DEEP LEARNING IN DRUG DISCOVERY

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INTRODUCTION

Artificial intelligence (AI) is touted as a transformational technology across sectors. Healthcare is often cited as one of the key applications of the technology for societal benefit. There are a series of AI applications in the field – from detecting anomalies in medical imaging, identifying cancerous and benign markings on skin, and identifying COVID-19 symptoms from CT scans.

The application of deep-learning models to improve the drug discovery process is one of the most promising current developments in healthcare and AI. Drug discovery requires significant resource investment. In spite of major upfront investments, a staggering 90% of developing drugs fail to reach approval for public distribution.[1] The path of translating biomedical research insights to new medicines (referred to as the "translational mechanism" or "translational industry" in this piece) is key to improving the overall efficiency of drug development.[2] Deep learning offers the potential to optimize drug discovery procedures.[3]

AI TECHNOLOGY IN DRUG DISCOVERY

AI algorithms, particularly deep learning, are usually employed to recognize potential drug targets after training by available data on chemical structure and binding properties — this same notion is also applied to identify potentially toxic drug interactions.[4]

AI technology is deployed across five fields of drug discovery:

- **finding new targets**
- **screening small molecules to find new candidates**
- ***de novo* drug design**
- **drug optimization and repurposing**
- **preclinical testing**

Data shows that until 2019, 40% of AI start-ups in drug discovery focused on drug screening, which can help leverage tremendous amount of research data and bypass a slow and expensive discovery process.[5]

MOTIVATION

In a moment when the geopolitical relationship between the United States and China is unravelling, examining existing successful cross-border research collaborations is important. One such collaboration between Atomwise Inc. (Atomwise), a US-based AI drug discovery company, and Hansoh Pharmaceutical Group Company Limited (Hansoh Pharma), a

Chinese pharmaceutical firm, has made significant progress in deploying AI to discover drug candidates.[6] While US-China collaboration in applying AI, including to healthcare-related fields, is met by increasing political tensions, ample opportunity for collaboration in terms of the drug discovery process continues to exist. Future bilateral and international cooperation has the potential to uncover novel healthcare solutions that could help patients around the world.

Examining the state of existing successful collaborative efforts in healthcare is important as it may help us imagine the landscape of future Sino-American collaboration in a post-COVID world. The case example of successful AI application to improve drug discovery may serve as a guideline to help leaders better place their AI strategy in future developments in healthcare, and across other sectors.

INTERNATIONAL CONTEXT AND STAKEHOLDERS

The collaboration between Atomwise and Hansoh reflects a global pattern of AI companies forming partnerships with the pharmaceutical industry. In 2019, the market size for AI in drug discovery was estimated at USD 253.8 million, and researchers predicted it would reach USD 2,127.9 million by 2027.[7] Around the world, hundreds of AI startup companies have emerged in recent years to provide better solutions for drug development.[8]

DRUG DISCOVERY IN THE UNITED STATES

The United States has a world-class pharmaceutical (pharma) industry that is well known for its innovative drug development. The pipeline of an approved innovative drug has several stages, spanning from basic research to clinical trial. The pharmaceutical company will "take the newly discovered potential targets identified by basic science, screen for potentially active compounds, and then selectively narrow the field down to a small number of potentially viable product candidates. After targets and product candidates have been identified, adequate preclinical evaluation of safety and pharmacology is required before the FDA allows testing in humans."[9]

The cost of each step increases as the drug candidates approach the late clinical trial, which can reach USD 50–100 million.[10] The public and private sectors contribute indispensably but differently to drug development. In the US free market system, much basic foundational research is funded by the federal government, but subsequent capital-intensive drug development procedures are performed within the pharmaceutical industry. Recently, this translational process has become increasingly slow and expensive, which is described as Eroom's Law (Moore's Law spelled inversely), indicating that "the number of new drugs approved per billion United States dollars spent on research and development has halved roughly every 9 years since 1950."[11] In recent years, this means that almost 90% of drugs have been washed out during the clinical trials

because they are either unsafe or ineffective. This low success rate and high risk of failing make decreased profitability a key challenge for US pharmaceutical companies.[12]

Because these principles have emerged from different stakeholders with unique histories and motivations, their style and substance vary. Some documents include recommendations or voluntary commitments, while a smaller subset includes binding agreements or enforcement mechanisms. Despite the differences, arguably a consensus has also been growing around key thematic trends, including privacy, accountability, safety and security, transparency and explainability (meaning that the results and decisions made by an AI system can be understood by humans), fairness and nondiscrimination, human control of technology, professional responsibility, and promotion of human values.[13] However, in the face of complex and growing geopolitical tensions, it is important to investigate the feasibility of any such "consensus" between the United States and China.

STATE ASSISTANCE IN DRUG DEVELOPMENT — SPILLOVER OF PUBLIC-FUNDED RESEARCH

Public-funded research programs are also important to drug development. Scholars have found a positive correlation between the amount of public funding in research (e.g., by NIH) and the number of approved drugs that go into the market.[14] About 70%–90% of biomedical patents, best sale drugs, and priority review can be attributed to the outcomes attained in the public-funded research programs.[15] Specifically, as many as 65% of FDA priority reviewed drugs grow from the important insights gained from the study of diseases or research apparatus discovered by public-funded research, and another 17% of priority review drugs and patents are direct results of public-funded research.[16]

The slow and costly translational process retains great potential for improvement from investment by the public sector. To improve the low approval rate, NIH established the National Center for Advancing Translational Sciences (NCATS) to "transform the translational science process so that new treatments and cures for disease can be delivered to patients faster."[17] The center is unique as it focuses on the common ground of different diseases and aims to improve the translational apparatus that adapts and optimizes the entire research community to work more efficiently.[18]

Although NCATS publicly reports focusing on innovation and data, as of September 2020, the center did not yet have programs that integrate artificial intelligence technology. This may be due to the relative nascence of AI being implemented in the translational industry.[19]

Interestingly, the lag in technological implementation may seem disjointed with the ambitious plan of the United States to lead the world in the field of AI. In February 2019, President Donald Trump signed an executive order called "The American AI Initiative," which aims to "continue American leadership in Artificial Intelligence."[20] Under this philosophy, the Trump administration has launched several programs to facilitate domestic AI development. On August 26, 2020, the White House announced its plan "to invest $765 million over the next 5 years in a dozen scientific centers dedicated to the study of artificial intelligence and quantum information science," which followed USD 1 billion plus commitment of research investment from private firms including IBM and Google.[21] Overall, in FY 2020, the federal government spent about USD 4 million on AI for defense purposes, and USD 1 million for nondefense ones.[22]

According to the budget of the federal government for FY 2021, in contrast with the increasing spending for AI, the funding for NIH and NSF were respectively cut 6% and 7%, resulting in a cut of more than 1,000 research programs aided by NIH.[23] This loss stops the five-year-long increase of NIH budgets since 2015. Though disappointing the biomedical research community, it creates great opportunities for deploying artificial intelligence in drug development.[24] This adjustment in US strategic focus could have negative impacts on drug development over the short term, but in the long run, it could induce more efficient translational mechanisms in the drug discovery process through the application of AI technologies. In fact, on the two ends of the translational mechanism, NIH and the Food and Drug Administration (FDA) launched respective plans for better integration of AI. In 2018, NIH issued "NIH Strategic Plan for Data Science" that paved the way for future development in AI and other data-hungry algorithms.[25] And in 2017, the FDA launched its "Digital Health Innovation Action Plan" that has been used to facilitate AI and machine learning in drug development.[26]

Coupled with state support, AI could be the catalyst of the next round of innovation in drug development; it has the potential to fill the needs of multiple federal agencies to improve the translation of research insights into clinical trials in drug discovery. President Management Agenda, 2019, a plan that benchmarks the federal services, sets the goal to "improve the transfer of technology from federally funded research and development to the private sector by [increasing] engagement with private sector technology development experts and investors [and supporting] innovative tools and services for technology transfer."[27] While this signals that potentially more efficient translational outcomes could be expected from the public sector, it also reminds the private sector about the opportunities that can be gained through the potential trajectory for more innovative technologies including AI. With a promising future that comes with increasing support of AI research and discovery of novel AI applications, the great potential to facilitate translational science in the United States lands at the intersection of AI and healthcare.

DRUG DISCOVERY IN CHINA

Drug approval is a vigorous process, and pharmaceutical companies in China face the same issues as their American counterparts in terms of cost and inefficiency. However, as an emerging market with a mix of public sector engagement on different levels, there are some key differences in the drug development process in China.

In contrast with the indirect approach to investing in basic biomedical research followed by the United States, the Chinese government takes the lead in developing its pharmaceutical industry through multiple apparatuses. In the past few years, compared with the mature US market, the Chinese drug market is not well regulated and sometimes raises safety concerns from the public. Thus, the Chinese government has pushed regulatory reform to ameliorate the safety problems caused by substandard drugs. From 2015 to 2017, the central government initiated more than 20 policies to regulate pharmaceutical production and promote high-quality development in both the short and long terms.[28] By setting more vigorous approval standards and strengthening market surveillance, these regulatory policies, in effect, pressure pharma companies to supply safer and more effective products to the market.[29]

Another challenge for the Chinese pharmaceutical industry is the lag in innovation on novel discoveries. In response to this issue, the Chinese government takes a more comprehensive approach through a mix of public guidance, funding initiatives, subsidies, and so on. Along with the well-known "Five-Year Plan," the Chinese government is believed to spend more than USD 600 million annually on biotech R&D.[30] Although this is still unscalable to the US investment in health-related research,[31] the state stimulus has quickly led to a boom in the quantity of biomedical research. In 2017, China had overtaken the United States in academic publication in pharmaceutics.[32]

However, the increase in research outcomes has not translated into an increased R&D capacity for the industry. The Chinese pharmaceutical industry is still dominated by active pharmaceutical ingredients (APIs) and nonproprietary medicines.[33] And there are many fewer novel drugs discovered in China in relation to those in the United States.[34] In short, China is still positioned at the lower end of the pharmaceutical value chain.

RATIONAL FOR LOW LEVEL OF INNOVATION IN CHINESE PHARMA INDUSTRY

1. **China's academic promotion system tends to fund research programs of trending topics in academia.** Until 2020, scholars were promoted based on publications of higher-impact factors—thus, the surge in research results produced in academia tends to be disproportionate to the most demanding needs of the pharmaceutical industry.[35]

2. **Sluggish R&D investment by the industry contributes to the low innovation rate.** Top-tier international pharmaceutical companies report spending "more than 10% of their revenue on R&D"; major Chinese pharmaceutical companies spend, on average, only 2%.[36] Within this limited budget, the most spending is channeled to generics research, which further hampers funding for innovative drug development.[37]

3. **Lack of high-level scientists in the pharmaceutical industry, particularly PhD holders, contributes to the slump in innovation**. This phenomenon may occur because graduates tend to remain in academic institutions rather than join pharmaceutical companies.[38]

The Chinese pharmaceutical industry has developed unevenly in different regions in terms of innovation and technological development, in part due to the role of local governments in industrial development. [39] The provincial government, on the local level, also tailors industrial policies to incentivize local economic growth and social development. As an example, Jiangsu province is nationally ranked first in production of new drugs and the scale of pharmaceutical clusters (Figure 1). In 2018, the Jiangsu provincial government issued "Opinions on Fostering High-Quality Development of Biomedical Industry", a comprehensive industrial policy that sets goals for local pharma companies and industrial clusters in terms of economic output, R&D capacities, manufacture standards, and so on.[40] To achieve these development objectives, the provincial government plans to issue subsidies, support local pharma companies that apply for national R&D grants, and encourage international collaboration.[41]

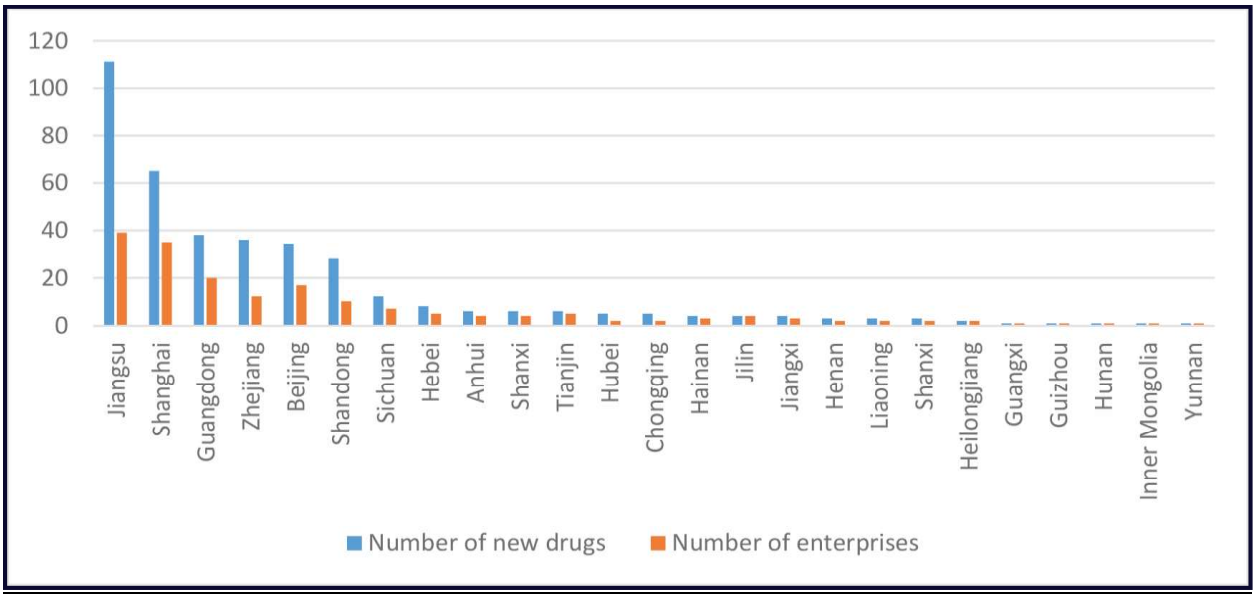


Figure 1: Regional Difference in Chinese Pharmaceutical Developments

Source: Lai et al. https://doi.org/10.1371/journal.pone.0233093

As in the United States, the Chinese government realizes the potential that AI can bring to its pharmaceutical industry. In 2017, the Chinese government published "New Generation Artificial Intelligence Development Plan," stressing the importance of integrating AI into drug development.[42] China has also adopted some direct approaches to fund key projects through the National Natural Science Foundation (国家自然科学基金) and National Key R&D Programs (国家重点研发计划).[43] To address the problem that basic research has not yet been effectively translated to pharmaceutical products, the government steers academic promotion criteria, encouraging "academia to transfer their research into commercialization."[44] Overall, recent estimates show that China's spending on AI in 2018 was about the same magnitude as the planned US AI spending for 2020, namely USD 5 billion.[45]

In short, Chinese AI and pharmaceutical companies are still far from closing the technological gap with their competitors abroad. However, following the current trajectory, innovative drug development capacity in China is growing, and an increasingly competitive AI sector is to be expected in the future.[46]

CASE STUDY - COLLABORATION BETWEEN ATOMWISE AND HANSOH PHARMA

Atomwise is an AI firm based in the San Francisco Bay Area of the United States. Founded in 2012, it has developed an AI system that uses deep-learning algorithms for small molecule drug discovery.[47] Known for partnerships with many major pharmaceutical firms, Atomwise has raised USD 174.3 million to continue to develop its AI technology.[48]

Atomwise's product, known as "AtomNet," is based on deep-learning convolutional neutral networks. This statistical algorithm "extracts the insights from millions of experimental affinity measurements and thousands of protein structures to predict the binding of small molecules to proteins."

Hansoh Pharma is based in Jiangsu, China. According to the China National Pharmaceutical Industry Information Center, Hansoh ranks among the top three for "R&D-driven Pharmaceutical companies in China."[49] It went public in 2019 and was the biggest biopharma IPO of the year.[50]

Hansoh Pharma can be seen as a microcosm of the recent progress made in the Chinese pharmaceutical industry. As an R&D-focused pharma company, Hansoh has become increasingly aware of the importance of innovation, devoting 12% of its revenue to R&D in recent years.[51] The company may have used preferential policies and subsidies given by the state. For example, it appears Hansoh is participating in multiple National Science and Technology Major Projects that aim to develop medicines key to public health in China.[52] The enterprise is also well supported by the Jiangsu provincial government and the Lianyungang Economic and Technological Development Zone Administrative Committee.

Responding to the need to improve innovation and efficiency in drug development, in November 2019, Hansoh Pharma and Atomwise began their collaboration by deploying AI technology in drug discovery. The collaboration deployed Atomwise's AI technology to screen billions of chemical compounds; in only four months, their joint efforts had found suitable drugs for several mutant forms of oncological targets.[53] As they expand their partnership to further drug discovery, their collaboration not only manifests the efficiency that AI can bring to the early drug development process but also symbolizes that Sino-American collaboration in terms of the drug discovery can indeed be successful.

ANALYSIS

The public investment in basic research of AI technology and biomedical science provides important synergies with the private sector in terms of new knowledge creation. For AI, the US federal government has recently increased its support by directly investing in scientific centers. For basic biomedical research, from 2015 to 2020, the overall trend has been a steady growth in public funding. While in the future the federal government may steer the public investment toward AI research and application, the intersection between translational mechanism and AI technology could be the catalyst for the next round of innovation in drug development.

In the fields of both pharmaceutical innovative capacity and AI technology, China has been left behind the United States. The Chinese government understands the importance of basic research, and the Chinese public sector plays an active role in the investment in basic research in these two areas. In addition, the Chinese government has adopted more comprehensive industrial policy measures to facilitate the development of AI and the pharmaceutical industry, in which China's state support differs greatly from the indirect US approach to influence the industry and the market.

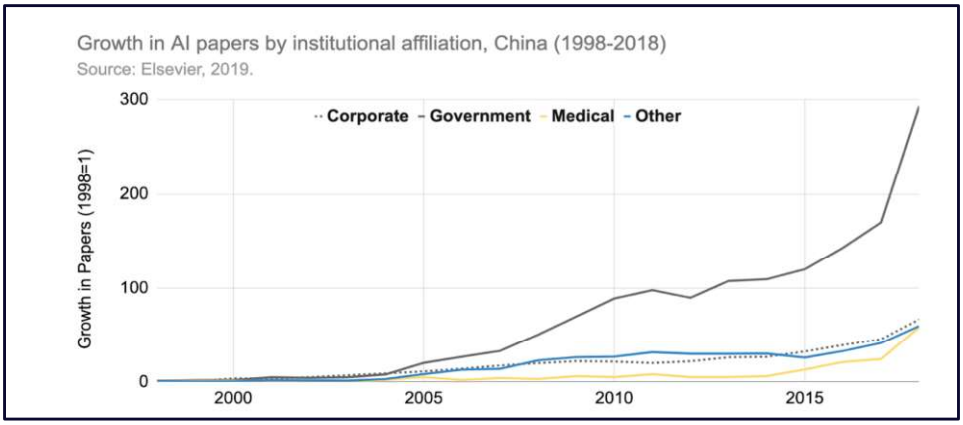
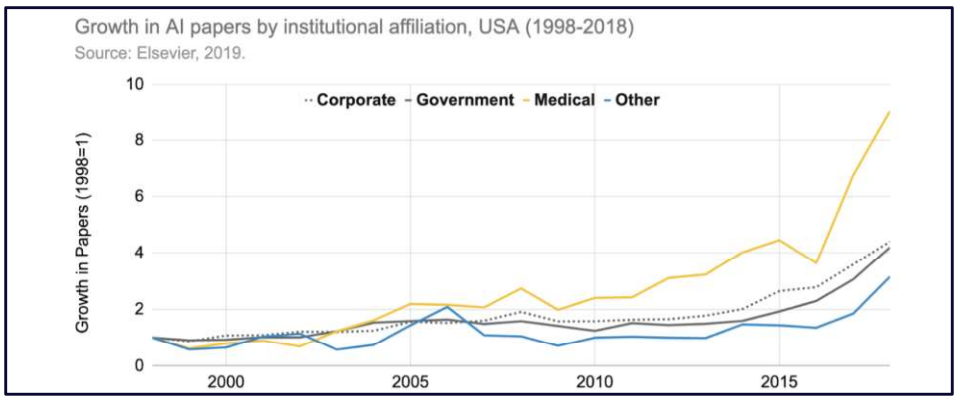


Figure 2a & 2b: Distinction in the Institutional Affiliation of US and Chinese AI Publications

Source: Elsevier, 2019. Retrieved from "The AI Index 2019 Annual Report," AI Index Steering Committee, Human-Centered AI Institute, Stanford University, Stanford, CA, December 2019, p. 186.



The collaboration between Atomwise and Hansoh Pharma poses questions from the disparate political economies of the United States and China: given the intensive state support to the Chinese pharmaceutical industry, why is cooperation in this increasingly competitive field still favored by both parties? Should collaboration be the norm for future US-China interaction in drug discovery? To answer these questions, it would be helpful to understand the implications of emerging Chinese pharmaceutics on the US government, market, and society.

Given the nature of Chinese industrial plans, a thriving Chinese pharmaceutical sector may not be able to impose a meaningful threat to US leadership in the pharmaceutical industry. Unlike some novel areas (e.g., 5G) that China aims to lead in global standard setting, drug development is a field in which China intends to embrace the current international standard. In fact, an important aspect of the Chinese pharmaceutical industrial plan is to play by the international standard, which, in practice, drives Chinese pharmaceutical companies to attain approval from the US FDA to be globally competitive. As long as the US drug approval standard is a credible benchmark for safety and efficacy and the US market remains attractive, Chinese innovative drug development should be placed under US regulation, and the US government has the final say on this.

For the global innovative drug market, given Chinese pharmaceutics' low position in the global value chain, they still seem unlikely to challenge the US "Big Pharma" over market dominance probably in decades. As an important indicator of innovation, only about 1% of pharmaceutical patents in major countries are issued to Chinese companies, way less than the US share of more than approximately 40%.[54] Though this does not seemingly harm today's US interests, some may raise concern of the possibility that industrial development in China will lead to a takeover of global innovative drug supply in the future. However, given today's disparity between US and Chinese pharmaceutical innovative capacities, this vision is very unlikely to come true in the foreseeable future. Rather than China creating innovative drugs, reducing US reliance on Chinese API would be a more legitimate concern. According to the FDA, in 2019, about 13% of API manufacturers supplying the US market were based in China, which doubled its share in 2010.[55]

On the social aspect, compared with an intangible threat to US leadership in the global pharmaceutical industry, the positive social externality brought by Chinese pharmaceutics will certainly benefit society with more diverse health solutions. The increase of novel medicine — meaning previously unknown — can save American lives, reflecting the great social impacts connected with improvements in healthcare.

Thus, helping Chinese pharmaceutics improve their innovative capacity tends to be a "Pareto improvement" that does not impose meaningful loss to other stakeholders. According to the American AI Initiative, as long as the cooperation aligns with US values and interests, it will not be opposed by the federal government, which aims to open oversea markets for American companies.

However, some may worry that the merger of AI and drug development will complicate the situation from a geopolitical perspective. Considering China's ambition in leading global AI technology, is it possible that the Chinese government will interfere in transactions because of a potential over-fascination with domestic AI firms?

From an institutional perspective, the Tiao-kuai (条块)[56] arrangement of the Chinese government prevents separate governmental units of the same rank from overriding one another's policies. As a result, the governmental units responsible for pharmaceutic development would have no institutional incentive to advance the AI initiative in pharmaceutical development. Furthermore, companies are registered under their local government, so their business is primarily influenced by local policies on a day-to-day basis. The central-local tension within the Tiao-kuai arrangement makes the local government prioritize local over national interests. In this case, the international AI competition is not the priority for the local government, compared with the pharmaceutical cluster that steadily brings in tax revenue and foreign investment; there is no further incentive to interfere with the free market decisions made by local pharmaceutics. In this sense, the co-development project using AI technology is unlikely to face arbitrary challenges from the state.

In reality, although Chinese AI firms may have been granted through state support, in drug discovery, they still experience a significant technological lag behind their international competitors. The existence of such a market gap makes Chinese pharmaceutical companies naturally see a foreign AI firm with a strong technical background as an attractive partner,[57] which is exactly what happened in the case of the Hansoh-Atomwise collaboration.

For the Chinese government, such collaborations should be beneficial as well. The acceleration in innovative drug development fits its national agenda; on the local level, it also brings positive externality to the economy and society. Although the foreign AI firms (e.g., Atomwise) can potentially gain tremendous profits from the collaboration, the collaboration also saves Chinese pharmaceutics (e.g., Hansoh) tremendous investment in the long and expensive drug development process, and it also fills in the market gap left by domestic AI firms. As a result, even from the perspective of government, Sino-American cooperation in drug discovery should be regarded as having positive prospects.

Moreover, AI in drug discovery is unique, as it does not face serious policy hurdles regarding privacy, compared with many other AI applications in healthcare. AI algorithms for drug discovery are based on the data of chemical compounds, which is far less sensitive than, for example, patients' medical records. While data security and privacy awareness appear to be global trends in public policy making, AI application in drug discovery can potentially bypass the barriers of protective policies in different countries. In addition to the relatively low political risk and high level of positive social impacts to both countries, such collaboration should be the norm for future interactions.

Though seen with great prospect, the potential of AI in drug discovery still needs time to be fully tested, as this is still a nascent field. Drug development takes time; even the foremost drug created with AI technology still sits in clinical trials waiting to be approved.[58] However, as we keep witnessing the progress brought by AI technologies, realizing its full potential in drug discovery may only be a matter of time.

Thus, the issue of improving the drug discovery process with AI technology can still be identified as a "**Green Light"** in accordance with Asia Society's Green-Yellow-Red (GYR) framework. In a foreseeable future under the current trajectories, cooperation for intelligent health solutions is deemed with prospects, and the world will enjoy its realization.

We should also note that the benefits of improved healthcare are not guaranteed without thoughtful, stable support from public agencies and an international political climate that is not intensely competitive. The contemporary political climate between the United States and China requires stakeholders be extra mindful of any changes in the international power landscape. In this sense, the cooperation between the AI and pharmaceutical industries risks being placed on a value-based decision that might avoid some of the structural realities inherent in the distinctive political economies of two countries. For the prospective collaborators, the extent of Chinese state intervention breeds uncertainty in international cooperation. Therefore, deploying AI in drug discovery bears the possibility of "**Green turning Yellow**." The implications of any future development rest on thoughtful inquiry and constant alert.

CONCLUSION

Recent trends show that both the United States and China are placing more resources on facilitating the development of the healthcare industry and its intersection with AI technology. As a result, an increasingly competitive international market should be expected in the coming years. While the implications of future skyrocketed market size and intensified competition remain uncertain, there are some key takeaways at this point.

KEY TAKEAWAYS

- **AI technologies have shown great potential to improve the efficiency of drug discovery.** Globally, the collaboration between AI firms and pharmaceutics in drug discovery has begun to harness some successes through the identification of drug candidates in the early development stage.

- **AI in drug discovery continues to be a nascent field.** AI's foremost progress in pharmaceutics is still far from attaining approval for entering the marketplace; its empirical evidence on overall cost-saving effects and implications on market pricing still await testing.

- **Policies in the United States and China regarding innovation in healthcare are not in opposition, and space for future cross-border cooperation exists.** The United States and China have issued guidelines and policies to facilitate the development and integration of AI technology. The current policies of these two countries are not in opposition to the collaboration between a US firm and a Chinese pharma company. The space for future cross-border cooperation in the two countries looks ample.

Today, the biomedical research community has grown increasingly globalized and connected. As sophisticated and enormous as the pharmaceutical industry is, any effect that obstructs international communication would be hazardous for the research community, the economy, and the general public. In this light, just as in many other fields that require a stable international environment, the future of deploying AI in drug discovery depends on the efforts made by decision makers today.

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