SIAF

ANNUAL REPORT 2017

University of Zurich[UZH]

Index

Schweizerisches Institut für Allergie- und Asthmaforschung SIAF

Über das SIAF

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

Bericht des Direktors

Prof. Dr. Cezmi A. Akdis

1988 wurde das Schweizerische Institut für Allergie- und Asthmaforschung (SIAF) in seiner heutigen Form von der Medizinischen Abteilung der Stiftung Schweizerisches Forschungsinstitut für Hochgebirgsklima und Medizin Davos (SFI) gegründet. Seit 1996 ist das Institut 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. Weiter ist das SIAF aktives Mitglied der Academia Raetica und der Graduate School Graubünden.

Die Forschung am SIAF konzentriert sich auf die patientenrelevante translationale Forschung und Untersuchung der immunologischen Grundlagen allergischer und asthmatischer Erkrankungen, die Ansatzpunkte für neue präventive und kurative Behandlungen zugunsten der Betroffenen schafft. Das SIAF setzt sich auch verstärkt für eine personalisierte Medizin ein, damit Behandlungsansätze entwickelt werden können, die besser auf den einzelnen Patienten zugeschnitten sind, und welche die individuelle Symptomausprägung des jeweiligen Patienten stärker berücksichtigt. Nicht nur massgeschneiderte Behandlungstherapien, sondern auch präzisere Diagnosen erhofft man sich von der personalisierten Medizin. 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), der Europäischen Akademie für Allergologie und klinische Immunologie (EAACI) sowie der Amerikanischen Akademie für Allergie, Asthma und Immunologie (AAAAI) eingebunden. Die EAACI ist die weltgrösste Akademie für allergische Erkrankungen und übernimmt eine wichtige Rolle in Bezug auf Wissenschaft, Weiterbildung, Kommunikation und Öffentlichkeitsarbeit. Mit der Universität Stanford (Sean Parker Asthma and Allergy Center) besteht eine intensive Zusammenarbeit.

Das SIAF hat über 1'200 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 45 Mitarbeitern weltweit zu den Besten in Bezug auf seine Grösse. In den letzten Jahren konnte eine signifikante Erhöhung der Anzahl Zitierungen erreicht werden. Es ist eine international bekannte Ausbildungsstätte für Doktoranden und Habilitanden.
2017 wurden 84 wissenschaftliche Arbeiten in begutachteten internationalen Fachzeitschriften mit “Impact Factor” veröffentlicht oder sind noch in Druck. 2017 erreichte das SIAF einen Gesamtwert des “Impact Factors” von 636.429 und einen Durchschnitt von 7.577 Punkten pro Publikation. Die neusten Ergebnisse wurden zudem in 31 Abstracts an verschiedenen Fachtagungen mitgeteilt. Unsere Mitarbeitenden wurden zu 84 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 28 verschiedenen Sessionen hatten SIAF-Mitarbeitende den Vorsitz. Zusätzlich werden 39 wissenschaftliche Ämter in internationalen Gesellschaften durch Wissenschaftler des SIAF besetzt. Desweiteren sind die Forscher des SIAF bei insgesamt 17 internationalen Zeitschriften als Mitglieder der redaktionellen Komitees tätig. Zudem hält Prof. C. A. Akdis seit März 2018 das Amt des Chefredaktors der Fachzeitschrift Allergy inne.

Das SIAF und das Christine-Kühne Center for Allergy Research and Education (CK-CARE) in Davos-Wolfgang spielen in ihren Bereichen je eine international tragende Rolle. Das SIAF ist eines der weltweit führenden Forschungsinstitute im Bereich der Allergien und Asthma; die CK-CARE ist ein privat finanziertes Allergieforschungs- und Ausbildungsprojekt. 2014 wurde im Zusammenhang mit der Lancierung der neuen Hochgebirgsklinik Davos-Wolfgang (HGK) entschieden, die Idee des SFI/SIAF, der CK-CARE AG und der HGK für einen gemeinsamen Campus für Allergie-und Asthmaforschung an diesem Standort umzusetzen. Auf dem Gelände der Klinik wird deshalb im Rahmen der gesamten Immobilienentwicklung an geeignetem Ort ergänzend ein neuer Campusteil für das SIAF und die CK-CARE erstellt, das Grundlagenforschung, klinische Forschung, klinische und ambulante Versorgung, Entwicklung von Therapien, Lehre/Edukation von Studierenden und Ärztinnen und Ärzten sowie Kongresse, Tagungen, Seminare und Workshops, an ein und demselben Ort vereint. Auch dank der räumlichen und organisatorischen Nähe kommen die Ergebnisse der Forschung direkt den Patienten in der Klinik zu Gute. Im Gegenzug profitiert die Forschung vom Zugang zu Behandlungsschwerpunkten. Die Erkenntnisse aus dieser einmaligen Kollaboration werden durch gezielte Aus- und Weiterbildungsmassnahmen in die Welt hinausgetragen. Dank der Unterstützung durch die CK-CARE konnten seit 2009 mehr als 42 wissenschaftliche Mitarbeitende eingestellt und über 68 akademische Gäste im Austauschprogramm aufgenommen werden. Darüber hinaus wurden 150 Publikationen in namhaften Zeitschriften veröffentlicht.

Personalisierte Medizin, «Big Data-» und Bioinformatik Projekte
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 Bedeutung 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 dem Gebiet von Allergien und Asthma antworten zu können. Die Anzahl Projekte nahm zu und wir weiteten diese in den letzten zwei Jahren auf andere Omics-Technologien 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, zwei Research Fellows, die sich auf die Forschung von Omics-Methoden konzentrieren und drei Research Fellows, welche sich der Hightech-Bioinformatik in der Medizin widmen. Nebst der wachsenden Anzahl dieser Projekte wird auch die Infrastruktur für diese Forschung angepasst und die Mitarbeiter weiter geschult.
In den letzten fünf Jahren haben wir eine starke Zusammenarbeit mit dem Functional Genomic Center der Universität Zürich und der Stanford University (Sean Parker Asthma and Allergy Center) aufbauen können. Das SIAF und die Stanford Universität pflegen eine starke Zusammenarbeit mit Austausch von Material und Daten, Veröffentlichung von Publikationen und Entwicklung von geistigem Eigentum.

Unser Verständnis über die pathophysiologischen Prozesse allergischer Erkrankungen hat dank fundamentaler Erkenntnisse in der Grundlagen- und Translationsforschung bedeutend zugenommen. Folglich hat sich die Sicht auf die Pathophysiologie von allergischen Erkrankungen von einem einfachen Ansatz mit Fokus auf Symptome und Organfunktionen in Richtung Wahrnehmung eines komplexen Netzwerkes von immunologischen und biochemischen Abläufen verbessert. Krankheiten, die sich in der Art der Entzündung und in der Komplexität der immunregulatorischen Netzwerken ähneln, zeigen einen neuen Ansatzweg zur präzisen Diagnostik und gezielten Behandlung auf. Die vier Schlüsselwörter Endotyp, Phänotyp, Theratyp und Biomarker sind heute die Forschungsschwerpunkte, die zu einer personalisierten Medizin und personalisierten Gesundheitsversorgung führen.
Von Endotyp spricht man in der Allergologie, wenn von den Mechanismen die Rede ist, die einer allergischen Erkrankung zugrunde liegen. Wohingegen der Phänotyp das Erscheinungsbild eines Organismus bezeichnet, d.h. seine tatsächlichen morphologischen und physiologischen Eigenschaften - unabhängig davon, ob sie vererbt oder erworben wurden. In diesem Zusammenhang spricht man oft auch von Biomarkern. Biomarker sind charakteristische biologische Merkmale, die objektiv gemessen werden können und auf einen normalen biologischen oder krankhaften Prozess im Körper hinweisen können und haben prognostische oder diagnostische Aussagekraft. Ein neues Schlüsselwort, das in diesem Kontext auftaucht, ist das Wort Theratyp. Es beschreibt die Gruppe von Patienten, welche aufgrund ihrer gleichen Symptome auch auf dieselbe Behandlung ansprechen. Diese vier Schlüsselwörter werden in Zukunft dem Ziel dienen, die Patientenversorgung zu revolutionieren, um so den Weg für die personalisierte Medizin und personalisierte Gesundheitsversorgung zu ebnen.

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, Lehrverpflichtungen, Kongress
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. Diese bestehen aus verschiedenen Vorlesungsstunden im Rahmen der Biochemie am Biochemischen Institut. Prof. R. Crameri ist zusätzlich 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 und Honorarprofessor an der Bezmialem Universität Istanbul. Prof. C. A. Akdis und Prof. M. Akdis haben zudem eine Honorarprofessur am Tungren Spital der Peking-Universität.

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 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. Die zusätzlichen Ausgaben wurden aus Erträgen von zusätzlichen kompetitiv eingeworbenen 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 wertvolle Unterstützung unseres Institutes.

Insbesondere möchte ich hier unsere fruchtbare Zusammenarbeit mit der CK-CARE betonen, welche uns patientenorientierte Forschung in der atopischen Dermatitis 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 kantonalen und Davoser Behörden, die die Forschung des SIAF unermüdlich unterstützen und das Institut in jeder Hinsicht fördern.

Davos, Juni 2018

Report of the director

Prof. Dr. Cezmi A. Akdis

The Swiss Institute for Allergy and Asthma Research (SIAF) was founded in 1988 in its present form by the Medical Department of the Swiss Research Institute for High Altitude Climate and Medicine Davos (SFI). Since 1996, the institute has been affiliated with the University of Zurich and since 2008 it is a member of the Life Science Zurich Graduate School, a joint post graduate education project of the University of Zurich and the ETH Zurich. Furthermore, the SIAF is an active member of the Academia Raetica and the Graduate School of the Canton of Grissons.

Research at the SIAF focuses on patient-relevant translational research and the study of the immunological basis of allergic and asthmatic diseases, which provides a starting point for new preventative and curative treatments in favor of those affected. The SIAF is also increasing its commitment to personalized medicine projects to develop treatment approaches that are better tailored to each patient and that take greater account of each patient's individual symptom severity.
The research in SIAF has been designed for direct cooperation with the clinics in Davos, the University of Zurich and other specialized institutes. The SIAF is also involved in the European Network of National Competence Centers (GA2LEN: Global Allergy and Asthma European Network of Excellence), the European Academy of Allergology and Clinical Immunology (EAACI) and the American Academy of Allergy, Asthma and Immunology (AAAAI). The EAACI is the world's largest academy for allergic diseases and plays an important role in science, education, communication and public relations. The collaboration with University of Stanford (Sean Parker Asthma and Allergy Center) is working intensively and several projects.

The SIAF has published over 1,200 research articles and is one of the most cited institutions of its size worldwide. The articles published by the SIAF have been cited more than 45'000 times. The institute with its approximately 45 employees is one of the best in terms of number of employees or citation divided by budget worldwide. In recent years, a significant increase in the number of citations has been achieved as an internationally renowned training center for doctoral students and post-doctoral candidates who join SIAF groups with their own country or institutional stipends.
In 2017, 84 scientific papers were published in peer-reviewed international journals with "Impact Factor" or are still in print. The SIAF achieved a total value of the impact factor of 636,429 and an average of 7,577 points per publication. The latest results were also communicated in 31 abstracts at various symposia. Our employees were invited to 84 different seminars and lectures at national and international congresses. SIAF co-workers chaired 28 different international sessions. In addition, 39 scientific posts in international organizations are being occupied by scientists of the SIAF. Furthermore, the SIAF researchers are members of the editorial committees of a total of 17 international journals. In addition, Prof. C. A. Akdis holds the position of Editor-in-Chief of the Allergy journal since March 2018.

The SIAF and the Christine-Kühne Center for Allergy Research and Education (CK-CARE) in Davos-Wolfgang each play an internationally leading role in their respective fields. The SIAF is one of the world's leading research institutes in the field of allergies and asthma; CK-CARE is a privately funded allergy research and education project. In 2014, in connection with the launch of the new high mountain clinic Davos-Wolfgang (HGK), it was decided to implement the idea of the SFI / SIAF, CK-CARE AG and HGK for a joint campus for allergy and asthma research at this location. For this reason, a new campus section for the SIAF and the CK-CARE is being created on the grounds of the clinic as part of the overall real estate development at a suitable location: basic research, clinical research, clinical and outpatient care, development of therapies, teaching / training of students and physicians, as well as congresses, meetings, seminars and workshops, united in the same place. Thanks to the spatial and organizational proximity, the results of the research will directly benefit the patients in the clinic. The findings from this unique collaboration are being carried out through targeted education and training measures in the area of allergic skin diseases, namely atopic dermatitis. Thanks to the support of CK-CARE, more than 42 scientific staff have been recruited since 2009 and more than 68 academic guests have joined the exchange fellowship program. 150 publications were published in high impact journals.

Personalized medicine, big data and bioinformatics projects
The SIAF has more than 15 years of experience in performing Gene Array Transcriptomic. As systems biology approaches and the analysis of large amounts of data became more important, four years ago, we began to apply omics methods, most of them the next-generation RNA sequencing transcriptomics, to address a range of important issues in the field of allergies and asthma. The number of projects has increased and we have extended these to other omics methods in the last two years.
Parallel to this, since 2013 the SIAF has established an efficient research group for high-tech medicine, bioinformatics and omics methods. There are currently two experts in bioinformatics at the SIAF, two research fellows focused on the research of omics methods and three research fellows dedicated to high technology bioinformatics in medicine. In addition to the growing number of these projects, the infrastructure for this research is being adapted and the students and post docs trained. Over the past five years, we have built strong collaboration with the Functional Genomic Center of the University of Zurich and Stanford University (Sean Parker Asthma and Allergy Center). The SIAF and Stanford University maintain a strong collaboration with sharing material and data, publishing and developing intellectual property together.

Our understanding of the pathophysiological processes of allergic diseases has significantly increased thanks to fundamental findings in basic and translational research. Consequently, the view of the pathophysiology of allergic diseases has improved from a simple approach focusing on symptoms and organ functions towards the perception of a complex network of immunological and biochemical processes. Diseases similar in the type of inflammation and in the complexity of the immunoregulatory networks show a new approach to precise diagnosis and targeted treatment. The four key words endotype, phenotype, theratype and biomarker are the main research areas that lead to personalized medicine and personalized healthcare.
Endotype is the term used in allergology when referring to the mechanisms underlying an allergic disease. Whereas the phenotype refers to the clinical visible property, whether inherited or acquired. In this context, biomarkers are characteristic biological features that can be measured objectively and indicate a normal biological or pathological process in the body and have prognostic or diagnostic value. A new keyword that appears in this context is the word theratype. It describes the group of patients who also respond to the same treatment because of their same symptoms. These four keywords will be used in the future to revolutionize patient care, paving the way for personalized medicine and personalized healthcare.

Clinical service
The SIAF offers to Davos and all other interested clinics and practicing physicians special cellular immunological diagnosis. By means of the flow cytometric analysis of blood, bronchoalveolar lavage (BAL), but also other tissue fluids, the different immune cells and subpopulations are measured in their development, their proportions and their activation state.

Education, teaching, congresses
An important task has been fulfilled by the SIAF in the education of PhD students as well as in postgraduate studies. At the same time, the SIAF fulfills teaching obligations at the University of Zurich. These consist of various lecture courses within the framework of biochemistry at the Biochemical Institute. Prof. R. Crameri is also involved in the block lecture "Molecular Genetic Foundations of Immunology" of the University of Salzburg. Prof. C. A. Akdis is a faculty member of the Medical Faculty of the University of Zurich with promotion rights in the Faculty of Mathematics and Natural Sciences and honorary professor at the Bezmialem University of Istanbul. Prof. C. A. Akdis and Prof. M. Akdis also hold an honorary professorship at the Tungren Hospital of Beijing University.

From 15 to 18 March 2017, the internationally reknown World Immune Regulation Meeting (WIRM) took place for the eleventh time in the Davos Congress Center. Around 600 scientists from 40 different countries came to this congress to discuss the latest findings in immunology and delivered 125 lectures and 238 abstracts. During the day participants took part in top-class scientific lectures. The evenings in the congress center were reserved to present scientific projects in the form of a poster exhibition. The congress and other SIAF activities generate around 4,000 overnight stays each year in the Davos hotels and holiday apartments.

Financial basis
The expenditures and the financial return of the SIAF have changed only insignificantly compared to the past years. A basic funding of the institute is currently ensured by the main sponsors. It mainly consists of a federal contribution (Forschungsförderungsgesetz Art. 15), contributions from the canton of Graubünden and the municipality of Davos, contributions by CK-CARE AG and the University of Zurich. The additional expenses were covered by additional competitive third-party funding and the WIRM Congress.

Thanks
I cordially thank all our employees for the great work and the good working atmosphere in the SIAF. At the same time, I would like to thank the Davos-based clinics, their chief physicians and their employees. I am extremely honoured with our continuous collaboration with the University of Zurich for the immense support of our institute.

In particular, I would like to emphasize here our fruitful collaboration with CK-CARE, which enables patient-oriented atopic dermatitis research in our institute. I would particularly like to thank Ms. and Mr. Kühne for their support, which enables our research to find sustainable solutions for better diagnosis and treatment of atopic dermatitis patients. Thanks to this support, many master's degrees and PhD titles have been obtained at the institute and in Davos.

My thanks go especially to the Foundation Swiss Research Institute for Mountain Climate and Medicine (SFI), its Foundation Council and Foundation Committee for the continuous support. Last but not least, I would like to thank the authorities in Cantonal and Davos institutions, who tirelessly support SIAF in every respect.

Davos, June 2018

Plenary Session during WIRM in the Congess Center Davos.

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Report of the director

Director
Akdis Cezmi A. Prof., MD ***

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Bärenfaller Katja PD, PhD, Head Molekulare Allergologie (from September 2017)
Crameri Reto Prof., PhD, Head Molecular Allergology * (- July 2017)
O'Mahony Liam PD, PhD, Head Molecular Immunology *
Rhyner Claudio PhD, Head Vaccine Development *

SIAF Administration
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Wirz Oliver	PhD student ***

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Geiger Lucas, Charité Berlin, Germany
Graversen Katrine, National Food Institute DTU Soeborg, Denmark
Jutel Marek, ALL-MED Medical Research Institute Breslau, Poland
Komlosi Zsolt, Semmelweis University Budapest, Hungary
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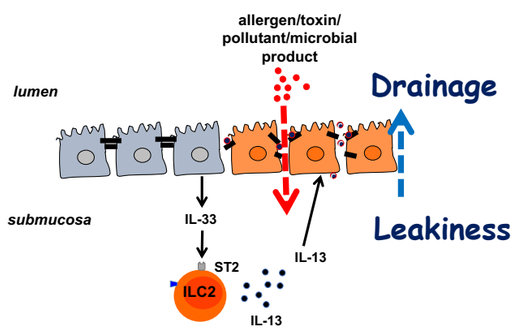
Salary paid by
* SIAF
** Swiss National Science Foundation
*** Other

Prof. Dr. Cezmi A. Akdis

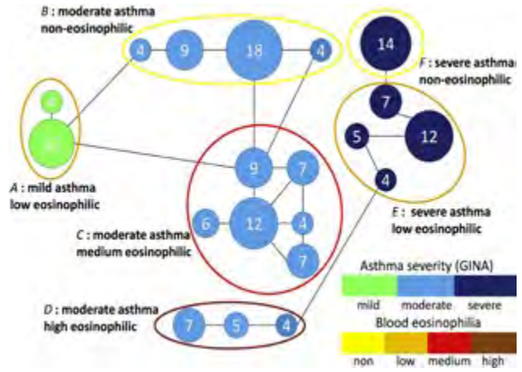
Type 2 innate lymphoid cells (ILC2s) contribute to lung inflammation and asthma development. They produce large amounts of IL-5 and IL-13 in response to alarmins, such as IL-25 and IL-33, thereby leading to eosinophilia and goblet cell hyperplasia at bronchial surfaces, both of which are critical for asthma pathogenesis. Moreover, ILC2s facilitate IgE and T cell responses to local TH2-inducing allergens and mediate TH2 cell differentiation through dendritic cells.

Their proximity to epithelial barriers and enrichment at these barriers enable ILC2s to respond rapidly to allergens on bronchial surfaces. Disruption of the epithelial barrier and responses to allergens or environmental pollutants are important early events in asthma development. Together with previous reports on mice and human subjects, these results provide evidence for the possible redundancy of the immunologic function of ILCs in the presence of the adaptive immune system. We have recently reported two important findings as summarized below, namely their role in epithelial barrier (Figure 1) and their interaction with NK cells.

ILC2s disrupt bronchial epithelial TJ barrier via IL-13



Asthma phenotypes describe clinical and morphologic characteristics, as well as unique responses to different treatments. Although potentially clinically relevant, phenotypes do not necessarily relate to or provide insights into the underlying physiopathologic processes, asthma endotypes uncover molecular mechanisms underlying phenotypes. Identification of corresponding molecular biomarkers for each pathogenic mechanism operating within a phenotype is required to link the phenotype to a disease endotype. We are also reporting below a new concept on multidimentional monitoring inflammatory heterogeneity with multiple biomarkers for multidimensional endotyping of asthma (Figure 2).



Type 3 innate lymphoid cells induce proliferation of CD94+ natural killer cells.
Li S, Morita H, Rückert B, Boonpiyathad T, Neumann A, Akdis CA.
J Allergy Clin Immunol. 2017 Oct;140(4):1156-1159
To understand how ILCs might bridge innate and adaptive immunity or further contribute to the expansion of innate immune cells, we asked whether ILCs might affect other immune cells within their surroundings. Using a coculture model, we discovered that ILC3s negative for natural cytotoxicity receptor NKp44 drive a rapid and dramatic expansion of CD94+ natural killer (NK) cells. Our findings suggest that ILC3s may also be involved in innate immunity against tumors and viral infections by rapid expansion of NK or NK-like cells. NK cell memory was reported in recent studies, but mechanisms remain unknown. ILC3 might play a role in NK cell memory development and/or recall. Such a link will provide opportunities for clinical translations, such as in allergy and cancer treatment.

Type 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions through IL-13 in asthmatic patients.
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.
J Allergy Clin Immunol. 2018 Jan;141(1):300-310.
Bronchial epithelial barrier leakiness and type 2 innate lymphoid cells (ILC2s) have been separately linked to asthma pathogenesis; however, the influence of ILC2s on the bronchial epithelial barrier has not been investigated previously. We investigated the role of ILC2s in the regulation of bronchial epithelial tight junctions (TJs) and barrier function both in bronchial epithelial cells of asthmatic patients and healthy subjects and general innate lymphoid cell- and ILC2-deficient mice. Cocultures of human ILC2s and bronchial epithelial cells were used to determine transepithelial electrical resistance, paracellular flux, and TJ mRNA and protein expressions. The effect of ILC2s on TJs was examined by using a murine model of IL-33-induced airway inflammation in wild-type, recombination-activating gene 2 (Rag2)-/-, Rag2-/-Il2rg-/-, and Rorasg/sg mice undergoing bone marrow transplantation to analyze the in vivo relevance of barrier disruption by ILC2s. ILC2s significantly impaired the epithelial barrier, as demonstrated by reduced transepithelial electrical resistance and increased fluorescein isothiocyanate-dextran permeability in air-liquid interface cultures of human bronchial epithelial cells. This was in parallel to decreased mRNAs and disrupted protein expression of TJ proteins and was restored by neutralization of IL-13. Intranasal administration of recombinant IL-33 to wild-type and Rag2-/- mice lacking T and B cells triggered TJ disruption, whereas Rag2-/-Il2rg-/- and Rorasg/sg mice undergoing bone marrow transplantation that lack ILC2s did not show any barrier leakiness. Direct nasal administration of IL-13 was sufficient to induce deficiency in the TJ barrier in the bronchial epithelium of mice in vivo. These data highlight an essential mechanism in asthma pathogenesis by demonstrating that ILC2s are responsible for bronchial epithelial TJ barrier leakiness through IL-13.

Monitoring inflammatory heterogeneity with multiple biomarkers for multidimensional endotyping of asthma.
Agache I, Strasser DS, Pierlot GM, Farine H, Izuhara K, Akdis CA.
J Allergy Clin Immunol. 2018 Jan;141(1):442-445.
In this study we used topological data analysis (TDA) to characterize adult asthmatic patients based on exhaustive clinical characterization and blood biomarkers. One hundred asthmatic patients underwent detailed clinical assessment, evaluation of asthma severity (Global Initiative for Asthma [GINA]) and control (Asthma Control Test). Measurement of lung function, fraction of exhaled nitric oxide levels, blood eosinophil and neutrophil counts, and levels of the following serum biomarkers: total IgE, IL-4, IL-5, IL-13, periostin, eotaxin-1, eosinophil-derived neurotoxin (EDN), dipeptidyl-peptidase 4 inhibitor (DPP4), IL-8, monocyte chemoattractant protein 1, TNF-α, IFN-γ, IFN-γ–induced protein 10, IL-17α, and IL-33. All evaluations were done outside an asthma exacerbation or a respiratory tract infection (minimum of 2-week washout period was required, including for oral corticosteroids). Six clusters of multidimentional endotypes were identified, such as mild non-eosinophilic, moderate non-eosinophilic, moderate medium eosinophilic, moderate high eosinophilic, severe non-eosinophilic, severe low eosinophilic asthma. Our study indicates that multidimensional endotyping is needed both for type 2 and non–type 2 asthma. Therefore, the use of multiple biomarkers is recommended to provide evidence that a certain pathway is the key driver for a given patient. In particular, additional biomarkers, such as IL-5, IL-13, DPP4, eotaxin, and periostin, might refine responder selection for type 2 targeted therapies.

miR-146b Probably Assists miRNA-146a in the Suppression of Keratinocyte Proliferation and Inflammatory Responses in Psoriasis.
Hermann H, Runnel T, Aab A, Baurecht H, Rodriguez E, Magilnick N, Urgard E, Šahmatova L, Prans E, Maslovskaja J, Abram K, Karelson M, Kaldvee B, Reemann P, Haljasorg U, Rückert B, Wawrzyniak P, Weichenthal M, Mrowietz U, Franke A, Gieger C, Barker J, Trembath R, Tsoi LC, Elder JT, Tkaczyk ER, Kisand K, Peterson P, Kingo K, Boldin M, Weidinger S, Akdis CA, Rebane A.
J Invest Dermatol. 2017 Sep;137(9):1945-1954.
miR-146a inhibits inflammatory responses in human keratinocytes and in different mouse models of skin inflammation. Little is known about the role of miR-146b in the skin. In this study, we confirmed the increased expression of miR-146a and miR-146b (miR-146a/b) in the lesional skin of patients with psoriasis. The expression of miR-146a was approximately twofold higher than that of miR-146b in healthy human skin, and it was more strongly induced by stimulation of proinflammatory cytokines in keratinocytes and fibroblasts. miR-146a/b target genes regulating inflammatory responses or proliferation were altered in the skin of patients with psoriasis, among which FERMT1 was verified as a direct target of miR-146a. In silico analysis of genome-wide data from >4,000 psoriasis cases and >8,000 controls confirmed a moderate association between psoriasis and genetic variants in the miR-146a encoding gene. Transfection of miR-146a/b suppressed and inhibition enhanced keratinocyte proliferation and the expression of psoriasis-related target genes. Enhanced expression of miR-146a/b-influenced genes was detected in cultured keratinocytes from miR-146a-/- and skin fibroblasts from miR-146a-/- and miR-146b-/- mice stimulated with psoriasis-associated cytokines as compared with wild-type mice. Our results indicate that besides miR-146a, miR-146b is expressed and might be capable of modulation of inflammatory responses and keratinocyte proliferation in psoriatic skin.

Highlights in immune response, microbiome and precision medicine in allergic disease and asthma.
Sokolowska M, Akdis CA. (Editorial for the Allergy Issue)
Curr Opin Immunol. 2017 Oct;48:iv-ix. doi: 10.1016/j.coi.2017.10.009.
Several recent key findings in immunology of allergic diseases that have led to a need of reassessment of our current thinking are reviewed in this issue of the journal. Recently developed strong evidence on the role of hygiene hypothesis in protection from allergic disease and its immune mechanisms is reviewed by Ober et al. The authors pointed out immunologic mechanisms of lower prevalence of asthma and allergic sensitization observed among Amish children living on traditional farms with higher endotoxin levels as compared to Hutterite children living on industrialized farms. Barcik et al. reviewed that biologically active histamine in humans is produced by certain bacteria in the gut in addition to several cells, and has broad immunoregulatory functions. Turcanu et al. reviewed immune mechanisms of a revolutionary change to protect from food allergy. The immunologic window of opportunity in the infants can be used to enable oral tolerance in severe allergy predisposed children. Accordingly, van de Veen et al. reviewed general mechanisms of allergen tolerance highlighting recent findings. Extensive usage of precision medicine due to emerging biologics is knocking

the doors of allergic diseases and asthma. Boyd et al. reviewed the existing and future "immune monitoring" approaches in the multiple omics perspective with the hope of identifying better correlates of disease status, predictors of therapeutic outcomes, and potential side-effects of treatment. Paul et al. reviewed newly uncovered innate and adaptive immunologic mechanisms that contribute to the pathogenesis of eosinophilic esophagitis. Further highlighting newly developing disease subgroups and precision medicine, Guttman-Yassky & Kruger reviewed clinical subtypes of atopic dermatitis and psoriasis, which may potentially benefit from newly developing highly efficient biologicals. Complementing this paper, Kabashima & Nomura reviewed similarities and distinctions in mouse models of atopic dermatitis and psoriasis.

Davos, June 2018

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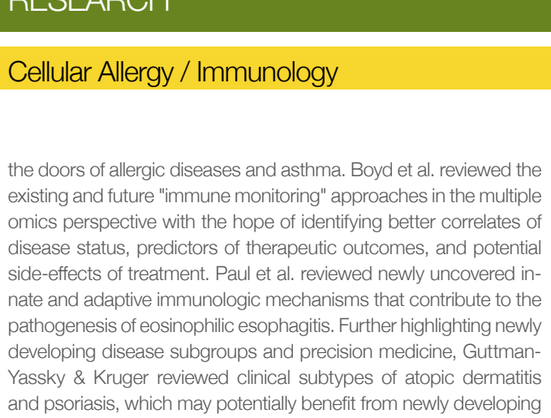

Prof. Dr. Mübeccel Akdis

Immune regulation by B cell subsets

An allergic reaction is characterized by the differentiation of T helper 2 (Th2) cells, which drive B cells to produce allergen-specific IgE antibodies. Immune tolerance to allergens, on the other hand, is characterized by changes in memory-type and allergen-specific T and B cell responses that lead to a healthy immune response. Several B cells subsets have been described that express distinct polarized cytokine profiles. The most prominent of these subsets are Breg cells, which secrete anti-inflammatory cytokines such as IL-10, IL-35 and TGF-β. Other effector B cell subsets have been reported, which produce distinct arrays of cytokines. B effector 1 (Be1) cells producing IFNγ, IL-12 and TNFα are induced by infection with TH1-inducing pathogens and have been shown to promote TH1 responses in mice. Be2 cells, which produce IL-4 have been found in mice infected with parasites and promote TH2 repsonses. More recently IL-17-producing a TH17 corresponding B cell subset has been identified in mice infected with Trypanosoma cruzi.

There is an increasing body of evidence supporting a functional role of Breg cells in the induction and maintenance of tolerance to allergens. Our group has significantly contributed to better understand the role of human Breg cells and IgE versus IgG4 regulation in allergic inflammation. Increased frequency of IL-10-expressing human B cells was first reported in patients with bee venom allergy who received AIT. Detailed evidence on the role of Breg cells in allergen tolerance was obtained when Breg cells were purified by isolation of live IL-10+ and IL-10- B cells. These inducible IL-10+ B cells were named B regulatory 1 (BR1) cells in analogy to inducible TR1 cells. BR1 cells potently suppressed antigen-specific T-cell proliferative responses via their secreted IL-10. Purified B-cell fractions were subsequently compared by using whole-transcriptome analysis, revealing that these inducible IL-10+ B cells were enriched among CD19+CD73-CD25+CD71+ cells. Furthermore, they expressed increased levels of CD274, also named PD-L1, which counteracts the activation of T cell through binding to PD-1. In addition, increased CD25 expression on human B cells has been associated with enhanced in vitro antigen-presenting capacity, as well as increased B-cell IL-10 production in a murine model of intestinal inflammation. CD71 mediates cellular uptake of iron as the major transferrin receptor. The increased expression of CD25 and CD71 reflects an increased activation state of T and B cells. CD73 is a cell-surface enzyme that converts adenosine monophosphate to adenosine, which has potent immunosuppressive effects. The frequency of inducible IL-10+ cells among B cells specific for the major bee venom allergen phospholipase A2 (PLA) showed a significant increase in patients with bee venom allergy several months after the start of venom immunotherapy. Their levels were comparable to healthy beekeepers. These observations support a functional role for IL-10–producing B cells in inducing and maintaining allergen tolerance and indicate that Breg cells expand in response to high-dose allergen exposure in vivo. In addition, CCR5 expression was also upregulated on PLA-specific B cells in patients after AIT and in healthy beekeepers.

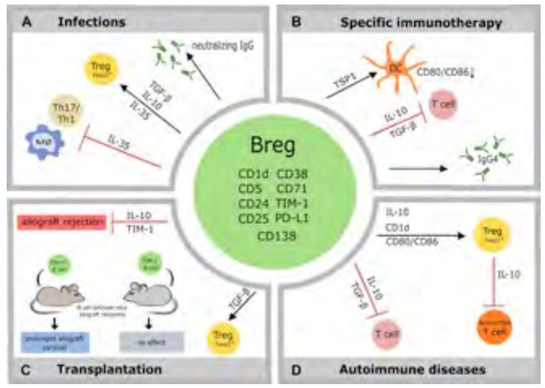

Figure 1: Multiple functions of Breg cells in immune tolerance to infectious agents, allergen-specific immunotherapy, organ transplantation and autoimmune diseases.

B cells have a short life span in vitro which makes it challenging to study these cells. A novel technology to generate long-living human memory B cell lines in vitro allows the expansion of B cells while keeping many of their key characteristics intact. This technology, which we have in the institute encompasses the introduction of the human BCL6 and BCL-xl genes into human memory B cells (This procedure is also referred to as transduction). BCL6 is involved in the maintenance of memory B cells. It suppresses key factors that drive terminal differentiation of B cells to plasma cells, which are end-stage, non-proliferating, antibody producing cells. BCL-xl is an anti-apoptotic molecule that prevents cells from apoptosis. Introducing BCL6 and BCL-xl into memory B cells leads to formation of long-living, highly proliferating, cell surface B cell receptor (BCR)-positive, immunoglobulin-secreting B cells.

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-specific 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.

Human rhinoviruses infect and regulate B cells

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. 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 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.

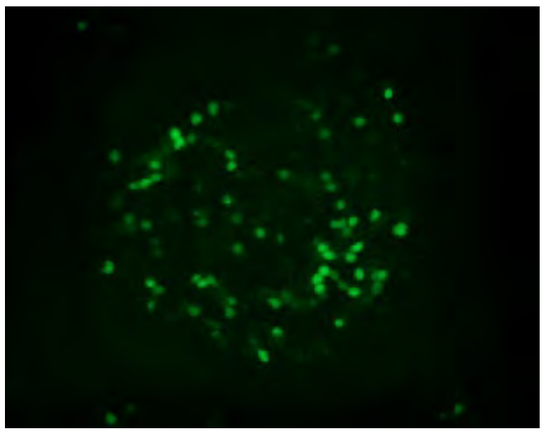

Figure 2: HELA-H1 cells are infected with HRV-16-GFP. Green cells are the cells that are infected by HRV16 and where the virus is propagating.

Role of Der p 1-specific Breg cells in immune tolerance during 2-year house dust mite-specific immunotherapy.
(T. Boonpiyathad et al. Manuscript is in revision JACI)
In this study, we characterized allergen-specific B cell responses during a 2-year house dust mite (HDM) AIT and compared between responder and non-responder patients. Peripheral blood mononuclear cells obtained from 25 patients before, after 10 weeks, 30 weeks and 2 years of AIT were analyzed. Major HDM allergen Der p 1-specific B cells were detected by double fluorescence-labeled allergen and flow cytometry. The role of IgA, IgG1 and IgG4-switching Der p 1-specific B cells, plasmablasts and IL-10- and IL-1RA-producing Breg cells were investigated. Clinical response was observed by visual analogue scale (VAS). Eleven AIT responder patients showed a successful response to AIT as demonstrated by decreased VAS. Skin prick test reactivity to HDM decreased in responders from 7.0±1.3 mm to 2.7±0.5 mm and in non-responders, 7.6±1.1 mm to 5.6±0.5 mm. Increased frequencies of Der p -1 specific B cells was observed in both groups. Increased frequencies of Der p 1-specific IgA+ and IgG4+ B cells were detected only in responder patients. After 2 years, only IgG4+ B cells revealed significantly higher levels compared to non-responder patients. There was no difference observed in Der p 1-specific IgG1+ B cells. The frequency of plasmablasts was higher among responders compared to non-responder patients after 2 years. The frequency of IL-10+, IL-1RA+ and IL-10+IL-1RA+ Breg cells was higher in responder compared to non-responder patients after 2 years. Increased frequency of Der p 1-specific IgG4+ B cells and IL-10-producing Breg cells significantly correlated with improved clinical symptoms over the course of AIT. In conclusion, we demonstrate in this study that AIT induces allergen-specific B cell tolerance in responder patients with increased IgA- and IgG4-expressing Der p 1-specific B cells after 2 years of AIT.

Regulation of IgE production in STAT3 Hyper IgE patients.
(W. van de Veen et al. Manuscript is submitted.)
TH2 cells promote IgE class switch recombination by providing CD40L and IL-4 signals to B cells. These T-dependent B cell responses are initiated in germinal centers in lymphoid tissues. T follicular helper cells are the driving factors in the formation of germinal centers with IL-21 production. IL-21 is a strong activator of the signal transducer and activator of transcription (STAT) 3 signaling pathway, which induces IgG class switch recombintion, and augments IgE production and proliferation in human naive B cells stimulated with CD40L and IL-4. We studied these mechanisms in patients with STAT3 hyper IgE syndrome (STAT3-HIES), an autosomal dominant immune deficiency caused by heterozygous mutations in the STAT3 gene. STAT3-HIES patients showed significantly reduced circulating memory B cells, while frequencies of naive mature B cells were elevated. The numbers of circulating memory B cells expressing IgA, IgG1, IgG2 and IgG3 were reduced while the IgG4- and IgE-switched memory B cell levels were normal in STAT3-HIES patients. In vitro proliferation and immunoglobulin production of naive B cells in response to IL-4 and CD40L were similar in STAT3-HIES and control samples, while IL-21 strongly increased these B cell responses only in controls. Although they showed only moderate proliferative responses to CD40L+IL-4+IL-21, the percentage of the cells that differentiated to plasma cells was significantly higher in STAT3-HIES compared to controls. Together with the observation of abundant IgE+ plasma cells in STAT3-HIES bone marrow, these data suggest a process of rapid switching to IgE and generation of plasma cells that migrate to bone marrow as the main reasons leading to hyper IgE in the circulation in STAT3-HIES patients.

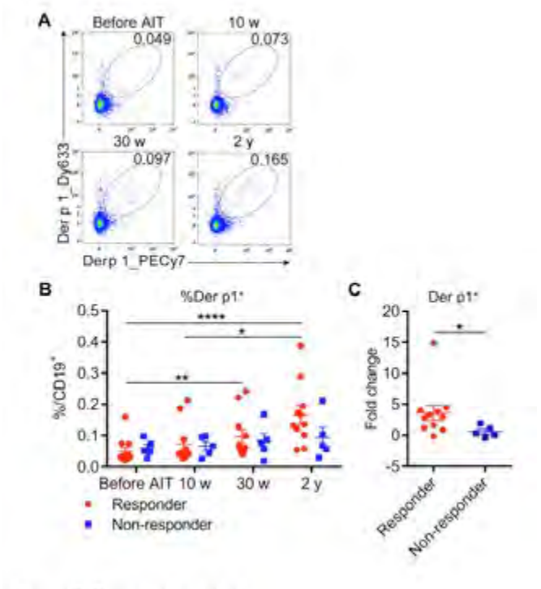

*Figure 3: Increased Der p 1-specific class-switched B cells in responder patients during allergen-specific immunotherapy (AIT). A, Representative dot plot of the responder patient. Cells were gated as CD19+IgM- and Der p 1-specific cells were identified as dual stained for Der p 1-Dy633+ and Der p 1-PECy7+. B, Frequency of Der p 1-specific class-switched B cells before, at 10 weeks (10 w), 30 weeks (30 w) and 2 years (2 y) of AIT. C, Fold change of Der p 1-specific class-switched B cells between before and after 2 years of AIT among responder patients (n = 11) and non-responder patients (n = 5). *p < 0.05, **p < 0.01, ***p < 0.0001.*

Acute Rhinovirus infection induces an extensive anti-viral, B cell receptor signaling and proinflammatory cytokine profiles in asthma.
(O.F. Wirz et al. Manuscript is under preparation)
Rhinovirus (RV) infections are among the most common respiratory viral infectionsassociated asthma exacerbations. The current study aimed at characterization of in vivo B cell responses in healthy and asthmatic individuals, before and after experimental acute rhinovirus infection. Asthmatic and healthy volunteers (control group) were intranasally infected with rhinovirus-A16. PBMCs were isolated and CD19+ B cells were purified using flow cytometry. Total RNA was isolated and next generation RNA-seq was performed for transcriptome profiling in vivo before and 3 days after the infection as well as in pure B cells cultured with RV and IFN-a in vitro. PBMC were stimulated with RV in vitro and cytokine-positive cells were measured using flow cytometry. At baseline, most differentially expressed genes between asthmatic and healthy subjects are involved in immune system processes including antiviral, type I interferon, cytokine and B cell receptor responses. Genes for IgG4 and IgE as well as IgG1, IgG2, IgG3 and IgA2 are more expressed in B cells of asthmatic patients. In addition, genes encoding inflammatory cytokines from the TNF-family, amphiregulin and IL6 are higher expressed in B cells from asthmatics. RV infection induces expression of antiviral genes including STAT1, EIF2AK2, IFIT1, and IFITM1 in B cells from both, healthy and asthmatic individuals. B cells from asthmatic patients express a higher number of antiviral genes and they are more strongly upregulated compared to control group. Most of the up-regulated antiviral genes can be induced by type-I-interferons, preferentially via the JAK/STAT-pathway. In vitro simulated B cells show that IFN-α is sufficient to induce the antiviral genes found in samples from experimentally infected subjects. The inflammatory cytokine IL-6 is increased in B cells of non asthmatic group upon RV infection up to a level which is comparable to steady-state expression in asthmatics before infection. Our data demonstrate that genes involved in the function of B cells are dysregulated in asthmatic subjects at steady-state. We provide evidence that short-term response (3 days) to type-I-interferons is an important mechanism for B cells during RV-infections and that this immune response is less regulated in asthmatics. Rhinovirus infection induces expression of inflammatory cytokines in B cells from healthy individuals, which resembles steady-state gene expression in asthmatics.

Allergic asthma and allergic rhinitis patients do not show regulatory B cell deficiency.
(by Wirz and Głobińska et al. Manuscript is in revision in Allergy)
In the present study, we compared the percentages of Breg subsets in peripheral blood from 14-15 years old longitudinal clinically-characterized allergic asthma, allergic rhinitis and healthy individuals using multicolor flow cytometry. Peripheral blood mononuclear cells were stained with antibodies specific for IL-10, CD1d, CD5, CD24, CD38, CD25, CD71 and CD73. We found no differences in numbers of peripheral Bregs both at baseline and after stimulation in asthmatic and allergic rhinitis patients compared to healthy controls. Since our study included patients with well-controlled asthma and allergic rhinitis, we conclude that induction of Bregs in asthmatic and allergic rhinitis patients in response to stimulation is not impaired in treated patients. Furthermore, no systemic Breg deficiency was observed in these two diseases. However, we cannot exclude that exacerbation of asthma or allergic rhinitis may influence the Breg responses.

Davos, June 2018

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.

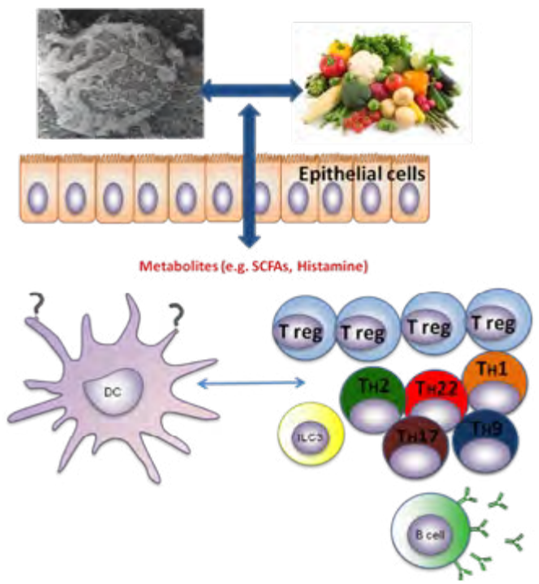

Figure 1. Microbes and their metabolites (e.g. short-chain fatty acids) directly influence DC maturation, activation and lymphocyte polarization.

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. 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, 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 particularly associated with exaggerated activation of invariant natural killer T cells (iNKT) within the lungs. 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. 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. In order to test this hypothesis, we cloned the hdc gene into an E. coli strain and examined the influence of bacterial-derived histamine on respiratory allergen-induced inflammation. Surprisingly, administration of the histamine-secreting bacterial strain, but not its isogenic control strain that doesn't secrete histamine, reduced inflammatory cell recruitment and cytokine secretion within the lung. This effect was partially dependent on H2R, as demonstrated in H2R knock-out animals.

(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. 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). 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. 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 EPS 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. In addition, infants with the highest levels of SCFAs, particularly butyrate, develop significantly less asthma, atopic dermatitis and food allergy by school age. Microbes also secrete biogenic amines following decarboxylation of dietary amino acids and these metabolites can influence immune responses. We have identified a wide range of bacterial species from the human gut microbiota that can generate biogenic amines when the substrate amino acid is present. In addition, biogenic amine levels in fecal samples and BALs from asthma patients are altered compared to healthy controls. We have identified a subset of microbe-derived biogenic amines that suppress dendritic cell activation and oral administration of these biogenic amines to mice have significant effects on airway inflammation. These molecular mechanisms highlight an important link between diet, composition of the gastrointestinal microbiota and regulation of mucosal immune responses.

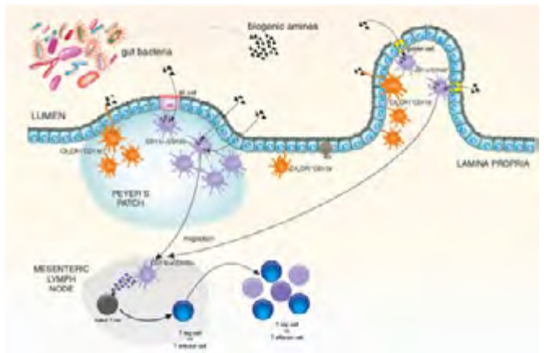

Figure 2. Biogenic amine secretion by the microbiota can influence epithelial cells, innate immune cells such as dendritic cells and polarization of naïve lymphocyte responses.

(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. 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 of fecal, oral, nasal and BAL samples 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.

Exopolysaccharide from Bifidobacterium longum subsp. longum 35624 modulates murine allergic airway responses.
Schiavi E, Plattner S, Rodriguez-Perez N, Barcik W, Frei R, Ferstl R, Kurnik-Lucka M, Groeger D, Grant R, Roper J, Altmann F, van Sinderen D, Akdis CA, O'Mahony L.
Benef Microbes. 2018 May 4:1-14.
Interactions between the host and the microbiota are thought to significantly influence immunological tolerance mechanisms at mucosal sites. We recently described that the loss of an exopolysaccharide (EPS) from Bifidobacterium longum 35624 eliminated its protective effects in colitis and respiratory allergy murine models. Our goal was to investigate the immune response to purified EPS from B. longum 35624, determine if it has protective effects within the lung and identify the protective mechanisms. Isolated EPS from B. longum 35624 cultures was used for in vitro, ex vivo and in vivo studies. Human monocyte-derived dendritic cells (MDDCs) were used to investigate in vitro immunological responses to EPS. Cytokine secretion, expression of surface markers and signalling pathways were examined. The ovalbumin (OVA) respiratory allergy murine model was used to evaluate the in vivo immunomodulatory potential of EPS. In addition, interleukin (IL)-10 knockout (KO) mice and anti-Toll-like receptor (TLR)-2 blocking antibody were used to examine the underlying protective mechanisms of intranasal EPS administration. Stimulation of human MDDCs with EPS resulted in IL-10 secretion, but not proinflammatory cytokines. IL-10 secretion was TLR-2-dependent. Eosinophil recruitment to the lungs was significantly decreased by EPS intranasal exposure, which was associated with decreased expression of the Th2-associated markers C-C motif chemokine 11 (CCL11), C-C chemokine receptor type 3 (CCR3), IL-4 and IL-13. TLR-2-mediated IL-10 secretion was shown to be required for the reduction in eosinophils and Th2 cytokines. EPS-treatment reduced eosinophil recruitment within the lung in a respiratory inflammation mouse model, which is both TLR-2 and IL-10 mediated. EPS can be considered as a novel molecule potentially reducing the severity of chronic eosinophil-related airway disorders.

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. 2018 Jan;141(1):382-390.
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 Nov;72(11):1744-1752.
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 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.
Allergy. 2017 Dec;72(12):1925-1935.
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.
Microb Ecol Health Dis. 2017 Jan 1;28(1):1353881.
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.

Mechanisms underlying induction of allergic sensitization by Pru p 3.
Tordesillas L, Cubells-Baeza N, Gómez-Casado C, Berin C, Esteban V, Barcik W, O'Mahony L, Ramirez C, Pacios LF, Garrido-Arandia M, Díaz-Perales A.
Clin Exp Allergy. 2017 Nov;47(11):1398-1408.
Recently, the nature of the lipid-ligand of Pru p 3, one of the most common plant food allergens in southern Europe, has been identified as a derivative of the alkaloid camptothecin bound to phytosphingosine. However, the origin of its immunological activity is still unknown. We sought to evaluate the role of the Pru p 3 lipid-ligand in the immunogenic activity of Pru p 3. In vitro cultures of different cell types (monocyte-derived dendritic cells [moDCs], PBMCs [peripheral blood mononuclear cells] and epithelial and iNKT-hybridoma cell lines) have been used to determine the immunological capacity of the ligand, by measuring cell proliferation, maturation markers and cytokine production. To study the capacity of the lipid-ligand to promote sensitization to Pru p 3 in vivo, a mouse model of anaphylaxis to peach has been produced and changes in the humoral and basophil responses have been analysed. The lipid-ligand of Pru p 3 induced maturation of moDCsc and proliferation of PBMCs. Its immunological activity resided in the phytosphingosine tail of the ligand. The adjuvant activity of the ligand was also confirmed in vivo, where the complex of Pru p 3-ligand induced higher levels of IgE than Pru p 3 alone. The immunological capacity of the Pru p 3 ligand was mediated by CD1d, as maturation of moDCs was inhibited by anti-CD1d antibodies and Pru p 3-ligand co-localized with CD1d on epithelial cells. Finally, Pru p 3-ligand presented by CD1d was able to interact with iNKTs. The Pru p 3 lipid-ligand could act as an adjuvant to promote sensitization to Pru p 3, through its recognition by CD1d receptors. This intrinsic adjuvant activity of the accompanying lipid cargo could be a general essential feature of the mechanism underlying the phenomenon of allergenicity.

Influence of fracture stability on Staphylococcus epidermidis and Staphylococcus aureus infection in a murine femoral fracture model.
Sabaté Brescó M, O'Mahony L, Zeiter S, Kluge K, Ziegler M, Berset C, Nehrbass D, Richards RG, Moriarty TF.
Eur Cell Mater. 2017 Nov 21;34:321-340.
Fracture-related infection (FRI) is a major complication in surgically fixed fractures. Instability of the fracture after fixation is considered a risk factor for infection; however, few experimental data are available confirming this belief. To study whether stable fractures led to higher infection clearance, mouse femoral osteotomies were fixed with either stable or unstable fixation and the surgical site was contaminated with either Staphylococcus epidermidis (S. epidermidis)or Staphylococcus aureus (S. aureus)clinical isolates. Infection progression was assessed at different time points by quantitative bacteriology, total cell counts in spleen and lymph node and histological analysis. Operated, non-inoculated mice were used as controls. Two inbred mouse strains (C57BL/6 and BALB/c) were included in the study to determine the influence of different host background in the outcome. Stable fixation allowed a higher proportion of C57BL/6 mice to clear S. epidermidis inoculation in comparison to unstable fixation. No difference associated with fixation type was observed for BALB/c mice. Inoculation with S. aureus resulted in a more severe infection for both stable and unstable fractures in both mouse strains; however, significant osteolysis around the screws rendered the stable group functionally unstable. Our results suggested that fracture stability could have an influence on S. epidermidis infection, although host factors also played a role. No differences were observed when using S. aureus, due to a more severe infection, leading to osteolysis and loss of stability in both groups. Further studies are required in order to address the biological features underlying the differences observed.

Microbiome and asthma.
Sokolowska M, Frei R, Lunjani N, Akdis CA, O'Mahony L.
Asthma Res Pract. 2018 Jan 5;4:1.
The mucosal immune system is in constant communication with the vast diversity of microbes present on body surfaces. The discovery of novel molecular mechanisms, which mediate host-microbe communication, have highlighted the important roles played by microbes in influencing mucosal immune responses. Dendritic cells, epithelial cells, ILCs, T regulatory cells, effector lymphocytes, NKT cells and B cells can all be influenced by the microbiome. Many of the mechanisms being described are bacterial strain- or metabolite-specific. Microbial dysbiosis in the gut and the lung is increasingly being associated with the incidence and severity of asthma. More accurate endotyping of patients with asthma may be assisted by further analysis of the composition and metabolic activity of an individual's microbiome. In addition, the efficacy of specific therapeutics may be influenced by the microbiome and novel bacterial-based therapeutics should be considered in future clinical studies.

Immune regulation by histamine and histamine-secreting bacteria.
Barcik W, Wawrzyniak M, Akdis CA, O'Mahony L.
Curr Opin Immunol. 2017 Oct;48:108-113.
Histamine is a biogenic amine with extensive effects on many immune cell types. Histamine and its four receptors (H1R-H4R) represent a complex system of immunoregulation with distinct effects dependent on receptor subtypes and their differential expression. In addition to mammalian cells, bacteria can also secrete histamine and the influence of microbiota-derived histamine on host immunological processes is only beginning to be described. However, it is clear that histamine-secreting microbes are present within the human gut microbiota and their levels are increased in asthma patients. Additional studies are required to fully understand the complex regulatory interactions between histamine and the host immune response to everyday microbial and environmental challenges.

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.

Pathogenic Mechanisms and Host Interactions in Staphylococcus epidermidis Device-Related Infection.
Sabaté Brescó M, Harris LG, Thompson K, Stanic B, Morgenstern M, O'Mahony L, Richards RG, Moriarty TF.
Front Microbiol. 2017 Aug 2;8:1401.
Staphylococcus epidermidis is a permanent member of the normal human microbiota, commonly found on skin and mucous membranes. By adhering to tissue surface moieties of the host via specific adhesins, S. epidermidis is capable of establishing a lifelong commensal relationship with humans that begins early in life. In its role as a commensal organism, S. epidermidis is thought to provide benefits to human host, including out-competing more virulent pathogens. However, largely due to its capacity to form biofilm on implanted foreign bodies, S. epidermidis has emerged as an important opportunistic pathogen in patients receiving medical devices. S. epidermidis causes approximately 20% of all orthopedic device-related infections (ODRIs), increasing up to 50% in late-developing infections. Despite this prevalence, it remains underrepresented in the scientific literature, in particular lagging behind the study of the S. aureus. This review aims to provide an overview of the interactions of S. epidermidis with the human host, both as a commensal and as a pathogen. The mechanisms retained by S. epidermidis that enable colonization of human skin as well as invasive infection, will be described, with a particular focus upon biofilm formation. The host immune responses to these infections are also described, including how S. epidermidis seems to trigger low levels of pro-inflammatory cytokines and high levels of interleukin-10, which may contribute to the sub-acute and persistent nature often associated with these infections. The adaptive immune response to S. epidermidis remains poorly described, and represents an area which may provide significant new discoveries in the coming years.

AllergoOncology: Opposite outcomes of immune tolerance in allergy and cancer.
Jensen-Jarolim E, Bax HJ, Bianchini R, Crescioli S, Daniels-Wells TR, Dombrowicz D, Fiebiger E, Gould HJ, Irshad S, Janda J, Josephs DH, Levi-Schaffer F, O'Mahony L, Pellizzari G, Penichet ML, Redegeld F, Roth-Walter F, Singer J, Untersmayr E, Vangelista L, Karagiannis SN.
Allergy. 2018 Feb;73(2):328-340.
While desired for the cure of allergy, regulatory immune cell subsets and nonclassical Th2-biased inflammatory mediators in the tumour microenvironment can contribute to immune suppression and escape of tumours from immunological detection and clearance. A key aim in the cancer field is therefore to design interventions that can break immunological tolerance and halt cancer progression, whereas on the contrary allergen immunotherapy exactly aims to induce tolerance. In this position paper, we review insights on immune tolerance derived from allergy and from cancer inflammation, focusing on what is known about the roles of key immune cells and mediators. We propose that research in the field of AllergoOncology that aims to delineate these immunological mechanisms with juxtaposed clinical consequences in allergy and cancer may point to novel avenues for therapeutic interventions that stand to benefit both disciplines.

Davos, June 2018

Dr. Claudio Rhyner

The activities of the SIAF Division Vaccine Development during the timeframe of reporting were focused on several projects and collaborations. The Commission of Technology and Innovation (CTI) granted project "PLATELETS" was finished in the middle of the year. 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. We performed also some work to round up older projects and academic and industrial collaborations.

Measuring of Bet v1 and Phl p5a-specific IgE and IgG4 with Evanescent field technology during allergen specific immunotherapy
Allergen specific immunotherapy (SIT) is an effective treatment for IgE-mediated allergic diseases. During immunotherapy there is an increase of allergen specific IgG4 which is regarded as a blocking antibody. The aim of the study is to show the usefulness of this diagnostic assay for the detection of allergen specific IgE during SIT which is not interfered by the blocking antibody IgG4.
The EVA-biosensor is a near patient testing (NPT) device based on the evanescent field technology that allow fast and quantitative measurements of minute amounts of biomolecules with no washing steps and a 10 min time-to-result unlike time consuming standard ELISA methods.
Two different formats based on evanescence biosensor technology were developed for measuring of Bet v1 and Phl p5a-specific IgE and IgG4 (see Fig. 1):
In the direct assay format the antigen (Bet v1 or Phl p5a) is immobilized to the solid phase of the EVA-chip, followed by serum and detected fluorescent-labeled antibodies against IgE or IgG4. In the evanescent field at the bottom of the EVA-chip, the increase in fluorescence intensity is proportional to the concentration of the analyte.
In the reverse assay format anti-human IgE or IgG4 is immobilized to the solid phase of an EVA-chip followed by IgE or IgG4 antibodies contained in the serum. The allergen (Bet v1 or Phl p5a) in this assay was preliminary labeled with fluorescent dye APC and is used to detect the amount of allergen specific antibody captured from the serum. The measurements in the evanescent field provide a very rapid method and the results from both assays allow the calculation of the blocking effect of IgG4.
A schematic of both assays is illustrated in Figure 1.

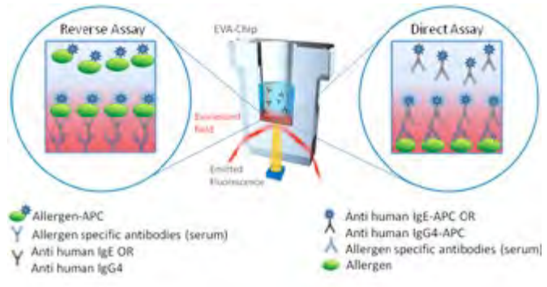

Figure 1: Assay formats

First of all were for both tests the optimal concentrations for antibody / antigen determined. With the optimal concentrations was the sensitivity of the tests terminated. To calculate the sensitivity of a test, serial dilutions of a serum pool calibrated against ImmunoCAP™ (Thermo Fisher) were measured. The limit of detection (LOD) for Phl p5a specific IgE was 0.29 kU/L for the direct assay and 0.29 kU/L for the reverse assay. The LOD for Bet v1 specific IgE was 0.27 kU/L for the direct assay and 0.33 kU/L for the reverse assay. Therefore, the requirements for a test detecting allergen specific antibodies is met, since the concentration of 0.35 kU/L, which is regarded as a cut-off level as defined by ImmunoCAP for sensitization can be detected. The direct assay measurements of specific IgG4 resulted in a LOD of 14.7 µg/L for Phl p5a and 116.6 µg/L for Bet v1.
To determine the influence of the blocking antibody IgG4 on IgE measurements, 138 serum samples from patients undergoing SIT were measured. For this purpose, we used the direct and reverse assays for the detection of Phl p5a / Bet v1 specific IgE and the direct assay for IgG4.
After the measurement of Phl p5a and Bet v1 specific antibodies, the sera were combined to groups based on their amount of Phl p5a / Bet v1 specific IgG4. Sera without specific antibodies were combined to the first group. In a second group, sera are containing specific IgE with absence of specific IgG4. The third group is composed of sera with specific IgE and IgG4. The results are depicted in Figure 2 and Figure 3.

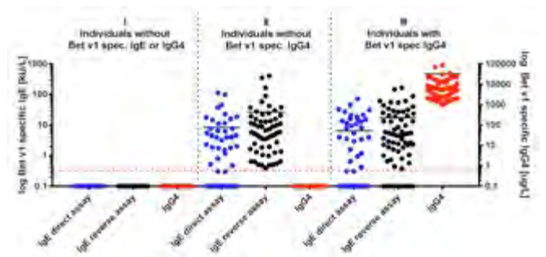

Figure 2: Bet v1-specific IgE and IgG4 measurements in 138 serum samples from a blinded study.

In both groups (II and III; with specific IgE) Bet v1-specific IgE levels differ between the direct and reverse assay and indicate the presence of IgG4 interference (Figure 2). In the second group was no Bet v1-specific IgG4 detected, the amount of IgG4 might be below the detection limit and could so not be detected.
For 50 serum samples could no Bet v1-specific IgE detected in the direct IgE assay, but Bet v1-specific IgE was detected in the reverse IgE assay for all the 50 samples. The IgG4 in these samples blocked the IgE binding in the direct assay.

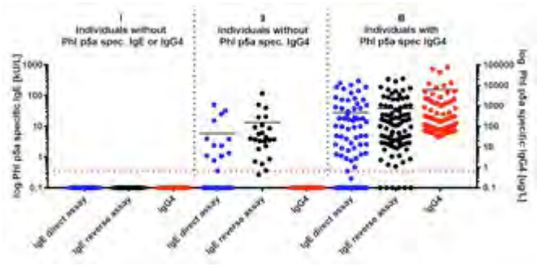

Figure 3: Phl p5a-specific IgE and IgG4 measurements in 138 serum samples from a blinded study.

In both groups (II and III) Phl p5a-specific IgE levels differ between the direct and reverse assay and indicate the presence of IgG4 interference (Figure 3). In the second group was no Phl p5a-specific IgG4 detected, the amount of IgG4 might be below the detection limit and could so not be determined.
For 36 serum samples could be no Phl p5a-specific IgE detected in the direct IgE assay, but Phl p5a-specific IgE was detected in the reverse IgE assay for all the 36 samples. The IgG4 in these samples blocked the IgE binding in the direct assay.
Here, we present a fast and sensitive method for the measurements of Bet v1 and Phl p5a specific antibodies in sera of allergic patients with and without SIT. Furthermore, we could show the blocking effect of Bet v1 / Phl p5a specific IgG4 on the measurements of Bet v1 / Phl p5a specific IgE in a direct assay. With the reverse assay, we developed a useful method for the detection of Bet v1 / Phl p5a specific IgE, which is not influenced by the presence of blocking antibody IgG4.

Improving sensitivity of EVA measurement with alternative allergen labeling

The conjugation of allergens with the fluorophore Allophycocyanin (APC) could reveal some problems. The activated fluorophore APC will bind to free primary amines, in the case of proteins, it is the surface exposed amino acid lysine. Depending on the content and the position of lysine in the allergen can the availability of antibody epitopes be impaired. Linking of allergens (e.g. Bet v1 18 kDa) with the 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 APC, to generate a proteoliposome, which could improve the signal intensity. The Bet v1 protein was produced as a Bet v1-6xHis tag-transmembrane helix (TMH) construct in E. coli BL21 cells, purified using immobilized metal affinity chromatography (IMAC) under denaturing conditions and refolded into the native stage. The proteoliposome was formed using a lipid to protein mixture of L-α-Phosphatidylcholine(PC):cholesterol:Bet v1-6xHis-TMH protein construct with 2 mg APC solution. The Bet v1 APC liposomes were sized after the forming using sonication and lipid extrusion. These Bet v1 APC proteoliposomes were compared with Bet v1 APC in EVA measurement.

In the EVA measurement showed both Bet v1 APCs and Bet v1 APC liposome comparable results. The preparation of Bet v1 APC liposomes will be optimized in terms of buffer (pH), additional salts, APC concentration (fluorescence self-quenching), lipid composition (PC and cholesterol), lipid-to-protein ratio, temperature and time of evaporation and sonication and extrusion parameters.

Investigation of fentanyl plasma levels after application of a fentanyl patch in different locations

Transdermal fentanyl patches are used to help relieve severe ongoing pain e.g. chronic pain in cancer patients or pain in orthopedic research models after surgery. The patches are attractive for dosing in animals because of its ease of application and supposed long duration of action. Fentanyl is a synthetic opioid and specific μ-agonist with approximately 100 times the potency of morphine.
A competitive binding assay for fentanyl determination in animal plasma samples was developed recently. The fast and sensitive immunoassay is based on real time measurement of a binding reaction using evanescent field excitation of bound fluorophores. During the measurement an evanescent field is generated at the bottom (~ 200 nm) of each well in the sensor chip due to total internal reflection of the excitation laser light. Only fluorophores that are present in this evanescent field will be excited and emit light.
In collaboration with the AO Research Institute Davos, we used the developed immunoassay to determine the fentanyl plasma levels in rabbits after application of a transdermal fentanyl patch in three different locations in order to refine postoperative pain management. Rabbits were randomly assigned to 3 groups (n=6 per group) in order to the patch location. The transdermal fentanyl patches (12 μg/h) were located on the following sites (i) inside of the ear, (ii) outside of the ear and (iii) the neck. Blood samples were collected from each rabbit at 12 different time points [h] and subsequently centrifuged for plasma collection. Plasma was stored at -20°C until assayed.

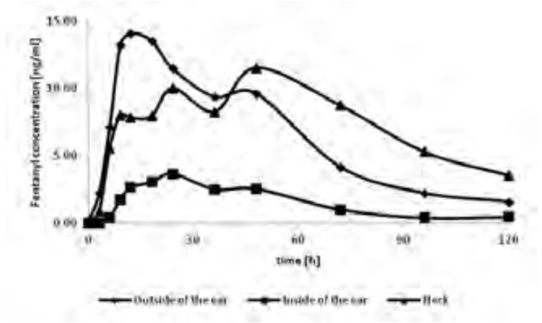

Figure 4: Plasma fentanyl levels at various time points [h] after application of a fentanyl patch at different locations. Curves displayed as mean values of 6 animals per time point and location.

We showed that the drug absorption from the fentanyl patch leads to higher plasma fentanyl levels when the patch is located “outside of the ear” compared to patch locations “inside of the ear” and “neck” in which the “inside of the ear” location shows the minimal absorption of the drug from the patch. Fentanyl levels measured in plasma samples indicate an increase in concentration during the first 24 h and a decrease after patch removal at 60h (Fig. 4).
This sensitive competitive immunoassay can be used for a rapid determination of fentanyl levels in plasma samples within 10 minutes, which is helpful for post-surgery surveillance and care of laboratory animals used in clinical trials.

Mouse IgG-Immunoassay

Immunoglobulins are heterotetrameric proteins produced by B lymphocytes. The protein complexes are composed of two heavy and two light chains which together form the Y-like shape. Heavy and light chains, can be separated functionally into variable domains, that bind antigens and constant domains that specify effector functions such as activation of complement or binding to Fc-receptors. IgG is the predominant isotype found in the blood and extracellular fluids.
We developed an immunoassay for the quantitative determination of mouse IgG in serum or plasma based on the evanescence field technology. IgG’s are detected in a sandwich immunoassay format, where in a first step mouse IgG is captured by an anti-mouse-IgG antibody coated well. The specific detection is performed with an anti-mouse-IgG antibody conjugated to the fluorophor Allophycocyanin (APC). The sensor chip is precoated with the capture antibody, pre-diluted sera or plasma needs to be mixed with the detection mix and the mixture is transferred to the well. The binding reaction is recorded in real time as fluorescence-time graph starting at time zero and ending at 10 minutes.
With this easy, fast and sensitive IgG detection assay it is possible to determine mouse IgG in serum or plasma within 10 minutes. There are ongoing investigations for specific mouse IgG subtypes (e.g. IgG1, IgG 2a and IgG 2b) immunoassay development.

Davos, June 2018

PD Dr. Katja Bärenfaller

Innovation Strategy

The activities of the new Molecular Allergology Group at SIAF were mainly focused on establishing and positioning the new group. This meant getting involved in implementing the research strategy of canton Graubünden, first focusing on profile field "Computational Biology". Working together with Heike Rölke and Bruno Studer from HTW Chur and Duri Bezzola from the Graduate School Graubünden we developed a concept termed DAViS Center (Center for data analysis, visualization and simulation) (Figure 1), which was submitted to the canton in December. Part of this concept were proposals for the development of novel computational methods for the analysis and interpretation of multi-dimensional biomedical datasets established in SIAF. If granted, the resources developed in the frame of the DAViS concept will strengthen and considerably enhance the bioinformatics and computational biology capacities of SIAF, which will be instrumental in future research efforts.

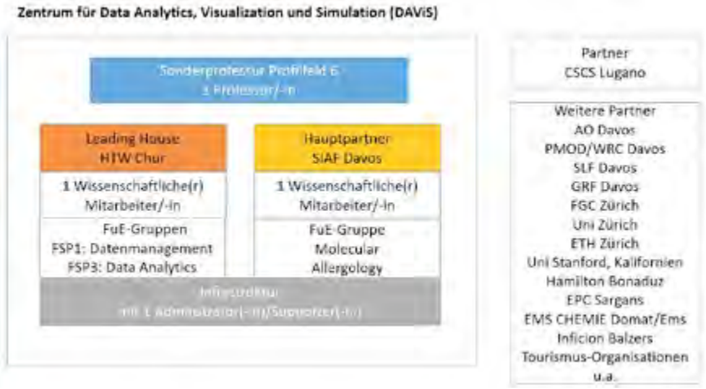

Figure 1: Organisational structure DAViS

Membership at the Swiss Institute of Bioinformatics (SIB)

Also with the aim to better position SIAF in the bioinformatics field, we applied for the group to become a member of the Swiss Institute of Bioinformatics (SIB), which was granted. From the beginning of 2018 the Molecular Allergology group has therefore become a group of the SIB (Figure 2), the SIAF became an institutional member (Figure 3) and Cezmi Akdis became a member of the Foundation Council.

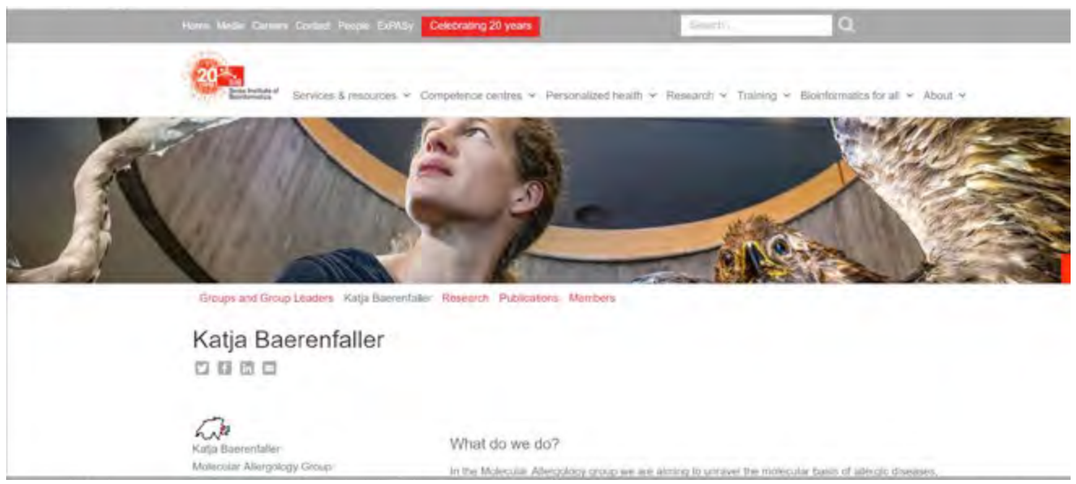

Figure 2: On-line presentation of the Group of Molecular Allergology at the SIB website (https://www.sib.swiss/baerenfaller-katja/katja-baerenfaller-sub), with a picture taken by Nicolas Righetti.

Figure 3: Institutional members of the SIB. With the SIAF the SIB is now also located in Eastern Switzerland.

Ongoing and concluded projects

Translation of non-protein coding RNA stretches

Through the widespread use of RNA sequencing it became evident that a large portion of the genome is transcribed, also regions without annotated protein coding capacity, such as long non-coding RNAs (lncRNAs). Some of these non-mRNAs are 5'-capped and 3'-polyadenylated and encode small open reading frames (sORFs). Furthermore, many mRNAs contain upstream ORFs (uORFs) present in the 5'-leader sequence of the main ORFs. The view that the translation of uORF and sORF sequences can give rise to peptides has been substantiated by experimental evidence obtained by ribosome footprinting in which those stretches of RNA that are buried inside elongating ribosomes are sequenced. In a collaboration with the group of Julia Bailey-Serres at the University of California we were previously provided with uORF- and sORF-encoded sequences with evidence for translation in ribosome footprinting data. These sequences were included in database-dependent searches of large-scale mass spectrometry data, which enabled the detection of several peptides indicative for translational and in vivo accumulation of sORF- and uORF-encoded peptides (Figure 4) (Bazin, Baerenfaller et al., 2017).

In my previous laboratory we had also acquired ribosome footprinting data of a cell culture challenged with flagellin 22 peptide, together with RNA sequencing and quantitative proteomics data and data on protein turnover. With the aim to identify the relative contributions of transcription, translation and protein degradation in the regulation of protein levels these data are currently modelled in collaboration with the group of Jörg Stelling at ETH Zürich (Ihmor et al., manuscript in preparation). The experience and expertise acquired in these projects will be instrumental in projects that are currently planned in SIAF.

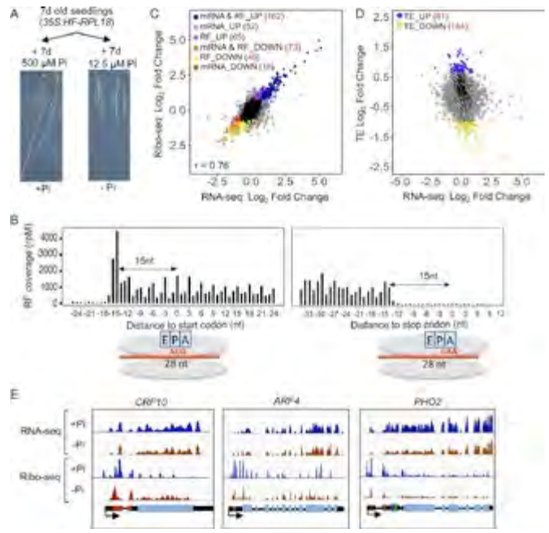

Figure 4: Part of Figure 1 as in Bazin, Baerenfaller et al., (2017) showing that the ribosome footprint (RF) coverage shows a characteristic pattern with RFs spanning a distance of around 15 nucleotides upstream of the start codon and an abrupt stop around 15 nucleotides upstream of the stop codon (B), which can be used to verify translation of non-protein coding RNA stretches, and that the correlation between RNA sequencing (RNA-Seq) and ribosome footprint sequencing (Ribo-Seq) can reveal cases of increased or decreased translational efficiency (TE) (D).

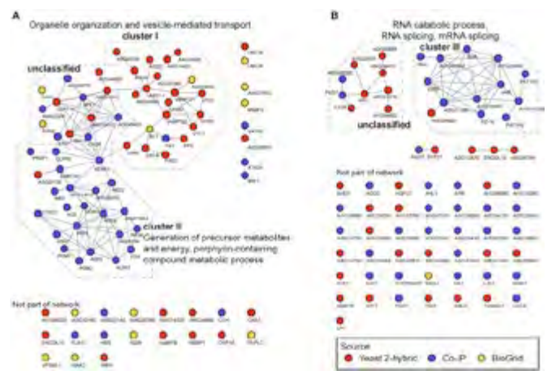

Figure 5: Part of Figure 2 as in Nintemann et al. (2017) showing a network analysis of interactors of CYP83A1, identified by yeast 2-hybrid, co-immunoprecipitation and the BioGrid database, built with the String database.

Identification of protein interaction networks
Building on previous proteomics work in which we identified proteins required in glucosinolate biosynthesis, we collaborated with the group of Meike Burow in Denmark to identify interaction partners for CYP83A1 and CYP83B1, two homologous enzymes specific for aliphatic and indole glucosinolate biosynthesis, respectively. In our group we performed the mass spectrometry measurements of the co-immunoprecipitations and contributed to data analysis, integration and interpretation. In this work we established a potential link between glucosinolate defense compounds and defense against biotrophic pathogens that is mediated by protein-protein interactions (Figure 5) (Nintemann et al., 2017). Identifying protein interaction networks of proteins central to immune regulation, as well as their post-translational modifications, is also part of experiments that are currently planned in the group.

The role of targeted protein degradation in defense response
In an ongoing SNF-funded project at ETH Zurich with PhD student Sebastian Peterson we aim to identify substrates and interaction partners for ubiquitin ligases known to be involved in defense response. To this end, homozygous Arabidopsis mutant plants not expressing the E3 ligases PUB17, PUB20 and PUB22/PUB23/PUB24 were generated and confirmed with genotyping and RT-PCR. These mutants were transformed with constructs in which the protein sequences are fused to tandem affinity tags. These plants can now be used to perform tandem affinity purification (TAP) experiments in different experimental conditions. Furthermore, Sebastian Peterson is working on the identification of the sites of ubiquitylation.

Unravelling Protein-Protein Interaction Networks Linked to Aliphatic and Indole Glucosinolate Biosynthetic Pathways in Arabidopsis.
Nintemann SJ, Vik D, Svozil J, Bak M, Baerenfaller K, Burow M, Halkier BA. Frontiers in Plant Science. 2017 Nov; 8: 2028
Within the cell, biosynthetic pathways are embedded in protein-protein interaction networks. In Arabidopsis, the biosynthetic pathways of aliphatic and indole glucosinolate defense compounds are well-characterized. However, little is known about the spatial orchestration of these enzymes and their interplay with the cellular environment. To address these aspects, we applied two complementary, untargeted approaches—split-ubiquitin yeast 2-hybrid and co-immunoprecipitation screens—to identify proteins interacting with CYP83A1 and CYP83B1, two homologous enzymes specific for aliphatic and indole glucosinolate biosynthesis, respectively. Our analyses reveal distinct functional networks with substantial interconnection among the identified interactors for both pathway-specific markers, and add to our knowledge about how biochemical pathways are connected to cellular processes. Specifically, a group of protein interactors involved in cell death and the hypersensitive response provides a potential link between the glucosinolate defense compounds and defense against biotrophic pathogens, mediated by protein-protein interactions.

Global analysis of ribosome-associated noncoding RNAs unveils new modes of translational regulation.
Bazin J, Baerenfaller K, Gosai SJ, Gregory BD, Crespi M, Bailey-Serres J. Proceedings of the National Academy of Sciences. 2017 Nov; 114(46), E10018-E10027
Eukaryotic transcriptomes contain a major non–protein-coding component that includes precursors of small RNAs as well as long noncoding RNA (lncRNAs). Here, we utilized the mapping of ribosome footprints on RNAs to explore translational regulation of coding and noncoding RNAs in roots of Arabidopsis thaliana shifted from replete to deficient phosphorous (Pi) nutrition. Homodirectional changes in steady-state mRNA abundance and translation were observed for all but 265 annotated protein-coding genes. Of the translationally regulated mRNAs, 30% had one or more upstream ORF (uORF) that influenced the number of ribosomes on the principal protein-coding region. Nearly one-half of the 2,382 lncRNAs detected had ribosome footprints, including 56 with significantly altered translation under Pi-limited nutrition. The prediction of translated small ORFs (sORFs) by quantitation of translation termination and peptidic analysis identified lncRNAs that produce peptides, including several deeply evolutionarily conserved and significantly Pi-regulated lncRNAs. Furthermore, we discovered that natural antisense transcripts (NATs) frequently have actively translated sORFs, including five with low-Pi up-regulation that correlated with enhanced translation of the sense protein-coding mRNA. The data also confirmed translation of miRNA target mimics and lncRNAs that produce trans-acting or phased small-interfering RNA (tasiRNA/phasiRNAs). Mutational analyses of the positionally conserved sORF of TAS3a linked its translation with tasiRNA biogenesis. Altogether, this systematic analysis of ribosome-associated mRNAs and lncRNAs demonstrates that nutrient availability and translational regulation controls protein and small peptide-encoding mRNAs as well as a diverse cadre of regulatory RNAs.

Photoperiodic control of the Arabidopsis proteome reveals a translational coincidence mechanism.
Seaton DD, Graf A, Baerenfaller K, Stitt M, Millar AJ, Gruissem W. Molecular Systems Biology. 2018 Mar; 14(3), e7962
Plants respond to seasonal cues such as the photoperiod, to adapt to current conditions and to prepare for environmental changes in the season to come. To assess photoperiodic responses at the protein level, we quantified the proteome of the model plant Arabidopsis thaliana by mass spectrometry across four photoperiods. This revealed coordinated changes of abundance in proteins of photosynthesis, primary and secondary metabolism, including pigment biosynthesis, consistent with higher metabolic activity in long photoperiods. Higher translation rates in the day than the night likely contribute to these changes, via an interaction with rhythmic changes in RNA abundance. Photoperiodic control of protein levels might be greatest only if high translation rates coincide with high transcript levels in some photoperiods. We term this proposed mechanism “translational coincidence”, mathematically model its components, and demonstrate its effect on the Arabidopsis proteome. Datasets from a green alga and a cyanobacterium suggest that translational coincidence contributes to seasonal control of the proteome in many phototrophic organisms. This may explain why many transcripts but not their cognate proteins exhibit diurnal rhythms.

Davos, June 2018

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O'Mahony L. The microbiome and immune tolerance. Paediatric Gastro-Allergy Symposium, Newcastle, 22nd May 2017.

O'Mahony L. Role of the microbiome in food allergy and asthma. Italian Proteomics Association XII Annual conference, Leece, 12th June 2017.

O'Mahony L. Obesity and allergy – the evidence? European academy of allergy and clinical immunology, Helsinki, 19th June 2017.

O'Mahony L. Tolerance mechanisms in allergy and asthma – implications in cancer. European academy of allergy and clinical immunology, Helsinki, 19th June 2017.

O'Mahony L. Immune-Bacterial-Dietary Interactions in the Gastrointestinal Tract. TUM seminar series, Munich, 1st August 2017.

O'Mahony L. Influence of the Microbiome on the Airways. 100ORL Meeting, Zürich, 1st September 2017.

O'Mahony L. Interplay between the Microbiota and Immune System: A Role for Probiotics? Paul Ehrlich Symposium, Bad Homburg, 9th September 2017.

O'Mahony L. How do Pre- and Probiotics Work? The Role of Receptors in Immune Modulation by Microbial Products. EAACI Food Allergy Training School, Manchester, 15th September 2017.

O'Mahony L. Microbiome & Metabolites in Mucosal Inflammatory Disorders. Seminar series of the Dermatology Department, University Hospital Zürich, Zürich, 21st September 2017.

O'Mahony L. Microbiota and microbiome: role in the immunology of asthma. Novartis Severe Asthma Symposium, Madrid, 22nd September 2017.

O'Mahony L. Immune Regulation by Microbes and their Metabolites. Seminar series at Galderma, Nice, 11th October 2017.

O'Mahony L. Prebiotics and probiotics: regulation of the immune response and inflammation in allergic disease. Nutricia-sponsored satellite symposium at PAAM, London, 26th October 2017.

O'Mahony L. EACCI PRACTALL on Microbiome – an overview. PAAM, London, 26th October 2017.

O'Mahony L. Microbiome-host immune system interactions and manifestations of allergies. PAAM, London, 28th October 2017.

O'Mahony L. Histamine Regulates Mucosal Inflammatory Reseponses. Signal Transduction Society Meeting, Weimar, 8th November 2017.

O'Mahony L. Allergy and Asthma. ISMA, Luxembourg, 9th November 2017.

O'Mahony L. Microbial Modulation of Mucosal Tolerance. Seminar seris of Linköping University, Sweden, 16th November 2017.

Rhyner C. Late Night with LRIG: Rapid-Fire Innovation Session: Quantitative Immunoassays in 10 minutes. SLAS Annual Conference, Washington DC, Feb 6–8 2017.

Rhyner C. Oral Abstract Session «IgE and allergens", Introductory lecture, EAACI Annual Congress, Helsinki, Finland, June 17-21 2017.

Rhyner C. Postgraduate Courses Immunology 'Omic' technologies in immunology – Advanced: Future: New perspectives in immunology, EAACI Annual Congress, Helsinki, Finland, June 17-21 2017.

Sokolowska M. Biomarkers for Allergen Specific Immunotherapy and Immune Tolerance. Allergopharma meeting, Reinbeck, Germany, 17th July 2017.

van de Veen W. B Regulatory Cells Role in Allergen-Specific Tolerance. AAAAI annual meeting, Atlanta GA, USA, 3-6 March 2017.

Wawrzyniak M. Influence of microbial metabolites on mucosal immune regulation and inflammation. MIKROBIOT 2017, 4th Workshop on Microbiology in Health and Environmental Protection, Łódź, Poland, 19–21 September 2017.

Wawrzyniak P. Defective epithelial barrier in respiratory diseases. The Finnish Society of Allergology and Immunology, Helsinki, Finland, October 27th, 2017.

2017

Chairs

Akdis CA. JACI Year in Review Workshop. AAAAI Annual Meeting, Atlanta, USA, 3-6 March 2017.

Akdis CA. Mechanisms of Immune Tolerance to Allergens. AAAAI Annual Meeting, Atlanta, USA, 3-6 March 2017.

Akdis CA. AIT: New Insights into Mechanisms. AAAAI Annual Meeting, Atlanta, USA, 3-6 March 2017.

Akdis CA. Immune tolerance. World Immune Regulation Meeting, Davos, Switzerland, 15-18 March 2017.

Akdis CA. Euphoria Oral Presentations: Feedback from Editors. European Summit Prevention and Self Management of Airway Diseases. EU parliament Brussels, Belgium, 29 March 2017.

Akdis CA. Innate lymphoid cells in allergy and chronic inflammatory diseases. EAACI Congress 2017, Helsinki, Finland, 17-21 June 2017.

Akdis CA. New immunological concepts in allergen-specific immunotherapy: Immune regulation beyond regulatory T cells? EAACI Congress 2017, Helsinki, Finland, 17-21 June 2017.

Akdis CA. Researchers and Editors interaction. European Rhinology Research Forum, Brussels, Belgium, 9-10 November 2017.

Akdis CA. Allergy Updates. National Congress for Allergology and Clinical Immunology, Antalya, Turkey, 18-22 November 2017.

Akdis M. Viral infections and inflammation. World Immune Regulation Meeting, Davos, Switzerland, 15-18 March 2017.

Akdis M. Novel roles of dendritic cells. EAACI Congress 2017, Helsinki, Finland, 17-21 June 2017.

Akdis M. New ways of coping with cat allergy. EAACI Congress 2017, Helsinki, Finland, 17-21 June 2017.

Akdis M. Researchers and Editors interaction. European Rhinology Research Forum, Brussels, Belgium, 9-10 November 2017.

Akdis M. Mucosal Immunity. National Congress for Allergology and Clinical Immunology, Antalya, Turkey, 18-22 November 2017.

Ferstl R. Mucosal tolerance and intestinal homeostasis. World Immune Regulation Meeting, Davos, Switzerland, 15-18 March 2017.

Frei R. Mucosal tolerance and intestinal homeostasis. World Immune Regulation Meeting, Davos, Switzerland, 15-18 March 2017.

O'Mahony L. EAACI Immunology winter school, Sierra Nevada, Spain, January 2017.

O'Mahony L. World Immune Regulation Meeting, Davos, Switzerland, 15-18 March 2017.

O'Mahony L. European academy of allergy and clinical immunology, Helsinki, 18-21 June 2017.

O'Mahony L. EAACI Food Allergy Training School, Manchester, 14-16 September 2017.

O'Mahony L. PAAM, London, 26-28 October 2017.

O'Mahony L. ISMA, Luxembourg, 9-11 November 2017

Rhyner C. Plenary Session Endotypes and allergy epidemics, World Immune Regulation Meeting, Davos, Switzerland, 15-18 March 2017.

Rhyner C. Oral Abstract Session IgE and allergens, Chair, EAACI Annual Congress, Helsinki, Finland, June 17-21 2017.

Rhyner C. Poster Discussion Session Functional genomics and proteomics, EAACI Annual Congress, Helsinki, Finland, June 17-21 2017.

Rhyner C. Thematic Poster Sessions Functional genomics and proteomics, , Chair, EAACI Annual Congress, Helsinki, Finland, June 17-21 2017.

Sokolowska M. Inflammatory mechanisms in the tissue. World Immune Regulation Meeting, Davos, Switzerland, 15-18 March 2017.

van de Veen W. B cell subsets and immune regulation. World Immune Regulation Meeting, Davos, Switzerland, 15-18 March 2017.

2017

Lectures

Lectures at University of Zurich

Akdis CA. BCH301. Innate Immunity
Akdis CA. BCH301. Antigen Presentation

Akdis M. BCH301. Innate Immunity
Akdis M. BCH301. Antigen Presentation

Baerenfaller K. UZH BIO390 'Introduction to Bioinformatics'; 2h lecture on 'RNA structure analysis'

O'Mahony L. BCH301. Innate Immunity
O'Mahony L. BCH301. Antigen Presentation

Lectures at University of Salzburg

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

Awards

Akdis CA. Honorary Member of the Swiss Society for Allergology and Immunology, June 2017.

Barcik W. Abstract Prize for best oral presentation, EAACI Congress in Helsinki, Finland, 17-21 June 2017.

Crameri R. EAACI Paul Ehrlich Award, EAACI Congress in Helsinki, Finland, 17-21 June 2017.

Frei R. Annual Allergy Price 2017, Allergie-Stiftung, Ulrich Müller-Gierok, Bern, Switzerland.

Frei R. Best Workshop Presentation Award. World Immune Regulation Meeting, Davos, Switzerland, 15-18 March 2017.

O'Mahony L. PhARF Award, EAACI Congress in Helsinki, Finland, 17-21 June 2017.

Radzikowska U. Travel Grant for abstract Human rhinovirus triggers activation of inflammasome in airway epithelium in asthma. EAACI Winter School 2017, Sierra Nevada, Spain, 26-29 January 2017.

Satitsuksanoa P. Long Term Research Fellowship 2017. European Acadamy of Allergy and Clinical Immunology (EAACI 2017), Swiss Institute of Allergy and Asthma (SIAF), 01.06.2017-31.05.2018.

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

Sokolowska M. 1st place. SIAF Science Day 2017, 14th December 2017.

van de Veen W. AAAAI In-training Member International Travel Grant Scholarship. AAAAI annual meeting, Atlanta GA, USA, 3-6 March 2017.

van Elst DP. Long Term Research Fellowship EAACI 2017. European Acadamy of Allergy and Clinical Immunology, SIAF, Davos, Switzerland 1 July 2017 - 30 June 2018.

Wawrzyniak M. The best oral presentation award. MIKROBIOT 2017, 4th Workshop on Microbiology in Health and Environmental Protection, Łódź, Poland, 19–21 September 2017.

Degrees

Sabaté Brescó M. Dissertation: Role of Implant Stability and Local Inflammatory Responses on the Development and Progression of Infection Associated with Internal Fixation Devices, University of Zurich, 18 August 2017.

Wawrzyniak P. Doctoral degree (PhD): Role of effector lymphocytes T type 2, cytokines IL-4, IL-13 and histone deacetylases on the bronchial epithelial cell integrity in asthma, University of Bialystok, Poland.

Ruchti F. Master Degree (MSc): Immunological analysis of innate lymphoid cells and antigenspecific T cells during allergenspecific immunotherapy. University of Zurich, 27 February 2017.

Hildebrand M. Master Degree (MSc), in collaboration with AO: Characterization of the Immune Response Following a Large Bone Defect in the Presence and Absence of a Human Xenograft in a Rat Model. University of Zurich, 27 February 2017.

Public Seminars

05.01.2017: Dr. Lindholm Bøgh K., Research Group for Gut Microbiology and Immunology, National Food Institute, Technical University of Denmark, Søborg, Denmark. Food Allergy: Mechanisms and Models.

03.02.2017: Allergopharma SIAF Partnership Meeting. Dr. Dr. Willers C., Dr. Kahlert H., Dr. Nandy A., Prof. Akdis CA., Prof. Akdis M., Dr. Sokolowska M., Dr. Boonpiyathad T., Ruchti F., Dreher A., Prof. Akdis CA: Welcome and introduction, tour in the institute., Dr. Sokolowska M.: Aims and set up of the study, Biomarker discovery program and T cell results., Ruchti F.: Innate lymphoid cells and monocytes., Sokolowska M.: Current molecular leads and optimization of proteomics, follow-up strategy for biomarker discovery, to do list., General discussion on strengthening partnership, back up experiments, biobanked material, future plans.

07.02.2017: Dr. Mantel PY., Institute of Anatomy, Department of Medicine, University of Fribourg, Extracellular vesicles† in the regulation of neutrophil dysfunction.

13.02.2017: Dr. Kündig T., Department of Dermatology, University Hospital Zurich, University of Zurich. Allergen immunotherapy: learning from pathogens.
Dr. Johansen P., Department of Dermatology, University Hospital Zurich, University of Zurich., Photosensitisers may shed new light on avenues towards effective CTL vaccines.
Hjálmsdóttir Á., Department of Dermatology, University Hospital Zurich, University of Zurich., B cell activation by a T cell independent liposomal vaccine and its potential therapeutic use.

16.02.2017: Univ.Prof. Dr. Bopp T., Head of Molecular Immunology, Institute for Immunology, University Medical Center of the Johannes GutenbergUniversity, Mainz, Germany, Context and Tissuespecific Regulation of Tolerance and Type 2 Immunity by Regulatory T cells.

17.02.2017: Prof. Boyman O., Department of Immunology, Laboratory of Applied Immunobiology, University Hospital Zurich, Modulation of immune responses by cytokines and anti-cytokine antibodies.

17.02.2017: 3rd traditional Boyman Lab meets Akdis Lab, University Hospital Zurich, Department of Immunology, Laboratory of Applied Immunobiology and Swiss Institute of Allergy and Asthma Research (SIAF) Davos, University of Zurich, Keynote Lecture: Prof. Boyman O.: Modulation of immune responses by cytokines and anti-cytokine antibodies., Sokolowska M.: Antigen-specific T cell regulation by allergen-specific immunotherapy., Impellizzieri D.: Characterization of tissue resident memory T cells., van de Veen W.: A novel antigen-specific B cell subset., Räberm M.: In vivo characterization of anti-tumor properties of different IL-2 complexes. Karakus U.: Development of TREG cell-stimulating IL-2/antibody complexes and how they modulate IL-2 receptor assembly., Nguyen T.: IL-2 complex in murine islets transplantation: A model to study the mechanism of long-term graft acceptance., Wawrzyniak P.: Epigenetic regulation of bronchial epithelial barrier., Altunbulakli C.: Links between skin microbiome and transcriptome in atopic dermatitis.

20.02.2017: PD Dr. Baerenfaller K., Department of Biology, ETH Zürich, Gene expression regulation from a protein point of view.

27.02.2017: Master Thesis Presention and Examination, Prof. Becher B., Institute of Experimental Immunology, University of Zurich, Chronic inflammation: how T cells talk to myeloid cells.
Ruchti F., SIAF, University of Zurich, Immunological analysis of innate lymphoid cells and antigenspecific T cells during allergenspecific immunotherapy.
Hildebrand M., AO Research Institute, Characterization of the immune response following a large bone defect in the presence and absence of a human xenograft in a rat model.

27.03.2017: Dr. Serra T., Musculoskeletal Regeneration, AO Research Institute Davos, Additive Manufacturing (3D bioprinting) in Medicine.
Dr. Eglin D. Musculoskeletal Regeneration, AO Research Institute Davos, Additive Manufacturing (3D bioprinting) at AO Research Institute Davos.

19.03. + 20.03.2017: Becton Dickinson Trainings Course with Dr. Bauhofer O.

30.06.2017: Rusch S., Research Assistant, Evaluation Office, University of Zurich, Information Event on the Evaluation Process of the University of Zurich.

03.07.2017: Prof. Agache I., President European Academy of Allergy & Clinical Immunology, Professor, Allergy & Clinical Immunology Transylvania University, Brasov, Romania, Endotypes of Allergic Diseases and Asthma. & How to handle best your junior years for a successful career development.

21.07.2017: Prof. Makowska J., Chief of the Department of Rheumatology, Medical University of Lodz, Poland, The role of airways in initiation and propagation of autoimmunity and inflammation in rheumatic diseases.

10.08.2017: Prof. Jutel M., Department of Clinical Immunology, Wroclaw Medical University, ALL-MED Medical Research Institute, Wroclaw, Poland, Prerequisites for Personalized or Precision Treatment using AIT.

25.08.2017: Prof. Ronchese F., Malaghan Institute of Medical Research, Immune Cell Biology Programme Wellington, New Zealand, Transcriptional characterization of dendritic cells during Th2 immune responses.
Prof. Le Gros G., Malaghan Institute of Medical Research, Allergic & Parasitic Diseases Programme Wellington, New Zealand, Regulation of Th2 subset differentiation.

21.09.2017: SIAF - UNIKA-T Meeting, Chairs: Traidl-Hoffmann, Akdis CA., Radzikowska U.: Role of rhinovirus infections and house dust mite on the activation of inflammasome and epithelial barrier in asthma., Gilles S., Rhinovirus infection and pollen., van de Veen W.: B-cell / IgE regulation., Reiger M. Skin microbiome / transcriptome.

29.09.2017: Dr. Järvinen-Seppo KM., Associate Professor of Pediatrics Chief, Pediatric Allergy and Immunology, Founders' Distinguished Professorship of Pediatric Allergy, UR Medicine / Golisano Children's Hospital, University of Rochester, USA, Human milk bioactives and development of food allergy in infants.

29.11. – 01.12.2017: Evaluation of the last 7 years of SIAF, conducted by the University of Zurich.

04.12.2017: Prof. Müller A., Professor of Experimental Medicine, Institute of Molecular Cancer Research, University of Zurich, Helicobacter pylori in health and disease.

04.12.2017: Prof. Straumann A., Chairman Swiss EoE Clinic, Department of Gastroenterology, University Hospital Zurich, Eosinophilic Esophagitis – Some Facts important for Clinicians and for Scientists.

07.12.2017: State Secretary for Education, Research and Innovation (SERI), Dr. Schaad N., Dr. Girardin C., Akdis CA, Epithelial barrier and allergy epidemic. O'Mahony L. Forgotten friends - Bacterial Protection from Allergic Diseases., Bärenfaller K., The Molecular Profile of Allergy., Akdis M., Immune tolerance to allergens: role of B cells. Frei R., Exposure to Non-Microbial N-Glycolylneuraminic Acid Protects Farmers' Children Against Airway Inflammation and Colitis., Wirz O., The role of B lymphocytes during rhinovirus infection.

13.12.2017: Prof. Hellings P., Professor at University Hospitals Leuven Belgium, Guest professor at Ghent University Belgium, Professor at Academic Medical Center, Amsterdam, Founding director of EUFOREA, News from the nose: understanding symptoms by novel immunologic insights.

30.06.2017: Retirement Symposium Prof. Reto Crameri

Crameri R.:	My commitment to allergy/immunology research
Akdis C.:	Molecular mechanisms of chronicity in allergic di seases
Carballido J.M.:	A T cell journey from allergy to autoimmunity se arching for patients' cure
Akdis M.:	Mechanisms of immune tolerance to allergens
O'Mahony L.:	Nature's solution to avoid allergy: bacterial cell wall products and metabolites
Rhyner C.:	The Evanescence Field Technology

Schmid-Grendelmeier P.: Atopic and non atopic dermatitis

Kündig T.:	Novel AIT vaccines
Renz H.:	The neonatal window for immune interventions
Lauener R.:	Molecular basis for immune interventions for the treatment of allergic diseases

Einladung
Abschiedssymposium Prof. Reto Crameri
Ort: Seminarraum Sunstar Alpine Hotel Davos
Zeit: Freitag, 30. Juni 2017, 14:00 Uhr

Universität Zürich
SIAF

SIAF Science Day
14.12.2017

Wirz O.: Modulation of B cell gene expression and function by rhinovirus infection.

Jansen K.: T regulatory cells during human rhinovirus infection.

Karaslaan C.: Immune Regulatory Role of Human Bocavirus I.

Wang M.: The effect of laundry detergents on barrier integrity and transcriptome of human bronchial epithelial cells.

Lunjani N.: Proteome and transcriptome of peadiatric atopic dermatitis.

Altunbulakli C.: Simultaneous skin microbiome and transcriptome analyses reveals a relation between staphylococci-dominated dysbiosis and barrier dysregulation in atopic dermatitis.

Rinaldi A., Simultaneous skin microbiome and transcriptome analyses reveals a relation between staphylococci-dominated dysbiosis and barrier dysregulation in atopic dermatitis.

Steelant B.: Resume of a potent HDAC inhibitor.

Sokolowska M.: Molecular and cellular signature of allergen-specific immunotherapy or mission impossible redefined.

van de Veen W.: Novel effector B cells and their role in immune regulation.

Globinska A.: Identification of novel angiogenesis-related B cell subset.

Barcik W.: Bacteria derived histamine-relevance to immune homeostasis.

Radzikowska U.: House dust mite exposure primes asthmatic bronchial epithelium for inflammasome activation after rhinovirus infection.

Boonpyiathad T.: Asthma phenotypes and immune response profiles during therapy response.

Winner of the SIAF Science Day 2017: Milena Sokolowska

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 Academy of Allergy Clinical Immunology (EAACI) - Member of Allergen Immunotherapy Guidelines

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

Editor In Chief - Journal of Allergy and Clinical Immunology (JACI)

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.
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.
Organizing committee member for the annual World Immune Regulation Meeting (WIRM).

Scientific program committee member for ISMA, Luxembourg (2017).

Organizing committee member for the annual EAACI Immunology Winter School (2017 & 2018).

Management Committee Member (Swiss representative) to EU COST Action FA1402 – Improving Risk Assessment Strategies for Food Allergens.

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

EAACI Executive Committee Member.

External examiner for the Trinity College Dublin MSc in Immunology.

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.
Allergy, Editor in Chief (March 2018)

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

Baerenfaller K.
Frontiers Topic Editor 'Proteomics of Food and Environmental Plant Allergens'

Associate Editor for Plant Proteomics in Frontiers in Plant Science

Crameri R.
Allergy, associate editor

Mycoses, deputy editor

The open Immunology Journal, editorial advisory board member

O’Mahony L.
Allergy, associate editor

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. T. Rothe, Dr. A. Speiser
- Zürcher Höhenklinik Davos Clavadel, Dr. C. Cardoso

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

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. S. Grad, Prof. M. Alini, Dr. F. Moriarty, Prof. R.G. Richards, Dr. B. Stanic, Dr. K. Thompson

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

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

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

Biochem. Institut, University of 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), Dr. S. Generelli, Dr. D. Ulrich

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

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

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

Forschungszentrum 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

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

Hacettepe University, Ankara (TR), Prof. O. Kalayci, Prof. E. Birben, Prof. C. Karaaslan

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

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

Kantonsspital Graubünden, Chur (CH), Dr. M. Kuhn, Prof. W. Reinhart, Prof. T. Fehr, Dr. E. Riedi, Dr. HB. Fahrner

Kantonsspital St. Gallen, Institute of Immunobiology (CH), Prof.

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

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

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

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 (PL), Prof. M. Kowalski, Prof. J. Makowska

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

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

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

Ostschweizer Kinderspital, St. Gallen (CH), Prof. R. Lauener, Dr. C. Roduit

Padua University Hospital, Italy (IT), Prof. A. Muraro

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, Dr. D. Potaczek

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

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 (AT), Prof. Emeritus M. Breitenbach

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

Universitätsspital Bern (CH)
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Schweizerisches Institut für Allergie- und Asthmaforschung

Bilanz per 31. Dezember 2017

(inklusive Drittmittel)

	31.12.2017	31.12.2016
	CHF	CHF
AKTIVEN		
Flüssige Mittel	1'153'230.73	1'606'386.74
Forderungen	171'137.30	96'641.70
Aktive Rechnungsabgrenzungen	278'149.22	274'267.15
	1'602'517.25	1'977'295.59
PASSIVEN		
Verbindlichkeiten	142'873.51	174'902.00
Kontokorrent SFI Stiftung	4'908.60	21'369.40
Passive Rechnungsabgrenzungen	998'139.77	1'203'688.57
Rückstellungen	236'439.56	357'179.81
Eigenkapital	220'155.81	220'155.81
	1'602'517.25	1'977'295.59

Schweizerisches Institut für Allergie- und Asthmaforschung

Betriebsrechnung 2017

(inklusive Drittmittel)

	Rechnung 2017	Budget 2017	Rechnung 2016
	CHF	CHF	CHF
ERTRAG			
Beitrag Bund Forschungsgesetz Art. 16	847'700.00	840'000.00	828'200.00
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	358'005.50	330'000.00	369'303.15
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	0	50'000.00	50'000.00
Beitrag Stiftungen/Drittmittel	67'977.60	0	54'703.60
Einnahmen Miete an AHPD	0	0	31'740.00
Overheadbeiträge	32'574.26	39'414.00	91'404.00
Ertrag aus Dienstleistung Asthmaforschung	0	2'500.00	0
Spenden	700'000.00	0	0
Übriger Ertrag	19'687.20	3'000.00	7'742.69
Finanzertrag	10'126.53	0	806.77
Auflösung von Rückstellungen	120'740.25	0	0
Ausserordentlicher Ertrag	22'976.87	0	34'063.50
WIRM-Kongress	300'823.83	350'000.00	319'188.76
Drittmittel	2'114'618.04	2'216'901.00	2'401'700.51
	5'569'790.08	4'806'375.00	5'163'412.98
AUFWAND			
Personalaufwand	2'848'146.65	2'691'900.00	3'086'478.58
Verbrauchsmaterial	843'293.99	1'216'615.00	976'583.22
Raumaufwand	186'736.55	182'760.00	180'397.90
Unterhalt/Reparaturen/Ersatz	171'210.13	115'500.00	124'722.80
Investitionen	981'094.32	0	211'298.25
Sachversicherungen/Abgaben	8'300.90	7'500.00	7'628.20
Energie- und Entsorgungsaufwand	63'866.31	72'000.00	62'442.45
Verwaltungsaufwand	100'427.75	149'600.00	119'705.62
Reisespesen	84'347.77	50'000.00	93'200.17
WIRM-Kongress	267'541.79	306'500.00	290'395.94
Übriger Betriebsaufwand	12'083.78	2'000.00	7'532.23
Finanzaufwand	2'711.48	2'000.00	2'328.30
Ausserordentlicher Aufwand	28.66	10'000.00	0
	5'569'790.08	4'806'375.00	5'162'713.66
Ergebnis	- 0.00	0	699.32
	5'569'790.08	4'806'375.00	5'163'412.98

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