New Hope For Severe Rare Muscle & Lung Disease Patients

Building a New Class of Medicines

Physiocrine Based Therapeutics To Promote Tissue Homeostasis

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Treating Rare Disease Patients with Agonists of Homeostatic Pathways

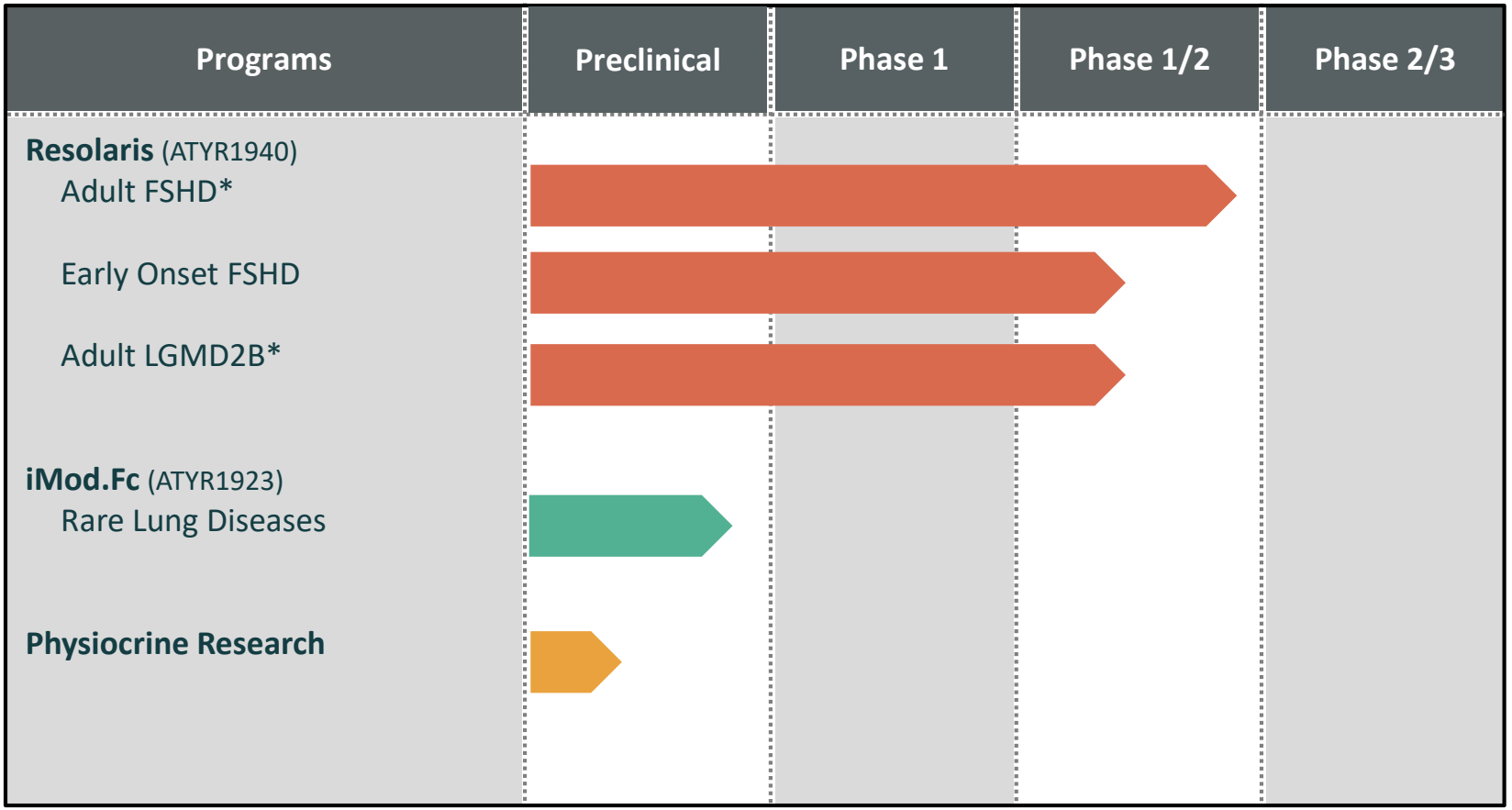
Physiocrine* Biology	• Pioneering new biology to provide new therapeutic intervention points • Human proteins evolved from gene family over more than 3 billion years
Resokine Pathway	• Potentially new treatment paradigm of immuno-modulation • In vivo, MOA and patient data suggest homeostatic role in muscle & lung
Resolaris: Drug Candidate For Multiple Rare Myopathies	• 1st Resokine pathway agonist muscular dystrophy trial completed • Potential activity signals in FSHD • 3 ongoing trial readouts expected in December 2016
Biologics Pipeline & Rare Disease Business Model	• 2nd Resokine agonist (iMod.Fc) for lung disease clinical trials in 2017 • Building franchises in rare diseases influenced by an immune component

**Proteins for life (physio) specific activity (crine)*

Harnessing the Power of Physiocrines for Patients

1st in class candidates for rare diseases with an immune or fibrotic component

aTyr Pipeline



Indications selected on basis of mechanism of action and biology along with potential for significant treatment effect

**FSHD = Fascioscapulohumeral Muscular Dystrophy*
**LGMD2B = Limb-Girdle Muscular Dystrophy 2B*

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New classes of biology have led to meaningful medicines

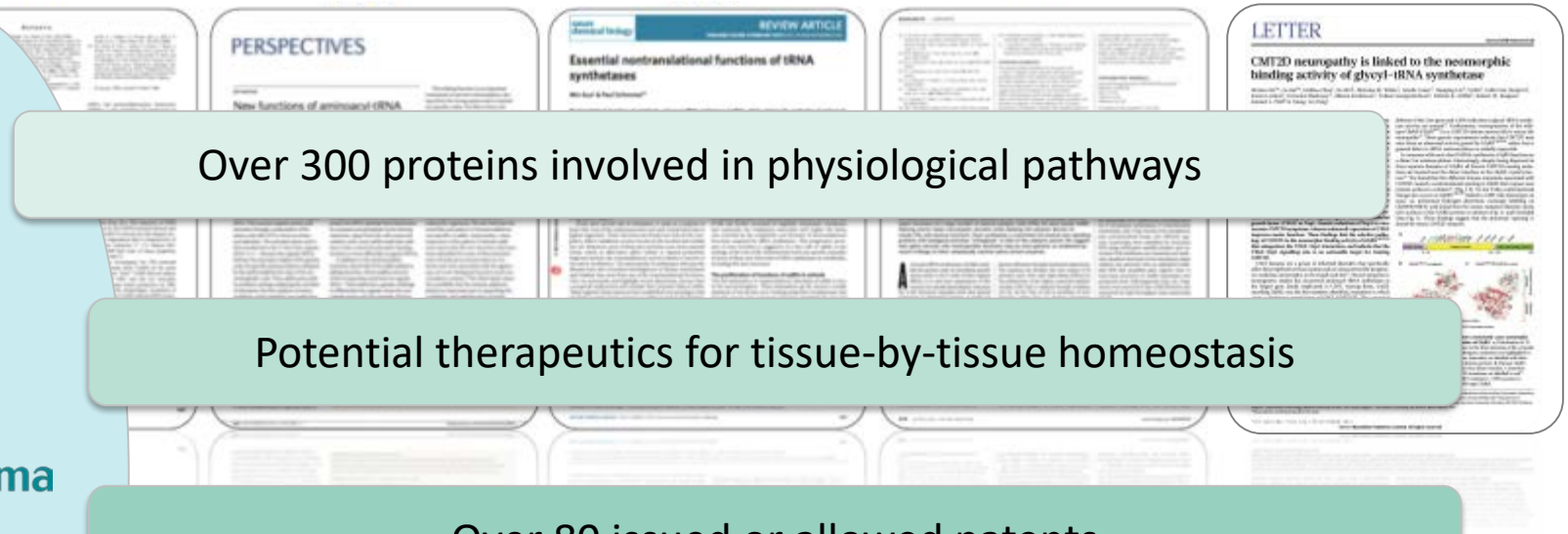
- ***TNF Inhibitors*** *(Humira® WW sales over $14B in 2015)*
- ***Complement inhibitors*** *(Soliris® net product sales over $2.6B in 2015)*
- ***Insulins*** *(used by over 3 million Americans to treat diabetes in 2012)*

Potential of Physiocrine Proteins

Discovery of a New Class of Proteins from Alternative Splicing of Ancient Genes

Pioneering New Biology for Meaningful Medicines

Science 1999 | **Nature 2010** | **Nature 2013** | **Science 2014** | **Nature 2015**



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Over 300 proteins involved in physiological pathways

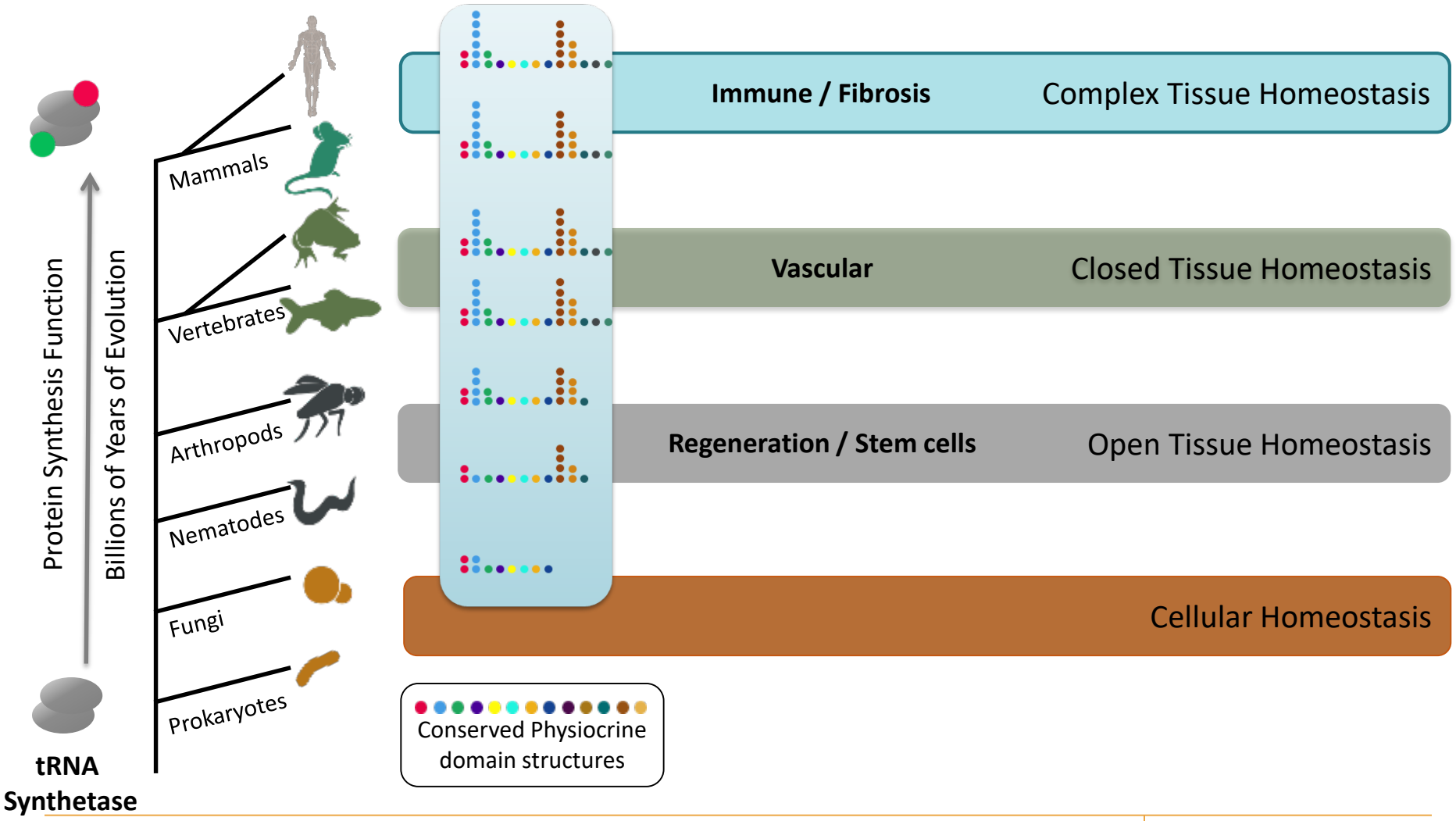
Potential therapeutics for tissue-by-tissue homeostasis

Over 80 issued or allowed patents

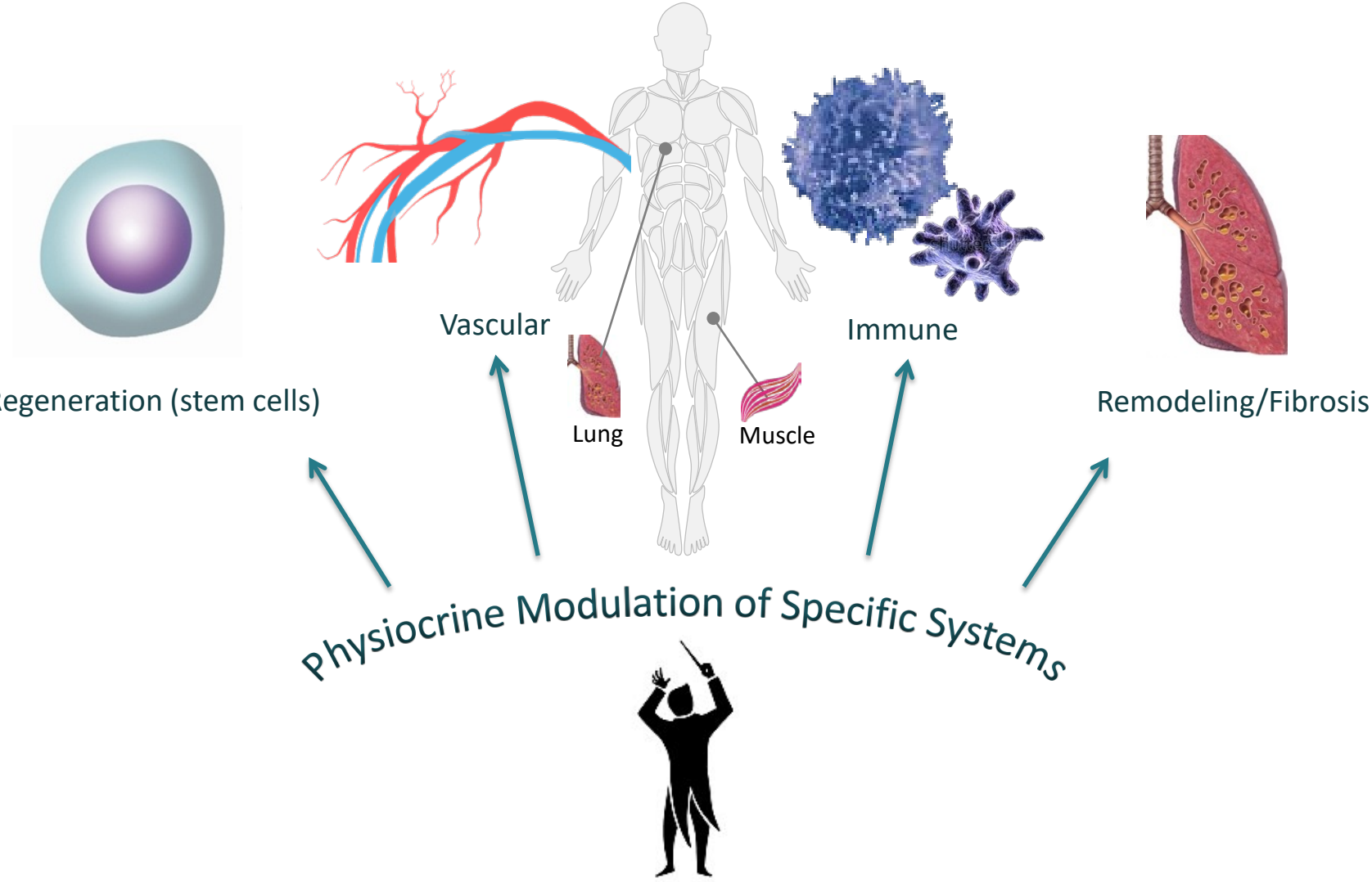
Focused on homeostasis related to immune & fibrotic pathways

Evolution of Homeostasis & Physiocrines

Physiocrine hypothesis: physiological modulation from primordial tissue homeostasis



Physiocrine Orchestration of Homeostasis



Harnessing the Resokine* Pathway

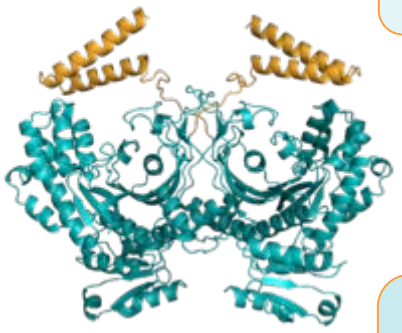
Natural Pathway From Skeletal Muscle to Treat Multiple Rare Muscle Diseases

**Resokine: for resolution of immune activity*

Resokine Pathway Paradigm

1st Physiocrine Pathway Modulated in the Clinic

An extracellular homeostatic pathway that sets T cell responses



Arising from histidine aminoacyl tRNA synthetase (HARS) gene

Changes activated T cell responses at levels <100pM

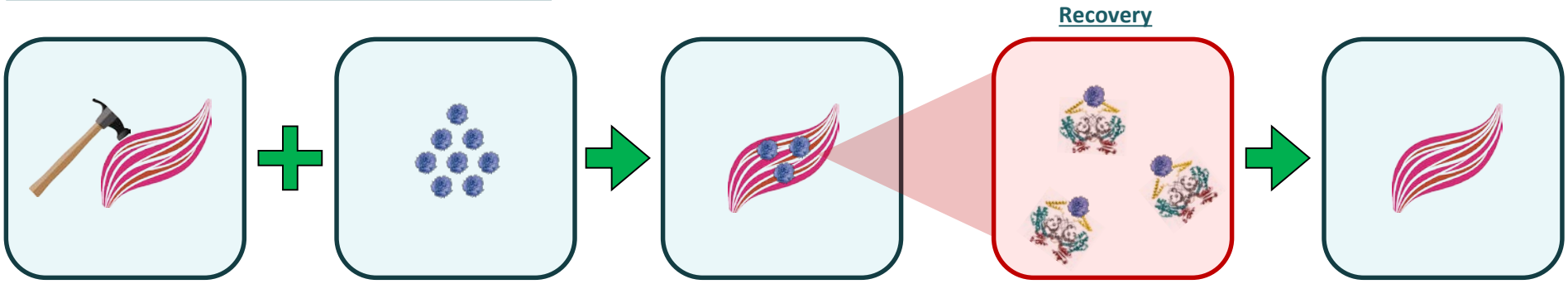
Resokine pathway disruption or insufficiency leads to inappropriate immune responses, contributing to muscle & lung disease

Resolaris, an agonist, plays a role in homeostasis & T cell responses in muscle

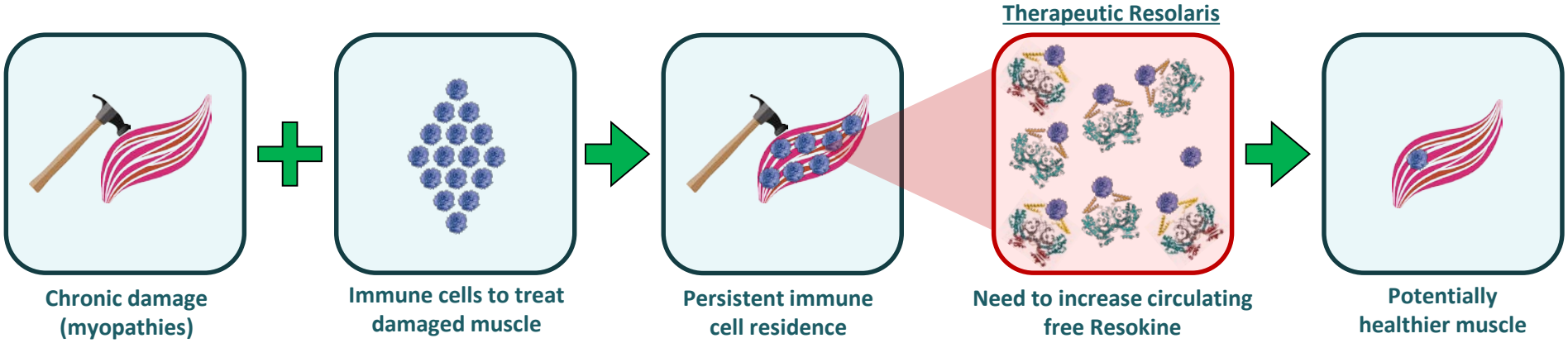
Model of Resokine Pathway

In skeletal muscle health and disease

Healthy Repair of Acute Skeletal Muscle Damage:



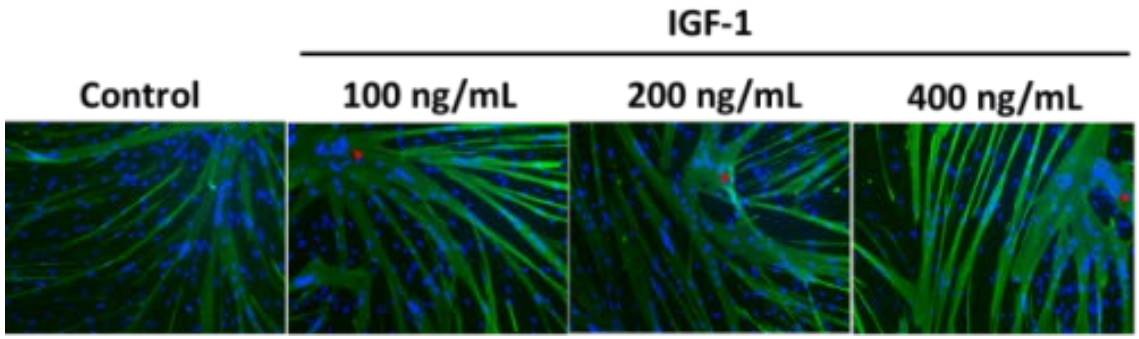
Our Hypothesis - Potential of Resolaris:



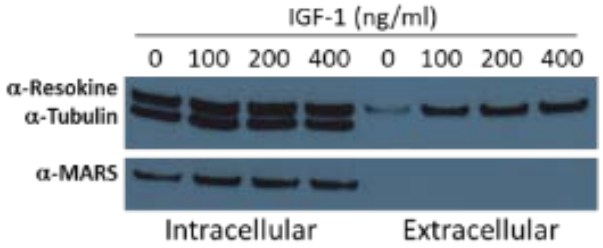
Resokine Release From Differentiating Myoblasts

Linking the Resokine pathway to muscle biology

PRE-CLINICAL

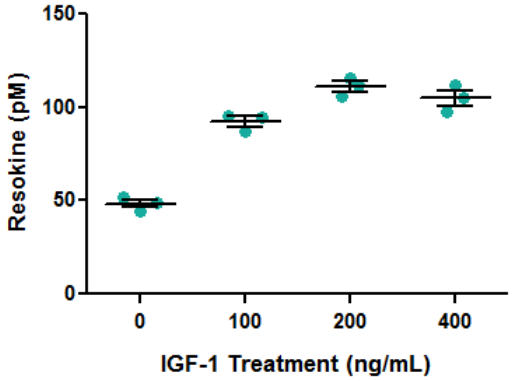


Resokine (Western Blot)



(~100pM Resokine)

Extracellular Resokine (ELISA)



Antibodies sufficient to block 100pM Resokine
block >50% of differentiation (slower)

Human myoblasts were isolated from a healthy volunteer properly consented and not in a clinical trial

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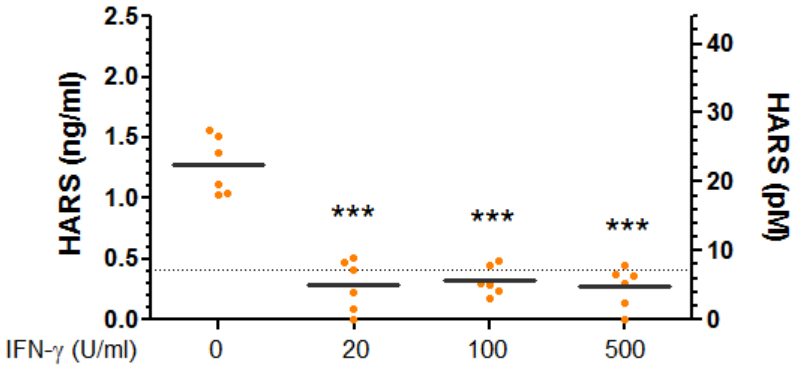
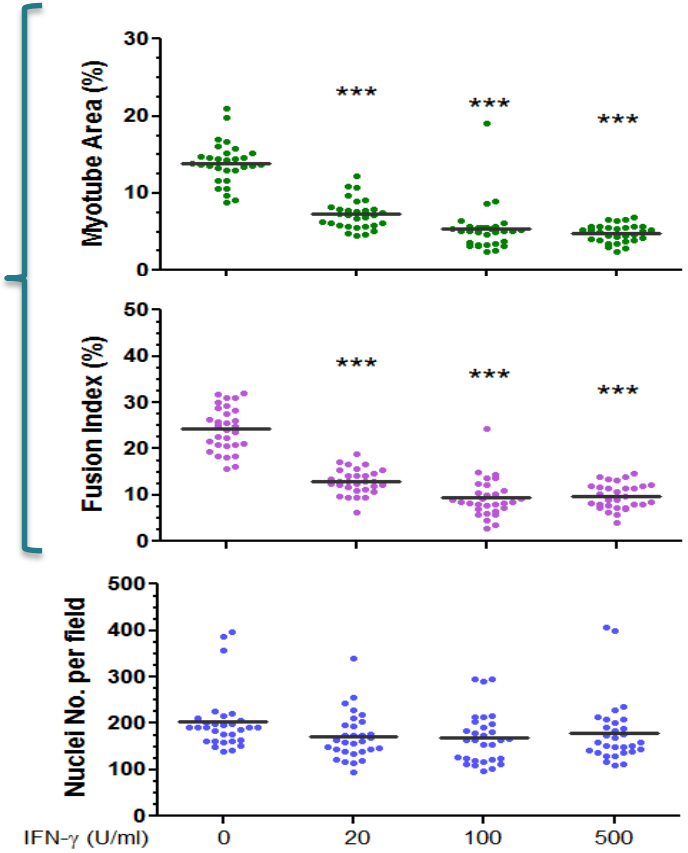
IFN-γ Reduces Resokine Release & Myotube Differentiation

Resokine Released from Myotubes



Myotube differentiation

Cell viability



*p<0.05, **p<0.01, ***p<0.001, n=6 (ELISA) or 30 (10 images/well×3 wells)

Human myoblasts were isolated from a healthy volunteer properly consented and not in a clinical trial

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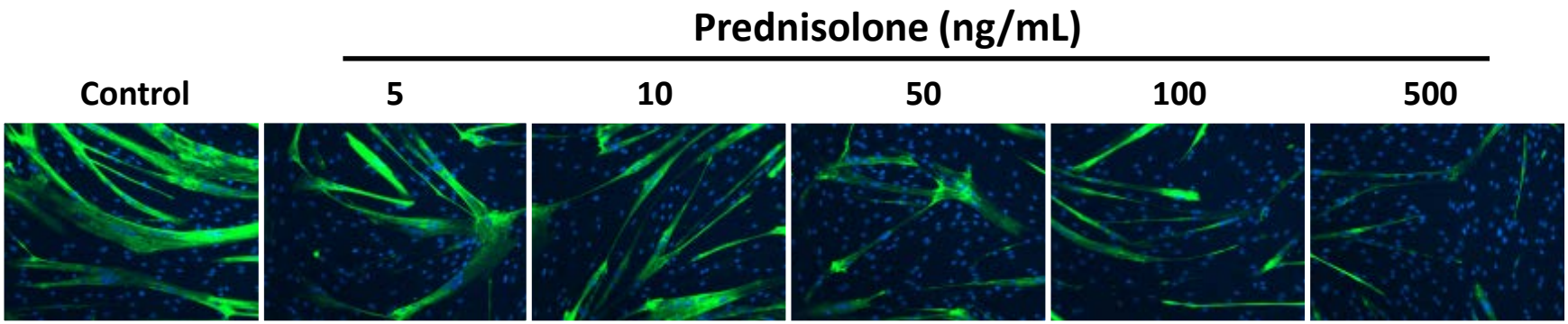
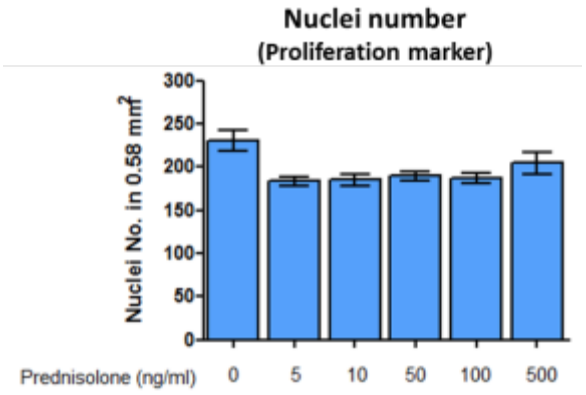
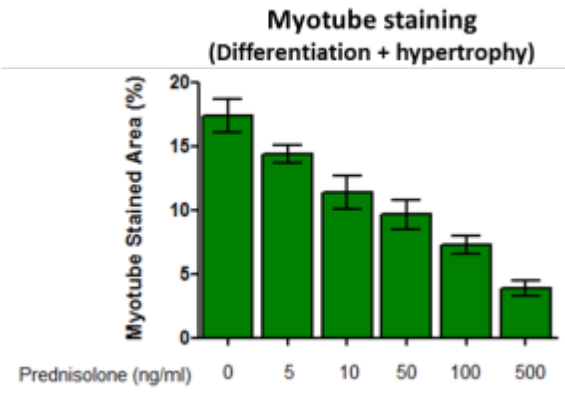
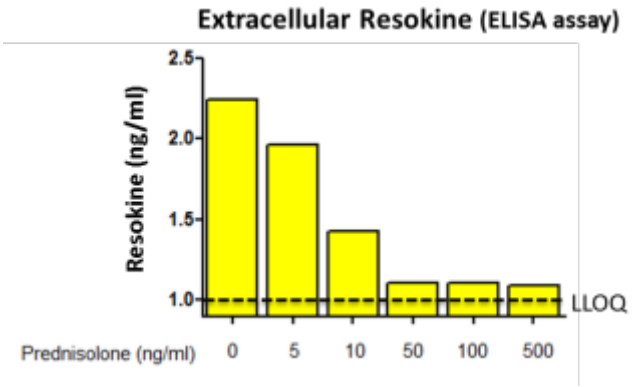
Steroid Treatment Decreases Muscle Growth & Resokine Release



Myotube (myosin)/Nuclei (Hoechst), Images at 10× magnification; **Differentiation Day 0-6**







Human myoblasts were isolated from a healthy volunteer properly consented and not in a clinical trial

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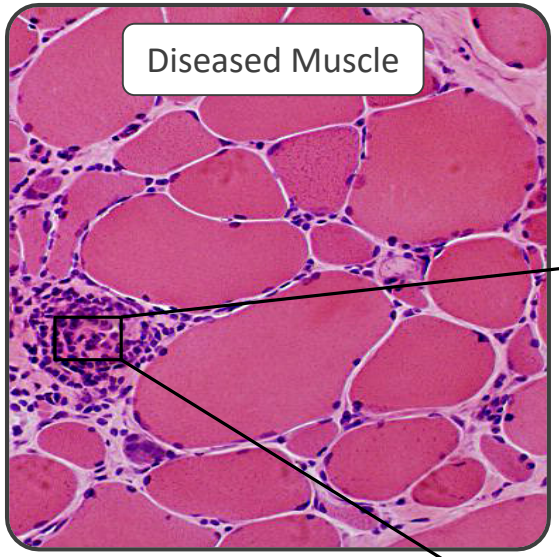
T Cell Release of Granzyme B Can Cause Muscle Damage

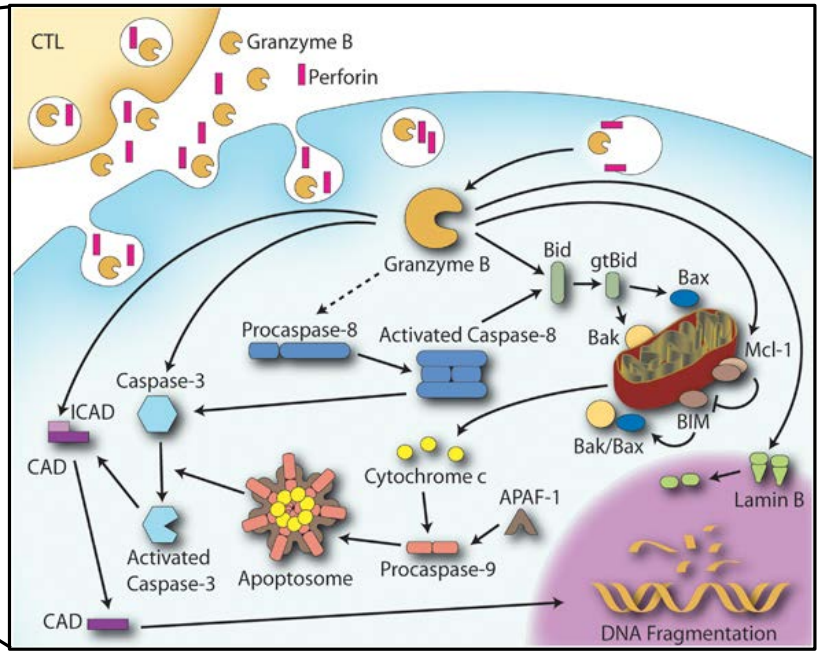
Excessive immune cell invasion contributes to a disease immune phenotype

Immune cell infiltration



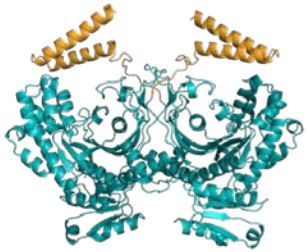
Granzyme B expressing cells cause muscle cell damage

Cell Death

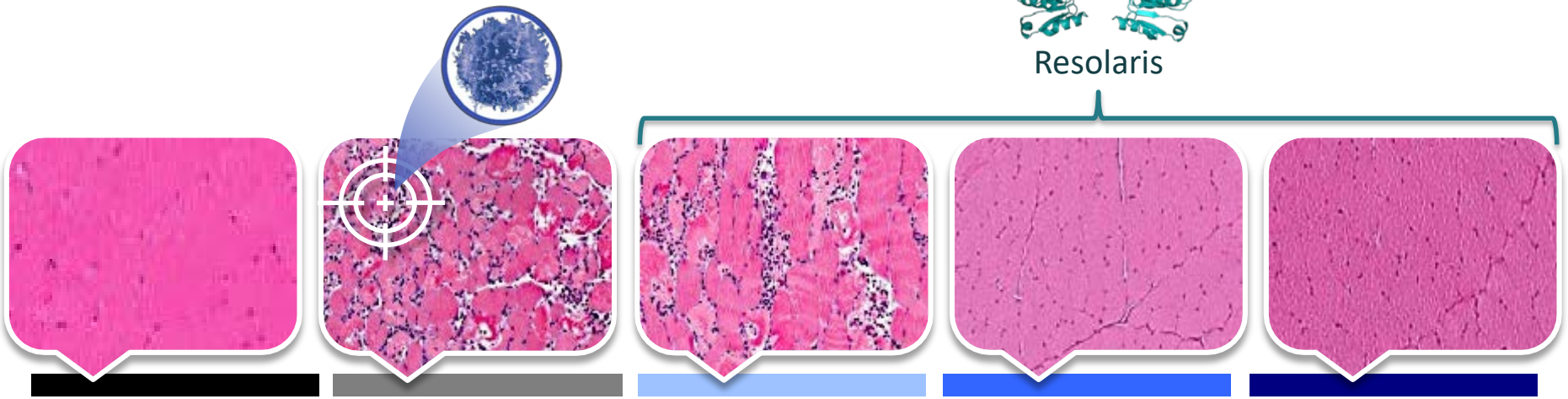


Treating Immune Cell Invasion in Skeletal Muscle

One week of therapeutic treatment in two week Statin myopathy model



Resolaris



Control	Statin days 1-14 (toxic dose)	0.3 mg/kg Resolaris days 7-14 Statin days 1-14	1.0 mg/kg Resolaris days 7-14 Statin days 1-14	3.0 mg/kg Resolaris days 7-14 Statin days 1-14

↓ Cytokines, ↓ T-cells and ↓ Monocytes
with Resolaris administration

aTyr unpublished data

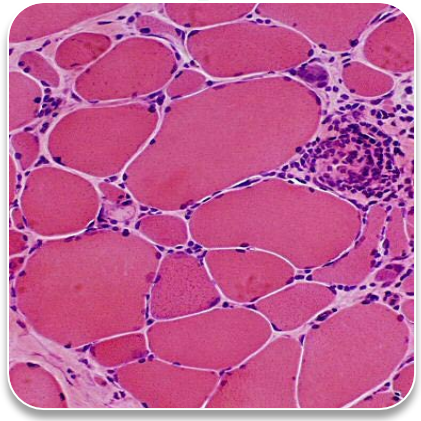
Resokine Pathway Linked to Rare Genetic Muscle Diseases

Aberrant proteins, immune invasion & deteriorated muscles

Facioscapulohumeral Muscular Dystrophy (FSHD)

Multiple aberrant proteins in muscle cells

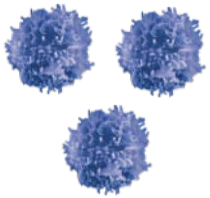
Genetic mutation



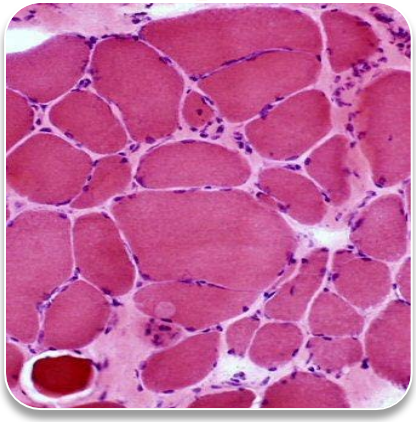
Limb Girdle Muscular Dystrophy (LGMD)

Aberrant proteins for each form of LGMD

Aberrant protein expression



T cell proliferation



Duchenne Muscular Dystrophy (DMD)

Aberrant dystrophin proteins

Immune cell infiltration

Frisullo *et al.*, J. *Clin. Immunol.*, 2011

Flanigan *et al.* Human Gene Therapy, 2013

Gallardo *et al.* Neurology, 2001

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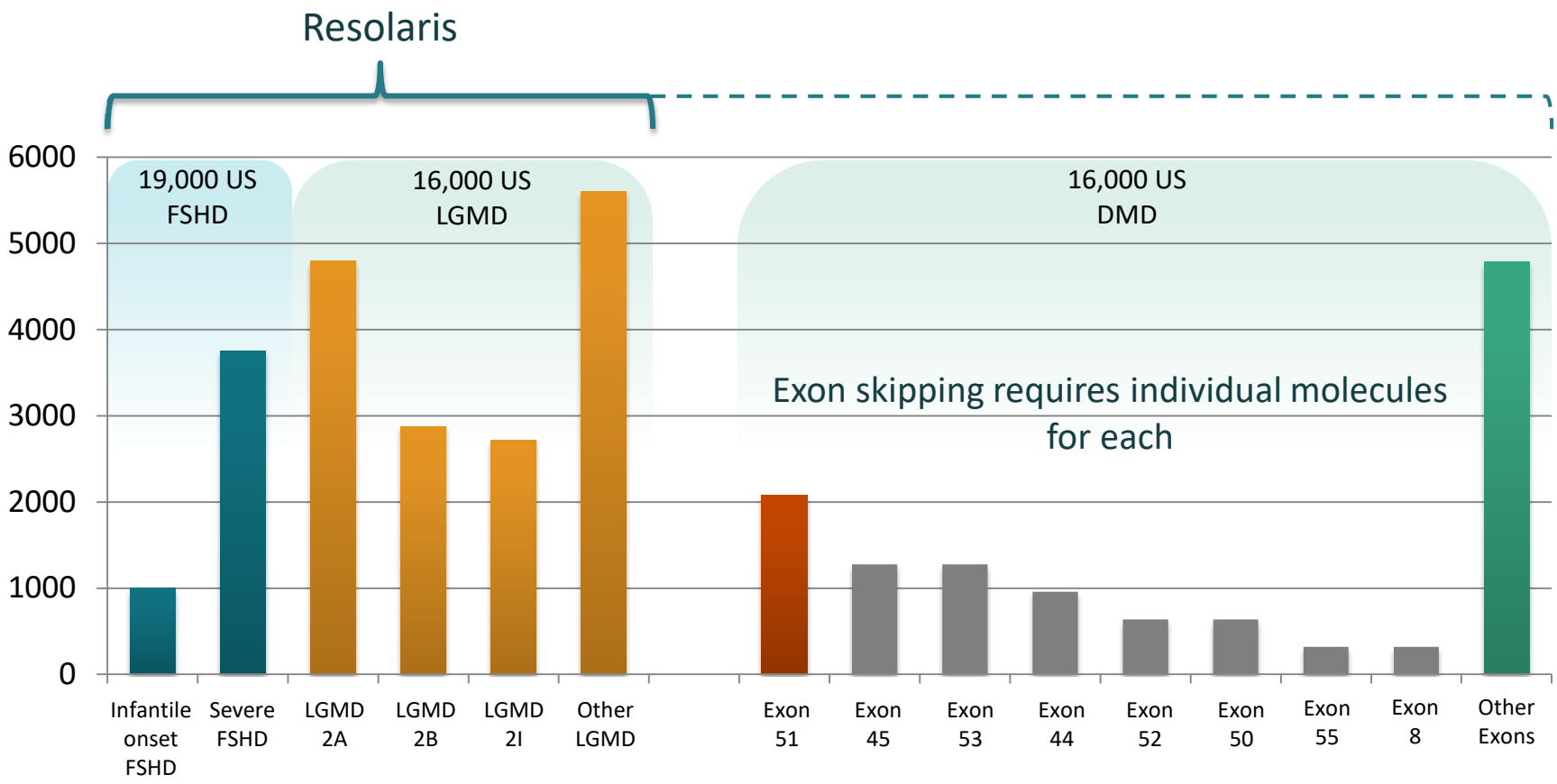
Resolaris: One Product, Multiple Rare Diseases

Promise for severely afflicted myopathy patients

MARKET OPPORTUNITY



- ✓ Leadership position in FSHD and LGMD2B clinical trials
- ✓ Leverage registries, sites, advocacy and common physician base
- ✓ Mechanism applicable to multiple rare myopathies

***FSHD**: Average prevalence rates of FSHD are approximately 1/17,000. Applying this rate to the US population based on recent census data equals approximately 19,000.*
***LGMD:** 16,000 cases estimated in US population. 1/20,000 Wickland and Kissel, Neural. Clin. 2014. Relative Prevalence of Limb Girdle Muscular Dystrophies in the United States Population. Wicklund et al., Neurology 2013.*
***DMD:** Prevalence of approximately 5/100,000. Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - May 2014 - Number 1*

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Resolaris Clinical Development

Potential New Therapy for Patients with Rare Muscle Diseases

Clinical Strategy for Resolaris in Skeletal Muscle

Staging rare muscle disease indications

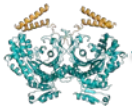
CLINICAL DEVELOPMENT

1st Physiocrine based therapeutic in clinic

To promote muscle homeostasis

Focus on Rare Myopathies with an Immune Component (RMIC)

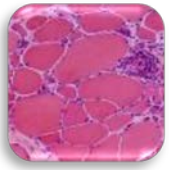
003, 004 & 005 data readouts expected in December 2016



Resolaris

Clinical Trials

RMIC	Preclinical	Phase 1	Phase 1b/2

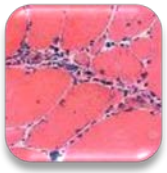


Adult FSHD[1]

- Phase 1b/2 Trial (002) – Completed
- Phase 1b/2 Trial (004) – Ongoing
- Phase 1b/2 ext. (005/006) – Ongoing

Early Onset FSHD

- Phase 1b/2 Trial (003) – Ongoing
- Phase 1b/2 ext. (006) – Ongoing



Adult LGMD2B[2]

- Phase 1b/2 Trial (004) – Ongoing
- Phase 1b/2 ext. (006) – Ongoing

Phase 1b/2 Patient Data to Best Inform Clinical Path Forward

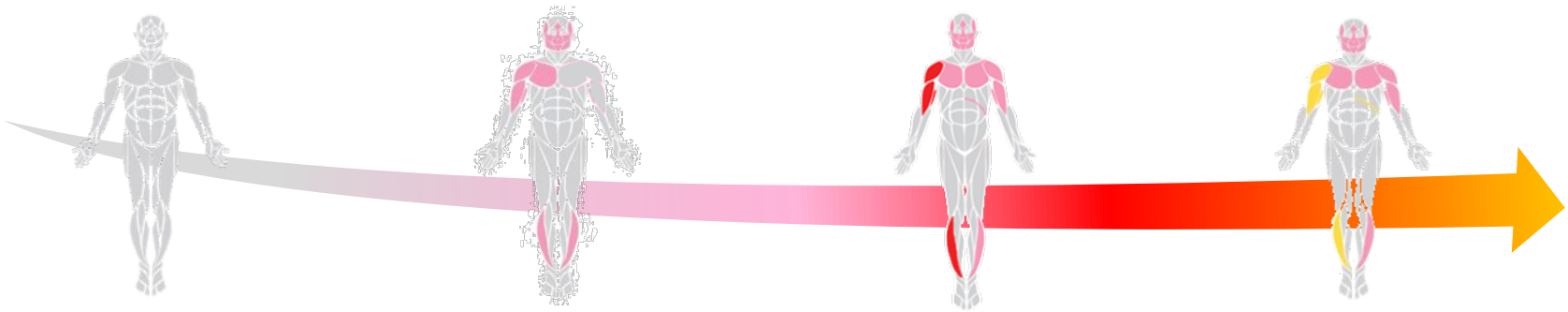
- Establishing data dossier on safety
- Exploring activity assessments such as PROs, biomarkers & muscle testing
- Directionality on endpoints for approval

[1] *Facioscapulohumeral Muscular Dystrophy*
[2] *Limb-girdle Muscular Dystrophy 2B*

Facioscapulohumeral Muscular Dystrophy (FSHD)

A progressive, debilitating muscular disease

Pathology	• Dominant/spontaneous toxic gain of function (↑ Dux4) • Immune infiltration by activated T cells [1], primarily $CD8^+$ • Defects in biochemical/physical/structural muscle components leading to tissue death
Clinical	• Debilitating, progressive skeletal muscle weakness • Severe pain, chronic fatigue and respiratory insufficiency • Often diagnosed before adulthood (early onset form) • May have visual or auditory impairment (early onset form)
Standard of care	• No therapeutic treatments • Only supportive care provided



"Unaffected muscle" in an FSHD Patient

Transition to immune activity

Muscle destruction

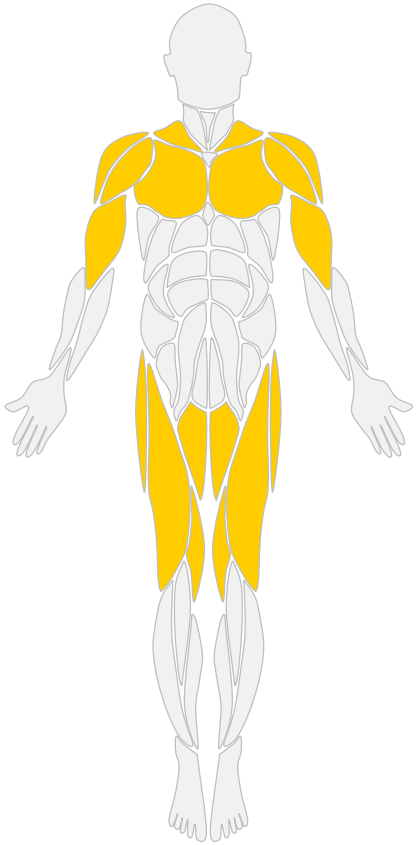
Infiltration of fat/atrophy

[1]*Frisullo et al. J Clin Immunol (2011) 31:155–166*

Limb-Girdle Muscular Dystrophy 2B (LGMD2B)

A severe muscle disease with a genetic loss of function

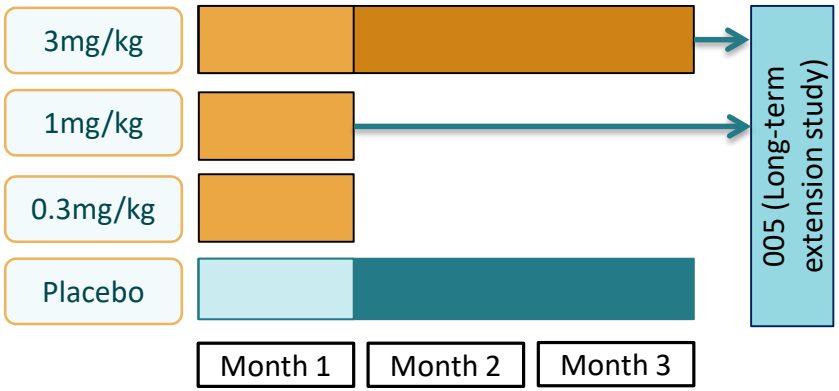
Pathology	• Toxic loss of function mutation (dysferlin) • Immune infiltrates consisting of $CD4^+$, $CD8^+$ and macrophages[1] • Muscle group progression
Clinical	• Debilitating, progressive skeletal muscle weakness • Challenges moving limbs • May have respiratory insufficiency
Standard of care	• No therapeutic treatments • Only supportive care provided



[1]*Gallardo et al. Neurology 2001;57:2136–2138; Yin et al. Int J Clin Exp Pathol 2015;8(3):3069-3075*

Adult FSHD (002) Trial

Study Design



- Double-blinded, placebo-controlled
- Multiple ascending doses
- N=20 (5 in each cohort)
- 3:1 Randomization (Resolaris:placebo)
- 4 sites in 4 countries

Study Objective

Evaluate Safety and Tolerability:

- Build safety dossier for Resolaris
- Generally well-tolerated at doses tested*

Evaluate Potential Activity Assessments:

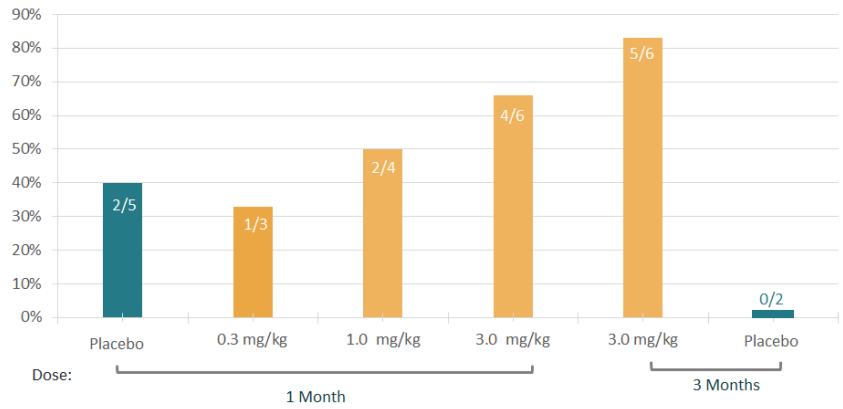
1. Manual Muscle Test (MMT):
   - Validated endpoint for functional strength
2. Individualized Neuromuscular Quality of Life (INQoL):
   - Validated patient reported outcome
3. Evaluate a new targeted MRI technique
4. Biomarker assessments

**One reversible infusion related reaction (IRR) patient in 002*

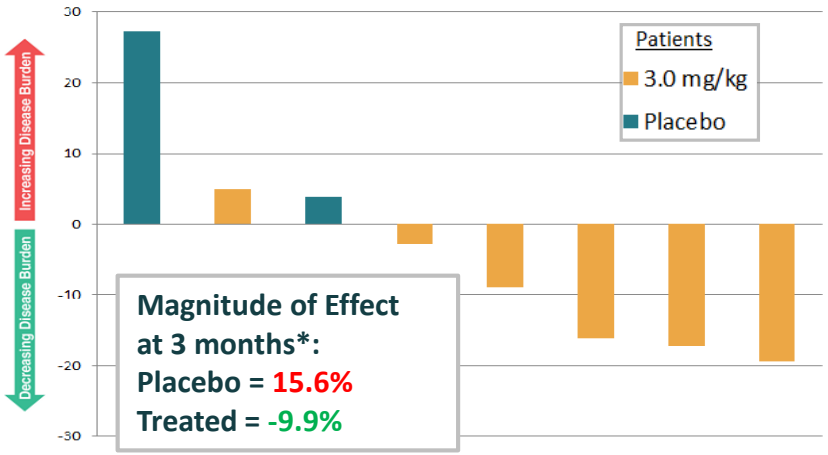
3 Month Adult FSHD (002) INQoL Results

Encouraging Improvement Signal in INQoL

% Responder Analysis:



Absolute Disease Progression by Patient:



INQoL: *Validated Patient Reported Outcome*

- Global systematic assessment used in clinical studies and trials (to test for increased disease burden)

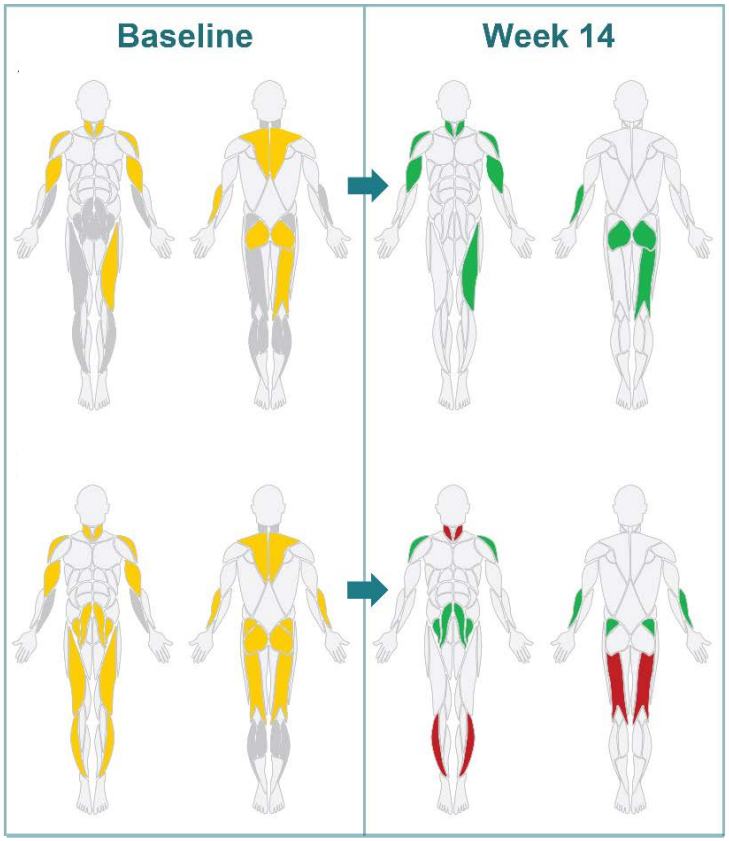
Encouraging Activity Signals:

- 5 of 6 patients in cohort 3 (3 mg/kg of Resolaris over 3 months) showed improvement in their INQoL score vs. 0 out of 2 patients on placebo
- Patients on Resolaris reported a **~9.9%** improvement in INQoL compared to a **~15.6%** worsening in the placebo group.
- Relative improvement v. 3.0 mg/kg cohort at 3 months was **~25.5%** *(p-value = 0.03)*

**Relative improvement placebo v. 3.0 mg/kg cohort at 3 months: 25.5% (p=0.03)*

Resolaris 3 Month Adult FSHD (002) MMT Results

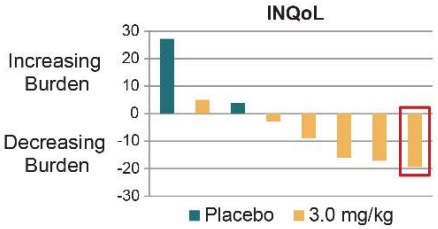
Sample of Patients' MMT scores on Resolaris



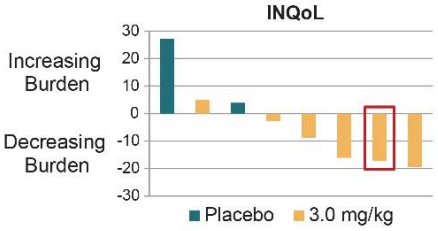
Non-impaired tested muscle
Impaired muscles

Improvement relative to baseline
Worsening relative to baseline

MMT % of Muscles Changed
Improved: 39.3
Stable: 60.7
Worse: 0.0



MMT % of Muscles Changed
Improved: 28.6
Stable: 50.0
Worse: 21.4



Manual Muscle Testing (MMT):

Validated Endpoint for Functional Strength

Encouraging Activity Signals:

- A trend for improvement was observed compared to placebo, especially in upper limbs
- 100% patients with an improved MMT score had an improved INQoL score

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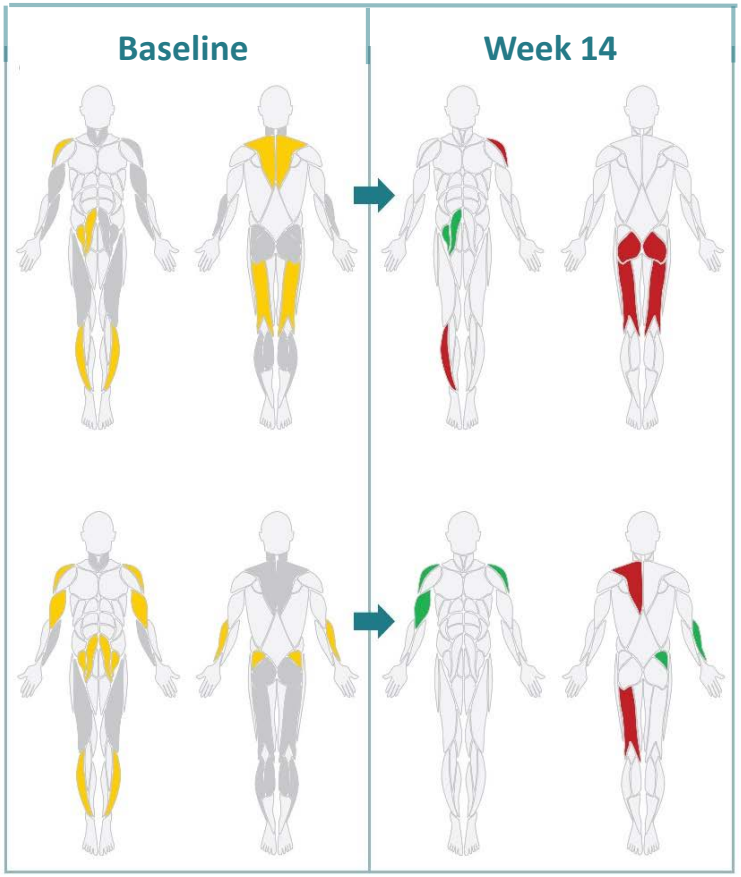
Placebo 3 Month Adult FSHD (002) MMT Results

Placebo Patient's MMT results

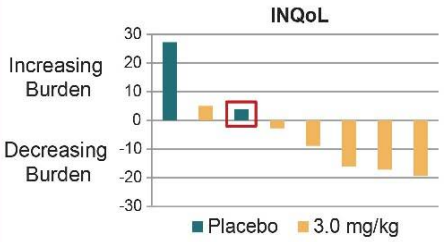


Non-impaired tested muscle
Impaired muscles

Improvement relative to baseline
Worsening relative to baseline

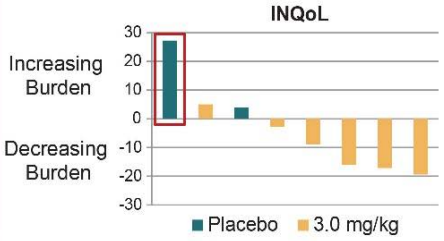
MMT % of Muscles Changed

Improved: 3.6
Stable: 75.0
Worse: 21.4



MMT % of Muscles Changed

Improved: 17.9
Stable: 75.0
Worse: 7.1



Manual Muscle Testing (MMT):

All patients on placebo, at 3 months, did not show trends for improvement in either INQoL or MMT

Resolaris Clinical Trial Summary 2016

Completion of Exploratory Trials

Trial	Indication(s)	Patients	Highest Dose	Design	Data Timing
002	Adult FSHD	3 dose cohorts (n=20 Total)	3mg/kg weekly	Placebo controlled, Double blinded; Interpatient Dose Escalation	Announced 1Q 2016
003	Early onset FSHD	Stage 1 (n=8) Stage 2 (n=8)	3mg/kg weekly	Open-label, Intrapatient Dose Escalation	4 pts. top-line Dec. 2016*
004	Adult LGMD2B, Adult FSHD	LGMD2B (n=10) FSHD (n=8)	3mg/kg biweekly	Open-label, Intrapatient Dose Escalation	18 pts. top-line Dec. 2016*
005	Adult FSHD	Rollover from 002	3mg/kg weekly	Long-term Safety Extension	Update Dec. 2016*
006	LGMD2B, FSHD, Early onset FSHD	Rollover from 003 & 004	3mg/kg weekly	Long-term Safety Extension	TBD

Ongoing Trial Objectives

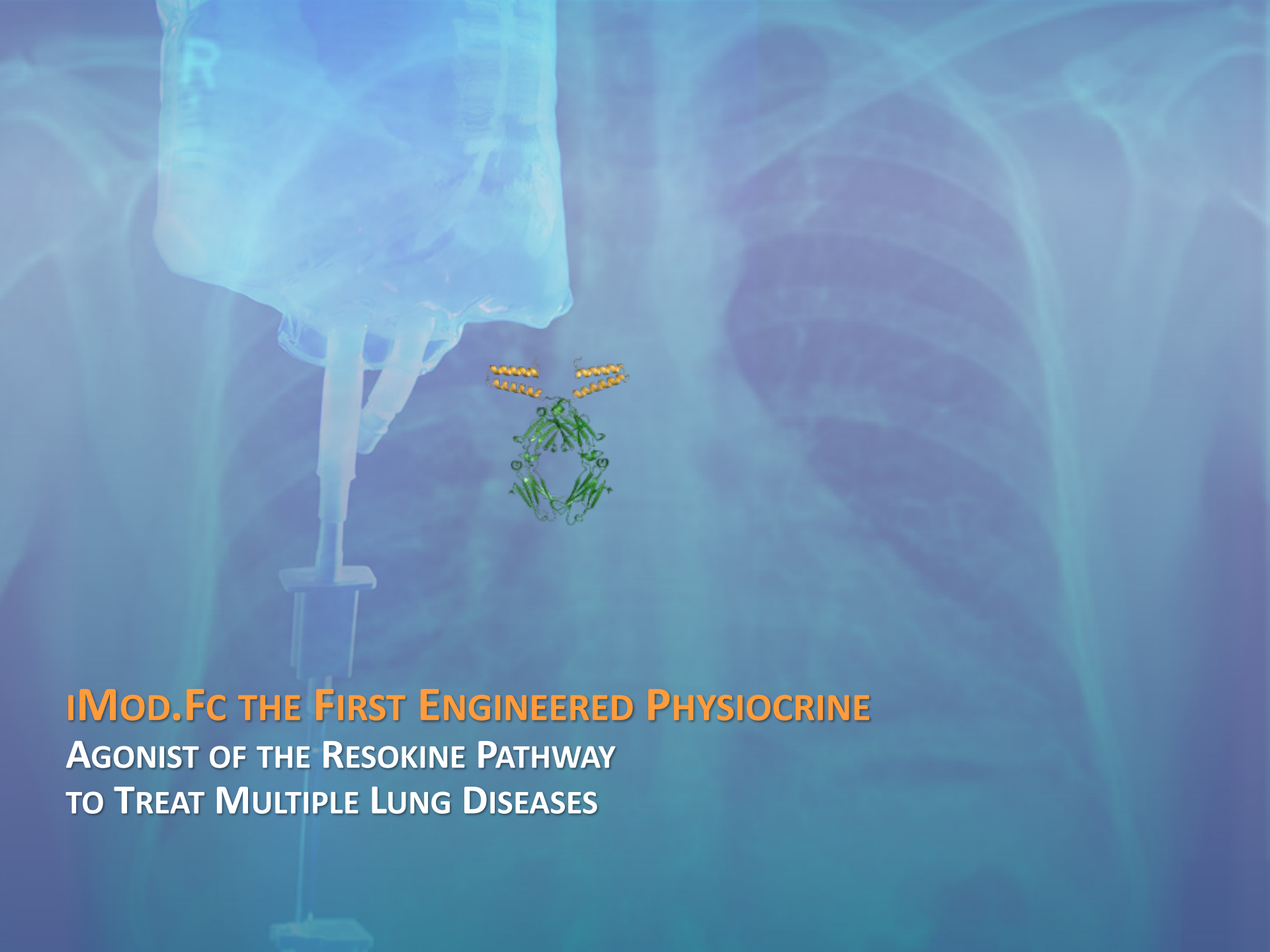
Evaluate Safety and Tolerability:

- Build safety dossier for Resolaris
- Explore multiple indications, different dosing regimens, longer duration

Evaluate Potential Activity Assessments:

1. Functional/Strength: MMT
2. Patient Reported Outcomes: INQOL
3. MRI / Biomarkers assessments

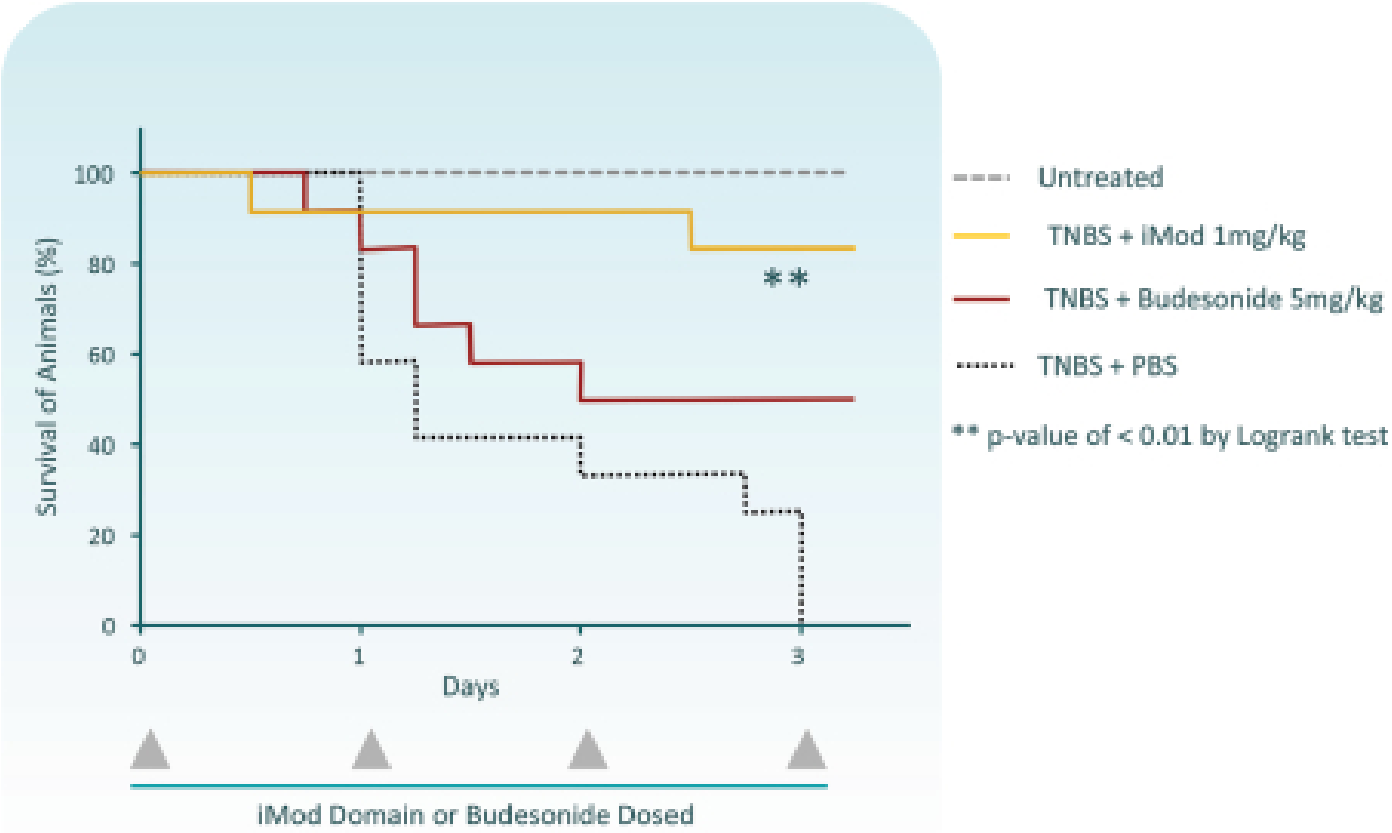
**According to current expectations*



iMod.Fc the First Engineered Physiocrine

Agonist of the Resokine Pathway to Treat Multiple Lung Diseases

Discovery of the Resokine iMod Domain



- Rodent model of severe immune cell activity induced by administration of trinitrobenzene sulfonic acid (TNBS)
- Animals administered the iMod domain survived longer than those given either the vehicle control phosphate buffer solution (PBS) or Budesonide ($p<0.01$)

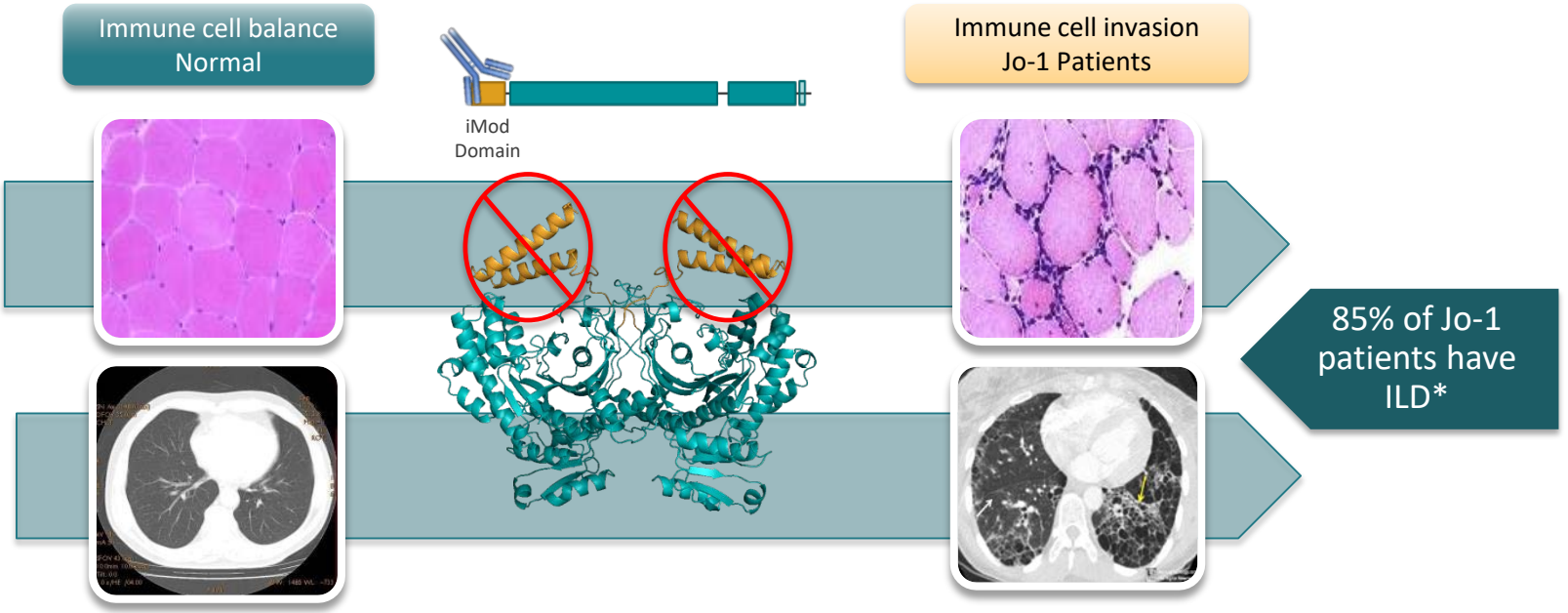
Blockade of Pathway in Muscle & Lung Disease

Anti-Synthetase syndrome provides evidence in humans of Resokine pathway

Patients start normal

Jo-1 Abs

18 of 18 Jo-1 patients tested positive for Antibodies to iMod Domain



*ILD = Interstitial Lung Disease

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Interstitial Lung Disease Overview

Collectively a heterogeneous group of disorders that involves pathology that begins in the interstitium

Many associated with extensive alteration of alveolar and airway architecture

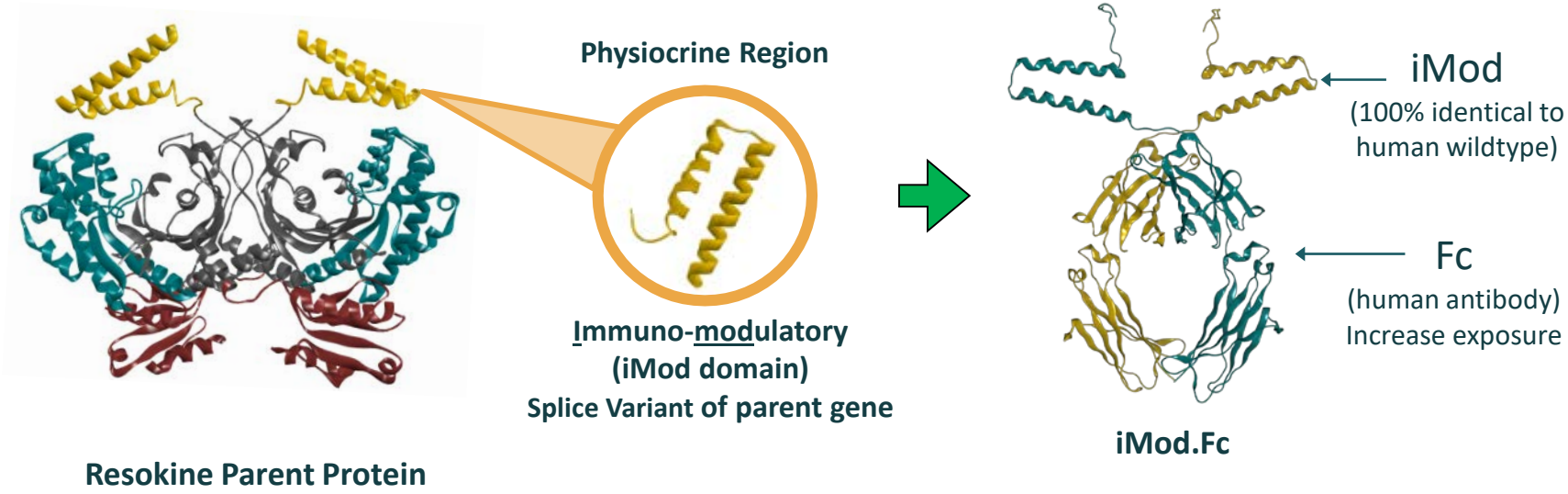
Share similar clinical, radiographic, physiologic and pathologic manifestations

Well over 100 different forms of ILD have been described, most of which involve an immune and/or fibrotic component

Source: Applied Chest Imaging Laboratory – Harvard University

iMod.Fc Leverages Knowledge of Splice Variant Biology

Harnessing the iMod. Domain

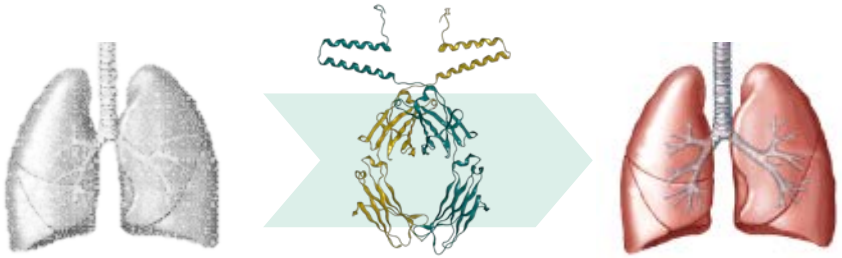


Rationale for iMod.Fc

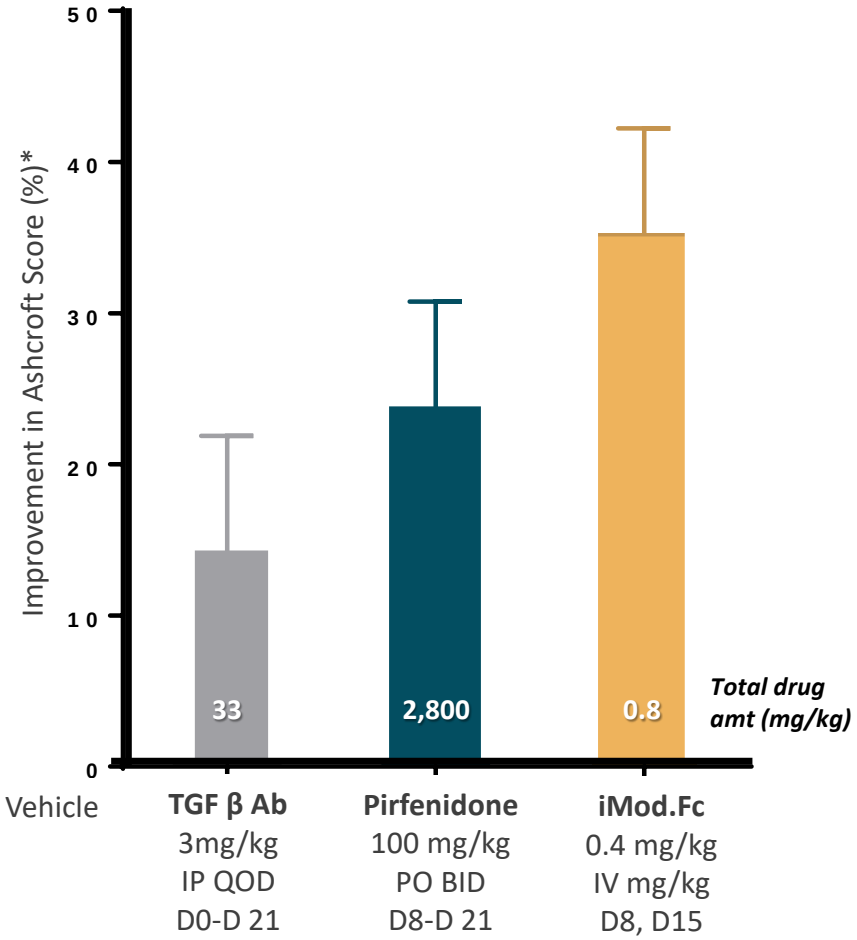
- iMod domain is a Resokine splice variant expressed in lung
- Lung requires a once-monthly dosing TPP
- iMod.Fc possesses ~350x increase in exposure compared to iMod alone

Two iMod.Fc Doses Outperform 28 Pirfenidone Doses

IPF Model Activity



- iMod.Fc 1/3500th of total Pirfenidone dose
- Better than 11 TGFβ Ab doses
- Established IPF rodent model
- Improves inflammation & fibrosis
- Differentiated mechanism



**The Ashcroft scale for the evaluation of bleomycin-induced lung fibrosis is the analysis of stained histological samples by visual assessment*

iMod.Fc an Engineered Physiocrine for Lung Disease

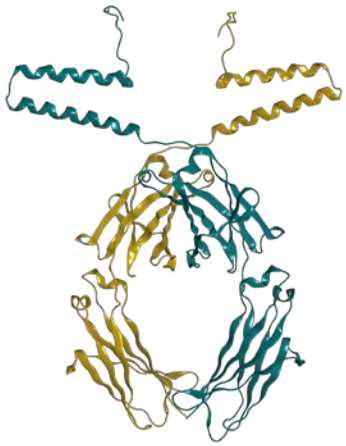
New Target Product Profile (TPP) and new molecule to open up lung indications

Preclinical Status and Goals

- ✓ Activity in industry proven model of IPF (approved drugs: Pirfenidone & Nintedanib)
- ✓ Immuno- & fibro- modulatory activity
- ✓ Successful *E. coli* production for low COGs
- ✓ Rat/non-human primate non-GLP safety & PK data support advancement to IND
- Expect to initiate clinical trial with iMod.Fc in 2017

Potential Therapeutic applications

- Rare pulmonopathies with an immune component (RPICs)
- Broader reach into RPICs and interstitial lung disease (ILD) indications



Building a New Class of Therapeutics

Foundation for the Future

Leadership Team

EXPERIENCED INDUSTRY VETERANS

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Chief Executive Officer

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Chief Business Officer

The Medicines Company · ASIAN HEALTH CARE FUND · RADIUS · BURRILL & COMPANY

Sanjay Shukla, M.D.
Chief Medical Officer

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SVP, Product Programs and Planning

CoDa Therapeutics, Inc. · AMGEN

Ashraf Amanullah, Ph.D.
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Genentech · GILEAD · MERCK

Andrew Cubitt, Ph.D.
VP, Product Protection

AnaptysBio · xceptor · Aurora Biosciences Corporation

John Blake, CPA
VP, Finance

VOLCANO · BD

Holly D. Chrzanowski
VP, Enterprise Talent and Organization

VERTEX · Aurora Biosciences Corporation

Upcoming Catalysts and Financial Guidance

Resolaris Readouts Dec. 2016*

- Early Onset FSHD (003) Trial – Data from first 4 patients in Stage 1
- LGMD2B/FSHD (004) Trial – Top-line results from 10 LGMD2B, 8 FSHD patients
- First Extension (005) Trial – Update from these patients

Prudently Advancing Pipeline:

- December 2016* data readout to select best advancement path for Resolaris
- iMod.Fc program on track for clinical trial initiation in 2017

Cash Position:

- $96.6M in cash, equivalents & investments as of 6/30/16
- Anticipate cash, equivalents & investments will fund operations into 2018

**According to current expectations*

Revolutionary Drugs Leveraging New Biology

Opportunity to own a new class of meaningful medicines