Artificial Intelligence in Drug Discovery

Believe the hype

May 2020

Advisors | MEHTA PARTNERS

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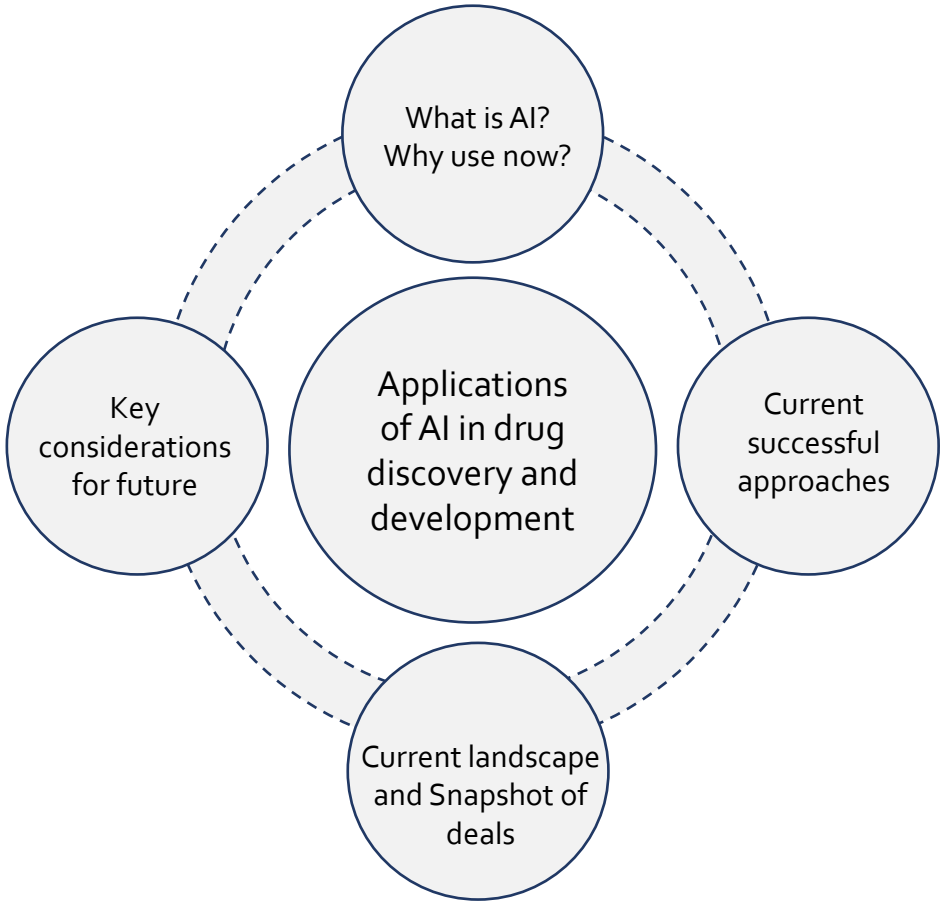
Executive summary

Key questions answered in the presentation



- Artificial Intelligence (AI) is a potential solution to the continuously declining efficiency of Biopharma R&D
  - AI algorithms learn from millions of data points to predict new drugs, optimize drug properties, repurpose existing drugs in new indications and optimize clinical trial design and execution
- Proven cases in hit identification and lead optimization, off-target toxicity predictions, biomarker establishment are already available
  - AI based target validation and lead discovery proven to be up to 15 times faster than traditional discovery methods, with lead generations in a matter of few months vs. 4- 6 years
- The AI drug discovery ecosystem is now maturing, with >200 AI based start ups working in different stages of drug discovery, >$3.5B in investments and early stage BioPharma partnerships
  - Promising results across indications in oncology, neurology and infectious diseases are already achieved
  - AI adoption is rapidly increasing, with more >45 pharma cos and CROs partnering with AI based startups with 100+ deals
  - Early stage drug discovery accounts for a significant share of overall number of deals
- In the coming decade, AI will be an integral part of drug discovery therefore, it is timely to consider embed AI-based tools in R&D initiatives
- MP Group has closely monitored this space and developed a deep understanding through interactions with several companies globally, that enables us to identify and evaluate prudent below-the-radar partnering opportunities in AI-drug discovery space

Biopharma is facing efficiency challenges – Can Artificial Intelligence (AI) be the required catalyst?

Biopharma's 'averse to change' mindset adopting age-old drug discovery and development methodology coupled with conservative regulatory guidelines has led to declining efficiency over the last decade

>$2.1 billion	**Average Cost** to get a drug approved and launched in the market[1]
10-12 years	**Time** for development of one drug from discovery to approval
~90%	**Failure rate** in clinical trials

Potential Considerations to Improve R&D Efficiency

- Comprehensive understanding of disease mechanism and the network of interacting proteins for a more efficient multi-target approach
- Availability of accurate three-dimensional structures of target proteins for structure specific drug design with higher binding affinity
- Better toxicity predictions to minimize the failures in late stage developments

These limiting factors usually leads to crowding of drugs against the same targets and often small incremental survival benefits not justifying the cost of such therapies.

Among the upcoming technologies, Artificial Intelligence (AI) based platforms demonstrate promise to improve R&D efficiency while reducing the rate of failures. A few early adopters of AI tools are already experiencing the positive impact across the drug discovery and development value chain

AI as a potential solution

AI is based on advanced algorithms that can 'learn' by analyzing big data and perform human-like tasks by predicting future outcomes at an unmatched speed

Asset Identification	AI utilizes complex algorithms to screen millions of data points to validate pharmacological targets and perform in-silico analysis for safety and efficacy predictions in a fraction of time, reducing costly manpower and experimental input
Asset prioritization	AI can automate pipeline prioritization depending on continuous monitoring of real-world evidence and build models on 'big data' to validate the hypothesis
Diversify pipelines	AI can assist in finding and navigating new niches for differentiated targets or 'rare-diseases' indications for competitive advantages
Clinical trial management	AI applications have been developed for improving patient recruitment, compliance monitoring and data analysis to evaluate population specific benefits

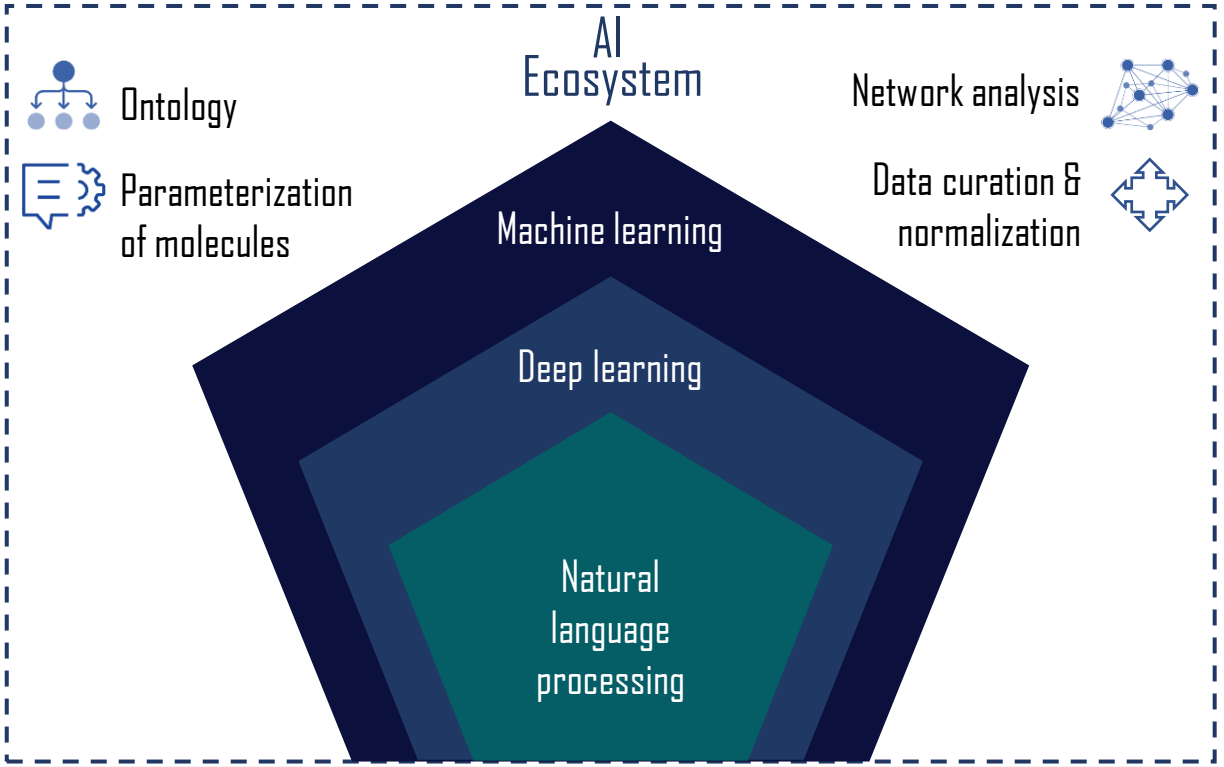
Source: [1]Measuring the return from pharmaceutical innovation 2018, Deloitte, MP Analysis

AI is a complex math algorithm that can 'learn'

Data quality is the secret sauce for success

Non-exhaustive data input

- **Literature**: Journals, books, patents, 3rd party sources & more
- **Patient data**: Patient samples, medical history, genomic data & more
- **Molecule libraries**: Chemical properties, 3D structures, ADME/QSAR
- **OMICS data:** Disease specific data, therapy specific, sub-population specific data, scaled microscopic images
- **Clinical trial data:** Patient population, doctor's notes, site specific patient availability etc



ML: Algorithms that feed on structured and unstructured data, identify buried patterns, and predict future outcomes

DL: ML algorithms that utilize a logic structure akin to the brain called neural 'networks'

NLP: Analysis and synthesis of structured data from natural language of notes and speech

Types of AI applications

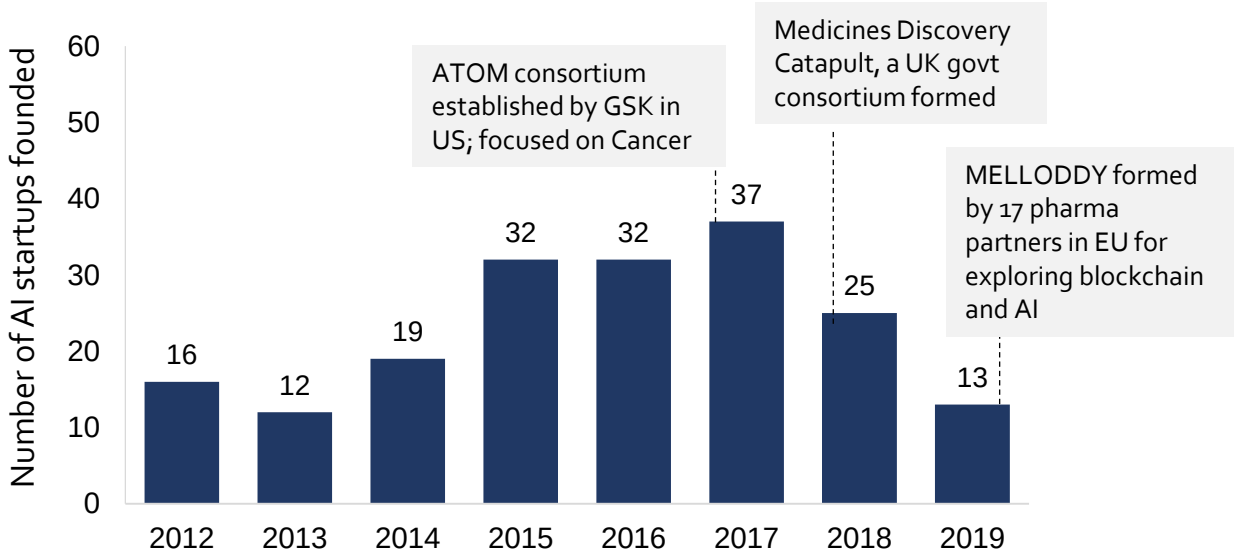
- Design and run preclinical experiments
- Data aggregation & analysis/hypothesis support
- Drug design and optimization
- Optimize clinical trial design, recruitment and analysis
- Understand mechanisms of diseases
- Repurpose existing drugs

A rush of AI-drug discovery start ups and venture funding witnessed in the last decade – The industry awaits maturity

230+ Start-ups using AI in drug discovery incorporated so far

The total number of start up boomed from about 40 pre-2012 to >200 by 2019. A decreasing trend is being observed in the last two years suggesting high competition albeit among early stage companies along with a few matured companies starting to dominate the space.

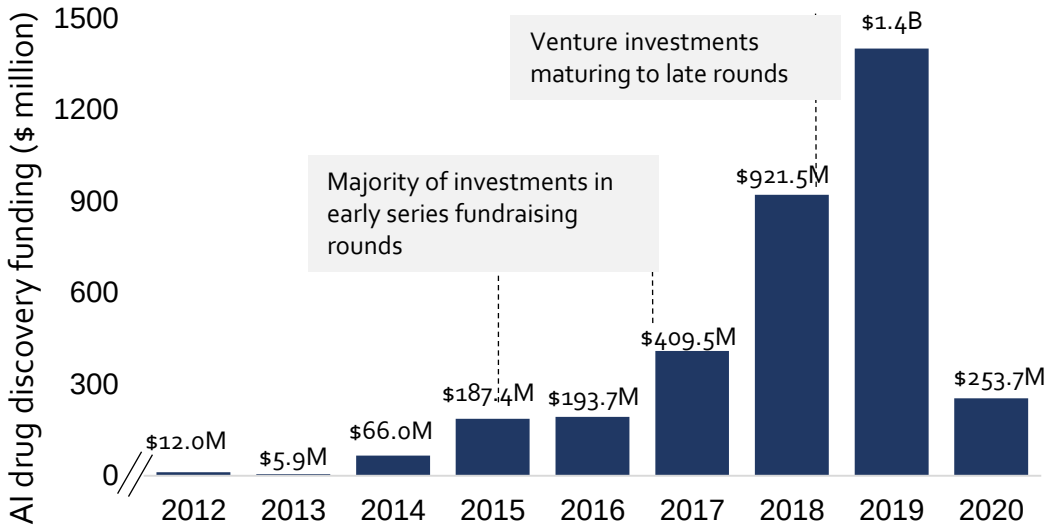
Consortiums to ensure data security are being formed in the US, EU and UK, thereby providing common resources to accelerate AI drug discovery applications



$3.5B+ Invested in AI based drug discovery start-ups

AI drug discovery has attracted VC groups, along with a strong involvement shown by venture groups of pharma as well as the tech giants like Google Ventures, Tencent, GE Ventures, etc.

The venture funding is shifting to late stage platforms/companies with established proof-of-concept. ~80% of the funding has gone to <10% of the companies



Source: BenchSci, MP Analysis

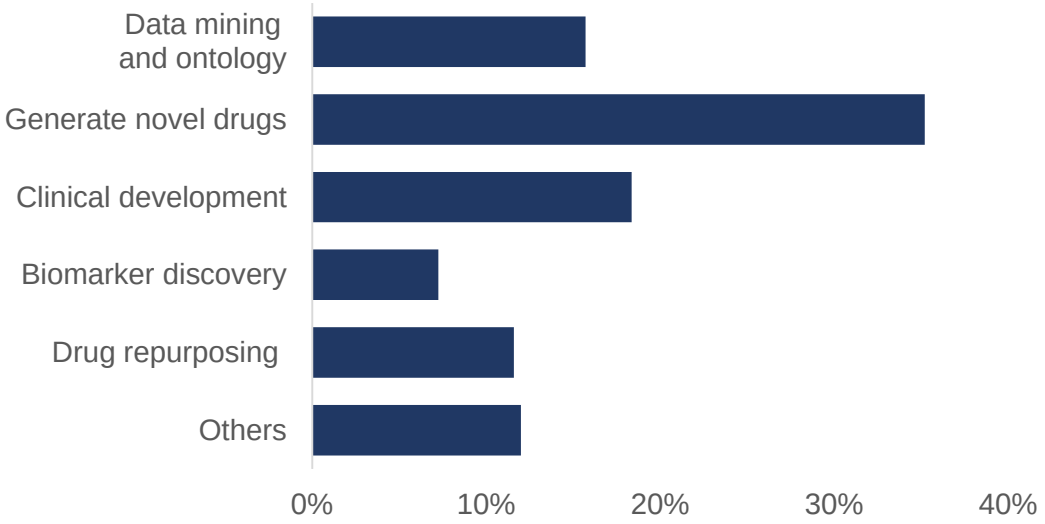
~50% of the AI-based companies focus on early stage drug discovery

Promising results already seen in oncology, infectious disease & neurology space

AI drug discovery companies by segment

Only a handful of companies have internal development programs, while majority of the companies work on a license-based model offering their software/AI platforms as a service

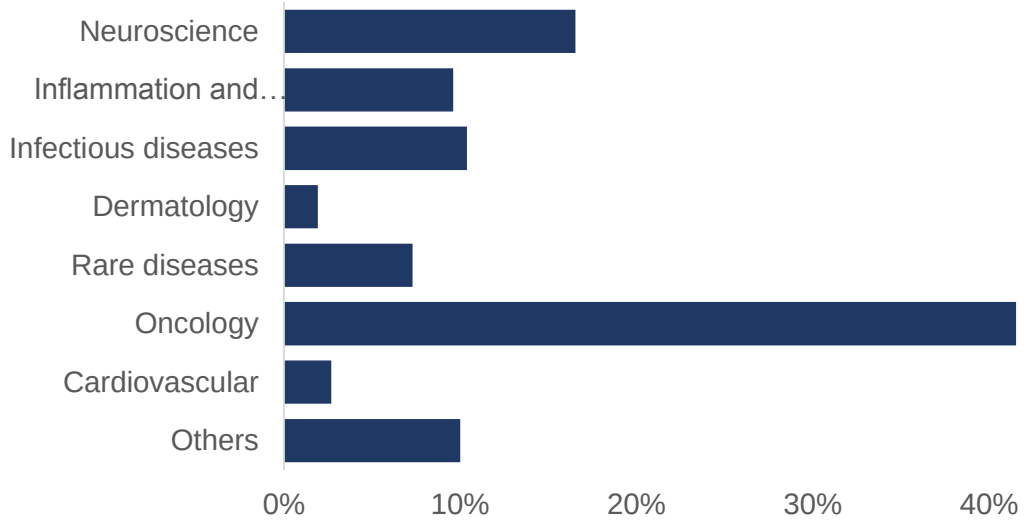
While most have capabilities specific to a vertical within the drug discovery or development value chain, a few companies have capabilities across all the functions. Some of these companies have already inked broad partnerships with Big Pharma



Source: BenchSci, MP Analysis

Pipeline of drugs using AI

Among 116 drug candidates identified using AI platforms at different stages (eg: ADMET prediction, sub-population identification) in development, several compounds focusing on Oncology, Neurology and Infectious Disease are in the late stage development. Results of completely AI driven and designed programs have also been recently reported
For e.g. Exscientia announced registration of a phase I trial for first completely AI-designed drug for obsessive compulsive disorder within 12 months of project initiation in collaboration with a Japanese pharma

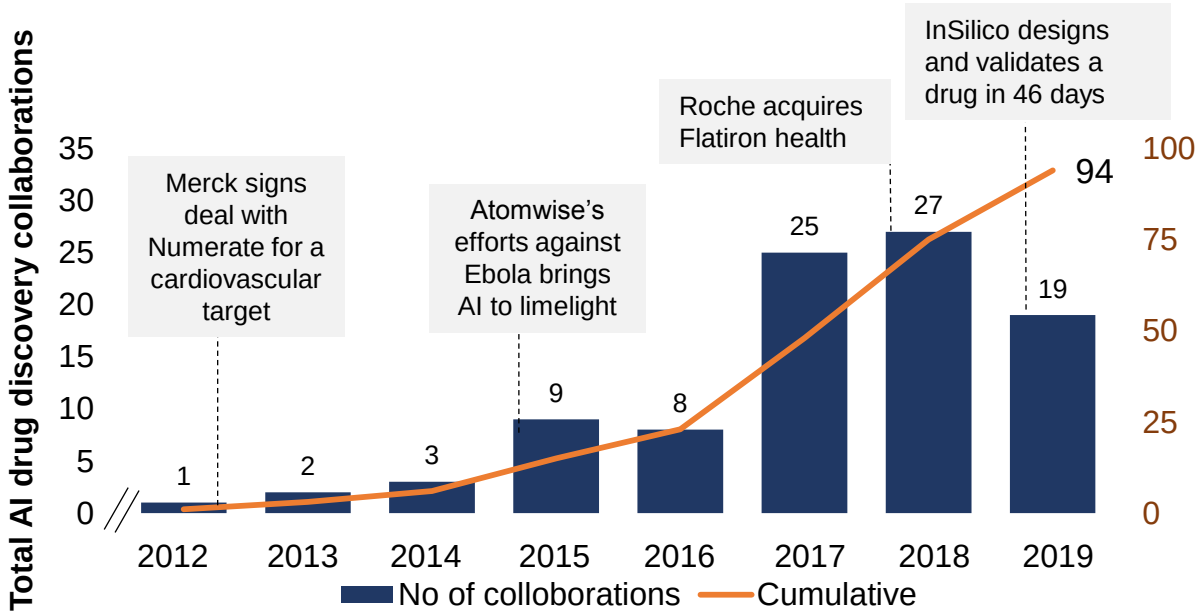


Pharma industry is rapidly adopting AI to boost efficiency

AI R&D market is expected to cross USD $20 billion by 2025

45+ **Pharma companies and CROs** partnering with one or more AI based start ups

Global pharma: Adoption of AI has been the highest in the US, followed by the UK
Japanese pharma: Adoption is increasing among large pharma companies
Indian pharma: Adoption is low, with only a few companies exploring AI



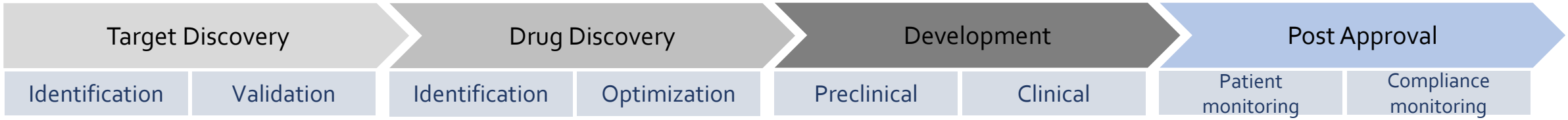
Source: Secondary Research, MP Analysis

100+ **Deals spanning** a wide variety of applications

Majority of the deals are concentrated in early discovery, including target identification, validation and hit/lead discovery

Applications of AI in drug discovery and development

AI platforms have the potential to save time and improve efficiency of several key steps across drug discovery and development value chain



- Extract knowledge from literature to generate insights on possible hidden variables that may be important
- Identify competitive whitespace
- Generate novel target ideas by understating underlying disease mechanisms
- Identify a polypharmacology/Multi-target approach
- Validate targets using various computational models

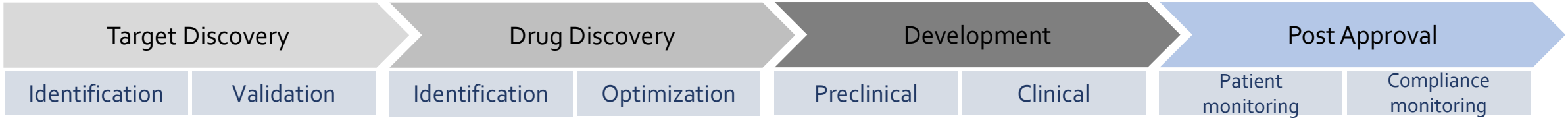
- Analyze data sets, form hypotheses and generate drug candidates
- Analyze data from patient samples in both healthy and diseased states to generate novel biomarkers and therapeutic targets
- Repurpose currently approved drugs to rapidly identify new indications
- Conduct experimental biology at scale by testing 1000+ of compounds on 100+ of cellular disease models simultaneously
- Predict 3D structures of protein targets
- Predict binding affinity, ADMET and other pharmacological properties of molecules

- Optimize clinical trial study design
- Transform diverse streams of biomedical and healthcare data into computer models representative of individual patients
- Deliver personalized medicine at scale by revealing optimal health interventions for individual patients
- Automate matching patients to clinical trials through personal medical records and genetic analysis
- Improve pathology and sub-group analysis
- Improve patient monitoring and compliance in real-world settings

Source: Secondary Research, MP Analysis

Snapshot of select deals across diverse applications

AI-enabled solutions are emerging as a crucial tool for transforming the process of drug discovery from identifying mechanisms of action to improving pharmacological properties of drugs to establishing biomarkers, etc.



BAI will combine its platforms with AstraZeneca's genomics, chemistry and clinical data to identify new targets in Idiopathic Pulmonary Fibrosis and Chronic Kidney Disease

AstraZeneca
BenevolentAI

charles river
Atomwise

Charles River will integrate Atomwise's AI technology to its drug discovery platform. It has the potential to significantly streamline the hit discovery, hit-to-lead, and lead optimization process for clients' research efforts

abbvie
AiCure

AbbVie used AiCure's AI-based patient monitoring platform to improve adherence in a phase 2 schizophrenia trial. AiCure announced study results demonstrating 90% adherence

Bristol-Myers Squibb
Concerto HealthAI

BMS's partnership with Concerto covers a range of data sources and activities, including clinical trials protocol design, and precision oncology treatments

Takeda
Numerate

Takeda tapped into Numerate's platform to develop new clinical candidates in oncology, gastroenterology, and CNS. It includes hit finding and expansion through lead design/ optimization to ADME/ toxicity predictions

Teva will use IBM Watson services for repurposing existing drugs. IBM will also help in improving chronic disease management and develop Real World Evidence E-health solutions

teva
IBM Watson

Source: Company Reports, MP Analysis

Insilico Medicine

Case study: Hit discovery and validation in 46 days

Uses Deep Learning to identify novel targets and design small molecules with desired properties

Target Discovery | Drug Discovery | Development | Post Approval

Founded: 2014

Location: Hong Kong (originally established in US, moved headquarters 2019)

Funding to date: $56 million;

Key partnerships: Pfizer, GSK, Jiangsu CTF Pharmaceutical, Novartis

Proprietary platform: Generative Tensorial Reinforcement Learning (GENTRL), which combines two distinct DL models, a generator and a discriminator. The 'imagined' output by one network is tested by the other network. Once a target is identified, DL algorithms design molecular structures with desired physical and chemical properties

Why watch? - Other than the collaborations, the company is working on internal programs in CNS, oncology, dermatology, fibrosis and aging. Company has over 150 partnerships, with more than 120 peer reviewed publications and has received several innovation awards

Molecules in pipeline: Oncology candidates in collaboration with A2A pharma disclosed

GENTRL Platform – A Case Study

The GENTRL platform has generated new drug hits against DDR1, a kinase involved in fibrosis. It took about 21 days for the AI system to design the molecules.

The total time for hit design, optimization, synthesis and validation in vivo was about 46 days. The time taken was 15-fold lesser than traditional biopharma process. The results were published in Nature Biotechnology (2019)

The current paper has its origin to a challenge posed by a team at Genentech, which took about 8 years to identify promising candidates against DDR1. Insilico Medicine's platform completed the hit discovery and validation within 46 days

The company believes that the platforms built on its technology has the potential to save millions of dollars in R&D costs, and significant time in small molecule discovery along with a better probability of success.

Source: Company Website

CYCLICA

Case study: Minimize toxicity of drugs - poly-pharmacology implications

Uses AI to consider-the polypharmacology and predict pharmacokinetics and structural pharmacogenomics

Target Discovery | **Drug Discovery** | Development | Post Approval

Founded: 2013

Location: Toronto

Funding to date: $7 million;

Key partnerships: Bayer, Merck KGA, WuXi Apptech, Tieos pharma

Proprietary platform: 2 platforms; 1) Ligand Design®, a platform which can uniquely de novo design chemical entities across a panel of desirable targets while avoiding undesirable anti-targets 2) Ligand Express®, a cloud-based platform that screens small-molecule drugs against repositories of structurally-characterized proteins or 'proteomes' to determine poly pharmacological profiles and provide insights into a compound's off-target interactions

Why watch? – Published several used cases in collaboration with the existing partners along with noteworthy contribution to the understanding of repurposed drugs used in Ebola treatment

Molecules in pipeline: Not disclosed

Ligand Express® - A Case Study

Cyclica's platform, Ligand Express® discovered the molecular reason leading to the fatal side effects exhibited by a chronic pain treatment drug candidate Decernotinib (Vertex Pharma) in clinical trials in 2016. Decernotinib disrupts the pro- inflammatory protein Janus Kinase 3 (JAK3). In addition Ligand Express® identified several off-target interactions, including with the isoforms of JAK1 and JAK2.

Implications for a multi-target approach:

Cyclica used its platform to identify binders to the panel of 5 proteins (SIRT1, SIRT2, SIRT3, PTP1B, MCL1) to design in Sirtuin 2 inhibitor. About 100,000 compounds were screened of which 22 were selected and tested in vitro to identify a selective hit. This entire study was executed within 20 business days

Source: Company Website

PHARNEXT

Case study: Repurposing drugs, What was old, is new again

Uses AI to screen and reposition known drugs in unrelated indications at new, lower doses

Repurposing

Target Discovery | Drug Discovery | Development | Post Approval

Founded: 2007

Location: France

Funding to date: $37 million;

Key partnerships: Ipsen, Tasly pharma (Beijing)

Proprietary platform: PLEOTHERAPY™ systematically identifies and develops new synergistic combinations of existing drugs repositioned for diseases with significant medical needs. These new therapeutic entities, called PLEODRUG™, are expected to have high levels of efficacy and safety. Indeed, these are formulated with new optimal doses of their constituents and simultaneously target several anomalies associated with a given disease

Why watch? – Focus on CNS discovery with 4 drugs in clinical pipeline, and one candidate in phase 3 having orphan drug status

Molecules in pipeline: Candidates for Alzheimer's Disease, Parkinson's, ALS and Charcot-Marie tooth disease

PLEOTHERAPY™ - A Case Study

Pharnext reported positive results for a Phase III trial of one of its drug combinations, PXT3003 for a neurodegenerative condition called Charcot-Marie-Tooth disease (CMT), a rare disorder.

PXT3003 is a low-dose fixed combination of baclofen, naltrexone and sorbitol, given twice a day as an oral solution. It has multiple mechanisms of action - inhibition of PMP22 gene associated with an improvement in myelination, preservation of the axon of the peripheral nerves and additional targets as identified by systems biology approaches

PTX3003 was granted orphan drug status by US FDA and EMA

Source: Company Website

AiCure

Case study: innovative use in patient monitoring in CNS

Uses AI to optimize patient engagement and establish digital biomarkers in clinical trials and post approval

Target Discovery | Drug Discovery | **Development** | Post Approval

Founded: 2010

Location: New York, US

Funding to date: $51.8 million

Key partnerships: Abbvie, Syneos health, Cerevel therapeutics

Proprietary platform: AiCure provides a clinically validated, scalable, and patient-centric technology platform which can see, hear, and understand how patients respond to treatment. It also has an advanced data analytics system that enables intelligent decision-making and improving health outcomes.

Why watch? – Already demonstrated POC in real world settings. Moreover the innovative algorithms enable assessment of responses in complex CNS diseases like Alzheimer's and Parkinson's disease

Company announced an alliance with Syneos health, a large CRO in the pharmaceutical industry

Molecules in pipeline: Not applicable

AiCure Platform – A Case Study

Abbvie tested AiCure's platform in a Phase 2 trial of an oral drug for schizophrenia. AiCure platform was introduced into 10 of 31 US sites. Subjects were monitored either by AiCure or by modified Directly Observed Therapy (mDOT) at least 3 times per week. Patients on AiCure's platform showed a 90% adherence as compared to 70% with mDOT in schizophrenia trials

Recently, the company also announced positive results of use of the platform to develop digital biomarkers based on vocal tremors in a Parkinson's trial by Cerevel Therapeutics

Source: Company Website

Indicative list of companies with AI-drug discovery focus

	Name	Founded	Funding $m	Molecules in Pipeline	Select Pharma Partners/ *CRO* *other undisclosed partners	Uses AI to…
Prominent names	**Atomwise**	2012		Not disclosed	Monsanto, Merck, Pfizer, Abbvie, Eli lilly, *Charles River Laboratories*	
	XtalPi	2014	67.5	Not disclosed	Pfizer, *Porton pharma solutions*,*	Predict the crystalized form of drug and understand the potential safety, stability, and efficacy
	Exscientia	2012	43.0	13	Janssen, GSK, Sanofi, Evotech, Sunovion pharma, Sumitomo Dainippon Pharma	Process drug discovery data and generate candidates in one-quarter the time of traditional approaches.
	TwoXAR	2014	14.3	19	Santen Pharmaceuticals, Ono pharmaceuticals, SK biopharmaceuticals	Screen compound libraries for efficacy, identify new drugs from a public library, and identify new targets
	Schrodinger	1990	193	5	Sun pharma, Bayer, WuXi Apptech, ono pharma	Ideate, optimize, and analyze drug candidates. Evaluate chemical compounds in silico ahead of synthesis and assay
Below the radar	**Globavir**	2011	7.5	2	Bio-Rad	Leverage existing data to develop therapies (currently focused on infectious disease diagnostics and treatments)
	Insitro	2018	100	-	Gilead	Generate cellular models from large, high-quality datasets
	Sirenas	2011	1.3	-	BMS	Analyze metabolomic and bioassay datasets to uncover insights into human health and establish biomarkers
	Carocure	2017	0.75	5	-	Predict toxicity to weed out toxic compounds and increase the efficiency of computational drug discovery
	X-37	2019	14.5	5	-	Develop drugs for hard-to-target proteins with high therapeutic value

Source: Secondary Research, MP Analysis

AI is the future of biopharma R&D

The promise of AI will have far-reaching impact on the pharma industry

Where are we?

- All major pharma companies have invested/partnered with an AI based company, with the primary focus on early stage discovery
- AI based target validation and lead discovery has demonstrated to be up to 15 times faster than traditional discovery methods, with lead generations in a matter of few months vs. 4-6 years
- Benefits in hit identification, lead optimization, off-target toxicity predictions, and biomarker establishment are already proven by case studies
- The number of new companies being formed has reduced suggesting a maturity in understanding and functioning of the AI ecosystem
- The recent approval of software for diagnosing diabetic retinopathy and heart conditions by the FDA highlights the flexibility of the regulators to consider AI-based solutions

The next 10 years

- The potential of hit identification and lead optimization within months with heavy reliance on AI-based platforms for early stage discovery
- AI based repurposing abilities will allow companies to explore multiple indications and virtual cellular models at low cost and reduced timelines, leading to diversification of pipelines
- Partnerships between virtual discovery AI start-ups and experimental CROs will lead to one-stop shops for early stage discovery companies
- Over the next 2-3 years, the results of current AI partnerships and programs will begin to un-fold, raise the bar for not only the collaborations but also for new entrants
- Adoption of digital AI-based platforms along with wearable technology in clinical trial stratification and analysis is likely to increase
- Regulatory guidelines are likely to evolve over the next 5 years favoring artificial drug with predicted pharmacological properties to reduce the clinical development timeline

Source: Secondary Research, MP Analysis

Why should Pharma cos consider adopting AI strategy?

Benefits of AI have already been observed across drug discovery value chain

- AI is already catalyzing a range of drug discovery initiatives, from target identification to hit/lead generation to ADMET prediction, to drug repurposing opportunities, identify repurposing opportunities, etc.
    - Several candidates in neurology, oncology, and anti-infectives developed using AI, have reached late phase clinical development, suggesting a high potential of technology-based disruption in the space
    - A molecule completely designed using AI with minimal pre-clinical intervention has recently entered clinical trials
- Therefore, it is timely for pharma cos to adopt AI strategy to improve R&D efficiency and therefore, expedite the pace of innovation, while reducing the risks associated with drug discovery. Some of the key areas for consideration are -
    - Reduce time and cost of drug development – Multiple-fold improvement in efficiency of hit to lead discovery, predicting ADMET properties and efficacy can save substantial time and cost
    - Drug Repurposing – Enhance pipeline diversification using the existing drugs for new indications, while reducing the chances of failure
    - Asset and indication prioritization for the current drug discovery and development projects, including exploring new indications for a fraction of cost and time
    - Clinical trial capabilities – Adopting AI to identify patient populations, trial site and data analysis can give significant impetus to your clinical development programs

Key considerations for adopting AI

A two-step framework that can help identify the right AI partner

Step 1

Internal Foundation

Identify the area of focus

- Identifying the key segments that AI can benefit is of prime importance
- Understanding potential disruptions feasible through AI platforms
- Understanding potential opportunities through partnerships, investments or licensing with AI companies

Informed Team

- Assess the organizational fit for AI
- Identify cross-functional teams and ensure continuous evolution of their understanding
- Establishing key parameters and performance indicators for monitoring growth

Data Security

- Data sharing in Biopharma is often a concern. Understanding data security and partners data is important
- Recent consortiums are working to achieve effective data sharing, while ensuring its security

Step 2

Finding the Right Partner – Key Parameters to Consider

Therapeutic area knowledge (Domain specific or service specific)	Platform capabilities (Stringent or Adaptable to diff. data)	Management and team (AI experts vs. Biology experts)
Proof of concept (publications, patents)	Data used for training algorithm (depth of data, proprietary vs. public)	Business models (Platform for use or partnerships)
Other Partnerships (other big pharma, consortiums)	Scalability and evolution (Future generations/improvement possible?)	Cost Benefit (Tangible and intangible returns)

Source: MP Analysis

MP Group can catalyze your AI initiative

With over 3 decades of diverse experience and integrated perspective in domestic and global BioPharma, and deep understanding of AI space, MP Group has the capabilities to help establish your AI initiative

MP Team will be happy to be an extension of the management team and help with one or more of the below initiatives:

- Asses the internal capabilities and identify the key business segments for potential disruption/augmentation by AI platforms
- Identify business segments for short-term and long-term benefit from AI interventions
- Identify partnering or investment opportunities unique to company's vision
- Assess best use cases for big data analytics
- Technical due diligence to investigate the AI platforms best suited for the need

We invite you to write to us -

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