Machine learning in drug development

Efficiency welcomed in a competitive market

Edison themes

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Biotech buzzwords do not come much bigger than those of artificial intelligence (AI) and machine learning (ML). With the promise of expediting routes to market and reducing costs, such platforms may very well find themselves cemented as critical components in future drug development toolboxes. The application of ML approaches in the pharma industry has now matured to a stage where the first purely ML generated candidates have entered clinical trials. However, we are still a way off from using solely ML to uncover completely new disease mechanisms of action or targets, which many would consider as the holy grail of applications. Leading the charge towards this ambition are focused biotechs leveraging ML that are not only applying their platforms to bolster internal pipelines but striking deals with big pharma, which are likely to be the main clients, utilising ML to boost their own portfolios.

Advancements in machine learning continue to rely on highly focused and specialised technology developed by small and nimble biotech companies. Mechanisms will continue to evolve and fuel advancements in targeted treatments and therapies with more broad-based offerings within large pharma portfolios.

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Companies mentioned in this report (Edison clients in bold)

Exscientia (EXAI: NASDAQ)
e-therapeutics (ETX: LSE)
Bristol Myers Squibb (BMY: NYSE)
IRLAB Therapeutics (IRLABA: Nasdaq Stockholm)
Merck (MRK: XETRA)
Recursion Pharmaceuticals (RXRX: NASDAQ)
Relay Therapeutics (RLAY: NASDAQ)
Sanofi (SNY: NASDAQ)

A climate fuelling the need for efficiencies

The pharma industry continues to evolve and, based on current macro pressures, we are likely to see different approaches to increase efficiency and expedite drug discovery. In our view, these efficiencies will be partly driven by an increased focus on ML technology, finding applications from the discovery through to clinical trial stages of development. Albeit still in their relative infancy, ML platforms and technology applications aim to improve complex drug development by scouring vast pharmaceutical datasets to identify trends or patterns that facilitate decision-making. Due to current funding challenges, methods that claim to de-risk drug candidate selection and reduce time to market are likely to gain heightened interest. It is not just technologies that are modernising either. In efforts to minimise animal testing, regulators are beginning to support the use of new methods to validate drugs before they enter the clinic, marked by the recent passing of the FDA Modernization Act 2.0. Change may not come quickly; however, the passing of the act will certainly help promote the use of alternative approaches that, in time, may predict drug safety and efficacy with even greater accuracy and cost efficiencies.

Building trust to support adoption will be key

On the face of it, the concept of harnessing big data to improve drug development efficiency seems like a no brainer. However, to truly disrupt the industry, awareness will need to be raised to drive change away from historically manual processes and more traditional mindsets that believe nothing can truly trump the knowledge of a medicinal chemist with 30 years' experience under their belt. Additionally, drug development failures are estimated to cost as much as c $700m, with failure rates of c 90%; if ML technologies produce results, it would certainly promote their usage. While the approval of drugs stemming from ML might seem in the distant future, we believe credibility and success in the more immediate term will be based on those platforms that bring drugs into clinical trials or that unveil new disease targets. Not only would this help support the wider adoption of such nascent technologies, but it would provide both big pharma and investors alike with opportunities to get in on the ground floor, before ML starts realising its potential of accelerating development and delivering clinical successes.

From concept to clinic, and big pharma are watching

Before we jump in to discuss ML and its place in drug development, an important point to clarify from the offset is what we mean by ML and AI? While ML and AI are closely related, with the terms often being used interchangeably, they are not quite the same. AI is a more holistic concept that refers to the creation of intelligent machines that simulate human thinking and behaviors. ML can be thought of as a subset of AI, which allows a machine to take datasets, learn from them using statistics to identify patterns and then apply those learnings to solve a problem and make predictions, with minimal human intervention. In the context of drug development, one problem that an ML platform might be asked is: based upon what you, the computer, knows about (ie the properties of) these 10,000 drug molecules, can you predict a new type of molecule that is going to bind most effectively to the disease target of interest?

This illustrates just why the application of ML in drug development is starting to generate quite considerable interest in the industry. Rather than pour resourcing into a medicinal chemistry workforce to make and then test thousands of new compounds to see which works best, companies may be able to use ML to get to the same, or even a better, answer more quickly. However, at this stage, it is important for expectations to be tapered somewhat as we are not currently at the point where we can push a button on a machine and out pops a fully polished candidate drug ready for the clinic. That being said, we are at a point where ML is more than simply an idea, as it has now been used to deliver therapeutic candidates deemed suitable for clinical trials, something that has caught the eye of big pharma, as illustrated in Exhibit 1.

Exhibit 1: Selected pharma partnerships with biotech that own proprietary ML drug discovery platforms

Selected companies leveraging ML	AstraZeneca	Bayer	Bristol-Myers Squibb	charles river	GSK	Lilly	IPSEN	MERCK	novo nordisk	Pfizer	Roche Genentech	SANOFI
Exscientia			■									■
Recursion pharmaceuticals		■									■	
Insitro			■									
Schrödinger			■									
Relay therapeutics											■	
Verge genomics						■						
e-therapeutics								■	■			
Nimbus therapeutics						■						
Benevolent AI	■											
BERG	■											
C4XD	■											■
IRLAB Therapeutics							■					
Insilico Medicine												■
Valo Health				■								
CytoReason								■		■		■
PathAI					■							

Source: Edison Investment Research. Note: Edison clients in bold.

A spotlight on biotechs

Exscientia led the way with the initiation of what was thought to be the world's first clinical study to investigate a purely AI designed drug (DSP-1181) in January 2020, closely followed by the world's second in April 2021 (EXS21546) and third in May 2021 (DSP-0038). Subsequently, the company announced high-profile collaborations with both Bristol Myers Squibb (BMS) and Sanofi, which are utilizing Exscientia's platform in multiple early stage discovery programs.

In line with our previous industry reports, we believe big pharma will look to tap into various domains of expertise housed across ML-focused biotechs, forging partnerships and deals even at the early stages of development. Such collaborations have included those of Merck and Novo Nordisk with Edison's client e-therapeutics. The pharma giants partnered with the company to use its computational biological platform and network-driven drug discovery approach to discover novel small molecules and identify therapeutic targets, which e-therapeutics has also delivered for smaller biopharma partners Galapagos and iTeos, across a variety of therapeutic areas.

Having developed a proprietary, liver targeting RNAi interference (RNAi) platform over the last two years, e-therapeutics has moved away from small molecules. This has further developed its proven computational expertise by focussing on one cell type in the liver – hepatocytes. The strategy of understanding biology as a first principle and doing so in hepatocytes enables e-therapeutics to train its deep learning algorithms and functional tools on comprehensive hepatocyte-specific data resources. This potentially provides more accurate disease/ biological process modelling, novel target identification and the ability to predict the behaviours of potential targets, as opposed to computational platforms applied to broader or more systemic disease approaches.

In addition to disease biology modelling, the company also apply artificial intelligence to expedite the design and production of novel RNAi therapies. RNAi based therapeutics are a rapidly evolving commercial-stage category of new drugs showing much promise as treatments for disease pathways and targets previously considered 'undruggable' through conventional small molecule medicines. Unlike small molecules, which target disease associated proteins, RNAi products aim to stop the production of these proteins altogether by targeting the root cause of the problem, that is the expression of the underlying genes that make them, much like targeting the roots of a weed. Such treatments have already been clinically validated, with the FDA having, to date, approved five RNAi therapies. With a platform that puts the identification of novel gene targets associated with hepatocyte disease biology at the forefront and a focus on discovering and bringing next-generation RNAi medicines into the clinic, e-therapeutics is well-positioned to create value from its platforms and differentiate it in the market, in our view.

Edison's client IRLAB Therapeutics is also leveraging ML, with its Integrative Screening Process (ISP) research platform sitting at the heart of the company's drug discovery efforts. The ISP platform is a database containing a wealth of biological, chemical and safety data of almost 1,400 central nervous system (CNS) drug-like compounds from known drug classes developed over 25 years. By drawing comparisons between these compound datasets, the machine learning tool is designed to guide and expedite the design of future drug candidates at an earlier stage. Importantly, this has translated into clinical-stage candidates and, since 2000, IRLAB has leveraged the ISP platform to progress eight drug candidates into clinical studies. Today, the company's pipeline consists of two-Phase II clinical assets, one of which (mesdopetam) has been out-licensed to Ipsen, and IRLAB expects a further two to enter the clinic in 2023.

In our recent overview of the coming year, we anticipate that large-cap pharma companies holding relatively large cash positions set 2023 up to potentially be a busy period for biotech deal activity. We believe that the focus may not solely be on pure drug development companies, but also on biotech companies fostering advanced ML capabilities aimed at expediting a drug's route to market.

The proof will be in the pudding

For a layperson, differentiating between ML platforms is challenging, with only a handful of people – often the designers – truly understanding the inner workings and nuances between one algorithm and another. However, we believe there are a few, perhaps easier, concepts to consider when weighing up the maturity of today's, and future, ML technologies:

- How is the ML biotech progressing with partnerships?
- Has the platform delivered clinical candidates? If the answer to this is yes,
  - How has the drug been discovered – has ML been used to develop it from scratch?
  - What is the drug target in the clinical program – is it well established or new?
  - How different is the drug candidate from known, marketed products?

This simplified checklist should provide readers with a handrail to assess how effectively individual companies are deploying ML to develop drugs.

Exscientia has set the clinical pace

Exscientia, a Nasdaq-listed, AI-driven biotech, is arguably one of the companies furthest ahead in the application of ML for drug design. However, while it has provided a critical proof of concept for the application of ML, the clinical programs that were initiated may not be particularly ground-breaking.

Firstly, the three candidates that the company's platform has produced (EXS21546, DSP-1181 and DSP-0038) are all, structurally, very similar to already well-known drug scaffolds. They are by no means completely new families of drug molecules or so novel in the chemical space that a traditional discovery team would not have considered making them against the desired targets. Secondly, the targets themselves in each program are all very well established and clinically validated disease targets, so again nothing completely new or that has not been thought of before. DSP-1181 and DSP-0038 (partnered for development with Sumitomo Pharma) both target serotonin receptors (5-HT), an area of the market that is awash with genericized 'me-too' drugs, while EXS21546 is an Adenosine 2a (A2a) antagonist, which has already been recognized as a potential target in immunoncology and is a well-known target in other disease areas. Additionally, the development of DSP-1181 has been discontinued; the news that the world's first pure AI-derived drug candidate no longer forms part of Sumitomo's pipeline was not widely publicized. This goes to show that even the use of innovative ML technology does not necessarily guarantee success.

While we are by no means diminishing Exscientia's platform – bringing the first AI-designed drug into the clinic is a major achievement – we highlight that there are existing limitations with today's technologies, even those considered to be front-runners. Although the company's platform may not, to date, have identified new clinical targets, it might be considered as a very useful patent-breaking tool for identifying new, patentable molecules in well-established areas of chemical space. Moreover, the similarity of EXS21546 and DSP-0038 to known scaffolds does not necessarily mean they will not be effective drugs; however, we will have to wait for future readouts from these clinical programs to surface before any claims can be made.

ML cannot run before it can walk, but it's getting there

The ultimate achievement for ML's application in drug development would be to have a platform that has the predictive power to provide completely new and accurate insight into human diseases such as, 'there is a 99.9% probability that this target, which has not garnered much attention previously, is the root cause of the disease' or 'if you can figure out how to interrupt this particular cellular pathway then it will have an impact on the disease'. This is not yet possible with current ML technologies, in our view, and if we were to get to such a point it would be truly revolutionary. There

have been significant advancements towards applying ML in the design of new and better drugs from scratch and identifying new disease targets; below we provide examples of how the technology is being applied to produce clinical candidates (Exhibit 2).

Exhibit 2: Selected clinical candidates discovered through ML applications

Company	ML candidates produced	Drug(s)	Clinical programs	Target/s	Indication
Benevolent AI	1	BEN2293	Phase I/II	Trk	Atopic dermatitis
BERG	1	BPM31510 (ubidecarenone)	Phase II	Cellular metabolic stimulator	Glioblastoma
C4X Discovery	1	C4X_3256 (INDV-2000)	Phase I*	OX1	Opioid use disorder
Exscientia	3	EXS21546	Phase I	A2a	High adenosine cancers
		DSP-0038	Phase I (to be initiated)**	5-HT2a/5HT1a	Alzheimer's related psychosis
		DSP-1181**	Phase I (Discontinued)	5-HT1a	Obsessive compulsive disorder
Nimbus Therapeutics	2	NDI-034858 (acquired by Takeda)	Phase II	TYK2	Psoriasis
		NDI 1150-101	Phase I/II	HPK1	Solid tumours
Pharos iBIO	1	PHI 101	Phase I	FLT3	Acute myeloid leukaemia
Recursion Pharmaceuticals	4	REC-3964	Phase I (trial initiated)	C difficile toxin B	Clostridium difficile infection
		REC-4881	Phase II	MEK1/MEK2	Familial adenomatous polyposis
		REC-994	Phase II	SOD mimetic	Cerebral cavernous malformation
		REC-2282	Phase II/III	Multiple HDACs	NF2 mutated meningiomas
Relay Therapeutics	3	RLY-1971	Phase I (Roche)	SHP2	Advanced solid tumours
		RLY-2608	Phase I	PI3Kα	Advanced solid tumours
		RLY-4008	Phase I/II	FGFR2	Advanced solid tumours
Insilico Medicine	1	INS018_055	Phase I	Undisclosed novel target	Idiopathic pulmonary fibrosis (IPF)
Valo Health	2	OPL-0401	Phase II	ROCK 1/2	Diabetic retinopathy
		OPL-0301	Phase II	S1P	Post-myocardial infarction
IRLAB Therapeutics	2	Mesdopetam	Phase II	D3 receptor	Levodopa induced dyskinesia
		Pirepemat	Phase II	5-HT7	Falls in Parkinson's disease

Source: Edison Investment Research. Note: *Collaboration with Indivior. **Jointly developed with Sumitomo Dainippon Pharma.

Relay Therapeutics is using its ML Dynamo platform to analyse the motion of drug targets, potentially uncovering new sites that may be 'druggable' by small molecules and that had not previously been considered. Recursion Pharmaceuticals is also applying ML in a slightly different way: drug repurposing, which uses ML algorithms to predict the potential use of known medications in new indications. This is how Recursion first applied its platform to generate candidates (REC-4881, REC-994 and REC-2282). The company has now expanded beyond repurposing and in September 2022 announced the initiation of a Phase I study, marking the company's first in-house developed drug designed purely by its ML technology (Recursion OS).

However, Insilico Medicine is perhaps one of the furthest along the ML evolutionary path. The private biotech initiated what is thought to be the world's first clinical study in February 2022 to investigate an ML-designed novel molecule for an ML-discovered novel target. This is a hugely significant breakthrough; however, what makes the feat even more impressive is that Insilico was able to accelerate from discovery through preclinical studies to a Phase I trial in idiopathic pulmonary fibrosis (IPF) in just 30 months. Considering the typical industry average for this process ranges between five and six years this is quite a remarkable achievement, in our view. Of further note, the company was able to complete its preclinical studies in under 18 months with a budget of just $2.6m, a fraction of the cost of a typical preclinical program of roughly $430m. This has been enough to attract Sanofi, which entered a strategic research collaboration with Insilico in November 2022, and the positive news flow has continued since. In December 2022 the company announced its second novel AI-designed preclinical candidate, with a novel AI discovered target (DGKA), this time in immunoncology, and in January 2023 it reported positive top-line safety and tolerability results from the Phase I IPF study. A Phase IIa trial is now expected to initiate in early 2023. Insilico's story not only provides the industry with a glimpse into a potential future where ML-aided drug and target discovery is commonplace, but is backed up with hard figures on time and cost savings.

Quris AI is pushing the ML boundaries even further

If Insilico's efforts are not impressive enough, Quris AI is another private biotech that is attempting to take the application of ML to the next level. While the use of ML in discovering new drugs and targets is a major advancement, it does not go quite as far to begin solving the age-old problem of accurately replicating human biology and having complete certainty of whether drugs will be safe when administered to humans. Clinical failure rates still sit at an astonishing 90% even when promising preclinical results are observed. The major issue is that in the preclinical setting there are simply no human relevant models and while animal testing is a necessity, the genetics and physiology of mice, which are heavily used in drug development, are fundamentally different from those of a human.

Quris AI's solution is its 'patients-on-a-chip' platform, which sounds like something out of a science fiction movie. The technology is essentially a miniaturised version of the human body where 'organs' are created from stem cells and interconnected by micro-sized blood-like circulations in a circuit (chip). The idea is that the chip can better replicate the complexity of human physiological processes compared to animals. The patient on a chip is then tested against thousands of drug compounds, responses are observed and the data captured is used to continuously train the ML model so that it can make better predictions about clinical safety. Quris's CEO certainly backs the platform, claiming that it has the potential to reduce clinical failure rates to 50% and generate clinical-stage drug candidates from the captured data and ML algorithms. While this is a bold statement, the technology is not just the stuff of science fiction, as the company is preparing for clinical studies in Fragile X syndrome to investigate the first drug to be developed from its Bio-AI clinical safety prediction platform. Quris's progress has also caught the eyes of some big names, with Merck entering a licensing option agreement in March 2022 and, more recently, AstraZeneca partnering with the company to support its transition from start-up to larger scale. Quris's ambition is to further develop its Bio-AI platform and to expand from clinical safety prediction to efficacy prediction; however, for now, the immediate focus is on safety modelling.

Interest in technologies such as Quris AI's is only set to ramp up, aided by the Biden administration's passing of new legislation (the FDA Modernization Act 2.0) at the end of 2022 that negates the mandatory requirement of animal studies before receipt of FDA approval. The FDA has also been supportive of the development of alternative approaches to drug testing, particularly with 'organ-on-chip' technologies (similar to 'patient-on-chip').

We believe animal testing is likely to still be the norm for quite some time; however, as ML matures and, like Insilico, if companies such as Quris AI can live up to their claims of finally bringing down the 90% failure rates, then a paradigm shift in drug development awaits.

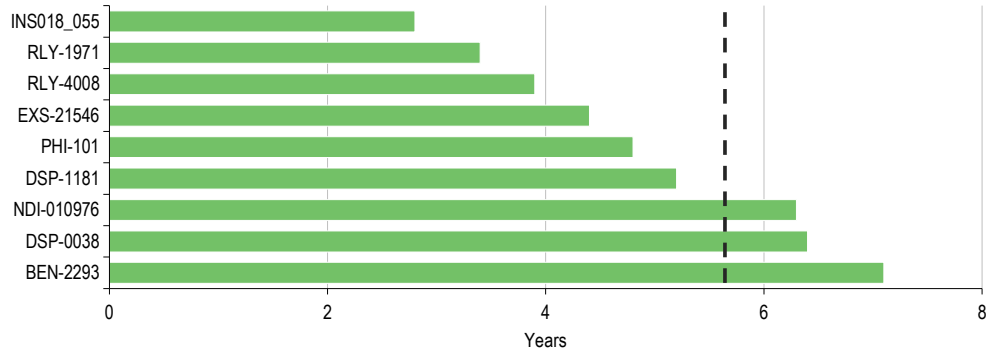
A challenging road but the concept has been proven

As we have continued to caution throughout this report, we have barely moved off the starting line of the ML race and the finish line of an industry with ML fully embedded is a long way off. The pace at which computational power and ML have grown has been frighteningly quick; however, no matter how advanced or smart computers get, they can only be trained on what they are given. It is this concept that has coined the well-known phrase within the data science community of 'garbage in, garbage out'. If the underlying training data that is input into a machine is unreliable, then the predictions it makes are not going to be accurate. With challenges around the ability to access clinical datasets and ensuring that data used to train ML models is of sufficient quality and quantity, pharmaceutical data integrity (discovery and clinical) provides one of the biggest obstacles ML will need to overcome.

A further challenge that may complicate ML is the potential for bias to be incorporated into the design of predictive models. This can stem from a variety of root causes such as the use of imbalanced or misrepresentative training data, the use of data that may have been influenced by human subjectivity or the replication of cognitive biases and human prejudices that cause models to mimic historical inequalities. A notable real-life example found significant racial bias to be embedded within an ML commercial algorithm, widely used in the US healthcare system, to predict the health status of individuals. The algorithm used health costs as a proxy for health needs; however, because of unequal access to care, less money is spent on black patients who have the same level of need as Caucasian patients. The result was an algorithm falsely concluding that black patients were healthier than equally sick Caucasian patients, despite the former patient group having higher disease severity indexes for life threatening conditions such as melanoma. It will be important to understand the strategies that ML biotech developers are taking to mitigate such bias in their platforms. One potential differentiator could be with those companies that have diverse data science teams possessing individuals from a range of backgrounds. Such diverse groups are possibly more likely to draw upon the various experiences of its team members to better spot uncertain hidden biases in clinical datasets that may not be spotted by less diverse teams, helping to develop much more relevant ML platforms.

The complex nature of drug development means that there is never going to be a magic bullet and ML's application in the pharmaceutical industry is undoubtedly going to be met with both successes and setbacks. However, a point we would like to stress is that even though ML technologies are still in the nascent stages, we are already beginning to see signs of the value it can potentially add. Based on an analysis conducted by Boston Consulting Group (BCG) that assessed company patent filings, publications and press releases, an approximate timeline from program start to clinical trials was constructed for five selected biotech companies (Relay Therapeutics, Exscientia, Pharos iBio, Nimbus Therapeutics and Benevolent AI) with ML-enabled clinical programs (Exhibit 3). While we acknowledge that this sample size may not be representative of the entire ML assisted clinical program landscape, considering the maturity of ML, to see examples of development timelines bettering those of the industry average provides encouraging signs for the future.

Exhibit 3: Approximate time from program start to clinical trial initiation of selected ML-enabled programs



Source: Boston Consulting Group (BCG), Nature Reviews Drug Discovery, Meir *et al*. Note: Dotted line represents industry average from target-to-hit until start of clinical trials. Edison Investment Research has also included Insilico's candidate INS018_055.

Clinical failures spark a turn to new technologies

If there is anything that we learned from 2022 it is that drug approvals are not getting any easier. New approvals were down by c 25% from 2021, bringing them to the lowest levels seen since 2016. The FDA's accelerated approval pathway has drawn some sharp criticism in recent times, with claims of drug efficacy being compromised at the expense of early access, and US regulators have

responded by tightening the clinical requirements of drugs taking this route to market. Today, late-stage clinical development (Phase III) sees failure rates sitting at c 40%, following hundreds of millions of dollars and years of investment, and we believe this provides opportunities for new methodologies to disrupt the traditional way in which companies approach drug development. While we may only be at the beginning of the ML life cycle, it has certainly come a long way in a relatively short period of time and, if it continues the same trajectory, we are likely to see more ML candidates enter the clinic followed by new ML determined disease targets, and we anticipate there may ultimately be regulatory approvals of ML-derived drug candidates.

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