July 5, 2022

Northwestern Unlocks Proteome

Highlights from our 4th Annual Biotech Summit

HEALTHCARE/BIOTECHNOLOGY

SUMMARY

Our 4th annual investor conference with Northwestern University Chemistry of Life Processes Institute (CLP) highlighted the emerging science of proteomics which has encouraging implications for the future of biotechnology. Director Neil L. Kelleher graciously hosted the virtual forum featuring Northwestern principal investigators sharing groundbreaking research, and corporate presentations providing unique industry perspectives (Genentech/Roche, AMGN). Additionally, *BioCentury* Senior Editor Karen Tkach Tuzman hosted a panel discussion with industry leaders on hot topics in protein therapeutics and technologies, and we hosted a panel discussion with distinguished investors on financing and investing in biotechnology companies during challenging market dynamics. CLP Institute enables a network of diverse and complementary approaches, and has contributed to launching commercially successful drugs and incubating 33 new companies raising $2.5B in total capital. CLP Institute also houses Northwestern Proteomics where Dr. Kelleher, world-leading expert in proteomics, is pioneering the Human Proteoform Project. We provide our key takeaways (video replay).

KEY POINTS

- CLP Institute faculty presentations included: 1) Shana Kelley's work on rare cell profiling for therapeutic discovery and development; 2) Elizabeth McNally's work on using genetic signals to develop new protein biologics for muscle diseases; 3) Peter Penzes' work on small-molecule kalirin antagonists for treating chronic neuropathic pain among other CNS conditions; and 4) Samuel Stupp's work on supramolecular peptide medicines with a wide array of applications.
- Genentech/Roche VP of Large Molecule Drug Discovery Arvind Rajpal discussed the evolution of antibody therapeutics. Antibodies have become the most successful drug class representing 8 of the top-20 drugs by sales in 2021. The numbers of antibodies being developed for broader therapeutic areas is driven by continued innovation in antibodies, ADCs, and bispecifics forming what Dr. Rajpal describes as the "protein therapeutic trifecta" which should continue to create value for patients and investors.
- AMGN VP of Research in Biologic Therapeutic Discovery Alan J. Russell discussed approaches to solving grand challenges of protein therapeutics. At AMGN, generative biology is deployed to address such challenges. Generative biology combines life science with data science to achieve the goal of revealing generalized principles to facilitate drug discovery and development processes.
- *BioCentury* Senior Editor Karen Tkach Tuzman hosted a panel discussion on hot topics in protein therapeutics and technologies with industry leaders. The discussion involved background on the emerging science of proteomics that could drive drug discovery and development upon further innovation, and the current challenges to develop tools including high-throughput screening to optimize therapeutic applicability.
- We hosted a panel discussion with distinguished investors on financing and investing in biotechnology during challenging market environments. We asked about the causes of prior outperformance and current underperformance of biotech vs. the broader market, which reflects a correction that we believe should benefit companies with financial discipline and high-quality assets. We also provide our analysis on trends in probabilities of success for clinical trials, M&A deals, and IPO activity across the biotech industry.

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Disseminated: July 5, 2022 06:00 EDT; Produced: July 1, 2022 15:45 EDT

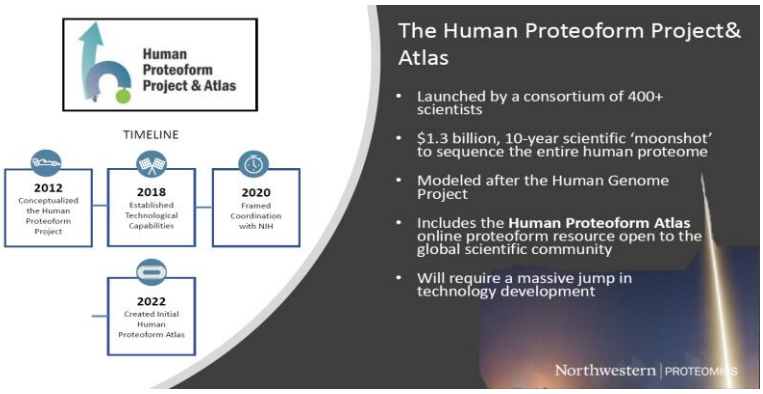
For analyst certification and important disclosures, see the Disclosure Appendix.

Introduction

Neil L. Kelleher, PhD

Neil L. Kelleher, Director of Northwestern Chemistry of Life Processes (CLP) Institute and Northwestern Proteomics, hosted our fourth annual investor conference in a virtual format featuring both academic and corporate presentations plus two expert panel discussions. Our event focused on the emerging science of proteomics, which studies the wide variety of molecular forms of proteins that are produced by cells, i.e. the proteoform. Dr. Kelleher noted that the Human Genome Project conducted by NIH identified ~20.3K genes that drive protein production, and believes that further elucidating the proteoform which drives phenotypic outcomes could have profound applications in medicine and drug discovery. Northwestern Proteomics within CLP Institute was established in 2015 to centralize innovation in proteomics, which includes the Human Proteoform Project & Atlas that seeks to map the entire human proteome, analogously to the Human Genome Project for genes (Exhibit 1). Dr. Kelleher describes the endeavor of sequencing the entire human proteome as a "scientific moonshot" involving a $1.3B investment over a 10-year horizon that could uncover new targets for treating disease, provide high-speed methods to analyze data, and improve the accuracy of diagnostics and biomarkers. CLP Institute uniquely provides the infrastructure for proteomics innovation with shared facilities, dedicated faculty, and collaboration between academics, investors, and industry leaders. Dr. Kelleher noted that CLP Institute has incubated 33 new biotech companies that ultimately received $2.5B in total investment, establishing Northwestern as a hub for biomedical innovation (Exhibit 2).

Exhibit 1. Northwestern Proteomics Is Unleashing the Power of the Human Proteoform



Source: Northwestern University

Exhibit 2. CLP Institute Has Built an Impressive Legacy of Innovation in Biotechnology

Source: Northwestern University

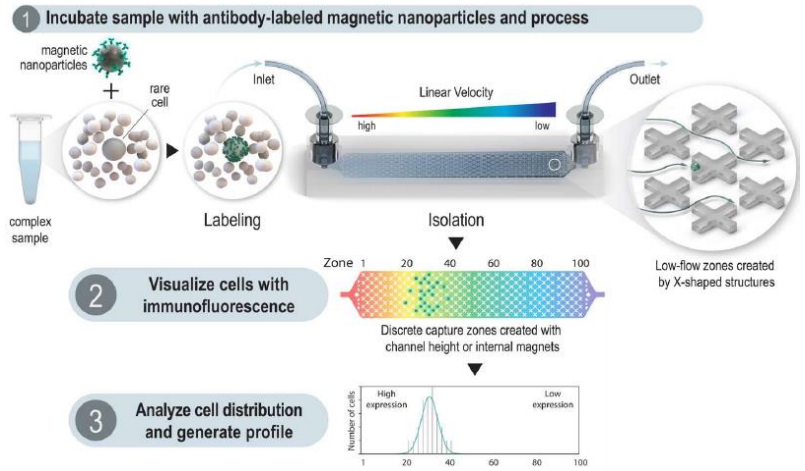
Shana Kelley, PhD

Rare Cell Profiling for Therapeutic Discovery and Development

Single-cell analysis provides a powerful tool to depict gene expression profile at the cellular level that enables the identification of different cell subpopulations, however, restrictions including the requirements for a minimal cell amount and sample purity often limit the application in rare cell populations in complex samples. The Kelley lab has developed a new magnetic ranking cytometry approach that allows high-resolution rare cell profiling. With magnetic ranking cytometry, cells expressing a marker of interest are coated with antibody-labeled magnetic nanoparticles and separated from cells without the marker using a microfluid device (Exhibit 3). Based on the expression levels of the marker and the corresponding levels of magnetic nanoparticles coated, cells can be further sorted and ranked for subsequent characterizations (e.g., cells can be subsequently cultured and expanded at high recovery and viability rates).

Magnetic ranking cytometry offers a unique strategy for therapeutic discovery and development. The LEAPFROG platform combines the magnetic ranking cytometry with CRISPR system that allows high-throughput phenotypic functional screens at scale (able to process more than 10^8 cells per hour). Currently, the LEAPFROG platform has several ongoing drug discovery and development programs, including KRAS modulators, autoimmune regulators, immune checkpoints, and antibody manufacturing. On the immune checkpoint front, the group has identified novel modulators of CD47, which represents a key macrophage immune checkpoint as a "don't eat me" signal. The top hit of the screen is glutaminyl cyclase (QPCTL), an enzyme critical for the N-terminus pyroglutamate modification of CD47 at the SIRPα binding site (Mair et al., 2019). This finding suggests that pharmacological interference with QPCTL could be a novel approach to modulate CD47-SIRPα signaling activity and enhance phagocytosis. The program has been partnered with EVO, and new checkpoint inhibitor screens are underway. Enabled by the LEAPFROG platform, the group also identified SMKM as a mutant KRAS G12V-specific regulator, and genetic interference of SMKM has been shown to inhibit the proliferation of KRAS G12V cells but not KRAS wild-type cells. The platform also suits well for the characterization of secreted proteins. For instance, the group is screening regulators of cytokine secretion relevant to autoimmune diseases. Initial results showed that inhibition of the top hit of the screen demonstrated protective effects on intestinal stem cells in an inflammatory bowel disease model. The group is also partnering with AMGN to discover regulators of antibody secretion for biologic manufacturing based on the LEAPFROG platform.

Exhibit 3. Magnetic Ranking Cytometry Allows High-Resolution Rare Cell Profiling



Source: Northwestern University.

Elizabeth McNally, MD, PhD

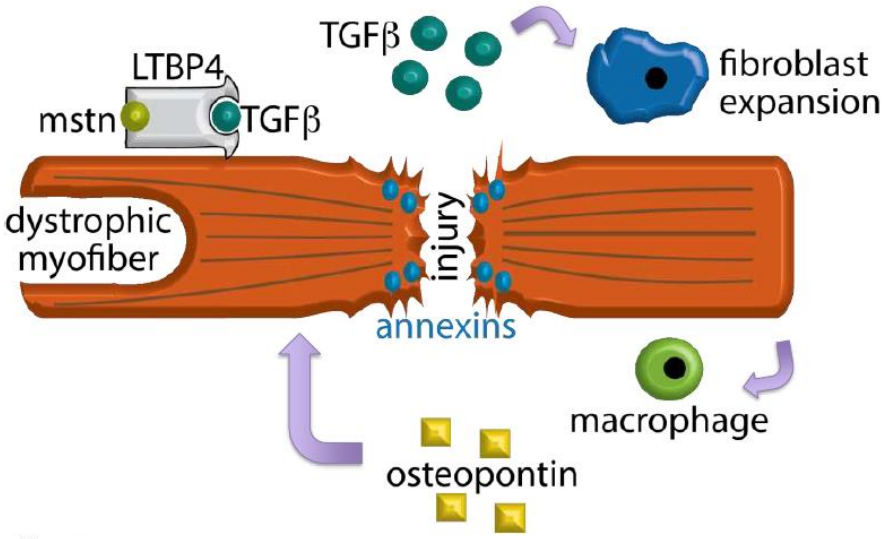
Using Genetic Signals to Develop New Protein Biologics for Muscle Disease

Muscular dystrophy is a group of inherited diseases characterized by progressive muscle weakness and degeneration. Using genome-wide quantitative trait locus (QTL) screen in mice, Dr. McNally and colleagues identified latent TGFβ binding proteins (LTBPs) as key modifiers of muscular dystrophy. LTBP4 is an extracellular matrix protein in muscle cells that binds and sequesters TGFβ. In mice muscular dystrophy models, excessive proteolytic cleavage at the hinge domain of LTBP4 leads to TGFβ release and enhanced TGFβ signaling (Exhibit 4). Blocking LTBP4 proteolytic cleavage, for instance using an antibody that targets the hinge domain, offers a novel therapeutic strategy to address the underlying disease.

Published recently in *Science Translational Medicine*, Dr. McNally's group developed a monoclonal antibody to human LTBP4 that binds the hinge domain of the protein, thus preventing LTBP4's proteolytic cleavage. In muscular dystrophy mice expressing human LTBP4, antibody treatment preserved muscle functions and reduced fibrosis. In addition, the combination of anti-LTBP4 antibody with prednisone had greater muscle protection from contraction-induced muscle injury, suggesting promising therapeutic potential of anti-LTBP4 antibody for the treatment of muscular dystrophy.

Another modifier region identified from the screen mapped to Annexin A6, a protein previously known to be involved in muscle injury and disease (Exhibit 4). Annexin A6 forms the repair cap at muscle membrane injury sites and can be added from the inside or outside of muscle cells to reduce muscle injury. The group has demonstrated that adding recombinant Annexin A6 could reduce injury in dystrophic muscle fibers and lower serum creatinine kinase level, a biomarker of the disease. Dr. McNally is the founder of Ikaika Therapeutics, a biotech company focused on first-in-class biologics for the treatment of muscular dystrophy and other fibrotic conditions. The company is developing a series of new antibodies for muscular dystrophy and is looking for additional investors.

Exhibit 4. Novel Modifiers Act on Multiple Levels to Regulate Muscle Cell Homeostasis and Functions



Source: Northwestern University

Peter Penzes, PhD

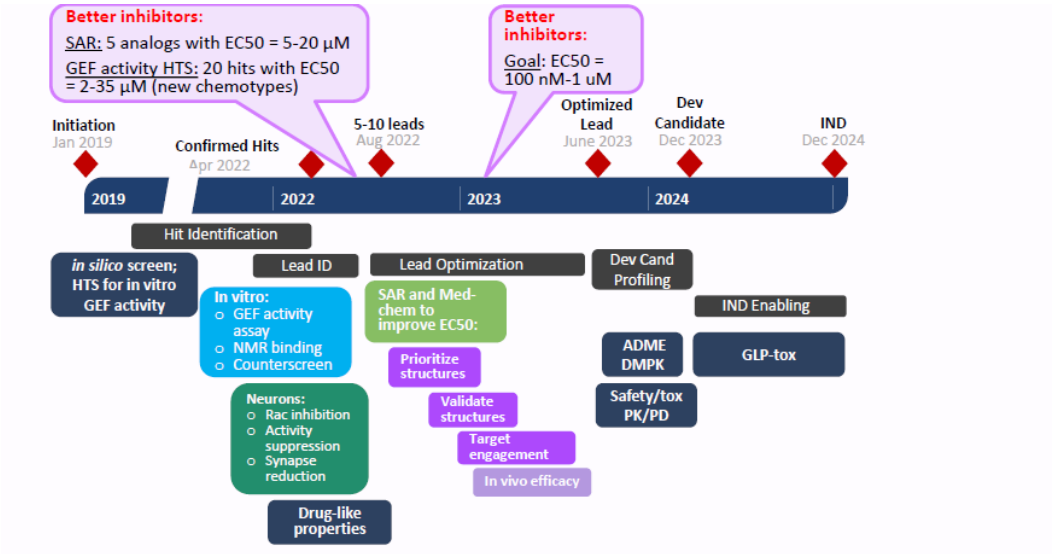
Small-molecule Kalirin Antagonists for the Treatment of Chronic Neuropathic Pain and Other Conditions

Neuropathic pain typically exhibits an acute phase which then progresses to a chronic phase that involves new synapse formation in the CNS. Kalirin, a Rac GTPase, activates Rac1 and plays an important role in the modulation of synaptic plasticity via actin cytoskeletal remodeling. Kalirin inhibitors have been shown to inhibit synapse activity and represent a novel non-opioid approach to treat chronic neuropathic pain. Previous studies demonstrated that Kalirin is highly expressed in the CNS with minimal expression in the periphery, making it an ideal target for pharmacological intervention with small molecules. In vitro data also show that Kalirin overexpression causes synapse formation while Kalirin knock-down leads to synapse elimination. Using different rodent models, Kalirin's upregulation has been shown to be necessary for the establishment of chronic pain.

Based on biological evidence, Dr. Penzes and the team performed primary in silico screens for Kalirin-Rac interaction inhibitors. One hit (PP01) was identified, and the optimized molecule has an EC50 of 2-30uM demonstrating dose-dependent inhibition of neural activity in vitro. Initial pharmacology characterization shows the small-molecule inhibitor has a promising safety/efficacy profile and demonstrates dose-dependent response of pain inhibition. Given the physiological functions of Kalirin, Dr. Penzes expects some levels of side effects of Kalirin inhibitors related to cognitive functions, but a more defined treatment window should address the potential safety concerns. Currently, Dr. Penzes and the team have selected moderate to severe chronic post-surgical pain as the lead indication where Kalirin inhibitor will be administrated around the surgery and can be discontinued after 1-2 months post-surgery. The team is also testing the therapeutic potential of Kalirin inhibitors in other chronic pain settings and in epilepsy.

Dr. Penzes co-founded Synaptomed, a company dedicated to the development of novel small-molecule drugs to treat human disorders by targeting small G-protein signaling. The company is currently conducting lead optimization with a goal to get a molecule with an EC50 of ~100nM (Exhibit 5). The company expects to proceed to IND-enabling studies in 1-2 years.

Exhibit 5. Discovery and Development Plan of Kalirin Inhibitors for Chronic Neuropathic Pain at Synaptomed



Source: Northwestern University.

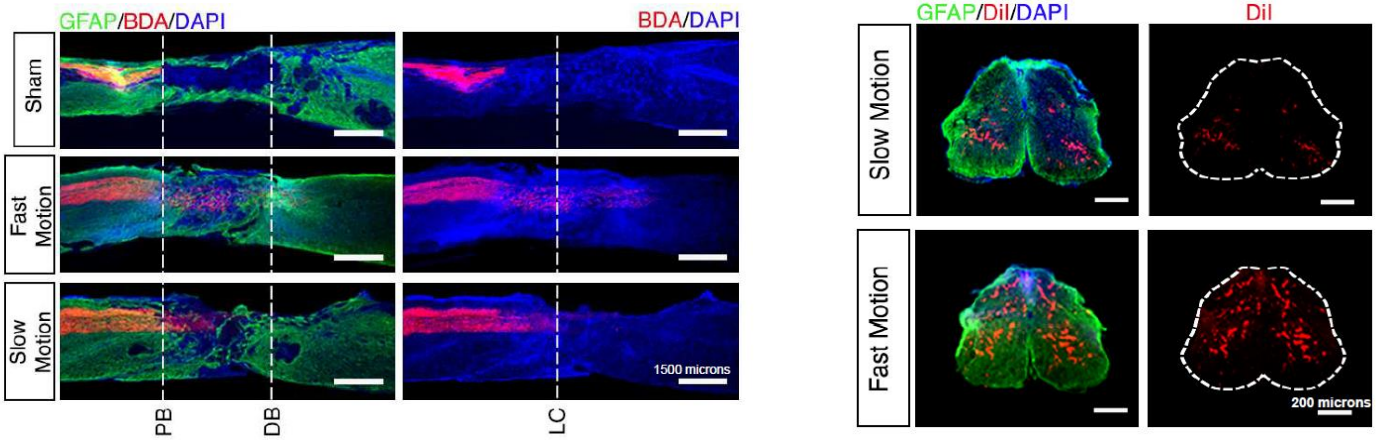
Samuel Stupp, PhD

Supramolecular Peptide Medicines

The Stupp lab focuses on the development of self-assembling organic materials and applicable functions in energy and medicine. In the area of medicine, the Stupp lab is interested in biomaterials for regenerative medicine of the brain, spinal cord, bone, cartilage and muscle, and also on targeted systemic drug delivery using nanostructures for cancer and cardiovascular applications. The organic supramolecular structures were built by non-covalent supramolecular polymerization of peptide amphiphile that can self-assemble by specific interactions. The supramolecular peptide/fiber allows protein signaling amplification by utilizing a similar bioactive functional signals designed in the peptide amphiphile, which can potentially outperform protein therapeutics with its longer half-life and versatility. In one example, the team developed a brain-derived neurotrophic factor (BDNF) mimetic based on peptide amphiphile supramolecular nanostructure. This novel BDNF mimetic is capable of activating the BDNF receptor TrkB and downstream signaling in primary cortical neurons in vitro. In a systemic setting, supramolecular nanofibers containing collagen-targeting motif and nitric oxide donor can be specifically detected at the site of angioplasty.

A new concept recognized by the team is that constant motion of supramolecular peptide/fiber could greatly increase the probability of the bioactive signals to encounter with receptors on the surface of cells. Using this concept, the team developed peptide amphiphile supramolecular that can activate both the transmembrane receptor β1-integrin and the basic fibroblast growth factor 2 receptor. The motion dynamics of the supramolecular nanostructure could be further adjusted or intensified by mutating the peptide sequence of the amphiphilic monomers. Tested in a mouse model of severe spinal cord injury, the supramolecular peptide/fiber facilitated axon regeneration and blood vessel formation at a greater degree in the fast motion state (Exhibit 6). In addition, improvements in vascular and neural functions were translated to functional recovery of paralyzed mice after severe spinal cord injury (video here). These results were published in *Science* last year, and the team hopes to advance the program into clinical studies in patients with spinal cord injury.

Exhibit 6. Supramolecular Motion Enhances Axon Regeneration (Left, Axons Labeled with BDA in Red) and Blood Vessel Formation (Right, Blood Vessels Labeled with DiI in Red) in Paralyzed Mice after Severe Injury



Source: Northwestern University.

Panel Discussion: *Hot Topics in Protein Therapeutics and Technologies*

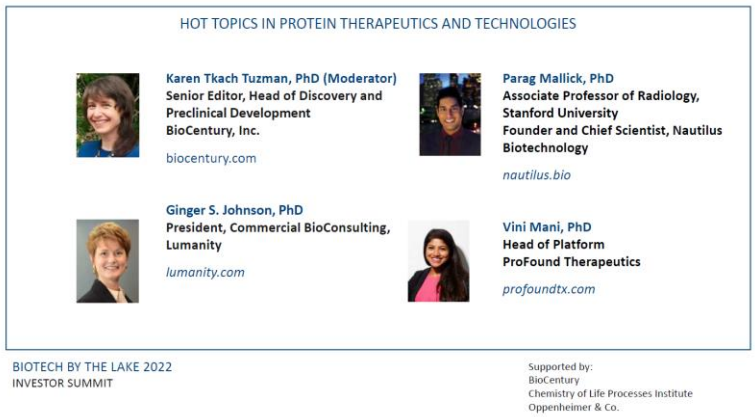
Karen Tkach Tuzman, Senior Editor, Head of Discovery & Preclinical Development at *BioCentury*

Karen Tkach Tuzman, Senior Editor at *BioCentury*, moderated an expert panel discussion featuring Vini Mani, Head of Platform at ProFound Therapeutics, Parag Mallick, Associate Professor of Radiology at Stanford University and Founder and Chief Scientist at Nautilus Biotechnology, and Ginger Johnson, President of Commercial BioConsulting at Lumanity (Exhibit 7). Karen opened the discussion by asking panelists about how protein innovation is involved in their work. Vini noted that ProFound Therapeutics was founded by VC firm Flagship Pioneering upon recognizing that prevailing proteomic technology required further innovation to discover new proteins for therapeutic application. Parag noted that his academic research led to founding Nautilus Biotechnology that seeks to introduce the first large-scale, single-molecule platform designed to quantify the proteome. Ginger noted that her work involves advising platform companies similarly focusing on new technology.

Panelists then discussed how proteomics is evolving and what challenges remain for potential medical application. Vini mentioned the ongoing need to gain better resolution of the human proteome to identify biological roles in disease states, and that evolution will be driven by applying new biological insights to drug discovery. Parag commented that some inherent challenges are that the proteome is dynamic while the genome is static, so new technologies with improved sensitivity to identify small targets within a large sample to capture "statefulness" could address this, e.g. innovative throughput analytics technology. Parag believes that the emergence of screening tools that could become as similarly routine as Next Gen. Sequencing (NGS) would enable more comprehensive investigations of new approaches. Vini also believes that standardization of integrating proteomics with NGS tools alongside currently routine tools e.g. mass spectrometry would drive innovation and biological understanding. Ginger added that she would advise companies to be prudent about investing in enabling technologies as opposed to waiting for their advent and losing a competitive edge on timing, and mentioned Illumina as a relevant example.

Karen lastly asked panelists about navigating the current biotech market and how current negative perceptions would affect investment. Vini believes that great science should still produce great opportunities, and advocated for the necessity of building new technology that provides long-term value despite short-term challenges. Parag noted that companies must prioritize their budget and customer needs while committing to their core mission.

Exhibit 7. BioCentury Panel Discussion Moderator and Participant Profiles



Source: Northwestern University.

Genentech/Roche (RHHBY)

Arvind Rajpal, Ph.D., Vice President Large Molecule Drug Discovery—Antibody Engineering & Protein Chemistry

Dr. Rajpal described a framework for conceptualizing next-generation antibody therapeutics while addressing this important modality as the largest and most successful class of protein therapeutics. He illustrated antibody progress with a comparison of the top 20 therapeutics by sales in 2021 vs 2011. In 2011, there were only 6 biologics on the list, among which there were only 3 antibodies, including Humira, Remicade, and Rituxan. By contrast, in 2021, more than half (11) of the top 20 pharmaceuticals were biologics among which 8 were antibodies, including Humira and Keytruda which are listed in the top 5. From a historical perspective, Dr. Rajpal noted that the antibody landscape began a period of rapid acceleration in 1998. Although currently approved mAbs are mostly in the areas of oncology and autoimmunity, we are seeing growing numbers of antibodies approved for infectious diseases, respiratory diseases, neurology, etc. (Exhibit 8). Dr. Rajpal described the current landscape of antibody therapeutics as "the antibody trifecta," including antibodies, bispecific antibodies and antibody-drug conjugates (ADCs).

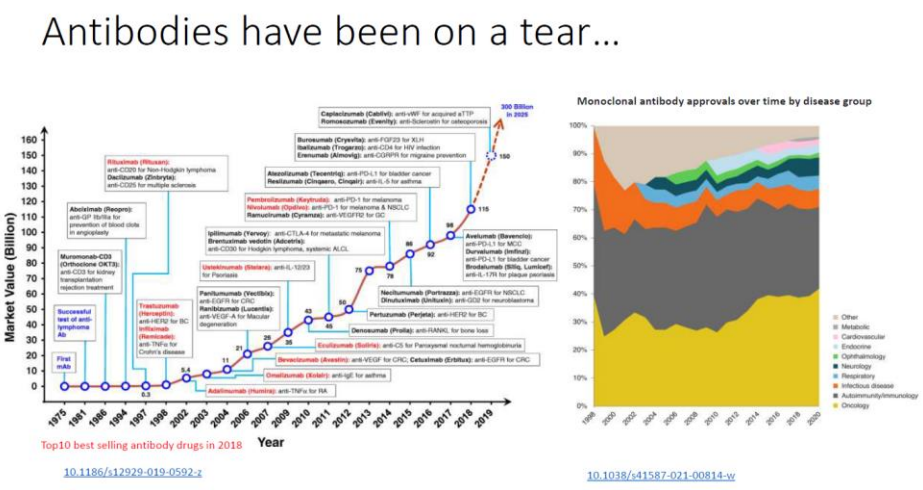
A number of current and emerging trends were identified within antibody dynamics. In the first theme of the trifecta, Dr. Rajpal discussed applications of AI/ML in the discovery and optimization of antibodies. Specifically, he mentioned a machine learning algorithm called Alphafold 2, which is designed to predict protein structures based on primary amino acid sequences and is now able to reach a level of sophistication and accuracy almost equivalent to experimentally determined structures. Dr. Rajpal compared Alphafold to Rosetta Fold, a purely physics-based method, and mentioned that while both methods predict the alpha helical structures well, Alphafold 2 does a better job than Rosetta in predicting the beta sheet structures of which the antigen-binding area of antibodies is mostly composed. He also noted there is more work to be done to optimize ML algorithms despite their significant potential. Next, Dr. Rajpal shared that by generating mutations in certain Fc regions, the function and exposure/half-life of antibody effectors can be enhanced. Apart from Fc gamma receptors (FcγRs), antibodies can also employ effector functions by binding to C1q and engaging complement-based cytotoxicity. As compared to IgG antibodies, IgM pentamers and hexamers cannot bind to FcγRs, so they can only rely on complement-based activation. But, antibody multimers have stronger avidity to antigens, and research has shown that IgGs can be induced to hexamerize with mutations in 3 positions, E345, E430, and E440. Furthermore, Dr. Rajpal mentioned an approach whereby antibodies can be conditionally activated. The approach allows antibodies to not bind to cells in the periphery but instead preferentially bind to tumor cells, subsequently increasing the therapeutic index.

For the second theme of the trifecta, Dr. Rajpal discussed bispecifics and emerging therapeutic approaches. He pointed out that bispecifics are primarily utilized in the treatment of cancer. Bispecifics can bring an effector cell close to a tumor cell and activate the killing of the latter. The most commonly used effector cell is T cells, but another approach is to explore the use of different cell types, such as NK cells, for example by Affimed. Since bispecifics have not been as successful in solid tumors, there is exploratory work being done to use co-stimulatory signals, such as 4-1BB, to enhance the efficacy of bispecifics. Dr. Rajpal then discussed the delivery of protein therapeutics specifically into the brain, where the blood-brain barrier (BBB) is the primary hindrance to transport. He noted that after being engineered for recognition by the transferrin receptors, more beta-secretase antibodies were transported into the brain through receptor-mediated transcytosis. Dr. Rajpal described multispecific drugs as the fourth wave of antibody-based drugs after the first three waves including random screening for active substances, rational drug discovery methodology, and recombinant protein-based therapeutic agents.

He demonstrated a few examples of mutispecifics' obligate mechanisms, including bridging cells, receptor activation/inhibition, co-factor mimetic, and piggybacking.

Third in the trifecta, Dr. Rajpal discussed antibody-drug conjugates. At the moment, most ADCs are targeted toward solid tumors. In terms of payloads, most are designed to promote mitotic arrest, and DNA damage. EGFR and HER2 are the most common targets. ADCs can be used to increase therapeutic indices by reducing the minimum efficacious dose and enhancing the maximum tolerated dose of cytotoxic chemotherapy. Dr. Rajpal noted that the modulation of ADCs can be fairly complicated, with multiple variables including tumor antigen, antibody, cytotoxic payload, and linker. Thus, site-specific conjugation is preferred which generates well-characterized molecules with a stable drug-antibody ratio (DAR). In his concluding remarks, Dr. Rajpal touched on the evolution of the classes of payloads that are used in ADCs, with some novel payloads including radionuclides and antibiotics.

Exhibit 8. Antibody Therapeutic Development Has Surged in Recent Decades



Source: Genentech/Roche company information

Amgen (AMGN)

Alan J. Russell, Ph.D, Vice President of Biologics at Amgen—Biologic Therapeutic Discovery

Dr. Russell pointed out that despite the enormity of time and capital invested in the drug discovery process, current scientific methodology has failed to eliminate the "grand challenges" in therapeutic protein engineering, which encompass reducing cost, increasing speed and efficiency, improving predictability, and quality of target production. He noted that with the traditional approach at hand, researchers usually spend years implementing the animal model to make a repertoire of potential leads and screening the molecule of interest only to find that the molecule still behaves differently during further development and manufacturing or even in the clinic. Thus, he underscored the importance of investing in "new science" that will enable us to drug challenging targets with high precision and specificity.

Dr. Russell believes only biotech companies that develop new science with dual capabilities in discovering molecules and selecting targets can progress in the discovery of unique, competitive therapeutics and lay claim as tomorrow's winners. Mainstream modalities emphasize selecting unique targets, whereas Biologics NeXT strategy platform at AMGN focuses on discovering novel molecules. He pointed out that biologic discovery today at AMGN has honed its expertise in traditional antibody discovery, conventional biologic manufacturing, development of first generation BiTEs (bispecific T-cell engager), centralized automation, and transactional informatics. But to solve the grand challenges present in the field, AMGN needs to identify and facilitate disruptive innovations including but not limited to in-silico discovery, assembly of next generation biologics, and automation and miniaturization with high throughput of data processing.

Dr. Russell transitioned to contrasting the traditional approach to protein drug discovery with the generative approach experimented with at AMGN. The traditional approach uses wet lab experiments following screening of molecules to test and finalize drug design. However, the generative approach instructs a computational model to predict candidate drug designs to test, resulting in a much higher success rate and more efficiency. He provided a contrast of the fundamental difference between biologics discovery and rocket science as rocket trajectory and design is predictable using physics, opening the door to exquisite targeting, while biologics lack central principles that map sequence to structure to function, thereby limiting the success of drug discovery. Dr. Russell reiterated that generative biology, leveraging AI for protein design, and utilizing automation and ultra-miniaturization for protein engineering, could specialize in generating lead molecules in discovery that have predictable manufacturability and clinical behavior while delivering biologics at high speed (Exhibit 9). He believes that the realization of these new applications is predicated on the maturation of digital biologics discovery.

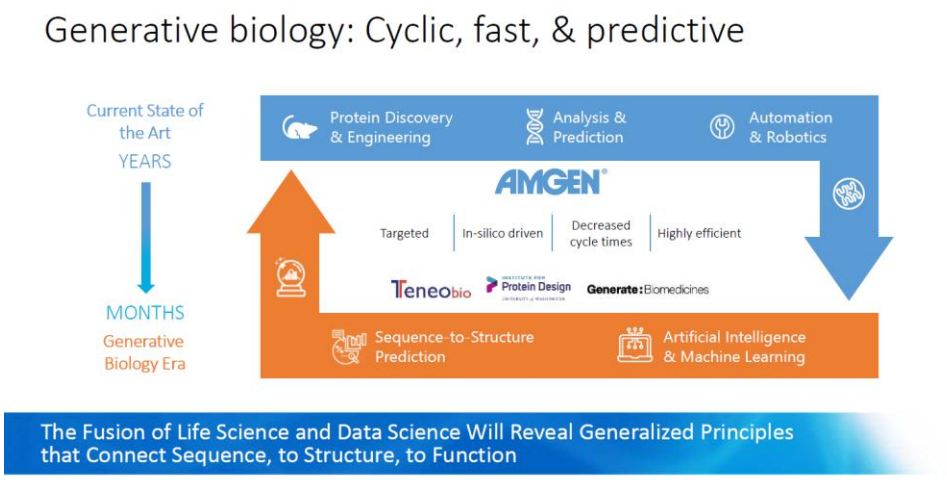
Dr. Russell noted that generative biology differs from the current state-of-the-art machinery in protein drug discovery as it evolves from developing AI algorithms that use sequences to predicting functions of proteins, conferring us with the ability to modify sequences to introduce desirable loss-of-function and gain-of-function properties. Furthermore, generative biology creates a series of corporate and academic partnerships that are open to learning from external sources, and reinforces cyclic learning where the algorithm learns from one program and adapts itself to enable and accelerate the execution of the next program.

Dr. Russell then touched upon a myriad of challenges in assembling AMGN's generative biology pipeline, including how to predict function from sequence, how sequence influences structure, if we could validate a virtual immune system, how we learn from historic data, if we could design allosteric proteins, and if we could make long strands of absolute sequence purity, etc.

He highlighted the key role of ML/AI modeling in optimizing selection of ideal molecule leads. The first example of sequence-based modeling is agnostic prediction of molecule aggregation behavior. Dr. Russell pointed out that failure of molecule leads lies in their tendency to aggregate. Using the predictive ML model to flag high aggregation molecules with ~90% accuracy could result in ~60% reduction in high aggregation candidates and ~20% less wet-lab experiments running time without losing low aggregation candidates. The second example is using ML on sequence and structure features to generalize prediction of antibody thermos-stability. If given 70% accuracy and assuming evenly distributed thermos-stabilities, applying these methods as a filter reduces the number of experimental sequence by >50%. The third example involved using AMGN's UNI-rat sequence-based discovery platform to enable us to conduct pure sequence-based discovery in an animal model. This platform uses microfluidic B-cell enrichment and deep repertoire sequencing to ensure rare sequences are captured, data-driven mining of lineages of interest to enable rational sequence section, and fit-for-purpose screening for validation and selection, thereby reducing antibody discovery timelines from 12-20 months to 6-9 months. He also mentioned that implementing Alphafold to compute the structure and regions of instability for proteins could remove unstable regions in a purpose-designed stable protein, and thus reduce the reagent timeline from >24 months to <2 months.

Last, Dr. Russell stressed that in the foreseeable future, biology will be and must be reliant on increasing computational power, including quantum computing, to stay ahead of competition and enhance problem-solving capabilities.

Exhibit 9. AMGN Is Investing Heavily in Efficient Drug Discovery Processes



Source: AMG company information

Panel Discussion: *Biotech Financing and Investing in Challenging Dynamics*

Jay Olson, CFA, Biotechnology Research Analyst at Oppenheimer & Co.

We hosted a panel discussion on financing and investing in the biotech sector featuring Margarita Chavez, MD at AbbVie Ventures, Scott Morenstein, MD at Blackstone, Bill Slattery, Partner at Deerfield, and Stefan Loren, MD at Oppenheimer & Co.'s Healthcare Investment Banking division (Exhibits 10-14)). Our panelists each provided a summary of their diverse backgrounds across prior financial, industry, and/or academic careers, and shared their motivations for becoming financiers or investors in biotechnology. We began the discussion by asking our panelists about the most promising areas for biotech investing. Margarita is an early-stage investor seeking differentiated assets for "drugging the undruggable" with novel targets. Bill seeks to minimize risk by seeking companies with a quantitative approach, and believes that companies like AMGN that are applying improving computational power will ultimately increase probabilities of success. Stefan believes that protein degraders are interesting and benefit from the FDA's increasingly accepting alternative forms of datasets.

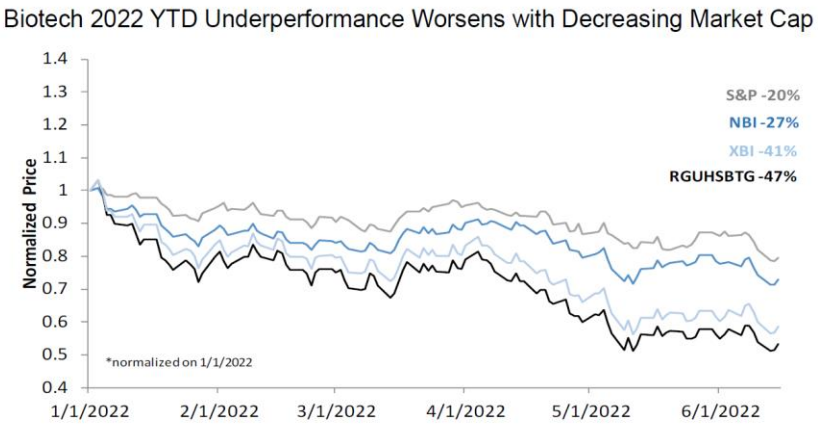
We asked our panelists about what they believe is driving the recent challenging market dynamics for biotech companies. Scott provided a comprehensive explanation: he notes that biotech investing had historically been relegated to specialists, but that generalists became attracted to biotech as companies pursued therapeutics to combat COVID-19 during the pandemic, which was also exacerbated by consequent expansionary policies that drove larger fund sizes and deployment of capital. He believes that a general lack of discipline among investors, bankers, and companies in the ecosystem led to a glut of new public companies at inflated valuations while management teams struggled to absorb the investment within their business models which led to unsustainable cash burn rates. As generalist investors began to focus on other asset classes driven by macro factors, public biotech companies became more illiquid and were continually sold even despite underlying positive catalysts, e.g. positive data events, reducing the perceived risk/reward. Many biotech companies now must raise dilutive capital, seek alternative financings, or risk bankruptcy. Scott also anticipates a similar fate for private companies. Stefan agrees and added that biotech market performance has been correlated with market cap size as large-cap companies have largely outperformed small-caps over the past one-year period. Essentially, our panelists believe that the biotech market is undergoing a sharp correction.

Last, we asked about when the biotech market would regain positive momentum and advice for new companies. Bill noted that increasing M&A would improve sentiment, although he noted that this takes time as boards must thoughtfully consider each deal. Stefan believes that positive data should support valuations, and that many companies must consider the difficult choices of reprioritizing R&D budgets or returning capital to shareholders. Scott advised that companies should assume a safety cushion for required capital as events may be negative despite expectations, and that capital efficiency is key. Margarita added that early-stage companies must preserve capital and maintain focus, which is enabled by alignment with long-term investors who share the same vision.

Exhibit 10. Our Panel Discussion Featured Financiers and Investors in Biotechnology

Source: Oppenheimer & Co.

Exhibit 11. Performance of Biotech Market Indices vs. the Broader Market

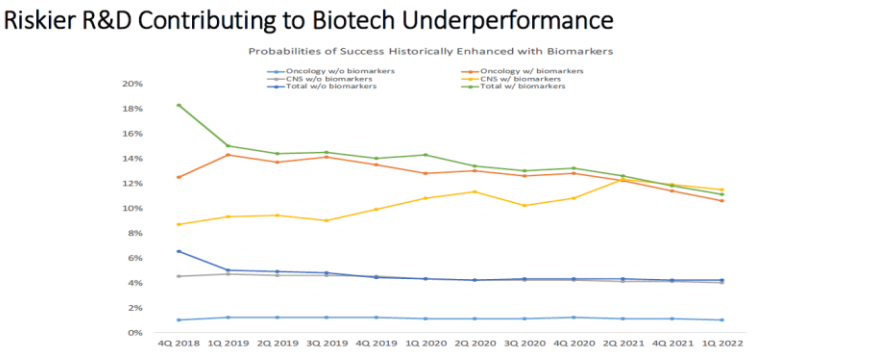


- **Investors increasingly concerned about binary events, single product risk and financing overhangs**

Source: Bloomberg, FactSet, Oppenheimer Research

Note: These results cannot and should not be viewed as an indicator of future performance.

Exhibit 12. Probabilities of Success across the Biotech Industry from 4Q18 to 1Q22



- **Clinical trial success rates steadily declining over the past 2 years with numerous prominent failures**
- **Limited support from Biomarkers which have historically boosted success rates**

Source: MIT Project Alpha, Oppenheimer Research

Exhibit 13. Biotech M&A Deals by Valuation Multiple and Aggregate Size from 2011 to 2022

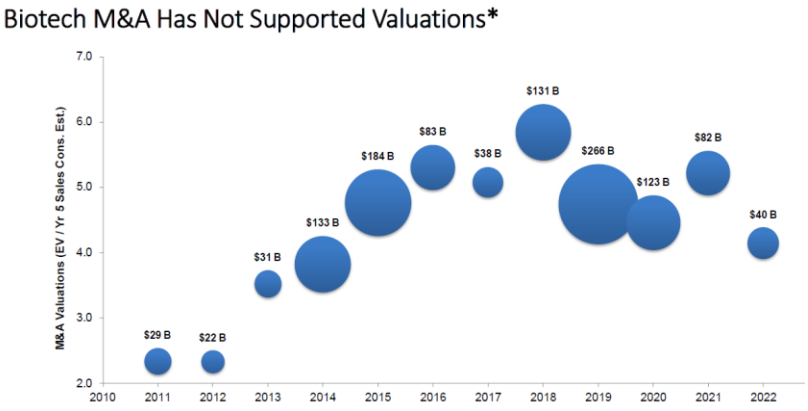
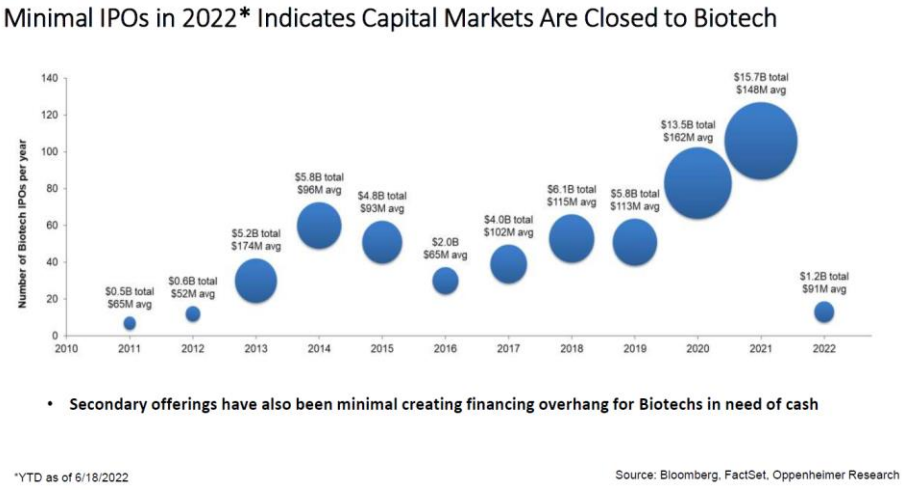


Exhibit 14. Biotech IPOs by Total Number and Aggregate Size from 2011 to 2021



Stock prices of other companies mentioned in this report (as of 6/30/2021):

Company	Ticker	Exchange	Closing Price (6/30/2022)	Oppenheimer Rating
AbbVie, Inc.	ABBV	NYSE	$154.14	Not Covered
Affimed N.V.	AFMD	NASDAQ	$2.81	Not Covered
Aptinyx Inc	APTX	NASDAQ	$0.56	Not Covered
Evotec SE Sponsored ADR	EVO	NASDAQ	$12.49	Not Covered
Illumina, Inc.	ILMN	NASDAQ	$186.43	Not Covered
Johnson & Johnson	JNJ	NYSE	$176.99	Not Covered
Merck & Co., Inc.	MRK	NYSE	$92.51	Not Covered
Nautilus Biotechnolgy, Inc.	NAUT	NASDAQ	$2.64	Not Covered
Roche Holding Ltd Sponsored ADR	RHHBY	US OTC	$41.81	Not Covered

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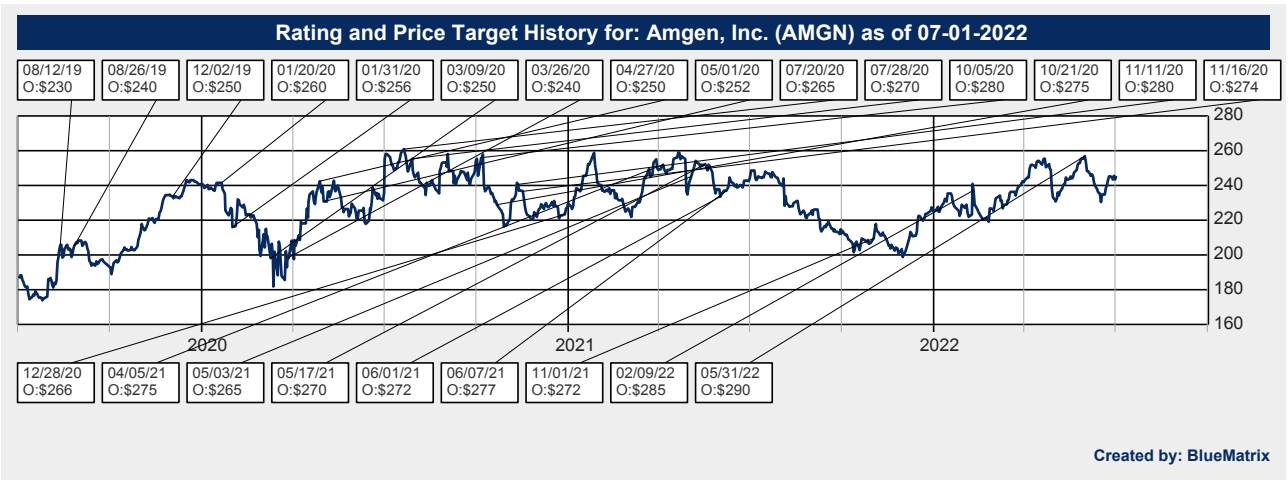
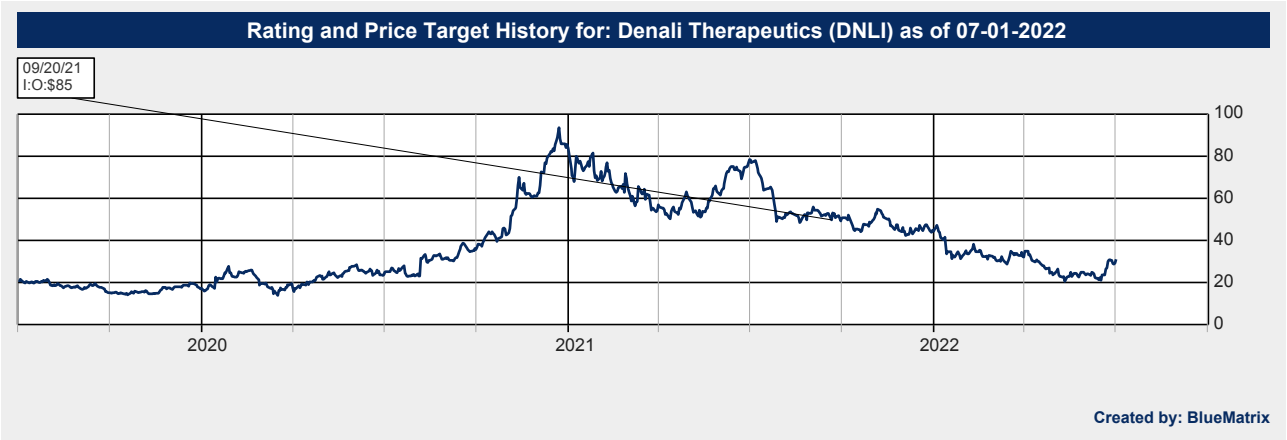
Stock Prices as of July 5, 2022

Amgen, Inc. (AMGN - NASDAQ, $245.55, OUTPERFORM)

Denali Therapeutics (DNLI - NASDAQ, $31.24, OUTPERFORM)





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Distribution of Ratings/IB Services Firmwide

			IB Serv/Past 12 Mos.	
Rating	Count	Percent	Count	Percent
OUTPERFORM [O]	525	73.12	294	56.00
PERFORM [P]	193	26.88	77	39.90
UNDERPERFORM [U]	0	0.00	0	0.00

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