where science meets humanity™

Biogen Gene Therapy

Junghae Suh, Ph.D., Head of Gene Therapy Accelerator Unit (GTxAU)

R&D Day
September 21, 2021

Biogen

Forward-looking statements

This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to: our strategy and plans; potential of, and expectations for, our commercial business and pipeline programs; capital allocation and investment strategy; clinical development programs, clinical trials, and data readouts and presentations; risks and uncertainties associated with drug development and commercialization; regulatory discussions, submissions, filings, and approvals and the timing thereof; the potential benefits, safety, and efficacy of our and our collaboration partners' products and investigational therapies; the anticipated benefits and potential of investments, collaborations, and business development activities; and our future financial and operating results. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "plan," "potential," "possible," "prospect," "will," "would," and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: our dependence on sales from our products; uncertainty of long-term success in developing, licensing, or acquiring other product candidates or additional indications for existing products; failure to compete effectively due to significant product competition in the markets for our products; failure to successfully execute or realize the anticipated benefits of our strategic and growth initiatives; difficulties in obtaining and maintaining adequate coverage, pricing, and reimbursement for our products; our dependence on collaborators, joint venture partners, and other third parties for the development, regulatory approval, and commercialization of products and other aspects of our business, which are outside of our full control; risks associated with current and potential future healthcare reforms; failure to obtain, protect, and enforce our data, intellectual property, and other proprietary rights and the risks and uncertainties relating to intellectual property claims and challenges; the risk that positive results in a clinical trial may not be replicated in subsequent or confirmatory trials or success in early stage clinical trials may not be predictive of results in later stage or large scale clinical trials or trials in other potential indications; risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, regulatory authorities may require additional information or further studies, or may fail to approve or may delay approval of our drug candidates; the occurrence of adverse safety events, restrictions on use with our products, or product liability claims; risks relating to the distribution and sale by third parties of counterfeit or unfit versions of our products; risks relating to the use of social media for our business; risks relating to technology failures or breaches; risks relating to management and key personnel changes, including attracting and retaining key personnel; failure to comply with legal and regulatory requirements; the risks of doing business internationally, including currency exchange rate fluctuations; risks relating to investment in our manufacturing capacity; problems with our manufacturing processes; fluctuations in our effective tax rate; the direct and indirect impacts of the ongoing COVID-19 pandemic on our business, results of operations, and financial condition; fluctuations in our operating results; risks related to investment in properties; the market, interest, and credit risks associated with our investment portfolio; risks relating to share repurchase programs; risks relating to access to capital and credit markets; risks related to indebtedness; change in control provisions in certain of our collaboration agreements; environmental risks; and any other risks and uncertainties that are described in other reports we have filed with the U.S. Securities and Exchange Commission (SEC).

These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.

Key messages

We are building **Biogen's Gene Therapy (GTx) R&D Engine** to drive innovation and to deliver a continuous pipeline of gene therapies

Gene Therapy Accelerator Unit (GTxAU)

External innovation is an important part of our strategy

Biogen's internal gene therapy manufacturing facility is underway

Building Biogen's gene therapy (GTx) R&D engine with aim of delivering both near- and long-term assets with greater probability of success

Technology Innovation ⟷ **Bidirectional alignment** ⟷ **Portfolio Delivery**

Focused **technology innovation** to increase probability of success of GTx

Focused **system innovation** to move GTx programs through pipeline

GTx Pillars	Capsid	Cargo	Vector Performance	Vector Production
Tech Innovation*	• Broad CNS, intravitreal, muscle-tropic capsids • Higher potency capsids	• Regulated/inducible promoters • Gene editing tools	• Routes of administration (ROA) • Immunogenicity, safety	• Increase overall yield • Increase scalability
Portfolio Delivery	• Capsid identification • Structure-activity mapping	• Cargo optimization • Human genetic evidence bioinformatics	• *In vitro* and *in vivo* cores • Bioanalytics, PK/PD modeling • *In vivo* imaging	• Small-/mid-scale production • Process development • Analytical development

*Goals and needs of gene therapy programs

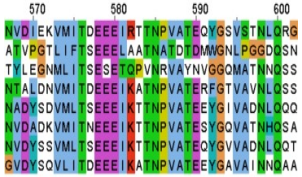
CNS = central nervous system; PK/PD = pharmacokinetics/pharmacodynamics

Gene Therapy Accelerator Unit (GTxAU)

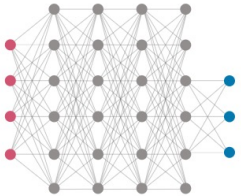
Identify and solve key rate-limiting steps in our **technologies**, **capabilities**, and drug discovery and development **processes** to accelerate gene therapy programs through the pipeline.

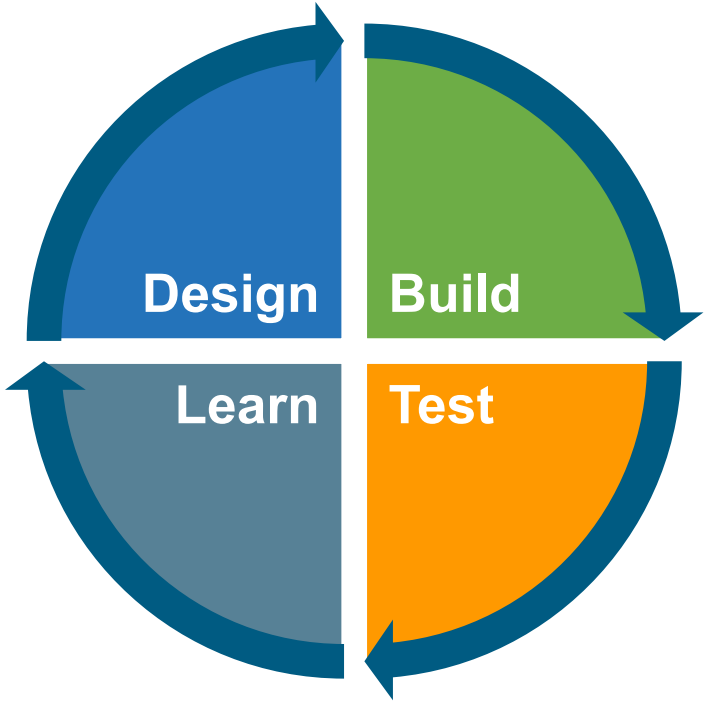
Gene therapy engineering cycle

Rational, Combinatorial, *in silico*

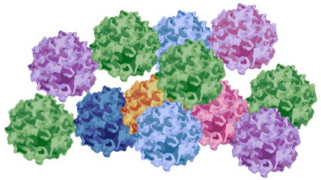


Data Science





Scalable Prototyping



Scalable Experiments

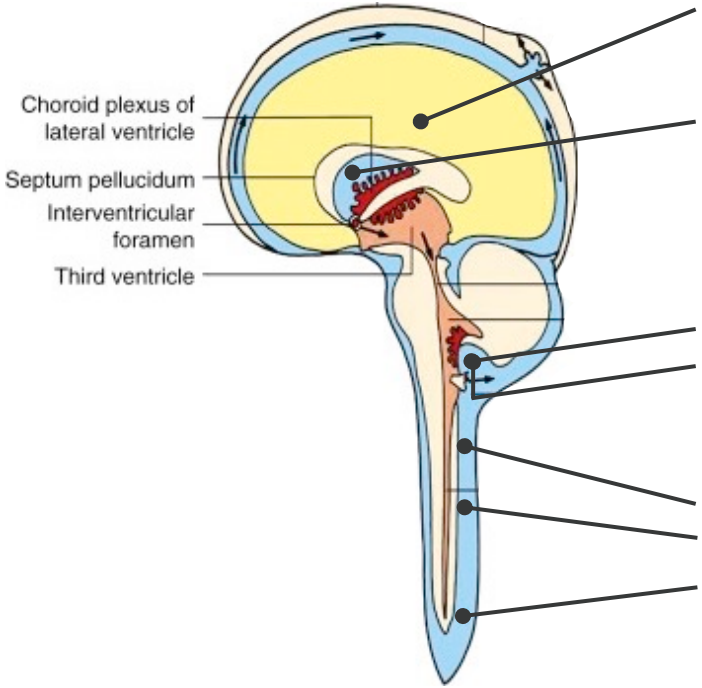
Challenges with delivery, safety, and immunogenicity continue to impact entire gene therapy Field

Challenges			Company	Events Routes of Administration (ROA): IT - intrathecal IV - intravenous IVT - intravitreal
Safety / Immuno	Delivery	Cargo Design		
✕	✕		Apic Bio	AAV-SOD1 IT resulted in **pain syndrome** caused by DRG tox observed by nerve conduction studies and post-mortem; Clear evidence of biological activity but observed clinical effect in one SOD1 patient did not suggest meaningful clinical efficacy (**2020**)
✕			Astellas	AAV-MTM1 IV resulted in **3 deaths** in highest dose group associated with complement activation (**2020**)
✕			Novartis	Zolgensma IT was on **partial clinical hold** due to DRG tox and questions on efficacy (**2020**)*
✕			Pfizer	AAV-DMD IV resulted in **acute kidney injury** and **thrombocytopenia** with atypical hemolytic uremic-like complement activation in 3 patients in high-dose group (**2020**)
✕	✕		Roche, 4DMT	AAV-CHM IVT **collaboration terminated** by Roche likely due to observed uveitis and insufficient retinal delivery with novel 4DMT capsid (**2021**)
	✕	✕	Sarepta	AAV-DMD IV **failed to meet primary functional endpoint** in Ph 1/2 trial, possibly due to design of mico-dystrophin, insufficient delivery and/or durability of cargo expression in muscle cells (**2021**)
	✕	✕	Solid Bio	AAV-DMD IV **unclear mixed results** in Ph 1/2 trial with no dose-response observed, possibly due to insufficient delivery and/or durability of cargo expression in muscle cells (**2021**)
✕			Biogen	BIIB089 program development **discontinued.** IND on clinical hold due to dorsal root ganglion toxicity (**2020**)

*Partial clinical hold lifted in 2021

AAV = adeno-associated virus; DRG = dorsal root ganglion; IND = investigational new drug; tox = toxicity

Gene delivery into CNS remains a major challenge



Intraparenchymal (IPa)
Various sites

Brain parenchyma

Intracerebroventricular (ICV)

Intra-cisterna magna (ICM)
Direct
Catheter

Intrathecal (IT)
Cervical
Thoracic
Lumbar
Direct
Catheter

Cerebrospinal fluid (CSF)

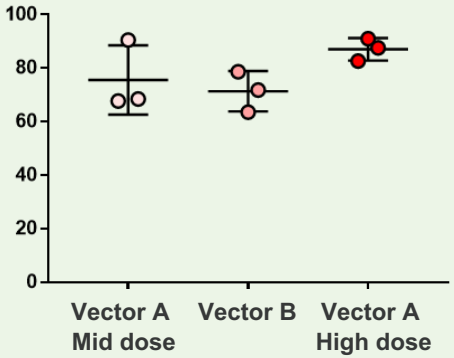
Intravenous (IV)

Blood

Intra-cisterna magna (ICM) injection of AAV gene therapy

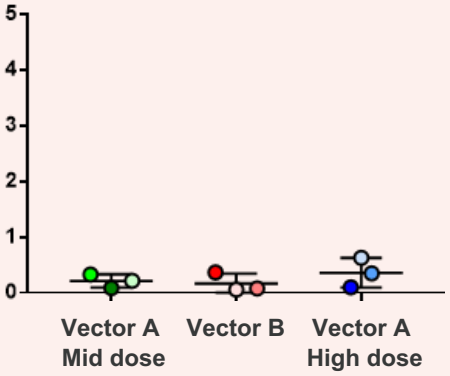
Spinal cord

% MNs Expressing Transgene



Putamen

% Neurons Expressing Transgene



Using current off-the-shelf components

Findings:

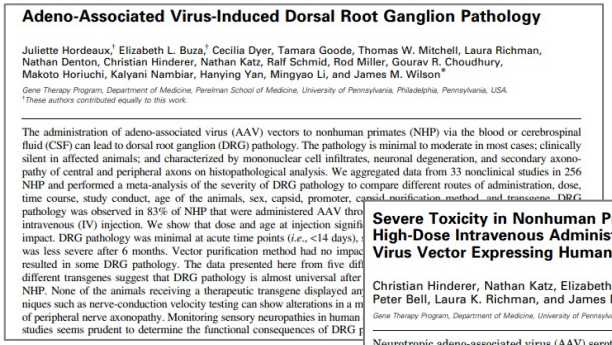
- ✓ High spinal cord motor neuron (MN) transduction in NHPs
- ✗ Low putamen transduction in NHPs
- ✗ DRG toxicity

Technology innovation may be needed

NHP = non-human primate

Dorsal root ganglion (DRG) toxicity

Observed for 5 capsids, 5 promoters, 20 transgenes

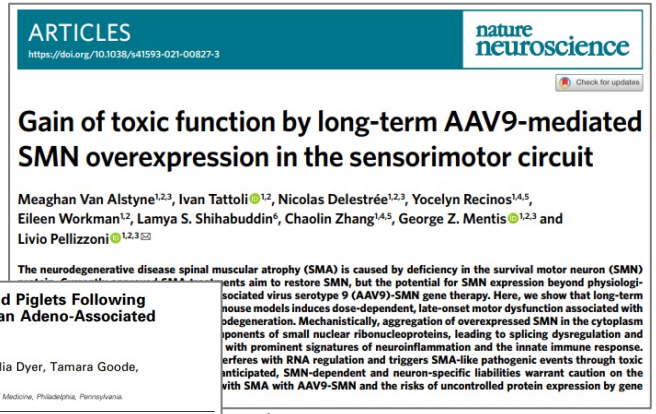


Adeno-Associated Virus-Induced Dorsal Root Ganglion Pathology

Juliette Hordeaux,† Elizabeth L. Buza,† Cecilia Dyer, Tamara Goode, Thomas W. Mitchell, Laura Richman, Nathan Denton, Christian Hinderer, Nathan Katz, Ralf Schmid, Rod Miller, Gourav R. Choudhury, Makoto Horiuchi, Kalyani Nambiar, Hanying Yan, Mingyao Li, and James M. Wilson*

Gene Therapy Program, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
†These authors contributed equally to this work.

The administration of adeno-associated virus (AAV) vectors to nonhuman primates (NHP) via the blood or cerebrospinal fluid (CSF) can lead to dorsal root ganglion (DRG) pathology. The pathology is minimal to moderate in most cases; clinically silent in affected animals; and characterized by mononuclear cell infiltrates, neuronal degeneration, and secondary axonopathy of central and peripheral axons on histopathological analysis. We aggregated data from 33 nonclinical studies in 256 NHP and performed a meta-analysis of the severity of DRG pathology to compare different routes of administration, dose, time course, study conduct, age of the animals, sex, capsid, promoter, capsid purification method, and transgene. DRG pathology was observed in 83% of NHP that were administered AAV thro
intravenous (IV) injection. We show that dose and age at injection signifi
impact. DRG pathology was minimal at acute time points (*i.e.*, <14 days),
was less severe after 6 months. Vector purification method had no impac
resulted in some DRG pathology. The data presented here from five dif
different transgenes suggest that DRG pathology is almost universal after
NHP. None of the animals receiving a therapeutic transgene displayed an
niques such as nerve-conduction velocity testing can show alterations in a m
of peripheral nerve axonopathy. Monitoring sensory neuropathies in human
studies seems prudent to determine the functional consequences of DRG p



ARTICLES
https://doi.org/10.1038/s41593-021-00827-3

nature neuroscience

Check for updates

Gain of toxic function by long-term AAV9-mediated SMN overexpression in the sensorimotor circuit

Meaghan Van Alstyne[1,2,3], Ivan Tattoli[1,2], Nicolas Delestrée[1,2,3], Yocelyn Recinos[1,4,5], Eileen Workman[1,2], Lamya S. Shihabuddin[6], Chaolin Zhang[1,4,5], George Z. Mentis[1,2,3] and Livio Pellizzoni[1,2,3]✉

The neurodegenerative disease spinal muscular atrophy (SMA) is caused by deficiency in the survival motor neuron (SMN)
ents aim to restore SMN, but the potential for SMN expression beyond physiologi-
sociated virus serotype 9 (AAV9)-SMN gene therapy. Here, we show that long-term
ouse models induces dose-dependent, late-onset motor dysfunction associated with
odegeneration. Mechanistically, aggregation of overexpressed SMN in the cytoplasm
ponents of small nuclear ribonucleoproteins, leading to splicing dysregulation and
with prominent signatures of neuroinflammation and the innate immune response.
erferes with RNA regulation and triggers SMA-like pathogenic events through toxic
nticipated, SMN-dependent and neuron-specific liabilities warrant caution on the
ith SMA with AAV9-SMN and the risks of uncontrolled protein expression by gene

Severe Toxicity in Nonhuman Primates and Piglets Following High-Dose Intravenous Administration of an Adeno-Associated Virus Vector Expressing Human SMN

Christian Hinderer, Nathan Katz, Elizabeth L. Buza, Cecilia Dyer, Tamara Goode, Peter Bell, Laura K. Richman, and James M. Wilson*

Gene Therapy Program, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania.

Neurotropic adeno-associated virus (AAV) serotypes such as AAV9 have been demonstrated to transduce spinal alpha motor neurons when administered intravenously (i.v.) at high doses. This observation led to the recent successful application of i.v. AAV9 delivery to treat infants with spinal muscular atrophy, an inherited deficiency of the survival of motor neuron (SMN) protein characterized by selective death of lower motor neurons. To evaluate the efficiency of motor neuron transduction with an AAV9 variant (AAVhu68) using this approach, three juvenile nonhuman primates (NHPs; aged 14 months) and three piglets (aged 7–30 days) were treated with an i.v. injection of an AAVhu68 vector carrying a human *SMN* transgene at a dose similar to that employed in the spinal muscular atrophy clinical trial. Administration of 2×10^{14} genome copies per kilogram of body weight resulted in widespread transduction of spinal motor neurons in both species. However, severe toxicity occurred in both NHPs and piglets. All three NHPs exhibited marked transaminase elevations. In two NHPs, the transaminase elevations resolved without clinical sequelae, while one NHP developed acute liver failure and shock and was euthanized 4 days after vector injection. Degeneration of dorsal root ganglia sensory neurons was also observed, although NHPs exhibited no clinically apparent sensory deficits. There was no correlation between clinical findings and T-cell responses to the vector capsid or transgene product in NHPs. Piglets demonstrated no evidence of hepatic toxicity, but within 14 days of vector injection, all three animals exhibited proprioceptive deficits and ataxia, which profoundly impaired ambulation and necessitated euthanasia. These clinical findings correlated with more severe dorsal root ganglia sensory neuron lesions than those observed in NHPs. The liver and sensory neuron findings appear to be a direct consequence of AAV transduction independent of an immune response to the capsid or transgene product. The present results and those of another recent study utilizing a different AAV9 variant and transgene indicate that systemic and sensory neuron toxicity may be general properties of i.v. delivery of AAV vectors at high doses, irrespective of the capsid serotype or transgene. Preclinical and clinical studies involving high systemic doses of AAV vectors should include careful monitoring for similar toxicities.

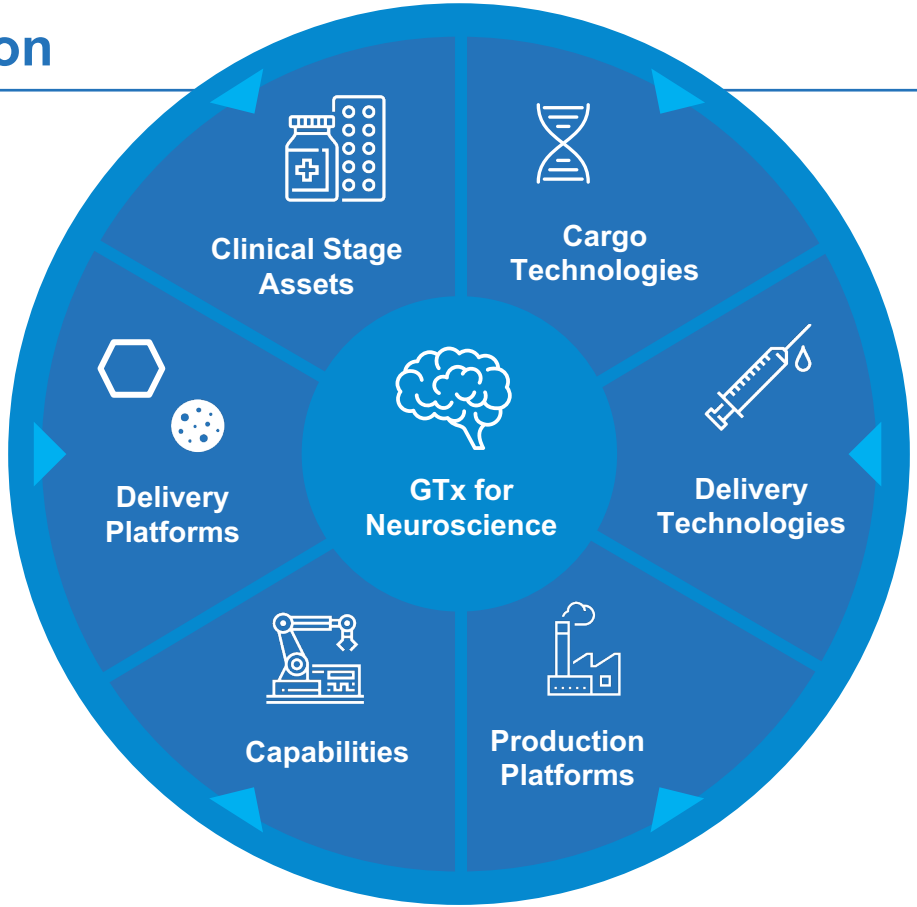
Observed with high-dose IV ROA

Transgene overexpression can lead to toxicity

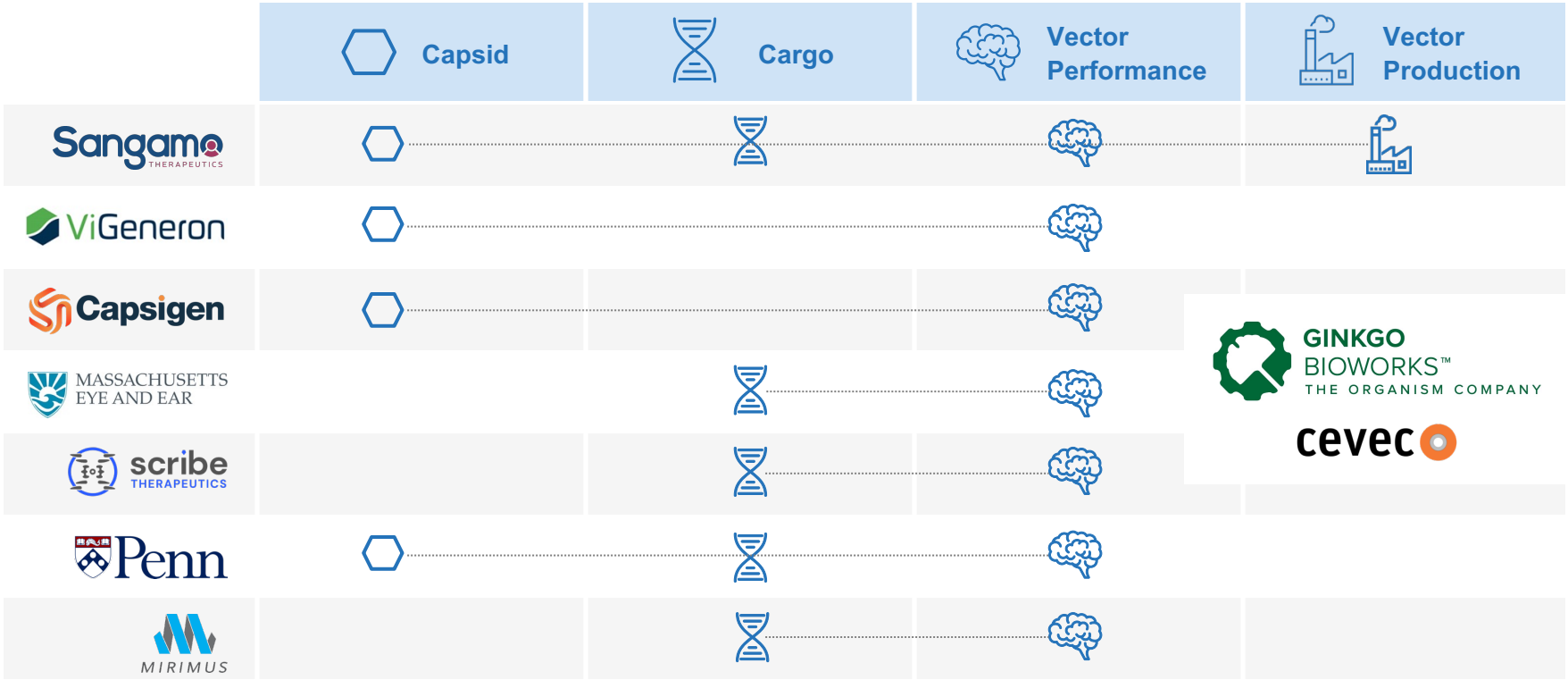
- May be due to **expression of AAV cargo**
  - Platform-related v. specific transgene-related
- Need to consider **Benefit/Benefit**
- Immuno-suppression, tech innovation

Accessing external innovation

Enhance our pipeline, technical expertise, capabilities and capacity through external investments



Gene therapy deals signed over last 2 years



Importance of getting GTx manufacturing right

Time

- For rare diseases, 1st to market may be critical
- Potential for accelerated clinical development pathways

Safety, Quality

- ‘The Process is the Product’
- Comparability, potency, data integrity
- Potential impact of process impurities and unknown structure-activity relationships
- Analytical approaches are still evolving

Workforce, Platform, Facility

- Limited workforce with deep know-how in gene therapy manufacturing
- Gene therapy production platforms are still evolving
- Limited CMO choices with long queues
- Limited ability to scale to supply commercial market

CMO = contract manufacturing organization

Biogen's GTx manufacturing facility – 200M, 175k Sq Ft

BIOGEN ANNOUNCES PLANS TO BUILD A NEW, STATE-OF-THE-ART GENE THERAPY MANUFACTURING FACILITY IN RESEARCH TRIANGLE PARK, NORTH CAROLINA

March 4, 2021 at 7:48 AM EST

- *The innovative and scalable gene therapy manufacturing facility will support Biogen's plan to advance its gene therapy portfolio*
- *The new facility is expected to employ approximately 90 people and to be operational by 2023*

CAMBRIDGE, Mass., March 04, 2021 (GLOBE NEWSWIRE) -- Biogen Inc. (Nasdaq: BIIB) today announced its plans to build a new gene therapy manufacturing facility at its Research Triangle Park (RTP) manufacturing campuses in North Carolina to support its growing gene therapy pipeline across multiple therapeutic areas.

Biogen's gene therapy preclinical pipeline

3

Ophthalmology

3

Neurodegenerative Diseases

6

Neuromuscular & Muscle Diseases

4

Genetic & Neurodevelopmental Disorders

Gene Therapy @ Biogen

01 **Gene Therapy R&D Engine**
Tech Innovation + Portfolio Delivery

02 **Gene Therapy Accelerator Unit**
Capsid, cargo, performance, production

03 **Accessing External Innovation**
Assets, technologies, capabilities

04 **Gene Therapy Manufacturing**
Internal facility