SIAF

ANNUAL REPORT 2016

University of Zurich[UZH]

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Das Schweizerische Institut für Allergie- und Asthmaforschung (SIAF) ist eine Abteilung der Stiftung Schweizerisches Forschungsinstitut für Hochgebirgsklima und Medizin Davos (SFI). Das Institut in seiner heutigen Form wurde von der Medizinischen Abteilung des SFI 1988 gegründet. Seit daher konzentrieren sich die Forschungsarbeiten des SIAF auf die Mechanismen und die Entwicklung für verbesserte Diagnose- und Behandlungsmöglichkeiten von Allergien und Asthma. Das SIAF ist ein assoziiertes Institut der Universität Zürich und Mitglied der Life Science Zurich Graduate School.

1905	Tuberculosis Research Institute Davos
	Medical Society Davos, Community of Davos, K. Turban
1907	Physical-Meteorological Observatory Davos, C. Dorno
1922	Swiss Research Institute for High Altitude Climate and Tuberculosis
1922-1933	A. Loewy, High Altitude Physiology
1934-1937	F. Roulet, Chemistry of Mycobacterium Tuberculosis
1938-1954	W. Berblinger, Pathology of Tuberculosis
1954-1960	W. A. Vischer, Resistance to Mycobacterium Tuberculosis
1961	Swiss Research Institute for High Altitude Climate and Medicine
1961-1985	E. Sorkin, Neuroendocrine-Immune Interactions
1985-1987	H. Basedowsky, Neuroendocrine-Immune Interactions
1988	Swiss Insitute of Allergy and Asthma Research (SIAF)
1988-2006	K. Blaser, Mechanisms of Allergy and Asthma
2006-present	C. A. Akdis, Mechanisms and Novel Methods for the Diagnosis and Treatment of Allergy and Asthma

Zimmer für Respirationsversuche

Erster bakteriologischer Raum

Bericht des Direktors

Prof. Dr. Cezmi A. Akdis

Das Schweizerische Institut für Allergie- und Asthmaforschung (SIAF) in seiner heutigen Form wurde 1988 von der Medizinischen Abteilung der Stiftung Schweizerisches Forschungsinstitut für Hochgebirgsklima und Medizin Davos (SFI) gegründet. Das SIAF ist seit 1996 der Universität Zürich angegliedert und seit 2008 Mitglied der Life Science Zurich Graduate School, einem gemeinsamen Ausbildungs-Projekt der Universität Zürich und der ETH Zürich. Diese Angliederung ermöglicht dem SIAF eine vollumfängliche PhD-Ausbidlung anzubieten.

Die Forschung ist auf eine direkte Kooperation mit den Kliniken in Davos, der Universität Zürich und weiteren spezialisierten Instituten ausgelegt. Ausserdem ist das SIAF in das europäische Netzwerk nationaler Kompetenzzentren (Projekt GA2LEN: Global Allergy and Asthma European Network of Excellence), in die Europäische Akademie für Allergologie und Klinische Immunologie (EAACI), in die Amerikanische Akademie für Allergie, Asthma und Immunologie (AAAAI) sowie in die World Allergy Organization (WAO), bei welcher Frau Prof. Dr. M. Akdis Mitglied des Verwaltungsrates ist, eingebunden. Die EAACI ist die weltgrösste Akademie für allergische Erkrankungen und übernimmt eine wichtige Rolle in Bezug auf Wissenschaft, Weiterbildung, Kommunikation und Öffentlichkeitsarbeit. Von 2008-2011 war Prof. C. A. Akdis Vizepräsident der EAACI. 2011 wurde er zum Präsidenten der Akademie gewählt. Seine Amtsperiode im Ausschuss dauerte bis 2015. PD Dr. L. O'Mahony ist Vorstandsmitglied der Sektion Immunologie. Prof. Dr. M. Akdis ist Mitglied der Biologicals Interest Group und Dr. C. Rhyner der Allergy Diagnostics Interest Group.

Das SIAF hat über 1'000 Fachbeiträge veröffentlicht und gehört zu den meistzitierten Instituten weltweit. Die vom SIAF publizierten Artikel wurden über 45'000 Mal zitiert. Das Institut gehört mit seinen rund 50 Mitarbeitern (im Vergleich zu Universitäten mit Tausenden von Forschern) weltweit zu den Besten bezüglich Anzahl Mitarbeiter oder Zitierung geteilt durch Budget. In den letzten Jahren konnte eine signifikante Erhöhung der Anzahl Zitierungen erreicht werden. Es ist eine international bekannte Ausbildungsstätte für Doktoranden und Habilitanden.

2016 wurden 72 wissenschaftliche Arbeiten in begutachteten internationalen Fachzeitschriften mit "Impact Factor" veröffentlicht. 2016 erreichte das SIAF einen Gesamtwert des "Impact Factors" von 502.069 und einen Durchschnitt von 6.973 Punkten. Die neusten Ergebnisse wurden zudem in 31 Abstracts an verschiedenen Fachtagungen mitgeteilt. Unsere Mitarbeitenden wurden zu 49 verschiedenen Seminaren und Vorträgen an nationalen und internationalen Kongressen eingeladen. Solche Einladungen sind wichtig für die Verbreitung der erzielten Ergebnisse und für die internationale Akzeptanz der Forschung des Instituts. Bei 26 verschiedenen Sessionen hatten SIAF-Mitarbeitende den Vorsitz. Zusätzlich werden 45 wissenschaftliche Ämter in internationalen Gesellschaften durch Wissenschaftler des SIAF besetzt. Desweiteren sind die Forscher des SIAF bei insgesamt 19 internationalen Zeitschriften als Mitglieder der redaktionellen Komitees tätig.

Zudem hält Prof. C. A. Akdis das Amt des Chefredaktors des Journal of Allergy and Clinical Immunology (JACI), welches einen Impact Factor von 12.485 aufweist, inne.

Im Juli 2009 hat die Kühne-Stiftung eine der europaweit grössten privaten Initiativen auf dem Gebiet der Allergologie, das Christine Kühne – Center for Allergy Research and Education (CK-CARE), mit den Standorten Davos, München und Zürich ins Leben gerufen. Ziel ist es, Forschung, Edukation und Prävention auf dem Gebiet der Allergien zu fördern und die Umsetzung der Forschungsergebnisse in der klinischen Versorgung zugunsten der betroffenen Patienten zu verbessern. Unser Workpackage hat das Ziel, die molekularen Vorgänge von externen und internen Faktoren besser zu verstehen, die bei der Entstehung, Entwicklung, Chronifizierung und dem Schweregrad atopischer Erkrankungen bzw. Neurodermitis eine Rolle spielen. Dieses Wissen ist von grundlegender Bedeutung und wird zur Entwicklung besserer Präventions- und Behandlungsstrategien sowie diagnostischer Biomarker für Neurodermitis führen. Seit 2009 konnten dank der Unterstützung durch die CK-CARE mehr als 38 wissenschaftliche Mitarbeitende eingestellt und über 60 akademische Gäste im Austauschprogramm aufgenommen werden. Darüber hinaus wurden 128 Publikationen in namhaften Zeitschriften veröffentlicht.

Personalisierte Medizin

Eine Therapie ist nicht bei allen Patienten gleich wirksam und kann bei einigen gar zu starken Nebenwirkungen führen. Bei der Behandlung von Allergien, wie bei anderen Erkrankungen auch, geht man klassischerweise nach der jeweiligen Leitlinie vor, also auf die medizinisch anerkannte Vorgehensweise in Bezug auf Diagnostik und Therapie. Es hat sich jedoch gezeigt, dass gerade bei allergischen Erkrankungen das Krankheitsbild in vielen verschiedenen Arten auftreten kann, wie bei Asthma, Heuschnupfen, Neurodermitis, etc. Deshalb ist es zwingend notwendig, dieser Diversität Rechnung zu tragen. Und hier kommt die personalisierte Medizin ins Spiel.

Bei der personalisierten Medizin geht es darum, zusätzlich zum Krankheitsbild weitere Kenntnisse über die biologischen Eigenschaften von Patienten zu nutzen, um in Zukunft bereits vor dem Beginn einer Behandlung einschätzen zu können, ob ein Patient auf eine bestimmte Therapie ansprechen wird. Biomarker sind in der Medizin messbare charakteristische biologische Merkmale, die auf einen normalen biologischen oder krankhaften Prozess im Körper hinweisen können und so für Prognose und Diagnose der Krankheit genutzt werden können. Bei Biomarkern kann es sich um Zellen, Gene, Genprodukte oder bestimmte Moleküle wie Enzyme oder Hormone handeln. Es ist enorm wichtig, Biomarker als Prädiktoren für den Behandlungserfolg verschiedener Krankheits-Endotypen zu entdecken, damit Protokolle für die personalisierte Medizin effizient bei der Behandlung von Asthma und Allergien angewendet werden können.

Das SIAF verfügt über mehr als 15 Jahre Erfahrung in der Durchführung von Gene Array Transcriptomic. Als die systembiologischen Ansätze und die Analyse grosser Datenmenge an Bedeu-

tung zunahm, haben wir vor vier Jahren damit begonnen, Omics-Methoden durchzuführen, mehrheitlich die Next-Generation-RNA-Sequencing-Transcriptomics, um auf eine Reihe wichtiger Fragen auf den Gebieten von Allergien und Asthma antworten zu können. Die Anzahl Projekte nahmen zu und wir weiteten diese in den letzten zwei Jahren auf andere Omics-Methoden aus.

Parallel dazu, hat das SIAF seit 2013 eine effiziente Forschungsgruppe für Hochtechnologiemedizin, Bioinformatik und Omics-Methoden etabliert. Am SIAF sind derzeit zwei Experten auf dem Gebiet der Bioinformatik tätig, zahlreiche Research Fellows, die sich auf die Forschung von Omics-Methoden konzentrieren und Research Fellows, welche sich der Hochtechnologiemedizin widmen. Nebst der wachsenden Anzahl dieser Projekte wird auch die Infrastruktur für diese Forschung angepasst und die Mitarbeiter weiter geschult.

In den letzten drei Jahren haben wir eine starke Zusammenarbeit mit dem Functional Genomic Center der Universität Zürich und der Stanford University, Department of Immunology, Sean Parker Asthma and Allergy Center für Omics-Methoden aufbauen können.

Klinische Dienstleistung

Das SIAF bietet den Davoser und allen weiteren interessierten Kliniken und praktizierenden Ärzten spezielle zelluläre immunologische Untersuchungen an. Mit Hilfe der durchfluss-zytometrischen Analyse (FACS Analyse) von Blut, bronchoalveolären Lavagen (BAL), aber auch weiteren Gewebsflüssigkeiten, werden die verschiedenen Immunzellen und Subpopulationen in ihrer Entwicklung, ihren Mengenverhältnissen und ihrem Aktivierungszustand gemessen.

Ausbildung und Lehrverpflichtungen

Eine wichtige Aufgabe erfüllt das SIAF in der Ausbildung von Studierenden sowie im Nachdiplomstudium. Gleichzeitig werden durch das SIAF Lehrverpflichtungen an der Universität Zürich erfüllt. Zudem ist Prof. R. Crameri an der Blockvorlesung „Molekulargenetische Grundlagen der Immunologie“ der Universität Salzburg beteiligt. Prof. C. A. Akdis ist Fakultätsmitglied der Medizinischen Fakultät der Universität Zürich mit Promotionsrecht in der Mathematischen und Naturwissenschaftlichen Fakultät. Prof. C. A. Akdis und Prof. M. Akdis haben zudem eine Honorarprofessur am Tungren Spital der Peking-Universität.

Kongressorganisation 2017

Bereits zum elften Mal fand vom 15. bis 18. März 2017 das international ausgeschriebene World Immune Regulation Meeting (WIRM) im Kongresszentrum Davos statt. Rund 600 Wissenschaftler aus 40 verschiedenen Länder trafen sich zu diesem Kongress, um sich über die neuesten Erkenntnisse in der Immunologie auszutauschen und trugen 125 Vorträge und 238 Abstracts vor. Tagsüber nahmen die Teilnehmer an hochkarätigen wissenschaftlichen Vorträgen teil. Die Abende im Kongresszentrum waren reserviert, um in ungezwungener Atmosphäre wissenschaftliche Projekte in Form einer Posterausstellung zu präsentieren. Der Kongress und weitere SIAF Aktivitäten generieren jährlich etwa 4’000 Übernachtungen in den Davoser Hotels und Ferienwohnungen.

Finanzielle Grundlage

Die Ausgaben und der finanzielle Ertrag des SIAF haben sich im Vergleich zu den vergangenen Jahren nur unwesentlich verändert. Eine Grundfinanzierung des Instituts ist durch die Hauptsponsoren gegenwärtig sichergestellt. Sie besteht vor allem aus einem Beitrag des Bundes (Forschungsförderungsgesetz Art. 15), Beiträge des Kantons Graubünden und der Gemeinde Davos, Beiträge der CK-CARE AG und der Universität Zürich sowie einem Beitrag der Stiftung vormals Bündner Heilstätte Arosa. Die zusätzlichen Ausgaben wurden aus Erträge von zusätzlichen Drittmitteln und des WIRM-Kongresses gedeckt.

Dank

Für die grossartige Arbeit und die gute Arbeitsatmosphäre im SIAF danke ich allen Mitarbeitenden herzlich. Gleichzeitig danke ich den Davoser Kliniken, ihren Chefärzten und deren Mitarbeitenden sowie der Universität Zürich für die stetige und wirkungsvolle Unterstützung unseres Institutes.

Insbesondere möchte ich hier unsere fruchtbare Zusammenarbeit mit der CK-CARE betonen, welche uns patientenorientierte Forschung ermöglicht. Ich danke speziell Frau und Herr Kühne für Ihre Unterstützung, welche unsere Forschung zur Findung von nachhaltigen Lösungen für bessere Diagnosen und Behandlungen von Neurodermitis-Patienten ermöglicht. Dank dieser Unterstützung konnten im Institut viele Master-Diplome und PhD-Titel erlangt werden.

Mein Dank geht vor allem auch an die Stiftung Schweizerisches Forschungsinstitut für Hochgebirgsklima und Medizin (SFI), dessen Stiftungsrat und Stiftungsratsausschuss für die stets gewährte Unterstützung. Nicht zuletzt gilt mein Dank den Behörden, die sich unermüdlich für die Forschung des SIAF interessieren und das Institut in jeder Hinsicht fördern.

Davos, Juni 2017

Vortrag während des WIRM im Kongresszentrum Davos.

Report of the director

Prof. Dr. Cezmi A. Akdis

The story of the Swiss Institute of Allergy and Asthma Research (SIAF) started in 1907 as the Tuberculosis Research Institute Davos and was founded on the request of Professor Karl Turban, the Davos Doctors' Association and the municipality of Davos. The Swiss Institute of Allergy and Asthma Research (SIAF) was developed as a department of the foundation Swiss Research Institutes for High Altitude Climate and Medicine Davos (SFI) in 1988. SIAF is an affiliated institute of the University of Zurich since 1996 and member of the Life Science Zurich Graduate School since 2008, a joint post graduate education program of the Swiss Federal Institute of Technology and the University of Zurich. SIAF members play leading roles in national and international organizations, such as European Academy of Allergy and Clinical Immunology (EAACI), World Allergy Organization (WAO) and in editorial boards and editorships of top Journals in the field of allergy asthma and clinical immunology. At the same time, SIAF group leaders fulfill teaching obligations in the University of Zurich and the University of Salzburg.

The research activities at SIAF have been focused on basic research in the field of allergies and asthma to develop approaches for new preventive and curative treatments for patients. Major research aims are to develop curative treatment and prevention of allergies and asthma with a focus on immune tolerance to allergens, allergen-specific immunotherapy, rapid diagnosis and microbiology. Human research has been pursued at the front level with a main emphasis given on patient-relevant research. SIAF has a large impact in the field of allergies and asthma with more than 45'000 citations to its more than 1'000 publications.

The research is based on a direct cooperation with the clinics in Davos and surrounding, the University of Zurich and other specialist institutions. Furthermore, SIAF is integrated in the Global Allergy and Asthma European Network of Excellence (GA2LEN), in the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Allergy, Asthma, and Immunology (AAAAI) and World Allergy Organization (WAO).

In July 2009, the Kühne Foundation has launched the Christine Kühne Center for Allergy Research and Education (CK-CARE), with locations in Davos, Munich and Zurich. The aim of this initiative has been highly qualified and well-connected research work in the field of allergies and education of medical professionals based on recent findings. The overriding objective of our workpackage in CK-CARE is to understand better the molecular processes of external and internal factors, which play a role in how atopic diseases occur, develop and become chronic, and in their degree of severity. This knowledge is fundamentally important and will lead to the development of better preventive and therapeutic strategies as well as diagnostic biomarkers for atopic diseases.

We had and will have series of publications in the area with the support of CK-CARE. So far 128 articles were published supported by CK-CARE. We could engage more than 38 scientific co-workers, and there were more than 60 academic guests working on the specific projects of CK-CARE in the short term exchange program.

The work at SIAF during the last year generated a total of 72 scientific publications (exclusive abstracts), which appeared in peer-reviewed international journals. The total average of impact factor is 6.973. In 2016, SIAF reached a total impact factor amounting to 502.069 and 31 abstracts were presented at different congresses. Members of SIAF were invited to 49 different seminars or lectures at international congresses, universities and other research institutions and chaired 26 sessions. In addition, SIAF members continued to take place in 45 scientific posts in international institutions and play a role in 19 editorial board and editorship activities. Several members of SIAF have teaching responsibilities at the Universities of Zurich and Salzburg. In 2015, Prof. C.A. Akdis and Dr. Z.K. Ballas have been chosen to serve as the next JACI Co-Editors-in-Chief. Having a European-based Editor-in-Chief in addition to a U.S.-based Editor-in-Chief is a historic first for the journal and reflects an increased international appeal demonstrating that JACI is a global journal that should have a global impact on all aspects of our specialty.

Precision Medicine

Precision medicine is essential in the management of asthma, rhinitis and atopic dermatitis (AD), providing tools for a better selection of responders to treatment, design of better clinical trials as well as risk prediction and disease-modifying strategies. The heterogeneity of allergic diseases and asthma in relation to patient characteristics (phenotype), underlying pathogenic mechanisms (endotype) and clinically significant outcomes, including response to treatment has been established beyond any doubt. Better management of asthma needs a refined understanding of disease heterogeneity.
One of the major problems in treating allergy and asthma is the lack of clear biomarkers for allergic diseases and asthma. In addition, while it is obvious that asthma is more than just one disease condition, there is lack of biomarkers for the different endotypes of asthma, and similarly for other allergy conditions. Without comprehensive knowledge on such biomarkers defining different disease endotypes, it will be very difficult to develop precision medicine in the field since different endotypes require different treatments. Finally, discovery of predictors for the success of treatment of different disease endotypes is required in order to have efficient precision medicine protocols to treat asthma and allergy.

SIAF has long term experience in performing gene array transcriptomics for more than 15 years. As the importance of systems biology approach and big data analysis had recently become evident, we had started 4 years ago to perform high throughput omics studies, mainly next generation RNA sequencing transcriptomics to answer a number of important questions in the fields of allergy and asthma. The number of projects had grown and expanded to other omics approaches (as detailed below) during the last two years. So far we had more than 25 omics projects related to "precision medicine" and more and larger, projects have been already approved or are in planning.

In parallel, SIAF had started in the beginning of 2013 to build a local bioinformatics and systems biology expert team to facilitate/perform multiple omics research. At the moment there is two bioinformatics experts at the SIAF, and many fellows that are mainly

dedicated to omics research and fellows that perform “Precision Medicine” studies. In parallel to rapidly growing number of omics / systems biology oriented projects, the team and equipment to support these activities is also on the rise.

In the first phase of our omics studies, we had concentrated on answering basic science questions related to asthma and allergy pathogenesis. In particular: what causes the development, and the break, of immune tolerance; what is the relationship between immune response and tissue pathology; and what are the virome and microbiome correlates of asthma and allergy. The second phase started and we are concentrating on precision medicine and biomarkers in allergic diseases and asthma.

During the last three years, we established a strong collaboration with the Functional Genomics Center of the University of Zurich and Stanford University, Department of Immunology, Sean Parker Asthma and Allergy Center for Precision Medicine Studies, which are both ongoing with full efficiency.

Congress Organization

The international World Immune Regulation Meeting (WIRM) belongs to one of the most important meetings in its area in the World. It attracts top-class senior scientists as well as junior researchers and provides the most efficient environment to meet the experts, fellows and old colleagues and organize top level of business meetings. This year, SIAF organized the WIRM for the eleventh time on 15-18 March 2017 at the Congress Center Davos. The congress was focused on “Development and Maintenance of Immune Tolerance and Role of Tissues in Immune Regulation” with approximately 600 participants from 40 countries with 125 presentations and 238 abstracts.

Acknowledgements

I would like to thank all SIAF co-workers for their productive work and most enjoyable work atmosphere. I would like to thank all Davos clinicians and University Zurich for the efficient collaboration and support.

I would like to mention in particular our fruitful cooperation with CK-CARE, which enables our patient-oriented research. I thank very much Mrs. and Mr. Kühne for their continuous support of our research for finding sustainable solutions for better diagnosis and treatment of atopic eczema patients. With this support so many masters and PhD degrees have been given in our institute.

Finally, I would like to thank all members of our foundation Swiss Research Institutes for High Altitude Climate and Medicine Davos (SFI). My gratitude also goes to the authorities in Davos and Canton, which are tirelessly interested in the research of SIAF and are supporting our institute in every way.

Davos, June 2017

Talk and interview at the EU parliament in Brussels on prevention of allergic diseases.

SIAF STAFF MEMBERS

2016

Director

Akdis Cezmi A.	Prof., MD ***

Group Leaders

Akdis Cezmi A.	Prof., MD, Head Immunology ***
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Prof. Dr. Reto Crameri

The activities of the Molecular Allergology Group at SIAF during the report period were focused on finishing the projects "Improving diagnosis and treatment of allergic diseases by avant-garde technologies" founded by the Swiss National Science foundation, "Allergy vaccination using novel drug delivery routes mediated via nanotechnology (ERANET EuroNanoMed2, NANOASIT II), "Pet ownership and matchmaking by allergen profiles in suitable breeds" (DIAPET, EUROSTARS E!8599) and the project "Rapid in vitro diagnosis for platelets" in collaboration with the Vaccine Development Group and Davos Diagnostics supported by the CTI. All these projects are thematically closely related and will terminate during 2017.

Poly-sensitization to allergens in Atopic Dermatitis

Atopic dermatitis (AD) is a complex chronic inflammatory skin disease with15–30% of children and 2–10% of adults being afflicted. The pathogenesis of AD is considered to result from a combination of a defective skin barrier and inappropriate immune responses with contribution of both genetic and environmental factors. Allergens are important in the pathogenesis of AD since they can act as specific triggering factors especially during exacerbation phases. AD has been classified into either an extrinsic or an intrinsic type according to the presence or to the absence of detectable allergen-specific serum IgE antibodies. Still, another subgroup of patients with AD has an autoimmune IgE-mediated reactivity against self-antigens in addition to sensitization against exogenous allergens.
In a complex study involving groups of severe (53) and moderate (126) AD patients we investigated the IgE-sensitization profiles of both groups to extracts of M. sympodialis, S. aureus, human epithelial cell extracts, and 120 purified natural or recombinant allergen components (Table1).

Table 1: Summary of allergen-specific IgE reactivities in the AD patients

IgE reactivity to the allergens/allergen components tested [a]	All AD n=179 (%)	Severe AD n=53 (%)	Moderate AD n=126 (%)
Any allergen/allergen component	154 (86%)	49 (92%)	105 (83%)
Mono-sensitized [b]	18 (10%)	3 (6%)	15 (12%)
Sensitized to 2-25 allergens/allergen components	109 (61%)	34 (64%)	75 (59%)
Sensitized to 26-55 allergens/allergen components	27 (15%)	12 (22%)	15 (12%)

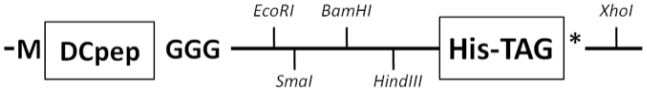
[a] Tested for IgE reactivity to 120 allergen components (MeDALL allergen chip), and to M. sympodialis, S. aureus and human epithelial cell extracts (immunoblotting).
[b] Mono-sensitised severe AD patients: M. sympodialis (n=3); Mono-sensitised moderate AD patients: Grass pollen (n=2), birch pollen (1), dog (1), cat (5), house dust mite (1), M. sympodialis (4), wasp venom (1).

The complex sensitization patterns of both, severe and moderate AD patients hardly allows to write firm conclusions about their influence on the pathophysiology of the disease except that the majority of the patients (76%) are poly-sensitized and 10% mono-sensitized.

Targeting antigens to dendritic cells (DC's) in vitro and in vivo

Professional antigen presenting cells like DC's play a pivotal role in the elicitation of immune responses. Therefore specific targeting of different DC subsets is assumed to have a big potential for the improvement of different vaccination strategies. Peptides targeting receptors displayed by DC's can be easily isolated from phage surface-displayed peptide libraries and used to construct fusion proteins which should be specifically taken up by DC's. We used a peptide (DC-Pep) and a tetramer thereof to generate fusion proteins with the murine OVA model of allergy (Fig. 1).

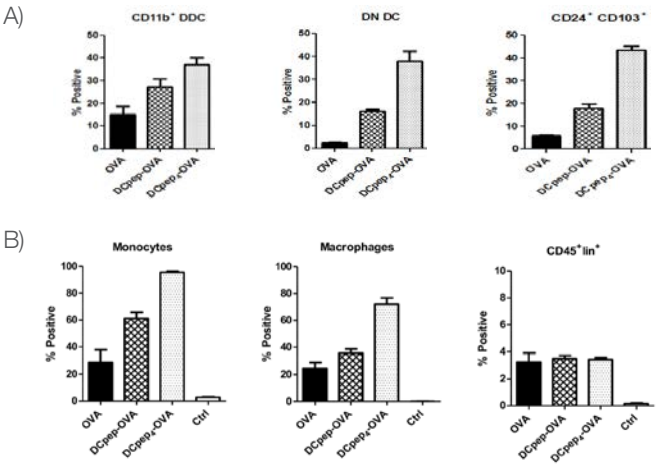
*Figure 1: Modified pET17b expression vector with DCpep and His-Tag used for the cloning of targeting. M, Methionine; G, Glycine; *, Stop-codon; restriction enzymes sites are shown in italic.*



In collaboration with the vaccine development group, our findings confirmed that DCpep represents an easy way to enhance antigen delivery to DCs in vitro.(Fig. 2A). However, the targeting benefit disappears after *in vivo* application of DCpep fusion proteins to the mouse skin due to a lack of specificity for professional antigen presenting cells. After injection to mouse skin DCpep constructs are preferentially taken up by dermal cells with poor antigen-presenting properties, such as macrophages and monocytes (Fig. 2B). These cells most likely act as a sort of antigen sink; efficiently removing the delivered DCpep constructs from the application site suggesting

that vaccines targeting DCs *in vitro* are preferentially phagocyted by cells with poor antigen-presenting properties *in vivo*.

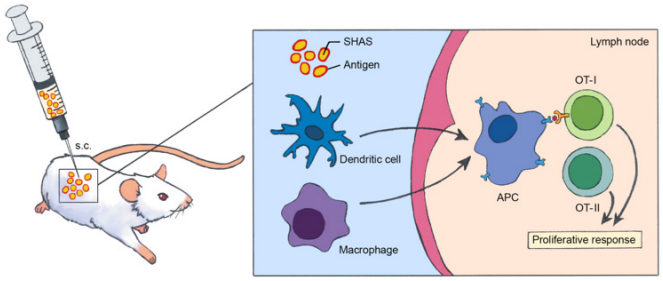
Figure 2: A) Efficient uptake of DCpep-OVA constructs by different subsets of dendritic cells in vitro. B) Efficient uptake of DCpep and DCpep4 OVA fusions by macrophages and monocytes injected the mouse ear dermis. No difference in (unspecific) uptake was observed for the other cell populations (CD45+lin+).



The use of nano-particles for allergen-specific immunotherapy

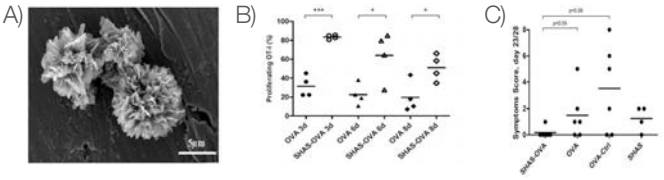
Allergens are very toxic already at low concentrations and, therefore, can only be applied in escalating doses requiring 30 to 80 injections over a period of 3 to 5 years. Nano- or microparticles can be injected subcutaneously to create a depot effect and a slow release of absorbed vaccines (Fig. 3). We tested this possibility using Fel d 1 loaded strontium-doped hydroxyapatite porous spheres (SHAS) in a mouse model of allergy.

Figure 3: Schematic representation of the experimental set up and expected results.



Scanning electron microscopy revealed that the synthesis procedure developed for the production of SHAS results in a highly homogeneous population of spheres (Fig. 4A). SHAS bound and released proteins such as ovalbumin (OVA) or the major cat allergen Fel d 1. In a mouse model of allergy OVA released from subcutaneously injected SHAS microspheres led to a sustained proliferation of both CD4+ and CD8+ T-cells (Fig. 4B) and a higher efficacy of the immunotherapeutic treatment, as assessed by the symptom score (Fig. 4C). We conclude that SHAS may constitute a suitable carrier and adjuvant for ASIT with great potential due to its unique protein-binding properties.

Figure 4: A) Electron microscopic picture of SHAS particles. B) Sustained proliferation of T-cells induced by subcutaneously injected OVA-loaded micro-particles. C) Improvement of the allergic symptoms after immunization with OVA-loaded SHAS particles.



Global Allergy Forum and 3rd Davos Declaration 2015: Atopic dermatitis/Eczema: challenges and opportunities toward precision medicine.

T. Bieber, C. Akdis, R. Lauener, C. Traidl-Hoffmann, P. Schmid-Grendelmeier, G. Schäppi, J.-P. Allam, C. Apfelbacher, M. Augustin, L. Beck, T. Biedermann, C. Braun-Fahrländer, F. T. Chew, T. Clavel, R. Crameri, U. Darsow, M. Deleuran, D. Dittlein, H.-W. Duchna, L. Eichenfeld, K. Eyerich, R. Frei, C. Gelmetti, U. Gieler, S. Gilles, M. Glatz, K. Grando, J. Green, J. Gutermuth, E. Guttman-Yassky, J. Hanifin, D. Hijnen, W. Hoetzenecker, A. Irvine, A. Kalweit, N. Katoh, E. Knol, H. Koren, M. Möhrenschlager, D. Münch, N. Novak, L. O'Mahony, A. S. Paller, C. Rhyner, C. Roduit, K. Schiesser, J. Schröder, D. Simon, H.-U. Simon, M. Sokolowska, P. Spuls, J.-F. Stalder, D. Straub, Z. Szalai, A. Taieb, R. Takaoka, G. Todd, A. Todorova, C. Vestergaard, T. Werfel, A. Wollenberg and J. Ring. Allergy 2016:71(5);588-592 (no Abstract available).

IgE Sensitization Profiles differ between Adult Patients with Severe and Moderate Atopic Dermatitis.

Mittermann I, Wikberg G, Johansson C, Lupinek C, Lundberg L, Crameri R, Valenta R, Scheynius, A. PLOS One 2016 |DOI:10.1371/journal.pone.0156077.

Background: Atopic dermatitis (AD) is a complex chronic inflammatory disease where allergens can act as specific triggering factors.

Aim: To characterize the specificities of IgE-reactivity in patients with AD to a broad panel of exogenous allergens including microbial and human antigens.

Methodology: Adult patients with AD were grouped according to the SCORAD index, into severe (n=53) and moderate AD (n=126). As controls 43 patients were included with seborrhoeic eczema and 97 individuals without history of allergy or skin diseases. Specific IgE reactivity was assessed in plasma using Phadiatop®, ImmunoCapTM, micro-arrayed allergens, dot-blotted recombinant Malassezia sympodialis allergens, and immune-blotted microbial and human proteins.

Results: IgE reactivity was detected in 92% of patients with severe and 83% of patients with moderate AD. Sensitization to cat allergens occurred most frequently, followed by sensitization to birch pollen, grass pollen, and to the skin commensal yeast M. sympodialis. Patients with severe AD showed a significantly higher frequency of IgE reactivity to allergens like cat (rFel d 1) and house dust mite (rDer p 4 and 10), to Staphylococcus aureus, M. sympodialis, and to human antigens. In contrast, there were no significant differences in the frequencies of IgE reactivity to the grass pollen allergens rPhl

p 1, 2, 5b, and 6 between the two AD groups. Furthermore the IgE reactivity profile of patients with severe AD was more spread towards several different allergen molecules as compared to patients with moderate AD.
Conclusion: The more broadly spread sensitization pattern and higher frequency of IgE reactivity observed in severe AD patients may be responsible for a more frequent boosting of the allergic immune response in these patients and explain why they suffer from more severe disease.

EAACI Molecular Allergology User's Guide.
P. M. Matricardi, J. Kleine-Tebbe, H. J. Hoffmann, R. Valenta, C. Hilger, S. Hofmaier, R. C. Aalberse, I. Agache, R. Asero, B. Ballmer-Weber, D. Barber, K. Beyer, T. Biedermann, M. B. Bilò, S. Blank, B. Bohle, P. P. Bosshard, H. Breiteneder, H. A. Brough, L. Caraballo, J. C. Caubet, R. Crameri, J. M. Davies, N. Douladiris, M. Ebisawa, P. A. Elgenmann, M. Fernandez-Rivas, F. Ferreira, G. Gadermaier, M. Glatz, R. G. Hamilton, T. Hawranek, P. Hellings, K. Hoffmann-Sommergruber, T. Jakob, U. Jappe, M. Jutel, S. D. Kamath, E. F. Knol, P. Korosec, A. Kuehn, G. Lack, A. L. Lopata, M. Mäkelä, M. Morisset, V. Niederberger, A. H. Nowak-We zgrzyn, N. G. Papadopoulos, E. A. Pastorello, G. Pauli, T. Platts-Mills, D. Posa1, L. K. Poulsen, M. Raulf, J. Sastre, E. Scala, J. M. Schmid, P. Schmid-Grendelmeier, M. van Hage, R. van Ree, S. Vieths, R. Weber, M. Wickman, A. Muraro, M. Ollert. Ped. Allergy Immunol. 2016;27 (Suppl 23):1-250.
The availability of allergen molecules ('components') from several protein families has advanced our understanding of immunoglobulin E (IgE)-mediated responses and enabled 'component-resolved diagnosis' (CRD). The European Academy of Allergy and Clinical Immunology (EAACI) Molecular Allergology User's Guide (MAUG) provides comprehensive information on important allergens and describes the diagnostic options using CRD. Part A of the EAACI MAUG introduces allergen molecules, families, extracts, databases, and diagnostic IgE, skin, and basophil tests. Singleplex and multiplex IgE assays with components improve both sensitivity for lowabundance allergens and analytical specificity; IgE to individual allergens can yield information on clinical risks and distinguish cross-reactivity from primary sensitization. Part B discusses clinical and molecular aspects of IgE-mediated allergies to foods (including nuts, seeds, legumes, fruits, vegetables, cereal grains, milk, egg, meat, fish, and shellfish), inhalants (pollen, molds, mites, animal dander), and Hymenoptera venom. Diagnostic algorithms and short case histories provide information for the clinical workup of allergic individuals targeted for CRD. Part C covers protein families containing ubiquitous, highly cross-reactive panallergens from plant (lipid transfer proteins, polcalcins, PR-10, profilins) and animal sources (lipocalins, parvalbumins, serum albumins, tropomyosins) and explains their diagnostic and clinical utility. Part D lists 100 important allergen molecules. In conclusion, IgEmediated reactions and allergic diseases, including allergic rhinoconjunctivitis, asthma, food allergy, and insect sting reactions, are discussed from a novel molecular perspective. The EAACI MAUG documents the rapid progression of molecular allergology from basic research to its integration into clinical practice, a quantum leap in the management of allergic patients.

Allergic bronchopulmonary aspergillosis (ABPA)
Crameri R. Ped. Allergy Immunol. 2016;27 (Suppl 23):81-83 (No abstract available).

Role of microbial allergens in atopic dermatitis.
Glatz M, Bosshard PP, Crameri R, Schmid-Grendelmeier P. Ped. Allergy Immunol. 2016;27 (Suppl 23):84-88.
We review the most relevant aspects of molecular allergens for atopic dermatitis (AD) that involve mostly microbial antigens. Recent investigations suggested a significant role of fungal allergens in the pathogenesis of AD. The most common fungi found on human skin are Malassezia spp. Malassezia is a genus of lipophilic yeasts that currently encompasses 14 species, nine of which are frequently isolated from human skin. Currently 14 immunogenic proteins (allergens) are characterized that are produced by Malassezia species, namely M. furfur, M. sympodialis, and M. globosa. These allergens elicit a specific IgE response. Furthermore, some of these allergens interact with human immune cells such as Dendritic cells or T cells, supposedly hrough Toll-like receptor 2, and elicit a pro-inflammatory immune response. For example, the allergen Mala s 11 from M. sympodialis is a manganese-dependent superoxide dismutase (MnSOD). The IgE-mediated sensitization to this protein correlates with the severity of AD, and this protein induces the release of proinflammatory cytokines such as interleukin (IL)-6, IL-8, IL12p70, and TNF-alpha by dendritic cells. Mala s 11 also activates autoreactive T cells that may act against its human homolog. The MnSOD from Aspergillus fumigatus (Asp f 6) is strongly crossreacting to Mala s 11. Asp f 6-specific IgE can be routinely determined in clinical settings, and may serve as a marker for autoreactivity in AD. Another species, M. globosa, produces the very recently characterized allergen MGL_1304 that induces the degranulation of mast cells and the release of IL-4 by basophils. Non-fungal microbial allergens with a supposed significance in AD are Der p 11 from Dermatophagoides pteronyssinus and enterotoxin B from Staphylococcus aureus. In conclusion, microbial allergens, particularly those from Malassezia spp., may be involved in the molecular mechanisms that lead to skin inflammationand may therefore be of significance for the course of AD.

Allergen-loaded strontium-doped hydroxyapatite spheres improve allergen-specific immunotherapy in mice.
M. Garbani, W. Xia, C. Rhyner, M. Prati, A. Scheynius, B. Malissen, H. Engqvist, M. Maurer, R. Crameri, D. Terhorst. Allergy 2016 Sep 3. doi: 10.1111/all.13041. [Epub ahead of print].
Background: Immunomodulatory interventions play a key role in the treatment of infections and cancer as well as allergic diseases. Adjuvants such as micro- and nanoparticles are often added to immunomodulatory therapies to enhance the triggered immune response. Here, we report the immunological assessment of novel and economically manufactured microparticle adjuvants, namely strontium-doped hydroxyapatite porous spheres (SHAS), which we suggest for the use as adjuvant and carrier in allergen-specific immunotherapy (ASIT). Methods and Results: Scanning electron microscopy revealed that the synthesis procedure developed for the production of SHAS results in a highly homogeneous population of spheres. SHAS bound and released proteins such as ovalbumin

(OVA) or the major cat allergen Fel d 1. SHAS-OVA were taken up by human monocyte-derived dendritic cells (mdDCs) and murine DCs and did not have any necrotic or apoptotic effects even at high densities. In a murine model of ASIT for allergic asthmatic inflammation we found that OVA released from subcutaneously injected SHAS-OVA led to a sustained stimulation of both CD4+ and CD8+ T-cells. ASIT with SHAS-OVA as compared to soluble OVA resulted in similar humoral responses but in a higher efficacy as assessed by symptom scoring. Conclusion: We conclude that SHAS may constitute a suitable carrier and adjuvant for ASIT with great potential due to its unique protein-binding properties.

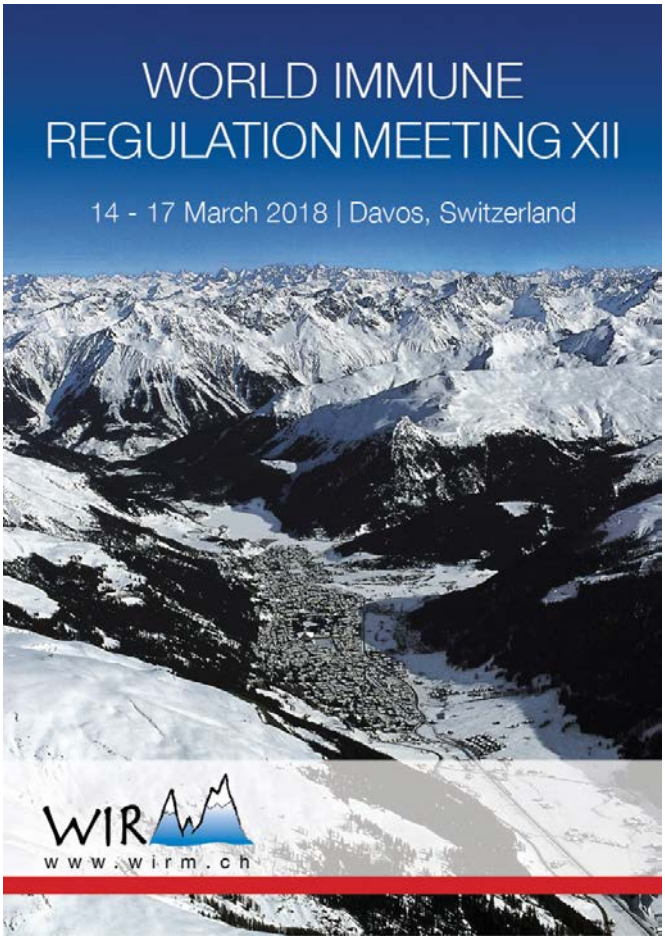
Artificial human sera: a breakthrough?
Crameri R. Allergy 2016;71(12):1549-1571. (No abstract available).

Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases.
Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, Duan S, Eiwegger T, Eljaszewicz A, Ferstl R, Frei R, Garbani M, Globinska A, Hess L, Huitema C, Kubo T, Komlosi Z, Konieczna P, Kovacs N, Kucuksezer UC, Meyer N, Morita H, Olzhausen J, O'Mahony L, Pezer M, Prati M, Rebane A, Rhyner C, Rinaldi A, Sokolowska M, Stanic B, Sugita K, Treis A, van de Veen W, Wanke K, Wawrzniak M, Wawrzyniak P, Wirz OF, Zakzuk JS, Akdis CA. J Allergy Clin Immunol 2016;138(4):984-1010.
There have been extensive developments on cellular and molecular mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumor development, organ transplantation, and chronic infections during the last few years. Better understanding the functions, reciprocal regulation, and counterbalance of subsets of immune and inflammatory cells that interact through interleukins, interferons, TNF-α, and TGF-β offer opportunities for immune interventions and novel treatment modalities in the era of development of biological immune response modifiers particularly targeting these molecules or their receptors. More than 60 cytokines have been designated as interleukins since the initial discoveries of monocyte and lymphocyte interleukins (called IL-1 and IL-2, respectively). Studies of transgenic or gene-deficient mice with altered expression of these cytokines or their receptors and analyses of mutations and polymorphisms in human genes that encode these products have provided essential information about their functions. Here we review recent developments on IL-1 to IL-38, TNF-α, TGF-β, and interferons. We highlight recent advances during the last few years in this area and extensively discuss their cellular sources, targets, receptors, signaling pathways, and roles in immune regulation in patients with allergy and asthma and other inflammatory diseases.

Direct determination of antibodies affinity to markers expressed on cell surface assessed by Quartz Crystal Microbalance (QMV) bio-sensing.
Prati M, Garbani M, Akdis CA, Crameri R, Rhyner C. (Submitted)

Evansescence wave-based technology for the rapid and sensitive quantification of biological analytes.
Schawaller M, Rhyner C, Wiki M, Huitema C, Quapil G, Zuberbier T, Akdis CA, Crameri R. (submitted)

Davos, June 2017



Cellular Allergy / Immunology

Prof. Dr. Cezmi A. Akdis

Epithelial tight junctions (TJ) consist of different transmembrane and scaffold adaptor proteins and form the most apical intercellular junction essential for barrier function between epithelial cells. They are responsible for the regulation of paracellular flux and epithelial impermeability. In addition, they prevent foreign particles, such as allergens, to enter into subepithelial layers. In addition to prevention and barrier function, opening of TJs can lead to drainage of inflammatory cells towards the lumen, supporting the resolution of inflammation. Tight junctions can be considered as gatekeepers that could contribute both to aggravation of inflammation related tissue damage or resolution of inflammation via drainage. Our research during the past few years demonstrated that epithelial barrier is leaky in allergic diseases and it is strongly regulated by innate and adaptive immune cells and their cytokines and environmental factors, which altogether opens a new window for further mechanistic research for better understanding and the development of novel ways for prevention and treatment.

Anionic surfactants and commercial detergents decrease tight junction barrier integrity in human keratinocytes
Xian M, Wawrzyniak P, Rückert B, Duan S, Meng Y, Sokolowska M, Globinska A, Zhang L, Akdis M, Akdis CA.
J Allergy Clin Immunol. 2016 Sep;138(3):890-893
As the largest organ of the body, skin acts as an essential barrier that protects and/ or minimizes damage from environmental and endogenous factors to keep an internal homeostasis. Skin barrier plays key roles in immune surveillance and in preventing penetration of microbes, toxins, pollutants, and allergens. This important barrier function resides mainly in the epidermis, which has two major barrier structures: stratum corneum and tight junctions (TJs), the latter seal adjacent keratinocytes in stratum granulosum. Recent data from human and animal studies have suggested the impairment of skin barrier as an important mechanism in allergen sensitization.We demonstrated in this study that even at trace concentrations, anionic surfactants as well as commercial detergents decreased the barrier integrity of air liquid interface cultured human keratinocytes through disruption of tight junctions and associated molecules, which may play a role in leaky barrier-related diseases including allergies.

Platelet-activating factor decreases skin keratinocyte tight junction barrier integrity
Duan S, Wanke K, Wawrzyniak P, Meng Y, Kast JI, Rückert B, Rebane A, Xian M, Bindslev-Jensen C, Broesby-Olsen S, Raap U, Werfel T, Akdis M, Zhang L, Akdis CA.
J Allergy Clin Immunol. 2016 Dec;138(6):1725-1728
Platelet-activating factor (PAF) is an important pro-inflammatory factor that is involved in allergic inflammation, and it is produced and secreted by several types of cells, including mast cells, monocytes, tissue macrophages, platelets, eosinophils, endothelial cells and neutrophils. In this study, we demonstrate the influence of PAF on skin barrier and keratinocyte tight junction integrity in atopic dermatitis and further analyze tight junction disruption in diseased skin for better understanding the molecular and cellular mechanisms in the regulation of TJ barrier integrity.

Cellular and molecular immunologic mechanisms in patients with atopic dermatitis
Werfel T, Allam JP, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E, Hoetzenecker W, Knol E, Simon HU, Wollenberg A, Bieber T, Lauener R, Schmid-Grendelmeier P, Traidl-Hoffmann C, Akdis CA.
J Allergy Clin Immunol. 2016 Aug;138(2):336-49
Atopic dermatitis (AD) is a complex skin disease frequently associated with other diseases of the atopic diathesis. Recent evidence supports the concept that AD can also recognize other comorbidities, such as chronic inflammatory bowel or cardiovascular diseases. These comorbidities might result from chronic cutaneous inflammation or from a common, yet-to-be-defined immunologic background leading to immune deviations. The activation of immune cells and their migration to the skin play an essential role in the pathogenesis of AD. In patients with AD, an underlying immune deviation might result in higher susceptibility of the skin to environmental factors. There is a high unmet medical need to define immunologic endotypes of AD because it has significant implications on upcoming stratification of the phenotype of AD and the resulting targeted therapies in the development of precision medicine. This review article emphasizes studies on environmental factors affecting AD development and novel biological agents used in the treatment of AD. Best evidence of the clinical efficacy of novel immunologic approaches using biological agents in patients with AD is available for the anti-IL-4 receptor α-chain antibody dupilumab, but a number of studies are currently ongoing with other specific antagonists to immune system players. These targeted molecules can be expressed on or drive the cellular players infiltrating the skin (eg, T lymphocytes, dendritic cells, or eosinophils). Such approaches can have immunomodulatory and thereby beneficial clinical effects on the overall skin condition, as well as on the underlying immune deviation that might play a role in comorbidities. An effect of these immunologic treatments on pruritus and the disturbed microbiome in patients with AD has other potential consequences for treatment.

Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthmatic patients

Wawrzyniak P, Wawrzyniak M, Wanke K, Sokolowska M, Bendelja K, Rückert B, Globinska A, Jakiela B, Kast JI, Idzko M, Akdis M, Sanak M, Akdis CA.

J Allergy Clin Immunol. 2017 Jan;139(1):93-103

Tight junctions (TJs) form a barrier on the apical side of neighboring epithelial cells in the bronchial mucosa. Changes in their integrity might play a role in asthma pathogenesis by enabling the paracellular influx of allergens, toxins, and microbes to the submucosal tissue. The expression, regulation, and function of TJs were determined in air-liquid interface (ALI) cultures of control and asthmatic primary human bronchial epithelial cells (HBECs) by means of analysis of transepithelial electrical resistance, paracellular flux, mRNA expression, Western blotting, and immunofluorescence staining. We demonstrated that HBECs from asthmatic patients showed a significantly low TJ integrity in ALI cultures compared with HBECs from healthy subjects. TH2 cell numbers and levels of their cytokines, IL-4 and IL-13, decreased barrier integrity in ALI cultures of HBECs from control subjects but not in HBECs from asthmatic patients. They induced a physical separation of the TJs of adjacent cells in immunofluorescence staining of the TJ molecules occludin and zonula occludens-1. We observed that expression of histone deacetylases (HDACs) 1 and 9, and Silent information regulator genes (sirtuins [SIRTs]) 6 and 7 were significantly high in HBECs from asthmatic patients. IL-4 and IL-13 significantly increased the expression of HDACs and SIRTs. The role of HDAC activation on epithelial barrier leakiness was confirmed by HDAC inhibition, which improved barrier integrity through increased synthesis of TJ molecules in epithelium from asthmatic patients to the level seen in HBECs from control subjects.

In conclusion, our data demonstrate that barrier leakiness in asthmatic patients is induced by TH2 cells, IL-4, and IL-13 and HDAC activity. The inhibition of endogenous HDAC activity reconstitutes defective barrier by increasing TJ expression.

Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics

Agache I, Strasser DS, Klenk A, Agache C, Farine H, Ciobanu C, Groenen PM, Akdis CA.

Allergy. 2016 Aug;71(8):1192-202

Molecular biomarkers that identify the phenotype of blood eosinophilia were evaluated in adult asthmatics, and their relationship with clinically significant asthma outcomes was assessed. Patients were clustered based on their molecular fingerprint. In this study, 64 patients were evaluated for phenotypic traits, sputum and blood eosinophilia, exhaled NO, serum cytokines and chemokines, total serum IgE, lung function (LF), and airway hyper-responsiveness (AHR). Within-patient changes were evaluated in 44 patients 6 weeks later. Lung function, asthma control, and monocyte chemotactic protein-1 (MCP-1) were identified as the most important distinguisher and blood eosinophilia as second most important identifier in principal component analysis. A robust relationship was observed between blood eosinophilia and IL-5, IL-13, and eosinophil-derived neurotoxin (EDN), which stayed consistent after 6 weeks. Serum IL-5 and IL-13 were the two best, followed by EDN as separators of high vs low blood eosinophilia. Periostin did not identify blood or sputum eosinophilia, even after stratification for total IgE, and did not correlate with IL-5, IL-13, eotaxin, or EDN. IL-5 and IL-13 showed strong correlations with AHR and monocyte chemoattractant protein (MCP)-1 with asthma severity and fast LF decline. The presence of high or low expression of MCP-1, eotaxin, and IL-8 identified two separate blood eosinophilia patient clusters linked to asthma severity. In conclusion, serum IL-5 and IL-13 are reliable biomarkers for the blood eosinophilia asthma phenotype. High or low expression of MCP-1, eotaxin, and IL-8 discriminates between eosinophilic asthma severity clusters.

Davos, June 2017

Multiple cells and cytokines involved in type 2 immunity. Feb. 2016 Cover of the Journal of Allergy & Clinical Immunology. Artist: Anna Globinska (SIAF)

Prof. Dr. Mübeccel Akdis

Effector and Regulatory Memory B cells

B lymphocytes display a unique role in immune response through the production of antibodies, representing the humoral arm of the adaptive immune response. A functional role for human regulatory B cells was further supported by the finding that B cell–depleting therapy was associated with exacerbations of colitis and psoriasis induction and neutropenia in patients undergoing organ transplantation. Furthermore, altered numbers, function, or both of regulatory B-cell subsets in patients with chronic inflammatory and autoimmune diseases, as well as insufficient antitumor immunity, was associated with locally increased numbers of IL-10–producing B cells. Allergen-specific immunotherapy typically leads to suppression of IgE and upregulation of IgG4 production, as well as increased IL-10 production, in allergen-specific T and B cells. These observations have stimulated scientific interest to study the role and capacity of regulatory B cells and their underlying immunosuppressive mechanisms. IL-10 is a pivotal anti-inflammatory cytokine that protects the host from excessive tissue damage during host defense to pathogens and acts as one of the key molecules critically involved in the development and maintenance of immune tolerance and homeostasis. IL-10 deficiency leads to the development of spontaneous colitis in mice. IL-10 suppresses the production of proinflammatory cytokines and chemokines, as well as antigen presentation. In B cells, IL-10 enhances survival, proliferation, and differentiation and modulates class-switch recombination through suppression of IL-4–induced IgE and induction of IgG4. Plasmid-driven IL-10 transfection was performed to reveal the role of IL-10 on the phenotype and functions of B cells. IL-10 overexpression was sufficient for acquisition of a notable immunoregulatory phenotype in B cells. In conjunction with secreted IL-10, these B cells further extend their immunosuppressive functions on both innate and adaptive immune responses.

Characterization of human antigen-specific B cells has been hampered by the fact that long-term culture of B cells is challenging. In this study we generated long-living allergen-specific memory B cell subsets to investigate their function in regulating immune responses. Immortalization of memory B cells by introducing Bcl-6 and Bcl-xl into peripheral memory B cells, leading to formation of highly proliferating, cell surface BCR-positive, immunoglobulin-secreting cells. B cells were isolated from non-allergic individuals, bee venom-allergic patients and beekeepers. Using labeled phospholipase A2 (PLA), the frequency of PLA-specific B cells and generated PLA-specific B cell clones was measured. Non-allergic individuals did not have detectable PLA-specific memory B cells, whereas frequencies of PLA-specific cells in beekeepers and BV-allergic patients reached up to 0.4%. Beekeeper-derived PLA-specific B cells mainly produced PLA-specific IgG4 and expressed mostly surface BCR of the IgG4 isotype. The frequency of IgG4+ cells within PLA-specific B cells from BV-allergic patients was significantly increased after beevenom-specific immunotherapy (SIT). Furthermore, IgG4+ B cell clones showed increased expression of HLA-DR and CD86 when compared to IgG1+ clones. Secretion of TNF-alpha, RANTES, IL-6, IP-10 and CCL4 were significantly reduced in IgG4-switched clones, indicating that IgG4+ cells may be efficient antigen-presenting cells.

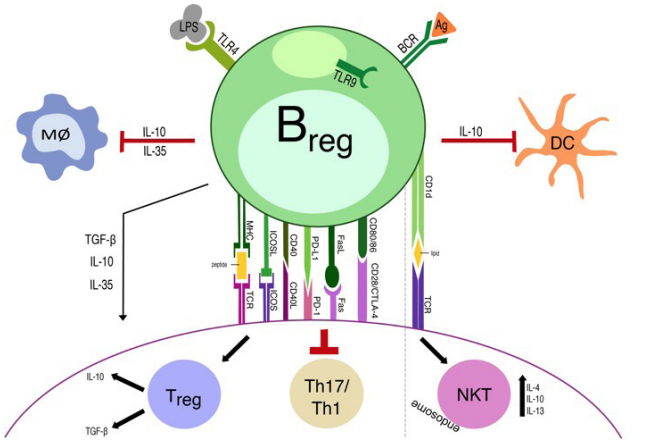


Figure 1: Mechanisms of suppression by Breg cells. Expression and secretion of suppressive mediators in Breg cells can be induced by TLR ligands, such as LPS and CpG, as well as BCR and CD40 signaling. Breg cells can regulate T-cell responses through inhibition of effector T-cell (in particular TH1 and TH17) responses while promoting Treg cell expansion. These effects are mediated by secreted factors, such as IL-10, TGF-b, and IL-35. Moreover, membrane-bound molecules at the interface between B cells and T cells include CD80, CD86, Fas ligand (FasL), CD40, inducible costimulator ligand (ICOS-L), and MHC-II on the B-cell side and T-cell receptor (TCR), cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), CD28, Fas, PD-1, CD40 ligand (CD40L), and inducible costimulator (ICOS) on the T-cell side. CD1d, which is expressed by certain Breg cells, can activate natural killer T (NKT) cells with suppressive function. Furthermore, Breg cells can inhibit DC and macrophage activation, primarily through secreted IL-10.

Mechanisms of allergen-specific immunotherapy

Allergen-specific immunotherapy (AIT) is currently the only available treatment that can lead to allergen tolerance. AIT can result in a reduction of allergic symptoms, disease severity, and decreased medication use. AIT for insect venoms, also known as venom immunotherapy (VIT) has been proven effective for preventing further allergic reactions to insect stings. Allergic patients receiving VIT as well as healthy nonallergic beekeepers represent valuable human in vivo models to study the mechanisms of immune tolerance induction to allergens. Beekeepers receive multiple bee stings during the beekeeping season in spring and summer, while they are not exposed to bee venom in autumn and winter. Within a week after the first bee stings of the season, the frequency of allergen-speci-

fic IL-10-producing T regulatory 1 (TR1) increases in beekeepers. Venom-specific Th1 and Th2 cells switch toward IL-10- secreting TR1 cells, which suppress T-cell responses through various mechanisms. IL-10 has a wide range of immunosuppressive functions including suppression of proinflammatory cytokine production, suppression of effector T-cell responses as well as augmentation of IgG4 production and suppression of IgE production by B cells. AIT also induces IL-10-secreting B regulatory 1 (BR1) cells, which can regulate immune responses through suppression of antigen-specific CD4+ T-cell proliferation and production of noninflammatory IgG4 antibodies. Allergen-specific IgG4 can interfere with allergen-mediated IgE cross-linking, thereby preventing mast cell and basophil degranulation. Furthermore, AIT can stimulate somatic hypermutation of allergen specific B cells, leading to generation of high-affinity antibodies. In response to AIT, typically a transient increase in circulating specific IgE is observed, followed by gradual decrease over subsequent months. In contrast, circulating specific IgG4 increases during AIT. However, the correlation between serum IgG4 and clinical outcome of AIT remains controversial, and allergen-specific B-cell responses have not been thoroughly studied. Interestingly, a recent study demonstrated a positive correlation between serum histamine levels and venom-specific IgG4 antibodies in beekeepers, associating high histamine levels in serum with a tolerant phenotype. Allergen-specific B cells are found in circulation at very low frequencies. Accurate detection of allergen-specific B cells therefore requires a thorough exclusion of nonspecific staining. It has been demonstrated that small fractions (<0.05%) of B cells express a B-cell receptor (BCR) that specifically recognizes fluorescent dyes such as Phycoerythrin or Allophycocyanin. Therefore, detection of allergen-specific B cells without inclusion of such dye-specific B cells may be more accurate when cells are stained with antigens labeled with two structurally unrelated fluorescent dyes. Chemokine receptors play a key role in the regulation of immune responses by coordinating chemotaxis of immune cells. B cells express a range of chemokine receptors including CXCR4, CXCR5, CCR6, and CCR7. CCR5 is not widely expressed on B cells but was of interest because it plays an important role in the functionality of Treg cells in immune tolerance. CXCR5 and CCR7 primarily regulate cell trafficking in lymphoid tissues, CXCR4 facilitates bone marrow homing and trafficking of B cells in lymph nodes, and CCR5 and CCR6 promote homing to peripheral sites of inflammation. There are still many open questions regarding the role of allergen-specific B cells in the induction of immune tolerance to allergens. In this study, we investigated the effect of VIT as well as natural tolerance induction on allergen-specific B cell responses. We used dual-color fluorescent staining to identify phospholipase A2 (PLA)-specific B cells. Using this method, we could isolate PLA-specific B cells and confirm their antigen specificity. Moreover, we used flow cytometry to characterize PLA-specific B cells. This approach revealed that allergen-specific memory B cells expand in response to high-dose allergen exposure both in patients as well as healthy individuals. Furthermore, B cells developed an immunoregulatory phenotype, characterized by elevated production of IL-10 and IgG4, and increased CCR5 expression, which may facilitate their migration to site of inflammation, where they can exert their regulatory function.

Increased Breg cells after VIT and live bee stings

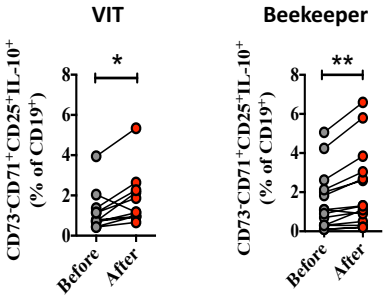


Figure 2: Frequencies of BR1 cells increase after bee venom immunotherapy in allergic patients and after multiple bee stings in beekeepers. Frequency of IL-10-producing BR1 cells (CD73-CD71+CD25+IL-10+) in VIT group (n = 11) (A) and in beekeeper group (n = 15) (B).

Breaking of allergen-specific tolerance by human rhinovirus infections

Respiratory infections with human rhinoviruses (HRV) pose severe health risks for patients with allergies and asthma, and represent the leading cause for their exacerbations. Respiratory viral infections negatively influence the dose increment phase and sometimes maintenance dose phase in allergen immunotherapies in general and oral immunotherapy of food allergy in particular. A susceptibility to viral infection, most often to HRV, characterizes allergic diseases (asthma, rhinitis and more), and is exaggerated in comorbid states. This common susceptibility facilitates viral evasion and/or host antiviral incompetence, leading to inappropriate inflammatory responses, clinically expressed as disease exacerbation and propensity to progression. In addition, there is both mechanistic and epidemiological evidence suggesting that viral infections are indeed a frequent co-factor in severe allergic reactions, such as anaphylaxis, thus causing major burden for patients. Effects of HRV on many cell types have already been described including epithelial cells and lymphocytes, such as CD4+ T cells. B cells are found in mucosal tissues that are frequently exposed to HRV. However, not much is known about the interaction of rhinovirus with B cells. We have demonstrated for the first time that B cells can be infected by HRV in an ICAM-1-dependent manner. This infection induced proliferation through endosomal receptors, most probably TLRs 3,7, and 8. We found both (+) and (-) viral RNA strands, suggesting that there is not only HRV inside or attached to the cells, but also that HRV is replicating in B cells. HRV can be detected inside the B cells already within one day after infection. Unlike in PBMC, the viral load stays mostly constant over an extended period of cell culture in B cells. To address, whether B cells could be a natural reservoir of HRV immortalized B cell lines will be infected and studied over an extended period of time. The integration of the mechanisms of acute exacerbations into a chronic allergic disease background and their link to breaking of allergen tolerance or changing the thresholds of immune tolerance remains to be elucidated. In addition to induction of asthma exacerbations, there is likely a causative link between HRV infections and the development of childhood asthma, but yet fundamental questions persist about mechanisms linking this common pathogen to the disease.

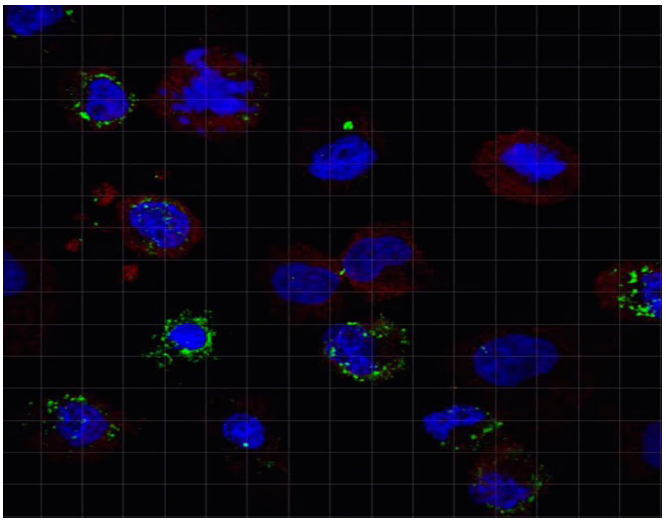


Figure 3: Visualization of HRV1B vRNA with in situ hybridization (ISH). HRV1B vRNA is designated with green, human beta-actin mRNA with red and DAPI with blue. (A) PBMCs were cultured with HRV1B and subjected to ISH analysis on 5th day.

Role of regulatory B cells in immune tolerance to allergens and beyond.

van de Veen W, Stanic B, Wirz OF, Jansen K, Globinska A, Akdis M. J Allergy Clin Immunol. 2016 Sep;138(3):654-65.

Immune tolerance to both self-antigens and innocuous non-self-antigens is essential to protect the host against chronic inflammatory diseases and tissue damage. A wide range of cell types and suppressive molecules are involved in induction and maintenance of tolerance. In addition to their key function in the production of immunoglobulins, B cells can regulate immune responses through their surface molecules and secretion of cytokines. Regulatory B (Breg) cells are characterized by their immunosuppressive capacity, which is often mediated through IL-10 secretion. However, IL-35 and TGF-β have also been associated with B cell-mediated immunosuppression. Several types of murine and human Breg cells have been described, such as mouse CD5(+)CD1d(hi) B10 cells, CD21(hi)CD23(hi)CD24(hi) transitional stage 2-like B cells, and CD138(+) plasma cells and plasmablasts. Human Breg cell types include CD27(+)CD24(high) B10 cells, CD24(hi)CD38(hi) immature transitional B cells, and CD73(-)CD25(+)CD71(+) BR1 cells and a subset of plasma cells. Support for the in vivo existence of allergen-specific human Breg cells comes from direct detection of their increase during the course of allergen-specific immunotherapy, as well as their increased expression in nonallergic but high-dose allergen-exposed beekeepers. Human BR1 cells selectively upregulate IgG4 antibodies on differentiation to plasma cells. This suggests an additional immune regulatory role because of the noninflammatory and blocking antibody function of IgG4. Taken together, Breg cells appear to be involved in mediating allergen tolerance, but many open questions remain to be answered.

High-dose bee venom exposure induces similar tolerogenic B cell responses in patients and healthy beekeepers

Boonpiyathad T, Meyer N, Moniuszko M, Sokolowska M, Eljaszewicz A, Wirz O.F, Tomasiak-Lozowska M. M, Bodzenta-Lukaszyk A, Ruxrungtham K, van de Veen W. Allergy. 2017 Mar;72(3):407-415.

The involvement of B cells in allergen tolerance induction remains largely unexplored. This study investigates the role of B cells in allergen tolerance induction to high-dose allergen exposure, and to compare B cell responses between allergic patients receiving allergen immunotherapy (AIT) and naturally exposed healthy beekeepers before and during the beekeeping season. Circulating B cells were characterized by flow cytometry. PLA-specific B cells were identified using dual color staining with fluorescently labeled phospholipase A2 (PLA). Expression of regulatory B cell-associated surface markers, interleukin-10, chemokine receptors and immunoglobulin heavy chain isotypes was measured. Specific and total IgG1, IgG4, IgA and IgE from plasma as well as culture supernatants of PLA-specific cells were measured by ELISA. Strikingly similar responses were observed in allergic patients and beekeepers after venom exposure. Both groups showed increased frequencies of plasmablasts, PLA-specific memory B cells and IL-10-secreting CD73-CD25+CD71+ BR1-cells. PLA-specific IgG4-switched memory B cells expanded after bee venom exposure. Interestingly, PLA-specific B cells showed increased CCR5 expression after high-dose allergen exposure while CXCR4, CXCR5, CCR6 and CCR7 expression remained unaffected. This study provides the first detailed characterization of allergen-specific B cells before and after bee venom tolerance induction. The observed B cell responses in both Venom immunotherapy-treated patients and naturally exposed beekeepers suggest a similar functional immunoregulatory role for B cells in allergen tolerance in both groups. These findings can be investigated in other AIT models to determine their potential as biomarkers of early and successful AIT responses.

Human Rhinoviruses Enter and Induce Proliferation of B Lymphocytes.

Aab A, Wirz O, van de Veen W, Söllner S, Stanic B, Rückert B, Aniscenko J, Edwards MR, Johnston SL, Papadopoulos NG, Rebane A ,Akdis CA, Akdis M. Allergy. 2017 Feb;72(2):232-243.

Human rhinoviruses (HRV) are one of the main causes of virus induced asthma exacerbations. Infiltration of B lymphocytes into the subepithelial tissue of the lungs has been demonstrated during rhinovirus infection in allergic individuals. However, the mechanisms through which HRVs modulate the immune responses of monocytes and lymphocytes are not yet well described. To study the dynamics of virus uptake by monocytes and lymphocytes, and the ability of HRVs to induce activation of in vitro cultured human peripheral blood mononuclear cells. Flow cytometry was used for the enumeration and characterization of lymphocytes. Proliferation was estimated using 3 H-thymidine or CFSE labelling and ICAM-1 blocking. We used bead based multiplex assays and quantitative PCR for cytokine quantification. HRV accumulation and replication inside B lymphocytes was detected by a combination of in situ hybridation (ISH), immunofluorescence and with PCR for positive strand and negative strand viral RNA. Cell images were acquired with imaging flow cytometry. By means of imaging flow cytometry,

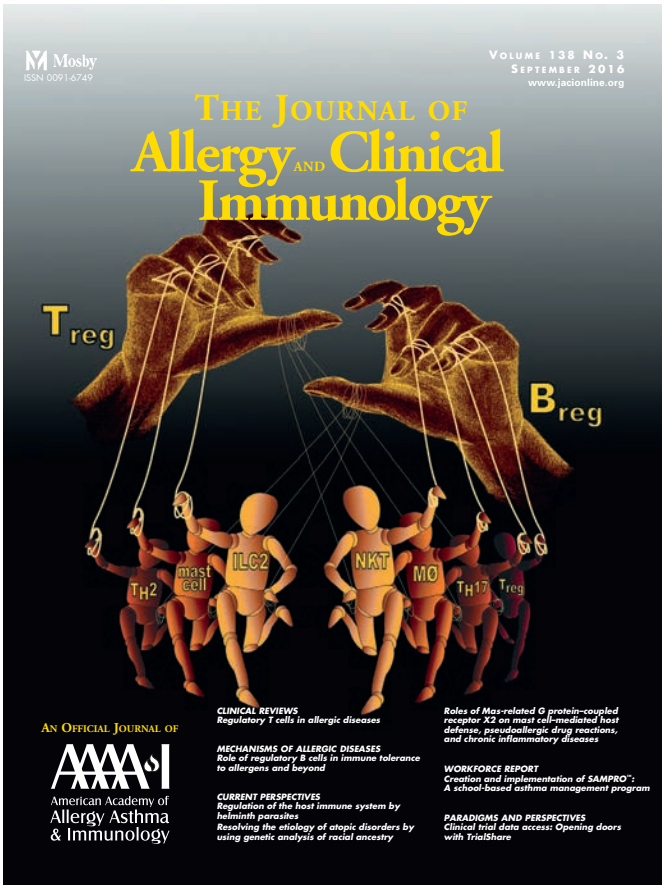
we demonstrate a strong and quick binding of HRV types 16 and 1B to monocytes, and slower interaction of these HRVs with CD4+ T cells, CD8+ T cells and CD19+ B cells. Importantly, we show that HRVs induce the proliferation of B cells while addition of anti-ICAM-1-antibody partially reduces this proliferation for HRV16. We prove with ISH that HRVs can enter B cells, form their viral replication centers and the newly formed virions are able to infect HeLa cells. In addition, we demonstrate that similarly to epithelial cells, HRVs induce the production of pro-inflammatory cytokines in PBMCs. Our results demonstrate for the first time that HRVs enter and form viral replication centers in B lymphocytes and induce the proliferation of B cells. Newly formed virions have the capacity to infect other cells (HeLa). These findings indicate that the regulation of human rhinovirus induced B cell responses could be a novel approach to develop therapeutics to treat the virus-induced exacerbation of asthma.

Increased microRNA-323-3p in IL-22/IL-17-producing T cells and asthma: a role in the regulation of the TGF-β pathway and IL-22 production.

Kärner J, Wawrzyniak M, Tankov S, Runnel T, Aints A, Kisand K, Altraja A, Kingo K, Akdis CA, Akdis M, Rebane A. Allergy. 2017 Jan;72(1):55-65.

IL-22- and IL-17-producing T cells have important roles in allergic diseases. microRNAs (miRNAs) are post-transcriptional regulators of gene expression and modulate numerous biological processes. Little is known about the functions of miRNAs in IL-22/IL-17-producing T cells. IL-22- and IL-17-positive T cells were sorted from human peripheral blood mononuclear cells (PBMCs) by intracellular staining and dual secretion assay. miRNA expression profiles were detected with TaqMan array microfluidic cards. T cells were transfected with miRNA mimics. Gene expression was analyzed using RT-qPCR and/or enzyme-linked immunosorbent assay in T cell subsets and PBMCs from patients with asthma and atopic dermatitis. The increased expression of miR-323-3p and non-coding RNA nc886 and reduced expression of miR-93, miR-181a, miR-26a and miR-874 were detected in IL-22-producing T cells. The pathway analysis of the putative targets suggested that these differentially expressed miRNAs could impact the proliferation, differentiation and effector functions of T cells. Further analyses showed the highest expression for miR-323-3p in IL-22- and IL-17-double-positive T cells and its capacity to suppress multiple genes from the transforming growth factor β pathway and the production of IL-22 in T cells. An increased expression of miR-323-3p in PBMCs from asthma patients and reverse correlation between miR-323-3p levels and IL-22 production in PBMCs cultured in T cell growth conditions was observed. Our data suggest that miR-323-3p acts in a negative feedback loop to control the production of IL-22 in IL-22/IL-17-producing T cells and might thus impact the T cell responses in asthma.

Davos, June 2017



Immune regulation by T and B regulatory cells. Sept. 2016 Cover of the Journal of Allergy & Clinical Immunology. Artist: Anna Globinska (SIAF)

Molecular Immunology

PD Dr. Liam O'Mahony

The molecular Immunology group is primarily focused on understanding the molecular mechanisms responsible for microbial and metabolite regulation of mucosal immune responses. In particular, regulation of the innate immune system is examined in detail. These innate immune cells are responsible for the initial acquisition of foreign particles and their interaction with T and B cells, leading to the development of adaptive immunity. Dendritic cells (DCs) are potent antigen presenting cells that are present at all mucosal surfaces and are central players in initiating and regulating adaptive immune responses. Microbial-derived metabolites such as short-chain fatty acids and biogenic amines significantly influence DC activation and lymphocyte polarization. Microbial dysbiosis and associated metabolic impairment may significantly contribute to the immunological dysfunction observed in allergy and asthma patients.

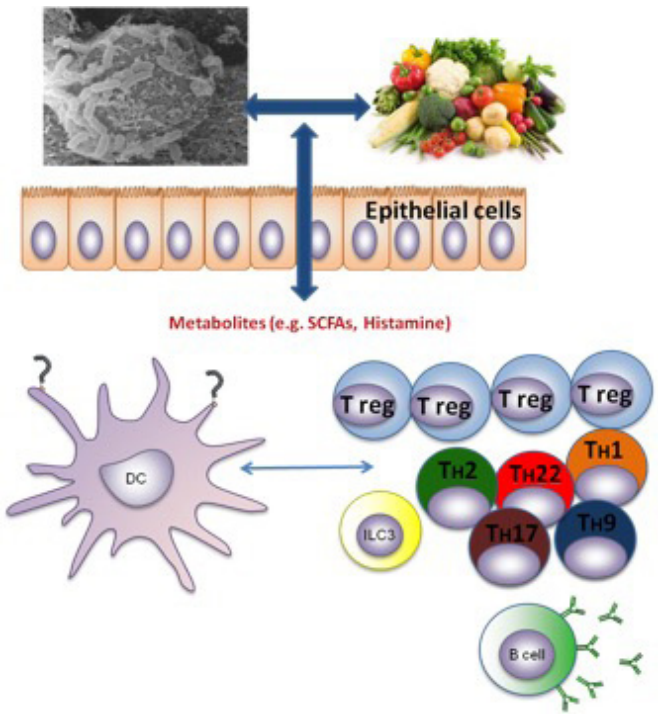


Figure 1. Microbes and their metabolites (e.g. short-chain fatty acids) directly influence DC maturation, activation and lymphocyte polarization.

DC activation, maturation and polarization are largely influenced by local factors within their micro-environment such as microbial components, cytokines and metabolic products (e.g. histamine or retinoic acid). DCs shape the functional differentiation of the dividing T cells into Th1, Th2, Th9, Th17 and Treg responses by producing cytokines such as IL-1β, IL-12, IL-18, IL-23, IL-11, IL-10 or TGF-β. The selection of an appropriate cytokine secretion pattern by dendritic cells is dependent on a number of factors, but is significantly influenced by the binding of microbial ligands, termed pathogen-associated molecular patterns (PAMPs), to pattern recognition receptors (PRRs) such as toll-like receptors (TLR) and C-type lectin receptors (CLR). PRR signaling is important in the context of asthma as increased household endotoxin exposure (in aerosol form) is a significant risk factor for the development of asthma in a subset of the population while household endotoxin levels positively correlate with disease severity. Deliberate administration of LPS to the lungs of asthma patients resulted in the rapid recruitment of multiple cell types, including mDCs and to a lesser extent pDCs. The differential binding of specific PRRs activates a number of intracellular signaling pathways, which ultimately result in cytokine secretion and/or cellular maturation. For example, human mesenteric lymph node dendritic cells preferentially secrete IL-10 and TGF-β to commensal microbes while pathogens stimulate TNF-α and IL-12 secretion. Certain intracellular pathways have been well described (e.g. TLR-4 activation by LPS) while others are still being explored. However, in vivo, multiple dendritic cell PRRs are simultaneously activated and the co-operation or competition between the resultant signaling cascades is not well understood. The specificity of these responses is achieved through the activation of a particular mosaic of PRRs, that is determined by the available PAMPs and the innate immune cells involved. pDCs preferentially express TLR-7, TLR-9 and DCIR while mDCs express TLR-1, TLR-2, TLR-4, TLR-5, TLR-8, DC-SIGN and Dectin 1. A number of regulatory mechanisms have been described which prevent PRR over-activation. These include intracellular inhibitors, such as IRAK-M and TAG, and other cell types, such as T regulatory cells, which can dampen PRR activation and prevent inflammatory damage to the host.

We are pursuing complementary research programs within our group in order to (i) identify the molecular basis and in vivo relevance for histamine-H2R interactions in respiratory and gastrointestinal inflammatory responses; (ii) identify bacterial bioactives that promote regulatory immune responses at mucosal sites; (iii) determine the interaction between diet, microbes and metabolites in regulating the immune response in obese and non-obese asthma patients.

(i) Histamine is a biogenic amine with extensive effects on many cell types including important immunological cells such as antigen-presenting cells (APCs), Natural Killer (NK) cells, epithelial cells, T lymphocytes and B lymphocytes. Histamine and its four receptors (H1R – H4R) represent a complex system of immunoregulation with distinct effects dependent on receptor subtypes and their differential expression. These are influenced by the stage of cell differentiation as well as micro-environmental influences, leading to the selective recruitment of effector cells into tissue sites accompanied by effects on cellular maturation, activation, polarization and effector functions

leading to tolerogenic or pro-inflammatory responses. H1R, H2R, and H4R are expressed by many cell types of the innate and adaptive immune system, including DCs, while expression of H3R is largely limited to the central nervous system. Histamine has diverse effects depending on the cell type and the repertoire of histamine receptors that are expressed. For example, Th1 cells predominantly express H1R while Th2 cells express H2R and activation of the H2R can suppress activation of both T cell lineages. H2R activation of human pDCs leads to a significant downregulation of IFN-α and TNF-α release following CpG stimulation. H4R has been shown to mediate mast cell, eosinophil, and dendritic cell chemotaxis and can modulate cytokine production from dendritic cells and T cells. H4R has also been shown to be upregulated on human T cells under Th2 polarizing conditions in vitro. H4R-/- mice and wild-type mice treated with a selective H4R antagonist display reduced disease activity following induction of airway inflammation. In contrast, H4R activation mediated by a selective agonist, delivered intratracheally, mitigated airway hyper-reactivity and inflammation. This effect was associated with a potent Foxp3+ T regulatory cell response in the lung. Thus, it is clear that histamine and its receptors play an important role in linking innate and adaptive immune responses.

As described in previous reports, histamine signaling through the H2R significantly alters the human dendritic cell immune response to bacterial ligands (such as TLR ligands). In addition, ovalbumin sensitized mice were co-treated with Famitodine (H2R antagonist) or Dimaprit (H2R agonist), resulting in a more severe allergic phenotype or protection from allergic sensitization, respectively. Furthermore, we have also demonstrated in H2R knock-out animals, that loss of this receptor results in more exaggerated allergic responses within the lung. This is characterized by enhanced recruitment of eosinophils and elevated cytokine release from tissue cells. In particular, CD1d expressing DC numbers are increased in the lung, while invariant natural killer T cells (iNKT) are also increased. Stimulation of iNKT cells by alphaGalCer within the lungs of H2R knock-out animals resulted in more severe respiratory inflammation, characterized by an enhanced Th17 response and recruitment of neutrophils. Lung challenge with Th2 promoting lipids resulted in a more pronounced eosinophil response. Identical results were observed in the house dust mite murine model. We generated a double knock-out mouse (H2R-/-CD1d-/-) to evaluate the specific contribution of iNKT cells to the exaggerated respiratory inflammatory response associated with the loss of H2R. OVA challenge of these animals did not result in increased inflammatory cells within BALs, compared to wild-type animals, confirming that H2R is a negative regulator of iNKT cell inflammatory activity within the lung. In humans, we have recently discovered that there are increased numbers of bacteria, which can secrete histamine, in the gastrointestinal tract of adult asthma patients. Histamine-secreting Escherichia coli, Lactobacillus vaginalis and Morganella morganii strains were isolated from the gut microbiome of asthma patients and patients with more severe disease had the highest levels of M. morganii. Histamine may also exert immunoregulatory effects in other inflammatory disorders, such as inflammatory bowel disease (IBD). Patients with IBD exhibit altered H2R expression on peripheral blood monocytes and the suppressive effect of H2R activation on TLR-induced cytokine responses is no longer effective in IBD patients. Within the gastrointestinal mucosa, histamine receptor expression is altered in inflamed tissue, compared to non-inflamed tissue from the same patient, and histamine receptor expression is directly correlated with proinflammatory cytokine expression. Utilising the SCID murine model of colitis, we observed that mice receiving lymphocytes from H2R-/- donors, or treated with famotidine, displayed more severe weight loss, higher disease scores and increased numbers of mucosal IFN-γ and IL-17+ T cells. Based on these murine and human observations, it is clear that host and bacterial-derived histamine mediates important immune regulatory effects in the gut and in the lung via H2R. An increase in histamine secreting microbes may therefore have protective effects if H2R is triggered, but may contribute to histamine-mediated pathologies if H1R or H4R are triggered.

(ii) The commensal microbiota is required for optimal host development and for ongoing immune homeostasis which involves an inter-dependence between microbes and immunity. This requires discriminative responses to commensals in comparison to pathogens to ensure tolerance and protective immunity respectively. A characteristic feature of mucosal tolerance is the induction and expansion of Foxp3+ T regulatory cells which limit excessive pro-inflammatory responses. We and others have identified specific microbes present within the gastrointestinal tract which selectively promote Foxp3+ polarization within the mucosa of mice. However, the in vivo mechanisms underpinning this response are not well understood.

Bifidobacterium longum 35624 (B. longum) is a commensal microbe originally isolated from the human gastrointestinal mucosa and has been extensively studied for its ability to regulate inflammatory responses, both in mice and humans. In order to understand the B. longum-associated molecules, which dampen inflammatory responses, we examined the bacterial genome and identified a unique gene cluster that encodes for the enzymatic machinery to produce an exopolysaccharide (EPS). The chemical composition and structure of the EPS was determined and found to be novel. A EPS knock-out mutant was generated and surprisingly the mutant induced a strong dendritic cell proinflammatory response, which was not observed for the parent strain expressing EPS. Administration of B. longum 35624 to the SCID colitis model prevented disease symptoms, whereas the EPS KO mutant did not protect against the development of colitis, with associated enhanced recruitment of IL-17+ lymphocytes to the gut. In addition, intranasal administration of the EPS KO mutant exaggerated the recruitment of TH17 cells to the lungs, while the wild-type bacterium did not. Isolated EPS induced IL-10 secretion from human DCs in vitro, which was TLR-2-dependent. Intranasal administration of the EPS during challenge with OVA significantly reduced the infiltration of eosinophils to the lungs, which was not observed in IL-10-deficient animals or when anti-TLR-2 neutralizing antibodies were used. These studies implicate the surface-associated exopolysaccharide of the B. longum 35624 cell envelope in the prevention of aberrant inflammatory responses.

In addition to immunoregulatory cell structures, microbes secrete metabolites that are immunoregulatory. Microbiota-derived short-chain fatty acids (SCFAs) are generated following microbial fermentation of dietary fibres and have been shown by others to possess immune-modulating properties. We have administered SCFAs to mice and observed a dramatic suppression of allergic airway responses. Microbes also secrete biogenic amines following decarboxylation of dietary amino acids and these metabolites can influence immune responses. We have measured biogenic amine levels in fecal samples and BALs from asthma patients and healthy controls. Preliminary results suggest a similar shift for both fecal samples and BALs towards an increase in proinflammatory biogenic amines in asthma patients. We have also identified a subset of microbe-derived biogenic amines that suppress dendritic cell activation and we are currently isolating and characterizing these microbes from healthy volunteers and asthma patients. These molecular mechanisms highlight an important link between diet, composition of the gastrointestinal microbiota and regulation of mucosal immune responses.

These studies are important for determining the role of novel dietary components and novel bacterial-derived immunoregulatory peptides, lipids and polysaccharide structures in managing allergic disorders. A clearer understanding of the mechanisms employed in vivo for the induction of oral tolerance by the microbiota will likely result in rational strategies to manipulate both T regulatory and effector cells, thereby influencing inflammatory disorders such as allergy and asthma. In addition, the identification of bacterial-derived components or metabolites which selectively activate the immune regulatory program will lead to the rationale design of new drugs for in vivo assessment.

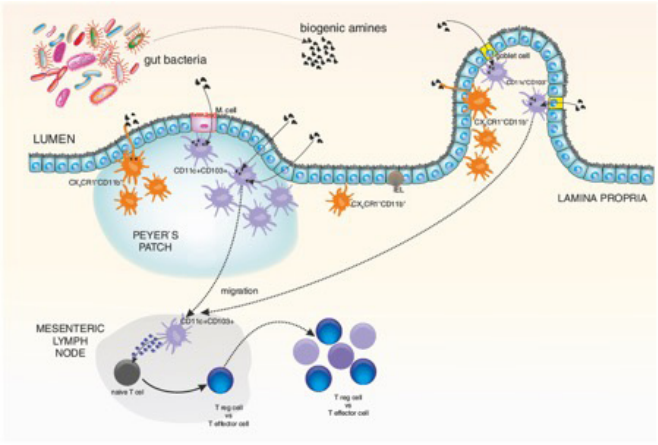


Figure 2. Biogenic amine secretion by the microbiota can influence epithelial cells, innate immune cells such as dendritic cells and polarization of naïve lymphocyte responses.

(iii) The incidence of obesity has risen dramatically during the last decades and obesity has been correlated with significant public health implications, including a well established link with an increased risk of developing diabetes, coronary artery disease and non-alcoholic steatohepatitis. More recent epidemiologic studies have demonstrated an increased risk of asthma associated with increasing obesity. The effect of obesity on the occurrence of asthma seems to be more prominent in women and non-allergic individuals, while there is a dose response effect of increasing body mass index (BMI) on asthma incidence. Interestingly, the interaction between obesity and asthma is not mediated by classical TH2 inflammation as suggested by cytokine profiling and exhaled nitric oxide studies. It is becoming increasingly evident that obesity is associated with a unique asthma phenotype that is characterized by more severe disease with variable response to conventional asthma therapies. Metabolic factors, such as free fatty acids (FFA) could also play a role in the increased risk for developing asthma. FFA can be derived from host metabolism or also from microbiota-associated metabolic processes. FFAs play important physiological roles in many tissues as an energy source and as signaling molecules in various cellular processes. We have recruited 201 patients and volunteers from the Pneumology Department, University Hospital Zürich (Dr. Kohler) and the Department of Clinical Immunology, Wroclaw Medical University, Poland (Prof. Jutel). Microbiome analysis has revealed surprising differences between the groups and with asthma disease severity. One microbial population is significantly decreased in patients with severe asthma and administration of this microbe to murine models is protective. Transcriptomic and functional analyses of peripheral and lung-derived cells clearly show activation of innate inflammatory processes in obese asthma patients compared to non-obese asthma patients. Significant differences in serum fatty acid levels were observed between obese and non-obese asthma patients, with a surprising decrease in the circulating levels of fatty acids, only in non-obese asthma patients. This correlated with a decrease in fatty acid desaturase activity. Experimental models in mice and human epithelial cells suggest that inhibition of desaturase activity leads to airway hyper-responsiveness and reduced anti-viral defense. SCD may represent a new target for therapeutic intervention in asthma patients.

Exposure to the non-microbial foreign sialic acid N-Glycolylneuraminic acid confers protection against human and murine allergic airway-inflammation.

Frei R, Ferstl R, Roduit C, Ziegler M, Schiavi E, Barcik W, Rodriguez N, Wirz O, Konieczna P, Bieli C, Loeliger S, Waser M, Scheynius A, van Hage M, Pershagen G, Doekes G, Riedler J, Sennhauser F, Depner M, Schaub B, Loss G, Genuneit J, Pfefferle P, Hyvärinen A, Karvonen AM, Dalphin JC, Pekkanen J, Akdis M, Akdis CA, von Mutius E, Braun-Fahrländer C, O'Mahony L, Lauener R. J Allergy Clin Immunol. in press, 2017.

Childhood exposure to a farm environment has been shown to protect against the development of inflammatory diseases such as allergy, asthma, and inflammatory bowel disease. We sought to investigate whether besides exposure to microbes also exposure to structures of non-microbial origin such as the sialic acid N-Glycolylneuraminic acid (Neu5Gc) may play a significant role. Exposure to Neu5Gc was evaluated by quantifying anti-Neu5Gc antibody levels in the sera of children enrolled in two farm studies: the PARSIFAL study (n=299) and the PASTURE birth cohort (cord blood (n=836), 1 year (n=734), 4.5 years (n=700) and 6 years (n=728)), and we associated them with asthma and wheeze. The effect of Neu5Gc was examined in murine airway inflammation and colitis models and the role of Neu5Gc in regulating immune activation was assessed by T helper cells and regulatory T cell activation in mice. In children, anti-

Neu5Gc IgG levels positively correlated with living on a farm and increased peripheral blood Foxp3 expression and inversely correlated with wheezing and asthma in non-atopic subjects. Exposure to Neu5Gc in mice resulted in reduced airway hyperresponsiveness and inflammatory cell recruitment to the lung. Furthermore, Neu5Gc administration to mice reduced the severity of a colitis model. Mechanistically, we found that Neu5Gc exposure reduced IL-17 positive T cells and supported differentiation of regulatory T cells. In addition to microbial exposure, increased exposure to non-microbial-derived Neu5Gc may contribute to the protective effects associated with the farm environment.

Altered Fatty Acid Metabolism and Reduced Stearoyl-Coenzyme A Desaturase Activity in Asthma.

Rodriguez-Perez N, Schiavi E, Frei R, Ferstl R, Wawrzyniak P, Smolinska S, Sokolowska M, Sievi NA, Kohler M, Schmid-Grendelmeier P, Michalovich D, Simpson KD, Hessel EM, Jutel M, Martin-Fontecha M, Palomares O, Akdis CA, O'Mahony L. Allergy. 2017 Apr 11.

Fatty acids and lipid mediator signaling play an important role in the pathogenesis of asthma, yet this area remains largely under-explored. The aims of this study were (i) to examine fatty acid levels and their metabolism in obese and non-obese asthma patients and (ii) to determine the functional effects of altered fatty acid metabolism in experimental models. Medium- and long-chain fatty acid levels were quantified in serum from 161 human volunteers by LC/MS. Changes in stearoyl-coenzyme A desaturase (SCD) expression and activity was evaluated in the ovalbumin (OVA) and house dust mite (HDM) murine models. Primary human bronchial epithelial cells from asthma patients and controls were evaluated for SCD expression and activity. The serum desaturation index (an indirect measure of SCD) was significantly reduced in non-obese asthma patients and in the OVA murine model. SCD1 gene expression was significantly reduced within the lungs following OVA or HDM challenge. Inhibition of SCD in mice promoted airway hyperresponsiveness. SCD1 expression was suppressed in bronchial epithelial cells from asthma patients. IL-4 and IL-13 reduced epithelial cell SCD1 expression. Inhibition of SCD reduced surfactant protein C expression and suppressed rhinovirus-induced IP-10 secretion, which was associated with increased viral titers. This is the first study to demonstrate decreased fatty acid desaturase activity in humans with asthma. Experimental models in mice and human epithelial cells suggest that inhibition of desaturase activity leads to airway hyperresponsiveness and reduced anti-viral defense. SCD may represent a new target for therapeutic intervention in asthma patients.

Histamine-secreting microbes are increased in the gut of adult asthma patients.

Barcik W, Pugin B, Westermann P, Rodriguez Perez N, Ferstl R, Wawrzyniak M, Smolinska S, Jutel M, Hessel E, Michalowich D, Akdis CA, Frei R, O`Mahony L. J Allergy Clin Immunol. 2016 Nov;138(5):1491-1494.

Alterations in the metabolites (i.e. histamine) derived from the gut microbiome may influence host immune responses. Histamine-secreting microbes are increased in the gut microbiome of adult asthma patients and histamine from these microbes may contribute to the effector responses in atopic asthma patients. Histamine-secreting Escherichia coli, Lactobacillus vaginalis and Morganella morganii strains were isolated from the gut microbiome of asthma patients.

Histamine Receptor 2 is Required to Suppress Innate Immune Responses to Bacterial Ligands in Inflammatory Bowel Disease Patients.

Smolinska S, Groeger D, Rodriguez Perez N, Schiavi E, Ferstl R, Frei R, Konieczna P, Akdis CA, Jutel M, O'Mahony L. Inflamm Bowel Dis. 2016 Jul;22(7):1575-86.

Histamine is a key immunoregulatory mediator in immediate type hypersensitivity reactions and chronic inflammatory responses, in particular histamine suppresses proinflammatory responses to bacterial ligands, via histamine receptor 2 (H2R). The aim of this study was to investigate the effects of histamine and H2R on bacterial-induced inflammatory responses in IBD patients. PBMCs were obtained from Crohn's disease patients, ulcerative colitis patients and healthy controls. PBMC histamine receptor expression was evaluated by flow cytometry. Cytokine secretion following TLR-2, TLR-4, TLR-5 or TLR-9 stimulation in the presence or absence of histamine or famotidine (H2R antagonist) was quantified. Biopsy histamine receptor gene expression was evaluated using RT-PCR. The in vivo role of H2R was evaluated in the T cell transfer murine colitis model. The percentage of circulating H2R+ monocytes was significantly reduced in IBD patients. Histamine effectively suppressed TLR-induced cytokine secretion from healthy volunteer PBMCs, but not for PBMCs from IBD patients. Famotidine reversed this suppressive effect. H1R, H2R and H4R gene expression was increased in inflamed gastrointestinal mucosa, compared to non-inflamed mucosa from the same patient and expression levels correlated with proinflammatory cytokine gene expression. Mice receiving lymphocytes from H2R-/- donors, or treated with famotidine, displayed more severe weight loss, higher disease scores and increased numbers of mucosal IFN-γ and IL-17+ T cells. IBD patients display dysregulated expression of histamine receptors, with diminished anti-inflammatory effects associated with H2R signaling. Deliberate manipulation of H2R-signalling may suppress excessive TLR responses to bacteria within the gut.

Histamine receptor 2 controls invariant natural killer T cell responses within the lung.

Ferstl R, Frei R, Konieczna P, Ziegler M, Zeiter S, Lauener R, Akdis CA, O'Mahony L. Under review.

Histamine is a key immunoregulatory mediator and can dampen proinflammatory responses via activation of histamine receptor 2 (H2R). The aim of this study was to determine the role of H2R in modulating lung inflammatory responses. H2R was blocked using famotidine or activated using dimaprit in both the ovalbumin (OVA) and house dust mite extract (HDM) murine models of respiratory inflammation. H2R-deficient animals and CD1d/ H2R-deficient animals were utilized to examine the CD1d presentation of lipid antigens (αGal-Cer or OCH) to invariant Natural Killer T (iNKT) cells. Famotidine treatment resulted in more severe airway disease in the OVA model, while dimaprit treatment significantly reduced disease severity. Both OVA and HDM-induced airway disease were more severe in H2R-deficient animals. Flow cytometric analysis of lung

tissue from H2R-deficient animals revealed increased numbers of CD1d+ dendritic cells and increased numbers of iNKT cells. In vitro, αGal-Cer-stimulated iNKT cells from H2R-deficient mice secreted higher levels of IL-4, IL-5 and GM-CSF. In vivo, αGal-Cer or OCH administration to the lung resulted in enhanced mucus secretion, inflammatory cell recruitment and cytokine production in H2R-deficient or famotidine-treated animals, while dimaprit dampened the lung iNKT cell response to αGalCer. Removal of iNKT cells in H2R-deficient (CD1d-/-H2R-/-) animals normalized the lung response to HDM. The deliberate activation of H2R, or its downstream signaling molecules, may represent a novel therapeutic target for chronic lung inflammatory diseases, especially when CD1d-mediated presentation of lipid antigens to iNKT cells are contributing to the pathology.

A Wide Diversity of Bacteria Produce and Degrade Biogenic Amines within the Human Gastrointestinal Tract.

Pugin B, Barcik W, Westermann P, Heider A, Wawrzyniak M, Hellings P, Akdis CA, O'Mahony L. Under review.

Biogenic amines (BAs) are metabolites produced by the decarboxylation of amino acids with significant physiological functions in eukaryotic and prokaryotic cells. BAs can be produced by bacteria in fermented foods, but little is known concerning the potential for microbes within the human gut microbiota to produce or degrade BAs. Objective: To isolate and identify BA-producing and BA-degrading microbes from the human gastrointestinal tract. Fecal samples from human volunteers were screened on multiple growth medias, under multiple growth conditions. Bacterial species were identified using 16S rRNA sequencing and BA production or degradation was assessed using Ultra Performance Liquid Chromatography (UPLC). A total of 74 BA-producing or BA-degrading strains were isolated from the human gut. These isolates belong to the genera Bifidobacterium, Clostridium, Enterococcus, Lactobacillus, Pediococcus, Streptococcus, Enterobacter, Escherichia, Klebsiella, Morganella and Proteus. While differences in production or degradation of specific BAs were observed at the strain level, our results suggest that these metabolic activities are widely spread across different taxa present within the human gut microbiota. The isolation and identification of microbes from the human gut with BA-producing and BA-degrading metabolic activity is an important first step in developing a better understanding of how these metabolites influence health and disease.

The Surface-Associated Exopolysaccharide of Bifidobacterium longum 35624 Plays an Essential Role in Dampening Host Proinflammatory Responses and Repressing Local TH17 Responses.

Schiavi E, Gleinser M, Molloy E, Groeger D, Frei R, Ferstl R, Rodriguez-Perez N, Ziegler M, Grant R, Moriarty TF, Plattner S, Healy S, O'Connell Motherway M, Akdis CA, Roper J, Altmann F, van Sinderen D, O'Mahony L. Appl Environ Microbiol. 2016 Nov 21;82(24):7185-7196.

The immune-modulating properties of certain bifidobacterial strains, such as Bifidobacterium longum subsp. longum 35624 (B. longum 35624), have been well described, although the strain-specific molecular characteristics associated with such immune-regulatory activity are not well defined. It has previously been demonstrated that B. longum 35624 produces a cell surface exopolysaccharide (sEPS), and in this study, we investigated the role played by this exopolysaccharide in influencing the host immune response. B. longum 35624 induced relatively low levels of cytokine secretion from human dendritic cells, whereas an isogenic exopolysaccharide-negative mutant derivative (termed sEPSneg) induced vastly more cytokines, including interleukin-17 (IL-17), and this response was reversed when exopolysaccharide production was restored in sEPSneg by genetic complementation. Administration of B. longum 35624 to mice of the T cell transfer colitis model prevented disease symptoms, whereas sEPSneg did not protect against the development of colitis, with associated enhanced recruitment of IL-17+ lymphocytes to the gut. Moreover, intranasal administration of sEPSneg also resulted in enhanced recruitment of IL-17+ lymphocytes to the murine lung. These data demonstrate that the particular exopolysaccharide produced by B. longum 35624 plays an essential role in dampening proinflammatory host responses to the strain and that loss of exopolysaccharide production results in the induction of local TH17 responses.

Genome Analysis and Characterisation of the Exopolysaccharide Produced by Bifidobacterium longum subsp. longum 35624.

Altmann F, Kosma P, O'Callaghan A, Leahy S, Bottacini F, Molloy E, Plattner S, Schiavi E, Gleinser M, Groeger D, Grant R, Rodriguez Perez N, Healy S, Svehla E, Windwarder M, Hofinger A, O'Connell Motherway M, Akdis CA, Xu J, Roper J, van Sinderen D, O'Mahony L. PLoS One. 2016 Sep 22;11(9):e0162983.

The Bifibobacterium longum subsp. longum 35624 strain (formerly named Bifidobacterium longum subsp. infantis) is a well described probiotic with clinical efficacy in Irritable Bowel Syndrome clinical trials and induces immunoregulatory effects in mice and in humans. This paper presents (a) the genome sequence of the organism allowing the assignment to its correct subspeciation longum; (b) a comparative genome assessment with other B. longum strains and (c) the molecular structure of the 35624 exopolysaccharide (EPS624). Comparative genome analysis of the 35624 strain with other B. longum strains determined that the sub-speciation of the strain is longum and revealed the presence of a 35624-specific gene cluster, predicted to encode the biosynthetic machinery for EPS624. Following isolation and acid treatment of the EPS, its chemical structure was determined using gas and liquid chromatography for sugar constituent and linkage analysis, electrospray and matrix assisted laser desorption ionization mass spectrometry for sequencing and NMR. The EPS consists of a branched hexasaccharide repeating unit containing two galactose and two glucose moieties, galacturonic acid and the unusual sugar 6-deoxy-L-talose. These data demonstrate that the B. longum 35624 strain has specific genetic features, one of which leads to the generation of a characteristic exopolysaccharide.

The microbiome in allergic disease: current understanding and future opportunities.
Huang Y, Marsland B, Bunyavanich S, O'Mahony L, Leung D, Muraro A, Fleisher TA. J Allergy Clin Immunol. 2017 Apr;139(4):1099-1110.
PRACTALL is a joint initiative of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology to provide shared evidence-based recommendations on cutting-edge topics in the field of allergy and immunology. PRACTALL 2017 is focused on what has been established regarding the role of the microbiome in patients with asthma, atopic dermatitis, and food allergy. This is complemented by outlining important knowledge gaps regarding its role in allergic disease and delineating strategies necessary to fill these gaps. In addition, a review of progress in approaches used to manipulate the microbiome will be addressed, identifying what has and has not worked to serve as a baseline for future directions to intervene in allergic disease development, progression, or both.

Biology of the Microbiome 1: Interactions with the Host Immune Response.
Smolinska S, Groeger D, O'Mahony L. Gastroenterol Clin North Am. 2017 Mar;46(1):19-35.
The intestinal immune system is intimately connected with the vast diversity of microbes present within the gut and the diversity of food components that are consumed daily. The discovery of novel molecular mechanisms, which mediate host-microbe-nutrient communication, have highlighted the important roles played by microbes and dietary factors in influencing mucosal immune responses. Dendritic cells, epithelial cells, innate lymphoid cells, T regulatory cells, effector lymphocytes, natural killer T cells, and B cells can all be influenced by the microbiome. Many of the mechanisms being described are bacterial strain or metabolite specific.

Current challenges facing the assessment of the allergenic capacity of food allergens in animal models.
Lindholm Bøgh K, van Bilsen J, Głogowski R, López-Expósito I, Bouchaud G, Blanchard C, Bodinier M, Smit J, Pieters R, Bastiaan-Net S, de Wit N, Untersmayr E, Adel-Patient K, Knippels L, Epstein MM, Noti M, Cecilie Nygaard U, Kimber I, Verhoeckx K, O'Mahony L. Clin Transl Allergy. 2016 Jun 16;6:21.
Food allergy is a major health problem of increasing concern. The insufficiency of protein sources for human nutrition in a world with a growing population is also a significant problem. The introduction of new protein sources into the diet, such as newly developed innovative foods or foods produced using new technologies and production processes, insects, algae, duckweed, or agricultural products from third countries, creates the opportunity for development of new food allergies, and this in turn has driven the need to develop test methods capable of characterizing the allergenic potential of novel food proteins. There is no doubt that robust and reliable animal models for the identification and characterization of food allergens would be valuable tools for safety assessment. However, although various animal models have been proposed for this purpose, to date, none have been formally validated as predictive and none are currently suitable to test the allergenic potential of new foods. Here, the design of various animal models are reviewed, including among others considerations of species and strain, diet, route of administration, dose and formulation of the test protein, relevant controls and endpoints measured.

The use of animal models for discovering immunological mechanisms underpinning sensitization to food allergens.
Smit JJ, Noti M, O'Mahony L. Drug Discovery Today: Disease Models, 2016;17-18: 63-69.
In almost all countries, food allergy is of growing concern affecting all age groups. Given the increased prevalence of food allergies, current research focuses on developing new treatment strategies and to predict allergenicity of novel and modified food proteins. The recent use of animal models has significantly contributed to a better understanding of the complex immunological and pathophysiological mechanisms of food allergies. Central to the development of food allergy is the allergic cascade driven by cells of the innate and adaptive immune system. These models can now be integrated into the risk assessment of possible allergenic proteins. In this review, we discuss the role of the immune system as a qualitative readout for the sensitizing potential and risk assessment of food proteins.

Influence of microbiome and diet on immune responses in food allergy models.
Barcik W, Untersmayr E, Pali-Schöll I, O'Mahony L, Frei R. Drug Discovery Today: Disease Models, 2016;17-18: 71-80.
The intestinal immune system is intimately connected with the vast array of microbes present within the gut and the diversity of food components that are consumed daily. The discovery of novel molecular mechanisms, which mediate host–microbe–nutrient communication, have highlighted the important roles played by microbes and dietary factors in influencing mucosal inflammatory and allergic responses. In this review, we summarize the recent important findings in this field, which are important for food allergy and particularly relevant to animal models of food allergy.

Microbiome-Host Immune System Interactions.
Smolinska S, O'Mahony L. Semin Liver Dis. 2016 Sep;36(4):317-326.
The intestinal immune system recognizes and responds to the vast diversity of microbes present within the gut. Highly sophisticated cellular and molecular networks are continuously coordinated to tolerate the presence of a large number and diversity of bacteria on mucosal surfaces. Different types of bacteria induce different immune responses, and bacterial metabolism of dietary factors generates metabolites that have significant effects on host immune responses. Dendritic cells, epithelial cells, innate lymphoid cells, T-regulatory cells, effector lymphocytes, natural killer T cells, and B-cell responses can all be influenced by the microbiome. Many of the mechanisms being described are bacterial strain or metabolite-specific. A better understanding of the mechanisms governing microbiome-host immune responses will likely lead to novel therapeutics for inflammatory disorders.

Monitoring immune responses in a mouse model of fracture fixation with and without Staphylococcus aureus osteomyelitis.
Rochford ETJ, Sabaté-Brescó M, Zeiter S, Kluge K, Poulsson A, Ziegler M, Richards RG, O' Mahony L, Moriarty TF. Bone. 2016 Feb;83:82-92.

In a trauma setting, where devices such as fracture fixation plates are used to repair fractured bones, the combined physiological response to the trauma, the surgically placed implant and the healing of the bone adds numerous dimensions to the host defense against infection. The aim of this study was to monitor the immune responses, healing and progression of Staphylococcus aureus infection in a clinically relevant murine fracture model. Skeletally mature C57bl/6 mice received a transverse osteotomy of the femur, which were treated with commercially available titanium fracture fixation plates. In the absence of infection, healing of the fracture was complete within 14-21 days, and was characterized by elevated interferon-gamma gene expression and Interleukin (IL)-4 secretion from bone cell suspensions. In contrast, mice inoculated with S. aureus could not heal the fracture and were found to develop typical signs of implant-associated bone infection, including biofilm formation on the implant and osteolysis of surrounding bone. The immune response to infection included an early peak in IL-10 secretion followed by a later increase in inflammatory IL-17 and KC secretion, as well as IL-1β gene expression. Lymph nodes of infected animals also displayed an increase in IL-17 positive lymphocytes from day 7. In this model, we characterize the kinetics of pro-inflammatory responses to infection, secondary to bone trauma and surgery. Divergent local immune polarization is evident in the infected versus non-infected animals, while the surprisingly late anti-bacterial immune response is not effective in clearing the S. aureus infection.

Davos, June 2017

Dr. Claudio Rhyner

The activities of the SIAF Division Vaccine Development during the timeframe of reporting were focused on several projects and collaborations. We performed some work to round up older projects and collaborations. The main focus was on the Commission of Technology and Innovation (CTI) granted project "PLATELETS". This CTI granted project requesting for the collaboration of industry and academia, where Davos Diagnostics figured as the industry part and the Vaccine Development Group as the academic partner.

Platelets

Platelets have a major function in hemostasis and wound healing. Their main physiological role is to sense injured vessels and to initiate blood clotting and consequently prevent excessive blood loss. Platelets carry glycoprotein complexes on their surfaces which are receptors for proteins involved in the adhesion to surfaces during the haemostatic response. These platelet glycoproteins are polymorphic in nature and genes encoding these glycoproteins have single nucleotide polymorphisms resulting in amino acid substitutions in ecto domains of the glycoproteins with no apparent functional consequences. These protein polymorphisms can give rise to allo-antibodies which can lead to complications. Post-transfusional Platelet Refractoriness (PR), Post-transfusion thrombocytopenic purpura (PTP) and Neonatal alloimmune thrombocytopenia (NAIT) are known as important clinical consequences of HPA allo-antibodies. Therefore fast and sensitive diagnostic assays are needed for the typing of platelets and the measurement of antibodies against glycoproteins. The development of these kind of assays were performed on a biosensor which is based on real time measurement of a binding reaction using evanescent field excitation of bound fluorophores. Due to the optical phenomenon of total internal reflection of a laser beam, evanescent field waves are generated at the bottom (~200 nm) of each well in the sensor chip. Only fluorophores that are present in this evanescent field will be excited and emit light.

Assays for the typing of HPA-1a/HPA-5b and a MAIPA assay has been developed recently using the evanescent field method. The scope of application of these assays mentioned above lies in the measurement of platelet allo- and autoantigens on platelet glycoproteins. The MAIPA-Assay can also be used for the detection of antibodies against these glycoproteins. Since the sample preparation for the MAIPA Assay includes several incubation- and washing steps there is a need for fast assays that can be used for the determination of antibodies against platelets. We tried to address this by developing screening assays using whole platelets for coating and for the detection. We could show that a detection of anti HPA-1a antibodies using an anti platelet antibody screen assay was feasible. The antibodies are captured in a first step in an HPA-1a or anti HPA-1b coated well. The specific detection is performed by using an anti human IgG conjugated to the fluorophor Allophycocyanin (APC).

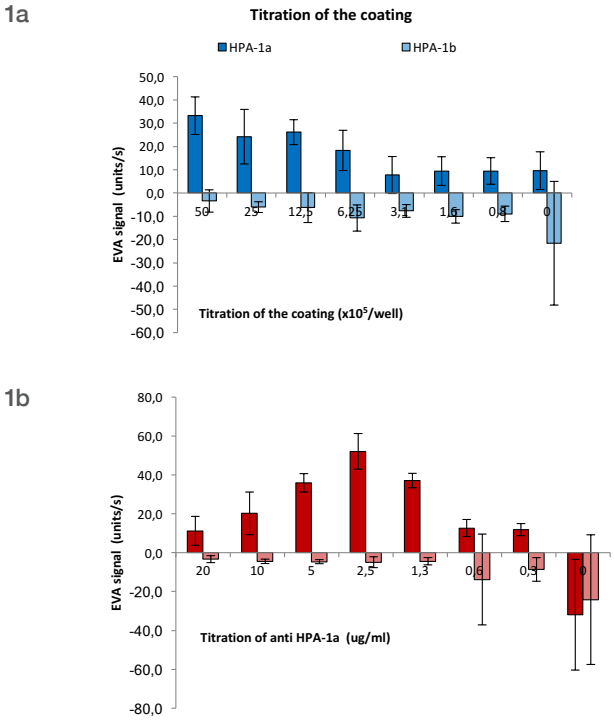


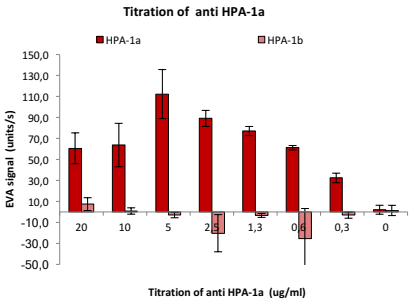
Figure 1: Platelet antibody screen Titration of coated platelets (A) as well as titration of the analyte anti HPA1A (B) was performed by using anti platelet antibody screen assay.

In a further development phase, liposomes instead of whole platelets were used, since a detection of antibodies which were catched by ~1µm big platelets in a 200 nm thick field is sub-optimal.

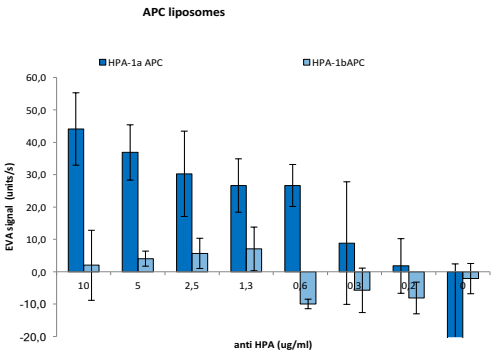
Proteoliosomes with membrane bound glycoproteins from platelets were prepared by the extrusion method followed by detergent removal. For the detection, either proteoliposomes loaded with Allophycocyanin or proteoliposomes coloured with a lipophilic dye were used.

An anti platelet antibody screen captures antibodies in a liposome coated well. The detection was performed by an anti human IgG-APC antibody. No false positive signals were observed, since no signal could be observed using HPA-1b coated wells (Figure2a; light red). A second Assay which has been developed is an antibody screening Assay which uses platelet coated wells and either APC loaded liposomes (B) or liposomes which were coloured with a lipophilic dye (C). Anti HPA-1a Titration experiments results in a dose dependent decrease of the signal.

2a Anti platelet antibody screen



2b



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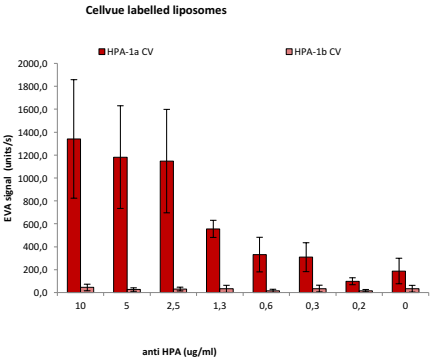


Figure 2: Titration of anti HPA-1a in an Anti platelet antibody screen(A) and in an antibody screening Assay usind APC loaded liposomes (B) and Liposomes coloured with a lipophilic dye (C).

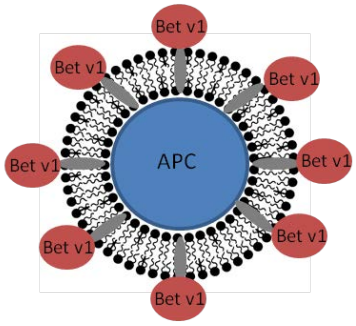
We could show that detection of anti HPA-1a was possible using either whole platelet coated wells or wells coated with liposomes. The preparation of liposomes leads to a more stable and reproducible Assay. Further, the usage of fluorescently labeled liposomes or liposomes loaded with fluorophore could be used as a detection molecule. Hereby we developed two different Assays which allow the fast and sensitive detection of antibodies without further sample preparation steps. To further improve the sensitivity of EVA assays for the detection of low abundant molecules, we aimed at transporting more fluorophore to the Evanescent field and set up a project described below.

Improving allergen labeling using proteoliposomes

To improve the sensitivity of assays to measure allergen specific IgE in patient sera, we are used anti-human IgE antibodies for the coating of the chips, followed by addition of serum (containing IgE antibodies) mixed with a detection reagent including the allergen conjugated to the fluorophore Allophycocyanin (APC) to specifically detect the allergen-specific IgE antibodies.

The conjugation of allergens with the APC fluorophore could reveal some problems. The activated fluorophre APC will bind to free primary amines, in the case of proteins, it is the surface exposed amino acid lysine. Depending on the content of lysine in the allergen and the position of the lysine (epitopes for binding of the antibodies), the availability of antibody epitopes can be impaired. The difference in the size from linking the “small” allergen (e.g. the major birch pollen allergen Bet v1 18 kDa) with the “large” APC molecule (100 kDa) can lead to sterical hindrance for the later binding of the antibody. A high amount of fluorophore linked to a protein can cause over labeling of the allergen, which decreases the fluorescent signal by quenching.

To overcome these problems, we are investigating the incorporation of a model allergen (Bet v1) genetically fused to a transmembrane helix into a liposome filled with fluorophore, to generate a proteoliposome, which we think to improve the signal intensity. The schematically proteoliposome is depicted below:



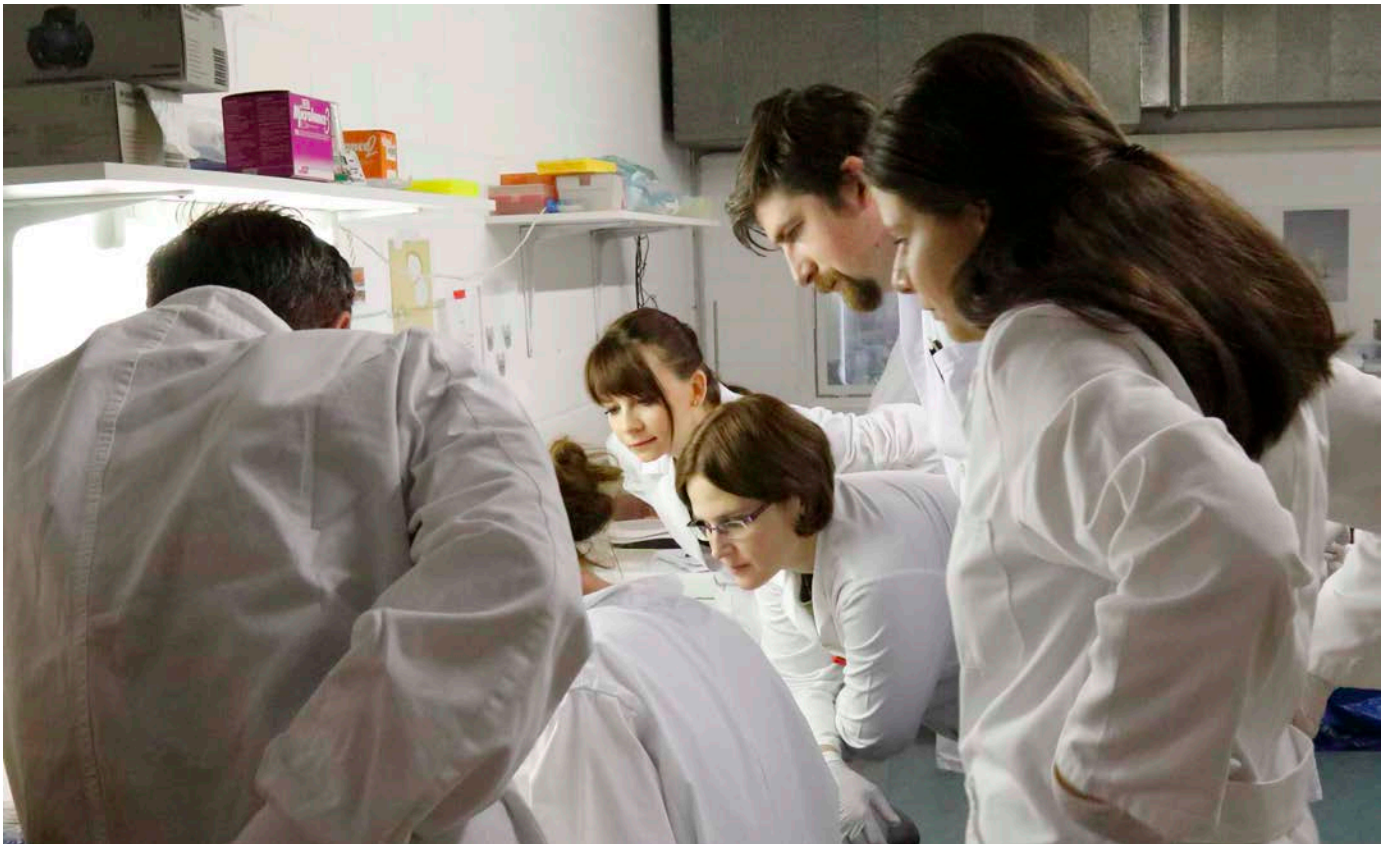
As a transmembrane helix the transmembrane 5 of GlpG was selected. GlpG is a multi-pass rhomboid intermembrane serine protease, found in E. coli and has six transmembrane domains (TMD). These DNA sequence coding for the transmembrane helix was supplemented with His6 tag C-terminally to the Bet v1 sequence. The protein was produced in E. coli BL21 cells. The protein could be purified using Immobilized metal affinity chromatography (IMAC) under denaturing conditions and refolded into the native stage. The purified and refolded protein will be used for forming proteoliposomes. As lipids we use L-α-Phosphatidylcholine (Egg, chicken) mixed with Cholesterol. The lipids will be dried using a rotary evaporator and then the lipid film rehydrated with an aqueous APC solution and proteoliposome will be formed by extrusion through membranes. These proteoliposomes will be tested in EVA measurements and compared to Bet v1 labelled APC.

Determination of Fentanyl Levels in plasma

Fentanyl is a synthetic narcotic analgesic of high potency and a short duration of action. It is used in clinical anesthesia and analgesia and in the treatment of chronic pain e.g. in cancer patients. Fentanyl binds to the μ-opioid receptors and is estimated to have 100 times the potency as morphin. The metabolization is especially in the liver trough cytromoxidase CYP3A4 to ineffective degradation products Hydroxyl- and Norfentanyl. The drug is available as a citrate salt for injection and as a transdermal patch containing 2.5-10mg Fentanyl for management of chronic pain.

In collaboration with the AO Foundation Research Institute, Davos we developed a fast and sensitive immunoassay, based on the evanescence field, to determine the concentration of Fentanyl in animal plasma after treatment of the animals with transdermal Fentanyl patches to manage the pain after surgery. The assay is based on a competitive binding assay, which is often used to measure small analytes. Fentanyl-BSA competes together with plasma Fentanyl or a Fentanly Standard for binding to the detection antibody conjugated to a fluorophore. The sensor chip is coated with Fentanyl-BSA, the add-in Fentanyl (sample/standard) mixed together with the detection buffer, containing the detection antibody, is transferred to the well and the fluorescence intensity is measured over 10 minutes in a 200nm evanescent field at the bottom of the EVA-Chip. As the concentration of add-in Fentanyl is increased, less detection antibody can bound to the coated Fentanyl-BSA and the measured signal decreases.
Plasma collected at different time points [h] was analyzed from 10 rabbits undergoing Fentanyl treatment after surgery. In result we could detect an increased Fentanyl concentration after a few hours which decrease at later time points. Here we developed a sensitive competitive assay which leads to a rapid determination of Fentanyl concentration in plasma within 10 minutes, which is helpful for post surgery surveillance and care of laboratory animals used in clinical trials to improve bone implants for human patients.

Davos, June 2017



Articles in peer reviewed journals 2016

Peer reviewed articles

Agache I, Akdis CA. Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine. Allergol Int. 2016 Jul;65(3):243-52. IPF: 2.355

Aab A, Wirz O, van de Veen W, Söllner S, Stanic B, Rückert B, Aniscenko J, Edwards MR, Johnston SL, Papadopoulos NG, Rebane A, Akdis CA, Akdis M. Human Rhinoviruses Enter and Induce Proliferation of B Lymphocytes. Allergy. 2016 May 11. IPF: 6.335

Agache I, Strasser DS, Klenk A, Agache C, Farine H, Ciobanu C, Groenen PM, Akdis CA. Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics. Allergy. 2016 Aug;71(8):1192-202. IPF: 6.335

Bieber T., C. Akdis, R. Lauener, C. Traidl-Hoffmann, P. Schmid-Grendelmeier, G. Schäppi, J.-P. Allam, C. Apfelbacher, M. Augustin, L. Beck, T. Biedermann, C. Braun-Fahrländer, F. T. Chew, T. Clavel, R. Crameri, U. Darsow, M. Deleuran, D. Dittlein, H.-W. Duchna, L. Eichenfeld, K. Eyerich, R. Frei, C. Gelmetti, U. Gieler, S. Gilles, M. Glatz, K. Grando, J. Green, J. Gutermuth, E. Guttman-Yassky, J. Hanifin, D. Hijnen, W. Hoetzenecker, A. Irvine, A. Kalweit, N. Katoh, E. Knol, H. Koren, M. Möhrenschlager, D. Münch, N. Novak, L. O'Mahony, A. S. Paller, C. Rhyner, C. Roduit, K. Schiesser, J. Schröder, D. Simon, H.-U. Simon, M. Sokolowska, P. Spuls, J.-F. Stalder, D. Straub, Z. Szalai, A. Taieb, R. Takaoka, G. Todd, A. Todorova, C. Vestergaard, T. Werfel, A. Wollenberg, J. Ring. Global Allergy Forum and 3rd Davos Declaration 2015: Atopic dermatitis/Eczema: challenges and opportunities toward precision medicine. Allergy 2016;71(5):588-592. IPF: 6.335

Boonpiyathad T, Meyer N, Moniuszko M, Sokolowska M, Eljaszewicz A, Wirz OF, Tomasiak-Lozowska MM, Bodzenta-Lukaszyk A, Ruxrungtham K, van de Veen W. High-dose bee venom exposure induces similar tolerogenic B-cell responses in allergic patients and healthy beekeepers. Allergy. 2016. IPF: 6.335

Bousquet J, Anto JM, Akdis M, Auffray C, Keil T, Momas I, et al. Paving the way of systems biology and precision medicine in allergic diseases: the MeDALL success story: Mechanisms of the Development of ALLergy; EU FP7-CP-IP; Project No: 261357; 2010-2015. Allergy. 2016 Nov;71(11):1513-1525. IPF: 6.335

Crameri R. Artificial human sera: a breakthrough? Allergy 2016;71(12):1549-1571. IPF: 6.335

Garbani M, Xia W, Rhyner C, Prati M, Scheynius A, Malissen B, Engqvist M, Maurer M, Crameri R, Terhorst D. Allergen-loaded strontium-doped hydroxyapatite spheres improve allergen-specific immunotherapy in mice. Allergy. 2016 Sep 3. [Epub ahead of print]. IPF: 6.335

Giavi S, Vissers YM, Muraro A, Lauener R, Konstantinopoulos AP, Mercenier A, Wermeille A, Lazzarotto F, Frei R, Bonaguro R, Summermatter S, Nutten S, Papadopoulos NG. Oral immunotherapy with low allergenic hydrolysed egg in egg allergic children. Allergy. 2016 Nov;71(11):1575-1584. IPF: 6.335

Kärner J, Wawrzyniak M, Tankov S, Runnel T, Aints A, Kisand K, Altraja A, Kingo K, Akdis CA, Akdis M, Rebane A. Increased microRNA-323-3p in IL-22/IL-17-producing T cells and asthma: a role in the regulation of the TGF-β pathway and IL-22 production. Allergy. 2017 Jan;72(1):55-65. IPF: 6.335

Mueller RS, Janda J, Jensen-Jarolim E, Rhyner C, Marti E. Allergens in veterinary medicine. Allergy. 2016 Jan;71(1):27-35. IPF: 6.335

Nurmatov U, Dhami S, Arasi S, Battista Pajno G, Fernandez-Rivas M, Muraro A, Roberts G, Akdis CA, Alvaro-Lozano M, Beyer K, Bindslev-Jensen C, Burks W, du Toit G, Ebisawa M, Eigenmann P, Knol E, Makela M, Nadeau K, O'Mahony L, Papadopoulos N, Poulsen LK, Sackesen C, Sampson H, Santos A, van Ree R, Timmermans F, Sheikh A. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy. 2017 Jan 6. doi: 10.1111/all.13124. [Epub ahead of print]. IPF: 6.335

Rodriguez-Perez N, Schiavi E, Frei R, Ferstl R, Wawrzyniak P, Smolinska S, Sokolowska M, Sevi N, Kohler M, Michalovich D, Simpson KD, Hessel EM, Jutel M, Martin-Fontecha MM, Palomares O, Akdis CA, O'Mahony L. Asthma is Associated with Altered Fatty Acid Metabolism and Reduced Stearoyl-Coenzyme A Desaturase Activity. Allergy. 2017 Apr 11. [Epub ahead of print]. IPF: 6.335

Schröder PC, Illi S, Casaca VI, Lluis A, Böck A, Roduit C, Depner M, Frei R, Genuneit J, Pfefferle PI, Roponen M, Weber J, Braun-Fahrländer C, Riedler J, Dalphin JC, Pekkanen J, Lauener R, von Mutius E, Schaub B; PASTURE study group. A switch in regulatory T cells through farm exposure during immune maturation in childhood. Allergy. 2016 Oct 12. IPF: 6.335

Wawrzyniak M, Ochsner U, Wirz O, Wawrzyniak P, van de Veen W, Akdis CA, Akdis M. A novel, dual cytokine-secretion assay for the purification of human Th22 cells that do not co-produce IL-17A. Allergy. 2016 Jan;71(1):47-57. IPF: IPF: 6.335

Wawrzyniak M, O`Mahony L, Akdis M. Role of regulatory cells in oral tolerance. Allergy Asthma Immunol Res. 2017 Mar;9(2):107-115. IPF: 2.3

Schiavi E, Gleinser M, Molloy E, Groeger D, Frei R, Ferstl R, Rodriguez-Perez N, Ziegler M, Grant R, Moriarty TF, Plattner S, Healy S, O'Connell Motherway M, Akdis CA, Roper J, Altmann F, van Sinderen D, O'Mahony L. The Surface-Associated Exopolysaccharide of Bifidobacterium longum 35624 Plays an Essential Role in Dampening Host Proinflammatory Responses and Repressing Local TH17 Responses. Appl Environ Microbiol. 2016; 82(24):7185-7196. IPF: 3.668

Braido F, Scichilone N, Lavorini F, Usmani OS, Dubuske L, Boulet LP, Mosges R, Nunes C, SÃ¡nchez-Borges M, Ansotegui IJ, Ebisawa M, Levi-Schaffer F, Rosenwasser LJ, Bousquet J, Zuberbier T, Canonica GW; Interasma Executive Board.; WAO Board of Directors.; ARIA.; GAÂ²LEN. Manifesto on small airway involvement and management in asthma and chronic obstructive pulmonary

disease: an Interasma (Global Asthma Association - GAA) and World Allergy Organization (WAO) document endorsed by Allergic Rhinitis and its Impact on Asthma (ARIA) and Global Allergy and Asthma European Network (GA(2)LEN). Asthma Res Pract. 2016 Oct 28;2:12. IPF: in process

Rochford ET, Sabaté Brescó M, Zeiter S, Kluge K, Poulsson A, Ziegler M, Richards RG, O'Mahony L, Moriarty TF. Monitoring immune responses in a mouse model of fracture fixation with and without Staphylococcus aureus osteomyelitis. Bone. 2016 Feb;83:82-92. IPF: 4.461

Walker SM, Akdis C, Dahlen SE, Djukanovic R, Edwards J, Garcia-Marcos L, Johnston S, Kupczyk M, Martin T, Myles D, Palkonen S, Papadopoulos N, Powell P, Riley J. Building the investment case for asthma R&D: the European Asthma Research and Innovation Partnership argument. Clin Exp Allergy. 2016 Sep;46(9):1136-8. IPF: 5.587

Bousquet J, Farrell J, Crooks G, Hellings P, Bel EH, Bewick M, et al. Scaling up strategies of the chronic respiratory disease programme of the European Innovation Partnership on Active and Healthy Ageing (Action Plan B3: Area 5). Clin Transl Allergy. 2016 Jul 29;6:29. IPF: in process

Calderon MA, Demoly P, Casale T, Akdis CA, Bachert C, et al. Allergy immunotherapy across the life cycle to promote active and healthy ageing: from research to policies: An AIRWAYS Integrated Care Pathways (ICPs) programme item (Action Plan B3 of the European Innovation Partnership on active and healthy ageing) and the Global Alliance against Chronic Respiratory Diseases (GARD), a World Health Organization GARD research demonstration project. Clin Transl Allergy. 2016 Nov 23;6:41. IPF: in process

Dhami S, Nurmatov U, Agache I, Lau S, Muraro A, Jutel M, Roberts G, Akdis C, Bonini M, Calderon M, Casale T, Cavkaytar O, Cox L, Demoly P, Flood B, Hamelmann E, Izuhara K, Kalayci Ã–, Kleine-Tebbe J, Nieto A, Papadopoulos N, Pfaar O, Rosenwasser L, Ryan D, Schmidt-Weber C, Szefler S, Wahn U, van Wijk RG, Wilkinson J, Sheikh A. Allergen immunotherapy for allergic asthma: protocol for a systematic review. Clin Transl Allergy. 2016 Feb 9;6:5. IPF: in process

Dhami S, Nurmatov U, Varga EM, Sturm G, Muraro A, Akdis CA, Antoli¬n-Amerigo D, Bilo MB, Bokanovic D, Calderon MA, Cichocka-Jarosz E, Elberink JN, Gawlik R, Jakob T, Kosnik M, Lange J, Mingomataj E, Mitsias DI, Mosbech H, Pfaar O, Pitsios C, Pravettoni V, Roberts G, Rueff F, Sin BA, Sheikh A. Allergen immunotherapy for insect venom allergy: protocol for a systematic review. Clin Transl Allergy. 2016 Feb 16;6:6. IPF: in process

Dhami S, Nurmatov U, Pajno GB, Fernandez-Rivas M, Muraro A, Roberts G, Akdis C, Alvaro-Lozano M, Beyer K, Bindslev-Jensen C, Burks W, du Toit G, Ebisawa M, Eigenmann P, Knol E, Makela M, Nadeau KC, O'Mahony L, Papadopoulos N, Poulsen L, Sackesen C, Sampson H, Santos A, van Ree R, Timmermans F, Sheikh A. Allergen immunotherapy for IgE-mediated food allergy: protocol for a systematic review. Clin Transl Allergy. 2016 Jul 5;6:24. IPF: in process

Lindholm Bøgh K, van Bilsen J, Głogowski R, López-Expósito I, Bouchaud G, Blanchard C, Bodinier M, Smit J, Pieters R, Bastiaan-Net S, de Wit N, Untersmayr E, Adel-Patient K, Knippels L, Epstein MM, Noti M, Cecilie Nygaard U, Kimber I, Verhoeckx K, Liam O'Mahony. Current challenges facing the assessment of the allergenic capacity of food allergens in animal models. Clin Transl Allergy. 2016 Jun 16;6:21. IPF: in process

Tan HT, Sugita K, Akdis CA. Novel Biologicals for the Treatment of Allergic Diseases and Asthma. Curr Allergy Asthma Rep. 2016 Oct;16(10):70. IPF: 3.127

Barcik W, Untersmayr E, Pali-Schöll I, O'Mahony L, Frei R. Influence of microbiome and diet on immune responses in food allergy models. Drug Discovery Today: Disease Models, 2016;17-18: 71-80. IPF: 5.625

Smit JJ, Noti M, O'Mahony L. The use of animal models to discover immunological mechanisms underpinning sensitization to food allergens. Drug Discovery Today: Disease Models, 2016; 17-18: 63-69. IPF: 5.625

Smolinska S, Groeger D, O'Mahony L. Biology of the Microbiome: Interactions with the Host Immune Response. Gastroenterol Clin North Am. 2017 Mar;46(1):19-35. IPF: 3.0

Ozdemir C, Kucuksezer UC, Akdis M, Akdis CA. Mechanisms of Aeroallergen Immunotherapy: Subcutaneous Immunotherapy and Sublingual Immunotherapy. Immunol Allergy Clin North Am. 2016 Feb;36(1):71-86. IPF: 1.818

Smolinska S, Groeger D, Perez NR, Schiavi E, Ferstl R, Frei R, Konieczna P, Akdis CA, Jutel M, O'Mahony L. Histamine Receptor 2 is Required to Suppress Innate Immune Responses to Bacterial Ligands in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016;22(7):1575-86. IPF: 4.464

Kubo T, Wawrzyniak P, Morita H, Sugita K, Wanke K, Kast JI, Altunubulakli C, Rueckert B, Akdis M, Akdis CA. CpG-DNA enhances the tight junction integrity of the bronchial epithelial cell barrier. Nihon Rinsho Meneki Gakkai Kaishi (Japanese Journal of Clinical Immunology). 2016;39(4):426b. IPF: in process

Akdis CA, Ballas ZK. Precision medicine and precision health: Building blocks to foster a revolutionary health care model. J Allergy Clin Immunol. 2016 May;137(5):1359-61. IPF: 12.485

Akdis CA, Ballas ZK; Associate Editors of the JACI. The Editors' Choice. J Allergy Clin Immunol. 2016 May;137(5):1362-3. IPF: 12.485

Akdis CA, Ballas ZK; Associate Editors of the JACI. The Editors' Choice. J Allergy Clin Immunol. 2016 Jun;137(6):1697-8. IPF: 12.485

Articles in peer reviewed journals 2016

Akdis CA, Ballas ZK; Associate Editors of the JACI. The Editors' Choice. J Allergy Clin Immunol. 2016 Jul;138(1):59-60. IPF: 12.485

Akdis CA, Ballas ZK; Associate Editors of the JACI. The Editors' Choice. J Allergy Clin Immunol. 2016 Aug;138(2):411-2. IPF: 12.485

Akdis CA, Ballas ZK; Associate Editors of the JACI. The Editors' Choice. J Allergy Clin Immunol. 2016 Sep;138(3):727-8. IPF: 12.485

Akdis CA, Ballas ZK; Associate Editors of the JACI. The Editors' Choice. J Allergy Clin Immunol. 2016 Oct;138(4):1014-1015. IPF: 12.485

Akdis CA, Ballas ZK; Associate Editors of the JACI. The Editors' Choice. J Allergy Clin Immunol. 2016 Nov;138(5):1299-1300. IPF: 12.485

Akdis CA, Ballas ZK; Associate Editors of the JACI. The Editors' Choice. J Allergy Clin Immunol. 2016 Dec;138(6):1559-1560. IPF: 12.485

Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, Duan S, Eiwegger T, Eljaszewicz A, Frestl R, Frei R, Garbani M, Globinska A, Hess L, Huitema C, Kubo T, Komlosi Z, Konieczna P, Kovacs N, Kucuksezer UC, Meyer N, Morita H, Olzhausen J, O'Mahony L, Pezer M, Prati M, Rebane A, Rhyner C, Rinaldi A, Sokolowska M, Stanic B, Sugita K, Treis A, van de Veen W, Wanke K, Wawrzyniak M, Wawrzyniak P, Wirz OF, Zakzuk JS, Akdis CA. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor b, and TNF-a: Receptors, functions, and roles in diseases. J Allergy Clin Immunol. 2016;138(4):984-1010. IPF: 12.485

Barcik W, Pugin B, Westermann P, Rodriguez-Perez N, Ferstl R, Wawrzyniak M, Smolinska S, Jutel M, Hessel EM, Michalovich D, Akdis CA, Frei R, O'Mahony L. Histamine-secreting microbes are increased in the gut of adult asthma patients. J Allergy Clin Immunol 2016; 138(5): 1491-1494.e7. IPF: 12.485

Bousquet J, Schuenemann HJ, Hellings PW, Arnavielhe S, Bachert C, Bedbrook A, et al; MASK study group*. MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. J Allergy Clin Immunol. 2016 Aug;138(2):367-374.e2. IPF: 12.485

Duan Su, Kerstin Wanke, Paulina Wawrzyniak, Yifan Meng, Jeannette I. Kast, Beate Rückert, Ana Rebane, Mu Xian, Carsten Bindslev-Jensen, Sigurd Broesby, Ulrike Raab, Thomas Werfel, Mübeccel Akdis, Luo Zhang, Cezmi A. Akdis. Platelet-activating factor decreases skin keratinocyte tight junction barrier integrity. J Allergy Clin Immunol, 2016, IPF: 12.485

Frei R, Ferstl R, Roduit C, Ziegler M, Schiavi E, Barcik W, Rodriguez N, Wirz O, Konieczna P, Bieli C, Loeliger S, Waser M, Scheynius A, van Hage M, Pershagen G, Doekes G, Riedler J, Sennhauser F, Depner M, Schaub B, Loss G, Genuneit J, Pfefferle P, Hyvärinen A, Karvonen AM, Dalphin JC, Pekkanen J, Akdis M, Akdis CA, von Mutius E, Braun-Fahrländer C, O'Mahony L, Lauener R. Exposure to the non-microbial foreign sialic acid N-Glycolylneuraminic acid confers protection against human and murine allergic airway-inflammation. J Allergy Clin Immunol. 2017 in press. IPF: 12.485

Huang Y, Marsland B, Bunyavanich S, O'Mahony L, Leung D, Muraro A, Fleisher TA. The microbiome in allergic disease: current understanding and future opportunities. J Allergy Clin Immunol. 2017 Apr;139(4):1099-1110. IPF: 12.485

Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, Cox L, Demoly P, Frew AJ, O'Hehir R, Kleine-Tebbe J, Muraro A, Lack G, Larenas D, Levin M, Martin BL, Nelson H, Pawankar R, Pfaar O, van Ree R, Sampson H, Sublett JL, Sugita K, Du Toit G, Werfel T, Gerth van Wijk R, Zhang L, Akdis M, Akdis CA. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol. 2016 Feb;137(2):358-68. IPF: 12.485

Lech Z, Chalubinski M, Kosinski S, Smorawska E, Bassin C, Akdis CA, Grzegorczyk J, Kowalski ML. Prostaglandin E2 and lipoxin A4 in PBMCs are associated with immune tolerance during venom immunotherapy. J Allergy Clin Immunol. 2016 Oct;138(4):1199-1202.e2. IPF: 12.485

Morita H, Moro K, Koyasu S. Innate lymphoid cells in allergic and nonallergic inflammation. J Allergy Clin Immunol. 2016;138(5):1253-1264. IPF: 12.485

Muraro A, Lemanske RF Jr, Hellings PW, Akdis CA, Bieber T, Casale TB, Jutel M, Ong PY, Poulsen LK, Schmid-Grendelmeier P, Simon HU, Seys SF, Agache I. Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2016 May;137(5):1347-58. IPF: 12.485

O'Mahony L, Akdis CA, Eiwegger T. Innate mechanisms can predict successful allergen specific immunotherapy. J Allergy Clin Immunol, 2016 Feb;137(2):559-61. IPF: 12.485

Sokolowska M, Chen LY, Liu Y, Martinez-Anton A, Logun C, Alsaaty S, Cuento RA, Cai R, Sun J, Quehenberger O, Armando AM, Dennis EA, Levine SJ, Shelhamer JH. Dysregulation of lipidomic profile and antiviral immunity in response to hyaluronan in patients with severe asthma. J Allergy Clin Immunol. 2016 Nov 5. pii: S0091-6749(16)31276-3. IPF: 12.485

Steelant B, Farré R, Wawrzyniak P, Belmans J, Dekimpe E, TothJ, Van Gerven L, Kortekaas Krohn I, Ceuppens JL, Akdis CA, Boeckxstaens G, Seys SF, Hellings PW. Impaired barrier function in patients with house dust mite-induced allergic rhinitis is accompanied by decreased occludin and zonula occludens-1 expression. J Allergy Clin Immunol, 2016 Apr;137(4):1043-53.e1-5. IPF: 12.485

Sugita K, Steer CA, Martinez-Gonzalez I, Altunbulakli C, Morita H, Castro-Giner F, Kubo T, Wawrzyniak P, Rückert B, Sudo K, Nakae

S, Matsumoto K, O'Mahony L, Akdis M, Takei F, Akdis CA. Group 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions. J Allergy Clin Immunol. 2017 Apr 6. [Epub ahead of print]. IPF: 12.485

van de Veen W, Stanic B, Wirz OF, Jansen K, Globinska A, Akdis M. Role of regulatory B cells in immune tolerance to allergens and beyond. J Allergy Clin Immunol. 2016;138(3): 654-65. IPF: 12.485

van de Veen W, Akdis M. Role of IgG4 in IgE-mediated allergic responses. J Allergy Clin Immunol. 2016;138(5):1434-1435. IPF: 12.485

Wawrzyniak P, Akdis CA, Finkelman FD, Rothenberg ME. Advances and highlights in mechanisms of allergic disease in 2015. J Allergy Clin Immunol, 2016 Jun;137(6):1681-96. IPF: 12.485

Wawrzyniak P, MSc, Marcin Wawrzyniak, PhD, Kerstin Wanke, PhD, Milena Sokolowska, MD PhD, Kreso Bendelja, PhD, Beate Rückert, Anna Globinska, MSc, Bogdan Jakiela, MD, PhD, Jeannette I. Kast, MSc, Marco Idzko, MD, Mübeccel Akdis, MD, PhD, Marek Sanak, MD, PhD, Cezmi A. Akdis, MD. Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthma. J Allergy Clin Immunol, 2016 May 11. IPF: 12.485

Werfel T, Allam JP, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E, Hoetzenecker W, Knol E, Simon HU, Wollenberg A, Bieber T, Lauener R, Schmid-Grendelmeier P, Traidl-Hoffmann C, Akdis CA. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. J Allergy Clin Immunol. 2016 Aug;138(2):336-49. IPF: 12.485

Xian Mu, Paulina Wawrzyniak, Beate Rückert, Su Duan, Yifan Meng, Milena Sokolowska, Anna Globinska, Luo Zhang, Mübeccel Akdis, Cezmi A. Akdis. Anionic surfactants and commercial detergents decrease tight junction barrier integrity in human keratinocytes. J Allergy Clin Immunol, 2016 Sep;138(3):890-893.e9. IPF: 12.485

Zuberbier T, Abelson MB, Akdis CA, Bachert C, Berger U, Bindslev-Jensen C, Boelke G, Bousquet J, Canonica GW, Casale TB, Jutel M, Kowalski ML, Madonini E, Papadopoulos NG, Pfaar O, Sehlinger T, Bergmann KC; Global Allergy and Asthma European Network (GA(2)LEN) European Union Network of Excellence in Allergy and Asthma. Validation of the Global Allergy and Asthma European Network (GA(2)LEN) chamber for trials in allergy: Innovation of a mobile allergen exposure chamber. J Allergy Clin Immunol. 2016 Sep 30. [Epub ahead of print] IPF: 12.485

Bachert C, Akdis CA. Phenotypes and Emerging Endotypes of Chronic Rhinosinusitis. J Allergy Clin Immunol Pract. 2016 Jul-Aug;4(4):621-8. IPF: 5.429

Bousquet J, Bewick M, Cano A, Eklund P, Fico G, Goswami N, et al. Building Bridges for Innovation in Ageing: Synergies between Action Groups of the EIP on AHA. Nutr Health Aging. 2017;21(1):92-104. IPF: 2.996

Crameri R. Allergic Bronchopulmonary Aspergillosis (ABPA). EAACI Molecular Alloegology User's Guide. Pediatr Allergy Immunol. 2016;27 (Suppl 23):81-83. IPF: 3.947

Glatz M, Bosshard PP, Crameri R, Schmid-Grendelmeier P. Role of Microbial Allergens in Atopic Dermatitis. EAACI Molecular Alloegology User's Guide. Pediatr Allergy Immunol. 2016;27 (Suppl 23):84-88. IPF: 3.947

Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, Aalberse RC, Agache I, Asero R, Ballmer-Weber B, Barber D, Beyer K, Biedermann T, Bilò MB, Blank S, Bohle B, Bosshard PP, Breiteneder H, Brough HA, Caraballo L, Caubet JC, Crameri R, Davies JM, Douladiris N, Ebisawa M, Elgenmann PA, Fernandez-Rivas M, Ferreira F, Gadermaier G, Glatz M, Hamilton RG, Hawranek T, Hellings P, Hoffmann-Sommergruber K, Jakob T, Jappe U, Jutel M, Kamath SD, Knol EF, Korosec P, Kuehn A, Lack G, Lopata AL, Mäkelä M, Morisset M, Niederberger V, Nowak-Węgrzyn AH, Papadopoulos NG, Pastorello EA, Pauli G, Platts-Mills T, Posa D, Poulsen LK, Raulf M, Sastre J, Scala E, Schmid JM, Schmid-Grendelmeier P, van Hage M, van Ree R, Vieths S, Weber R, Wickman M, Muraro A, Ollert M. EAACI Molecular Alloegology User's Guide. Pediatr Allergy Immunol. 2016;27 (Suppl 23):1-250. IPF: 3.947

Schröder PC, Casaca VI, Illi S, Schieck M, Michel S, Böck A, Roduit C, Frei R, Lluis A, Genuneit J, Pfefferle P, Roponen M, Weber J, Braun-Fahrländer C, Riedler J, Lauener R, Vuitton DA, Dalphin JC, Pekkanen J, von Mutius E, Kabesch M, Schaub B; PASTURE Study group. IL-33 polymorphisms are associated with increased risk of hay fever and reduced regulatory T cells in a birth cohort. Pediatr Allergy Immunol. 2016 Nov;27(7):687-695. IPF: 3.947

Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, Halken S, Katz Y, Ebisawa M, Eichenfield L, Sampson H, Lack G, Du Toit G, Roberts G, Bahnson H, Feeney M, Hourihane J, Spergel J, Young M, As'aad A, Allen K, Prescott S, Kapur S, Saito H, Agache I, Akdis CA, Arshad H, Beyer K, Dubois A, Eigenmann P, Fernandez-Rivas M, Grimshaw K, Hoffman-Sommergruber K, Host A, Lau S, O'Mahony L, Mills C, Papadopoulos N, Venter C, Agmon-Levin N, Kessel A, Antaya R, Drolet B, Rosenwasser L. Consensus Communication on Early Peanut Introduction and Prevention of Peanut Allergy in High-Risk Infants. Pediatr Dermatol. 2016 Jan;33(1):103-6. IPF: 1.015

Altmann F, Kosma P, O'Callaghan A, Leahy S, Bottacini F, Molloy E, Plattner S, Schiavi E, Gleinser M, Groeger D, Grant R, Rodriguez Perez N, Healy S, Svehla E, Windwarder M, Hofinger A, O'Connell Motherway M, Akdis CA, Xu J, Roper J, van Sinderen D, O'Mahony L. Genome Analysis and Characterisation of the Exopolysaccharide Produced by Bifidobacterium longum subsp. longum 35624™. PLoS One. 2016;11(9):e0162983. IPF: 3.234

Mittermann I, Wikberg G, Johansson C, Christian Lupinek C, Lundeberg L, Crameri R, Valenta R, Scheynius A. Molecular IgE sensitization profiles differ between patients with severe and moderate atopic dermatitis. PLOSONE May 26,201; 2016. IPF: 3.057

2016

Steelant B, Seys SF, Boeckxstaens G, Akdis CA, Ceuppens JL, Hellings PW. Restoring airway epithelial barrier dysfunction: a new therapeutic challenge in allergic airway disease. Rhinology. 2016 Sep;54(3):195-205. IPF: 1.686

Morita H, Saito H, Matsumoto K, Nakae S. Regulatory roles of mast cells in immune responses. Semin Immunopathol. 2016;38(5):623-629. IPF: 6.394

Smolinska S, O'Mahony L. Microbiome-Host Immune System Interactions. Semin Liver Dis. 2016 Sep;36(4):317-326. Epub 2016 Dec 20. IPF 5.7

Jonsdottir S, Svansson V, Stefansdottir SB, Schüpbach G, Rhyner C, Marti E, Torsteinsdottir S. A preventive immunization approach against insect bite hypersensitivity: Intralymphatic injection with recombinant allergens in Alum or Alum and monophosphoryl lipid A. Vet Immunol Immunopathol. 2016 Apr;172:14-20. IPF: 1.664

Braido F, Scichilone N, Lavorini F, Usmani OS, Dubuske L, Boulet LP, et al.; for Interasma Executive Board.; ARIA.; GA2LEN. Manifesto on small airway involvement and management in asthma and chronic obstructive pulmonary disease: an Interasma (Global Asthma Association - GAA) and World Allergy World Allergy Organ J. Organization (WAO) document endorsed by Allergic Rhinitis and its Impact on Asthma (ARIA) and Global Allergy and Asthma European Network (GA(2)LEN). World Allergy Organ J. 2016 Oct 28;9(1):37. IPF: 1.04

Kowalski ML, Ansotegui I, Aberer W, Al-Ahmad M, Akdis M, et al. Risk and safety requirements for diagnostic and therapeutic procedures in allergology: World Allergy Organization Statement. World Allergy Organ J. 2016 Oct 12;9(1):33. IPF: 1.04

Submitted

Ferstl R, Frei R, Konieczna P, Ziegler M, Zeiter S, Lauener R, Akdis CA, O'Mahony L. Histamine receptor 2 controls invariant natural killer T cell responses within the lung. Submitted.

Pugin B, Barcik W, Westermann P, Heider A, Wawrzyniak M, Hellings P, Akdis CA, O'Mahony L. A Wide Diversity of Bacteria Produce and Degrade Biogenic Amines within the Human Gastrointestinal Tract. Submitted.

Book chapters

Akdis CA, Palomares O. Immunology of the Asthmatic Response. In: Pediatric Allergy. Editors: Leung DYM, Szefler SJ, Bonilla FA, Akdis CA, Sampson HA. Elsevier 2016.

Crameri R. Allergic bronchopulmonary aspergillosis (ABPA). In: Handbook of Molecular Allergology. European Academy of Allergy and Clinical Immunology. (in press).

Glatz M. Bosshard PP, Crameri R, Schmid-Grendelmeier P. Role of recombinant allergens in atopic dermatitis. In: Handbook of Molecular Allergology. European Academy of Allergy and Clinical Immunology. (in press).

Kubo T, Morita H, Sugita K, Akdis CA. Introduction to Mechanisms of Allergic Diseases. In: Middleton's Allergy Essentials, 2016.

Abstracts

Altunbulakli C. Analysis Of Barrier Molecules And Histone Modifying Enzymes In Atopic Dermatitis Lesions. EAACI winter school 2016, Cortina d'Ampezzo, Italy, 4-7 February 2016.

Altunbulakli C. Transcriptomic analysis of epidermal barrier molecules, cytokines and growth factors in atopic dermatitis lesions. ESDR Congress, Munich, Germany, 7-10 September 2016.

Altunbulakli C. Epidermal barrier dysregulation in human skin after exposure to p-Phenylenediamine. ESCD Congress, Manchester, United Kingdom, 14-17 September 2016.

Barcik W., Benoit Pugin, Remo Frei, Ruth Ferstl, Liam O`Mahony. Microbiota-Derived Histamine - Relevance to Mucosal Immune Homeostasis. SWIFCOB 16 «Macht Biodiversität gesund?», Bern, Switzerland, 15th January 2016.

Barcik W., Frei R., Ferstl R., Pugin B., Rodriguez N., O`Mahony L. Microbiota-Derived Histamine - Relevance To Mucosal Immune Homeostasis. EAACI Winter School, Cortina d'Ampezzo, Italy, 4-7 February 2016.

Barcik W., Benoit Pugin, Remo Frei, Noelia Rodriguez Perez, Ruth Ferstl, Liam O`Mahony. Microbiota-Derived Histamine - Relevance to Mucosal Immune Homeostasis. WIRM-X, Davos, Switzerland, 16 - 19 March 2016.

Eljaszewicz A., Wawrzyniak P., Globinska A., Sokolowska M., Akdis C. Role of NOD-, RIG-I, AIM2-liker receptors in airway epithelium in asthma. WIRM X, Davos Platz, Switzerland, 16-19 March 2016.

Eljaszewicz A., Radzikowska U., Wawrzyniak P., Globinska A., Sokolowska M., Akdis C. Role of NOD-, RIG-I and AIM2-like receptors in airway epithelium in asthma. Graubünden Forscht, Davos Platz, Switzerland, 14-15 September 2016.

Morita H. Mast cells suppress IL-33 induced airway inflammation by promoting regulatory T cells expansion. EAACI 2016, Vienna, Austria, 11-15 June 2016.

Olzhausen J, Schawaller M, Klimek L, Crameri R, Akdis CA, Rhyner C. Rapid and sensitive measurement of allergen specific antibodies during allergen specific immunotherapy. WIRM X, Davos Platz, Switzerland, 16-19 March 2016.

Olzhausen J, Schawaller M, Merieux Y, Crameri R, Rhyner C. Fast and sensitive method for HPA-1a and HPA-5b Allo–Antigen Typing in Whole blood. ESPGI, Stockholm, Sweden, 26-28 May 2016.

Olzhausen J, Schawaller M, Klimek L, Crameri R, Akdis CA, Rhyner C. Rapid and sensitive measurement of allergen specific antibodies during allergen specific immunotherapy. Graubünden Forscht, Davos Platz, Switzerland, 14-15 September 2016.

Mittermann I, Wikberg G, Johansson C, Christian Lupinek C, Lundeberg L, Crameri R, Valenta R, Scheynius A. IgE Sensitization Profiles differ between Adult Patients with Severe and Moderate. Atopic Dermatitis. KI Inflammation and immunology network KiiM, Stockholm, Sweden, 13-14 October 2016.

Mittermann I, Wikberg G, Johansson C, Christian Lupinek C, Lundeberg L, Crameri R, Valenta R, Scheynius A. IgE Sensitization Profiles differ between Adult Patients with Severe and Moderate. Atopic Dermatitis. 2nd Inflammatory Skin Disease Summit, New York, USA, November 16-19 2016.

Pugin B, Barcik W, Wawrzyniak M, Westermann P, O'Mahony L. A rapid and simple culture -dependent approach for the isolation and characterization of biogenic amines producing bacteria from gut microbiota. WIRM, Davos, Switzerland, 16-19 March 2016

Radzikowska U. Role of NOD-, RIG-I and AIM2-like receptors in airway epithelium in asthma. 5th Conference Graubünden Forscht, Davos, Switzerland, 14-15 September 2016.

Rhyner C. Novel microparticles create a slow releasing depot for long-term immunostimulation in allergen-specific immunotherapy. 43rd Annual Meeting of the Arbeitsgemeinschaft-Dermatologische-Forschung-e-V (ADF), Vienna, Austria, 10-12 March 2016.

Rhyner C. Promotion of a regulatory immune response induced by an allergen-fused dendritic cell-binding peptide in combination with MPLA. EAACI Annual congress, Vienna, Austria, 11-15 June 2016.

Rösner, LM, Wieschowski, S, Vauth, M, Valenta, R, Crameri, R, Werfel, T. Autoantigene bei atopischer Dermatitis weisen auf Ebene der immundominanten Epitope Homologien zu mikrobiellen Antigenen auf. 11th Deutche Allergiekongress, Berlin, Deutschland, 29 September – 01 Oktober 2016.

Sokolowska M, Chen L-Y, Liu Y, Martinez-Anton A, Logun C, Alsaaty S, Cuento RA, Cai R, Sun J, Quehenberger O, Armado AM, Dennis EA, Levine SJ, Shelhamer JH. Dysregulation of lipidomic profile and antiviral immunity in response to hyaluronan in severe asthma. 10th World Immune Regulation Meeting, 16-19 March 2016, Davos, Switzerland.

Sokolowska M, Chen L-Y, Liu Y, Martinez-Anton A, Logun C, Alsaaty S, Cuento RA, Cai R, Sun J, Quehenberger O, Armado AM, Dennis EA, Levine SJ, Shelhamer JH. Dysregulation of lipidomic profile and antiviral immunity in response to hyaluronan in severe asthma. „Graubünden forscht – Young Scientists in Contest", 14-15 September 2016, Davos, Switzerland.

Sokolowska M, Chen L-Y, Liu Y, Martinez-Anton A, Logun C, Alsaaty S, Cuento RA, Cai R, Sun J, Quehenberger O, Armado AM, Dennis EA, Levine SJ, Shelhamer JH. Hyaluronan-induced lipid mediators influence antiviral and antibacterial immunity in severe asthmatics. 3rd International Severe Asthma Forum (ISAF), 17-19 November 2016, Manchester, United Kingdom.

van de Veen W. Identification of novel human effector memory B cell subsets. World Immune Regulation Meeting, Davos, Switzerland, March 2016.

van de Veen W. Allergen-specific B cell responses to allergen-tolerance induction are characterized by expansion of BR1 cells, IgG4-class switch recombination and CCR5 expression. 31st Symposium of the Collegium Internationale Allergologicum, Charleston SC, United States, April 2016.

van de Veen W. High-dose bee venom exposure induces similar tolerogenic B cell responses in patients and healthy beekeepers. EAACI Congress, Vienna, Austria, June 2016.

Wawrzyniak P. Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthma. EAACI Winter School, Cortina d'Ampezzo, Italy, 04-06 February 2016.

Wawrzyniak P, Marcin Wawrzyniak, Kerstin Wanke, Milena Sokolowska, Kreso Bendelja Beate Rückerta, Anna Globinska, Bogdan Jakiela, Jeannette I. Kast, Marco Idzko, Mübeccel Akdis, Marek Sanak, Cezmi A. Akdis. Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthma. World Immune Regulation Meeting X - WIRM 2016, Davos, Switzerland, 16-19 March 2016.

Wawrzyniak P. Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthma. Graubünden forscht - Young Scientists Contest, Davos, Switzerland, 14-15 September 2016.

Wirz OF, Van de Veen W, Aab A, Altunbulakli C, Morita H, Johnston SL, Glanville N, Akdis C, Akdis M. The Role Of B Cells In Human Rhinovirus Infection. 14th EAACI Immunology Winter School, Cortina d'Ampezzo, Italy, 4-7 February 2016.

Wirz OF, Van de Veen W, Altunbulakli C, Aab A, Morita H, Johnston SL, Glanville N, Papadopoulos NG, Akdis C, Akdis M. The Role of B cells in Human Rhinovirus Infection. 10th World Immune Regulation Forum (WIRM X), Davos Platz, Switzerland, 16-19 March 2016.

Wirz OF, van de Veen W, Mirer D, Morita H, Altunbulakli C, Johnston SL, Glanville N, Papadopoulos NG, Akdis CA, Akdis M. The role of B cells in rhinovirus infection. WAO International Scientific Conference (WISC), Jerusalem, Israel, 6-9 December 2016.

Seminar and congress talks

Akdis CA. Mechanism of Tolerance to Venom Induced By Immunotherapy. Annual Meeting American Academy of Allergy Asthma & Immunology (AAAAI), Los Angeles, USA, 4-7 March 2016.

Akdis CA. Immunologic Mechanisms of Novel Allergen-Specific Immunotherapies. Annual Meeting American Academy of Allergy Asthma & Immunology (AAAAI), Los Angeles, USA, 4-7 March 2016.

Akdis CA. Role of group 2 innate lymphoid cells and IL-13 in bronchial epithelial cell tight junction barrier leakiness. 31st Symposium of the Collegium Internationale Allergologicum (CIA), Charleston, USA, 3-8 April 2016.

Akdis CA. Role of Epithelial Barrier in Allergic Diseases. Luxemburg Research Institute, 14 April 2016.

Akdis CA. Endotypes of Asthma. Pediatric Allergy and Asthma Academy Meeting, Marmaris, Turkey 24-26 April 2016.

Akdis CA. Regulation of chronicity in diseases by immune system interaction with resident tissue cells. International Molecular Immunology & Immunogenetics Congress (MIMIC), Belek/Antalya, Turkey, 27-30 April 2016.

Akdis CA. Tissue response in Chronic Rhinosinusitis Rhinocamp, Bodrum, Turkey, 25-28 May 2016.

Akdis CA. Could microRNAs be the future biomarkers of allergies and asthma? EAACI congress 2016, Vienna, Austria, 11-15 June 2016.

Akdis CA. Role of epithelial barrier in asthma. International edcational course on respiratory diseases, Catania, Italy, 16-18 June 2016.

Akdis CA. Mechanisms of Immunological Tolerance to Allergens. 9th Allergy Convention, Hong Kong, 8-9 October 2016.

Akdis CA. Personalized care based on molecular, immunologic and functional endotyping of the allergic disease. 9th Allergy Convention, Hong Kong, 8-9 October 2016.

Akdis CA. Immune mechanisms underpinning successful allergen-specific immunotherapy. EAACI Master Class on Translational Immunology in Allergic Diseases, Zurich, Switzerland, 21-22 October 2016.

Akdis CA. From phenotypes to endotypes: basic concepts. European Rhinology Research Forum, Brussels, Belgium, 17-18 November 2016.

Akdis CA. Publish your work in high IF journals (researchers & editors interaction). European Rhinology Research Forum, Brussels, Belgium, 17-18 November 2016.

Akdis CA. Advances in mechanisms and clinical implications. WAO International Scientific Conference (WISC), Jerusalem, Israel, 6-9 December 2016.

Akdis M. IL-10 Expressing B Cells Regulate Innate and Adaptive Immune Responses. Annual Meeting American Academy of Allergy Asthma & Immunology (AAAAI), Los Angeles, USA, 4-7 March 2016.

Akdis M. Immunological Routes We Can Influence to Enhance Tolerance. Annual Meeting American Academy of Allergy Asthma & Immunology (AAAAI), Los Angeles, USA, 4-7 March 2016.

Akdis M. Mechanisms of inducing and breaking allergen tolerance. 31st Symposium of the Collegium Internationale Allergologicum (CIA), Charleston, USA, 3-8 April 2016.

Akdis M. Inducing and breaking of allergen specific tolerance. International Molecular Immunology & Immunogenetics Congress (MIMIC), Belek/Antalya, Turkey, 27-30 April 2016.

Akdis M. Asthma and breaking of immune tolerance to allergens. International edcational course on respiratory diseases, Catania, Italy, 16-18 June 2016.

Akdis M. Immunotherapy of allergic diseases. PhD Days, University of Copenhagen, Denmark, 22 June 2016.

Akdis M. New treatments for allergen immunotherapy. 9th Allergy Convention, Hong Kong, 8-9 October 2016.

Akdis M. Induction of tolerance: role of regulatory T cells. EAACI Food Allergy and Anaphylaxis Meeting (FAAM), Rome, Italy, 13-15 October 2016.

Akdis M. Induction and breaking of immune tolerance and asthma. EAACI International Severe Asthma Forum (ISAF), Manchester, UK, 17-19 November 2016.

Akdis M. Role of B Reg cells in allergen tolerance during allergen immunotherapy (AIT). WAO International Scientific Conference (WISC), Jerusalem, Israel 6-9 December 2016.

Akdis M. Modifying the Immune Response: Specific Immunotherapy. WAO International Scientific Conference (WISC), Jerusalem, Israel 6-9 December 2016.

Barcik W. Microbiota-Derived Histamine - Relevance to Mucosal Immune Homeostasis. EAACI Winter School 2016, Cortina d`Ampezzo, Italy, 11.02.2016.

Barcik W. Microbiota-Derived Histamine - Relevance to Mucosal Immune Homeostasis. Graubünden forscht - Young Scientists Contest, Davos, Switzerland, 12.09.2016.

Crameri R. Biotechnologie zwischen Frankenstein und Allheilsmittel. TechDay, Bündner Kantonsschule, Chur, Switzerland, 26 February 2016.

Crameri R. Engineering optimal allergy vaccines and development of a diagnostic chip to monitor the success of allergen-specific immunotherapy. Nanoasit II meeting, Davos, Switzerland, 14 March 2016.

Crameri R. Report Molecular Allergology Group. Scientific Advisory Board Meeting, Davos, Switzerland, 21 March 2016.

Crameri R. Allergy vaccination using novel drug delivery routes mediated via nanotechnology. Nanoasit II meeting, Stockholm, Sweden, 27 September 2016.

Frei R. Short-chain fatty acids in prevention of the development of inflammatory diseases. World Immune Regulation Meeting, Davos, Switzerland, March 2016.

Morita H. Roles of innate lymphoid cells in allergic inflammation. Istanbul University, Istanbul, Turkey, June 2016.

Morita H. Roles of innate lymphoid cells (ILC) in allergic inflammation. IEM Lecture Series 2016 at UNIKA-T, Augsburg, Germany, June 2016.

O'Mahony L. Microbiome and dietary factors leading to immune tolerance. Nestle Research Centre, Lausanne, 26 January 2016.

O'Mahony L. Influence of Microbes and their Metabolites on Immune Tolerance. Hannover Medical School, Hannover, 10 February 2016.

O'Mahony L. Microbiota and food in the intestinal immune response. European academy of allergy and clinical immunology, Vienna, 13 June 2016.

O'Mahony L. Microbes: Good or Bad. International Congress on Pediatric Pulmonology, Naples, 24 June 2016.

O'Mahony L. Probiotics for Allergic and Respiratory Diseases in Children. International Congress on Pediatric Pulmonology, Naples, 25 June 2016.

O'Mahony L. The Gut Microbiota and its Role in Allergic Disease. British Society for Allergy and Clinical Immunology, Telford, 30 September 2016.

O'Mahony L. The Developing Gut in Early Life. British Society for Allergy and Clinical Immunology, Telford, 30 September 2016.

O'Mahony L. Shaping the infant microbiota. Food Allergy and Anaphylaxis Meeting (FAAM), Rome, 15 October 2016.

SEMINAR AND CONGRESS TALKS

2016

O'Mahony L. Novel microbiome targets in allergy and asthma. Translational Immunology in Allergic Diseases, Zurich, 22 October 2016.

O'Mahony L. Microbiota, diet and allergies. Imparas, Vienna, 30 November 2016.

Rhyner C. PG 9 Inflammation and immune biomarkers in childhood non-communicable diseases. Monitoring inflammation: Benefits and challenges of immune biomarkers. EAACI Annual congress, Vienna, Austria, 11-15 June 2016.

Rhyner C. GA²LEN Research improves precision medicine. Prediction: Biomarkers of allergy in precision medicine. EAACI Annual congress, Vienna, Austria, 11-15 June 2016.

Sokolowska M. Immunoregulatory roles of eicosanoids in inflammatory diseases. University of Lausanne; Department of Biochemistry invited seminar, 05 July 2016.

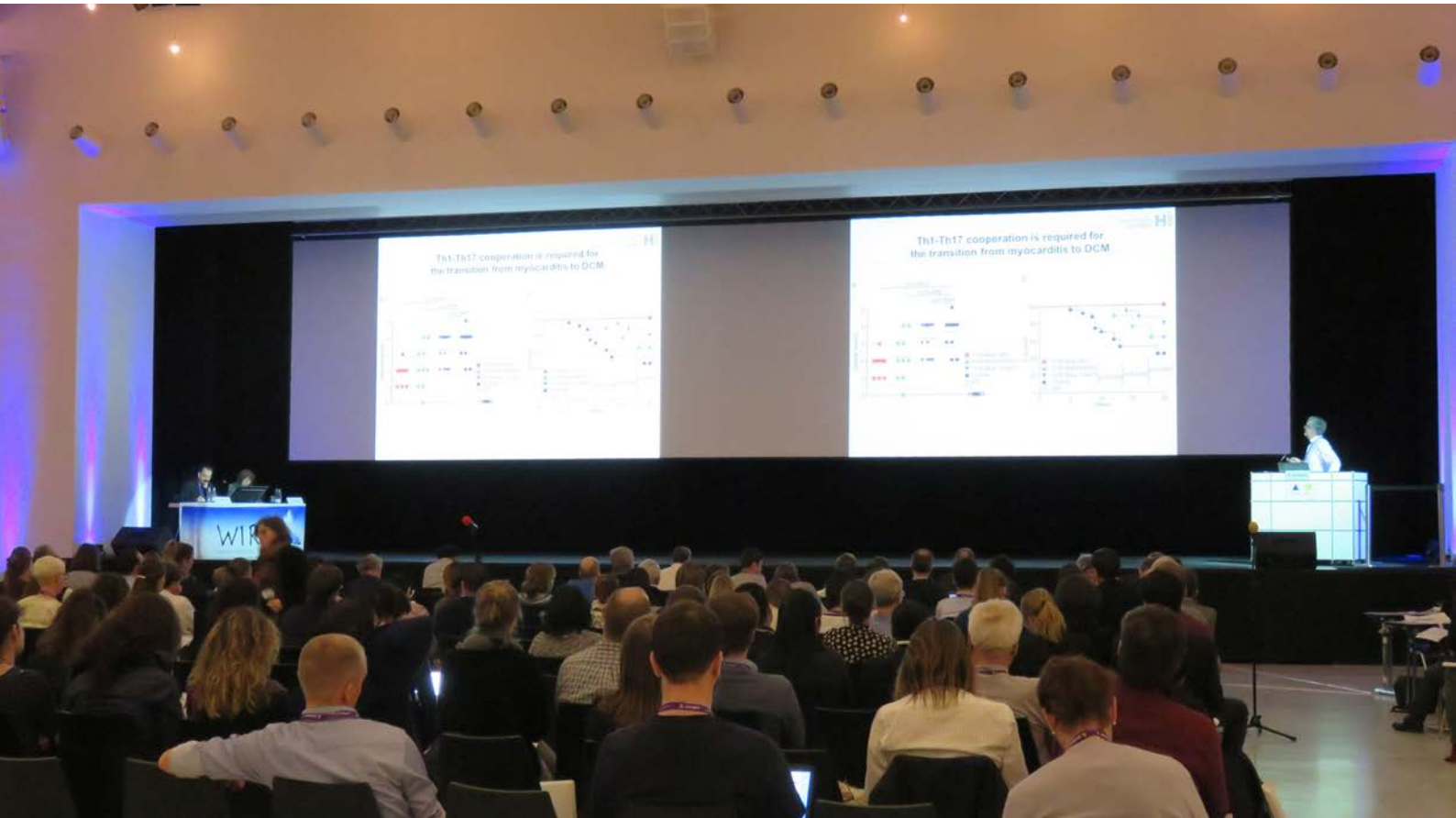
Sokolowska M. Dysregulation of lipidomic profile and antiviral immunity in response to hyaluronan in severe asthma. „Graubünden forscht – Young Scientists in Contest",Davos, Switzerland, 14-15 September 2016.

Sokolowska M. Hyaluronan-induced lipid mediators influence antiviral and antibacterial immunity in severe asthmatics. 3rd International Severe Asthma Forum (ISAF), Manchester, United Kingdom, 17-19 November 2016.

Steengaard SS, Altunbulakli C, Johansen JD, Bonefeldt CM, Akdis CA. Skin changes after allergen exposure in hair color allergic individuals and tolerant individuals. GSI, Copenhagen, Denmark, September 2016.

Steengaard SS, Altunbulakli C, Akdis CA, Johansen JD, Bonefeldt CM. Immunology of hairdye allergy and tolerance. National Allergy Research Center, Copenhagen, Denmark, December 2016.

van de Veen W. (Regulatory) B cells and tolerance to allergens. HSM-2 Symposium on Immunotolerance, Zürich, Switzerland, May 2016.



Chairs

Akdis CA. JACI: Year-in-Review. Annual Meeting American Academy of Allergy Asthma & Immunology (AAAAI), Los Angeles, USA, 4-7 March 2016.

Akdis CA. B-Regulatory Cells: No Longer Playing Second Fiddle to T Regs. Annual Meeting American Academy of Allergy Asthma & Immunology (AAAAI), Los Angeles, USA, 4-7 March 2016.

Akdis CA. Cellular Mechanisms. 31st Symposium of the Collegium Internationale Allergologicum (CIA), Charleston, USA, 3-8 April 2016.

Akdis CA. Immune Mechanisms of Allergy. Rhinocamp, Bodrum, Turkey, 25-28 May 2016.

Akdis CA. Year In Review. Rhinocamp, Bodrum, Turkey, 25-28 May 2016.

Akdis CA. Treating allergy with biologicals. EAACI congress 2016, Vienna, Austria, 11-15 June 2016.

Akdis CA. PRACTALL on precision medicine in allergy and asthma. EAACI congress 2016, Vienna, Austria, 11-15 June 2016.

Akdis CA. Horizons in food allergy. EAACI Food Allergy and Anaphylaxis Meeting (FAAM), Rome, Italy, 13-15 October 2016.

Akdis CA. Emerging cells in allergy. WAO International Scientific Conference (WISC), Jerusalem, Israel 6-9 December 2016.

Akdis CA. WAO International Scientific Conference (WISC), Jerusalem, Israel 6-9 December 2016.

Akdis M. Pathophysiology of allergic disorders, barrier function, inflammation and remodeling. 31st Symposium of the Collegium Internationale Allergologicum (CIA), Charleston, USA, 3-8 April 2016.

Akdis M. The intrigues of the asthmatic lung – women in science. EAACI congress 2016, Vienna, Austria, 11-15 June 2016.

Akdis M. Regulatory pathways in allergen-specific immunotherapy. EAACI congress 2016, Vienna, Austria, 11-15 June 2016.

Crameri R. Vaccine development. Nanoasit II meeting, Davos, Switzerland, 14 March 2016.

Crameri R. Regulation of immune response and immune pathology. WIRM, Davos, Switzerland, 16-19 March 2016.

Crameri, R. Medical and Life Sciences, oral presentations. Young Scientists in context, Davos, Switzerland, 14-15 September 2016.

Crameri R. WP 3: Eigineering optimal allergy vaccines and development of a diagnostic chip to monitor the success of ASIT. Nanoasit II meeting, Stockholm, Sweden, 27 September 2016.

O'Mahony L. EAACI winter school, February 2016, Cortina, Italy.

O'Mahony L. Imparas meeting, March 2016, Barcelona, Spain.

O'Mahony L. WIRM, March 2016, Davos, Switzerland.

O'Mahony L. Neutrophils: too long ignored in allergy. EAACI congress 2016, Vienna, Austria, 11-15 June 2016.

O'Mahony L. T-sing out the role of T cells. EAACI congress 2016, Vienna, Austria, 11-15 June 2016.

O'Mahony L. Immunology Section. EAACI Master Class on Translational Immunology in Allergic Diseases, Zurich, Switzerland, 21-22 October 2016.

Rhyner C. Plenary Session 9: Novel treatments and immune mechanisms. WIRM-X, Davos, Switzerland, 16-19 March 2016.

Rhyner C. Postgraduate Courses 9: Inflammation and immune biomarkers in childhood non-communicable diseases – Advanced. EAACI Annual congress, Vienna, Austria, 11-15 June 2016.

Rhyner C. Poster Session 22: Functional genomics and immunogenomics. EAACI Annual congress, Vienna, Austria, 11-15 June 2016.

Rhyner C. Poster Discussion Session 2: Effector cells. EAACI Annual congress, Vienna, Austria, 11-15 June 2016.

Sokolowska M. Innate Immunity. 10th World Immune Regulation Meeting, Davos, Switzerland, 16-19 March 2016.

van de Veen W. B cell subsets and immune regulation. World Immune Regulation Meeting, Davos, Switzerland, March 2016.

Lectures

Lectures at University of Zurich

Akdis CA. HS 2016 Nr. 1180. Klinisch-experimentelle Konferenz zur Allergologie
Akdis CA. HS 2016 Nr. 1215 e. Mechanisms of Allergic Diseases
Akdis CA. HS 2016 Nr. BCH301.1. Vorlesung Molekulare Zellbiologie
Akdis M. HS 2016 Nr. 1180. Klinisch-experimentelle Konferenz zur Allergologie
Akdis M. HS 2016 Nr. 1215 e. Mechanisms of Allergic Diseases
Akdis M. HS 2016 Nr. BCH301.1. Vorlesung Molekulare Zellbiologie
Crameri R. HS 2016 Nr. 1180. Klinisch-experimentelle Konferenz zur Allergologie
Crameri R. HS 2016 Nr. 1215 e. Mechanisms of Allergic Diseases
Crameri R. HS 2016 Nr. BCH301.1. Vorlesung Molekulare Zellbiologie

Lectures at University of Salzburg

Crameri R. SS 2016: MOD.259. Mastermodul.: Molekulare Zellbiologie als Analyseplattform in Medizin und Industrie
Crameri R. SS 2016: Nr. 439.006. Molekulare Zellbiologie in der Medikamentenentwicklung
Crameri R. SS 2016: Nr. 439.007. Molekulare Interaktionen als Target für therapeutische Interventionen

Awards

Sokolowska M. European Respiratory Society Long-term Fellowship Award, extension 01.10.2016-31.03.2017.

van de Veen W. Alain de Weck Travel Grant for the 31st Symposium of the Collegium International Allergologicum, Charleston, SC United States, May 2016.

Wirz OF. Outstanding Abstract Award. WAO International Scientific Conference (WISC 2016) in Jerusalem, Israel, 6-9 Dec 2016.

Degrees

Habilitation (Venia Legendi, PD):
O'Mahony L. Microbiot and Metabolite Regulation of Mucosal Immune Homeostasis, Universität Zurich

Public Seminars

05.01.2016: Ping-Chih Ho. Department of Fundamental Oncology, Ludwig Center for Cancer Research, University of Lausanne, Switzerland. Metabolically rewiring immune cells in cancer immunotherapy.

20.01.2016: Jeffrey M. Drazen. Editor-in-Chief, New England Journal of Medicine. Distinguished Parker B. Francis Professor of Medicine, Harvard Medical School, USA. Biophysical Characteristics of Airway Epithelial Cells.

14.03.2016: Davis Simoes. CellASIC ONIX the life cell imaging platform. Merck & Cie.

19.04.2016: CK-CARE Minisymposium
Dirk Haller, Technical University Munich, Germany, Chair Biofunctionality of Food. Microbiota Health and Disease.
Claudia-Tradl Hoffmann, Direktorin Institut für Umweltmedizin, Technische Universität München und Helmholtzzentrum München. Chefärztin Ambulanz für Umweltmedizin, Klinikum Augsburg. Skin and Microbiota.
Thomas Bieber, Chair, Department of Dermatology and Allergy, University of Bonn. Mechanisms of Atopic Dermatitis.

06. & 07.06.2016: Course on Practical Statistics for Biology / Medical Research
Avidan Neumann, Swiss Institute for Allergy and Asthma Research (SIAF), Davos, Switzerland.

21.06.2016: Zhikang Peng, University of Manitoba, College of Medicine, Faculty of Health Sciences, Department of Pediatrics and Child Health and Department of Immunology, Manitoba, Winnipeg, Canada. Therapeutic vaccines for treatment of allergic and autoimmune diseases.

04.07.2016: M. Selim Ünlü, Distinguished Professor of Engineering, Boston University, Boston, USA. Interferometric Reflectance Imaging Sensor (IRIS)—A Platform Technology for Multiplexed Diagnostics and Digital Detection.

08.07.2016: Emmanuella Guenova-Hötzenecker, Department of Dermatology/Allergology, Cantonal Hospital St. Gallen, Department of Dermatology, University Hospital Zurich.IL-4 in innate immunity and immunotherapy.
Wolfram Hötzenecker, Department of Dermatology/Allergology, Cantonal Hospital St. Gallen. From psoriasis to sepsis - the role of ROS in immunomodulation.

19.07.2016: Simone Oberhänsli, Roche Diagnostics International, Switzerland.The wheat powdery mildew genome.

21.07.2016: Hadi Jorjani, Department of Bioinformatics, Biozentrum, University of Basel, Switzerland. Swiss Institute of Bioinformatics, Switzerland. Computational Analysis of Next Generation Sequencing Data: From Transcription Start Sites in Bacteria to Human Non-coding RNAs.

22.07.2016: Alban Ramette, Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland. NGS analyses and biostatistics: from environmental microbes to paediatric epidemiology of respiratory diseases.

25.07.2016: Mari Mar Martín-Fontecha, Department of Organic Chemistry I, School of Chemistry, Complutense University of Madrid, Spain. Chemoproteomic approach to explore the target profile of GPCR ligands: application to 5-HT1A and 5-HT6 receptors.
Oscar Palomares, Department of Biochemistry and Molecular Biology I, School of Chemistry, Complutense University of Madrid, Spain. Cannibinoid sytem and immune regulation.

11.08.2016: Paul L. Bigliardi, A*STAR - Agency for Science, Technology and Research, Senior Consultant NUHS, Director of Academic Dermatology and Allergology NUHS, Board certified in Dermatology & Allergology/Clin Immunology, Director of Clinical Research Unit for Skin, Allergy and Regeneration CRUSAR/IMB, Senior PI Experimental Dermatology IMB/A*STAR, Singapore
Mei Bigliardi-Qi, Team leader Experimental Dermatology group IMB/A*STAR, Head of Operations Clinical Research Unit for Skin Allergy & Regeneration (CRUSAR), Singapore. Role of opioids in skin homeostasis and wound healing.

12.08.2016: Harald Renz, Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics, Philipps University Marburg, University Hospital Giessen and Marburg GmbH, Germany. Development of asthma – hygiene hypothesis, microbes and early life.

16.09.2016: R. Gerth van Wijk, Head Section of Allergology, Internal Medicine, Allergology, University Medical Center Rotterdam, The Netherlands, EAACI Past President. Positive and negative Allergen Immunotherapy trials. What makes the difference?

11.10.2016: Trevor Lockett, Commonwealth Scientific and Industrial Research Organisation (CSIRO),
Australia. Feeding the hungry gut microbiome for improved health.

24.10.2016: Emmanuel Karouzakis, Department of Rheumatology, University Hospital of Zurich,
Switzerland. The role of hydroxylmethylation and TET proteins in inflammation.

14.11.2016: Hubert Rehrauer, Head of Genomie Informatics, Functional Genomics Center Zurich,
ETH Zurich / University of Zurich, Switzerland. Developments in single cell technologies and data analysis in next generation sequencing.

30.11.2016: Máté Manczinger, Department of Dermatology and Allergology, University of Szeged, Hungary. The role of epitope-binding promiscuity of MHC II molecules in the adaptation to environmental pathogens.

02.12.2016: Minisymposium on immune-mediated skin diseases.
Sinem Bagci, Ludwig-Maximilian University, Department of Dermatology and Allergology, Munich, Germany. Ankara 29 Mayis Hospital, Department of Dermatology, Ankara, Turkey. Bullous pemphigoid - clinical spectrum, immunopathogenesis and treatment.
Thomas Ruzicka, Ludwig-Maximilian University, Department of Dermatology, Munich, Germany. Modern management of Atopic eczema.

13.12.2016: Christine Hosp, Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, Germany. Successful immunotherapy in a newly established mouse model of wasp venom allergy.

SIAF Science Day
15.12.2016
Altunbulakli C. Interaction between the microbiome and the transcriptome in lesional and non-lesional skin in atopic dermatitis patients.

Barcik W. Microbiota derived histamine - relevance to mucosal homeostasis.

Globinska A. Identification of angiogenesis-related B cell subsets.

Groeger D. Introducing a potentially novel anti viral fraction.

Rinaldi A. Epithelial barrier and its assessment by electrical impedance measurements.

Sabate Bresco M. Gene expression in a murine fracture model with and without infection.

Sokolowska M. Unique gene signature of allergen-specific CD4+T cells and Treg cells in allergic patients.

van de Veen W. B cell responses in STAT3 hyper-IgE patients.

Wawrzyniak M. Microbial-derived biogenic amines can influence host immune responses.

Wawrzyniak P. The role of CpG methylation in bronchial epithelial cells barrier integrity.

Wirz O. Rhinovirus infection in B cells.

Winner of the SIAF Science Day 2016: David Groeger

Scientific Posts

Akdis CA.
American Academy of Allergy, Asthma & Immunology (AAAAI) - Eczema Atopic Dermatitis Committee Member

American Academy of Allergy, Asthma & Immunology (AAAAI) - Cells and Mediators Committee, Board Member

Christine Kuehne - Center for Allergy Research and Education (CK-CARE) – Directorium member

COST Action BM0806 - Recent advances in histamine receptor H4 research member

National Institute of Health, USA - Scientific Advisory Board, Food Allergy, Allergen-Specific Immunotherapy

European Academy of Allergy Clinical Immunology (EAACI) - Executive Committee Member (2003-), President 2011-2013, Past President 2013-2015

European Asthma Research and Innovation Partnership (EARIP) - Member

Global Allergy and Asthma European Network GA2LEN - Member

World Immune Regulation Meeting - Chairman

Stanford University, School of Medicine, Department of Immunology, Sean Parker Allergy Center - Scientific Advisory Board Member

Akdis M.
Member of Life Sciences Zurich Graduate School-Zurich

World Immune Regulation Meeting - Member of the organizing committee

European Union Research Project, MedALL - Secretary General, Executive Committee Member, Work package leader

European Union Research, PreDicta - Steering board member, Work package leader

Stanford University, School of Medicine, Sean Parker Allergy Center - Scientific Advisory Board Member

Member of the World Allergy Organization Board of Directors.

Scientific Programme Committee Member, WISC, Jerusalem

Crameri R.
Academia Raetica - Co-founder and vice president (until May 25, 2016)

Graduate School Graubünden - Co-founder and vice president (until May 25, 2016)

Euronanomed Program “NANOASIT II” - Steering board member

Euronanomed Program “NANOASIT II” - Work package leader

Eurostars Projekt 8599 DIAPET - Steering board member

Eurostars Projekt 8599 DIAPET - Work package leader

Life Science UNI / ETH Zürich, PhD Program in Microbiology & Immunity - Member and Principal Investigator

EAACI CRD “Task Force on IgE assays in Allergy Diagnosis” - Member

Global Allergy Forum Davos - Member

Naturforschende Gesellschaft Davos - Advisory board member and treasurer

World Immune Regulation Meeting - Member of the organizing committee

Davos Diagnostics AG – Member of the board of directors

O’Mahony L.
EAACI Immunology Section Board Member 2011-2017

EAACI Immunology Section Chair 2015-2017

EAACI Executive Committee Member 2015-2017

Co-chair of the EAACI task force on “Role of Nutritional Factors in Immunomodulation” (2016-2017)

Management Committee Member to EU COST Action FA1402 – Improving Risk Assessment Strategies for Food Allergens (2014-2018)

Group leader for working group 3 in the EU COST Action FA1402 – Improving Risk Assessment Strategies for Food Allergens

World Immune Regulation Meeting - Member of the organizing committee

Scientific program committee member for the annual EAACI meeting, Vienna (2016)

Scientific program committee member for the 4th Food Allergy and Anaphylaxis Meeting (FAAM), Rome (2016)

Organizing committee member for the EAACI Immunology Winter School, Cortina (2016)

Scientific program committee member for ISMA, Luxembourg (2017)

Organizing committee member and Chair for the EAACI Master Class on Translational Immunology, Zürich (2016)

Rhyner C.
EAACI Interest Group „Omics and systems medicine", Secretary of the board

Member of Life Sciences Zurich Graduate School-Zurich

World Immune Regulation Meeting - Member of the organizing committee

Editorial Activities

Akdis CA.
Current Opinion in Immunology, editorial board member

European Journal of Immunology, editorial board member

Expert Opinion on Emerging Drugs, editorial board member

International Reviews of Immunology, editorial board member

Journal of Allergy and Clinical Immunology, co-editor-in-chief

Journal of Investigational Allergology and Clinical Immunology, editorial board member

Akdis M.
Allergy, editorial board member

International Archives of Allergy and Immunology, editorial board member

European Journal of Immunology, editorial board member

Journal of Allergy Clinical Immunology, editorial board member

Crameri R.
Allergy, associate editor

Mycoses, deputy editor

The open Immunology Journal, editorial advisory board member

O'Mahony L.
Allergy, member of the editorial board

Clinical and Translational Allergy, member of the editorial board

Rhyner C.
Allergy, member of the editorial board

Collaborations with the Clinics of Davos

- Hochgebirgsklinik Davos-Wolfgang (Prof. H.W. Duchna, Dr. M. Möhrenschlager, Dr. A. Kalweit, Prof. R. Lauener, Dr. C. Steiner, Dr. A. Kirsch)
- Nederlands Astmacentrum (Dr. L.H.M. Rijssenbeek-Nouwens)
- Spital Davos (Dr. J. Mattli, Dr. A. Speiser)
- Zürcher Höhenklinik Davos, Davos Clavadel (Dr. T. Rothe)

Collaborations outside Davos

Academic Medical Center, Amsterdam (NL)
-Deptartment of Cell Biology and Histology, (Prof. H. Spits)
-Department of Experimental Immunology, (Prof. H. Spits)
-Department of Pathology, (Prof. C. van Noesel)

Akdeniz University, Human Gene Therapy Unit, Antalya, (TR), (Prof. S. Sanlioglu)

ALK, Copenhagen (DK), (Dr. H. Jacobi, Dr. K. Lund, Dr. A. Millner, Dr. M. Spangfort, Dr. P.A. Würtzen)

Allergopharma GmbH & Co. KG., Reinbek (DE), (Dr. A. Nandy, Dr. C. Willers, Dr. H. Kahlert, Dr. Nadine Karschuk)

Allergy and Pulmonology Department, Postgraduate Center for Medical Education, Warsaw (PL), (Prof. M. Pirozynski)

Allgem. Krankenhaus (AKH) Wien (AT), Institut für Allgemeine und Experimentelle Pathologie, (Prof. H. Breiteneder, Dr. P. Ebersteiner, Prof. E.-J. Jarolim, Dr. S. Natter, Prof. O. Scheiner, Prof. R. Valenta, Dr. S. Vrtala)

AO Research Institute Davos, AO Foundation, Davos Platz (CH), (Dr. F. Moriarty, Prof. M. Alini, Dr. K. Thompson)

Beckman Research Institute, Department of Molecular and Cellular Biology, City of Hope, Duarte, CA (US), (Dr. M. Boldin)

Benaroya Research Institute at Virginia Mason; Department of Medicine, University of Washington, Seattle, WA, (US) (Dr. W. Kwok, Dr. E. James)

Bilkent University, Ankara (TR), (Prof. I. Gürsel)

Biochem. Institut, University of Zürich, Zürich (CH), (Prof. M. Grütter, Dr. P. Mittl)

Center for Inflammation Research, University of Edinburgh (UK), (Prof. J. Schwartze)

Centre Suisse d'Electronique et Microtechnique SA (CSEM) Landquart (CH), (S. Generelli)

Children's Hospital Srebrnjak, Department of Translational Medicine, Zagreb (HR), (Prof. M. Mercep)

Complutense University Madrid (ES), (Dr. O. Palomares, Dr. M. Martin-Fonseca)

Consejo Superior de Investigaciones Cientificas (CSIC), Madrid (ES), (Dr. C. Bernabéu)

East Switzerland Children's Hospital, St. Gallen (CH), (Prof. R. Lauener)

ETH Zürich (CH)
-Departement Pharmazie, (Prof. G. Folkers)
-Department of Biotechnology, (Prof. C. Lacroix)

Food Allergy Referral Centre Veneto Region, Padua General University Hospital, Padua (IT), (Prof. A. Muraro)

Forschungszentrum Borstel, Borstel (DE), (Prof. U. Jappe, Prof. H. Fehrenbach, Prof. Dr. O. Holst)

Functional Genomic Center Zurich (CH), (Prof. Dr. R. Schlapbach, Dr. H. Rehrauer, Dr. C. Aquino, Dr. F. Castro Giner, Dr. W. Wolski, Dr. P. Nanni, Dr. C. Fortes, Dr. G. Tan)

GlaxoSmithKline (GSK), Stevenage (UK), (Dr. E. Hessel, Dr. D. Michalovich)

Hacettepe University, Dept. Pediatrics, Ankara (TR), (Prof. O. Kalayci, Prof. C. Sackesen, Prof. E. Birben)

Icahn School of Medicine at Mount Sinai Immunology Institute, Department of Medicine, Division of Clinical Immunology, New York (US), (Prof. A. Cerutti)

Immunologie et Neurogénétique Expérimentales et Moléculaires (INEM) UMR7355, Department of Molecular Immunology, Orleans (FR), (Prof. B. Ryffel, Dr. D. Togbe)

Imperial College, London (UK), (Prof. S. Durham, Dr. K. Nouri-Aria, Dr. MH Shamji, Prof. S. Johnston)

Institut de Génétique et de Biologie Moléculaire et Cellulaire, Centre National de la Recherche Scientifique/Institut National de la Santé et de la Recherche Médicale/Université de Strasbourg, Illkirch, (FR), (Dr. M. Li)

Institut Pasteur, Paris (FR), (Prof. J.P. Latgé, Dr. S. Paris)

Jagiellonian University, Krakow (PL), (Prof. M. Sanak, Dr. B. Jakiela)

Kantonsspital Basel, Abt. Dermatologie (CH), (Prof. A. Bircher)

Kantonsspital Chur, Department ENT, Chur (CH), (Dr. HB. Fahrner)

Karolinska Hospital, Stockholm (SE), (Prof. Dr. G. Gavfelin, Dr. H. Grönlund, Prof. O. Rasool, Prof. A. Scheynius, Prof. M. van Hage, Dr. S. Thunberg)

Ludwig Maximilians Universität, Department of Pathology, Munich (DE), (PD Dr. J. Neumann)

Marmara University, Istanbul (TR), (Prof. T. Akkoç, Prof. C. Özdemir)

Max-Planck Institute for Molecular Genetics, Berlin-Dahlem (DE), (Dr. Z. Konthur, Prof. H. Lehrach)

Medical University of Bialystok, Department of Regenerative Medicine and Immune Regulation (PL), (Prof. M. Moniuszko, Dr. A. Eljaszewicz)

Medical University of Brasov, (RO), (Prof. I. Agache, Dr. C. Agache)

Medical University of Lodz, Lodz (PL), (Prof. M. Kowalski)

Medical University of Vienna, Au, Department of Pediatrics, Vienna (AT), (Dr. T. Eiwegger, Prof. Z. Scephaluzi)

Monash University, Department of Immunology, Melbourne (AU), (Dr. M. van Zelm)

Novartis, Basel (CH), (Dr. C.H. Heusser)

Paul-Ehrlich-Institut, Langen (DE), (Dr. E. Flory, Prof. S. Vieths)

Paul Scherrer Institute (CH), (Prof. R. Schibli, Dr. R. Waibel)

Philipps University of Marburg, Medical Faculty Marburg (DE), (Prof. H. Garn and Prof. H. Renz)

Rätisches Kantons- und Regionalspital, Chur (CH), (Dr. M. Kuhn, Prof. W. Reinhart, Prof. T. Fehr, Dr. E. Riedi)

Red Cross Finland, Blood Service, Stem Cell, Transplantation Services, Research Laboratory, Helsinki (FI), (Dr. N. Woolley)

Sean N. Parker Center for Allergy Research at Stanford University (US), (Prof. K. Nadeau)

Stanford University, Department of Pathology (US), (Dr. S. Boyd)

Swiss EoE Research Network, Olten, (CH), (Prof A. Straumann)

Tartu University Hospital, Dermatology Clinic, Tartu (EE) (Prof. K. Kingo)

Technische Universität München (DE)
- Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, (Prof. J. Ring)
- Forschungszentrum für Umwelt und Gesundheit, (Prof. C. Schmidt-Weber, Prof. Dr. E. Renner, Prof. Dr. C. Traidl-Hoffmann) The Hospital for Sick Children, Cancer and Blood Research Program, Toronto (CN), (Dr. M. Letarte)

The Netherlands Cancer Institute, Divison of Cellular Biochemistry, Amsterdam (NL), (Prof. P. ten Dijke, Dr. S. Itoh)

Uludag University of Bursa, Bursa (TR), (Prof. H.B. Oral, Prof. F. Budak)

Universität Bern, Dept. Clinical Vet. Medicine (CH), (PD Dr. E. Marti, Prof. A. Zurbriggen)

Universität Graz (AT)
-Deptartement of Pediatrics, (Dr. E.M. Varga)
-Inst. Pharm. Chem., (Prof. A. Kungl)

Universitätsklinikum Freiburg, COPD & Asthma Researchgroup (CARG), Abtl. für Pneumologie, Freiburg (DE), (PD Dr. M. Idzko)

Universität Salzburg, Salzburg (AT), (Prof. Emeritus M. Breitenbach)

Universität Zürich, Clinical Trials Center (CH), (PD Dr. G. Senti)

Universitätsspital Bern (CH)
- Kinderklinik, Inselspital, (Prof. R. Kraemer, Dr. C. Aebischer-Casaulta, Prof. M.H. Schöni)
- Universitätsklinik für Rheumatologie, Immunologie und Allergologie, Inselspital, (Prof. A. Helbling, Dr. A. Gschwend)
- Universitätsklinik für Hals-, Nasen- und Ohrenkrankheiten, Kopf- und Halschirurgie, (Dr. U. Borner, Dr. S. Negoias, Dr. S.-L. Hool)

Universitätsspital Zürich (CH)
- Abteilung für Klinische Immunologie, (Prof. Dr. O. Boyman)
- Abteilung ENT, (PD Dr. D. Holzmann, PD Dr. M. Soyka)
- Abfteilung Pneumologie, (Prof. Dr. M. Kohler, PD Dr. C. Clarenbach)
- Abteilung Gastroenterologie, (Prof. R. Gerhard)
- Abteilung Kardiologie, (Prof. F. Duru, Dr. D. Akdis)
- Dermatologische Klinik, (Prof. R. Dummer, PD Dr. Th. Kündig, PD Dr. P. Schmid-Grendelmeier, PD Dr. B. Ballmer-Weber, PD Dr. E. Guenova, PD Dr. G. Hofbauer, Prof. L. Frenc)
- Kinderspital, (Prof. J. Reichenbach, Prof. R. Lauener, Dr. C. Roduit, Dr. A. Jung)
- Vetsuisse Fakultät, (Prof. Dr. C. Favrot, Dr. A. Rostaher)

University of Cape Town, Department of Dematology (ZA), (Assoc Prof. M. Levin, Dr. C. Hlela)

University College Cork, Alimentary Pharmabiotic Centre (IE), (Prof. F. Shanahan and Prof. D. van Sinderen)

University of Istanbul, Institute of Experimental and Medical Research, Istanbul (TR), (Prof. G. Deniz, Prof. Dr. G. Erten, Prof. Dr. U. Kücüksezer)

University of Lausanne, Department of Biochemistry, Lausanne (CH), (Prof. M. Thome, Prof. G. Guarda)

University of Natural Resources and Life Sciences, BOKU Wien (AT), (Dr. F. Altmann)

University of Szeged, Department of Dermatology and Allergology, Szeged (HU) (Dr. N. Nagy, Prof. L. Kemeny)

University of Tartu, Institute of Biomedicine and Translational Medicine, Tartu (EE), (Dr. A. Rebane, Prof. P. Peterson)

Wroclaw Medical University, Wroclaw (PL), (Prof. M. Jutel, Dr. S. Smolinska, Dr. P. Gajdanowicz)

Schweizerisches Institut für Allergie- und Asthmaforschung

Bilanz per 31. Dezember 2016

(inklusive Drittmittel)

	31.12.2016	31.12.2015
	CHF	CHF
AKTIVEN		
Flüssige Mittel	1'606'386.74	1'976'206.35
Forderungen	96'641.70	170'272.04
Aktive Rechnungsabgrenzungen	274'267.15	368'924.84
	1'977'295.59	2'515'403.23
PASSIVEN		
Verbindlichkeiten	174'902.00	226'343.83
Kontokorrent SFI Stiftung	21'369.40	77'486.25
Passive Rechnungsabgrenzungen	1'203'688.57	1'634'936.85
Rückstellungen	357'179.81	357'179.81
Eigenkapital	220'155.81	219'456.49
	1'977'295.59	2'515'403.23

Schweizerisches Institut für Allergie- und Asthmaforschung

Betriebsrechnung 2016

(inklusive Drittmittel)

	Rechnung 2016	Budget 2016	Rechnung 2015
	CHF	CHF	CHF
ERTRAG			
Beitrag Bund Forschungsgesetz Art. 16	828'200.00	840'000.00	843'000.00
Beitrag Kanton Graubünden	290'000.00	290'000.00	290'000.00
Beitrag Gemeinde Davos	424'560.00	424'560.00	424'560.00
Beitrag Universität Zürich	369'303.15	330'000.00	657'078.70
Beitrag Stiftung SFI Villa Fontana	100'000.00	100'000.00	100'000.00
Beitrag Stiftung SFI Mieterlass	160'000.00	160'000.00	160'000.00
Beitrag Stiftung vormals Bündner Heilstätte Arosa	50'000.00	75'000.00	75'000.00
Beitrag Stiftungen/Drittmittel	54'703.60	0	233'000.00
Einnahmen Miete an AHPD	31'740.00	19'200.00	0
Overheadbeiträge	91'404.00	92'507.00	99'767.00
Ertrag aus Dienstleistung Asthmaforschung	0	2'500.00	- 400.00
Übriger Ertrag	7'742.69	3'000.00	55'428.57
Finanzertrag	806.77	0	41.35
Ausserordentlicher Ertrag	34'063.50	0	0
WIRM-Kongress	319'188.76	450'000.00	351'235.26
Drittmittel	2'401'700.51	2'053'943.00	2'468'864.36
	5'163'412.98	4'840'710.00	5'757'575.24
AUFWAND			
Personalaufwand	3'086'478.58	2'730'420.00	2'997'068.68
Verbrauchsmaterial	976'583.22	985'001.00	1'131'649.61
Raumaufwand	180'397.90	182'760.00	170'077.70
Unterhalt/Reparaturen/Ersatz	124'722.80	115'500.00	109'144.02
Investitionen	211'298.25	195'000.00	737'402.41
Sachversicherungen/Abgaben	7'628.20	7'500.00	8'162.85
Energie- und Entsorgungsaufwand	62'442.45	77'029.00	67'537.40
Verwaltungsaufwand	119'705.62	156'500.00	142'932.14
Reisespesen	93'200.17	75'000.00	103'456.52
WIRM-Kongress	290'395.94	306'500.00	268'146.18
Übriger Betriebsaufwand	7'532.23	3'000.00	14'394.50
Finanzaufwand	2'328.30	1'000.00	3'006.15
Ausserordentlicher Aufwand	0	5'500.00	4'597.08
	5'162'713.66	4'840'710.00	5'757'575.24
Ergebnis	699.32	0	0
	5'163'412.98	4'840'710.00	5'757'575.24

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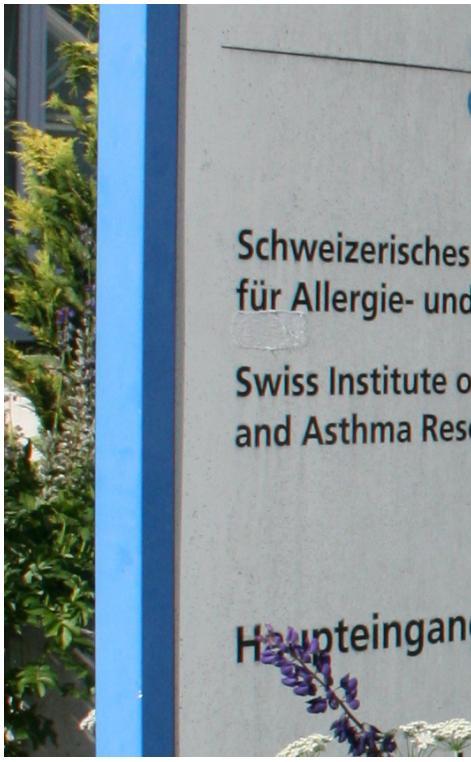

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