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Immunomodulatory protein ATYR1923 disrupts an *in vitro* model of sarcoid granuloma formation

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Tuesday, September 7, 2021

Conflict of Interest Disclosure



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Acknowledgements



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1. To educate the audience on ATYR1923, aTyr's lead product candidate, that is currently in clinical development as a potential therapeutic to treat pulmonary sarcoidosis and other interstitial lung disease (ILD)
2. To demonstrate that Neuropilin-2 (NRP2), the selective binding partner to ATYR1923, is highly upregulated under inflammatory conditions and is highly expressed in granulomas found within the lungs of sarcoidosis patients
3. To demonstrate that ATYR1923 exerts its immunomodulatory functions through both antigen presenting cells (APCs) and CD4+ T cells and that both cells types express NRP2 in the lung tissue of sarcoidosis patients

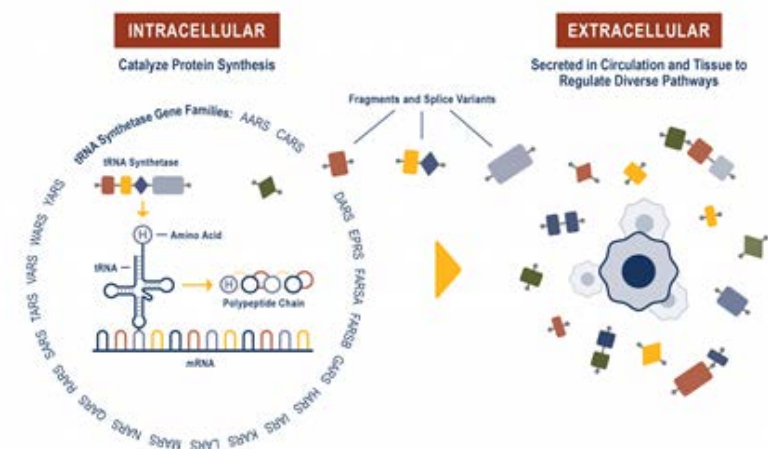
ATYR1923 Background Information



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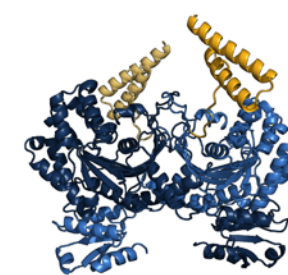
- ATYR1923 is a clinical stage immunomodulatory protein
- ATYR1923 comprises the N-terminal immunomodulatory domain of Histidyl-tRNA synthetase (HARS) fused to Human IgG1 Fc
- ATYR1923 selectively binds to NRP2 (Ref #1) and exerts some of its immunomodulatory functions by affecting T cell activation & cytokine release (Ref#2)
- ATYR1923 was shown to play a role in LPS induced ARDS and RA-ILD inflammatory models (Ref#3, 4)
- The primary effects of ATYR1923 are on APCs and T cells, which are implicated in the immunopathology of sarcoidosis, and are known key contributors of granuloma formation

A) Novel Functions of tRNA Synthetases

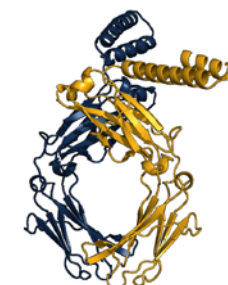


ATYR1923 Structure

B)



HARS



ATYR1923

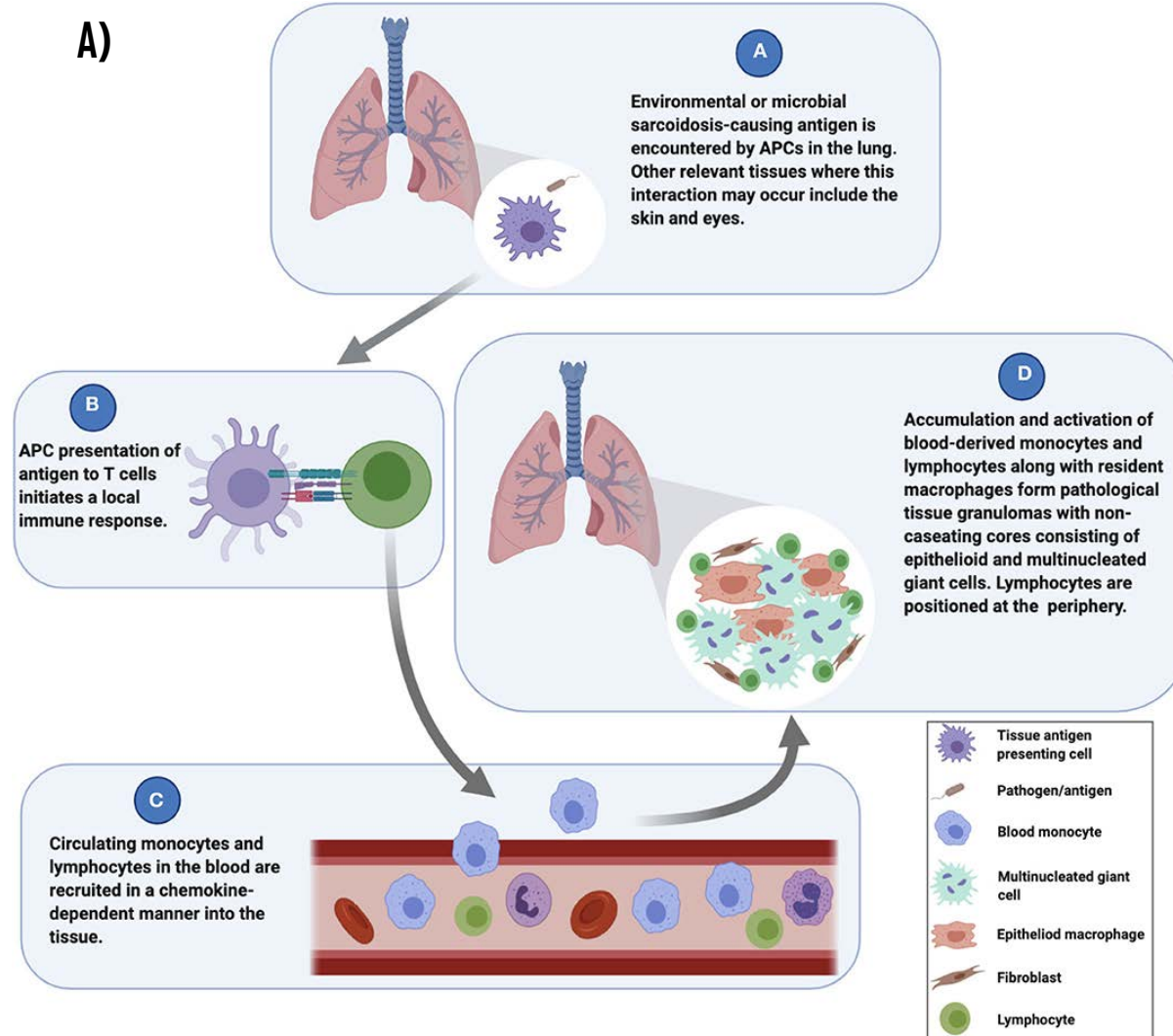
N-Terminal of HARS

hIgG1 Fc

Cellular Organization of Pulmonary Sarcoidosis Granulomas

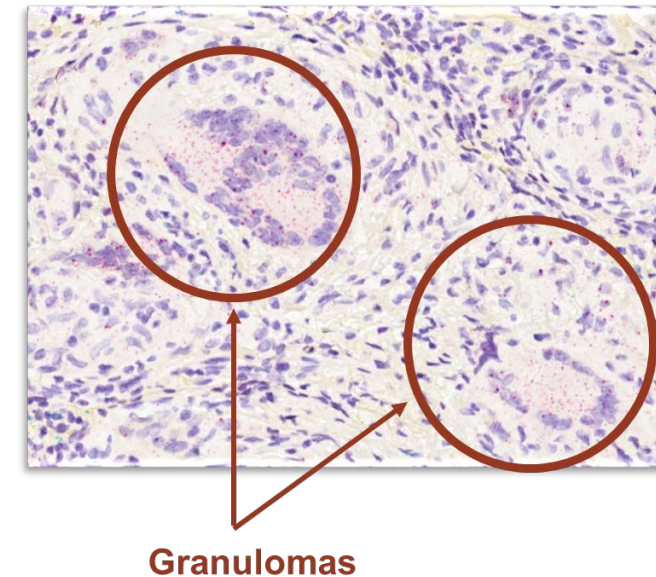


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- Granulomas contain epithelioid cells (resemble APCs such as $M\Phi$, but are not able to phagocytose), Macrophages, Multinucleated Giant Cells (MGC), Lymphocytes (B & T cells), and fibroblasts

B) NRP2 mRNA expression measure by *in situ hybridization* (ISH)

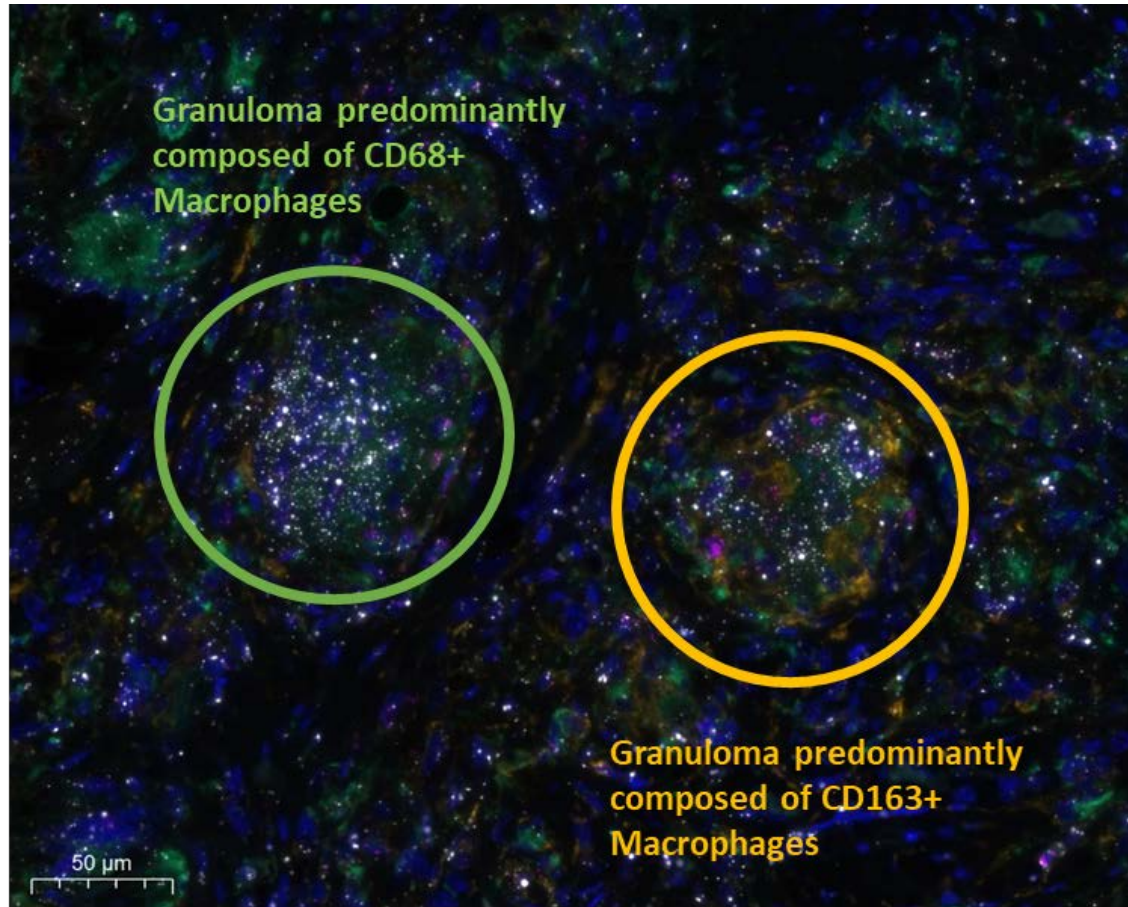


NRP2 is Highly Expressed in Myeloid Cells Found Within Granulomas of Sarcoidosis Patients



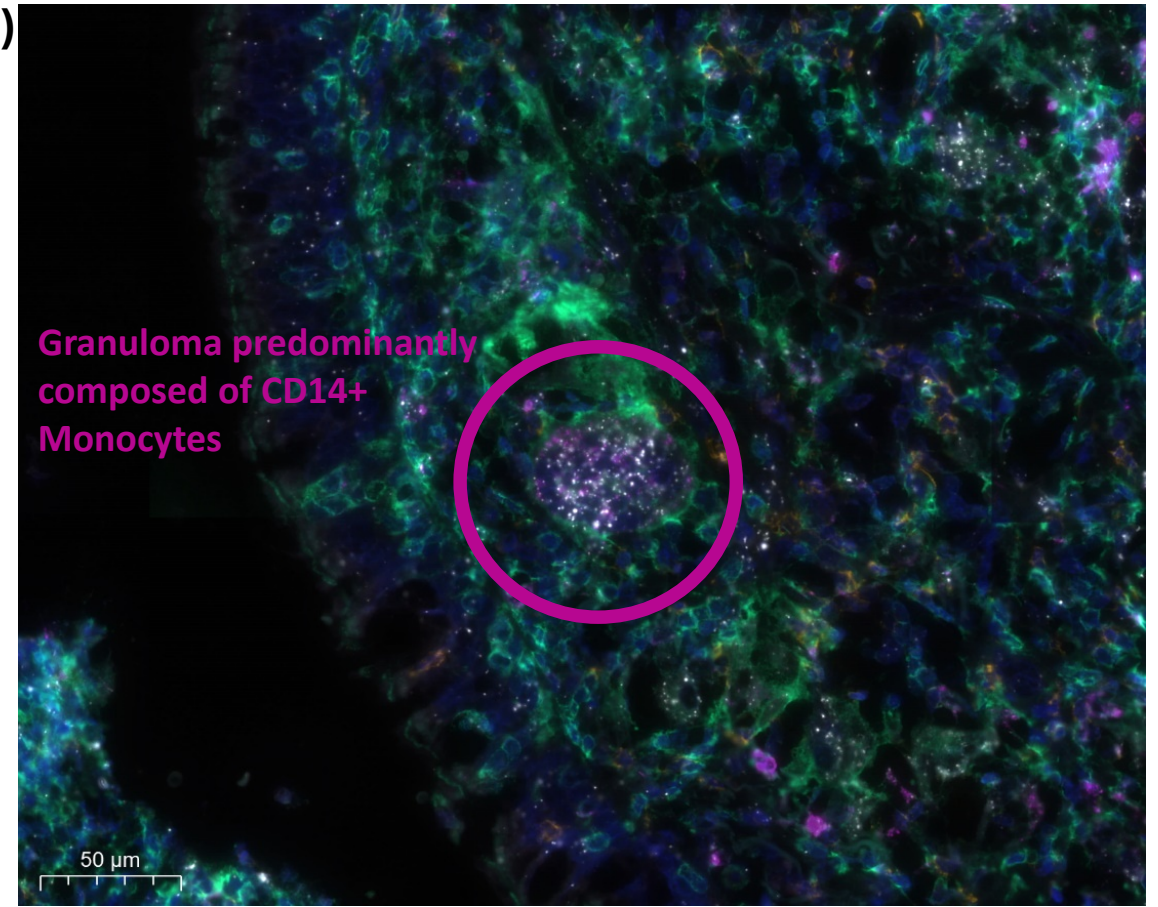
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A)



DAPI	NRP2	CD68	CD163	ITGAM
	FISH RNA	IF Protein	IF Protein	FISH RNA

B)



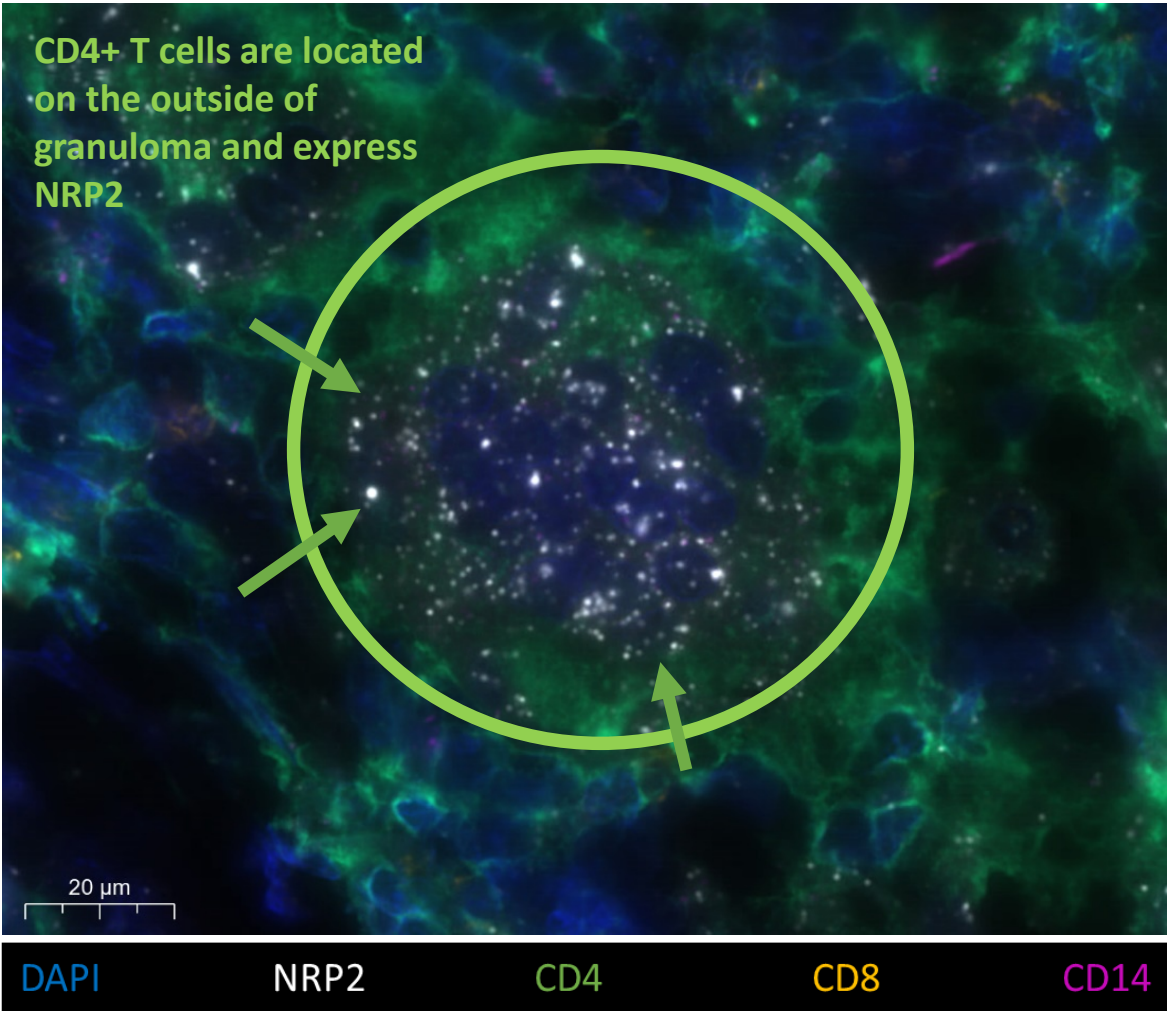
DAPI	NRP2	CD4	CD8	CD14
	FISH RNA	IF Protein	IF Protein	FISH RNA

FISH = fluorescent *in situ* hybridization, IF = immunofluorescence

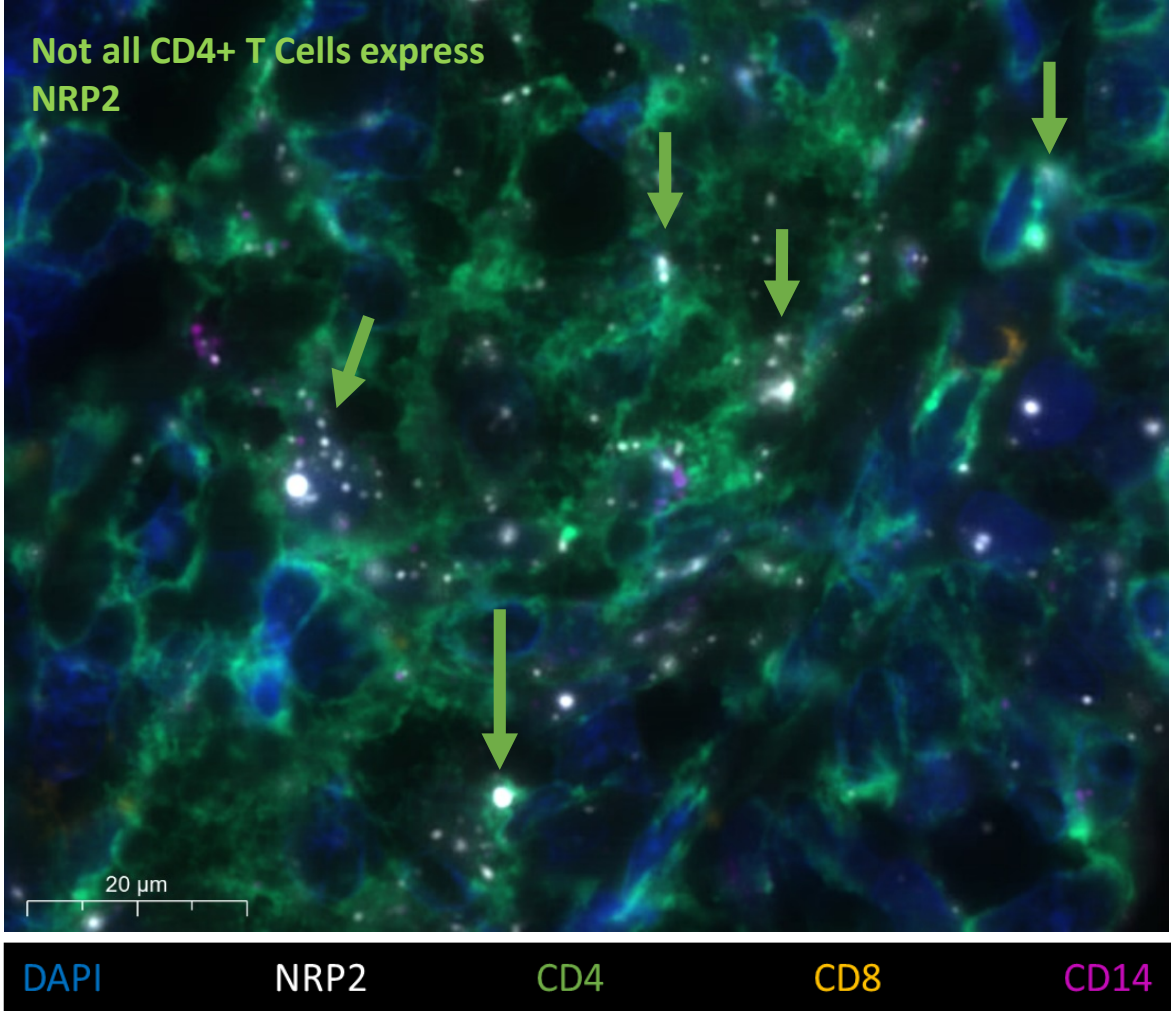
NRP2 is Expressed in T cells From Lung Tissue of Sarcoidosis Patients



A)



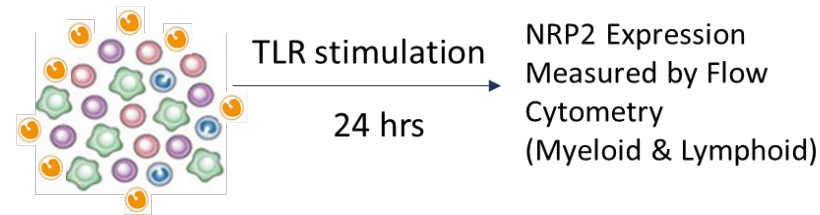
B)



NRP2 Expression on Myeloid and CD4+ T Cells is Upregulated Following TLR Activation



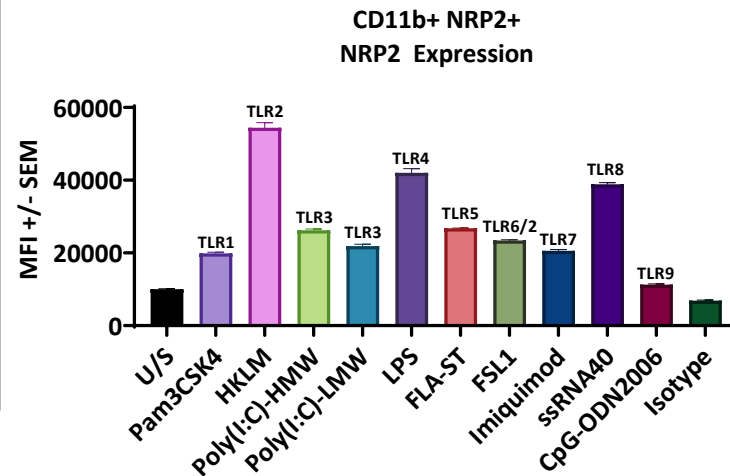
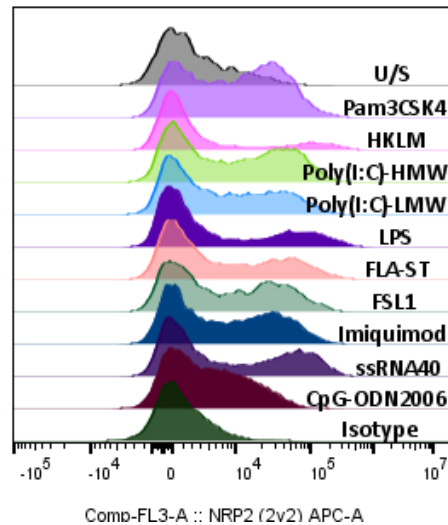
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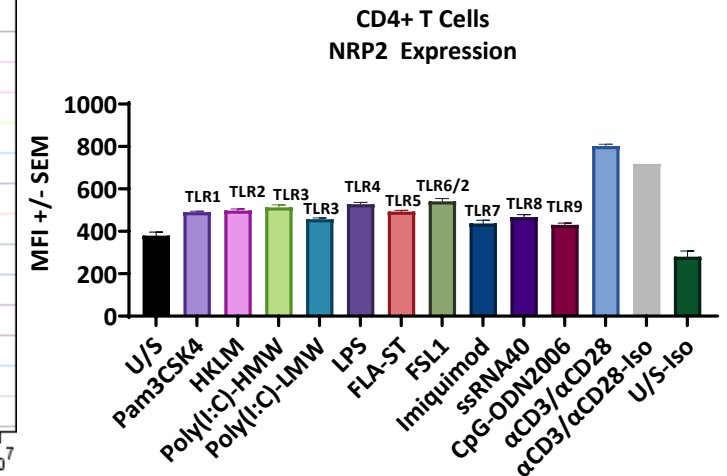
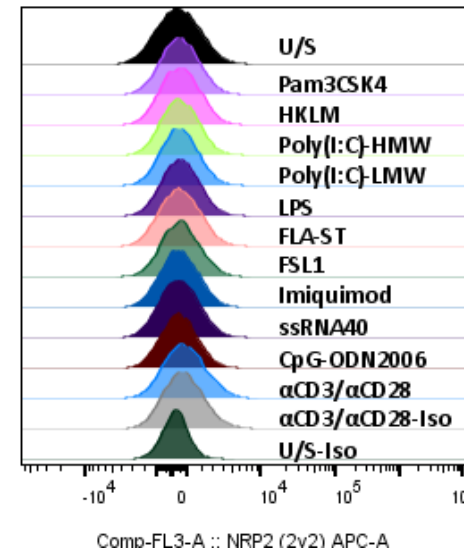
PBMCs from Healthy Volunteers

Myeloid Cells (CD11b+)

A)



B)



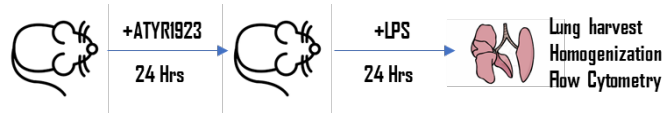
NRP2 is Expressed on Murine Alveolar MΦ (AM) and CD4+ T Cell; Treatment with ATYR1923 Reduces AM & CD4+ T cells in the Lungs of Diseased Animals



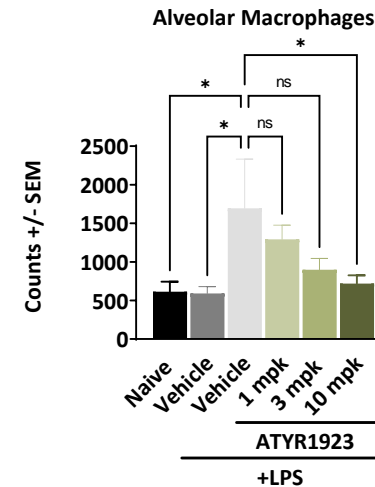
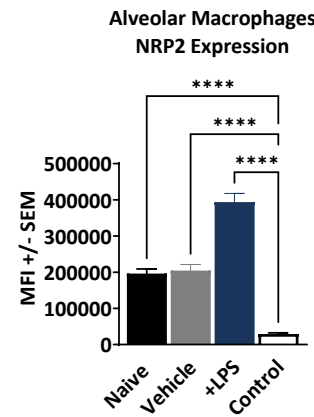
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ARDS/ALI

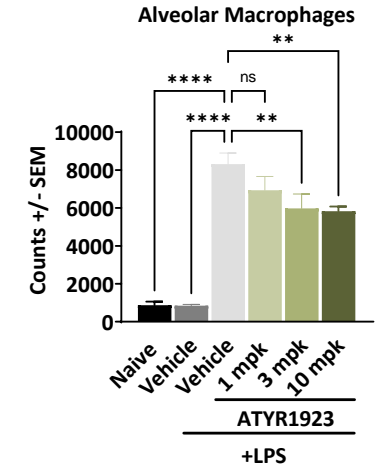
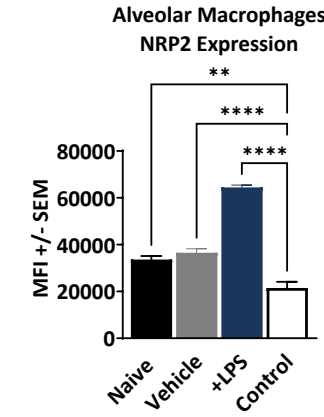
Acute Lung Injury Model



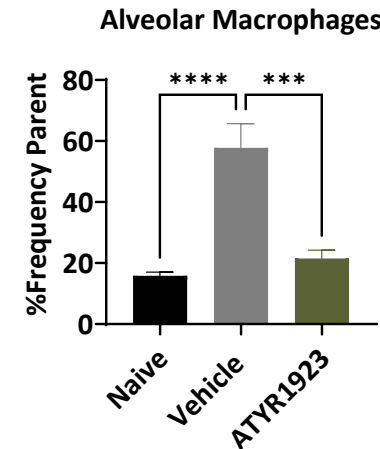
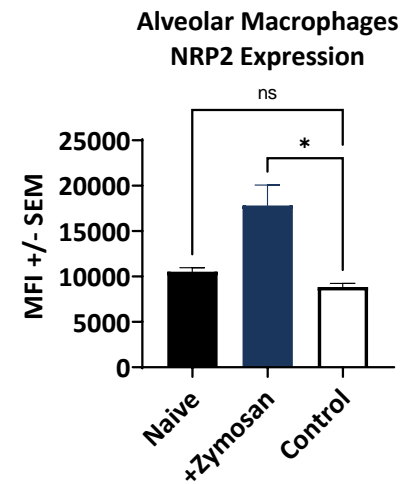
A) BAL (Bronchoalveolar Lavage)



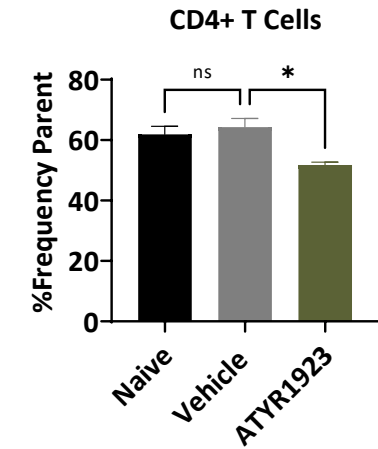
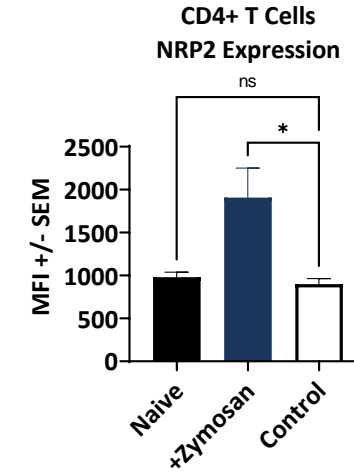
B) Lung tissue



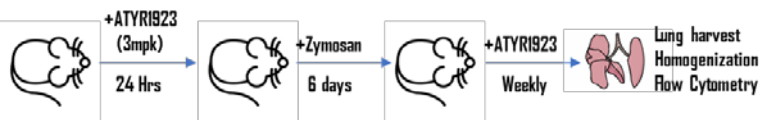
C) Lung Tissue



D) Lung Tissue



RA-ILD Inflammatory Model

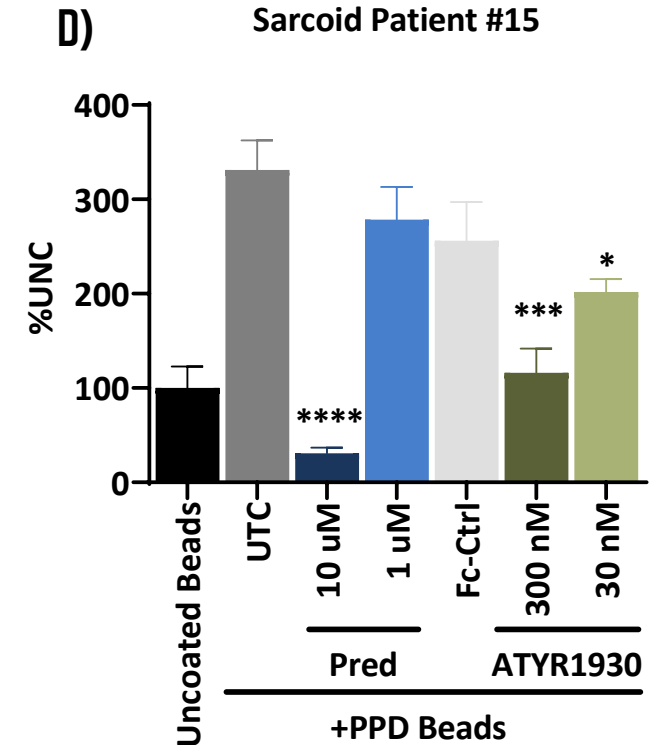
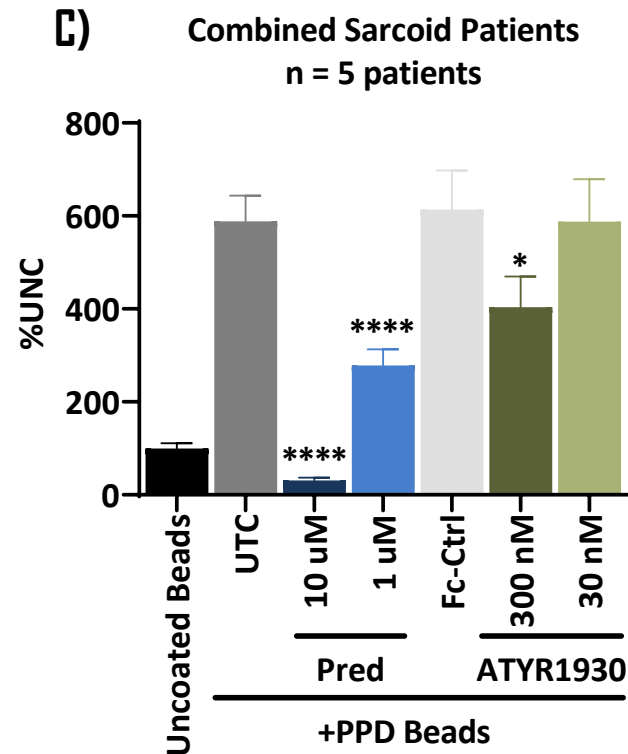
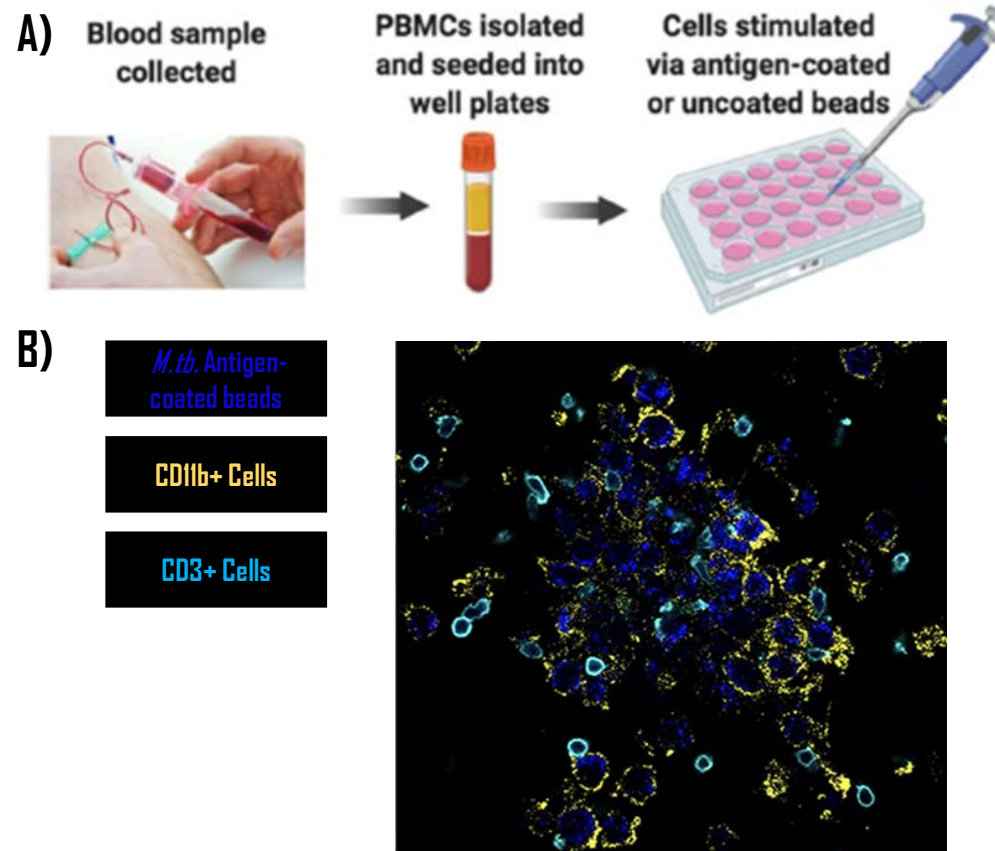


ARDS/ALI = Acute respiratory distress syndrome / Acute lung injury

ATYR1930 Prevents Granuloma Formation in a human *In Vitro* Granuloma Formation Assay



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- ATYR1930 contains the same exact the N-terminal domain of human HARS as ATYR1923, but fused to a mouse IgG1 Fc fragment



- ATYR1923 is a potential first-in class, disease modifying therapy for patients with inflammatory lung diseases with high unmet medical needs
- ATYR1923 works by selectively binding to the NRP2 receptor, which is highly expressed in granulomas from lung samples obtained from pulmonary sarcoidosis patients and more specifically expressed in macrophages
- CD4+ T cells and myeloid cells/macrophages express NRP2 in human and mouse systems
- TLR stimulation leads to a very pronounced upregulation of NRP2 in myeloid cells
- ATYR1923 treatment leads to reduction of alveolar macrophages in two mouse lung inflammatory models (LPS & RA-ILD)
- ATYR1923 treatment also reduced the number of CD4+T cells detected in the lungs of RA-ILD mouse model
- ATYR1930 significantly blocks granuloma formation *in vitro*

These findings confirm the role of ATYR1923 in controlling lung inflammation, underline its inhibitory effects on granuloma formation, and highlight the potential of ATYR1923 in regulating disease drivers in pulmonary sarcoidosis and other ILD

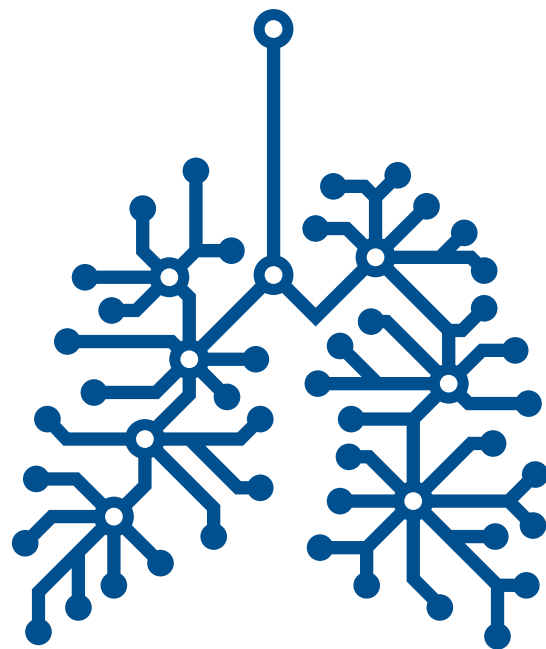
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