The Future of Rare at Insmed:

Functional Genes, AI-Enhanced Proteins, Glowing Algae, and More

Forward Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. "Forward-looking statements," as that term is defined in the Private Securities Litigation Reform Act of 1995, are statements that are not historical facts and involve a number of risks and uncertainties. Words herein such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "intends," "potential," "continues," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) may identify forward-looking statements.

The forward-looking statements in this presentation are based upon the Company's current expectations and beliefs, and involve known and unknown risks, uncertainties and other factors, which may cause the Company's actual results, performance and achievements and the timing of certain events to differ materially from the results, performance, achievements or timings discussed, projected, anticipated or indicated in any forward-looking statements. Such risks, uncertainties and other factors include, among others, the following: failure to obtain, or delays in obtaining, regulatory approvals for ARIKAYCE outside the U.S., Europe or Japan, or for the Company's product candidates in the U.S., Europe, Japan or other markets, including separate regulatory approval for the Lamira® Nebulizer System in each market and for each usage; failure to successfully commercialize ARIKAYCE, the Company's only approved product, in the U.S., Europe or Japan (amikacin liposome inhalation suspension, Liposomal 590 mg Nebuliser Dispersion, and amikacin sulfate inhalation drug product, respectively), or to maintain U.S., European or Japanese approval for ARIKAYCE; business or economic disruptions due to catastrophes or other events, including natural disasters or public health crises; impact of the COVID-19 pandemic and efforts to reduce its spread on the Company's business, employees, including key personnel, patients, partners and suppliers; risk that brensocatib or TPIP does not prove to be effective or safe for patients in ongoing and future clinical studies, including, for brensocatib, the ASPEN study; uncertainties in the degree of market acceptance of ARIKAYCE by physicians, patients, third-party payors and others in the healthcare community; the Company's inability to obtain full approval of ARIKAYCE from the U.S. Food and Drug Administration, including the risk that the Company will not successfully or in a timely manner complete the study to validate a patient reported outcome tool and the confirmatory post-marketing clinical trial required for full approval of ARIKAYCE; inability of the Company, PARI or the Company's other third-party manufacturers to comply with regulatory requirements related to ARIKAYCE or the Lamira® Nebulizer System; the Company's inability to obtain adequate reimbursement from government or third-party payors for ARIKAYCE or acceptable prices for ARIKAYCE; development of unexpected safety or efficacy concerns related to ARIKAYCE, brensocatib, TPIP or the Company's other product candidates; inaccuracies in the Company's estimates of the size of the potential markets for ARIKAYCE, brensocatib, TPIP or the Company's other product candidates or in data the Company has used to identify physicians, expected rates of patient uptake, duration of expected treatment, or expected patient adherence or discontinuation rates; the risks and uncertainties associated with, and the perceived benefits of, the Company's secured senior loan with certain funds managed by Pharmakon Advisors, LP and the Company's royalty financing with OrbiMed Royalty & Credit Opportunities IV, LP, including our ability to maintain compliance with the covenants in the agreements for the senior secured loan and royalty financing and the perceived impact of the restrictions on the Company's operations under these agreements; the Company's inability to create an effective direct sales and marketing infrastructure or to partner with third parties that offer such an infrastructure for distribution of ARIKAYCE or any of the Company's product candidates that are approved in the future; failure to obtain regulatory approval to expand ARIKAYCE's indication to a broader patient population; risk that the Company's competitors may obtain orphan drug exclusivity for a product that is essentially the same as a product the Company is developing for a particular indication; failure to successfully predict the time and cost of development, regulatory approval and commercialization for novel gene therapy products; failure to successfully conduct future clinical trials for ARIKAYCE, brensocatib, TPIP and the Company's other product candidates due to the Company's limited experience in conducting preclinical development activities and clinical trials necessary for regulatory approval and its potential inability to enroll or retain sufficient patients to conduct and complete the trials or generate data necessary for regulatory approval, among other things; risks that the Company's clinical studies will be delayed or that serious side effects will be identified during drug development; failure of third parties on which the Company is dependent to manufacture sufficient quantities of ARIKAYCE or the Company's product candidates for commercial or clinical needs, to conduct the Company's clinical trials, or to comply with the Company's agreements or laws and regulations that impact the Company's business or agreements with the Company; the Company's inability to attract and retain key personnel or to effectively manage the Company's growth; the Company's inability to successfully integrate its recent acquisitions and appropriately manage the amount of management's time and attention devoted to integration activities; risks that the Company's acquired technologies, products and product candidates are not commercially successful; the Company's inability to adapt to its highly competitive and changing environment; risk that the Company is unable to maintain its significant customers; risk that government healthcare reform materially increases the Company's costs and damages its financial condition; deterioration in general economic conditions in the U.S., Europe, Japan and globally, including the effect of prolonged periods of inflation, affecting the Company, its suppliers, third-party service providers and potential partners; the Company's inability to adequately protect its intellectual property rights or prevent disclosure of its trade secrets and other proprietary information and costs associated with litigation or other proceedings related to such matters; restrictions or other obligations imposed on the Company by agreements related to ARIKAYCE or the Company's product candidates, including its license agreements with PARI and AstraZeneca AB, and failure of the Company to comply with its obligations under such agreements; the cost and potential reputational damage resulting from litigation to which the Company is or may become a party, including product liability claims; risk that the Company's operations are subject to a material disruption in the event of a cybersecurity attack or issue; business disruptions or expenses related to the upgrade to the Company's enterprise resource planning system; the Company's limited experience operating internationally; changes in laws and regulations applicable to the Company's business, including any pricing reform, and failure to comply with such laws and regulations; the Company's history of operating losses, and the possibility that the Company may never achieve or maintain profitability; goodwill impairment charges affecting the Company's results of operations and financial condition; inability to repay the Company's existing indebtedness and uncertainties with respect to the Company's ability to access future capital; and delays in the execution of plans to build out an additional third-party manufacturing facility approved by the appropriate regulatory authorities and unexpected expenses associated with those plans.

The Company may not actually achieve the results, plans, intentions or expectations indicated by the Company's forward-looking statements because, by their nature, forward-looking statements involve risks and uncertainties because they relate to events and depend on circumstances that may or may not occur in the future. For additional information about the risks and uncertainties that may affect the Company's business, please see the factors discussed in Item 1A, "Risk Factors," in the Company's Annual Report on Form 10-K for the year ended December 31, 2022 and any subsequent Company filings with the Securities and Exchange Commission (SEC).

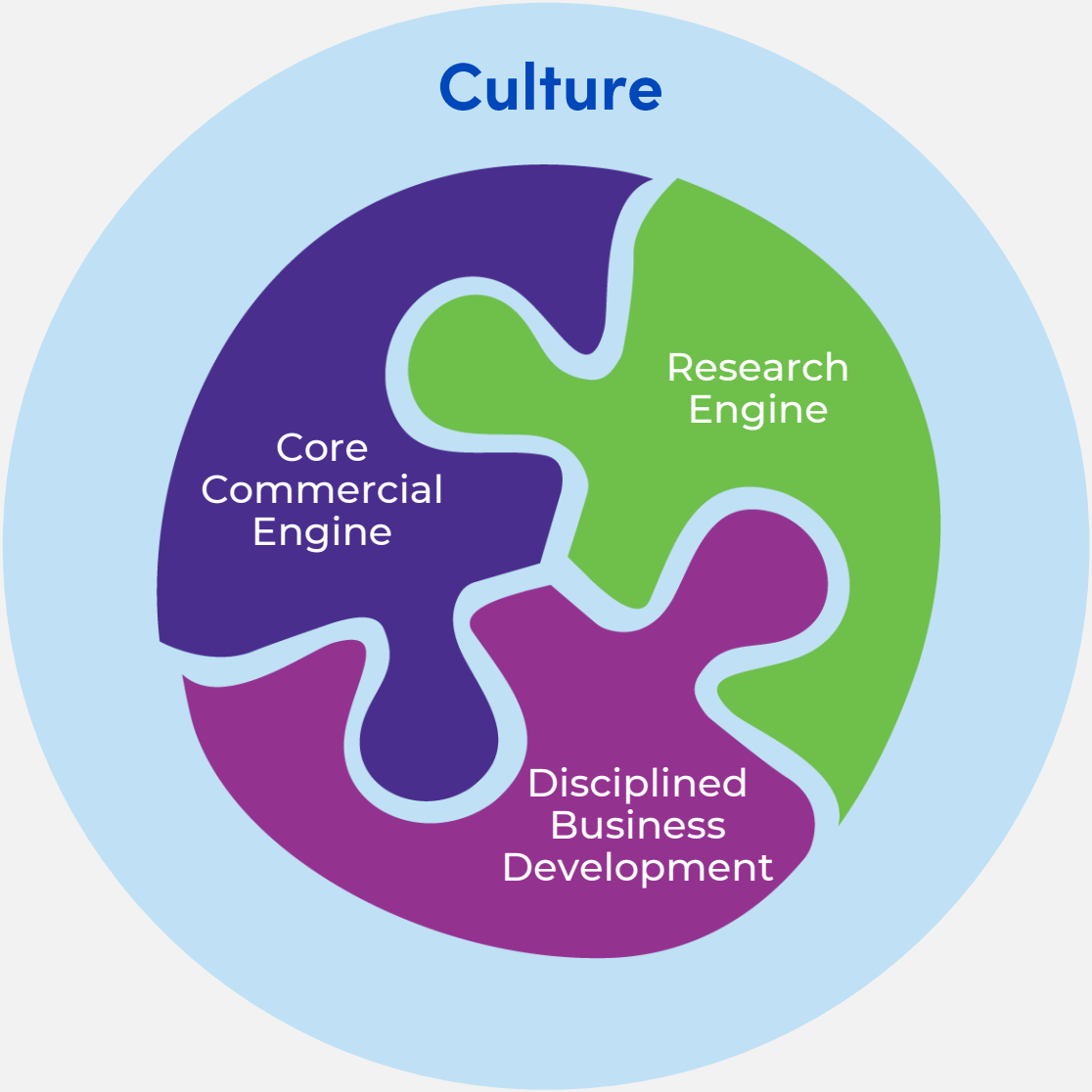
The Company cautions readers not to place undue reliance on any such forward-looking statements, which speak only as of the date of this presentation. The Company disclaims any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

Will Lewis

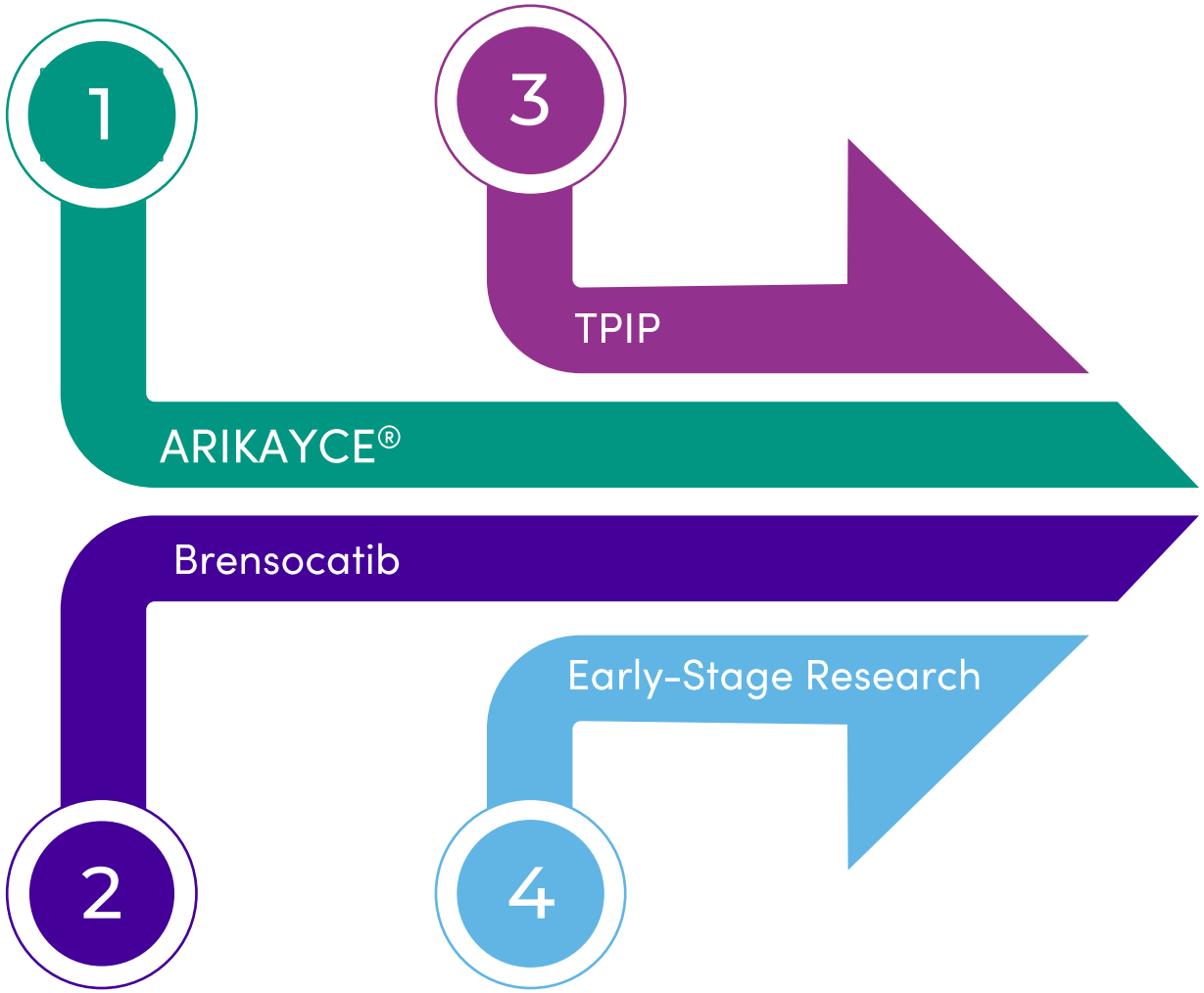
Chair and Chief Executive Officer

Insmed is Assembling the Key Pieces from Which All Successful Biotechnology Companies are Made

- **Commercial Engine:** Global scale with ability to support business **(Pillars 1 – 3)**
- **Research Engine:** Technologies, platforms, and talent that work synergistically to yield impactful therapies **(Pillar 4)**
- **Business Development:** Disciplined and committed to clear criteria that maximize the likelihood for success
- **Unifying Culture:** Mission, Vision, Values

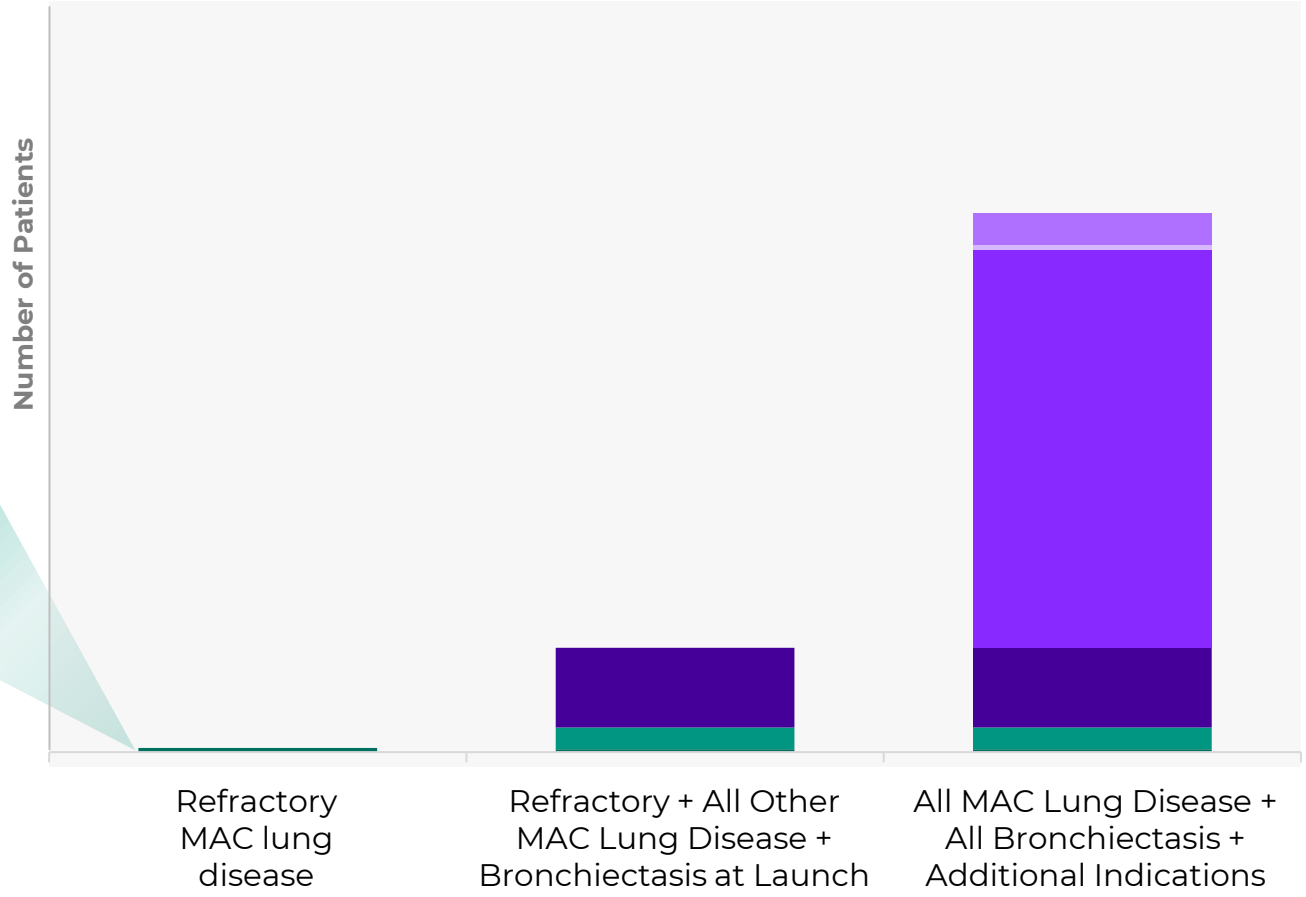


Accelerating the Transformation of Insmed



Potential Addressable Patient Populations: Pillars 1 & 2

2023 Revenue guidance of $285M to $300M for Refractory MAC lung disease



BRENSOCATIB
- CRSsNP
- CF
- Additional BE
- BE

ARIKAYCE
- All Other MAC
- Refractory MAC

Near-term readouts for **ARIKAYCE** and **brensocatib** potentially unlock the commercial value of these assets, steer the company towards profitability, and fund early-stage research

Few Have Accomplished Our Proven Success at Each Stage of Drug Development

Research	Clinical	Regulatory	Commercial
ARIKAYCE developed in our labs	Advanced ARIKAYCE through all stages	ARIKAYCE – approved in US, EU and JP	ARIKAYCE top 10 rare disease launches (US)
TPIP developed in our labs	Advanced brensocatib into pivotal Phase 3	Brensocatib – PRIME & BTD	Commercial infrastructure in US, EU and Japan
Brensocatib diligence by research team	Advanced TPIP into multiple Phase 2s		

Our Drug Development is Focused on Having the Highest Impact to Patients

	1 ARIKAYCE		2 Brensocatib*				3 TPIP*	
	Refractory MAC Lung Disease (Ref MAC)	**All MAC Lung Disease** (All MAC)	**Non-CF Bronchiectasis** (NCFBE)	**Chronic Rhinosinusitis without Nasal Polyps** (CRSsNP)	**Cystic Fibrosis** (CF)	**Hidradenitis Suppurativa** (HS)	**Pulmonary Hypertension associated with Interstitial Lung Disease** (PH-ILD)	**Pulmonary Arterial Hypertension** (PAH)
First-In-Disease	●	●	●	●				
First-In-Class			●	●	●	●		
Best-In-Class**	●	●	●	●	●	●	●	●

Core Respiratory/Inflammation Commercial Engine

insmed

* Potentially, if approved. Brensocatib and TPIP are investigational products that have not been approved for sale by the FDA or any international regulatory agency.
** Best-in-class indicates a profile that could be considered more attractive than other treatment options in the class. Head-to-head clinical trials are not anticipated.

Pillar 4 Aims to Bring 'First-in-Class' & 'Best-in-Class' Gene Therapies and Therapeutic Proteins to Patients*

4 Early-Stage Research

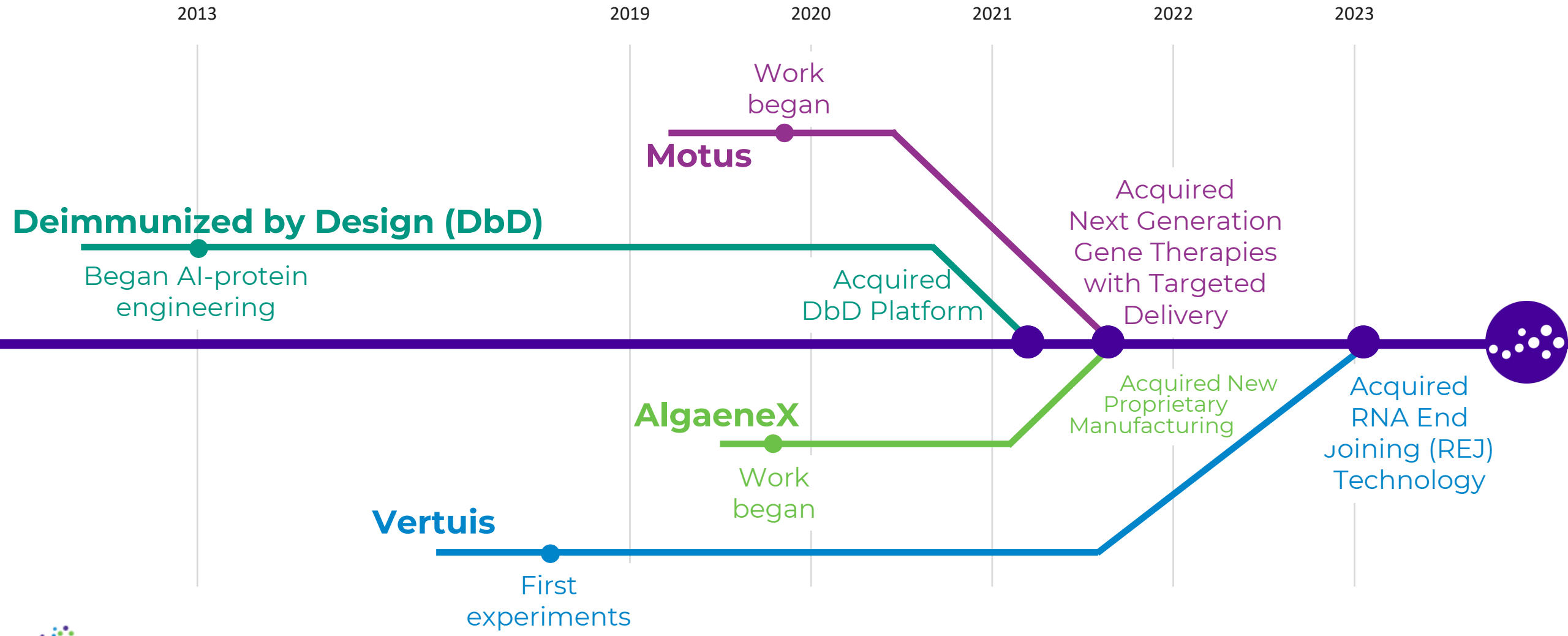
	Duchenne Muscular Dystrophy[1] (DMD)	**Stargardt Disease[1]** (STGD)	**Chronic Refractory Gout[2]** (CRG)	**Argininosuccinic Aciduria[1]** (ASA)
First-In-Disease		●		
First-In-Class		●		●
Best-In-Class**	●	●	●	●

Scientific Technology, Platforms, and Talent

* Potentially, if approved. All of our early-stage research candidates are in preclinical development and have not been approved for sale by the FDA or any international regulatory agency.
** Best-in-class indicates a profile that could be considered more attractive than other treatment options in the class. Head-to-head clinical trials are not anticipated.
[1] Next Generation Gene Therapies [2] Deimmunized Therapeutic Protein

Our Principles for Business Development Have Guided How We Built our Pillar 4

Recent Acquisitions Potentially Position Us to Bring Gene Therapies and Therapeutic Proteins to Market Faster and Cheaper

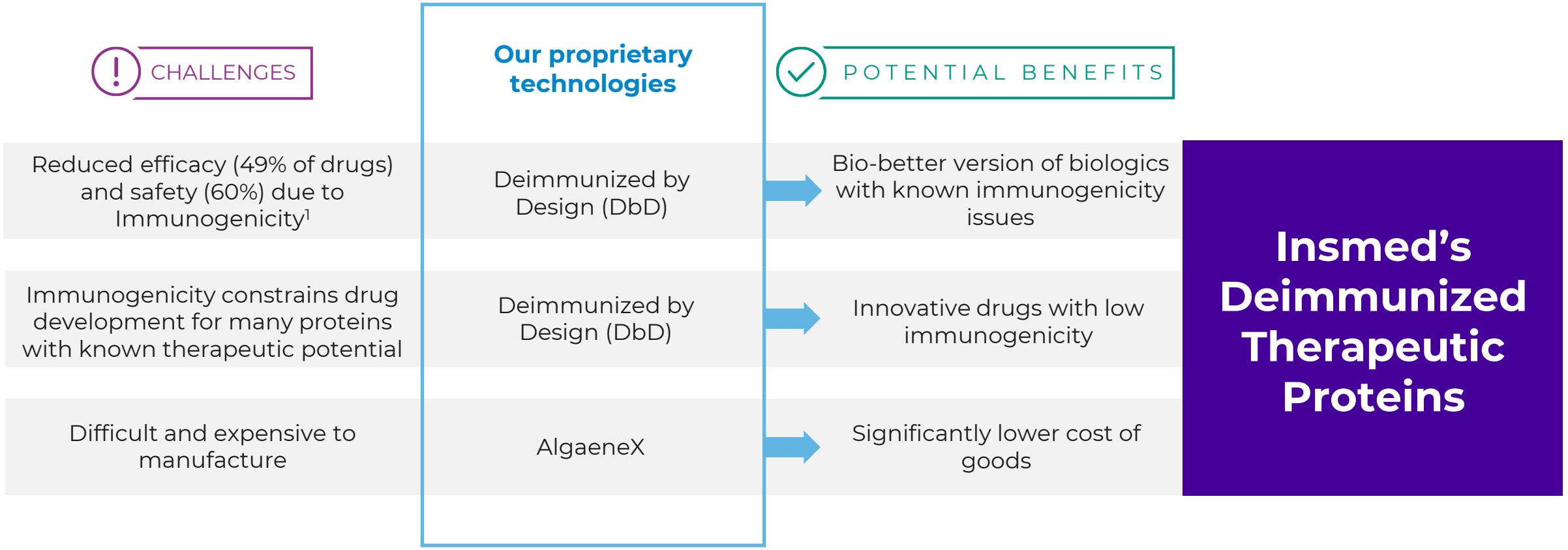


Our Next-Generation Gene Therapies Could Leapfrog Current Approaches

CHALLENGES	Our proprietary technologies	POTENTIAL BENEFITS
Inconsistency between batches and dose measurements	Internally developed assays & manufacturing processes	Every batch can be precisely controlled for dose strength
High doses – linked to adverse safety outcomes	Targeted Delivery (e.g. intrathecal)	10 to 50-fold dose reduction
Cannot target genes >4kbs	RNA End Joining (REJ)	Large size gene delivery
Immunogenicity against viral capsids	Deimmunized by Design (DbD)	Repeat dosing
Difficult and expensive to manufacture	AlgaeneX	AAV in 1/3rd the time, at fraction of the cost

Insmed's Next-Generation Gene Therapies

Deimmunized Therapeutic Proteins Could Overcome Immunogenicity and Cost Challenges Facing Biologics



[1] Wang YM, Wang J, Hon YY, Zhou L, Fang L, & Ahn HY. (2016). Evaluating and reporting the immunogenicity impacts for biological products-A clinical pharmacology perspective. The AAPS Journal, 18(2), 395–403

Brian Kaspar, PhD

Chief Scientific Officer

Next-Generation Gene Therapy

World-leading expertise and differentiated approach in GTx

Gene Therapy Can Have a Truly Transformational Impact on Patients, as Past Success Has Shown

- **Spinal muscular atrophy (SMA):** genetic neuromuscular disease affecting children
- **Children born with SMA** rarely reach the age of 2
- **Evelyn's story:** Now 7 ½ years post-treatment with gene therapy

Evelyn, shown here at nearly 3 years of age.

70+ Years of Biotech Experience

THE INSMED SAN DIEGO FOUNDING TEAM

Samit Varma

SVP, Gene Therapy

- Former CEO and Co Founder of Celenex (acquired by Amicus)
- Investor & Board member of Advanced Cell Technology (ACTC) (acquired by Astellas)
- Investor & Board member of Cynvenio
- Founder and Managing Director - Troy Capital & Quid Capital, VC/PE firms with $1.2B AUM

Brian Kaspar

Chief Scientific Officer

- Co-Founder & former Chief Scientist at AveXis (acquired by Novartis), Celenex (acquired by Amicus), and Milo Biotechnology
- Formerly Endowed Chair in Pediatrics and Professor at The Center for Gene Therapy at NCH & OSU's College of Medicine
- Ph.D. from UCSD – over 110 scientific articles published

James L'Italien

SVP, Regulatory Affairs

- Former SVP and Chief Regulatory Officer at AveXis (acquired by Novartis).
- Former SVP of Regulatory at Intermune.
- Multiple global successes on submitted NDA including Zolgensma for Spinal Muscular Atrophy
- PhD in Biology from Boston University.

Allan Kaspar

VP, Research & Gene Therapy

- 1st scientist hired at AveXis (acquired by Novartis) – served as SVP of Research and Development
- Principal Scientist at Pfizer
- Significant Experience in Manufacturing Science & Technology
- Ph.D. in Immunology from Stanford with post-doctoral training at the Burnham Institute

Gretchen Thomsen

Executive Director, Gene Therapy

- Former Principal Scientist, AveXis, Inc. (acquired by Novartis) focused on bringing AAV-based gene therapies to clinical setting
- Former Assistant Professor, Regenerative Medicine Institute Cedars-Sinai Medical Center
- PhD in Neuroscience from UCLA, Postdoctoral training at Cedars-Sinai Medical Center

Rare and debilitating genetic disorders with no effective treatment options

Gap in expertise and experience bringing GTx programs to market

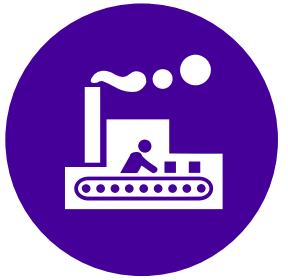
Challenges in manufacturing at scale with robust quality and analytical capabilities

Insmed Is Uniquely Positioned To Address Challenges In GTx Landscape With Game Changing, Novel, Proprietary Technologies

High doses, inherent systemic toxicities, low efficacy, and off-target transduction

Inability to treat diseases requiring delivery of large genes

Immunogenicity and inability to target diseases requiring redosing



High production costs with low yields

Insmed's Targeted Up-Front Investment And Focus On CMC, Quality, And Analytics Designed to Ensure A Locked Commercial Process To Supply The Market with Control And Understanding Of The Product

At-scale 1000L manufacturing process defined prior to IND submission to ensure locked commercial process to supply market

In House GMP QC Lab with 25 state-of-the-art assays to ensure quality and robust analytical understanding of manufactured Gene Therapy Products

Insmed is Uniquely Positioned to Address Challenges in GTx Landscape with Game-Changing, Novel, Proprietary Technologies

Next Generation Gene Therapies With Targeted Delivery

Enhanced safety profile with similar/better efficacy

10 to 50-fold reduction in dose (vs. Systemic delivery)

RNA End Joining Technology (REJ)

Unlocks new GTx market opportunities with no competition

Large size gene delivery through traditional AAVs

Deimmunized by Design (DbD) platform

Redosable viral vectors

Deimmunized biobetters & derisked innovator drugs

Repeat dosing of gene therapies and overcoming immunogenicity

AlgaeneX

New, Proprietary Manufacturing

Lowest cost of goods for Insmed's gene therapy portfolio

Opportunity to license technology

Significant reduction in AAV manufacturing time and cost

Duchenne Muscular Dystrophy

John W. Day, M.D., PhD
Professor of Neurology, Pediatrics, and Pathology
Stanford University

Duchenne Muscular Dystrophy (DMD)

Loss of Dystrophin – Kunkel, 1986

- Largest Gene in Human Genome - >2.2MBp
- One of the largest human proteins – 427KD

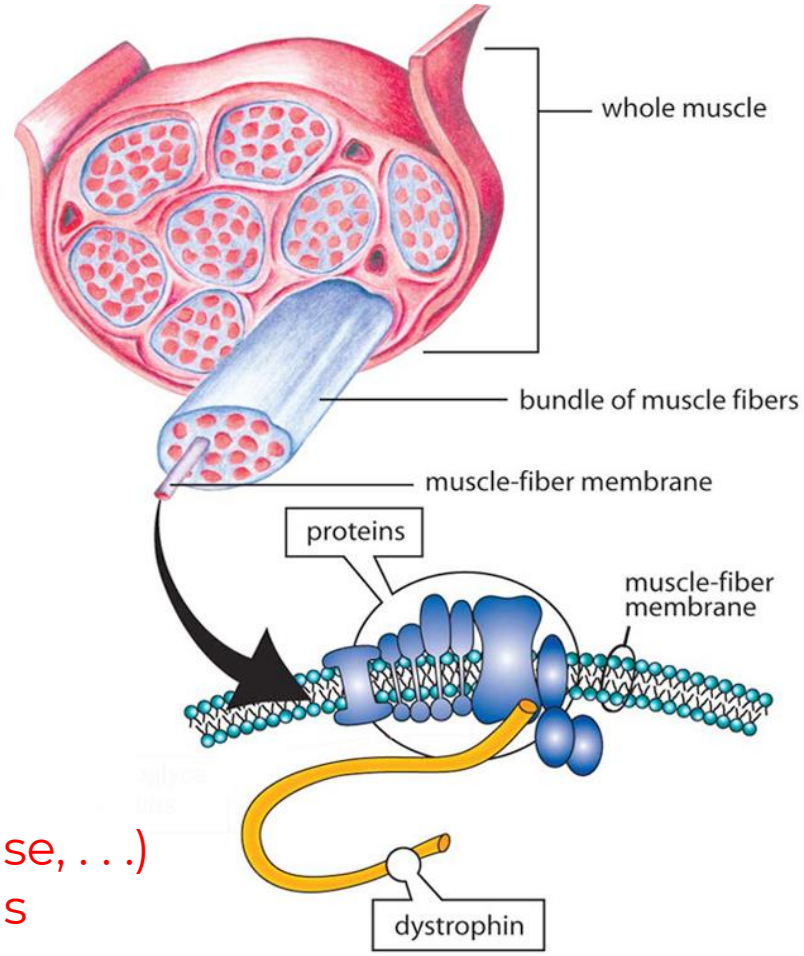
Stereotypical Clinical Course

- Genetically diagnosable at birth
- Weakness clinically evident by 3-4yo
- Non ambulatory by 11-13yo
- Ventilatory Insufficiency by 15-20yo
- Severe cardiomyopathy by 15-30yo

Relatively Common

- 1 in 3500 male births worldwide
- >30% of patients have de novo mutation

But – Genetic Heterogeneity (deletions, duplication, missense, . . .)
Led to clinical heterogeneity, and difficult clinical trials



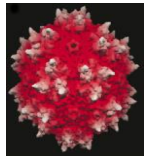
Improving Treatment Landscape for DMD

Chronic Steroids Slow Disease Progression

- Boys remain ambulatory for 2-3y longer
- Significant weight gain and other side effects

Gene Modification Treatments Have Shown Modest Effects

- Antisense modification of genetic splicing useful for 20-30% of patients
- Nonsense mutation suppression useful for 10% of patients
- Effect size has been modest



IV AAV Gene Replacement Treatment for DMD

- High dose infusion results in good expression of micro-dystrophin product
- Signs of improved functional course
- Dose-related side-effects (if combining all DMD AAV GRT trials)
  - Severe early innate immune response – 2 deaths in week 1 out of ~200 patients total
  - Severe late adaptive immune response – liver failure, myocarditis, other severe reactions
  - Requires 3 months of careful monitoring before risk clearly abates

IV AAV-GRT Challenges and INSMED Opportunity

Prevalent Cases if Approved for All Ambulatory ≥ 3yo

- 4000-5000 boys in USA eligible on day 1
- 500 more boys eligible annually
- If 50 centers treating 1 patient weekly = 3 years to treat prevalent and new cases
- More likely 2 patients /mo. @ 50 sites = 6 years to treat prevalent and new cases

Risks of IV AAV GRT

- If 1% death rate persists – 12-25 deaths / y
- Some factors could increase risk
  - Treating older boys with pre-existing heart and breathing weakness
  - Treating heavier boys with larger viral load (vg/kg)
  - Involvement of additional less experienced centers

Ways to mitigate risk and increase effect of AAV-GRT – INSMED Opportunity

- Significant reduction of dose
- Reduced AAV immunogenicity
- Benefit of larger dystrophin construct

Brian Kaspar, PhD

Chief Scientific Officer

Insmed Has Developed A Targeted Delivery System To Circumvent Challenges Within The DMD Landscape

High doses

Inherent systemic toxicities

Low efficacy

Off-target transduction

Insmed Value Proposition & Solution

Next Generation Gene Therapies With Targeted Delivery

Enhanced safety profile with similar/better efficacy

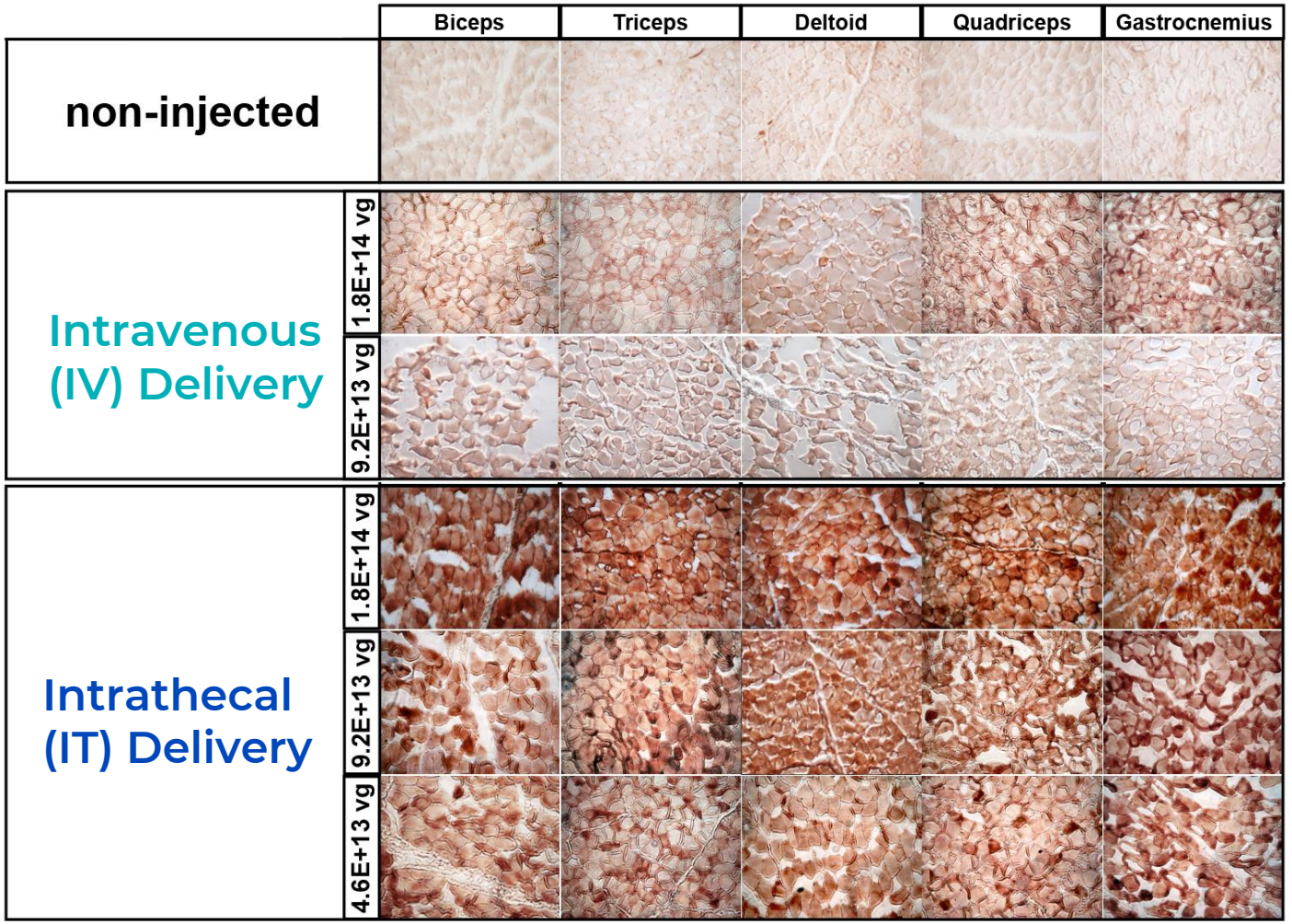
10 to 50-fold reduction in dose (vs. Systemic delivery)

Insmed's IT-Delivery of AAV9-GFP Shows Greatly Improved Muscle Targeting When Compared To Systemic (IV) Dosing

ONE-TIME INTRATHECAL DELIVERY PLATFORM: AAV9-GFP IN NHP

NovaRed immunostaining for GFP expression *(Vector® HRP substrate)*

**Doses are expressed as total vector genomes administered per animal*



No dose

Minimal expression & limited targeting

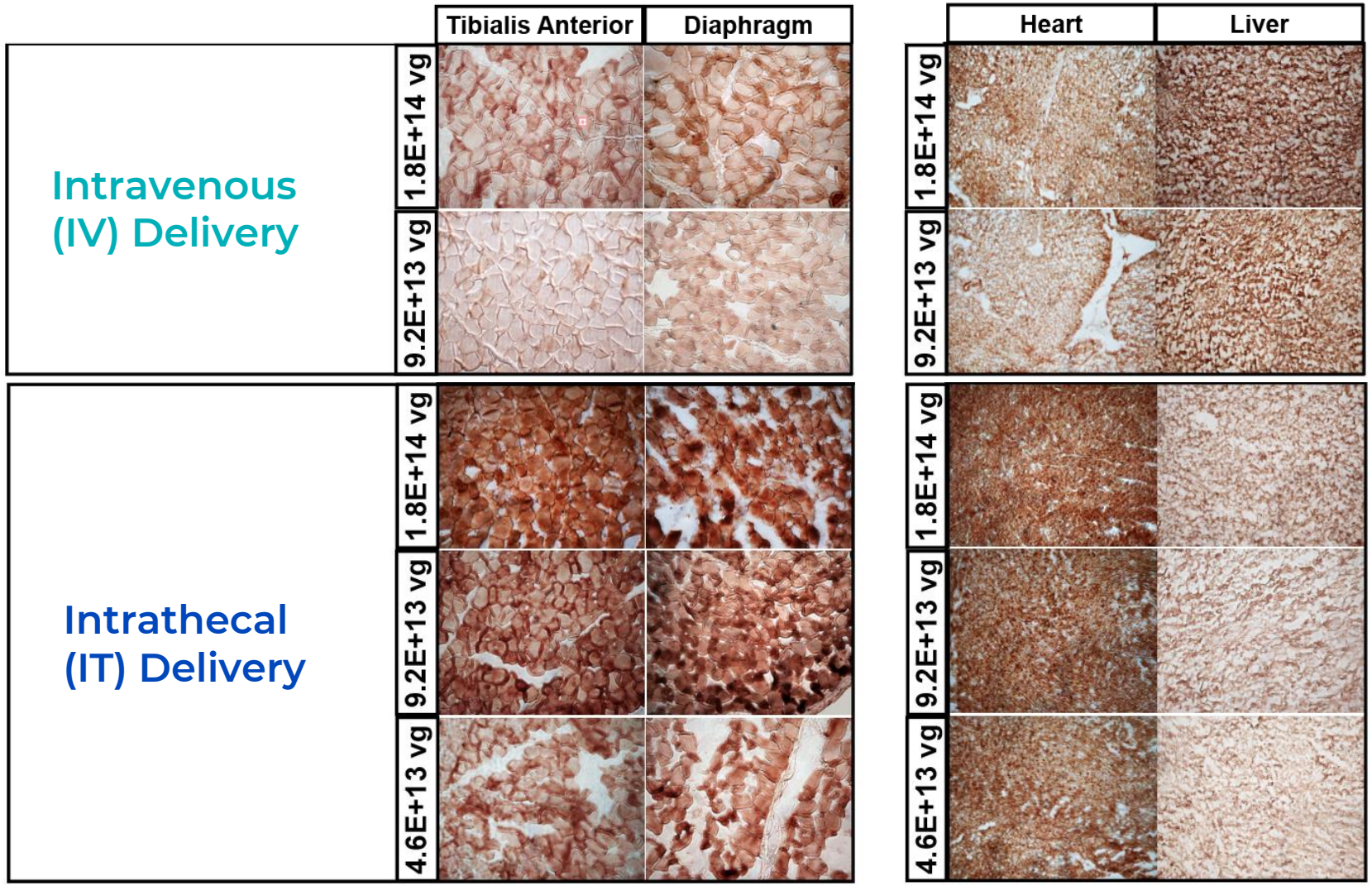
Robust expression & tactical targeting

Insmed's IT Delivery Shows Enhanced Targeting Of Skeletal And Cardiac Muscle With Lower Liver Expression Relative To Systemic (IV) Delivery

ONE-TIME INTRATHECAL DELIVERY PLATFORM: AAV9-GFP IN NHP

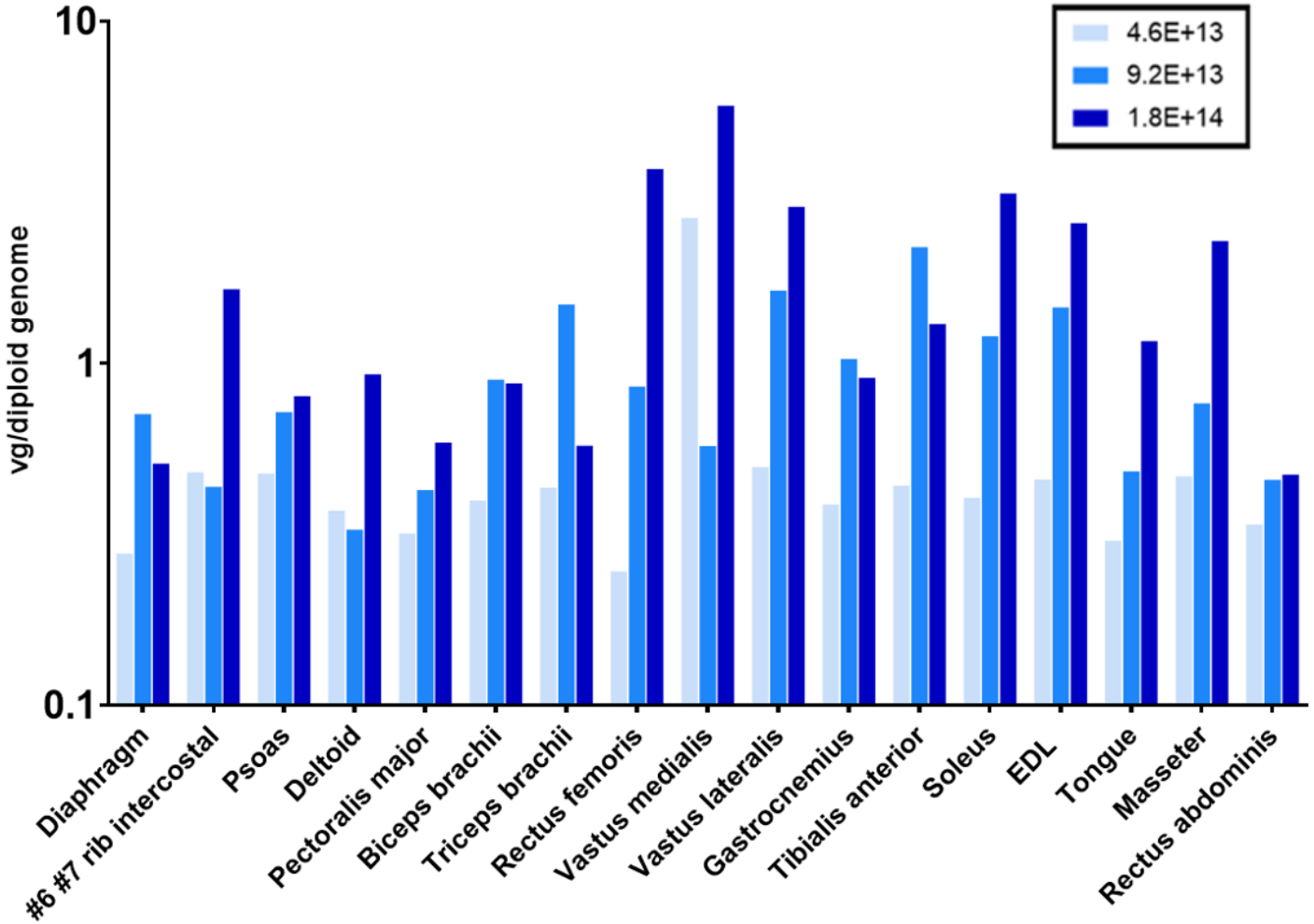
NovaRed immunostaining for GFP expression *(Vector® HRP substrate)*

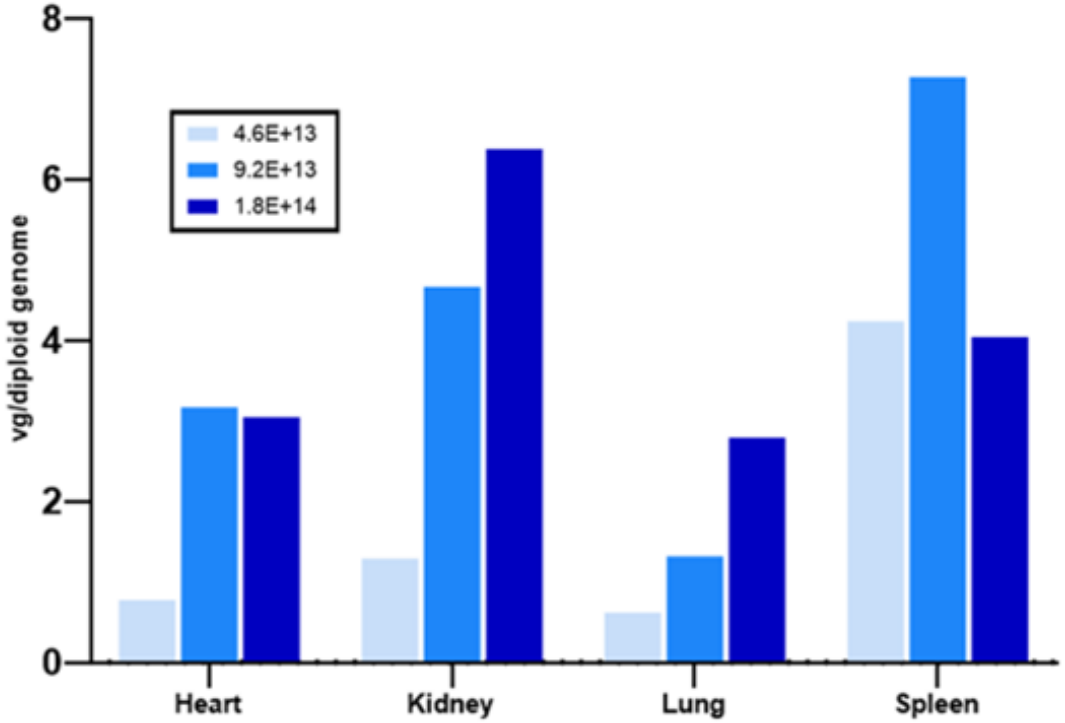
**Doses are expressed as total vector genomes administered per animal*



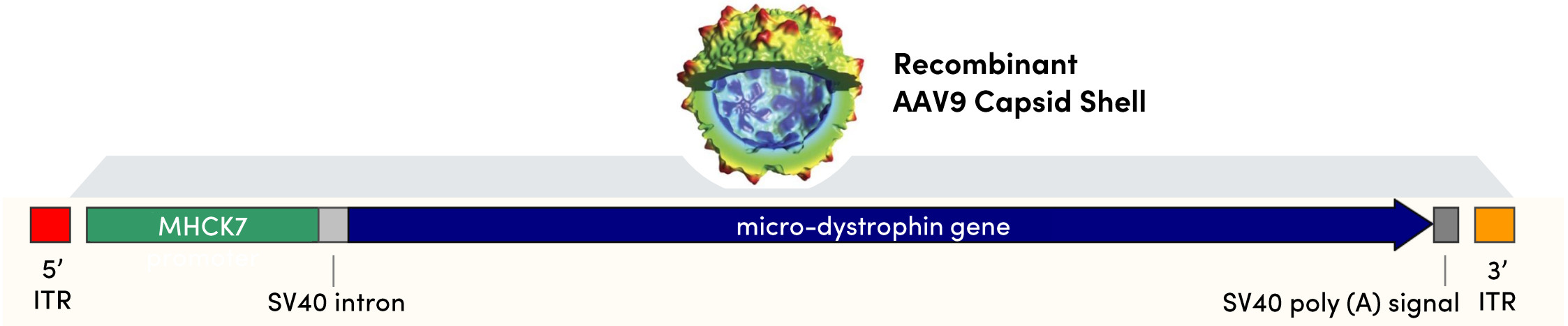
Insmed's IT-Delivery Shows Efficient DNA Biodistribution in Skeletal And Cardiac Muscles

ONE-TIME INTRATHECAL DELIVERY PLATFORM: NHP AAV9-GFP ddPCR





Innovative Gene Construct (INS1201) Specifically Designed for DMD



Treatment involves a **one-time administration** of AAV9-Micro-Dystrophin in human DMD patients to replace missing dystrophin protein and promote muscle function

The constructs contain **unique** promoter, enhancer, intron, and **micro-dystrophin** elements packaged in the AAV9 Capsid

The *mdx* mouse, lacking functional dystrophin, is the **most commonly used** model to study DMD

Preclinical Proof of Concept Study

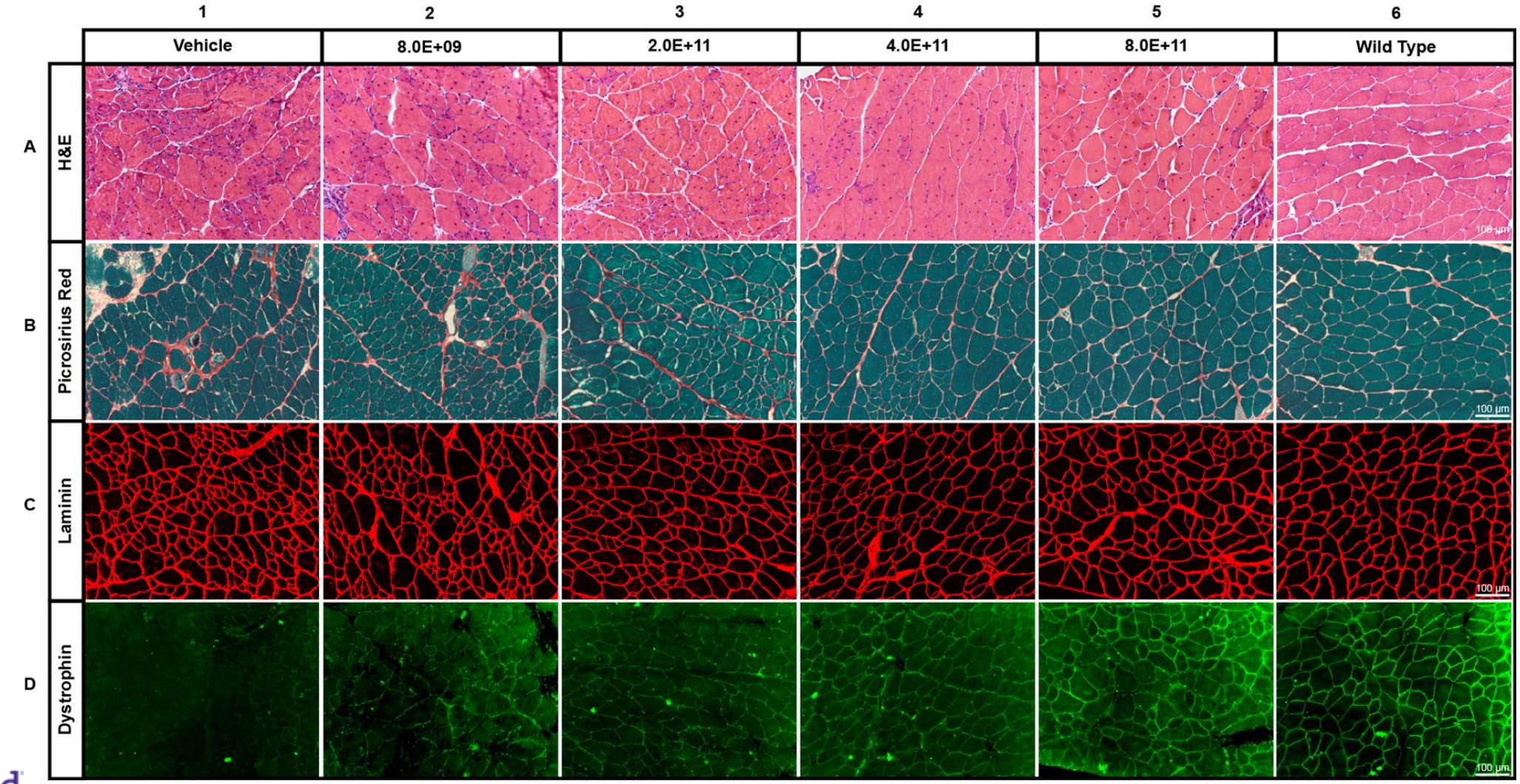
The goal of this study is to evaluate a dose response of INS1201 on protein expression and efficacy in the mdx mouse model using a GMP produced engineering lot of INS1201

Intracerebroventricular (ICV) Injections of INS1201

ICV injection of INS1201 at P28 (postnatal day 28) in *mdx* mice

Tissue analyzed for dystrophin expression and correction of histopathological DMD features at various time points

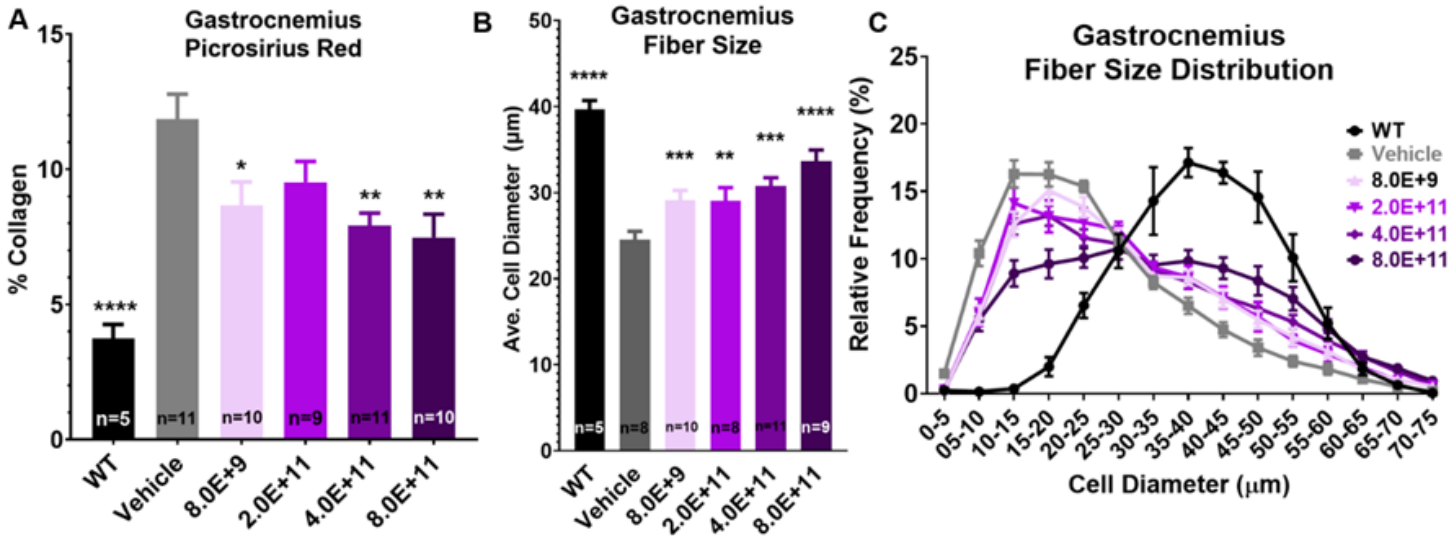
INS1201-Treated *mdx* Mice Demonstrate Substantial Improvement of Dystrophic Pathology in a Dose-Dependent Manner (Muscle: Gastrocnemius)



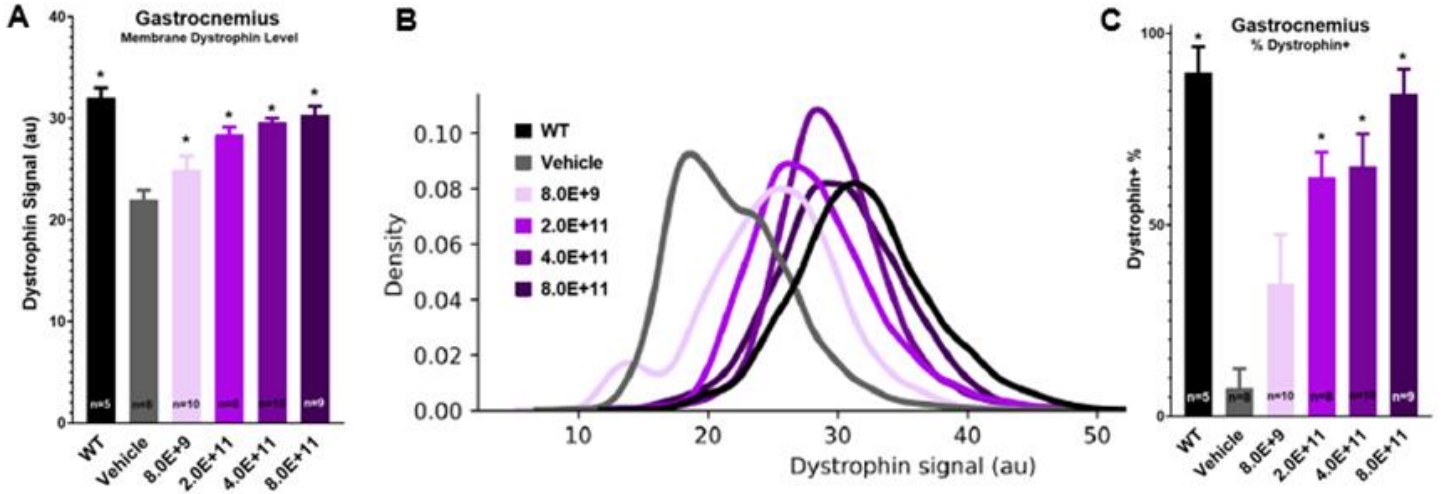
INS1201-Treated *mdx* Mice Demonstrate Substantial Improvement of Dystrophic Pathology in a Dose-Dependent Manner

(Muscle: Gastrocnemius)

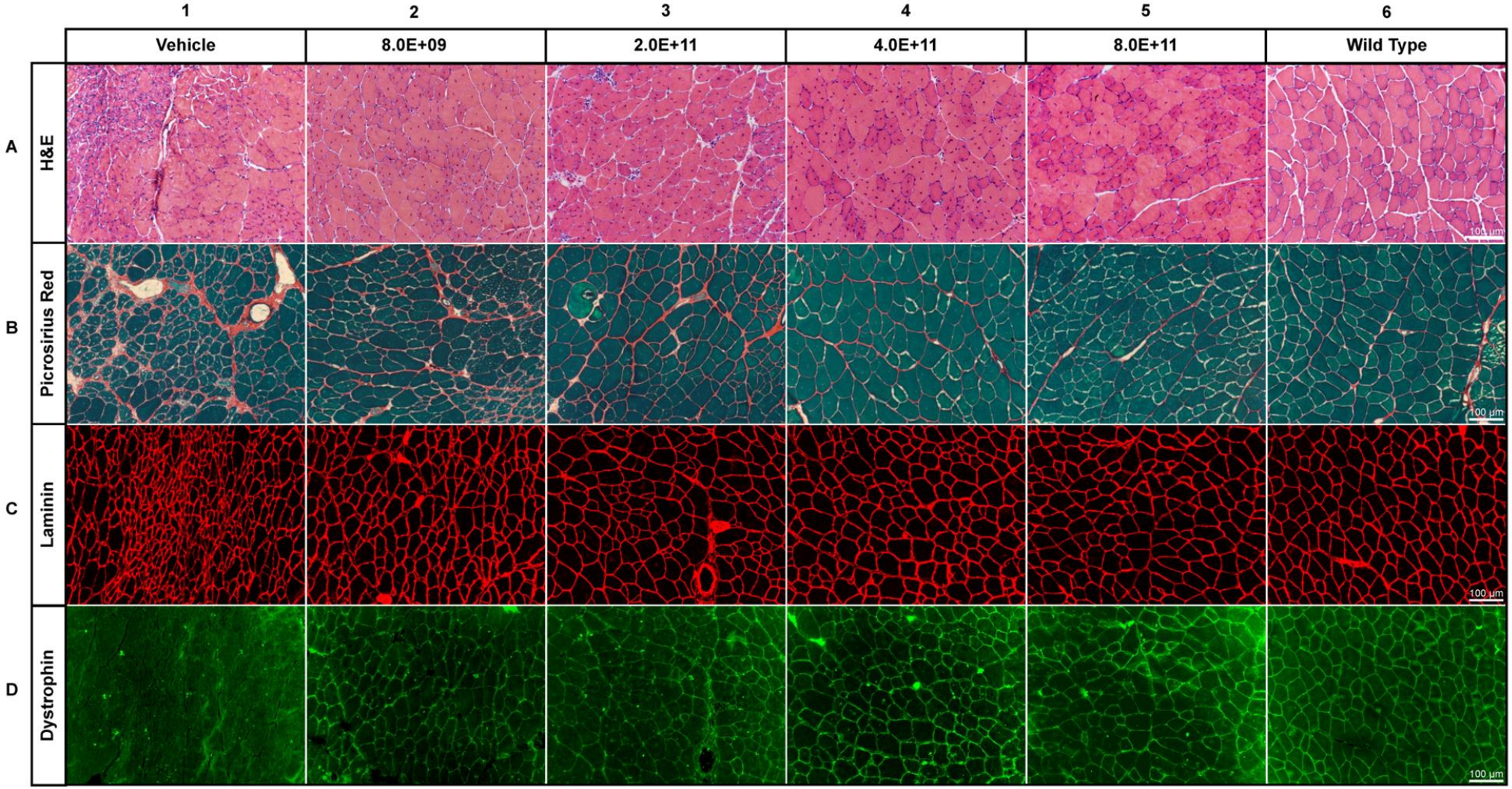
Reduced Fibrosis and Increased Fiber Size



Dystrophin Expression in up to 84% of cells



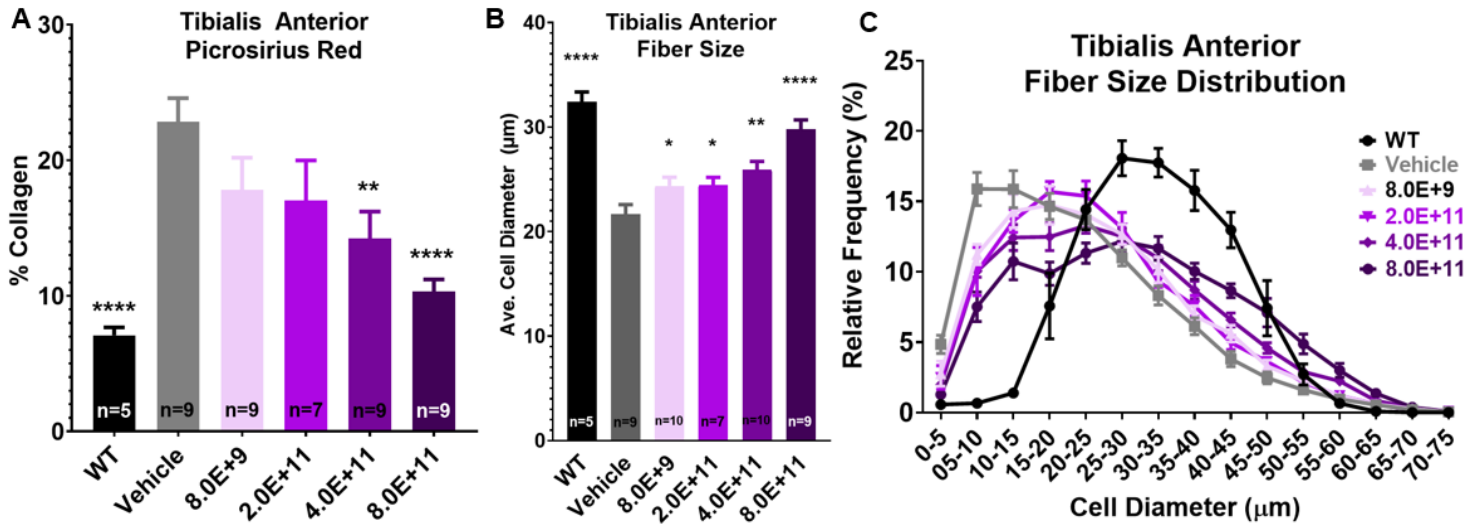
INS1201 Treated *mdx* Mice DemonstrateSubstantial Improvement of Dystrophic Pathology in a Dose-Dependent Manner (Muscle: Tibialis Anterior)



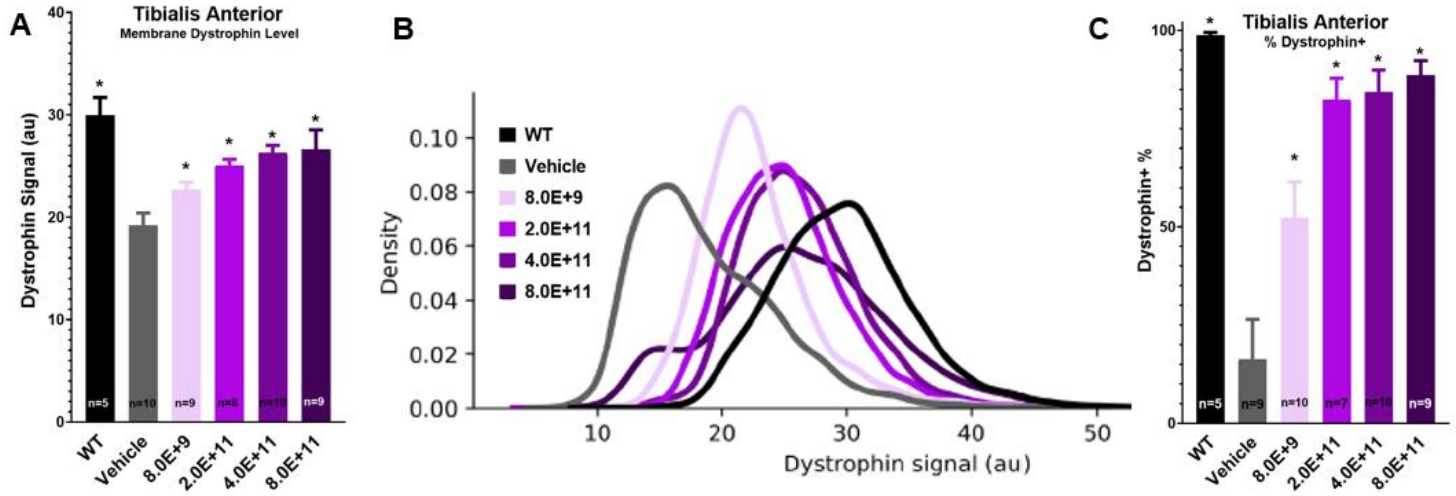
INS1201-Treated *mdx* Mice Demonstrate Substantial Improvement of Dystrophic Pathology in a Dose-Dependent Manner

(Muscle: Tibialis Anterior)

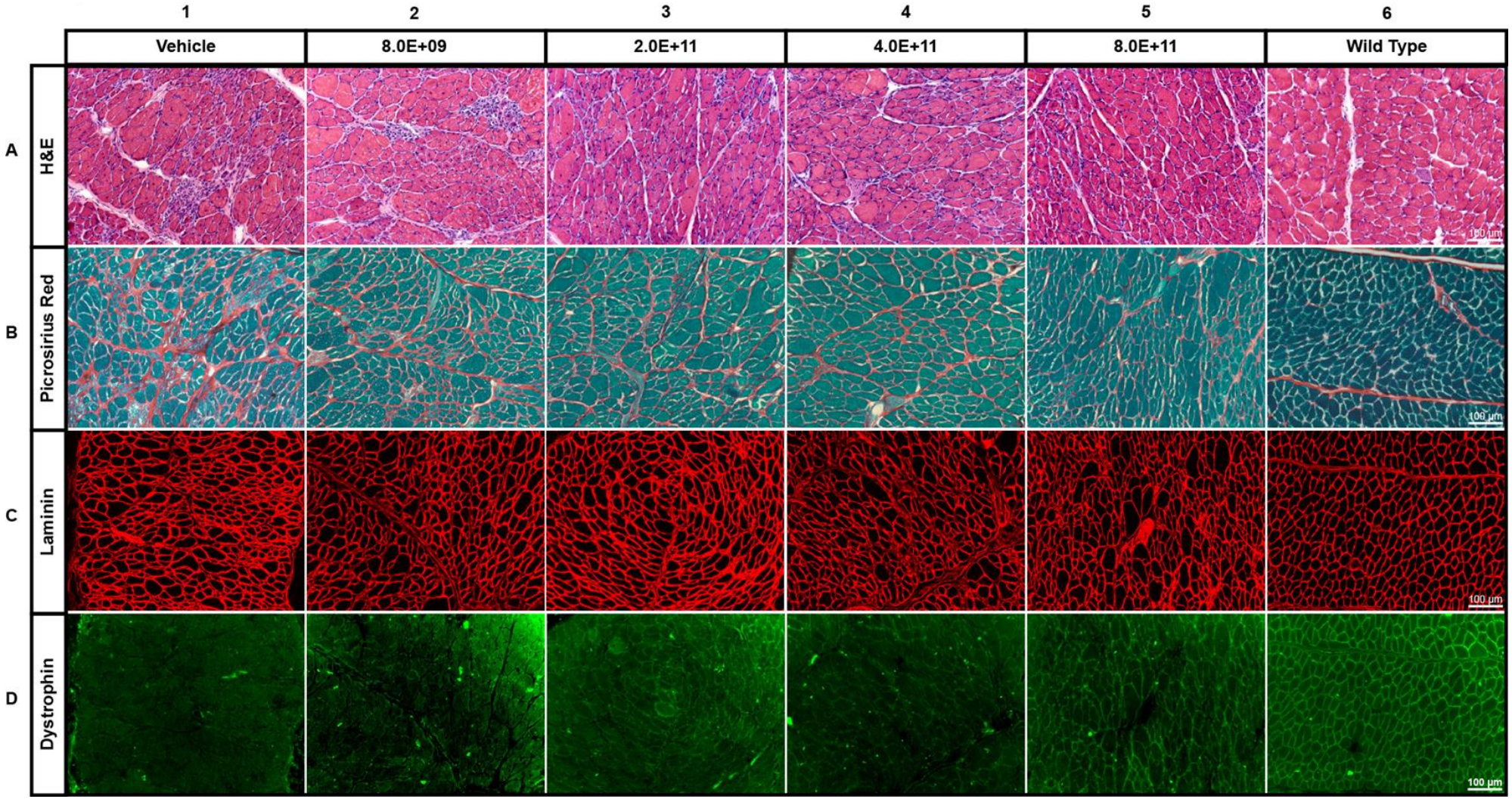
Reduced Fibrosis and Increased Fiber Size



Dystrophin Expression in up to 89% of cells



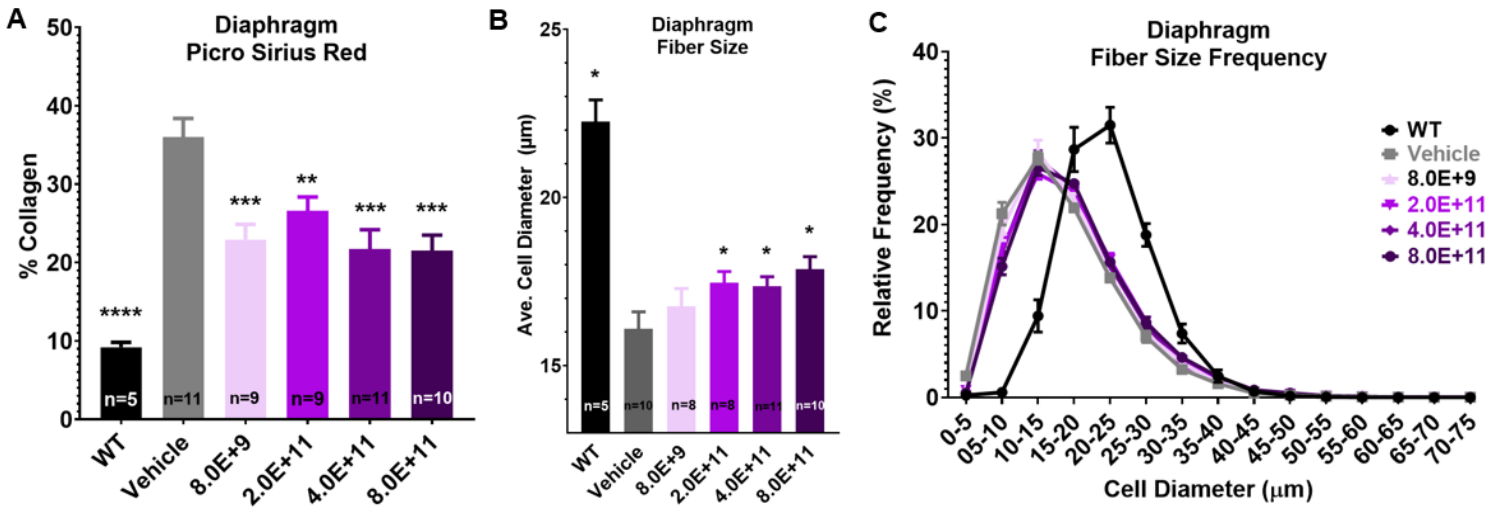
INS1201 Treated *mdx* Mice Demonstrate Substantial Improvement of Dystrophic Pathology in a Dose-Dependent Manner (Muscle: Diaphragm)



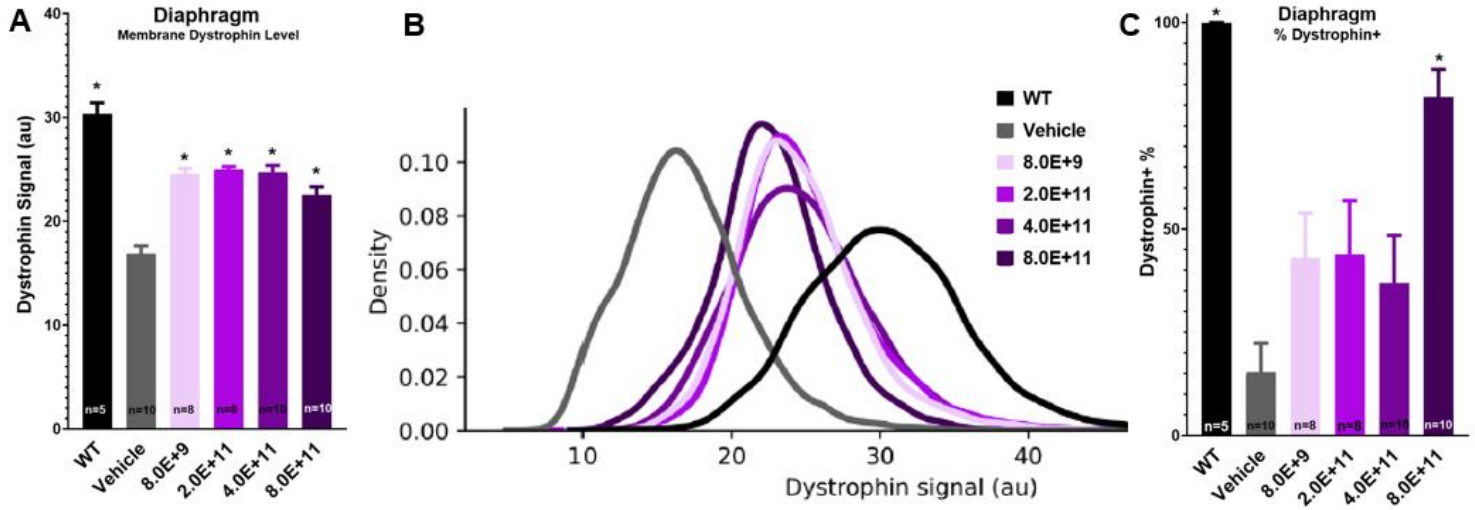
INS1201-Treated *mdx* Mice Demonstrate Substantial Improvement of Dystrophic Pathology in a Dose-Dependent Manner

(Muscle: Diaphragm)

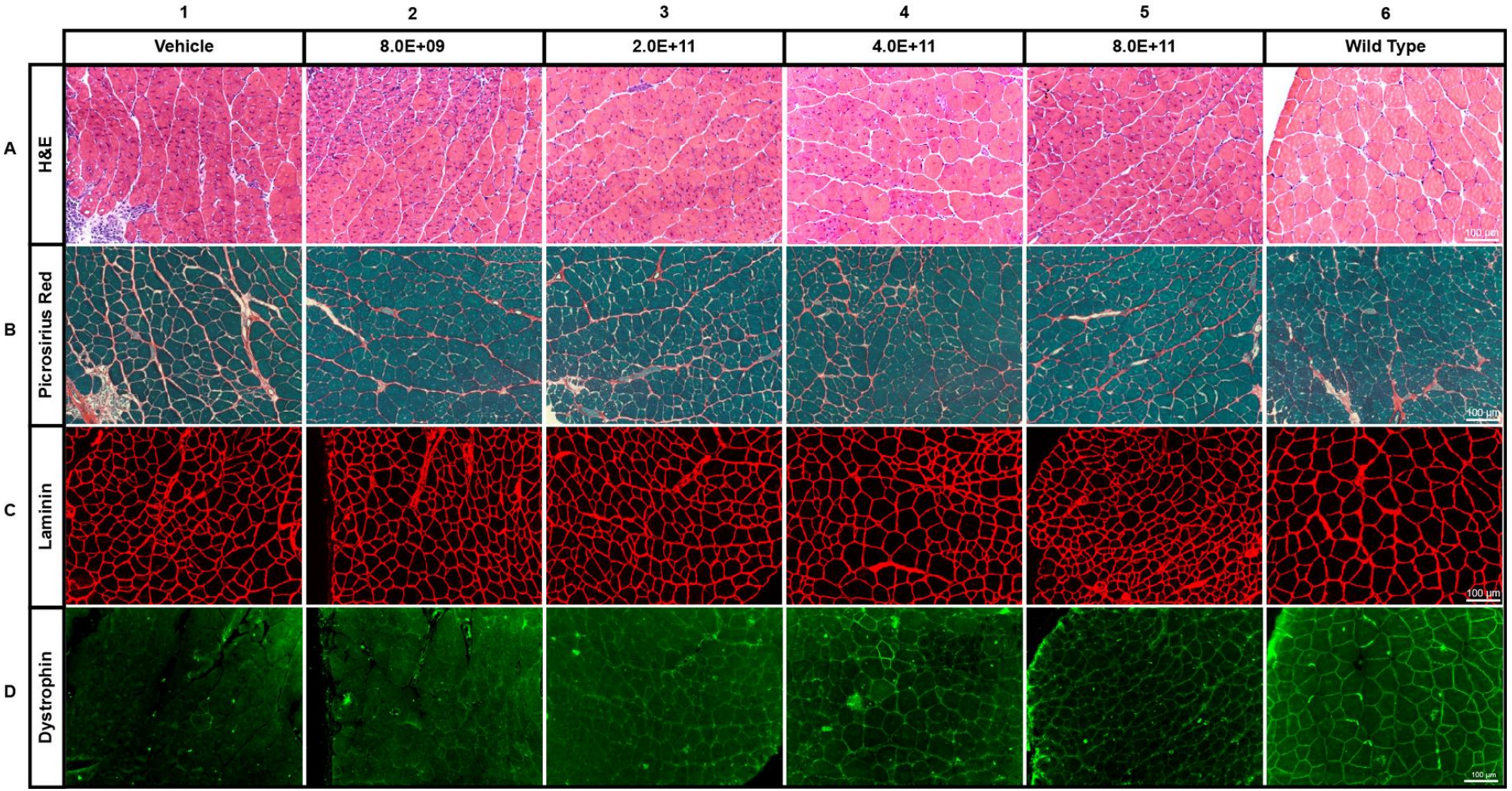
Reduced Fibrosis and Increased Fiber Size



Dystrophin Expression in up to 81% of cells



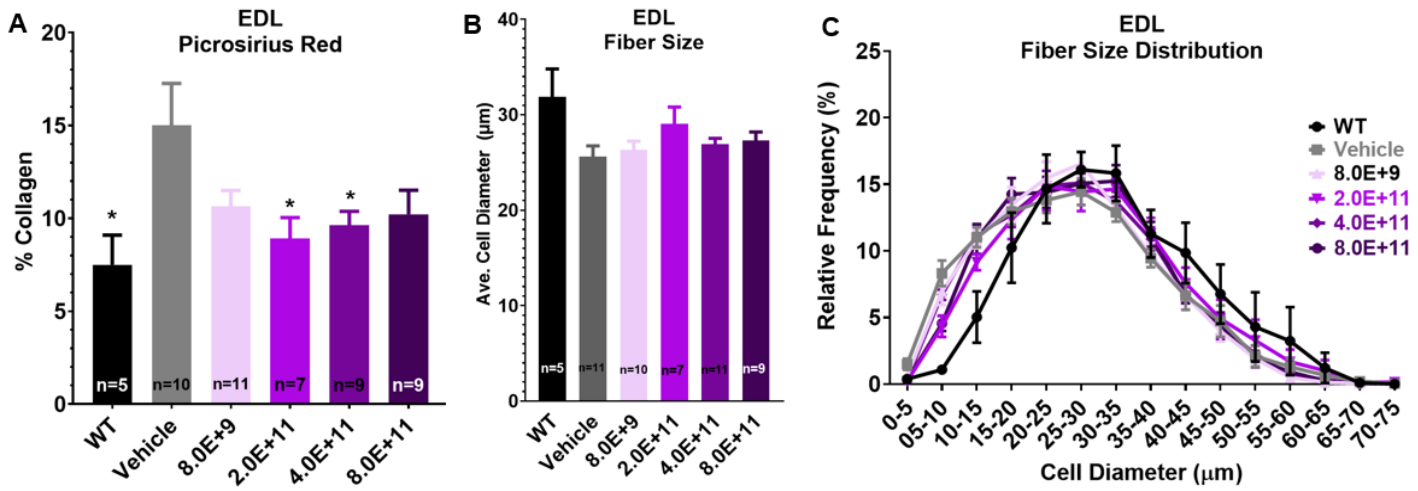
INS1201 Treated *mdx* Mice Demonstrate Substantial Improvement of Dystrophic Pathology in a Dose-Dependent Manner (Muscle: EDL)



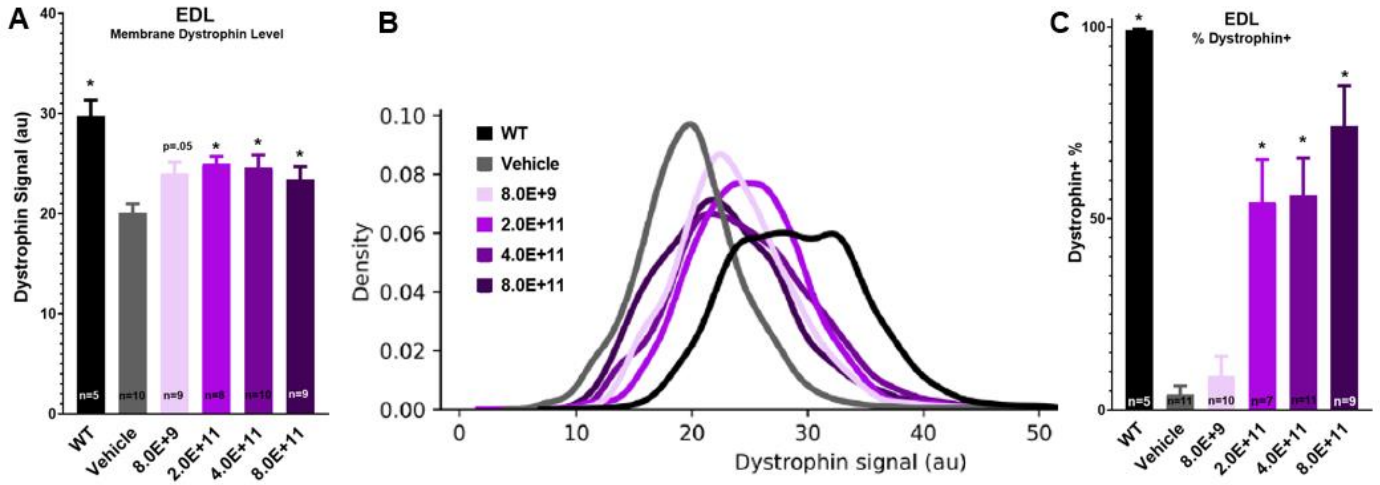
INS1201-Treated *mdx* Mice Demonstrate Substantial Improvement of Dystrophic Pathology in a Dose-Dependent Manner

(Muscle: EDL)

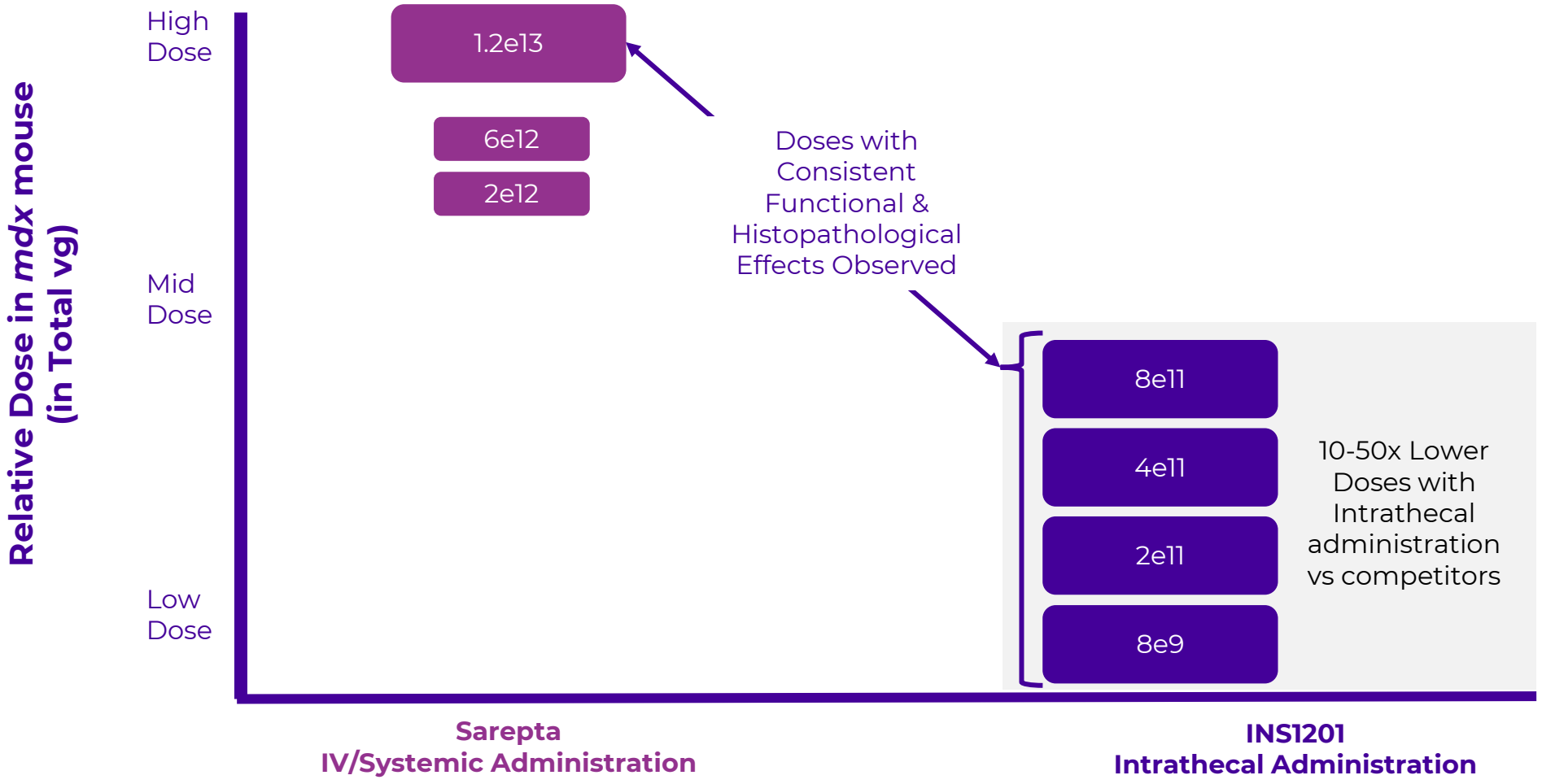
Reduced Fibrosis and Increased Fiber Size



Dystrophin Expression in up to 74% of cells



Consistent Functional & Histopathological Effects Observed Following Intrathecal Administration Of INS1201 With 10 To 50-fold Reduction In Dose Compared To Systemic Delivery In *mdx* Mouse



No claim of comparative safety or effectiveness relative to INS1201 is made or implied. INS1201 has not yet been studied in clinical trials.

Brief Study Design

The overall goal of this GLP study is to evaluate toxicology and biodistribution of GMP produced engineering lot of INS1201 in wild type mice

Timing Cohort	n
12-week	72
6-week	60
3-week	60
Total Animals:	**192**

Intracerebroventricular (ICV) Injections of INS1201

ICV injection of INS1201 at P28 (postnatal day 28) in wild type (C57BL/6J) mice

Protocol Group	Dosing Group	Dose (total vg)
Group 1	vehicle	0.0E+00
Group 2	Dose 1	8.0E+11
Group 3	Dose 2	4.0E+11
Group 4	Dose 3	2.0E+11
Group 5	Naïve/untreated	0.0E+00

N = 15 total per each injected group, 12 naïve untreated included in 12-week cohort

INS1201 Mouse GLP Toxicology Study Shows Clean Safety Profile With No Off-Target Transduction

Normal Body Weight Gain

Normal Blood Chemistry/Hematology

Normal Clinical Observations

No Concerning Histopathology Associated With INS1201 Delivery

Observed mono-nuclear cell infiltrates around blood vessels in the brain, associated with virus delivery, not dose-dependent and appears to resolve over time

No Unexpected Deaths In Any Treatment Groups

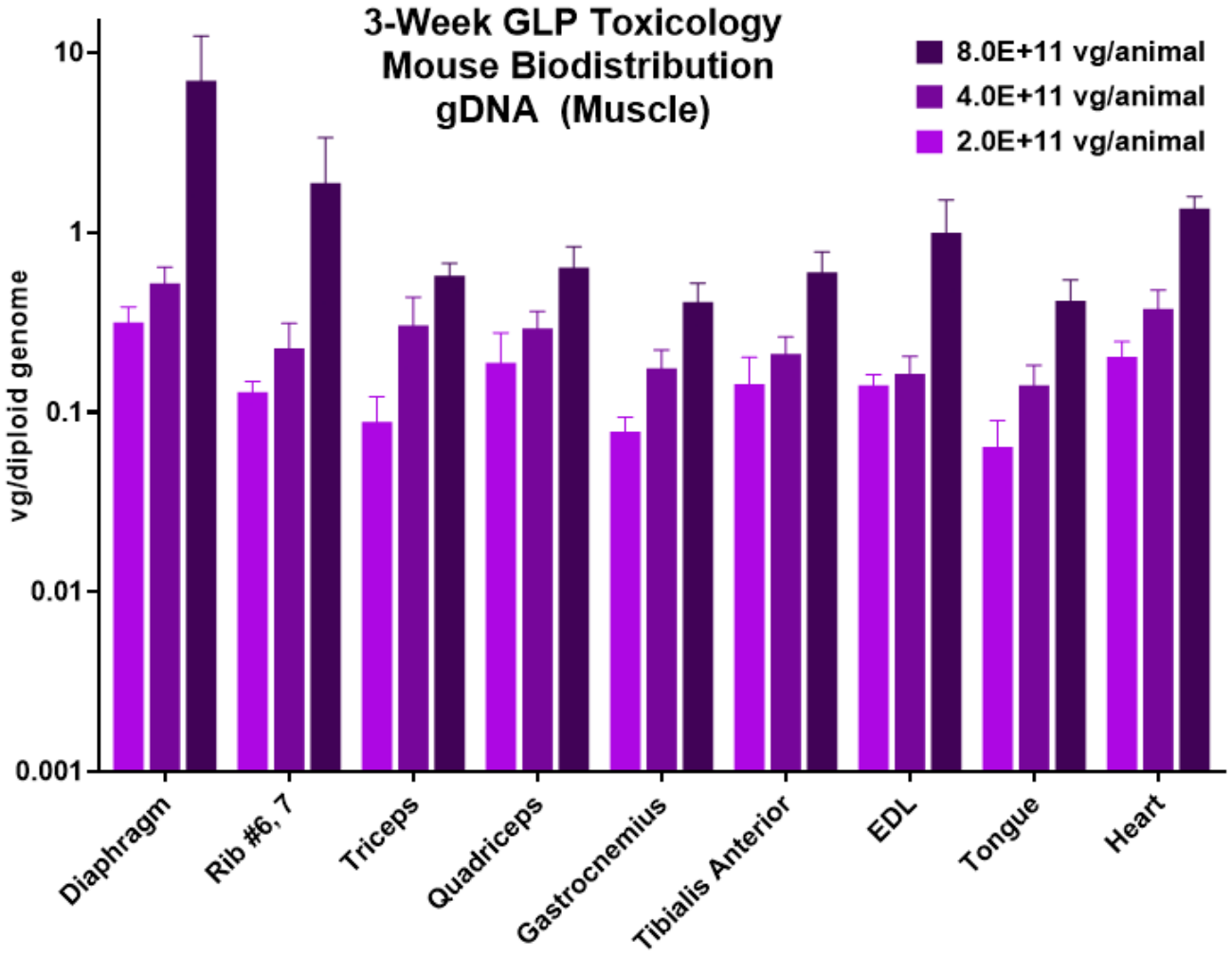
1 unexpected death *in the vehicle control group*

The NOAEL* was 8.0+E11 vg, which was the highest dose tested in the study

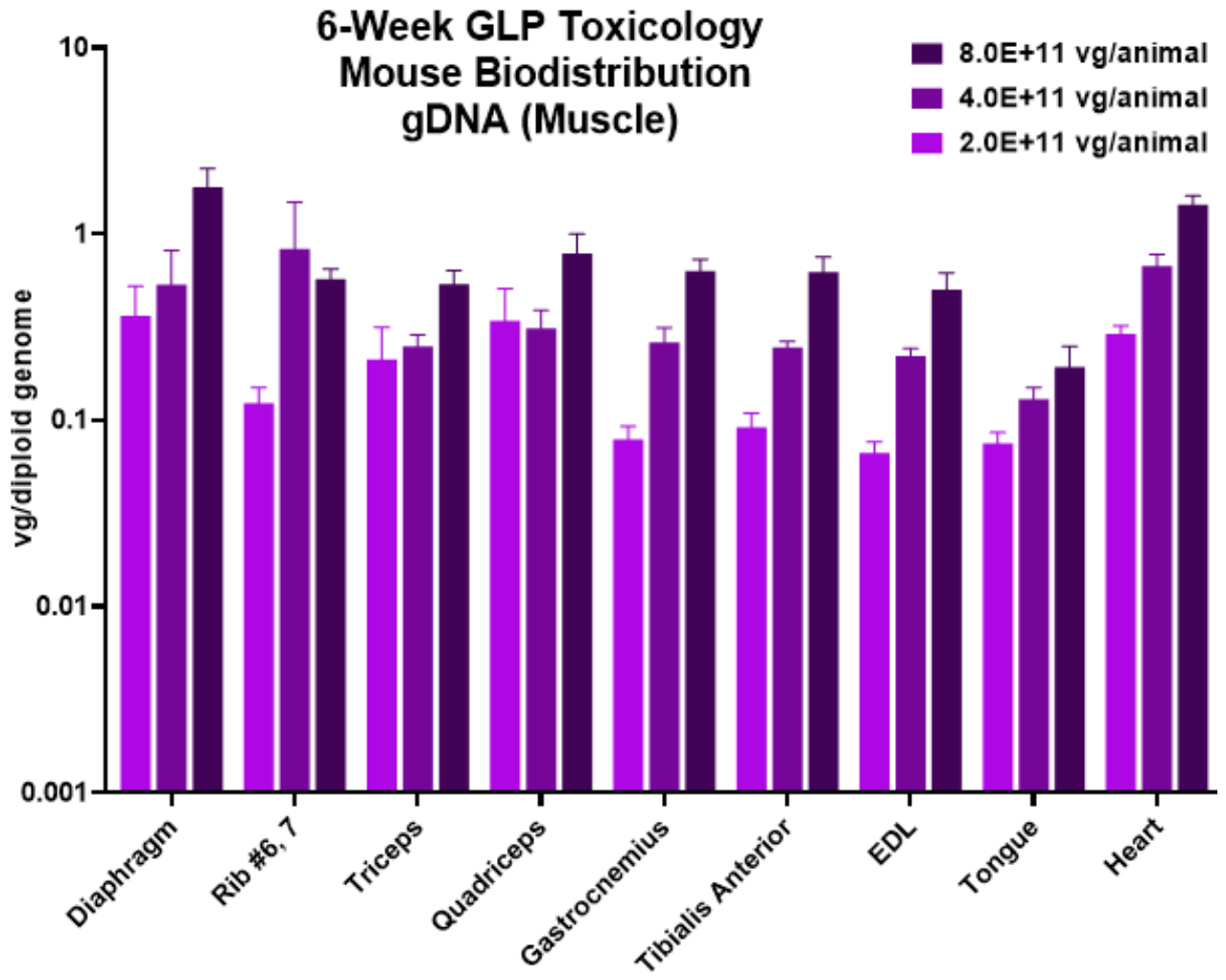
insmed

**No Observed Adverse Effect Level*

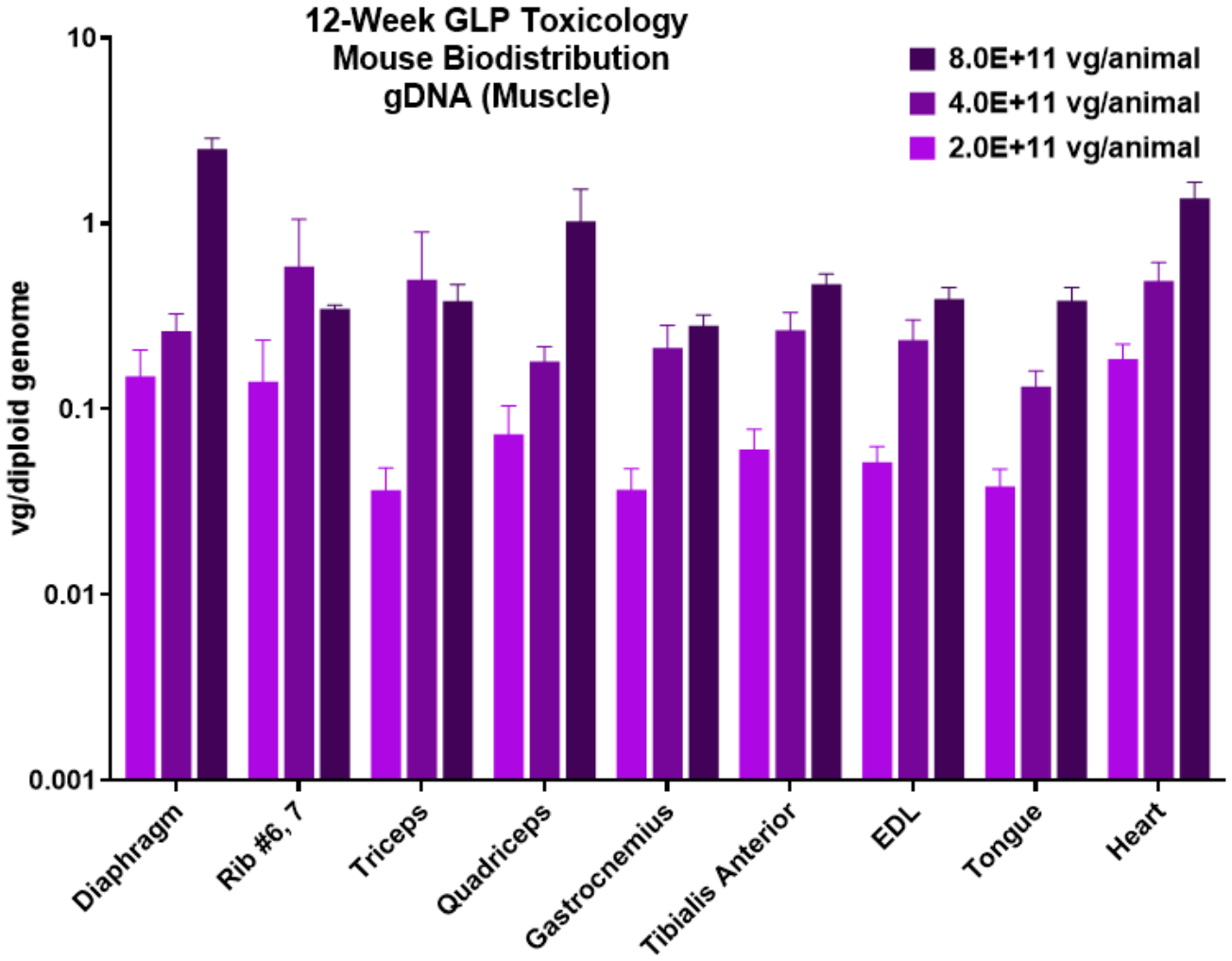
Muscle Biodistribution of INS1201 Demonstrates a Dose Response and Robust Muscle Targeting in 3-week GLP Toxicology Study in Wild Type Mice



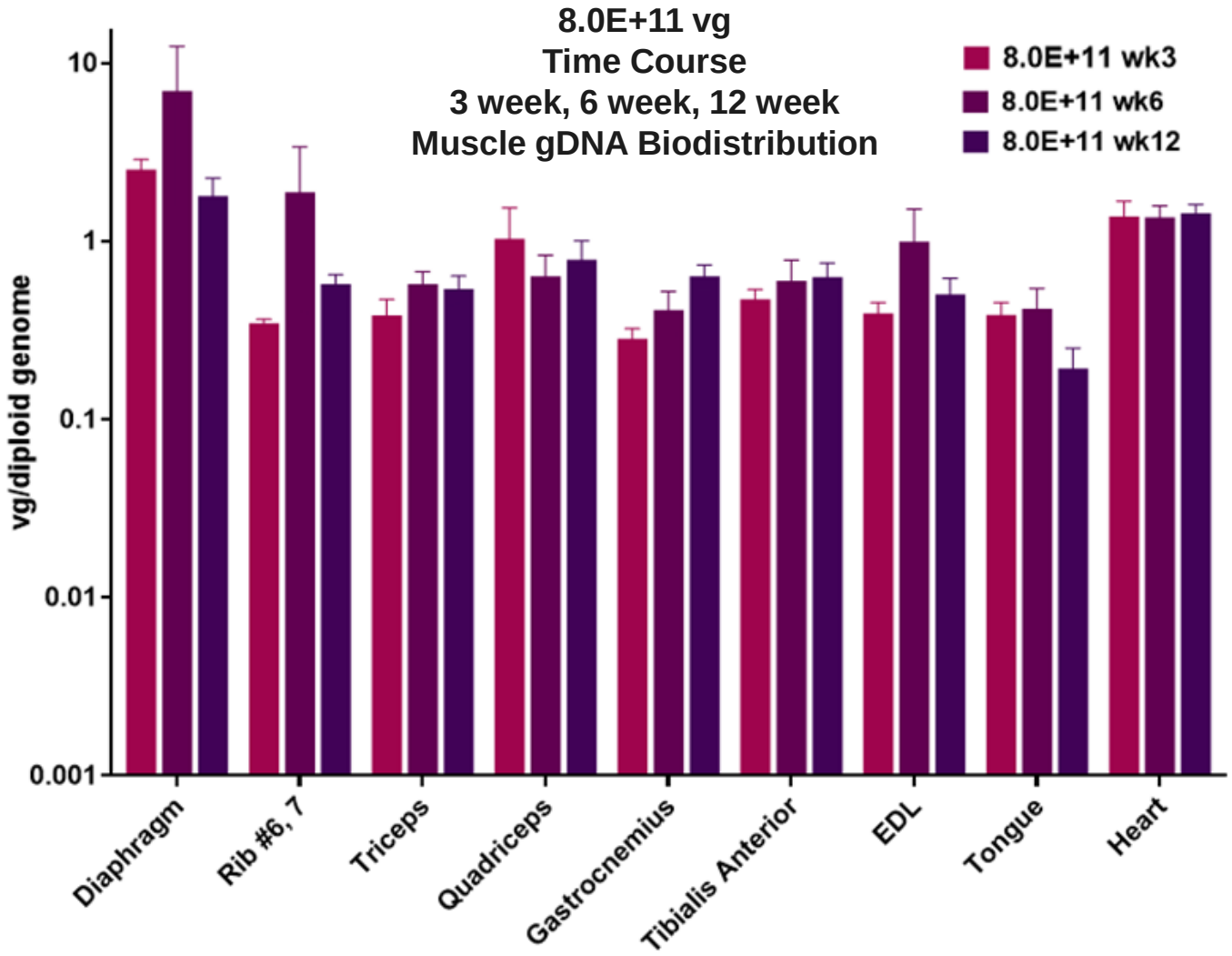
Muscle Biodistribution of INS1201 Demonstrates a Dose Response and Robust Muscle Targeting in 6-week GLP Toxicology Study in Wild Type Mice



Muscle Biodistribution of INS1201 Demonstrates a Dose Response and Robust Muscle Targeting in 12-week GLP Toxicology Study in Wild Type Mice



Muscle Biodistribution of INS1201 Demonstrates Durability Throughout Twelve Weeks and Effective Targeting of the Heart



Brief Study Design

The overall goal of this study is to evaluate the Biodistribution of INS1201 in Non-Human Primates (NHP) Using GMP Produced Engineering Lot of INS1201

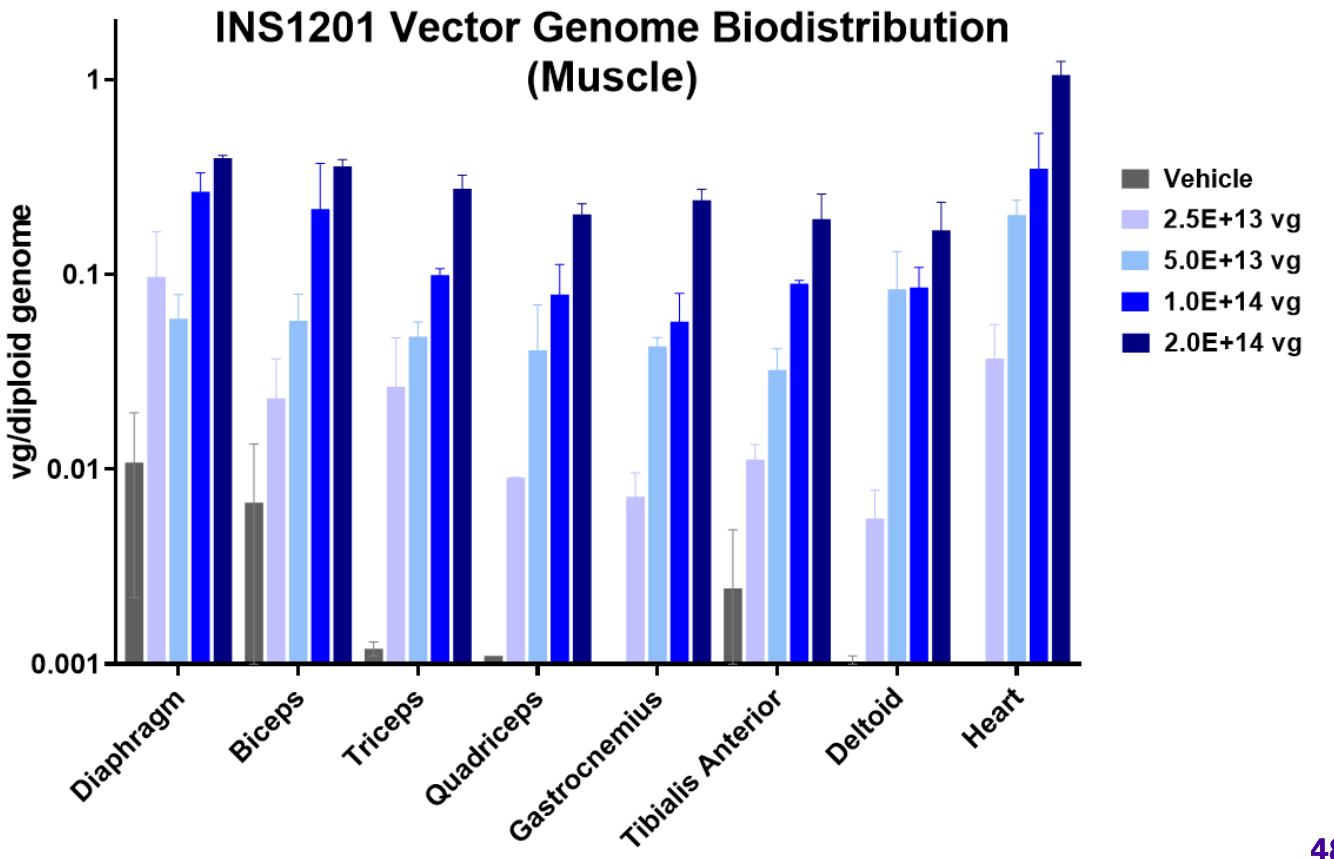
Intrathecal (IT) Injections of INS1201

IT injection of INS1201 in 10 NHP between 2-3 years

Tissue analyzed at 21 days post treatment

Muscle Biodistribution of INS1201 Demonstrates a Dose Response and Robust Muscle Targeting in Non-Human Primates

- Normal Body Weight Gain
- Normal Clinical Observations
- Normal Blood Chemistry/Hematology
- No mortality or moribundity in any NHPs dosed with INS1201



Brief Study Design

The overall goal of this study is to evaluate INS1201 efficacy in newborn *mdx* mice

Intracerebroventricular (ICV) Injections of INS1201

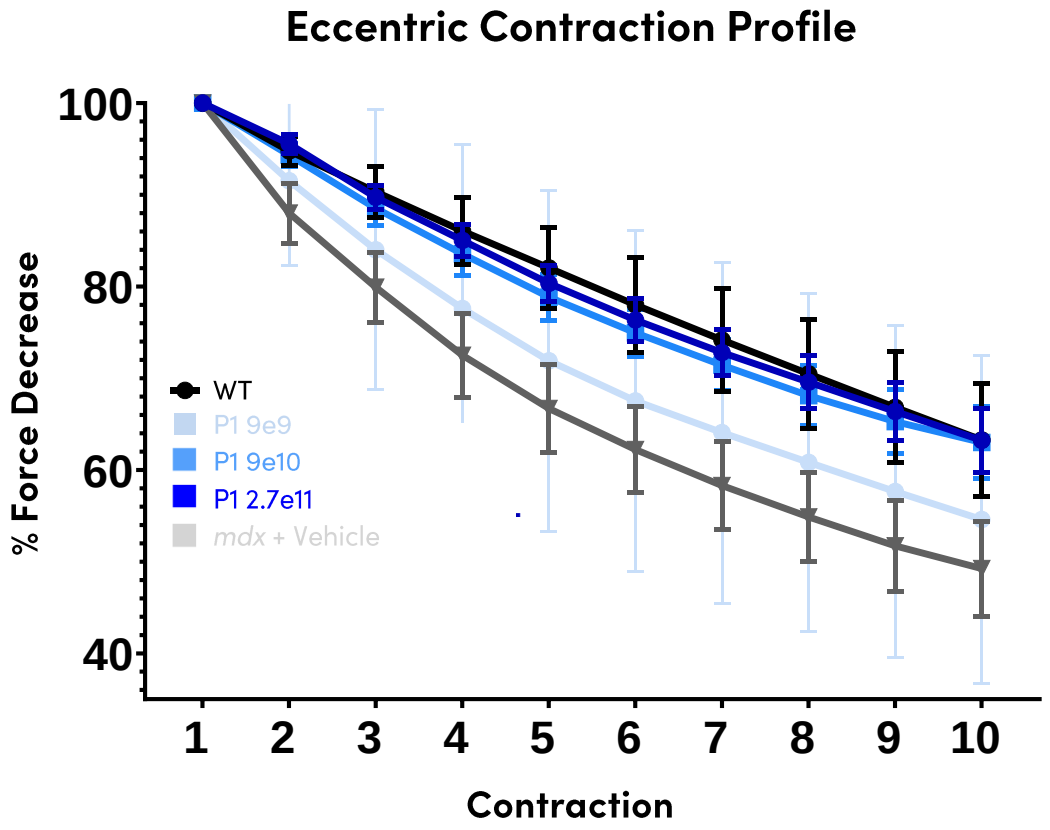
ICV injection of INS1201 at P1 (postnatal day 1) in *mdx* mice

EDL muscle analyzed by physiology

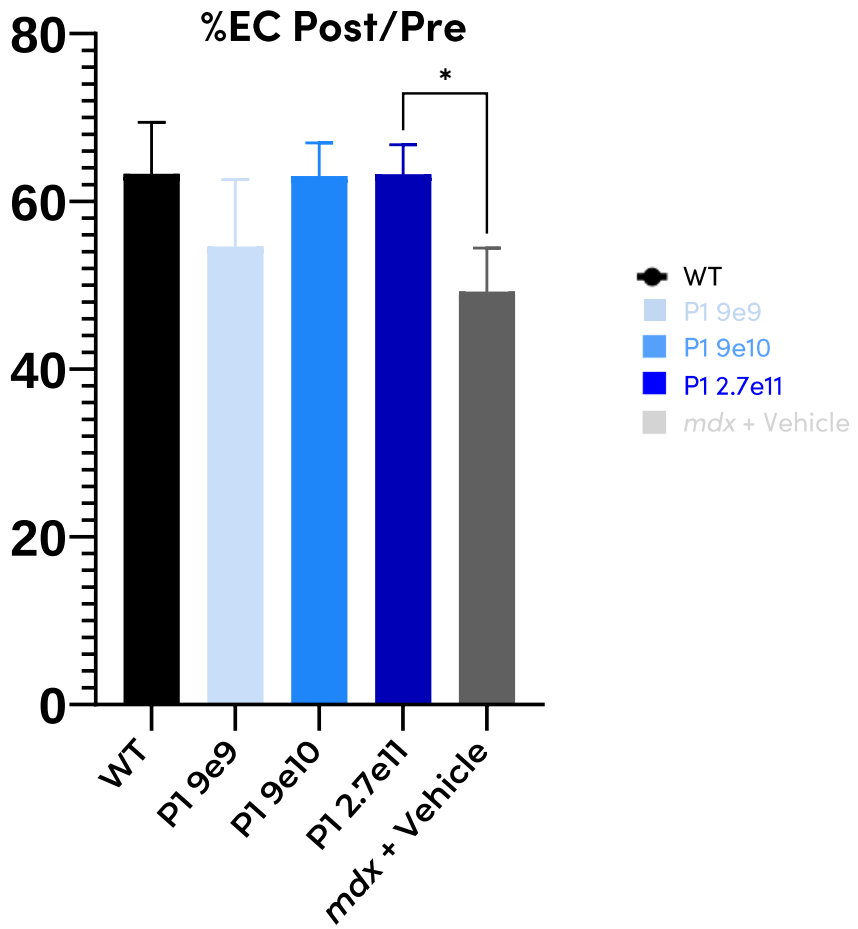
Substantial Improvement in Muscle Physiology by Early Intervention in P1 *mdx* Mice Treated with INS1201

EXTENSOR DIGITORUM LONGUS (EDL) MUSCLE

A

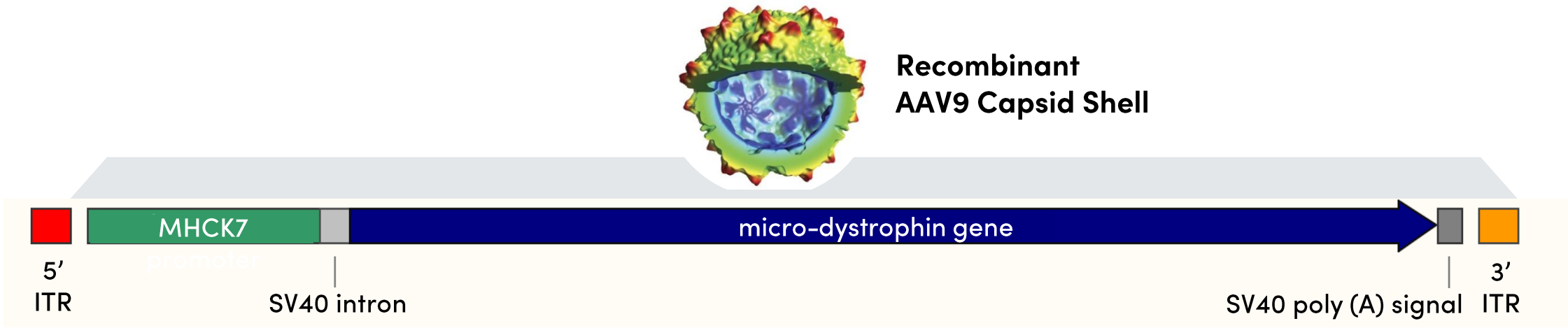


B

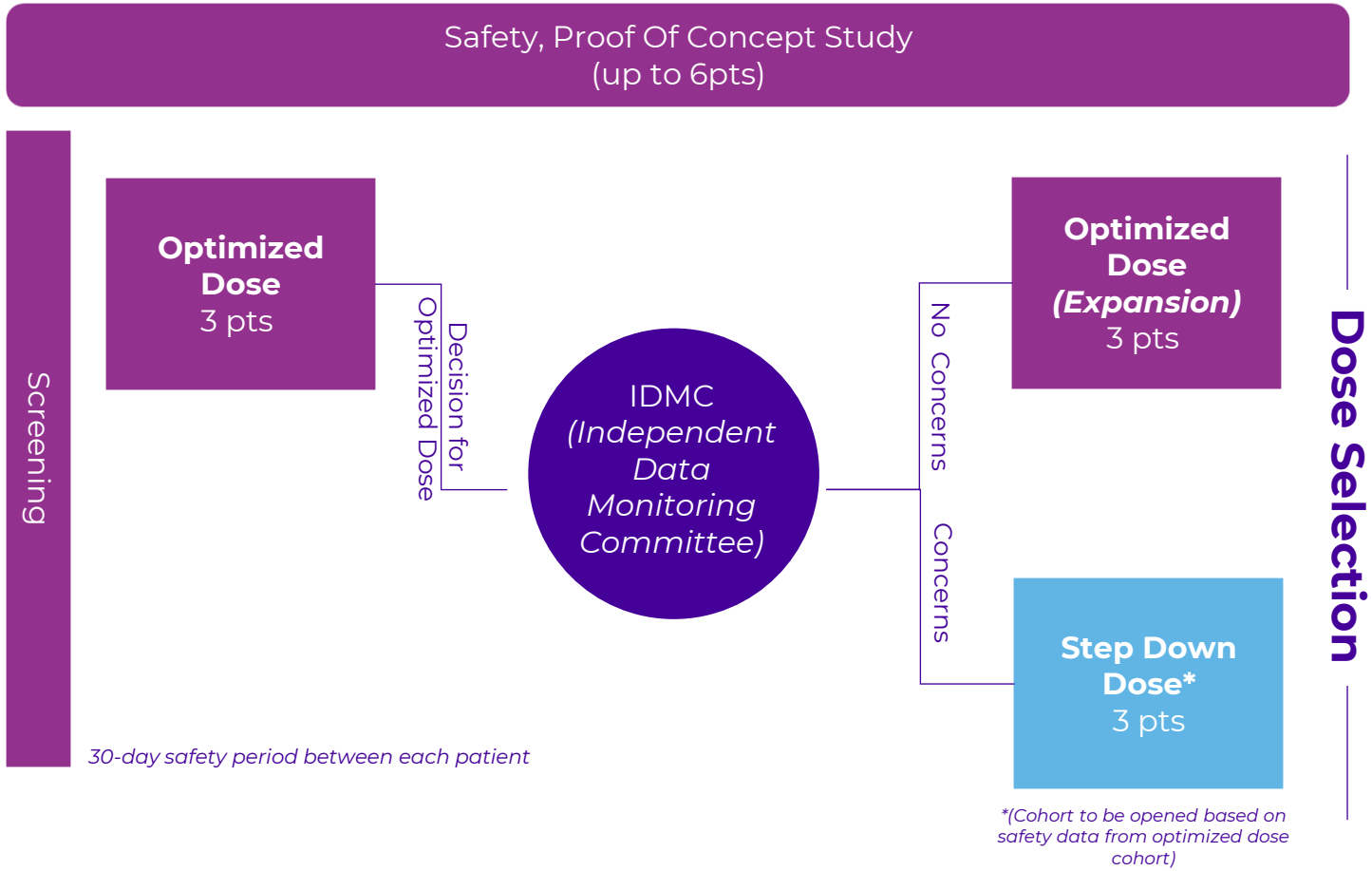


Insmed Is Well-Positioned To Initiate An Early Intervention Study Once Newborn Screening Is Available

Insmed Plans to Initiate a Clinical Trial for INS1201 in 2H2023



Insmed Will Initiate A Phase 1, Multicenter, Open-Label, Study to Investigate the Safety and Biodistribution of INS1201 in Male Toddlers for the Treatment of Duchenne Muscular Dystrophy



Muscle Biopsy and Biomarker Data Expected To Be Available 1H2024

Single dose; Intrathecal administration

Insmed Gene Therapy Welcomes Its Executive Medical Director For Clinical Development & Safety

Jessica Eisner, M.D.

Jessica Eisner, M.D. has over 20 years of leadership experience in regulated medical product development in both industry and the government. She has worked in multiple therapeutic areas including rare diseases, infectious diseases, cardiology, and oncology.

Dr. Eisner's previous positions include Senior Medical Officer at the FDA (both CDER & CDRH) where she was the primary medical reviewer for over 150 industry product submissions (e.g. INDs/ 510(k)s/PMAs and NDAs). She also previously held the position of Deputy Director of the Military Infectious Disease Research Program for the US Department of Defense and medical leadership positions at Takeda and Abbott Laboratories.

Dr. Eisner was a member of the Board of Trustees for Group Health in the Pacific Northwest where she provided strategic and financial oversight for this HMO with over 500,000 members and $2.5 billion dollars revenue. She is currently a medical expert for International Standard Organization (ISO) drug delivery device standards committees.

Dr. Eisner received her BA from Cornell College in Iowa. She earned her medical degree from the University of California, San Diego and completed her residency at the University of Washington in Seattle.

Insmed is Uniquely Positioned to Address Challenges in GTx Landscape with Game-Changing, Novel, Proprietary Technologies

Next Generation Gene Therapies With Targeted Delivery

Enhanced safety profile with similar/better efficacy

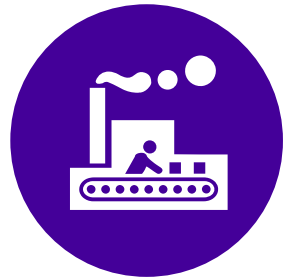
10 to 50-fold reduction in dose (vs. Systemic delivery)

RNA End Joining Technology (REJ)

Unlocks new GTx market opportunities with no competition

Large size gene delivery through traditional AAVs

Immunogenicity and inability to target diseases requiring redosing



High production costs with low yields

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Inability to treat diseases requiring delivery of large genes

Insmed Value Proposition & Solution

RNA End Joining Technology (REJ)

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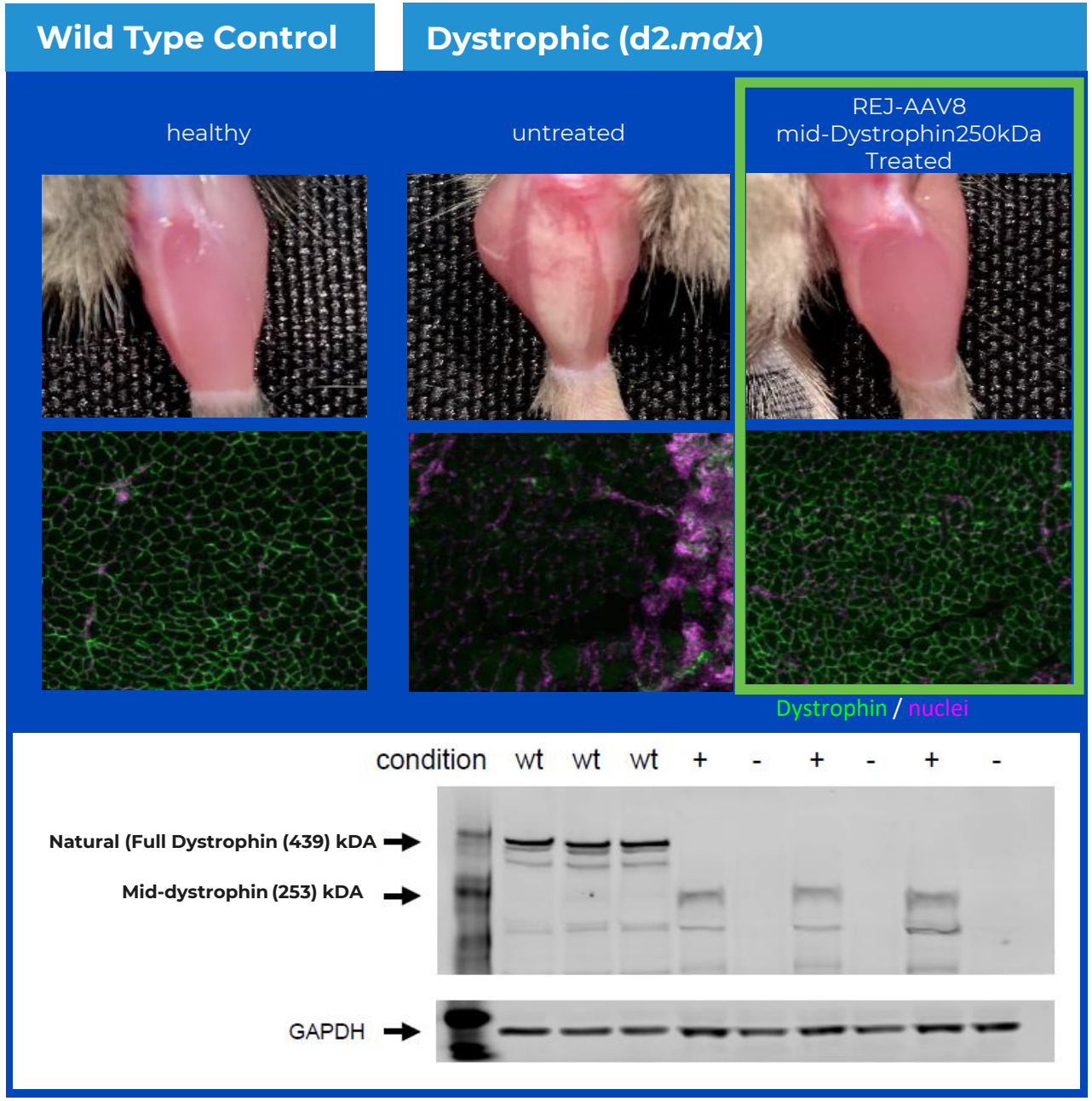
Novel RNA End Joining Technology Enables Treatment With Larger Mid-Dystrophin Variants

INTRAMUSCULAR DELIVERY OF AAV8-REJ-MID-DYSTROPHIN

AAV8-REJ-mid-dystrophin

An ~8kb/253kDa truncated dystrophin; improved efficacy/functionality, particularly for cardiac function



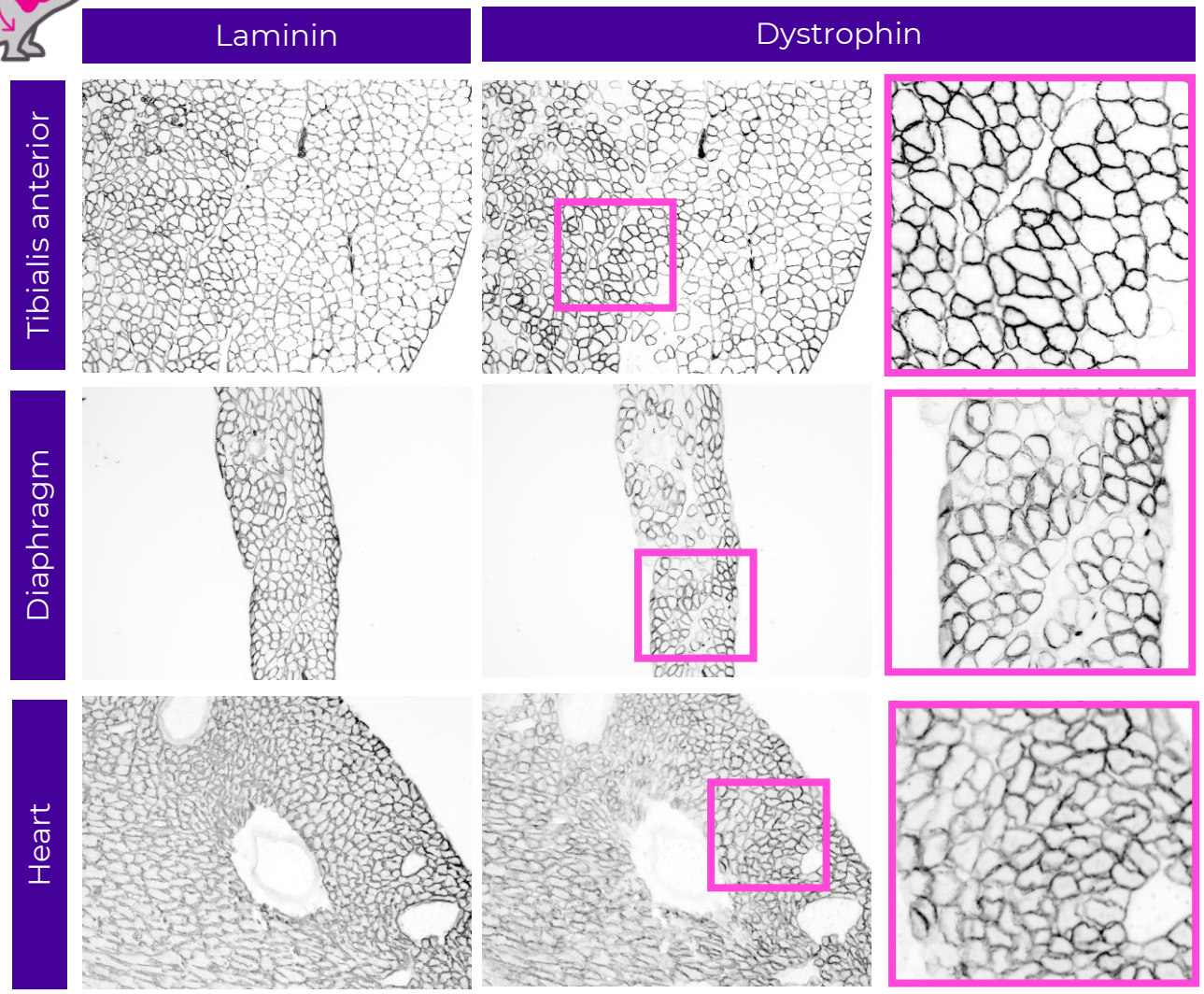
ICV Dual REJ-AAV9 Mid-Dystrophin^{250kDa} Results in Widespread Gene Replacement

NEXT-GENERATION
DYSTROPHIN REPLACEMENT

Approach: Combination of two of Insmed's key inventions: (1) ICV AAV administration for widespread distribution and (2) RNA-end joining for expanded AAV capacity.

Result: ICV injection of dual REJ-AAV9 mid-Dystrophin^{250kDa} results in widespread Dystrophin replacement with an expanded 250kDa mid-gene.

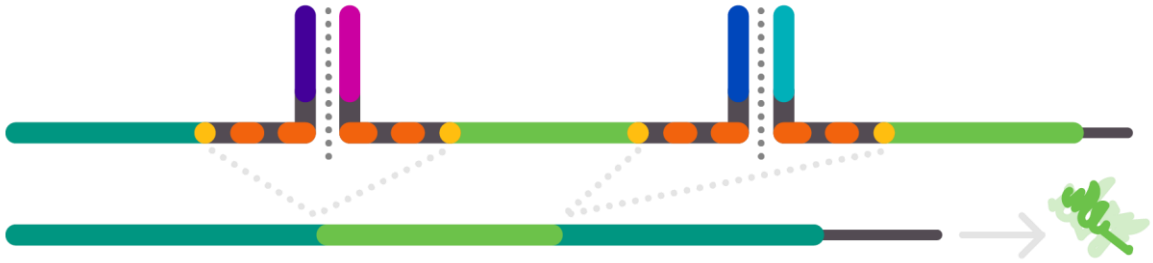
Dystrophin expression in key muscle tissues including skeletal muscle (e.g. Tibialis anterior), the diaphragm and the heart.

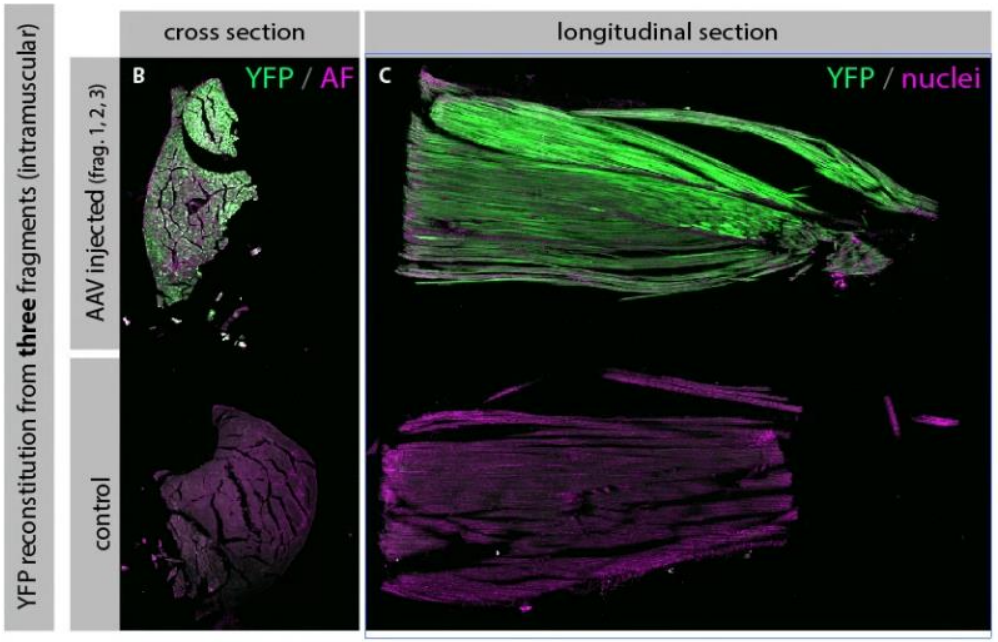


Full-Length Dystrophin Replacement With Triple REJ-AAV Approach

TRIPLE REJ-AAV APPROACH FOR ULTRA-LARGE GENE REPLACEMENT

- Reconstitution of full length YFP from three vectors using REJ technology
- Three vector approach allows for ~12kb CDS





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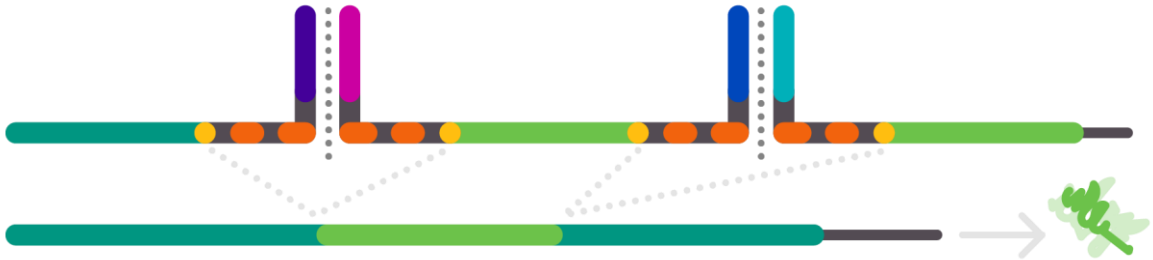
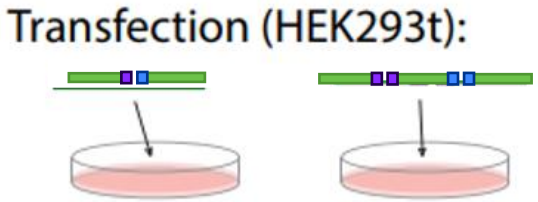
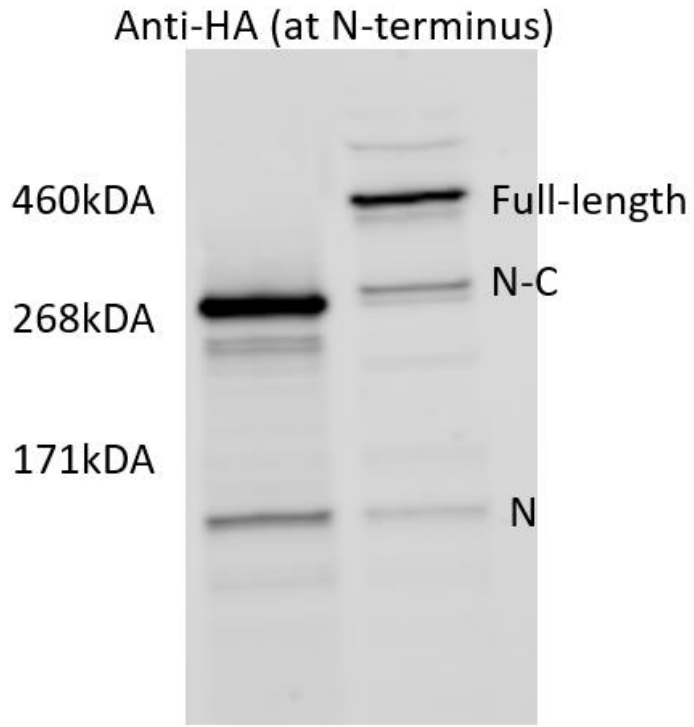






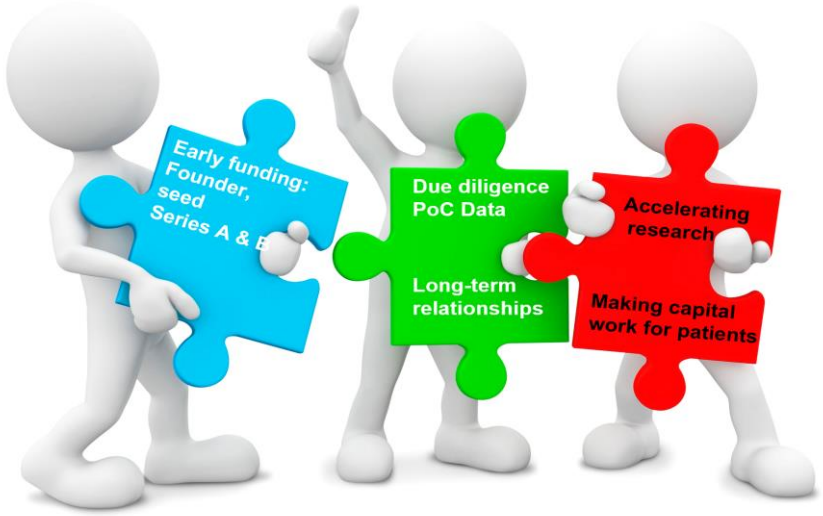
Cure Duchenne

Michael G. Kelly, PhD
Chief Scientific Officer
CureDuchenne

CureDuchenne Ventures

CureDuchenne Ventures was established to find, fund and de-risk innovative research programs, advance them to the clinic to accelerate the approval of life-changing treatments for all Duchenne/Becker patients.

- Early funder, substantial due diligence and de-risk projects to attract further investments.
- Cultivate long-term strategic relationships providing deep domain expertise, insight and support.
- Our investments have attracted approximately $3B in follow-on funding for DMD from VC firms and public markets.
- Seventeen CureDuchenne-funded projects have advanced to clinical trials.



Supporting Innovation - Growing a Pipeline of Therapeutic Opportunities

Our investments are targeted and impactful:

- We invest with an emphasis on treatments that restore dystrophin in addition to approaches that provide a “stand-alone” benefit for Duchenne and Becker muscular dystrophy patients.
- “Combination therapy” is expected to become the standard-of-care as new drugs are approved.

The pipeline has evolved to target the disease from multiple angles:

- Our investments have supported DNA editing, RNA modulation, gene therapy, new muscle targeted AAV’s, solutions for nAb’s and AAV redosing, non-viral gene delivery, muscle and bone sparing agents, and novel anti-inflammatories etc.

RNA Targeting/Exon Skipping

PROSENSA BIOMARIN · PTC THERAPEUTICS · SAREPTA THERAPEUTICS · AVIDITY BIOSCIENCES · PepGen · Dyne THERAPEUTICS · entrada THERAPEUTICS · hC Bioscience, Inc

Gene Editing

exonics THERAPEUTICS · VERTEX · ShapeTX

AAV Gene Therapy

Bamboo therapeutics · Pfizer · CHAMELEON BIOSCIENCES INC. · NATIONWIDE CHILDREN’S *When your child needs a hospital, everything matters.* · 4DMT · AskBio MAKING HISTORY

Exosomes & Non-Viral Delivery

Capricor Therapeutics™ · code bio™ · Gennao · Myosana Therapeutics

Anti-inflamm, Muscle & Bone Preserving

ReveraGen BioPharma · santhera THEIR FUTURE - OUR FOCUS · MyoTherix · RASRx · Mesentech · Edgewise THERAPEUTICS

Activating Private Capital & Public Markets

We've invested alongside many VC and biotech funds to drive innovation.

- New technologies targeting DNA/RNA have emerged that will dramatically impact many monogenetic diseases.
- The “next-generation” cell-penetrating muscle-targeted exon-skipping approach's have entered the clinic.
- Approval of the first gene therapy products are anticipated.

But significant challenges remain to more effectively treat DMD

We Still Need Breakthroughs To Get Closer To Our Goal

Gaps and opportunities exist within the current gene therapy pipeline.

- **Delivery & cost**: improved muscle targeting for AAV and non-viral approaches.
  - Lower AAV dose - reduce manufacturing burden & cost of goods and improve safety
- **Gene size**: larger dystrophin transcripts will be needed for more effective treatment.
  - Larger “mid-length” BMD transcripts associated with mild/asymptomatic phenotypes.
  - Full-length dystrophin protein is our ultimate goal.
- **Treatment** needs to begin at diagnosis.
  - Newborn screening.
  - Redosing - solutions needed for nAb’s.

CureDuchenne Ventures/Insmed

CD Ventures held separate meetings over the past few years with Motus Bio & Vertuis Bio.

- **Vertuis Bio**: utilized RNA end joining technology to deliver larger dystrophin transcripts - efficiently produced mid-length (ca. 8kb, 253 kDa) BMD constructs and full-length dystrophin protein (ca. 12kb, 439 kDa).
  - More potent, targeted AAV were required to fully unlock the potential of REJ technology for DMD.
- **Motus Bio**: IT-delivered μdys-gene therapy targeted muscle with 10 to 50-fold dose reduction compared to i.v. delivery.
  - This presented an exciting stand-alone opportunity that addressed gaps in the current GT landscape.
- The merging of these approaches offers Insmed a unique opportunity to go beyond where GT is today.

CureDuchenne is delighted to announce its enthusiastic support for this program and an investment in Insmed to help potentially bring this opportunity to Duchenne patients

Brian Kaspar, PhD

Chief Scientific Officer

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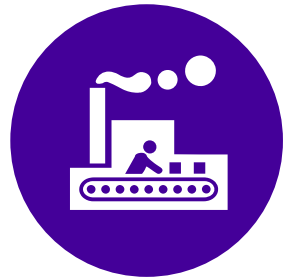

High production costs with low yields

Lukas Bachmann, PhD

Director, Research

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Inability to treat diseases requiring delivery of large genes

Insmed Value Proposition & Solution

RNA End Joining Technology (REJ)

Unlocks new GTx market opportunities with no competition

Large size gene delivery through traditional AAVs

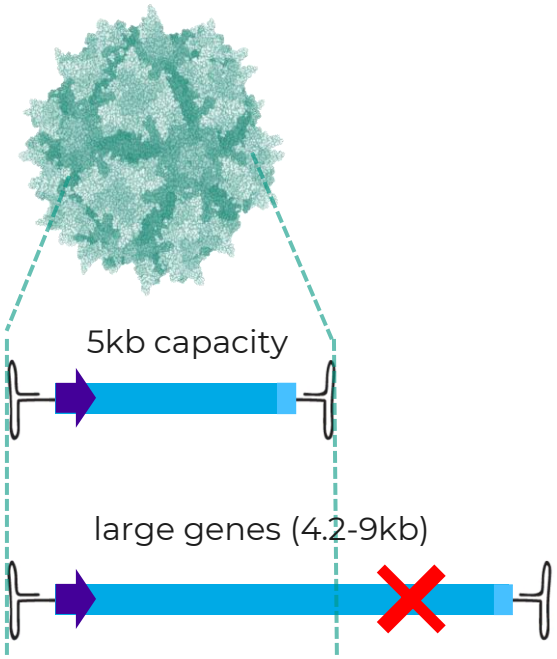
Insmed's Proprietary RNA-End Joining (REJ) Technology Could Enable Large Gene Delivery Using AAV

OVERCOMING THE CAPACITY CHALLENGE: AN RNA PLATFORM FOR NEXT GENERATION GENE THERAPY

CHALLENGE

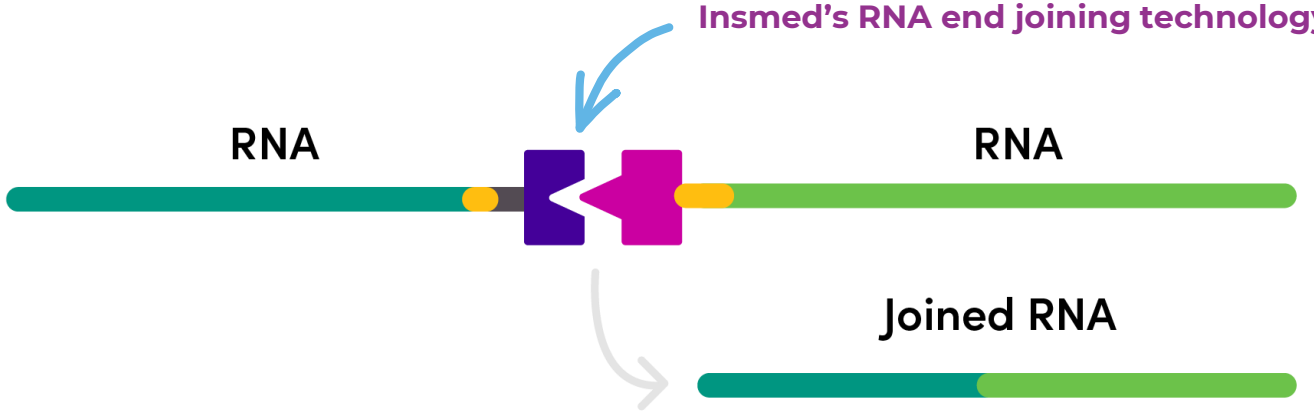
Current challenge in AAV gene therapy:

- AAV: favored gene therapy vector but has limited cargo capacity
- Many **large disease/effector genes (or large regulatory sequences)** cannot fit within AAV
- **High unmet need for patients** with diseases caused by large genes.



POTENTIAL SOLUTION

High-capacity REJ dual AAV approach



Highly efficient, precise, and universal

Plug-and-play

Allows for **dual AAV** up to 8-9kb CDS (triple AAV up to 12kb CDS)

Insmed's Proprietary REJ Platform is Designed to Allow For Two Vector Delivery Of Split Genes With Efficient, Precise Reconstitution Of RNA While Maintaining Suppression Of Un-joined Protein Fragment Expression

REJ Technology in Action:

(1) Gene can be split anywhere

(2) Split-gene is packaged in two AAVs; any serotype or promoter can be used

(3) Co-infection of a cell is readily achieved

(4) Split RNA transcribed from two AAVs

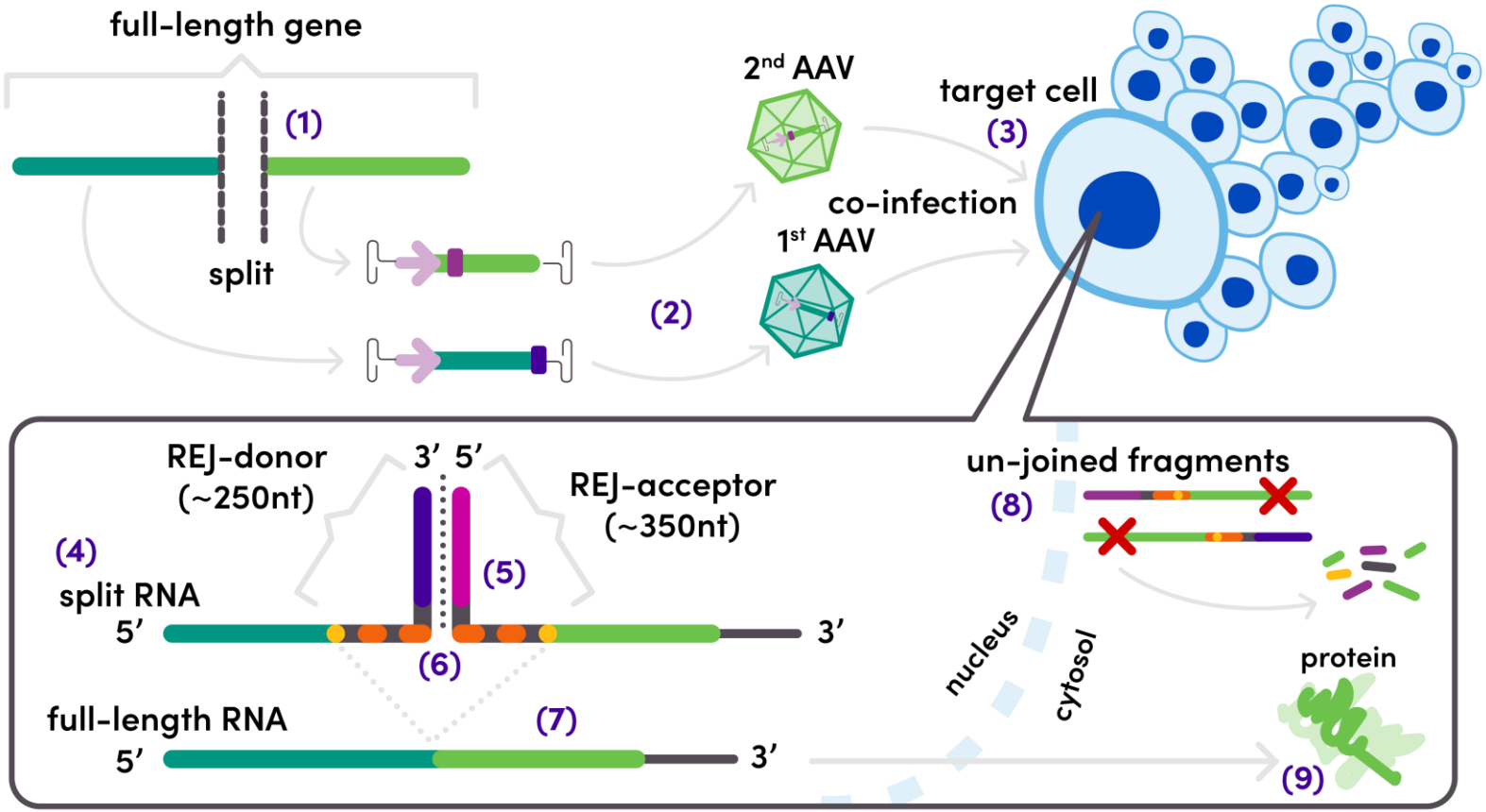
(5) Structured RNA dimerization domains mediate non-covalent binding

(6) REJ domains are designed for efficient spliceosome recruitment

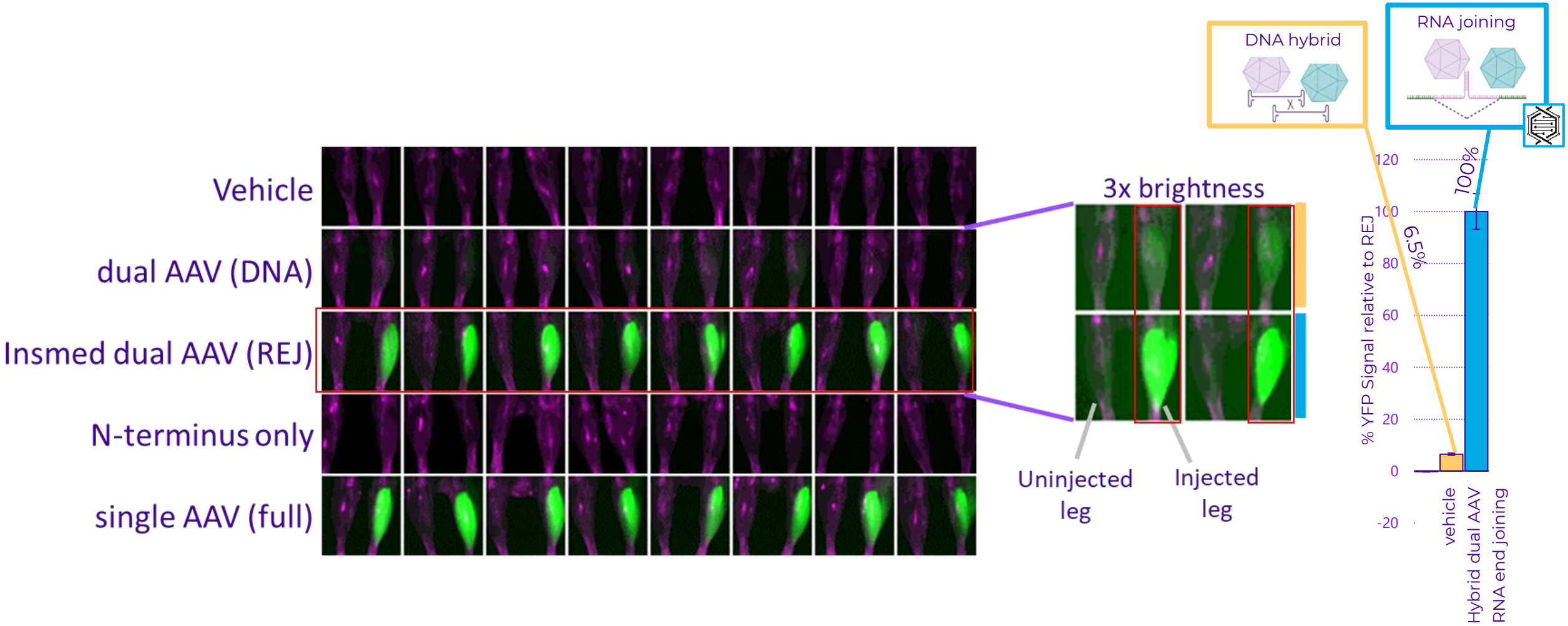
(7) Spliceosome mediates RNA-end joining

(8) Protein expression from un-joined fragments is suppressed

(9) Desired full-length protein is translated

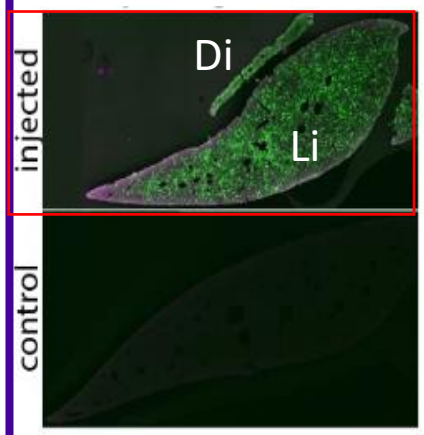


Insmed's Proprietary REJ Platform Is ~15x More Efficient At Gene Reconstitution Than DNA Hybrid Technology

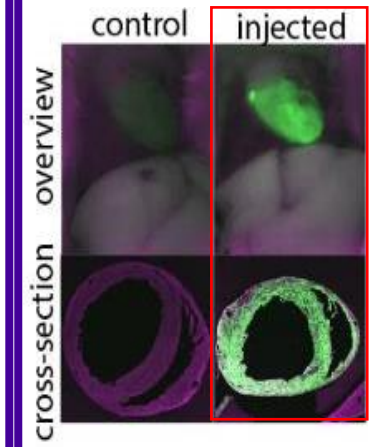


Insmed's Proprietary REJ Platform Produces High Levels of Functional Protein Across Tissue and Cell Types

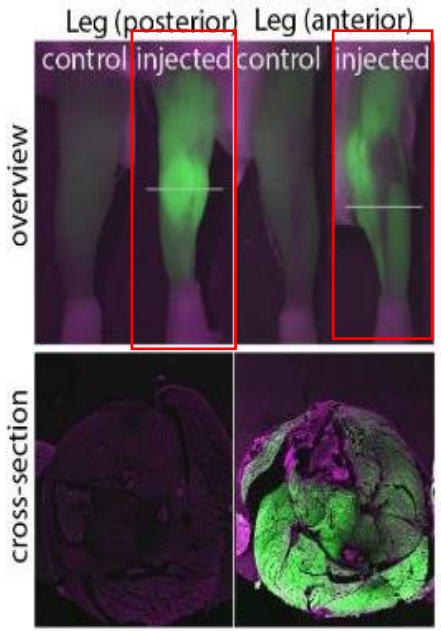
Liver
Diaphragm



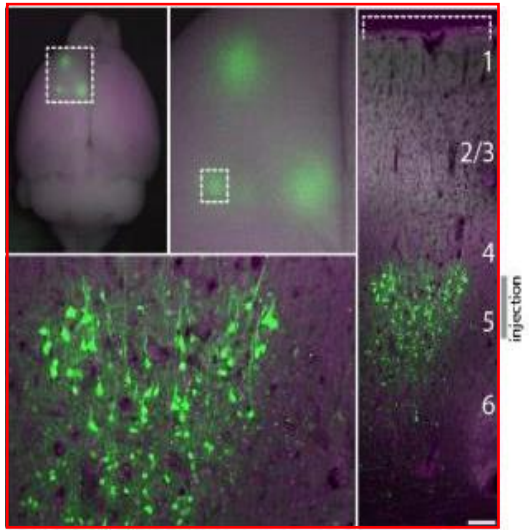
Heart



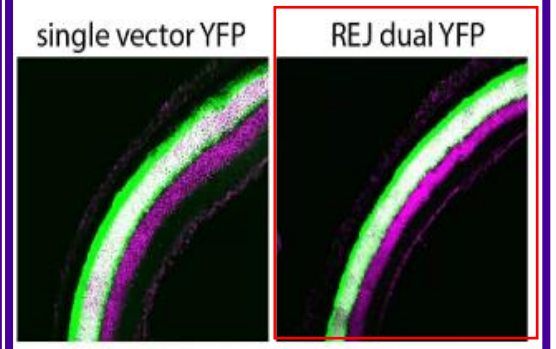
Skeletal
Muscle



Neurons



Retinal
Photoreceptors



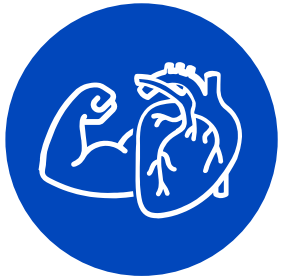
Systemic delivery

Local delivery

Insmed's Proprietary REJ Platform Could Unlock Gene Therapy Whitespace

REJ Platform is designed to enable delivery of large genes with AAV

Muscular/Cardiac

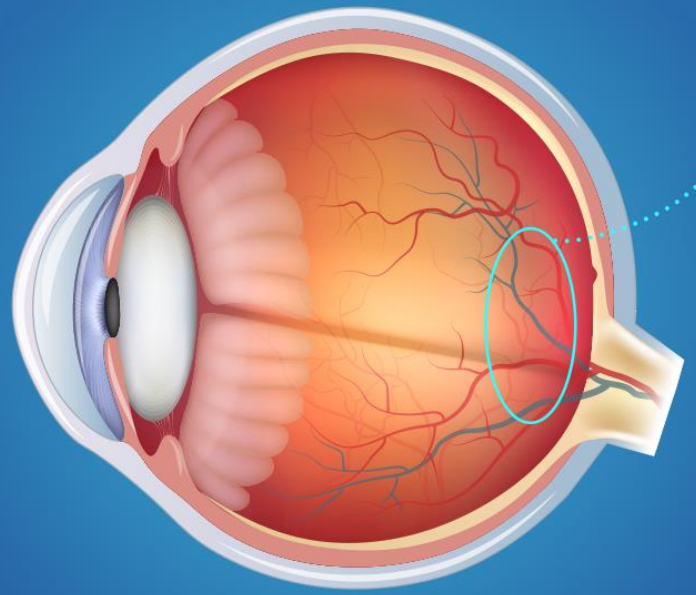


Retinal Disease

Respiratory

Nervous System

Other Systems



Stargardt disease is a hereditary retinal disease leading to progressive degeneration of the Retinal Pigment Epithelium (RPE) and choriocapillaris, finally leading to loss of vision and progressive visual field defects.[1]

- **Caused by mutations in the ABCA4 gene** - gene affects how body uses vitamin A
- **Vision loss usually starts in childhood** - some people don't start to lose their vision until they're adults
- **No treatment available** - current management focused on alleviating symptoms and optimizing remaining sight
- **Prevalence of 1 in 8,000 to 10,000[2]** - most common inherited macular dystrophy

[1] National Eye Institute. Stargardt Disease, Available at: https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/stargardt-disease (Accessed: 31 March 2023)
[2] https://doi.org/10.1167/iovs.09-3611

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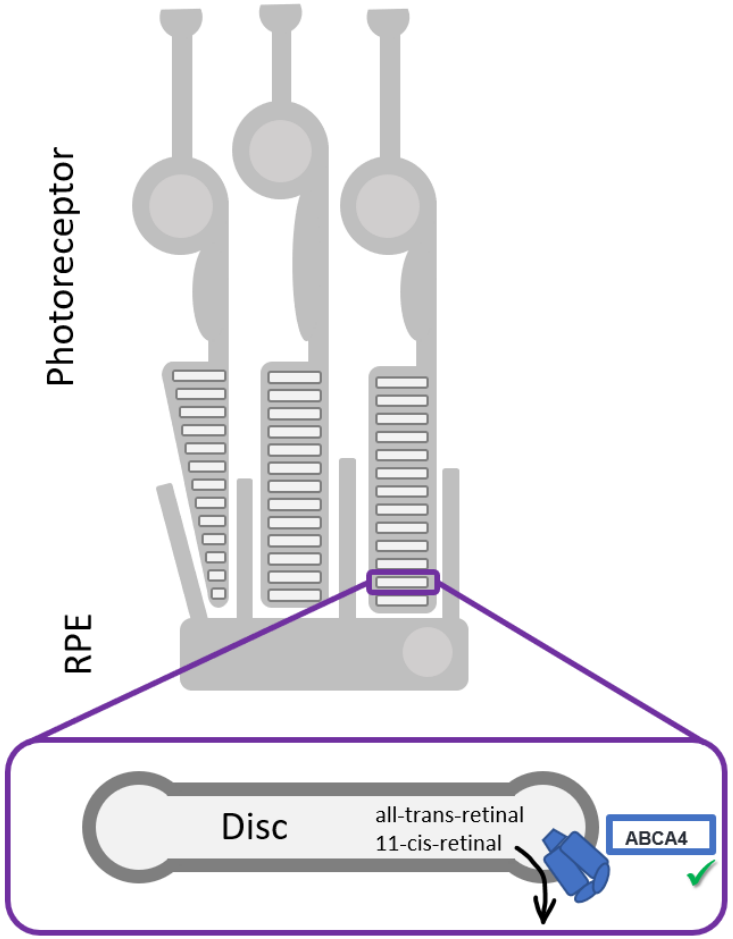
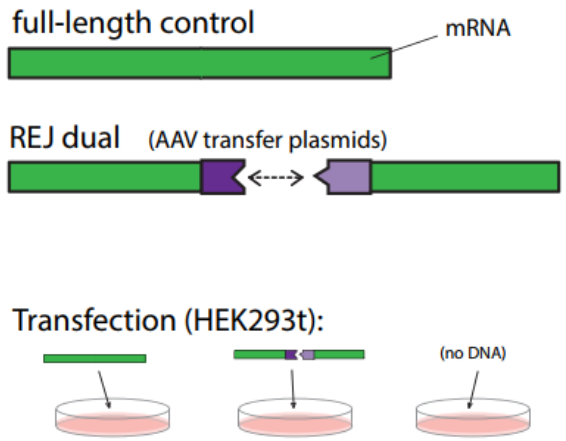
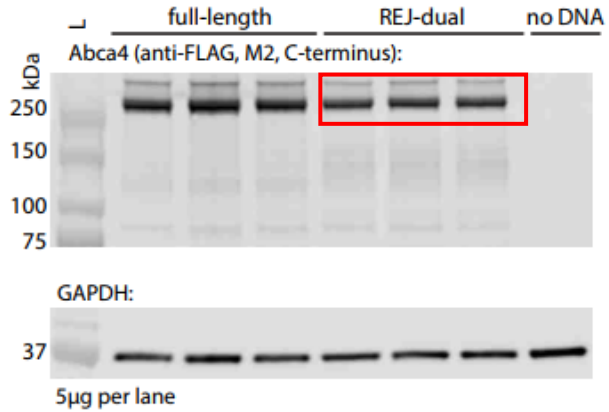
Stargardt Disease: REJ Produces a Full Length Abca4 Protein *in vitro*



A Experimental Setup



B Full Length Abca4 by REJ



Stargardt Disease: REJ Produces a Full Length Abca4 Protein *in vivo*

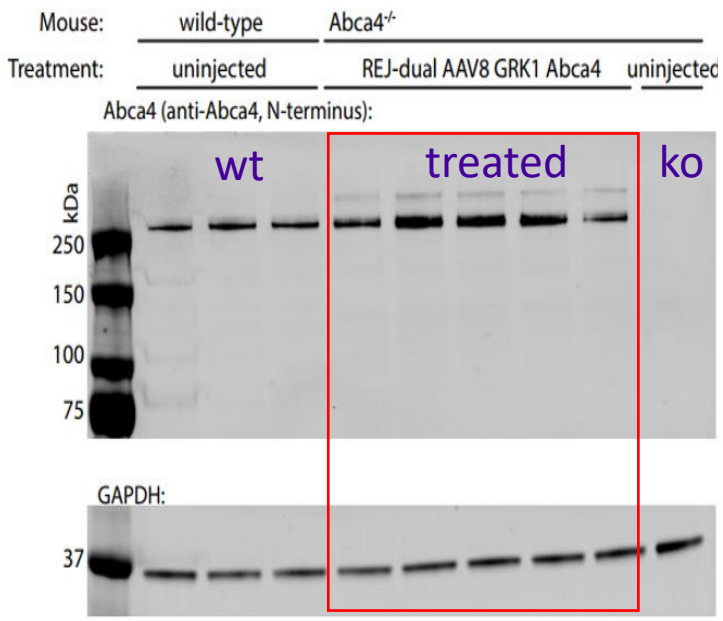
SUBRETINAL DELIVERY OF AAV8-REJ-Abca4

REJ dual AAV8 Abca4 generates (more than) physiological levels of Abca4 in photoreceptors when injected sub-retinally in the Stargardt's Disease model mouse

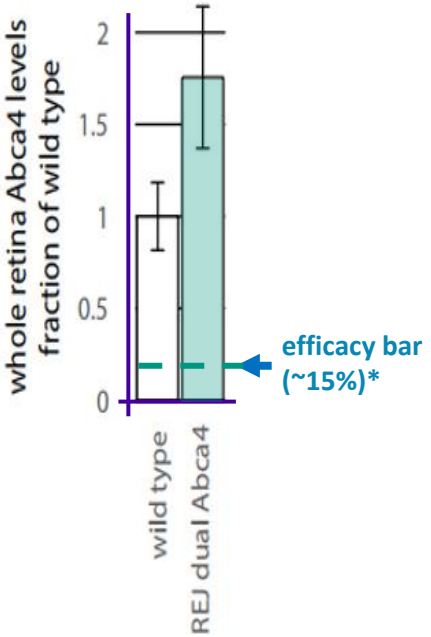
In contrast, Intein dual AAV approach only reached ~10-15% of wild type at the comparable dose

REJ dual AAV8 Abca4 levels are more than 10x above the threshold for efficacy

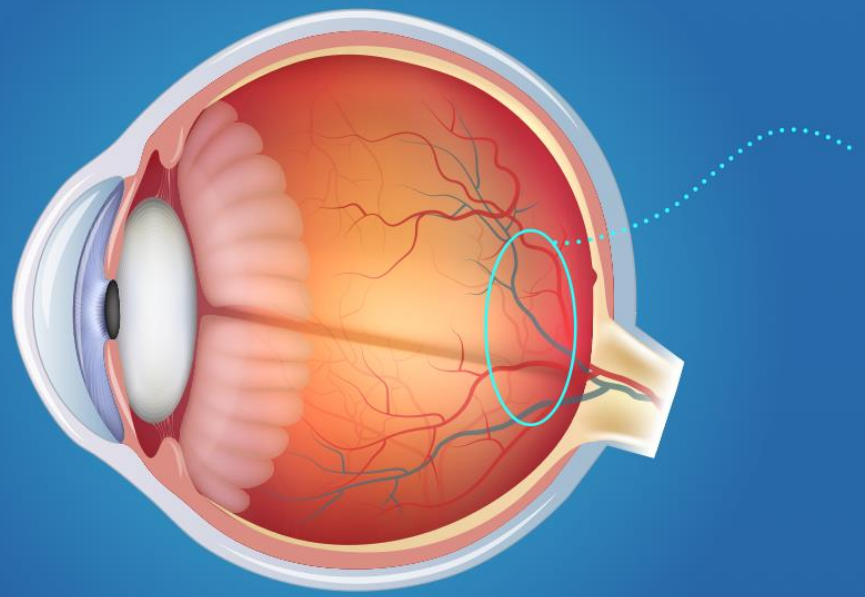
REJ's higher efficiency allows for reduction in dose which improves safety profile



Western Blot



* As observed in Tornabene et al., 2019



Insmed Plans To Submit An IND For The Treatment Of Stargardt Disease by the End of 2024

10-Minute Intermission

Karl Griswold, PhD

Executive Director, Biologics Research & NH Site Lead

Chris Bailey-Kellogg, PhD

Executive Director, Computational Biology

Insmed is Uniquely Positioned to Address Challenges in GTx Landscape with Game-Changing, Novel, Proprietary Technologies

Next Generation Gene Therapies With Targeted Delivery

Enhanced safety profile with similar/better efficacy

10 to 50-fold reduction in dose (vs. Systemic delivery)

RNA End Joining Technology (REJ)

Unlocks new GTx market opportunities with no competition

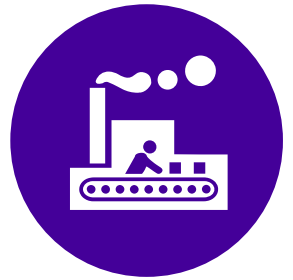
Large size gene delivery through traditional AAVs

Deimmunized by Design (DbD) platform

Redosable viral vectors

Deimmunized biobetters & derisked innovator drugs

Repeat dosing of gene therapies and overcoming immunogenicity



High production costs with low yields

Insmed is Uniquely Positioned to Address Challenges in GTx Landscape with Game-Changing, Novel, Proprietary Technologies

Immunogenicity

Inability to target diseases requiring redosing

Insmed Value Proposition & Solution

Deimmunized by Design (DbD) platform

Redosable viral vectors

Deimmunized biobetters & derisked innovator drugs

Repeat dosing of gene therapies and overcoming immunogenicity

A Deep Bench of Multidisciplinary Scientists and Engineers Empower Insmed Research

Chris Bailey-Kellogg

Executive Director, Computational Biology

- PhD, Computer & Information Science, Ohio State University
- Professor, Computer Science, Dartmouth
- Co-founder of Stealth Biologics
- Joined Insmed in 2021

Karl Griswold

Executive Director, Biologics Research

- PhD, Chemistry, University of Texas
- Professor, Thayer School of Engineering, Dartmouth
- Co-founder of Stealth Biologics
- Joined Insmed in 2021

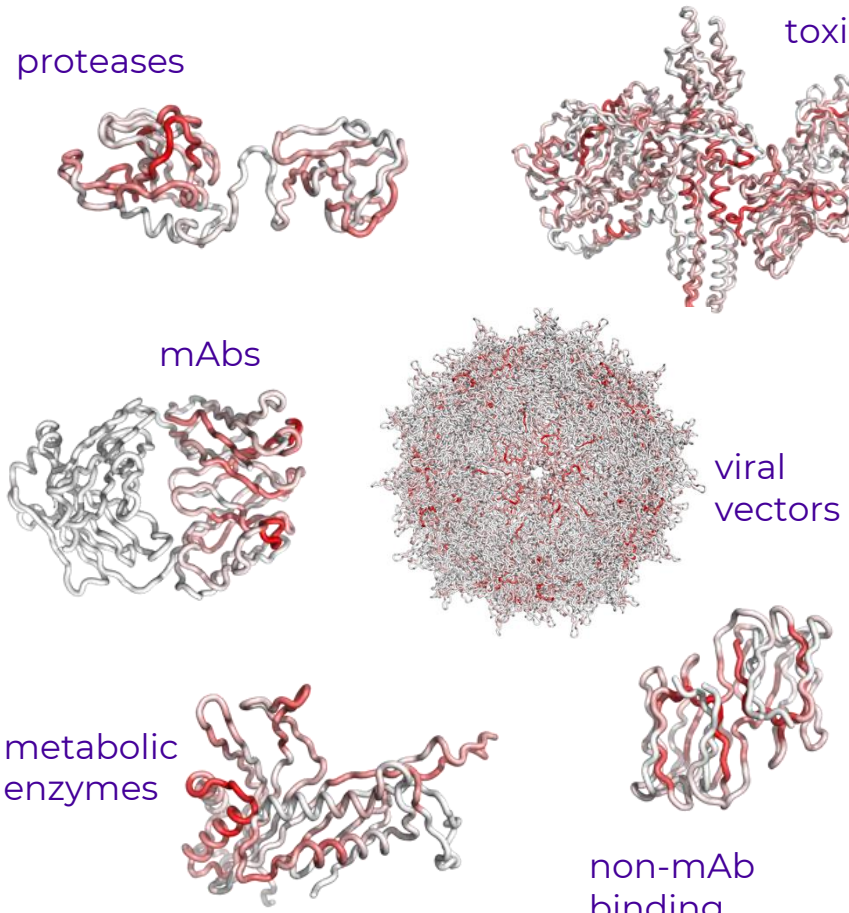
Franziska Leifer

Director, Biologics Research

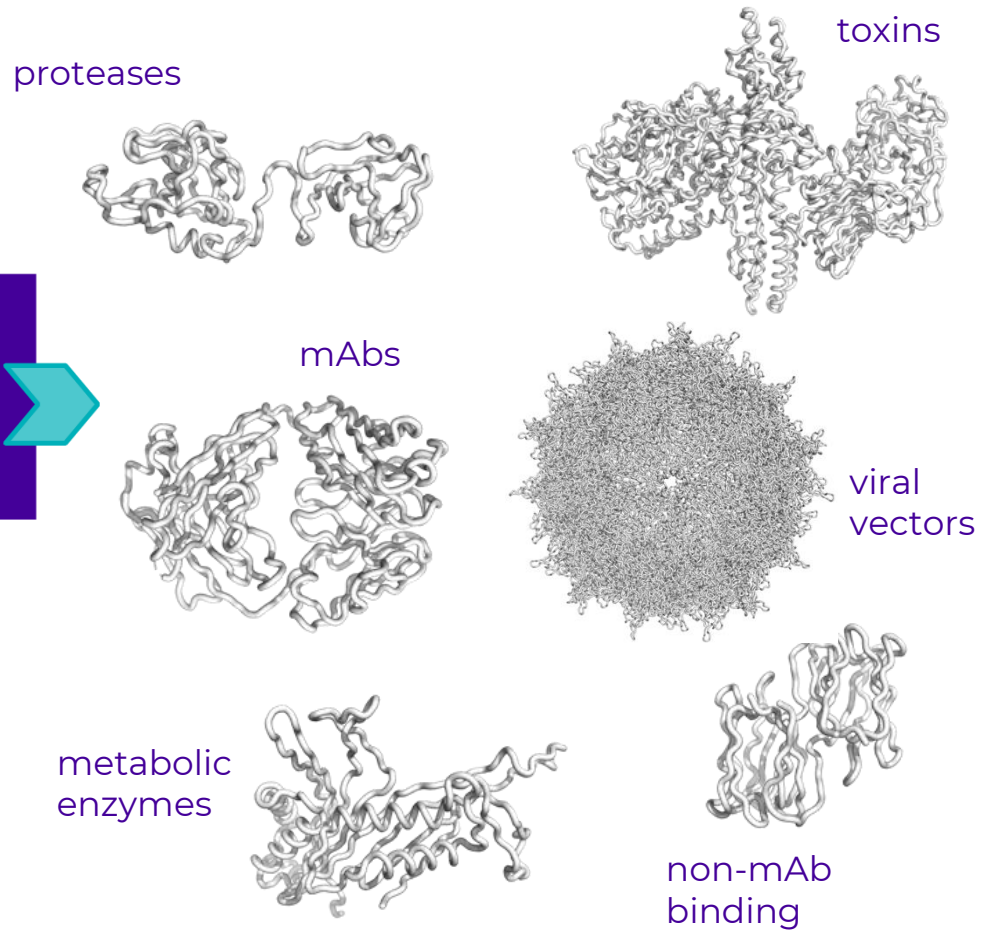
- PhD, Biological Sciences in Public Health, Harvard University
- Preclinical lead, gene therapies for inherited metabolic disorders
- Joined Insmed in 2012

Transforming Potent but Immunogenic Biotherapies into High-Performance, Immunologically Stealthy Drugs

Our proprietary Deimmunized by Design® platform represents a unique technology for engineering safer and more effective biotherapeutic candidates, with relevance to a broad array of indications.

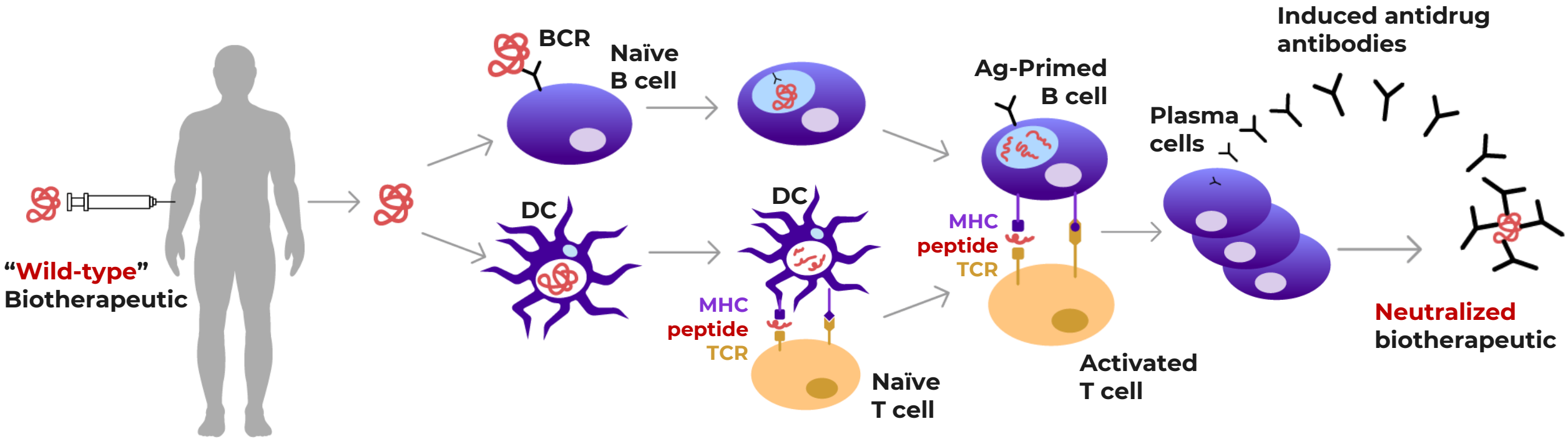


DbD Platform



CHALLENGE

Immune Surveillance Can Undermine Biotherapeutic Efficacy



Consequences of Antidrug Antibodies

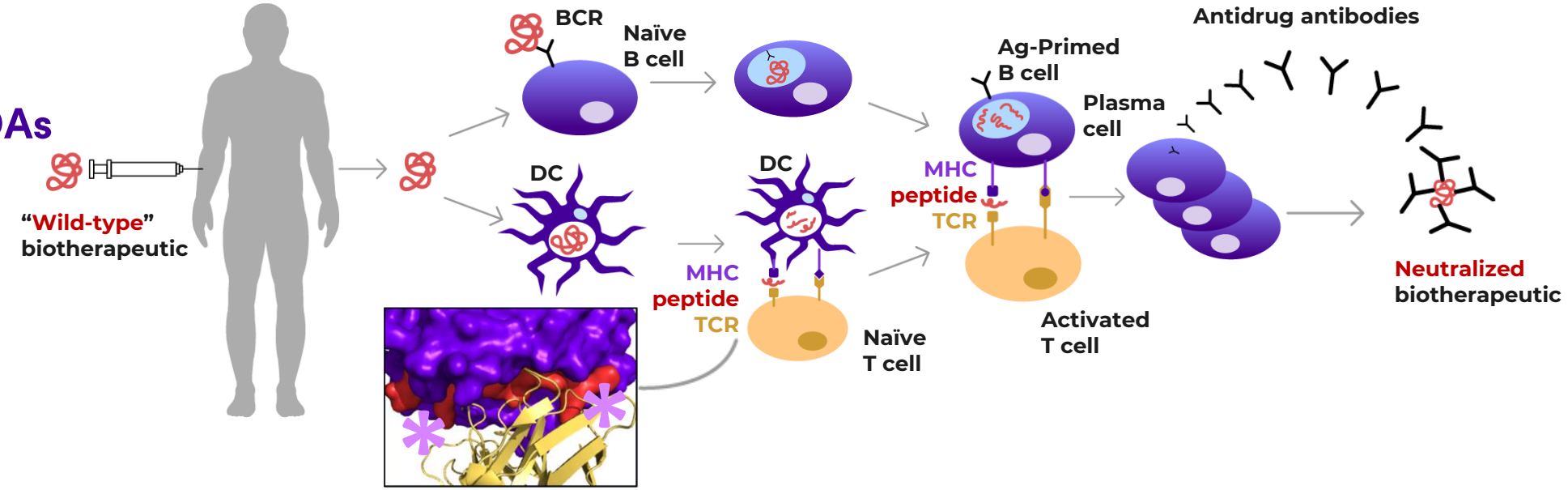
- Drug inhibition
- Discontinuation of therapy
- Exclusion from treatment options
- Immune complex associated toxicity
- Infusion reactions
- Altered pharmacokinetics

(Abbreviations: DC-dendritic cell; MHC-major histocompatibility complex; TCR-T cell receptor; BCR-B cell receptor, Ag-antigen)

Deleting T Cell Epitopes of Immunogenic Biotherapies Blunts Development of Antidrug Antibodies, Enabling Effective Redosing

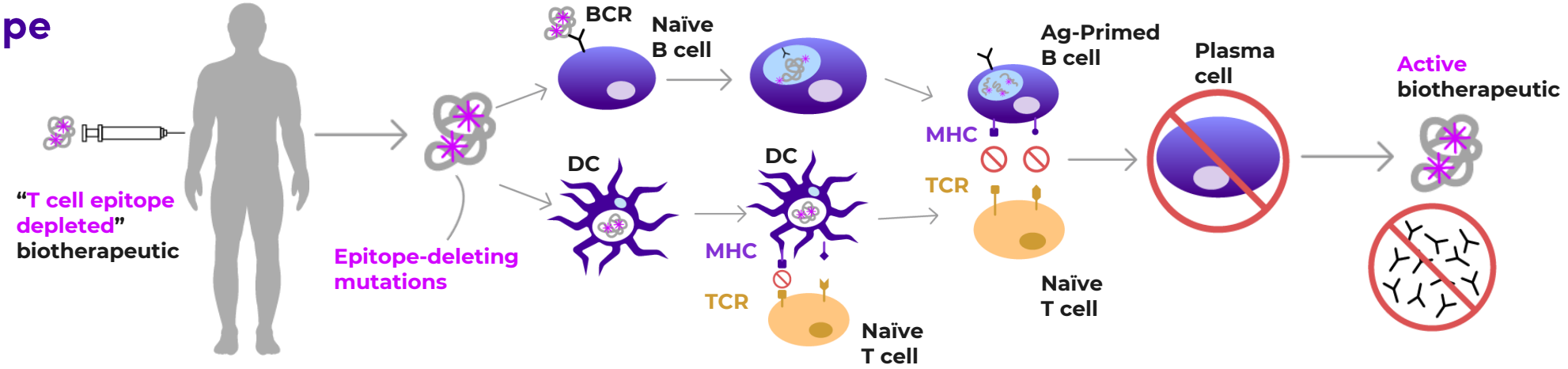
Induced ADAs

CHALLENGE



T cell Epitope Deletion

POTENTIAL SOLUTION

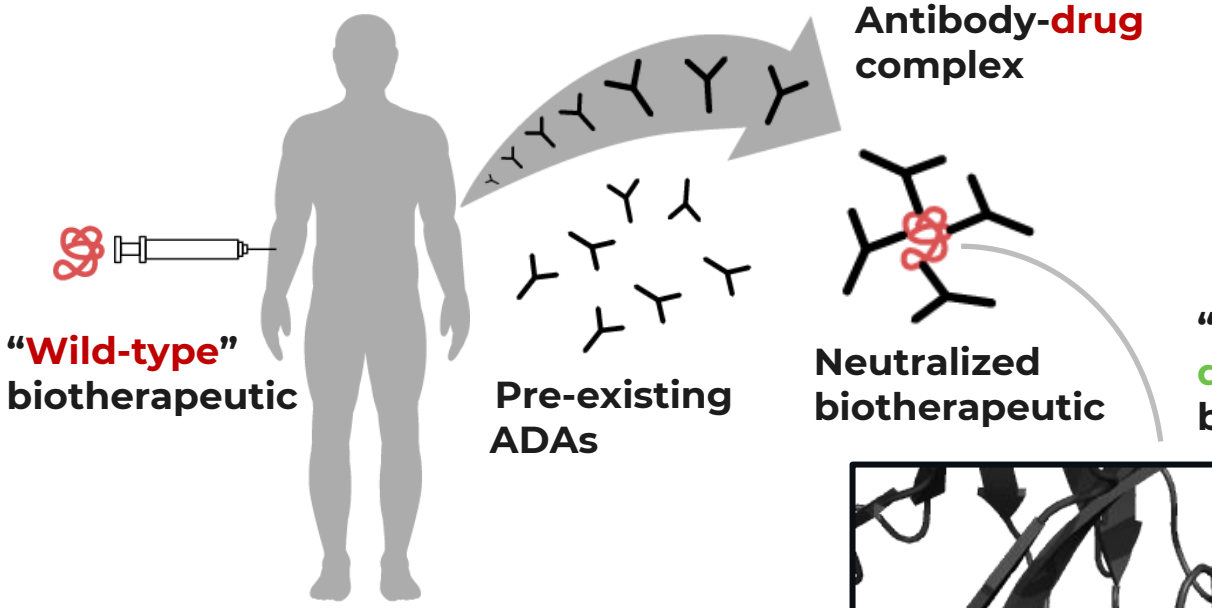


(Abbreviations: iDC-immature dendritic cell; mDC-mature dendritic cell; MHC-major histocompatibility complex; TCR-T cell receptor; BCR-B cell receptor, ADA-antidrug antibodies)

Deleting B Cell Epitopes of Immunogenic Biotherapies Enables Effective Treatment in the Context of Pre-Existing Antidrug Immunity

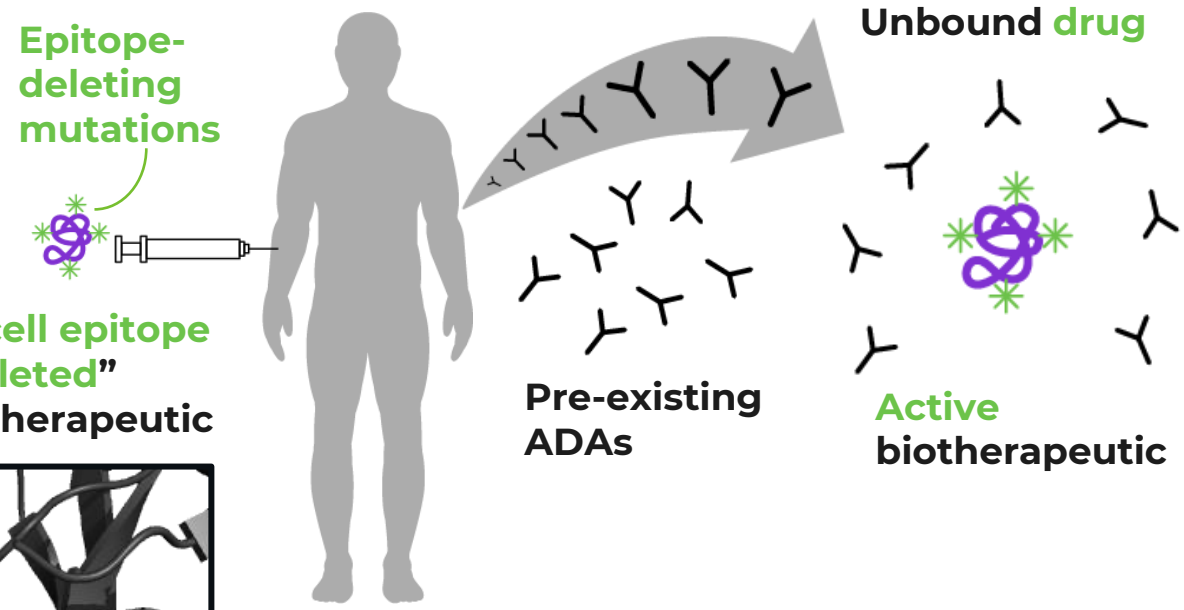
Pre-existing ADAs

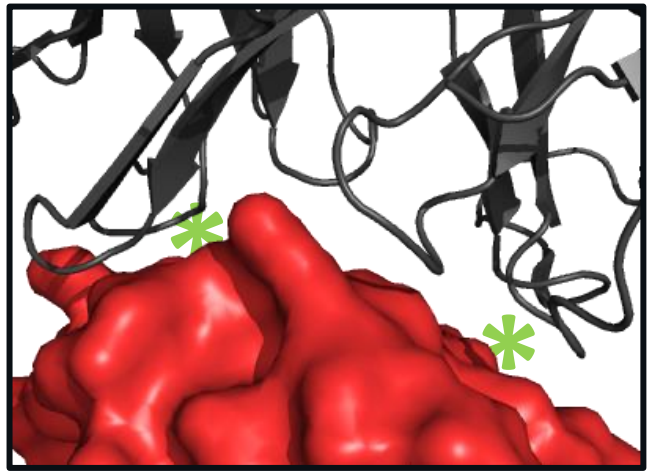
CHALLENGE



B cell Epitope Deletion

POTENTIAL SOLUTION





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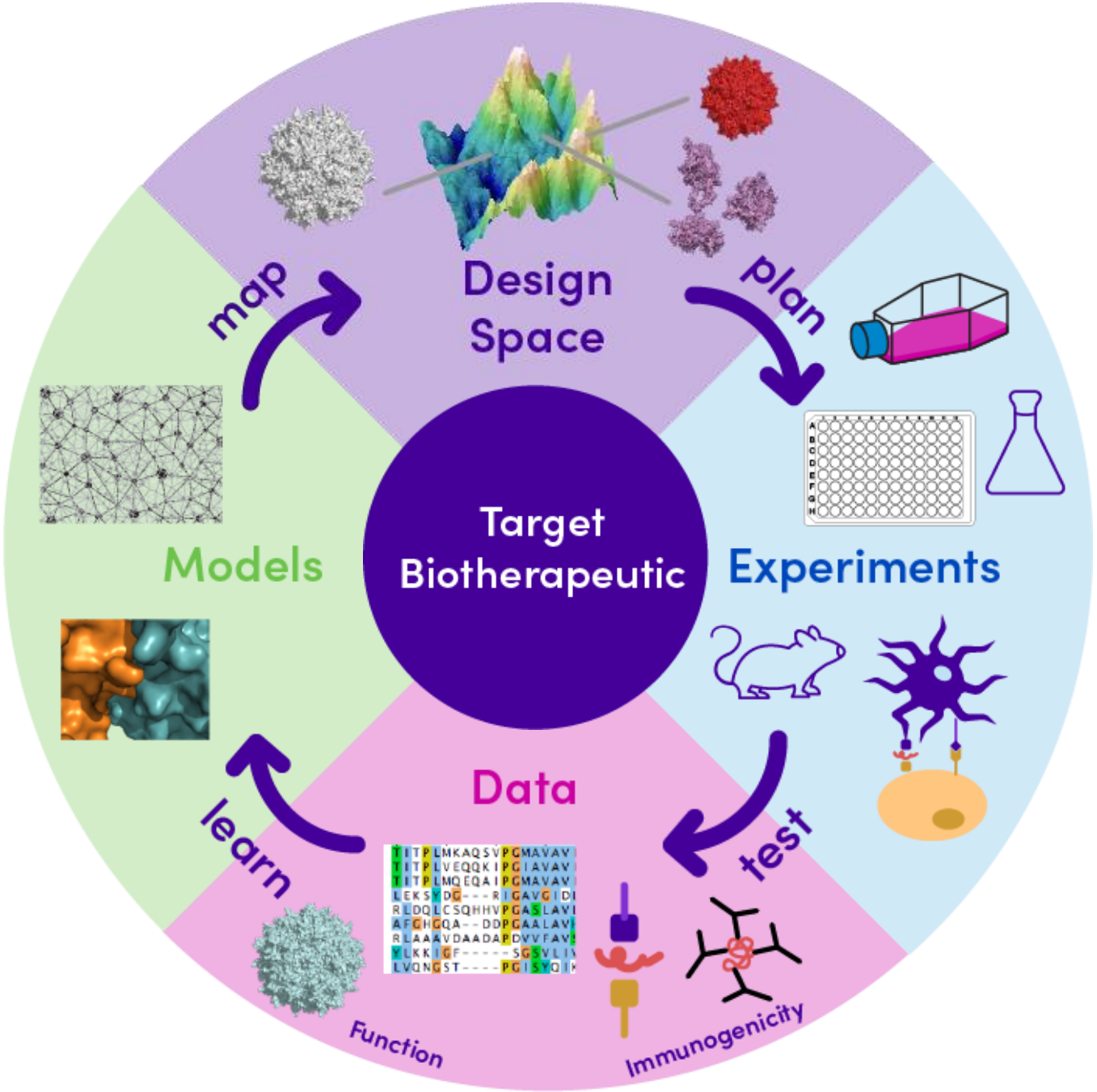
(Abbreviations: ADA-antidrug antibodies)

Deimmunized by Design®

An AI-driven protein engineering platform designed to enable **functional deimmunization** of therapeutic proteins

- **Machine learning** methods **learn models** from prior **data** regarding protein **function** and **immunogenicity**
- **AI methods map** the complex **design space** of protein variants, balancing **function** and **immunogenicity**
- **AI methods plan experiments** to explore and exploit the mapped design space
- **Experiments test** variant **function** and **immunogenicity,** and the **data** drives **iterative improvement** of models and subsequent designs



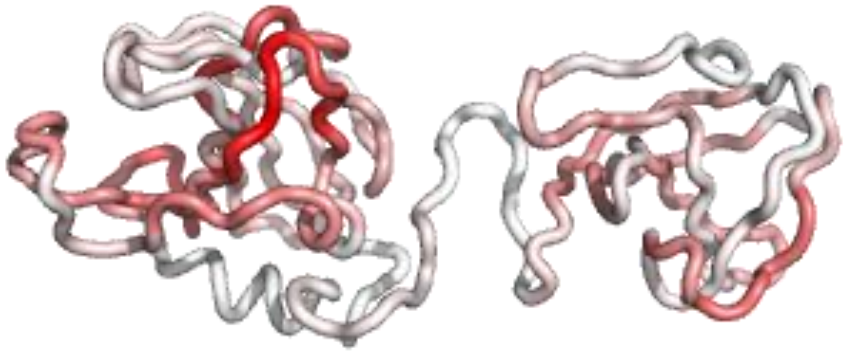
PROOF OF PRINCIPLE:

Deimmunized Lysostaphin for MRSA Infections

Transforming Potent but Immunogenic Biotherapies into High-Performance, Immunologically Stealthy Drugs

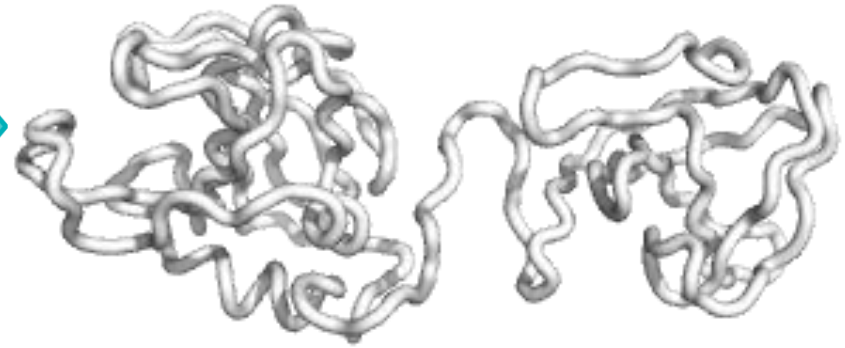
Our proprietary Deimmunized by Design® platform represents a unique technology for engineering safer and more effective biotherapeutic candidates, with relevance to a broad array of indications.

proteases



DbD Platform

next-generation anti-infectives



SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

Globally deimmunized lysostaphin evades human immune surveillance and enables highly efficacious repeat dosing

Hongliang Zhao[1]*, Seth A. Brooks[1]*, Susan Eszterhas[1], Spencer Heim[1], Liang Li[2], Yan Q. Xiong[2], Yongliang Fang[1,3], Jack R. Kirsch[1], Deeptak Verma[4], Chris Bailey-Kellogg[3,4,5], Karl E. Griswold[1,3,5†]

Zhao *et al.*, *Sci. Adv.* 2020; **6** : eabb9011 2 September 2020

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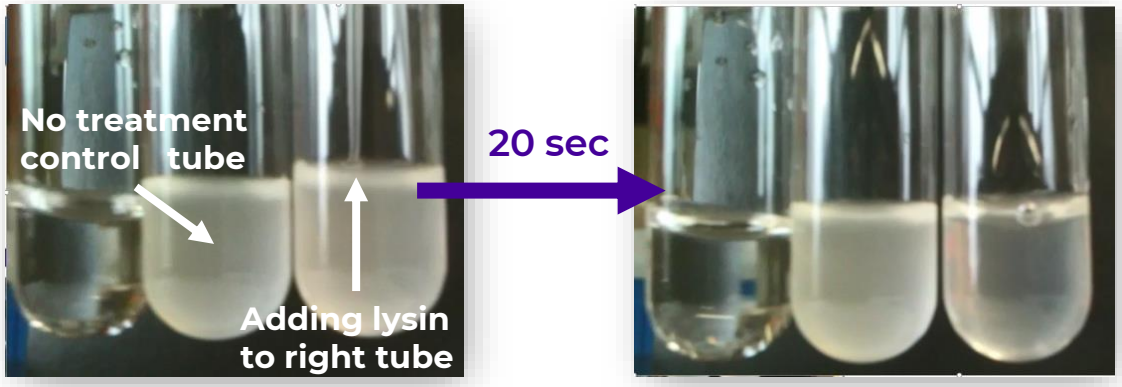
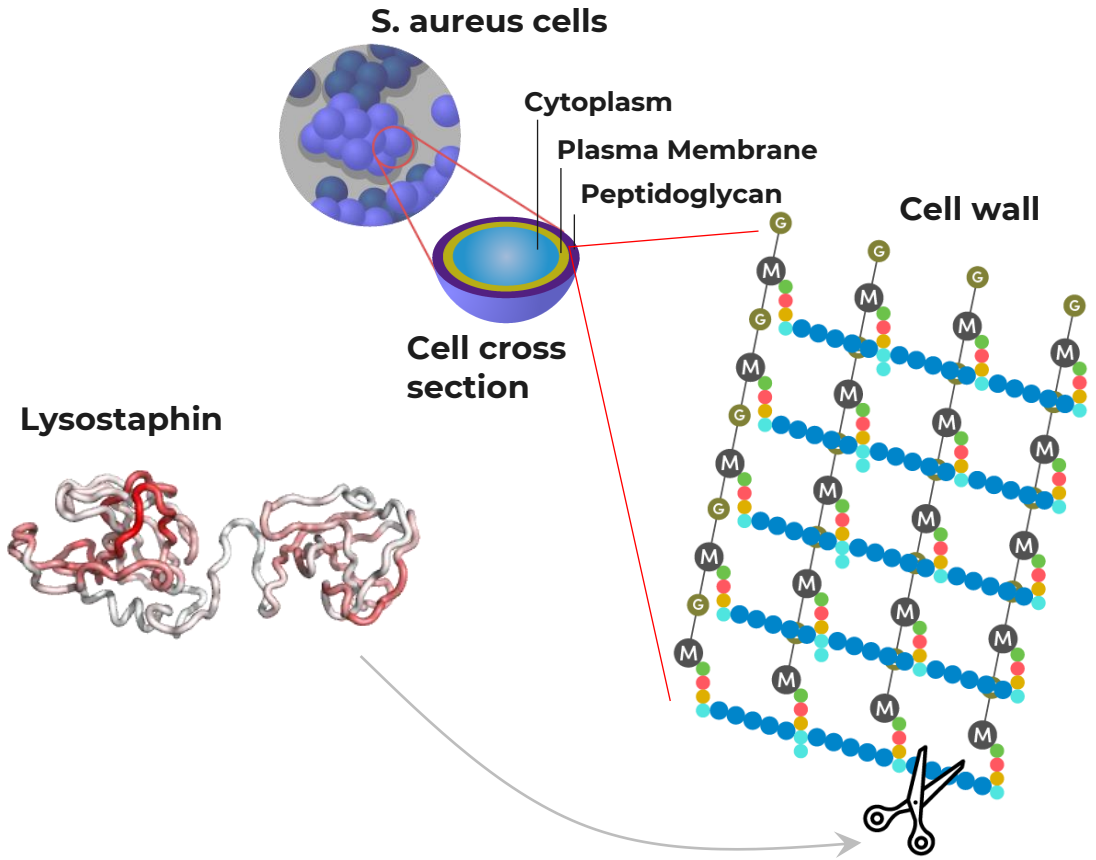
Lysostaphin is a Potent Anti-Staphylococcal Agent, but its Clinical Potential is Limited by Immunogenicity Issues

BACKGROUND

- Rapid onset of action and potent killing of *S. aureus*
- Effective against MSSA, MRSA, VISA, VRSA, LRSA, DRSA
- Synergy with other conventional antibiotics; re-sensitizes MRSA to beta-lactam drugs
- Specific MOA => minimal off-target => spares patient microbiome
- Proven efficacy in clinic, but potential is limited by immunogenicity

Rapid Bacterial Lysis





Lysostaphin hydrolyzes cell wall peptidoglycan resulting in rapid bacterial lysis and death

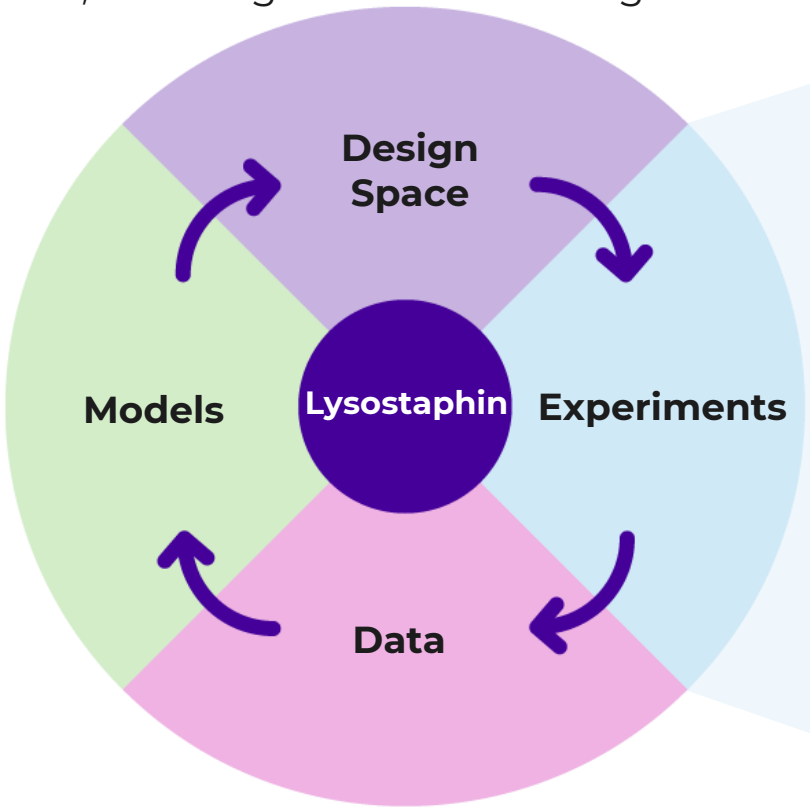
Adapted from: https://lazarillo.info/2018/cell-wall-function-structure-and-importance.tech

MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*; VISA: vancomycin-intermediate *Staphylococcus aureus*; VRSA: vancomycin-resistant *Staphylococcus aureus*; LRSA: linezolid-resistant *Staphylococcus aureus*; DRSA: daptomycin-resistant *Staphylococcus aureus*; SOC: standard of care; MOA: mechanism of action

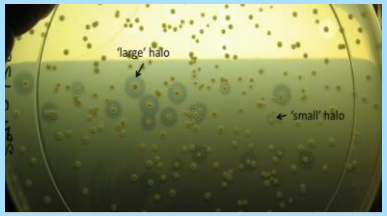
The DbD AI Design Platform has Generated LYT100, a High-Performance, Deimmunized Antibiotic for MRSA

Goal: T cell epitope deletion

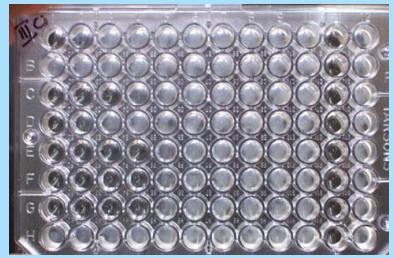
Blunt development of ADAs in naïve subjects, enabling effective redosing



Radial Diffusion Screen

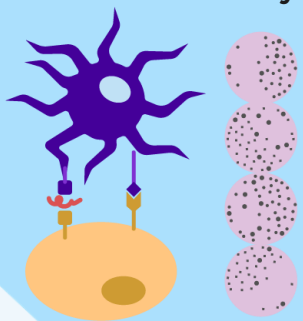


In vitro potency assays



In vivo efficacy & immunogenicity

Ex vivo PBMC Assays



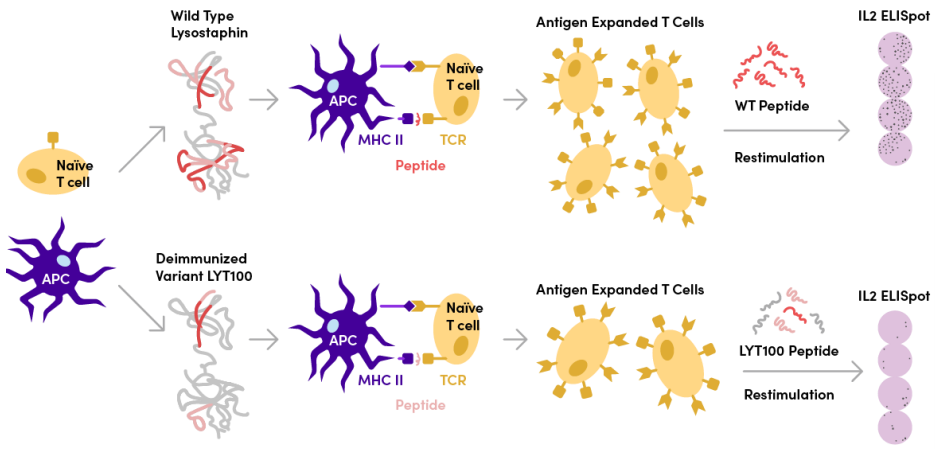
Results

DbD => ↓T cell epitopes => ↓ADAs => ↑redosable efficacy

LYT100 Evades Human T cell Surveillance

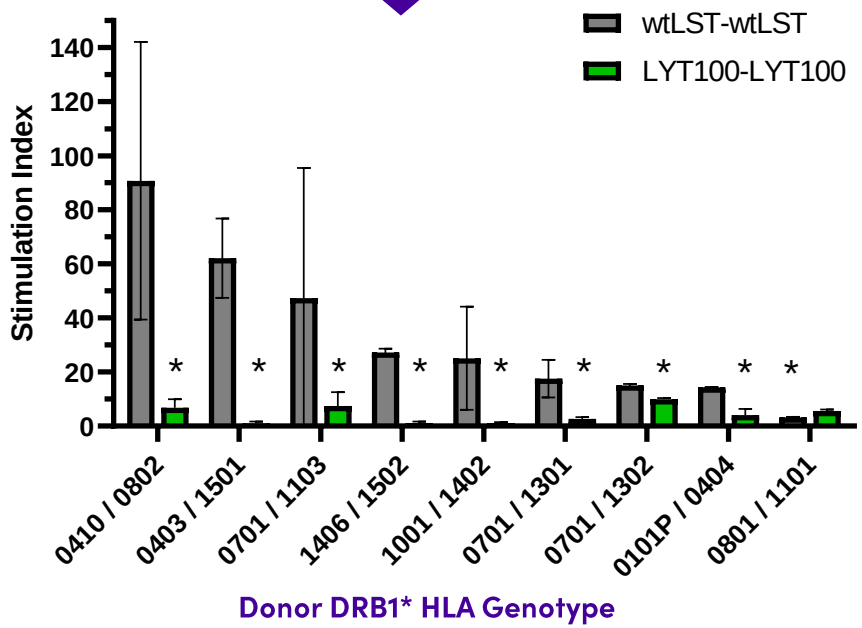
DEIMMUNIZED LYSOSTAPHIN LYT100 SILENCES HUMAN T CELL ACTIVATION

Schematic of the Human PBMC Assay



Human PBMC Assays

Matched Antigen Expansion and Restimulation



(Abbreviations: APC-antigen presenting cell; MHC-major histocompatibility complex; TCR-T cell receptor; wtLST-wild type lysostaphin; LYT100-deimmunized lysostaphin; HLA-human leukocyte antigen, or human MHC II)

Wild type lysostaphin activates immune cells in genetically diverse donors

- Consistent with prior clinical experience

LYT100 evades immune cell activation in a head-to-head comparison using the same donors

- Significant differences by t tests, correcting for multiple comparisons

Note on Interpretation
Higher stimulation index indicates higher immunogenic potential

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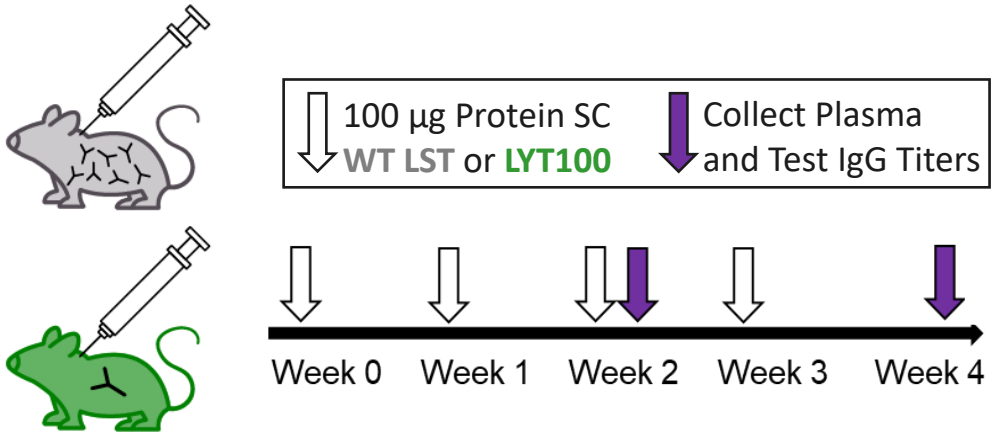
Science Advances (2020) Vol. 6, no. 36, eabb9011

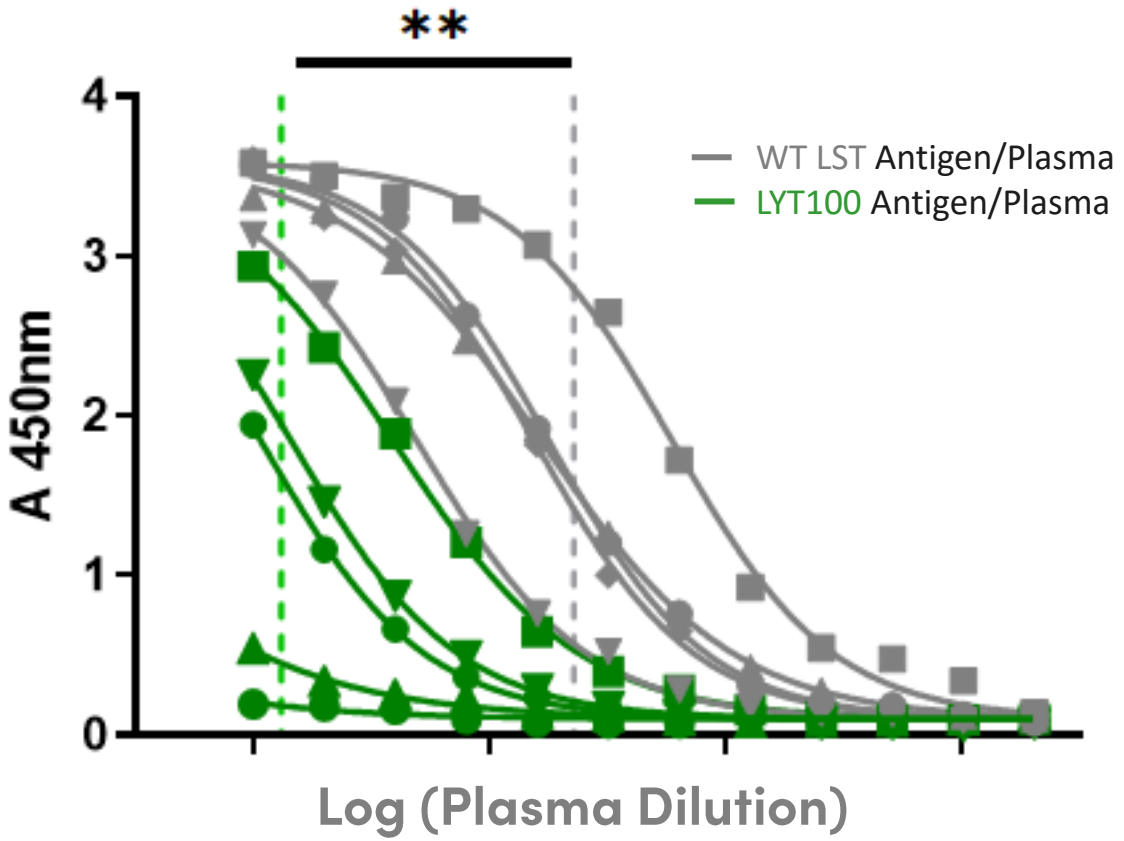
LYT100 Dampens Antidrug Antibody (ADA) Response

DEIMMUNIZED LYSOSTAPHIN LYT100 DAMPENS ANTIDRUG ANTIBODY RESPONSES IN HUMANIZED HLA TRANSGENIC MICE



DR4 mice express human MHC II allele DRB1*0401

DR4 DAY 28 Antidrug Antibody Titers



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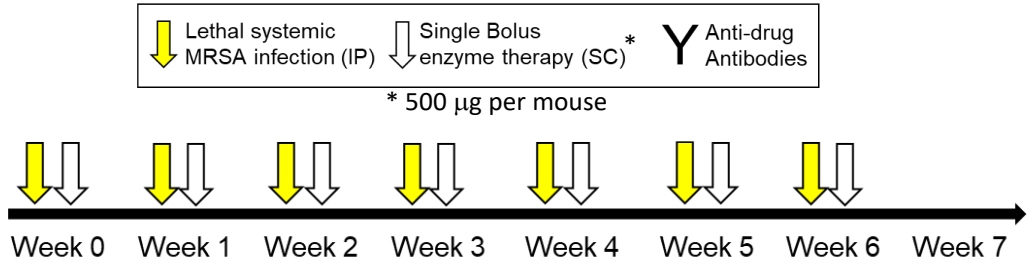
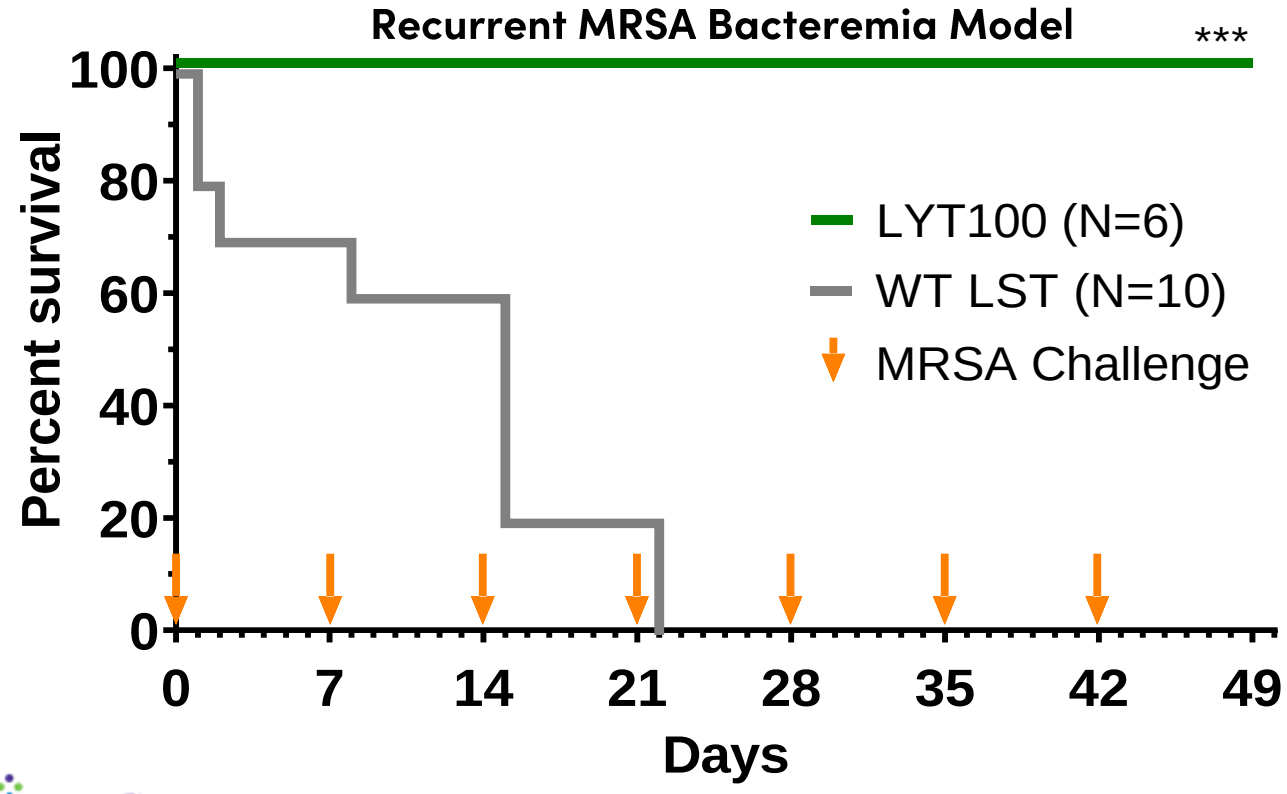
LYT100 Enables Efficacious Repeat Dosing for Recurrent MRSA Infections

Humanized DR4
HLA Transgenic Mice





Deimmunized LYT100 enables highly efficacious repeat dosing in humanized HLA transgenic mice

MRSA: methicillin-resistant *Staphylococcus aureus*

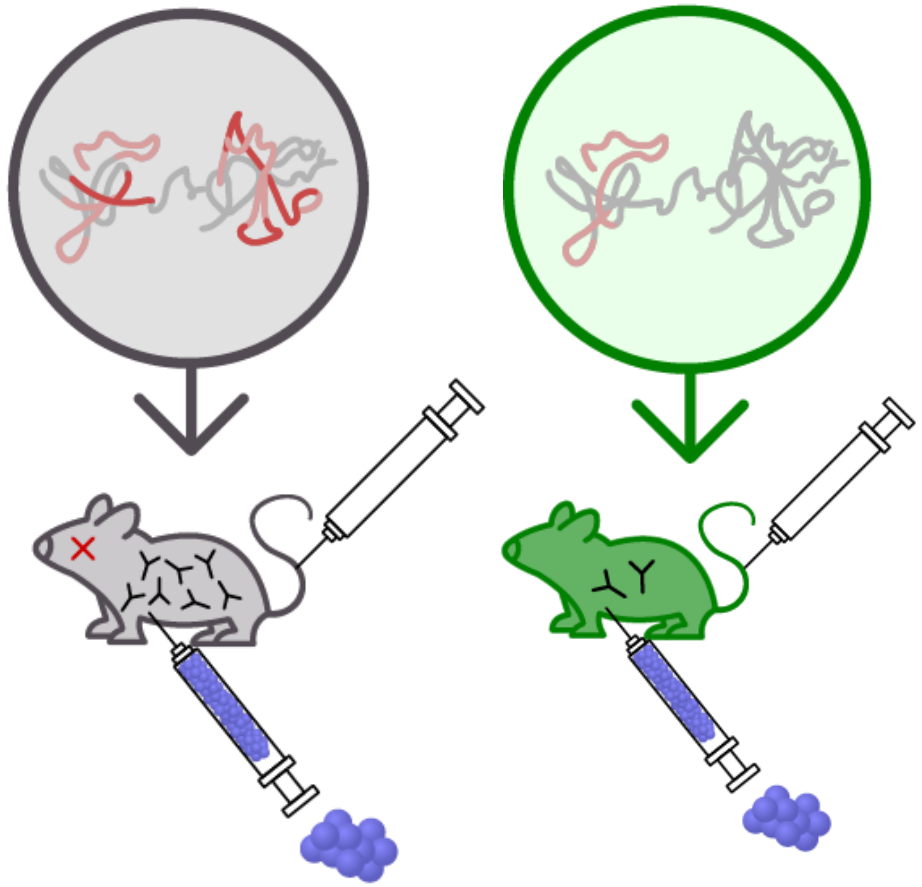
Science Advances (2020) Vol. 6, no. 36, eabb9011

Initial Studies Demonstrated Animal Proof-of-Concept for LYT100

T cell epitopes *can* be depleted while maintaining function

T cell epitope deletion *does* lead to reduced antibody titers

Reduced antibody titers *do* lead to improved efficacy



LYT100 program demonstrated success in deimmunizing lysostaphin as the initial proof of principle for the DbD platform:

- ✓ Reduced immunogenicity
- ✓ Repeat dosing with little to no toxicity
- ✓ Enhanced efficacy against multidrug-resistant *Staphylococcus aureus*

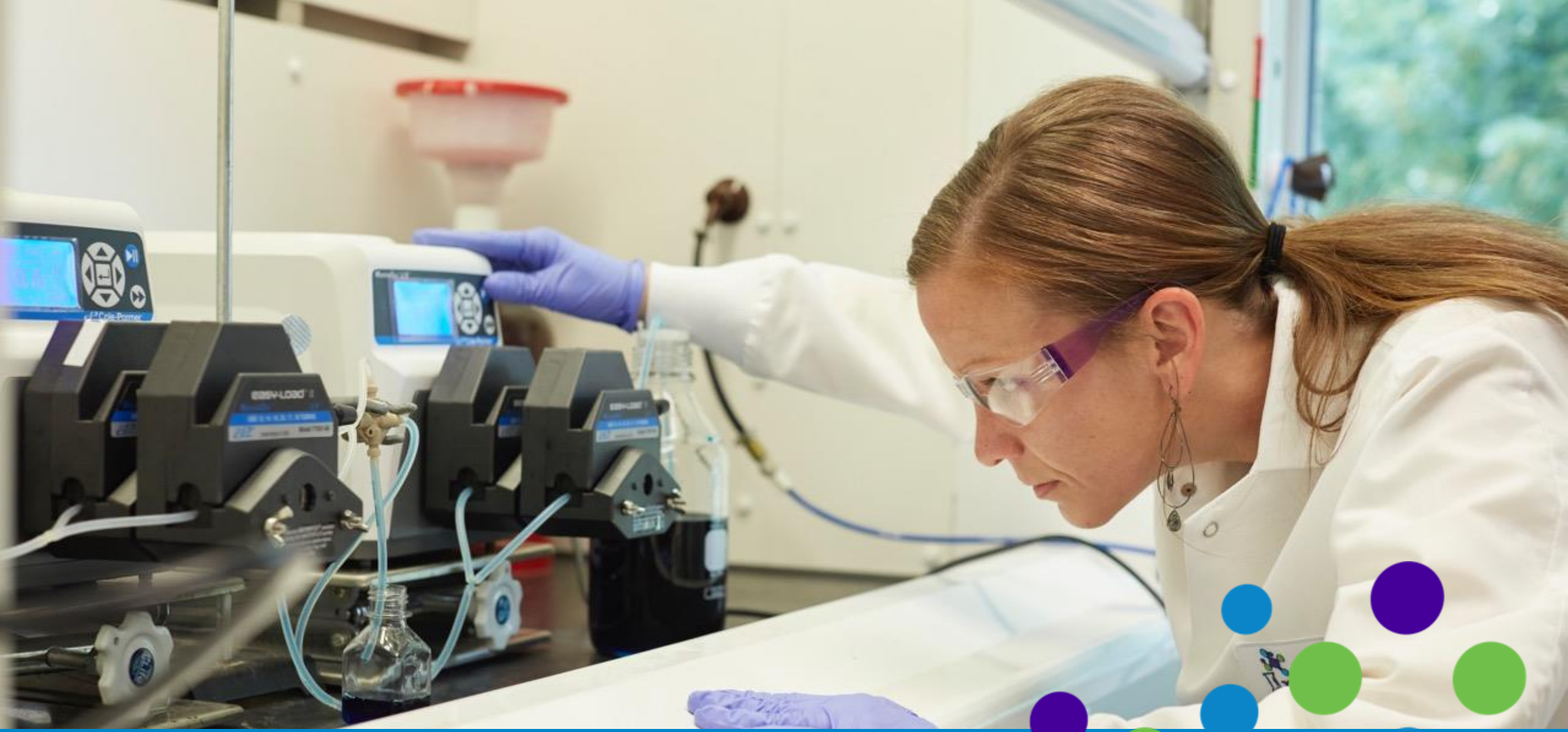
Based on this encouraging data Insmed acquired the Deimmunized by Design® technology and has expanded its application to other high-need indications

Note: Despite promising POC data which validated the platform, clinical development of LYT100 is not actively being pursued due to portfolio prioritization

Further data available in the following LYT100 publications:

1. ***Electrostatic-Mediated Affinity Tuning of Lysostaphin Accelerates Bacterial Lysis Kinetics and Enhances In Vivo Efficacy***. *Zhao H, Eszterhas S, Furlon J, Cheng H, Griswold KE. Antimicrob Agents Chemother. 2021 Mar 18;65(4):e02199-20. PMID: 33468459*

2. ***Deimmunized Lysostaphin Synergizes with Small-Molecule Chemotherapies and Resensitizes Methicillin-Resistant Staphylococcus aureus to β-Lactam Antibiotics***. *Fang Y, Kirsch JR, Li L, Brooks SA, Heim S, Tan C, Eszterhas S, Cheng HD, Zhao H, Xiong YQ, Griswold KE. Antimicrob Agents Chemother. 2021 Feb 17;65(3):e01707-20. PMID: 33318001 .*

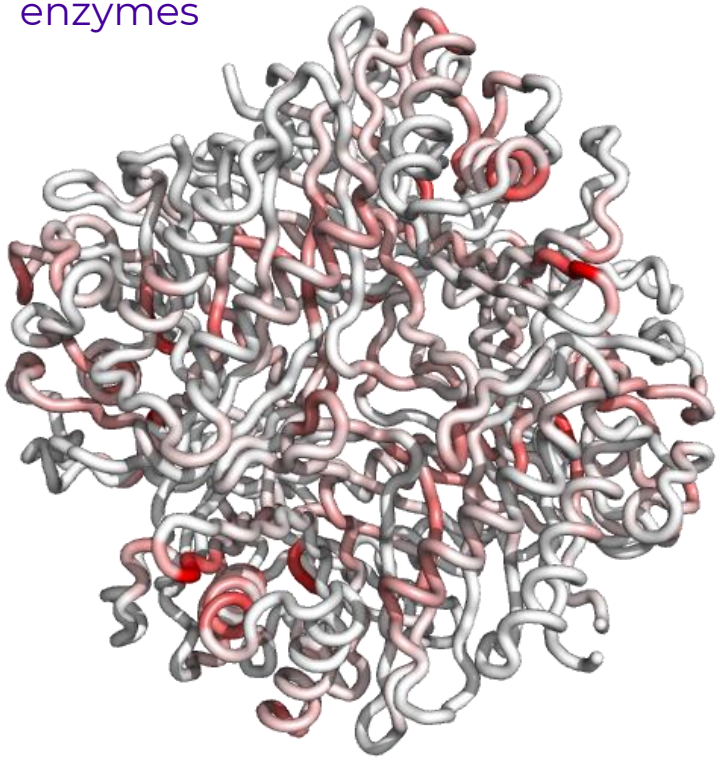


DbD Therapeutic Proteins Example: Uricase

Transforming Potent But Immunogenic Biotherapies into High-Performance, Immunologically Stealthy Drugs

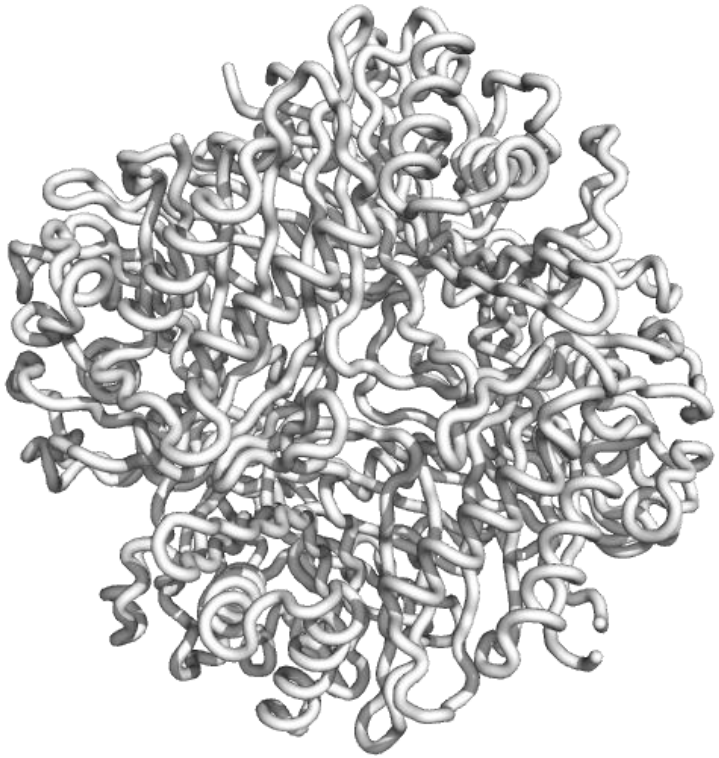
Our proprietary Deimmunized by Design® platform represents a unique technology for engineering safer and more effective biotherapeutic candidates, with relevance to a broad array of indications.

metabolic enzymes



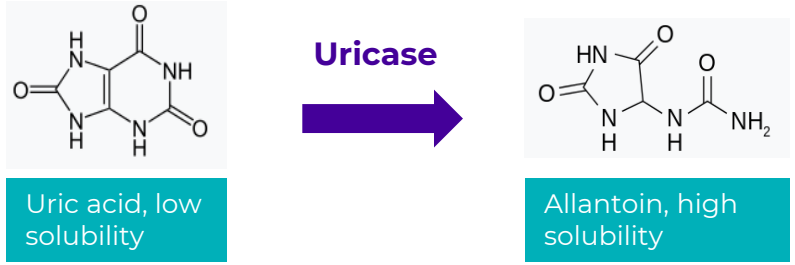
DbD Platform

rheumatology



Pegloticase (a Pegylated Uricase) is an Example of a Marketed Therapeutic Protein Where Immunogenicity Limits its Utility

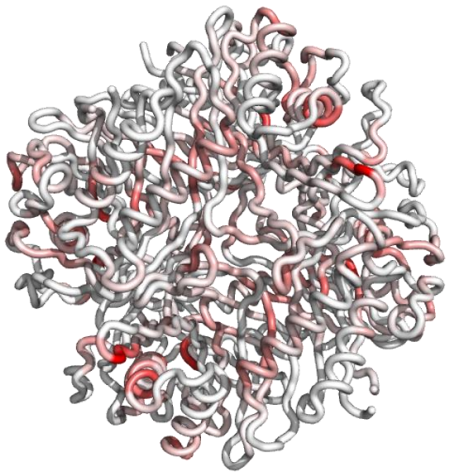
- Perceived as the most effective urate-lowering therapy, especially for tophi resolution
- The only agent specifically indicated for treatment of chronic refractory gout



However…

- ~90% of patients developed ADAs in pivotal trials (41% high-titer)
- ADA titers correlate with loss of efficacy
- Black box warning for anaphylaxis and infusion reactions
- Recent label update codifies pre- and concomitant treatment with methotrexate to improve patient response and reduce infusion reactions
- An alternative approach to suppressing the immune system (employed with a different uricase) does not completely solve for loss of response

There is a key unmet need for novel effective agents with low immunogenicity to treat chronic refractory gout

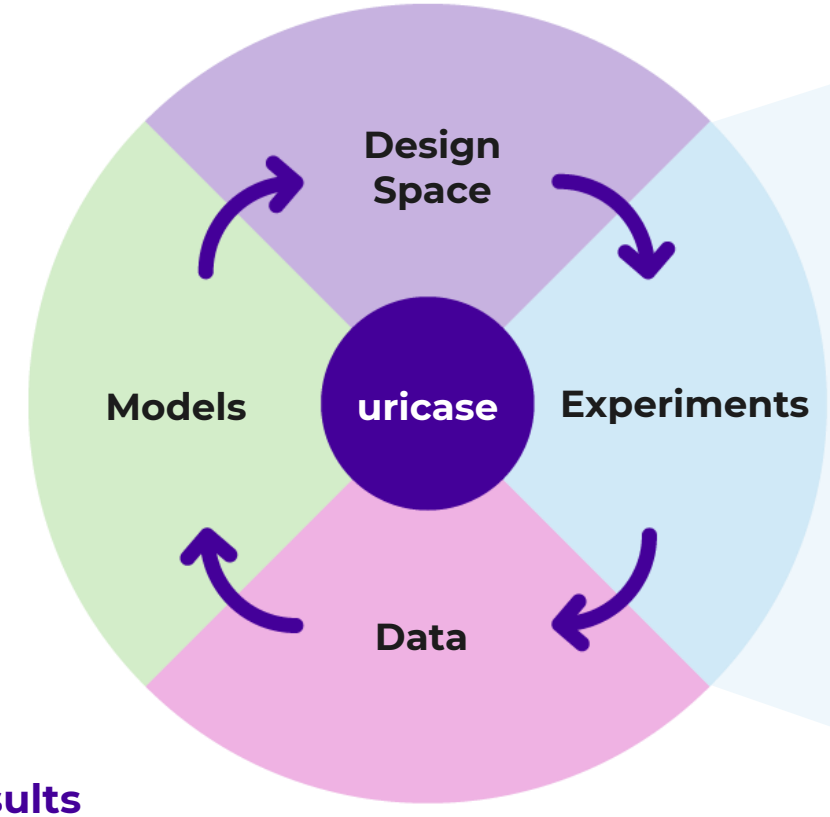


Sources: Schlesinger. Semin Arthritis Rheum. 2020; Nyborg. PLoS One. 2016; Lipsky. Arthritis Res Ther. 2014; Horizon Therapeutics Press Release 3/1/23; Evaluate Pharma; Insmed market research

The DbD AI Design Platform has Generated High-Performance, Deimmunized Uricase Variants for Refractory Gout

Goal: T cell epitope deletion

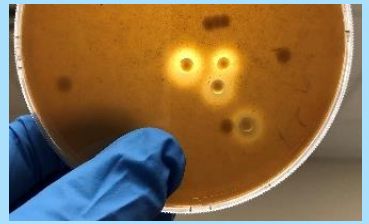
Blunt development of ADAs in naïve subjects, enabling effective redosing



Results

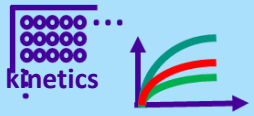
DbD => ↓T cell epitopes and ↑function

Halo Screen

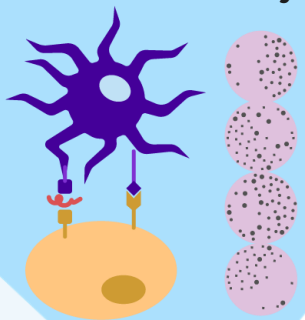


Results from First Round

Colonies screened	~14,000
Selected high activity clones	135
Top candidates identified	4



Ex vivo PBMC Assays



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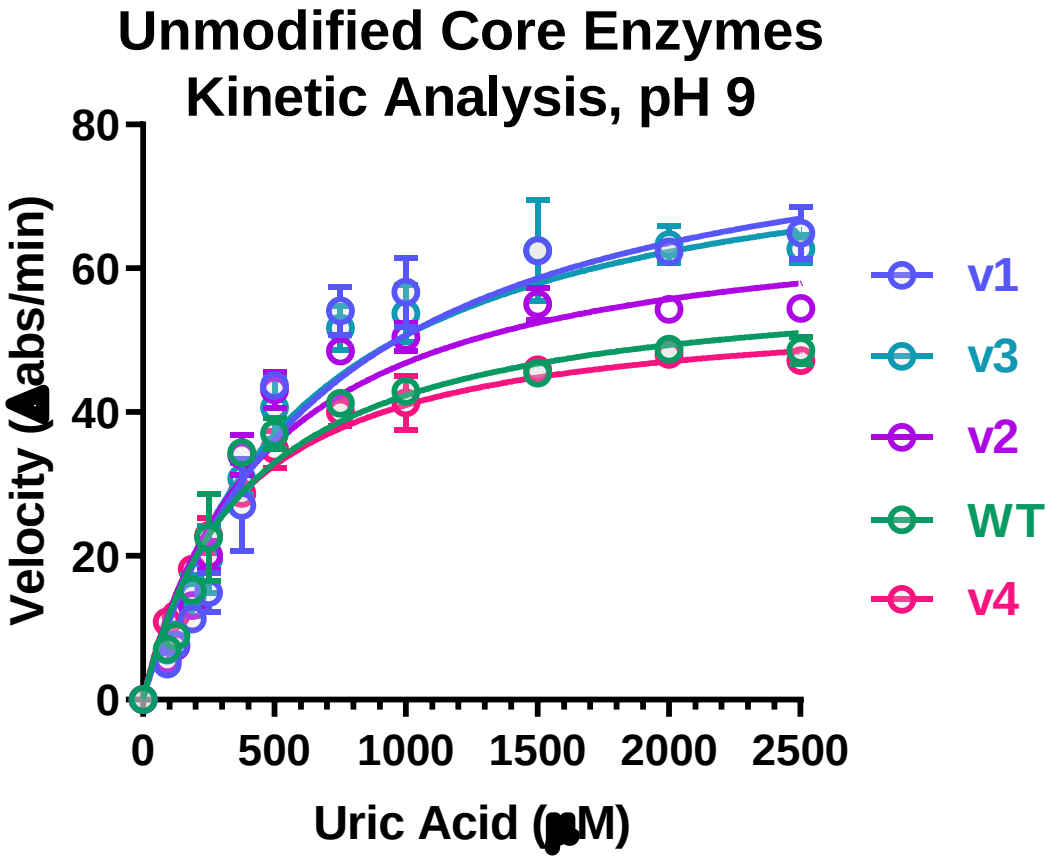
Round 1 Candidates Exhibit Wild Type or Better Activity

FUNCTIONAL ANALYSIS OF FIRST CAMPAIGN DEIMMUNIZED URICASE CANDIDATES



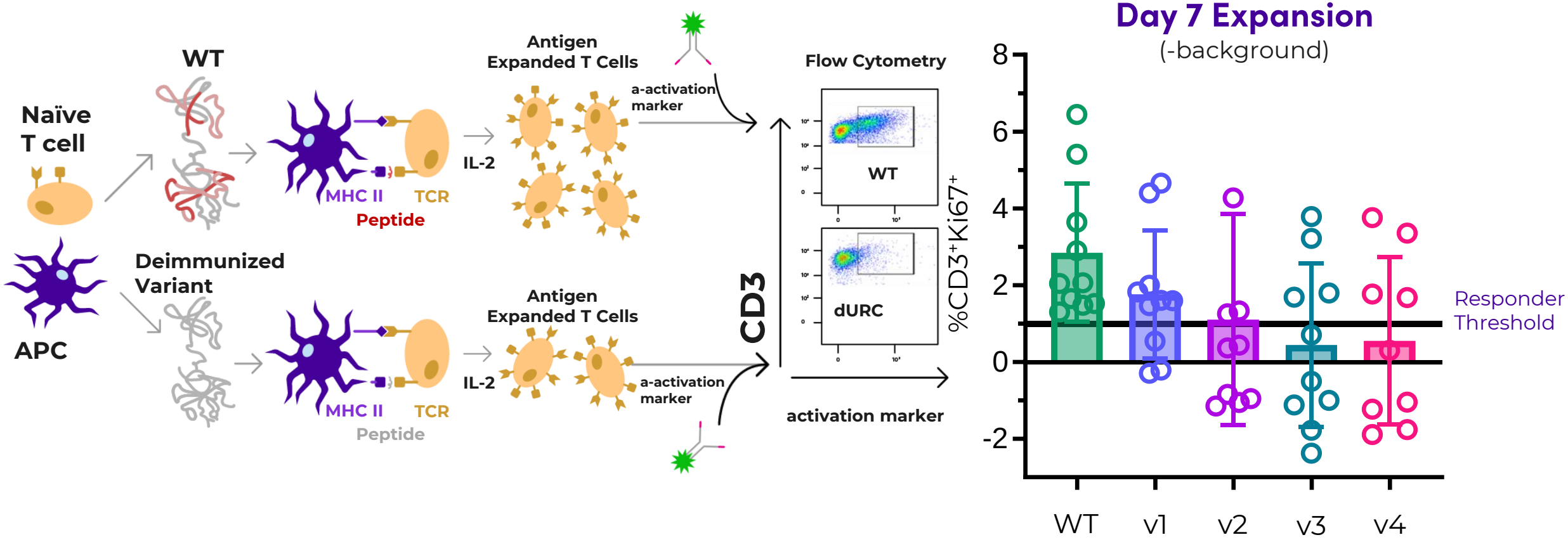
Preliminary Kinetic Parameters

	Reaction Velocity (arbitrary units)	K_M (μM)
v1	43±2	700±100
v3	40±2	600±70
v2	34±1	470±60
WT	30±1	400±50
v4	28.0±0.5	350±20

(Abbreviations: WT-wild type Krystexxa enzyme; v1/v2/v3/v4-deimmunized Krystexxa variants)

Round 1 Candidates Evade Human T Cell Surveillance

PRELIMINARY STUDY WITH A SMALL PANEL OF HEALTHY HUMAN PBMC DONORS



(Abbreviations: WT-wild type uricase enzyme; v1/v2/v3/v4-deimmunized uricase variants; Note: Ki67 is a marker of cell proliferation)

Peer-Reviewed Papers Demonstrate the Breadth of DbD Utility for Engineering Deimmunized Biotherapies

PARTIAL LIST OF TEAM'S PEER-REVIEWED PAPERS ON PROTEIN DEIMMUNIZATION BY T CELL EPITOPE DELETION

1. Salvat…Bailey-Kellogg, Griswold (2015) "*Mapping the Pareto Optimal Design Space for a Functionally Deimmunized Biotherapeutic Candidate*." **PLoS Computational Biology** 11(1): e1003988

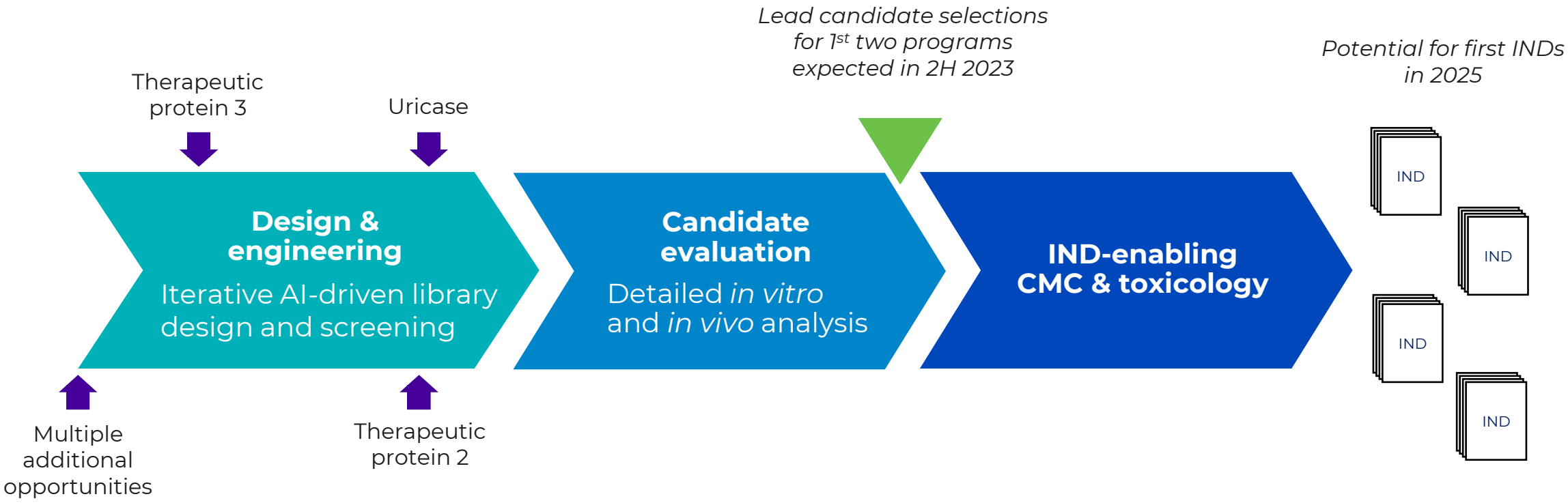
2. Zhao …Bailey-Kellogg, Griswold (2015) "*Depletion of T cell epitopes in lysostaphin mitigates anti-drug antibody response and enhances antibacterial efficacy in vivo*." **Chemistry & Biology**; 22: 629-639

3. Salvat …Bailey-Kellogg, Griswold (2017) "*Computationally optimized deimmunization libraries enable efficient discovery of highly mutated enzymes with low immunogenicity and enhanced activity*." **Proceedings of the National Academy of Sciences USA** 114(26): e5085-e5093

4. Zhao …Bailey-Kellogg, Griswold (2020) "*Globally deimmunized lysostaphin evades human immune surveillance and enables highly efficacious repeat dosing*." **Science Advances** 6(36): eabb9011

5. Fang …Bailey-Kellogg, Griswold (2023) "*Functional Deimmunization of Botulinum Neurotoxin Protease Domain via Computationally Driven Library Design and Ultrahigh-Throughput Screening*." **ACS Synthetic Biology** 12(1):153-163

We are Currently Deimmunizing Three Therapeutic Proteins in Parallel and Have Additional Opportunities in Queue



Deimmunizing AAV Capsids for Gene Therapy

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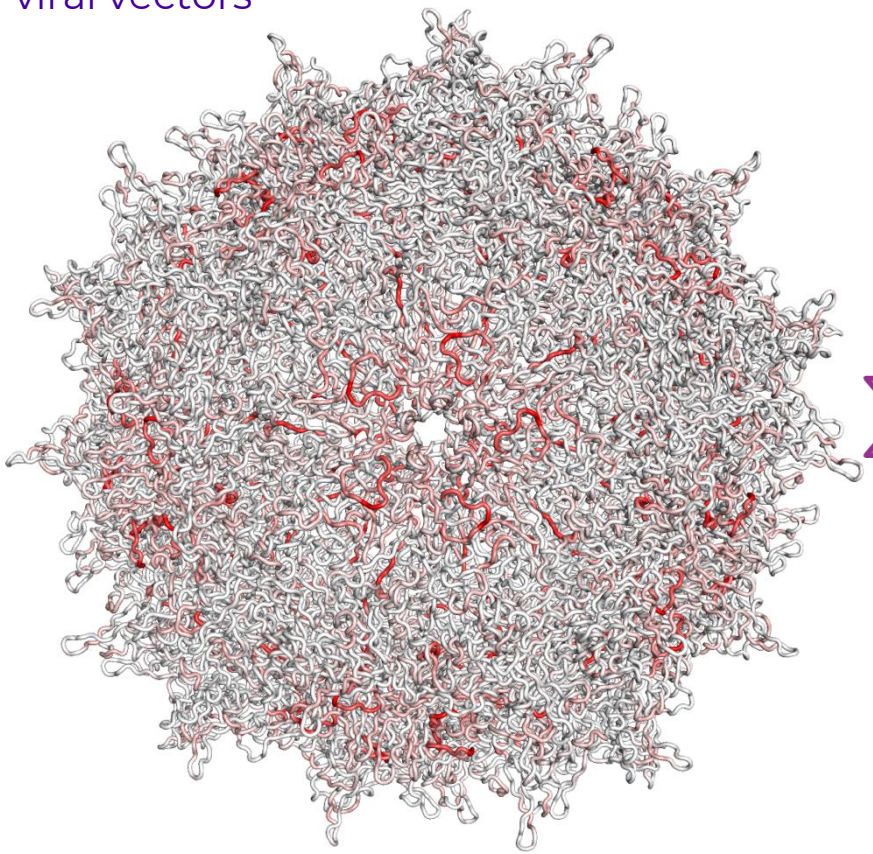
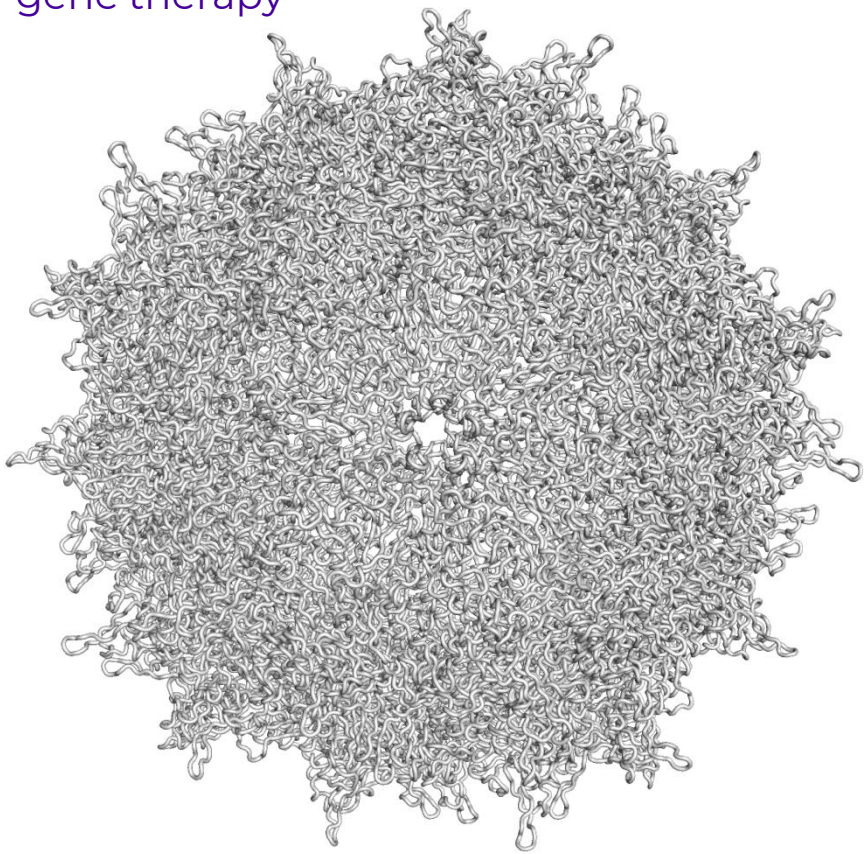
Our proprietary Deimmunized by Design® platform represents a unique technology for engineering safer and more effective biotherapeutic candidates, with relevance to a broad array of indications.

viral vectors



DbD Platform

gene therapy



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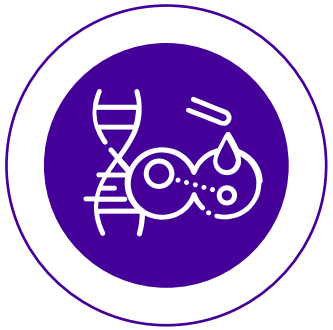
Enabling Redosable AAV Gene Therapy Can Unlock New High Unmet Need Disease Targets for Gene Therapy

Pediatric onset diseases involving organs with high cell turnover

- Transgene loss over time would be expected, leading to waning efficacy
- Redosable gene therapy could provide for continued therapeutic effect

Diseases with on-target toxicity

- On-target toxicity creates risks if transgene expression is too high
- Redosable gene therapy can enable a “dose to effect” paradigm

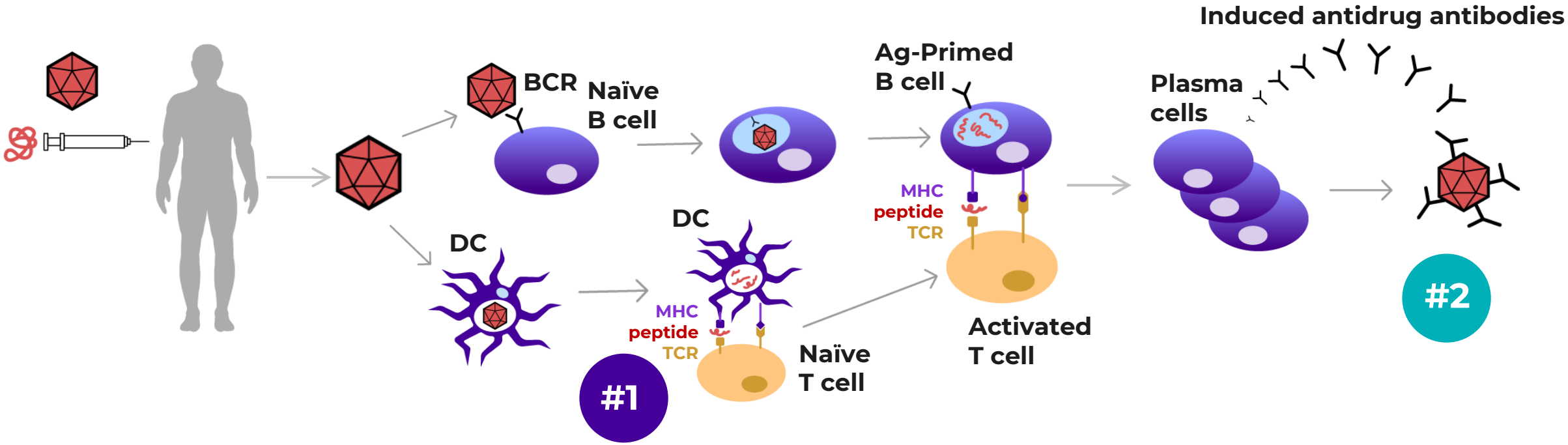


Diseases requiring high doses of transgene

- High doses of currently available AAV capsids entail significant safety risks
- Redosable gene therapy can enable doses to be spread out over time

Next-Gen DbD Viral Capsids for Multi-Dose Gene Therapy

PRIORITIZED ENGINEERING OBJECTIVES



#1 Delete CD4+ T cell epitopes from AAV capsids

Enable repeat dosing of AAV-vectored gene therapies for AAV-naïve patients

#2 Delete B cell epitopes on surface of AAV capsids

Enable AAV-vectored gene therapy for immune experienced patients

- prior natural AAV infection
- prior wild-type AAV gene therapy

… Additional capsid, transgene, and transgene product engineering goals

Improving transduction efficiency, transgene stability, and durability of therapeutic effect

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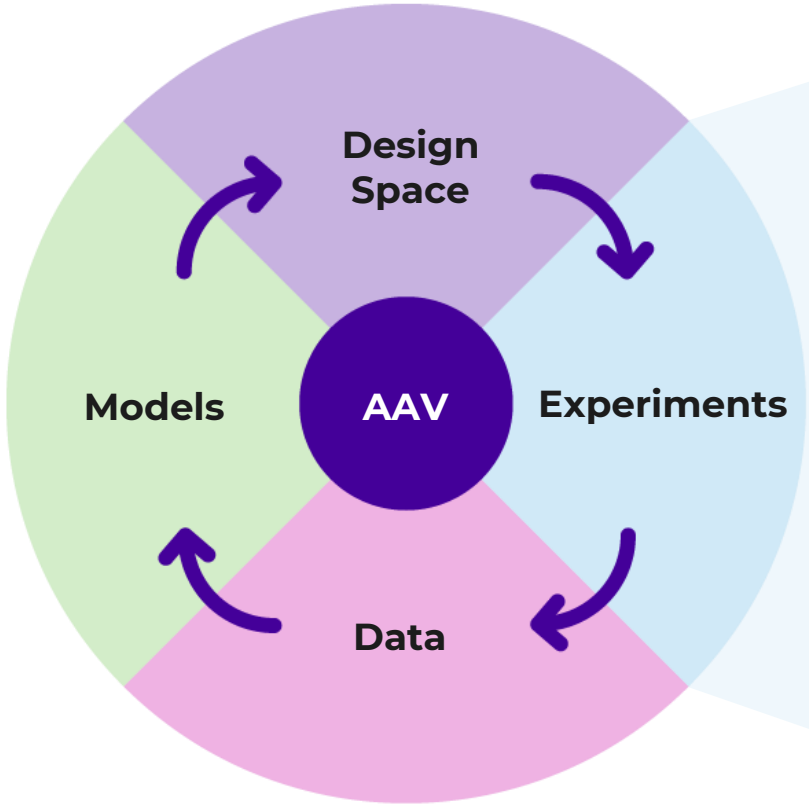
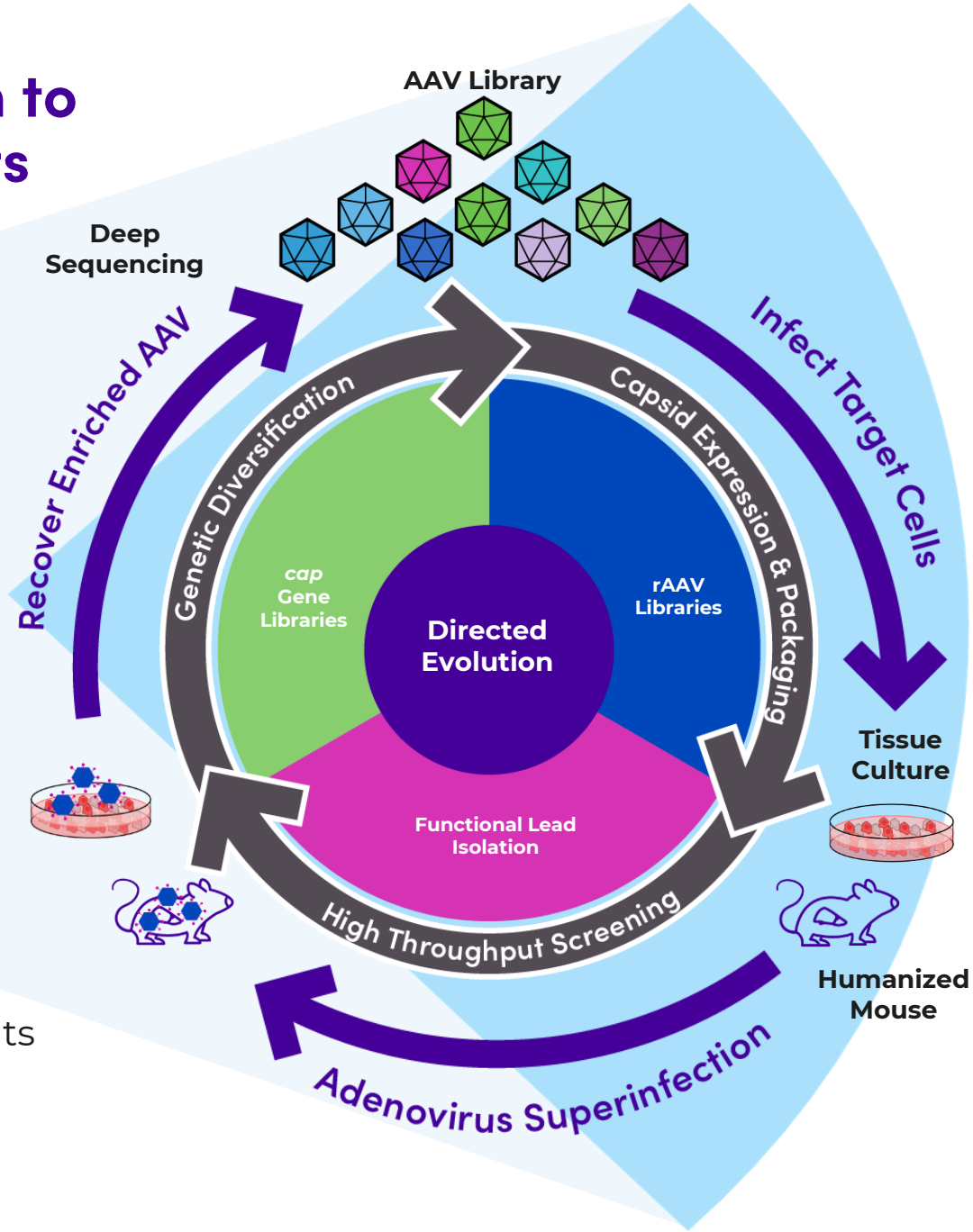
https://pubmed.ncbi.nlm.nih.gov/23596044/

AI-Driven AAV T Cell Epitope Depletion to Enable Repeat Dosing of Naïve Patients

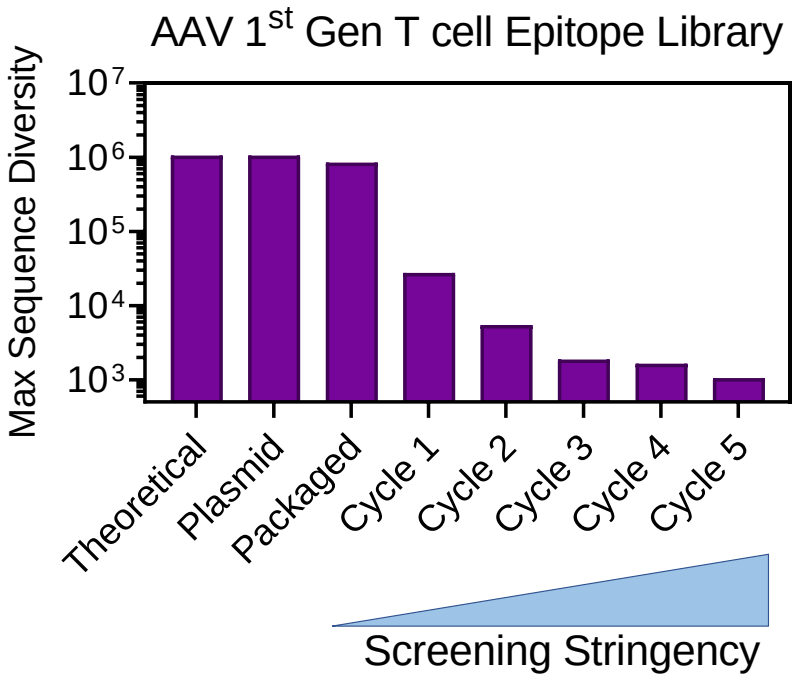




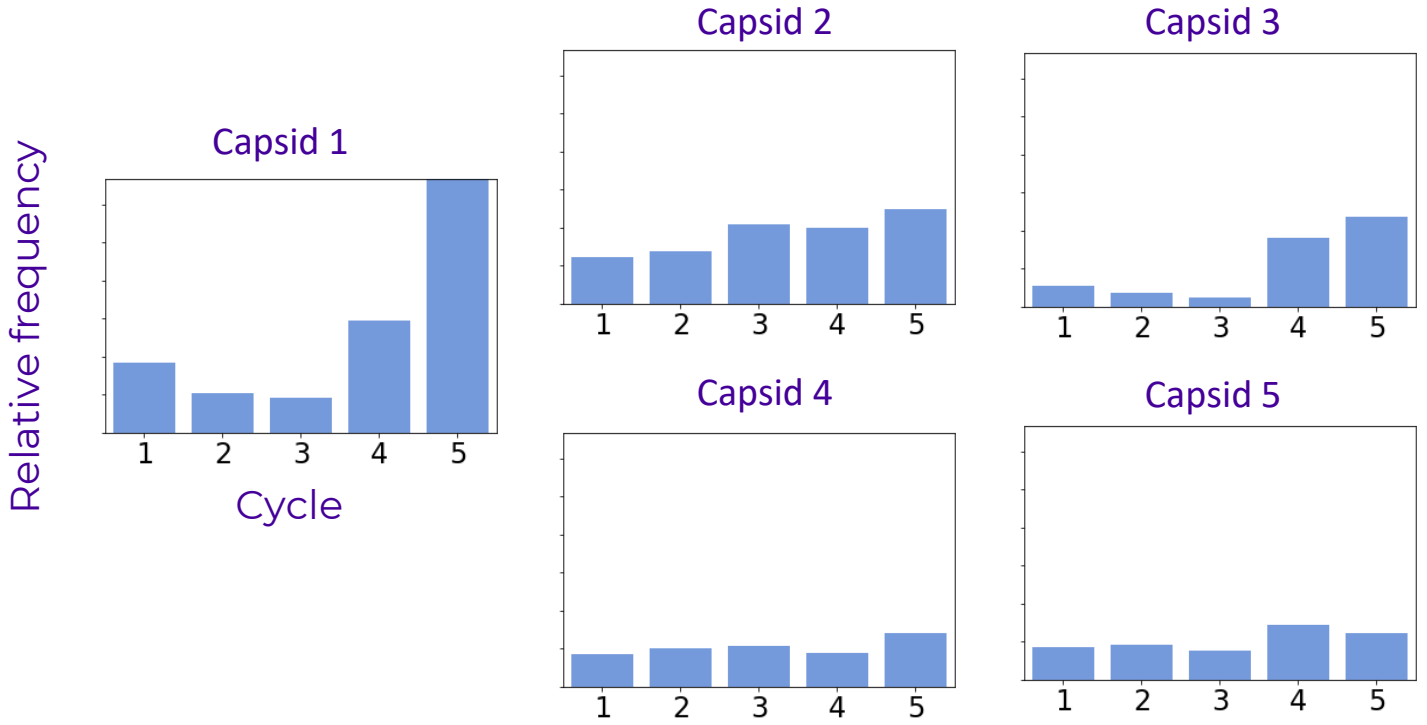
- Each learn-map-design-test *round* employs multiple experimental screening *cycles* to select the fittest variants
- Results shown from first round's experimental cycles

Capsids with Combinations of Deimmunizing Mutations are Functionally Enriched Over Screening Cycles

Population-wide Sequence Diversity



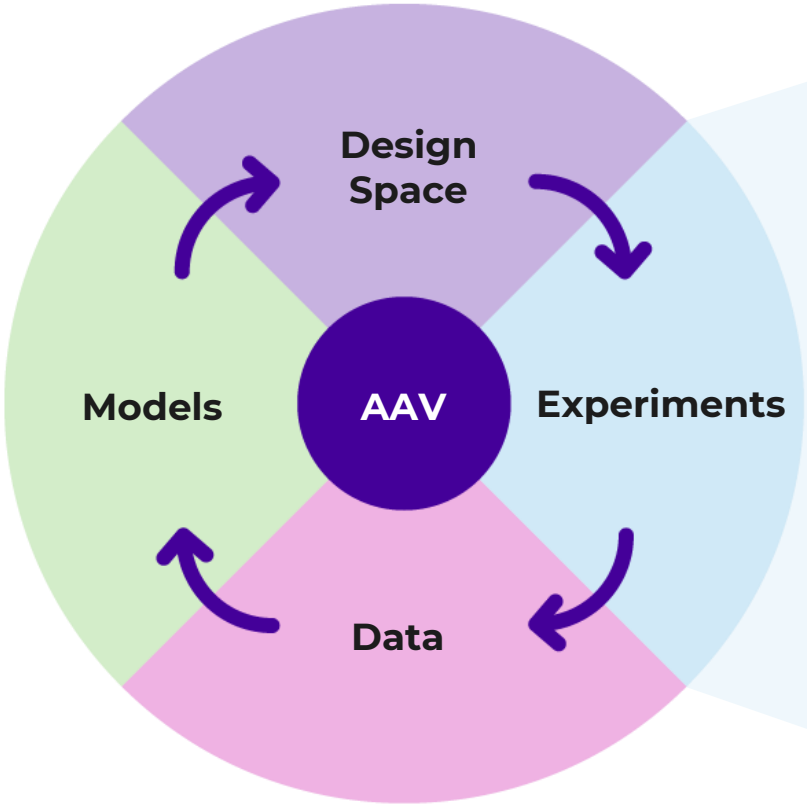
Example capsid fitness profiles

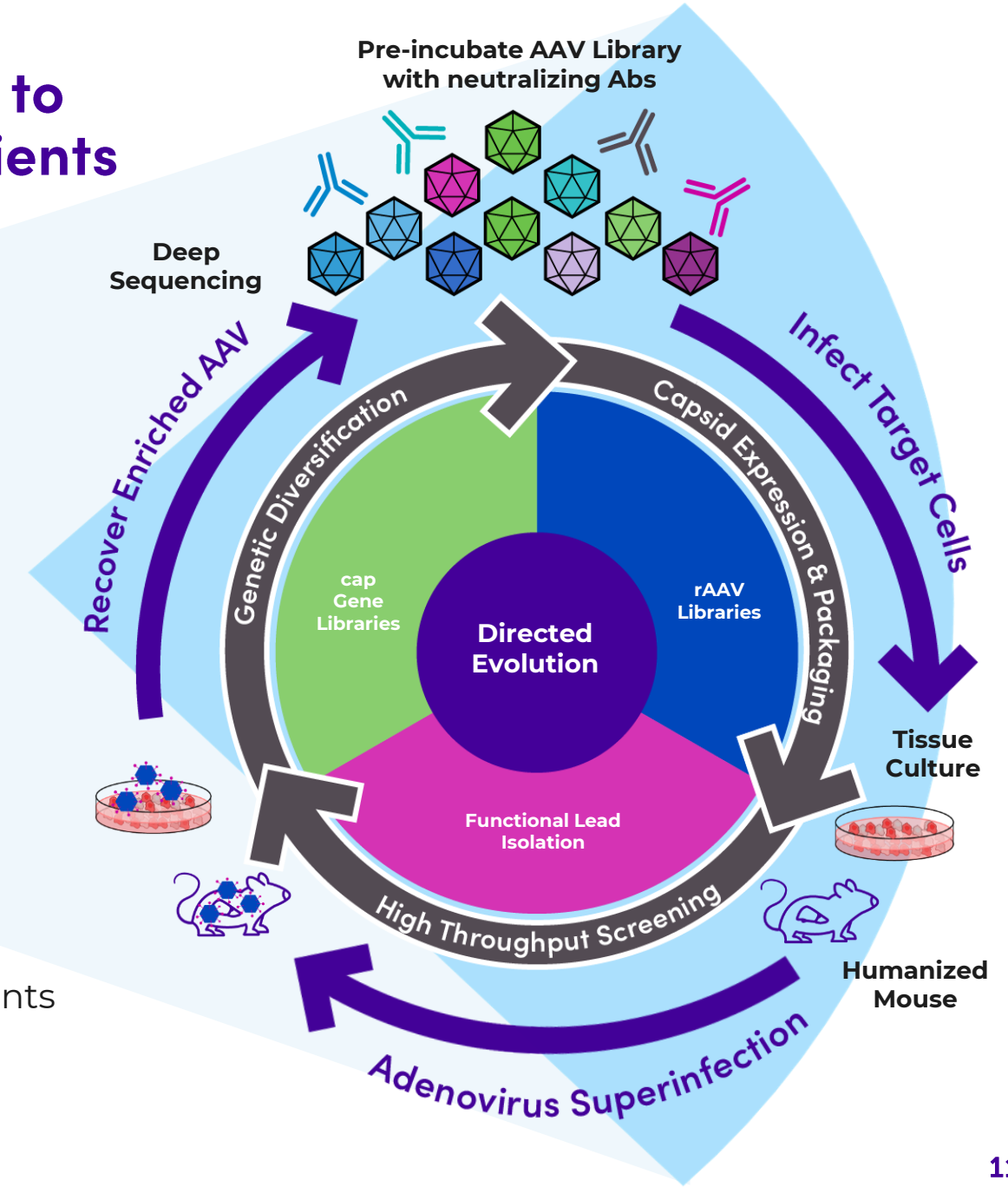


A population of highly functional yet diverse capsids is selected over cycles of screening

Within the functionally enriched population are individual capsids that by design combine deimmunizing mutations

AI-Driven AAV B Cell Epitope Deletion to Enable Treatment of Seropositive Patients

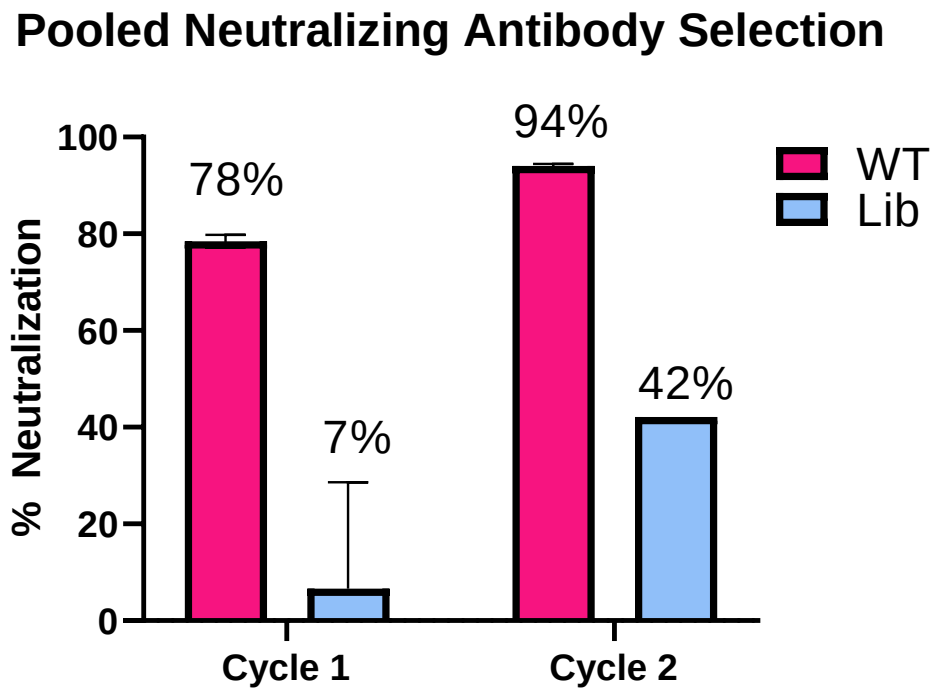




- Each learn-map-design-test *round* employs multiple experimental screening *cycles* to select the fittest variants
- Results shown from first round's experimental cycles

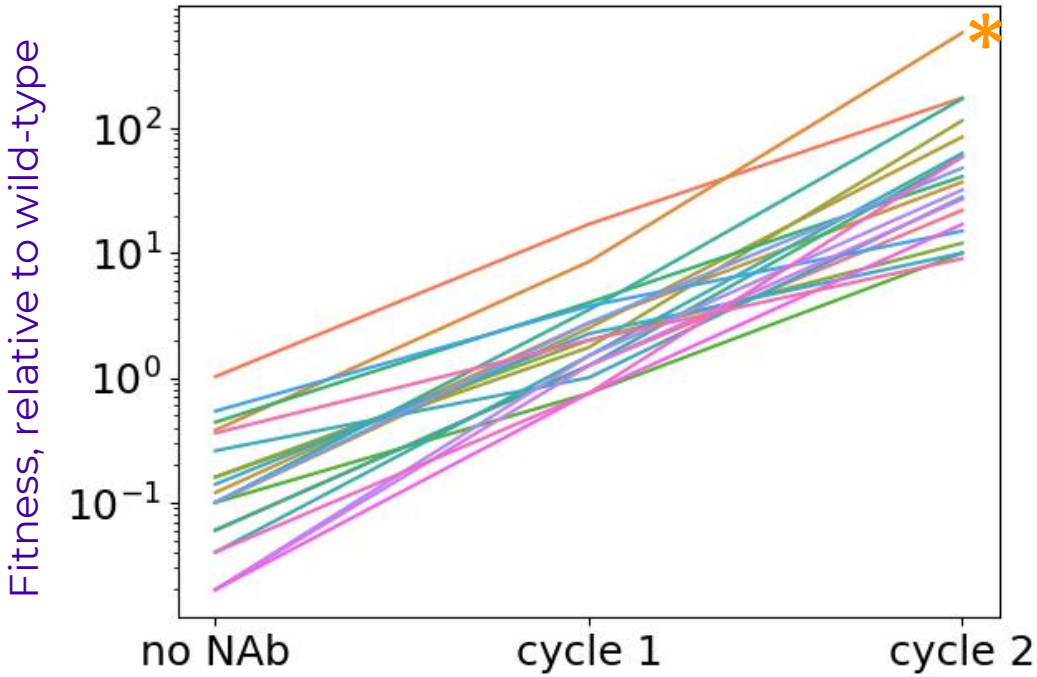
Functional Screening Identifies Highly Fit, Antibody-Evading Capsids

Population fitness analysis



Library population contains large numbers of capsids that evade increasingly stringent NAb selection pressure

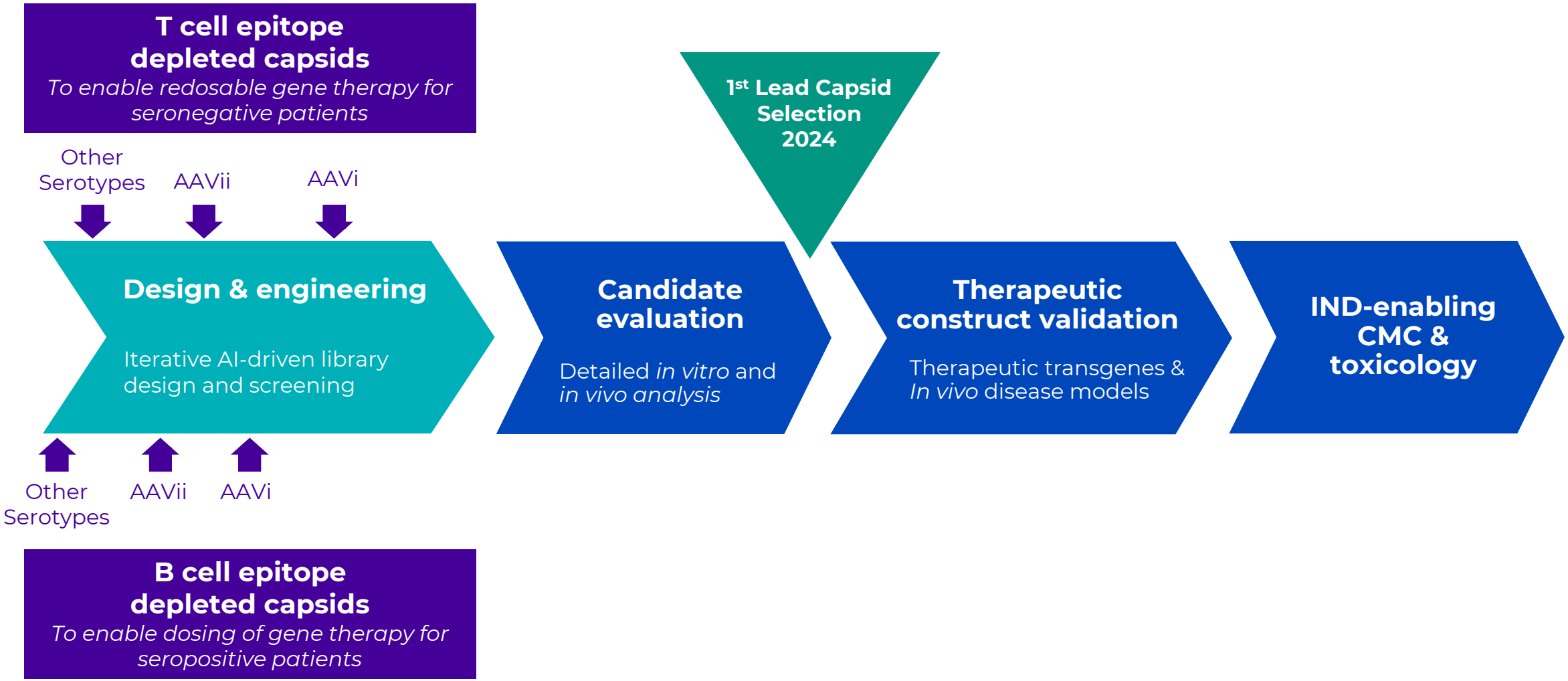
Individual capsid fitness analysis



Iterative library selection yields highly-mutated individual capsids with up to 600-fold greater fitness (*) under NAb pressure that neutralizes ~94% of wild-type AAV.

(Abbreviations: Nab-neutralizing antibody; WT-wild-type)

Multiple Staged Programs Aim to Create Redosable AAV Gene Therapies for Diverse Indications and Patient Populations



Franziska Leifer, PhD

Director, Biologics Research

Argininosuccinic Aciduria is Ideally Suited to Demonstrate the Expected Benefit of Redosable Gene Therapy

Argininosuccinic Aciduria (ASA)

- 2nd most common urea cycle disorder[1, 2]
- Pediatric onset[3]
- Caused by deficiency of argininosuccinate lyase (ASL)[1]
- High unmet need with recurring metabolic crises and high incidence of cognitive impairment despite SOC[1, 3]
- Part of standard newborn screening in the US[1, 2]

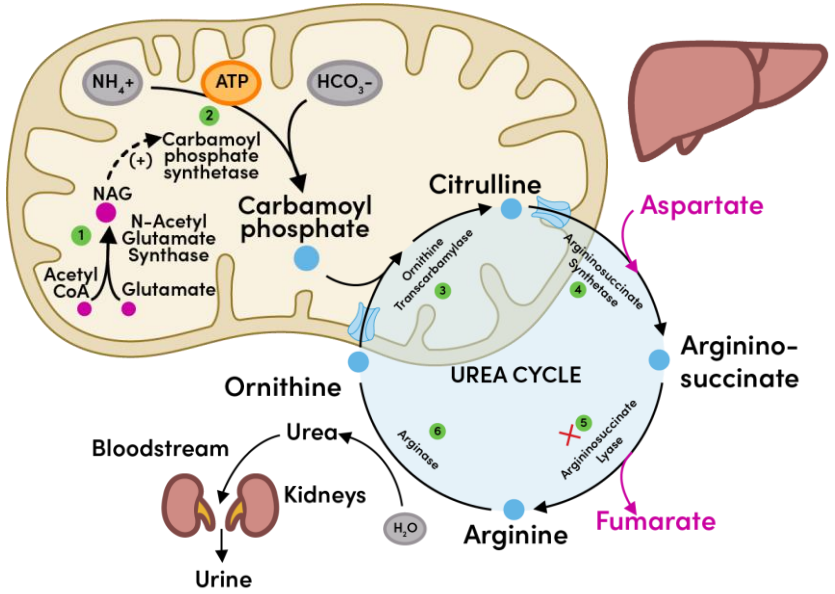


Figure adapted from Molecular Genetics and Metabolism 131 (2020) 289–298

- As AAV capsid reengineering proceeds, we are developing therapeutic transgene constructs for target diseases to streamline later development
- Our hASL therapeutic transgene construct shows strong efficacy in a mouse model of argininosuccinic aciduria

[1]J Inherit Metab Dis. 2019;42:1147–1161.
[2]Genetics in Medicine. 2012; 14:501-507
[3]Molecular Genetics and Metabolism 98 (2009) 273–277

“ASA Mice” Recapitulate Human Disease

ASA mouse WT

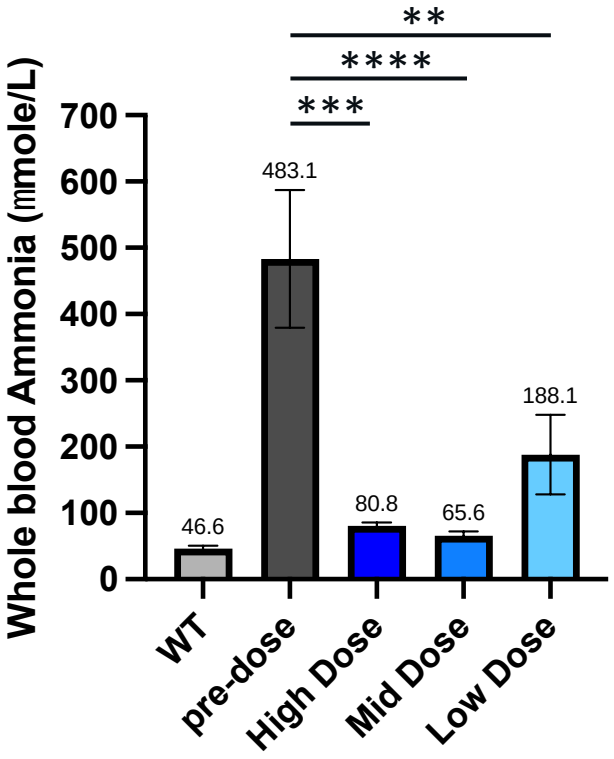
18 days old

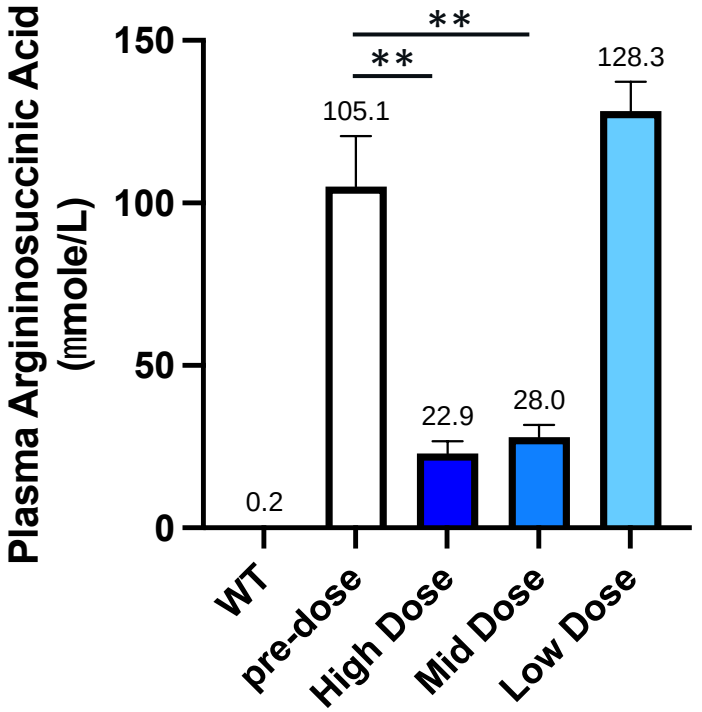
- 15% residual argininosuccinate lyase (ASL) activity[1]
- Hyperammonemia[1]
- Elevation of urea cycle intermediates argininosuccinic acid and citrulline[1]
- Abnormal hair patterning[1]
- Severely stunted growth[1]
- Dramatically shortened life span[1]

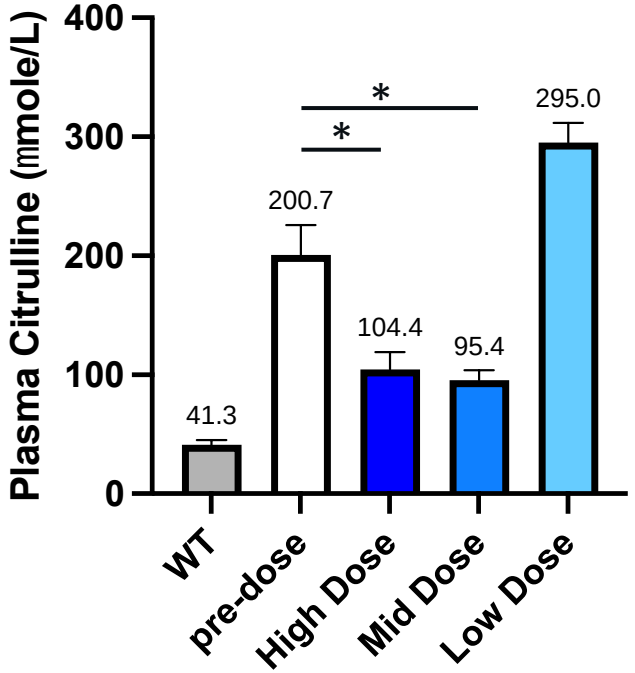
ASA mice = B6.129S7-*Asl*^{tm1Brle}/J, ASL $^{neo/neo}$

[1]Erez et al. 2011. Nature Med. Vol 17:12

ASA AAV GTx Nearly Normalizes Metabolic Parameters of ASA Mice







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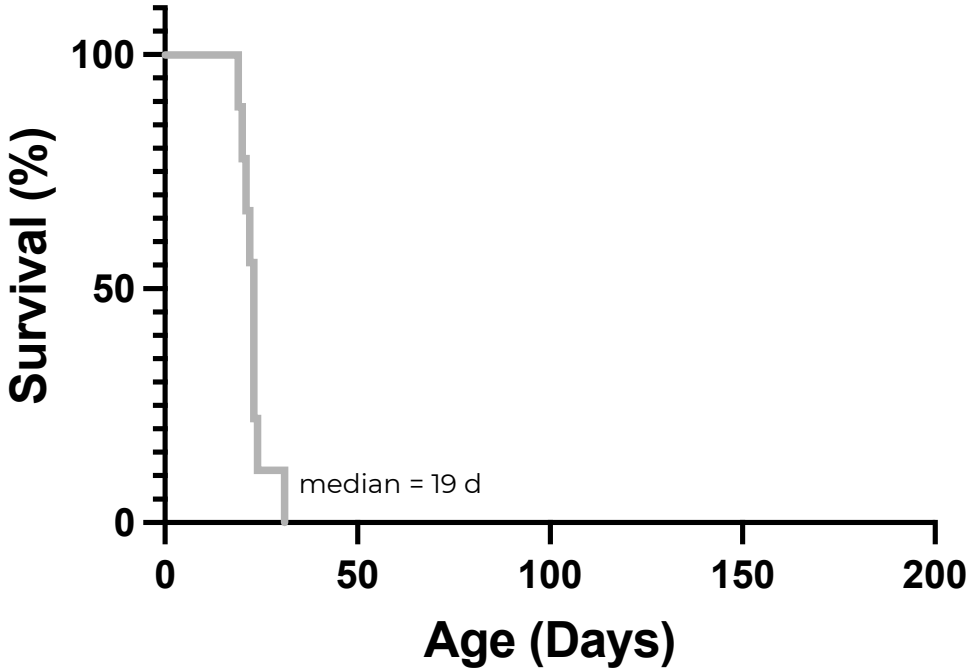
ASA AAV GTx Results in Strong Survival and Growth Benefit in ASA Mice



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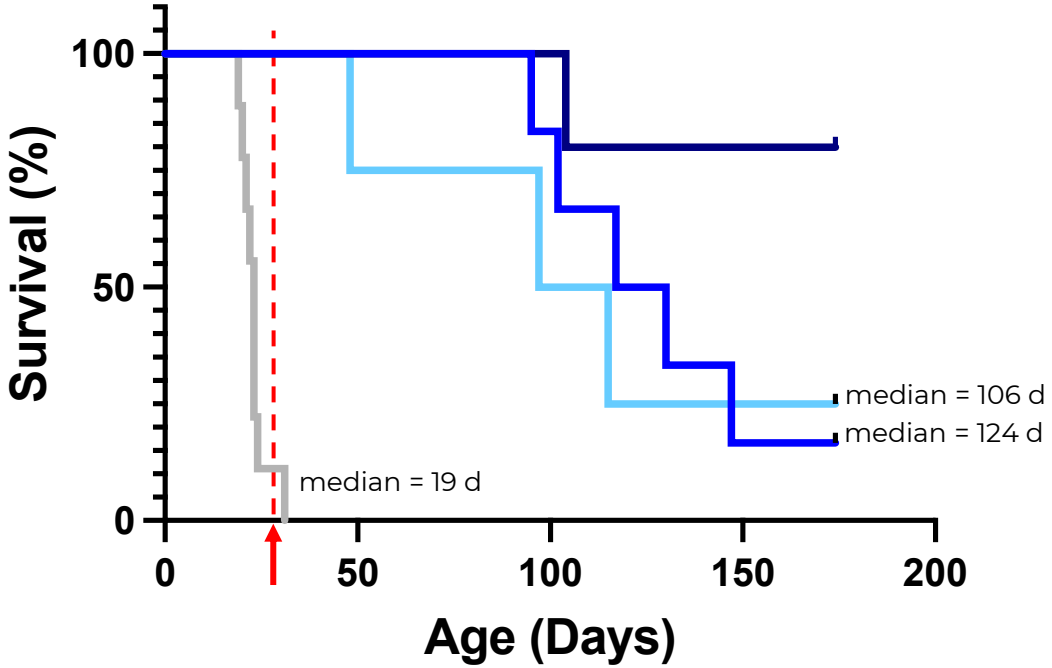
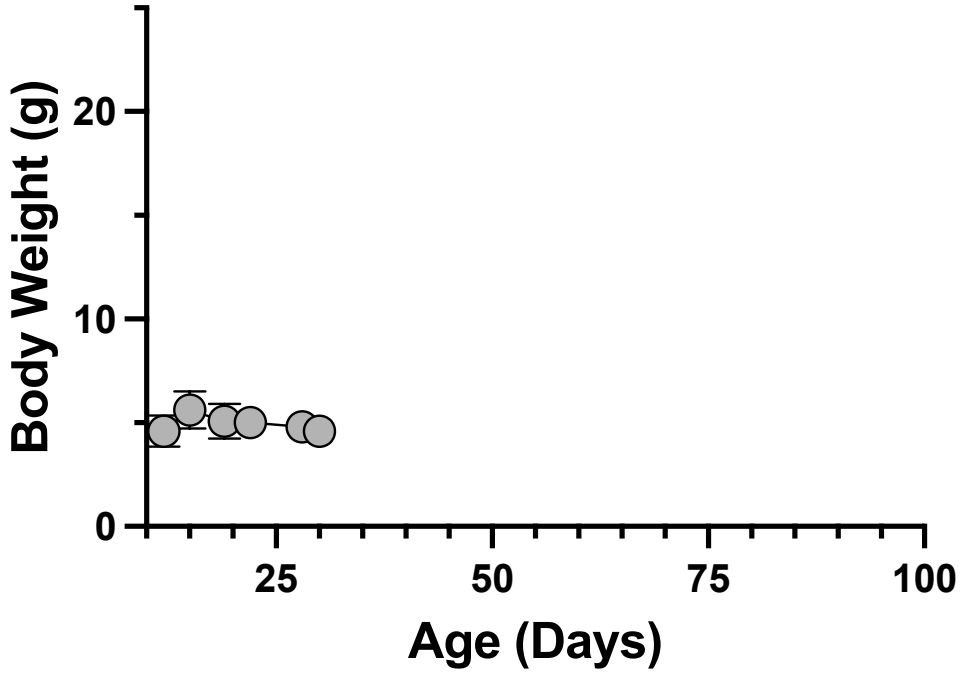




High Dose (1e14 vg/kg, 7e11 vg/mouse)

Mid Dose (5e13 vg/kg, 3.5e11 vg/mouse)

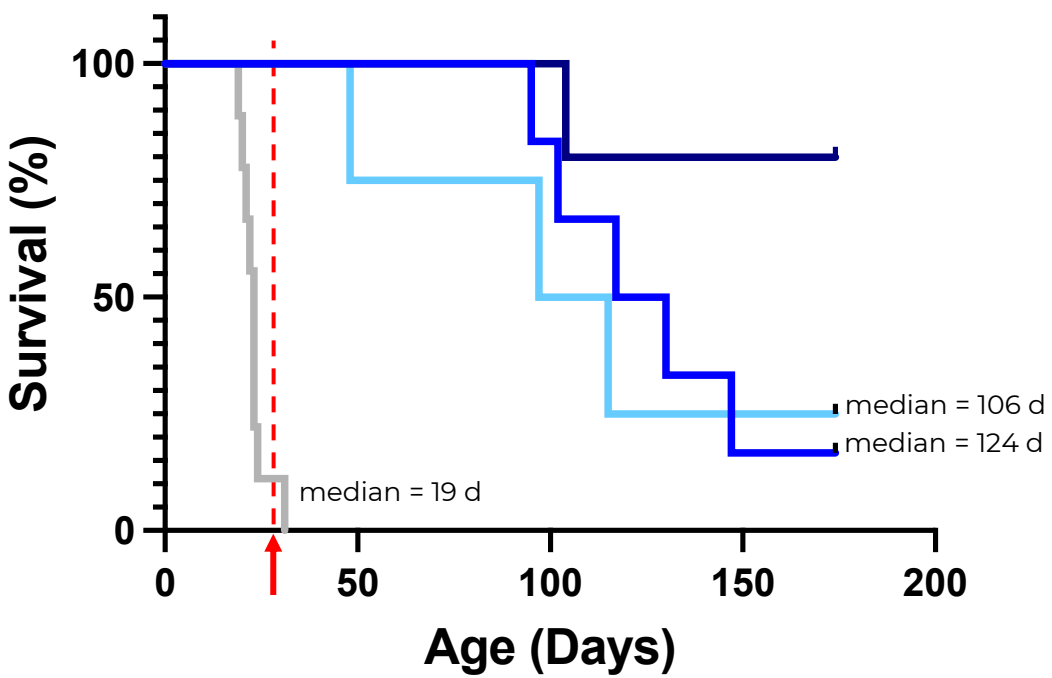
Low Dose (1e13 vg/kg, 7e10 vg/mouse)

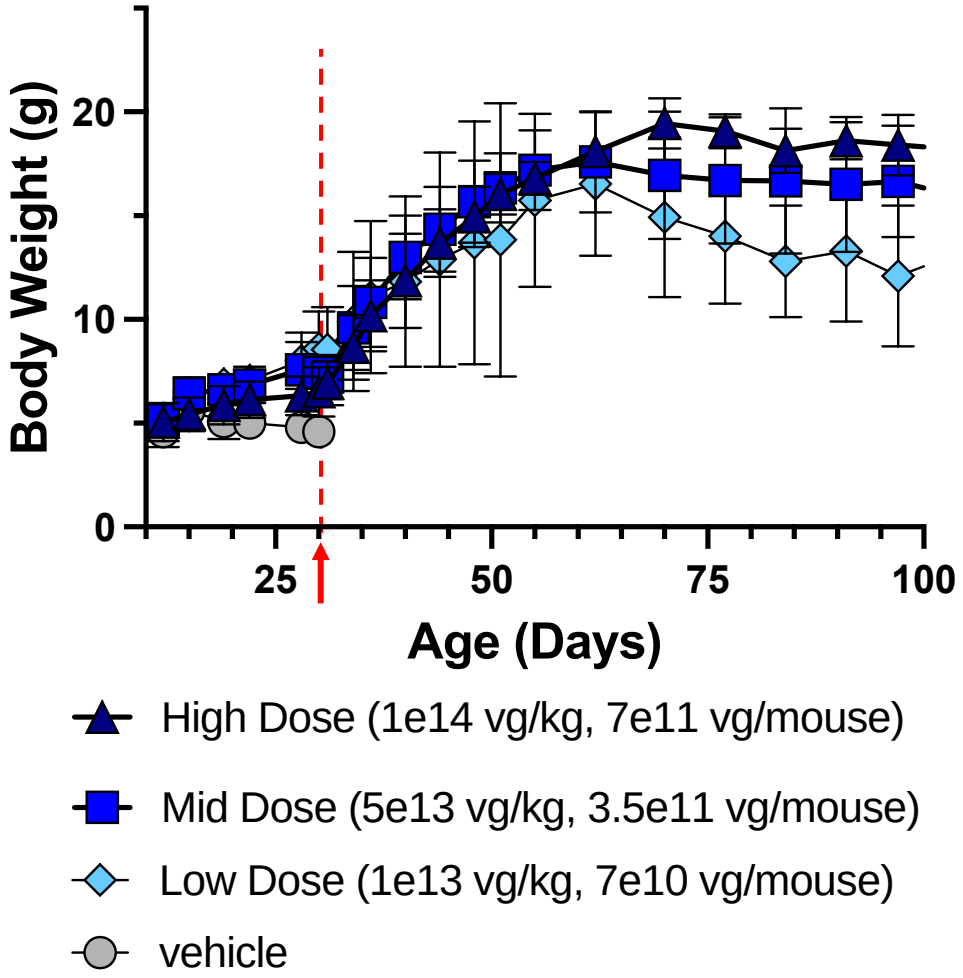
Vehicle

vehicle

Error bars = STDEV

ASA AAV GTx Results in Strong Survival and Growth Benefit in ASA Mice





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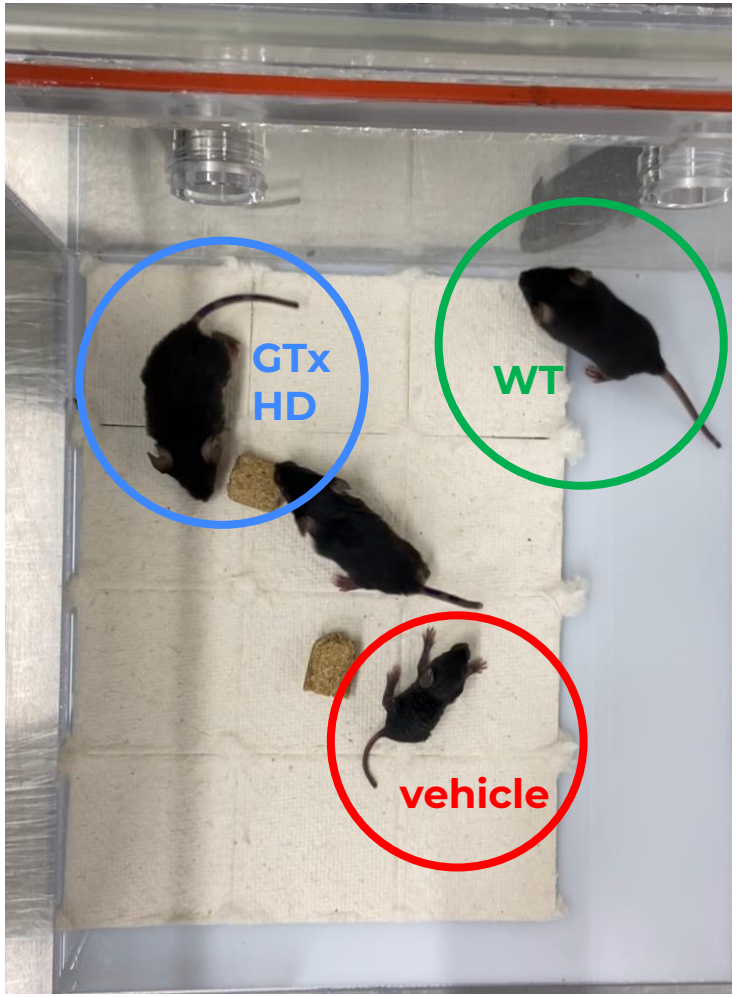
ASA AAV GTx Shows Remarkable Clinical Effect Lasting More Than 100 Days in ASA Mice

Video of 19-day-old ASA mice treated at birth

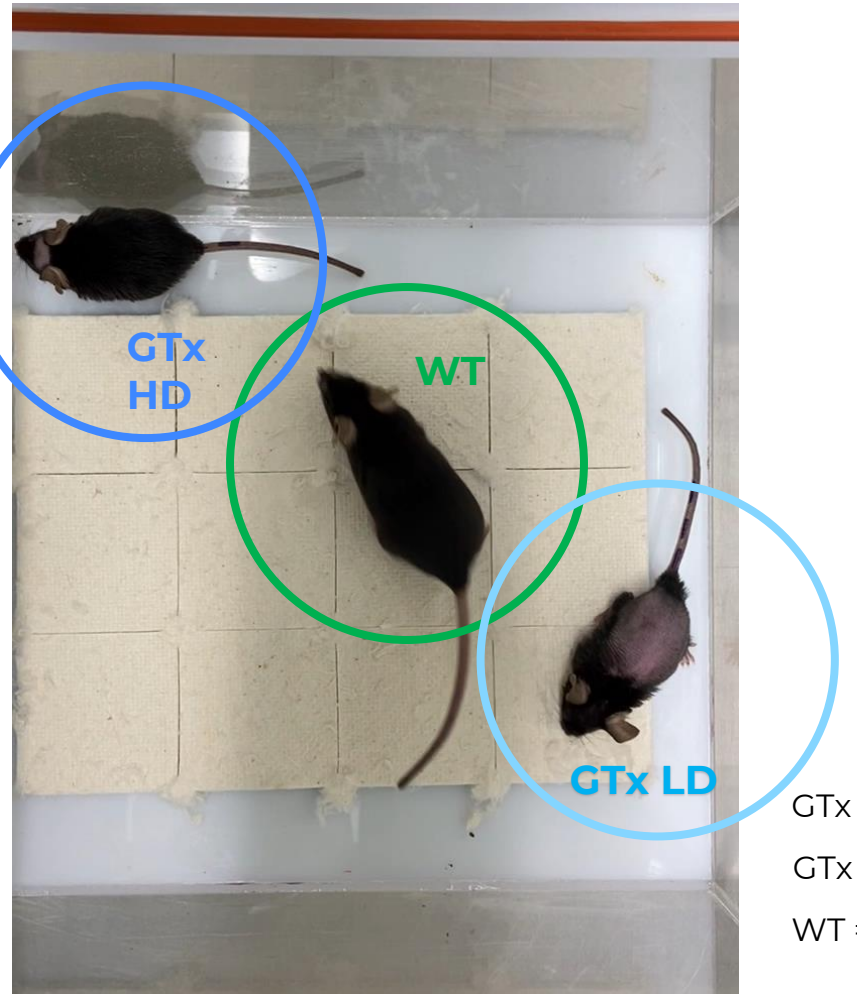


GTx HD = 3 dashes

WT = clean tail

vehicle = clean tail

Video of 100-day-old ASA mice treated at birth



GTx HD = 1 dash

GTx LD = 3 dashes

WT = clean tail

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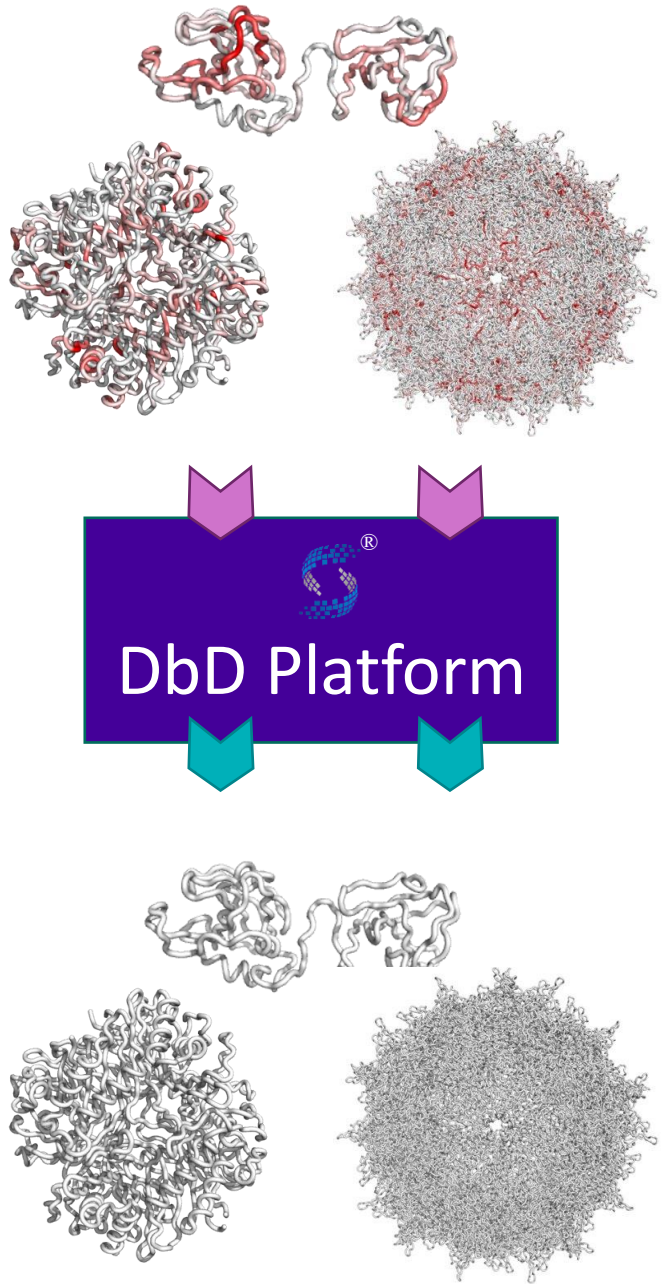
Insmed's hASL Transgene Construct Shows Compelling Therapeutic Efficacy in a Mouse Model of ASA

- This data provides **strong support for the potential utility of AAV gene therapy** in the treatment of ASA.
- Delivering the hASL transgene construct with a ***redosable* deimmunized AAV capsid** could lead to a **durable and highly effective treatment** for even the youngest ASA patients.
- **A similar strategy could be applied to other urea cycle disorders and inherited metabolic disorders**.
- Next steps include **in vivo proof of concept** studies of ***redosable* AAV gene therapy**

DbD – Key Takeaways

- Immunogenicity is a **major challenge** with many biotherapeutics.
- **Deimmunized by Design®** is a **proprietary AI-driven platform** for **reengineering immunogenic biotherapies** into **immunologically stealthy drugs**.
- The platform has been **validated preclinically** with lysostaphin and several other therapeutic proteins.
- We are **actively deimmunizing several therapeutic proteins**, which could yield multiple INDs over the coming years.
- **Deimmunizing AAV capsids** could **unlock the potential for redosable gene therapy**, and we intend to demonstrate clinical proof of concept in **diseases that are amenable to gene therapy but likely to require redosing** for sustained effect.



Brian Kaspar, PhD

Chief Scientific Officer

Insmed is Uniquely Positioned to Address Challenges in GTx Landscape with Game-Changing, Novel, Proprietary Technologies

Next Generation Gene Therapies With Targeted Delivery

Enhanced safety profile with similar/better efficacy

10 to 50-fold reduction in dose (vs. Systemic delivery)

RNA End Joining Technology (REJ)

Unlocks new GTx market opportunities with no competition

Large size gene delivery through traditional AAVs

Deimmunized by Design (DbD) platform

Redosable viral vectors

Deimmunized biobetters & derisked innovator drugs

Repeat dosing of gene therapies and overcoming immunogenicity

AlgaeneX

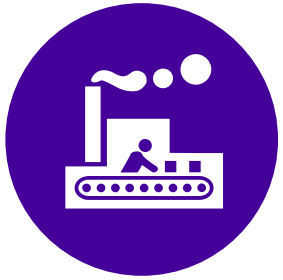
New, Proprietary Manufacturing

Lowest cost of goods for Insmed's gene therapy portfolio

Opportunity to license technology

Significant reduction in AAV manufacturing time and cost

Insmed is Uniquely Positioned to Address Challenges in GTx Landscape with Game-Changing, Novel, Proprietary Technologies



High production costs with low yields

Insmed Value Proposition & Solution

AlgaeneX

New, Proprietary Manufacturing

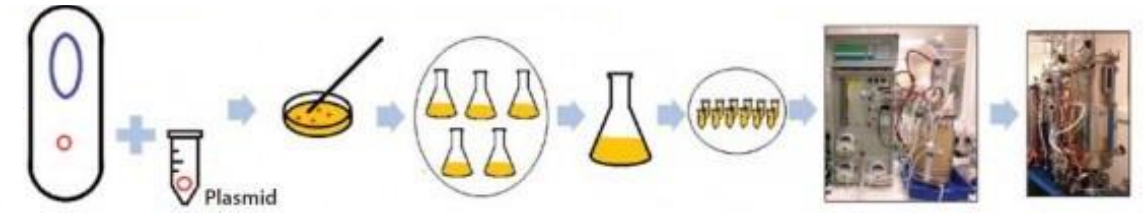
Lowest cost of goods for Insmed's gene therapy portfolio

Opportunity to license technology

Significant reduction in AAV manufacturing time and cost

The Arduous Process of AAV Gene Therapy Manufacturing

Creating functional genes for specific disease targeting is extremely slow & expensive…



1

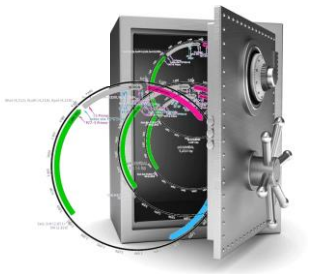
Development

Create a gene construct for an appropriate disease target

2

Construction

Production of AAV recombinant plasmid containing gene construct



3

Storage

A plasmid bank holds the construct

4

Production

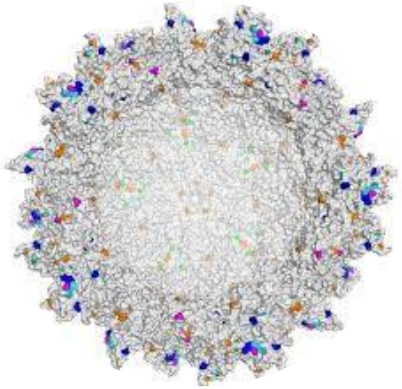
Production in the bioreactor requires a complicated scale-up in cell number and up to a week in the reactor before harvest

Anthony Berndt, PhD

Senior Scientist

The AlgaeneX Solution:

ALGAE FOR MASS GENE THERAPY PRODUCTION



Standard HEK293 Cell Production

Current state of the art

HEK293 **cell takes ~33 hours to double one-time** in a bioreactor

CHALLENGES

- Relatively slow growth
- Requires transfection
- Expensive bioreactors and media
- Need for maintenance and skilled manpower

Algae Cell Production

Potential future of GTx production

Algae cells take **~11 hours to double one-time**

POTENTIAL BENEFITS

- Rapid scalability to larger volumes
- No transfection required
- Low production cost; no expensive bioreactors or media required
- Ease of culturing and maintenance

OUR SOLUTION

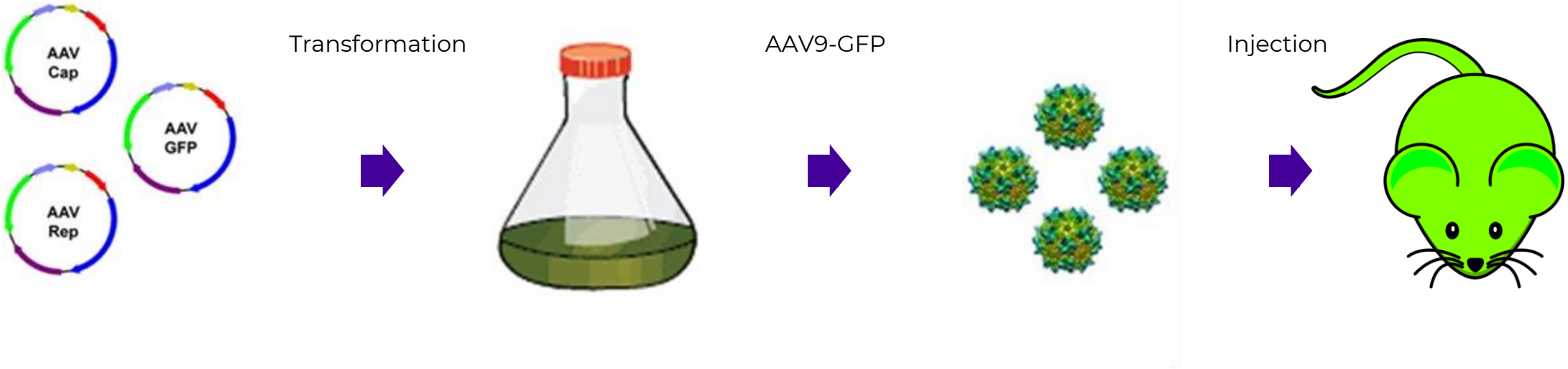
Use Simple Algae Cell For Mass Production

Microalgae have been successfully utilized to produce human recombinant proteins

Inherent low cost of goods and capitalization costs

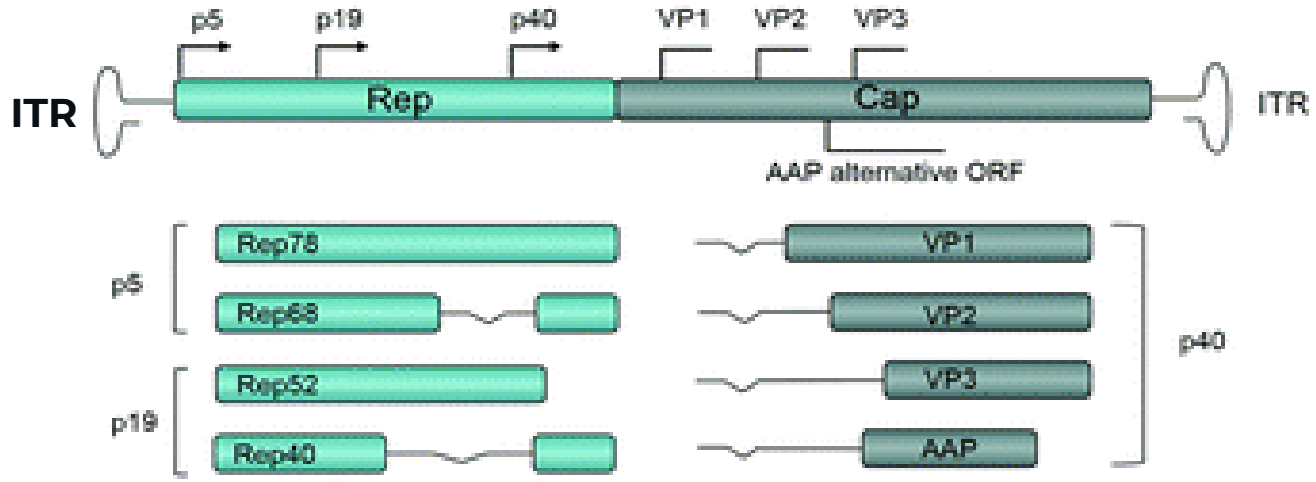
Simple production process and fast growth rate

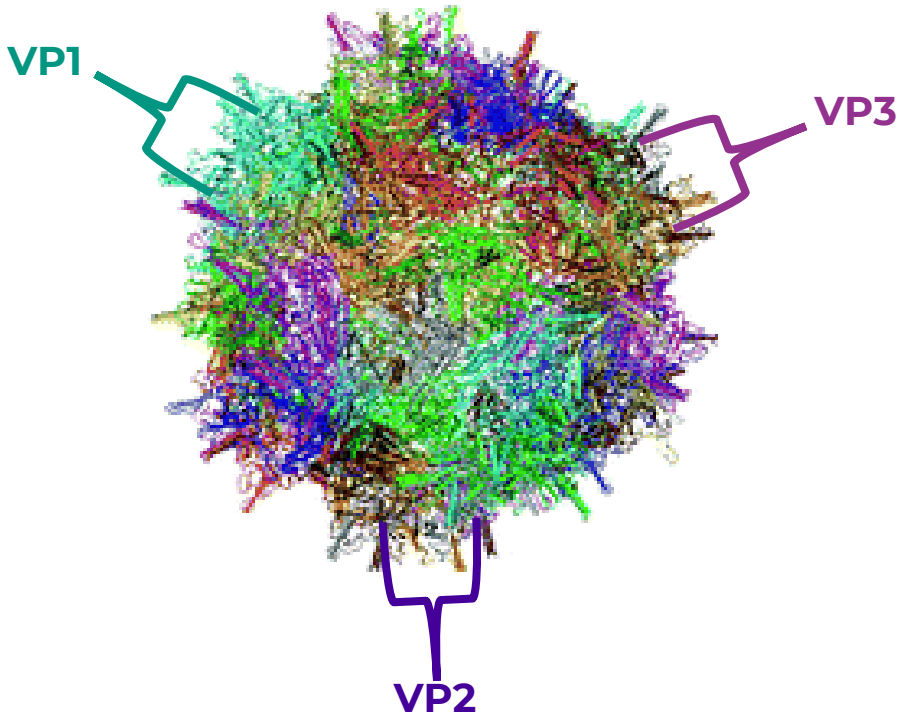
Overview of AAV9 production in Microalgae



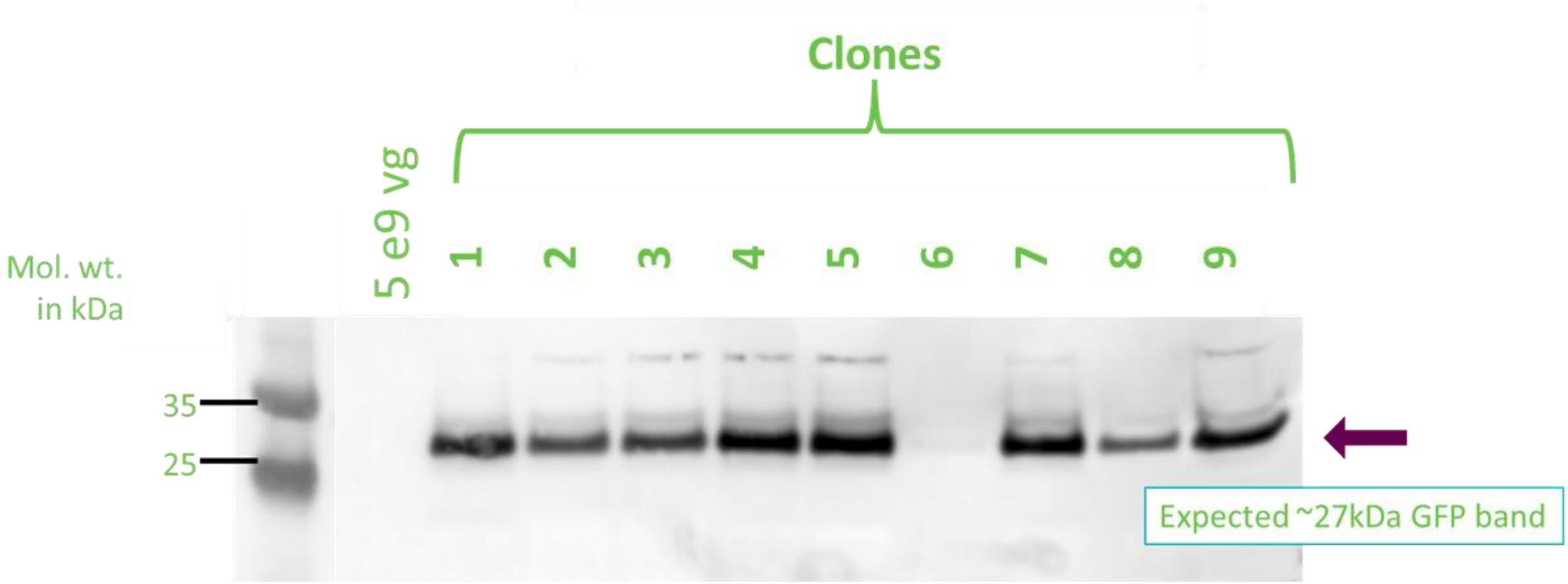
Minimum Necessary Components To Make An Infectious AAV

- Viral coat proteins: VP1, VP2, VP3
- Replication Factors: Rep78, Rep52
- ITR-flanked gene (payload)

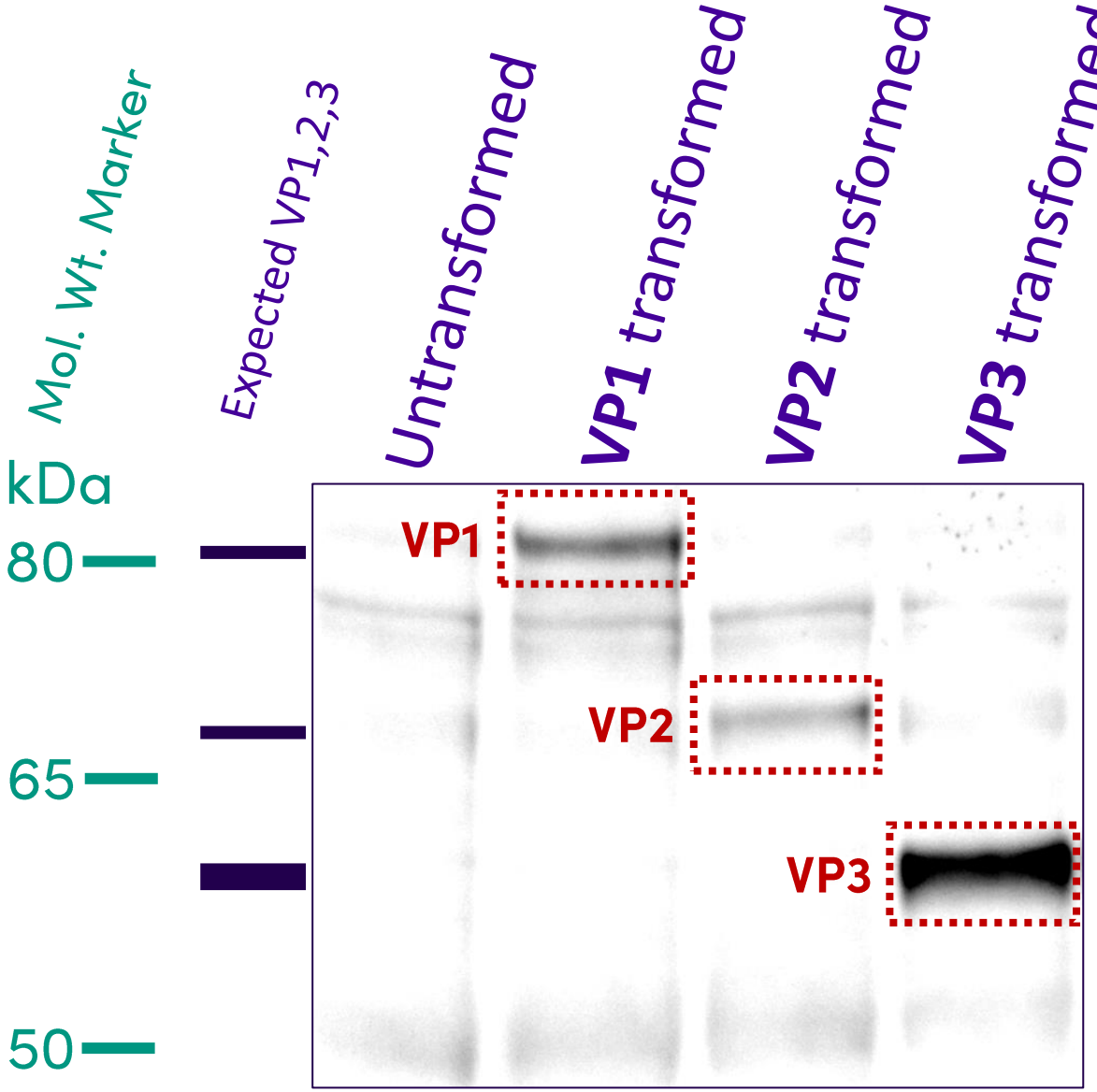




Insmed Has Successfully Expressed GFP Protein Using The AlgaeneX Next-Generation Manufacturing Solution

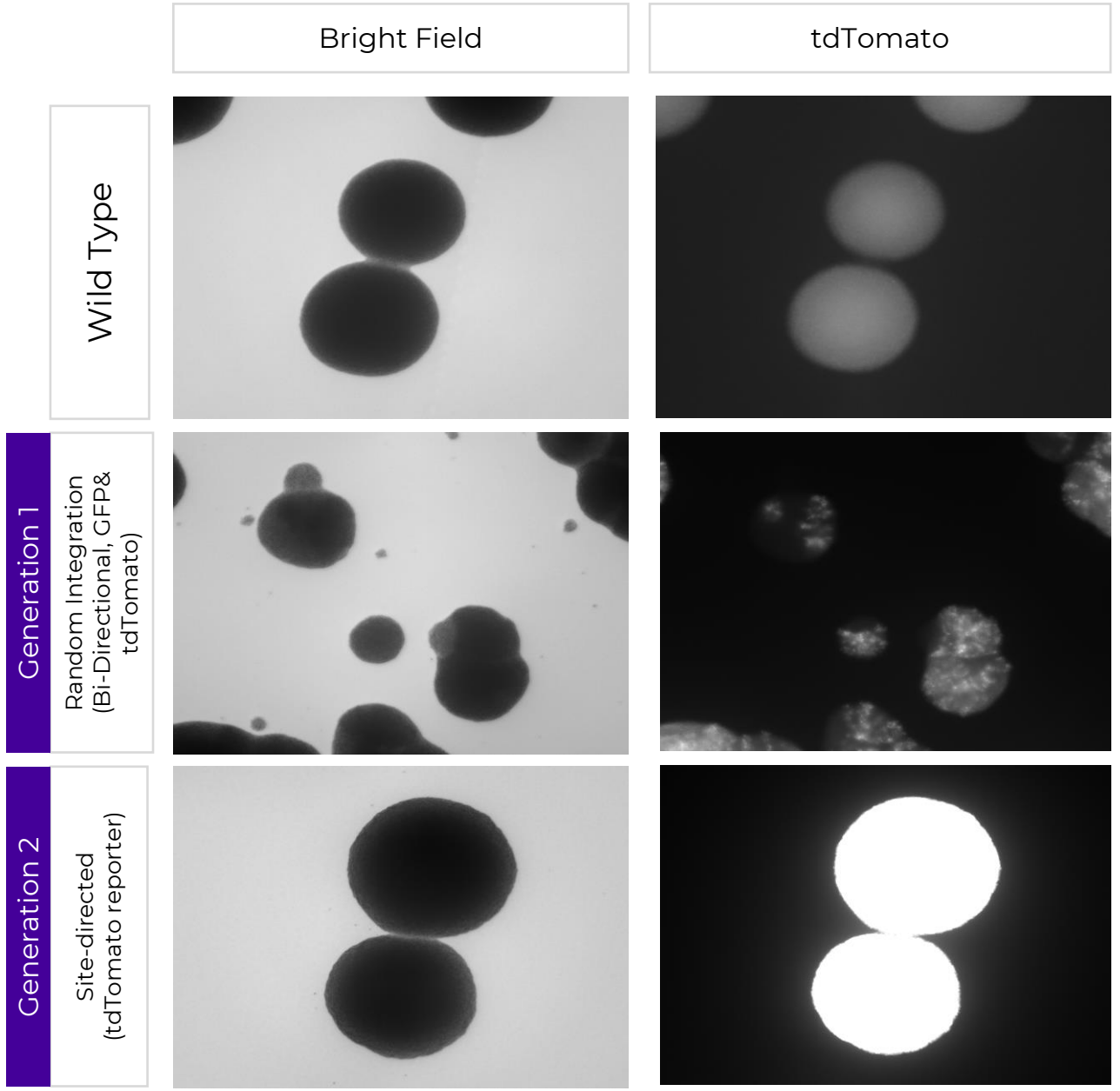


Insmed Has Successfully Expressed AAV9 VP1, VP2, and VP3 Using The AlgaeneX Next-Generation Manufacturing Solution



Anti-VP1/2/3 antibody on algae lysates

Insmed Is Building A Differentiated, Next-Generation Production Platform And Genetic Tool Kit That is Intended to Allow For Low-Cost Cultivation While Maintaining High Yield



Roger Adsett

Chief Operating Officer

Insmed Strategically Positioned to Answer “What’s Next?”

Potential ‘First-in-Disease’ or ‘Best-in-Disease’

- **Potential First-in-Disease/Best-in-Disease medicines** in areas of significant unmet need
- **Solving key issues** facing gene therapy – safety, cost of goods, durability of effect, and delivery of large genes

Rare Disease Focus

- **Exempt from Medicare price negotiation** under IRA

Faster to Market and Durable Revenue

- **≥6 INDs by end of 2025, with potentially shortened time** from IND to approval
- **Durable revenue potential**, leveraging ‘Top 10’ commercial launch engine

Game-Changing Platform Technologies with Multiple Revenue Stream Opportunities

Next Generation Gene Therapies with Targeted Delivery

- Potentially improved safety profile
- Significantly lower cost of goods

RNA End Joining (REJ) Technology

- Unlocks GTx for diseases caused by large gene mutations

Deimmunized by Design (DbD) Platform

- Redosable viral vectors
- Biobetter versions of biologics with known immunogenicity issues
- Innovative drugs with low immunogenicity

New Proprietary Manufacturing (AlgaeneX)

- Significant reduction in manufacturing time and cost
- Broad application beyond gene therapy
- Potential licensing opportunity

Initial GTx INDs Targeting Potential First-in-Disease or Best-in-Disease

Duchenne Muscular Dystrophy (DMD)

Source: cureduchenne.org

Stargardt Disease

Source: fightingblindness.org

Argininosuccinic Aciduria (ASA)

Source: gosh.nhs.uk

$1+B Potential Annual Market Opportunity for Newly Diagnosed Patients with DMD

	Aiming to be the preferred gene therapy for newly diagnosed DMD patients …	… and gene therapy of choice for existing patients
	Estimated DMD Annual Incidence	Estimated DMD Prevalence
US	400-600	10,500-13,000
EU4+UK	300-400	10,000-10,500
Japan	80-120	3,000-4,000
TOTAL (7 major markets)	**750-1,100**	**23,500-27,500**

Source: Insmed analysis based on published epi (2019) and UN population estimates (2022)

Substantial Stargardt Disease Opportunity: Large Eligible Patient Pool Addressed with Potentially the Only Approved Gene Therapy

	Estimated Stargardt Incidence[1]	Estimated Stargardt Prevalence[2]
US	550-600	34,000-42,000
EU4+UK	500-550	32,000-40,000
Japan	150-200	12,000-15,000
TOTAL (7 major markets)	**1,200-1,350**	**78,000-97,000**

~40% may be eligible for GTx based on visual acuity[3]

[1] Runhart, et. al, Stargardt disease: monitoring incidence and diagnostic trends in the Netherlands using a nationwide disease registry, Acta Ophthalmol. 2022 Jun; 100(4): 395–402
[2] Based on prevalence of 1:8000-10,000, and UN 2023 population estimate
[3] 36% of patients had no/mild visual impairment at baseline in the ProgStar retrospective study; pubmed.ncbi.nlm.nih.gov/26786511

GTx Redosing for Babies Born with ASA is a Paradigm Shift Towards Lifelong Gene Therapy

	Estimated Argininosuccinic Aciduria Incidence[1]	Estimated Argininosuccinic Aciduria Prevalence[2]
US	20-50	1,000-2,500
EU4+UK	15-40	750-2,000
Japan	5-10	250-500
TOTAL (7 major markets)	**40-100**	**2,000-5,000**

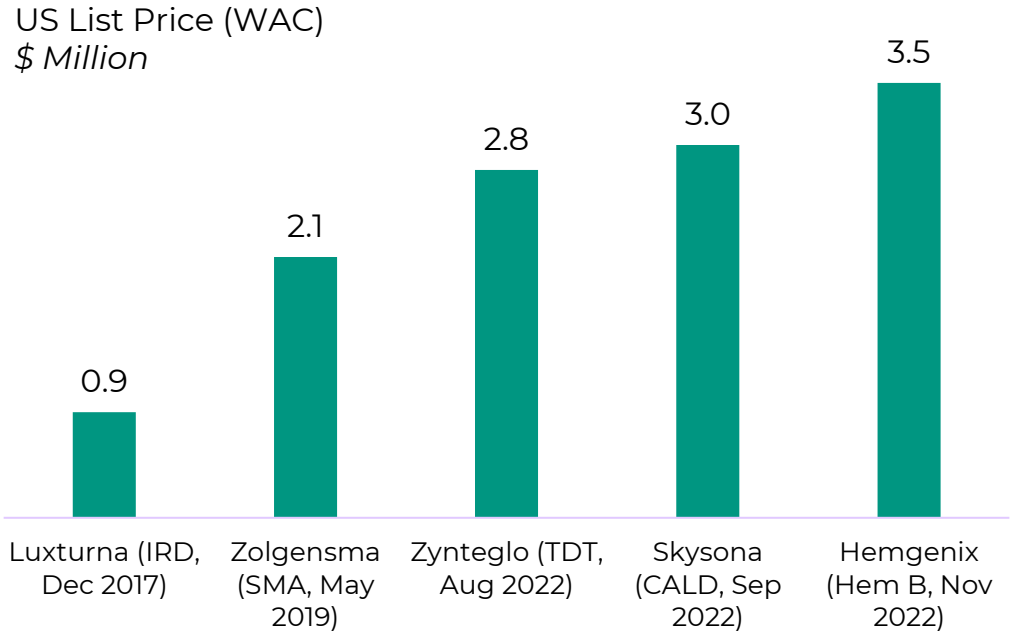
[1] Based on prevalence of 1:70,000-218,000 newborns, and UN 2023 population estimate
[2] Assuming median life expectancy of 50 years

Gene Therapies will Transform Patient Outcomes While Reducing Costs to Healthcare System

Transforming rare disease treatment with gene therapy

- 8 in 10 rare diseases are genetic in origin
- Insmed's gene therapies overcome key issues facing gene therapy
  - Safety
  - Durability of effect
  - Cost of goods
  - Delivery of large genes

US prices for approved GTxs* anchored on clinical evidence and cost offsets



IRD: Inherited Retinal Disease; SMA: Spinal Muscular Atrophy; TDT: Transfusion Dependent Beta Thalessemia; CALD: Cerebral Adrenoleukodystrophy (CALD); Hem B: Hemophilia B
* For genetic disorders

Anticipated Upcoming Milestones* from Pillar 4

SUBSET OF PILLAR 4 PIPELINE

4 Early-Stage Research

Innovative Treatments	2H 2023	2024	2025
Duchenne Muscular Dystrophy[1] (DMD)	FIH (2H)	Clinical Data (1H)	
Stargardt Disease[1] (STGD)		IND	Clinical Data
Chronic Refractory Gout[2] (CRG)	Candidate Selection	Preclinical Data	IND
Argininosuccinic Aciduria[1] (ASA)		Preclinical Data	IND
New Proprietary Manufacturing (AlgaeneX)		Full Capsid Production	Scale up to commercial manufacturing

[1] Next Generation Gene Therapies
[2] Deimmunized Therapeutic Protein

* May be revised as research and clinical development progresses

Key Takeaways

1

Multibillion annual revenue potential from first 3 GTxs

- **Leapfrog current GTx approaches** to emerge as market leader
- **Initial GTx INDs targeting First in Class/Best in Class:**
  - Duchenne Muscular Dystrophy (DMD)
  - Stargardt Disease
  - Argininosuccinic Aciduria (ASA)

2

Potentially game-changing platform with multiple revenue streams

- **Solving key issues facing gene therapy** – safety, cost of goods, durability of effect, and delivery of large genes
- **Platform technologies with multiple revenue stream opportunities**
  - AI driven Deimmunized proteins and AAV capsid library
  - Manufacturing platform

3

Insmed strategically positioned for success

- **First in Disease/Best in Disease medicines** in areas of significant unmet need
- **Focus on rare diseases, BLAs** – ensures patient access under the IRA
- **≥ 6 INDs by end of 2025**, with potentially shortened time from IND to approval

Lean Pillar 4 operations with <20% of total Insmed expenditures

Infinite potential.
One patient at a time.

Count us in.

Key Pipeline Catalysts