



## A New Path to Medicine

H.C. Wainwright Global Life Sciences Conference

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March 9-10, 2021

# Forward Looking Statements

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# aTyr: A New Path to Medicine

**Mission:** Develop a new class of medicines based on proprietary biology platform with a novel approach for identifying target receptors for extracellular tRNA synthetase fragments from an IP portfolio covering protein derivatives from all 20 tRNA synthetase gene families

## **ATYR1923**

- Immunomodulator for severe inflammatory lung diseases
- Pulmonary sarcoidosis trial enrollment completed – data expected Q3 2021
- Positive topline data reported January 2021 in COVID-19 pts

## **NRP2 Antibodies**

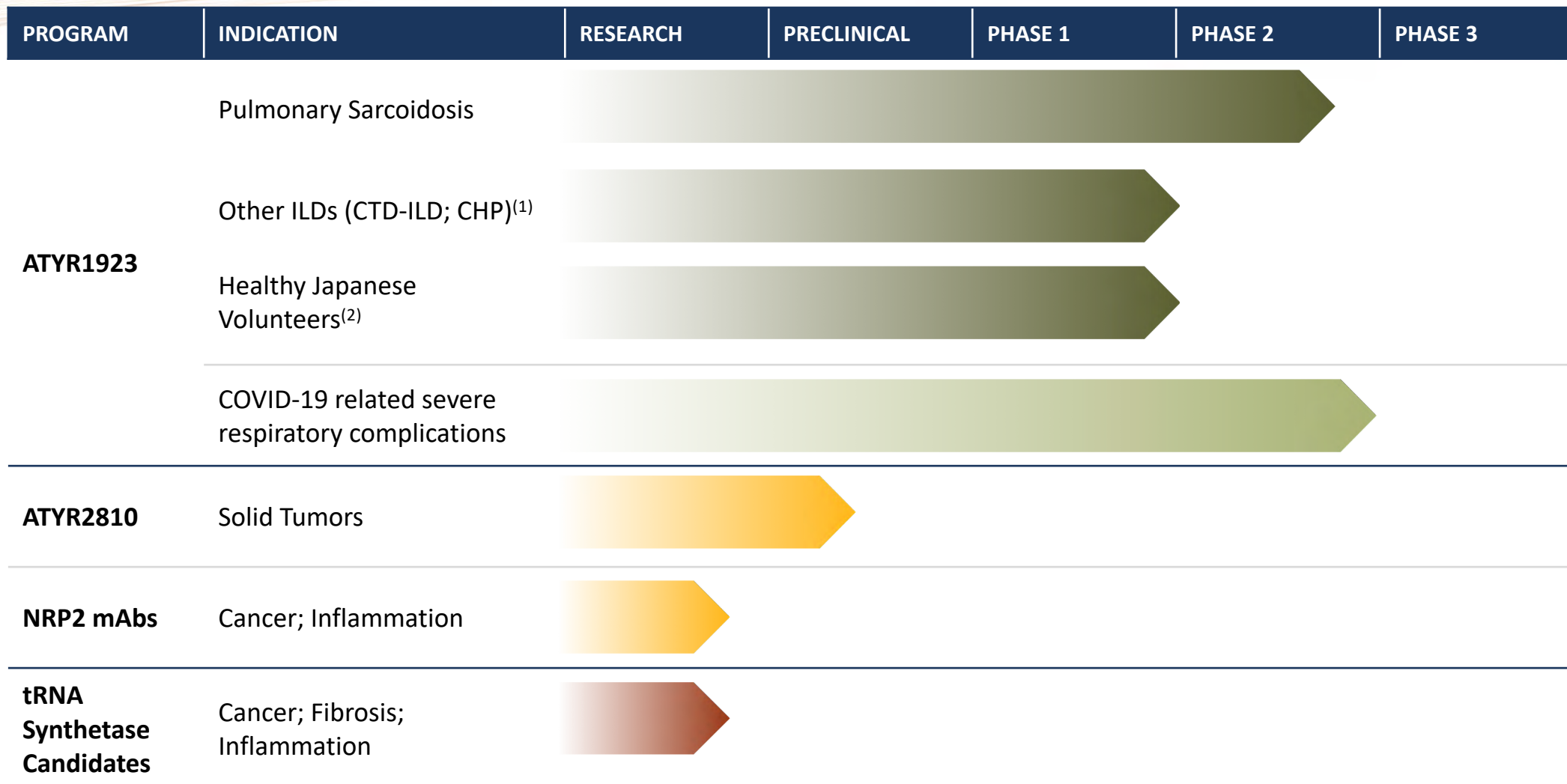
- ATYR2810: first anti-neuropilin-2 (NRP2) antibody for cancer – IND-enabling activities initiated
- NRP2 antibody research program for distinct therapeutic applications

## **tRNA Synthetase Candidates**

- Receptors identified for two new tRNA synthetases from our pipeline
- Discovery programs targeting cancer and NK cell biology

**Financials:** Cash, cash equivalents and investments at \$36.1m as of September 30, 2020

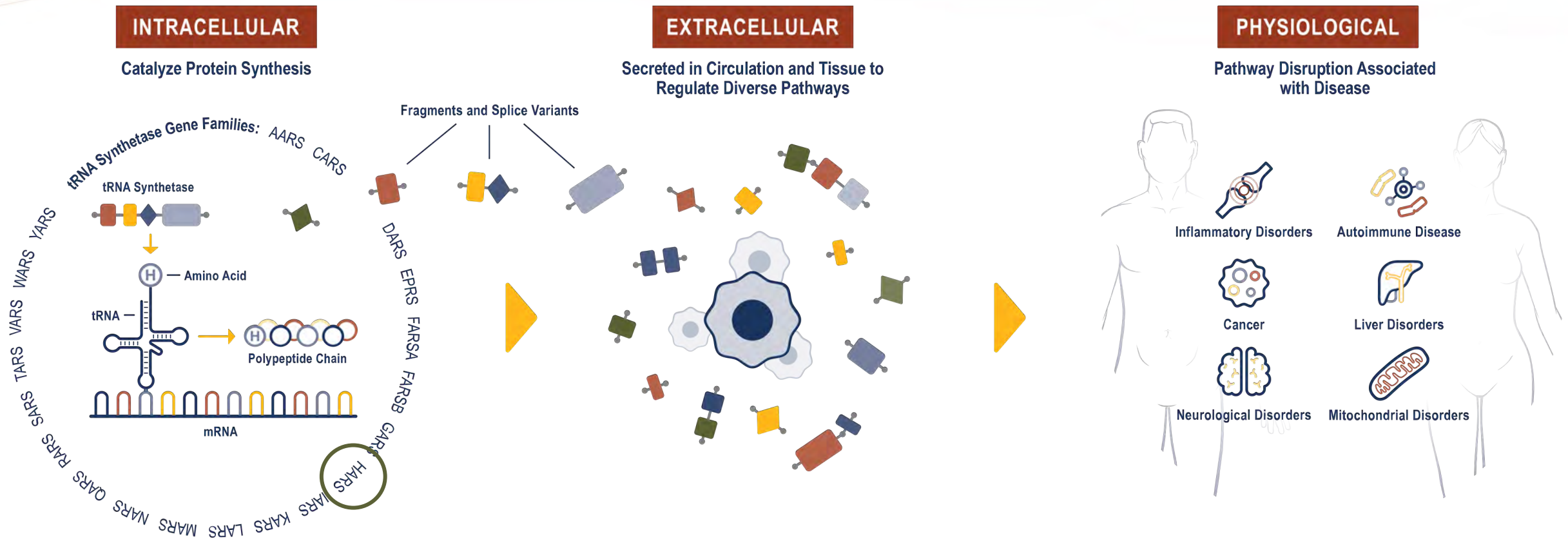
# aTyr Development Pipeline



(1) CTD-ILD: connective tissue disease-related ILD (e.g. Scleroderma-related ILD); CHP: chronic hypersensitivity pneumonitis

(2) In partnership with Kyorin Pharmaceutical Co., Ltd.

# tRNA Synthetases May Have Novel Functions Extracellularly



tRNA synthetases are secreted extracellularly and occur in novel forms which lose their canonical function

Extracellular tRNA synthetase disruption (genetic/ autoimmune) is associated with disease in humans

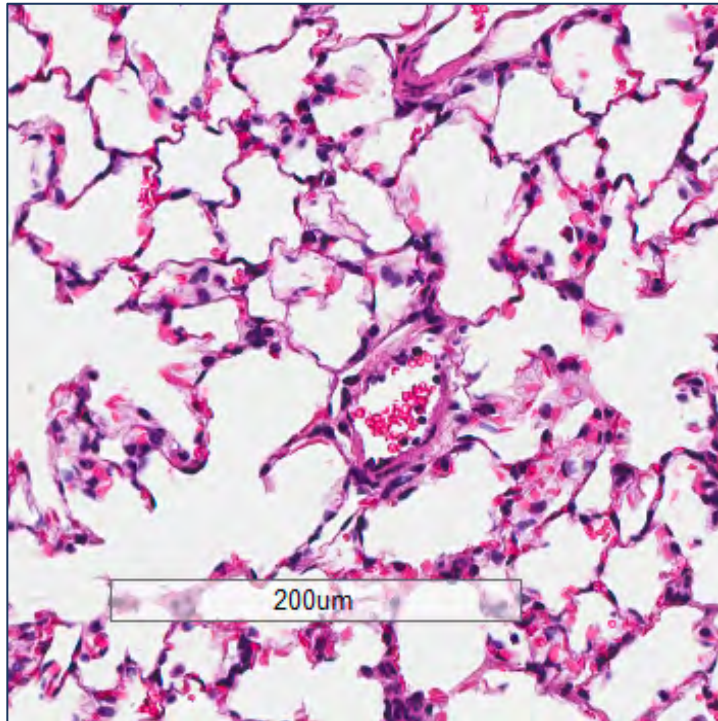


ATYR1923

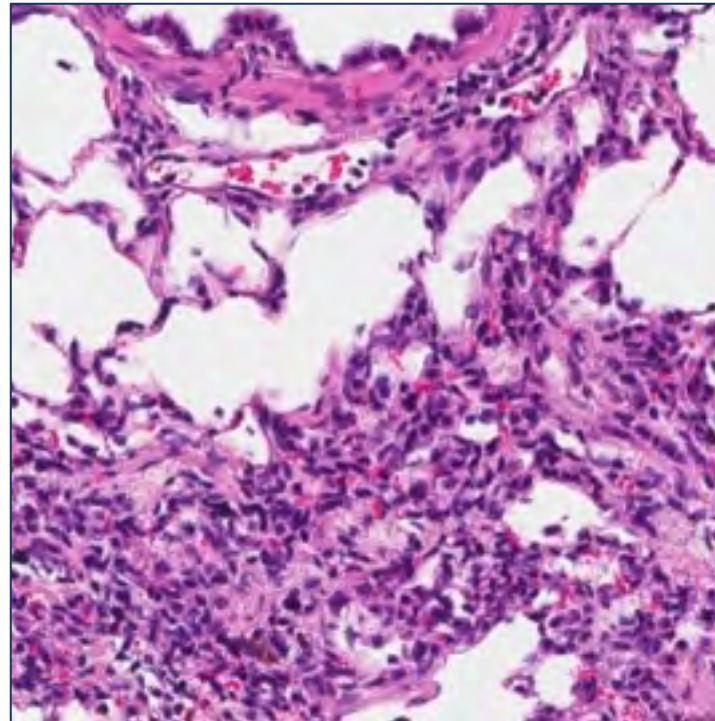
A Novel Immunomodulator for Inflammatory Lung Disease

# A Novel Mechanism to Treat Inflammation

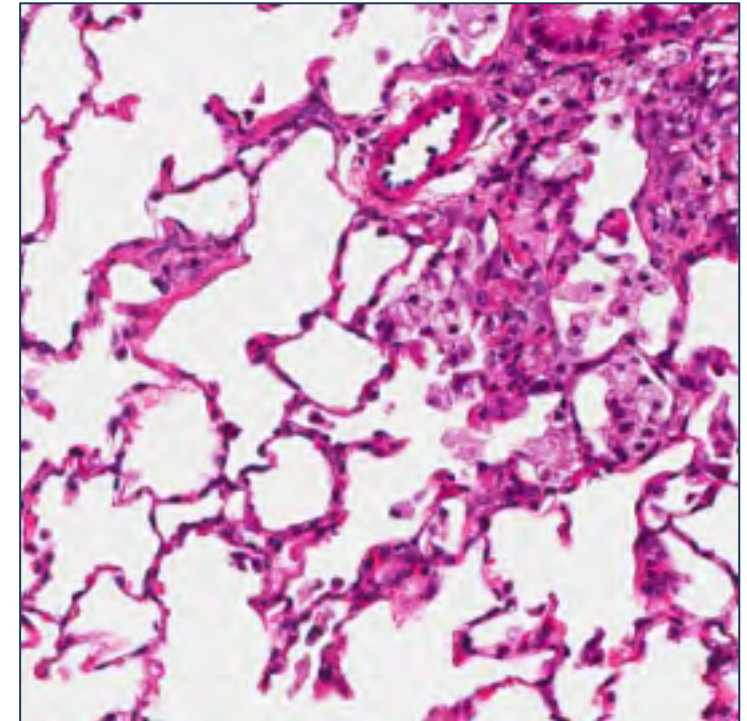
**Healthy lung**



**Injured lung**



**ATYR1923 treated**



# ATYR1923: Early Data Supports Therapeutic Potential in Immune-Mediated Lung Disease

- Fc fusion protein, based on naturally occurring splice variant of the lung-enriched histidyl-tRNA synthetase (HARS) fragment, recombinantly expressed in *E. coli*
- Receptor screen identified selective binding to NRP2, a cell surface receptor upregulated on key immune cells during inflammation and is enriched in inflamed lung tissue
  - NRP2 expression is detected in granulomas associated with human sarcoidosis of the lung and skin
  - Lung tissue from patients who died from COVID-19 related respiratory failure shows increased NRP2
- Downregulates inflammatory and pro-fibrotic cytokine and chemokine levels as well as histological inflammation and fibrosis in pre-clinical models
- Phase 1 study in healthy volunteers PK supports with once-monthly intravenous dosing
- Well tolerated in patients and subjects dosed to date with exposure up to 24 weeks

# Demonstrated Effect in Animal Lung Injury Models



*P. acnes* (Sarcoidosis)

↓ pro-fibrotic proteins

*S. Rectivirgula* (CHP)

↓ tissue cytokines/chemokines and enzymes

Sclerodermatous GvHD (SSc-ILD)

↓ fibrosis

SKG mice (RA-ILD)

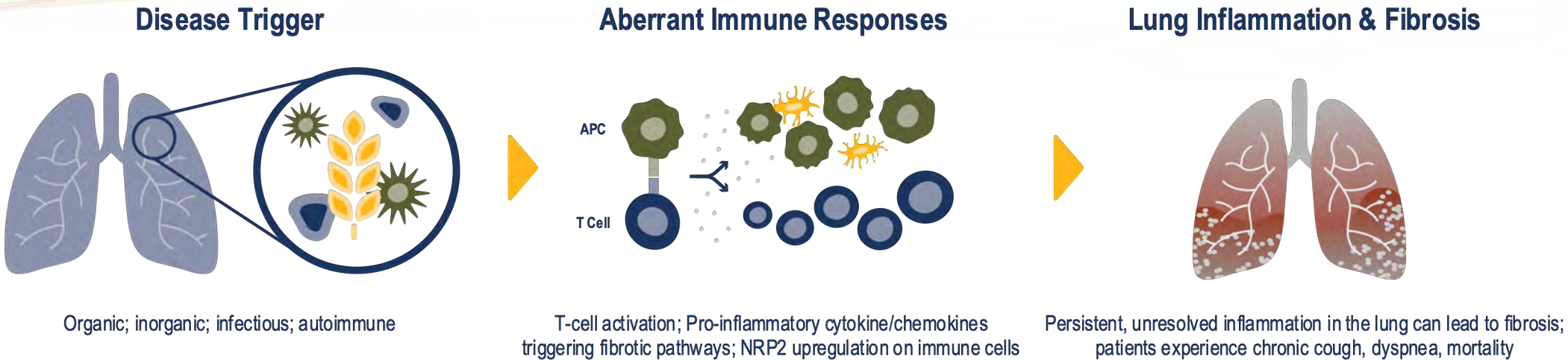
↓ immune infiltrates

Bleomycin-Induced Lung Fibrosis (IPF)

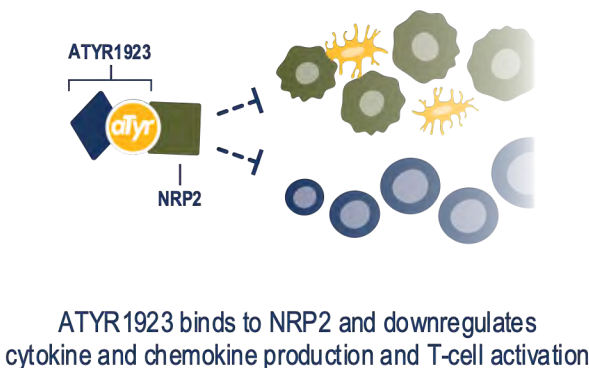
↓ inflammation / fibrosis

Consistent downregulation of pro-inflammatory cytokines including IL-6, MCP-1, and IFN- $\gamma$

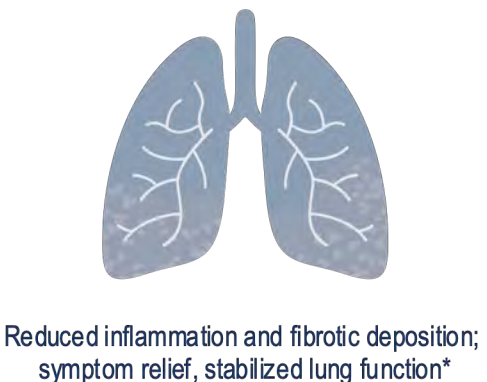
# ATYR1923 Mechanism of Action in Inflammatory Lung Disease



## ATYR1923 Dampens Immune Responses



## Stabilized Lung

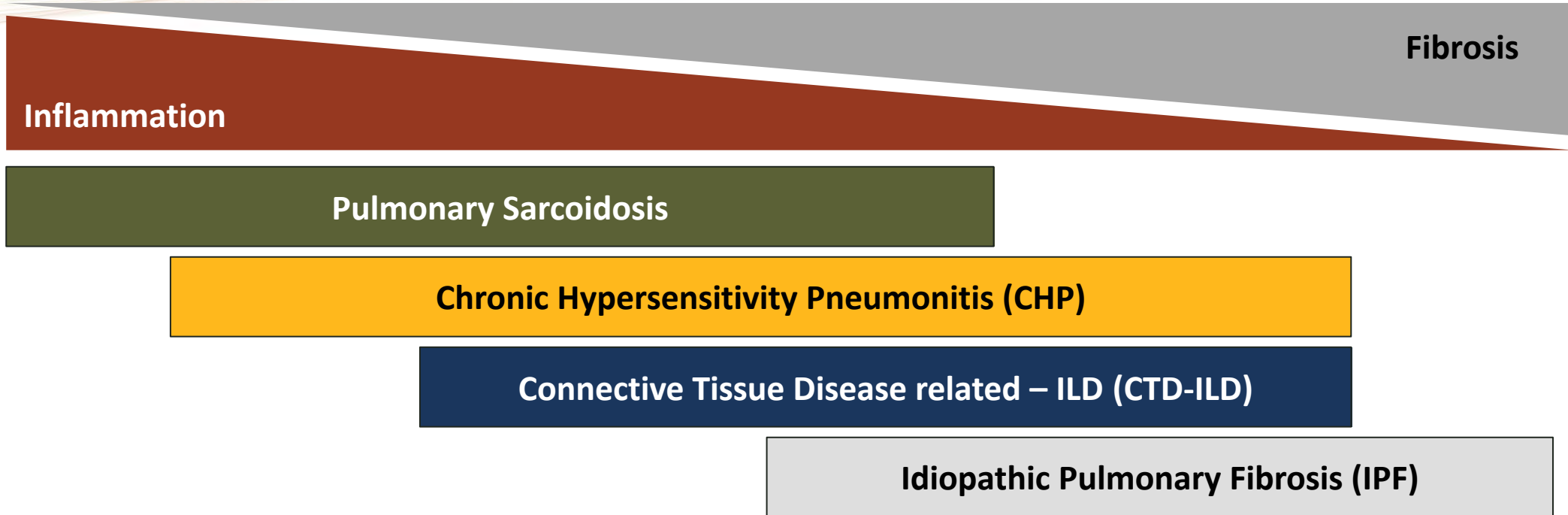




ATYR1923

Interstitial Lung Disease

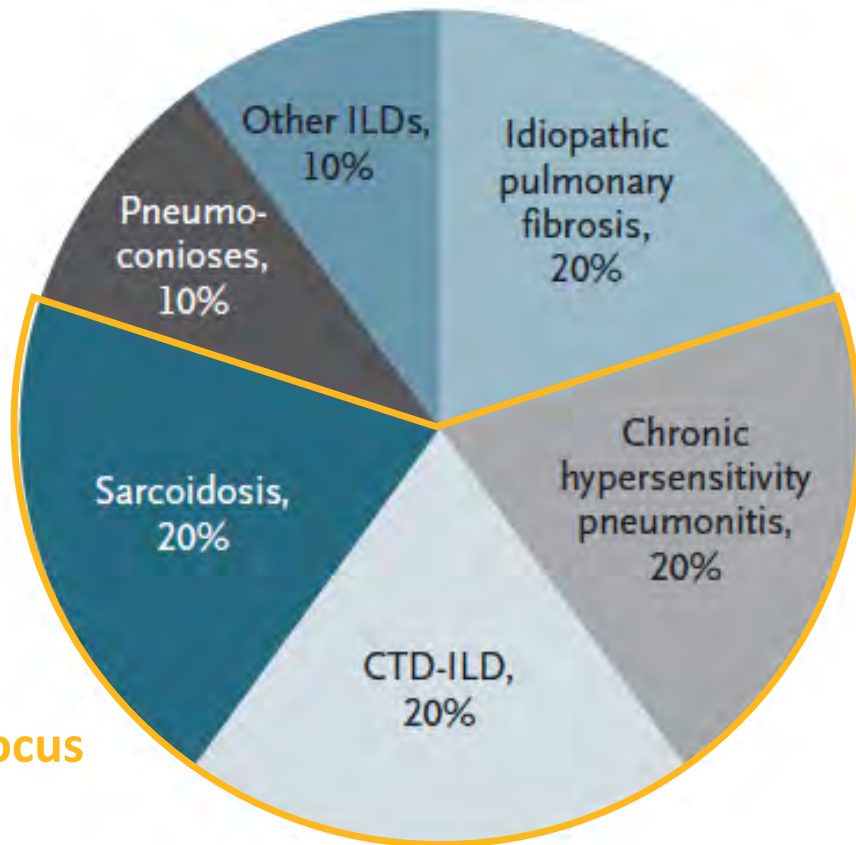
# ILDs Share Common Immune Pathology Leading to Fibrosis



- ILDs lie on a spectrum of inflammation and fibrosis, but all share an immune pathology
- Progression to fibrosis is a key driver of morbidity and mortality
- By targeting aberrant immune response driving fibrosis, ATYR1923 has potential to improve outcomes in multiple ILDs

# Market Opportunity in Inflammatory Interstitial Lung Disease

## Relative Distribution of ILDs in the USA<sup>(1)</sup>



aTyr focus

- >200 types of ILD: 4 major types comprise 80% of patients
- Limited standard of care with substantial morbidity and mortality
- aTyr focused on 3 most inflammatory types: ~500-600k US patients<sup>(2)</sup>; ~3m globally
- \$2-3b global market opportunity<sup>(3)</sup>

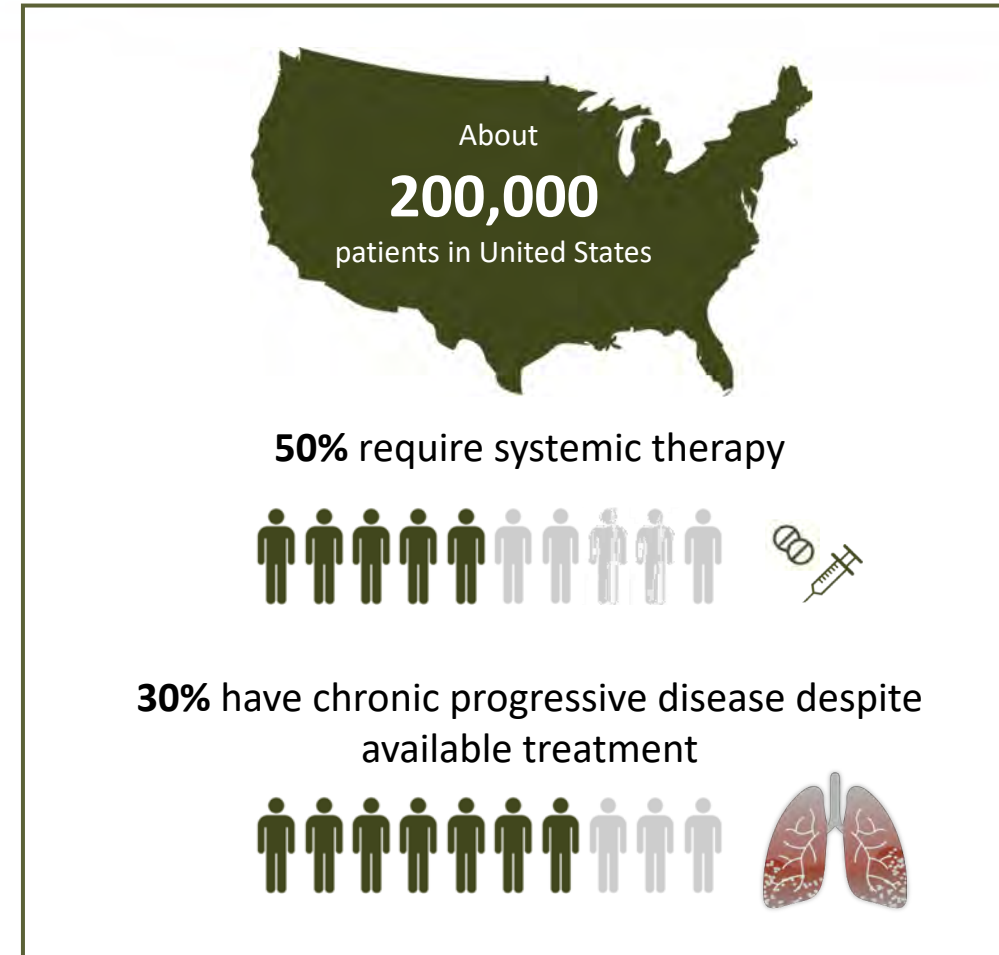
(1) Lederer, Martinez. NEJM 2018

(2) All ILDs individually have potential for orphan status

(3) aTyr estimates for ATYR1923 in Pulmonary Sarcoidosis, CHP, CTD-ILD; excludes IPF

# First ATYR1923 Indication: Pulmonary Sarcoidosis

- Inflammatory disease of unknown etiology characterized by the formation of granulomas (clumps of immune cells)
- T cell driven: CD4+ (Th1 / Th17)
- Pulmonary sarcoidosis occurs in ~90% of all sarcoidosis patients
- Treatment options are limited with associated toxicity: Corticosteroids, antimetabolite immunosuppressants, TNF inhibitors

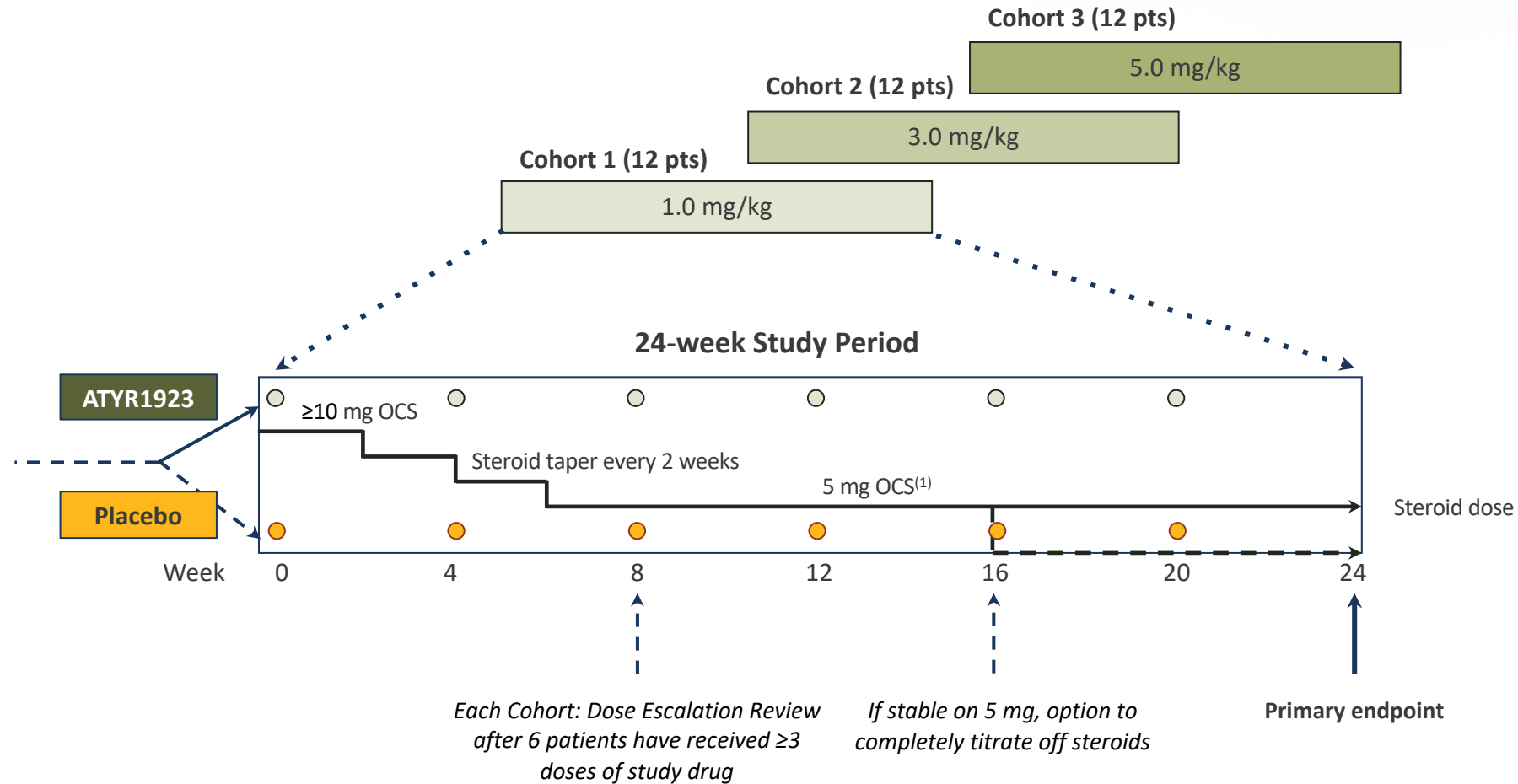


# Phase 1b/2a Study in Pulmonary Sarcoidosis Ongoing

<b>Design</b>	<ul style="list-style-type: none"><li>• Randomized (2:1), double-blind, placebo-controlled, multiple ascending dose</li><li>• 6 IV doses of ATYR1923 being tested at 1.0, 3.0, and 5.0 mg/kg</li><li>• Forced steroid taper to 5.0 mg by week 8; taper to 0 mg possible at week 16 in responders</li></ul>
<b>Population</b>	<ul style="list-style-type: none"><li>• 37 histologically confirmed pulmonary sarcoidosis patients</li><li>• ≥10 mg stable oral corticosteroid treatment</li><li>• Symptomatic/active disease at baseline</li></ul>
<b>Primary Endpoint</b>	<ul style="list-style-type: none"><li>• Safety and tolerability of multiple ascending IV ATYR1923 doses</li></ul>
<b>Secondary Endpoints</b>	<ul style="list-style-type: none"><li>• Steroid-sparing effect</li><li>• Immunogenicity</li><li>• Pharmacokinetics (PK)</li><li>• Exploratory efficacy measures: FDG-PET/CT imaging; Lung function (FVC); Serum biomarkers; Health-related quality of life scales</li></ul>

Target enrollment completed  
Data expected Q3 2021

# Phase 1b/2a Pulmonary Sarcoidosis Study Schema



# ATYR1923 Japan Collaboration

## Kyorin Overview

- Founded: 1923
- Focus: Respiratory, ENT, Urology
- 1600 employees: incl. 350 in R&D; 750 sales reps covering top respiratory centers in Japan
- Sales: ~\$1b USD
- Market cap: \$1.2b USD (4569:JP TSE)

## Key Terms

- Scope: ATYR1923; Japan; ILD
- Upfront payment: \$8m
- Development, regulatory and commercial milestones: \$167m
- Tiered sales royalties into double digits
- Kyorin to fund all development and commercial activities in Japan

Last subject visit completed for Phase 1 study to evaluate the safety, pharmacokinetics and immunogenicity in Japanese healthy volunteers



ATYR1923

COVID-19 Related Severe Respiratory Complications

# Phase 2 Study in COVID-19 Related Severe Respiratory Complications

<b>Rationale</b>	<ul style="list-style-type: none"><li>• COVID-19 associated lung inflammation is driven by pathways effected by ATYR1923's mechanism of action</li></ul>
<b>Objective</b>	<ul style="list-style-type: none"><li>• Evaluate safety and preliminary efficacy of ATYR1923 in subjects hospitalized with COVID-19-related severe respiratory complications</li></ul>
<b>Design</b>	<ul style="list-style-type: none"><li>• Randomized, double-blind, placebo controlled, single dose (not powered for statistical significance)</li></ul>
<b>Population</b>	<ul style="list-style-type: none"><li>• 32 adult patients with severe respiratory complications related to COVID-19 infection requiring supplemental oxygen but not mechanically ventilated (WHO score 4, 5)</li></ul>
<b>Doses</b>	<ul style="list-style-type: none"><li>• Randomized 1:1:1 - Single dose of 1.0 or 3.0 mg/kg ATYR1923 or Placebo</li></ul>
<b>Endpoints</b>	<ul style="list-style-type: none"><li>• Primary: Safety and Tolerability</li><li>• Secondary: Time to recovery (WHO score <math>\leq 3</math> or hospital discharge without supplemental oxygen); proportion of patients achieving recovery within a week; all cause mortality</li><li>• Exploratory: Clinical biomarkers; 60 day follow up</li></ul>

Topline data reported January 2021

Full data set, including biomarker analysis, expected Q1 2021

# Highlights of Topline Results for Safety and Key Recovery Metrics

## **Study Met Primary Safety Endpoint in Moderate to Severe Hospitalized Patients**

- ATYR1923 was generally safe and well-tolerated in both the 1.0 and 3.0 mg/kg treatment groups
- Adverse events were mostly mild or moderate in severity and there were no drug-related SAEs

## **Preliminary Signal of Activity Seen in 3.0 mg/kg Cohort<sup>(1)</sup>**

- 3.0 mg/kg cohort experienced a median time to recovery of 5.5 days (95% CI: 3,6) compared to 6 days (95% CI: 2,12) in placebo group
- 83% vs 56% of patients achieved recovery by day 6 in the 3.0 mg/kg ATYR1923 and placebo groups, respectively

# Key Insights from Preliminary Demographics and Baseline Characteristics

- Demographics and baseline disease characteristics were largely balanced except for some key risk factors which were disproportionately randomized to ATYR1923 groups:
  - More patients over the age of 65
  - More patients with severe hypoxia
  - More baseline comorbidities and more patients with multiple baseline comorbidities
- Imbalances suggest a sicker patient population in ATYR1923 treatment groups and may have contributed to an overperformance in the placebo arm
- All patients in the study received remdesivir and/or dexamethasone



NRP2 Antibodies

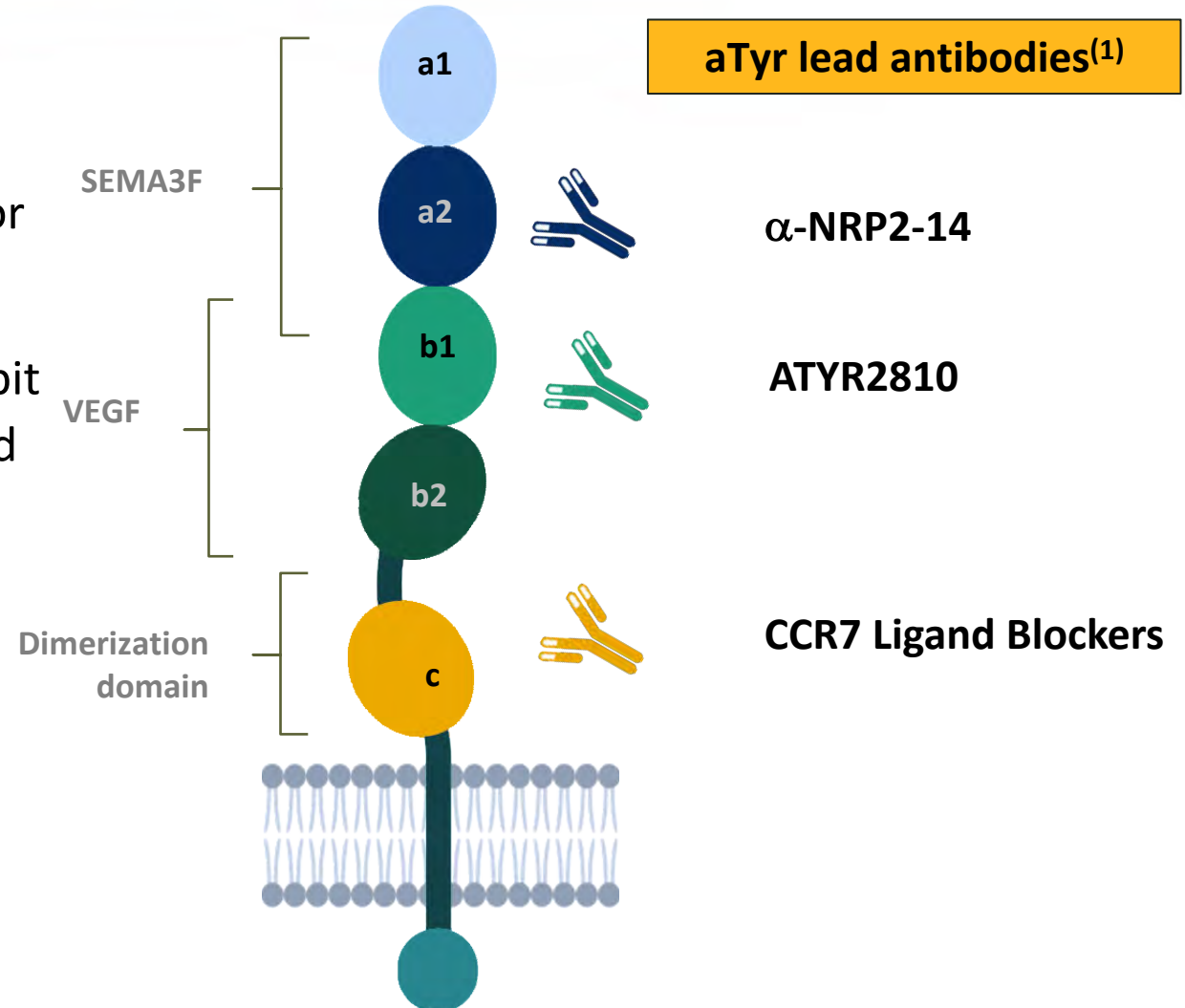
Regulating Diverse Disease Pathways

# NRP2: A Novel Therapeutic Target

- NRP2 is a potentially novel drug target for cancer and inflammatory disorders
- Acts as a co-receptor for VEGF, semaphorins and certain chemokines (e.g., CCL21)
- Highly expressed on certain solid tumors, such as breast and lung
- Tumor expression is associated with worse outcomes in many cancers

# aTyr is Developing Humanized NRP2 Antibodies Targeting Diverse Pathways

- aTyr has developed a panel of antibodies to selectively target different NRP2 epitopes for diverse therapeutic applications
- aTyr anti-NRP2 monoclonal antibodies exhibit superior specificity and sensitivity compared to commercially available antibodies

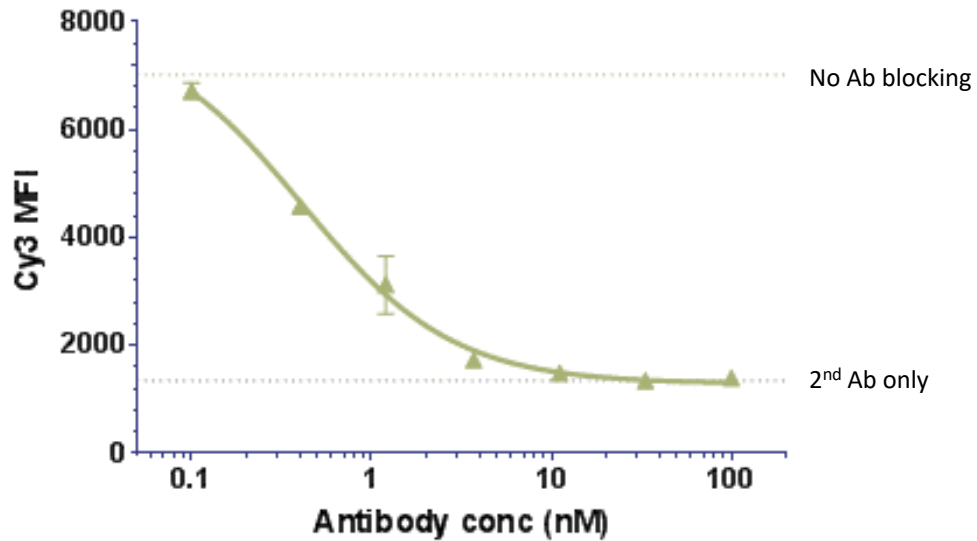


# ATYR2810: Lead Anti-Neuropilin-2 Antibody IND Candidate for Cancer

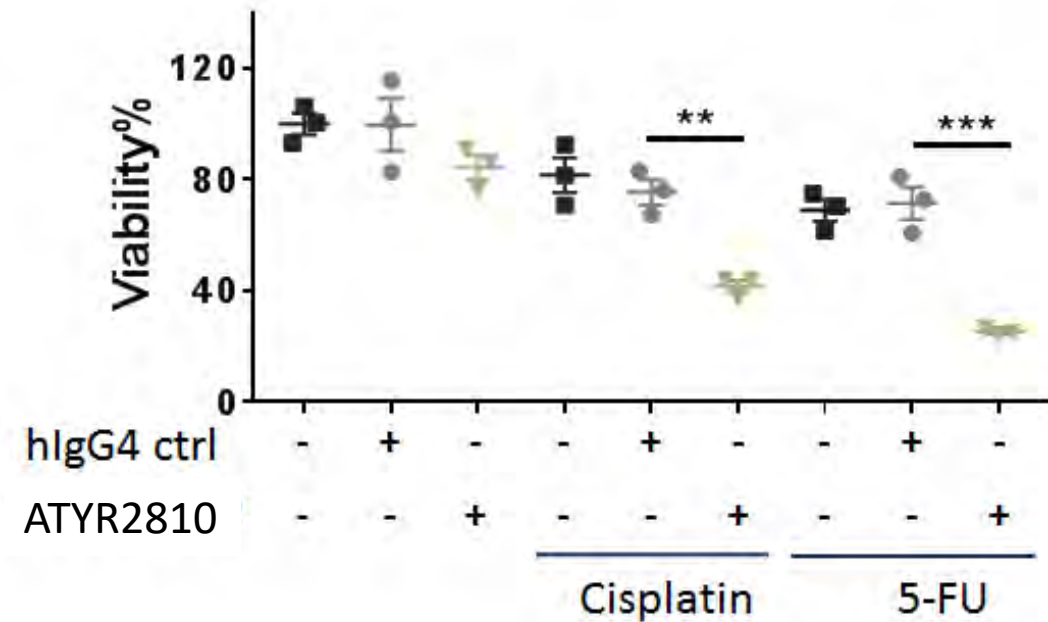
- ATYR2810 is a humanized monoclonal antibody that specifically and functionally blocks the interaction between NRP2 and VEGF
- The role of NRP2 and VEGF signaling in the tumor microenvironment and its importance in the progression of certain aggressive cancers is becoming increasingly validated
- Preclinical data in models of triple-negative breast cancer suggest that ATYR2810 could potentially be effective in certain aggressive solid tumors <sup>(1)</sup>
  - Blocks VEGF-C binding to NRP2
  - Shows tumor inhibitory effects
  - Increases sensitivity to chemotherapy

# Early Pre-clinical Data Support Development in Oncology

## Blocks VEGF binding to NRP2



## Increases Sensitivity to Chemotherapy in Triple-Negative Breast Cancer Model

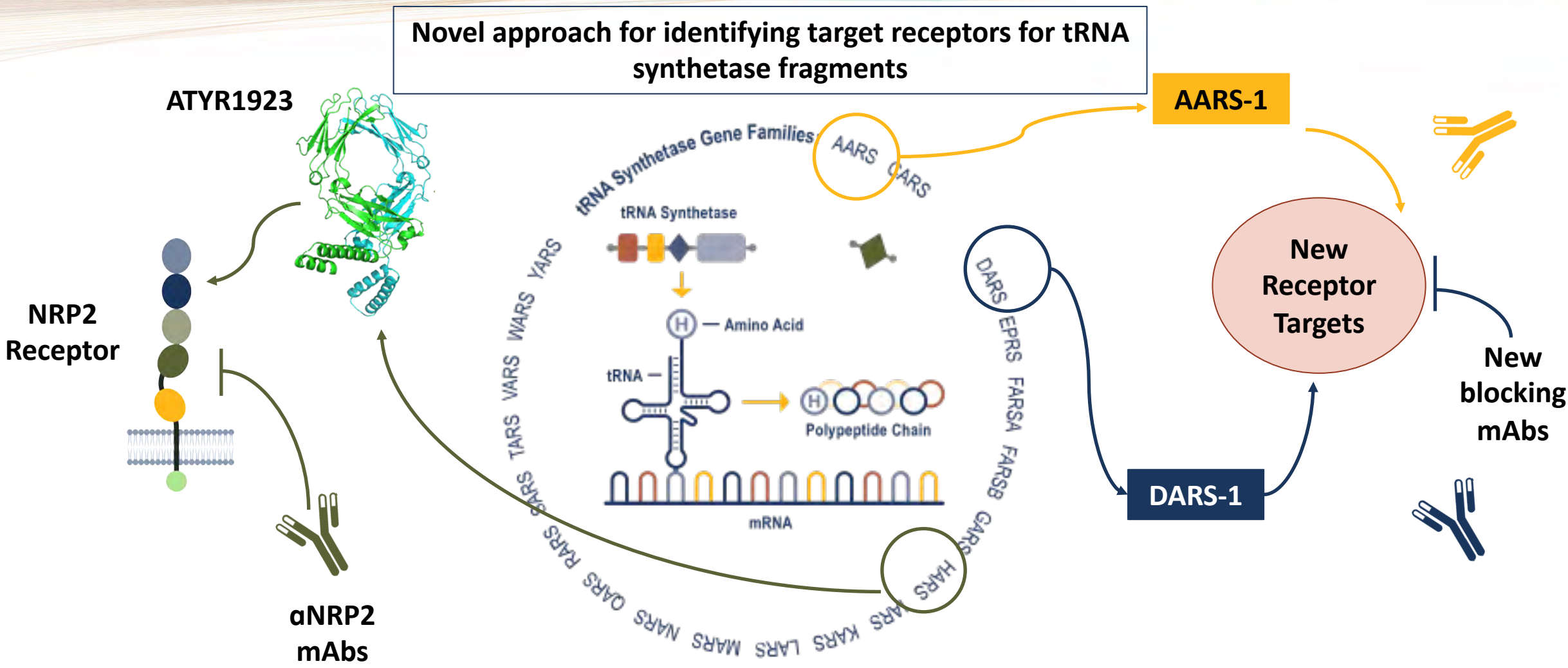




tRNA Synthetases

A Potential New Therapeutic Protein Class

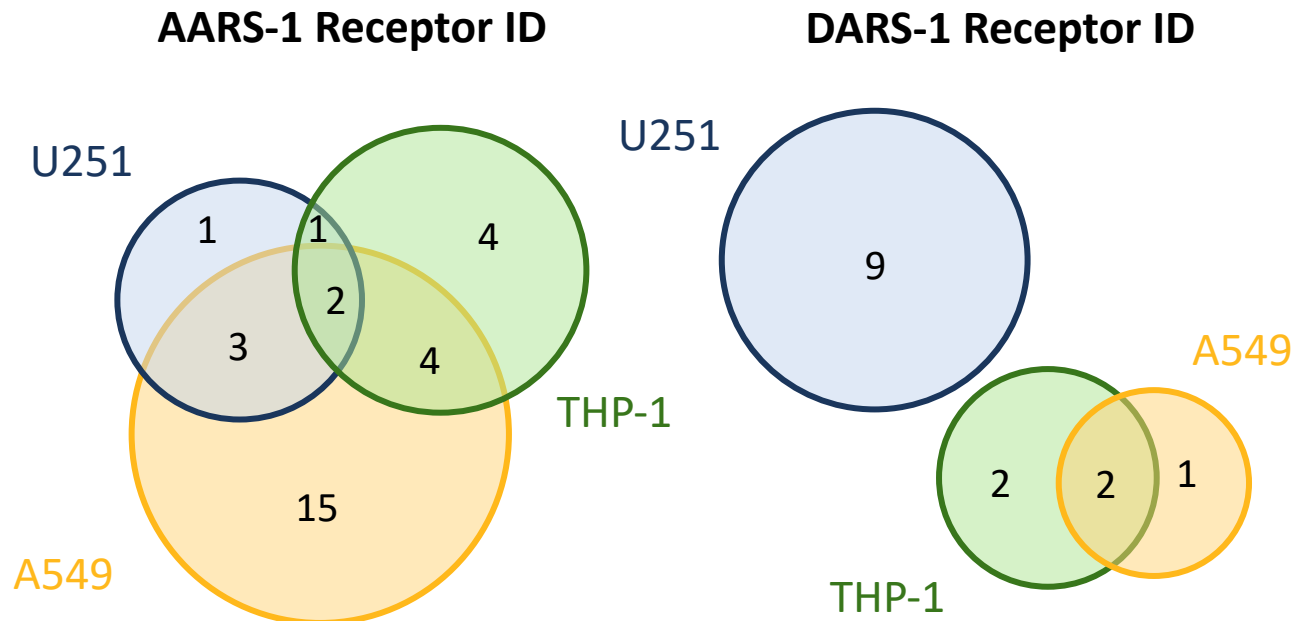
# aTyr Biology Platform



**aTyr owns IP covering all 20 tRNA synthetase gene families**

# New Discovery Programs Initiated from tRNA Synthetase Library

- New discovery programs initiated around select fragments of alanine- (AARS) and aspartyl- (DARS) tRNA synthetases from our platform library
- Multiple binding targets identified using novel approach, with potential implications in immunology, fibrosis and cancer
- Initial focus on NK cells for cancer



## Differential Cell Binding

	Human cell type	Differentiation state	AARS-1	DARS-1
Innate Immune cells	Monocyte THP-1	Naïve	+	+
	Primary monocytes (classical)	Naïve	-	-
	Primary monocytes (classical)	Activated (PMA)	++	++
	Monocyte THP-1	M0 (PMA)	+	+
	Monocyte THP-1	M1 (PMA/LPS/IFN $\gamma$ )	-	-
	Primary macrophages	All	-	+
	Natural Killer NK-92	Naïve	-	++
Adaptive Immune cells	Primary NK cells	Naïve	+	+
	T cell Jurkat	Naïve	+	+
	T cell Jurkat	Activated ( $\alpha$ CD3/ $\alpha$ CD28)	+	+
	T cell Jurkat	Activated (PMA)	-	-
	Primary CD4+ T-cells	CD4+	-	-
	Primary CD8+ T-cells	CD8+	+	+
	Primary NK-T cells	Naïve	+	+
Oncology	Glioblastoma U251	Naïve	++	++
	Glioblastoma U87	Naïve	+	+
	Lung adenocarcinoma A549	Naïve	++	++



A New Path to Medicine

# aTyr: A New Path to Medicine

- Platform of proprietary new biology
- Phase 2 clinical program: ATYR1923
  - Novel MOA for inflammatory lung disease
  - Demonstrated effect in multiple animal lung injury models
  - Phase 1b/2a clinical study in pulmonary sarcoidosis completed enrollment in US – positive interim safety data reported Dec 2019
  - Kyorin collaboration for ILD in Japan with total deal value up to \$175m – completed last subject visit for Phase 1 study
  - Phase 2 trial in COVID-19 patients with severe respiratory complications completed – positive topline results reported January 2021
- Preclinical program: ATYR2810
  - Lead anti-NRP2 antibody IND candidate for cancer shows anti-tumor effects in triple-negative breast cancer model
- Discovery stage programs in cancer, inflammation and immunology
  - NRP2 antibody research program for distinct therapeutic applications
  - Discovery programs for tRNA synthetases AARS and DARS primarily targeting cancer and initially focusing on NK cell biology
- Cash, cash equivalents, and investments at \$36.1m as of September 30, 2020

# Upcoming Catalysts

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## **ATYR1923**

- Phase 1b/2a results in pulmonary sarcoidosis patients expected Q3 2021
  - Phase 2 full data set in COVID-19 patients expected Q1 2021
- 

## **ATYR2810**

- IND enabling activities for the first anti-NRP2 antibody
- 

## **NRP2 Antibodies**

- Potential new pipeline opportunities internally and through academic collaborations
- 

## **tRNA Synthetase Candidates**

- Presentation of scientific findings related to new receptor targets for AARS and DARS
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Thank You