

# **Pulmonary Sarcoidosis and ATYR1923**

**Educational Webinar  
October 8, 2018**



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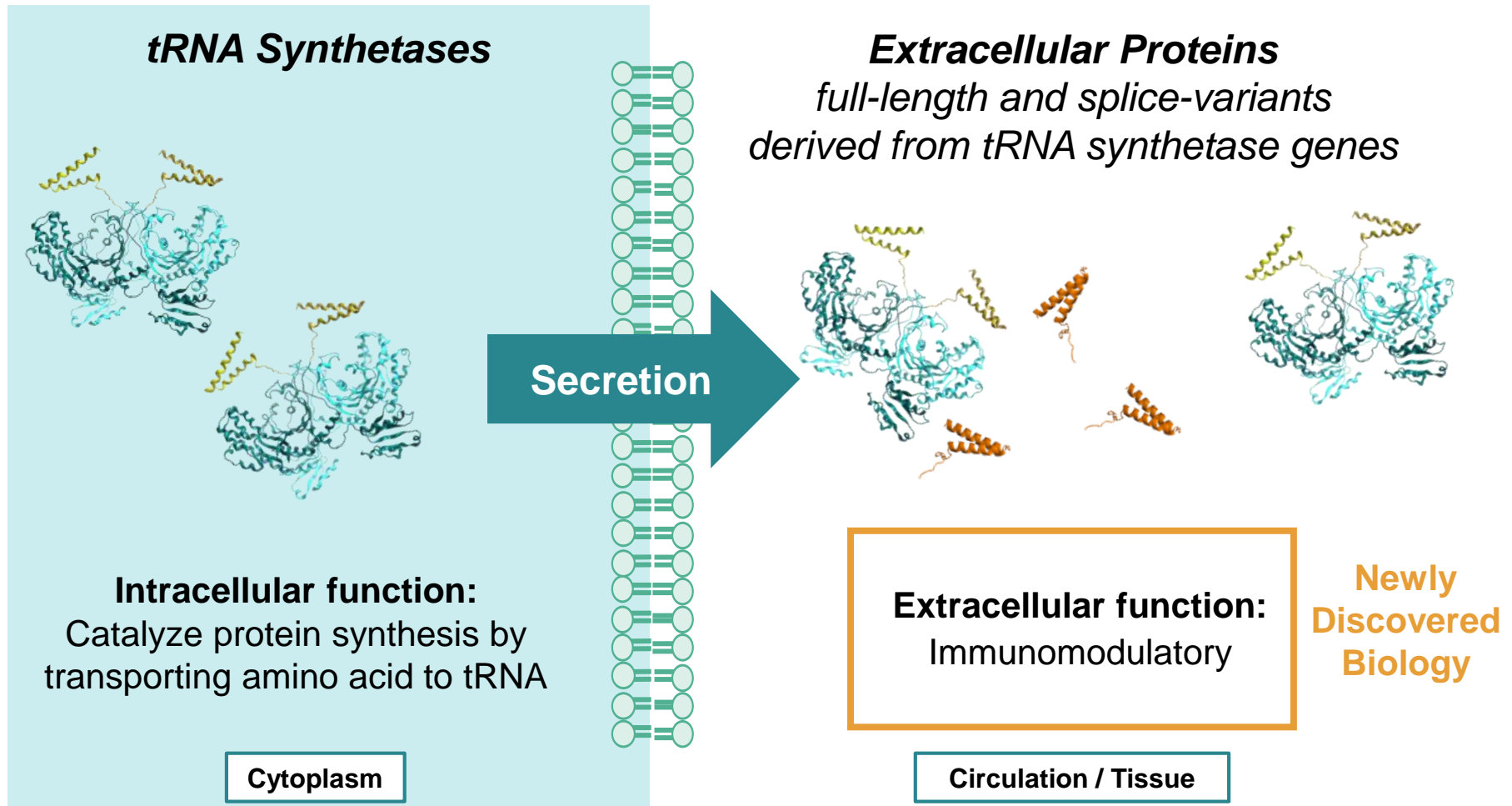
# aTyr Pharma

## Corporate Overview

# 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)*

# New Biology: Functionality of Extracellular tRNA Synthetase Proteins



# ATYR1923

*Extracellular HARS splice variant “iMod domain”  
fused to Fc domain of human antibody*

## **iMod Domain of HARS:**

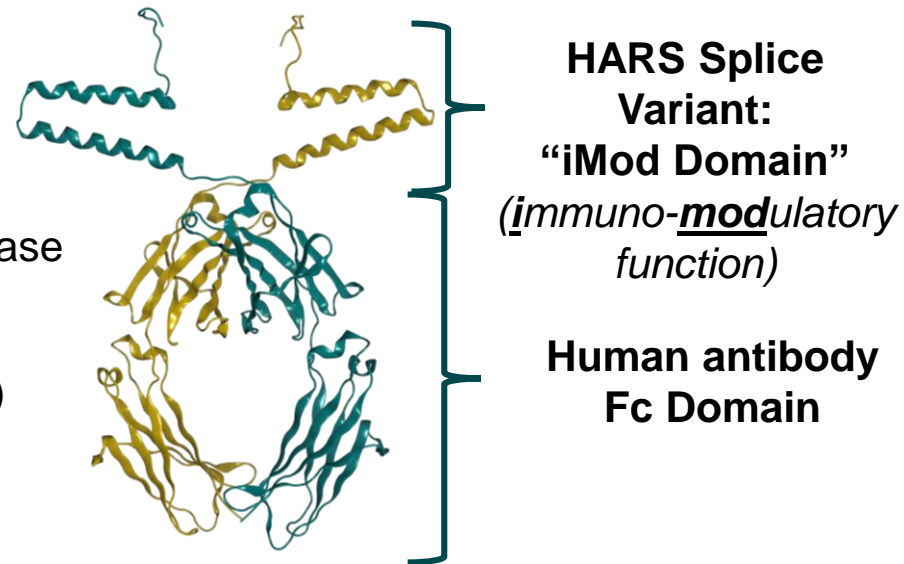
- Enriched in the human lung
- Inhibits human T cell activation/cytokine release

## **Receptor/Mechanism of Action:**

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

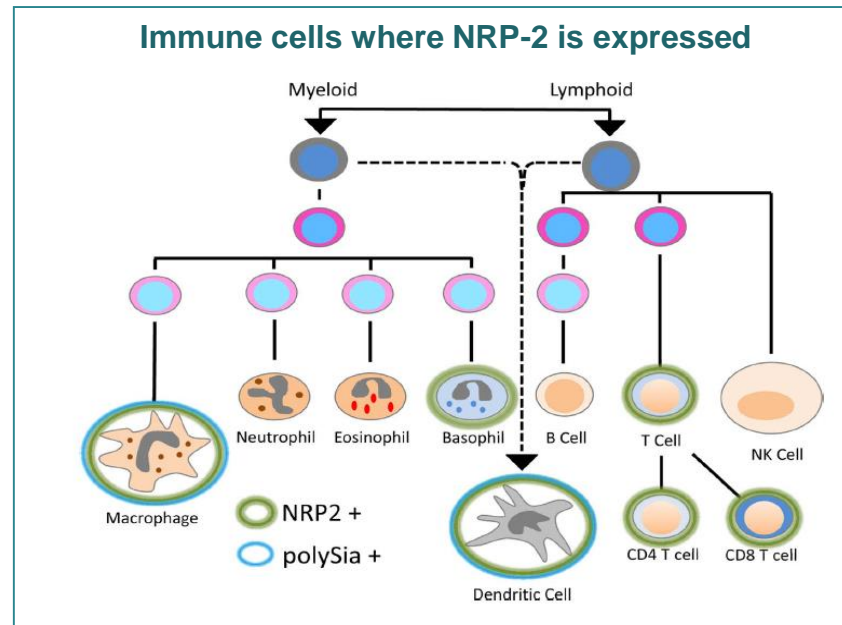
## **Fc Domain of Human Antibody:**

- 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**



# Pre-Clinical Translational Estate Supports Clinical Development in ILD

## **1923 Provides Therapeutic Activity in Bleomycin-induced Lung Fibrosis Model**

- Mouse model comparing pirfenidone\* vs. dexamethasone 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**

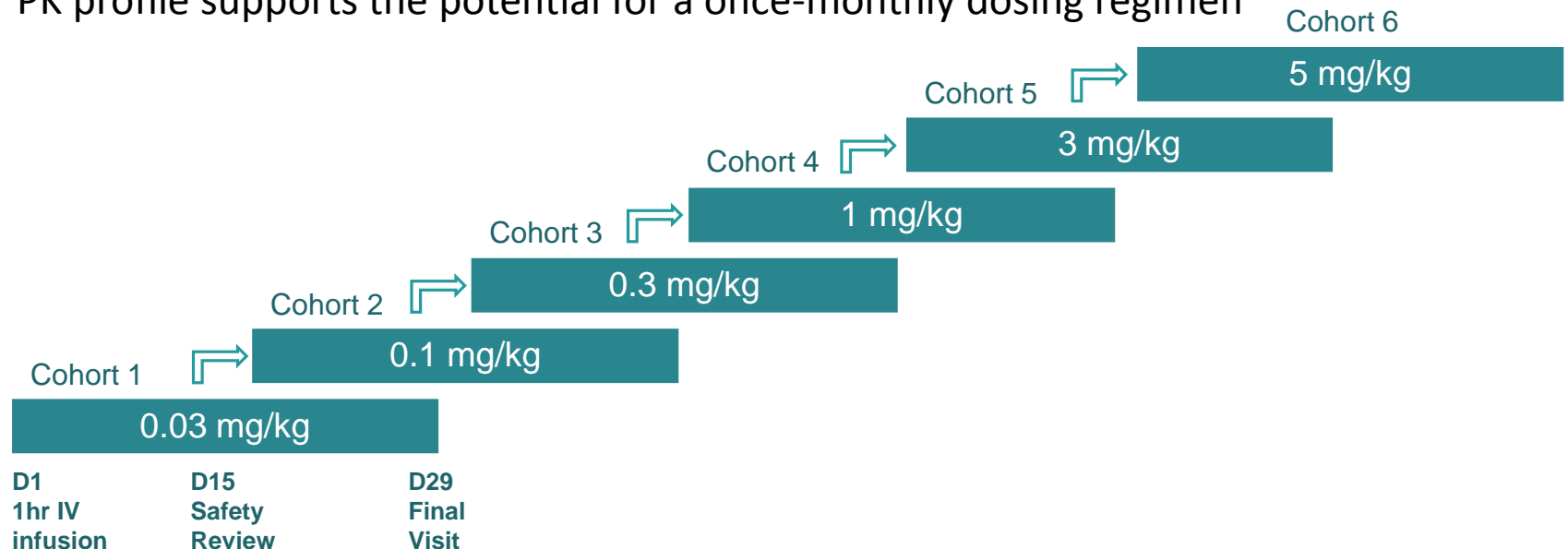
- Mouse model comparing nintedanib\*\* vs. ATYR1923
- 1923 has robust activity when treatment initiated early (day 7)
- Presented at Scleroderma Foundation Patient Conference, July 2018



# Phase I: Healthy Volunteer Study

## Positive Phase 1 Data Announced in June 2018

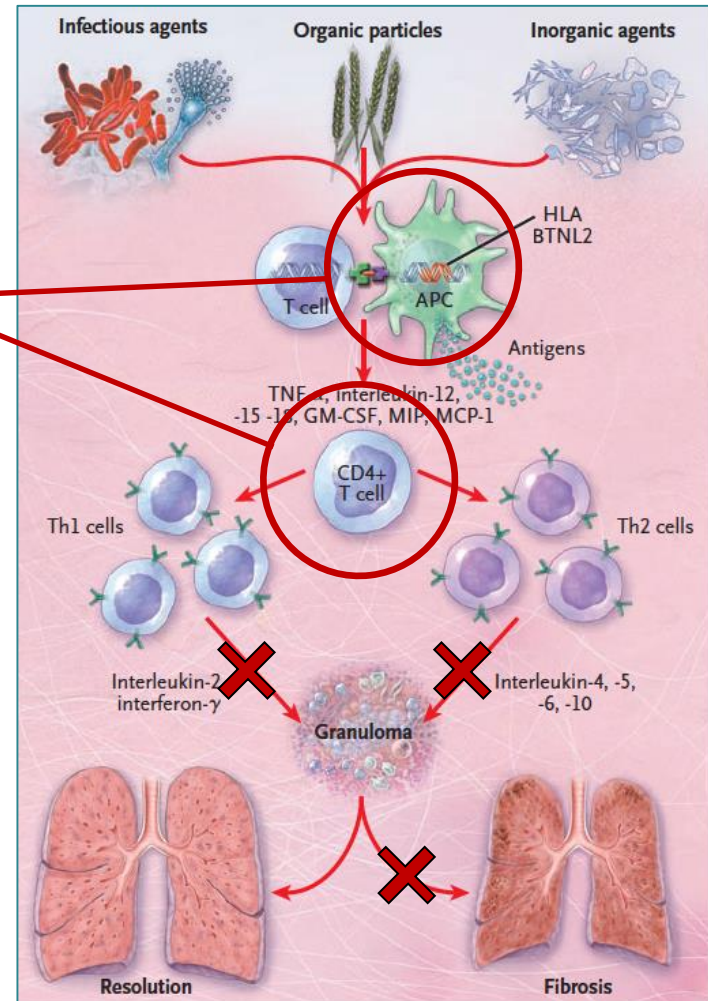
- Randomized, double-blind, placebo-controlled, single ascending dose (N=36 HVs)
- ATYR1923 was generally well-tolerated with no significant adverse events
- PK profile supports the potential for a once-monthly dosing regimen



# ATYR1923 Intervention in Pulmonary Sarcoidosis

## ATYR1923 Therapeutic Hypothesis:

Downregulate inflammatory insult and prevent progression to fibrosis



# Mission: Generate Value for Shareholders and Patients

- ✓ aTyr owns IP estate directed to a potential pipeline of proteins derived from 20 tRNA synthetase genes
- ✓ ATYR1923 *in-vitro* and *in-vivo* studies support clinical development in ILD
- ✓ Identification of NRP-2 receptor for ATYR1923 elucidates greater understanding of MOA
- ✓ 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

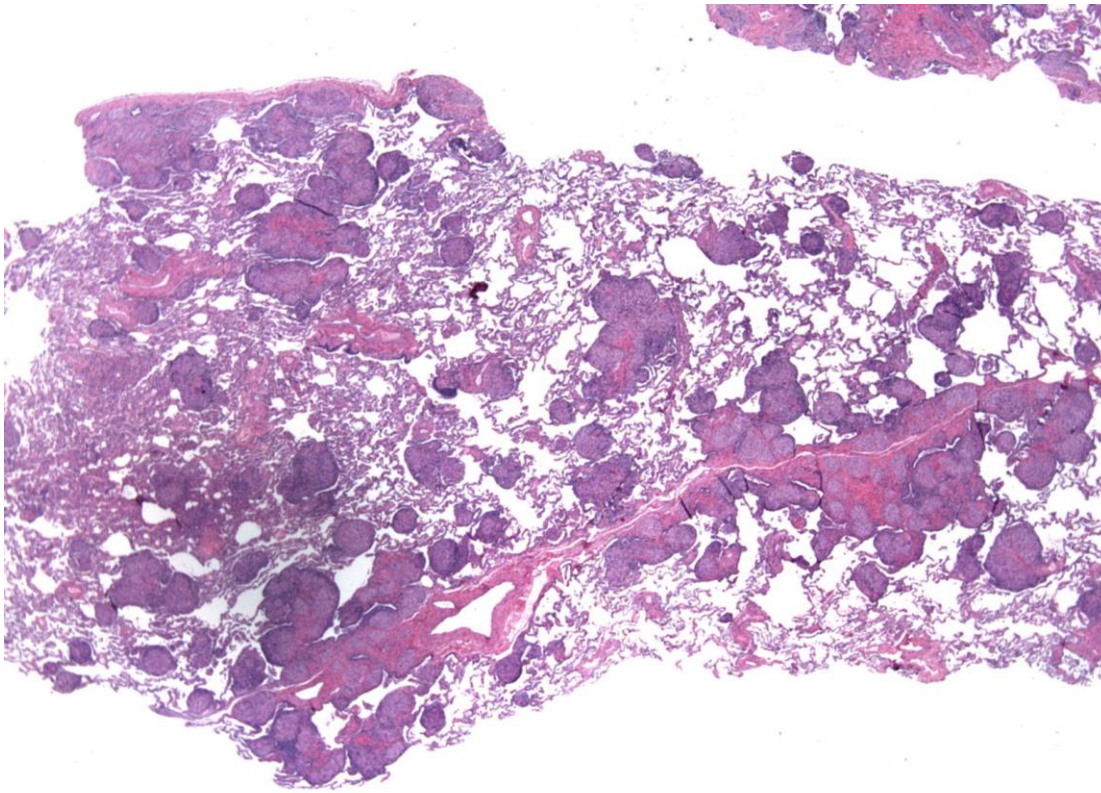
# Sarcoidosis

Daniel A. Culver, DO  
Cleveland Clinic



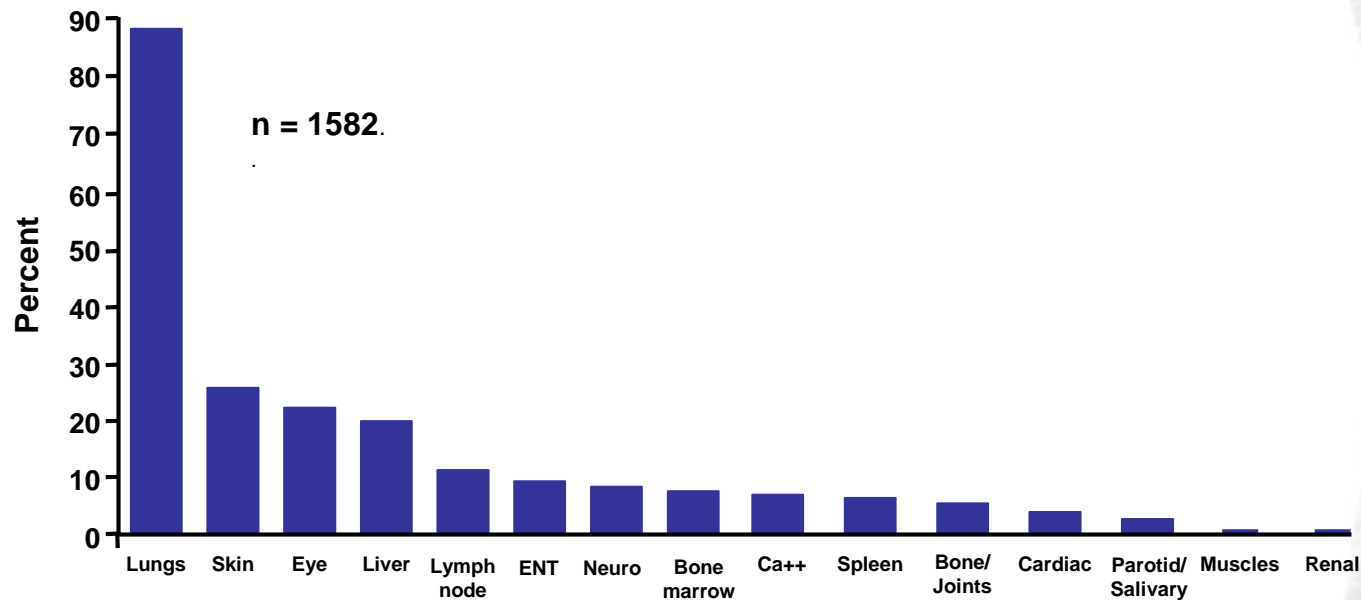
# Sarcoidosis is:

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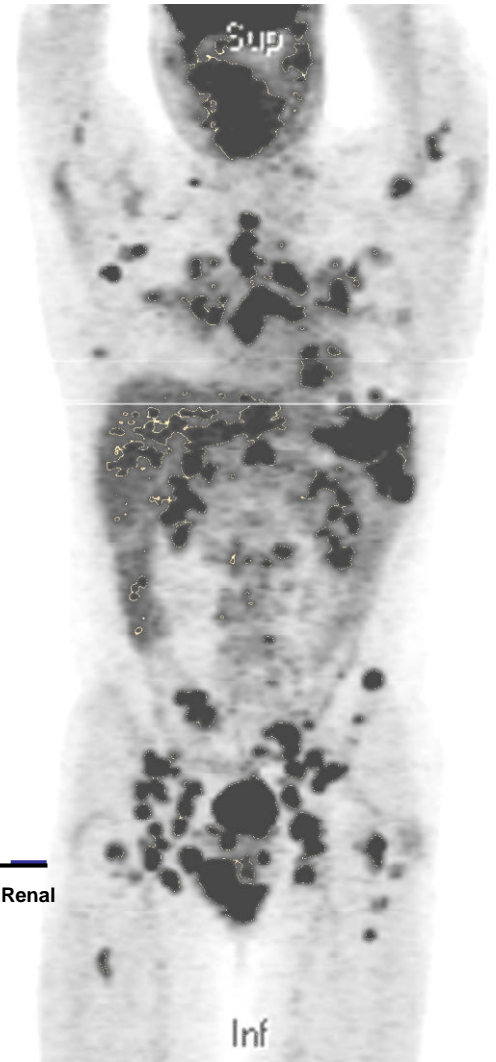


- Granulomatous
- Caused by an unknown trigger
- Multisystem

# Organ involvement in a US sarcoidosis clinic

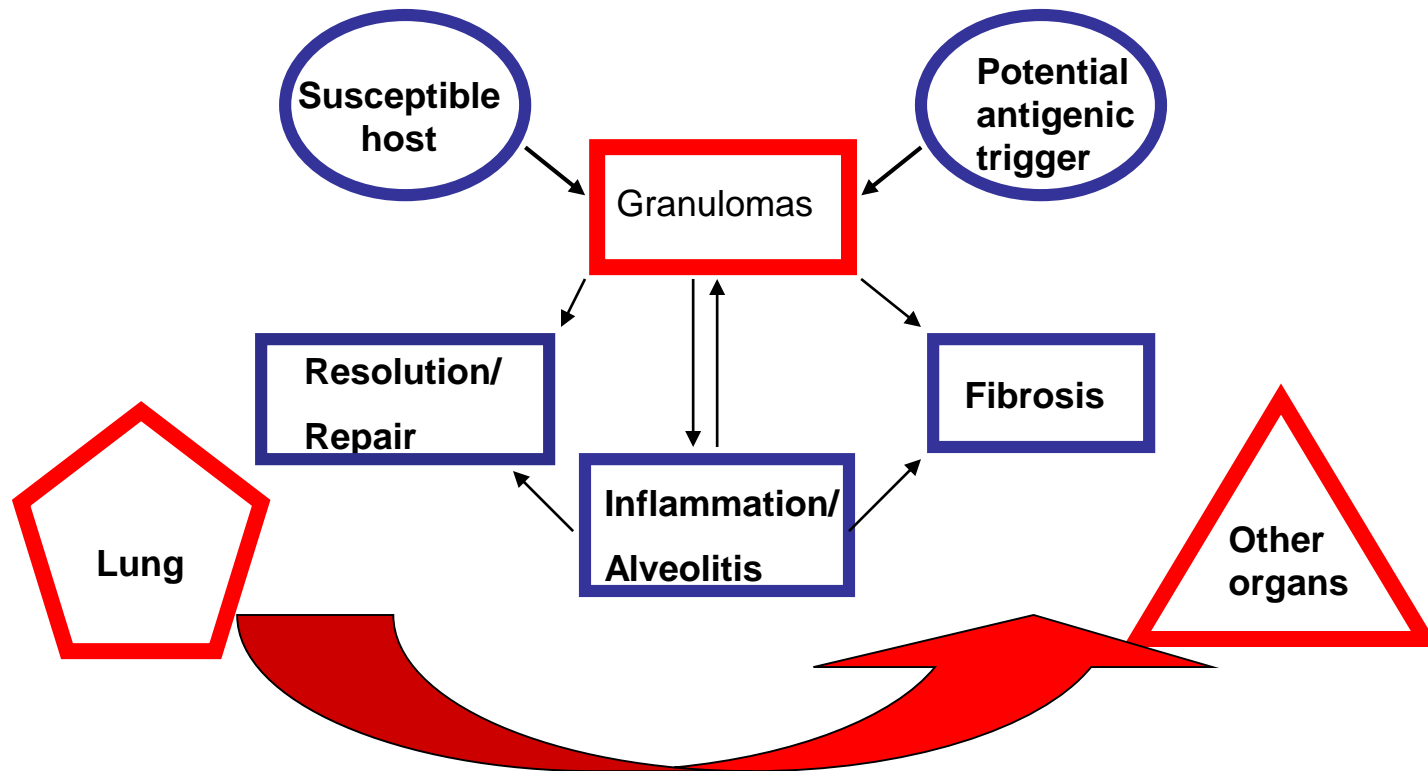


Judson MA. Sarcoidosis Vasc Diffuse Lung Dis 2012



# ***Pathogenesis and Natural History of Sarcoidosis: Current Paradigm and Key Issues***

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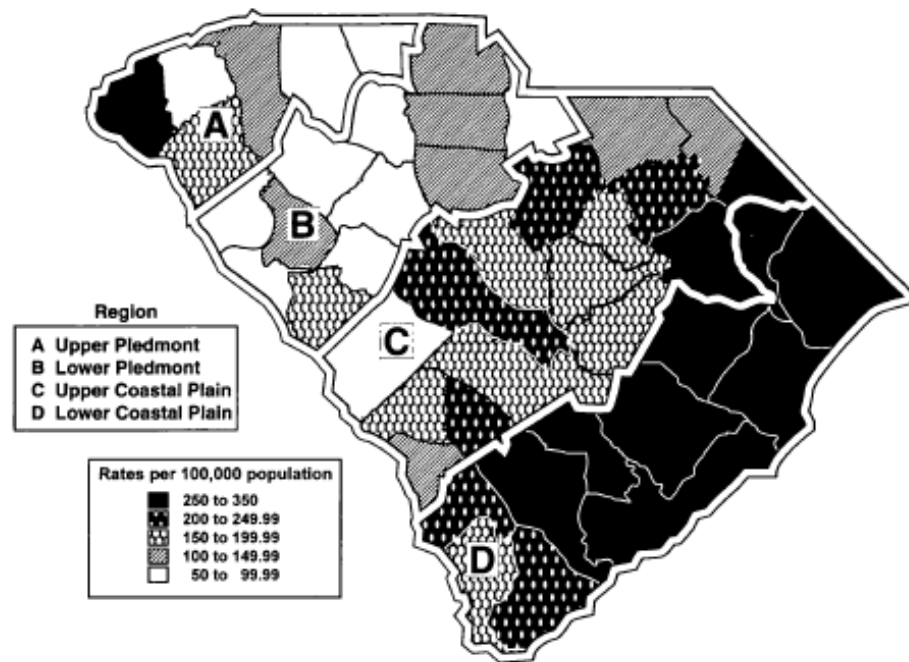
# Key clinical features of sarcoidosis syndrome

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- *Sine qua non* is the granuloma
- Multisystem by definition
- Cases are concentrated in space and time
- Spontaneous remission is common
- Persistent disease does not always progress
- Racial and ethnic heterogeneity



# Geographic variance: hospitalization for sarcoidosis



Kajdasz DK. Am J Epidemiol 1999

# Association with rural exposures

Exposure	Exposure profile	% cases (n = 44) <sup>a</sup>	% controls (n = 88) <sup>a</sup>	Unadjusted OR with 95% CI	Adjusted OR <sup>b</sup> with 95% CI
Use of a coal stove	Yes	22.7	4.5		
	No	77.3	95.5	6.2 [1.7, 22.7]	3.3 [0.9, 12.8]
Use of a wood stove	Yes	63.6	27.3		
	No	34.1	72.7	4.1 [1.9, 9.0]	3.7 [1.5, 8.8]
Use of a fireplace	Yes	54.5	26.1		
	No	43.2	73.9	5.5 [2.0, 14.9]	6.8 [2.1, 21.8]
Use of or exposure to insecticides and/or herbicides other than for home extermination	Yes	31.8	17.0		
	No	68.2	83.0	2.1 [0.9, 4.7]	2.0 [0.8, 5.1]
Use of well or spring water	Yes	50.0	29.5		
	No	47.7	70.5	2.2 [1.1, 4.7]	2.4 [1.0, 5.6]
Living or working on a farm	Yes	27.3	10.2		
	No	70.5	89.8	3.4 [1.2, 9.1]	3.1 [1.1, 8.9]

Kajdasz DK. Ann Epidemiol 2001

# Photocopier use and risk of sarcoidosis

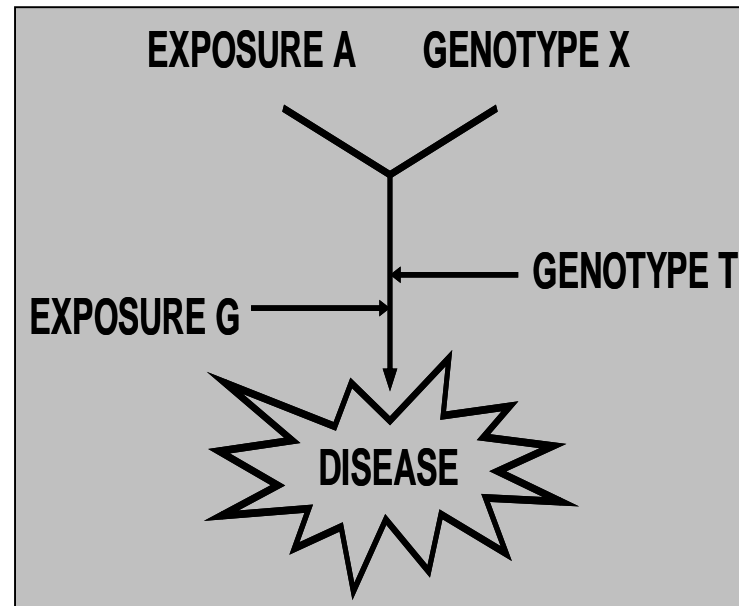
PHOTOCOPIER USE	TERTILE	ODDS RATIO <sup>1</sup>	P VALUE
		(95% CONFIDENCE INTERVAL)	
Duration of use (years)	0	1	Reference
	1 – 7	1.37 (0.82, 2.31)	0.234
	> 7	2.01 (1.18, 3.42)	0.010
	Overall trend	–	0.012
Frequency of use (times per Week)	0	1	Reference
	1 – 3	1.10 (0.63 – 1.91)	0.746
	> 3	2.19 (1.31 – 3.65)	0.003
	Overall trend	–	0.003
Duration of use (min per episode)	0	1	Reference
	1 – 2	1.26 (0.72 – 2.20)	0.415
	> 2	1.83 (1.11, 3.02)	0.018
	Overall trend	–	0.018
Total lifetime exposure (hours)	0	1	Reference
	1 – 60	1.07 (0.61, 1.88)	0.824
	> 60	1.98 (1.18, 3.35)	0.010
	Overall trend	–	0.012

<sup>1</sup>adjusted for age, sex, method of data collection and history of clerical work

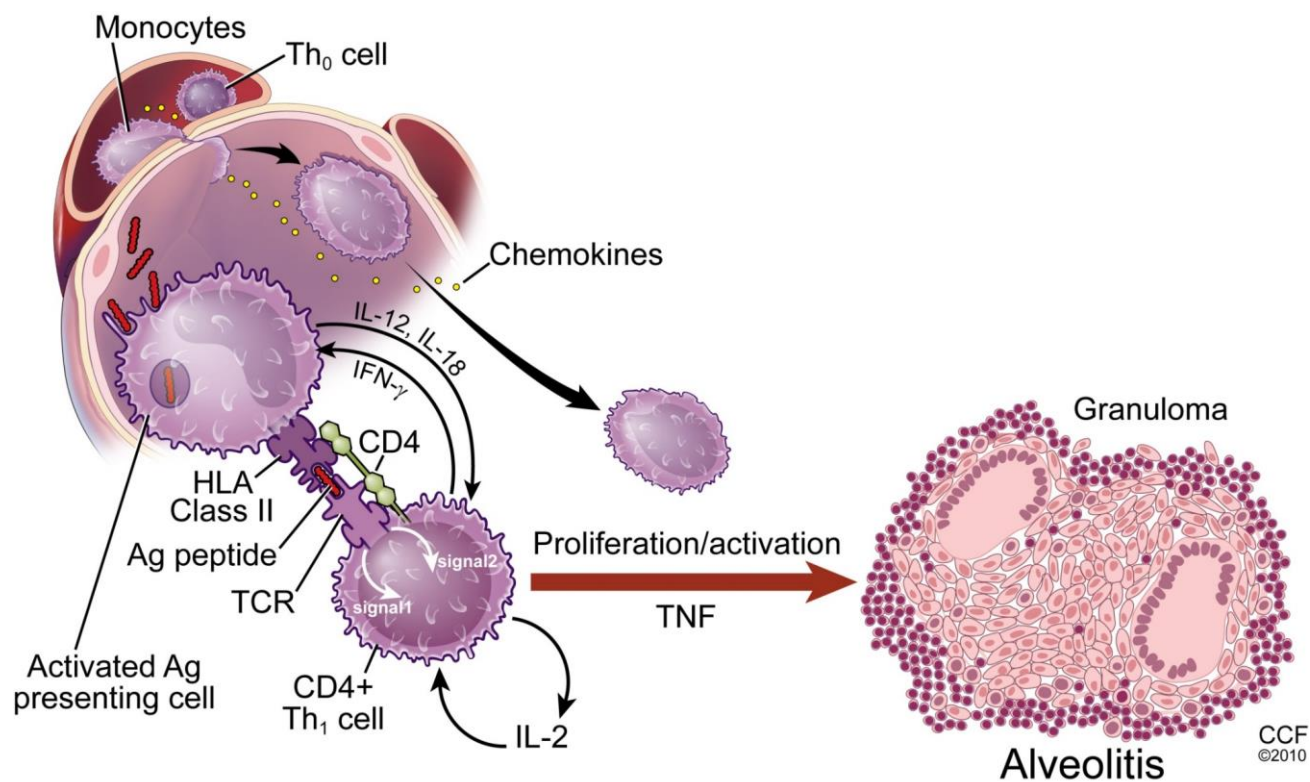
Rybicki BA. Sarcoidosis Vasc Diffuse Lung Dis 2004

# Etiologic and modifier exposures and genes

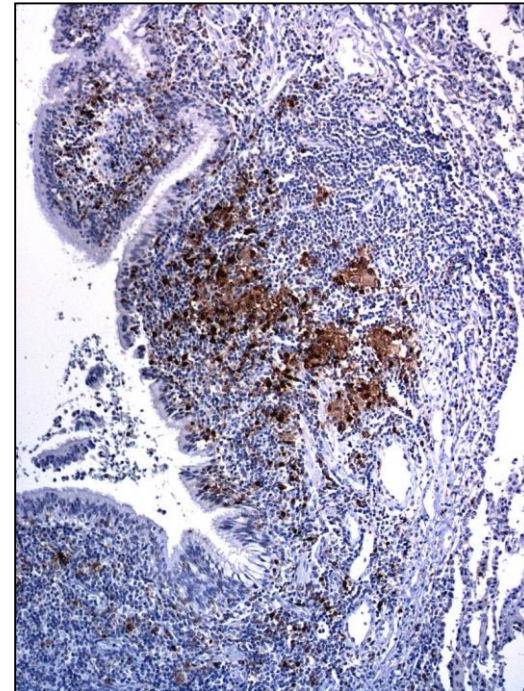
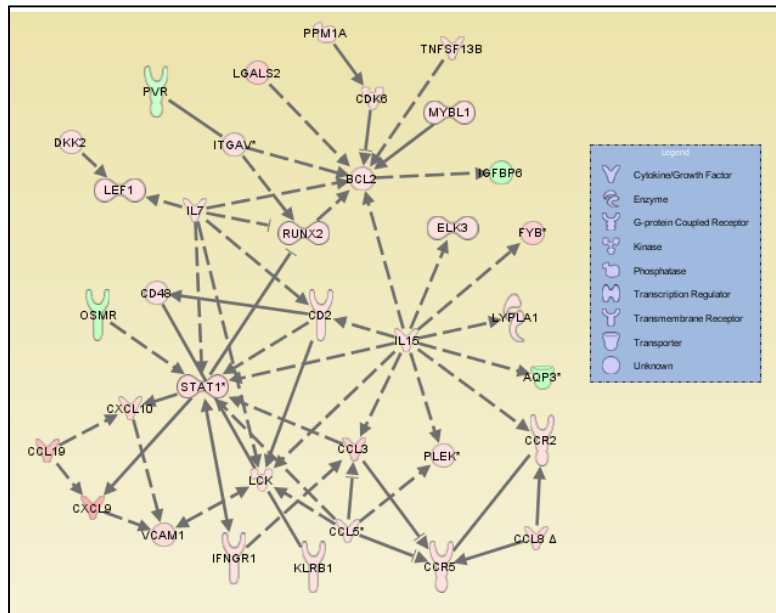
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# Pathobiology 101

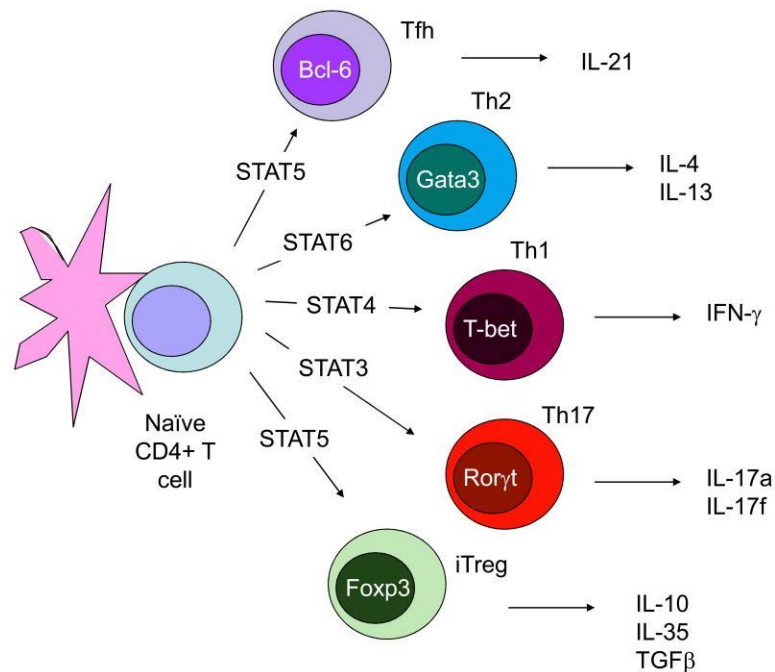


# STAT1 plays a central role in sarcoidosis



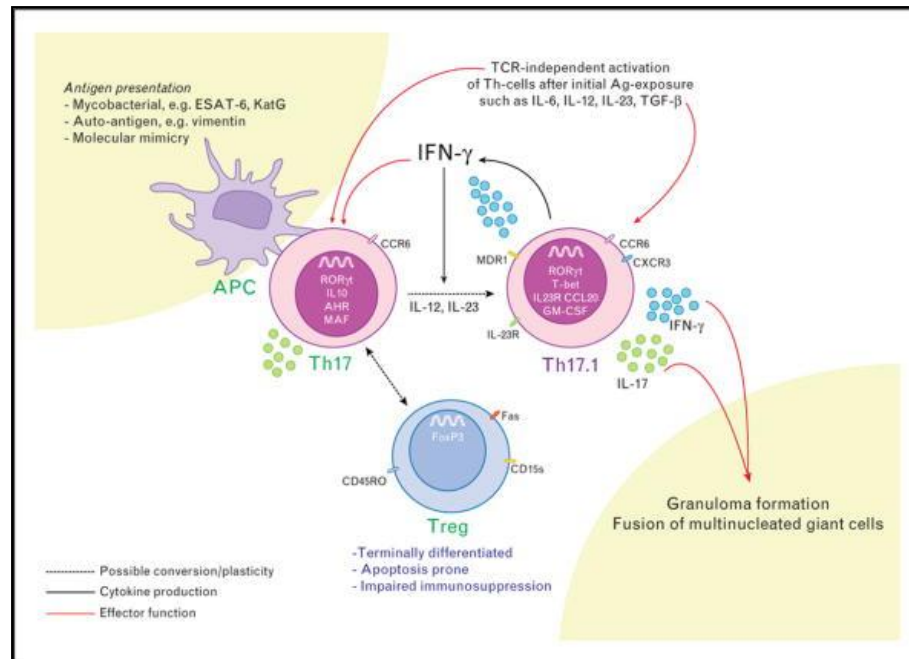
Crouser ED, Culver DA. Am J Respir Crit Care Med 2009

# Are there more than Th1 cells involved in sarcoidosis?



O'Shea JJ. Science 2010

# Th17.1 cells are the primary source of interferon gamma

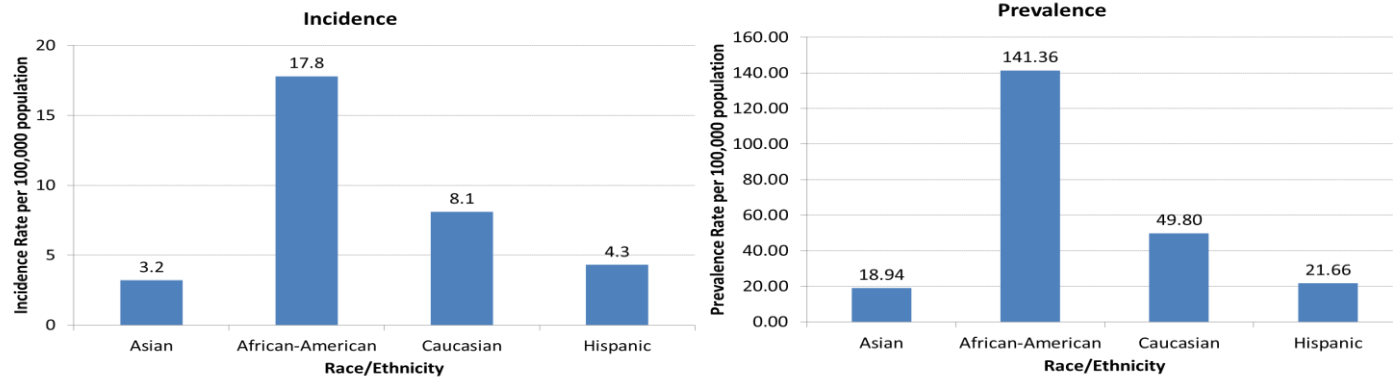


Broos CE. Curr Opin Pulm Med 2016



# Sarcoidosis in the US

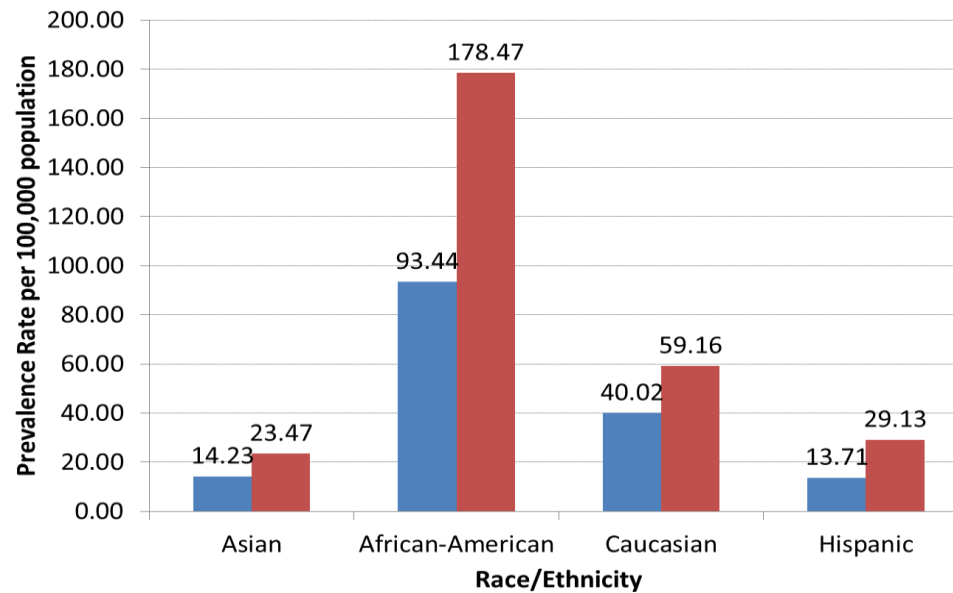
2010-2013 Optum Database



Baughman RP. Ann Am Thorac Soc 2016

# Female predilection

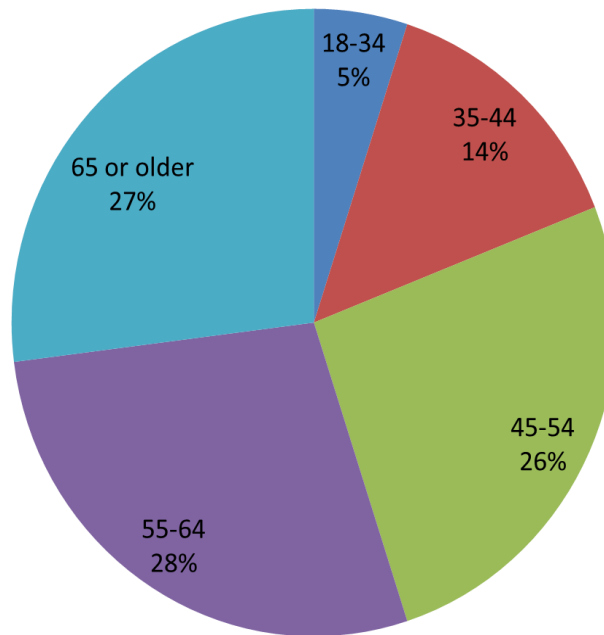
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Baughman RP. Ann Am Thorac Soc 2016

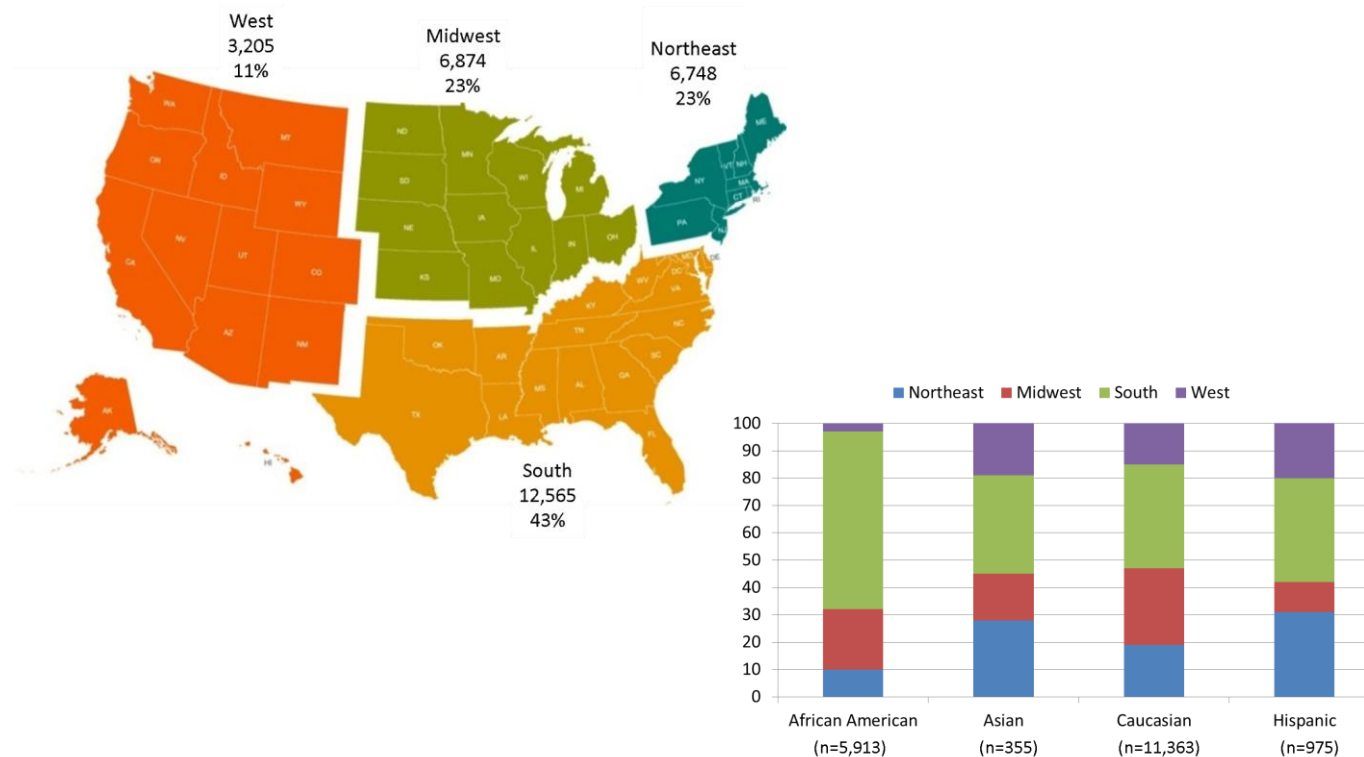
# Most patients are >55 at the time of diagnosis now

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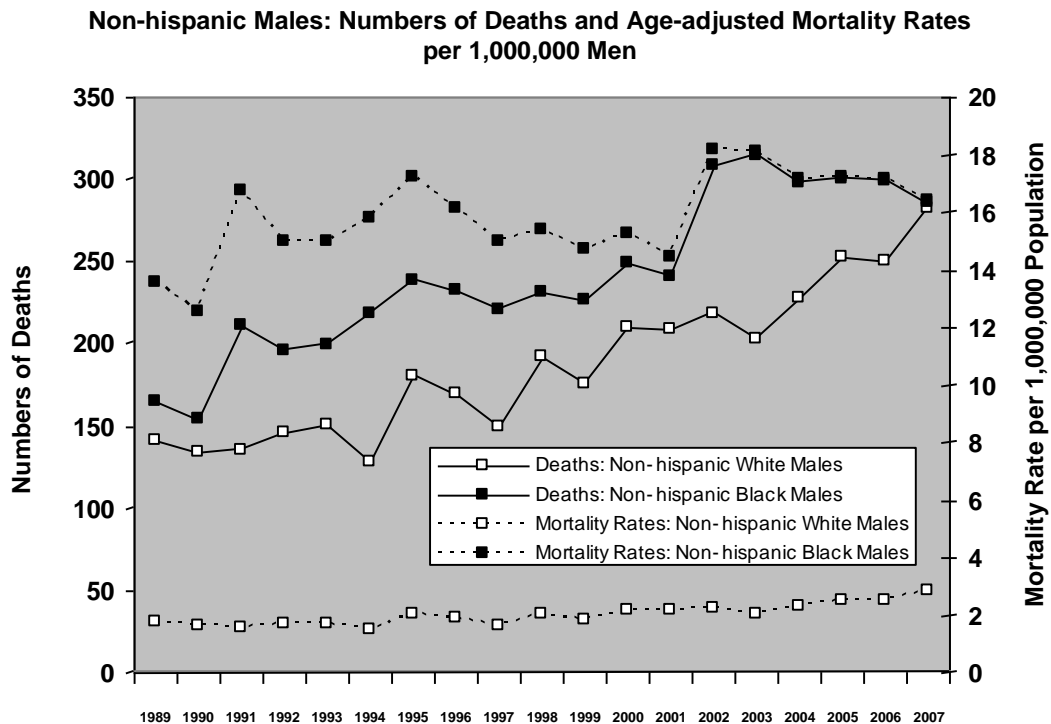
Baughman RP. Ann Am Thorac Soc 2016

# Sarcoidosis less common in the West



Baughman RP. Ann Am Thorac Soc 2016

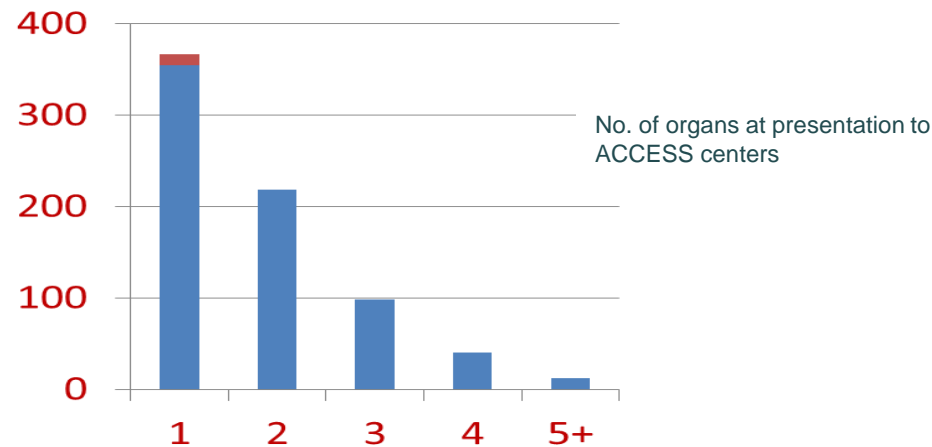
# Rising sarcoidosis mortality in the US



Swigris JJ. AJRCCM 2011

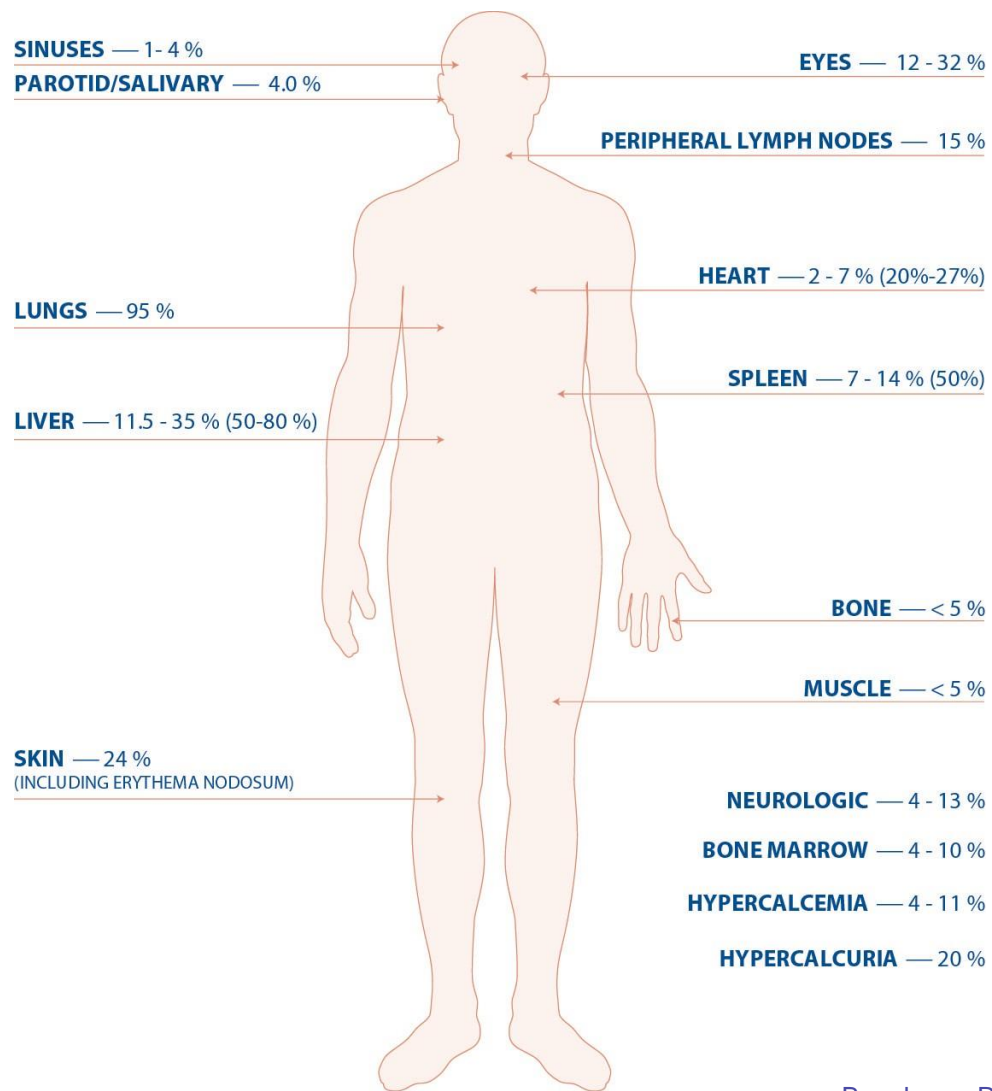
# Sarcoidosis is a systemic disease

- About half of US sarcoidosis involves more than one organ



- 23% of involved organs were not evident at the time of diagnosis

Baughman RP. AJRCCM 2001



Baughman RP. AJRCCM 2001

# Prognosis versus clinical features

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<b>Characteristics Associated with Worse Prognosis</b>
<b>Age &gt; 40 at onset</b>
<b>African American</b>
<b>Requirement for steroids</b>
<b>Extrapulmonary involvement</b> Cardiac Neurologic (except isolated CN palsy) Lupus pernio Splenomegaly Hypercalcemia Osseous disease
<b>Pulmonary Involvement</b> Stage 3-4 chest radiograph Pulmonary hypertension Significant lung function impairment Moderate to severe dyspnea on presentation BAL neutrophilia at presentation



# Prognostic markers

- Increasing number of organs versus outcome†

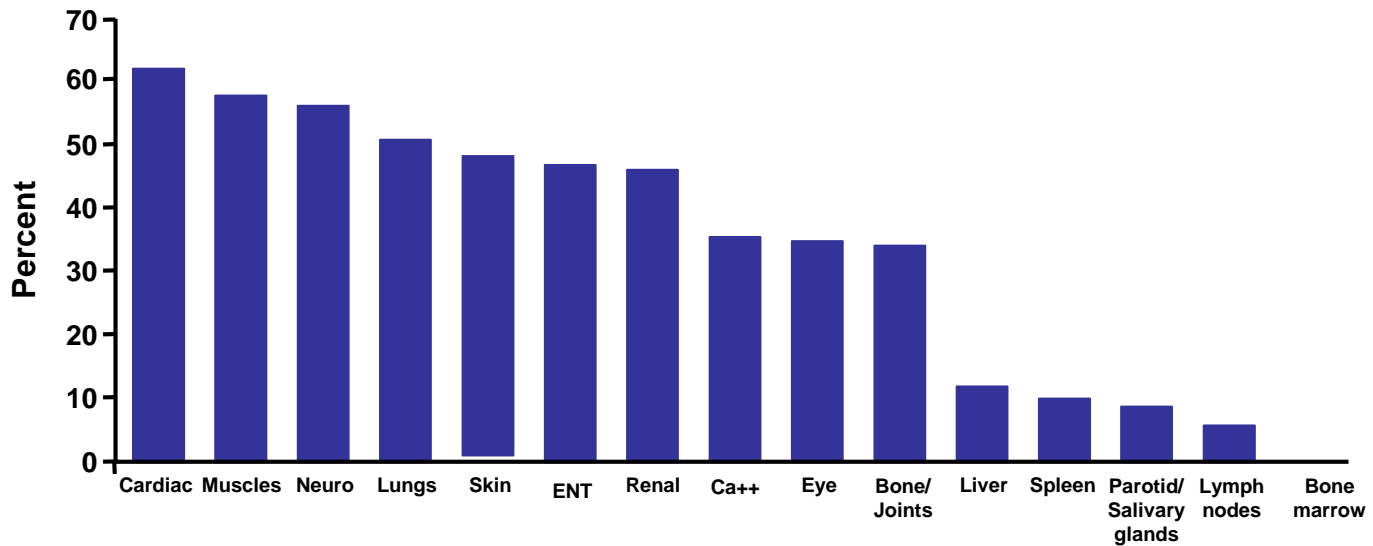
Outcome at 2-5 yrs	1 organ (n=44)	2-3 organs (n=198)	4+ organs (n=53)
No important issue	64%	46%	13%
Significant organ function impairment	30%	43%	64%
Required assistance	7%	6%	23%

- Presence of neurosarcoidosis increases risk of concomitant ophthalmologic and cardiac sarcoidosis

Neville E. QJM 1983; Lower EE. Arch Intern Med 1997; Sones M. Am J Med 1960; Israel HL. Ann NY Acad Sci 1986; Takada K. J Clin Epidemiol 1993†

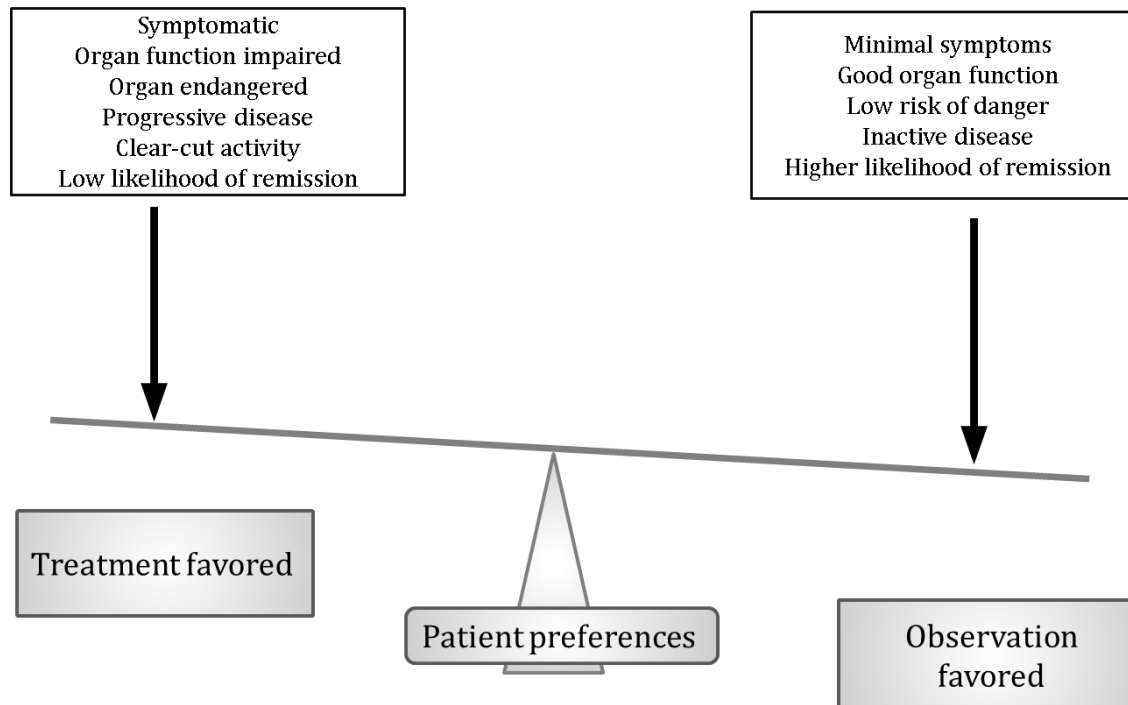
# Frequency of treatment requirement

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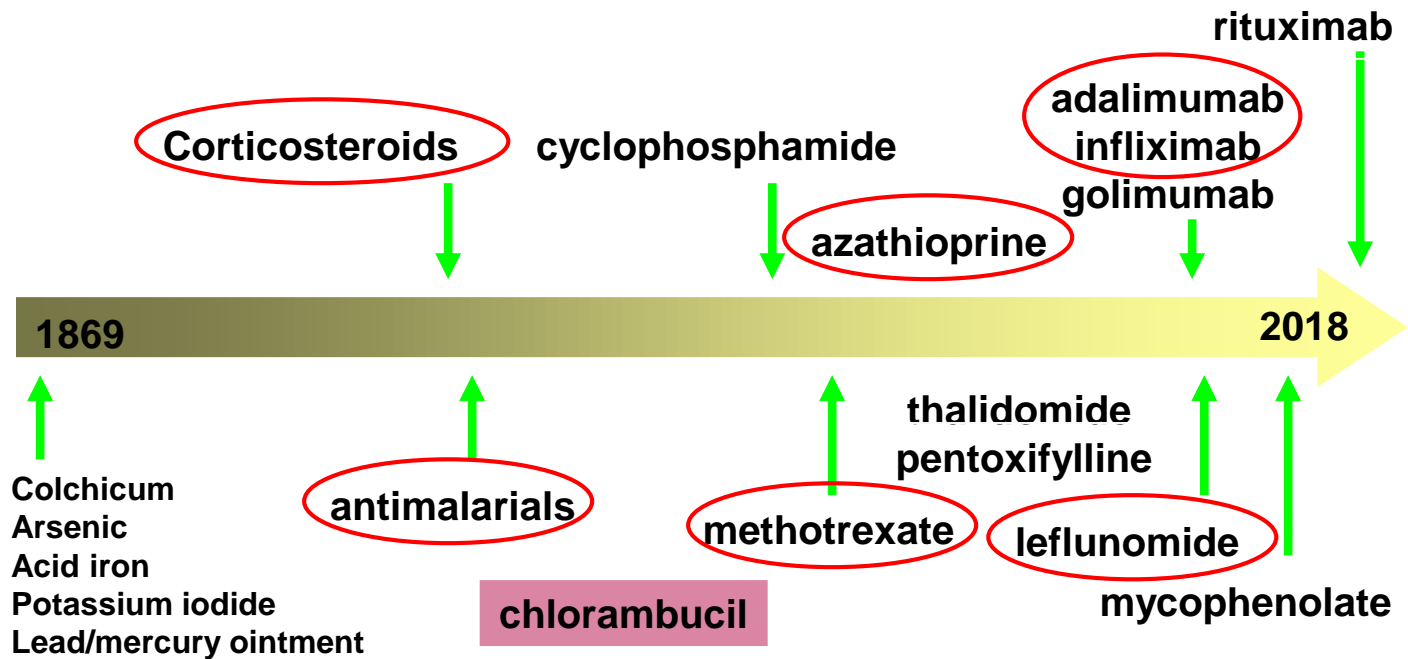
Judson MA. Sarcoidosis Vasc Diffuse Lung Dis 2012

# The decision to treat

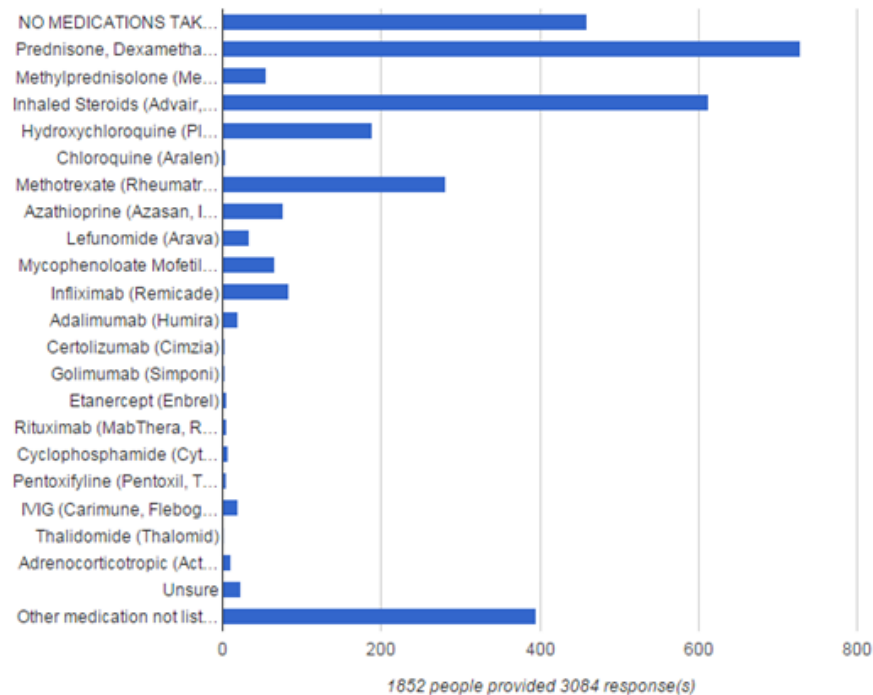


Wijsenbeek MS. Clin Chest Med 2015

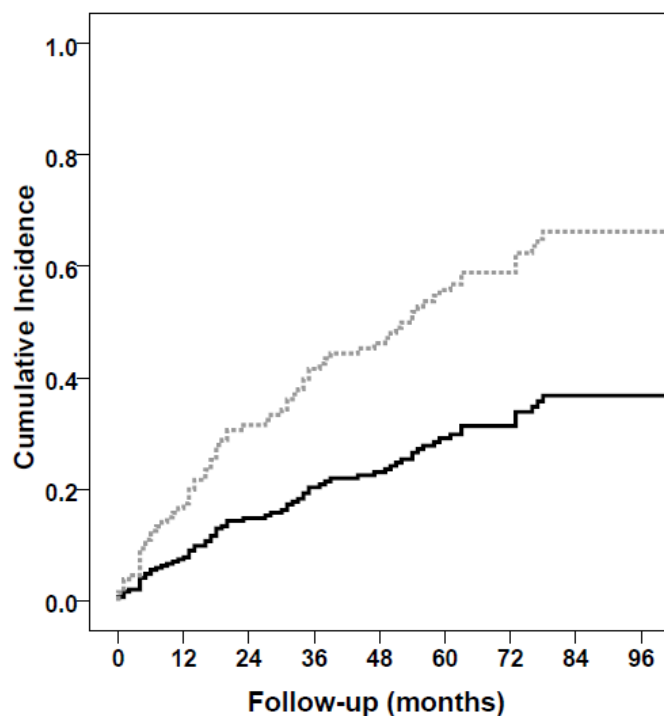
# Main immunosuppressive options



# Medications in FSR registry population



# Cumulative risk of steroid complications



Hazard ratio: 2.37 (1.34-4.17)

## Other covariates

Age/yr 1.021 (1.001-1.041)

Pre-existing disease 2.27 (1.33-3.89)

Duration of steroids (mos)  
1.023 (1.013-1.033)

Cumulative dose (grams)  
1.038 (1.019-1.056)

# Quality of life and use of steroids are opposite

**Table 3—Differences in Predicted HRQL Scores Between Patient Groups Based on Oral Corticosteroid Treatment\***

Group	Unadjusted Score	p Value	Adjusted Score†	p Value	Adjusted Score‡	p Value
SGRQ total						
Steroid users (n = 56)	52 (45–58)	<0.0001	49 (43–56)§	0.031	48 (44–53)	0.011
No steroids (n = 55)	37 (31–43)		39 (33–44)		39 (35–44)	
SF36-PCS						
Steroid users (n = 56)	31 (28–34)	0.011	32 (29–35)¶	0.048	32 (29–35)#	0.044
No steroids (n = 55)	37 (34–40)		37 (34–40)		37 (34–40)	
SF36-MCS						
Steroid users (n = 56)	42 (39–46)	0.055				
No steroids (n = 55)	47 (44–50)					

Cox CE. Chest 2004

# Unmet needs

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- Better understanding of the pathogenesis
  - Extant models just coming online will be helpful
- Prognostic stratification and targeted management
  - GRADS study, Gen-Phen study, and others will provide new insights
- Better therapies, with quicker onset of action and less toxicity





# ATYR1923

Proposed Phase 1b/2a Study for  
Patients with Pulmonary Sarcoidosis

# ATYR1923 Proposed Phase 1b/2a Study in Pulmonary Sarcoidosis\*

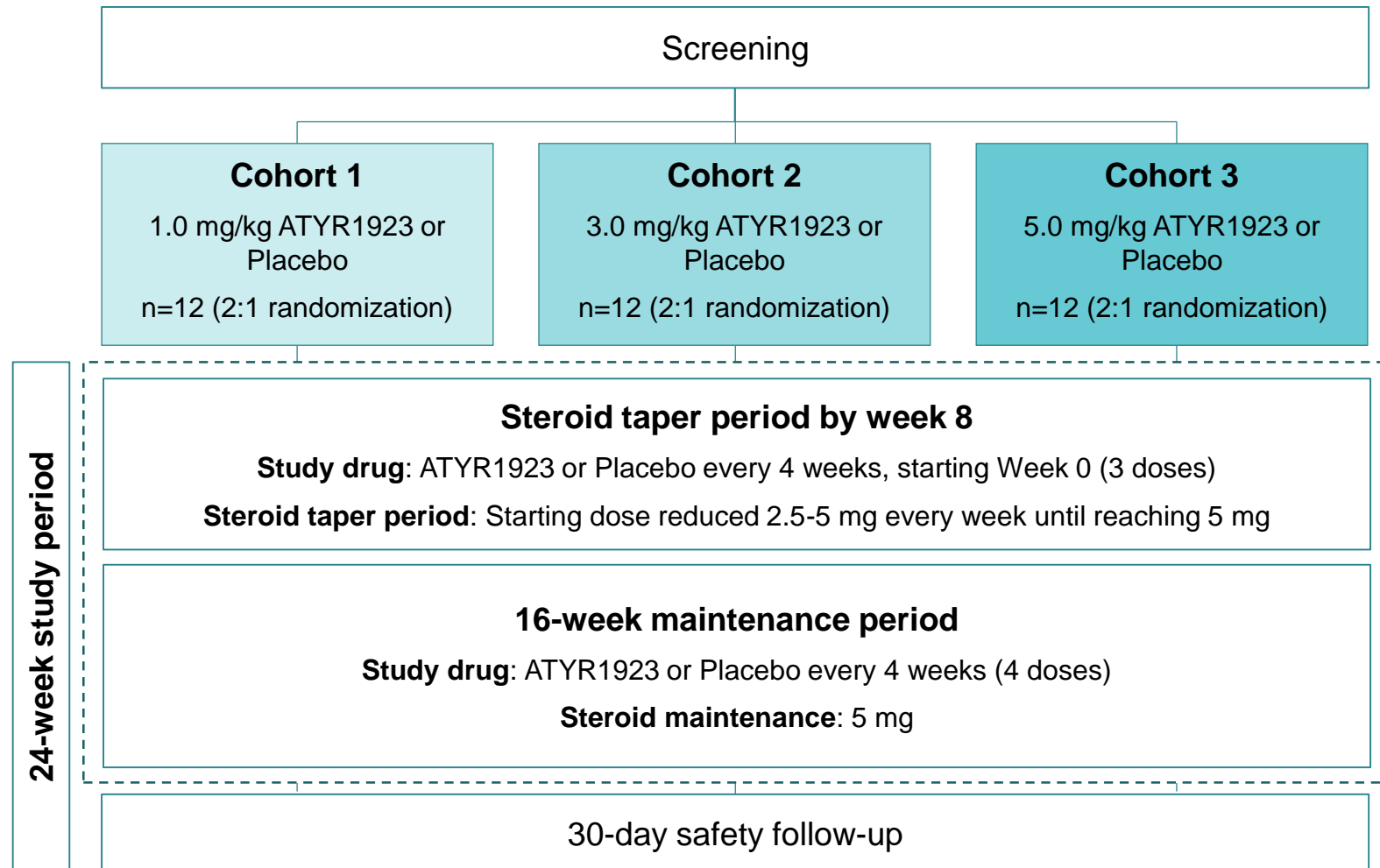
<b>Study Objectives</b>	<ul style="list-style-type: none"><li>• Evaluate safety, tolerability, PK, and immunogenicity of multiple ascending doses of ATYR1923</li><li>• Evaluate signals of drug activity through steroid dose reduction and FDG-PET/CT changes</li></ul>
<b>Design</b>	<ul style="list-style-type: none"><li>• Randomized, double-blind, placebo-controlled, multiple ascending dose</li></ul>
<b>Patient Population</b>	<ul style="list-style-type: none"><li>• Histologically confirmed pulmonary sarcoidosis</li><li>• Requiring <math>\geq 10</math> mg prednisone (steroid) treatment; capable of steroid taper</li><li>• Symptomatic/active disease at baseline by <math>^{18}\text{F}</math>-FDG-PET/CT, Pulmonary Function Tests</li></ul>
<b>Study Drug Dosing/Cohorts</b>	<ul style="list-style-type: none"><li>• 3 sequential cohorts, 12 subjects each</li><li>• 2:1 randomization</li><li>• Possible ATYR1923 doses: 1.0, 3.0, and 5.0 mg/kg</li></ul>
<b>Treatment Duration</b>	<p>24-week Treatment Period</p> <ul style="list-style-type: none"><li>• Steroid taper phase down to 5 mg by week 8</li><li>• 16-week maintenance phase</li></ul>
<b>Sites</b>	<ul style="list-style-type: none"><li>• 8-10 leading pulmonary sarcoidosis centers in US</li></ul>

# ATYR1923 Proposed Phase 1b/2a Study in Pulmonary Sarcoidosis\*

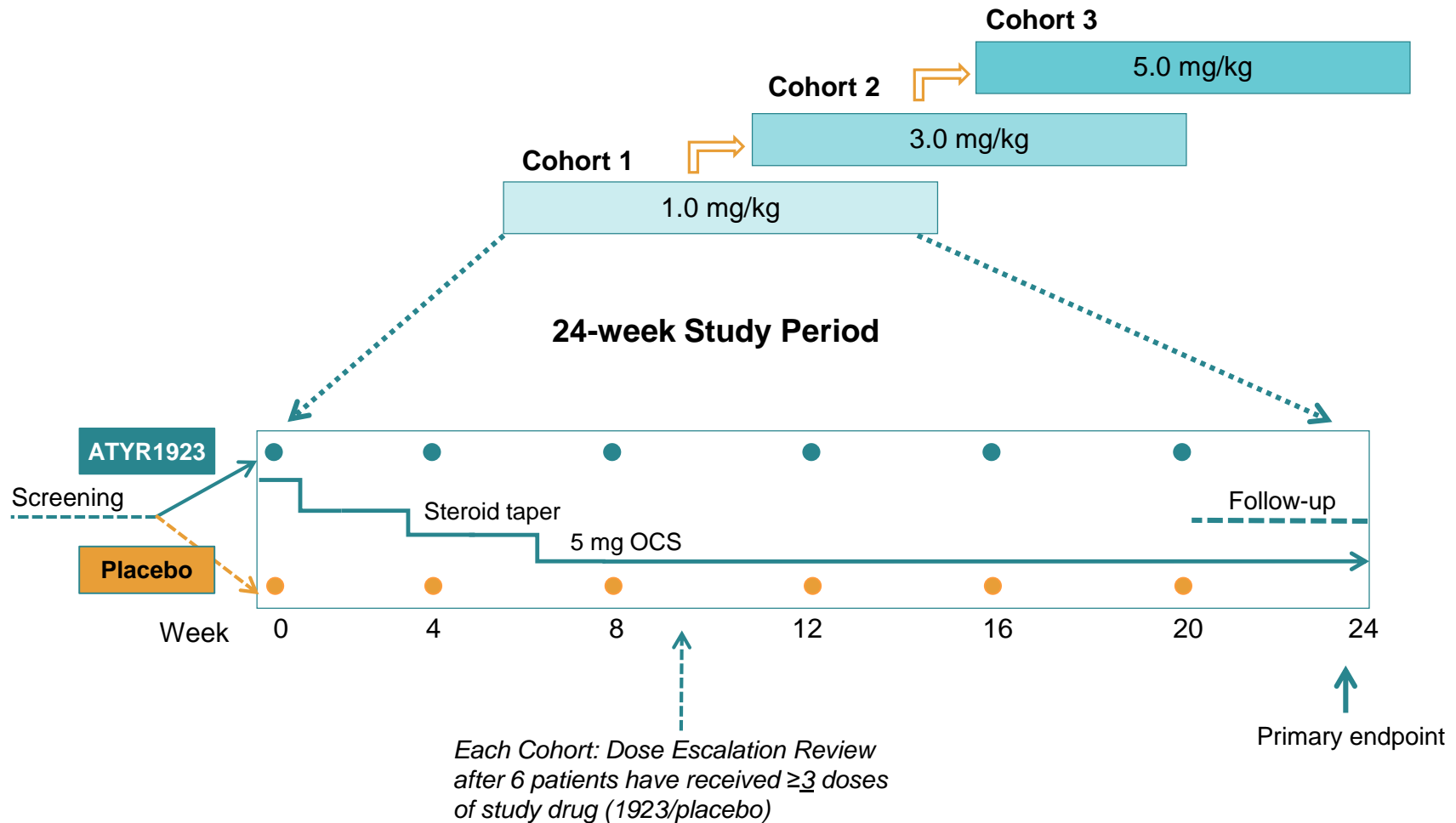
## Endpoints

- To evaluate the safety and tolerability of multiple ascending intravenous doses
- To assess the potential steroid-sparing effect
- To assess the potential immunogenicity
- To characterize the pharmacokinetics (PK)
- To explore the preliminary efficacy by evaluating changes over time in:
  - Disease activity (pulmonary parenchymal inflammation), assessed by  $^{18}\text{F}$ -fluorodeoxyglucose positron-emission tomography combined with computed tomography ( $^{18}\text{F}$ -FDG-PET/CT)
  - Lung function, assessed by percent predicted forced vital capacity (FVC)
  - Serum biomarkers, including angiotensin converting enzyme (ACE), neopterin and soluble IL-2 receptor (sIL-2R)
  - Health-related quality of life scales, including the Sarcoidosis Assessment Tool (SAT), St. George's Respiratory Questionnaire (SGRQ), Leicester Cough Scale, Fatigue Assessment Scale (FAS), and the self-administered computerized Baseline/Transitional Dyspnea Indices (SAC BDI-TDI)

# ATYR1923 Proposed Phase 1b/2a Study in Pulmonary Sarcoidosis\*



# Proposed ATYR1923 Phase 1b/2a Study Schema\*



\* Subject to regulatory review

# 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

## Phase 1b/2a Milestones:

- ☐ Initiate Clinical Trial – 4Q 2018\*
- ☐ Interim Results – 4Q 2019\*\*
  - ☐ Final Results – TBD



**Thank You**