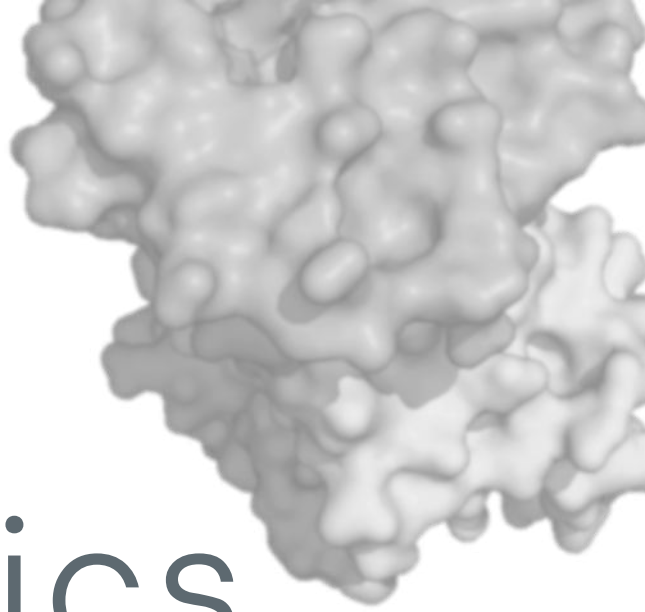

Toleris Biotherapeutics

AutoImmunity Modifying Biologicials - inspired by pregnancy

non-confidential slide deck 6/2024

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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)
- Asset: 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)
- Intellectual property:

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

Toleris leadership team, partners, funding and awards

Toleris management team

Dr. rer. nat. **Valentin Bruttel**

immunologist and bioengineer, co-inventor AIM platform technology

Prof. Dr. **Jörg Wischhusen**

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

Prof. Dr. Dr. **Jürgen Engel**

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

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

public funding and awards:

eXIST

Bundesministerium für Wirtschaft und Klimaschutz

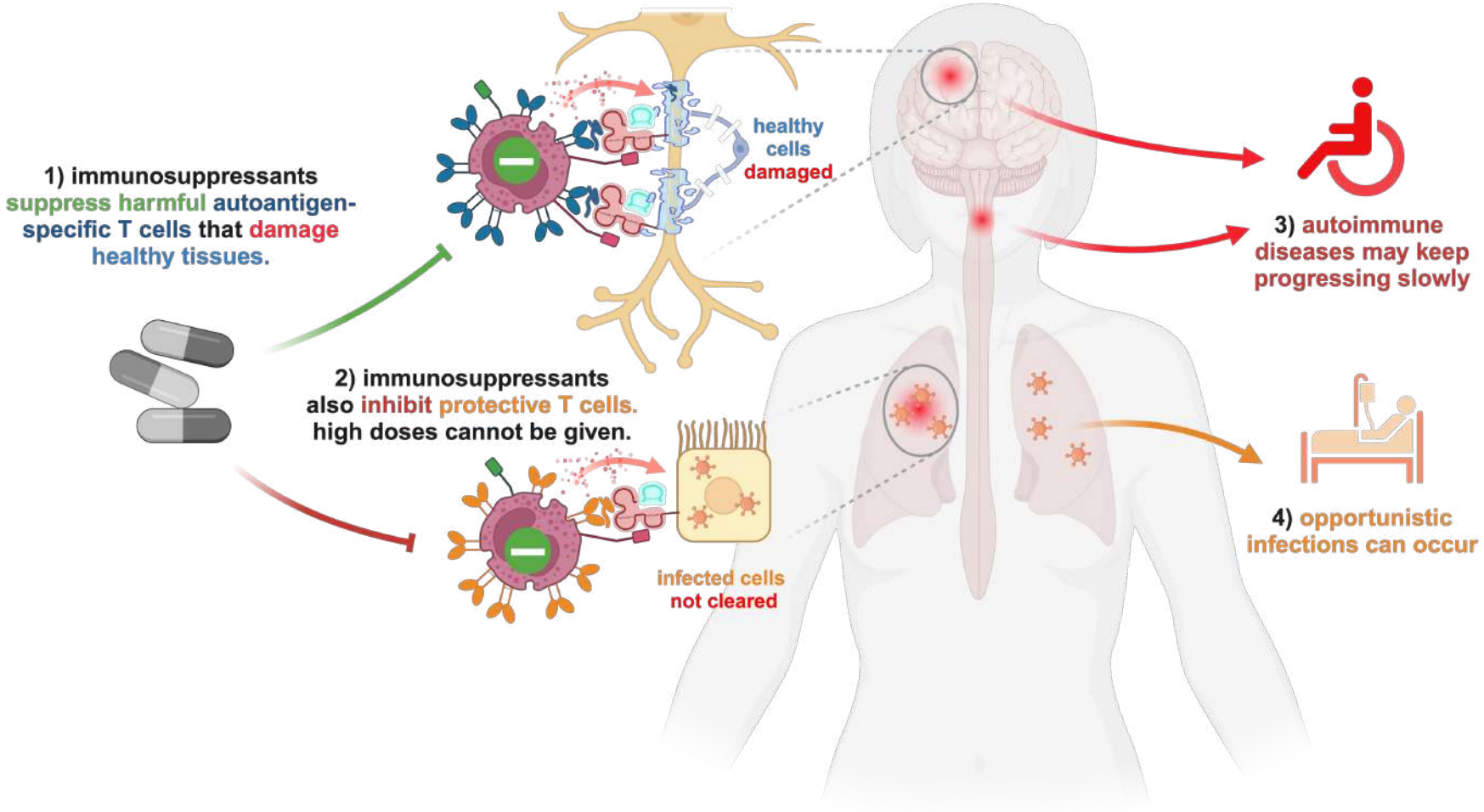
m⁴ Award

Bayerisches Staatsministerium für Wirtschaft, Landesentwicklung und Energie

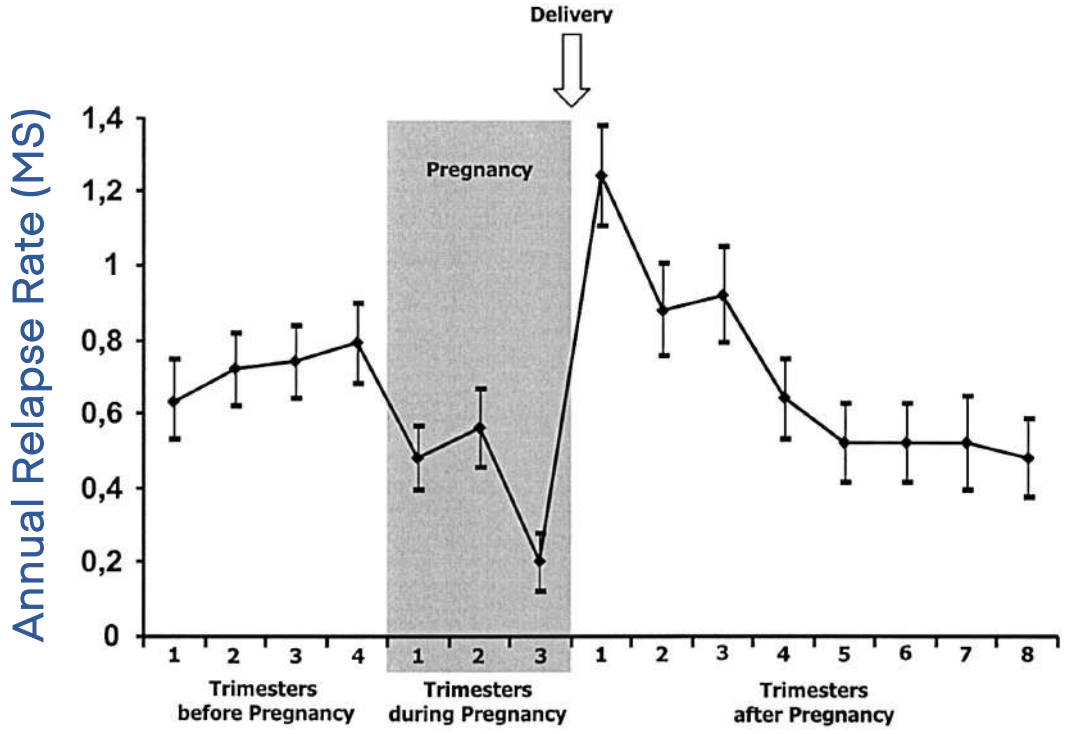
Innovationspreis 2022

BioRegionen in Deutschland

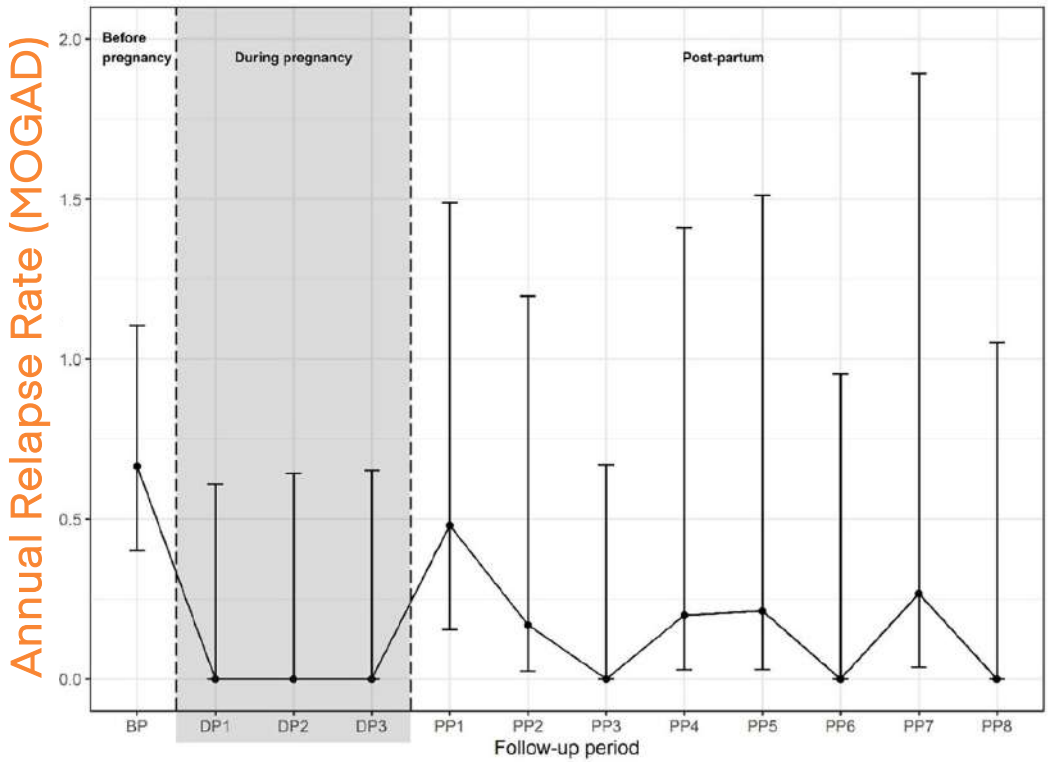
The key challenge in autoimmune therapy: precision



Autoimmune disease symptoms vanish during pregnancy



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

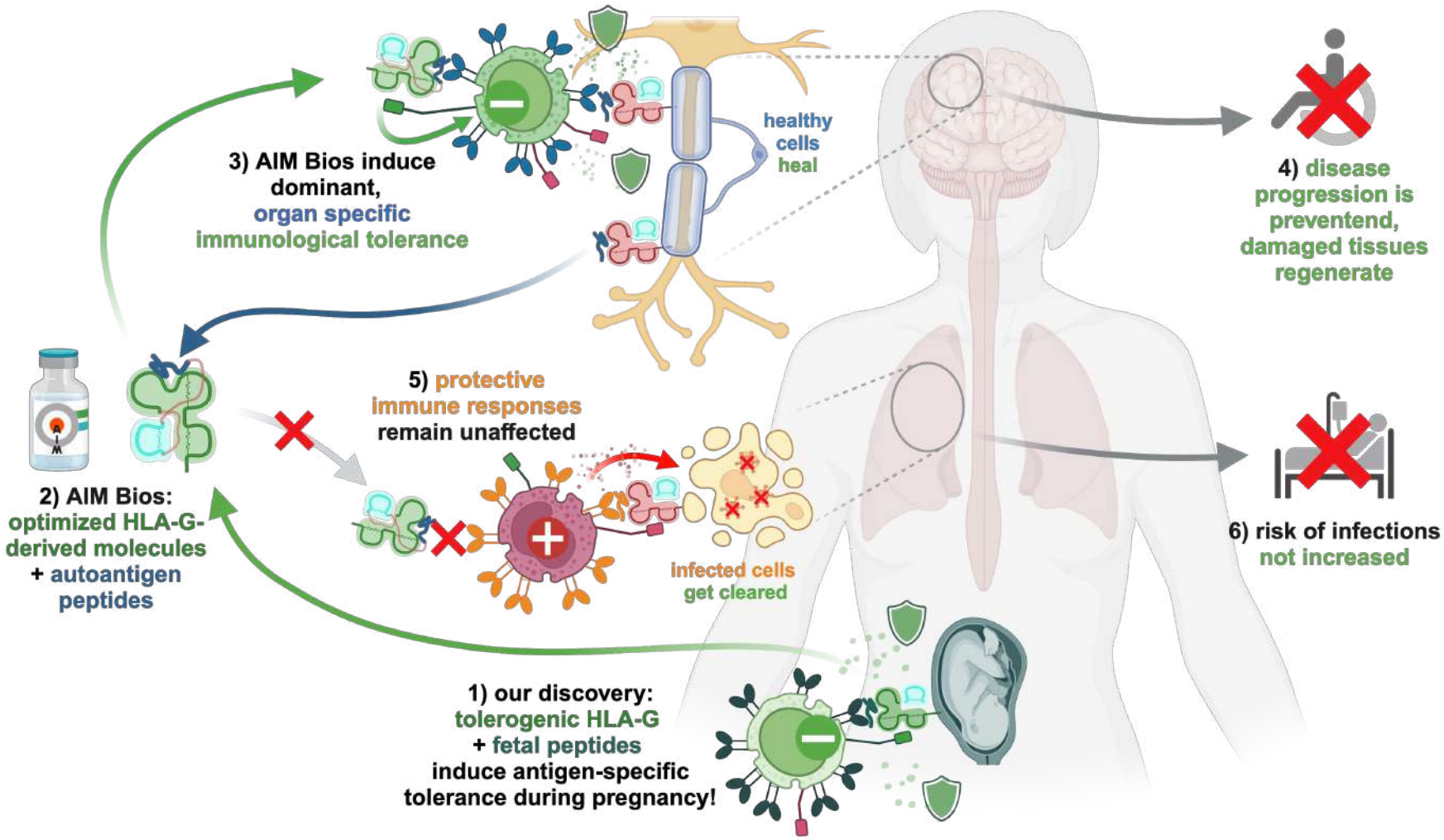


Carra-Dallière C. et al., Multiple Sclerosis Journal. 2023;29(2):270-276

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

Shao et al., Science, September 2023

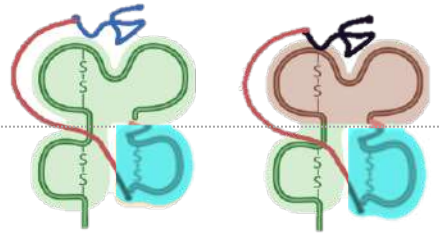
Our solution: mimicking natural targeted tolerance



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.

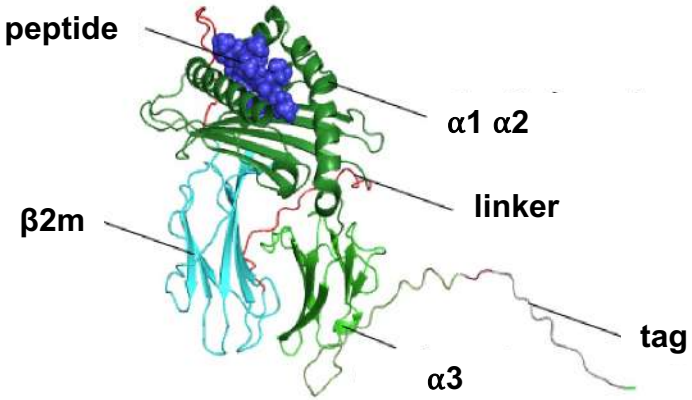
structural and functional domains in AIM Bios



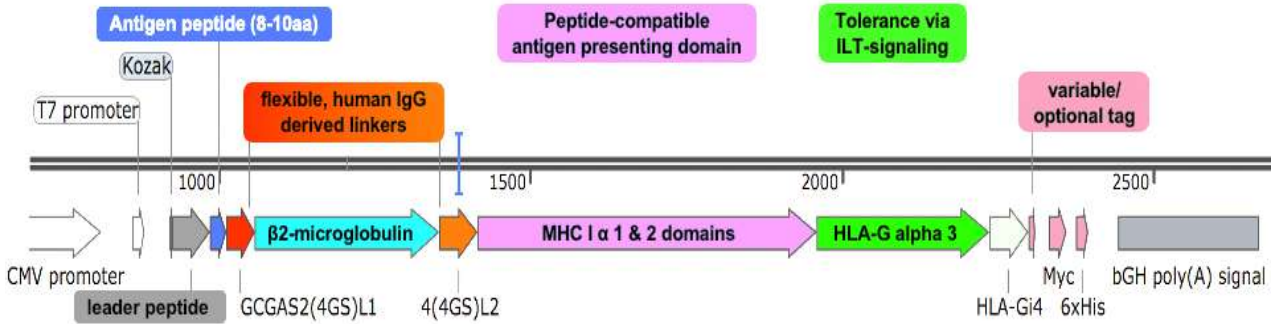
Peptide and matching antigen-presenting domains define the specificity

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

predicted 3D structure



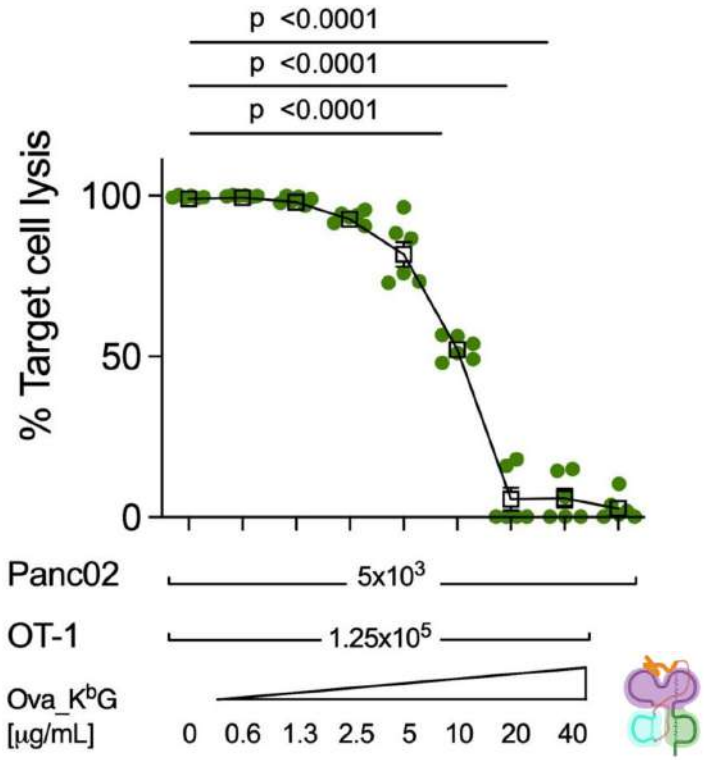
key genetic elements in AIM Bio production plasmids



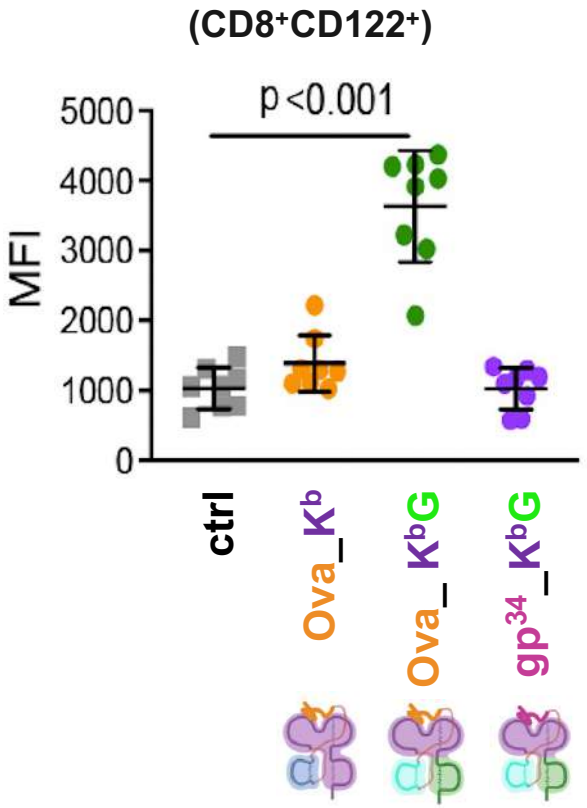
PoC: AIM Bios induce protective, antigen specific Treg

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

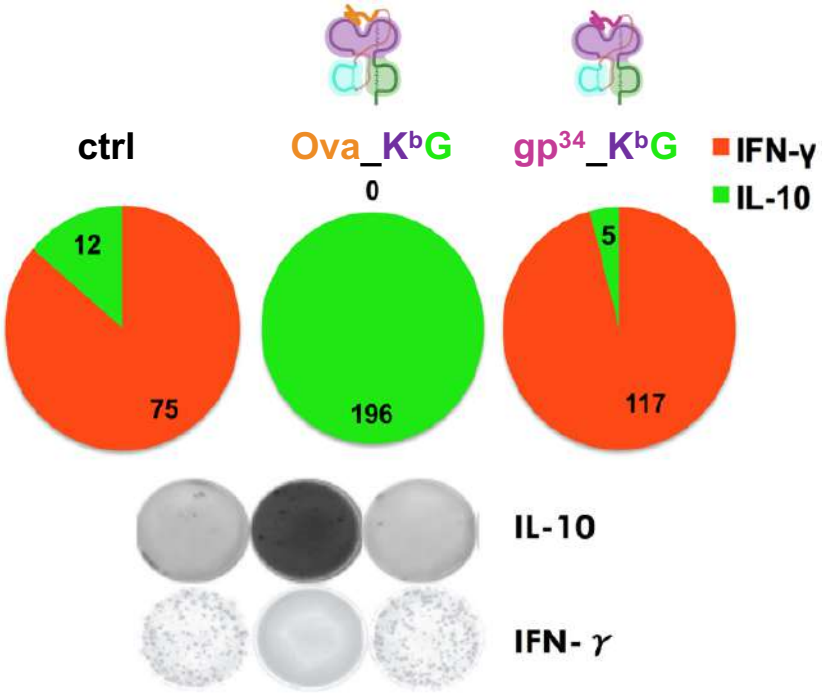
→ suppression of cytotoxicity



→ induction of tolerogenic cytokines



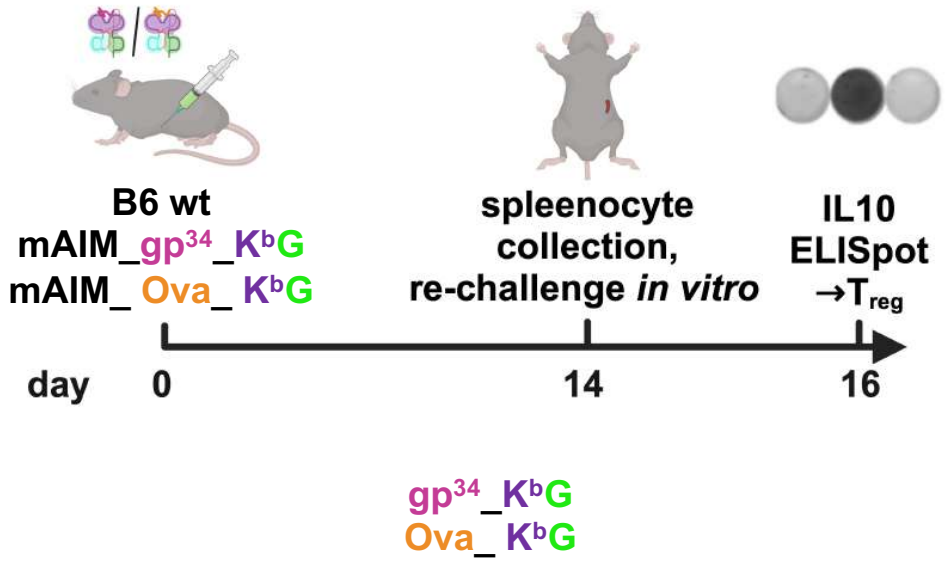
→ upregulated T_{reg} markers



AIM Bios induce Treg specific for presented peptides *in vivo*

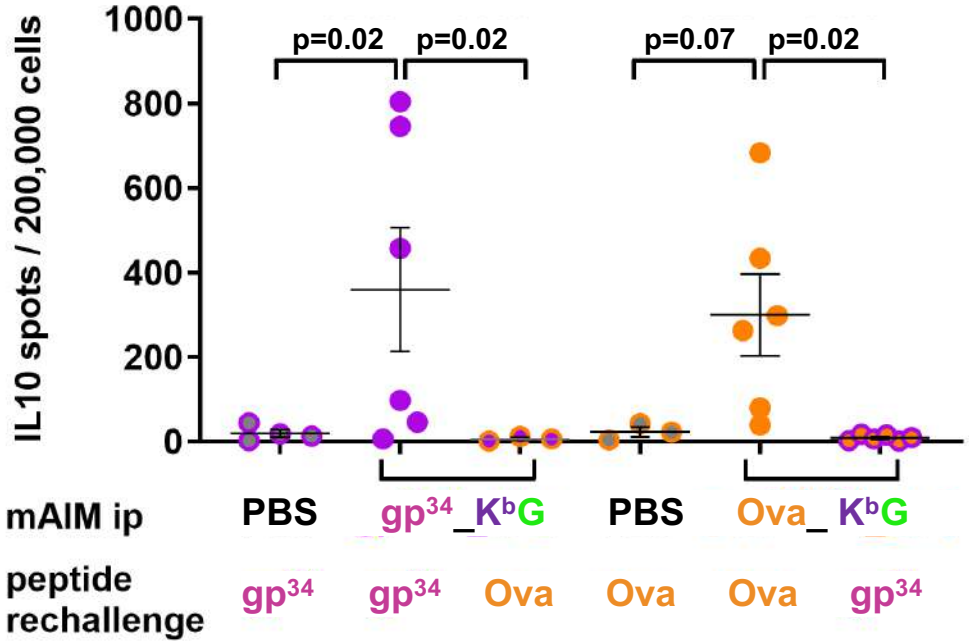
Experimental setup

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



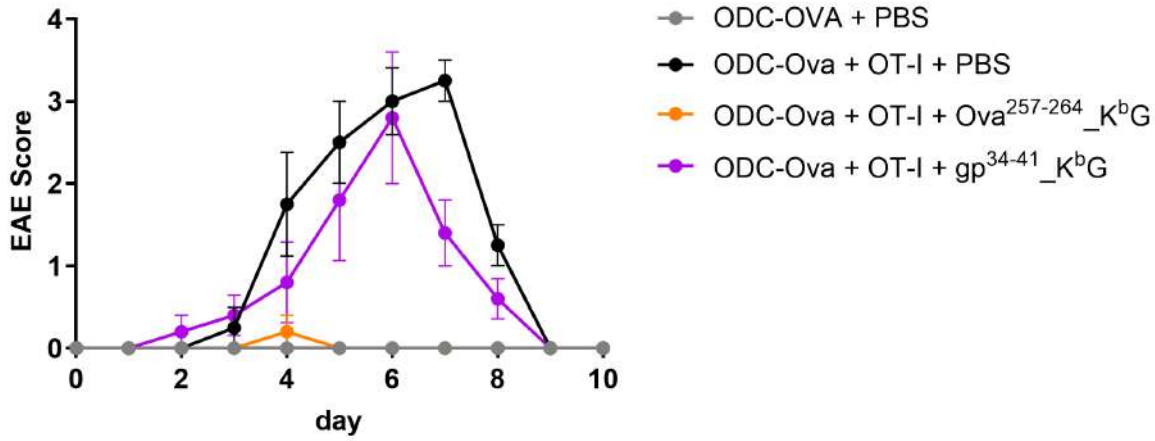
AIM Bios fully prevent MS symptoms in mice

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.

Results

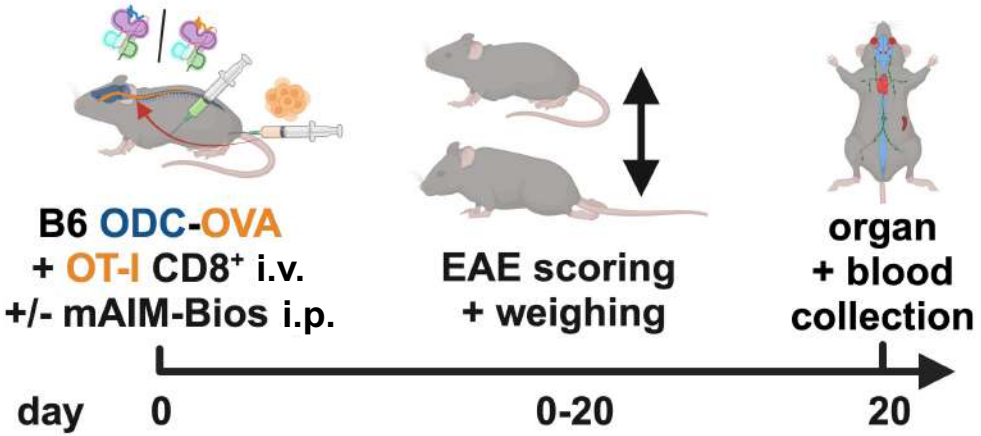
Mice treated with AIM Bios presenting the targeted Ova peptide were completely protected from severe paralysis (EAE)



AIM Bios induce dominant organ-specific tolerance

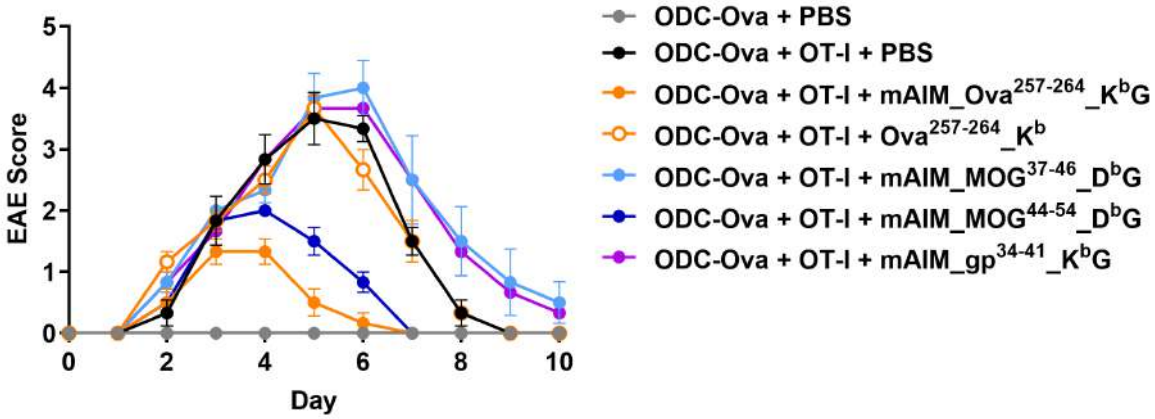
Experimental setup

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

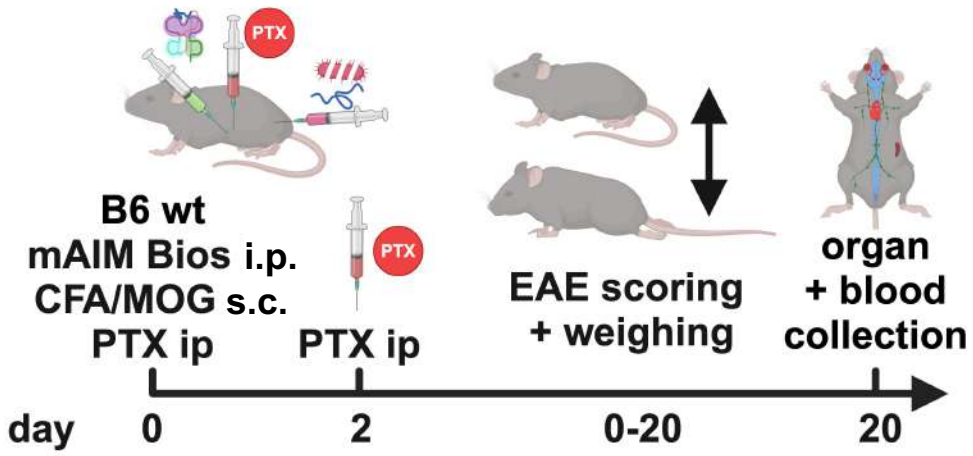
Mice treated with one MOG-tolerance inducing AIM Bio were protected almost as well against paralysis as mice treated with Ova tolerance inducing AIM Bios.



AIM Bios prevent autoantibody development

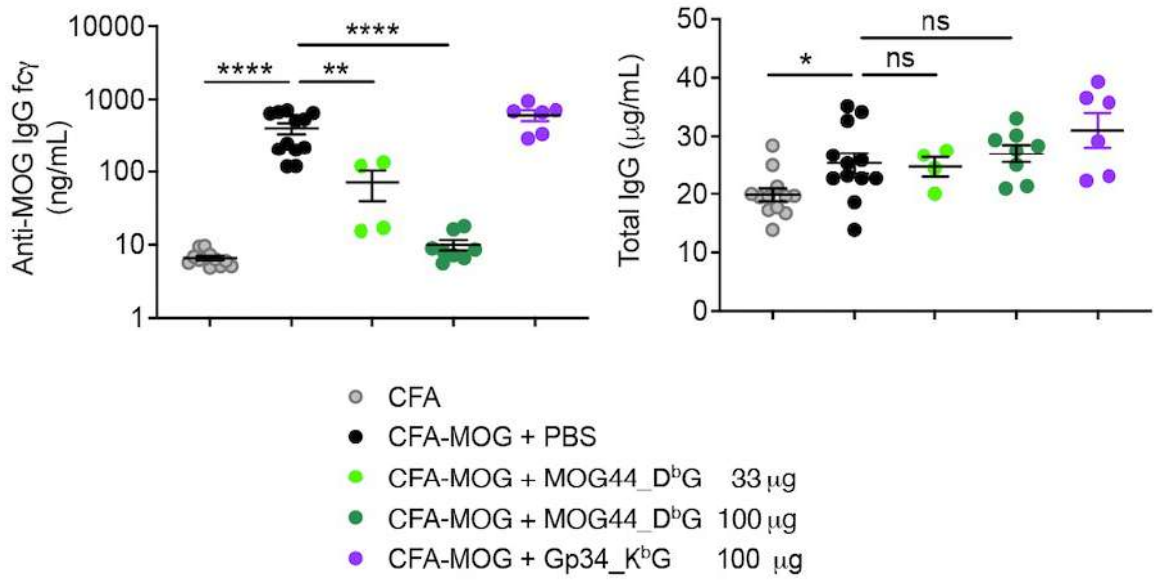
Experimental setup

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

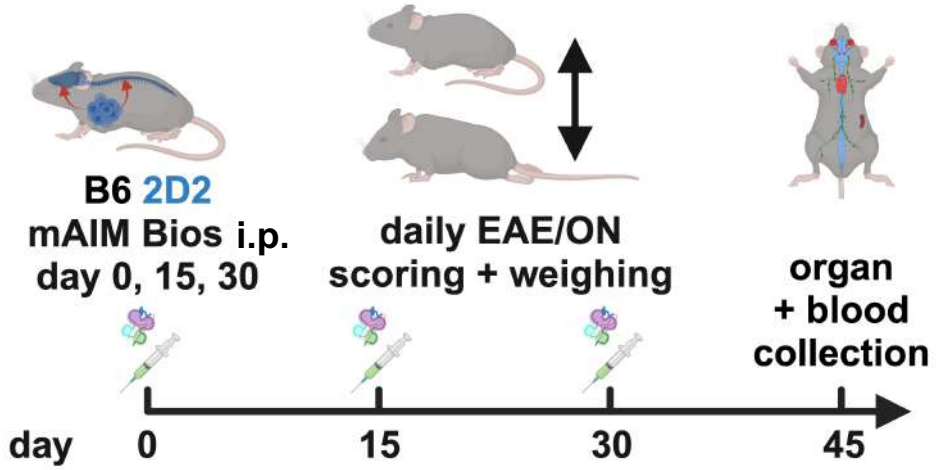
mice treated with one MOG-tolerance inducing AIM Bios developed significantly less MS symptoms (not shown) and prevented the development of autoantibodies in a dose-dependent manner. Other, protective antibodies (total IgG) were not affected.



AIM Bios reduce pre-existing disease symptoms

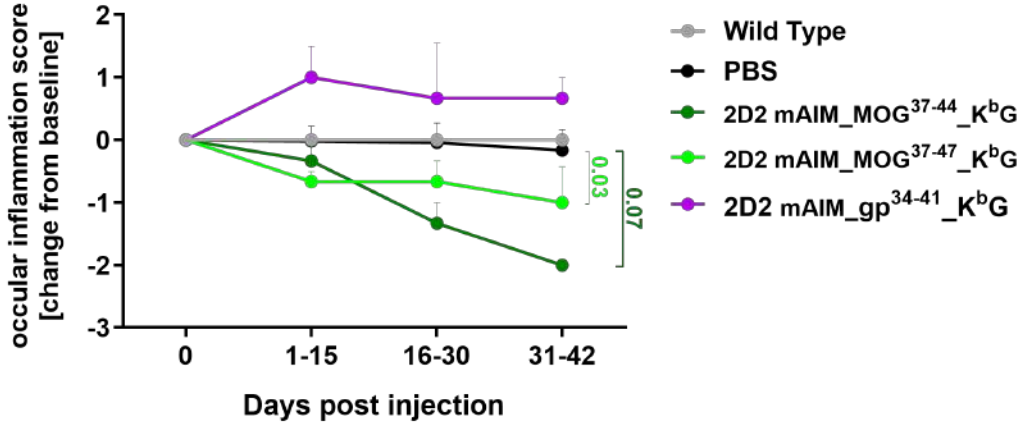
Experimental setup

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).

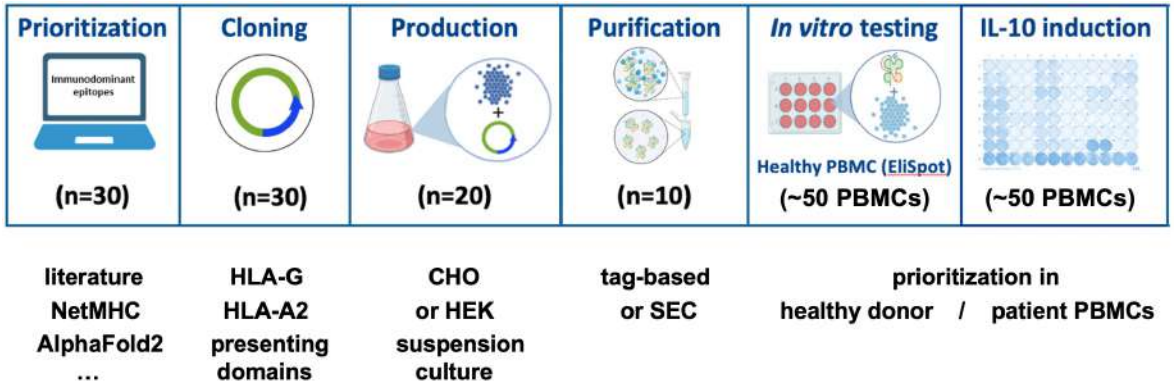


optic neuritis scoring examples

AIM candidates efficiently induce Treg in patient cells

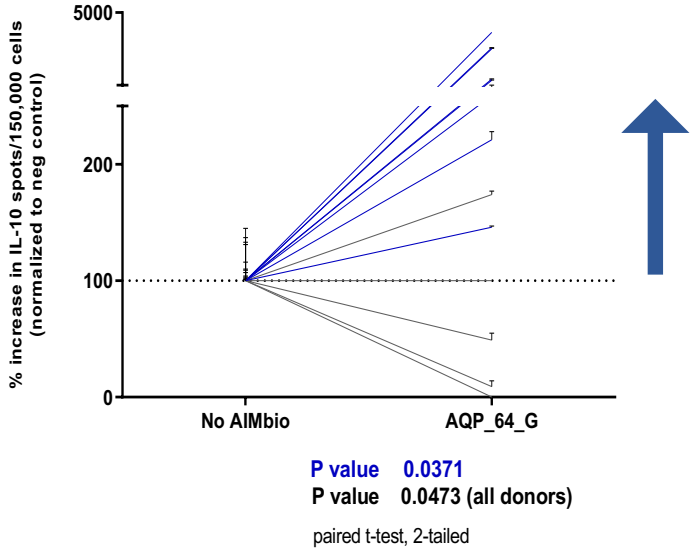
Human therapeutic candidate prioritization

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 heathy donor or patient PBMCs



Results

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. An induction of Treg was also observed in all tested high quality patient samples.



Data presented at the Harvard Medical School MOGAD Symposium 2023. Patient samples provided by Friedemann Paul and Patrick Schindler, Charité Berlin

USP: physiological targeted tolerance induction

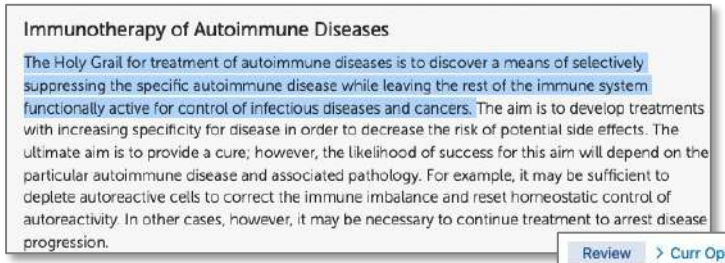
Antigen-specific tolerance induction has been considered to be the “holy grail” for immunotherapy of autoimmune diseases for more than a decade.

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.

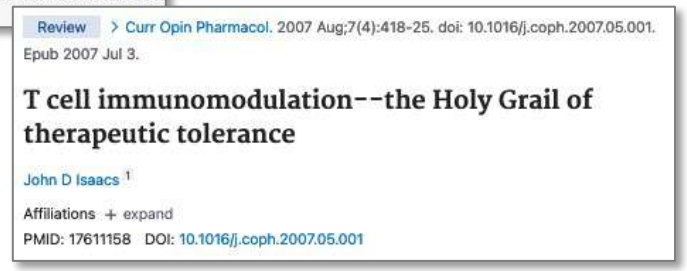
To our knowledge, AIM Biologicals are the only immunosuppressants under development that combine tolerance-inducing domains and specific antigens in an almost completely physiological molecule, which evolved over millions of years to safely and reliably induce immunological tolerance during pregnancy.



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.

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



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]

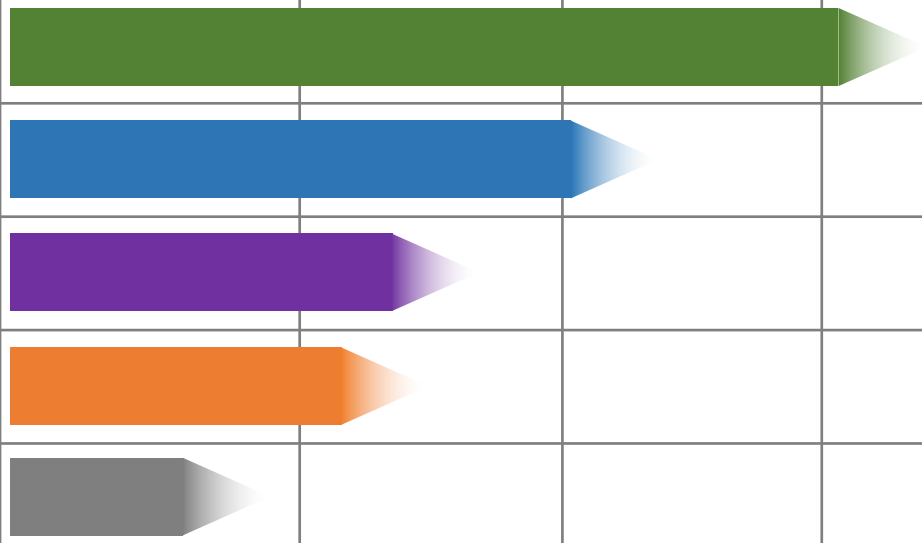
Affiliations + expand

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

	therapeutic approach	effective	targeted	complexity/cost
AG-specific therapeutics	**antigen** alone	-	+/-	+
	tolerogenic **vaccination**	-	+/-	+
	regulatory **cells**	+	+	-
	physiological 2-signal protein	+	+	+

Toleris pipeline overview

disease	candidate(s)	predicted candidates	prioritized candidate	PoC *in vivo*	*IND filing*	Phase I	Phase II	Phase III
MS/MOGAD	AIM_MOG1							
type 1 diabetes	several							
confidential 1								
confidential 2								
confidential 3								



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

Conclusion

- patented and disruptive platform for targeted immunosuppressants
- multi-billion-dollar opportunity to disrupt a growing global market
- almost completely physiological therapeutics design reduces risks
- experienced and highly motivated leadership team
- potential to address huge unmet medical needs and significantly improve patient lives
- clear and fast clinical development strategy in orphan indication and several backup positions

We are looking for investors or pharmaceutical and biotech partners to further develop the AIM Bio platform in lead or additional indications! Please contact us via info@toleris.com !