# Company profile

Insilico

Insilico Medicine, founded in 2014, focuses on generative models, reinforcement learning (RL), and other modern machine learning techniques for the generation of new molecular structures with specified parameters, generation of synthetic biological data, target identification, prediction of clinical trial outcomes, and applications in aging research. Since its inception, Insilico Medicine has raised over $310 million from expert biopharmaceutical and technology investors, established R&D centres in 6 countries or regions, nominated preclinical candidates for novel targets for major diseases, published over 130 peer-reviewed scientific papers, applied for over 30 patents, generated millions in revenue from partnerships with pharmaceutical companies and received multiple industry awards.

Alex Zhavoronkov, the founder and CEO of Insilico Medicine, comes from a computer science background specializing in graphics processing unit (GPU) and neuroscience. Since 2004, Alex switched his focus to aging research and drug discovery receiving a Master's degree at Johns Hopkins University, a PhD from Moscow State University, and managing the regenerative medicine and sequencing and bioinformatics laboratories at the Centre for Paediatric Haematology, Oncology, and Immunology. At the dawn of the deep learning revolution in 2013-2014, Alex Zhavoronkov with a co-founder, Alex Aliper (Endpoints top 20 under 40 biotechnology executives), refocused on the applications of deep neural networks to target identification, chemistry and clinical trial prediction problems. Currently, the company has a wide geographical presence in multiple countries and regions with headquarters based in Hong Kong and over 160 scientists worldwide.

Insilico's technology platform, Pharma.AI, uses AI to link together generative chemistry and biology to cover every step of target discovery and expedite the drug discovery process. Traditional drug discovery starts with the testing of thousands of small molecules, followed by further testing and synthesis of hundreds of molecules in order to get to just a few lead-like molecules appropriate for preclinical studies, of which only about one in ten of these molecules pass clinical trials in human patients. Incredibly slow and expensive, the overall process on average often totals over ten years of development and billions of dollars, with each of the processes costing millions of dollars. Further compounding the hurdles in bringing a new drug to market are the massive number of R&D steps involved – each costing millions of dollars – often disconnected and conducted by different companies or different business units in the pharmaceutical ecosystem.

Insilico's technology platform, Pharma.AI, starts with PandaOmics, a proprietary target discovery system designed to identify therapeutic targets through deep feature selection, causality inference and de novo pathway reconstruction. Then Insilico's generative chemistry platform for drug discovery, Chemistry42, generates hit compounds from scratch for the chosen target of interest. By using Pharma.AI, Insilico can assess the probability of success for a given clinical or preclinical program. Taken together, this forms a unique ecosystem of AI tools that is able to significantly accelerate the drug discovery process, specifically in the field of chronic age-related diseases.

Insilico's team firmly believes that AI has transformative potential in the process of
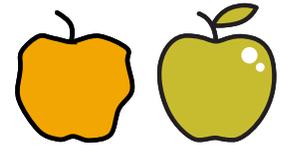
discovering and validating new drugs and is confident its platform can make the pharmaceutical drug discovery and development process more efficient. Insilico has multiple milestones for integrating more AI engines into its end-to-end pipeline as well as plans to expand its collaborations with the robotics drug discovery companies and to build its own robotics facility.

Through its AI platform, Insilico has developed a rich pipeline of therapeutic programs including several antifibrotics, anti-cancer, and metabolic disease programs as well as programs targeting CNS diseases, and the basic process of senescence. In addition, Insilco has multiple collaborations with pharmaceutical companies where it is identifying new targets and pathways implicated in senescence or supports novel chemistry generation efforts. In the next few years, Insilico plans to progress more of these programs into human clinical trials.

Insilico's flagship program is a novel antifibrotic targeting senofibrosis. In the context of senescence, the company developed a target and pathway discovery engine and consequently a multi-step combination therapy. Senescent cells and the SASP have been identified in multiple pathologies of skin, liver and lung and in experimental models. For the first time, using many interconnected deep learning models and other advanced AI approaches, Insilico has managed to link biology and chemistry to build a platform for novel biological target discovery and novel small molecule generation for multiple modalities of senescence-related therapeutics. Insilico proposes a 5R (Rescue, Remove, Replenish, Reinforce, Repeat) strategy for managing cellular senescence (a driving cause of multiple pathologies) by selectively rescuing pre-senescent cells, removing senescent cells, replenishing and reinforcing with new healthy cells and repeating the procedure. The platform itself and the 5R approach related IP is protected.

One of Insilico's most important key partnerships for senolytic drug discovery is that with Taisho Pharmaceutical from Japan, announced in October of 2020. This collaboration brings together Insilico's state-of-the-art AI technologies with Taisho's expertise in drug development. Insilico Medicine will be responsible for early research phase target identification and molecular generation and Taisho will work collaboratively with Insilico in validating the results in various in vitro and in vivo assays.

Insilico's first published work in senescence-related target discovery dates back to 2016 and consisted of basic experimental validation with a company called BioTime (now AgeX Therapeutics). Insilico also has a long story of collaboration with one of the leading nutraceutical companies in longevity field – Life Extension Foundation with two products on the market since 2017. These collaborations allowed Insilico to scale up its internal capabilities in the development of therapeutics targeting senescence. Currently, Insilico has a variety of internal drug development programs in pre-clinical stage with 3 IND-enabling studies planned in 2022. The major area of those studies is fibrosis. The distinct feature of the majority of the current programs is that they rely on novel molecules and novel targets identified by Insilico's proprietary AI platform. The platform itself generates licensing deals resulting in a decent revenue and aids in engaging with the leaders of the industry potentiating the future licensing and co-development deals.
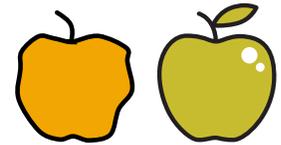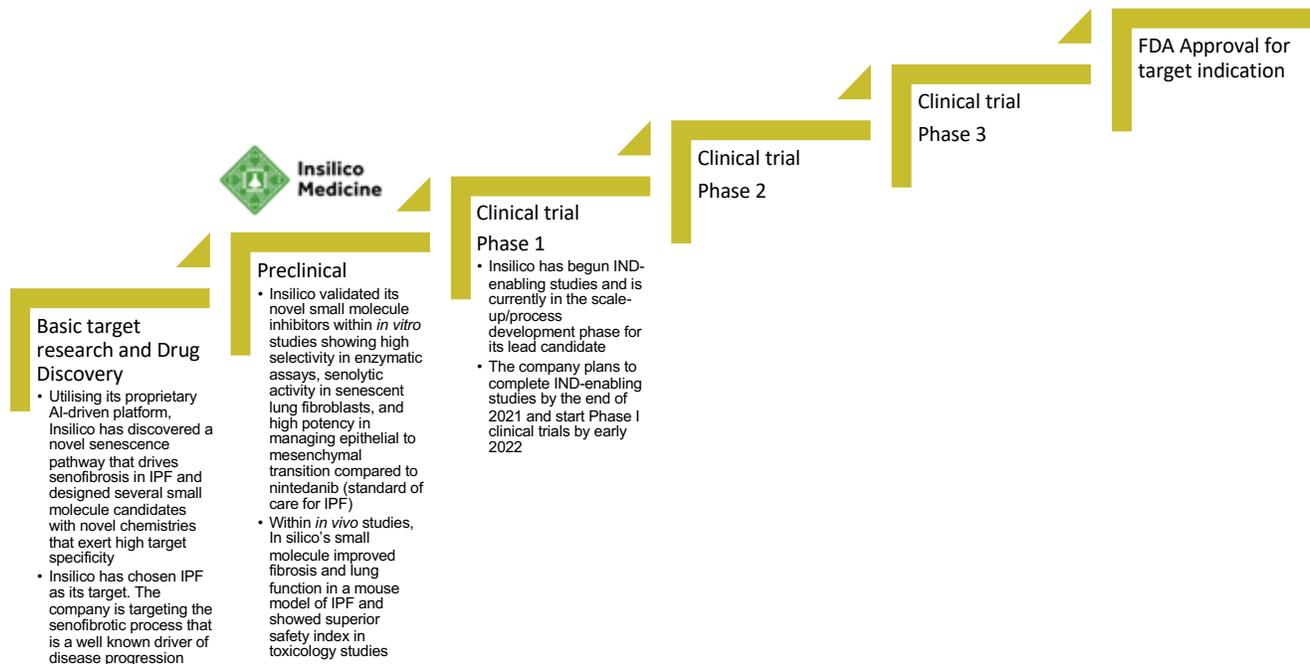
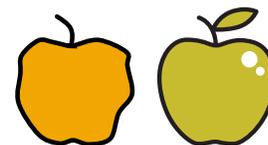## Longevity Potential: Senolytic compounds for Idiopathic Pulmonary Fibrosis

Insilico has applied its end-to-end AI platform to tackle Idiopathic Pulmonary Fibrosis (IPF). IPF is a broad medical condition that is limited to the lungs and primarily affects older adults. As the disease progresses, the health of the patient gradually deteriorates leading to a potentially life-threatening condition.

Fibrosis is one of the main aging-associated disease processes, and often the term senofibrosis is used to describe the development of fibrous connective tissue under influence of senescent cells. Through its AI platform, Insilico used deep neural networks trained on age, and different types of fibrosis, to identify a range of targets and small molecule therapies. Its flagship product for IPF works through a completely novel target regulating the progression of senofibrotic condition by clearing senescent cells and reducing the SASP. In essence, the compound targets the pathological consequences of the senofibrotic effect by mitigating the accumulation of senescent cells in lung tissues which normally leads to increased inflammatory signalling (driven by SASP) and the progression of fibrotic transformation in lungs. The effect of targeting this novel pathway is that of a combined senolytic and senomorphic that eliminates senescent cells from lung tissue and at the same time reduces the levels of SASP markers. This ensures that not only is the disease process halted, but the effects of inflammatory signalling are remediated so the tissue has the energy and resources to recover.

Pre-Clinical and Clinical Studies

Basic target research and Drug Discovery
- Utilising its proprietary AI-driven platform, Insilico has discovered a novel senescence pathway that drives senofibrosis in IPF and designed several small molecule candidates with novel chemistries that exert high target specificity
- Insilico has chosen IPF as its target. The company is targeting the senofibrotic process that is a well known driver of disease progression

Preclinical
- Insilico validated its novel small molecule inhibitors within *in vitro* studies showing high selectivity in enzymatic assays, senolytic activity in senescent lung fibroblasts, and high potency in managing epithelial to mesenchymal transition compared to nintedanib (standard of care for IPF)
- Within *in vivo* studies, In silico's small molecule improved fibrosis and lung function in a mouse model of IPF and showed superior safety index in toxicology studies

Clinical trial Phase 1
- Insilico has begun IND-enabling studies and is currently in the scale-up/process development phase for its lead candidate
- The company plans to complete IND-enabling studies by the end of 2021 and start Phase I clinical trials by early 2022

Clinical trial Phase 2

Clinical trial Phase 3

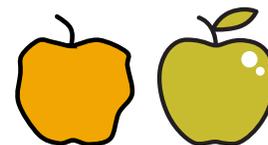**FDA Approval for target indication**

Insilico utilised its platform AI technologies to generate a set of small molecules that were validated to be selective, bioavailable, metabolically stable, capable of oral administration, safe, and effective. Within in vitro studies their molecules were proven to be highly selective and potent against the novel target identified in enzymatic assays. Further, the company confirmed senolytic activity in a mitomycin-c (MMC) induced senescence model within lung fibroblasts. As part of their in vitro preclinical data, Insilico utilised cell-based assays to confirm lower IC50 in Collagen 1 and alpha-SMA readouts in comparison to Nintedanib (standard of care for IPF). These results indicate increased potency in reducing tissue fibrogenesis. Overall, Insilico's compounds showed a 5-to-16-fold greater potency managing fibroblasts-to-myofibroblasts and epithelial mesenchymal transition, a major driver of fibrotic diseases, in comparison to Nintedanib.

In follow-up in vivo studies, Insilico's molecules were shown to improve fibrosis in a Bleomycin-induced mouse lung fibrosis model, leading to further improvement in lung function. These compounds also demonstrated a good safety profile in a 14-day repeated mouse dose range-finding (DRF) study. No significant adverse effects were observed in mice and the therapeutic had a safety index of 8-10 (in non-GLP, 2-week toxicity studies), indicating the therapeutic dose is much lower than the toxicity threshold. Greater tolerability is planned to be confirmed in pivotal toxicology studies.

The best-performing molecule from their AI-generated set of compounds was nominated as a preclinical drug candidate in December 2020 for IND-enabling studies that will lead to clinical investigations. IND-enabling studies have started, and currently, the scale-up/process development of the candidate is ongoing. Insilico plans to complete the IND-enabling studies by the end of 2021 and start phase I clinical trials by the end of the year or early next year.

Technology Platform Analysis	Description	Insilico
Class of Senotherapeutic	Senolytic, Senomodulator, SA-immunomodulator, Senoblocker.	Senolytic: Targeting cellular pathways that make senescent cells vulnerable to death. Senomodulator: Modulating the aberrant signalling cascade driven by SASP.
Target specificity	Features of therapeutic that facilitate targeting of senescent cells without off-target effects; dependent on senescent biomarkers	Insilico utilises a proprietary AI-driven platform technology to discover senescence specific target pathways and design therapeutics with a high level of specificity towards the target. Their platform technology has the capabilities of designing novel molecules with desired "targeting" properties that may not exist in the known chemical space.
Delivery	Approaches (local or systemic), technologies (delivery vehicle), and formulations needed to safely and reliably deliver therapeutic to its target.	Insilico utilises its AI-driven platform technology to design its small molecule therapies to optimise molecular structure and chemical properties for increased stability and bioavailability for oral delivery.
Adaptability	Foundational technology that can be utilised to systematically improve, or build upon, robustness of therapeutic.	Insilico's AI driven platform technology, Pharma.AI, was developed to constantly optimise senescence target discovery and therapeutic development based on evolving data within the field. The company's proprietary technology can even make novel inferences to discover target pathways and design therapeutics that are unprecedented in the field.
Regulation	Context specific control over therapeutic action once it has reached its target (spatial, temporal, sensitivity, degradation).	The nature of Insilico's flagship product and target pathways within senescent cells has not been revealed, so there is not enough information to evaluate regulatory capabilities. That being said, Insilico's AI-platform has every capability to confer regulatory capabilities through novel chemistries and target identification.
Toxicity	Level of damage that therapeutic can cause to organism; can include, but not limited to: off-target effects, on-target side effects, immunogenicity, etc.	Insilico's AI driven platform allows them to discover senescence specific target pathways and design therapeutics with a high level of specificity. This in turn helps avoid undesired toxic and side effects.
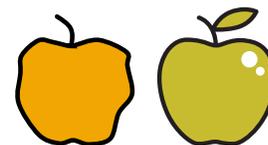
Insilico's AI-driven drug discovery platform is powered by Pharma.AI which combines the synergistic activity of the PandaOmics novel target discovery engine with Chemistry42 deep generative reinforcement learning system. PandaOmics can elucidate novel senescence associated therapeutic targets through deep feature selection, causality inference, and de novo pathway reconstruction and Chemistry42 allows for de novo design of novel molecules that can target these pathways. Chemistry42 has the added advantage of designing molecules with desired properties that do not exist in the known chemical space. Both of these systems are combined with the InClinico engine which predicts the probability of success for a given preclinical / clinical program. Together, Insilico's AI-powered platform forms a powerful end-to-end system for the generation of promising clinical candidates for senescence associated chronic diseases.

Significantly, Insilico utilised its platform technology to complete its therapeutic discovery and validation process, from hypothesis to preclinical drug candidate, in just under 18 months and at a budget of around 2 million dollars. This accomplishment is several orders of magnitude faster and cheaper when compared to the traditional drug discovery process. With AI tools like our PandaOmics and Chemistry42, combined in one integrated workflow, organizations can streamline their efforts and accelerate the translation of ideas into actual clinical candidates and further on. Insilico is receptive to strategic partnerships and collaborations with companies seeking to enhance their drug pipelines and accelerate their therapeutic candidates through preclinical and clinical trials. Beyond its senotherapeutic candidate, Insilico achieved an incredible validation milestone by being able to identify a completely new target out of an automatically generated hypothesis and a drug candidate that is a first-in-class molecule, all in under 18 months.

Safety and Risks

Insilico's AI-driven platform allows them to discover senescence specific target pathways and design therapeutics with a high level of specificity. This in turn helps avoid undesired toxic and side effects. The ability to validate their preclinical candidates with InClinico allows the company to include an extra layer of evaluation to ensure their therapeutic has increased potential for superior safety and efficacy when tested in humans within clinical trials.

Insilico's AI-generated molecules demonstrated a good safety profile in a 14-day repeated mouse DRF studies and no significant adverse effects were observed in mice. This combined with a superior safety index is a promising sign for the safety of Insilico's therapeutic candidates. The company plans to further build on this safety data in further within more comprehensive toxicology studies throughout the year.

The company's lead candidate acts through the combined effect of clearing senescent cells (senolytic) and mitigating the consequences of chronic SASP signalling (senomodulatory). This holds potential to lead to both significant reductions in the accumulation of senescent cells throughout the system and halt the pathogenic cascade of effects driven by senescent signalling. More comprehensive than either senotherapeutic modality alone, this holds potential to improve senotherapeutic regimens as well as long term safety and efficacy for patients with senescence associated chronic diseases.

Target Market

Idiopathic Pulmonary Fibrosis (IPF) is a broad medical condition that has a market size valued at $2 billion in 2018 and is estimated to expand at a CAGR of 12.7% over the forecast period, amounting to $5.2 billion by 2027. The growing burden of IPF is further accelerated by the global impact of the pandemic as data shows that SARS-
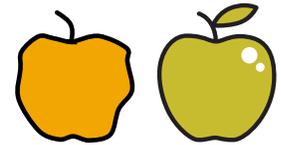
Cov2 preferentially targets senescent lung tissue and drives further cellular senescence in the lungs. This makes individuals with IPF more vulnerable to getting infected by SARS-Cov2 as well as having more severe COVID-19 outcomes.

IPF pathology is typically limited to the lungs and primarily affects older adults. As the disease progresses, the health of the patient gradually deteriorates leading to a potentially life-threatening condition. Fibrosis is one of the main aging-associated disease processes that drives disease progression. The heterogeneity of fibrosis also means that IPF can be stratified based on disease subpopulations with specific metabolic subtypes. Through the process of validating INS001 to target senofibrosis, Insilico is also developing a companion diagnostic biomarker strategy facilitating the identification of patients projected to be susceptible to their therapy. IPF is associated with significant costs covered by both families and healthcare systems. Novel anti-fibrotic therapies, such as the one Insilico is developing, may result in both direct and indirect savings for the affected populations.

Success Factors

Team and Reputation

- Alex Zhavoronkov is founder and CEO of Insilico and has extensive experience in longevity, AI, oncology, bioinformatics and entrepreneurship. Alex is the founder and/or C-suite executive of several successful companies including Deep Longevity, The International Aging Research Portfolio, and NeuroG;

- Alex Aliper is President of Insilico and is an expert in oncology, bioengineering, and bioinformatics;

- Insilico founders Alex Zhavoronkov and Alex Aliper spent years building and integrating hundreds of AI models to generate what they believe is the most comprehensive drug design platform on the market. Together, they have over 100 peer-reviewed publications overall with about 25% specifically related to aging and senescence;

- Dr. Feng Ren is recently appointed CSO of Insilico and is in charge of leading a team of over 20 expert drug hunters and developers responsible for taking the AI-discovered drugs into human clinical trials and creating a broad portfolio of preclinical assets. Dr. Ren was former Senior VP of biology and chemistry at Medicilon and Head of chemistry at GSK before joining Insilico;

- Insilico has a strong record of previous and current partnerships in the longevity and pharmaceutical space including collaborations in senescence-related target discovery with AgeX as well as collaborations with Life Extension Foundation which led to the launch of two nutraceutical products;

- In 2020, Insilico announced three big pharma collaborations in the field of target discovery including Pfizer, Boehringer Ingelheim, and Taisho Pharmaceutical. The collaboration with the latter brings together Insilico's state-of-the-art AI technologies in drug discovery with Taisho's expertise in drug development to develop novel senolytic treatments that extend human healthspan;

- The company's team expanded significantly over the years and is planning on further expansion after the coming financing round. Insilico plans to utilize this financing to further develop its pipeline in senotherapeutics, fibrosis, NASH, immunology and CNS for the purposes of partnering with pharmaceutical companies on specific therapeutic programs.

Intellectual Property

- Since its inception in 2014, Insilico has published over 130 peer-reviewed papers and has applied for over 30 patents;

- Insilico's proprietary technology platform, Pharma.AI, can reveal novel wide-indication targets and corresponding drug candidates in under 18 months and at roughly 1/10th of the typical cost associated with similar compounds;
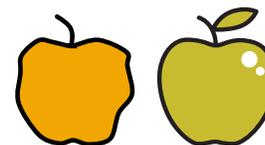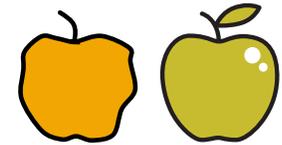
- This platform and Insilico's 5R strategy for managing senescence (Rescue, Remove, Replenish, Reinforce, Repeat) are IP protected and can be utilised to generate a rich pipeline of therapeutic programs – both in-house and through strategic collaborations;

- The company already demonstrated the first case of AI identifying a novel target for IPF, generating novel molecules for that novel target, and completing preclinical experiments to nominate a preclinical candidate (INS001) for IND-enabling studies that will lead to clinical investigations;

- INS001 operates via a combinatorial effect of senolytic and senomodulatory activity that has been shown to effectively clear senescent lung fibroblasts in vitro and mitigate progression of disease pathology within in vivo models;

- IND-enabling studies have commenced and the company is currently engaging in the scale-up/ process development of the candidates. Insilico plans to complete IND-enabling studies and start phase I clinical studies by early 2022 and welcomes collaborations with pharmaceutical companies to co-develop the drug candidate after phase II;

- The company is working on optimizing its candidates for additional routes of delivery (on top of oral administration) as well as additional indications. These endeavours are inspired by the observation that they observe pan-fibrotic effects of their flagship product;

- Insilico is also making its technologies available for licensing for the leading pharmaceutical and biotechnology companies looking to gain a head start in AI and accelerate their drug discovery programs. One such collaboration that holds particular promise is the partnership with Taisho Pharmaceutical that aims to develop novel senolytic targets and compounds that extend human healthspan;

- Insilico's AI-powered platform technology combined with its prolific partnerships with large pharmaceutical and small, innovative biotech companies alike sets the company up to be an IP generating machine;

- The company's platform technology facilitates the designing of molecules with desired properties that do not exist in the known chemical space setting them up for a rich pipeline of therapeutic programs and technologies within the senotherapeutics space.

Funding

- Since its inception in 2014, Insilico medicine has raised over $310 million from expert pharmaceutical and technology investors;

- The company completed a $37 million funding series B round and recently closed a $255 million series C financing round led by Warburg Pincus and joined by Eight Roads Ventures, BOLD Capital Partners, Formic Ventures, Qiming Venture Partners and Sage Partners among others;

- The series C funding will be used to commercialize the validated generative chemistry and target identification technology. The company will also build up a senior management team with pharmaceutical experience and further develop its pipeline in senotherapeutics, fibrosis, NASH, immunology and CNS for the purposes of partnering with pharmaceutical companies on specific therapeutic programs;

- Insilico's AI drug discovery platform facilitates generation of revenue through software licensing and service projects but the highest growth potential relates to the development of internal programs;

- Insilico's platform technology facilitates the discovery of novel, wide-indication targets and corresponding therapeutic candidates in under 18 months and at roughly 1/10th of the typical cost associated with similar programs;

- The company's ultimate exit strategy is IPO which they plan to implement within a 2-3 year time scale.

Insilico: success grid

Intellectual property:

Insilico's proprietary technology platform, Pharma.AI, can generate novel wide-indication targets and corresponding drug candidates in a proven unprecedented 18 months. This platform, and Insilico's 5R strategy for managing senescence, are IP protected and can be utilised in a rich pipeline of therapeutic programs.

Team:

The current team has a strong breadth of knowledge, covering computer science, senescence, chemistry and drug discovery. The team has expanded to over 160 scientists and drug developers, in multiple countries, to take AI-discovered drugs into human clinical trials. Further expansion is planned following the coming round of financing.

Unique value proposition:

Insilico's technology platform, Pharma.AI, uses AI to link together generative chemistry and biology to cover every step of target discovery and expedite the drug discovery process. This comprehensive drug design platform significantly cuts the costs and time taken to get a drug candidate to market.

Efficacy:

Insilico states its lead candidate, an AI-generated small molecule inhibitor of a novel biological candidate, has shown the ability to regulate the fibroblast-to-myofibroblast transition. Further, in vivo studies showed evidence the candidate can improve fibrosis in a Bleomycin-induced mouse lung fibrosis model, leading to further improvement in lung function. Currently progressing the candidate for IND-enabling studies and phase I clinical trials, Insilico is targeting clinical studies by early 2022, which will provide further evidence.

Competitive advantage:

Insilico has 3 big pharma collaborations in the field of target discovery including Pfizer, Boehringer Ingelheim and Taisho Pharmaceutical. The collaboration with the latter brings together Insilico's state-of-art artificial intelligence (AI) technologies in drug discovery with Taisho's expertise in drug development.

Target:

IPF had a 2018 market size valuation of $2 billion and is predicted to expand at a CAGR of 12.7% until 2026. This forecast does not consider COVID-19, which is likely to heighten IPF cases further. IPF is associated with significant costs covered by the families and healthcare systems. Insilico's small molecule has shown 5-to-16 fold greater potency in comparison with the standard care drug for IPF.

Platform analysis:

Insilico's AI-powered platform facilitates discovery of novel senescent targets and the design of potent therapeutic candidates at a fraction of the time and cost of the conventional process. Importantly, Pharma.AI can make de novo inferences to design pipelines that are unprecedented in the field.

Channels:

Insilico is focused on clinical endpoints and is not currently focused on addressing alternative markets.

Runway:

Insilico has over $310 million in funding to date. Its June 2021 $255M Series C round was led by Warburg Pincus to progress the company's current therapeutic programmes into human clinical trials, initiate multiple new programmes for novel and difficult targets and further develop its AI and drug discovery capabilities.

Inflection point:

IND-enabling studies have started, and currently, the scale-up/process development of the candidate is ongoing. IND-enabling studies are to be completed by the end of this year and phase I clinical trials to begin in late 2021 or early 2022. IPO is an ultimate exit strategy and is planned on a 2-3 years time scale.

■ = Positive progress　■ = Work-in-progress　■ = Needs attention