A novel disruptive IgE inhibitor: Efficacy assessment in non-human primate and human precision-cut lung slices

J. Wichmann[1,2], S. Jiménez-Delgado[1], E. Cabral Serrão[1,2], C. Curths[1,2], A. Schmitt[2], S. Dunker[1], D. Jonigk[3], P. Braubach[3], F.-J. Kaup[2], A. Braun[1], A. Eggel[4], F. Dahlmann[1,2], K. Sewald[1,*], S. Knauf[2,*]

[1] Fraunhofer Institute for Toxicology and Experimental Medicine, Member of the German Center for Lung Research (DZL), Biomedical Research in Endstage and Obstructive Lung Disease (BREATH) research network, Member of the Cluster of Excellence Regenerative Biology to Reconstructive Therapy (REBIRTH), Hannover, Germany; [2] German Primate Center, Leibniz-Institute for Primate Research, Göttingen, Germany; [3] Hannover Medical School, Hannover, Germany; [4] University Hospital Bern, Bern, Switzerland

* Contributed equally

Introduction

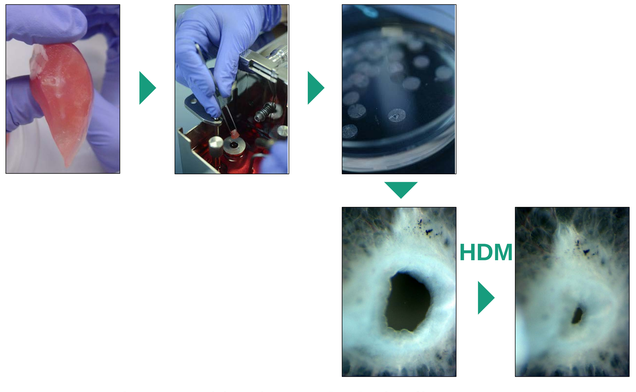
- Asthma effects 334 million people worldwide. To counteract IgE-dependent asthmatic symptoms, the new disruptive inhibitor DARPin bi53_79 was developed. It binds free and releases receptor-bound IgE.
- To test new therapeutics specific for human IgE, suitable animal models are needed.
- Precision-cut lung slices (PCLS) offer a promising tool to assess early airway reaction (EAR) *ex vivo*.

Hypothesis:

- It is possible to sensitize mast cells in PCLS of humans, cynomolgus macaques (*Macaca fascicularis*), and common marmosets (*Callithrix jacchus*).
- Early airway reaction can be counteracted by omalizumab and the novel, disruptive IgE inhibitor DARPin bi53_79.

Methods

- Lungs were filled with 1.5 % agarose and medium and processed with a Krumdieck tissue slicer to achieve precision-cut lung slices (PCLS) containing central airways.



- For passive sensitization, PCLS duplicates were incubated in human allergic plasma containing IgE directed against house dust mite (HDM). Control PCLS were placed in human non-allergic plasma.
- Omalizumab was incubated overnight. Additionally, Omalizumab, DARPInbi53_79, or control DARPin were incubated for 2 h before HDM challenge. After HDM exposure, the airway area of PCLS was recorded for 20 minutes and supernatants were analyzed for histamine release.

Results

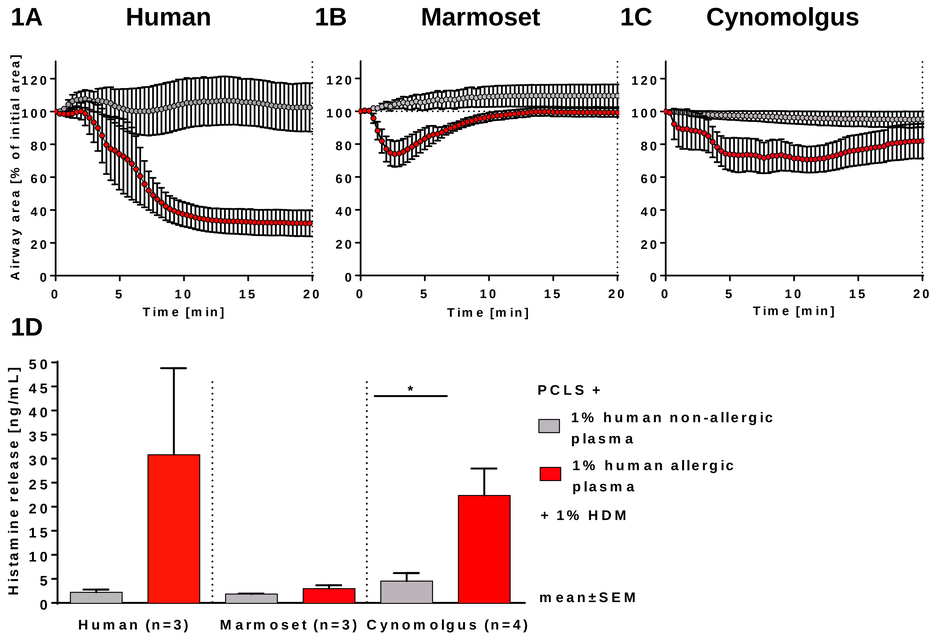


Figure 1. Allergen provocation induces bronchoconstriction in PCLS. Incubation in human allergic plasma resulted in HDM-induced reduction of initial airway area from 100% to 31.9±8.0% in human (1A), 74.0±7.8% in marmoset (1B), and 70.7±7.9% in cynomolgus PCLS (1C). In comparison to PCLS incubated in non-allergic plasma, histamine levels were only increased in sensitized PCLS (1D) (human: 30.8±18.0 ng/ml; marmoset: 2.0±0.7 ng/ml; cynomolgus: 21.4±5.6 ng/ml; mean±SEM).

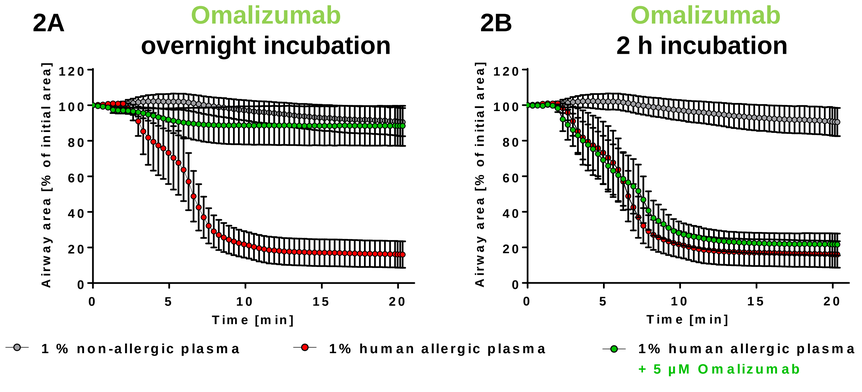


Figure 2. Anti-IgE inhibitor Omalizumab does not prevent bronchoconstriction in pre-sensitized human PCLS. 5 µM Omalizumab prevented bronchoconstriction when incubated during sensitization of human PCLS (2A). In contrast, an incubation for 2 h did not inhibit bronchoconstriction (2B). n=3, mean±SEM.

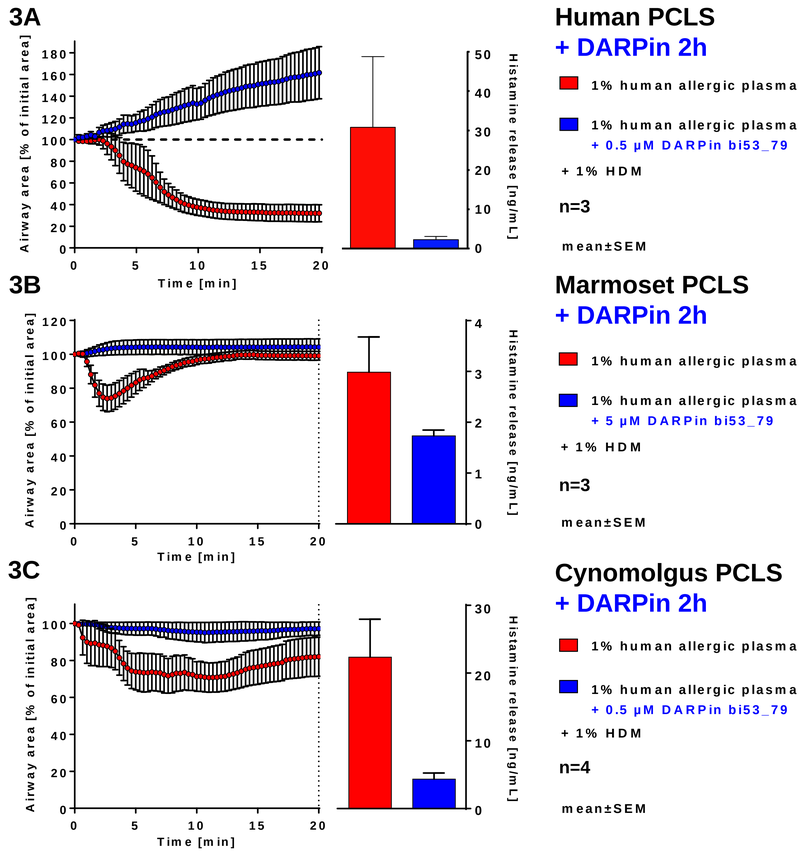


Figure 3. Preincubation with DARPin bi53_79 prevents broncho-constriction and reduces histamine release. Bronchoconstriction was prohibited at a concentration of 5 µM in human (3A) and cynomolgus (3C) PCLS and 0.5 µM in marmoset PCLS (3B), respectively.

Conclusion

- Non-human primate PCLS and human PCLS can be passively sensitized with human allergic plasma and are a model for early airway reaction (EAR)
- Omalizumab only inhibits EAR if inoculated during sensitization
- The anti-IgE DARPin bi53_79 prevents EAR in human, marmoset, and cynomolgus PCLS.
- Data of cynomolgus PCLS are comparable to those of human.

Contact

- Fraunhofer ITEM, Nikolai-Fuchs-Str.1, 30625 Hannover, Germany
- fdahlmann@dpz.eu
- Funded by the German Research Foundation