



Small molecules and their impact in drug discovery: A perspective on the occasion of the 125th anniversary of the Bayer Chemical Research Laboratory

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The year 2021 marks the 125th anniversary of the Bayer Chemical Research Laboratory in Wuppertal, Germany. A significant number of prominent small-molecule drugs, from Aspirin to Xarelto, have emerged from this research site. In this review, we shed light on historic cornerstones of small-molecule drug research, discussing current and future trends in drug discovery as well as providing a personal outlook on the future of drug research with a focus on small molecules.

Keywords: Small molecule therapeutics; Drug discovery; Medicinal chemistry; New modalities; Artificial intelligence; Societal impact

Introduction

The year 2021 marks the 125th anniversary of the Bayer Chemical Research Laboratory in Wuppertal, Germany (Fig. 1).^{1,2} This research facility has been vital for Bayer's continuing development. When the Chemical Research Laboratory was founded in 1896, Bayer was mainly a producer of synthetic dyes for the booming textile industry. The dyes were synthesized from the rich source of organic coal-tar intermediates in the region. Around that time, it was also discovered that several of these small-molecule dyes and intermediates showed unexpected biological activity. These findings led to the invention of some of the first synthetic pharmaceutical drugs and opened a new field of business for the still-young chemical industry.^{3,4} Among the many dye factories at that time, only innovative companies with their own research facilities were able to address new market opportunities and to survive over the long term. In the following years and decades, Bayer expanded its pharmaceutical research and directed it toward a growing number of indications, starting from analgesics and anesthetics, to anti-infectives and



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Lars Baerfacker was awarded his PhD in chemistry by the University of Dortmund, Germany, after which he carried out post-doctoral research at the University of Minnesota, USA. After joining Bayer in 2000, he contributed to drug discovery programs in various therapeutic areas as a medicinal chemist and project leader. From 2011, he spent 3.5 years in Berlin focusing on oncological research, after which he returned to Wuppertal to focus on target identification as a Senior Science

Fellow.

fellows for tropical diseases, to cardiovascular, central nervous, and oncological medicines, to name just a few. Since its inception, the Bayer Chemical Research Laboratory in Wuppertal has contributed to the invention of more than 125 small-molecule medications reaching the patients.

Small molecules have consistently enabled medical breakthroughs and tackling unmet medical needs, thus saving countless lives. Moreover, small molecules have been vital as chemical probes in biomedical research, aiding understanding of disease biology. Traditional small-molecule drugs have been the dominant modality in drug research over the past century. However, newer modalities, such as proteolysis-targeting chimeras (PROTACs) and RNA-targeting small molecules (RSMs), as well as biological approaches, such as antibody-based therapy and cell and gene therapy, have been added to the drug discovery toolbox. Most big pharmaceutical companies are now embracing drug research in a more modality-agnostic manner.

What will be the role of small molecules in future drug research and how will small molecules continue to address the future needs of patients? In this review, we take an opportunity to look back and shed light on some historical cornerstones of small-molecule drug research, discussing current and future trends in drug discovery, and providing a personal outlook on the future of drug research with a focus on small molecules.

From Aspirin to now: A historical look back at some prominent small-molecule drugs

Throughout history, many small-molecule drugs have contributed to medical progress and improved the lives of patients (Fig. 2). Some of these early drugs are still in use today, whereas others have disappeared from the market, but were instrumental in paving the way for improved treatments in their specific indication. While the history of drugs has been reviewed elsewhere in more detail,⁵ here we provide selected examples illustrating the impact and fascinating role of small molecules in drug research, medicine, and society throughout time. The bias in this selection of drugs invented by Bayer and others is owed to the happy occasion of this article in combination with personal experiences of the authors and can hopefully be forgiven by the reader (Fig. 3).

1899: Aspirin

Aspirin (acetylsalicylic acid) is one of the earliest synthetic pharmaceutical drugs and is still widely used around the world (Fig. 3). It was first synthesized in stable and pure form by Bayer in Wuppertal, Germany, and registered in 1899 as a readily available way to provide relief from pain and fever. Acetylsalicylic acid is a prodrug and the more tolerated acetyl derivative of salicylic acid, an active ingredient from the bark of the willow tree, which had been known as an herbal medicine since ancient times.⁶ It took until the early 1970s to identify the inhibition of prostaglandin biosynthesis as the primary mode of action of acetylsalicylic acid.⁷ Sune K. Bergström, Bengt I. Samuelsson, and John R. Vane were awarded the Nobel Prize in Physiology or Medicine in 1982 for this discovery, which also led the way for the use of low-dose Aspirin as an antiplatelet agent for the prevention of cardiovascular diseases, such as coronary artery disease, heart attack, and stroke.⁸ Persistent claims of potential benefits in additional indications add to the perception of Aspirin as a ‘wonder drug’.^{9,10}

1941: Penicillin

Penicillin is a naturally occurring antibiotic produced by fungi that has saved many millions of lives (Fig. 3). It was discovered by Scottish researcher Alexander Fleming in 1928 serendipitously when returning to his laboratory after a holiday. Fleming noticed that, in one of his petri dishes, an airborne fungus had prevented his staphylococci cultures from growing. A decade later, pure penicillin was isolated from mold fermentations and successfully administered



Drug Discovery Today

FIGURE 1

The original Bayer Chemical Research Laboratory in Wuppertal. The picture shows Hall 2 of the Chemical Research Laboratory in 1908.

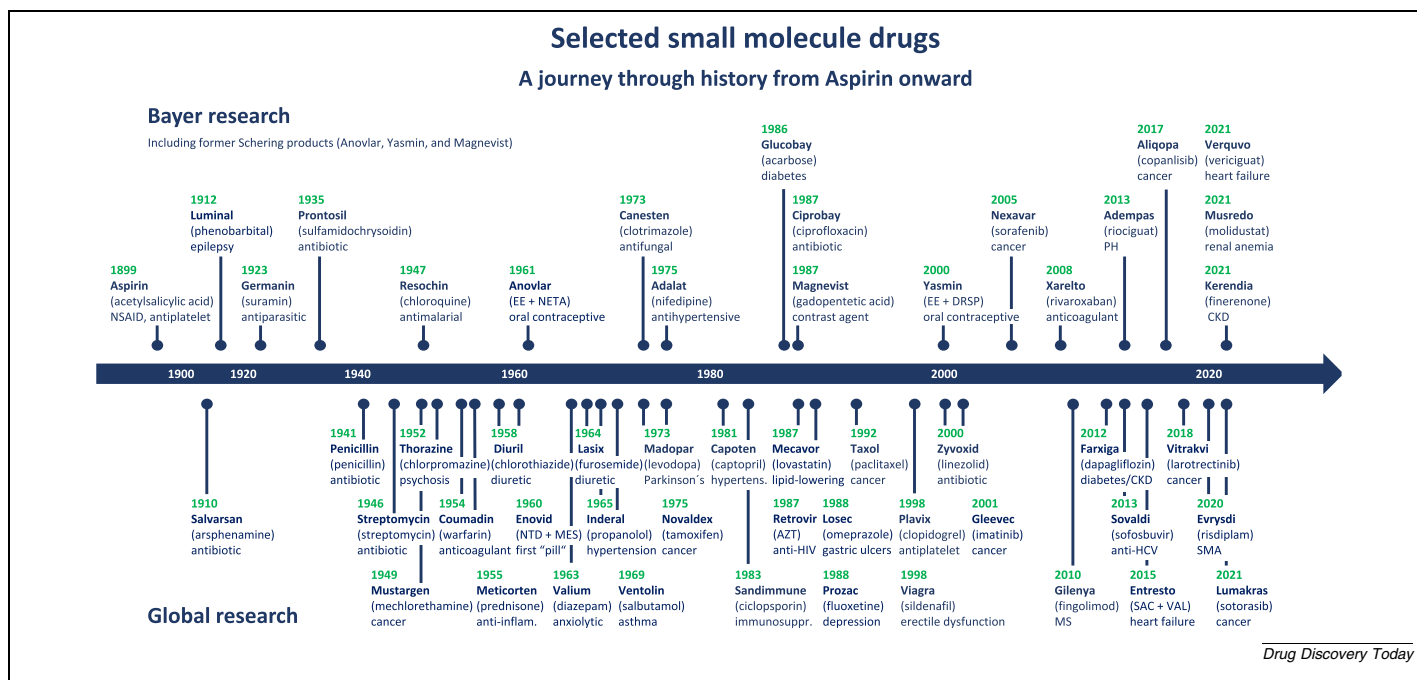
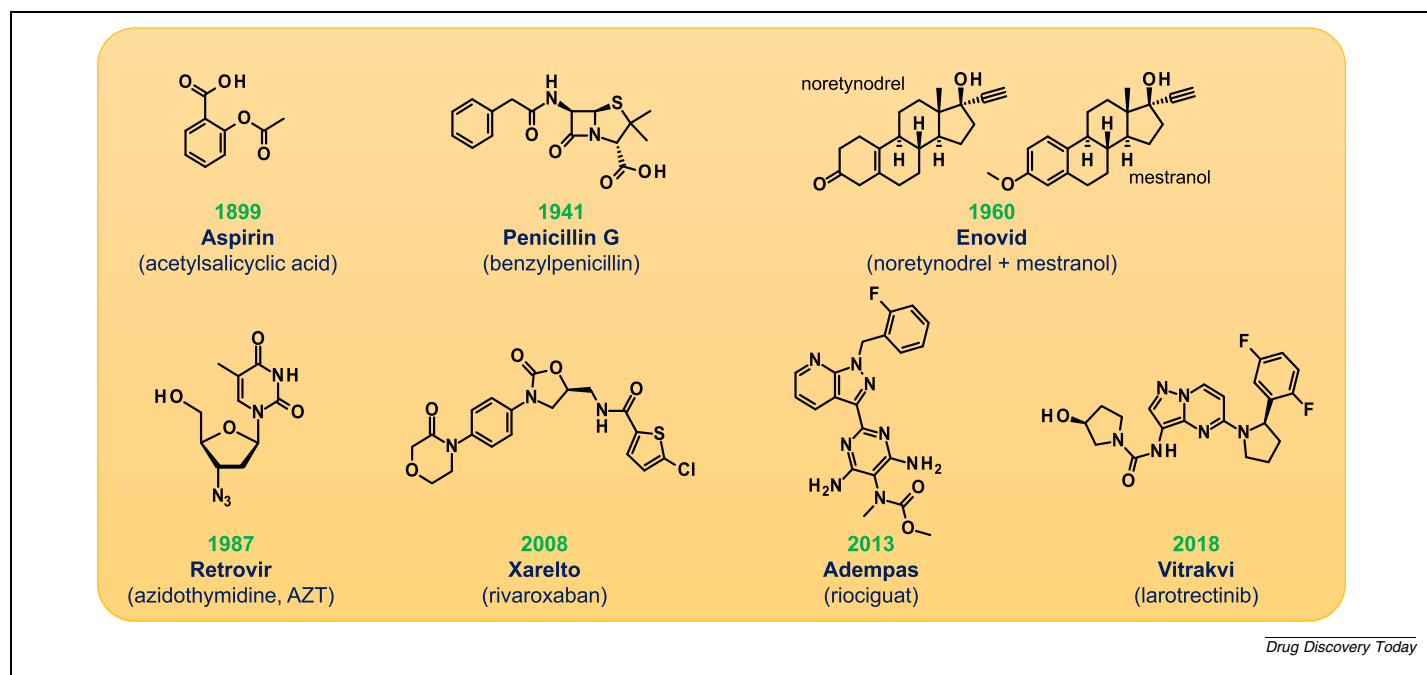


FIGURE 2

Time chart of selected small-molecule drugs from Aspirin onward, demonstrating the wide scope of small molecules as therapeutics, without any claim to comprehensiveness. Year dates indicate first clinical use or market launch anywhere in the world. Brand names beginning with capital letters are selected from one of the known brands and do not necessarily represent the brand under which the drug was launched first. The drug names in brackets are the international nonproprietary names (INN). Several drugs and indications are not listed because of lack of space. Vitakvi is now marketed by Bayer. Abbreviations: CKD, chronic kidney disease; EE + DRSP, ethinylestradiol + drospirenone; EE + NETA, ethinylestradiol + norethisterone acetate; HCV, hepatitis C virus; MS, multiple sclerosis; NSAID, nonsteroidal anti-inflammatory drug; NTD + MES, noretynodrel + mestranol; PH, pulmonary hypertension; SAC + VAL, sacubitril + valsartan; SMA, spinal muscular atrophy.



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FIGURE 3

Chemical structures of prominent small-molecule drugs invented by Bayer and others mentioned in the historical section of the main text.

to the first patient in 1941, after which it was used to heal bacterial wound infections during World War II.¹¹ Along with Salvarsan (1910) and Prontosil (1935), the introduction of penicillin marked the beginning of the antibiotic era.¹² After the unique and synthetically challenging β -lactam structure of penicillin had been revealed by X-ray crystallography in 1945, it was not until 12 years later that its first total synthesis was achieved.¹³ Despite inevitable emergence of bacterial resistance, penicillin and a multitude of structural analogs are still in use today.

1960: Enovid, the first 'pill'

Enovid (noretynodrel and mestranol) was the first hormonal birth control pill and arguably impacted society more than any other drug (Fig. 3). It was introduced by Searle in the USA in 1960 for contraceptive use as a combination of two steroids: noretynodrel and mestranol. For the first time, a medication was available that provided reliable and reversible control of pregnancy. By enabling women to control their fertility, the 'pill' significantly contributed to changes in the status of women in the following decades and was part of a global movement for women's emancipation and self-determination.¹⁴ Enovid was discontinued in 1988 and has been replaced by various generations of oral contraceptives with lower doses, different compositions, and improved safety profiles.¹⁵ Today, modern contraception comprises a growing list of various methods,¹⁶ with the 'pill' still taken by around 150 million women worldwide.¹⁷

1987: Retrovir, the first anti-HIV drug

Retrovir (zidovudine, azidothymidine, AZT) was the first anti-HIV drug and the starting point of a remarkable medical success story in which a deadly viral infection was gradually turned into

a manageable chronic condition (Fig. 3).¹⁸ Retrovir was introduced in 1987 by Burroughs-Wellcome (now GlaxoSmithKline) by repurposing a failed cancer agent from the 1960s. It was the first treatment for patients with an at-the-time mysterious illness, later called AIDS, that had initially emerged in the USA in 1981. Today, a combination of mostly small molecules from several drug classes are used in antiretroviral therapy, effectively reducing the viral load to a minimum and enabling a near-normal life under medication.¹⁹ In a different indication, in the fight against the hepatitis C virus (HCV), small-molecule antivirals have recently celebrated their greatest success with cure rates above 90%.²⁰ By contrast, for the latest viral challenge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pioneering first small-molecule antiviral treatments Paxloxy (remdesivir, a repurposed Ebola virus drug candidate), Paxlovid [nirmatrelvir plus ritonavir, a main protease (Mpro) inhibitor plus a cytochrome P450 inhibitor], and Lagevrio (molnupiravir, a repurposed drug candidate for Venezuelan equine encephalitis virus and influenza) have been approved only recently.^{21–23}

2008: Xarelto

Xarelto (rivaroxaban) was the first direct factor Xa inhibitor and is approved for more cardiovascular indications than any other direct oral anticoagulant (DOAC) (Fig. 3).²⁴ It was invented at Bayer in Wuppertal, and introduced in 2008 as a new antithrombotic medication.^{25,26} Cardiovascular diseases have developed into the leading cause of death globally, driven by a change in life style and an increase in life expectancy over the course of the 20th century.²⁷ By preventing the formation of undesired blood clots, anticoagulants help reduce the risk of life-threatening thromboembolic events, such as heart attacks or strokes. With the introduction of DOACs, which are selective inhibitors of activated factor Xa (rivaroxaban, apixaban, edoxa-

ban, and betrixaban) or thrombin (dabigatran), patients benefit from a more manageable oral anticoagulant treatment compared with the former standard of vitamin K antagonists (warfarin and phenprocoumon).²⁸

2014: Adempas

Adempas (riociguat) is used to treat two forms of pulmonary hypertension as a serious condition of high blood pressure in the arteries of the lungs (Fig. 3).^{29,30} It was introduced in 2014 by Bayer as the first marketed stimulator of soluble guanylate cyclase (sGC). sGC acts as the receptor for nitric oxide (NO), a short-lived vasodilatory gas used in medicine for over a hundred years. However, the discovery that NO is also an important natural signaling molecule in the cardiovascular system was revolutionary and the reason for the Nobel Prize in Physiology or Medicine being awarded to Robert F. Furchgott, Louis J. Ignarro and Ferid Murad in 1998. Riociguat stimulates sGC independently of NO and leads to an increase in cGMP, thus offering a long-lasting mode of action with broad therapeutic potential.

The fundamental NO-sGC-cGMP axis can also be addressed by the cGMP-stabilizing PDE5 inhibitors (sildenafil, vardenafil, and tadalafil), which were initially introduced as effective oral treatments of erectile dysfunction.

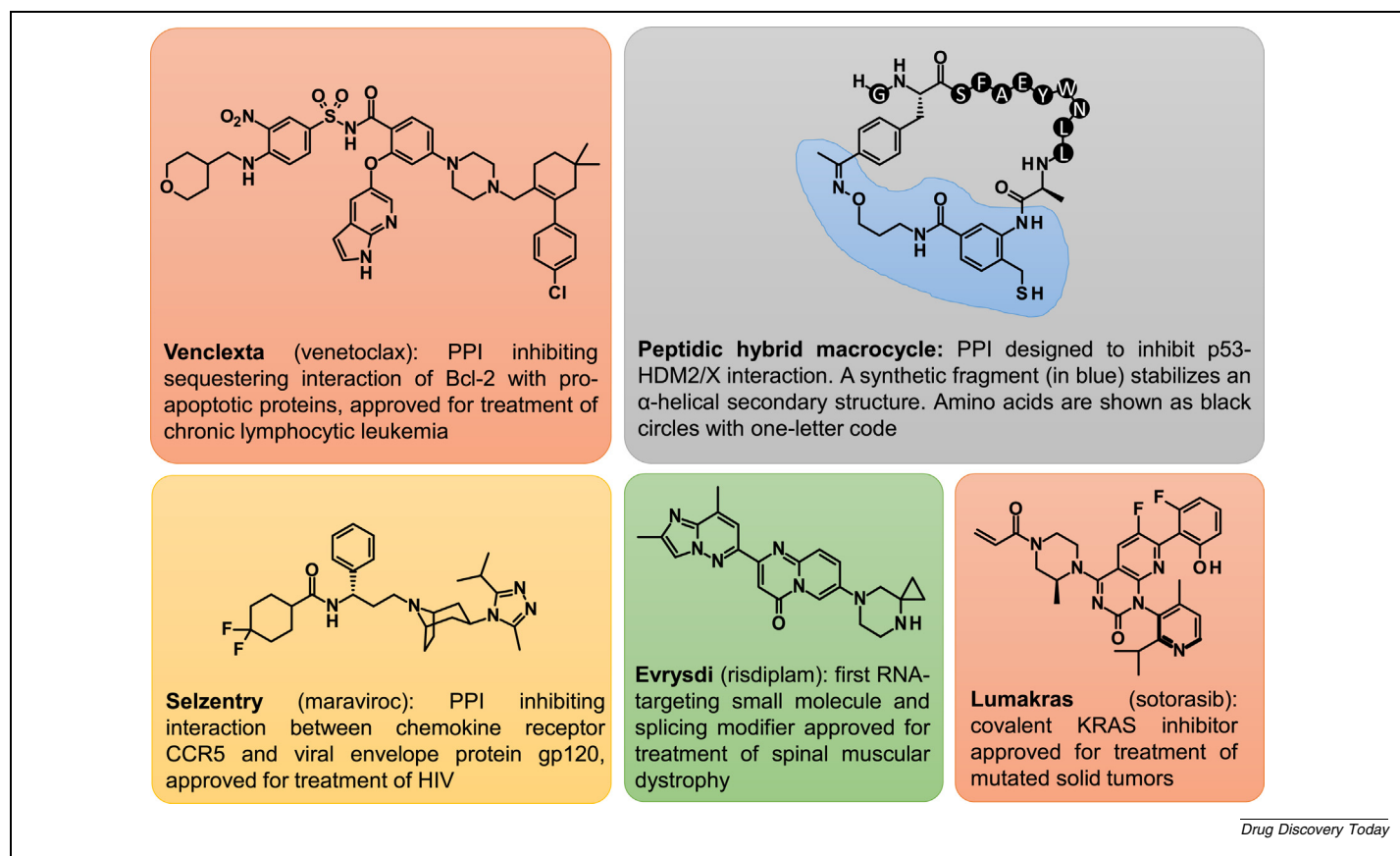
2018: Vitrakvi

Vitrakvi (larotrectinib) is the first tumor type-agnostic small-molecule cancer drug and represents a new milestone in precision oncology (Fig. 3).³¹ This selective TRK kinase inhibitor was first identified by Array BioPharma, then licensed to Loxo Oncology, and finally sublicensed and marketed by Bayer in 2018. Cancer is the second leading cause of death globally. Historically, small molecules have initiated the era of chemotherapy, with alkylating agents during the 1940s,³² and later championed the path to targeted cancer therapy, pioneered by Novaldex (tamoxifen, 1977) and Gleevec (imatinib, 2001).^{33–35} Cancer treatments have traditionally been centered around specific organs or tissues, for example in the treatment of breast or lung cancer. By contrast, tumor type-agnostic therapy targets a specific genetic

TABLE 1

Key properties of small molecules impacting their use in drug discovery.

| Property | Small molecule |
|------------------------------------|--|
| Biological target space | Very diverse: e.g., proteins (enzymes, ion channels, receptors, etc.), RNA, DNA, (glyco-)lipids |
| Functional interaction with target | Intracellular and extracellular targets Diverse: inhibitor, activator, antagonist, agonist, (allosteric) binder, etc. Reversible physical binding (i.e., no chemical modification of the biological target) versus irreversible chemical binding (i.e., permanent chemical modification of the biological target) Tunable properties |
| Target selectivity | Can be optimized to reach high target selectivity Tunable to address multiple (related) targets |
| Drug combinations | Can be combined with other drugs |
| Immunogenicity | Typically not |
| Permeability | Ability to cross biological barriers Good tissue penetration Cell permeable, intracellular targets accessible Tunable properties, e.g., to avoid crossing of blood–brain barrier |
| Metabolic stability | Tunable stability, from low to high Sufficiently high to allow oral application and prolonged systemic exposure |
| Application routes | No limitations; all application routes |
| Formulation and drug delivery | Compatible with standard and specialized formulations and drug delivery technologies From conventional instant-release tablets to sophisticated delivery systems (liposomes/exosomes, organic nanocrystals, nanoparticles, nanotubes, albumin conjugates, etc.) |
| Shelf-life stability | High stability in most cases Typically no demanding storage or transport conditions required |
| Chemical structure | Small to mid-size synthetic organic molecules Natural product or natural product-derived organic molecules Peptide or chemically modified peptides Macrocytic and other shapes Variable complexity, both in terms of chemical structure and function (e.g., bifunctional drug conjugates) Modular structure, easily accessible for optimization of properties |
| Production by chemical synthesis | Mature technology, from laboratory to industrial scale Provides great flexibility, in terms of molecular structure and synthesis approaches Facilitates rapid analoging and derivatizations during drug discovery Cost of goods usually not critical |
| Driver of innovation | Expanding biological target space: e.g., protein surfaces in PPIs, RNA Orally bioavailable and cell-permeable peptides Protein degraders to induce removal of biological target, rather than its functional modulation Huge DNA-encoded small-molecule libraries for lead finding in drug discovery, making use of PCR technology for hit deconvolution Suitable for AI/ML-supported lead optimization in drug discovery |

**FIGURE 4**

Examples of the successful expansion of the biological target space of small molecules mentioned in the main text. Venclexta, Selzentry, and the designer peptidic hybrid macrocycle represent protein–protein inhibitors (PPIs); Evrysdi represents an RNA-targeting small molecule; and Lumakras represents a covalent inhibitor.

alteration independent of the site of origin of the tumor and, therefore, is effective in a variety of different cancers. This new treatment paradigm offers hope especially for patients with rare, genetically defined cancers who would otherwise only have limited treatment options.

Small molecules: unique properties enabling multiple applications in drug discovery

Key properties of small molecules

As described above, small molecules have been providing medical breakthroughs for human diseases for more than a century. To a large part, their success as drugs has been due to their inherent properties, including their ability to cross biological barriers and to modulate an array of different biological targets. Oral bioavailability is a key feature of most small-molecule drugs, enabling standard oral delivery as a tablet. This convenience aspect is a huge advantage compared with biologics, even if the pharmacological effect size might be similar. Examples are the small-molecule inhibitors of hypoxia-inducible factor prolyl hydroxylase (HIF-PH), which can replace the recombinant biologic erythropoietin (EPO) in the treatment of renal anemia, thus replacing injection/infusion administration with a pill.³⁶ Another important feature of small molecules is their modular

structure and their ease of accessibility via chemical synthesis. This allows for rapid variation of the chemical structure and for systematic improvement of their properties. Drug products in most cases contain the unmodified small molecule as the active ingredient. However, suitable reversible chemical modifications (prodrugs) can be designed to address potential shortcomings, such as low aqueous solubility. After administration to the patient, prodrugs are converted back to the active form via biological activation, such as enzymatic hydrolysis or oxidative cleavage, or by bioorthogonal methods, such as irradiation. A similar strategy can be applied for targeted activation or targeted delivery of a pharmacological ingredient toward a tissue of interest. Finally, small molecules usually show high shelf-life stability and are compatible with most drug formulations and administration routes. Several more key characteristics of small molecules are summarized in Table 1.

Teaching an old dog new tricks: The new modalities

Small molecules continuously expand to new modes of action and conquer new target spaces, enlarging the classical toolbox for drug discovery. New chemical modalities and new ways of using small molecules have emerged that address biological targets previously deemed undruggable.^{37,38} Here, we highlight

some of the new tricks the ‘old dog’ small molecule can be taught.

Targeted covalent inhibitors

Small molecules can be designed in such a way that they either noncovalently bind to their biological target via intermolecular forces, such as hydrogen bonds and van der Waals forces, or engage in covalent bonding modifying the target permanently, and anything in-between. Early examples of covalent drugs include Aspirin and penicillin. Acetylsalicylic acid covalently modifies cyclooxygenase by transferring an acetyl group to an active-site serine residue, and penicillin covalently binds a serine residue of penicillin-binding protein via a β -lactam ring-opening mechanism. Although the covalent binding mode of these early examples is based on serendipity and was revealed only in retrospect, targeted covalent inhibition (TCI) has recently become an increasingly relevant approach, supported by advances in protein mass spectroscopy.^{39–42} Prominent examples include Imbruvica (ibrutinib), a covalent binder to Bruton's tyrosine kinase (BTK) for the treatment of B cell cancers, launched in 2013, and Lumakras (sotorasib), a covalent KRAS inhibitor for the treatment of solid tumors with G12C mutation, launched in 2021 (Fig. 4).^{43–45} The KRAS proteins have long been known as especially difficult targets. Covalent inhibitors manage to tackle KRAS successfully by binding to a cysteine residue that is present only in the mutated form.

Protein–protein interactions

Interactions between proteins are essential for many cellular processes, and both stabilization and disruption of protein–protein interactions (PPIs) constitute attractive targets for therapeutic intervention. Although antibody-based PPI modulators domi-

nate the field in terms of the number of known therapeutic entities, small molecules are increasingly gaining attention for some of the reasons described above, namely their good oral bioavailability, better tissue penetration, lower risk of immunogenicity, and lower cost in research and development.⁴⁶ Given the reduced size of small molecules compared with the large binding surface areas of proteins, potent small-molecule PPI modulators are more challenging to design than are small-molecule enzyme or receptor binders. In this regard, an interesting approach is to stabilize protein-binding motifs, such as α -helices, via cyclic peptide hybrid molecules (Fig. 4).⁴⁷ Several molecular starting points for small-molecule PPI modulators have been identified via screening and some have been optimized successfully into clinical candidates.⁴⁶ Selzentry (maraviroc) was the first small-molecule inhibitor of a PPI (viral gp120/CCR5), approved in 2007 for the treatment of HIV (Fig. 4).⁴⁸ Venclexta (venetoclax), an inhibitor of Bcl-2/Bax PPI for the treatment of chronic lymphocytic leukemia (CML), was introduced to the market in 2016 (Fig. 4).⁴⁹

RNA-targeting small molecules

Although most drug targets are proteins, RNA-targeting small molecules (RSMs) are emerging as a new treatment modality. For a long time, human RNA was thought to be undruggable because of the perceived absence of suitable binding sites. It is now known that RNA, despite being more flexible than a protein, can assume discrete secondary and tertiary structures, which create binding sites for small molecules to interact with.^{50,51} It was only in 2020 that the first human RSM drug, Evrysdi (risdiplam), was introduced to the market for the treatment of spinal muscular atrophy (SMA) (Fig. 4).⁵² SMA is a genetic disease caused by decreased levels of survival motor neuron (SMN) protein, result-

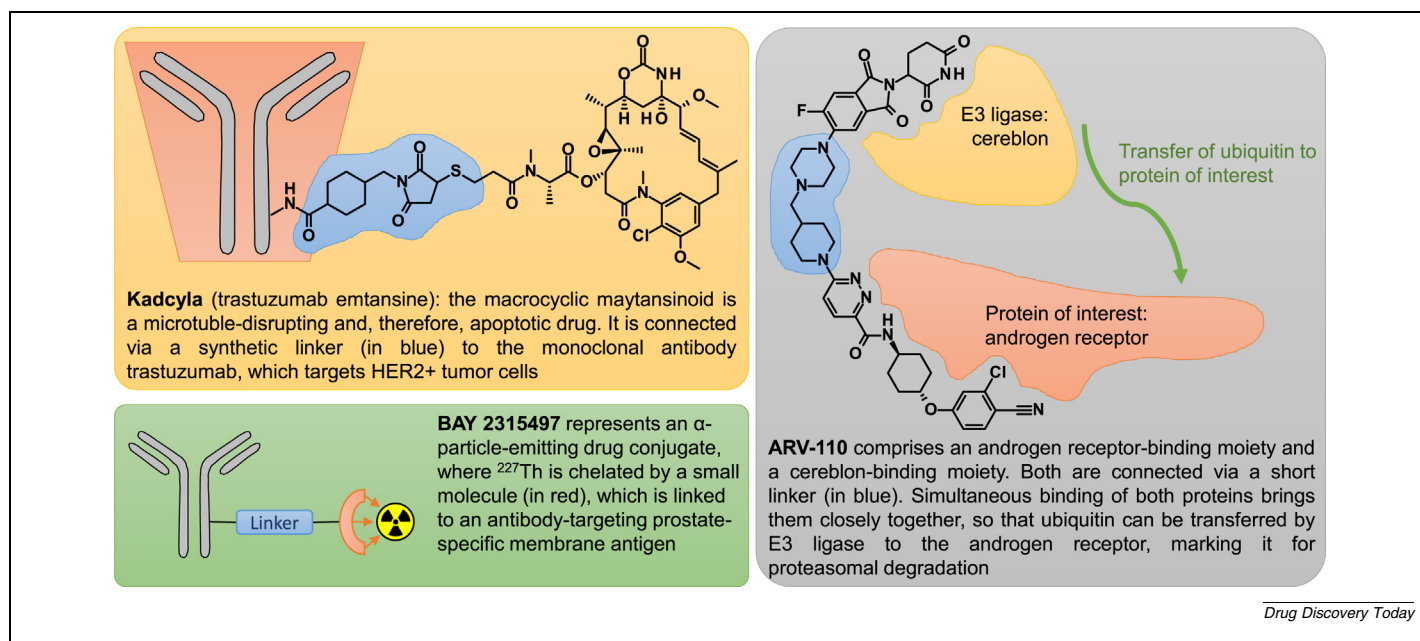


FIGURE 5

Examples of bifunctional small-molecule conjugates mentioned in the main text. Kadcylla and BAY 2315497 represent antibody–drug conjugates; ARV-110 represents a protein degrader.

ing in severe muscle weakness. Risdiplam acts as a splicing modifier on SMN2 mRNA to include exon 7 into the transcript, resulting in an increase in functional SMN protein. Thus, risdiplam involves a truly disease-modifying mode of action and its approval created a lot of excitement. Apart from addressing mRNA encoding disease-relevant proteins, as in the case of risdiplam, a potentially even larger target space is provided by non-coding mRNAs, the regulatory function and disease-driving potential of which we are only beginning to understand.

Antibody–drug conjugates

A small-molecule drug conjugate comprises a small molecule covalently attached to a second molecular moiety with a distinct biological function. This bifunctional molecule concept has matured considerably over the past few decades. The task of one molecular part is to direct the conjugate to the intended site of action so that the other part can exert its pharmacological activity with high specificity. Antibody–drug conjugates (ADCs) are prominent examples that involve the use of highly selective antibodies to direct the conjugate to the target site. After internalization of the ADC and intracellular cleavage of the small molecule from the antibody, a high local concentration of the pharmacologically active small molecule is generated in a microenvironment-specific manner.⁵³ The enhanced local concentration offers the opportunity to reduce the systemic drug concentration in the body, leading to an overall improved side effect profile. Eleven ADC drugs have been approved for treatment of hematological and solid tumors thus far. The first was Mylotarg (gemtuzumab ozogamicin) which was initially introduced in 2000 (and later withdrawn and relaunched), followed by Adcetris (brentuximab vedotin) and Kadcyla (trastuzumab emtansine, Fig. 5).⁵⁴ Most US Food and Drug Administration (FDA)-approved ADC drugs were only introduced in 2019 or later. They comprise highly efficacious small-molecule components with often intercalating or microtubule-disrupting properties. A special case of an ADC is a radiopharmaceutical agent being covalently attached to an antibody. BAY 2315497 is a recent example in which the small-molecule component of the conjugate is a strong chelator of thorium-227, based on a 3-hydroxy-2-pyridone motif (Fig. 5). The antibody component targets prostate-specific membrane antigen (PSMA) and delivers α -particle-emitting [²²⁷Th] to PSMA-expressing prostate tumor cells. BAY 2315497 is currently in Phase 1 trials for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).⁵⁵ Similar approaches addressing PSMA involve actinium-225.

PROTACs, LYTACs, and molecular glues

PROTACs are protein-degrading bifunctional drug conjugates containing two small-molecule moieties covalently linked to each other: one binds to a target protein of interest and the other to an E3 ligase.⁵⁶ E3 ligases transfer ubiquitin to their natural protein substrates, thereby marking them for proteasomal degradation. A PROTAC can hijack this mechanism by bringing the target protein of the PROTAC close to the ligase, which transfers ubiquitin to the target protein even if it is not a natural substrate of the utilized ligase. Consequently, the protein of interest can be degraded by the cellular proteasome, removing it from the cell

rather than just modulating its function. Given their molecular setup as bifunctional molecules, PROTACs are larger than conventional small molecules, which poses potential challenges with respect to oral bioavailability and cell permeability. Furthermore, optimization is complex, because not every PROTAC molecule reaches productive interactions with both target protein and E3 ligase alike. Despite these hurdles, the first PROTACs have already been transferred to the clinic successfully. In 2019, ARV-110 and ARV-471 entered clinical trials for cancer indications (Fig. 5).⁵⁷ ARV-110 targets the androgen receptor for the treatment of mCRPC and ARV-471 targets the estrogen receptor for treatment of locally advanced or metastatic ER⁺/HER2⁻ breast cancer. Both compounds are orally bioavailable and reportedly reach exposure levels in patients that correspond to efficacious levels in preclinical models.

Molecular glues can also induce protein degradation but work slightly differently from PROTACs. They act by binding to an E3 ligase and enhancing its binding interaction with a protein of interest via sticking to the protein–protein interface.⁵⁶ Molecular glues are monofunctional and, therefore, usually smaller than PROTACs, and have rather traditional small-molecule properties. Approved molecular glues are thalidomide and its derivatives, the mode of action of which was only discovered in retrospect.

Lysosomal-targeting chimeras (LYTACs) target membrane and extracellular proteins, which cannot be addressed by PROTACs and molecular glues. LYTACs were first reported in 2020 and engage the lysosome pathway for protein degradation as an interesting approach for potential future applications.⁵⁸

Modified peptides and peptidomimetics

Therapeutic peptides often display high potency and selectivity for their target. However, their therapeutic application is typically hampered by low oral bioavailability, low plasma stability, and low membrane permeability.⁵⁹ Formulation approaches, including the addition of small-molecule permeation enhancers, and several chemical modification techniques are available to address these shortcomings. One key strategy is to stabilize peptides by designing cyclic, stapled, stitched, or otherwise constrained peptides that improve the pharmacokinetic and tissue/cell-penetrating properties. In many of these cases, small molecule-type structural features have been included in the peptide. Similarly, conjugation of peptides with polyethylene glycol (PEGylation) or fatty acids (lipidation) can prolong their half-life without compromising potency. The first orally bioavailable peptide, Rybelsus (oral semaglutide), was approved in 2019 for the treatment of type 2 diabetes mellitus. Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that is structurally related to natural GLP-1. The most striking chemical variation is the addition of a fatty acid moiety connected via a synthetic linker, leading to increased protein binding and prolonged circulation half-life.⁶⁰ In the oral product Rybelsus, semaglutide is co-formulated with an absorption enhancer to enable once-daily oral administration.

Small molecules as chemical probes in chemical biology

Small molecules serve as scientific tools to elucidate (patho-) physiological mechanisms on a molecular level and to identify or validate drug targets. This interdisciplinary field of drug

research is termed ‘chemical biology’, and has matured considerably over the past 25 years, establishing itself at the intersection of chemistry, biology, physiology, and medicine. Small molecules used as chemical probes do not necessarily differ fundamentally from small molecules used as medicines, but they do not usually need to be fully optimized with respect to properties such as their *in vivo* efficacy or *in vivo* pharmacokinetics. Depending on their specific purpose, they can also be tagged for identification or enrichment in separation processes or can be decorated with additional functional groups for covalent binding (e.g., in chemoproteomics studies). Noteworthy, a growing number of chemical probes is being generated by the scientific community, supported by the open science initiatives, such as EUBOPEN and Structural Genomics Consortium (SGC), with partners from academia and industry.^{61,62} The global open science movement Target 2035 aims to identify probes for the entire human genome, thus facilitating the quest for the discovery of new medicines for human diseases.^{63–65}

Small molecules as facilitators of cell and gene therapy

There is arguably no other treatment modality today that receives so much attention in the media, creates such high hopes in patients, and fires the imagination of industry leaders as cell and gene therapy. The FDA currently counts 22 approved cell and gene therapy products.⁶⁶ By providing breakthroughs for the treatment of diseases with unmet medical need, these novel therapeutic modalities hold the promise of becoming the next-generation therapy of the future. However, also in cell and gene therapy, small molecules are of growing importance, namely by improving the safety, efficacy, and manufacturing of these new treatments at different stages.⁶⁷

In cell therapy, small-molecule additives can ensure product quality during cell expansion, cryopreservation, and formulation and can lead to improved toxicological profiles and enhanced therapeutic efficacy of the intervention. An early example is the tool compound pluripotin (SC1), a small-molecule kinase inhibitor of ERK1 and RasGAP. It is used for the propagation of embryonic stem cells in an undifferentiated, pluripotent state.⁶⁸ Further examples include the BET inhibitor JQ1⁶⁹ and the GSK3 β inhibitor TWS119,⁷⁰ which are used to expand T cells and to control their phenotype. To prevent cryopreservation-induced cell death, the protein kinase A inhibitor H89 can be applied.⁷¹ Another interesting example is the c-Rel inhibitor IT-603, which is used to control the immune response on the host side and to prevent graft-versus-host disease without compromising the antitumor activity of T cell therapies in preclinical models.⁷² Furthermore, the PD-L1/2 and VISTA immune checkpoint blocker CA-170 can be used for the *in vivo* inhibition of T cell suppression, leading to increased therapeutic efficacy of the cell therapy. These examples are currently in clinical or preclinical development stages for their cell therapy application.

In gene therapy, a broad range of small molecules have been developed to improve the therapeutic efficacy following different modes of action. The vectors that are applied to genetically modify cells *ex vivo* or *in vivo* offer a lot of opportunities, but timing and precision are key for efficacy and safety. Important applications of small molecules in gene therapy are the enhancement of vector internalization, the targeting of intracellular pathways

involved in transduction, and the blocking of cellular antiviral pathways.^{73,74} Transduction is a complex process that is still not completely understood; therefore, phenotypic screening remains the method of choice to identify chemical matter. The small-molecule protein kinase C agonist phorbol 12-myristate 13-acetate (PMA) enhances lentiviral transduction of human hematopoietic cell lines and CD34 + hematopoietic stem cells.⁷⁵ For adeno-associated virus-based vectors, the marketed proteasome inhibitors Velcade (bortezomib) and Kyprolis (carfilzomib) represent important tool compounds in gene therapy with the potential to enhance transduction efficacy.⁷⁶

The discovery of the clustered regularly interspaced short palindromic repeats (CRISPR) gene-editing technology has significantly broadened the overall scope of gene therapeutic approaches. Small molecules have been shown to improve the precision of CRISPR/Cas gene editing, thus facilitating its future therapeutic use.⁷⁷

Small molecules as diagnostic agents

A nontherapeutic but clinically highly relevant application is the use of small molecules as diagnostic agents.⁷⁸ Small molecules find widespread use for imaging purposes, such as positron emission tomography (PET) tracers and as X-ray, magnetic resonance imaging (MRI), ultrasound, and near-infrared contrast agents. The diversity of roles that small molecules can assume mirrors the diversity of the applications themselves. PET tracers are bioactive molecules tagged with a positron-emitting radionuclide, such as the frequently used ¹⁸F-labeled fluorodeoxyglucose (FDG), approved in 1994 for PET imaging.⁷⁸ As MRI contrast agents, small molecules show metal-chelating properties, as in the first Gd³⁺-based MRI agent Magnevist (gadopentetic acid), introduced in 1987.⁷⁹ In near-infrared spectroscopy, small molecules act as organic dyes, such as indocyanine green, approved for clinical use in 1959.⁸⁰

Small molecules as facilitators of organ transplantation

Small molecules can be used to enable or improve nonpharmacological interventions, such as organ transplantation. As immunosuppressive drugs, small molecules are administered to patients to control rejection of the transplanted organ.⁸¹ An important immunosuppressant used after organ transplantation is Prograf (tacrolimus/FK-506), a macrocyclic lactone derived from bacteria that binds the FK binding protein, inhibiting calcineurin and reducing T cell activity.⁸² Apart from suppressing rejection of the implanted organ, small molecules can also be used to preserve the quality of the organ by protecting it from the deleterious effects of hypoxia and nutrient deprivation during storage and transport.⁸³ The optimization of organ preservation media via small molecule-based additives remains a subject of continued research.

Leveraging artificial intelligence for small-molecule drug discovery

Digitalization and artificial intelligence (AI) are revolutionizing all industries and have likewise begun to transform the drug discovery sector. Small molecules are especially suited for machine-learning (ML) approaches. For one part, this is because of their

modular chemical structure, which can be translated into machine-readable formats. For the other part, vast historically grown data sets of synthetic methods, physicochemical characteristics, and protein–target interactions are widely available.⁸⁴ The challenge and art is to ‘integrate everything’⁸⁵ by further developing computational tools, leveraging compound data, and seamlessly incorporating efficient digital workflows to support medicinal chemists to invent new therapeutic drugs for the patient.

Retrosynthetic planning driven by machine learning

Despite their relatively simple chemical structure and the vast arsenal of available methods, synthetic access to new, specific small molecules often remains a bottleneck.⁸⁶ Therefore, that machines are beginning to learn the language of organic chemistry is a major step forward. Initial attempts to approach retrosynthesis in a computerized manner were made by E.J. Corey, who developed the concept of retrosynthetic analysis during the 1960s and was later awarded the Nobel Prize in Chemistry. His program, Logic and Heuristics Applied to Synthetic Analysis (LHASA), used a systematic way of breaking bonds of a given molecule, thus simplifying it step by step and tracing it back to commercially available building blocks.⁸⁷ However, at that time, computers were not capable of adequately mastering the complexity of chemistry.

Meanwhile, modern digital retrosynthesis planning tools have been made available.^{88–91} The more traditional approach is based on retrosynthesis rules, which are hand-encoded by human chemistry experts. Based on this technology, the retrosynthesis tool SYNTHIA was validated in 2018 in the laboratory by successfully putting synthesis routes into practice that had been proposed by the computer.⁹² Also in 2018, it was demonstrated that a machine could extract chemical transformation rules from millions of mapped single-step reactions and apply them to new synthetic problems.⁹³ The combination of artificial neuronal networks (ANNs) and Monte Carlo tree search (MCTS) that had once made the game software ‘AlphaGo’ invincible, was shown to also be applicable to chemical synthesis. As a major advantage of this approach, manual rule extraction could entirely be avoided. Today, automated rule generation algorithms are part of commercially available retrosynthesis tools in the Reaxys⁹⁴ and SciFinder⁹⁵ platforms, as well as in open-source tools, such as ASKCOS, provided by the Machine Learning for Pharmaceutical Discovery and Synthesis (MLPDS) Consortium.^{96,97} Further advances in retrosynthesis technology arise from representing molecular structures as graphs^{98,99} and from the idea of organic chemistry as a language.¹⁰⁰ In the latter case, the relation between starting materials and products can be described as a translation problem between text sequences, such as Simplified Molecular-Input Line-Entry Systems (SMILES).^{101,102} This fully data-driven deep learning ‘end-to-end’ model can learn organic chemistry naturally like a human language without depending on any transformation rules or reaction schemes. Thus, it can also predict ‘new’ chemistry outside its chemistry training data set.

ML depends on training data with both positive and negative examples. However, commercial reaction databases have a strong bias toward the positives. This is why large corporate reaction

databases of well-documented both positive and negative reaction outcomes can be regarded as a treasure trove.¹⁰³ With the inhouse ‘AI4Synthesis’ project, Bayer is leveraging the potential of its historically grown chemical database of almost 5 million chemical reactions suitable for ML purposes.

Medicinal chemistry powered by artificial intelligence

Compound optimization in medicinal chemistry is the art of systematically improving the desired properties of a molecule while keeping the undesirable properties at bay.¹⁰⁴ However, inventing the right molecule is usually a complex and time-consuming endeavor, which involves years of multiparameter optimization along numerous iterative learning cycles. The aim is to speed up this drug-hunting process with help of ML and computational methods, thus providing optimized candidate compounds in a much shorter time.¹⁰⁵ During the past few decades, ML-assisted methods of predicting physicochemical and pharmacokinetic properties of small molecules have considerably improved.¹⁰⁶ Likewise, the task to find the optimal balance of several, often conflicting, properties simultaneously has been well addressed by a today ML-assisted technique called Pareto optimization.¹⁰⁷ One important application of these innovative methods is the design of new screening compounds that serve as high-quality molecular starting points for compound optimization. The idea is that screening hits with favorable built-in properties, such as high solubility and oral bioavailability, will consequently lead to less complex compound optimization tasks and, thus, dramatically shorten lead optimization project timelines. Believing in the sustainable success of small-molecule drug discovery, Bayer recently added half a million exclusively designed compounds with novel scaffolds to its corporate screening library.¹⁰⁸

One inherent feature of small molecules is their modular nature and the almost infinite possibilities to generate biologically active molecules from new combinations of their components. For successful small-molecule drug discovery over the long term, it will be necessary to skillfully address the virtual chemical space not only with human imagination, but also via computational methods and AI. With $\sim 10^{60}$ theoretically existing drug-like small molecule compounds, the virtual chemical space is incredibly vast.¹⁰⁹ Although this breathtaking number of compounds is too big to be handled by even the most powerful computers, the enumeration of virtual compound libraries in the range of 10^9 molecules has become routine.¹¹⁰ Computational techniques, such as scaffold hopping, functional group variations, and similarity searches, are frequently used to expand a virtual library around an initial compound hit set, a process often referred to as ‘hit expansion’. Importantly, special attention has been paid in recent years to improve the synthetic feasibility of these libraries by ML approaches, as described above. In addition, the emergence of huge commercially available compound libraries on demand, as offered for instance by companies such as Enamine and WuXi AppTec, have facilitated virtual screening approaches worldwide.^{110–113}

A successful example of fusing ML and small-molecule library approaches was recently published in a joint study by ZebiAI, Google Accelerated Science (GAS), and X-Chem.¹¹⁴ Starting with a chemically synthesized DNA-encoded library (DEL), the researchers used screening data obtained from DEL affinity selec-

tion to establish effective ML models and successfully predict hits with similar chemical structures outside this library from a commercially available catalog of 88 million compounds.

AI techniques, such as deep learning, have also led to advances in *de novo* drug design.^{115,116} In *de novo* design, small molecules are designed ‘from scratch’ (e.g., based on available 3D-structural information of their protein targets).¹⁰⁵ A well-known traditional design technique that exploits the modular nature of small molecules is the ‘growing’ of weakly active fragments into fully fledged drug-like molecules by gradually fitting them into the protein binding pocket. Special opportunities can be anticipated by the combination of *de novo* molecular design techniques and so-called free energy perturbation (FEP) simulations.¹¹⁷ FEP simulations are used to predict the binding affinity of a small-molecule ligand to its protein target, which can be regarded as the ‘holy grail’ in computer-aided drug design.¹¹⁸ Massively increased computing power and improved statistical and biophysical-based algorithms have led to more accurate FEP predictions, which, in some cases, have reached sufficient predictive quality to guide synthesis prioritization decisions in compound optimization projects.

To leverage the huge potential of AI in small-molecule drug discovery, big pharmaceutical companies, including Bayer, have announced partnerships with specialized computational and AI-based providers, such as Schrödinger and Exscientia.^{84,119} One focus of these collaborations are ‘holistic approaches’, which combine various tools under one roof, thus ‘integrating everything’⁸⁵ into automated molecular design solutions, such as the approach recently published by GlaxoSmithKline.¹²⁰ The era of AI in small-molecule drug discovery has undoubtedly begun, illustrated also by the announcement that the first three small molecules created with the aid of AI have reached clinical trials: a 5-HT_{1A} receptor agonist (DSP-1181) for obsessive compulsive disorder; an A2a receptor antagonist (EXS-21546) for immunoncology; and a dual-targeted 5-HT_{1A} agonist/5-HT_{2A} antagonist (DSP-0038) for Alzheimer’s disease psychosis.¹²¹

Societal aspects

For more than 120 years, novel small-molecule drugs have not only positively affected life expectancy and quality of life for humans individually, but also impacted society on a global scale. During the first half of the 20th century, drug discovery largely focused on the fight against infectious diseases. Whereas, in 1900, the average life expectancy at birth was 47 years even in the industrialized world, this had increased to 68 years in the USA by 1950,¹²² largely attributable to the introduction of antibiotics during the 1940s.¹² The success of penicillin antibiotics was driven, to a large extent, by governmental support during World War II, thus giving US companies a leading position at that time. The ‘Golden Age’ of pharmaceutical industry (the 1940s to the mid-1970s) in the USA, Europe, and Japan was fueled by strong investments in research and development, massive improvements in the standard of living, and a general optimism regarding scientific and technological progress. Novel small-molecule drugs from this era, such as antidepressants, antipsychotics, and oral contraceptives, were beginning to exert their influence on medical treatment, life style, and society as a whole.^{123,124}

The increased life expectancy in combination with lifestyle changes led to a dramatic increase in cardiovascular diseases throughout western civilizations. Changes in diet, a steadily growing number of smokers, and a decrease in exercise and regular physical activity were shown to be associated with an increase in coronary atherosclerosis, resulting in coronary heart disease.¹²⁵ Whereas at the beginning of the 20th century, heart disease was a rather rare cause of death, it became the most common cause of death in the USA by the middle of the last century, peaking during the mid-1960s. Coronary heart disease was referred to as the ‘epidemic of the 20th century’.¹²⁵ Between the 1960s and 1980s, scientific advancements changed the drug discovery process. Drug research was now focusing on small molecules directed toward specific physiological processes on a molecular target level, thus offering therapies for better control of blood pressure and heart rate, such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers, and angiotensin II receptor blockers (ARBs).

During the late 1980s, a new class of cholesterol-lowering medications, called statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, became available. Eight statins received approval from the 1980s to 1990s. As indicated in a recent meta-analysis, use of any statin in moderate dose leads to a reduction in low-density lipoprotein C (LDL-C) levels by 20–40% and significantly reduces major cardiovascular events and mortality to a similar extent.^{126,127} Accordingly, the introduction of statins changed the treatment of cardiovascular diseases and decreased the humanistic and economic burden on both the individual and societal level by reducing the number of myocardial infarctions and revascularization procedures, respectively. However, whereas all statin compounds were comparably efficacious, marketing strategies became a major factor for commercial success. First approved in 1997, Lipitor (atorvastatin) was not the first statin on the market but commercially by far the most successful. Notably, Lipitor evolved into the best-selling small-molecule drug of all time, with peaks sales of over US\$13 billion in 2006 and overall sales of US\$120 billion until patent expiration in 2011.¹²⁸ The commercial success of statins can be marked as a turning point for the pharmaceutical industry. The cost for patent-protected medication became an increasing burden for healthcare systems. Today, healthcare providers and payers are no longer capable or willing to afford premium prices for drugs that cannot prove therapeutic benefits over the standard of care in the respective indication. As a consequence, cost-containment policies of various types have been introduced.¹²⁹

Since the 1980s, the growing biotechnology sector has contributed to major scientific innovations and societal transformations.¹³⁰ Fundamental discoveries in molecular biology, such as the decoding of the human genome between 1990 and 2003, were made. Likewise, important medical breakthroughs were achieved for treatments in indications with relatively low therapeutic standards, such as in some cancers and rheumatoid arthritis. By 2020, half of the top-selling drugs were biologics, with the antirheumatic antibody Humira (adalimumab) leading the list, with annual sales of more than US\$20 billion. However, the therapeutic benefits of the new biologics have translated into high prices, thus putting healthcare systems and payers under even

further pressure. For example, in 2017, only 2% of prescriptions in the USA comprised biologics, but these accounted for 37% of net drug spending.¹³¹ Another example is the annual cost for the biologic Humira, which, in the USA, is more than double that for the small-molecule Olumiant (baricitinib), in the same indication of rheumatoid arthritis.¹³² This example reveals an ethical dilemma: that not always the potentially best possible therapy might be available for all patients in need because of cost constraints.

Cost projections also have a major role in the public discussion on breakthrough cell and gene therapies.^{133–135} With prices of several million US dollars per single administration, it becomes apparent that healthcare systems will likely not be capable of providing these high-cost medicines for all patients. It has been suggested that, if gene therapies were made available for only one-tenth of people with genetic conditions (~1% of the US population), the budget impact could equal US\$3 trillion, which represents the overall healthcare spending of the USA.¹³⁶ As illustrated also in the ongoing Coronavirus 2019 (COVID-19) pandemic, affordability and sustainability discussions will likely become an even more prominent topic for many societies around the globe in the near and mid-term future. In this situation, small molecules might have an increasing role in flexibly securing the best possible population health within given willingness-to-pay considerations and potential budgetary constraints.

In aging societies, dementia and neurodegenerative diseases have become more prevalent and a major public health concern.¹³⁷ There is currently neither a cure nor disease-modifying treatment for Alzheimer's disease, and therapeutics can only temporarily reduce symptoms. Notably, more than a hundred disease-modifying drug candidates are in clinical trials, with a high percentage (70%) of small molecules.¹³⁸ Therefore, one can be cautiously optimistic that better future therapies will become available for Alzheimer's disease as one of the most urgent health problems of our age.

Concluding remarks and outlook

Small molecules have been vital as milestone drugs in the history of medicine and have impacted both medical progress and societal changes. For medicinal chemists, small molecules have been the perfect modality to optimize the potency and selectivity of drugs and to fine-tune overall molecular properties. Given the modular nature of small molecules and the almost infinite possibilities to combine their structural components and to yield biologically active molecules, there seem few limits regarding new applications, including addressing the formerly undruggable target space. With the aid of AI, general prospects for compound synthesis and property optimization have reached a new dimension. Currently, machines are learning the language of organic chemistry and are serving as digital assistants to human medicinal chemists during lead optimization. However, the application

of small molecules in medicine goes far beyond direct therapeutic use. Small molecules can be used as diagnostics, as scientific tools for chemical biology, and as facilitators in novel breakthrough technologies, such as cell and gene therapy.

In the era of modern medicine, new biological technologies, such as CRISPR/Cas, have begun to further revolutionize our understanding of diseases. A more causative treatment paradigm has emerged along with highly personalized medical approaches, such as cell and gene therapy. Delivering on these promises will be vital for patients with, thus far, untreatable diseases. At the same time, these new technologies have raised the bar for drug discovery approaches in general. In the past, interventions providing a symptomatic relief were often attractive enough to drive ideation for new drug discovery projects. Today, the innovation level needs to be of a more transformative nature. Excitingly, we are witnessing a dynamic scientific development in which small molecules address new modes of action and access new target space. Small molecules have recently learned to target proteins via degradation in addition to traditional modulation of their function, as well as to address PPIs and RNAs. While tremendous progress has been made in these new areas, significant hurdles remain and a lot of work needs to be done.

Today, the pharmaceutical industry is aiming at a broad mix of modalities to tackle human diseases, including small molecules, antibodies, nucleic acids, glycans, and cell and gene therapy, among others. The decision for a specific modality is preferentially driven in a patient-centric manner considering the pros and cons in a given disease context. However, for many diseases, small molecules often remain the modality of choice.

Adding to the intrinsic advantages of small molecules, such as flexible modes of action and adaptable administration routes, they also offer a path beyond mono-targeted treatment options via combination therapy with other drugs, thus increasing clinical effect size. The generally long shelf-life of small molecules enables this modality to reach out to more patients in need than any other modality in a highly sustainable way for healthcare systems. As illustrated throughout medical history on multiple occasions, small molecules are highly suited to address unmet medical needs. It is anticipated that they will remain drivers of innovation in future drug research, thus continuing to improve the lives of patients.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors are employees of Bayer AG.

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References

1. Bayer AG. Overview: History of Bayer. www.bayer.com/en/history [accessed February 17, 2022].
2. Anon., 100 Jahre CWL in Wuppertal, *Nachr Chem Tech Lab* 44 (1996) 1195–1196.

3. M. Wainwright, Dyes in the development of drugs and pharmaceuticals, *Dyes Pigm* 76 (2008) 582–589.
4. A.W. Jones, Early drug discovery and the rise of pharmaceutical chemistry, *Drug Test Anal* 3 (2011) 337–344.
5. M.C. Gerald, *The Drug Book. From Arsenic to Xanax, 250 Milestones in the History of Drugs*, Publishing, New York; Sterling, 2013.
6. M.J.R. Desborough, D.M. Keeling, The aspirin story – from willow to wonder drug, *Br J Haematol* 177 (2017) 674–683.
7. A. Harding, Sir John Robert Vane, *The Lancet* 364 (2004) 2090.
8. V. Fuster, J.M. Sweeny, *Aspirin Circulation* 123 (2011) 768–778.
9. P.C. Elwood, G. Morgan, C. Delon, Aspirin and cancer survival: a systematic review and meta-analyses of 118 observational studies of aspirin and 18 cancers, *E cancer* 15 (2021) 1258.
10. P. Savarapu, N. Baral, G. Adhikari, M. Akanbi, B. Abdelazeem, S.O. Isa, et al. Aspirin use is associated with decreased mortality in patients with COVID-19: a systematic review and meta-analysis. *medRxiv*. Published online July 10, 2021. <http://dx.doi.org/10.1101/2021.07.08.21260236>.
11. R. Gaynes, The discovery of penicillin—new insights after more than 75 years of clinical use, *Emerg Infect Dis* 23 (2017) 849–853.
12. M.I. Hutchings, A.W. Truman, B. Wilkinson, Antibiotics: past, present and future, *Curr Opin Microbiol* 51 (2019) 72–80.
13. K.C. Nicolaou, S. Rigol, A brief history of antibiotics and select advances in their synthesis, *J Antibiot* 71 (2018) 153–184.
14. C. De Costa, The pill: a short history, *O&G Mag* 22 (2020) 1.
15. Wikipedia. Combined oral contraceptive pill. https://en.wikipedia.org/wiki/Combined_oral_contraceptive_pill#cite_note-Speroff_2011a-114 [accessed February 18, 2022].
16. M.P.R. Festin, Overview of modern contraception, *Best Pract Res Clin Obstet Gynaecol* 66 (2020) 4–14.
17. United Nations Digital Library. Contraceptive use by method 2019: data booklet. <https://digitallibrary.un.org/record/3849735> [accessed February 18, 2022].
18. A. Park, The story behind the first AIDS drug. <https://time.com/4705809/first-aids-drug-azt/> [accessed February 18, 2022].
19. E.J. Arts, D.J. Hazuda, HIV-1 antiretroviral drug therapy, *Cold Spring Harb Perspect Med* 2 (2012).
20. S. Chaudhuri, J.A. Symons, J. Deval, Innovation and trends in the development and approval of antiviral medicines: 1987–2017 and beyond, *Antiviral Res* 155 (2018) 76–88.
21. A. Mullard, 2021 FDA approvals. *Nat Rev Drug Discov*. Published online January 4, 2022. <http://dx.doi.org/10.1038/d41573-022-00001-9>.
22. M. Cully, A tale of two antiviral targets — and the COVID-19 drugs that bind them, *Nat Rev Drug Discov* 21 (2022) 3–5.
23. Zimmer C, Wu KJ, Corum J, Kristoffersen M. Coronavirus drug and treatment tracker. www.nytimes.com/interactive/2020/science/coronavirus-drugs-treatments.html [accessed February 18, 2022].
24. Johnson&Johnson. FDA approves two new indications for XARELTO (rivaroxaban) to help prevent and treat blood clots in pediatric patients. www.jnj.com/fda-approves-two-new-indications-for-xarelto-rivaroxaban-to-help-prevent-and-treat-blood-clots-in-pediatric-patients [accessed February 17, 2022].
25. S. Roehrig, A. Straub, J. Pohlmann, T. Lampe, J. Pernerstorfer, K.-H. Schlemmer, et al., Discovery of the novel antithrombotic agent 5-chloro-N-((5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl)methyl)thiophene-2-carboxamide (BAY 59–7939): an oral, direct factor Xa inhibitor, *J Med Chem* 48 (2005) 5900–5908.
26. E. Perzborn, S. Roehrig, A. Straub, D. Kubitz, F. Misselwitz, The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor, *Nat Rev Drug Discov* 10 (2011) 61–75.
27. A.M. Wendelboe, G.E. Raskob, Global burden of thrombosis: epidemiologic aspects, *Circ Res* 118 (2016) 1340–1347.
28. M. Franchini, G.M. Liumbruno, C. Bonfanti, G. Lippi, The evolution of anticoagulant therapy, *Blood Transfus* 14 (2016) 175–184.
29. M. Follmann, N. Griebenow, M.G. Hahn, I. Hartung, F.J. Mais, J. Mittendorf, et al., The chemistry and biology of soluble guanylate cyclase stimulators and activators, *Angew Chem Int Ed* 52 (2013) 9442–9462.
30. P. Sandner, D.P. Zimmer, G.T. Milne, M. Follmann, A. Hobbs, J.-P. Stasch, Soluble guanylate cyclase stimulators and activators, in: H.H.H.W. Schmidt, P. Ghezzi, A. Cuadrado (Eds.), *Reactive Oxygen Species: Network Pharmacology and Therapeutic Applications*, Springer International Publishing, Berlin, 2021, pp. 355–394.
31. J.J. Adashek, V. Subbiah, R. Kurzrock, From tissue-agnostic to n-of-one therapies: (r)evolution of the precision paradigm, *Trends Cancer* 7 (2021) 15–28.
32. L. Falzone, S. Salomone, M. Libra, Evolution of cancer pharmacological treatments at the turn of the third millennium, *Front Pharmacol* 9 (2018) 1300.
33. L. Zhong, Y. Li, L. Xiong, W. Wang, M. Wu, T. Yuan, et al., Small molecules in targeted cancer therapy: advances, challenges, and future perspectives, *Signal Transduct Target Ther* 6 (2021) 201.
34. P.L. Bedard, D.M. Hyman, M.S. Davids, L.L. Siu, Small molecules, big impact: 20 years of targeted therapy in oncology, *Lancet* 395 (2020) 1078–1088.
35. S. Santhosh, P. Kumar, V. Ramprasad, A. Chaudhuri, Evolution of targeted therapies in cancer: opportunities and challenges in the clinic, *Future Oncol* 11 (2015) 279–293.
36. H. Beck, M. Jeske, K. Thede, F. Stoll, I. Flamme, M. Akbaba, et al., Discovery of molidustat (BAY 85-3934): a small-molecule oral HIF-prolyl hydroxylase (HIF-PH) inhibitor for the treatment of renal anemia, *ChemMedChem* 13 (2018) 988–1003.
37. M.J. Blanco, K.M. Gardinier, New chemical modalities and strategic thinking in early drug discovery, *ACS Med Chem Lett* 11 (2020) 228–231.
38. E. Valeur, S.M. Guéret, H. Adihou, R. Gopalakrishnan, M. Lemurell, H. Waldmann, et al., New modalities for challenging targets in drug discovery, *Angew Chem Int Ed* 56 (2017) 10294–10323.
39. J. Singh, R.C. Pette, T.A. Baillie, A. Whitty, The resurgence of covalent drugs, *Nat Rev Drug Discov* 10 (2011) 307–317.
40. R. Lonsdale, R.A. Ward, Structure-based design of targeted covalent inhibitors, *Chem Soc Rev* 47 (2018) 3816–3830.
41. A.K. Ghosh, I. Samanta, A. Mondal, W.R. Liu, Covalent inhibition in drug discovery, *ChemMedChem* 14 (2019) 889–906.
42. Bayer AG. Bayer strengthens drug discovery platform through acquisition of Vividion Therapeutics. <https://media.bayer.com/baynews/baynews.nsf/id/Bayer-strengthens-drug-discovery-platform-through-acquisition-of-Vividion-Therapeutics> [accessed February 18, 2022].
43. A.T. Voice, G. Tresadern, R.M. Twidale, H. van Vlijmen, A.J. Mulholland, Mechanism of covalent binding of ibrutinib to Bruton's tyrosine kinase revealed by QM/MM calculations, *Chem Sci* 12 (2021) 5511–5516.
44. NIH National Institute of Health. FDA approval of KRAS inhibitor sotorasib for lung cancer hailed as milestone. www.cancer.gov/news-events/cancer-currents-blog/2021/fda-sotorasib-lung-cancer-kras [accessed February 17, 2022].
45. B.A. Lanman, J.R. Allen, J.G. Allen, A.K. Amegadzie, K.S. Ashton, S.K. Booker, et al., Discovery of a covalent inhibitor of KRASG12C (AMG 510) for the treatment of solid tumors, *J Med Chem* 63 (2020) 52–65.
46. H. Lu, Q. Zhou, J. He, Z. Jiang, C. Peng, R. Tong, et al., Recent advances in the development of protein–protein interactions modulators: mechanisms and clinical trials, *Signal Transduct Target Ther* 5 (2020) 213.
47. J.M. Smith, J.R. Frost, R. Fasan, Designer macrocyclic organo-peptide hybrids inhibit the interaction between p53 and HDM2/X by accommodating a functional α -helix, *Chem Commun* 50 (2014) 5027–5030.
48. P. Dorr, M. Westby, S. Dobbs, P. Griffin, B. Irvine, M. Macartney, et al., 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) 4721–4732.
49. A. Korycka-Wolowiec, D. Wolowiec, A. Kubiak-Mlonka, T. Robak, Venetoclax in the treatment of chronic lymphocytic leukemia, *Expert Opin Drug Metab Toxicol* 15 (2019) 353–366.
50. A.E. Hargrove, Small molecule–RNA targeting: starting with the fundamentals, *Chem Commun* 56 (2020) 14744–14756.
51. M.G. Costales, J.L. Childs-Disney, H.S. Haniff, M.D. Disney, How we think about targeting RNA with small molecules, *J Med Chem* 63 (2020) 8880–8900.
52. H. Ratni, M. Ebeling, J. Baird, S. Bendels, J. Bylund, K.S. Chen, et al., Discovery of risdiplam, a selective survival of motor neuron-2 (SMN2) gene splicing modifier for the treatment of spinal muscular atrophy (SMA), *J Med Chem* 61 (2018) 6501–6617.
53. P. Khongorzul, C.J. Ling, F.U. Khan, A.U. Ihsan, J. Zhang, Antibody-drug conjugates: a comprehensive review, *Mol Cancer Res* 18 (2020) 3–19.
54. J.T.W. Tong, P.W.R. Harris, M.A. Brimble, I. Kavianinia, An insight into FDA approved antibody–drug conjugates for cancer therapy, *Molecules* 26 (2021) 5847.
55. S. Hammer, U.B. Hagemann, S. Zitzmann-Kolbe, A. Larsen, C. Ellingsen, S. Geradue, et al., Preclinical efficacy of a PSMA-targeted thorium-227 conjugate (PSMA-TTC), a targeted alpha therapy for prostate cancer, *Clin Cancer Res* 26 (2020) 1985–1996.

56. S.B. Alabi, C.M. Crews, Major advances in targeted protein degradation: PROTACs, LYTACs, and MADTACs, *J Biol Chem* 296 (2021).
57. B. Halford, Drug Discovery, Arvinas unveils PROTAC structures C&EN 99 (2021) 5.
58. S.M. Banik, K. Pedram, S. Wisnovsky, G. Ahn, N.M. Riley, C.R. Bertozzi, Lysosome-targeting chimaeras for degradation of extracellular proteins, *Nature* 584 (2020) 291–297.
59. A.T. Zizzari, D. Pliatsika, F.M. Gall, T. Fischer, R. Riedl, New perspectives in oral peptide delivery, *Drug Discov Today* 26 (2021) 1097–1105.
60. C. Granhall, F.L. Søndergaard, M. Thomsen, T.W. Anderson, Pharmacokinetics, safety and tolerability of oral semaglutide in subjects with renal impairment, *Clin Pharmacokinet* 57 (2018) 1571–1580.
61. EUBOPEN. Enabling & unlocking biology in the open. www.eubopen.org/ [accessed February 17, 2022].
62. SGC. Structural Genomics Consortium. www.thesgc.org/ [accessed February 17, 2022].
63. Target 2035. www.target2035.net/ [accessed February 17, 2022].
64. A.J. Carter, O. Kraemer, M. Zwick, A. Mueller-Fahrnow, C.H. Arowsmith, A.M. Edwards, Target 2035: probing the human proteome, *Drug Discov Today* 24 (2019) 2111–2115.
65. S. Müller, S. Ackloo, A. Al Chawaf, B. Al-Lazikani, A. Antolin, J.B. Baell, et al., Target 2035 – update on the quest for a probe for every protein, *RSC Med Chem* 13 (2022) 13–21.
66. FDA. Approved cellular and gene therapy products. www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products [accessed February 17, 2022].
67. L.L. Brayshaw, C. Martinez-Fleites, T. Athanasopoulos, T. Southgate, L. Jespers, C. Herring, The role of small molecules in cell and gene therapy, *RSC Med Chem* 12 (2021) 330–352.
68. S. Chen, J.T. Do, Q. Zhang, S. Yao, F. Yan, E.C. Peters, et al., Self-renewal of embryonic stem cells by a small molecule, *Proc Natl Acad Sci USA* 103 (2006) 17266–17271.
69. P. Georgiev, Y. Wang, E.S. Muise, M.L. Bandi, W. Blumenschein, M. Sathe, et al., BET bromodomain inhibition suppresses human T cell function, *ImmunoHorizons* 3 (2019) 294–305.
70. M. Sabatino, J. Hu, M. Sommariva, S. Gautam, V. Fellowes, J.D. Hocker, et al., Generation of clinical-grade CD19-specific CAR-modified CD8+ memory stem cells for the treatment of human B-cell malignancies, *Blood* 128 (2016) 519–528.
71. L. Zhang, Y. Xu, J. Xu, Y. Wei, X. Xu, Protein kinase A inhibitor, H89, significantly enhances survival rate of dissociated human embryonic stem cells following cryopreservation, *Cell Prolif* 49 (2016) 589–598.
72. Y. Shono, A.Z. Tuckett, S. Ouk, H.-C. Liou, G. Altan-Bonnet, J.J. Tsai, et al., A small-molecule c-Rel inhibitor reduces alloactivation of T cells without compromising antitumor activity, *Cancer Discov* 4 (2014) 578–591.
73. J.W. Schott, D. León-Rico, C.B. Ferreira, K.F. Buckland, G. Santilli, M.A. Armant, et al., Enhancing lentiviral and alpharetroviral transduction of human hematopoietic stem cells for clinical application, *Mol Ther Methods Clin Dev* 14 (2019) 134–147.
74. S. Pillay, J.E. Carette, Host determinants of adeno-associated viral vector entry, *Curr Opin Virol* 24 (2017) 124–131.
75. J.M. Johnston, G. Denning, R. Moot, D. Whitehead, J. Shields, J.M. Le Doux, et al., High-throughput screening identifies compounds that enhance lentiviral transduction, *Gene Ther* 21 (2014) 1008–1020.
76. A.M. Mitchell, R.J. Samulski, Mechanistic insights into the enhancement of adeno-associated virus transduction by proteasome inhibitors, *J Virol* 87 (2013) 13035–13041.
77. N. Bischoff, S. Wimberger, M. Maresca, C. Brakebusch, Improving precise CRISPR genome editing by small molecules: is there a magic potion?, *Cells* 9 (2020) 1318.
78. T. Opacic, V. Paefgen, T. Lammers, F. Kiessling, Status and trends in the development of clinical diagnostic agents, *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 9 (2017).
79. V.C. Pierre, M.J. Allen, P. Caravan, Contrast agents for MRI: 30+ years and where are we going?, *J Biol Inorg Chem* 19 (2014) 127–131.
80. P. Liu, X. Mu, X.-D. Zhang, D. Ming, The near-infrared-II fluorophores and advanced microscopy technologies development and application in bioimaging, *Bioconjug Chem* 31 (2020) 260–275.
81. P.F. Halloran, Immunosuppressive drugs for kidney transplantation, *N Engl J Med* 351 (2004) 2715–2729.
82. T. Kino, H. Hatanaka, M. Hashimoto, M. Nishiyama, T. Goto, M. Okuhara, et al., FK-506, a novel immunosuppressant isolated from a Streptomyces. I. Fermentation, isolation, and physico-chemical and biological characteristics, *J Antibiot (Tokyo)* 40 (1987) 1249–1255.
83. Y. Chen, J. Shi, T.C. Xia, R. Xu, X. He, Y. Xia, Preservation solutions for kidney transplantation: history, advances and mechanisms, *Cell Transplant* 28 (2019) 1472–1489.
84. N. Savage, BioPharm Dealmakers. Tapping into the drug discovery potential of AI, *Nature* Published online May 27 (2021), <https://doi.org/10.1038/d43747-021-00045-7>.
85. D.J. Cummins, M.A. Bell, Integrating everything: the molecule selection toolkit, a system for compound prioritization in drug discovery, *J Med Chem* 59 (2016) 6999–7010.
86. D.C. Blakemore, L. Castro, I. Churcher, D.C. Rees, A.W. Thomas, D.M. Wilson, et al., Organic synthesis provides opportunities to transform drug discovery, *Nat Chem* 10 (2018) 383–394.
87. E.J. Corey, W.T. Wipke, Computer-assisted design of complex organic syntheses, *Science* 166 (1969) 178–192.
88. Y. Shen, J.E. Borowski, M.A. Hardy, R. Sarpong, A.G. Doyle, T. Cernak, Automation and computer-assisted planning for chemical synthesis, *Nat Rev Methods Primers* 1 (2021) 23.
89. C.M. Williams, M.A. Dallaston, The future of retrosynthesis and synthetic planning: algorithmic, humanistic or the interplay?, *Aust J Chem* 74 (2021) 291–326.
90. S. Genheden, A. Thakkar, V. Chadimová, J.-L. Reymond, O. Engkvist, E. Bjerrum, AiZynthFinder: a fast, robust and flexible open-source software for retrosynthetic planning, *J Cheminform* 12 (2020) 70.
91. A.F. de Almeida, R. Moreira, T. Rodrigues, Synthetic organic chemistry driven by artificial intelligence, *Nat Rev Chem* 3 (2019) 589–604.
92. B. Mikulak-Klucznik, P. Gołębiewska, A.A. Bayly, O. Popik, T. Klucznik, S. Szymkuć, et al., Computational planning of the synthesis of complex natural products, *Nature* 588 (2020) 83–88.
93. M.H.S. Segler, M. Preuss, M.P. Waller, Planning chemical syntheses with deep neural networks and symbolic AI, *Nature* 555 (2018) 604–610.
94. Elsevier. Reaxys predictive retrosynthesis. www.elsevier.com/solutions/reaxys/predictive-retrosynthesis [accessed February 17, 2022].
95. American Chemical Society. Retrosynthetic analysis and synthesis planning in SciFinder[®]. www.cas.org/solutions/cas-scifinder-discovery-platform/cas-scifinder/retrosynthesis-planning [accessed February 17, 2022].
96. Massachusetts Institute of Technology. ASKCOS: software tools for organic synthesis. <https://askcos.mit.edu/> [accessed February 17, 2022].
97. T.J. Struble, J.C. Alvarez, S.P. Brown, M. Chytil, J. Cisar, R.L. Desjarlais, et al., Current and future roles of artificial intelligence in medicinal chemistry synthesis, *J Med Chem* 63 (2020) 8667–8682.
98. C.W. Coley, W. Jin, L. Rogers, T.F. Jamison, T.S. Jaakkola, W.H. Green, et al., A graph-convolutional neural network model for the prediction of chemical reactivity, *Chem Sci* 10 (2019) 370–377.
99. L. David, A. Thakkar, R. Mercado, O. Engkvist, Molecular representations in AI-driven drug discovery: a review and practical guide, *J Cheminform* 12 (2020) 56.
100. A. Cadeddu, E.K. Wylie, J. Jurczak, M. Wampler-Doty, B.A. Grzybowski, Organic chemistry as a language and the implications of chemical linguistics for structural and retrosynthetic analyses, *Angew Chem Int Ed* 53 (2014) 8108–8112.
101. K. Lin, Y. Xu, J. Pei, L. Lai, Automatic retrosynthetic route planning using template-free models, *Chem Sci* 11 (2020) 3355–3364.
102. P. Schwaller, T. Gaudin, D. Lányi, C. Bekas, T. Laino, 'Found in Translation': predicting outcomes of complex organic chemistry reactions using neural sequence-to-sequence models, *Chem Sci* 9 (2018) 6091–6098.
103. E.M. Gale, D.J. Durand, Improving reaction prediction, *Nat Chem* 12 (2020) 509–510.
104. J.P. Hughes, S. Rees, S.B. Kalindjian, K.L. Philpott, Principles of early drug discovery, *Br J Pharmacol* 162 (2011) 1239–1249.
105. P. Schneider, W.P. Walters, A.T. Plowright, N. Sieroka, J. Listgarten, R.A. Goodnow, et al., Rethinking drug design in the artificial intelligence era, *Nat Rev Drug Discov* 19 (2020) 353–364.
106. A.H. Göller, L. Kuhnke, F. Montanari, A. Bonin, S. Schneckener, A. ter Laak, et al., Bayer's in silico ADMET platform: a journey of machine learning over the past two decades, *Drug Discov Today* 25 (2020) 1702–1709.
107. C.A. Nicolaou, N. Brown, Multi-objective optimization methods in drug design, *Drug Discov Today: Technol* 10 (2013) e427–e435.

108. M. Follmann, H. Briem, A. Steinmeyer, A. Hillisch, M.H. Schmitt, H. Haning, et al., An approach towards enhancement of a screening library: the next generation library initiative (NGLI) at Bayer — against all odds?, *Drug Discov Today* 24 (2019) 668–672.
109. R.S. Bohacek, C. McMartin, W.C. Guida, The art and practice of structure-based drug design: A molecular modeling perspective, *Med Res Rev* 16 (1996) 3–50.
110. T. Hoffmann, M. Gastreich, The next level in chemical space navigation: going far beyond enumerable compound libraries, *Drug Discov Today* 24 (2019) 1148–1156.
111. Enamine. Real Space, <https://enamine.net/compound-collections/real-compounds/real-space-navigator> [accessed February 17, 2022].
112. WuXi AppTec. Virtual library. https://wuxi-rsd.com/FTE_Chemistry_Services/Virtual_Library [accessed February 17, 2022].
113. W.P. Walters, Virtual chemical libraries, *J Med Chem* 62 (2019) 1116–1124.
114. K. McCloskey, E.A. Sigel, S. Kearnes, L. Xue, X. Tian, D. Moccia, et al., Machine learning on DNA-encoded libraries: a new paradigm for hit finding, *J Med Chem* 63 (2020) 8857–8866.
115. V.D. Mouchlis, A. Afantitis, A. Serra, M. Fratello, A.G. Papadiamantis, V. Aidinis, et al., Advances in de novo drug design: from conventional to machine learning methods, *Int J Mol Sci* 22 (2021) 1676.
116. R. Gupta, D. Srivastava, M. Sahu, S. Tiwari, R.K. Ambasta, P. Kumar, Artificial intelligence to deep learning: machine intelligence approach for drug discovery, *Mol Divers* 25 (2021) 1315–1360.
117. R. Abel, L. Wang, E.D. Harder, B.J. Berne, R.A. Friesner, Advancing drug discovery through enhanced free energy calculations, *Acc Chem Res* 50 (2017) 1625–1632.
118. D. Clark, Charles River Laboratories. Eureka a dose of science. Free energy calculations in drug discovery. www.criver.com/eureka/free-energy-calculations-in-drug-discovery [accessed February 17, 2022].
119. D.H. Freedman, Hunting for new drugs with AI, *Nature* 576 (2019) S49–S53.
120. D.V.S. Green, S. Pickett, C. Luscombe, S. Senger, D. Marcus, J. Meslamani, et al., BRADSHAW: a system for automated molecular design, *J Comput Aided Mol Des* 34 (2020) 747–765.
121. K. Parkins, Verdict Media Limited. Clinical trials arena. Exscientia's third AI-discovered molecule to enter trials. www.clinicaltrialsarena.com/news/exscientias-third-ai-discovered-molecule-to-enter-trials/ [accessed February 17, 2022].
122. CDC/National Center for Health Statistics/Division of Analysis and Epidemiology. Health, United States, 2019 – Data Finder. www.cdc.gov/nchs/hus/contents2019.htm#Table-004 [accessed February 17, 2022].
123. Pharmaphorum Media Limited. A history of the pharmaceutical industry. https://pharmaphorum.com/r-d/a_history_of_the_pharmaceutical_industry/ [accessed February 17, 2022].
124. R.M. Baum, C&EN Global Enterprise. Policy. Top pharmaceuticals. <https://cen.acs.org/articles/83/i25/Top-Pharmaceuticals.html?PageSpeed=noscript> [accessed February 17, 2022].
125. J.E. Dalen, J.S. Alpert, R.J. Goldberg, R.S. Weinstein, The epidemic of the 20(th) century: coronary heart disease, *Am J Med* 127 (2014) 807–812.
126. T.J. Wilt, H.E. Bloomfield, R. MacDonald, D. Nelson, I. Rutks, M. Ho, et al., Effectiveness of statin therapy in adults with coronary heart disease, *Arch Intern Med* 164 (2004) 1427–1436.
127. I. Pinal-Fernandez, M. Casal-Dominguez, A.L. Mammen, Statins: pros and cons, *Med Clin (Barc)* 150 (2018) 398–402.
128. UKEssays. Blockbuster drugs in the pharmaceutical industry. <https://www.ukessays.com/essays/business/blockbuster-drugs-pharmaceutical-3063.php> [accessed February 17, 2022].
129. N. Stadhouders, F. Kruse, M. Tanke, X. Koolman, P. Jeurissen, Effective healthcare cost-containment policies: A systematic review, *Health Policy* 123 (2019) 71–79.
130. R. Evens, K. Kaitin, The evolution of biotechnology and its impact on health care, *Health Aff (Millwood)* 34 (2015) 210–219.
131. A. Roy, Forbes. Biologic medicines: the biggest driver of rising drug prices. <https://www.forbes.com/sites/theapothecary/2019/03/08/biologic-medicines-the-biggest-driver-of-rising-drug-prices/?sh=24ddcc0018b0> [accessed February 17, 2022].
132. F.D. Makurvet, Biologics vs. small molecules: drug costs and patient access, *Med Drug Discov* 9 (2021).
133. M. Herper, Forbes. Patient advocate says Novartis' \$475,000 breakthrough should cost just \$160,000. www.forbes.com/sites/matthewherper/2018/02/08/patient-advocate-says-novartis-475000-breakthrough-should-cost-just-160000/?sh=35a0b4245152 [accessed February 17, 2022].
134. J. Cohen, Forbes. At over \$2 million Zolgensma is the world's most expensive therapy, yet relatively cost-effective. www.forbes.com/sites/joshuacohen/2019/06/05/at-over-2-million-zolgensma-is-the-worlds-most-expensive-therapy-yet-relatively-cost-effective/?sh=2c71377045f5 [accessed February 17, 2022].
135. ICER. Institute for Clinical and Economical Review. Update. A look at spinraza and zolgensma for spinal muscular atrophy. https://icer.org/wp-content/uploads/2020/10/SMA-RAAG_060519.pdf [accessed February 17, 2022].
136. G. Hampson, A. Towse, S.D. Pearson, W.B. Dreitlein, C. Henshall, Gene therapy: evidence, value and affordability in the US health care system, *J Comp Eff Res* 7 (2018) 15–28.
137. A. Abbott, Dementia: a problem for our age, *Nature* 475 (2011) S2–S4.
138. J. Cummings, G. Lee, K. Zhong, J. Fonseca, K. Taghva, Alzheimer's disease drug development pipeline: 2021, *Alzheimer's Dement Transl Res Clin Interv* 7 (2021).