

# Artificial intelligence makes a splash in small-molecule drug discovery

Companies applying artificial intelligence tools in small-molecule drug discovery have recently attracted substantial financing and a multitude of large pharma partners.

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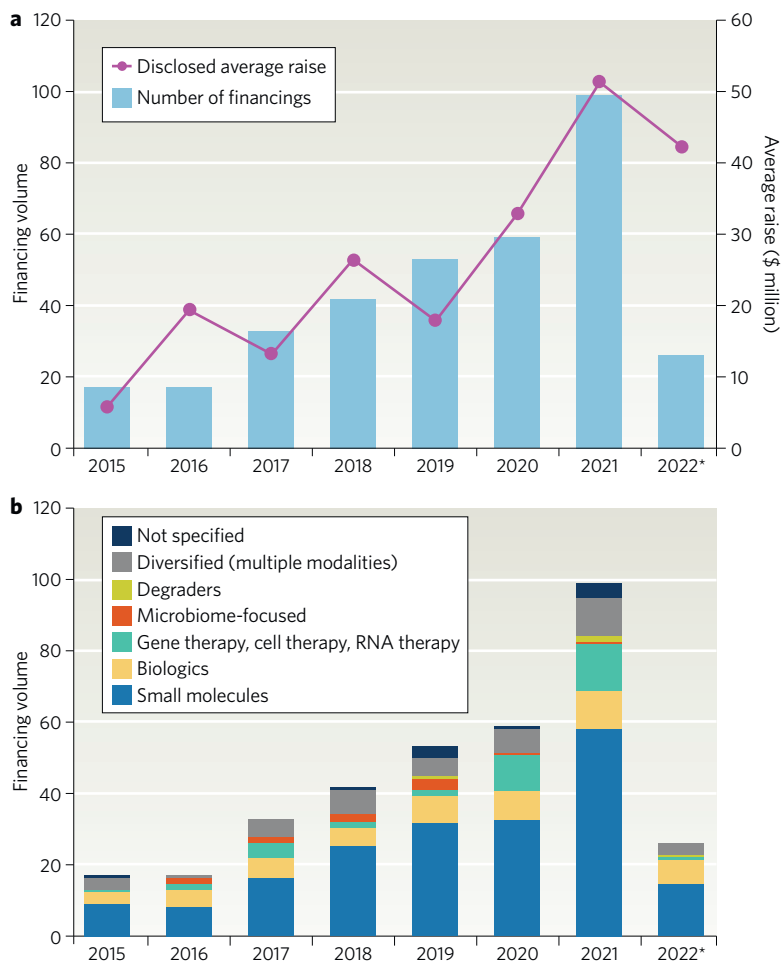
In the past five years, interest in applying artificial intelligence (AI) approaches in drug research and development (R&D) has surged. Driven by the expectation of accelerated timelines, reduced costs and the potential to reveal hidden insights from vast datasets, more than 150 companies with a focus on AI have raised funding in this period, based on an analysis of the field by Back Bay Life Science Advisors (Fig. 1a). And the number of financings and average amount raised soared in 2021.

At the forefront of this field are companies harnessing AI approaches such as machine learning (ML) in small-molecule drug discovery, which account for the majority of financings backed by venture capital (VC) in recent years (Fig. 1b), as well as some initial public offerings (IPOs) for pioneers in the area (Table 1). Such companies have also attracted large pharma companies to establish multiple high-value partnerships (Table 2), and the first AI-based small-molecule drug candidates are now in clinical trials (*Nat. Rev. Drug Discov.* 21, 175–176; 2022). These pioneering AI-focused companies are the focus of this article, which highlights some of the trends in the field based on recent major company financings and deals.

## Spectrum of strategies

The spectrum of approaches for the application of AI in small-molecule drug discovery can be illustrated by a selection of companies that have raised substantial funding (Table 1) and/or signed major deals with large pharma companies (Table 2) in the past two years. Some of these companies are mainly focused on a particular stage of the drug discovery pipeline, such as target identification or compound screening, while others are aiming to establish end-to-end platforms in which AI tools are at the core in each step.

One of the companies using AI for drug target identification is BenevolentAI, which agreed to go public at a €1.5 billion valuation in Amsterdam through what was billed as Europe's largest ever special purpose acquisition company (SPAC) deal in December 2021 (Table 1). BenevolentAI's approach is based on a knowledge graph that integrates a wide range of publicly available biomedical and chemical data with in-house data, which can be mined with AI tools to generate target hypotheses. For example, the company has been collaborating with AstraZeneca since 2019 on target identification for chronic kidney disease and idiopathic pulmonary fibrosis, and expanded the partnership to include heart failure and systemic lupus erythematosus in January 2022.



**Fig. 1 | Recent financings for companies engaged in AI/ML-enabled drug discovery and development. a** | Venture-capital-backed private financings with disclosed raises for companies from seed stage to series D. **b** | Financing by disclosed modality when specified; biologics includes peptides, vaccines, antibodies, bispecific molecules and medium-sized macrocycles. Analysis provided by Mavra Nasir, Peter Bak and Ron Thompson at Back Bay Life Science Advisors based on data sourced from Pitchbook on 170 companies categorized as working in drug discovery and development, for the period from 1 January 2015 through to 17 March 2022. \*Data for 2022 are partial. AI, artificial intelligence; ML, machine learning.

**Table 1 | Select recent financings for companies engaged in AI-based small-molecule drug discovery**

Date	Company	Headline
July 2020	Relay Therapeutics	Relay raises \$460 million in an IPO
August 2020	Atomwise	Atomwise raises \$123 million in a series B financing round co-led by B Capital Group and Sanabil
March 2021	Valo Health	Valo Health closes its series B financing round at \$300 million, including a \$110 million investment from Koch Disruptive Technologies
March 2021	Insitro	Insitro raises \$400 million in a series C financing round led by Canada Pension Plan Investment Board
April 2021	Recursion	Recursion raises \$436 million in an IPO
June 2021	Insilico Medicine	Insilico Medicine raises \$225 million in a series C financing round led by Warburg Pincus
August 2021	XTalPi	XTalPi raises \$400 million in a series D financing round co-led by OrbiMed Healthcare Fund Management and HOPU Investments
October 2021	Exscientia	Exscientia raises \$510 million from a \$350 million IPO and a concurrent \$160 million private placement led by SoftBank
December 2021	BenevolentAI	BenevolentAI announces it will merge with Amsterdam-listed Odyssey Acquisition in a deal that is expected to raise around €390 million

AI, artificial intelligence; IPO, initial public offering. Source: company websites; financings are from 1 July 2020 to 1 March 2022.

A second company that has recently established a major pharma collaboration based on novel target identification is Verge Genomics. In July 2021, Eli Lilly signed a deal potentially worth more than \$700 million with Verge focused on identifying targets for amyotrophic lateral sclerosis (ALS) using Verge's AI-enabled platform, which is based on a proprietary collection of patient brain transcriptomes across multiple neurodegenerative diseases.

There are high hopes that AI-derived insights might provide a starting point for therapeutic breakthroughs for neurodegenerative diseases such as ALS, which have seen little medical progress in decades and many clinical trial failures. The AI-driven platform company Insitro is also working on the identification of novel targets for ALS with its partner Bristol Myers Squibb, with which it agreed a deal potentially worth more than \$2 billion in October 2020 (Table 2). Insitro has raised substantial financing in the past two years too, with a \$400 million series C round in March 2021 following shortly after a \$143 million series B round in May 2020.

Insitro was founded in 2018 around a strategy to address one of the key challenges in the application of ML approaches for drug discovery: the quality of the data being analysed by the ML tools (*Nat. Rev. Drug Discov.* **18**, 576–577; 2019). Public datasets can be highly heterogeneous, as well as polluted with erroneous or mislabeled data, and Insitro is generating its own high-quality biological datasets from cellular disease models at high throughput.

Recursion Pharmaceuticals, founded in 2013, is another company with a strong focus on generating bespoke high-quality data from cellular models and applying ML to gain insights that may not be obvious to human experts—for example, by using image-based profiling of cellular disease models treated with a library of potential drug leads (*Nat. Rev. Drug Discov.* **18**, 653–655; 2019). In one of the biggest deals in the field so far in December 2021, with a potential value of \$12 billion, Recursion agreed to collaborate with Genentech and Roche to use its AI-guided high-content screening platform to identify novel targets and medicines for up to 40 research programs in neuroscience and oncology (Table 2). This came just a few months after Recursion raised \$436 million in an upsized IPO in April 2021 (Table 1).

Exscientia, a pioneer in applying AI to small-molecule drug design, had a hefty IPO in 2021 as well, raising \$510 million in October from a \$350 million IPO and a \$160 million concurrent private placement led by Softbank (Table 1). This followed on

the heels of a \$100 million series C round in March 2021 and a \$225 million series D round in April 2021 led by Softbank Vision Fund 2, with the potential to access a further \$300 million at Exscientia's discretion. The company has raised substantial funding through deals too. In May 2021, it signed a potential \$1.2 billion deal with Bristol Myers Squibb to discover small-molecule drug candidates in areas including oncology and immunology, followed by a potential \$5.2 billion deal with Sanofi in January 2022 focused on oncology and immunology, with the two deals together bringing in a total of \$150 million in upfront payments (Table 2).

### Towards the clinic

The AI strategy being applied by Exscientia, in which vast virtual libraries of small molecules are computationally analysed based on various characteristics such as predicted specificity for particular drug targets in order to identify a small subset to test in lab experiments, has recently led to multiple drug candidates entering clinical trials.

Exscientia was among the first companies to report the entry of an AI-generated small-molecule drug candidate into the clinic. In January 2020, the company announced that DSP-1181, a long-acting serotonin 5-HT<sub>1A</sub> receptor agonist that is intended to treat obsessive-compulsive disorder, had been progressed into a phase 1 trial by its collaborator Sumitomo Dainippon Pharma. Exscientia reported a rapid timeline for the exploratory research phase—less than 12 months compared to a historical benchmark of around 4.5 years for these steps.

Insilico Medicine, which raised \$225 million in a series C financing round in June 2021 (Table 1), is another company that has recently reported speedy timelines for AI-enabled preclinical research. In February 2022, Insilico announced the initiation of a phase 1 trial of the small-molecule inhibitor ISM001-055, a drug candidate for idiopathic pulmonary fibrosis. The company highlighted the role of its end-to-end platform, with both the undisclosed target and the drug candidate being identified by using its AI tools, leading to a total time of less than 30 months from the initiation of target discovery through to initiation of the phase 1 trial. A deal that Insilico signed with Fosun Pharma in January 2022 focused on immuno-oncology (Table 2) also quickly led in February to the nomination of the preclinical drug candidate ISM004-1057D, which is a potential first-in-class small-molecule inhibitor of the enzyme QPCTL, a regulator of the CD47–SIRPα pathway.

**Table 2 | Select recent AI-based small-molecule drug discovery partnerships with disclosed terms**

Date	Licensor	Licensee	Deal summary
September 2020	Recursion	Bayer	Recursion and Bayer establish collaboration to discover small-molecule drug candidates for fibrotic diseases by using Recursion's AI-guided screening platform and Bayer's small-molecule compound library. Recursion will receive an upfront payment of \$30 million, as well as a \$50 million equity investment as part of Recursion's series D financing round, and is eligible for potential milestone payments of \$100 million per program for more than 10 programs.
October 2020	Insitro	Bristol Myers Squibb	Insitro partners with Bristol Myers Squibb to use its AI-supported screening platform in the identification of novel targets and candidate drugs for amyotrophic lateral sclerosis and frontotemporal dementia. Insitro will receive an upfront payment of \$50 million and is eligible for more than \$2 billion in potential milestone payments.
November 2020	Schrödinger	Bristol Myers Squibb	Schrödinger announces a collaboration with Bristol Myers Squibb that will use Schrödinger's physics-based computational drug discovery capabilities to identify small-molecule drugs for targets in oncology, immunology and neurological disorders. Schrödinger will receive \$55 million upfront and is eligible for up to \$2.7 billion in potential milestone payments.
December 2020	Relay Therapeutics	Genentech	Relay signs deal with Genentech to partner on the development of RLY-1971, an inhibitor of SHP2 identified using Relay's platform, which harnesses AI to analyse protein dynamics. Genentech will pay \$75 million upfront and up to \$720 million in potential milestone payments, and will take responsibility for the clinical development of RLY-1971, including with Genentech's investigational KRAS inhibitor GDC-6036.
May 2021	Exscientia	Bristol Myers Squibb	Exscientia enters collaboration with Bristol Myers Squibb to discover small-molecule drug candidates in therapeutic areas including oncology and immunology. Bristol Myers Squibb will provide up to \$50 million in upfront funding, and potential milestone payments could take the total value of the deal to more than \$1.2 billion.
July 2021	Verge Genomics	Eli Lilly	Verge Genomics partners with Lilly to discover novel therapies for amyotrophic lateral sclerosis using its AI-driven platform. Verge will receive up to \$25 million in upfront, equity investment and potential near-term payments, and is eligible for up to \$694 million in additional milestone payments.
December 2021	Recursion	Genentech/Roche	Recursion collaborates with Roche and Genentech to use Recursion's AI-guided high-content screening platform to identify novel targets and medicines in key areas of neuroscience, as well as an oncology indication. Recursion will receive an upfront payment of \$150 million and potential milestone payments of \$300 million each for up to 40 research programs.
January 2022	Insilico Medicine	Fosun Pharma	Insilico Medicine enters collaboration with Fosun Pharma to work on four undisclosed disease targets, and Fosun will also co-develop Insilico's QPCTL inhibitor program in immuno-oncology. The deal includes an upfront payment of \$13 million to Insilico Medicine, as well as an undisclosed equity investment and potential milestones.
January 2022	Exscientia	Sanofi	Sanofi partners with Exscientia to develop up to 15 drug candidates in oncology and immunology using Exscientia's AI-based personalized medicine platform. Exscientia will receive an upfront payment of \$100 million and potential milestone payments worth up to a total of \$5.2 billion.

AI, artificial intelligence. Source: company websites; deals are from 1 July 2020 to 1 March 2022.

Candidates being developed by companies that are applying AI tools in concert with other computational screening approaches are also advancing in the clinic. Relay Therapeutics, which has a focus on identifying drug candidates based on insights into protein dynamics, raised \$460 million through an IPO in July 2020 (Table 1). Its SHP2 inhibitor RLY-1971, which is being developed in partnership with Genentech through a deal signed in December 2020 (Table 2), is in phase 1 trials for cancer.

A recent analysis of AI-focused companies (*Nat. Rev. Drug Discov.* **21**, 175–176; 2022) noted that signs of the impact of AI

in small-molecule drug discovery so far are typically related to greater efficiency and accelerated timelines in early-stage research, with some examples of drug candidates with novel chemical structures for major targets or that target novel biology. As the pool of these drug candidates grows and they progress through the clinic in the next few years, it will become clear how well AI could fulfil its wider promise to increase clinical success rates and reduce drug R&D costs.

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