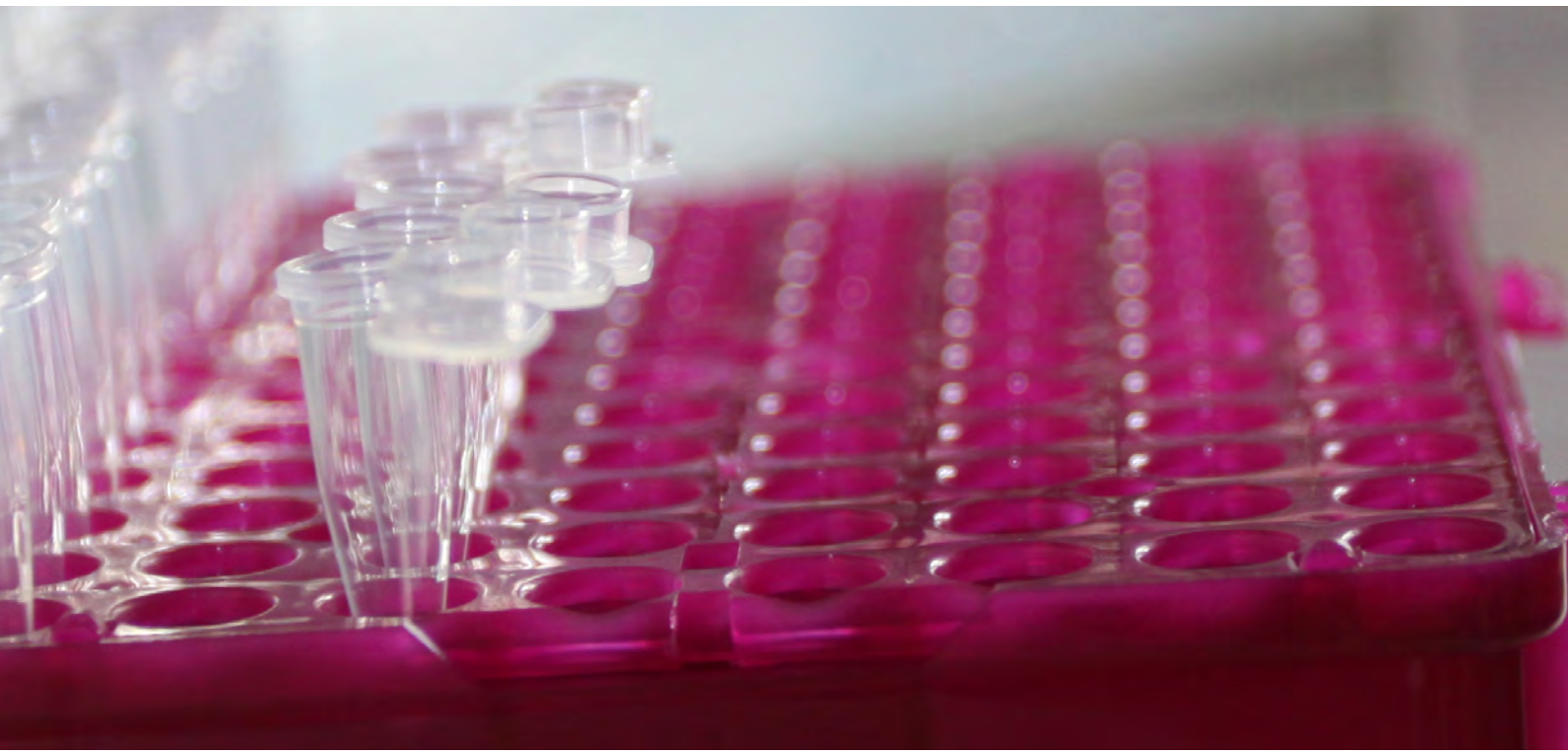
SIAF

ANNUAL REPORT 2014



University of Zurich[UZH]

Schweizerisches Institut für Allergie- und Asthmaforschung SIAF

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

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

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Bericht des Direktors

Prof. Dr. med. Cezmi A. Akdis

Die weltweit steigende Belastung aufgrund von Krankheiten wie allergische Rhinitis, Asthma und atopisches Ekzema wurde als die „allergische Epidemie“ definiert. Bis 2050 wird die Weltbevölkerung 9 bis 10 Milliarden zählen, davon werden 2 bis 4 Milliarden Menschen an einer allergischen Erkrankung leiden. Die Prävalenz in der Schweiz von allergischer Rhinitis liegt bei ca. 25%, bei Asthma und atopischer Dermatitis sind es rund 10%. All diese Erkrankungen erzeugen eine hohe sozio-ökonomische Belastung und müssen mit intensiver Forschung und Entwicklung angeganen werden.

Das Wort „Allergie“ kommt aus dem Altgriechischen und bedeutet Fremdreaktion, das heisst, dass das Immunsystem auf bestimmte und normalerweise harmlose Umweltstoffe viel zu intensiv reagiert. Diese Reaktion kann sich beispielsweise gegen Pollen, Kosmetika, Lebensmittel oder Insektengifte richten und kann so stark ablaufen, dass der Organismus dabei geschädigt wird: Atemprobleme, allergisches Asthma, Hautausschläge, Schleimhautreizungen, Durchfall, Erbrechen und viele weitere Symptome. Leider führen Allergien oft zu schweren gesundheitlichen Belastungen, welche die Lebensqualität von Betroffenen stark einschränken und auch das familiäre, gesellschaftliche und berufliche Umfeld stark belasten kann.

Das Schweizerische Institut für Allergie- und Asthmaforschung (SIAF) in seiner heutigen Form wurde 1988 von der Medizinischen Abteilung der Stiftung Schweizerisches Forschungsinstitut für Hochgebirgsklima und Medizin Davos (SFI) gegründet. Das SIAF ist seit 1996 der Universität Zürich angegliedert und seit 2009 Mitglied der Life Science Zurich Graduate School, einem gemeinsamen Ausbildungs-Projekt der Universität Zürich und der ETH Zürich. Diese Angliederung ermöglicht dem SIAF eine vollumfängliche PhD Ausbidlung anzubieten. Die Mitarbeiter des SIAF nehmen in nationalen und internationalen Organisationen sowie in Redaktionen von Top-Fachzeitschriften in den Bereichen Allergie, Asthma und klinische Immunologie eine führende Rolle wahr. Zusätzlich erfüllt das SIAF Lehrverpflichtungen an der Universität Zürich und der Universität Salzburg. Das Institut organisiert seit Jahren das international angesehene World Immune Regulation Meeting (WIRM) in Davos, das weltweit zu den attraktivsten Kongressen dieser Art zählt.

Es ist von enormer Wichtigkeit, dass sich die Forschung speziell der Verbesserung des Gesundheitszustandes der Betroffenen widmet. Denn das hohe Auftreten von Allergien und Asthma geht mit einer hohen sozialen wie auch wirtschaftlichen Belastung der Gesellschaft einher. Die medizinischen Gesamtkosten allergischer Erkrankungen in industrialisierten Ländern liegen im Milliardenbereich. Aus diesen Gründen werden dringend neue diagnostische, präventive und therapeutische Ansätze zur Behandlung von Allergien benötigt.

Die Allergieforschung am SIAF konzentriert sich auf die Untersuchung der immunologischen Grundlagen allergischer und asthmatischer Erkrankungen sowie allergischer Hautkrankheiten. Dabei stehen die zellulären, molekularen und biochemischen Vorgänge bei der Regulation der allergischen Immunreaktion und die Wirkung der aktivierten Immunzellen im Gewebe der betroffenen Organe im Mittelpunkt. In den letzten Jahren wurde der Zusammenhang zwischen den Vorgängen der Immunaktivierung und der Immuntoleranz überzeugend belegt. Diese Vorgänge bieten einen Ansatzpunkt für neue kurative und präventive Behandlungen. Um diese Behandlungen entwickeln zu können, muss das Verständnis der Mechanismen der Entzündungs- oder Toleranzentwicklung in allergischen Erkrankungen verbessert werden.

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 Klinischen Immunologie (EAACI) sowie der Amerikanischen Akademie für Allergie, Asthma und Immunologie (AAAAI) eingebunden.

Die EAACI ist die weltgrösste Akademie für allergische Erkrankungen und übernimmt eine wichtige Rolle in Bezug auf Wissenschaft, Weiterbildung, Kommunikation und Öffentlichkeitsarbeit. Zudem organisiert sie in Zusammenarbeit mit dem SIAF und der CK-CARE AG die in Davos jährlich stattfindenden EAACI Davos Schools mit rund 100 jungen Teilnehmern. Ich war in den Jahren 2008-2011 Vizepräsident der EAACI. 2011 wurde ich zum Präsidenten der Akademie gewählt. Meine Amtsperiode im Ausschuss dauert bis 2015. Dr. L. O‘Mahony ist Vorstandsmitglied der Sektion Immunologie. PD Dr. M. Akdis ist Mitglied der Biologicals Interest Group und Dr. C. Rhyner der Allergy Diagnostics Interest Group.

Das SIAF hat über 800 Fachbeiträge veröffentlicht und gehört zu den meistzitierten Instituten weltweit. Die vom SIAF publizierten Artikel wurden über 35‘000 Mal zitiert. Das Institut gehört mit seinen rund 45 Mitarbeitern (im Vergleich zu Universitäten mit Tausenden von Forschern) weltweit zu den Besten bezüglich Anzahl Mitarbeiter oder Zitierung geteilt durch Budget. In den letzten Jahren konnte eine signifikante Erhöhung der Anzahl Zitierungen erreicht werden. Es ist eine international bekannte Ausbildungsstätte für Doktoranden und Habilitanden.

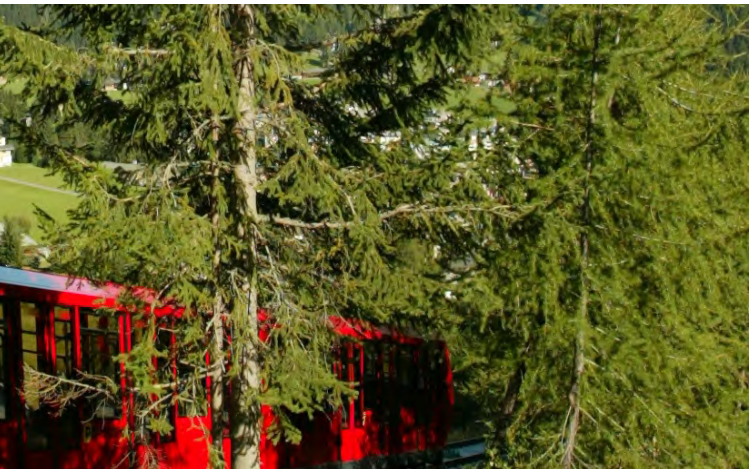
2014 wurden 52 wissenschaftliche Arbeiten publiziert. 50 wurden in begutachteten internationalen Fachzeitschriften mit “Impact Factor” veröffentlicht. 2014 erreichte das SIAF einen Gesamtwert des “Impact Factors” von 358.811 und einen Durchschnitt von 7.176 Punkte. Die neusten Ergebnisse wurden zudem in 45 Abstracts

an verschiedenen Fachtagungen mitgeteilt. Unsere Mitarbeitende wurden zu 80 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 31 verschiedenen Sessionen hatten SIAF-Mitarbeitende den Vorsitz. Zusätzlich werden 45 wissenschaftliche Ämter in internationalen Gesellschaften durch Wissenschaftler des SIAFs besetzt. Desweiteren sind die Forscher des SIAF bei insgesamt 24 internationalen Zeitschriften als Mitglieder der redaktionellen Komitees tätig.

In den letzten 6 Jahren haben sich beachtliche Fortschritte in der Aufklärung der grundlegenden Mechanismen, welche zu allergischen Erkrankungen führen, erzielen lassen. Nach wie vor besteht allerdings ein grosses Bedürfnis, das theoretische Wissen und die Alltagserfahrungen der Betroffenen und ihres Umfeldes zu vereinen. Das Allergieforschungsprojekt „CK-CARE Christine Kühne – Center for Allergy Research and Education“ wurde 2009 ins Leben gerufen mit dem Ziel, aus einer engen Zusammenarbeit exzellenter internationaler Forschungsgruppen heraus wissenschaftliche Erkenntnisse im Allergiebereich zu fördern und zugleich die entsprechende Ausbildung von Fachpersonen zu unterstützen und die Versorgung zugunsten der betroffenen Patienten zu verbessern. Das SIAF spielt in der CK-CARE eine tragende Rolle. In unserem Arbeitsbereich in der CK-CARE werden diejenigen Vorgänge erforscht, welche bei schweren Allergikern und Asthmatikern, die trotz therapeutische Behandlung nach dem modernsten Stand der Wissenschaft zur Entwicklung von Krankheitssymptomen führen. Mit der Unterstützung der CK-CARE werden wir in den nächsten 5 Jahren unsere Forschung auf die Barriere und Immuntoleranz fokusieren.
Seit 2009 konnten dank der Unterstützung durch die CK-CARE 35 wissenschaftliche Mitarbeitende eingestellt und 30 akademische Gäste im Austauschprogramm aufgenommen werden, die an den folgenden Projekten gearbeitet und 72 Publikationen in namhaften Zeitschriften veröffentlicht haben:

Die folgenden Forschungsgebiete werden aktuell am SIAF bearbeitet und durch den Schweizerischen Nationalfonds, die CK-CARE AG, MeDALL, PREDICTA, ALLFUN, NANOASIT, das Swiss-Polish Kooperationsprogramm, Marie Curie, die Kommission für Technologie und Innovation KTI sowie durch andere private Stiftungen und Firmen gefördert:

- Im Falle einer Allergie ist die Funktion des Epithels (äusserste Zellschicht von Haut, Nase oder Lunge) gestört und vermehrt durchlässig. Wir haben herausgefunden, dass die sogenannten Tight Junctions - kurz TJs – dafür verantwortlich zu sein scheinen. TJs sind schmale Bänder aus Proteinen, welche vereinfacht gesagt die Epithelzellen eng zusammenhalten und dadurch eine Barriere bilden. Die TJs verhindern ein Eindringen von Stoffen aus der Umwelt wie etwa Allergene, Pathogene, Schadstoffe und bakterielle Gifte. Defekte in den TJs stören diesen wichtigen Schutzmechanismus. Dank dieser Erkenntnisse können in Zukunft neue Massnahmen für die Prävention und Behandlung von Asthma entwickelt werden. Es wurde herausgefunden, dass die Durchlässigkeit der Barriere eine wichtige Rolle bei der Entwicklung von Asthma und Neurodermitis spielt. Wir haben ein neues Konzept entwickelt, das eine neue Therapieform zum der Barrierefunktion ermöglicht und eine frühere Diagnose sowie die Entwicklung von neuen Biomarkern ermöglicht.



- Allergische Erkrankungen sind komplexe Krankheiten, die aus verschiedenen Krankheitsbilder/-varianten und verschiedenen Mechanismen unterliegenden Subtypen bestehen. Das grösste Problem bei der Verbesserung der Behandlung ist vermutlich das begrenzte Verständnis über die Mechanismen dieser Untergruppen der Erkrankung. Eine bessere Erkennung der Untergruppen könnte eine individualisierte Behandlung, also eine auf den Patienten zugeschnitte Therapie, die gezielt gegen die Mechanismen dieser Erkrankungen gerichtet werden kann, ermöglichen. Damit kann man eine effektivere Behandlung erreichen und bessere Erfolge bei der Therapie der Patienten erzielen.

- Es wurden neue Labormethoden entwickelt, die mit nur 5ml Blut innerhalb von 45 Minuten zur Diagnose und Identifikation von Subgruppen von Neurodermitis und schlimmer Asthmaschüben eingesetzt wird. Dies führt zu einer individualisierten Medizin.

- Signifikante Fortschritte haben wir bei der Entdeckung neuer Wechselwirkungen zwischen dem Wirt und den mikrobiellen Erregern gemacht. Unter anderem haben wir entdeckt, dass gewisse Bakterien Histamin sekretieren und mikrobielles Histamin den TLR-Signalweg in den dendritischen Zellen des Wirts beeinflusst. Histamin senkt die entzündliche Reaktion gegenüber mikrobieller Liganden über den Histamin-2-Rezeptor.

- Das Projekt MeDALL „Mechanismen der Entstehung von Allergien“ hat zum Ziel, die Gründe für die Allergie-Epidemie zu verstehen, damit der Gesundheitszustand der europäischen Bevölkerung verbessert werden kann und soll bahnbrechende Erkenntnisse betreffend Ursachen und Mechanismen von allergischen Erkrankungen eröffnen. MeDALL hat europaweit 42‘000 Kinder zu einer Geburtskohorte zusammen gebracht. Leider endet das Projekt 2015. Wir haben zusammen mit dem MeDALL Netzwerk mehr als 10 Artikel publiziert, welche massgeblich zu unserem Verständnis über die Entwicklung von Allergien beigetragen haben.

- Das Projekt NANOASIT ist ein vom SNF im Rahmen der Europäischen Initiative EuroNanoMed unterstütztes Forschungsprojekt und hat die Entwicklung neuartiger Vakzinierungskonzepte zur Be-

handlung allergischer Erkrankungen basierend auf Nano-Partikeln zum Ziel. Dafür werden wir neuartiger Vakzine entwickeln, welche die Fähigkeit besitzen, selektiv von dendritischen Zellen (DC) aufgenommen zu werden. Dazu werden wir aus Peptidbibliotheken solche Peptide isolieren, die von dendritischen Zellen spezifisch aufgenommen werden. Die gentechnologische Fusion dieser Peptide mit rekombinanten Allergenen wird es erlauben, DC-spezifische Vakzine zu entwickeln, die nach chemischer Kopplung mit Nano-Partikeln subkutan injiziert werden, um einen lang anhaltenden Depot-Effekt zu erzielen.

- Die Hauptthese des Projektes PREDICTA besteht darin, dass wiederholte akute Vireninfektionen die angeborene, adaptive und/oder regulatorische Immunantwort so verändern, dass ein chronisches Entzündungsmuster entstehen kann. Diese Studie untersucht die Regulierung von Entzündungen durch akute Infektionen in Patientenkohorten. Es sollen Strategien entwickelt werden, um die Progredienz/Persistenz von Krankheiten zu verzögern und/oder zu verhindern, indem man sich auf ursächliche oder spezifische Elemente von Entzündungsabläufen fokussiert.

- Die allergen-spezifische Immunotherapie (SIT) wird seit mehr als einem Jahrhundert als desensibilisierende Therapie für allergische Krankheiten eingesetzt und ist die einzige kurative Behandlungsmethode. Jedoch tragen die derzeitigen Allergen-SIT-Impfstoffe und die Behandlungsprotokolle Nachteile mit sich. Diese beziehen sich auf den Inhalt des Impfstoffs, des Anwendungswegs, die lange Behandlungsdauer, Nebenwirkungen und teils auf eine eingeschränkte Wirksamkeit. Unser KTI-Projekt konzentriert sich in Zusammenarbeit mit zwei Industriepartnern auf ein neues diagnostisches Verfahren, das mittels Biomarker den Erfolg der SIT dokumentiert und verbesserte und sicherere Ansätze für die zukünftige Prävention und Heilung allergischer Erkrankungen erarbeitet.

- Beim Projekt TEAM EPIC werden die Funktionsmechanismen von EPS (Extrazelluläre Polysaccaride von Bakterien), isoliert von Bifidobacterium infantis, untersucht. Des Weiteren wird überprüft, was EPS für eine Aktivität innerhalb des Immunsystems bei In vitro- und In vivo-Modellen hat.

- Seit dem Anfang beschäftigt sich das SIAF mit Pilzallergien, ein nach wie vor ungelöstes Problem. Die Europäische Kommission erkannte dieses Problem und bewilligte im Rahmen des 7th Framework Programms ein Grossprojekt unter dem Titel ALLFUN (Fungi in the setting of inflammation, allergy and autoimmune diseases: Translating basic science to clinical practices). In diesem Forschungsprojekt nimmt das SIAF eine führende Rolle ein. Dies erlaubt uns, während der nächsten Jahre diese Forschungsrichtung zu verstärken.

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.
Das SIAF bietet als einziges Institut im gesamten Kanton Graubünden Davoser und allen weiteren interessierten Kliniken und praktizierenden Ärzten spezielle zelluläre immunologische Untersuchungen an. Für die Durchführung dieser Untersuchungen besitzt das SIAF eine vom Gesundheitsamt Graubünden ausgestellte Bewilligung zum Betreiben eines „Immunologischen Laboratoriums“ und ein vom Schweizerischen Zentrum für Qualitätskontrolle (CSCQ) erteiltes Zertifikat, das mit einer regelmässigen Kontrolle durch ein anerkanntes, externes Kontrollinstitut verbunden ist.

Ausbildung und Lehrverpflichtungen

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

Am SIAF werden zahlreiche Seminare und Workshops mit eingeladenen Referenten durchgeführt. Die Fortbildungsveranstaltungen sind im Vorlesungsverzeichnis der Universität Zürich aufgeführt und werden der obligatorischen Facharztweiterbildung angerechnet. Sie sind jeweils sehr gut besucht und vereinigen die Grundlagenforscher mit den Klinikern und praktizierenden Ärzten von Davos.

Kongressorganisation 2015

Das World Immune Regulation Meeting fand vom 18. bis 21. März 2015 bereits zum neunten Mal im Kongresszentrum Davos statt. Rund 600 Wissenschaftler aus 37 verschiedenen Länder trafen sich zu diesem Kongress, um sich über die neuesten Erkenntnisse in der Immunologie auszutauschen und trugen 133 Vorträge und 235 Abstracts vorgestellt. Tagsüber nahmen die Teilnehmer an hochkarätigen wissenschaftlichen Vorträgen teil. Die Abende im Kongresszentrum waren reserviert, um in ungezwungener Atmosphäre wissenschaftliche Projekte in Form einer Posterausstellung zu präsentieren. Der Kongress und weitere SIAF Aktivitäten generieren jährlich etwa 5'000 Übernachtungen in den Davoser Hotels und Ferienwohnungen.

Personal

Gegenwärtig beschäftigt das SIAF 51 Mitarbeitende. Davon zählen 47 zum wissenschaftlichen Stab. Derzeit führen am SIAF 13 Doktoranden eine naturwissenschaftliche Doktorarbeit durch. Insgesamt 17 Wissenschafter aus verschiedensten Ländern waren im letzten Jahr zu Gast im SIAF. Eine Administrationsleiterin sowie eine Kongressassistentin, eine 80%- und eine Halbtagesstelle für den Unterhalt und die Reinigung des Gebäudes vervollständigen das

Personal. Die Buchhaltung und Lohnauszahlungen werden durch das Treuhandbüro Wälti Treuhand und Revisionen AG in Bad Ragaz erledigt.

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. 16), Beiträge des Kantons Graubünden und der Gemeinde Davos, Beiträge der CK-CARE AG und der Universität Zürich sowie einem Beitrag der Stiftung vormals Bündner Heilstätte Arosa. Die zusätzlichen Ausgaben wurden aus Erträge von zusätzlichen Drittmitteln und des WIRM-Kongresses gedeckt.

Dank

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

Insbesondere möchte ich hier unsere fruchtbare Zusammenarbeit mit der CK-CARE betonen, welche uns patientenorientierte Forschung ermöglicht. Ich danke speziell Frau und Herr Kühne für Ihre Unterstützung, welche unsere Forschung zur Findung von nachhaltigen Lösungen für bessere Diagnosen und Behandlungen von Neurodermitis-Patienten ermöglicht.

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

Davos, Juni 2015

Report of the director

Prof. Dr. med. Cezmi A. Akdis

With an epidemic rise during the last 60 years, today, allergic diseases are affecting the lives of more than one billion people worldwide, and their prevalence is expected to reach up to 4 billion in 2050. The prevalence of allergic diseases and socioeconomic impact are particularly on the rise in urbanizing regions and globalizing world in association with environmental and lifestyle changes. Apart from individual suffering of patients, allergic diseases present a very high socioeconomic burden to health care systems and families. In addition, patient care and access to diagnosis and treatment is inadequate in many developing regions and countries. Effective policies and strategy development are needed to fill this gap at the global, regional, national level.

The efforts to overcome high numbers of unmet needs in allergic diseases can be grouped in three directions:
- Research and development should be synergized and prioritized in order to achieve sustainable results on prevention, biomarkers, curative treatment, anti-viral vaccines, and novel drug development. There are a number of barriers and obstacles in grant giving bodies to be solved, particularly to support human immunology and allergy research. They can be listed as: Lack of political awareness and low understanding and priority setting for the allergy epidemics; curative approaches and research for prevention has not been so far efficiently supported; small quantities of grants have been given to hypothesis-based research, although the real need is for large scale, non hypothesis based, in dept research, which is now possible with the novel developments in next generation DNA and RNA sequencing, exposome and epigenetic analysis and biomarkers; human research is receiving relatively less funding in many grant giving bodies compared to animal models; many major grant giving bodies had to decrease their budgets due to economical conditions in the US and Europe during the last years .
- Improved patient care at the global level requires a worldwide approach to identify barriers for prevention and cure, develop patient registries and next generation guidelines, improve access to diagnosis and essential drugs in low income countries, implement full environment control, provide psychological help directly and routinely without any need for consultation and implement every aspect of education of patients, primary care physicians and allied health employees.
- To increase the public awareness, it is now essential to publicly position allergic diseases and asthma as one of the most important causes of chronic morbidity and health care burden. Allergy and asthma focused patient organizations should be immediately established in all countries. A significant number of international alliances, societies, networks and academies are working on this. Intensive efforts should be performed at the level of local governments, United Nations, WHO, EU etc.

A worldwide strategy to fight and manage allergic diseases should be developed as follows.
- All stakeholders including specialists, primary care physicians, nurses, dieticians, psychologists, pharmacists, patient organizations, educators, industry, and policy makers should be involved.
- The specialty of “Allergology” should be strengthened as a full specialty and should be world wide harmonized.
- Modern global guidelines should be developed and implemented for the management of allergic diseases, asthma and co-morbidities. The new generation guidelines should provide structured, multidisciplinary, region and environment-oriented and individual patient-focused solutions, with full considerations on differences across cultures.
- There is substantial experience of already established strategies and associations. We should avoid reinventing the wheel and utilize and implement the existing know how. For example, one of the most valuable experiences in our fight with allergies is the success of the Finnish Allergy and Asthma Programs. It is now fundamental to disseminate the Finnish experience to the whole world, collect feedback and further improve.
- Global management of allergic diseases should be integrated with the “One Health” concept that acknowledges the systemic interconnections of human, animal and environmental health in close relationship with food and water safety and security (Global Risk Forum, Davos). In an era of climate change, resource depletion, land degradation, food insecurity and development challenges, an integrative approach is needed to ensure sustainable health. This concept strongly applies to all chronic inflammatory diseases, because of a strong scientific basis of epigenetic regulation of the disease genes with the influence of changing environment. Human health, animal health, plant health, healthy air, water and earth, food safety & security are integrative components of the “One Health” concept.
- A fully integrated World Allergy and Asthma Network should be established with all national asthma centers and already established networks, alliances, societies, academies aiming at worldwide allergy surveillance, strategy development and education. Prioritization of allergies should take place more and more in the EU, United Nations, WHO and national political agendas.

We have finalized the first six years of our CK-CARE research and education activities. Our CK-CARE research focused on the identification of molecular and cellular mechanisms that play a role in severity of asthma. Most asthmatic patients can be adequately managed according to practice guidelines, however, there is a minority group of patients with so called severe and refractory asthma, who remain poorly controlled despite high-dose treatment with inhaled glucocorticoids and β2-mimetics. Apart from classifications based on asthma severity and control, a number of clinical and pathological asthma phenotypes have also been distinguished. Remodeling in asthma, which might be the consequence of excessive repair processes following repeated airway injury, includes increased deposition of several extracellular matrix proteins in the reticular basement membrane and bronchial mucosa, as well as increases in airway smooth muscle mass, goblet-cell hyperplasia and new blood vessel formation. Consequently, the airway wall in asthma is usually characterized by increased thickness and markedly and permanently reduced airway caliber.

In addition, we demonstrated in the CK-CARE that the epithelium of asthmatics and patients with atopic dermatitis shows an abnormally high permeability through defects in the formation of tight junctions and is capable of cytokines and to produce growth factors, the in-

flammatory process and the conversion processes influence below the basement membrane. Better understanding of asthma phenotypes and endotypes to address the complexities of the disease related to severity is very important and distinguishing phenotypes with regard to the severity or duration of the disease is essential. An asthma phenotype covers the clinically relevant properties of the disease, but does not show the direct relationship to the pathophysiology. Different pathogenetic mechanisms are addressed by the term, endotype. Classification of asthma based on endotypes provides advantages for epidemiological, genetic, and drug particularly recent biological-related studies. A successful definition of endotypes and identification of corresponding molecular biomarkers for individual pathogenic mechanism underlying subgroups within a phenotype is essentially important. Thus, our research on better understanding asthma endotypes and their relationship to phenotypes will be more and more important in the future for clinical practice. We had and will have series of publications in the area with the support of CK-CARE. So far 72 articles were published supported by CK-CARE. We could engage more than 35 scientific co-workers. In the short term exchange program, there were 30 academic guests working on the specific projects of CK-CARE. The project MeDALL stands for “Mechanisms of the Development of ALLergy” and aims at improving the health of European citizens by understanding the causes of the allergy epidemic. MeDALL has been continuously generating groundbreaking knowledge on the causes and mechanisms of allergic diseases (including asthma, allergic rhinitis, atopic dermatitis, and food allergy, particularly in children). There is more than 43’000 children involved in MeDALL cohorts and SIAF takes it as great advantage to work with these cohorts and lead this work package. Our recent data provided a significant contribution to the understanding mechanisms of immune regulation particularly by novel B regulatory cell subset that produces IL-10 as well as turns into IgG4 producing plasma cells.

The 7th frame work EU research PREDICTA is that repeated, acute rhinovirus infection-mediated events may reprogram the innate, adaptive and/or regulatory immune responses to predispose towards a chronic inflammation pattern. This study demonstrated the modulation of inflammatory patterns by rhinovirus strains for the disease chronicity and demonstrated that human B cells are important responders to rhinovirus infections. In addition, we demonstrated that human tonsils with and without rhinoviruses show distinct patterns of immune regulation and an antiviral immune response in atopic Individuals clusters with IL-13 production that may play a role in asthma exacerbation.

The human microbiome contains an enormous diversity of different bacterial strains, with an equally astonishing number of genes conferring an array of metabolic functions that influence immunoregulatory mechanisms of the host. The Molecular Immunology group has made significant progress in discovering novel microbial-host immunoregulatory interactions. We have identified that certain commensal microbes promote retinoic acid metabolism within human dendritic cells and this mechanism is responsible for the polarization of naïve lymphocytes into regulatory T cells. In addition, we have discovered that certain microbes secrete histamine and microbial-derived histamine modulates TLR signaling pathways in host dendritic cells. Histamine decreases the pro-inflammatory response to microbial ligands via the histamine 2 receptor.

During the last two decades, SIAF has been investigating mechanisms and diagnosis of fungal allergies. Although we had significant developments, there is still unmet needs. Under the 7th Framework Program, the European Commission has now recognized the problem and a major project ALLFUN under the title “Fungi in the setting of inflammation, allergy and autoimmune diseases: Translating basic science to clinical practices has been approved. In this project SIAF has investigated the chemical structure and biochemical properties of allergens and produce highly pure recombinant allergens through gene cloning and biotechnological methods.

NANOASIT (Novel drug delivery routes mediated via nanotechnology: targeting allergy vaccination) is a research project founded by the Swiss National Science Foundation in the frame of the European Initiative EuroNanoMed. Aim of this three year project is to develop novel methods for an efficient vaccination against allergic diseases based on nanoparticles. We have developed different approaches for a direct targeting of the MHC class II antigen presentation pathway, successfully tested in a Phase I/IIa clinical study. In the frame of NANOASIT, based on our experience in allergen cloning and production, we will develop novel recombinant allergens able to target directly dendritic cells (DC) by selection of DC targeting peptides from phage surface display libraries. Fusion of these peptides to recombinant allergens will allow generating DC-targeting allergy vaccines, which will be delivered subcutaneously after chemical coupling to nanoparticles to obtain a long lasting depot effect.

The Swiss Polish research collaboration continued to investigate Factors contributing exacerbations of the asthma symptoms include respiratory infections (viral, bacterial, atypical), allergens (aeroallergens, food additives and food allergens), exposures (occupational allergens, drugs), and miscellaneous factors (β-adrenergic receptor polymorphisms and non-respiratory factors). To address these questions in a clinical setting, we used multicolor flow cytometry for the evaluation of phenotypical changes in CD4+ T cells in asthmatic subjects during acute episodes and remission compared to the control group.

The work at SIAF during the last year generated a total of 52 scientific publications (exclusive abstracts), of which 50 appeared in peer-reviewed international journals. The total average of impact factor is 7.176. In 2014 SIAF reached a total impact factor amounting to 358.811 and 45 abstracts were presented at different congresses. Members of SIAF were invited to 80 different seminars or lectures at international congresses, universities and other research institutions and chaired 38 sessions. In addition, SIAF members continued to take place in 45 scientific posts in international institutions and play a role in 24 editorial board and editorship activities. Several members of SIAF have teaching responsibilities at the Universities of Zurich and Salzburg.

Report of the director

Organization of WIRM-IX

The international World Immune Regulation Meeting (WIRM) belongs to one of the most important meetings in its area in the World. It attracts top-class senior scientists as well as junior researchers and provides the most efficient environment to meet the experts, fellows and old colleagues and organize top level of business meetings. This year, SIAF organized the WIRM for the ninth time on 18-21 March 2015 at the Congress Center Davos. The congress was focused on “Development and Maintenance of Immune Tolerance and Role of Tissues in Immune Regulation” with approximately 600 participants from 37 countries with 133 presentations and 235 abstracts.

Acknowledgements

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

I would like to mention in particular our fruitful cooperation with CK-CARE, which enables us patient-oriented research. I thank very much Mrs. and Mr. Kühne for their continuous support of our research for finding sustainable solutions for better diagnosis and treatment of atopic eczema patients.

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

Davos, June 2015

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Molecular Allergology

Prof. Reto Crameri

The activities of the Molecular Allergology Group at SIAF during 2014 were focused on finishing the projects "Fungi in the setting of inflammation, allergy and autoimmune diseases: translating basic science into clinical practices (ALLFUN), Novel drug delivery routes mediated via nanotechnology; targeting allergy vaccination (NANOASIT I) supported by the European Union and the project "SIT-monitor" in collaboration with the Vaccine Development Group and Davos Diagnostics supported by the CTI. In parallel the projects "Improving diagnosis and treatment of allergic diseases by avant-garde technologies" funded by the Swiss National Science foundation, "Allergy vaccination using novel drug delivery routes mediated via nanotechnology (ERANET EuroNanoMed2, NANOASIT II), "Pet ownership and matchmaking by allergen profiles in suitable breeds" (DIAPET, EUROSTARS E!8599) and the project "Rapid in vitro diagnosis for platelets" in collaboration with the Vaccine Development Group and Davos Diagnostics supported by the CTI were started. All new projects are thematically closely related and represent a consequent continuation and extension of our research activities started more than two decades ago.

The core technology used in all projects has been developed at Davos Diagnostics AG, a spin-off of SIAF, during the last three years and is based on evanescence biosensor technology consisting of two components: the EVA-biosensor chip and the EVA-reader allowing running immuno-tests in ten minutes or less, the fastest system worldwide we are aware of.

Technological background

1) The EVA-biosensor Chip

The "EVA"-Chip (Figure 1) is made by injection molding of polystyrene: the upper part with of eight wells and the lower part consisting of a high optical quality prism. Each well can be bio-functionalized for the detection of an analyte of choice. In contrast to ELISA tests which are end point measurements, the EVA-technology allows kinetic measurements which are practically background-free.

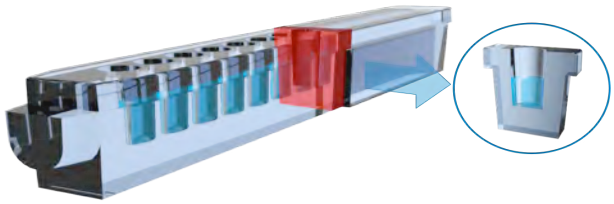


Figure 1: The EVA-Biosensor Chip

2) The EVA-Reader

The EVA-reader is based on evanescence excitation of fluorophors bound to the EVA-Chip surface at the interface between the liquid in the upper well and the lower prism. A diode laser light beam is directed against the side wall of the prism where it is reflected. The light beam further travels in the prism, hits the evanescent surface at the bottom of the well, and exits on the other side of the prism without penetrating the liquid above the bottom of the well following the classical optic rules of total internal reflection. Fluorescently labelled molecules present in the thin 200 nm layer at the bottom of the well are excited and only the photons emitted through the bottom of the prism are collected, filtered and counted in a time dependent mode (Figure 2).

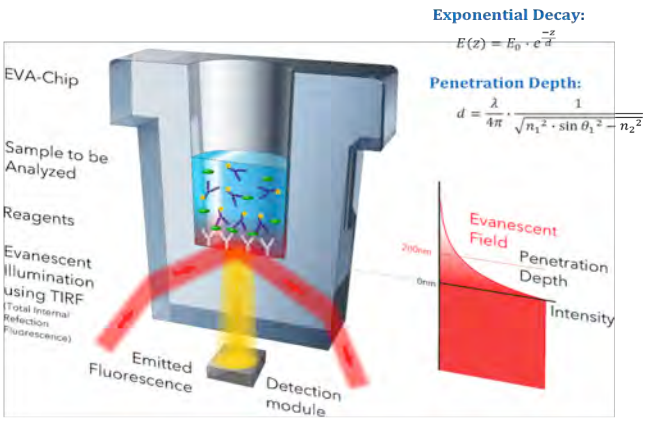


Figure 2: EVA-Biosensor Technology: The exciting light beam is reflected at the liquid - solid interface at the bottom of a well of a biosensor chip and registered by the detector.

Photon counts for each well are automatically plotted in 8 different graphs as function of the time on the X-axis and cumulative photon counts on the Y-axis. For diffusion-limited assays, where all parameters are kept constant the Fick's second diffusion law applies and the slope (dFt/dt) is directly proportional to the concentration of the analyte (Figure 3).

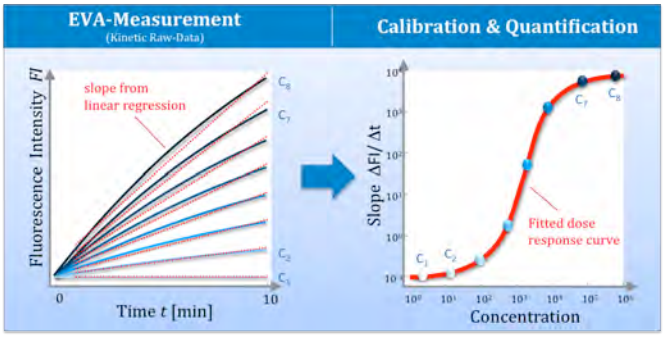


Figure 3: From the slope to a sigmoidal dose-response curve.

The innovative biosensor technology platform has the potential to replace all ELISA-based immunoassays with a comparable high sensitivity and specificity. The EVA-Biosensor overcomes the major disadvantages of ELISA – especially the long measurement time is shortened from hours to minutes, and the multiple washing and manipulation steps are reduced to few simple steps. This technology is suitable for simultaneous multiple parameter testing as required in many biosensor tests. The EVA-Biosensor chips use a design with 8 independent wells avoiding biochemical crosstalk and mixing up of reagents between the wells and has been used to develop more than 30 different project-related assays. As an example thereof we report here the performance of the EVA-technology for the detection of total serum IgE compared to the "gold standard" daily used in clinical practice (Figure 4).

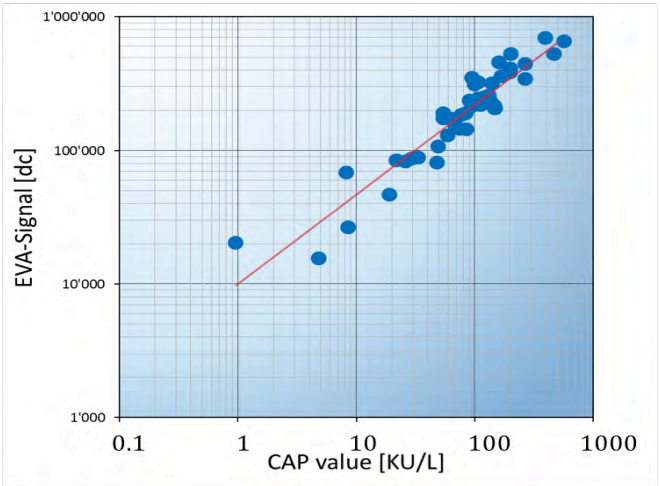


Figure 4: Detection of total IgE in serum of 40 A. fumigatus allergic patients compared to the ImmunoCAP test (correlation R2 = 0.89)

This and other tests for the detection of allergen-specific IgE and IgG4 developed together with the Vaccine Development Group during the SIT-Monitor project have been forward to Davos Diagnostics AG which is currently optimizing the industrial production and packaging of the corresponding EVA-chips which will be ready for β-testing during 2015.

Here, I would like to thank all my co-workers at SIAF and Davos Diagnostics for the exceptional engagement and especially the SFI Foundation and the SIAF director, Cezmi Akdis, who continuously supported the idea of a public/private partnership aiming to strengthen and extend the research activities in Kanton Graubünden.

Fungi : the neglected allergenic sources

Crameri R, Garbani M, Rhyner C, Huitema C. Allergy 69, 176-185, 2014.

Allergic diseases are considered the epidemics of the 21th century estimated to affect more than 30% of the population in industrialized countries with a still increasing incidence. During the past two decades the application of molecular biology allowed cloning, production and characterization of hundreds of recombinant allergens. In turn, knowledge about molecular, chemical, and biologically relevant allergens contributed to increase our understanding of the mechanisms underlying IgE-mediated type I hypersensitivity reactions. It has been largely demonstrated that fungi are potent sources of allergenic molecules covering a vast variety of molecular structures including enzymes, toxins, cell wall components and phylogenetically highly conserved cross-reactive proteins. Despite the large knowledge accumulated and the compelling evidence for an involvement of fungal allergens in the pathophysiology of allergic diseases, fungi as a prominent source of allergens are still largely neglected in basic research as well as in clinical practice. This review aims to highlight the impact of fungal allergens with focus on asthma and atopic dermatitis.

Histamine and Gut Mucosal Immune Regulation

Smolinska S, Jutel M, Crameri R, O'Mahony L. Allergy 69, 273-281, 2014.

Histamine is a biogenic amine with extensive effects on many cell types, mediated by activation of its four receptors (H1R – H4R). Distinct effects are dependent on receptor subtypes and their differential expression. Within the gastrointestinal tract, histamine is present at relatively high concentrations, particularly during inflammatory responses. In this review, we discuss the immunoregulatory influence of histamine on a number of gastrointestinal disorders, including food allergy, scombroid food poisoning, histamine intolerance, irritable bowel syndrome and inflammatory bowel disease. It is clear that the effects of histamine on mucosal immune homeostasis are dependent on expression and activity of the four currently known histamine receptors, however, the relative protective or pathogenic effects of histamine on inflammatory processes within the gut are still poorly defined and require further investigation.

Global Allergy Forum and 2nd Davos Declaration of 2013 Summit: Barriers to cure – challenges and actions to be taken
Ring J, Akdis C, Lauener R, Schäppi G, Traidl-Hoffmann C, Akdis M, Ammann W, Behrendt H, Bieber T, Biedermann T, Bienenstock J, Blaser K, Braun-Fahrländer1 C, Brockow K, Buters J, Crameri R, Darsow U, Denburg J, Eyerich K, Frei R, Galli S, Gutermuth J, Holt P, Koren H, Leung D, Müller U, Muraro A, Ollert M, O'Mahony L, Pawankar R, Platts-MillsT, Rhyner C, Rosenwasser L, Schmid-Grendelmeier P, Schmidt-Weber C, Schmutz W, Simon D, Simon HU, Sofiev M, van Hage M, van Ree R. Allergy. 69, 978-982, 2014.

The contribution of biotechnology towards progress in diagnosis, management, and treatment of allergic diseases
Palomares O, Crameri R, Rhyner C. Allergy 69, 1588-1601, 2014.
"Biotechnology" has been intuitively used by humans since thousands of years for the production of foods, beverages and drugs based on experience without any scientific background. However, the golden era of this discipline emerged only during the second half of the last century. Incredible progresses have been achieved on all fields starting from the industrialization of the production of foods, to the discovery of antibiotics, the decipherment of the genetic code, and rational approaches to understand and define the status, we now call "health". The extremely complex interactions between genetic background, life style and environmental factors influencing our continuously increasing life span become more and more evident, and steadily generate new questions which are only partly answered. Here we try to summarize the contribution of biotechnology to our understanding, control, and cure of IgE-mediated allergic diseases.

Structural aspects of fungal allergens
Crameri R. Seminars Immunol Immunopathol. 2015 Mar;37(2):117-21. doi: 10.1007/s00281-014-0458-0.
Despite the increasing number of solved crystal structures of allergens, the key question why some proteins are allergenic and the vast majority are not remains unanswered. The situation is not different for fungal allergens which cover a wide variety of proteins with different chemical properties and biological functions. They cover enzymes, cell wall, secreted, and intracellular proteins which, except cross-reactive allergens, does not show any evidence for structural similarities at last at the three dimensional level. However, from a diagnostic point of view, pure allergens biotechnologically produced by recombinant technology can provide us, in contrast to fungal extracts, which are hardly producible as standardized reagents, with highly pure perfectly standardized diagnostic reagents.

Differential cytokine induction by the human skin-associated autoallergen thioredoxin in sensitized patients with atopic dermatitis and controls
Hradetzky S, Roesner LM, Heratizadeh A, Crameri R, Garbani M, Scheynius A, Werfel T. J Allergy Clin Immunol 2015 May;135(5):1378-80.e1-5. doi: 10.1016/j.jaci.2014.10.038.

Davos, June 2015

Prof. Dr. med. Cezmi A. Akdis

The importance of Barrier in Allergy

Epithelial barrier function of bronchial epithelial cells in the asthmatic lung, sinus epithelial cells in the sinus tissue of chronic rhinosinusitis patients as well as keratinocytes in the skin of atopic dermatitis patients have been demonstrated to be defective. Tissue integrity is disturbed in patients and allergens, bacterial toxins and other particles are able to penetrate the epidermis and the lung epithelium, where they may activate the immune system leading to severe chronic inflammation in both diseases. Therefore, paracellular sealing of keratinocytes and bronchial epithelial cells appears to be very important to prevent the infiltration of subepithelial tissues by factors that induce allergic inflammation. Epithelial tight junctions (TJ) consist of different transmembrane and scaffold adaptor proteins and form the most apical intercellular junction essential for barrier function between epithelial cells. They are responsible for the regulation of paracellular flux and epithelial impermeability. In addition, they prevent foreign particles, such as allergens, to enter into subepithelial layers. In contrast, opening of TJs can lead to drainage of inflammatory cells towards the lumen, supporting the resolution of phlogistic processes. Consequently, they can be considered as gatekeepers that could contribute both to aggravation of inflammation related tissue damage or resolution of inflammation via drainage. In conclusion, the balance between inflammation inducing factors, keep away factors, wash away factors and suppression factors plays a decisive role in the remission, exacerbation and chronicity of allergic inflammation. Recent studies, including ours in this context, open a window for novel treatment and prevention modalities.

A little difference in the airway epithelial barrier could lead to a large impact on disease susceptibility or outcome as it was shown in several airway diseases. Proximal bronchial epithelium is composed of the columnar-cilated cells, mucus-secreting goblet cells supported by basal cells. Mature apical junctional complexes in epithelial cells, comprise the most apical TJs, underlying adherent junctions and the desmosomes. Depending on the protein composition, TJs define the barrier characteristics and maintain cell polarity. TJs are composed of transmembrane, peripheral and cytoskeletal proteins including junctional adhesion molecules, claudins, occludin, tricellulins, and adaptor proteins. It has been shown that in vitro exposure to Der p 1 or inhalation exposure of ovalbumin in sensitized mice cause epithelial TJ disruption. However, the impact of the complex allergen, such as house dust mite (HDM), containing molecules activating pattern recognition receptors (PRR) on components of TJs has not been reported. Additionally, it has been shown that TJs are disrupted in airways of patients with asthma as assessed by biopsies, as well as in air liquid interface cultures of epithelial cells cultures from the asthmatic bronchi. However, the impact of these changes on the cellular composition of airway inflammation in vivo or the regulation of the epithelial TJs proteins expression remain to be extensively analyzed.

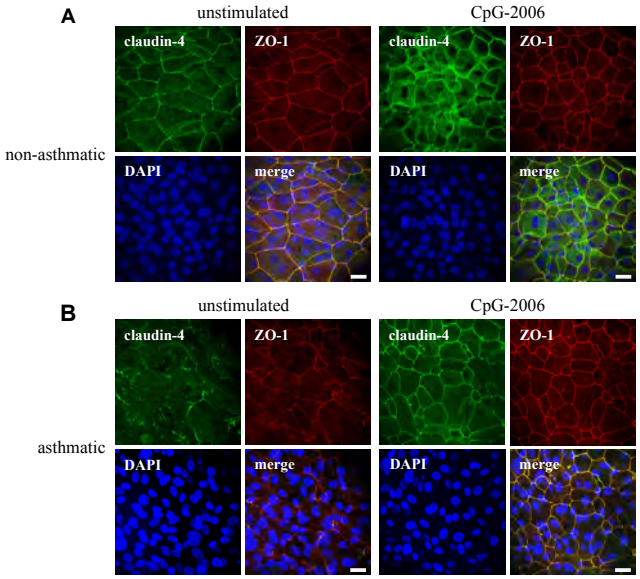
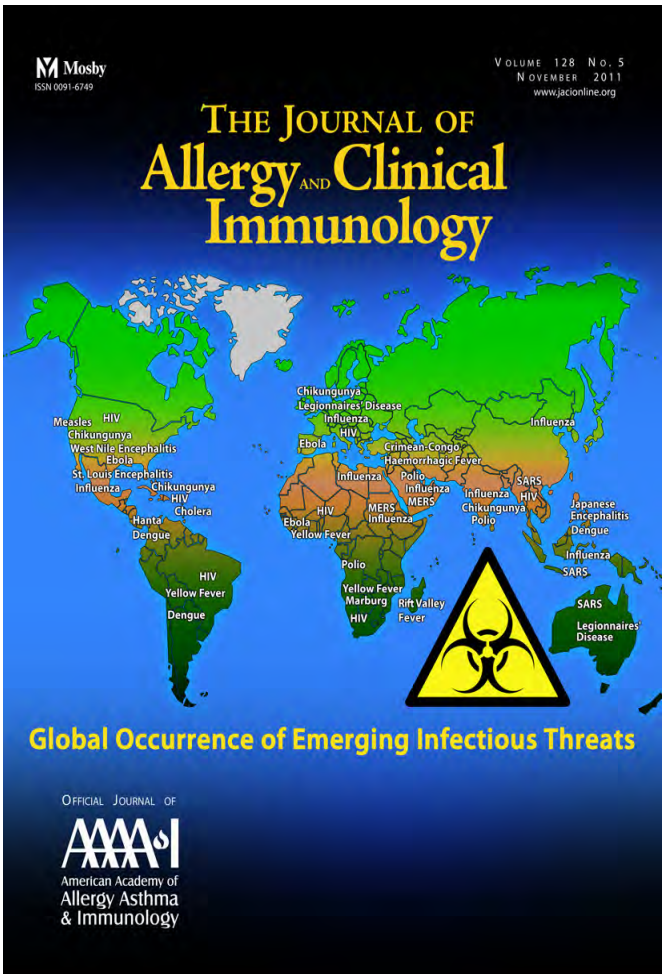


Figure 1: Immunofluorescence detection of claudin-4 (green) and ZO-1 (red) in non-asthmatic (A), and asthmatic (B) bronchial epithelial cells. CpG-2006-stimulated bronchial epithelial cells from non-asthmatic donors had higher ZO-1 and claudin-4 immunofluorescence at the cell boundary as compared with unstimulated control (A). CpG-2006 stimulation remarkably restored the impaired TJ immunostaining of the bronchial epithelia from asthma patients (B). Bar= 20 µm. Journal of Allergy and Clinical Immunology 2015.

In chronic allergic inflammation, dermis in the atopic skin and submucosa in the asthmatic lung turn into a lymphatic organ-like organization, where professional dendritic cells, T cells, B cells and innate lymphoid cells contact each other and a second step of antigen-presentation, activation and inflammation takes place in the inflamed tissue. Persistent airway inflammation and irreversible structural changes of the bronchial wall, defined as airway remodelling are crucial processes in the asthma development. These changes involve an altered expression and/or function of a large variety of proinflammatory cytokines, growth factors and their receptors, as well as a dysregulation in the differentiation, proliferation, and apoptosis of multiple cell types resulting in epithelial damage, subepithelial basement membrane thickness, subepithelial fibrosis, leukocyte, particularly eosinophils and T cell infiltrates as well as mucous gland and smooth muscle cell hypertrophy and/or hyperplasia. In particular, the increase in smooth muscle cell content can

explain the mechanical consequences of airway remodeling, such as airway luminal narrowing and the permanent reduction of the airway caliber. Basement membrane (lamina reticularis) thickening, allergen-specific secretory IgA are tissue events that try to keep the allergens away from submucosal immune system cells (keep away effects). There is clear evidence that lamina reticularis thickening starts very early in asthma, even at the time of first diagnosis, suggesting that a barrier between activated epithelium or mucosal allergens and inner tissues i.e. immune system cells occurs with the aim of down-regulation of the allergen-induced inflammatory response. The efforts of the immune system, epithelial cells and lung fibroblasts to increase lamina reticularis thickness might be indeed aiming to make a mechanical barrier between the allergens (mites and pollens) and the submucosal immune system. It is now very important to investigate these mechanisms, which resemble features of immune response to chronic helminth infections in order to decrease antigenic burden of the helminths and mechanically keep them away from tissues. For example, keeping them in fibrous sacks etc. As a part of remodelling, increases in airway smooth muscles occur in children with chronic inflammatory lung diseases that include cystic fibrosis and asthma. Our current research tools are suitable to answer these questions and the development and utilization of artificial 3D lung tissues will enable to ask human in vivo relevant questions.



The induction of IL-33 in the sinus epithelium and its Influence on T helper cell responses

Soyka MB, Holzmann D, Basinski TM, Wawrzyniak M, Bannert C, Bürgler S, Akkoc T, Treis A, Rückert B, Akdis M, Akdis CA, Eiwegger T. PLoS One. 2015 May;10, doi: 10.1371

Chronic rhinosinusitis (CRS) is characterized by epithelial activation and chronic T-cell infiltration in sinonasal mucosa and nasal polyps. IL-33 is a new cytokine of the IL-1 cytokine family that has a pro-inflammatory and Th2 type cytokine induction property. The role of IL-33 in the pathomechanisms of CRS and its interaction with other T cell subsets remain to be fully understood. IL-33 was mainly induced by IFN-γ in primary sinonasal epithelial cells, and induced a typical CRSwNP Th2 favoring cytokine profile upon co-culture with T-helper cell subsets. IL-33 and its receptor ST2 were highly expressed in the inflamed epithelial tissue of CRS patients. While IL-33 was significantly up-regulated in the epithelium for CRSsNP, its receptor was higher expressed in sinus tissue from CRSwNP. The present study delineates the influence of IL-33 in upper airway epithelium and a potential role of IL-33 in chronic inflammation of CRSwNP by enhancing Th2 type cytokine production, which could both contribute to a further increase of an established Th2 profile in CRSwNP.

Asthma, allergy and the olympics: a 12-year survey in elite athletes

Bonini M, Gramiccioni C, Fioretti D, Ruckert B, Rinaldi M, Akdis CA, Todaro A, Palange P, Carlsen KH, Pelliccia A, Rasi G, Bonini S; AIDA and the Italian Unit of the GA2LEN Olympic Study. Curr Opin Allergy Clin Immunol. 2015 Apr:184-92. doi: 10.1097

This 12-year survey aims to evaluate several clinical, functional and immunological parameters in order to assess features, trend and burden of asthma, allergy, infections and autoimmune diseases, in a large homogeneous population of six hundred and fifty-nine Italian Olympic athletes. The prevalence of asthma and/or exercise-induced bronchoconstriction was 14.7%, with a significant increase (P=0.04) from 2000 (11.3%) to 2008 (17.2%). The prevalence of rhinitis, conjunctivitis, skin allergic diseases and anaphylaxis was 26.2%, 20.0%, 14.8% and 1.1%, respectively. Sensitization to inhalant allergens was documented in 49.0% of athletes, being 32.7% in 2000 and 56.5% in 2008 (P<0.0001). Food, drug and venom allergy was present in 7.1%, 5.0% and 2.1% of athletes, respectively. The high prevalence of asthma and allergy was associated with recurrent upper respiratory tract (10.3%) and herpes (18.2%) infections, an abnormal T cell subset profile and a general down-regulation of serum cytokines with a significantly lower IFN-γ/IL-4 ratio. In conclusion, our findings demonstrated a chronic and intense physical exercise may cause that transient immunodepression with a preferential shift to a Th2 response, associated with abnormalities of the respiratory tract.

T-cell regulation during viral and nonviral asthma exacerbations

Wegrzyn AS, Jakiela B, Rückert B, Jutel M, Akdis M, Sanak M, Akdis CA.

J Allergy Clin Immunol. 2015 Jan. doi: 10.1016/j

Immune mechanisms underlying acute episodes of asthma are

poorly understood. We developed a multicolor flow cytometry panel for the evaluation of phenotypical changes in CD4+ T cells in asthmatic subjects during acute episodes and stable asthma compared to the control group. We demonstrate that virus-induced and non- virus-induced asthma exacerbations show distinct activation patterns in peripheral blood T cells. Virus-induced asthma exacerbations present with increased IL-17A production in T cells, non virus-induced asthma exacerbations show a highly significant decrease in CD4+CD25+CD127-FOXP3+, Helios+ T reg cells with an increase in IL-4+ Th2 cells.

Mechanisms of immune tolerance to allergens: role of IL-10 and Tregs

Akdis CA, Akdis M. J Clin Invest. 2014 Nov;124(11):4678-80

During the past 20 years, major advances have been made in understanding the molecular and cellular mechanisms of allergen tolerance in humans. This article summarizes major contributions of our group. The demonstration of T cell tolerance, particularly that mediated by the immune-suppressive functions of IL-10, led to a major conceptual change in this area. Currently, the known essential components of allergen tolerance include the induction of allergen-specific regulatory subsets of T and B cells, the immune-suppressive function of secreted factors, such as IL-10 and TGF-β, the production of IgG4 isotype allergen-specific blocking antibodies, and decreased allergic inflammatory responses by mast cells, basophils, and eosinophils in inflamed tissues.

MicroRNA-146a alleviates chronic skin inflammation in atopic dermatitis through suppression of innate immune responses in keratinocytes

Rebane A, Runnel T, Aab A, Maslovskaja J, Rückert B, Zimmermann M, Plaas M, Kärner J, Treis A, Pihlap M, Haljasorg U, Hermann H, Nagy N, Kemeny L, Erm T, Kingo K, Li M, Boldin MP, Akdis CA. J Allergy Clin Immunol. 2014 Oct;134(4):836-847

MicroRNAs (miRNAs) are short, single-stranded RNA molecules that silence genes via the degradation of target mRNAs or inhibition of translation. The aim of this study was to investigate the role of miR-146a in skin inflammation in AD. We demonstrated that miR-146a expression is increased in keratinocytes and chronic lesional skin of patients with AD. miR-146a inhibited the expression of numerous proinflammatory factors, including IFN-γ-inducible and AD-associated genes CCL5, CCL8, and ubiquitin D (UBD) in human primary keratinocytes stimulated with IFN-γ, TNF-α, or IL-1β. In a mouse model of AD, miR-146a-deficient mice developed stronger inflammation characterized by increased accumulation of infiltrating cells in the dermis, elevated expression of IFN-γ, CCL5, CCL8, and UBD in the skin, and IFN-γ, IL-1β, and UBD in draining lymph nodes. Both tissue culture and in vivo experiments in mice demonstrated that miR-146a-mediated suppression in allergic skin inflammation partially occurs through direct targeting of upstream nuclear factor kappa B signal transducers caspase recruitment domain-containing protein 10 and IL-1 receptor-associated kinase 1. In addition, human CCL5 was determined as a novel, direct target of miR-146a. In conclusion, miR-146a controls nuclear factor kappa B-dependent inflammatory responses in keratinocytes and chronic skin inflammation in AD.

EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy

Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, Cardona V, Dubois A, duToit G, Eigenmann P, Fernandez Rivas M, Halken S, Hickstein L, Høst A, Knol E, Lack G, Marchisotto MJ, Niggemann B, Nwaru BI, Papadopoulos NG, Poulsen LK, Santos AF, Skypala I, Schoepfer A, Van Ree R, Venter C, Worm M, Vlieg-Boerstra B, Panesar S, de Silva D, Soares-Weiser K, Sheikh A, Ballmer-Weber BK, Nilsson C, de Jong NW, Akdis CA; EAACI Food Allergy and Anaphylaxis Guidelines Group. Allergy. 2014 Aug;69(8):1008-25

Food allergy can result in considerable morbidity, impact negatively on quality of life, and prove costly in terms of medical care. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Guidelines for Food Allergy and Anaphylaxis Group, building on previous EAACI position papers on adverse reaction to foods and three recent systematic reviews on the epidemiology, diagnosis, and management of food allergy, and provide evidence-based recommendations for the diagnosis and management of food allergy. While the primary audience is allergists, this document is relevant for all other healthcare professionals, including primary care physicians, and pediatric and adult specialists, dieticians, pharmacists and paramedics. Current understanding of the manifestations of food allergy, the role of diagnostic tests, and the effective management of patients of all ages with food allergy is presented in a series of publications.

Distinct regulation of tonsillar immune response in virus infection

Jartti T, Palomares O, Waris M, Tastan O, Nieminen R, Puhakka T, Rückert B, Aab A, Vuorinen T, Allander T, Vahlberg T, Ruuskanen O, Akdis M, Akdis CA. Allergy. 2014 May;69(5):658-67

This study demonstrates that tonsillar cytokine expression is closely related to existing viral infections, age, and allergic illnesses and shows distinct clusters between antiviral and immune regulatory genes. Palatine tonsil samples were obtained from 143 elective tonsillectomy patients. Fifty percent of subjects reported allergy, 59% had ≥1 nasopharyngeal viruses, and 24% had ≥1 intratonsillar viruses. Tonsillar virus detection showed a strong negative association with age; especially rhinovirus or parainfluenza virus detection showed positive association with IFN-γ and Tbet expressions. IL-37 expression was positively associated with atopic dermatitis, whereas IFN-α, IL-13, IL-28, and Tbet expressions were negatively associated with allergic diseases. Network analyses demonstrated strongly polarized clusters of immune regulatory (IL-10, IL-17, TGF-β, FOXP3, GATA3, RORC2, Tbet) and antiviral (IFN-α, IFN-β, IL-28, IL-29) genes. These two clusters became more distinctive in the presence of viral infection or allergy. A negative correlation between antiviral cytokines and IL-10, IL-17, IL-37, FOXP3, and RORC2 was observed only in the presence of viruses, and interestingly, IL-13 strongly correlated with antiviral cytokines.

Th2-type cytokine-induced mucus metaplasia decreases susceptibility of human bronchial epithelium to rhinovirus infection

Jakiela B, Gielicz A, Plutecka H, Hubalewska-Mazgaj M, Mastalerz L, Bochenek G, Soja J, Januszek R, Aab A, Musial J, Akdis M, Akdis CA, Sanak M. Am J Respir Cell Mol Biol. 2014 Aug;51(2):229-41

A characteristic feature of asthmatic epithelium is goblet cell metaplasia and mucus hypersecretion. Bronchial epithelium is also an important source of lipid mediators, including pro- and antiinflammatory eicosanoids. By using air-liquid interface cultures of airway epithelium from patients with asthma and nonasthmatic control subjects, we compared rhinovirus16 replication-induced changes in mRNA expression of asthma candidate genes and eicosanoid production in the epithelium with or without IL-13-induced mucus metaplasia. Mucus metaplastic epithelium was characterized by a 20-fold less effective replication of RV16 and blunted changes in gene expression; this effect was seen to the same extent in patients with asthma and control subjects. We identified ciliary cells as the main target for RV16 by immunofluorescence imaging and demonstrated that the numbers of ciliary cells decreased in RV16-infected epithelium. RV16 infection of mucociliary epithelium resulted in overexpression of genes associated with bronchial remodeling (e.g., MUC5AC, FGF2, and HBEGF), induction of cyclooxygenase-2, and increased secretion of prostaglandins. These responses were similar in both studied groups. These data indicate that structural changes associated with mucus metaplasia renders airway epithelium less susceptible to RV infection. Thus, exacerbations of the lung disease caused by RV may result from severe impairment in mucociliary clearance or activation of immune defense rather than from preferential infection of mucus metaplastic epithelium.

Davos, June 2015

PD Dr. Mübeccel Akdis

Mechanisms of allergen-specific immunotherapy

Substantial progress in understanding mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumors, organ transplantation and chronic infections has led to a variety of targeted therapeutic approaches. Allergen-specific immunotherapy (AIT) has been used for 100 years as a desensitizing therapy for allergic diseases and represents the potentially curative and specific way of treatment. AIT represents the only curative and specific way for the treatment of allergic diseases, which have reached a pandemic dimension in industrial countries affecting up to 20-30% of the population. Currently, AIT is performed with vaccines based on allergen extracts that can cause severe, often life threatening, anaphylactic reactions as well as new IgE sensitization to other allergens present in the extract. Low patient adherence and high costs due to long duration (3 to 5 years) of treatment have been commonly reported. Several strategies have been developed to tackle these issues and it became possible to produce recombinant AIT vaccines with reduced allergenic activity.

A novel vaccine was developed for the treatment of cat allergy, a common cause of rhinoconjunctivitis and asthma. The major cat allergen, Fel d 1, is an 18-kDa heterodimer protein produced in cat saliva and sebaceous glands and is responsible for symptoms in more than 90% of cat-allergic individuals. The vaccine consisted of three functional elements of the modular allergen translocation (MAT) technique, which was fused to form a single recombinant protein. First, a cell membrane translocation module, the Trans-Activator of Transcription (TAT) peptide of human immunodeficiency virus, was used, which enables the vaccine to pass through the cell membrane and to accumulate inside antigen-presenting cells (APCs). Second, an MHC class-II targeting module, truncated invariant chain domain, which directs the processing of the MAT molecule within the APC and improves the presentation of the allergen and its components to the immune system via the MHC class-II pathway. Finally, the allergen, el d 1 in this case to which the patient is allergic determines the specificity of the induced immune response. In a randomized double-blind placebo-controlled trial MAT-Fel d 1 was injected into inguinal lymph nodes (ILIT) of cat allergic patients. Our group evaluated mechanisms of immune regulation by MAT vaccines in vitro and in AIT of cat allergic rhinitis patients, who received 3 inguinal intralymphnode injections of MAT-Fel d 1 vaccine. The data demonstrate that early T cell activation was followed by allergen-specific peripheral T cell tolerance one year later induced by multiple mechanisms that suggest the in vivo generation of allergen-specific Treg cells.

It is generally accepted that allergen-specific peripheral T-cell tolerance is characterized mainly by generation of allergen-specific Treg cells and initiated by IL-10, which is increasingly produced by the antigen-specific Treg cells. Subsets of Treg cells with distinct phenotypes and mechanisms of action include the CD4+ CD25+ FoxP3+ Treg cells, and the CD4+ IL-10-producing Tr1 cells. Different studies show roles for both subsets, suggesting an overlap particularly in the inducible subsets of Treg cells in human subjects. It has been shown that CD4+ CD25+ Treg cells from atopic donors have a reduced capability to suppress the proliferation of CD4+CD25- T cells. The presence of local FOXP3+ CD25+ CD3+ cells in the nasal mucosa, their increased numbers after immunotherapy, and their association with clinical efficacy and suppression of seasonal allergic inflammation strengthen the concept of allergen tolerance based on Treg cells in human subjects.

Still, current allergen-SIT approaches have inadequacies in terms of potential side effects, long duration, patient compliance, and insufficient outcomes in some patients. Further developments in the field of mechanisms of peripheral tolerance to allergens will guide future treatment options in allergic diseases.

Increased rapid internalization of MAT-Fel d 1

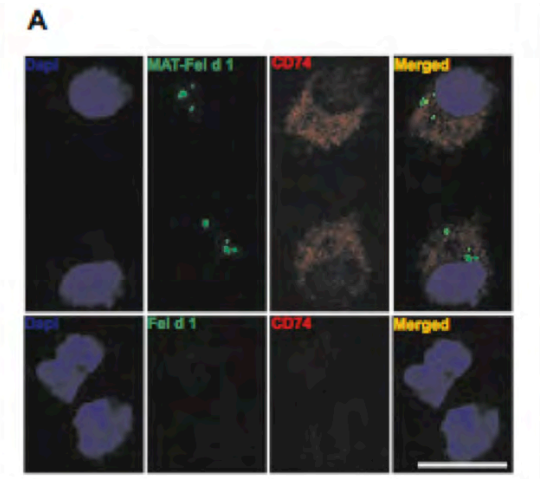


Figure 1: MAT-vaccines aggregate inside the cells after internalization. Allergy 2014;69:1262.

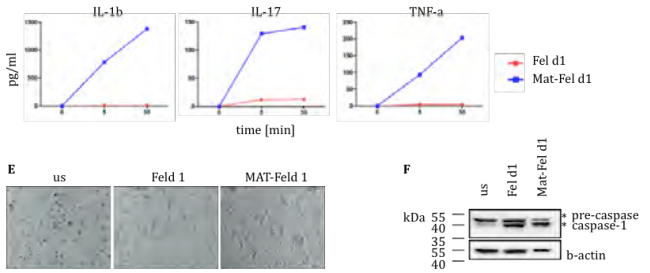


Figure 2: MAT-vaccines activate inflammasome. Pre-caspase and caspase-1 protein expression was assessed in THP-1 cells after stimulation for 120 min with Fel d 1 or MAT-Fel d 1. PBMC were incubated with Fel d 1 and MAT-Fel d 1 and secreted IL-1β was measured. Allergy 2014;69:1262.

Induction of allergen-specific IgG4 is a hallmark of successful peripheral tolerance induction, as observed in allergen SIT. Our findings demonstrate that PLA-specific B cells from beekeepers mainly express IgG4. PLA-specific and non–PLA-specific B cells were isolated from peripheral blood and directly analyzed without in vitro culture. The increased IgG4 expression in PLA-specific B cells indicates that these cells mainly represent circulating IgG4-switched PLA-specific memory B cells. Interestingly, IL-10 mRNA expression was also significantly higher in these cells, suggesting that in vivo circulating PLA-specific B cells in beekeepers have increased IL-10 production. Furthermore, when stimulated in vitro with TLR9-L, PLA-specific B cells showed higher IL-10 secretion than non–PLA-specific B cells. This increased frequency of IL-10+ cells among PLA-specific B cells was not observed in patients with bee venom allergy. However, after SIT, the frequency of PLA-specific IL-10+ B cells significantly increased to the same level seen in beekeepers. PLA-specific IgG4 was detected at high concentrations in sera of nonallergic beekeepers, which showed greater than 1000 times lower PLA-specific IgE/IgG4 ratios than sera from allergic subjects. Allergen SIT and high-dose allergen tolerance has been linked to increased serum IgG4 and IL-10 production from T cells. Our data demonstrate that particularly CD27–IL-10+ B cells are precursors of IgG4-producing cells. In addition, the ongoing immune response of memory B cells contributes to IgG4 production. We found increased IgG4 expression and an increased frequency of IL-10+ cells among PLA-specific B cells in bee venom–tolerant subjects. This suggests that in these subjects there exists a PLA-specific IgG4-switched memory B-cell compartment that retains high IL-10 expression and might play a role in maintenance of tolerance.

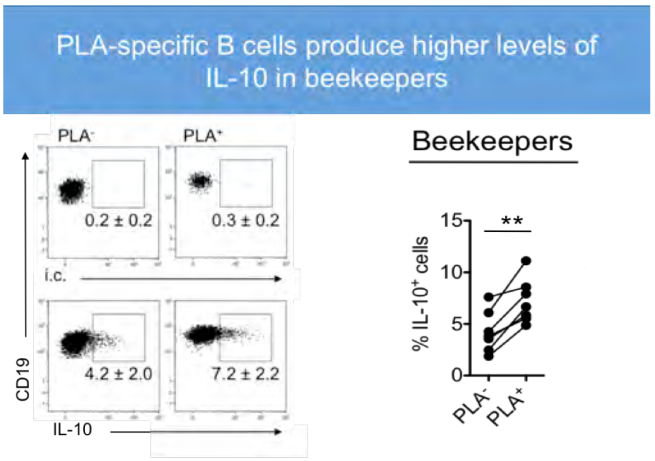


Figure 3. Enrichment of PLA-specific B cells and higher numbers of PLA-specific B cells express IL-10 from beekeepers.

Th22 cells

The regulation of IL-22 is poorly understood and has been mostly studied as part of Th17 differentiation process. It is clear that IL-22 is also expressed independently of IL-17 and that TGF-β, a major driver of Th17 development, suppresses IL-22 production. On the other hand, various transcription factors known to drive Th17 differentiation, such STAT3, RORγt, or aryl hydrocarbon receptor (AhR) have been implicated as positive regulators of IL-22. This is evidenced by the fact that mice deficient in either of those factors show a severe impairment in their ability to produce IL-22, but the precise molecular mechanisms by which these factors regulate IL-22 expression are largely unknown in human.

As a first step in the characterization of these different T cell populations, we sorted IL-22+ and IL22- cells and performed a whole genome microarray expression analysis. This provides insight in the mechanisms underlying the differential regulation of IL-22 production. Interleukin-22 uses the IL-22R1/IL-10R2 complex to mediate its biological effect – crosstalk between leukocytes and tissue epithelia. We have established several primary human tonsillar and bronchial epithelial cell lines from asthmatic and healthy donors. They will be differentiated in air liquid interface cultures (ALI) cultures. We showed that IL-22 is decreasing transepithelial resistance of tonsillar epithelial cells. Our preliminary data suggests that IL-22 influences epithelial cells integrity and could be responsible for the development of immune response in tonsils.

Breaking of antigen-specific tolerance in tonsil cells

Human tonsils are organs of immune tolerance in which the generation and maintenance of allergen-specific Treg cells occur. Supporting these findings, recently reported that in human tonsils extrathymic T-cell development programs are imprinted. Although it is becoming more clear that the observed increment in the incidence of allergic diseases is due to the loss of peripheral T-cell tolerance to allergens, the mechanisms or specific cytokines or innate immune response stimulating factors involved in such processes remain largely unknown. Dendritic cells (DC) play a pivotal role in the orchestration of immune responses by linking innate and adaptive immunity. In human subjects, circulating DCs can be broadly divided into 2

main groups: myeloid dendritic cells (mDC) and plasmacytoid dendritic cells (pDC). Both mDCs and pDCs are equipped with a specific repertoire of Toll-like receptors (TLRs). mDCs express TLR2 to TLR6 and TLR8, whereas pDCs express TLR7 and TLR9. DCs can control the suppressive activity of Treg cells in several ways through the release of proinflammatory cytokines, such as IL-1b or IL-6, after TLR-dependent responses to pathogen-associated molecular patterns. Although recent studies have demonstrated that triggering of TLRs can directly regulate Treg cell functions, there is still scarce information about the role played by specific TLR ligands (TLR-Ls) or proinflammatory cytokines in breaking allergen-specific T-cell tolerance, especially in human subjects.

We identified molecular mechanisms involved in breaking allergen-specific T-cell tolerance. We demonstrated that triggering of TLR4 or TLR8, as well as IL-1beta or IL-6, is able to enhance allergen-specific CD4+ T-cell responses in human tonsils and peripheral blood. We showed mDCs as the main DC subset mediating such effects through mechanisms partially dependent on MyD88 and upregulation of costimulatory molecules. Our findings demonstrate that specific stimuli that are able to activate innate immunity also condition specific adaptive immune responses to allergens, suggesting a mechanism that explains how healthy subjects can have allergic diseases after encountering microbes or inflammatory conditions. The identification of the factors leading to the loss of peripheral allergen-specific T-cell tolerance and the better understanding of the pathways involved in such mechanisms will allow the design of alternative strategies aimed at preventing the development of allergic diseases, as well as improving the current treatment modalities.

Regulatory B cells

The current findings demonstrate an essential role for B cells in the induction and maintenance of immunologic tolerance. B lymphocytes display a unique role in immunity through the production/secretion of antibodies confining humoral arm of adoptive immune response, necessary for neutralization and final clearance of (harmful) dangerous substances and pathogens and their products. Nevertheless, B cells also substantially contribute to the full magnitude and fate of normal immune response through antigen presentation and co-stimulation, cytokine secretion and lymphoid tissue organization.

As well as in normal immune response, the importance of complex B cell biology was recognized in altered/non-adequate pathological immune responses: asthma and atopic diseases (chronic immune reactivity to non-harmful antigens in sensitized individuals primarily mediated through IgE), autoimmunity (lack of control, excessive response) anti-tumor immunity/defense (insufficient response).

Different subsets of B regulatory cells have been described in both mice and humans, differing in their surface markers profile, but all of them secreting interleukin-10. In order to address the suppressive capacity of IL-10 producing B cells, over expression of human IL-10 in normal human B cells was established and optimized. Purified human B cells were transfected with pORF-hIL-10 or pORF-mcs control vector using nucleofection. Significant transcription of IL-10 was detected in cell lysates by qPCR as well as secreted IL-10 protein in cell culture supernatants. There was no influence on B cell survival and apoptosis. In order to test the effect of IL-10-producing B cells on innate immune response, human B cells over expressing IL-10 were co-cultured with autologous PBMC prior to activation with different TLR ligands (TLR2-, TLR3-, TLR4- and TLR9- ligands). Along with marked increase in IL-10 secretion, all secreted cytokines induced on TLR-2, TLR-3, TLR-4 and TLR-9 pathways were substantially inhibited, particularly TNF-a, IL-1b IL-6, IL-8, G-CSF, IFN-g, as well as GM-CSF and IL-8, compared to control vector transfected B cell co-cultures. These data demonstrate the suppressive role of high IL-10 expressing B cells on innate immune response. These findings particularly confirm the role of B cells in the maintenance of peripheral tolerance and their contribution to immune homeostasis.

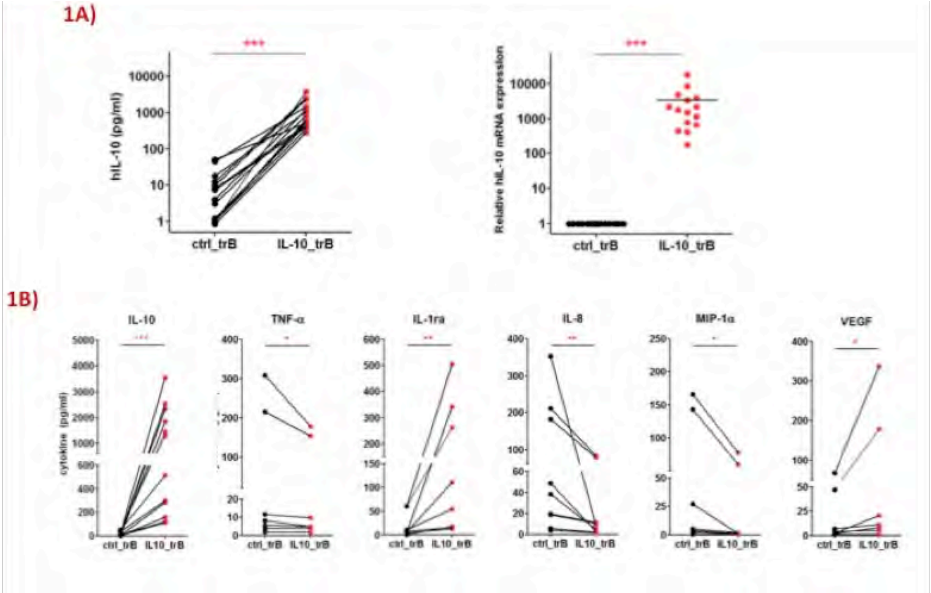


Figure 4: Overexpression of human IL-10 and profile of cytokine secreted from IL-10 overexpressing B cells. (A) B cells were transfected with pORF-hIL-10 (IL10_trB) or pORF-mcs (ctrl_trB) and cultured in medium for 24h. Secreted human IL-10 and relative human IL-10 mRNA expression were measured. (B) Secretion of other cytokines, chemokines and growth factors was quantified using beads-based multiplex cytokine measurement.

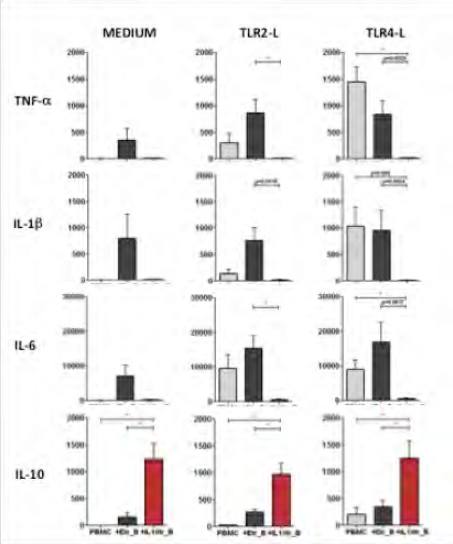


Figure 5: Cytokine secretion from PBMC co-incubated with TLR9-L pretreated and transfected B cells upon TLR2-L or TLR4-L stimulation.

MeDALL (Mechanisms of the Development of ALLergy)
Rationale
The causes explaining the epidemic of IgE-associated (allergic) diseases are unclear. The prediction of allergy and preventive strategies are currently insufficient to abate the epidemic.

Objectives
MeDALL (Mechanisms of the Development of ALLergy) aims to generate novel knowledge on the mechanisms of initiation of allergy from early childhood to young adulthood, in order to propose early diagnosis, prevention and targets for therapy. A novel definition of phenotypes of allergic diseases and an integrative translational approach are needed to understand how a network of molecular and environmental factors can lead to complex allergic phenotypes.

Predicta (Post-infectious immune reprogramming and its association with persistence and chronicity of respiratory allergic diseases)
Immunodermatology group of SIAF is the WP5 in predicta.
Main ideas behind PreDicta
•Rising incidence of asthma and rhinitis in Europe with high socioeconomic burden
•Urgent need for novel preventive, diagnostic and therapeutic approaches
•Strong recent evidence associating rhinovirus infections with the origins, triggering and persistence of asthma
•Need for understanding the pathophysiological mechanisms linking infections to inflammation persistence in asthma and rhinitis
•Need to explore an in deterministic approach in the persistence of asthma/ respiratory allergies
•Gap between scientific discoveries and their rendition into clinical practice
•Consortium with translational focus, including clinical cohorts and experimental models, strong track record, unique resources and technologies

Immune regulation by intralymphatic immunotherapy with modular allergen translocation MAT vaccine
Anna Zaleska, Thomas Eiwegger, Özge Soyer, Willem van de Veen, Claudio Rhyner, Michael B. Soyka, Cemalettin Bekpen, Duygu Demiröz, Angela Treis, Stefan Söllner, Oscar Palomares, , William W. Kwok, Horst Rose, Gabriela Senti, Thomas M. Kündig, Marek Jutel, Cezmi A. Akdis, Reto Crameri, Mübeccel Akdis. Allergy. 2014 Sep;69(9):1162-70.
Allergen-specific immunotherapy (SIT) faces problems related to side effects and limited efficacy. Direct administration of allergen extracts into lymph nodes induces increased specific IgG production and T-cell responses using significantly lower allergen doses. In this study mechanisms of immune regulation by MAT vaccines in vitro and in allergen-SIT of cat allergic rhinitis patients, who received 3 inguinal intralymphnode injections of MAT-Fel d 1 vaccine was investigated in PBMC and cell cultures for specific T cell proliferation, Fel d 1-tetramer-specific responses and multiple immune regulatory molecules. MAT-Fel d 1 vaccine was efficiently internalized by antigen-presenting cells. This was followed by pre-caspase 1 cleavage to caspase 1 and secretion of IL-1β, indicating inflammasome activation. Mat-Fel d 1 induced specific T cell proliferation and an IL-10- and IFN-g-dominated T cell responses with decreased Th2 cytokines at 100 times lower doses than Fel d 1. Induction of immune tolerance by MAT-Fel d 1 ILIT involved multiple mechanisms of immune suppression. Early Fel d 1-specific T cell activation was followed by full T cell unresponsiveness to allergen after 1 year in the MAT-Fel d 1 group, characterized by increased allergen-specific T regulatory cells, decreased circulating Fel d 1 tetramer-positive cells, increased IL-10 and FOXP3 expression and change in the HR2/HR1 ratio towards HR2. The present study demonstrates induction of allergen tolerance after 3 intralymph node injections of MAT-Fel d 1 vaccine, mediated by increased cellular internalization of the allergen, activation of inflammasome and generation of allergen-specific peripheral T cell tolerance.

Human IL-10-overexpressing B cells exibit complex immunoregulatory phenotype and possess extensive regulatory capacity toward both innate and adoptive arm of immune response
Barbara Stanic, Willem van de Veen, Oliver Wirz, Beate Rückert, Stefan Söllner, Cezmi A. Akdis, and Mübeccel Akdis. J Allergy Clin Immunol. 2015 Mar;135(3):771-80.
Distinct human IL-10-producing B cells with immunoregulatory properties demonstrated in vivo were described. However, the broader spectrum of their direct cellular targets and mechanisms of suppression have not yet been extensively reported, particularly in the light of direct and indirect solely IL-10 mediated functions. To characterize regulatory phenotype and, based on solely IL-10 intrinsic properties, to assess the immunosuppressive capacity of IL-10 producing cells on TLR- stimulated innate responses in PBMC, maturation of dendritic cells and antigen-specific proliferation using IL-10-overexpressing normal human B cells. Highly purified IL-10-overexpressing B cells were phenotypically characterized in terms of their profile of cytokine and immunoglobulin produc-

tion, antigen presentation and co-stimulation capacity, transcription factors signature, and chemokine receptor profile (by quantitative PCR and flow cytometry). Effects of IL-10-overexpresing B cells on PBMC and MDDC were addressed in co-cultures with autologous cells under stimulatory conditions. Cytokine release from TLR2- and TLR4-triggered PBMCs, cytokine production and co-stimulatory molecules expression from TLR4-L stimulated maturation of MDDC and antigen-specific stimulation of PBMC were assessed. Our data show that under IL-10 overexpression normal human B cells are quickly able to acquire prominent immunoregulatory profile with reduced activation (CD19loCD27lo) that comprise enhanced expression of surface GARP and transcription factor HELIOS, molecules expressed on regulatory T cells, and intracellular SOCS3 probably responsible for reduced production of TNF-a, IL-8 and MIP-1a, and enhanced secretion of IL-1RA and VEGF. IL-10 overexpression was found associated with decrease in co-stimulatory potential retaining antigen presentation. Furthermore, IL-10-overexpressing cells induce IRF-4 and XBP-1 transcription factors and CD38 and CD138 surface markers, which depict reduced activated B cell transition to antibody secreting plasmablasts with no significantly skewed isotype secretion. When co-cultured with autologous PBMC, IL-10-overexpressing B cells potently reduce the secretion of proinflamatory cytokines induced by TLR2 and TLR4 stimulation, cause shift of MDDC to less differentiated stage and remarkably downregulate their co-stimulatory capacity by reducing expression of CD80, CD86 and CD83, while inducing the expression of PD-L1 molecule important for induction of regulatory T cells. IL-10-overexpressing B cells substantially inhibit antigen specific proliferation of PBMC. Our data demonstrate prominent role of IL-10 in inducing complex immunoregulatory phenotype of B cells capable to exert substantial anti-inflammatory functions as well as to significantly contribute immune response providing tolerance-inducing environment.

Advances in allergen immunotherapy: aiming for complete tolerance to allergens

Akdis CA, Akdis M. Sci Transl Med. 2015 Mar 25;7 (280): 280ps6.

Allergen-specific immunotherapy (AIT) has been used for more than 100 years as a tolerance-inducing therapy for allergic diseases and represents a potentially curative method of treatment. AIT functions through multiple mechanisms, including regulating T and B cell responses, changing antibody isotypes, and decreasing mediator release and migration of eosinophils, basophils, and mast cells to affected tissues. Despite the relative success of AIT, attempts are being made to improve this therapy in order to overcome problems in standardization, efficacy, safety, long duration of treatment, and costs. These have led to the development of biotechnological products with successful clinical results.

EAACI Interest Group Biologicals task force paper on the use of biologic agents in allergic disorders

Boyman O, Kaegi C, Akdis M, Bavbek S, Bossios A, Chatzipetrou A, Eiwegger T, Firinu D, Harr T, Knol E, Matucci A, Palomares O, Schmidt-Weber C, Simon HU, Steiner UC, Vultaggio A, Akdis CA, Spertini F. Allergy. 2015 Mar 26.

Biologic agents (also termed biologicals or biologics) are therapeutics that are synthesized by living organisms and directed against a specific determinant, for example, a cytokine or receptor. In inflammatory and autoimmune diseases, biologicals have revolutionized the treatment of several immune-mediated disorders. Biologicals have also been tested in allergic disorders. These include agents targeting IgE; T helper 2 (Th2)-type and Th2-promoting cytokines, including interleukin-4 (IL-4), IL-5, IL-9, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP); pro-inflammatory cytokines, such as IL-1β, IL-12, IL-17A, IL-17F, IL-23, and tumor necrosis factor (TNF); chemokine receptor CCR4; and lymphocyte surface and adhesion molecules, including CD2, CD11a, CD20, CD25, CD52, and OX40 ligand. In this task force paper of the Interest Group on Biologicals of the European Academy of Allergy and Clinical Immunology, we review biologicals that are currently available or tested for the use in various allergic and urticarial pathologies, by providing an overview on their state of development, area of use, adverse events, and future research directions.

Davos, June 2015


SIAF
Schweizerisches Institut
für Allergie- und Asthmaforschung
Swiss Institute of Allergy
and Asthma Research

Dr. Liam O´Mahony

The molecular Immunology group is primarily focused on the molecular and cellular mechanisms underpinning the interactions between host immune cells and the microbiome. 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. In humans, allergen challenge leads to an accumulation of myeloid (mDCs) within the airways of asthmatics, concomitantly with a reduction in circulating CD11c+ cells, suggesting that these cells are recruited from the bloodstream in response to allergen challenge. The plasmacytoid DCs (pDCs) subset have also been described within the bronchoalveolar lavage (BAL) fluid of asthma patients but their role in ongoing allergen-specific responses in asthma is currently unknown.

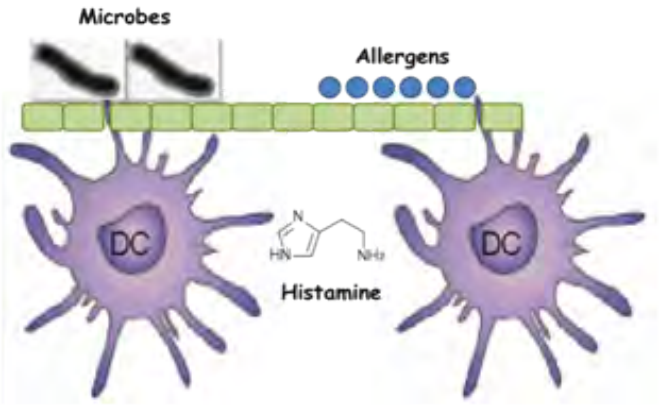


Figure 1. Microbes, allergens and metabolites (e.g. histamine) directly influence DC maturation, activation and lymphocyte polarization.

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

We are pursuing complementary research programs within our group in order to (i) identify the molecular basis and in vivo relevance for histamine-H2R interactions in respiratory and gastrointestinal inflammatory responses; (ii) identify bacterial bioactives that promote regulatory immune responses at mucosal sites; (iii) determine the role of G protein-coupled receptors (GPCRs) in regulating the immune response in asthma patients.

(i) Histamine is a biogenic amine with extensive effects on many cell types including important immunological cells such as antigen-presenting cells (APCs), Natural Killer (NK) cells, epithelial cells, T lymphocytes and B lymphocytes. Histamine and its four receptors (H1R – H4R) represent a complex system of immunoregulation with distinct effects dependent on receptor subtypes and their differential expression. These are influenced by the stage of cell differentiation as well as micro-environmental influences, leading to the selective recruitment of effector cells into tissue sites accompanied by effects on cellular maturation, activation, polarization and effector functions leading to tolerogenic or pro-inflammatory responses. H1R, H2R, and H4R are expressed by many cell types of the innate and adaptive immune system, including DCs, while expression of H3R is largely limited to the central nervous system. Histamine has diverse effects depending on the cell type and the repertoire of histamine receptors that are expressed. For example, Th1 cells predominantly express H1R while Th2 cells express H2R and activation of the H2R can suppress activation of both T cell lineages. H2R

activation of human pDCs leads to a significant downregulation of IFN-α and TNF-α release following CpG stimulation. H4R has been shown to mediate mast cell, eosinophil, and dendritic cell chemotaxis and can modulate cytokine production from dendritic cells and T cells. H4R has also been shown to be upregulated on human T cells under Th2 polarizing conditions in vitro. H4R-/- mice and wild-type mice treated with a selective H4R antagonist display reduced disease activity following induction of airway inflammation. In contrast, H4R activation mediated by a selective agonist, delivered intratracheally, mitigated airway hyper-reactivity and inflammation. This effect was associated with a potent Foxp3+ T regulatory cell response in the lung. Thus, it is clear that histamine and its receptors play an important role in linking innate and adaptive immune responses.

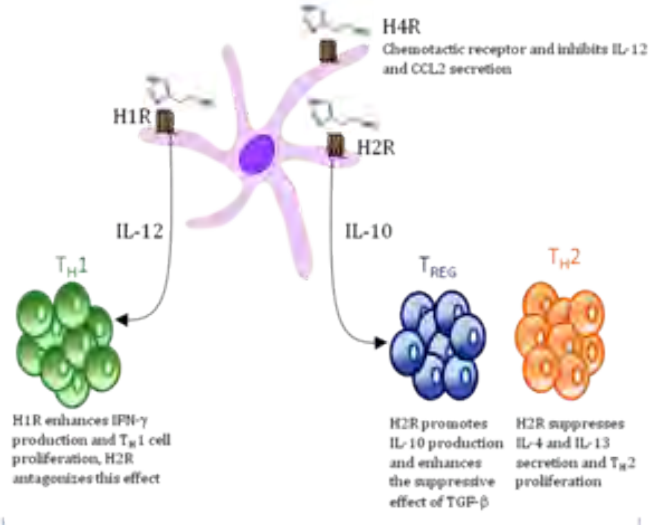


Figure 2. Histamine influences DCs and lymphocytes via their expression of different histamine receptors.

As described in previous reports, histamine signaling through the H2R significantly alters the human dendritic cell immune response to bacterial ligands (such as TLR ligands). In addition, ovalbumin sensitized mice were co-treated with Famitodine (H2R antagonist) or Dimaprit (H2R agonist), resulting in a more severe allergic phenotype or protection from allergic sensitization, respectively. Furthermore, we have also demonstrated in H2R knock-out animals, that loss of this receptor results in more exaggerated allergic responses within the lung. This is characterized by enhanced recruitment of eosinophils and elevated cytokine release from tissue cells. Interestingly, the balance between regulatory cells and effector cells within the lung is severely disrupted, even prior to allergen sensitization and challenge. In particular, CD1d expressing DC numbers are increased in the lung, while invariant natural killer T cells (iNKT) are also increased. Stimulation of iNKT cells by alphaGalCer within the lungs of H2R knock-out animals resulted in more severe respiratory inflammation, characterized by an enhanced Th17 response and recruitment of neutrophils. Lung challenge with other Th2 promoting lipids resulted in a more pronounced eosinophil response. Identical results were observed in the house dust mite murine model. Our group is currently dissecting these cellular interactions in order to further define the molecular basis for this defect in immunoregulation, in particular the lung-associated iNKT cell hyper-reactivity. Thus, our results to date suggest that histamine signaling via H2R suppresses the pro-inflammatory response and may represent a novel intervention target in the treatment of allergy and asthma.

Histamine may also exert immunoregulatory effects in other inflammatory disorders, such as inflammatory bowel disease (IBD). Patients with IBD exhibit altered H2R expression on peripheral blood monocytes and the suppressive effect of H2R activation on TLR-induced cytokine responses is no longer effective in IBD patients. Within the gastrointestinal mucosa, histamine receptor expression is altered in inflamed tissue, compared to non-inflamed tissue from the same patient, and histamine receptor expression is directly correlated with proinflammatory cytokine expression. A more detailed histological and functional analysis of mucosal biopsies from IBD patients is ongoing, in order to better define the specific role for histamine signaling within the gastrointestinal tract.

(ii) The commensal microbiota is required for optimal host development and for ongoing immune homeostasis which involves an inter-dependence between microbes and immunity. This requires discriminative responses to commensals in comparison to pathogens to ensure tolerance and protective immunity respectively. A characteristic feature of mucosal tolerance is the induction and expansion of Foxp3+ T regulatory cells which limit excessive pro-inflammatory responses. We and others have identified specific microbes present within the gastrointestinal tract which selectively promote Foxp3+ polarization within the mucosa of mice. However, the in vivo mechanisms underpinning this response are not well understood and it is not clear if results obtained in the murine system are also applicable to humans.
Within the mucosa, both mDCs and pDCs are in close contact with microbes and are responsible for presenting microbial and dietary antigens to the adaptive immune system thereby influencing polarization of the adaptive response via cytokine and metabolite production. Thus, the decision to induce Foxp3+ T cells is significantly influenced by activation of dendritic cell pattern recognition receptors (PRRs) which program dendritic cell gene expression and subsequent T cell polarization. Co-ordination between PRR signaling pathways is important for the induction of the appropriate dendritic cell and T cell response. For example, TLR-2 recognition of zymosan results in the secretion of retinoic acid and IL-10 leading to Foxp3+ induction while dectin-1 activation by zymosan leads to IL-23 secretion and Th17 induction. In addition, TLR-2 activation was demonstrated to inhibit TLR-3 associated inflammatory responses within the skin in a TRAF-1 dependant mechanism.

Bifidobacterium infantis 35624 (B. infantis) is a commensal microbe originally isolated from the human gastrointestinal mucosa and has been extensively studied for its ability to regulate inflammatory responses, both in mice and humans. We selected this bacterium as a model Foxp3 inducing organism. B. infantis induction of regulatory cytokines, such as IL-10, is dependent on DC-SIGN and TLR-2 recognition by mDCs but TLR-9 is required for pDC activation. In addition to regulatory cytokines, DCs regulatory metabolic proces-

ses become activated, which are also required for the induction of Foxp3+ CD4 cells by B. infantis-stimulated mDCs and pDCs. However, the mechanisms of Foxp3 induction differ for mDCs and pDCs. We have now shown that both TLR-2 and DC-SIGN are important for immunoregulatory responses to another microbe, Lactobacillus rhamnosus JB-1, suggesting that the combination of TLR-2 and DC-SIGN activation may be critical for immunoregulatory responses to commensal microbes. Interestingly, recent findings by our group on microbiota-derived short-chain fatty acids suggest that we may have previously underestimated the importance of the relationship between diet and the microbiota. Current collaborations with Prof Lauener, Dr Frei and Dr Roduit are examining the role for novel dietary components in managing allergic disorders. In addition, we are isolating and identifying novel biogenic amine (e.g. histamine) secreting microbes from the human microbiome, that exert immunoregulatory activity both in vitro and in vivo. Furthermore, the identification of novel bacterial-derived immunoregulatory peptides, lipids and polysaccharide structures is ongoing and exciting results demonstrate that these bacterial-derived molecules exert potent immunoregulatory activities. A clearer understanding of the mechanisms employed in vivo for the induction of oral tolerance by the microbiota will likely result in rational strategies to manipulate both T regulatory and effector cells, thereby influencing inflammatory disorders such as allergy and asthma. These molecular mechanisms also highlight an important link between diet (e.g. vitamin A, which is required for DC metabolism to retinoic acid), composition of the gastrointestinal microbiota and regulation of intestinal immune responses. The identification of bacterial-derived components or metabolites which selectively activate the immune regulatory program will lead to the rationale design of new drugs for in vivo assessment.

(iii) The incidence of obesity has risen dramatically during the last decades and obesity has been correlated with significant public health implications, including a well established link with an increased risk of developing diabetes, coronary artery disease and non-alcoholic steatohepatitis. More recent epidemiologic studies have demonstrated an increased risk of asthma associated with increasing obesity. The effect of obesity on the occurrence of asthma seems to be more prominent in women and non-allergic individuals, while there is a dose response effect of increasing body mass index (BMI) on asthma incidence. Interestingly, the interaction between obesity and asthma is not mediated by classical TH2 inflammation as suggested by cytokine profiling and exhaled nitric oxide studies. It is becoming increasingly evident that obesity is associated with a unique asthma phenotype that is characterized by more severe disease with variable response to conventional asthma therapies. Metabolic factors, such as free fatty acids (FFA) could also play a role in the increased risk for developing asthma. FFA can be derived from host metabolism or also from microbiota-associated metabolic processes. FFAs play important physiological roles in many tissues as an energy source and as signaling molecules in various cellular processes. We have currently recruited 161 patients and volunteers from the Pneumology Department, University Hospital Zürich (Dr. Kohler) and the Department of Clinical Immunology, Wroclaw Medical University, Poland (Prof. Jutel). Microbiome composition and microbial metabolites are significantly altered in obese individuals, compared to non-obese individuals. Asthma is also associated with alterations in metabolite levels, while microbiome analysis has revealed surprising differences between the groups and these differences in microbial populations are currently being examined for their functional significance in in vitro and murine models.

Histamine and gut mucosal immune regulation.

Smolinska S, Jutel M, Crameri R, O'Mahony L.

Allergy. 2014 Mar;69(3):273-81

Histamine is a biogenic amine with extensive effects on many cell types, mediated by the activation of its four receptors (H1R-H4R). Distinct effects are dependent on receptor subtypes and their differential expression. Within the gastrointestinal tract, histamine is present at relatively high concentrations, particularly during inflammatory responses. In this review, we discuss the immunoregulatory influence of histamine on a number of gastrointestinal disorders, including food allergy, scombroid food poisoning, histamine intolerance, irritable bowel syndrome, and inflammatory bowel disease. It is clear that the effects of histamine on mucosal immune homeostasis are dependent on expression and activity of the four currently known histamine receptors; however, the relative protective or pathogenic effects of histamine on inflammatory processes within the gut are still poorly defined and require further investigation.

Salmonella adhesion, invasion and cellular immune responses are differentially affected by iron concentrations in a combined in vitro gut fermentation-cell model.

Dostal A, Gagnon M, Chassard C, Zimmermann MB, O'Mahony L, Lacroix C.

PLoS One. 2014 Mar 27;9(3):e93549.

In regions with a high infectious disease burden, concerns have been raised about the safety of iron supplementation because higher iron concentrations in the gut lumen may increase risk of enteropathogen infection. The aim of this study was to investigate interactions of the enteropathogen Salmonella enterica ssp. enterica Typhimurium with intestinal cells under different iron concentrations encountered in the gut lumen during iron deficiency and supplementation using an in vitro colonic fermentation system inoculated with immobilized child gut microbiota combined with Caco-2/HT29-MTX co-culture monolayers. Colonic fermentation effluents obtained during normal, low (chelation by 2,2'-dipyridyl) and high iron (26.5 mg iron/L) fermentation conditions containing Salmonella or pure Salmonella cultures with similar iron conditions were applied to cellular monolayers. Salmonella adhesion and invasion capacity, cellular integrity and immune response were assessed. Under high iron conditions in pure culture, Salmonella adhesion was 8-fold increased compared to normal iron conditions while invasion was not affected leading to decreased invasion efficiency (-86%). Moreover, cellular cytokines IL-1β, IL-6, IL-8 and TNF-α secretion as well as NF-κB activation in THP-1 cells were attenuated under high iron conditions. Low iron conditions in pure culture increased Salmonella invasion correlating with an increase in IL-8 release. In fermentation effluents, Salmonella adhesion was 12-fold and inva-

sion was 428-fold reduced compared to pure culture. Salmonella in high iron fermentation effluents had decreased invasion efficiency (-77.1%) and cellular TNF-α release compared to normal iron effluent. The presence of commensal microbiota and bacterial metabolites in fermentation effluents reduced adhesion and invasion of Salmonella compared to pure culture highlighting the importance of the gut microbiota as a barrier during pathogen invasion. High iron concentrations as encountered in the gut lumen during iron supplementation attenuated Salmonella invasion efficiency and cellular immune response suggesting that high iron concentrations alone may not lead to an increased Salmonella invasion.

Histamine 2-receptor is a key influence in immune responses to intestinal histamine-secreting microbes.
Ferstl R, Frei R, Schiavi E, Konieczna P, Barcik W, Ziegler M, Lauener RP, Chassard C, Lacroix C, Akdis CA, O'Mahony L.
J Allergy Clin Immunol. 2014 Sep;134(3):744-746.
Mucosal expression of histamine receptor 2 is critical for immunomodulatory responses to bacterial-derived histamine. Histamine-secreting microbes may be important intervention targets in patients with mucosal inflammatory disorders, while the selection of enteric microbes for potential probiotic use needs to be conducted more in depth than is currently routinely performed.

Prebiotics, probiotics, synbiotics, and the immune system: experimental data and clinical evidence.
Frei R, Akdis M, O'Mahony L.
Curr Opin Gastroenterol. 2015 Mar;31(2):153-8.
The intestinal immune system is constantly exposed to foreign antigens, which for the most part should be tolerated. Certain probiotics, prebiotics, and synbiotics are able to influence immune responses. In this review, we highlight the recent publications that have substantially progressed this field. The immunological mechanisms underpinning probiotics, prebiotics, and synbiotics effects continue to be better defined with novel mechanisms being described for dendritic cells, epithelial cells, T regulatory cells, effector lymphocytes, natural killer T cells, and B cells. Many of the mechanisms being described are bacterial strain or metabolite specific, and should not be extrapolated to other probiotics or prebiotics. In addition, the timing of intervention seems to be important, with potentially the greatest effects being observed early in life.
In this review, we discuss the recent findings relating to probiotics, prebiotics, and synbiotics, specifically their effects on immunological functions.

Intestinal dendritic cells.
Schiavi E, Smolinska S, O'Mahony L.
Curr Opin Gastroenterol. 2015 Mar;31(2):98-103.
The intestinal immune system is constantly exposed to foreign antigens, which for the most part should be tolerated, but the immune system retains the ability to react rapidly and effectively to eliminate pathogens. Dendritic cells are at the front line in maintaining intestinal integrity as they are widely distributed within the intestinal lamina propria, Peyer's patches and mesenteric lymph nodes. The identification of dendritic cell subsets and phenotypic markers within the healthy and diseased intestine has progressed significantly, including improved identification of dendritic cell subsets within the human intestine. Recently, the role for dietary factors and the microbiome in modulating the intestinal dendritic cell functions has begun to be better investigated, resulting in a number of new findings relating to retinoic acid metabolism, pattern recognition receptor triggering and G-protein-coupled receptor activation. In addition, the interactions between goblet cells and mucin with intestinal dendritic cells are being better defined.
In this review, we discuss the recent findings relating to intestinal dendritic cells, in particular the importance of dendritic cells in sensing the intestinal microenvironment and the consequences for health and disease.

Human dendritic cell DC-SIGN and TLR-2 mediate complementary immune regulatory activities in response to Lactobacillus rhamnosus JB-1.
Konieczna P, Schiavi E, Ziegler M, Groeger D, Healy S, Grant R, O'Mahony L.
PLoS One. 2015 Mar 27;10(3):e0120261.
The microbiota is required for optimal host development and ongoing immune homeostasis. Lactobacilli are common inhabitants of the mammalian large intestine and immunoregulatory effects have been described for certain, but not all, strains. The mechanisms underpinning these protective effects are beginning to be elucidated. One such protective organism is Lactobacillus rhamnosus JB-1 (Lb. rhamnosus JB-1). Lb. murinus has no such anti-inflammatory protective effects and was used as a comparator organism. Human monocyte-derived dendritic cells (MDDCs) were co-incubated with bacteria and analysed over time for bacterial adhesion and intracellular processing, costimulatory molecule expression, cytokine secretion and induction of lymphocyte polarization. Neutralising antibodies were utilized to identify the responsible MDDC receptors. Lb. rhamnosus JB-1 adhered to MDDCs, but internalization and intracellular processing was significantly delayed, compared to Lb. murinus which was rapidly internalized and processed. Lb. murinus induced CD80 and CD86 expression, accompanied by high levels of cytokine secretion, while Lb. rhamnosus JB-1 was a poor inducer of costimulatory molecule expression and cytokine secretion. Lb. rhamnosus JB-1 primed MDDCs induced Foxp3 expression in autologous lymphocytes, while Lb. murinus primed MDDCs induced Foxp3, T-bet and Ror-γt expression. DC-SIGN was required for Lb. rhamnosus JB-1 adhesion and influenced IL-12 secretion, while TLR-2 influenced IL-10 and IL-12 secretion. Here we demonstrate that the delayed kinetics of bacterial processing by MDDCs correlates with MDDC activation and stimulation of lymphocytes. Thus, inhibition or delay of intracellular processing may be a novel strategy by which certain commensals may avoid the induction of proinflammatory responses.

Systemic Inflammatory Markers and Disease Severity in Chronic Obstructive Pulmonary Disease——The Effect of Acute Exercise and Pulmonary Rehabilitation.
El Gammal AI, O'Farrell R, O'Mahony L, Shanahan F, Killian K, O'Connor TM.
Open Journal of Respiratory Diseases, Vol.05 No.01(2015), Article ID:53567

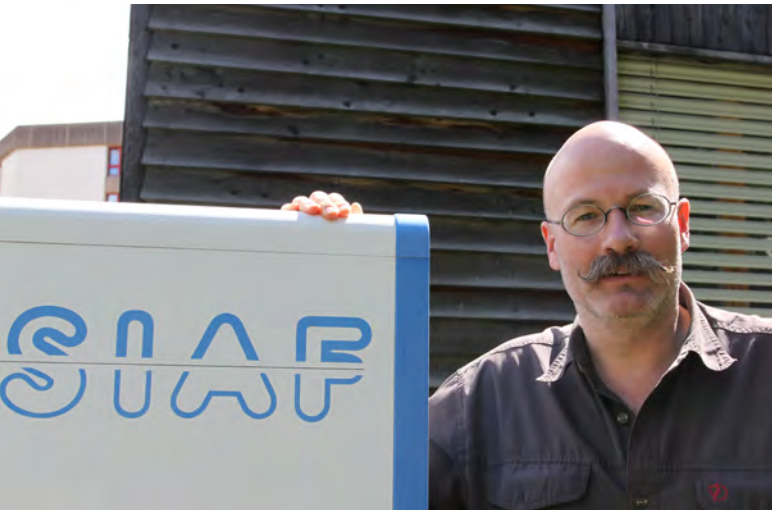
Decreased physical capacity and increased systemic inflammatory response are frequently observed in patients with chronic obstructive pulmonary disease (COPD). The relationship between the inflammatory response and disease severity and the immunological response to exercise were addressed in COPD. The first objective was to identify systemic biomarkers and their relationship with COPD severity. The second objective was to examine the effect of both acute exercise and pulmonary rehabilitation on these biomarkers. Forty subjects participated in the study. Thirty-two patients with moderate or severe COPD and 8 healthy non- smokers completed the study. Spirometry was preformed. Physical capacity was determined by a progressive symptom-limited cycle ergo meter (incremental) test. Blood samples were analyzed for C-reactive protein (CRP), pro-inflammatory cytokines (IL-6, TNF-α), pro-fibrotic cytokines (TGF-β) and oxidative burst in circulating leukocytes before and after exercise, and before and after pulmonary rehabilitation. IL-6, CRP, WCC and TGF-β were higher in COPD ($p < 0.05$) than eight healthy controls. WCC, IL-6, TNF-α, CRP and TGF-β were negatively related to forced expiratory volume in 1 s (FEV1) ($r = 0.4054$, 0.3221, 0.1528, 0.1846 and 0.1187, respectively). Acute exercise increased circulating leucocytes and oxidative stress in both groups ($p = 0.000$, 0.0049 respectively), while IL-6 was increased in COPD group (($p = 0.0115$) and circulating TNF-α in healthy control ($p = 0.0369$). Pulmonary rehabilitation didn't modify the levels of inflammatory mediators. Reduced lung function is associated with increased levels of systemic inflammatory markers and acute exercise can further increase this inflammatory response. However pulmonary rehabilitation is unlikely to exacerbate systemic inflammation in COPD.

Monitoring immune responses in a mouse model of fracture fixation with and without Staphylococcus aureus osteomyelitis.
Rochford ETJ, Sabaté-Brescó M, Zeiter S, Kluge K, Poulsson A, Ziegler M, Richards RG, O' Mahony L, Moriarty TF.
Submitted.
In a trauma setting, where devices such as fracture fixation plates are used to repair fractured bones, the combined physiological response to the trauma, the surgically placed implant and the healing of the bone adds numerous dimensions to the host defense against infection. The aim of this study was to monitor the immune responses, healing and progression of Staphylococcus aureus infection in a clinically relevant murine fracture model. Skeletally mature C57bl/6 mice received a transverse osteotomy of the femur, which were treated with commercially available titanium fracture fixation plates. In the absence of infection, healing of the fracture was complete within 14-21 days, and was characterized by elevated interferon-gamma gene expression and Interleukin (IL)-4 secretion from bone cell suspensions. In contrast, mice inoculated with S. aureus could not heal the fracture and were found to develop typical signs of implant-associated bone infection, including biofilm formation on the implant and osteolysis of surrounding bone. The immune response to infection included an early peak in IL-10 secretion followed by a later increase in inflammatory IL-17 and KC secretion, as well as IL-1β gene expression. Lymph nodes of infected animals also displayed an increase in IL-17 positive lymphocytes from day 7. In this model, we characterize the kinetics of pro-inflammatory responses to infection, secondary to bone trauma and surgery. Divergent local immune polarization is evident in the infected versus non-infected animals, while the surprisingly late anti-bacterial immune response is not effective in clearing the S. aureus infection.

Davos, June 2015

Vaccine Development

Dr. Claudio Rhyner



The activities of the SIAF Division Vaccine Development during the timeframe of reporting were focused on several projects and collaborations. The Swiss National Science Foundation Project "Targeted elimination of IgE memory B cells and serum IgE through active vaccination" 310030_138251/1 and a Commission of Technology and Innovation (CTI) granted project "PLATELETS". The first project is performing research in the development and application of our MAT Vaccine technology to address two of the key players in allergic reactions, IgE positive B cells and serum IgE. The latter one is a CTI granted project requesting for the collaboration of industry and academia, where Davos Diagnostics figured as the industry part and the Vaccine Development Group as the academic partner. We also integrated some novel technologies (e.g. quartz crystal microbalance and ultra performance liquid chromatography) available at the institute into our workflow.

Allergic diseases have reached a pandemic dimension where up to 25-30% of the population in industrialized countries is suffering from allergic rhinoconjunctivitis, allergic asthma or atopic dermatitis/eczema. Allergen-specific immunotherapy (AIT) is currently the only treatment able to cure these diseases. The success of AIT is, however, limited to relatively simple sensitization patterns like those occurring in insect sting and pollen allergy. For the majority of multisensitized patients, symptomatic treatments based on corticosteroids or other short-term-acting drugs remains as therapeutic treatment. Because the common hallmark of all allergic diseases is related to the production of allergen-specific IgE, prophylactic approaches aimed at eliminating IgE responses before they can establish, could be an optimal therapy for severe forms of IgE-mediated diseases. Both, poly-sensitization and hyper IgE syndrome can be considered as "orphan" diseases not causally treatable with the current therapeutic options.

We proposed to investigate the possibility to develop a broad applicable vaccination therapy based on the targeted elimination of B cells responsible for the establishment of IgE memory immune responses and target IgE directly by a vaccination against the receptor binding site. Based on our previous results, we could show that passive immunization with antibodies specific for the extracellular proximal domain of membrane bound IgE (EMPD) on the surface of B cells can suppress the establishment of an allergen-specific IgE response in naïve mice. Our novel vaccination system (modular antigen translocation, MAT) has been successfully proven in clinical studies to develop protective antibody responses in patients suffering from cat allergy. As a logical extension of our previous work, we proposed to develop an active prophylactic vaccination concept aimed at suppressing the establishment of IgE memory B cells and to target soluble IgE.

We started from the interaction interface of FcεRI bound IgE, which is is known from the solved crystal structure in the human system, to model and identify the situation in mice. The first decision was to clone the full Cε23 sequences of the humans and mice domains into our modular antigen translocation vectors (MAT). However, it turned out, that the yield of soluble Cε23 protein was low (<2mg/l). We therefore decided to clone only Cε3 alone, which is highly soluble and hence allows more controllable LPS content. The vaccine for the EMPD sequence was cloned into MAT vectors as hexamer of the murine and human EMPD sequences, respectively, to achieve better immunization. In the initial phase of this project, we also engineered six-time repeated murine and human EMPD synthetic genes, which were cloned into a vector and expressed as N-terminally [His]6-tagged fusion protein in E. coli. In collaboration with the University of Salzburg, we have generated specific hybridoma cell lines by immunizing mice with both EMPD-peptides. Four single hybridomas were identified as α-EMPD secreting clones of the IgG1 isotype. One murine- (mAbA9) and three human-EMPD specific hybridomas (mAbC6, mAbC33, mAbC20) were selected for production, purification, and characterization of the corresponding monoclonal antibodies. Quartz crystal microbalance (QCM) biosensing on Attana Cell200TM was used to determine the affinity (KD) constant of the mAb's. All antibodies in a concentration of 66 nM were compared against the human and the murine EMPD recombinant proteins. Association (Kon) and dissociation (Koff) rate constants were then generated by the software from the fitted curves. The results confirmed that mAbC20 and mAbC33 were the antibodies, which associate the best also with the mouse recombinant protein, suggesting a cross-reactivity, although they rapidly dissociate.

The affinities of the specific interactions between mAb's and EMPD were also tested in cell based assays. The affinity constants against both the recombinant proteins and the transfected cells were then compared. The fact that the a-EMPD mAb's bind better to the recombinant proteins might be due to sterical reasons. However, the range around 10-9 is an expected value for high-affinity antibodies. The mAb specific for the human EMPD domain with higher specificity and affinity (mAbC20, KD ~ 10 10), was then labeled and used to target IgE+ memory B cells. B cells were purified from PBMCs of allergic patients and assessed by FACS analysis. Usually the frequency of IgE+ B cells is very low, and as expected we could detect a very small EMPD+ CD19+ population. mAbC20, compared to some commercially available antibodies, detect only a tiny percentage (about 0.3 %) of the total B cells. These preliminary results have been confirmed by repeating the experiment, and the assay has been optimized by using the second best monoclonal antibody (mAbC33) which was shown to bind better to cells. The original idea was to immortalize these B cells with a very innovative method developed by collaborators of the University of Amsterdam (Spits, H) and transferred to our institute.

We aimed to immortalize the IgE+ B cell pool, propagate it and use the propagated B cell pool to sort for allergen specific cells with labeled allergen. In close collaboration with other members of the institute (M. Akdis, W. van de Veen) we were able to identify several IgG4+ clones from beekeepers and IgG2a positive clones from mice derived from vaccination experiments with OVA (R. Ferstl), but neither in the human nor in the murine system, we were able to identify an IgE+ B cell population in a way which was suitable to be characterized in terms of specificity. However, several clones were rescued via PCR, cloned in antibody expression vectors (pFUSEss) and ready for affinity determinations by QCM. Starting from that experience, we re-directed the work power originally dedicated for the characterization of the IgE clones to an important field in the topic.
Monitoring and understanding interactions occurring around and within biological systems is nowadays becoming of essential interest to extend our knowledge in understanding cellular functions, regulation, metabolism, signaling pathways, and immune responses. The QCM instrument Attana Cell200TM can be used for studying interactions between biomolecules, including peptides, proteins, lipids, or nucleic acids, as well as interactions on cells. From the work on characterization of B cells, we realized, that direct affinity characterization of the B cell receptor could be of major interest and we developed a novel method to capture non adherent cells on a biosensor surface and to examine the interactions between analytes (e.g mAb's) with specific ligands (e.g receptors) on the cell surface. This study (in submission) reports for the first time the suitability of the QCM devices for the determination of antibody affinity on cells. A method suitable for both, adherent and non-adherent cells was developed, consisting of mounting the quartz sensor in a cytospin device, and subsequent centrifugation and fixation of the cells of interest. This opens the possibility for cell-based affinity measurements on immunologically relevant cells such as B-cells or T-cells. Moreover, no culture step on the biosensor chip is needed, resulting in the opportunity for measurements on primary cells that cannot be cultured in vitro. By using HeLa cells transfected with the C-type lectin CLEC7A/Dectin-1 as a model system, we showed for the first time the possibility to measure the affinity of antibodies for epitopes located in the plasma membrane of whole adherent or suspended cells fixed on polystyrene surfaces and we provided general protocol guidelines for the optimization of the assay. Additionally, we showed the importance to complement standard with on-cell affinity measurement by comparing the results obtained with the purified extracellular domain of Dectin-1 with the ones obtained with the transfected protein for two different anti-Dectin-1 mAb's. Specifically, anti-Dectin-1 mAb's from different clones showed similar Kon values for the on-cell and the on-protein measurement, but different on-cell Koff values indicating an equally fast, but less-affine binding leading to faster detachment of the bound antibodies and a decreased overall affinity constant KD (manuscript in submission).
In parallel to the QCM studies, we produced and purified several murine MAT vaccine constructs and ran experiments in a mouse asthma model. We used the classical OVA-induced asthma-like mouse model to investigate the possibility to target IgE antibodies in vivo. Briefly, BALB/c mice were immunised with three injections of OVA-alum i.p. on days 0, 14, and 21 followed by different regimens of vaccinations (between days 25 till 38). On days 49, 50, and 51, mice were challenged by OVA inhalations. BALB/c mice were sacrificed at day 52, some organs, BALs, and blood were collected and serum was analysed for the presence of antigen-specific antibodies by ELISA. In response to intraperitoneal immunization, our results showed that a humoral immune response was induced by both MAT-mEMPD and MAT-mCε23 vaccines. Our results show an induction of protective IgG2a antibody response, and a reduction of serum IgE levels as well as B cell numbers in blood and spleen. Significant decrease in BAL cells and eosinophils were also observed after vaccination. The MAT-vaccines were also tested in a prophylactic in vivo murine model of asthma. Also in this case, the data show a decrease of the total serum IgE levels as well as B cell numbers in the blood and in the lungs. The establishment of the murine asthma model and the optimisation of the vaccination regimen took more time than originally expected. However, we were able to successfully prove a significant reduction in the number of total cells and eosinophils in BAL fluid (Figure 1 a, b), and a reduction in specific and total IgE in serum (Figure 1 c, d).

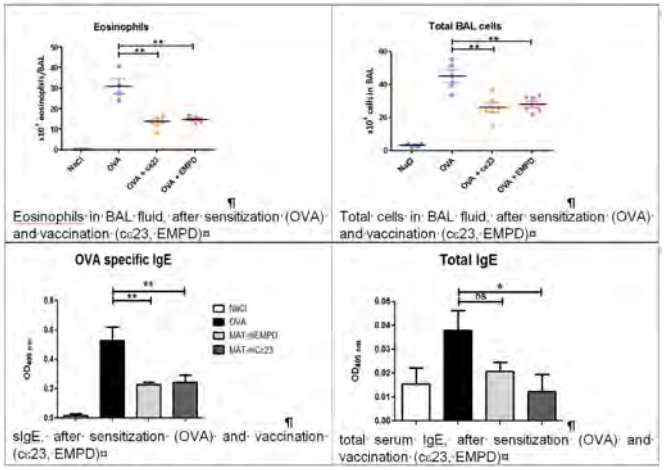


Figure 1: Decreased BAL eosinophils, Ova-specific IgE and total IgE in mouse model of asthma by MAT-m ce23-EmPD vaccine.

Platelets

Blood is a biological fluid consisting of serum and cellular components. The cellular components of blood are mainly red cells (erythrocytes), white cells (leucocytes) and platelets (thrombocytes). Blood is the source of some important therapeutics such as plasma, plasma proteins and cellular blood components, like red cells and platelets. The largest number of cellular products from blood are red cell concentrates followed by platelet bags, the ratio between the two products is about one platelet concentrate for ten red cell concentrates. All blood cells have proteins and sugar molecules on their surface. These sugar molecules and proteins can vary from individual to individual and are called allo-antigens. Well known for over 100 years are the blood groups A and B but there are also donor to donor differences and these are the minor blood group antigens such as Kell, Duffy, MNS, Lewis etc. When the blood of the donor has different allo-antigens than the blood cells of the recipient, these allo-antigens can lead to an immunization of the recipient and the formation of allo-antibodies. Platelets are also carriers of allo-antigens, namely the major blood antigens (AB0) but also so-

me minor allo-antigens. As platelet transfusions or pregnancies can lead to unwanted immunizations in a manner similar to red cells due to allo-antigen incompatibilities, the detection of platelet antibodies and typing of platelet allo-antigens has become a specialized field in immune hematology. Blood banks have established platelet diagnostic laboratories in addition to the classical red cell immune hematology labs, the HLA laboratories and the infectious disease testing labs. The evanescence biosensor system to be used for diagnostic applications allows simplifying the labor intensive multistep ELISA tests to simple one or two step assays giving a result in a short time.

MAIPA is considered the gold standard methodology for platelet antibody detection and conversely can be used to type a patient by the use of polyclonal sera. A MAIPA is a two step method with a cellular part and a detection part, traditionally done by ELISA. The cellular part involves first incubating platelets with the human serum to be analyzed for anti platelet IgG and allowing the IgG bind to the platelet glycoproteins. The reaction is split into four tubes and to each of the four tubes an anti platelet glycoprotein specific antibody is added as follows; tube 1 anti gpIIbIIa, tube 2 anti gpIaIIa, tube 3 anti gpIbIX and tube four anti beta-2-microglobulin / HLA. After incubation and binding of the monoclonal antibodies excess reagents are washed away from the platelets by repeated centrifugation and resuspension steps in washing buffer. The remaining washed platelet pellet is solubilized with detergent and trimolecular complexes composed of mouse gp specific IgG – platelet gp – human IgG are solubilized. These trimolecular complexes are then analyzed in the second MAIPA step using a two step ELISA procedure. A MAIPA allows the detection of antibodies in plasma (indirect MAIPA) and the detection of antibodies already bound to platelets (direct MAIPA). The evanescence biosensor technology can be used here to improve the detection step. The classical two step 3h ELISA used for the detection step in the MAIPA can be replaced by a 15 minute no wash evanescence detection step.

For antibody screening assays, preliminary evidence shows the feasibility of developing a one-step antibody test for platelet antibodies by coating intact platelets on the biosensor surface. This preliminary work has to be validated by a larger number of patients with allo-antibodies.

Davos, June 2015

Peer reviewed articles

Akdis CA, Akdis M. Mechanisms of immune tolerance to allergens: role of IL-10 and Tregs. J Clin Invest. 2014 Nov 3;124(11):4678-80. IPF: 13.765

Akdis CA, Akdis M. Advances in allergen immunotherapy: aiming for complete tolerance to allergens. Sci Transl Med. 2015 Mar 25;7(280) IPF: 15.843

Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. World Allergy Organ J. 2015 May 14;8(1):17.

Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol. 2014 Mar;133(3):621-31. IPF: 11.248

Akdis M. New treatments for allergen immunothereapy. World Allergy Organ J. 2014 Sep 24;7(1):23.

Bonini M, Gramiccioni C, Fioretti D, Ruckert B, Rinaldi M, Akdis C, Todaro A, Palange P, Carlsen KH, Pelliccia A, Rasi G, Bonini S; AIDA and the Italian Unit of the GA2LEN Olympic Study. Asthma, allergy and the Olympics: a 12-year survey in elite athletes. Curr Opin Allergy Clin Immunol. 2015 Apr;15(2):184-92. IPF: 3.659

Bousquet J, Anto JM, Berkouk K, Gergen P, Antunes JP, Augé P, Camuzat T, Bringer J, Mercier J, Best N, Bourret R, Akdis M, Arshad SH, Bedbrook A, Berr C, Bush A, Cavalli G, Charles MA, Clavel-Chapelon F, Gillman M, Gold DR, Goldberg M, Holloway JW, Iozzo P, Jacquemin S, Jeandel C, Kauffmann F, Keil T, Koppelman GH, Krauss-Etschmann S, Kuh D, Lehmann S, Carlsen KC, Maier D, Méchali M, Melén E, Moatti JP, Momas I, Nérin P, Postma DS, Ritchie K, Robine JM, Samolinski B, Siroux V, Slagboom PE, Smit HA, Sunyer J, Valenta R, Van de Perre P, Verdier JM, Vrijheid M, Wickman M, Yiallouros P, Zins M. Developmental determinants in non-communicable chronic diseases and ageing. Thorax. 2015 Jun;70(6):595-7. doi: 10.1136/thoraxjnl-2014-206304. Epub 2015 Jan 23. IPF: 8.562

Bousquet J, Anto JM, Wickman M, Keil T, Valenta R, Haahtela T, Lodrup Carlsen K, van Hage M, Akdis C, Bachert C, Akdis M, Auffray C, Annesi-Maesano I, Bindslev-Jensen C, Cambon-Thomsen A, Carlsen KH, Chatzi L, Forastiere F, Garcia-Aymerich J, Gehrig U, Guerra S, Heinrich J, KoppelmanGH, Kowalski ML, Lambrecht B, Lupinek C, Maier D, Melén E, Momas I, Palkonen S, Pinart M, Postma D, Siroux V, Smit HA, Sunyer J, Wright J, Zuberbier T, Arshad SH, Nadif R, Thijs C, Anderson N, Arsanoj A, Balardini N, Ballereau S, Bedbrook A, Benet M, Bergstrom A, Brunekreef B, Burte E, Calderon M, De Carlo G, Demoly P, Eller E, Fantini MP, Hammad H, Hohman C, Just J, Kerkhof M, Kogevinas M, Kull I, Lau S, Lemonnier N, Mommers M, Nawijn M, Neubauer A, Oddie S, Pellet J, Pin I, Porta D, Saes Y, Skrindo I, Tischer CG, Torrent M, von Hertzen L. Are allergic multimorbidities and IgE polysensitization associated with the persistence or re-occurrence of foetal Type 2 signalling? The MeDALL hypothesis. Allergy. 2015 Apr 24. doi: 10.1111/all.12637. [Epub ahead of print] IPF: 5.995

Boyman O, Kaegi C, Akdis M, Bavbek S, Bossios A, Chatzipetrou A, Eiwegger T, Firinu D, Harr T, Knol E, Matucci A, Palomares O, Schmidt-Weber C, Simon HU, Steiner UC, Vultaggio A, Akdis CA, Spertini F. EAACI IG Biologicals task force paper on the use of biologic agents in allergic disorders. Allergy. 2015 Jul;70(7):727-54. IPF: 5.995

Cavkaytar O., Akdis CA, Akdis M. Modulation of immune responses by immunotherapy in allergic diseases. Curr Opin Pharmacol. 2014 Jul 22;17C:30-37. IPF: 4.227

Crameri R, Garbani M, Rhyner C, Huitema C. Fungi: the neglected allergenic sources. Allergy 2014;69(2):176-185. IPF: 5.995

Crameri R. Structural aspect of fungal allergens. Sem Immunol Immunopathol 2014; Nov 21. [Epub ahead of print]. IPF: 6.428

Demoly P, Tanno LK, Akdis CA, Lau S, Calderon MA, Santos AF, Sanchez-Borges M, Rosenwasser LJ, Pawankar R, Papadopoulos NG. Global classification and coding of hypersensitivity diseases - An EAACI - WAO survey, strategic paper and review. Allergy. 2014 May;69(5):559-70. IPF: 5.995

de Silva D, Geromi M, Halken S, Host A, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Cardona V, Dubois AE, Poulsen LK, Van Ree R, Vlieg-Boerstra B, Agache I, Grimshaw K, O'Mahony L, Venter C, Arshad SH, Sheikh A. Primary prevention of food allergy in children and adults: systematic review. Allergy 2014 May;69(5):581-9. IPF: 5.995

Dostal A, Gagnon M, Chassard C, Zimmermann MB, O'Mahony L, Lacroix C. Salmonella adhesion, invasion and cellular immune responses are differentially affected by iron concentrations in a combined in vitro gut fermentation-cell model. PLoS One 2014 Mar 27;9(3):e93549. IPF 4.5

Ferstl R, Frei R, Schiavi E, Konieczna P, Barcik W, Ziegler M, Lauener RP, Chassard C, Lacroix C, Akdis CA, O'Mahony L. Histamine receptor 2 is a key influence in immune responses to intestinal histamine-secreting microbes. J Allergy Clin Immunol. 2014 Sep;134(3):744-746.e3. IPF: 11.248

Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, Halken S, Katz Y, Ebisawa M, Eichenfield L, Sampson H, Lack G, Du Toit G, Roberts G, Bahnson H, Feeney M, Hourihane J, Spergel J, Young M, As'aad A, Allen K, Prescott S, Kapur S, Saito H, Agache I, Akdis CA, Arshad H, Beyer K, Dubois A, Eigenmann P, Fernandez-Rivas M, Grimshaw K, Hoffman-Sommergruber K, Host A, Lau S, O'Mahony L, Mills C, Papadopoulos N, Venter C, Agmon-Levin N, Kessel A, Antaya R, Drolet B, Rosenwasser L. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. J Allergy Clin Immunol. 2015 [Epub ahead of print], IPF: 11.248

Articles in peer reviewed journals 2014

Frei R, Roduit C, Bieli C, Loeliger S, Waser M, Scheynius A, van Hage M, Pershagen G, Doekes G, Riedler J, von Mutius E, Sennhauser F, Akdis CA, Braun-Fahrländer C, Lauener RP; as part of the PARSIFAL study team. Expression of genes related to anti-inflammatory pathways are modified among farmers' children. PLoS One. 2014 Mar 6;9(3):e91097. IPF 4.5

Frei R, Akdis M, O'Mahony L. Prebiotics, probiotics, synbiotics and the immune system; experimental data and clinical evidence. Curr Opin Gastroenterol. 2015 Mar;31(2):153-8. IPF 4.1

Hradetzky S, Roesner LM, Heratizadeh A, Crameri R, Garbani M, Scheynius A, Werfel T. Differential cytokine induction by the human skin-associated autoallergen thioredoxin in sensitized patients with atopic dermatitis and healthy control subjects. J Allergy Clin Immunol. 2015 May;135(5):1378-1380.e5. doi: 10.1016/j.jaci.2014.10.038. Epub 2014 Dec 6. IPF: 11.248

Hunt T, Hunt T, Stanciu LA, Khaitov M, Bartlett NW, Edwards MR, Kon OM, Mallia P, Papadopoulos NG, Akdis CA, Westwick J, Edwards MJ, Cousins DJ, Walton RP, Johnston SL. IL-33-Dependent Type 2 Inflammation during Rhinovirus-induced Asthma Exacerbations In Vivo. Am J Respir Crit Care Med. 2014 Dec 15;190(12):1373-82. IPF: 11.986

Jackson DJ, Makrinioti H, Rana BM, Shamji BW, Trujillo-Torralbo MB, Footitt J, Del-Rosario J, Telcian AG, Nikonova A, Zhu J, Aniscenko J, Gogsadze L, Bakhsoliani E, Traub S, Dhariwal J, Porter J, Hunt D, Jutel M, Akdis CA. Novel immunotherapy vaccine development. Curr Opin Allergy Clin Immunol. 2014 Dec;14(6):557-63. IPF: 3.659

Jakiela B, Gielicz A, Plutecka H, Hubalewska-Mazgaj M, Mastalerz L, Bochenek G, Soja J, Januszek R, Aab A, Musial J, Akdis M, Akdis CA, Sanak M. Th2-type cytokine induced mucous metaplasia decreases susceptibility of human bronchial epithelium to rhinovirus infection. Am J Respir Cell Mol Biol. 2014;51:229-241. IPF: 4.109

Jartti T, Palomares O, Waris M, Tastan O, Nieminen R, Puhakka T, Rückert B, Aab A, Vuorinen T, Allander T, Vahlberg T, Ruuskanen O, Akdis M, Akdis CA. Distinct regulation of tonsillar immune response in virus infection. Allergy. 2014 May;69(5):658-67. IPF: 5.995

Kubo T, Wawrzyniak P, Morita H, Sugita K, Wanke K, Kast JI, Altunbulakli C, Rückert B, Jakiela B, Sanak M, Akdis M, Akdis CA. CpG-DNA enhances the tight junction integrity of the bronchial epithelial cell barrier. J Allergy Clin Immunol. 2015 [Epub ahead of print] IPF: 11.248

Martín-Fontecha M, Eiwegger T, Jartti T, Rueda-Zubiaurre A, Tiringer K, Stepanow J, Puhakka T, Rückert B, Ortega-Gutiérrez S, López-Rodríguez ML, Akdis M, Akdis CA, Palomares O. The expression of cannabinoid receptor 1 is significantly increased in atopic patients. J Allergy Clin Immunol. 2014 Mar;133(3):926-9.e2. IPF: 11.248

Meyer N, Nuss SJ, Rothe T, Siebenhüner A, Akdis CA, Menz G. Differential serum protein markers and the clinical severity of asthma. J Asthma Allergy. 2014 Apr 25;7:67-75.

Meyer N, Dallinga JW, Nuss S, Moonen E, van Berkel J, Akdis C, van Schooten F, Menz G. Defining adult asthma endotypes by clinical features and patterns of volatile organic compounds in exhaled air. Respir Res. 2014 Nov 28;15(1):136. IPF: 3.642

Morita H, Arae K, Unno K, Miyauchi K, Toyama S, Nambu A, Oboki K, Ohno T, Motomura K, Matsuda A, Yamaguchi S, Narushima S, Kajiwara N, Iikura M, Suto H, McKenzie AN, Takahashi T, Karasuyama H, Okumura K, Azuma M, Moro K, Akdis CA, Gali SJ, Koyasu S, Kubo M, Sudo K, Saito H, Matsumoto K, Nakae S. An Interleukin-33-Mast cell-interleukin-2 Axis Suppress Papain-Induced Allergic Inflammation by Promoting Regulatory T Cell Numbers. Immunity 2015. In press. IPF: 19.748

Muraro A, Agache I, Clark A, Sheikh A, Roberts G, Akdis CA, Borrego L, Higgs J, Hourihane J, Jorgensen P, Mazon A, Parmigiani D, Said M, Schnadt S, van Os-Medendorp H, Vlieg-Boestra B, Wickman M. EAACI Food Allergy and Anaphylaxis Guidelines. Managing patients with food allergy in the community. Allergy. 2014 Aug;69(8):1046-57. IPF: 5.995

Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, Cardona V, Dubois A, duToit G, Eigenmann P, Fernandez Rivas M, Halken S, Hickstein L, Høst A, Knol E, Lack G, Marchisotto MJ, Niggemann B, Nwaru BI, Papadopoulos NG, Poulsen LK, Santos AF, Skypala I, Schoepfer A, Van Ree R, Venter C, Worm M, Vlieg-Boerstra B, Panesar S, de Silva D, Soares-Weiser K, Sheikh A, Ballmer-Weber BK, Nilsson C, de Jong NW, Akdis CA; EAACI Food Allergy and Anaphylaxis Guidelines Group. EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. Allergy. 2014 Aug;69(8):1008-25. IPF: 5.995

Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, Eigenmann PA, Grimshaw KE, Hoest A, Lack G, O'Mahony L, Papadopoulos NG, Panesar S, Prescott S, Roberts G, de Silva D, Venter C, Verhasselt V, Akdis AC, Sheikh A. EAACI Food Allergy and Anaphylaxis Guidelines. Primary prevention of food allergy. Allergy. 2014 May;69(5):590-601. IPF: 5.995

Muraro A, Hoffmann-Sommergruber K, Holzhauser T, Poulsen L, Gowland M, Akdis CA, Mills E, Papadopoulos N, Roberts G, Schnadt S, van Ree R, Sheikh A, Vieths S. EAACI Food Allergy and Anaphylaxis Guidelines. Protecting consumers with food allergies: understanding food consumption, meeting regulations and identifying unmet needs. Allergy. 2014 Nov;69(11):1464-72. IPF: 5.995

Palomares O, Crameri R, Rhyner C. The contribution of biotechnology toward progress in diagnosis, management, and treatment of allergic diseases. Allergy. 2014;69(12): 1588-601. IPF: 5.995

Palomares O, Martín-Fontecha M, Lauener R, Traidl-Hoffmann C, Cavkaytar O, Akdis M, Akdis CA. Regulatory T cells and immune

regulation of allergic diseases: roles of IL-10 and TGF-β. Genes Immun. 2014 Dec;15(8):511-20. doi: 10.1038/gene.2014.45. Epub 2014 Jul 24. IPF: 3.789

Rebane A, Akdis CA. MicroRNAs in allergy and asthma. Curr Allergy Asthma Rep. 2014 Apr;14(4):424. IPF: 2.450

Rebane A, Runnel T, Aab A, Maslovskaja J, Rückert B, Zimmermann M, Plaas M, Kärner J, Treis A, Pihlap M, Haljasorg U, Hermann H, Nagy N, Kemeny L, Erm T, Kingo K, Li M, Boldin MP, Akdis CA. MicroRNA-146a alleviates chronic skin inflammation in atopic dermatitis through suppression of innate immune responses in keratinocytes. J Allergy Clin Immunol. 2014 Oct;134(4):836-847. e11. IPF: 11.248

Ring J, Akdis C, Lauener R, Schäppi G, Traidl-Hoffmann C, Akdis M, Ammann W, Behrendt H, Bieber T, Biedermann T, Bienenstock J, Blaser K, Braun-Fahrländer C, Brockow K, Buters J, Crameri R, Darsow U, Denburg JA, Eyerich K, Frei R, Galli SJ, Gutermuth J, Holt P, Koren H, Leung D, Müller U, Muraro A, Ollert M, O'Mahony L, Pawankar R, Platts-Mills T, Rhyner C, Rosenwasser LJ, Schmid-Grendelmeier P, Schmidt-Weber CB, Schmutz W, Simon D, Simon HU, Sofiev M, van Hage M, van Ree R. Global Allergy Forum and Second Davos Declaration 2013. Allergy: Barriers to cure - challenges and actions to be taken. Allergy 2014;69 8):978-982. IPF: 5.995

Roduit C, Frei R, Depner M, Schaub B, Loss G, Genuneit J, Pfefferle P, Hyvärinen A, Karvonen AM, Riedler J, Dalphin JC, Pekkanen J, von Mutius E, Braun-Fahrländer C, Lauener R; PASTURE study group. Increased food diversity in the first year of life is inversely associated with allergic diseases. J Allergy Clin Immunol. 2014 Apr;133(4):1056-64. IPF: 11.248

Sahiner UM, Jusufagic AS, Curtin JA, Birben E, Belgrave D, Sackesen C, Simpson A, Yavuz TS, Akdis CA, Custovic A, Kalayci O. Polymorphisms of endotoxin pathway and endotoxin exposure: in-vitro IgE synthesis and replication in a birth cohort. Allergy. 2014 Dec;69(12):1648-58. doi: 10.1111/all.12504. Epub 2014 Sep 20. IPF: 5.995

Schieck M, Sharma V, Michel S, Toncheva AA, Worth L, Potaczek DP, Genuneit J, Kretschmer A, Depner M, Dalphin JC, Riedler J, Frei R, Pekkanen J, Tost J, Kabesch M. A polymorphism in the TH 2 locus control region is associated with changes in DNA methylation and gene expression. Allergy. 2014 Sep;69(9):1171-80. IPF: 5.995

Smits HH, Akdis CA. In utero priming by worms protects against respiratory allergies. J Allergy Clin Immunol. 2014 Dec;134(6):1280-1. (Editorial) IPF: 11.248

Smolinska S, Jutel M, Crameri R, O'Mahony L. Histamine and gut mucosal immune regulation. Allergy 2014;69(3): 273-281. IPF: 5.995

Soyka MB, van de Veen W, Holzmann D, Akdis M, Akdis CA. Scientific foundations of allergen-specific immunotherapy for allergic disease. Chest. 2014 Nov 1;146(5):1347-57. IPF: 7.132

Soyka MB, Holzmann D, Basinski TM, Wawrzyniak M, Bannert C, Bürgler S, Akkoc, T, Treis A, Rückert B, Akdis M, Akdis CA, Eiwegger T. The Induction of IL-33 in the Sinus Epithelium and Its Influence on T-Helper Cell Responses. PLoS One. 2015 May 1;10(5):e0123163. IPF 4.5

Stanic B, van de Veen W, Wirz OF, Rückert B, Morita H, Söllner S, Akdis CA, Akdis M. IL-10-overexpressing B cells regulate innate and adaptive immune responses. J Allergy Clin Immunol. 2015 Mar;135(3):771-80. IPF: 11.248

Tanno LK, Calderon MA, Goldberg BJ, Akdis CA, Papadopoulos NG, Demoly P. Categorization of allergic disorders in the new World Health Organization International Classification of Diseases. Clin Transl Allergy. 2014 Nov 28;4:42. IPF: 2.53

Tiringer K, Treis A, Kanolzer S, Witt C, Ghanim B, Gruber S, Schmidthaler K, Renner S, Dehlink E, Nachbaur E, Frischer T, Klepetko W, Akdis CA, Szépfalusi Z, Eiwegger T. Differential expression of IL-33 and HMGB1 in the lungs of stable cystic fibrosis patients. Eur Respir J. 2014 Sep;44(3):802-5. IPF: 7.125

Wegrzyn AS, Jakiela B, Rückert B, Jutel M, Akdis M, Sanak M, Akdis CA. T-cell regulation during viral and nonviral asthma exacerbations. J Allergy Clin Immunol. 2015 Jan 17. pii: S0091-6749(14)03659-8. doi:10 .1016/j.jaci.2014.12.1866. [Epub ahead of print] IPF: 11.248

Yorgancioglu A, Cruz AA, Bousquet J, Khaltaev N, Mendis S, Chuchalin A, Bateman ED, Camargos P, Chavannes NH, Bai C, Deleanu D, Kolek V, Kuna P, Laurendi G, Masjedi MR, Mele S, Mihaltan F, Pinto JR, Samolinski B, Scalera G, Sooronbaev T, Tageldin MA, Tuyetlan le T, Yusuf O, Akdis C, Baigenzhin A, Cagnani CB, Fletcher M, Gemicioglu B, Muhammed Y, Sagra H, To T, Wagner AH. The Global Alliance against Respiratory Diseases (GARD) Country Report. Prim Care Respir J. 2014 Mar;23(1):98-101. IPF: 2.909

Zaleska A, Eiwegger T, Soyer O, van de Veen W, Rhyner C, Soyka MB, Bekpen C, Demiröz D, Treis A, Söllner S, Palomares O, Kwok WW, Rose H, Senti G, Kündig TM, Ozoren N, Jutel M, Akdis CA, Crameri R, Akdis M. Immune regulation by intralymphatic immunotherapy with modular allergen translocation MAT vaccine. Allergy. 2014 Sep;69(9):1162-70. IPF: 5.995

BOOK CHAPTERS

2014

Book chapters

Akdis CA. The underlying mechanisms in allergy. In: Global Atlas of Allergy; Akdis CA, Agache I (Editors), European Academy of Allergy and Asthma Research, 2014.

Akdis CA., Agache I. Endotypes of allergic diseases. In: Global Atlas of Allergy; Akdis CA, Agache I (Editors), European Academy of Allergy and Asthma Research, 2014.

Akdis CA. Vision and roadmap to fight with allergies. In: Global Atlas of Allergy; Akdis CA, Agache I (Editors), European Academy of Allergy and Asthma Research, 2014.

Crameri R. I In vitro allergy diagnosis – allergen-specific IgE. In: Global Atlas of Allergy. European Academy of Allergy and Clinical Immunology (Agache I, Akdis C, eds), pp 166-167, 2014.

Frei R, O'Mahony L. Animal models of allergic disease. In: Global Atlas of Allergy; Akdis CA, Agache I (Editors), European Academy of Allergy and Asthma Research, 2014.

Lötval J., Ledford D., Akdis CA., iCAALL Chairs. iCAALL: International Collaboration in Asthma, Allergy and Immunology. In: Global Atlas of Allergy; Akdis CA, Agache I (Editors), European Academy of Allergy and Asthma Research, 2014.

van de Veen W. IgE Receptor. In: Encyclopedia of Medical Immunology - Allergic Diseases. Editors: Ian R. Mackay, Noel R. Rose, Dennis K. Ledford, Richard F. Lockey. Springer 2014.

van de Veen W. Specific IgE. In: Encyclopedia of Medical Immunology - Allergic Diseases. Editors: Ian R. Mackay, Noel R. Rose, Dennis K. Ledford, Richard F. Lockey. Springer 2014.

van de Veen W. Induction of IgE Synthesis: Cellular Interactions and Molecular Events. In: Encyclopedia of Medical Immunology - Allergic Diseases. Editors: Ian R. Mackay, Noel R. Rose, Dennis K. Ledford, Richard F. Lockey. Springer 2014.

van de Veen W. IgE Isotype Switching. In: Encyclopedia of Medical Immunology - Allergic Diseases. Editors: Ian R. Mackay, Noel R. Rose, Dennis K. Ledford, Richard F. Lockey. Springer 2014.

van de Veen W., Akdis M. Mechanisms of immune regulation in allergy. In: Global Atlas of Allergy; Akdis CA, Agache I (Editors), European Academy of Allergy and Asthma Research, 2014.

Abstracts

Aab A, van de Veen W, Söllner S, Wirz O, Stanic B, Altunbulakli C, Johnston S, Rebane A, Akdis CA, Akdis M. Immune Response to Rhinoviruses and Their Link to Asthma Exacerbations. Annual meeting of AAAAI, San Diego, March, 2014.

Akdis M. New Treatments for Allergen Immunotherapy. World Allergy organisation, Rio de Janeiro, Brasil, 2014.

Akdis M. Human novel effector and regulatory subsets of memory B cells. CIA, Petersberg, Germany, 2014.

Akdis M. Allergen specific Immunotherapy –mechanistic insights and practical aspects. Japanise society of Allergology, Kyoto, Japan, 2014.

Crameri R. Component-resolved diagnosis for inhalant allergies. Annual Meeting AAAAI, San Diego, USA, 28 February-14 March 2014.

Crameri R. New adjuvants. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Garbani M, Terhorst D, Xia W. Prati M, Rhyner C, Malissen B, Engquist H, Crameri R. Prolonged immune stimulation mediated by allergen-loaded calcium phosphate spheres. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Groeger D, O'Mahony L, Murphy EF, Wycherley C, Malik M, Moriarty B, Kiely B, Shanahan F, Bourke J, Quigley E. Inflammatory and Metabolic markers in Psoriasis. Probiota, Amsterdam, Netherlands, 4-5 February 2014.

Groeger D, O'Mahony L, Murphy EF, Wycherley C, Malik M, Moriarty B, Kiely B, Shanahan F, Bourke J, Quigley E. Inflammatory & Metabolic Markers in Psoriasis: Baseline Characteristics & Response to a Probiotic Bifidobacterium infantis 35624. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Huitema C, Schawaller M, Akdis C.A, Rhyner C, Crameri R. Rapid quantification of antigen-specific serum immunoglobulins. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Huitema C, Akdis CA, Crameri R, Rhyner C, Schawaller M. Quantitative measurements of antigen-specific immunoglobulins using an evanescent biosensor. Graubünden forscht: Young Scientists in Contest. Davos, Switzerland, 11-12 September 2014.

Hradetzky S, Rösnert LM, A Heratizadeh A, Mittermann I, R Valenta R, Crameri R, Scheynius A, Werfel T. Cytokine effects induced by the human autoallergens thioredoxin and α-NAC. International Symposium on Atopic Dermatitis/8th Georg Rajka Symposium 21-23 May 2014.

Hradetzky S, Roesner LM, Heratizadeh A, Crameri R, Scheynius A, Werfel T. The human autoallergen thioredoxin induces more IL-13 and less IL-10 in immune cells from atopic dermatitis patients sensitized to Malassezia. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Kenk M, Romer K, Schawaller M, Akdis CA, Huitema C, Rhyner C, Crameri R. Detection of tryptophan and tryptophan metabolites by evanescence technology. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Kenk M, Romer K, Schawaller M, Akdis CA, Huitema C, Rhyner C, Crameri R. HPA-1a Allo-Antigen Typing in Whole Blood- Discrimination of a Single Amino Acid Change in a Minute One-Step Assay. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Mittermann I, Wikberg G, Johansson C, Lupinek C, Crameri R, Valenta R, Scheynius A. Molecular IgE sensitization profiles differ between patients with severe and moderate atopic dermatitis. Inflammatory skin disease summit: The translational revolution. Vienna, 19-21 November 2014.

Olzhausen J, Schawaller M, Akdis CA, Jutel M, Crameri R, Rhyner C. Comparative measurements of allergen specific antibodies using the evanescent field method. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Olzhausen J, Schawaller M, Akdis CA, Crameri R, Wiki M, Rhyner C. Rapid aptamer-based assay for the detection of pathogenis bacteria. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Olzhausen J, Schawaller M, Wiki M, Akdis CA, Jutel M, Crameri R, Rhyner C. Evanescent field-based fast measurements of antigen and allergen specific antibodies during SIT. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Olzhausen J, Akdis CA, Crameri R, Jutel M, Rhyner C, Schawaller M. Measurements of allergen specific antibodies during allergen specific immunotherapy using the evanescent field method: A. Comparison. Graubünden forscht: Young Sientists in Contest. Davos, Switzerland, 11-12 September 2014.

Prati M, Crameri R, Ferstl R, Frei R, Garbani M, Rhyner, C. Preventive/therapeutic vaccines in a murine model of allergy. Graubünden forscht: Young Sientists in Contest. Davos, Switzerland, 11-12 September 2014.

Prati M, Garbani M, Ferstl R, Frei R, Crameri R, Rhyner C. Targeted elimination of IgE memory B cells and serum IgE through active vaccination in a murine model of allergy. Keystone Symposia - The Modes of Action of Vaccine Adjuvants, Seattle, Washington, 8–13 October 2014.

Romer K, Kenk M, Schawaller M, Akdis C.A, Huitema C, Crameri R, Rhyner C. Blood, Sweat and Tears – different biological fluids for use in evanescence biosensor tests. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Romer K, Kenk M, Akdis C.A, Huitema C, Rhyner M, Schawaller M, Crameri R. Simple, Specific, Sensitive, and Rapid Detection of Toxoplasma. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Sabaté Brescó M, Kluge K, Ziegler M, Richards G, O'Mahony L, Moriarty F. Immune response during bone healing in a murine fracture model with osteomyelitis: role of biomechanical stability. 5th International Conference on Osteoimmunology, 15-20 June, Kos, Greece.

Sabaté Brescó M, Kluge K, Ziegler M, Richards G, Moriarty F, O'Mahony L. Immune response during bone healing in a murine fracture model with osteomyelitis: role of biomechanical stability. 7th MIM Retreat, 4-6 September 2014, Wildhaus, Switzerland.

Sabaté Brescó M, Kluge K, Ziegler M, Richards G, O'Mahony L, Moriarty F. Assessing the role of implant stability on the development of staphylococcal osteomyelitis in a murine fracture model. Graubünden forscht 2014: Young Scientists in Contest, 10th-11th September, Davos, Switzerland.

Sabaté Brescó M, Kluge K, Ziegler M, Richards G, O'Mahony L, Moriarty F. Staphylococcus epidermidis infection increases in the presence of unstable fixation: evidence in a murine fracture model. The European Bone & Joint Infection Society (EBJIS), 11th-13th September, Utrecht, The Netherlands.

Schawaller M, Kenk M, Romer K, Akdis C.A, Huitema C, Rhyner C, Crameri R. Analytic performance of evanescence technology for drugs of abuse tests. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Schiavi E, Plattner S, Grant R, Groeger D, Rodriguez-Perez N, Ziegler M, Healy S, O'Mahony L. Immunomodulatory properties associated with Bifidobacteriuminfantis 35624 exopolysaccharides. WIRM VIII 2014, Davos, Switzerland, March 2014.

Schiavi E, Plattner S, Grant R, Groeger D, Rodriguez-Perez N, Ziegler M, Healy S, O'Mahony L. Immunomodulatory properties associated with Bifidobacteriuminfantis 35624 exopolysaccharides. EAACI Congress, Copenhagen June 2014.

Stanic B, van de Veen W, Wirz O, Söllner S; Rückert B, Akdis C, Akdis M. Immunoregulatory capacity of human IL-10 overexpressing B cells. 12th EAACI Immunology Winter School. Poiana Brasov, Romania, 30 January-2 February 2014.

Treis A., Bekpen C., Rückert B., Rebane A., Remes M., Akdis CA. Characterization and Functional Analysis of SMA, a Novel Gene in Human Core Duplicons. EAACI Winter School, Poiana Brasov, Romania, 30 January-2 February 2014.

Treis A., Bekpen C., Rückert B., Rebane A., Remes M., Akdis CA. Characterization and Functional Analysis of SMA, a Novel Gene in Human Core Duplicons. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

van de Veen W, Wirz OF, de Jong MAWP, Stanic B, van Splunter M, Kwakkenbos M, Spits H, Akdis C, Akdis M. Generation and characterization of human allergen-specific memory B cell clones. EAACI Winter School, Poiana Brasov, Romania, 30 January - 2 February 2014.

van de Veen W, Wirz OF, de Jong MAWP, Stanic B, van Splunter M, Kwakkenbos M, Spits H, Akdis C, Akdis M. Characterization of human allergen-specific B cell subsets. WIRM VIII, Davos, 19 – 22 March 2014.

van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Teca S, Ruckert B, Akdis D, Akdis CA, Akdis M. Regulation of B cell Activation and Antibody Production. Annual meeting of AAAAI, San Diego, March, 2014

van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Teca S, Ruckert B, Akdis D, Akdis CA, Akdis M. New Aspects of the Involvement of B and T Cells in the Mechanisms of Immunotherapy. Annual meeting of AAAAI, San Diego, March, 2014.

van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Teca S, Ruckert B, Akdis D, Akdis CA, Akdis M. Tolerance mechanisms to allergens. MIMIC II, Antalya, Turkey, April, 2014

van de Veen W, Wirz OF, de Jong MAWP, Stanic B, Ochsner U, van Splunter M, Kwakkenbos M, Spits H, Akdis C, Akdis M. Generation and characterization of human allergen-specific B cell clones. Graubünden Forscht – Young Scientists in Contest, Davos, 10 – 11 September 2014.

van de Veen W, Wirz OF, Stanic B, de Jong MAWP, van Splunter M, Spits H, Akdis CA, Akdis M. Generation and characterization of allergen-specific B cell clones from tolerant and allergic individuals. CIA, 30th symposium, Petersberg, 13 – 18 September 2014.

Wanke K. Treg cells and their cytokine TGFbeta control tight junction and brochial epithelial integrity in asthma. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Wawrzyniak M., Wawrzyniak P., Breedveld A., Rebane A., Ruckert B., Akdis CA., Akdis M. Isolation and characterization of IL-22 producing T cells. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Wawrzyniak M., Wawrzyniak P., Breedveld A., Rebane A., Ruckert B., Akdis CA., Akdis M. Isolation and characterization of IL-22 producing T cells. Graubunden forscht – Young Scientists in Contest 2014, Davos Switzeraland, 10-11 September 2014.

Wawrzyniak P, Wawrzyniak M, Wanke K, Rückert B, Jakiela B, Bandelja K, Kast JI, Akdis M, Sanak M, Akdis CA. Epigenetic mechanisms for weaker expression of tight junctions in bronchial epithelial cells from asthmatic individuals. CK-CARE Meeting, Davos, Switzerland, 10 September 2014.

Wiki M, Schawaller M, Akdis C.A, Rhyner C, Rohmann S, Crameri R. Replacing ELISA tests with ultra-rapid evanescence field-based technology. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Seminar and congress talks

Akdis CA. Aspects of the immune system in anaphylaxis. ORCA Meeting, Odense, Denmark, 10-11 January 2014.

Akdis CA. Tolerance to allergens: how it develops and how it can be induced. AAAAI Annual Meeting, San Diego, USA, 28 February-4 March 2014.

Akdis CA. Mechnisms of allergic rhinitis, rhinosinusitis and novel treatments. Rhinocamp Winter, St.Moritz, Switzerland, 13-15 March 2014.

Akdis CA. Mechanisms of chronicity in allergic diseases. 9th National Allergy and Asthma Congress, Turkish Republic of Northern Cyprus, 23-26 April 2014.

Akdis CA. Resident tissue cells in immune tolerance and chronicity. 2nd International Molecular Immunology and Immunogenetics Congress, Antalya, Turkey, 27-30 April 2014.

Akdis CA. Molecular and cellular mechanisms of chronicity in asthma. 26th Spring Meeting of Japanese Society of Allergology, Kyoto, Japan, 9-11 May 2014.

Akdis CA. Biologicals in asthma and endotypes. 26th Spring Meeting of Japanese Society of Allergology, Kyoto, Japan, 9-11 May 2014.

Akdis CA. Epithelial barrier function in asthma, atopic dermatitis and chronic rhinosinusitis. JIKEI allergy Seminar, Tokyo, Japan, 13 May 2014.

Akdis CA. Immunologische Wirkmechanismen der spezifischen Immuntherapie: Was wissen wir wirklich? 10. Allergologie im Kloster Eberbach, Eltville/Rheingau, Germany, 23-24 May 2014.

Akdis CA. Regulation of tight junctions. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Akdis CA. Research results on understanding immune tolerance to allergens. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Akdis CA. Defective epithelial barrier in allergy. EAACI Allergy School, Brindisi, Italy, 2-5 July 2014.

Akdis CA. Epithelial barrier in patients with chronic rhinosinusitis. ERS International Congress, Munich, Germany, 6-10 September 2014.

Akdis CA. „Life in Science“ Breakfast Discussion. CIA, Petersberg, Germany, 13-18 September 2014.

Akdis CA. Epigenetic mechanisms for the regulation of barrier integrity and bronchial epithelial tight junctions in asthma. CIA, Petersberg, Germany, 13-18 September 2014.

Akdis CA. Role of tissue cells in immune tolerance. Inmunoterapia IV State of the Art 2014, Mexico City, 26-27 September 2014.

Akdis CA. Overview of biologics in allergic diseases. Inmunoterapia IV State of the Art 2014, Mexico City, 26-27 September 2014.

Akdis CA. Immunotherapy: Mechanism, Outcomes and Markers. National Allergy and Clinical Immunology Congress, Bodrum, Turkey, 25-29 October 2014.

Akdis CA. How to write and how to review for top journals. National Allergy and Clinical Immunology Congress, Bodrum, Turkey, 25-29 October 2014.

Akdis CA. Suggestions to young scientists from the Editor of JACI. National Allergy and Clinical Immunology Congress, Bodrum, Turkey, 25-29 October 2014.

Akdis CA. The future role(s) of biomarkers in AIT. FASIT Workshop, Hamburg, Germany, 27-29 November 2014.

Akdis CA. Role of Tissue Cell Respones in Chronicity and Severity in Allergic Diseases. WAO International Scientific Conference, Rio de Janeiro, Brazil, 6-9 December 2014.

Akdis M, Role of B cells in AIT, MeDALL annual meeting, 2014.

Akdis M. Mechanisms of immune tolerance to allergens. Department of Pathology Stanford University School of Medicine, Stanford University medical Center, January 2014.

Akdis M. Immune response to rhinoviruses and their link to asthma exacerbations. AAAAI Annual Meeting, San Diego, USA, 28 February-4 March 2014.

Akdis M. New aspects of the involvement of B and T cells in the mechanisms of Immunotherapy. AAAAI Annual Meeting, San Diego, USA, 28 February-4 March 2014.

Akdis M. Regulation of B cell activation and antibody production. AAAAI Annual Meeting, San Diego, USA, 28 February-4 March 2014.

Akdis M. Mechanisms of immune tolerance to allergens. Rhinocamp Winter, St.Moritz, Switzerland, 13-15 March 2014.

Akdis M. Mechanisms of immune tolerance to allergens. 9th National Allergy and Asthma Congress, Turkish Republic of Northern Cyprus, 23-26 April 2014.

Akdis M. Peripheral tolerance mechnanisms. 2nd International Molecular Immunology and Immunogenetics Congress, Antalya, Turkey, 27-30 April 2014.

Akdis M. Mechanisms of immune tolerance to allergens. 26th Spring Meeting of Japanese Society of Allergology, Kyoto, Japan,

9-11 May 2014.

Akdis M. Mechanisms of breaking allergen-specific T cell tolerance. 26th Spring Meeting of Japanese Society of Allergology, Kyoto, Japan, 9-11 May 2014.

Akdis M. Human B regulatory cells and immune tolerance. JIKEI allergy Seminar, Tokyo, Japan, 13 May 2014.

Akdis M. Regulatory T cells: state of the art. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Akdis M. B-cell regulation by innate immune signals. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Akdis M. Mechanisms of immune response to allergens. EAACI Allergy School, Brindisi, Italy, 2-5 July 2014.

Akdis M. Human novel effector and regulatory subsets of memory B cells. CIA, Petersberg, Germany, 13-18 September 2014.

Akdis M. „Life in Science" Breakfast Discussion. CIA, Petersberg, Germany, 13-18 September 2014.

Akdis M. Mechanisms of immune tolerance to allergens. Inmunoterapia IV State of the Art 2014, Mexico City, 26-27 September 2014.

Akdis M. SIT Intralynphatic, Epicutaneous, Peptides and allergen components. Inmunoterapia IV State of the Art 2014, Mexico City, 26-27 September 2014.

Akdis M. T and B cell responses in immunotherapy. National Allergy and Clinical Immunology Congress, Bodrum, Turkey, 25-29 October 2014.

Akdis M. Mechanisms of peripheral tolerance to allergens. 23rd Semmelweis Symposium, Budapest, Hungary, 6-8 November 2014.

Akdis M. Overview of Allergen Immunotherapy and Tolerance. WAO International Scientific Conference, Rio de Janeiro, Brazil, 6-9 December 2014.

Crameri, R. The Swiss Institute of Allergy and Asthma Research. Audit by the KTI, Davos, Switzerland, 09 Januar 2014.

Crameri R. The Swiss Institute of Allergy and Asthma Research. Visit Amt für Wirtschaft und Tourismus des Kantons Graubünden, Davos, Switzerland, 21 January 2014.

Crameri R. Rapid and simple diagnostics. Meeting with Endotell AG, Zürich, Switzerland, 27 January 2014.

Crameri R. Rapid and simple diagnostics. Visit at Neurotune AG, Zürich, Switzerland, 27 January 2014.

Crameri R. From recombinant proteins to an universal immunodiagnostic platform. Visit, Heat of the Novartis Institutes for BioMedical Research at SIAF, Davos, Switzerland, 31 January 2014.

Crameri R. Component resolved diagnosis for inhalant allergies. Annual AAAAI Meeting, San Diego, USA, 27 February-04 March 2014.

Crameri R. From recombinant proteins to an universal immunodiagnostic platform. Visit at BioLegend, San Diego, USA, 4 February 2014.

Crameri R. Molecular Allergology. SIAF Scientific advisory board meeting. Davos, Switzerland, 18 March 2014.

Crameri R. Allergy vaccination using novel drug delivery routes mediated via nanotechnology. Nanoasit II Kick-off meeting, Davos, Switzerland, 18 March 2014.

Crameri R. Development of a evanescense-field based device for the rapid diagnosis of allergy and inflammation. ALLFUN final meeting, Borgo Riccio, Italy, 13-15 April 2014.

Crameri R. New perspectives in immunodiagnostics. Euresearch guided visit at SIAF Davos, Switzerland, 27 May 2014.

Crameri R. Development of new adjuvants. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Crameri R. Evanescent wave fluorescence technology: substituting ELISA with fast real time background free diagnostic tests. Forschungszentrum Borstel, Germany, 01 July 2014.

Garbani M. Novel drug delivery routes mediated by nanotechnology. EuroNanoMed-II 2nd Review Seminar for funded projects, Düsseldorf, Germany, 29-30 January 2014.

Garbani M. Prolonged immune stimulation mediated by allergen-loaded calcium phosphate spheres.
WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Grant RA. Dissecting a probiotic: biochemical and immunological aspects. International Probiotics Association (IPA) World Congress 2014, Athens, Greece, May 2014.

Neumann AU. Bioinformatics analysis of T-cell repertoire next generation deep sequencing – promises and pitfalls. SIAF, Davos, Switzerland, February 2014.

Neumann AU, Jurchott K. Workshop on bioinformatics analysis of gene expression. SIAF, Davos, Switzerland. February, 2014.

Neumann AU. Bioinformatics analysis of T-cell repertoire next generation deep sequencing – promises and pitfalls. Technical University Munich, Germany, December 2014.

O'Mahony L. Microbiome and food allergy: where is the link? Swiss Society for Allergology and Immunology (SSAI) Annual Meeting, Davos, March 2014.

O'Mahony L. Explanations for the high prevalence of asthma and allergy – influence of bacteria? EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

O'Mahony L. Microbes & metabolites as immunoregulators. Seminar series of the Pharmacology Department, University of Bern, June 2014.

O'Mahony L. Immune regulation at the intestinal mucosa. University of Leuven Summer School, Leuven, September 2014.

O'Mahony L. Pre- and pro- biotics and the development of tolerance. Food Allergy and Anaphylaxis Meeting (FAAM), Dublin, October 2014.

Prati M. Preventive/therapeutic vaccines in a murine model of allergy. Graubünden forscht: Young Scientists in Contest - Academia Raetica Symposium, 10–11 September 2014.

Rhyner, C. KTI Project "SIT-Monitor". Audit by the KTI, Davos, Switzerland, 09 Januar 2014.

Rhyner, C. Vaccine Development. SIAF Scientific advisory board meeting. Davos, Switzerland, 18 March 2014.

Rhyner, C. Evanescent field-based fast measurements of allergen specific antibodies during SIT. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Schawaller M. Evanescence technology: rapid point of care diagnostics. Swiss-Polish annual expert meeting, Davos, Switzerland, 20 June 2014.

Schiavi E. Study of Bifidobacterium infantis 35624 exopolysaccharides on immune cells. Swiss-Polish Annual Expert Meeting, SIAF, 20 June 2014.

van de Veen W. Generation and characterization of human allergen-specific memory B cell clones. EAACI Winter School, Poiana Brasov, Romania, 30 January-2 February 2014.

van de Veen W. Characterization of human allergen-specific B cell subsets. WIRM VIII, Davos, 19 – 22 March 2014.

van de Veen W. Generation and characterization of allergen-specific B cell clones from tolerant and allergic individuals. CIA, 30th symposium, Petersberg, 13 – 18 September 2014.

van de Veen W. Generation and characterization of human allergen-specific B cell clones. Graubünden Forscht – Young Scientists in Contest, Davos, 10 – 11 September 2014.

Wawrzyniak P. Epigenetic mechanisms for weaker expression of tight junctions in bronchial epithelial cells from asthmatic individuals. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Wawrzyniak P. Role of Th2 cells and cytokines in epithelial barrier function in asthma. Swiss-Polish Annual Expert Meeting, SIAF, Davos, Switzerland, 20 June 2014.

Wawrzyniak P. Epigenetic mechanisms for weaker expression of tight junctions in bronchial epithelial cells from asthmatic individuals. Graubünden forscht – Young Scientists in Contest, Davos, Switzerland, 10–11 September 2014.

Chair at congresses

Akdis CA. EAACI: Novel developments in asthma exacerbations. AAAAI Annual Meeting, San Diego, USA, 28 February-4 March 2014.

Akdis CA. Rhinocamp Winter, St.Moritz, Switzerland, 13-15 March 2014.

Akdis CA. Essentials of immune regulation in the innate immune response. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Akdis CA. Viruses and drug hypersensitivity. EAACI Drug Hypersensitivity Meeting, Bern, Switzerland, 9-12 April 2014.

CHAIR AT CONGRESSES

2014

Akdis CA. Immune system and allergy. 9th National Allergy and Asthma Congress, Turkish Republic of Northern Cyprus, 23-26 April 2014.

Akdis CA. Emerging issues in the adaptive immune system. 2nd International Molecular Immunology and Immunogenetics Congress, Antalya, Turkey, 27-30 April 2014.

Akdis CA. IgE paradigm in the immune system. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Akdis CA. FOCIS Symposium: highlighting translational immunology. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Akdis CA. CK-CARE Allergy School, Davos, Switzerland, 10-12 September 2014.

Akdis CA. Pathogenesis of Allergic Disease: Role of Cytokine Families. WAO International Scientific Conference, Rio de Janeiro, Brazil, 6-9 December 2014.

Akdis M. Rhinocamp Winter, St.Moritz, Switzerland, 13-15 March 2014.

Akdis M. B cell regulation. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Akdis M. Regulatory cells of immune system. 2nd International Molecular Immunology and Immunogenetics Congress, Antalya, Turkey, 27-30 April 2014.

Akdis M. Novel interleukins regulating tissue inflammation. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Akdis M. AIT mechanisms. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Akdis M. Women in science: genetics and epigenetics of allergy and asthma. EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Akdis M. Allergen Specific Immunotherapy. CIA, Petersberg, Germany, 13-18 September 2014.

Akdis M. TH-22, Thymic Stromal Lymphopoietin (TSLP) and Fractalkine: New Targets in Atopic Dermatitis? WAO International Scientific Conference, Rio de Janeiro, Brazil, 6-9 December 2014.

Akdis M. Mechanisms of Asthma and Allergic Inflammation. WAO International Scientific Conference, Rio de Janeiro, Brazil, 6-9 December 2014.

Crameri, R. RaptaDIAG WP2: Evanescence biosensors, overview of the progress. 4th Project Meeting, Davos, Switzerland, 11-12 February 2014.

Crameri R. Vaccine development. Nanoasit II Kick-off meeting, Davos, Switzerland, 18 March 2014.

Crameri R. Regulation of immune response and immune pathology. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Crameri R. Common immunogenic molecules and auto-antigens: towards an universal diagnosis. ALLFUN final meeting, Borgo Riccio, Italy, 13-15 April 2014.

Frei R. Dendritic cells II. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Komlosi Z. NK cells and innate lymphoid cells. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Mercep M. Biologicals and in vivo immune modulation. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

O'Mahony L. EAACI Immunology Winter School, Brasov, Romania, January 2014.

O'Mahony L. Microbiome-immune interactions. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

O'Mahony L. EAACI annual meeting, Copenhagen, Denmark, June 2014.

O'Mahony L. University of Leuven Summer School on Immunology, Leuven, Belgium. September 2014.

Palomares O. Dendritic cells I. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Rhyner C. Metabolism and immune response I. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Rhyner C. Poster Session: „Allergy diagnosis". EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Rhyner C. Oral Abstract Session: „Allergic immune responses". EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Rhyner C. Symposium: „Immunotherapy preparations". EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Rhyner C. Poster Session: „Vaccines". EAACI Congress, Copenhagen, Denmark, 7-11 June 2014.

Schawaller M. In vitro diagnostic methods and biomarkers. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

van de Veen W. T and B cell subsets. WIRM VIII, Davos, Switzerland, 19-22 March 2014.

Lectures

Lectures at University of Zurich

Akdis CA. FS/HS 2014 Nr. 1290/1253, Klinisch-experimentelle Konferenz zur Allergologie.
Akdis CA. FS/HS 2014 Nr. 1324/1289, Mechanisms of Allergic Diseases.
Akdis CA. HS 2014 Nr. 3695, Vorlesung Molekulare Zellbiologie.

Akdis M. FS/HS 2014 Nr. 1290/1253, Klinisch-experimentelle Konferenz zur Allergologie.
Akdis M. FS/HS 2014 Nr. 1324/1289, Mechanisms of Allergic Diseases.
Akdis M. HS 2014 Nr. 3695, Vorlesung Molekulare Zellbiologie.

Crameri R. FS/HS 2014 Nr. 1290/1253, Klinisch-experimentelle Konferenz zur Allergologie.
Crameri R. FS/HS 2014 Nr. 1324/1289, Mechanisms of Allergic Diseases.
Crameri R. HS 2014 Nr. 3695, Vorlesung Molekulare Zellbiologie.

O'Mahony L. FS/HS 2014 Nr. 1290/1253, Klinisch-experimentelle Konferenz zur Allergologie.
O'Mahony L. FS/HS 2014 Nr. 1324/1289, Mechanisms of Allergic Diseases.
O'Mahony L. HS 2014 Nr. 3695, Vorlesung Molekulare Zellbiologie.

Lectures at University of Salzburg

Crameri R. SS 2014: MOD.259, Mastermodul.: Molekulare Zellbiologie als Analyseplattform in Medizin und Industrie.
Crameri R. SS 2014: Nr. 439.006, Molekulare Zellbiologie in der Medikamentenentwicklung.
Crameri R. SS 2014: Nr. 439.007, Molekulare Interaktionen als Target für therapeutische Interventionen.

Awards

Akdis CA. The Elliot Middleton Memorial Lectureship Award. Annual Meeting AAAAI, San Diego, USA, March 2014.

Akdis CA. Election as member of the Swiss Academy of Medical Sciences (SAMS), Switzerland, May 2014.

Olzhausen J. Poster Prize. Graubünden forscht–Young Scientists in Congress. Davos, Switzerland, September 2014.

Palomares O. AAAAI International Young Investigator Award. Annual Meeting AAAAI, San Diego, USA, March 2014.

Sabaté Brescó M. Travel Award. 5th International Conference on Osteoimmunology, Kos, Greece, June 2014.

Sabaté Brescó M. Best Oral presentation in Medical Sciences. Graubünden forscht 2014: Young Scientists in Contest, Davos, Switzerland, September 2014.

Smolinska S. Young investigator award. Histamine Research Society 43rd Annual Meeting, Lyon, France, May 2014.

Smolinska S. Student bursaries. Histamine Research Society 43rd Annual Meeting, Lyon, France, May 2014.

Smolinska S. 2 Poster Prizes. EAACI-WAO Congress 2014, Copenhagen, Denmark, June 2014.

Smolinska S. Alain de Weck Travel Grant Award. 30th Symposium of the Collegium Internationale Allergologicum, Petersberg, Germany, September 2014.

Sokolowska M. European Respiratory Society/EMBO, Long Term Research Fellowship.

Sokolowska M. European Academy of Allergy and Clinical Immunology, Long Term Research Fellowship.

Treis A. Travel Grant. EAACI Winter School, Poiana Brasov, Romania, February 2014.

van de Veen W. Certificate of Merit from Academia Raetica for contribution to scientific excellence by means of dissertation.

Degreees

Rhyner C. Executive diploma in the management of small and mid-sized enterprises, University of St. Gallen, Switzerland, 2014.

Wanke K. PhD. Thesis: Regulation of Tight Junctions in Asthma. University of Zürich, Faculty of Science, Swiss Institute of Allergy and Asthma Research, October 2014.

Public Seminars

24./25.02.2014

Prof. Avidan U. Neumann, Head Systems Biology Group, BCRT, Charite University Hospital Berlin, Germany. Research Seminar: Next generation TCR repertoires – regulatory and conventional T-cells – to share or not to share?" Lectures: Biostatistics refresher - applied statistics for biological research. Introduction to Bioinformatics - microarray analysis. Introduction to biomathematics - analysis and modeling of kinetic data.

11.03.2014

Dr. Andreas Tobler, PhD, Sequencing Sales Specialist at Life Technologies, Zurich, Switzerland. Ion torrent: Single cell expression analysis from FACS sorted cells using Next Generation Sequencing.

03.04.2014

Dr. Catharine Aquino Fournier. Functional Genomics Center Zurich. Main issues you need to know before doing next generation sequencing.
Dr. Lennart Opitz. Functional Genomics Center Zurich. Getting informative summaries for millions of reads.
Hideaki Morita, SIAF. Innate lymphoid cells and histamine.
Willem Van de Veen / Oliver Wirz, SIAF. Human B cell subsets.
Jeannette Kast, SIAF. Allergen-specific T cells.
Can Altunbulakli, SIAF. Rhinovirus infected epithelial cells and asthma and rhinitis.
Paulina Wawrzyniak, SIAF. Epigenetics of bronchial epithelial barrier function.

19.05.2014

Professor Avidan Neumann, PhD, Institute for Theoretical Biology (ITB), Humboldt University and Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charite University Hospital, Berlin, Germany and Dr. Karsten Jürchott, PhD, Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charite University Hospital, Berlin, Germany. Next Generation RNA Sequencing Transcriptome.

27.05.2014

Prof. Hans Jürgen Hoffmann, Dept Pulmonary Medicine B, Institute for Clinical Medicine, Aarhus University, Denmark. Rapid Desensitization of Human primary Basophil Granulocytes and cultured Mast Cells.

27.05.2014

Eurosearch Guided Visit
Cezmi Akdis, SIAF. Epithelial barrier function and allergic diseases.
Reto Crameri, SIAF. New perspectives in immunodiagnostics.
Mübeccel Akdis, SIAF. Mechanisms of peripheral tolerance to allergens.
Claudio Rhyner, SIAF. Evanescent field-based fast measurements of allergen specific antibodies during SIT.
Ray Grant, SIAF. Bacterial exopolysaccharides for the treatment of inflammatory conditions.

20.06.2014

Swiss-Polish Annual Expert Meeting
Workshops on Rhinovirus experiments metaplastic and Epithelial junctional network experiments.
Marek Sanak, Jagiellonian University. Production of lipid mediators during bronchial provocations in aspirin-exacerbated respiratory disease.
Bogdan Jakieła, Jagiellonian University. Response to rhinovirus infection in mucociliary differentiated and mucous metaplastic bronchial epithelium.
Mübeccel Akdis, SIAF. Novel developments in the immune response to rhinovirus infections.
Manfred Schawaller, Davos Diagnostics. Evanescence technology: rapid point of care diagnostics.
Barbara Stanic, SIAF. Introduction to Breg cells: IL-10-overexpressing B cells regulate innate and adaptive immune responses.
Cezmi Akdis, SIAF. Introduction to epithelial barrier.
Paulina Wawrzyniak, SIAF. Role of Th2 cells and cytokines in epithelial barrier function in asthma.
Roger Lauener, Ostschweizer Kinderspital. Influences of genes and environment on allergic phenotypes.
Ray Grant, Alimentary Health Pharma Davos. Immunoregulatory responses to microbial factors.
Elisa Schiavi, SIAF. Exopolysaccharides modulate inflammatory responses.
Can Altunbulakli, SIAF. Analyses of next generation data in AD lesion formation.

17.07.2014

Dr. Francesc Castro-Giner, PhD. Molecular and Population Genetics Group, Wellcome Trust Centre for Human Genetics, University of Oxford, UK. Complex disease genetics: from candidate genes to whole-genome sequencing.

21.07.2015

Prof. Dr. Harald Renz, Professor and Director, Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics, Philipps University Marburg, University Hospital Giessen and Marburg, Germany. Epigenetics and allergy.

28.07.2014

Dr. Marcin Fraczek, The University of Manchester, Institute of Inflammation & Repair, UK. Aspergillus fumigatus as a human pathogen and the role of host defence against the fungus.

08.10.2014

Prof. Dr. Nicole Joller, Institute of Experimental Immunology, University of Zurich, Switzerland. Immune regulation through the co-inhibitory molecule TIGIT.

15.10.2014

Dr. Simmon Hofstetter, PhD, Department of Renewable Resources, University of Alberta, Canada. Isolating Microorganisms: Challenges and Strategies.

15.10.2014
Dr. Mathias Hauri-Hohl, MD PhD, Children's Hospital Zurich, Switzerland, Department of Stem Cell Transplantation and Immunology, Postdoctoral Research Associate, Benaroya Research Institute at Virgina Mason, Seattle WA, USA. Making a good thing better? - On the role of TGF-beta in regulating central tolerance.

05.11.2014
Prof. Dr. Thorsten Buch, Institute of Laboratory Animal Science, University of Zurich, Switzerland, Institute for Medical Microbiology, Immunology and Hygiene, Technische Universität München, Germany. TGFbeta receptor in tolerance, autoimmunity and allergy.

11.11.2014
Dr. Tuomas Jartti, M.D., Head of Pediatric Allergy and Asthma Unit, Turku University Hospital, Turku, Finland. Etiology of viral wheeze determines the risk of childhood asthma.

14.11.2014
Prof. Dr. Wolfgang Pfützner, Clinic of Dermatology and Allergology, Universitätsklinikum Gießen und Marburg, Germany. Long-term effects of specific immunotherapy.
Prof. Dr. Michael Zemlin, Pediatric Allergy and Immunology, Universitätsklinikum Gießen und Marburg, Germany. Antibodies in allergies.

17.11.2014
Dr. med. Norbert Meyer, Universitätsklinik für Rheumatologie, Immunologie und Allergologie, Universitätsspital Bern, Switzerland. Allergen-specific Immunotherapie – Clinical aspects and novel highlights.

01.12.2014
Dr. Christoph Kornfeld, Beckman Coulter. Kaluza Aquisition Software Demonstration.

17.12.2014
Rainer Warth, PhD, Foundation biobank-suisse, Lausanne, Switzerland. Biospecimens with associated data for biomedical research in the genomic era.

SIAF Science Day
18.12.2014
Microbial molecules - relevance to immune homeostasis. Barcik W.

Allergen specific T and B cells in allergic patients. Boonpiyathad T.

Potential role of Short-chain fatty acids in allergy prevention of children. Frei R.

Role of TLR9 in preserving bronchial epithelial integrity. Kubo T.

Retinoic acid convert ILC2 into „regulatory ILC". Morita H.

Quantitative measurements using the evanescent field technology. Olzhausen J.

Kinetics on cells – Bridging the gap between traditional biosensors and cell based assays. Prati M.

Group 2 innate lymphoid cells promote human bronchial epithelial cell barrier disruption. Sugita K.

Human antigen-specific B cell subsets. Van de Veen W.

Characterization of IL-22 producing T cells. Wawrzyniak M.

Epigenetic mechanism for leaky barrier and regulation of tight junctions in asthma. Wawrzyniak P.

Something about B cells. Wirz O.

Winner of the SIAF Science Day 2014: Remo Frei

Scientific Posts
Akdis CA.
Allergopharma Award - Committee member

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) - Director and Speaker

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

International Coalition in Allergy and Asthma, a collaborative network between EAACI, AAAAI, ACAAI, WAO (iCAALL) - Chair

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

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

European Asthma Research and Innovation Partnership (EARIP) - Member

Global Allergy and Asthma European Network GA2LEN - Executive Committee Member

World Allergy Organization Research Council - Council Member

World Immune Regulation Meeting - Chairman

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

Akdis M.
Clemens von Pirquet-prize for Allergology, The Austrian Society of Allergol. and Immunol. - Reviewer

Immunotherapy consultant, Workshop is “in focusing and prioritizing future research that will lead to the development of more effective and safer modes of immunotherapies to prevent and treat allergic diseases” in the National Institute of Allergy and Infectious Diseases. Bethesda, Maryland, October, 2012.

World Immune Regulation Meeting - Member of the organizing committee

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

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

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

Crameri R.
Academia Raetica - Co-founder and vice president

Academia Raetica Symposium, „Graubünden forscht: Young Scientists in Contest” - Member of organizing committee

18th Congress of the “International Society for Human and Animal Mycology” (ISHAM), Berlin - Member of the organizing committee
2nd International Workshop on Allergen Vaccines, Cuba - Member of the organizing committee

7th Framework Program ALLFUN - Steering board member

7th Framework Program ALLFUN - Work package leader (Common immunogenic fungal molecules and cross-reactive structures: towards a universal diagnosis)

Euronanomed Program NANOASIT - Steering board member, Work package leader (Engineering optimal allergy vaccines)

Naturforschende Gesellschaft Davos - Advisory board member and treasurer

Satellite Meeting SM5 “Fungi in the setting of inflammation, allergy and autoimmune diseases: translating basic science into clinical practices” of the 15th International Congress of Immunology, Perugia, Italy - Member of the organizing committee

World Immune Regulation Meeting - Member of the organizing committee

O’Mahony L.
EAACI Immunology Section - Board Member 2011-2015

EAACI Immunology - Section Secretary 2013-2015

EAACI Immunology winter school, Brasov, Romania, Jan 2014 - Organizer

EAACI Food Allergy and Anaphylaxis Guidelines - Group member

EU COST Action BM0806 – Histamine H4 Receptor - Management Committee Member

COST BM0806 - Financial Rapporteur

World Immune Regulation Meeting - Member of the organizing committee

Annual EAACI meeting, Copenhagen 2014 - Scientific Program Committee member

Rhyner C.
EAACI interest group "Functional Genomics and proteomics" - Member of the Board

Academia Raetica - Member

British Biochemical Society - Member

World Immune Regulation Meeting - Member of the organizing committee

2nd International Workshop on Allergen Vaccines, Cuba - Member of the organizing committee

Editorial Activities
Akdis CA.
Current Opinion in Immunology, editorial board member

European Journal of Immunology, editorial board member

Expert Opinion on Emerging Drugs, editorial board member

International Reviews of Immunology, editorial board member

Journal of Allergy and Clinical Immunology, associate editor

Journal of Allergy and Clinical Immunology, co-editor-in-chief (July 2015)

Journal of Investigational Allergology and Clinical Immunology, editorial board member

Clinical Translational Allergy, associate editor

Nature Scientific Reports, editorial board member

Akdis M.
Allergy, editorial board member

International Archives of Allergy and Immunology, editorial board member

Recent patents in inflammation, allergy and drug discovery, editorial board member

Journal of Allergy Clinical Immunology, editorial board member

Crameri R.
Allergy, associate editor

Biochemical Journal, editorial board member

International Archives of Allergy and Immunology, editorial board member

Mycoses, deputy editor

The Open Allergy Journal, editorial board member

The Open Immunology Journal, editorial board member

The Open Mycology Journal, editorial board member

Collaborations with the Clinics of Davos

Hochgebirgsklinik Davos-Wolfgang (Prof. G. Menz, H.W. Duchna, Dr. M. Möhrenschlager, Dr. A. Kalweit, Prof. R. Lauener, Dr. C. Steiner, Dr. A. Kirsch)

Nederlands Astmacentrum (Dr. A. Bron, Dr. J. Romeijin)

Spital Davos (Dr. J. Mattli, Dr. A. Speiser)

Zürcher Höhenklinik Davos, Davos Clavadel (Dr. T. Rothe)

Collaborations outside Davos

Academic Medical Center, Dept. of Cell Biology and Histology, Amsterdam (NL), (Porf. H. Spits)

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

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

Allergopharma, Reinbek (D), (Dr. A. Nandy, Dr. S. Klysner)

Allgem. Krankenhaus (AKH) Wien (A), 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)

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

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

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

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

Centre Suisse d'Electronique et Microtechnique SA (CSEM) Landquart (CH), (Silvia Generelli, Stephane Follonier)

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

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

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

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

ETH Zürich, Departement Pharmazie (CH), (Prof. G. Folkers)

ETH Zürich, Department of Biotechnology (CH), (Prof. C. Lacroix)

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

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

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

Immunologie et Neurogénétique Expérimentales et Moléculaires (INEM) UMR7355, Department of Molecular Immunology, Orleans (FR), (Prof. Bernhard Ryffel)

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

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

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

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

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

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

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

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

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

Medical University of Bialystok, Department of Regenerative Medicine and Immune Regulation (PL), (Prof. Marcin Moniuszko)

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

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

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

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

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

Paul Scherrer Institute (CH), (Prof. R. Schibli, Dr. R. Waibel)
Philipps University of Marburg, Medical Faculty Marburg (DE), (Prof. Holger Garn and Prof. Harald Renz)

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

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

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

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

Technische Universität München, Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, München (D), (Prof. J. Ring)

Technische Universität München, Forschungszentrum für Umwelt und Gesundheit, München (D), (Prof. C. Schmidt-Weber, Prof. Dr. C. Traidl-Hoffmann)

The Hospital for Sick Children, Cancer and Blood Research Program, Toronto (CAN), (Dr. M. Letarte)

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

Tytgat Institute of Intestinal and Liver Research, Academic Medical Center, Amsterdam (NL), (Prof. H. Spits)

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

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

Universität Graz, Dept. of Pediatrics, Graz (A), (Dr. E.M. Varga)

Universität Graz, Inst. Pharm. Chem., Graz (A), (Prof. A. Kungl)

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

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

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

Universitätsklinik Zürich, Dermatologische Klinik, Zürich (CH), (Prof. R. Dummer, PD Dr. Th. Kündig, PD Dr. P. Schmid-Grendelmeier, PD Dr. B. Ballmer-Weber, PD Dr. G. Hofbauer, Prof. L. Frenc)

Universitätsspital Bern, Kinderklinik, Inselspital, Bern (CH), (Prof. R. Kraemer, Dr. C. Aebischer-Casaulta, Prof. M.H. Schöni)

Universitätsspital Zürich, Vetsuisse Fakultät, Zürich (CH), (Prof. C. Fauvrat, Dr. A. Rostaher)

Universitätsspital Zürich, Abteilung für Klinische Immunologie, Zürich (CH), (Prof. O. Boyman)

Universitätsspital Zürich, Abteilung ENT, Zürich (CH), (PD Dr. D. Holzmann, Dr. M. Soyka)

Universitätsspital Zürich, Kinderklinik, Zürich (CH), (Prof. R. Lauener, Dr. C. Roduit, Dr. A. Jung)

Universitätsspital Zürich, Abteilung Pneumologie, Zürich (CH), (Dr. M. Kohler)

Universitätsspital Zürich, Abteilung Gastroenterologie, Zürich (CH), (Prof. R. Gerhard)

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

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

University of Lausanne, Department of Biochemistry, Lausanne (CH), (Prof. Margot Thome)

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

University of Szeged, Department of Dermatology and Allergology, Szeged, (HUN) (Dr. Nikoletta Nagy, Prof. Lajos Kemeny)

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

Wroclaw Medical University, Wroclaw (PL), (Prof. M. Jutel)

Schweizerisches Institut für Allergie- und Asthmaforschung

Bilanz per 31. Dezember 2014

(inklusive Drittmittel)

	31.12.2014	31.12.2013
	CHF	CHF
AKTIVEN		
Flüssige Mittel	1'615'787.49	1'018'206.05
Forderungen	23'796.55	77'414.34
Aktive Rechnungsabgrenzung	259'880.36	497'761.11
	1'899'464.40	1'593'381.50
PASSIVEN		
Verbindlichkeiten	113'780.47	208'026.69
Kontokorrent SFI Stiftung	212'756.40	6'945.35
Passive Rechnungsabgrenzung	1'215'523.20	1'057'046.95
Rückstellungen	137'947.84	101'906.02
Eigenkapital	219'456.49	219'456.49
	1'899'464.40	1'593'381.50

Schweizerisches Institut für Allergie- und Asthmaforschung

Betriebsrechnung 2014

(inklusive Drittmittel)

	Rechnung 2014	Budget 2014	Rechnung 2013
	CHF	CHF	CHF
ERTRAG			
Beitrag Bund Forschungsgesetz Art. 16	840'000.00	840'000.00	810'000.00
Beitrag Kanton Graubünden	146'050.00	146'050.00	146'050.00
Beitrag Gemeinde Davos	424'560.00	424'560.00	424'560.00
Beitrag Universität Zürich	326'180.90	300'000.00	306'228.00
Beitrag Stiftung SFI Villa Fontana	100'000.00	100'000.00	100'000.00
Beitrag Stiftung vormals Bündner Heilstätte Arosa	75'000.00	75'000.00	75'000.00
Overheadbeiträge	90'693.00	15'000.00	155'171.42
Ertrag aus Dienstleistung Asthmaforschung	2'721.04	5'000.00	7'193.16
Übriger Ertrag	32'500.80	19'300.00	2'991.89
Finanzertrag	84.28	0	137.24
Ausserordentlicher Ertrag	0	0	6'984.05
WIRM-Kongress	401'363.93	430'000.00	382'542.60
Drittmittel	2'755'376.25	2'578'286.00	2'787'724.15
	5'194'530.20	4'933'196.00	5'204'582.51
AUFWAND			
Personalaufwand	3'079'722.59	3'031'805.00	3'063'039.32
Verbrauchsmaterial	997'574.51	1'019'223.00	1'094'863.69
Raumaufwand	17'521.41	38'760.00	14'338.20
Unterhalt/Reparaturen/Ersatz	138'319.02	114'000.00	101'010.65
Investitionen	327'880.76	25'408.00	258'021.73
Sachversicherungen/Abgaben	7'358.70	7'500.00	7'971.35
Energie- und Entsorgungsaufwand	66'110.95	83'000.00	68'999.85
Verwaltungsaufwand	118'403.61	170'500.00	146'682.56
Reisespesen	119'939.86	73'000.00	101'588.36
WIRM-Kongress	299'853.88	365'000.00	334'391.03
Übriger Betriebsaufwand	4'933.45	2'000.00	5'076.67
Finanzaufwand	2'092.87	3'000.00	2'853.57
Ausserordentlicher Aufwand	14'818.59	0	5'745.53
	5'194'530.20	4'933'196.00	5'204'582.51
Ergebnis	0	0	0
	5'194'530.20	4'933'196.00	5'204'582.51

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