TABLE OF CONTENTS

HEALTHCARE MARKET REVIEW AND OUTLOOK

Healthcare made a slight comeback during the second quarter, outperforming global markets, as the MSCI World Healthcare Index rose 9.1%, compared with 7.4% for the MSCI World Index. All subindustries contributed about equally to the strong performance. Notably, small- and mid-caps finished the quarter strongly, although they were still under pressure during April and May; this performance mainly benefited biotechs, in particular gene-editing and vaccine players. Over the quarter, however, small- and mid-cap healthcare names lagged significantly, with the Russell 2000 Healthcare Index rising only 2.7%. At this time, the small- and mid-cap rebound we saw in June looks more like a pause in the market rotation from momentum to value than the beginning of a new trend. Looking at the globe, we note that emerging-market healthcare companies performed strongly after a cautious start to the year. The MSCI Emerging Markets Healthcare Index rose 14.1%, bringing year-to-date performance to

INDEX	CLOSE 6/30/2021	RETURN					ANNUALIZED VOLATILITY	
		1 MONTH	3 MONTH	6 MONTH	9 MONTH	12 MONTH	30 DAY	90 DAY
MSCI World Index (all country)	368.6	1.3%	7.4%	12.3%	28.8%	39.3%	7%	10%
MSCI World Index	9053.3	1.5%	7.7%	13.0%	28.8%	39.0%	7%	11%
MSCI World Healthcare Index	475.5	3.0%	9.1%	9.9%	17.4%	23.0%	9%	10%
MSCI World Pharma	295.3	3.4%	8.4%	7.8%	11.6%	14.6%	11%	10%
MSCI World Biotech	1999.1	5.2%	9.9%	9.8%	12.9%	8.9%	14%	15%
MSCI World Equip and Supplies	889.7	2.8%	8.8%	8.9%	19.8%	34.8%	12%	14%
MSCI World Healthcare Prov & Serv	903.2	-2.5%	6.7%	15.5%	30.6%	32.9%	11%	14%
MSCI Emerging Market Healthcare	881.2	1.1%	14.1%	8.9%	29.8%	32.3%	16%	21%
MSCI Emerging Markets	670.6	0.2%	5.0%	7.4%	28.6%	40.9%	9%	14%

8.9%. This growth trailed the MSCI World Healthcare Index, which increased +9.9% YTD only slightly.

We want to remphasize the view expressed in our previous Newsletter: Expect markets to continue to fluctuate between the good news — COVID and the recovery — and the bad news — inflation, debt, (lack of) recovery, and political unrest. Given the solid year-to-date performance after the Q2 run, we would not be surprised to see weaker markets over the summer, as valuations suggest much of the good news has been baked into the financial cake.

GROWTH P.A. 2021-2023E					
	SALES	EPS	PE21E	EV/SALES21E	COGS
MSCI World Pharma	3%	7%	16x	4.3x	30%
MSCI World Biotech	2%	2%	16x	6.0x	17%
MSCI World Equip and Supplies	6%	10%	32x	6.4x	40%
MSCI World Healthcare Providers	6%	11%	15x	0.7x	82%

Thus, we remain cautious. We continue to see healthcare as a good place to invest for the short run — it is a safe haven — as well as for the long — it is a steady grower. The main themes of its long-term growth remain innovation, digitalization, and the growing demand in emerging economies. We believe these themes are best refelected in the small- and mid-cap spaces, although larger caps represent a more stable opportunity in the short term.

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Chief Investment Officer

SOURCES:
Sectoral Asset Management
Bloomberg

INNOVATION IN DRUG DISCOVERY: THE EMERGING ROLE OF ARTIFICIAL INTELLIGENCE

The hallmark of biotechnology is innovation, the discovery of new targets and technology platforms for the development of safe and effective therapies to treat human disease. Exciting examples of these approaches, a number of which have already been launched or are progressing through clinical development, include gene and cellular therapies. These novel agents deliver into the body either a protein or mechanism to correct a disease-causing gene, while cellular therapies for cancer, such as chimeric antigen receptor T cells (CAR-T), involve the collection, modification, and re-administration of a patient's own immune cells to fight cancer. In addition to the pursuit of new therapeutics, the biotech industry is also advancing the technologies used to develop drugs, and an emerging subsector of biotechnology is applying artificial intelligence (AI) and machine learning (ML) to the process. Since 2020, a small number of companies in the field have entered the public markets through successful IPOs, with the featured companies closing between 74-195% above their IPO prices on their first day of trading, compared with an average 39% gain for biotech IPOs in 2020[1]. Notably, this performance surpassed their biotech IPO peers during a period in which biotech IPO activity and performance was robust: 92 biotech IPOs reported an average return of +89% in 2020[1]. Clearly, investors are paying attention and view AI to be a disruptive and transformational adjunct to drug discovery.

In this review, we will explore biotech innovations in drug discovery, taking a panoramic view of the emerging role of AI, and highlighting the proprietary technologies and capabilities of leading AI-driven biotechnology companies that have recently entered the public markets. Considering the breadth of therapeutic modalities, we will focus on the drug discovery of small molecules (chemical compounds), the most established area of research and development and the target of much AI-based innovation. This new subsector is continuing to advance; in so doing, it is validating its disruptive potential. Overall, the ongoing innovation provides further support for our positive long-term view of the biotechnology industry.

The promise of AI in drug discovery

John McCarthy, the father of AI, defines it as the science and engineering behind the making of intelligent computer programs.[2]. Machine learning, a subset of AI, is the method of developing algorithms to derive insights from datasets for decision-making and includes such methods as supervised, unsupervised, and reinforcement learning. Speech and image recognition are areas in which AI has shown much progress; indeed, these technologies are now omnipresent in our everyday lives: our conversations with Siri and Alexa, and our smartphones' ability to recognize when our pets are before the camera lens are only the most obvious examples of the range of AI platforms.

To truly comprehend how AI and ML can be applied to drug development, we need to understand the process, which includes target identification and validation, lead generation and optimization, and their shortcomings (Figure 1). The drug-development process for small molecules begins with identifying a biological target of interest implicated in the onset of a disease, followed by the application of animal and cell-based disease models to validate the target as one with the potential of offering therapeutic gain.

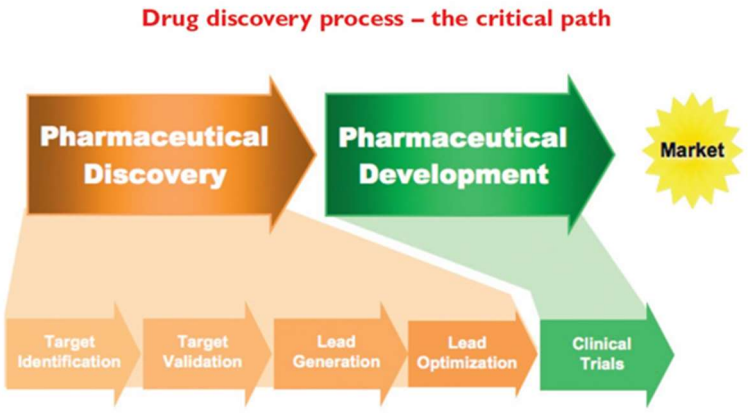

Figure 1: Components of the drug discovery and development process.[3]

After validating the target, a company then moves to lead generation, which involves either the screening of novel chemical compounds synthesized by medicinal chemists or the use of one (or more) of the millions of created compounds. After the large number of compounds have been screened, high-throughput (ie, automated) techniques are used to identify 'hit' compounds (ie, those that show activity against a target) that can be advanced to lead optimization. This step involves taking the 'hits' and evaluating compounds with similar chemical structures or modifying side chains to identify or create a molecule with optimal properties of ADMET: absorption, distribution, metabolism, excretion, and toxicity. Preclinical studies in cells and animals are also required for evaluating such essential properties as safety, mode of administration, interactions with other molecules, and efficacy. In other words, lead optimization is one of the most challenging and time consuming steps in the drug-development process, particularly as multiple, potentially opposing, properties must be evaluated and balanced (Figure 2). Once a lead compound is identified and preclinical studies are completed, the agent will advance into human clinical trials.

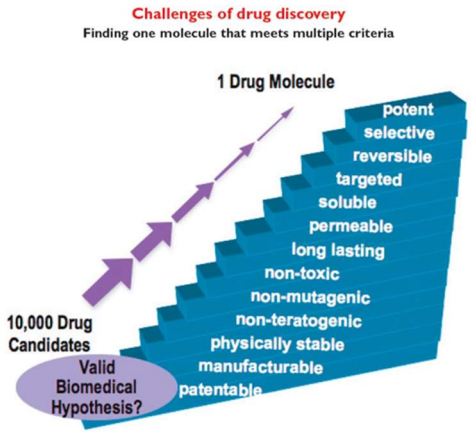

Figure 2: Challenges of lead optimization in the drug discovery process.[3]

Drug discovery and development are time-consuming, costly, and uncertain processes, with studies citing a 96% failure rate, a span of 14 years (on average) from start to finish, and a cost of USD2.6bn before the developmental drug reaches the market (Figure 3).[4,5]

Historical Biopharma R&D Metrics

	Success rate	Time (years)	Capitalized R&D spend per approval
Drug Discovery	51%	4.5	$881-$1,098
Preclinical	69%	1	
Clinical & FDA Review	8-14%	8-11	$954-$1,460
Overall	<4%	~14	$1,778-$2,558

Figure 3: The high cost of drug development .[4,5,6]

As decisions are made at each step of the drug discovery process, AI can be employed throughout, with computation-based screening enabling the assessment of a broader set of chemical compounds, while obviating the need for their synthesis. Moreover, ML algorithms have the power to analyze multiple datasets and parameters for decision-making (Figure 4). The lead-optimization phase is exceptionally costly and time consuming, as it requires multiple iterations of chemical synthesis and characterization and is complicated by the need to balance potency and drug-like characteristics, which are often in conflict. By applying ML to large chemical libraries in lead generation and optimization, AI promises to improve drug discovery by screening more molecules, thereby identifying drug candidates with better potency, safety, and drug-like properties. The end result is a greater likelihood of success, by bringing fewer compounds into lead optimization and shortening the development time. Taken together, the benefit reshapes the drug-development funnel, producing more screening with reduced optimization, both of which lowers the cost of drug development (Figure 5). These objectives are further aided by the addition of advanced computing and automation. The emergence of big data and its improved accessibility has also driven a need for AI to extract information and draw conclusions, particularly with large '-omics' datasets, which include the large-scale study of proteins (proteomics), transcription of RNA to proteins (transcriptomics), and phenotypic or physical changes to cells (phenomics), among others.

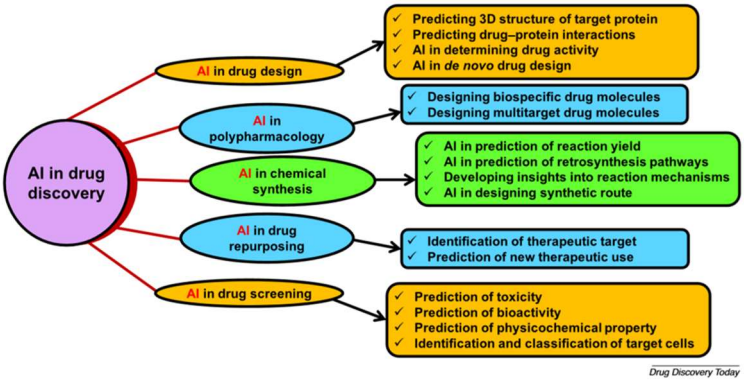

Figure 4: Potential applications of AI across drug discovery.[7]

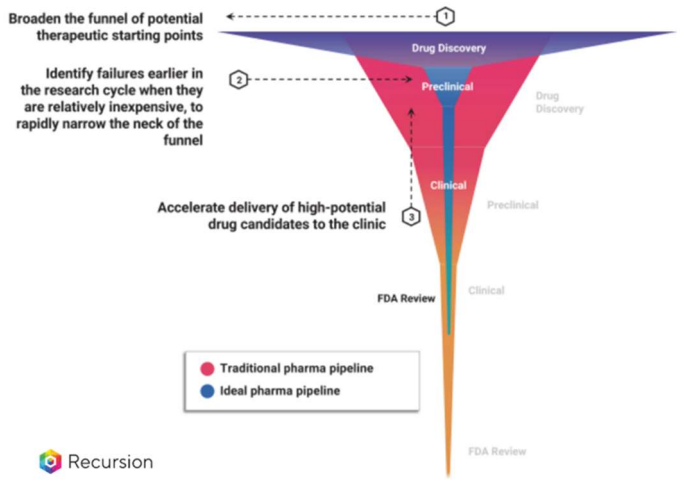

Figure 5: Recursion Pharmaceuticals' AI-driven approach to reshaping the drug-discovery funnel.[6]

Early biotech adopters of AI and computational approaches to drug development

BioXcel Therapeutics, founded in 2017 as a subsidiary of the leading big-data/AI corporation BioXcel Corporation, is a clinical-stage biotechnology company and one of the first to adopt an AI-driven approach to drug discovery.[1] Focusing on drug repurposing through their EvolverAI platform, which performs a comprehensive and unbiased evaluation of the pharmacological research environment (eg, clinical data, publications, and patent literature), BioXcel has the ability to identify drug candidates for development in new indications. EvolverAI identified dexmedetomidine, an IV-administered drug approved for the sedation of intubated and mechanically ventilated patients, as a potential therapy for agitation. BioXcel reformulated the drug as a thin film for sublingual delivery and recently concluded a successful Phase 3 trial in schizophrenia/bipolar patients with agitation.[8] (Regulatory

approval is anticipated in 2022.) In this case, BioXcel was able to repurpose an approved drug, shortening development time by up to seven years. Bypassing the discovery and optimization stages and moving directly into clinical trials saved billions. While BioXcel aims to identify candidates and progress from clinical trials to approval in 4-5 years, no new development candidates have been announced since their 2018 IPO, placing their two-leading clinical-stage assets in the sight of investors. Still, the company aims to re-emphasize its discovery engine by hosting an "R&D day" later this year, during which it plans to announce new programs in neurology and oncology.

One of the pioneers of computation-based target discovery, Compugen Ltd. uses a predictive computational discovery platform introduced in 1997.[9] This platform evaluates data from public and proprietary genomics, transcriptomics, and proteomics datasets, and is augmented with scientific expertise. Their computational approach was applied to target discovery, and it identified a new pathway of immune-checkpoint inhibition in 2009, resulting in novel drug targets, including TIGIT, a high-value immune receptor that biopharma has pursued aggressively. (Remember that cancer immunotherapies are an immense market, USD21bn in 2020).[1,10] Compugen's lead assets include two early-stage antibodies that mediate the TIGIT pathway. As Compugen has announced limited target-discovery news since a 2013 collaboration with Bayer for two new pathways, the clinical development of their lead assets is the primary focus among investors.[11]

Emerging biotech companies advancing AI in drug discovery

A number of biotech companies exploiting AI in drug discovery have entered the public markets since 2020 and with great success. Their valuations reflect the importance of AI, either for its potentially transformational discovery platforms or the biological insights that are generated, both of which can yield differentiated clinical assets in their pipelines. Compared with early adopters, these companies are attempting to maximize the capabilities of AI to revolutionize drug development.

Relay Therapeutics

Relay Therapeutics is leveraging their Dynamo computational drug-discovery platform, which incorporates advanced machine-learning models and molecular-dynamics simulations into identifying new targets derived from simulated protein motion.[12] This singular approach allows candidate molecules to probe biologically active conformations and yield drug candidates that might offer superior efficacy or safety, relative to competing drugs. In addition, the method has the potential to address receptors that, to date, could not be targeted because they lack a unique binding pocket for small-molecule inhibition. Relay's lead clinical candidate targets FGFR2 mutations in cancer and aims to improve upon the safety profile of the two FDA-approved FGFR2 inhibitors.[12] These drugs have high discontinuation rates due to excessive rates of diarrhea and elevated blood-phosphate levels, the latter of which is suspected of arising from the concomitant binding with FGFR1. Using the Dynamo platform, Relay has gained additional insights into the conformation of FGFR2 versus FGFR1. Through motion-based molecular simulations, their researchers have discovered that one conformation is adopted more frequently by FGFR1, relative to FGFR2. Relay has incorporated these dynamic differences into the design of their lead asset to improve FGFR2 specificity (Figure 6). Promising data from animal models shows lower serum phosphate levels and increased tumor shrinkage, compared with competitor compounds. Initial clinical data is expected later in 2021, and positive efficacy and safety data will provide meaningful initial validation for the AI-directed approach. At the same time, Relay is continuing to advance the capabilities of its Dynamo platform, acquiring ZebiAI in April 2021 for an USD85m upfront payment.[13] ZebiAI has developed ML to analyze DNA encoded libraries, a technique that monitors the binding of drug candidates to protein targets by tagging the molecules with a small DNA fragment for identification.

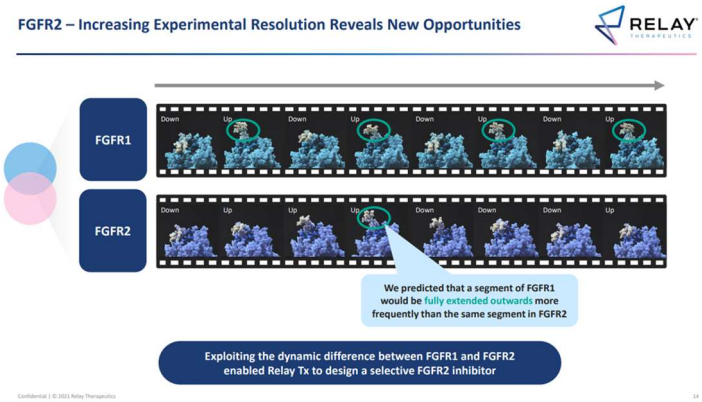

Figure 6: Unique insights gained from Relay Therapeutics' Dynamo, which incorporates protein dynamics into molecular modelling simulations.[12]

Recursion Pharmaceuticals

Recursion Pharmaceuticals is advancing technology-enabled drug discovery through their Recursion OS platform.[6] The system, which incorporates automation, AI, and ML, aims to reconfigure drug discovery by increasing the probability of success, speeding development, and, as a consequence, reducing costs. Recursion OS incorporates automated wet-lab experimentation into the platform, yielding high-throughput microscopy of cells interacting with library compounds. This monitoring of the physical and biochemical changes to cell properties produced through drug interactions can generate important new insights. The system incorporates automated imaging, data analysis, and robotics for sample manipulation. Recursion's burgeoning data universe is another core asset, as

the platform has been conducting 1.5 million new experiments per week. Leveraging this wide-ranging discovery tool, Recursion has identified four clinical-stage assets that are being repurposed for new therapeutic indications. The company plans to re-enter clinical trials in 2021 or 2022.[14]

As an illustration of the capability of Recursion OS, consider the case of REC-4881. Millenium Pharmaceuticals previously investigated this agent as a cancer therapy but discontinued development in Phase 1 due to a lack of efficacy. (Notably, the safety profile was acceptable.) Through a "brute-force" search, which involves the unbiased testing of a compound against all available targets, Recursion OS identified activity in familial adenomatous polyposis (FAP), a rare tumor syndrome with no approved therapies. With the drug's preliminary safety profile already sketched in Millenium's phase 1 study, REC-4881 will enter directly into Phase 2 clinical study. Leveraging Recursion OS, the company also has created a large pipeline of 33 early discovery or preclinical-stage assets in such diverse therapeutic areas as oncology, rare genetic and infectious diseases, inflammation and immunology, and neuroscience.[6] With such a varied pipeline, Recursion has the potential to form development and discovery partnerships with biopharma, even as the company advances its internal pipeline. In fact, the first such deal was signed last year, as Recursion joined with Bayer to explore new agents for use in fibrosis. More such agreements may be expected in the future.

Abcellera Biologics

In contrast with the aforementioned companies, which work in small-molecule discovery, Abcellera has developed an AI-powered, high-throughput discovery platform for antibodies. The business model here offers discovery services to biopharma and biotech for royalties, discovery fees, and/or milestones. Abcellera's platform integrates proprietary technologies across all steps of antibody discovery, incorporating engineering, microfluidics, single-cell analysis, high-throughput genomics, machine learning, and hyperscale computing to enhance the speed of development and probability of success.[15]

Unlike its peers, Abcellera's approach has been validated by its recent success, the discovery of bamlanivimab, the first antibody approved in North America for the treatment of COVID-19.[15] Abcellera delivered the agent to Eli Lilly for clinical development only 90 days after receiving a sample from one of the first US patients to recover from the disease. In this case, Abcellera screened 5.8 million immune cells in the patient's blood sample in three days, identifying 500 cells that excrete antibodies against COVID-19, and then tested them against assays to select 24 potential development candidates (Figure 7). (The company noted that traditional approaches to antibody development would have identified a mere handful in 2-3 months.[16]) These unprecedented screening capabilities leverage AI-based image algorithms and proprietary single-cell microfluidics chamber technology, enabling the discovery of cells that excrete antibodies with the desired properties.

Figure 7: Abcellera's antibody discovery capabilities were successfully applied to COVID-19 antibody discovery.[17]

Schrodinger

Schrodinger is a leading biotech drug-discovery player, offering a suite of software solutions for predictive modelling in target identification and validation, hit discovery, and lead optimization.[18] Schrodinger's business model differs from competitors, as they operate a dedicated, revenue-generating software business with biopharma customers paying for access. Based on revenues from Q1 2021, the business generates annualized revenues of about USD100m, with a growing base of more than 1200 customers.[19] As the name suggests, Schrodinger incorporates physics-based methods and ML to rapidly calculate free-energy perturbations (FEP+), a clear mark of distinction from competitors and traditional approaches to drug discovery. FEP+ involves molecular simulations to predict binding affinities or drug potency (relative to the target) and is used to computationally generate the most promising new leads, in the course of which FEP+ can analyze billions of molecules. In contrast, a more traditional approach would synthesize and analyze only several thousand molecules. Thanks to Schrodinger's FEP+ solution, medicinal chemists will save time and synthesize fewer unsuccessful compounds, improving optimization from the lead-generation step and shortening the discovery stage by years (Figure 8). In addition to the proven commercial success of its software business, Schrodinger's strategy has been validated by the 25 external collaborations it has created with biopharma companies (including Relay Therapeutics), which pay fees, milestones, and/or future royalties. Notably, collaboration with Agios has led to two approved oncology drugs. While Schrodinger also has a pipeline of five preclinical stage therapeutics addressing high-value oncology targets, these are still in the early stages of development. Thus, we believe Schrodinger's USD5bn valu-

ation reflects its leading position in the biotech drug-discovery industry and investors' appreciation of the transformational potential of their software suite.

In sum, we view this emerging subsector as another example of ongoing innovation in biotechnology, which underpins our bullish long-term view of the sector.

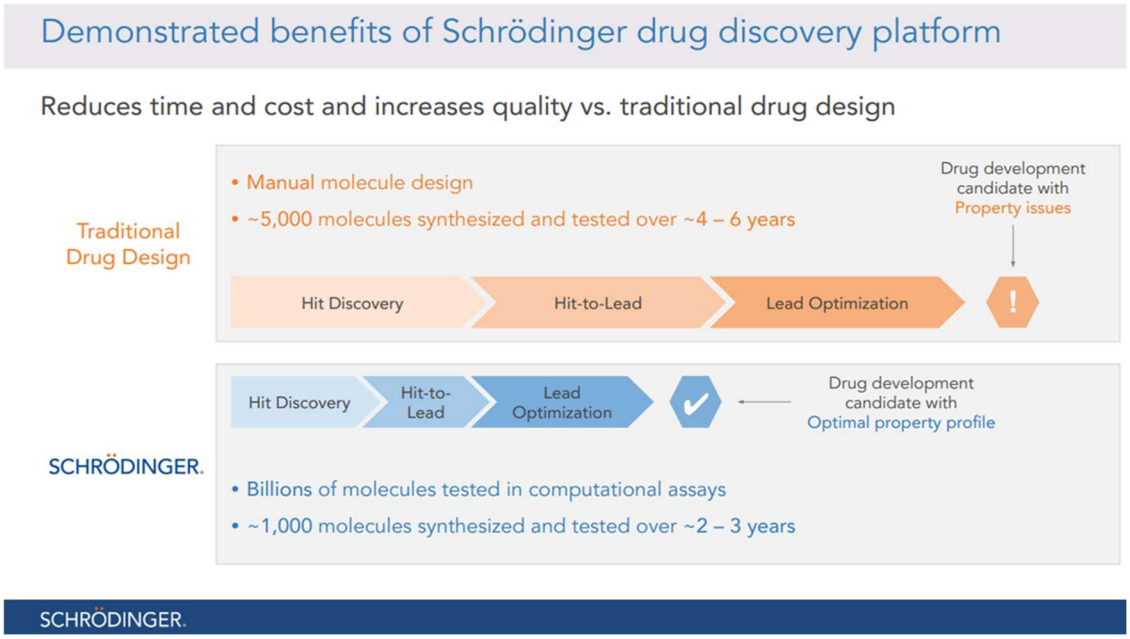

Figure 8: Benefits of Schrodinger drug discovery platform over traditional drug design.[18]

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Conclusion

As this overview suggests, we see many early markers of AI's substantive value, which have already generated new biological insights and differentiated compounds, enhanced lead optimization, and improved the pace of drug discovery. It is no surprise that the application of AI is multi-faceted, and company objectives vary, with some aiming to advance novel drug candidates derived through AI insights, while others refine their discovery tools for widespread adoption across biopharma. The early wins we have seen, including the rapid adoption of software solutions and the approval of bamlivanimab for COVID-19, support AI-driven drug discovery, and further validation from Relay's pipeline is expected in 2021. However, many questions remain, among them the extent to which AI can disrupt biopharma's processes, the willingness of biopharma to incorporate new technologies, and AI's ability to derive new biological insights and increase the druggable space. With some 170 companies involved in AI drug discovery, according to a 2020 Jefferies analysis (privately held), we expect to see an inflection in adoption of AI. The extent of this disruption will correlate with the industry's ability to deliver on the promise of AI-driven drug discovery by producing concrete examples of better molecules, faster development, and more clinical success. With companies maturing and entering public markets, we look for new capabilities and catalysts that will drive value creation by supporting the reproducibility and scalability of technologies.

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