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Thanks to generative AI we can double Big Pharma's R&D productivity in a very small biotech setting

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Fresh from the news that one of its AI-designed and discovered drug candidates has entered Phase II human clinical trials - the first time that such a project has made it to that development stage - Insilico Medicine's Alex Zhavoronkov sat down with PharmaBoardroom to discuss a range of topics. These included consolidation in the AI-driven drug discovery industry, how the attitudes of Big Pharma and regulatory agencies towards AI have shifted in recent years, and why we are only at the beginning of a potential AI-driven revolution in preclinical drug discovery work.



What has changed for Insilico Medicine since our last conversation three years ago?

We have changed pretty dramatically in the last three years. Prior to 2020, we were an algorithm and software company driven by generative artificial intelligence (AI), but we now have a much stronger focus on drug discovery, thanks in large part to my now co-CEO Dr Feng Ren. I first met Dr Ren in 2020 when he was SVP and head of biology and chemistry at the contract research organization (CRO) Medicilion, a multibillion-dollar company he helped grow and list on the market. Dr Ren has a PhD from Harvard in chemistry, spent 11 years at GSK, and had thousands of people reporting to him in a very important role at Medicilion. However, he wanted to go beyond the traditional CRO service model and do real drug discovery. CROs are usually a few years behind innovative drug companies, only conducting services that are already established.

Dr Ren became an advisor to Insilico in 2020 and in February 2021 joined the firm as our chief scientific officer to help us build a drug R&D team and established our pipeline of therapeutics utilising generative AI. After he joined the company, we transformed beyond recognition. Insilico nominated nine preclinical candidates in 2022 alone, contributing to 14 preclinical candidates in total since Dr Ren joined. Following setting several industry records and advancing the pioneer pipeline into the clinical stage, we promoted Dr Ren to co-CEO.

Now a dominant force at Insilico, Dr Ren and I have become a yin-yang of drug discovery and AI. Most of the companies in our sector without an equal focus on both drug discovery and AI have failed in one of the two fields, which has led to quite significant industry consolidation. In 2020 there were hundreds of companies claiming to do ‘AI drug discovery,’ but there are only perhaps less than ten companies with a tangible offering left.

This industry consolidation led to the rise of Insilico as pharma companies realized the productivity we were able to offer. Big Pharma, utilizing its traditional model of small molecule chemistry and internal R&D can generally generate four or five preclinical candidates in the same amount of time that our AI-driven approach is able to generate nine. This means that thanks to generative AI we can double Big Pharma’s R&D productivity in a very small biotech setting. Generative AI allows us to rapidly discover targets, formulate the shortest path from the target to the patient, and generate chemistry with the right properties from scratch instead of searching for a compound with those said properties.

Insilico now has four clinical stage assets in both Phase I and – in a first for an AI-designed and discovered candidate – Phase II human clinical trials. This is probably the most famous Phase II trial in the world, with a feature on the front page of the Financial Times and was the subject of a lengthy discussion by former FDA commissioner Scott Gottlieb on CNBC, which is very cool and shows the power of generative AI in pharma.

Why is this AI-designed and discovered drug moving into Phase II clinical trials such an important milestone?

This is the first true example of a drug reaching Phase II trials where AI has been used for target discovery, chemistry, and prediction of clinical trial outcomes. The modern concept of AI is actually reasonably new, dating back to around 2014, and goes far beyond the older idea of machine learning. The deep learning revolution a decade ago demonstrated that AI could outperform humans in many tasks, especially image recognition.

However, AI has propagated very slowly in pharma due to the difficulty in bridging the expertise between deep learning and pharmaceutical drug discovery. There are very few people who know deep learning really well and very few who know the entire end-to-end process of drug discovery really well. We were lucky to be born in the age of deep learning and cut our teeth working with many pharmaceutical companies before they acquired armies of AI scientists and went into generative AI in 2016. Our leadership in this category is clear; ask ChatGPT what the top three AI drug discovery companies are, and Insilico will undoubtedly feature. For generative AI-driven drug discovery, our strength is even more profound.

While some of AIDD companies have experienced severe declines and laid off considerable numbers of employees, Insilico is growing rapidly. I would not categorise many of these so-called AIDD companies as true AI companies. There are very few ‘AI biotechs’ like Insilico with their own software on the market which other companies can use and with pipelines developing in the pre-clinical and clinical stages.

Has this candidate been brought all the way to Phase II trials by Insilico alone or is it a program acquired from another company?

This program has been fully developed by Insilico and we have documented every step along the way. We started with target identification, tangibly demonstrating how we discovered the target, then generating small molecules from scratch. Through this synthetic route planning, we completed *in vivo* and *in vitro* studies to nominate two preclinical candidates for kidney fibrosis and for lung fibrosis. We did a Phase 0 study in Australia with eight healthy volunteers because the target is new and to better understand whether we should invest in it, before rolling out a fully-blown Phase I study with 78 healthy volunteers in New Zealand and 43 in China. We are now

running two Phase II arms, with 60 patients in China and 60 in the US.

These timelines are much more expedited than traditional pharmaceutical R&D. How confident are you that the next stages of clinical development are going to be similarly speedy?

While we are able to accelerate preclinical development, it is impossible to accelerate late-stage clinical, development. To use an analogy, we are able to make a better bullet with a higher probability of reaching its target and aim it more precisely, but once it is fired, we cannot make it travel any faster.

At Insilico, we do not promise magic and replacing late-stage preclinical work or human clinical trials is not our aim. However, an AI-driven approach can have an impact on the probability of success. 95-99 percent of candidates that start from a novel target fail and there is 30-40 percent failure rate in late-stage preclinical trials. Good Laboratory Practice (GLP) documents are needed at this stage because usually some toxicity signals show up, meaning that Phase I approval will not be granted. We have been able to speed up the traditional timeframe of this process for novel targets from four years to 18 months. High novelty programs usually come with longer timelines because the assays and chemistry are not available.

Soon after we began achieving some success with our methodology, other companies began claiming to be doing end-to-end discovery using generative AI, but Insilico is the only company that has tangible proof of having done so. We publish research papers at a rate of two per month, which are cited in top academic journals and media publications, and which clearly document how ahead of the field we were – and are – in AI-driven drug discovery.

How has Big Pharma’s receptiveness and approach to AI-driven drug discovery evolved over the past few years?

Pharma’s approach to AI comes in waves; some have been too early and some too late. Novartis, for example, went too big on AI too soon back in 2016, hiring hundreds of AI engineers and by 2018 had more AI heads than Insilico had AI scientists, according to LinkedIn; over half of which have now been let go. While AI is used in some way in almost all drug discovery work, there are very few end-to-end AI-driven use cases.

Sanofi has thus far been more successful. The French firm, which recently announced that it was going “all in” on AI, is led by Paul Hudson, who spent a considerable amount of time at Novartis and has been able to learn from his previous company’s mistakes. He decided that instead of hiring armies of AI scientists, they should realise where their key strengths are and where they need to rely on partners. Now they are perhaps the leading Big Pharma in terms of AI integration and picked up several AI partners – including Insilico – along the way.

How does this collaboration with Sanofi manifest? Does Insilico act as something of a CRO/service provider in its partnerships with Big Pharma?

Today, Insilico does collaborations more than CRO work. When the company was starting out, we did act as a CRO in some cases, but now if we do not have a participation in the molecule, we do not do the work. In the Sanofi deal, we received USD 21.5 million up front, with up to USD 1.2 billion in milestones, and single- to double-digit royalties. This goes far above and beyond the traditional CRO model.

Our collaboration with Sanofi represents a landmark deal in terms of size and no other AI-powered biotech in Asia has done anything at this level from scratch. There have been some big deals in antibody-drug conjugates (ADCs) and other hot areas but from a later starting point. While I cannot expand further on the collaboration at this moment, I think it will be one of our most successful and there are already some success stories emanating from it.

Our Big Pharma partnership strategy has been influenced by the fact that management changes in these companies often have a seismic impact on R&D strategy. Sometimes they partner with a biotech and then a new leader comes in and the partnership is deprioritised. For this reason, our business model is now based only around partnering on assets that have already progressed. To use another analogy, we bake the cookies, and then sell them, instead of helping other people bake them. We, of course, also sell cookie baking software but this helps us make our own cookies better. The more of our platforms are used, the more we know what works and what does not, and the more updates we are able to create.

Another achievement delivered in a big pharma collaboration of Insilico, our Fosun Pharma-partnered candidate is now in Phase I trials. When we began this partnership, the candidate was still in the preclinical stages and subject to a bidding war, showing that the quality of AI-driven assets is increasingly being recognised. Fosun won out and we received USD 13 million upfront, still own 50 percent of the molecule, and there is another USD 82 million available based on

milestones. This is one of my favourite deals that we have been able to strike and also shows that partnering with Chinese Big Pharma companies can also be quite successful.

The eventual goal of many biotechs is to be acquired by a Big Pharma. Is this the case for Insilico and might it even become a pharma company itself in the future?

I never say never. Generative AI tools which can act as a professional journalist, doctor, or lawyer can learn from credible scientific literature; understand the difference in data presented in clinical trials and in preclinical work; and could help patients and doctors to find the best treatment. There is strong potential for generative AI to outperform humans in many aspects, thereby increasing the opportunity for a company like ours to cut out the middleman and become a Pharma, getting products to patients faster, but this is not part of our plan. The current plan is to be the bakery of high-quality preclinical and clinical assets that satisfy unmet medical needs, and at the same time, have the perfect balance of novelty, confidence, and commercial attractiveness.

We also want to debias target selection. Our lab is built to allow for genuine scientific exploration by AI. Instead of just doing the phenotypic screening, for example, it makes target decisions using 60 different target discovery philosophies, tests those decisions very quickly, and comes up with promising targets. We assess commercial suitability and even if other companies are pursuing those targets, we may be able to outperform them with a higher quality candidate thanks to AI.

Insilico aims to substantially increase the number of drugs on the market. The best way to do that is to take those drugs to a certain level and then license out to companies that specialise in drug development and can do combinations. I want to evangelise the partnering model, where the partnering is done at the preclinical candidate stage because then you can partner with a pharma company to create the best clinical pathway for the preclinical candidate and ensure that the probability of reaching the patient and maximising patient benefit is maximised. Moreover, pharma companies are usually better at clinical study design than AI drug discovery companies because they can do more arms and combinations.

How sceptical are regulatory bodies towards AI-driven drug discovery today?

We are not asking for any regulatory shortcuts and are following rules as a traditional biotech with no requests for additional help. I take my hat off to the US Food & Drug Administration (FDA) because years of patient advocacy have resulted in a very efficient system, with guidelines for a

response within 30 days. There are few bureaucratic holdups within the FDA process and there is a clear willingness to see candidates succeed while ensuring that the drug is safe and effective.

The Chinese equivalent, the National Medical Products Administration (NMPA) with the Center for Drug Evaluation (CDE) underneath it, was previously much harsher than the US FDA. However, in recent years the NMPA CDE has begun to create a more efficient system with guidelines and norms for responses. At the very least, if a biotech has good data in hand, the regulatory pathway can be mapped out.

Once regulators see more good clinical results from AI-driven companies, we can begin to work on achieving additional regulatory speed-ups, especially in rare diseases. Automobile manufacturers first try out their most advanced technologies in Formula 1 racing cars before then rolling them out to their expensive, but mainstream, commercially available supercars. Regulators in both the US and China could pursue a similar tack on AI-driven drug R&D, partnering up with the few leading companies to find innovative ways to deliver drugs faster.

Could you sum up why Insilico's mission is so important to the future of drug development?

From the very beginning, we have had a much bigger goal than most other companies. We aim to understand and solve ageing and age-related diseases and that is why we train much of our biology engines on basic human biology that changes in time. All of us come into this world, compete, reproduce, take care of our young, reach our peak, decline, and die. Even those lucky enough not to contract diseases lose a lot of function as they age.

To go after this lofty goal, we need to accelerate drug discovery and create effective tools that allow for the rapid identification and development of interesting targets with real chemistry. The idea is to quickly tap into new areas of biology that are commercially attractive, but at the same time novel, and may address chronic diseases via potentially blockbuster drugs.

So far, we have managed to make many goals that seemed too big to swallow for a small company look achievable. And the team united behind this goal, at that time it was, considered to be a crazy idea. But now you can see that this is a source of competitive advantage – having an end-to-end system that can go from zero to one, even allowing us to branch into many different areas. For example, we also collaborate with companies in the agriculture, petrochemistry, and skincare sectors to better understand different types of chemistry and the human body.

All of this has allowed us to progress considerably in many areas of cancer and chronic diseases, but this is just the beginning. We have demonstrated that we can be a credible player with ambitious goals and claims and when we make a statement, we usually deliver. Conversely, if we fail, we tell people that we have failed. Now what we really need to see is something of an industry transformation, where pharma companies and biotechs start focusing on their respective core competencies. With this transformation in place, pharma companies can swiftly gain access to promising early-stage and late-stage preclinical pipelines and focus on what they do best: drug development and clinical trials.

Currently, the best time for any pharma company to partner with an AI company is at the preclinical candidate stage, because that way their teams can contribute to clinical study design which is the part they specialize in. Instead, by not making those ultra-early-stage bets, Pharma can significantly de-risk their pipelines. Novartis – the most productive Big Pharma of the past two decades – has only been able to deliver 20 drugs that can be traced back to internal R&D, for example.

How internationalised is Insilico today and how does it draw on the different geographies in which it has a footprint?

We have infrastructure across the world. In the US, Insilico has business development (BD), communications, operations, and clinical trial teams in both San Francisco and New York, with the latter collaborating closely with stakeholders in Boston, which has become the main venue for partnering. We do all our high-level AI work in Montreal, Canada as well as a good deal of AI research and development in Abu Dhabi, UAE. Elsewhere in Asia, target discovery is based out of Hong Kong, new drug and business development team is in Taipei, we utilise AI to discover drugs in Shanghai, and our robotics facility is located in Suzhou. For BD purposes, we also have staff in Switzerland, Japan, the UK, Sweden, and France.

Internationalisation can be costly to sustain, is Insilico looking to raise further funds to support it?

We experienced a 500 percent increase in revenue last year and while we are not yet profitable, we are not burning through as much capital as many other companies in our field. The company submitted a listing application to the Hong Kong Stock Exchange in June this year.

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