Translating New Immune Pathways into Meaningful Medicines

Cantor Fitzgerald 2018 Global Healthcare Conference

Sanjay S. Shukla, M.D., M.S., President & CEO

October 2, 2018

aTyr Pharma

Forward-Looking Statements

The following slides and any accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” “opportunity,” or “continue,” and other similar expressions are intended to identify forward-looking statements. For example, all statements we make regarding the potential therapeutic benefits of proteins derived from tRNA synthetase genes and our product candidates, including ATYR1923 and any product candidates from our other pipeline programs, the ability to successfully advance our pipeline or product candidates, the timing within which we expect to initiate, receive and report data from, and complete our planned clinical trials, our ability to receive regulatory approvals for, and commercialize, our product candidates, our ability to identify and discover additional product candidates, and the ability of our intellectual property portfolio to provide protection are forward-looking statements. All forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected. These risks, uncertainties and other factors are more fully described in our filings with the U.S. Securities and Exchange Commission, including our Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q, and in our other filings. The forward-looking statements in this presentation speak only as of the date of this presentation and neither we nor any other person assume responsibility for the accuracy and completeness of any forward-looking statement. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

Corporate Overview - aTyr

Founded:	2005 by Paul Schimmel, Ph.D. and Xiang-Lei Yang, Ph.D, leading tRNA synthetase researchers at *The Scripps Research Institute (TSRI)*
Science:	Discovering and developing novel therapeutics based on our understanding of the extracellular functionalities of tRNA synthetase genes
Patents:	Global intellectual property estate directed to a potential pipeline of protein compositions derived from 20 tRNA synthetase genes
Located:	San Diego, CA
Subsidiary:	Pangu BioPharma (98%), founded in Hong Kong in 2007, affiliated with tRNA synthetase research at *Hong Kong University of Science & Technology (HKUST)*

Accelerating Value Creation from Novel Biology

Platform of New Biology:

Discover innovative therapeutic candidates based on proprietary knowledge of extracellular functions of tRNA synthetase genes

Lead Product Candidate: ATYR1923

Engineered protein, based on the HARS* gene, for the treatment of pulmonary sarcoidosis

Financials:

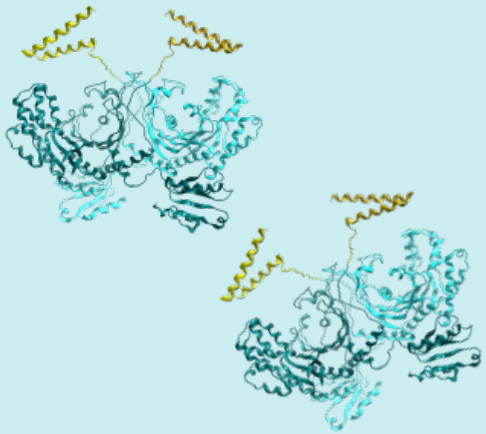
Cash, cash equivalents and investments at $64.3M as of 6/30/2018

Upcoming Clinical Catalysts:

- ✓ ATYR1923 Phase 1 data – 2Q 2018
- ❑ Initiate Phase 1b/2a – 4Q 2018
- ❑ Results Phase 1b/2a – TBD

New Biology: Functionality of Extracellular tRNA Synthetase Proteins

tRNA Synthetases

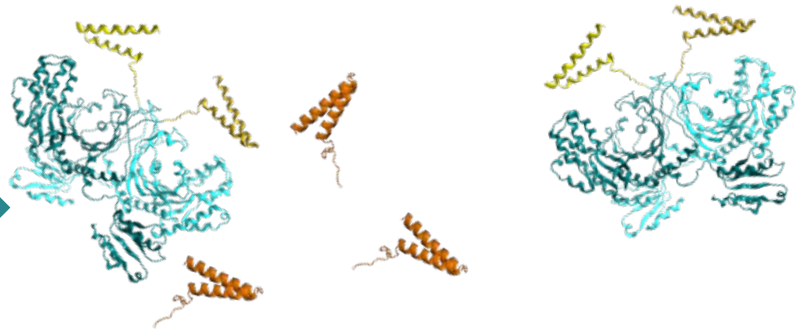


Intracellular function:
Catalyze protein synthesis by transporting amino acid to tRNA

Cytoplasm

Secretion

Extracellular Proteins
full-length and splice-variants derived from tRNA synthetase genes

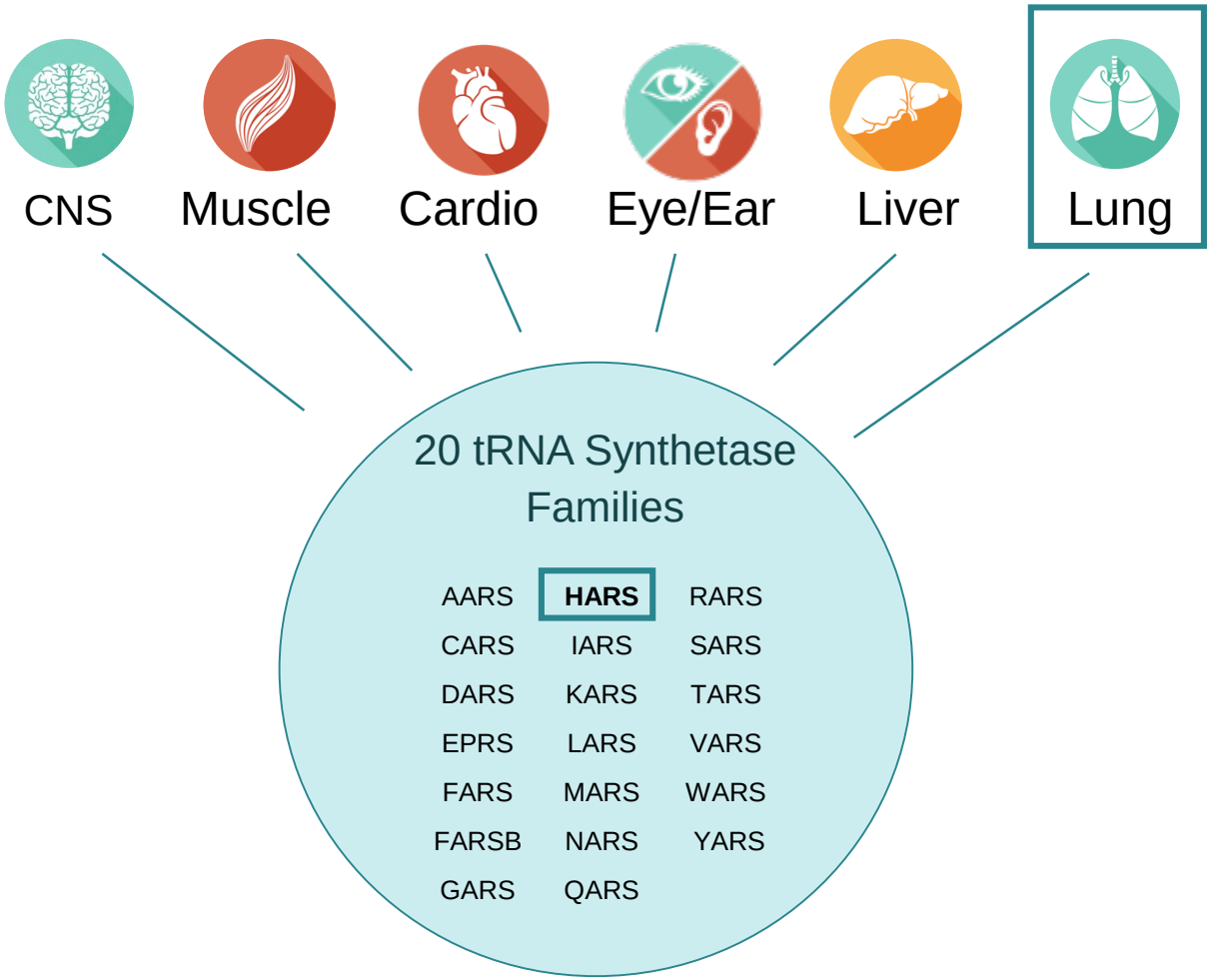


Extracellular function:
Immunomodulatory

Circulation / Tissue

Newly Discovered Biology

Extracellular tRNA Synthetase Biology Associated with Disease in Multiple Tissues



HARS = Histidyl tRNA Synthetase

ATYR1923

Extracellular HARS splice variant "iMod domain"

fused to Fc domain of human antibody

iMod Domain of HARS:

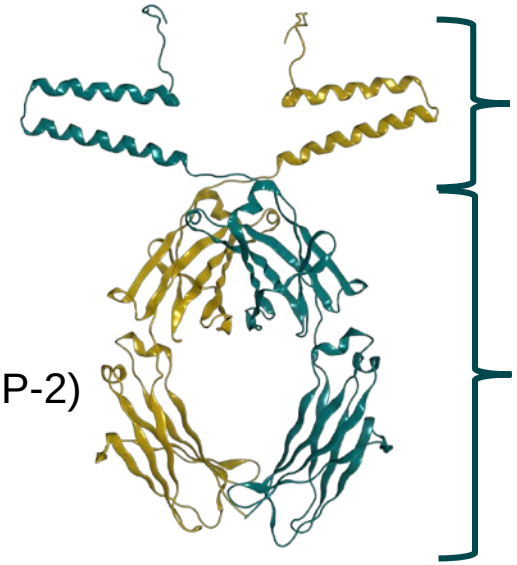
- Enriched in the human lung
- Inhibits human T cell activation

Receptor/Mechanism of Action:

- "iMod domain" binds to Neuropilin-2 (NRP-2)
- Regulates immune system

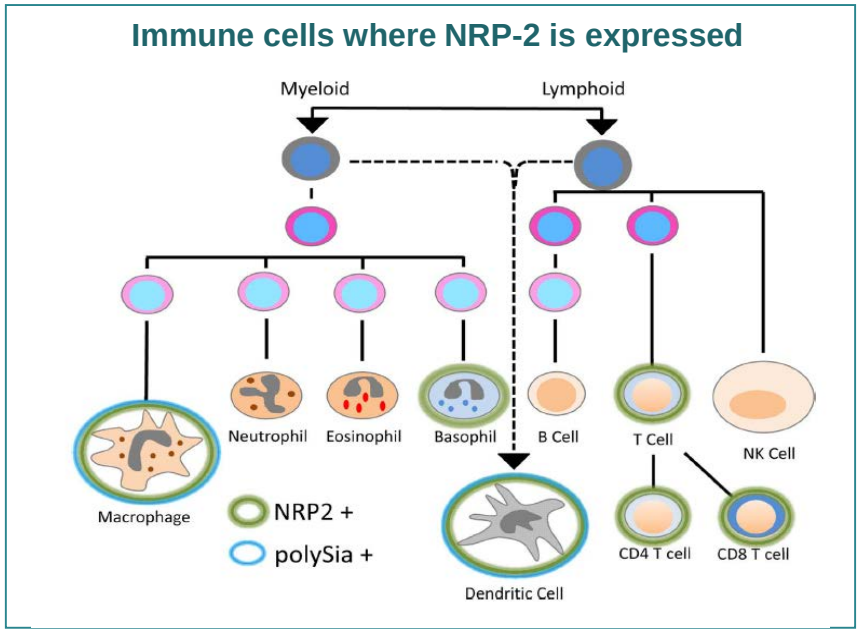
Fc Domain of Human Antibody:

- Used to extend half-life
- Once-monthly dosing regimen



Receptor: Importance of NRP-2 as a Binding Partner for ATYR1923

- Pleiotropic receptor that can bind to a number of different ligands
- Well-established role in the development of the neural and lymphatic systems
- Emerging role in the **immune system**; present on a number of immune cell types
- Expressed on alveolar macrophages, may play role in **regulating lung inflammation**



Schellenberg et al. *Role of Neuropilin-2 in the immune system.* Mol. Immunol. 90, 239-244. 2017

NRP-2 Connections to T Cell Biology

Immunomodulatory Effects of Neuropilin-2 On T Cells

H. Nakayama,[1,2] N. Kochupurakkal,[1] S. Bruneau,[1] D. Bielenberg,[2] M. Klagsbrun,[2] D. Briscoe.[1]

[1]Transplant Research Program, Boston Children's Hospital, Boston, MA
[2]Vascular Biology Program, Boston Children's Hospital, Boston, MA.

Meeting: 2015 American Transplant Congress

Abstract number: 139

OPEN ACCESS Freely available online PLOS | ONE

Semaphorin 3F and Neuropilin-2 Control the Migration of Human T-Cell Precursors

Daniella Arêas Mendes-da-Cruz[1,2¤], Anne Colette Brignier[1,3¤], Vahid Asnafi[4], Frederic Baleydier[4], Carolina Valença Messias[2], Yves Lepelletier[1,5], Nawel Bedjaoui[4], Amedée Renand[1], Salete Smaniotto[6], Danielle Canioni[4,6], Pierre Milpied[1], Karl Balabanian[8], Philippe Bousso[9], Stéphane Leprêtre[10], Yves Bertrand[11], Hervé Dombret[12], Norbert Ifrah[13], Mireille Dardenne[1], Elizabeth Macintyre[4], Wilson Savino[2], Olivier Hermine[1,4,5]*

Emerging area of immunology implicated in multiple organ systems:

- Lung
- Lymphatics
- Smooth Muscle

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Regulation of mTOR Signaling by Semaphorin 3F-Neuropilin 2 Interactions *In Vitro* and *In Vivo*

Received: 13 March 2015
Accepted: 04 June 2015
Published: 09 July 2015

Hironao Nakayama[1,2,3,4], Sarah Bruneau[1,5], Nora Kochupurakkal[1,5], Silvia Coma[1,3], David M. Briscoe[1,2,3,*] & Michael Klagsbrun[1,2,3,*]

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 282, NO. 42, pp. 30346–30356, October 19, 2007

Polysialylated Neuropilin-2 Is Expressed on the Surface of Human Dendritic Cells and Modulates Dendritic Cell-T Lymphocyte Interactions*

Received for publication, April 9, 2007, and in revised form, July 24, 2007 Published, JBC Papers in Press, August 15, 2007, DOI 10.1074/jbc.M702965200

Sabrina Curreli[‡], Zita Arany[§], Rita Gerardy-Schahn[¶1], Dean Mann[§], and Nicholas M. Stamatos[‡‖2]

From the [‡]Institute of Human Virology, University of Maryland, Baltimore, Maryland 21201, [§]Department of Pathology and [‖]Division of Infectious Diseases, Department of Medicine, University of Maryland Medical System, Baltimore, Maryland 21201, and [¶]Zentrum Biochemie, Abteilung Zellulare Chemie, Medizinische Hochschule Hannover, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany

ATYR1923

For the Treatment of Pulmonary Sarcoidosis

High Unmet Need in Interstitial Lung Disease

Pulmonary Sarcoidosis

- Systemic inflammatory disorder characterized by non-caseating granulomas (CD4+ T cell driven)
- US prevalence: ~150k to 200k
- ~30% have chronic progressive disease unresponsive to steroids; definable subset with high mortality
- Current SOC: steroids - cytotoxic agents - TNF inhibitors (as disease progresses)

Chronic Hypersensitivity Pneumonitis (CHP)

- Exaggerated immune response to environmental antigen
- US prevalence: ~60k
- 5-year mortality: ~20%
- No effective therapeutic options

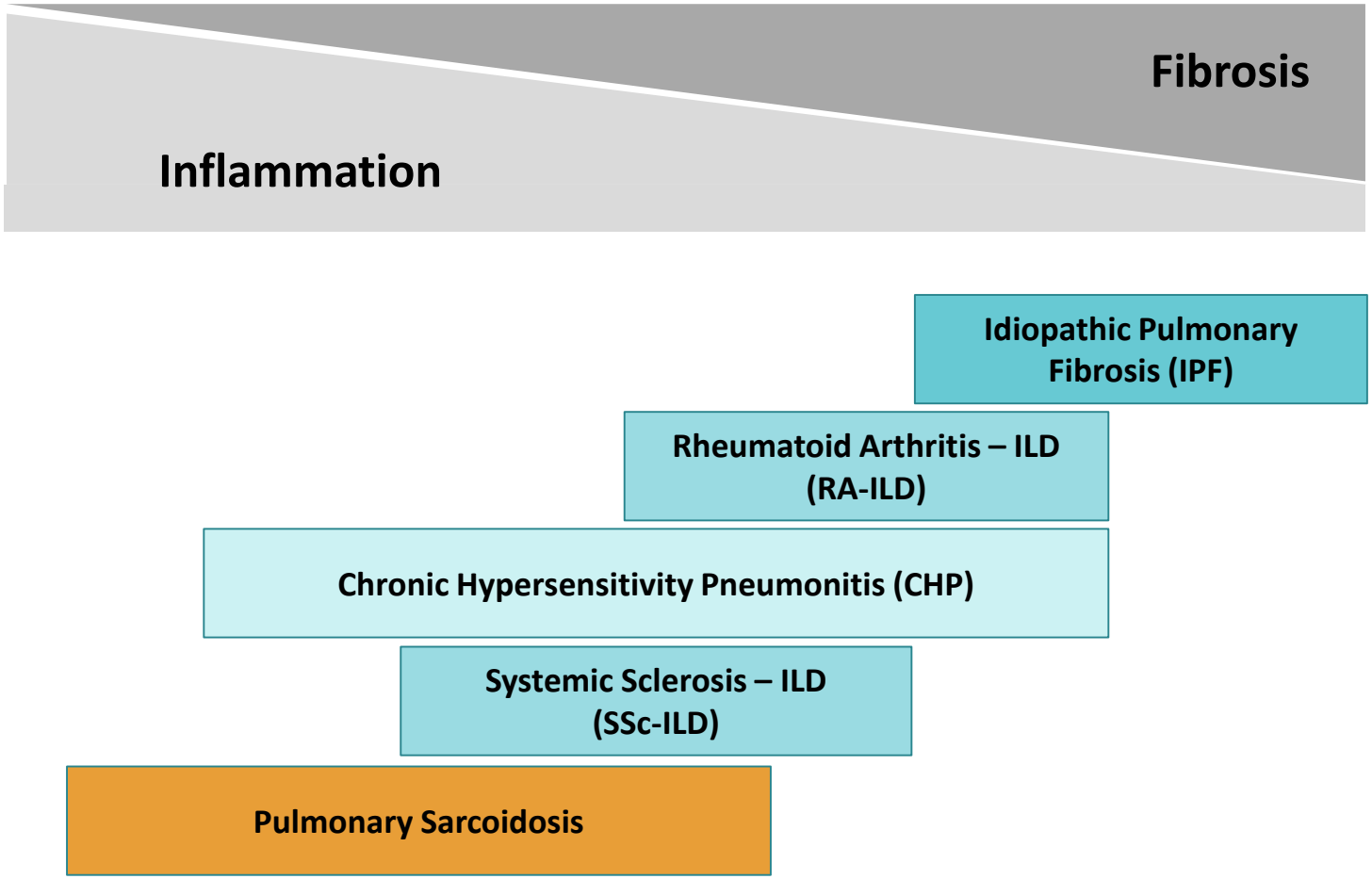
Connective Tissue Disease Associated-ILD (CTD-ILD)

- Common manifestation in CTD: Rheumatoid Arthritis - 10% with clinical symptoms; Systemic Sclerosis - <50% with lung involvement)
- US prevalence: ~150k
- 5-year mortality: ~20%
- Current SOC: Mycophenolate mofetil or cyclophosphamide for SSC-ILD; no consensus for RA-ILD

Idiopathic Pulmonary Fibrosis (IPF)

- Irreversible, progressive fibrotic disease of unknown cause
- US prevalence: ~135k
- 5-year mortality: ~60-80%
- Current SOC: Nintedanib or pirfenidone (>$2B combined 2017 sales)

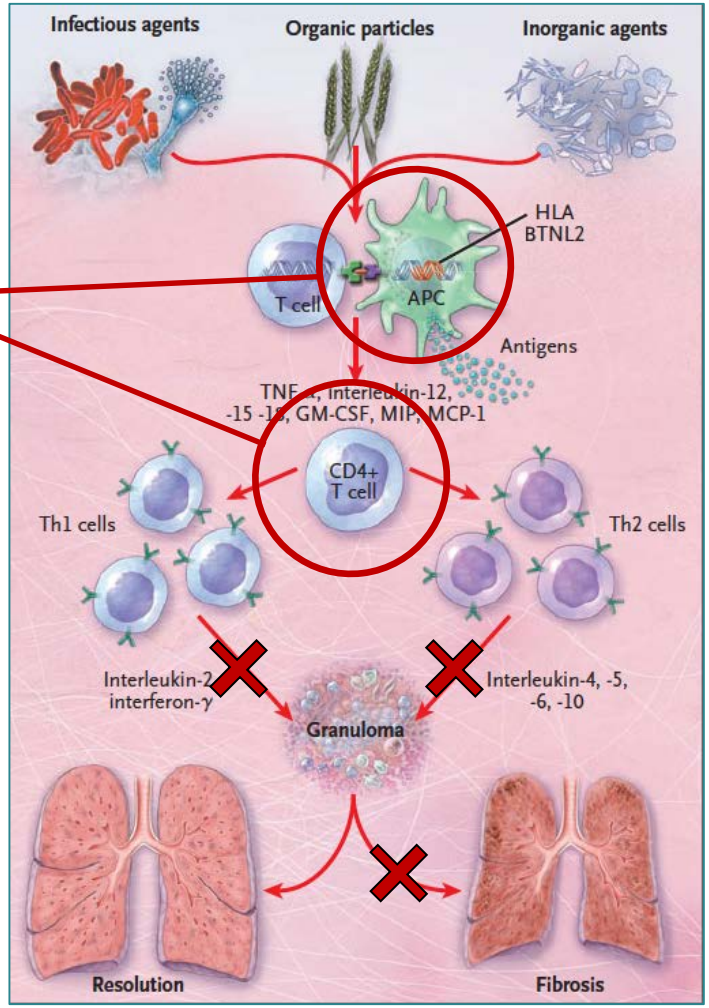
Interstitial Lung Diseases Share Persistent Immune Engagement



Slide adapted from Dr. Steven Nathan, Medical Director, Advanced Lung Disease and Transplant Program at Inova Fairfax Hospital, Falls Church, VA

ATYR1923 Intervention in Pulmonary Sarcoidosis Pathogenesis

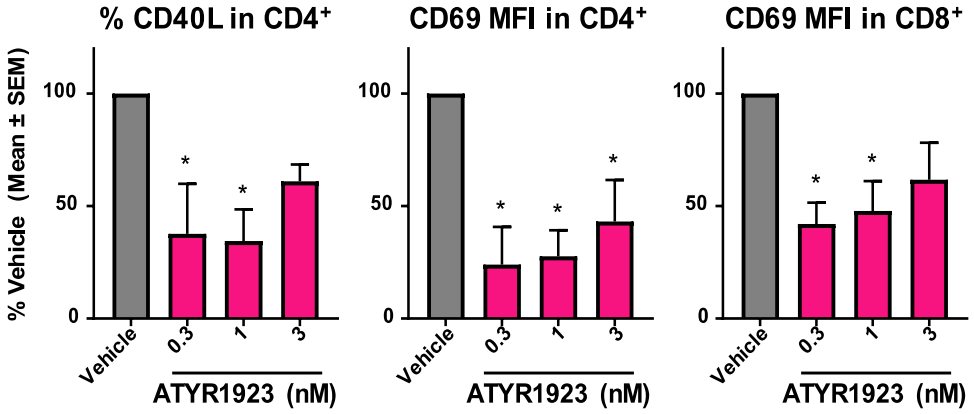
ATYR1923 Therapeutic Hypothesis:
Downregulate inflammatory insult and prevent progression to fibrosis



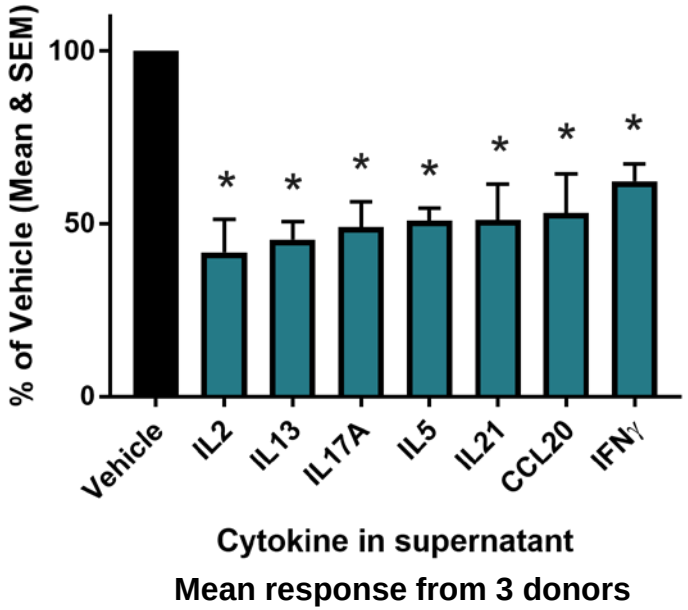
Hypothesized Immunopathogenesis of Sarcoidosis adapted from Iannuzzi et al, NEJM, 2007

Mechanism of Action: ATYR1923 Inhibits T Cell Activation In Vitro

Effect of ATYR1923 on T Cell Activation Markers



Effect of 0.3 nM ATYR1923 on T Cell Cytokine Release



aTyr is currently exploring the interaction with ATYR1923 and NRP-2 across multiple immune cell types

*$P < 0.05$

Note: Presented in a poster at the American Academy of Immunology Annual Meeting in May 2018

Pre-Clinical Translational Estate Supports Clinical Development in ILD

1923 Provides Therapeutic Activity in Bleomycin-induced Lung Fibrosis Model

- Mouse model comparing pirfenidone* vs. dexamethasome vs. ATYR1923
- 1923 was efficacious and ameliorated lung fibrosis
- Presented at ATS, May 2017

1923 Improves Lung Function in Model

- Rat model comparing nintedanib** vs. ATYR1923
- 1923 was efficacious in additional bleomycin-induced lung fibrosis
- Presented at ATS, May 2018

1923 Ameliorates Dermal and Pulmonary Fibrosis in Model

- Mouse model comparing nintedanib** vs. ATYR1923
- 1923 has robust activity when treatment initiated early (day 7)
- Presented at Scleroderma Foundation Patient Conference, July 2018

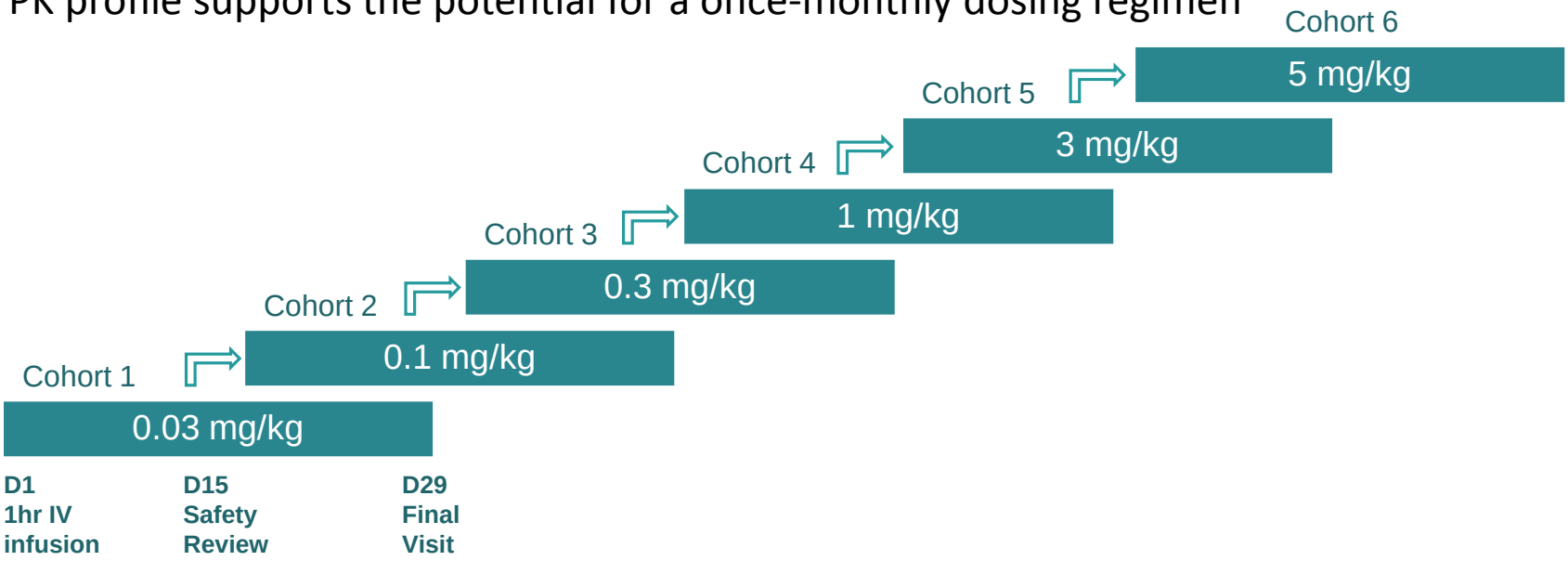
*2017 annual sales of Esbriet® (pirfenidone) ~869 CHF, 13% increase YoY

**2017 annual sales of Ofev® (nintedanib) ~920 Euros, 52.3% increase YoY

Phase I: Healthy Volunteer Study

Positive Phase 1 Data Announced in June 2018

- Randomized, double-blind, placebo-controlled, single ascending dose (N=36 HVs)
- ATYR1923 was generally well-tolerated with no significant adverse events
- PK profile supports the potential for a once-monthly dosing regimen



First-in-Patient Trial in Pulmonary Sarcoidosis

Preliminary Design:

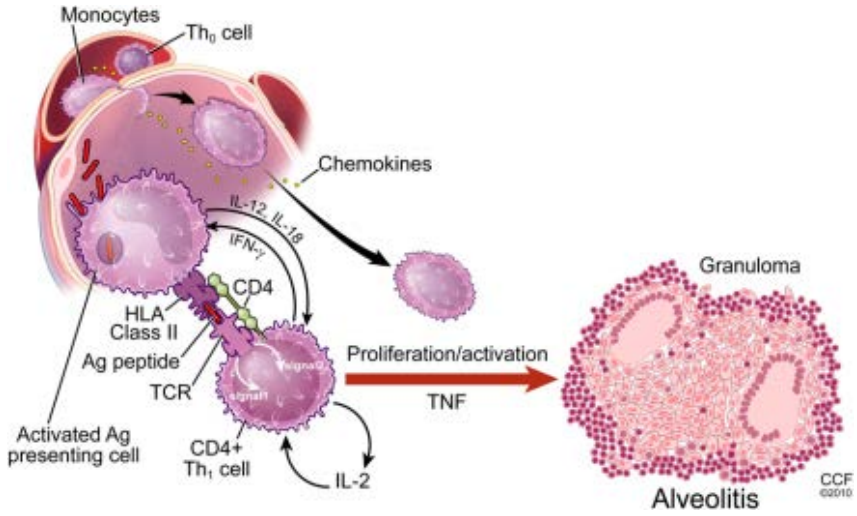
- Phase 1b/2a multiple-ascending dose, placebo controlled, first-in-patient study in pulmonary sarcoidosis
- Evaluate safety, tolerability and immunogenicity of multiple doses of 1923
- Evaluate established clinical endpoints and potential biomarkers to assess preliminary activity of ATYR1923

Upcoming Milestones:

- ✓ Announced Phase 1b/2a indication of pulmonary sarcoidosis
- ❑ Educational webinar on October 8th to provide disease education with Dr. Daniel Culver and overview of Phase 1b/2a study design
- ❑ Initiate trial in 4Q 2018

First-in-Patient Population: Pulmonary Sarcoidosis

- Systemic inflammatory disorder characterized by the formation of granulomas (clumps of inflammatory cells) in one or more organs of the body
- Usually begins in the lungs, skin or lymph nodes
- Sarcoidosis in the lungs is called pulmonary sarcoidosis and occurs in ~90% of patients
- ~30% of patients have chronic, unremitting inflammation with progressive organ impairment
- US Prevalence: ~150k to 200k patients



Mission: Generate Value for Shareholders and Patients

- ✓ aTyr owns the full potential pipeline of proteins derived from 20 tRNA synthetase genes
- ✓ Identification of NRP-2 receptor for ATYR1923 elucidates greater understanding of MOA
- ✓ ATYR1923 *in-vitro* and *in-vivo* studies support clinical development in ILD
- ✓ HARS-based therapeutics safety profile includes 92 subjects
- ❑ Goal is to demonstrate safety and preliminary clinical activity in ATYR1923 pulmonary sarcoidosis trial
- ❑ Potential to expand into other ILD indications

Thank You