

“The better the AI gets, the harder it is to ignore”

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Hong Kong based Insilico Medicine, a pioneer in AI-based drug discovery, has made significant strides in recent years. Two of their candidates have reached clinical trials, with INS018-055 leading the pack as the first AI-discovered drug designed by generative AI to enter phase 2 clinical trials for idiopathic pulmonary fibrosis (IPF). Back in 2014, when the company began, AI for drug discovery was relatively unheard of, but now it's an indispensable part of the drug discovery process. Insilico's partnerships with major pharmaceutical firms like Janssen underscore the growing importance of AI in this field. Dr Alex Zhavoronkov, Founder and CEO of Insilico Medicine, sheds light on the industry's evolving response to AI in drug discovery, partnerships, regulatory reforms etc. and also shares the company's future plans.

Insilico Medicine has garnered attention for its innovative utilisation of artificial intelligence (AI) in drug discovery. Could you provide insights into how the industry's response to AI-based drug discovery has evolved since your inception in 2014?

In the early days, when I presented at conferences on how generative AI technology could be applied to chemistry, there was a lot of scepticism. I had discovered through my research that generative adversarial networks (GANs) combined with deep reinforcement learning (the same AI learning strategy used in AlphaGo) could generate novel molecules that could be used to treat disease. Since that time, AI drug discovery has undergone enormous acceleration, fueled both by advances in AI technology and in massive stores of data. While there are still no AI-designed drugs on the market, there are a number of companies with these drugs in advanced clinical trials, including our own lead drug for idiopathic pulmonary fibrosis, the drug with an AI-discovered target and designed by generative AI now in Phase II trials with patients.

Although the pharma industry has moved cautiously, the inherent risks in drug discovery (99 per cent of the drugs fail in the early discovery phase and 90 per cent of the drugs fail in clinical trials) and the validation of AI developed drugs to reach advanced trials, means that pharma companies are more actively pursuing partnerships and developing their own internal AI programmes. We have major partnerships with Exelixis, Sanofi and Fosun Pharma to develop new therapies, for instance.

Recently, your two candidates INS018_055, ISM8207 have entered phase II and phase I respectively. Can you share the significance of reaching these stages in the drug development process, and what key milestones do you hope to achieve during these trials?

To our knowledge, Insilico's lead drug for IPF – INS018-055 - is the first drug for an AI-discovered target and designed by generative AI to reach Phase 2 clinical trials with patients.

AI was used in every stage of the process. Insilico Medicine used its AI target-discovery engine, <https://insilico.com/pandaomics>, to process large amounts of data – including omics data samples, compounds and biologics, patents, grants, clinical trials, and publications – to discover a new target (called “Target X”) relevant for a broad range of fibrosis indications. We then used this newly discovered target as the basis for the design of a potentially first-in-class novel small molecule inhibitor using its generative AI drug design platform, Chemistry42.

Insilico's molecule – INS018_055 - demonstrated highly promising results in multiple preclinical studies including in vitro biological studies, pharmacokinetic, and safety studies. The compound improved myofibroblast activation, a contributor to the development of fibrosis, with a novel mechanism and was shown to have potential relevance in a broad range of fibrotic indications, not just IPF.

The current phase II study is a randomised, double-blind, placebo-controlled trial to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of 12-week oral INS018_055 dosage in subjects with IPF divided into 4 parallel cohorts. To further evaluate the candidate in wider populations, the company plans to recruit 60 subjects with IPF at about 40 sites in both the US and China.

If our phase IIa study is successful, the drug will then go to phase IIb with a larger cohort. This is also the stage where our primary objective would be to determine whether there is significant response to the drug. The drug will go on to be evaluated in a much larger group of patients – typically hundreds – in phase III studies to confirm safety and effectiveness before it can be approved by the FDA as a new treatment for patients with that condition. We expect to have results from the current phase II trials next year.

Advancing ISM8207 is also significant – both because it is the first clinical milestone reached in our partnership with Fosun, and also because it is the first of our cancer drugs to advance to the clinic, and cancer represents the largest disease category in Insilico's pipeline. This drug is a novel QPCTL inhibitor, designed to treat advanced malignant tumours, and works by blocking the tumour cells' 'don't eat me' signal. We entered into phase I clinical trials to assess the drug's safety in healthy volunteers in July 2023.

You have had quite successful partnerships with Exelixis, Fosun etc. Can you provide insights into Insilico's approach to forming strategic partnerships? How do you approach deal making?

We have the advantage of being able to produce and advance new, high quality small molecules that have been optimised to treat diseases much more quickly than traditional drug discovery methods. That's because our generative AI system can optimise across 30 parameters at once based on desired criteria when generating molecules, rather than the traditional method of screening libraries to find a potential compound, and then working to optimise it for each desired property in a linear fashion. As we speed up the drug discovery process on these high-quality molecules – we now have 31 in our pipeline – we look to find partners who have specific disease expertise and clinical experience to advance these molecules into later

stage clinical studies, and, we hope, to market where they can begin helping patients.

Our most recent partnership with Exelixis is a perfect example. We just announced an exclusive global licence agreement with Exelixis with \$80 million upfront – granting Exelixis the right to develop and commercialise ISM3091, an AI designed cancer drug and potentially best-in-class small molecule inhibitor of USP1 that received IND approval from the FDA in April 2023. This company is expert in cancer and cancer drug development and discovery, and has an expert drug hunting team. Because it's an extremely innovative company, they already have substantial revenue coming from best-in-class cancer therapeutics and they are strengthening this pipeline and making bets on innovative cancer drugs.

If we were to look at one of your AI-designed drugs versus a traditionally designed drug candidate, is there a telltale signature?

Our AI-designed drugs will often have a novel structure or work via a novel mechanism compared to existing drugs. By optimising across these 30 different parameters to design molecules with just the right structure and properties to provide the best likelihood of treatment without toxicity and minimal side effects, we are essentially designing ideal new drug-like molecules from scratch. There may be other drugs that are designed to act on those same targets, but ours are optimised through structure or mechanism to be most efficacious, first-in-class, or best-in-class.

Until recently perhaps, big pharma was somewhat sceptical or resistant to AI. What has been responsible for this growing appetite to embrace AI as a fundamental part of the drug discovery process?

There are a number of reasons pharma is now embracing AI. Traditional drug discovery is an incredibly slow and expensive process that fails in clinical trials 90 per cent of the time. AI improves all three of those roadblocks – improving speed, lowering cost, and optimising molecules to have the greatest likelihood of clinical trial success. Our AI engine known as PandaOmics can sift through trillions of data points quickly to identify new targets for disease that humans might not find. Then, our generative AI Chemistry42 platform can design brand-new molecules that are optimised to interact with those targets without causing adverse effects, scoring them based on which are likely to work the best. Finally, using our InClinico tool, we can predict how these drugs will likely fare in clinical trials to reduce the time and money lost on failed trials.

There is also now significant validation that this method of developing new drugs is producing very high quality new drugs for hard-to-treat diseases and even diseases that were considered “undruggable.” And a number of these AI-designed drugs are now in later stage clinical trials.

Finally, the technology is itself progressing and improving with additional use and data via reinforcement learning and expert human feedback. The better the AI gets, the harder it is to ignore.

How sceptical are regulatory bodies towards AI-driven drug discovery? How are regulations evolving to support such developments?

Data privacy and protection are critical to any businesses utilising AI, as is compliance with all international laws and regulations. I expect that these measures will become more stringent in coming years and they are essential to building and maintaining public trust. Insilico Medicine uses only publicly available data and employs privacy by design and by default. We facilitate security of our systems by thorough security analysis on each phase of development. All Insilico data hubs are contained in Amazon Web Services (AWS) or Microsoft Azure cloud.

In addition, there are several checks and balances in place to ensure continuous data integrity, protection and privacy. For example, clients' data is not used in any internal environments of the platform, and a firewall is separated for the clients' access to the platform versus everyone else's access. All data is encrypted, and data privacy is managed according to Insilico Medicine's privacy policy.

What does the future hold for Insilico over the next few years?

We're eager to see our clinical stage programmes progress, and the continued advancement of our lead drug for IPF. It's a terrible, chronic condition with a very poor prognosis and patients are in desperate need of new treatment options.

I also hope that our latest deal with Exelixis marks a trend of pharma companies partnering earlier in the drug development process with highly optimised AI-designed molecules as we continue to expand our pipeline, so that we can truly accelerate the process of delivering new treatments to patients in need.

We will also continue to expand the capabilities of our end-to-end generative AI platform, through new data, reinforcement learning, and expert human feedback; and augment those capabilities with our AI-powered robotics lab as well as incorporating the latest technological tools into our platform, including AlphaFold and quantum computing – both of which we've published papers on.

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