Targeting Novel Immunological & Homeostatic Pathways
For Patients With Severe Immune Mediated Diseases

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aTyr Pharma, Inc.
Jefferies Healthcare Conference
June 9, 2017
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**LIFE Value Proposition**

- **Pioneers of new, fundamental immunology targets**
  - **Promote Tissue Homeostasis**

- Resolaris in 2 rare muscular dystrophies
- **Favorable safety profile and potential muscle improvement**

- Advancing iMod.Fc, **2nd Physiocrine**, program for rare lung diseases
- **Initiate first-in-human clinical trial 2H 2017**

- 3rd Physiocrine-based Program in a 3rd therapeutic area
- **Potential 2017 IND candidate, 3rd Modality**

- **Pursuing partnership(s)** for one or more programs to accelerate clinical and preclinical pipeline

- >190 issued/allowed patents
- **Strong Leadership Team** associated with 18 approved drugs

- **$61.9M** cash and investments as of 3/31/2017
- Sufficient to fund anticipated operations into **3Q 2018**
New Immunology Pathway: Resokine

Evolved from Cellular Homeostasis Genes over 400 Million Years
Resokine: Potential Key Regulator of Homeostasis

Evolved with system complexity

Physiocrines

- Mammals
- Vertebrates
- Arthropods
- Nematodes
- Fungi
- Prokaryotes

Protein Synthesis Function

- tRNA Synthetase

Conserved Physiocrine domain structures

DNA insertions

Complex Tissue Homeostasis

Closed Tissue Homeostasis

Open Tissue Homeostasis

Cellular Homeostasis
Resokine Pathway Evolved Early

**Human HARS** (Histidyl tRNA Synthetase)

Splice variant 9: “iMod” Domain

<table>
<thead>
<tr>
<th>First evolved (~M years)</th>
<th>human iMod</th>
<th>human IL-6</th>
<th>human IGF-1</th>
<th>human Myostatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
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<td>85%</td>
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<td>96%</td>
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<td>70%</td>
<td>31%</td>
<td>72%</td>
<td>76%</td>
</tr>
<tr>
<td>408</td>
<td>50%</td>
<td>-</td>
<td>58%</td>
<td>69%</td>
</tr>
</tbody>
</table>
Ancient, Fundamental Immune Motifs in Resokine

Resokine iMod domain entered the genome of animals before IL-6 and related cytokine family.
Resokine Agonists Change T Cell Phenotype

Unique MOA to orchestrate immune homeostasis in activated T cells

- Shifts trafficking & residence closer to a resting T cell
- Stimulatory pathways at levels close to a resting T cell
- Effector functions at levels close to a resting T cell
- Without in vivo immunosuppression
Resolaris MOA: Tempers Activated T cells

Demonstrated effect as an immuno-modulator

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.

Resolaris with Activated T-cells Promotes a More Resting T-cell Phenotype
How T Cells Participate in Pathology & Disruption of Homeostasis

Release of Granzyme B

Muscle Disease

Induces Cell Death

Lung Disease

Boivin et al., Lab Invest., 2009
Chen et al., Immunity, 2013
LIFE’s Therapeutic Paradigm

Homeostasis → Resokine insufficiency → Disease → Resokine agonists → Healthier Patients
Evidence for Homeostatic Role of Resokine in Humans

Disrupting the Resokine Pathway Promotes Muscle and Lung Disease

Homeostasis

Disease-antibodies

Imbalance

Healthy muscle
Healthy lung

Diseased Muscle
Diseased Lung

↑ Immune cell invasion/activity

100% (18 of 18) anti-synthetase syndrome patients tested positive for antibodies for Resokine proteins
Free Resokine Pathway in Anti-Synthetase Patients is Diminished

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

69% at or below limit of detection
Agonists of the Resokine Pathway in Immune Driven Models

Balancing the immune response to tissue insults

<table>
<thead>
<tr>
<th>Disease Model</th>
<th>Resokine Homeostatic Effect</th>
<th>Immune Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal Muscle</td>
<td></td>
<td>CD4/CD8 &amp; macrophages</td>
</tr>
<tr>
<td>Statin Induced Myopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>Th17/CD4</td>
</tr>
<tr>
<td>Bleomycin Induced Lung Fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td>Th17/CD4</td>
</tr>
<tr>
<td>TNBS Induced Colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>Th17/CD4</td>
</tr>
<tr>
<td>IL23 Induced Psoriasis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

“Native Approach”
to agonize Resokine pathway

Muscle homeostasis

No observed signs of immunosuppression
Signals of potential improved muscle function

Rare muscular dystrophies

iMod.Fc

“Engineered Agonist”
Splice variant of Resokine pathway fused to Fc of antibody

Lung homeostasis

Functional knockout disrupts lung homeostasis
IPF rodent model data compared to Pirfenidone & Nintedanib

Interstitial lung disease

ORCA

3rd Modality

Tissue homeostasis

Preclinical activity

Pan therapeutic area potential

IPF = Idiopathic Pulmonary Fibrosis
RESOLARIS PROGRAM
HARNESSING THE RESOKINE PATHWAY
TO TREAT MULTIPLE RARE MUSCLE DISEASES
Rare Myopathies with an Immune Component

*Chronic damage, homeostasis disrupted*

- **Genetic Mutation**
  - FSHD
  - LGMD2B
  - DMD

- **Aberrant Protein Expression**
  - Inappropriate Proteins in muscle
  - Mutated Dysferlin proteins in muscle
  - Mutated Dystrophin proteins in muscle

- **Localized T Cell Invasion/Engagement**
  - Untapped therapeutic intervention point

Potential to link genotype to specific T cell phenotype
All debilitating diseases with little or no therapeutic treatments

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FSHD = Facioscapulohumeral Muscular Dystrophy. LGMD2B = Limb Girdle Muscular Dystrophy 2B. DMD = Duchenne Muscular Dystrophy.
## Resolaris in Adult LGMD, Adult FSHD & Early Onset FSHD

### Evaluate Safety and Tolerability
- ✓ Build safety dossier
- ✓ Across doses
- ✓ Different patients

### Evaluate Potential Activity Assessments*
- ✓ Functional / Strength: MMT
- ✓ Patient Reported Outcomes: INQoL
- ± MRI / Biomarkers assessment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Highest Dose</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>002</td>
<td>Adult FSHD (n=20), ages 18-70</td>
<td>3.0 mg/kg Weekly (12 weeks)</td>
<td>Placebo controlled, Double blinded</td>
</tr>
<tr>
<td>003</td>
<td>Early onset FSHD (n=8), ages 16-20</td>
<td>3.0 mg/kg Weekly (6 weeks)</td>
<td>Open-label, Intra-patient Dose Escalation for 12 weeks</td>
</tr>
<tr>
<td>004</td>
<td>Adult LGMD2B (n=10), ages 18-70 Adult FSHD (n=8), ages 18-70</td>
<td>3.0 mg/kg Biweekly (4 weeks)</td>
<td>Open-label, Intrapatient Dose Escalation for 12 weeks</td>
</tr>
</tbody>
</table>

*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 Patients Manual Muscle Strength Progressively Declines

Manual Muscle Strength Score
% Change from Baseline Over Time

Time (Months)

Change from Baseline (%)

Placebo
Deflazacort

Percentage of Patients with Muscle Worsening at 6 and 12 Months

Patients with CIDD Worsening (%)

No treatment
Deflazacort

19%
67%

Deflazacort treatment 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)
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; Manual Muscle Testing (MMT) a validated assessment of muscle function/strength in 14 muscle groups
† One patient in 004 Trial did not have an MMT measurement due to being wheelchair bound at baseline
Manual Muscle Test (MMT) Scores LGMD2B & FSHD Patients

004 Study: Individual Patient Changes from Baseline (%)

Week 14 MMT*
LGMD2B (n=9†) & FSHD (n=8)

*1-week follow-up is earlier than week 14 for 2 early discontinuations; Manual Muscle Testing (MMT) a validated assessment of muscle function/strength in 14 muscle groups
† One patient in 004 Trial did not have an MMT measurement due to being wheelchair bound at baseline
MMT Scores Early Onset FSHD Patients

Individual Patient Changes from Baseline (%)

Week 14 MMT*
Early Onset FSHD (n=8)
Patient age range 16 to 20

Note: Patient with 2.2% improved from baseline originally was reported as 1% change in December interim analysis and was corrected for this presentation.

*Manual Muscle Testing (MMT) a validated assessment of muscle function/strength in 14 muscle groups
Compiled Data from Three Phase 1b/2 Clinical Trials
Relatively Stable or Improved Muscle Function Observed

**Overall Mean MMT* Change Week 14 by Dose Group**
*FSHD & LGMD2B Patients From 002, 003, 004 Trials*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Condition</th>
<th>Dose (mg/kg)</th>
<th>Type</th>
<th>Baseline Mean Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>002</td>
<td>FSHD</td>
<td>Placebo</td>
<td>Placebo-controlled</td>
<td>-2.5</td>
</tr>
<tr>
<td>004</td>
<td>FSHD</td>
<td>1.0</td>
<td>Open-label</td>
<td>3.0</td>
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<tr>
<td>004</td>
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<tr>
<td>002</td>
<td>FSHD</td>
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<tr>
<td>004</td>
<td>LGMD*</td>
<td>3.0</td>
<td>Open-label</td>
<td>6.5</td>
</tr>
</tbody>
</table>

- *Manual Muscle Testing (MMT) a validated assessment of muscle function/strength in 14 muscle groups

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

Generally 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

*as of December 2016
Resolaris: One Product, Multiple RMICs
Promise for severely afflicted myopathy patients

Resolaris has broad potential across 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.
- **DMD**: Prevalence of approximately 5/100,000. Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - May 2014 - Number 1

Exon skipping requires individual molecules for each mutation set.
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

✓ Clinical Results: Early Onset FSHD Patient Trial (003)
MOA: Introduce Mechanistic/PD Assay
Clinical Trial: Kick off next randomized controlled trial post partnership*

*Partner for one or more programs
iMod.Fc Program
Lung Physiocrine Engineered
To Treat Multiple Pulmonary Diseases
ILDs Characterized by T Cell Infiltration

**Sarcoidosis**

![Graph showing mRNA-positive cells in BAL fluid for IL-2 and IFN-γ](image)

- Healthy control
- Non-active sarcoidosis
- Active sarcoidosis

**Hypersensitivity Pneumonitis**

**Idiopathic Pulmonary Fibrosis**

![Graph showing CD4/CD8 ratio](image)

- Controls
- Subacute
- Chronic

References:
- Balestro et al. PLOS ONE. 2016
- Barrera et al.: Functional Diversity of T Cells in HP 2007
- Solomon et al. J Bras Pneumol. 2011
Resokine Promotes Lung Homeostasis

**Perturbation**
- Injury
- Infection
- Genetic

**Epithelial damage**
- Pro-inflammation
- IL-1β, TNF, IFNγ

**Pro-inflammation**
- Neutrophil
- Macrophage
- Mast Cell
- T Cell
- Neutrophil

**IL-13, TGFβ, TNF, IL-1β**

**Fibrocytes**
- EMT
- Fibroblasts

**Severe tissue remodeling**
- Excess deposition of ECM

**Natural Resokine levels**
- Pro-inflammation
- IL-1β, TNF, IFNγ

**Natural restoration of tissue homeostasis and resolution of immune engagement**

**Pharmacologic restoration of tissue homeostasis and resolution of immune engagement**

**Resokine agonist therapy**

**Circulation**

**Natural Resokine levels**
- Pro-inflammation
- IL-1β, TNF, IFNγ
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

* p < .05
iMod.Fc Tempers Activated Human T Cells at High Affinity

Th2 Cytokine (pg/ml)

**iMod.Fc 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
iMod.Fc Outperforms Current Treatments
Established Rodent Model for Idiopathic Pulmonary Fibrosis (IPF)

**Superior activity in established IPF fibrotic model**

iMod.Fc outperformed pirfenidone at $1/3500^{th}$ total dose

Two doses of iMod.Fc 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*
Significant Untapped Opportunity in ILD

**Limited available options for patients**

**IPF**

**Irreversible, progressive lung disease**
- Chronic progressive fibrotic process
- Acute episodes

**Very high unmet medical need**
- 2-3 year median survival
- Significant functional and QoL impairment

~135k patients in US

**Other ILDs**

**>100 disorders**
- Primary & secondary
- Various disease patterns

**High unmet medical need**
- Heterogeneous, many have grave prognosis
- SOC has limited evidence of safety and efficacy

>450k patients in US across all forms of ILD*

*including IPF
# iMod.Fc: 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:**

- **MOA:** Introduce mechanistic/PD assay
- **IND Enabling:** Complete preclinical safety studies
- **GMP Manufacturing:** Complete initial 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

John Blake, CPA
SVP, Finance

Andrea Cubitt, Ph.D.
VP, Product Protection

Ashraf Amanullah, Ph.D.
VP, Manufacturing

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

- $61.9M cash and investments as of 3/31/2017
- 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