Technische Universität München

Macrophage-targeted RNA therapeutics

27th DGRA Annual Congress
May 8th -9th, 2025
Bonn

Stefan Engelhardt
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Technical University of Munich (TUM)

Acknowledgement and disclosures

Christina Beck, PhD

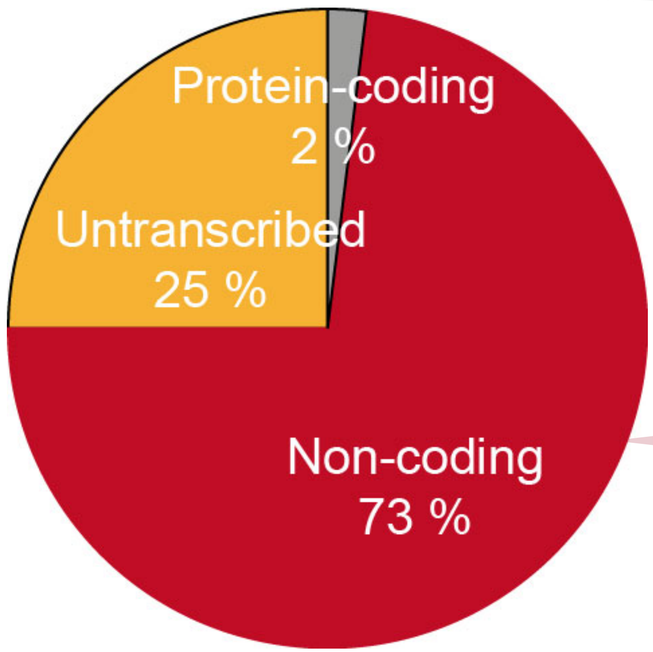
Deepak Ramanujam, PhD

Disclosures

TUM filed patent application on therapeutic use of carbohydrate-coupled inhalation RNA therapeutics

RNATICS GmbH (Founder)

RNAs as drug targets



Human genome
% transcribed)

Current state of drug development

- Approx. 2700 drugs approved
- Directed against approx. 650 proteins
- Further 2500-4500 proteins considered druggable
- Development costs >1 billion/drug approved

Nucleic acid/RNA therapeutics

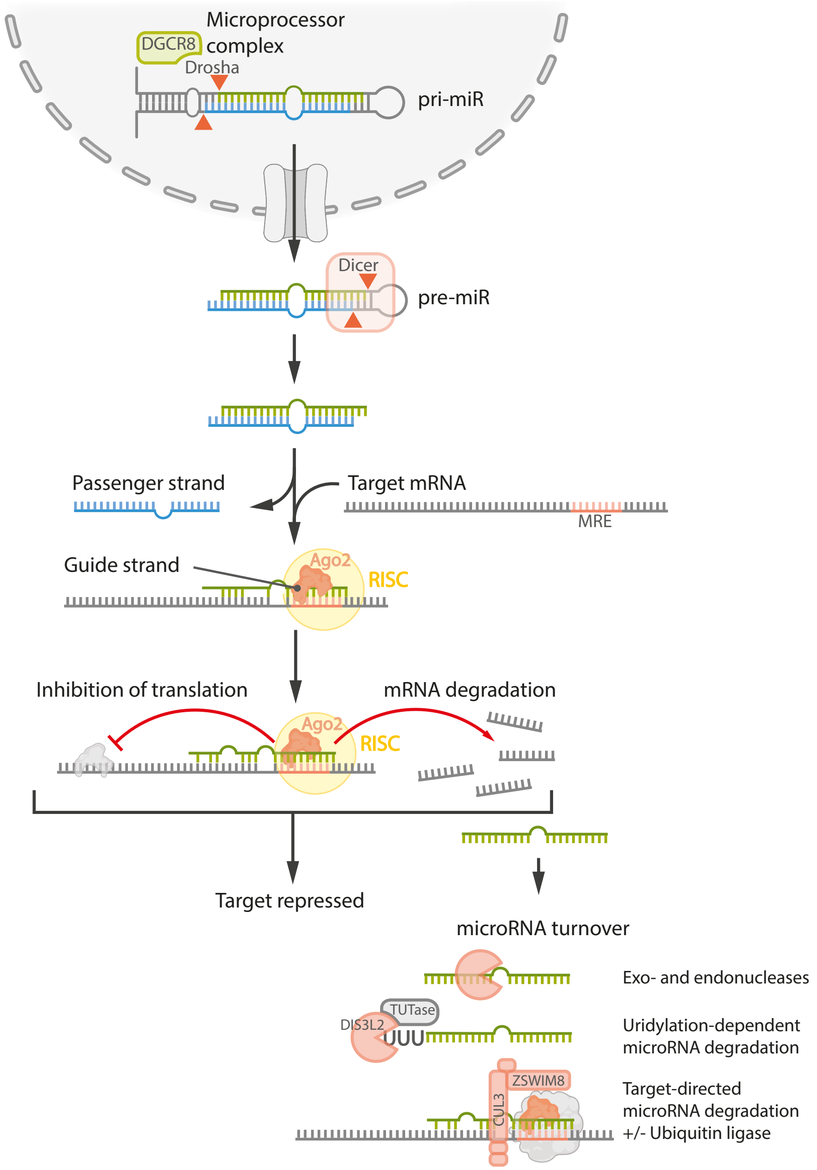
In principle: all proteins druggable as mRNAs

Plus > 20.000 ncRNAs

Long non-coding RNAs (lncRNAs) > 30,000
- Long intervening (lincRNAs)
- Intronic
- Natural antisense (NATs)
- Enhancer (eRNAs)
- Circular (circRNAs)

Short non-coding RNAs
- micro (miRNAs)
- structural (rRNAs, tRNAs)
- other (Y, pi, sno etc.)

MicroRNAs are pervasive regulators of gene expression



- Small, single-stranded, non-coding RNA molecules (approx. 21-22 nt)
- >2000 miRNAs suggested (500-700 functional)
- MiRNAs base-pair with complementary sequences within the 3'UTR of mRNA molecules (targets - targetome)
- Induce degradation or translational silencing of target mRNAs
- up to 50% of human mRNAs are regulated by miRNAs

Laggerbauer & Engelhardt. *J Clin Invest* 2022

Background to antimiR-21 as therapeutic strategy in inflammatory tissue fibrosis

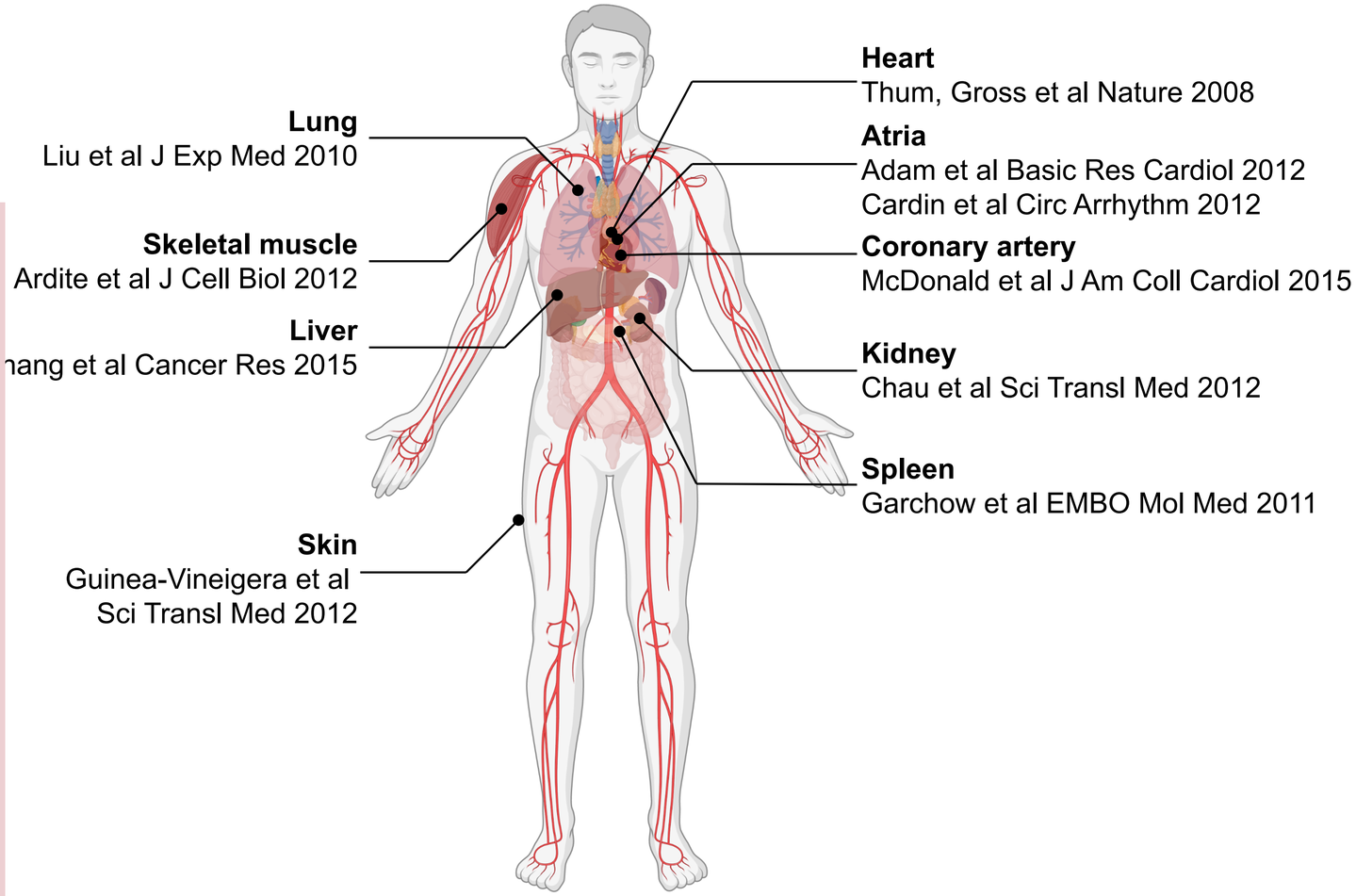
LETTERS

MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts

Thomas Thum[1,2]*, Carina Gross[3]*, Jan Fiedler[1,2], Thomas Fischer[3], Stephan Kissler[3], Markus Bussen[5], Paolo Galuppo[1], Steffen Just[6], Wolfgang Rottbauer[6], Stefan Frantz[1], Mirco Castoldi[7,8], Jürgen Soutschek[9], Victor Koteliansky[10], Andreas Rosenwald[4], M. Albert Basson[11], Jonathan D. Licht[12], John T. R. Pena[13], Sara H. Rouhanifard[13], Martina U. Muckenthaler[7,8], Thomas Tuschl[13], Gail R. Martin[5], Johann Bauersachs[1] & Stefan Engelhardt[3,14]

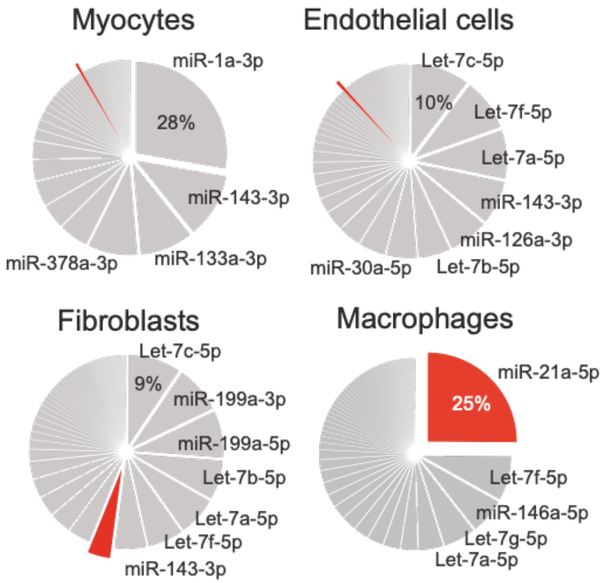
miR-21 drives inflammatory tissue fibrosis in many organs

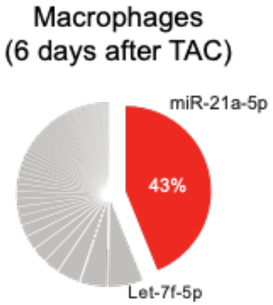
- miR-21 generally upregulated in organ fibrosis
- Pharmacological and genetic inhibition of miR-21 prevents fibrosis

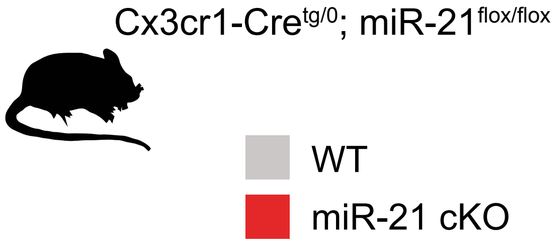


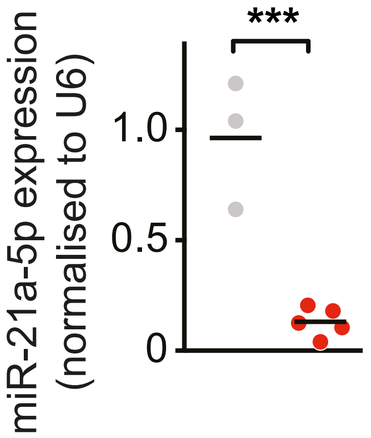
Thum*, Gross* et al. *Nature* 2008; Thum et al. *J Clin Invest* 2011; Ramanujam et al. *Mol Ther* 2016; Hinkel et al. *JACC* 2020

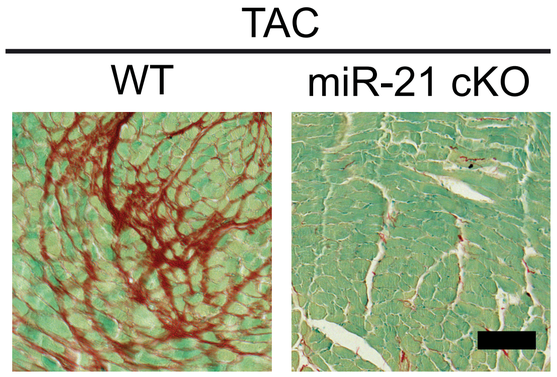
Genetic deletion of miR-21 selectively in macrophages prevents from cardiac fibrosis and heart failure in mice

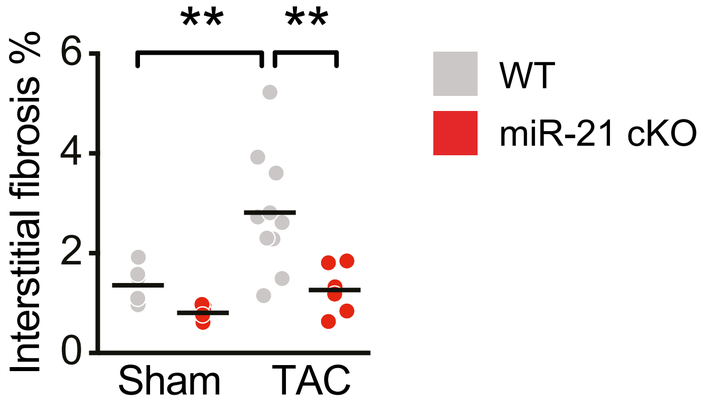






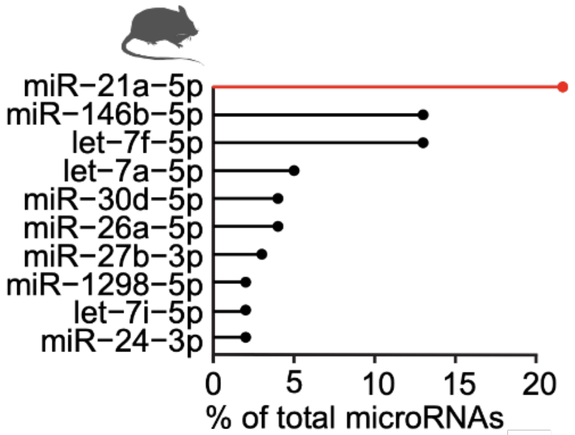


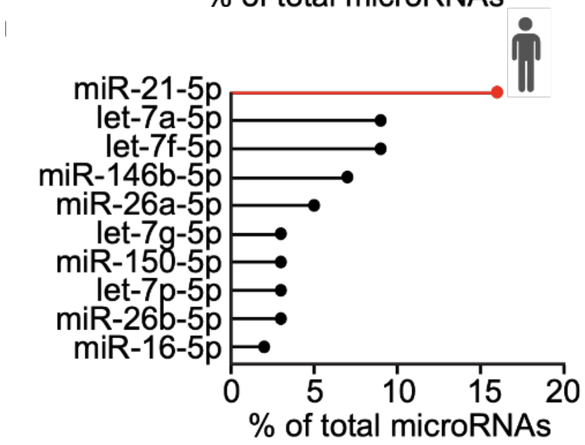




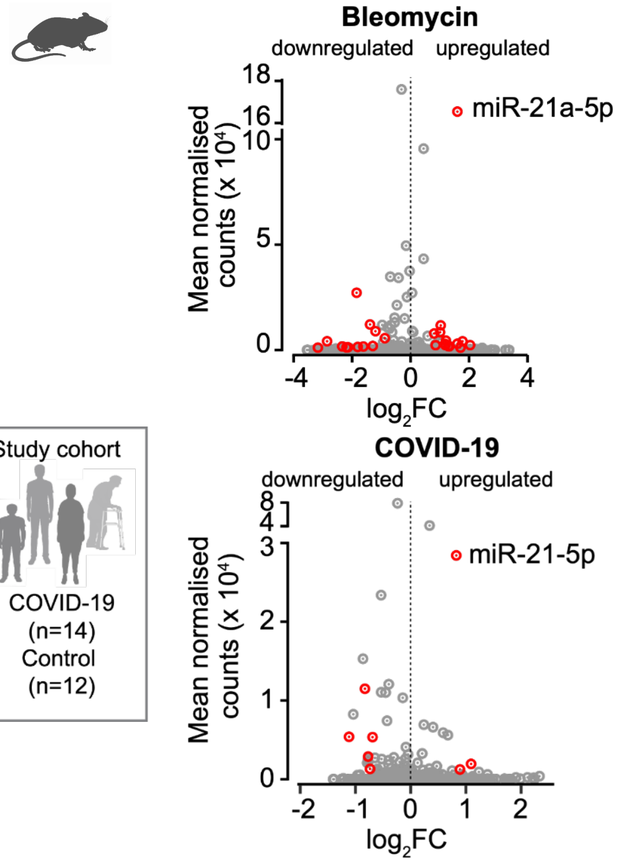
miR-21 in macrophages determines inflammatory lung damage

miR-21 is ..highest expressed miR in alveolar macrophages

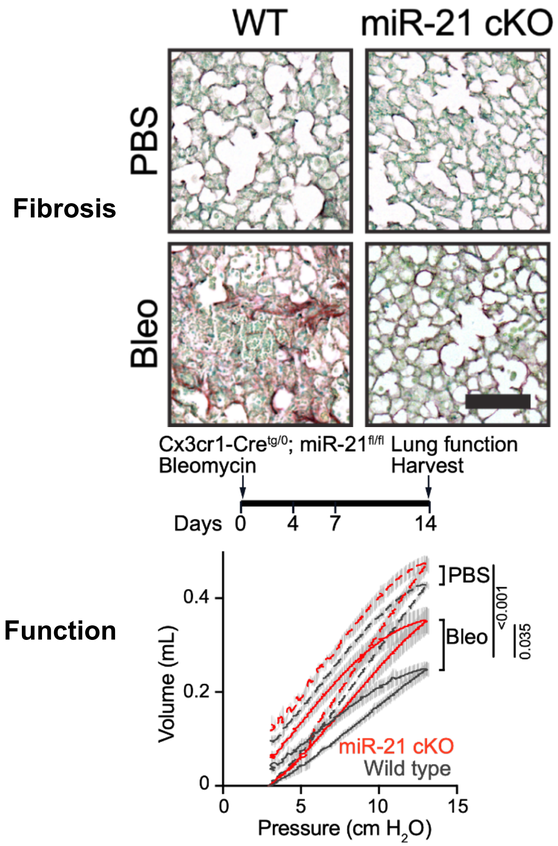




..upregulated in acute inflammatory lung diseases

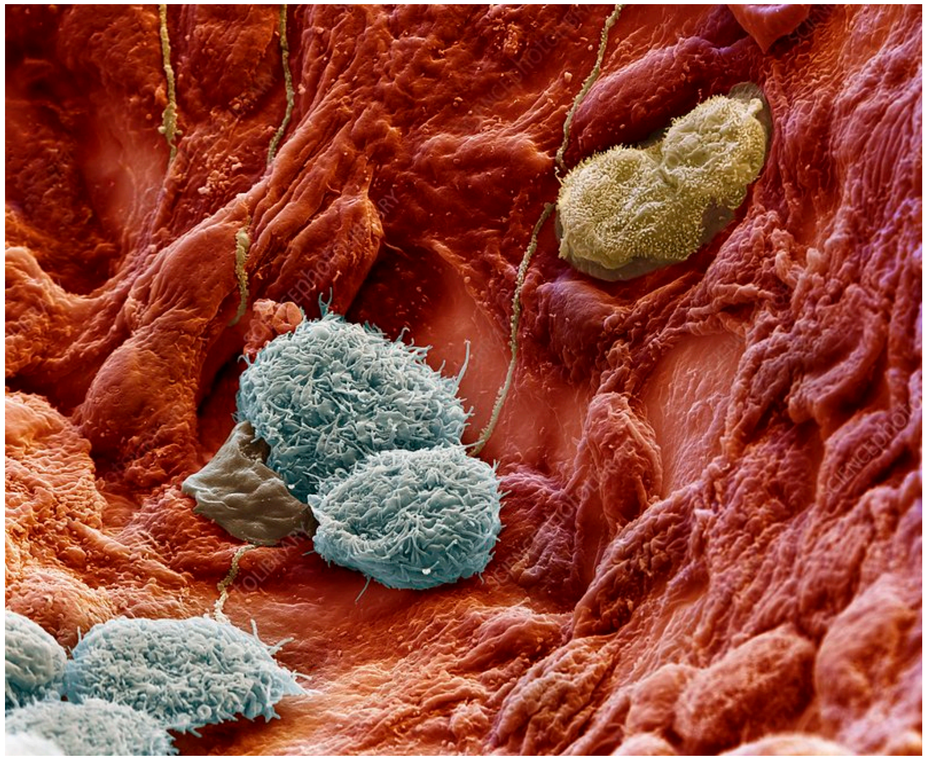


..required for pulmonary fibrosis and dysfunction



Beck, Ramanujam et al. *Nat Commun* 2023

Can we extend the spectrum of targeted oligonucleotide therapeutics to macrophages?



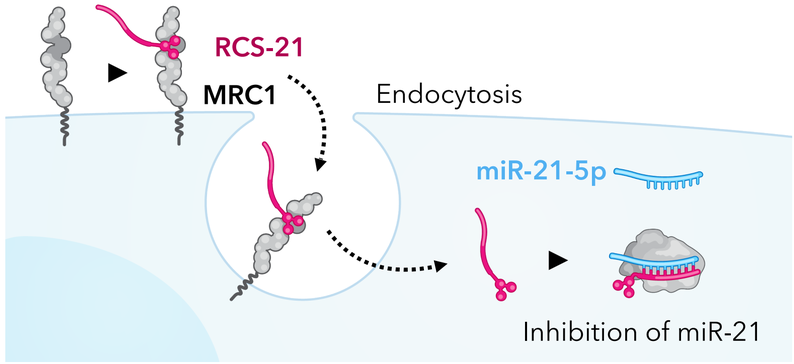
Credit: Science stock

Alveolar macrophages are key drivers of lung damage and fibrosis[1]

Role model: GalNac-coupling of siRNA for targeted delivery to hepatocytes (Alnylam)

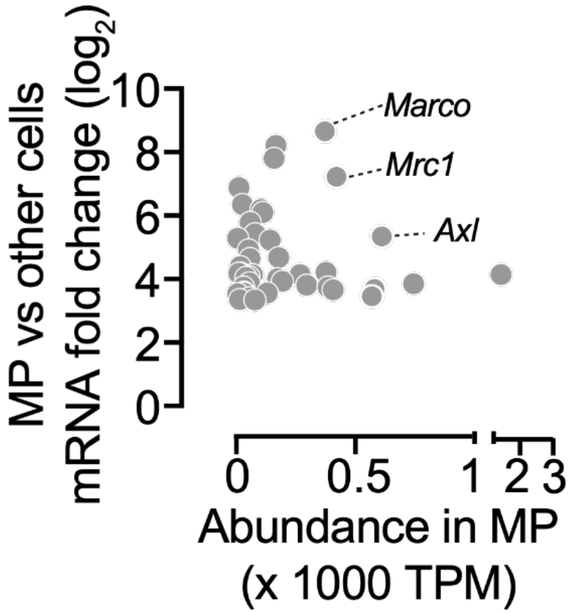
Alnylam® PHARMACEUTICALS

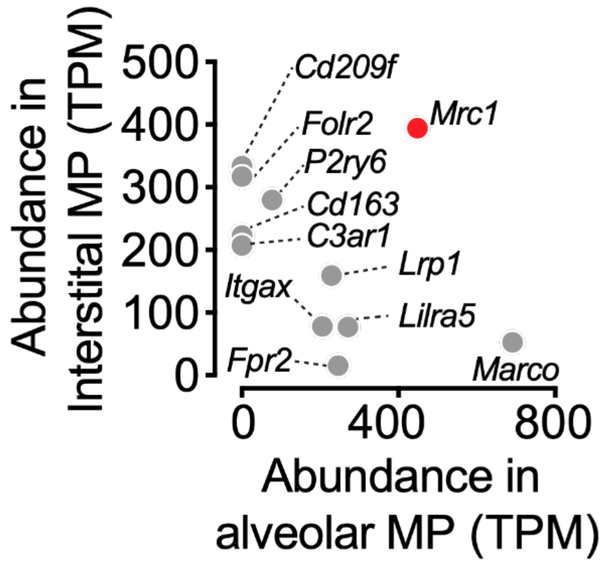
Solution: Trimannose carbohydrate-coupling for first-in-class, targeted delivery of RNA therapeutics to macrophages

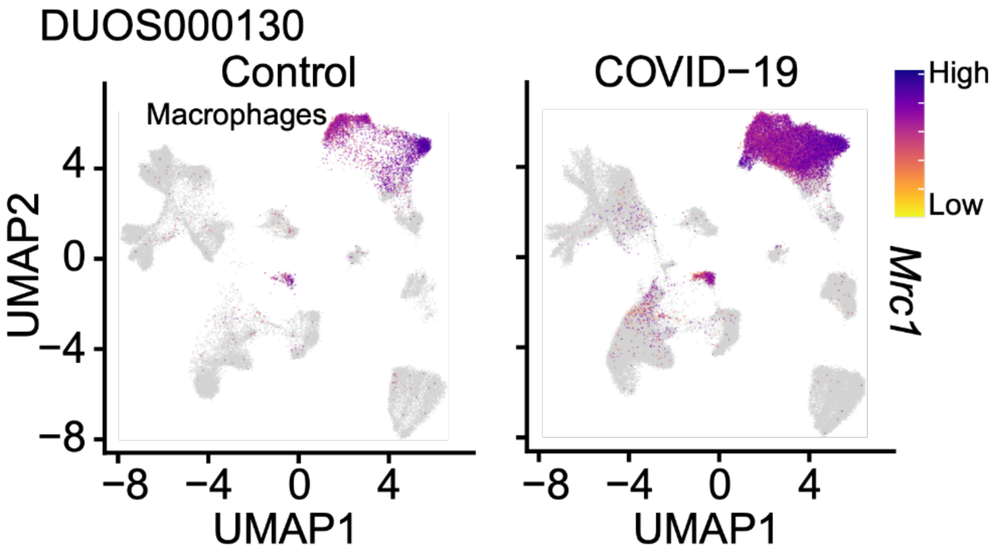


[1]COVID-19 scSeq studies: *Delorey et al, Nature 2021, Melms et al, Nature 2021, Wendisch et al, Cell 2021*

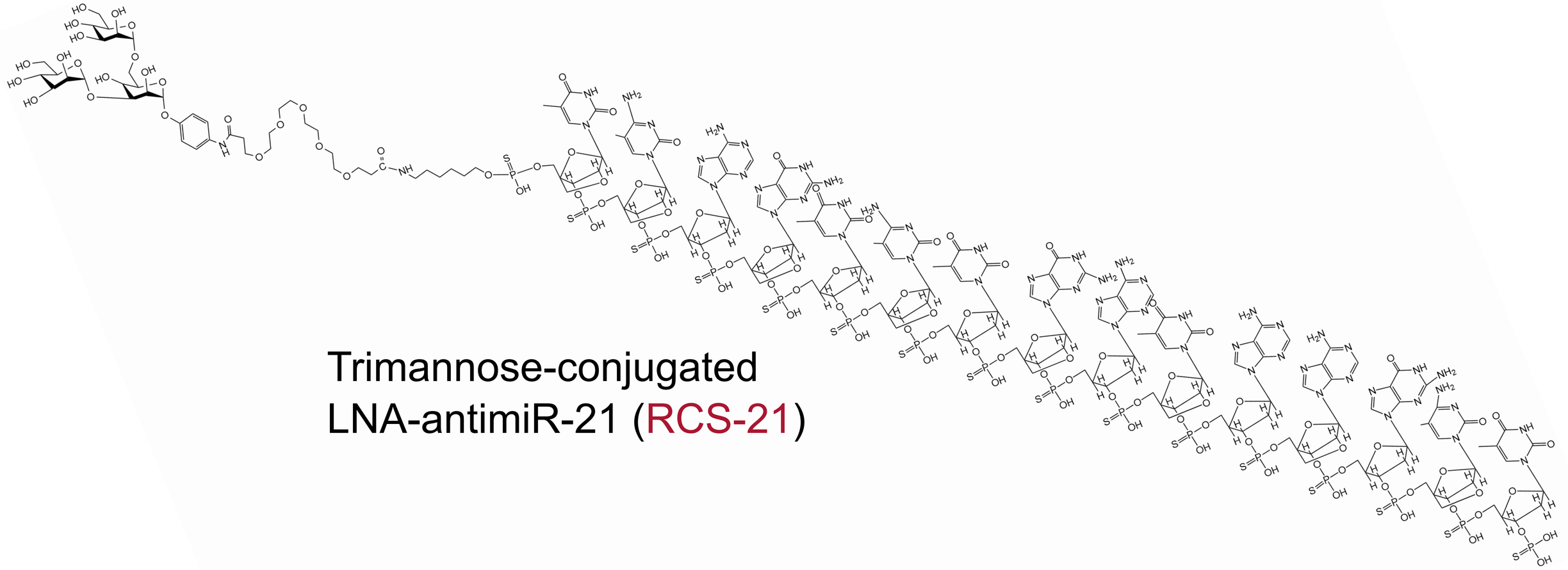
scRNA Seq-based stratification of cell surface receptors specific for macrophages







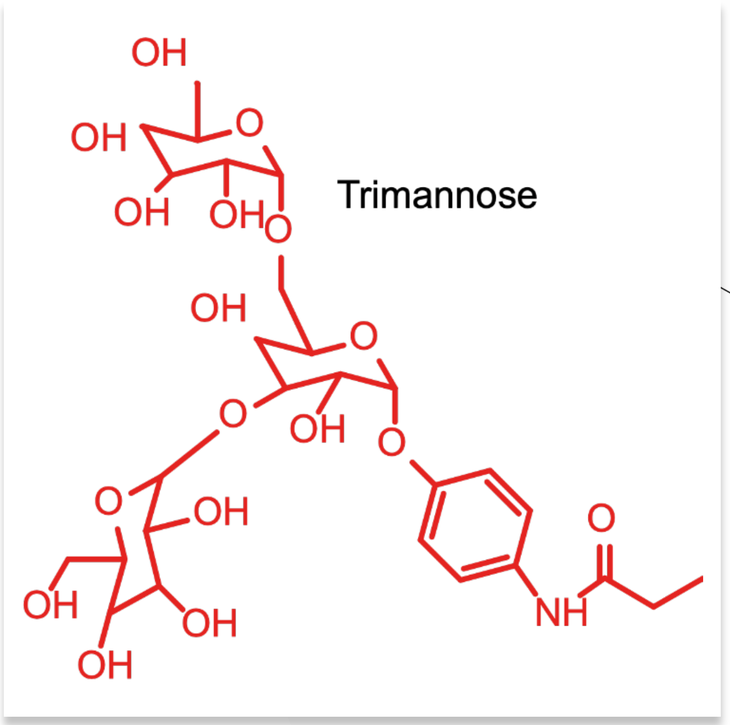
Trimannose-coupling for macrophage-targeted delivery of oligonucleotides

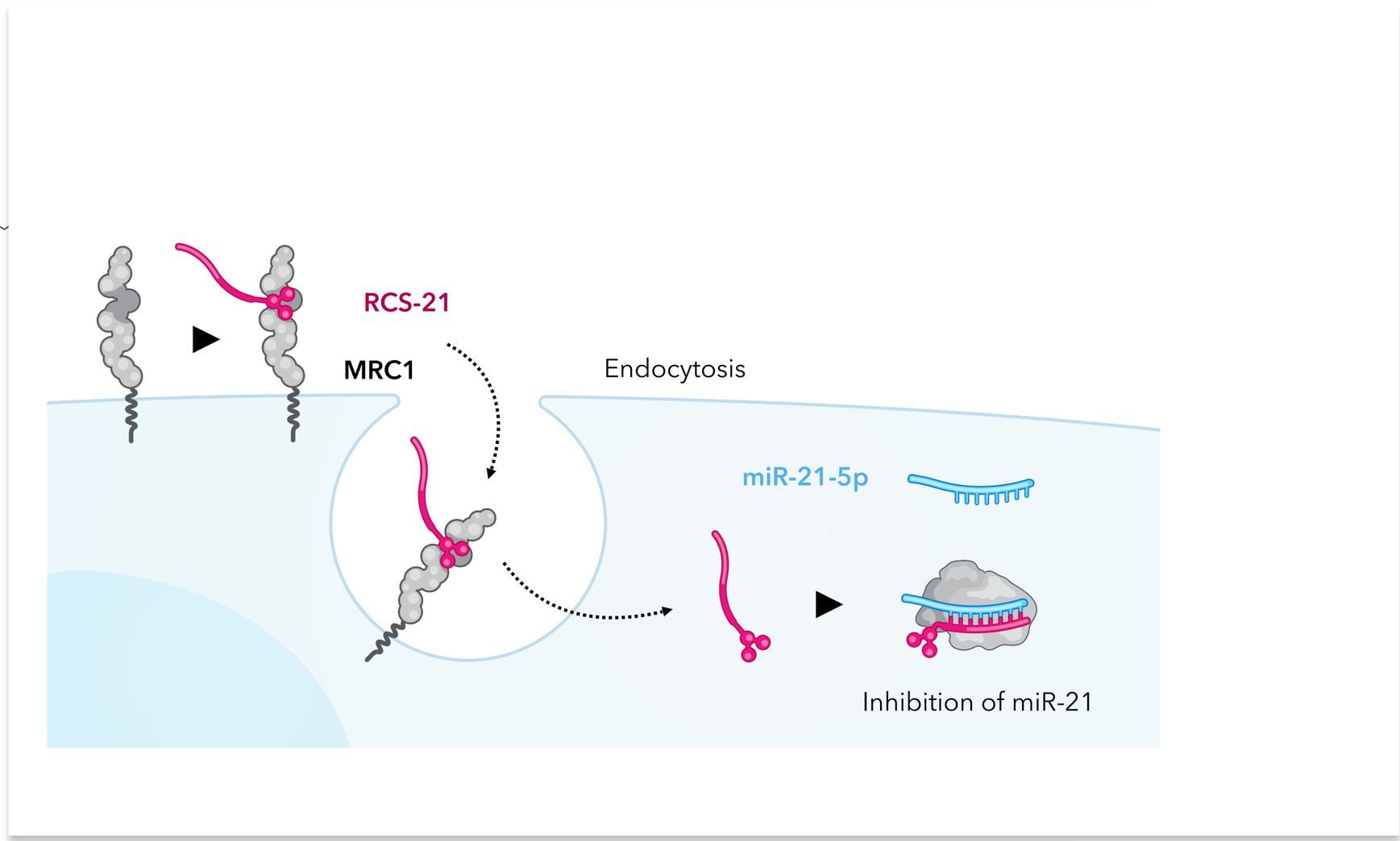


Trimannose-conjugated
LNA-antimiR-21 (RCS-21)

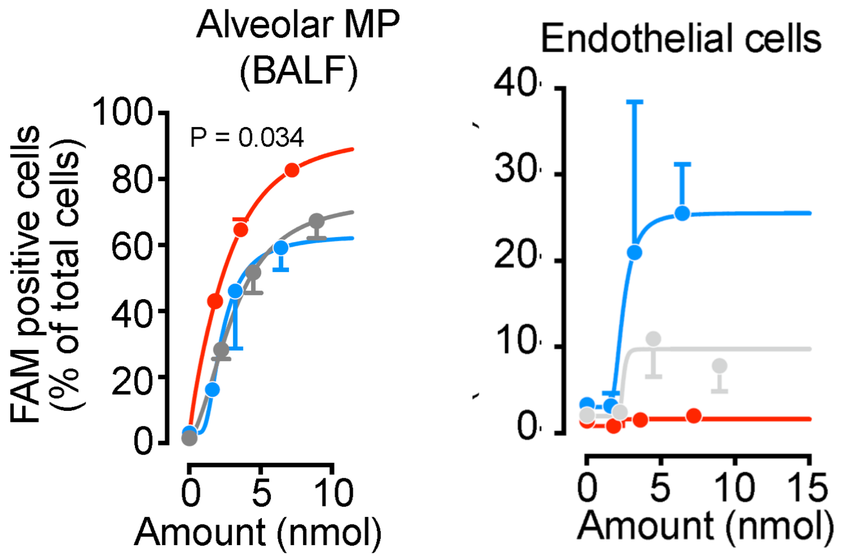
PCT/EP2021/059360

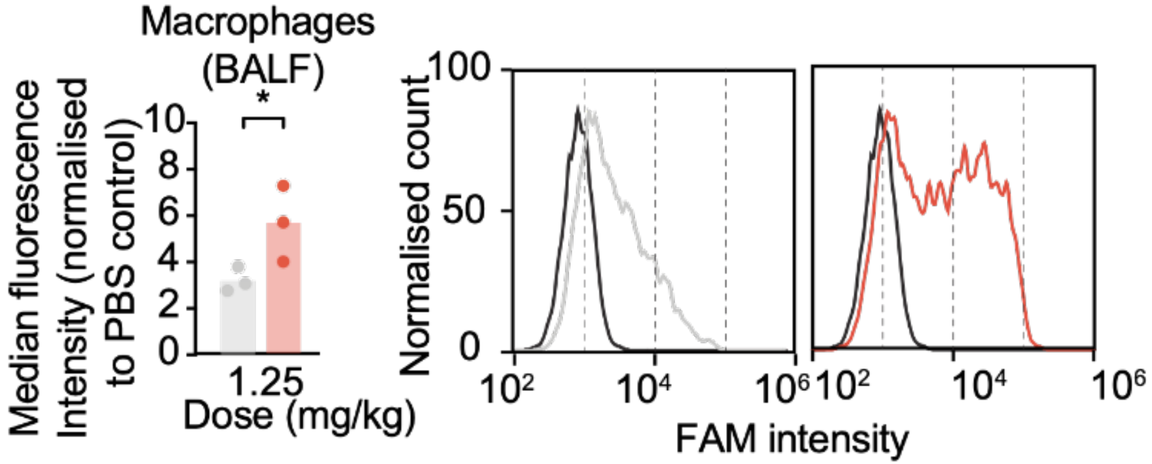
Trimannose-coupling for macrophage-targeted delivery of oligonucleotides

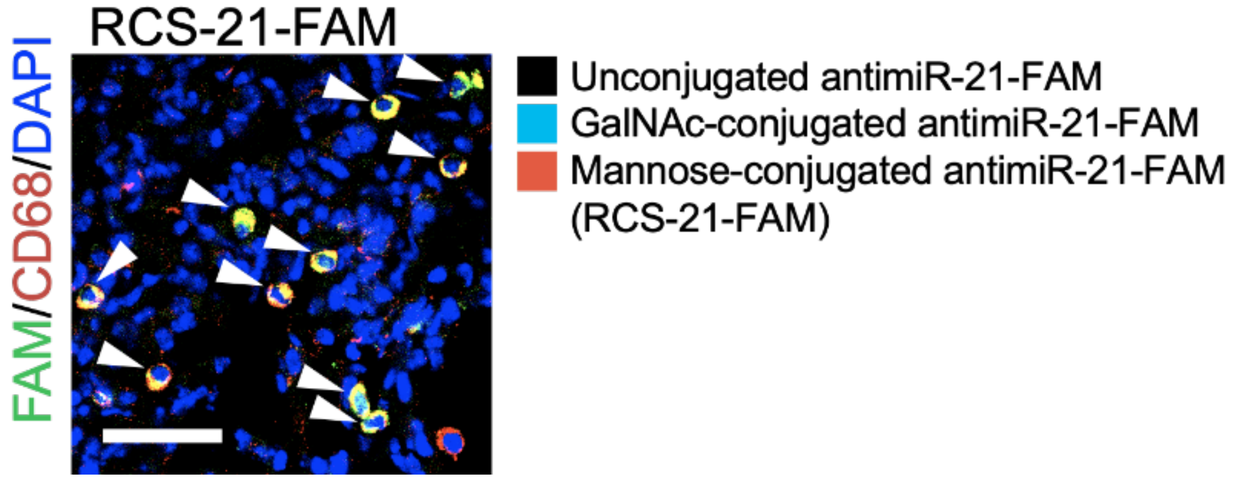




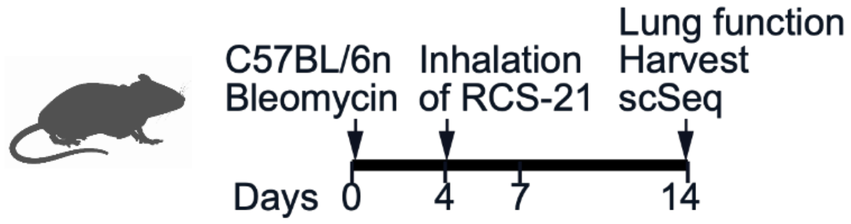
Delivery: inhaled macrophage-targeted antimiR-21 (RCS-21) achieves rapid and efficient delivery to pulmonary macrophages in vivo



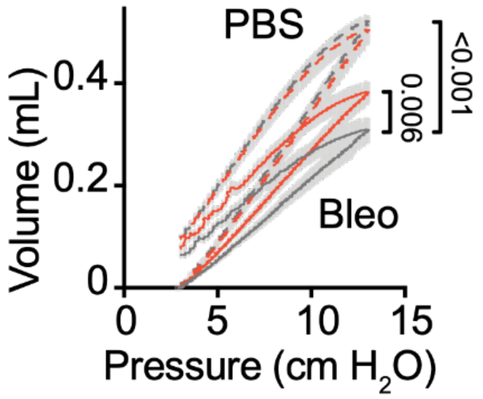




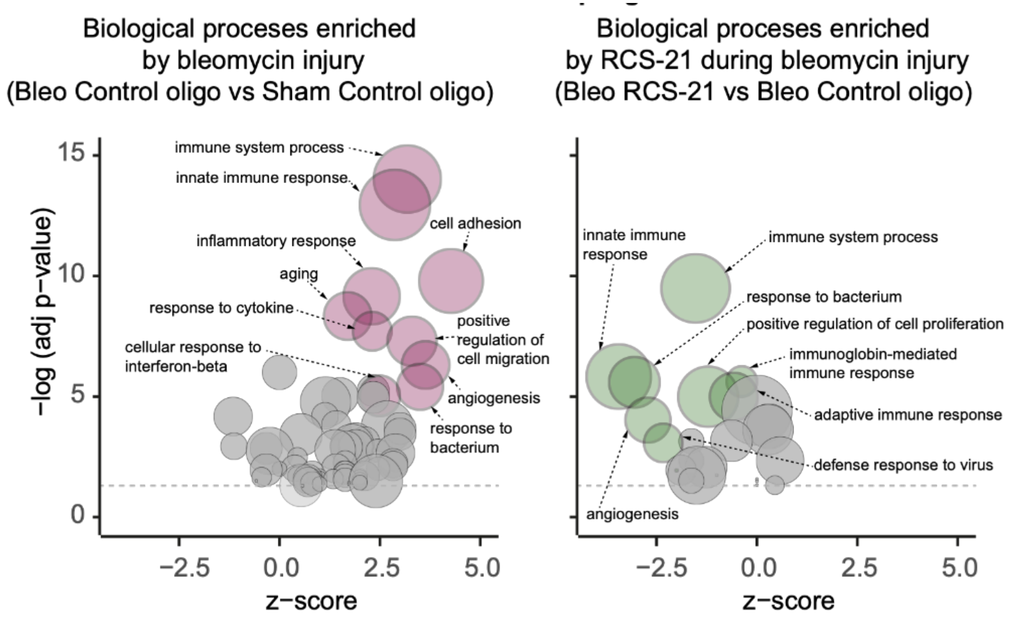
Therapeutic proof-of-concept: RCS-21 in acute inflammatory lung damage (bleomycin model)



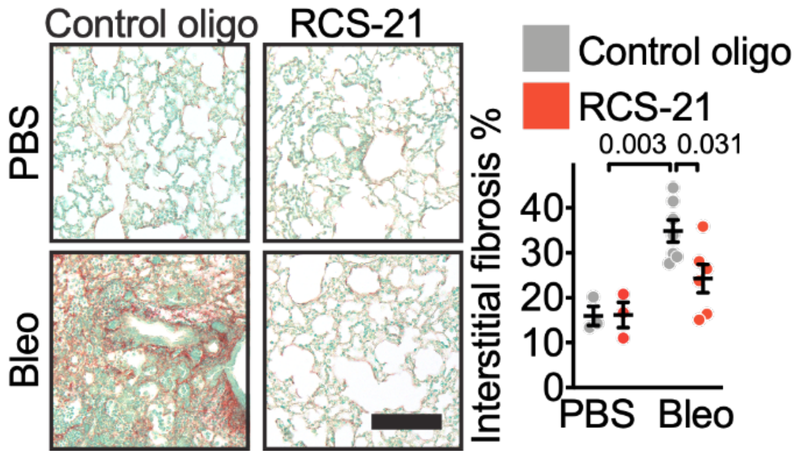
Pulmonary function



Macrophage transcriptome signature

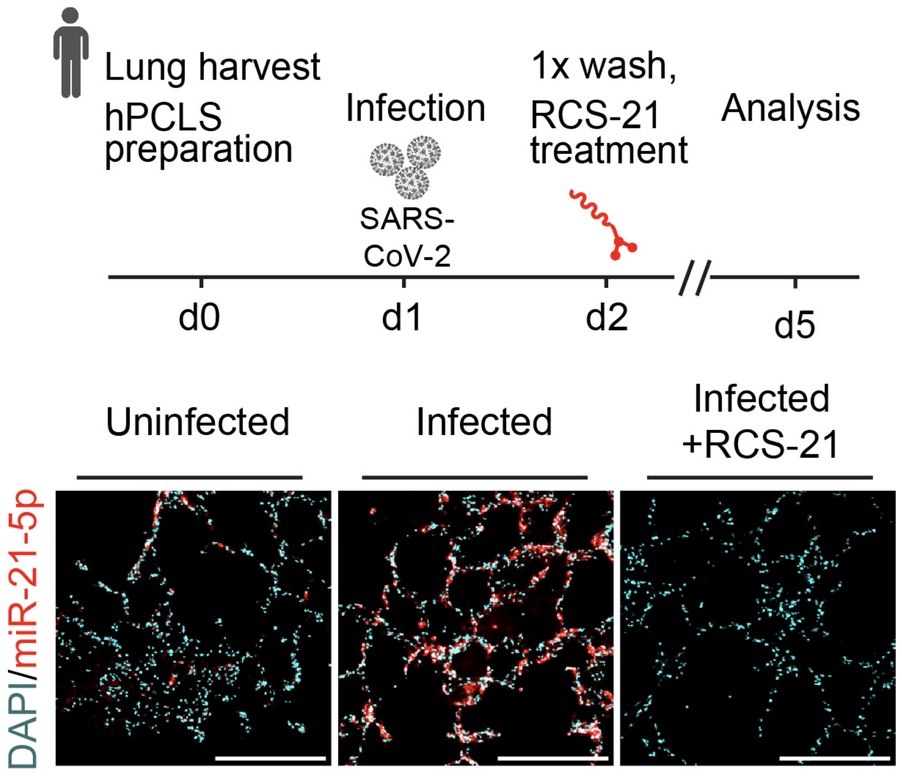


Pulmonary fibrosis

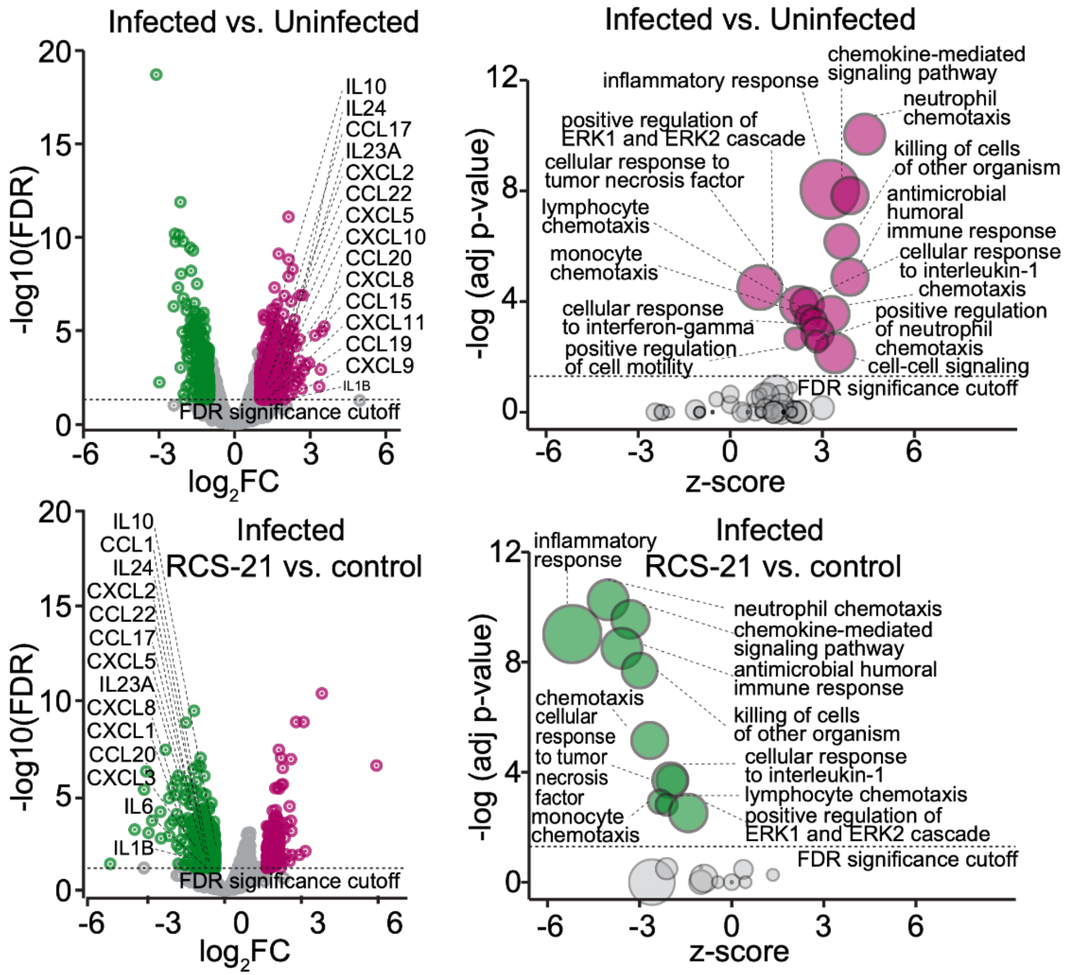


Beck, Ramanujam et al., *Nat Commun* 2023

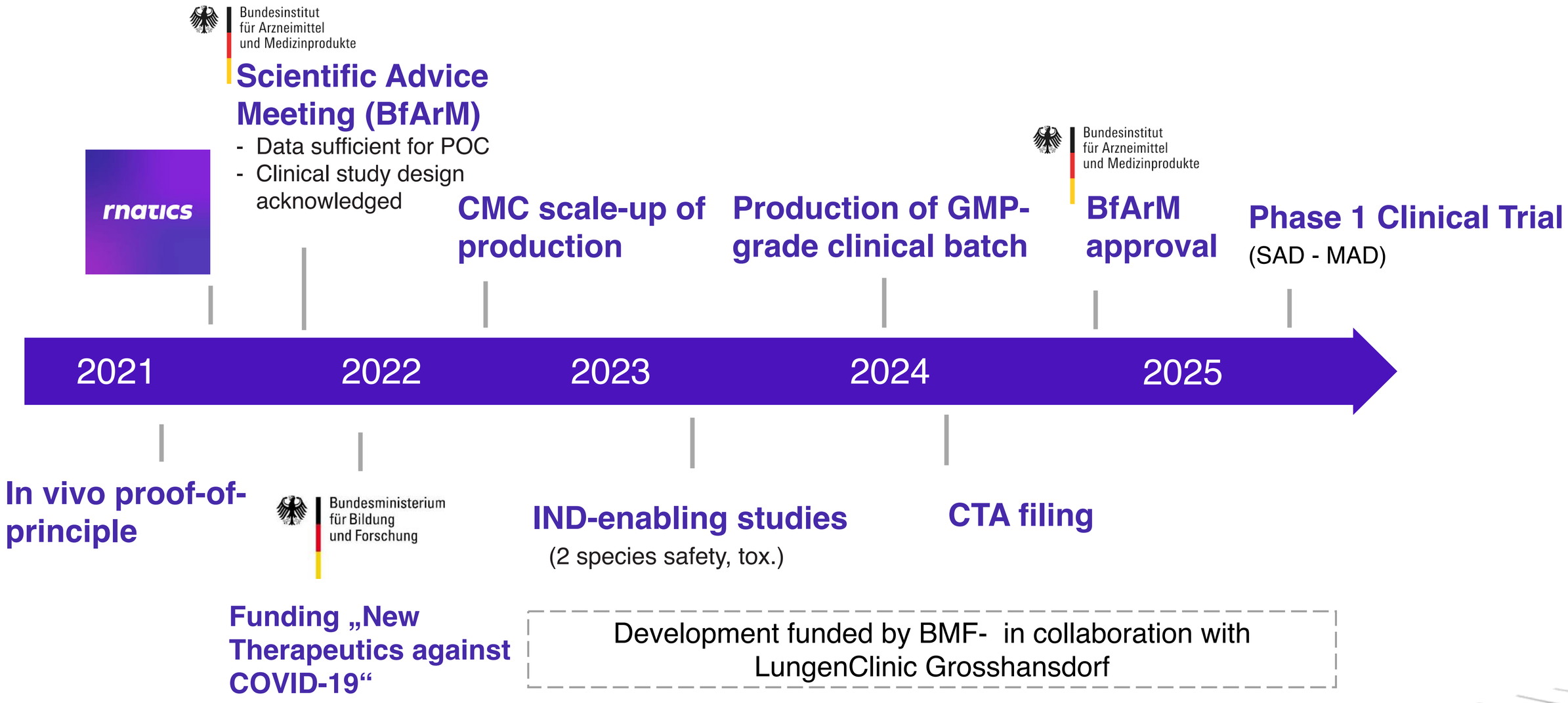
Human tissue: RCS-21 prevents the exaggerated inflammatory response to SARS-CoV-2 in human lung



Transcriptome signature



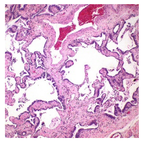
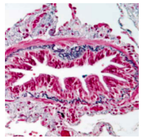
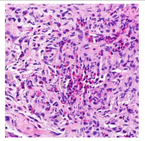
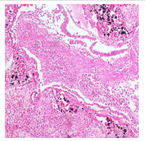
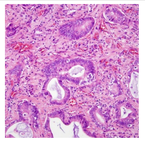
Development steps to bring RCS-21 into the clinic



Development funded by BMF- in collaboration with LungenClinic Grosshansdorf

Future strategy for anti-miR-21 therapy

We intend to address macrophage-dependent lung diseases in 5 areas :

	AREA	INDICATION		# OF PATIENTS[1]	DEVELOPMENT STAGE
1	Interstitial lung diseases	virus-triggered acute exacerbations (AE-ILD)		~95k yearly	
2	Chronic Obstructive Pulmonary Disease (COPD)	Exacerbating COPD		~4M yearly	
3	Orphan diseases	Pulmonary Histiocytosis		25k – 50k	
4	Viral infections	Influenza, RSV, COVID-19, other SARI		~1.2M yearly	
5	Lung cancer	Non-Small Cell Lung Cancer (NSCLC)		~600k yearly	

Direct to Phase II efficacy trial

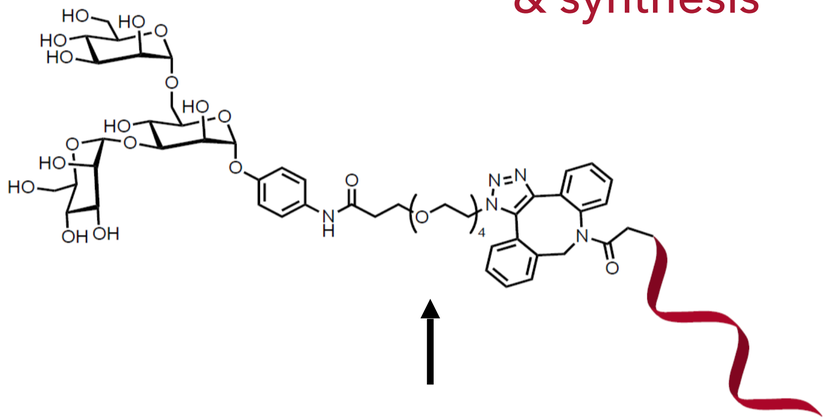
Discovery | Pre-clinical | Phase I | Phase II

- *We aim to establish miR-21 in macrophages as ubiquitous nexus of the inflammatory response*

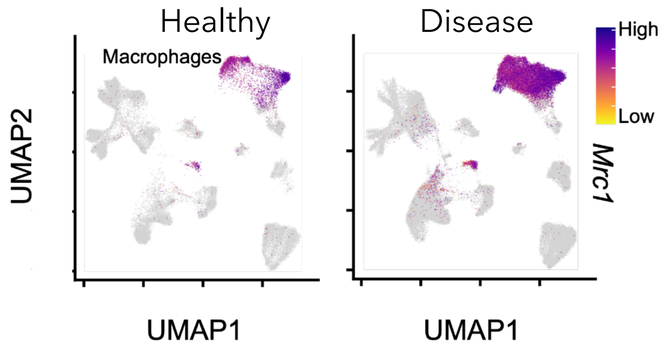
1 EU25+Switzerland, UK, Israel, North America, Australia/New Zealand/Japan

Summary: Trimannose-coupling of antisense oligomers to target macrophages

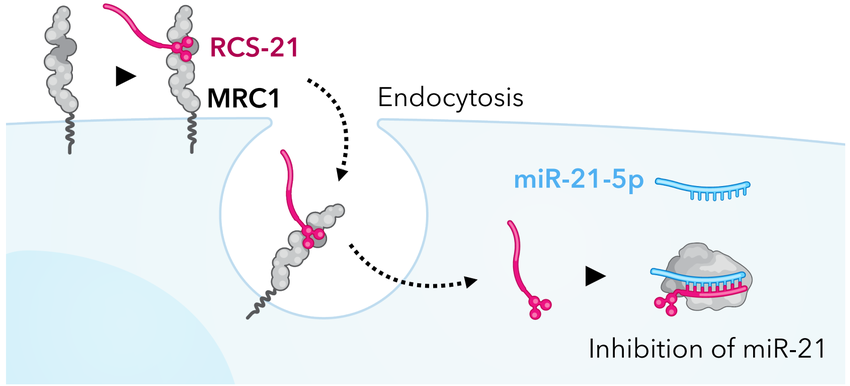
NA chemistry, lead optimization & synthesis



Receptor identification



Targeted delivery



A first-in-class, macrophage-targeted inhalation RNA therapeutic

rnatics

BfArM approval 11/2024
Phase 1 scheduled 2025

Acknowledgement

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CNATM Cluster for Nucleic Acid Therapeutics Munich

Cardiovascular ncRNA TRR 267

DZHK Deutsches Zentrum für Herz-Kreislauf-Forschung

Federal Ministry of Education and Research

ISAR BIOSCIENCE

Bayerische Forschungsstiftung