Advancing New Therapeutic Horizons For Patients With Imbalanced Immune Systems

Harnessing Novel Pathways in Immunology to Promote Homeostasis

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Senior Vice President, Finance
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Needham and Company Healthcare Conference
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aTyr Pharma
NASDAQ: **LIFE**

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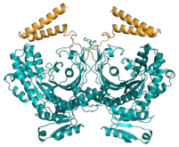
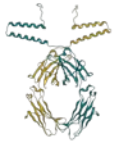
LIFE Value Proposition

Pioneers of new therapeutic intervention points in immunology
The World of Physiocrines & Homeostasis



Favorable safety profile and potential clinical activity from
1st Physiocrine program, Resolaris, in 2 rare muscular dystrophies



Advancing **2nd Physiocrine** program for rare lung diseases,
Stalaris, into human trials this year

Potential **3rd Physiocrine**-based opportunity
as a 2017 IND candidate in a 3rd therapeutic area

Pursuing partnership(s) for one or more of the above programs
to accelerate clinical and preclinical pipeline

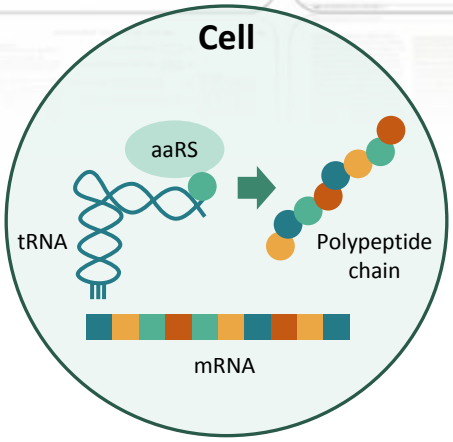
>175 issued/allowed patents
Strong Leadership Team associated with **18** approved drugs
$76M cash 2016 EOY

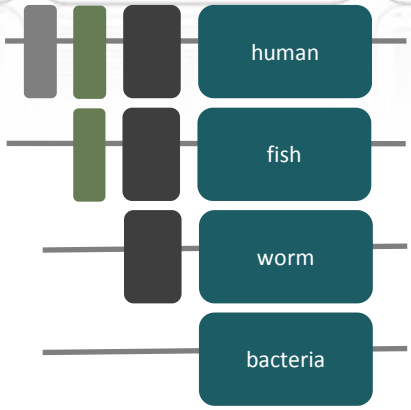
The Power of Physiocrines Orchestrating Homeostasis

New Class of Proteins from Alternative Splicing of Ancient Genes

What are ***Physiocrines?*** *Extracellular Signaling Regions*

Science 1999	Nature 2010	Nature 2013	Science 2014	Nature 2015
Intracellular 23 genes in humans		**Extracellular signaling** 4 billion years of evolution		**Extracellular function** ~300 Physiocrines
Original Primordial Function		***Physiocrine regions of tRNA synthetases in a gene***		***Systems evolved with species***
Protein synthesis		**Evolution**		**Tissue homeostasis**





Immune System
Complex Tissue Homeostasis

Vascular Systems
Closed Tissue Homeostasis

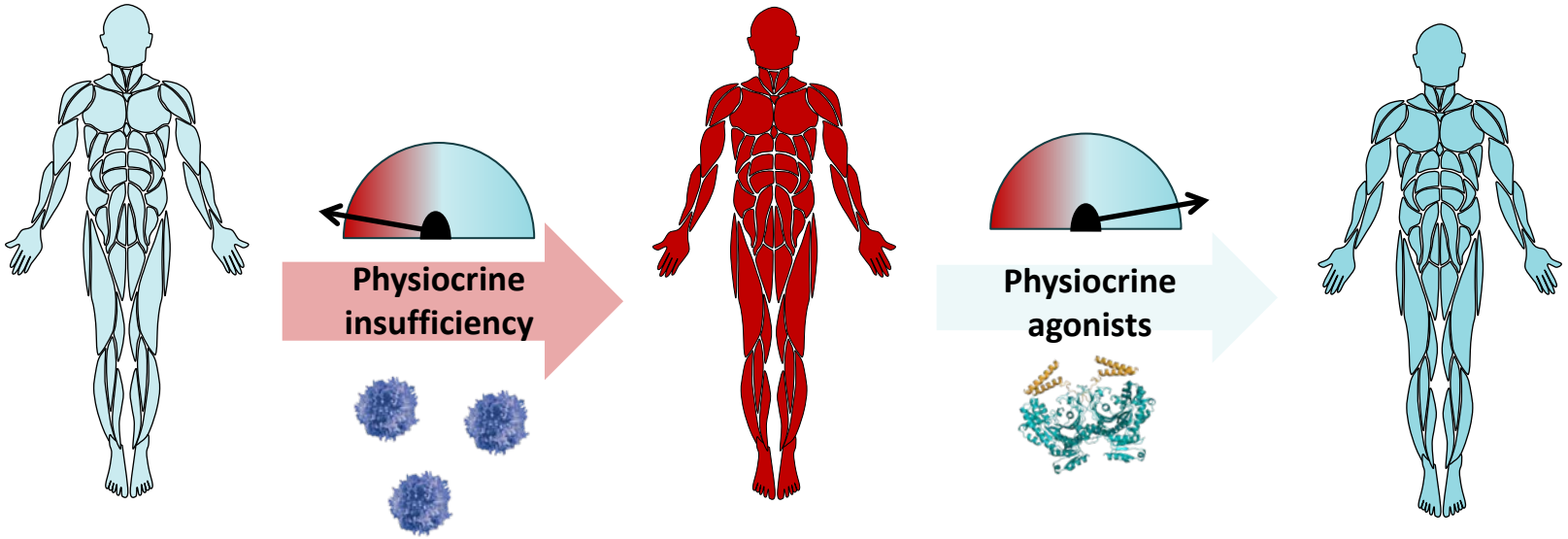
Regenerative Systems
Open Tissue Homeostasis

Bacteria
Protein synthesis

Schimmel et al. Human tRNA Synthetase Catalytic Nulls with Diverse Functions. Science, 2014.

LIFE's Therapeutic Paradigm

PROMOTE HOMEOSTASIS



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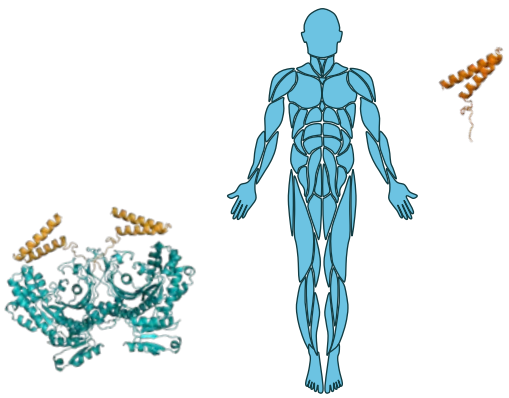
Evidence for Homeostatic Role of a Physiocrine in Humans

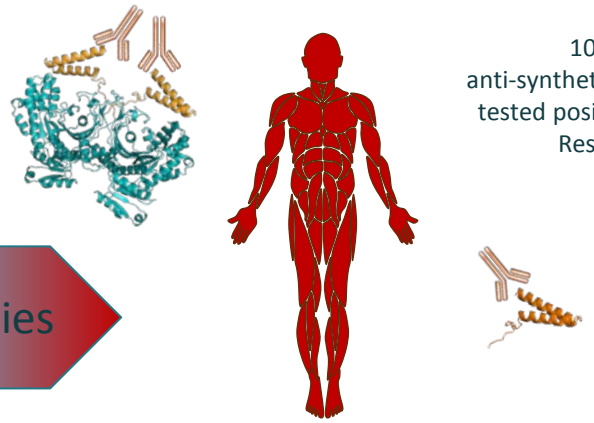
Disrupting the Resokine Pathway Promotes Muscle and Lung Disease

Homeostasis

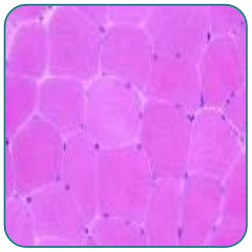


Disease-antibodies

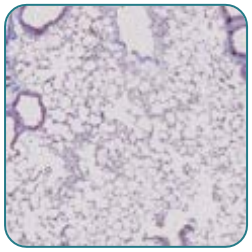
Imbalance



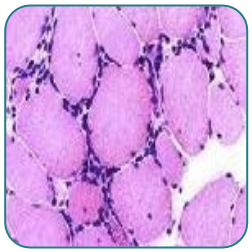
100% (18 of 18) anti-synthetase syndrome patients tested positive for antibodies for Resokine proteins



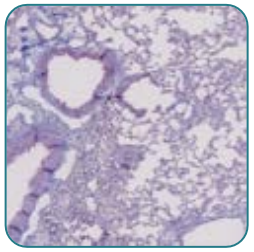
Healthy muscle



Healthy lung



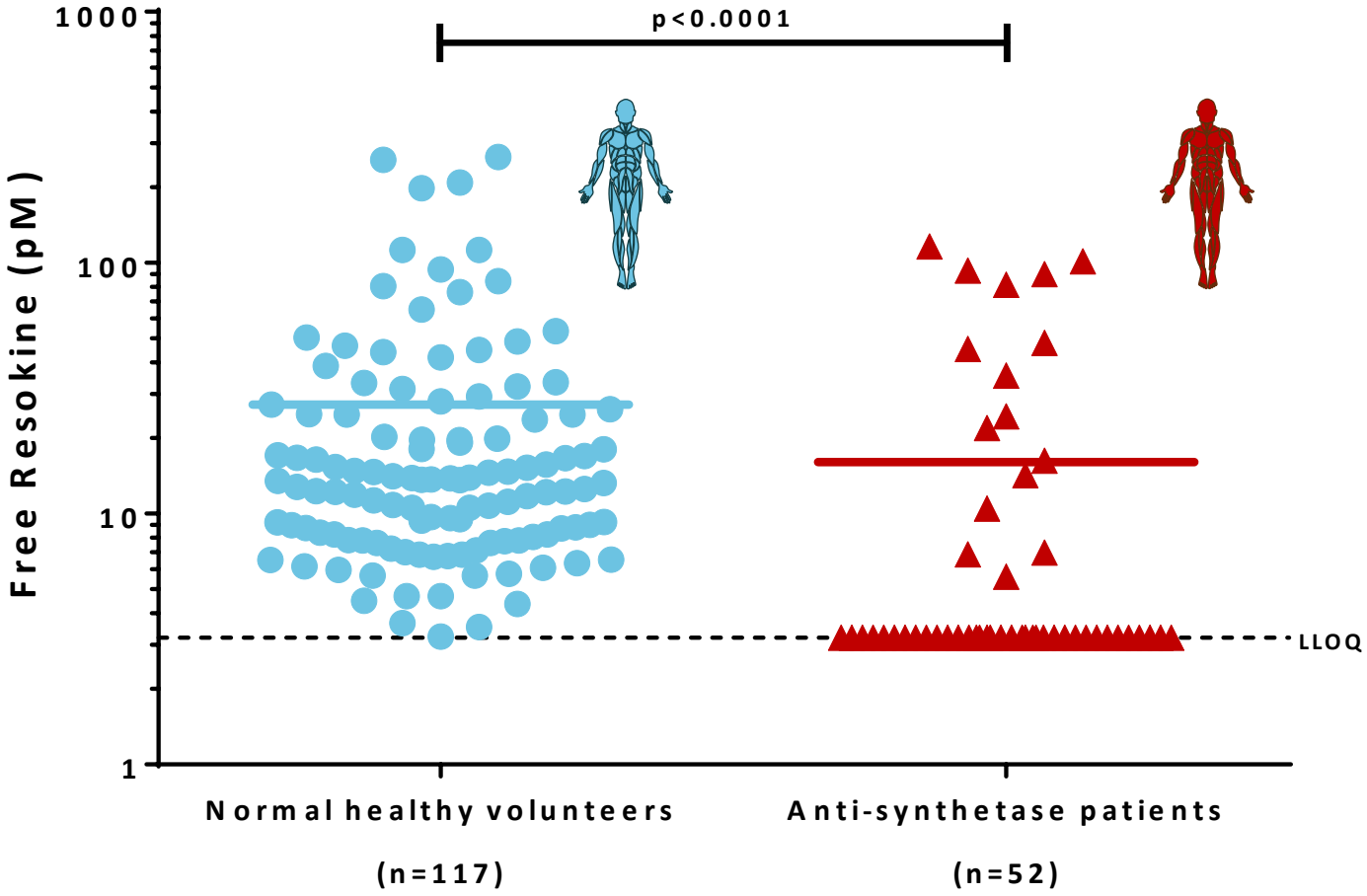
Diseased Muscle



Diseased Lung

↑ Immune cell invasion/activity

Free Resokine Pathway in Anti-Synthetase Patients Diminished



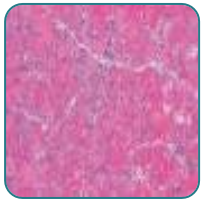
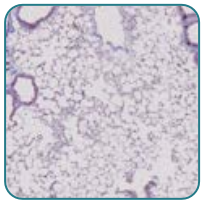
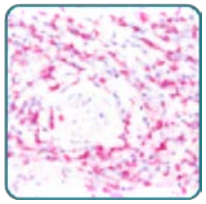
Resokine Pathway Antagonized

69% at or below limit of detection

Unpublished data from aTyr and collaborator
Statistics: Mann-Whitney test

Agonists of the Resokine Pathway in Immune Driven Models

Balancing the immune response to tissue insults

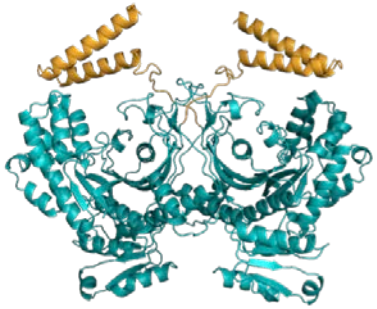
Disease Model	Resokine Homeostatic Effect	Immune Targets
Skeletal Muscle Statin Induced Myopathy		**CD4/CD8 & macrophages**
Lung Bleomycin Induced Lung Fibrosis		**Th17/CD4**
Colon TNBS Induced Colitis		**Th17/CD4**
Skin IL23 Induced Psoriasis		**Th17/CD4**

In vivo administration of Resokine proteins to animal models of T cell driven disease states.
Cell type indicates type of cells involved but may not be limited to these cells.

RESOLARIS

HARNESSING THE RESOKINE PATHWAY TO TREAT MULTIPLE RARE MUSCLE DISEASES

First Physiocrine For Patients: Resolaris



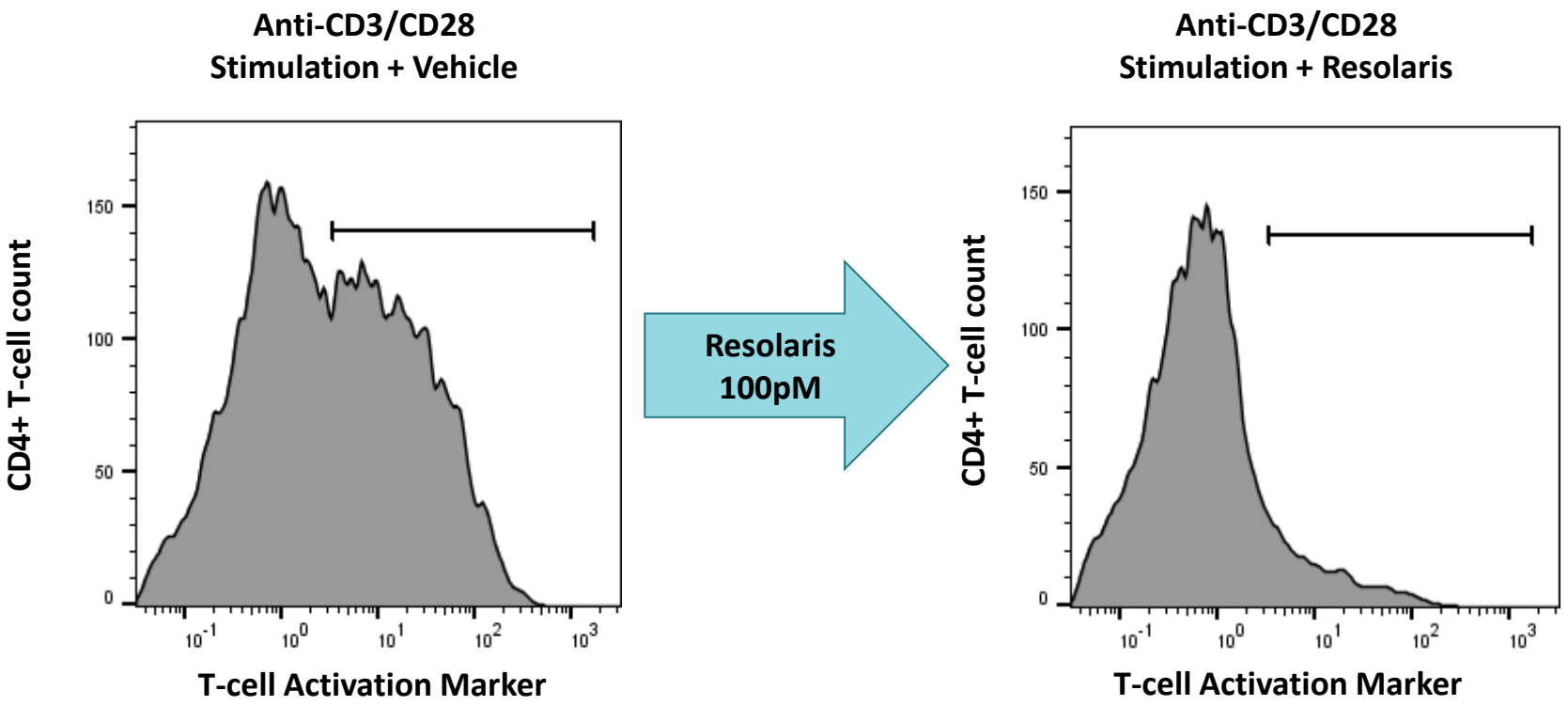
Derived from **Resokine:** a naturally occurring protein, the histidine aminoacyl tRNA synthetase (HARS)

- Skeletal muscle secretes Resokine
- Resokine, an agonist, plays a role in homeostasis & T cell responses in muscle
- Recombinant version of Resokine
- Demonstrated favorable safety profile and potential clinical activity in two rare muscular dystrophy indications
- Therapeutic potential for rare myopathies with an immune component (RMIC), **over 20** potential indications

➢ **Strategy:** Establish broad utility in multiple indications

Resolaris Tempers Activated T cells

Demonstrated effect as an immuno-modulator



*Resolaris with **Activated** T-cells Promotes a More **Resting** T-cell Phenotype*

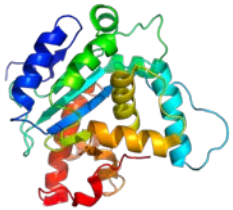
On the Left: *Gated on CD4⁺ T cells. Resolaris at 100 pM. 24 hours stimulation with anti-CD3/CD28 Abs.*

On the Right: *T cells were stimulated with anti-CD3/CD28 antibodies in the presence of vehicle or Resolaris . After 24 h, supernatants were collected and analyzed by ELISA, Statistics by T test*

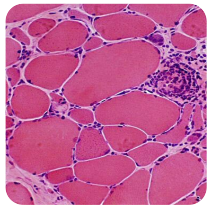
Rare Myopathies with an Immune Component

Chronic damage, homeostasis disrupted

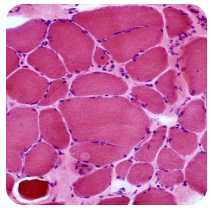
Untapped therapeutic intervention point



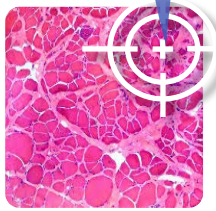
Genetic Mutation	Aberrant Protein Expression	Localized T Cell Invasion/Proliferation
FSHD	Multiple proteins	
LGMD2B	Dysferlin proteins	
DMD	Dystrophin proteins	



FSHD



LGMD2B



DMD

Potential to link genotype to specific T cell phenotype

All debilitating diseases with little or no therapeutic treatments

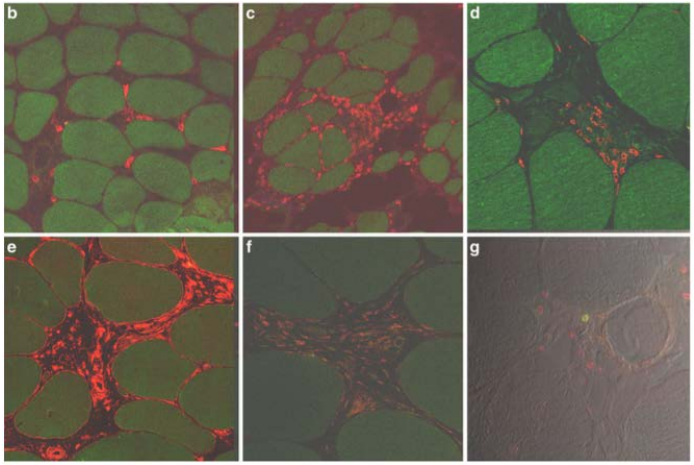
Frisullo et al., J. Clin. Immunol., 2011. Gallardo et al. Neurology, 2001. Flanigan et al. Human Gene Therapy, 2013.

***FSHD** = Facioscapulohumeral Muscular Dystrophy (FSHD). **LGMD2B** = Limb Girdle Muscular Dystrophy 2B.*

***DMD** = Duchenne Muscular Dystrophy.*

T Cells Central to Pathophysiology of RMICs

FSHD



Endomysial infiltrates, in which CD8+ cells predominated (Fig. 2b–d), and perivascular infiltrates, mainly constituted by CD4+ cells (Fig. 2f) in all samples

LGMD2B

Cells	Polymyositis	Dysferlinopathy
CD8+	46.5 ± 10.3	11.1 ± 6.6
CD4+	27.3 ± 11.5	40.6 ± 22.8
Macrophages	27.7 ± 7.6	36.7 ± 23.7

Endomysial mononuclear cell infiltrates in clusters (cell count per cluster)
5/12 dysferlinopathy patients originally diagnosed with inflammatory myopathy

LGMD2B & DMD

Cells	Polymyositis	Dysferlinopathy	DMD/BMD
CD8+	3.3 ± 1.8	1.3 ± 1.1	2.0 ± 1.6
CD4+	12.3 ± 6.4	5.7 ± 4.4	4.9 ± 5.7
Macrophages	10.8 ± 6.5	7.8 ± 4.3	3.7 ± 3.1

Comparison of inflammatory cells in muscle biopsy samples of dysferlinopathy, DMD/BMD and polymyositis patients (average cell count per muscle section)

Frisullo et al. J Clin Immunol 2011
Gallardo et al. Neurol. 2001
Yin et al.Int J Clin Exp Pathol 2015

Resolaris Phase 1b/2 Clinical Trials

Objectives

Evaluate Safety and Tolerability

- ✓ Build safety dossier for Resolaris
- ✓ Multiple indications, different dosing regimens, longer duration

Evaluate Potential Activity Assessments*

- ✓ Functional / Strength: MMT
- ✓ Patient Reported Outcomes: INQoL
- ± MRI / Biomarkers assessments

Evaluate three potential indications: Adult LGMD2B, Adult FSHD, & Early Onset FSHD

Trial	Indication(s)	Patients	Highest Dose	Design
002	Adult FSHD	3 dose cohorts (n=20 Total)	3.0 mg/kg Weekly (12 weeks)	Placebo controlled, Double blinded; Interpatient Dose Escalation up to 12 weeks
003	Early onset FSHD	Stage 1 (n=8)	3.0 mg/kg Weekly (6 weeks)	Open-label, Intrapatient Dose Escalation for 12 weeks
004	Adult LGMD2B, Adult FSHD	LGMD2B (n=10) FSHD (n=8)	3.0 mg/kg Biweekly (4 weeks)	Open-label, Intrapatient Dose Escalation for 12 weeks

**MMT* = Manual Muscle Testing, a validated assessment tool that measures muscle function/strength*

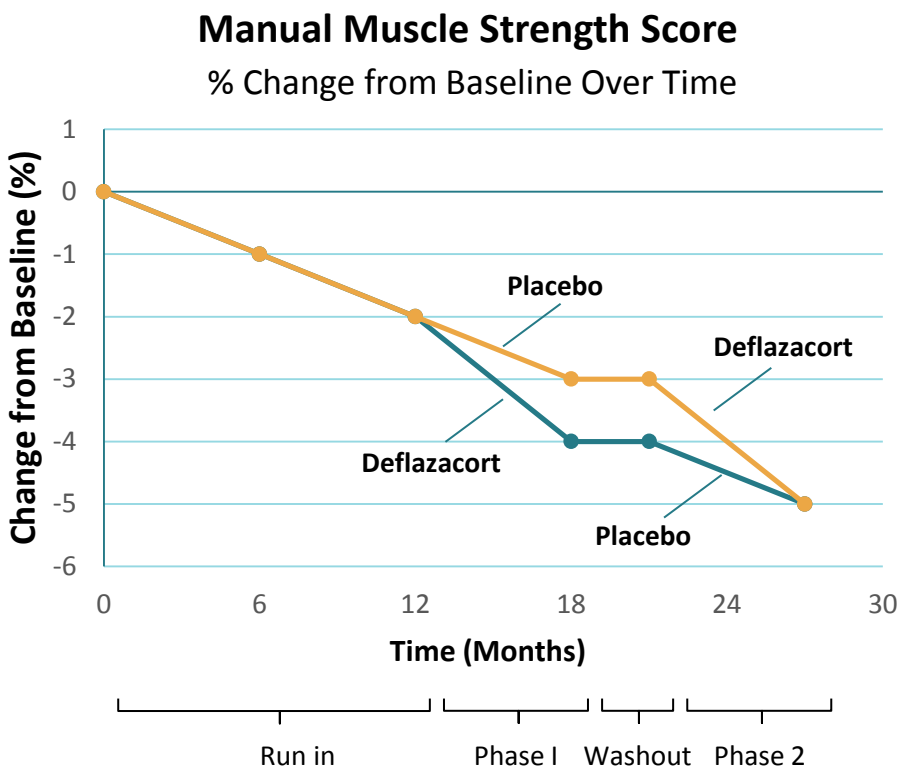
***INQoL** = Individualized Neuromuscular Quality of Life, a patient reported outcome measure designed specifically for neuromuscular disease*

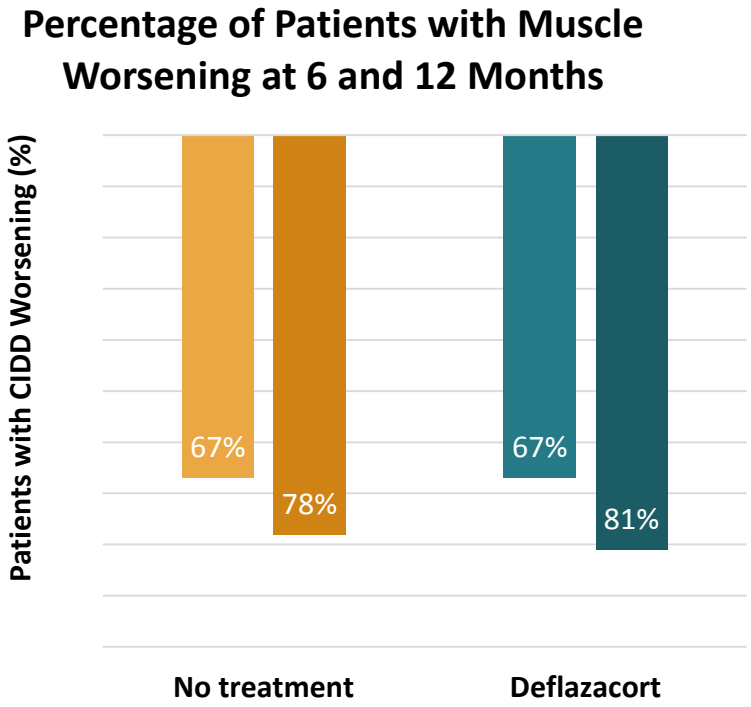
LGMD2B Disease Progression Case History

	First symptoms	Misdiagnosed w/ polymyositis	LGMD2B Diagnosis	Part time wheelchair-bound	Full time wheelchair-bound	Full dependency due to severe physical disability
Age	<15	16 – 18		19 – 27		28 - 34
	• Walks normally, active childhood	• Abnormal gait • Knees locked • Difficulty climbing stairs and running	• Difficulty rising from a chair, raising hands above head • Uses a cane and leg braces	• Slight improvement when steroids stopped • Unable to rise from a chair	• Requires assistance in daily living	• Unable to turn over in a bed or raise hands above head • Uses service dog for daily activities

https://www.youtube.com/watch?v=JLqHis1yPUI
http://mwtn2013blisswelch.blogspot.com/

LGMD Patients Manual Muscle Strength Progressively Declines





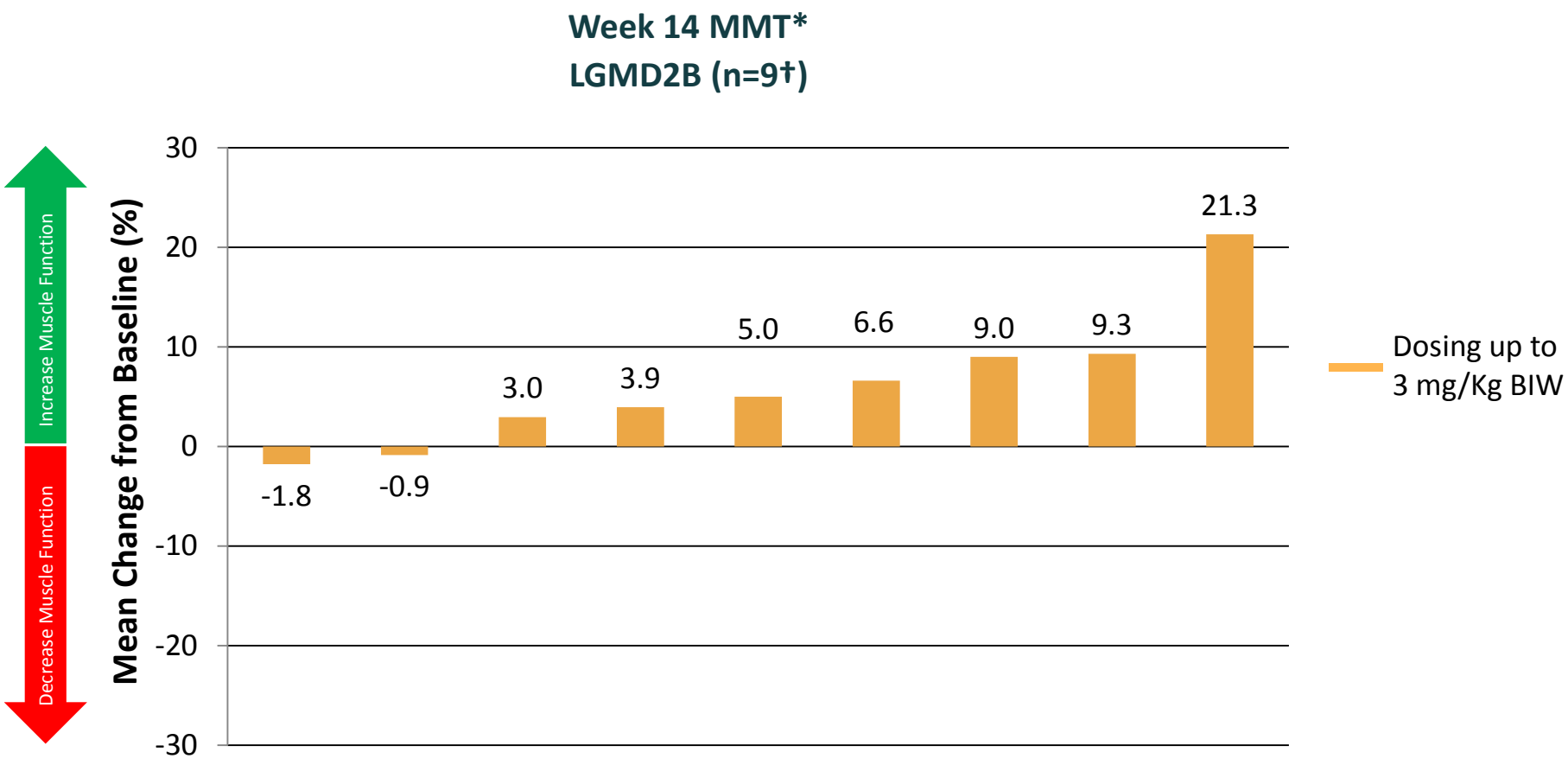
Treatment with Deflazacort was for 6 months in each arm. Single site, placebo controlled, cross over design (n=25)

Manual muscle strength assessed bilaterally by the modified Medical Research Council Scales (MRC)
CIDD (Clinical Investigation of Duchenne Dystrophy) score, graded from 0 (worst) to 10 (best)

Walter et al, Orphanet Journal of Rare Diseases, 2013

Manual Muscle Test (MMT) Scores LGMD2B Patients

004 Study: Individual Patient Changes from Baseline (%)



1-week follow-up is earlier than week 14 for 2 early discontinuations

† One patient in 004 Trial did not have an MMT measurement due to being wheelchair bound at baseline

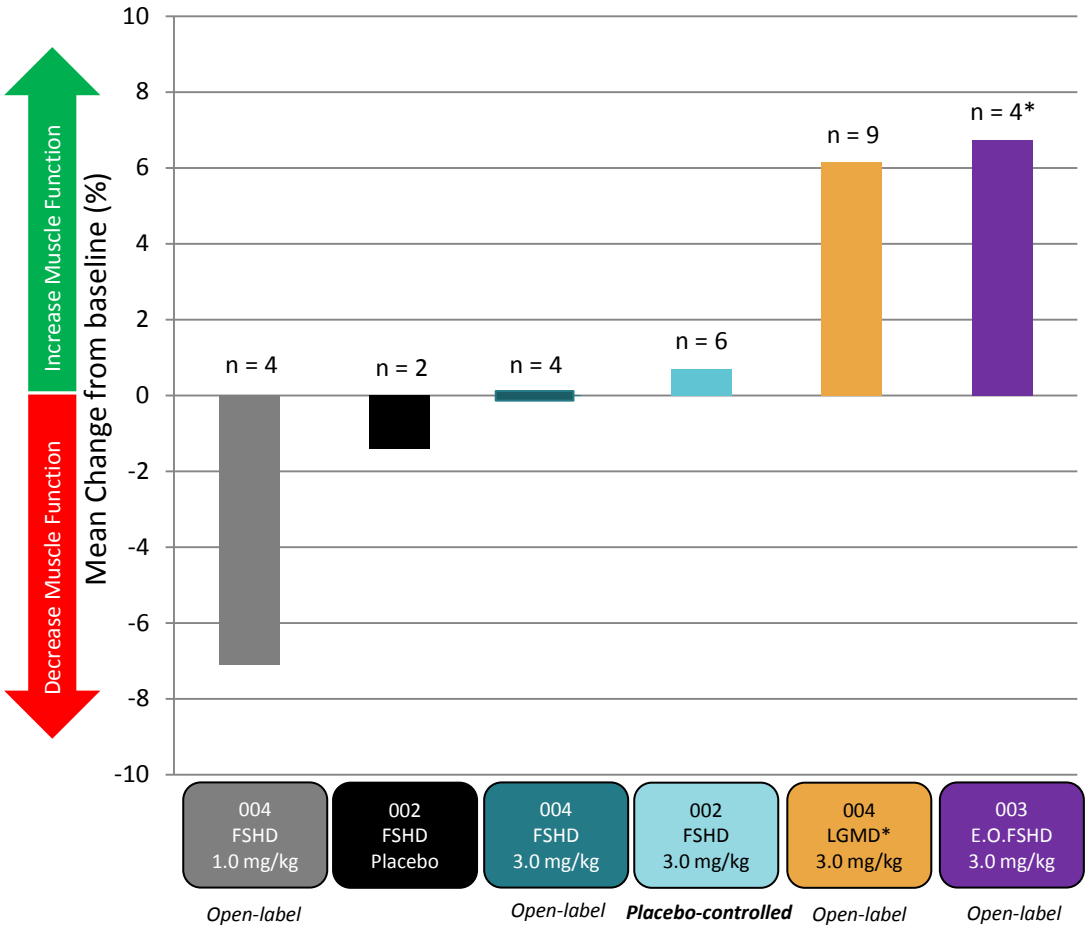
Compiled Data from Three Phase 1b/2 Clinical Trials

Relatively Stable or Improved Muscle Function Observed

RESOLARIS PROGRAM

Overall Mean MMT Change Week 14 by Dose Group

FSHD & LGMD2B Patients From 002, 003, 004 Trials



Manual Muscle Testing (MMT):
A measure of muscle function/strength

50% to 78% of patients in Resolaris dose groups had increased MMT scores

No placebo patients had increased MMT scores

3.0 mg/kg weekly identified as an active dose

**Early onset FSHD (003) Trial represents interim data results (4 patients of a total of 8)*

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Robust Safety & Tolerability Dossier

44 patients have received Resolaris for a total drug exposure of 149 patient months

No observed signs of general immunosuppression

Consistent with a homeostatic pathway working at a tissue level

Well-tolerated across all doses tested:
Multiple myopathies; various age-groups; long-term exposure
No serious adverse events reported by investigators

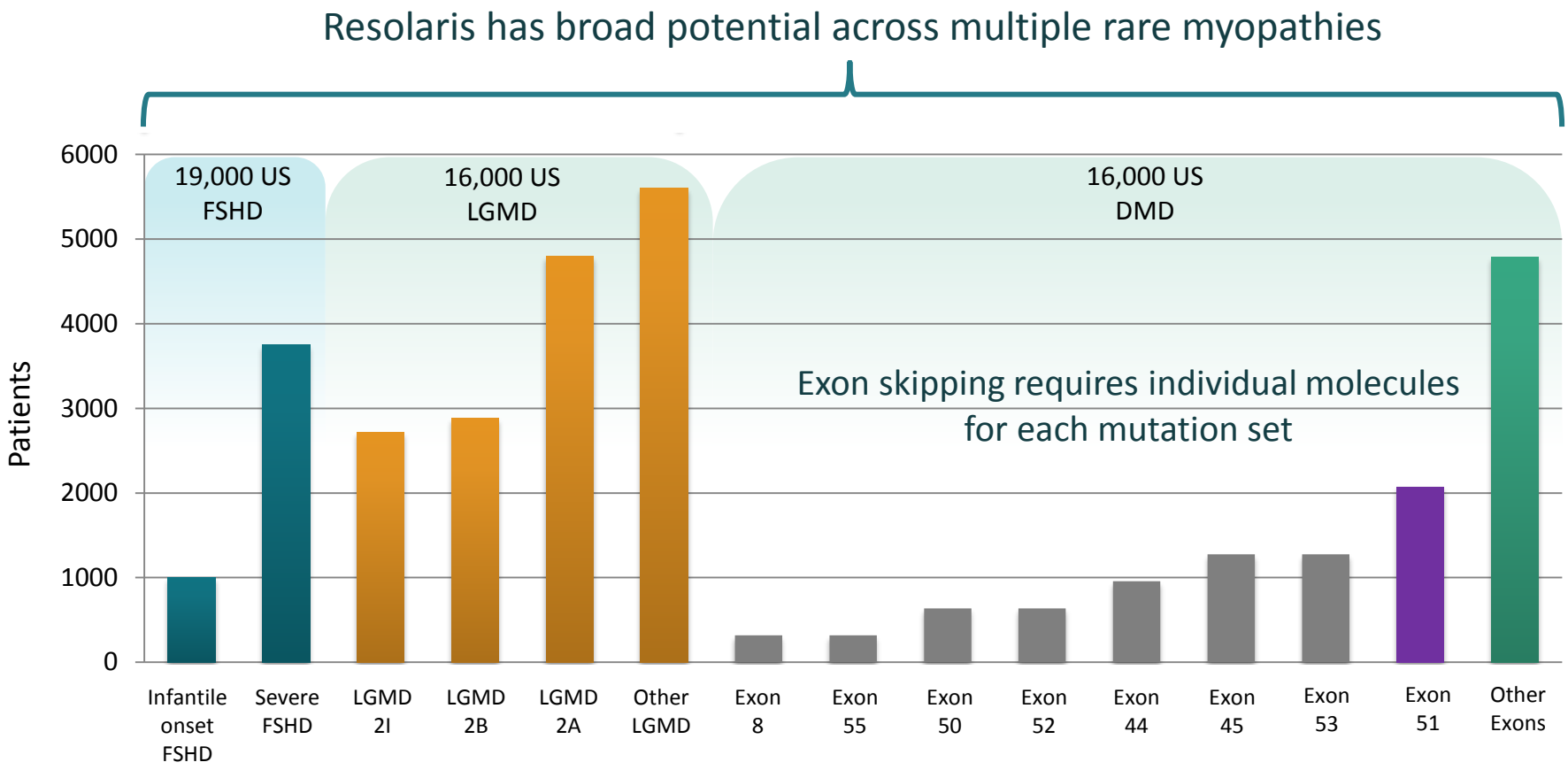
Low-level anti-drug antibody assay signals did not result in clinical symptoms
Protocol discontinuations primarily driven by transient infusion related reactions

Target Product Profile (Discontinuation Rate ≤ 10%)

- *Potential to pre-medicate patients*
- *Potentially relax cut-off criteria for discontinuations*

Resolaris: One Product, Multiple RMICs

Promise for severely afflicted myopathy patients



***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. 20`14. 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*

Resolaris Status and 2017 Development Goals

Milestones

- ✓ Muscle Function Signals: Adult LGMD2B; Early onset FSHD* > Adult FSHD
- ✓ Established a favorable safety profile and identified an active dose
- ✓ Commercial scale manufacturing to be ready for future larger randomized controlled trials
- ✓ Fast Track designations for Resolaris to treat FSHD and LGMD2B

2017 Development Goals

First Half

Clinical Results: Early Onset FSHD Patient Trial (003)

Biomarker/MOA: Introduce Mechanistic/PD Assay

Second Half

Clinical Trial: Kick off next trial post partnership**

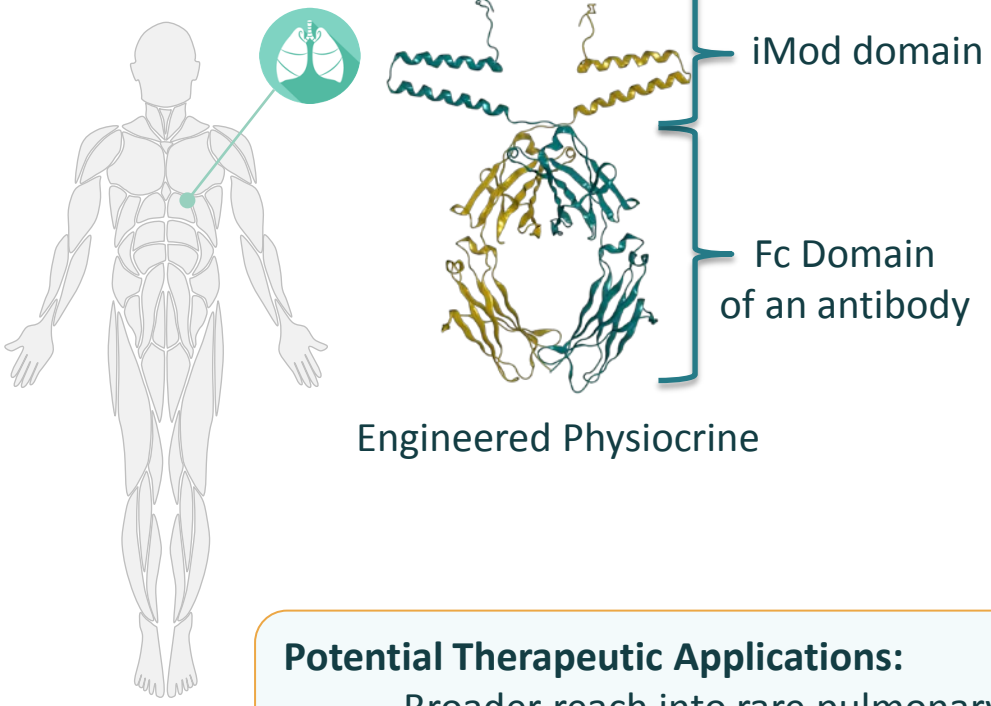
**Based on interim data reported in December 2016*
***Partner for one or more programs*

Stalaris

Lung Physiocrine Engineered to Treat Multiple Pulmonary Diseases

Stalaris Program: Opportunity for Lung Patients

Leverages Knowledge of Resokine Pathway in Lung



Engineered Physiocrine

- **Human iMod domain:** Resokine splice variant relatively more expressed in ***lung*** than other tissues
- **Human Fc Domain:** increased exposure to potentially enable:

  Target Product Profile of ***once-monthly dosing in humans***
- **Engineered result:** Stalaris ~350x increased exposure vs. iMod; while retaining T cell modulation activity
- **1st molecule** from internal Fc platform

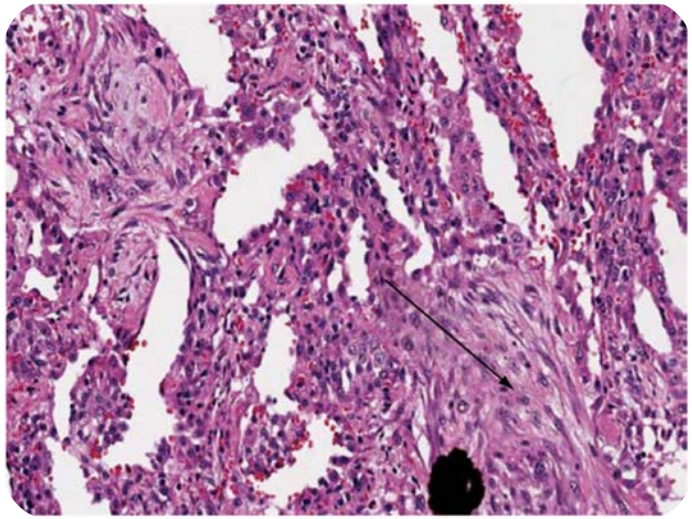
Potential Therapeutic Applications:

Broader reach into rare pulmonary diseases characterized by immune cell infiltration including several rare interstitial lung disease (ILD) indications

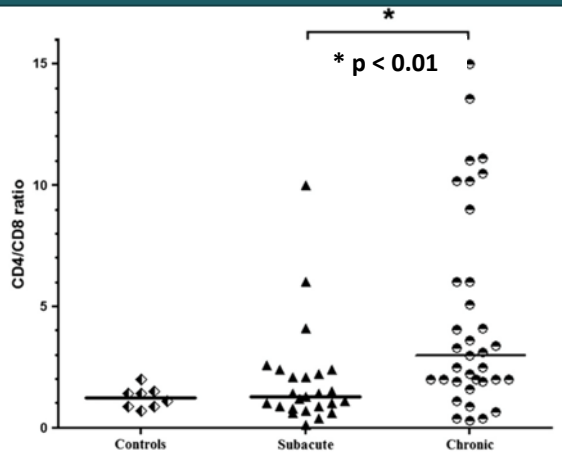
Stalaris from Greek, statera for balance

ILDs Characterized by T Cell Infiltration

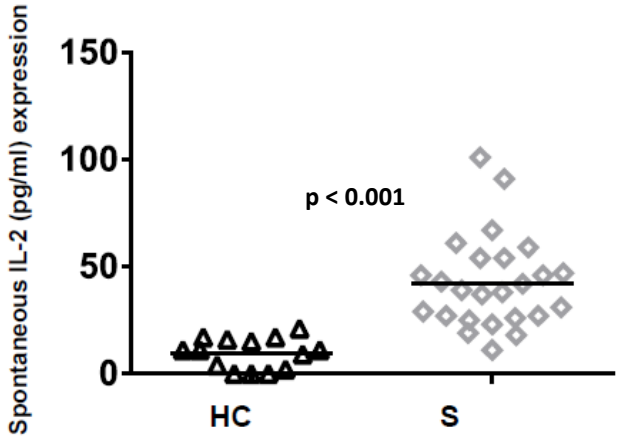
Myositis w/ Anti-Synthetase Syndrome



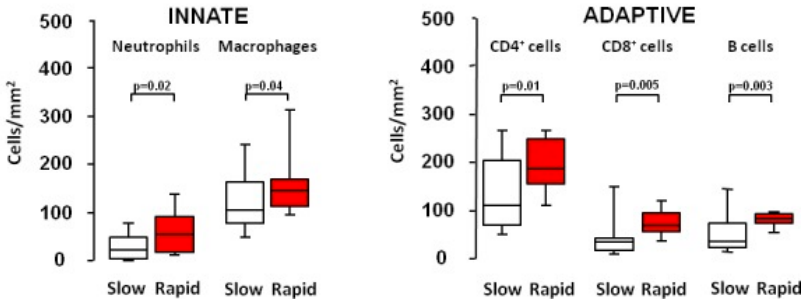
Hypersensitivity Pneumonitis



Sarcoidosis



Idiopathic Pulmonary Fibrosis

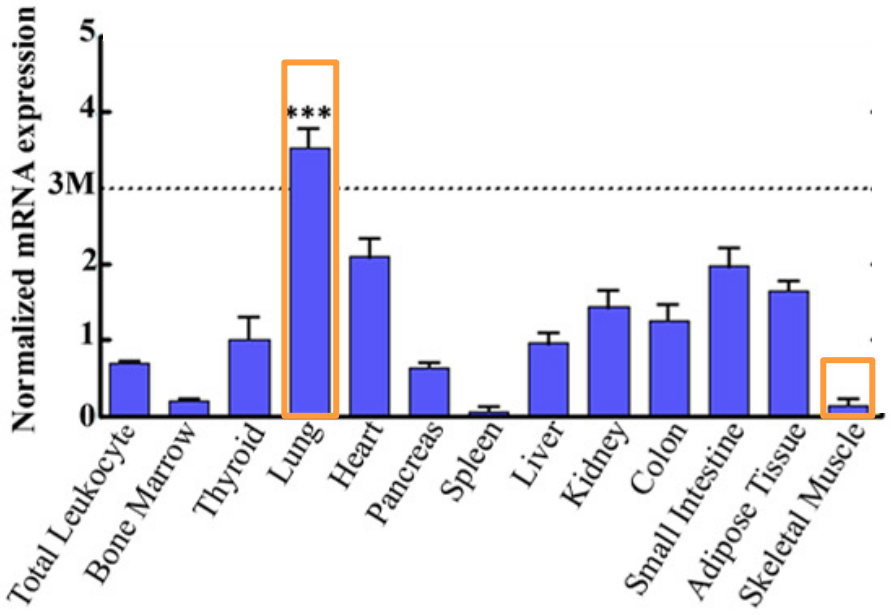


Balestro et al. PLOS ONE. 2016
Barrera et al.: Functional Diversity of T Cells in HP 2007
Solomon et al. J Bras Pneumol. 2011

Braun et al. Amer J Resp Crit Care Med 2014

iMod Domain in Lung

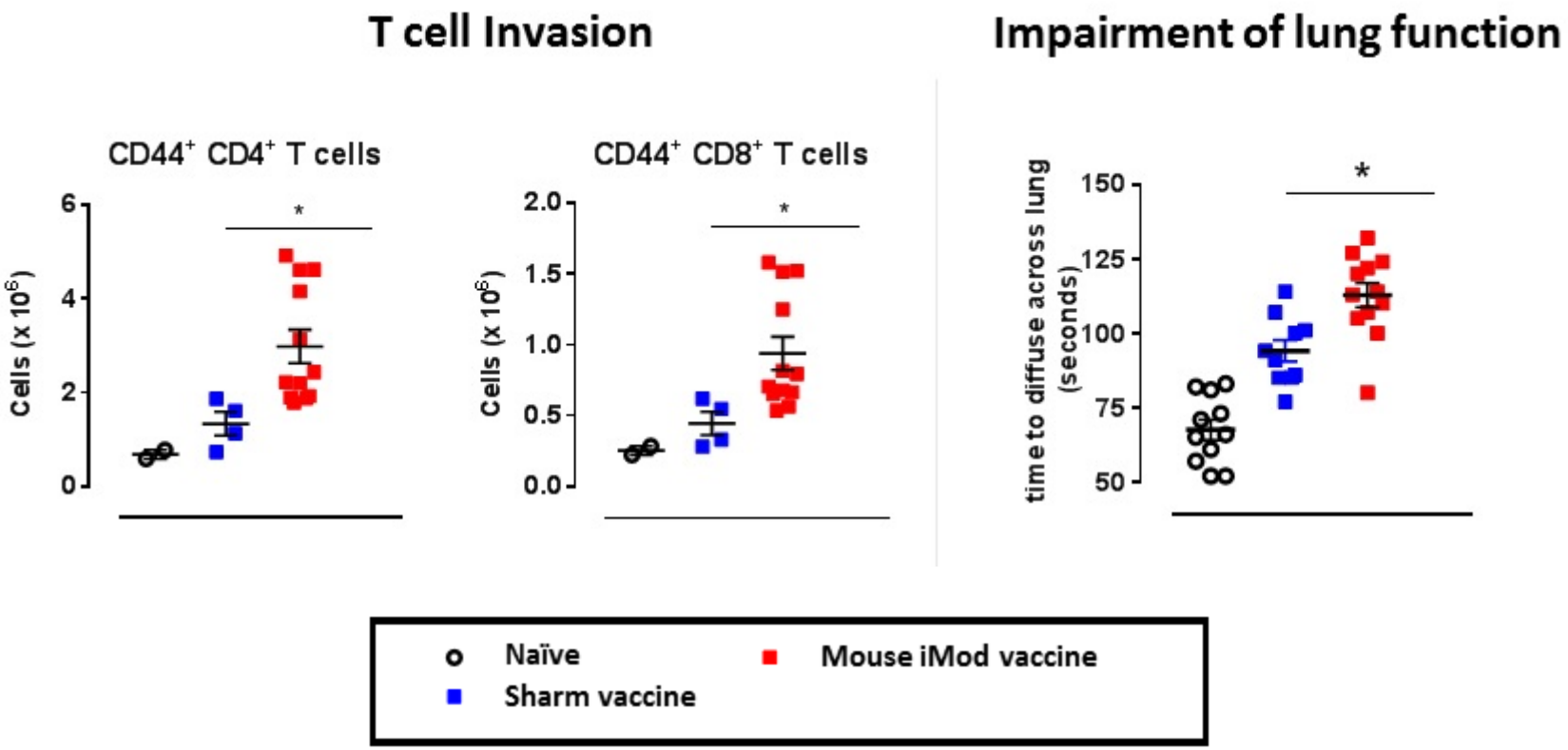
Splice Variant Express Data for iMod in Lung



Splice variant for the **iMod domain** is relatively more expressed in **lung** than other tissues

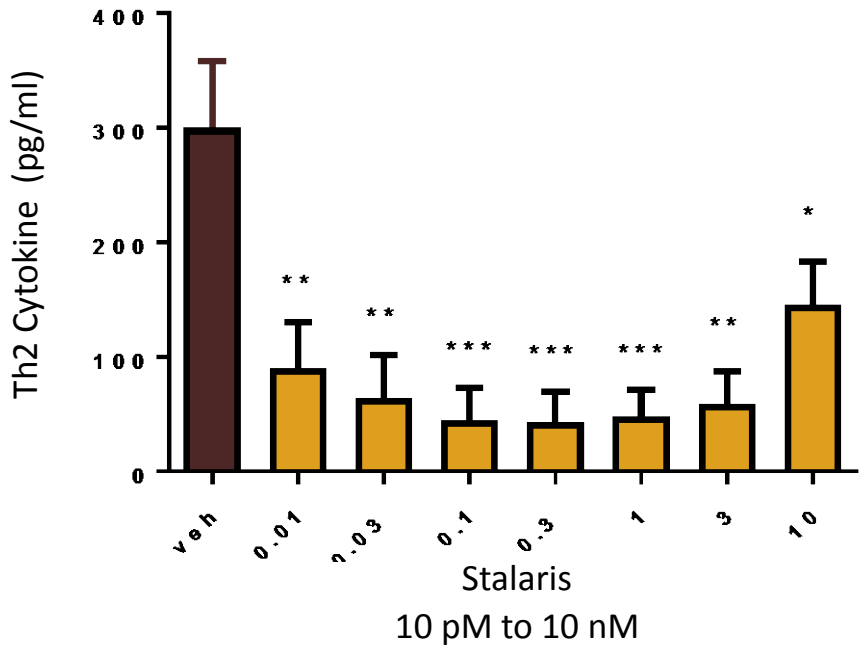
Knockout of Resokine Pathway Increases T Cell Invasion Post Disease Induction

Rodent functional knockout inducing idiopathic pulmonary disease using Bleomycin



* $p < .05$

Stalaris Tempers Activated T Cells at High Affinity

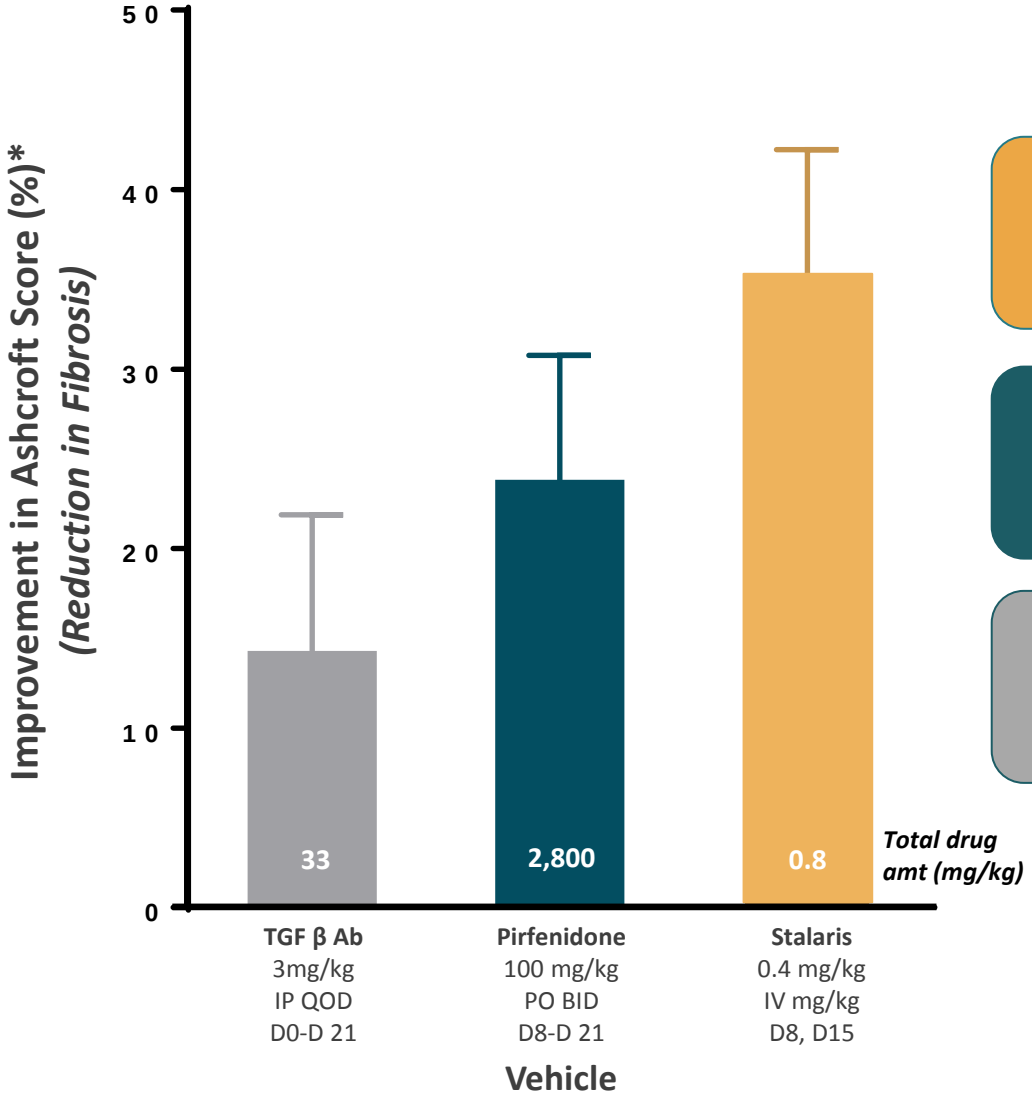


- Stalaris inhibits Th2 type cytokines from activated T cells
- Th2 cytokines play a role in promoting **fibrosis** in certain interstitial lung diseases

**** p < .001; ** p <.01; * p < .05*

Stalaris Outperforms Current Treatments

Established Rodent Model for Idiopathic Pulmonary Fibrosis (IPF)



Superior activity
in established IPF fibrotic model

Stalaris **outperformed pirfenidone** at **1/3500th** total dose

Two doses of Stalaris **outperformed 11 TGFβ Ab** doses

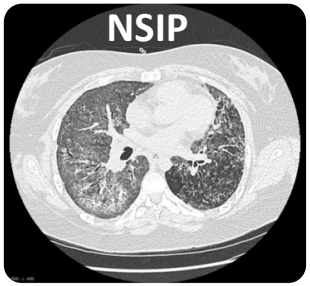
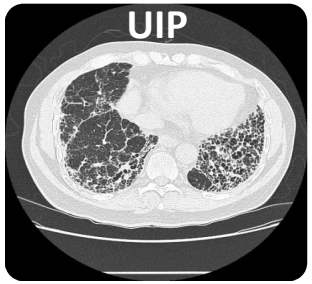
**The Ashcroft scale for the evaluation of bleomycin-induced lung fibrosis is the analysis of stained histological samples by visual assessment*

Interstitial Lung Disease Opportunity

Driven by a combination of immunological and fibrotic pathways

PATIENTS

UNMET NEED

Interstitial Lung Disease (ILD)	Over 100 different specific disease types
Standard of Care	Steroids and immuno-suppressants Approved therapies for IPF*: Pirfenidone & Nintedanib
Pathology	T cells involved in various diseases
Pattern of Disease	  Pattern of disease, e.g. usual interstitial pneumonia (UIP) vs. non-specific interstitial pneumonia (NSIP), to determine diagnosis/prognosis
Prognosis	Poor prognosis for these patients e.g. 2-3 year median survival for IPF

Adapted from: Thannickal VJ, et al. Ann Rev Med. 2004;55:395-417 (and) 2013 ATS Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

***IPF =** Idiopathic Pulmonary Fibrosis*

aTyr Pharma

Stalaris: Status and 2017 Development Goals

Milestones:

- ✓ Activity in industry proven model of IPF (approved drugs Pirfenidone & Nintedanib)
- ✓ GMP manufacturing kicked off
- ✓ Rat/non-human primate non-GLP safety & PK data support advancement to IND

2017 Development Goals:

First Half

- **Biomarker/MOA:** Introduce mechanistic/PD assay
- **IND Enabling:** Initiate preclinical safety studies

Second Half

- **GMP Manufacturing:** Complete clinical trial supply
- **Clinical Trial:** Initiate First in human clinical trial


Building a New Class of Therapeutics For Patients
Foundation for the Future

LIFE Leaders

John Mendlein, Ph.D.
Chief Executive Officer

Sanuj Ravindran, M.D.
Chief Business Officer

Sanjay Shukla, M.D.
Chief Medical Officer

David King, Ph.D.
SVP, Research

Grove Matsuoka
SVP, Product Programs and Planning

Ashraf Amanullah, Ph.D.
VP, Manufacturing

Andrea Cubitt, Ph.D.
VP, Product Protection

John Blake, CPA
SVP, Finance

Holly D. Chrzanowski
VP, Enterprise Talent and Organization

Nancy Krueger
VP, Legal Affairs

LIFE 2017 Goals and Financial Guidance

2017 Goals

- Partner One or More Programs
- Advance Pipeline with Two Molecules in the Clinic
- Declare 3rd IND Candidate from Physiocrine Discovery Engine

Financial Guidance

- $76M cash 2016 EOY
- Operations funded into 3Q 2018 without any partnerships
- ~30% expected reduction in operational cash burn compared to 2016*

**Operational cash burn only, excludes cash from financings*


Gracias
Merci
多謝
Спасибо
متشكرم
תודה.
Sukria
ありがとう
Efharisto
谢谢
Shukran
Danke
Mahalo
Khop Khun Mak Kha
Grazie
Obrigado
Spasiba
감사합니다
Dziekuje
Thank you!
Takk
Terima kasih
Nandri