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Modulating undruggable targets to overcome cancer therapy resistance

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ABSTRACT

Many cancer patients frequently fail to respond to anti-cancer treatment due to therapy resistance which is the major obstacle towards curative cancer treatment. Therefore, identification of the molecular mechanisms underlying resistance is of paramount clinical and economic importance. The advent of targeted therapies based on a molecular understanding of cancer could serve as a model for strategies to overcome drug resistance. Accordingly, the identification and validation of proteins critically involved in resistance mechanisms represent a path towards innovative therapeutic strategies to improve the clinical outcome of cancer patients. In this review, we discuss emerging targets, small molecule therapeutics and drug delivery strategies to overcome therapy resistance. We focus on rational treatment strategies based on transcription factors, pseudokinases, nuclear export receptors and immunogenic cell death strategy. Historically, unliganded transcription factors and pseudokinases were considered undruggable while blocking the nuclear export *e.g.*, through inhibition of the nuclear export receptor CRM1 was predicted as highly toxic. Recent success inhibiting Gli-1, HIF-1α, HIF-2α and reactivating the tumor suppressor transcription factors p53 and FOXO illustrates the feasibility and power of this targeting approach. Similarly, progress has been made in modulating the activity of pseudokinase proteins implicated in therapy resistance including members of the Tribbles protein family. On the other hand, the recent clinical approval of Selinexor, a specific inhibitor of CRM-1, a protein that mediates the transport of cargos with leucine-rich nuclear export signals and known to be a driver of drug resistance, represents the proof-of-concept for inhibiting the nuclear export as a feasible strategy to overcome therapy resistance.

The ever-growing capacity to target resistance mechanisms with judiciously selected small molecules, some of which are being formulated within smart nanoparticles, will pave the way towards the improvement of the clinical outcome and realize the full potential of targeted therapies and immunotherapies.

Introduction

Our understanding of the molecular basis of cancer has increased exponentially in the past 4 decades beginning with the discovery of oncogenes and tumor suppressor genes in the 1980s (Capdeville et al., 2002; Hanahan and Weinberg, 2011, 2000) and started to result in novel targeted treatments in 2001 with the FDA approval of Imatinib (Capdeville et al., 2002). The molecular groundwork required to discover new anti-cancer medicines nowadays is significantly higher than in the case of the traditional chemotherapeutic drugs which were sometimes identified empirically without pre-existing knowledge of their molecular mechanism of action (Drews, 2000; Ferreira et al., 2015; Link, 2018) whereas others were rationally based (Assaraf, 2007; Gonen and Assaraf, 2012; Assaraf et al., 2014). The latest achievements of this new knowledge-based drug discovery paradigm are the immune checkpoint inhibitors (ICIs) which markedly improved the clinical outcome of several solid tumors (Diesendruck and Benhar, 2017; Kon and Benhar, 2019; Leonetti et al., 2019; Dal Bo, 2020). However, the efficacy of virtually all these novel cancer therapies is limited by pre-existing or acquired drug resistance and, as a consequence, tumor relapse. Somewhat surprisingly, recent research revealed that chemotherapeutics, targeted and immunotherapeutic agents share many of the molecular

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mechanisms underlying drug resistance despite their distinct modes of action (Housman et al., 2014). The strategy to discover new medicines based on in-depth knowledge of the disease has just begun to impact the clinic in the last decade but it is safe to say that it is highly successful. In parallel, drug development technologies evolved to a point that enables targeting proteins that were historically considered as intractable (Dang et al., 2017). Ras proteins represent a paradigmatic example of this process. Ras proteins were identified as oncogenes in the early 1980s and despite more than three decades of intensive effort to find specific inhibitors, they were perceived as undruggable targets. Cumulative scientific and technological advances led to the development of allele-specific covalent inhibitors of KRAS (Moore et al., 2020) and to the approval of Sotorasib for its clinical use to treat patients with non-small-cell lung cancer (NSCLC) (Hong et al., 2020). Accordingly, the molecular understanding of the mechanisms driving resistance will guide the path to develop means to overcome adaptive responses of the tumor and reap the full benefit of anti-cancer therapies.

Therapy resistance in cancer

Anticancer drug resistance has been recently declared as the biggest challenge in cancer treatment (Kozar et al., 2019) and as such surmounting such multidrug resistance modalities is of paramount importance in curative cancer therapeutics (Kathawala et al., 2015; Iwasaki et al., 1989; Narayanan et al., 2020; Wang et al., 2021). Many cancer patients fail to respond to therapy or develop resistance after initial treatment. If cancer cells become unresponsive to treatments, the patient relapses and eventually dies, generally due to metastasis. Therapy resistant tumors kill most cancer patients. Therapy resistance is known to occur for most of cancer types and for all modes of treatments including conventional chemotherapeutic drugs as well as for modern targeted drugs or ICIs (Groenendijk and Bernards, 2014). The treatment of advanced melanoma represents a paradigmatic example for this observation. For decades, treatment of metastatic melanoma included high-dose interleukin-2 or the alkylating chemotherapeutic drug dacarbazine (DTIC) ((Ugurel et al., 2013), associated with response rates between 10–20 % and severe side effects (Gray-Schopfer et al., 2007). The analysis of genomic alterations revealed that the kinase ERK is hyperactivated by mutated BRAF or mutated NRAS in up to 90 % of human melanoma (Akbani et al., 2015; Gray-Schopfer et al., 2007). These findings provided the rational to develop specific inhibitors of mutant BRAF and MEK, the kinase that acts downstream of BRAF to activate ERK, as therapeutics for advanced melanoma (Henriques et al., 2018). On the other hand, Nobel-prize awarded research on the regulation of T cell activity paved the way to develop ICIs aimed at unleashing anti-tumor T cell responses (Sharma and Allison, 2015). The BRAF inhibitors vemurafenib or dabrafenib and the MEK inhibitors trametinib, cobimetinib and binimetinib approved for the treatment of advanced melanomas with mutated BRAF, significantly improved the clinical success of the treatment (Luke et al., 2017; Luke and Hodi, 2013). The ICIs ipilimumab, nivolumab or pembrolizumab are widely used for the treatment of different tumor types nowadays, but due to its high mutational burden and consequently the presence of immunogenic tumor antigens, they have been particularly successful in melanoma (Davis et al., 2018). While both, small molecule inhibitors targeting components of the MAPK pathway and ICIs have yielded unprecedented clinical responses, most patients fail to respond or acquired resistance to these treatments (Kozar et al., 2019). As drug resistance limits the efficacy of all of these treatments *via* intrinsic or acquired resistance modalities, deciphering and targeting the underlying molecular mechanisms is of pivotal importance to reap the full benefit of anti-cancer therapeutics and develop combinatory and synergistic strategies.

Mechanisms of therapy resistance

Resistance mechanisms can operate within a cancer cell independent of other cells in a cell autonomous fashion (Gottesman, 2002). Conversely, non-cell-autonomous resistance mechanisms depend on the interaction of different cells (Ferreira et al., 2017). While intrinsic resistance refers to the innate capacity of cancer cells to escape therapy due to pre-existing factors, acquired resistance develops during the treatment to which the tumor was initially susceptible. These different types of resistance mechanisms operate in melanoma malignancies and most other cancer entities promoting a highly unresponsive phenotype. Therapeutic challenges drive tumor cells to exploit both genetic and phenotypic adaptive responses. Therapy resistant might occur upstream, downstream and at the level of the therapeutic drug target (Holohan et al., 2013). Before a drug can exert a therapeutic effect, it has to reach its cellular target in the cancer cells or in the tumor microenvironment. Poor absorption, rapid metabolism or low tissue penetration might prevent a systemically administered drug to be at the side of action in the required concentration. This is especially true for lipophilic molecules which include most organic molecule drugs. Moreover, some drugs need to be metabolically processed to be active against cancer cells and therefore, inefficient activation can also limit the efficiency of drug treatment (Kaur et al., 2020; Aghi et al., 2000; Rochat, 2005; Townsend and Tew, 2003). As these pharmacokinetic host factors, decreased cellular influx *via* impaired influx transporters (Giovannetti et al., 2017; Rothem et al., 2002; Rothem et al., 2003, 2004; Ifergan et al., 2003; Kaufman, 2006) and increased efflux through multidrug efflux pumps, such as the ATP-binding cassette (ABC) superfamily (Borst et al., 1999; Choi, 2005; Li et al., 2016; Wang et al., 2021) represent therapy resistance mechanisms that operate upstream of the therapeutic drug target. Drug action also depends on the presence of the target and therefore alterations in the expression level (Assaraf et al., 1989, 1992) or mutation of the target can render a cancer cell unresponsive to treatment (O'Hare et al., 2007). But even when the drug reaches its cellular target at a sufficient concentration, the cancer cell might still escape the therapeutic effects reactivating the same signalling pathway further downstream or activating alternative signal cascades (Paraiso et al., 2011). In addition, enhanced DNA damage repair (Lord and Ashworth, 2012) and dysfunctional apoptosis signalling (Mohammad et al., 2015) (Shahar and Larisch, 2020; Levin et al., 2021; Gao et al., 2021) can limit the efficacy of anti-cancer drugs. Several of these resistance mechanisms might co-exist in different cells that comprise a tumor. Consequently, tumor heterogeneity has been considered as a key driver of therapy resistance representing an ideal scenario to adapt to selective pressure arising from anti-cancer drug treatment. In particular, cancer stem cells (CSC), a small subpopulation of cells within the tumor with the ability to self-renew, differentiate and promote tumor growth have been suggested as the main source of drug resistance (Dean et al., 2005; Shibue and Weinberg, 2017; Erin et al., 2020; Assaraf et al., 2019; Sharifzad et al., 2019; Koren and Fuchs, 2016). CSCs are thought to be resistant to chemotherapy through the increased expression of drug efflux pumps, enhanced DNA repair and attenuated apoptotic signalling and therefore responsible for tumor relapse. CSCs have been identified and characterized in almost all solid tumors and their capacity to dynamically switch between CSC and non-CSC states has been shown recently (de Sousa e Melo et al., 2017d; Shimokawa et al., 2017). This remarkable phenotypic plasticity suggests that drug resistance mechanisms do not need to be hardwired into the cancer genome, as phenotypic adaptation can mediate tumor cell survival. The capability to adapt through the transition between different cellular phenotypes increases the likelihood of cell survival upon anti-cancer therapy. Another phenotypic transition state is the epithelial-to-mesenchymal transition (EMT) which is closely associated with therapy resistance (Shibue and Weinberg, 2017; Erin et al., 2020; Santoro et al., 2017). EMT is an evolutionary conserved reversible cellular program by which epithelial cells transiently adopt migratory and invasive properties typical of mesenchymal cells during

embryonic development and wound healing, immune evasion and metastasis. Similar to the above-mentioned pharmacokinetic host factors, the tumor microenvironment can provide non-cell autonomous instructive signals to neighboring tumor cells promoting their survival under treatment pressure (Lu et al., 2012; Straussman et al., 2012; Trédan et al., 2007).

In this review, we aimed to focus on molecular target classes that have been shown to play a role in cancer drug resistance but were considered as undruggable such as transcription factors and pseudokinases or their inhibition was predicted to be associated with significant toxicity as the export receptor CRM1. Finally, among the cancer immunotherapy approaches recently introduced into the clinics and showing remarkable therapeutic potentials, it was discovered that some of the conventional chemotherapeutics could also exert immunomodulatory activities which might be exploited to synergistically enhance their anticancer effects *via* the so-called "immunogenic cell death" (ICD) (Terenzi et al., 2016). We will show through significant examples how this strategy can also be employed to overcome multidrug resistance (MDR).

Emerging targets to overcome therapy resistance

In the knowledge-based drug discovery paradigm, target identification and target validation are the most innovative and riskiest steps of the drug development process and a major reason for drug attrition (Benson et al., 2006; Link, 2018). There is no reason to believe that this is any different in targeting therapy resistance. The molecular mechanisms outlined above reveal several obvious targets to be considered. As several adaptive responses to drug treatment rely on modifications of the drug target itself or reactivation of the same pathway further downstream or even redundant parallel signaling cascades, the targets to eradicate drug resistant tumors include many components of known oncogenic signaling pathways such as Her2, EGFR, PI3K, AKT, mTOR, Ras, Raf, Mek, Wnt and β-catenin. Inhibition of ATP-binding cassette (ABC) transporters responsible for enhanced drug efflux and MDR (Choi, 2005), the detoxification enzymes Glutathione S-transferases (GSTs) (Zhang et al., 2014) and uridine diphospho-glucuronosyltransferase (UGT) (Guillemette, 2003; Rowland et al., 2013) as well as the monooxygenase cytochrome P450s responsible for the activation of several prodrugs, are considered as possible therapeutic strategies to overcome therapy resistance. Targeting components of signaling pathways such as the Notch, Wnt or the Hedgehog pathways involved in the maintenance of stem cell properties have been proposed as a therapeutic modality to eliminate the CSC subpopulation within the tumor as a source of resistance and relapse. Recently, some emerging targets in cancer drug resistance have been discussed (Kumar et al., 2019).

In the current review article, we focus on several therapeutic targets that have emerged in recent years and represent promising options to surmount therapy resistance in cancer. These targets including pseudokinases, unliganded transcription factors and nuclear export receptors (Fig. 1) have been traditionally considered as difficult to target or "undruggable" as they might lack binding pockets or experimental procedures to measure their functional activity. However, progress in technologies relevant for drug development such as structure-based drug design, proteolysis targeting chimeras (PROTACs) or hydrophobic tagging (HyT) (Bondeson et al., 2015; Burslem and Crews, 2020; Neklesa et al., 2011), however, have changed our concept of druggability (Gashaw et al., 2011; Hajduk et al., 2005) and increased the availability of difficult targets. PROTAC and HyT represent approaches that take advantage of the cellular protein destruction machinery and promote small-molecule-induced proteolysis of specific protein targets. PROTACs are bifunctional molecules that connect a ligand that binds to a protein of interest to an E3 ubiquitin ligase-recruiting ligand. Similarly, HyT is based on a target-specific ligand coupled to a hydrophobic moiety that mimics a partially unfolded protein and elicits an unfolded protein response to remove the target protein (Cromm and Crews, 2017). For both methods, ligands that specifically bind to the target protein are essential starting points for PROTAC and HyT based drug development. Therefore, recent progress in targeting technologies have rendered undruggable proteins into promising therapeutic targets to overcome drug resistance. In addition, we discuss immunogenic cell death as a strategy to eliminate therapy resistant cancer cells.

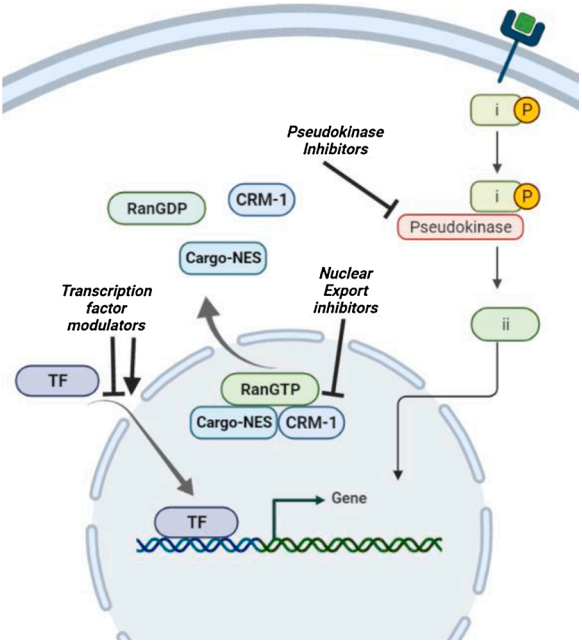

Fig. 1. Overview of the emerging therapeutic targets discussed in the current review and their functional role in cellular signaling.

Small molecule therapeutics

Targeting transcription factors to eradicate drug resistant tumors

Cancer cells respond to drug treatment with the expression of genes that are involved in drug resistance. This transcriptional response is orchestrated by multiple transcription factors (Kohno et al., 2005). Most transcription factors were long time considered as "undruggable" targets (Bushweller, 2019). Transcription factors regulate gene expression programs involved in several diseases including cancer, neurodegenerative diseases, and diabetes. Indeed, transcription factors have been estimated to account for 20 % of oncogenes in cancer (Vaquerizas et al., 2009). Targeting transcription factors has become an attractive strategy for the development of "personalized" therapy based on specific managing of the transcriptome. Transcription factors are activated or inhibited during several cancer treatments, leading inhibition of cancer cell growth or cell death, with significant impact on the therapeutic treatment. Current strategies to modulate the activity of transcription factors with small molecules or peptide-mimetics may be viewed as falling into four major strategies (Hagenbuchner and Ausserlechner, 2016): (1) inhibition of protein/protein interactions; (2) direct targeting of the binding of the transcription factor to DNA; (3) targeting chromatin remodeling/epigenetic reader proteins, and (4) blockage of protein/DNA-binding. Transcription factors may modulate gene transcription, either directly or indirectly, by forming complexes with identical or different transcription factor proteins: only these homo- or heterodimers can recognize the specific DNA sequences. Typical examples are the transcription factors p53 which associates with DNA as a tetramer, MYC/MAX dimers, STAT3 and HIF1. FOXO transcription factors may cooperate with SMAD, p53 or MYC and in part modulate target gene promoters that lack typical FOXO sites. These protein–protein interactions have attracted medicinal chemists on p53 as a target for

the design of specific inhibitors (Stiewe and Haran, 2018a; Cao et al., 2020; Frezza and Martins, 2012).

The p53 tumor suppressor regulates the transcription of target genes, responds to DNA damage, leading to cell cycle arrest, apoptosis or senescence (Horn and Vousden, 2007; Stiewe ad Haran, 2018). p53 is frequently inactivated, due to mutations, in various cancers (Petitjean et al., 2007), and its reactivation has become a robust challenge in designing anticancer drugs (Martins et al., 2006; Vazquez et al., 2008; Stiewe ad Haran, 2018; Cao et al., 2020; Frezza and Martins, 2012). Modulation of p53-mediated transcription (Yoon et al., 2002) depends on the abundance of p53 that correlates with the following biological outputs including apoptosis (Clarke et al., 1994). The tumor suppressor gene TP53 lies on the short arm of chromosome 17 (17p13.1) (Isobe et al., 1986). TP53 encodes for the p53 protein (43.7 kDa, 393 amino acids). The main role of p53 is to prevent alterations in the genome and to manage the expression of target genes; on the contrary, mutations in p53 play a key role in cancer formation (Mantovani et al., 2019; Stiewe and Haran, 2018a). Mutations in TP53 often reduce the expression of the p53 protein or may cause the production of inactive variants of p53, hence affecting its tumor suppressor activity. The antitumor agent doxorubicin (**1**) (Chart 1), a member of the anthracycline family, behaves as a topoisomerase II inhibitor, breaking the DNA at single or double strand level, thus interfering with DNA replication and transcription (Yang et al., 2014). The administration of doxorubicin would be responsible for the emergence of MDR due to loss of function p53 mutations and overexpression of MDR efflux pumps (Robey et al., 2018; Wijdeven et al., 2016). Drug resistance against doxorubicin and paclitaxel demonstrated that the cross-resistance between both drugs was induced by introduction of the p53 R248Q mutation in hepatocellular Hep3B cells. Such mutations could prompt the up-regulation of P-gp (ABCB1) expression (Chan and Lung, 2004). On the other hand, the p53 R273H mutation would be responsible for cross-resistance to doxorubicin and methotrexate by down-regulating procaspase-3 expression (Wong et al., 2007). Cisplatin (**2**) oxaliplatin and DACH-Pt the 3 platin derivatives, widely used as first line anticancer agents, are alkylating agents that interfere with DNA replication, linking primarily to guanine, causing apoptosis and failure of DNA repair (Chen and Chang, 2019). p53 plays a key role, managing multiple factors responsible for the development of cisplatin drug resistance. After an initial high response to platinum agents, the majority of cancer patients eventually exhibit the emergence of alterations in TP53 that is associated with the development of drug resistance (Chen and Chang, 2019; Singh et al., 2019). The nuclear transcription factor erythroid 2-related factor 2 (Nrf2) is downregulated by wild type p53 and upregulated by mutated p53 (Lisek et al., 2018). The expression by p53 of the apoptosis regulators BCL2, BCL2-like 1 (Bcl-XL), and hemeoxygenase 1 (HO-1), by regulating Nrf2, results in Nrf2-mediated resistance to cisplatin. This resistance could be reduced by BCL2 antagonists (Tung et al., 2015). The antimetabolite 5-fluorouracil (5-FU, **3**) behaves as an inhibitor of thymidylate synthase, inducing cancer cell death by blocking dTMP biosynthesis. The intrinsic (primary) and acquired (secondary) resistance to 5-FU results from various mechanisms of drug resistance, including, among other, loss of function mutations in p53 (Deng et al., 2017; Marjaneh et al., 2019). Paclitaxel (**4**) is a first line anticancer agent which acts as a β-tubulin stabilizer causing the disruption of spindle formation and mitosis. Paclitaxel resistance of lung NSCLC cells developed upon over-activation of the p38 MAPK-EGFR signaling pathway, could be overcome by inhibiting the activity of p38 MAPK or EGFR through the induced degradation of MDM2 and consequent p53 stabilization (Park et al., 2016).

The transcription factor Nuclear Factor-kappa B (NF-κB) is directly involved in innate and adaptive immune functions and plays as a key

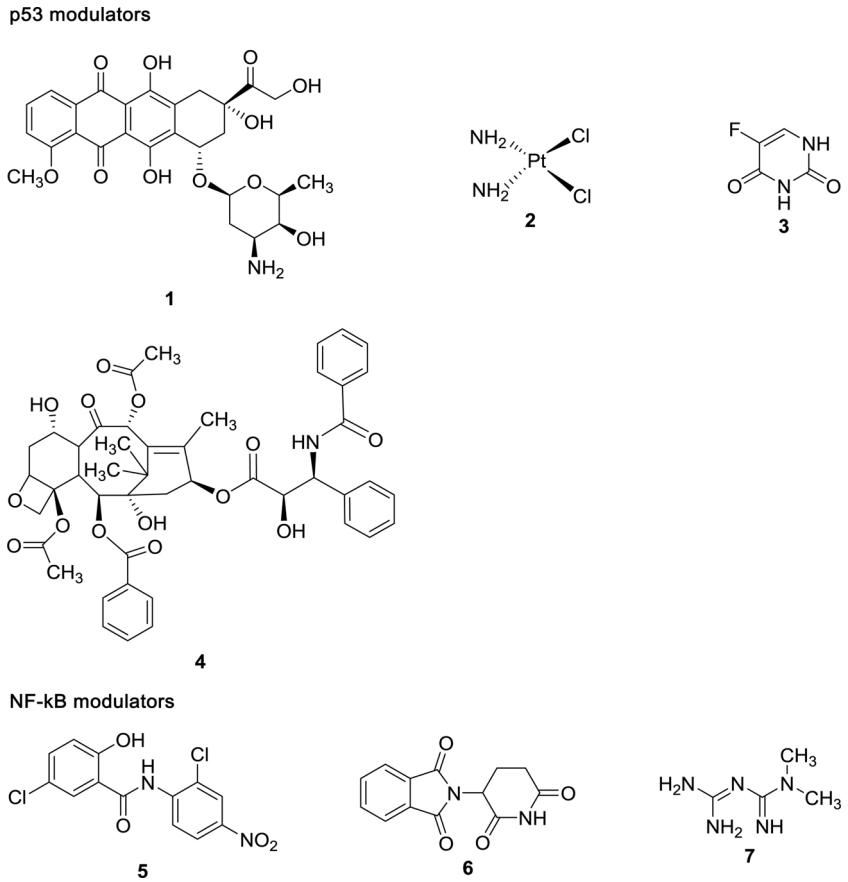

Chart 1. Chemical structures of p53 (**1-4**) and NF-kB modulators (**5-7**).

mediator of inflammatory responses. NF-κB prompts the expression of several pro-inflammatory genes, including those encoding for cytokines and chemokines, and also participates in inflammasome regulation. Moreover,

NF-κB regulates the survival, activation and differentiation of innate immune cells and inflammatory T cells (Liu et al., 2017). Upon activation, the NF-κB transcription factor translocases to the nucleus and initiates transcription of various genes including inflammatory cytokines or results in activation of cell apoptosis or necrosis pathways (Van Quickelberghe et al., 2018). Tumor Necrosis Factor (TNF) is a major inflammatory cytokine activating the transcription factor NF-κB, but TNF is also able to induce apoptosis and necroptosis (Cabal-Hierro and Lazo, 2012; Wertz, 2014). TNF signaling is required to maintain tissue homeostasis and prevents inflammatory pathology (Brenner et al., 2015). Most inflammatory effects of TNF are mediated through the TNF Receptor 1 (TNFR1), and inhibition of TNFR1-NF-κB signaling pathway, as seen with TNF antagonists, possesses beneficial effects in autoimmune and inflammatory syndromes (Puimège et al., 2014; Varfolomeev and Vucic, 2018; Workman and Habelhah, 2013). TNF is expressed as a transmembrane protein (memTNF) that can be processed into a soluble form (sTNF) (Locksley et al., 2001). Protein-protein interactions of the sTNF/TNFR1 type are typically considered undruggable not only because of the high affinity of the protein pairs, but also because of the perception that only a broad distribution of poorly contoured interactions exists across the binding partners (Lang et al., 2016; Xu et al., 2017). Thanks to recent developments in modern drug discovery, an increasing number of crystal structures and homology models are available, thereby allowing application of computational tools to quantify protein interfaces (Tian et al., 2018). The introduction of small molecules to influence the protein-protein interaction of TNF-α with its receptor has been reviewed (Richmond et al., 2015; Song and Buchwald, 2015). Resistance to drugs that target DNA derives from DNA-repair proteins as a result of NO nitrosation and denaturation of several proteins by NO that are involved in DNA repair, leading to an enhanced drug cytotoxicity (Kim et al., 2017). Furthermore, NO also regulates the chemosensitivity of cancer cells by nitrosylating, and therefore inhibiting, the NF-κB pathway (Huerta-Yepez et al., 2013). Several studies performed on a variety of MDR cell lines showed that high NO levels can overcome drug resistance. For example, NO was capable of reversing cisplatin resistance in tumor cells as the downregulation of NF-κB/Snail/YY1/ RKIP circuitry after epithelial-to-mesenchymal transition (Bonavida et al., 2008; Bonavida and Baritaki, 2011; Wottrich et al., 2017; Hays and Bonavida, 2019). The inducible nitric oxide synthase (iNOS) produces endogenous NO that may also reverse the MDR phenotype. Silencing RhoA, a small GTPase of the Rho family, activates the NF-κB pathway and iNOs activity; the consequent accumulation of doxorubicin in both HT29 and HT29-dx colon cancer cells leads to the surmounting of drug resistance (De Boo et al., 2009).

The repurposing of drugs has been applied in several chemotherapeutic strategies to treat human health disorders such as cancer (Antoszczak et al., 2020; Armando et al., 2020; Dinić et al., 2020; Kopecka et al., 2020; Mudduluru, 2016). The antiparasitic drug niclosamide (**5**) was shown to act as a multitargeted drug against both cancer cells and cancer stem cells (CSCs). Niclosamide inhibited the Wnt/β-catenin, mTORC1, STAT3, NF-κB, NFAT and Notch signaling pathways, targeting glutathione biosynthesis and mitochondria in cancer cells and, thereby induced cell growth inhibition and apoptosis (Hamdoun et al., 2017; Li et al., 2014).

The antitumor activity of thalidomide (**6**) was initially attributed to its potential antiangiogenic effects through the inhibition of both basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) (D'Amato et al., 1994). Further evidence demonstrated that thalidomide also suppressed the production/expression of proangiogenic factors, such as TNF-α, NF-κB, IGF-1, IL-6, IL-8, PGE2, chemokine receptor type 4 (CXCR4) and stromal cell-derived factor-1 (SDF-1) (Bouyssou et al., 2016). Thalidomide displays immunomodulatory and anti-inflammatory activity due to its capability to modulate the production and activity of several cytokines, including interleukins IL-6, IL-10, IL-12, IL-1β, and TNF-α. It was demonstrated that thalidomide downregulates NFκB, a key transcription factor for TNF and other cytokines, by suppressing the activity of IκB kinase (Keifer et al., 2001). These modulatory effects affect the antiangiogenic and anti-proliferative effects of thalidomide.

Antidiabetic drugs have also been investigated for potential anticancer activity (Klil-Drori et al., 2017). The effect on MDR mediated by the diabetic drug metformin (**7**), was attributed to the modulation of ATM/LKB1/AMPK signaling, which regulates downstream proteins, such as mTOR, MAPKs and transcription factors including NF-κB, FOXO and p53 (Kamarudin et al., 2019). The anti-cancer properties of metformin rely on its capacity to decrease ATP production and modulate mitochondrial activity (Saraei et al., 2019; Vial et al., 2019). In mouse models of triple-negative breast cancer (TNBC), metformin inhibits CSCs (Hirsch et al., 2009). Metformin is capable to reverse the MDR phenotype in a variety of cancer models. Metformin decreased the DOX-induced expression of P-gp/MDR1/ABCB1 and HIF-1α in MCF7-DOX breast cancer cells and, similarly, in a breast cancer xenograft model derived from a patient tumor (Davies et al., 2017). In a model of drug resistant MCF7-FU cells, metformin reversed MDR through AMPK pathway activation and inhibition of EMT (Qu et al., 2014). Drug combination of DOX and metformin co-encapsulated in nanoparticles showed increased accumulation of DOX and cytotoxicity in MCF-7 cells which was superior to the free drug combination (Shafiei-Irannejad et al., 2018).

HIF is an oxygen-sensitive transcription factor that plays a key role in adaptation of cells to oxygen stress by regulating transcriptional programs involving cell viability, metabolism, proliferation, and angiogenesis (Olenyuk et al., 2004). Orchestration of these key programs generally results in human diseases such as cancer, anemia, ischemia and hypoxic-ischemic diseases (Higashijima et al., 2013; Jain et al., 2018). Overexpression of the HIF pathway has been correlated to invasive cancer and resistance to radiation in patients with advanced tumors (Masoud and Li, 2015). On the other hand, hypoxia and HIF pathway have been correlated to a large proportion in solid tumors (Warfel and El-Deiry, 2014). Small molecules interfering with the HIF pathway have become a promising approach to treat a variety of solid tumors, such as breast cancer, lung cancer, multiple myeloma, and renal cell carcinoma. Such compounds may include degradation promoters of the HIF-1α protein, disrupters of the of the HIF-α/ HIF-β interaction, and, most importantly, blockers of the HIF-α/p300 interaction (Li et al., 2019; Wei et al., 2018).Distal hypoxia response elements (HREs) regulate HIF target genes such as erythropoietin (Orlando et al., 2020). HIF consists of two subunits: HIF-α, made by three isoforms, HIF-1α, HIF-2α, and HIF-3α (Ema et al., 1997; Gu et al., 1998) is regulated by oxygen, as well as HIF-β (only one subtype) that is constitutively expressed. HIF-1, consisting of HIF-1α and HIF-β subunits, is the most extensively investigated HIF isoform (Li et al., 2019). HIF-1α overexpression in cancer progression has been correlated with NF-kB pathway, accumulation of p53 (Sang et al., 2002), and recruitment of the transcriptional HIF-1 co-activator p300 (Semenza, 2002). Inhibition of HIF-1 and inhibition of HIF-2 are the principal reported strategies to down-regulate the HIF pathway. LW6 (**8**, Chart 2) (Boovanahalli et al., 2007) and PX-478 (**9**) (Schwartz et al., 2010) behave as indirect regulators through suppression of hypoxia-induced transcriptional activity and modulate of HIF-α translation and stabilization leading to a reduction in HIF protein levels. In search for selective HIF-1α inhibitors focused on the protein-protein interaction between HIF-1α C-terminal transactivation domain (C-TAD) and the co-transcription factor p300/coactivator protein CBP (Arany et al., 1996; Hay et al., 2014). Chetomin (**10**) (Kung et al., 2004) and the KCN1 derivative **11** (Yin et al., 2012) exert direct inhibition of the HIF-1α/p300 interaction with no apparent effect on the intracellular levels of HIF-1α. Both **10** and **11** showed little toxicity *in vivo*, indicating that they have potential as drugs for the treatment of vascular disease

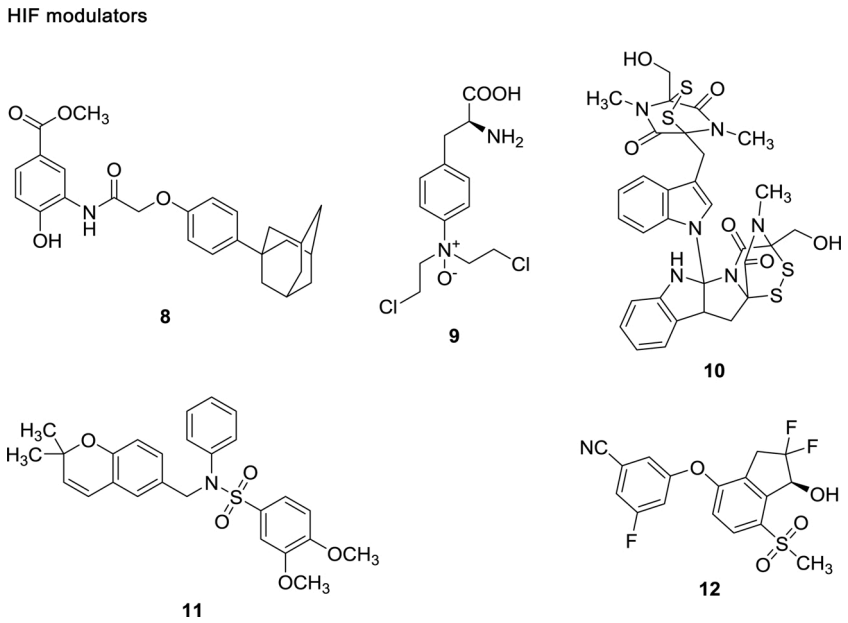

Chart 2. Chemical structures of HIF modulators (**8-12**).

and cancers. The development of selective HIF-1α and HIF-2α inhibitors was hampered by the fact that these subtypes share 48 % amino acid homology. The potent and selective HIF-2α inhibitor PT2385 (**12**) showed appreciable activity in phase I clinical studies, paving the way for the development of a new class of HIF-2α-specific inhibitors (Wehn et al., 2018).

The Wnt signaling pathway is one of the majors signaling mechanisms regulating tissue homeostasis and has been found to be deregulated in a variety of human diseases. Nuclear DNA-binding TCF/LEF proteins and their transcriptional co-activator β-catenin represent key components of the canonical Wnt signaling pathway (Hrckulak et al., 2016). In the absence of Wnt ligand, β-catenin is phosphorylated in the cytoplasm through the destruction complex, and then ubiquitinated by β-transducing repeats-containing proteins (β-TrCP) and degraded by the proteasome or, alternatively, phosphorylated by the destruction complex and followed by β-TrCP ubiquitination. In the presence of a Wnt ligand, after interaction with frizzled receptor, β-catenin translocates into the nucleus, where it activates the expression of TCF/LEF target genes (Clevers et al., 2014; Clevers and Nusse, 2012). The aberrant deregulation of β-catenin in tumor cells boosts the transcription of many oncogenes, resulting in the development of various cancers, such as colon cancer, hepatocellular carcinoma, pancreatic cancer, lung cancer

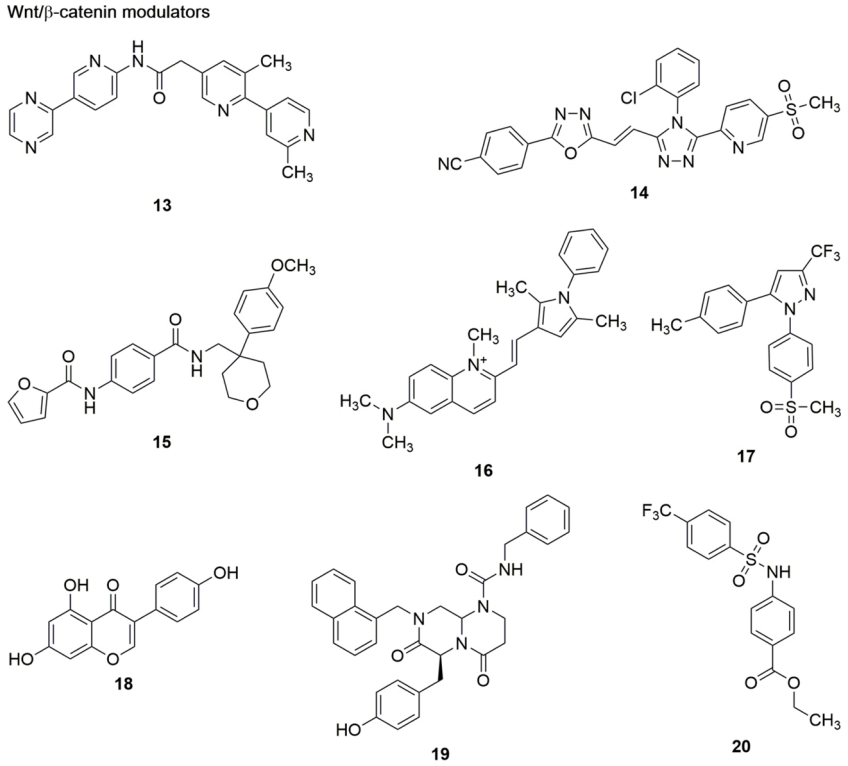

Chart 3. Chemical structures of Wnt/β-catenin modulators (**13-20**).

and ovarian cancer (Shang et al., 2017). Anticancer drugs that interfere with the Wnt/β-catenin signaling pathway have not been approved so far. Known inhibitors targeting Wnt ligand, its receptor, β-catenin subcellular localization or β-catenin transcriptional complex are viewed as falling into five main classes: small molecules, peptides, antibodies, RNA interference and natural compounds (Shang et al., 2017).

LGK974 (**13**) (Chart 3) is a potent small-molecule Wnt ligand and receptor inhibitor of membrane-bound o-acyltransferases-porcupine (PORCN) that showed efficacy in multiple tumor models, such as murine breast cancer and human head and neck squamous cell carcinoma *in vivo* (Liu et al., 2013). Some antibodies targeting Wnt ligands, such as OMP-18R5, OTSA-101 and OMP-54F28, have been selected for clinical trials (Sebio et al., 2014). G007-LK (**14**) and JW55 (**15**) are tankyrase 1/2 inhibitors (Huang et al., 2009) in preclinical research which show stabilizer activity on Axin2, thus causing an increase of β-catenin degradation (Lau et al., 2013; Waaler et al., 2012). Pyrvinium (**16**) is a small molecule that activates the phosphorylation of β-catenin by casein kinase 1 (CK1) to promote its degradation (Thorne et al., 2010). The non-steroidal anti-inflammatory drug (NSAID) celecoxib (**17**) reduces the auto-phosphorylation of c-Met, a tyrosine kinase receptor, resulting in GSK3β activation and β-catenin degradation (Tuynman et al., 2008). The phytoestrogen genistein (**18**) was found to promote β-catenin degradation through activation of GSK3β (Su and Simmen, 2009). Small peptide derivatives proved to hamper the protein–protein interaction of β-catenin with specific import chaperones in some tumor types, *i.e.*, by disruption of the BCL9/ β-catenin complex, resulting in reduced accumulation of β-catenin in the nucleus and suppression of its transcriptional activity (Takada et al., 2012). ICG-001 (**19**) is a small molecule targeting β-catenin-cyclic AMP response element-binding protein (CBP) (but not β-catenin-p300) capable of downregulating the expression of β-catenin-TCF-responsive genes (Emami et al., 2004). TSAH-BCL9 (**19**) is an α helix stabilizer that disassembles native β-catenin-BCL9 complexes and selectively suppresses Wnt transcription, leading to an antitumor effect (Takada et al., 2012, p. 9). Ethyl 4-((4-(trifluoromethyl) phenyl)sulfonamido)benzoate (compound **20**) inhibits the effect on Wnt reporter with an IC_{50} value of 7.0 μM, significantly reduces c-MYC levels, inhibits HCT116 colon cancer cell growth (IC_{50} = 20.2 μM), does not violate Lipinski and Veber rules, and shows predicted Caco-2 and MDCK cell permeability Papp>500 nms^{-1} (Di Magno et al., 2020). Transcription factors belonging to the Gli family contain DNA binding zinc finger domains and represent the transcriptional effectors of Hedgehog (Hh) signaling pathway. Constitutive activation of Hh has been shown in several cancer types and is a driver of chemoresistance (Scales and de Sauvage, 2009). Major progress has been made in the development of Hh pathway inhibitors for the treatment of patients with cancer (Amakye et al., 2013). In particular, Infante et al. identified Glabrescione B as the first small molecule binding to Gli1 zinc finger and impairing Gli1 activity by interfering with its interaction with DNA (Infante et al., 2015).

FOXO proteins are transcription factors that are involved in numerous physiological processes and in various pathological conditions, including cardiovascular disease, cancer, diabetes and chronic neurological diseases (Calissi et al., 2021). FOXO transcription factors bind to the promoter regions of a wide range of target genes (Link and Fernandez-Marcos, 2017) and play a key role in the regulation of cellular homeostasis. Their activity is regulated through post-translational modifications (PTMs) such as phosphorylation, acetylation, ubiquitylation and methylation (Eijkelenboom and Burgering, 2013; van der Horst and Burgering, 2007v). The PI3K/AKT signaling pathway represents the major inhibitory input to FOXO activity, while FOXO proteins are activated by cellular stress signaling (Brown and Webb, 2018). FOXO proteins have emerged as longevity genes, in particular FOXO3 (Martins et al., 2016), and are known to be involved in senescence, autophagy, stem cell maintenance and ageing (Calissi et al., 2021 and references therein). FOXO proteins can behave as tumor suppressors and frequently get inactivated in several human tumors (Dansen and Burgering, 2008; Paik et al., 2007). Enzymes regulate FOXO activity mostly *via* post-translational modifications (PTMs). These findings raise the possibilities to modulate FOXO activity as an ideal target to achieve a therapeutic benefit. Large screening programs have been conducted in search for FOXO targeting small molecules to treat several human diseases. Several compounds from different sources, including natural products, synthetic and semi-synthetic or drugs already in use have been evaluated for their capacity to modulate FOXO activities. Such compounds may either maintain, stimulate or inhibit FOXO activity (Hornsveld et al., 2018).

Selinexor (KPT-330, **21**, Chart 4) is a karyopherin chromosome region maintenance-1 (CRM1, also termed XPO1) inhibitor and has been approved for its clinical use to treat patients with multiple myeloma (Ferreira et al., 2020a, p. 1). CRM1 participates in the nuclear export of FOXO1, which finely modulates the effect of **21** and marginally of the combination with cisplatin (Gounder et al., 2016). These findings provide preclinical evidence of potential clinical impact on ovarian carcinoma and highlight the interest in **21**-based combination therapies designed to enhance the cell death of tumor cells. Likely, given the role of CRM1 in the localization of cellular proteins, it could affect the cellular response of ovarian cancer cells to cisplatin and its combination with **21** (Corno et al., 2018).

ETP-45658 (**22**), dactolisib (NVP-BEZ235, **23**) and capivasertib (AZD5363, **24**) increase nuclear localization of FOXO3. Compound **22** is a potent and selective inhibitor of phosphoinositide 3-kinases synthesized after computational and structure-activity relationship studies of a pyrazolopyrimidine scaffold that demonstrated a desired mechanism of action in tumor cell lines and *in vivo* in treated mice (Link et al., 2009). The phosphoinositide 3-kinase (PI3K)/AKT pathway is activated in a variety of solid and non-solid tumors (Vivanco and Sawyers, 2002). Such activation is frequently mediated by mutations in PI3Kα with enhanced production of phosphatidyl 3,4,5-trisphosphate (PIP3) (Zhao and Vogt, 2008), or by mutations/deletions in the tumor suppressor phosphatase and tensin homolog (PTEN). The activated form of AKT phosphorylates several effector molecules including the FOXO transcription factors (Burgering, 2008; Calnan and Brunet, 2008). Upon cell treatment, compound **22** decreased the phosphorylation of AKT at Ser473, of FOXO at Thr32 and of p70S6K at Thr389 in cells after treatment with the compound. It induced the nuclear translocation of FOXO tagged with green fluorescent protein (GFP) with an EC_{50} value of 45 nM, and, consistently, inhibited the PI3K with an IC_{50} of 22 nM. Compound **22** showed anti-proliferative activity in a variety of tumor-derived cell lines, and this activity appeared to be independent on the PI3Kα and PTEN mutational status (Link et al., 2009). Compound **23** is a dual inhibitor of the PI3K and downstream mammalian target of rapamycin (mTOR) that inhibits the activation of the downstream effectors AKT, S6 ribosomal protein, and 4EBP1 in breast cancer cells. Compound **23** inhibited the PI3K/mTOR axis and results in anti-proliferative and antitumor activity in cancer cells with both wild-type and mutated p110-α (Serra et al., 2008). Compound **24** is a potent inhibitor of AKT. Tumor types with PIK3CA mutation, PTEN mutation, or HER2 gene amplification, without coincident RAS mutation, exhibit the highest frequency of response to **24** *in vitro*. Compound **24** has also the potential to overcome resistance or increase the sensitivity to HER2 inhibitors in breast cancer, and greatly sensitizes to docetaxel chemotherapy, resulting in tumor regression *in vivo* (Davies et al., 2012). Very recently, health-promoting compounds have been assessed for their capacity to induce the activity of FOXO3 and the natural occurring alkaloids harmine and piperlongumine were identified as potent activators of FOXO3 nuclear localization (Jimenez et al., 2021).

Several other compounds have been reported to interfere with FOXO activity. For example, tanzawanic acid D (**25**) behaves as a stabilizer of FOXO1 binding to DNA; AS1842856 (**26**) reduced FOXO1 activity by binding directly to the protein; carbenoxolone repressed FOXO3 activity by binding to the FOXO3 DNA binding domain; the proteasome inhibitor bortezomib (velcade) behaves as a FOXO stabilizer. Therefore,

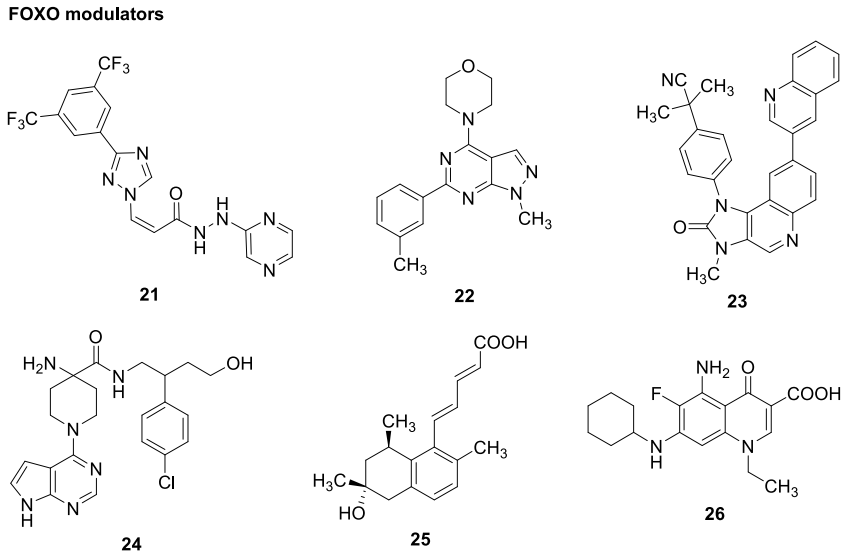

Chart 4. Chemical structures of FOXO modulators (**21-26**).

modulation of FOXO proteins through the design and synthesis of targeted small molecules appears as an attractive approach towards the development of targeted anticancer drugs (Link et al., 2009).

Pseudokinases, an emerging group of druggable targets

There is growing evidence that several kinases possess non-catalytic functions in addition to their catalytic role (Jacobsen and Murphy, 2017; Kung and Jura, 2019, 2016; Shaw et al., 2014). It was predicted from analysis of the human genome that about 10 % of all protein kinases do not play catalytic activity and that they play a role in signaling pathway through different mechanisms (Manning et al., 2002). These kinases bear mutations that render their catalytic site inactive. This family of kinases are called pseudokinases (Kung and Jura, 2019), and, similarly to the other kinases, play key roles in cellular function and signaling, and are found often altered in several diseases (Boudeau et al., 2006; Reiterer et al., 2014).

Most importantly, the nucleotide binding site of pseudokinases was shown to host small molecules with drug-like properties, thus making it an attractive target for drug design (Kung and Jura, 2016). Moreover, several pseudokinases are unable to bind a nucleotide, and lack a binding site for small molecules that are competitive with the ATP (Kung and Jura, 2016). Murphy and co-workers identified four classes of pseudokinases: class 1 of pseudokinases lack the ability to bind traditional ligands, such as nucleotides and metal cations, in their pseudoactive sites (Murphy et al., 2014); class 2 pseudokinases bind nucleotides in the absence of cations, such as Mg^{2+} that enables nucleotide binding to the kinase active site, and are required for ATP coordination and transfer of the phosphate groups (Zheng et al., 1993); several pseudokinases of this group are able to bind to ATP even in the absence of cations, meanwhile the binding to the nucleotide binding site is inhibited in the presence of Mg^{2+} (Bailey et al., 2015; Cui et al., 2017); class 3 pseudokinases bind divalent cations but not nucleotides or ATP-competitive small molecules (Murphy et al., 2014); class 4 include pseudokinases able to bind both nucleotides and divalent cations. These pseudokinases show detectable catalytic activity, but to a lesser extent compared to the fully active kinases (Jura et al., 2009).

TX1-85-1 is a selective Her3 ligand that forms a covalent bond with Cys721 located in the ATP-binding site of Her3. Her3 is recognized as an anti-cancer target but is thought to be 'undruggable' using ATP-competitive small molecules due to the lack of significant kinase activity. Compound TX1-85-1 was manipulated by introducing an adamantane moiety to generate the bivalent ligand TX2-121-1 (**27**, Chart 5

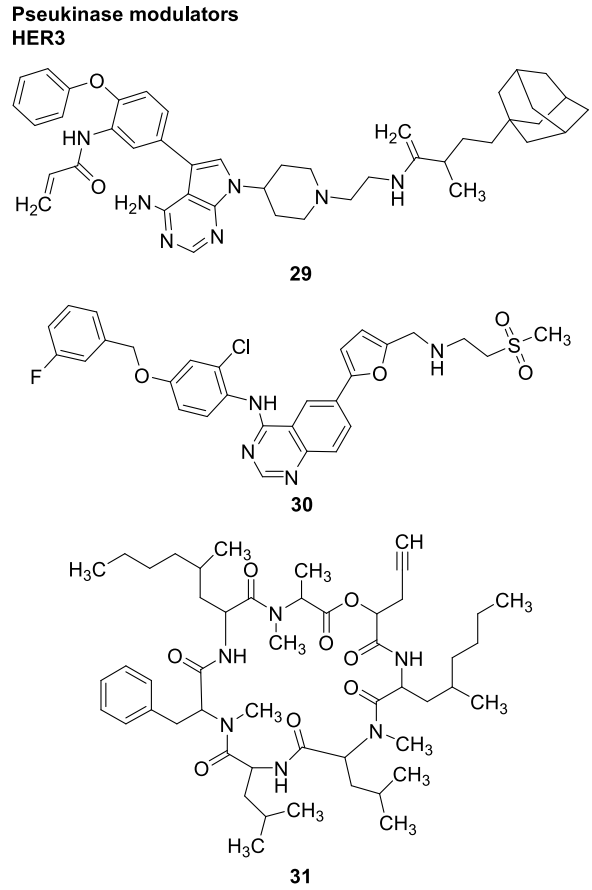

Chart 5. Chemical structures of HER modulators (**29-31**).

). Treatment of cells with TX2-121-1 induced partial degradation of Her3 and interfered with heterodimerization between Her3 with either Her2 or c-Met (Xie et al., 2014). Lapatinib (**28**) is an ATP-competitive inhibitor of HER2 that is able to induce cell proliferation cooperatively with the HER3 ligand neuregulin by promoting atypical HER2-HER3 heterodimerization.

Compound **28** drives the formation of the HER2-HER3 complex by stabilizing a particular HER2 conformer. Formation of these dimers

activates a proliferative outcome as a response to neuregulin (Claus et al., 2018). CT8 (**29**) binds the Sec61 transposon thus preventing the initial translational translocation of the nascent HER3 protein. As a result, HER3 but none of the other HER proteins is degraded. Treatment with **29** suppresses the induction of HER3 during lapatinib treatment in cancers with HER2 gene amplification and increases the apoptotic effects of lapatinib (Ruiz-Saenz et al., 2015).

Kinase suppressor of Ras (KSR), a Ras-mitogen activated protein kinase (MAPK) scaffold that is an early event in many different cancers and a key driver of resistance to targeted therapies, may be allosterically modulated through dimerization with RAF proto-oncogene serine/threonine-protein kinase (RAF). Based on mutations that selectively suppress oncogenic Ras signaling, Dhawan and co-workers developed a class of KSR stabilizers, APS-2-79 (**30**, Chart 6). This compound was able to modulate KSR-dependent MAPK signaling by antagonizing RAF heterodimerization as well as the conformational changes required for phosphorylation and activation of KSR-bound mitogen-activated protein kinase (MEK), and to increase the potency of several MEK inhibitors specifically within Ras-mutant cell lines by antagonizing the release of negative feedback signaling (Dhawan et al., 2016).

ASC24 is a KSR2 inhibitor that, presumably, causes a conformational change in KSR2, mimicking the binding to KSR Arg718 by BRAF. MEK1 alteration leads to its increased phosphorylation consistently with its capacity to disrupt the KSR2(KD) homodimer interface. Thus, a KSR–MEK complex inhibitor and BRAF antagonist could behave analogously to the Ras suppressor: the KSR(R718 H) mutation (Brennan et al., 2011; Statsuk et al., 2008). Hildebrand and co-workers showed that the MLKL pseudokinase domain acts as a latch to restrain the *N*-terminal four-helix bundle (4HB) domain and that unleashing this domain results in formation of a high-molecular-weight, membrane-localized complex and cell death. Cpd 1 (GW806742X, **31**) was reported as a type II kinase inhibitor that reportedly binds to the MLKL pseudokinase domain and prevents necroptosis (Hildebrand et al., 2014). Ma and co-workers measured protein conformational changes using second harmonic generation (SHG) to confirm that **31** is a non-selective type II inhibitor that also inhibits the upstream kinase RIPK1 (Ma et al., 2016). The *R*-enantiomer cpd 4 (**32**) was found to bind selectively to MLKL with KD = 230 nM without binding RIPK1 or RIPK3; its *S*-enantiomer showed a weaker binding to MLKL with KD = 7600 nM. In contrast to Hildebrand and co-workers (Hildebrand et al., 2014), these studies indicated that an ATP-pocket inhibitor of the MLKL pseudokinase domain does not have any impact on the necroptosis pathway. Neither the MLKL selective analog **32** (*R*-enantiomer) nor the truncated versions of **31** with better selectivity against RIPK1 rescued cells from necroptosis (Ma et al., 2016).

The anti VEGF and PDGF ATP-competitive agent sunitinib (**33**) inhibited both RNase L and PKR with IC_{50} values of 1.4 and 0.3 μM, respectively. It had no effect on encephalomyocarditis virus growth in cells lacking both PKR and RNase L. Also, **33** reduced mean survival times from 12 to 6 days in virus-infected WT mice while having no effect on survival of mice lacking both RNase L and PKR (Jha et al., 2011).

Tribbles 2 (TRIB2) is a cancer-associated pseudokinase with a diverse interactome, includes MEK1 and AKT as binding partners. There is substantial evidence that human TRIB2 promotes survival and drug resistance in solid tumors (Ferreira et al., 2021; Mayoral-Varo et al., 2021) and hematological cancers (Stein et al., 2015) and therefore is of interest as a therapeutic target. The TRIB2 destabilizing agent afatinib (**34**) caused rapid TRIB2 degradation in human AML cancer cells (Foulkes et al., 2018) providing the proof of concept for the druggability of the TRIB2 oncoprotein. In addition, harmine and piperlongumine have been shown to induce inverse matched signatures compared to TRIB2-mediated transcriptional signatures as determined by connectivity map-based analysis (Machado et al., 2020). These data together with the FOXO3 activating effect of both alkaloid compounds mentioned above are in line with the role of TRIB2 as a FOXO repressor protein (Zanella et al., 2010)

Targeting the nuclear export receptor CRM1

Chromosome region maintenance 1 (CRM1, also reported as XPO1 or exportin 1) is an export protein of the karyopherin-β family of transport receptors that mediates the nuclear exports of proteins that contain

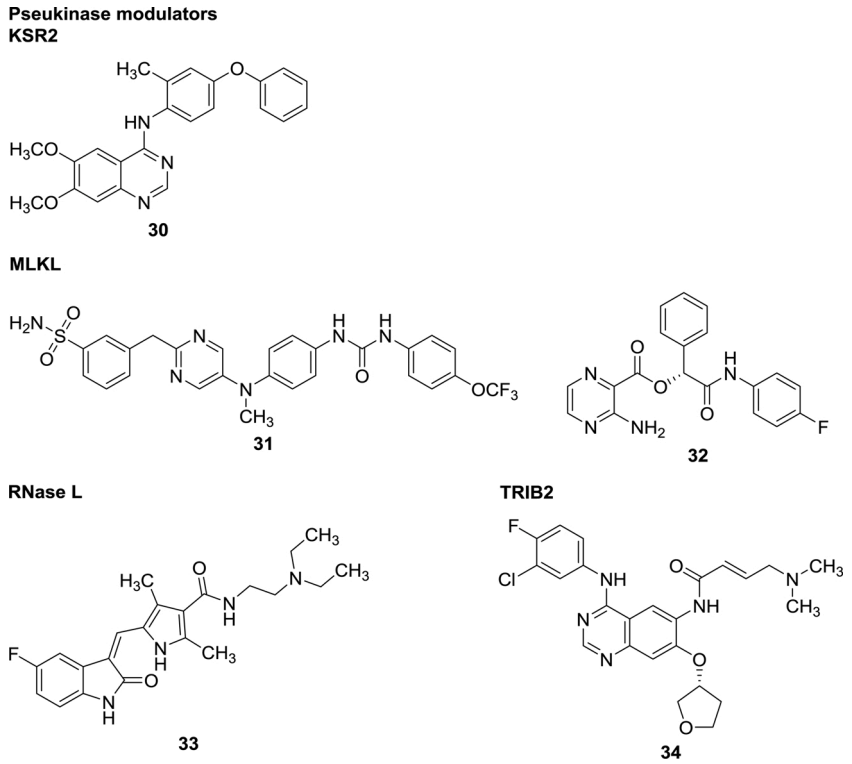

Chart 6. Chemical structures of KSR2 (**30**), MLKL (31,32), RNase L (**33**) and TRIB2 (**34**) modulators.

leucine-rich nuclear export signal (NES) (Ferreira et al., 2020b; Fornerod et al., 1997; Fukuda et al., 1997). CRM1 is involved in the nuclear export of several proteins with tumor suppressor and oncogenic activity, for example retinoblastoma, APC, FOXO proteins, INI1/hSNF5, galectin-3, Bok, NPM1, RASSF2, Merlin, p53, p21CIP, p27KIP1, N-WASP/FAK, estradiol receptor, Tob, BRCA1, BCR–ABL and eIF4E. Worthy to note, such proteins appear to be spread inside the tumor cells (Hill et al., 2014). In a wide variety of both solid and blood tumor types the expression of CRM1 was found to be remarkably increased (Gao et al., 2015; Inoue et al., 2013; Kojima et al., 2013; Lapalombella et al., 2012; Noske et al., 2008; Schmidt et al., 2013, p. 1; Shen et al., 2009; Tai et al., 2014; van der Watt et al., 2014v, 2009, p. 1; Yao et al., 2009, 2009; Yoshimura et al., 2014; Zheng et al., 2014; Zhou et al., 2013). Accordingly, the expression of high level of CMR1 correlates with size and spread of distant metastasis of the tumor (Turner et al., 2012; Turner and Sullivan, 2008). Due to the crucial regulatory role and the alteration in human cancer, CRM1 has emerged as a therapeutic target for anti-cancer therapy. Several nuclear export inhibitors (NEIs) have proven to sensitize drug-resistant cancer cells to anti-cancer treatments (Ferreira et al., 2020c, p. 1). They are natural products and synthetic; natural product NEIs are derived from bacterial, plant, fungal or animal sources (Sun et al., 2016).

Leptomycin B (LMB, elactocin, **35**, Chart 7) is a natural product isolated from *Streptomyces spp* originally discovered as an antifungal agent (Hamamoto et al., 1983). LMB was identified as a CRM1 inhibitor by Kudo (Kudo et al., 1998). Compound **35** forms a covalent bond with Cys528 of the human CRM1 in the NES-binding groove through a reaction type Michael addition involving its 5,6-dihydro-2*H*-pyran-2-one moiety (Dickmanns et al., 2015; Kudo et al., 1999). The covalent bond with Cys528 inhibits the formation of the NES-CRM1-RanGTP complex and thereby the export of the cargo protein to the cytoplasm. In clinical trial, compound **40** showed systemic toxicity, despite its appreciable anticancer activity, possibly due to a permanent block of nuclear export of essential macromolecules (Newlands et al., 1996). Some analogs of **35**, the Anguinomycins isolated from *Streptomyces* sp. *Ratjadone*, form a covalent bond with Cys238, show EC_{50} values at nanomolar concentrations, and are also highly cytotoxic (Sun et al., 2013, p. 1).

1'S-1'-acetoxychavicol (galangal) acetate (**36**) was isolated from the rhizomes of *Alpinia galanga*. Compound **36** inhibited Rev transport at a low concentration by binding to CRM 1 and accumulating full-length HIV-1 RNA in the nucleus, resulting in a block in HIV-1 replication in peripheral blood mononuclear cells (Ye and Li, 2006).

Valtrate (**37**) was obtained after separation of the extract of *Valeriana Radix*, and it was shown to inhibit the export from the nucleus to cytoplasm of the *Schizosaccaromyces* pombe fused protein at 3 μg/mL (Murakami et al., 2002). To compare the mode of action of **37** and callystatin (**38**) a polyketide isolated from a marine sponge by the same group, the authors considered the simplified compound **39**, a Rev-transport inhibitor with a MIC of 3.8 μM.

Compound **37** was presumed to inhibit Rev transport from the nucleus to cytoplasm through direct binding to the Cys-529 in CRM1. In order to compare the modes of action between **37** and **38**, a biotinylated probe was synthesized. The analysis of the binding protein demonstrated

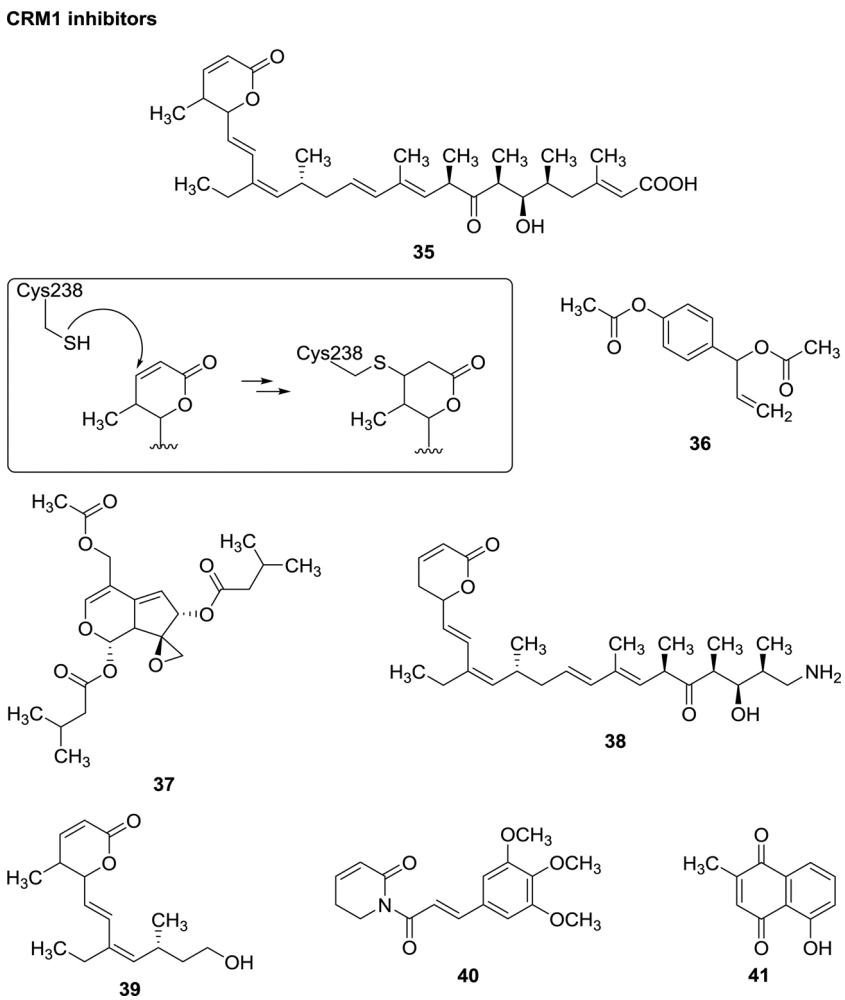

Chart 7. Chemical structures of CRM1 inhibitors (**35-41**).

that both **37** and **38** inhibit Rev-transport in the same fashion (Murakami et al., 2002).

Watanabe and colleagues examined CRM1 inhibitors, and found that both **36** and **37** are potent inhibitors of influenza virus replication (Watanabe et al., 2011).

Piperlongumine (**40**) is a natural alkaloid of *Piper longum* endowed with anti-microbial, anti-inflammatory and platelet aggregation inhibitory properties (Adams et al., 2012). Niu reported that compound **40** may behave as nuclear export inhibitor though retention of tumor suppressor proteins and inhibition of the interactions between CRM1 and these proteins. It could directly bind to the conserved Cys528 of CRM1; notably, cancer cells expressing the CRM1 C528S mutation are resistant to **40** (Niu et al., 2015b).

Plumbagin (**41**) is a naphthoquinone derivative extracted from the plant *Plumbago zeylanica* endowed with anti-proliferative activity in both cellular and animal models. Liu reported that cells incubated with **41** accumulated tumor-suppressor proteins in the nuclei and hampered the interaction of these proteins with CRM1. Consistent with the weaker cytotoxicity, **41** suppressed the nuclear export at higher concentrations than 35. Compound **41** binds directly to the conserved Cys528 of CRM1, like **35**, but not to the Cys528 mutated peptide. In this respect, cells bearing the CRM1 C528S mutation were resistant to **41**. Nuclear retention of FOXO1 could be observed in the presence of **35** or **41**; in contrast, cytoplasmic FOXO1 was observed only in CRM1-Cys528 mutant cells (Liu et al., 2014).

In search for new Rev inhibitors of HIV, Daelemans identified a new small molecule antiviral agent, PKF050-638 (**42**, Chart 8) that behaves as an inhibitor of the CRM1-mediated Rev nuclear export and inhibits in a dose-dependent manner Rev-dependent mRNA expression in a cellular assay for Rev function. The authors demonstrated that **42** disrupts CRM1-NES interaction using a quantitative *in vitro* CRM1-nuclear export signal cargo-binding assay and reversibly interferes with the colocalization of CRM1 and Rev in the nucleolus. Similarly to **35**, the mode of action of **42** is through a direct and reversible interaction with Cys539 (Daelemans et al., 2002). Sakakibara reported that CBS9106 (**43**) is an inhibitor of CRM1-dependent nuclear export that causes cell cycle arrest and induces apoptosis in a broad spectrum of cancer cells, including multiple myeloma. Compound **43** leads to a significant reduction of CRM1 protein levels without any apparent effect on CRM1 mRNA expression. After oral administration, compound **43** suppressed significantly tumor growth and prolonged survival in mice bearing human tumor xenografts (Sakakibara et al., 2011).

Kau performed a phenotypic screen in order to identify small molecule inhibitors of nuclear export of the transcription factor FOXO1a. The study led to the identification of 19 novel compounds that promote retention of FOXO1a in the nucleus. These molecules block the nuclear export of RevGFP and FOXO1a by selective targeting CRM1. Of the 19 compounds in this class, 5219668 (**44**) was the most potent CRM1 inhibitor, although less potent than compound **35** (Kau et al., 2003). Similarly, Cautain et al., performed a high content screening of 14,000 different microbial extracts, purified the fungal metabolite MDN-0105 and characterized it as a potent CRM-1 inhibitor capable of inducing FOXO3 and NFkB2 nuclear translocation (Cautain et al., 2014).

Niu investigated S109 (**45**), a novel reversible CRM1 inhibitor in colorectal cancer cells that inhibited cell proliferation and induced cell cycle arrest. Compound **45** has shown nuclear retention of major tumor suppressor proteins. The reduction of CRM1 protein level was likely mediated through a reversible mechanism involving the proteasome pathway. The Cys528 mutation of CRM1 prevented the ability of **45** to block nuclear export (Niu et al., 2015a, p. 1).

Selective Inhibitors of Nuclear Export (SINEs) are characterized by slow and reversible binding. The Cys528 mutation confers resistance to SINE compounds, meanwhile the E571 K mutation does not induce resistance *via* CRM1-mediated nuclear export (García-Santisteban et al., 2016). The CRM1 antagonist, selinexor (KPT-330, **21**, see also above) promoted rapid apoptosis at low nanomolar concentrations in a panel of

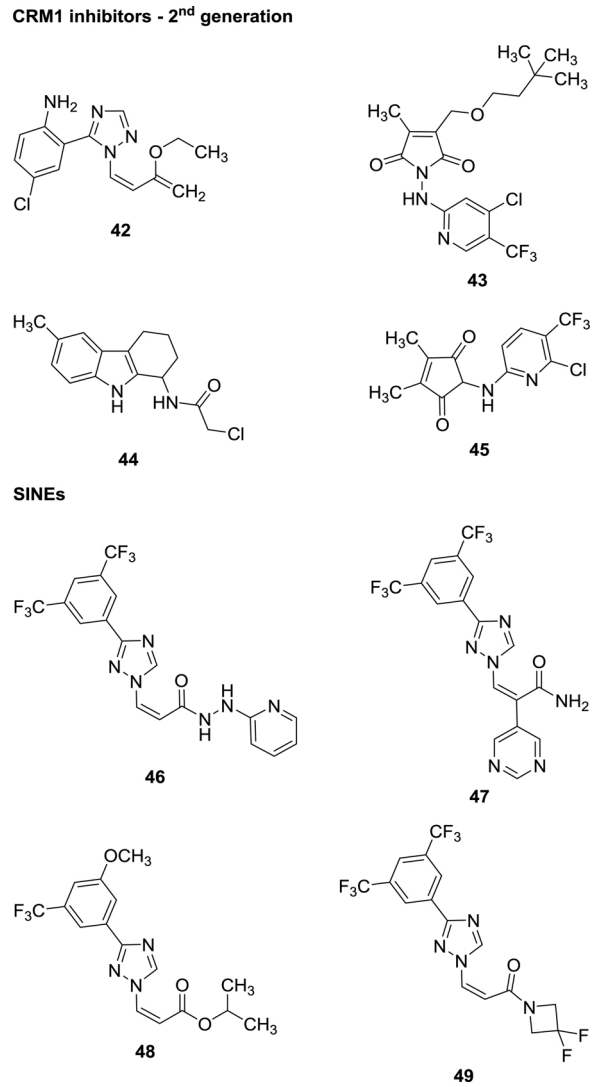

Chart 8. Chemical structures of CRM1 inhibitors (2nd generation) (**42-45**) and SINEs (**46-49**).

human T-cell acute lymphoblastic leukemia (T-ALL) cell lines, and arrested cell cycle in the G1 phase. Compound **21** demonstrated prominent growth suppression *in vivo* of T-ALL cells and demonstrated high activity against acute myeloid leukemia (AML) cells, with little toxicity to normal murine hematopoietic cells (Etchin et al., 2013).

Verdinexor (KPT-335, **46**) is an orally bioavailable, selective CRM1 inhibitor. Compound **46** is being evaluated in a variety of viral indications as well as autoimmune and inflammatory diseases. Compound **46** inhibited CRM1-mediated transport and reduced respiratory syncytial virus (RSV) replication *in vitro*. It proved to be effective against both strains A and B of RSV and reduced viral replication following prophylactic or therapeutic administration. The mechanism of inhibition was through a combined effect of reduced CRM1 expression, disruption of the nuclear export of RSV M protein, and inactivation of the NF-kB signaling pathway (Jorquera et al., 2019). It has the potential to treat viral diseases through inhibition of viral replication and suppression of inflammatory cytokine-mediated symptoms.

Eltanexor (*Z*-isomer, KPT-8602, **47**) showed an improved tolerability profile compared to compound **21** due to its reduced brain penetration, with attenuation of the central nervous system mediated side effects of anorexia and weight loss. Compound **47** showed promising anticancer activity in preclinical models of colorectal cancer (CRC). It exhibited anti-leukemic efficacy against leukemic blasts and leukemia initiating

cells (LICs) in AML patient-derived xenograft models. Importantly, normal hematopoietic stem and progenitor cell frequency is not significantly reduced by **47**, providing a therapeutic window for the elimination of relapse-driving LICs while sparing normal HSPCs (Etchin et al., 2017). Compound **47** displayed a strong synergism with dexamethasone on human B-ALL and T-ALL cell lines as well as *in vivo* in three patient-derived ALL xenografts (Verbeke et al., 2020).

The treatment of tumors with mutations in the epidermal growth factor receptor (EGFR) with tyrosine kinase inhibitors (TKIs) represents one of the major breakthroughs in lung cancer management. The acquired T790 M mutation accounts for the majority of resistance cases. In addition to the acquired T790 M mutation, the resistant PC9GR cells had very different transcription programs from the sensitive PC9 cells. KPT-185 (**48**) suppressed growth, caused apoptosis, and inhibited migration of the PC9GR cells at similar (or better) rates as the sensitive PC9 cells in a dose-dependent manner (Wei et al., 2020). Both compounds **48** and **49** (KPT-276) were investigated for the antileukemic activity *in vitro* and *in vivo* in AML. Compound **48** displayed potent anti-proliferative activity with IC_{50} values of 100–500 nM, induced apoptosis, cell cycle arrest, and myeloid differentiation in AML cell lines and patient blasts. In a FLT3-ITD–positive MV4-11 xenograft murine model, compound **49** significantly prolonged survival of leukemic mice (Ranganathan et al., 2012).

It is important to note that apart from CRM-1, there is a broad range of nuclear import and export receptors with different affinities to cellular substrates involved in cancer progression and therapy resistance and that most of these potential targets are completely unexplored (Hill et al., 2014).

Immunogenic cell death strategy

Cancer immunotherapy has recently emerged as an important alternative strategy to treat MDR positive cancers by leveraging the cytotoxic potential of the human immune system.Indeed, multiple factors can be related to immunotherapy resistance as characteristics of the tumor microenvironment (TME), presence of tumor infiltrating lymphocytes (TILs) such as CD8 + T lymphocytes associated with treatment-response, or presence of tumor associated macrophages (TAMs). In addition, the activation of a number of regulators and the presence of other specific molecules or cells has also been described (Pérez-Ruiz et al., 2020). On their side, MDR cells are characterized by a high immune-evasive capacity since they have poor immune-activating molecules on their surface. They can also produce immuno-suppressive metabolites that do not allow the host immune system to mount an anti-tumor response. The main reason for chemo-immune-resistance of MDR cancer cells is due to their ability to adapt to stressors, this phenotype being part of a multi-stress resistance phenotype. In this respect, one strategy to overcome MDR could consist of restoring oxidative stress sensitivity of MDR cells (Riganti and Contino, 2019). Indeed, ROS play a central role in cancer cells by regulating and inducing apoptosis, thereby modulating cancer cell proliferation, cell survival and drug resistance. The levels of ROS and the activity of scavenging/antioxidant enzymes in drug resistant cancer cells are typically increased compared to non-MDR cancer and normal cells. Consequently, MDR cancer cells may be more susceptible to alterations in ROS levels (Cui et al., 2018).

More particularly, immunogenic cell death (ICD), any type of cell death eliciting an immune response, was discovered following a vaccination effect exerted by cancer cells dying from pre-treatment with certain chemotherapeutics in a murine syngeneic tumor model *in vivo*. ICD is likely to be of great relevance in cancer therapy. Interestingly, only a minority of drugs is able to trigger ICD without a clear-cut relation to chemical structures or their primary modes-of-action. Nevertheless, generation of ROS and induction of endoplasmic reticulum (ER) stress are clearly linked to ICD. Some clinically established chemotherapeutics have recently emerged as being particularly efficient in causing ICD. In the list of molecules in current clinical studies as ICD-inducing chemotherapy, doxorubicin, the first molecule in Chart 1 appears as playing a major role together with four other molecules, cyclophosphamide (**50**), oxaliplatin (**51**), epirubicin (**52**) and bortezomib (**53**) (Vanmeerbeek et al., 2020) (Chart 9).

Although cisplatin (**2**, Chart 1) and oxaliplatin (**51**) exhibit strong structural similarities, only the latter but not the former is an ICD inducer. An iron metallo-drug, P722 (**54**) has also been included in this list for the following reasons. This molecule belongs to a family of molecules called ferrocifens, that are based on the structure of hydroxy tamoxifen (OH-Tam), the antiestrogen of reference classically used to cure hormone dependent breast cancer (Jaouen et al., 2015; Top et al., 2003; Vessieres, 2019). In members of the ferrocifens family, the phenyl ring of tamoxifen has been replaced by a ferrocenyl unit.

Presence of this organometallic unit confers unique redox properties to these molecules. These are associated, in cancer cells, with a high and rapid production of ROS and generation of quinone methides, highly reactive molecules able to interact with key enzymes such as thioredoxin reductase (Citta et al., 2014) and to induce cell damage leading to cell death by senescence or apoptosis (Jaouen et al., 2015; Vessières et al., 2021). As a consequence, some members of the family exhibit strong anti-proliferative effects, both *in vitro* and *in vivo*, associated with a cytotoxic activity while hydroxy tamoxifen shows only an anti-hormonal effect (Allard et al., 2008; Jaouen et al., 2015; Lainé et al., 2014). This is for example the case for P722 (**54**, Chart 9) which has been identified so far as the most cytotoxic member of the family, on MDA-MB231, triple negative breast cancer cells ($IC_{50} = 35$ nM) and to be highly cytotoxic also on several MDR cell lines (Idlas et al., 2021; Wang et al., 2019). ROS production observed with ferrocifens (Jaouen et al., 2015) make them potential candidates as agent capable of inducing ICD (Terenzi et al., 2016). Indeed, in a recent paper, it has been shown that P722 formulated in lipid nanocapsules (LNCs) was able to induce an activation of CD8 + T lymphocytes potentially associated with an ICD inducer effect (Topin-Ruiz et al., 2021).

Drug delivery strategies

Nanoparticulate drug delivery systems (NPs) intended to treat pathologies such as cancer or infections can provide various advantages as a high active drug loading capacity, low toxicity, targeted delivery, increased uptake by tumor cells, and optimized pharmacokinetic patterns of traditional drugs. They are expected to overcome multidrug resistance in cancer therapy. Indeed, nanotechnology holds great promise in establishing efficacious and innovative strategies to facilitate complementary treatments and cancer diagnostics, with various NPs demonstrating encouraging results (Livney and Assaraf, 2013; Cohen et al., 2021; Bar-Zeev et al., 2017; Engelberg et al., 2019). In the current review we focus on NPs adapted for the treatment of MDR tumors in the context of the emerging targets and ICD described above, which currently seem to represent innovative and promising strategies. As the bibliography is very large in this field, a focus will be put on NPs able to encapsulate the small molecules previously described in and summarized in Table 1. Table 2 presents these specific drug delivery systems as well as their *in vitro* and *in vivo* applications, when they exist.

Many reviews have broadly and recently described the different types of NPs (Fig. 2) applied to cancer therapy, including resistant cancers (Doroudian et al., 2021; Khot et al., 2021; Lepeltier et al., 2020; Mirza and Karim, 2021; Zhu et al., 2021a; Zhu et al., 2021b). Whether NPs are organic, inorganic or hybrid, they can be classified according to their shape (*e.g.*, spherical, cylindrical, cubic), their size (between a few tens of nm and 1 μm), their chemical composition (polymers, lipids, gold…) and their applications. Drugs can be entrapped within, physically adsorbed, or form chemically covalent or electrostatic bonds at the surface of the nanocarrier. Some applications can be local as, for example, in the brain by convection- enhanced delivery (Allard et al., 2010) or by *in situ* injection when tumors are directly accessible

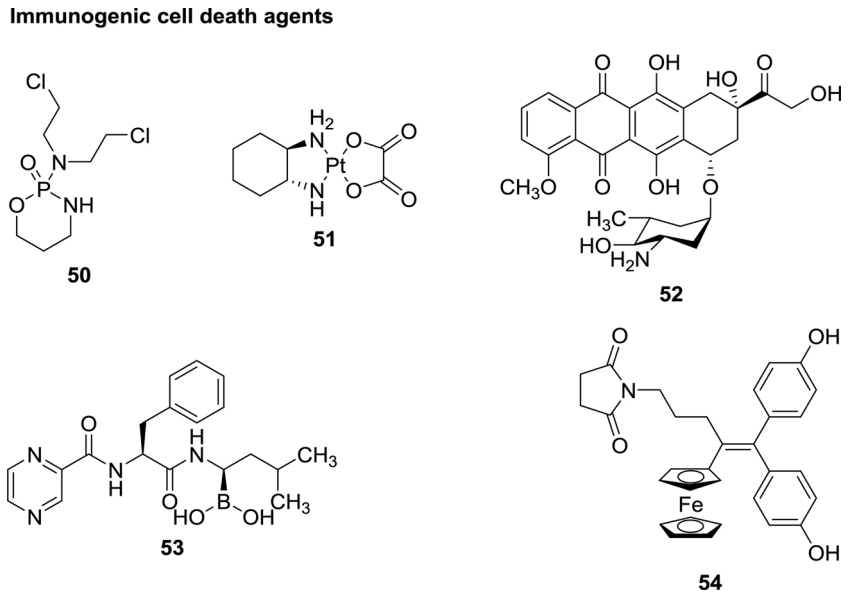

Chart 9. Chemical structures of molecules involved in immunogenic cell death (**50-54**).

(Andrade et al., 2021).

For systemic anticancer treatments, two modes of action characterize NPs according to the type of targeting they are able to achieve: passive or active targeting (Hirsjarvi et al., 2011).

Controversial for the past few years (Björnmalm et al., 2017; Danhier, 2016), it is nevertheless in relation with the enhanced permeability and retention (EPR) effect, characteristic of tumors that the passive targeting has been mainly evaluated (Maeda, 2021). EPR is related to the rapid and disordered growth of tumor cells by hypervascularity in a pathophysiological TME, subject to impaired lymphatic drainage. This leads to the presence of large spaces between endothelial cells and excessive secretion of vascular permeability factors allowing the NPs to specifically accumulate at the tumor site, when they are able to circulate long enough in the vascular system. To prolong this circulation, NPs are made stealth, *i.e.* able to escape the immune system which is prompt to eliminate them rapidly from the circulation (Bao et al., 2021). The polymer most commonly used at the surface of NPs in this context is the poly(ethylene glycol) or PEG (D'souza and Shegokar, 2016; Vonarbourg et al., 2006), but other surface coating with poly(2-oxazoline), poly (zwitterions) (Fam et al., 2020) or polysaccharides as chitosan (Moraru et al., 2020) have been employed. These molecules are generally low in charge, biocompatible and very flexible. The influence of the composition, size and conformation of these surface molecules has been widely described in the literature (Ozer et al., 2017; Vonarbourg et al., 2006). With such a protective layer and thanks to a steric effect, NPs are able to repel the absorption of opsonin proteins and block the uptake by macrophages.

However, by passive targeting, a high untoward toxicity can be observed through the action of NPs on the healthy cells of the TME, resulting in significant side effects (Attia et al., 2019; Bazak et al., 2015; Izci et al., 2021; Pérez-Herrero and Fernández-Medarde, 2015). To achieve greater specificity, active targeting can be attained by conjugation of targeting ligands (*e.g.* antibodies, peptides, small molecule ligands) to the NPs (Ashfaq et al., 2017) or through the use of an external or internal stimulus to the desired location (Liu et al., 2020). Different targeting moieties, such as albumin, folic acid, somatostatin, and transferrin, can be attached to NP surface with a particular affinity for transmembrane receptors present at the surface of tumor cells, allowing an enhancement of the site-specificity and receptor-mediated endocytosis (Yu et al., 2012) (Pinhassi et al., 2010; Assaraf et al., 2014). Efficient binding and internalization require that receptors are expressed exclusively on target cancer cells relative to normal cells, and expression should be homogenous across all targeted cells (Peer et al., 2007). Targeted NPs offer innovative therapeutic strategies to overcome the various limitations of conventional chemotherapy, enabling enhanced selectivity, early and more precise cancer diagnosis, individualized treatment as well as overcoming of MDR (Bar-Zeev et al., 2017).

Although more advanced technologies are needed to assess the interactions between NPs and biological systems, new treatments are emerging by combining different strategies involving NPs. Indeed, multicomponent or multifunctional systems (one or more drugs, bioactive moieties reacting with extern or intern stimuli, and imaging functions) combined with different types of therapeutics (radiation, photodynamic therapy, gene therapy, immunotherapy, *etc.*) can increase the effective concentration of chemotherapeutic drugs in tumor cells as well as minimize the risk of resistance, improving therapeutic efficacy by modulating the different pathways involved (Chen et al., 2020; Gao et al., 2020; Liu et al., 2018). Drug combination therapy has long been adopted as the standard first-line treatment of several malignancies to improve the clinical outcome and combination with NPs has been shown to generally induce synergistic activity and sometimes prevent the onset of drug resistance (Gurunathan et al., 2020). Indeed, NPs-based combination therapy can deliver multiple therapeutic agents with different physicochemical and pharmacological properties. For example, one drug will reverse or abolish the development of drug resistance, whereas the other will concurrently kill cancer cells. Different examples using ferrocifen LNCs proved that the action of the active drug was improved when external radiotherapy was applied (Allard et al., 2010) or when BCL-2 gene therapy was associated *via* the siRNA co-encapsulation with the iron-based drug (Resnier et al., 2017).

Accumulating evidence shows that the expression of biomarkers related to stemness is crucial for tumor maintenance as they are also the mediators of drug resistance. This evidence is of special relevance since cancer stem-like cells (CSC) have been shown to be drivers of metastasis, associated with a more invasive and aggressive cancer phenotype (Garcia-Mayea et al., 2020). Thus, the phenomenon of cancer MDR can be related both to rapidly proliferating cells constituting the bulk of the tumor but also to CSC localized in tumor niches, difficult to target, able to survive to conventional therapy and leading to recurrent disease. These cells have a natural tendency to migrate and distribute within the tumor mass with a specific tropism. As an example, "marrow-isolated adult multilineage inducible" cells (MIAMI cells), a subpopulation of mesenchymal stromal cells, were able to efficiently incorporate LNCs without altering their stem cell properties or their migration capacity.

Table 1
List of the compounds and their molecular targets (formulated molecules with*).

Mode of Action/ Targets	Compound	N°	References
P53 modulators*	doxorubicin*	1	(Yang et al., 2014)
	cisplatin*	2	(Tiwari and Wilson, 2019)
	5-fluorouracil	3	(Deng et al., 2017; Marjaneh et al., 2019)
	paclitaxel*	4	(Park et al., 2016)
NF-kB modulators	niclosamide	5	(Hamdoun et al., 2017; Li et al., 2014)
	thalidomide	6	(D'Amato et al., 1994)
HIF-alpha modulators	metformin*	7	(Klil-Drori et al., 2017)
	LW6	8	(Boovanahalli et al., 2007)
	PX-478	9	(Schwartz et al., 2010)
	chetomin	10	(Kung et al., 2004)
	KCN1 derivative	11	(Yin et al., 2012)
	PT2385	12	(When et al., 2018)
Wnt/b-catenin modulators	LGK974	13	Liu et al., 2013)
	G007-LK*	14	(Huang et al., 2009)
	JW55	15	(Huang et al., 2009)
	pyrvinium	16	(Thorne et al., 2010)
	celecoxib	17	(Tuynman et al., 2008)
	genistein	18	(Su and Simmen, 2009)
	ICG-001	19	(Emami et al., 2004)
	ethyl 4-((4-(trifluoromethyl) phenyl) sulfonamido) benzoate	20	(Di Magno et al., 2020)
FOXO modulators	selinexor (KPT330)*	21	(Ferreira et al., 2020b)
	ETP-45658	22	(Link et al., 2009)
	dactolisib (NVP-BEZ235)	23	(Serra et al., 2008)
	capivasertib (AZD5363)*	24	(Davies et al., 2012)
	tanzawaic acid D	25	(Link et al., 2009)
	AS1842856	26	(Link et al., 2009)
Pseudokinase inhibitors	TX2-121-1	27	(Xie et al., 2014)
	lapatinib*	28	(Claus et al., 2018)
	CT8	29	(Ruiz-Saenz et al., 2015)
	APS-2-79	30	(Dhawan et al., 2016)
	GW806742X	31	(Hildebrand et al., 2014)
	R-enantiomer cpd 4	32	(Ma et al., 2016)
	sunitinib	33	(Ma et al., 2016)
	afatinib	34	(Foulkes et al., 2018)
Nuclear export receptor CRM1 (1st generation)	leptomycin B	35	(Hamamoto et al., 1983; Kudo et al., 1998)
	1'S-1'-acetoxychavicol (galangal) acetate	36	(Ye and Li, 2006)
	valtrate	37	(Murakami et al., 2002)
	callystatin	38	(Murakami et al., 2002)
	the simplified 39	39	(Murakami et al., 2002)
	piperlongumin*	40	(Niu et al., 2015a)
	plumbagin	41	(Liu et al., 2014)
Nuclear export receptor CRM1 (2nd generation)	PKF050-638	42	(Daelemans et al., 2002)
	CBS9106	43	(Sakakibara et al., 2011)
	5219668	44	(Kau et al., 2003)
	S109	45	(Niu et al., 2015a)
Nuclear export receptor CRM1 (SINEs)	verdinexor (KPT-335)	46	(Jorquera et al., 2019)
	eltanexor (Z-isomer, KPT-8602)	47	(Verbeke et al., 2020)
	KPT-185	48	(Wei et al., 2020)
	KPT-276	49	(Ranganathan et al., 2012)
Immunogenic Cell Death (ICD)	cyclophosphamide	50	(Vanmeerbeek et al., 2020)
	oxaliplatin (DACH-Pt)*	51	(Vanmeerbeek et al., 2020)
	epirubicin	52	(Vanmeerbeek et al., 2020)
	bortezomib	53	(Vanmeerbeek et al., 2020)
	ferrocifen P722*	54	(Jaouen et al., 2015; Top et al., 2003; Vessieres, 2019)

* among other mechanisms.

MIAMI cells loaded with LNCs containing a ferrocifen produced a significant cytotoxic effect on U87MG glioma cells *in vitro* and *in vivo* after intratumor injection in a heterotopic U87MG glioma model in nude mice (Clavreul et al., 2015; Roger et al., 2012).

Based on all this data, the development of "quadrugnostic" NPs as proposed by Shapira et al., (Shapira et al., 2011) harboring i) a selective targeting moiety, ii) a diagnostic imaging component, iii) an anticancer drug and iv) an anti MDR agent, will allow novel personalized medicine treatment modalities able to surmount distinct and well-defined mechanisms of anticancer drug resistance (Assaraf et al., 2019). To achieve the most out of NPs therapy in cancer treatment, new delivery systems have also to be selected based on the characteristics of the tumor. Personalized treatments according to the characteristics of the TME showing high intra- and inter-tumor variability, can be adapted to enhance tumor penetration by developing different design parameters in accordance with the tumor physiology (Swetha and Roy, 2018). Many reviews detail the characteristics of the TME and the various strategies that can be deployed to take advantage of it (Baghban et al., 2020). For example, modification of NP surface by pH-sensible polymers can represent a way to increase the cellular uptake in the acidic TME, enhancing tumor sensitivity to anticancer drugs (Donahue et al., 2019; Pautu et al., 2021). Finally, as emerging components of the tumor-host interaction, tumor-derived circulating materials as exosomes are increasingly recognized as professional carriers of information in TME and as pivotal molecular entities involved in tumorigenic microenvironment setup (Wu et al., 2019). Furthermore, they can also be used as cancer diagnostic tools to precisely predict and monitor the outcome of therapy. Recently, widely described in the literature and somewhat marginal to our purpose, this topic will not be developed in this review (Le Saux et al., 2020; Lepeltier et al., 2020; Li et al., 2020; Mashouri et al., 2019; Wortzel et al., 2019).

Metastatic lesions show genetic instability that gives rise to mutations also conferring drug resistance. They usually show heterogeneous subpopulations of cells, different from the original primary tumor cells, with differential gene expression patterns, growth properties, cell surface proteins, and enzyme/protein functions. Furthermore, the molecular and cellular signatures can vary both within single metastases and among different metastases. As a consequence, among drugs showing high cytotoxic effect *in vitro* and *in vivo* in preclinical mouse models, only a few reached clinical trials due to the lack of sensitivity of metastatic cells (Banerjee et al., 2019). Multiple ongoing clinical trials are directed towards nanomedicine-based strategies including combination therapies with the specific objective of eliminating the tumor and its metastasis (combination of chemotherapeutic agents, ICIs, inhibitors of angiogenesis, a process that is often associated with metastasis). Currently, more than a dozen of clinically approved NPs is successfully used for various types of cancer treatments. Majority of NPs are derived from liposomes and polymers (Table 2). Complexity of chemical synthesis or multistage processes, posing a significant challenge in obtaining consistent physical and chemical properties (size, composition over time) at affordable price, can compromise the successful clinical translation. A better understanding of the tumor type-specific pathophysiology, more connections between research and treatment and NP design based on patient characteristics (biomarker preselection strategies, treatment combinations with a clinical focus on the target disease as it develops in patients) must be implemented to achieve this success (Nayak et al., 2021).

Nanoparticulate drug delivery systems (NPs) used to deliver some of the selected drugs

As previously described, the mechanisms by which cancer cells develop MDR are well known and among them are: (i) enhanced tumor cell proliferation and pro-survival signals, (ii) increased drug efflux, (iii) decreased drug uptake, (iv) drug inactivation, (v) evasion of drug-induced apoptosis, (vi) activation of DNA repair, (vii) acquired DNA

Table 2
Formulation of molecules.

N°*	Compound	Formulation	Indication/ Research stage	References
Transcription factors				
1	doxorubicin (alone)	Pegylated liposomes (Doxil®, Caelyx®, Lipdox®)	Chemotherapy for ovarian, metastatic breast cancer, myeloma	(Barenholz, 2012)
2	cisplatin	Liposomal cisplatin: Lipoplatin™	FDA approved; orphan drug for pancreatic cancer	(Boulikas, 2009, 2004; Stathopoulos and Boulikas, 2012)
		Cremophor®EL-Paclitaxel	Chemotherapy for NSCLC, breast cancer and ovarian cancer	(Gelderblom et al., 2001)
4	paclitaxel	Nano albumin-bound paclitaxel (Abraxane®, nab-paclitaxel)	Chemotherapy for breast, lung and pancreatic cancers	(Miele et al., 2009; Stinchcombe, 2007)
		Paclitaxel in LNCs (Labrafac®, PEG-HS solutol®HS15)	*In vitro* and *in vivo* on glioma cancer cells	(Garcion et al., 2006)
7	metformin	Formulated with DOX in PLGA-TPG nanoparticles	*In vitro* reversion of multidrug resistance on MCF-7/DOX breast cancer	(Shafiei-Irannejad et al., 2018)
14	G007-LK	Formulated in a mixture 10 % DMSO, 60 % PEG400, 30 % saline for iv and in 15 % DMSO, 17.5 Cremophor EL, 8.75 % ethanol, 8.75 % Miglyol 810 N, 50 % PBS for ip	*In vitro* and *in vivo* on CRC (colorectal cancer)	(Lau et al., 2013)
24	AZD5363 (Capivasertib)	Solution containing 10 % DMSO, 25 % W/v Kleptose HPB (Roquette) buffer	*In vivo* on xenografted breast cancer tumors (BT474c, KPL-41 and HGC)	(Davies et al., 2012)
Pseudokinase inhibitors				
		Dextran sulfate-chitosan nanoparticles	*In vitro* and *in vivo* on xenografted BT 474 cells (HER^{+} human breast cancer)	(Mobasseri et al., 2017)
28	lapatinib	Polymer nanoparticles with a coordination complex of tannic acid and iron; used for lapatinib alone or for codelivery with paclitaxel	*In vitro* on OVCA-432 (ovarian cancer cell line); synergistic effect with paclitaxel	(Levit et al., 2020)
		PEG-PBC nanoparticles for codelivery of lapatinib and doxorubicin	*In vitro* and *in vivo* on xenografted breast cancer tumors (MCF-7 and resistant MCF-7/ADR)	(Wang et al., 2014)
Nuclear export receptors CRM1				
21	selinexor	Formulation in Pluronic F-68 (non-ionic surfactant and PVP (polyvinyl pyrrolidone) K-29/32	Phase IB study for advanced refractory bone or soft tissue sarcoma	(Corno et al., 2018; Gounder et al., 2016)
40	piperlongumin	Formulation in ChitoPEGse NPs obtained by crosslinking ChitoPEG [methoxy poly(ethylene glycol)-grafted chitosan] using selenocystine-acetyl histidine (Ac-histidine)	*In vitro* on A549 and CT26 cells and *in vivo* on CT26 cell; pulmonary metastasis mouse model	(Lee et al., 2018)
		Encapsulation of PL in PLGA nanoparticles; co delivery with TRAIL, chemically conjugated to the surface of liposomes	*In vitro* on PC3 prostate and HCT116 colon cancer cells and *in vivo* on HCT116 cells	(Sharkey et al., 2016)
Associated with Immunogenic Cell Death (ICD)				
1	doxorubicin	Recombinant chimeric polypeptides including doxorubicin (CP-DOX)	*In vitro* and *in vivo* on 4T1-luc (murine mammary carcinoma) and LL/2-luc-M38 (Lewis lung carcinoma)	(MacKay et al., 2009; Mastria et al., 2018)
		Ultrasound controlled release of doxorubicin-liposome-microbubble complex (MbDOX)	*In vitro* and *in vivo* on LL/2 and CT26 cancer cells	(Deng et al., 2014; Huang et al., 2018)
51	oxaliplatin (DACH-Pt)	Mesoporous silica nanoparticle (MSNPs) loaded with oxaliplatin and subsequently encapsulated in silicasome (coated lipid bilayer)	*In vivo* on orthotopic Kras-derived pancreatic cancer model	(Liu et al., 2021)
		Nano-Folox: a precipitate of the aqueous form of oxaliplatin and FnA (folinic acid), formulated into an (aminoethyl anisamide) PEGylated lipid nanoparticle	*In vivo* on orthotopic CRC (colorectal cancer model)	(Guo et al., 2020)
		Polymer oxaliplatin prodrug nanoparticles associated with a flurorophore allowing imaging guided immunotherapy	*In vivo* on colorectal cancer cells	(Zhu et al., 2021a; Zhu et al., 2021b)
54	ferrocifen P722	LNCs (Labrafac®, Lipoid®, PEG-HS Kolliphor®HS15) surrounded by DSPE-mPEG 2000	*In vivo* on B16F10 mice- xenografted melanoma	(Topin-Ruiz et al., 2021)

BLPP: biotin-/lactobionic acid-modified poly(ethylene glycol)-poly(lactic-co-glycolic acid)-poly(ethylene glycol); CRC: colorectal cancer; NPC: nasopharyngeal carcinoma; NSCLC: non-small cell lung cancer; PEG-PBC [poly(ethylene glycol)-block-poly(2-methyl-2-benzocarbonylpropylene carbonate)]; PLGA: polylactic-co-glycolic acids; SCCHN: squamous cell carcinoma of the head and neck; TRAIL: tumor necrosis factor-related apoptosis inducing ligand.

mutation, (viii) epithelial to mesenchymal phenotype transition, (ix) epigenetic modifications. One main advantage of NPs is their ability to harbor a very wide spectrum of small anti-cancer molecules. This is especially true for hydrophobic drugs, molecules with a low therapeutic index or even unstable (Da Silva et al., 2017). Among the 54 molecules detailed in Table 1, we will focus on 11 of them requiring formulation in NPs for *in vitro* and *in vivo* studies on MDR tumor cells. Formulation used for these molecules ranges from simple to very sophisticated ones

(Table 2). Most of the time, NPs are fully characterized by their size, zeta potential, drug loading, encapsulation efficiency and release kinetics. Numerous formulations of three blockbusters listed in Table 1 (doxorubicin, paclitaxel, and cisplatin) have been published in the literature including co-formulations with other molecules. This is for example the case for doxorubicin (**1**) and paclitaxel (**4**) which have been encapsulated with targeting moieties improving prostate cancer treatment (Cohen et al., 2021). Here, we will focus on representative formulation of these drugs alone, or co-encapsulated with other drugs from our panel and associated with the 4 targets previously identified (non-liganded transcription factors, pseudokinases, nuclear export receptors and immune cell death regulators).

NPs and molecules associated with transcription factors

This first series contains the highest number of molecules (6 molecules). The first one in the list is doxorubicin (DOX), the first antitumor agent whose formulation in PEGylated liposomes was approved in 1995 for cancer treatment (Barenholz, 2012). The need for formulation of DOX was imposed because of its high cardiotoxicity. In this first formulation marketed under the names CAELYX®, DOXIL®, LIPODOX®, DOX is solubilized in a liposome which is then protected by a PEG layer. This formulation is used for chemotherapeutic treatment of multiple cancers for example ovarian cancer, endometrial cancer, metastatic breast cancer, multiple myeloma and lymphoma. Two formulations enhancing the ICD effect of DOX have been published and will be described below. The second molecule in the list is cisplatin (**2**), a potent metallodrug used to treat many forms of cancers (metastatic testicular, ovarian, NSCLC, cervical cancers, and head and neck cancer). It is usually given by infusion of its saline solution. However, due to its numerous side effects, the search for nanoformulations aimed at reducing its toxicity has been explored. The main successful one so far is a liposomal cisplatin formulation, called Lipoplatin™ which is FDA-approved (Boulikas, 2009, 2004; Stathopoulos and Boulikas, 2012; Xu et al., 2018). This formulation was achieved by formation of reverse micelles between cisplatin and DPPG (dipalmitoyl phosphatidyl glycerol) under special conditions of pH, ethanol and ionic strength. The cisplatin-DPPG reverse micelles were subsequently converted into liposomes by interaction with neutral lipids (mPEG 2000-DSPE). The nanoparticles, 110 nm in diameter, have the ability to target tumors and metastasis following intravenous administration. (Boulikas, 2009, 2004; Stathopoulos and Boulikas, 2012). Lipoplatin has been granted "orphan drug formulation" for pancreatic cancer treatment by the European Medicine Agency. Lipoplatin has 14-fold better radiosensitizing activity than cisplatin. Many preclinical and clinical trials on lipoplatin have been carried out over the past 2 decades. A recent meta-analysis of five clinical trials on NSCLC (non-small cell lung cancer) and SCCHN (squamous cell carcinoma of the head and neck) cells revealed that this formulation offers significant advantages regarding progression of the disease and reduced toxicities relative to cisplatin (Xu et al., 2018).

The third molecule in the list is paclitaxel (**4**), a highly lipophilic molecule. Actually, after the identification of this molecule as the active ingredient in crude ethanolic extracts of the bark of the pacific Yew tree against several tumors, its development was suspended for more than a decade due to problems associated with its solubility. Paclitaxel is insoluble in water (less than 0.03 mg/mL) but soluble in Cremophor ® EL (CrEL) a non-ionic surfactant (Gelderblom et al., 2001). CrEL is produced by the reaction of castor oil with ethylene oxide and consists mainly of oxylated triglycerides of ricinoleic acid. In its pharmaceutical form, paclitaxel is dissolved in a mixture of CrEL and dehydrated ethanol (1:1 v/v). Paclitaxel is prescribed for many cancers including MDR ones (ovarian, metastatic breast cancer, multiple myeloma). An albumin-bound formulation of paclitaxel (nab-paclitaxel, Abraxane®,) was published in 2007 (Miele et al., 2009; Stinchcombe, 2007). This CrEL free formulation is prepared by high-pressure homogenization of paclitaxel in the presence of serum albumin into a nanoparticle (average size 130 nm) colloidal suspension. This formulation eliminates the impact of CrEL on paclitaxel pharmacokinetics and utilizes the endogenous albumin transport mechanisms to concentrate Abraxane® within the tumor. Abraxane® is used as a chemotherapeutic agent for breast, lung and pancreatic cancer. Abraxane® anticancer activity has been studied in association with other chemotherapeutic agents or radiotherapy in various clinical I and II trials (Banerjee et al., 2019). Paclitaxel has also been formulated in lipid nanocapsules (LNCs) consisting of an oily core of triglycerides (Labrafac®) able to solubilize paclitaxel, surrounded by lecithin (Lipoid®) and a surfactant (PEG-HS Solutol® HS15) (Garcion et al., 2006). These paclitaxel-LNCs have been tested *in vitro* and *in vivo* on glioma cells and were found more efficient than the commercially available paclitaxel formulation. The fourth molecule, Metformin (**7**) has been recently co-encapsulated with DOX in PLGA-TPG nanoparticles [poly(lactide-co-glycolide)-D-alpha-tocopheryl polyethylene glycol nanoparticles] (Shafiei-Irannejad et al., 2018). This NPs were tested, *in vitro*, on MCF-7/DOX cancer cells resistant to DOX and a synergistic effect of the two drugs was observed. The fifth molecule G007-LK (**14**), has been formulated in a mixture of 10 % DMSO, 60 % PEG400, 30 % saline for i.v. administration as well as in 15 % DMSO, 17.5 % CrEL, 8.75 % ethanol, 8.75 % Miglyol 810 N, 50 % PBS for intraperitoneal injection (Lau et al., 2013). G007-LK NPs were found to inhibit tumor growth of APC-mutant colorectal cancer cells both *in vitro* and *in vivo*. AZD5363 (Capivasertib; **24**), the sixth molecule is an orally active and potent pan-AKT kinase inhibitor. It has been formulated in a solution containing 10 % DMSO, 25 % w/v Kleptose HPB (Roquette) buffer and is administered by oral gavage (Davies et al., 2012). In line with its mode of action, the growth inhibitory effect of AZD5363 is more pronounced in cells with PIK3CA and PTEN mutations but less pronounced in cells with RAS mutations. In addition, it enhances the activity of HER2 inhibitors and docetaxel *in vivo*.

NPs and molecules associated with pseudokinase inhibitors

Lapatinib (**28**) is the only molecule in this series. It is a TKI marketed under the trade name of TYKERB® and administered as lapatinib ditosylate monohydrate in an oral form (Lapatinib, 2015). However, its clinical use is restricted because of its extensive albumin binding capacity and poor oral bioavailability (Bonde et al., 2018). Consequently, numerous formulations of lapatinib have been developed. For example, lapatinib has been formulated in dextran sulfate-chitosan NPs (Mobasseri et al., 2017) or in polymer NPs (Levit et al., 2020). In this case, flash nano precipitation (FNP) is used to self-assemble PEG nanoparticles (PS-b-PEG; polystyrene-b-polyethylene glycol) with lapatinib and a

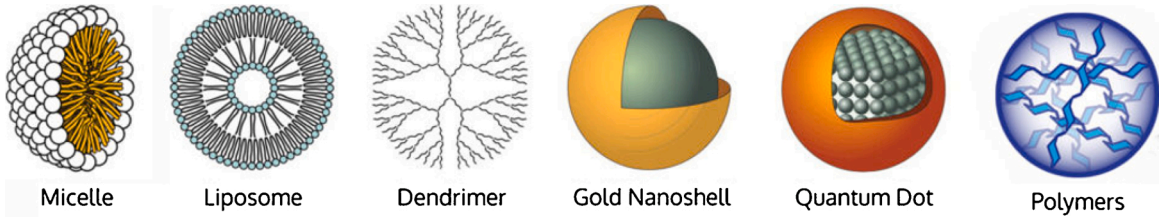

Fig. 2. Different types of nanoparticles (adapted from standardnano.com).

coordination complex of tannic acid and iron. This formulation has also been used for codelivery of paclitaxel and lapatinib (Levit et al., 2020) and a synergistic effect of the two drugs was observed. Another formulation was also developed for the codelivery of doxorubicin and lapatinib (Wang et al., 2014). This time, the two drugs were encapsulated in polymer micelles of PEG-PBC [poly(ethylene glycol)-block-poly (2-methyl-2-benzocarbonylpropylene carbonate)] and lapatinib was used as an adjuvant sensitized drug in breast cancer cells resistant to doxorubicin (MCF-7/ADR) (Wang et al., 2014).

NPs and molecules associated with nuclear export receptors CRM1

Two molecules belong to this category. The first one is selinexor (KPT-330, **21**) which is formulated in a non-ionic surfactant (Pluronic F-68) and a polymer (Plasdone K-29/32 PVP). A synergistic interaction between cisplatin and selinexor has been observed in ovarian carcinoma cells (Corno et al., 2018). The second one is piperlongumine (PL, **40**). Two formulations exist for this molecule. In the first one, PL is encapsulated in nanoparticles of chitosan as follows: chitoPEG [methoxy poly (ethylene glycol)-grafted chitosan] are crosslinked using selenocystine-acetyl histidine (Ac-histidine) conjugates thus giving ChitoPEGse (Lee et al., 2018). ChitoPEGse NPs are delivered to cancer cells in an acidic- or redox state-sensitive manner, allowing their efficient targeting of pulmonary metastasis of cancer cells (CT26) in a mouse model. In the second one, PL is encapsulated in PLGA nanoparticles and used to deliver a combination of two drugs, namely PL and TRAIL (tumor necrosis factor-related apoptosis inducing ligand) chemically conjugated to the surface of liposomes (Sharkey et al., 2016). Higher apoptotic rates were observed for HTC116 tumor cells that received the dual nanoparticle therapy compared to individual stages of the therapy alone.

NPs and molecules associated with immunogenic cell death (ICD)

Three molecules are in this category; the first one is DOX, already cited in the part concerning transcription factors. Actually, two specific formulations have been described in connection with ICD. The first one, is a sophisticated formulation, where DOX is encapsulated in NPs consisting of two segments, a hydrophilic, biodegradable elastin-like polypeptide and a short segment for the attachment of DOX through a pH labile linker. Chimeric polypeptides (CPs) self-assemble into CP-DOX (sub-100 nm in size) (MacKay et al., 2009). When used to deliver DOX to murine cancer model, these NPs have a fourfold higher maximal dose than the free drug and induce nearly complete tumor regression after a single dose. These NPs were also found to enhance antitumor immunity compared to free DOX and to re-establish host antitumor immunity through the generation of ICD (Mastria et al., 2018). In the second formulation, DOX-liposome-microbubble complexes (DLMC) were prepared through conjugation of DOX liposomes (DL) to the surface of microbubbles (made of perfluoropropane C3F8) *via* the high affinity biotin-streptavidin binding (Deng et al., 2014). These NPs, activated by ultrasound, were able to induce ICD more efficiently than free doxorubicin (Huang et al., 2018). Oxaliplatin is the second drug in the list; oxaliplatin (DACH-Pt) is one of the three platinum drugs classically prescribed in cancer chemotherapy. Oxaliplatin is often administered without formulation but recently three formulations have been published and are associated with the effect of the drug as an ICD inducer. The first one consists of the preparation of mesoporous silica nanoparticles (MSNPs) loaded with oxaliplatin through the use of electrostatic and coordination chemistry under weak basic pH conditions. These MSNPs are then encapsulated in a coated lipid bilayer (silicasome) to improve its stability after i.v. injection (Liu et al., 2021). These NPs induce ICD but interestingly, are also associated with a dramatic reduction in bone marrow toxicity (Liu et al., 2021). The second one is Nano-Folox, a formulation derived from FOLFOX, the combination of oxaliplatin with 5-fluorouracil (5-FU) and folinic acid (FnA) used as standard treatment of CRC. In Nano-Folox, the active hydrolysed form of oxaliplatin, $[Pt(DACH)(H_2O)_2]^{2+}$, is precipitated with FnA then formulated into an (aminoethyl anisamide) PEGylated lipid nanoparticle (Guo et al., 2020). Nano-Folox significantly promoted blood circulation of the NPs and induced a stronger chemotherapeutic response than that of FOLFOX in an orthotopic CRC mouse model (Guo et al., 2020). The third formulation is an oxaliplatin prodrug NPs with near-infrared fluorescence properties (Zhu et al., 2021a; Zhu et al., 2021b). This formulation elicits antitumor immune response and allows near infrared fluorescence imaging-guided for photothermal therapy (Guo et al., 2020). The last component in this series is P722 (**54**), a member of the ferrocifen family. These molecules are lipophilic thus they can be *in vivo* administered only after formulation. It has been shown by Passirani and her group that lipid nanocapsules are a very well-suited formulation for this family of molecules (Idlas et al., 2021). These nanoparticles present a hybrid structure between polymer NPs and liposomes and are prepared by a solvent-free process. They are composed of an oily core allowing dissolution of the lipophilic entity, surrounded by a shell of lecithin and PEG surfactant (Heurtault et al., 2002). These LNCs loaded with P722 have been tested on B16F10 melanoma mouse model (Topin-Ruiz et al., 2021). *In vivo*, a significant improvement in the survival rate and tumor progression was observed with P722-loaded LNCs in comparison with anti-CTLA4 mAb, the treatment of reference, identifying an immune-preventive approach of P722.

Conclusion and future perspectives

Proteins lacking catalytic activities, or ligand-binding pockets or for which no experimental three-dimensional structure are available, have been considered undruggable. Progress in drug discovery and development technologies including artificial intelligence, computer-based drug design, RNA therapeutics, targeted protein degradation, peptide-based and protein-based drugs are currently and will continue to broadening the landscape of druggability. As a consequence, a variety of historically undruggable, clinically meaningful therapeutic proteins will become important novel pharmacological targets. Indeed, the very concept of "undruggable" will vanish in the near future. The current review article provided some paradigmatic examples for this process.

A broad range of diverse chemical inhibitors and small molecule modulators of the activity of transcription factors and pseudokinase function have been identified to interfere with these targets. Several of these drug candidates are in different phases of development. The identification of compounds interfering with the activity of FOXO proteins has made significant progress (Calissi et al., 2021). FOXO proteins are becoming an attractive target for researcher from both academia and pharma industry. The importance of pseudokinases, that are unusual types of kinases, is growing since their role in normal physiological processes and in the onset of diseases are increasingly understood. Much of what we have learned from drugging active kinases can be applied to targeting pseudokinases and *vice versa* (Kung and Jura, 2019). Efforts have been made towards the development of inhibitors of the nuclear export receptor protein CRM1 as it was recognized that cells become vulnerable to cancer after the nuclear export of many tumor suppressors and oncoproteins by CRM1 (Nguyen et al., 2012). As non-liganded transcription factors and pseudokinases, CRM-1 lacks catalytic activity and operates *via* biomolecule interactions.

Here we proposed a knowledge-based strategy towards the discovery of targeted anti-cancer drugs in order to overcome drug resistance and render drug resistant cancer cells responsive to therapy. Recent progress in drug development technologies facilitated the targeting of difficult protein targets such as pseudokinases, unliganded transcription factors and nuclear export receptors thereby realizing the therapeutic potential of these approaches.

The continued development of nanomedicines has the potential to provide numerous benefits, including improved efficacy, bioavailability

and targeting ability of undruggable molecules, compared to conventional medicines. In the examples described in this review, we have shown that NPs present new opportunities to improve safety and efficacy of conventional therapeutics. It also opens the possibility of delivering drugs with low bioavailability.

Application of these new strategies in the treatment of patients is related to the development of personalized medicine or individualized medicine. This approach aims to analyze the characteristics of individual tumors and thus identify those that are likely to respond to a targeted therapy. Interest of this approach has been highlighted, for example, in the treatment of prostate cancer (Cohen et al., 2021), glioblastoma (Vessières et al., 2021b) and colorectal cancer (Kim et al., 2012). It is becoming increasingly important in the treatment of patients.

Declaration of Competing Interest

The authors declare no conflict of interest. The authors R.S., C.P., A. V. and G. La R. declare no conflict of interest. Wolfgang Link is the scientific co-founder of Refoxy Pharmaceuticals GmbH, Berlin and is required by his institution to state so in his publications. The funders had no role in the design and writing of the manuscript.

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