



Increased Laminin Binding Through $\alpha 7 \beta 1$ Integrin Activation Protects Dystrophic Muscle

2022 NEW DIRECTIONS IN BIOLOGY AND DISEASE
OF SKELETAL MUSCLE CONFERENCE

Scott Turner, Ph.D.

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About Pliant Therapeutics

The Company



- Founded in 2015
- Based in South San Francisco
- 110 employees
- June 2020 IPO (Nasdaq: PLRX)

Programs Targeting High Unmet Medical Need



- PLN-74809 in Phase 2a development in IPF and PSC
 - Topline data in IPF expected mid-2022
- IND submission in DMD expected by YE 2022

Industry-Leading Fibrosis Platform








- Built on integrin-mediated inhibition of TGF- β pathway
- Proprietary drug discovery platform based on novel in-house compound library of integrin binders

Strategic Partnership with Novartis



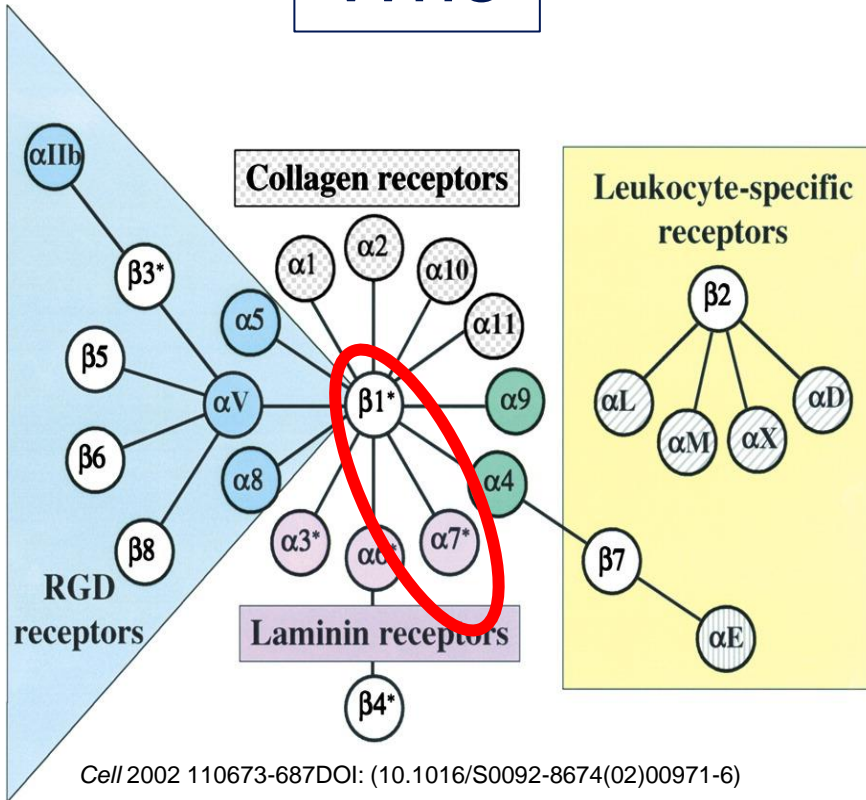
- Partnered NASH program currently in Phase 2
- Broad multi-target research collaboration
 - Next generation anti-fibrotic molecules targeting novel integrins

Pliant Development Pipeline

	Program	Indication	Preclinical	Clinical			Anticipated Milestone	Global Rights
				Phase I	Phase II	Phase III		
WHOLLY OWNED	PLN-74809	Idiopathic Pulmonary Fibrosis	INTEGRIS-IPF Enrollment Complete				Phase 2a Topline Data Expected Mid-2022	 PLIANT
	Dual selective inhibitor of $\alpha_V\beta_8/\alpha_V\beta_1$	Primary Sclerosing Cholangitis					Phase 2a Data Expected 1H 2023	 PLIANT
	Oncology	Solid Tumors					IND Filing Expected YE 2022	 PLIANT
	Muscular Dystrophies	DMD Other Muscular Dystrophies					IND Filing Expected YE 2022	 PLIANT
PARTNERED	PLN-1474	NASH-Associated Liver Fibrosis					Phase 2 Initiation	 NOVARTIS
	Selective inhibitor of $\alpha_V\beta_1$							

The Integrin Family: Who, What, Where, When and How

Who



24 **heterodimeric** cell adhesion receptors

Remember: $\beta 1$ is not an integrin, it's a gene product looking for a friend

What

- Regulate the cell-matrix interaction
- Promote cell adhesion and migration
- Activate intracellular signals
- Activate extracellular signals (eg: TGF- β)

Where

- Everywhere
 - Cell type
 - Organ
 - Disease

When

- Always
 - Embryogenesis to Cancer

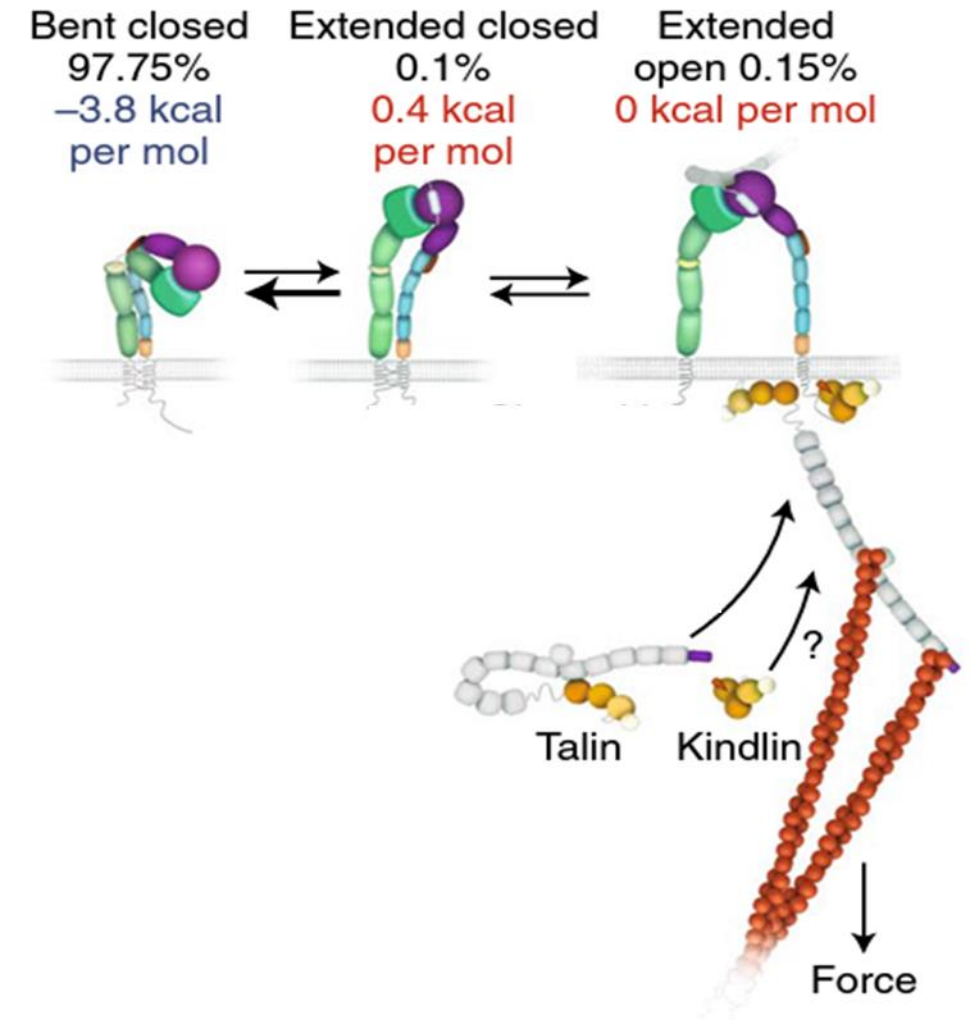
How

- Kinase signaling
- Interaction with other integrin pairs
- Interaction with other cell surface receptors (VEGFR, FGF)
- Mechano-transduction

Caution: generalizations about integrins are usually wrong

The Integrin Family: Who, What, Where, When and How

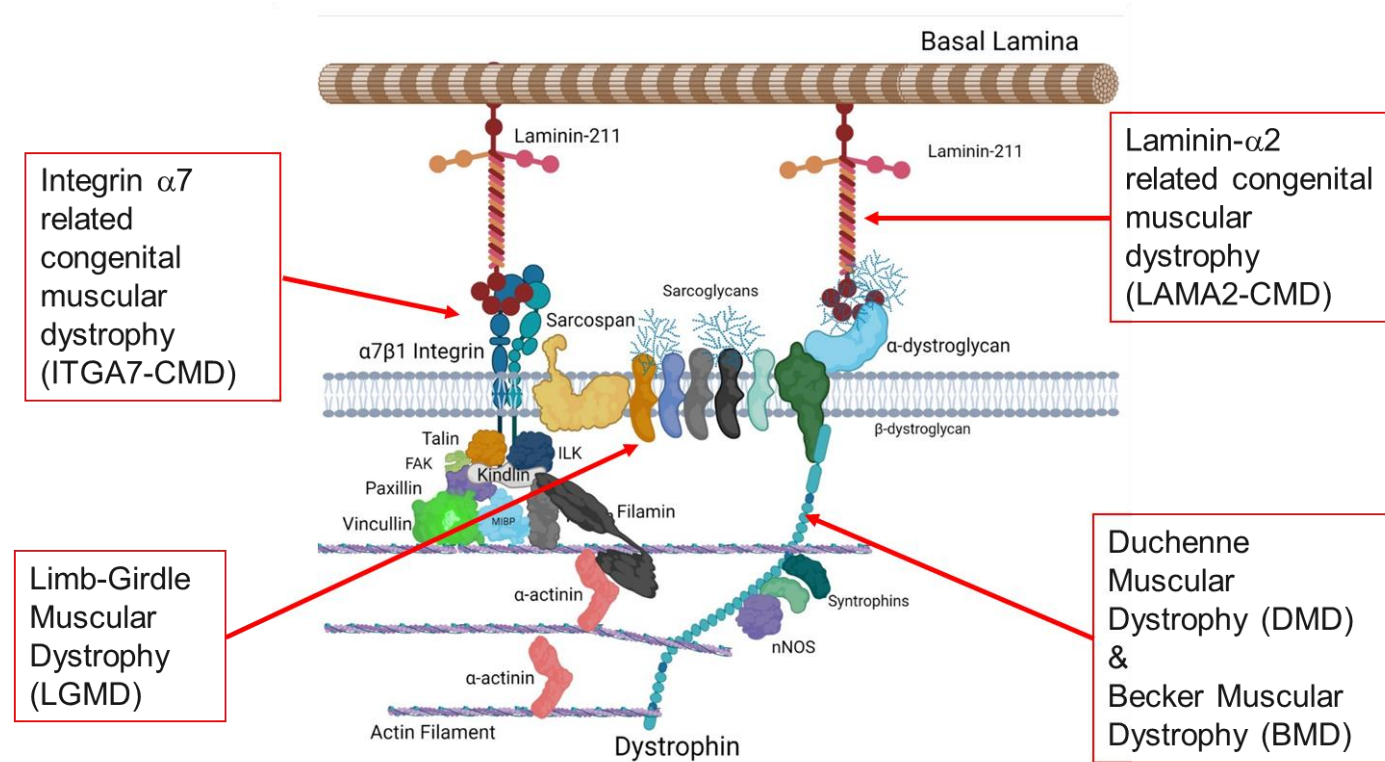
- Most integrins have 3 conformational states
 - Predominant state is the bent closed conformation
 - Extended open conformation can increase ligand binding up to 5000x
- Inside-out signals through Talin and Kindlin induce conformation changes
- Ligand binding induces outside-in signaling through the β chain
- Ligand specificity is determined by the α chain



Nature Cell Biology 21, 25–31 (2019) |

$\alpha 7\beta 1$: A Drug Target in Muscular Dystrophies

- Predominantly expressed in skeletal, heart and smooth muscle
- $\alpha 7\beta 1$ strong genetic modifier in MDX mice
 - Lack of $\alpha 7\beta 1$ worsens disease phenotype
 - Over expression increases survival and improves function.
- Pharmacological agents that increase expression show similar effects.
- Human mutations in $\alpha 7\beta 1$ result in congenital MD
- ITGA7 frameshift (heterozygous, nonfunctional mutation is associated with lean muscle volume reduction (UK Biobank)



Dean J Burkin, PhD and Ryan Wuebbles, PhD
Generated using BioRender

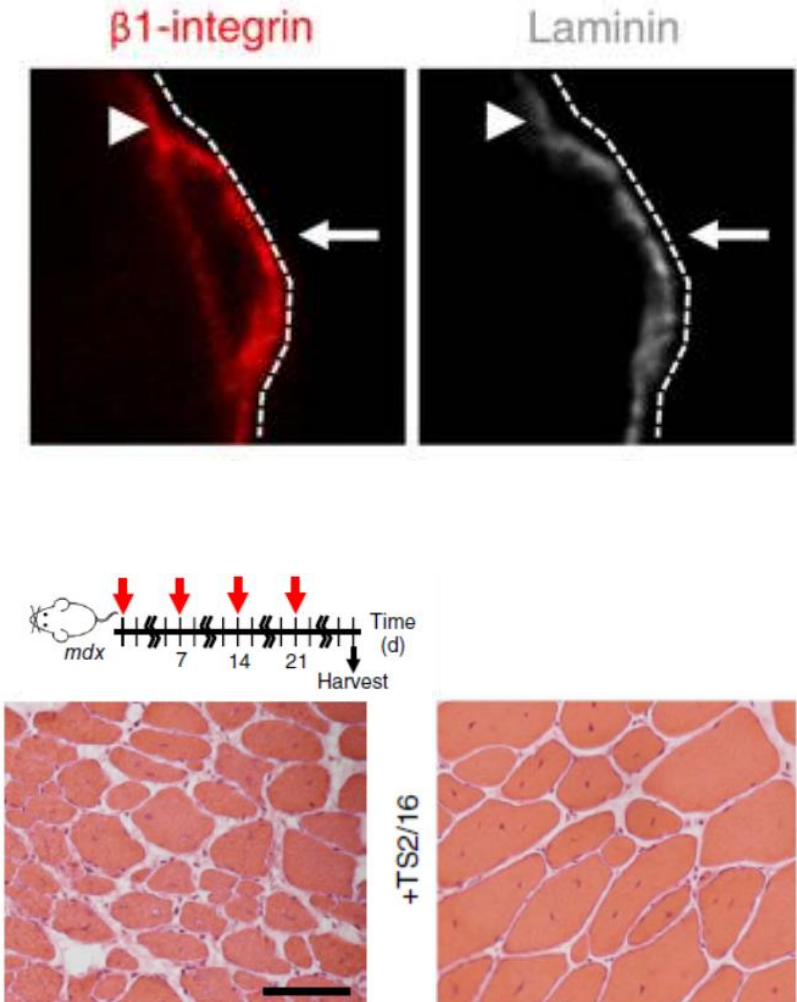
Antibody Activation of Muscle $\beta 1$ Integrins

Targeting $\beta 1$ -integrin signaling enhances regeneration in aged and dystrophic muscle in mice

Michelle Rozo, Liangji Li & Chen-Ming Fan

Nature Medicine 22, 889–896 (2016) | [Cite this article](#)

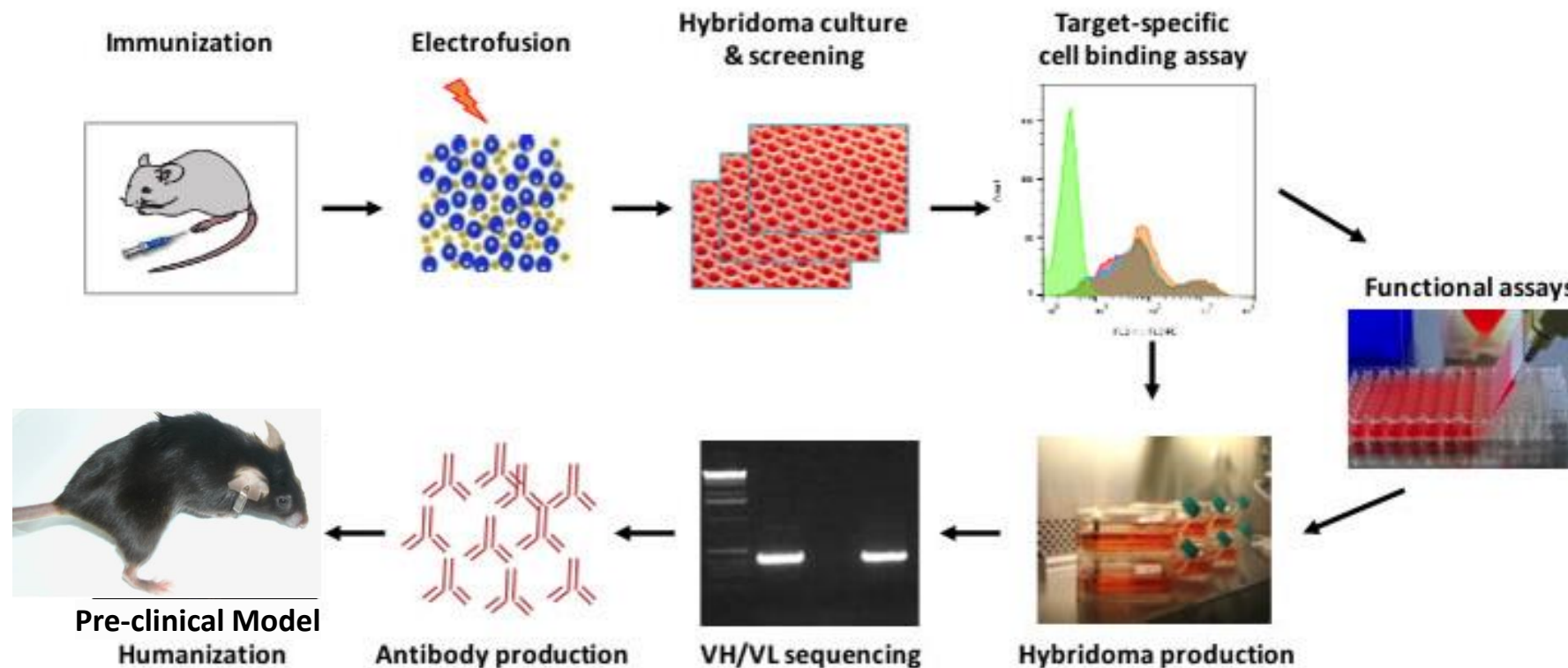
- TS2/16 is an allosteric activating antibody of $\beta 1$ integrins
 - Increases laminin binding of satellite cells
 - 4 main laminin binding integrins in muscle are $\alpha 7\beta 1$, $\alpha 6\beta 1$, $\alpha 6\beta 4$, $\alpha 3\beta 1$
- Intramuscular injections improve dystrophic muscle
 - Systemic activation of $\beta 1$ integrin is not safe due to wide distribution of $\beta 1$ integrin



Discovery of an $\alpha 7$ Integrin Specific Agonist Antibody

Antigen: human integrin $\alpha 7 \beta 1$ ectodomain

110 clones were picked as integrin $\alpha 7 \beta 1$ binders (from total of 9000 clones)



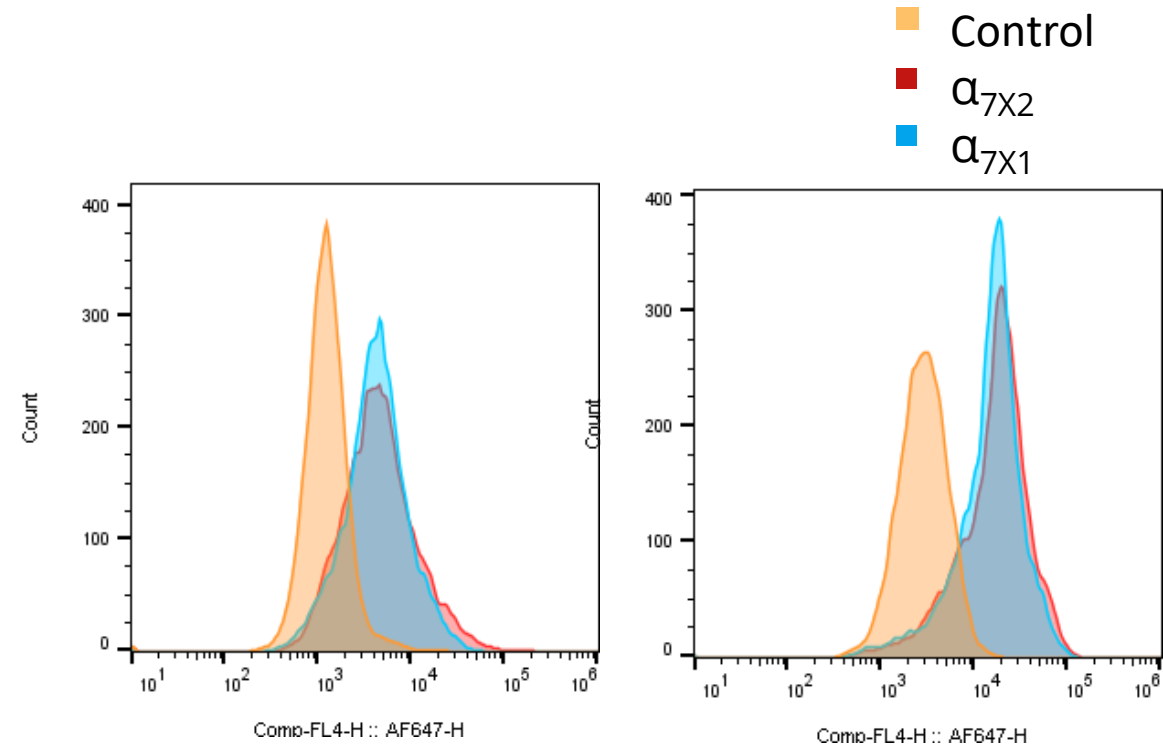
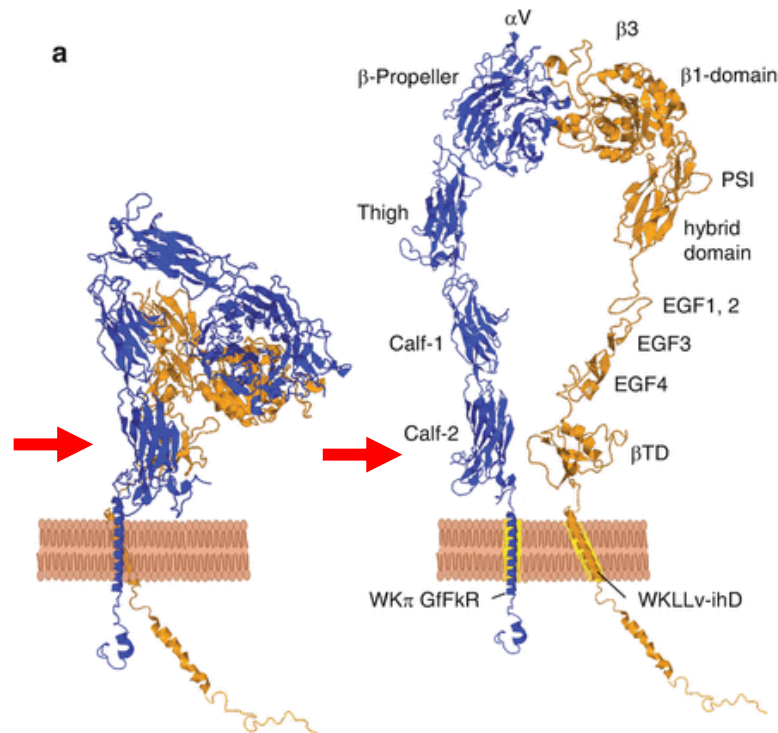
Four agonist Abs:
Two bind to $\beta 1$;
Two bind to $\alpha 7$

Multiple
antagonist Abs

Discovery of an Integrin $\alpha 7$ Specific Agonist Antibody

- Epitope mapping identified Calf-2 as the agonist antibody binding site
- High homology across species
- Binding site is not altered in any known $\alpha 7\beta 1$ splice variants

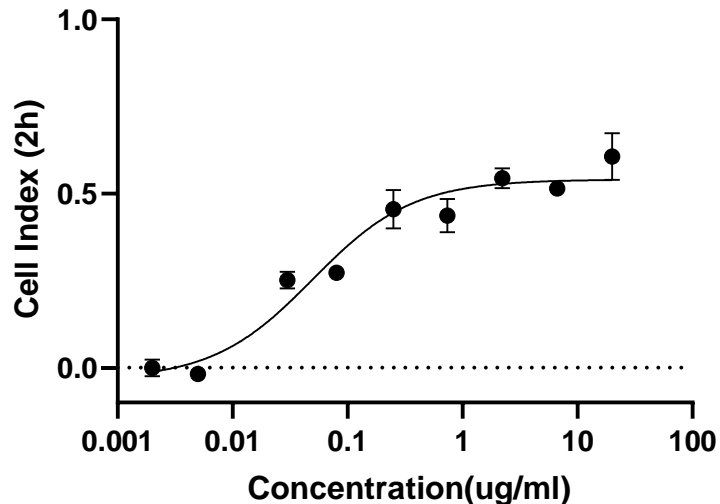
- The $\alpha 7$ integrin subunits are expressed in two cytoplasmic ($\alpha 7A$ and $\alpha 7B$) and two extracellular splice variants ($\alpha 7X1$ and $\alpha 7X2$)
 - No difference in binding to splice variants



Discovery of an $\alpha 7$ Integrin Specific Agonist Antibody

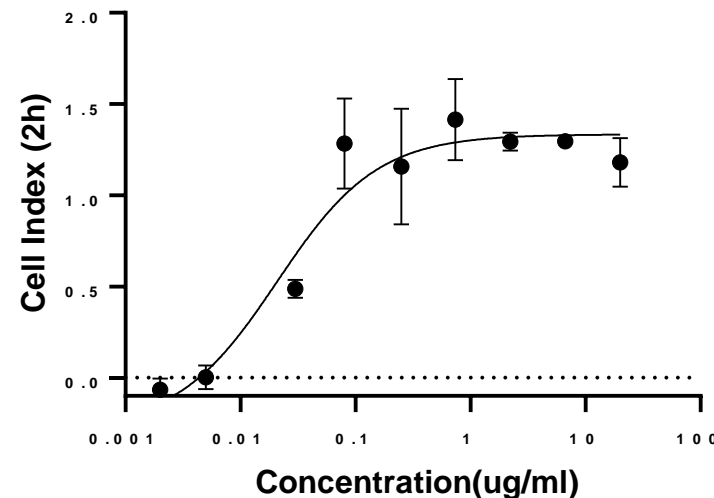
- Lead mAb increases healthy and DMD myoblast adhesion to laminin 211
- K562 cells expressing $\alpha 7 \times 2$ adhere to laminin 211 which can be reversed by an $\alpha 7$ blocking antibody;
 - Both TS2/16 and $\alpha 7$ agonist can enhance the ligand binding

Control Cell Adhesion on LN211



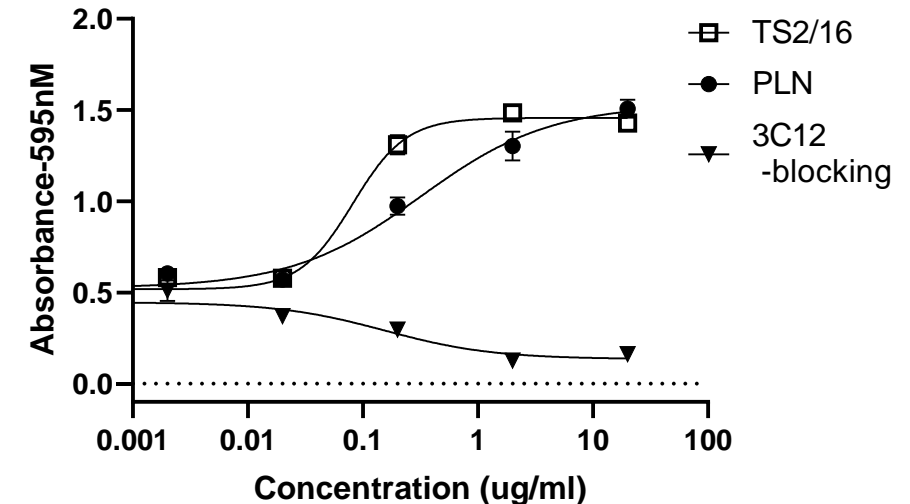
Health control myoblast is provided by Dr. Lee Sweeney;

AB1071DMD Cell Adhesion on LN211



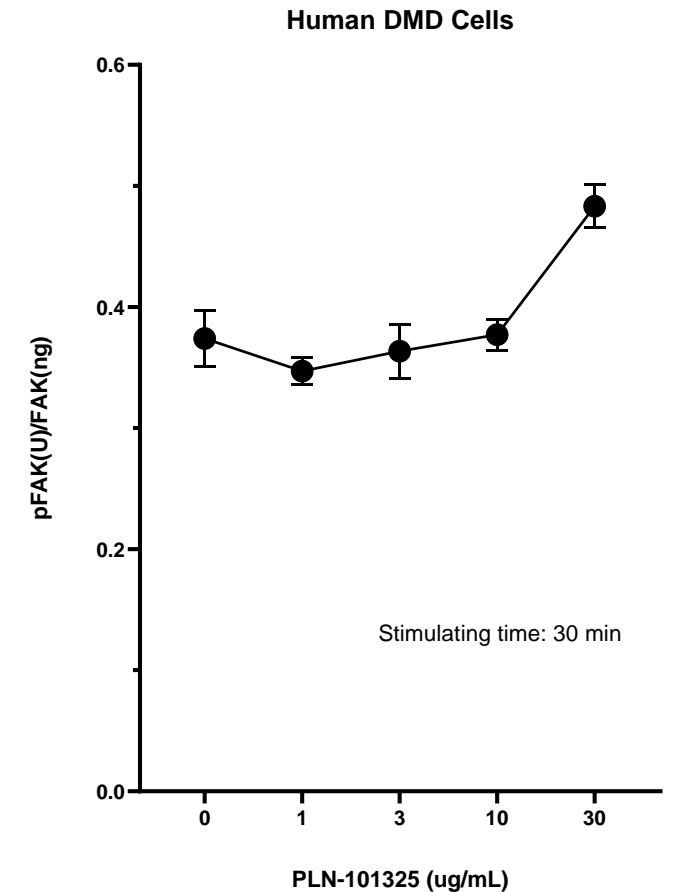
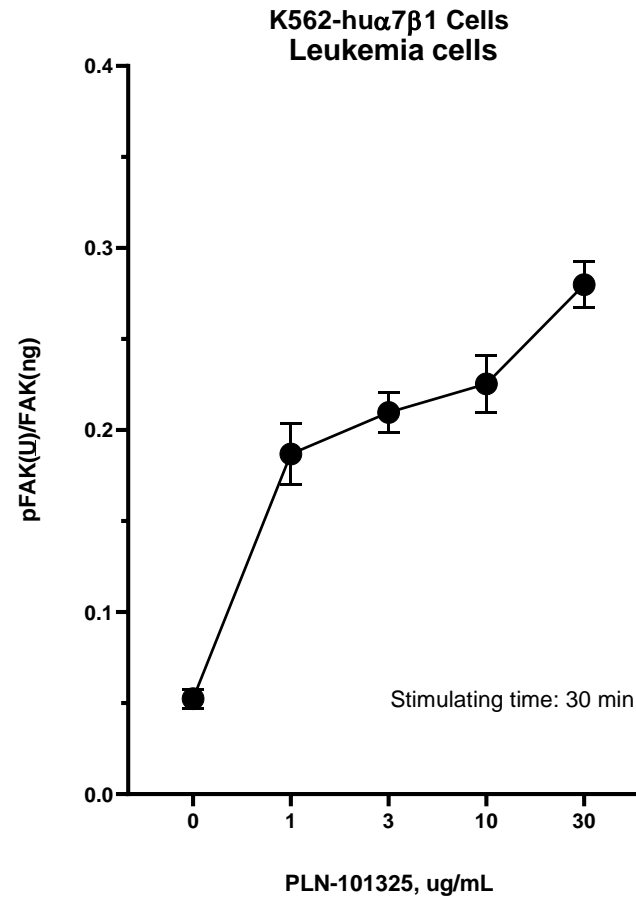
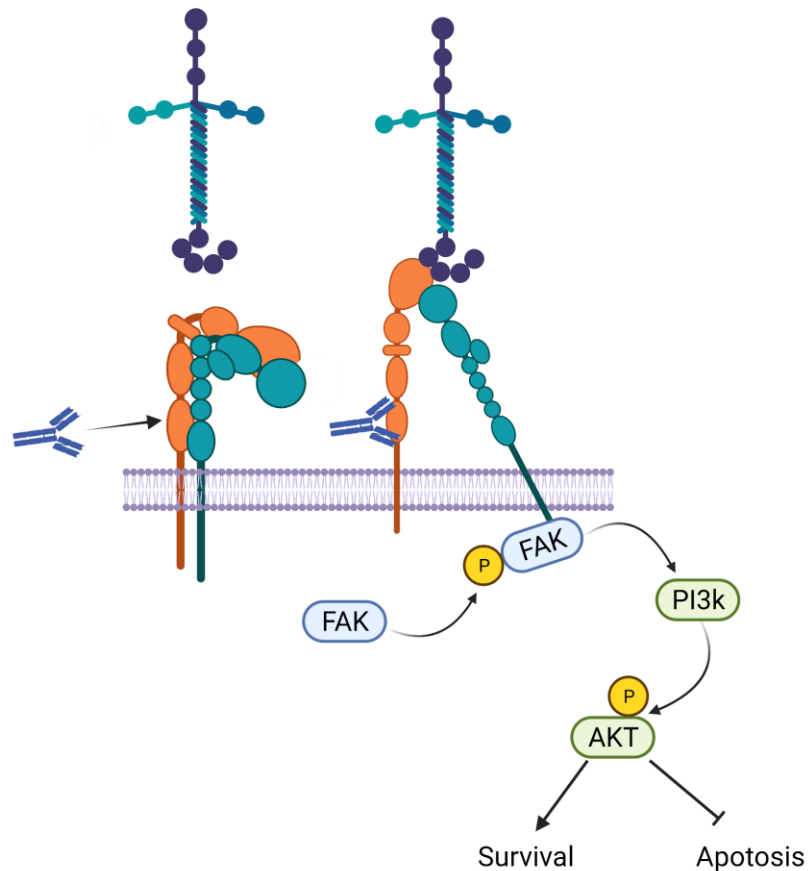
DMD myoblast from Dr. Vincent Mouly (AB1071DMD; mutation deletion exon 45-52; 13Y males)

K562/Hu $\alpha 7 \times 2$ Cell Adhesion on LN211



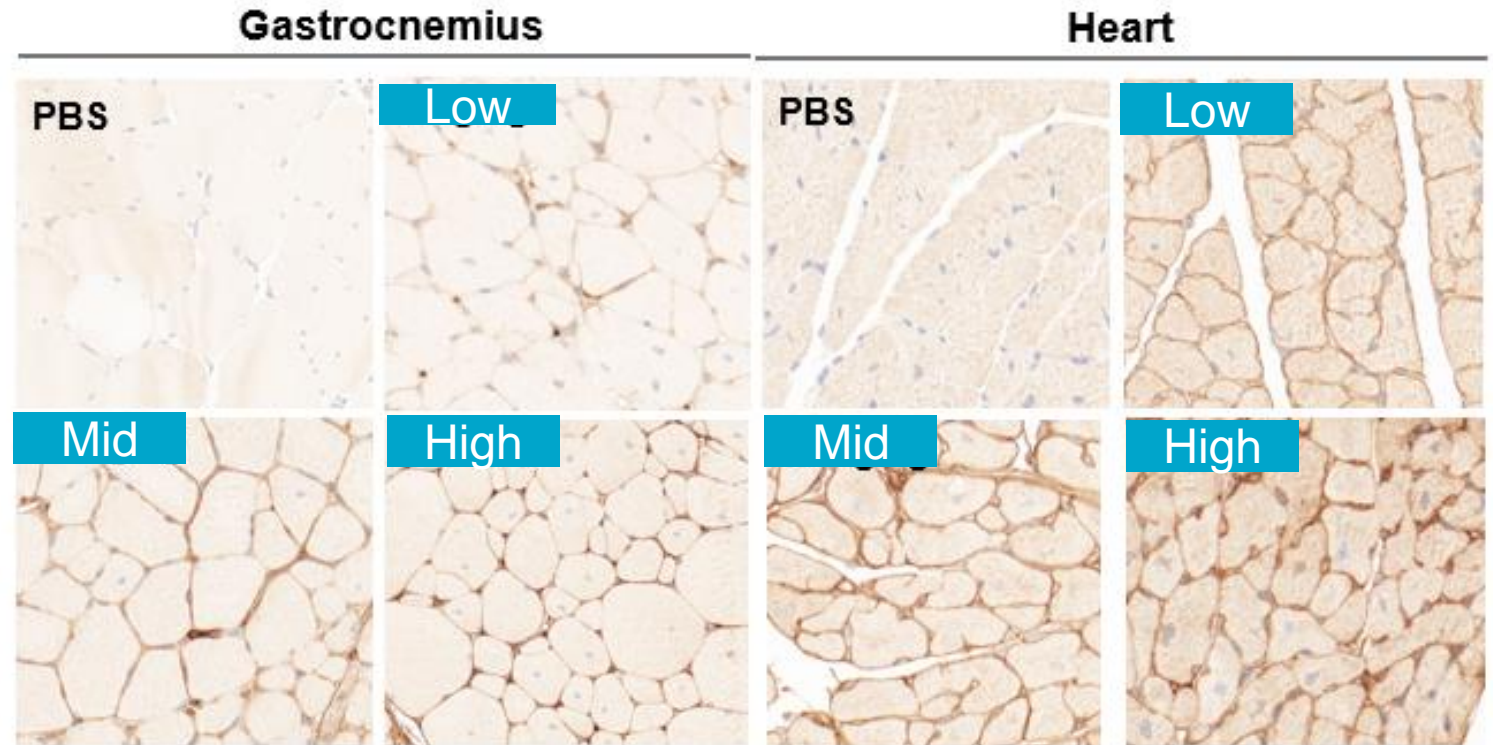
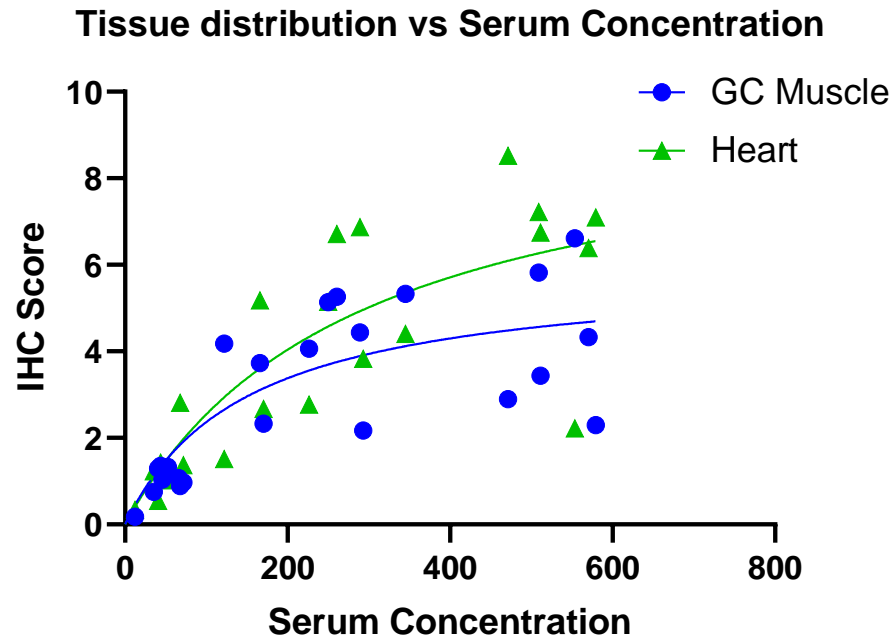
Discovery of an $\alpha 7$ Integrin Specific Agonist Antibody

Activation of $\alpha 7 \beta 1$ increases intracellular integrin signaling through phospho-FAK



Target Occupancy in the D2-mdx Model In Both GC Muscle and Heart

- D2-Mdx mice were dosed 2x IP/wk for 4wk
- PLN-101325 tissue distribution was measured by anti-human IgG4 IHC.



The target engagement data shows sarcolemmal distribution and greater binding in heart at higher doses

PLN-101325: An $\alpha 7$ Integrin Specific Agonist Antibody

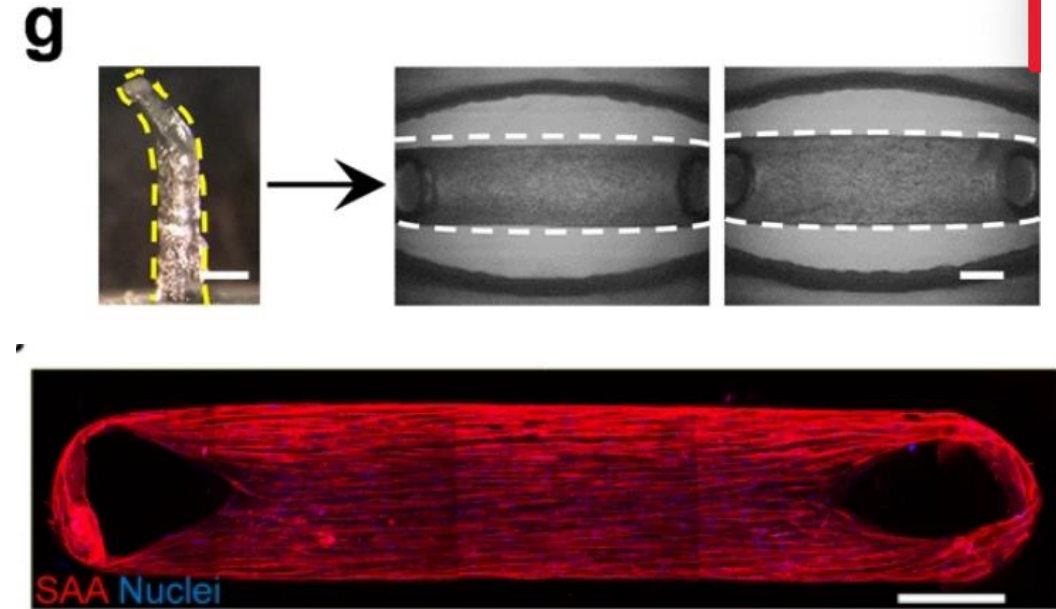
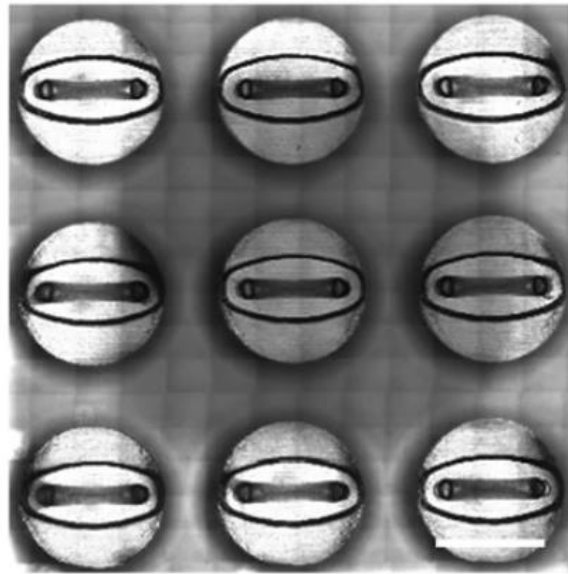
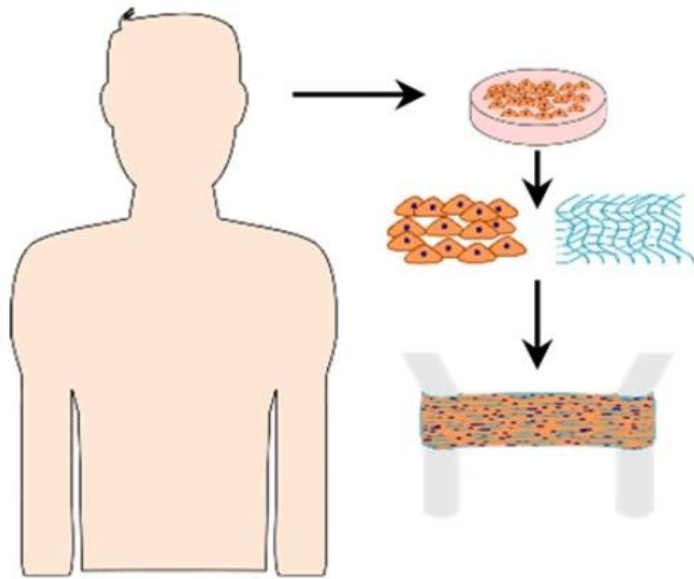
- Single digit nm EC50 and Kd - more potent in human vs. mouse
- IgG4 fully humanized antibody
- ~200h half-life in Cynomolgus monkeys (consistent with other IgG4 drugs)
- No off target/non-specific binding
- No internalization
- Low immunogenicity risk
- Strong, dose responsive target engagement

Evaluating the Effects of a Pliant Therapeutics Humanized $\alpha 7 \beta 1$ Integrin Antibody on DMD Muscle Cell Structure & Function in 3D Culture

A 96-well culture platform enables longitudinal analyses of engineered human skeletal muscle microtissue strength

Mohammad E. Afshar, Haben Y. Abraha ... Penney M. Gilbert

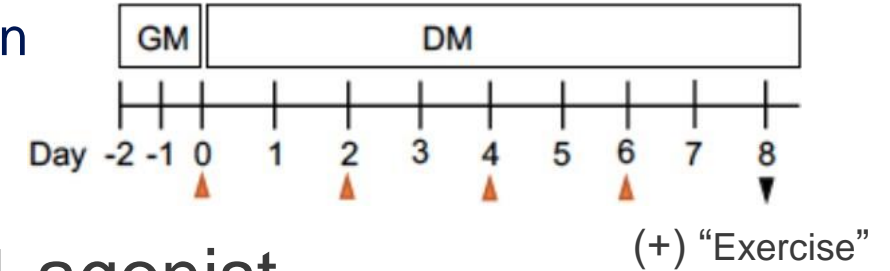
Research | Open Access | 24 Apr 2020 | Scientific Reports | Volume: 10, P: 1-16



Integrin $\alpha 7 \beta 1$ Agonist Antibody Promotes Muscle Maturation

- AB1071 hMMTs treated with 1 $\mu\text{g/ml}$ or 10 $\mu\text{g/ml}$ Pliant antibody contain myotubes with substantially improved sarcomere organization that can withstand tetanic stimulation compared to IgG4 control.

Treatment Regime

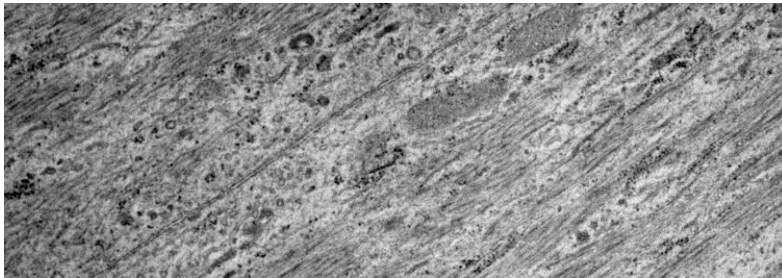


IgG4

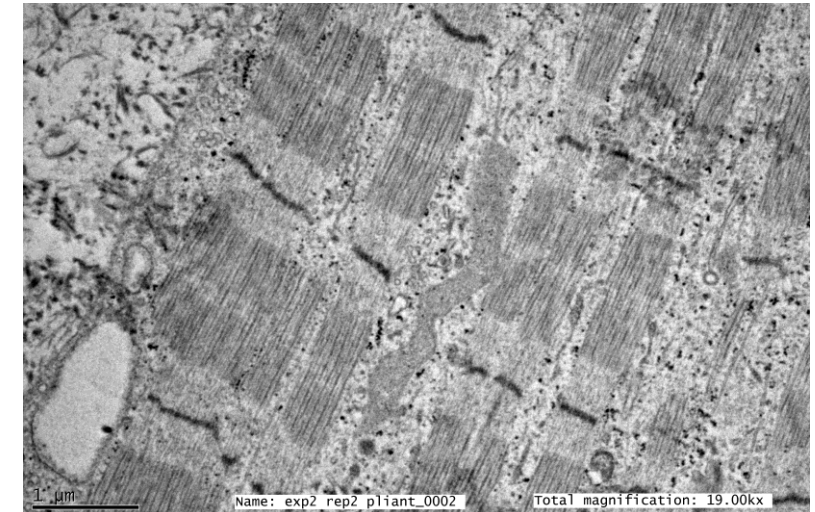
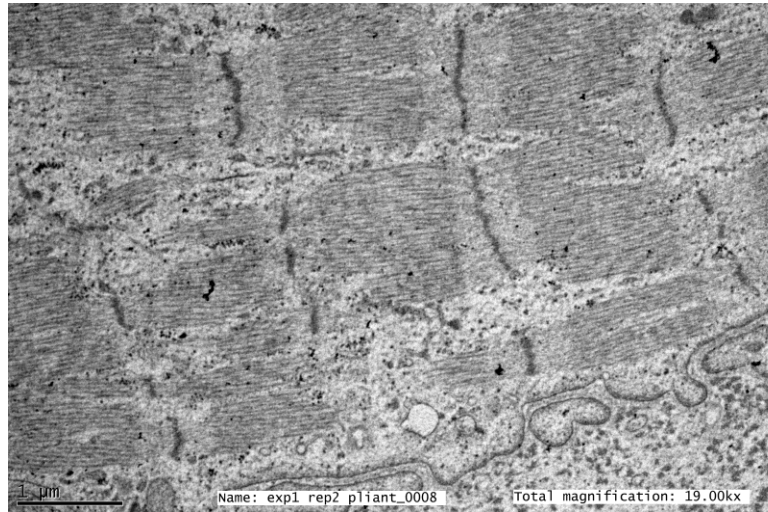
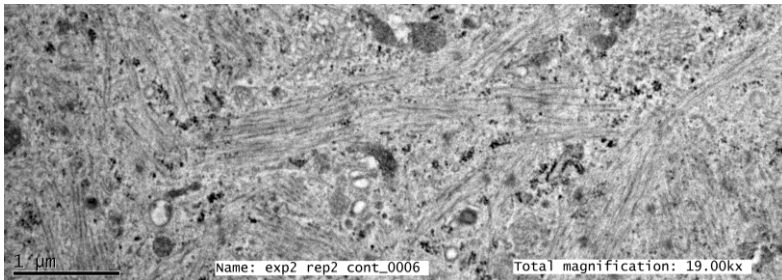
1 $\mu\text{g/ml}$ $\alpha 7 \beta 1$ agonist

10 $\mu\text{g/ml}$

1 $\mu\text{g/ml}$



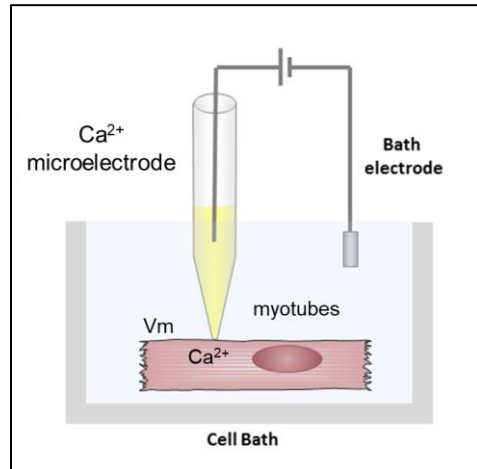
10 $\mu\text{g/ml}$



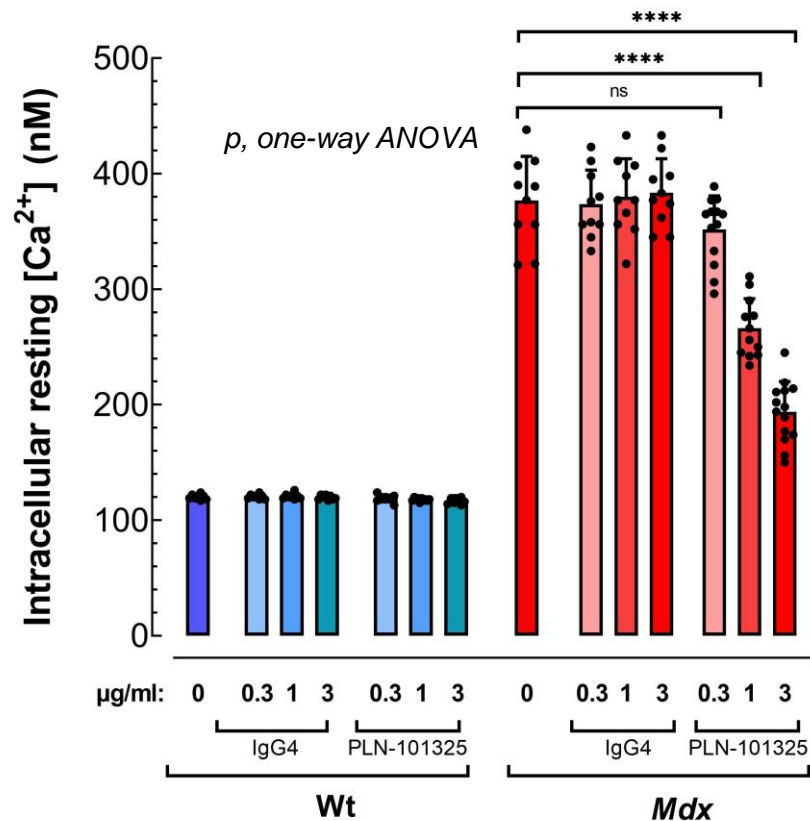
Institute of Biomedical Engineering
UNIVERSITY OF TORONTO

Effect of PLN-101325 in Ca²⁺ Homeostasis and Resting Membrane Potential of B10-mdx Myotubes

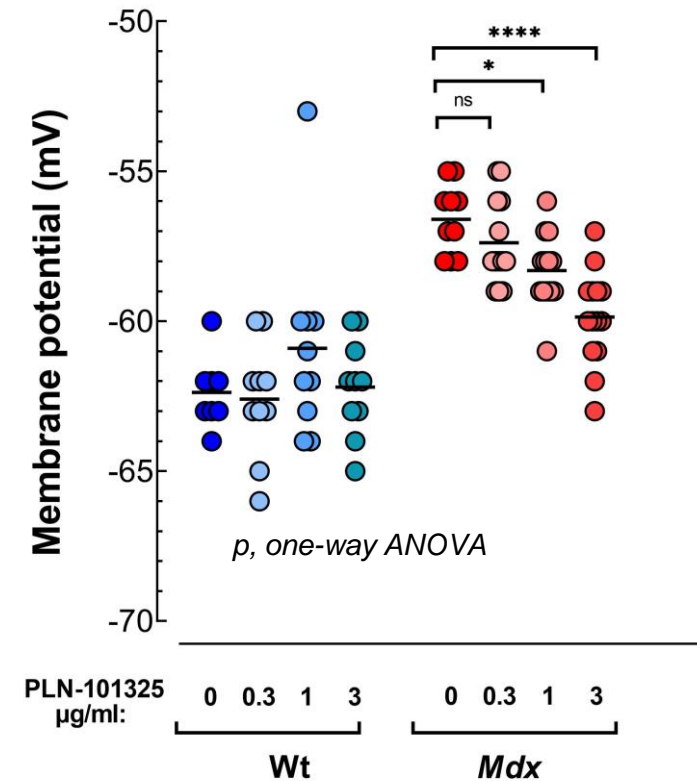
Reduced intracellular resting calcium and hyperpolarization of the membrane potentially support improved plasmalemmal integrity by PLN-101325



Intracellular resting Ca²⁺



Resting membrane potential



Dr. Jose R. Lopez

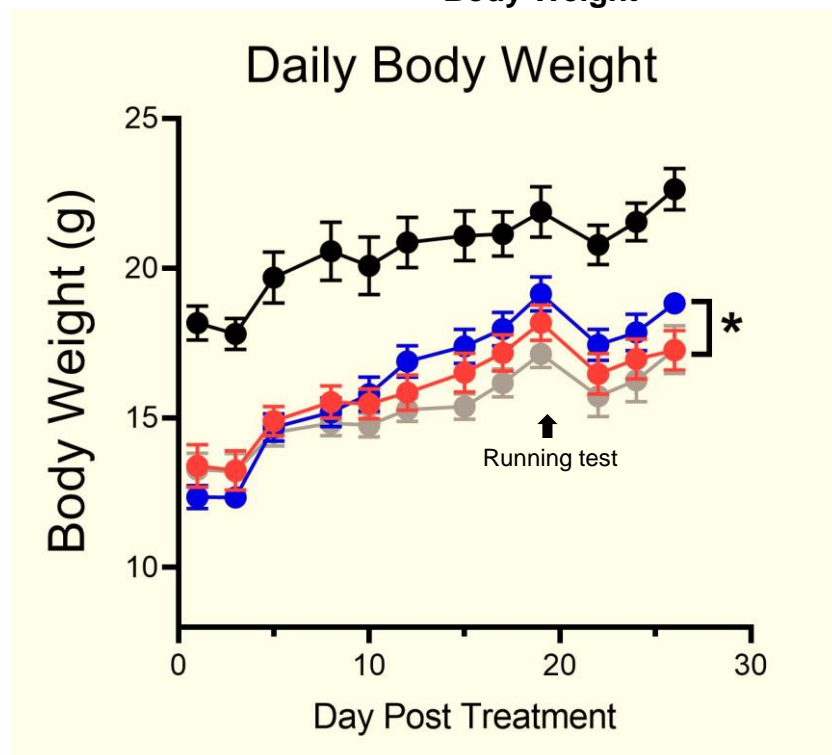
Mount Sinai
MEDICAL CENTER

Body Weight Improvement at 4 and 12 Weeks of Treatment

PLN-101325 3x/ wk IP
5-6 wk old D2-MDX mice

4-week

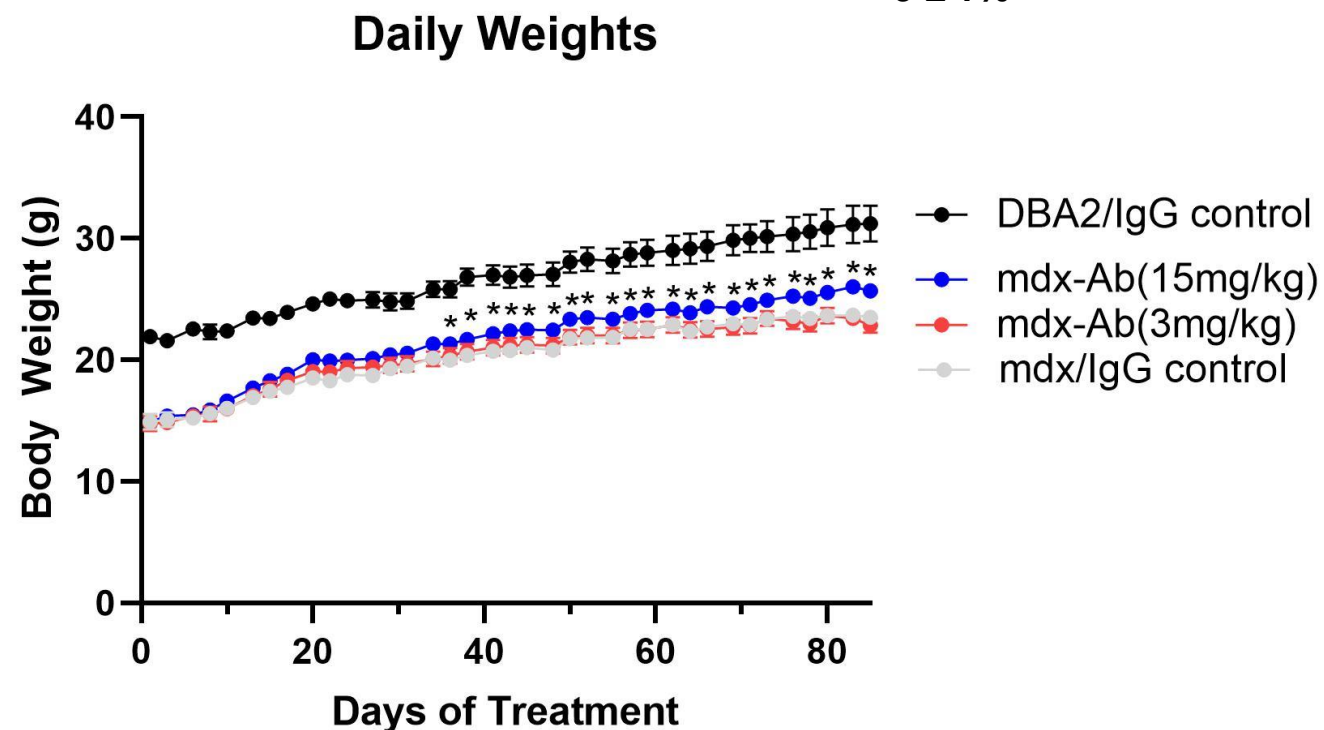
$8 \pm 3\%$ Increase in
Body Weight



12-week

$9 \pm 1\%$ Increase in
Body Weight

Weight Increase
 $9 \pm 1\%$



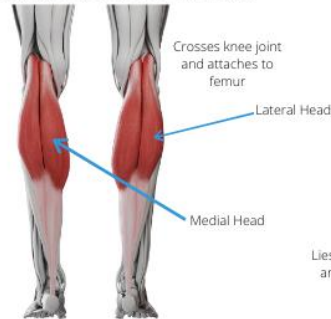
Improved Response to Post Eccentric Injury at 4 and 12 Weeks of Treatment

Plantar flexion test

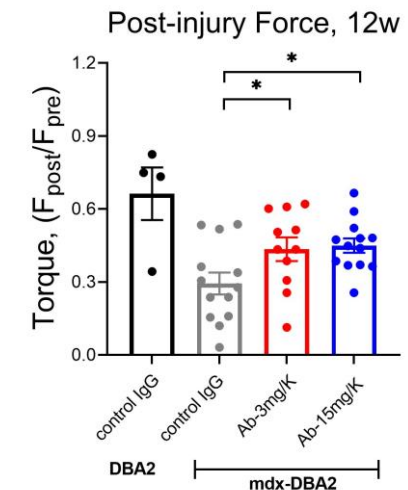
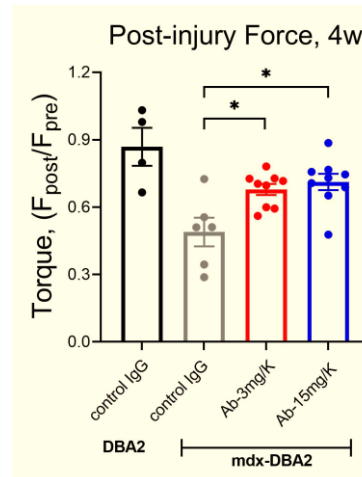
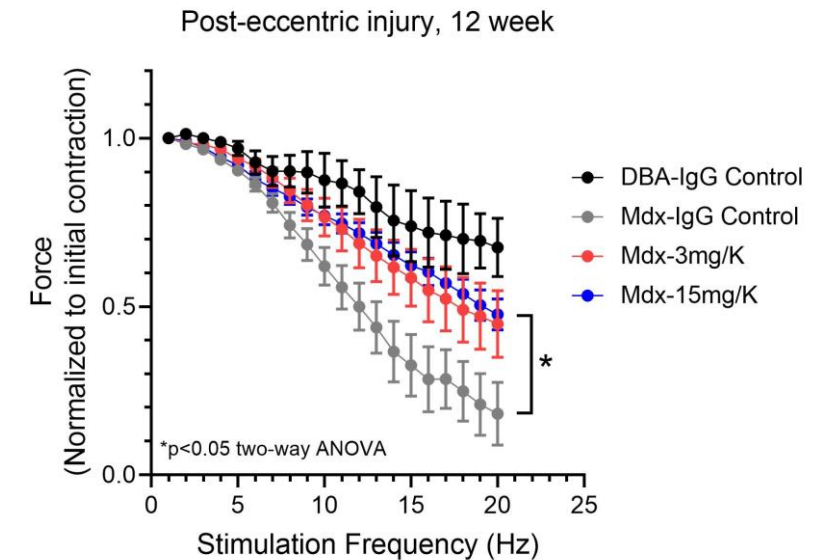
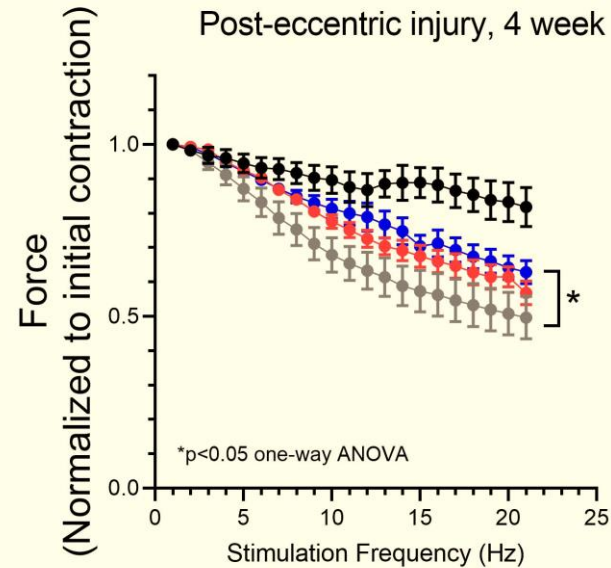
- Gastrocnemius (GC): Premier mover muscle for plantar flexion.
- GC only muscle to join both ankle and knee.



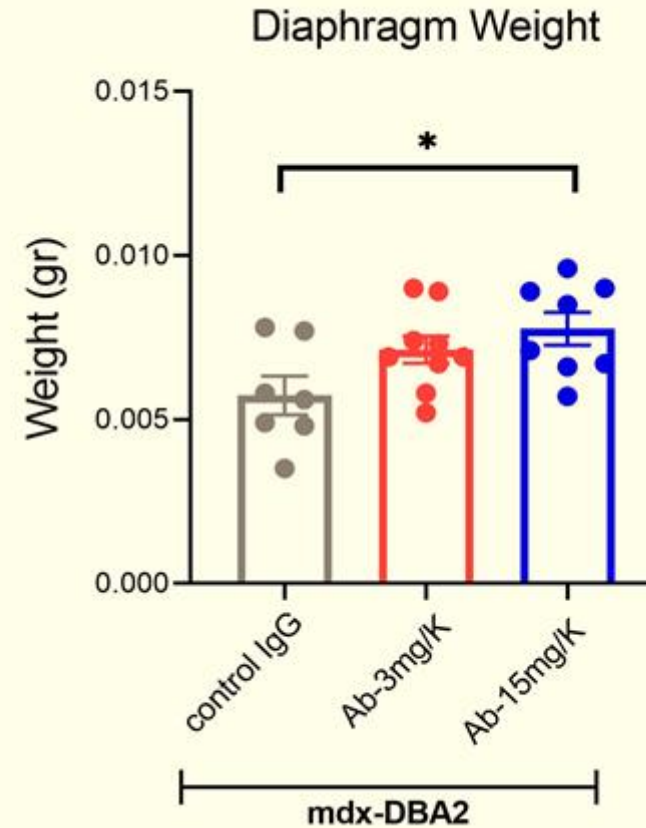
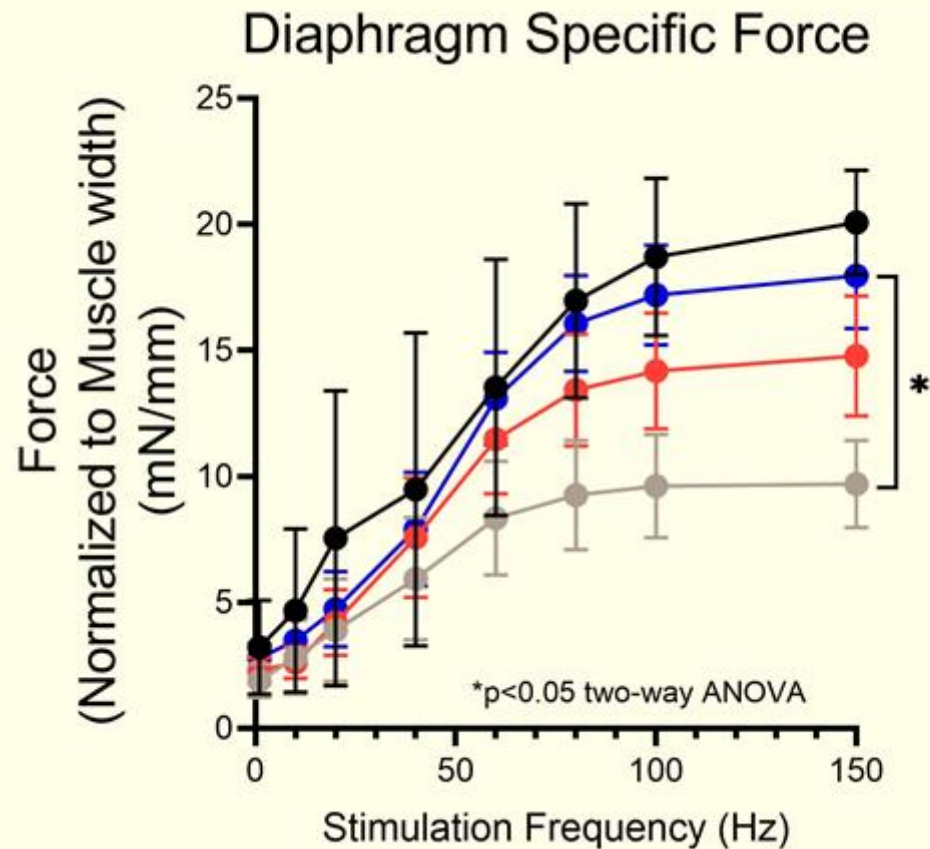
Gastrocnemius



Eccentric muscle injury protocol: A series of 20 tetanic stimulations (80Hz, 0.2ms pulse, 500ms duration) are delivered at 0.1Hz frequency. The foot is rotated against the direction of contraction by 10° over 250ms, resulting in an eccentric contraction



Diaphragm Force Significantly Improved at 4 weeks



277 Serum Proteins Differed Between MDX and Control Mice and Were Improved with PLN-101325 Treatment



somalogic

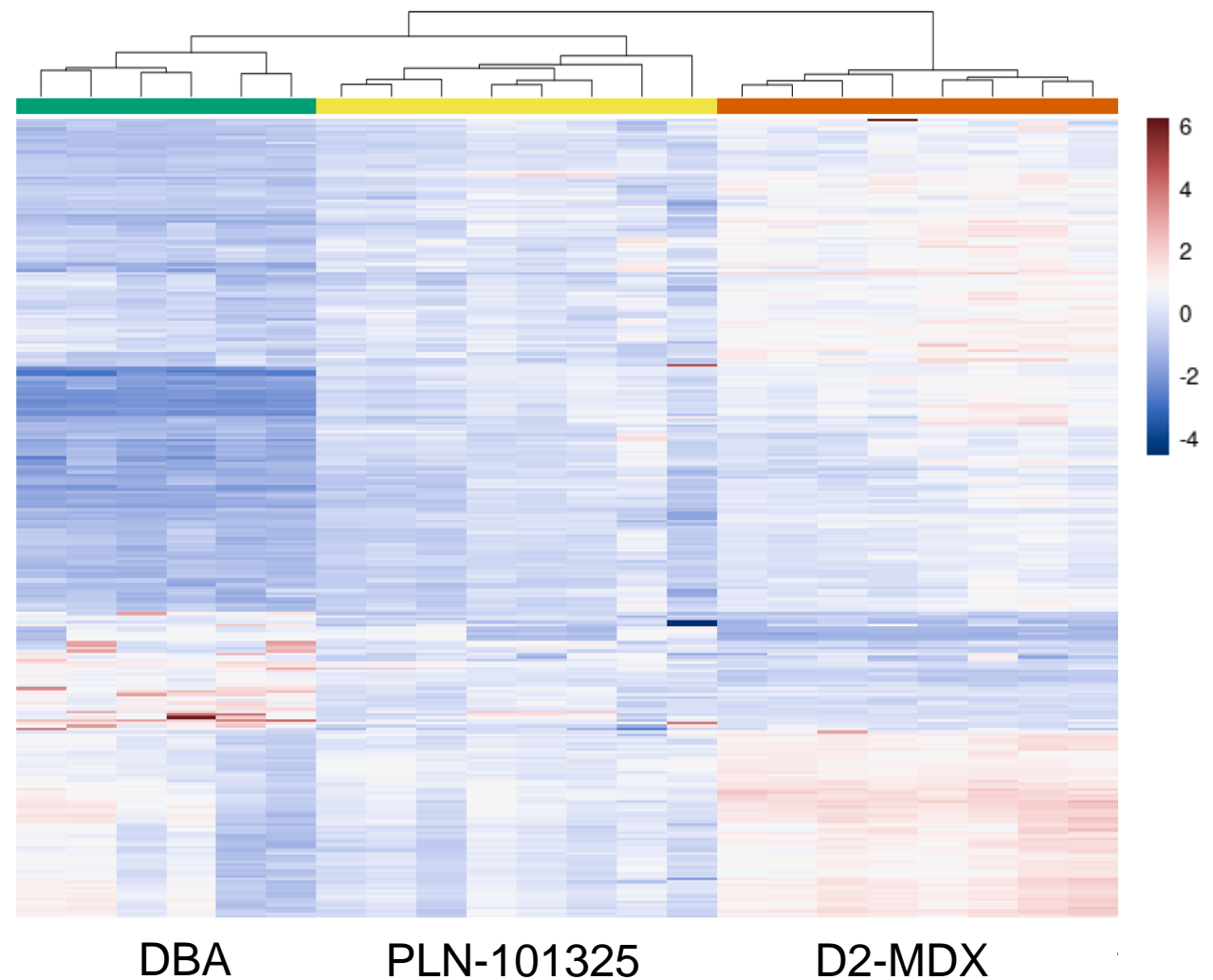
SOMAscan protein
biomarker discovery assay
7,596 human proteins
(not all detect mouse)

- 277 proteins were different between MDX and DBA
- PLN-101325 moved protein levels toward normal

FDR ≤ 0.25

$\text{abs}(\log_2\text{FC}) \geq 1$

Unsupervised hierarchical clustering with euclidean distance

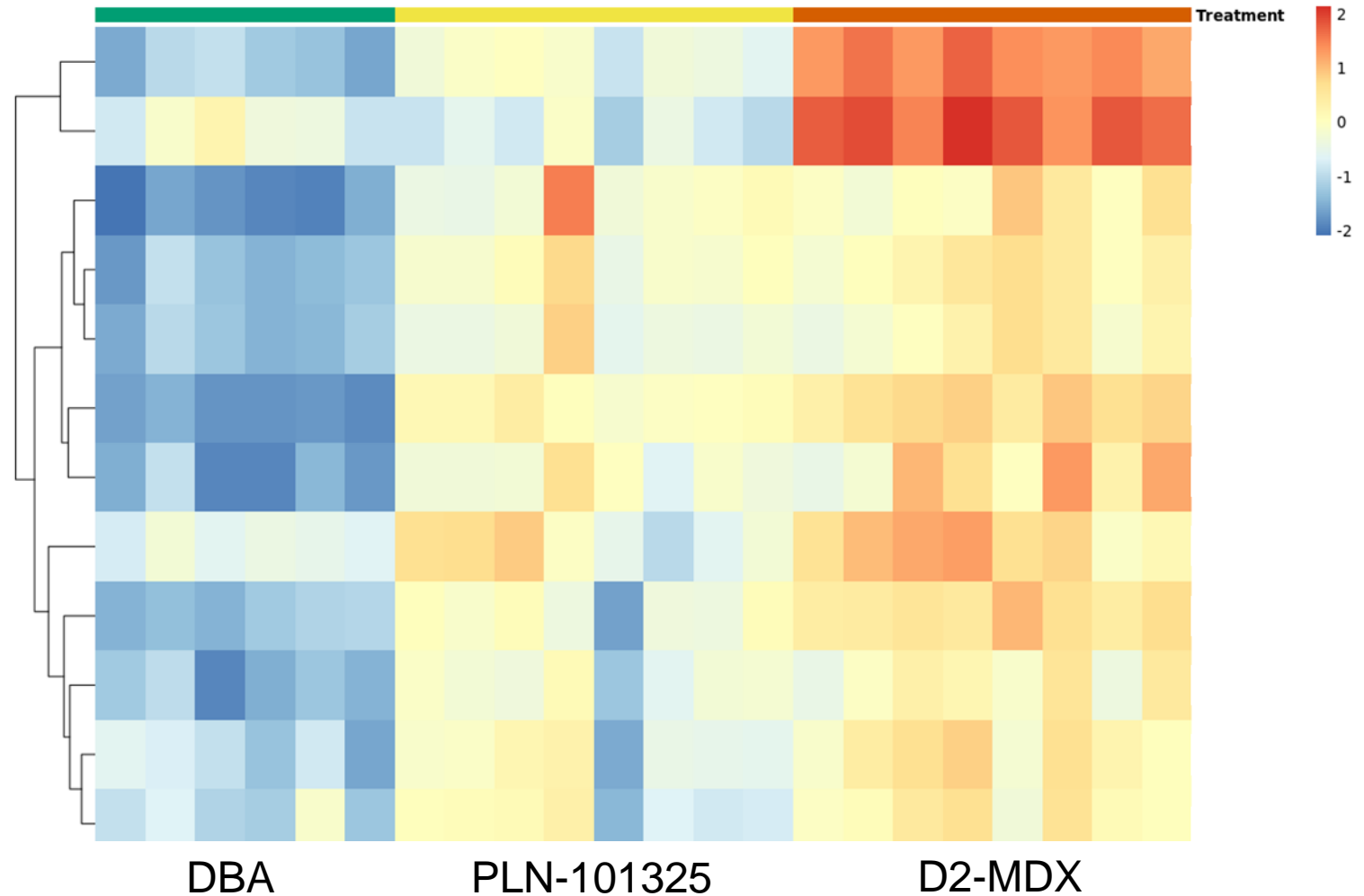


Glycolysis and Gluconeogenesis Proteins



somalogic

- PLN-101325 reduced circulating biomarkers of glycolysis and gluconeogenesis
- May reflect reduced injury in glycolytic (fast) muscle fibers



PLN-101325: A Novel Disease Modifying Approach in DMD

- Increasing $\alpha7\beta1$ -laminin binding can compensate for loss of dystrophin in myofibers as well as satellite cells
- Potential for clinical benefit in DMD in combination with current standard of care as well as gene targeted therapies.
- Improvement in respiratory and potentially cardiac function can address older patients who may not be good candidates for gene therapy
- May have benefit in other muscular dystrophies (Congenital MD's & LGMD)
- Clinical trials expected to begin in 2023





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