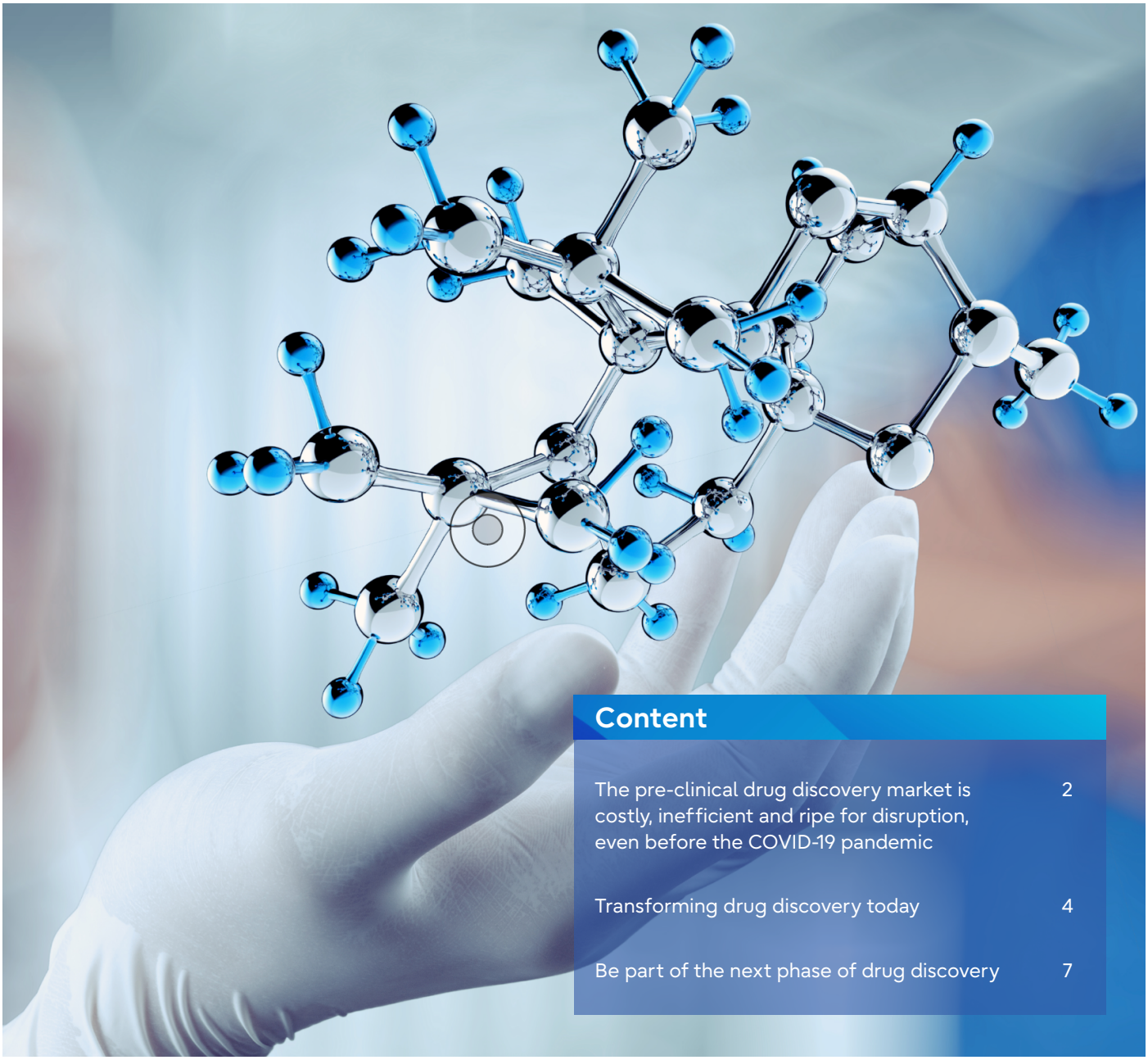
White paper

Disrupting and accelerating drug discovery for faster and more accurate lead identification



Content

The pre-clinical drug discovery market is costly, inefficient and ripe for disruption, even before the COVID-19 pandemic

The pre-clinical drug discovery market is plagued by inefficiencies and often spiraling costs. Yet it is fundamental to the existence and survival of the pharmaceutical industry.

Research and development (R&D) spending continues to increase exponentially, set to reach forecasted levels of $200 billion per year by 2024. The discovery of new therapeutic drugs is a slow, laborious and costly process taking many years to develop new treatments. From target identification to launching a new treatment in the market takes 12-15 years per drug.

This is impacting the industry, the medical profession and the health of millions of people across the world. The need for industry disruption was clear and critical before the current pandemic and is even more so now. The question is how?

Today, Fujitsu is using unique, quantum-inspired technologies and our global expertise to disrupt and expedite the traditional pre-clinical drug discovery market by blurring the lines between drug discovery and lead optimization. An initial drug discovery process that once took years, can now be completed in just seven to eight weeks, while complex protein identification can be handled in seconds.

In this paper, we illustrate how co-creation partnerships are innovating to disrupt and re-imagine the pharmaceutical industry right now. From King's College London and Polaris[qb], both in the race against the clock to find a COVID-19 therapeutic treatment with Polaris[qb] also making great inroads in finding a solution for dengue fever, to Toray Industries Inc. who has achieved great success in accelerating the drug discovery process.

Currently, 81% of business leaders believe quantum-inspired technologies could enable the discovery of new, disruptive business capabilities.[1] Discover how Fujitsu's Quantum-Inspired Optimization Services, through the power of the Digital Annealer, is the way of the future in drug discovery.

The essential early stages of the drug discovery process

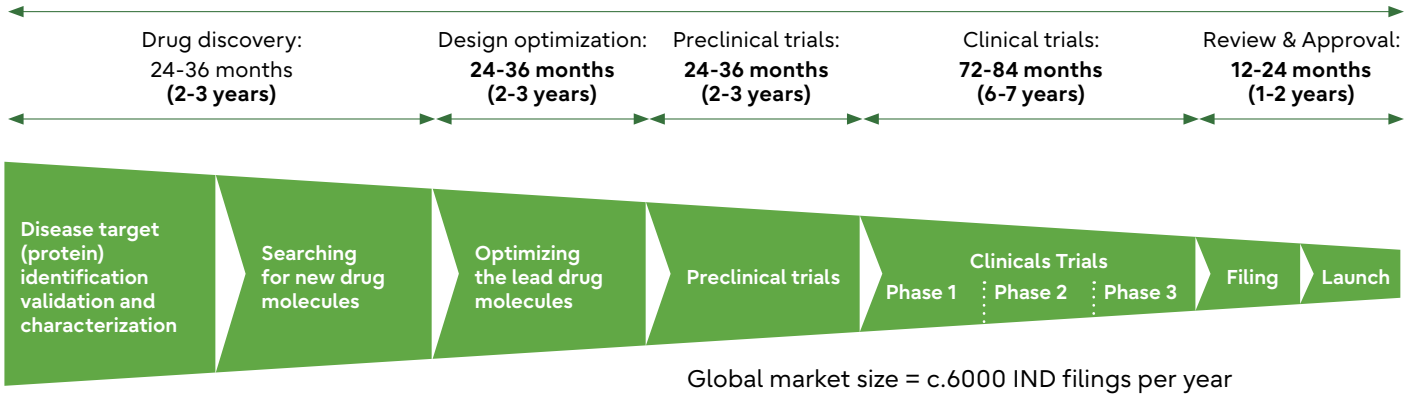
Disease-causing pathogens often contain specific proteins that are responsible for their infection; blocking these proteins is the key to stopping the disease. Early stages of the drug discovery process involve the identification of small molecules (known as "hits") which are capable of blocking these proteins by binding to them.

There is an almost infinite number of molecules to assess, and potentially only one of these molecules will bind with the protein - finding the right one is like looking for a needle in a haystack. Current library searching solutions are only capable of reviewing up to a few tens of millions of molecules and the existing process takes at least two years.

The use of quantum-inspired computing enables the screening of trillions of molecules and reduces the hit molecule search timeline to just eight weeks. This increased speed of analysis means the range of targets can be progressively reduced, leaving just a core of high value candidates, significantly lowering the risk of trial failure.

If ever there was a legitimate, non-hype time to use the term 'disruption', this is it. The technology is already being utilized for rapid therapy development and as part of a new program to address dengue fever and more recently COVID-19.

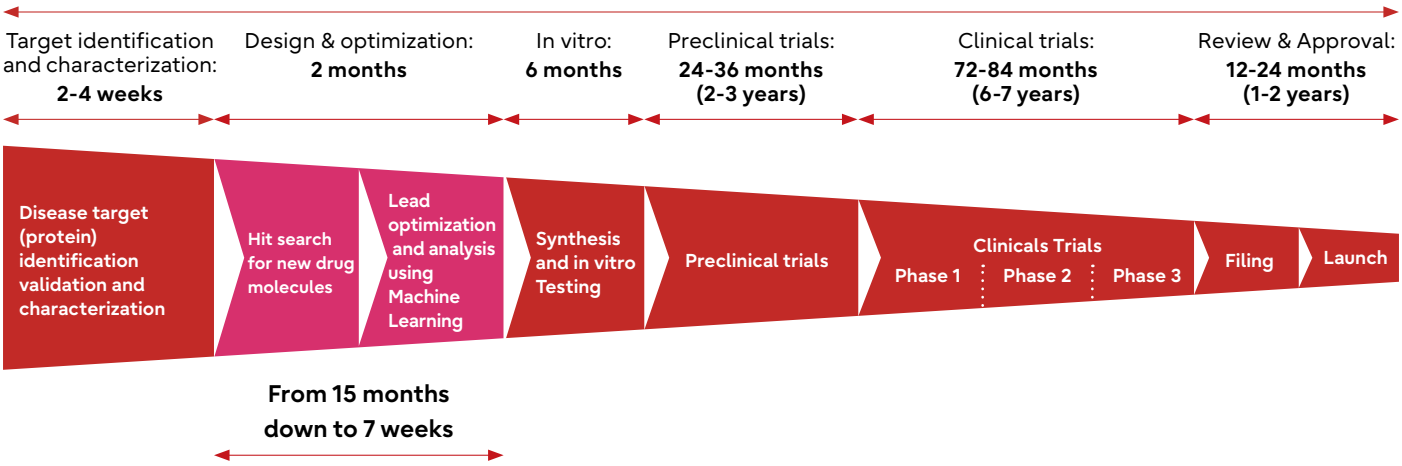
Traditional Drug Discovery Timeline - Total: 12-15 years



Global market size = c.6000 IND filings per year

*Sources: Wong, C. H., Siah, K. W., & Lo, A. W. (2018). Estimation of clinical trial success rates and related parameters. Biostatistics, 2018. Mestre-Ferrandiz, J., Sussex, J., & Towse, A. (2012). The R&D cost of a new medicine. Monographs.

Disrupted Drug Discovery Timeline - Total: 9-10 years



From mass-screening to virtual-screening

Traditionally drug discovery has required pharmaceutical companies to mass-screen large libraries of previously discovered and manufactured physical molecules, which is a laborious and costly process.

Computational advances and a better understanding of the molecular mechanisms of pathogenicity have led to the ability to 'virtually mass-screen' libraries of target molecules based on their relevant therapeutic characteristics.

In the latest advance in drug development, we are able to build libraries of large chemical spaces relevant to the target protein and rapidly constrain it to drug-like properties by assessing the likely efficacy, toxicity and manufacturability of molecules. This process uses a fragment-based combinatorial library of potential molecules built by researchers. They are seeking to identify small molecules, with shapes that are compatible with the target binding pockets; these small molecules are made up of "fragments". The number of possible fragments that could bind to amino acid residues in a binding pocket is extraordinarily large and these fragments can be combined in different ways resulting in trillions of potential lead molecules. Virtual combinatorial screening thus allows us to identify or rule out lead molecules without having to discover and manufacture them first.

Virtual screening of combinatorial libraries moves the goal posts in favor of smaller or nimbler pharma companies, who no longer need extensive libraries of actual molecules or the manpower and financial resources needed for mass screening.

It also means researchers start with a much larger initial set of molecular candidates, funneled to a much smaller number of higher quality assets. Overall, this results in a considerable cost saving over mass screening.

Optimized drug discovery - the difference in numbers

Quantum-inspired drug discovery is radically different from current virtual screening:

1. Today's standard virtual screening of 100 million molecules requires half a million CPU hours and results in a large range of approximately 4,000 candidates. The 15-month screening process requires further analysis of about six months to take these candidates to preclinical testing.

2. With quantum-inspired drug discovery, Fujitsu has illustrated the ability to run trillions of combinatorial options for drug candidate optimization in just eight weeks. This decreases the combined discovery and optimization time needed to reach preclinical testing to just eight months.

Transforming drug discovery today

The dramatic benefits of quantum-inspired computing in drug discovery sound futuristic, but are already being leveraged by innovators to carve out important new market positions. Moreover, through collaboration and co-creation comes the opportunity to disrupt and re-shape the industry.

The global race in the search for a COVID-19 treatment

Given the drastic impacts from the recent COVID-19 pandemic, the search for a treatment is on across the globe. Fujitsu was determined to support this widespread endeavor in as many ways as possible.

Fujitsu partnered with The School of Immunology & Microbial Sciences (SIMS) at King's College London who are a multi-disciplinary research, teaching and training facility focusing on innovation and knowledge development in the areas of immunobiology, inflammation and infectious diseases. With the recent global pandemic situation, SIMS is adding to the efforts against COVID-19 and is carrying out research into understanding the immunobiology of disease, the host response and SARS-CoV-2 diagnostics. In order to accelerate their research, the Dept. Infectious Diseases within SIMS are collaborating with Fujitsu using their Quantum-Inspired technology, Digital Annealer to find similarities among already approved molecules and desired properties for future COVID-19 treatments.

The recent pandemic has already caused damage to economies around the world and requires a fast and accurate resolution. There are several ways of tackling the virus that range from blocking its entry into cells to inhibiting its replication. Either way, a treatment is urgently needed. Considering the length of time required for a new drug to be approved, repurposing approved drugs is a valuable option to accelerate the drug discovery process.

Virtual screening plays an important role at the early stages of drug discovery. This process generally takes a long time to execute since it typically relies on measuring similarities among molecules. This is a computationally heavy and expensive exercise, and a major challenge for today's computers. Most of the well-known methods for this type of evaluation use 2D molecular fingerprints to encode structural information. Although they are efficient in terms of execution times, these methods lack the consideration of relevant aspects of molecular structures.

Considering 3D structural properties of molecules increases the accuracy of the results, at the expense of higher computing times. By using Digital Annealer, the mathematical model is able to manage this kind of information while having shorter executing times. Additionally, the solutions provided by Digital Annealer consider the percentage of similarity between the molecules being compared as well as the specific domains that are similar. The latter information is key helping experts to review the results, and better inform decision making for further validation, therefore significantly reducing times and optimizing the entire process.

Dr Rocio T Martinez-Nunez, Principal Investigator Dept. Infectious Diseases at Kings: "Our collaboration was founded on the need and will from all parties to provide a different solution to COVID-19 drug target research. Thanks to the efforts of the team at Fujitsu in employing Digital Annealer, and by combining this with our current knowledge on SARS-CoV-2, we hope that we will be in a position to test novel approved drugs that are predicted to target the virus in our laboratories very soon".

Albert Mercadal, Head of Fujitsu's Advanced Analytics CoE: "We have been able to speed up the process of finding molecules candidates for new COVID-19 new treatments thanks to the use of Digital Annealer. Now SIMS is able to run a 3D screening process more efficiently and accurately compared with traditional methods in this ever-so important hunt for a treatment.

Polaris[qb] and Fujitsu create a faster, more accurate drug discovery platform

A co-creation project between Polaris[qb] and Fujitsu has seen the development of a drug discovery platform that expands the size of the searchable chemical space from the current market-best of 10 million molecules, to trillions of molecules, thereby increasing the likelihood of finding novel, viable drug candidates.

Previously the traditional preclinical trial process including protein identification, hit molecule identification, lead molecule design and optimization was lengthy and convoluted. Polaris[qb] and Fujitsu's new solution cuts drug discovery and lead optimization timelines from up to 48 months, down to just eight.

Polaris[qb], a Research Triangle Park-based start-up and spin-out from Cloud Pharmaceuticals, uses machine learning combined with quantum mechanics/molecular mechanics (QM/MM) simulations to improve the speed and chemical diversity of small molecule lead discovery. The resulting molecules have strong binding affinities and desirable drug properties for a specific target and therapeutic profile. By partnering with Fujitsu, it has further accelerated the performance and capabilities of its pioneering new drug discovery platform.

The platform is being piloted in tests on the dengue fever polymerase, and now also COVID-19. The aim is to find a cure where other efforts in research and drug development have been unsuccessful.

Dengue fever is a mosquito-borne viral disease, causing flu-like symptoms with sometimes life-threatening complications such as the dengue hemorrhagic fever or the dengue shock syndrome. The disease is widespread in over 100 countries and four continents worldwide, threatening up to 40% of the world's population.

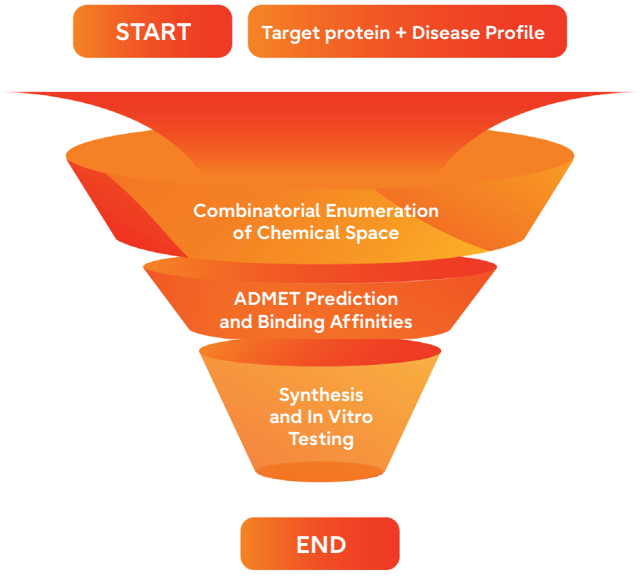
> **"Fujitsu's new solution cuts drug discovery and lead optimization timelines from up to 48 months, down to just eight."**

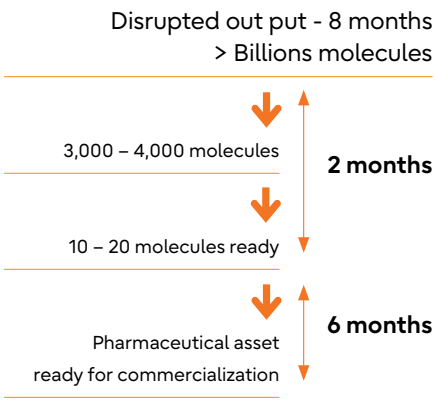
Dengue fever outbreaks are a recurrent theme in most tropical countries. According to the World Health Organization (WHO), there are as many as 50-100 million infections, with 500,000 cases of severe dengue and 22,000 deaths every single year. The first case of dengue contracted in the United States was discovered in Miami in 2019 and based on predicted climate changes, the mosquito vector of dengue is moving toward unprotected populations.

Thanks to this ground-breaking new technology, a cure for dengue fever is now closer than ever before. Polaris[qb] and Fujitsu's new solution quickly assesses whether the molecules discovered possess all the properties that a new drug for dengue fever requires, such as low toxicity, synthesizability and being biologically active.

With drug discovery and lead optimization now just an eight month process, and billions of molecules searched, years cut off research time and costs dramatically reduced, industry disruption has now become a reality.

"Polaris[qb] and Fujitsu's new solution cuts drug discovery and lead optimization timelines from up to 48 months, down to just 8", Patrick Stephenson, Director of Innovation and Health, Fujitsu.





How Toray Industries, Inc. increased its competitive agility in drug discovery

Toray Industries, Inc. is a multinational corporation, headquartered in Japan, well known for its textile, plastic, and carbon fiber businesses, and increasingly for its life science business.

To create a disruptive advantage in this market, Toray collaborated with Fujitsu, to develop a new model for drug discovery optimization. This new way of working represents a shift from in vivo (animal experiments) through to in vitro (test tube experiments) and now to in silico (computer experiments).

Toray's objective was to achieve greater precision in drug lead identification, with fewer, more compelling candidates to take into wet chemistry.

"By narrowing numbers of evaluating methods down through the computation as much as possible, we hope to reduce the number of possibilities down to 1,000 or even 100." Dr. Ryuji Tanimura, Group Leader Pharmaceutical Research Laboratory/Digital Life Science Group at Toray.

To achieve this, first the known optimal combinations of side chain conformations for small protein structures are compared with the optimal combination solutions for the same proteins provided by the Digital Annealer, to confirm that they matched. Next, the technology predicted the structures of large proteins that previously were unable to be realistically computed. For example, with 100 side chains with 10 different conformations there would be 10,100 possible combinations when identifying proteins.

> **"With 100 side chains with 10 different conformations there would be 10,100 possible combinations when identifying proteins."**

"The problem of the large proteins, which a general-purpose computer failed to solve after three to four hours of computation, was solved in about 20 seconds by the Digital Annealer. We were able to arrive at answers which were out of reach using conventional methods."

Dr. Ryuji Tanimura

Be part of the next phase in reimagining drug discovery

The move to in silico drug design is well underway. But the opportunities to win prizes for novel drug discovery are no longer unfairly tilted towards organizations with the biggest molecule banks, the largest computing facilities or the deepest pockets. We are entering a new era of drug discovery, driven in Dr. Tanimura's words, by "a contest of intelligence rather than scale and size".

This is an opportunity for companies to make giant steps forward in the speed and accuracy of drug pipeline development. It can reduce the cost of development and avoid the huge costs of failed trials.

With drugs reaching the market faster, at lower cost, more people can be treated for life-threatening conditions.

But that's only part of the story. With Fujitsu Quantum-Inspired Optimization Services, the possibility now exists for smaller companies or for small project teams in larger organizations to tackle some of the world's most intractable illnesses, with rapid development of therapies for pandemics, as we've highlighted in the cases of treating dengue fever and COVID-19.

> **"Quantum-inspired computing is a key organizational priority for over 80% of business leaders."**

Solving the world's health problems just became easier and faster and the race is now on for research and business leaders to identify the targets they want to solve for humanity.

"Fujitsu's Quantum-Inspired Optimization Services is a truly pioneering technology that will radically improve the drug discovery process", Patrick Stephenson, Director of Innovation & Health, Fujitsu.

Find out how we dramatically accelerated the drug discovery process with Polaris[qb] in our technical white paper.

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