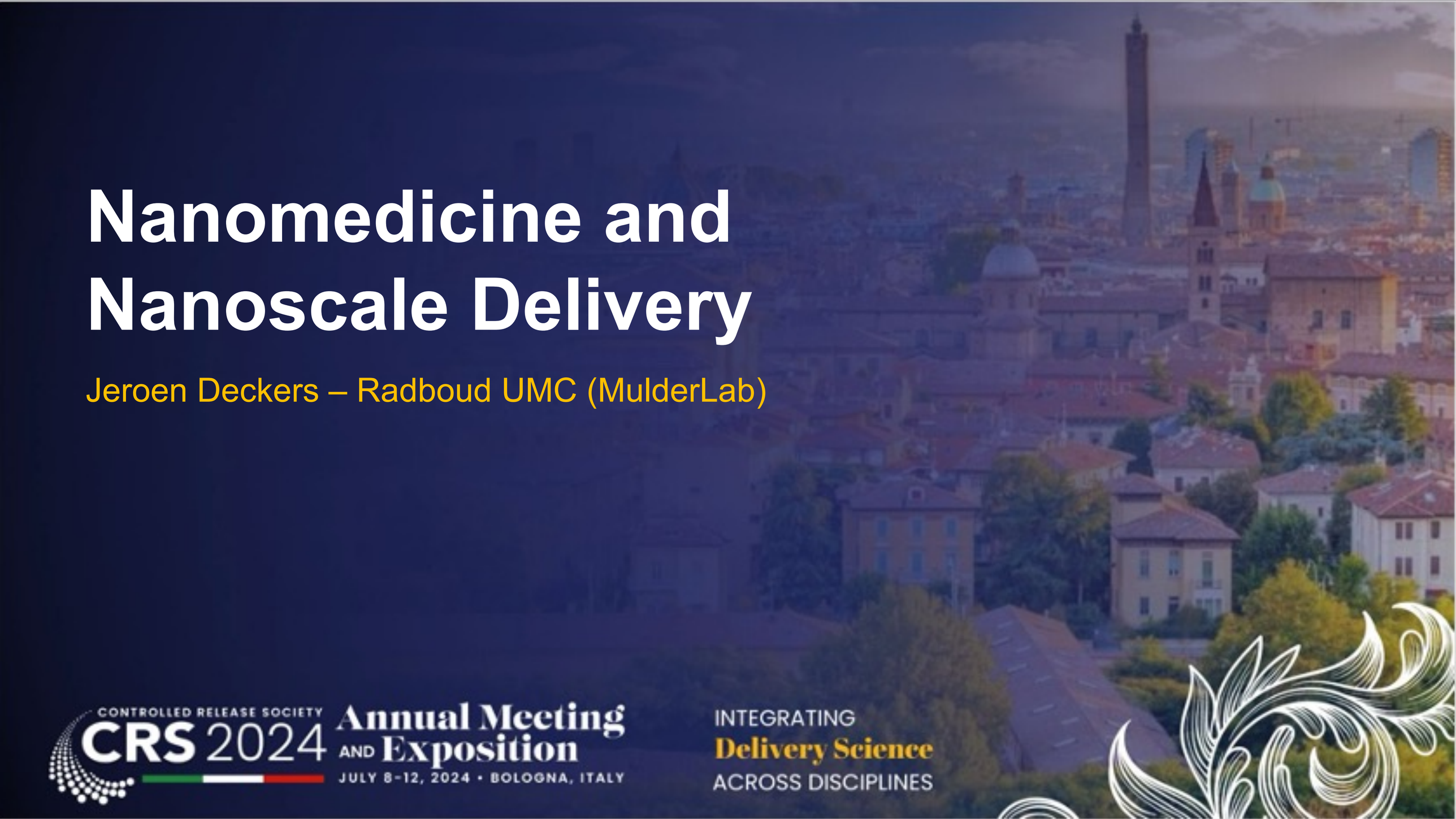
Nanomedicine and Nanoscale Delivery

Jeroen Deckers – Radboud UMC (MulderLab)



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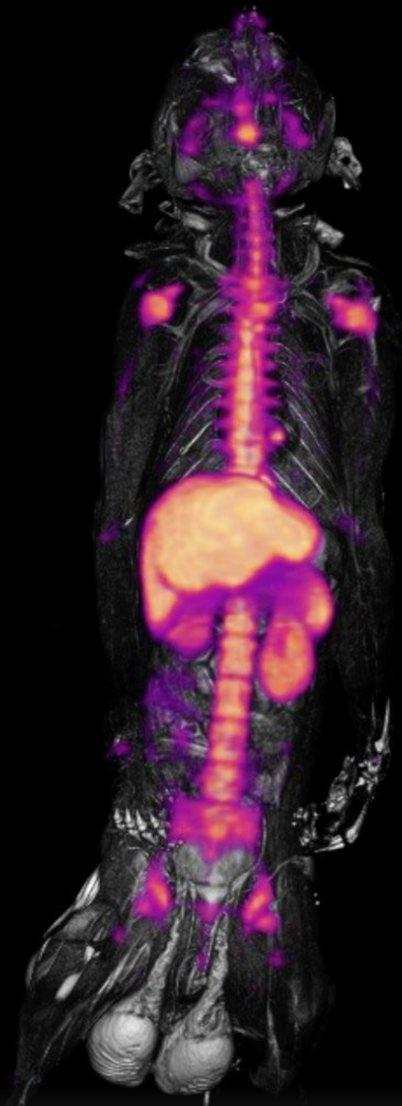
Resolving sepsis-induced immunoparalysis via trained immunity by targeting interleukin-4 to myeloid cells



Jeroen Deckers

PhD Candidate
Department of Internal Medicine
Radboud University Medical Center

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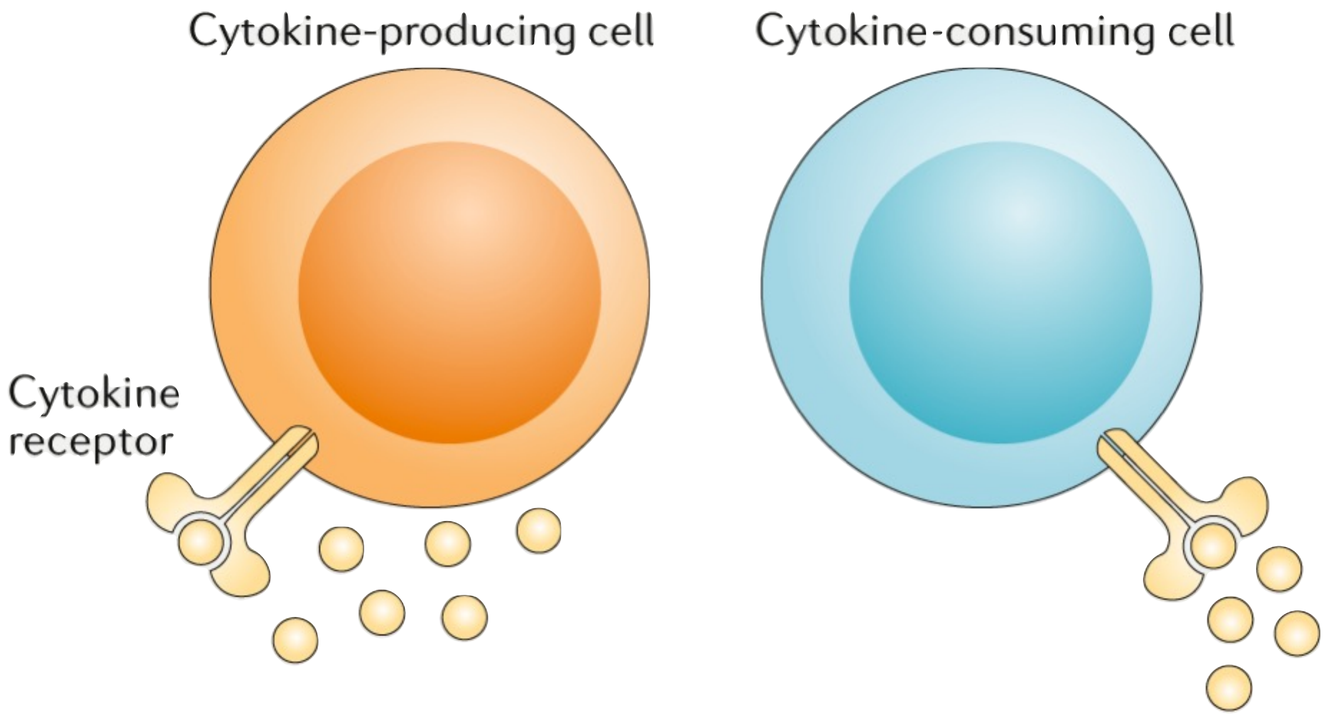
Radboudumc

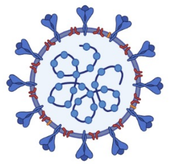
Cytokines are key regulators of host responses

Infection, immune responses, inflammation, and trauma

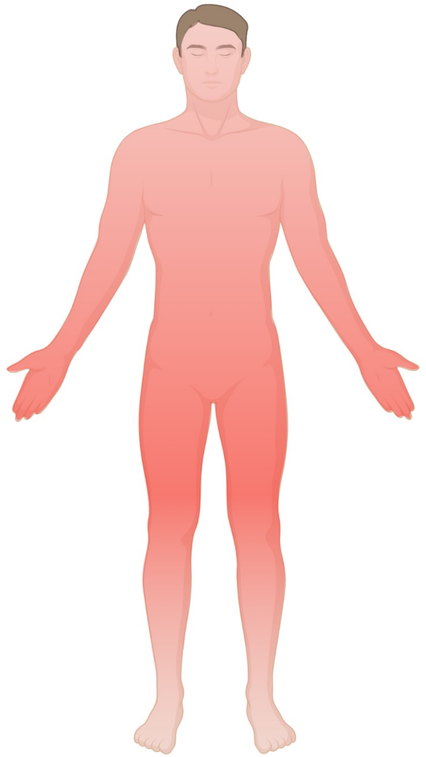


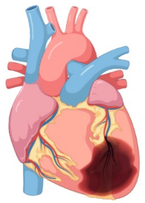
Altan-Bonnet, G., Mukherjee, R. *Nat Rev Immunol* (2019)

Hyperinflammation and immunoparalysis



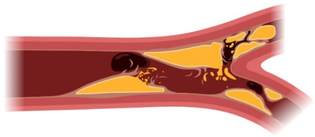
Covid-19





Myocardial infarction

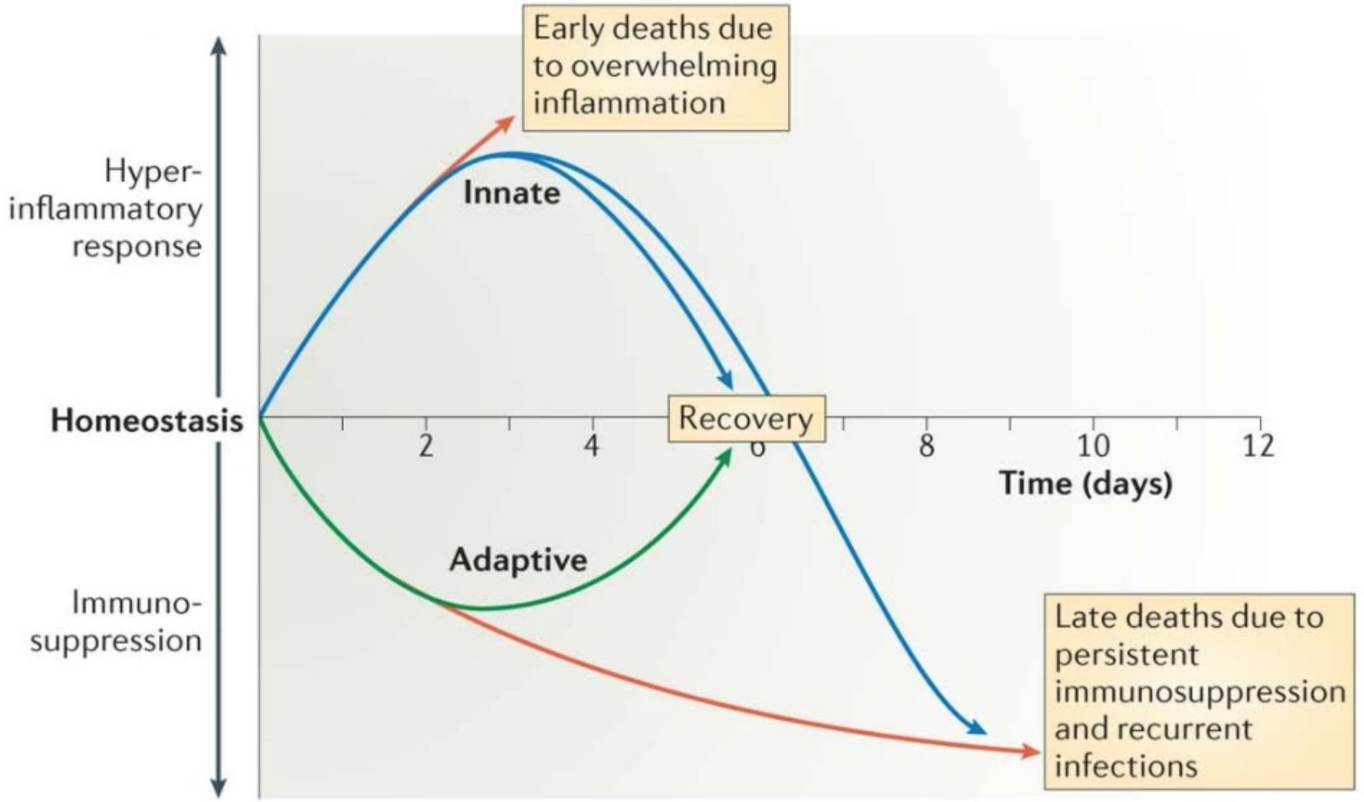
Stroke



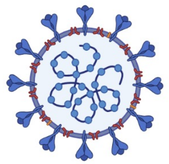
Trombosis

E. coli

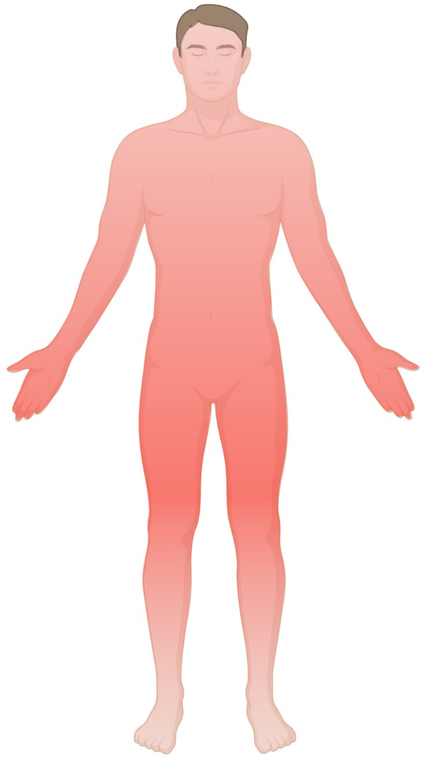
Staphylococcus

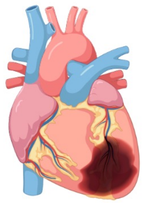


Hyperinflammation and immunoparalysis



Covid-19





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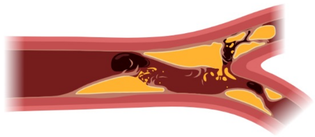
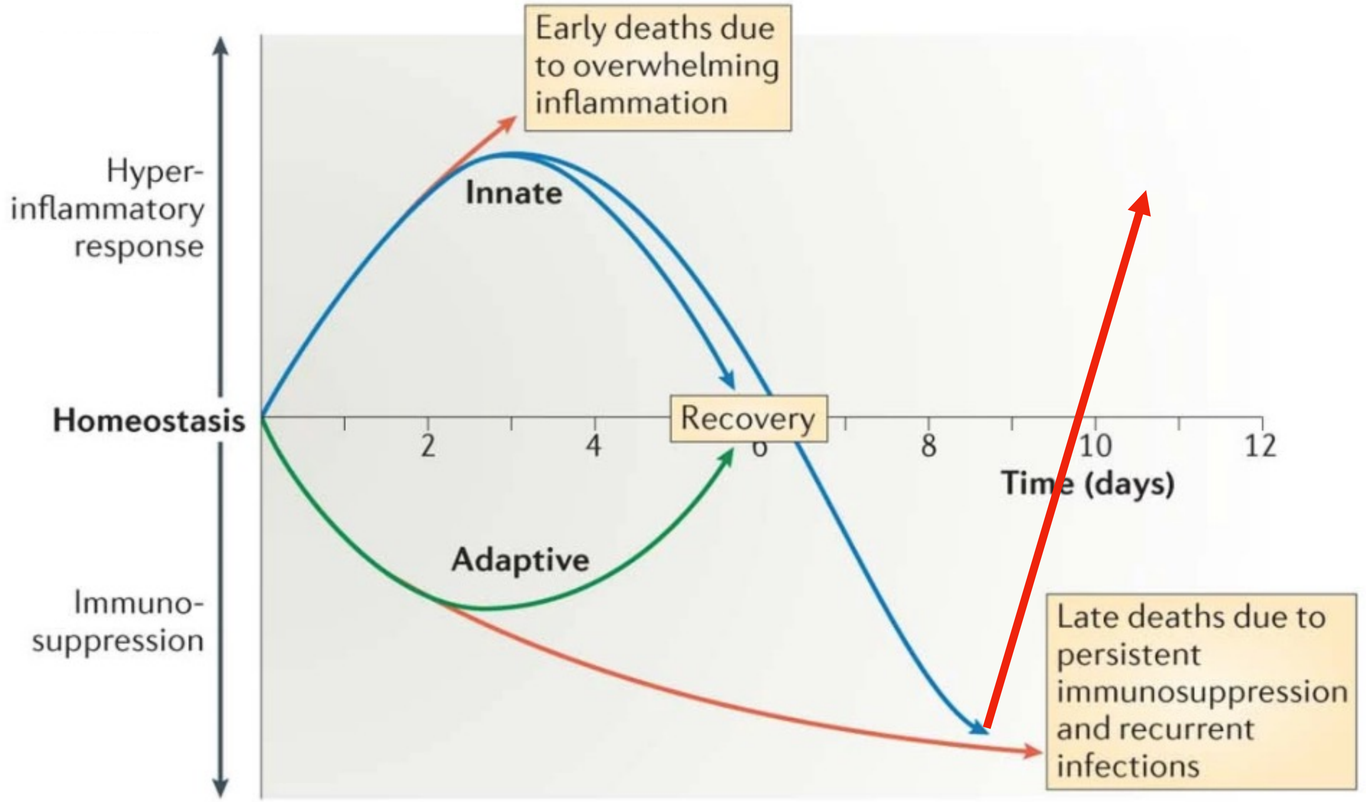
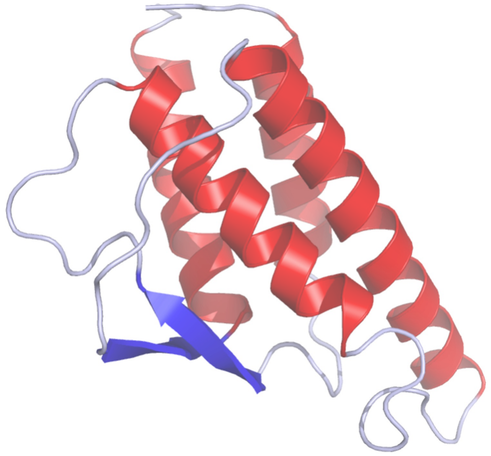


Trombosis

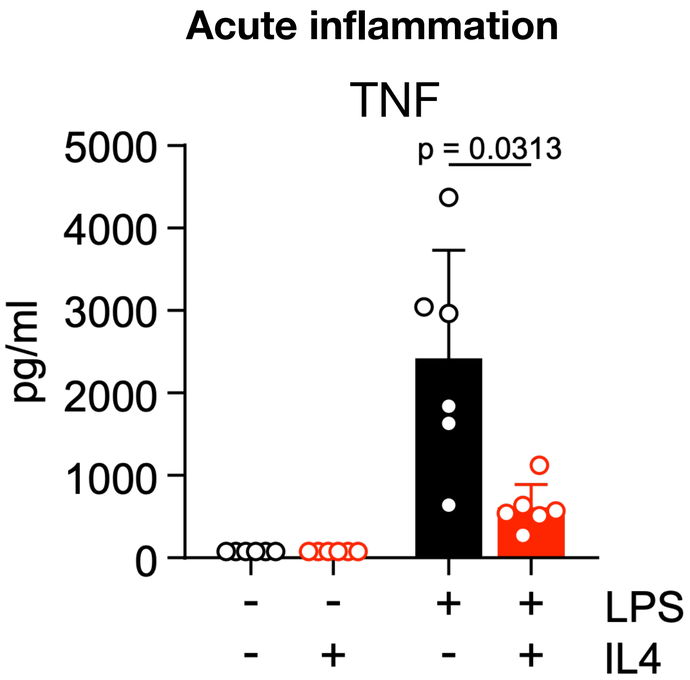


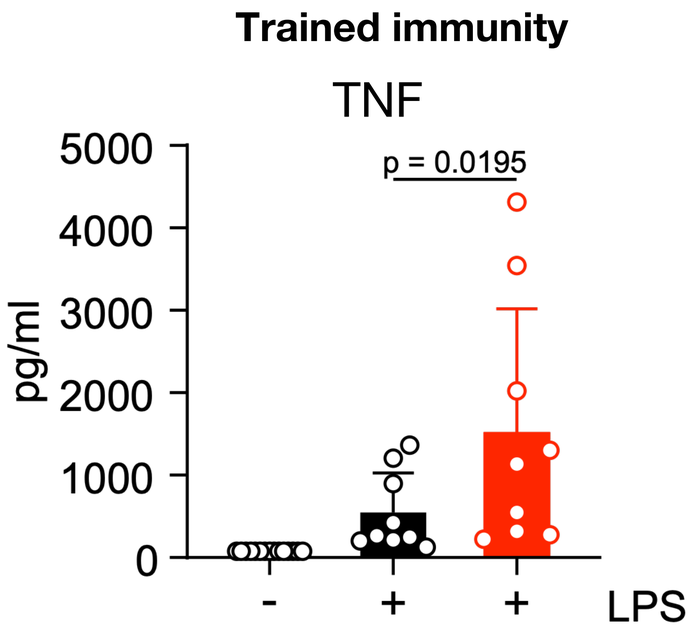
Interleukin-4



In a controlled *in vitro* context IL4 simultaneously

- Inhibits acute inflammation
- Induces trained immunity





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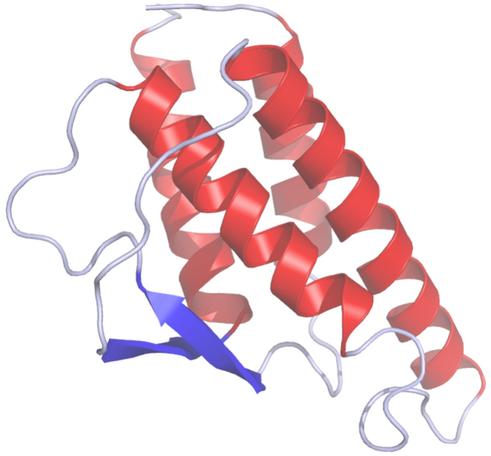
Schrijver D.P., Röring R.J. et al. Nat. Biomed. Eng (2023)

Interleukin-4



In a controlled *in vitro* context IL4 simultaneously

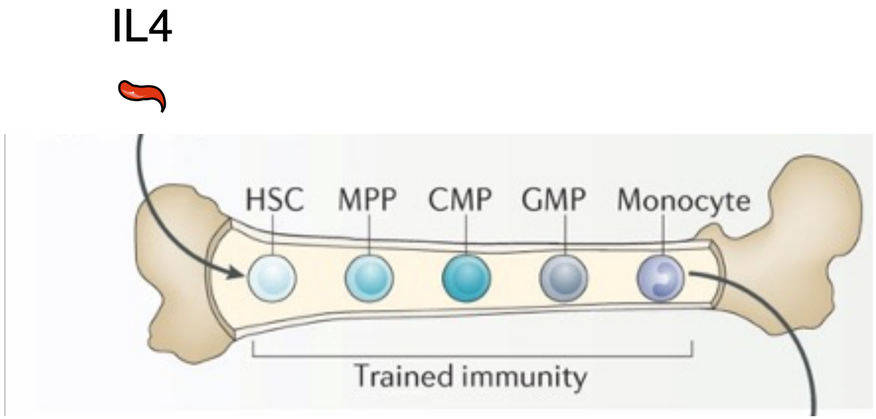
- Inhibits acute inflammation
- Induces trained immunity

To take advantage of these properties *in vivo* IL4 must be

- Routed to myeloid cells

Our strategy

- Myeloid cell-avid IL4-nanoparticles



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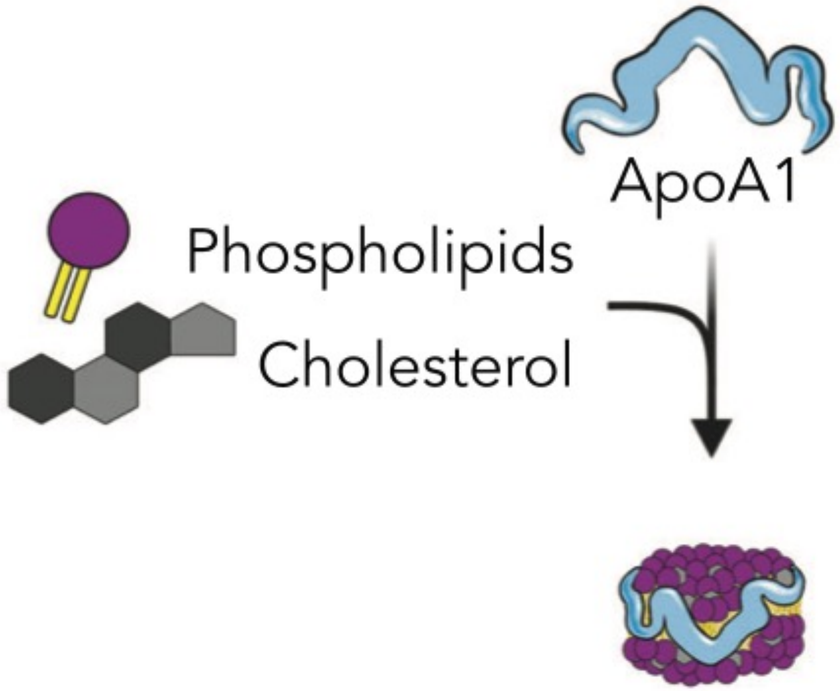
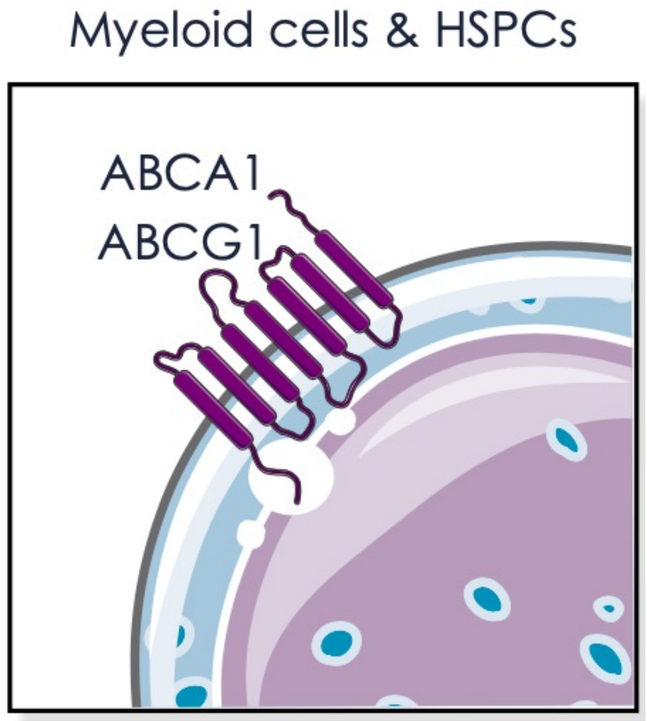
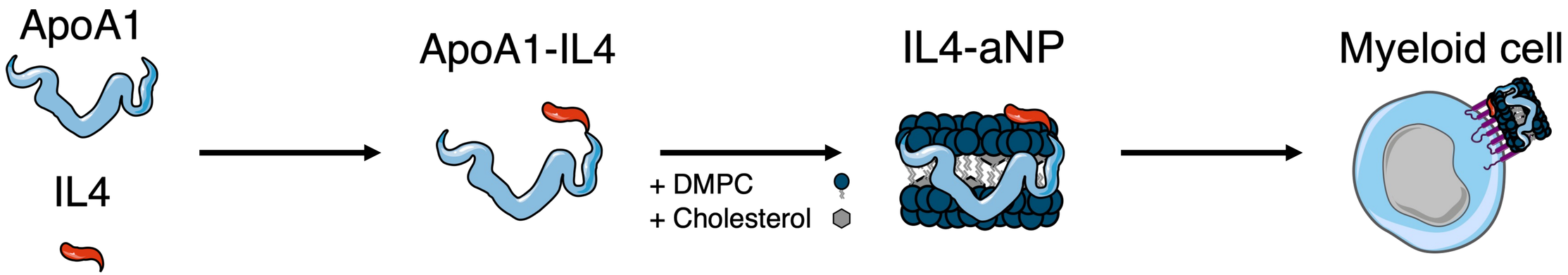
Netea, M.G., Domínguez-Andrés, J., Barreiro, L.B. *et al.* Nat Rev Immunol (2020)

ApoA1 NP


ApoA1
Phospholipids
Cholesterol

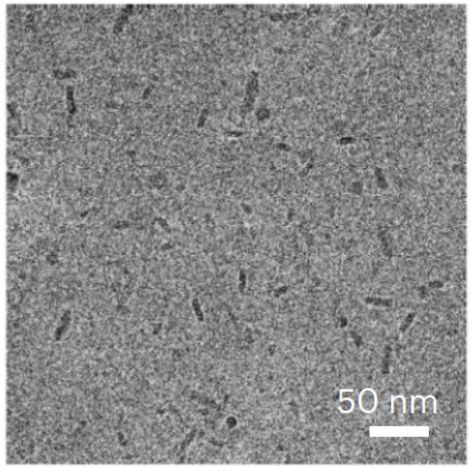

Myeloid cells & HSPCs
ABCA1
ABCG1

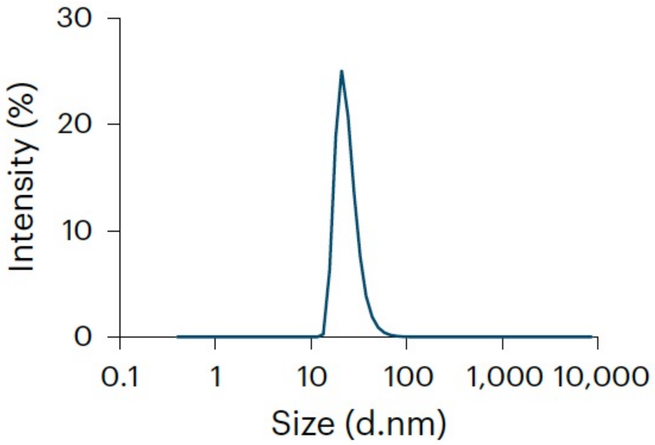
Myeloid cell-avid IL4-nanoparticles

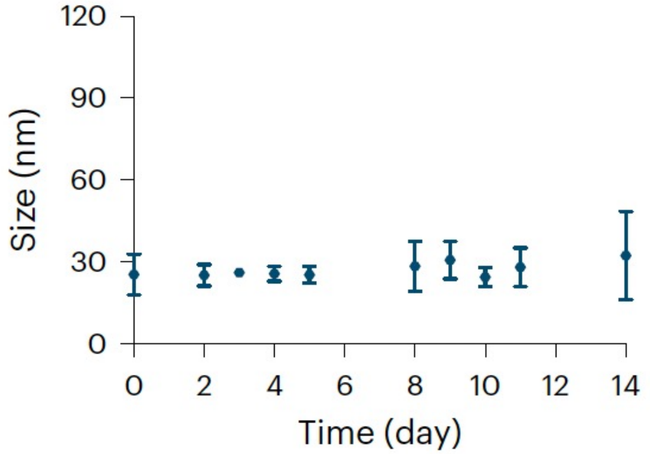


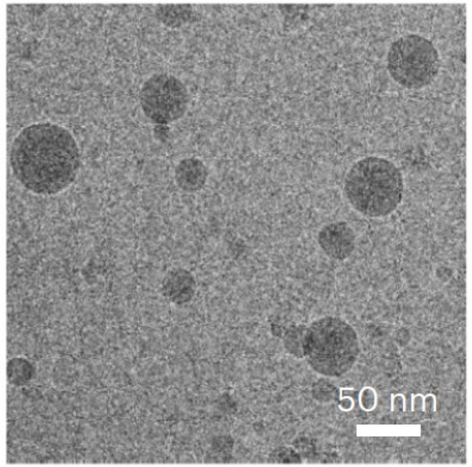
Schrijver D.P., Röring R.J. et al. Nat. Biomed. Eng (2023)

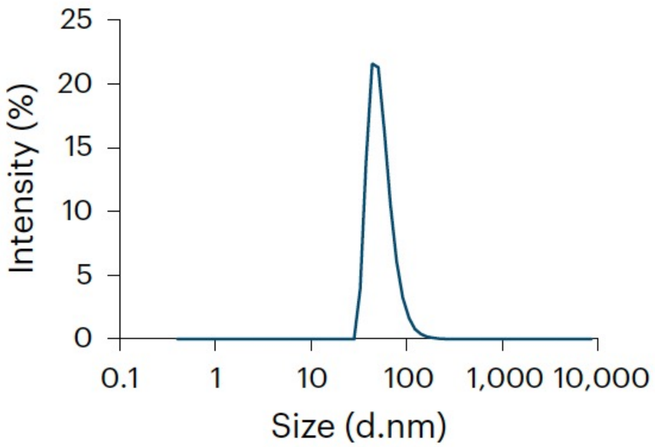
ApoA1-IL4 integrates in aNPs

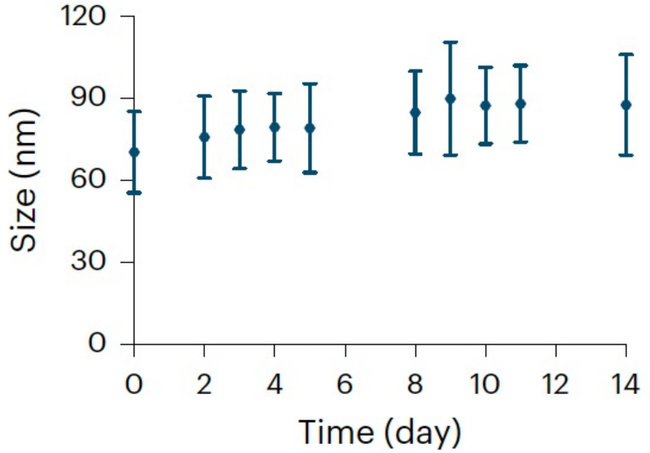












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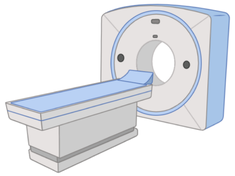
In vivo behavior of IL4 versions

IL4

ApoA1-IL4

Spherical IL4-aNP

Discoidal IL4-aNP



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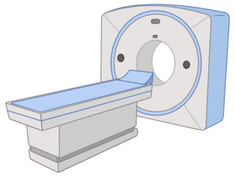

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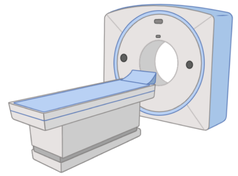

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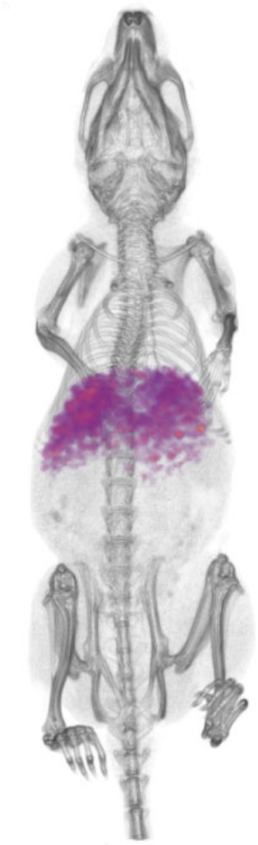

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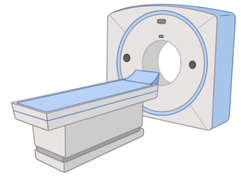

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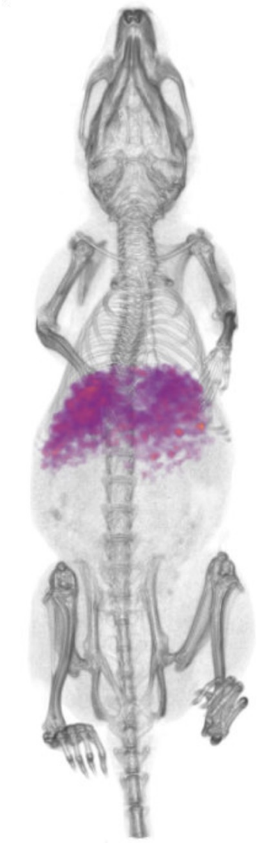

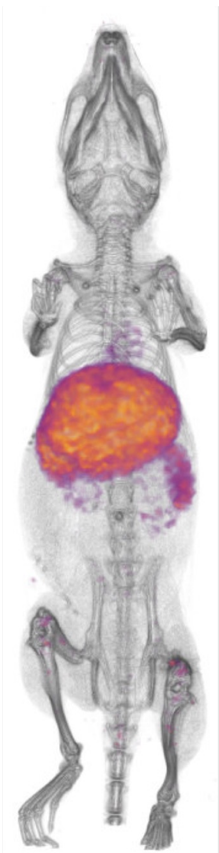

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In vivo behavior of IL4 versions

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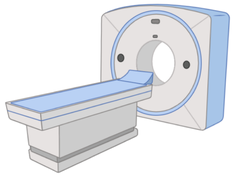

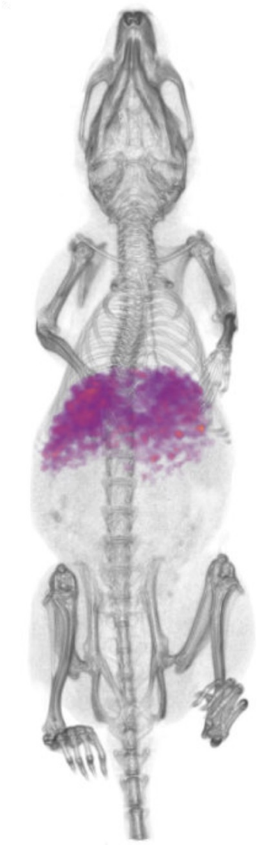

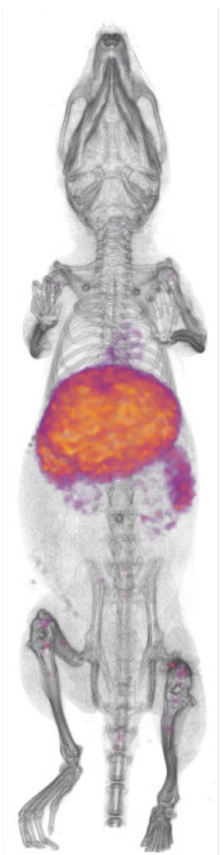

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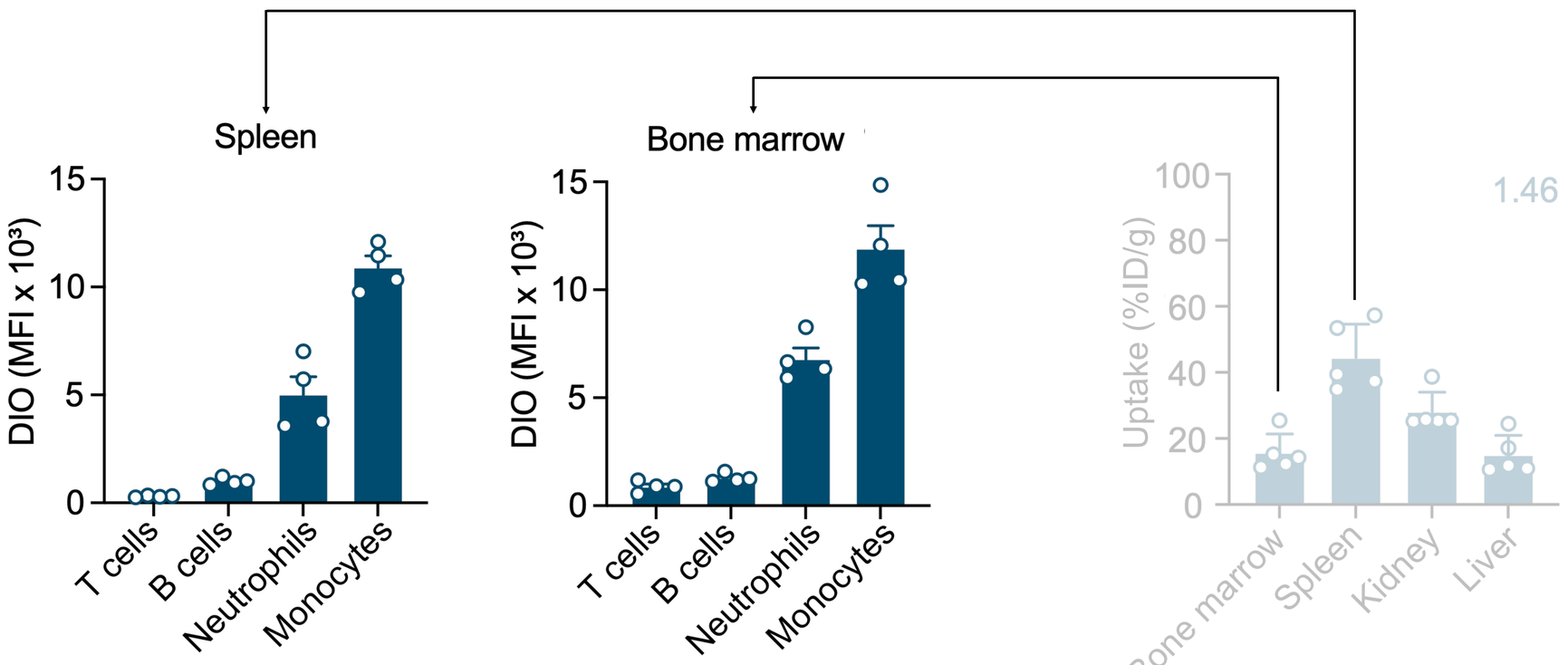
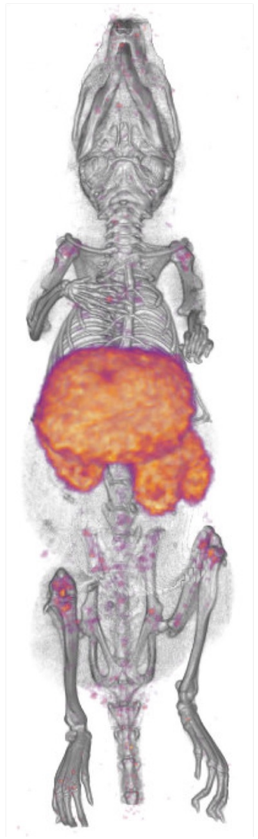
Specific uptake in myeloid cells

Discoidal
IL4-nanobiologic





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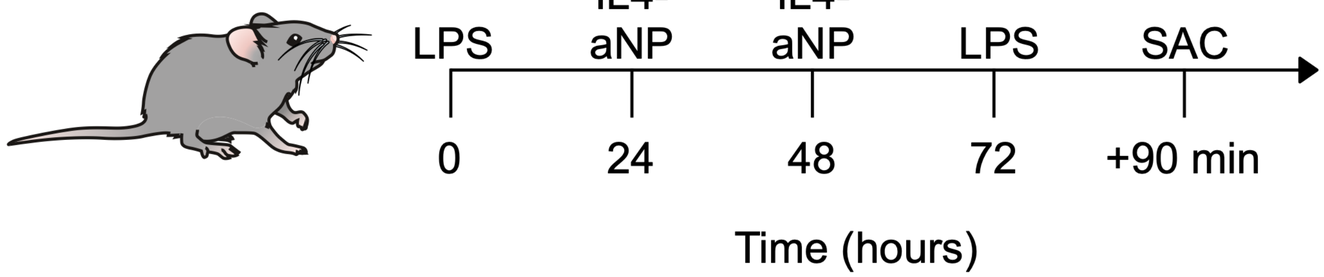
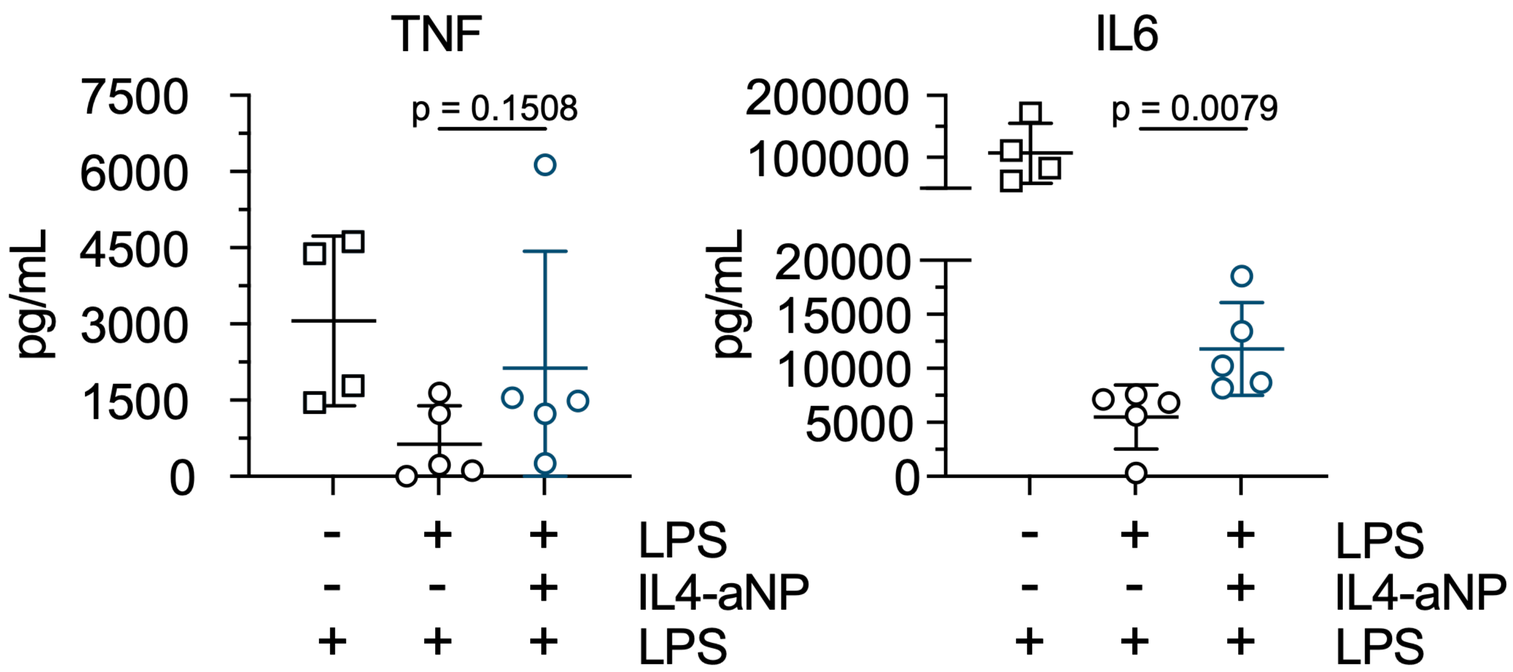
IL4(-aNPs) reverses tolerance in vivo





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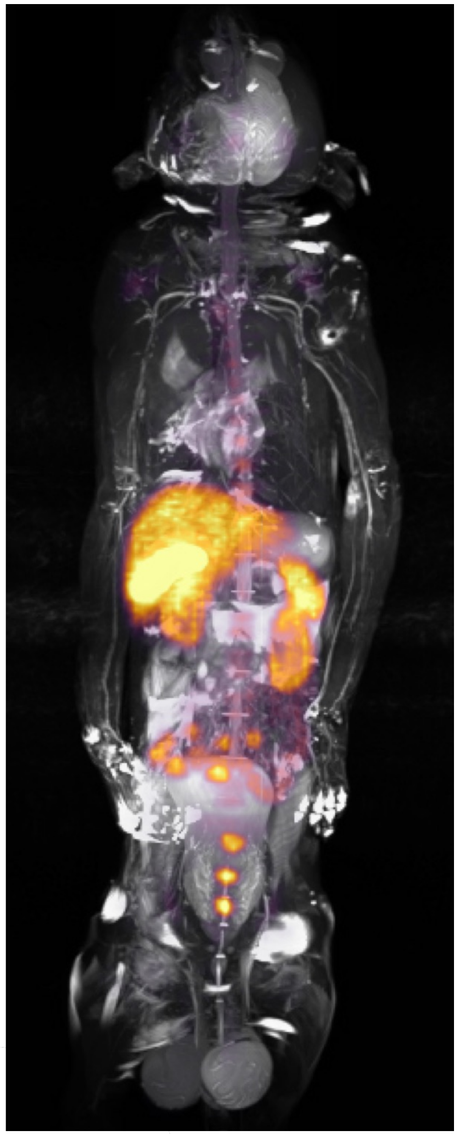
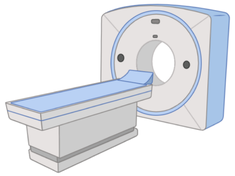
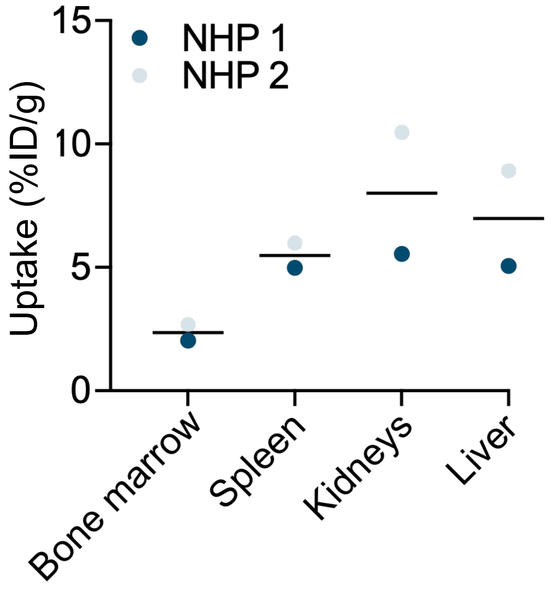
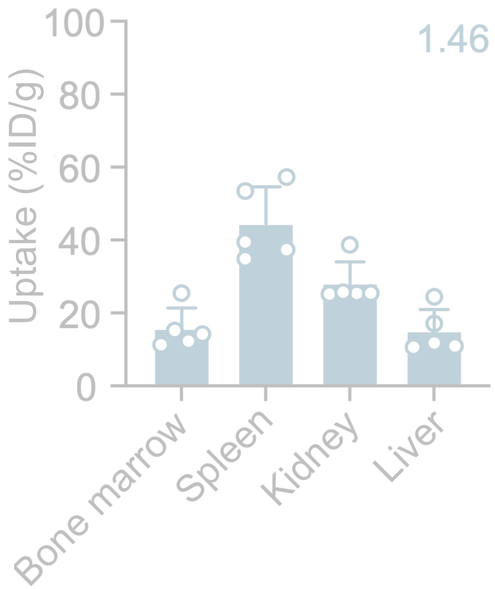
IL4-aNPs in non-human primates

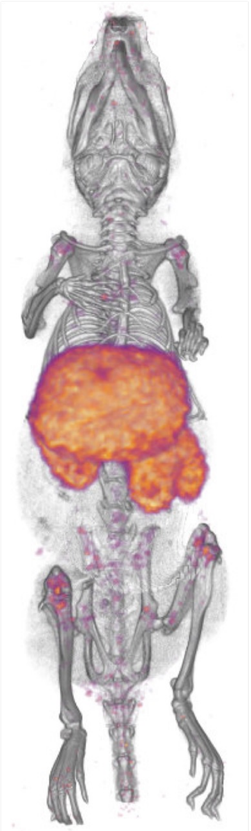




Discoidal IL4-aNP







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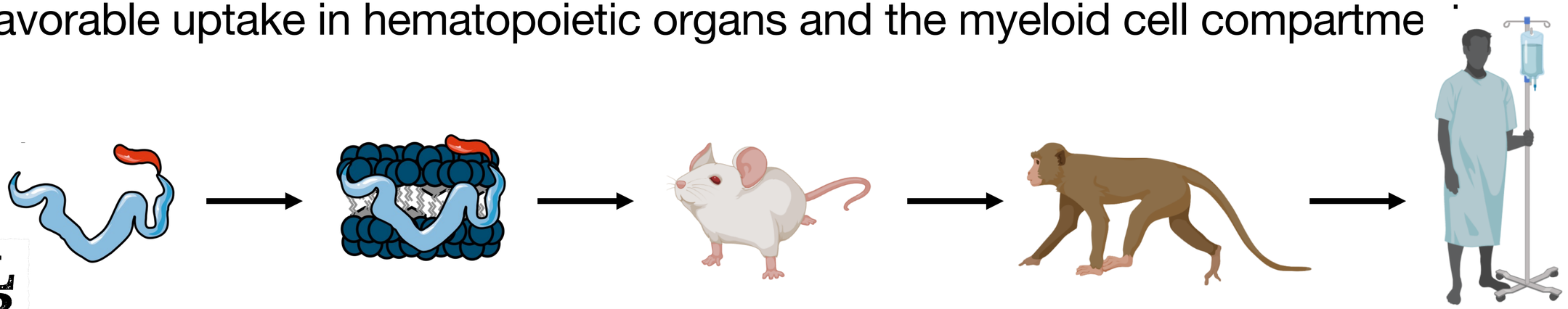
Summary

- IL4(-aNPs) unique biology
  - Reduces acute inflammation
  - Induces trained immunity
  - Reverses LPS induced tolerance

- ApoA1-IL4 integrates in lipid nanoparticles to form IL4-aNPs

- Favorable uptake in hematopoietic organs and the myeloid cell compartme



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Acknowledgements

TU/e

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MulderLab

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Prof. Dr. Leo Joosten

Dr. Rutger Röring

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NYU

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