CHEMICAL REVIEWS

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Review

Colorectal Cancer at the Crossroads: The Good, the Bad, and the Future of Platinum-Based Drugs

Jia Xuan Kee,[‡] Jia Ning Nicolette Yau,[‡] Ram Pravin Kumar Muthuramalingam, Xinyi Wang, Wei Heng Chng, Alvaro Lopez-Sanchez, Kevin Kuang Wei Tay, Lih-Wen Deng, Dan Gibson, Helene C. Bertrand, Giulia Adriani, Wee Han Ang,* and Giorgia Pastorin*

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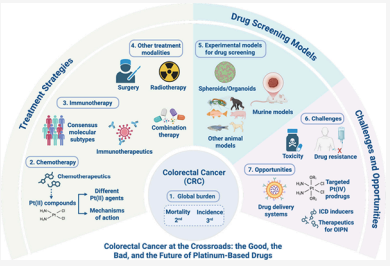
ABSTRACT: Colorectal cancer (CRC) remains a significant global health challenge, ranking third in incidence and second in mortality among cancers worldwide. This review addresses the complex landscape of CRC, focusing on incidence, mortality trends, preventive strategies, and the evolving therapeutic approaches, particularly highlighting the role of platinum-based drugs like oxaliplatin (OXP). It also underscores the increasing burden of CRC, with factors such as westernized diets, aging populations, and genetic predispositions contributing to its prevalence. Therapeutically, early detection greatly enhances survival rates, emphasizing the importance of regular colonoscopies and stool tests. For advanced CRC, chemotherapy remains pivotal, with OXP as a cornerstone treatment despite its associated chemotherapy-induced peripheral neurotoxicity (CIPN). The review explores innovative strategies to overcome challenges related to chemotherapy, such as drug resistance and side effects, highlighting recent developments in the field, such as Pt(IV) prodrugs and immunotherapeutic approaches to enhance efficacy while minimizing toxicity. Additionally, this manuscript examines experimental models for drug screening, emphasizing the role of murine models and advanced 3D *in vitro* systems in CRC research. Overall, the review advocates for a comprehensive approach, integrating prevention, early detection, and personalized treatments to alleviate the global burden of CRC.



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1. GLOBAL BURDEN OF COLORECTAL CANCER (CRC)

1.1. Incidence and Mortality Trends Associated with CRC

Colorectal cancer (CRC) is among the most lethal and prevalent cancers globally, ranking third in incidence and second in overall mortality, with similar incidences and mortality rates in both genders (Table 1). CRC accounted for 1.9 million new cases in 2020,[1] and is projected to exceed 3 million cases by 2040.[2] CRC incidence and mortality vary considerably among different countries. Generally, cases have increased in tandem with socioeconomic development, particularly in countries with an increasing human development index (HDI),[3] due to growing risk factors such as a more westernized diet, population aging, smoking and physical inactivity.[4] Consequently, in Asia, the incidence and mortality of CRC have also been increasing steadily and were the highest globally in 2018.[4] Of note, the incidence of CRC is significantly higher in Chinese populations compared to other ethnicities in multiracial countries within Southeast Asia,[5] suggesting genetic factors might predispose Chinese to CRC more than other ethnicities. However, no specific genetic markers have been found exclusively or significantly more expressed in Chinese CRC patients.[6] Other factors contributing to this higher incidence of CRC in Chinese population (i.e., host, environmental, and endogenous factors) are currently under investigation.[7]

Table 1. Top Five Most Common and Deadly Cancers Globally in 2022[8] (NA, Not Applicable/Not Available)

	incidence (%)		mortality rate (%)	
cancer type	male	female	male	female
breast	<1	23.8	NA	15.4
colorectal	10.4	8.9	9.2	9.4
lung	15.2	9.4	22.7	13.6
liver	5.8	2.7	9.6	5.5
prostate	14.2	NA	7.3	NA

1.2. Clinical Guidelines on the Treatment of CRC

CRC slowly develops from an abnormal growth, often referred to as a polyp, on the inner lining of the rectum or colon. Polyps can form a tumor and expand into blood vessels, facilitating cancer metastasis.[9] CRC cases can be subdivided based on the location of the developed tumor such as colon and rectal cancer or left-sided and right-sided tumors (Figure 1). These classifications help to systematically guide diagnosis, identify suitable treatment options, and provide estimated prognosis based on comprehensive clinical practice guidelines issued by leading oncology networks, such as the National Comprehensive Cancer Network (NCCN). Right-sided tumors, for instance, are more common in females whereas left-sided tumors are more predominant in male patients.[10]

The standard of care for detection and treatment of CRC in early stages (i.e., stage I–III) is surgical resection with curative intent (Table 2, section 4.1) for the removal of polyps (i.e., polypectomy) and tumors (i.e., colectomy).[11−13] These

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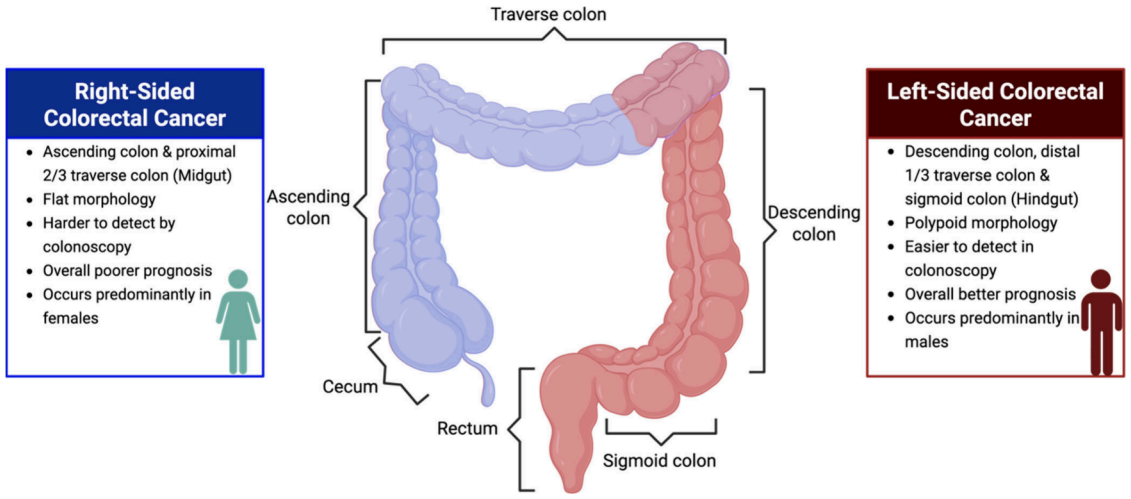

Figure 1. Diagram of human colon and differences between right- and left-sided CRC.[10] Figure created with BioRender.com.

Table 2. General Treatment Strategies for Different Stages of CRC[17]

	treatment (% total)		
stage	I and II	III	IV
polypectomy	3	<1	<1
colectomy	84	31	12
colectomy and chemotherapy	10	67	36
chemotherapy	<1	<1	30
others	2	<1	21

surgeries are often supplemented with neoadjuvant, adjuvant, or perioperative systemic therapies in order to reduce recurrence risk and improve patient survival by up to 90% (Table 3).[14] Advanced CRC cases that are diagnosed at late stages (i.e., stage IV), when the disease is symptomatic and has metastasized to other tissues and organs,[15,16] are associated with poorer prognosis (Table 3).[12,13] For advanced metastatic CRC (mCRC), systemic therapies such as chemotherapy (ca., 66−67%, section 2) and immunotherapy (section 3) are the cornerstones of treatment, aiming for outcomes ranging from potential cure to palliation and life prolongation.[11−13] Platinum (Pt)-based chemotherapeutics (section 2.1), particularly oxaliplatin (**OXP**)(section 2.1.3), play a crucial role in current clinical regimens owing to their unique mechanisms of action (section 2.2). On the other hand, immunotherapies using immune checkpoint inhibitors (ICIs) offer an effective alternative for specific advanced CRC patient subsets (i.e., deficient DNA mismatch repair (dMMR)/ microsatellite instability (MSI)-high) (section 3.4−3.6).

In addition, EGFR inhibitors (such as cetuximab and panitumumab) are best used in metastatic colorectal cancer patients whose tumors are KRAS and NRAS wild-type and located on the left side of the colon, as these patients benefit most; they are ineffective in tumors with KRAS or NRAS mutations and less effective for right-sided tumors. VEGF and VEGFR inhibitors (such as bevacizumab, ramucirumab, and aflibercept) can be used in metastatic colorectal cancer regardless of RAS or BRAF mutation status or tumor location, and are typically given in combination with chemotherapy, provided there are no contraindications such as bleeding risk or uncontrolled hypertension.

Table 3. Brief Summary on the Stages of CRC and Associated Frequency of Diagnosis and 5-Year Survival Rate[a].[20]

stage	description[15,21,22]	frequency of diagnosis[b]	5-year survival rate[b]
I (localized)	tumor has invaded submucosa no regional lymph node metastases nor distant metastases detected	24.9%	≥90%
II (localized)	tumor has invaded through the muscularis propria no regional lymph node metastases nor distant metastases detected	24.4%	≥80%
III (regional)	tumor has invaded through the muscularis propria into the subserosa	28.5%	≤70%
IV (metastatic)	tumor has directly invaded other organs or structures, or perforates visceral peritoneum metastases in multiple regional lymph nodes and/or distant metastases detected	22.2%	≤20%

[a]Other than primary tumor (T), the staging of CRC is also dependent on the status of regional lymph nodes (N) and distant metastases (M) in the TNM staging system.. [b]Statistics of stage at diagnosis and 5-year survival rate of CRC from 2016 to 2020 across 9 countries in Europe.

Despite these advances, significant challenges remain (section 6). The efficacy of current CRC chemotherapeutics (e.g., **OXP**) for mCRC is often diminished by major dose-limiting toxicities (e.g., **OXP**-induced peripheral neuropathy) and the emergence of drug resistance (section 6.1−6.3), which restrict therapeutic options and impact patients' quality of life. Additionally, the differences in the tumor microenvironment (TME) between primary and metastasized tumors affect tumor sensitivity toward systemic treatments such as chemotherapies and immunotherapies.[18,19] As a result, the majority of the advanced CRC patients do not benefit from ICI therapies due to low response rates, resistance development as well as immune-related adverse events (section 6.4). Consequently, treatment decisions are increasingly reliant on patient-specific molecular profiling for optimal treatment regimens (section

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3.2−3.3). These limitations underscore the critical need for innovative therapeutic strategies that can enhance efficacy, overcome resistance mechanisms, reduce systemic toxicities, and potentially offer novel combination approaches. Emerging strategies include targeted Pt-based chemotherapeutics (section 7.1), Pt-based chemoimmunotherapeutics (section 7.2), and innovative drug delivery strategies (section 7.3) which could represent promising alternatives to overcome these challenges. Furthermore, the development and application of suitable experimental models are crucial for optimizing the evaluation and accelerating the discovery of novel Pt-based drug candidates with clinical potential (section 5).

2. CHEMOTHERAPY

Chemotherapy is often provided either before (neoadjuvant therapy) or after (adjuvant therapy) surgery to reduce the risk of recurrence and improve patients' survival (Table 4).[23] In stage IV CRC (i.e., mCRC) and in patients with unresectable tumors, chemotherapy becomes the primary treatment, essential for increasing overall survival (OS) rates.[24,25] Chemotherapeutic drugs typically suppress tumor growth by interfering with cellular function, which eventually induces apoptosis in cancer cells.[26] Patients abstaining from chemotherapy typically observe a short median survival, ranging from 0 to 5 months.[27] The main classes of chemotherapeutics approved for treating CRC include fluoropyrimidines, folic acid derivative, deoxyribonucleic acid (DNA) topoisomerase I inhibitors, angiogenesis inhibitors and platins (Table 5 and Figure 2).

Other classes of drugs including nucleosides, antibiotics, anthracyclines, and mitogen-activated protein kinase (MAPK) signaling pathway inhibitors, while approved for other cancers, are still under clinical evaluation for treating CRC patients (Table 5). Recently, drugs that target specific cancer-associated gut microbiota have been proposed as a new approach to treating CRC. The *Fusobacterium nucleatum* (*F. nucleatum*) bacteria in tumor tissue, for instance, have been linked to increased chemoresistance,[32] reduced T-cell infiltration,[33] and poor patient survival.[34] Consequently, targeting *F. nucleatum* using an antibiotic like metronidazole can reduce cancer cell proliferation and tumor growth.[35] However, this approach is still preliminary and has yet to reach clinical trials.

Table 4. Common Chemotherapy Regimens for Treating CRC

regimen	chemotherapeutic drugs	dosing	median survival (months)
FOLFOX[28]	leucovorin	200 mg/m^2 on days 1 and 2	19.5
	5-fluorouracil	400 mg/m^2 bolus, 600 mg/m^2 on days 1 and 2	
	OXP	85 mg/m^2 on day 1	
FOLFIRI[29]	5-fluorouracil	400 mg/m^2 bolus, 600 mg/m^2 on days 1 and 2	17.4
	irinotecan	180 mg/m^2 on day 1	
	leucovorin	200 mg/m^2 on day 1	
FOLFOXIRI[30]	5-fluorouracil	400 mg/m^2 bolus, 600 mg/m^2 on days 2 and 3	21.9
	irinotecan	150 mg/m^2 on day 1	
	leucovorin	200 mg/m^2 on days 2 and 3	
	OXP	65 mg/m^2 on day 2	
CAPOX[31]	capecitabine	1000 mg/m^2 bid daily	16.8
	OXP	70 mg/m^2 on days 1 and 8	

For the clinical management of CRC, various chemotherapy drugs that target different cellular pathways are available (Figure 2), such as 5-fluorouracil (5-FU), irinotecan (Camptosar), oxaliplatin (**OXP**, Eloxatin), trifluoridine−tipiracil (Lonsurf), and capecitabine (Xeloda). However, single-agent chemotherapy regimen is not commonly used for advanced CRC management.[36] Instead, combination therapies such as FOLFOX (leucovorin calcium + 5-FU + **OXP**),[37,38] FOLFIRI (leucovorin calcium + 5-FU + irinotecan),[39−41] FOLFOXIRI (leucovorin calcium + 5-FU + **OXP** + irinotecan),[42,43] and CAPOX (capecitabine + **OXP**)[44,45] are more routinely used as first-line treatment for advanced CRC to improve their overall efficacy by working synergistically or additively according to their mechanisms of action (Table 4).[41,46,47]

One example is the combination of 5-FU, a commonly used chemotherapeutic agent for CRC treatment, with leucovorin (LV) (i.e., a reduced folate compound). 5-FU is a fluoropyrimidine that interferes with ribonucleic acid (RNA) synthesis as well as DNA synthesis and repair.[48,49] However, the reported response rate of 5-FU is less than 20%, with median survival time of less than 9 months. As a result, LV is added on top of 5-FU to enhance its cytotoxicity by acting as an external source to increase the intracellular levels of reduced foliate cofactors, which can stabilize the binding of 5-FU metabolite (i.e., 5-fluorodeoxyuridine monophosphate) to thymidylate synthase, resulting in pronounced and prolonged inhibition of DNA synthesis.[50,51] Indeed, a meta-analysis of 3300 patients from 19 randomized trials found that a combined treatment of 5-FU and LV was more likely to induce at least a 50% reduction in tumors and statistically improve the OS rate when compared to 5-FU alone in CRC patients.[52] The addition of the Pt(II) drug **OXP** further improved the mean survival from 17.4 (FOLFIRI) to 21.9 months (FOLFOXIRI) (Table 4).[30] Complementary to chemotherapy, targeted therapies are available in CRC such as antibodies targeting Epidermal Growth Factor (EGF) or the vascular endothelial growth factor (VEGF) (Table 5).

2.1. Pt(II) Chemotherapeutics for CRC

Since their discovery in the 1960s−1970s,[92,93] *cis*-Pt(II) drugs, in which at least 2 identical ligands are on the same side of the molecule, have been highly effective in treating various solid tumors (Figure 2, Table 6). **Cisplatin** (**CDP**), **carboplatin** (**CBP**), and **oxaliplatin** (**OXP**) are first-line chemotherapeutic agents for various cancers.[94] Nearly half of all chemotherapeutic regimens involve the use of these Pt(II) drugs.[95]

2.1.1. Cisplatin (CDP). **CDP** is a first-generation Pt compound with a simple *cis*-square planar structure consisting of two chlorido and two ammine ligands (Figure 2). It is used to treat several cancers through intravenous (IV) administration (Table 6).[94] However, the lack of specificity for cancer cells also makes **CDP** highly toxic, being associated with severe side-effects (e.g., chronic nephrotoxicity, ototoxicity, gastrointestinal toxicity and neuropathy) that can persist long

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Table 5. Chemotherapeutics and Targeted Therapeutics for CRC, Either in Clinical Trials or FDA-Approved

class	drug	clinical status	mechanism of action
fluoropyrimidines[53,54]	5-FU	approved	inhibit thymidylate synthase, rate-limiting enzyme in pyrimidine nucleotide synthesis to disrupt DNA-replication and repair and initiate apoptosis
	capecitabine	approved	replace uracil for incorporation into DNA and RNA to cause DNA/RNA fragmentation
	trifluridine	approved	
	tipiracil	approved	
folic acid derivative	leucovorin calcium	approved	serves as additional source of reduced folate cofactors to stabilize binding between 5-fluorodeoxyuridine monophosphate to thymidylate synthase
fluoropyrimidine prodrugs	thymectacin	trial (NCT00031616)	prodrug of brivudine monophosphate
	tegafur	trial (NCT03448549)	prodrug of 5-FU: contains gimeracil to enhance the bioavailability of 5-FU and oteracil to reduce gastrointestinal toxicity
DNA topoisomerase I inhibitors[55,56]	irinotecan	approved	inhibit topoisomerase I that catalyzes breakage and rejoining of DNA strands, causing DNA fragmentation that initiates apoptosis
	camptothecin	trial (NCT04744831)	
angiogenesis inhibitors[57]	bevacizumab	approved	inhibit development of blood vessels that support tumor growth by inhibiting growth factors such as VEGF
	aflibercept	approved	interfere with signaling pathways required for cellular proliferation that support angiogenesis
	ramucirumab	approved	
	regorafenib	trial (NCT03657641)	VEGF inhibitors
	vandetanib	trial (NCT00500292)	
	cediranib	trial (NCT00384176)	
	HLX04	trial (NCT04547166)	
	sorafenib	trial (NCT00780169)	
	MKC-1	trial (NCT00016250)	interfere with the AKT/mTOR pathway
	everolimus	trial (NCT01387880)	
	SU011248	trial (NCT00806663)	tyrosine kinase inhibitor
	NGR-hTNF	trial (NCT00483080)	interferes with pro-survival signaling pathways (Ras, Erk and Akt)
EGFR inhibitors[58]	cetuximab	approved	selectively inhibit EGFR to disrupt signaling pathways for cellular growth and proliferation necessary for tumor growth
	panitumumab	approved	
	CMAB009	trial (NCT03206151)	
	SCT200	trial (NCT03405272)	
	lapatinib	trial (NCT00574171)	
Pt drugs[59]	**OXP**	approved	form irreparable Pt-DNA adducts that interrupt DNA replication and initiate apoptosis
mitogen-activated protein kinase (MAPK) signaling pathway inhibitors	vemurafenib	trial (NCT03727763)	selectively inhibit mutated BRAF V600E
	cobimetinib	trial (NCT02788279)	mitogen-activated protein kinase (MAPK) inhibitors
	binimetinib	trial (NCT03693170)	
	docetaxel	trial (NCT02039336)	
nucleosides	gemcitabine	trial (NCT01909830)	incorporate into DNA strand to interfere with DNA replication and induce apoptosis

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Table 5. continued

class	drug	clinical status	mechanism of action
	decitabine	trial (NCT00879385)	
antibiotics	mitomycin C	trial (NCT00294359)	form cross-links with DNA strands to interfere with DNA replication and induce apoptosis
anthracyclines	epirubicin	trial (NCT03251612)	cause DNA damage to induce apoptosis

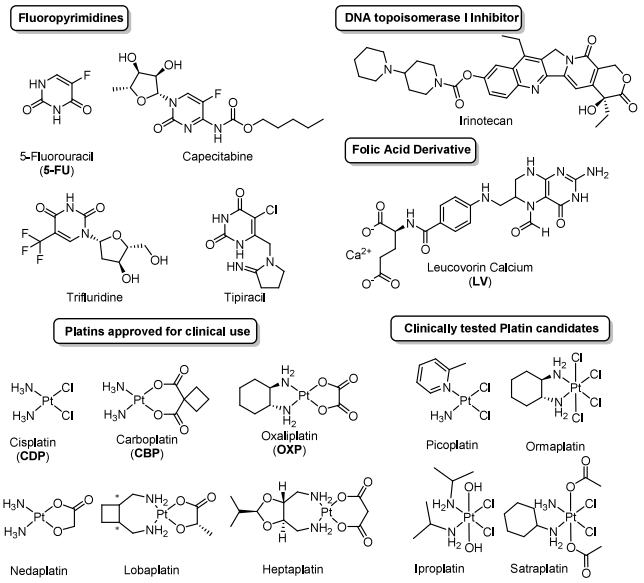

Figure 2. Structures of small molecule chemotherapeutics frequently used to treat CRC as well as Pt drugs used in the clinic and/or clinically trialled.

after chemotherapy ends (please refer to section 6.1 for more details).[94]

2.1.2. Carboplatin (CBP). **CBP** is a second-generation *cis*-Pt compound that replaces the chlorido ligands in **CDP** with a cyclobutane-1,1-dicarboxylate leaving group (Figure 2).[96,97] This makes **CBP** less reactive than **CDP**, resulting in milder toxicity mainly in the form of myelosuppression in patients and higher maximum tolerated dose (MTD) by the patients (Table 6).[98] **CBP** treatment is comparable to **CDP** treatment both as a single agent and in combination chemotherapy for lung and ovarian cancers.[98−100] However, **CDP** treatment has been shown to remain superior to **CBP** for germ cell tumor, bladder, head and neck cancers despite its poorer toxicity profile.[98,101] **CBP** is typically used in treating ovarian cancer with combination chemotherapy and is selected over **CDP** in palliative care to maximize the patients' quality of life.[102−104]

2.1.3. Oxaliplatin (OXP). **OXP** is a *cis*-Pt compound containing *trans*-(1*R*,2*R*)-diaminocyclohexane (DACH) (Figure 2) and oxalate ligands. The oxalate ligand reduces the reactivity of **OXP** compared to **CDP**, resulting in much fewer associated toxicities than **CDP** (Table 6).[59] However, acute chemotherapy-induced peripheral neuropathy (CIPN), a persistent pain sensation from peripheral neurons, is a key challenge to the therapeutic use of **OXP** (please refer to section 6.3 for more details).[105] **OXP** has been more effective for treating CRC compared to other Pt(II) drugs,[59] but the molecular mechanisms behind the higher CRC-specificity is not well-understood.[106,107] Several studies suggest that **OXP** is more efficiently transported into CRC cells due to its higher affinity for the organic cation transporters.[108109,110] Additionally, **OXP** forms bulkier and more hydrophobic Pt-DNA adducts *via* its DACH ligand, enhancing its ability to inhibit DNA synthesis and cellular proliferation as well as reducing its cross-resistance with **CDP** and **CBP**.[111−113] Consequently, **OXP** has demonstrated to be more effective than **CDP** and **CBP** in inhibiting cellular proliferation in 6 out of 8 CRC cell lines (i.e., DLD-1, HCT116, HCT-15, HT-29, KM20L2, SW620) taken from the National Cancer Institute (Bethesda, Maryland, USA) automated screening panel.[111] Currently, chemotherapy regimens for treating mCRC include FOLFOX, the systemic administration of **OXP**, 5-FU, and LV (Table 4). The addition of **OXP** to the cocktail improved the average response rate and OS rate of patients.[31,114] **OXP** alone demonstrated low responses rates of around 20% in clinical trials, but in combination with LV and 5-FU (i.e., FOLFOX), the responses rates increased up to ca. 60%, with an increased progression-free survival (PFS) and OS. **OXP** can be used both as first-line and adjuvant therapy in CRC. The combination regimen depends on factors such as tumor type, stage, and burden. Unlike FOLFIRI (Table 4) treatment, FOLFOX is effective in an adjuvant setting, leading to its use in postoperative therapy. FOLFOX and CAPOX (Table 4) regimens are the most frequently used in metastatic conditions. In addition, **OXP** is also being evaluated in clinical trials for the treatment of gastric, pancreatic, breast and non-small cell lung cancers, though no official outcome has been made available yet.[115] The detailed mechanisms and advantages of **OXP** for CRC treatments have been extensively discussed by O'Dowd et al.[116]

2.1.4. Other Clinically Relevant Pt(II) Drugs. Other Pt(II) drugs that have been approved for use in other countries include **nedaplatin** in Japan (for esophageal, ovarian, cervical, bladder, lung, head and neck cancers) (Table 6 and Figure 2), **lobaplatin** in China (for chronic myelogenous leukemia and inoperable, metastatic breast and small cell lung cancer) and **heptaplatin** in Korea (for advanced gastric cancer).[65] **picoplatin** is another promising Pt(II) drug candidate designed to circumvent glutathione-mediated cellular resistance mechanism.[117] **Picoplatin** demonstrated promising preclinical efficacy in **CDP**- and **OXP**-resistant ovarian and colorectal cell lines (i.e., A2780, CH1, 41M, HCT116, HT-29), respectively, and can be administered orally, which is attractive for improving patient compliance.[118,119] While picoplatin has undergone various phase I−II clinical trials (e.g., NCT00465725 and NCT00478946) for the treatment of CRC, it has yet to demonstrate significant improvement to warrant clinical approval.

2.2. Mechanisms of Action of Pt(II) Drugs in CRC

2.2.1. Uptake and Efflux Mechanisms. Passive diffusion across the cell membrane was initially proposed as the main mode of internalizing Pt(II) drugs in cells. However, physical

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Table 6. Pt(II) Chemotherapeutics That Have Received Approval or Currently in Clinical Trials for Various Types of Cancer

Pt(II) drug	clinical status	indications	dose	common toxicities
cisplatin (CDP)[59−62]	approved[63]	ovarian	up to 200 mg/m^2 per cycle administered intravenously	nephrotoxicity
		testicular		ototoxicity
		bladder		gastrointestinal toxicity
carboplatin (CBP)[64,65]	approved[63]	ovarian	up to 2400 mg/m^2 per cycle administered intravenously	myelosuppression
oxaliplatin (OXP)[65,66]	approved[63]	colorectal	up to 175 mg/m^2 per cycle administered intravenously	chemically induced neuropathy
nedaplatin[65,67−71]	approved (Japan)	head and neck	up to 120 mg/m^2 per cycle administered intravenously	
	phase I−IV	cervical	NA	
lobaplatin[65,72−78]	approved (China)	lung	up to 60 mg/m^2 per cycle administered intravenously	
		leukemia		
	phase I−IV	colorectal	NA	
		ovarian		
		liver		
heptaplatin[65,79−81]	approved (Korea)	gastric	up to 400 mg/m^2 per cycle administered intravenously	
	phase I−III	head and neck	NA	
picoplatin[82−91]	phase I−II	CRC	up to 150 mg/m^2 per cycle administered intravenously	interim analysis determined modest improvement in median overall survival but clinical trials currently ongoing in US
		prostate		
		lung		
		bladder		
		breast		
		ovarian		
		pancreatic		
		head and neck		

characterizations of Pt(II) drugs (e.g., **CDP**, **CBP**, and **OXP**) indicated that they are hydrophilic, which disfavors their diffusion across the lipophilic cell membrane.[120] Membrane transporters have been implicated as key players in the cellular accumulation of Pt drugs, directly influencing the anticancer efficacy of Pt(II) drugs.[120,121] Several membrane transporters, in particular, have been recognized as common transporters for all Pt(II) compounds.[122]

The copper transporter 1 (CTR1) is the most well-known substrate transporter for **CDP**, **OXP** and **CBP** in mammalian cells.[123,124] The genetic knockout and reduced expression of the *SLC31A1* gene that encodes for CTR1 are associated with decreased cellular accumulation of and sensitivity to **CDP**, **OXP**, and **CBP** in cancer cell lines.[123−127] Clinically, the efficacy of Pt chemotherapy correlates well with the expression level of CTR1, suggesting that the CTR1 expression can be used as a prognostic marker of patient response to Pt chemotherapy. For example, **CDP** treatment was more effective, extending PFS by 20 months, in ovarian cancer patients with a 2-fold increased of CTR1 messenger RNA (mRNA) expression in tumor tissue.[128]

Other copper transporters involved in cellular uptake of Pt(II) drugs include the copper transporter 2 (CTR2) and the P-type ATPase copper transporters (e.g., ATP7A and ATP7B), which utilize energy from adenosine triphosphate (ATP) hydrolysis to transport copper(I) across cellular membranes by conductance.[122] Pt agents bind to the *N*-terminus of the methionine-rich motifs of CTR1/2 and are transported into cells *via* endocytosis.[129] *In vitro*, *in vivo*, and clinical studies found that decreased CTR2 expression correlated to increased intracellular Pt and greater efficacy of Pt chemotherapy.[128,130,131] Conversely, overexpression of ATP7A and ATP7B on the cell surface is associated with increased Pt resistance in ovarian cancer cell lines (e.g., 2008/EV and 2008/MNK) and patients with ovarian cancer.[132,133] These findings suggest that the overexpression of ATP7A and ATP7B represent a cellular response when developing resistance mechanisms to Pt. As transporters, CTR2, ATP7A and ATP7B are likely responsible for the efflux of Pt out of the cell, thereby reducing the sensitivity of the cells to Pt.

The volume-regulated anion channels (VRACs), a membrane transporter family that facilitates the exchange of osmolytes, such as chloride, to maintain cellular homeostasis,[134,135] have recently been found to play a major role in the cellular uptake of **CDP** and **CBP**. The VRACs are formed by at least 2 different leucine-rich repeat containing 8 (LRRC8) subunits, one of which is LRRC8A. Specific combinations of LRRC8 augment the permeability of the resulting pore, thereby modifying the regulated osmolyte for which the channel is responsible. Planells-Cases and coworkers found that up to 50% of cellular **CDP** and **CBP** entered cells *via* the VRACs, and the cellular Pt content was

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significantly reduced in cells with malformed VRACs.[136] Consequently, increased LRRC8A and LRRC8D expression correlated with increased survival in ovarian cancer patients undergoing Pt-based chemotherapy.[136] While the importance of the VRACs for cellular uptake of **OXP** was not evaluated, the authors postulated that VRACs could accommodate any molecular compound small enough to fit through the 12−14 Å channel diameter.[137]

Organic cation transporters 1−3 (OCTs 1−3), which facilitate the transport of a broad spectrum of organic cations of 60−350 kDa, represent another class of transporters for Pt(II) drugs. Although the OCTs are not as well-investigated as the copper transporters, current studies suggest that each Pt(II) drug has a preferred OCT for transport into the cell. For example, **CDP** relies on OCT1 for cellular transport. Studies by Yonezawa et al. and Zhang et al. showed improved intracellular accumulation of **CDP** and **CBP** in human embryonic kidney (HEK-293) cells overexpressing human (h) OCT1 but no change was observed upon overexpression of hOCT3.[68,110] Interestingly, Yonezawa et al. found that overexpression of hOCT2 improved the cellular accumulation of **CDP**, whereas Zhang et al. found no significant influence of the same channel on **CDP** accumulation. Critically, Yonezawa et al. performed Pt accumulation studies using much higher concentrations (i.e., 100−1000 μM) than Zhang et al. (i.e., 6 μM). These differences account for the distinct kinetics of transport *via* the OCTs. **OXP** is a good substrate for all OCTs, displaying improved accumulation in the cells overexpressing OCT1, OCT2, and OCT3, which have been reported to be overexpressed in CRC tumors, contributing to the greater efficacy of **OXP** in treating CRC compared to the other Pt compounds.[109,110]

2.2.2. Pt-DNA Adduct Formation. After cell entry, Pt compounds undergo aquation to form electrophilic Pt(II) aqua species that preferentially react at nucleophilic N7 positions of purine residues (Figure 3). Reactivity with guanine is preferred due to H-bonding interactions between the ammine ligands and the exocyclic guanine-O6, giving rise to a majority of 1,2-d(GpG) and 1,2-d(ApG) intrastrand Pt-DNA adducts (ca., 80−90%) in the major groove, with the remaining Pt-DNA adducts constituted by 1,3-intrastrand and interstrand cross-links (ca., 10%).[138−140] These adducts distort DNA through local unwinding and interfere with cell function by inhibiting RNA transcription and DNA replication.[141,142]

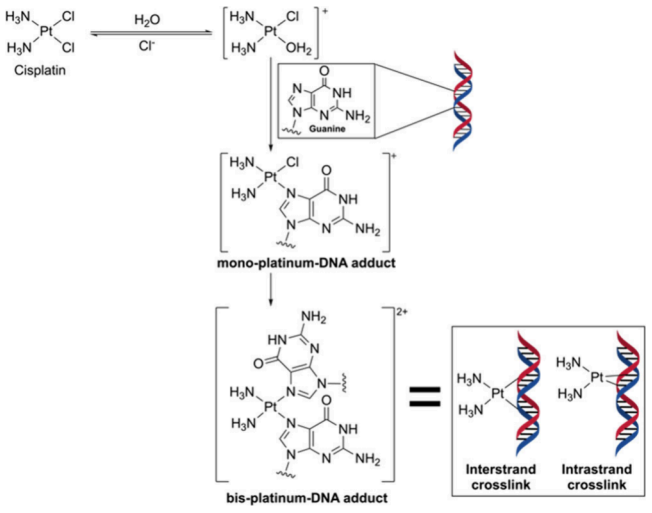

Figure 3. Mechanism of Pt−DNA adduct formation.

While nuclear DNA has long been regarded as the primary target of Pt drugs, mitochondrial DNA (mtDNA) has been recently implicated in the mechanism of action of **CDP**.[143] Unlike nuclear DNA, mtDNA lacks histones, making the structure more vulnerable to oxidative damage.[144] Additionally, absence of the nucleotide excision repair (NER) pathway in mtDNA makes it more sensitive to damage induced by Pt drugs.[145] LeDoux and co-workers observed that, while nearly 70% of Pt-DNA adducts were removed from nuclear DNA within 24 h, there was comparatively minimal repair of the same damage in mtDNA of Chinese hamster ovary cells.[146] The distortion of the mtDNA compromises mitochondrial function (e.g., hydrolysis of ATP), thereby activating apoptotic pathways.[147]

2.2.3. Nucleolar Stress Induction. Certain Pt(II)-based drugs have recently been found to cause cell death by triggering nucleolar stress. Nucleoli are the largest subnuclear structures in eukaryotic cells. Their primary role is the biosynthesis of ribosomes, the intricate cellular machines pivotal for translating mRNA into proteins. This complex process involves the coordination of approximately 200 proteins to synthesize ribosomal RNA (rRNA) and assembles it with ribosomal proteins. However, the homeostasis of ribosome biogenesis can be impaired by morphological alterations in nucleoli, such as segmentation or disruption, a condition recently termed "nucleolar or ribosomal stress". These changes can ultimately trigger the activation of the p53 signaling pathway, leading to cell cycle arrest and apoptosis.[148,149] Pt(II) drugs containing a cyclic diamino bidentate ligand, like **OXP** and other Pt(II)-DACH derivatives, have been observed to induce nucleolar stress by inhibiting rRNA transcription.[150] On the other hand, Pt(II) complexes with monodentate or alkyl-based bidentate amino ligands, such as **CDP** or **CBP**, have been predominantly seen to operate by DNA-adduct formation.

2.2.4. Oxidative Stress Induction. A third axis to comprehend the cellular activity of Pt(II) complexes is oxidative stress, characterized by an imbalance between the production and accumulation of reactive oxygen species (ROS) such as hydroxyl radical (•OH), superoxide anion (O_2•$^-$) or hydrogen peroxide (H_2O_2), and the ability to detoxify these byproducts by antioxidant defenses.[151,152] ROS are known to have a two-edged sword-like behavior in cancer: malignant cells usually display higher ROS levels than healthy cells, and the homeostasis of these species, regulated by generally overexpressed antioxidant defenses, can promote proliferation and tumor growth.[153] However, a sharp increase in the intracellular levels of ROS can easily overwhelm the inefficient antioxidant arsenal of cancer cells and induce oxidative stress-mediated apoptosis.[154]

After aquation, the formed Pt(II) center is a soft Lewis acid, providing a highly electrophilic species prone to react with several nucleophilic biological targets, especially sulfur-containing moieties. For example, glutathione (GSH), an important metabolite for maintaining intracellular redox potential and nonenzymatic ROS scavenger, can be depleted through Pt-GSH binding, resulting in oxidative stress induction.[155] Oxidative stress can also be generated due to the formation of adducts with mtDNA. Due to the lack of repair mechanisms, **OXP**-DNA adducts formed within

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mitochondria cannot be repaired. This ultimately leads to mitochondrial dysfunction and the generation of ROS.

2.2.5. Immunogenic Cell Death (ICD). Immunogenic cell death (ICD) is a form of regulated cell death (RCD) that induces the activation of both innate and adaptive immune responses. It involves the release of damage-associated molecular patterns (DAMPs) from dying cells and their subsequent recognition by pattern-recognition receptors (PRRs) on immune cells, generating specific antitumor immune responses.[156] Doxorubicin was the first ICD inducer found to regress tumor in immunocompetent mice through ICD-mediated immune responses.[157] Since then, extensive research has been done to elucidate the molecular and cellular mechanisms of ICD. One of the key factors that initiates ICD is organelle and cellular stress. In particular, ROS overgeneration by various means, such as photogeneration or redox reactions, is strongly associated with the onset of endoplasmic reticulum (ER) stress, which in turn triggers ICD.[158−161] Once initiated, ICD leads to the orderly exposure and release of DAMPs or alarmins from dying cancer cells, in a time- and space-dependent manner. Some of the key DAMPs and biological hallmarks found to be responsible for ICD include the exposure of calreticulin (CRT) on the cell membrane,[162−167] heat-shock proteins (HSPs) on the cell membrane or released passively,[168,169] the passive release of high-mobility group box 1 (HMGB1),[170−174] surface exposure of annexin A1 (ANXA1),[175−178] and the active or passive release of ATP.[166,179,180] These DAMPs interact with their respective PRRs on antigen-presenting cells such as dendritic cells (DCs), which ultimately leads to the activation of both the innate and adaptive immune systems through a network of cytokines and chemokines.[181−185] This can lead to the activation and recruitment of immune cells to the site of the cancer, which helps in tumor elimination. For example, the main "eat me" signal is represented by the cell surface exposure of CRT, which interacts with low-density lipoprotein receptor-related protein 1 (LRP1) on DCs.[186] ICD inducers can be broadly divided into two groups: (a) Type I inducers, which primarily target intracellular organelles excluding the ER, initiating DAMP-related signaling *via* subsequent ER stress responses; and (b) type II inducers, which involve ER as the primary target organelle.[187] As it was observed that Type II ICD inducers generally display higher levels of DAMPs and require simpler DAMPs trafficking, they are presumed to be more efficient ICD inducers than their type I counterparts.[188,189]

OXP is the first metal-based chemotherapeutic shown to elicit ICD-mediated immune response in CRC and has been classified as a type I ICD inducer.[190] Besides DNA-adduct formation, it is widely accepted that the other determinant for **OXP**'s anticancer efficacy is ICD induction.[191,192] In contrast, **CDP** does not induce preapoptotic CALR exposure *via* the PKR-like endoplasmic reticulum kinase (PERK)/eukaryotic initiation factor 2 alpha (eIF2α)/caspase 8/ B-cell receptor-associated protein 31 (Bap31) that is required for ICD induction.[190,193] **OXP** treatment has also shown to have longer lasting antitumor protection in CRC *in vivo* as compared to **CDP**,[190] consistent with the ICD-inducing ability of **OXP**.[193−197] **CDP** only induces extracellular release of HMGB1 protein, which is similar to **OXP**, but it does not cause ICD unless combined with ER stress inducers such as thapsigargin.[193] **OXP** treatment has been found to reverse immunosuppressive TME by (a) enriching TME with infiltration of innate and adaptive immune cells such as $CD8^+$ T cells,[198−203] natural killer (NK) cells,[199,204] and DCs,[205] and (b) depleting immunosuppressive cells such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs).[203,206]

The importance of *trans*-(1*R*,2*R*)-DACH ligand structure on **OXP** immunomodulatory activity has been explored by substituting it with different *cis*-1,3-diaminocycloalkanes. The results show that Pt(*cis*-1,3-diaminocyclobutane)Cl_2 displays comparable cytotoxicity and ICD features with **OXP** in microsatellite stable (MSS) CT26 cell line.[207] Macrophage-mediated antigen presentation to effector cells such as helper T cells (Th) is a key factor in tumor immunity. While **OXP** can effectively induce ICD DAMPs, it has been shown in various *in vitro* phagocytosis assays that **OXP** does not induce macrophage phagocytosis.[208,209] Interestingly, Pt(*cis*-1,3-diaminocyclobutane)Cl_2 increased J774 macrophage phagocytosis markedly, implying that it could be a better ICD inducer than **OXP**, since macrophage-mediated antigen presentation to effector cells such as Th cells is a key factor in tumor immunity.

In addition to the favorable immunostimulatory effect associated with the structural change of *trans*-(1*R*,2*R*)-DACH ligand, substitution using other isomers such as *cis*-1,4-DACH[210] and *trans*-1,2-diamino-4-cyclohexene (DACHEX)[211] has also demonstrated comparable or superior cytotoxicity against a range of cancer cell lines, including **OXP**-resistant CRC cells, relative to **CDP** and **OXP**. These improvements, particularly in overcoming **OXP** resistance, are likely driven by altered mechanisms of action resulted from ligand substitution. These include the formation of distinct DNA adducts that are less efficiently recognized and repaired by cellular DNA repair pathways,[212] enhanced inhibition of DNA polymerases,[213] and induction of metabolic stress.[211] Moreover, Pt(IV) complexes incorporating DACHEX-based ligands demonstrate that axial ligands modifications can further enhance cellular uptake and activation, through modulation of lipophilicity and reduction potential, ultimately leading to an increased *in vitro* potency against both **OXP**-sensitive and **OXP**-resistant CRC cell lines.[214] Notably, the chirality of these DACH ligands has also been found to have significant impact on their anticancer efficacy, depending on the final structure of the Pt(II) or Pt(IV) complexes.[215]

3. IMMUNOTHERAPY

3.1. Immunoediting and Immune Escape Process of CRC

Immunotherapy for CRC has shown promise, yet its effectiveness can be significantly influenced by the immune escape process, which highlights the complexity of the interplay between tumor cells and the immune system within the cancer-immunity cycle. The theory of cancer immunosurveillance,[216] which was first formalized by Sir Frank MacFarlane Burnet in 1970, proposes that the host's immune system has the capacity to identify and eliminate emerging tumor cells. However, subsequent evidence demonstrated that tumors can still develop in immunocompetent hosts.[221] More recently, evading immune destruction has been identified as one of the main hallmarks of cancer.[222] This phenomenon arises because the immune system functions as a double-edged sword. On one hand, it protects the host by eradicating tumors through immunogenic mechanisms. On the other hand, it exerts immune pressure on genetically unstable tumor cells,

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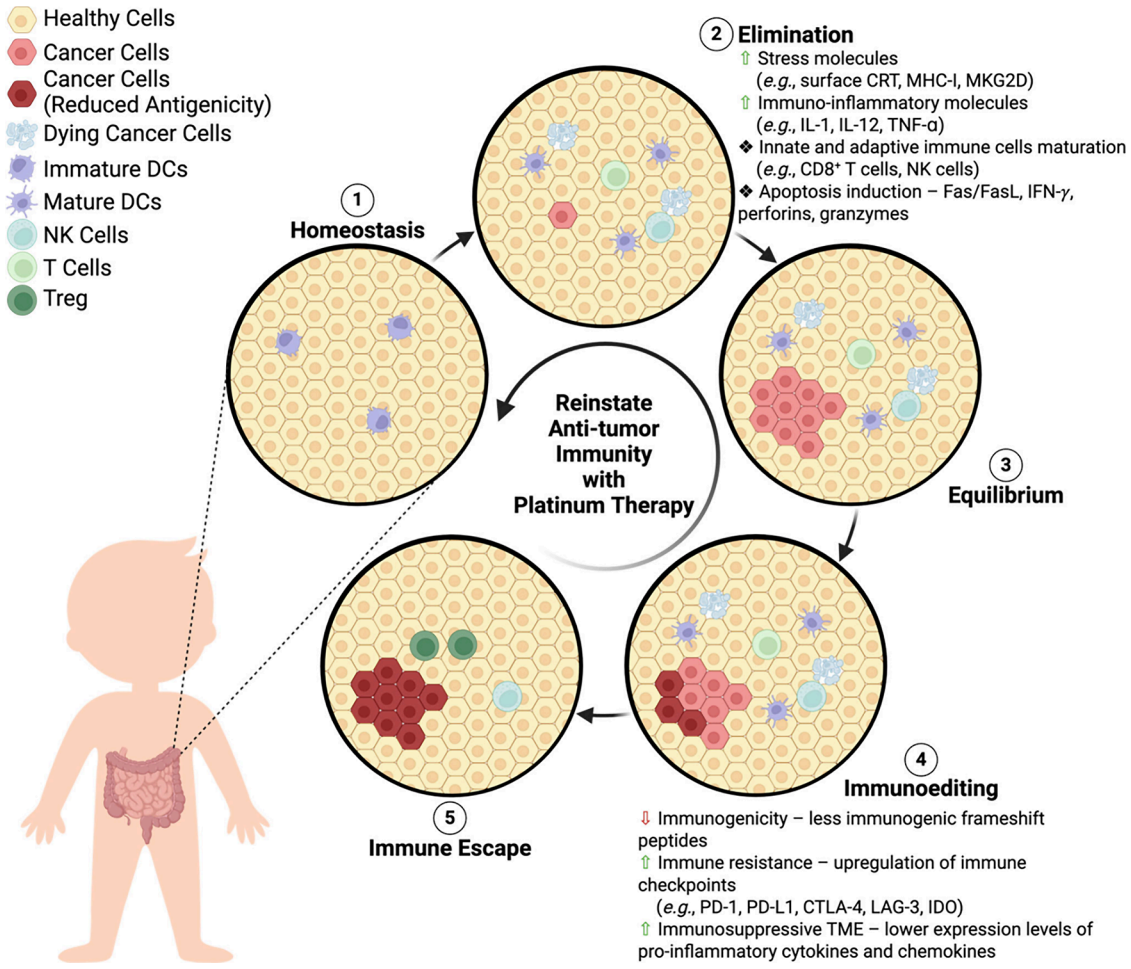

Figure 4. Depiction of the typical immune escape mechanisms involved in the tumorigenesis of CRC.[217−220] Restoration of antitumor immunity is achievable by employing immunomodulatory Pt complexes, which are capable of activating the adaptive immunity within the TME. Figure created with BioRender.com.

leading to the emergence of immunosuppressive variants through a process called immunoediting. Immunoediting results in tumor cells capable of thriving and progressing by avoiding immune recognition (i.e., low immunogenicity), increasing immunity resistance, or suppressing immune responses (i.e., immunosuppressive TME).[217] The dynamic process of immune escape unfolds in five phases: (1) homeostasis, (2) elimination; (3) equilibrium, (4) immunoediting, and (5) immune escape (Figure 4).[218]

Unsurprisingly, the tumorigenesis of CRC also involves different phases of the immune escape process. In the elimination phase, tumor cells express stress-induced molecules such as surface CRT, peptide-major histocompatibility class I (MHC-I), and NK group 2 member D (NKG2D) ligands that can attract immune cells to undergo cytotoxic activities. Tumor cells that survive the elimination phase then progress into the equilibrium phase, marked by a delicate balance between cancer cells and the immune system. These surviving cancer cells eventually transition from equilibrium phase into the escape phase, driven by the immunoediting process under constant immune pressure. For instance, it has been found that MSI-High CRC with intact antigen presentation machinery can survive immune selection by producing immunogenic frameshift peptides that are less detectable by the immune system.[219] Furthermore, highly immunogenic MSI CRC has also been reported to overcome the innate and adaptive immune systems by overexpressing immune checkpoints such as programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), and indoleamine 2,3-dioxygenase (IDO), compared to CRC with higher microsatellite stability.[220] As a result, the high immune cells infiltration in CRC with MSI is counteracted by the overexpression of immunosuppressive immune checkpoints, resulting in "exhausted" immune cell populations, and consequently the depletion of antitumor immunity.

Other studies also revealed that CRC subpopulations associated with more favorable prognosis exhibit elevated expression levels of chemokines such as chemokine (C−C motif) ligand (CCL) 5, chemokine (C−X−C motif) ligand (CXCL) 9, and CXCL10[226] as well as cytokines such as interleukin (IL)-7, IL-8, IL-15, IL-18, and IL-1β[227] that promote the immune inflammatory profile as compared to other CRC subpopulations. Therefore, it is evident that the immunoediting process generates tumor cells that are poorly immunogenic, rendering them more "invisible" to the immune system and facilitating their immune escape.

3.2. CRC Consensus Molecular Subtypes and Their Immune Landscape

The prognosis and treatment outcome of CRC immunotherapy are strongly linked with its phenotype and immune status.

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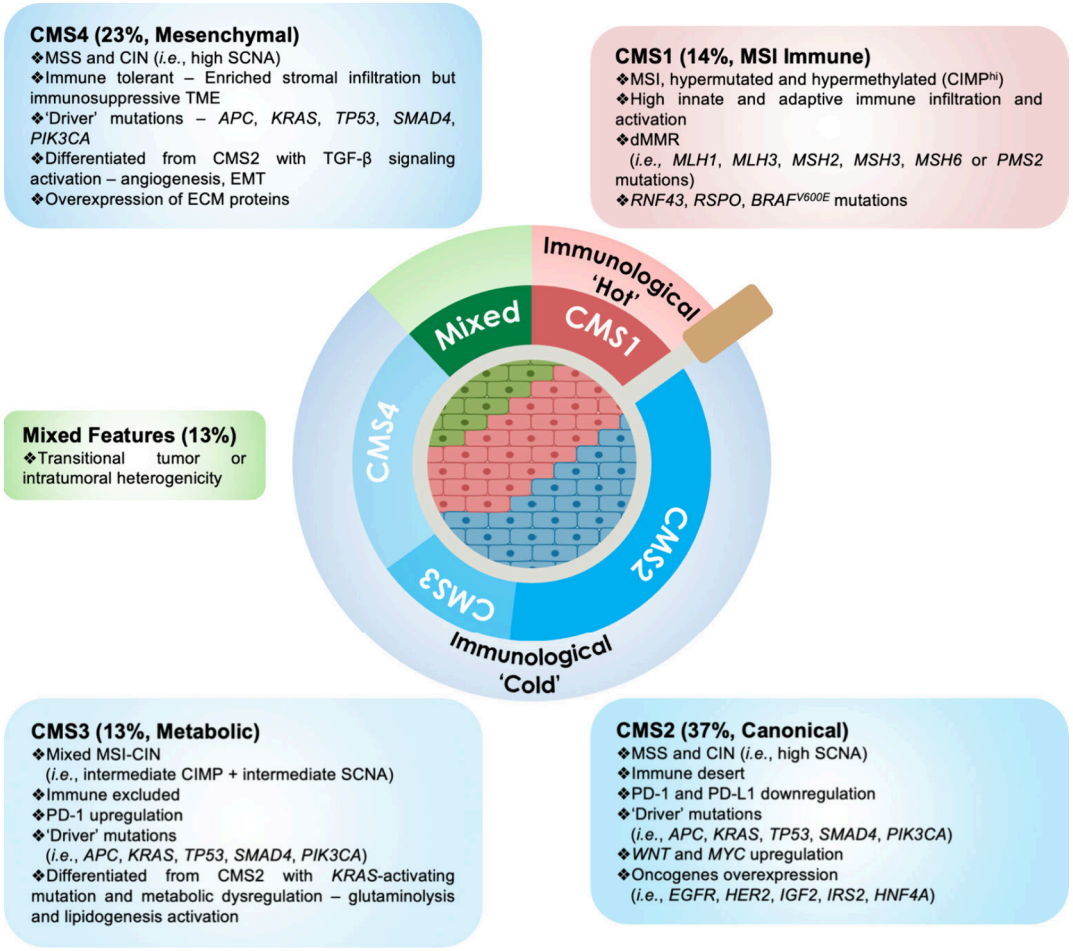

Figure 5. Visual representation underscores the interplay between consensus molecular subtypes (CMSs) and immune landscape of CRC,[223−225] which dictates therapeutic sensitivity toward immune checkpoint inhibitor (ICIs) monotherapy. Understanding the association between them is critical and offers valuable insights for clinical decision-making and treatment optimization.

Therefore, stratifying CRC into distinct subpopulations based on their variations in genetic and immune landscape would greatly enhance the clinical decision-making process (Figure 5). The CRC consensus molecular subtypes (CMSs) represent one such approach in classifying CRC subpopulations. In CMSs, CRC is divided into four major subtypes that remain the current best transcriptome-based descriptor for CRC.[223]

CMS1 "MSI Immune" phenotype, which accounts for about 14% of early stage CRC cases, has a faulty DNA mismatch repair (MMR) system due to the loss of function of genes such as *MLH1*, *MLH3*, *MSH2*, *MSH3*, *MSH6* or *PMS2*,[228] similar to other dMMR/MSI-High tumors. This results in hypermutation and hypermethylation of CpG islands. CMS1 CRC also has significant mutations in ring finger protein 43 (*RNF43*), *R-spondin*[229] and $BRAF^{V600E}$ genes.[223] CMS1 CRC is considered to be immunologically 'hot' as it exhibits strong activated immune cell infiltration in the TME, especially by $CD8^+$ T cells, $CD4^+$ Th1 cells, NK cells, and $CD68^+$ macrophages.[224]

Other CRC subtypes are categorized into CMS2 to CMS4, which originate from chromosomal instability (CIN) and have a MSS status. They follow the classical model of CRC progression, involving "driver" mutations in *APC*, *KRAS*, *TP53*, *SMAD4*, and *PIK3CA* genes.[230−232] The highest proportion (ca., 37%) of CRC patients falls into the category of CMS2 "canonical". While CMS2 is indistinguishable from CMS4 in terms of CIN and MSS, CMS2 is differentiated from CMS4 due to the aberrant activation of *WNT* and *MYC* pathway (i.e., canonical pathway)[233] as well as overexpression of oncogenes (e.g., *EGFR*, *HER2*, *IGF2*, *IRS2*, *HN4FA*).[223] CMS2 is also known as an immune desert subtype due to its reduced immune cell activation and low number of infiltrating lymphocytes and monocytes, explained by minimal transcription of leukocyte chemotaxis and activation genes.[223,225] Only a few memory B and Th cells and naive $CD4^+$ cells were found in these tumors, albeit without the ability to mount an antitumor response.[225] Moreover, low-level expression of PD-1 and PD-L1, which are common traits among immunodeficient tumors, also characterizes the CMS2 molecular phenotype.[224]

CMS3 "metabolic" subtype contributes to about 13% of CRC cases and is identified by prominent metabolic dysregulation and *KRAS*-activating mutations.[223] These mutations and alterations are thought to occur early in CRC tumorigenesis, with a unique combination of *KRAS* mutations and copy number events resulting in distinct metabolic deregulation profile.[234] Like CMS2, CMS3 possesses a quiescent tumor immune microenvironment (TIME). Th17 and resting T cell infiltrations reinforce the immunological dormancy of this subtype and mark it as "immune excluded". Unlike CMS2, intratumoral cells of CMS3 tumors reveal PD-1 upregulation.[224,225] CMS4 "mesenchymal" tumors, which represents about 23% of CRC, are driven by the unusual activation of the transforming growth factor-β (TGF-β)

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signaling pathway, which induces angiogenesis, tissue remodeling, and epithelial−mesenchymal transition.[223,235] CMS4 tumors have a high stromal content and a complex immune landscape, with a predominance of immunosuppressive cells (e.g., MDSCs, Treg, Th17), cytokines (e.g., TGF-β, CXCL12), and chemokines (e.g., IL-23, IL-17).[224,236] As a result, despite high levels of immune infiltration, CMS4 tumors are considered as immunologically "cold" and have low sensitivity toward mono-ICI therapy.[237] Finally, 13% of early stage CRC have no clear subtype classification and show mixed features from the other subtypes, suggesting that they are either transitional or heterogeneous tumors.[223]

3.3. Tumor Immune Microenvironment (TIME) in CRC Development and Progression

One of the key strategies that tumor cells use to evade immune surveillance is to modify the TME to achieve suppression of antitumor immunity. The CRC TME, as with many other solid tumors, comprises of both cellular and noncellular components, each with distinct functions that also interact to make the TME a dynamically evolving entity throughout different stages of cancer progression. As our comprehension of the TME in CRC progression and metastasis advances, the significance of each constituent within this complex system is increasingly recognized. Therefore, studying of the roles and mechanisms governing the interplay between TME remodeling and CRC evolution has received substantial attention over the past decade, as it holds promise for enhancing current anticancer strategies, particularly in the development of novel immunotherapies.

The TME comprises key elements like the extracellular matrix (ECM) and cellular components including stromal cells (e.g., cancer-associated fibroblasts, pericytes), immune cells, endothelial cells (e.g., blood vessels), and lymphatic vascular networks.[238] In addition, these cellular components also secrete noncellular soluble products to the extracellular environment such as chemokines, cytokines, growth factors, and extracellular vesicles to communicate immunostimulatory or immunosuppressive signals.[239] Notably, CRC cells interface with the gut microbiota, consisting of trillions of microorganisms,[240] and are considered essential for understanding CRC development and treatment response.[241] Indeed, some microbial species and microbial metabolites, such as *Enterotoxigenic Bacteroides fragilis*, *Escherichia coli*, and *Fusobacterium nucleatum* have been implicated in promoting colorectal carcinogenesis and therapy resistance.[242−244]

Immune cells, fibroblasts, and endothelial cells play pivotal roles within the CRC TME. Tumor-infiltrating lymphocytes,[245] comprising $CD4^+$ T cells, $CD8^+$ T cells, B cells, and NK cells, contribute to both immune evasion and tumor elimination. Notably, the Immunoscore, developed for routine clinical assessment, enables a prognosis by characterizing cytotoxic and memory T cell infiltration into TME of individual CRC patients.[246,247] Additional studies have also shown the roles played by a specific subtype of T cells in the prognostic outcome of CRC patients.[248−251] For example, in addition to the traditional lymphoid cells, another subset known as group 3 innate lymphoid cells (ILC3) has been shown to regulate the balance between the immune system and gut microbes to prevent CRC progression and resistance to immunotherapy.[252] Unlike $CD8^+$ T cells, naïve $CD4^+$ T cells require priming by antigen-presenting cells displaying peptide-major histocompatability class II (MHC-II) complexes before they can expand and differentiate into various $CD4^+$ Th cell subsets. The main Th cell subsets identified in the TME of CRC are Th1, Th2, Th17, Th22, follicular helper T (Tfh) cells, and regulatory T (Treg) cells, which can be either immunostimulatory or immunosuppressive. For example, Th1 cells and their cytokines can infiltrate CRC and suppress cancer cell proliferation through mechanisms such as $CD8^+$ T cells recruitment, apoptosis induction, angiogenesis reduction, and senescence induction.[253−255] Moreover, tumor necrosis factor alpha (TNF-α) and IL-6 can promote the differentiation of naïve $CD4^+$ T cells into Th22 cells, which are correlated with better outcome in human CRC.[266] High Tfh cells abundance has also been associated with positive CRC prognosis.[267] Another study in mice demonstrated that IL-21, produced by Tfh cells, can regulate $CD8^+$ T cell responses and enhance interferon gamma (IFN-γ) and granzyme B production.[268]

TAMs are another key cellular component of the CRC TIME that communicates with tumor cells through exosomes or cytokines to influence tumor immunity.[269−271] Based on their phenotype and function, TAMs are divided into two major distinct subsets, namely, M1- and M2-like macrophages.[272] Depending on the immunomodulatory signal received from the tumor, the TME, and external treatments such as chemotherapy and radiation, macrophages rapidly polarize between M1 and M2 phenotypes. In contrast to other tumors, the contribution of TAMs to CRC outcome is controversial. TAMs have been shown to support CRC progression through interactions with cancer cells, supporting cancer cell stemness and modulation of the immune response.[273−275] However, TAM density and their prognostic role change with tumor stage.[276] Despite the documentation of phospholipase D4 (PLD4) from TAMs and protein kinase C alpha (PKCα) from CRC in promoting M1-like macrophage polarization and CRC regression,[277,278] most solid tumors, including CRC, have a TME that favors the M2-like polarization of TAMs, which facilitates tumor growth. For instance, EGF secreted by CRC can induce M2 polarization of TAMs *via* the epidermal growth factor receptor (EGFR)/Phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/ mammalian target of rapamycin (mTOR) pathway.[279] Likewise, paxillin can activate the PI3K/AKT pathway and increase the proliferation and invasion of CRC cells by modulating M2 polarization.[280] Moreover, the "Warburg effect" in proliferating tumor cells can trigger the expression of VEGF and arginase 1 (ARG1) in TAMs, resulting in macrophage recruitment and M2 polarization.[281] In addition, TAMs can secrete CCL2 to attract Treg cells, which inhibit antitumor function of T cells and NK cells,[282−284] and interfere with immune cell interactions, creating an immunosuppressive TME in CRC.[269−271]

A crucial component of the innate immune system is represented by the NK cells, which are cytotoxic lymphocytes that can recognize and eliminate foreign cells, similar to the cytotoxic T cells of the adaptive immune system. NK cells are divided into two main subsets: (a) immature $CD56^+CD16^-$ cells that secrete cytokines such as IFN-γ and TNF-α, and (b) mature $CD56^-CD16^+$ cells that perform cytotoxic functions.[285,286] The cytotoxic function of NK cells is a well-established prognostic factor in reduced cancer risk[287] and CRC recurrence.[288] Several studies have also demonstrated that a high infiltration of NK cells within the tumor was associated with a favorable prognosis in CRC.[236,276,289]

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Table 7. FDA Approved Immune Checkpoint Inhibitors (ICIs) as Immunotherapy Options for Various Stages and Phenotypes of CRC

drug	target	clinical status	ref
dostarlimab	PD-1/PD-L1 pathway	approved for dMMR/MSI-digh advanced CRC	256
ipilimumab	CTLA-4 pathway	approved in combination with nivolumab for dMMR/MSI-high advanced CRC	257−260
nivolumab	PD-1/PD-L1 pathway	approved in combination with ipilimumab for dMMR/MSI-high advanced CRC	257−259
pembrolizumab	PD-1/PD-L1 pathway	approved as first-line treatment for dMMR/MSI-high advanced CRC with high tumor mutational burden (TMB)	261−265

However, some CRC patients show modified NK cell phenotypes in the tumor and peripheral blood, with reduced expression of activating receptors and increased expression of inhibitory receptors, which compromise their cytotoxic functions.[290−292] These receptors, such as killer cell immunoglobulin-like receptors, and their ligands, are part of the complex network that regulates NK cells activities.[293−296] If this network is disrupted, the tumor cells may evade the immune system more easily.

MDSCs control antitumor immunity by restricting T cell growth and promoting Treg differentiation.[297] MDSCs found in the blood of CRC patients can restrain T cells proliferation *in vitro*,[298,299] and neutralizing MDSCs activity restored IFN-γ secretion by T cells.[300] This is because T cell proliferation and activity is negatively affected by the depletion of L-arginine in the TME, which is being consumed by high levels of ARG1 expressed on MDSCs.[301,302] Similarly, MDSCs have also been found to affect T cell activation through regulation of O_2 production and inducible nitric oxide synthase (iNOS) activities.[298,303,304]

Cancer-associated fibroblasts (CAFs) in CRC are plastic cells that respond to cytokines and are influencing matrix remodeling and supporting cancer stemness through Wnt signaling.[305,306] Interleukin-1 receptor type 1 $(IL1R1)^+$ CAFs in CRC contribute to an immunosuppressive environment and T cell exclusion.[307] Tumor-associated endothelial cells (TECs) produce factors, significantly contributing to angiogenesis in the TME and influencing CRC stemness, metastasis, and chemoresistance.[308]

Noncellular components within the ECM, consisting of proteins like collagen and fibronectin, shape the TME stiffness and cellular functions, ultimately influencing CRC progression. Within the TME there are many signaling molecules that modulate tumor progression, such as the cytokine TGF-β that is released by various cells including macrophages and fibroblasts with immunoregulatory activity in CRC.[309] Exosomal microRNAs (miRNAs) also mediate cellular communication within the TME, affecting CRC development, antitumor immunity and serving as potential biomarkers.[310,311]

3.4. Current Immunotherapy Landscape for CRC

The first clinical success of immunotherapy (NCT00094653) with ipilimumab (anti-CTLA-4) for metastatic melanoma in 2010[312] marked the rise of ICIs as a promising immunotherapeutic strategy, compared to other methods such as IL-2 or α-interferon-based cancer vaccines, or chimeric antigen receptor (CAR) T-cell therapies that have shown limited effectiveness along with high toxicities.[313−319] Unlike the conventional approval of other anticancer regimens, the fast-track approval granted by US FDA for ICIs to treat advanced solid tumor such as mCRC[262] is based on tumor-agnostic, dMMR/MSI-high biomarker-driven approach, irrespective of the tumor origin or type (Table 7).[320]

The efficacy of pembrolizumab (anti-PD-1), nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4), and dostarlimab (anti-PD-1), in dMMR/MSI-high advanced CRC were substantiated by positive data from several clinical trials including KEYNOTE-016 (NCT01876511),[261,262] KEYNOTE-028 (NCT02054806),[265] KEYNOTE-164 (NCT02460198),[263,264] KEYNOTE-177 (NCT02563002),[321] Checkmate 142 (NCT02060188),[257−259] GARNET (NCT02715284),[256] and NICHE (NCT03026140),[260] which demonstrated that these ICIs could induce lasting responses in patients with dMMR/MSI-high advanced CRC. Furthermore, ICIs treatments have also shown promising results in addressing dMMR/MSI-high tumors of other types, as evidenced by the findings from KEYNOTE-012 (NCT01848834), KEYNOTE-158 (NCT02628067), and GARNET (NCT02715284).[256] Beyond therapeutic benefits, pembrolizumab exhibited low immunogenicity and favorable safety profile for advanced solid tumor patients.[322] Notably, the increased tumor mutational burden (TMB)[323] and T-cell inflamed gene-expression profile[324] have been associated with clinically significant improvement in the efficacy of pembrolizumab monotherapy. The compelling efficacy demonstrated across various clinical trials unequivocally establishes the capability of ICIs in inducing durable and safe responses in patients with dMMR/MSI-high CRC.

It is unfortunate that the majority of CRC patients (ca., 85%)[325] that are characterized by proficient MMR (pMMR), MSS, or MSI-low tumors have poor responses to ICI treatments.[259,261,262,326−330] MSS CRCs are usually considered to be immunologically "cold" tumors, with lower TMB than MSI CRCs, posing a major challenge for ICI therapy.[220] However, some studies have suggested otherwise: some MSS tumors are reported to have intermediate (75% MSS vs 83% MSI) and high (21% MSS vs 45% MSI) immunoscore,[246,331] albeit lower than MSI tumors. Moreover, some patients with large immune infiltrates have shown a pathological response to ICI therapy.[246,247,260,262] Additionally, *POLE* mutations affecting DNA polymerase ε, which facilitate lead strand DNA replication, have been found in MSS mCRC patients who respond to pembrolizumab treatment.[332] The tumor regression observed in CRC patients with *POLE* mutation may be due to greater $CD8^+$ T cell infiltration and enhanced expression of effector cytokines and cytotoxic T-cell markers.[333] However, clinical efficacy of ICI therapy is still limited in MSS tumors, with only up to 25% patients responding positively, potentially due to low immunogenicity.[246,247,260,262] Immunologically "hot" MSI CRC also suffers from moderate outcomes from treatment with ICIs with about 50% patients responding positively.[262] MSI CRC could develop resistance to immunotherapy *via* various mechanisms,

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such as low neoantigen presentation, expression of multiple immune checkpoints, neutrophil and Treg immunosuppression, and inflammation and immunosuppression.[223,225,334] To address these challenges, efforts have been made toward developing combinatorial therapies and identifying predictive biomarkers to maximize the benefits of ICI therapies. Currently, suitable patients to receive ICI therapy are selected based on three FDA-approved predictive biomarkers, namely dMMR/MSI status, TMB, and immune checkpoint PD-L1 expression, as well as emerging biomarkers such as the immunoscore and the hematology index, to achieve optimal therapeutic efficacy.[335]

3.5. Combination Therapy to Enhance CRC Immunotherapy Efficacy

Due to the limited eligibility of CRC patients for immunotherapy, current research mainly focuses on investigating the combination of immunotherapy with other treatments such as chemotherapy, radiotherapy, targeted therapy, and vaccines. This strategy seeks to address treatment resistance and broaden the scope of potential benefits to a more extensive CRC patient population, ultimately improving overall treatment outcomes.

The synergy between chemotherapy and immunotherapy is based on the observation that chemotherapeutic drugs can lead to the overexpression of tumor-associated antigens and stimulate tumor antigen-specific T-cell responses. Clinical trials combining chemotherapy with immunotherapy, such as the GOLFIG regimen (i.e., granulocyte macrophage colony-stimulating factor and low-dose interleukin-2, following gemcitabine + FOLFOX-4), have shown promising results in terms of response rates, disease control, and PFS.[336−338] These studies reported the effect of chemotherapy on immune cells, specifically the reduction in Treg, and enhanced tumor-specific T-cell responses. However, conflicting results have emerged regarding the impact of chemotherapy on intratumoral T-cell densities, emphasizing the necessity for further clinical trials to elucidate the precise mechanisms involved.

The integration of radiation therapy with ICI therapy has shown potential in overcoming immune resistance of pMMR mCRC.[339] Studies have also demonstrated improved survival rates for CRC patients undergoing complete liver metastasis resection when treated with radiotherapy combined with monoclonal antibodies against carcinoembryonic antigens.[340]

Recent advancements in targeted therapies, particularly antiangiogenic drugs, are being integrated into the clinical treatment of various tumors, including CRC. These therapies have demonstrated immune-enhancing effects offering a potential improvement in clinical outcomes in combination with immunotherapy for resistant MSS tumors. For example, studies have shown increased immune cell infiltration in CRC patients responding to bevacizumab (VEGF inhibitor) or chemotherapy with cetuximab (EGFR inhibitor), both of which are antibodies rather than small molecules.[341,342] In contrast, results from trials involving MAPK/extracellular signal-regulated kinase (ERK) (MEK) inhibitors and PD-L1 inhibitors have failed to achieve improved outcomes,[343,344] emphasizing the need for further investigation and optimization of the combination strategies for low immunoscore tumors. Cetuximab, in combination with NK cells, has also demonstrated antitumor effects by inducing antibody-dependent cell-mediated cytotoxicity (ADCC), representing another promising combination approach for CRC patients.[345,346]

Promising outcomes from human clinical trials of therapeutic cancer vaccines are prompting investigations into whether combining ICI therapy with vaccination could enhance efficacy beyond ICI monotherapy in dMMR/MSI-high CRC and potentially induce responses in pMMR/MSS CRCs, which are typically unresponsive to ICI therapy alone.

3.6. Combining CRC Immunotherapy with Clinical Pt Drugs

A variety of combination strategies have been investigated to enhance the efficacy of ICI therapy in MSS CRC patients who have low response rates, and in MSI CRC patients who could develop resistance to ICI therapy. These strategies include combining ICI therapy with another ICI, chemotherapy, anti-VEGF therapy, anti-EGFR therapy, antiangiogenic therapy, radiotherapy, oncogenic pathway inhibitors, bispecific antibodies, and cancer vaccines. Many of the clinical trials for these combinations have been thoroughly discussed in previous reviews,[347−350] hence we will focus on the attempts in combining ICI therapy with Pt-based chemotherapy to enhance the response rate of CRC patients to ICI immunotherapy, especially for pMMR/MSS phenotype.

As previously mentioned in section 2.1, the primary clinical treatment for advanced CRC typically involves combinatorial chemotherapies (Table 4). These cocktail regimens aim to enhance overall chemotherapy efficacy through synergistic or additive effects. Another reason for the combination of chemotherapeutics of different classes is that their combination can enhance immunomodulation in various ways, on top of their cytotoxic effects. For instance, the combination of 5-FU and **OXP** in FOLFOX regimen can improve tumor immunity by selectively inhibiting MDSCs[351,352] and inducing tumor cells ICD,[190] respectively. In a CT26 murine CRC model, FOLFOX treatment increased $CD8^+$ T cell infiltration and decreased exhausted $CD8^+$ T cell population.[353] FOLFOX therapy also reversed the immunosuppressive TME by reducing the expression of inhibitory receptor such as PD-1 and T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3)[354] to enhance the cytotoxic IFN-γ and TNF-α secretion.[355] At the same time, an *in vivo* CT26 model exposed to FOLFOX showed upregulation of PD-L1 induced by high levels of IFN-γ and TNF-α, indicating that FOLFOX treatment could trigger tumor adaptive immune resistance.[355]

Therefore, it is conceivable that these immunostimulatory effects induced by **OXP** combination chemotherapy regimens may expand the potential beneficiaries of ICI therapy among CRC patients, including those with pMMR/MSS CRC or dMMR/MSI-high CRC that do not respond to ICI immunotherapy. In particular, CT26 cell line, representative of pMMR/MSS tumors, has been extensively studied for its immunological response to chemotherapy and demonstrated encouraging antitumor effects when combined with ICIs. Recently, it was found that immune checkpoints CD47 and PD-L1 were upregulated in CT26 cells post-treatment with either FOLFOX or **OXP** alone, both *in vitro* and *in vivo*.[356] Remarkably, the combination of anti-CD47, anti-PD-L1, and FOLFOX *in vivo* demonstrated a significant improvement in mice survival and tumor regression. This combination also promoted immunoinflammatory TME through reduction in Tregs and MDSCs, as well as elevation in $CD8^+$ INF-γ^+ lymphocytes and M1/M2 macrophage ratio. Similar positive outcomes were also observed in the studies combining **OXP** with anti-PD-L1 antibodies in the CT26 mice model, showing

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Table 8. Summary of Ongoing and Completed Clinical Trials for Combination Therapy Using Both Pt-Based Chemotherapy and Immune Checkpoint Blockade Therapy in Various Advanced CRC Patient Populations Such as pMMR/MSS, dMMR/MSI-high, and RAS/BRAF-Mutant[a]

identifier	phase	treatment regime	patient population	outcome	status	ref
METIMMOX (NCT03388190)	II	FLOX ± nivolumab	pMMR/MSS CRC (metastatic)	mPFS (control vs experimental) = 5.6 months vs 6.6 months	active not recruiting	63
METIMMOX-2 (NCT05504252)	II	FLOX + nivolumab	pMMR/MSS CRC (metastatic)	PFS = YTR	recruiting	
COLUMBIA-1 (NCT04068610)	Ib/II	FOLFOX + bevacizumab ± (durvalumab + oleclumab)	pMMR/MSS CRC (metastatic)	ORR (control vs experimental) = 44.0% vs 61.5% mOS (control vs experimental) = NR vs 19.1 months mPFS (control vs experimental) = 11.1 months vs 10.9 months	terminated	361
KEYNOTE-651 (NCT03374254)	Ib	mFOLFOX7 + pembrolizumab ± binimetinib	pMMR/MSS CRC (metastatic)	ORR = 61%m PFS = 8.6 months mOS = 28.6 months	completed	362
AVETRIC (NCT04513951)	II	mFOLFOXIRI + cetuximab + avelumab	pMMR/MSS CRC (metastatic with *RAS* wild-type)	mPFS = 14.1 months ORR = 82% DCR = 98% R0RR = 21%	active not recruiting	363
AVETUX (NCT03174405)	II	mFOLFOX6 + cetuximab + avelumab	pMMR/MSS CRC (metastatic with *RAS/BRAF* wild-type)	mPFS = 11.1 months mOS = 32.9 months ORR = 79.5% DCR = 92.3%	completed	364,365
MEDITREME (NCT03202758)	Ib/II	FOLFOX + durvalumab + tremelimumab	pMMR/MSS CRC (metastatic with *RAS* mutant)	PFS (3-months) = 90.7% PFS (6-months) = 60% mPFS (historical vs experimental) = 6 months vs 8.2 months ORR = 63% OS = NR	completed	366,367
BBCAPX (NCT05171660)	III	XELOX + bevacizumab ± sintilimab	pMMR/MSS CRC (metastatic with *RAS* mutant)	mPFS = 18.2 months DCR = 100% ORR = 84%	recruiting	368−370
APHRODITE (NCT04653480)	II	OXP/irinotecan + surufatinib + toripalimab	pMMR/MSS CRC (metastatic with *RAS/BRAF* mutant)	ORR = YTR	recruiting	
POCHI (NCT04262687)	II	XELOX + bevacizumab + pembrolizumab	pMMR/MSS CRC (metastatic with high immune infiltrate)	PFS = YTR	recruiting	371
NSABP FC-10 (NCT03626922)	I	pembrolizumab + pemetrexed ± OXP	pMMR/MSS CRC (metastatic with chemo-refractory)	CBR = 50% ORR = 12.5%	active not recruiting	372
COBP (NCT05585814)	II	CAPOX + pembrolizumab + bevacizumab	pMMR/MSS CRC (local advanced)	R0RR = YTR PRR = YTR TRG = YTR	yet to recruit	373
BASKETII (NCT04895137)	II	mFOLFOX6 + bevacizumab + sintilimab	pMMR/MSS CRC (local advanced)	pCR = YTR	recruiting	
NCT05588297	II	CAPOX + nivolumab + bevacizumab	pMMR/MSS CRC (with liver metastases)	R0RR = YTR PRR = YTR TRG = YTR	yet to recruit	
ATOMIC (NCT02912559)	III	FOLFOX ± atezolizumab	dMMR/MSI-high CRC (metastatic)	DFS = YTR	active	

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Table 8. continued

identifier	phase	treatment regime	patient population	outcome	status	ref
					not recruiting	
COMMIT (NCT02997228)	III	atezolizumab ± (mFOLFOX6 + bevacizumab)	dMMR/MSI-high CRC (metastatic)	PFS = YTR	recruiting	
HCRN GI14-186 (NCT02375672)	Ib/II	mFOLFOX6 + pembrolizumab	CRC (metastatic)	ORR = 56.7% mPFS = 8.8 months mOS = NR	completed	374,375
CheckMate 9 × 8 (NCT03414983)	II/III	mFOLFOX6 + bevacizumab ± nivolumab	CRC (metastatic)	mPFS (control vs experimental) = 11.9 months vs 11.9 months ORR (control vs experimental) = 46% vs 60% DCR (control vs experimental) = 84% vs 91% mOS (control vs experimental) = NR vs 29.2 months	completed	376
AtezoTRIBE (NCT03721653)	II	FOLFOXIRI + bevacizumab ± atezolizumab	CRC (metastatic)	ORR (control vs experimental) = 59.0% vs 64.0% mPFS (control vs experimental) = 13.1 months vs 11.5 months mOS = NR	Completed	377−380
NIVACOR (NCT04072198)	II	FOLFOXIRI + bevacizumab + nivolumab	CRC (metastatic with *RAS*/*BRAF* mutant)	ORR = 76.7% DCR = 97.3% mDOR = 8.4 months mPFS = 10.1 months	completed	381,382

[a]Note: CBR, clinical benefit rate; DCR, disease control rate; DFS, disease free survival; DLT, dose limiting toxicities; mDOR, median duration of response; mPFS, median progression-free-survival; mOS, median overall survival; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response rate; PRR, pathological complete response rate; PFS, progression-free survival; R0RR, R0 recession rate; TRG, tumor regression grade; YTR, yet to report.

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an increase in survival, inhibition of tumor growth, and a favorable TME for antitumor immune responses.[357,358] Furthermore, a synergistic effect was noted when FOLFOX was combined with anti-PD-1 treatment, leading to a complete tumor regression in both CT26 and MC38 CRC mouse models that were resistant to monoanti-PD-1 therapy.[355] The synergism observed was associated with enhanced tumor infiltration by activated PD-1$^+$CD8$^+$ T-cells and increased IFN-γ induced PD-L1 expression on tumor cells. Notably, CRC patients in the same study also displayed induced PD-L1 expression and high CD8$^+$ T-cell infiltration in the TME. In another MC38 *in vivo* mice model that is resistant to ICI therapy, the combination of ICI therapy (i.e., anti-CTLA-4 plus anti-PD-1) with **OXP** treatment successfully invoked an antitumor response.[202] Moreover, trifluridine/tipiracil with **OXP** demonstrated the ability to induce ICD in a panel of murine and human pMMR/MSS CRC cell models, namely CT26, SW620, Caco-2, and Colo-320, both *in vitro* and *in vivo*.[359] This combination resulted in improved CD8$^+$ T-cell infiltration and activation through M2 TAMs elimination. The adaptive immune resistance involving PD-L1 expression on tumor cells and PD-1 induction on CD8$^+$ T cells was overcome when anti-PD-1 was coadministered with trifluridine/tipiracil and **OXP**, resulting in enhanced antitumor efficacy. These preclinical findings provide compelling evidence that the synergy between Pt-based chemotherapeutics and ICIs can offer significant benefits to cancer patients currently unresponsive to ICI therapy, not only in CRC but also in other cancers such as lung cancer[200,201] as well as head and neck cancer.[360]

To comprehend and investigate the safety and efficacy of employing Pt-chemotherapeutics for sensitizing pMMR/MSS mCRC patients toward ICI therapy, numerous clinical trials have been initiated, exploring diverse combinatorial treatment regimens involving both Pt-based chemotherapeutics and ICIs (Table 8).

As a start, METIMMOX (NCT03388190) assessed the efficacy of FLOX (5-FU + leucovorin + **OXP**) with or without nivolumab (anti-PD-1) in pMMR/MSS mCRC patients. Preliminary results revealed a modest improvement in median PFS (i.e., 5.6 months vs 6.6 months) between control arm and experimental arm, suggesting that short-course **OXP**-based chemotherapy could indeed sensitize pMMR/MSS mCRC patients to ICI therapy.[63] Another study, COLUMBIA-1 (NCT04068610) investigated the combination of FOLFOX and bevacizumab (anti-VEGF) with or without durvalumab (anti-PD-L1) and oleclumab (anti-CD73) in pMMR/MSS mCRC patients.[361] Although the addition of durvalumab and oleclumab to FOLFOX plus bevacizumab in the experimental arm significantly increased the objective response rate (ORR) (44.0% vs 61.5%), median PFS remained unaffected (11.1 months vs 10.9 months) compared to the control arm. Additionally, cohorts B and D in KEYNOTE-651 (NCT03374254), which received the combination of mFOLFOX7 and pembrolizumab with or without beinimetinib, reported median PFS of 8.6 months and median OS of 28.6 months with no new safety concerns emerged for using this regimen in pMMR/MSS mCRC patients.[362]

AVETRIC (NCT04513951) examined the combination of mFOLFOXIRI, cetuximab (EGFR inhibitor), and avelumab (anti-PD-L1) in pMMR/MSS mCRC patients with wild-type RAS, and met its primary end point with median PFS of 14.1 months, a ORR of 82%, a disease control rate (DCR) of 98%, and a R0 recession rate of 21%.[363] AVETUX (NCT03174405) trialed the combination of mFOLFOX6, cetuximab, and avelumab as a novel strategy to increase the immunogenicity of pMMR/MSS tumors in mCRC patients with wild-type rat sarcoma viral oncogene homologue (RAS)/B-Raf proto-oncogene, serine/threonine kinase (BRAF), and achieved a final median PFS of 11.1 months, median OS of 32.9 months, ORR of 79.5%, and DCR of 92.3%.[364]

Notably, follow up analysis of AVETUX found that tumor clonality and diversity could serve as potential biomarkers for predicting the response to chemo-immunotherapy combination in pMMR/MSS mCRC treatment.[365]

Several clinical trials have investigated the efficacy and safety of combining immunotherapy with chemotherapy and/or targeted therapy in patients with mutant variants of pMMR/MSS mCRC. For example, the triple combination of durvalumab (anti-PD-L1), tremelimumab (anti-CTLA-4), and mFOLFOX6 for RAS mutant pMMR/MSI-Low mCRC patients in MEDITREME (NCT03202758) demonstrated favorable PFS of 90.7% and 60% for 3 months and 6 months, respectively.[366,367] MEDITREME also reported higher median PFS (6 months vs 8.2 months) and ORR (63%) in the treatment group compared to historical FOLFOX control group. Immunological analysis also demonstrated that this triple combination regimen could enhance the tumor-specific neoantigen immune response in both tumor and peripheral tissues. BBCAPX (NCT05171660) assessed the combination of sintilimab (anti-PD-1), CAPOX, and bevacizumab in RAS/BRAF mutant pMMR/MSS mCRC patients, reporting an impressive ORR of 84%, disease control rate of 100%, and median PFS of 18.2 months with a tolerable safety profile.[368−370] Biomarker assessment analysis indicated that some patients transitioned to an immunologically "hot" subtype after receiving the combination therapy. Furthermore, heavily pretreated chemorefractory patients with pMMR/MSS mCRC were treated with combinatorial therapy of pembrolizumab and pemetrexed with or without **OXP** in NSABP FC-10 (NCT03626922)[372] and achieved clinical benefit rate (CBR) of 50% and ORR of 12.5%, comparable to those reported in KEYNOTE-016 (NCT01876511).[261,262]

HCRN GI14-186 (NCT02375672) evaluated the efficacy and safety of mFOLFOX6 and pembrolizumab in mCRC patients.[374,375] The trial reported median PFS of 8.8 months, median OS of 19.9 months, and ORR of 56.7%, which are similar to the historical data of FOLFOX alone (i.e., median PFS = 9.0 months, median OS = 16.2 months). This suggests that the combination is well tolerated and does not compromise the activity of FOLFOX. CheckMate 9 × 8 (NCT03414983) compared mFOLFOX6 plus bevacizumab with or without nivolumab in mCRC patients.[376] The trial did not meet its primary end point of median PFS (11.9 months vs 11.9 months), but it revealed that the addition of nivolumab causes improvements for PFS, median OS (i.e., 29.2 months), ORR (i.e., 46% vs 60%), and DCR (i.e., 84% vs 91%) after 12 months, when compared to the control arm. AtezoTRIBE (NCT03721653) tested FOLFOXIRI plus bevacizumab with or without atezolizumab in mCRC patients.[377−380] The trial demonstrated that the combination of atezolizumab was safe and increased both ORR (i.e., 59.0% vs 64.0%) and median PFS (i.e., 11.5 months vs 13.1 months) against the control arm. Moreover, the trial identified potential responders for this combination from the patient pool based on high immunoscore or high TMB. NIVACOR (NCT04072198) investigated

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Table 9. 3D CRC-on-a-Chip and Bioprinted Models

3D culture	source material	description	applications	ref
spheroids	commercial cell lines	culture of aggregated cells that do not adhere to any culture substrate	drug screening	421,422,444−446
patient-derived tumoroids or organoids	patient tissue		nanomedicine evaluation	423,424,447−449
			disease modeling	
			personalized medicine	
bioprinted tissue/organs	bioink: biomaterials (commercial/patient cells, cell aggregates, decellularized matrix components, microcarriers, hydrogels)	additive manufacturing (3D printing) of tissues or organs by building layer-by-layer using bottoms-up approach	drug screening	450−452
			toxicology	
			disease modeling	
			regenerative medicine	
			personalized medicine	

the combination of FOLFOXIRI, bevacizumab, and nivolumab in RAS/BRAF-mutated mCRC patients regardless of their MSI status, and achieved a high ORR of 76.7%, median PFS of 10.1 months, DCR of 97.3% and median duration of response (DOR) of 8.4 months.[381,382]

Efforts to enhance therapeutic efficacy and overcome resistance to ICI therapy among CRC patients persist with ongoing clinical trials, such as METIMMOX-2 (NCT05504252, FLOX + nivolumab), APHRODITE (NCT04653480, **OXP**/irinotecan + surufatinib + toripalimab), POCHI (NCT04262687, XELOX + bevacizumab + pembrolizumab),[371] COBP (NCT05585814, CAPOX + pembrolizumab + bevacizumab),[373] BASKETII (NCT04895137, mFOLFOX6 + bevacizumab + sintilimab), NCT05588297 (CAPOX + nivolumab + bevacizumab), ATOMIC (NCT02912559, FOLFOX ± atezolizumab), and COMMIT (NCT02997228, atezolizumab ± (mFOLFOX6 + bevacizumab)). Even though the combination between immunotherapy and chemotherapy is still not a standard treatment option in patients who are MSS or TMB-low, as well as many trials have yet to report their results, the synergistic potential of combining Pt-based chemotherapeutics with ICIs seems to be promising in addressing challenges associated with ICI therapy.

4. OTHER CRC TREATMENT MODALITIES

4.1. Surgery

Surgery is the primary treatment for localized and regional CRC cases (Tables 2 and 3). Most patients with early stage (stage I−II) CRC can be treated with polypectomy (ca. 3%) or colectomy (ca. 84%), surgical removal of polyps and diseased part of the colon, respectively (Table 2).[17] Surgical resection of primary tumors and affected tissues can achieve complete remission in approximately 50% of CRC patients.[383] However, the benefit and effectiveness of surgery decrease as the disease progresses, with the 5-year survival rate dropping to as low as 30% at stage III.[384] At stage IV, surgical resection of the primary tumor is typically reserved for treating symptoms such as bowel obstruction, although this palliative benefit is offset by the increased mortality and risk of postoperative complications in mCRC patients with weakened immune systems.[385] As this review focuses on discussing Pt drugs for treating CRC, please refer to reviews by Shinji et al. for recent advances in surgical techniques for CRC patients.[386]

4.2. Radiotherapy

Various radiotherapy techniques, such as stereotactic ablative radiotherapy[387] and selective internal radiotherapy, are commonly employed for CRC patients to achieve local control of inoperable liver and lung colorectal metastases, respectively.[388−390] In addition, neoadjuvant radiotherapy, either in a short course (SC-RT, 5 × 5 Gy) or long course with concurrent chemotherapy (LC-CRT, 45−50.4 Gy, 25−28 fractions), are the current standard-of-care for locally advanced rectal cancer (LARC, stage II−III), which carries a higher risk of local recurrence and a poorer overall prognosis.[391−394] SC-RT has demonstrated a significant reduction in local recurrence rates (LRR) from 26% to 9% ($p < 0.001$) and an increased OS from 30% to 38%.[391] Furthermore, preoperative SC-RT has been shown to improve the quality of total mesorectal excision surgery by substantially reducing LRR as compared to just surgery alone.[395,396] Similarly, long-course chemoradiotherapy, often followed by total mesorectal excision surgery, is associated with improved curative surgery and reduced LRR.[397] Typically, patients receive chemoradiotherapy that utilizes fluoropyrimidine-based (e.g., 5-FU or capecitabine) chemotherapy as a radiosensitizer in combination with radiotherapy, followed by total mesorectal excision surgery.[398,399]

Despite the evident benefits of providing preoperative chemoradiotherapy in conjunction with total mesorectal excision surgery for rectal cancers, this combination does not completely eliminate local recurrences and distant metastasis in patients.[400] Furthermore, radiotherapy can result in unwanted side effects, including radiation injury and hematological toxicity.[401] Moreover, the application of Stereotactic ablative body radiotherapy[387] in CRC liver metastasis is constrained due to its suboptimal efficacy and potential harm to healthy liver cells.[402] For greater insights into the advances and efficacy of radiotherapy for CRC patients, please refer to a review by Tam et al.[403]

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5. EXPERIMENTAL MODELS FOR CRC DRUG SCREENING AND DEVELOPMENT

5.1. 3D *in Vitro* Cancer Models

Currently, conventional chemotherapeutic drug development strategies follow progressive evaluations of lead compounds *in vitro*, then preclinical *in vivo* models and, finally, clinical trials.[404] However, this lengthy process has a low 6.7% success rate of developing a clinically approved drug from phase I.[405] This is largely attributed to the inadequate recapitulation of true pathological conditions in preclinical two-dimensional (2D) *in vitro* models, causing poor predictions of the patient outcomes.[406] 2D cell cultures present an oversimplified scenario, where cells are uniformly exposed to nutrients or drugs due to a high surface area-to-volume ratios.[407] This neglects the complex reality of solid tumors, where drugs must navigate through tumor vasculature and penetrate tissue to reach all cancer cells. These processes delay drug exposure, significantly impairing the anticancer efficacy of short half-lives therapeutics.[408] Furthermore, 2D cell culture lacks key characteristics of the TME that can be mimicked in 3D culture (Table 9), such as 3D spatial arrangements within the ECM of different cell types and the presence of an hypoxic environment, which influence drug sensitivity.

Local inflammation is a significant promoter of CRC tumorigenesis,[409] attracting stromal cell populations which, along with immune cells, tumor-associated vasculature and the ECM (Figure 6, Table 10), form the CRC TME.[410,411] In turn,

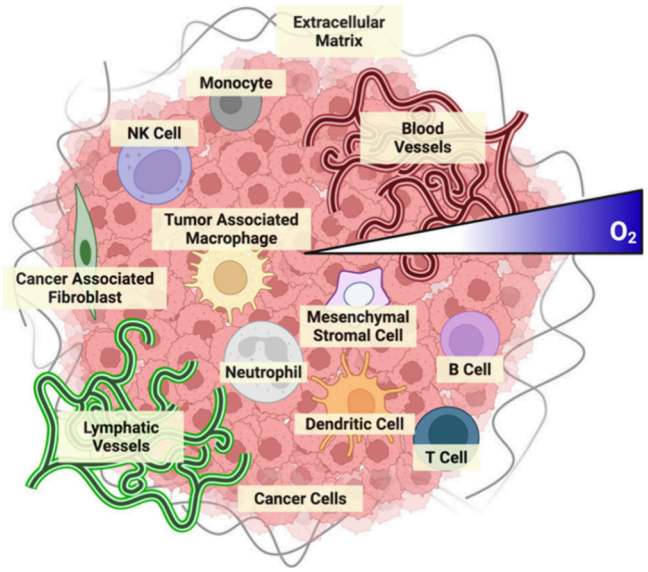

Figure 6. Major players of the TME recapitulated in 3D cultures including blood vessels, lymphatic vessels subpopulations of various immune cells, fibroblasts, endothelial cells, and an extracellular matrix. Figure created with BioRender.com.

interactions between tumor, stromal and immune cells further promote CRC progression.[412−414] For example, CAFs adjacent to CRC cells overexpress IL-6 and serine protease inhibitor Kazal type 3 (SPINK3), which promote tumor angiogenesis and cancer cell growth while suppress tumor inhibition.[409,415] The inability of 2D cell cultures to recapitulate these critical TME elements represents a significant limitation, contributing to discrepancies between *in vitro* drug efficacies and clinical outcome with inevitable failures of clinical trials. Therefore, 3D *in vitro* CRC models were developed to better mimic the complex tumor TME.[229,416−419]

These 3D models, such as spheroids and organoids, offer improved recapitulation of cell-cell and cell-matrix interactions, as well as spatial organization of tumors. Further, they allow for the incorporation of multiple cell types, including stromal and immune cells, to more accurately represent the heterogeneous nature of tumors. To further bridge the gap between *in vitro* models and *in vivo* conditions, organ-on-a-chip or microphysiological systems (MPS) have emerged as advanced platforms that integrate microfluidics with 3D cell culture techniques.[420−422] CRC tumor MPS provides additional human-relevant complexity to the TME, ultimately aiming at improving the rate of success in translation of preclinical findings to clinics.[422−424] Moreover, advancements in bioprinting technologies, in which tissues or organs are manufactured additively layer by layer, enable greater customization over biological characteristics in 3D cultures.[425,426] For more extensive reviews on 3D models for CRC, please refer to the following reviews by Vitale et al. and others for 3D models to better emulate the complexity of the tumor tissues;[427,428] and reviews by Reidy et al. and others for 3D models for screening novel therapeutics.[427,429,430]

5.2. Why Murine as an Experiment Model for CRC?

Despite the fact that extensive research has been done on CRC in the past decades, there are still substantial issues that need to be addressed, like difficulties in early detection of micrometastases and resistance to treatment. The animal models are therefore crucial assets to address these challenges. Since the rodent models enable researchers to concurrently assess and measure a complicated disease including CRC, they provide a valuable contribution to knowledge advancement. The affordability, ease of management, short gestation period, anatomical similarities, and accessibility of genetic modification, as well as their classification as mammals are among the benefits when utilizing murine models.[431] The current understanding of tumor biology, carcinogenesis, and the effects of specific molecular processes on colon biology might all be enhanced by the use of murine models.[432] These murine models make it possible to comprehend and track the disease progression, as well as to find and create novel preventive measures that could potentially be implemented in clinical trials in the future. An ideal murine model of a human disease should be easy to understand, inexpensive, and able to replicate the disease's pathology, the biological behaviors and the biochemical changes.[433] Although animal research cannot take the place of human clinical trials, it can be employed as a prescreening approach in order to make human trials more targeted in view of their key recapitulative features.[434]

The development, structure, and functions of the murine and human intestinal tracts are almost identical (Figure 7A). The rectum, anus, colon, and cecum are components of the large intestine, which is in charge of absorbing salt and water from digested food before preparing the faecal matter.[433] A curled blind bag called the cecum discharges into the proximal colon, supporting bacterial fermentation. Compared to murine, the cecum in humans is significantly smaller and forms a continuous portion of the proximal colon located distal to the ileocecal valve. Histologically, the murine mucosal folds vary by region; the cecum and proximal colon mucosa are transverse, distal colon and rectum mucosa are longitudinal, and midcolon mucosa has no folds and is flat. Also, the human

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Table 10. Major Players of the TME Involved in Tumor Progression, Metastasis, and Chemoresistance That Are Mimicked in 3D Tumor Models

elements of TME	role in TME	srategies for recapitulation in *in vitro* cultures	ref
extracellular matrix (ECM)	soluble proteins and interactions with cell-surface integrins stimulate signaling pathways that promote chemoresistance, regulate proliferation, differentiation, migration, apoptosis and metastasis	cultures grown on hydrogels mimicking ECM	453−455
	forms physical barrier impeding drug transport to tumor cells		
cancer associated fibroblasts (CAFs)	CAF-soluble factors stimulate signaling pathways that promote tumor invasion, metastasis that consequently promote chemoresistance	cocultures of cancer cells with optimized ratios of noncancer cell types	456−460
endothelial cells (ECs)	soluble factors from tumor cells induce morphological changes in ECs that promote angiogenesis to support tumor development	cocultures of cancer cells with optimized ratios of noncancer cell types	456,458,461
tumor associated macrophages (TAMs)	soluble factors from anti-inflammatory M2-like macrophages promote chemoresistance, tumor growth, angiogenesis, migration, invasion and metastasis	cocultures of cancer cells with optimized ratios of noncancer cell types	457,458,462−464
	TAM-soluble factors stimulate a positive feedback loop that stimulates immunosuppression in the TME		
tumor induced hypoxia	hypoxia-induced factors (HIF-1α, HIF-2α) upregulate the expression of multiple genes that mediate chemoresistance, angiogenesis, metabolic reprogramming, and immunosuppression	induced concentration gradients of nutrient and oxygen transport in large 3D cultures (determination of hypoxia by expression of hypoxia induced factors (HIF)	458,465−469
	hypoxia induces metabolic rewiring that promotes tumor survival	hypoxic chambers	
	hypoxic conditions activate pro-tumor progression signaling pathways		

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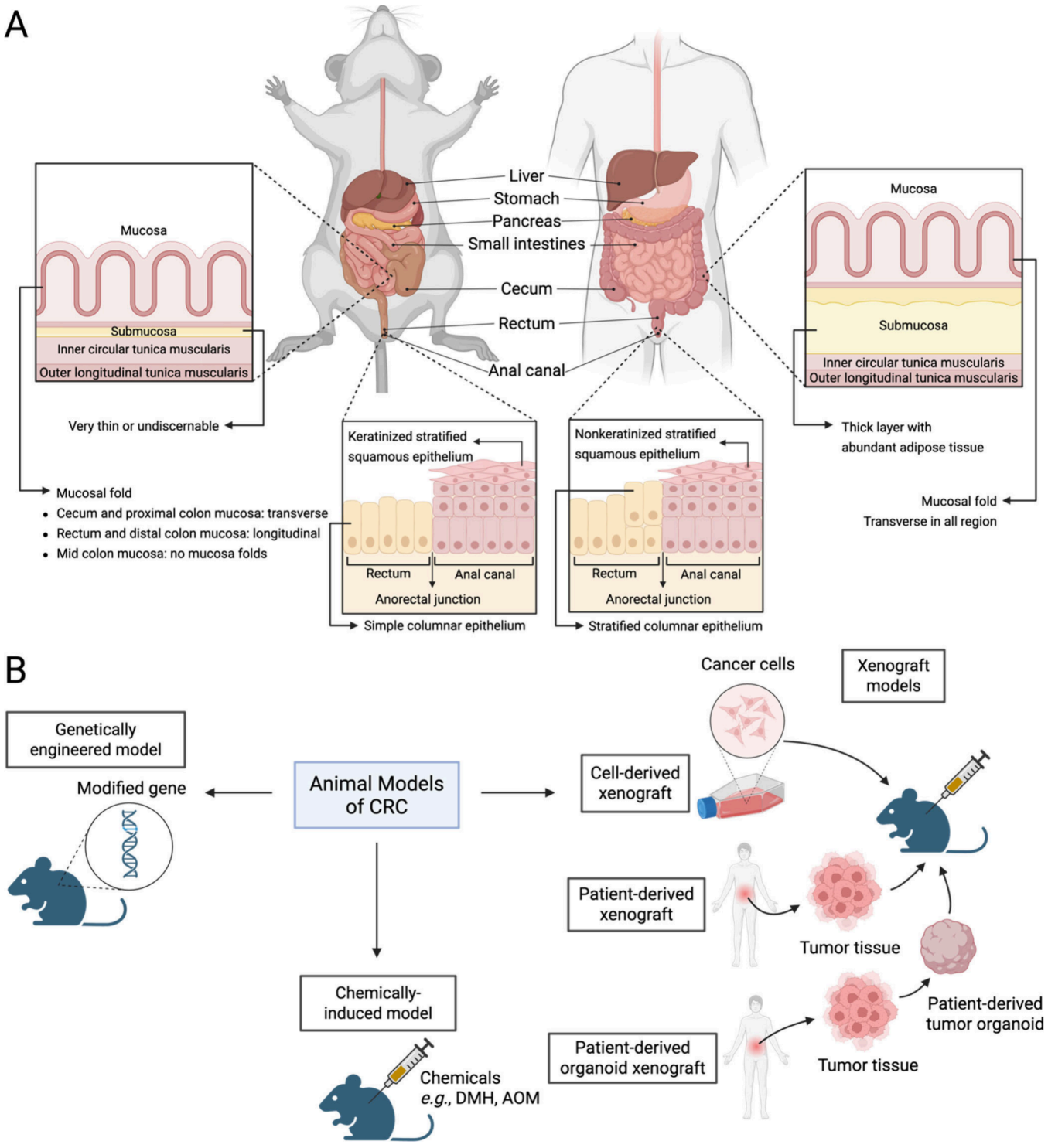

Figure 7. (A) Anatomical similarities between rodent and human GI tract. (B) Graphical representation of various murine models of CRC. Figure created with BioRender.com.

mucosal fold is transverse in all regions. The murine anal canal is bordered by a keratinized, stratified squamous epithelium, while the human anal canal is bordered by a stratified squamous epithelium and nonkeratinized lines.[435] Despite the comparable histology between rodents and humans, rats and mice lack adipose tissue in their submucosa, in contrast to humans.[433]

The first model that successfully used carcinogens to induce CRC was the *APC* (Adenomatous polyposis coli) Min/+ model, where chemical mutagenesis was used to create the diseased animal.[436] These models are useful in recapitulating the early phases of tumor carcinogenesis, due to their low rate of developing tumors. However, only a small percentage of the mice under such circumstances develop tumors, and even if they do, their location, dissemination, and differentiation vary greatly.[437]

5.2.1. Diet Induced Models (DIMs). Compelling epidemiological data associate obesity resulting from diet,

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excess body and abdominal fat with a higher incidence of colon cancer and a lower prognosis following diagnosis. The relationship between eating a high-fat diet and obesity and the incidence and spread of colon cancer has been studied in murine models in an effort to simulate the human condition. The intake of a high-fat diet leads to obesity, which is associated with elevated tumorigenesis, reduced apoptosis and rapid proliferation of tumor cells.[438] The main advantage of this model is the development of carcinoma in the proximal colon, cecum, and small intestine. Nonetheless, the time required for tumor development is long, and there is a high risk of failure to develop tumors. Also, there is currently no description of dietary mutations, and few animals acquire neoplastic cancers.[439]

5.2.2. Chemical Induced Models (CIMs). The first mouse intestinal tumor model was successfully established by feeding mice with methylcholanthrene. Later, colon carcinoma was induced in rats by feeding them with radioactive yttrium (Y).[434,440] A decade after these models, hydrazines were found to be colon carcinogenic agents and adenocarcinoma was induced to rats upon treatment with excessive amount of cycad flour, which contains a form of methylazoxymethanol (MAM), often referred as cycasin.[433] In general, chemically induced models (CIMs) are noninvasive and do not metastasize; tumors formed in this way represent the transition of adenoma to adenocarcinoma from aberrant crypt foci. They have an advantage of enabling different routes of administration, including oral gavage, intraperitoneal (IP), intramuscular (IM), and subcutaneous (SC) injections. Even though the CIMs are easy and good models of CRC, they are not thought to be relevant for recapitulating the immune response and the TME.[436] The chemically induced tumors in rodents randomly exhibit pathological and genetical similarities with human CRC. Since the tumor progression must occur from normal cells to adenocarcinoma or carcinoma in this model, establishing a successful model requires a significant amount of time. Apart from this, the development of adenocarcinoma or carcinoma is highly influenced by the rodent's age, gender and genetic background. Furthermore, the effective local concentration of carcinogenic substances might result in interference with their metabolism caused by the gut flora, diet, and immune status of rodents.[431] The different chemicals used to induce the CRC model, their doses and/or concentrations, routes of administration to murine and the strain/species used are reported in Table 11.

5.2.3. Limitations of Induced Models. Various risk factors, such as poor eating habits, the environment, exposure to carcinogenic substances, and other variables, are associated with higher incidence of CRC. Even though the chemically induced rodent models of CRC are useful for exploring new therapy strategies and for the identification of diagnostic and prognostic markers, generating these models requires longer experimental cycles and duration.[441] These models have a low carcinogenic efficiency, a low modeling rate, and a variable molding time. Also, CIMs cannot be used alone as they have low carcinogenic effect and require multiple administrations. Since the quantification of treatment volume is challenging, they usually cannot be utilized to analyze CRC metastases, and the induced mutations are random.[442]

5.3. Metastasis Models

Understanding the etiology of CRC and the roles that various genetic and genomic alterations play in its onset and progression is necessary for target authentication (Table 12).

To comprehend how mutations behave in the natural environment, most of the research has focused on developing genetically engineered mice models (GEMMs) that precisely represent late-stage diseases. Researchers are now able to identify a gene's pathophysiological significance by creating genetically engineered autochthonous mouse models (GEAMMs) using clustered regularly interspaced short palindromic repeats (CRISPR)-associated Protein 9 (CRISPR-Cas9) technology, in which a tumor develops from healthy cells.[443]

Despite these advances, the lack of a mouse model that accurately mimics the course of human disease, from adenoma and adenocarcinoma to metastasis or changes in the microenvironment remains a common issue. The most widely employed models of GEMMs and GEAMMs include adenomatous polyposis mouse models (APMM) and hereditary nonpolyposis colon cancer mouse models (HNPCC). While HNPCC is the consequence of genetic changes to the MMR genes, APMM is mainly caused by germline mutations of the *APC* gene, a tumor suppressor gene. When it comes to comprehending the molecular pathways and therapeutic targets involved in the onset and evolution of CRC, APMM has proven to be particularly valuable. Hereditary nonpolyposis CRC, or Lynch syndrome (LS), is a prevalent syndrome predisposing to cancer that is caused by germline pathogenic mutations in MMR genes. HNPCC models provide a platform for researching the processes underlying drug resistance and for testing novel combinations of immunotherapies and targeted therapies. However, the creation of these models is costly and time-consuming, and environmental influences may cause variations in the mice's phenotypes.[431] In these APMM and HNPCC models, various genes such as oncogenes like C-*myc*, *SRC*, *Kras*, etc., tumor suppressor genes like DCC, MDD, *p53*, *Apc*, etc., and DNA repair genes like *hMsh1*, *hMsh2*, *hMlh6*, *hPms1*,and *hPms2* are used to create a successful CRC model. Each of the genes plays a distinct role in the development of CRC, and mutations in two or more of those genes are commonly linked to the malignant phenotype of CRC.[439] The most prevalent model, which accounts for 86% of human CRC cases, is a mouse with a mutant *Kras* gene.[500] This model is used to explore the onset, course, and efficacy of possible therapies for CRC. Mice with mutations in the *Apc* gene, which is present in 90% of human CRC[501] and mice with mutations in the *p53* gene, which is present in 60% of human CRC,[502] are the other common GEMMs that are used in CRC research. The advantages and disadvantages of modifying the different genes to induce CRC model in murine species are summarized in Table 12.

Taking into account all the genes involved in the development of the genetic model, these GEMMS and GEAMMs aid in the growth of *in situ* tumors and replicate the early phases of oncogenesis including stage I and II. Since gene alterations occur at the biological level, these models depict the clinical circumstances of cancer in terms of the natural immune system. This is because of a well-known genetic event, and the cancer cells and stroma are from the same species. However, the creation of these models is costly and time-consuming, and metastases are seldom created. The complete replication of human cancer differs from that of the

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Table 11. Most Used Carcinogens to Induce CRC; IP = Intraperitoneal; SC = Subcutaneous; IR = Intrarectal; OG = Oral Gavage; IG = Intragastric

carcinogen used	dose/concentration	species/strain and route of administration	CRC induction rate	ref
1,2-dimethylhydrazine (DMH)	2 mg to 200 mg/kg	male Wistar rats: SC and IR male Balb/C mice: IP, SC female Wistar rats, SC female CD1 Swiss Albino Mice: SC	~60% induction of CRC with SC injection once a week for 20 weeks	470−475
1,2-dimethylhydrazine (DMH) and dextran sulfate sodium (DSS)	20−40 mg/kg of DMH and 2−3% of w/v of DSS in drinking water	male Wistar rats: IP male BALB/c mice: IP male F344 rats: IP	~80% induction of CRC after 12 with IP injection of DMH once a week for 8 weeks and DSS water up to 12 weeks	476−478
1,2-dimethylhydrazine (DMH) and 2,4,6-tririnitrobenzenesulfonic acid (TNBS)	20−40 mg/kg of DMH and 10 mg of TNBS in 0.25 mL of 50% ethanol	male Wistar rats: SC and IR for TNBS	~60% induction of CRC after 25 weeks with SC injection of DMH 4 times a week for 2 weeks and 1 time IR administration of TNBS	479
azoxymethane (AOM)	7−15 mg/kg	male C57BL/6 mice: IP male Balb/c mice: IP male Wistar rats: SC male Sprague-Dawley rats: SC female A/J mice: SC	~60% induction of CRC with IP injection once a week for 12−16 weeks	480−484
azoxymethane (AOM) and dextran sulfate sodium (DSS)	10−15 mg/kg of AOM and 2−4% of w/v of DSS in drinking water	male C57BL/6 mice: IP male Wistar rats: SC male F344 rats: IP female Balb/C and C57/Bl6 mice: IP female FVB/NJ mice: IP	100% adenocarcinoma induction after 20 weeks with IP injection of AOM once and 1 week DSS in water	485−489
azoxymethane (AOM) and 2,4,6-trinitrobenzenesulfonic acid (TNBS)	10 mg/kg of AOM and 2.5 mg of TNBS in 0.15 mL of 50% ethanol	C57BL/6 mice: SC and IR for TNBS IFN-$\gamma^{-/-}$ and IL-4$^{-/-}$ mice: SC and IR for TNBS	~90% adenocarcinoma induction after 16 weeks with SC injection of AOM once a week for 6 weeks and 1 dose TNBS	490,491
N-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG)	100 mg/kg and 4 continuous dose of 5 mg/mL in 0.1 mL twice a week for 2 weeks	male BALB/c mice: IR male C57/BL6 mice: IR female C57BL6 mice: IR	100% induction of CRC with once week IR instillation for 20 weeks	492−494
methyl nitroso urea (MNU)	8−10 mg/kg	male Wistar rats: IR male Sprague-Dawley rats: IR male F344/DuCrj rats: IR	78% induction of CRC with thrice a week IR instillation for 10 weeks	495−497
2-amino-1-methyl-6-phenylimidazo(4,5-*b*) pyridine (PhIP)	0.01−200 mg/kg in 1.5% w/v of DSS	hCYP1A mice: OG and IG	did not induce colon cancer, but forms colonic aberrant crypt foci and lymphomas	498,499

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Table 12. Most Commonly Modified Genes to Induce CRC in Murine Species

modified gene	advantages	disadvantages	ref
APC gene	useful for understanding the process by which CRC develops, evaluating therapeutic and/or chemo preventative agents, and simulating the cellular and tissue milieu of malignancies that are inherited, such as Lynch syndrome (LS), also called as hereditary nonpolyposis CRC (HNPCC) and Familial adenomatous polyposis (FAP).	inadequate ability to stop the cells at the crypt base from multiplying; the early development of CRC may complicate the assessment of treatment interventions and necessitates the use of additional animals in APC gene mutation-based cancer models	516,517
Kras gene	studies on the KRAS signaling pathway have shown that adenocarcinomas that express consistently *Kras* genes show uniform high-grade dysplasia	metastases are not developed	518
Apc^{CKO}/LSL-*Kras* genes	the germline has FAP and LS genetic alterations; useful to study the mTOR pathway and metastatic models	for the development of metastases, 20−24 weeks are required	519
$Msh2^{-/-}$ gene	useful to develop the CRC tumors with defects in DNA mismatch repair, which mimics the LS models	all body cells have the Msh2 mutation, and mice are more likely to develop lymphomas	520
$Smad4^{TKO}$	the beginning of spontaneous colitis-associated CRC (CAC) by six months of age is correlated with IFN-expression	metastases are not developed	521
villin-Cre /$KrasG12D^{Dint}$/ $Ink4a/Arf^{-/-}$	target gene knockout and tissue-specific promoters in the intestinal mucosa; some invasive adenocarcinomas have the potential to target oncogenes or tumor-suppressor genes	this model needs recombinant adenovirus expressing *Cre* to be administered into the rectal cavity	522
$Apc^{\Delta 716}$ $Kras^{G12D}$ $Apc^{\Delta 716}$ $Trp53^{R270H}$ $Apc^{\Delta 716}$ $Kras^{G12D}$ $Tgfbr^{-/-}$ $Apc^{\Delta 716}$ $Kras^{G12D}$ $Fbxw^{-/-}$	effective metastases model through a combination of TGF suppression, *Kras* activation, and *Wnt* activation	although the gene mutation serves as an effective model for metastases (induced metastases), it does not lead to the development of spontaneous metastases	523−525
$Dpc4^{\pm}$ $Apc^{+/\Delta 716}$	suitable model for FAP CRC investigation since tumor histology characteristics are the same as humans	metastases are not developed	526
$Fbw7^{flox/flox}$ $P53^{flox/flox}$villin-Cre	a valuable resource for the investigations on the etiology and management of chromosomally unstable and metastatic CRC	the latency period which is the interval between the genetic alteration (e.g., mutation, knockout, or transgene activation) and the appearance of measurable cancer or metastasis in an animal model is long	527

animal model due to secondary mutations, even though the immune system remains untouched. Since the imaging of disease assessment in these models requires costly and user-dependent (i.e., high skill required) techniques like magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), endoscopy and so on, one of the primary limitations of these models is their limited noninvasive imaging options.[503]

5.4. Xenograft Models

Human tumor cells or tumor fragments are grafted into immunocompromised animals to create xenograft models. Xenograft refers to the transplantation of tissue including fresh human tumor, intact or single cell from one species into another. SC, intrasplenic, and orthotopic transplantation are the three types of transplantation routes. Orthotopic transplantation involves delivering cancer cells to the same tissue or anatomic site where a tumor type originated.[504] To create syngeneic models, animal tumor cell lines like CT26 or any commercially available immortalized cells are transplanted into animals that share the same genetic heritage as the cell line.[505] It is also feasible to distinguish between orthotopic and heterotopic models in this context.

5.4.1. Cell Derived Xenograft Model (CDX). Owing to its ease, accessibility, and high tumor growth, SC injection (i.e., heterotopic model) is one of the most popular techniques; however, the TME differs from that of the colon, and metastases do not form. Considering its low level of technical requirements, ease of seeing tumor growth, low cost of maintaining colonies, high yield generation, and tolerable tumor latency, CDX model is widely used at the injection site. Commonly used mice are typically naked (i.e., athymic) mice strains and the severe combined immunodeficient (SCID) mice, which are devoid of either T cells or both B and T lymphocytes, respectively. Moreover, NOD/SCID animals lack NK cells in comparison to SCID mice.[506] However, this model cannot replicate the genetic heterogeneity of the original tumor because of the loss of original inheritance and the absence of relevant TME components during *in vitro* passage. Additionally, modifications at the genomic and epigenetic levels may arise from repeated passaging with enrichment for specific subclones.[507] There are advantages of injecting cells into the intestinal serosa of immune-deficient animals for orthotopic xenografts of CRC cell lines. The advantages of this approach are comparable to those of the SC model; however, certain cell lines metastasise to the liver, and the CRC cells are housed in a more natural milieu. Nonetheless, a significant limitation of these models for immuno-oncology investigations is their inability to support studies on checkpoint blockade treatments, cytotoxic T cells, or adaptive immunity.[508]

5.4.2. Patient Derived Xenograft Model (PDX). To address the weaknesses of the CDX model, PDX models have been established to deepen the understanding of tumor biology and to develop novel medicines for the treatment of cancer. PDX models are developed by grafting human tumors or tumor cells onto murine species. The outcomes of drug evaluation using PDX model is the most similar to clinical settings, and the kind of immunodeficient mice employed and the mode of administration influence the engraftment rate. Evidence has shown that in CRC, PDX models maintain the heterogeneity of the underlying tumor and the most popular method for promoting engraftment is to monitor and treat the tumor after SC implantation.[431] The most frequently

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employed original source is surgical specimens since the quantity of initial tumor material greatly influences the outcome of PDX engraftment. The highest percentage of engraftment (ca., 60−100%) in CRC is observed in PDX models with 89% of the hosts being Balb/c nude mice with orthotopic implantation; however, nonobese diabetic (NOD)/SCID and NOD/SCID/IL2rγ^{null} (NSG) mice are used as hosts in the PDX model with 76% with subcutaneous injection.[509−511] Compared to 2D cultured cancer cell lines, the PDX model has a higher stromal component, which could be useful for studying the interactions between cancer cells and TME. Studies have shown that PDX preserves the human donor tumor's global gene-expression patterns, mutational status, metastatic potential, histological differentiation, and histopathological subtypes.[512] The CRC humanized PDX model has been utilized in numerous studies to evaluate the efficacy of immunotherapy medications and other systemic chemotherapeutic medicines. It has also been used to identify drugs and biomarkers, generate cell lines, construct colospheric structures, and gain additional insights into the biology of tumor. A strong foundation for examining the biology of metastases and the response to treatment in CRC is offered by PDX orthotopic models. However, orthotopic implantation requires a high level of technical skills, and this model's capacity and reproducibility are limited. Recently, fluid from malignant ascites or pleural effusions, circulating tumor cells (CTCs), or both have been used to construct PDXs that maintain tumorigenicity in mice. Therefore, it is possible to analyze the genetic evolution of tumors and evaluate how new therapies are responding to tumors using CTC-derived PDX models.[513] The PDX model has some drawbacks, such as high costs, longer tumor production time and poor engraftment rate. Establishing a viable PDX model is challenging, and the possibility of gene mutations further complicates the process.

5.4.3. Patient Derived Organoid Xenograft Model (PDOX). Since the PDX model is known to be a tedious and expensive process, patient-derived organoid xenograft (PDOX) may be able to help with these problems. Patient derived organoids (PDOs) are created from patients' stem cell collections or isolated organ progenitor cells, which result in clusters of three-dimensionally cultured multicellular aggregates. Investigations have demonstrated that PDOX model preserves the original matrix's characteristics as well as the functions of the tissues. Also, PDOs perfectly replicate the *in vivo* tissues in both the healthy and diseased conditions, including CRC. This model can be genetically edited and is easy to maintain. It has been shown that PDOs preserve the parental tumors' histological, transcriptomic, and genetic characteristics.[514] In other words, the PDOX model preserves the essential cell signaling pathways to sustain the growth of the tumor cells while removing any chance of the tumor cells being rejected because it lacks an adaptive immune system. The PDOX model's capacity to precisely mimic the tumor biology and histology in patients, as well as preserve driver mutations from the original tumor, represent key advantages. As a result, pharmacological efficacy and toxicities can be realistically evaluated in an *in vivo* model that closely mimics the clinical setting. Since PDOX implantation has a tumor formation rate of 60% in the colon wall and 100% in the cecum, respectively, it offers a strong basis for more accurate CRC murine models.[515] Since the concept is still in its infancy, PDOX technology validation and standardization processes are still lacking. These models might not be appropriate for producing results that can be applied to other patient populations because they are based on individual patients. Nonetheless, it is still less costly to establish a PDOX setup compared to PDX models.

5.5. Inferences and Implications on Murine Models

Animal models play a critical role in biomedical research, particularly in understanding disease mechanisms and evaluating therapeutic interventions. Their performance depends on how well they mimic the pathophysiology, progression, and treatment responses of human diseases. The overview of the performance of various models has been discussed in (Table 13).

Table 13. Overview of the Performance of Various Animal Models

Features	Induced model	GEMMs and GEAMMs	CDX model	PDX model	PDOX model
Time consumption	Medium	High	Medium	High	High
Cost	Low	High	Medium	High	High
Metastases	Low	Medium	Medium	Medium	Medium
TME	High	High	Low	Low	Medium
Engraftment rate	High	Medium	Medium	Medium	High
Translational ability	Medium	High	Medium	Medium	High
Tumor heterogenicity	High	Medium	Medium	High	High
Surgical skill	Low	Medium	Medium	High	High
Immuno-oncology	Medium	High	Medium	Low	Medium
Drug discovery	High	Medium	High	Medium	Medium
Biomarker discovery	Medium	High	Medium	High	High

Understanding the advantages and disadvantages of CRC models, as well as how to apply them most effectively for medication development and studies into the origins and evolution of tumors, is essential for CRC researchers. Even though there are a few animal models available for the study of CRC, none can be considered as a perfect model; rather, they are all valuable resources for understanding the etiology of colon cancer in humans and other animals as well. Nonetheless, the selection of the model should take into account the objectives of the study, the costs, and the benefits and drawbacks of each model, animal strain, and gender.

Over the past few decades, human cell lines and xenograft models have been widely used because they are inexpensive and simple to use. However, the heterogeneity of CRC tumors cannot be replicated by these models used individually. Every animal model has benefits and drawbacks. While certain models are effective at inducing carcinogenesis on their own, in other situations combining two induction methods yields the most representative results for human carcinogenesis. By combining two induction methods, researchers can create models that more accurately represent human diseases, improving the predictive value of preclinical studies. An example is the combination of genetic mutation plus carcinogen exposure. Such a combination can be achieved through the use of an *APC* gene mutation model, such as the *Apc* Min/+ mouse, which predisposes animals to develop tumors and Administration of a chemical carcinogen like

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azoxymethane (AOM), which induces DNA damage and accelerates tumor formation. As discussed, certain individual animal models are considered particularly suitable for research on CRC because they closely replicate the pathophysiology of the disease in humans. These models provide valuable insights into tumor initiation, progression, and metastasis, as well as responses to various therapeutic strategies. It should be highlighted, nonetheless, that the majority of models necessitate the combination of at least two CRC strategies. This is because CRC is a complex condition, meaning that a number of variables, including hereditary and environmental factors, can contribute to its development. To summarize, a model that fully captures the pathophysiology of CRC is still needed. Murine CRC models remain a valuable resource for advancing our knowledge and management of this disease.

5.6. Other *in Vivo* CRC Models

5.6.1. Fruit Fly Model (*Drosophila melanogaster*). *Drosophila melanogaster*, a common fruit fly, has evolved into a useful tool for research on cancer (Figure 8). WNT, HIPPO, JAK/STAT, RAS, NOTCH, HEDGEHOG, BMP, and TGF-β are just a few of the important elements in cancer-related pathways that have been successfully identified using Drosophila as a pathway discovery platform.[528] About 75% of the genes associated with human diseases are reported to have functional homologues in Drosophila.[529] The fruit fly contains important genes related to the cell cycle, differentiation, migration, polarity, adhesion, and apoptosis in the setting of cancer. It is important to note that, compared to mammals, Drosophila exhibits less genetic redundancy, which results in a lower frequency of these genes.[530] Therefore, compared to conventional 2D *in vitro* cell culture systems, fruit flies can more precisely reflect the cancer state. The organism can produce a lot of offspring and has a quick life cycle (ca.,10 days). It is also reasonably priced and simple to care for. Furthermore, 96-well microtiter plates can accommodate both larvae and mature adults because of their small size and also the organism may be used to screen wide pharmacological libraries at high throughput screening.[531] Despite lacking a colon, Drosophila can be used as a model to study the cellular and genetic processes that contribute to CRC. By altering *APC*, *Ras*, and other genes linked to cancer, gene-editing techniques can shed light on the origin of epithelial tumors. Owing to their short life cycles and low cost, Drosophila models are especially useful for high-throughput screening and fundamental mechanistic research.

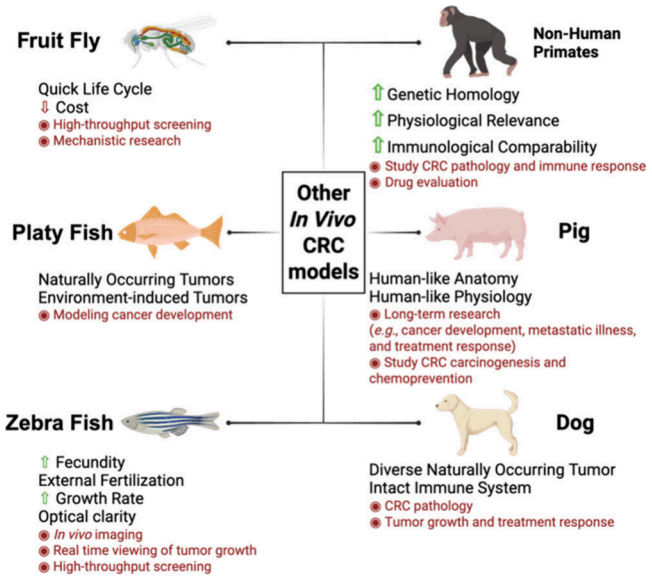

Figure 8. Other *in vivo* animal models of CRC: advantages are indicated in black above where the applications in CRC are reported in red. Figure created with BioRender.com.

5.6.2. Platy Fish Model (Xiphophorus Fish). Classically, Xiphophorus fish were used to successfully develop melanoma models (Figure 8). Xiphophorus hybrids have been used in a number of attempts to model cancer development following exposure to toxins. Utilizing well-known carcinogens with potent mutagenesis properties, the tests successfully induced a wide range of distinct cancer histotypes, which replicated numerous known human tumor entities. Even in the absence of carcinogens, certain strains of Xiphophorus produce other forms of neoplasia, such as thyroid and ocular tumors, although these results were not investigated further.[532] Smaller models of xiphophorus fish that display both naturally occurring and environmental-induced tumors are helpful in comprehending the genetics of CRC and the biology of malignancies. Understanding how genetic and environmental factors combine to generate CRC is made possible by the ease with which species with different susceptibilities to the disease can be crossbred.

5.6.3. Zebrafish Model (*Danio rerio*). The zebrafish, or *Danio rerio*, is an animal model that was first employed in studies of developmental biology in the early 1980s (Figure 8). As early as 1982, it was also used in studies on cancer. Numerous factors, including high fecundity and external fertilization, rapid growth, and optical clarity throughout the larval stage, made zebrafish one of the most widely used animal models in study.[533] Furthermore, the genomes of zebrafish and humans have 70% of similarities, including the preservation of even some epigenetic markers.[532] Zebrafish provides numerous opportunities for the research of invasion and dissemination by enabling *in vivo* imaging to track the interactions among the implanted cancer cells. Furthermore, the interaction between endothelium and cancer cells can be studied *in vivo* using angiographic zebrafish models, such as the Tg(fli:eGFP) zebrafish line, a transgenic animal containing GFP-labeled blood vessels.[534] Because of their transparent embryos, which enable *real time* viewing of tumor growth, zebrafish are being used more and more in CRC research. Research into gene functions, metastasis, and treatment responses is made possible by genetic modification and xenografts, particularly PDXs. Zebrafish models are perfect for high-throughput drug screening because of their quick reproduction and genetic resemblance to humans.

5.6.4. Dog Model. One of the most significant animal models of human cancer is spontaneous cancer in dogs (Figure 8).[535] Unlike most genetically modified or xenograft mouse models, they capture the essence of human cancer since they are naturally occurring, diverse, and their immune system is intact. Additionally, dogs are more biologically similar to humans than mice, with similar telomere and telomerase activity and a higher incidence of spontaneous malignancies of epithelial origin.[536] In an effort to support the dog-human molecular similarity, researchers identified copy number aberrations (CNAs) in the genomes of canine CRC.[537] Furthermore, they have successfully developed a novel dog–human comparison technique for cancer driver and passenger

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amplified/deleted gene discrimination.[538] The significance of canine models in promoting drug discovery for personalized oncology is shown by the fact that a number of targeted medicines created for humans are linked to a favorable prognosis when applied to canine tumors with certain genomic abnormalities.[539] Given that some dog breeds are more naturally prone to spontaneous CRC, researchers can examine CRC pathology in a setting more similar to human diseases, particularly with relation to spontaneous tumor growth. Dogs with CRC are a good model to investigate tumor growth and treatment responses because they share genetic and environmental risk factors with humans.

5.6.5. Pig Model. Considering the numerous similarities to humans in terms of longevity, size, organ anatomy, physiology, drug metabolism, genetics, and immunology, the pig is a promising alternative model organism (Figure 8).[540] Pigs and humans have comparable small intestinal structure, but the pig's large intestine differs slightly because of its bigger cecum, absence of an appendix, and spiral colon.[541] Crucially, since pigs are larger than rodents, there are more options for longitudinal sampling and, consequently, for tracking the progression of tumors throughout therapy. The onco-pig model is an intriguing disease model for intestinal types of cancer, since it provides a variety of opportunities for long-term research on intestinal cancer development, metastatic conditions, and treatment response.[542] Pigs are valuable in CRC research for their anatomical and physiological similarities to humans, especially in the digestive system. These models help study CRC carcinogenesis and chemoprevention. CRISPR-Cas9 has enabled the creation of genetically engineered pigs with mutations in *APC* and other CRC-related genes, providing a unique approach to understanding tumor progression and drug effects.

5.6.6. Nonhuman Primates Model. The heterogeneous environment of cancer requires a validated and reliable preclinical model for the successful clinical translation of the research. Rhesus and cynomolgus macaques are examples of nonhuman primates (NHPs), which are similar to humans in many ways, including physiology, genetics and, most importantly, immune cell populations, immune regulatory systems, and protein targets (Figure 8).[543] NHPs have been a vital tool for analyzing pathogenic pathways and evaluating the effectiveness of vaccines against a variety of human infections, highlighting significant parallels between the immune systems of humans and NHPs.[544] In rhesus macaques, palpable abdominal mass, intermittent diarrhea, weight loss, hypoproteinemia, microcytic anemia, and fecal occult blood are typical clinical indications of CRC.[545] Since tumor targeting, tumor regression, PKPD biodistribution, intratumoral metabolic activity, and immunogenicity can all be similarly examined in tumor bearing monkeys, the evaluation of drug candidates in these preclinical models is similar to that done clinically in patients.[543] Nonhuman primates offer a high degree of genetic, physiological, and immunological similarity to humans, providing a unique model for studying CRC's pathology and immune response. Though ethical and logistical limitations reduce their frequent use, NHPs are valuable for preclinical validation of therapies where translational fidelity is critical. Monkeys with tumors could help close the experimental gap between clinical patients and preclinical models.

6. CHALLENGES FOR CURRENT TREATMENT MODALITIES IN CRC

6.1. Toxicities and Side Effects of Pt(II) Drugs

Apart from the emergence of acquired resistance,[546] particularly notable for **CDP**, Pt(II)-based chemotherapy is associated with severe dose-limiting systemic side effects,[547] that can persist long after chemotherapy ends.[94] This results from the lack of specificity of Pt(II) drugs for cancer cells. Pt(II) complexes are highly reactive toward both cancerous and healthy cells, and interact with biomolecules beyond DNA, such as proteins (e.g., metallothioneins (MTs), albumin) or small molecules (e.g., GSH). It has been shown that less than 10% of the Pt administered intravenously, whether through bolus IV injection or slow IV infusion, attaches to nuclear DNA.[548]

While various toxicity profiles are associated with different Pt(II) complexes (Table 6), they arise from the aforementioned mechanisms of action within healthy cells.[547] An illustration can be given with **CDP**-induced nephrotoxicity. Nephrotoxicity can manifest in various ways, with the most critical and prevalent form being acute kidney injury (AKI), affecting roughly 20−30% of all patients.[549] Pt accumulation in kidneys, stemming from variations in the expression of OCT2 or CTR1 transporters, is a factor contributing to **CDP**-induced nephrotoxicity by facilitating **CDP**-transport to renal tubular cells after filtration at the glomerulus.[550−552] Subsequently, **CDP** can disrupt cellular function by interfering with the cell cycle through Pt-DNA adduct formation,[553] and/or by inducing the production of ROS.[554] This activates MAPK, inducing apoptosis,[555] and stimulates inflammation and fibrogenesis,[61] causing nephrotoxicity. Mitochondrial dysfunction has been identified as a contributor to nephrotoxicity, given the high mitochondrial density in kidney cells.[556] Notably, a correlation has been established between intracellular Pt levels and mitochondrial content in ovarian cancer cells.[557] Other factors, including inflammation and interactions with components of the immune system, may also contribute to the development of AKI.[549] Apart from renal cells, **CDP** can disrupt similar processes in other healthy cells that give rise to ototoxicity, gastrointestinal toxicity and so on. Consequently, the tubular damage and tubular dysfunction with Na^+, K^+, and Mg^{2+} wasting can progress from acute to chronic even after the suspension of treatment.[550] However, in the context of CRC, a focus will be given to **OXP**-induced peripheral neuropathy (OIPN), a major challenge in the treatment of CRC, in section 6.3.1.

6.2. Drug Resistance Mechanisms in CRC against Pt(II) Drugs

Although significant progresses have been made in systemic combination of chemotherapy and targeted therapy, resistance to chemotherapy and tumor recurrence remain the main issues and challenges in CRC treatment and management.[558] The resistance phenomena in tumors can be intrinsic or acquired.[559] Intrinsic resistance is associated with factors such as tumor heterogeneity, drug inactivation, and genetic mutations.[560] Acquired resistance occurs in a large majority (ca., 90%) of patients with metastatic cancer.[561] The associated mechanisms can differ depending on the chemotherapy, but acquired resistance to one cytotoxic agent can confer resistance to other drugs, leading to multidrug resistance. An increase in the tumor size typically leads to an increase in the occurrence of metastases and resistance. The constant evolution of cancer

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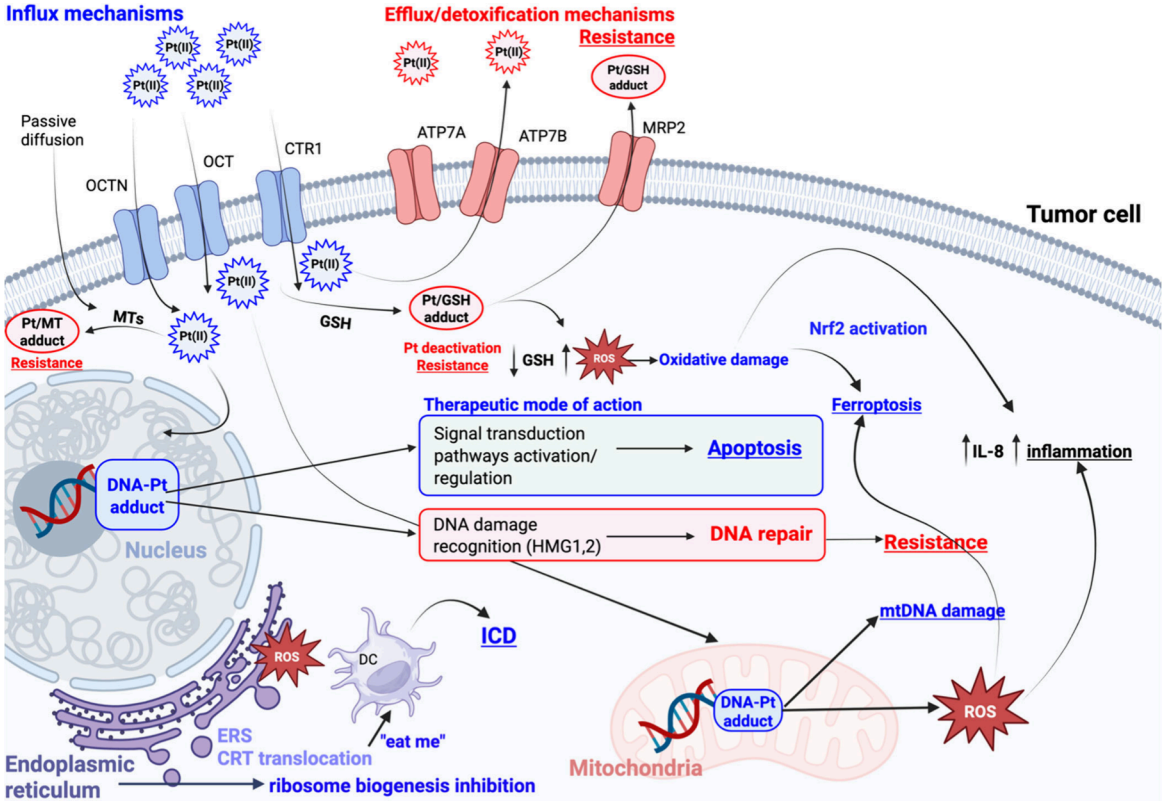

Figure 9. Resistance mechanisms to OXP. Figure created with BioRender.com.

Table 14. Main Mechanisms of Resistance to OXP in CRC

component	pathway	mechanism	ref
cancer cells	OCT transporters	decreased expression levels leading to decreased influx	564,570
	multidrug resistance protein (MRP)	increased expression leading to enhanced excretion	565,566
	GSH	enhanced levels of GSH inactivating Pt, contributing to increased export	
	ERCC1 and 2	upregulation leading to increased DNA repair (NER)	568
TME (CAFs)	IL6	activation of pathways leading to inhibition of apoptosis	571
	TGF-β	activation associated with poor prognosis	571
epigenetic modulations	DNA methylation of SRBC gene	inactivation of SRBC leading to resistance	572
	EMT markers and EMT-inducing transcription factors	facilitating the EMT transition, associated with resistance	573

cells drives heterogeneity in tumors, with cell populations showing differences in metabolism, proliferation or morphology. It is accompanied by various modifications at molecular levels, driving the acquisition of resistance.[562] In the context of this review, CRC is characterized by a high intratumor and intertumor heterogeneity.

Resistance to Pt-based chemotherapy is a multifactorial process and can be acquired through general mechanisms such as a decrease in the cell uptake, an increase in the drug efflux, changes in metabolic enzymes, or reduced sensitivity to the drug(s) caused by genetic or epigenetic modifications (Figure 9). Acquired resistance is also associated with changes in the TME (please refer to section 6.2.1. for more details).[563] The cellular uptake of Pt drugs is mediated/regulated by ATP-binding cassette (ABC) transporters and P-type ATPase copper transporters such as ATP7A and ATP7B. Additionally, Pt drugs are substrates of the copper transporter CTR1 and of the organic cation transporters OCT1−3, members of the solute carrier family 22 (SLC22) transmembrane transporters family, that contribute to Pt cellular uptake. OCT1−3 transporters and their expression levels are involved in Pt accumulation in CRC cells, and thus they have a role in acquired resistance mechanisms.[564]

Additionally, Pt drugs form covalent conjugates with GSH, which contributes to the inactivation of the drug. Enhanced GSH levels are often encountered in resistant cells. It has been shown that upon conjugation of **OXP** with GSH, the expression level of multidrug resistance-associated protein 2 (MRP2) increases, contributing to enhanced drug efflux.[565,566]

The NER mechanism relies on proteins such as excision repair cross-complementation group 1 (ERCC1) and excision repair cross-complementation group 2 (ERCC2) for DNA-adducts recognition and base excision. ERCC1 has been shown to be upregulated in **OXP**-resistant tumors. High levels of ERCC1 mRNA is observed in 5-FU resistant tumors with poor response to FOLFOX.[567] This supports the notion that

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enhanced DNA repair diminishes sensitivity to Pt drugs and may be an acquired resistance mechanism.[568] The NER system can therefore be considered a predictive factor in the treatment of CRC. However, the resistance mechanisms of **OXP** slightly differ compared to those of **CDP** and **CBP**.[569] For example, inactivation or mutation of *p53* alters **CDP**'s cytotoxic activity, but such an effect is observed to a lesser extent for **OXP**-treated CRC lines.[569]

Deregulation of signaling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), is another mechanism leading to resistance. This transcription factor regulates the expression of genes involved in numerous pathways involved in CRC progression, such as apoptosis, proliferation, inflammation, angiogenesis, invasion, and metastasis. NF-κB is constitutively activated in CRC and other tumors, leading to antiapoptotic genes upregulation. Consequently, NF-κB and its associated survival pathway have been considered as therapeutic targets for resistance reversion.[574] For a more in-depth discussion on the cellular mechanisms of resistance to Pt(II) chemotherapeutics, please refer to the review by O'Dowd et al.[116]

6.2.1. Resistance and TME. Apart from cancer cells, the TME comprises multiple other types of cells such as stromal cells such as CAFs, epithelial, immune cells such as TAMs and MDSCs, and blood vessels (Table 14). CAFs have been linked to the development of resistance. The activation of the TGF-β pathway in these stromal cells is a hallmark of poor prognosis in CRC. In addition, the secretion of soluble factors such as IL-6, associated with an increase in CAFs, activates pathways (e.g., PI3K/AKT and JAK/STAT) that cause apoptosis inhibition. Accumulation of Pt in CAFs upon long-term exposure to Pt drugs was proposed to facilitate drug resistance.[571] The TME also contains other elements such as ECM and growth factors. The components of the TME enable the development of the tumor and their response to anticancer drugs significantly impacts the development of resistance. These contributing components include a hypoxic environment, pH, levels of growth factors, inflammatory factors, and angiogenic factors.[571]

6.2.2. Resistance and Epigenetic Modifications. Besides alterations in genes expression, epigenetic changes have been shown to be involved in the development of resistance (i.e., intrinsic and acquired), in CRC and other types of tumors (Table 14).[575] For example, DNA methylation of cytosine, which is one of the epigenetic regulations, catalyzed by DNA methyltransferases in CpG dinucleotides, is known to induce resistance to 5-FU in CRC. DNA hypermethylation is another hallmark in CRC and considered as a predictive biomarker. In the context of resistance, epigenetic modifications affect drug efflux and the ability of the cells to evade chemotherapy-induced cell death (e.g., apoptosis, autophagy and ferroptosis). For example, the inactivation of the BRCA1 interactor *SRBC* gene by DNA methylation is associated with **OXP**-resistance and shorter PFS in CRC.[572]

Epigenetic changes can occur in other TME-associated cells (e.g., CAFs, TAMs, and MDSCs), leading to TME reprogramming and contributing to immune evasion, survival, and resistance.[575] In the context of tumor heterogeneity, epigenetic modifications can promote the development of drug-tolerant cells that are able to survive chemotherapies. Epigenetic modulations of some signaling pathways regulate the generation of cancer stem cells (CSCs) that are described as an important factor in chemotherapy resistance.[576] CSCs are a subpopulation of cells (ca. 5% of tumor cells) with the ability of self-renewal and differentiation. Epigenetic processes facilitating the epithelial-mesenchymal transition (EMT)[235] such as epigenetic regulation of EMT markers (e.g., E-cadherin) or EMT-inducing transcription factors (EMT-TFs), contribute to resistance mechanisms and to the formation of cells with a mesenchymal phenotype generally more resistant to chemotherapy in CRC.

6.2.3. Resistance Reversion. Numerous compounds and formulations were evaluated in the reversion of **OXP**-acquired resistance. Curcumin, for example, was shown to enable reversion in CRC cell lines mediated by CXC-chemokine/NF-κB signaling pathway.[574] Epigenetic drugs have also been evaluated in CRC treatment, in preclinical and clinical trials, with some success. 5-Aza-2′-deoxycytidine (decitabine) and 5-azacytidine are FDA-approved inhibitors of DNA methyltransferases (DNMTs) to treat myelodysplastic syndrome (MDS). Decitabine was shown to improve the activity of **OXP** on CRC cells in an *in vitro* study.[577,578] Some clinical activity of azacytidine along with CAPOX was also described in mCRC patients (NCT01193517).

Histone deacetylase inhibitors (HDACi) were also explored in CRC treatments. Histone deacetylases (HDACs) are often overexpressed in CRC, and are one of the main mechanisms of resistance to **OXP** in CRC cells. The combination of the HDACi suberoylanilide hydroxamic acid (SAHA or Vorinostat)[426] with **OXP** reduced HDAC2 levels and induced mitotic cell death, suggesting that HDACi could potentially be used to revert chemotherapy resistance.[579] Other targets for epigenetic drugs to potentially reverse chemotherapy resistance in CRC include histone methyltransferases (HMTs) and histone demethylases (HDMs), as deregulated histone methylation in CRC has been linked to tumor recurrence and poor survival rates. Consequently, proliferation of **OXP**-resistant CRC cells was significantly reduced upon treatment with a combination of **OXP** with the KDM6A/6B histone demethylase inhibitor GSK-J4.[580] Targeting dysregulated miRNAs is also explored as a therapeutic strategy to overcome resistance. As an example, dichloroacetate (DCA) inhibits the miR-543/PTEN/Akt/mTOR pathway and improves **OXP** sensitivity in CRC cells.[581,582] Mimicking the downregulated tumor-suppressive miRNAs, such as miR-483-3p, is also another interesting approach to revert **OXP** resistance in CRC.[582]

6.2.4. Prediction of Response to OXP Resistance. Predicting the response to **OXP**-based therapy in CRC is challenging due to the complex molecular and genetic heterogeneity of tumors. Generally, variations in DNA repair pathways such as MMR and NER influence **OXP** sensitivity, while factors like immune infiltration and EMT further complicate prediction (Table 14).

Advancements in multiomics have led to the identification of various biomarkers in CRC, including genomic, epigenetic, transcriptomic, proteomic markers, and those related to the gut microbiome (e.g., metagenomics) and metabolomics.[583] Liquid biopsies, which detect CTCs and nucleic acids, have emerged as promising noninvasive tools for early detection and predicting treatment outcomes. However, translating these biomarkers into clinical practice remains difficult. Despite the discovery of numerous biomarkers, only a few have been FDA-approved for clinical use.[584] Comprehensive overviews of established, promising, and potential biomarkers, along with omics technologies used in CRC, are provided in recent reviews.[583−586] This discussion focuses on biomarkers related to **OXP**-based therapy in CRC.

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While FOLFOX regimen is a standard first-line therapy for mCRC, many advanced CRC patients develop chemoresistance, reducing the 5-year survival rate to 14%.[587] Understanding the mechanisms behind **OXP**-resistance is crucial for improving treatment outcomes. Guinney et al. identified four CMSs for colon cancer, which are useful for predicting patient prognosis.[223] Cancers classified as CMS4 (i.e., mesenchymal tumor) are linked to the poorest OS and relapse-free survival (RFS).[223,588] Although standard adjuvant therapies (e.g., FOLFOX) for stage III are recommended, CMS4 cancers do not benefit from systemic adjuvant treatments.[589]

Few studies have developed gene signatures to predict **OXP**-resistance. Lin et al. identified 495 resistance-related genes by analyzing data from resistant and nonresistant cell lines in the Gene Expression Omnibus (GEO) database and developed a four-gene (i.e., *ALCAM*, *CD22*, *CASP1*, and *CISH*) signature that predicted OS.[590] High-risk patients showed poorer outcomes, with a 5-year OS prediction area under the receiver operating characteristic (ROC) curve of 0.72. Using a similar systems biology approach, Cheraghi-shavi et al. analyzed differentially expressed genes (DEGs) between sensitive and **OXP**-resistant CRC cells, identifying upregulation of transglutaminase 2 (TGM2) and high-mobility group AT-hook 2 (HMGA2) and downregulation of FXYD domain containing ion transport regulator 3 (FXYD3) and Galectin 4 (GALS4), which may serve as novel therapeutic targets.[591] A recent study by Zhang et al. in 2024 integrated data from a microarray data set of CRC patients, an **OXP**-resistant CRC cell data set from GEO, and RNA-sequencing (RNA-seq) data from The Cancer Genome Atlas Program (TCGA) to establish a prognostic model for **OXP**-resistant CRC.[592] This model evaluated both the immune landscape and prognostic risk. Notably, prostate transmembrane protein androgen induced 1 (PMEPA1), $CD8^+$ T cells, and M0 macrophages emerged as key biomarkers, suggesting potential therapeutic targets for overcoming **OXP** resistance and reducing disease progression in CRC patients.

OXP-resistance is associated with DNA repair mechanisms, particularly NER and MMR pathways. High expression levels of ERCC1, X-ray cross-complementing group 1 (XRCC1) and xeroderma pigmentosum group D (XDP) correlate with **OXP** resistance and can serve as drug sensitivity indicators.[593] Studies suggest that patients with dMMR or MSI-high in colon cancer have better survival rates than those with pMMR or MSI-Low.[594,595] Additionally, activation of the Wnt/β-catenin signaling pathway and TGF-β1-induced EMT contribute to FOLFOX resistance.[596−598] KIAA1199 promotes resistance by inhibiting apoptosis through poly(ADP-ribose) polymerase 1 (PARP-1) upregulation and reducing endoplasmic reticulum stress.[599] Other biomarkers, such as pyruvate kinase M2 (PKM2) and Williams−Beuren syndrome chromosomal region 22 (WBSCR22) protein, further predict resistance and outcomes.[600,601]

miRNAs, long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) have gained significant attention as predictive factors for CRC due to their roles in gene regulation.[602−605] For instance, miR-128-3p is a key regulator in tumorigenesis and a potential marker for **OXP**-based chemotherapy, as it decreases B cell-specific Moloney murine leukemia virus integration site 1 (BMI1) and MRP5, enhancing chemosensitivity in CRC.[606] Li et al. reported that miR-34a is significantly downregulated in **OXP**-resistant CRC patients and multidrug-resistant cells.[607] Similarly, Ning et al. found that exosomal miR-208b promotes Treg expansion by targeting programmed cell death 4 (PDCD4), contributing to tumor growth and **OXP** resistance.[608] Circulating miR-208b is a promising noninvasive biomarker for predicting FOLFOX sensitivity and a potential immunotherapy target. Zhuang et al. also identified miR-5000-3p as upregulated in CRC and **OXP**-resistant cells, modulating drug resistance by targeting ubiquitin-specific peptidase 49 (USP49).[609]

Several oncogenic lncRNAs, including lncRNA GIHCG and lncRNA ARSR, regulate **OXP** resistance in CRC.[610,611] Another lncRNA, lnc-RP11-536 K7.3, is associated with **OXP** resistance and poor prognosis by recruiting SRY-box (SOX) 2 to activate ubiquitin-specific protease 7 (USP7) expression and stabilize hypoxia-inducible factor 1-alpha (HIF-1α).[612] Knockdown of lnc-RP11-536 K7.3 improves chemosensitivity and reduces tumor proliferation, making it a potential therapeutic target for reversing **OXP** resistance. Moreover, lncRNA cancer susceptibility candidate 15 (*CACS15*), which promotes the expression of ATP-binding cassette, subfamily C, member 1 (*ABCC1*) involved in Pt drug efflux, was shown to be upregulated in **OXP**-resistant CRC cells and associated with poorer prognosis in patients.[613] Furthermore, lncRNA taurine upregulated gene 1 (*TUG1*) induces **OXP** resistance in CRC stem cells and inhibits apoptosis by interacting with GATA-binding factor 6 (GATA6).[614] Colorectal cancer-associated lncRNA (CCAL) and lncRNA H19, found enriched in exosomes generated from CAFs, play a role in the regulation of the extracellular matrix and contribute to **OXP**-resistance in CRC.[575] The expression of circRNAs has also been linked to CRC progression and drug resistance. circHIPK3 promotes **OXP** resistance in CRC cells by inhibiting autophagy and activating the B-cell lymphoma (Bcl)-2/Beclin-1 signaling pathway through signal transducer and activator of transcription 3 (STAT3) expression.[615] Lin et al. demonstrated that **OXP**-resistant CRC cells express higher levels of oncogenic circRNA CCDC66, and its expression is mediated by **OXP**-induced cellular stress *via* DHX9 phosphorylation.[616] Moreover, Pan et al. showed that circATG4B is upregulated in **OXP**-resistant CRC cells, increasing autophagy.[617]

Developing reliable biomarkers to predict treatment outcomes is essential for stratifying patients based on their likelihood of response, personalize treatments, and improving clinical outcomes. However, the clinical relevance of many emerging biomarkers is still under investigation, requiring further research and validation in larger patient cohorts.

6.3. Chemotherapy-Induced Peripheral Neuropathy (CIPN)

CIPN[618] is one of the main off-target toxicities of systemic chemotherapies, affecting the peripheral nervous system (PNS). Generally speaking, the peripheral neuropathy leads to numerous highly debilitating symptoms that may differ with the type of affected nerve fibres. Damages of small nerve fibres, either unmyelinated such as C-fibres (related to the perception of heat, thermal pain) or thinly myelinated such Aδ (related to cold thermal pain), which are involved in the conduction of information associated with mechanical and thermal pain, are associated with burn sensations, tingling, hyperalgesia or allodynia. Damages of myelinated fibres of larger diameters (e.g., Aβ fibres) are associated with sensory dysfunctions such as numbness and loss of balance or motor impairments. CIPN

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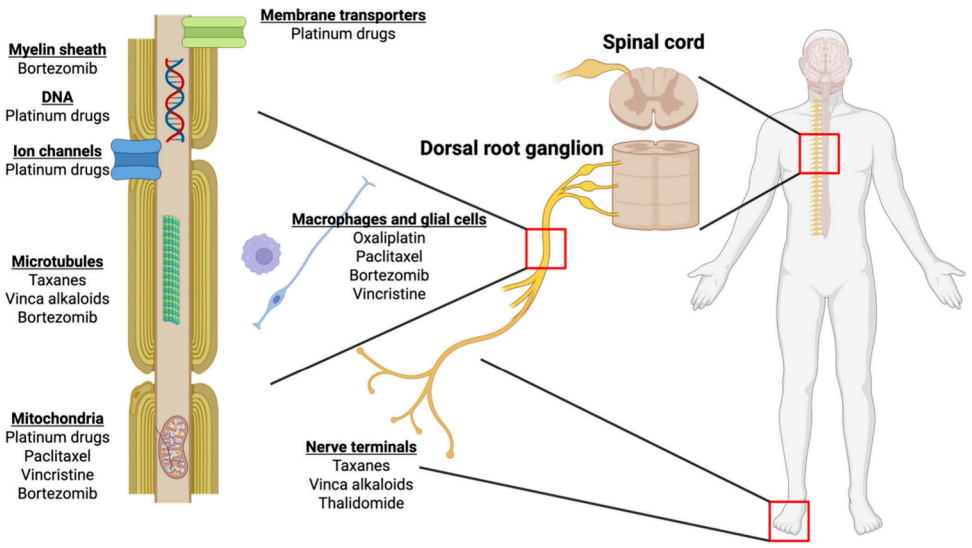

Figure 10. PNS and the main targets of chemotherapies in CIPN. Figure created with BioRender.com.

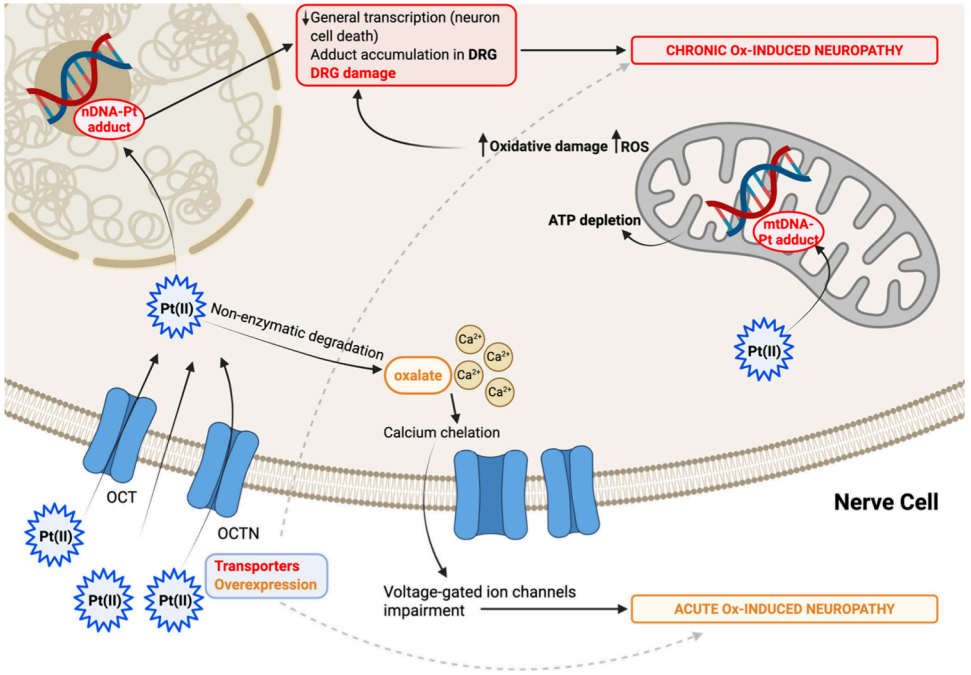

Figure 11. Mechanisms of OIPN in neuronal cells. Figure created with BioRender.com.

patients show paraesthesia and dysesthesia with a typical "sock-and-glove" distribution.

The PNS targets of CIPN are the dorsal root ganglia (DRG), the nerve fibers, and their components, until the distal nerve terminations. The main targets, the neurotoxicity mechanisms and the symptoms vary according to the chemotherapeutic agent (Figure 10).

The prevalence of CIPN depends on factors such as age, environmental/habit factors or genetic conditions/factors.[619] The severity of the symptoms depends on the administered chemotherapeutic drug, the injection schedule and the cumulative dose. In general, the higher the dose and the frequency of the administered neurotoxic agent, the higher the incidence of CIPN.

Its evaluation also varies with the clinical assessment method. Due to the variety of symptoms, diagnoses and evaluations are still difficult and a matter of debate. The clinical evaluations include sensory and motor clinical examinations and neurophysiology studies of sensible nerve conduction velocity (NCV), where a reduction of sensible nerve action potential amplitude (SNAP) reflects axonal damage. Different grading scales are used in clinical diagnosis of CIPN, such as the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CIPN20, among others.[620,621]

Around 68% of cancer patients receiving chemotherapy develop CIPN in the first month of treatment.[387] CIPN severely affects the patients' quality of life and often leads to the reduction of administered doses or even to treatment discontinuation, jeopardizing the treatment outcome. Managing and reducing CIPN through treatment or prevention is therefore a major public health issue. Despite intense efforts to decipher the multifactorial mechanisms of CIPN and identify

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molecular strategies toward their reduction, no preventive or therapeutic clinically approved solution is currently available, although clinical practice guidelines are available.[622,623]

6.3.1. OXP-Induced Peripheral Neuropathy (OIPN). Among the Pt-based anticancer agents, **OXP** shows the highest neurotoxicity, associated with an acute form of OIPN possibly evolving in a chronic OIPN.[624] The **OXP**-specific acute, transient peripheral neuropathy appears during or a few hours after administration, and typically disappears 48−72 h post treatment but it recurs with subsequent administrations.[625] Acute OIPN affects around 85−95% of all patients. Its main symptoms are cold allodynia along with paresthesia and dysesthesia in both hands and feet.[626] Although not dose-limiting, the degree of acute peripheral neuropathy has been thought to correlate with the development of chronic peripheral neuropathy.[619,627] This observation is important since it may lead to dose limitation or arrest. Continuous administration of **OXP** and subsequent bioaccumulation can lead to the development of chronic peripheral neuropathy, in approximately 40−93% of patients (at cumulative doses superior to 780−850 mg/m^3),[626] its incidence and severity depending on the cumulated **OXP** dose. Comparable to **CDP**-induced peripheral neuropathy but occurring in a more prominent and larger extent, as described by Joseph et al. in a rat model,[628] its main symptoms include numbness, tingling in hands and feet, and motor dysfunctions (e.g., loss in proprioception) leading, in some cases, to disability.[629] The reversibility of these symptoms is rare, and they can persist years after the cessation of the treatment,[630] severely impacting the patients' quality of life. In chronic OIPN, a "coasting" phenomenon (i.e., a worsening of the symptoms after the cessation of treatment) is also often observed. Different mechanisms are believed to be involved in acute or chronic OIPN.

6.3.2. OIPN Mechanisms. The neurotoxicity of **OXP** derives from its lack of specificity for cancer cells and a preferential accumulation in the DRG sensory neurons, facilitated by the absence of blood−nerve barrier in the DRG. Different transporters have been involved in the accumulation of **OXP** in DRG neurons (Figure 11). OCT transporters, particularly OCT2, expressed in DRG neuronal cells, were shown to play a role in the uptake.[631] Huang et al. reported that, after a single injection of **OXP** (10 mg/kg), wild-type mice (C57BL/6, FVB, or DBA strains) reported acute OIPN-like symptoms, while the mice deficient in OCT1/2 transporters did not display such symptoms. This was not the case for OCT3-deficient mice, suggesting that this transporter is less implicated in the accumulation of **OXP** in DRG. The same results were obtained in a model of chronic OIPN, supporting the hypothesis that OCT1/2 transporters could be a valuable therapeutic target. CTR1 and multidrug and toxin extrusion protein 1, efflux (MATE1)[632] were also shown to be involved in **OXP**'s cellular accumulation *in vitro*. Organic cation transporter novel types 1 and 2 (OCTN1/2)[631] were recently suggested as key mediators for the preferential accumulation of **OXP** in PNS components, particularly in DRG.[633] *In vitro*, both OCTN1 and OCTN2 impacted **OXP**'s uptake in cells, and their knockout led to reduced toxicity in neurite PC12 and primary cultured DRG cells. *In vivo*, only OCTN1 levels seemed to affect **OXP**'s accumulation in rats' DRG, its inhibition reducing Pt accumulation in DRG and improving **OXP**-induced mechanical hypersensitivity.[632]

Once internalized in the neuronal cells, mechanisms of action similar to those in cancer cells occur. Having less efficient DNA repair systems, DRG sensory neurons display a strong sensitivity to the generation of DNA adducts. Targeting of mitochondrial DNA and subsequent events including mitochondrial swelling, dysfunction and damage, eventually leads to caspase activated apoptosis.[634] **OXP** also provokes the generation of elevated ROS levels in neurons.[635] Additionally, Calls et al. reported, in 2022, an increase in the levels of pro-inflammatory cytokines and NF-κB p65 protein (implicated in cellular responses to stress, among others) in DRG neurons upon treatment with **OXP**, suggesting that a transient inflammatory response is involved in OIPN.[636] Through activation of glial cells, **OXP** induces the activation of immune cells and an increase in the levels of pro-inflammatory markers and cytokines such as IL-6 and IL-1β or TNF-α. Oxidative stress and neuroinflammation[637] are therefore widely accepted mechanisms in the case of chronic OIPN as a result of Pt accumulation in peripheral nerves and dorsal root ganglia.[638,639]

OXP also targets sensory axons, where it leads to a disruption of ion channels activation. Acute OIPN would arise from axonal hyperexcitability leading to the described symptoms of acute neurotoxicity. Acute OIPN has been reported to directly depend on Na_v voltage-gated sodium channel activation impairments,[640] that were suggested to be induced by oxalate, a byproduct resulting from the non-enzymatic degradation of **OXP**,[641,642] which acts as a well-known calcium chelator. Disrupting calcium levels homeostasis alters the function and kinetics of voltage-gated sodium channels, leading to increased sodic currents and both neuronal and peripheral nerve hyperexcitability.[643,644] Sodium oxalate alone was shown to induce cold allodynia (acute neuropathy) in animal models but no mechanical allodynia contrary to chronic OIPN.[645] Other ion channels have been involved in **OXP**-induced neuron toxicity. Transient receptor potential (TRP) channels are nonselective cationic channels involved in the detection of mechanical, thermal and chemical signals. The overactivation of these channels leads to an axonal hyperexcitability. Members of this family such a transient receptor potential ankyrin 1 (TRPA1), transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential melastatin 8 (TRPM8) were shown to be overexpressed after **OXP** treatment in DRG sensory neurons in rats, and thought to be associated with cold hyperesthesia.[646]

Long-term exposure to **OXP** induces axonal demyelinisation and degenerescence, leading to mechanical allodynia. Chronic OIPN has often been associated with a loss in the density of intraepidermal nerve fibres (IENF), small nociceptive non-myelinated fibres located in the extremities, in mice (from skin in hind paws). Demyelinization in sciatic nerves is also a neuropathic marker.[647] However, the mechanisms involved are not yet fully uncovered and additional mechanisms might be involved in both acute and chronic peripheral neuropathy. A summary of the key mechanisms contributing to OIPN is depicted in Figure 11.

6.4. Role of CRC TME in Response and Resistance to Cancer Immunotherapy

In the CRC TME, various cell types play crucial roles in shaping the response to immunotherapy. In the context of dMMR CRCs, some sensitivity to immunotherapy is attributed to the high TMB and the generation of multiple neoantigens

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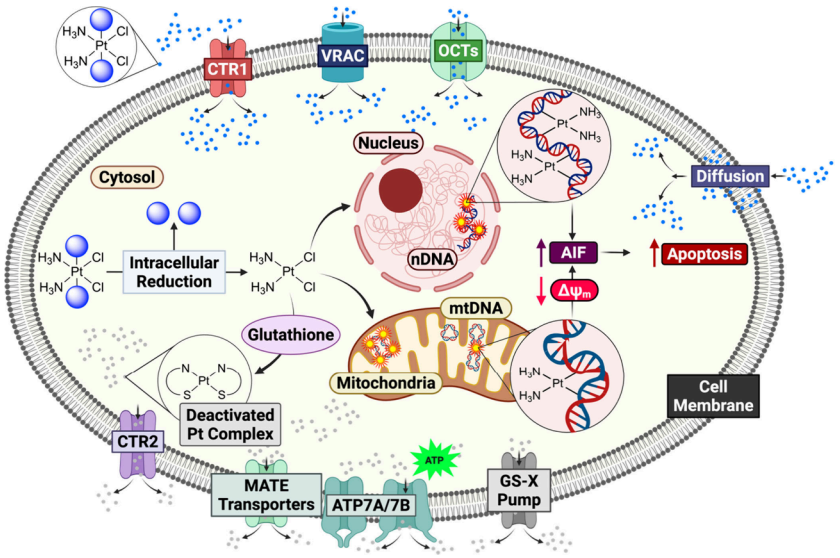

Figure 12. Intracellular fate of Pt(IV) compound. Figure created with BioRender.com.

resulting from genomic mutations due to defective MMR genes (e.g., *MLH1*, *SH2*, *MSH6*, *PMS2*) that fail to rectify errors in the DNA microsatellite regions during replication.[228] $CD8^+$ T cells have the capability to recognize these neoantigens as foreign, allowing them to selectively target and attack cancer cells while sparing healthy cells. Furthermore, T cells, macrophages, and NK cells are abundant in dMMR/MSI-high tumors, where cell surface inhibitory checkpoint molecules, such as PD-1 on lymphocytes and PD-L1 on tumor cells, are increased, enhancing the tumor response to ICI therapies.[648] In contrast, pMMR/MSS CRCs that are found in the majority of patients, present a significant lower antitumor immune response. This is because they are unable to be recognized by cytotoxic immune cells, a consequence of the low mutational profile of these tumors, ultimately leading to resistance to ICI therapies.[649] In addition to T cells, MDSCs enriched in pMMR/MSS CRCs also contribute to the creation of an immunosuppressive state through various mechanisms,[650] including the release of immunosuppressive cytokines, such as TGF-β.[298] This is consistent with *in vivo* data, where mice injected with MSI-high CRC experienced greater tumor regression and T-cell infiltration than MSI-low or intermediate CRC when treated with anti-PD-1 therapy.[651] While dMMR CRCs are generally more sensitive to immunotherapy than pMMR/MSS CRCs, it is still possible for dMMR CRC patients to develop immunotherapy resistance.[652−654]

TAMs are also involved in immunosuppression by releasing cytokines, such as IL-10 and TGF-β, inducing the expression of immune checkpoint molecules, and modulating metabolism that may compromise the energy and function of antitumor T cells. These mechanisms lead to a reduction of immunotherapy effectiveness, although the prognostic significance of TAMs exhibits great variability based on both the stage and type of cancer, necessitating the evaluation of their functionality. Ongoing research focuses on reprogramming TAMs toward a pro-inflammatory phenotype or inhibiting their immunosuppressive functions to enhance the success of immunotherapy. Recent studies on tertiary lymphoid structures (TLSs) have also suggested that B cells contribute to creating an intratumor immunity cycle that increases tumor sensitivity to immunotherapies for solid tumors, including CRC, and are considered as potential prognostic markers.[661−663]

Beyond immune cells, CAFs and endothelial cells (ECs), that constitute a large part of the cancer in CRC CMS4 ("mesenchymal") tumors, may also influence immunotherapy responses through secretion of immunosuppressive and angiogenic factors such as TGF-β, CXCL12, or VEGF.[664,665] These factors support an inflammatory environment and impact immune cell function and tumor growth. Research targeting the interaction between CAFs/ECs and immune cells aims to enhance immunotherapy responses.[666]

The ECM and its components play a significant role in influencing sensitivity or resistance to immunotherapy in several ways within the TME. First, the ECM can act as a physical barrier, limiting the infiltration of immune cells into the tumor. The composition and stiffness of the ECM can impact immune cell function. Certain ECM components, such as collagen and fibronectin, can create a stiffer matrix, that promote CRC progression,[667] affecting the behavior and function of immune cells and ultimately contributing to immune suppression and resistance to immunotherapy. Understanding the complex cell−cell and cell−ECM interactions within the CRC TME is crucial for overcoming potential resistance and developing comprehensive and effective immunotherapeutic strategies in CRC.

7. OPPORTUNITIES FOR EMERGING TREATMENT MODALITIES IN CRC

7.1. Targeted Chemotherapeutic Approaches Using Pt(IV) Prodrug Strategy

The Pt(IV) pro-drug strategy has been propelled as a solution to address the high systemic toxicities associated with Pt(II) drugs.[547] Pt(IV) complexes, containing two additional axial ligands, are relatively inert outside cells and are activated mainly intracellularly by endogenous small molecular (e.g., ascorbate, glutathione, L-methione, L-cysteins, deoxyguanosine monophosphate, metallothionein, serum albumin) or macromolecular reducing agents.[668] Upon reduction, the Pt(II) moiety and the two axial ligands are released (Figure 12).

The resulting active Pt(II) species interferes with cell survival by inducing DNA damage. The two axial ligands can

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Table 15. Summary of Lead Pt(IV) Compounds That Reached Clinical Trials

Pt(IV) drugs in clinical trials	improved characteristics	reduction half-life in plasma	treatment for cancer type	stage of clinical trial (indication)	status	ref
Ormaplatin (Tetraplatin)	*in vivo* and *in vitro* efficacy against CDP-resistant cancers	<1 min	various malignant solid tumors	phase I (solid tumors)	suspended due to observed severe neurotoxicity	655,656
Iproplatin	highly water soluble and more resistant to reduction than ormaplatin in plasma	1.2 h	ovarian cancer, various malignant solid tumors	phase III (ovarian cancer)	suspended due to lack of observed improved efficacy over CDP	657,658
Satraplatin	suitable for oral administration	5.3 h	prostate, breast, lung, ovarian, head, and neck cancer	phase III (prostate cancer)	suspended due to lack of observed improved efficacy over CDP	659,660

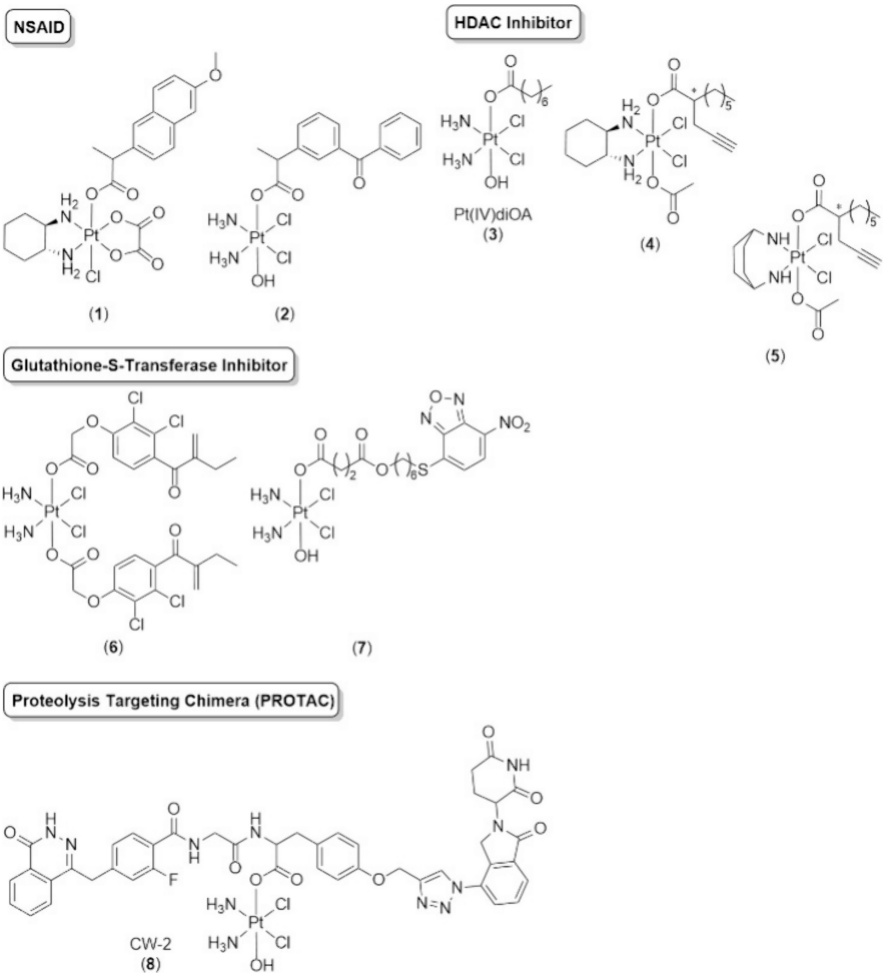

Figure 13. Dual- and multiaction Pt(IV) complexes.

be utilized to improve the pharmacological properties of the prodrugs. These ligands can, for instance, enhance lipophilicity, solubility, facilitate tumor or intracellular targeting, impart imaging properties, inhibit cellular processes, or display antiproliferative properties, making them multitargeting prodrugs.[669−671] The tumor targeting strategies using Pt(IV) scaffold is further discussed in greater details in sections 7.1.4.

7.1.1. Pt(IV) Prodrugs in Clinical Trials. Currently, a few Pt(IV) compounds have reached clinical trials, the most notable being **ormaplatin** (phase I), **iproplatin** (phase III), and **satraplatin** (phase III) (Table 15, Figure 2). Of the three, satraplatin has demonstrated the most promising potential, as patients displayed a decrease in Pt-associated toxicity compared to **CDP** in clinical trials.[672] Moreover, **satraplatin** can be administered orally, significantly improving patient compliance and quality of life compared to IV administration of Pt(II) drugs.[672] However, **satraplatin** did not offer any improvement in OS compared to existing clinical treatments for prostate cancer and therefore did not receive FDA approval for clinical use.[673] Similarly, other Pt(IV) compounds in clinical trials did not receive approval due to the lack of longer OS compared to existing Pt drugs,[659] despite some improvements in oral stability,[674,675] cellular uptake,[674] and toxicity profiles.[676] Satraplatin is also rapidly reduced in whole blood, with a half-life of about 1−2 h, largely due to efficient reduction by hemoglobin. This process converts satraplatin into its active Pt(II) form.

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One potential explanation for the limited success of the Pt(IV) compounds reported in Table 15 is that the Pt(IV) compounds were easily reduced extracellularly, resulting in premature release of the bioactive Pt(II) drug. Studies have demonstrated that the complexity of the axial groups determines the resulting reduction mechanism and half-lives of each Pt(IV) complex: compounds carrying less electrophilic axial ligands are the most resistant to reduction.[677−679] **Ormaplatin**, for instance, is reduced within 1 min (Table 15), thereby releasing the active Pt(II) species rapidly, contributing to high systemic toxicity.[655] In comparison, satraplatin and iproplatin are less easily reduced, as evident from their comparatively longer half-lives (1.2 and 5.3 h, respectively) and consequently they are less associated with systemic toxicities (Table 15). Despite their longer half-lives, these Pt(IV) compounds were still discontinued, indicating that there are additional contributing factors to the limited success of these Pt(IV) compounds in clinical trials.

Another hypothesis to the observed lack of improvement in the OS stems from the simplicity of the axial ligands, with no functionality to improve the efficacy of the drugs. As such, recently developed Pt(IV) compounds contain more complex axial ligands that confer benefits to their anticancer efficacies such as targeting to disease areas,[680] synergistic activity to Pt,[681] overcoming of chemoresistance,[682] complementing photodynamic therapy (PDT)[670] as well as expanding the molecular targets of Pt.[676]

7.1.2. Dual- and Multi-Action Pt(IV) Complexes for CRC. Pt(IV) prodrugs represent a promising strategy to enhance therapeutic efficacy and circumvent resistance mechanisms, leveraging on improved cellular accumulation facilitated by lipophilic axial payloads as well as the capacity for synchronous targeting of multiple biological pathways offered by bioactive axial ligands. The conjugation of ancillary or "innocent" ligands such as halides, hydroxides, or carboxylate derivatives or onto Pt(IV) scaffold results in increased cellular uptake and eventual enhancement in anticancer efficacy.[683−687] Other than "innocent" ligands, a diverse array of bioactive agents have also been conjugated onto the Pt(IV) scaffold, including cytotoxic drugs, nonsteroidal anti-inflammatory drugs (NSAIDs),[688−700] epigenetic modulators (e.g., histone deacetylase inhibitors),[701−713] metabolic enzyme inhibitors (e.g., glutathione S-transferase inhibitor,[682,714−716] pyruvate dehydrogenase kinase inhibitor,[717,718] carbonic anhydrase IX inhibitor),[719] DNA repair inhibitor (e.g., nucleotide excision repair inhibitor),[720] signaling pathway modulators (e.g., NF-κB inhibitor),[721,722] antimetabolites,[723,724] antimetastatic agents,[725−728] antimicrotubule agents,[729−733] vitamin analogues,[734] and even proteolysis targeting chimeras (PROTACs).[735,736] Advancement in novel Pt(IV) scaffold synthesis and linker technologies continues to support future expansion on repertoire of conjugatable molecules, further enhancing the versatility of the Pt(IV) prodrug approach.[713,737,738] While numerous excellent comprehensive reviews have covered multiaction Pt(IV) complexes,[739−742] this section will specifically highlight several prominent examples that have demonstrated promising efficacy and mechanisms of action relevant to CRC models. (Figure 13)

Being one of the hallmarks of cancer, chronic inflammation not only promotes the proliferation and progression of tumors, but also causes a immunosuppressive TME. As a result, NSAIDs have become a popular choice for conjugation onto Pt(IV) scaffold with examples include aspirin,[688,689] carprofen,[695] etodolac,[695] diclofenac,[700] flurbiprofen,[693,700] ibuprofen,[690−692] indomethacin,[690,691] ketoprofen,[696,699] naproxen,[694,696−698,700] and sulindac.[695] These Pt(IV)-NSAID conjugates generally exhibited comparable or enhanced antiproliferative efficacy against CRC cell lines (i.e., HCT116, SW480, CT26), as compared to their corresponding Pt(II) precursors.[690−693,696,697,699] While improved cellular accumulation *via* increased lipophilicity or nanostructure formation was initially thought to be the primary contributor to the enhanced potency,[690−693,696] recent studies revealed more complex mechanisms of action.[697,699] Notably, recent *in vitro* and *in vivo* investigations using CT26 CRC model demonstrate that **1** and **2** possess reduced systemic toxicity and significant antimetastatic properties compared to their parent compounds.[697,699] The antimetastatic effect is likely attributed to the cyclooxygenase-2 (COX-2) inhibition exerted by the NSAID payload, leading to the downrefulation of matrix metalloproteinase-9 (MMP-9).[697,699]

HDACi constitutes another prominent class of bioactive axial payloads incorporated into dual-action Pt(IV) prodrugs, with examples including valproic acid (VPA),[701−705] octanoic acid (OA),[702,706] 2-(2-propynyl)octanoic acid (POA),[707−709] 4-phenylbutyric acid (PhB),[710−712] and SAHA.[713] Similar to Pt(IV)-NSAIDs, the increased lipophilicity of these Pt(IV)-HDACi conjugates translates to enhanced antiproliferative efficacy compared to the parent compounds across various cancer cell lines, including CRC models (i.e., HCT116, HCT-15, HT-29, SW480, LoVo).[706,707,709,710,712] Intriguingly, Osell and Brabec found that their Pt(IV) octanoato compound (**3**) can induce global DNA methylation independent of the enzymatic activity of HDAC on CRC model.[706] This discovery is similar to what have been found on another Pt(IV)-VPA complex on human ovarian cancer cells.[704] Furthermore, the therapeutic potential of these Pt(IV)-HDACi complexes extends to overcoming drug resistance, as exemplified by Pt(IV)-POA (**4** and **5**) conjugates that effectively circumvented **OXP** resistance in **OXP**-resistant LoVo-**OXP** CRC cell line.[709] Contrastingly, some other types of Pt(IV)-HDACi complexes with PhB as bioactive axial payload have successfully demonstrated significant HDAC enzymatic activity inhibition.

The development of resistance to Pt-based chemotherapeutics is frequently mediated by cancer-associated metabolic enzymes, such as glutathione S-transferases (GSTs),[682,714−716] pyruvate dehydrogenase kinase (PDK),[717,718] and Carbonic anhydrase IX (CAIX),[719] among others. These enzymes employ distinct resistance mechanisms such as GST-mediated drug inactivation and efflux *via* glutathione conjugation, PDK-mediated metabolic reprogramming toward glycolysis influencing cellular energy production and stress responses, and CAIX-mediated modulation of the TME to promote cancer cell survival and adaptation. Therefore, incorporating inhibitors of these metabolic enzymes as bioactive axial payloads within Pt(IV) prodrugs presents a rational strategy to enhance therapeutic efficacy and potentially circumvent Pt-drug resistance. For example, two Pt(IV)-GSTi complexes have successfully demonstrated improved potency against CRC cell lines (i.e., HT-29 and HCT116) in antiproliferative assays using ethacrynic acid (**6**) and 6-(7-nitro-2,1,3-benzoxadiazol-4-ylthio)hexanol (NBDHEX) (**7**) as the axial payload.[682,714] Notably, **6** was observed to exhibit a faster onset of cytotoxic activity compared to its parent Pt complex.[714]

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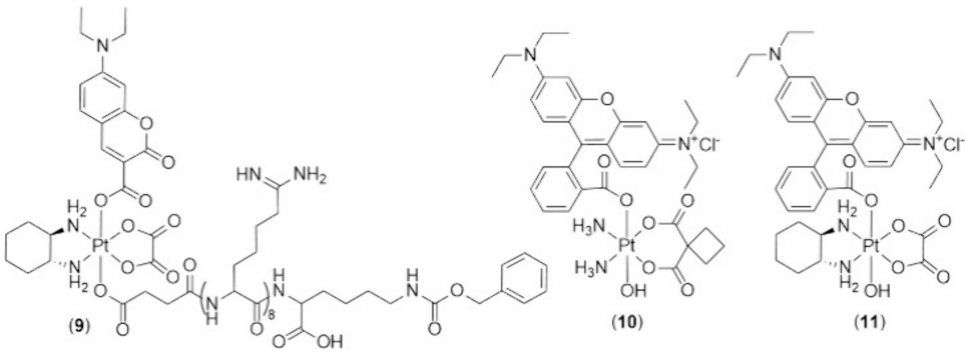

Figure 14. Photoactivatable Pt(IV) complexes that have shown activity against CRC models.

In recent times, PROTACs has emerged as a new class of anticancer agent through targeted protein degradation (TPD) rather than conventional target inhibition. PROTACs offer advantages over traditional small molecule inhibitors including the targeting of "undruggable" molecules and the ability to overcome resistance caused by target protein overexpression or mutations. Very recently, PROTACs for two protein targets (i.e., BRD4 and PARP-1) have been attached onto the Pt(IV) scaffold in order to improve the potency of Pt(IV) prodrugs and overcome Pt-based chemoresistance.[735,736] In particular, **CW-2** (**8**) has demonstrated about 4-fold increase in antiproliferative efficacy when tested in HCT116 CRC cell line.[735] Furthermoer, **CW-2** conjugated with olaparib PROTAC as PARP-1 degrader has also managed to resensitized **CDP**-resistant cell line to Pt-based therapy. This is likely attributed to the degradation of PARP-1 that plays a crucial role in cellular DNA repairs.

The octahedral geometry of the Pt(IV) prodrug scaffold features two modifiable axial ligands that open up possibilities for multiaction prodrugs designs. A common approach involves the conjugation of two or more bioactive ligands with distinct mechanisms of action, in order to achieve enhanced therapeutic effects. Combinations incorporating previously discussed classes such as NSAIDs, HDACi, and metabolic enzyme inhibitors have been reported and shown improved anticancer efficacy.[737,743,744] Alternatively, these axial sites can be exploited for targeted delivery, where one position is occupied by a therapeutic payload while the other incorporates a tumor-targeting moiety, such as biotin, intended to promote selective accumulation within cancer cells.[745,746] Furthermore, the versatility of the axial sites has been leveraged in more complex designs, including the development of bimetallic Pt(IV) complexes aimed at achieving superior anticancer activity or enabling stimuli-responsive prodrug activation.[747,748]

7.1.3. Photoactivatable Pt(IV) Complexes for CRC. Enhancing the clinical effectiveness of Pt(IV) chemotherapeutic prodrugs can be achieved by controlled activation using external physical stimuli. Light, as a stimulus, stands out due to its convenience and noninvasive nature, offering a considerable edge over other forms of stimuli for prodrug activation. Furthermore, the precise spatiotemporal control offered by photoactivation further allows for site-directed activation of Pt(IV) prodrugs at the tumor site while maintaining high dark stability. This targeted approach not only enhances therapeutic efficacy but also minimizes adverse side effects and systemic toxicities to healthy tissues. Advancement in the field of photoactivated prodrugs has also been propelled by developments in light delivery technologies, including laser- or light emitting diodes (LEDs)-based planer, injectable, and optical-fiber devices.[749] These technologies can cater for tumors located superficially or within internal organs, such as the colon, head, neck, esophagus, lung, bladder, and cervix.

Many photoactivatable Pt(IV) complexes have been synthesized through modifications in their axial, leaving, and nonleaving ligands, a topic that has been extensively reviewed in many literatures.[116,750,751] Here, our review is focused on photoactivatable Pt(IV) complexes that have demonstrated effectiveness in CRC models (Figure 14). For instance, **Coumaplatin** (**9**), that is axially conjugated to a coumarin derivative and incorporates **OXP** as the Pt(II) scaffold, has shown remarkable dark stability and significant photocytotoxicity *in vitro* when compared to **OXP**.[752] This is particularly evident in CRC models such as HCT116 $p53^{+/+}$ and HT-29, where the half-maximal inhibitory concentration (IC_{50}) values are 32- and 14-fold lower, respectively, than those of **OXP**. Additionally, **Coumaplatin** displayed the ability to overcome Pt drug resistance in HCT116 $p53^{-/-}$, with an IC_{50} value that is 96 times lower than that of **OXP**. When activated with blue light at 450 nm, **Coumaplatin**, which accumulates in the nucleolus, releases **OXP**. **OXP** released in the nucleolus induces cellular senescence and initiates ICD through a p53-independent mechanism involving E2F1, in addition to causing p21-mediated cell cycle arrest and apoptosis.

Another example of photoactivatable Pt(IV) drugs was developed by conjugating rhodamine B to the axial position on **CBP** and **OXP**-derived Pt(IV) precursors (**10** and **11**). The design was based on the hypothesis that the oxidation potential of photoexcited rhodamine B is sufficient to reduce the majority of traditional Pt(IV) prodrugs.[753−756] Subsequent experiments confirmed that rhodamine B conjugation can significantly enhance the activation of both **CBP**- and **OXP**-based **Rhodaplatins**. This is evidenced by the marked increase in their photocytotoxicity in HCT116 CRC model under low-dose visible light irradiation (400−760 nm, 4 $mW{\cdot}cm^{-2}$), as compared to **CBP** and **OXP**. Notably, the **OXP**-based variant of **Rhodaplatins** demonstrated selective mitochondrial accumulation, which in turn induced mtDNA damage and subsequently cell apoptosis.

7.1.4. Incorporation of Targeting Ligands. The efficacy of Pt drugs in the treatment of CRC depends on the level of accumulation at the tumor site. The biodistribution of Pt drugs can be altered to favor tumor accumulation by taking advantage of the structural differences between normal physiological tissues and tumors. By directing the Pt drugs to their intended site of action, it is possible to reduce off-target

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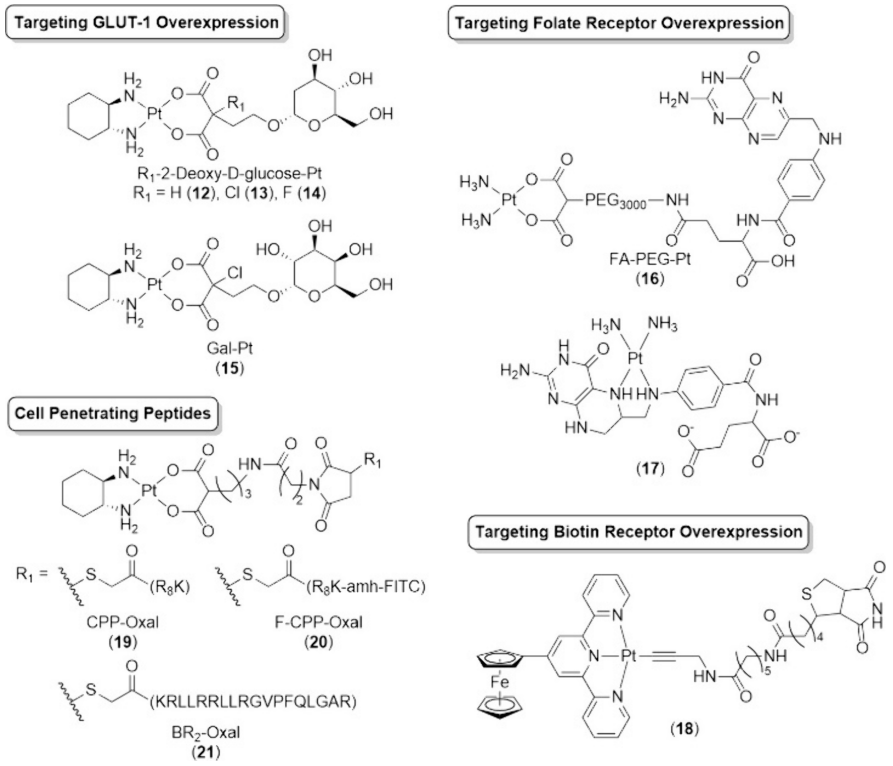

Figure 15. Pt(II)-based anticancer complexes with direct incorporation of targeting ligands.

accumulation and, consequently, their associated side effects. Moreover, the genetic differences between healthy cells and cancer cells can also be exploited to increase the uptake of Pt drugs by CRC cells.

There are several strategies to enhance the efficacy of Pt drugs: (1) incorporating targeting ligands on the chemical structure of Pt(II) and/or Pt(IV) compounds, (2) loading of Pt drugs into nanoparticle-based formulations (including surface engineering of these nanoparticles), and (3) administering Pt drugs through alternative routes.

The incorporation of tumor targeting ligands into anticancer Pt complexes offers a promising strategy for enhancing selectivity toward cancer cells while minimizing toxicity to healthy tissue. In the case of square-planar Pt(II) complexes, which typically feature two nonleaving and two leaving ligands, tumor-targeting functionality can be introduced through chemical modification of the leaving groups. On the other hand, the octahedral geometry of Pt(IV) complexes presents additional opportunities for functionalization; specifically, the axial positions offer expanded chemical space for the conjugation of tumor-targeting moieties. The targeting properties arise from the differences between normal healthy cells and cancerous cells. Some of these differences include the overexpression of membrane proteins. For instance, there are reports that glucose membrane transporters, such as GLUT1, is overexpressed in CRC.[757] The overexpression of glucose membrane transporters can be attributed to increased glycolysis of cancer cells. As such, Pt(II) drugs can be designed to incorporate ligands of these overexpressed proteins to improve the selectivity toward the tumor. Some of the substituents include sugars to target glucose membrane transporters (**12**−**15**). Specifically, **12**−**15** have shown significant improvement in *in vitro* antiproliferative activity against HT-29 CRC cells (ca., 4- to 6-fold lower IC_{50}).[758,759] **15** shows further efficacy in *in vivo* HT-29 CRC xenograft with superior therapeutic index and growth inhibitory activity.[759] Figure 15 shows a list of certain Pt(II) compounds that were designed to improve selectivity toward the tumor. While some of the examples such as folate receptors targeting (**16** and **17**)[760,761] and biotin targeting (**18**)[762] were not directly tested on CRC, it is expected that similar targeting mechanisms could make these tumor-targeting drugs accumulate in CRC tumors.

Among these examples, it is interesting to note that the conjugation of folate ligands did not give rise to an increase in anticancer efficacy. Despite the introduction of folate ligands to target the folate receptors on the cancer cells, the cytotoxicity of the folate-targeted Pt drug **16** was lower than **CBP** and the nontargeting Pt drug.[760] To explain this phenomenon, Aronov et al. quantified the cellular Pt content, and the formation of Pt-DNA adducts *in vitro*. Despite a higher accumulation of Pt, there was less formation of Pt-DNA adducts. It was then hypothesized that the folate receptor-mediated endocytosis may inhibit the release of the drug to the cytosol and hence affect the overall efficacy of the drug. Despite the efforts to modify the structure of Pt drugs chemically to target the tumor cells, it is also important to consider the biological implications (in terms of drug uptake mechanism and intracellular release of the drug). Moreover, the pharmacokinetics of the modified drugs may also be altered depending on the hydrophobicity of the new chemical structure, which may affect the overall efficacy of the Pt drug. This may explain the difficulty encountered when designing next generation Pt-based drugs with higher efficacy and lower toxicity as well as the reasons why, despite the development of novel Pt-based compounds with tumor-targeting features, none of them has been translated into the clinics yet.

Moreover, peptides can also be introduced to increase the efficacy of Pt(II) compounds. For instance, Singh et al.

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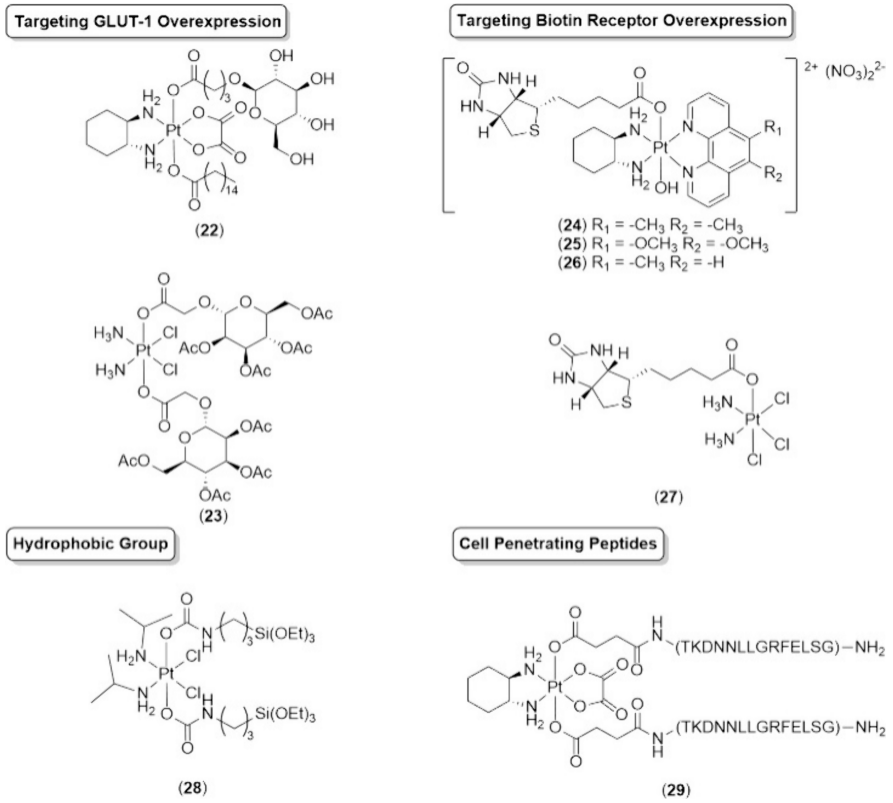

Figure 16. Pt(IV)-based anticancer complexes with direct incorporation of targeting ligands.

synthesized **OXP** conjugated with a cell-penetrating peptide (CPP) (peptide sequence: RRRRRRRR) (**19** and **20**).[763] The addition of CPP drastically increased the accumulation of Pt *in vitro* and improved the efficacy of treatment both *in vitro* and *in vivo*. Moreover, Sepay et al. also showed that **OXP** conjugated with a cell-penetrating, cancer-specific peptide BR2 (peptide sequence: RAGLQFPVGRLLRRLLR) (**21**) could improve selectivity toward cancer cells over normal healthy cells.[764] As a result of this selectivity, there was an increased accumulation in the tumor, leading to a greater tumor suppression *in vivo*.

Targeting ligands can be incorporated to direct the compounds to their intended site of action. Similar to Pt(II) compounds, these ligands could target the overexpression of membrane proteins on the cancer cells (Figures 16 and 17). For instance, sugars, such as glucose, galactose, or mannose, can be conjugated onto the Pt drugs. Interestingly, Pt(IV) prodrugs conjugated with the unacetylated sugars can enhance cellular uptake by targeting GLUT1 transporters on cancer cell lines, unlike Pt(IV) drugs that are conjugated with acetylated sugars (**22** and **23**).[680,765] The introduction of a glucoside group (targeting the overexpression of GLUT-1 on tumor cells) and a hexadecanoic chain (that could bind to human serum albumin) (**22**) reduced the toxicity while maintaining the efficacy of the chemotherapeutic treatment *in vivo*.[680] It should be noted that GLUT1-targeting Pt(II) complexes are not specific for CRC. They are designed to target any malignancy with high GLUT1 expression, which includes but is not limited to CRC. Their use in human patients is experimental and not limited to a particular cancer type. Besides the addition of a sugar molecule, biotin was also conjugated onto the Pt(IV) structure (**24**−**27**) to target the biotin receptors on tumor cells. Similar to the Pt(II) counterparts, the incorporation of biotin increases the

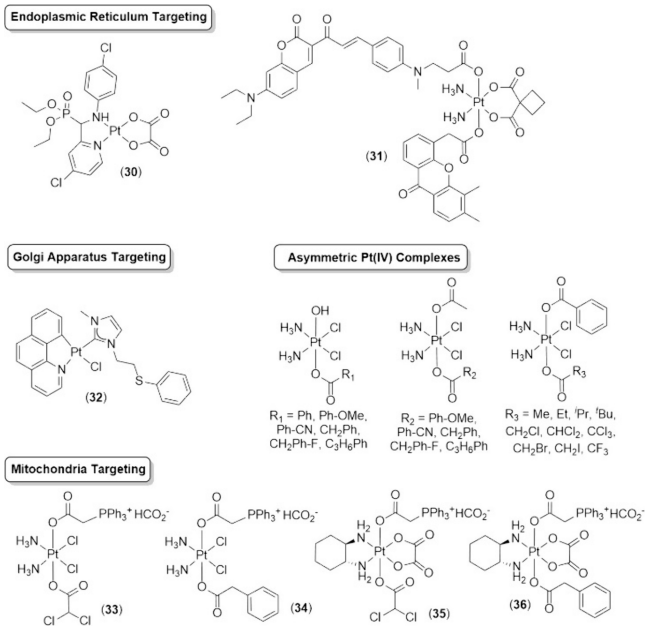

Figure 17. Pt(IV) complexes that possess subcellular-targeting properties and asymmetric Pt(IV) complexes for SAR studies.

cytotoxicity against tumor cells with an overexpression of biotin receptors (**27**).[766,767] A recent study involved the introduction of bis-organosilane groups to improve selectivity toward cancer cells and lower toxicity.[768] With the addition of tri(ethylene glycol) silane groups, the resultant complex is more hydrophobic, which facilitates the transport across biological membranes. The cytotoxicity of Pt(IV)-biSi-2 (**28**) was higher toward HCT116 CRC cells compared to HIEC6

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nontumorigenic intestinal cells. Pt(IV)-biSi-2 was also effective in inhibiting HCT116 xenograft tumor growth while reducing renal and hepatic toxicity, which are commonly associated with **CDP** treatment.

Similarly, peptides can also be introduced on the axial positions to improve the accumulation and uptake of these drugs. It was discovered that tumor cells, including CRC cells, have a selective expression of HSP70. These HSP70-positive cancer cells can be targeted with a 14-mer tumor penetrating peptide (TKDNNLLGRFELSG). McKeon et al. conjugated this 14-mer peptide onto a Pt(IV) complex (**29**), which showed a higher cytotoxicity toward HT-29 CRC cells with a high membrane expression of HSP70.[769]

The capacity to include additional ligands also provides the opportunity for multiple functionalized Pt(IV) drugs. Other chemotherapeutics, such as gemcitabine, paclitaxel and estramustine, can be conjugated onto the axial positions of Pt(IV) structures.[737] The conjugated complex showed a higher tumor growth inhibition as compared to a coadministration of the individual drugs, implying some synergistic effects. Similarly, niflumic acid, a NSAID, conjugated onto **CDP** and **OXP** Pt(IV) scaffold, can increase cell apoptosis, reduce cell migration and have the potential to work on metastases of HCT116 CRC cells.[770]

Besides improving the selectivity toward tumor cells, ligands can be introduced to target other intracellular components that could further inhibit cell proliferation. These Pt(IV) prodrugs have additional mechanism of actions and could overcome Pt resistance. As various organelle-targeting Pt complexes have been extensively discussed in previous reviews,[771−776] we will focus on new Pt complexes that have been reported recently to localize in the ER and Golgi apparatus. For instance, a Pt(II) complex containing an aminophosphonate ester ligand was found to selectively enrich in the ER, likely due to the high affinity of this type of ligand toward the high Ca^{2+} levels in the ER (**30**).[777,778]

Similar to **Pt-NHC** and **PlatinER**, this complex could effectively trigger ER stress and display ICD DAMPs, likely due to its mitochondria targeting properties. The antitumor activity and vaccination effect of Pt(II)-aminophosphonate were validated *in vivo* using an immunocompetent mouse bearing MB49 bladder cancer model, which also exhibited increased $CD3^+CD8^+$ T-cells infiltration compared to **OXP** treatment. This example demonstrated that the rational design of Pt(II) complex ligand is another promising way to achieve desired subcellular targeting properties. More recently, a Pt(IV) complex that can undergo oxygen-independent activation using near-infrared (NIR) irradiation has been developed and shown to selectively accumulate in the ER (**31**).[779]

The ER targeting capability of this complex synergises with its ability to act as a photooxidant, to induce severe oxidative stress and disrupt intracellular pH balance. The generation of a large amount of ROS causes the rapid oxidation of intracellular biomolecules, which subsequently triggers ER stress and initiates ICD. This has been evidenced by the detection of ICD DAMPs, and the enhancement of $CD4^+$ and $CD8^+$ T-cell infiltration in a 4T1 mouse xenograft model.[779]

A novel Pt(II) compound that selectively targets Golgi apparatus has also been recently developed and exhibits a potent anticancer activity by inducing Golgi stress and modulating the balance between autophagy and apoptosis (**32**).[780] This monochlorinated Pt(II) compound incorporated monoaza phenanthrene and *N*-heterocyclic carbenes (NHC) as ligands. Interestingly, the complex showed remarkable anticancer activity when encapsulated in lipid-based nanovesicles called liposomes. It completely eradicated LLC tumors in immunocompetent mice, but only inhibited A549 tumors growth in immunocompromised mice. This suggests that the complex could stimulate the host immune response and demonstrates the potential of modulating Golgi-related signaling pathways for cancer treatment, offering a novel design strategy for the development of new Pt-based drugs by working synergistically with immunotherapies.

Previously, some of us reported the development of a library of mitochondria-targeting Pt(IV) compounds for human ovarian cancer cells (A2780).[676] These Pt(IV) compounds, based on either a **CDP** or **OXP** scaffold, were modified with the inclusion of a chemosensitizer which are PhB or dichloroacetic acid (DCA)[676] and a mitochondria-targeting triphenylphosphonium (TPP) ligand (**33**−**36**). These modifications enhanced the sensitivity of cancer cells toward the chemotherapeutics and increased Pt-induced DNA-damage to mtDNA. Although these Pt(IV) drugs demonstrated similar anticancer efficacy as the parent Pt(II) drugs *in vitro* (**CDP** and **OXP**, respectively), they were more efficient in inhibiting tumor development *in vivo* than **CDP** by abrogating mitochondrial function.[676] Consequently, by enhancing mtDNA damage, these drugs could be effective in suppressing tumorigenesis in a CRC mice model, where the fidelity of mtDNA (decreased mutagenesis) is enhanced (due to the reduction of ROS in cancer cells) and is better correlated with disease progression.[781]

7.2. Activation of CRC TME Using Immunochemotherapeutic Pt Complexes

Pt complexes are versatile compounds that can exhibit both cytotoxic and immunomodulatory effects in cancer therapy.[782] Although classical cytotoxic Pt(II)-based anticancer drug such as **CDP** or **CBP** were considered to impair the immune system due to their immuno- and myelosuppressive nature that negatively affect the numbers of lymphoid and myeloid cells,[783−785] growing evidence has led to the belief that anticancer Pt complexes can also exploit the host immunity to enhance their antitumor efficacy. Some of the immunomodulatory effects of **CDP** that have been discovered[786−788] include (1) decreased frequency of MDSCs;[789] (2) upregulation of immune stimulatory molecules (e.g., MHC-I);[790] (3) modulation of STAT signaling;[791,792] and (4) regulation of tumor-specific antigen (e.g., PD-L1).[793,794] Besides immunomodulatory Pt(II) complexes, several advantages offered by the Pt(IV) platform including better biological inertness, lower side effects, reduced systemic toxicities, and greater utilization of chemical spaces, could prove to be a silver bullet in tackling issues with conventional immunotherapy of CRC. Other than being useful for tuning chemical properties, the extra chemical spaces in the Pt(IV) complexes can be used to integrate bioactivate molecules that can influence the antitumor immunity or alter the immunosuppressive TME. As a result, new Pt(IV) complexes with different modes of action that target immunologically "cold" tumors have been developed. Therefore, we envision that Pt-based chemo-immunotherapeutics could be the novel way forward for improving the treatment of immunologically "cold" tumors such as pMMR/MSS CRC.

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7.2.1. OXP- and CDP-Based Pt(IV) Complexes. OXP can paradoxically promote immune escape by upregulating IDO expression,[795] an enzyme that causes local immune suppression *via* kynurenine production.[796] Upregulation of IDO also resulted in tryptophan depletion to trigger amino-acid sensing signal-transduction pathways such as GCN2 kinase and mTOR, which are responsible for inhibiting proliferation and differentiation of cytotoxic T cells (e.g., $CD8^+$ and $CD4^+$) and activating Treg.[797]

Recently, an **OXP**-based triplet prodrug (Figure 18) (**37**)[798] was designed to overcome immunosuppression induced by

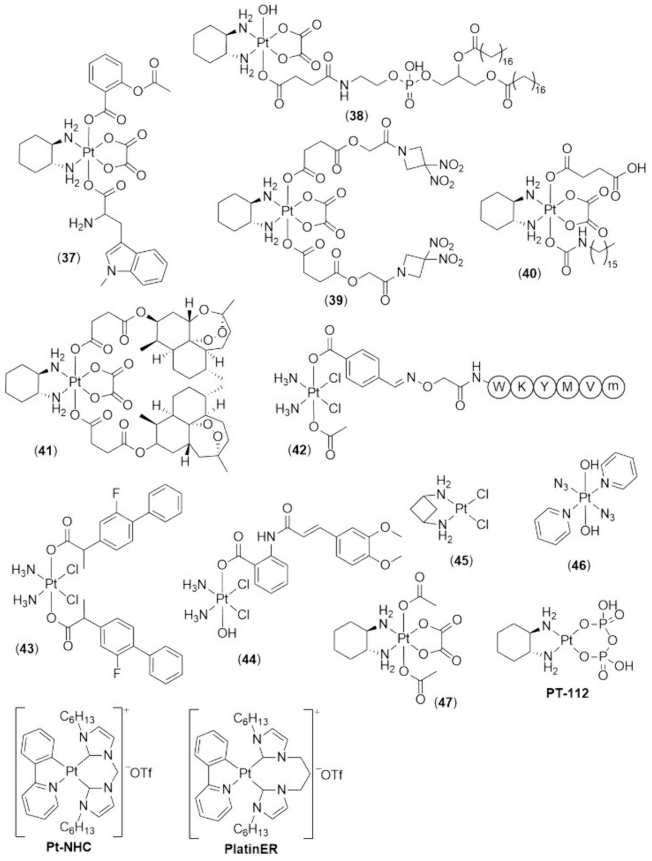

Figure 18. Molecular structures of Pt complexes tested for immunotherapeutic and chemoradiotherapeutic efficacies.

kynurenine biosynthesis through incorporating aspirin (i.e., COX-2 inhibitor)[799] and 1-methyl-tryptophan (i.e., IDO inhibitor). While there are already several other publications with IDO-Pt(IV) complexes in literature, compound **37** enhanced the anti-PD-1 immunotherapy in the CT26 mouse model by increasing the infiltration and activation of $CD8^+$ T cells, NK cells, and effector memory $CD8^+$ T cells, as well as the production of IFN-γ and TNF. It also reduced the number of Treg cells in the tumor. These effects were not observed when **OXP** and inhibitors were treated simultaneously. Similar approaches using dual-functional liposomes with **OXP** (IV)-conjugated phospholipid (**38**) and IDO inhibitor (i.e., NLG919)[800] or metformin[801] also achieved effective ICD induction and reversal of immunosuppressive TME in CT26 mouse models such as enhanced DC maturation, increased intratumoral $CD8^+$ T-cells infiltration, decreased Treg, and secretion of TNF-α and IFN-γ. **Met-OXP(IV)-liposome** was also found to stimulate M1-like macrophage polarization and synergise with anti-PD-1 immune checkpoint blockade therapy.[801]

Another approach that has shown to be effective in enhancing the phagocytic clearance of **OXP**-treated cancer cells is compound **39**, which combines RRx-001, a nitric oxide donor, with **OXP**.[802] RRx-001 modulates TAM polarization from immunosuppressive M2 to immunoinflammatory M1,[803] and reduces the expression of CD47, a "do not eat me" signal, on cancer cells.[804] Compound **39** significantly reduced CD47 levels and increased the ratio of CRT/CD47 on the surface of CT26 cells *in vitro* and *in vivo*. Moreover, compound **39** effectively reduced the hypoxic TME mediated by HIF-1α, increased the ratio of M1/M2 macrophages, enhanced the infiltration of $CD3^+$ and $CD8^+$ T cells, decreased Treg cells, and increased the production of immunostimulatory cytokines such as IL-12, TNF-α, and IFN-γ, thereby reversing the immunosuppressive hypoxic TME of CT26 *in vivo*.

A novel nanomedicine approach, compound **40**, was developed to overcome the immunosuppressive TME that limits the effectiveness of ICI therapy.[805] Compound **40** is composed of polymeric all-*trans*-retinoic acid (ATRA) and a Pt(IV) prodrug of **OXP**. The design rationale is to combine **OXP** with the immune activation by ATRA, which has been previously reported to stimulate inflammatory TME by promoting $CD8^+$ T Cell proliferation and inhibiting MDSCs.[245,806,807] *In vitro*, compound **40** delivered **OXP** to MC38 cells and induced all ICD hallmarks. *In vivo*, treatment of compound **40** in MC38 mouse model significantly reduced the immunosuppressive MDSCs and increased the pro-inflammatory M1 macrophages and $CD8^+$ T cells. It has been found that the antitumor effect of compound **40** was mainly mediated by $CD8^+$ T cells rather than direct cytotoxicity and was enhanced by cotreatment with anti-PD-L1 immune checkpoint blockade. Refer to section 7.3.1 for other examples of Pt drug encapsulation in delivery systems.

An **OXP**-based prodrug that combines **OXP** with a triggering receptor expressed on myeloid cells 2 (TREM2) inhibitor (i.e., artesunate) to target and inhibit TREM2 expression on TAMs was reported (**41**). This concept of exploting therapeutic activation of pro-inflammatory macrophages to enhance antitumor immunity is similar to a formyl peptide receptors (FPRs) binding ligand conjugated **CDP**-based prodrug **Pt(IV)-WKYMVm**[501] (**42**) that has been previously developed by Ang and coworkers.[808]

Compound **41** demonstrated that it can effectively inhibit TREM2 expression on macrophages both *in vitro* and *in vivo* for CRC.[834] TAMs in human tumors express high levels of TREM2, which triggers immune reprogramming that favors tumor survival and reduces antitumor immunity. Patients with high TREM2 expression have worse outcomes and survival rates. Even though the reduction efficiency of compound **41** under chemical reductive environment is low, it can still cause significant DNA damage to HCT116 cells. Compound **41** also reshapes the immunosuppressive TME in MC38 *in vivo* mouse model by inducing THP-1 macrophage M1 polarization, encouraging DCs maturations, and enhancing immune infiltration of $CD8^+$ T cells and NK cells.

In addition to IDO upregulation, **OXP** and **CDP** treatments were also found to upregulate PD-L1 and PD-L2 expression in various cancer and myeloid cells.[200,203,356,358,835,836] High PD-L1 levels can impair the T-cells cytotoxicity and antitumor immunity of tumor cells and DCs,[835] but also sensitize tumor cells to ICI therapies. As a result, PD-L1 is currently a FDA-

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approved prognostic marker for ICI therapies.[335] Flurbiprofen, a COX inhibitor and NSAID, can bind to PD-L1 and reverse immunosuppressive TME to enhance cancer treatment efficacy. A **CDP**-based Pt(IV) prodrug (**43**) with flurbiprofen on both axial positions was developed and found to inhibit tumor growth and spread by suppressing inflammation.[837] Other than activating the mitochondrial apoptosis pathway, this complex can also stimulate T-cell immunity by increasing $CD8^+$ T cell infiltration and reducing PD-L1 expression in CT26 tumors *in vivo*.

Tranilast, a drug approved clinically for inflammatory disorders and allergies, has been reported for its efficacy in preventing human breast cancer metastasis and cytostatic activity in various cancers. Although unclear, the antiproliferative mechanism of Tranilast is suspected to be involving inflammatory pathways such as TGF-β pathway, MMP-2/9 production, or activation of NF-kB, PKC and MAPK. Compound **44** is a Pt(IV) prodrug derived from **CDP** and Tranilast.[838] Compound **44** exhibited enhanced cytotoxicity against colon and lung cancer cells *in vitro* compared to **CDP**, but reduced toxicity against immune cells. Moreover, compound **44** was evaluated *ex vivo* using tumor explants from CRC patients and demonstrated strong induction of intratumoral cytotoxicity and increased the infiltration of $CD45^+$ immune cells.

7.2.2. Immunogenic Cell Death (ICD) Inducers. **PT-112** (Imifoplatin) is a novel Pt(II) anticancer agent that is structurally analogous to **OXP**, but with the oxalate ligand replaced with pyrophosphate.[839] Despite its lower intracellular uptake,[839,840] **PT-112** exhibits higher potency against **CDP**- and **CBP**-resistant cell lines due to its unique mode of action.[839,841−843] Notably, **PT-112** efficiently induces ICD in HCT116 human colon cancer cells *in vitro* by emitting ICD-associated DAMPs.[872] The ability for **PT-112** to act as an ICD inducer was further demonstrated in CT26 and MC38 *in vivo*, which resulted in enhanced immune infiltrations and synergism with anti-PD-1 blockade immunotherapy.[873,874] The antiproliferative and immunostimulatory effects of **PT-112** is likely to be the result of nucleolar stress and ribosomal biogenesis (RiBi) interruption, which led to nucleolar protein relocalization and increase of free ribosomal proteins, respectively.[875] Additionally, these effects can also cause ER stress and pro-apoptotic protein transportation to the mitochondria. **PT-112** has been tested in clinical trials (i.e., NCT02266745 and NCT03409458) and has shown remarkable and durable responses in patients with advanced lung, liver, and prostate cancers who did not respond to other standard treatments.[876−878] This may be due to the fact that the pyrophosphate ligand confers greater biochemical stability, resulting in enhanced pharmacokinetic and pharmacodynamic properties, as well as accumulation in the lung, liver, and bones.[872,876,877,879] This could also explain the reduced side effects of **PT-112** when administered to patients. Furthermore, **PT-112** has shown promising results in combination with avelumab, an ICI that targets PD-L1, in clinical trials.[876−878]

The ability of a series of Pt-based anticancer drugs, both existing and emerging, to trigger ICD was screened based on CT26 *in vitro* assays performance such as J774A.1 macrophage phagocytosis efficacy, ICD-related DAMPs expression, and ER ROS production.[209] Among the library, **Pt-NHC**, an ER targeting compound that was originally designed to cause ER stress,[880] emerged as the most potent ICD inducer, as it significantly increased the uptake of tumor cells by cocultured J774 macrophages compared to other Pt complexes. **Pt-NHC** also exhibited all three biological markers of ICD induction (e.g., ecto-CRT exposure, extracellular HMGB1 and ATP release). It was then discovered that ER ROS, rather than cytotoxicity, was correlated with phagocytosis ability. Furthermore, phagocytosis activity could be modulated by coating recombinant CRT on the surface or blocking it with a CRT blocking peptide.

After successfully identifying **Pt-NHC** as a potent type II ICD inducer, structural optimization of **Pt-NHC** led to the discovery of **PlatinER** with superior ICD properties.[881] By using similar *in vitro* testing strategies in CT26 cells, **PlatinER** displayed comparable performance with equipotent **Pt-NHC** in terms of phagocytotic ability, extracellular HMGB1 release and ecto-CRT exposure. Similar to **Pt-NHC**, **PlatinER** triggered partial ER stress response through the PERK/eIF2a pathway. However, **PlatinER** additionally elicited ecto-HSP90 expression as an additional "eat-me" signal, which was not observed from Pt-NHC.

Another Pt(IV) complex that has been found to be able to induce ICD in CRC is the photoactivable *trans,trans,trans*-$[Pt(N_3)_2(OH)_2(py)_2]$ (**46**).[208] Other than its DNA binding ability,[882,883] compound **46** can release products such as azidyl radicals, hydroxyl radicals, nitrene, and singlet oxygen that can trigger other biochemical pathways.[884,885] Furthermore, ROS and reactive nitrogen species (RNS) produced during the photoactivation of compound **46** could also contribute to the ICD induction. While the biological ICD hallmarks were confirmed on human ovarian A2780 cell line, the irradiation of 420 nm blue light on *trans,trans,trans*-$[Pt(N_3)_2(OH)_2(py)_2]$ treated CT26 cells significantly induced phagocytosis by cocultured J774.A1 macrophages.

7.3. Drug Delivery Strategies for CRC

7.3.1. Encapsulation into Drug Delivery Systems. Conventional development of chemotherapeutics, including Pt drugs, is challenged by the lack of replication of drug efficacy between *in vitro* and *in vivo* models.[212,219,655,656] For instance, 56MESS, a Pt(II) scaffold of compound **24**, was significantly more potent than **CDP** in inhibiting cellular viability *in vitro* but demonstrated no significant antitumoral activity compared to **CDP** *in vivo*.[657] Similarly, another Pt(II) complex demonstrated nearly 8-fold improved anticancer potency compared to **CDP** *in vitro* but observed no significant improvement of the antitumor efficacy *in vivo*.[658] An attributing reason to this discrepancy between *in vitro* and *in vivo* efficacy is the limited amount of active that reaches the tumor site. In order to address this limitation, alternative strategies are required to enhance the availability of the drug at the diseased area and thus the *in vivo* efficacy of Pt(IV) complexes. Nanoparticles have been used clinically for the treatment of various forms of cancers. By virtue of their dimensions (i.e., 50−200 nm), intravenously injected nanoparticles are able to accumulate at the tumor tissue passively over time through the enhanced permeability and retention (EPR) effect (Figure 19).[886] This phenomenon arises from the rapid angiogenesis of tumor tissue, creating leaky vasculature through which nanoparticles are able to extravasate from the circulatory system and reach the tumor tissue. The poor lymphatic drainage system at the tumor also reduces the clearance of the nanoparticles, allowing them to accumulate over time.[887] Moreover, nanoparticles can impart beneficial attributes to otherwise unfavorable drugs such as increased

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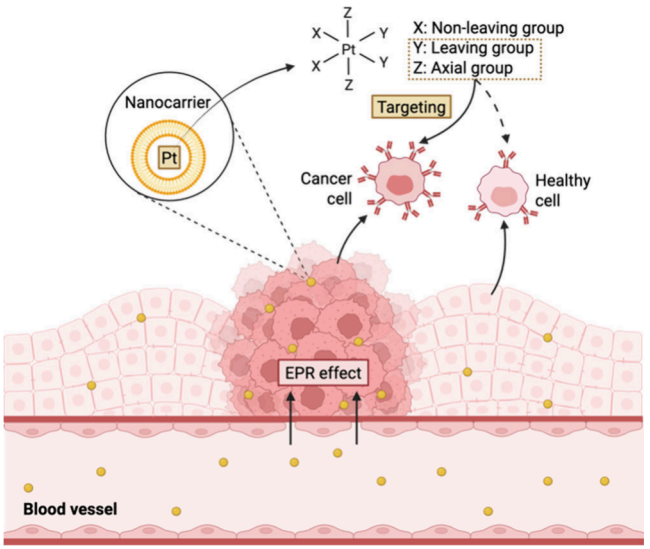

Figure 19. Enhancing Pt drug efficacy through enhanced permeability and retention effect and drug targeting properties toward cancerous cells. Figure created with BioRender.com.

aqueous solubility, longer circulation time, increased bioavailability,[888,889] and codelivery of several bioactive agents for combination therapy.[890]

Several nanomedicines have been successfully developed and received FDA approval for treating various cancers (Table 16). **Doxil** was one of the first successful nanoparticle formulations that is used for the treatment of solid tumors from ovarian cancer, Kaposi's sarcoma, and myeloma.[891] **Doxil** is able to mitigate the cardiotoxicity of doxorubicin (DOX) through distinctively increasing the relative accumulation of DOX at the tumor compared to the heart. Likewise, other nanoparticle formulations approved by the FDA significantly reduce the toxicity as well as improve the plasma availability and circulation time of the chemotherapeutic drugs (Table 16), resulting in improved overall survival and quality of life for patients.

Interestingly, nanoformulation that includes Pt drugs as the chemotherapeutic agents have yet to be approved by the FDA. However, several **CDP**-encapsulated nanoparticles, such as **LiPlaCis** and **Nanoplatin**, are undergoing clinical trials for various solid tumors (Table 17).[830−832] **LiPlaCis**, a novel liposome for **CDP**, was designed to be degraded by secretory phospholipase A2 that is relatively abundant in tumor tissue.[827] The selective and targeted release of **CDP** in tumor tissue enabled by this formulation was designed to significantly reduce the associated systemic toxicity from off-target Pt accumulation.

Besides those in clinical trials, further developments are being made for the loading and delivery of Pt drugs in other forms of nanoparticles (Table 18). These include lipid-based nanoparticles (e.g., nanostructured lipid carriers), polymer-based nanoparticles (e.g., polymersomes), carbon-based nanoparticles (e.g., graphene-based nanoparticles), and gold-based nanoparticles (Figure 20). For instance, Tummala et al. delivered **OXP** using hybrid lipid-polymer nanoparticles conjugated with anti-TRAIL antibodies. The nanoparticle formulation demonstrates strong tumor growth inhibition as compared to free **OXP**. Moreover, the anti-TRAIL antibodies on the surface of the nanoparticles result in a synergistic antiapoptotic effect by both targeting the HT-29 CRC cells and activating the death receptors.[867]

Besides solely loading Pt-based drugs, multiple drugs can be coloaded into nanoformulations for synergistic effects. For instance, Li et al. coloaded **CBP** and paclitaxel into phosphonated calixarenes, which are a macrocycles or cyclic oligomers.[871] Interestingly, Guo et al. formulated a nanoprecipitate of **OXP** and folinic acid into a PEGylated lipid nanoparticle.[855] The lipid nanoparticles were also decorated with aminoethyl anisamide to target the CRC cells. The targeted nanoformulation with 5-FU was able to induce stronger synergistic chemo-immunotherapy without significant toxicity as compared to the free drugs mixture.

Moreover, the anticancer mechanism is not limited to the promotion of cell death of cancer cells. These loaded Pt-based nanoformulation can also suppress the growth of blood vessels within the solid tumor. Abu-Lila et al. utilized the PEGylated cationic liposomes loaded with **OXP** to suppress angiogenesis in dorsal air sac model.[851] Additionally, the use of metal nanoparticles, such as gold-based nanoparticles, provides the potential for photothermal therapy. Lee et al. utilized gold nanoshells loaded with **Pt(DACH)Cl$_2$** for the treatment of HT-29 xenograft tumor.[854] The tumors were irradiated with 1W/cm^2 NIR (808 nm) for 10 min after the IV administration of the loaded gold nanoshells. The combination of chemotherapy and photothermal therapy suppressed the growth of tumor over a period of 30 days. Gold nanoparticles can also contribute to radiosensitization. In a separate study, liposomes loaded with gold nanoparticles and **CBP**, together with 10 Gy of radiation, significantly slowed HCT116 human CRC xenograft tumor growth progression.[857]

Additionally, surface functionalization of nanoparticles can enhance their delivery capabilities. Targeting ligands on the nanoparticles' surface to target cells facilitates preferential uptake of nanoparticles through diffusion and/or receptor-mediated endocytosis,[892] potentially overcoming chemoresistance mechanisms by disfavoring cellular uptake. Some of these receptors overexpressed by CRC cells include transferrin receptors, EGFR and hyaluronic acid (HA) receptors. The incorporation of transferrin on the **OXP**-loaded liposomal surface reduced Colon-26 tumor growth progression *in vivo*.[893] Liposomes can also be decorated with cetuximab or cetuximab-Fab′ fragments to target EGFR-overexpressing CRC cells. **OXP** encapsulated in cetuximab-Fab′ fragment-liposomes exhibited higher accumulation in the tumor.[894] Moreover, the use of EGFR-targeted liposomes inhibited the growth of SW480 colorectal xenograft tumor.[894] HA is also used as a targeting molecule to target HA-overexpressing CRC cells. HA-coupled chitosan nanoparticles loaded with **OXP** showed enhanced accumulation in the colon and tumor within 24 h of oral administration, effectively delaying HT-29 tumor growth in the colon.[844]

However, surface functionalization can often be expensive and challenging to perform, depending on the specificity of the ligand chosen and its physical and chemical compatibility with the nanoparticles. In this regard, nanoparticles originated from biological sources (e.g., cells) can demonstrate intrinsic targeting toward cancer cells and could represent an attractive option in drug delivery.[895,896] These biomimetic systems include extracellular vesicles and cell-derived vesicles, where the cell membranes of natural cells are used to imbue nanoparticles with characteristics of the original cell. Erythrocyte-cloaked nanoparticles (e.g., polymeric nanopar-

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Table 16. List of FDA-Approved Nanoformulations of Chemotherapeutics

formulation name	nanoparticle	drug	nanoparticle advantage	clinical indication	ref
Doxil	liposome (PEGylated) (lipid bilayered nanoparticle)	doxorubicin (DOX)	significant reduction of cardiotoxicity of DOX	ovarian cancer, Kaposi's sarcomas, and multiple myeloma	809−811
			increased localization of DOX in tumors	undergoing clinical trials for other cancer types	
Abraxane	albumin bound nanoparticle (protein-based micelles)	paclitaxel	reduced toxicity of taxol	pancreatic, lung, and metastatic breast cancer	810−812
			improved tumor inhibition	undergoing clinical trials for other cancer types	
Onivyde	liposome (PEGylated)	Irinotecan	reduced toxicity of Irinotecan	metastatic pancreatic cancer	810,811,813,814
			improved localization of Irinotecan in tumors	undergoing clinical trials for other cancer types	
MEPACT	liposome (non-PEGylated)	mifamurtide	improved long-term survival rate of patients with osteosarcoma	osteosarcoma	810,811,815
				undergoing clinical trials for other osteosarcomas	
Marqibo	liposome (non-PEGylated)	vincristine	reduced toxicity of vincristine	Philadelphia chromosome-negative acute lymphoblastic leukemia	810,811,816
			enhanced bioavailability of vincristine over prolonged period	undergoing clinical trials for other cancer types	
DaunoXome	liposome (non-PEGylated)	daunorubicin	reduced systemic toxicity of danorubicin	Kaposi's sarcoma	810,811,817
			increased delivery of danuorubicin to tumors	undergoing clinical trials for other types of leukemia	
VYXEOS	liposome	cytarabine and daunorubicin (5:1 molar ratio)	enabled targeted codelivery of chemotherapeutic cocktail	acute myeloid leukemia	810,811,818,819
			improved remission rate and overall survival	undergoing clinical trials for other types of leukemia	
Eligard	polymeric micelle	leuprolide acetate	reduced frequency of testosterone surge (hot flushes)	prostate cancer patients in palliative care	810,811,820,821
			improved bioavailability of leuprolide acetate		
Ontak	protein-based micelles	IL-2 fused to diphtheria toxin	enabled specific targeting of T-cells specificity enable lysosomal escape	cutaneous T-cell lymphoma	810,811,822−824
				undergoing clinical trials for other cancer types	
Nanotherm	inorganic nanoparticles	iron oxide	enabled specific thermal treatment of tumor	glioblastoma	810,811,825,826
			improved overall survival	undergoing clinical trials for prostate cancer.	

ticles, iron oxide nanoparticles, mesoporous nanoparticles, and gold nanocages), for instance, enable long circulation time by "camouflaging" the nanoparticles from the mononuclear phagocytotic system.[897,898] Extracellular vesicles isolated from milk have been used to deliver **OXP** to SNU-C5 colorectal tumor xenograft.[864] Additionally, these biomimetic systems can be further engineered to enhance the accumulation within the tumor. The addition of GE11 peptide targeting EGFR has shown to improve the therapeutic efficacy of **OXP**-loaded milk extracellular vesicles in the treatment of SNU-C5 colorectal tumor xenograft.[864]

7.3.2. Targeted Administration and Delivery. **OXP**, which is currently FDA-approved for the treatment of CRC, is administered by IV infusion. **OXP** is administered to patients over a 2 h period, often in combination with other chemotherapeutics such as 5-FU and LV. Although IV injections ensure the highest blood concentrations, patients are subjected to rounds of injections during treatment. The efficacy of the treatment is also dependent on the biodistribution of the drugs and their uptake and accumulation inside the cancerous cells. There are also associated hematological harmful effects and toxicity to healthy organs caused by off-target accumulation.[899]

Besides the IV route, it could be advantageous to administer Pt drugs through alternative means to target the colorectal area more efficiently. The administration of Pt drugs through alternative methods has been tested in clinical trials for other forms of cancer. For instance, a sustained release lipid inhalation releasing **CDP** was evaluated for the treatment of lung cancer.[900] Recent developments also demonstrate that

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Table 17. List of Nanoformulations Containing Pt Drugs under Clinical Trials

formulation name	nanoparticle	drug	composition[827]	size [827]	indication	phase of clinical trial	ref
lipoplatin	PEGylated liposome	**CDP**	hydrogenated soy phosphatidylcholine (HSPC), cholesterol, dipalmitoyl phosphatidyl glycerol (DPPG), and methoxy-polyethylene glycol-distearoylphosphatidylethanolamine (DSPE-PEG2000)	110 nm	nonsmall cell lung cancer pancreatic cancer ovarian cancer	phase III	828
aroplatin	liposome	**CDP**	1,2-dimyristoylphosphatidylcholine (DMPC) and 1,2-dimyristoylphosphatidylglycerol (DMPG)	1−5 μm	metastatic CRC advanced solid tumors	phase II	829
LiPlaCis	liposome with specific degradation-controlled drug release	**CDP**	1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1,2-distearoyl-sn-glycero-3-phospho-(1′-*rac*-glycerol) (sodium salt) (DSPG) and DSPE-PEG2000 ($sPLA_2$-triggered targeted release of CDP)		metastatic breast cancer prostate cancer skin cancer	phase I−II	830
NC-6004 Nanoplatin	polymeric micelles	**CDP**	PEG-*b*-poly (l-glutamic acid)	30 nm	pancreatic cancer head and neck cancer	phase I−II	831,832
Lipoxal	liposome	**OXP**			CRC gastric cancer pancreatic cancer	phase I	833

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Table 18. Preclinical Studies of Pt-Based Drugs on Nanoformulations

nanocarrier	composition	Pt drug	size	efficacy	ref
chitosan nanoparticles (coated with Eudragit S100)	chitosan	**OXP**	136 (±6.0 nm)	delay tumor growth (HT-29 human colon cancer cells)	844
	hyaluronic acid-conjugated chitosan		152 (±5.2 nm)		
PEG-*b*-poly(glutamic acid) micelles	PEG-*b*-poly(glutamic acid)	**Pt(DACH)Cl_2**	37−41 nm	improve antitumor effect without significant toxicity	845
stearic acid-*g*-chitosan oligosaccharide micelles	stearic acid-*g*-chitosan oligosaccharide	**OXP**	90 nm	suppress growth of HT-29 and SW620 CRC cells xenograft	846
poly lactic-*co*-glycolic acid microsphere	poly lactic-*co*-glycolic acid	**OXP**		suppress growth of HCT116 human CRC cell xenograft	847
PEGylated multiwalled carbon nanotubes	carbon nanotubes functionalized with PEG600	**OXP**	length of few hundred nm to few μm, outer diameter of 40 to 50 nm, thickness of 15 nm	increase cytotoxicity toward HT-29 human CRC cells	848
PEGylated liposomes	lecithin or cholesterol and DSPE-PEG2000	**OXP**	100−200 nm	suppress growth of SW480 human CRC cell xenograft	849,850
PEGylated cationic liposomes	HSPC, cholesterol, mPEG2000-DSPE and *O*,*O*′-ditetradecanoyl-*N*-(*α*-trimethyl ammonio acetyl) diethanolamine chloride (DC-6−14)	**OXP**	around 250 nm	suppress angiogenesis in dorsal air sac mouse model	851−853
gold nanoshells	poly[2-(*N*,*N*-dimethylamino)ethyl methacry-late]-poly(*ε*-caprolactone) copolymer PEGylated gold nanoshell	**Pt(DACH)Cl_2**	90.8−100.1 nm (micelles) 144.3−298.6 nm (micelles coated into gold nanoshell)	suppress growth of HT-29 human CRC cell xenograft	854
PEGylated lipid nanoparticle	1,2-dioleoyl-*sn*-glycero-3-phosphate (DOPA), 1,2-dioleoyl-3-trimethylammonium propane (DOTAP), cholesterol and DSPE-PEG/DSPE-PEG-aminoethyl anisamide	**OXP**	120 nm	suppress growth of CT26 mice CRC cell xenograft	855,856
liposomes	DOTAP, DSPC and cholesterol	**CBP** with gold nanoparticles	134.33 (±0.27 nm)	suppress growth of HCT116 human CRC cell xenograft	857
poly(acrylic acid) hydrogel grafted cellulose nanocrystals	cellulose nanocrystals conjugated with acrylic acid	**CDP**		slow and sustained release of CDP *in vitro*	858
liposomes	HSPC, cholesterol and mPEG2000-DSPE	**OXP**	180 (±52 nm)	suppress growth of CT26 mouse colon cancer cells preserve $CD8^+$ T-cell mediated antitumor immunity through decreasing immune suppressor cells	859
gelatin-based nanoparticles	gelatin	**CBP**	16 nm	increase cytotoxicity toward HCT116 human CRC cells	860
biological chemotaxis-guided self-thermophoretic nanoplatform (*S. aureus* membrane coated mesoporous silica nanoparticles)	mesoporous silica functionalized with PEG and glucose	**CDP**	81.1 (±4.9 nm)	suppress growth of CT26 mouse CRC cells xenograft	861
self-assembled nanoparticle (ROS-sensitive polymer and lipid polymer)	mPEG2000-DSPE	**CDP**	97.47 nm	suppress growth of CT26 mouse CRC cells xenograft	862
nanostructured lipid carriers	myristyl myristate, capric triglyceride, Poloxamer 188 and riboflavin	**8-oxyquinolinate-Pt(II)**	146.5 (±1.6 nm)	increase cytotoxicity toward HT-29 human CRC cells	863
milk extracellular vesicles		**OXP**		suppress growth of SNU-C5 human CRC cells xenograft	864
PEAP-2 polymersomes	poly[(methoxy-poly(ethylene glycol)) (*N*-[bis(2-amino ethyl) ethyl amino] amino phenyl amide) phosphazene]	**CBP**	150−200 nm	suppress growth of CT26 mouse CRC cells xenograft	865
ZnO nanoparticles	zinc oxide	**CBP**	69−82 nm	increase cytotoxicity toward HT-29 human CRC cells	866

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Table 18. continued

nanocarrier	composition	Pt drug	size	efficacy	ref
lipid-polymer hybrid nanoparticles	cholesterol, soyalecithin, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(polyethylene glycol)-3400] (DSPE-PEG-3400-mal), mPEG2000-DSPE and chitosan	**OXP**	95 (±0.01 nm)	suppress growth of HT-29 human CRC cells xenograft	867
lipid nanoparticles	D-α-tocopheryl polyethylene glycol 1000 succinate	**OXP**	158 (±3.15 nm)	increase cytotoxicity toward HT-29 human CRC cells	868
dendrimers	PEGylated polyamidoamine G4 conjugated with folic acid	**OXP**	7.8−14.1 nm	increase cytotoxicity toward SW480 human CRC cells	869
PEGylated multiwalled carbon nanotubes	carbon nanotubes functionalized with superparamagnetic iron oxide and PEG	**OXP**		slow and sustained release of CDP *in vitro*	870
P4C6 phosphonated calixarenes	calix[4]arene with four ionizable phosphonic acid groups attached to the upper rim and four sixcarbon alkyl moieties attached to the lower rim	**CBP** + paclitaxel	119 (±13 nm)	suppress growth of HT-29 human CRC cells xenograft	871

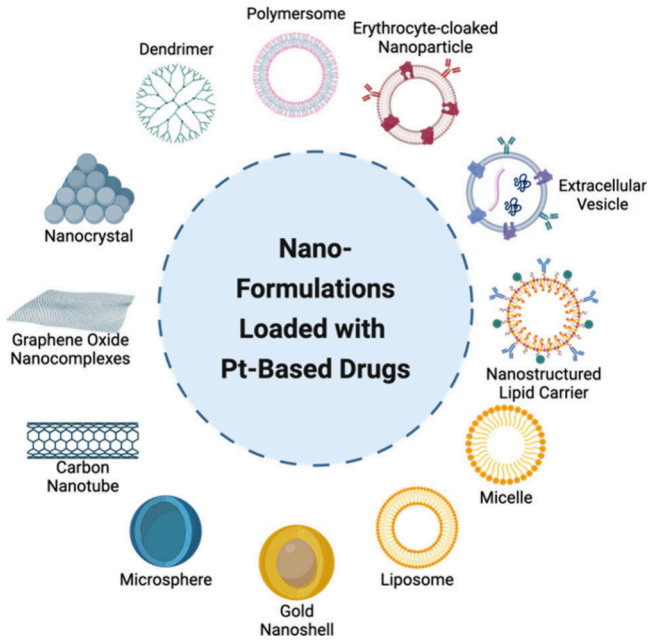

Figure 20. Preclinical studies of nanoformulation loaded with Pt-based drugs. Figure created with BioRender.com.

CDP aerosol therapy can be delivered to the lymph nodes in Stage II lung cancer patients.[901]

Instead of the parenteral route, administration through the enteral route could allow a direct targeting to the colon and rectum. Although it is not well-studied clinically, we propose that the oral administration of Pt-based chemotherapeutics may have added advantages in the treatment of CRC. The design and development of colon-targeted oral formulations for Pt-based chemotherapeutics could target the colon directly, increasing the efficacy while reducing off-target side effects.[902] Some strategies include designing Pt compounds that could survive the gastrointestinal tract or the loading of Pt compounds into colon-targeted oral drug delivery systems. Such colon-targeted oral drug delivery systems take advantage of the physiological conditions of the colon and have a pH-triggered (e.g., Eudrajit), microbiota-triggered (e.g., polysaccharides or azo polymers) or time-controlled release (e.g., hydroxypropyl methylcellulose) of the active drug.[903,904]

A few Pt-based chemotherapeutics have been designed and developed for oral administration. Even if it was not tested for CRC, **Satraplatin** was the first orally active Pt drug to be used in clinical trials.[905,906] The lipophilicity and stability of **satraplatin** allows for oral administration.[906] Moreover, the efficacy of **satraplatin** is comparable to **CDP** and **CBP** with a reduced toxicity. **Satraplatin** has been tested in the treatment of various cancers in clinical trials, including prostate cancer, metastatic breast cancer, lung cancer, and brain tumors. Similarly, Ang and colleagues have developed and screened a series of **asymmetric mono/bis-carboxylated Pt(IV)** complexes (Figure 17), which have shown potential in preclinical studies involving CRC, both *in vitro* and *in vivo*.[907] The effectiveness of the Pt(IV) complexes in the colitis-induced *in vivo* CRC model is likely attributed to their retention in a prodrug form postoral administration, thereby enhancing cellular uptake and thus therapeutic effectiveness.

Additionally, other clinically approved chemotherapeutics (e.g., capecitabine and trifluridine/tipiracil) have demonstrated the feasibility to use orally administered tablets for CRC

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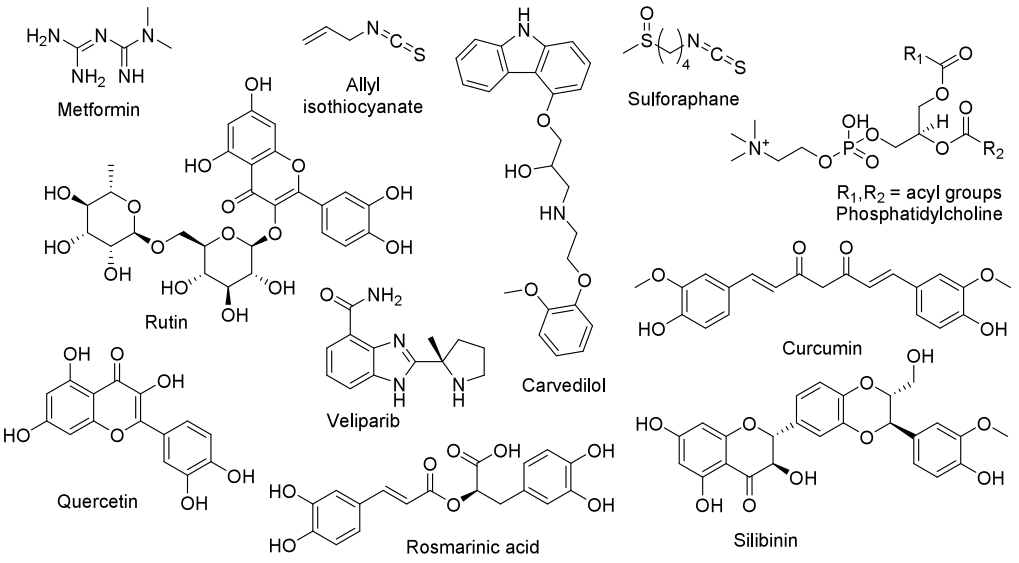

Figure 21. A list of pharmacological treatments evaluated in clinical trials of **OXP**-based chemotherapy-treated patients.

treatments. Using similar approach, Pt-based drugs can also be formulated into oral dosage forms. For instance, Urbanska et al. loaded **OXP** into lipidoid encapsulated in alginate microcapsules.[908] The oral delivery of **OXP**-loaded capsules increases the OS rate. Another study by Kim et al. demonstrated that tablets containing **OXP** loaded using fat employing supercritical nano system was able to further reduce HT-29 xenograft tumor growth as compared to IV route.[909] More recently, Pangeni et al. developed a solid formulation of **OXP** for oral administration to treat CRC.[910] A permeation enhancer was used to complex with **OXP** and then mixed with dispersing agents to form a solid amorphous oral formulation. With this oral formulation, there is a further inhibition in CT26 and HCT116 xenograft tumor growth as compared to the maximum tolerable dose by IV injection. This signifies the potential of oral administration in the treatment of CRC while reducing the adverse side effects associated to chemotherapy.

7.3.3. HIPEC and PIPAC for mCRC. Peritoneal metastases (PMs) are common for late-stage gastrointestinal cancers, including mCRC, and associated with poor prognosis.[911] PMs respond poorly to systemic chemotherapy and adversely affect patients' quality of life. Intraperitoneal chemotherapy (IPC) has been developed as an alternative delivery modality to treat PMs that could improve drug concentrations at the affected tissue and reduce systemic toxicities.[912] In IPC, chemotherapeutic drug solutions are typically administered at high concentrations directly into the peritoneal cavity *via* catheters and irrigated using a perfusion machine. In the case of **OXP**, the drug solutions are also heated to 41−43 °C during treatment as higher temperature has been shown to improve therapeutic outcomes through increasing cytotoxicity and ensuring better tissue penetration. This modality of delivering **OXP** at elevated temperatures is known as hyperthermic intraperitoneal perioperative chemotherapy (HIPEC), and it is typically performed in conjunction with cytoreductive surgery (CRS).[913] This is in part due to the need to install catheters, which would require surgical access to the patient's abdomen. A typical HIPEC procedure ranges from 30 to 120 min and the peritoneal cavity is flushed with saline after treatment. It should be noted that there are conflicting data on the effectiveness of **OXP**-based HIPEC for treatment of PMs arising from mCRC following CRS vs CRS alone, despite its wide adoption.[914−916]

The invasive nature of HIPEC has led to the development of other ways of delivering **OXP** into the peritoneal cavity. One such technique known as pressurized intraperitoneal aerosol chemotherapy (PIPAC) involves nebulizing **OXP** solution into an aerosol and then introducing it into the patient's abdomen *via* laparoscopy.[917,918] It is a significantly less invasive procedure since only small incisions are required for the trocar and nebuiliser injector. Several clinical trials have established the efficacy, safety and tolerance of PIPAC, with minimal systemic uptake.[919−921] At this time, PIPAC is only indicated for patients with advanced peritoneal carcinomatosis when other options such as CRS or systemic chemotherapy are not viable.[922]

7.4. Chemoradiotherapy as an Emerging Strategy

The hypoxic TME is known to contribute significantly to the development of radioresistance for cancer radiotherapy.[923,924] Consequently, a variety of radiosensitizers have been integrated into clinical treatment regimens to enhance therapeutic efficacy of radiotherapy. For instance, 5-FU was among the first compounds recognized for its enhanced efficacy in conjunction with radiotherapy compared to radiotherapy alone for the treatment of CRC.[925] On top of it, transition metal compounds have also been designed to be radiosensitizers for cancer radiotherapy.[926] In addition to radiosensiting effects, chemoradiotherapeutic agents could be designed to maximize eradication of tumor cells while simultaneously minimize the negative impacts on surrounding healthy tissues.

A novel class of chemoradiotherapeutic prodrugs activated by radiotherapy has emerged in recent times.[927−930] **OXP** has shown promise as a chemoradiotherapeutic agent as supported by *in vitro* and *in vivo* results from preclinical studies,[931−934] although the clinical outcomes have been inconsistent.[399,935−939] Recent discovery found that hydrated electrons (e^-_{aq}) generated from radiotherapy dose of X-ray can be used as a reliable source of reductant to efficiently reduce and activate Pt(IV) prodrugs (**47**).[940] Upon X-ray irradiation, these Pt(IV) prodrugs can readily release their active Pt(II) precursors (e.g., **CDP**, **OXP**, **CBP**, **nedaplatin**, **picoplatin**,

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Table 19. Summary of the Variety of Schedules and Studies in Rodent Models for OXP-Induced Neurotoxicity[a,b]

strain	sex	administration	cumulated dose (mg Ox/kg)	nerve conduction studies	behavioral tests results	morphology changes
human	M	IV	27.54	Y	C	
C57BL/6	M	IP	20, 30, 80	Y (80)	M, M/C	struc, mol, struc/mol
	M	IV	28	Y	M/C	struc/mol
Swiss	M	IV	9, 18		M/C	mol, struc/mol
Balb/C	M	IP	30, 45, 48, 60, 80, 90	Y (80)	M, C, M/C	mol, struc, struc/mol
	F	IP	30, 48	Y	M/C	struc
	M	IV	28	Y	M/C	struc, struc/mol
CD-1	M	IP	24, 36		M, C, M/C	
	M	IV	28	Y	M+, C=	struc, mol
AJ	M	IV	28	Y	M/C	struc, mol
FVB	M	IV	28	Y	M/C	struc, mol
DBA/2J	M	IV	28	Y	M/C	struc, mol
ICR	M	IP	30, 32		M/C	
Wistar	F	IP	29.6, 36, 40, 48, 70	Y	M (36)	struc (36, 48)
	M	IP	18, 24, 32, 36		M, M/C	struc
	F	IV	18, 24, 27	Y		mol, struc/mol
	M	IV	12, 20		M/C	
Sprague-Dawley	M	IP	6, 16, 18, 20, 21, 24, 30, 32, 36, 48, 64, 90	Y (6, 16, 32, 36, 48)	M, C, M/C	struc, mol, struc/mol
	F	IV	9, 36		M/C	
	M	IV	32		M	struc/mol

[a]Sex: M, Male; F, Female. Route: IP, intraperitoneally; IV, intravenously. Nerve conduction studies; Y, yes (cumulated dose used in the study). Behavioral tests: M, mechanical stimulation; C, cold stimulation; M/C, both. Morphology changes studied: struc, at anatomic structural level (fiber/body neuron); mol, at molecular level. Weight range for mice, 18−35 g; weight range for rats, 150−380 g; Human dose estimate is based on a 60 kg male with a body surface area of 1.62 m^2, and the dose is converted to mg/kg from the standard dose of 85 mg/m^2. [b]Adapted with permission from ref 640. Copyright 2020 Elsevier.

lobaplatin, **transplatin**), along with their associated axial ligands such as (3-carboxypropyl) triphenyl phosphonium (CTPP), coumarin, succinic acid in physiologically related solvents. Moreover, **OXP**-derived Pt(IV) compounds have demonstrated markedly enhanced anticancer activity when exposed to radiotherapy-dose X-ray (i.e., 4 Gy) on CRC models like HCT116 and HT-29 both *in vitro* and *in vivo*, outperforming the non-irradiated controls. Additionally, the hypoxic TME appears to have minimal impact on the release of active **OXP** from the Pt(IV) prodrugs by radiation. These discoveries underscore the potential of radiotherapy-induced Pt(IV) prodrugs activation as a compelling strategy for *in situ* prodrug activation, complementing chemotherapy's efficacy when combined with radiotherapy.

7.5. Therapeutic Strategies Against OIPN

The onset of OIPN in patients depends on numerous factors, among which the administered dose at each cycle and the cumulative dose. In patients with acute OIPN, depending on the neurological assessment between consecutive cures and to avoid the appearance of chronic OIPN, the administered dose may be diminished, the chemotherapy protocol changed or the treatment stopped. While no clinically approved preventive or therapeutic solution exists, numerous approaches to prevent, treat, or alleviate OIPN and its symptoms have been evaluated over the last decades, including both pharmacological (Figure 21) or nonpharmacological methods, following the identification of OIPN mechanisms.[637,941,942] To mitigate the systemic toxicities caused by Pt(II) drugs, a wide range of strategies, including combination therapies, have been explored. In the context of CRC, various medications have been developed to prevent or manage OIPN, among which antioxidants, anti-inflammatory agents or ion channel modulators have been proposed. Although significantly less explored, other strategies, such as the use of Pt(IV) prodrugs, are also being actively developed for this purpose.

7.5.1. Nonpharmacological Approaches against OIPN. Several nonpharmacological approaches have been evaluated against CIPN. Among those that have reached clinical evaluations, reviewed elsewhere recently,[629] could be cited, for example, acupuncture (NCT05882396, NCT0585-0130, NCT04505553), ultrasound therapy (NCT03958747), physical exercise (NCT03515356), or compression therapy. A short focus will be given here to cryotherapy.

Before being evaluated in the context of CIPN, cryotherapy received attention for its beneficial effect in alleviating other chemotherapy-induced side-toxicity, in particular alopecia, oral mucositis and nail toxicity.[943] After decades of studies, scalp cooling devices received FDA approval to reduce chemotherapy-induced hair loss. Cryotherapy consists in cooling the extremities of the patients while they receive chemotherapeutic treatment. The vasoconstrictive effect of the cooling is hypothesized to limit the local delivery and accumulation of the chemotherapy and therefore its toxicity to the nerves in the

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extremities. Several studies and clinical trials evaluated the efficacy and the safety of different cryotherapy implementations, mostly involving taxane-based chemotherapies (e.g., paclitaxel, docetaxel).[944] Most of the studies support the use of cryotherapy to reduce CIPN symptoms in paclitaxel-receiving patients, leading this method to progress in clinical practice and considered as a preventive approach.[622,976]

In the context of Pt-based chemotherapies, a recent trial involving breast cancer patients that received **CBP** reported that patients using ice gloves and boots showed milder CIPN symptoms than patients not receiving cryotherapy.[977]

Relative to taxanes, and because of the induced cold hypersensitivity (the patients being advised to avoid cold touch), the available data on the use of cryotherapy in the context of **OXP** treatment is more limited (Table 21). In a study evaluating the use of frozen gloves in **OXP**-treated patients, no significant beneficial effects were observed but the discontinuation rates of the patients receiving cryotherapy (one-third in total due to discomfort) was not different whether they received **OXP** or taxanes.[978] A recent phase II clinical trial on **OXP**-receiving patients with cancers in the digestive system evaluated cryotherapy using a continuous cooling of hands and feet at a constant temperature, named hilotherapy.[978] This approach was described to be well tolerated and to reduce acute OIPN symptoms. More work is needed to further evaluate the potential benefits of cryotherapy in the context of OIPN and to develop cryotherapy methods combining patients' compliance and ease of implementation.

7.5.2. Rodent Models for OIPN Studies. This section briefly discusses the most widely used *in vivo* immunocompetent rodent models in the study and assessment of OIPN.[640,979] Detailed information on these models can be found in the 2020 review from Calls et al.[640]

Different animal strains have been used in *in vivo* models of OIPN, among which C57BL/6 and Balb/C mice are the most frequent and Balb/C mice being the most susceptible to neurotoxicity development.[980] Rat models, generally more prone to **OXP**'s toxicity than mice, include Wistar and Sprague-Dawley strains. Intraperitoneal (IP) injections are more frequent although IV administration was also described. There is little established consensus on OIPN models and evaluation, and models differ in animals' species, strains, age, sex, cumulated dose, and injection schedules (Table 19).[981] Because of this variation, phenotypic outcomes obtained with behavioral tests can be contradictory for the same species. In the case of Balb/C mice, most experiments have been performed on healthy animals without a tumor xenograft, and cumulated doses typically vary from 30 to 90 mg of **OXP**/kg of body weight. The durations of the experiments also vary depending on injection schedules and range from 2 weeks to 3 months. Most experiments were performed on adult male individuals, even though it has been reported that female individuals are more sensitive to OIPN.[981]

Classically performed behavioral tests comprise the Von Frey test to evaluate mechanical hypersensitivity,[982,983] and the cold plate and acetone test to measure cold hypersensitivity (acute symptoms).[984] Contradictory results between hyperalgesia and hypoesthesia have been published and such behavioral tests only reflect some of the OIPN clinical symptoms associated with pain. Neuropathy assessment includes the quantification of the loss in IENF density in skin biopsies of hind paws (immunohistological IHC studies with PGP9.5 antibody),[985] studies on DRG samples and sections (IHC studies), and isolated sciatic nerves to characterize axonal damage and demyelination (IHC with Luxol Blue staining, determination of G-ratio, shown to increase, confocal microscopy). Important features are nerve conduction studies, which are however not systematically carried out and if so, with significant variability across studies. The variability in the described models including variations in the injection schedules and administration route, the cumulative total doses, the animal strains/age/sex that show different sensitivities and behaviors,[981] and the different neuropathy assessment methods (behavioral tests, molecular characterizations of OIPN) (Table 19), makes systematic comparisons between studies unrealistic.

Finally, most of the *in vivo* models consist of healthy animals and very few models have been used to evaluate neuropathy in rodents with tumors (CT26 xenograft in Balb/C mice).[956,957,986] The presence of a solid tumor can alter the evaluated drugs' pharmacokinetics and such a model appears more clinically relevant. The same administration schedules, duration of the experiments and therefore accessible stages of neuropathy, are however more restrained in tumor-bearing models. We believe both healthy and tumor-bearing mice models provide complementary information and the latter should be further implemented in order to determine the systemic side effects of the newly developed chemotherapeutic agents.

7.5.3. Combination Treatments for OIPN. The combination treatments' approaches against OIPN include targeting molecular mechanisms and pathways, such as sodium, potassium or TRP channels, glutamate or monoamine nervous systems, oxidative stress, inflammatory responses and Pt transporters, and have been extensively reviewed.[619,623,987,988]

A number of *in vitro* models using tumor-derived neuron-like cells of human or murine origin have been described and used for the study of the mechanisms of **OXP** neurotoxicity and to evaluate therapeutic approaches against OIPN.[640] Different *in vivo* models for preclinical studies of OIPN have also been described,[640,979] as briefly introduced above in section 7.5.2.

Na^+ and K^+ have been reported to display crucial roles in the development of acute peripheral neuropathy. Na^+ channels have been traditionally related to the induction of acute cold hypersensitivity, and K^+ channels regulate sensory neuronal pain and excitability. The expression of K^+ channels such as TWIK-related K^+ channel 1 (TREK-1) and TWIK-related arachidonic acid-stimulated K^+ channel (TRAAK) has been shown to be altered by **OXP** in the DRG of rodents.[975,989] Ion channel modulators are therefore potential therapeutic options for alleviating OIPN. In this regard, several drugs known for their voltage-gated sodium or calcium channels inhibitory properties, have been reported to display neuroprotective activities in the context of CIPN.[619,623,987,988] Analgesics like capsaicin,[990] lidocaine,[991] and morphine,[992] antidepressants such as amitriptyline,[993] cholinesterase inhibitors such as donepezil,[964,994] renin−angiotensin system modulators such as Ramipril,[995] among others, can reduce symptoms by acting on neurotransmission. Anticonvulsants such as carbamazepine or gabapentine reduce excitatory neurotransmitters and target voltage-gated calcium channels. However, all these drugs show secondary deleterious effects. More recently, Alberti et al. reported prevention of **OXP**-induced both acute and chronic

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peripheral neuropathy in female Wistar rats when treated in combination with topiramate, another voltage-gated sodium channel modulator.[627] In this study, acute neuropathy was assessed through sensory nerve's threshold observation, while chronic neuropathy was evaluated at neurophysiological, behavioral, and neuropathological levels. Since topiramate is already clinically approved for the treatment of epilepsy and migraines and shows minimal detrimental effects,[996] it presents a promising candidate for further preclinical investigations in the context of OIPN.

As extensively covered by Stankovic et al. in 2020,[997] exogenous antioxidants usually employed as supplementation treatments were investigated, including vitamins (e.g., C, E, or K), minerals (e.g., manganese, selenium or zinc), carotenoids, and other molecules such as lipoic acid, D-methionine, carnosine or omega-3-fatty acids. Supplementation of ROS scavengers in combination with **OXP** might compensate for **OXP**-induced glutathione depletion and re-establish redox homeostasis in healthy cells.

Antioxidants of synthetic origin have also been largely evaluated to reduce oxidative stress in neurons in rodent models, with some encouraging results.[988] Among them, (Mn)-based complexes, mimicking superoxide dismutase (SOD) enzyme and therefore able to catalyze the dismutation of two superoxide anions ($O_2^{\cdot-}$) into H_2O_2 and dioxygen,[998] have been widely studied in anticancer strategies[999,1000] and in OIPN prevention (**48**−**51**).[955] **Mangafodipir**, an MRI contrast agent also displaying SOD-mimicking properties, has been shown to improve the therapeutic index of **OXP** and prevent OIPN under both preclinical and clinical studies.[647,1001] The preventive use of SOD mimics based on different scaffolds was further explored in OIPN animal models by Guillaumot et al. in 2019[956] and Prieux-Klotz et al. in 2022.[957] The open-chain diamine complex **Mn1** (**49**) was an excellent candidate due to its antioxidant and anti-inflammatory properties in various *in vitro* and *in vivo* models.[1002,1003] Remarkably, when combined with **OXP** in CT26-bearing Balb/C mice, Mn1 displayed neuroprotective activity as observed in behavioral tests and electrophysiological recordings.[956] This Mn(II) complex and its derivatives, all bearing a positive charge, could display improved cell penetrative properties with respect to mangafodipir and are therefore excellent candidates for further preclinical investigations. Table 20 and Figure 21 present selected examples of antioxidants that have shown a neuroprotective activity in preclinical models of OIPN in mice or rats.

Nuclear factor-erythroid 2-related factor 2 (Nrf2), a transcription factor that regulates the expression of antioxidant enzymes and detoxification proteins, is an interesting target in the prevention of OIPN. Dimethyl fumarate, an electrophilic Nrf2 activator approved for multiple sclerosis, was shown to protect against axonal degeneration of rats' sciatic nerves.[1004−1006] Anti-inflammatory agents such as minocycline or rapamycin prevented neuronal damage in rats. Inhibitors of Pt transporters involved in Pt accumulation in DRG were also evaluated. Cimetidine and dasatinib,[631] OCT2 inhibitors, showed some prevention of mechanical allodynia in mice, and ergothioneine,[1007] an OCTN1 inhibitor, showed a beneficial effect on mechanical allodynia in rats. Of note, inhibition of OCTN2 by L-carnithine, failed to do so. A significant number of clinical trials involving molecular approaches mentioned above were also conducted without much success, and are covered in a few recent reviews.[637,988]

A list of pharmacological treatments evaluated in clinical trials of **OXP**-based chemotherapy-treated patients is proposed in Table 21. Among these, Duloxetine, a serotonin−norepinephrine reuptake inhibitor used to treat depressive disorders, is the only recommended drug (moderately recommended) by the American Society of Clinical Oncology, to treat neuropathic pain, although its efficacy is still debated.[1008] To counteract oxalate's effect on sodic channels, calcium/magnesium infusions were evaluated without success.[969,1009−1011] Goshajinkigan, a traditional Japanese medicine acting on TRP channels, gave contradictory results.[1012−1014]

Antioxidants such as α-lipoic acid, glutathione or vitamin E, or the anti-inflammatory minocycline failed to show any improvement in neuropathy or pain score. The Ca^{2+} channel inhibitor pregabalin was studied in several clinical trials that gave differential results. Further validation of its potential efficacy is therefore needed. Calmangafodipir reached phase III trials (POLAR A and M) in CRC patients, although it gave negative results, with no OIPN reduction after 9 months.[973] The negative charge of the complex was suspected to cause low cell penetration and possible redox reactions between the Mn(II) and Pt(II) centers, due to a very close in time administration, were presumably the causes of the negative effect in the last clinical trial.[973,1015] Riluzole, which inhibits the accumulation of glutamate, has entered a phase II trial.[975]

In summary, many strategies have been studied in animal models of OIPN, with some success, most of them alleviating acute OIPN symptoms and only a few showing preventive activity. These drugs must neither reduce **OXP** antitumoral efficacy nor generate additional side effects. There remains a gap between preclinical animal studies and clinical trials, where only a few compounds have been evaluated with very limited positive outcomes. Although efficient solutions have yet to be developed, some target candidates for neuroprotection and prevention of nerve damage have been identified.[1016] More efforts are necessary to evaluate and characterize the mode of action of potential preventive strategies and to develop assessment methods in animal models that better reflect clinical symptoms in order to bridge that gap.[624]

7.5.4. Pt(IV) Strategy in the Context of OIPN. Although vastly less explored, other strategies, such as the use of Pt(IV) prodrugs are also under current development. The Pt(IV) strategy can also be exploited in the context of OIPN prevention for several reasons. First, mediated uptake of Pt(IV) prodrugs might differ from that of their Pt(II) counterparts. The toxicity profiles of Pt(IV) prodrugs are far from being completely deciphered and their neurotoxicity, including accumulation in DRG, has been poorly characterized so far. For instance, unlike **CDP**, it has been reported that **dicarboxylato CDP**-based Pt(IV) prodrugs are not substrates for CTR1 transporters.[1017] However, **OXP** and its Pt(IV) derivatives seem to be equally internalized *via* OCTs.[1018] Furthermore, the uptake of **CDP**-based Pt(IV) complexes *via* OCT2 might be dependent on the symmetric or unsymmetric functionalization of such complexes.[1019] The role of solute and membrane transporters for Pt(IV) complexes is, nevertheless, less explored than for their Pt(II) analogs. Overexpression of transporters in certain tissues (e.g., OCT2 is typically expressed in neurons and is thought to play an essential role in **OXP** accumulation in DRG)[631] might drastically modify the therapeutic consequences of said prodrugs. Such parameters

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Table 20. Antioxidant and/or Anti-inflammatory Agents Tried As Combination Treatment with OXP in the Context of OIPN in Murine Models

compound	mechanism of action	model	schedule	outcome
Metformin[945]	inhibition of mitochondrial oxidative phosphorylation antidiabetic	Sprague-Dawley male rats (250 g)	**OXP** (4 mg/kg IP) injections in two consecutive days every week, for 4 weeks Metformin (250 mg/kg, IP) injections daily for 4 weeks	prevented degeneration of intraepidermal fibers and altered sensitivity
Carvedilol[946]	ROS scavenger anti-inflammatory	Male Sprague−Dawley rats (200−250 g)	**OXP** (4 mg/kg IP) twice a week for four weeks in a total of nine injections (total cumulative dose 36 mg/m^2) carvedilol at 10 mg/kg, po	prevented deficits in peripheral nerves, reduced ROS
phosphatidylcholine[947]	aldehydes scavenger	male Sprague-Dawley rats (5 weeks old, 180 g)	**OXP** (4 mg/kg) + PC group injected IP with **OXP** twice a week for 4 weeks and orally administered PC (300 mg/kg) five times a week for 4 weeks	reduced peripheral neuropathy by oxidative stress reduction
PARP inhibitor[948]	PARP inhibitor	male C57BL6J mice (10−12 weeks old, 24−26 g)	**OXP** (3.0 mg/kg, IP), injections for 5 days, followed by 5 days of rest, for two weekly cycles; total cumulative dose 30 mg/kg PARP inhibitor (50 mg/kg or 25 mg/kg, IP), injections two days prior to treatment with **OXP**	reduced sensory neuropathy
curcumin[949]	antioxidant	male Wistar rats		
rutin, quercetin[950]	antioxidant	male Swiss mice	**OXP** (1 mg/kg, IV), injections twice a week (total of nine injections) rutin and quercetin (25−100 mg/kg, IP), injections 30 min before each OXP injection.	decreased oxidative stress, prevention of thermal and mechanical hypersensitivity
rosmarinic acid[951]	polyphenol	rats	rosmarinic acid (25 and 50 mg/kg, po)	reduced mitochondrial dysfunction
allyl-isothiocyanate[952]	H_2S-releasers	male CD-1 albino mice (22−25 g)	**OXP** (2.4 mg /kg, IP) 1−2, 5−9, 12−14 (10 IP injections) compounds (1.33, 4.43, 13.31 and 38 μmol/kg, corresponding to 0.1, 0.33, 1 and 3 mg/kg, sc or 4.43 nmol/mouse by icv route)	reduced hypersensitivity
sulforaphane[953]	Nrf2 activator	male CD-1 albino mice (22−25 g)	**OXP** (2.4 mg /kg, IP) 1−2, 5−9, 12−14 (10 IP injections) sulforaphane (1.33, 4.43, 13.31 μmol/kg)	reduced neuropathic pain
silibinin[954]	antioxidant	rats		reduced thermal and mechanical hypersensitivity
MnL4[955]	SOD mimic	male Sprague-Dawley rats (200−250 g)	**OXP** (2.4 mg /kg, IP) injections 5 consecutive days every week for 3 weeks (15 IP injections) MnL4 continuous subcutaneous (sc) delivery, daily dose of 15 mg/kg for 21 days	reduced hypersensitivity
Mn1 (Figure 22)[956]	SOD mimic	CT26 xenograph BALB/c female mice (6 weeks)	**OXP** (10 mg/ kg, IP), cumulated dose 30 mg/kg Mn1 (10 mg/kg, IP)	neuroprotective activity without anticancer activity loss

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Table 20. continued

compound	mechanism of action	model	schedule	outcome
Mn1C1 (Figure 22)[957]	SOD mimic	CT26 xenograph BALB/c female mice (6 weeks)	**OXP** (10 mg/ kg, IP), cumulated dose 30 mg/kg Mn1C1 (10 mg/kg, IP)	OIPN reduction without anticancer activity loss

are key for understanding Pt(IV) complexes' off-target effects.[671]

On the other hand, the further functionalization achieved by the introduction of two additional axial ligands enables the introduction of neuroprotective moieties (Figure 22).[671] In this regard, the only Pt(IV) prodrugs described for this purpose up to date were reported by Prieux-Klotz et al. in 2022 and were bearing a Mn(II) complex derived from SOD mimic Mn1 (**PtC1Mn*x***) (**50** and **51**).[957] Although poor stability upon Mn(II) coordination was shown, **PtC1Mn1** reported lower antitumoral activity mainly due to a lower effective Pt dose but an improved therapeutic index (in terms of asthenia, alopecia, diarrhea and weight loss).

The evaluation of Pt(IV) complexes in the context of neurotoxicity and peripheral neuropathy is still in its infancy. They present a very interesting opportunity to combine optimized antitumoral activity along with a better toxicity profile with reduced neurotoxicity arising from reduced accumulation in the PNS components and protective activity in healthy cells provided by the axial ligands. This deserves active investment from Pharma companies.

8. CONCLUSION AND OUTLOOK

In this review, we have described the current approaches in treating colorectal cancer (CRC) and the drawbacks and shortcomings of the various methods, focusing on the roles that Pt anticancer agents play as first-line treatment in several malignancies. Although Pt(II) anticancer drugs are simple cytotoxic agents that lack selectivity for cancer cells and cause severe side effects, they have been effectively used in the clinic for over four decades. Remarkably, even today, amid the era of targeted drugs, precision medicine and immunotherapy, nearly half of all chemotherapy regimens include at least one Pt drug.

Nonetheless, the primary challenges with traditional Pt drugs include the lack of selectivity, severe side effects (e.g., nephrotoxicity and neurotoxicity), and the development of drug resistance. **OXP**, commonly used for CRC, is particularly associated with peripheral neuropathy. The severity of the undesirable side effect is further complicated by the interplay among TME, TIME, and Pt drugs. This is because TME and TIME play significant roles in influencing the efficacy of Pt-based drugs in CRC. For instance, the dense structure and abnormal vasculature of the TME can impede drug delivery to tumor cells and the extracellular matrix (ECM) can act as a physical barrier, while hypoxia can alter cellular metabolism and promote survival pathways that counteract the effects of Pt drugs. Moreover, tumors can create an immunosuppressive TIME by recruiting Tregs, MDSCs, and producing inhibitory cytokines, which can reduce the effectiveness of chemotherapy. Recent strategies that modify the TME or TIME to enhance drug delivery and immune response are being explored. These include using agents that normalize blood vessels, modify ECM components, or modulate immune cell activity. Understanding and targeting these environments can potentially improve treatment outcomes and overcome resistance.

The discovery of immunomodulatory roles of **OXP** and other clinical Pt agents has led to numerous clinical trials exploring the combination of Pt chemotherapeutics with immunotherapeutics. This discovery has also broadened the potential use of immunologically active Pt compounds as small molecule chemo-immunotherapeutics. Contrary to previous beliefs that classical cytotoxic Pt(II) anticancer drugs are detrimental to the patients' immune system, recent evidence

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Table 21. Pharmacological Treatments against OIPN in Clinical Trials in OXP-Treated Patients

identifier	title	drug	chemotherapy	number of patients	last updated	study design[a]	status
NCT05866653[958]	effect of lidocaine transdermal patch as add-on therapy in treatment of **OXP** induced peripheral neuropathy in CRC patients	lidocaine	**OXP**	90	2023-05-23	phase 2	recruiting
NCT05624138	the possible protective role of ketotifen against **OXP** induced peripheral neuropathy	ketotifen (antihistaminic)	FOLFOX-6	64	2024-11-21	phase 3	recruiting
NCT05404230	prevention of **OXP**-induced nerve damage in the body's extremities	n-3 PUFA (polyunsaturated fatty acids)		120	2024-10-08	NA masking: triple	recruiting
NCT05680870[959]	the possible protective role of omeprazole against **OXP** induced neuropathy in cancer patients	omeprazole	FOLFOX-4,6,7 or mFOLFIRINOX	46	2023-01-11	phase 3 masking: none	not yet recruiting
NCT02024191[960]	the role of glutamine for preventing **OXP**-induced peripheral neuropathy	glutamine	mFOLFOX6	80	2013-12-32	phase 3 masking: single	unknown (ineffective)
NCT02590367	estimate the efficacy of HD6610 granule for **OXP**-induced peripheral neuropathy	HD6610	FOLFOX	64	2015-12-02	phase 2−3 PP: treatment	unknown
NCT05590117	protective effect of pentoxifylline against chemotherapy induced toxicities in patients with CRC	pentoxifylline (anti-inflammatory)	FOLFOX-6	48		early phase 1 nasking: none	unknown
NCT03812523	comparing lorcaserin versus duloxetine for the treatment of chemotherapy-induced peripheral neuropathy	lorcaserin (R-HT2c receptor antagonist FDA-approved weight loss drug) Duloxetine	**OXP**	50	2019-04-04	phase 2 PP: treatment masking: triple	unknown
NCT04690283[961]	Yiqi Wenjing prescriptions preventive efficacy of OIPN clinical trial	traditional Chinese medicine	mFOLFOX6 or FOLFOX4 or XELOX	360	2020-12-30	phase 3	unknown
NCT05291286	BXQ-350 pharmacokinetic/pharmacodynamic study in cancer patients	BXQ-350 (antineoplastic agent, saposin C, human lysosomal protein, and phospholipid dioleoylphosphatidyl-serine (DOPS)		21	2024-08-28	early phase 1 PP: supportive care	active, not recruiting

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Table 21. continued

identifier	title	drug	chemotherapy	number of patients	last updated	study design[a]	status
						masking: quadruple	
NCT04137107	duloxetine to prevent OIPN in patients with stage II–III CRC	duloxetine	**OXP**	220	2024-07-31	phase 2–3 PP: supportive care IM: sequential assignment	active, not recruiting
NCT02808624[962]	L-carnosine prophylactic effect on **OXP** induced peripheral neuropathy in GIT cancer patients	L-carnosine	FOLFOX-6	65	2017-04-24	phase 1–2 masking: none	completed
NCT05510856	comparative clinical study evaluating the possible efficacy of duloxetine, gabapentin and lacosamide on OIPN in cancer patients	duloxetine or gabapentin or lacosamide	FOLFOX-4	93	2024-11-22	phase 4 masking: double	completed
NCT00112996	α-lipoic acid in preventing peripheral neuropathy in patients receiving chemotherapy for cancer	α-lipoic acid		244	2014-04-08	phase 3 PP: supportive care masking: triple	completed
NCT03254394[963]	lidocaine for **OXP**-induced neuropathy	lidocaine	mFOLFOX6	26	2022-03-09	phase 1–2 masking: quadruple	completed
NCT05254639[964]	Donepezil for **OXP**-induced neuropathy peripheral neuropathy: proof of concept study	Donepezil (acetylcholinesterase inhibitor use for Alzheimer's disease)		77	2024-04-05	phase 2 PP: treatment masking: quadruple	completed
NCT01450163[965]	evaluate the efficacy and safety of pregabalin in prevention, reduction of **OXP**-induced painful neuropathy	pregabalin	FLOX	200	2017-05-09	phase 3 masking: quadruple	completed
NCT01775449[105]	prevention of **OXP**-induced neuropathic pain by a specific diet	polyamine deprived diet, polydol (oral alimentation without polyamines)	FOLFOX4	80	2017-07-11	phase 3	completed

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Table 21. continued

identifier	title	drug	chemotherapy	number of patients	last updated	study design[a]	status
						masking: single	
NCT01611155 (MC11C4NCI-2012-00318) [966]	venlafaxine in preventing chronic **OXP**-induced neuropathy in patients receiving combination chemotherapy	venlafaxine (Effexor)	FOLFOX ([m] FOLFOX6 or FOLFOX4)	50	2019-09-26	NA PP: supportive care	completed
NCT02792842[967]	exploratory study of ART-123 for the prevention of cancer treatment related symptoms in patients with postoperative stage II/III colon cancer	ART-123 (thrombomodulin α)	mFOLFOX6	79	2024-04-04	phase 2	completed
NCT01523574[968]	vitamin E for OIPN prophylaxis	vitamin E	FLOX, FOLFOX, XELOX	38	2012-02-01	phase 2 masking: quadruple	completed
NCT01099449[969]	calcium gluconate and magnesium sulfate in preventing neurotoxicity in patients with colon cancer or rectal cancer receiving **OXP**-based combination chemotherapy	Ca/Mg	FOLFOX	362	2022-11-03	phase 3 PP: supportive care	completed
NCT00058071[970]	amifostine in treating peripheral neuropathy in patients who have received chemotherapy for cancer	Amifostine	Pt-based chemotherapy	100	2013-07-09	phase 3 PP: supportive care	completed
NCT02251977[971]	effect of GM1 in prevention of **OXP** induced neurotoxicity in stage II/ III CRC	monosialotetrahexosylganglioside (GM1)	mFOLFOX6 or XELOX	196		phase 3 masking: quadruple	completed
NCT04034355[972]	preventive treatment of **OXP** induced peripheral neuropathy in adjuvant CRC	PledOx (Calmangafodipir)	mFOLFOX6	301	2022-01-26	phase 3 masking: triple	terminated
NCT03654729[973]	preventive treatment of **OXP** induced peripheral neuropathy in metastatic CRC (POLAR-M)	PledOx (Calmangafodipir)	mFOLFOX6	291	2021-12-17	phase 3 masking: triple	terminated (clinical hold)
NCT05251727	assess safety and tolerability of ART-123 + FOLFOX + Bevacizumab in metastatic CRC patients	ART-123 (thrombomodulin alfa)	leucovorin/5-fluorouracil/OXP and bevacizumab	77	2024-08-19	phase 1	terminated (Business decision)

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Table 21. continued

identifier	title	drug	chemotherapy	number of patients	last updated	study design[a]	status
						masking: quadruple	
NCT00603577[974]	role of xaliproden on recovery rate from severe neuropathy in patients who have completed adjuvant chemotherapy With **OXP**-based regimens	Xaliproden		102	2016-05-05	phase 3 PP: treatment	terminated (dvt of product discontinued)
NCT02560740	a study of the efficacy and safety of perox quench on the prevention of **OXP** treatment induced neuropathy	PerOx Quench		9	2016-12-14	NA	terminated (subjects' not-well compliance)
NCT04282590	a study to investigate the safety and efficacy of TRK-750 for the treatment of patients with CIPN (Chopin study)	TRK-750		0	2022-03-15	phase 2 PP: treatment IM: crossover assignment masking: triple	withdrawn (COVID-19)
NCT04205071	Lorcaserin in treating chemotherapy-induced peripheral neuropathy in patients with stage I–IV gastrointestinal or breast cancer	Lorcaserin		0	2021-01-19	phase 1 PP: treatment A: N/A IM: single group assignment masking: none	withdrawn (PI decision)
NCT04492436	a trial measuring ART-123 ability to prevent sensory neuropathy in unresectable mCRC subjects w/**OXP**-based chemo	ART-123 (thrombomodulin alfa)	chemotherapy	0	2022-02-18	phase 2 masking: quadruple	withdrawn (change in study design)
NCT03722680[975]	effectiveness assessment of Riluzole in the prevention of **OXP**-induced peripheral neuropathy	Riluzole	simplified FOLFOX4	80	2024-11-04	masking: quadruple	suspended (lack of treatment, sponsor decision)

[a]Note: unless otherwise indicated: primary purpose (PP), prevention; allocation (A), randomized; interventional model (IM), parallel assignment; masking (M), double.

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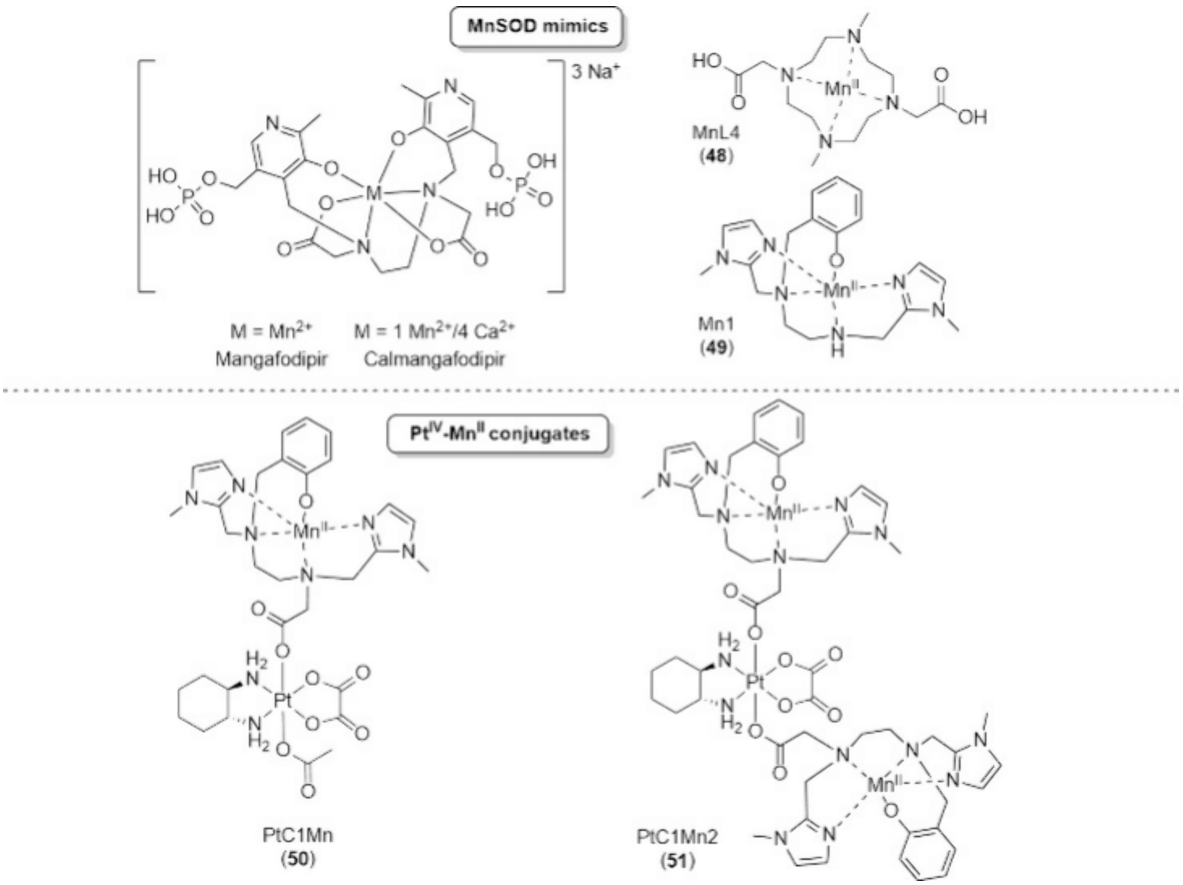

Figure 22. Chemical structures of MnSOD mimics **mangafodipir** and **Mn1** derivatives (top) and **OXP**-Pt(IV) conjugates of MnSOD mimics (bottom).

that have surfaced support their roles in promoting anticancer immunity. For instance, several Pt(II) complexes (e.g., **OXP**, **Pt-NHC**, **PlatinER**, and **PT-112**) have been found to activate the TIME as immunogenic cell death (ICD) inducers effective against CRC.

Recent research has focused on developing Pt(IV) prodrugs which are designed to be more stable and less toxic compared to their Pt(II) counterparts. These prodrugs can be reduced in the cancer cell to release the active drug, potentially targeting tumors more effectively while reducing damage to healthy cells. New strategies involve designing Pt(IV) complexes that not only deliver the cytotoxic Pt but also release additional therapeutic agents (e.g., inhibitors of specific cancer-promoting pathways) upon reduction. Researchers are also exploring new Pt complexes with modified ligands to increase efficacy, reduce toxicity, and overcome resistance. These new analogs are designed to have better pharmacokinetic properties and target specific cancer cell mechanisms. This multiaction approach aims to enhance anticancer efficacy and reduce resistance.

In addition, the Pt(IV) platform extends the potential application of immunomodulatory Pt(II) anticancer agents by adding pro-inflammatory payloads that can reverse the immunosuppressive TIME or compliment and enhance the immunological effects of the Pt(II) active core. Therefore, chemo-immunotherapeutic Pt(II) and Pt(IV) complexes appear to be promising candidates in targeting immunologically "cold" tumors that are inherently resistant to immunotherapy, such as pMMR/MSS or dMMR/MSI-Low CRC.

Advances have also been made in developing nanoparticles and other delivery systems that encapsulate Pt drugs to improve their selectivity for cancer cells. These systems can exploit the EPR effect in tumors or utilize targeting ligands to direct the drugs specifically to cancer cells. Moreover, combining Pt-based drugs with other treatments, such as immunotherapies or targeted therapies, is being explored to overcome resistance and improve efficacy. For instance, combining **OXP** with immune checkpoint inhibitors (ICIs) is under investigation to enhance immune response against tumors such as lung, head and neck cancers. With regards to the latter, traditional chemotherapy works by targeting rapidly dividing cells, which include cancer cells. It generally lacks specificity, affecting both cancerous and healthy cells, which leads to side effects. Immunotherapies instead enhance the immune system to recognize and destroy cancer cells in a more targeted approach. Hence, while chemotherapy remains the standard treatment for many types of CRC, particularly in the adjuvant and metastatic settings, immunotherapy has shown to be particularly effective in dMMR/MSI-High CRCs. For these subtypes, immunotherapy can lead to durable responses and potentially better outcomes, with side effects that are no longer associated with the intrinsic toxicity of the compounds, but rather to immune activation (e.g., skin rashes, diarrhea, fatigue etc.). Nonetheless, Pt-based drugs remain suitable (and more affordable!) for a broad range of CRC patients, including those with stable disease and various molecular profiles. On the other hand, immunotherapy has the potential to lead to long-term remission in specific subsets of patients (particularly those with

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specific genetic markers like MSI-High or dMMR). Hence, future research should focus on expanding the use of immunotherapy to a broader range of CRC patients, including those with MSS CRC tumors. This will involve combining immunotherapy with other treatments like chemotherapy, targeted therapies, or radiation to improve efficacy.

While developing new therapeutic modalities that could address the shortcoming of Pt drugs, it is also imperative to address some of the crucial challenges of current treatments: specifically for CRC, a key priority would be to overcome oxaliplatin-induced peripheral neuropathy (OIPN). Possible approaches could include reducing the **OXP** dose or altering the treatment schedule to mitigate the severity of OIPN without significantly compromising efficacy, as well as coadministering neuroprotective agents such as calcium (Ca) and magnesium (Mg) infusions to reduce acute neurotoxicity. More recently, glutamate modulators like riluzole have shown a promising role by modulating neuronal excitability, and even vitamin E and glutathione proved to be beneficial by reducing the oxidative stress associated with OIPN. In addition, compounds with central effects, including antidepressants (duloxetine and venlafaxine) and antiepileptic drugs such as gabapentin seem to help alleviate neuropathic pain and improve quality of life for patients with OIPN. Emerging strategies have also been explored by our team, including SOD mimetics that reduce oxidative damage to nerves.[956,998] Alternative approaches, such as gene therapy, acupuncture and physical therapy hold some promise, too. Overall, overcoming OIPN requires a multifaceted approach involving preventive strategies, symptomatic treatments, and ongoing research to develop more effective therapies. The goal is to maintain the efficacy of Pt drugs in treating CRC while minimizing its impact on patients' quality of life.

Very recently, several biomarkers have been studied to predict the response to Pt-based chemotherapy in CRC. These biomarkers can help tailor treatments to improve efficacy and reduce unnecessary toxicity. Among these, the DNA MMR status and MSI are of particular relevance as dMMR/MSI-High CRC tumors are known to have a better prognosis and are typically more sensitive to immunotherapy, but their response to Pt-based chemotherapy can vary. Alternatively, ERCC1 is involved in the NER pathway, which repairs Pt-induced DNA damage. High levels of ERCC1 expression may be associated with resistance to Pt-based chemotherapy, as the cells can effectively repair the DNA cross-links caused by the drugs.

Alternatively, specific miRNAs have been linked to chemotherapy resistance or sensitivity. They can modulate gene expression post-transcriptionally and have been explored as potential biomarkers for predicting response to Pt-based drugs. Lastly, tumor-infiltrating lymphocytes[245] and immune markers, in which certain immune signatures may correlate with better responses to Pt-based treatments, represent a valuable tool to predict treatment responses. While these biomarkers show promise, it is important to note that their clinical application requires further validation through research and clinical trials. Only the successful integration of these biomarkers into clinical practice, combined with personalized treatment plans, will be able to improve the overall outcomes for CRC patients.

Taken all these aspects into consideration, the underlying question is whether we can develop a novel Pt complex that on the one hand will retain the efficacy of the current Pt drugs and on the other, will overcome their shortcomings, particularly toxicities and acquired resistance. This is quite a formidable challenge and, despite many attempts and several clinical trials of Pt(IV) complexes, the FDA has not approved a new Pt drug for over two decades. So how should chemists go about designing such novel drugs? The structure−activity relationship (SAR) rules for developing square planar Pt(II) anticancer drugs, described in 1973, resulted in seven Pt(II) drugs approved for use in humans. Conversely, because no Pt(IV) complexes were approved for use in humans, to date, there is no roadmap for the design of octahedral Pt(IV) prodrugs. The Pt(IV) complexes that entered the clinical trials were all unpretentious prodrugs of the Pt(II) complexes with simple axial ligands that were devoid of any anticancer activity. They were not multitargeting prodrugs. Nevertheless, there are some important take-home lessons for the design of novel drugs that can be obtained from the clinical trials of satraplatin, which completed phase III. **Satraplatin** was administered orally, attesting to the stability and inertness of Pt(IV) compared with more reactive Pt(II) drugs that are administered intravenously. A logical starting point to treat CRC would be to design and prepare dual-action Pt(IV) derivatives of **OXP** with 5-FU, irinotecan or capecitabine that are coadministered with **OXP** in the clinic. Designing reduction-resistant, light-activated dual-action Pt(IV) derivatives of **OXP**, is another attractive approach. Photo- or radioactivable Pt complexes are designed to become activated only upon exposure to light or radiation, which can trigger the release of the Pt species directly at the tumor site. There is ongoing research to optimize these complexes in terms of their activation wavelengths, tissue penetration, and stability. Advances in this area could lead to more effective and safer chemotherapy options.

Taken together, the ability to enhance efficacy by incorporating the appropriate bioactive ligands in the axial positions of Pt(IV) complexes, coupled with reduced side effects, makes multiaction Pt(IV) prodrugs good candidates for treating CRC. Pt(IV) prodrugs can also be modified to make them amenable to encapsulation in drug delivery systems, which should further enhance their efficacy and reduce toxicities. While promising, these technologies are still in the experimental stages and they are not yet ready to replace small molecule Pt agents entirely. Instead, they may complement existing therapies as part of a broader arsenal of treatment options. Hence, it is unlikely that small molecule Pt agents will be completely replaced in the near future. Instead, they may be integrated with new therapies to enhance outcomes. For instance, combining Pt drugs with immunotherapy or using them as part of a multimodal approach involving photo- or radio-activation could improve efficacy. The future likely involves a more personalized approach, where treatment is tailored based on the genetic and molecular makeup of the tumor, as well as patient-specific factors. This could mean selecting the most appropriate therapy or combination of therapies for each individual patient. Advances in personalized medicine and combination therapies are expected to shape the future landscape of CRC treatment. Until then, Pt-based chemotherapy remains a cornerstone of treatment for most CRC patients.

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AUTHOR INFORMATION

Corresponding Authors

Giorgia Pastorin − *Department of Pharmacy and Pharmaceutical Sciences, Faculty of Science, National University of Singapore, Singapore 117544, Singapore; Integrative Sciences and Engineering Programme, NUS Graduate School, National University of Singapore, Singapore 119077, Singapore;* orcid.org/0000-0002-2568-0626; Phone: +6565161876; Email: phapg@nus.edu.sg

Wee Han Ang − *Department of Chemistry, Faculty of Science, National University of Singapore, Singapore 117544, Singapore; Integrative Sciences and Engineering Programme, NUS Graduate School, National University of Singapore, Singapore 119077, Singapore*; Phone: +6565165131; Email: ang.weehan@nus.edu.sg

Authors

Jia Xuan Kee − *Department of Chemistry, Faculty of Science, National University of Singapore, Singapore 117544, Singapore;* orcid.org/0009-0006-8008-2924

Jia Ning Nicolette Yau − *Department of Pharmacy and Pharmaceutical Sciences, Faculty of Science, National University of Singapore, Singapore 117544, Singapore; Integrative Sciences and Engineering Programme, NUS Graduate School, National University of Singapore, Singapore 119077, Singapore;* orcid.org/0000-0002-5478-001X

Ram Pravin Kumar Muthuramalingam − *Department of Pharmacy and Pharmaceutical Sciences, Faculty of Science, National University of Singapore, Singapore 117544, Singapore;* orcid.org/0000-0002-2120-7620

Xinyi Wang − *Department of Pharmacy and Pharmaceutical Sciences, Faculty of Science, National University of Singapore, Singapore 117544, Singapore*

Wei Heng Chng − *Department of Pharmacy and Pharmaceutical Sciences, Faculty of Science, National University of Singapore, Singapore 117544, Singapore*

Alvaro Lopez-Sanchez − *Laboratoire Chimie Physique et Chimie du Vivant CPCV, Département de Chimie, Ecole Normale Supérieure, PSL University, Sorbonne Université, CNRS, 75005 Paris, France;* orcid.org/0000-0003-1528-9938

Kevin Kuang Wei Tay − *Gleneagles Hospital, Singapore 228510, Singapore; Mount Elizabeth Hospital, Singapore 258500, Singapore*

Lih-Wen Deng − *Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117596, Singapore; NUS Center for Cancer Research, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117599, Singapore*

Dan Gibson − *Institute for Drug Research, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem 91120, Israel;* orcid.org/0000-0002-1631-4018

Helene C. Bertrand − *Laboratoire Chimie Physique et Chimie du Vivant CPCV, Département de Chimie, Ecole Normale Supérieure, PSL University, Sorbonne Université, CNRS, 75005 Paris, France;* orcid.org/0000-0002-3841-022X

Giulia Adriani − *Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (A*STAR), Singapore 138648, Singapore; Department of Biomedical Engineering, National University of Singapore, Singapore 117583, Republic of Singapore; Lee Kong Chian School of Medicine (LKC Medicine), Nanyang Technological University, Singapore 308232, Singapore;* orcid.org/0000-0002-7505-1668

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.chemrev.5c00041

Author Contributions

‡J.X.K. and J.N.N.Y. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Jia Xuan Kee graduated with a B.Sc. (Hons) in Chemistry from the National University of Singapore (NUS) with the Singapore National Institute of Chemistry Prize (2020). He is currently a Ph.D. candidate in Prof. Wee Han Ang's lab at NUS under the President's Graduate Fellowship, focusing on the development of novel Pt(IV) prodrugs and the elucidation of their mechanisms of actions.

Jia Ning Nicolette Yau received her Ph.D. in Pharmacy in 2024 from the National University of Singapore. She is currently an internal editor of the Multidisciplinary Digital Publishing Institute.

Ram Pravin Kumar Muthuramalingam is a Ph.D. candidate at the Department of Pharmacy, National University of Singapore. His research focuses on platinum(IV) prodrugs and biohybrid nanocarriers for targeted cancer therapy. He holds a Master's in Pharmacology and a Bachelor's in Pharmacy from The Tamil Nadu Dr. M.G.R. Medical University, India. With prior experience as a Research Assistant at NUS and Lecturer at PSG College of Pharmacy, his expertise spans in vivo pharmacology, extracellular vesicle-based delivery systems, and molecular techniques. He has coauthored several interdisciplinary publications in nanomedicine, oncology, and drug delivery, and is a recipient of the NUS-IRP scholarship.

Xinyi Wang graduated from Ocean University of China with a bachelor's degree in biotechnology. Currently she is a Ph.D. student in Prof. Giorgia Pastorin's lab, focusing on developing patient-derived immune-competent *in vitro* 3D models for colorectal cancer drug screening.

Wei Heng Chng received his Ph.D. from the National University of Singapore (NUS) in 2023. As a research fellow at NUS Department of Pharmacy and Pharmaceutical Sciences, he conducted research on the use of nanodrug delivery systems to deliver various drugs, including platinum-based compounds, to treat colorectal cancer. His area of research also includes the use of various nanoparticles, such as extracellular vesicles, for both therapeutic and drug delivery purposes.

Alvaro Lopez-Sanchez earned his Ph.D. in Molecular Chemistry in 2024 from Sorbonne Université, under the supervision of Dr. Hélène Bertrand. He is currently an American Cancer Society Postdoctoral Fellow in the laboratory of Prof. María Contel at Brooklyn College, The City University of New York. His research focuses on the design and biological evaluation of transition metal complexes as chemotherapeutic agents.

Dr. Kevin Kuang Wei Tay is a Senior Consultant Medical Oncologist at the Oncocare Cancer Center since 2013. He currently holds American Board certifications for the practice of Internal Medicine and Medical Oncology. Dr. Tay completed his medical oncology training in 2009 at the National Cancer Institute (NCI) in USA. Upon returning to Singapore, Dr. Tay joined the Department of

Medical Oncology at National Cancer Center in Singapore from 2010 to 2013. He was part of the core translational research group at the National Cancer Center Singapore, that was awarded the prestigious center grant by the National Medical Research Council of Singapore. His main interests are in hematological cancers (lymphoma and multiple myeloma), women's cancers (breast and gynaecological cancers), and rare cancers such as sarcomas and melanomas.

Lih-Wen Deng received her Ph.D. in Biochemistry from the University of Cambridge in 2000 and completed her postdoctoral training at Harvard University. She joined the National University of Singapore in 2004 and is currently an Associate Professor at the Yong Loo Lin School of Medicine at National University of Singapore. She also serves as Co-Research Director at the NUS Centre for Cancer Research and is an affiliated member of the National University Cancer Institute of Singapore. Her research focuses on genomic instability, therapy resistance, and targeting cancer metabolism and the tumor microenvironment for therapeutic intervention.

Dan Gibson received his Ph.D. in Chemistry in 1983 from the Hebrew University of Jerusalem (Israel). From 1983 to 1986, he was a postdoctoral fellow with Prof. S. Lippard at MIT. He joined the Department of Medicinal Chemistry in the School of Pharmacy in the Faculty of Medicine at the Hebrew University of Jerusalem in 1986. He retired as a full professor of Medicinal Chemistry in 2020. His research focuses on the development of novel multitargeting platinum based anticancer agents.

Helene C. Bertrand received her Ph.D. in Molecular Chemistry at Sorbonne University in 2008 with Dr. M.-P. Teulade Fichou and D. Fichou. She carried out her postdoctoral research at the School of Pharmacy (University College London) with G. Wells between 2009 and 2011 and at the Institut des Sciences Moléculaires in Bordeaux (2011) with S. Quideau, before joining Sorbonne University as an Assistant Professor in 2011. She is currently a Full Professor at Sorbonne University at the Laboratoire Chimie Physique et Chimie du Vivant (https://ens-bic.fr/). Her research interests lie in the field of bioinorganic medicinal chemistry and include chemotherapy-induced peripheral neuropathy.

Giulia Adriani received her Ph.D. in Engineering of Machines under the Biomedical and Biomechanical Engineering program from the Polytechnic of Milan, Bari, and Turin (Italy) in 2012, with research at The Methodist Hospital Research Institute in Houston (USA). She held positions at the National University of Singapore (NUS) and the Singapore−MIT Alliance for Research and Technology. Currently, she is Principal Scientist at the Singapore Immunology Network, by the Agency for Science, Technology, and Research, with adjunct appointments at NUS and Nanyang Technological University. Her research includes advanced human-relevant microphysiological systems to model the tumor microenvironment and improve cancer therapy screening.

Wee Han Ang received his B.Sc. (Hons) from Imperial College of London (1995) and Ph.D. from Ecole Polytechnique Federale de Lausanne (2007) under the supervision of Prof. Paul Dyson. After a postdoctoral stint with Prof. Stephan Lippard at Massachusetts Institute of Technology, he joined the National University of Singapore (2009) as a principal investigator and has been there since. His current research focusses on the investigation and development of metal complexes, particularly those based on platinum group metals, for chemo- and immunotherapy.

Giorgia Pastorin received her Ph.D. in Medicinal Chemistry in 2004 from the University of Trieste (Italy). After being a research fellow at the Centre National De La Recherche Scientifique (CNRS) in Strasbourg (France), she joined the Department of Pharmacy at the National University of Singapore in 2006 as Assistant Professor. She is currently a Full Professor and Head of the Department of Pharmacy and Pharmaceutical Sciences in the same university. Her area of research includes platinum-based prodrugs and their release through innovative drug delivery systems. For the work performed by her BioNanoTechnology team, she has received both National and International awards.

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ABBREVIATIONS

2D, two-dimensional; 5-FU, 5-fluorouracil; ABC, adenosine triphosphate-binding cassette; ABCC1, ATP-binding cassette, subfamily C, member 1; ADCC, antibody-dependent cell-mediated cytotoxicity; AKI, acute kidney injury; AKT, protein kinase B; ANXA1, annexin A1; AOM, azoxymethane; APMM, adenomatous polyposis mouse models; ATP, adenosine triphosphate; ATRA, all-*trans*-retinoic acid; Bap31, B-cell receptor-associated protein 31; Bcl, B-cell lymphoma; CACS15, cancer susceptibility candidate 15; CAF, cancer-associated fibroblast; CAIX, carbonic anhydroase IX; CAR, chimeric antigen receptor; CBP, carboplatin; CBR, clinical benefit rate; CCAL, colorectal cancer-associated long non-coding ribonucleic acid; CCL, chemokine (C-C motif) ligand; CDP, cisplatin; CDX, cell derived xenograft model; CIM, chemical induced model; CIN, chromosomal instability; CIPN, chemotherapy-induced peripheral neuropathy; circRNA, circular ribonucleic acid; CMS, consensus molecular subtype; CNA, copy number aberration; COX-2, cyclooxygenase-2; CPP, cell-penetrating peptide; CRC, colorectal cancer; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9; CRS, cytoreduction surgery; CRT, calreticulin; CSC, cancer stem cell; CT, computed tomography; CTC, circulating tumor cell; CTLA-4, cytotoxic T-lymphocyte associated protein 4; CTPP, (3-carboxypropyl)triphenylphosphonium; CTR1, copper transporter 1; CTR2, copper transporter 2; CXCL, chemokine (C-X-C motif) ligand; DACH, diaminocyclohexane; DACHEX, diamino-4-cyclohexane; DAMP, damage-associated molecular pattern; DC, dendritic cell; DCA, dichloroacetic acid; DCR, disease control rate; DEG, differentially expressed gene; DIM, diet induced model; DMH, 1,3-dimethylhydrazine; dMMR, deficient DNA mismatch repair; DNA, deoxyribonucleic acid; DNMT, DNA methyltransferase; DOR, duration of response; DOX, doxorubicin; DRG, dorsal root ganglia; DSS, dextran sulfate sodium; EC, endothelial cell; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; eIF2α, eukaryotic initiation factor 2 alpha; EMT, epithelial−mesenchymal transition; EORTC,

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European Organization for Research and Treatment of Cancer; EPR, enhanced permeability and retention; ER, endoplasmic reticulum; ERCC1, excision repair cross-complementation group 1; ERCC2, excision repair cross-complementation group 2; ERK, extracellular signal-regulated kinase; FPP, formyl peptide receptor; FXYD3, FXYD domain containing ion transport regulator 3; GALS4, galectin 4; GATA6, GATA-binding factor 6; GEAMM, genetically engineered autochthonous mouse model; GEMM, genetically engineered mice model; GEO, Gene Expression Omnibus; GST, glutathione S-transferase; HA, hyaluronic acid; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; HDI, human development index; HDM, histone demethylase; HIF-1α, hypoxia-inducible factor 1-alpha; HIPEC, hyperthermic intraperitoneal perioperative chemotherapy; HMGA2, high-mobility group AT-hook 2; HMGB1, high-mobility group box 1; HMT, histone methyltransferase; HNPCC, hereditary nonpolyposis colon cancer mouse model; HSP, heat-shock protein; IG, intragastric; IM, intramuscular; IP, intraperitoneal; IR, intrarectal; IV, intravenous; IC_{50}, half-maximal inhibitory concentration; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; IDO, indoleamine 2,3-dioxygenase; IENF, intraepidermal nerve fiber; IFN-γ, interferon gamma; IL, interleukin; ILC, innate lymphoid cell; iNOS, inducible nitric oxide synthase; IPC, intraperitoneal chemotherapy; LAG-3, lymphocyte-activation gene 3; LARC, locally advanced rectal cancer; lncRNA, long noncoding ribonucleic acid; LRP1, low-density lipoprotein receptor-related protein 1; LRR, local recurrence rate; LRRC8, leucine-rich repeat containing 8; LS, Lynch syndrome; LV, leucovorin; MAM, methylazoxymethanol; MAPK, mitogen-activated protein kinase; MATE1, multidrug and toxin extrusion protein 1, efflux; mCRC, metastatic colorectal cancer; MDS, myelodysplastic syndrome; MDSC, myeloid-derived suppressor cell; MHC-I, peptide-major histocompatibility class I; MHC-II, peptide-major histocompatibility class II; miRNA, microribonucleic acid; MMP-9, matrix metalloproteinase-9; MMR, DNA mismatch repair; Mn, manganese; MNNG, *N*-methyl-*N*-nitro-*N*-nitrosoguanidine; MNU, methyl nitroso urea; MPS, microphysiological system; MRI, magnetic resonance imaging; mRNA, messenger ribonucleic acid; MRP2, multidrug resistance-associated protein 2; MSI, microsatellite instability; MSS, microsatellite stable; MTD, maximum tolerated dose; mtDNA, mitochondria DNA; mTOR, mammalian target of rapamycin; NCCN, National Comprehensive Cancer Network; NER, nucleotide excision repair; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cell; NHC, *N*-heterocyclic carbene; NHP, nonhuman primate; NIR, near-infrared; NK, natural killer; NOD, nonobese diabetic; Nrf2, nuclear factor-erythroid 2-related factor 2; NSAID, nonsteroidal anti-inflammatory drug; OG, oral gavage; OA, octanoic acid; OCT, organic cation transporter; OCTN1, organic cation transporter novel type 1; OCTN2, organic cation transporter novel type 2; OIPN, oxaliplatin-induced peripheral neuropathy; ORR, objective response rate; OS, overall survival; OXP, oxaliplatin; PARP-1, poly(ADP-ribose) polymerase 1; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PDCD4, programmed cell death 4; PDK, pyruvate dehydrogenase kinase; PDO, patient derived organoid; PDOX, patient derived organoid xenograft model; PDX, patient derived xenograft model; PERK, PKR-like endoplasmic reticulum kinase; PET, positron emission tomography; PFS, progression-free survival; PhB, 4-phenylbutyric acid; PhIP, 2-amino-1-methyl-6-phenylimidazo(4,5-*b*)pyridine; PI3K, phosphatidylinositol-3-kinase; PIPAC, pressurised intraperitoneal aerosol chemotherapy; PKCα, protein kinase C alpha; PKM2, pyruvate kinase M2; PLD4, phospholipase D4; PM, peritoneal metastasis; PMEPA1, prostate transmembrane protein androgen induced 1; pMMR, proficient deoxyribose nucleic acid mismatch repair; PNS, peripheral nervous system; POA, 2-(2-propynyl)octanoic acid; PROTAC, proteolysis targeting chimera; PRR, rattern-recognition receptor; Pt, platinum; RCD, regulated cell death; RFS, relapse-free survival; RiBi, ribosomal biogenesis; RNA, rinobucleic acid; RNA-Seq, ribonucleic acid sequencing; RNS, reactive nitrogen species; ROC, receiver operating characteristic; ROS, reactive oxygen species; rRNA, ribosomal ribonucleic acid; SC, subcetaneous; SAHA, suberoylanilide hydroxamic acid; SC-RT, short-course radiotherapy; SCID, severe combined immunodeficient; SLC22, solute carrier family 22; SNAP, sensible nerve action potential amplitude; SOD, superoxide dismutase; SOX, SRY-box; SPINK3, serine protease inhibitor Kazal type 3; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TCGA, The Cancer Genome Atlas Program; TEC, tumor-associated endothelial cell; Tfh, follicular helper T cell; TGF-β, transforming growth factor-β; TGM2, transglutaminase 2; Th, helper T cell; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; TIME, tumor immune microenvironment; TLS, tertiary lymphoid structure; TMB, tumor mutational burden; TME, tumor microenvironment; TNBS, 2,4,6-trinitrobenzenesulfonic acid; TNF-α, tumor necrosis factor alpha; TPD, targeted protein degradation; TPP, triphenylphosphonium; TRAAK, TWIK-related arachidonic acid-stimulated K^+ channel; Treg, regulatory T cell; TREK-1, TWIK-related K+ channel 1; TREM2, triggering receptor expressed on myeloid cells 2; TRP, transcient receptor potential; TRPA1, transcient receptor potential ankyrin 1; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanilloid 1; TUG1, taurine upregulated gene 1; USP49, ubiquitin-specific peptidase 49; USP7, ubiquitin-specific protease 7; VEGF, vascular endothelial growth factor; VPA, valproic acid; VRAC, volume-regulated anion channel; WBSCR22, Williams–Beuren syndrome chromosomal region 22; XDP, xeroderma pigmentosum group d; XRCC1, X-ray cross-complementing group 1

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