Pharma's AlphaGo Moment: For First Time AI Has Designed and Validated a New Drug Candidate in Days

Insilico Medicine has succeeded in using AI to design a new molecule from scratch in 21 days and validate it in 25 days. This is the first time that the true transformative and disruptive potential of AI for the Pharma industry has been validated in practice, turning its potential from theory into reality.

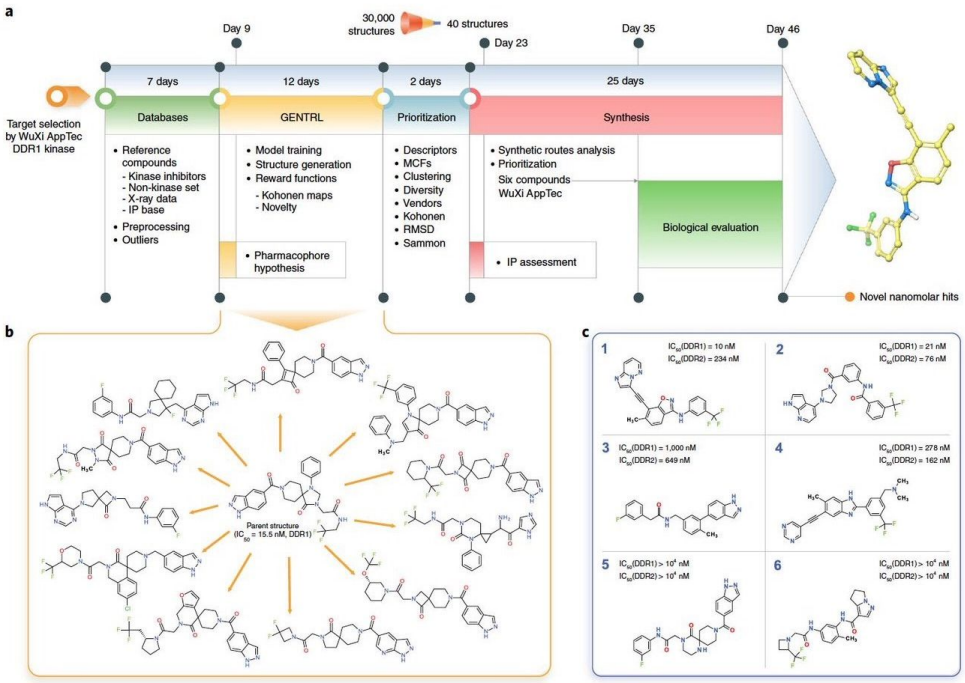
This is Pharma's *AlphaGo moment* when the potential for AI to radically transform the operating procedures and business models of the entire Pharma industry has become obvious to the public. The original AlphaGo moment occurred in 2015 when DeepMind succeeded in developing AlphaGo, the first AI that was capable of beating a human Go champion at Go. This study by Insilico Medicine may be an analogous game-changing moment for Pharma. While it typically takes 2-3 years to go from initial drug discovery to preclinical validation, Insilico Medicine has done this in less than 2 months end-to-end. This is 15x faster than Pharma companies that are capable of conducting the most efficient R&D processes.

In a landmark study published in Nature Biotechnology on September 2, 2019, Insilico Medicine showed that they designed a drug candidate from scratch in 21 days and validated it in 25 days. This achievement demonstrates the true power of AI to accelerate the pace of scientific R&D. This is the first time that GAN-RL technology, which is a combination of Generative Adversarial Networks and Reinforcement Learning, was used to generate novel small molecules for a protein target that were validated in vitro and in vivo.

"The drug discovery process consists of many phases and often takes decades. In preclinical phases the failure rates are over 99%. Our AI can be used in all phases and in some cases lead to superhuman results. Our AI is exceptionally good at finding the molecular targets in specific diseases and inventing new chemistry. We intend to use this in a big way."

Alex Zhavoronkov PhD, Founder & CEO, Insilico Medicine

We expect that this will have a big impact on the Pharma industry generally, and incentivize an increasing number of large Pharma corporations to on-board AI in a very integral manner. We might even see this news create the beginning of a kind of arms race in drug development, whereby the largest Pharma and Tech corporations begin to compete to acquire the strongest AI in Drug Discovery companies. The promise that AI holds to reduce the 99% preclinical failure rate and expedite the time it takes to go from R&D to real treatments has been a major topic of discussion for years. But thus far, no drugs designed or developed using AI having actually reached the market. This new study is the closest that the industry has come to demonstrating the real-world potential of AI in drug discovery and development in a tangible, material way. This is Insilico's most important publication to date because it shows that the molecules "imagined" using the Generative Reinforcement Learning approach work in vitro and in vivo.



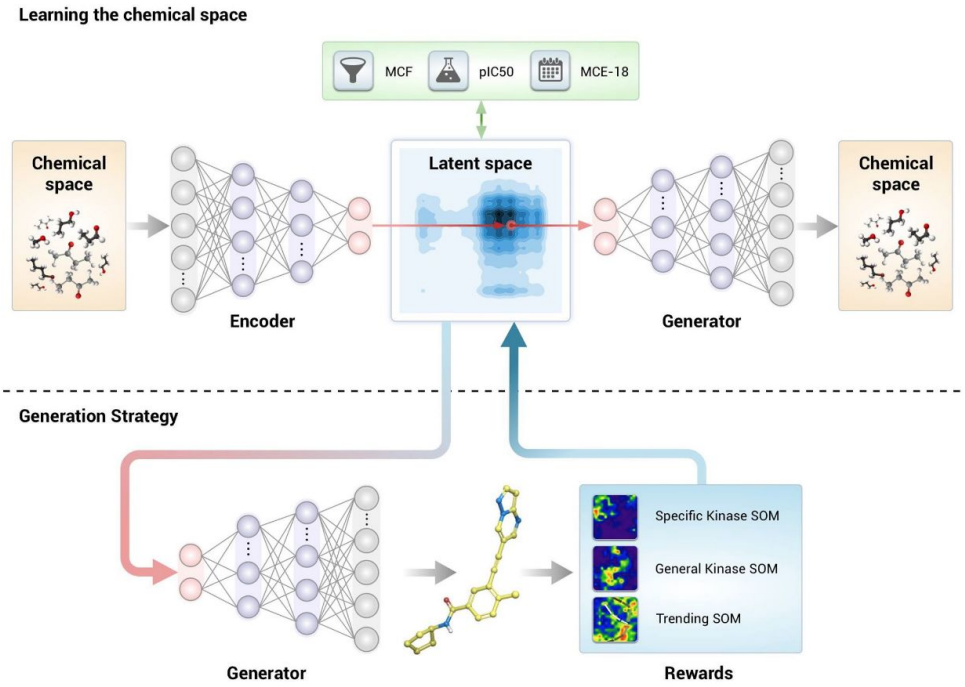
Insilico Medicine is known for validated science - they announce every achievement they make. Insilico has published over 150 scientific papers with over 3000 citations. They strive to be transparent in showing that their methodology and their solutions really work. Most AI companies offering similar services barely have a few released papers or a proof of concept derived from their technology. Insilico is known worldwide for being a pioneer in cutting edge solid science backed up by transparency and credibility. The company employs over 85 AI experts and scientists in 6 countries and collaborates with 150 academic and industry partners worldwide. Insilico's team includes bioinformatics, computational and structural biology experts, and highly experienced medicinal chemists and deep learning engineers, who work with massive amounts of biomedical data and practical problems in drug discovery.

"The platforms built on this technology may save from millions to tens of millions in R&D costs and 1-2 years in small molecule discovery time. And since the molecules are generated with the specific conditions and objectives in mind including safety, it is likely that these molecules will have better chances of passing through clinical trials."

Alex Zhavoronkov PhD, Founder & CEO, Insilico Medicine

Deep Knowledge Ventures provided Insilico Medicine's initial funding round in 2014, and has remained a close advisor in the company's journey towards becoming a global leader in the application of advanced AI for aging research. Insilico Medicine is one of our most promising portfolio companies, not only in terms of its potential ROI, but also of its potential impact on serious problems facing humanity. Methods like GAN-RL could expedite drug discovery dramatically so that life saving treatments could reach doctors and patients sooner, reducing suffering and saving human lives.

Deep Knowledge Ventures continues to make the AI for Drug Discovery sector a major priority for its strategic agenda, and will soon be launching a new subsidiary fund, AI-Pharma, which will use hybrid investment technologies combining the profitability of venture funds with the liquidity of hedge funds, significantly de-risking the interests of LP's and simultaneously providing the best and most promising AI companies with a relevant amount of investment.



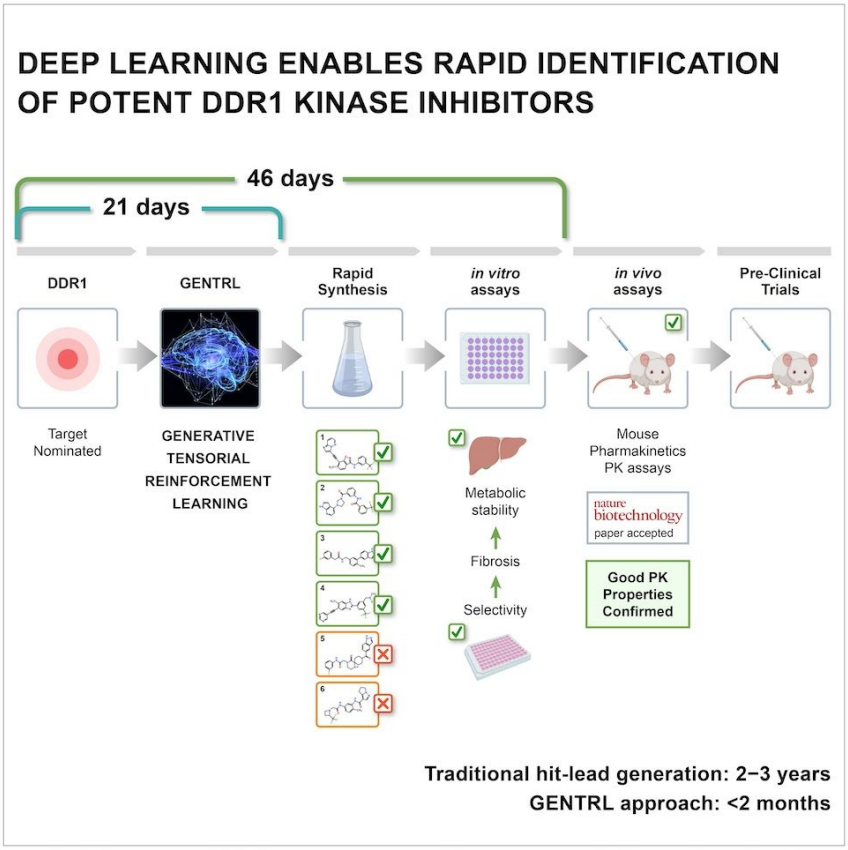
This is basic graphical representation of GENTRL approach. It generates the molecules with specific conditions and learns to generate molecules with the specific objectives.

AI-Driven Molecule Design in 2016 to AI-Driven Molecule Validation in 2019

This game-changing accomplishment is the culmination of Insilico Medicine's efforts in pioneering the use of cutting-edge techniques in AI and Deep Learning, specifically, the combination of GANS and Reinforcement Learning, for drug discovery and biomarker development, which began more than 2 years ago. The concept of GANs is relatively new and is sometimes referred to as the AI Imagination. Conceptually it is a competition between two deep neural networks, where one, the generator, is generating novel content with the desired set of criteria and another, the discriminator, is testing whether the output of the generator is true or false.

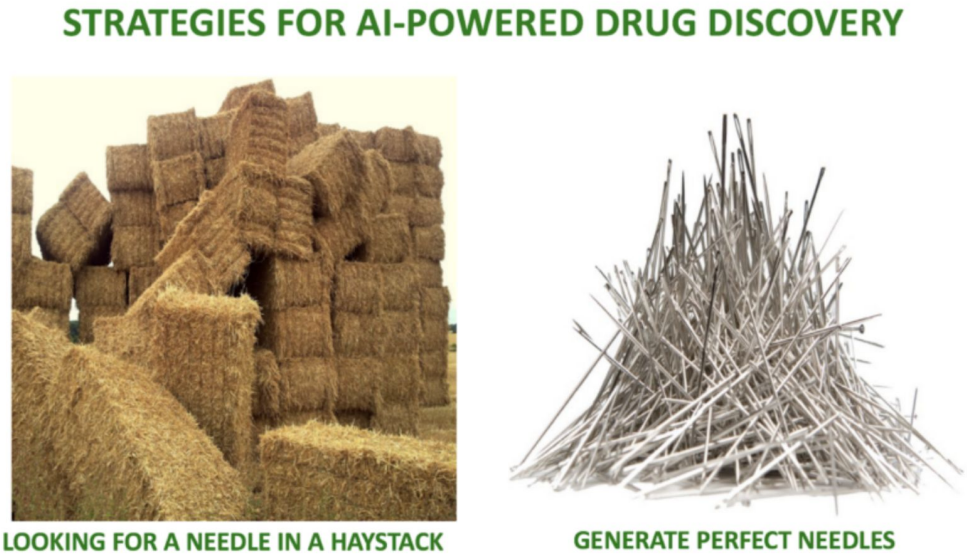
Insilico Medicine was the first to utilize GANs to generate novel molecules in 2016, and since then has spent two years developing the theoretical base for the combined use of GANs and RL, documented in 15+ papers and 80+ conference presentations. Now, for the first time, these efforts have been utilized to design, synthesize and validate a novel DDR1 kinase inhibitor both in vivo and in vitro, end-to-end, in just 26 days. Insilico Medicine screens potential drug candidates using GANs, which create synthetic datasets that are indistinguishable from real datasets by having two neural networks compete against each other. One neural network generates the data and the other compares it to a real data set in iterative cycles so that the

degree of error in the synthetic data set is gradually decreased. Rather than using trial and error when looking for molecular leads, requests are made to the network to generate specific leads and leads are generated on demand.



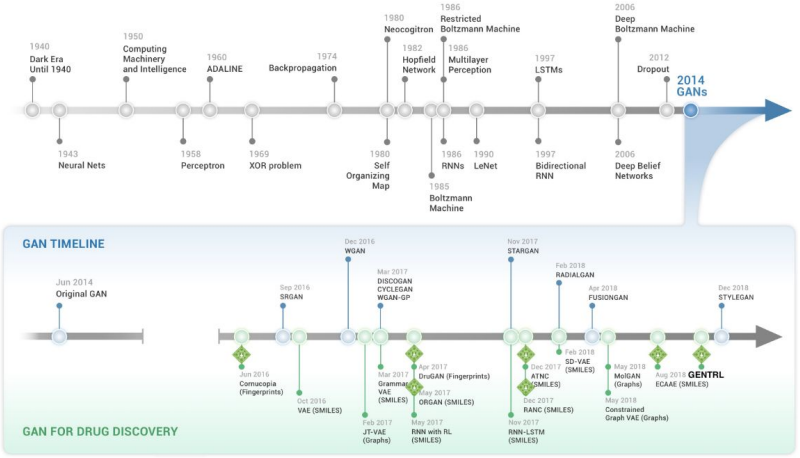
How Insilico Applies Deep Learning to Drug Discovery

So, how exactly does this work in practice? The process begins with identification of a protein target. Once a target is identified, scientists use a deep learning algorithm to design molecular structures with desired physical and chemical properties. This is a brand new approach to drug design. The traditional method is to screen existing molecule libraries against specific targets. Insilico Medicine spent two years developing the theoretical base for this method, a deep generative model called GENTRL. Deep generative models are machine learning techniques that use neural networks to produce new data objects. This technique generates objects with specific properties so it's well-suited to discover drug candidates. This new model optimizes for synthetic feasibility and biological activity. Insilico Medicine performed a challenging experiment where they timed the process from target nomination, small molecule design, synthesis, disease-relevant models, and animal pharmacokinetics for lead-like molecule development.



How Insilico identified new small molecule kinase inhibitors in 46 days

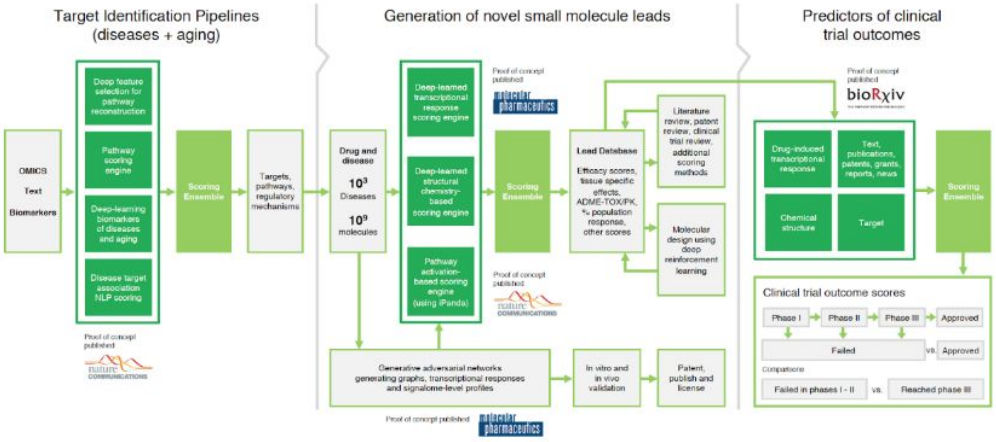
Researchers at Insilico Medicine mapped the chemical space to a continuous space of 50 dimensions, and then explored the space with reinforcement learning to discover new compounds. They used three distinct self-organizing maps as reward functions and used six datasets to build the model. By day 23 after target selection, they had identified 6 lead candidates, and by day 35 the molecules had been successfully synthesized. As a final experimental validation of GENTRL's potential as a valuable tool, they tested one compound in a rodent model. This study demonstrates the utility of Insilico Medicine's deep generative model for the successful, rapid design of compounds. The company plans to develop this technology so that it can be used as a useful tool to identify drug candidates.



A timeline summarizing the key advances towards the development of machine and deep learning and a timeline of the release of the successive GAN-based models. Insilico Medicine was among the first companies to publish the proof of concept of such models for molecular generation. The company has published several models for that purpose over the last five years. (Source: Insilico Medicine)

Molecules "imagined" using advanced AI show promising results in preclinical experiments

By using AI in drug development, it's possible to accurately predict which drugs will be safe and effective for specific patient subgroups. AI accelerates the drug development cycle by generating drug candidates for which we already have some evidence of effectiveness. Traditional pharma companies screen through a large number of candidates and test each one with the hope that one will work. Insilico Medicine starts with molecular leads that have been specifically designed, in terms of their pharmacokinetic and pharmacodynamic properties, and therefore have a higher probability of being effective for specific disease targets. Insilico Medicine's drug discovery engine is trained on massive amounts of structural, functional, and phenotypic data in order to predict the biological activity of compounds. Insilico Medicine has published seminal papers in *Oncotarget* and *Molecular Pharmaceutics*. Another paper, published in *Molecular Pharmaceutics* in 2016, demonstrated the proof of concept of the application of deep neural networks for predicting the therapeutic class of the molecule using the transcriptional response data.



Every Drug Can Be Made and Every Disease Can Be Treated

This new study, submitted in November of 2018 and published on September 2nd 2019 in Nature Biotechnology, was a close collaboration between Insilico Medicine and WuXi AppTec. WuXi AppTec is a leading global pharmaceutical and medical device open-access capability and technology platform company with global operations. WuXi AppTec is committed to enabling innovative collaborators to bring innovative healthcare products to patients, and to fulfilling WuXi's dream that every drug can be made and every disease can be treated.

WuXi AppTec and Insilico Medicine share a mutual vision that AI and machine learning will optimize the drug discovery process by increasing the probability of success at the preclinical level. Insilico Medicine's domain expertise in next-generation AI coupled with WuXi AppTec's capability platform, can potentially improve the efficiency of drug discovery and increase the productivity to serve partners. By combining WuXi AppTec's comprehensive platform and services with Insilico Medicine's hallmark expertise in AI for drug discovery they hope to make dramatic paradigm shifts in the drug development process. By focusing on slashing inefficiencies in the preclinical drug design stage of drug development, cutting development time and cost.

When Deep Knowledge Ventures chose to provide Insilico Medicine's initial funding round in 2014, we did so because we saw their potential to increase Quality-Adjusted Life Years for the betterment of humanity as a whole. Since then, they have been the first to use cutting edge deep learning techniques like GANS to design novel drug candidates from scratch with specified molecular properties, and succeeding in designing, synthesizing and validating a new drug end-to-end in less than 2 months. We are thrilled by the fact that this paper shows what Insilico

Medicine has been developing in R&D all the way back to 2017, and submitted for publication in 2018. Perhaps they have made even greater progress in applying next-generation AI techniques for drug design, which might be publicly disclosed in 2020.

Comments From Key Opinion Leaders

“This paper is certainly a really impressive advance and likely to be applicable to many other problems in drug-design. Based on state-of-the-art reinforcement learning, I am also very impressed by the breadth of this study involving as it does molecular modeling, affinity measurements, and animal studies"

- **Michael Levitt, PhD, professor of structural biology, Stanford University. Dr. Levitt received the Nobel Prize in Chemistry in 2013**

"Using Advanced GANs in the discovery of drugs is a great example of cutting edge application of AI in the pharmaceutical industry - it speeds up a critical process from years to just weeks."

- **Christian Guttmann, PhD, Executive Director Nordic AI Institute, Sr Research Fellow AI, Karolinska Institute**

“Zhavoronkov et al. show that AI techniques can be used to guide our search for good drug molecules in the vastness of chemical space, one of the key challenges in drug discovery today. The work provides compelling evidence that AI can learn from historical datasets to generate novel molecular compounds with drug-like properties, and helps clarify how AI can be used to improve the speed of drug development."

- **Mark DePristo, PhD, former Head of Genomics at Google Brain, Co-founder and CEO, BigHat Biosciences**

"I met Alex when working at OpenAI and have been excited to see him pioneer the use of GANs/RL for the pharmaceutical industry since 2016. One major criticism of GANs is that their usefulness has been limited to image editing applications, so I'm glad that Alex and his team are finding ways to use them for molecular generation,"

- **Ian Goodfellow, PhD, the original inventor of GANs**

“The generative tensorial reinforcement learning in this paper substantially advances the efficiency of biochemistry implementation in drug discovery. Yet to be further experimented at scale, this method signals a breakthrough of pharmaceutical artificial intelligence at industrial level, and may bring significant social and economic impact to our society,”

- **Kai-Fu Lee, PhD, founder of Sinovation Ventures, former executive of Microsoft and Google, and the original inventor of multiple AI technologies**

“This is an important demonstration of the power of AI, using a GAN approach, to markedly accelerate the design and experimental validation of a new molecule, no less one targeting fibrosis, a major unmet medical need.”

- **Eric Topol, MD, Executive Vice-President of Scripps Research and Founder and Director of the Scripps Research Translational Institute (Dr. Eric Topol has no relationship with the company in question nor its authors).**

"I interacted with many AI startups in the past and Insilico was the only deep learning company with impressive, demonstrated capabilities integrating target identification and small molecule discovery. They did a lot of theoretical work in GANs from the very beginning and this experimental validation is a significant demonstration that this technology may improve and accelerate drug discovery,"

- **John Baldoni, PhD, CTO of a stealth AI-powered drug development startup and former SVP of Platform Technology and Science at GSK.**

"In a recent Nature Biotechnology article, Zhavoronkov et al., experimentally demonstrate the utility of their novel GENerative Tensorial Reinforcement Learning (GENTRL) strategy for de novo drug design. In this study, GENTRL was used to design novel compounds against Discoidin Domain Receptor Tyrosine Kinase 1 (DDR1), a pro-inflammatory receptor tyrosine kinase involved in idiopathic pulmonary fibrosis and breast cancer. Of most interest, six DDR1 compounds were designed, synthesized, and experimentally tested all within only 46 days. By coupling advanced deep generative AI models, such as GENTRL with robust causal dependency structure prediction of multi-omics data in drug target discovery studies, we now hold the potential to revolutionize the pharmaceutical industry."

- **Tom Chittenden, PhD, DPhil, PStat, Chief AI Scientist and Founding Director, Advanced AI Research Laboratory, WuXi NextCODE Genomics**

" This study is a significant step forward in the field of de novo small molecule design. GAN has been used before for generating new molecules but A. Zhavoronkov and colleagues have developed Generative Tensorial Reinforcement Learning framework where they have shown how GAN can be complemented with reinforcement learning and prioritize regenerated structure using self-organizing maps strategies. Moreover, what amazes me is the timeline within which lead compounds are generated which are both in vivo and in vitro validated. I appreciate Insilico Medicine's efforts for sharing their code repository to the open-source community, I'm confident this study will open many avenues towards the research activities within AI in drug discovery."

- **Gopal Karemore, PhD, Principal Data Scientist, Novo Nordisk**

"Exhilarating news in Nature Biotechnology today, as scientists from Insilico Medicine report that an AI process called GENTRL, has facilitated the identification of new small molecule kinase inhibitors, DNA damage response (DDR1) inhibitors, in a two month time frame, reducing the current non-AI early 'research/preclinical development' time estimates for new drugs by approximately 94%. The cost savings for biomarker drugs using AI processes is huge. Not only is the end-to-end development time reduced, but so too are the costs related to R&D scientific, professional and technical personnel, which account for approximately 29% of the total cost to develop a drug, according to Tufts CSDD. Since the FDA fast tracks many drugs for serious conditions, there is incredible potential to reduce overall development costs while increasing the speed which novel drugs can be approved for very sick patients waiting for them. This welcome news comes at a time when soaring costs for drug development, arguably are being recouped in high prices of novel innovative therapies hitting the market."

- **Barbara Gilmore, Senior Consultant, Transformational Health, Frost & Sullivan**

"Deep Knowledge Ventures provided Insilico Medicine's initial funding round in 2014, and has remained a close advisor in the company's journey towards becoming a global leader in the application of advanced AI for aging research. Insilico Medicine is one of our most promising portfolio companies, not only in terms of its potential ROI, but also of its potential impact on serious problems facing humanity. Deep learning helps advance aging research and aging research helps make deep learning more interpretable. Aging is similar to other diseases, but its progression is slower. Aging is the biggest risk factor for developing many diseases - few breakthroughs would make as profound an impact on humanity as curing aging. Delaying aging would have a greater impact on society than curing cancer. Deep Knowledge Ventures continues to make the AI for Drug Discovery sector a major priority for its strategic agenda, and will soon be launching a new subsidiary fund, AI-Pharma, which will use hybrid investment technologies combining the profitability of venture funds with the liquidity of hedge funds, significantly de-risking the interests of LP's and simultaneously providing the best and most promising AI companies with a relevant amounts of investment."

- **Margaretta Colangelo, Managing Partner, Deep Knowledge Ventures**

"It is extremely exciting seeing Deep Learning and other techniques being used to help pinpoint drug discovery in a matter of days. In particular, exploiting large, publicly-available data sets to accelerate this process can give huge benefits for low cost. The data-driven approach will give better and faster results than the traditional methods, leading to faster drug discovery and safer, more reliable results than clinical trials on their own. While it's unlikely that AI will replace the

current methods overnight, it's obvious that organizations which add AI to their methods will quickly replace those who do not. It is vital these organizations 'Uber' themselves before they get Kodaked"

- **David Whewel, former Director of Architecture & Software Innovation, Merck Group**

"This newest achievement made by Insilico Medicine, a leading AI for drug discovery and longevity company and an official partner of Ageing Research at King's, demonstrates the truly disruptive potential that AI holds in terms of accelerating the pace of progress in drug discovery. Furthermore, this is just the latest step in a much grander agenda of applying AI for ageing and longevity R&D, and to the accelerated translation of that research into real-world therapies for human patients. It is also quite notable that the team released the code behind their algorithm in an open-source format, allowing other researchers to apply their techniques and build upon their achievements for the advancement of the entire field of AI for drug design, ageing research and longevity"

- **Richard Siow, PhD, Director of Ageing Research at King's and former Vice-Dean (International), Faculty of Life Sciences & Medicine, King's College London**

"As far as I know, this marks the first ever demonstration that AI can generate entirely novel, synthesizable, active molecules against a specific pharmacological target. In my view, the fact that they were able to generate entirely novel, pharmacologically viable compounds using AI is the most amazing achievement here. Of course it's even more amazing that they established this ground-breaking proof of concept in just 46 days!"

- **Olivier Elemento, PhD, Director of the Englander Institute for Precision Medicine & Associate Director of the Institute for Computational Biomedicine at Weill Cornell Medicine**

"Besides cost savings, vendors need to demonstrate high-quality results that can be measured and compared against standard practices potentially reducing the burden on sponsors. Within the drug discover space Insilico Medicine is one such successful company that leverages Deep Learning Platform solutions for Drug Repurposing and Biomarker Development. Through their commercial partnerships and peer-reviewed publications the company has clearly demonstrated its strong position. AI is becoming a significant source of competitive advantage and differentiation. Frost & Sullivan finds a moderate level of investment towards appropriate AI products and services for R&D can provide up to 5x-8x times returns on investment. For example, deep learning and GANs (Generative adversarial networks) are providing opportunities for reducing the timeline for molecule hit discovery in

a matter of weeks when compared to years with the traditional approach. Target validation, compound discovery, and repurposing supported by Deep Learning and Big Data will lead to further advances and recognizable benefits. With advances in Deep neural networks based models, the field of de novo drug design will start to produce truly novel drug candidates."

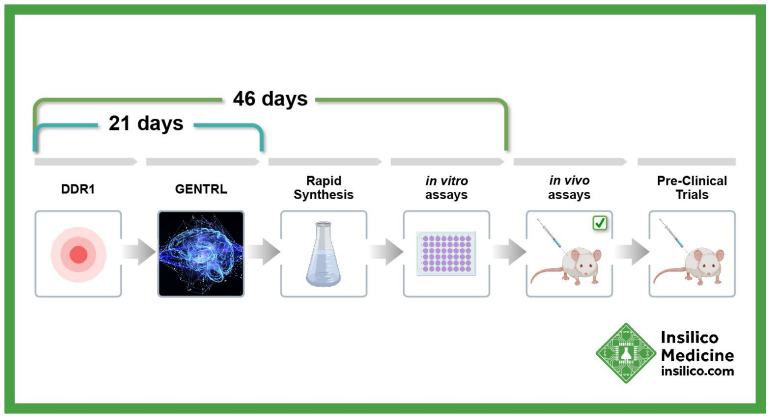
- **Kamaljit Behera, Senior Industry Analyst for Transformational Health at Frost & Sullivan**

“This is the first time that an AI company has designed a novel drug from scratch, synthesized it and pre clinically validated it end-to-end in days rather than years - 15 times faster than the approach used by even the most efficient big pharma players. This is a true game changer, and proves that AI will be the central driver in drug development for years to come.”

- **Robin Starbuck Farmanfarmaian, author of *The Patient as CEO: How Technology Empowers the Healthcare Consumer***

“When Deep Knowledge Ventures chose to provide Insilico Medicine's initial funding round in 2014, we did so because we saw their potential to increase Quality-Adjusted Life Years (QALY) for the betterment of humanity as a whole. Since then they have been the first to use cutting edge deep learning techniques like Generative Adversarial Networks to design novel drug candidates from scratch with specified molecular properties in 2016, and in 2018 to succeed in designing, synthesizing and validating a new drug end to end in less than 2 months. I am also thrilled by the fact that this article visualizes what Insilico Medicine has been making in their R&D already back in 2017 and submitted for publication in 2018. I would not be surprised to find out that since then they have made even greater progress in applying next-generation AI techniques for drug design, which might be publicly disclosed in 2020”

- ***Dmitry Kaminskiy, General Partner, Deep Knowledge Ventures***



Press Coverage

An AI system identified a potential new drug in just 46 days, MIT Technology Review

AI may help speed up drugs development and could have ‘immense’ impact in China, study finds, South China Morning Post

Novel molecules designed by artificial intelligence in 21 days are validated in mice, Eureka Alert

AI system can create novel drug candidates in just 46 days, study finds, STAT

AI designed, synthesised and validated new drug in 46 days, Drug Target Review

A Molecule Designed By AI Exhibits 'Druglike' Qualities, Wired

This Startup Used AI To Design A Drug In 21 Days, Forbes

Insilico Medicine Develops and Validates Powerful AI System To Transform Drug Discovery, BioSpace

AI study led by Insilico's Alex Zhavoronkov bolsters case for faster, cheaper drug discovery, Endpoints News

Study shows AI potential to drastically speed drug development in China, TechNode

A New Era Beckons as First Drug Is Created by AI, Leaf Science

AI helped design a promising drug in 21 days flat, Economic Times

Deep Learning Techniques Speed Drug Discovery, Science & Enterprise

Novel Molecules Designed by Artificial Intelligence May Accelerate Drug Discovery, SciTech Daily

Experimental validation confirms the ability of artificial intelligence to accelerate drug discovery, Pharma News EU

Insilico Medicine Pioneers Use of Artificial Intelligence in the System of Drug Development, CloudWedge

Insilico Medicine develops new AI drug discovery system, Pharmaceutical Technology

AI-designed molecule shows medicinal properties, International Business Times

AI system expedites drug discovery from years to days, Pharma Business International

Novel Molecules Designed By AI In 21 Days Are Validated In Mice, Eurasia Review

This article was written by Margaretta Colangelo and Dmitry Kaminskiy

Dmitry Kaminskiy is General Partner of Deep Knowledge Ventures, Founding Partner of Longevity Capital, Founder of Aging Analytics Agency, and Founder of Deep Knowledge Analytics. Dmitry is the Head of International Development of the Secretariat for the UK All-Party Parliamentary Group for Longevity and Managing Trustee of the Biogerontology Research Foundation. Dmitry is based in London.

Margaretta Colangelo is Managing Partner of Deep Knowledge Ventures and Managing Partner of Longevity Capital. She is Co-Founder of Aging Analytics Agency, Co-founder of Deep Knowledge Analytics, and Co-founder of Longevity Capital. Margaretta serves on the Advisory Board of the AI Precision Health Institute at the University of Hawai'i Cancer Center. Margaretta is based in San Francisco.

About Deep Knowledge Ventures

Deep Knowledge Ventures is a leading investment fund focused on the synergetic convergence of DeepTech, frontier technologies and technological megatrends, known for its use of sophisticated analytical system for investment target identification and due-diligence. Major investment sectors include AI, Precision Medicine, Longevity, Blockchain and InvestTech. Deep Knowledge Ventures led Insilico Medicine's seed funding round in 2014, and has remained a close advisor in the company's journey towards becoming a global leader in the application of advanced AI for aging research and the extension of healthy human longevity. DKV has since formed a fund to focus exclusively on investments in the areas of Geroscience, longevity research, AI for advanced bioscience. DKV's AI-Pharma Specialized Fund combines the

profitability of venture funds with the liquidity of hedge funds significantly de-risking the interests of LP's and simultaneously providing the best and most promising AI companies with a relevant amount of investment.@DeepTech_VC

About Deep Knowledge Analytics Pharma Division

The Pharma Division of Deep Knowledge Analytics is the leading analytical agency specifically focused on deep intelligence of the pharma industry and the AI for Drug Discovery sector, and a specialized department of Deep Knowledge Analytics, a DeepTech-focused analytical company focusing on advanced industry analytics on the topics of Artificial Intelligence, GovTech, Blockchain, FinTech, Invest-Tech and Frontier Technologies. Its proprietary and open-access reports have been covered by top-tier tech, business and finance media including Forbes, Financial Times, The Guardian, The Telegraph, and acknowledged by many other authoritative entities such as MIT Review.

About Deep Knowledge Analytics

Deep Knowledge Analytics, a DeepTech-focused analytical subsidiary of Deep Knowledge Ventures, specializing in conducting special case studies and producing advanced industry analytical reports on the topics of Artificial Intelligence, GovTech, Blockchain, FinTech and Invest-Tech. This entity has produced a number of comprehensive analytical reports in coordination with the UK All-Parties Parliamentary Group on AI and on Blockchain, including its AI in UK Landscape Overview 2018 and Blockchain in UK Landscape Overview 2018.