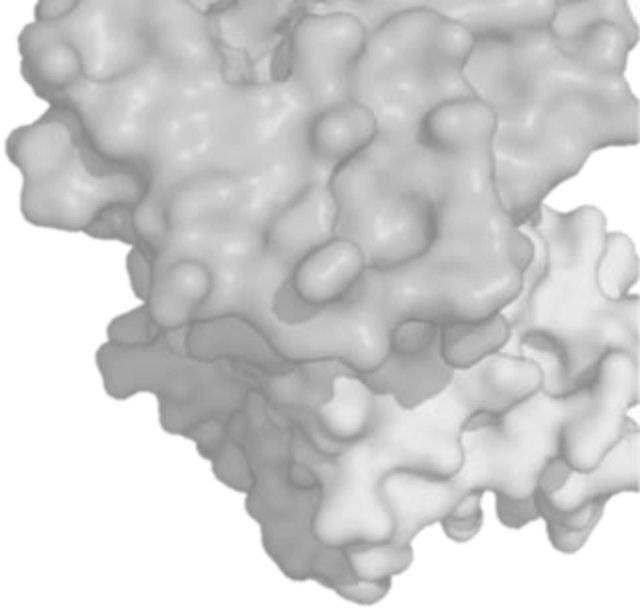


Toleris Biotherapeutics

AutoImmunity Modifying Biologicials - inspired by pregnancy

non-confidential slide deck 9/2024

disclaimer

Neither this presentation nor the information contained herein may constitute a contract or commitment of any kind. This presentation may contain indications about the objectives of or the business sector in which Toleris operates. These indications may be identified by use of the future and conditional tense or forward-looking statements such as 'thinks', 'aims', 'expects', 'should', 'intends', 'plans', 'estimates', 'believes', 'hopes', 'could' etc. This information is based on data, assumptions and estimates that Toleris considers reasonable, but which may prove not to be correct. Actual results or events suggested by those indications are difficult to predict, and the data assumptions or estimates on which such indications are based may change or be modified as a result of uncertainties relating in particular to the economic, financial, competitive and regulatory environment. Toleris does not make any commitments or give any guarantees concerning the attainment of any objectives set out in the presentation, the accuracy of the assumptions and estimates used or the updating of the information contained herein to reflect such changes and amendments.

Toleris Biotherapeutics: about us

Established January 2024 as a spin off from the University of Würzburg, Germany

Founders/shareholders:

- Prof. Jürgen Engel (CEO), Dr. Valentin Bruttel (CSO), Prof. Jörg Wischhusen (Chief Scientific Advisor)

Assets:

- exclusive worldwide license for innovative biotherapeutics platform AutoImmunity Modifying Biologicals (AIM Bios)
  (excluding NMOSD and Parkinson´s disease, which the founders co-develop with an industry partner)
- proof of concept in 4 animal models in 3 indications
- prioritized candidate molecules for MS/MOGAD and type 1 diabetes, other indications in preparation

Intellectual property:

- platform patent filed in major countries in 2017
- applications for MOGAD/MS and type 1 diabetes filed in 2022 and 2023

Toleris leadership team, partners, funding and awards

Toleris management team

Valentin Bruttel

immunologist and bioengineer, co-inventor AIM platform technology

Jörg Wischhusen

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

Markus Haake

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

Sigrid Müller-Deubert

immunologist, public funding and project coordination

Jürgen Engel

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

funding/awards:

eXIST

Bundesministerium für Wirtschaft und Klimaschutz

m⁴ Award

Bayerisches Staatsministerium für Wirtschaft, Landesentwicklung und Energie

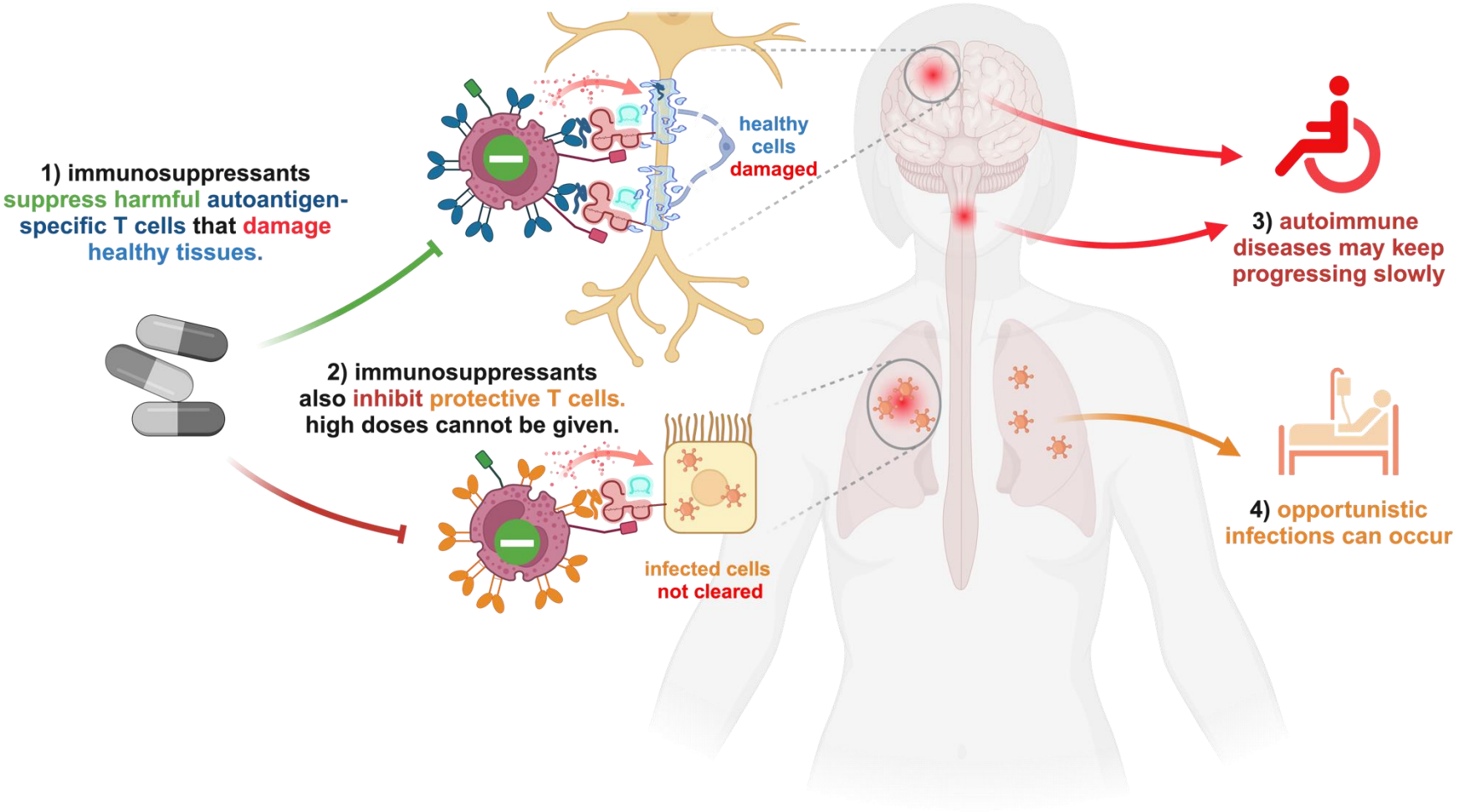
Innovationspreis 2022

BioRegionen in Deutschland

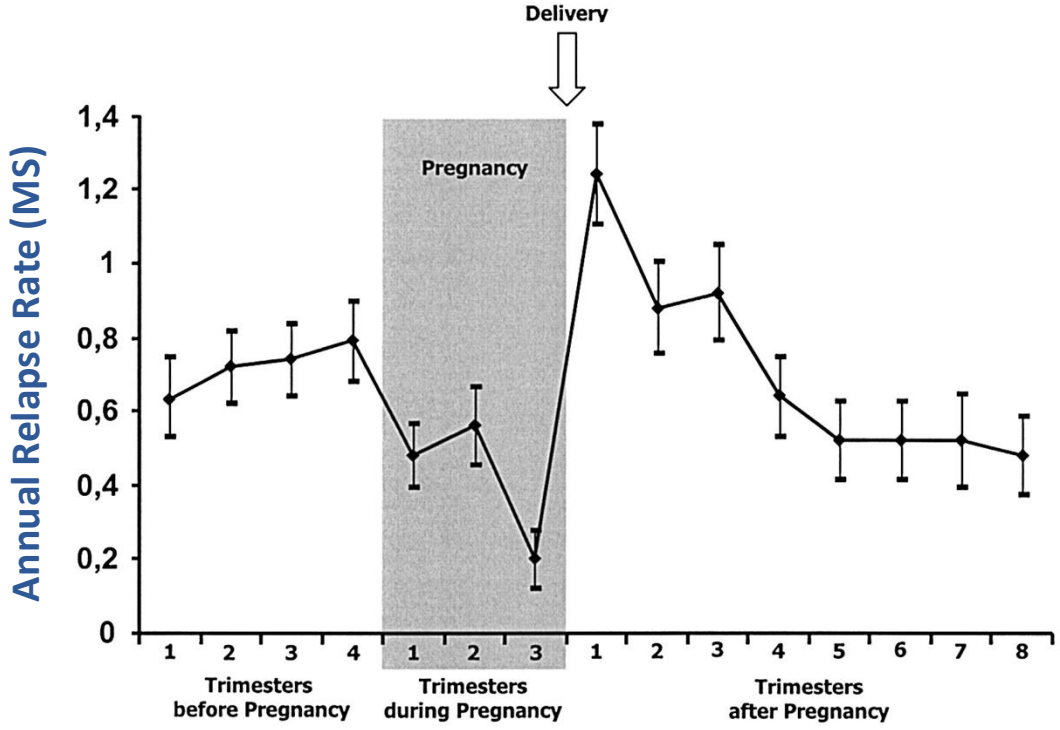
Collaboration partners:

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

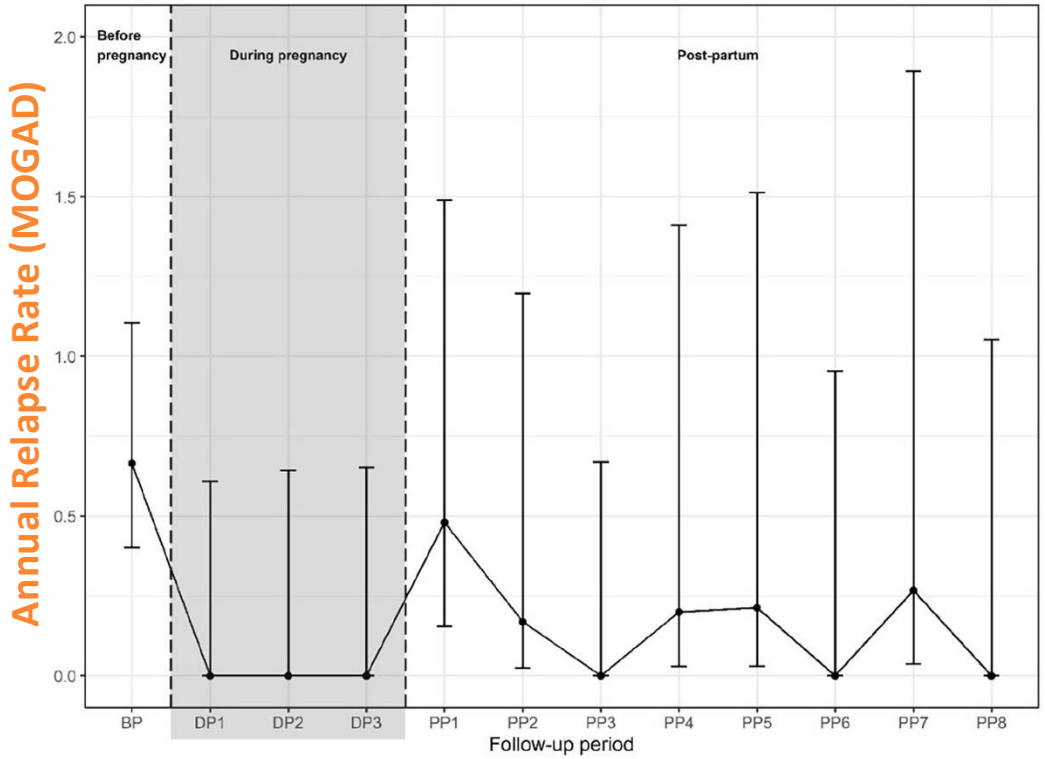
The key challenge in autoimmune therapy: precision



Autoimmune disease symptoms vanish during pregnancy



Brain, Volume 127, Issue 6, June 2004, Pages 1353–1360

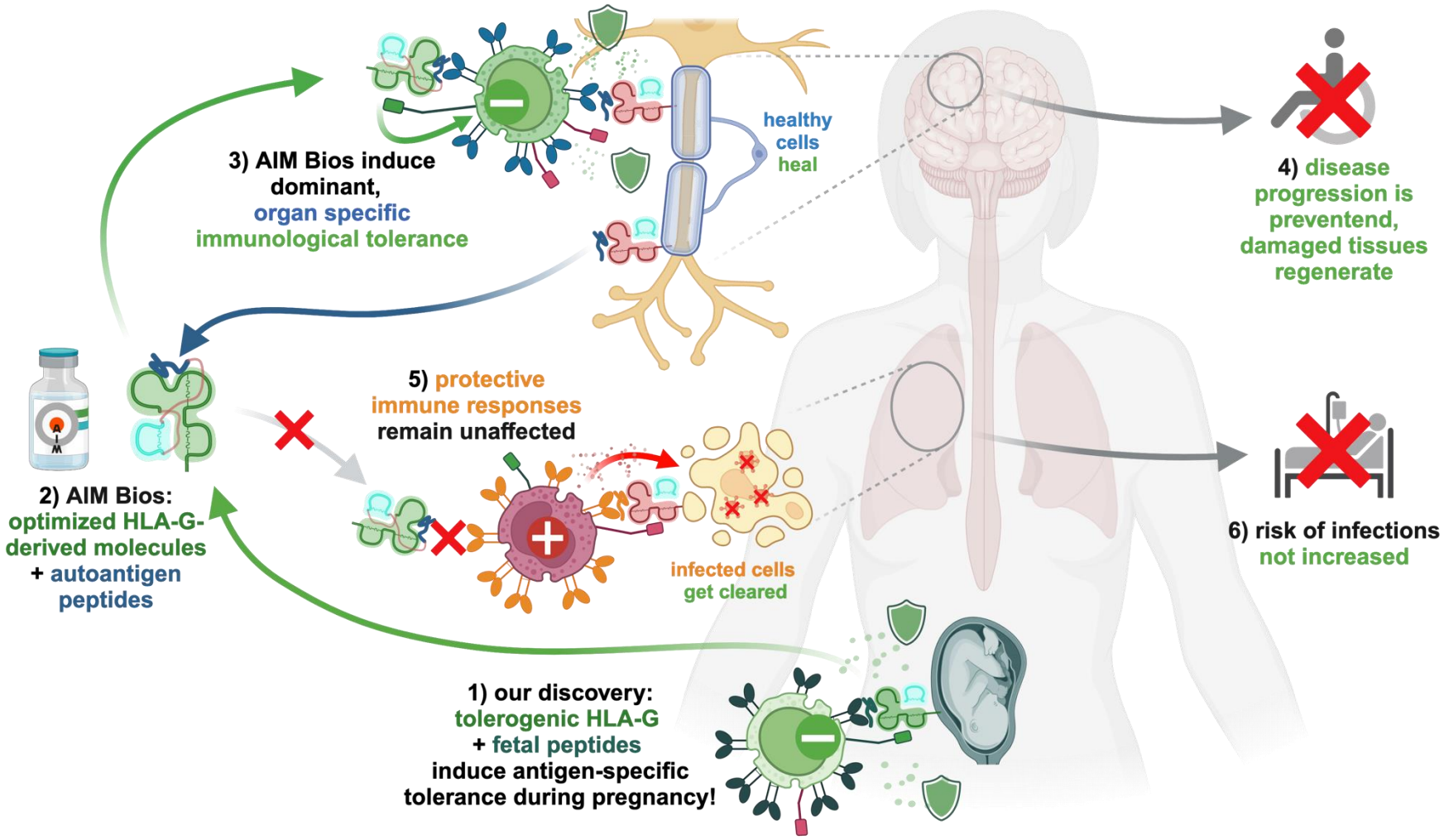


Carra-Dallière C. et al., Multiple Sclerosis Journal. 2023;29(2):270-276

Embryonic cells in maternal blood induce and maintain regulatory T cells!

Shao et al., Science, September 2023

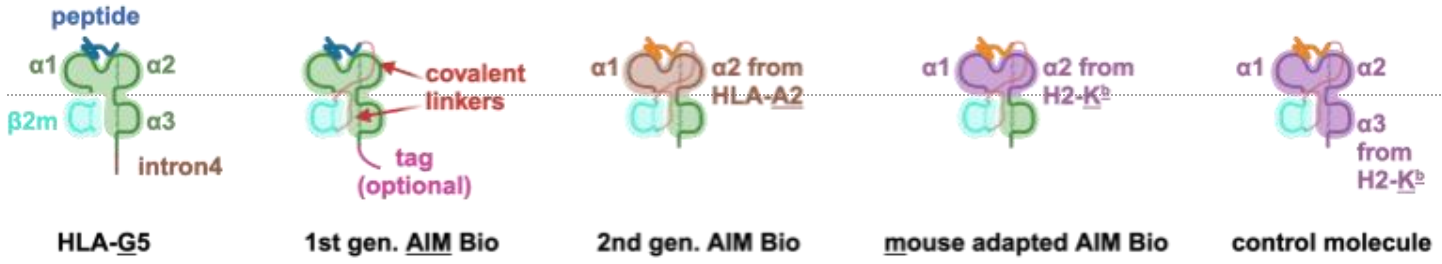
Our solution: mimicking natural targeted tolerance



AIM Bios: adaptable to induce tolerance to any protein

AIM Bios are soluble, HLA-G derived molecules in which the presented peptide antigen, the presenting domains, β2-microglobulin and the tolerance-inducing HLA-G α3 domain are covalently linked.

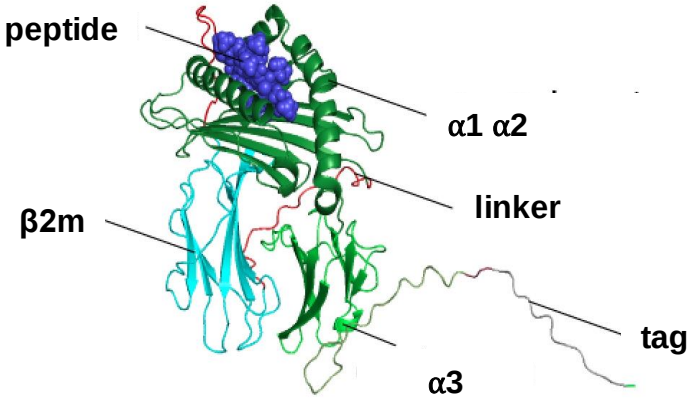
structural and functional domains in AIM Bios



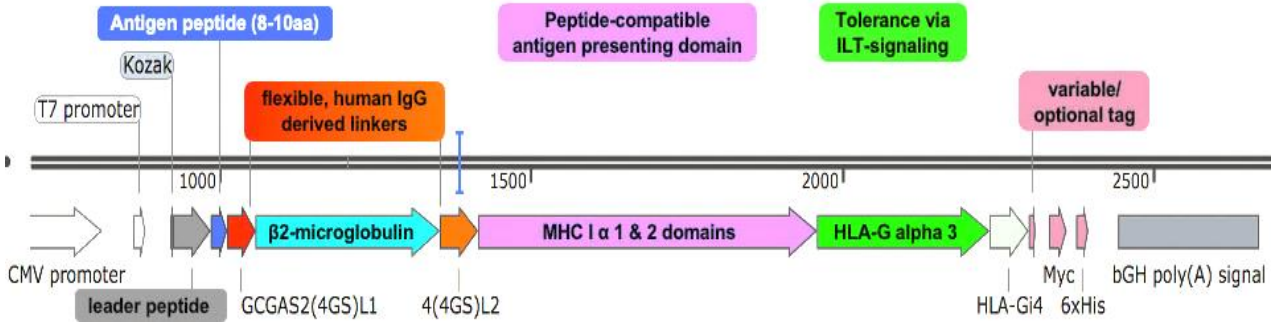
Peptide and matching antigen-presenting domains
→ define the specificity

β2-microglobulin and HLA-G α3 domain
→ provide stability and induce tolerance

predicted 3D structure



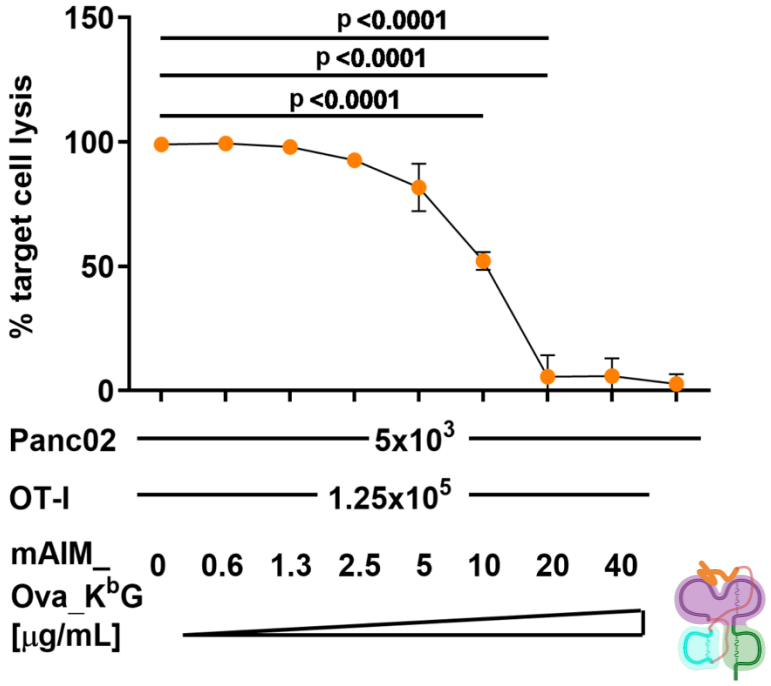
key genetic elements in AIM Bio production plasmids



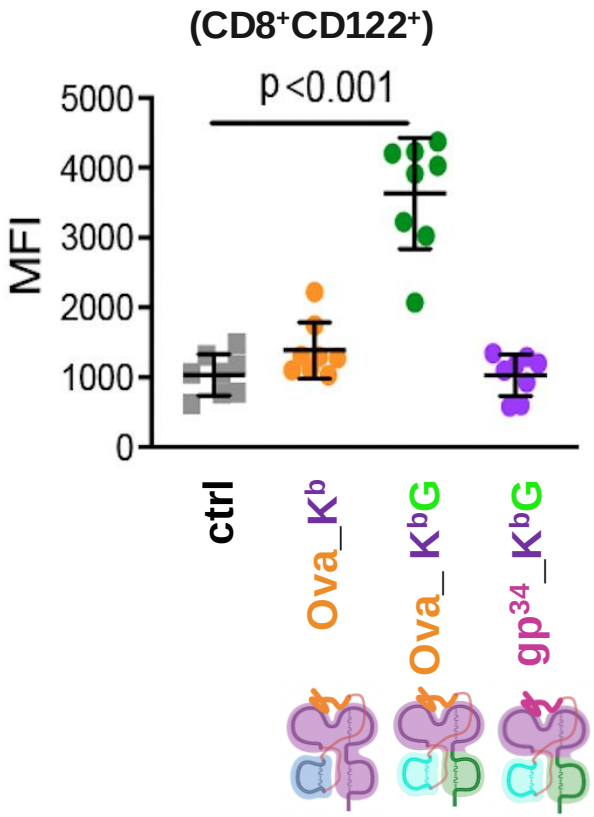
PoC: AIM Bios induce protective, antigen specific Treg

Only cognate, Ovalbumin-presenting mouse adapted AIM Bios induce protective Treg in OT-I splenocytes

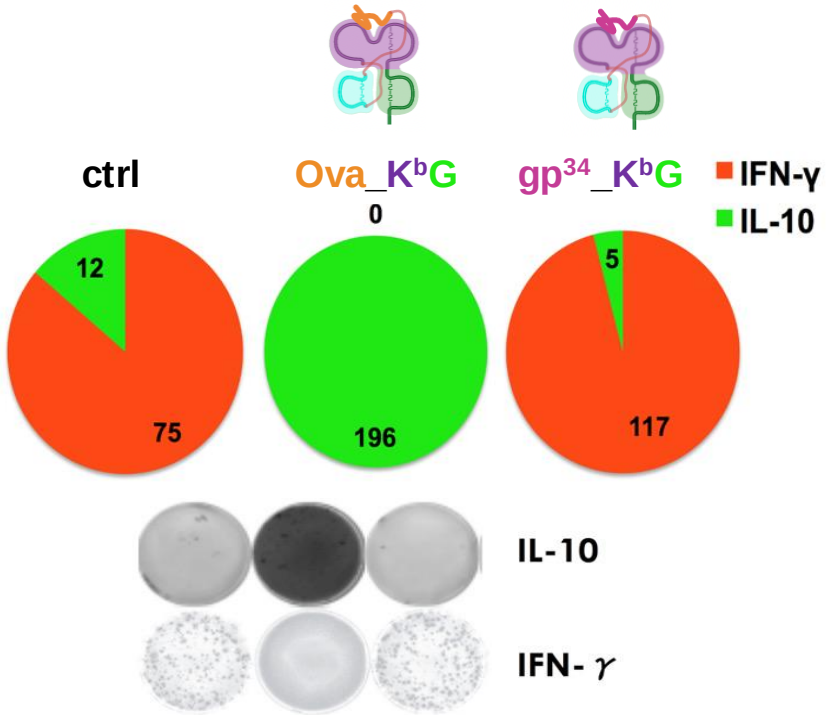
→ suppression of cytotoxicity



→ more regulatory T cells



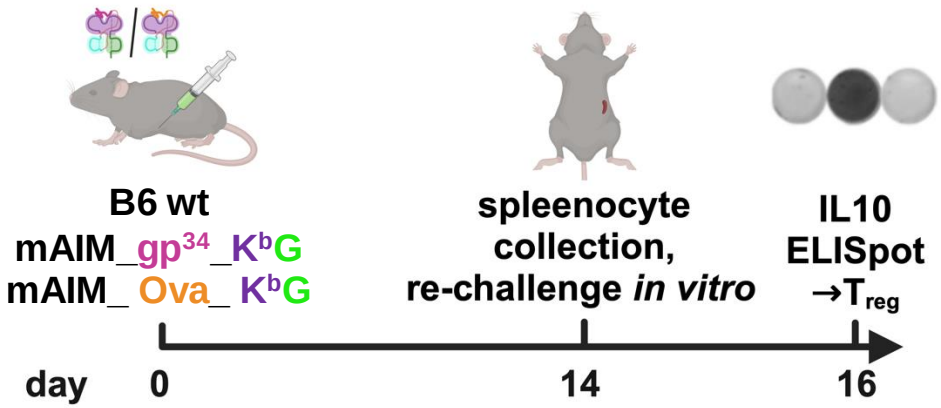
→ shift to tolerogenic cytokines



AIM Bios induce antigen specific Treg *in vivo*

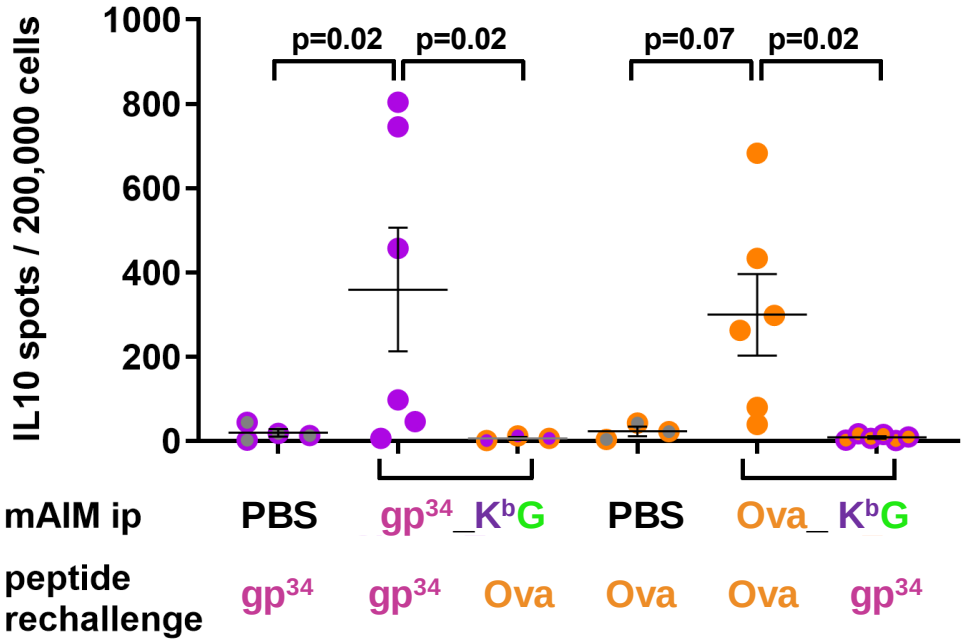
Experimental setup

Mice were injected with AIM Bios inducing tolerance to one of 2 model peptide antigens.



Results

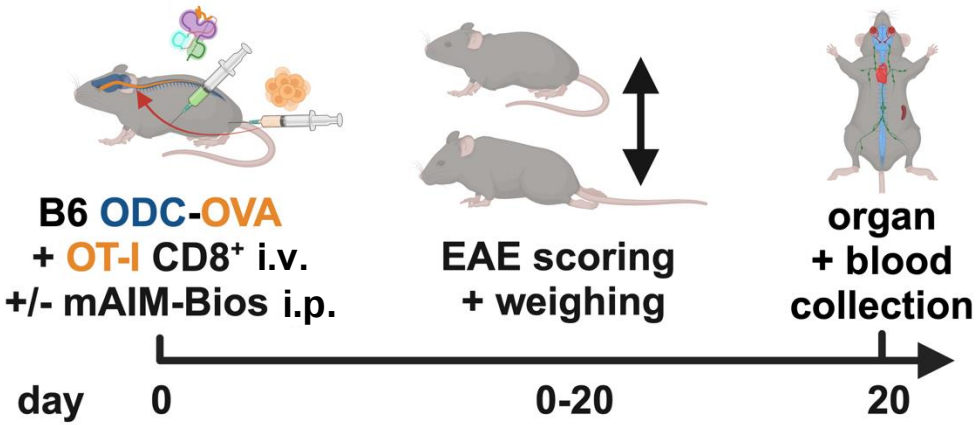
After 14 days, splenocytes collected from the treated mice secreted immunomodulatory IL10 when re-challenged with the same antigen presented on AIM Bios



AIM Bios fully prevent MS symptoms in mice

Experimental setup

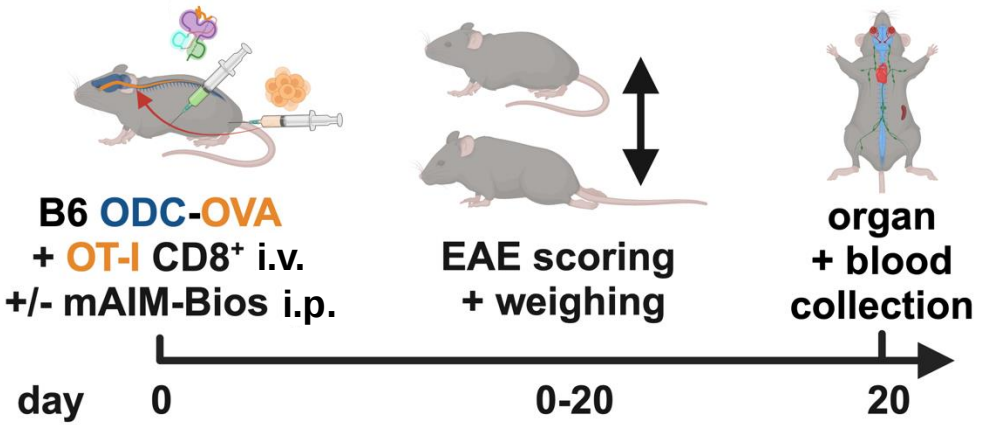
Oligodendrocytes are attacked in MS patients. Mice expressing the Ova model antigen in oligodendrocytes were injected with Ova-specific T cells and mouse adapted AIM Bios.



AIM Bios fully prevent MS symptoms in mice

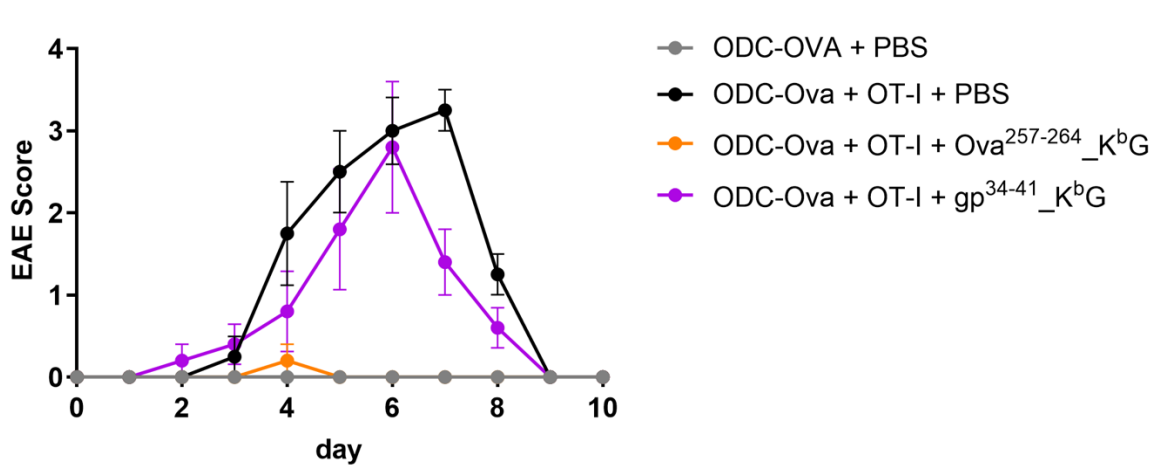
Experimental setup

Oligodendrocytes are attacked in MS patients. Mice expressing the Ova model antigen in oligodendrocytes were injected with Ova-specific T cells and mouse adapted AIM Bios.



Results

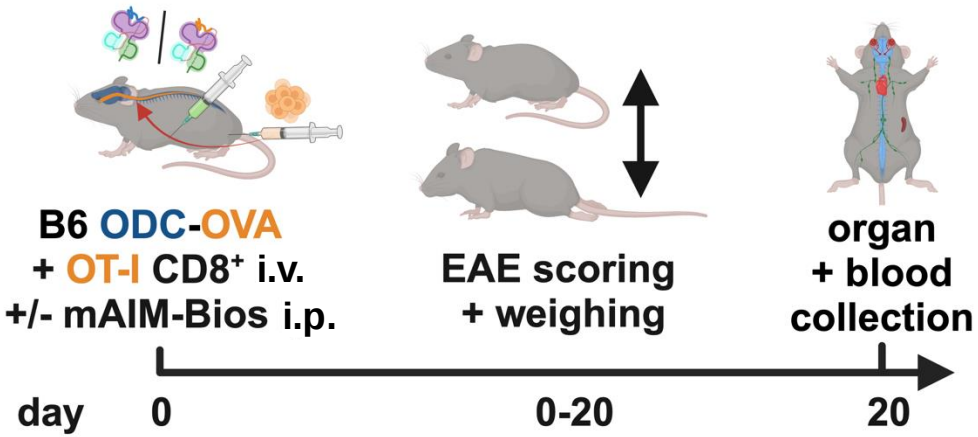
Mice treated with AIM Bios presenting the targeted Ova peptide were completely protected from severe paralysis (EAE)



AIM Bios induce dominant organ-specific tolerance

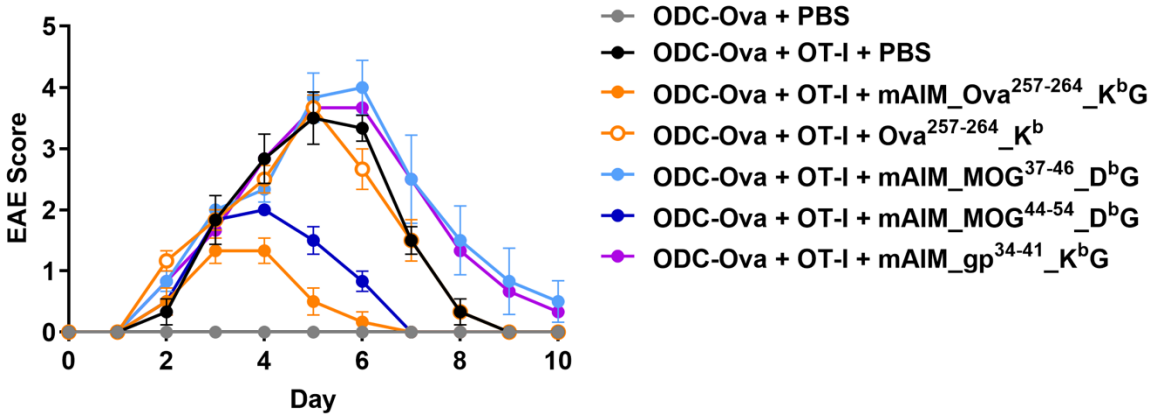
Experimental setup

The targeted autoantigen peptides always vary between patients. Thus, we tested if AIM Bios inducing tolerance towards the oligodendrocyte antigen MOG protect mice in which the disease is caused by Ova-specific T cells.



Results

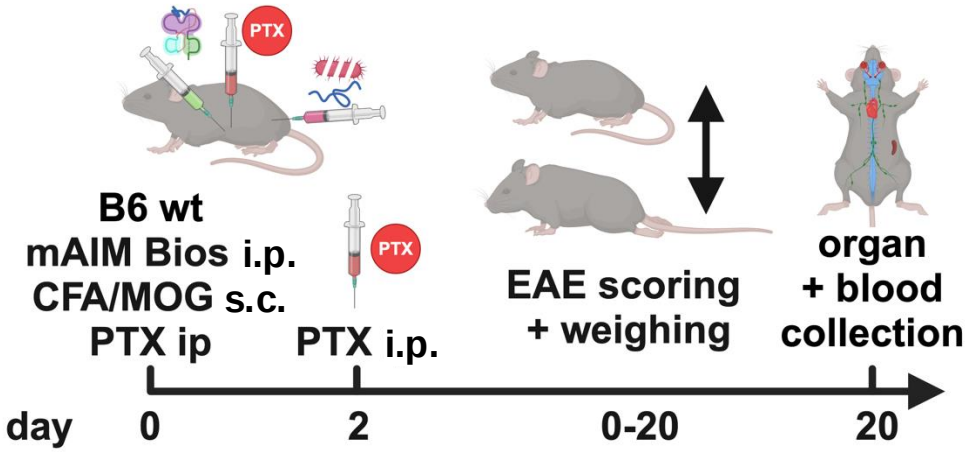
Mice treated with one MOG-tolerance inducing AIM Bio were protected almost as well against paralysis as mice treated with Ova tolerance inducing AIM Bios.



AIM Bios prevent autoantibody development

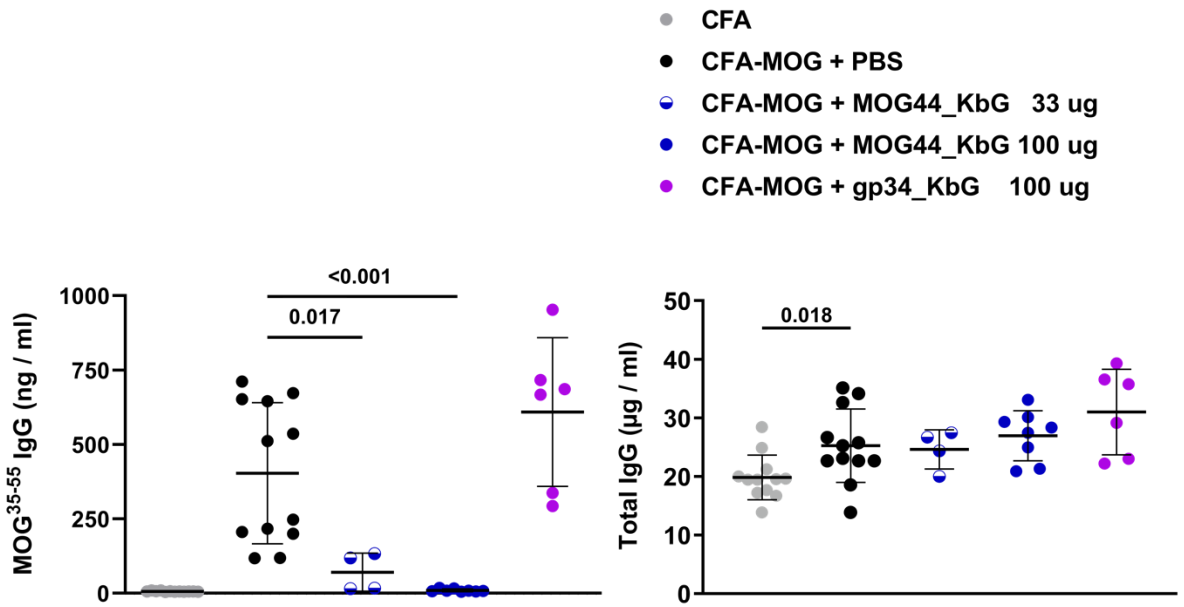
Experimental setup

Wildtype mice were injected with a MOG peptide, a strong adjuvant and a toxin attacking the blood-brain barrier to induce MS symptoms (EAE) and MOG specific autoantibodies.



Results

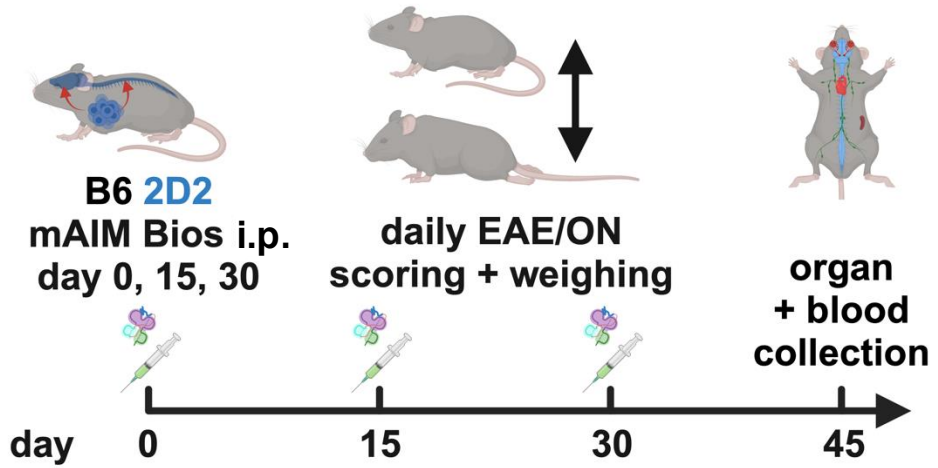
Mice treated with one MOG-tolerance inducing AIM Bios developed significantly less MS symptoms (not shown) and prevented the development of autoantibodies in a dose-dependent manner. Other, protective antibodies (total IgG) were not affected.



AIM Bios reduce pre-existing disease symptoms

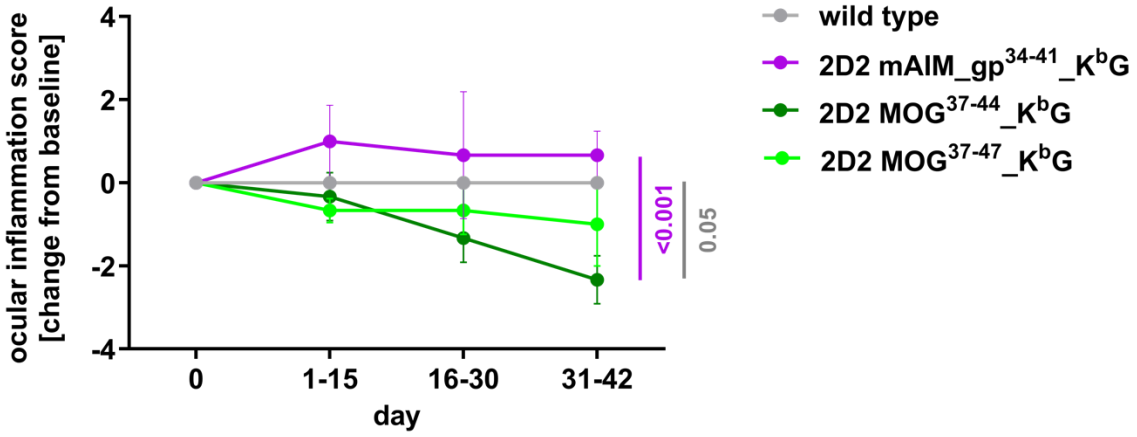
Experimental setup

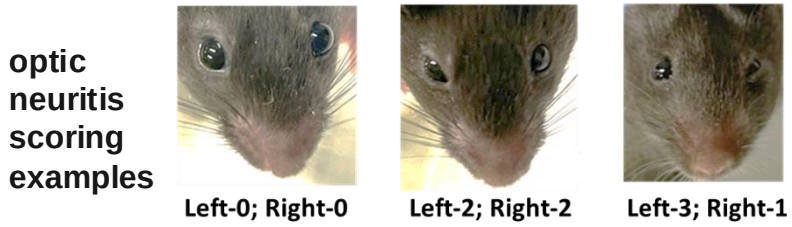
2D2 mice express a MOG-specific T cell receptor on every T cell and spontaneously develop MOG Antibody Disease (MOGAD) like symptoms including paralysis and optic neuritis (ON). These mice were treated with MOG tolerance-inducing AIM Bios after disease onset.



Results

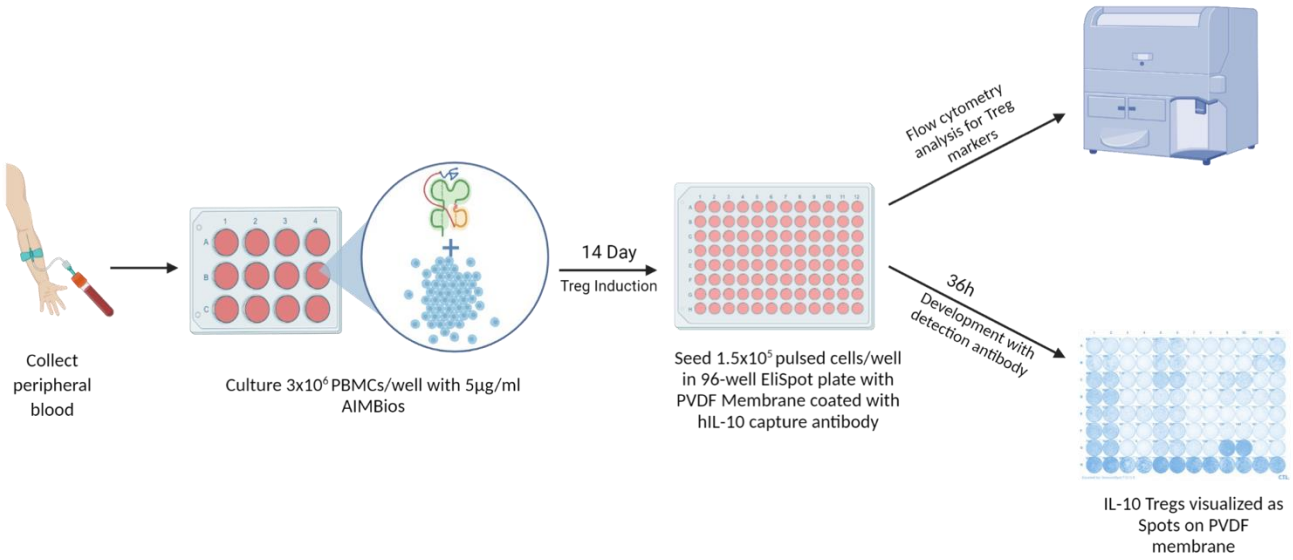
A MOG-tolerance inducing AIM Bio reduced pre-existing optic neuritis in 2D2 mice. Paralysis and cell death in the retina, optic nerve and spinal cord were completely prevented (data not shown).

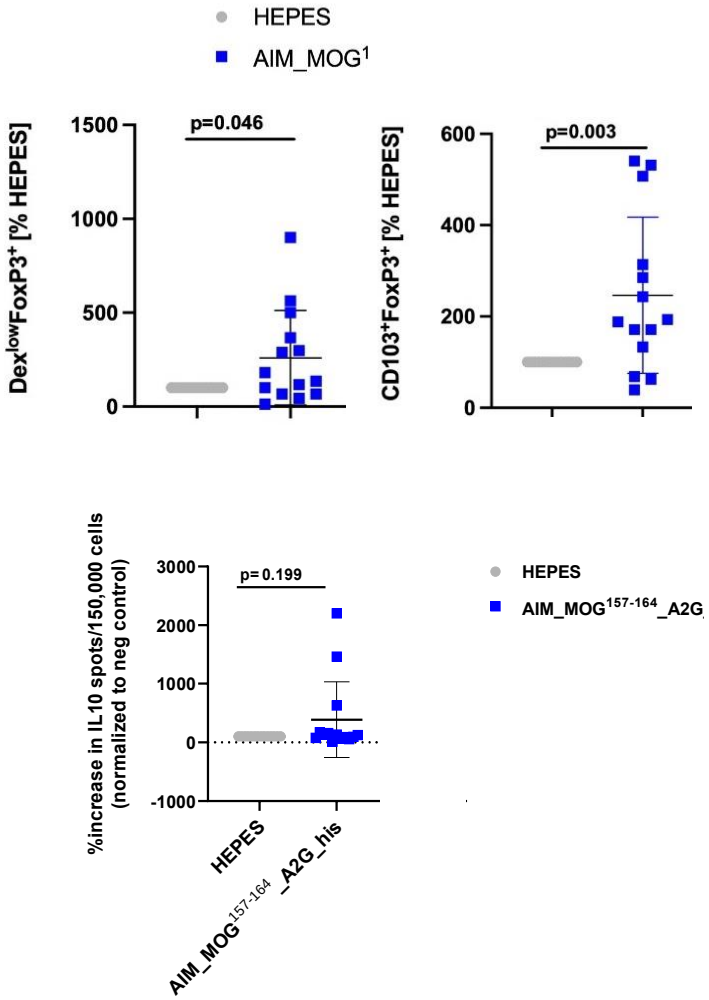




AIM candidates efficiently induce Treg in patient cells

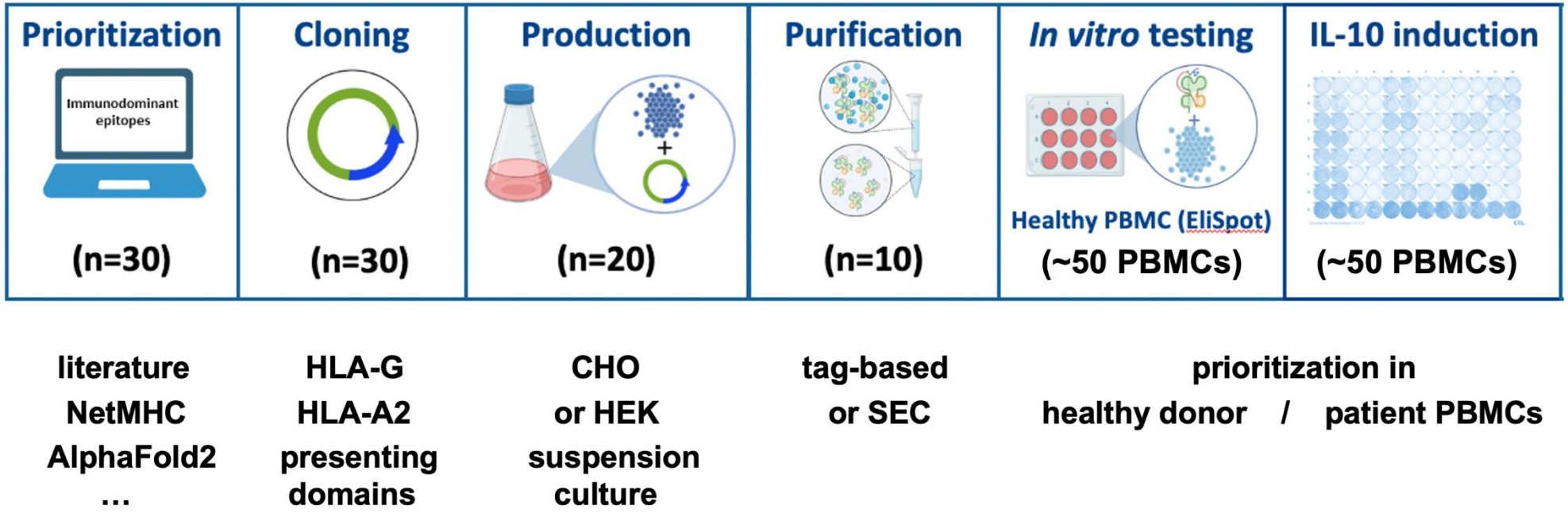
Lead compounds for type I diabetes, multiple sclerosis and MOGAD have been identified. An induction of Treg can be observed in 60-80% of tested healthy donor PBMCs. A significant induction of Treg was observed in PBMCs from MS patients.



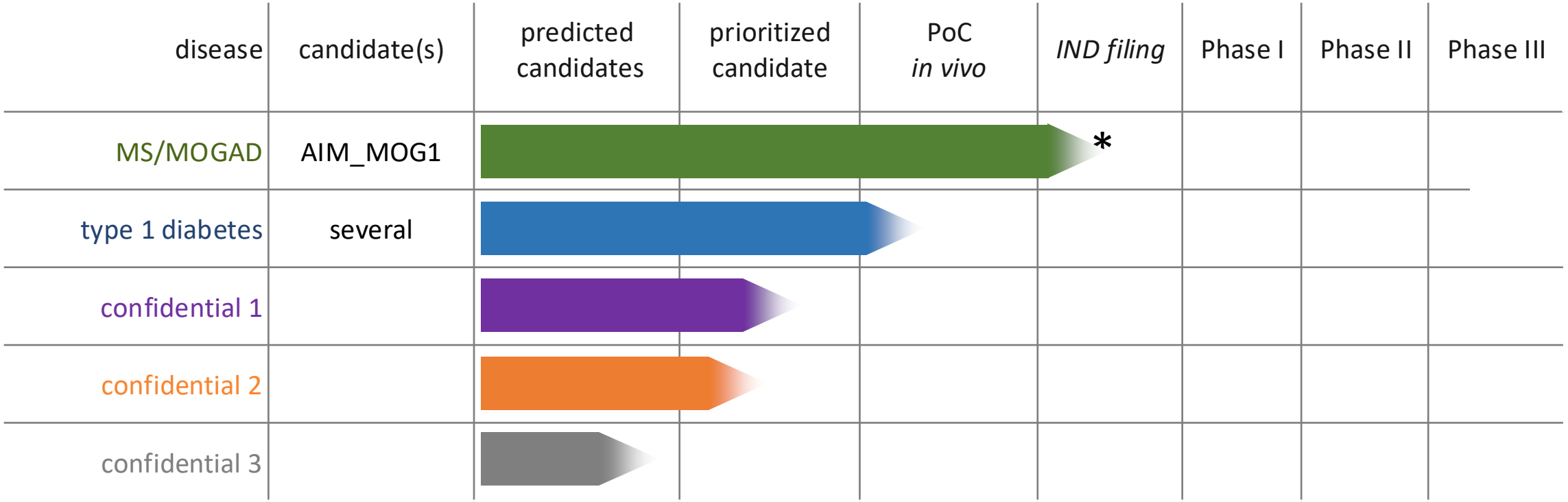


AIM Biologicials technology platform

Human candidate molecule development:
Immunodominant and functional HLA-G or HLA-A2 restricted epitopes in autoimmunity target proteins are predicted in silico. AIM Bios are cloned into mammalian expression vectors. Transient transfection in suspension cell lines produces similar yields and purities as seen in monoclonal antibodies. Candidates are then prioritized based on yields, thermal stability, HLA-G receptor binding and the capacity to induce Treg in healthy donor or patient PBMCs.



Toleris pipeline overview



* current status: Toleris IND-filing program for AIM_MOG1 supported by Paul-Ehrlich-Institute in scientific advice meeting.

autoimmune disease market landscape

- Platform technology allows for entering numerous multi-billion $ markets (MS, T1D, RA, IBD, …)
- MOGAD is an orphan disease (prevalence 1.3–2.5/100,000[1]) with high medical need, for which no approved therapeutics exist. This should facilitate and accelerate the approval process.
- Extension of use of the MOGAD lead compound for MS appears feasible. This may allow for entering this major market without the need for additional tox or clinical phase I studies
- T1D: is a common autoimmune disease (prevalence 59/100,000[2]) with a high medical need (~10 years lower life expectancy[3]) and therapeutic options that strongly impair the daily lives of patients. AIM Bios could stop disease initiation or progression and reduce the number of injections needed to one in three months.

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

USP: physiological targeted tolerance induction

Antigen-specific tolerance induction has been considered to be the “holy grail” for immunotherapy of autoimmune diseases for more than a decade.

Many competitors simply administer peptides in the absence of co-stimulation, which induces tolerance in allergies (hyposensitation), but thus far failed in autoimmune disease patients.

This evolved into encapsulating antigens liposomes or nanoparticles, which led to further technical hurdles, and thus far also did not function in patients. RNA-based antigen delivery may activate the immune system via TLR3.

Clinical success was seen with experimental cell based therapies. However, this requires individually tailored cell therapy products which are very expensive and challenging to produce and have thus not been applied commercially.

To our knowledge, AIM Biologicals are the only immunosuppressants under development that combine tolerance-inducing domains and specific antigens in an almost completely physiological molecule, which evolved over millions of years to safely and reliably induce immunological tolerance during pregnancy.

David C. Wraith, The Future of Immunotherapy:
A 20-Year Perspective, Frontiers in Immunology, 2017

Immunotherapy of Autoimmune Diseases

The Holy Grail for treatment of autoimmune diseases is to discover a means of selectively suppressing the specific autoimmune disease while leaving the rest of the immune system functionally active for control of infectious diseases and cancers. The aim is to develop treatments with increasing specificity for disease in order to decrease the risk of potential side effects. The ultimate aim is to provide a cure; however, the likelihood of success for this aim will depend on the particular autoimmune disease and associated pathology. For example, it may be sufficient to deplete autoreactive cells to correct the immune imbalance and reset homeostatic control of autoreactivity. In other cases, however, it may be necessary to continue treatment to arrest disease progression.

Review > Curr Opin Pharmacol. 2007 Aug;7(4):418-25. doi: 10.1016/j.coph.2007.05.001.
Epub 2007 Jul 3.

T cell immunomodulation--the Holy Grail of therapeutic tolerance

John D Isaacs [1]

Affiliations + expand

PMID: 17611158 DOI: 10.1016/j.coph.2007.05.001

partnering and investment opportunities

IND enabling / early clinical development partnerships / investments

Toleris is looking for biotech or pharmaceutical companies interested in co-developing or venture capital partners interested in investing in our more advanced therapeutic programs. These are MS and MOGAD, for which we have received regulatory scientific advice, and type 1 diabetes, for which we have prioritized human candidates.

Preclinical development partnerships / early investments

Toleris is looking for early investors, biotech and academic partners to adapt the AIM Biologicals to novel indications. We offer extensive experience in human candidate or surrogate AIM Bio design, production and prioritization, and have successfully collaborated with academic and clinical partners in Europe and the US. Opportunities include myasthenia gravis, pemphigus vulgaris, stiff person syndrome, rheumatoid arthritis and many other autoimmune diseases with defined autoantigens.

Please contact us via info@toleris.com !