A New Approach to Inflammatory Diseases

8th Annual Antifibrotic Drug Development Summit AFDD

Harnessing Cross-Fibrosis Disease Insights from Discovery to Early Clinical Development

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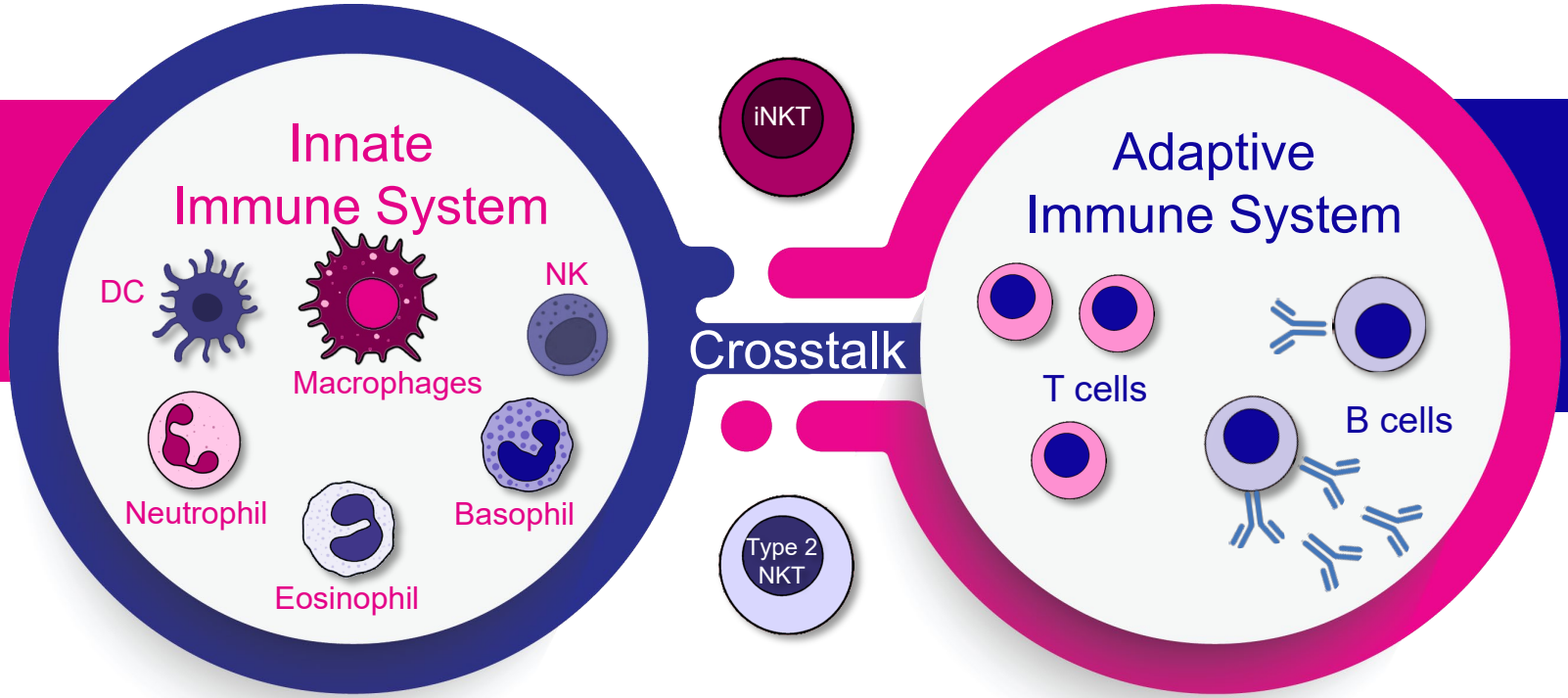
NKT Cells for Immune Regulation

Novel Immune Mechanism to Regulate the Adaptive-Innate Immune Axis & Reset Dysfunctional Immune Responses

Innate Immunity

- Non-specific
- Fast to respond (hours)
- Activated by 'danger' signals
- First line of defense



Adaptive Immunity

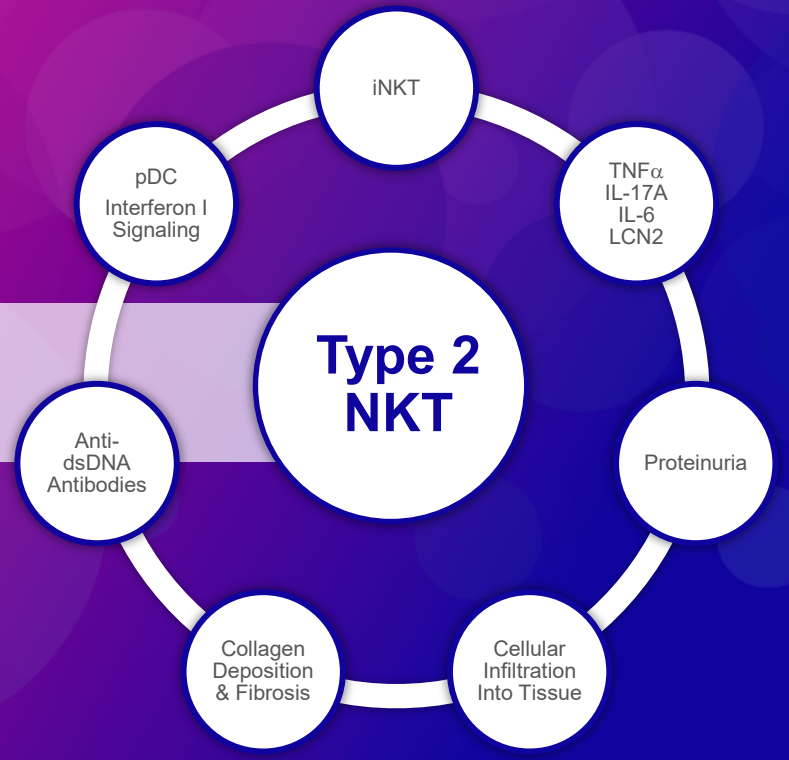
- Specific
- Slow to respond (days)
- Activated by specific pathogen recognition
- Generates immune memory

Regulating NKT Cells is a Selective Approach to Immunomodulation via Resetting the Immune Response

Natural Killer T Cells

Immune Cells that Bridge the Innate and Adaptive Immune Responses

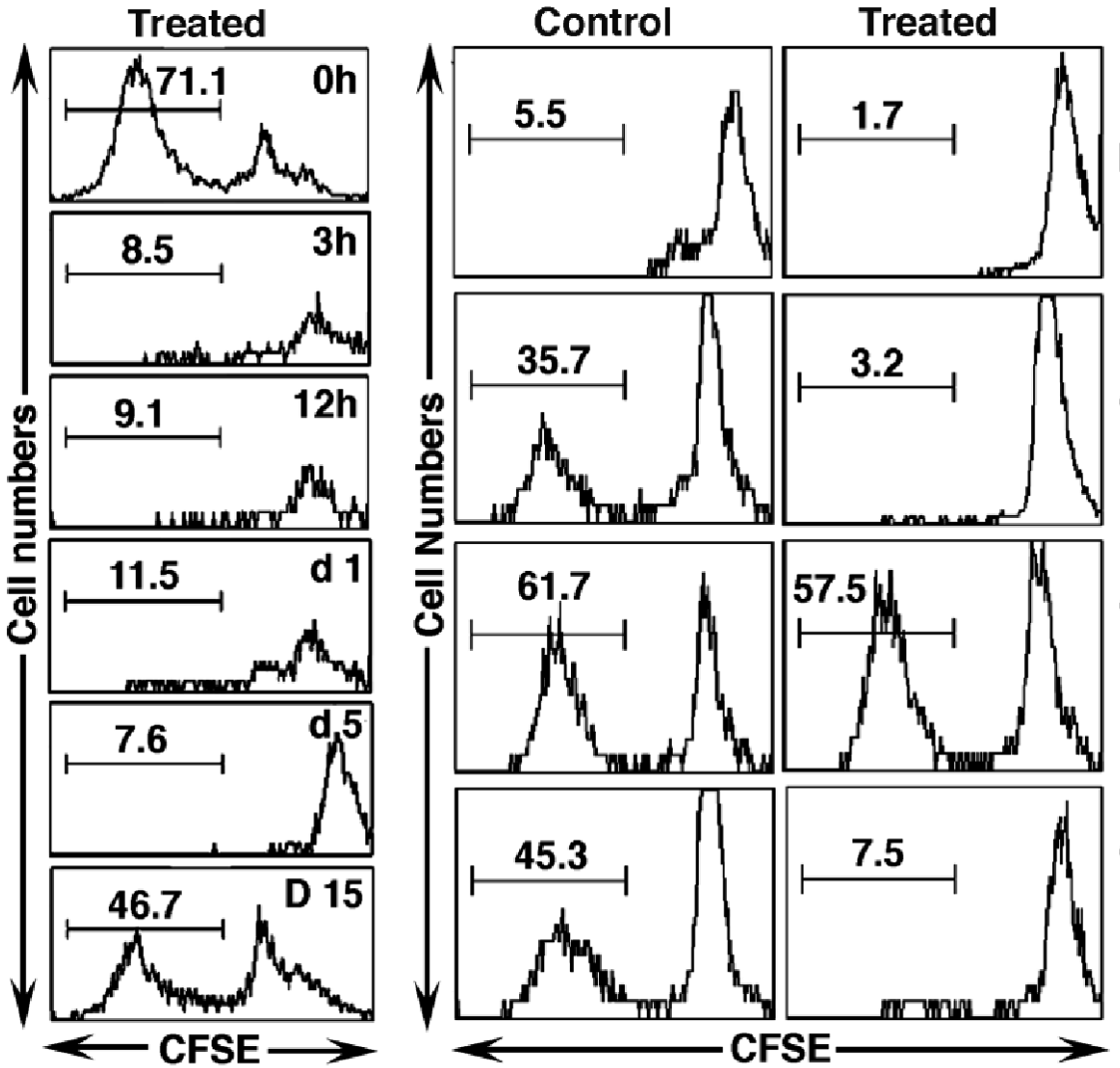
Two Types:
iNKT
and
Type 2 NKT



Significantly Increased in Patients with Chronic Inflammatory Conditions

Regulate the Activity of Other Immune Cells and 'Reset' an Aberrantly Activated Immune Response

Activated Type 2 NKT Cells Induce Anergy in iNKT Cells



Anergic iNKT cells recover by day 15

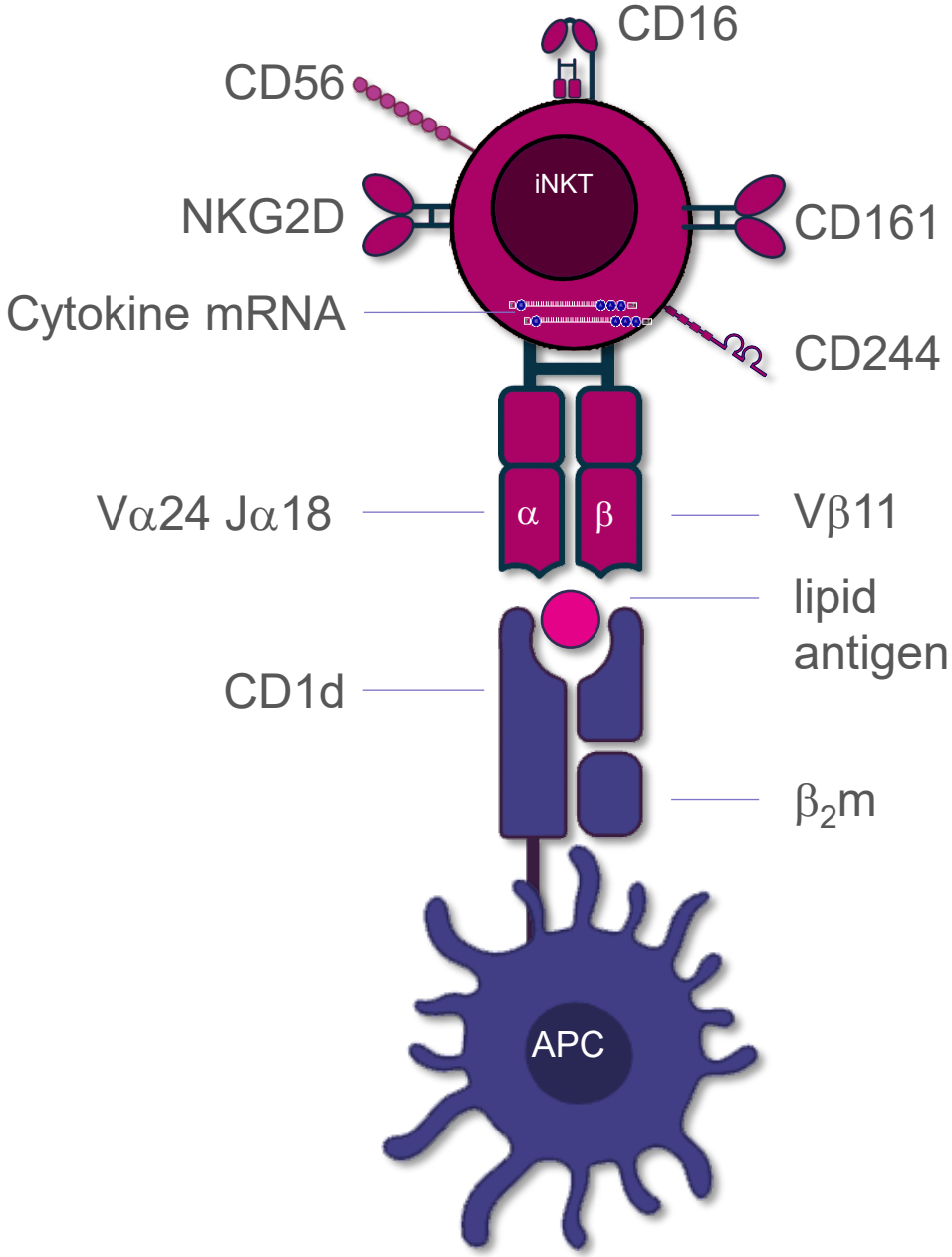
iNKT from type 2 NKT agonist-treated mice do not proliferate after α-GalCer stimulation

IL-2, but not IL-12, rescues anergic iNKT cells

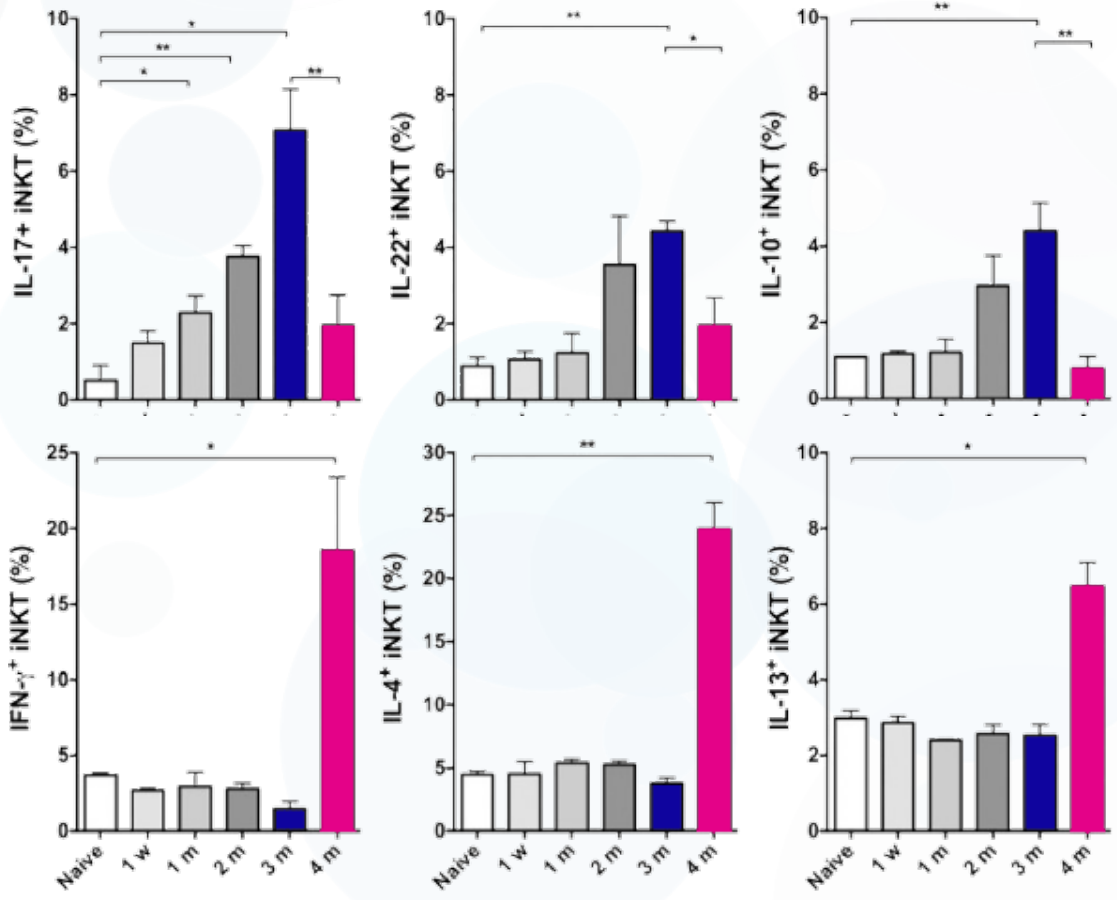
Halder et al. J Clin Invest (2007) 117: 2302

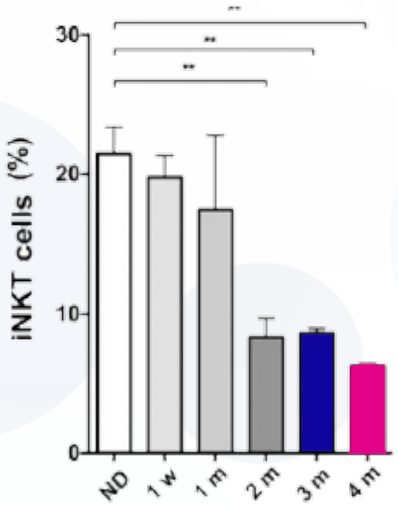
Human αβ T vs iNKT cells

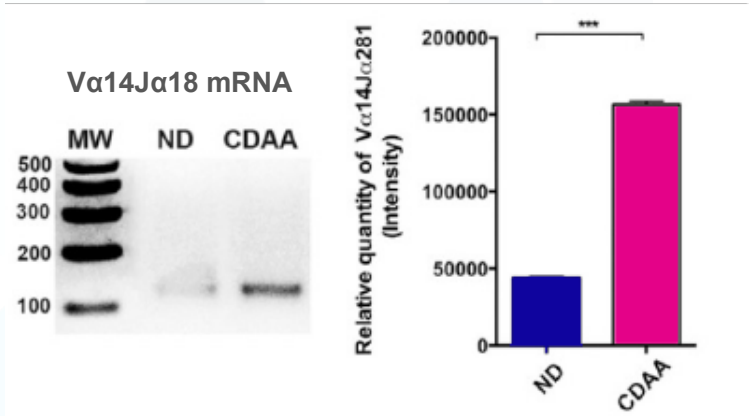
	αβ T cell	iNKT
% PBMC	45-70%	0.01 - 3%
TCR	highly diverse	Vα24-Jα18 Vβ11
Antigen	peptides, diverse	glycolipids
Restriction element	HLA polymorphic	CD1d non-polymorphic
T cell markers	CD3 CD4 CD8	CD3 CD4 CD8
NK markers	n/a	CD56
Subsets	Th1, Th2, Th17	NKT1, NKT2, NKT17
Activation	TCR	TCR, Cytokines KIR, NLR, TLR
Cytokines	after priming	pre-formed mRNA
Activation timing	3-5 days, peak weeks	hours, peak days



iNKT Cells Are Chronically Activated in CDAA Model of MASH

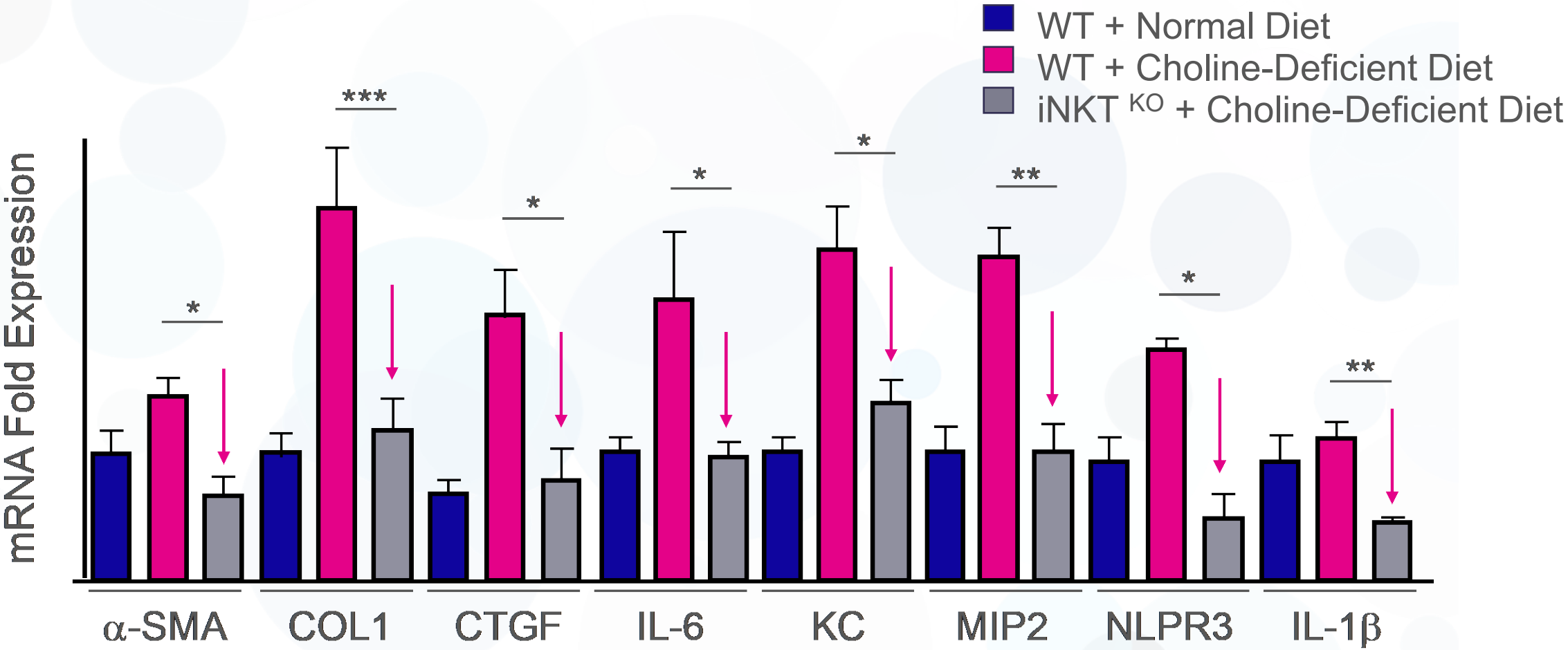




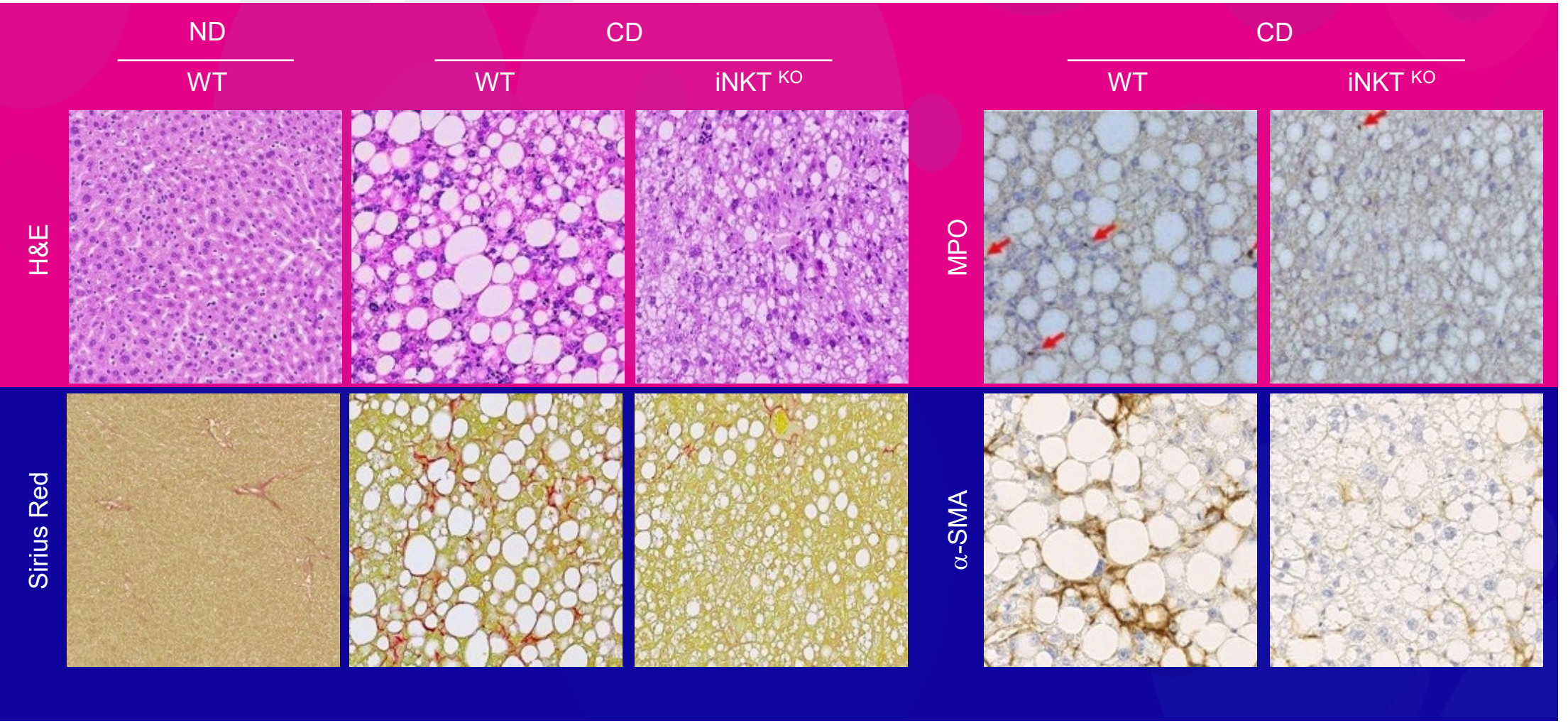


Maricic et al. J Immunol (2018)

iNKT Cell Deficiency Inhibits Pro-Inflammatory & Fibrogenic Genes in a Hepatic Fibrosis Model

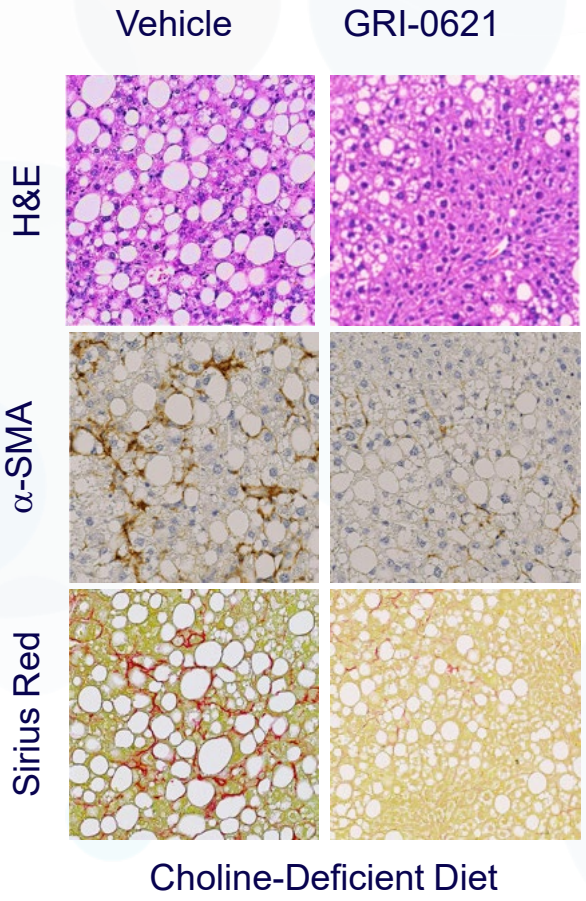


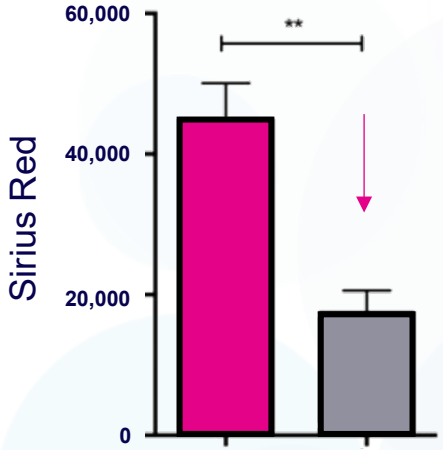
iNKT Cell Deficiency Prevents Inflammation, Steatosis & Fibrosis in MASH Model

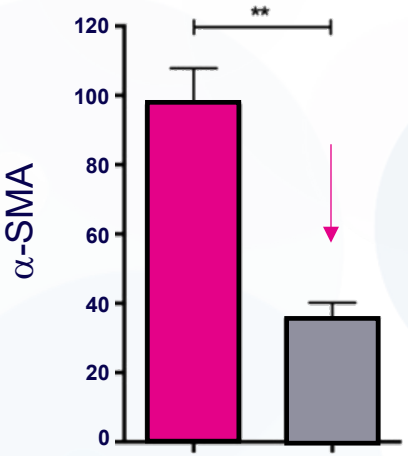


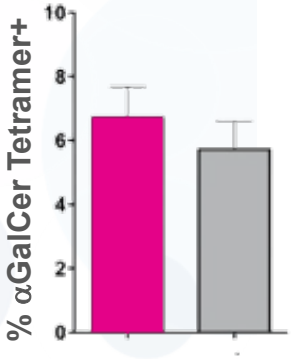
ND = Normal diet
CD = Choline-deficient diet
WT = Wild Type mice
iNKT ^{KO} = Jα18$^{-/-}$ iNKT deficient mice

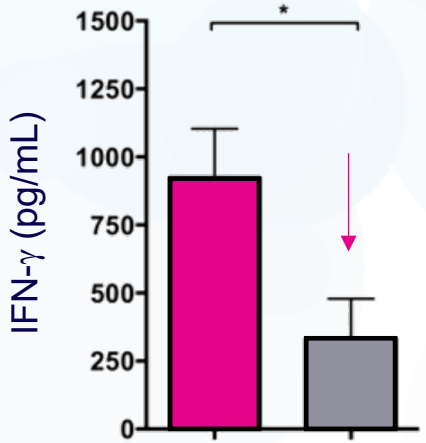
GRI-0621 Reduces Inflammation, α-SMA and Hepatic Fibrosis

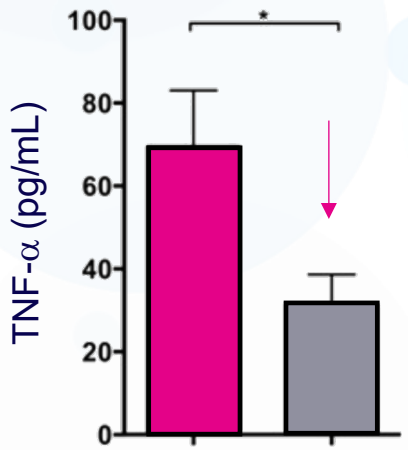


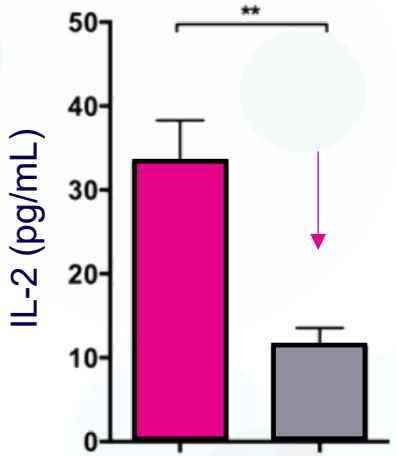


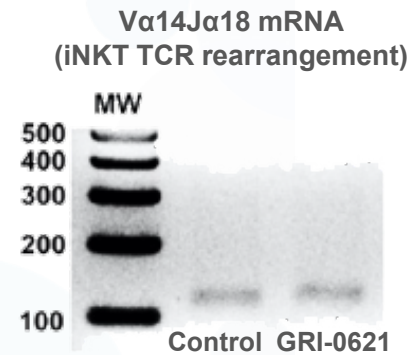




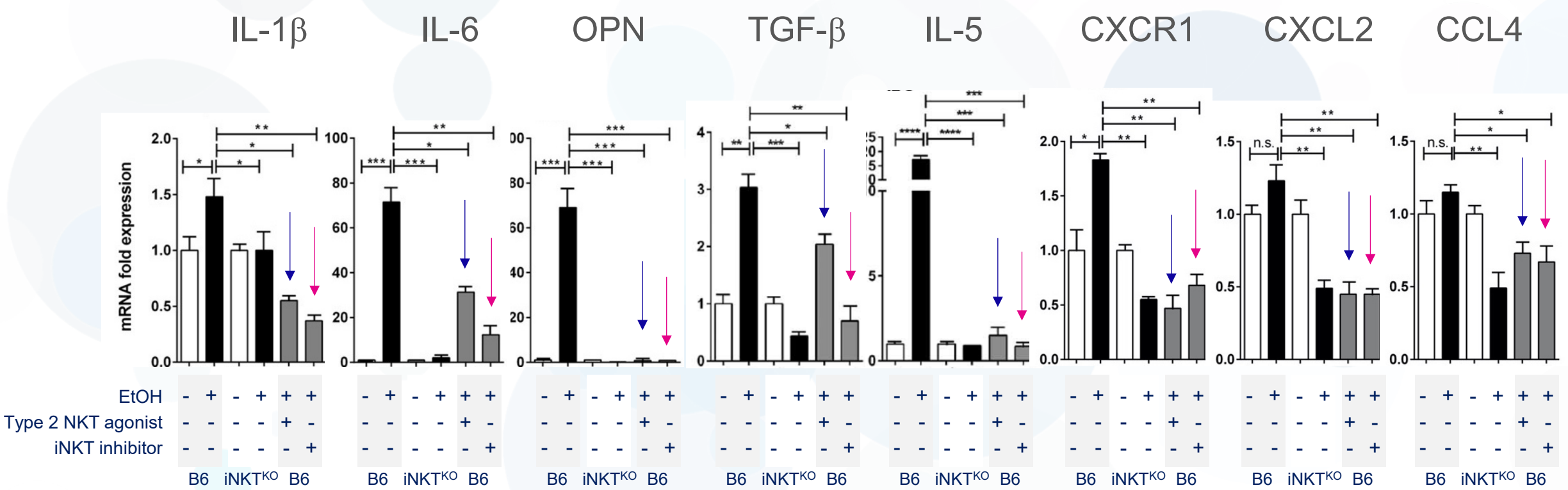








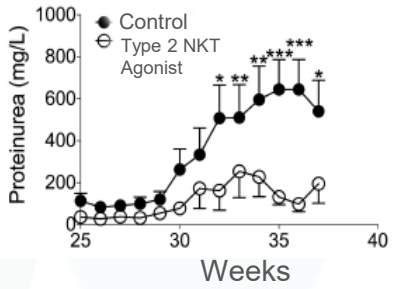
iNKT Inactivation, via iNKT inhibitors or Type 2 NKT Agonists, Inhibit Key Inflammatory Pathways

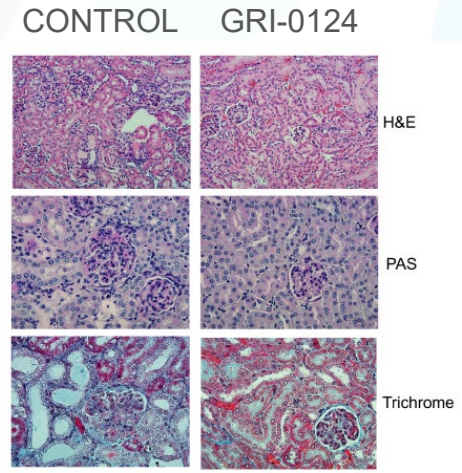


Maricic et al. Hepatology (2015)

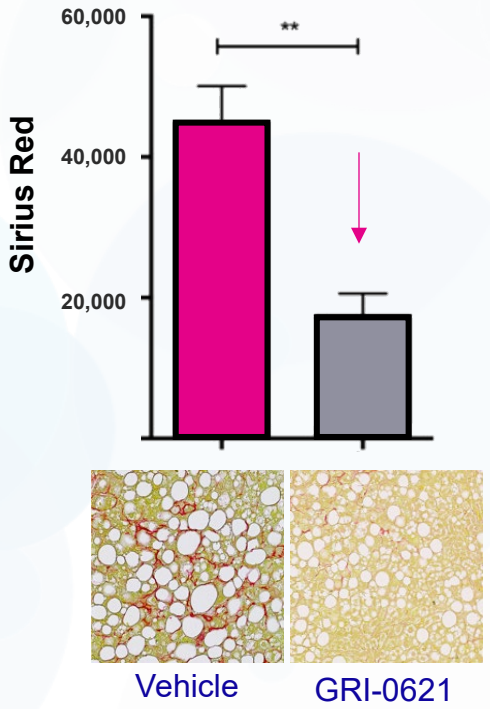
Observed Reduction of Fibrosis in Disease Models

NZBWF1

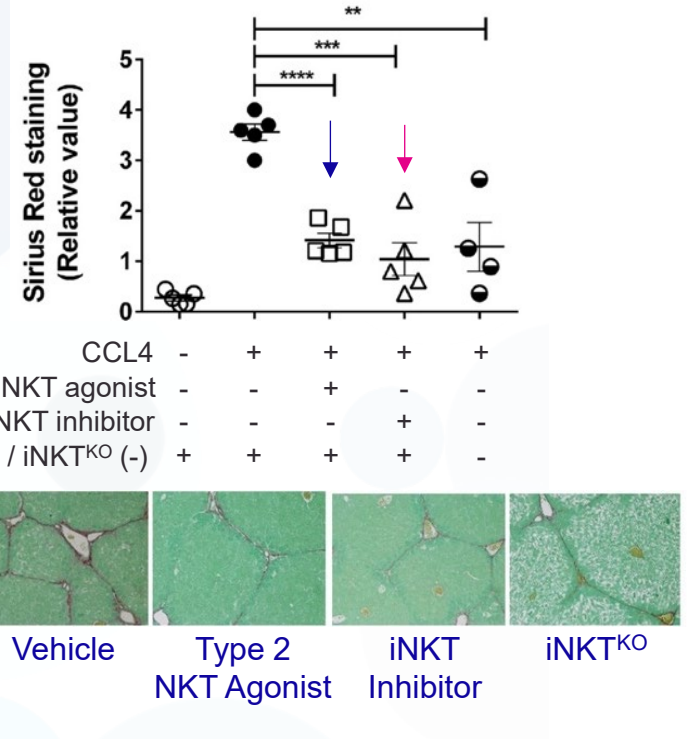




CDAA



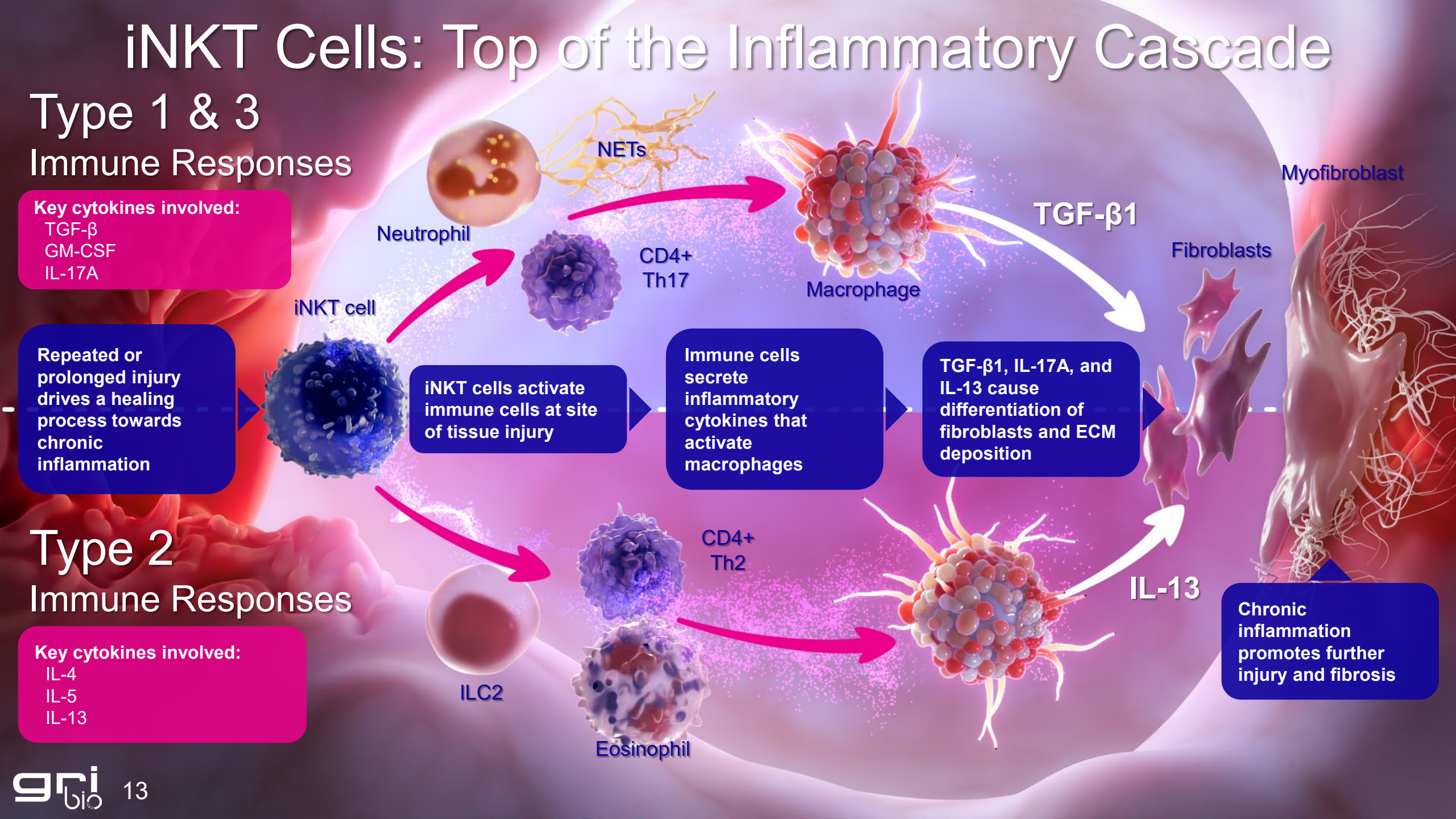
CCL4



iNKT Cells: Top of the Inflammatory Cascade

Type 1 & 3 Immune Responses

Key cytokines involved:
- TGF-β
- GM-CSF
- IL-17A



Type 2 Immune Responses

Key cytokines involved:
- IL-4
- IL-5
- IL-13

GRI-0621 Targets iNKT to Restore Homeostasis

Type 1 & 3
Immune Responses

GRI-0621

Macrophage

TGF-β1

Most current therapies work through TFG-β regulation and fail to address type 2 immune responses

Fibroblasts

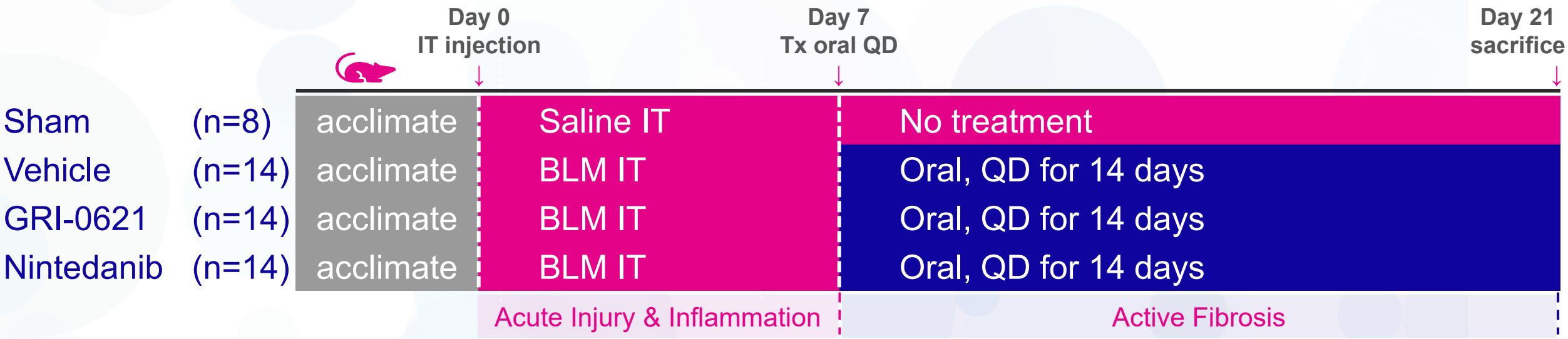
GRI-0621 inhibits the activity of iNKT cells early in the inflammatory cascade to prevent cytokine release, cellular infiltration, and interrupts disease progression at the source

Type 2
Immune Responses

IL-13

Resolution of chronic inflammatory response and immune system returning to homeostasis without systemic immunosuppression

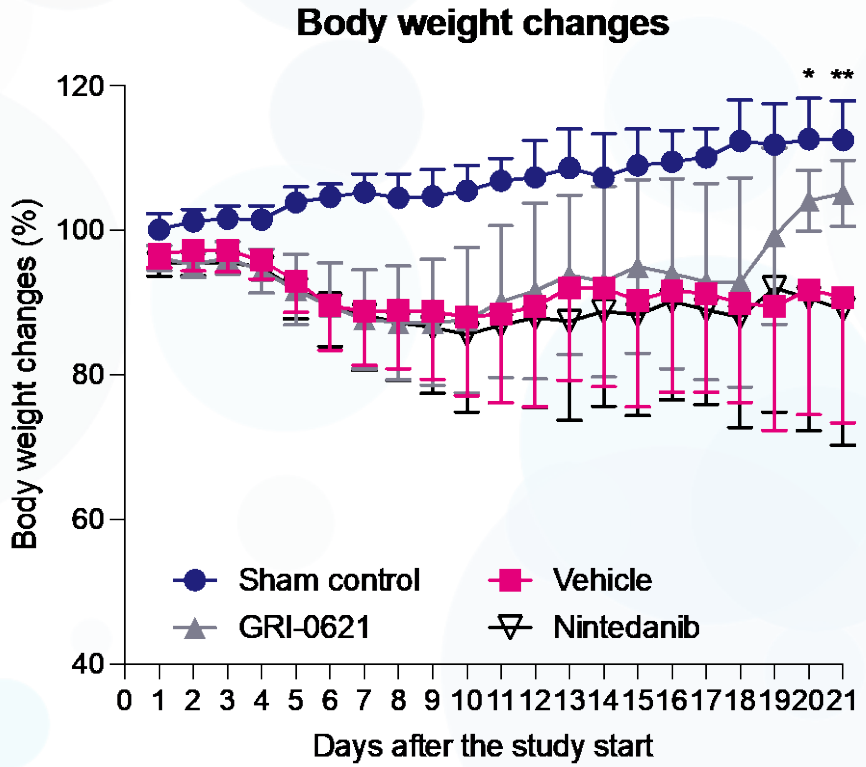
Pulmonary Fibrosis Treatment Model



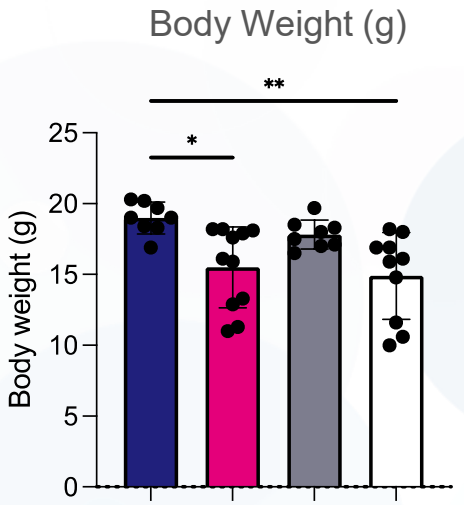
Mouse IPF Model: Pulmonary fibrosis induced on day 0 in 8-week old C57BL/6 mice with intratracheal bleomycin (3.0 mg/kg). Vehicle*, GRI-0621 (1.0mg/kg), or nintedanib (100mg/kg) was administered for 14 days beginning on day 7. Studies conducted at SMC Laboratories (Tokyo, JP).

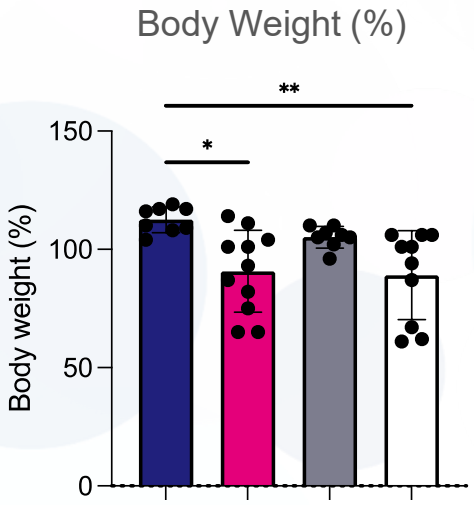
*GRI-0621 vehicle: 5% DMSO, 0.1% Tween 80 in PBS
Nintedanib vehicle: 1% methylcellulose

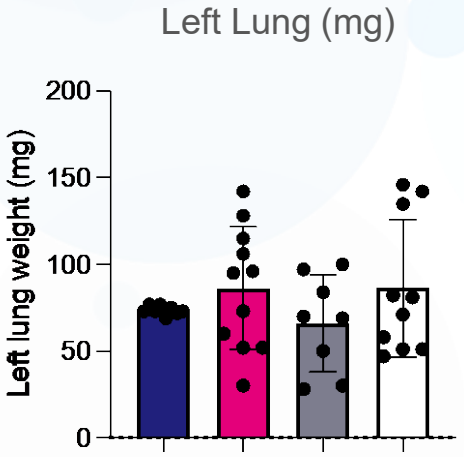
GRI-0621 Reduces Weight Loss & Lung Weight

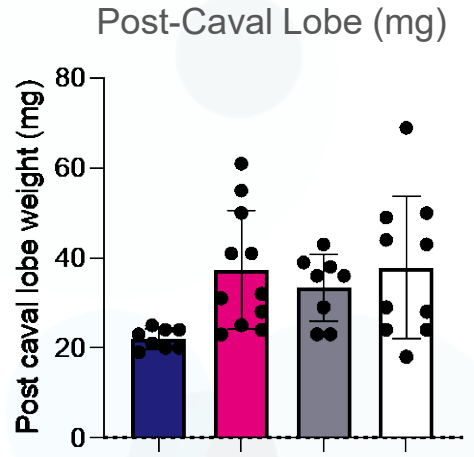


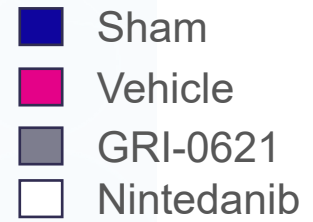
Body weight: Vehicle vs GRI-0621
* p<0.05, ** p<0.01





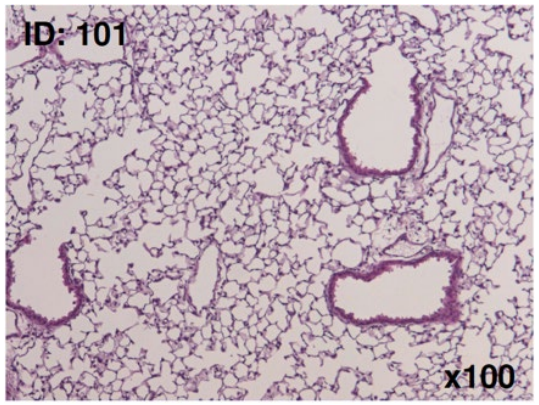




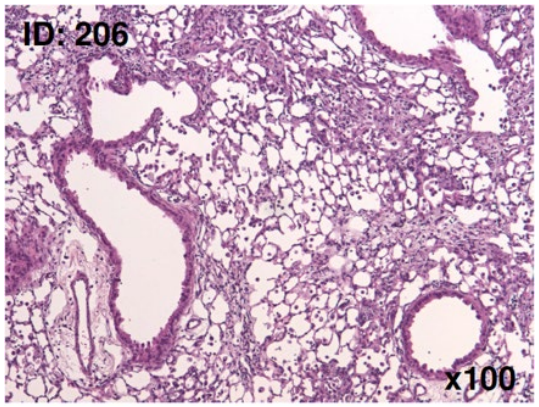


GRI-0621 Reduces Lung Infiltrates & Injury

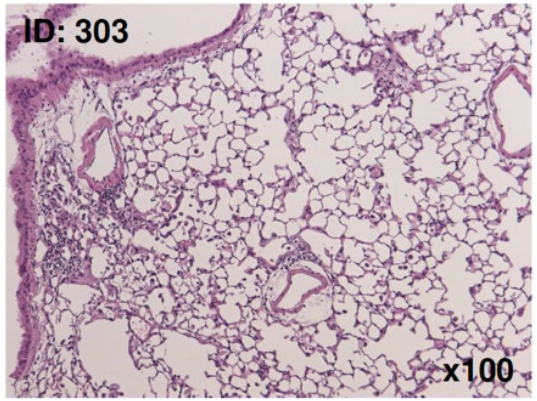
Sham



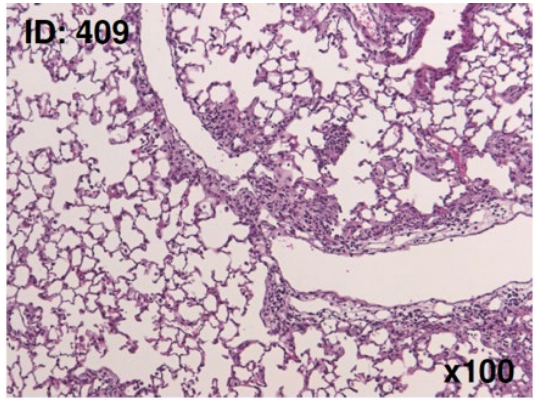
Vehicle



GRI-0621

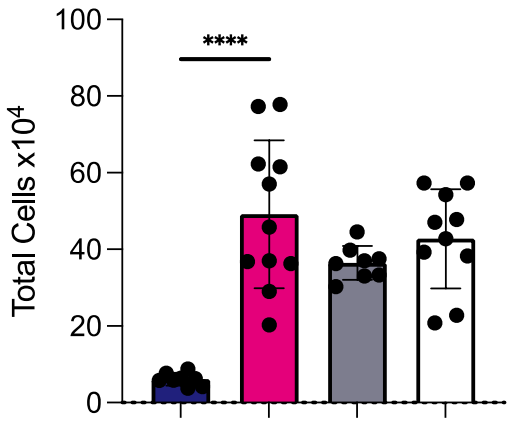


Nintedanib

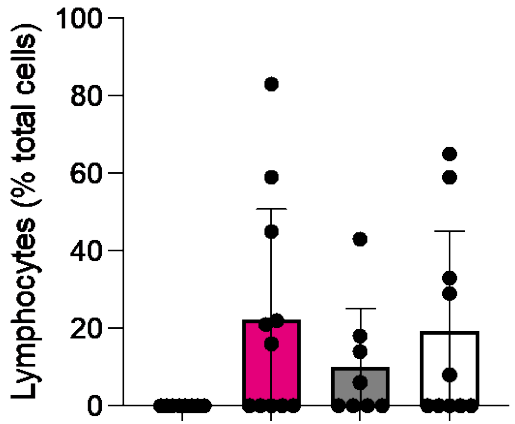


H&E Staining

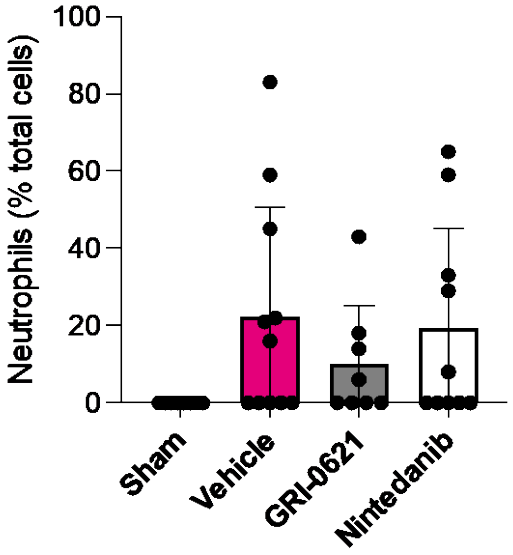
Total Lung Cells



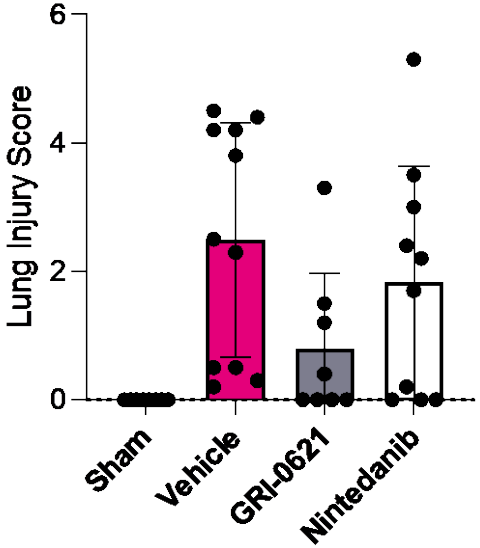
Lymphocytes



Neutrophils

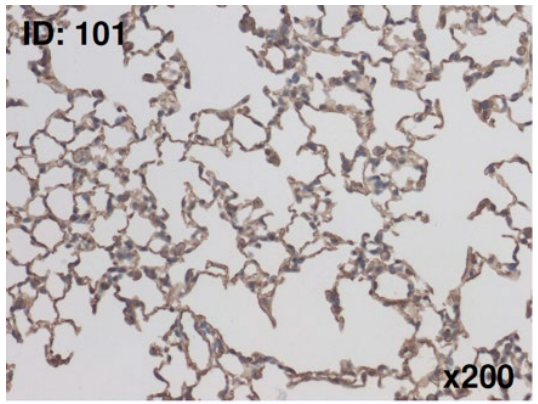


Lung Injury

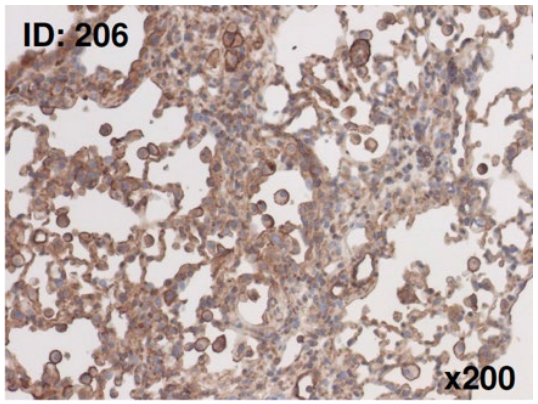


GRI-0621 Inhibits Myofibroblast Activation

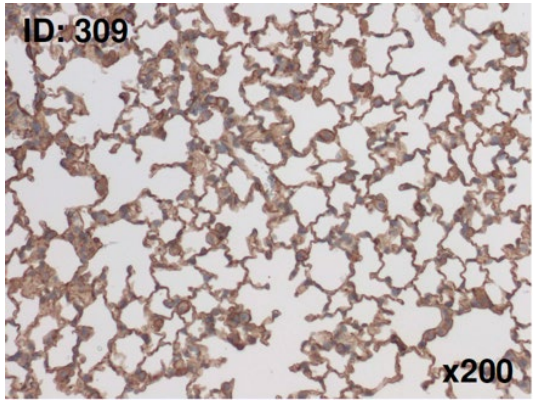
Sham



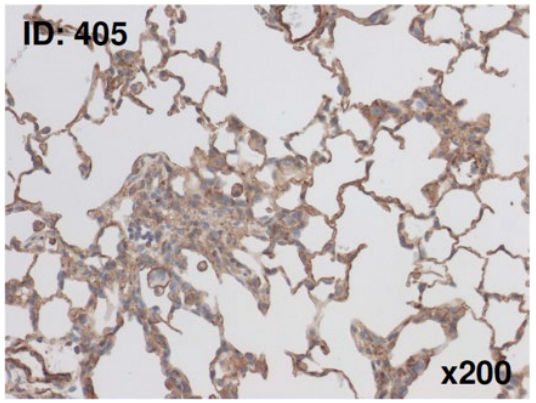
Vehicle



GRI-0621

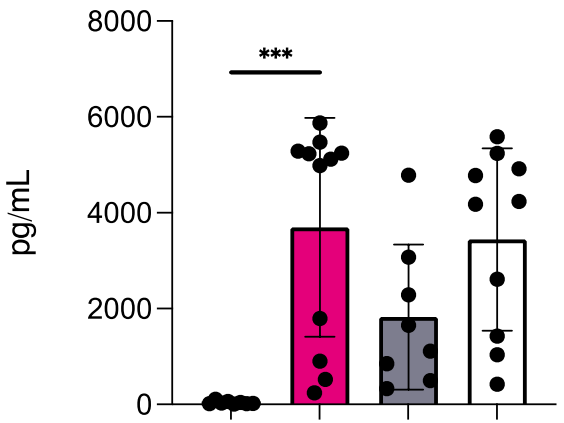


Nintedanib

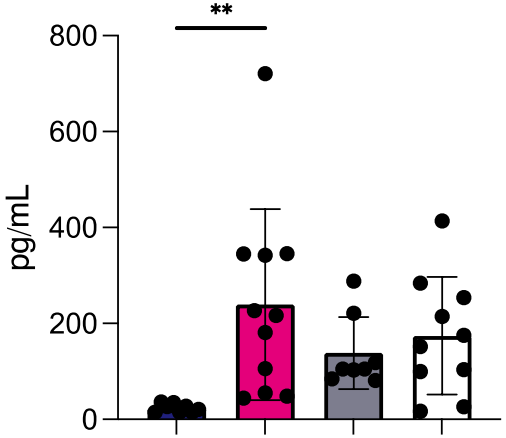


α-SMA Staining

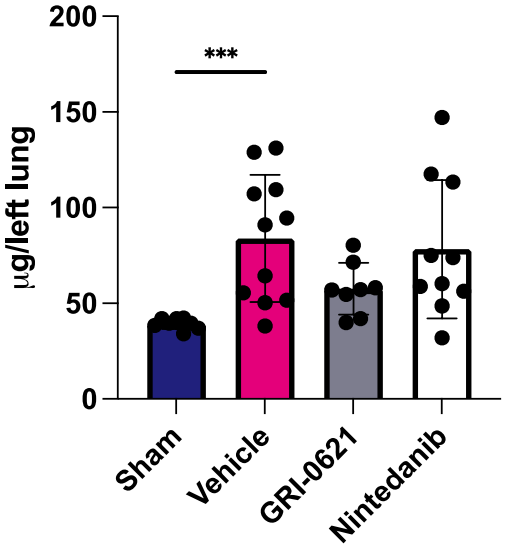
TIMP-1



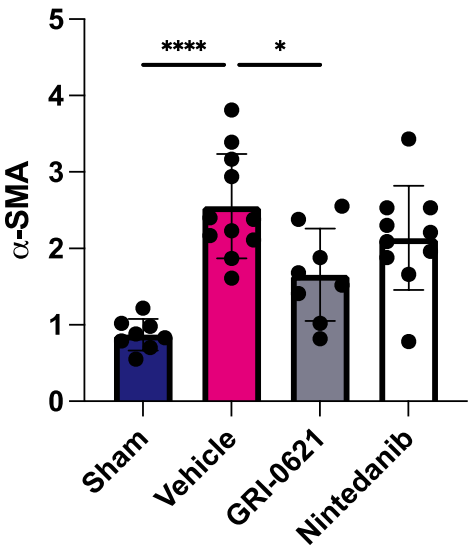
TGF-β



Hydroxyproline

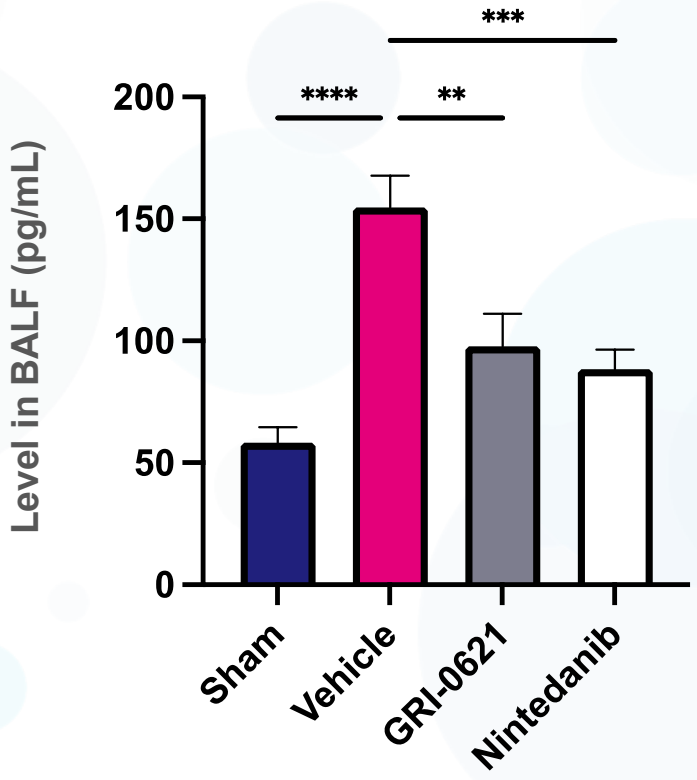


α-SMA



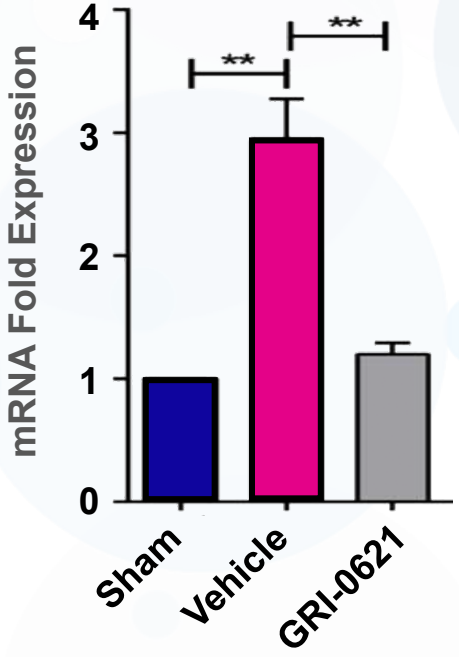
Observed Reduction of TGF-β in Fibrotic Models

Pulmonary Fibrosis



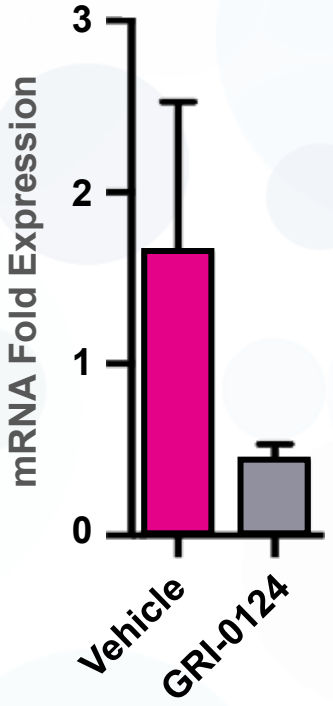
Bleomycin

Hepatic Fibrosis



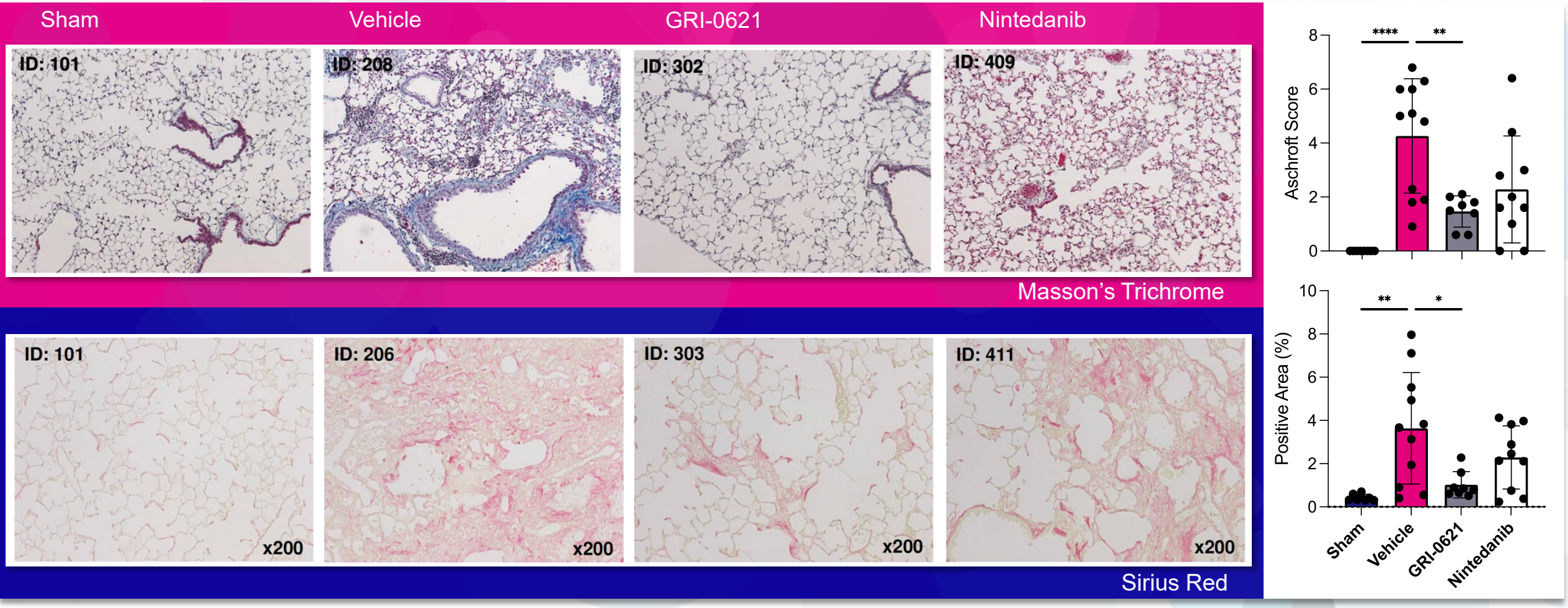
Lieber-DeCarli

Renal Fibrosis

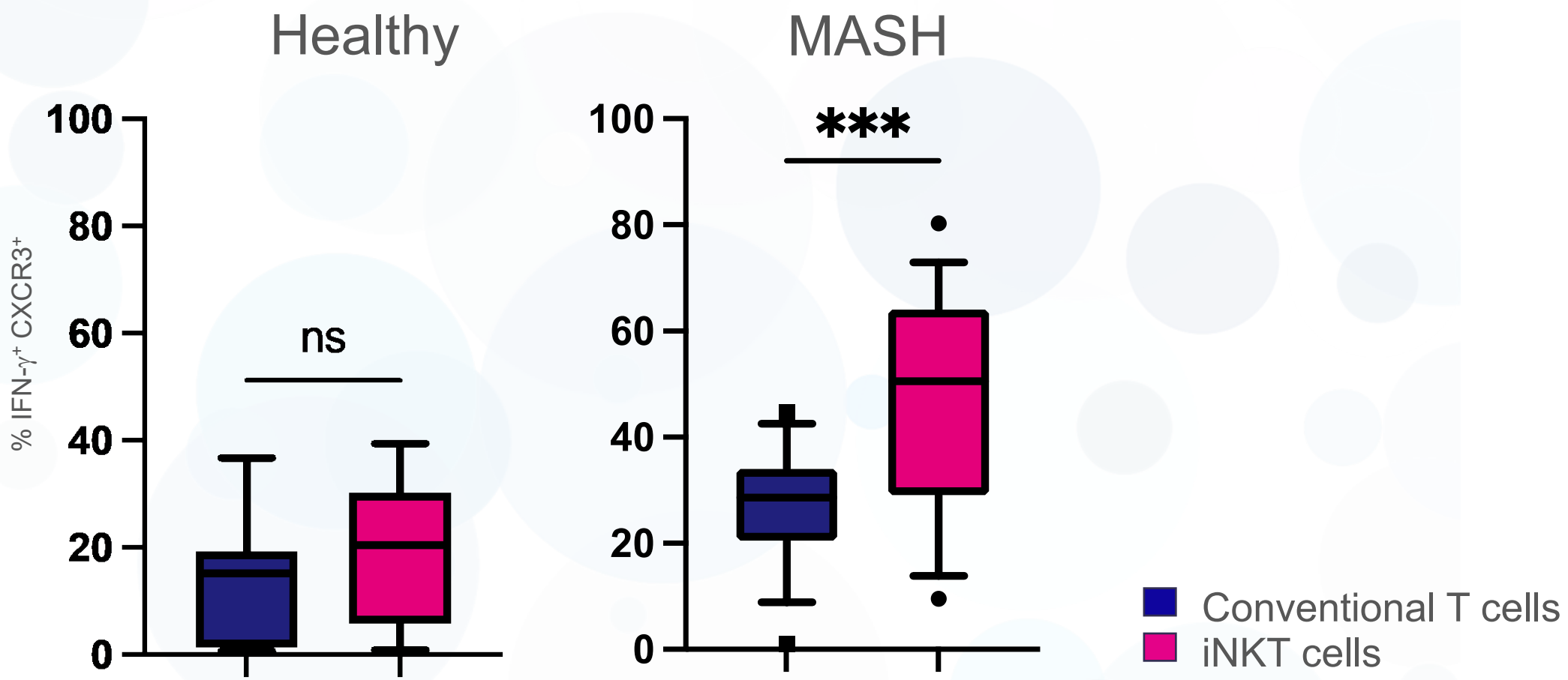


NZB/W F1

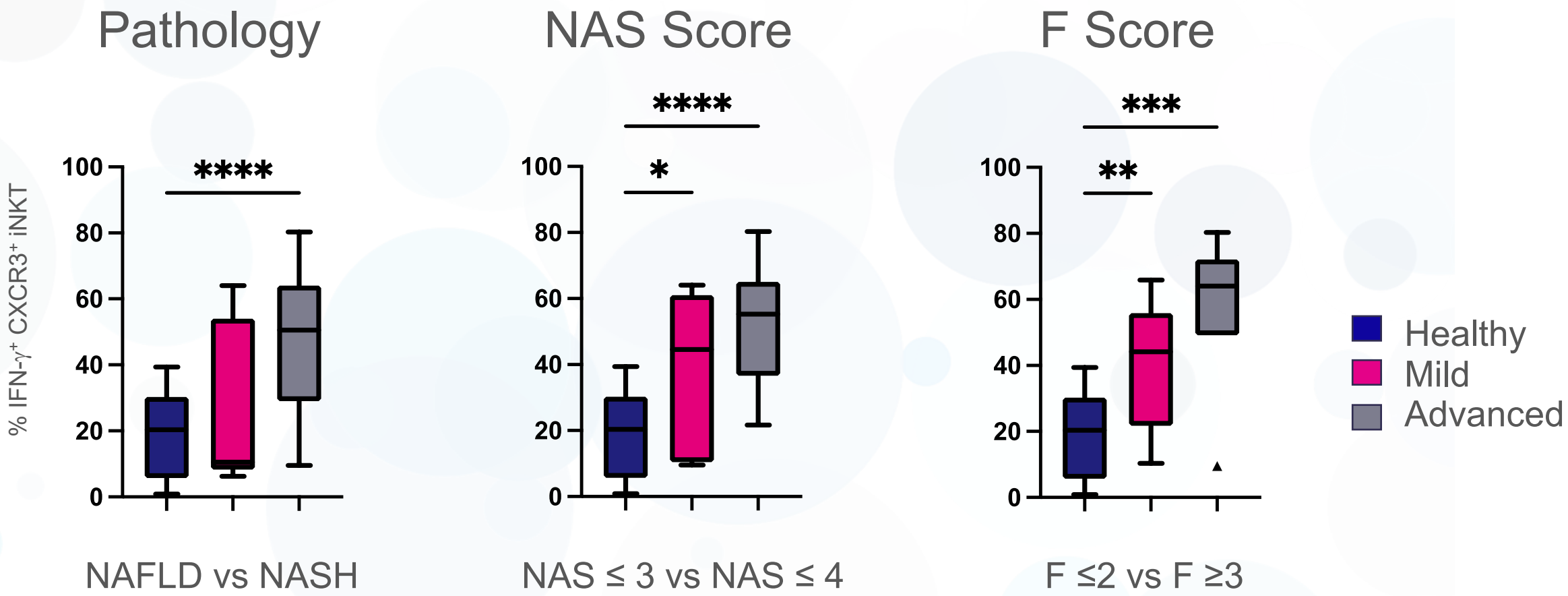
GRI-0621 treatment significantly reduces fibrosis



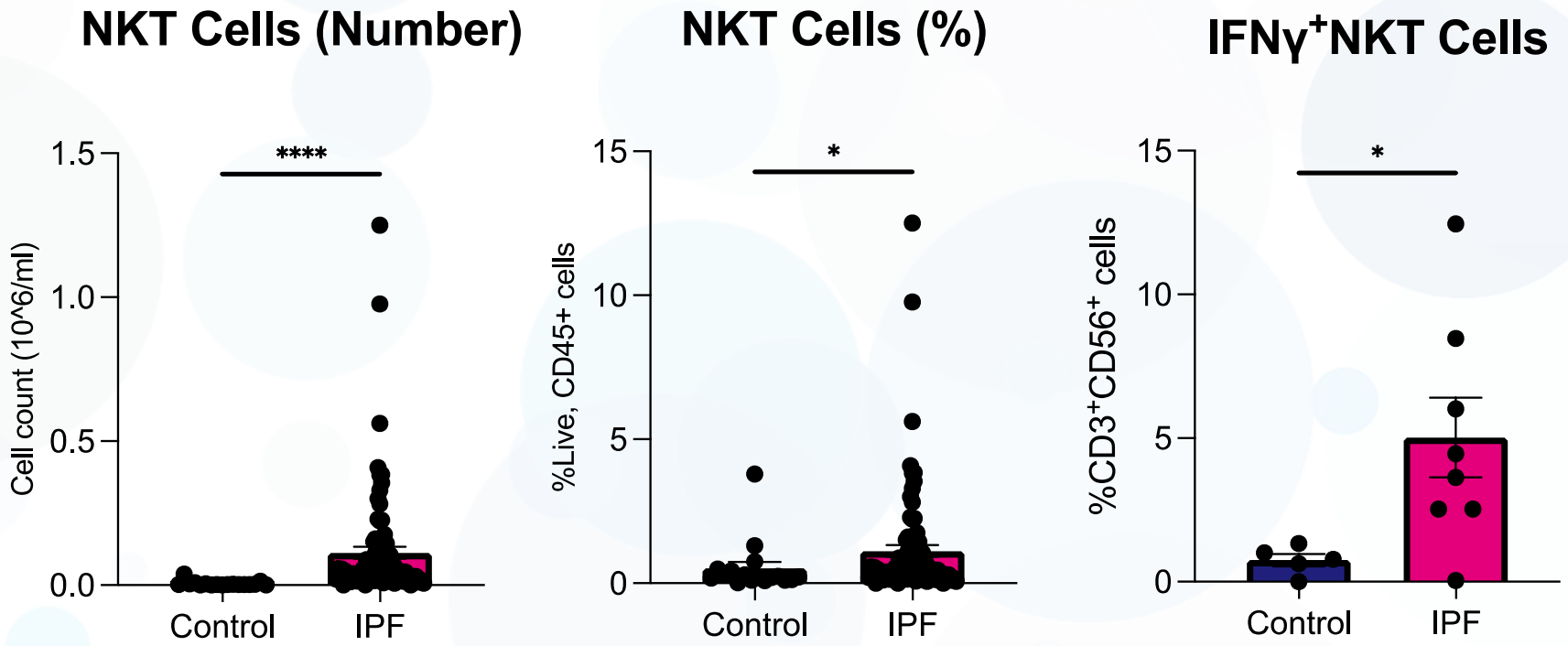
Pro-Inflammatory iNKT Cells Accumulate in Fatty Liver Disease Patients



Pro-Inflammatory iNKT Cells Correlate with Progressive Advanced Disease



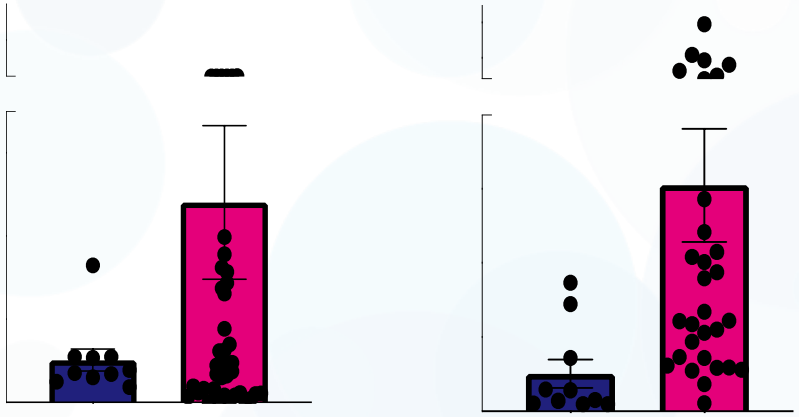
Proportion and Number of NKT Cells Significantly Increased in BAL of IPF Patients



$CD3^+CD56+$ NKT-like cells correlate with progressive IPF, and are part of a proposed immune cell composite to identify progressive IPF patients at baseline

- *Mendoza et al. Int. J. Mol. Sci (2023)*

Increased Expression of and iNKT cells and Pro-Fibrotic Factors in BAL from IPF Patients

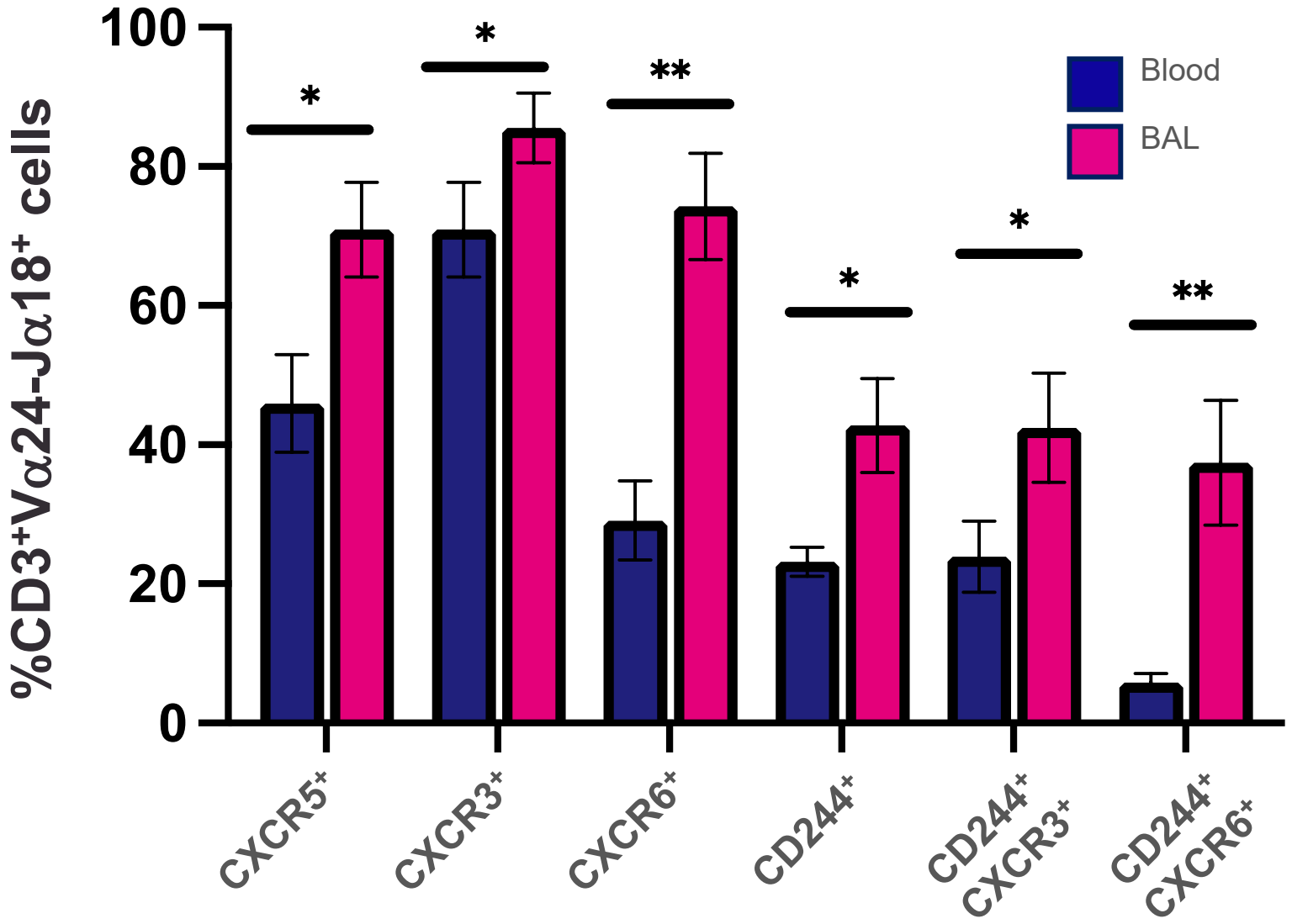


No significant difference in CXCR3, TNF, IL-4, IL-5 and IL-13 in healthy (n=10) vs. IPF patients (n=29)

Increased expression of iNKT TCR, Col1α1, OPN, and TGF-β genes in IPF patients

Significant Activation of iNKT cells (Vα24⁺Jα18⁺) in BAL of IPF Patients

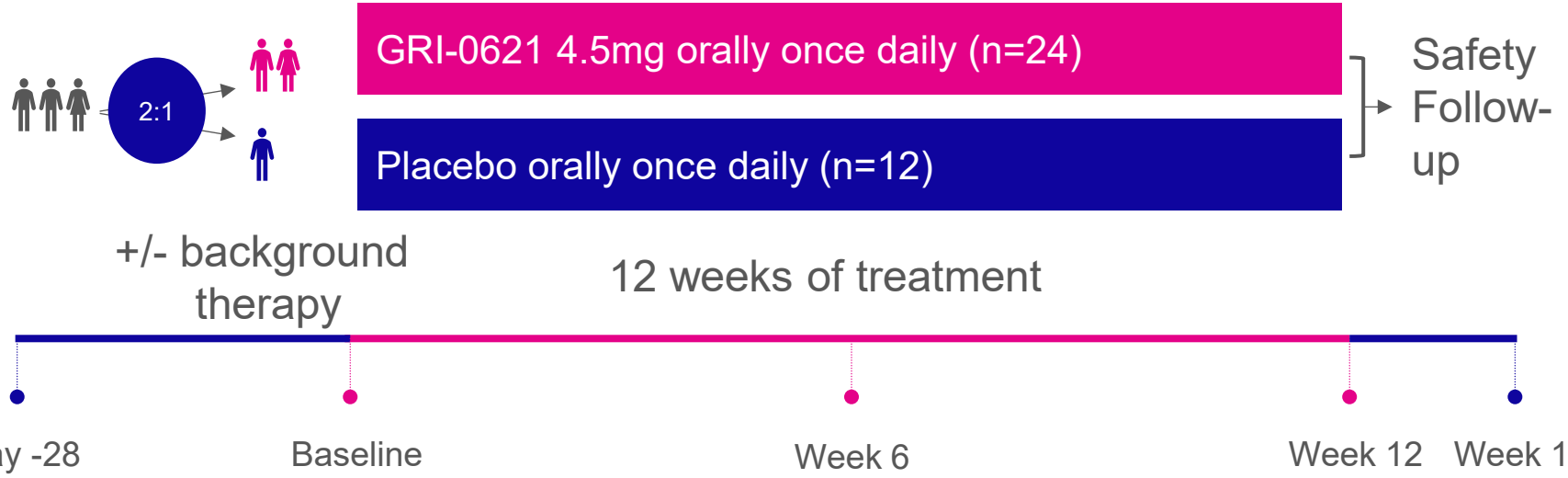
CD244+CXCR6+ iNKT cells are circulating in peripheral tissues, including lung



KEY INCLUSION CRITERIA

1. Men or women 40-85 yrs
2. Confirmed IPF diagnosis
3. FVC > 50% predicted
4. FEV1/FVC > 0.65
5. DLCOc > 30% predicted
6. Life expectancy of at least 12-months
7. Subjects on approved IPF therapy must remain on their current medication from Screening until the last study visit

Ongoing Phase 2 Study in IPF



Interim Analysis

iNKT inhibition, biomarker change from baseline and pulmonary function

PRIMARY & SECONDARY ENDPOINTS

- Safety, tolerability and PK
- Biomarkers change from baseline
- To determine the PD activity of oral GRI-0621 as measured by inhibition of iNKT cell activation in blood after 6 & 12 weeks and from BAL after 12 weeks of treatment in a sub-study

EXPLORATORY ENDPOINTS

Effect of GRI-0621 on pulmonary function (FEV1, FVC and FEV1/FVC ratio) at baseline and after 6 and 12 weeks of treatment

GRI-0621-IPF-02 Biomarker Analysis

iNKT cell activity as a PD biomarker for fibrotic disease

Serum biomarkers change from baseline

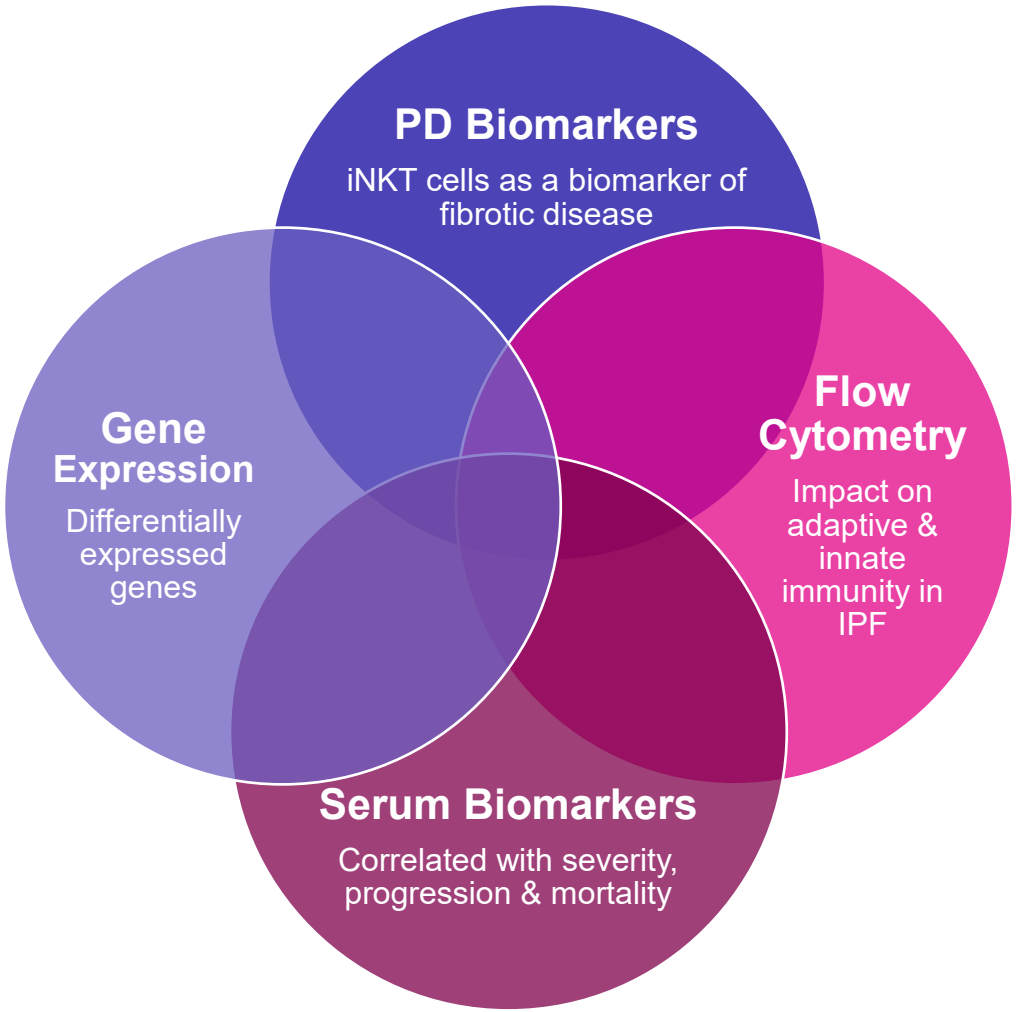
- PRO-C3, PRO-C6, C1m, C3M, C6M, VICM, CPa9-HNE, PRO-C4, CT-III, ELP-3, and C4Ma3

Flow Cytometry

- B cells, CD4/CD8 T cells (Th1, Th2, Th17, Treg), $CD56^{+}$ T cells (iNKT, MAIT, $\gamma\delta$ T), NKT1, NKT2, NKT17, circ & tissue-resident iNKT, NK, monocytes, MØ, eosinophils, and neutrophils

Gene Expression

- Genes associated with iNKT cell activity, adaptive & innate immunity, tissue remodeling, fibrosis, and IPF progression



Summary of iNKT cell involvement in Fibrosis

- iNKT cells have an activated phenotype in MASH & IPF patients and correlate with progressive disease
- Enhanced iNKT activity correlates with progression of fibrosis in MASH patients and with macrophage accumulation and key proinflammatory genes in BAL from IPF patients
- iNKT cells are activated and accumulate in liver and lung in experimental fibrosis models
- iNKT promote Type 1, Type 2 and Type 3 immune pathways involved in fibrosis
- iNKT-deficient mice have reduced inflammatory damage and fibrosis
- Daily oral administration of GRI-0621 in experimental animals
  - Inhibits key pro-inflammatory cytokines and inflammation
  - Decreases accumulation of neutrophils and proinflammatory macrophages
  - Inhibits key fibrogenic cytokines including TGF-β
- Phase 2 study with GRI-0621 in IPF patients to examine iNKT activity along with key biomarkers, differential gene expression, flow cytometry and pulmonary function

A New Approach to Inflammatory Diseases

Thank You!

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