SIAF

Swiss Institute of Allergy and Asthma Research

ANNUAL REPORT 2018

University of Zurich[UZH]

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The Swiss Institute of Allergy and Asthma Research (SIAF) is a department of the foundation Swiss Research Institutes for High Altitude Climate and Medicine Davos (SFI) and an affiliated institute of the University of Zurich and member of the Life Science Zurich Graduate School. The institute in its current form arised from the medical department of SFI in 1988. Since this time the research activities at SIAF are focused on basic research in the field of allergies and asthma.

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

SIAF

Schweizerisches Institut für Allergie- und Asthmaforschung

Eröffnung des Schweizerischen Instituts für Allergie- und Asthmaforschung Davos, 16./17. Juni 1989

Seit weit über 100 Jahren spielt der weltberühmte Höhenkurort Davos für Lungenkranke eine bedeutende Rolle. Waren es anfänglich weitgehend Tuberkulosepatienten, die in den zahlreichen Davoser Kliniken auf Besserung hofften, besuchen heute in erster Linie Asthmatiker und Allergiker den Kurort in den Bündner Alpen. Es ist daher kein Zufall, dass ausgerechnet Davos als Sitz des neueröffneten Schweizerischen Instituts für Allergie- und Asthmaforschung (SIAF) bestimmt wurde.

Die Kenntnisse auf dem Gebiet der allergischen Krankheiten sind noch sehr lückenhaft. Die Hauptaufgabe des SIAF ist deshalb die Erforschung der zellulären und molekularen Zusammenhänge, die zu allergischen Erkrankungen führen. Unter der Leitung des Berner Privatdozenten Dr. phil. nat. Kurt Blaser, werden rund 20 Forscher in drei Gruppen unterteilt, dieser anspruchsvollen Frage nachgehen.
An der Eröffnungsfeier, der über 200 Gäste aus aller Welt beiwohnten, drückten zahlreiche Redner ihre Genugtuung darüber aus, dass mit der Gründung der SIAF eine Stätte geschaffen wurde, an der Betroffene wie Interessierte, das heisst, Patienten wie Forscher, in klinischer Form gemeinsam Problemlösungen erarbeiten können.

Bericht des Direktors

Prof. Dr. med. 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. Mit der Universität Stanford (Sean Parker Asthma and Allergy Center) besteht eine intensive Zusammenarbeit.

Das SIAF hat über 1'250 Fachbeiträge veröffentlicht und gehört zu den meistzitierten Instituten weltweit. Die vom SIAF publizierten Artikel wurden über 44‘000 Mal zitiert. Das Institut gehört mit seinen rund 45-50 Mitarbeitern weltweit zu den Besten in Bezug auf seine Grösse. Es ist eine international bekannte Ausbildungsstätte für Doktoranden und Habilitanden.
2018 wurden 75 wissenschaftliche Arbeiten in begutachteten internationalen Fachzeitschriften mit “Impact Factor” veröffentlicht oder sind noch in Druck. 2018 erreichte das SIAF einen Gesamtwert des “Impact Factors” von 572.662 und einen Durchschnitt von 7.635 Punkten pro Publikation. Die neusten Ergebnisse wurden zudem in 36 Abstracts an verschiedenen Fachtagungen mitgeteilt. Unsere Mitarbeitenden wurden zu 71 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 32 verschiedenen Sessionen hatten SIAF-Mitarbeitende den Vorsitz. Zusätzlich werden 33 wissenschaftliche Ämter in internationalen Gesellschaften durch Wissenschaftler des SIAF besetzt. Des Weiteren sind die Forscher des SIAF bei insgesamt 18 internationalen Zeitschriften als Mitglieder der redaktionellen Komitees tätig. Zudem hält Prof. C. A. Akdis seit 2018 das Amt des Chefredaktors der Fachzeitschrift Allergy inne. Als Folge seiner international höchst angesehenen wissenschaftlichen Publikationen wurde Prof. Dr. C. A. Akdis 2018 zum dritten Jahr in Folge von Thomson Reuters in die Gruppe der 1‘000 meistzitierten Forscher aus allen wissenschaftlichen Fachbereichen weltweit aufgenommen.

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. Die Hochgebirgsklinik Davos (HGK) konnte unter einem neuen Betriebskonzept neu ausgerichtet werden, mit dem Ziel eine der führenden Kliniken im Allergiebereich zu formen, nicht zuletzt dank der Nähe zur Forschung.
Das neue Gebäude wird mit 3’136 m2 Fläche für Labor- und Büroräume für 75 Mitarbeiter ausgelegt sein. Die Labore werden mit modernster Technologie ausgestattet. Die Grundsteinlegung fand am 04. Mai 2018 statt. Das beauftragte Architekturbüro OOS AG hat mit diesem Projekt schon vor der Inbetriebnahme den renommierten Real Estate Award 2018 gewonnen. Der Bezug der Räumlichkeiten ist per Frühsommer gesichert. Das SIAF wird Anfangs August seine Forschungstätigkeiten in den neuen Laboren aufnehmen können. Am 06. September 2019 wird die offizielle Eröffnung stattfinden. Ein Tag danach ist der Tag der offenen Tür für alle interessierten Einheimischen und Gästen geplant, damit der Bevölkerung ein Einblick in den Medizincampus gewährt werden kann.
Dank der Unterstützung durch die CK-CARE konnten seit 2009 mehr als 45 wissenschaftliche Mitarbeitende eingestellt und über 70 akademische Gäste im Austauschprogramm aufgenommen werden. Darüber hinaus wurden 170 Publikationen in namhaften Zeitschriften veröffentlicht.

Atopische Dermatitis (AD auch als Neurodermitis bekannt) ist eine entzündliche Hauterkrankung, von der weltweit bis zu 20% der Kinder und 5% der Erwachsenen betroffen sind – Tendenz steigend. Die Epithelbarriere, die das innere Gewebe üblicherweise schützt, ist bei AD-Patienten gestört. Aufgrund der Defekte in der Epithelbarriere dringen also diese gewebeschädigenden Stoffe ins Gewebe ein und wirken direkt auf das Immunsystem ein.
Unser Ziel ist es, ein *in-vivo*-Verfahren zur Beurteilung der epithelialen Barrierefunktion zu entwickeln. Dies mit Hilfe einer neueren Technik zur Charakterisierung von Epithelgewebe – die elektrische Impedanzspektroskopie. Mit dieser Messtechnik wird ein harmloses elektrisches Signal durch die Haut gesendet und so die elektrischen Eigenschaften wie Form, Ausrichtung und Grösse des Gewebes analysiert. Die Messungen haben gezeigt, dass bei einer defekten Barriere die elektrische Impedanz passend mit dem Grad der Schädigung verringert ist. Aufgrund dieser Erkenntnisse haben wir eine klinische Studie an der Hochgebirgsklinik Davos Wolfgang initiiert, in der die elektrische Impedanz und andere biologische Parameter in Patienten mit atopischer Dermatitis gemessen wurden, die sich in der Klinik einer 21-tägigen Therapie unterzogen. Wir haben festgestellt, dass die Werte für die elektrische Impedanz in Patienten mit atopischer Dermatitis deutlich niedriger sind als in gesunden Probanden, und dass ihre Haut geschädigt ist.
Wir sind uns sicher, dass dieses *in-vivo*-Verfahren zur Beurteilung von Hautbarrieredefekten der Frühdiagnose für die Vorhersage einer Entwicklungsgefahr für atopische Dermatitis bereits im Kindesalter dient und damit frühzeitig geeignete Präventivmassnahmen ergriffen werden können.

Das SIAF hat bis heute wichtige patienten-relevante Erkenntnisse auf diesem Gebiet beitragen können. So konnten umfassende Analysen mit den Patienten in der HGK durchgeführt werden. Diese Analysen wurden unter Verwendung der personalisierten Medizin und der Identifikation von Patientensubgruppen durchgeführt. Weiter wurde ein CK-CARE-Panel für Blutproben entwickelt, die mittels Durchflusszytometrie direkt nach Blutentnahme und ohne Zellkultur gemessen werden können. Wir erwarten, dass die Allergiesubgruppe der Patienten in der HGK dank dieser Methode innerhalb von 2-3 Stunden nach ihrer Aufnahme analysiert werden können.

Allgemein wird angenommen, dass Asthma und Allergien im Zusammenhang mit der heutigen Lebensumwelt steht, denn ihre Prävalenz ist in den Industrieländern höher.
Es ist hinlänglich dokumentiert, dass eine erhöhte Belastung durch verschiedene Umweltfaktoren wie Schadstoffe, Atemwegsviren, Tabakrauch, Allergene in der Luft, Duftstoffe, Konservierungsmittel, Metalle und Ernährung zur Entwicklung und Verschlechterung von Neurodermitis, Asthma und anderen Allergien beitragen kann. Es zeichnet sich zunehmend ab, dass Personen, die am Arbeitsplatz und zu Hause vermehrt Reinigungsmittel ausgesetzt sind, ein grösseres Risiko für die Entwicklung von Allergien und Asthma haben. Dies könnte ein nicht zu unterschätzendes Problem für das öffentliche Gesundheitswesen darstellen.
Wir haben die Rolle von Waschmitteln auf die Funktion der Schleimhaut- und Hautbarriere und die Wirkung von Waschmitteln auf die Molekülveränderungen sowie Zelltod und Toxizität in humanen Epithelzellen der Lunge intensiv untersucht. Unsere Daten zeigen, dass Waschmittel und Waschmittelrückstände eine toxische Wirkung haben und die Barriereintegrität stören.
Die Epithelzellen formen eine Schutzbarriere gegen das Eindringen von Umweltstoffen, die eingeatmet werden. Aus unseren CK-CARE-Studien gibt es immer mehr Hinweise darauf, dass eine gestörte Epithelbarriere eine Eigenschaft ist, die bei vielen chronischen Entzündungskrankheiten vorkommt. Weiter konnten wir beweisen, dass die Tenside (Hauptbestandteil in Waschmitteln) die Integrität der Barriere in menschlichen Hautzellen zerstören. Dies könnte das Risiko eines Eindringens von Allergenen und die darauffolgende Hautentzündung erhöhen.

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 zwölften Mal fand vom 14. bis 17. März 2018 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 127 Vorträge und 242 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, Mai 2019

Report of the director

Prof. Dr. med. 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 Grisons.

Allergic diseases showed an epidemic rise during the last several decades and are affecting the lives of more than one billion people worldwide. Their prevalence continues to increase in developing countries in parallel to urbanization and industrialization. It is expected to reach to 4 billion patients in 2050, when the world pupulation reaches to 10 billion. Currently, 300 million people (4.2%) suffer from asthma, 500 million (6.5%) from atopic dermatitis, 900 million (12 %) from allergic rhinitis and 700 million (9%) from food allergy worldwide.

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 1'250 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 44'000 times. The institute with its approximately 45-50 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.

This year, SIAF members received 16 awards and Honors including the Distinguished fellowship of the American College and the Ulrich Müller-Gierok Allergy Prize.

In 2018, 75 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 572.662 and an average of 7.635 points per publication. The latest results were also communicated in 36 abstracts at various symposia. Our employees were invited to 71 different seminars and lectures at national and international congresses. SIAF co-workers chaired 32 different international sessions. In addition, 33 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 18 international journals. In addition, Prof. C. A. Akdis holds the position of Editor-in-Chief of the Allergy journal.

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 Hochgebirgsklinik Davos (HGK) was realigned under a new operating concept with the aim of becoming one of the leading clinics in the allergy, not least thanks to the proximity of the research. The new building on the Hochgebirgsklinik Davos Wolfgang will have 3’136 m2 of laboratory and office space for 75 coworkers. The labs will be equipped with the most modern technology. The foundation stone was laid on 04 May 2018 and as of today the building is completed with extremely front laboratories and equipment including a biosafety level 3 lab. The moving into the new building is planned for the beginning of July 2019. SIAF will be able to run his research activities from the beginning of August 2019 on. On 06 September 2019, the official opening will have place and one day later, all local people are invited to gain an insight of the new Campus. Thanks to the support of CK-CARE, more than 45 scientific staff have been recruited since 2009 and more than 70 academic guests have joined the exchange fellowship program. More than 170 publications were published in high impact journals.

The new building at the Medizincampus Davos Wolfgang

SIAF has focused on direct patient-relevant human immunology and cell biology during the last several years with a series of projects on immune regulatory aspects and particularly allergen tolerance; regulation of tissue cells and tissue barriers; novel methods for the detection of tissue barriers; regulatory aspects of noncoding DNA and development of novel vaccines. Main projects are listed below:

Laundry detergents directly disrupt barrier integrity in human bronchial epithelial cells

It is generally accepted that asthma and allergy are associated with environment of modern life since their prevalence being higher in developed countries. It is well documented that increased exposure to multiple environmental factors such as air pollutants, respiratory viruses, tobacco smoke, allergens in the air, fragrances, preservatives, metals and diet contribute to the development and exacerbation of asthma and other allergic diseases. Growing evidence showed that people high exposed to cleaning agents both in the workplace and at home were at high risk of developing allergy and asthma, which may represent an important public health issue. The popularizing of synthetic laundry detergents coincided with the uprising of allergic diseases over the past few decades. Laundry detergent contain numerous ingredients which may be irritants (surfactants, bleaches) or sensitizers (fragrances, enzymes) and may cause asthma and other allergic diseases. Allergic disease symptoms in domestic cleaning women are associated with exposure to bleaches and other irritant agents. Several studies reported occupational asthma due to EDTA or enzymes in detergent factory, which also suggested the issue of sensitisation outside detergent manufacture should be pay attention.

The epithelial cells form a barrier to defense against inhaled environmental insults. We demonstrated that defective epithelial barrier function is a feature of many chronic inflammatory diseases. Our findings suggested that the allergenicity of inhaled substances depends on their potential to disrupt epithelial barriers. We also showed that surfactants, one of the main constituents of detergents, disrupted the barrier integrity of human skin cells which may increase the risk of allergen penetration and the succeeding skin inflammatory reaction.

We extensively investigated the roles of laundry detergent on mucosal and skin barrier function and the effects of laundry detergent on molecular changes and cell death and toxicity in human bronchial epithelial cells. Our data demonstrated that laundry detergents and laundry residues showed a toxic effect and a directly disruptive effect on barrier integrity.

Direct assessment of skin epidermal barrier by electrical impedance spectroscopy

Several skin and mucosal inflammatory disorders, such as atopic dermatitis (AD), have been associated with an impaired epithelial barrier function, which allows allergens, pollutants or microbes to enter the tissue and activate the immune response. The aim of this study was to establish a method to directly assess the *in vivo* status of epithelial barrier function by electrical impedance (EI) spectroscopy. After transmitting a harmless electrical signal through the skin, electrical impedance is measured within 8 seconds.

In a recently completed study epidermal barrier of mice was damaged by epicutaneous application of several proteases and cholera toxin and by tape stripping. EI and transepidermal water loss (TEWL) were measured before and after the application. Furthermore, histological analysis, IHC and quantitative RT-PCR were performed in skin biopsies of the mice to evaluate the epidermal barrier. In addition, mice skin was treated with some commercially available laundry detergents, previously described to disrupt the barrier integrity. After the treatment with proteases tape strip or detergent, a dose dependent reduction of EI was detected. Simultaneously, an increase of TEWL was observed, showing a significant negative correlation with EI, demonstrating that changes of EI were directly linked to epidermal barrier defects. Barrier disruption was confirmed by histological analysis, which showed an impaired stratum corneum and inflammation after papain application, and by IHC and qPCR, which showed downregulation of filaggrin and other proteins involved in the barrier function.

A clinical study is ongoing for the analyses of skin barrier to establish a reliable and efficient method to directly assess the *in vivo* status of the epidermal barrier by EI spectroscopy to develop a new tool for diagnosis and monitoring of the treatment. AD patients were followed during a 21 days' clinical treatment at the High Altitude Clinic in Davos, Switzerland. EI spectroscopy and TEWL were measured in both lesional and non-lesional skin.

EI values were detected in atopic dermatitis patients within 8 seconds single touch of the microchip head of the Navisense instrument, without any pain, or side effects. Apparently, EI spectroscopy is a good candidate as an *in vivo* diagnostic method to determine barrier defects, useful for the clinical assessment of the nature of the pathology for the identification of certain disease endotypes and phenotypes related to barrier deficiency, in particular atopic dermatitis. In addition, this technology can help identifying atopic dermatitis patients at risk of relapse, thus indicating the necessity to reinforce topical therapy to enhance the skin barrier in order to prevent exacerbations. Furthermore, EI appers as a suitable tool to detect children at risk of developing AD, allowing the application of preventive measures.

In depth analysis of food allergen-specific B cell responses in allergic and tolerant children

The prevalence of food allergy is an increasing public health concern affecting millions of people worldwide. The role of allergen-specific B cells in the development of tolerance to food allergy and their production of allergen-inducing IgE antibodies remain unclear. Therefore, we aim to perform an in-depth study on the role of allergen-specific B cell during food-immune tolerance induction and oral immunotherapy. As a model, we focus on cow's milk allergy in children. B cells specific for the major cow's allergen, αS1-casein were isolated from the blood of natural tolerance and allergic individuals. The RNA-sequencing was performed for quantitative transcriptomics and differential gene expression between these groups.

Probing the allergen-specific B cell repertoire in human models of high-dose allergen exposure-induced immune tolerance

Understanding the mechanisms of tolerance induction to allergens is critical for the development of targeted therapies for treatment of allergies. Beekeepers, who are frequently exposed to high-doses of bee venom allergens, represent a unique human in vivo model for studying the immunological mechanisms underlying development of allergen tolerance in response to high-dose allergen exposure. Using cutting edge techniques we isolate, immortalize and characterize bee venom allergen-specific B cells in healthy beekeepers and bee venom allergic individuals who receive allergen-specific immunotherapy. This will result in detailed understanding of the allergen-specific B cell development in healthy and allergic individuals and may lead to the discovery of therapeutic antibodies for treatment of allergies.

Immunometabolism in allergy, asthma and immune tolerance

Due to environmental and lifestyle changes, there is an increasing frequency of allergies, autoimmune disorders and chronic respiratory diseases. Immune cells need to engage in a wide array of energetically demanding metabolic processes in order to respond correctly to allergens, viruses or bacteria. Understanding the link between the dysregulated systemic and cellular metabolism with the incorrect function of immune system will provide novel targets for effective treatments in these diseases. Therefore, using high throughput transcriptomic, proteomic and metabolomic methods, coupled with gene editing, multi-color flow cytometry and forefront imaging we will uncover immune and metabolic reprogramming of immune cells in health and in disease.

Novel mechanisms and biomarkers of allergen immunotherapy (AIT)

Allergen immunotherapy is the only curative treatment for patients suffering from allergic diseases by inducing allergen-specific immune tolerance. As prediction of long-term treatment efficacy of AIT remains difficult, there is a great need to discover biomarkers to monitor clinical efficacy of AIT. Similarly, molecular mechanisms of acquiring and maintaining tolerance to specific allergens on the single cell level remain incompletely understood. Thus, we are conducting clinical studies involving patients receiving subcutaneous AIT and healthy controls. By combining cutting edge multi-omics analyses of allergen-specific T cells, B cells and innate immune cells as well as plasma and tissue samples with precise monitoring of clinical efficacy we aim to uncover and validate novel mechanisms on a single cell level and provide novel predictive biomarkers.

House dust mite priming enhances rhinovirus-induced inflammasome activation in asthma

Common environmental factors such as viruses and allergens can lead to asthma development, disease progression and exacerbations. Viral infections combined with allergen sensitization and exposure in asthmatics cause significant increase in the incidence of emergency hospitalizations. We are studying molecular mechanisms of combined exposures to common respiratory viruses and allergens in primary human bronchial epithelium *in vitro* as well as in *in vivo* experimental viral infection in healthy subjects and asthmatic patients. Deeper understanding of novel innate immune mechanisms linking rhinovirus and house dust mite exposures will provide novel targets for effective treatment of asthma exacerbations and progression.

Towards a molecular view on allergies

In a new project started in the group of PD Dr. Katja Baerenfaller, translational regulation as a mechanism to change gene expression during CD4+ T cell differentiation and activation is investigated. The focus here will be to identify translation events of short open reading frames (sORFs) encoded on transcribed non protein-coding RNAs (ncRNAs). Other research efforts will concentrate on studying cellular proteotpyes of different immune cell types in health and allergic diseases. Here, the first targets will be to study the production of alternative protein N-termini and the regulation of protein turn-over through polyubiquitylation events.

The Molecular Allergology group furthermore works together with HTW Chur, the leading house in this project as appointed by the Canton of Graubünden, in establishing the Center for Data analytics, Visualization and Simulation (DAViS). Our aim here will be to add modern computational methods, such as machine learning, to the tools of how to analyze life science data containing several variables and various data types. A first project analyzing existing data on allergic and healthy children already started, including the mutual training at the interface between biology and informatics.

Development of the Allergy Office in SIAF

Allergy is a more than 70 years old Journal which is the flagship journal of EAACI European Academy of Allergy and Clinical Immunology (13'000) members. Prof. Cezmi A. Akdis has been appointed as the Editor-in-Chief of Allergy. Managing editor, graphics editor and social media editor have been appointed and an office has been established in SIAF premises. A new board of associate editors and editorial board have been selected. Many new developments and sections have been initiated and implemented, such as a fully colourful journal, new cover, graphical abstracts, original figures of cells and tissues by allergy graphics, letters to the editor, algorithms in allergy, recent patents, extensive reviews, new table of contents. Recently, Allergy has been selected into the ten Journals of Wlley because of its performances throughout 2018.

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. 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 14 to 17 March 2018, the internationally reknown World Immune Regulation Meeting (WIRM) took place for the twelfth 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 127 lectures and 242 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 honored 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. Finally, I would like to thank the authorities in Cantonal and Davos institutions, who tirelessly support SIAF in every respect.

Davos, May 2019

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O'Mahony Liam	PD, PhD, Head Molecular Immunology * (- July 2018)
Rhyner Claudio	PhD, Head Vaccine Development *
Sokolowska Milena	PhD, Head Immune Metabolism * (since October 2018)

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Cellular Allergy / Immunology

Prof. Dr. Cezmi A. Akdis, MD

With an epidemic rise during the last 60 years, allergic diseases of the skin and mucosa are affecting the lives of more than one billion people worldwide. Their prevalence continues to increase in developing countries in parallel to urbanization and industrialization. Currently, 300 million people (4.2%) suffer from asthma, 500 million (6.5%) from atopic dermatitis, 900 million (12 %) from allergic rhinitis and 700 million (9%) from food allergy worldwide.

All of the above mentioned diseases are more common in industrialized countries compared to developing countries. The difference in this prevalence has been linked to hygiene, having less bacterial infections, having less worm infections, high dose of allergen exposure, westernized lifestyle. It is nowadays well documented that increased exposure to multiple environmental factors associates with the development and exacerbation of asthma and other allergies.

An intact functional skin and mucosal barrier is considered to be crucial for the maintenance of tissue homeostasis as it protects the host tissues from infections and exposure to noxious environmental toxins and allergens. Recent data demonstrated the contribution of barrier dysfunction to the development of inflammatory diseases in the skin, airways, esophagus and gut. A defective barrier has been documented in asthma, atopic dermatitis, chronic rhinosinusitis, eosinophilic esophagus, allergic rhinitis, and inflammatory bowel disease.

Personalized Medicine.

Atopic dermatitis (AD) is an inflammatory skin disorder that affects up to 20% of children and 5 % of adults. The epithelial barrier, which normally protects the internal tissues from environmental stresses, by minimizing water loss and preventing the entry of pathogens, pollutants and allergens, results impaired in AD. Hence, defects in the epithelial barrier allow tissue-damaging factors to enter the tissue and thus activate the immune response.

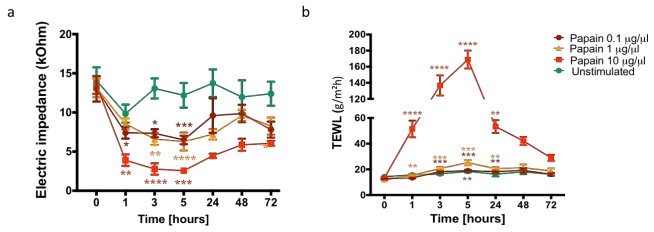
SIAF has specifically contributed to direct patient relevant findings and personalized medicine in this area so far, which can be listed as extensive analyses of HGK patients with personalized medicine techniques and identification of patient subtypes and development of CK-CARE panels for direct flow cytometry of patient blood samples immediately after it was taken from patients without any cell cultures. The panel consists of upto 100 antibodies for cell surface molecules and aims to type blood cells with extreme front knowledge applied to sub groups of patients.

SIAF has licence from the Canton to perform these patient analyses and has been giving service to klinics in Davos and Engadin. This service has now extremely improved to very detailed individual analyses to identify patient sub groups. One major patient subgroup is identified as a specific molecule CRTH2 high patients. This molecule was demonstrated to be functional and high in several subgroups of immune system cells in highly allergic patients who show eosinophilia. We expect a bed to bench analyses will be possible for HGK patients for subgrouping of their allergies at the time of admission within 2-3 hours.

Direct assessment of skin epithelial barrier by electrical impedance spectroscopy.

Rinaldi AO, Morita H Wawrzyniak P, Dreher A, Grant S, Svedenhag P, Akdis CA.

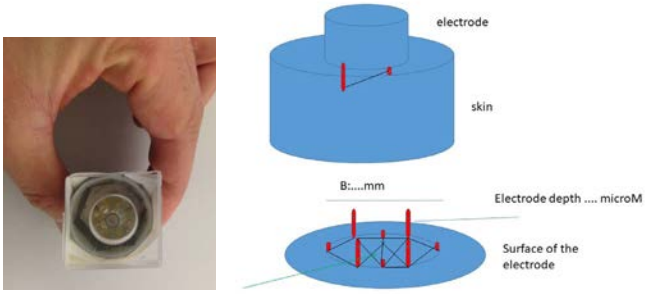
This study aims to establish a method to assess the epithelial barrier function *in vivo* by electrical impedance (EI) spectroscopy, a recent technique for the characterization of epithelial tissues. By this technique, a harmless electrical signal is sent through the skin and the response of the tissue is analyzed, which is influenced by several cellular properties, such as shape, orientation and size. In order to validate this technique, we treated the skin of mice with some molecules able to destroy the epithelial barrier. We observed that, after damaging the barrier, a decrease of the electrical impedance could be detected, consistent with the type and degree of the damage.



Epicutaneous administration of increasing concentrations of papain damages the epithelial barrier, causing a dose-dependent decrease of EI and increase of TEWL of skin.

WT C57BL/6 mice were depilated on their back by using a depilatory cream. Three days after depilation, 100 µl of a solution containing different doses of the protease papain (0.1µg/µl, 1µg/µl and 10µg/µl), or PBS as control (unstimulated), were applied by means of a skin patch. EI (a) and TEWL (b) measurements were performed before treatment and 1, 3, 5, 24, 48, 72 hours after the treatment. Electrical impedance is expressed in kOhm, at the frequency of 1000 Hz. TEWL is expressed in g/m2h. Data are shown as mean ± SD (n=8). *: p<0.05, **: p<0.01, ***: p<0.001, ****: p<0.0001.

Electrical impedance is measured by Nevisense® device, which allows measurements at four different depths in only 8 seconds. The electrode is composed of five bars furnished of 225 microscopic micro-invasive pins (45 pins per electrode bar). The electrical signal is sent between the bars at 35 different frequencies, between 1 kHz to 2.5 MHz, and in different combination to create measurement data at different areas and different depths.



First Prototype of the Electric Impedance Chip Electrode Designed by Cezmi Akdis in 2014, produced in CSEM, Landquart.

Based on these results, we have started a clinical study at HGK clinic in Davos, where EI and other biological parameters have been measured in AD patients during a 21 days' clinical treatment they receive at the clinic. We have noticed that AD patients present significantly decreased EI values compared to healthy subjects and AD lesions are characterized by a decrease of EI, if compared to non-lesional skin. Moreover, lesional skin shows an increase of EI during the 21 days treatment and SCORAD (the clinical score for assessing the severity of AD) negatively correlates with EI: when SCORAD is high, which means that the patient has a severe condition, then EI is low. Now we are planning a multicenter study that aims to early detection of skin barrier defects in children. Infantile eczema is taking place in more than 10% of the children and early detection of barrier defects. The mutation of the genes requires DNA analyses and is relatively costly. Our aim is to disseminate this method worldwide for early screening of atopy prone children. Obviously, there is a huge direct contribution to the patients expected. These front studies are not covered by the insurance systems and require sponsorships in the early stages of development.

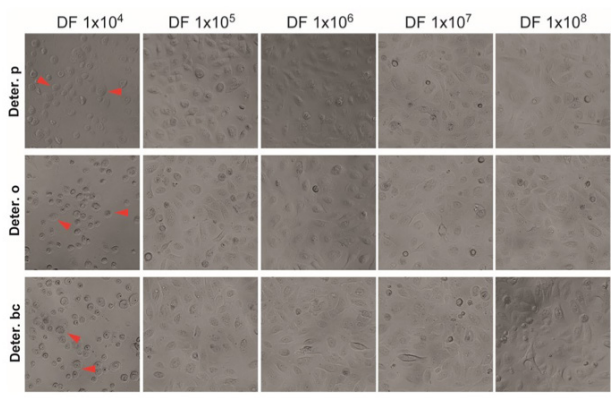
In conclusion, our data suggest that this technique is an *in vivo* method to assess skin barrier defects and is a good candidate as an early diagnostic tool for the prediction of the risk to develop atopic dermatitis in young subjects, allowing the possibility to apply possible preventive measures. In addition, the technique is suitable for the assessment and the evaluation of a given therapy during the patient hospitalization, and it might help to identify AD patients at risk of relapse, thus indicating the necessity to reinforce the topical therapy in order to prevent exacerbations.

Laundry detergents and detergent residue after rinsing directly disrupt tight junction barrier integrity in human bronchial epithelial cells.

Wang M, Tan G, Eljaszewicz A, Meng Y, Wawrzyniak P, Acharya S, Altunbulakli C, Westermann P, Dreher A, Yan L, Wang C, Akdis M, Zhang L, Nadeau KC, Akdis CA.

J Allergy Clin Immunol. 2018 Nov 27. pii: S0091-6749(18)31665-8.

Defects in the epithelial barrier have recently been associated with asthma and other allergies. The influence of laundry detergents on human bronchial epithelial cells (HBECs) and their barrier function remain unknown. We investigated the effects of laundry detergents on cytotoxicity, barrier function, the transcriptome, and the epigenome in HBECs. Air-liquid interface cultures of primary HBECs from healthy control subjects, patients with asthma, and patients with chronic obstructive pulmonary disease were exposed to laundry detergents and detergent residue after rinsing. Cytotoxicity and epithelial barrier function were evaluated. RNA sequencing, Assay for Transposase Accessible Chromatin with high-throughput sequencing, and DNA methylation arrays were used for checking the transcriptome and epigenome. Laundry detergents and rinse residue showed dose-dependent toxic effects on HBECs, with irregular cell shape and leakage of lactate dehydrogenase after 24 hours of exposure. A disrupted epithelial barrier function was found with decreased transepithelial electrical resistance, increased paracellular flux, and stratified tight junction (TJ) immunostaining in HBECs exposed to laundry detergent at 1:25,000 dilutions or rinse residue at further 1:10 dilutions. RNA sequencing analysis showed that lipid metabolism, apoptosis progress, and epithelially derived alarmin-related gene expression were upregulated, whereas cell adhesion-related gene expression was downregulated by laundry detergent at 1:50,000 dilutions after 24 hours of exposure without substantially affecting chromatin accessibility and DNA methylation. In conclusion, our data demonstrate that laundry detergents, even at a very high dilution, and rinse residue show significant cell-toxic and directly disruptive effects on the TJ barrier integrity of HBECs without affecting the epigenome and TJ gene expression.



Dose dependent cytotoxicity and disruption of barrier integrity in HBECs in response to laundry detergents. Cytotoxicity of monolayer cultured HBECs treated by commercial detergents at different dilutions. Representative phase-contrast images of monolayer cultured HBECs treated by detergent A or detergent B. Dilution factors are labeled on the top. Doses of 1:10'000 dilutions are toxic and are visibly killing the cells.

Staphylococcus aureus enhances the tight junction barrier integrity in healthy nasal tissue, but not in nasal polyps.
Altunbulakli C, Costa R, Lan F, Zhang N, Akdis M, Bachert C, Akdis CA. J Allergy Clin Immunol. 2018 Aug;142(2):665-668.e8. doi: 10.1016/j.jaci.2018.01.046.
Epithelial tight junctions (TJ) consist of different transmembrane, scaffold-adaptor proteins and signaling molecules and form the apical-most intercellular junction between epithelial cells. Epithelial barrier function of epithelial cells in the sinus tissue of chronic rhinosinusitis patients have been demonstrated to be defective with major contributions from our group.These studies suggest that tissue integrity is disturbed in patients; and allergens, bacterial toxins and other particles are able to penetrate the epithelium, where they may activate the immune system leading to severe chronic inflammation in both diseases. Therefore, paracellular sealing of sinus epithelial cells in chronic rhinosinusitis appears to be very important to prevent the infiltration of the subepithelial tissues by factors that induce allergic inflammation. Tight junctions are responsible for the regulation of paracellular flux and epithelial impermeability. In addition, they prevent foreign particles, such as allergens, to enter into subepithelial layers. Consequently, they can be considered as gatekeepers that could contribute both to aggravation of inflammation related tissue damage or resolution of inflammation via drainage. Healthy nasal tissue response to S. aureus is in the direction of tightening the barrier, whereas in diseased tissues the leakiness of epithelium increases because of S aureus exposure.

Der p 1-specific regulatory T-cell response during house dust mite allergen immunotherapy.
Boonpiyathad T, Sokolowska M, Morita H, Rückert B, Kast JI, Wawrzyniak M, Sangasapaviliya A, Pradubpongsa P, Fuengthong R, Thantiworasit P, Sirivichayakul S, Kwok WW, Ruxrungtham K, Akdis M, Akdis CA.
Allergy. 2018 Nov 28. doi: 10.1111/all.13684. [Epub ahead of print]
Allergen-specific immunotherapy (AIT) is the only available treatment for allergic diseases that can induce specific immune tolerance to allergens. The key mechanisms involved in this process include changes in allergen-specific regulatory T (Treg) cells. We studied 25 allergic rhinitis patients undergoing subcutaneous house dust mite-specific immunotherapy. Peripheral blood mononuclear cells were studied before and after 10, 30 weeks, and 3 years of AIT. Der p 1-specific T regulatory cell responses were investigated by characterization of Der p 1-MHC class II tetramer-positive cells and correlated with nasal symptom score. Twelve of 25 AIT patients matched with their MHC class II expression to the Der p 1 peptide-MHC class II tetramers. A significant increase in the numbers of Der p 1-specific FOXP3+ Helios+ CD25+ CD127- Treg cells after 30 weeks was observed, which slightly decreased after 3 years of AIT. In contrast, Der p 1-specific immunoglobulin-like transcript 3 (ILT3)+ CD25+ Treg cells decreased substantially from baseline after 3 years of AIT. ILT3+ Treg cells displayed compromised suppressive function and low FOXP3 expression. In addition, Der p 1-specific IL-10 and IL-22 responses have increased after 30 weeks, but only IL-10+ Der p 1-specific Treg cells remained present at high frequency after 3 years of AIT. Increased number of FOXP3+ Helios+ and IL-10+ and decreased ILT3+ Treg cell responses correlated with improved allergic symptoms.
In conclusion, these results indicate that AIT involves upregulation of the activated allergen-specific Treg cells and downregulation of dysfunctional allergen-specific Treg cell subset. Correction of dysregulated Treg cells responses during AIT is associated with improved clinical response.

Davos, May 2019

WORLD IMMUNE REGULATION MEETING XIV

4 - 7 March 2020 | Davos, Switzerland

„Immune Activation, Effector Functions and Immune Tolerance with a special focus on Autoimmunity and Allergy“

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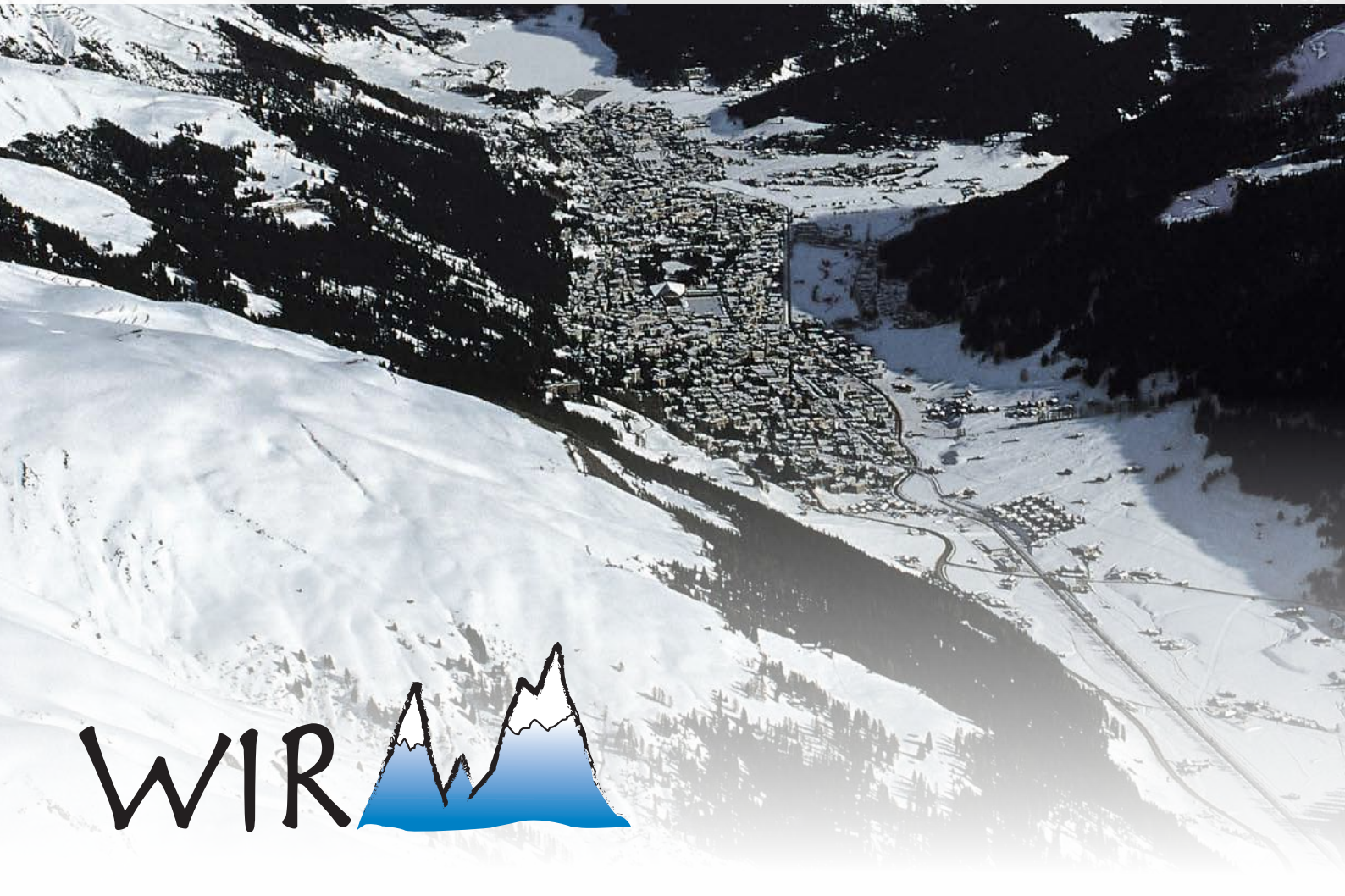


WIR

Immunodermatology

Prof. Dr. Mübeccel Akdis, MD, PhD

Regulatory and effector B cell subsets

Induction of immune tolerance has become a prime target for prevention and treatment for many diseases that involve dysregulation of the immune system, including asthma, allergy, autoimmunity, cancer, organ transplantation, chronic infections, and infertility. However, antigen-specific tolerance induction has achieved varying success in these different areas, with allergen immunotherapy of allergic diseases being the one of the most established.

It is generally accepted that allergen-specific peripheral T-cell tolerance is characterized mainly by generation of allergen-specific Treg cells and IL-10, a major responsible cytokine from immune tolerance is increasingly produced by the specific Treg cells. B cells contribute to immune responses essentially through antigen presentation to T cells, secretion of cytokines and production of antibodies after differentiation to plasma cells. Human B cells express several toll like receptors (TLR) including TLR1, 6, 7, 8, 9 and 10. TLR7 (activated by single stranded RNA) and TLR9 (activated by hypomethylated CpG DNA) are the highest expressed TLRs on B cells. IL-10 is a key regulator of inflammatory responses and protects the host from tissue damage as a result of excessive inflammation. IL-10 enhances the survival, proliferation, differentiation and isotype switching of human B cells. IL-10 augments IgG4 production, whereas it inhibits IL-4-induced IgE class switch recombination. IL-10-mediated immunosuppressive functions of B cells have been described in murine models of autoimmunity, infection, and cancer. Patients treated for rheumatoid arthritis with the B cell depleting antibody rituximab showed exacerbation of ulcerative colitis and development of psoriasis illustrating the relevance of immune regulatory functions of human B cells. Interestingly, an increase in IL-10-producing B cells also occurs during ultra-rush high dose allergen-specific immunotherapy of venom allergic individuals by bee venom. Regulatory B cells expressing IL-10 suppress immune responses and the lack or loss of regulatory B cells leads to exacerbated symptoms in experimental autoimmune encephalitis, chronic colitis, contact hypersensitivity, collagen-induced arthritis and non-obese diabetic mouse models. Another B cell-related immune regulatory response restricted to humans is induction of non-inflammatory IgG4 antibodies, which is characteristic for high dose antigen tolerance models. Several molecules including CD25 and PD-L1 were upregulated in IL-10-producing B cells. Br1 cells potently suppressed antigen-specific CD4+ T cell proliferation, whereas other B cells did not. Furthermore, we demonstrate that human Br1 cells show selectively increased production of IgG4. B cells specific for the major bee venom allergen phospholipase A2 that were isolated from beekeepers had increased expression of IL-10 and were from the IgG4 isotype. Human Br1 cells may regulate humoral and cellular immunological tolerance through suppression of T cell responses and production of anti-inflammatory IgG4 antibodies. Several B cells subsets have been described that express distinct polarized cytokine profiles. B cells were immortalized by transduction with Bcl6 and Bcl-XL, allowing *in vitro* expansion of B cells under IL-21 and CD40L stimulation. Clones were generated from immortalized B cell pools and transcriptomes were measured using RNAseq. Hierarchical clustering based on cytokine expression profiles was performed followed by differential expression analysis between clusters. A cluster of IgG4 clones that expressed pro-angiogenic cytokines including VEGF, CYR61, ADM, FGF2, PDGFA and MDK was identified. Supernatants from these clones efficiently promoted HUVEC tube formation demonstrating their pro-angiogenic potential. Further characterization led to identification of CD49b and CD73 as surface markers associated with pro-angiogenic B cells. The *in vivo* relevance of this novel B cell sunset was demonstrated by the observation that circulating CD49b+CD73+ B cells showed significantly increased frequency in melanoma patients and eosinophilic esophagitis patients, two diseases that are associated with angiogenesis. In conclusion, here we demonstrated a novel B cell subset with angiogenic property.

Mechanisms of allergen-specific immunotherapy; Role of antigen-specific B cells

Allergen-specific immunotherapy (AIT) is the only curative treatment inducing clinical and immunologic tolerance to causative allergens in allergic patients. Investigation of B-cell responses among patients receiving venom immunotherapy and naturally exposed beekeepers suggested a similar functional immunoregulatory role for B cells, enhanced IL-10–secreting regulatory B (BR1) cells, and IgG4-secreting phospholipase A2–specific B cells in allergen tolerance. AIT also induces IL-10–producing regulatory B (Breg) cells and allergen-specific IgG4. IL-10 is produced by TR1 and BR1 cells and also produced by TH2 cells in combination with TH2 cytokines. IL-10 has multiple functions in the regulation of immune responses by suppressing antigen-presenting cells, eosinophils, and basophils and allergen-specific CD4+ T cells through direct and indirect mechanisms and induction of IgG4 isotype antibodies by B cells. Allergen-specific IgG4 can function as a blocking antibody by preventing allergen-IgE binding, thereby inhibiting mast cell and basophil degranulation. Its production is selectively regulated by TR1 and BR1 cells. In addition, AIT can induce somatic mutation of IgG4-switched allergen-specific B cells, leading to generation of high-affinity antibodies. Furthermore, AIT results in reduced expression of antigen-specific IgE and increased expression of allergen-specific IgA as a delayed response after months to years. Increased allergen-specific IgA2 responses correlating with increased local TGF-b expression and increased monocyte IL-10 expression have also been reported. IL-1 is a potential mediator of inflammation

and tissue damage in multiple organs. The IL-1 family is a group of 11 cytokines,14 with IL-1a and IL-1b as the most studied members. IL-1 receptor antagonist (IL-1RA) binds to IL-1 receptor and thereby prevents binding of IL-1a and IL-1b and reduces the inflammation related to IL-1 in patients with various diseases. IL-1RA deficiency causes a very rare autoinflammatory disease with an inappropriate lack of control of inflammation. IL-1RA is produced by monocytes, macrophages, neutrophils, epithelial cells, fibroblasts, and mesenchymal stem cells. House dust mite (HDM) is a common cause of perennial allergy. Dust mites can survive throughout the year in warm and humid indoor conditions. Der p 1 is the major HDM allergen inducing IgG and specific IgE antibody synthesis. Its cysteine protease activity cleaves CD40 on dendritic cells, plays a role in directing dendritic cells to induce TH2 differentiation, and stimulates the epithelial mesenchymal transition in airway epithelial cells, leading to airway remodeling. Intranasal administration of proteolytic active Der p 1 to sensitized mice leads to enhanced inflammatory cellular infiltration in the lung and systemic production of IgE compared with inactive Der p 1, which has no effect. Der p 1 can activate protease-activated receptor 2 signaling pathway through Akt and pp65 to increase IL-6 and IL-8 expression. Moreover, Dermatophagoides pteronyssinus can be endocytosed into dendritic cells through dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN) and reduces DC-SIGN expression to change the polarization of dendritic cells, leading to the TH2 cytokine immune response. Allergen-specific B cells are present in circulation at very low frequencies. Small fractions (<0.05%) of B cells express a B-cell receptor (BCR) that binds fluorescent dyes, such as phycoerythrin (PE).24 Therefore accurate detection of allergen-specific B cells requires staining with antigens labeled with 2 structurally unrelated fluorescent dyes. Multicolor flow cytometry was used to determine and follow-up the immunoglobulin isotype expressed by Der p 1–specific B cells during 2 years of HDM AIT. It was possible to identify AIT responders and non-responders after 2 years and demonstrated that especially IgA+ and IgG4+ Der p 1–specific B cells, as well as plasmablasts, expanded in patients who responded to therapy. In parallel, CD73-CD25+CD71+ expressing Breg cells, which also produce IL-10 and IL-1RA, increased *in vivo* during AIT. Numbers of allergen-specific IgG4+ B cells, plasmablasts, and IL-10+ and/or IL-1RA+ Breg cells positively correlated with improved clinical response during AIT (Figure 1).

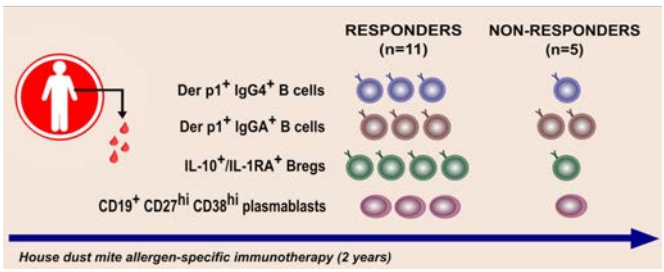


Figure 1: Allergen-specific B cells in patients responding to AIT are characterized by increased numbers of IgA- and IgG4- expressing Der p 1–specific B cells, plasmablasts, and IL-10+ and/or IL-1RA+ Breg cells.

Human rhinoviruses infect and regulate immune system cells

Human rhinoviruses (RV) are non-enveloped (+)-stranded picoRNA viruses that are the most common cause for viral induced respiratory disease. Rhinovirus infections are non-life-threatening infections for healthy individuals. However, in juveniles and in immune compromised individuals rhinovirus can lead to more severe symptoms. In addition to this there is a strong correlation between rhinovirus infections and asthma exacerbations. Furthermore, it was shown that 90% of the children that were suffering from rhinovirus-induced wheezing illness at year 3 develop asthma at the age of 6.

The relation between the mechanisms of asthma exacerbations and their link to breaking of tolerance remains to be elucidated. Understanding the mechanisms of viral infection-induced exacerbations and breaking of allergen tolerance could lead to new therapies and to general understanding of our immune system. So far, most of the research on virus induced asthma exacerbations have focused on epithelial cells. It has been shown that asthma is linked to a decrease in epithelial barrier function, which makes subjects more prone to have severe viral respiratory infections, and thereby increase the risk of an exacerbation. However which role lymphocytes play in these viral exacerbations is not clear. So far it has been shown that Rhinovirus has the ability to infect B cells, CD4+ and CD8+ T cells and that Rhinovirus induces proliferation in these cell types. However, it is unknown, if Rhinovirus also has the ability to specifically infect Tregs and have the capacity to change the functionality of their suppressive mechanisms. The hypothesis here is that due to the decreased epithelial barrier function in asthmatics, T regulatory cells might come in contact with Rhinovirus and that this could change their suppressive function. Indeed, it was demonstrated for the first time that T regulatory cells can be infected with RV. Furthermore, T regulatory cells are strongly affected upon rhinovirus infection *in vivo*. Tregs from healthy and asthmatic individuals share an anti-viral response, but have many genes that respond different to viral stimulation, which might affect Treg functions or viral clearance. It was shown that the differentially expressed genes in asthmatics are all highly connected to each other, which indicates an 'immune panic' response, while this is not the case for healthy individuals. All together these data suggest that Treg functions might be altered or impaired during HRV infections in asthmatics (Figure 2).

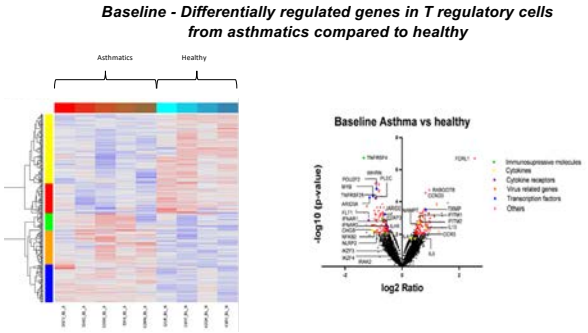


Figure 2: Baseline - Differentially regulated genes in T regulatory cells from asthmatics compared to healthy. (A) Heathmap showing all differentially expressed genes (325 with a p>0.01). (B) Volcano plot showing differentially expressed genes (DEG) in red, non significant genes in black and the most significant genes from specified groups : immunosupressive molecules (green), cytokines (yellow)s, cytokine receptors (purple) , virus related genes (orange) , transcription factors (blue) and others (pink).

Role of Der p 1-specific Breg cells in immune tolerance during 2-years of house dust mite-specific immunotherapy

(T. Boonpiyathad et al. J Allergy Clin Immunol. 2019 Mar;143(3):1077-1086.)

Background: Long-term follow-up of allergen-specific B cells in terms of immunoglobulin isotype expression, plasmablast differentiation, and regulatory B (Breg) cell development during allergen-specific immunotherapy (AIT) has not been reported. Objective: Allergen-specific B-cell responses during 2 years of house dust mite AIT were compared between responder and nonresponder patients. Methods: B cells specific for Der p 1 were detected by using the fluorochrome-labeled allergen method. The frequency of IgA-, IgG1- and IgG4-switched Der p 1–specific B cells, plasmablasts, and IL-10– and IL-1 receptor antagonist (IL-1RA)–producing Breg cells were investigated and correlated to clinical response to AIT.

Results: Sixteen of 25 patients completed the 2-year study. Eleven responder patients showed a successful response to AIT, as measured by a decrease in symptom-medication scores from 13.23 6 0.28 to 2.45 6 0.24 (P 5 .001) and a decrease in skin prick test reactivity to house dust mite from 7.0 6 1.3 to 2.7 6 0.5 mm (P 5 .001). IgG4+ and IgA+ Der p 1–specific B cells showed a significant increase after AIT, with a significantly greater frequency in responders compared with nonresponders in the IgG4+ but not the IgA+ fraction. The frequency of plasmablasts and IL-10– and/or IL-1RA–producing Breg cells was greater among responders compared with nonresponders after 2 years. The increased frequency of Der p 1–specific IgG4+ B cells, plasmablasts, and IL-10+ and dual-positive IL-10+IL- 1RA+ Breg cells significantly correlated with improved clinical symptoms over the course of AIT. Conclusion: Allergen-specific B cells in patients responding to AIT are characterized by increased numbers of IgA- and IgG4- expressing Der p 1–specific B cells, plasmablasts, and IL-10+ and/or IL-1RA+ Breg cells.

The use of biologics for immune modulation in allergic disease

(van de Veen W, Akdis M. Journal of Clinical Investigation. 2019 Mar 18;130.)

The rising prevalence of allergies represents an increasing socioeconomic burden. A detailed understanding of the immunological mechanisms that underlie the development of allergic disease, as well as the processes that drive immune tolerance to allergens, will be instrumental in designing therapeutic strategies to treat and prevent allergic disease. Improved characterization of individual patients through the use of specific biomarkers and improved definitions of disease endotypes are paving the way for the use of targeted therapeutic approaches for personalized treatment. Allergen-specific immunotherapy and biologic therapies that target key molecules driving the Th2 response are already used in the clinic, and a wave of novel drug candidates are under development. In-depth analysis of the cells and tissues of patients treated with such targeted interventions provides a wealth of information on the mechanisms that drive allergies and tolerance to allergens. Here, we aim to deliver an overview of the current state of specific inhibitors used in the treatment of allergy, with a particular focus on asthma and atopic dermatitis, and provide insights into the roles of these molecules in immunological mechanisms of allergic disease (Figure 3).

The use of biologics for immune modulation in allergic disease

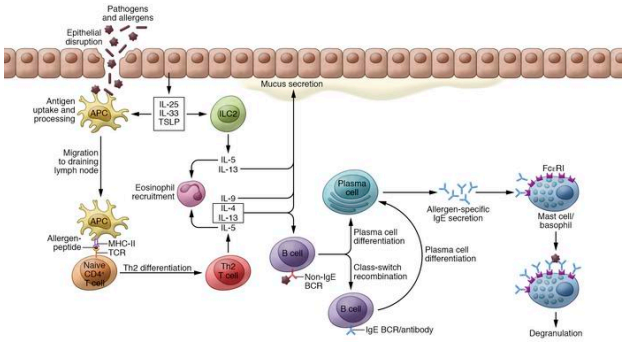


Figure 3: Key cellular and molecular players in allergic sensitization. Allergens and pathogens that have passed the skin or mucosal epithelium are phagocytosed by antigen-presenting cells (APCs). These APCs mature as a result of cytokines produced by epithelial cells, then migrate to draining lymph nodes, where they present allergen-derived peptides to CD4+ T cells and induce differentiation to Th2 cells. ILC2s are also activated by epithelial cell–derived cytokines such as IL-25, IL-33, and TSLP. Th2 cells and ILC2s produce type 2 cytokines such as IL-4, IL-13, IL-5, and IL-9. IL-4 and IL-13 drive IgE class switch recombination of B cells, leading to allergen-specific IgE production. Allergen-specific IgE binds to FcεRI on mast cells and basophils. IL-4, IL-9, and IL-13 promote mucus secretion by goblet cells, whereas IL-5 is instrumental in eosinophil recruitment. TCR, T cell receptor.

Regulation of IgE production in STAT3 Hyper IgE patients

(W. van de Veen et al. Under last revision in Allergy)

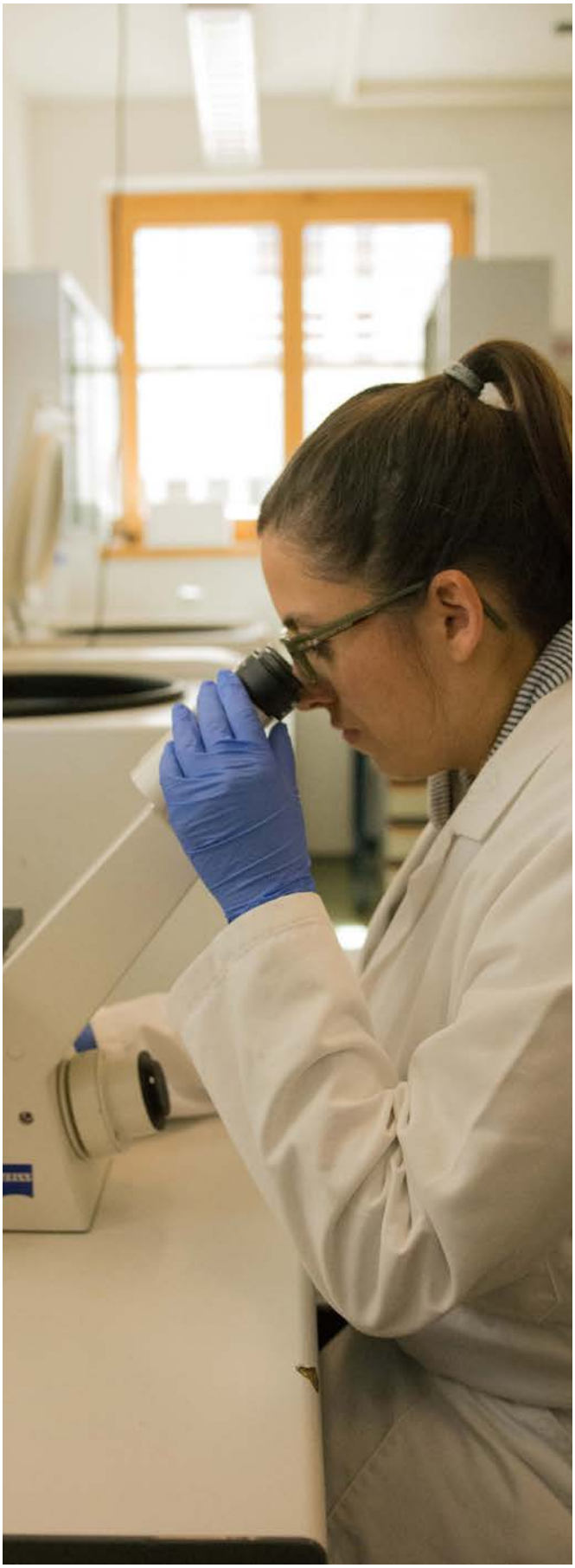
TH2 cells promote IgE class switch recombination by providing CD40L and IL-4 signals to B cells. These T-dependent B cell responses are initiated in germinal centers in lymphoid tissues. T follicular helper cells are the driving factors in the formation of germinal centers with IL-21 production. IL-21 is a strong activator of the signal transducer and activator of transcription (STAT) 3 signaling pathway, which induces IgG class switch recombintion,89 and augments IgE production and proliferation in human naive B cells stimulated with CD40L and IL-4.90-92 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.93-95 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.

Allergic asthma and allergic rhinitis patients do not show regulatory B cell deficienc

(by Wirz and Głobińska et al. Allergy. 2018 Nov 18.)

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, May 2019



Molecular Allergology

PD Dr. Katja Bärenfaller, PhD

DAViS Center (Center for Data Analytics, Visualization and Simulation)

The concept of the DAViS Center had been developed to implement the research strategy of canton Graubünden in profile field "Computational Science". On 20 November 2018 the canton issued the order to establish the DAViS Center to HTW Chur as leading house with SIAF as primary partner. From the beginning of 2019 on we will therefore join efforts with HTW Chur to analyze large-scale multi-dimensional life science data. The first project here will be MLM-SOS-ALL, where we will attempt to use novel computational methods to identify features that are responsible for the development and the increasing prevalence of allergic diseases.

Membership at the Swiss Institute of Bioinformatics (SIB)

From the beginning of 2018, the Molecular Allergology group is a group of the Swiss Institute of Bioinformatics (SIB) and SIAF became an institutional member. As 2018 also marked the SIB's 20th anniversary, the SIB published the book "Science Fiction", which combines portraits of researchers and significant advances in science made possible by bioinformatics (Figure 1).

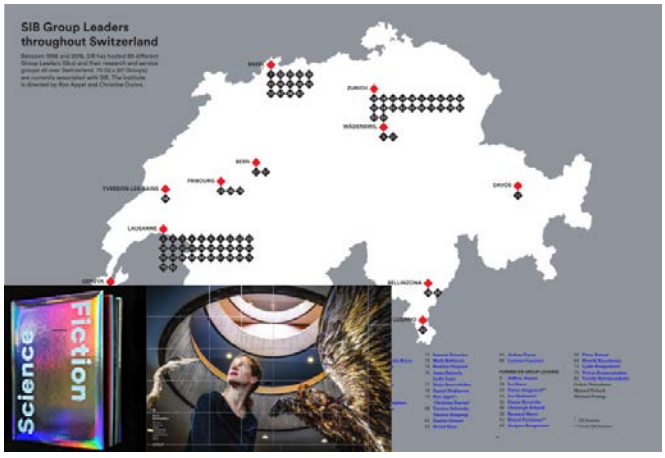


Figure 1: "Science Fiction": Discover science in a different way; book cover, and pages 17 and 88 inside the book, displaying the representation of Davos in the Swiss bioinformatics landscape.

The molecular profile of T cell differentiation and activation

In previous research efforts, we managed to detect several peptides encoded in open reading frames in non-protein coding RNAs (Bazin, Baerenfaller et al., PNAS, 2017). Based on this experience, we started in 2018 a new project to study the effect of translational regulation and small peptides on T cell differentiation and activation with PhD student Jana Koch, who is funded by "Stiftung vormals Bündner Heilstätte Arosa". CD4+ T cell differentiation into the different cell lineages and T cell activation play important roles in the pathophysiology of allergic diseases and in autoimmunity, as the decision between Th1 and Th2 lineage differentiation and the induction of suppressive Treg cells critically determine allergen tolerance. In this project, we aim at identifying events of differential translation and the sequences of peptides generated through the translation of sORFs and uORFs on non-protein coding RNA sequences, followed by immunologic assays to confirm their role in the differentiation and activation of T cells. A preliminary experiment with Th0, Th1 and Th2 cells after induction of differentiation and after re-stimulation has already been performed and the data are currently analyzed.

One switch to control them all, or how a 'translational coincidence' mechanism can explain photoperiod-dependent regulation of protein levels based on clock-dependent, daily mRNA level changes.

The regulation of gene expression still harbors a lot of secrets. One is the long-known anomaly that the transcripts of more than 50% of plant genes are expressed in a rhythmic way across the day, but that the levels of most of the encoded proteins remain stable. So why do transcript levels change if not for the sake of changing protein levels? In the context of the FP7 collaborative TiMet project, the group of Andrew J Millar from the University of Edinburgh, UK, developed a mathematical model based on coincidence detection in our proteomics and transcriptomics data. The best-known coincidence detector so far is for the control of flowering, which only occurs if the diurnal peaks of transcript expression of genes controlling flowering coincide with longer daylight hours as environmental trigger, and hence prevents premature flowering. Yet the adjustments to seasonally changing daylight hours requires many more shifts, including the remodeling of metabolism and energy use, and plants even manage to not only adapt, but to anticipate predicable changes in daylength. Here it was found that proteins with clock-regulated, evening-peaking RNA levels tended to increase in abundance under longer daylengths, whereas proteins with morning-peaking RNAs did not. This could be predicted with the so-called translational coincidence model, because high, light-induced translation rates will coincide with high levels of an evening-expressed RNA only under long days, but not short days (Figure 2). Many clock-controlled genes might therefore actually gain seasonal control of protein levels via translational coincidence. The translational coincidence model thus revealed a regulatory mechanism that contributes to changes in protein abundance across photoperiods based on daily mRNA level changes and light-dependent translation efficiency differences.

Link to video abstract: https://www.youtube.com/watch?v=C5l2d-QXOnU

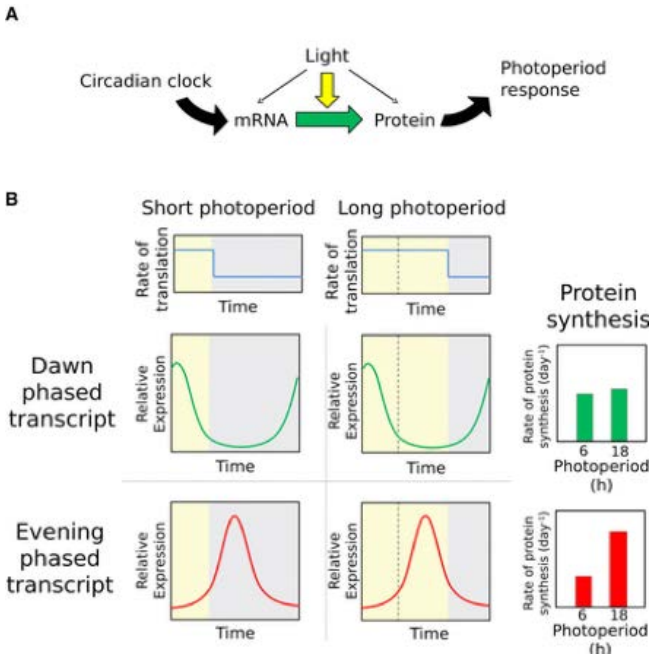


Figure 2: As in Figure 5 of Seaton, Graf, Baerenfaller et al. (2018): Expected effects of the changing coincidence of protein synthesis with transcript. A) Schematic of translational coincidence. B) Idealized representation of translational coincidence for two different transcripts. Light maintains high rates of protein synthesis for longer in longer photoperiods (top panels), which is expected to be without consequence for protein synthesis from dawn-phased transcripts (centre panels), but results in a boost of protein synthesis from transcripts expressed late in the day (bottom panels).

The role of targeted protein degradation in defense response

In line with our aim to study proteostasis, i.e. the regulation of proteins, we advanced in our efforts to identify substrates and interaction partners for ubiquitin ligases involved in defense response in an ongoing SNF-funded project at ETH Zurich with PhD student Sebastian Peterson. In the experiments performed in this project, ubiquitylated proteins will be identified with affinity enrichment using wild type or ubiquitin ligase mutant seedlings stimulated or not with the flagellin22 peptide. In addition, interaction partners for the ubiquitin ligases are identified using deficient mutant lines transformed with the respective TAP-tagged ubiquitin ligases. Establishing all the required mutant lines and methods needed a lot of preparation and preliminary experiments, yet this has been completed and the experiments are currently running.

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, May 2019

Molecular Immunology

PD Dr. Liam O'Mahony, PhD

The molecular Immunology group has been 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.

We have been 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.

We previously described that there was an increase in the number of histamine secreting bacteria, within the gut microbiome of adult asthma patients. In order to better understand the potential roles for gut bacterial-derived histamine on lung inflammatory responses, we cloned a gene encoding the enzyme required for conversion of histidine to histamine (histidine decarboxylase), into E.coli. Using murine models or respiratory allergic inflammation, we observed that the histamine secreting E. coli mutant significantly suppressed cytokine secretion and inflammatory cell recruitment to the lung. These responses were partially H2R-dependent, but were also influenced by expression of histamine degrading enzymes and histamine receptor expression. This study highlights the impact of metabolites that are secreted by bacteria within the gut, on immune reactivity on distant sites such as the lung (Figure 1). In addition to histamine, we have also examined the role of other bacterial-derived metabolites, such as short-chain fatty acids (SCFAs). Bacterial-derived SCFAs are generated following microbial fermentation of dietary fibres and have been shown by us and others to possess immune-modulating properties. Infants with the highest levels of SCFAs, particularly butyrate, are less likely to develop asthma, atopic dermatitis and food allergy by school age. Levels of butyrate correlated with consumption of yoghurt, fist, fruit and vegetables. In addition, our murine models showed that oral administration of butyrate increased the number of T regulatory cells within the lung, suggesting that butyrate may protect against the development of allergic disorders due to its support of T regulatory cell polarization (Figure 2).

These molecular mechanisms are important examples that highlight the important links between diet, composition of the gastrointestinal microbiota and regulation of mucosal immune responses.

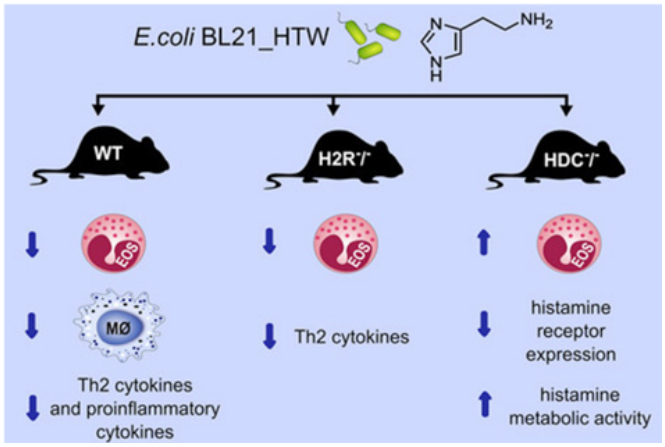


Figure 1. Gut bacterial-derived histamine influences immune responses within the lung (Graphical Abstract from Barcik et al., 2018)

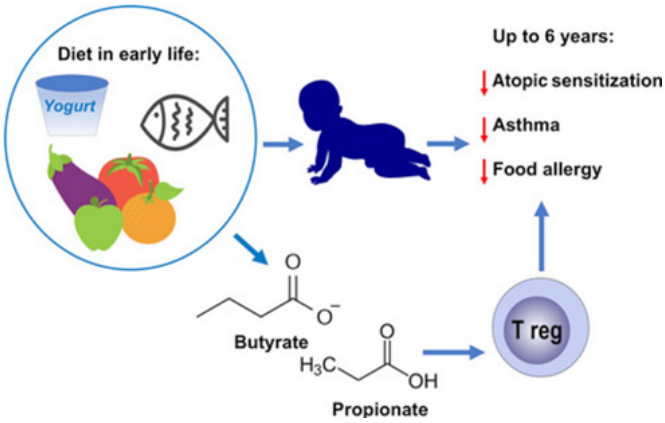


Figure 2. SCFAs generated by microbes protect against atopic disorders (Graphical Abstract from Roduit et al., 2019)

Bacterial secretion of histamine within the gut influences immune responses within the lung.

Barcik W, Pugin B, Brescó MS, Westermann P, Rinaldi A, Groeger D, Van Elst D, Sokolowska M, Krawczyk K, Frei R, Ferstl R, Wawrzyniak M, Altunbulakli C, Akdis CA, O'Mahony L.

Allergy. 2018 Dec 27.

Histamine is an important immunomodulator influencing both the innate and adaptive immune system. Certain host cells express the histidine decarboxylase enzyme (HDC), which is responsible for catalysing the decarboxylation of histidine to histamine. We and others have shown that bacterial strains can also express HDC and secrete histamine; however, the influence of bacterial-derived histamine on the host immune responses distant to the gut is unclear. The Escherichia coli BL21 (E coli BL21) strain was genetically modified to express the Morganella morganii (M morganii)-derived HDC gene (E coli BL21_HTW). E coli BL21 and E coli BL21_HTW were gavaged to ovalbumin (OVA) sensitized and challenged mice to investigate the effect of bacterial-derived histamine on lung inflammatory responses. Oral administration of E coli BL21_HTW, which is able to secrete histamine, to wild-type mice reduced lung eosinophilia and suppressed *ex vivo* OVA-stimulated cytokine secretion from lung cells in the OVA respiratory inflammation mouse model. In histamine receptor 2 (H2R)-deficient mice, administration of histamine-secreting bacteria also reduced inflammatory cell numbers in bronchoalveolar lavage (BAL). However, the suppressive effect of bacterial-derived histamine on BAL inflammation was lost in HDC-deficient mice. This loss of activity was associated with increased expression of histamine degrading enzymes and reduced histamine receptor expression. Histamine secretion from bacteria within the gut can have immunological consequences at distant mucosal sites, such as within the lung. These effects are influenced by host histamine receptor expression and the expression of histamine degrading enzymes.

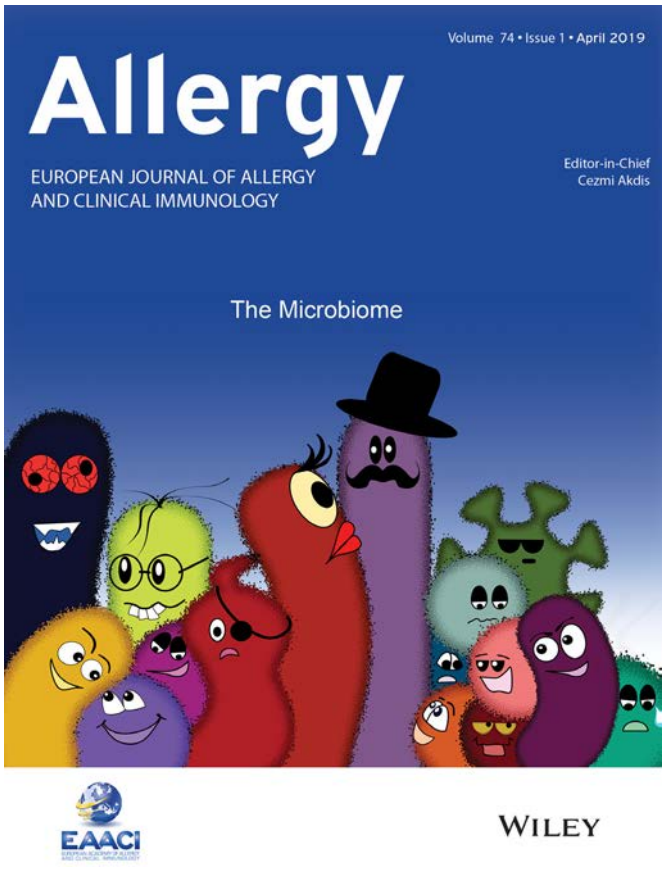
High levels of butyrate and propionate in early life are associated with protection against atopy

Roduit C, Frei R, Ferstl R, Loeliger S, Westermann P, Rhyner C, Schiavi E, Barcik W, Rodriguez-Perez N, Wawrzyniak M, Chassard C, Lacroix C, Schmausser-Hechfellner E, Depner M, von Mutius E, Braun-Fahrländer C, Karvonen AM, Kirjavainen PV, Pekkanen J, Dalphin JC, Riedler J, Akdis C, Lauener R, O'Mahony L.

Allergy. 2019 Apr;74(4):799-809.

Dietary changes are suggested to play a role in the increasing prevalence of allergic diseases and asthma. Short-chain fatty acids (SCFAs) are metabolites present in certain foods and are produced by microbes in the gut following fermentation of fibers. SCFAs have been shown to have anti-inflammatory properties in animal models. Our objective was to investigate the potential role of SCFAs in the prevention of allergy and asthma. We analyzed SCFA levels by high-performance liquid chromatography (HPLC) in fecal samples from 301 one-year-old children from a birth cohort and examined their association with early life exposures, especially diet, and allergy and asthma later in life. Data on exposures and allergic diseases were collected by questionnaires. In addition, we treated mice with SCFAs to examine their effect on allergic airway inflammation. Significant associations between the levels of SCFAs and the infant's diet were identified. Children with the highest levels of butyrate and propionate (≥95th percentile) in feces at the age of one year had significantly less atopic sensitization and were less likely to have asthma between 3 and 6 years. Children with the highest levels of butyrate were also less likely to have a reported diagnosis of food allergy or allergic rhinitis. Oral administration of SCFAs to mice significantly reduced the severity of allergic airway inflammation. Our results suggest that strategies to increase SCFA levels could be a new dietary preventive option for allergic diseases in children.

Davos, May 2019



Vaccine Development

Dr. Claudio Rhyner, PhD

Cloning and Expression of Human Rhinovirus (HRV) 16 Viral protein (VP) 1

The main trigger of asthma exacerbations in children and adults are respiratory viruses, particularly HRV. Surface exposed capsid proteins (VP1, VP2, and VP3) are important for binding of HRV to human epithelial cells. HRVs attach to cellular receptors such as ICAM-1, which promotes vial uncoating and release of viral RNA into cells. ICAM-1 interacts mainly with VP1 and VP2.

VP1 is naturally intertwined and very unstable individually, making purification of the individual protein extremely difficult. The VP1 is not soluble and remain in inclusion bodies. With this background in mind, we cloned the VP1 protein in-frame with a N-terminal glutathione-S-transferase (GST) tag. The use of GST as a fusion tag is desirable, because it can act as a chaperone to facilitate protein folding and frequently the fusion protein can be expressed as a soluble protein rather than in inclusion bodies. The RNA of the HRV16 was isolated using the RNeasy Micro Plus Kit (Qiagen GmbH). With the isolated RNA was the cDNA synthesized using the Thermo Scientific Revert Aid RT Kit (Thermo Scientific) and Oligo dT primers. The gene for the HRV16VP1 (aa 565-853) was amplified with gene-specific primers flanked by recognition sites for restriction endonucleases and the additionally applied AviTag sequence for later use of biotinylation of the protein. The plasmid map and the reading frame of the whole protein are depicted below:

The cloned plasmid was finally transformed into E. coli Rosetta™ 2 cells (BL21 derivative designed to enhance the expression of eukaryotic proteins). The protein was purified via GST affinity chromatography. After GST elution a TEV-cleavage was performed.

The eluted protein was cleaved with TEV-protease. The protein will be biotinylated using a Biotin ligase adding one Biotin molecule to the AviTag linker.

The produced VP 1 protein is used for labelling of RV-specific B cells and for future B- or Treg cell stimulation experiments.

Reversed phase (C18) ultra performance liquid chromatography (UPLC) analysis

We developed Reversed phase chromatography methods on the Acquity UPLC H-Class Bio System equipped with an C18 columns to detect Sodium dodecyl benzene sulfonate (SDBS) in laundry detergent and rinsing fluid, Tartrazine in dishwashing detergent, SGI1027 (Histone deacetylase inhibitor) in cell culture media and Bisphenol-A in plastics and cell culture media. These methods allow for the identification of bioactive substances in the environment.

Bacteriophages

Bacteriophages (phages) are viruses able to infect bacteria. They are currently considered not only as natural regulators of bacterial populations, but also potential modulators of the immune responses. It has been described that bacteriophages reside in the human microbiome, skin, urinary tract, gut and lungs. Phages interact with mucosal surfaces and are able to cross epithelial cell layer to disseminate throughout the body. To date, little is known about the nature of interactions between phages and immune cells.

Large quantities of identical phages are prepared trough infection of bacterial host cells. We optimized the protocol of phage propagation in order to obtain high-titer phage formulations of 1010. Sb-1 phages propagated in the host bacterium Staphylococcus aureus. Characterized Phage preparations for experiments with immune cells were obtained.

Phage preparations are contaminated by macromolecules derived from the host bacteria, such as lipopolysaccharide (endotoxin) from the outer membrane of gram-negative bacteria. Endotoxin elicits a wide variety of pathophysiological effects and interacts with immune cells. To perform experiments with cells of the immune system, LPS has to be removed from the preparations. We developed a methodology to wash away Endotoxin and other inmate immune response stimulators from phage preparations.

In order to localize phage within the layers of pseudostratified airway epithelium, we generated fluorescently-labelled phages. Figure 1 visualize bacteria infected with fluorescently-labelled phage. Ethidium bromide stained bacteria are visible as clusters of spherical cells. Bacteria infected with SYBR Gold labeled phages are visible as bright green spherical cells.

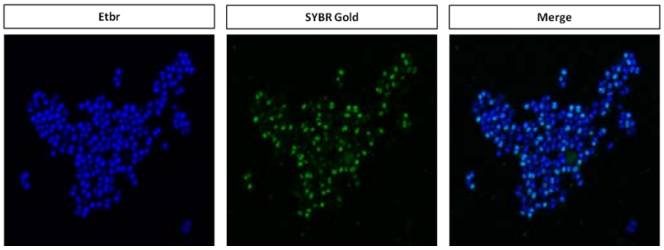


Figure 1: Visualization of SYBR-Gold labelled Sb-1 phages on Staphylococcus aureus (blue) after 5minutes of infection. Magnification x63.

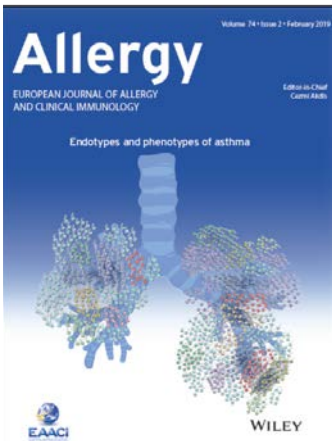
Davos, May 2019

Dr. Milena Sokolowska, MD, PhD

Due to environmental and lifestyle changes, there is an increasing frequency of allergies and respiratory viral and bacterial infections. These further lead to an increase in the prevalence of asthma, rhinitis, food allergy and atopic dermatitis. It is still not well understood why the same substances are leading to the development of allergic inflammation in some people, while being well tolerated by others. Several reasons are postulated, such as lack of proper microbiome stimulation early in life, recurrent viral infections with common respiratory viruses and exposure to environmental pollutants. In addition, central metabolic disorders such as obesity or even an unhealthy diet itself also influence the proper regulation of immune responses. All of those factors impact the proper cross-talk between innate and the adaptive immunity responses on the metabolic level. Immune cells need to engage in a wide array of energetically demanding intracellular processes in order to respond to external stimuli, such as allergen, virus or bacteria. These processes encompass changing the expression of a large number of genes, translating proteins, synthesis of lipids, activation of intracellular signaling cascades, altering cytoskeleton, and as a result production of cytokines, lipid mediators and proliferation or migration. To be competent to perform all those duties, the cell needs active metabolic processes, shifting nutrients into different pathways-a process called metabolic reprogramming. The role of immunometabolism in the development of allergy and asthma is not well understood. Therefore, our group applies high throughput transcriptomic, proteomic, metabolomic and lipidomic methods, coupled with gene editing, multi-color flow cytometry and confocal microscopy to understand immune and metabolic reprogramming of innate and adaptive immune cells. Our aim is to understanding immune and metabolic crosstalk in **(1)** different endotypes and phenotypes of asthma and other allergic diseases, **(2)** in the course of allergen-specific immunotherapy (AIT), and **(3)** in response to allergen, respiratory viruses and microbiota.

1. Phenotypes and endotypes of asthma and chronic obstructive pulmonary disease

Chronic airway diseases are amongst the most common causes of death worldwide. The prevalence of these diseases is increasing.



Asthma and COPD are complex, heterogenous diseases and their treatment should be tailored specifically according to their various endotypes. Therefore, we are studying the heterogeneity of chronic respiratory diseases on the level of immune responses, metabolic changes and microbiome alterations *in vivo* in animal models, *in vitro* in primary cells and in clinical cohorts of patients with asthma and COPD (Fig.1).

Figure 1: Cover of February 2019 issue of Allergy, depicting bioinformatic analysis of transcriptome data of different endotypes and phenotypes of asthmatic inflammation (Based on Tan et al, 2019).

Tight junction, mucin, and inflammasome-related molecules are differentially expressed in eosinophilic, mixed, and neutrophilic experimental asthma in mice.

Tan HT, Hagner S, Ruchti F, Radzikowska U, Tan G, Altunbulakli C, Eljaszewicz A, Moniuszko M, Akdis M, Akdis CA, Garn H, Sokolowska M. Allergy 2019 Feb;74(2):294-307. doi: 10.1111/all.13619. Epub 2018 Nov 5.

Asthma is a chronic respiratory disease with marked clinical and pathophysiological heterogeneity. Specific pathways are thought to be involved in the pathomechanisms of different inflammatory phenotypes of asthma; however, direct *in vivo* comparison has not been performed. We developed mouse models representing three different phenotypes of allergic airway inflammation-eosinophilic, mixed, and neutrophilic asthma via different methods of house dust mite sensitization and challenge. Transcriptomic analysis of the lungs, followed by the RT-PCR, western blot, and confocal microscopy, was performed. Primary human bronchial epithelial cells cultured in air-liquid interface were used to study the mechanisms revealed in the *in vivo* models. By whole-genome transcriptome profiling of the lung, we found that airway tight junction (TJ), mucin, and inflammasome-related genes are differentially expressed in these distinct phenotypes. Further analysis of proteins from these families revealed that Zo-1 and Cldn18 were downregulated in all phenotypes, while increased Cldn4 expression was characteristic for neutrophilic airway inflammation. Mucins Clca1 (Gob5) and Muc5ac were upregulated in eosinophilic and even more in neutrophilic phenotype. Increased expression of inflammasome-related molecules such as Nlrp3, Nlrc4, Casp-1, and IL-1β was characteristic for neutrophilic asthma. In addition, we showed that inflammasome/Th17/neutrophilic axis cytokine-IL-1β- may transiently impair epithelial barrier function, while IL-1β and IL-17 increase mucin expressions in primary human bronchial epithelial cells.

Our findings suggest that differential expression of TJ, mucin, and inflammasome-related molecules in distinct inflammatory phenotypes of asthma may be linked to pathophysiology and might reflect the differences observed in the clinic (Fig. 2).

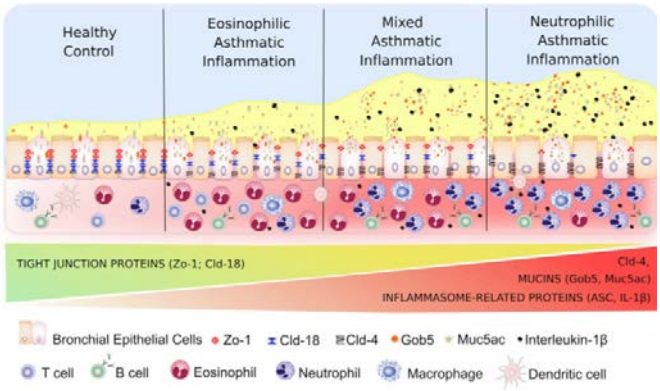


Figure 2: Tight junction, mucin and inflammasome-related molecules are differentially expressed in the lungs in distinct inflammatory phenotypes of allergic airway inflammation. (Graphical abstract from Tan et al, Allergy 2019).

Immunological and molecular fingerprints of chronic respiratory flow limitations: asthma and chronic obstructive pulmonary disease (COPD). A multicenter case control study.

In collaboration with three clinics in Davos (Zürcher RehaZentrum (ZRH) Davos, Hochgebirgsklinik Davos (HGK) and Spital Davos), we initiated the study which aims at unbiased identification of differences in local and systemic inflammatory reactions and the definition of the various endotypes of asthma and COPD. We will assess the frequency, and repertoire of various cell subsets, microbiome diversity and the expression, regulation and function of genes and proteins in the airways, in the blood and in the gut of patients with asthma and COPD as compared to healthy controls. We have already received approval from the Cantonal Ethical Committee to perform this study. We will study molecular and immunological mechanisms that are able to identify separate subgroups of asthma and COPD patients (endotypes) and their changes over time. This will allow the identification of potential new biomarkers for better treatment of these diseases.

Key points for moving the endotypes field forward: from Implementing Precision Medicine in Best Practices of Chronic Airway Diseases.

Sugita K., Sokolowska M., Akdis CA., Elsevier (2019), (I. Agache, P. Hellings, eds.) ISBN: 9780128134719 . 1st Edition.

We described here the taxonomy and the current state of the art on various endotypes and phenotypes of different allergic diseases. Moreover, we present the range of currently existing and emerging measurable indicators of different disease characteristics, called biomarkers. Finally, discussing the technological advances, such as next generation sequencing, other omics technologies and big data handling in research and clinical aspects, we propose further steps and directions in the field of precision and personalized medicine in allergy and clinical immunology. All those aspects are crucial in further development of an individual patient-oriented concept of precision health.

2. Immunometabolism in allergy and immune tolerance. Novel mechanisms and biomarkers of allergen-specific immunotherapy

Allergic immune response in T cells is characterized, among others, by increased secretion of pro-inflammatory mediators by Th2 effector cells. The main suppressors of this response are allergen-specific regulatory T cells (Tregs) as demonstrated in the steady state and in allergen-specific immunotherapy (AIT). Little is known about the metabolic requirements of allergen-specific and non-specific effector T cells and Tregs to carry out their functions *in vivo*. The aim of our studies is to identify essential metabolic pathways for regulatory and effector populations of allergen-specific and non-specific memory T cells *in vivo* in humans, their potential alterations in allergic disease, as well as their changes during allergen-specific immunotherapy. We found that allergen-specific memory CD4 T cells are significantly different between healthy controls and allergic patients in terms of lipid metabolism and fatty acid signaling, which is coupled to their abnormal type-2 cytokine and transcription factor signature. Interestingly, we found that AIT induced significant changes in previously dysregulated immune and metabolic pathways and led to induction of tolerance programs in allergen-specific CD4+ T cells and Treg cells. However, allergen-specific Treg cells in non-responders to AIT still displayed aberrant type 2 gene, protein and metabolic profiles, coupled with the corresponding plasma and nasal inflammatory milieu, in parallel to functional impairment of their suppressive capacities.

Serum proteomics reveals novel candidate biomarkers of the efficacy of allergen immunotherapy.

Van Elst D. and Agache I. et al. In preparation.

Allergen immunotherapy (AIT) is the only curative treatment for patients suffering from allergic diseases such as allergic rhinitis (AR) and allergic asthma by inducing allergen-specific immune tolerance. To find potential biomarkers of efficacy of AIT, we implemented an untargeted proteomics comparison of serum obtained 2 years after the start of AIT against house dust mite, grass pollen or cat antigens, from adults and children suffering from AR and allergic asthma. The control group included age- and gender-matched healthy controls. Serum proteomics data, obtained by mass spectrometry in a data-independent mode were compared between non-responders (NR) and responders to the therapy (R), and between NR and controls. Biomarker assessment and network association analyses were performed to investigate activated pathways and protein interactions. We detected 166 serum proteins in adults and 223 in children. In adults, six proteins were differentially expressed in NR as compared to R. No differentially expressed proteins were detected between NR and R in children. When comparing enriched process networks in NR versus R, several inflammation and the immune response-related processes were significantly enriched. Interestingly, we found that distinctly identified biomarker candidates contribute to these processes. Identified potential biomarkers in the present study could provide an important step in understanding the long-term effects of AIT and in implementing a personalised medicine approach allowing selection of responders to AIT.

Dynamic changes in the composition of innate immune cells compartments in the course of allergen-specific immunotherapy.

Eliaszewicz A and Ruchti F. et al. In preparation.

Allergen-specific immunotherapy (AIT) is recognized as the only available causative treatment for allergic rhinitis and allergic asthma patients. The vast majority of studies focused on the mechanisms of adaptive immune responses in AIT, while innate immune mechanisms still remain elusive. Innate immune cells such as monocytes/macrophages, dendritic cells (DCs) and innate lymphoid cells (ILCs) and NK cells may orchestrate adaptive immune responses through direct (contact-mediated) and indirect (soluble factor-mediated) mechanisms. We found that AIT induces substantial changes in the phenotype of innate immune changes distinct from seasonal changes observed in healthy non-allergic donors. AIT treatment induced a shift from proinflammatory to the regulatory phenotype of monocytes and dendritic cells. In detail, we observed decrease in non-classical CD14+CD16++ monocytes and increase in intermediate CD14++CD16+monocytes, as well as pDCs. Moreover, we observed significant reduction of ILC2s and shifted proportion towards ILC1s and ILC3s during AIT, with no changes in NK cells compartment. Our research is the first to describe comprehensive effects of AIT on systemic changes of innate immune cell compartments in long term observations. Our data suggest an essential role of specific subsets of monocytes, dendritic cells and ILCs in the induction of tolerance and reduction of inflammatory potential in AIT- treated patients. More importantly, observed shifts in the composition of circulating innate immune cells may open a new window for more precision monitoring of AIT treatment response.

3. Immunologic and metabolic responses to allergen, viruses and microbiota in airway epithelium

House dust mite priming enhances rhinovirus-induced inflammasome activation in asthma.

Radzikowska U. and Eljaszewicz A. et al. In preparation

Environmental exposures such as house dust mite (HDM) and rhinovirus (HRV16) play an important role in asthma development and in exacerbations. To date the mechanistic link of those factors with inflammasome activation in asthmatic bronchial epithelium is not fully understood. Air-liquid interphase cultures of primary human bronchial epithelial cells (HBE) from healthy controls and asthmatic patients were treated with HDM and HRV16. Mouse models of HDM-induced asthma and poly-IC-induced lung inflammation were analysed by next generation sequencing, real-time-PCR, Western-blotting and confocal microscopy to evaluate mechanisms of inflammasome activation. Bronchial brushings and bronchoalveolar lavage fluid (BAL) samples from control and asthmatic subjects at baseline and after experimental *in vivo* HRV16 infection were analysed using gene array, confocal microscopy and multiplex immunoassays to extend findings from *in vitro* and animal models to man. We found full activation of inflammasome in response to HRV16, represented by enhanced secretion of IL-1β, formation of ASC specks (Fig.3,A) and presence of activated caspase-1, which was further increased by HDM stimulation especially in asthmatic HBE. Release of IL-1β was decreased by caspase-1 inhibitor and ICAM-1 blocking, but not by specific NLRP3 inflammasome inhibitor. RIG-I was the sensor molecule for inflammasome activation during rhinovirus infection as detected by its co-immunoprecipitation with ASC (Fig.3,B). Observed *in vitro* polarized apical production of IL-1β reflected increased IL-1β levels in BAL fluid from asthmatic patients and *ex vivo* apical expression of ASC and RIG-I protein in epithelium in human lung biopsies. Upregulation of genes encoding RIG-I, caspase-1, IL-1β in *in vitro* HRV16-infected HBE, was mirrored by similar gene and protein expression patterns in bronchial brushings after experimental *in vivo* HRV16 infection in humans and in animal models. In conclusion, HDM priming enhances HRV16-induced inflammasome activation in asthmatic bronchial epithelium.

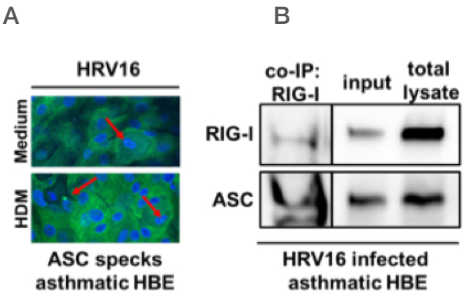


Figure 3: Activation of inflammasome in human bronchial epithelium (HBE) upon HDM exposure and human rhinovirus 16 (HRV16) infection. (A) Formation of ASC specs; (B) Co-immunoprecipitation of RIG-I with ASC.

Ozone exposure induces respiratory barrier biphasic injury and inflammation controlled by IL-33.

Michaudel C., Mackowiak C., Maillet I., Fauconnier L., Akdis CA., Sokolowska M., Dreher A., Tan HT., Quesniaux VF., Ryffel B., Togbe D. J Allergy Clin Immunol. 2018 Jan 10. pii: S0091-6749(18)30028-9

We have shown here that interleukin-33 has a protective role in ozone induced lung inflammation through its capacity to activate tight junction expression, maintain pulmonary barrier integrity and reduce neutrophil recruitment.

Microbiome and asthma.

Sokolowska M., Frei R., Lunjani N., Akdis CA., O'Mahony L. Asthma Res Pract. 2018 Jan 5;4:1. doi: 10.1186/s40733-017-0037-y. eCollection 2018.

We have thoroughly reviewed here the data linking microbial dysbiosis in the gut and the lung with the incidence and severity of asthma.

Davos, May 2019

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Satitsuksanoa P, van de Veen W and Akdis M. Mechanisms of immune tolerance to food allergens. World Immune Regulatory Meeting XII (WIRM) 2018, Davos, Switzerland, 14-17 March 2018.

Sokolowska M. Transcriptomic and proteomic signature of allergen-specific CD4+T and regulatory T cells during AIT. Gordon Research Conference: Food Allergy, Ventura, CA, US, 7-12 January 2018.

Sokolowska M. Transcriptomic and proteomic signature of allergen-specific CD4+T and regulatory T cells during AIT. WIRM 2018, Davos, Switzerland, 14-17 March 2018.

Sokolowska M. Transcriptomic and proteomic profile of allergen-specific CD4+T and regulatory T cells is precisely targeted by allergen-specific immunotherapy. EAACI annual congress 2018, Munich, Germany, 26-30 May 2018.

Sokolowska M. Immunometabolic changes in allergen-specific CD4+T and regulatory T cells during allergen-specific immunotherapy. Cell Symposium: Translational Immunometabolism, Basel, Switzerland, 24-26 June 2018.

Sokolowska M. Transcriptomic and proteomic signature of allergen-specific CD4+T and regulatory T cells during allergen-specific immunotherapy. Collegium Internationale Allergologicum, Palma, Mallorca, Spain, 30 September-5 October 2018.

van de Veen W. Identification of a novel pro-angiogenic effector B cell subset in EoE and Melanoma. Food Allergy Gordon Research Conference, Ventura, CA, USA, 7-12 January 2018.

van de Veen W. Probing the allergen-specific B cell repertoire in a human model of high-dose allergen exposure-induced immune tolerance. World Immune Regulation Meeting XII, Davos, Switzerland, 14-17 March 2018.

van de Veen W. Impaired germinal center reaction in STAT3-HIES patients favors development of IgE-producing B cells and plasma cells. 32nd Symposium of the Collegium Internationale Allergologicum, Mallorca, Spain, 30 September - 5 October 2018.

van de Veen W. Studying the regulation of IgE antibody production in patients with a mutation in the STAT3 gene. 6th conference “Graubünden forscht – The Young Researchers Convention”, Davos, Switzerland, 19-20 September 2018.

Wallimann A, Thompson K, O'Mahony L, Moriarty TF. The influence of microbial-derived metabolites on bone health. Graubünden forscht 2018, Davos, Switzerland, 19-20 September 2018.

Wawrzyniak P., Krzysztof Krawczyk, Francesc Castro Giner, Marcin Wawrzyniak, Emmanuel Karouzakis, Bogdan Jakiela, Ge Tan, Ming Wang, Can Altunbulakli, Marek Sanak, Liam O‘Mahony, Cezmi A. Akdis. Inhibition of CpG methylation improve the barrier integrity of bronchial epithelial cells in asthma. WIRM 2018, Davos, Switzerland, 14-17 March 2018.

Wirz OF. *In-vivo* regulation of B cells during human experimental rhinovirus challenge. Gordon Research Conference on Food Allergy, Ventura California, USA, 7-12 January 2018.

Wirz OF. Modulation of B cell gene expression and function by rhinovirus infection. World Immune Regulation Meeting XII, Davos Platz, 14-17 March 2018.

Wirz OF. Experimental human rhinovirus infection induces exaggerated anti-viral and B cell receptor gene expression in peripheral B cells from asthmatics. Conference “Graubünden forscht – The Young Researchers Convention 2018, 19-20 September 2018.

Seminar and congress talks

Akdis CA. Role of epithelial barrier and allergic diseases. Gordon Research Conference on Food Allergy, Ventura California, USA, 7-12 January 2018.

Akdis CA. Epithelial genes in allergic inflammation. AAAAI/WAO Joint Congress, Orlando Florida, USA, 2-5 March 2018.

Akdis CA. Accepting a manuscript: what do editors look for? AAAAI/WAO Joint Congress, Orlando Florida, USA, 2-5 March 2018.

Akdis CA. Epithelium in allergic diseases. AAAAI/WAO Joint Congress, Orlando Florida, USA, 2-5 March 2018.

Akdis CA. Innate lymphoid cells and asthma phenotypes. 12th Greek Congress of Allergy and Clinical Immunology, Athens, Greece, 29 March – 1 April 2018.

Akdis CA. Immune tolerance dynamics. 1st Borstel Asthma and Allergy Conference, Germany, 9-10 April 2018.

Akdis CA. What editors want. 13. International Congress of Allergy and Asthma, Fethiye, Turkey, 20-23 April 2018.

Akdis CA. Epithelial barrier leakiness and its regulation in asthma and allergic diseases. Highlights and novel developments in asthma, Istanbul, Turkey, 28 April 2018.

Akdis CA. Role of epithelial barrier in allergic diseases. KAAACI-EAAS-SERIN ASIA Joint Congress, Seoul, Korea, 10-12 May 2018.

Akdis CA. Meet the Expert Session: What editors expect: Reviewing and writing papers for top journals. KAAACI-EAAS-SERIN ASIA Joint Congress, Seoul, Korea, 10-12 May 2018.

Akdis CA. Innate lymphoid cells in allergic diseases. KAAACI-EAAS-SERIN ASIA Joint Congress, Seoul, Korea, 10-12 May 2018.

Akdis CA. What do editors expect: how to write and review for high impact journals. 67th Annual Meeting of Japanese Society of Allergology, Chiba, Japan, 22-24 June 2018.

Akdis CA. Epithelial barrier in allergy. 67th Annual Meeting of Japanese Society of Allergology, Chiba, Japan, 22-24 June 2018.

Akdis CA. Meet the professors. 67th Annual Meeting of Japanese Society of Allergology, Chiba, Japan, 22-24 June 2018.

Akdis CA. Epithelial barrier. National Center for Child Health and Development, Tokyo, Japan, 25 June 2018.

Akdis CA. Opening talk: Epithelial barrier in allergic diseases. International Congress of Immunology, Lima, Peru, 26-28 September 2018.

Akdis CA. Monitoring of allergen immunotherapy. International Congress of Immunology, Lima, Peru, 26-28 September 2018.

Akdis CA. What's in the crystal ball for future immunotherapy for food allergy. FAAM Copenhagen, Denmark, 18-20 October 2018.

Akdis CA. Meet the Expert: tips for successful publishing in the EAACI journals. FAAM Copenhagen, Denmark, 18-20 October 2018.

Akdis CA. Skin and mucosal barrier in allergic diseases. CAG Allergy Meeting, Copenhagen, Denmark, 31 October 2018.

Akdis CA. Innate and adaptive pathways in severe asthma: interactions & pathogenesis. International Severe Asthma Forum ISAF, Madrid, Spain, 8-10 November 2018.

Akdis CA. Epithelial barrier and its regulation in upper and lower airways. 27th Annual John Hopkins Allergy and Clinical Immunology Fall Symposium, Baltimore, USA, 16 November 2018.

Akdis CA. Novel therapeutic approaches for allergy and asthma. ACAAI Annual Scientific Meeting, Seattle, USA, 15–19 November 2018.

Akdis CA. Immunological mechanisms of allergy and asthma development. National Congress SIAAIC/WISC, Florence, Italy, 6-9 December 2018.

Akdis CA. The laboratory in patients with allergic and immune-mediated disorders treated with biologics. National Congress SIAAIC/WISC, Florence, Italy, 6-9 December 2018.

Akdis M. Induction and breaking of allergen tolerance, role of T and B regulatory cells. Gordon Research Conference on Food Allergy, Ventura California, USA, 7-12 January 2018.

Akdis M. Role of B Cells in Maintaining Tolerance. 16th EAACI Immunology Winter School, Saas-Fee, Switzerland, 25-28 January 2018 .

Akdis M. B cell biologics: effects on immune function. AAAAI/WAO Joint Congress, Orlando Florida, USA, 2-5 March 2018.

Akdis M. Effector and regulatory B cell subsets. AAAAI/WAO Joint Congress, Orlando Florida, USA, 2-5 March 2018.

Akdis M. T and B cells in allergy and immune tolerance to allergens. 12th Greek Congress of Allergy and Clinical Immunology, Athens, Greece, 29 March – 1 April 2018.

Akdis M. Mechanisms of inducing and breaking allergen tolerance. Munich Lung Conference, Munich, Germany, 12-14 April 2018

Akdis M. Mechanisms of inducing and breaking allergen tolerance. 13. International Congress of Allergy and Asthma, Fethiye, Turkey, 20-23 April 2018.

Akdis M. Novel B cell subsets, in inflammation versus immne tolerance. 13. International Congress of Allergy and Asthma, Fethiye, Turkey, 20-23 April 2018.

Akdis M. Immune tolerance to allergens and type 2 inflammation. Highlights and novel developments in asthma, Istanbul, Turkey, 28 April 2018.

Akdis M. Mechanisms of induction and breaking allergen tolerance. KAAACI-EAAS-SERIN ASIA Joint Congress, Seoul, Korea, 10-12 May 2018.

Akdis M. Meet the Expert Session: Life in science: at the frontier of allergy and immunology research. KAAACI-EAAS-SERIN ASIA Joint Congress, Seoul, Korea, 10-12 May 2018.

Akdis M. Novel mechanisms in immune tolerance. EAACI, Munich, Germany, 26-30 May 2018.

Akdis M. Mechanisms of allergen-specific tolerance. 67th Annual Meeting of Japanese Society of Allergology, Chiba, Japan, 22-24 June 2018.

Akdis M. Mechanisms of inducing and breaking allergen tolerance. 67th Annual Meeting of Japanese Society of Allergology, Chiba, Japan, 22-24 June 2018.

Akdis M. Meet the professors. 67th Annual Meeting of Japanese Society of Allergology, Chiba, Japan, 22-24 June 2018.

Akdis M. Allergen tolerance. National Center for Child Health and Development, Tokyo, Japan, 25 June 2018.

Akdis M. Mechanisms of inducing and breaking allergen tolerance. Cutting Edge Topics in Immunology and Infection Biology" at the Irchel Camupus. Zurich, 18 September 2018.

Akdis M. Mechanisms of immune tolerance to allergens. International Congress of Immunology, Lima, Peru, 26-28 September 2018.

Akdis M. New vaccines for allergen immunotherapy. International Congress of Immunology, Lima, Peru, 26-28 September 2018.

Akdis M. The role of IgG4 in IgE-mediated allergic responses. ACAAI Annual Scientific Meeting, Seattle, USA, 15–19 November 2018.

Akdis M. PLENARY SYMPOSIUM - WINAIT (Allergy Immunotherapy) - Respiratory Allergy - Immune response to AIT. SIAAIC / WISC, 6-9 December 2018.

Barcik W , Pugin B, Brescó MS, Westermann P, Rinaldi A, Groeger D, Van Elst D, Sokolowska M, Krawczyk K, Frei R, Ferstl R, Wawrzyniak M, Altunbulakli C, Akdis CA, O'Mahony L. Bacterial derived histamine - its influence on mucosal immune homeostatsis, XII WIRM, Davos , Switzerland, March 2018.

Frei R. Metabolic links between obesity and asthma. EAACI Congress, Munich, Germany from 26-30 May 2018.

Globinska A. Phage effect on barrier. 1st General Assembly of the Horizon 2020 project “Constructing a ‘Eubiosis Reinstatement Therapy’ for Asthma (CURE-731944)”, Tbilisi, Georgia, 24 September 2018.

Jansen K. The effect of Human Rhinovirus on T regulatory cells. Stanford University, Palo Alto, United states of America, 17 January 2018.

Jansen K. The effect of Human Rhinovirus on T regulatory cells. WIRM 2018, Davos, Switzerland, 14 March 2018.

Karaaslan C.The role of viruses in asthma pathogenesis. 21st Annual congress of the Turkish Thoracic Society , Antalya, Turkey, 11-15 April 2018.

Komlosi ZI. Human CD40L-expressing type 3 innate lymphoid cells induce IL-10-producing immature transitional regulatory B cells. European Respiratory Society (ERS) International Congress, Paris, France, 15-19 September 2018.

Lunjani N. Novel Biomarkers for Atopic Dermatitis. 13. International Congress of Allergy and Asthma, Fethiye, Turkey, 20-23 April 2018.

O’Mahony L. The Microbiome and Allergic Disorders, AIU, Grindelwald, 4th February 2018.

O’Mahony L. Bidirectional Microbiome-Immune Communication in Obesity and Asthma, WIRM, Davos, 17th March 2018.

O’Mahony L. Microbial Based Treatments of Allergy and Asthma, Seminar seris at University of Salzburg, Austria, 26th March 2018.

O’Mahony L. The Role of the Microbiome in Upper and Lower Airways and the Effect of Treatment, EAACI Masterclass on Biologicals, Prague, 13th April 2018.

O’Mahony L. Microbiome and Inflammatory Interactions in Obese Asthma, 13th Pediatric Allergy and Asthma Congress, Fethiye, Turkey, 22nd April 2018.

O’Mahony L. Microbiome and Allergy. What's the Connection? 13th Pediatric Allergy and Asthma Congress, Fethiye, Turkey, 22nd April 2018.

O’Mahony L. Microbiome-Immune System Interactions in the 21st

2018

Century - Old Friends and New Terrorists, Seminar seris at Trinity College Dublin, Ireland, 26th April 2018.

O'Mahony L. Microbiome and Immune Tolerance, Seminar series of Winterthur Hospital, 14th May 2018, Diet-Microbiome Interactions, EAACI annual conference, Munich, 28th May 2018.

O'Mahony L. The Gut Microbiome and its Role in Early Immune Development and Allergies, EAACI annual conference, Munich, 28th May 2018.

O'Mahony L. Environment and the Epigenome Affecting the Balance between Sensitisation and Tolerance, EAACI annual conference, Munich, 30th May 2018.

O'Mahony L. Innate and Adaptive Immune Responses in Food Allergy, Imparas Training School, Vienna, 5th June 2018.

Sokolowska M. Transcriptomic and proteomic signature of allergen-specific CD4+T and regulatory T cells during AIT. WIRM 2018, Davos, Switzerland, 14-17 March 2018.

Sokolowska M. Year in Review: Immune Tolerance in prevention of allergic disease. EAACI annual congress 2018, Munich, Germany, 26-30 May 2018.

Sokolowska M. Immunoregulatory roles of lipid mediators in asthma and allergy. European Congres of Immunology, Amsterdam, Netherlands, 2-5 September 2018.

van de Veen W. B cells as immune regulators in allergy and beyond. Seminars in Experimental Medicine, Kantonsspital St. Gallen, Switzerland, 11 October 2018.

van de Veen W. The role of B cells in the regulation of allergic immune responses. Seminar, Wageningen University and Research, Wageningen, The Netherlands.

Chairs

Akdis CA. Poster Session: Basic Immunology. 16th EAACI Immunology Winter School, Saas-Fee, Switzerland, 25-28 January 2018.

Akdis CA. Highlights in allergy. 13. International Congress of Allergy and Asthma, Fethiye, Turkey, 20-23 April 2018.

Akdis CA. New advances in allergy. 13. International Congress of Allergy and Asthma, Fethiye, Turkey, 20-23 April 2018.

Akdis CA. Pathophysiology of allergy and allergic disorders. 67th Annual Meeting of Japanese Society of Allergology, Chiba, Japan, 22-24 June 2018.

Akdis CA. Oral abstract session: Food allergens. FAAM Copenhagen, Denmark, 18-20 October 2018.

Akdis CA. Asthma Symposium. National Congress SIAAIC/WISC, Florence, Italy, 6-9 December 2018.

Akdis M. Oral abstract presentations from participants. 16th EAACI Immunology Winter School, Saas-Fee, Switzerland, 25-28 January 2018.

Akdis M. Poster Session: Adaptive immunity. 16th EAACI Immunology Winter School, Saas-Fee, Switzerland, 25-28 January 2018.

Akdis M. The epithelium as boss: lessons from the AADCRC. AAAAI/WAO Joint Congress, Orlando Florida, USA, 2-5 March 2018.

Akdis M. Mechanisms and the future of allergen-specific immunotherapy. 13. International Congress of Allergy and Asthma, Fethiye, Turkey, 20-23 April 2018.

Akdis M. Symposium, The origin and fate of IgE-producing cells. EAACI, Munich, Germany, 26-30 May 2018.

Akdis M. Thematic poster session, Hymenoptera allergy: Allergens and basic science. EAACI, Munich, Germany, 26-30 May 2018.

Akdis M. Allergen sensitization and immunotherapy. 67th Annual Meeting of Japanese Society of Allergology, Chiba, Japan, 22-24 June 2018.

Akdis M. Workshop, manipulation of tolerance by FOX P3+ T regs. European Congress of Immunology. Amsterdam, Holland, 2-5 September 2018.

Akdis M. Poster presentation, MHC, Stem cell transplantation and regulation. European Congress of Immunology. Amsterdam, Holland, 2-5 September 2018.

Baerenfaller K. Novel mechanisms of autoinflammation. World Immune Regulation Meeting XII (WIRM), Davos, Switzerland, 14-17 March 2018.

Baerenfaller K. Life Sciences and Medical Sciences. Graubünden forscht – The Young Researchers Convention, Davos, Switzerland, 19-20 September 2018.

Barcik W, XII WIRM, poster session, Davos, Switzerland, March 2018.

Frei R. World Immune Regulation Meeting, Davos, Switzerland, 14-18 March 2018.

O'Mahony L., Regulation of innate immunity, World Immune Regulation Meeting, Davos, Switzerland, 14-18 March 2018.

O'Mahony L., EAACI Masterclass on Biologicals, Prague, April 2018.

O'Mahony L., EAACI annual conference, Munich, May 2018.

Rhyner C. T and B cell responses in vaccination, food allergy and helminth infection. World Immune Regulation Meeting XII (WIRM), Davos, Switzerland, 14-17 March 2018.

Rhyner C. "Junge Forscher gesucht": international Jury: Finals, Innsbruck, 19-20 April 2018.

Satitsuksanoa P, Altunbulaki C. Genetics of chronic diseases. World Immune Regulatory Meeting XII (WIRM) 2018, Davos, Switzerland, 14-17 March 2018.

Sokolowska M. Role of B Cells in Maintaining Tolerance. EAACI Immunology Winter School, Saas-Fee, Switzerland, 25-28 January 2018.

Sokolowska M. Lymphocytes. EAACI Immunology Winter School, Saas-Fee, Switzerland, 25-28 January 2018.

Sokolowska M. Systems biology. WIRM 2018, Davos, Switzerland, 14-17 March 2018.

Sokolowska M. Asthma: From bench to bedside. EAACI annual congress 2018, Munich, Germany, 26-30 May 2018.

van de Veen W. Allergy and Asthma session. World Immune Regulation Meeting XII, Davos, Switzerland, 14-17 March 2018.

Wawrzyniak P. Poster Session 2: Epithelium and tissue response. World Immune Regulation Meeting XII, Davos, Switzerland, 14-17 March 2018.

LECTURES, AWARDS AND DEGREES

2018

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. Advanced Block Course: Computational Biology' of the Life Science Zurich Graduate School, Topic: Large data sets: Transcriptomics and Proteomics
Baerenfaller K. BIO390. Indroduction to Bioinformatics, Topic: Proteomics

Awards

Akdis M. International Distinguished Fellow, ACAAI Annual Scientific Meeting, Seattle, USA, 18 November 2018.

Frei R. Allergy Prize of the 'Allergie-Stiftung Ulrich Müller-Gierok' 2018.

Jansen K. Poster prize winner. EAACI winterschool 2018, Saas Fee, Switzerland, 25-28 January 2018.

Jansen K. Best presentation Award. WIRM 2018, Davos, Switzerland, 14 March 2018.

Jansen K. Best presentation. Graubünden Forscht, Davos, Switzerland, 19-20 September 2018.

Radzikowska U. Oral Session Prize. World Immune Regulation Meeting 2018, Davos, Switzerland, 14-17 March 2018.

Radzikowska U. Travel Grant. EAACI Annual Congress 2018, Munich, Germany, 26-30 May 2018.

Radzikowska U. Travel Grant. International Severe Asthma Forum (ISAF), Madrid, Spain, 8-10 November 2018.

Radzikowska U. Poster Prize. International Severe Asthma Forum (ISAF), Madrid, Spain, 8-10 November 2018.

Satitsuksanoa P. 1st place at SIAF Science Day 2018, Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland, 14 Dec 2018.

Wirz OF. Travel grant for 17th EAACI Immunology Winter School in Tryil, Norway, 24-27 January 2019.

Wirz OF. BioLegend Best Presentation Award – WIRM XII Workshop 4: B cell Subsets and Immune Regulation, 14-17 March 2018.

Wirz OF. Academic Award for oral presentation "Experimental human rhinovirus infection induces exaggerated anti-viral and B cell receptor gene expression in peripheral B cells from asthmatics" – Conference "Graubünden forscht – The Young Researchers Convention 2018", 19-20 September 2018.

Wirz OF. Certificate of Merit for the dissertation "The Influence of Respiratory Viruses on B lymphocytes" by Graduate School Graubünden, 19 September 2018.

Wirz OF. Early Postdoc.Mobility Fellowship Stipend, Nr. P2ZHP3_184081, Swiss National Science Foundation, November 2018.

Degrees

Altunbulakli C. Doctoral Degree (PhD): Microbiome and Transcriptome Interactions in Epithelial Tissues in the Context of Allergic Diseases. University of Zurich, 09 March 2018.

Baerenfaller K. Umhabilitation (Venia Legendi, PD): Correlation of Transcript and Protein Level Changes: A Special Case in Gene Expression Regulation, Universität Zürich, 31 October 2018.

Barcik W. Doctoral degree (PhD): Microbiota-Derived Histamine - Relevance to Mucosal Immune Homeostasis. University of Zurich, 23 March 2018.

Globinska. Doctoral degree (PhD): The immune response to viral infection in nasal epithelial cells from patients with allergic rhinitis. Medical University of Lodz, 21 March 2018, Poland.

Wirz O. Doctoral degree (PhD): The role of B cells during rhinovirus infections. University of Zurich, 09 March 2018.

Public Seminars
2 February 2018
Prof. Johann Christian Virchow: Novel Treatments for Severe Asthma
Prof. Roy Gerth van Wijk: Reasons of Success and Failure in Clinical Trials

22 and 23 February 2018
Workshop: Introduction clinical flow cytometry

19 March 2018
Prof. Kari Nadeau: Air and water pollution effects on immune cells involved in asthma and allergies
Prof. Scott Boyd: Human B cell repertoire responses in vaccination and infection

6 April 2018
Prof. Peter Hellings: Upper airways inflammation: what is needed for the future?

16 April 2018
Dr. Lukas Flatz: Mechanisms of checkpoint blockade induced toxicity in cancer immunotherapy

17 April 2019
Dr. Domingo Barber Hernandez: Profilin severe allergy model. A way to understand disease evolution

Dr. Sonja Wipf: Higher, faster, taller, more – climate change and Europe's alpine summit flora

25 May 2018
Science Rally Davos (SIAF, GRF, AO, SLF, PMOD)

6 June 2018
Dr. Sebastian L. Johnston: Immune mechanisms of respiratory viral invections in asthma

21 August 2018
Dr. Mohamed Shamji: Mechanisms and predictive biomarkers of grass pollen immunotherapy: what's new?

14 November 2018
Dr. Sandra Blaszkiewicz from Becton Dickinson: Presentation LSM Fortessa

SIAF Science Day
14.12.2018

Radzikowska U.: Activation of inflammasome upon rhinovirus infection in asthmatic airway epithelium is enhanced by house dust mite exposure.

Rinaldi A.: Direct assessment of skin epithelial barrier by electrical impedance spectroscopy.

Rodriguez J.: A travel in metabolomics.

van de Veen W.: CD73+CD49b+ B cells promote angiogenesis

Satitsuksanoa P.: Functional and phenotypic analysis of allergen-specific B cells in cow's milk allergy and tolerance

Jansen K.: Tregs - Out of Control!

Wirz OF.: Novel insights into the B cell response to rhinovirus infections.

Allergy Team: How Allergy stole Christmas.

Winner of the SIAF Sciene Day 2018: Pattraporn Satitsuksanoa

Scientific Posts

Akdis CA.
Academia Raetica - Member and Board Member

Allergy, Editor in Chief (since 2018)

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

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

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

World Immune Regulation Meeting - Chairman

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

Akdis M.
European Academy of Allergy Clinical Immunology (EAACI)

Member of Life Sciences Zurich Graduate School Zurich

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

World Allergy Organization (WAO) Board Member

World Immune Regulation Meeting - Member of the organizing committee

World Allergy Organization Congress - 2021 Scientific Chair

Baerenfaller K.
Group leader of the Swiss Institute of Bioinformatics (SIB) (from 1.1.2018)

Member of Life Sciences Zurich Graduate School Zurich

World Immune Regulation Meeting - Member of the organizing committee

O'Mahony L.
EAACI Executive Committee (Member at large)

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

Member of Life Sciences Zurich Graduate School Zurich

World Immune Regulation Meeting - Member of the organizing committee

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

Sokolowska M.
EAACI Basic and Clinical Immunology Section Board Member (2017-2019)

Organizing committee member for the annual EAACI Immuology Winter School (2018 & 2019)

Secretary of the EAACI Task Force on Public Outreach in Immunology (2018-2019)

Secretary of the EAACI Task Force on Eicosanoids in the Treatment of Asthma and Allergic Diseases (2018-2019)

Member of the EAACI Task Force on Nutritional Factors in Immunomodulation (2017-2018)

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, past 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

O'Mahony L.
Allergy, associate editor

Rhyner C.
Allergy, editorial board member

International Archives of Allergy and Immunology, editorial board member

Sokolowska M.
Clinical and Molecular Allergy, journal board member

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 Berek

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, Prof. M. Stoddart

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, I-Ting Chow

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

CURE partners: Prof. N. Papadopoulous, Assistant Prof. P. Xepapadaki, Dr. S. Taka, Assistant Prof. N. Rovina, Prof. D. Robertson, Dr. T. Gilman, Dr. S. Megremis, Dr. E. Andreakos, Prof. KB. Marcu, Dr. I. Galani, Prof. ML. Kowalski, Prof. X. Thibert-Plante, Dr. N. Cahnishivili, Dr. M. Goderdzishvili, G. De Carlo

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

Institute for Research in Biomedicine, Bellinzona (CH), Prof. G. Guarda

Instituto de Salud Carlos III, Madrid (SP), Dr. D. Barber, Dr. M.M. Escribese

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

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Schweizerisches Institut für Allergie- und Asthmaforschung

Bilanz per 31. Dezember 2018

(inklusive Drittmittel)

	31.12.2018	31.12.2017
	CHF	CHF
AKTIVEN		
Flüssige Mittel	1’416’724.04	1’153’230.73
Forderungen	152’238.32	171’137.30
Kontokorrent SFI Stiftung	59’015.05	Passiv
Aktive Rechnungsabgrenzungen	261’192.58	278’149.22
	1’889’169.99	1’602’517.25
PASSIVEN		
Verbindlichkeiten	218’248.89	142’873.51
Kontokorrent SFI Stiftung	Aktiv	4’908.60
Passive Rechnungsabgrenzungen	767’464.44	998’139.77
Rückstellungen	683’300.85	236’439.56
Eigenkapital	220’155.81	220’155.81
	1’889’169.99	1’602’517.25

Schweizerisches Institut für Allergie- und Asthmaforschung

Betriebsrechnung 2018

(inklusive Drittmittel)

	Rechnung 2018	Budget 2018	Rechnung 2017
	CHF	CHF	CHF
ERTRAG			
Beitrag Bund Forschungsgesetz Art. 16	818'100.00	818'100.00	847'700.00
Beitrag Kanton Graubünden	520'000.00	290'000.00	290'000.00
Beitrag Gemeinde Davos	424'560.00	424'560.00	424'560.00
Beitrag Universität Zürich	361'629.20	330'000.00	358'005.50
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	9'016.00	50'000.00	0
Beitrag Stiftungen/Drittmittel	52'480.95	0	67'977.60
Overheadbeiträge	86'981.00	60'000.00	32'574.26
Spenden	0	0	700'000.00
Übriger Ertrag	23'408.45	3'000.00	19'687.20
Finanzertrag	845.60	0	10'126.53
Auflösung von Rückstellungen	0	0	120'740.25
Ausserordentlicher Ertrag	17'680.07	0	22'976.87
WIRM-Kongress	319'892.70	350'000.00	300'823.83
Drittmittel	1'527'528.90	1'910'212.00	2'114'618.04
	4'422'122.87	4'495'872.00	5'569'790.08
AUFWAND			
Personalaufwand	2'580'916.95	2'361'726.00	2'848'146.65
Verbrauchsmaterial	504'068.59	1'058'847.00	843'293.99
Raumaufwand	183'071.38	182'760.00	186'736.55
Unterhalt/Reparaturen/Ersatz	124'702.99	115'500.00	171'210.13
Investitionen	19'148.63	147'500.00	981'094.32
Sachversicherungen/Abgaben	7'408.40	7'500.00	8'300.90
Energie- und Entsorgungsaufwand	65'948.35	70'000.00	63'866.31
Verwaltungsaufwand	132'645.06	142'500.00	100'427.75
Reisespesen	88'041.22	65'000.00	84'347.77
WIRM-Kongress	254'627.70	306'500.00	267'541.79
Übriger Betriebsaufwand	12'799.78	31'039.00	12'083.78
Finanzaufwand	1'794.13	6'000.00	2'711.48
Bildung von Rückstellungen	446'949.69	0	0
Ausserordentlicher Aufwand	0	1'000.00	28.66
	4'422'122.87	4'495'872.00	5'569'790.08
Ergebnis	0	0	0
	4'422'122.87	4'495'872.00	5'569'790.08

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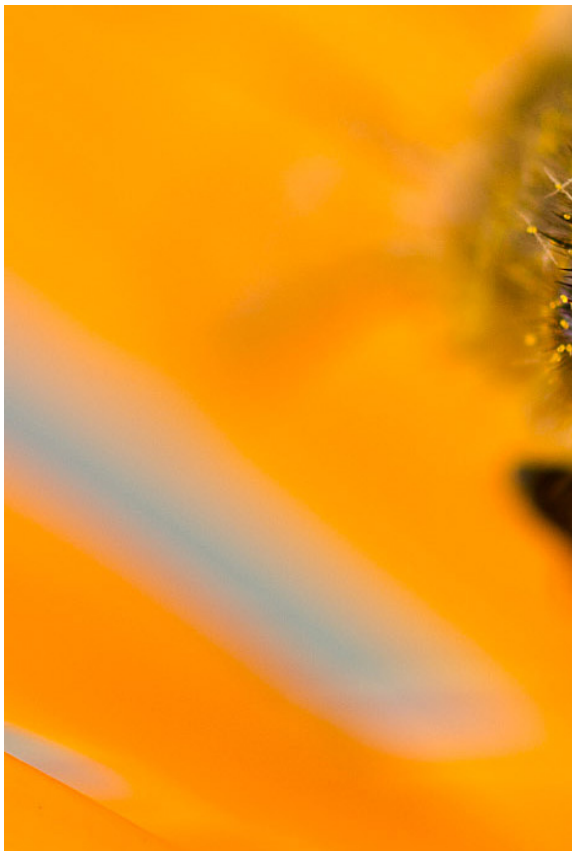

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