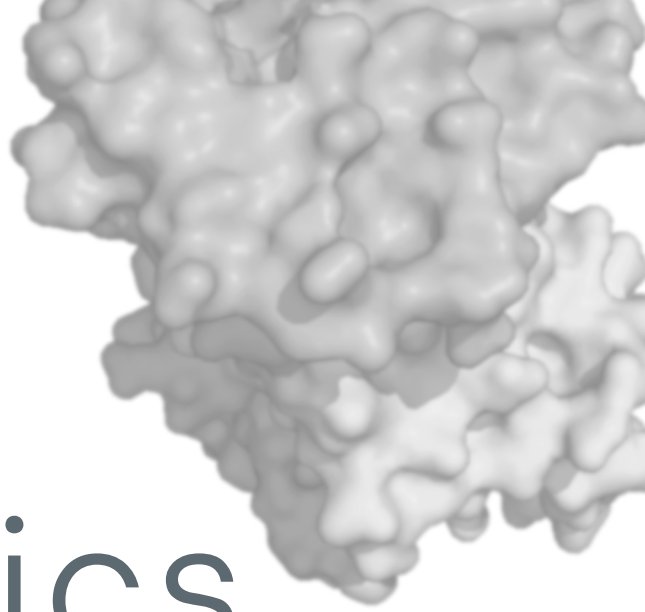


Toleris Biotherapeutics

AutoImmunity Modifying Biologicals - inspired by pregnancy

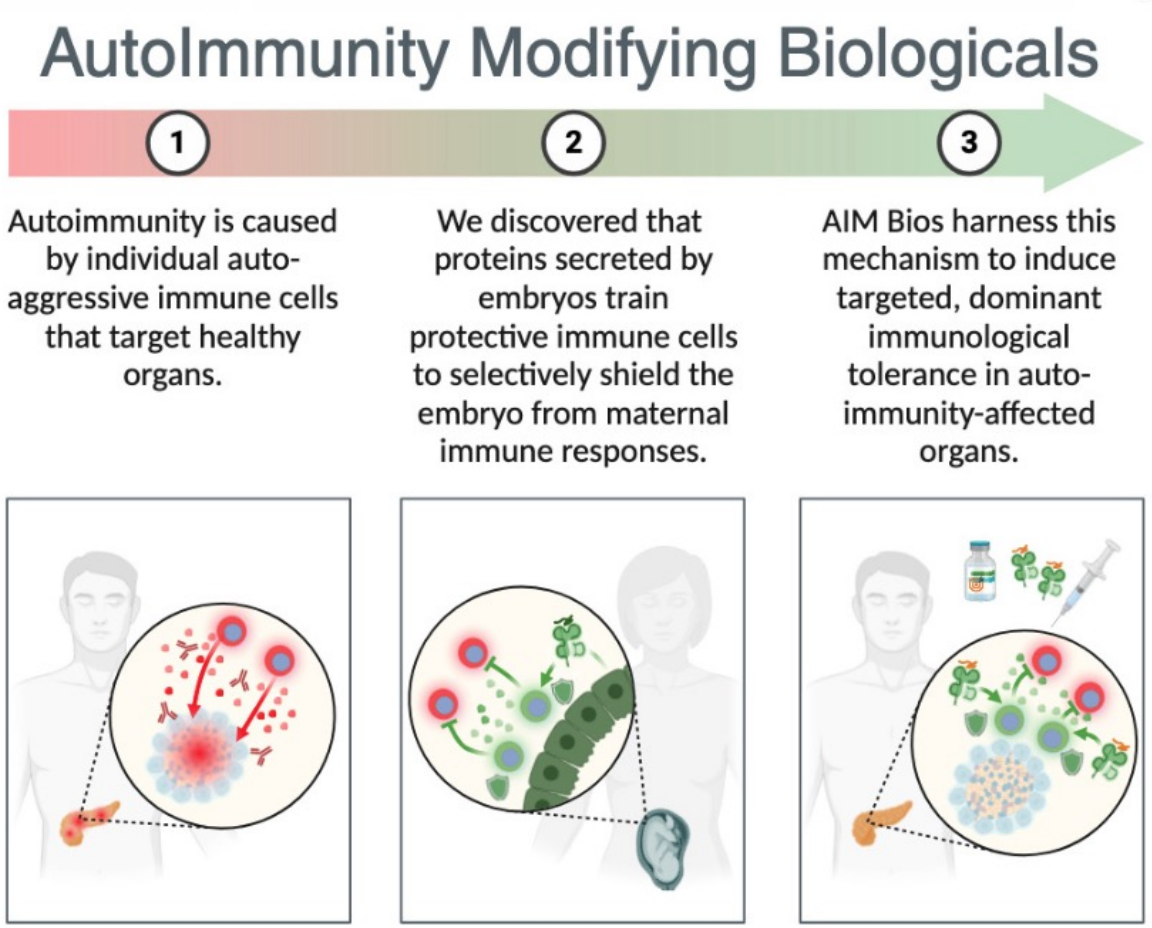
non-confidential pitch deck 04/2025

Toleris: mimicking potent & targeted natural tolerance

Autoimmune diseases are driven by autoaggressive immune cells. Current therapies suppress these harmful cells but also compromise protective immune responses, increasing vulnerability to infections.

Selective tolerance is achieved in pregnancy, when embryos succesfully reprogram the maternal immune system to tolerate paternal antigens without inducing generalized immunosuppression.

Toleris' scientists have discovered a novel mechanism that likely plays a crucial role in this selective immune tolerance. Leveraging this discovery, Toleris is pioneering AutoImmunity Modifying Biologicals (AIM Bios) - a new class of targeted therapeutics designed to induce robust, antigen-specific immune tolerance only in affected organs, without broad immunosuppression.

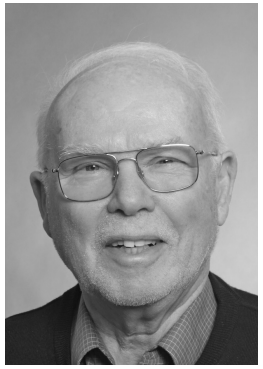


Toleris Biotherapeutics: at a glance

- spin off from the University of Würzburg, Germany established January 2024
- worldwide license for innovative biotherapeutics platform AutoImmunity Modifying Biologicals (AIM Bios), first right of refusal for NMOSD and Parkinson's disease
- Development candidates for MOGAD/MS, NMOSD, Parkinson's disease and type 1 diabetes
- successful proof of concept in 5 animal models in 3 indications
- platform patent in major countries filed 2017, eight disease specific patents filed 2022 and 2023
- fully owned by founders

Toleris team & funding

Toleris management team



Jürgen Engel

CEO

strategic consultant, former CEO of Nasdaq listed company, successful development of several drugs, in- and out-licensing, M&A, public financing

Valentin Bruttel

CSO

immunologist and bioengineer, co-inventor AIM platform technology

Jörg Wischhusen

CSA

chief scientific advisor, PI, co-inventor AIM platform technology, Scientific founder Catalym

Markus Haake

SVP Preclin Dev

drug discovery and non-clinical development, co-founder Catalym

funding/awards:

eXIST
Bundesministerium für Wirtschaft und Klimaschutz

m⁴ Award

Bayerisches Staatsministerium für Wirtschaft, Landesentwicklung und Energie

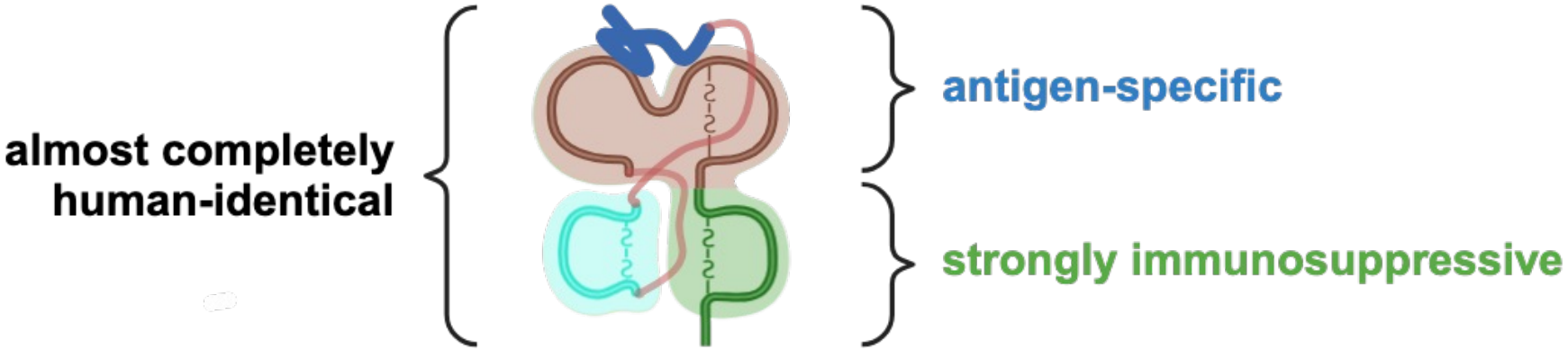
Innovationspreis 2022

BioRegionen in Deutschland

Collaboration partners:Prof. Michael Levy (Harvard Medical School), Prof. Friedemann Paul (Charité Berlin)

USP: physiological, potent & targeted tolerance

Antigen-specific tolerance induction has been considered to be the "**holy grail**" for immunotherapy of autoimmune diseases for decades. Our discovery that antigen presentation in the presence of the HLA-G α3 domain induces antigen-specific tolerance enabled us to develop a new platform named **a**uto**i**mmunity-**m**odifying (AIM) biologicals.

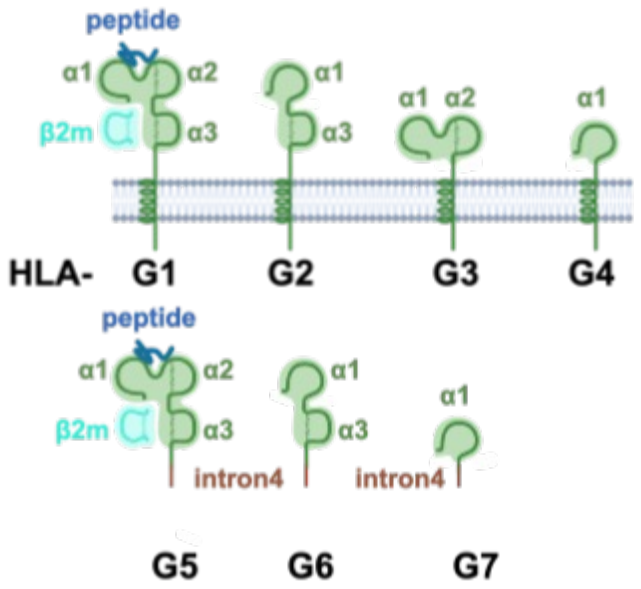


IP: e.g. WO2018215340A1

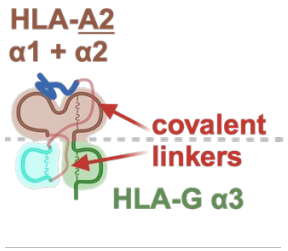
→ To our knowledge, **AIM Bios are the only therapeutics that combine antigen peptides and a very potent immunosuppressive mechanism in almost completely physiological proteins.**

HLA-G biology and AIM Bio design

HLA-G has numerous published immunosuppressive effects on immune cells. Unlike other MHCs, HLA-G possesses hardly any allelic variants that affect the protein sequence. Both membrane-bound and soluble variants are known.



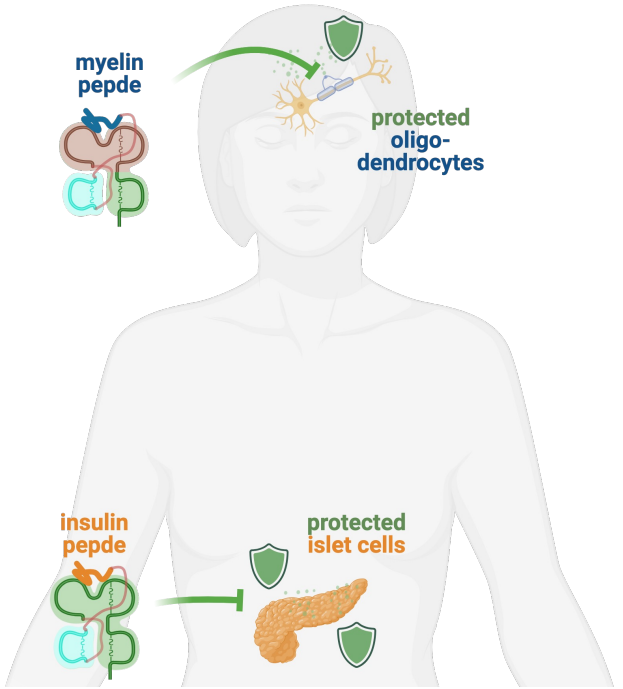
AIM Bios are soluble molecules derived from HLA-G, combining a peptide antigen, antigen-presenting domains, β2-microglobulin, and the tolerance-inducing HLA-G α3 domain in a single, covalently linked protein.



Peptide and matching antigen-presenting domains → define the specificity

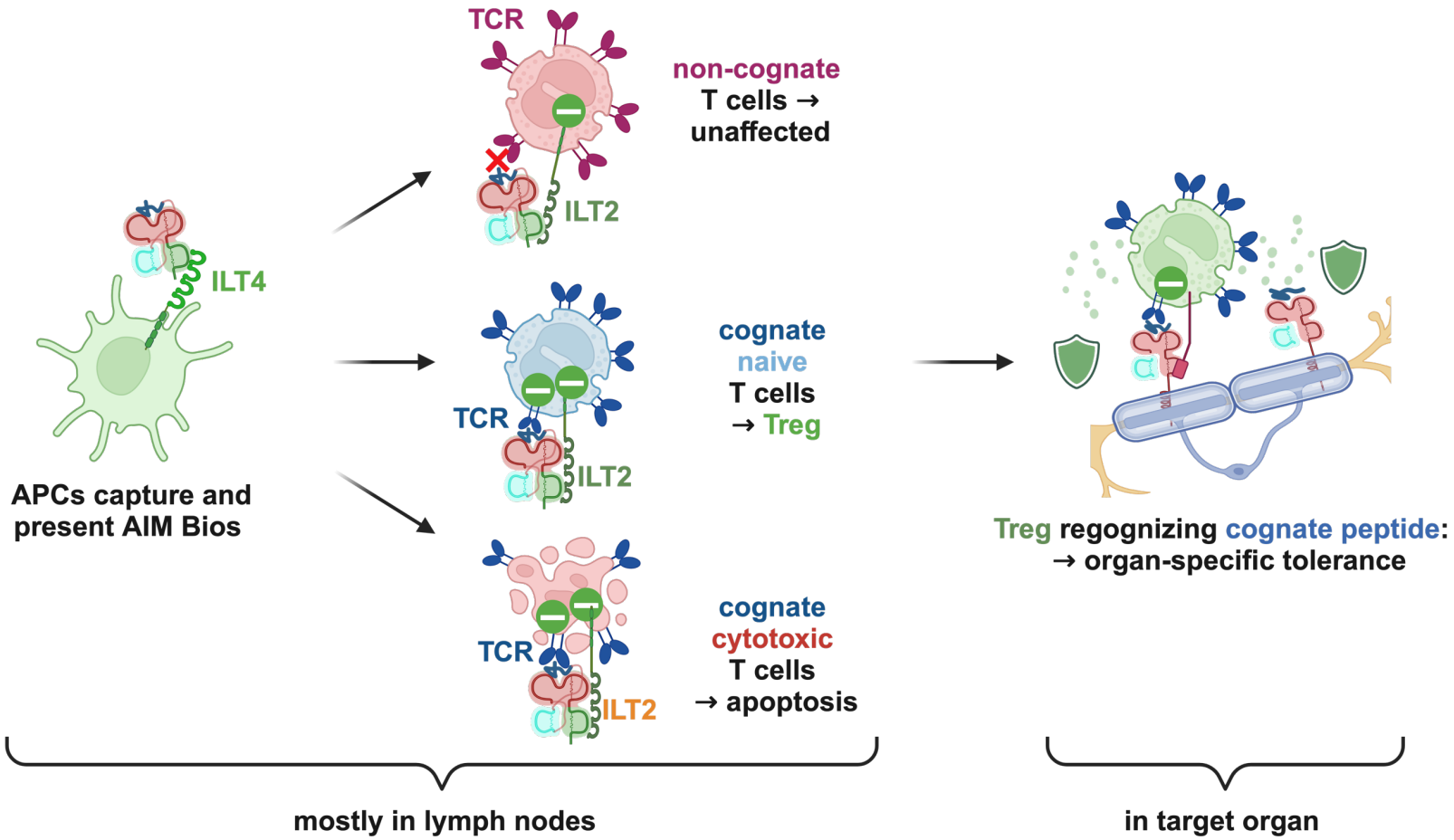
β2-Microglobulin and HLA-G α3 domain → induce tolerance

Peptide antigens and presenting domains are customized for specific organs or animal models, while immunological tolerance is driven by the potent HLA-G α3 domain, which remains constant.



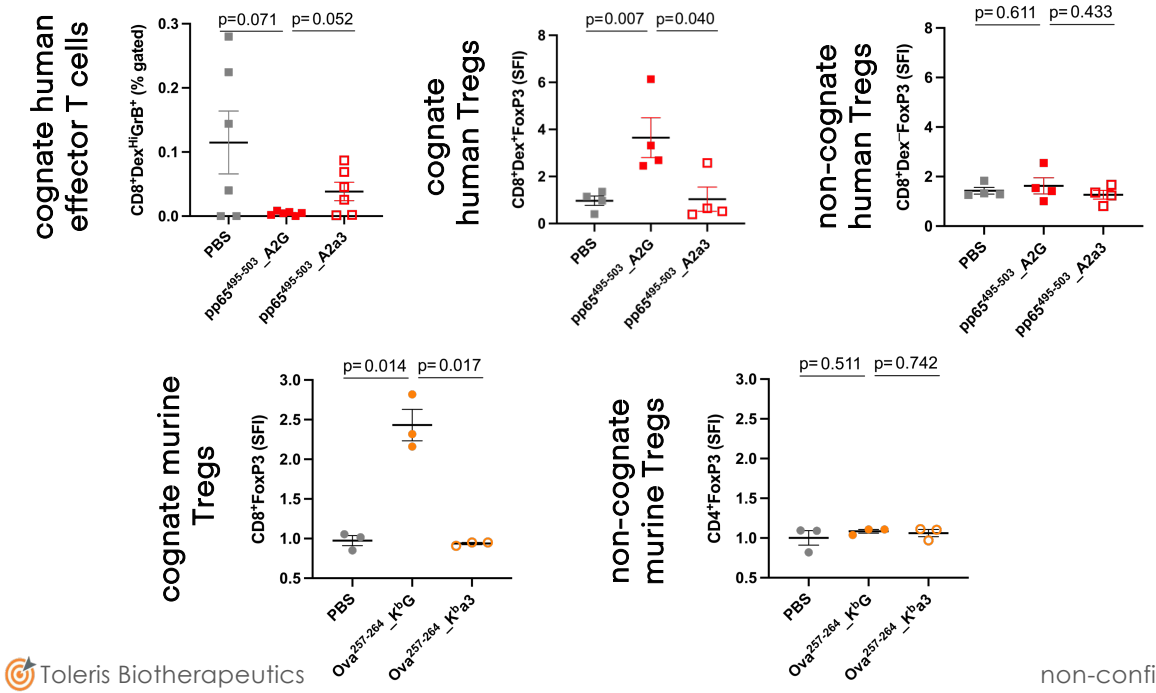
AIM Bio mode of action

Soluble AIM Bios are captured by antigen-presenting cells (APCs) in the lymph nodes via ILT4. Non-cognate effector T cells remain unaffected by AIM Bios. In contrast, highly activated cognate effector T cells undergo apoptosis. Meanwhile, naïve cognate T cells are polarized into tolerogenic regulatory T cells (Tregs). These Tregs, upon recognizing their cognate peptide in the affected organ, induce robust local immunosuppression to mitigate autoimmunity.

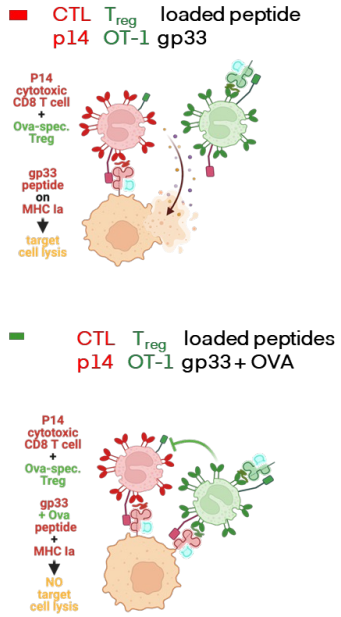


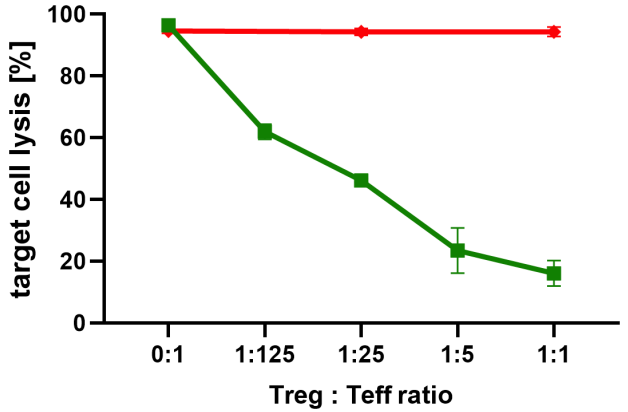
proof-of-concept *in vitro*

To evaluate the effects of AIM Bios, human PBMCs reactive to a viral model peptide and mouse splenocytes reactive to an ovalbumin peptide were treated with AIM Bios presenting the corresponding peptides or control molecules. AIM Bios selectively reduced $CD8^+$ cognate granzyme B^+ effector T cells while inducing $CD8^+$ $CD103^+$ and $FoxP3^+$ antigen-specific regulatory T cells.



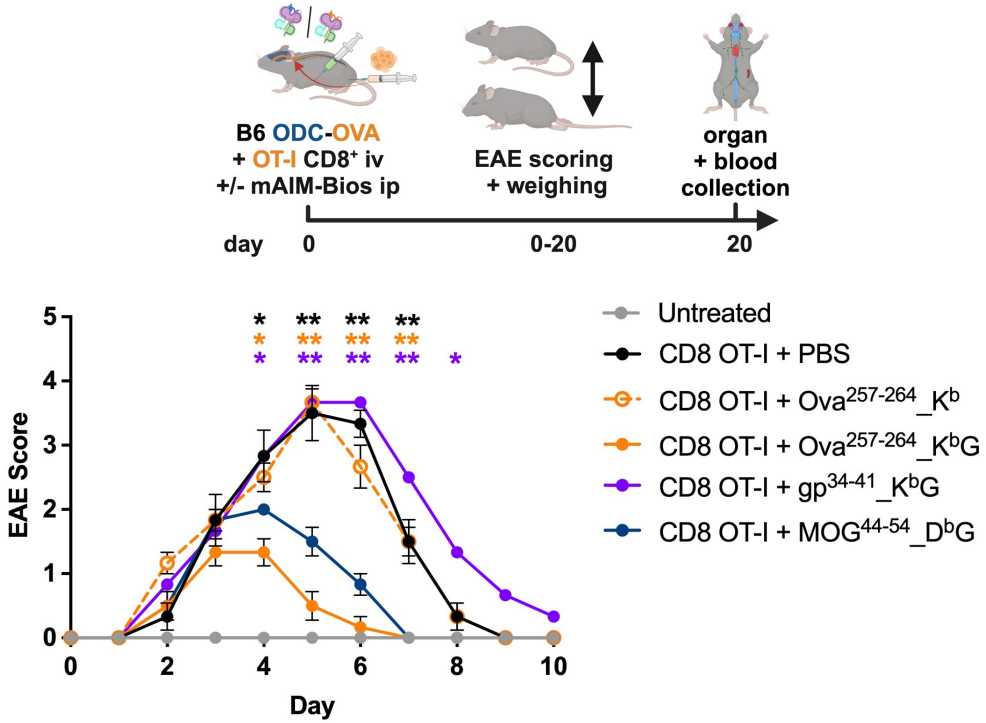
Mouse-adapted AIM Bios loaded with cognate peptides inhibit cytotoxic T cells, while AIM Bios with other peptides have no effects (not shown). Furthermore, AIM Bio-induced Tregs suppress effector T cell-mediated lysis of target cells even very low Treg-to-Teff ratios of 1:125, but only if target cells present the peptide recognized by Treg (bystander suppression).



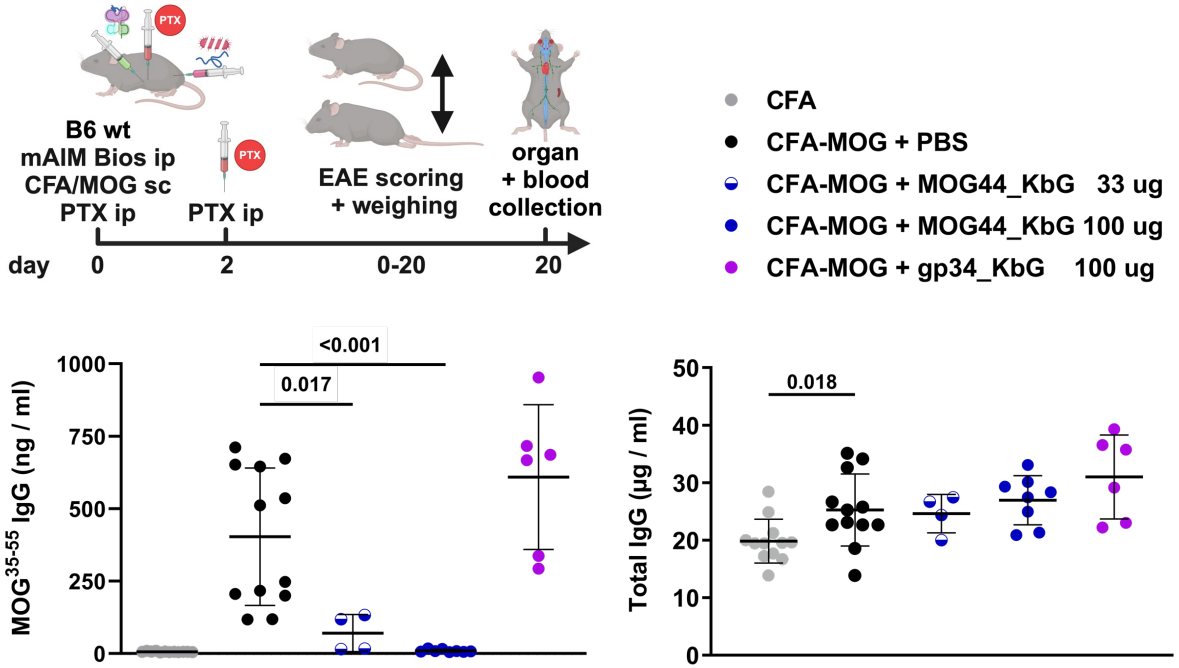


proof-of-concept *in vivo*

In mice in which MS-like symptoms are caused by T cells targeting a model antigen, AIM Bios that induce tolerance towards the model antigen or towards other antigens expressed by oligodendrocytes prevent severe disease symptoms.

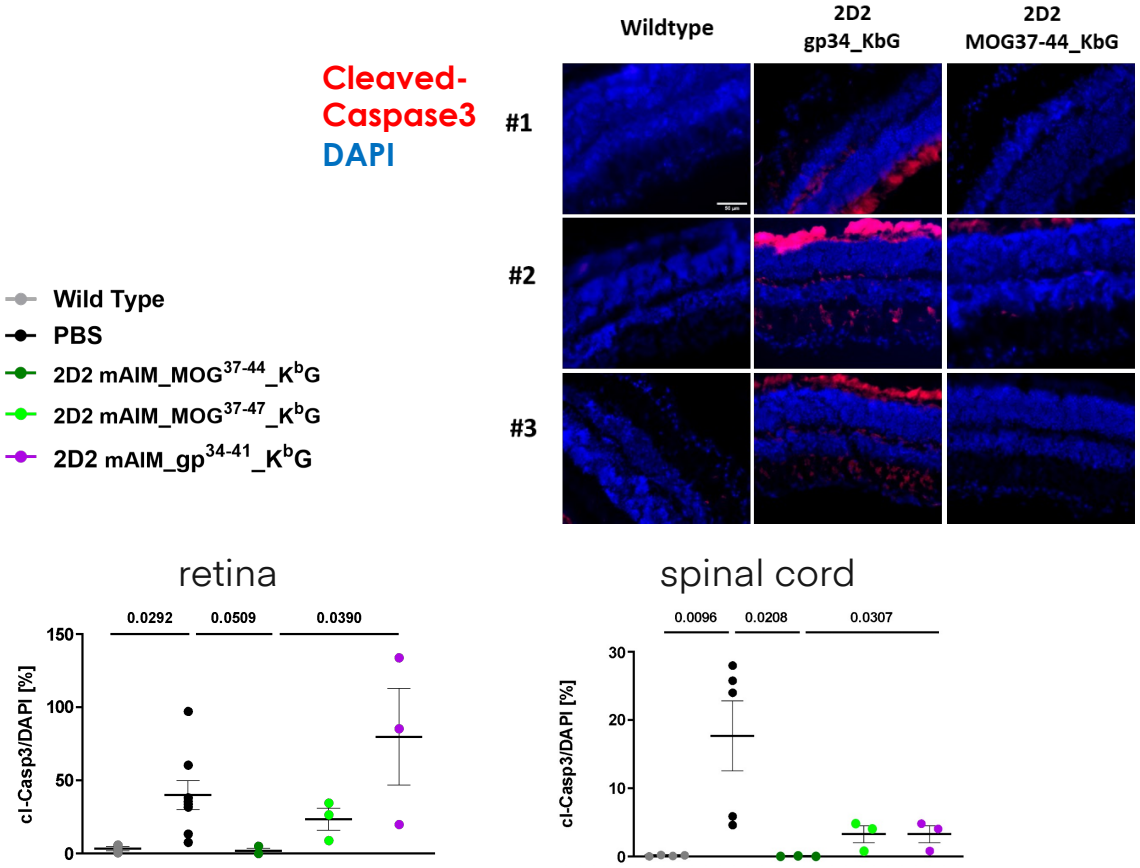


Wildtype mice with EAE induced by MOG peptide, adjuvant, and toxin were treated with MOG-tolerance-inducing or control AIM Bios. **MOG-specific AIM Bios reduced symptoms and prevented MOG-specific autoantibodies without affecting total IgG levels.**

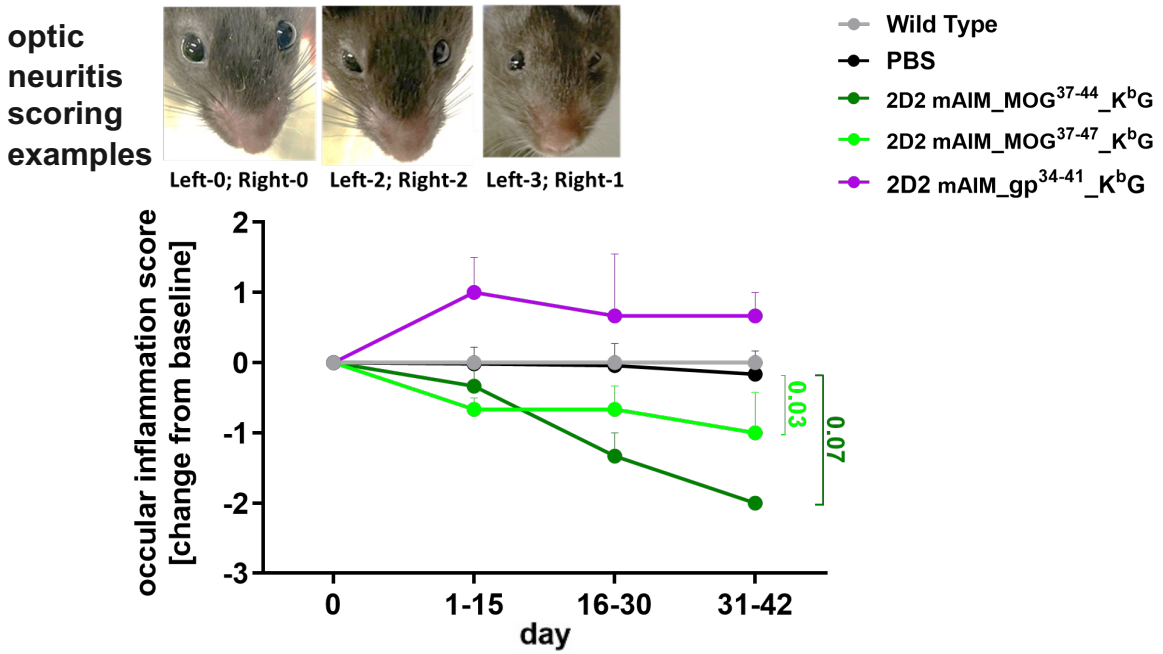


MOGAD: AIM Bios have therapeutic effects

MOG AIM Bios completely prevent cell death (red = apoptosis) in all organs predominantly affected by MS/MOGAD in 2D2 mice.



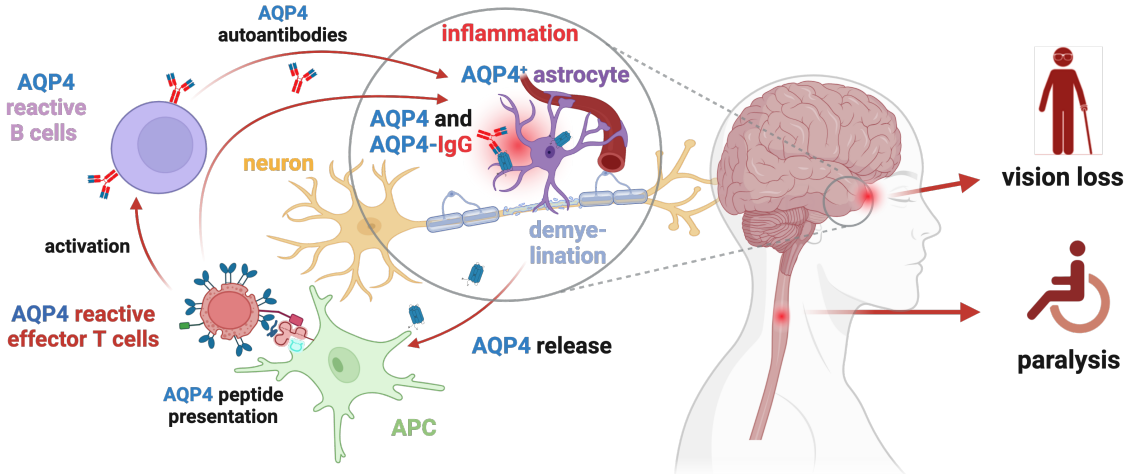
Even after significant swelling of the eyes, a **MOG-tolerance inducing AIM Bios reduced pre-existing optic neuritis** in 2D2 mice.



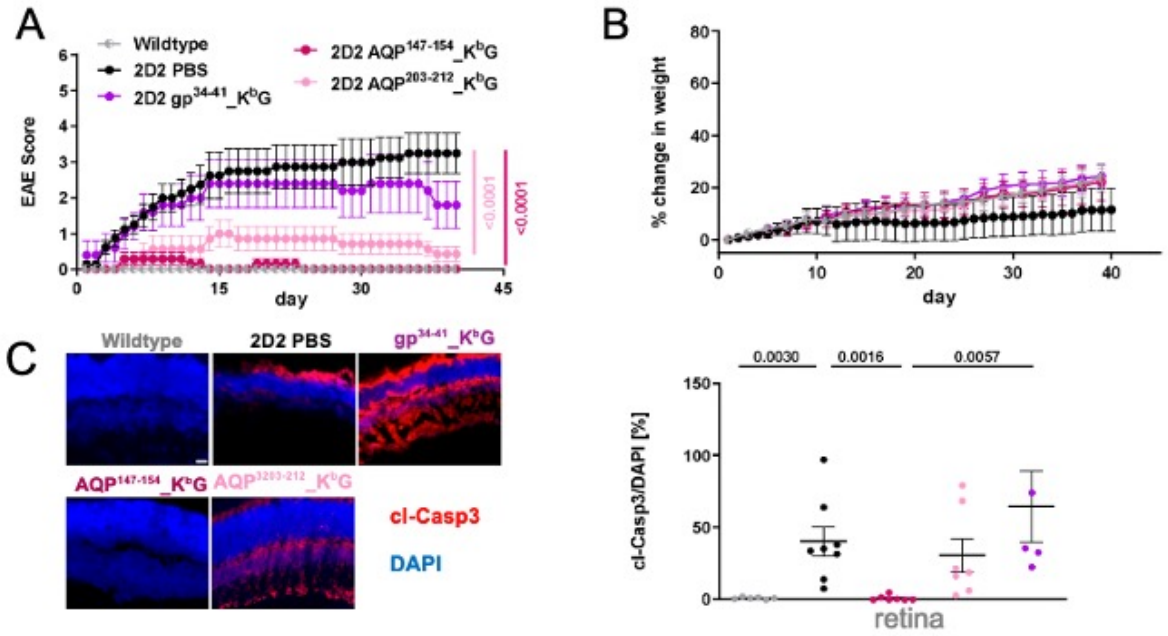
→ human lead compound TOL101 induces Treg in patient cells

NMOSD: AIM Bios prevent EAE & neuron loss

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a severe autoimmune condition caused by aquaporin-4 (AQP4) specific immune cells and antibodies. These drive astrocyte damage and cause smoldering disease despite acute treatment.



AQP4-specific AIM Bios completely prevent EAE symptoms (A), **weight loss** (B) **and neuron loss in the retina** (C) **and optic nerve and spinal cord** (not shown) in the 2D2 optic neuritis mouse model.

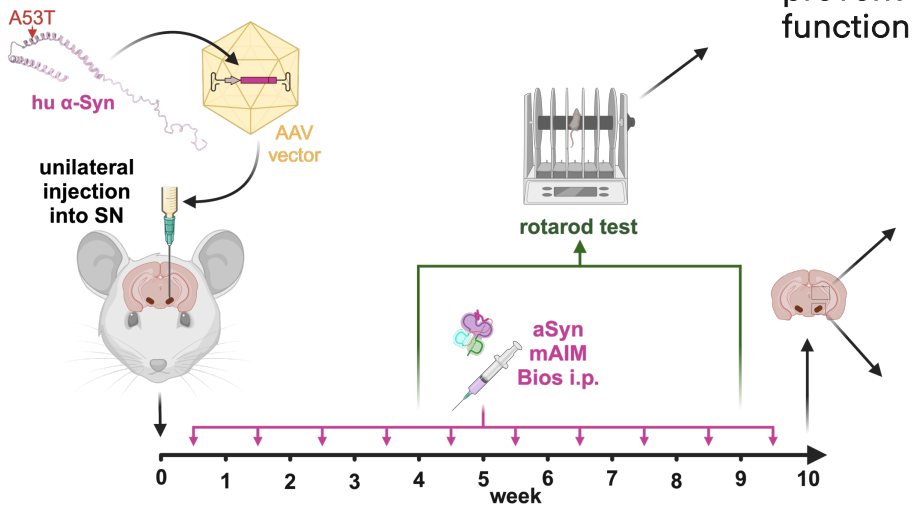


→ prioritized AQP4 tolerance inducing human candidate molecule TOL201

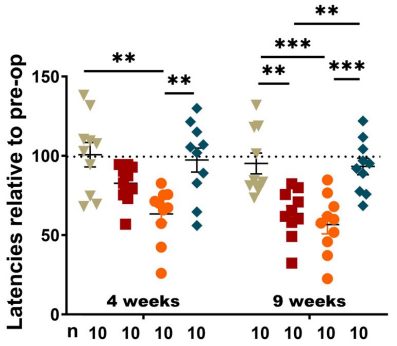
PD: AIM Bios completely prevent symptoms

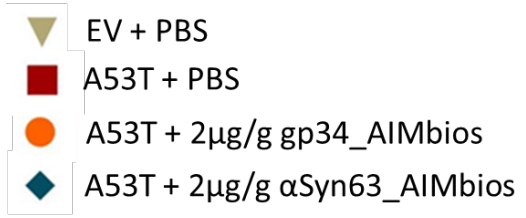
Parkinson's disease (PD) is a neurodegenerative disorder marked by the accumulation of α-synuclein (aSyn) aggregates (Lewy bodies) and neuroinflammation. In an AAV-aSynA53T PD mouse model, α-synuclein-targeted AIM Bios completely prevented PD symptoms.

see Karikari, ..., Bruttel, ..., Wischhusen, ..., Ip , Brain, Behavior, and Immunity 101 (2022) 194–210

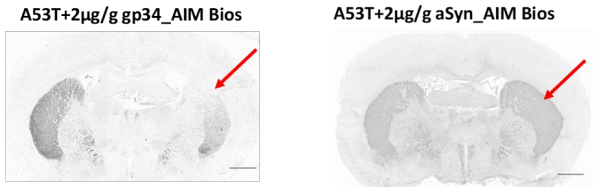


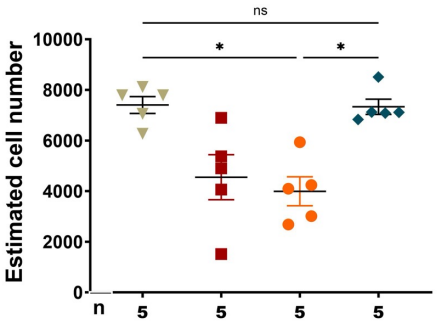
aSyn AIM Bios prevent motor function deficits



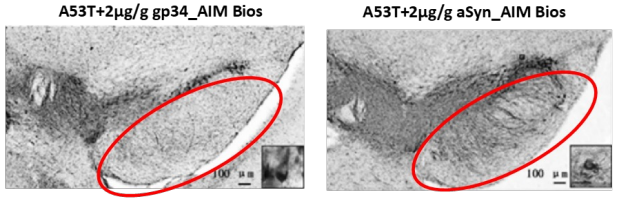


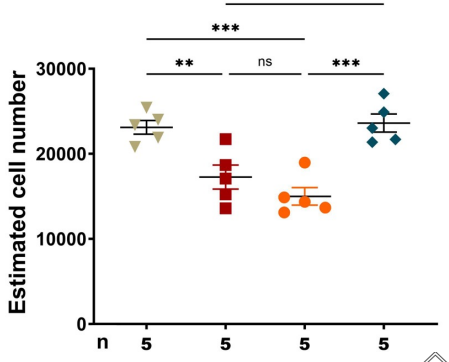
aSyn AIM Bios prevent loss of dopaminergic terminal fibers





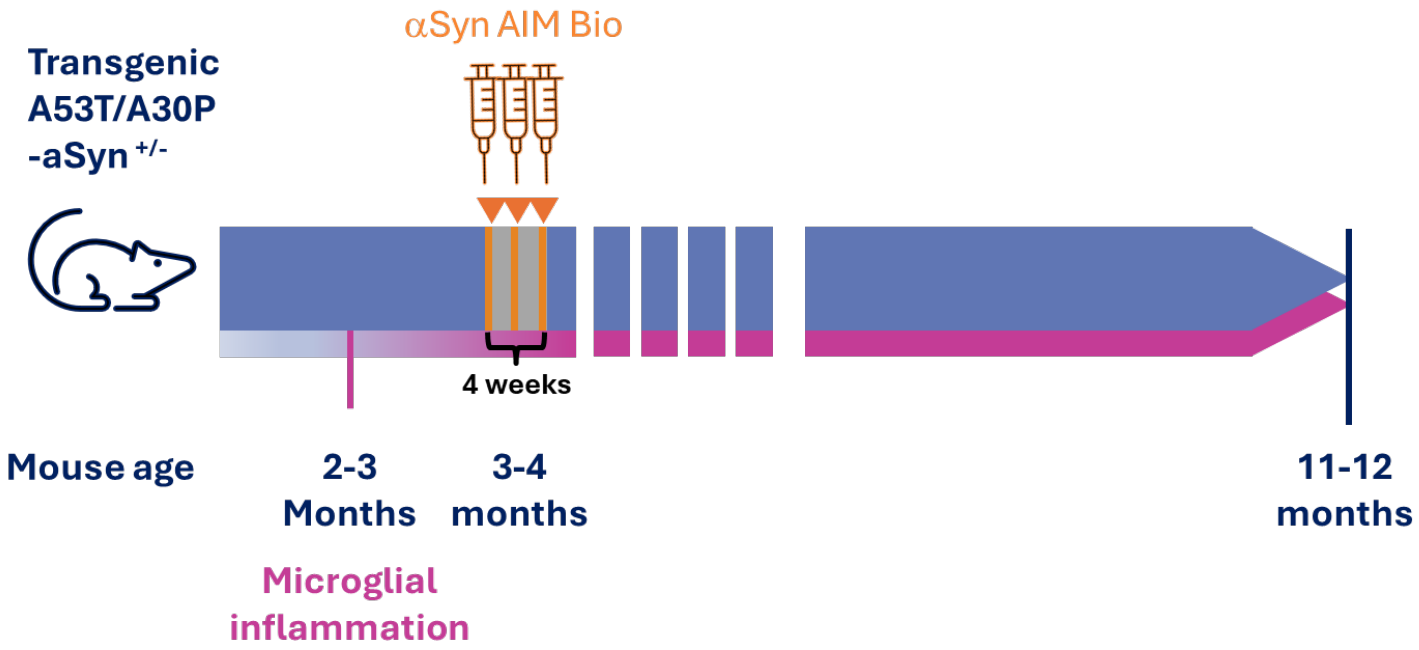
aSyn AIM Bios prevent loss of substantia nigra neurons

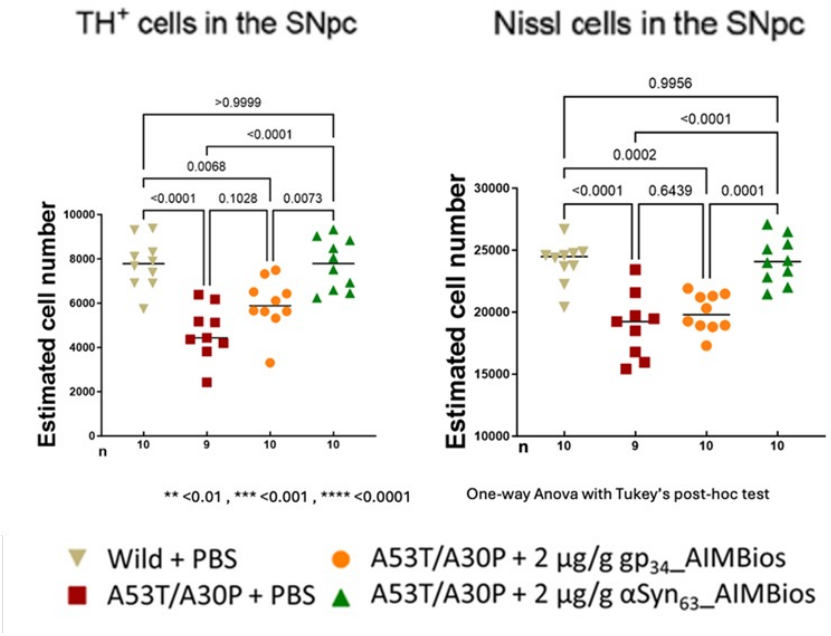




PD: AIM Bios confer long-term protection

Genetic A53T/A30P-αSyn model





→ a brief treatment with murine aSyn AIM Bios completely protects substantia nigra neurons and terminals even 7-8 months after the last injection

→ human candidate TOL301 induces tolerance to aSyn in T cells from PD patients

Key facts on AIM Bios

1. Engineered antigen-presenting HLA-G-like AutoImmunity Modulating Biologicals inspired by feto-maternal immune tolerance

2. Induce autoantigen-specific $CD8^+$ regulatory T cells and inhibit cytotoxic $CD8^+$ T cells (mouse and men)

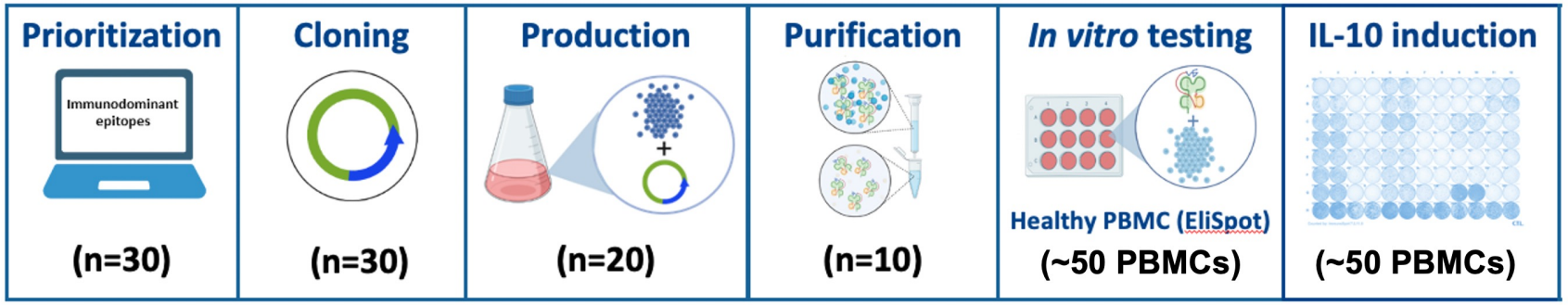
3. Acting upstream of the autoimmune inflammatory cascade, preventing pathogenic T cell actions and reducing autoreactive antibodies

4. $CD8^+$ Tregs secure an immune-privileged area around the organ affected by the autoimmune pathology (bystander effect)

5. Activity and tolerability in various animal models for MOGAD, multiple sclerosis, NMOSD and Parkinson´s disease

AIM Bio human candidate prioritization workflow

Immunodominant and functional AIM Bio peptide antigens are first predicted in silico, including folding analysis. Promising candidates are then cloned, expressed in mammalian systems, and purified. The production protocols, yields, and thermal stability are comparable to those of monoclonal antibodies and have been validated by CDMOs. Candidates are prioritized based on production yield, thermal stability, HLA-G receptor binding, and their ability to induce Tregs in PBMCs from healthy donors or patients.



Toleris AIM Bio platform pipeline overview

disease	developmentc andidate	predicted candidates	prioritized AIM Bios	PoC *in vivo*	*IND filing*	Phase I	Phase II	Phase III
MS/MOGAD*	TOL101							
NMOSD**	TOL201							
Parkinson's disease**	TOL301							
type 1 diabetes	t.b.d.							
myasthenia gravis	t.b.d.							
pemphigus & others	t.b.d.							

*current status: Toleris IND-filing program for TOL101 supported by Paul-Ehrlich-Institute in scientific advice meeting.

** currently first right of refusal for IP from University of Würzburg

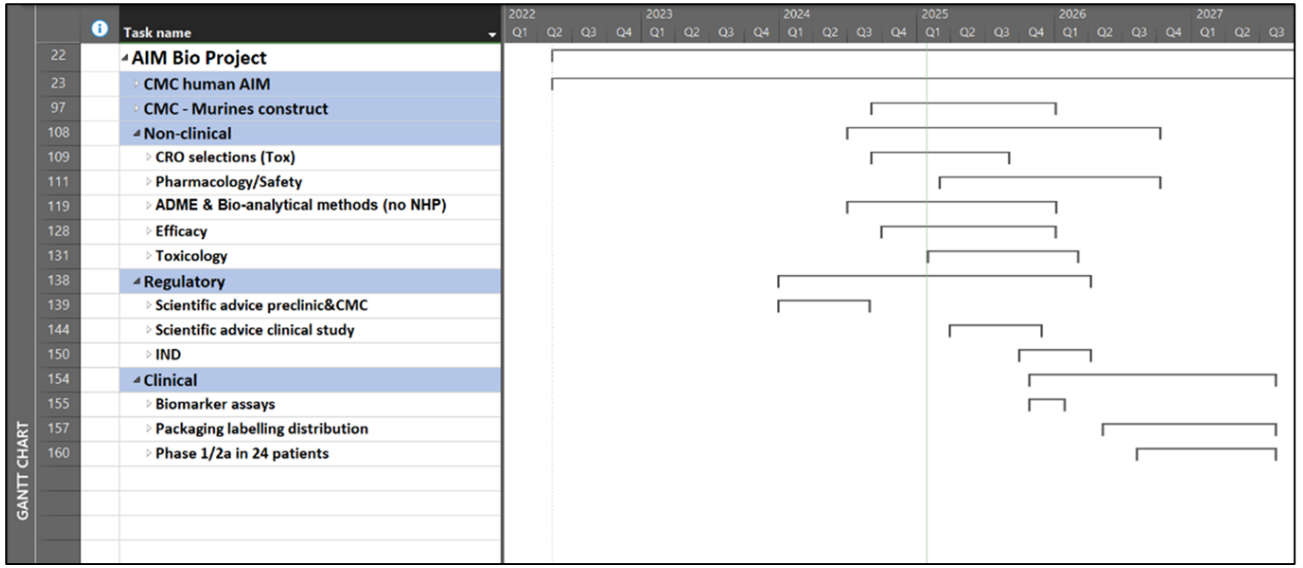
autoimmune disease market landscape

- AIM Bios are a platform technology with potential to revolutionize treatment options in numerous multi-billion $ disease markets (MS, PD, T1D, RA, IBD, ...)
- MOGAD and NMOSD are orphan diseases (prevalence 1.3–2.5 100,000[1]) with high medical need, and in the case of MOGAD no approved therapeutics. This should facilitate clinical entry and accelerate approval.
- Extension of use of the MOGAD compound for MS appears feasible.
- MS, T1D and PD are common autoimmune diseases with a high medical need (~10 years lower life expectancy in T1D[3]). Current therapeutics strongly impair the daily lives of patients. AIM Bios could stop disease progression and extend intervals between treatments to several months.

References: 1 PMID: 37789888; 2 PMID: 32296622; 3 PMID: 36804193

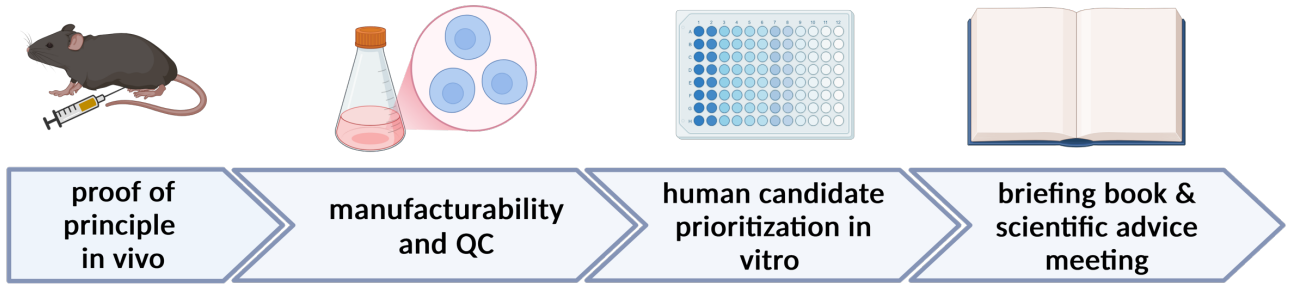
investment opportunities

Toleris' next key milestone to be achieved with a Series A round is the completion of a first clinical Phase 1a/b study in MOGAD or an alternative lead indication. This requires ~15-20 Mio €.



Budget estimate	
CMC:	~5M€
Non-clinical:	~3M€
Regulatory:	~1M€
Clinical:	~4M€
Other Activities: (IP,SAB):	~1M€

In parallel, we aim to complete *in vivo* proof of principle studies and human candidate prioritization in 1-2 additional indications. This requires ~1.5 Mio € per indication.



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