Pharma's AlphaGo Moment: For the First Time, Artificial Intelligence Has Designed and Validated a New Drug in Days

Insilico Medicine succeeds in using AI to design a new molecule from scratch in just 21 days, and validate it in just 25 days, compared to 2-3 years required currently for pharma industry

This is Pharma's AlphaGo moment.
In 2015 DeepMind succeeded in developing the first AI capable of beating a human Go champion in Go. This may be an analogous game-changing moment for Pharma. The potential for AI to radically transform Pharma is obvious.

While it typically takes 2-3 years to go from initial drug discovery to preclinical validation, one AI for Drug Discovery company has done the same in less than 2 months end-to-end, which is 15 times faster compared what it typically takes even for the best pharma corporations capable to conduct the most efficient R&D process.

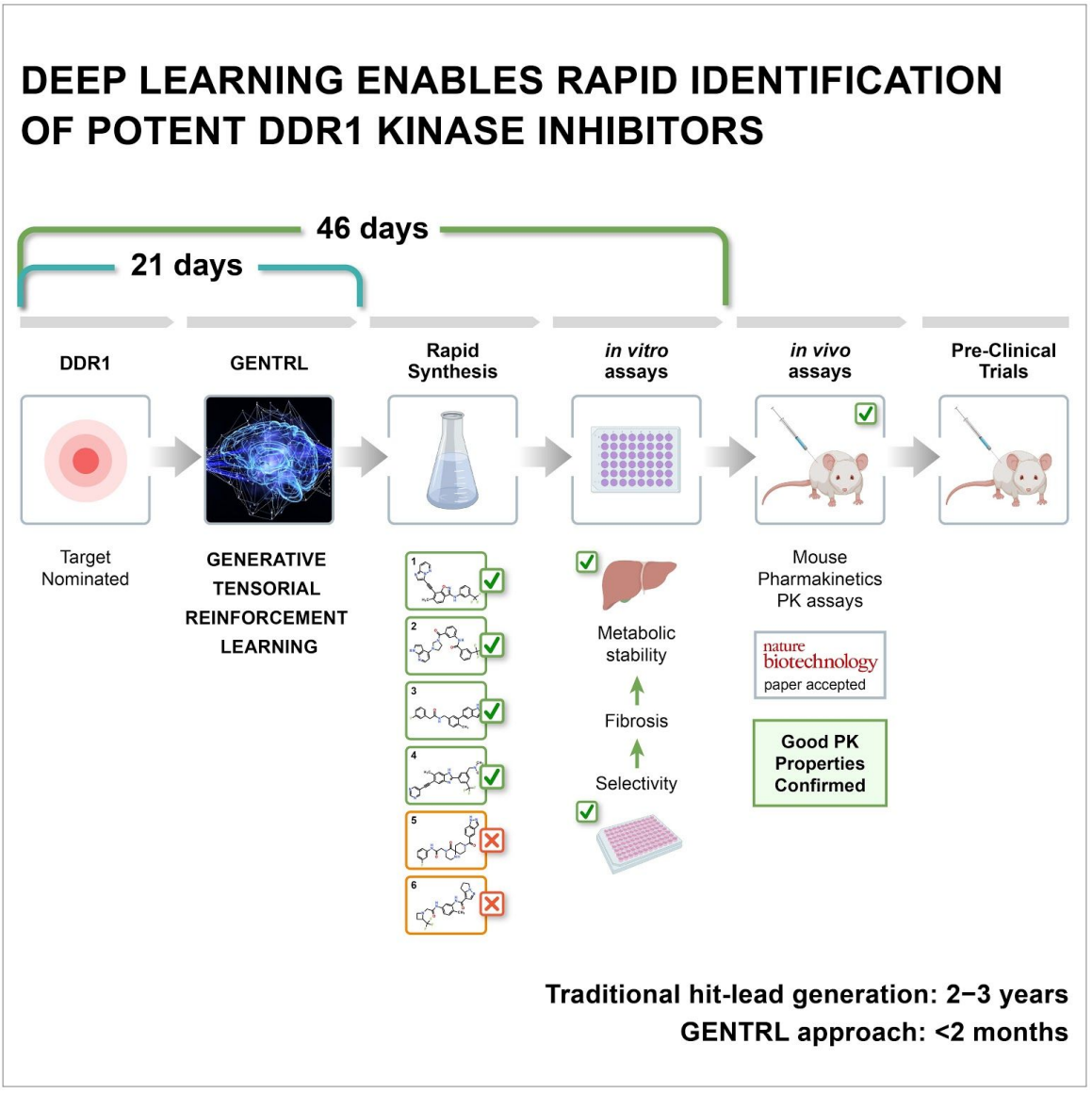
In a landmark study published in *Nature Biotechnology* on September 2nd, 2019, Insilico Medicine showed that they generated and validated a novel small molecule in just 46 days, and designed the drug from scratch based on specified molecular properties in just 21 days.

"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" ***said*** **Alex Zhavoronkov, CEO of Insilico Medicine.**

This is the first time that GAN-RL technology (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. Methods like GAN-RL could expedite

drug discovery dramatically so that life saving treatments could potentially reach doctors and patients sooner, reducing suffering and saving human lives.

And, more importantly, 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. The promise that AI holds in reducing the 99% preclinical failure rate in pharma and expediting the time it takes to go from R&D in drug discovery to real treatments in the hands of patients has been a major topic of discussion among investors, researchers and the media for years. But thus far, the proof behind these potentials has been lacking, with zero drugs designed or developed by AI having actually reached the market. But 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.



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

In some sense, this can be thought of as Pharma's AlphaGo moment, when the potential for AI to radically transform the normal operating procedures and business models of the industry becomes tangibly obvious to the public. In the case of the AI industry, this was when the AI company DeepMind (acquired by Google for $0.5 billion) succeeded to develop the first computer program capable of beating a professional human Go world champion. In the case of the Pharma industry, this may very well be its analogous moment.

"*Exhilarating news in Nature Biotechnology today, as scientists from Insilico Medicine (Hong Kong), 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 bio-marker 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. In addition to the reduced development time and costs, drugs potentially get to market sooner, generating revenues for the companies who developed the drugs. DDR inhibitors are being studied for the treatment of cancer. Since the FDA fast tracks many drugs for serious conditions, there is incredible potential to reduce overall developments costs while increase 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*." **said Barbara Gilmore, Senior Consultant on Transformational Health at Frost & Sullivan.**

We can predict that this news will have a large 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.

"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

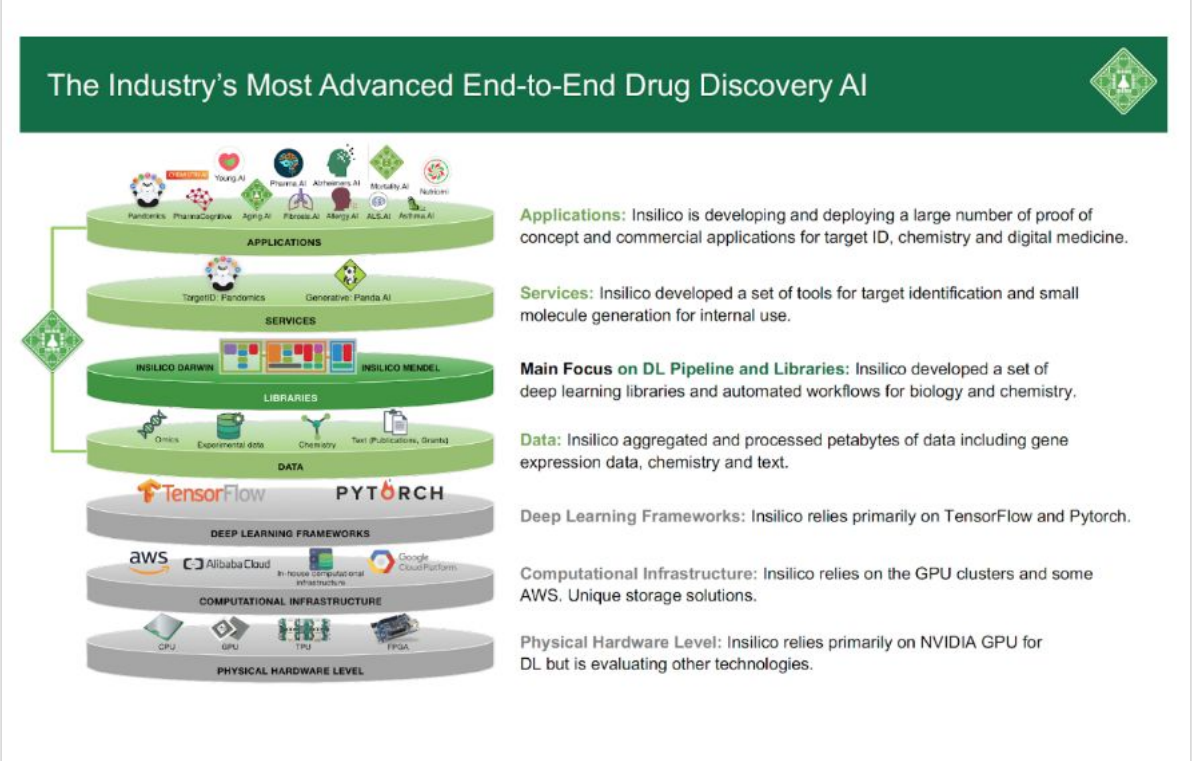
providing the best and most promising AI companies with a relevant amounts of investment." **said Margaretta Colangelo, Managing Partner of Deep Knowledge Ventures**

Insilico Medicine's Journey from 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 Generative Adversarial Networks and Reinforcement Learning) for drug discovery and biomarker development, which began more than 2 years ago.

"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." **said Christian Guttmann, Executive Director Nordic AI Institute, Professor AI at the University of New South Wales, and Senior AI Research Fellow AI at Karolinska Institute.**

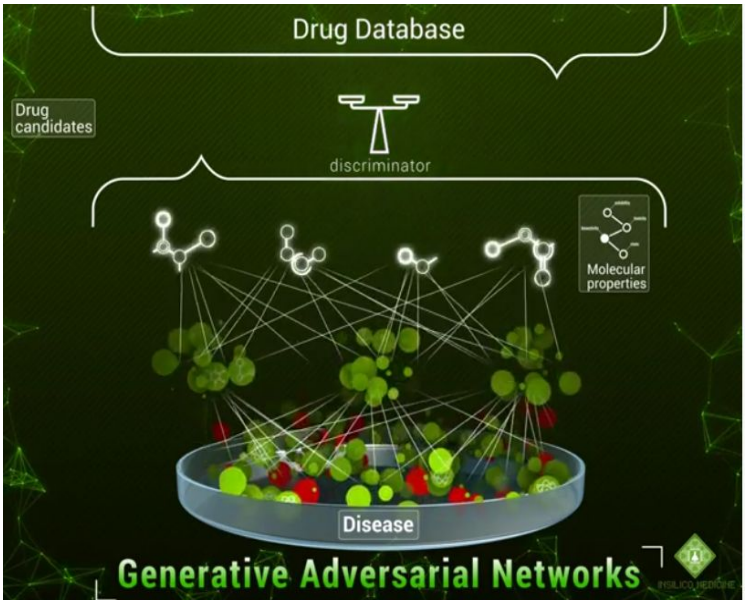
The company was the first to utilize Generative Adversarial Networks (GANs) to generale novel molecules in 2016, and since then have spent two years developing the theoretical base for the combined use of GANs and RL, documented in 15+ papers and 80+ conference presentations. Now, for the first time, these efforts have been utilized to design, synhesize and validate a novel DDR1 kinase inhibitor both in vivo and in vitro, end-to-end, in just 26 days.



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

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.



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.

"This is the first time that an AI company has designed a novel drug from scratch, synthesized it and preclinically 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." **said Robin Starbuck Farmanfarmaian, author of *The Patient as CEO: How Technology Empowers the Healthcare Consumer.***

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.

"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 organisations which add AI to their methods will quickly replace those who do not. It is vital these organisations 'Uber' themselves before they get Kodaked" **said David Whewel, former Director of Architecture and Software Innovation at Merck Group.**

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 pharmaceutical companies screen through a large number of candidates and test each one with the hope that one will work. Traditional pharmaceutical companies screen through many possible leads, testing each one and hoping that one works. 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.

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

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.

“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." **said Kamaljit Behera, Senior Industry Analyst for Transformational Health at Frost & Sullivan.**

In 2018, Frost & Sullivan awarded Insilico Medicine the *AI for Aging Research & Drug Development Innovation* award. This award was part their 2018 Best Practices Awards for developing an AI product with innovative features and functionality that is gaining rapid market acceptance. Frost & Sullivan created a new award category for this specific area of research and development is indicative of the interest and support that AI for drug discovery is garnering from the drug development community. Insilico Medicine’s work is so transformational that Frost and Sullivan created a whole new category for the award.

"I think 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 to share their code repository to the open-source community. I'm confident that his study will open many avenues towards research activities within AI in drug discovery." ***said Gopal Karemore, Principal Data Scientist at Novo Nordisk.***

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.

"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!" ***said Olivier Elemento, Director of the Englander Institute for Precision Medicine & Associate Director of the Institute for Computational Biomedicine at Weill Cornell Medicine.***

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 our 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 (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" ***said Dmitry Kaminskiy, General Partner of Deep Knowledge Ventures.***

Reference to the paper:

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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.

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.