OPPENHEIMER

June 27, 2021

HEALTHCARE/BIOTECHNOLOGY

Neuroscience Shines by the Lake

Highlights from our Focus on Brain Health with CLP

SUMMARY

Our third annual investor conference with Northwestern University Chemistry of Life Processes (CLP) Institute showcased the latest breakthroughs in neuroscience drug development, with fortuitous timing shortly following FDA approval of BIIB's Aduhelm for AD. CLP Institute Acting Director Neil L. Kelleher graciously hosted the virtual forum featuring CLP Institute principal investigators sharing their groundbreaking research, and corporate presentations providing unique industry perspectives (MRK, Genentech/Roche). Additionally, BioCentury Senior Editor Lauren Martz hosted a panel discussion with industry leaders on hot topics in CNS therapeutics and technology, and we hosted a panel discussion with distinguished investors on financing and investing in biotechnology companies focused on CNS. CLP Institute is an interdisciplinary network of diverse and complementary approaches with 65 dedicated faculty members across 20 departments, and has contributed to launching commercially successful drugs and incubating 27 new companies raising $2.3B in total capital. This report highlights our key takeaways (video replay).

KEY POINTS

- CLP Institute faculty presentations included: 1) P. Hande Ozdinler's work in collaboration with Neil Kelleher in developing protein-based biomarkers to stratify upper motor neuron diseases and develop personalized therapeutic approaches; 2) William Klein's research in Aβ oligomer antibodies that supports novel candidate ACU193; 3) Yevgenia Kozorovitskiy's progress in developing high-precision screens for pharmacological traction of neuroplasticity; and 4) Richard Silverman's work in protein aggregation and development of novel candidate NU-9 for upper-motor neuron diseases.

- MRK Executive Director of Neuroscience Drug Discovery Sean M. Smith highlighted the large unmet need for treating CNS disorders and outlined MRK's focus on discovering novel therapeutics. MRK is primarily focused on drug discovery in three areas including neurodegeneration, neuroimmunology, and diseases related to aging. MRK's approach is exemplified by autophagy, and MRK is currently conducting preclinical studies of TRPML1 agonists for neurodegenerative diseases.

- Genentech/Roche VP & Head of Neuroscience Research Casper Hoogenraad provided an overview of Genentech/Roche's long history in CNS drug development and its current pipeline of 14 novel candidates across five areas of CNS research with focus on indications including AD, MS, PD, ALS, FTD, and tauopathies. Dr. Hoogenraad noted that bepranemab for AD targets the mid-domain of tau. A Ph2 study is expected to initiate in 2021.

- BioCentury Senior Editor Lauren Martz hosted a panel discussion on hot topics in CNS drug development with industry leaders. The discussion ranged from implications of FDA approval of BIIB's Aduhelm to other CNS biotech companies, other areas of large unmet need, precision medicine approaches in CNS, and new modalities with promising potential. Excitement is building for CNS biotech.

- We hosted a panel discussion with distinguished investors on financing and investing in biotechnology focused on CNS disorders. We asked about the impact of FDA approval of BIIB's Aduhelm on CNS research and investment approaches, new areas in CNS biotech that are gaining enthusiasm, and advice to emerging CNS biotech companies. We also provided our analysis on trends in FDA approvals, M&A deals, and IPO activity across the biotech industry.

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

Introduction

Neil L. Kelleher, PhD

Acting Director of Northwestern University Chemistry of Life Processes (CLP) Institute, Neil L. Kelleher, hosted our third annual investor conference in a virtual format featuring both academic and corporate presentations plus two expert panel discussions focused on neuroscience drug development. Our event enjoyed fortuitous timing that followed recent FDA approval of BIIB's Aduhelm for Alzheimer's disease (AD) which became a key theme. CLP Institute was founded in 2004 with the mission to create an interdisciplinary network of diverse and complementary approaches to drive productive collaborations leading to drug discovery, clinical development, and ultimately commercialization. CLP Institute has 65 dedicated faculty members across 20 departments and has contributed to launching commercially successful drugs, such as Lyrica from Dr. Richard Silverman's laboratory, and developing novel drug candidates, such as Acumen's ACU193 (Aβo antibody) for AD from Dr. William Klein's laboratory. CLP has advanced over 75 novel drug candidates and has incubated 27 new companies raising $2.3B in total capital. Prof. Kelleher noted a ~20x ROI and attributed this success to CLP Institute's distinguished technology platform and shared resources, enabled by bringing together all the faculty and essential facilities within one place on campus at Silverman Hall. CLP Institute's executive advisory board provides expert guidance and comprises academics, investors, and industry leaders from the Chicago, IL area—an emerging hub for biotechnology innovation.

Exhibit 1. CLP Institute Functions as an Interdisciplinary Network for Drug Discovery

Source: Northwestern University.

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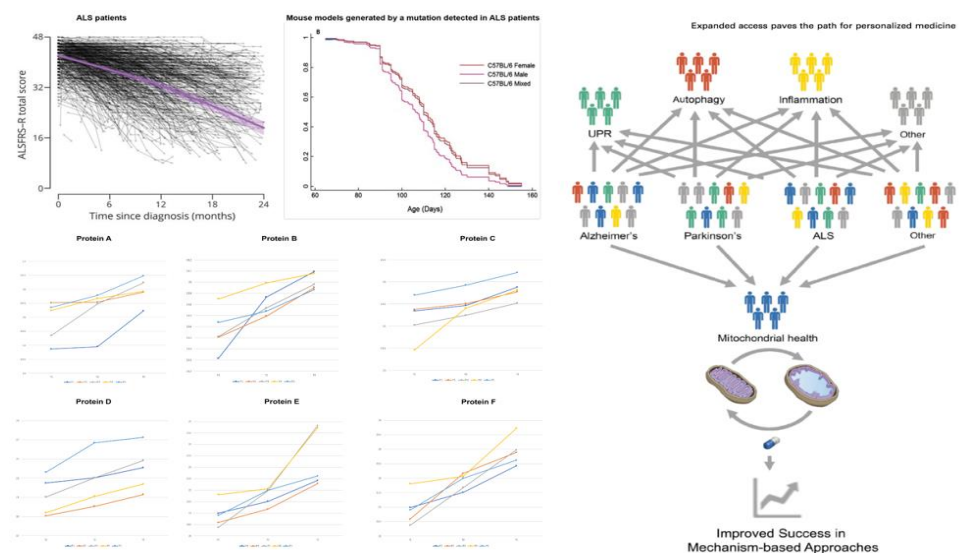

Source: Northwestern University.

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P. Hande Ozdinler, PhD

Improving Success Rate of Clinical Trials by Proteomics

Neurodegenerative diseases are heterogeneous in nature and many clinical trials are conducted in patients grouped by diseases based on clinical phenotypes. As we learn more about the disease pathology, a more rational approach to clinical development in neurodegenerative diseases might be to conduct trials in patient subgroups based on underlying disease mechanisms rather than clinical manifestations. Upper motor neuron (UMN) degeneration is a key feature in several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia (HSP), and primary lateral sclerosis (PLS). At the Ozdinler lab, researchers focus on understanding the cellular and molecule basis of UMN degeneration as the underlying disease mechanism with the ultimate goal of developing effective treatment strategies.

A key challenge of clinical development in neurodegenerative diseases is translatability from preclinical studies to clinical studies. Although humans and mice differ greatly at the behavioral level, neurons in mice and humans share many common features. The Ozdinler lab tackles the translatability challenge by focusing on the affected neurons to inform underlying disease mechanisms at the cellular level. The Ozdinler lab developed the first reporter line for UMNs that, once crossed into ALS mouse models, provides valuable information on UMNs under various disease conditions. Using proteomics, isolated UMNs from ALS mouse models can be studied at the protein level from a top-down approach, allowing a more comprehensive understanding of misregulated protein-protein interactions, splicing variations, and protein modifications driven by different mechanisms. With access to ALS patients' blood samples at Northwestern, Dr. Ozdinler also found that important UMN proteins are shared in mice and humans, and proteins involved in lipid and protein homeostasis, DNA damage repair, and cytoskeletal dynamics are important for the proper function of motor neurons. Additionally, combining proteomics with longitudinal sample studies also reveals serum protein dynamics in ALS patients, which can inform the development of biomarkers and therapeutic target for ALS. All together, these efforts are supported by the promise of understanding and revealing neurodegenerative diseases mechanisms, and enabling personalized medicine in neurodegenerative diseases based on mechanisms (Exhibit.4). A next step at the Ozdinler lab is to develop biomarkers for ALS.

Exhibit 3. With Proteomics, biomarkers that inform disease mechanisms can be identified and used to subgroup patients to improve success rate of clinical trials.

Source: Northwestern University.

William Klein, PhD

Next Generation Alzheimer's Immuno-Rx: Targeting the Toxins that Trigger Brain Damage

Dr. Klein is one of the leading experts in Alzheimer's disease research and is a co-founder of Acumen Pharmaceuticals, a clinical-stage biotech company focusing on developing targeted therapies for the treatment of Alzheimer's disease.

Dr. Klein's early research revealed the correlation between memory loss in Alzheimer's patients and soluble amyloid beta oligomers (Aβo) that are neurotoxic and cause structural and functional neurodegeneration. Mice injected with Aβo demonstrated memory dysfunction in hippocampal task and cortical task compared to mice injected with vehicle. In Alzheimer's patients, Aβo level in the brain is closely correlated with the disease stage and the severity of clinical symptoms. Dr. Klein and his team also detected amyloid-β-derived diffusible ligands (ADDLs) in patients' cerebral spinal fluid (CSF), and ADDL concentrations were consistently elevated in patients vs. non-demented age-matched controls. These seminal discoveries provide a new approach to developing targeted therapeutics to Alzheimer's disease in conjunction with the CSF biomarker.

Whereas mAbs that bind to amyloid-beta monomers or plaques have lower affinity to Aβo, Dr. Klein and scientists at Acumen developed ACU193, a humanized mAb that is highly selective to Aβo and less selective to other amyloid-beta species. Preclinical studies showed that treatment of ACU193 could rescue memory dysfunction in a 5xFAD mouse model (Exhibit.5). ACU193 is currently Ph1-ready, with data expected in late-2022.

Exhibit 4. Treatment of ACU193 rescues memory dysfunction in a 5xFAD mouse model.

Source: Northwestern University.

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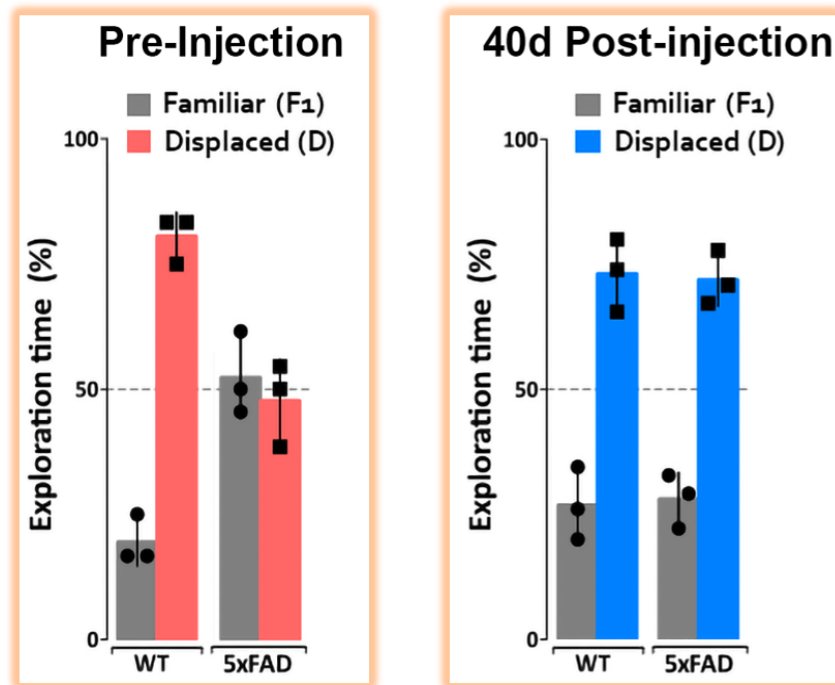
Yevgenia Kozorovitskiy, PhD

## High Precision Screens for Pharmacological Traction of Neuroplasticity

Dr. Kozorovitskiy and her team are interested in understanding the neuromodulatory control of neuronal plasticity, and developing new tools for visualizing, measuring and controlling neural structure and functions.

Dendritic spines are neuronal protrusions that receive inputs typically from one excitatory synapse. These spines contain neurotransmitter receptors and signaling systems essential for synaptic function and plasticity. Loss of dendritic spines is correlated with neurodegeneration and aging. Dr. Kozorovitskiy and others developed microscopic two-photon uncaging of glutamate to study neuronal plasticity. Early studies have shown that uncaged glutamate can evoke de novo spinogenesis, and newly formed dendritic spines are functional and carry synaptic current. The two-photon uncaging of the glutamate system provides a robust platform to study neuromodulatory control of neuronal plasticity.

Ketamine can elicit rapid antidepressant effects in MDD patients, but to what extent ketamine modulates neural plasticity is less understood. Using two-photon uncaging of the glutamate system, Dr. Kozorovitskiy and her team found that ketamine rapidly enhanced glutamate-evoked spinogenesis in the medial prefrontal cortex through dopamine Drd1 receptor activation. The onset of spinogenesis matched the behavioral effects induced by ketamine, providing mechanistic insights into the rapid onset of ketamine and tools to identify and evaluate new drugs with antidepressant potential.

While two-photon imaging has proven powerful in studying neuronal plasticity at the cellular level, it is not ideal for large-scale screens. Dr. Kozorovitskiy and her team developed neural plasticity-dependent reporter lines suitable for high-throughput screening assays based on florescent signals. As expected, a few molecules including forskolin, ketamine, and gabazine with known neuromodulatory ability were shown to elicit strong fluorescent signals (Exhibit.6).

Exhibit 5. Structural plasticity modulation screening in primary mouse neurons with neuronal plasticity dependent reporter lines.
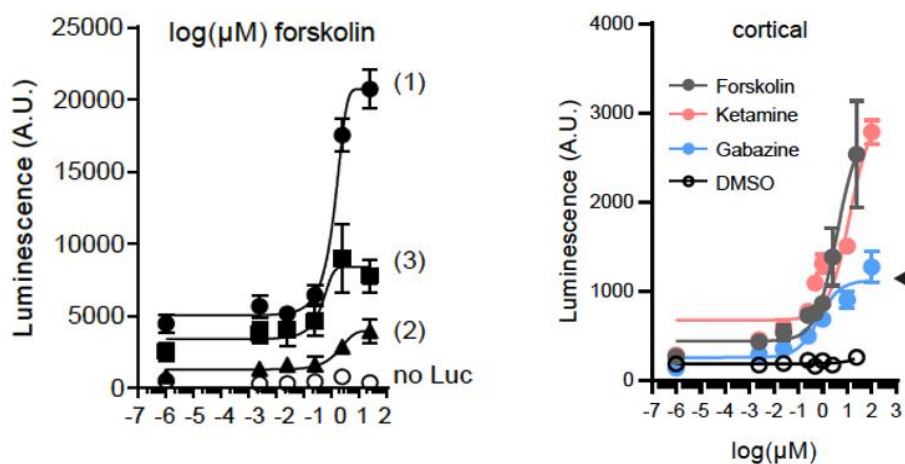
Source: Northwestern University.

Building on proof-of-concept for the reporter system, a large-scale screening of drug libraries can be conducted to identify novel molecules that elicit strong neural plasticity. Once identified, the top-hit can subsequently be validated by the two-photon uncaging glutamate imaging based on glutamate-evoked spinogenesis.

Richard B. Silverman, PhD

Protein Aggregation and the Development of NU-9 for Upper Motor Neuron Diseases

Abnormal protein aggregation is a hallmark of many neurodegenerative diseases including ALS. About 10-15% of ALS cases are inherited, and about 25% of them are caused by mutations in the *SOD1* gene. The mutant SOD1 protein or the TAR-DNA binding protein TDP-43 can aggregate in motor neurons and cause neurodegeneration.

Previous efforts by Dr. Silverman and the team have led to a couple of high-throughput screens for mutant SOD1 protein aggregation and toxicity protection. After years of development and optimization, NU-9, a small molecule that can significantly reduce mutant SOD1 aggregates with promising PK profile, has been selected for further development. Toxicology studies in mice showed NU-9 has a promising safety profile, and NU-9 treatment extended the lifespan of G93A SOD1 ALS mice.

We now know, from Dr. Ozdinler's presentation, the challenge in translating preclinical findings into clinic outcomes in neurodegenerative diseases and more importantly, the potential solution to address the challenge. Since ALS is characterized by upper motor neuron dysfunction and degeneration, Dr. Silverman's team and Dr. Ozdinler's team are working together to test NU-9 in ALS mouse models carrying the UMN reporter line.

The collaboration has been fruitful. Two teams showed NU-9 restored the health of diseased UMNs in vivo in ALS mouse models. When NU-9 was given to SOD1 ALS mice 60 days after birth (typically when ALS symptoms begin to manifest), a dose-dependent increase in healthy UMNs was observed (Exhibit.7). UMNs in treated mice had more healthy apical dendrites and increased axon length, concomitantly, misfolded SOD1 levels in UMNs were reduced with increasing doses of NU-9. Mitochondrial and ER health in ALS mice were also improved with the treatment of NU-9. Similar results were observed in TDP-43 ALS mice. Lastly, ALS mice treated with NU-9 also performed better in functional tests (latency to fall hanging upside down from wire grid) vs. non-treated mice.

The teams are currently conducting IND-enabling studies for NU-9, and Dr. Silverman expects another 18-24 months of work before NU-9 enters the clinic.

Exhibit 6. NU-9 treatment rescues the health of upper motor neurons in the motor cortex of G93A SOD1 ALS mice in a dose-dependent manner
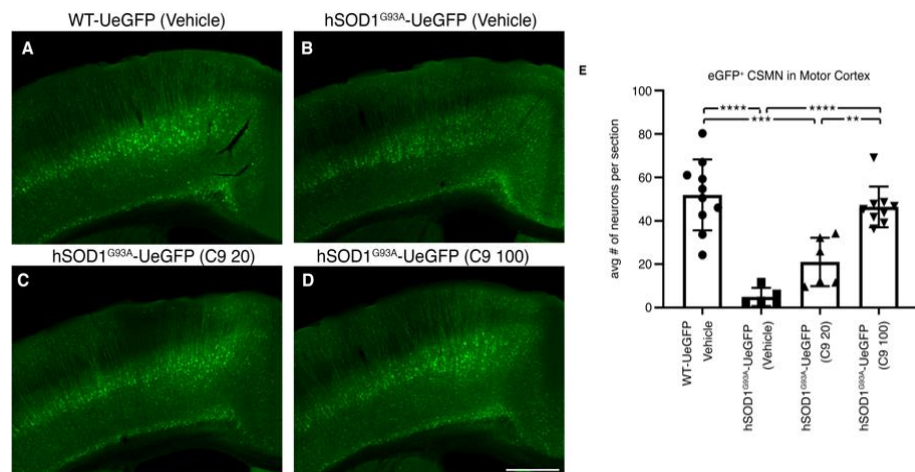
Source: Northwestern University.

Panel Discussion: *Hot Topics in Neurological Disorder Therapeutics and Technologies*

Lauren Martz, Senior Editor, Head of Translation & Clinical Development at BioCentury

Lauren Martz of BioCentury moderated a panel discussion featuring Sarah Bhagat of Sofinnova Investments, Ginger S. Johnson of Cello Health BioConsulting, Norbert Riedel of APTX, and Myung Shin of MRK. Lauren Martz began the discussion by asking about the implications of FDA's decision to approve BIIB's Aduhelm for other CNS companies. Sarah Bhagat believes that while this decision is positive as a reflection of FDA working closely with the industry to provide access to treatments for large unmet needs e.g. AD, the post-marketing Ph4 trial requirement within nine years could challenge the Aβ MOA class until more definitive clinical results become available. Meanwhile, FDA's decision should motivate CNS companies to focus more on biomarkers that correlate with clinical outcomes in AD, and the question remains which biomarkers may be more promising than Aβ plaque, so further research is necessary. Lauren Martz then asked Norbert Riedel about other areas in CNS drug development that need more focus. Norbert Riedel noted that numerous areas other than neurodegeneration involve cognitive impairment such as neuropsychiatry e.g. PTSD. SSRIs were approved over 20 years ago yet remain the SOC despite an inadequate benefit/risk profile for many patients, so large unmet need persists which should drive novel approaches. APTX has a pipeline of three novel compounds for chronic pain, PTSD, and cognitive impairment in PD and DLB. Lauren Martz then asked Ginger S. Johnson about the progress of precision medicine applications in neurology, and she mentioned gene therapy for SMA as the immediate example. Ginger S. Johnson also believes that FDA approval of Aduhelm sets a precedent for biomarker approaches, although she believes that investors are more likely to focus on biomarkers that correlate directly with clinical benefit to minimize risk, which are primarily in rare diseases such as SOD1 ALS and HTT HD. BIIB notably has an opportunity to determine clinical benefit by funding the required Ph4 trial with Aduhelm sales generated in the interim, which provides an example of commercial viability with relatively lower risk. Lauren Martz lastly asked Myung Shin about new modalities and related potential impact in neurology. Myung Shin sees enthusiasm for new modalities such as RNAi and gene therapy that could address areas that small molecules or antibodies have had previous difficulty. Each panelist finally commented on how hot topic ideas could potentially move into more prevalent indications, agreeing that progress should arise from deeper understanding of genetics and biology.

Exhibit 7. BioCentury Panel Discussion Moderator and Participant Profiles

HOT TOPICS IN NEURODEGENERATIVE DISORDER THERAPEUTICS AND TECHNOLOGIES

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Chemistry of Life Processes Institute
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Source: Northwestern University.

Merck (MRK)

Sean M. Smith, Ph.D., Executive Director of Discovery Neuroscience

Dr. Smith outlined MRK's focus on discovering novel therapeutics for neurodegenerative diseases and psychiatric disorders. Dr. Smith noted that CNS disorders rank second for top therapeutic areas by global disability, reflecting large unmet need as populations grow with longer overall life-expectancy while many SOC therapies for CNS remain inadequate. Other reasons for historical difficulty in developing therapeutics for CNS disorders involve restricted access of small molecules into the brain, and target engagement measurements also have been difficult until more recently as technologies improve. Dr. Smith believes that greater understanding of CNS biology along with biomarker approaches are required. One recent example is LLY's donanemab for AD which showed modest disease-modifying efficacy, which reflects increased understanding of disease staging and patient selection. Dr. Smith also cited schizophrenia as another example of where better understanding of pathophysiology should drive better therapies that also could address residual symptoms. Recent improvements in CNS drug development are reflected by FDA approvals in 2020 when CNS therapies were second only to oncology. Dr. Smith approaches the discovery of novel therapeutics in CNS at MRK by combining human genetics understanding with protein selection to identify targets, then studying how PK relates to potential biomarkers, which then could be applied to later-stage clinical studies. Since common mechanisms of pathology may underlie multiple diseases, MRK focuses on broader buckets of varying CNS biology with research groups organized by different buckets, each at three locations: in West Point, PA, MRK works on neurodegeneration, neuronal signaling, and sensory biology; in Boston, MA, MRK works on neuroimmunology with emphasis on myeloid cell biology; and in London, UK, MRK works on diseases related to aging with an approach involving mitophagy and oxidative stress. Dr. Smith described autophagy as one example of how this approach has led to novel insights. Autophagy uses degradation to clear toxic proteins, which define AD, PD, HD, ALS, and other neurodegenerative diseases, and new evidence demonstrates that enhancing autophagy and lysosomal function may protect against neurodegeneration. Specifically, TFEB (transcription factor EB) has emerged as an important target to modulate autophagy and lysosomal function, and TRPML1 has now been identified is the most tractable drug target for TFEB modulation. MRK is currently conducting preclinical studies of TRPML1 agonists from its acquisition of Calporta, which Dr. Smith expects to enter the clinic within the next few years.

Exhibit 8. MRK's Approach to Neuroscience Drug Development Exemplified by Autophagy

Genetics and Pathological Data Link Deficits in Autophagy to Neurodegenerative Disease

- Autophagy is a powerful process for removing toxic proteins and damaged organelles to maintain cellular homeostasis.
  - Autophagy drives clearance through proteolytic degradation of cytosolic components at the lysosome.
- Dysfunction of autophagy is a defining hallmark of almost all neurodegenerative diseases characterized by the accumulation of toxic protein aggregates.
  - *Alzheimer's (β-Amyloid, Tau) Parkinson's (α-Synuclein), Huntington's (Htt) and ALS (TDP-43)*
- Evidence has accumulated to support that enhancing lysosome function and autophagy may protect against neurodegeneration.
  - **TFEB** (transcription factor EB) has emerged as an important target to modulate autophagy and lysosomal function. TRPML1 is the most tractable drug target for TFEB modulation.
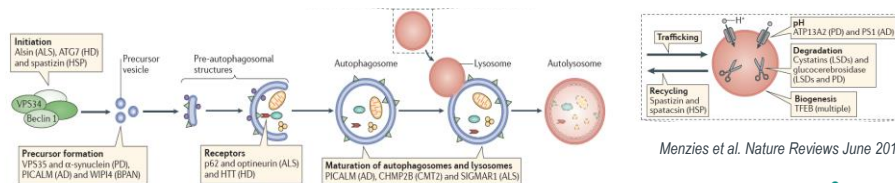
Menzies et al. Nature Reviews June 2015

Source: MRK Presentation.

Genentech / Roche (RHHBY)

Casper Hoogenraad, Ph.D., Vice President, Head of Neuroscience Research

Dr. Hoogenraad provided an overview of Genentech/Roche's history in CNS research and drug development and its current pipeline of novel candidates with promising clinical data. Neuroscience remains an area of great unmet need, posing challenges to the healthcare system that is burdened by over 600 neurological diseases with ~$800B in annual costs. Genentech and parent company Roche employ over 4,000 neuroscientists focused on developing 14 investigational compounds in over 150 clinical trials globally. As a pioneer, Roche's history in CNS drug development dates back to 1963 when Valium for anxiety was first approved, followed by Madopar i.e. levodopa and decarboxylase for PD in 1973, Activase for stroke in 1996, and Ocrevus for MS in 2017 and Evrysdi for SMA in 2020 as more recent examples of innovative approaches to large unmet needs in CNS disorders. Genentech/Roche's current pipeline is organized into five main areas of CNS research consisting of neuroimmunology, neurodegeneration, neuromuscular, neurodevelopmental, and neuropsychiatric disorders with 14 candidates across various therapeutic modalities and development stages. Dr. Hoogenraad described Genentech/Roche's mission as preventing or slowing progression of neurodegenerative diseases through early treatment, repairing and regenerating nervous system damage via remyelination and cell therapy, and transforming the treatment of severe chronic pain and other neurological disorders by understanding human genetics and the underlying biology. Core and adjacent indication areas are AD, MS, PD, and glaucoma in Tier-1, and ALS, FTD, and tauopathies in Tier-2. Genentech/Roche's approach is characterized by four themes: protein aggregation and homeostasis; neuroimmunological communication; modulation of neuronal circuitry; and protection, repair, and regeneration of neuronal damage. Dr. Hoogenraad highlighted tau pathology correlation with disease severity as evidence that distribution and density of tau are associated with AD, which supports ongoing clinical studies of anti-tau antibodies bepranemab targeting the mid-domain of tau protein with Ph2 study initiating in 2021 and semorinemab targeting the N-terminus with Ph2 study ongoing in moderate AD, which may provide better results than the prior Ph2 study in prodromal/mild AD patients. Other examples of new approaches to historically difficult drug targets include small molecules, ASO-antisense technology, RNAi, and cell and gene therapies. Dr. Hoogenraad described a heavy reliance on genetic insights, biomarker strategies, and new disease models e.g. iPSC-derived human microglia cells, and noted key alliances with academic institutions.

Exhibit 9. Genentech/Roche's Pipeline Features 14 Novel Candidates for CNS Disorders

Source: Genentech/Roche Presentation.

Panel Discussion: *Financing and Investing in Neuroscience Biotechnology*

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

We hosted a panel discussion featuring Jamil M. Beg of 5AM Ventures, Margarita Chavez of AbbVie Ventures, Jingwen Wang of Veriton Fund Management, and Michael Margolis, Oppenheimer & Co.'s Co-Head of Healthcare Investment Banking. 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 CNS biotechnology, overlapping with a passion for contributing their expertise towards an area with an accelerating pace of innovation. We began the discussion by asking panelists about how FDA approval of BIIB's Aduhelm impacts their view of financing and investing in CNS biotechnology. Margarita Chavez and Jamil M. Beg both believe that while there is gaining enthusiasm for the novel treatment for AD, the FDA decision does not change how research or investment strategy is done, although it should motivate more research and investment into AD drug development which provides smaller biotech companies focusing on CNS with more options. Michael Margolis commented on the resulting halo effect seen in increasing valuations of comparable companies, and he believes that investors should maintain cautious optimism. Jingwen Wang noted the inherent uncertainty and subjectivity of clinical endpoints in clinical trials for CNS drugs, which directs her investment outlook towards precision medicine approaches, e.g. gene therapy for SMA, and drug candidates that show high magnitude of efficacy vs. placebo in Ph1/2 studies, e.g. ketamine for MDD. Our panelists all agreed on the importance of novel targets that could be validated with biomarkers and platform expertise to support an investment thesis for neurodegeneration. We asked about new areas that our panelists are most enthusiastic about in CNS therapy, and Jamil M. Beg noted BlueRock's recent initiation of Ph1 study in cell therapy for PD, and ABBV's collaboration with Capsida on developing viral vectors for CNS gene therapy. For neuroinflammation, approaches to microglia biology should become an emerging field as well. Margarita Chavez noted that ABBV's acquisition of AGN provided novel targets for psychiatric disorders, and also expressed her enthusiasm of nitration enzymes for PD and biomolecular condensates for ALS that Nitrome Biosciences and Faze Medicines are pursuing, respectively. Jingwen Wang views new modalities that show target engagement as important, such as tau antibodies with optimized binding profiles, and is enthusiastic about novel approaches to psychiatry e.g. psychedelics that FDA and industry are now considering more seriously. Michael Margolis agreed that psychedelics are promising for psychiatry, especially for TRD, and is enthusiastic about the overall gravitation of investors towards CNS therapeutics within the last five years. Lastly, we asked our panelists about advice to early-stage CNS biotech companies, and all agreed that portfolio prioritization, differentiated targets, strong management, and reliable investors are crucial for success.

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

FINANCING AND INVESTING IN NEUROSCIENCE

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abbvie.com/partnerships/abbvie-ventures.html

Jingwen Wang, PhD
Portfolio Manager
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Supported by:
BioCentury
Chemistry of Life Processes
Institute
Oppenheimer & Co.

Source: Oppenheimer & Co.

Exhibit 11. FDA Approvals of BLAs and NDAs from 1995 to 2020 Show Recent Strength
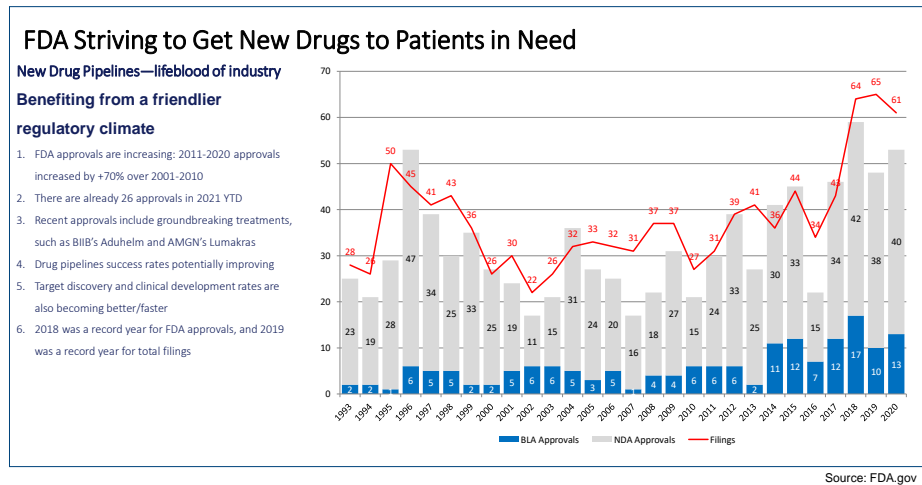

FDA Striving to Get New Drugs to Patients in Need

New Drug Pipelines—lifeblood of industry

Benefiting from a friendlier regulatory climate

1. FDA approvals are increasing: 2011-2020 approvals increased by +70% over 2001-2010
2. There are already 26 approvals in 2021 YTD
3. Recent approvals include groundbreaking treatments, such as BIIB's Aduhelm and AMGN's Lumakras
4. Drug pipelines success rates potentially improving
5. Target discovery and clinical development rates are also becoming better/faster
6. 2018 was a record year for FDA approvals, and 2019 was a record year for total filings

Source: FDA.gov

Exhibit 12. Biotech M&A Deals by Valuation Multiple and Aggregate Size from 2011 to 2021

Biotech M&A is Gaining Steam in 2021*

1. 2021 YTD total deal value at ~$81B is comprised of 60 deals across multiple treatment areas, which include notable targets such as GWPRF and PAND
2. 2020 Biotech M&A dynamics were decent despite the global pandemic and market volatility, with total transaction value of $123B driven by 67 deals
3. 2019 was a record year for Biotech M&A with $266B in total value across 41 deals, dominated by large mergers (CELG, AGN, ARRY, LOXO, and MDCO) and strategic asset sales (Upjohn, Otezla)
4. We anticipate continuing momentum in deal pace throughout 2021 based on strong tailwinds
5. Our longer-term forecast of the M&A environment for Biotech is favorable based on significant patent cliffs, increasing competition, and an uncertain payer environment that encourages larger scale

*YTD as of 6/18/2020

Source: FactSet, Oppenheimer Research

Exhibit 13. Biotech IPOs by Total Number and Aggregate Size from 2011 to 2021

Biotech IPOs in 2021* Already Looking to Beat Records Set in 2020

*YTD as of 6/18/2020

Source: Bloomberg, FactSet, Oppenheimer Research

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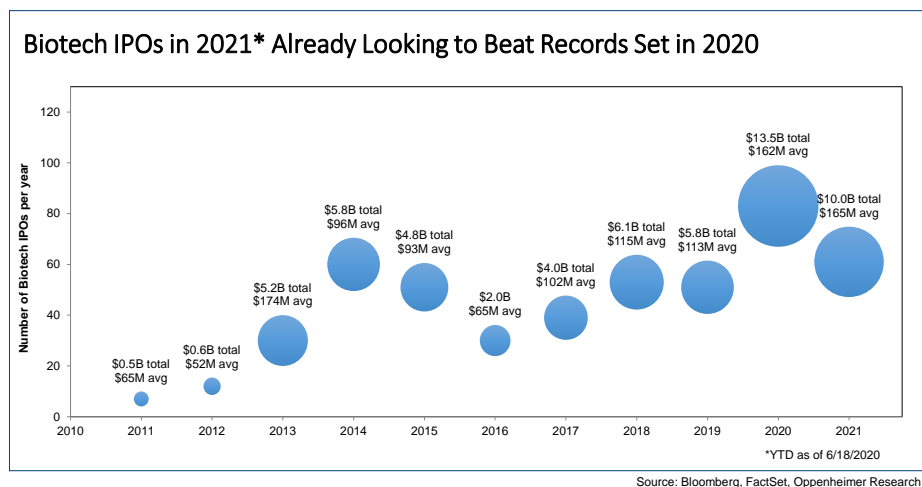
Stock prices of other companies mentioned in this report (as of 6/25/2020):

AbbVie, Inc. (ABBV-NYSE; $112.82; Not Covered)

Aptinyx Inc (APTX-NASDAQ; $2.88; Not Covered)

Merck & Co. (MRK-NYSE; $76.66; Not Covered)

Roche Holdings Ltd. Sponsored ADR (RHHBY-OTC; $46.95; Not Covered)

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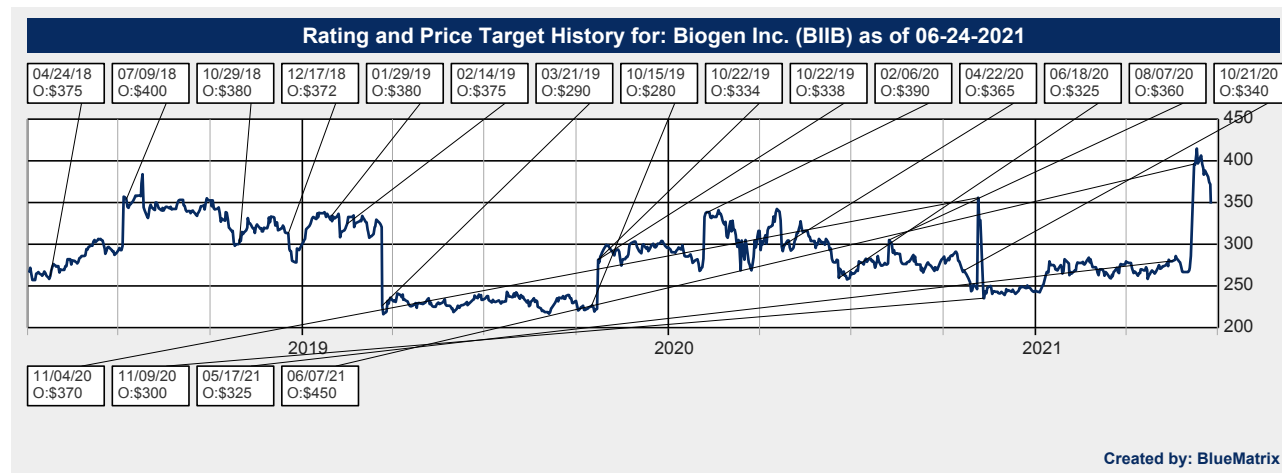
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Stock Prices as of June 27, 2021
Biogen Inc. (BIIB - NASDAQ, $347.93, OUTPERFORM)

Rating and Price Target History for: Biogen Inc. (BIIB) as of 06-24-2021

| 04/24/18 O:$375 | 07/09/18 O:$400 | 10/29/18 O:$380 | 12/17/18 O:$372 | 01/29/19 O:$380 | 02/14/19 O:$375 | 03/21/19 O:$290 | 10/15/19 O:$280 | 10/22/19 O:$334 | 10/22/19 O:$338 | 02/06/20 O:$390 | 04/22/20 O:$365 | 06/18/20 O:$325 | 08/07/20 O:$360 | 10/21/20 O:$340 |

| 11/04/20 O:$370 | 11/09/20 O:$300 | 05/17/21 O:$325 | 06/07/21 O:$450 |

Created by: BlueMatrix

All price targets displayed in the chart above are for a 12- to- 18-month period. Prior to March 30, 2004, Oppenheimer & Co. Inc. used 6-, 12-, 12- to 18-, and 12- to 24-month price targets and ranges. For more information about target price histories, please write to Oppenheimer & Co. Inc., 85 Broad Street, New York, NY 10004, Attention: Equity Research Department, Business Manager.

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Oppenheimer & Co. Inc. Rating System as of January 14th, 2008:

Outperform(O) - Stock expected to outperform the S&P 500 within the next 12-18 months.

Perform (P) - Stock expected to perform in line with the S&P 500 within the next 12-18 months.

Underperform (U) - Stock expected to underperform the S&P 500 within the next 12-18 months.

Not Rated (NR) - Oppenheimer & Co. Inc. does not maintain coverage of the stock or is restricted from doing so due to a potential conflict of interest.

Oppenheimer & Co. Inc. Rating System prior to January 14th, 2008:

Buy - anticipates appreciation of 10% or more within the next 12 months, and/or a total return of 10% including dividend payments, and/or the ability of the shares to perform better than the leading stock market averages or stocks within its particular industry sector.

Neutral - anticipates that the shares will trade at or near their current price and generally in line with the leading market averages due to a perceived absence of strong dynamics that would cause volatility either to the upside or downside, and/or will perform less well than higher rated companies within its peer group. Our readers should be aware that when a rating change occurs to Neutral from Buy, aggressive trading accounts might decide to liquidate their positions to employ the funds elsewhere.

Sell - anticipates that the shares will depreciate 10% or more in price within the next 12 months, due to fundamental weakness perceived in the company or for valuation reasons, or are expected to perform significantly worse than equities within the peer group.

Distribution of Ratings/IB Services Firmwide

Rating	Count	Percent	IB Serv/Past 12 Mos. Count	Percent
OUTPERFORM [O]	466	70.93	248	53.22
PERFORM [P]	191	29.07	70	36.65
UNDERPERFORM [U]	0	0.00	0	0.00

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