

# Immuno Delivery I

Presenter: Rianne Maas

## Promoting organ transplant survival with trained immunity-inhibiting nanobiologics

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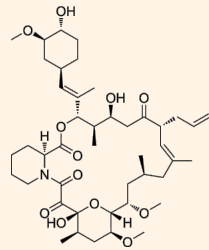
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# Organ transplant rejection: adaptive to innate

## Current anti-rejection therapeutics

Target adaptive immunity

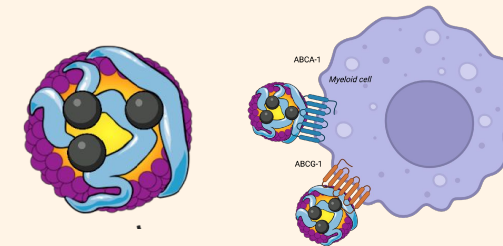


**Tacrolimus**

- Suboptimal survival rates
- Daily use
- Impaired host defense & adverse events
- Toxicity

## Our nanotherapeutic approach

Target innate immunity

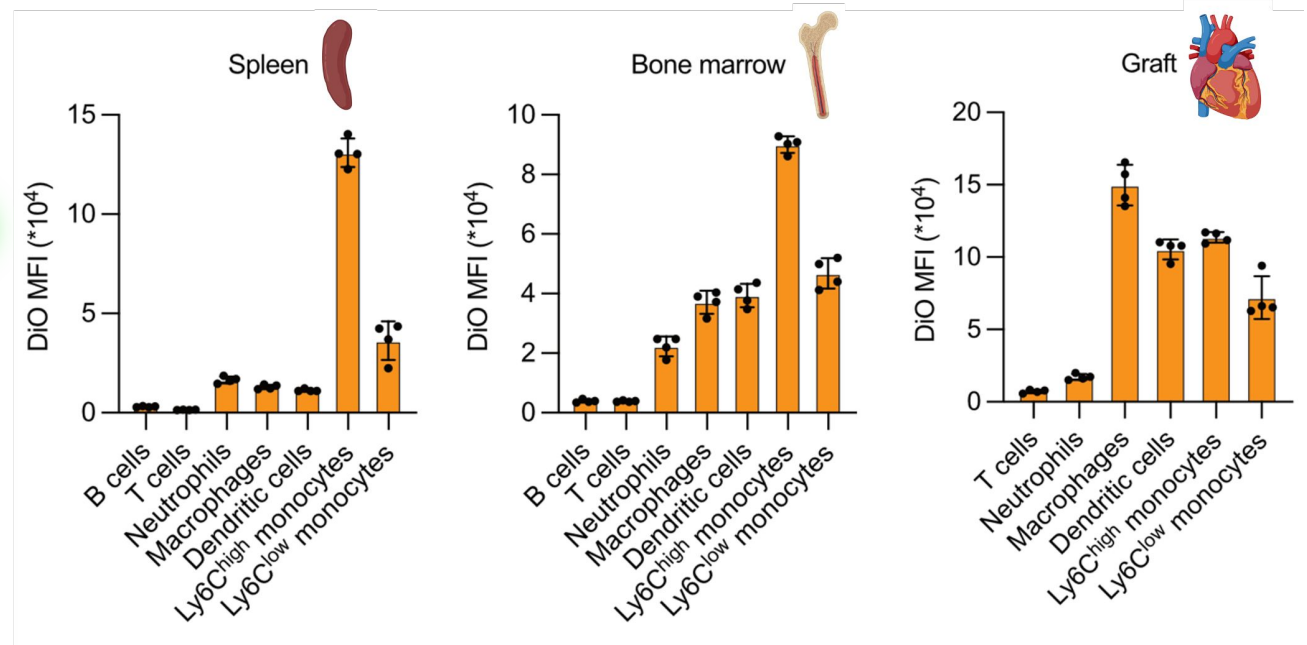
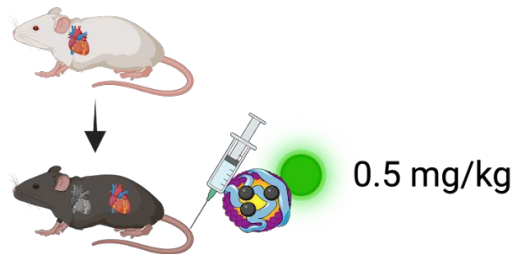


**Tacrolimus-loaded  
apolipoprotein A1 nanobiologics**



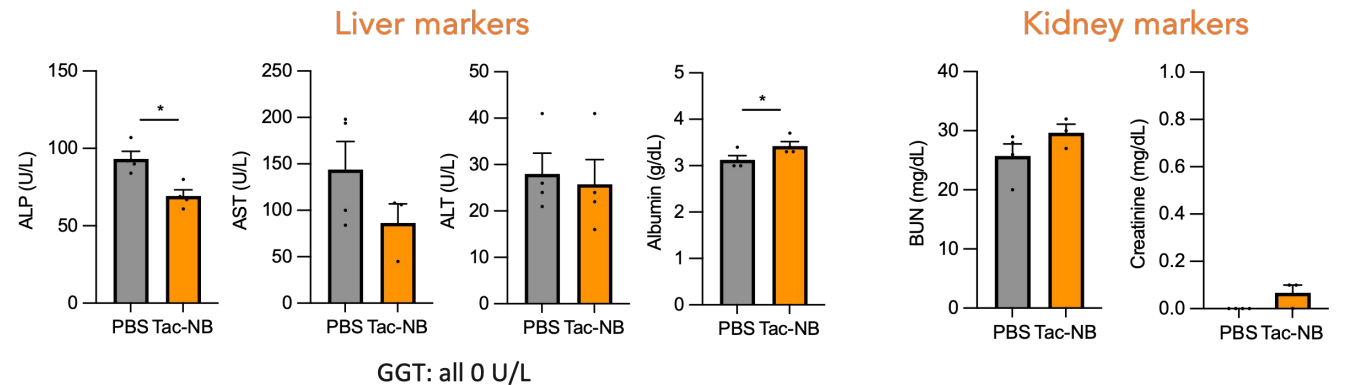
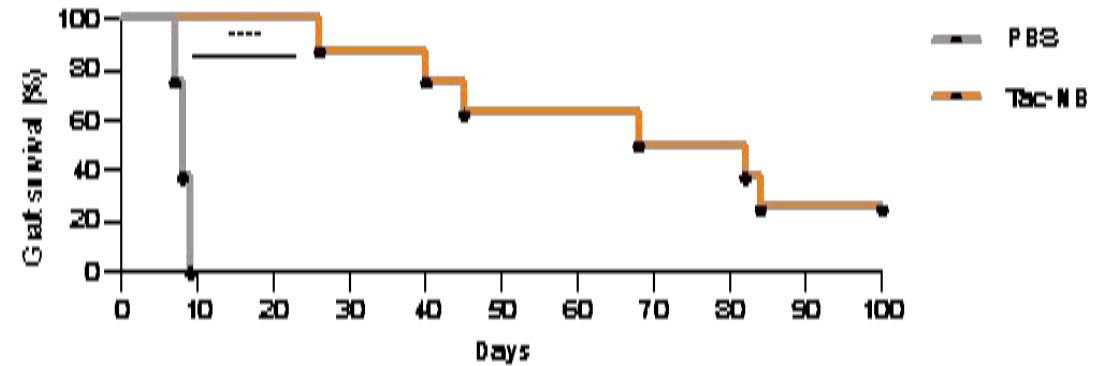
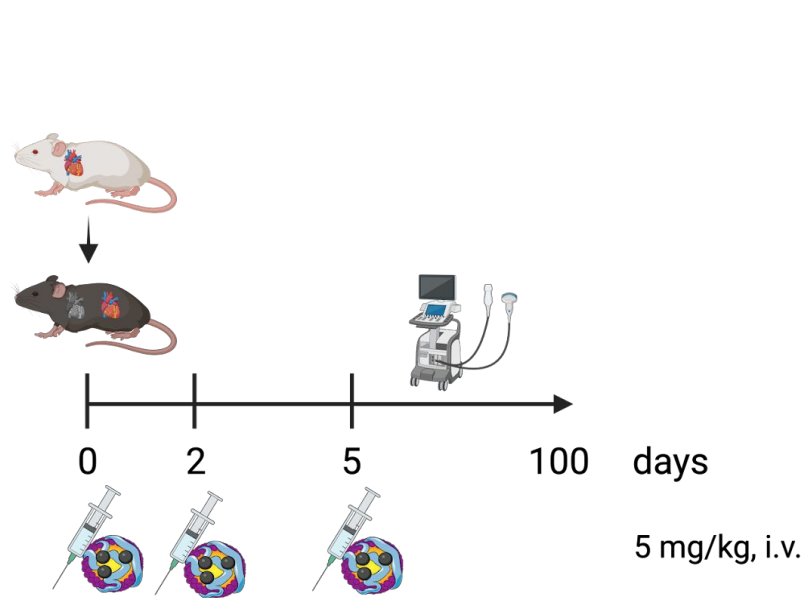
# Results

## *In vivo* cellular uptake of tacrolimus-nanobiologics



# Results

## Therapeutic effect on allograft survival and toxicity



# Conclusions & Outlook

- ✓ Tacrolimus-nanobiologics are specifically taken up by innate immune cells
- ✓ Delivering tacrolimus to innate immune cells promotes organ transplant survival
- ✓ *In vitro* mechanistic data: innate immune memory
- Investigate the drug release and NB behavior
- *In vivo* mechanistic data
- Comparison with bare tacrolimus

Promoting organ transplant survival by targeting the innate immune system by apolipoprotein A1 nanotherapeutics is a promising avenue





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# Promoting organ transplant survival with trained immunity-inhibiting nanobiologics

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## Introduction

Traditionally, organ transplant rejection is prevented with immunosuppressive drugs that inhibit adaptive immune responses. However, innate immune responses also play a critical role in allograft rejection, but currently no therapeutics are available that target innate immune cells.

Here, we developed an anti-rejection therapeutic aimed at inhibiting innate immunity. More specifically, we target trained immunity, a de facto memory of innate immune cells, which makes them hypersensitive to secondary stimuli. For drug delivery, we use an apolipoprotein A1-based nanobiologic platform with inherent affinity for innate immune cells.

## Objective

Apply our well-established apolipoprotein A1 nanobiologic platform to deliver tacrolimus to the innate immune cells and explore its potential for preventing organ transplant rejection and its underlying mechanism.

## Engineering tacrolimus-nanobiologics

Tacrolimus-loaded nanobiologics (Tac-NBs) were formulated by microfluidic mixing. The nanotherapeutics' size and tacrolimus loading incorporation efficiency were determined by dynamic light scattering and nuclear magnetic resonance, respectively.

## In vivo cellular uptake of tacrolimus-nanobiologics

Allogeneic heart transplant recipients were injected with DOX-labeled NBs (i.v., 0.5 mg/kg) and tissues of interest were measured by flow cytometry.

- NBs are predominantly taken up by monocytes, macrophages, and dendritic cells.

## In vivo toxicity of tacrolimus-nanobiologics

Naive mice were treated with Tac-NBs (i.v., 5 mg/kg) on days 0, 2, and 5 post-transplantation.

• The proposed dose regimen for the therapeutic studies is not toxic.

## Allograft survival in a heart transplant mouse model

Allogeneic recipients were treated with Tac-NBs (i.v., 5 mg/kg) on days 0, 2, and 5 post-transplantation and monitored by ultrasound.

• Graft survival was significantly prolonged by the Tac-NBs.

## Effect on trained immunity in human immune cells

Human peripheral blood mononuclear cells were stimulated with heat-killed *Candida albicans* (HKCA). Tac-NBs (10 mg/ml) were added during and after stimulation with HKCA. Candida responses upon stimulation with lipopolysaccharide (LPS) or Pam3CSK4 (P3K) were quantified by ELISA.

• Tac-NBs inhibit and revert trained immunity.

## Conclusions

- Tacrolimus-nanobiologics are specifically taken up by innate immune cells.
- Delivering tacrolimus to innate immune cells promotes organ transplant survival.
- Tacrolimus-nanobiologics inhibit and revert the innate immune memory.

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