Pharmacological Research 211 (2025) 107544

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Targeting protein-protein interactions in drug discovery: Modulators approved or in clinical trials for cancer treatment

Cristina Camps-Fajol [a,b,c], Debora Cavero [a,c], Jordi Minguillón [d,e], Jordi Surrallés [a,b,c,f,g,*]

[a] Unitat Mixta de Recerca en Medicina Genòmica, Universitat Autònoma de Barcelona (UAB)-IR SANT PAU, Barcelona, Spain
[b] Institut de Bioenginyeria de Catalunya (IBEC), Barcelona, Spain
[c] Centro de Investigación Biomédica en Red de Enfermedades Raras, Instituto de Salud Carlos III (CIBERER, ISCIII), Madrid, Spain
[d] CIBERER-ISCIII, IdiPAZ-CNIO Translational Research Unit in Pediatric Hemato-Oncology, La Paz University Hospital Research Institute; Spanish National Cancer Center, Madrid, Spain
[e] Hematopoietic Innovative Therapies Division, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Madrid, Spain
[f] Servei de Genètica, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[g] Departament de Genètica i Microbiologia, Universitat Autònoma de Barcelona, Spain

ARTICLE INFO

Keywords:
Protein-protein interaction
PPI
Modulators
Approved
Clinical trials
Cancer treatment

ABSTRACT

Protein-protein interactions (PPIs) form complex cellular networks fundamental to many key biological processes, including signal transduction, cell proliferation and DNA repair. In consequence, their perturbation is often associated with many human diseases. Targeting PPIs offers a promising approach in drug discovery and ongoing advancements in this field hold the potential to provide highly specific therapies for a wide range of complex diseases. Despite the development of PPI modulators is challenging, advances in the genetic, proteomic and computational level have facilitated their discovery and optimization. Focusing on anticancer drugs, in the last years several PPI modulators have entered clinical trials and venetoclax, which targets Bcl-2 family proteins, has been approved for treating different types of leukemia. This review discusses the clinical development status of drugs modulating several PPIs, such as MDM2–4/p53, Hsp90/Hsp90, Hsp90/CDC37, c-Myc/Max, KRAS/SOS1, CCR5/CCL5, CCR2/CCL2 or Smac/XIAP, in cancer drug discovery.

Abbreviations: ADT, androgen deprivation therapy; AML, acute myeloid leukemia; Bak, Bcl-2 homologous antagonist/killer; Bcl-2, B-cell lymphoma; Bcl-X_L, B-cell lymphoma extra-large; BiFC, bimolecular fluorescence complementation; BIR, baculovirus IAP repeat domain; BLI, bio-layer interferometry; BRET, bioluminescence resonance energy transfer; CLL, chronic lymphocytic leukemia; CTD, C-terminal homodimerization domain; CRC, colorectal cancer; DH, Dbl homology; ECLs, extracellular loops; EGFR, epidermal grow factor receptor; EMA, European Medicines Agency; ERK1-2, extracellular signal-regulated kinases 1 and 2; FBDD, fragment-based drug discovery; FDA, Food and Drug Administration; FP, fluorescent polarization; FRET, fluorescence resonance energy transfer; FSH, follicle-stimulating hormone; γc, gamma chain; GEF, guanine nucleotide exchange factor; GIST, gastrointestinal stromal tumor; GLP-1, glucagon-like peptide of type 1; GLP-2, glucagon-like peptide of type 2; GnRH, gonadotropin-releasing hormone; GnRHR, GnRH receptors; GUCY2C, receptor guanylyl cyclase C; HCC, hepatocellular carcinoma; HFs, histone folds; HNSCC, head and neck squamous cell carcinoma; HAS, human serum albumin; Hsp90, heat shock protein 90; HSR, heat shock response; HTRF, homogeneous time-resolved fluorescence; HTS, high throughput screening; HTLV-1, human T-lymphotropic virus 1; IAPs, inhibitors of apoptosis proteins; ICLs, intracellular loops; ITC, isothermal titration calorimetry; LBVS, ligand-based virtual screening; LDLR, low-density lipoprotein receptor; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; Max, Myc-associated factor X; MDM2-4, murine double minute 2-4; MS, mass spectrometry; MSS, microsatellite stable; NMR, nuclear magnetic resonance; NSCLC, non-small cell lung cancer; NTD, N-terminal ATP-binding domain; P53, tumor protein p53; PAINS, pan-assay interference compounds; PCSK9, proprotein convertase subtilisin/kexin type 9; PDAC, pancreatic ductal adenocarcinoma; PH, pleckstrin homology; PMMR, mismatch repair proficient; PPI, protein-protein interaction; PR, proline-rich; PROTAC, proteolysis targeting chimera; REM, RAS exchanger motif; SBDD, structure-based drug design; SBVS, structure-based virtual screening; SCLC, small cell lung cancer; SOS, son of sevenless; SPR, surface plasmon resonance; T-LGLL, T-cell large granular lymphocyte leukemia; TME, tumor microenvironment; TNBC, triple-negative breast cancer; VS, virtual screening.

* Correspondence to: Joint Research Unit on Genomic Medicine, Universitat Autònoma de Barcelona (UAB)-IR SANT PAU. DNA repair and Cancer Predisposition Syndromes Group, Carrer de Sant Quintí, 77, Barcelona 08041, Spain.
E-mail addresses: jsurralles@santpau.cat, jordi.surralles@uab.cat (J. Surrallés).

https://doi.org/10.1016/j.phrs.2024.107544
Received 16 October 2024; Received in revised form 27 November 2024; Accepted 9 December 2024
Available online 11 December 2024
1043-6618/© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Protein-protein interactions (PPIs) can be defined as stable or transient physical contacts established between two or more proteins as a result of biomolecular forces. PPIs in cells form a complex network that has been called the 'interactome', which is estimated to include between 130,000 and 650,000 types of PPIs [1–3]. This high amount of PPIs contrasts with the presence of only around 20,000 protein coding genes, representing about 1.5 % of the genome [4]. PPIs are essential to protein functions and play a central role in a multitude of key biological processes, including signal transduction, cell proliferation, differentiation, DNA repair and apoptosis. In consequence, their perturbation can be associated to many human diseases, such as cancer or neurodegenerative disorders [5,6]. The identification and characterization of critical hubs and nodes in PPI networks related to certain diseases may reveal unique opportunities for novel therapeutic intervention [7,8].

Several types of modulators targeting PPIs are currently either being studied in the clinical setting or already approved. Firstly, many monoclonal antibodies are being used to treat various diseases, including cancer (e.g., PD-1/PDL1 inhibitors pembrolizumab, nivolumab, atezolizumab, etc.) and autoimmune disorders. These antibodies selectively target cell surface antigens in cancer cells, inhibiting downstream signaling and leading to cancer cell death [9]. The main concerns related to these drugs include their potential for immunotoxicity, high production costs and the appearance of resistance [10]. Small molecules are also being used to disrupt PPIs. These compounds often target pockets within the protein interface, avoiding its interaction with another protein [11]. Several small-molecule inhibitors are being studied in clinical trials and the Bcl-2 inhibitor venetoclax has been approved for different types of leukemia. Peptidomimetics are synthetic molecules designed to mimic the structural and functional properties of natural peptides or proteins. These compounds are able to disrupt PPIs by binding to the protein interface and blocking the interaction to its protein partner. Several peptidomimetics have been approved for different diseases and some others are being evaluated in clinical trials, such as the c-Myc/Max inhibitor OmoMyc, that is being studied for cancer treatment (NCT04808362). Another type of peptide that can inhibit PPIs are stapled peptides. These are a type of synthetic mini-proteins that are stabilized by chemical cross-linking to adopt and maintain specific secondary structures, typically α-helical. They disrupt PPIs by mimicking native peptides in complex with their target protein interfaces. Some stapled peptides have progressed into clinical trials for cancer treatment (e.g., the dual MDM4/MDM2 inhibitor ALRN-6924, NCT02264613). Some of the limitations that both peptidomimetics and stapled peptides can face are that they often exhibit low stability in vivo and that they tend to be sensitive to proteolysis by peptidases, what reduces their half-life and makes them poor drug candidates [12,13]. Proteolysis Targeting Chimeras (PROTACs) are small molecules composed of two ligands joined by a linker that act as a bridge that engages an E3 ubiquitin ligase with the protein of interest, leading to its ubiquitination and subsequent proteasomal degradation. Molecular glues (e.g., thalidomide and its analogues [14]) are another type of targeted protein degraders that act by enhancing the formation of the PPI complex between an E3 ligase and the target protein [15]. Several PROTACs and molecular glues, such as ARV-471 (Phase III clinical trial, NCT05909397) and avadomide (Phase II clinical trial, NCT03834623 and Phase I clinical trial NCT01421524), are in preclinical or clinical development for various diseases, including cancer [15]. However, off-target effects resulting from their degradation of other targets need to be carefully studied, as they could cause long-term side effects [16]. Finally, RNA interference (RNAi)-based therapies are another type of technology that can indirectly target PPIs. This technique employs small RNA molecules to silence the expression of specific genes, including those encoding proteins involved in PPIs. RNAi approaches are being studied for different diseases and a few of them have been approved. An example of an RNAi targeting a PPI is the small interfering RNA (siRNA) inclisiran, that is approved for the treatment of hypercholesterolemia, by causing *PCSK9* gene silencing and therefore preventing the PCSK9/LDLR interaction to take place [17]. Challenges related to this therapy include efficient systemic delivery of RNAi molecules, off-target effects, and the need to achieve sustained knockdown [18,19].

2. Targeting PPIs with small molecules

Classically, drug discovery using small synthetic molecules generally focused on interactions between ligands and individual proteins such as receptors, ion channels or enzymes, since they contain well-defined binding sites (around 300–500 $Å^2$) [11,20–23]. However, this model has strong limitations, including unexpected side effects related to other functions of the protein or reduced efficacy due to the homeostatic compensation through other pathways. To avoid this, drug discovery approaches should be directed not only to the targeting of individual proteins but also to the consideration of their interaction network [3,24].

As PPIs are essential for many cellular functions and their dysregulation leads to several diseases, the modulation of PPIs offers a great opportunity to directly target entire signaling networks involved in these diseases. This modulation includes both the classic approach of inhibiting the interaction between both proteins and the less common tactic of stabilizing the PPI. PPIs were in the past regarded as 'undruggable' due to many reasons. For instance, numerous protein crystal structures, specially from globular proteins, show flat interaction interfaces reaching 1500–3000 $Å^2$, what is larger than the traditional receptor-ligand contact area, such as enzyme binding sites [23–25]. Moreover, the interface of PPIs usually contains highly hydrophobic residues [26] and a few grooves or pockets, hence making it difficult to identify suitable cavities that could be targeted with small molecules [24,25]. Besides, many of these PPI modulators exhibit higher molecular weight (>400 Da) than traditional small molecule inhibitors (200–500 Da), and therefore often violate traditional drug-likeness criteria such as Lipinski's Rule of five [27,28].

The long-sought goal of modulating PPIs was achieved with several monoclonal antibodies and peptidomimetics, but their generally low cell permeability and oral bioavailability did not make them very attractive for therapeutic purposes. Contrarily, targeting PPIs with small molecules showed many more advantages over large protein competitors, especially from a kinetic perspective, even if their discovery was considered challenging [29]. The development of small molecules targeting PPIs was made possible by the discovery of specific amino acids, the so-called hotspots, within the large binding interfaces of PPIs. These residues contribute to the binding free energy, tend to distribute mainly in the center of the PPI interface, are often located nearby sub-pockets and are complementary on both sides of the interface [23,24,30]. Additionally, when small molecules interact with the binding site, small conformational changes may make the pocket deeper [31]. These hotspots are identified through point mutation experiments. More concretely, the amino acid residues involved on PPIs are mutated into alanine, and the resulting change of the binding free energy is analyzed to identify the residues that are mainly responsible for this binding free energy [30,32]. Indeed, the term "hotspot" has been defined as a key residue that contributes significantly to the binding of two proteins and its substitution with an alanine leads to a remarkable increase in the binding free energy of the complex of more than 2 kcal/mol. The most frequently represented amino acids in hotspots are tryptophan, arginine and tyrosine [11,23].

Targeting hotspot residues at PPIs with small molecules seems to be a reasonable strategy to disrupt PPIs. Although the interface of PPIs is relatively large, by targeting hotspots a small molecule could break critical interactions and disrupt the PPI. Moreover, changes in protein conformations may create transient pockets in the protein surface that could be targeted with small molecules [24]. To this must be added that apart from binding the protein-protein interface (orthosteric

modulation), these compounds could also interact with sites outside the contact surface area between the two proteins, resulting in an allosteric modulation. Orthosteric approaches are useful for those PPIs with hotspots gathering together forming pockets, whereas allosteric methods may help on those cases where hotspots do not form pockets or in those PPIs without hotspots [11,33]. Approaches that target both types of modulation should also be considered. Finally, a myth that has been associated with small molecules is that native protein complexes have higher affinity than protein–small molecule complexes and cannot be competed away. This has been refuted by the fact that in many cases small molecules bind with affinity values comparable to those of native protein-protein complexes [29].

3. PPI characterization

There is high demand for techniques that allow to identify, monitor or better characterize PPIs. Many genetic, proteomic, biochemical, biophysical, structural biology and computational technologies have been developed to contribute to gain knowledge about protein interfaces (Fig. 1). Genetic approaches comprise the yeast two-hybrid system [34], phage display [35] and synthetic lethality analysis using RNAi [36]. Proteomic assays may use protein microarrays [37] or mass spectrometry-based methods coupled with several biochemical techniques, such as co-immunoprecipitation, pull-down, co-elution, cross--linking and affinity purification [38,39]. Biophysical techniques include isothermal titration calorimetry (ITC), which allows to directly measure the amount of heat released or absorbed during protein association; fluorescent polarization (FP), where a change on the rotation of a protein attached to a fluorophore upon protein-protein binding is detected [40]; Bio-layer Interferometry (BLI), which allows to detect biomolecular interactions by analyzing the shifts in the wavelength of white light reflected from the surface of a biosensor tip [41]; and surface plasmon resonance (SPR), a real-time label-free optical technique that measures changes in the refractive index upon binding of the analyte with the immobilized ligand at the surface of a sensor chip [42]. Other biophysical methods include dual polarization interferometry [43], light scattering [44] and circular dichroism methods [45]. Also employed for PPI characterization are the proximity-based assays fluorescence resonance energy transfer (FRET), that uses the non-radiative (dipole-dipole) energy transfer from an excited donor fluorophore to an acceptor when both of them are in close proximity; homogeneous time-resolved fluorescence (HTRF), which combines standard FRET with time-resolved measurement of fluorescence; bioluminescence resonance energy transfer (BRET), which is similar to FRET, but is based on a luciferase reaction that requires the fusion of the donor (luciferase) and the acceptor (fluorescent) to the proteins of interest; amplified luminescent proximity homogeneous assay screen (Alpha Screen), a bead-based technology that detects in a microplate format the energy transfer between two beads that are bound to the proteins of interest when these last interact with each other [46,47]; and bimolecular fluorescence complementation (BiFC), based on the formation of a fluorescent complex upon interaction between the non-fluorescent N-terminal and C-terminal fragments of a fluorescent protein fused to the two proteins of study [48]. Some other experimental methods such as NMR, cryo-electron microscopy (cryo-EM) and X-ray crystallography are useful to determine the three-dimensional structures of protein-protein complexes, and together with mutational analysis can also be employed to identify and study the so-called hotspots in PPIs [30, 49,50].

Thanks to the results provided by these experimental techniques massive PPI data on different organisms has been compiled in several online databases. Some of the most popular repositories including

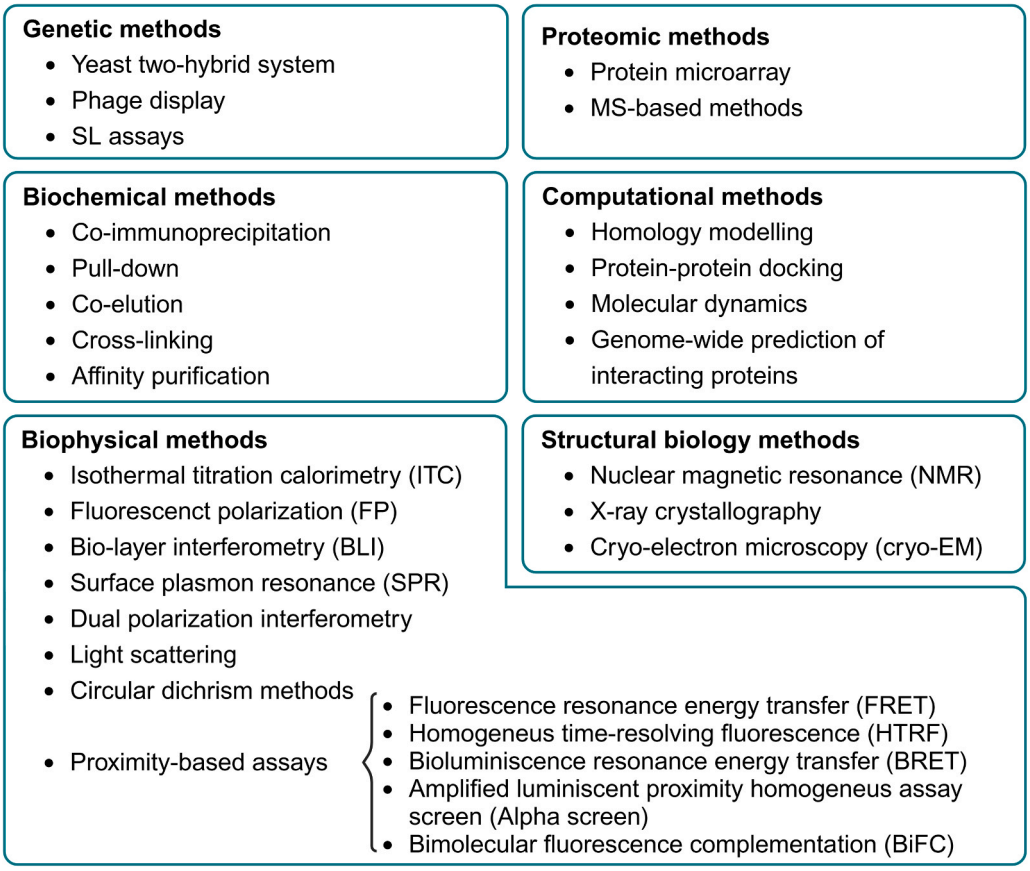

Fig. 1. Approaches for PPI characterization. Amongst the approaches that have been employed recently for PPI characterization are numerous genetic, proteomic, biochemical, computational, biophysical and structural biology methods. Figure created in BioRender.

massive protein-protein interaction data of various organisms are the General Repository for Interaction Database (BioGrid), the Biomolecular Relations in Information and Transmission and Expression (KEGG BRITE) database, the Mammalian Protein-Protein Interaction (MPPI) database, the PRotein Interaction and Molecular Information database (PRIME), the Database of Interacting Proteins (DIP), the Molecular Interaction Database (MINT), UniProt and the Search Tool for the Retrieval of Interacting Genes/proteins (STRING) [51,52]. This information is being used by different computational methods such as homology modelling, protein-protein docking, molecular dynamics and artificial intelligence, that can be based on genomic context and structural information, network topology, text mining and literature mining (or database mining) and machine learning algorithms employing heterogeneous genomic or proteomic features [49,53]. Some of the servers and software tools for visualizing and analyzing PPI networks are AlphaFold 3, SWISS-MODEL, RoseTTAfold, PRISM, HDOCK and Interactome3D, amongst others [53]. These tools can help for instance to predict the structure of a protein only from its amino acid sequence or to model both homo- and heteromeric complexes by utilizing the amino acid sequences of the interacting partners [54]. However, these methods still harbor a lot of limitations, as biases exist in these databases towards well-studied genes and proteins, and they may not be fully up to date. One of the reasons for these biases may be the fact that some homologous structures have not yet been fully experimentally resolved. Collaboration between databases to improve data heterogeneity, the advancement of experimental technologies such as cryo-EM, X-ray crystallography and NMR, the deposition of other characterized protein complexes in the ProteinData Bank (PDB), the improvement of protein structure prediction tools and the incorporation of new technologies based for instance on deep learning may help to better predict and characterize PPIs [54,55]. Additionally, the druggability of PPI interfaces can be assessed using different computational tools, such as SiteMap [56], PocketQuery [57] and TACTICS [58], amongst others.

Finally, data obtained from all these experimental and computational techniques may be used for the genome-wide inference of PPIs [59].

4. Approaches for the identification of PPI modulators

The above-mentioned characteristics of PPIs have hindered the discovery of modulators of these targets through conventional medicinal chemistry methods used for classical drug targets. Consequently, the design of new efficient drug discovery approaches that take into account the nature of PPIs is required. Numerous strategies have been employed recently to screen and identify PPI modulators in the initial stages of drug discovery processes (Fig. 2).

Firstly, high throughput screening (HTS), a method often used for traditional drug targets, has been broadly applied to the discovery of modulators of different PPIs. However, because of the nature of PPI interfaces typical compound libraries used for conventional HTS may not be appropriate for the screening of PPI modulators, as they do not contain enough chemical diversity. In fact, the success of this technique depends on screening large compound libraries that include high diversity, complexity and biological relevance [46]. For instance, HTS has been proven useful at the initial state of the discovery of inhibitors of the MDM2/p53 interaction [60].

Another approach that has been employed recently for the discovery of PPI modulators is structure-based drug design (SBDD), sometimes referred to as rational drug design or more simply rational design. SBDD uses the binding site of either one of the two protein partners to rationally design the associate PPI modulator. This method relies on the knowledge of the 3D structure of the target obtained through methods such as X-ray crystallography, nuclear magnetic resonance (NMR), cryo-electron microscopy or homology modelling. SBDD may be divided into different strategies. One of them is based on the structure of hotspots and uses bioisosterism and *de novo* design to obtain novel modulators [11].

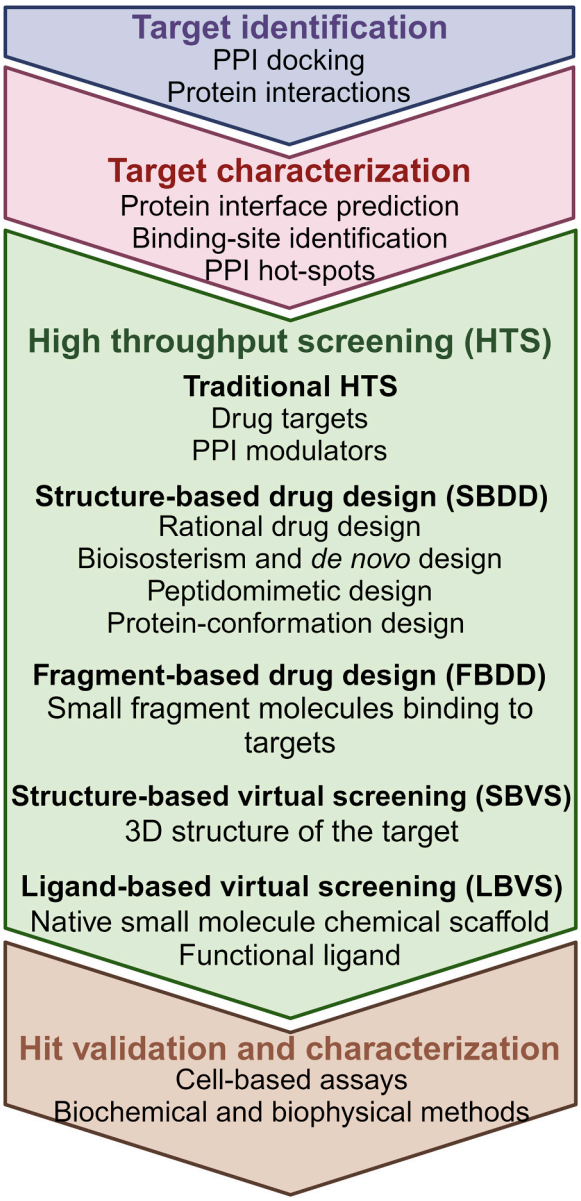

Fig. 2. Initial stages of the drug discovery process. The drug discovery process includes different steps: target identification, target characterization, hit identification by, for instance, high throughput screening and hit validation and characterization. Figure created in BioRender.

Another one is peptidomimetic design and mainly relies on computer modelling and the optimization of the amino acid sequence of a peptide derived from the natural binding epitope or a phage-derived peptide [11,46]. Other strategies may be related to the design of mimetics of protein secondary structures or the use of conformationally constrained peptides and miniproteins [46]. Several PPI modulators have been successfully identified using this method, including Bcl-X_L/Bak [61] and MDM2/p53 [62] inhibitors. The ERK1/2 inhibitor AZD0364, which is currently being tested in a Phase I clinical trial (NCT04305249), was also discovered using this approach [63].

Fragment-based drug discovery (FBDD) has also been applied for the discovery of PPI modulators. This method aims to identify small fragment molecules binding to targets. Compared to HTS, FBDD is considered a better approach to design PPI modulators because the PPI interface often consists of discontinuous hotspots and the binding of a fragment may reveal a new chemical space that may be explored to obtain a drug lead [11,33]. The initial fragment hits typically exhibit a

weak binding affinity to the target, but it may be enhanced after hit identification through introducing several chemical modifications. The overall chemical diversity of the library may also be improved by using a pharmacophore-based selection. Promising lead compounds have also been found when combining FBDD with SBDD, including the dual ROCK-AKT inhibitor AT13148 [64], which was investigated in a Phase I clinical trial against solid tumors (NCT01585701). However, it did not progress further due to its narrow therapeutic index and an unfavorable pharmacokinetic profile [65]. Another classic example of FBDD that was improved by SBDD is the development of the Bcl-X_L inhibitor ABT-737 [66].

These three approaches though face another challenge specific to PPIs. There are several protein-protein complexes that have not yet been properly experimentally defined. Recent developments to overcome this include new computational tools, such as protein docking and homology modelling, that are combined with the available low-resolution experimental approaches to, for instance, better predict and characterize hotspots [46,67]. Computer-based virtual screening (VS) is a powerful approach that allows to identify binding compounds using very large compound libraries with an appealing cost-effectiveness, compared to the massive working burden related to experimental screening approaches [68]. VS uses professional application software with filters to exclude pan-assay interference compounds (PAINS), which are compounds that often cause false-positive assay results and should be eliminated before applying biophysical screening methods [69]. Several compound databases of experimentally validated PPI inhibitors have become available, such as the TIMBAL [70], the iPPI-DB [71], the $2P2I_{DB}$ [72] and the Fr-PPIChem [73] database. These databases allow not only to store these PPI inhibitors, but also to determine their physicochemical properties. These characteristics can be used to build statistical models based on different training sets, molecular descriptors and machine learning in order to select putative PPI inhibitors from large commercial compound collections. Medicinal chemistry filters can also be applied to remove PAINS and improve drug likeness. The Fr-PPIChem library, for instance, can be then plated in 384-well plates in order to be validated by the scientific community willing to discover and develop new therapeutic drugs [73,74]. In fact, the validation of the most promising candidates may be then performed using several biophysical and biochemical techniques such as SPR, thermal shift, ITC, MST NMR, X-ray crystallography and mass spectrometry (MS) [11,69]. As described in Section 3., when seeking for PPI inhibitors, the druggability of PPI interfaces can be also analyzed using different computational tools, such as SiteMap [56]. Molecular descriptors may also be used by applying machine-learning approaches to discriminate between compounds that prefer to bind to deep binding pockets (buried compounds) from molecules that remain solvent-exposed at the surface of a target [75].

VS approach may be divided into 2 categories: structure-based virtual screening (SBVS) and ligand-based virtual screening (LBVS). SBVS docks the molecules to a well-defined 3D structure of the target and then ranks them according to their predicted binding affinity or complementarity to the binding site. Therefore, this strategy requires the availability of high-resolution structural information of the biological target. In the absence of high-resolution structure and/or homology model data, the LBVS strategy uses a native small molecule chemical scaffold or a functional ligand as a reference and seeks for compounds with chemical or conformational similarity within compound databases. In summary, one of the main advantages of using VS as a pre-screen is that it may limit the number of possible compounds in a manageable number for more efficient synthesis and further experimental validation [68]. Several examples of the successful application of this approach for drug discovery of PPI modulators include inhibitors of Ubc13/Uev1 [76], Hsp90/CDC37 [77] and MDM2/p53 [78].

5. PPI modulators approved or in clinical trials for cancer treatment

Focusing on anticancer drugs, several PPI modulators have entered clinical trials in the last years, and a few of them have been recently approved by regulatory agencies. A selection of small molecule PPI modulators FDA-approved or in more advanced clinical phases for cancer treatment has been listed on Table 1. A more thorough register of clinically developed PPI modulators can be found on Table S1.

5.1. Inhibitors of MDM2–4/p53 interactions

The tumor suppressor gene *TP53* is the most frequently mutated gene in cancer (~50 % of human cancers), what results in the inactivation of p53 protein [79]. P53 protein functions as a transcription factor that is activated upon multiple stress stimuli, including oncogenic and oxidative stress, DNA damage or metabolic dysfunction, and induces the transcription of a large number of protein-coding genes directed to suppress tumor development [80]. In unstressed cells under normal conditions, p53 protein levels are low through a negative feedback loop caused by the E3 ubiquitin-protein ligase MDM2, which targets p53 for proteasome-mediated degradation [81] (Fig. 3A). Direct gene alterations in *TP53* can also result in the inactivation of p53 function [82]. Cellular stress caused by DNA damage or hypoxia, amongst other factors, disrupts this binding leading to p53 accumulation and activation [81]. Therefore, recovery of the p53 function as tumor suppressor through the inhibition of MDM2/p53 interaction represents a potential approach for cancer treatment.

Deeper knowledge of the MDM2/p53 PPI has been obtained thanks to X-ray crystallography data (Fig. 3B). This PPI involves 4 key hydrophobic hotspots (Phe 19, Leu 22, Trp 23 and Leu 26) in a short amphipathic helix formed by p53 and a small but deep hydrophobic pocket in MDM2 [82]. An effective strategy to block this interaction would be to design a small molecule targeting the identified hotspots in p53, what would result in the competition to bind to MDM2. Different screening strategies have been employed to achieve this goal, such as peptide-like design, HTS and SBDD [62,83,84]. Remarkably, a series of cis-imidazoline analogues called nutlins were identified by HTS [60]. Nutlins, as it was seen in the crystal structure of the binding, were able to bind to the deep hydrophobic pocket in MDM2, and therefore, displace recombinant p53 protein from its complex with MDM2. Nutlin-1, −2 and −3 displayed in vitro IC_{50} on MDM2/p53 interaction of 260, 140 and 90 nM, respectively, hence being nutlin-3 the one selected as lead compound. Roche posteriorly optimized nutlin-3 applying several structural modifications obtaining the compound RG7112. HTRF studies revealed that RG7112 had an IC_{50} of 18 nM, being 5 times more potent than nutlin-3 [85]. RG7112 was the first MDM2 inhibitor to enter clinical trials for the treatment of advanced solid tumors (NCT00559533) and hematologic malignancies (NCT00623870). Later on, some other MDM2 antagonists were developed. Idasanutlin (RG7388) is another small-molecule inhibitor of MDM2 that progressed to a Phase III clinical trial for the treatment of AML but was terminated due to lack of efficacy at the interim analysis (NCT02545283). Multiple Phase I or II clinical trials are ongoing with this compound (e.g., NCT03662126, NCT05797831, NCT04029688, etc.). The oral MDM2 antagonist navtemadlin (AMG232 or KRT-232) is being studied in Phase II/III clinical trials for patients with myelofibrosis who no longer benefit from treatment with a JAK inhibitor (NCT03662126) and as maintenance therapy for *TP53* WT advanced or recurrent endometrial cancer (NCT05797831). This drug is also undergoing several other Phase I or II trials for different cancers alone or associated with radiotherapy (NCT03217266), chemotherapy (NCT04190550), chemotherapy and the Bcl-2 inhibitor venetoclax (NCT03041688), the BTK inhibitor TL-895 (NCT02825836) or immunotherapy (NCT03787602). Anoter Phase Ib/II study of navtemadlin combined with pembrolizumab as maintenance therapy in locally advanced and metastatic NSCLC has

Table 1
Selection of small molecule PPI modulators approved and in clinical trials for cancer treatment.

PPI	Drug	Related condition	Phase	Sponsor	Status	Clinical trial identifier
MDM2/ p53	**Idasanutlin (RG7388)**	*MDM2*-amplified *TP53* WT solid tumors	II	Hoffmann-La Roche	R	NCT04589845 (TAPISTRY)
	Navtemadlin (AMG232/ KRT−232)	Myelofibrosis	II/III	Kartos Therapeutics	R	NCT03662126 (BOREAS)
		TP53 WT endometrial cancer	II/III	Kartos Therapeutics	R	NCT05797831
		Myelofibrosis	II	Kartos Therapeutics	R	NCT04878003
	Alrizomadlin (APG−115)	Leukaemia	IIa	Ascentage Pharma Group	R	NCT04496349
Bcl−2/ Bax	**Venetoclax (ABT−199)**	Leukaemia	A	AbbVie	A	–
	Navitoclax (ABT−263)	Myelofibrosis	III	AbbVie	ANR	NCT04472598 (TRANSFORM−1)
		Myelofibrosis	III	AbbVie	ANR	NCT04468984 (TRANSFORM−2)
		Myelofibrosis	II	AbbVie	ANR	NCT03222609 (REFINE)
		Leukaemia	II	AbbVie	C	NCT01557777
		Ovarian cancer	II	Centre Francois Baclesse	C	NCT02591095 (MONAVI−1)
		Leukaemia	II	Genentech	C	NCT01087151
	Lisaftoclax (APG−2575)	Leukaemia	II	Ascentage Pharma Group	R	NCT05147467
		Leukaemia	IIa	Ascentage Pharma Group	R	NCT04496349
XIAP/ caspase−9	**LCL−161**	Multiple myeloma	II	Mayo Clinic	C	NCT01955434
		Myelofibrosis	II	M.D. Anderson Cancer Center	C	NCT02098161
		TNBC	II	Novartis	C	NCT01617668
	Debio1143 (xevinapant/ AT−406)	HNSCC	III	EMD Serono Research and Development Institute	R	NCT05386550
		HNSCC	III	EMD Serono Research and Development Institute	ANR	NCT04459715
Hsp90/ ATP	**Tanespimycin (17-AAG/ KOS−953)**	Thyroid cancer	II	NCI	C	NCT00118248
		Advanced malignancies	II	Bristol-Myers Squibb	C	NCT00779428
		Kidney Cancer	II	Memorial Sloan Cancer Center	C	NCT00093405
		Kidney Cancer	II	NCI	C	NCT00088374
		Lymphoma	II	NCI	C	NCT00117988
		Multiple myeloma	II/III	Bristol-Myers Squibb	C	NCT00514371
		Multiple myeloma	III	Bristol-Myers Squibb	C	NCT00546780
		Systemic mastocytosis	II	National Institutes of Health Clinical Center	C	NCT00132015
		Melanoma	II	Cancer Research UK	C	NCT00104897
		Pancreatic cancer	II	NCI	C	NCT00577889
		Ovarian cancer	II	NCI	C	NCT00093496
		Prostate cancer	II	NCI	C	NCT00118092
	Retaspimycin (IPI−504)	Hormone-resistant prostate cancer	II	Infinity Pharmaceuticals	C	NCT00564928
		NSCLC	II	Infinity Pharmaceuticals	C	NCT01362400
	Luminespib (AUY922)	Gastrointestinal stromal tumor	II	SCRI Development Innovations	C	NCT01404650
		NSCLC with exon 20 EGFR mutations	II	Massachusetts General Hospital	C	NCT01854034
		NSCLC	II	National Taiwan University Hospital	C	NCT01922583
		ALK+ NSCLC	II	Massachusetts General Hospital	C	NCT01752400
		NSCLC	II	Novartis	C	NCT01124864
		Gastric cancer	II	Novartis	C	NCT01084330
	Ganetespib (STA−9090)	Gastrointestinal stromal tumor	II	Synta Pharmaceuticals	C	NCT01039519
		Breast cancer	II	Synta Pharmaceuticals	C	NCT01677455
		ALK+ NSCLC	II	Synta Pharmaceuticals	C	NCT01562015
		NSCLC	II	Synta Pharmaceuticals	C	NCT01031225
		Ocular melanoma	II	Dana-Farber Cancer Institute	C	NCT01200238
		SCLC	II	David M. Jackman	C	NCT01173523
		HR+ breast cancer	II	Dana-Farber Cancer Institute	C	NCT01560416
		CRC	II	Memorial Sloan Cancer Center	C	NCT01111838
		Breast cancer	II	Memorial Sloan Cancer Center	C	NCT01273896
		Esophagogastric cancer	II	Massachusetts General Hospital	C	NCT01167114
		HR+ prostate cancer	II	Barbara Ann Karmanos Cancer Institute	C	NCT01270880
		Breast cancer	II	QuantumLeap Healthcare Collaborative	R	NCT01042379 (I-SPY)
	BIIB021	HR+ breast cancer	II	Biogen	C	NCT01004081
		Gastrointestinal stromal tumor	II	Biogen	C	NCT00618319
Hsp90/ Hsp90	**Sulforaphane**	Prostate cancer	II	OHSU Knight Cancer Institute	C	NCT01228084
		Breast cancer	II	Evgen Pharma	C	NCT02970682
CCR5/ CCL5	**Maraviroc**	HIV-related Kaposi's Sarcoma	II	University of California	C	NCT01276236
	Vicriviroc (MK−7690)	MSS/pMMR CRC	II	Merck Sharp & Dohme LLC	C	NCT03631407
CCR2–5/ CCL2–5	**BMS−813160**	NSCLC, HCC	II	Icahn School of Medicine at Mount Sinai	C	NCT04123379
		Renal cell carcinoma	II	Bristol-Myers Squibb	C	NCT02996110

Data extracted from clinicaltrials.gov. Clinical trial status: C, completed; R, recruiting; ANR, active not recruiting; A, approved.

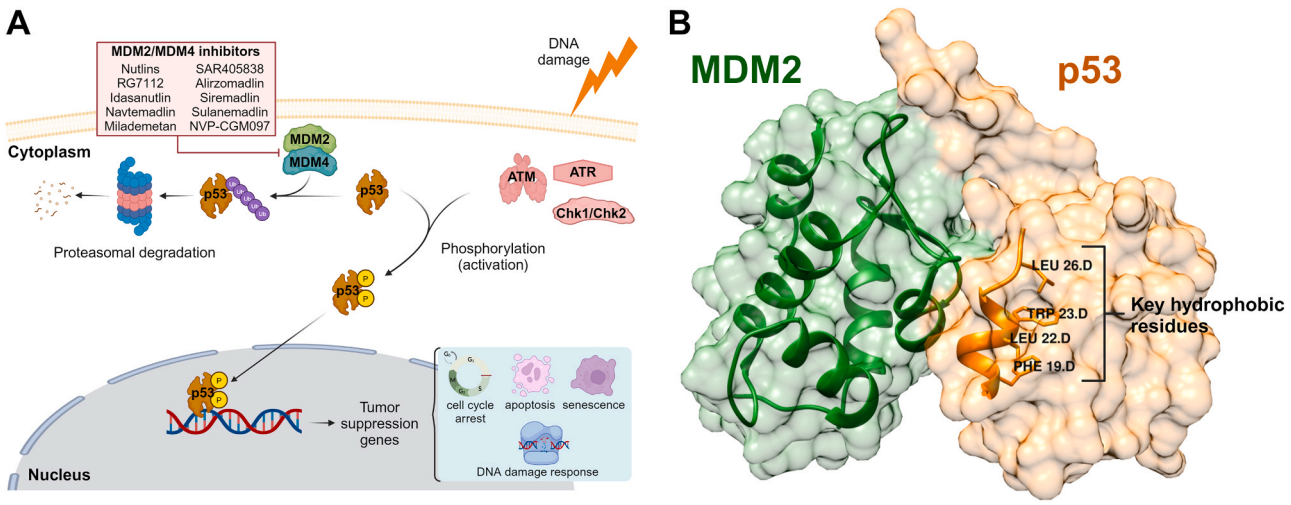

Fig. 3. MDM2–4/p53 PPI. A. The p53 protein functions as a transcription factor that activates different tumor suppressor genes in response to multiple stress stimuli (i.e., oncogenic and oxidative stress, DNA damage or metabolic dysfunction). In normal conditions, p53 protein levels are low through a negative feedback loop caused by the E3 ubiquitin-protein ligase MDM2, which in cooperation with MDM4 targets p53 for proteasome-mediated degradation. Cellular stress disrupts this binding leading to p53 accumulation and activation via ATM-Chk2 or ATR-Chk1-dependent phosphorylation. MDM2–4 inhibitors result in the inhibition of the proteasome-mediated degradation of p53 and, therefore, cause the activation of tumor suppression genes. B. The PPI between MDM2 and P53 (PDB: 4HFZ) involves 4 key hydrophobic hotspots (Phe 19, Leu 22, Trp 23 and Leu 26) in a short amphipathic helix formed by p53 (in orange) and a small but deep hydrophobic pocket in MDM2 (in green). Figure created in BioRender.

been recently withdrawn (NCT05705466). Miladematan is another MDM2 inhibitor that was being investigated for liposarcomas in a Phase III clinical trial compared to trabectedin but has been terminated due to a sponsor's decision (NCT04979442). A Phase II clinical trial of this drug in patients with solid tumors characterized by MDM2 dependence and wildtype *TP53* has been also recently terminated for the same reason (NCT05012397). Some other MDM2 antagonists, such as SAR405838, are still in Phase I clinical trials (NCT01985191 and NCT01636479), but the SAR405838 small-molecule analogue alrizomadlin (APG-115) has already progressed to Phase I/II and II clinical trials (e.g., NCT04496349, NCT04358393, NCT03611868). This compound is an orally active MDM2 antagonist that restores p53 tumor suppressive function via induction of apoptosis in WT *TP53* tumor cells [86]. Preliminary results from the Phase I/II trial (NCT03611868) have shown that alrizomadlin, combined with pembrolizumab, is well tolerated and exhibits antitumor activity in patients with highly refractory unresectable or metastatic cutaneous melanoma that had progressed on PD-1/PD-L1 immunotherapy [87]. Siremadlin (NVP-HDM201), developed by Novartis, is another MDM2 small molecule inhibitor that has just completed a Phase II clinical trial for the treatment of AML (NCT05155709). This drug is also currently undergoing Phase II clinical trials for other human cancers (e.g., NCT05180695, NCT04097821, etc.). Novartis has also developed NVP-CGM097, an orally bioavailable MDM2 inhibitor that was tested in a Phase I clinical trial in solid tumors and showed manageable tolerability (NCT01760525).

Another closely related protein to MDM2 that binds to the same p53 epitope is MDM4 (MDMX) [88]. MDM2 and MDM4 cooperate in the negative regulation of the p53 tumor suppressor [89]. In spite of the high structural similarity between both proteins, all previous compound scaffolds that had been published were proven highly specific for MDM2 and exhibited no or very low MDM4 binding [90]. MDM4 antagonists were also developed using different approaches, including FBDD [90] and SBDD [91]. The majority of them were peptides or peptidomimetics and after improving their cell permeability several candidates with different potency and selectivity against MDM4 and MDM2 were identified [92–94]. Another reported compound is sulanemadlin (ALRN-6924), a dual MDM4/MDM2 stapled peptide inhibitor that has progressed to a Phase II clinical trial (NCT02264613) in patients with advanced solid tumors or lymphomas with WT *TP53* [95]. This p53-based peptidomimetic exhibited remarkably better activity than the MDM2 inhibitor idasanutlin in different cell lines. Moreover, results from the clinical trial also showed a potential synergistic effect between sulanemadlin and immunotherapy [96]. In view of the promising antitumor activities observed by peptide-based dual MDM4/MDM2 antagonists, efforts have been made in the discovery of dual small molecule inhibitors of this target. Multiple compounds have been identified with variable potency and selectivity against MDM2 and MDM4 [97]. None of these compounds has yet undergone clinical trials, although some of the anti-MDM2 small molecules that are being tested in clinical trials exhibit moderate-low activity against MDM4, such as NVP-CGM097 [98].

5.2. *Inhibitors of Bcl-2/Bax or Bak interaction*

The Bcl family consists of different proteins that are involved in the regulation of apoptotic cell death. They can be subclassified into different groups based on their primary function: anti-apoptotic proteins (Bcl-2, Bcl-w, Bcl-X_L, Mcl-1, Bfl-1/A1, etc.) and pro-apoptotic proteins (Bax, Bok, Bak, Bid, Bad, Bmf, Noxa, Puma, Hrk, etc.). These two types of members of the Bcl family usually operate in the form of dimers to exert their role as an apoptotic switch. Specifically, the function of these pro-apoptotic proteins is blocked when they interact with the anti-apoptotic proteins and, therefore, inhibition of the PPI between both types of proteins may prevent tumor cells from escaping apoptosis [11]. Pro-apoptotic proteins can be further divided into effectors (Bak, Bax, Bok), direct activators (Bid, Bim and PUMA) and de-repressors/sensitizers (Bad, Bik, Bmf, Hrk and Noxa) [99,100]. Activators and de-repressors/sensitizers share only the Bcl-2 homology region 3 (BH3), while effectors and anti-apoptotic proteins share 4 Bcl-2 homology regions, BH1–BH4 (Fig. 4A). In general, the members of the BH3-only subfamily regulate the other two classes by directly activating the pro-apoptotic effectors or by blocking the activity of the anti-apoptotic proteins without directly engaging the pro-apoptotic effectors [99] (Fig. 4B). Taking as an example the Bcl-X_L/Bak interaction, two central hydrophobic α-helices in Bcl-2 (anti-apoptotic) are surrounded by six amphipathic α-helices, forming a hydrophobic BH3 groove that binds to Bak (pro-apoptotic effector) (Fig. 4C). Structural studies have shown that four conserved hydrophobic amino acids on Bak insert into 4 hydrophobic pockets named P1–P4 within the hydrophobic

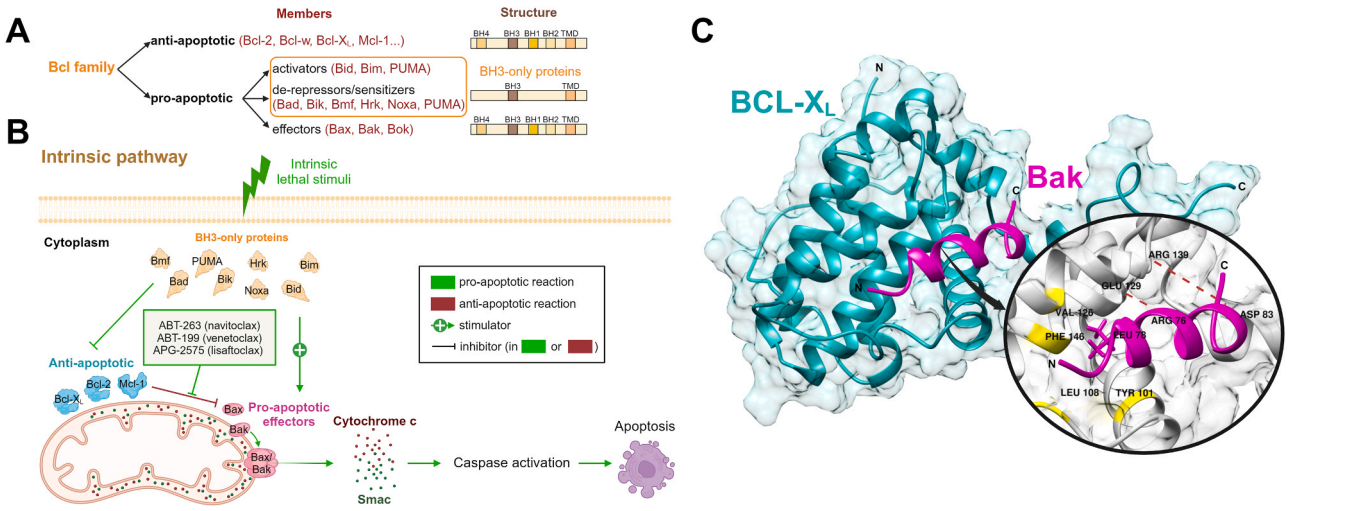

Fig. 4. Bcl-2/Bax or Bak PPI. A. The Bcl family consists of different proteins involved in apoptosis regulation. These proteins operate in the form of dimers to exert their role as an apoptotic switch. More concretely, the function of these pro-apoptotic proteins (Bax, Bok, Bak, Bid, etc.) is blocked when they bind to the anti-apoptotic proteins (Bcl-2, Bcl-w, Bcl-X_L, etc.). Pro-apoptotic proteins can be further divided into direct activators (Bid, Bim and PUMA), de-repressors/sensitizers (Bad, Bik, Bmf, Hrk and Noxa) and effectors (Bak, Bax, Bok). Activators and de-repressors/sensitizers share only the Bcl-2 homology region 3 (BH3), while effectors and anti-apoptotic proteins share 4 Bcl-2 homology regions, BH1–BH4. B. When intrinsic lethal stimuli occur in cells, members of the BH3-only subfamily directly activate pro-apoptotic effectors and block anti-apoptotic proteins. This results in cytochrome c and Smac (/Diablo) release from the inner membrane space of the mitochondria into the cytosol, what activates caspases that ultimately lead to apoptotic cell death. Several inhibitors of the Bcl-2/Bax or Bak interaction, such as navitoclax, venetoclax or lisaftoclax, have been discovered. This inhibition of the PPI between Bcl-2 (anti-apoptotic) and Bax or Bak (pro-apoptotic) may prevent tumor cells from escaping apoptosis by directly blocking the anti-apoptotic effect that Bcl-2 exhibits over the pro-apoptotic effectors Bax and Bak. Green lines represent pro-apoptotic reactions and red lines anti-apoptotic reactions. C. Taking the published structure of the BCL-X_L/Bak PPI (PDB: 1BXL) as an example, the Bak peptide interacts with BCL-X_L through the BH3 region. This region forms an amphipathic α-helix that establishes high affinity hydrophobic and electrostatic interactions with a hydrophobic groove in BCL-X_L. Figure created in BioRender.

groove, while an aspartate interacts with an arginine residue on Bcl-X_L [101] (Fig. 4C). Once activated, a BH3-only protein inserts its α-helical BH3 domain into the hydrophobic groove of the proapoptotic protein. The design of small-molecule mimetics of the BH3 domain of proapoptotic proteins thus enables these proteins to be targeted directly, neutralizing their functional activity [102].

Abbott researchers used a high-throughput NMR-based screening method for lead compound discovery called 'SAR by NMR' and a fragments library to identify small molecules that bind to the hydrophobic BH3-binding groove of Bcl-X_L. They obtained two small molecules, 4-fluoro-biphenyl-4-carboxylic acid and 5,6,7,8-tetrahydro-naphtalen-1-ol, that interacted with two small relatively independent hydrophobic pockets within the Bcl-X_L protein. Several modifications of the first small molecule led to a 3-nitro-4-(2-phenylthioethyl)aminophenyl group that was named compound 1. Compound 1 bound with high affinity to Bcl-X_L (K_i of 36 ± 1.6 nM), occupying both hydrophobic pockets. This affinity was though reduced in the presence of 1 % human serum albumin (HSA). To reduce binding to HSA they then applied a SBDD approach and added polar substituents. Additionally, they improved the binding to Bcl-2 by including a lipophilic group that allowed access to a deep, well-defined pocket in Bcl-2, identified in 3D structures of Bcl-2/inhibitor complexes. The resultant compound, ABT-737 binds with high affinity ($K_i \leq 1$ nM) to Bcl-X_L Bcl-2 and Bcl-w and nanomolar activity was retained in the presence of 10 % HSA [66]. The ABT-737 has been widely used in biological studies associated with apoptosis and also in preclinical studies for the treatment of lymphoma, small cell lung cancer (SCLC) and chronic lymphocytic leukemia (CLL). However, its clinical application is limited by its poor oral bioavailability [103].

The ABT-263 (navitoclax) is a second generation orally bioavailable inhibitor of Bcl-2 based on the structure of ABT-737. It targets and binds with high affinity ($K_i \leq 1$ nM) to multiple antiapoptotic Bcl-2 family proteins including Bcl-X_L, Bcl-2, Bcl-w and Bcl-B. Preclinical studies have demonstrated potent cytotoxic activity of navitoclax in human tumor cell lines derived from T- and B-cell lymphoid malignancies that overexpress Bcl-2. It also showed rapid and complete tumor regression in xenograft models [1,103]. Several Phase I clinical studies have shown anti-tumor activity of navitoclax in lymphoid malignancies and solid tumors alone and in combination with other antineoplastic agents (NCT00887757, NCT00891605). Thrombocytopenia was the main dose-limiting toxicity and was due to inhibition of Bcl-X_L [104–107]. This was confirmed in Phase II clinical trials (NCT01087151, NCT00406809) [108,109]. Two Phase III clinical trials of oral navitoclax in combination with oral ruxolitinib to assess change in spleen volume in adult myelofibrosis patients are ongoing (NCT04468984; NCT04472598).

Researchers then focused on obtaining a more selective Bcl-2 inhibitor that avoided the thrombocytopenia induced by ABT-263. Navitoclax and related structures were modified through the systematic removal or replacement of key binding elements and the complex of these compounds with Bcl-2 was studied. The introduction of an indole group enhanced the binding to the P4 hotspot in Bcl-2 through a hydrophobic interaction. Adding an azaindole as a new P4-binding moiety, along with a structural change in the P2-binding portion of the compound, produced the highly potent and Bcl-2-selective (not affecting Bcl-X_L) ABT-199, also known as venetoclax. Venetoclax showed an excellent inhibitory effect on CLL cells with high expression of Bcl-2 (EC_{50} = 8 nM). Compared with navitoclax, venetoclax significantly reduced the antiplatelet activity [110]. Based on significant activity as monotherapy in a Phase III trial in CLL (NCT02242942), the FDA approved venetoclax for CLL with 17p deletion in April 2016, becoming the first small molecule PPI inhibitor approved for marketing. Posteriorly, the FDA and the EMA approved several other indications for venetoclax alone or in combination for the treatment of different types of leukemia [11,109].

Recently, lisaftoclax (APG-2575), an orally bioavailable Bcl-2 selective inhibitor (Ki < 0.1 nM), was developed through computational modeling and showed strong antitumor activity in preclinical models of hematologic malignancies [111]. This compound is currently undergoing several clinical trials as a single agent or in combination for different hematologic neoplasms (e.g., NCT04215809, NCT04260217, NCT05147467, NCT04501120, NCT04964518, NCT04942067,

NCT04496349) and ER-positive breast cancer and advanced solid tumors (NCT04946864).

5.3. Stimulators of Smac/XIAP interaction

Inhibitors of apoptosis proteins (IAPs), such as XIAP, represent an important class of endogenous negative regulators of apoptosis that are characterized by the presence of at least one baculovirus IAP repeat (BIR) domain [112,113]. The binding of IAP to caspase or other pro-apoptotic proteins causes the inhibition of these proteins, leading to their degradation. Caspases implement apoptosis through two pathways, the extrinsic, mediated by caspase-8, and the intrinsic, which is mediated by cytochrome c/caspase-9 (Fig. 5A). The BIR3 domain of the metalloprotein XIAP is responsible for binding to pro-apoptotic caspase-9, thereby inhibiting it and suppressing apoptosis. Smac (also known as DIABLO) is an endogenous inhibitor of the XIAP-caspase-9 PPI that binds with its N-terminal amino acids, alanine-valine-proline-isoleucine (AVPI), to the BIR3 domain of XIAP so that it can no longer interact with caspase-9 [114] (Fig. 5B).

The crystal structure of the interaction between Smac and XIAP-BIR3 domain was deeply analyzed identifying potential targets for drug screening [115]. This knowledge led to the discovery of the first Smac simulator GDC-0152, through the combination of a peptidomimetic approach and several HTS campaigns [116]. This compound progressed to Phase I clinical trials in solid tumors but was terminated for reasons unrelated to patients' safety or anti-cancer activity (NCT00977067). GDC-0917 (CUDC-427) is another Smac mimetic that entered Phase I clinical trials for patients with advanced solid tumors and lymphomas and did not show severe toxicities [117]. Another Smac mimetic, TL32711 (birinapant), showed good pharmacokinetics and tolerability alone and in combination with multiple chemotherapeutic drugs in Phase I/II clinical trials (e.g., NCT01188499, NCT00993239, etc.). Clinical benefit from this compound was notably better when combined with irinotecan, what may be related to irinotecan as a TNFα-inducing agent [118]. Some other Smac mimetics that have reached Phase I/II clinical trials are LCL-161 and HGS1029 (e.g., NCT01955434, NCT00708006, etc.). Finally, the Smac mimetic Debio1143 (xevinapant or AT-406) was discovered employing a SBDD strategy using the crystal structure of Smac in complex with XIAP BIR3 protein [119]. Xevinapant plus cisplatin showed superior efficacy benefits, including markedly improved 5-year survival in a Phase II clinical trial (NCT02022098) enrolling patients with unresected locally advanced head and neck squamous cell carcinoma (HNSCC) [120]. For this reason, this compound is currently being tested in two Phase III clinical trials with HNSCC patients (NCT05386550, NCT04459715).

In a different approach, Astex Pharmaceuticals discovered using FBDD ASTX-660 (tolinapant), which is a dual small molecule antagonist of both XIAP and cIAP1/2 [121–123], that is currently being tested in different clinical trials. In the Phase I/II study (NCT02503423) it demonstrated a manageable safety profile and exhibited evidence of preliminary clinical activity at the 180 mg/day recommended Phase II dose [124]. The Phase II part of this study in advanced solid tumors and lymphomas is ongoing. Another Phase I trial (NCT05082259) of this compound in combination with pembrolizumab in patients with immune-refractory solid tumors is enrolling. Another Phase I/II study of tolinapant in combination with oral decitabine/cedazuridine in participants with peripheral T-cell lymphoma is also ongoing (NCT05403450).

5.4. Inhibitors of Hsp90/Hsp90 or Hsp90/CDC37 interactions

Molecular chaperones include different families of proteins that are crucial for maintaining the integrity of the proteome. One of them, the heat shock protein 90 (Hsp90) is a widely conserved molecular chaperone that is considered essential in eukaryotes and in some bacteria under stress conditions [125–127]. This protein contains four isoforms: Hsp90α and β, which can be found at the cytoplasm and nucleus, TRAP1 in the mitochondria, and GRP94 in the endoplasmic reticulum [128]. Hsp90 has many protein substrates (or 'clients') involved in different cellular processes, including cell proliferation and viability [129]. In particular, Hsp90 has been found highly expressed in cancer, indicating a relevant role of this protein in tumor growth and survival [130,131].

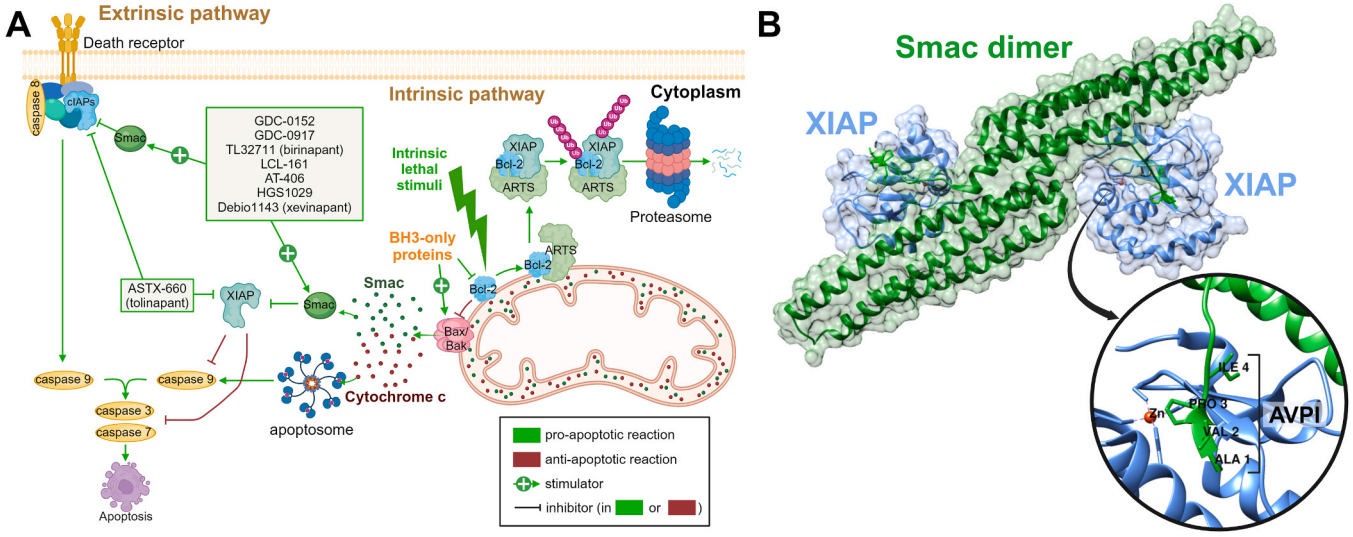

Fig. 5. Smac/XIAP PPI. A. The intrinsic mitochondrial pathway is initiated by ARTS forming a complex with XIAP and Bcl-2, what stimulates their proteasome-mediated degradation. Moreover, the BH3-only proteins directly activate pro-apoptotic effectors (Bak, Bax, etc.) and block anti-apoptotic proteins (eg., Bcl-2), resulting in the cytochrome c and Smac (/Diablo) release from the inner membrane space of the mitochondria into the cytosol. Once in the cytoplasm, Smac binds to XIAP resulting in the blocking of its cellular function of caspase inhibition, and cytochrome c interacts with Apaf-1 and forms the apoptosome which further activates caspase 9 to initiate apoptosis. Smac also participates in the extrinsic pathway by blocking the inhibitory effect that exhibit cIAPs over caspase 8. This further results in a cascade of caspases that ultimately lead to apoptosis. XIAP inhibitors and Smac stimulators therefore allow caspase activation and therefore result in apoptosis. Green lines represent pro-apoptotic reactions and red lines anti-apoptotic reactions. B. Considering the published structure of the PPI between Smac and XIAP-BIR3 domain (PDB: 1G73), Smac (also known as DIABLO) binds with its N-terminal amino acids, alanine-valine-proline-isoleucine (AVPI), to the BIR3 domain of XIAP so that it can no longer interact with caspase-9. Figure created in BioRender.

Amongst Hsp90's protein substrates several key protein kinases and transcription factors involved in cancer cell growth and apoptosis, such as HER2, VEGF, mutant p53, CDK4, HIF-1α, Raf-1 and AKT, are included. Hsp90 prevents their ubiquitinated-mediated degradation, resulting in the stabilization in the active form and the consequent promotion of tumor growth and metastasis [11,132–134]. Hsp90 is also regulated by a group of co-chaperones and accessory proteins [133]. Further, Hsp90 acts as a dimer where each protomer is formed by three conserved domains, including the N-terminal ATP-binding domain (NTD), the middle domain (MD), that consists of a large hydrophobic surface that serves as both nuclear localization sequences and client protein-binding site, and the C-terminal homodimerization domain (CTD), that contains the main dimerization interface [134,135]. It has been proposed that co-chaperones first interact with clients, followed by association with the Hsp90 dimer in an opened state [136]. Subsequent binding and hydrolysis of ATP and other substrates induce large distinct conformational rearrangements in the structure of Hsp90 dimers that may form different dynamic pockets [137–139] (Fig. 6A and B).

One of the main functions of Hsp90 is to regulate the use of ATP by its client proteins. This is such a crucial function for many normal proteins that the inhibition of the ATP binding to the Hsp90 N-terminal domain, using for instance the natural product geldanamycin, results in high toxicity [140]. Hsp90 inhibitors that block the binding of ATP to the Hsp90 N-terminal domain are classified as type 1 inhibitors and include geldanamycin analogs (e.g., tanespimycin, retaspimycin hydrocloride, IPI-493, etc.), radicicol, luminespib (AUY922), ganetespib (STA-9090), onalespib (AT13387) and other resorcinol-type compounds [139,141,142]. Some of these inhibitors targeting the N-terminal ATP pocket, apart from some initial promising results, have shown clinical hurdles such as induction of the heat-shock response, retinopathy, and gastrointestinal tract toxicity, raising concerns about their future development [143]. Tanespimycin (also called 17-AAG), a synthetic derivative of the antibiotic geldanamycin, is a first generation selective inhibitor of Hsp90 that reached Phase III clinical trials for the treatment of multiple myeloma in association with bortezomib (NCT00546780, NCT00514371). Unfortunately, its clinical development did not further progress due to non-clinical reasons. A second pocket is formed in the Hsp90 structure when the ATP binding site adopts a helical form [135]. Purine analogs, such as BIIB021 and SNX-5422 (pro-drug of SNX-2112), interact with both the N-terminal ATP pocket and this second pocket [139,144,145]. These compounds that bind to both pockets, and also moderately inhibit GRP94 and TRAP-1, have been classified as type 2 inhibitors. These purine-based compounds have reached Phase II clinical trials (NCT00618319, NCT01004081), but some of them have been terminated due to business reasons (NCT02612285). Despite this high amount of effort and progress made in the discovery of N-terminal inhibitors of Hsp90, none of them have yet reached the market. One of the reasons of that is in terms of toxicity, as these compounds induce a strong cellular heat shock response (HSR), which includes the overexpression of other Hsp proteins, requiring dose escalation [146–148]. TAS-116 (pimitespib) is a second generation Hsp90α/β inhibitor that binds to the ATP-binding domain and the second pocket, and also to a novel hydrophobic pocket (third pocket). This compound was generated by FBDD [149] and is highly specific for Hsp90α/β without causing the inhibition of other Hsp90 family proteins such as GRP94 in the endoplasmic reticulum or TRAP-1 in the mitochondria. In consequence, it shows higher efficacy and better safety margins than previous Hsp90 inhibitors [150,151]. This compound, discovered and developed by Taiho Pharmaceutical Co., received approval in June 2022 in Japan for gastrointestinal stromal tumors (GISTs) refractory to standard treatments (https://www.taiho.co.jp/en/release/2022/20220620.html). This approval was based on results of a Phase III trial that evaluated its efficacy and safety for this unmet medical need (JapicCTI-184094) [152]. Pimitespib is currently undergoing Phase I clinical trials for the treatment of GISTs in the USA (NCT05245968).

In contrast to classic Hsp90 inhibitors, the coumarin antibiotic novobiocin and its derivatives bind to the C-terminus interfering with Hsp90 dimerization without triggering the undesired HSR [147,148,153,154]. Apart from this effect over Hsp90, novobiocin was identified through an HTS as a specific POLθ inhibitor that selectively kills homologous recombination repair deficient tumor cells both in vitro and in vivo [155]. Thanks to these results, novobiocin is currently being

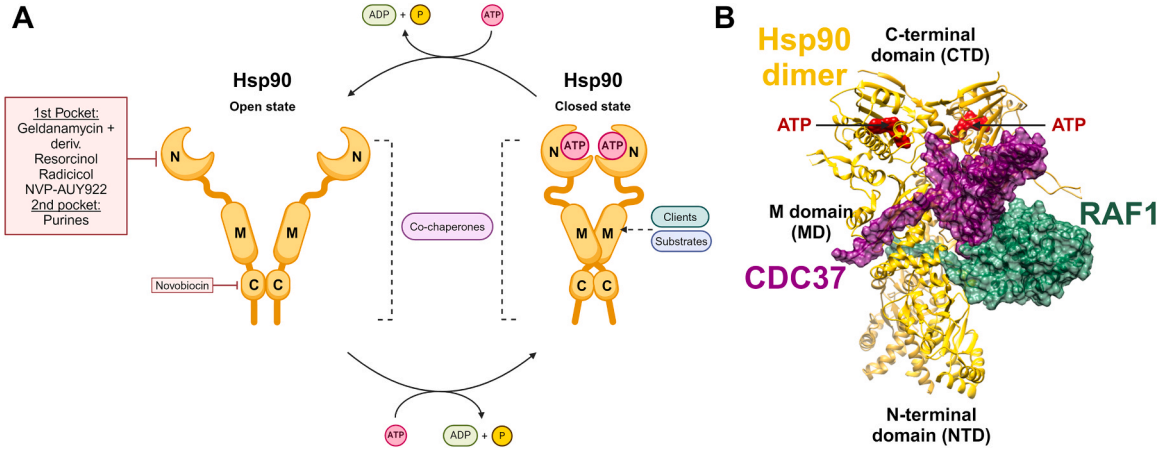

Fig. 6. Hsp90/Hsp90 or CDC37 PPI. A. Hsp90 is a molecular chaperone that acts as a dimer where each protomer is formed by three conserved domains: the N-terminal domain (NTD), that includes the nucleotide binding site (ATP/ADP), the middle domain (MD), that consists of a large hydrophobic surface that serves as both nuclear localization sequences and client and co-chaperones binding site, and the C-terminal domain (CTD), that contains the main dimerization interface. In the absence of ATP and client, Hsp90 exists as a protomer in an open conformation bound by the CTD. Co-chaperones that regulate Hsp90 firstly interact with clients, followed by association with the Hsp90 dimer. Subsequent binding of ATP to the CTD causes Hsp90's transition from an open to a closed state. Upon ATP hydrolysis and client phosphorylation, client is released and Hsp90 returns to its open 'V-shaped' state. Inhibitors of the Hsp90 /ATP or Hsp90/co-chaperones interaction have been identified. Geldanamycin and its derivatives, resorcinol, radicicol and NVP-AUY922 bind to the so-called 1st pocket domain, while purins to the 2nd pocket in the NTD, resulting in blocking ATP binding. Novobiocin and its derivatives bind to the CTD of Hsp90. B. Focusing in the described PPI structure between Hsp90 and CDC37 and RAF1 in a closed state (PDB: 5FWK), the co-chaperone CDC37 (in purple) first interacts with clients, such as the kinase RAF1 (also known as C-RAF, in green), followed by association with the MD of both Hsp90 protomers (in yellow). The Hsp90-CDC37 complex promotes RAF1 phosphorylation preventing its degradation. Subsequent binding of ATP (in red) to the CTD induces large conformational rearrangements in Hsp90 dimers transitioning from an open to a closed state that may form different dynamic pockets. Upon ATP hydrolysis and RAF1 phosphorylation, RAF1 is released and Hsp90 returns to its open 'V-shaped' state. Once phosphorylated RAF1 participates as a direct KRAS effector in the activation of the MAPK signaling pathway. Figure created in BioRender.

studied in a Phase I trial in patients with tumors with alterations in DNA repair genes (NCT05687110). Another reported inhibitor of the CTD domain is the natural product silibinin, obtained from the milk thistle (*Silybum marianum*). This compound, that has been widely used in several pharmacological formulations for its anti-hepatotoxic effects, has also shown activity as anti-cancer agent [156,157].

Researchers believe that a more challenging, but potentially far more specific, approach is to develop agents that block the interaction between Hsp90 and its client or accessory proteins [133]. Considering the co-chaperones of Hsp90, CDC37 plays a significant role in loading kinases like EGFR, CDK and AKT to Hsp90 [158,159], and thus, disrupting this interaction may deactivate the kinase clients and result in the inhibition of tumor proliferation and growth. The resolving of the crystal structure of the Hsp90/CDC37 core complex provided a solid structural basis for the development of inhibitors of this target [160]. A screening was then performed by SPR assays to find inhibitors of Hsp90 protein using triazine derivatives, and DCZ3112 was selected, which exhibited a K_D of 4.98 μM and did not inhibit ATPase activity [161]. By molecular docking researchers observed that the compound competitively bound to the N-terminal domain of Hsp90 and disrupted its binding to CDC37. Moreover, DCZ3112 inhibited the proliferation of HER2-positive breast cancer cells and xenografts and exhibited enhanced anti-tumor activity when combined with the anti-HER2 antibody trastuzumab. It also produced synergistic in vitro activity in inhibiting cell proliferation, inducing G1-phase arrest and apoptosis, and reducing AKT and ERK phosphorylation. Posteriorly, a SBVS was performed using four small molecule libraries to identify potential disruptors of the Hsp90/CDC37 interaction [77]. After successive molecular docking through high throughput virtual screening, standard precision and extra precision considering the free binding energy of the standard compound (DCZ3112) as cut-off, followed by in silico pharmacokinetics and binding interaction analyses, four molecules were proposed as crucial to inhibit this PPI. In another screening, cascade docking was employed to identify within a commercial database compounds that disrupted the Hsp90/CDC37 PPI, followed by experimental validation using HTRF. After several chemical modifications of the selected compounds, they obtained DDO-5936. This compound remarkably decreased CDK4 expression and caused the consequent inhibition of cell proliferation through CDC37-dependent cell cycle arrest [162]. Several compounds extracted from plants, such as celastrol (extracted from *Tripterygium wilfordii*), sulforaphane (dietary component from broccoli sprouts) or withaferin A (extracted from *Withania somnifera*), also inhibit the Hsp90/CDC37 PPI reducing the proliferation of cancer cells [163–165]. Withaferin A is being studied in a Phase I/II clinical trial in combination with doxorubicin for the treatment of recurrent ovarian cancer (NCT05610735). The chemopreventive effect of sulforaphane has also been tested in the clinical setting (NCT00982319, NCT03232138).

5.5. Inhibitors of c-Myc/Max interaction

MYC is a proto-oncogene that plays a critical role in cancer development and maintenance [166]. The c-Myc transcription factor, encoded by *MYC*, is the prototype member of the Myc family of proteins that also include n-Myc and l-Myc in mammalian cells, all of which are highly homologous but exhibit different expression patterns. Most functional studies of the Myc family of proteins to date have focused on the c-Myc product [167]. c-Myc is a highly conserved protein with helix structure, that is found largely overexpressed in the majority of human cancers and has therefore become a focus of attention to design new therapeutic strategies in oncology [166,168,169]. The activity of c-Myc depends on the formation of the c-Myc/Max dimer, via an interaction between their basic-helix-loop-helix zipper (bHLH-Zip) domains. This dimer recognizes a CACGTG enhancer box (E-box) in the target DNA and enhances the transcription of genes involved in cell growth and proliferation. The transactivation activity of c-Myc/Max is counteracted by Mad, which also dimerizes with Max to repress transcription and induces cell growth arrest and differentiation. The function of Max homodimers is still unclear, although it seems that they passively repress transcription by competing for DNA-binding elements with the heterodimers [170–172]. Therefore, the balance between the expression of c-Myc/Max or Mad/-Max determines whether the cell will divide and proliferate (c-Myc/-Max) or differentiate and become quiescent (Mad/Max) [173–175] (Fig. 7A and B). In fact, it has been hypothesized that interfering with c-Myc dimerization by inhibiting the c-Myc/Max PPI may block the activation or transcription of oncogenes, leading to an anti-tumoral effect [11]. Several small molecules that interfere with c-Myc/Max dimerization and show interesting in vivo effects have been discovered.

10074-G5, a small molecule inhibitor of the c-Myc/Max PPI, was reported [176]. It binds and stabilizes c-Myc in its monomeric form with an IC_{50} of 146 μM. After determining the pharmacophore, it was optimized leading to JY-3–094, which was almost 5 times as potent (IC_{50} = 33 μM) but could not enter the cell due to a charged carboxylic acid group. This was remedied by esterifying the carboxylic acid to generate a series of ester pro-drugs with low micromolar IC_{50} values, that were converted by intracellular esterases to JY-3–094. However, its activity was still limited by the carboxylic acid metabolite. To solve this, they combined 10074-G5 and JY-3–094, leading to 3jc48–3, that exhibited an IC_{50} value of 34.8 μM and was active cellularly. Further optimizations will be needed to increase its resistance to cellular hydrolysis and increase its short plasma half-life ($t_{1/2}$ = 37 min). Mycro3 is another small molecule inhibitor of c-Myc/Max dimerization that showed efficacy in increasing the survival of mice with pancreatic cancer upon oral administration [177]. A series of small molecule c-Myc inhibitors were also developed by coupling the in silico screening of a large chemical library to an in vivo screen in mice. An improved analogue with better tolerability, MYCi975, was finally identified [178]. This compound showed IC_{50} between 2.49 and 7.73 μM in a panel of 14 breast cancer cell lines and when combined with either paclitaxel or doxorubicin in preclinical investigations enhanced cell growth inhibition was observed [179]. KJ-Pyr-9 is another inhibitor of c-Myc that was identified from a Kröhnke pyridine library. This compound decreased survival of primary human colorectal cancer (CRC) [180], non-small cell lung cancer (NSCLC) [181] and endometrial cancer [182] cell lines.

MYCMI-6, a compound that exhibited strong selective inhibition of c-Myc/Max interaction both biochemically and in cell-based experiments, was identified through a cell-based protein interaction screen [183]. SPR results showed that MYCMI-6 bound selectively to the c-Myc bHLH-Zip domain with a K_D of 1.6 ± 0.5 μM. It also inhibited tumor cell growth in a c-Myc-dependent manner with IC_{50} concentrations of 0.5 μM and reduced proliferation and induced massive apoptosis in tumor tissue from a c-Myc-driven xenograft model. MYCMI-6 was also found to inhibit cell growth (IC_{50} values: 0.3–10 μM) and induce apoptosis in breast cancer cell lines [184].

Last but not least, the contribution of single amino acids to the c-Myc/Max PPI was analyzed by molecular modelling and mutagenesis and a mutant c-Myc with altered dimerization properties, OmoMYC, was constructed [173]. This mini-protein interacts with both c-Myc and Max but it preferentially binds to the latter. Due to its small size, it can easily enter the nucleus and function like a Mad1/Max heterodimer or a Max homodimer to inhibit Myc-mediated transcription. Moreover, OmoMYC has been found to compete with the 3 Myc family members (c-Myc, n-Myc and l-Myc) for binding to their target promoters [169,185–187] and has shown efficacy in various experimental models of SCLC and NSCLC harboring different oncogenic mutation profiles [188,189]. OmoMYC (OMO-103) has been tested in a Phase I/IIa clinical trial (NCT04808362) for the treatment of advanced solid tumors that has been recently terminated as sponsor decided to change strategy to a combination study. Results from this trial have shown that OmoMYC administered intravenously once a week has few side effects, is tolerable and stabilizes disease in some patients. The recommended Phase II dose was determined [190]. Another Phase Ib clinical trial to evaluate the safety, pharmacokinetics, and efficacy of OmoMYC administered

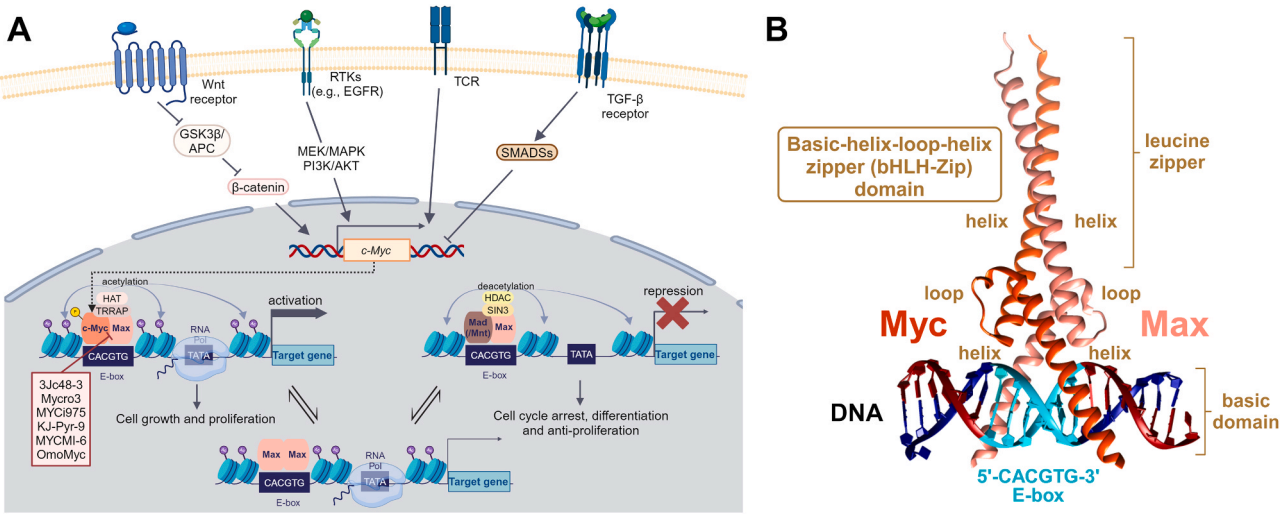

Fig. 7. c-Myc/Max PPI. A. Several growth signaling pathways including Wnt, receptor tyrosine kinases (RTKs) and TGF-β activate c-Myc expression. The activity of c-Myc depends on the formation of the c-Myc/Max dimer. This dimer recognizes a CACGTG enhancer box (E-box) in the target DNA and enhances the transcription of genes involved in cell growth and proliferation. The transactivation activity of c-Myc/Max is counteracted by Mad or Mnt, which also dimerize with Max to repress transcription and induce cell cycle arrest, differentiation and anti-proliferation. The function of Max homodimers is still unclear, although it seems that they passively repress transcription by competing for DNA-binding elements with the heterodimers. Therefore, the balance between the expression of c-Myc/Max or Mad/Max or Mnt/Max determines whether the cell will divide and proliferate (c-Myc/Max) or differentiate and become quiescent (Mad/Max or Mnt/Max). Several inhibitors of the c-Myc/Max interaction have been reported, what results in cell cycle arrest, differentiation and anti-proliferation. B. Using the Myc and Max PPI (PDB: 1NKP), Myc is a highly conserved protein with helix structure whose activity depends on the formation of the c-Myc/Max dimer, via an interaction between their basic-helix-loop-helix zipper (bHLH-Zip) domains. This dimer recognizes a 5'-CACGTG-3' E-box in the target DNA and enhances the transcription of genes involved in cell growth and proliferation. Figure created in BioRender.

intravenously in combination with the standard regimen gemcitabine/nab-paclitaxel in patients with pancreatic ductal adenocarcinoma (PDAC) is recruiting (NCT06059001).

5.6. Inhibitors of KRAS/SOS1 interaction

RAS proteins (KRAS, NRAS and HRAS) act as binary on-off switches that cycle between active GTP-bound and inactive GDP-bound states. Oncogenic *RAS* is found mutated in approximately 19 % of human

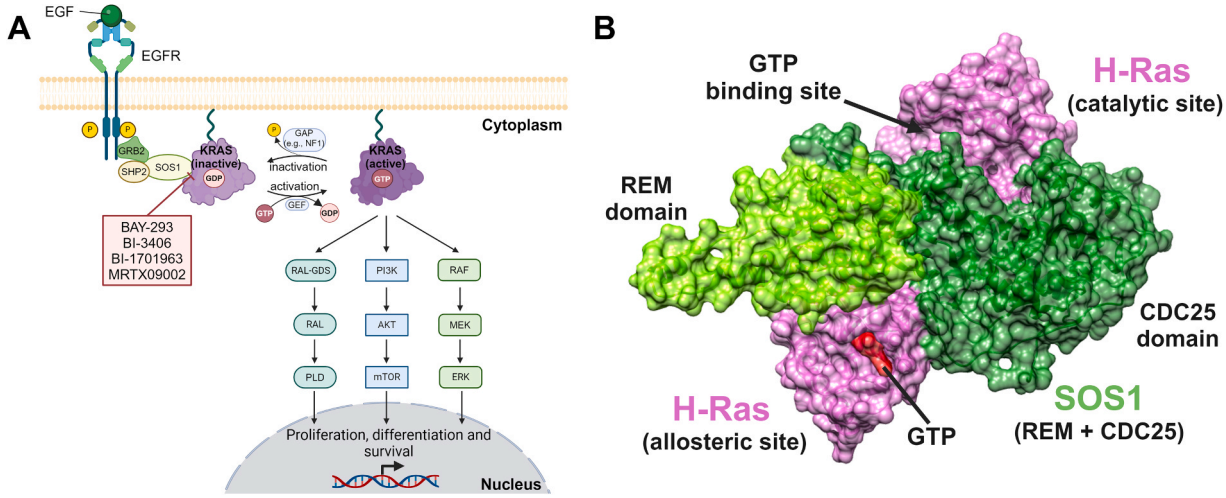

Fig. 8. KRAS/SOS1 PPI. A. KRAS acts as a binary on-off switch that cycles between active GTP-bound and inactive GDP-bound states. Upon EGFR stimulation, GRB2 adaptor protein associates with EGFR and recruits cytosolic SOS1 to the cell membrane, through binding of its SH3 domains to the C-terminal PR domain of SOS1. Inactive KRAS binds then to the CDC25 domain of SOS1 that catalyzes GDP-to-GTP exchange. GTP-bound KRAS can further activate SOS1 through binding at the exposed allosteric site resulting in increased Ras nucleotide exchange activity. Activated RAS stimulates downstream signaling pathways, such as RAL-GDS/RAL/PLD, RAF/MEK/ERK and PI3K/AKT/mTOR signaling, leading to cell proliferation, differentiation and survival. Several inhibitors of the KRAS/SOS1 PPI have been discovered and some of them have entered clinical trials for cancer. B. Taking the published HRAS/SOS1 PPI (PDB: 1NVW) as an example, SOS1 is a large multidomain protein composed by: an N-terminal region, which contains two tandem histone folds (HFs), a Dbl homology (DH) domain and a pleckstrin homology (PH) domain, and joined by a helical linker, the C-terminal domain, that includes a RAS exchanger motif (REM) domain (in light green), a CDC25 domain (in dark green), and a proline-rich (PR) region containing SH3-binding motifs. Inactive HRAS interacts with the CDC25 domain of SOS1, resulting in GTP (in red) binding and conversion of inactive GDP-bound state of HRAS to active GTP-bound. This GTP-bound HRAS further activates SOS1 through interaction with the exposed allosteric site found between REM and CDC25. Oncogenic mutations in RAS disrupt the guanine exchange cycle, typically by 'locking' RAS in the active GTP-bound state. Figure created in BioRender.

cancers [191]. These mutations result in the disruption of the guanine exchange cycle, typically by 'locking' RAS in the active GTP-bound state. Activated RAS consequently activates downstream signaling pathways, such as RAL-GDS/RAL/PLD, RAF/MEK/ERK and PI3K/AKT/mTOR signaling, leading to cell proliferation, differentiation and survival [192–194] (Fig. 8A). These pathways are frequently found over-activated in carcinogenesis [195,196]. The RAS pathway is also activated by mutations in genes encoding RAS regulatory proteins (*NF1*, *SOS1* and the SHP2-encoding *PTPN11* gene) [197–199] and downstream mediators (BRAF, RAF1) [200,201]. Investigators have sought an effective RAS inhibitor for more than three decades, but due to the challenging biochemical properties of RAS itself and redundancies in downstream signalling, RAS has been thought to be 'undruggable' [193]. Among the different RAS proteins, KRAS is often mutated in different cancers, especially in a large proportion of pancreatic cancers [202]. Targeting KRAS signaling has become an important field in anticancer drug discovery. Mainly two strategies can be followed to inhibit KRAS: the direct targeting of the signaling pathway of KRAS or the inhibition of its association to the plasma membrane [11,203,204]. However, only the first approach has obtained compounds that are already in clinical trials.

As for the signaling activity of KRAS, an approach that has been suggested is related to the inhibition of KRAS regulatory proteins. Son of Sevenless (SOS) is a guanine nucleotide exchange factor (GEF) that activates KRAS by promoting conversion of inactive GDP-bound state of KRAS to active GTP-bound (Fig. 8B). Two homologs of SOS exist, SOS1 and SOS2, being SOS1 functionally prevalent in different cellular processes [205,206]. Moreover, SOS1 has been reported to participate in a negative feedback loop within the KRAS pathway [207]. SOS1 is a large multidomain protein whose structure is composed of an N-terminal region, which contains two tandem histone folds (HFs), a Dbl homology (DH) domain and a pleckstrin homology (PH) domain, and joined by a helical linker, the C-terminal domain, that includes a RAS exchanger motif (REM) domain, a CDC25 domain, and a proline-rich (PR) region containing SH3-binding motifs. SOS1 can accommodate two Ras molecules: one at the allosteric site between REM and CDC25 domains, and the other one at the catalytic site (active site) in the CDC25 domain [198, 208,209]. Upon EGFR stimulation by EGF, GRB2 adaptor protein associates with EGFR and recruits cytosolic SOS1 to the cell membrane, through binding of its SH3 domains to the C-terminal PR domain of SOS1 [210,211]. Concerning RAS activation, inactive KRAS binds to the CDC25 domain of SOS1 that catalyzes GDP-to-GTP exchange. GTP-bound KRAS can further activate SOS1 through binding at the exposed allosteric site resulting in increased Ras nucleotide exchange activity [212,213].

Several attempts have been made to inhibit the KRAS/SOS1 interaction by using peptidomimetics of the RAS-interacting α-helix of SOS1 [214,215] or small molecule inhibitors discovered by NMR-based fragment screens [216,217]. However, none of these compounds have advanced to the clinical setting to date. Interestingly, some of these researchers also tried to identify compounds that activated the SOS1-mediated nucleotide exchange, what resulted in biphasic modulation of RAS signaling through negative feedback on SOS1 [218–223].

Further research has been performed to discover compounds that cause a reduction in KRAS activity via SOS1. Small molecule inhibitors of SOS1 were reported [224], focusing on its interaction with the oncogenic mutant $KRAS^{G12C}$ due to its clinical importance in lung cancer related to tobacco smoke exposure [225,226]. In this case, they took an HTS approach combining results from FBDD and crystallization of the structures of the $KRAS^{G12C}$–SOS1 complex and of SOS1 in complex with inhibitors, amongst others. They finally obtained compound 23 (BAY-293), which selectively inhibits KRAS–SOS1 interaction with an IC_{50} of 21 nM [224]. This compound showed synergy with drugs targeting specific vulnerabilities of *KRAS*-mutated pancreatic cancer cell lines [227]. With a similar structure as BAY-293, another orally bioavailable small molecule SOS1 inhibitor, BI-3406, was discovered by SBDD [228]. This compound binds to the catalytic domain of SOS1 with low nanomolar affinity, avoiding its interaction with KRAS and suppressing tumor growth in xenograft models of KRAS-driven cancers. Moreover, BI-3406 was able to attenuate adaptive resistance to MEK inhibitors induced by feedback reactivation, suggesting that combined SOS1 and MEK inhibition may represent a novel therapeutic approach to manage KRAS-driven tumors [229]. Interestingly, both BAY-293 and BI-3406 contain the same quinazoline scaffold as many EGFR inhibitors, such as erlotinib. In order to avoid binding to EGFR and achieve selectivity for SOS1 a 2-methyl substituent was included in their structure.

The small molecule BI-1701963 developed by Boehringer Ingelheim was the first SOS1 inhibitor reported to have entered clinical trials. Binding of this compound to the catalytic site of SOS1 blocks its interaction with RAS–GDP, thereby avoiding RAS activation. Treatment with BI-1701963 has shown cytostasis of cancer cells addicted to KRAS signaling in preclinical studies. The first Phase I trial testing BI-1701963 either alone or in combination with trametinib (MEK inhibitor) is ongoing for *KRAS*-mutated solid tumors (NCT04111458) [230]. Two other Phase I clinical trials studied BI-1701963 combined with irinotecan (NCT04627142) or the MEK inhibitor BI-3011441 (NCT04835714) for the treatment of solid tumors but were prematurely terminated due to non-clinical reasons. Moreover, another Phase I trial that evaluated BI-1701963 in combination with the irreversible $KRAS^{G12C}$ inhibitor MRTX849 (adagrasib) in patients with $KRAS^{G12C}$-mutated advanced solid tumors has been completed but results have not yet been published (NCT04975256). BI-1701963 is also being tested in a Phase I clinical trial combined with the $KRAS^{G12C}$ inhibitor BI-1823911 (NCT04973163). Finally, Boehringer Ingelheim established clinical collaboration with Amgen to perform a Phase Ib/II clinical trial of BI-1701963 in combination with the $KRAS^{G12C}$ inhibitor sotorasib in patients with $KRAS^{G12C}$-mutated advanced solid tumors (NCT04185883). MRTX0902 is another inhibitor of the SOS1/KRAS PPI that is currently being tested in a Phase I/II clinical trial alone or in combination with adagrasib in patients with advanced solid tumor malignancy with mutations in the KRAS or MAPK pathways (NCT05578092). This brain-penetrant and orally bioavailable compound exhibited almost complete tumor regression in xenografts models of pancreatic cancer when administered in combination with sub-maximal doses of adagrasib [207].

5.7. Inhibitors of CCR5/CCL5 and/or CCR2/CCL2

Emerging resistance to classical antiretroviral agents for HIV has led to the need to develop drugs with novel mechanisms of action. Maraviroc (UK-427857) is an orally bioavailable CCR5 antagonist approved for the treatment of HIV infection in combination with other antiretroviral drugs. This small molecule acts by blocking the binding of the gp-120 glycoprotein from the viral envelope to CCR5 chemokine receptor on the surface of certain immune cells, thereby preventing fusion of the viral membrane with the membrane of these cells and the consequent viral entry. By blocking this entry point, maraviroc helps reduce viral load in individuals with HIV and slows down disease progression [231] (Fig. 9A). Several others CCR5 antagonists are undergoing clinical trials (e.g., leronlimab, cenicriviroc, vicriviroc, etc.). Based on reported relevance of CCR5 activation in cancer initiation and progression, several of these antagonists that were initially developed for HIV therapy, are now being studied in the oncology field.

The CCR5 receptor, also known as C-C chemokine receptor type 5, is a chemokine receptor belonging to the family of G protein-coupled receptors. As a member of this family, it is composed of seven transmembrane helical domains linked by three extracellular loops (ECLs) and three intracellular loops (ICLs). The ECLs together with the N-terminus of CCR5 participate in chemokine (e.g., CCL5, CCL3, CCL4 and CCL8) binding, whereas the ICLs and the C-terminal domain play an important role in G protein-mediated signal transduction [232,233] (Fig. 9B). As described before, CCR5 is mainly found in immune cells and

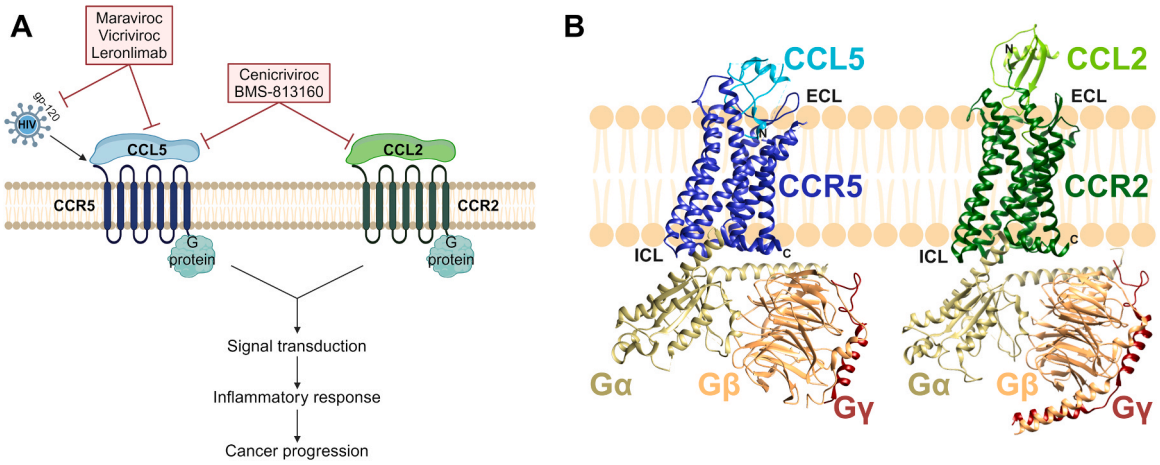

Fig. 9. CCR5/CCL5 and CCR2/CCL2 PPI. A. CCR5 and CCR2 are chemokine receptors expressed in immune cells, fibroblasts and neurons. Their respective ligands, CCL5 and CCR2 trigger signaling cascades associated with inflammation. Elevated expression of these receptors is observed in various cancer types, promoting oncogenic transformation, cancer progression and metastasis. Antagonists targeting these receptors are crucial in HIV treatment, inhibiting viral membrane interaction with CCR. Additionally, they play a pivotal role in mitigating inflammatory responses and restraining cancer progression. B. As for the CCR5/CCL5 PPI (PDB: 7F1R), the CCR5 receptor is a chemokine receptor belonging to the family of G protein-coupled receptors composed of seven transmembrane helical domains linked by three extracellular loops (ECLs) and three intracellular loops (ICLs). The ECLs together with the N-terminus of CCR5 participate in chemokine (e.g., CCL5 or RANTES) binding, whereas the ICLs and the C-terminal domain play an important role in G protein-mediated signal transduction. Thanks to preclinical data showing an involvement of the CCL5/CCR5 axis in cancer progression and metastasis, CCR5 inhibitors are being studied at the clinical setting for cancer treatment. Concerning the CCR2/CCL2 PPI (PDB: 7XA3), CCR2 is another chemokine receptor structurally related to CCR5. CCR2 also binds to some of the same chemokines as CCR5, being CCL2 the most potent and only selective ligand. The CCL2/CCR2 signaling axis has also been related to the metastatic process. Since both CCR5 and CCR2 seem to intervene in cancer pathogenesis, dual inhibitors of these two receptors have been developed and have progressed to clinical trials. Figure created in BioRender.

plays a fundamental role in the inflammatory response by directing cells to sites of inflammation [234]. This receptor has been found overexpressed in different cancer types [235–237] in a mechanism that seems to be induced by oncogenic transformation [220]. Among CCR5 ligands, the chemokine CCL5 (also called RANTES) has also been found overexpressed in different tumor types and together with CCR5 seems to be associated with cancer progression and metastasis [235,238–241] and the building of an immunosuppressive tumor-promoting tumor microenvironment (TME) [242,243]. Treatment with maraviroc or other CCR5 small molecule (vicriviroc, TAK-779, etc.) or monoclonal antibody (leronlimab) antagonists inhibited CCL5 activation reducing the invasiveness and metastatic potential of different cancer cell types [236,237,244,245]. In fact, maraviroc has shown to be particularly effective for treating CRC and pancreatic liver metastases [242,246] and mammary lung metastases [236,247]. In the molecular level, CCR5 blockade induced apoptosis and arrest in the G1 phase of the cell cycle [242,245,246,248]. Maraviroc and vicriviroc also enhanced DNA damage induced by different chemotherapeutic agents exerting synergistic effects [249,250]. High levels of both CCR5 and its ligand, CCL5, have been detected in patients with chronic liver disease and fibrosis [251], and maraviroc seemed to reduce the development of hepatocellular carcinoma (HCC) in a murine chronic liver disease model [252]. Thanks to all these preclinical data showing involvement of the CCL5/CCR5 axis in cancer progression and metastasis, CCR5 inhibitors progressed to clinical trials for cancer treatment.

Several clinical trials with the CCR5 antagonists maraviroc, leronlimab (PRO 140) and vicriviroc alone or in combination with chemotherapy, in Kaposi's sarcoma (maraviroc, Phase II, NCT01276236), CRC with liver metastases (maraviroc, Phase I, MARACON trial, NCT01736813), CCR5 + locally advanced or metastatic solid tumors (leronlimab, Basket study, NCT04504942) and triple-negative breast cancer (TNBC) (leronlimab, Phase Ib/II, NCT03838367) are completed, ongoing or recruiting. More concretely, in the MARACON trial no significant side effects for maraviroc treatment were observed in previously treated metastatic CRC patients and partial responses were achieved in patients with previously refractory disease [253]. Leronlimab in combination with carboplatin seems to be also well tolerated and has demonstrated promising preliminary results in the Phase Ib/II clinical trial (NCT03838367) for patients with CCR5 + metastatic TNBC [254]. Some of these compounds are being or have been clinically investigated in association with immunotherapy (anti-PD-1) for metastatic CRC (maraviroc, Phase I, PICASSO trial, NCT03274804; maraviroc, Phase I, LUMINESCENCE trial, NCT04721301; vicriviroc, Phase II, NCT03631407) and pancreatic cancer (maraviroc, Phase I, NCT03274804). In the PICASSO trial (NCT03274804), therapy with maraviroc combined with pembrolizumab exhibited a beneficial toxicity pattern but did not show relevant clinical activity in patients with refractory mismatch repair proficient CRC. However, the high response rates or disease stabilizations observed to poststudy exposure to cytotoxic treatment require further investigation [255]. The combination of vicriviroc plus pembrolizumab employed in the Phase II trial (NCT03631407) for treating advanced or metastatic microsatellite stable (MSS)/mismatch repair proficient (pMMR) CRC also showed limited antitumor activity with manageable toxicity [256].

CCR2 is another chemokine receptor structurally related to CCR5. Genes codifying for CCR2 and CCR5 share significant sequence homology [257], probably indicating that they arose from a gene duplication [258]. While CCR5 is expressed on a broad range of immune cells, neurons, fibroblasts and other cell types, normal CCR2 expression is almost restricted to monocytes, NK and T lymphocytes. CCR2 also binds to some of the same chemokines as CCR5, being CCL2 the most potent and only selective ligand [259]. The CCL2/CCR2 signaling axis has been related to the pathogenesis of many inflammatory and neurodegenerative diseases such as atherosclerosis, autoimmune diseases and cancer [258–262]. In the case of cancer, this axis has been shown to be especially relevant for the metastatic process. CCL2 can be synthesized by both stromal and tumor cells in the TME, where it recruits immune cells and modulates angiogenesis and tumor extravasation, growth and progression [260,263–265]. Since both CCR5 and CCR2 seem to intervene in the pathogenesis of cancer and other diseases, dual inhibitors of these two receptors have been developed. On the one hand, cenicriviroc (TAK-652), which was first developed for the treatment of HIV infection

[266], is a first-in-class dual CCR2/CCR5 antagonist that has been studied in clinical trials for different indications but specially to treat liver fibrosis in adults with nonalcoholic steatohepatitis (CENTAUR trial, NCT02217475; AURORA trial, NCT030287400), which is a high-risk condition for developing hepatocellular carcinoma. However, the Phase III AURORA trial did not demonstrate the efficacy of cenicriviroc for treating liver fibrosis [267]. On the other hand, BMS-813160 is another dual CCR2 and CCR5 antagonist that exhibited good preclinical results [268] and entered clinical trials for different types of cancer. This compound was tested in a Phase II trial in combination with nivolumab for advanced renal cell carcinoma (FRACTION-RCC trial, NCT02996110). Soon afterwards another Phase Ib/II study studied BMS-813160 in combination with chemotherapy or nivolumab in patients with advanced solid tumors (NCT03184870). BMS-813160 is also being tested in two Phase I/II trials for the treatment of PDAC associated with nivolumab, gemcitabine and paclitaxel (NCT03496662) and with neoadjuvant and adjuvant nivolumab with or without the cancer vaccine GVAX (NCT03767582). Preliminary results from this second clinical trial associating 300 mg of BMS-813160 orally twice a day with neoadjuvant and adjuvant nivolumab with or without GVAX (NCT03767582), have shown that this combination is safe, and neoadjuvant use does not lead to a delay in surgery [269]. Moreover, a Phase II study analyzing neoadjuvant nivolumab combined with BMS-813160 for NSCLC or HCC has just been completed (NCT04123379).

5.8. Other peptide drugs modulating PPIs for cancer treatment or prevention

Peptides were once almost discarded as potential lead compounds because of their generally low half-life, poor physicochemical stability and challenging oral administration due to proteolytic degradation, amongst other reasons. The improvement in, for instance, peptide synthesis and purification techniques, as well as the incorporation of non-native amino acids has ameliorated their pharmaceutical profiles and has led to the gaining attention of peptides as promising new drugs. In fact, more than 70 therapeutic peptides have been to date approved and marketed and more than 140 are currently being tested in clinical trials [270,271]. Recently, one of the most successful examples of these types of drugs are the glucagon-like peptide of type 1 (GLP-1) analogues, liraglutide and semaglutide, approved for the treatment of type 2 diabetes and obesity, that exceeded 23 B$ net sales in 2023 [272]. Moreover, according to several market studies the peptide therapeutic segment is expected to suffer important growth in the following years, from an estimated 43 B$ market size in 2024 to reaching 60 B$ by 2029. This significant growth is mostly due to new developments of peptide drugs for cancer treatment. However, market growth will probably be restrained by instability issues, high costs of development and rigorous regulatory requirements [273].

Related to Section 5.7., balixafortide is a synthetic cyclic peptide that acts as a potent and selective antagonist of the chemokine receptor CXCR4, which also belongs to the superfamily of the seven-transmembrane G-protein coupled receptors. This receptor is expressed by numerous tissues, including hematopoietic and endothelial cells. The natural ligand of CXCR4 is the chemokine SDF-1 (also named CXCL12), that regulates multiple physiological processes, including embryonic development and organ homeostasis [274]. CXCR4 has been found overexpressed in several cancer cell lines [275–277], and this overexpression has been related to poor prognosis [278]. SDF-1 has also been highly expressed in cancer-associated fibroblasts, suggesting a role in cell survival, metastasis and chemoresistance via activation CXCR4 receptor [277,279]. In this context, balixafortide was studied in a Phase III clinical trial, which was early terminated due to failure to meet the primary endpoint, in combination with eribulin versus eribulin alone in HER2-negative patients with locally recurrent or metastatic breast cancer (NCT03786094). It was also analyzed in a more recent dose-escalation Phase I trial also in associated with eribulin for HER2-negative metastatic breast cancer (NCT01837095) [280].

Cancer progression and tumorigenesis can be also brought on by dysregulation of interleukin signaling or production [281]. In fact, the upregulation of several interleukins has been associated with many tumors [282–284]. BNZ-1 (also known as BNZ132–1–40) is a pegylated helical peptide that selectively inhibits interleukins IL-2, IL-9, and IL-15 by blocking their binding to their cellular receptor complex involving the gamma chain (γc) [285]. IL-15 and IL-2 have been shown to drive T-cell-mediated malignancies including T-cell large granular lymphocyte leukemia (T-LGLL) and HTLV-1 driven adult T-cell leukemia [286]. This peptide was studied in a Phase I/II dose-ranging trial to characterize the safety, tolerability, preliminary efficacy, and pharmacokinetics/pharmacodynamics of up to four dose levels of BNZ-1 in patients with T-LGLL or refractory cutaneous T-cell lymphoma (NCT03239392). Results from this study showed that BNZ-1 demonstrated clinical partial responses in 20 % of patients with T-LGLL with minimal toxicity and that T-LGL leukemic cells were dependent on IL-15 [287].

VT1021 is a first-in-class cyclic peptide that has been shown to inhibit tumor growth via stimulation of thrombospondin-1 (Tsp-1) and reprogramming the TME in preclinical models [288]. Tsp-1 is a secreted protein that acts by inhibiting angiogenesis, stimulating tumor cell migration, and regulating antitumor immunity and the activity of extracellular proteases and growth factors within the TME [289]. An open-label Phase I trial of VT1021 in patients with advanced solid tumors is ongoing (NCT03364400). Preliminary results have shown that this peptide is safe and well-tolerated and partial response and stable disease with tumor shrinkage has been observed in multiple patients [290]. Another Phase II/III trial to evaluate multiple regimens in newly diagnosed and recurrent glioblastoma is currently recruiting (NCT03970447).

ALM201 is a therapeutic peptide derived from FKBPL, which is a protein involved in many cellular processes like cell cycle progression, signaling and differentiation and angiogenesis. At the cellular level FKBPL interacts with Hsp90, resulting in p21 stabilization and the regulation of estrogen receptor, androgen receptor and glucocorticoid receptor signaling [291–293]. Additionally, it has a critical extracellular role in angiogenesis by a mechanism that seems to be CD44-dependent [294,295]. ALM201 was the resultant peptide of improving the structure of AD-01, which was unstable [296]. AD-01 had demonstrated anti-angiogenic effects and reduced cancer stem cells using breast cancer cell lines, primary patient samples, and xenografts [297]. The second generation peptide, ALM201, exhibited promising antiangiogenic effects with potency in the low picomolar range in in vitro and ex vivo assays [298]. ALM201 was studied in a Phase I dose-escalation study in patients with advanced ovarian cancer and other solid tumors (EudraCT number: 2014–001175–31; NCT03427073), that showed that doses up to 300 mg of ALM201 subcutaneously were feasible and well-tolerated [296]. Furthermore, ALM201 was designated orphan drug status in 2017 by the FDA in ovarian cancer.

Tyroserleutide is a tripeptide compound with inhibitory effects on hepatocellular carcinoma, by downregulating calmodulin and protein expression of PI3K subunits p85 and p110, intervening in the signal transduction pathway in tumor cells and overcoming the dysfunctional PI3K activity in tumors [299]. This peptide is being tested in two Phase III trials in hepatocellular carcinoma patients (NCT01489566 and NCT03516448).

Foxy-5 is a formylated Wnt-5a-derived hexapeptide that triggers cytosolic free calcium signaling without affecting β-catenin activation and impairs epithelial cancer cells migration and invasion [300]. Dysregulation of the non-canonical member of the Wnt family Wnt-5a has been associated with cancer progression, but differences in its function have been observed in different types of cancer. In fact, the axis formed by Wnt5a and its receptor Ror2 has been found constitutively activated in some cancer cells, conferring invasive properties, but it also exhibits a tumor-suppressive function in other cancers [301]. Foxy-5 is currently

being tested in a Phase II study as neo-adjuvant therapy in subjects with Wnt-5a low colon cancer (NCT03883802).

Several peptides are also being developed to treat cancer types associated with the endocrine system. Gonadotropin-releasing hormone (GnRH), also called luteinizing hormone-releasing hormone (LHRH), is a decapeptide that is secreted in pulses by hypothalamic neurons and then binds and stimulates the G-protein coupled receptors, GnRH receptors (GnRHR), on pituitary gonadotrophs so that they synthesize and secrete the gonadotropin hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH are secreted into the systemic circulation and exert their effect on the ovaries and testes to control gonadal production of gametes and the sex steroids testosterone in the testes and estradiol and progesterone in the ovaries [302]. Androgen deprivation therapy (ADT) is a critical treatment for prostate cancer that can be performed as surgical castration or medical castration using GnRH agonists or antagonists. Agonists, which are the most commonly used medications for ADT, act by downregulating GnRHR in the pituitary gland, and in consequence, testosterone. Some disadvantages related to their mechanism of action have appeared, such as long-term cardiovascular risks, the development of diabetes, the appearance of tumor flares, a potential increase in non-cancer mortality, an initial testosterone surge and testosterone microsurges on repeated administration. Antagonists, conversely, directly inhibit the androgen receptor in the pituitary gland, avoiding testosterone surges [303,304]. Ozarelix is a novel fourth generation antagonist of the GnRH, that showed an immediate and complete suppression of testosterone in vivo. It also significantly sensitized androgen-independent prostate cancer cell lines to TRAIL or anti-CD95-mediated apoptosis resulting in a synergistic effect [305]. Ozarelix was tested in a Phase II trial to assess the safety and efficacy of a monthly regimen of subcutaneous ozarelix versus goserelin depot also administered subcutaneously in men with prostate cancer (NCT01252693).

EP-100 is a synthetic lytic peptide that targets the GnRHR on cancer cells. This receptor has been found to be overexpressed in many human tumors (e.g., breast, ovarian, endometrial, prostate, bladder and colorectal cancers), but not highly expressed or only at low levels in adjacent normal tissues [306–308]. The mechanism of action of EP-100 seems to be related with its interaction with a negatively charged tumor cell membrane, causing cell death through membrane lysis within a few minutes. A synergistic effect between olaparib and EP-100 was also observed, indicating a promising therapeutic strategy for ovarian cancer [308,309]. EP-100 was studied in a Phase II clinical trial in combination with paclitaxel versus paclitaxel alone in patients with ovarian cancer (NCT01485848).

Some other peptide drugs have been tested in the clinical setting for cancer prevention. Some examples are fexapotide triflutate, dolcanatide, BBT-401 and elsiglutide. Fexapotide triflutate (also referred to as NX-1207) is a first-in-class peptide that stimulates caspase pathways, tumor necrosis factor pathways and BCL pathways in prostate glandular epithelial cells [310] that has been studied in several Phase III clinical trials for managing benign prostatic hyperplasia (e.g., NCT01438775, NCT01846793). Dolcanatide (also named SP-333) is an oral uroguanylin analog structurally modified for enhanced stability and extended persistence to activate the tumor-suppressing receptor guanylyl cyclase C (GUCY2C) in small and large intestine. This compound was tested in a Phase II trial to assess its safety and efficacy for the treatment of opioid-induced constipation (NCT01983306) and in a Phase I study for preventing colorectal cancer in healthy volunteers (NCT03300570). BBT-401 is an orally available tetra-peptide that specifically binds to Pellino-1, an E3 ubiquitin ligase involved in innate immune response, and that has been tested in Phase II clinical trials for ulcerative colitis treatment (NCT04596293) [311]. Finally, elsiglutide is a selective glucagon-like peptide of type 2 (GLP-2) derivative that was developed as adjuvant to chemotherapy to reduce chemotherapy-induced diarrhea [312]. This peptide has completed two Phase II clinical trials for preventing chemotherapy-induced diarrhea (NCT02383810, NCT01543451).

6. Conclusions

Classical drug discovery approaches usually focused on the development of compounds that targeted interactions between ligands and individual proteins such as receptors, ion channels or enzymes, since they contained well-defined binding sites. However, these approaches often lacked the perspective on the target landscape, what lead to the appearance of undesired side effects derived from other functions of the target or to the homeostatic compensation of the effect of these drugs through other pathways and the resultant reduction in their efficacy. For this reason, current drug discovery approaches consider not only the targeting of individual proteins but also information on their interaction network. Although PPIs were in the past considered 'undruggable', recent advances in the genetic, proteomic and computational level amongst others, have improved the available knowledge about protein interfaces, leading to an increasing number of clinical trials that include PPI modulators for the treatment of different diseases. Nevertheless, PPI networks are highly dynamic, and further studies should be performed for better understanding of the evolution of these systems. Moreover, there is an urgent need for the resolution of additional PPI interfaces that can be targeted by PPI modulators and for the improvement of the computational tools assessing the druggability of these PPIs and the identification of novel hotspots or druggable sites. Related to the available databases collaborative efforts should be taken to overcome challenges, such as data heterogeneity and the lack of data standardization, multi-omics data should be integrated, and new tools related to deep learning and artificial intelligence should be incorporated in these databases to ameliorate the predictions.

When screening for PPI modulators, several authors have employed the HTS approach. However, the success of this technique has been shown to depend on the use of large compound libraries that contain enough chemical diversity, complexity and biological relevance. SBDD, another approach that uses one of the target proteins to rationally design the PPI modulator, has also been commonly used and has led to the discovery of promising compounds, such as the Smac mimetic Debio1143 or the SOS1 inhibitor BAY-293. Another approach that uses the knowledge on the PPI interface is the FBDD approach. In this case, after the identification of a specific small fragment that exhibits weak target binding, several chemical modifications can be introduced to enhance this binding. All these methods can also be combined altogether in order to improve the screening design, such as in the discovery of the dual ROCK-AKT inhibitor AT13148. However, several limitations can be faced when trying to employ these three methods for drug screening, such as the fact that several protein complexes lack experimental data on their 3D structure. Recent developments to overcome these limitations include the use of new computational tools, including protein docking and homology modelling, combined with low-resolution experimental techniques. These tools have the potential to help on the identification of suitable cavities in protein-protein interfaces through molecular dynamic simulations that may serve as starting points for further docking or VS studies, and also as a pre-screen to prioritize compounds for their experimental evaluation. Moreover, the discovery of hotspot residues within PPI interfaces has revolutionized the discovery of PPI inhibitors using small molecules, as the targeting of these hotspots often induce the breakage of critical interactions or small conformational changes that make the pocket deeper. The study of hotspots within PPIs has helped as a starting point, for instance, on the discovery of the MDM2/p53 inhibitors nutlins or the BCL-2-inhibitor approved for treating leukemia, venetoclax. All these methods should also be improved by incorporating machine-learning and artificial intelligence tools to maximize the potential of identifying interesting candidates for PPI modulation. Finally, as for the experimental analysis of the most promising candidates, the biophysical and biochemical techniques employed to date should also be optimized and additional validating techniques should be developed

and implemented for the successful discovery of PPI modulators.

In summary, several challenges can be faced when seeking for PPI inhibitors for cancer treatment. However, the approval of venetoclax and the presence of an expanding-amount on clinical trials and in preclinical phases, offers hope that a better knowledge of PPI interfaces and PPI networks, and the improvement of the existing methods added with new emerging approaches, will lead to the development of novel specific PPI inhibitors for a wide range of diseases, including cancer, neurodegenerative disorders, and autoimmune conditions.

Funding

This work, integrated into the framework of PERTE for Vanguard Health, has been co-financed by the Spanish Ministry of Science, Innovation and Universities with funds from the European Union NextGenerationEU, from the Recovery, Transformation and Resilience Plan (PRTR-C17.I1) and from the Autonomous Community of Catalonia within the framework of the Biotechnology Plan Applied to Health (PI-G7180 HSP). It has also been funded by: the project 'The Fanconi anemia/BRCA pathway: Genomic medicine and advanced therapies' (FABRAT, PID2021-122411OB-I00/AEI/10.13039/501100011033/FEDER, UE); the project 'Valorización y prueba de concepto de un inhibidor de la reparación del DNA por la via Fanconi/BRCA para el tratamiento del cáncer por letalidad sintética (Fanconinib)' (Prueba de Concepto, PDC2022-133233-I00/AEI/10.13039/501100011033/Unión Europea NextGenerationEU/PRTR); Instituto de Salud Carlos III (ISCIII) through the project ICI22/00076 and co-funded by the European Union; the ICREA-Acadèmia program (Fundació Institució Catalana de Recerca i Estudis Avançats); Agència de Gestió d'Ajuts Universitaris i de Recerca (2021-SGR-00835, 2023-2025); Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER) and the Fanconi Cancer Foundation.

CRediT authorship contribution statement

Cristina Camps-Fajol: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Conceptualization. **Jordi Surrallés:** Supervision, Project administration, Funding acquisition. **Jordi Minguillón:** Supervision, Resources, Methodology, Conceptualization. **Debora Cavero:** Writing – review & editing, Visualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jordi Surralles reports financial support was provided by PERTE Vanguard Health by the Spanish Ministry of Science, Innovation and Universities with funds from the NextGenerationEU, from the Recovery, Transformation and Resilience Plan (PRTR-C17.I1) and from the Autonomous Community of Catalonia (PI-G7180 HSP). Jordi Surralles reports financial support was provided by Spanish Ministry of Science, Innovation and Universities. Jordi Surralles reports financial support was provided by Instituto de Salud Carlos III (ISCIII) project ICI22–00076. Jordi Surralles reports financial support was provided by Fundació Institut Catalana de Recerca i Estudis Avançats. Jordi Surralles reports financial support was provided by Government of Catalonia Agency for Administration of University and Research Grants, (2021-SGR-00835, 2023–2025). Jordi Surralles reports financial support was provided by Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER). Jordi Surralles reports financial support was provided by Fanconi Cancer Foundation. Jordi Surralles reports a relationship with Rocket Pharmaceuticals Inc that includes: consulting or advisory and funding grants. Jordi Surralles reports a relationship with Roche Diagnostics Corporation that includes: funding grants. Jordi Surralles reports a relationship with Boehringer Ingelheim GmbH that includes: non-financial support. Jordi Surralles reports a relationship with Merck & Co Inc that includes: consulting or advisory. Jordi Surralles reports a relationship with Moderna Inc that includes: funding grants. Jordi Surralles reports a relationship with Glaxo Smith Kline Eesti OÜ that includes: consulting or advisory. Jordi Surralles reports a relationship with Pfizer that includes: consulting or advisory. Jordi Surralles has patent Repurposing of Afatinib issued to IR Sant Pau, UAB and CIBER. No If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank all financial instiutions for supporting this study: the Spanish Ministry of Science, Innovation and Universities (PRTR-C17.I1; FABRAT, PID2021–122411OB-I00/AEI/10.13039/501100011033/FEDER, UE; Prueba de Concepto, PDC2022–133233-I00/AEI/10.13039/501100011033/Unión Europea NextGenerationEU/PRTR), the Autonomous Community of Catalonia (PI-G7180 HSP), the Instituto de Salud Carlos III (ISCIII) (ICI22/00076), the ICREA-Acadèmia program (Fundació Institut Català de Recerca i Estudis Avançats), the Agència de Gestió d'Ajuts Universitaris i de Recerca (2021-SGR-00835, 2023–2025), the Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER) and the Fanconi Cancer Foundation.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2024.107544.

Data Availability

No data was used for the research described in the article.

References

[1] M.P.H. Stumpf, T. Thorne, E. De Silva, R. Stewart, J.A. Hyeong, M. Lappe, C. Wiuf, Estimating the size of the human interactome, Proc. Natl. Acad. Sci. USA 105 (2008), https://doi.org/10.1073/pnas.0708078105.

[2] K. Venkatesan, J.F. Rual, A. Vazquez, U. Stelzl, I. Lemmens, T. Hirozane-Kishikawa, T. Hao, M. Zenkner, X. Xin, K.Il Goh, M.A. Yildirim, N. Simonis, K. Heinzmann, F. Gebreab, J.M. Sahalie, S. Cevik, C. Simon, A.S. de Smet, E. Dann, A. Smolyar, A. Vinayagam, H. Yu, D. Szeto, H. Borick, A. Dricot, N. Klitgord, R.R. Murray, C. Lin, M. Lalowski, J. Timm, K. Rau, C. Boone, P. Braun, M.E. Cusick, F.P. Roth, D.E. Hill, J. Tavernier, E.E. Wanker, A. L. Barabási, M. Vidal, An empirical framework for binary interactome mapping, Nat. Methods 6 (2009), https://doi.org/10.1038/nmeth.1280.

[3] M. Vidal, M.E. Cusick, A.L. Barabási, Interactome networks and human disease, Cell 144 (2011), https://doi.org/10.1016/j.cell.2011.02.016.

[4] S. Nurk, S. Koren, A. Rhie, M. Rautiainen, A.V. Bzikadze, A. Mikheenko, M. R. Vollger, N. Altemose, L. Uralsky, A. Gershman, S. Aganezov, S.J. Hoyt, M. Diekhans, G.A. Logsdon, M. Alonge, S.E. Antonarakis, M. Borchers, G. G. Bouffard, S.Y. Brooks, G.V. Caldas, N.C. Chen, H. Cheng, C.S. Chin, W. Chow, L.G. de Lima, P.C. Dishuck, R. Durbin, T. Dvorkina, I.T. Fiddes, G. Formenti, R. S. Fulton, A. Fungtammasan, E. Garrison, P.G.S. Grady, T.A. Graves-Lindsay, I. M. Hall, N.F. Hansen, G.A. Hartley, M. Haukness, K. Howe, M.W. Hunkapiller, C. Jain, M. Jain, E.D. Jarvis, P. Kerpedjiev, M. Kirsche, M. Kolmogorov, J. Korlach, M. Kremitzki, H. Li, V.V. Maduro, T. Marschall, A.M. McCartney, J. McDaniel, D.E. Miller, J.C. Mullikin, E.W. Myers, N.D. Olson, B. Paten, P. Peluso, P.A. Pevzner, D. Porubsky, T. Potapova, E.I. Rogaev, J.A. Rosenfeld, S. L. Salzberg, V.A. Schneider, F.J. Sedlazeck, K. Shafin, C.J. Shew, A. Shumate, Y. Sims, A.F.A. Smit, D.C. Soto, I. Sovi, J.M. Storer, A. Streets, B.A. Sullivan, F. Thibaud-Nissen, J. Torrance, J. Wagner, B.P. Walenz, A. Wenger, J.M.D. Wood, C. Xiao, S.M. Yan, A.C. Young, S. Zarate, U. Surti, R.C. McCoy, M.Y. Dennis, I. A. Alexandrov, J.L. Gerton, R.J. O'Neill, W. Timp, J.M. Zook, M.C. Schatz, E. E. Eichler, K.H. Miga, A.M. Phillippy, The complete sequence of a human genome, Science 376 (2022) 1979, https://doi.org/10.1126/science.abj6987.

[5] A.W. White, A.D. Westwell, G. Brahemi, Protein - protein interactions as targets for small-molecule therapeutics in cancer, Expert Rev. Mol. Med. 10 (2008), https://doi.org/10.1017/S1462399408000641.

[6] L.L. Blazer, R.R. Neubig, Small molecule protein-protein interaction inhibitors as CNS therapeutic agents: current progress and future hurdles, Neuropsychopharmacology 34 (2009), https://doi.org/10.1038/npp.2008.151.

[7] Y. Zhou, W. Shi, D. Zhao, S. Xiao, K. Wang, J. Wang, Identification of immune-associated genes in diagnosing aortic valve calcification with metabolic syndrome by integrated bioinformatics analysis and machine learning, Front. Immunol. 13 (2022), https://doi.org/10.3389/fimmu.2022.937886.
[8] H.J. Azeez, F. Neri, M.A. Hosseinpour Feizi, E. Babaei, Transcriptome profiling of HCT-116 colorectal cancer cells with RNA sequencing reveals novel targets for polyphenol nano curcumin, Molecules 27 (2022), https://doi.org/10.3390/molecules27113470.
[9] A. Coulson, A. Levy, M. Gossell-Williams, Monoclonal antibodies in cancer therapy: mechanisms, successes and limitations, West Indian Med. J. 63 (2014), https://doi.org/10.7727/wimj.2013.241.
[10] P. Torka, M. Barth, R. Ferdman, F.J. Hernandez-Ilizaliturri, Mechanisms of resistance to monoclonal antibodies (mAbs) in lymphoid malignancies, Curr. Hematol. Malig. Rep. 14 (2019), https://doi.org/10.1007/s11899-019-00542-8.
[11] H. Lu, Q. Zhou, J. He, Z. Jiang, C. Peng, R. Tong, J. Shi, Recent advances in the development of protein–protein interactions modulators: mechanisms and clinical trials, Signal Transduct. Target Ther. 5 (2020), https://doi.org/10.1038/s41392-020-00315-3.
[12] J. Vagner, H. Qu, V.J. Hruby, Peptidomimetics, a synthetic tool of drug discovery, Curr. Opin. Chem. Biol. 12 (2008), https://doi.org/10.1016/j.cbpa.2008.03.009.
[13] A.M. Ali, J. Atmaj, N. Van Oosterwijk, M.R. Groves, A. Dömling, Stapled peptides inhibitors: a new window for target drug discovery, Comput. Struct. Biotechnol. J. 17 (2019), https://doi.org/10.1016/j.csbj.2019.01.012.
[14] V. Oleinikovas, P. Gainza, T. Ryckmans, B. Fasching, N.H. Thomä, From thalidomide to rational molecular glue design for targeted protein degradation, Annu. Rev. Pharmacol. Toxicol. 64 (2024) 291–312, https://doi.org/10.1146/annurev-pharmtox-022123-104147.
[15] M. Békés, D.R. Langley, C.M. Crews, PROTAC targeted protein degraders: the past is prologue, Nat. Rev. Drug Discov. 21 (2022), https://doi.org/10.1038/s41573-021-00371-6.
[16] T.M. Nguyen, V. Sreekanth, A. Deb, P. Kokkonda, P.K. Tiwari, K.A. Donovan, V. Shoba, S.K. Chaudhary, J.A.M. Mercer, S. Lai, A. Sadagopan, M. Jan, E. S. Fischer, D.R. Liu, B.L. Ebert, A. Choudhary, Proteolysis-targeting chimeras with reduced off-targets, Nat. Chem. 16 (2024), https://doi.org/10.1038/s41557-023-01379-8.
[17] C. Liu, J. Chen, H. Chen, T. Zhang, D. He, Q. Luo, J. Chi, Z. Hong, Y. Liao, S. Zhang, Q. Wu, H. Cen, G. Chen, J. Li, L. Wang, PCSK9 inhibition: from current advances to evolving future, Cells 11 (2022), https://doi.org/10.3390/cells11192972.
[18] X. Chen, L.S. Mangala, C. Rodriguez-Aguayo, X. Kong, G. Lopez-Berestein, A. K. Sood, RNA interference-based therapy and its delivery systems, Cancer Metastas. Rev. 37 (2018), https://doi.org/10.1007/s10555-017-9717-6.
[19] Z. Tian, G. Liang, K. Cui, Y. Liang, Q. Wang, S. Lv, X. Cheng, L. Zhang, Insight into the prospects for RNAi therapy of cancer, Front Pharm. 12 (2021), https://doi.org/10.3389/fphar.2021.644718.
[20] O.B. McManus, HTS assays for developing the molecular pharmacology of ion channels, Curr. Opin. Pharm. 15 (2014), https://doi.org/10.1016/j.coph.2014.01.004.
[21] R. Santos, O. Ursu, A. Gaulton, A.P. Bento, R.S. Donadi, C.G. Bologa, A. Karlsson, B. Al-Lazikani, A. Hersey, T.I. Oprea, J.P. Overington, A comprehensive map of molecular drug targets, Nat. Rev. Drug Discov. 16 (2016), https://doi.org/10.1038/nrd.2016.230.
[22] K. Sriram, P.A. Insel, G protein-coupled receptors as targets for approved drugs: how many targets and how many drugs? : Mol. Pharm. (2018) https://doi.org/10.1124/mol.117.111062.
[23] X. Wang, D. Ni, Y. Liu, S. Lu, Rational design of peptide-based inhibitors disrupting protein-protein interactions, Front Chem. 9 (2021), https://doi.org/10.3389/fchem.2021.682675.
[24] M. Rosell, J. Fernández-Recio, Hot-spot analysis for drug discovery targeting protein-protein interactions, Expert Opin. Drug Discov. 13 (2018), https://doi.org/10.1080/17460441.2018.1430763.
[25] H. Jubb, T.L. Blundell, D.B. Ascher, Flexibility and small pockets at protein-protein interfaces: new insights into druggability, Prog. Biophys. Mol. Biol. 119 (2015), https://doi.org/10.1016/j.pbiomolbio.2015.01.009.
[26] A. Berchanski, B. Shapira, M. Eisenstein, Hydrophobic complementarity in protein-protein docking, Protein. Struct. Funct. Genet. 56 (2004), https://doi.org/10.1002/prot.20145.
[27] M.Q. Zhang, B. Wilkinson, Drug discovery beyond the "rule-of-five", Curr. Opin. Biotechnol. 18 (2007) https://doi.org/10.1016/j.copbio.2007.10.005.
[28] P. Buchwald, Small-molecule protein-protein interaction inhibitors: therapeutic potential in light of molecular size, chemical space, and ligand binding efficiency considerations, IUBMB Life 62 (2010), https://doi.org/10.1002/iub.383.
[29] J.A. Wells, C.L. McClendon, Reaching for high-hanging fruit in drug discovery at protein-protein interfaces, Nature 450 (2007), https://doi.org/10.1038/nature06526.
[30] B.S. Zerbe, D.R. Hall, S. Vajda, A. Whitty, D. Kozakov, Relationship between hot spot residues and ligand binding hot spots in protein-protein interfaces, J. Chem. Inf. Model 52 (2012), https://doi.org/10.1021/ci300175u.
[31] D.K. Johnson, J. Karanicolas, Druggable protein interaction sites are more predisposed to surface pocket formation than the rest of the protein surface, PLoS Comput. Biol. 9 (2013), https://doi.org/10.1371/journal.pcbi.1002951.
[32] K.S. Thorn, A.A. Bogan, ASEdb: a database of alanine mutations and their effects on the free energy of binding in protein interactions, Bioinformatics 17 (2001), https://doi.org/10.1093/bioinformatics/17.3.284.
[33] J. Oláh, T. Szénási, A. Lehotzky, V. Norris, J. Ovádi, Challenges in discovering drugs that target the protein–protein interactions of disordered proteins, Int. J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms23031550.
[34] J.H. Wong, M. Alfatah, M.F. Sin, H.M. Sim, C.S. Verma, D.P. Lane, P. Arumugam, A yeast two-hybrid system for the screening and characterization of small-molecule inhibitors of protein-protein interactions identifies a novel putative Mdm2-binding site in p53, BMC Biol. 15 (2017), https://doi.org/10.1186/s12915-017-0446-7.
[35] C.H. Wu, I.J. Liu, R.M. Lu, H.C. Wu, Advancement and applications of peptide phage display technology in biomedical science, J. Biomed. Sci. 23 (2016), https://doi.org/10.1186/s12929-016-0223-x.
[36] J. Luo, M.J. Emanuele, D. Li, C.J. Creighton, M.R. Schlabach, T.F. Westbrook, K. K. Wong, S.J. Elledge, A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the ras oncogene, Cell 137 (2009), https://doi.org/10.1016/j.cell.2009.05.006.
[37] A. Montero-Calle, R. Barderas, Analysis of protein-protein interactions by protein microarrays, Methods Mol. Biol. (2021), https://doi.org/10.1007/978-1-0716-1562-1_6.
[38] B. Turriziani, A. von Kriegsheim, S.R. Pennington, Protein-protein interaction detection via mass spectrometry-based proteomics, Adv. Exp. Med Biol. (2016), https://doi.org/10.1007/978-3-319-41448-5_18.
[39] A.L. Richards, M. Eckhardt, N.J. Krogan, Mass spectrometry-based protein–protein interaction networks for the study of human diseases, Mol. Syst. Biol. 17 (2021), https://doi.org/10.15252/msb.20188792.
[40] L. Soini, S. Leysen, J. Davis, C. Ottmann, A biophysical and structural analysis of the interaction of BLNK with 14-3-3 proteins, J. Struct. Biol. 212 (2020), https://doi.org/10.1016/j.jsb.2020.107662.
[41] H. Müller-Esparza, M. Osorio-Valeriano, N. Steube, M. Thanbichler, L. Randau, Bio-layer interferometry analysis of the target binding activity of CRISPR-cas effector complexes, Front Mol. Biosci. 7 (2020), https://doi.org/10.3389/fmolb.2020.00098.
[42] I. Moscetti, S. Cannistraro, A.R. Bizzarri, Surface plasmon resonance sensing of biorecognition interactions within the tumor suppressor P53 network, Sens. (Switz.) 17 (2017), https://doi.org/10.3390/s17112680.
[43] S. Ricard-Blum, L.L. Peel, F. Ruggiero, N.J. Freeman, Dual polarization interferometry characterization of carbohydrate-protein interactions, Anal. Biochem 352 (2006), https://doi.org/10.1016/j.ab.2006.02.011.
[44] M.A. Woldeyes, C. Calero-Rubio, E.M. Furst, C.J. Roberts, Light scattering to quantify protein–protein interactions at high protein concentrations, Methods Mol. Biol. (2019), https://doi.org/10.1007/978-1-4939-9678-0_2.
[45] N.J. GreenfieldCircular dichroism (CD) analyses of protein-protein interactions, in: Protein-Protein Interactions: Methods and Applications2015, https://doi.org/10.1007/978-1-4939-2425-7_15.
[46] L.G. Milroy, T.N. Grossmann, S. Hennig, L. Brunsveld, C. Ottmann, Modulators of protein-protein interactions, Chem. Rev. 114 (2014) 4695–4748, https://doi.org/10.1021/cr400698c.
[47] K. Titeca, I. Lemmens, J. Tavernier, S. Eyckerman, Discovering cellular protein-protein interactions: technological strategies and opportunities, Mass Spectrom. Rev. 38 (2019), https://doi.org/10.1002/mas.21574.
[48] T.K. Kerppola, Bimolecular fluorescence complementation (BiFC) analysis as a probe of protein interactions in living cells, Annu Rev. Biophys. 37 (2008), https://doi.org/10.1146/annurev.biophys.37.032807.125842.
[49] Y. Haddad, V. Adam, Z. Heger, Ten quick tips for homology modeling of high-resolution protein 3D structures, PLoS Comput. Biol. 16 (2020), https://doi.org/10.1371/journal.pcbi.1007449.
[50] B. Kobe, G. Guncar, R. Buchholz, T. Huber, B. Maco, N. Cowieson, J.L. Martin, M. Marfori, J.K. Forwood, Crystallography and protein–protein interactions: biological interfaces and crystal contacts, Biochem Soc. Trans. 1 36 (6) (2008) 1438–1441, https://doi.org/10.1042/BST0361438.
[51] G. Gao, J.G. Williams, S.L. Campbell, Protein-protein interaction analysis by nuclear magnetic resonance spectroscopy, in: H. Fu (Ed.), Protein-Protein Interactions. Methods in Molecular Biology, Humana Press, 2004, https://doi.org/10.1385/1-59259-762-9:079.
[52] N.A. Kutchy, O.B. Morenikeji, A. Memili, M.R. Ugur, Deciphering sperm functions using biological networks, Biotechnol. Genet. Eng. Rev. 40 (4) (2023) 3743–3767, https://doi.org/10.1080/02648725.2023.2168912.
[53] J. Zahiri, J.H. Bozorgmehr, A. Masoudi-Nejad, Computational prediction of protein-protein interaction networks: algo-rithms and resources, Curr. Genom. 14 (6) (2013) 397–414, https://doi.org/10.2174/1389202911314060004. PMID: 24396273; PMCID: PMC3861891.
[54] G. Grassmann, M. Miotto, F. Desantis, L. Rienzo, G.G. Tartaglia, A. Pastore, G. Ruocco, M. Monti, E. Milanetti, Chem. Rev. 124 (7) (2024) 3932–3977, https://doi.org/10.1021/acs.chemrev.3c00550.
[55] M. Athar, A. Manhas, N. Rana, A. Irfan, Computational and bioinformatics tools for understanding disease mechanisms, Biocell 48 (2024) 1–10, https://doi.org/10.32604/biocell.2024.049891.
[56] L. Alzyoud, R.A. Bryce, M. Al Sorkhy, N. Atatreh, M.A. Ghattas, Structure-based assessment and druggability classification of protein–protein interaction sites, Sci. Rep. 12 (2022) 7975, https://doi.org/10.1038/s41598-022-12105-8.
[57] D.R. Koes, C.J. Camacho, PocketQuery: protein-protein interaction inhibitor starting points from protein-protein interaction structure, Nucleic Acids Res. (2012) W387–W392, https://doi.org/10.1093/nar/gks336.
[58] D.J. Evans, R.A. Yovanno, S. Rahman, D.W. Cao, M.Q. Beckett, M.H. Patel, A. F. Bandak, A.Y. Lau, Finding druggable sites in proteins using TACTICS, J. Chem. Inf. Model. 61 (6) (2021) 2897–2910, https://doi.org/10.1021/acs.jcim.1c00204.

[59] Q.C. Zhang, D. Petrey, L. Deng, L. Qiang, Y. Shi, C.A. Thu, B. Bisikirska, C. Lefebvre, D. Accili, T. Hunter, T. Maniatis, A. Califano, B. Honig, Structure-based prediction of protein-protein interactions on a genome-wide scale, Nature 490 (2012), https://doi.org/10.1038/nature11503.
[60] L.T. Vassilev, B.T. Vu, B. Graves, D. Carvajal, F. Podlaski, Z. Filipovic, N. Kong, U. Kammlott, C. Lukacs, C. Klein, N. Fotouhi, E.A. Liu, In vivo activation of the p53 pathway by small-molecule antagonists of MDM2, Science (1979) 303 (2004), https://doi.org/10.1126/science.1092472.
[61] H. Yin, G.I. Lee, K.A. Sedey, O. Kutzki, H.S. Park, B.P. Orner, J.T. Ernst, H. G. Wang, S.M. Sebti, A.D. Hamilton, Terphenyl-based Bak BH3 α-helical proteomimetics as low-molecular-weight antagonists of Bcl-xL, J. Am. Chem. Soc. 127 (2005), https://doi.org/10.1021/ja050122x.
[62] L. Chen, H. Yin, B. Farooqi, S. Sebti, A.D. Hamilton, J. Chen, p53 α-helix mimetics antagonize p53/MDM2 interaction and activate p53, Mol. Cancer Ther. 4 (2005), https://doi.org/10.1158/1535-7163.MCT-04-0342.
[63] R.A. Ward, M.J. Anderton, P. Bethel, J. Breed, C. Cook, E.J. Davies, A. Dobson, Z. Dong, G. Fairley, P. Farrington, L. Feron, V. Flemington, F.D. Gibbons, M. A. Graham, R. Greenwood, L. Hanson, P. Hopcroft, R. Howells, J. Hudson, M. James, C.D. Jones, C.R. Jones, Y. Li, S. Lamont, R. Lewis, N. Lindsay, J. McCabe, T. McGuire, P. Rawlins, K. Roberts, L. Sandin, I. Simpson, S. Swallow, J. Tang, G. Tomkinson, M. Tonge, Z. Wang, B. Zhai, Discovery of a potent and selective oral inhibitor of ERK1/2 (AZD0364) that is efficacious in both monotherapy and combination therapy in models of nonsmall cell lung cancer (NSCLC), J. Med Chem. 62 (2019), https://doi.org/10.1021/acs.jmedchem.9b01295.
[64] G. Saxty, S.J. Woodhead, V. Berdini, T.G. Davies, M.L. Verdonk, P.G. Wyatt, R. G. Boyle, D. Barford, R. Downham, M.D. Garrett, R.A. Carr, Identification of inhibitors of protein kinase B using fragment-based lead discovery, J. Med Chem. 50 (2007), https://doi.org/10.1021/jm070091b.
[65] R. McLeod, R. Kumar, D. Papadatos-Pastos, J. Mateo, J.S. Brown, A.H. Ingles Garces, R. Ruddle, S. Decordova, S. Jueliger, R. Ferraldeschi, O. Maiques, V. Sanz-Moreno, P. Jones, S. Traub, G. Halbert, S. Mellor, K.E. Swales, F. I. Raynaud, M.D. Garrett, U. Banerji, First-in-human study of AT13148, a Dual ROCK-AKT inhibitor in patients with solid tumors, Clin. Cancer Res. 26 (2020), https://doi.org/10.1158/1078-0432.CCR-20-0700.
[66] T. Oltersdorf, S.W. Elmore, A.R. Shoemaker, R.C. Armstrong, D.J. Augeri, B. A. Belli, M. Bruncko, T.L. Deckwerth, J. Dinges, P.J. Hajduk, M.K. Joseph, S. Kitada, S.J. Korsmeyer, A.R. Kunzer, A. Letai, C. Li, M.J. Mitten, D. G. Nettesheim, S.C. Ng, P.M. Nimmer, J.M. O'Connor, A. Oleksijew, A.M. Petros, J.C. Reed, W. Shen, S.K. Tahir, C.B. Thompson, K.J. Tomaselli, B. Wang, M. D. Wendt, H. Zhang, S.W. Fesik, S.H. Rosenberg, An inhibitor of Bcl-2 family proteins induces regression of solid tumours, Nature 435 (2005), https://doi.org/10.1038/nature03579.
[67] T.L. Nero, C.J. Morton, J.K. Holien, J. Wielens, M.W. Parker, Oncogenic protein interfaces: small molecules, big challenges, Nat. Rev. Cancer 14 (2014), https://doi.org/10.1038/nrc3690.
[68] Y. Qiu, X. Li, X. He, J. Pu, J. Zhang, S. Lu, Computational methods-guided design of modulators targeting protein-protein interactions (PPIs), Eur. J. Med. Chem. 207 (2020), https://doi.org/10.1016/j.ejmech.2020.112764.
[69] P. Kirsch, A.M. Hartman, A.K.H. Hirsch, M. Empting, Concepts and core principles of fragment-based drug design, Molecules 24 (2019), https://doi.org/10.3390/molecules24234309.
[70] A.P. Higueruelo, H. Jubb, T.L. Blundell, TIMBAL v2: update of a database holding small molecules modulating protein-protein interactions, Database (Oxf.) 13 (2013) (2013) bat039, https://doi.org/10.1093/database/bat039.
[71] C.M. Labbé, G. Laconde, M.A. Kuenemann, B.O. Villoutreix, O. Sperandio, iPPI-DB: a manually curated and interactive database of small non-peptide inhibitors of protein-protein interactions, Drug Discov. Today 18 (19-20) (2013) 958–968, https://doi.org/10.1016/j.drudis.2013.05.003.
[72] M.J. Basse, S. Betzi, X. Morelli, P. Roche, 2P2Idb v2: update of a structural database dedicated to orthosteric modulation of protein-protein interactions, Database. J. Biol. Database. Curation (2016) baw007, https://doi.org/10.1093/database/baw007.
[73] N. Bosc, C. Muller, L. Hoffer, D. Lagorce, S. Bourg, C. Derviaux, M.E. Gourdel, J. C. Rain, T.W. Miller, B.O. Villoutreix, M.A. Miteva, P. Bonnet, X. Morelli, O. Sperandio, P. Roche, Fr-PPIChem: an academic compound library dedicated to protein-protein interactions, ACS Chem. Biol. 15 (6) (2020) 1566–1574, https://doi.org/10.1021/acschembio.0c00179.
[74] B.I. Díaz-Eufracio, J.L. Medina-Franco, Machine learning models to predict protein–protein interaction inhibitors, Molecules 27 (22) (2022) 7986, https://doi.org/10.3390/molecules27227986.
[75] D. Trisciuzzi, O. Nicolotti, M.A. Miteva, B.O. Villoutreix, Analysis of solvent-exposed and buried co-crystallized ligands: a case study to support the design of novel protein-protein interaction inhibitors, Drug Discov. Today 24 (2) (2019) 551–559, https://doi.org/10.1016/j.drudis.2018.11.013.
[76] J. Scheper, M. Guerra-Rebollo, G. Sanclimens, A. Moure, I. Masip, D. González-Ruiz, N. Rubio, B. Crosas, Ó. Meca-Cortés, N. Loukili, V. Plans, A. Morreale, J. Blanco, A.R. Ortiz, À. Messeguer, T.M. Thomson, Protein-protein interaction antagonists as novel inhibitors of non-canonical polyubiquitylation, PLoS One 5 (2010), https://doi.org/10.1371/journal.pone.0011403.
[77] P.P. Dike, S. Bhowmick, G.E. Eldesoky, S.M. Wabaidur, P.C. Patil, M.A. Islam, In silico identification of small molecule modulators for disruption of Hsp90–Cdc37 protein–protein interaction interface for cancer therapeutic application, J. Biomol. Struct. Dyn. 40 (2022), https://doi.org/10.1080/07391102.2020.1835714.
[78] H.R. Lawrence, Z. Li, M.L. Richard Yip, S.S. Sung, N.J. Lawrence, M. L. McLaughlin, G.J. McManus, M.J. Zaworotko, S.M. Sebti, J. Chen, W.C. Guida, Identification of a disruptor of the MDM2-p53 protein-protein interaction facilitated by high-throughput in silico docking, Bioorg. Med Chem. Lett. 19 (2009), https://doi.org/10.1016/j.bmcl.2009.04.124.
[79] B.J. Aubrey, G.L. Kelly, A. Janic, M.J. Herold, A. Strasser, How does p53 induce apoptosis and how does this relate to p53-mediated tumour suppression? Cell Death Differ. 25 (2018) https://doi.org/10.1038/cdd.2017.169.
[80] B.J. Aubrey, A. Strasser, G.L. Kelly, Tumor-suppressor functions of the TP53 pathway, Cold Spring Harb. Perspect. Med 6 (2016), https://doi.org/10.1101/cshperspect.a026062.
[81] V.J.N. Bykov, S.E. Eriksson, J. Bianchi, K.G. Wiman, Targeting mutant p53 for efficient cancer therapy, Nat. Rev. Cancer 18 (2018), https://doi.org/10.1038/nrc.2017.109.
[82] S. Shangary, S. Wang, Small-molecule inhibitors of the MDM2-p53 protein-protein interaction to reactivate p53 function: A novel approach for cancer therapy, Annu Rev. Pharm. Toxicol. 49 (2009) 223–241, https://doi.org/10.1146/annurev.pharmtox.48.113006.094723.
[83] Q. Ding, Z. Zhang, J.J. Liu, N. Jiang, J. Zhang, T.M. Ross, X.J. Chu, D. Bartkovitz, F. Podlaski, C. Janson, C. Tovar, Z.M. Filipovic, B. Higgins, K. Glenn, K. Packman, L.T. Vassilev, B. Graves, Discovery of RG7388, a potent and selective p53-MDM2 inhibitor in clinical development, J. Med. Chem. 56 (2013), https://doi.org/10.1021/jm400487c.
[84] N. Atatreh, M.A. Ghattas, S.K. Bardaweel, S. Al Rawashdeh, M. Al Sorkhy, Identification of new inhibitors of Mdm2-p53 interaction via pharmacophore and structure-based virtual screening, Drug Des. Devel Ther. 12 (2018), https://doi.org/10.2147/DDDT.S182444.
[85] B. Vu, P. Wovkulich, G. Pizzolato, A. Lovey, Q. Ding, N. Jiang, J.J. Liu, C. Zhao, K. Glenn, Y. Wen, C. Tovar, K. Packman, L. Vassilev, B. Graves, Discovery of RG7112: a small-molecule MDM2 inhibitor in clinical development, ACS Med. Chem. Lett. 4 (2013) 466–469, https://doi.org/10.1021/ml4000657.
[86] H. Chen, D. Luo, L. Zhang, X. Lin, Q. Luo, H. Yi, J. Wang, X. Yan, B. Li, Y. Chen, X. Liu, H. Zhang, S. Liu, M. Qiu, D. Yang, N. Jiang, Restoration of p53 using the novel MDM2-p53 antagonist APG115 suppresses dedifferentiated papillary thyroid cancer cells, Oncotarget 8 (2017), https://doi.org/10.18632/oncotarget.17398.
[87] M.F. Shaheen, J.M. Segar, B. Chmielowski, J.J. Drabick, M. McKean, J.A. Reeves, C.S. Karapetis, M.M. Orloff, A.W. Tolcher, J.T.T. Beck, B. Gastman, A. De, B. Paudyal, R.E. Winkler, M. Li, M. Ahmad, D. Yang, Y. Zhai, A phase 2 study of alrizomadlin (APG-115) in combination with pembrolizumab in patients with unresectable or metastatic cutaneous melanoma that has failed immuno-oncologic (IO) drugs, J. Clin. Oncol. 41 (2023), https://doi.org/10.1200/jco.2023.41.16_suppl.9559.
[88] A. Czarna, G.M. Popowicz, A. Pecak, S. Wolf, G. Dubin, T.A. Holak, High affinity interaction of the p53 peptide-analogue with human Mdm2 and Mdmx, Cell Cycle 8 (2009), https://doi.org/10.4161/cc.8.8.8185.
[89] S. Francoz, P. Froment, S. Bogaerts, S. De Clercq, M. Maetens, G. Doumont, E. Bellefroid, J.C. Marine, Mdm4 and Mdm2 cooperate to inhibit p53 activity in proliferating and quiescent cells in vivo, Proc. Natl. Acad. Sci. USA 103 (2006), https://doi.org/10.1073/pnas.0508476103.
[90] A. Boltjes, Y. Huang, R. Van De Velde, L. Rijkee, S. Wolf, J. Gaugler, K. Lesniak, K. Guzik, T.A. Holak, A. Dömling, Fragment-based library generation for the discovery of a peptidomimetic p53-Mdm4 inhibitor, ACS Comb. Sci. 16 (2014), https://doi.org/10.1021/co500026b.
[91] J. Phan, Z. Li, A. Kasprzak, B. Li, S. Sebti, W. Guida, E. Schönbrunn, J. Chen, Structure-based design of high affinity peptides inhibiting the interaction of p53 with MDM2 and MDMX, J. Biol. Chem. 285 (2010), https://doi.org/10.1074/jbc.M109.073056.
[92] F. Bernal, M. Wade, M. Godes, T.N. Davis, D.G. Whitehead, A.L. Kung, G.M. Wahl, L.D. Walensky, A stapled p53 helix overcomes HDMX-mediated suppression of p53, Cancer Cell 18 (2010), https://doi.org/10.1016/j.ccr.2010.10.024.
[93] Y.S. Chang, B. Graves, V. Guerlavais, C. Tovar, K. Packman, K.H. To, K.A. Olson, K. Kesavan, P. Gangurde, A. Mukherjee, T. Baker, K. Darlak, C. Elkin, Z. Filipovic, F.Z. Qureshi, H. Cai, P. Berry, E. Feyfant, X.E. Shi, J. Horstick, D.A. Annis, A. M. Manning, N. Fotouhi, H. Nash, L.T. Vassilev, T.K. Sawyer, Stapled α-helical peptide drug development: a potent dual inhibitor of MDM2 and MDMX for p53-dependent cancer therapy, Proc. Natl. Acad. Sci. USA 110 (2013), https://doi.org/10.1073/pnas.1303002110.
[94] Y. Ben-Nun, H.S. Seo, E.P. Harvey, Z.J. Hauseman, T.E. Wales, C.E. Newman, A. M. Cathcart, J.R. Engen, S. Dhe-Paganon, L.D. Walensky, Identification of a structural determinant for selective targeting of HDMX, Structure 28 (2020), https://doi.org/10.1016/j.str.2020.04.011.
[95] L.A. Carvajal, D.Ben Neriah, A. Senecal, L. Benard, V. Thiruthuvanathan, T. Yatsenko, S.R. Narayanagari, J.C. Wheat, T.I. Todorova, K. Mitchell, C. Kenworthy, V. Guerlavais, D.A. Annis, B. Bartholdy, B. Will, J.D. Anampa, I. Mantzaris, M. Aivado, R.H. Singer, R.A. Coleman, A. Verma, U. Steidl, Dual inhibition of MDMX and MDM2 as a therapeutic strategy in leukemia, Sci. Transl. Med. 10 (2018), https://doi.org/10.1126/scitranslmed.aao3003.
[96] X. Zhou, M. Singh, G.S. Santos, V. Guerlavais, L.A. Carvajal, M. Aivado, Y. Zhan, M.M.S. Oliveira, L.S. Westerberg, D.A. Annis, J.I. Johnsen, G. Selivanova, Pharmacologic activation of p53 triggers viral mimicry response thereby abolishing tumor immune evasion and promoting antitumor immunity, Cancer Discov. 11 (2021), https://doi.org/10.1158/2159-8290.CD-20-1741.
[97] S. Zhang, Z. Yan, Y. Li, Y. Gong, X. Lyu, J. Lou, D. Zhang, X. Meng, Y. Zhao, Structure-Based Discovery of MDM2/4 dual inhibitors that exert antitumor

activities against MDM4-overexpressing cancer cells, J. Med. Chem. 65 (2022), https://doi.org/10.1021/acs.jmedchem.2c00095.
[98] S. Jeay, S. Gaulis, S. Ferretti, H. Bitter, M. Ito, T. Valat, M. Murakami, S. Ruetz, D. A. Guthy, C. Rynn, M.R. Jensen, M. Wiesmann, J. Kallen, P. Furet, F. Gessier, P. Holzer, K. Masuya, J. Würthner, E. Halilovic, F. Hofmann, W.R. Sellers, D. Graus-Porta, A distinct p53 target gene set predicts for response to the selective p53- HDM2 inhibitor NVP-CGM097, Elife 4 (2015), https://doi.org/10.7554/eLife.06498.
[99] T. Moldoveanu, A.V. Follis, R.W. Kriwacki, D.R. Green, Many players in BCL-2 family affairs, Trends Biochem Sci. 39 (2014), https://doi.org/10.1016/j.tibs.2013.12.006.
[100] F. Llambi, Y.M. Wang, B. Victor, M. Yang, D.M. Schneider, S. Gingras, M. J. Parsons, J.H. Zheng, S.A. Brown, S. Pelletier, T. Moldoveanu, T. Chen, D. R. Green, BOK is a non-canonical BCL-2 family effector of apoptosis regulated by ER-associated degradation, Cell 165 (2016), https://doi.org/10.1016/j.cell.2016.02.026.
[101] A.M. Petros, E.T. Olejniczak, S.W. Fesik, Structural biology of the Bcl-2 family of proteins, Biochim Biophys. Acta Mol. Cell Res. 1644 (2004), https://doi.org/10.1016/j.bbamcr.2003.08.012.
[102] C. Billard, Design of novel BH3 mimetics for the treatment of chronic lymphocytic leukemia, Leukemia 26 (2012), https://doi.org/10.1038/leu.2012.88.
[103] C. Tse, A.R. Shoemaker, J. Adickes, M.G. Anderson, J. Chen, S. Jin, E.F. Johnson, K.C. Marsh, M.J. Mitten, P. Nimmer, L. Roberts, S.K. Tahir, Y. Xiao, X. Yang, H. Zhang, S. Fesik, S.H. Rosenberg, S.W. Elmore, ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor, Cancer Res. 68 (2008), https://doi.org/10.1158/0008-5472.CAN-07-5836.
[104] W.H. Wilson, O.A. O'Connor, M.S. Czuczman, A.S. LaCasce, J.F. Gerecitano, J. P. Leonard, A. Tulpule, K. Dunleavy, H. Xiong, Y.L. Chiu, Y. Cui, T. Busman, S. W. Elmore, S.H. Rosenberg, A.P. Krivoshik, S.H. Enschede, R.A. Humerickhouse, Navitoclax, a targeted high-affinity inhibitor of BCL-2, in lymphoid malignancies: a phase 1 dose-escalation study of safety, pharmacokinetics, pharmacodynamics, and antitumour activity, Lancet Oncol. 11 (2010), https://doi.org/10.1016/S1470-2045(10)70261-8.
[105] L. Gandhi, D.R. Camidge, M.R. De Oliveira, P. Bonomi, D. Gandara, D. Khaira, C. L. Hann, E.M. McKeegan, E. Litvinovich, P.M. Hemken, C. Dive, S.H. Enschede, C. Nolan, Y.L. Chiu, T. Busman, H. Xiong, A.P. Krivoshik, R. Humerickhouse, G. I. Shapiro, C.M. Rudin, Phase I study of navitoclax (ABT-263), a novel bcl-2 family inhibitor, in patients with small-cell lung cancer and other solid tumors, J. Clin. Oncol. 29 (2011), https://doi.org/10.1200/JCO.2010.31.6208.
[106] A.W. Roberts, J.F. Seymour, J.R. Brown, W.G. Wierda, T.J. Kipps, S.L. Khaw, D. A. Carney, S.Z. He, D.C.S. Huang, H. Xiong, Y. Cui, T.A. Busman, E.M. McKeegan, A.P. Krivoshik, S.H. Enschede, R. Humerickhouse, Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease, J. Clin. Oncol. 30 (2012), https://doi.org/10.1200/JCO.2011.34.7898.
[107] M. Puglisi, L.R. Molife, M.J.A. De Jonge, K.H. Khan, L.Van Doorn, M.D. Forster, M. Blanco, M. Gutierrez, C. Franklin, T. Busman, J. Yang, F.A.L.M. Eskens, A Phase i study of the safety, pharmacokinetics and efficacy of navitoclax plus docetaxel in patients with advanced solid tumors, Future Oncol. 17 (2021), https://doi.org/10.2217/fon-2021-0140.
[108] T.J. Kipps, H. Eradat, S. Grosicki, J. Catalano, W. Cosolo, I.S. Dyagil, S. Yalamanchili, A. Chai, S. Sahasranaman, E. Punnoose, D. Hurst, H. Pylypenko, A phase 2 study of the BH3 mimetic BCL2 inhibitor navitoclax (ABT-263) with or without rituximab, in previously untreated B-cell chronic lymphocytic leukemia, Leuk. Lymphoma 56 (2015), https://doi.org/10.3109/10428194.2015.1030638.
[109] S. de Vos, J.P. Leonard, J.W. Friedberg, J. Zain, K. Dunleavy, R. Humerickhouse, J. Hayslip, J. Pesko, W.H. Wilson, Safety and efficacy of navitoclax, a BCL-2 and BCL-XL inhibitor, in patients with relapsed or refractory lymphoid malignancies: results from a phase 2a study, Leuk. Lymphoma 62 (2021), https://doi.org/10.1080/10428194.2020.1845332.
[110] A.J. Souers, J.D. Leverson, E.R. Boghaert, S.L. Ackler, N.D. Catron, J. Chen, B. D. Dayton, H. Ding, S.H. Enschede, W.J. Fairbrother, D.C.S. Huang, S. G. Hymowitz, S. Jin, S.L. Khaw, P.J. Kovar, L.T. Lam, J. Lee, H.L. Maecker, K. C. Marsh, K.D. Mason, M.J. Mitten, P.M. Nimmer, A. Oleksijew, C.H. Park, C. M. Park, D.C. Phillips, A.W. Roberts, D. Sampath, J.F. Seymour, M.L. Smith, G. M. Sullivan, S.K. Tahir, C. Tse, M.D. Wendt, Y. Xiao, J.C. Xue, H. Zhang, R. A. Humerickhouse, S.H. Rosenberg, S.W. Elmore, ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets, Nat. Med 19 (2013), https://doi.org/10.1038/nm.3048.
[111] J. Deng, A. Paulus, D.D. Fang, A. Manna, G. Wang, H. Wang, S. Zhu, J. Chen, P. Min, Y. Yin, N. Dutta, N. Halder, G. Ciccio, J.A. Copland, J. Miller, B. Han, L. Bai, L. Liu, M. Wang, D. McEachern, S. Przybranowski, C.Y. Yang, J.A. Stuckey, D. Wu, C. Li, J. Ryan, A. Letai, S. Ailawadhi, D. Yang, S. Wang, A. Chanan-Khan, Y. Zhai, Lisaftoclax (APG-2575) is a novel BCL-2 inhibitor with robust antitumor activity in preclinical models of hematologic malignancy, Clin. Cancer Res. 28 (2022), https://doi.org/10.1158/1078-0432.CCR-21-4037.
[112] M.J. Birnbaum, R.J. Clem, L.K. Miller, An apoptosis-inhibiting gene from a nuclear polyhedrosis virus encoding a polypeptide with Cys/His sequence motifs, J. Virol. 68 (1994), https://doi.org/10.1128/jvi.68.4.2521-2528.1994.
[113] H. Cong, L. Xu, Y. Wu, Z. Qu, T. Bian, W. Zhang, C. Xing, C. Zhuang, Inhibitor of apoptosis protein (IAP) antagonists in anticancer agent discovery: current status and perspectives, J. Med. Chem. 62 (2019), https://doi.org/10.1021/acs.jmedchem.8b01668.
[114] E.N. Shiozaki, J. Chai, D.J. Rigotti, S.J. Riedl, P. Li, S.M. Srinivasula, E.S. Alnemri, R. Fairman, Y. Shi, Mechanism of XIAP-mediated inhibition of caspase-9, Mol. Cell 11 (2003), https://doi.org/10.1016/S1097-2765(03)00054-6.
[115] G. Wu, J. Chai, T.L. Suber, J.W. Wu, C. Du, X. Wang, Y. Shi, Structural basis of IAP recognition by Smac/DIABLO, Nature 408 (2000), https://doi.org/10.1038/35050012.
[116] J.A. Flygare, M. Beresini, N. Budha, H. Chan, I.T. Chan, S. Cheeti, F. Cohen, K. Deshayes, K. Doerner, S.G. Eckhardt, L.O. Elliott, B. Feng, M.C. Franklin, S. F. Reisner, L. Gazzard, J. Halladay, S.G. Hymowitz, H. La, P. Lorusso, B. Maurer, L. Murray, E. Plise, C. Quan, J.P. Stephan, S.G. Young, J. Tom, V. Tsui, J. Um, E. Varfolomeev, D. Vucic, A.J. Wagner, H.J.A. Wallweber, L. Wang, J. Ware, Z. Wen, H. Wong, J.M. Wong, M. Wong, S. Wong, R. Yu, K. Zobel, W. J. Fairbrother, Discovery of a potent small-molecule antagonist of inhibitor of apoptosis (IAP) proteins and clinical candidate for the treatment of cancer (GDC-0152), J. Med. Chem. 55 (2012), https://doi.org/10.1021/jm300060k.
[117] A.W. Tolcher, J.C. Bendell, K.P. Papadopoulos, H.A. Burris, A. Patnaik, W. J. Fairbrother, H. Wong, N. Budha, W.C. Darbonne, F. Peale, M. Mamounas, S. Royer-Joo, R. Yu, C.C. Portera, J.R. Infante, A phase i dose-escalation study evaluating the safety tolerability and pharmacokinetics of CUDC-427, a potent, oral, monovalent IAP antagonist, in patients with refractory solid tumors, Clin. Cancer Res. (2016), https://doi.org/10.1158/1078-0432.CCR-16-0308.
[118] N.N. Senzer, P. LoRusso, L.P. Martin, R.J. Schilder, R.K. Amaravadi, K. P. Papadopoulos, Z.E. Segota, D.E. Weng, M. Graham, A.A. Adjei, Phase II clinical activity and tolerability of the SMAC-mimetic birinapant (TL32711) plus irinotecan in irinotecan-relapsed/refractory metastatic colorectal cancer, 3621–3621, J. Clin. Oncol. 31 (2013), https://doi.org/10.1200/jco.2013.31.15_suppl.3621.
[119] Q. Cai, H. Sun, Y. Peng, J. Lu, Z. Nikolovska-Coleska, D. McEachern, L. Liu, S. Qiu, C.Y. Yang, R. Miller, H. Yi, T. Zhang, D. Sun, S. Kang, M. Guo, L. Leopold, D. Yang, S. Wang, A potent and orally active antagonist (SM-406/AT-406) of multiple inhibitor of apoptosis proteins (IAPs) in clinical development for cancer treatment, J. Med. Chem. 54 (2011), https://doi.org/10.1021/jm101505d.
[120] Y. TAO, X.S. Sun, Y. Pointreau, C. Le Tourneau, C. Sire, M.C. Kaminsky, A. Coutte, M. Alfonsi, B. Calderon, P. Boisselier, L. Martin, J. Miroir, J.F. Ramee, J.P. Delord, F. Clatot, F. Rolland, J. Villa, N. Magne, O. Elicin, E. Gherga, F. Nguyen, C. Lafond, G. Bera, V. Calugaru, L. Geoffrois, B. Chauffert, L. Damstrup, P. Crompton, A. Ennaji, K. Gollmer, H. Nauwelaerts, J. Bourhis, Extended follow-up of a phase 2 trial of xevinapant plus chemoradiotherapy in high-risk locally advanced squamous cell carcinoma of the head and neck: a randomised clinical trial, Eur. J. Cancer 183 (2023), https://doi.org/10.1016/j.ejca.2022.12.015.
[121] G. Chessari, I.M. Buck, J.E.H. Day, P.J. Day, A. Iqbal, C.N. Johnson, E.J. Lewis, V. Martins, D. Miller, M. Reader, D.C. Rees, S.J. Rich, E. Tamanini, M. Vitorino, G. A. Ward, P.A. Williams, G. Williams, N.E. Wilsher, A.J.A. Woolford, Fragment-based drug discovery targeting inhibitor of apoptosis proteins: discovery of a non-alanine lead series with dual activity against cIAP1 and XIAP, J. Med. Chem. 58 (2015) 6574–6588, https://doi.org/10.1021/acs.jmedchem.5b00706.
[122] G.A. Ward, E.J. Lewis, J.S. Ahn, C.N. Johnson, J.F. Lyons, V. Martins, J.M. Munck, S.J. Rich, T. Smyth, N.T. Thompson, P.A. Williams, N.E. Wilsher, N.G. Wallis, G. Chessari, ASTX660, a novel non-peptidomimetic antagonist of cIAP1/2 and XIAP, potently induces TNFα-dependent apoptosis in cancer cell lines and inhibits tumor growth, Mol. Cancer Ther. 17 (2018), https://doi.org/10.1158/1535-7163.MCT-17-0848.
[123] C.N. Johnson, J.S. Ahn, I.M. Buck, E. Chiarparin, J.E.H. Day, A. Hopkins, S. Howard, E.J. Lewis, V. Martins, A. Millemaggi, J.M. Munck, L.W. Page, T. Peakman, M. Reader, S.J. Rich, G. Saxty, T. Smyth, N.T. Thompson, G.A. Ward, P.A. Williams, N.E. Wilsher, G. Chessari, A Fragment-derived clinical candidate for antagonism of X-linked and cellular inhibitor of apoptosis proteins: 1-(6-[(4-Fluorophenyl)methyl]-5-(hydroxymethyl)-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl)-2-[(2 R,5 R)-5-methyl-2-([(3R)-3-methylmorpholin-4-yl]methyl) piperazin-1-yl]ethan-1-one (ASTX660), J. Med. Chem. 61 (2018) 7314–7329, https://doi.org/10.1021/acs.jmedchem.8b00900.
[124] M.M. Mita, P.M. LoRusso, K.P. Papadopoulos, M.S. Gordon, A.C. Mita, R. Ferraldeschi, H. Keer, A. Oganesian, X.Y. Su, S. Jueliger, A.W. Tolcher, A phase I study of ASTX660, an antagonist of inhibitors of apoptosis proteins, in adults with advanced cancers or lymphoma, Clin. Cancer Res. 26 (2020) 2819–2826, https://doi.org/10.1158/1078-0432.CCR-19-1430.
[125] D. Picard, B. Khursheed, M.J. Garabedian, M.G. Fortin, S. Lindquist, K. R. Yamamoto, Reduced levels of hsp90 compromise steroid receptor action in vivo, Nature 348 (1990), https://doi.org/10.1038/348166a0.
[126] K.A. Borkovich, F.W. Farrelly, D.B. Finkelstein, J. Taulien, S. Lindquist, hsp82 is an essential protein that is required in higher concentrations for growth of cells at higher temperatures, Mol. Cell Biol. 9 (1989), https://doi.org/10.1128/mcb.9.9.3919.
[127] O. Ostrovsky, C.A. Makarewich, E.L. Snapp, Y. Argon, An essential role for ATP binding and hydrolysis in the chaperone activity of GRP94 in cells, Proc. Natl. Acad. Sci. USA 106 (2009), https://doi.org/10.1073/pnas.0902626106.
[128] A.S. Sreedhar, É. Kalmár, P. Csermely, Y.F. Shen, Hsp90 isoforms: functions, expression and clinical importance, FEBS Lett. 562 (2004), https://doi.org/10.1016/S0014-5793(04)00229-7.
[129] A.J. McClellan, Y. Xia, A.M. Deutschbauer, R.W. Davis, M. Gerstein, J. Frydman, Diverse cellular functions of the Hsp90 molecular chaperone uncovered using systems approaches, Cell 131 (2007), https://doi.org/10.1016/j.cell.2007.07.036.
[130] E. Pick, Y. Kluger, J.M. Giltnane, C. Moeder, R.L. Camp, D.L. Rimm, H.M. Kluger, High HSP90 expression is associated with decreased survival in breast cancer, Cancer Res. 67 (2007), https://doi.org/10.1158/0008-5472.CAN-06-4511.
[131] S. Zhang, S. Guo, Z. Li, D. Li, Q. Zhan, High expression of HSP90 is associated with poor prognosis in patients with colorectal cancer, PeerJ 2019 (2019), https://doi.org/10.7717/peerj.7946.

[132] A. Citri, D. Harari, G. Shohat, P. Ramakrishnan, J. Gan, S. Lavi, M. Eisenstein, A. Kimchi, D. Wallach, S. Pietrokovski, Y. Yarden, Hsp90 recognizes a common surface on client kinases, J. Biol. Chem. 281 (2006), https://doi.org/10.1074/jbc.M512613200.
[133] L.H. Pearl, C. Prodromou, P. Workman, The Hsp90 molecular chaperone: an open and shut case for treatment, Biochem. J. 410 (2008), https://doi.org/10.1042/BJ20071640.
[134] Y. Miyata, H. Nakamoto, L. Neckers, The therapeutic target Hsp90 and cancer hallmarks, Curr. Pharm. Des. 19 (2012), https://doi.org/10.2174/138161213804143725.
[135] L. Wright, X. Barril, B. Dymock, L. Sheridan, A. Surgenor, M. Beswick, M. Drysdale, A. Collier, A. Massey, N. Davies, A. Fink, C. Fromont, W. Aherne, K. Boxall, S. Sharp, P. Workman, R.E. Hubbard, Structure-activity relationships in purine-based inhibitor binding to HSP90 isoforms, Chem. Biol. 11 (2004), https://doi.org/10.1016/j.chembiol.2004.03.033.
[136] L.I. Finci, M. Chakrabarti, G. Gulten, J. Finney, C. Grose, T. Fox, R. Yang, D. V. Nissley, F. McCormick, D. Esposito, T.E. Balius, D.K. Simanshu, Structural dynamics of RAF1-HSP90-CDC37 and HSP90 complexes reveal asymmetric client interactions and key structural elements, Commun. Biol. 7 (2024), https://doi.org/10.1038/s42003-024-05959-3.
[137] T.O. Street, L.A. Lavery, D.A. Agard, Substrate binding drives large-scale conformational changes in the hsp90 molecular chaperone, Mol. Cell 42 (2011), https://doi.org/10.1016/j.molcel.2011.01.029.
[138] J. Chen, J. Wang, F. Lai, W. Wang, L. Pang, W. Zhu, Dynamics revelation of conformational changes and binding modes of heat shock protein 90 induced by inhibitor associations, RSC Adv. 8 (2018), https://doi.org/10.1039/c8ra05042b.
[139] C. Yoshimura, S. Nagatoishi, D. Kuroda, Y. Kodama, T. Uno, M. Kitade, K. Chong-Takata, H. Oshiumi, H. Muraoka, S. Yamashita, Y. Kawai, S. Ohkubo, K. Tsumoto, Thermodynamic dissection of potency and selectivity of cytosolic Hsp90 inhibitors, J. Med Chem. 64 (2021), https://doi.org/10.1021/acs.jmedchem.0c01715.
[140] J.G. Supko, R.L. Hickman, M.R. Grever, L. Malspeis, Preclinical pharmacologic evaluation of geldanamycin as an antitumor agent, Cancer Chemother. Pharm. 36 (1995), https://doi.org/10.1007/BF00689048.
[141] G. Floris, R. Sciot, A. Wozniak, T. Van Looy, J. Wellens, G. Faa, E. Normant, M. Debiec-Rychter, P. Schöffski, The novel HSP90 inhibitor, IPI-493, is highly effective in human gastrostrointestinal stromal tumor xenografts carrying heterogeneous KIT mutations, Clin. Cancer Res. 17 (2011), https://doi.org/10.1158/1078-0432.CCR-11-0562.
[142] K. Jhaveri, T. Taldone, S. Modi, G. Chiosis, Advances in the clinical development of heat shock protein 90 (Hsp90) inhibitors in cancers, Biochim Biophys. Acta Mol. Cell Res. 1823 (2012), https://doi.org/10.1016/j.bbamcr.2011.10.008.
[143] G. Garg, A. Khandelwal, B.S.J. Blagg, Anticancer Inhibitors of Hsp90 Function: Beyond the Usual Suspects, in: Adv Cancer Res., Academic Press Inc., 2016, pp. 51–88, https://doi.org/10.1016/bs.acr.2015.12.001.
[144] S. Hall, A. Barabasz, T. Barta, L. DuBois, J. Eaves, P. Fadden, B. Foley, T. Freed, G. Hanson, L. Hinkley, M. Hu, M. Jenks, M. Lewis, W. Ma, J. Partridge, B. Pronk, J. Rice, A. Scott, M. Silinski, J.-P. Strachan, P. Steed, J. Veal, K. Verleysen, T. Haystead, Chemoproteomics-driven drug discovery: identification of novel hsp90 inhibitors, Cancer Res. 67 (2007) 4177.
[145] K. Lundgren, H. Zhang, J. Brekken, N. Huser, R.E. Powell, N. Timple, D.J. Busch, L. Neely, J.L. Sensintaffar, Y.C. Yang, A. McKenzie, J. Friedman, R. Scannevin, A. Kamal, K. Hong, S.R. Kasibhatla, M.F. Boehm, F.J. Burrows, BIIB021, an orally available, fully synthetic small-molecule inhibitor of the heat shock protein Hsp90, Mol. Cancer Ther. 8 (2009), https://doi.org/10.1158/1535-7163.MCT-08-0758.
[146] R. Bagatell, G.D. Paine-Murrieta, C.W. Taylor, E.J. Pulcini, S. Akinaga, I. J. Benjamin, L. Whitesell, Induction of a heat shock factor 1-dependent stress response alters the cytotoxic activity of Hsp90-binding agents, Clin. Cancer Res. 6 (2000).
[147] Y. Wang, Y.C. Koay, S.R. McAlpine, Redefining the phenotype of heat shock protein 90 (Hsp90) inhibitors, Chem. - A Eur. J. 23 (2017), https://doi.org/10.1002/chem.201604807.
[148] S. Terracciano, A. Russo, M.G. Chini, M.C. Vaccaro, M. Potenza, A. Vassallo, R. Riccio, G. Bifulco, I. Bruno, Discovery of new molecular entities able to strongly interfere with Hsp90C-terminal domain, Sci. Rep. 8 (2018), https://doi.org/10.1038/s41598-017-14902-y.
[149] S. Ohkubo, H. Muraoka, A. Hashimoto, S. Ito, K. Ito, Y. Shibata, A. Kanoh, M. Kitade, K. Yonekura, T. Utsugi, 291 TAS-116, a novel, orally bioavailable HSP90a/β selective inhibitor demonstrates highly potent antitumor activity in preclinical models with a favorable PK profile, Eur. J. Cancer 48 (2012), https://doi.org/10.1016/s0959-8049(12)72089-0.
[150] Y. Kodama, H. Hitotsumachi, Y. Shibata, T. Suzuki, M. Sakuragi, M. Kitade, F. Morita, K. Yonekura, S. Ohkubo, T. Utsugi, 290 TAS-116, a novel, orally bioavailable highly potent HSP90a/β selective inhibitor demonstrates favorable tissue distribution properties which lead to minimized ocular toxicity, Eur. J. Cancer 48 (2012), https://doi.org/10.1016/s0959-8049(12)72088-9.
[151] S. Ohkubo, Y. Kodama, H. Muraoka, H. Hitotsumachi, C. Yoshimura, M. Kitade, A. Hashimoto, K. Ito, A. Gomori, K. Takahashi, Y. Shibata, A. Kanoh, K. Yonekura, TAS-116, a highly selective inhibitor of heat shock protein 90α and β, demonstrates potent antitumor activity and minimal ocular toxicity in preclinical models, Mol. Cancer Ther. 14 (2015), https://doi.org/10.1158/1535-7163.MCT-14-0219.
[152] Y. Honma, Y. Kurokawa, A. Sawaki, Y. Naito, S. Iwagami, H. Baba, Y. Komatsu, T. Nishida, T. Doi, Randomized, double-blind, placebo (PL)-controlled, phase III trial of pimitespib (TAS-116), an oral inhibitor of heat shock protein 90 (HSP90), in patients (pts) with advanced gastrointestinal stromal tumor (GIST) refractory to imatinib (IM), sunitinib (SU) and regorafenib (REG), J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/jco.2021.39.15_suppl.11524.
[153] M.G. Marcu, A. Chadli, I. Bouhouche, M. Catelli, L.M. Neckers, The heat shock protein 90 antagonist novobiocin interacts with a previously unrecognized ATP-binding domain in the carboxyl terminus of the chaperone, J. Biol. Chem. 275 (2000), https://doi.org/10.1074/jbc.M003701200.
[154] R.K. Allan, D. Mok, B.K. Ward, T. Ratajczak, Modulation of chaperone function and cochaperone interaction by novobiocin in the C-terminal domain of Hsp90: evidence that coumarin antibiotics disrupt Hsp90 dimerization, J. Biol. Chem. 281 (2006), https://doi.org/10.1074/jbc.M512406200.
[155] J. Zhou, C. Gelot, C. Pantelidou, A. Li, H. Yücel, R.E. Davis, A. Färkkilä, B. Kochupurakkal, A. Syed, G.I. Shapiro, J.A. Tainer, B.S.J. Blagg, R. Ceccaldi, A. D. D'Andrea, A first-in-class polymerase theta inhibitor selectively targets homologous-recombination-deficient tumors, Nat. Cancer 2 (2021), https://doi.org/10.1038/s43018-021-00203-x.
[156] N. Priego, L. Zhu, C. Monteiro, M. Mulders, D. Wasilewski, W. Bindeman, L. Doglio, L. Martínez, E. Martínez-Saez, S.R.Y. Cajal, D. Megías, E. Hernández-Encinas, C. Blanco-Aparicio, L. Martínez, E. Zarzuela, J. Muñoz, C. Fustero-Torre, E. Piñeiro-Yáñez, A. Hernández-Laín, L. Bertero, V. Poli, M. Sanchez-Martinez, J. A. Menendez, R. Soffietti, J. Bosch-Barrera, M. Valiente, STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis article, Nat. Med. 24 (2018), https://doi.org/10.1038/s41591-018-0044-4.
[157] E. Cuyàs, S. Verdura, V. Micol, J. Joven, J. Bosch-Barrera, J.A. Encinar, J. A. Menendez, Revisiting silibinin as a novobiocin-like Hsp90 C-terminal inhibitor: computational modeling and experimental validation, Food Chem. Toxicol. 132 (2019), https://doi.org/10.1016/j.fct.2019.110645.
[158] P.J. Gray, T. Prince, J. Cheng, M.A. Stevenson, S.K. Calderwood, Targeting the oncogene and kinome chaperone CDC37, Nat. Rev. Cancer 8 (2008), https://doi.org/10.1038/nrc2420.
[159] M. Taipale, I. Krykbaeva, M. Koeva, C. Kayatekin, K.D. Westover, G.I. Karras, S. Lindquist, Quantitative analysis of Hsp90-client interactions reveals principles of substrate recognition, Cell 150 (2012), https://doi.org/10.1016/j.cell.2012.06.047.
[160] S.M. Roe, M.M.U. Ali, P. Meyer, C.K. Vaughan, B. Panaretou, P.W. Piper, C. Prodromou, L.H. Pearl, The mechanism of Hsp90 regulation by the protein kinase-specific cochaperone p50cdc37, Cell 116 (2004), https://doi.org/10.1016/S0092-8674(03)01027-4.
[161] X. Chen, P. Liu, Q. Wang, Y. Li, L. Fu, H. Fu, J. Zhu, Z. Chen, W. Zhu, C. Xie, L. Lou, DCZ3112, a novel Hsp90 inhibitor, exerts potent antitumor activity against HER2-positive breast cancer through disruption of Hsp90-Cdc37 interaction, Cancer Lett. 434 (2018), https://doi.org/10.1016/j.canlet.2018.07.012.
[162] L. Wang, L. Zhang, L. Li, J. Jiang, Z. Zheng, J. Shang, C. Wang, W. Chen, Q. Bao, X. Xu, Z. Jiang, J. Zhang, Q. You, Small-molecule inhibitor targeting the Hsp90-Cdc37 protein-protein interaction in colorectal cancer, Sci. Adv. 5 (2019), https://doi.org/10.1126/sciadv.aax2277.
[163] T. Zhang, A. Hamza, X. Cao, B. Wang, S. Yu, C.G. Zhan, D. Sun, A novel Hsp90 inhibitor to disrupt Hsp90/Cdc37 complex against pancreatic cancer cells, Mol. Cancer Ther. 7 (2008), https://doi.org/10.1158/1535-7163.MCT-07-0484.
[164] Y. Yu, A. Hamza, T. Zhang, M. Gu, P. Zou, B. Newman, Y. Li, A.A.L. Gunatilaka, C. G. Zhan, D. Sun, Withaferin A targets heat shock protein 90 in pancreatic cancer cells, Biochem Pharm. 79 (2010), https://doi.org/10.1016/j.bcp.2009.09.017.
[165] Y. Li, G.E. Karagöz, Y.H. Seo, T. Zhang, Y. Jiang, Y. Yu, A.M.S. Duarte, S. J. Schwartz, R. Boelens, K. Carroll, S.G.D. Rüdiger, D. Sun, Sulforaphane inhibits pancreatic cancer through disrupting Hsp90-p50Cdc37 complex and direct interactions with amino acids residues of Hsp90, J. Nutr. Biochem. 23 (2012), https://doi.org/10.1016/j.jnutbio.2011.11.004.
[166] C.V. Dang, MYC on the path to cancer, Cell 149 (2012), https://doi.org/10.1016/j.cell.2012.03.003.
[167] W.P. Tansey, Mammalian MYC proteins and cancer, N. J. Sci. 2014 (2014), https://doi.org/10.1155/2014/757534.
[168] B. Gurel, T. Iwata, C.M. Koh, R.B. Jenkins, F. Lan, C. Van Dang, J.L. Hicks, J. Morgan, T.C. Cornish, S. Sutcliffe, W.B. Isaacs, J. Luo, A.M. De Marzo, Nuclear MYC protein overexpression is an early alteration in human prostate carcinogenesis, Mod. Pathol. 21 (2008), https://doi.org/10.1038/modpathol.2008.111.
[169] D. Massó-Vallés, L. Soucek, Blocking myc to treat cancer: reflecting on two decades of omomyc, Cells 9 (2020), https://doi.org/10.3390/cells9040883.
[170] S.J. Berberich, M.D. Cole, Casein kinase II inhibits the DNA-binding activity of Max homodimers but not Myc/Max heterodimers, Genes Dev. 6 (1992), https://doi.org/10.1101/gad.6.2.166.
[171] M. Cañelles, M.D. Delgado, K.M. Hyland, A. Lerga, C. Richard, C.V. Dang, J. León, Max and inhibitory c-Myc mutants induce erythroid differentiation and resistance to apoptosis in human myeloid leukemia cells, Oncogene 14 (1997), https://doi.org/10.1038/sj.onc.1200948.
[172] P. Brownlie, T.A. Ceska, M. Lamers, C. Romier, G. Stier, H. Teo, D. Suck, The crystal structure of an intact human Max-DNA complex: new insights into mechanisms of transcriptional control, Structure 5 (1997), https://doi.org/10.1016/S0969-2126(97)00207-4.
[173] L. Soucek, M. Helmer-Citterich, A. Sacco, R. Jucker, G. Cesareni, S. Nasi, Design and properties of a Myc derivative that efficiently homodimerizes, Oncogene 17 (1998), https://doi.org/10.1038/sj.onc.1202199.
[174] S.K. Nair, S.K. Burley, X-ray structures of Myc-Max and Mad-Max recognizing DNA: molecular bases of regulation by proto-oncogenic transcription factors, Cell 112 (2003), https://doi.org/10.1016/S0092-8674(02)01284-9.

[175] J.R. Whitfield, L. Soucek, The long journey to bring a myc inhibitor to the clinic, J. Cell Biol. 220 (2021), https://doi.org/10.1083/jcb.202103090.
[176] J. Chauhan, H. Wang, J.L. Yap, P.E. Sabato, A. Hu, E.V. Prochownik, S. Fletcher, Discovery of methyl 4'-methyl-5-(7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)-[1,1'-biphenyl]-3-carboxylate, an improved small-molecule inhibitor of c-Myc-max dimerization, ChemMedChem 9 (2014), https://doi.org/10.1002/cmdc.201402189.
[177] D. Stellas, M. Szabolcs, S. Koul, Z. Li, A. Polyzos, C. Anagnostopoulos, Z. Cournia, C. Tamvakopoulos, A. Klinakis, A. Efstratiadis, Therapeutic effects of an anti-Myc drug on mouse pancreatic cancer, J. Natl. Cancer Inst. 106 (2014), https://doi.org/10.1093/jnci/dju320.
[178] H. Han, A.D. Jain, M.I. Truica, J. Izquierdo-Ferrer, J.F. Anker, B. Lysy, V. Sagar, Y. Luan, Z.R. Chalmers, K. Unno, H. Mok, R. Vatapalli, Y.A. Yoo, Y. Rodriguez, I. Kandela, J.B. Parker, D. Chakravarti, R.K. Mishra, G.E. Schiltz, S.A. Abdulkadir, Small-molecule MYC inhibitors suppress tumor growth and enhance immunotherapy, Cancer Cell 36 (2019), https://doi.org/10.1016/j.ccell.2019.10.001.
[179] M. Tang, S. O'Grady, J. Crown, M.J. Duffy, MYC as a therapeutic target for the treatment of triple-negative breast cancer: preclinical investigations with the novel MYC inhibitor, MYCi975, Breast Cancer Res. Treat. 195 (2022) 105–115, https://doi.org/10.1007/s10549-022-06673-6.
[180] J. Schulte am Esch, B.A. Windmöller, J. Hanewinkel, J. Storm, C. Förster, L. Wilkens, M. Krüger, B. Kaltschmidt, C. Kaltschmidt, Isolation and characterization of two novel colorectal cancer cell lines, containing a subpopulation with potential stem-like properties: treatment options by MYC/NMYC inhibition, Cancers 12 (2020) 2582, https://doi.org/10.3390/cancers12092582.
[181] B.A. Windmöller, M. Beshay, L.P. Helweg, C. Flottmann, M. Beermann, C. Förster, L. Wilkens, J.F.W. Greiner, C. Kaltschmidt, B. Kaltschmidt, Novel primary human cancer stem-like cell populations from non-small cell lung cancer: inhibition of cell survival by targeting nf-κb and myc signaling, Cells 10 (2021), https://doi.org/10.3390/cells10051024.
[182] I.L. Hsin, H.P. Shen, H.Y. Chang, J.L. Ko, P.H. Wang, Suppression of pi3k/akt/mtor/c-myc/mtp53 positive feedback loop induces cell cycle arrest by dual pi3k/mtor inhibitor pqr309 in endometrial cancer cell lines, Cells 10 (2021), https://doi.org/10.3390/cells10112916.
[183] A. Castell, Q. Yan, K. Fawkner, P. Hydbring, F. Zhang, V. Verschut, M. Franco, S. M. Zakaria, W. Bazzar, J. Goodwin, G. Zinzalla, L.G. Larsson, A selective high affinity MYC-binding compound inhibits MYC:MAX interaction and MYC-dependent tumor cell proliferation, Sci. Rep. 8 (2018), https://doi.org/10.1038/s41598-018-28107-4.
[184] D. AlSultan, E. Kavanagh, S. O'Grady, A.J. Eustace, A. Castell, L.G. Larsson, J. Crown, S.F. Madden, M.J. Duffy, The novel low molecular weight MYC antagonist MYCMI-6 inhibits proliferation and induces apoptosis in breast cancer cells, Invest N. Drugs 39 (2021), https://doi.org/10.1007/s10637-020-01018-w.
[185] M. Savino, D. Annibali, N. Carucci, E. Favuzzi, M.D. Cole, G.I. Evan, L. Soucek, S. Nasi, The action mechanism of the Myc inhibitor termed Omomyc may give clues on how to target Myc for cancer therapy, PLoS One 6 (2011), https://doi.org/10.1371/journal.pone.0022284.
[186] M.J. Demma, C. Mapelli, A. Sun, S. Bodea, B. Ruprecht, S. Javaid, D. Wiswell, E. Muise, S. Chen, J. Zelina, F. Orvieto, A. Santoprete, S. Altezza, F. Tucci, E. Escandon, B. Hall, K. Ray, A. Walji, J. O'Neil, Omomyc reveals new mechanisms to inhibit the MYC oncogene, Mol. Cell Biol. 39 (2019), https://doi.org/10.1128/mcb.00248-19.
[187] M.J. Duffy, S. O'Grady, M. Tang, J. Crown, MYC as a target for cancer treatment, Cancer Treat. Rev. 94 (2021), https://doi.org/10.1016/j.ctrv.2021.102154.
[188] F.P. Fiorentino, E. Tokgün, S. Solé-Sánchez, S. Giampaolo, O. Tokgün, T. Jauset, T. Kohno, M. Perucho, L. Soucek, J. Yokota, Growth suppression by MYC inhibition in small cell lung cancer cells with TP53 and RB1 inactivation, Oncotarget 7 (2016), https://doi.org/10.18632/oncotarget.8826.
[189] M.E. Beaulieu, T. Jauset, D. Massó-Vallés, S. Martínez-Martín, P. Rahl, L. Maltais, M.F. Zacarias-Fluck, S. Casacuberta-Serra, E.S. Del Pozo, C. Fiore, L. Foradada, V. C. Cano, M. Sánchez-Hervás, M. Guenther, E.R. Sanz, M. Oteo, C. Tremblay, G. Martín, D. Letourneau, M. Montagne, M.Á.M. Alonso, J.R. Whitfield, P. Lavigne, L. Soucek, Intrinsic cell-penetrating activity propels omomyc from proof of concept to viable anti-myc therapy, Sci. Transl. Med. 11 (2019), https://doi.org/10.1126/scitranslmed.aar5012.
[190] E. Garralda, M.E. Beaulieu, V. Moreno, S. Casacuberta-Serra, S. Martínez-Martín, L. Foradada, G. Alonso, D. Massó-Vallés, S. López-Estévez, T. Jauset, E. Corral de la Fuente, B. Doger, T. Hernández, R. Perez-Lopez, O. Arqués, V. Castillo Cano, J. Morales, J.R. Whitfield, M. Niewel, L. Soucek, E. Calvo, MYC targeting by OMO-103 in solid tumors: a phase 1 trial, Nat. Med. 30 (2024), https://doi.org/10.1038/s41591-024-02805-1.
[191] I.A. Prior, F.E. Hood, J.L. Hartley, The frequency of ras mutations in cancer, Cancer Res. 80 (2020), https://doi.org/10.1158/0008-5472.CAN-19-3682.
[192] W. Kolch, Meaningful relationships: the regulation of the Ras/Raf/MEK/ERK pathway by protein interactions, Biochem. J. 351 (2000), https://doi.org/10.1042/0264-6021:3510289.
[193] A.R. Moore, S.C. Rosenberg, F. McCormick, S. Malek, RAS-targeted therapies: is the undruggable drugged? Nat. Rev. Drug Discov. 19 (2020) https://doi.org/10.1038/s41573-020-0068-6.
[194] C. Cuesta, C. Arévalo-Alameda, E. Castellano, The importance of being PI3K in the RAS signaling network, Genes 12 (2021), https://doi.org/10.3390/genes12071094.
[195] V. Pandey, V.K. Bhaskara, P.P. Babu, Implications of mitogen-activated protein kinase signaling in glioma, J. Neurosci. Res. 94 (2016), https://doi.org/10.1002/jnr.23687.
[196] J.A. Herman, R.R. Romain, P. Hoellerbauer, H.K. Shirnekhi, D.C. King, K. F. DeLuca, E.O. Nishimura, P.J. Paddison, J.G. DeLuca, Hyper-active RAS/MAPK introduces cancer-specific mitotic vulnerabilities, Proc. Natl. Acad. Sci. USA 119 (2022), https://doi.org/10.1073/pnas.2208255119.
[197] C. Philpott, H. Tovell, I.M. Frayling, D.N. Cooper, M. Upadhyaya, The NF1 somatic mutational landscape in sporadic human cancers, Hum. Genom. 11 (2017), https://doi.org/10.1186/s40246-017-0109-3.
[198] D. Kessler, D. Gerlach, N. Kraut, D.B. McConnell, Targeting son of sevenless 1: the pacemaker of KRAS, Curr. Opin. Chem. Biol. 62 (2021), https://doi.org/10.1016/j.cbpa.2021.02.014.
[199] C.M. Niemeyer, C. Flotho, Juvenile myelomonocytic leukemia: who's the driver at the wheel? Blood 133 (2019) https://doi.org/10.1182/blood-2018-11-844688.
[200] M. Dankner, A.A.N. Rose, S. Rajkumar, P.M. Siegel, I.R. Watson, Classifying BRAF alterations in cancer: new rational therapeutic strategies for actionable mutations, Oncogene 37 (2018), https://doi.org/10.1038/s41388-018-0171-x.
[201] M. Drosten, M. Barbacid, Targeting the MAPK pathway in KRAS-driven tumors, Cancer Cell 37 (2020), https://doi.org/10.1016/j.ccell.2020.03.013.
[202] J. Luo, KRAS mutation in pancreatic cancer, Semin Oncol. 48 (2021), https://doi.org/10.1053/j.seminoncol.2021.02.003.
[203] Y. Jiang, C. Zhuang, L. Chen, J. Lu, G. Dong, Z. Miao, W. Zhang, J. Li, C. Sheng, Structural biology-inspired discovery of novel KRAS-PDEδ inhibitors, J. Med Chem. 60 (2017), https://doi.org/10.1021/acs.jmedchem.7b01243.
[204] L. Huang, Z. Guo, F. Wang, L. Fu, KRAS mutation: from undruggable to druggable in cancer, Signal Transduct. Target Ther. 6 (2021), https://doi.org/10.1038/s41392-021-00780-4.
[205] J.M. Rojas, J.L. Oliva, E. Santos, Mammalian son of sevenless guanine nucleotide exchange factors: old concepts and new perspectives, Genes Cancer 2 (2011), https://doi.org/10.1177/1947601911408078.
[206] F.C. Baltanás, N. Zarich, J.M. Rojas-Cabañeros, E. Santos, SOS GEFs in health and disease, Biochim Biophys. Acta Rev. Cancer 1874 (2020), https://doi.org/10.1016/j.bbcan.2020.188445.
[207] J.M. Ketcham, J. Haling, S. Khare, V. Bowcut, D.M. Briere, A.C. Burns, R.J. Gunn, A. Ivetac, J. Kuehler, S. Kulyk, J. Laguer, J.D. Lawson, K. Moya, N. Nguyen, L. Rahbaek, B. Saechao, C.R. Smith, N. Sudhakar, N.C. Thomas, L. Vegar, D. Vanderpool, X. Wang, L. Yan, P. Olson, J.G. Christensen, M.A. Marx, Design and discovery of MRTX0902, a potent, selective, brain-penetrant, and orally bioavailable inhibitor of the SOS1:KRAS protein-protein interaction, J. Med. Chem. 65 (2022), https://doi.org/10.1021/acs.jmedchem.2c00741.
[208] S.M. Margarit, H. Sondermann, B.E. Hall, B. Nagar, A. Hoelz, M. Pirruccello, D. Bar-Sagi, J. Kuriyan, Structural evidence for feedback activation by Ras·GTP of the Ras-specific nucleotide exchange factor SOS, Cell 112 (2003), https://doi.org/10.1016/S0092-8674(03)00149-1.
[209] Y.K. Lee, S.T. Low-Nam, J.K. Chung, S.D. Hansen, H.Y.M. Lam, S. Alvarez, J. T. Groves, Mechanism of SOS PR-domain autoinhibition revealed by single-molecule assays on native protein from lysate, Nat. Commun. 8 (2017), https://doi.org/10.1038/ncomms15061.
[210] T.J. Liao, H. Jang, R. Nussinov, D. Fushman, High-affinity interactions of the nSH3/cSH3 domains of Grb2 with the C-terminal proline-rich domain of SOS1, J. Am. Chem. Soc. 142 (2020), https://doi.org/10.1021/jacs.9b10710.
[211] C.W. Lin, L.M. Nocka, B.L. Stinger, J.B. DeGrandchamp, L.J.N. Lew, S. Alvarez, H. T. Phan, Y. Kondo, J. Kuriyan, J.T. Groves, A two-component protein condensate of the EGFR cytoplasmic tail and Grb2 regulates Ras activation by SOS at the membrane, Proc. Natl. Acad. Sci. USA 119 (2022), https://doi.org/10.1073/pnas.2122531119.
[212] H. Sondermann, S.M. Soisson, S. Boykevisch, S.S. Yang, D. Bar-Sagi, J. Kuriyan, Structural analysis of autoinhibition in the Ras activator son of sevenless, Cell 119 (2004), https://doi.org/10.1016/j.cell.2004.10.005.
[213] J. Gureasko, W.J. Galush, S. Boykevisch, H. Sondermann, D. Bar-Sagi, J.T. Groves, J. Kuriyan, Membrane-dependent signal integration by the Ras activator Son of sevenless, Nat. Struct. Mol. Biol. 15 (2008), https://doi.org/10.1038/nsmb.1418.
[214] A. Patgiri, K.K. Yadav, P.S. Arora, D. Bar-Sagi, An orthosteric inhibitor of the Ras-Sos interaction, Nat. Chem. Biol. 7 (2011), https://doi.org/10.1038/nchembio.612.
[215] E.S. Leshchiner, A. Parkhitko, G.H. Bird, J. Luccarelli, J.A. Bellairs, S. Escudero, K. Opoku-Nsiah, M. Godes, N. Perrimon, L.D. Walensky, Direct inhibition of oncogenic KRAS by hydrocarbon-stapled SOS1 helices, Proc. Natl. Acad. Sci. USA 112 (2015), https://doi.org/10.1073/pnas.1413185112.
[216] T. Maurer, L.S. Garrenton, A. Oh, K. Pitts, D.J. Anderson, N.J. Skelton, B. P. Fauber, B. Pan, S. Malek, D. Stokoe, M.J.C. Ludlam, K.K. Bowman, J. Wu, A. M. Giannetti, M.A. Starovasnik, I. Mellman, P.K. Jackson, J. Rudolph, W. Wang, G. Fang, Small-molecule ligands bind to a distinct pocket in Ras and inhibit SOS-mediated nucleotide exchange activity, Proc. Natl. Acad. Sci. USA 109 (2012), https://doi.org/10.1073/pnas.1116510109.
[217] Q. Sun, J.P. Burke, J. Phan, M.C. Burns, E.T. Olejniczak, A.G. Waterson, T. Lee, O. W. Rossanese, S.W. Fesik, Discovery of small molecules that bind to K-Ras and inhibit Sos-mediated activation, Angew. Chem. Int. Ed. 51 (2012), https://doi.org/10.1002/anie.201201358.
[218] M.C. Burns, Q. Sun, R.N. Daniels, D. Camper, J.P. Kennedy, J. Phan, E. T. Olejniczak, T. Lee, A.G. Waterson, O.W. Rossanese, S.W. Fesik, Approach for targeting Ras with small molecules that activate SOS-mediated nucleotide exchange, Proc. Natl. Acad. Sci. USA 111 (2014), https://doi.org/10.1073/pnas.1315798111.

[219] J.E. Howes, D.T. Akan, M.C. Burns, O.W. Rossanese, A.G. Waterson, S.W. Fesik, Small molecule–mediated activation of ras elicits biphasic modulation of phospho-erk levels that are regulated through negative feedback on sos1, Mol. Cancer Ther. 17 (2018), https://doi.org/10.1158/1535-7163.MCT-17-0666.
[220] M.C. Burns, J.E. Howes, Q. Sun, A.J. Little, D.M.V. Camper, J.R. Abbott, J. Phan, T. Lee, A.G. Waterson, O.W. Rossanese, S.W. Fesik, High-throughput screening identifies small molecules that bind to the RAS:SOS:RAS complex and perturb RAS signaling, Anal. Biochem. 548 (2018), https://doi.org/10.1016/j.ab.2018.01.025.
[221] J.R. Abbott, T.R. Hodges, R.N. Daniels, P.A. Patel, J.P. Kennedy, J.E. Howes, D. T. Akan, M.C. Burns, J. Sai, T. Sobolik, Y. Beesetty, T. Lee, O.W. Rossanese, J. Phan, A.G. Waterson, S.W. Fesik, Discovery of aminopiperidine indoles that activate the guanine nucleotide exchange factor SOS1 and modulate RAS signaling, J. Med. Chem. 61 (2018), https://doi.org/10.1021/acs.jmedchem.8b00360.
[222] T.R. Hodges, J.R. Abbott, A.J. Little, D. Sarkar, J.M. Salovich, J.E. Howes, D. T. Akan, J. Sai, A.L. Arnold, C. Browning, M.C. Burns, T. Sobolik, Q. Sun, Y. Beesetty, J.A. Coker, D. Scharn, H. Stadtmueller, O.W. Rossanese, J. Phan, A. G. Waterson, D.B. McConnell, S.W. Fesik, Discovery and structure-based optimization of benzimidazole-derived activators of SOS1-mediated nucleotide exchange on RAS, J. Med Chem. 61 (2018), https://doi.org/10.1021/acs.jmedchem.8b01108.
[223] D. Sarkar, E.T. Olejniczak, J. Phan, J.A. Coker, J. Sai, A. Arnold, Y. Beesetty, A. G. Waterson, S.W. Fesik, Discovery of sulfonamide-derived agonists of SOS1-mediated nucleotide exchange on RAS using fragment-based methods, J. Med. Chem. 63 (2020), https://doi.org/10.1021/acs.jmedchem.0c00511.
[224] R.C. Hillig, B. Sautier, J. Schroeder, D. Moosmayer, A. Hilpmann, C.M. Stegmann, N.D. Werbeck, H. Briem, U. Boemer, J. Weiske, V. Badock, J. Mastouri, K. Petersen, G. Siemeister, J.D. Kahmann, D. Wegener, N. Böhnke, K. Eis, K. Graham, L. Wortmann, F. Von Nussbaum, B. Bader, Discovery of potent SOS1 inhibitors that block RAS activation via disruption of the RAS–SOS1 interaction, Proc. Natl. Acad. Sci. USA 116 (2019), https://doi.org/10.1073/pnas.1812963116.
[225] I.A. Prior, P.D. Lewis, C. Mattos, A comprehensive survey of ras mutations in cancer, Cancer Res. 72 (2012), https://doi.org/10.1158/0008-5472.CAN-11-2612.
[226] R. Veluswamy, P.C. Mack, J. Houldsworth, E. Elkhouly, F.R. Hirsch, KRAS G12C–mutant non–small cell lung cancer: biology, developmental therapeutics, and molecular testing, J. Mol. Diagn. 23 (2021), https://doi.org/10.1016/j.jmoldx.2021.02.002.
[227] A. Plangger, B. Rath, S. Stickler, M. Hochmair, C. Lang, L. Weigl, M. Funovics, G. Hamilton, Cytotoxicity of combinations of the pan-KRAS SOS1 inhibitor BAY-293 against pancreatic cancer cell lines, Discov. Oncol. 13 (2022), https://doi.org/10.1007/s12672-022-00550-w.
[228] J. Ramharter, D. Kessler, P. Ettmayer, M.H. Hofmann, T. Gerstberger, M. Gmachl, T. Wunberg, C. Kofink, M. Sanderson, H. Arnhof, G. Bader, K. Rumpel, A. Zöphel, R. Schnitzer, J. Böttcher, J.C. O'Connell, R.L. Mendes, D. Richard, N. Pototschnig, I. Weiner, W. Hela, K. Hauer, D. Haering, L. Lamarre, B. Wolkerstorfer, C. Salamon, P. Werni, S. Munico-Martinez, R. Meyer, M.D. Kennedy, N. Kraut, D. B. McConnell, One Atom Makes All the Difference: Getting a Foot in the Door between SOS1 and KRAS, J. Med. Chem. 64 (2021), https://doi.org/10.1021/acs.jmedchem.0c01949.
[229] M.H. Hofmann, M. Gmachl, J. Ramharter, F. Savarese, D. Gerlach, J.R. Marszalek, M.P. Sanderson, D. Kessler, F. Trapani, H. Arnhof, K. Rumpel, D.A. Botesteanu, P. Ettmayer, T. Gerstberger, C. Kofink, T. Wunberg, A. Zoephel, S.C. Fu, J.L. Teh, J. Böttcher, N. Pototschnig, F. Schachinger, K. Schipany, S. Lieb, C.P. Vellano, J. C. O'connell, R.L. Mendes, J. Moll, M. Petronczki, T.P. Heffernan, M. Pearson, D. B. McConnell, N. Kraut, Bi-3406, a potent and selective sos1–kras interaction inhibitor, is effective in kras-driven cancers through combined mek inhibition, Cancer Discov. 11 (2021), https://doi.org/10.1158/2159-8290.CD-20-0142.
[230] E. Gort, M.L. Johnson, J.J. Hwang, S. Pant, U. Dünzinger, K. Riemann, T. Kitzing, P.A. Janne, A phase I, open-label, dose-escalation trial of BI 1701963 as monotherapy and in combination with trametinib in patients with KRAS mutated advanced or metastatic solid tumors, J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/jco.2020.38.15_suppl.tps3651.
[231] P. Dorr, M. Westby, S. Dobbs, P. Griffin, B. Irvine, M. Macartney, J. Mori, G. Rickett, C. Smith-Burchnell, C. Napier, R. Webster, D. Armour, D. Price, B. Stammen, A. Wood, M. Perros, Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity, Antimicrob. Agents Chemother. 49 (2005), https://doi.org/10.1128/AAC.49.11.4721-4732.2005.
[232] M.A. El-Zohairy, D.P. Zlotos, M.R. Berger, H.H. Adwan, Y.M. Mandour, Discovery of novel CCR5 ligands as anticolorectal cancer agents by sequential virtual screening, ACS Omega 6 (2021), https://doi.org/10.1021/acsomega.1c00681.
[233] H. Zhang, K. Chen, Q. Tan, Q. Shao, S. Han, C. Zhang, C. Yi, X. Chu, Y. Zhu, Y. Xu, Q. Zhao, B. Wu, Structural basis for chemokine recognition and receptor activation of chemokine receptor CCR5, Nat. Commun. 12 (2021), https://doi.org/10.1038/s41467-021-24438-5.
[234] B. Molon, G. Gri, M. Bettella, C. Gómez-Moutón, A. Lanzavecchia, C. Martínez-A, S. Mañes, A. Viola, T cell costimulation by chemokine receptors, Nat. Immunol. 6 (2005), https://doi.org/10.1038/ni1191.
[235] G.G. Vaday, D.M. Peehl, P.A. Kadam, D.M. Lawrence, Expression of CCL5 (RANTES) and CCR5 in prostate cancer, Prostate 66 (2006), https://doi.org/10.1002/pros.20306.
[236] M. Velasco-Velázquez, X. Jiao, M. De La Fuente, T.G. Pestell, A. Ertel, M. P. Lisanti, R.G. Pestell, CCR5 antagonist blocks metastasis of basal breast cancer cells, Cancer Res. 72 (2012), https://doi.org/10.1158/0008-5472.CAN-11-3917.
[237] S.K. Singh, M.K. Mishra, I.E.A. Eltoum, S. Bae, J.W. Lillard, R. Singh, CCR5/CCL5 axis interaction promotes migratory and invasiveness of pancreatic cancer cells, Sci. Rep. 8 (2018), https://doi.org/10.1038/s41598-018-19643-0.
[238] G. Luboshits, S. Shina, O. Kaplan, S. Engelberg, D. Nass, B. Lifshitz-Mercer, S. Chaitchik, I. Keydar, A. Ben-Baruch, Elevated expression of the CC chemokine regulated on activation, normal T cell expressed and secreted (RANTES) in advanced breast carcinoma, Cancer Res. 59 (1999).
[239] H.K. Kim, K.S. Song, Y.S. Park, Y.H. Kang, Y.J. Lee, K.R. Lee, H.K. Kim, K.W. Ryu, J.M. Bae, S. Kim, Elevated levels of circulating platelet microparticles, VEGF, IL-6 and RANTES in patients with gastric cancer: Possible role of a metastasis predictor, Eur. J. Cancer 39 (2003), https://doi.org/10.1016/S0959-8049(02)00596-8.
[240] S. Tsukishiro, N. Suzumori, H. Nishikawa, A. Arakawa, K. Suzumori, Elevated serum RANTES levels in patients with ovarian cancer correlate with the extent of the disorder, Gynecol. Oncol. 102 (2006), https://doi.org/10.1016/j.ygyno.2006.01.029.
[241] H. Sugasawa, T. Ichikura, M. Kinoshita, S. Ono, T. Majima, H. Tsujimoto, K. Chochi, S. Hiroi, E. Takayama, D. Saitoh, S. Seki, H. Mochizuki, Gastric cancer cells exploit CD4+ cell-derived CCL5 for their growth and prevention of CD8+ cell-involved tumor elimination, Int. J. Cancer 122 (2008), https://doi.org/10.1002/ijc.23401.
[242] H. Huang, M. Zepp, R.B. Georges, M. Jarahian, M. Kazemi, E. Eyol, M.R. Berger, The CCR5 antagonist maraviroc causes remission of pancreatic cancer liver metastasis in nude rats based on cell cycle inhibition and apoptosis induction, Cancer Lett. 474 (2020), https://doi.org/10.1016/j.canlet.2020.01.009.
[243] L.F. Gao, Y. Zhong, T. Long, X. Wang, J.X. Zhu, X.Y. Wang, Z.Y. Hu, Z.G. Li, Tumor bud-derived CCL5 recruits fibroblasts and promotes colorectal cancer progression via CCR5-SLC25A24 signaling, J. Exp. Clin. Cancer Res. 41 (2022), https://doi.org/10.1186/s13046-022-02300-w.
[244] B. Cambien, P. Richard-Fiardo, B.F. Karimdjee, V. Martini, B. Ferrua, B. Pitard, H. Schmid-Antomarchi, A. Schmid-Alliana, CCL5 neutralization restricts cancer growth and potentiates the targeting of PDGFRβ in colorectal carcinoma, PLoS One 6 (2011), https://doi.org/10.1371/journal.pone.0028842.
[245] A. Pervaiz, M. Zepp, S. Mahmood, D.M. Ali, M.R. Berger, H. Adwan, CCR5 blockage by maraviroc: a potential therapeutic option for metastatic breast cancer, Cell. Oncol. 42 (2019), https://doi.org/10.1007/s13402-018-0415-3.
[246] A. Pervaiz, M. Zepp, R. Georges, F. Bergmann, S. Mahmood, S. Faiza, M.R. Berger, H. Adwan, Antineoplastic effects of targeting CCR5 and its therapeutic potential for colorectal cancer liver metastasis, J. Cancer Res. Clin. Oncol. 147 (2021), https://doi.org/10.1007/s00432-020-03382-9.
[247] E.C. Halvorsen, M.J. Hamilton, A. Young, B.J. Wadsworth, N.E. LePard, H.N. Lee, N. Firmino, J.L. Collier, K.L. Bennewith, Maraviroc decreases CCL8-mediated migration of CCR5+ regulatory T cells and reduces metastatic tumor growth in the lungs, Oncoimmunology 5 (2016), https://doi.org/10.1080/2162402X.2016.1150398.
[248] A. Pervaiz, S. Ansari, M.R. Berger, H. Adwan, CCR5 blockage by maraviroc induces cytotoxic and apoptotic effects in colorectal cancer cells, Med. Oncol. 32 (2015), https://doi.org/10.1007/s12032-015-0607-x.
[249] X. Jiao, M.A. Velasco-Velazquez, M. Wang, Z. Li, H. Rui, A.R. Peck, J.E. Korkola, X. Chen, S. Xu, J.B. DuHadaway, S. Guerrero-Rodriguez, S. Addya, D. Sicoli, Z. Mu, G. Zhang, A. Stucky, X. Zhang, M. Cristofanilli, A. Fatatis, J.W. Gray, J. F. Zhong, G.C. Prendergast, R.G. Pestell, CCR5 Governs DNA damage repair and breast cancer stem cell expansion, Cancer Res. 78 (2018), https://doi.org/10.1158/0008-5472.CAN-17-0915.
[250] N. Casagrande, C. Borghese, D. Aldinucci, In classical Hodgkin lymphoma the combination of the CCR5 antagonist maraviroc with trabectedin synergizes, enhances DNA damage and decreases three-dimensional tumor-stroma heterospheroid viability, Haematologica 107 (2022), https://doi.org/10.3324/haematol.2021.279389.
[251] M.L. Berres, R.R. Koenen, A. Rueland, M.M. Zaldivar, D. Heinrichs, H. Sahin, P. Schmitz, K.L. Streetz, T. Berg, N. Gassler, R. Weiskirchen, A. Proudfoot, C. Weber, C. Trautwein, H.E. Wasmuth, Antagonism of the chemokine Ccl5 ameliorates experimental liver fibrosis in mice, J. Clin. Investig. 120 (2010), https://doi.org/10.1172/JCI41732.
[252] A.M. Passman, R.P. Strauss, S.B. McSpadden, M. Finch-Edmondson, N. Andrewartha, K.H. Woo, L.A. Diepeveen, W. Zhao, J. Fernández-Irigoyen, E. Santamaría, L. Medina-Ruiz, M. Szpakowska, A. Chevigné, H. Park, R. Carlessi, J.E.E. Tirnitz-Parker, J.R. Blanco, R. London, B.A. Callus, C.L. Elsegood, M. V. Baker, A. Martínez, G.C.T. Yeoh, L. Ochoa-Callejero, Maraviroc prevents hcc development by suppressing macrophages and the liver progenitor cell response in a murine chronic liver disease model, Cancers 13 (2021), https://doi.org/10.3390/cancers13194935.
[253] N. Halama, I. Zoernig, A. Berthel, C. Kahlert, F. Klupp, M. Suarez-Carmona, T. Suetterlin, K. Brand, J. Krauss, F. Lasitschka, T. Lerchl, C. Luckner-Minden, A. Ulrich, M. Koch, J. Weitz, M. Schneider, M.W. Buechler, L. Zitvogel, T. Herrmann, A. Benner, C. Kunz, S. Luecke, C. Springfeld, N. Grabe, C.S. Falk, D. Jaeger, Tumoral immune cell exploitation in colorectal cancer metastases can be targeted effectively by anti-CCR5 therapy in cancer patients, Cancer Cell 29 (2016), https://doi.org/10.1016/j.ccell.2016.03.005.
[254] M. Cristofanilli, N. Chittoria, S. Ehsani, H. Rui, M. Dolezal, L. Stork-Sloots, F. de Snoo, C. Recknor, V. Abramson, Abstract P5-17-08: a phase Ib/II study of leronlimab combined with carboplatin in patients with CCR5+ metastatic triple-

negative breast cancer (mTNBC), Cancer Res. 82 (2022), https://doi.org/10.1158/1538-7445.sabcs21-p5-17-08.
[255] G.M. Haag, C. Springfeld, B. Grün, L. Apostolidis, S. Zschäbitz, M. Dietrich, A. K. Berger, T.F. Weber, I. Zoernig, M. Schaaf, L. Waberer, D.W. Müller, S.E. Al-Batran, N. Halama, D. Jaeger, Pembrolizumab and maraviroc in refractory mismatch repair proficient/microsatellite-stable metastatic colorectal cancer – the PICCASSO phase I trial, Eur. J. Cancer 167 (2022), https://doi.org/10.1016/j.ejca.2022.03.017.
[256] A. Bessudo, A.M. Haseeb, J.A. Reeves, X. Zhu, L. Wong, V. Giranda, L. Suttner, F. Liu, M. Chatterjee, S. Sharma, Safety and efficacy of vicriviroc (MK-7690) in combination with pembrolizumab in patients with advanced or metastatic microsatellite stable colorectal cancer, Clin. Colorectal Cancer (2024), https://doi.org/10.1016/j.clcc.2024.05.003.
[257] G. Kothandan, C.G. Gadhe, S.J. Cho, Structural insights from binding poses of CCR2 and CCR5 with clinically important antagonists: a combined in silico study, PLoS One 7 (2012), https://doi.org/10.1371/journal.pone.0032864.
[258] J. Wang, D.L. Adelson, A. Yilmaz, S.H. Sze, Y. Jin, J.J. Zhu, Genomic organization, annotation, and ligand-receptor inferences of chicken chemokines and chemokine receptor genes based on comparative genomics, BMC Genom. 6 (2005), https://doi.org/10.1186/1471-2164-6-45.
[259] L. Fantuzzi, M. Tagliamonte, M.C. Gauzzi, L. Lopalco, Dual CCR5/CCR2 targeting: opportunities for the cure of complex disorders, Cell. Mol. Life Sci. 76 (2019), https://doi.org/10.1007/s00018-019-03255-6.
[260] S.Y. Lim, A.E. Yuzhalin, A.N. Gordon-Weeks, R.J. Muschel, Targeting the CCL2-CCR2 signaling axis in cancer metastasis, Oncotarget 7 (2016) 28697–28710, https://doi.org/10.18632/oncotarget.7376.
[261] F. Moadab, H. Khorramdelazad, M. Abbasifard, Role of CCL2/CCR2 axis in the immunopathogenesis of rheumatoid arthritis: latest evidence and therapeutic approaches, Life Sci. 269 (2021), https://doi.org/10.1016/j.lfs.2021.119034.
[262] H. Zhang, K. Yang, F. Chen, Q. Liu, J. Ni, W. Cao, Y. Hua, F. He, Z. Liu, L. Li, G. Fan, Role of the CCL2-CCR2 axis in cardiovascular disease: pathogenesis and clinical implications, Front Immunol. 13 (2022), https://doi.org/10.3389/fimmu.2022.975367.
[263] S. Gazzaniga, A.I. Bravo, A. Guglielmotti, N. Van Rooijen, F. Maschi, A. Vecchi, A. Mantovani, J. Mordoh, R. Wainstok, Targeting tumor-associated macrophages and inhibition of MCP-1 reduce angiogenesis and tumor growth in a human melanoma xenograft, J. Invest. Dermatol. 127 (2007), https://doi.org/10.1038/sj.jid.5700827.
[264] B.Z. Qian, J. Li, H. Zhang, T. Kitamura, J. Zhang, L.R. Campion, E.A. Kaiser, L. A. Snyder, J.W. Pollard, CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis, Nature 475 (2011), https://doi.org/10.1038/nature10138.
[265] M. Gschwandtner, R. Derler, K.S. Midwood, More than just attractive: how CCL2 influences myeloid cell behavior beyond chemotaxis, Front Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.02759.
[266] M. Baba, K. Takashima, H. Miyake, N. Kanzaki, K. Teshima, X. Wang, M. Shiraishi, Y. Iizawa, TAK-652 inhibits CCR5-mediated human immunodeficiency virus type 1 infection in vitro and has favorable pharmacokinetics in humans, Antimicrob. Agents Chemother. 49 (2005), https://doi.org/10.1128/AAC.49.11.4584-4591.2005.
[267] Q.M. Anstee, B.A. Neuschwander-Tetri, V. Wai-Sun Wong, M.F. Abdelmalek, G. Rodriguez-Araujo, H. Landgren, G.S. Park, P. Bedossa, N. Alkhouri, F. Tacke, A. J. Sanyal, Cenicriviroc lacked efficacy to treat liver fibrosis in nonalcoholic Steatohepatitis: AURORA Phase III randomized study, Clin. Gastroenterol. Hepatol. 22 (2024), https://doi.org/10.1016/j.cgh.2023.04.003.
[268] R.J. Cherney, P. Anjanappa, K. Selvakumar, D.G. Batt, G.D. Brown, A.V. Rose, R. Vuppugalla, J. Chen, J. Pang, S. Xu, M. Yarde, A.J. Tebben, V.R. Paidi, M. E. Cvijic, A. Mathur, J.C. Barrish, S. Mandlekar, Q. Zhao, P.H. Carter, BMS-813160: a potent CCR2 and CCR5 dual antagonist selected as a clinical candidate, ACS Med Chem. Lett. 12 (2021), https://doi.org/10.1021/acsmedchemlett.1c00373.
[269] E. Christenson, S.J. Lim, H. Wang, A. Ferguson, R. Parkinson, Y. Cetasaan, C. Rodriguez, R. Burkhart, A. De Jesus-Acosta, J. He, R.B. Klein, K. Lafaro, D. Laheru, D.T. Le, C. Shubert, N. Zaidi, E.M. Jaffee, W. Burns, A. Narang, L. Zheng, Nivolumab and a CCR2/CCR5 dual antagonist (BMS-813160) with or without GVAX for locally advanced pancreatic ductal adenocarcinomas: results of phase I study, J. Clin. Oncol. 41 (2023), https://doi.org/10.1200/jco.2023.41.4_suppl.730.
[270] K. Fosgerau, T. Hoffmann, Peptide therapeutics: current status and future directions, Drug Discov. Today 20 (1) (2015) 122–128, https://doi.org/10.1016/j.drudis.2014.10.003.
[271] W. Cabri, P. Cantelmi, D. Corbisiero, T. Fantoni, L. Ferrazzano, G. Martelli, A. Mattellone, A. Tolomelli, Therapeutic peptides targeting PPI in clinical development: overview, mechanism of action and perspectives, Front. Mol. Biosci. 8 (2021) 697586, https://doi.org/10.3389/fmolb.2021.697586.
[272] Novo Nordisk Annual Report (2023). ⟨https://www.novonordisk.com/investors/annual-report.html⟩ (Accessed November 25, 2024).
[273] Mordor Intelligence, Peptide Therapeutics Market Size & Share Analysis - Growth Trends & Forecasts (2024 - 2029). ⟨https://www.mordorintelligence.com/industry-reports/peptide-therapeutics-market⟩ (Accesed November 25, 2024).
[274] M.Z. Ratajczak, E. Zuba-Surma, M. Kucia, R. Reca, W. Wojakowski, J. Ratajczak, The pleiotropic effects of the SDF-1–CXCR4 axis in organogenesis, regeneration and tumorigenesis, Leukemia 20 (2006) 1915–1924, https://doi.org/10.1038/sj.leu.2404357.
[275] P. Staller, J. Sulitkova, J. Lisztwan, H. Moch, E.J. Oakeley, W. Krek, Chemokine receptor CXCR4 downregulated by von Hippel-Lindau tumour suppressor pVHL, Nature 425 (6955) (2003) 307–311, https://doi.org/10.1038/nature01874.
[276] K.N. Kremer, K.L. Peterson, P.A. Schneider, X.W. Meng, H. Dai, A.D. Hess, B. D. Smith, C. Rodriguez-Ramirez, J.E. Karp, S.H. Kaufmann, K.E. Hedin, CXCR4 chemokine receptor signaling induces apoptosis in acute myeloid leukemia cells via regulation of the Bcl-2 family members Bcl-XL, Noxa, and Bak, J. Biol. Chem. 288 (32) (2013) 22899–22914, https://doi.org/10.1074/jbc.M113.449926.
[277] A. Orimo, P.B. Gupta, D.C. Sgroi, F. Arenzana-Seisdedos, T. Delaunay, R. Naeem, V.J. Carey, A.L. Richardson, R.A. Weinberg, Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion, Cell 121 (3) (2005) 335–348, https://doi.org/10.1016/j.cell.2005.02.034.
[278] I. Spinello, M.T. Quaranta, R. Paolillo, E. Pelosi, A.M. Cerio, E. Saulle, F.Lo Coco, U. Testa, C. Labbaye, Differential hypoxic regulation of the microRNA-146a/CXCR4 pathway in normal and leukemic monocytic cells: impact on response to chemotherapy, Haematologica 100 (9) (2015) 1160–1171, https://doi.org/10.3324/haematol.2014.120295.
[279] L. Xiao, H. Zhu, J. Shu, D. Gong, D. Zheng, J. Gao, Overexpression of TGF-β1 and SDF-1 in cervical cancer-associated fibroblasts promotes cell growth, invasion and migration, Arch. Gynecol. Obstet. 305 (2022) 179–192, https://doi.org/10.1007/s00404-021-06137-0.
[280] S. Pernas, M. Martin, P.A. Kaufman, M. Gil-Martin, P. Gomez Pardo, S. Lopez-Tarruella, L. Manso, E. Ciruelos, J.A. Perez-Fidalgo, C. Hernando, F. O. Ademuyiwa, K. Weilbaecher, I. Mayer, T.J. Pluard, M. Martinez Garcia, L. Vahdat, J. Perez-Garcia, A. Wach, D. Barker, S. Fung, B. Romagnol, J. Cortes, Balixafortide plus eribulin in HER2-negative metastatic breast cancer: a phase 1, single-arm, dose-escalation trial, Lancet Oncol. 19 (6) (2018) 812–824, https://doi.org/10.1016/S1470-2045(18)30147-5.
[281] M. Samadi, A. Kamrani, H. Nasiri, N. Shomali, J.A. Heris, P. Shahabi, K. Ghahremanzadeh, R. Mohammadinasab, M. Sadeghi, S. Sadeghvand, S. S. Shotorbani, M. Akbari, Cancer immunotherapy focusing on the role of interleukins: a comprehensive and updated study, Pathol., Res. Pract. 249 (2023) 154732, https://doi.org/10.1016/j.prp.2023.154732.
[282] A. Litmanovich, K. Khazim, I. Cohen, The role of interleukin-1 in the pathogenesis of cancer and its potential as a therapeutic target in clinical practice, Oncol. Ther. 6 (2) (2018) 109–127, https://doi.org/10.1007/s40487-018-0089-z.
[283] Y. Yang, A. Lundqvist, Immunomodulatory effects of IL-2 and IL-15; implications for cancer immunotherapy, Cancers 12 (12) (2020) 3586, https://doi.org/10.3390/cancers12123586.
[284] D. Briukhovetska, J. Dörr, S. Endres, P. Libby, C.A. Dinarello, S. Kobold, Interleukins in cancer: from biology to therapy, Nat. Rev. Cancer 21 (2021) 481–499, https://doi.org/10.1038/s41568-021-00363-z.
[285] T. Nata, A. Basheer, F. Cocchi, R. van Besien, R. Massoud, S. Jacobson, N. Azimi, Y. Tagaya, Targeting the binding interface on a shared receptor subunit of a cytokine family enables the inhibition of multiple member cytokines with selectable target spectrum, J. Biol. Chem. 290 (37) (2015) 22338–22351, https://doi.org/10.1074/jbc.M115.661074.
[286] T.T. Wang, J. Yang, Y. Zhang, M. Zhang, S. Dubois, K.C. Conlon, Y. Tagaya, C. E. Hamele, S. Dighe, T.L. Olson, D.J. Feith, N. Azimi, T.A. Waldmann, T. P. Loughran, IL-2 and IL-15 blockade by BNZ-1, an inhibitor of selective γ-chain cytokines, decreases leukemic T-cell viability, Leukemia 33 (5) (2019) 1243–1255, https://doi.org/10.1038/s41375-018-0290-y.
[287] J.E. Brammer, K. Ballen, L. Sokol, C. Querfeld, R. Nakamura, A. Mishra, E. M. McLaughlin, D. Feith, N. Azimi, T.A. Waldmann, Y. Tagaya, T. Loughran, Effective treatment with the selective cytokine inhibitor BNZ-1 reveals the cytokine dependency of T-LGL leukemia, Blood 142 (15) (2023) 1271–1280, https://doi.org/10.1182/blood.2022017643.
[288] J.J. Chen, M. Vincent, D.M. Peereboom, R. Watnick, S. Fyfe, W. Li, S. Wang, J. Mahoney, M. Cieslewicz, J. Watnick, Immune profiling in patients with glioblastoma treated with VT1021 in a phase I/II expansion study, 2021-2021, J. Clin. Oncol. 41 (2023), https://doi.org/10.1200/JCO.2023.41.16_suppl.2021.
[289] J.S. Isenberg, D.D. Roberts, THBS1 (thrombospondin-1), Atlas Genet. Cytogenet. Oncol. Haematol. 24 (8) (2020) 291–299, https://doi.org/10.4267/2042/70774.
[290] D. Mahalingam, W. Harb, A. Patnaik, A. Bullock, R.S. Watnick, M.Y. Vincent, J. J. Chen, S. Wang, H. Pestana, J. Chao, J. Mahoney, M. Cieslewicz, J. Watnick, First-in-human phase I dose escalation trial of the first-in-class tumor microenvironment modulator VT1021 in advanced solid tumors, Commun. Med. 4 (1) (2024) 10, https://doi.org/10.1038/s43856-024-00433-x.
[291] T. Jascur, H. Brickner, I. Salles-Passador, V. Barbier, A. El Khissiin, B. Smith, R. Fotedar, A. Fotedar, Regulation of p21(WAF1/CIP1) stability by WISp39, a Hsp90 binding TPR protein, Mol. Cell 17 (2) (2005) 237–249, https://doi.org/10.1016/j.molcel.2004.11.049.
[292] H.D. McKeen, K. McAlpine, A. Valentine, D.J. Quinn, K. McClelland, C. Byrne, M. O'Rourke, S. Young, C.J. Scott, H.O. McCarthy, D.G. Hirst, T. Robson, A novel FK506-like binding protein interacts with the glucocorticoid receptor and regulates steroid receptor signaling, Endocrinology 149 (11) (2008) 5724–5734, https://doi.org/10.1210/en.2008-0168.
[293] H.D. McKeen, C. Byrne, P.V. Jithesh, C. Donley, A. Valentine, A. Yakkundi, M. O'Rourke, C. Swanton, H.O. McCarthy, D.G. Hirst, T. Robson, FKBPL regulates estrogen receptor signaling and determines response to endocrine therapy, Cancer Res. 70 (3) (2010) 1090–1100, https://doi.org/10.1158/0008-5472.CAN-09-2515.
[294] A. Yakkundi, R. Bennett, I. Hernández-Negrete, J.M. Delalande, M. Hanna, O. Lyubomska, K. Arthur, A. Short, H. McKeen, L. Nelson, C.M. McCrudden, R. McNally, L. McClements, H.O. McCarthy, A.J. Burns, R. Bicknell,

A. Kissenpfennig, T. Robson, FKBPL is a critical antiangiogenic regulator of developmental and pathological angiogenesis, Arterioscler. Thromb. Vasc. Biol. 35 (4) (2015) 845–854, https://doi.org/10.1161/ATVBAHA.114.304539.
[295] A. Valentine, M. O'Rourke, A. Yakkundi, J. Worthington, M. Hookham, R. Bicknell, H.O. McCarthy, K. McClelland, L. McCallum, H. Dyer, H. McKeen, D. J. Waugh, J. Roberts, J. McGregor, G. Cotton, I. James, T. Harrison, D.G. Hirst, T. Robson, FKBPL and peptide derivatives: novel biological agents that inhibit angiogenesis by a CD44-dependent mechanism, Clin. Cancer Res. 17 (5) (2011) 1044–1056, https://doi.org/10.1158/1078-0432.CCR-10-224.
[296] A. El Helali, R. Plummer, G.C. Jayson, V.M. Coyle, Y. Drew, N. Mescallado, N. Harris, A.R. Clamp, J. McCann, H. Swaisland, R.D. Kennedy, A.N. Cranston, R. H. Wilson, A first-in-human Phase I dose-escalation trial of the novel therapeutic peptide, ALM201, demonstrates a favourable safety profile in unselected patients with ovarian cancer and other advanced solid tumours, Br. J. Cancer 127 (1) (2022) 92–101, https://doi.org/10.1038/s41416-022-01780-z.
[297] L. McClements, A. Yakkundi, A. Papaspyropoulos, H. Harrison, M.P. Ablett, P. V. Jithesh, H.D. McKeen, R. Bennett, C. Donley, A. Kissenpfennig, S. McIntosh, H. O. McCarthy, E. O'Neill, R.B. Clarke, T. Robson, Targeting treatment-resistant breast cancer stem cells with FKBPL and its peptide derivative, AD-01, via the CD44 pathway, Clin. Cancer Res. 19 (14) (2003) 3881–3893, https://doi.org/10.1158/1078-0432.CCR-13-0595.
[298] M. O'Rourke, A. Valentine, E. McLean, N. Page, G. Cotton, A. Marques, J. Worthington, T. Robson, D. Hirst, T. Harrison, I. James, The anti-tumour efficacy of the novel peptide inhibitor of angiogenesis ALM201, Abstract 3288, Almac. Discov. (2024), ⟨https://www.almacgroup.com/wp-content/uploads/2012/06/AACR-2010-Poster.pdf⟩. Abstract 3288.
[299] L. Zhao, Q. Zhao, R. Lu, Z. Fu, Z. Zhu, J. Jia, S. Wang, L. Shi, X. Jian, Z. Yao, Effects of tyroserleutide on gene expression of calmodulin and PI3K in hepatocellular carcinoma, J. Cell. Biochem. 103 (2) (2008) 471–478, https://doi.org/10.1002/jcb.21409.
[300] A. Säfholm, K. Leandersson, J. Dejmek, C.K. Nielsen, B.O. Villoutreix, T. Andersson, A formylated hexapeptide ligand mimics the ability of Wnt-5a to impair migration of human breast epithelial cells, J. Biol. Chem. 281 (5) (2006) 2740–2749, https://doi.org/10.1074/jbc.M508386200.
[301] M. Endo, M. Nishita, M. Fujii, Y. Minami, Insight into the role of Wnt5a-induced signaling in normal and cancer cells, Int. Rev. Cell Mol. Biol. 314 (2015) 117–148, https://doi.org/10.1016/bs.ircmb.2014.10.003.
[302] S. Shacham, D. Harris, H. Ben-Shlomo, I. Cohen, D. Bonfil, F. Przedecki, H. Lewy, I.E. Ashkenazi, R. Seger, Z. Naor, Mechanism of GnRH receptor signaling on gonadotropin release and gene expression in pituitary gonadotrophs, Vitam. Horm. 63 (2001) 63–90, https://doi.org/10.1016/s0083-6729(01)63003-6.
[303] H. Van Poppel, P.A. Abrahamsson, Considerations for the use of gonadotropin-releasing hormone agonists and antagonists in patients with prostate cancer, Int. J. Urol. Off. J. Jpn. Urol. Assoc. 27 (10) (2020) 830–837, https://doi.org/10.1111/iju.14303.
[304] L. Boccon-Gibod, E. van der Meulen, B.E. Persson, An update on the use of gonadotropin-releasing hormone antagonists in prostate cancer, Ther. Adv. Urol. 3 (3) (2011) 127–140, https://doi.org/10.1177/1756287211414457.
[305] C. Festuccia, D. Dondi, M. Piccolella, A. Locatelli, G.L. Gravina, V. Tombolini, M. Motta, Ozarelix, a fourth-generation GnRH antagonist, induces apoptosis in hormone-refractory androgen receptor-negative prostate cancer cells modulating expression and activity of death receptors, Prostate 70 (12) (2010) 1340–1349, https://doi.org/10.1002/pros.21169.
[306] M. Fekete, J.L. Wittliff, A.V. Schally, Characteristics and distribution of receptors for [D-TRP6]-luteinizing hormone-releasing hormone, somatostatin, epidermal growth factor, and sex steroids in 500 biopsy samples of human breast cancer, J. Clin. Lab. Anal. 3 (3) (1989) 137–147, https://doi.org/10.1002/jcla.1860030302.
[307] A.V. Schally, N.L. Block, F.G. Rick, Discovery of LHRH and development of LHRH analogs for prostate cancer treatment, Prostate 77 (9) (2017) 1036–1054, https://doi.org/10.1002/pros.23360.
[308] S. Ma, S. Pradeep, A. Villar-Prados, Y. Wen, E. Bayraktar, L.S. Mangala, M.S. Kim, S.Y. Wu, W. Hu, C. Rodriguez-Aguayo, C. Leuschner, X. Liang, P.T. Ram, K. Schlacher, R.L. Coleman, A.K. Sood, GnRH-R-targeted lytic peptide sensitizes BRCA wild-type ovarian cancer to PARP inhibition, Mol. Cancer Ther. 18 (5) (2019) 969–979, https://doi.org/10.1158/1535-7163.MCT-18-0770.
[309] C. Leuschner, A. Coulter, C. Giardina, H.W. Alila, Abstract 2829: activity of EP-100 in Non-Hodgkin's Lymphoma - synergy in combination, Cancer Res. 72 (8_ement) (2012) 2829, https://doi.org/10.1158/1538-7445.AM2012-2829.
[310] N. Shore, R. Tutrone, M. Efros, M. Bidair, B. Wachs, S. Kalota, S. Freedman, J. Bailen, R. Levin, S. Richardson, J. Kaminetsky, J. Snyder, B. Shepard, K. Goldberg, A. Hay, S. Gange, I. Grunberger, Fexapotide triflutate: results of long-term safety and efficacy trials of a novel injectable therapy for symptomatic prostate enlargement, World J. Urol. 36 (5) (2018) 801–809, https://doi.org/10.1007/s00345-018-2185-y.
[311] G. Lee, Y. Lee, M. Chang, S.U. Kang, J.-H. Ryou, J.-J. Lim, A. Imran, S.-H. Park, K. Lee, Y.-H. Lee, P120 BBT-401 is a selective Pellino-1 protein-protein interaction inhibitor in clinical development targeting a first-in-class drug for UC treatment, Gastroenterology 156 (3) (2019) S82, https://doi.org/10.1053/j.gastro.2019.01.190.
[312] B.J. Mayo, K.R. Secombe, A.D. Wignall, E. Bateman, D. Thorpe, C. Pietra, D. M. Keefe, J.M. Bowen, The GLP-2 analogue elsiglutide reduces diarrhoea caused by the tyrosine kinase inhibitor lapatinib in rats, Cancer Chemother. Pharmacol. 85 (4) (2020) 793–803, https://doi.org/10.1007/s00280-020-04040-0.