SIAF

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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. Cezmi A. Akdis

Die Auswirkungen von Allergien auf Gesundheit und Lebensqualität sind für viele Menschen gravierend. Allergien wie allergisches Asthma, allergische Rhinitis, atopisches Ekzema und Nahrungsmittelallergien sind allein in Europa mit geschätzten Kosten von jährlich mehr als 200 Milliarden Euro zudem zu einer grossen sozio-ökonomischen Herausforderung geworden.

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 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.

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. Von 2008-2011 war Prof. CA. Akdis Vizepräsident der EAACI. 2011 wurde er zum Präsidenten der Akademie gewählt. Seine Amtsperiode im Ausschuss dauerte bis 2015. PD Dr. L. O'Mahony ist Vorstandsmitglied der Sektion Immunologie. Prof. Dr. M. Akdis ist Mitglied der Biologicals Interest Group und Dr. C. Rhyner der Allergy Diagnostics Interest Group.

Das SIAF hat über 850 Fachbeiträge veröffentlicht und gehört zu den meistzitierten Instituten weltweit. Die vom SIAF publizierten Artikel wurden über 45'000 Mal zitiert. Das Institut gehört mit seinen rund 45 Mitarbeitern (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.

2015 wurden 58 wissenschaftliche Arbeiten in begutachteten internationalen Fachzeitschriften mit "Impact Factor" veröffentlicht. 2015 erreichte das SIAF einen Gesamtwert des "Impact Factors" von 363.361 und einen Durchschnitt von 7.267 Punkten. Die neusten Ergebnisse wurden zudem in 28 Abstracts an verschiedenen Fachtagungen mitgeteilt. Unsere Mitarbeitenden wurden zu 60 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 41 verschiedenen Sessionen hatten SIAF-Mitarbeitende den Vorsitz. Zusätzlich werden 45 wissenschaftliche Ämter in internationalen Gesellschaften durch Wissenschaftler des SIAF besetzt. Desweiteren sind die Forscher des SIAF bei insgesamt 24 internationalen Zeitschriften als Mitglieder der redaktionellen Komitees tätig. Zudem hält CA. Prof. Akdis das Amt des Chefredaktors des Journal of Allergy and Clinical Immunology (JACI) inne.

Auch wenn in den letzten Jahren beachtliche Fortschritte in der Aufklärung der grundlegenden Mechanismen, welche zu allergischen Erkrankungen führen, erzielen lassen haben, besteht nach wie vor ein grosses Bedürfnis, das theoretische Wissen und die Alltagserfahrungen der Betroffenen und ihres Umfeldes zu vereinen.

Im Juli 2009 hat die Kühne-Stiftung eine der europaweit grössten privaten Initiativen auf dem Gebiet der Allergologie, das Christine Kühne – Center for Allergy Research and Education (CK-CARE), mit den Standorten Davos, München und Zürich ins Leben gerufen. Ziel ist es, Forschung, Edukation und Prävention auf dem Gebiet der Allergien zu fördern und die Umsetzung der Forschungsergebnisse in der klinischen Versorgung zugunsten der betroffenen Patienten zu verbessern. Nach einer erfolgreichen externen Evaluation der erbrachten Leistungen wurde die Initiative 2014 um die Standorte Augsburg, Bonn und St.Gallen erweitert und für weitere fünf Jahre verlängert. Das SIAF spielt in der CK-CARE eine tragende Rolle. In unserem Workpackage ist das Ziel, die molekularen Vorgänge von externen und internen Faktoren besser zu verstehen, die bei der Entstehung, Entwicklung, Chronifizierung und dem Schweregrad atopischer Erkrankungen eine Rolle spielen. Dieses Wissen ist von grundlegender Bedeutung und wird zur Entwicklung besserer Präventions- und Behandlungsstrategien sowie diagnostischer Biomarker für atopische Erkrankungen führen. Wir legen höchste Priorität auf die In-vivo-Relevanz unserer Forschungsergebnisse, damit neue Präventions-, Diagnose- und Behandlungsmethoden entwickelt werden können. Im Berichtszeitraum haben wir uns schwerpunktmässig mit Barrierestörungen, Prävention und Behandlung von atopischen Erkrankungen befasst.

Seit 2009 konnten dank der Unterstützung durch die CK-CARE mehr als 35 wissenschaftliche Mitarbeitende eingestellt und über 50 akademische Gäste im Austauschprogramm aufgenommen werden. Darüber hinaus wurden 101 Publikationen in namhaften Zeitschriften veröffentlicht haben.

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

Mikrobiome in Allergien und Asthma
Bis vor nicht allzu langer Zeit galt die Lunge als steril. Jedoch ist nun klar, dass dem nicht so ist und wir sind daran interessiert das Lungenmikrobiom in Asthmapatienten zu ermitteln und dieses mit gesunden Proben zu vergleichen. Zusätzlich werden wir eine detaillierte Untersuchung der zellulären Immunantwort in der Lunge vornehmen. Diese Untersuchung umfasst auch die lymphozytische Antwort, Makrophagen und dendritische Zellen, invariante natürliche T-Killerzellen (iNKT) und die innate lymphoid cells (ILC). Neue Mikroben werden isoliert und in Mausmodellen verabreicht, um ihre Wirkung auf die Lungenantwort zu bestimmen.

Adipositas, Entzündungen, Asthma und Allergien
Fettleibigkeit birgt viele Risiken für Krankheiten wie Asthma. Ein erhöhter Bodymass-Index ist mit erhöhten IgE-Werten verbunden. Wir untersuchen die Mikrobiome, den Entzündungsstoffwechsel und die metabolische Störung von übergewichtigen Personen, um auf zellulärer und molekularer Ebene die biologische Grundlage dieser Wechselwirkungen bei adipösen Patienten besser zu verstehen. Wir sind insbesondere an den G-Protein-gekoppelten Rezeptoren (GPCRs) und ihre Aktivierung durch die Mikrobiome oder nahrungsabhängige Liganden interessiert.

Regulation der Immunantwort durch antigen-spezifische regulatorische B-Zellen und Effektor-B-Zellen in Allergien
Im Menschen findet man verschiedene Zytokin-produzierende B-Zellen-Subtypen, die verschiedene Funktionen wie entzündungsfördernde, entzündungshemmende sowie effektorische und regulatorische Funktionen übernehmen. Funktionelle menschliche B-Zellen-Subtypen zeigen in vivo klonale Expansion und könnten die Profile der Zytokine während der Entwicklung von Allergentoleranz umstellen, die mittels allergen-spezifischer Immunotherapie und als Folge einer Exposition mit einer hohen Allergendosis induziert werden kann. Die Bestimmung von Effektor-B- und regulatorischen B-Zellen-Subtypen nebst den T-Zellen-Subtypen mittels mehrfarbiger Durchflusszytometrie können zur immunologischen Untersuchung von Entzündungskrankheiten eingesetzt werden.
Unser Ziel ist es, neue menschliche regulatorische B-Zellen und Effektor-B-Zellen, ihre funktionellen Phäntoypen und in vivo Relevanz zu identifizieren, die Rolle dieser Zellen in der Immuntoleranz gegenüber Allergenen aufzuzeigen und ihre Subtypen-spezifischen Eigenschaften der Zellen-Oberflächen und sezernierende Moleküle zu entdecken und zu charakterisieren.

Verminderte Toleranz gegenüber Allergen durch menschliche Rhinovirus-Infektionen
Wir werden die molekularen Mechanismen bei viralen Infektionskrankheiten bestimmen, welche die Toleranz gegenüber Allergenen vermindern, indem die suppressive Funktion der Treg-Zellen unterbunden wird. Studien über die allergen-spezifische Immunotherapie gegen Bienengiftallergien und bei Imkern, die einer hohen Allergendosis ausgesetzt sind, deuten darauf hin, dass in vivo ein T-Zellenwechsel von Th2-Zellen zu regulatorischen/suppressiven T-Zellen stattfinden kann. Regulatorische T-Zellen könnten sich in Patienten mit einer Virusinfektion in Th2-, Th1- oder Th17-Zellen verwandeln und somit könnten die suppressiven Eigenschaften von regulatorischen T-Zellen vermindert sein. Wir werden die infektionsbedingten molekularen Mechanismen von humanen Rhinoviren (HRV) bestimmen, welche die regulatorischen B- und Effektor-B-Zellen-Subtypen stimulieren, indem sie zielgerichtet auf die Systembiologie zurückgreifen. Die vorläufigen Daten zeigen, dass die HRV humane B-Zellen direkt stimulieren und befallen können. Eingehende Studien über die Rolle von HRV-aktivierten B-Zellen und insbesondere von regulatorischen B-Zellen sowie die Brechung von Allergentoleranz werden helfen, die Asthmapathogenese besser zu verstehen und damit zur Entwicklung von gegen diese Zellen gerichtete Wirkstoffen verhelfen.

Gestörte Funktion der epithelialen Barriere in Asthma, atopischer Dermatitis, allergischer Rhinitis und chronischer Rhinosinusitits
Kürzlich haben verschiedene Studien, unsere mit einberechnet, zeigen können, dass die Barrierenfunktion in den Epithelzellen der Lunge von Asthmapatienten, in den Epithelzellen von Patienten mit chronischer Rhinosinusitis sowie in der Keratinozyten der Haut von Patienten mit atopischer Dermatitis gestört ist. Wenn die Integrität der Barriere gestört ist, können Allergene, bakterielle Stoffe und andere Partikel in das Epithel eindringen, dort das Immunsystem aktivieren und schwere chronische Entzündungen hervorrufen. Wir konnten viele Beiträge in diesem Forschungsfeld leisten und unser Ziel ist es, die wichtigsten Aspekte zu klären, die eine Rolle bei der Deregulierung der epithelialen Barrierefunktion in den verschiedenen allergischen Krankheiten spielen. Wir haben die Faktoren untersucht, welche die angeborene Immunantwort beeinflussen, mit besonderen Augenmerk auf die Rezeptoren. Weiter wurden wir die Regulierung der Expression von Tight Junction-Molekülen, die Rolle in der Barriereintegrität von T-Zell- und B-Zell-Subtypen sowie von Innate Lymphoid Cells und deren wichtigsten Zytokinen untersuchen. Die Untersuchungen werden mittels Air-liquid-Kulturen von primären menschlichen Zellen und Mausmodellen vorgenommen. Zudem werden neue diagnostische Methoden zur Bestimmung von Barriereundichtigkeit versus Integrität und neue Behandlungsansätze ermittelt.

Epigenetische Regulation bei bronchialer Barriereundichtigkeit in Allergien und Asthma
Zur Bestimmung der molekularen Mechanismen bei bronchialer Barriereundichtigkeit in Asthma und atopische Dermatitis verfolgen wir zwei Hypothesen: a) allgemeine Transkriptionsregulation aufgrund genetisch bedingter Defekte; b) epigenetische Veränderungen aufgrund der Umweltexposition und deren Interaktion mit dem Immunsystem, insbesondere die epigenetischen Veränderungen, die zu einer Undichtigkeit der Barriere führen. Die epigenetischen Veränderungen der DNA, der Histone und der RNA werden in Patienten mit Asthma, atopische Dermatitis und gesunden Probanden mittels standardisierter molekularbiologischen Methoden und Next-Generation-Sequenzierung untersucht. Neue Moleküle sollen bestimmt und neue Behandlungsmethoden verfolgt werden.

Entwicklung von künstlich hergestelltem 3D-Lungengewebe und 3D-Haut
Zur Untersuchung der zellulären und molekularen Interaktionen der epithelialen Barrierefunktion in der Lunge wird ein human-relevantes in vivo Modell benötigt. Die Entwicklung von künstlich hergestellten 3D-Organen wird die Untersuchung von Zellen und Mediatoren von Entzündungen in Asthma und anderen allergischen Entzündungskrankheiten ermöglichen. Wir planen, unsere bronchialen und dermalen Air-liquid Interface Kulturen auf künstlich hergestellte 3D-Lungenschleimhaut auszubauen. Zur Untersuchung von Pathomechanismen der atopischen Dermatitis haben wir künstlich herstellte 3D-Haut benutzt. Neue Entwicklungen in der regenerativen Medizin und Scaffold Technologie werden es erlauben, robustere 3D-Lungenschleimhaut und 3D-Haut (Epidermis und Dermis) herzustellen. Diese Modelle werden es uns ermöglichen, unsere Forschung in Primärzellen noch mehr getreu der in vivo Situation weiterzuführen und die Remodellierungsaskpekte von Asthma und atopischer Dermatitis zu untersuchen.

Antibody Engineering
Die immunologische Steuerung der Antikörperantwort im Verlauf einer allergischen Reaktion oder während einer Immuntherapie ist eine wichtige Frage. Wir führen Klonierungen von Antikörpergenen (aus sehr wenigen Zellen) und Anschlussexperimente durch, einschließlich Affinitätsmessungen und wollen diese Technologien weiter verbessern. Darüber hinaus werden wir konstante, schwere Ketten von Antikörpern für optimierte Markierungsverfahren mit Fluorophoren verändern, welche in der Assay-Entwicklung für die SIAF Ausgründung Davos Diagnostics AG Anwendung finden.

Evanescent field technology
Wir haben ein Projekt begonnen, um die Typisierung von menschlichen Blutplättchen und Bestimmung von Allo-Antikörpern in Humanplasma zu entwickeln. Dies ist eine Zusammenarbeit mit Davos Diagnostics AG. Unser Ziel ist es Antikörper für die Typisierung zu optimieren und wir planen neue Reagenzien und Reaktionssysteme zur Bestimmung von Allo-Antikörper bis zur Marktreife zu entwickeln.

Verbesserung der Diagnose und Behandlung allergischer Erkrankungen durch Spitzentechnologien
IgE ist das Schlüsselmolekül für die Diagnose und Behandlung allergischer Krankheiten. Bei der Diagnose wird das Vorhandensein von allergen-spezifischem IgE nachgewiesen und therapeutische Interventionen zielen auf die Reduktion der IgE Konzentration sowie auf die Induktion von schützenden Antikörper und T-Zell Antworten. Hauttestungen werden routinemässig eingesetzt um eine Sensibilisierung des Patienten in vivo nachzuweisen, sind aber von der Erfahrung des testenden Arztes abhängig und deshalb schwer zu standardisieren. Der Nachweis von allergen-spezifischem IgE in Serum hingegen ist hoch sensitiv, generiert aber häufig falsch positive Resultate als Folge des Vorhandenseins klinisch irrelevantes IgE gerichtet gegen Zuckerreste vieler Glykoproteine. Beide Verfahren müssen besser standardisiert werden um zuverlässigere Diagnosen stellen zu können. Auf der therapeutischen Seite wäre die Haut eine hervorragende Route um Vakzine zu applizieren, weil dieses Organ reich an Antigen-präsentierenden Zellen ist. Wie auch immer, das grösste Problem dieser Applikationsroute besteht in der reproduzierbaren Permeabilisierung des Stratum Corneum, die natürliche Barriere der Haut.

Standardisierung von Hauttestungen und trans-dermale Applikation von Vakzinen
Wir schlagen vor, eine genaue Lasertechnologie anzuwenden um in der Haut reproduzierbare, standardisierte Mikroporenreihen zu generieren für: Standardisierung von Hauttests und für eine effiziente transdermale Applikation von Vakzinen.

Verbesserung des in vitro-Nachweises von allergen-spezifisches IgE
Hier schlagen wir vor, eine neue Plattformtechnologie basierend auf evanescente Fluorimetire zu entwickeln und anzuwenden. Diese Technologie erlaubt, in Kombination mit spezifischen Inhibitoren, welche irrelevantes gegen Zuckerreste gerichtetes IgE maskieren und dadurch eine genaue Bestimmung des pathologisch relevanten IgE's in Serum ermöglichen.

Patienten-orientierte Forschung und bedeutungsvolle Demonstration von menschlicher in vivo Relevanz der Ergebnisse
Unsere geplanten Experimente haben zum Ziel, die wichtigen Mechanismen zu Prävention und Behandlung allergischer Erkrankungen und Asthma aufzuzeigen. Bei der Erforschung der molekularen und zellulären Mechanismen der Barriereintegrität, Mikrobiome, Immunregulation, Biomarker und biologischen Studien werden wir der Demonstration von menschlicher in vivo Relevanz unserer Ergebnisse höchste Priorität geben, damit diese zur Entwicklung von Präventions- und Behandlungsmöglichkeiten zu Gunsten der Patienten führen können. In den letzten drei Jahren hat sich das SIAF ein grosses Wissen im Verfahren mit Genomik und Proteomik und Erzeugung sowie Organisation von grossen Datenmengen aneignen können. Die direkte Analyse der Transkriptome und der epigenetischen Regulation von Biopsien ohne Kulturen, stellt eine Vorreiterrolle für ein besseres Verständnis der wesentlichen Merkmale für unsere zukünftigen Forschungsaktivitäten dar.

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 Prof. 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 2016
Bereits zum zehnten Mal fand vom 16. bis 19. März 2016 das international ausgeschriebene World Immune Regulation Meeting (WIRM) im Kongresszentrum Davos statt. Rund 600 Wissenschaftler aus 40 verschiedenen Länder trafen sich zu diesem Kongress, um sich über die neuesten Erkenntnisse in der Immunologie auszutauschen und trugen 115 Vorträge und 218 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 4'000 Übernachtungen in den Davoser Hotels und Ferienwohnungen.

Personal
Gegenwärtig beschäftigt das SIAF 45 Mitarbeitende. Davon zählen 41 zum wissenschaftlichen Stab. Derzeit führen am SIAF 14 Doktoranden eine naturwissenschaftliche Doktorarbeit durch. Insgesamt 9 Wissenschafter aus verschiedensten Ländern waren im letzten Jahr zu Gast im SIAF. Eine Administrationsleiterin sowie eine Kongressassistentin, eine 80%- und eine Tagesstelle 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. 15), Beiträge des Kantons Graubünden und der Gemeinde Davos, Beiträge der CK-CARE AG und der Universität Zürich sowie einem Beitrag der Stiftung vormals Bündner Heilstätte Arosa. Die zusätzlichen Ausgaben wurden aus Erträge von zusätzlichen Drittmitteln und des WIRM-Kongresses gedeckt.

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

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

Mein Dank geht vor allem auch an die Stiftung Schweizerisches Forschungsinstitut für Hochgebirgsklima und Medizin (SFI), dessen Stiftungsrat und 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 2016

Report of the director

Prof. Dr. Cezmi A. Akdis

The effects of allergies on health and quality of life have been severe for many patients. 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 and families, allergic diseases and asthma present a very high socioeconomic burden to health care systems with yearly costs of over EUR 200 billions in Europe alone.

The story of the Swiss Institute of Allergy and Asthma Research (SIAF) started in 1907 as the Tuberculosis Research Institute Davos and was founded on the request of Professor Karl Turban, the Davos Doctors' Association and the municipality of Davos. The Swiss Institute of Allergy and Asthma Research (SIAF) was developed as a department of the foundation Swiss Research Institutes for High Altitude Climate and Medicine Davos (SFI) in 1988. SIAF is an affiliated institute of the University of Zurich since 1996 and member of the Life Science Zurich Graduate School since 2009, a joint post graduate education program of the Swiss Federal Institute of Technology and the University of Zurich. SIAF members play leading roles in national and international organizations, such as European Academy of Allergy and Clinical Immunology and in editorial boards and editorships of top Journals in the field of allergy asthma and clinical immunology. At the same time, SIAF fulfills teaching obligations in the University of Zurich and the University of Salzburg. SIAF organizes the international World Immune Regulation Meeting (WIRM) every year in Davos, which is one of the most important meetings in its area in the world.

The research activities at SIAF have been focused on basic research in the field of allergies and asthma to develop approaches for new preventive and curative treatments for patients. Major research aims are to develop curative treatment and prevention of allergies and asthma with a focus on immune tolerance to allergens, allergen-specific immunotherapy, rapid diagnosis and microbiology. Human research has been pursued at the front level with a main emphasis given on patient-relevant research. SIAF has a large impact in the field of allergies and asthma with more than 45'000 citations to its more than 850 publications.

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

In July 2009, the Kühne Foundation has launched the Christine Kühne Center for Allergy Research and Education (CK-CARE), with locations in Davos, Munich and Zurich. The aim of this initiative has been highly qualified and well-connected research work in the field of allergies and education of medical professionals based on recent findings. After a successful external evaluation of the services provided, the initiative has been expanded to the locations of Bonn, Augsburg and St. Gallen and extended in 2014 for another five years. SIAF is playing an essential role in the CK-CARE.
The overriding objective of our workpackage is to understand better the molecular processes of external and internal factors, which play a role in how atopic diseases occur, develop and become chronic, and in their degree of severity. This knowledge is fundamentally important and will lead to the development of better preventive and therapeutic strategies as well as diagnostic biomarkers for atopic diseases. We give top priority to the in vivo relevance of our research results so that new methods of prevention, diagnosis and treatment can be developed. In the reporting period, we primarily addressed barrier disruptions, prevention and treatment of atopic diseases.
We had and will have series of publications in the area with the support of CK-CARE. So far 101 articles were published supported by CK-CARE. We could engage more than 35 scientific co-workers. There were more than 50 academic guests working on the specific projects of CK-CARE in the short term exchange program.

Asthma and allergy lung microbiome
Not too long ago, the lung was considered sterile. However, this is clearly not the case and we are interested in characterizing the lung microbiome of asthma patients and comparing this microbiome to healthy controls. In addition, detailed analysis of lung cellular responses, associated with distinct lung microbiome profiles will be performed. This analysis will include lymphocyte responses, macrophage and dendritic cells, invariant natural killer T cells (iNKT) cells and innate lymphoid cells (iNKT) cells. Novel microbes will be isolated and administered to murine models to determine their effects on lung responses.

Inflammation and obesity
Obesity is associated with an increased risk of many disorders, including asthma. Indeed, increasing body mass index is associated with increasing levels of serum IgE. We are examining the microbiome, inflammatory pathways and metabolic disturbances of obese individuals in order to better understand, at a cellular and molecular level, the biological basis for these aberrant interactions in obese individuals. We are particularly interested in g protein coupled receptors (GPCRs) and their activation by microbiome or dietary-derived ligands.

Regulation of immune response by antigen-specific regulatory and effector memory B cells
Different cytokine-producing human B cell subsets exist in humans and may show different pro-inflammatory, anti-inflammatory as well as immune effector and immune regulatory functions. Functional human B cell subsets show in vivo clonal expansion and may switch cytokine profiles during development of allergen-tolerance, which can be induced during allergen-specific immunotherapy and high dose allergen exposure. Determination of effector and regulatory B cell subsets in addition to T cell subsets by multicolor flow cytometry can be used for immune monitoring of inflammatory diseases.
We aim to identify novel human effector and regulatory B cell subsets, their functional phenotypes, in vivo skew between these subsets, demonstrate the role of these cells in immune tolerance to allergens, discover and characterize their subset specific novel cell

surface and secreted molecules.

Breaking of allergen-specific tolerance by human rhinovirus infections

The identification of infection-related molecular mechanisms that break allergen tolerance by overcoming the suppressive function of Treg cells is one of the main focuses of our research. Studies on allergen-specific immunotherapy of bee venom allergy and natural high dose allergen exposure in bee keepers suggest that a T cell switch from Th2 cells to regulatory/suppressor T cells may occur in vivo. Whether a memory Treg cell can turn into Th2, Th1 and Th17 cells in virus-infected individuals and the possibility that Treg cells may acquire a restricted suppressive property by selective silencing of activated effector genes during an anti-viral response. We are currently identifying HRV infection-related molecular mechanisms that stimulate effector and regulatory memory B cell subsets by using both systems biology and a targeted approach. Our preliminary data demonstrated that HRV can directly stimulate and also can infect human B cells. In depth study of the role of HRV-activated B cells and particularly Breg cells and breaking of allergen tolerance will help to better understand asthma pathogenesis and lead to the design of effective drugs targeting these cells.

Dysregulated epithelial barrier function in asthma, atopic dermatitis, allergic rhinitis and chronic rhinosinusisitis

Epithelial barrier function of bronchial epithelial cells in the asthmatic lung, sinus epithelial cells in chronic rhinosinusitis patients as well as keratinocytes in the skin of atopic dermatitis patients have been recently demonstrated to be defective in several studies including ours. When the barrier integrity is disturbed in patients, allergens, bacterial toxins and other particles are able to penetrate the epithelium, where they may activate the immune system leading to severe chronic inflammation. We had many major contributions in the area and we aim to clarify several essential aspects that play a role in the dysregulation of bronchial epithelial barrier in asthma and atopic dermatitis. We have investigated the role of innate immune response factors, particularly NOD-like receptors, RIG-1-like receptors, AIM2-like receptors. We will investigate the regulation of the expression of tight junction molecules, the role of T cell subsets, B cell subsets, innate lymphoid cell subsets and their major cytokines to barrier integrity, both in air-liquid interface cultures of human primary epithelial cells as well as in various mouse models. Novel diagnostic methods to detect barrier leakiness versus integrity and novel treatment modalities are extensively being investigated.

Epigenetic regulation of bronchial epithelial leakiness in asthma

In the follow up to determine molecular mechanisms of our interesting observation of the epithelial leakiness in asthma and atopic dermatitis, two hypothesis can be generated, such as a) general transcriptional regulation due to inherited genetic defects, b) epigenetic changes due to environment exposure and interaction with the immune system that continue during passages. Particularly, the epigenetic changes that lead to leaky barrier are being addressed in this section. The epigenetic modifications of DNA, histones, and RNA are being distinguished between asthmatic, atopic dermatitis and healthy epithelium using both standard molecular biology techniques and next-generation whole-genome sequencing approach. Novel molecules have been identified and novel treatment modalities are being pursued.

Development of human artificial 3D lung and skin

A human relevant in vivo model is needed to investigate cellular and molecular interactions in bronchial epithelial barrier function. The development of human artificial 3D organs will enable to investigate cells and mediators of inflammation in asthma and other allergic inflammatory diseases. We plan to expand our bronchial epithelial and skin air-liquid interface cultures to artificial 3D bronchial mucosa. We have used artificial 3D skins to investigate pathomechanisms of atopic dermatitis. Novel developments in regenerative medicine and scaffold technology will enable the production of more robust 3 dimensional bronchial mucosa and submucosa and skin (epidermis and dermis). These models will enable us to perform our research in primary cells in a way, which is more close to the in vivo situation and also to study remodeling aspects of asthma and AD.

Antibody engineering

The immunological biasing of the antibody response in the course of an allergic response or during immunotherapy requests for deeper characterization of this phenomenon. We established antibody rescue cloning (from very few cells) and downstream experiments, including affinity measurements to the antigen, these technologies will be further improved. Furthermore, we will engineer antibody constant heavy chains for optimized labeling procedures with fluorophors for the usage in assay development for the SIAF spin-off company DavosDiagnostics AG.

Evanescent field technology

We have an ongoing project to establish the typing of human blood platelets and determination of allo-antibodies in human plasma. This research has been performed through a a collaboration with DavosDiagnostics AG. We aim to use optimized antibodies for the detection and we will develop novel reagents for the determination of several diagnostic tools.

Improving diagnosis and treatment of allergic diseases by novel technologies

IgE is the key molecule for both, diagnosis and treatment of allergic diseases. While allergy diagnosis aims at demonstrating the presence of allergen-specific IgE, therapeutic interventions aim at reducing IgE levels and inducing protective antibody and T cell responses. Skin tests are routinely used to demonstrate allergen sensitization in vivo but are strongly dependant on the tester's skill and therefore hard to standardize, while serologic determinations of allergen-specific serum IgE may generate false positive results due to the presence of clinically irrelevant IgE directed against carbohydrate determinants. Both procedures need to be improved for more reliable diagnoses. On the therapeutic site the skin would be a potent route for vaccination due to the high density of antigen presenting cells present. However, the main problem using this route of application is to reproducibly render permeable the stratum corneum, the practically impermeable natural barrier of the skin.

We propose to use precise laser technology to create reproducible arrays of aqueous micro-pores on the skin for the standardization of skin tests and for an efficient trans-dermal delivery of allergy vaccines.
In addition, we propose to develop a novel platform technology based on evanescence fluorimetry, which allows background free determinations of antibody levels in combination with specific inhibitors that avoid the interference of clinically irrelevant carbohydrate-specific IgE with pathologic allergen-specific IgE.

Patient oriented research and high emphasis on demonstration of human in vivo relevance of the findings

Our planned experiments aim to demonstrate essential mechanisms in the prevention and treatment of allergic diseases and asthma. In the investigation of molecular and cellular mechanisms of barrier integrity, microbiome, immune regulation, biomarkers and biologicals studies, we will give a very high priority to the demonstration of the human in vivo relevance of our findings so that it may lead to development of a prevention and treatment modality for patients. Our research always had a priority for direct analysis of the relevant changes or differences in the affected tissues. The direct transcriptome and further confirmation of the expression profiles are proposed to be followed by the demonstration of in vivo relevance of the protein expression of new genes. We will be able to demonstrate which genes are expressed in which cells by multicolor immune histology and confocal microscopy. Direct analyses of biopsies, mouse models and three-dimensional tissues will be given a very high priority to demonstrate the human in vivo status. There is substantial requirement to develop human artificial 3D organs to investigate cells and mediators of inflammation in asthma and other allergic inflammatory diseases. During the last three years our institute has gained a huge knowhow in multiple omics and generation and expansion of big data. Direct analysis of transcriptome and epigenetic regulation from biopsies without any culture in a significant number of these samples represent a very front approach to better understand essential features of our future research activities.

The work at SIAF during the last year generated a total of 58 scientific publications (exclusive abstracts), which appeared in peer-reviewed international journals. The total average of impact factor is 7.267. In 2015, SIAF reached a total impact factor amounting to 363.361 and 28 abstracts were presented at different congresses. Members of SIAF were invited to 60 different seminars or lectures at international congresses, universities and other research institutions and chaired 41 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. In 2015, Prof. CA. Akdis and Dr. ZK. Ballas have been chosen to serve as the next JACI Co-Editors-in-Chief. Having a European-based Editor-in-Chief in addition to a U.S.-based Editor-in-Chief is a historic first for the journal and reflects an increased international appeal demonstrating that JACI is a global journal that should have a global impact on all aspects of our specialty.

Organization of WIRM-X

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 tenth time on 16-19 March 2016 at the Congress Center Davos. The congress was focused on “Development and Maintenance of Immune Tolerance and Role of Tissues in Immune Regulation” with approximately 600 participants from 40 countries with 115 presentations and 218 abstracts.

Acknowledgements

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

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

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

Davos, June 2015

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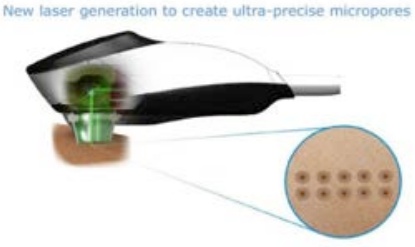
Molecular Allergology

Prof. Dr. Reto Crameri

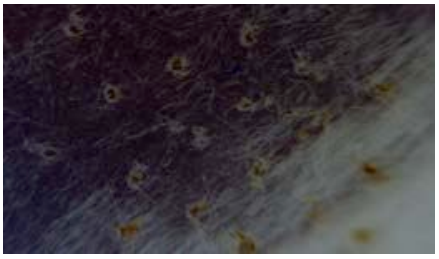
The activities of the Molecular Allergology Group at SIAF during the report period were focused on the projects "Improving diagnosis and treatment of allergic diseases by avant-garde technologies" founded by the Swiss National Science foundation, "Allergy vaccination using novel drug delivery routes mediated via nanotechnology (ERANET EuroNanoMed2, NANOASIT II), "Pet ownership and matchmaking by allergen profiles in suitable breeds" (DIAPET, EUROSTARS E!8599) and the project "Rapid in vitro diagnosis for platelets" in collaboration with the Vaccine Development Group and Davos Diagnostics supported by the CTI. All these projects are thematically closely related and represent a consequent continuation and extension of our research.
The core methods used were focused on the EVA-technology developed at the SIAF spin-off Davos Diagnostics AG described in the last report, and on the laser-assisted intradermal delivery of vaccines. Of course both technologies are not limited to applications on the field of allergy and asthma and can be used for the diagnosis a wide range of diseases, and for the intradermal delivery of any kind of vaccines and small molecules, respectively.

Laser-assisted intradermal delivery of vaccines
The Precise Laser Epidermal System (P.L.E.A.S.E) developed by Pantec Biosolutions has the capability to create micropores in the stratum corneum - the superficial impermeable layer of the skin - and the epidermis (Figure 1), allowing topical delivery not only of small molecules like drugs but also of antibodies or antigens with a molecular weight > than 150 kDa.

Figure 1: The P.L.E.A.S.E device (a) and its use (b)



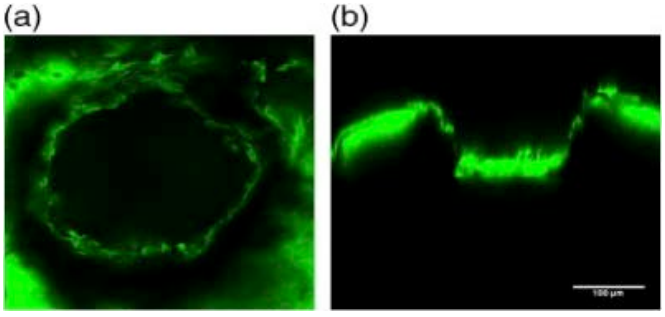
a) The please device



b) Micropore arrays created in mouse skin

Depending of the energy applied, user-defined arrays of almost identical, fast healing cylindrical pores with a diameter around 150-200 µm and a pore depth ranging from a few µm to 200 µm can be created in a few seconds (Figure 2). The unit functions with a predetermined set of operating parameters (pulse with, energy density, and repetition rate) warrant precise and fast microporation of the skin without carbonization and thermal damage.

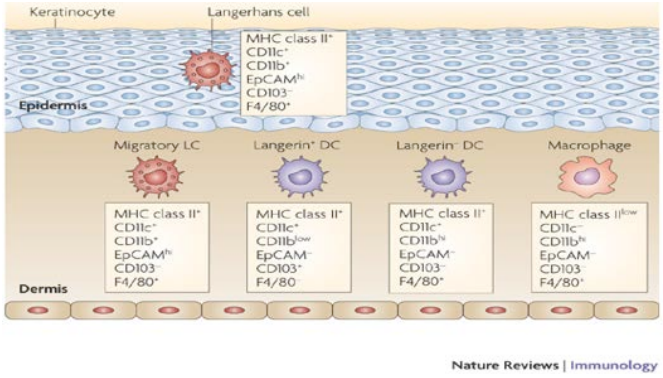
Figure 2: Confocal images showing the distribution of FITC fluorescence in the (a) XY- and (b) XZ-planes following P.L.E.A.S.E.® poration of full thickness porcine skin (courtesy of Dr. Y.N. Kalia)



The dramatically increased skin permeability generated by the micropores enables specific forms of topically applied substances to penetrate much faster and more deeply into the targeted skin layer. By sequential fractional ablation the device allows the unique opportunity to access different skin layers and, therefore, to target different cell type subsets such as Langerhans cells or dermal dendritic cells present in different layers of dermis and epidermis (Figure 3).

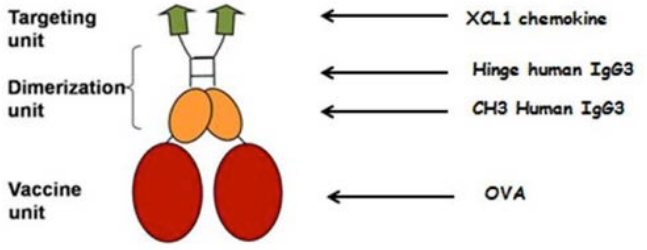
Targeting different subsets of dendritic cells in the skin
The skin (Figure 3) represents the first mechanical barrier protecting the body from environmental exposure and contains different subsets of potent antigen-presenting cells expressing different surface markers.

Figure 3: Anatomy of human skin and distribution of antigen presenting cells. Langerhans cells are mainly present in the epidermis, whereas different subsets of dendritic cells, including XCR1+ DC's are located in the dermis. (Merad M, Ginhoux F, Collin M. Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells. Nature Reviews Immunology; Dec. 2008; 8, 935-947.)



Dendritic cells (DCs) expressing the XCR1 chemokine receptor are located in the dermis and excel in presentation of extracellular antigens to CD8+ T cells. Studies aiming at harnessing such cross-presentation potential relied on intravenous injection of antigens conjugated to XCL1 – the ligand of XCR1 - or to antibodies specific for XCR1+ DCs. Due to its high DC content, including XCR1+ DCs, the skin dermis is an attractive site for vaccine administration. To assess the efficacy of creating laser-generated micropores through the epidermis for targeting dermal XCR1+ DCs we engineered a model homodimeric vaccibody (Figure 4) to be uses in a murine tumor model.

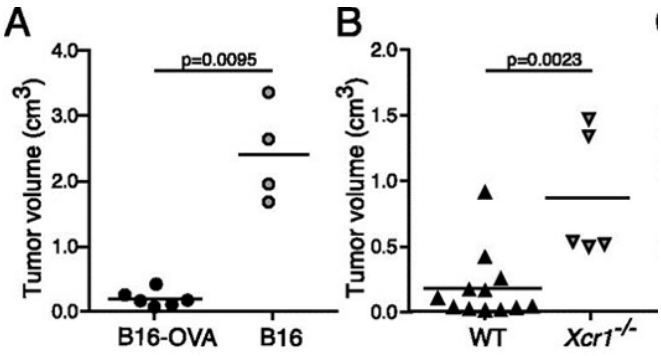
Figure 4 : Homodimeric chimeric vaccibody consisting of the XCL1 chemokine, a dimerization unit derived from the hinge and CHZ3 domain of human IgG3, and Ovalbumin as antigen.



We used B16 (B16F10), a highly aggressive metastatic and poorly immunogenic melanoma and its ovalbumin (OVA) expressing variant (B16-OVA), to investigate the in vivo anti-tumor efficacy of laser-assisted dermal delivery of OVA-containing vaccibodies without any adjuvant.

B6 (WT) mice were subcutaneously inoculated with B16-OVA or B16 melanoma cells, and immunized 3 days later with XCL1-OVA vaccibodies using laser assisted dermal delivery. 11 days after immunization the volume of the tumor developing in each mouse was determined. As shown in Figure 5 A mice immunized with B16-OVA vaccibodies were not able to control the growth of B16 melanoma but fully controlled its OVA-expressing variant. To demonstrate the dependence of tumor growth control on the expression of XCR1, B6 (WT) and Xcr1-/- mice were immunized as described above. The results (Figure 5B) demonstrate that tumor growth control is dependent on the expression of XCR1.

Figure 5: A) Tumor growth in each single mouse inoculated with B16 or B16-OVA expressing melanoma cells followed by immunization with XLR1-OVA vaccibodies. B) Lack of tumor control in Xcr1--knock-out mice treated as in A).



In conclusion, a single laser-assisted intradermal local delivery of a model antigen fused to the XCLC1 chemokine in an adjuvant-free setting is sufficient to target dermal XCR1+ dendritic cells and harness their cross-presentation capacity to induce a systemic protection against melanoma tumor growth in mice. Therefore local, needle-free intradermal delivery of antigens targeting ermal XCR1+ dendritic cells represent a promising way for the development of potent vacines. The existence in human of functionally equivalent XCR1+ dermal DCs should permit the translation of topic, needle-free intradermal delivery of antigens targeting XCR1+ DCs to human cutaneous vaccinations.

Currently, we are developing an array of XCR1 targeting vaccibodies fused to different allergens to evaluate the potential of laser-assisted intradermal delivery of allergens for the control of allergic and asthmatic diseases.

Structural aspects of fungal allergens.

Crameri R. Seminars Immunol Immunopathol. 37(2), 117-121, 2015.

Despite the increasing number of solved crystal structures of allergens, the key question why some proteins are allergenic and the vast majority is 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. 135(5), 1378-1380, 2015 (no Asstract available).

Laser-assisted intradermal delivery of adjuvant-free vaccines targeting XCR1+ dendritic cells induces potent antitumoral responses.
Terhorst D, Fossum E, Baranska A, Tamoutounour S, Malosse C, Garbani M, Braun R, Lechat E, Crameri R, Bogen B, Henri S, Malissen B. J Immunol. 194(12), 5895-5902, 2015.
The development of vaccines inducing efficient CD8(+) T cell responses is the focus of intense research. Dendritic cells (DCs) expressing the XCR1 chemokine receptor, also known as CD103(+) or CD8α(+) DCs, excel in the presentation of extracellular Ags to CD8(+) T cells. Because of its high numbers of DCs, including XCR1(+) DCs, the skin dermis is an attractive site for vaccine administration. By creating laser-generated micropores through the epidermis, we targeted a model protein Ag fused to XCL1, the ligand of XCR1, to dermal XCR1(+) DCs and induced Ag-specific CD8(+) and CD4(+) T cell responses. Efficient immunization required the emigration of XCR1(+) dermal DCs to draining lymph nodes and occurred irrespective of TLR signaling. Moreover, a single intradermal immunization protected mice against melanoma tumor growth in prophylactic and therapeutic settings, in the absence of exogenous adjuvant. The mild inflammatory milieu created in the dermis by skin laser microporation itself most likely favored the development of potent T cell responses in the absence of exogenous adjuvants. The existence of functionally equivalent XCR1(+) dermal DCs in humans should permit the translation of laser-assisted intradermal delivery of a tumor-specific vaccine targeting XCR1(+) DCs to human cancer immunotherapy. Moreover, considering that the use of adjuvants in vaccines is often associated with safety issues, the possibility of inducing protective responses against melanoma tumor growth independently of the administration of exogenous adjuvants should facilitate the development of safer vaccines.

Global Allergy Forum and 3rd Davos Declaration 2015: Atopic dermatitis/Eczema: challenges and opportunities toward precision medicine.
T. Bieber, C. Akdis, R. Lauener, C. Traidl-Hoffmann, P. Schmid-Grendelmeier, G. Schäppi, J.-P. Allam, C. Apfelbacher, M. Augustin, L. Beck, T. Biedermann, C. Braun-Fahrländer, F. T. Chew, T. Clavel, R. Crameri, U. Darsow, M. Deleuran, D. Dittlein, H.-W. Duchna, L. Eichenfeld, K. Eyerich, R. Frei, C. Gelmetti, U. Gieler, S. Gilles, M. Glatz, K. Grando, J. Green, J. Gutermuth, E. Guttman-Yassky, J. Hanifin, D. Hijnen, W. Hoetzenecker, A. Irvine, A. Kalweit, N. Katoh, E. Knol, H. Koren, M. Möhrenschlager, D. Münch, N. Novak, L. O'Mahony, A. S. Paller, C. Rhyner, C. Roduit, K. Schiesser, J. Schröder, D. Simon, H.-U. Simon, M. Sokolowska, P. Spuls, J.-F. Stalder, D. Straub, Z. Szalai, A. Taieb, R. Takaoka, G. Todd, A. Todorova, C. Vestergaard, T. Werfel, A. Wollenberg and J. Ring. Allergy 2016:71(5);588-592 (no Abstract available).

IgE Sensitization Profiles differ between Adult Patients with Severe and Moderate Atopic Dermatitis.
Mittermann I, Wikberg G, Johansson C, Lupinek C, Lundberg L, Crameri R, Valenta R, Scheynius, A. PLOS One 2016 (in press).
Background: Atopic dermatitis (AD) is a complex chronic inflammatory disease where allergens can act as specific triggering factors.
Aim: To characterize the specificities of IgE-reactivity in patients with AD to a broad panel of exogenous allergens including microbial and human antigens.
Methodology: Adult patients with AD were grouped according to the SCORAD index, into severe (n=53) and moderate AD (n=126). As controls 43 patients were included with seborrhoeic eczema and 97 individuals without history of allergy or skin diseases. Specific IgE reactivity was assessed in plasma using Phadiatop®, ImmunoCapTM, micro-arrayed allergens, dot-blotted recombinant Malassezia sympodialis allergens, and immune-blotted microbial and human proteins.
Results: IgE reactivity was detected in 92% of patients with severe and 83% of patients with moderate AD. Sensitization to cat allergens occurred most frequently, followed by sensitization to birch pollen, grass pollen, and to the skin commensal yeast M. sympodialis. Patients with severe AD showed a significantly higher frequency of IgE reactivity to allergens like cat (rFel d 1) and house dust mite (rDer p 4 and 10), to Staphylococcus aureus, M. sympodialis, and to human antigens. In contrast, there were no significant differences in the frequencies of IgE reactivity to the grass pollen allergens rPhl p 1, 2, 5b, and 6 between the two AD groups. Furthermore the IgE reactivity profile of patients with severe AD was more spread towards several different allergen molecules as compared to patients with moderate AD.
Conclusion: The more broadly spread sensitization pattern and higher frequency of IgE reactivity observed in severe AD patients may be responsible for a more frequent boosting of the allergic immune response in these patients and explain why they suffer from more severe disease.

Davos, June 2016

Prof. Dr. Cezmi A. Akdis

Epithelial cells in the skin and airways constitute the first line barrier to prevent penetration of environmental agents such as allergens and pollutants to the inner tissues, and they mount an innate immune response against infectious agents. The epithelial barrier is predominantly formed by tight junctions (TJs) located at the most apical part of the intracellular junctional complexes between the neighboring epithelial cells. They consist of transmembrane proteins: claudins, occludin, junctional adhesion molecules (JAMs), peripheral membrane proteins e.g. zonula occludens (ZO-1, ZO-2, ZO-3) and cingulin, gap and adherens junctions, which allow the transmembrane proteins to organize in the membrane and attach to the cytoskeleton. First observation of differences in TJ structures in asthma were performed by electron microscopy in 1988 showing that varying degrees of TJ abnormalities were observed in bronchial epithelium of normal, bronchitic and asthmatic subjects. Recent studies have shown that barrier function of the epithelium is impaired in various inflammatory diseases including asthma, atopic dermatitis and chronic rhinosinusitis. Disruption of the bronchial epithelial TJ integrity leads to the loss of barrier function, enabling passage of pro-inflammatory and tissue-damaging agents such as allergens and toxins from the lumen into the airway parenchyma. 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 recently demonstrated to be defective. When the barrier integrity is disturbed in patients, allergens, bacterial toxins and other particles are able to penetrate the epithelium, where they may activate the immune system leading to severe chronic inflammation. Epithelial TJs 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, TJs can be considered as gatekeepers that could contribute both to aggravation of inflammation-related tissue damage or resolution of inflammation via drainage. Although barrier leakiness has been detected as a phenomenon in asthma, its pathophysiological mechanisms have not been demonstrated so far.

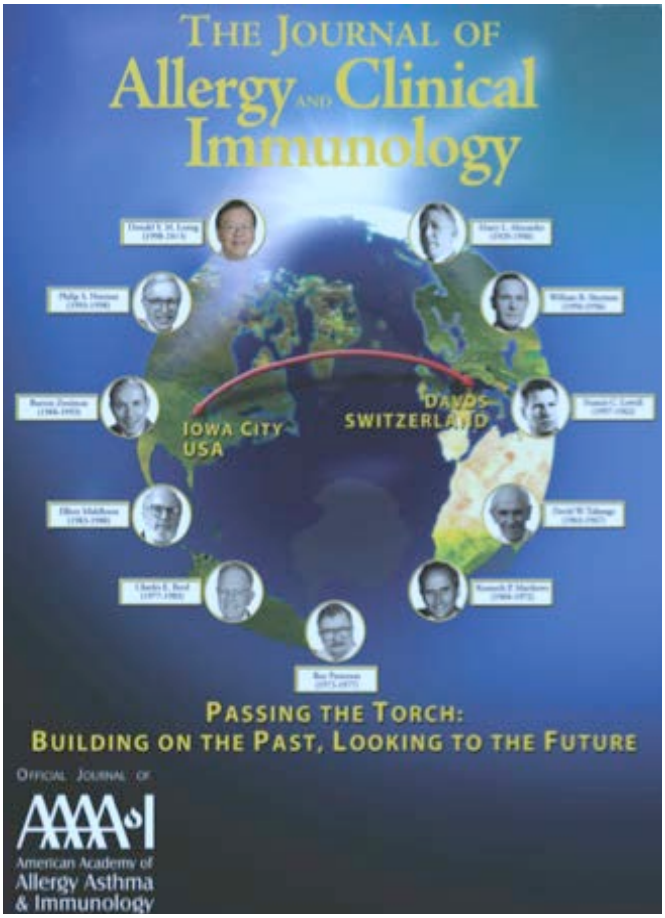


Figure. Davos in the world map on the cover of the inaugural issue of January 2016 that Cezmi Akdis took over the Co-Editor-in-Chief position.

A small 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. 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, containing molecules activating pattern recognition receptors 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 ALI epithelial cells cultures from the asthmatic bronchi. However the impact of these changes on the cellular composition of airway and skin inflammation in vivo or the regulation of the epithelial TJs proteins expression remain to be extensively analyzed.

CpG-DNA enhances the tight junction integrity of the bronchial epithelial cell barrier.
Kubo T, Wawrzyniak P, Morita H, Sugita K, Wanke K, Kast JI, Altunbulakli C, Rückert B, Jakiela B, Sanak M, Akdis M, Akdis CA.
J Allergy Clin Immunol. 2015 Nov;136(5):1413-6.e1-8.
Bronchial epithelial cells are at the forefront of tissue defense and

the innate immune response, preventing invasion of tissues as a physical barrier. Tight junctions (TJs) located at the most apical region of the lateral cell membrane seal the epithelium and form an essential part of the barrier between inner tissues and the external environment. In the present study we demonstrated that CpG-DNA improved and restored human bronchial barrier integrity through increased expression of TJ-related molecules and their proper allocation. Our data suggest that administration of CpG-DNA could be a useful intervention and demonstrate an additional explanation for the hygiene hypothesis in both the prevention and treatment of asthma by restoring impaired epithelial barrier.

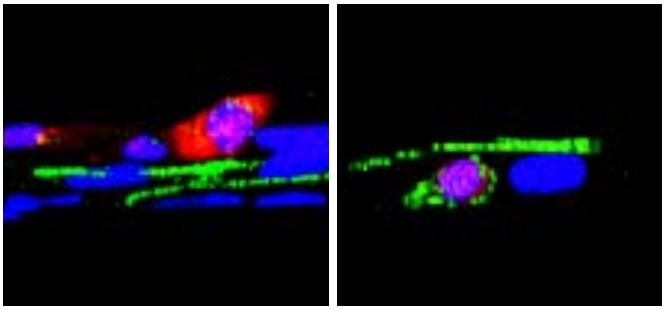


Figure: A) An immune system cell sits over the epithelial tight junctions after it is added to air-liquid interface cultures. B) The cell migrates towards the tight junctions after 24h and has also expressed tight junction molecules.

The expression of gingival epithelial junctions in response to subgingival biofilms.
Belibasakis GN, Kast JI, Thurnheer T, Akdis CA, Bostanci N.
Virulence. 2015;6(7):704-9.
Periodontitis is an infectious inflammatory disease that destroys the tooth-supporting tissues. It is caused by the formation of subgingival biofilms on the surface of the tooth. Characteristic bacteria associated with subgingival biofilms are the Gram-negative anaerobes Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola, collectively known as the „red complex“ species. Inter-epithelial junctions ensure the barrier integrity of the gingival epithelium. This may however be disrupted by the biofilm challenge. The aim of this in vitro study was to investigate the effect of subgingival biofilms on the expression of inter-epithelial junctions by gingival epithelia, and evaluate the relative role of the red complex. Multilayered human gingival epithelial cultures were challenged with a 10-species in vitro subgingival biofilm model, or its variant without the red complex, for 3 h and 24 h. A low-density array microfluidic card platform was then used for analyzing the expression of 62 genes encoding for tight junctions, gap junctions, adherens junctions, and desmosomes. Although there was a limited effect of the biofilms on the expression of tight, adherents and gap junctions, the expression of a number of desmosomal components was affected. In particular, Desmoglein-1 displayed a limited and transient up-regulation in response to the biofilm. In contrast, Desmocollin-2, Desmoplakin and Plakoglobin were down-regulated equally by both biofilm variants, after 24 h. In conclusion, this subgingival biofilm model may down-regulate selected desmosomal junctions in the gingival epithelium, irrespective of the presence of the „red complex.“ In turn, this could compromise the structural integrity of the gingival tissue, favoring bacterial invasion and chronic infection.

Impaired barrier function in patients with house dust mite-induced allergic rhinitis is accompanied by decreased occludin and zonula occludens-1 expression.
Steelant B, Farré R, Wawrzyniak P, Belmans J, Dekimpe E, Vanheel H, Van Gerven L, Kortekaas Krohn I, Bullens DM, Ceuppens JL, Akdis CA, Boeckxstaens G, Seys SF, Hellings PW.
J Allergy Clin Immunol. 2016 Apr;137(4):1043-1053
Tight junction (TJ) defects have recently been associated with asthma and chronic rhinosinusitis. The expression, function, and regulation of nasal epithelial TJs remain unknown in patients with allergic rhinitis (AR).
We investigated the expression, function, and regulation of TJs in the nasal epithelium of patients with house dust mite (HDM)-induced AR and in an HDM-induced murine model of allergic airway disease. Air-liquid interface cultures of primary nasal epithelial cells of control subjects and patients with HDM-induced AR were used for measuring transepithelial resistance and passage to fluorescein isothiocyanate-dextran 4 kDa (FD4). Ex vivo transtissue resistance and FD4 permeability of nasal mucosal explants were measured. TJ expression was evaluated by using real-time quantitative PCR and immunofluorescence. In addition, the effects of IL-4, IFN-γ, and fluticasone propionate (FP) on nasal epithelial cells were investigated in vitro. An HDM murine model was used to study the effects of allergic inflammation and FP treatment on transmucosal passage of FD4 in vivo. A decreased resistance in vitro and ex vivo was found in patients with HDM-induced AR, with increased FD4 permeability and reduced occludin and zonula occludens-1 expression. AR symptoms correlated inversely with resistance in patients with HDM-induced AR. In vitro IL-4 decreased transepithelial resistance and increased FD4 permeability, whereas IFN-γ had no effect. FP prevented IL-4-induced barrier dysfunction in vitro. In an HDM murine model FP prevented the allergen-induced increased mucosal permeability. In conclusion, in addition to asthma, atopic dermatitis and chronic rhinosinusitis, this study demonstrates impaired nasal epithelial barrier function in patients with HDM-induced AR, with lower occludin and zonula occludens-1 expression. IL-4 disrupted epithelial integrity in vitro, and FP restored barrier function. Better understanding of nasal barrier regulation might lead to a better understanding and treatment of AR.

An interleukin-33-mast cell-interleukin-2 axis suppresses papain-induced allergic inflammation by promoting regulatory T cell numbers.
Morita H, Arae K, Unno H, 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, Galli SJ, Koyasu S, Kubo M, Sudo K, Saito H, Matsumoto K, Nakae S.
Immunity. 2015 Jul 21;43(1):175-86.

House dust mite-derived proteases contribute to allergic disorders in part by disrupting epithelial barrier function. Interleukin-33 (IL-33),

produced by lung cells after exposure to protease allergens, can induce innate-type airway eosinophilia by activating natural helper (NH) cells, a member of group 2 innate lymphoid cells (ILC2), to secrete Th2 type-cytokines. Because IL-33 also can induce mast cells (MCs) to secrete Th2 type-cytokines MCs are thought to co-operate with NH cells in enhancing protease or IL-33-mediated innate-type airway eosinophilia. However, we found that MC-deficient Kit(W-sh/W-sh) mice exhibited exacerbated protease-induced lung inflammation associated with reduced numbers of regulatory T (Treg) cells. Moreover, IL-2 produced by IL-33-stimulated MCs promoted expansion of numbers of Treg cells, thereby suppressing development of papain- or IL-33-induced airway eosinophilia. We have thus identified a unique anti-inflammatory pathway that can limit induction of innate-type allergic airway inflammation mediated by NH cells.

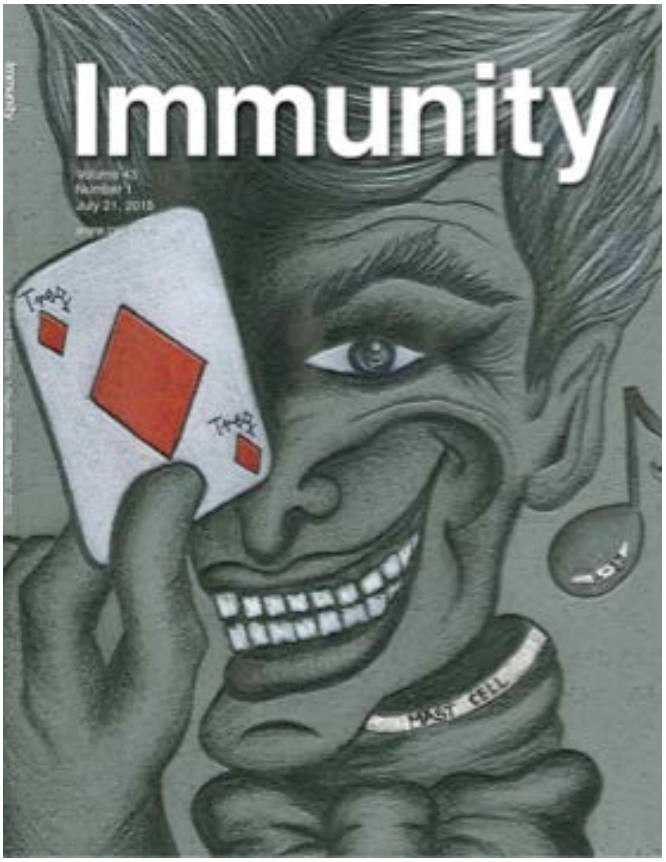


Figure. September 2015 cover of Immunity, developed by Anna Globinska (SIAF), depicting the interrelationship of mast cells, Treg cells and IL-33.

International consensus on allergy immunotherapy.
Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, Cox L, Demoly P, Frew AJ, O'Hehir R, Kleine-Tebbe J, Muraro A, Lack G, Larenas D, Levin M, Nelson H, Pawankar R, Pfaar O, van Ree R, Sampson H, Santos AF, Du Toit G, Werfel T, Gerth van Wijk R, Zhang L, Akdis CA.
J Allergy Clin Immunol. 2015 Sep;136(3):556-68.
Allergen immunotherapy (AIT) has been used to treat allergic disease since the early 1900s. Despite numerous clinical trials and meta-analyses proving AIT efficacious, it remains underused and is estimated to be used in less than 10% of patients with allergic rhinitis or asthma worldwide. In addition, there are large differences between regions, which are not only due to socioeconomic status. There is practically no controversy about the use of AIT in the treatment of allergic rhinitis and allergic asthma, but for atopic dermatitis or food allergy, the indications for AIT are not well defined. The elaboration of a wider consensus is of utmost importance because AIT is the only treatment that can change the course of allergic disease by preventing the development of asthma and new allergen sensitizations and by inducing allergen-specific immune tolerance. Safer and more effective AIT strategies are being continuously developed both through elaboration of new allergen preparations and adjuvants and alternate routes of administration. A number of guidelines, consensus documents, or both are available on both the international and national levels. The international community of allergy specialists recognizes the need to develop a comprehensive consensus report to harmonize, disseminate, and implement the best AIT practice. Consequently, the International Collaboration in Asthma, Allergy and Immunology, formed by the European Academy of Allergy and Clinical Immunology; the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the World Allergy Organization, has decided to issue an international consensus on AIT.

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.

Davos, June 2016

Immunodermatology

Prof. Dr. Mübeccel Akdis

Mechanisms of allergen-specific immunotherapy

Induction of immune tolerance has become a prime target for prevention and treatment for many diseases that involve dysregulation of the immune system, including asthma, allergy, autoimmunity, cancer, organ transplantation, chronic infections, and infertility. Immune tolerance induction has achieved varying success in these different areas, with allergen immunotherapy (AIT) being the one of the most established. AIT is routinely applied in the clinic either subcutaneously (SCIT) or sublingually (SLIT) and is suitable for both children and adults for a variety of allergens, such as pollen, cat and dog, house dust mite, and venom. AIT affects symptoms of allergic inflammation but also has been documented to modify disease pathology long-term, resulting in less drug usage, decreased disease severity, long-term curative effect after stopping the treatment, and prevention of additional allergen sensitization. Although disease-modifying effects are essential, patient nonadherence to long-term medication regimens is a common challenge in AIT. Indeed, 55 to 82% of the patients on SLIT and 13 to 89% on SCIT have shown to be noncompliant. Increasing safety while maintaining or even augmenting efficiency is the main goal of research in vaccine development and drives efforts of improving treatment schemes in AIT.

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.

Induction of allergen-specific IgG4 is a hallmark of successful peripheral tolerance induction, as observed in allergen SIT. Our findings demonstrate that major bee venom allergen 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 cells showed higher IL-10 secretion compared to 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 compared to bee venom allergic subjects. 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. Plasmid-driven IL-10 transfection was performed to reveal the role of IL-10 on the phenotype and functions of B cells. IL-10 overexpression was sufficient for acquisition of a notable immunoregulatory phenotype in B cells. In conjunction with secreted IL-10, these B cells further extend their immunosuppressive functions on both innate and adaptive immune responses. These findings demonstrate 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.

Th22 cells in humans

Adaptive immune responses mediated by CD4+ T cells are necessary to eliminate viral, fungal or bacterial infections. They activate other immune cells by releasing T-cell cytokines, assist B cells to produce antibodies and regulate the immune system and tissue cells. CD4+ T cells can be characterized according to their cytokine production patterns. Although new subsets of T helper cells were described during the last decade, including Th17 and Th22 cells. There is still an ongoing debate and no clear distinction between Th17 and Th22 cells in humans, because the main cytokine of Th22 cells, IL-22, can be also produced by Th17 cells. Most of the confusion in the assigning IL-22 as Th17 rather than Th22 cytokine comes from discrepancy between mouse and human data. Among mouse T helper subsets, Th17 cells are the major source of IL-22 and IL-22 is named as Th17 cytokine. In contrast, IL-22 production by human cells does not correlate with either RORγt or IL-17A and only 10–18% of IL-22-producing T cells in blood co-express IL-17A.

There is no consensus on the functions of single- IL-17 or IL-22 producing cells or IL-17A/IL-22-co-producing cells so far. One of the factors that may determinate the pro-inflammatory vs protective outcome of IL-22 action is the presence of IL-17A. For example, in the bleomycin-induced acute airway inflammation model in mice, where Th17 cells co-produce IL-17A and IL-22, the disease is ameliorated in anti-IL-22-treated WT mice or IL-22-/- mice. Additionally, IL17-A-/- knockout mice are protected from airway inflammation, suggesting that IL-17A synergizes with IL-22 in this model. These studies explain why it is important to understand the mechanisms of regulation of the production of both cytokines and the effects of single cytokine-producing vs IL-17A- and IL-22-co-producing cells.

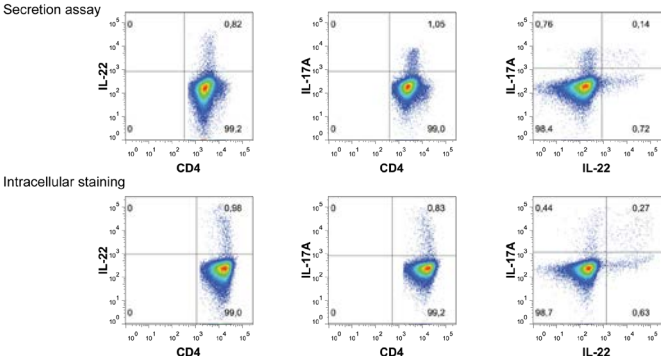


Figure 1: Comparison of cytokine production detected by secretion assays and intracellular staining.

We have recently developed a combined IL-17A/IL-22 secretion assay allowing to purify and characterize single IL-22-producing-Th22 cells, IL-17A-producing-Th17 cells and IL-22, IL-17A-co-producing Th17/Th22 cells.

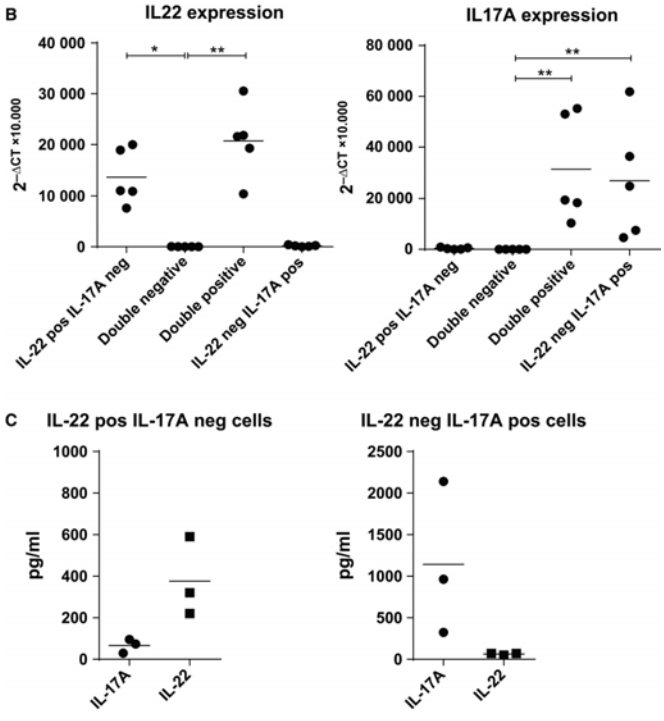


Figure 2: A novel, dual cytokine-secretion assay for the purification of human Th22 cells that do not co-produce IL-17A.

This method is now expected to improve our understanding of the physiological and pathogenic functions of cells co-producing cytokines or producing them individually in various diseases and can be used to identify other cell subsets co-expressing major cytokines.

Th22 cells are involved in the regulation of immune responses and epidermal remodeling in atopic dermatitis (AD). High numbers of skin-homing IL-22-positive cells are characteristic to adult patients and in severe AD. We analyzed the expression of miRNAs in IL-22-positive T cells and peripheral blood mononuclear cells (PBMCs) from patients with asthma and AD. We demonstrate increased expression of miR-323-3p in IL-22/IL-17-producing T cells, its capacity to suppress STAT3 mRNA and multiple factors from the TGF-β pathway, as well as IL-22 production by T cells. In addition, we report increased expression of miR-323-3p in PBMCs from patients with asthma and reverse correlation between miR-323-3p expression and IL-22 protein levels in PBMCs cultured in T-cell growth conditions.

Breaking of allergen-specific tolerance by human rhinovirus infections

Respiratory infections with human rhinoviruses (HRV) pose severe health risks for patients with allergies and asthma, and represent the leading cause for their exacerbations. Respiratory viral infections negatively influence the dose increment phase and sometimes maintenance dose phase in allergen immunotherapies in general and oral immunotherapy of food allergy in particular. A susceptibility to viral infection, most often to HRV, characterizes allergic diseases (asthma, rhinitis and more), and is exaggerated in comorbid states. This common susceptibility facilitates viral evasion and/or host antiviral incompetence, leading to inappropriate inflammatory responses, clinically expressed as disease exacerbation and propensity to progression. In addition, there is both mechanistic and epidemiological evidence suggesting that viral infections are indeed a frequent co-factor in severe allergic reactions, such as anaphylaxis, thus causing major burden for patients.

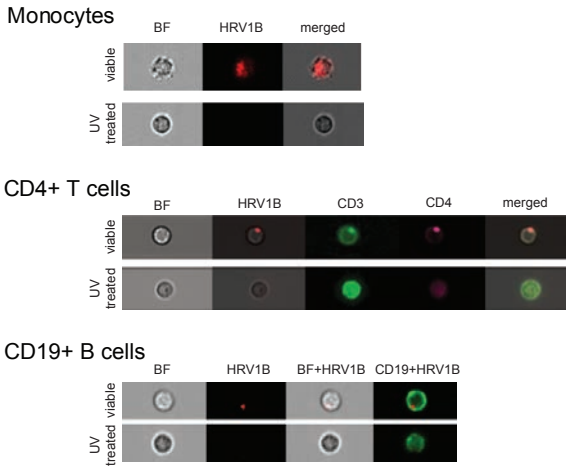


Figure 3: Imaging of HRV internalization by with monocytes, T and B cells.

The integration of the mechanisms of acute exacerbations into a chronic allergic disease background and their link to breaking of allergen tolerance or changing the thresholds of immune tolerance remains to be elucidated. In addition to induction of asthma exacerbations, there is likely a causative link between HRV infections and the development of childhood asthma, but yet fundamental questions persist about mechanisms linking this common pathogen to the disease.

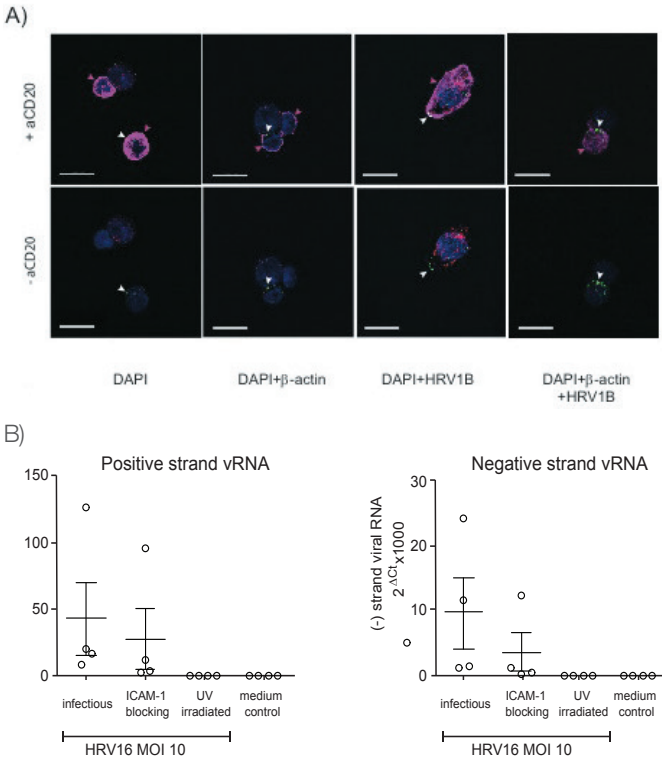


Figure 5. Visualization of HRV1B vRNA with in situ hybridization (ISH). HRV1B vRNA is designated with green, human beta-actin mRNA with red, DAPI with blue, and anti-CD20 (purple arrow) as the marker for B-cells with purple color. (A) PBMCs were cultured with HRV1B and subjected to ISH analysis on 5th day. (B) HRV can successfully replicate in PBMCs and produce infectious virions, which are able to infect HELA cells. Expression of positive strand and negative strand viral RNA in HELA cells after co-culture with pre HRV incubated PBMCs for three days are shown.

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 are

•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 indeterministic 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

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

Boonpiyathad T, Meyer N, Moniuszko M, Sokolowska M, Eljaszewicz A, Wirz O.F, Tomasiak-Lozowska M. M, Bodzenta-Lukaszyk A, Ruxrungtham K, van de Veen W.

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

Human 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.

IL-10-overexpressing B cells were phenotypically characterized in terms of their profile of human cytokine and immunoglobulin production (using specific ELISA, beads-based multiplex cytokine and isotyping measurement), 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 myeloid derived dendritic

cells (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 molecule expression from TLR4-L stimulated maturation of MDDC and antigen-specific stimulation of PBMC were assessed (by beads-based multiplex cytokine measurement, flow cytometry and by incorporation of 3H-thymidine). Our data show that under IL-10 overexpression normal human B cell 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, caused shift of MDDC to less differentiated stage and remarkably downregulate their co-stimulatory capacity by reducing expression of CD80, CD86 and CD83, while inducing 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 a 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 immunomodulation of immune response providing tolerance-inducing environment.

Human Rhinoviruses Enter and Induce Proliferation of B Lymphocytes.

Aab A, Wirz O, van de Veen W, Söllner S, Stanic B, Rückert B, Aniscenko J, Edwards MR, Johnston SL, Papadopoulos NG, Rebane A ,Akdis CA, Akdis M. Allergy. 2016 May 11. [Epub ahead of print]

Human rhinoviruses (HRV) are one of the main causes of virus induced asthma exacerbations. Infiltration of B lymphocytes into the subepithelial tissue of the lungs has been demonstrated during rhinovirus infection in allergic individuals. However, the mechanisms through which HRVs modulate the immune responses of monocytes and lymphocytes are not yet well described. To study the dynamics of virus uptake by monocytes and lymphocytes, and the ability of HRVs to induce activation of in vitro cultured human peripheral blood mononuclear cells. Flow cytometry was used for the enumeration and characterization of lymphocytes. Proliferation was estimated using 3 H-thymidine or CFSE labelling and ICAM-1 blocking. We used bead based multiplex assays and quantitative PCR for cytokine quantification. HRV accumulation and replication inside B lymphocytes was detected by a combination of in situ hybridation (ISH), immunofluorescence and with PCR for positive strand and negative strand viral RNA. Cell images were acquired with imaging flow cytometry. By means of imaging flow cytometry, we demonstrate a strong and quick binding of HRV types 16 and 1B to monocytes, and slower interaction of these HRVs with CD4+ T cells, CD8+ T cells and CD19+ B cells. Importantly, we show that HRVs induce the proliferation of B cells while addition of anti-ICAM-1-antibody partially reduces this proliferation for HRV16. We prove with ISH that HRVs can enter B cells, form their viral replication centers and the newly formed virions are able to infect HeLa cells. In addition, we demonstrate that similarly to epithelial cells, HRVs induce the production of pro-inflammatory cytokines in PBMCs. Our results demonstrate for the first time that HRVs enter and form viral replication centers in B lymphocytes and induce the proliferation of B cells. Newly formed virions have the capacity to infect other cells (HeLa). These findings indicate that the regulation of human rhinovirus induced B cell responses could be a novel approach to develop therapeutics to treat the virus-induced exacerbation of asthma.

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

Kärner J, Wawrzyniak M, Tankov S, Runnel T, Aints A, Kisand K, Altraja A, Kingo K, Akdis CA, Akdis M, Rebane A. Allergy. 2016 Apr 5. [Epub ahead of print]

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

A novel, dual cytokine-secretion assay for the purification of human Th22 cells that do not co-produce IL-17A.

Wawrzyniak M, Ochsner U, Wirz O, Wawrzyniak P, van de Veen W, Akdis CA, Akdis M. Allergy. 2016 Jan;71(1):47-57.

Interleukin-22 is produced by certain T helper cells subsets (Th17, Th22) and at lower levels by γ-δ T cells, NKT and innate lymphoid cells. Th22 cells are unique immune cells that regulate tissue responses by IL-22 production. The exact discrimination between Th17 cells that co-produce IL-22 and single IL-22-producing Th22 cells

has not been possible until the present study. Isolation of pure Th22 cells without co-expression of cytokines of other T-cell subsets is essential to better understand their function in humans. The aim of this study is the isolation and characterization of viable, human IL-22-producing CD4+ T cells that do not produce IL-17A. Isolation of viable Th22 cells was performed with the combination of two cytokine secretion assays detecting IL-17A- and IL-22-producing cells in a single purification step. The newly developed cytokine secretion assay consists of anti-IL-22 and anti-IL-17A catch antibodies, which via biotin-streptavidin interaction are bound to the biotinylated surface of the target cell, and anti-IL-22 and IL-17A detection antibody labelled with a fluorescent dye, which detects cytokines bound to these catch antibodies. A unique population of human Th22 cells, which do not produce IL-17A, was sorted, and cytokine expression pattern was confirmed by quantitative PCR analysis and ELISA. The presented technique allows the detection and isolation of pure human Th22 cells. This technique may allow the purification of any single cytokine-producing cell subset, and the combination of several different cytokine secretion assays can be used to purify and characterize novel and unique cell subsets.

Davos, June 2015

PD Dr. Liam O'Mahony

The molecular Immunology group is primarily focused on understanding the molecular mechanisms responsible for microbial and metabolite regulation of mucosal immune responses. In particular, regulation of the innate immune system is examined in detail. These innate immune cells are responsible for the initial acquisition of foreign particles and their interaction with T and B cells, leading to the development of adaptive immunity. Dendritic cells (DCs) are potent antigen presenting cells that are present at all mucosal surfaces and are central players in initiating and regulating adaptive immune responses. 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.

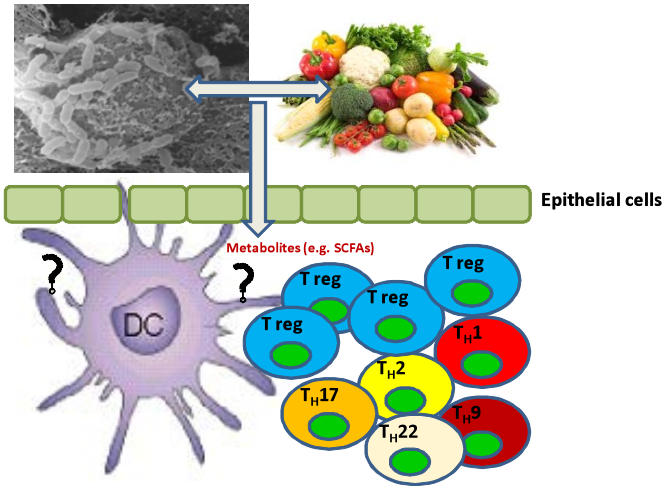


Figure 1. Microbes and their metabolites (e.g. short-chain fatty acids) directly influence DC maturation, activation and lymphocyte polarization.

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

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

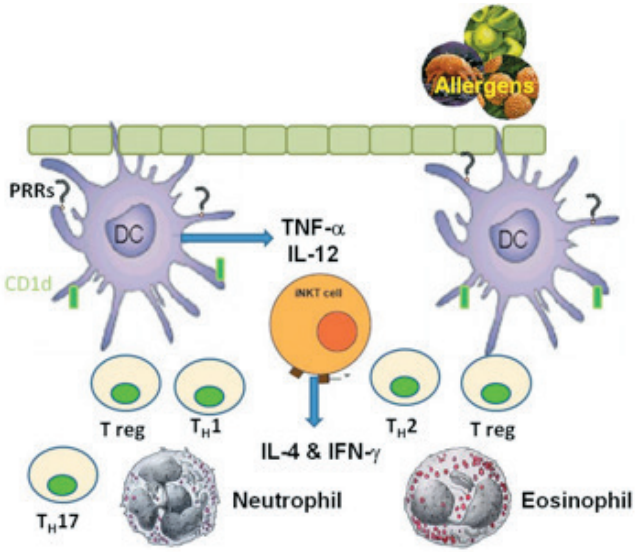


Figure 2. When mice lack the H2R in the lung, dendritic cells and iNKT cells are activated, which influences lymphocyte polarization and recruitment of Neutrophils and Eosinophils to the lung.

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. Thus, our results to date suggest that histamine signaling via H2R suppresses pro-inflammatory responses and may represent a novel intervention target in the treatment of allergy and asthma. Interestingly, we have recently discovered that there are increased numbers of bacteria, which can secrete histamine, in the gastrointestinal tract of adult asthma patients. Histamine-secreting Escherichia coli, Lactobacillus vaginalis and Morganella morganii strains were isolated from the gut microbiome of asthma patients and patients with more severe disease had the highest levels of M. morganii. Based on these observations, we speculate that increased levels of bacterial-derived histamine in certain adult asthma patients may contribute to histamine-mediated pathologies due to a higher systemic level of histamine, which then reduces the level required for host-derived histamine to drive allergic responses following allergen exposure.

Histamine may also exert immunoregulatory effects in other inflammatory disorders, such as inflammatory bowel disease (IBD). Patients with IBD exhibit altered H2R expression on peripheral blood monocytes and the suppressive effect of H2R activation on TLR-induced cytokine responses is no longer effective in IBD patients. Within the gastrointestinal mucosa, histamine receptor expression is altered in inflamed tissue, compared to non-inflamed tissue from the same patient, and histamine receptor expression is directly correlated with proinflammatory cytokine expression. Utilising the SCID murine model of colitis, we observed that mice receiving lymphocytes from H2R-/- donors, or treated with famotidine, displayed more severe weight loss, higher disease scores and increased numbers of mucosal IFN-γ and IL-17+ T cells. IBD patients display dysregulated expression of histamine receptors, with diminished anti-inflammatory effects associated with H2R signaling. Deliberate manipulation of H2R-signalling may suppress excessive TLR responses to bacteria within the gut.

(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 longum 35624 (B. longum) is a commensal microbe originally isolated from the human gastrointestinal mucosa and has been extensively studied for its ability to regulate inflammatory responses, both in mice and humans. In order to understand the B. longum-associated molecules, which dampen inflammatory responses, we examined the bacterial genome and identified a unique gene cluster that encodes for the enzymatic machinery to produce an exopolysaccharide (EPS). The chemical composition and structure of the EPS was determined and found to be novel. A EPS knock-out mutant was generated and surprisingly the mutant induced a strong dendritic cell proinflammatory response, which was not observed for the parent strain expressing EPS. Administration of B. longum 35624 to the SCID colitis model prevented disease symptoms, whereas the EPS KO mutant did not protect against the development of colitis, with associated enhanced recruitment of IL-17+ lymphocytes to the gut. These studies implicate the surface-associated exopolysaccharide of the B. longum 35624 cell envelope in the prevention of aberrant inflammatory responses.

In addition to immunoregulatory cell structures, microbes secrete metabolites that are immunoregulatory. Microbiota-derived short-chain fatty acids (SCFAs) are generated following microbial fermentation of dietary fibres and have been shown by others to possess immune-modulating properties. We have administered SCFAs to mice and observed a dramatic suppression of allergic airway responses. Microbes also secrete biogenic amines following decarboxylation of dietary amino acids (e.g. putrescine and cadaverine) and these metabolites can influence immune responses. We have identified a subset of microbe-derived biogenic amines that suppress dendritic cell activation and we are currently isolating and characterizing these microbes from healthy volunteers and asthma patients. These molecular mechanisms highlight an important link between diet, composition of the gastrointestinal microbiota and regulation of intestinal immune responses. Current collaborations with Prof Lauener, Dr Frei and Dr Roduit are examining the role for novel dietary components in managing allergic disorders. In addition, the identification of novel bacterial-derived immunoregulatory peptides, lipids and polysaccharide structures is ongoing and preliminary results suggest 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. In addition, the identification of bacterial-derived components or metabolites, which selectively activate the immune regulatory program will lead to the rationale design of new drugs for in vivo assessment.

(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 199 patients and volunteers from the Pneumology Department, University Hospital Zürich (Dr. Kohler) and the Department of Clinical Immunology, Wroclaw Medical University, Poland (Prof. Jutel). Preliminary results show that significant alterations in microbial metabolism are evident in obese individuals, compared to non-obese individuals. Asthma is also associated with alterations in metabolite levels, which is exaggerated in the obese asthmatics. Microbiome analysis has revealed surprising differences between the groups and these differences in microbial populations are currently being examined for their functional significance.

Histamine-secreting microbes are increased in the gut of adult asthma patients.
Barcik W, Pugin B, Westermann P, Rodriguez Perez N, Ferstl R, Wawrzyniak M, Smolinska S, Jutel M, Hessel E, Michalowich D, Akdis CA, Frei R, O'Mahony L. J Allergy Clin Immunol. 2016, in press.
Alterations in the metabolites (i.e. histamine) derived from the gut microbiome may influence host immune responses. Histamine-secreting microbes are increased in the gut microbiome of adult asthma patients and histamine from these microbes may contribute to the effector responses in atopic asthma patients. Histamine-secreting Escherichia coli, Lactobacillus vaginalis and Morganella morganii strains were isolated from the gut microbiome of asthma patients.

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

Smolinska S, Groeger D, Rodriguez Perez N, Schiavi E, Ferstl R, Frei R, Konieczna P, Akdis CA, Jutel M, O'Mahony L. Inflammatory Bowel Diseases 2016, in press.

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

Current challenges facing the assessment of the allergenic capacity of food allergens in animal models.

Lindholm Bøgh K, van Bilsen J, Głogowski R, López-Expósito I, Bouchaud G, Blanchard C, Bodinier M, Smit J, Pieters R, Bastiaan-Net S, de Wit N, Untersmayr E, Adel-Patient K, Knippels L, Epstein MM, Noti M, Cecilie Nygaard U, Kimber I, Verhoeckx K, O'Mahony L. Clinical and Translational Allergy 2016, in press.

Food allergy is a major health problem of increasing concern. The insufficiency of protein sources for human nutrition in a world with a growing population is also a significant problem. The introduction of new protein sources into the diet, such as newly developed innovative foods or foods produced using new technologies and production processes, insects, algae, duckweed, or agricultural products from third countries, creates the opportunity for development of new food allergies, and this in turn has driven the need to develop test methods capable of characterizing the allergenic potential of novel food proteins. There is no doubt that robust and reliable animal models for the identification and characterization of food allergens would be valuable tools for safety assessment. However, although various animal models have been proposed for this purpose, to date, none have been formally validated as predictive and none are currently suitable to test the allergenic potential of new foods. Here, the design of various animal models are reviewed, including among others considerations of species and strain, diet, route of administration, dose and formulation of the test protein, relevant controls and endpoints measured.

Monitoring immune responses in a mouse model of fracture fixation with and without Staphylococcus aureus osteomyelitis.

Rochford ETJ, Sabaté-Brescó M, Zeiter S, Kluge K, Poulsson A, Ziegler M, Richards RG, O' Mahony L, Moriarty TF. Bone. 2016 Feb;83:82-92.

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

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 (within the last 2 years) 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.

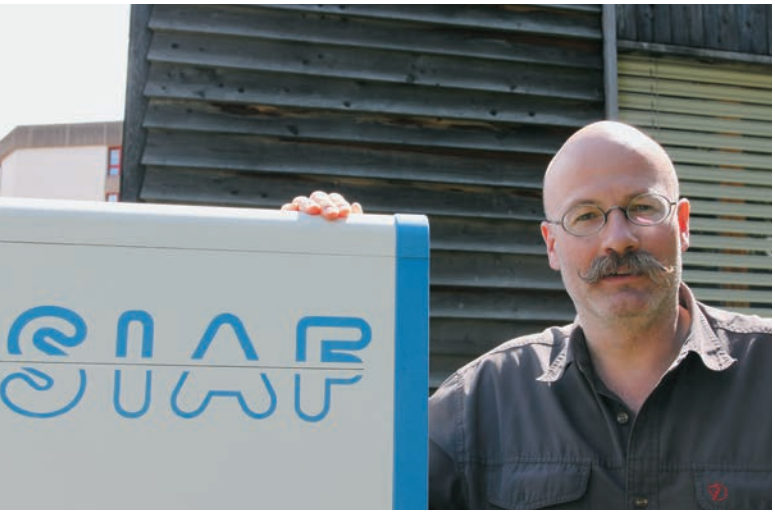
Human dendritic cell DC-SIGN and TLR-2 mediate complementary immune regulatory activities in response to Lactobacillus rhamnosus JB-1.
Konieczna P, Schiavi E, Ziegler M, Groeger D, Healy S, Grant R, O'Mahony L. PLoS One. 2015 Mar 27;10(3):e0120261.
The microbiota is required for optimal host development 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.

Davos, June 2016

Vaccine Development

Dr. Claudio Rhyner



The activities of the SIAF Division Vaccine Development during the last year were focused on several projects and collaborations. The main focus was on the Commission of Technology and Innovation (CTI) granted project "PLATELETS". This CTI granted project was 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.

Targeted elimination of IgE+ Bmem cells and serum IgE.
Since IgE antibodies play a key role in allergic disorders, a number of approaches to inhibit IgE antibody production are currently being explored. We aimed at providing strategies to control or permanently suppress IgE-mediated hyper-reactivity reactions by application of our modular antigen translocation (MAT) vaccine thechnology. The new therapeutic strategy is based on active vaccination and induction of a T cell-dependent antibody response against IgE in the classical OVA-induced asthma-like mouse model. Two main approaches have been considered during this study, (i) we targeted the humoral arm of the IgE response by blocking the interaction of IgE with the Fcε Receptor by constitutive inhibition of sIgE, and also (ii) the cellular counterpart by depleting IgE+ memory B cells through extracellular targeting of the membrane-bound IgE as part of the B-cell receptor (BCR), thus suppressing new IgE responses. We could demonstrate that humoral immune responses against self antigens can be elicited. Our results showed an induction of protective IgG2a antibody responses, and a reduction of B cell numbers in the blood and spleen, as well as a significant reduction in specific and total serum IgE levels. Significant decrease in BAL fluid of the number of total cells, and eosinophil counts in particular, were also observed after vaccination. The MAT-vaccines were also tested in a prophylactic in vivo murine model of asthma, where, also in this case, we could observe a decrease of total IgE in serum and of B cell numbers in the blood and in the lungs. These vaccination strategies principally aim at providing a long-lasting protection. Improvement in this context could open a new therapeutic opportunity to cure allergic diseases in a short time, representing a promising strategy to improve the development of potent allergy vaccines.

Affinity determinations on cells by QCM
Interactions between antibodies and proteins or cells are crucial in many biological processes and for the development and characterization of novel biologicals, such as therapeutic or diagnostic monoclonal antibodies. Quartz crystal microbalance (QCM) technology offers the opportunity to measure affinities over thicker layers of interaction partners, allowing direct label-free measurements of affinities on cells. The aim of our work has been to determine antibody kinetics and affinity for molecules on cell surfaces and provide comparisons between the on-cell results and the affinity constants obtained using recombinant proteins directly coating the biosensor chip of the QCM cell biosensor Attana CellTM 200. As a model system we employed the dendritic cell-associated C-type lectin-1 receptor (CLEC7A/Dectin-1, Dec1) either expressed on HeLa cells by transfection or recombinantly produced in a human cell line as soluble extracellular domain, and two different monoclonal antibodies. Dec1 exserts relevant immunoregulatory functions both in innate and adaptive immunity, because it is expressed predominantly by myeloid cells such as monocytes, macrophages, neutrophils and dendritic cells. Dec1 may represent an appropriate immunotherapeutic target, and deeper knowledge of the affinity of ligands and antibodies for Dec1 may therefore provide new insights facilitating the future development of immunotherapies. With Dec1 and HeLa cells as a model system, we aim at providing a new tool for an accurate measurement of kinetic rate constants and affinity of antibody-epitope interactions on membranes in a physiologically relevant environment (the cell surface), and new insights on how QCM measurements of antibody affinity on cells can be optimized, avoiding the laborious procedures needed for the purification of membrane proteins.

Platelets
The human Platelet Allo-Antigens HPA-1a and HPA-5b are bimorphic proteins with a single amino acid change (Leu33Pro and Glu505Lys) in the platelet specific glycoprotein gpIIIa and gpIa, respectively. These protein polymorphisms can give rise to alloantibodies which can lead to complications. Post-transfusional Platelet Refractoriness (PR), Post-transfusion thrombocytopenic purpura (PTP) and Neonatal alloimmune thrombocytopenia (NAIT) are known as important clinical consequences of HPA allo-antibodies. Therefore fast and sensitive diagnostic assays are advantageous to test patients receiving platelet transfusions for their respective platelet phenotype and to efficiently type platelet preparations. For the HPA-1a and HPA-5b Typing Assays, we used an evanescence biosensor, which is based on real time measurement of a binding reaction using evanescent field excitation of bound fluorophores. Due to the optical phenomenon of total internal reflection of a laser beam, evanescent field waves are generated at the bottom (~200 nm) of each well in the sensor chip. Only fluorphores that are present in this evanescent field will be excited and emit light. HPA-1a and HPA-5b platelet typing assays are sandwich immunoassays, which in a first step capture human platelets in an anti-GPIIbIIIa respectively or an anti-GPIa/IIa coated well. The specific detection is performed with anti-HPA-1a respectively or anti-HPA-5b monoclo-

nal antibodies conjugated to the fluorophor Allophycocyanin (APC). The sensor chip contains all necessary reagents. After mixing one part of EDTA blood with two parts of lysis buffer, 20 ul of this mix are transferred to the well and the result is shown after ten minutes on the reader. Only HPA-1a and HPA-5b positive blood samples bind both the well surface and the detection conjugate and give a detectable fluorescence signal.

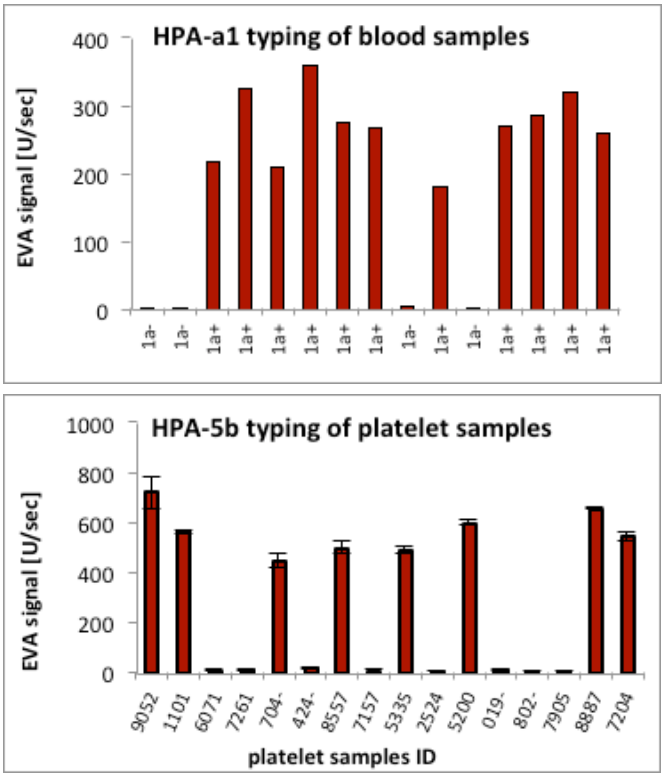


Figure 1: HPA-1a typing using whole blood 4/14 tested samples where negative for human platelet allo-antigen and in concordance with genotyping(A) and HPA-5b typing using HPA typed platelets 8/16 tested samples where negative for human platelet allo-antigen HPA-5b and in concordance with genotyping (B).

We show 14 typing samples for HPA-1a and 16 typing samples for HPA-5b, with genotyped human platelet and blood samples, resulting in no false positive or false negative result (Fig 1A+B). Larger studies in blood banks and transfusion centers are currently under progress. Here we present easy, fast, and sensitive typing assays for the human Platelet allo-antigens HPA-1a and HPA-5b. These one-step typing assays determine the allo-antigen type of platelets within ten minutes. We consider them useful tool in blood banks and transfusion medicine centers and for quick phenotyping of platelet recipients.

For the detection of platelet reactive antibodies, the MAIPA (monoclonal antibody specific immobilization of platelet antigens) represents the golden standard, which is used in laboratories as well as in blood banks. The MAIPA assay consists of a cellular part in which the complex composed of the glycoprotein (patient sample), the antibody against HPA (patient sample) and an antibody against the glycoprotein (catching antibody for the test) is prepared. In an ELISA based detection part, the detection of the prepared complex by an anti human IgE antibody is performed. We transferred this detection part to the EVA system and developed Assays for the detection of anti HPA 1a antibodies. A lysate of a trimolecular complex (formed by platelet gpIIbIIIa–mouse anti-gpIIbIIIa-human anti HPA-1a) with increasing concentrations of the analyte human anti-HPA-1a IgG is directly added to the anti-mouse IgG coated EVA-chip to catch the complex. Using an anti-human IgG-APC as a detection molecule, leads to an assay with a detection limit (LOD) of 2.33 ng/ml (Fig. 2A). Ready-to-use chips (dried chips) were precoated with anti-mouse IgG and these chips are containing the detection antibody anti-human IgG-APC. Adding the trimolecular complex with increasing concentrations of HPA-1a antibody leads to an assay with an LOD of 14.8 ng/ml (Fig. 2B). Furthermore, the time needed for thedetection part of a MAIPA Assay could be reduced from several hours to ten minutes.

Allergen specific antibodies during SIT

Currently, allergen specific immunotherapy (SIT) represents the only curative treatment for allergic diseases. Increasing doses of an allergen are applied to an allergic patient to induce peripheral T-cell tolerance and a shift from a TH2 to a TH1/Treg-biased immune response. During immunotherapy there is an increase of allergen specific IgG4 which is regarded as a blocking antibody. This can have an influence on the measurements of allergen specific IgE in assays which uses the allergen as a catching reagent. The aim of this study is the development of diagnostic assays for the detection of allergen specific IgE during SIT which is not influenced by the blocking antibody IgG4. For this purpose, we were using serum samples from birch pollen allergic patients undergoing SIT.

To calculate the sensitivity of a test, serial dilutions of a serum pool calibrated against ImmunoCAP™ (Thermo Fisher) were measured, resulting in a Limit of detection of 0.24 kU/L for the direct assay and 0.27 kU/L for the reverse assay, respectively (Fig 3A). Therefore the requirements for a test detecting allergen specific antibodies is met, since the concentration of 0.35 kU/L, which is regarded as a cut-off level for sensitization can be detected. Comparative measurements of 20 serum samples were performed with EVA and ImmunoCAP, showing a correlation of r=0.98 for the direct assay and r=0.82 for the reverse assay, respectively.

To determine the LOD of the direct Bet v1 IgG4 assay, serial dilutions of a serum calibrated against ImmunoCAP™ (Thermo Fisher) were measured. These measurements resulted in a LOD of 0.26 µg/L Bet v1 specific IgG4. To determine the influence of the blocking antibody IgG4 on IgE measurements, 164 serum samples from a blinded study were measured. For this purpose we used reverse and direct assays for the detection of Bet v1 specific IgE and a direct IgG4 assay.

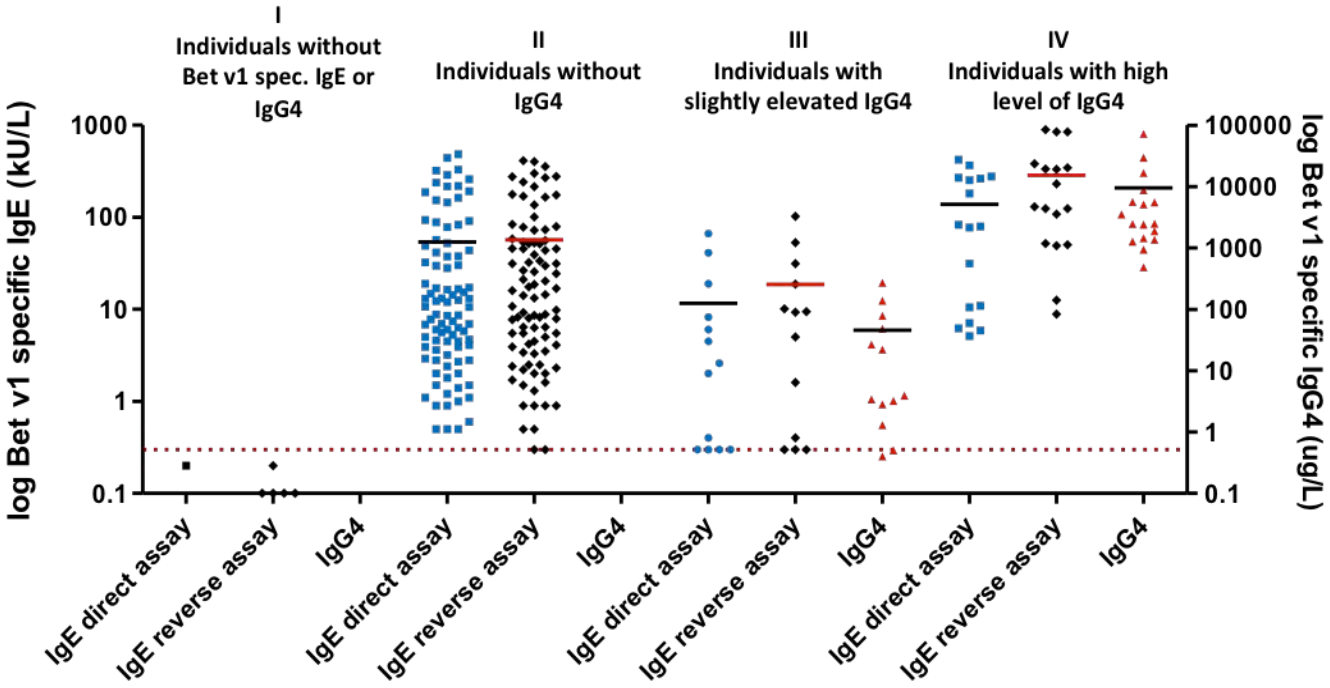


Figure 2: Bet v1-specific IgE and IgG4 measurements in 164 serum samples from a blinded study.

After the measurement of Bet v1-specific antibodies, the sera were combined to groups based on their amount of Bet v1-specific IgG4. Sera without Bet v1-specific antibodies were combined to the first group. In a second group, sera are containing Bet v1-specific IgE with absence of Bet v1-specific IgG4. Only in the groups with slightly elevated and highly elevated Bet v1-specific IgG4, the measurements of Bet v1-specific IgE levels differ between the direct and reverse assay and indicate the presence of IgG4 interference (Fig. 2). Here, we present a fast and sensitive method for the measurements of Bet v1-specific antibodies in sera of human allergic patients with and without birch-pollen specific Immunotherapy. Furthermore, we could show the blocking effect of Bet v1-specific IgG4 on the measurements of Bet v1-specific IgE in a direct assay. With the reverse assay, we developed a useful method for the detection of Bet v1-specific IgE, which is not influenced by the presence of blocking antibody IgG4.

Davos, June 2016

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Sumbitted and book chapters 2015

Submitted

Altmann F, Kosma P, O'Callaghan A, Leahy S, Bottacini F, Molloy E, Schiavi E, Gleinser M, Groeger D, Grant R, Rodriguez Perez N, Plattner S, Healy S, Wozny K, O'Connell Motherway M, Akdis CA, Xu J, Roper J, van Sinderen D, O'Mahony L. Identification and characterisation of the exopolysaccharide produced by Bifidobacterium longum subsp. longum 35624. Submitted.

Barcik W, Untersmayr E, Pali-Schöll I, O'Mahony L, Frei R. Influence of microbiome and diet on immune responses in food allergy models. Submitted.

Barcik W, Pugin B, Westermann P, Rodriguez Perez N, Ferstl R, Wawrzyniak M, Smolinska S, Jutel M, Hessel E, Michalowich D, Akdis CA, Frei R, O`Mahony L. Histamine-secreting microbes are increased in the gut of adult asthma patients. Submitted.

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

Ferstl R, Frei R, Barcik W, Schiavi E, Wanke K, Ziegler M, Rodriguez Perez N, Groeger D, Konieczna P, Zeiter S, Nehrbass D, Lauener R, Akdis CA, O'Mahony L. Histamine Receptor 2 Restrains Invariant NKT Cell Responses within the Lung. Submitted.

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

Schiavi E, Gleinser M, Groeger D, Frei R, Ferstl R, Rodriguez Perez N, O'Callaghan A, Leahy S, Bottacini F, Molloy E, Ziegler M, Grant R, Moriaty F, Plattner S, Healy S, O'Connell Motherway M, Akdis CA, Roper J, Altmann F, van Sinderen D, O'Mahony L. Expression of the surface-associated exopolysaccharide by Bifidobacterium longum 35624 is decisive in mediating appropriate host-microbe communication. Submitted.

van de Veen W, Akdis M. Role of IgG4 in IgE-mediated allergic responses. JACI, Editorial. Submitted.

Wawrzyniak M, O`Mahony L, Akdis M. Role of regulatory cells in oral tolerance. Submitted.

Book chapters

Akdis CA, Agache I, Editors
Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis. Published by European Academy of Allergy and Clinical Immunology.

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

Crameri R. Specific IgE and diagnosis of allergic rhinitis. In: Global Atlas of allergic rhinitis and chronic rhinosinusitis, European Academy of Allergy and Clinical Immunology (Akdis CA, Hellings P, Agache I (eds), pp. 165-166, 2015.

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

Frei R, Roduit C, Lauener RP. From gene expression measurements to epidemiological studies. Global Atlas of Allergic rhinitis and chronic Rhinosinusitis; European Academy of Allergy and Asthma Research, 2015.

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

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

O'Mahony L. Animal models of rhinitis. In: EAACI Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis; Akdis CA, Agache I (Editors), European Academy of Allergy and Asthma Research, 2015.

Sokolowska M, Akdis CA. New diagnostic and research techniques in allergic rhinitis and chronic rhinosinusitis. In: Global Atlas of Rhinitis and Chronic Rhinusinusitis; Akdis CA, Hellings PW, Agache I (Editors), European Academy of Allergy and Asthma Research, 2015.

van de Veen W, Morita H, Akdis M. Mechanisms of immune regulation in allergic rhinitis. In: Global Atlas on Allergic Rhinitis and Chronic Rhinosinusitis. Akdis C.A., Hellings P.W. and Agache I. European Academy of Allergy and Asthma Research, 2015.

Wawrzyniak P, Kubo T, Altunbulakli C, Sugita K, Wawrzyniak M, Akdis M, Akdis CA. Regulation of Epithelial Barrier in Asthma. Proceedings of the proceeding of the Collegium Internationale Allergologicum (CIA), 2015.

Abstracts

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

Barcik W., Frei R., Ferstl R., Pugin B., Rodriguez N., O`Mahony L. Microbiota-Derived Histamine - Relevance To Mucosal Immune Homeostasis. 1st Type 2 Immunity Meeting Bern, 16 December 2015.

Hradetzky S, Roesner LM, Heratizadeh A, Crameri R, Garbani M, Scheynius A, Werfel T. Differentielle Zytokinregulation durch das Autoallergen humans Thioredoxin bei sensibilisierten Patienten mit atopischer Dermatitis und gesunden Kontrollspendern. Kongress „Allergie in Fokus", Kassel, Germany, 17-18 April 2015.

Kubo T, Wawrzyniak P, Morita H, Sugita K, Wanke K, Kast JI, Altunubulakli C, Rückert B, Akdis M, Akdis CA. Role of TLR9 in restoring bronchial epithelial integrity. EAACI Winter School, Les Arcs 1800, France, 5-8 February 2015.

Kubo T, Wawrzyniak P, Morita H, Sugita K, Wanke K, Kast JI, Altunubulakli C, Rückert B, Akdis M, Akdis CA. Role of TLR9 in restoring bronchial epithelial integrity. World Immune Regulation Meeting, Davos, Switzerland, 18-21 March 2015.

Mittermann I, Wikberg G , Johansson C, Lupinek C, Lundeberg L, Crameri R, Valenta R, Scheynius A. Differences in molecular sensitization profiles of patients with severe and moderate atopic dermatitis. 4th European Congress of Immunology, Vienna, Austria, 6-9 September 2015.

Morita H, Sugita K, Kubo T, Akdis M, Akdis CA. Mechanisms of immune tolerance to allergens. EAACI Winter School, Les Arcs, France, 5-8 February 2015.

Morita H, Ferstl R, Frei R, Sugita K, Kubo T, Wirz O, Wawrzyniak M, van de Veen W, Stanic B, Ochsner U, Rückert B, O'Mahony L, Akdis M, Akdis CA. The effect of histamine on type 2 innate lymphoid cells. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Morita H, Sugita K, Ferstl R, Frei R, Kubo T, van de Veen W, Wawrzyniak M, Wirz O, Rückert B, O'Mahony L, Akdis M, Akdis CA. The effect of histamine on type 2 innate lymphoid cells. EAACI Congress 2015, Barcelona, Spain, 6-10 June 2015.

Morita H, Sugita K, Akdis M, Akdis CA. The effect of histamine on type 2 innate lymphoid cells (ILC2), CK-CARE meeting, Davos, Switzerland, 28 June-1 July 2015.

Myrset H, Olzhausen J, Peroza E, Maaike D, Rhyner C, Crameri R. Development of an evanescence-based method for the quantification of tropomyosin-specific IgE in ten minutes. 13th EAACI Immunology Winter School, Les Arcs, France, 5-8 February 2015.

Myrset H, Olzhausen J, Peroza E, Dooper M, Rhyner C, Crameri R. Development of an evanescence-based method fort he quantification of tropomyosin-specific IgE in ten minutes. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Myrset H, Olzhausen J, Peroza E, Dooper M, Rhyner C, Crameri R. Development of an evanescence-based method fort he quantification of tropomyosin-specific IgE in ten minutes. EAACI Congress, Barcelona, Spain, 8-11 June 2015.

Olzhausen J, Schawaller M, Akdis CA, Crameri R, Rhyner C. Monoclonal antibody specific immobilization of platelet antigens (MAIPA): A rapid and sensitive assay for the identification of platelet-reactive antibodies. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

O'Mahony L. Short chain fatty acid (SCFA) – G Protein coupled receptor (GPCR) interactions as central regulators of innate immune deviation in obese asthma patients. 16th Course AIU Grindelwald, Switzerland, January 2015.

Peroza E, Wiki M, Schawaller M, Akdis CA, Rhyner C, Crameri R. Ultimate innovation in immunodiagnostics: replacing ELISA tests with ultra-rapid evanescence field-based technology. Annual Congress SSAI-SGAI, Basel, Switzerland, 12-13 March 2015.

Peroza E, Rhyner C, Grönlund H, Crameri R. Matching pets to their owners: Tests to define suitable animal breeds for pet allergic individuals. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Prati M., Garbani M., Crameri R., Rhyner C. Interactions of biological molecules with cell-bound markers based on Quartz Crystal Microbalance biosensing. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Prati M, Garbani M, Crameri R, Rhyner C. Detection of molecular interactions between ligands and cell-bound receptors based on Quartz Crystal Microbalance biosensing. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Rhyner C, Prati M, Garbain M, Crameri R. quantification of molecular interactions on cell-surface receptors based on Quartz Crystal Microbalance Biosensor. EAACI Congress, Barcelona, Spain, 8-11 June 2015.

Sokolowska M, Chen L-Y, Liu Y, Martinez-Anton A, Logun C, Alsaaty S, Cuento RA, Cai R, Sun J, Quehenberger O, Armado AM, Dennis EA, Levine SJ, Shelhamer JH. Dysregulation of lipidomic profile and antiviral immunity in response to hyaluronan in severe asthma. 13th European Respiratory Society Lung Science Conference, Estoril, Portugal, 13-15 March 2015.

Sokolowska M, Chen L-Y, Liu Y, Martinez-Anton A, Qi H-Y, Logun C, Alsaaty S, Park YH, Kastner DL, Chae JJ, Shelhamer JH. Prostaglandin E2 inhibits NLRP3 inflammasome activation through EP4

receptor and intracellular cAMP in human macrophages. 9th World Immune Regulation Meeting, Davos, Switzerland, 18 - 21 March 2015.

Sokolowska M, Chen L-Y, Liu Y, Martinez-Anton A, Qi H-Y, Logun C, Alsaaty S, Park YH, Kastner DL, Chae JJ, Shelhamer JH. Prostaglandin E2 inhibits NLRP3 inflammasome activation through EP4 receptor and intracellular cAMP in human macrophages. European Respiratory Society International Congress, Amsterdam, Netherlands, 26-30 September 2015.

van de Veen W. Human Memory B Cell Subsets in Allergic and Healthy Individuals. World Immune Regulation Meeting, Davos, Switzerland, 18–21 March 2015.

van de Veen W. Characterisation of B cell responses in healthy and allergic individuals using allergen- specific B cell clones. ESF-EMBO Symposium Be there or die? The role of the microenvironment in B cell behaviour in health and disease, Sant Feliu de Guixols, Spain, 16 – 21 May 2015.

van de Veen W. Allergen-specific B cell subsets in healthy and allergic individuals. EAACI Congress, Barcelona, Spain, 6–10 June 2015.

Wawrzyniak M. Isolation and characteraization of IL-22-producing T cells. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Wawrzyniak P, Wawrzyniak M, Wanke K, Beate Rückert, Jakiela B, Bandelja K, Kast JI, Akdis M, Sanak M, Akdis CA. Regulation of leaky epithelial barrier and tight junctions in asthma. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Seminar and congress talks

Akdis CA. Role of epithelial barrier function in atopic diseases. Philipps University Marburg, Germany, 14 January 2015.

Akdis CA. Mechanisms of allergen-specific immunotherapy: immune tolerance versus vaccination. Annual Congress SGAI/SSAI, Basel, Switzerland, 12-13 March 2015.

Akdis CA. Role of Epithelial Barrier in Allergic Diseases. International Immunology Meeting, Antalya. 27 April 2015.

Akdis CA. Mechanisms of leakiness of epithelial barrier in allergic diseases. Scottish Allergy and Respiratory Academy Minisymposium on Allergy Research. University of Edinburgh, Scottland, 6 May 2015.

Akdis CA. Principles of airway inflammation. Rhino Camp, Bodrum, Turkey, 27-31 May 2015.

Akdis CA. Take home messages of the day. Rhino Camp, Bodrum, Turkey, 27-31 May 2015.

Akdis CA. Novel concepts in tissue injury, remodelling and chronicity. International Symposium of Musculoskeletal Regeneration Research Network, Karolinska Institutet Stockholm, Sweden, 1-2 June 2015.

Akdis CA. Mechanisms of allergen tolerance. EAACI Congress, Barcelona, Spain, 6-10 June 2015.

Akdis CA. Clinical implications of studies on mechanisms of AIT. EAACI Congress, Barcelona, Spain, 6-10 June 2015.

Akdis CA. Immune tolerance mechanisms in tissues during chronic inflammatory diseases. eCM XVI conference, Davos, Switzerland, 24-26 June 2015.

Akdis CA. Immune deviation. Global Allergy Forum, Davos, Switzerland, 28 June–1 July 2015.

Akdis CA. Novel Concepts in Tissue Injury, Remodelling and Chronicity. 1st International Symposium of Musculoskeletal Regeneration Research Network (MRN), Karolinska Institutet, Stockholm, Sweden, 1-2 June 2015.

Akdis CA. The epithelial barrier and chronic inflammation. International scientific-practical conference „Modern problems of allergology, immunology and genomic technologies“, Tashkent, Uzbekistan, 18-19 September 2015.

Akdis CA. Toleranzinduktion: Aus Sicht des Immunologen. 10. Deutscher Allergie Kongress, Köln, Germany, 1-3 October 2015.

Akdis CA. Epithelial barrier integrity in atopic diseases. TongRen International Forum of Rhinology and Allergy. Beijing, China, 9-10 October 2015.

Akdis CA. Mechanistic approach to define immune intolerance to allergens. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Akdis CA. Defective epithelial barrier function and the role of tight junctions. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Akdis CA. Opening Conference: past-present-future in immunology and allergology. National Allergy and Clinical Immunology Congress XXII, Belek/Antalya, Turkey, 28 November–02 December 2015.

Akdis CA. Atopic diseases and the role of epithelial barriers. National Allergy and Clinical Immunology Congress XXII, Belek/Antalya, Turkey, 28 November–02 December 2015.

Akdis M. Immune regulation. PreDicta Consortium Meeting, Castle of Rauischholzhausen, Germany, 12-13 January 2015.

Akdis M. Mechanisms of immune tolerance to allergens. Philipps University Marburg, Germany, 14 January 2015.

Akdis M. Th2 signaling unifying hypothesis. MeDALL meeting, Paris, France, 5-6 February 2015.

Akdis M. Role of Immune cells in the skin: balance between tolerance and sensitization. AAAAI Annual Meeting, Houston, Texas, USA, 20-24 February 2015.

Akdis M. Mechanisms of immune tolerance to allergens. Scottish Allergy and Respiratory Academy Minisymposium on Allergy Research. University of Edinburgh, Scottland, 6 May 2015.

Akdis M. Introduction to immunology: Dentritic cells, T and B cells. Rhino Camp, Bodrum, Turkey, 27-31 May 2015.

Akdis M. Mechanisms of inducing and breaking allergen tolerance in asthma. EAACI Congress, Barcelona, Spain, 6-10 June 2015.

Akdis M. Mechanisms of immune tolerance to allergens. International scientific-practical conference „Modern problems of allergology, immunology and genomic technologies“, Tashkent, Uzbekistan, 18-19 September 2015.

Akdis M. Mechanisms of immune tolerance to allergens in allergen immunotherapy and natural high dose exposure. TongRen International Forum of Rhinology and Allergy. Beijing, China, 9-10 October 2015.

Akdis M. Novel insights into the mechanisms of immunotherapy. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Akdis M. Regulatory B cells. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Akdis M. Allergen tolerance mechanisms in athma. National Allergy and Clinical Immunology Congress XXII, Belek/Antalya, Turkey, 28 November–02 December 2015.

Crameri R. Engineering optimal allergy vaccines and development of a diagnostic chip to monitor the success of allergen-specific immunotherapy. Nanoasit II meeting, Davos, Switzerland, 17 March 2015.

Crameri R. Substituting ELISA with evanescence-based technology. SIAF – AO Exchange Meeting. Davos, Switzerland 14 April 2015.

Crameri R. Development and production of a portable EVA-Reader. RaptaDiag Meeting, Madrid, Spain, 22-24 April 2015.

Crameri R. Allergic bronchopulmonary aspergillosis (ABPA). Meeting of the EAACI CRD Task Force, Berlin, Germany, 16-18 April 2015.

Crameri, R. Evanescent wave fluorescence technology: substituting ELISA with fast real time diagnostic tests. University of Zürich, Switzerland, 03 June 2015.

Crameri R. Schweizerisches Institut für Allergie- und Asthmaforschung. Besuch der Mitarbeiter der HTW Chur, Davos, 16 August 2015.

Morita H. Mast cells and itch. CK-CARE Allergy Education Week 2015, Davos, Switzerland, 9-11 September 2015.

Morita H. Role of Interleukin-22 in innate type immune cells in allergy. World Allergy Congress 2015, Seoul, Korea, 14-17 October 2015.

Neumann AU. T-cell repertoire kinetics on single clone level. E:Med Systems Medicine congress, Heidelberg, Germany, 26-28 October 2015.

O'Mahony L. Histamine Regulation of Inflammatory Responses. MIM Introductory Course, Zurich, Switzerland, January 2015.

O'Mahony L. Probiotic Immunomodulatory Mechanisms. Yakult symposium, Berlin, Germany, April 2015.

O'Mahony L. Microbiome effects on immune tolerance. Seminar series of the Rheumatology Department, University Hospital Zürich, Zürich, Switzerland, May 2015.

O'Mahony L. Microbiome and immunity. European Academy of Allergy and Clinical Immunology, Barcelona, Spain, June 2015.

O'Mahony L. Bacterial infections – friends or foes? European Academy of Allergy and Clinical Immunology, Barcelona, Spain, June 2015.

O'Mahony L. Immunoregulatory Microbes and their Metabolites. Seminar seris of the Service de Pneumologie, Centre Hospitalier

Universitaire Vaudois (CHUV), Lausanne, Switzerland, July 2015.

O'Mahony L. Molecular basis of host-bifidobacteria dialogue. APC Microbiome Institute Symposium, University College Cork, Cork, Ireland, August 2015.

O'Mahony L. Preventing allergy with probiotics and bacterial lysates. Pediatric Allergy and Asthma Meeting (PAAM), Berlin, Germany, October 2015.

O'Mahony L. Dysbiosis: a concept of dysfunctional intestinal microbiota. Pediatric Allergy and Asthma Meeting (PAAM), Berlin, Germany, October 2015.

O'Mahony L. Microbiome and Immunity. Alimentazione ambiente ed allergia: rischi ed opportunità AAITO, Bergamo, Italy, October 2015.

O'Mahony L. Regulatory cells in allergy. 10th Symposium on Specific Allergy (SOSA), Rome, Italy, November 2015.

O'Mahony L. What's wrong in Atopy & Allergy? D-A-CH-Symposium Allergy and Asthma, St. Gallen, Switzerland, December 2015.

O'Mahony L. Microbial and metabolite triggers of mucosal immune polarization. Type 2 Immunity Meeting (T2IMB), Bern, Switzerland, December 2015.

Peroza E. Ultimate innovation in immunodiagnostics: replacing ELISA tests with ultra-rapid evanescence field-based technology. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Rhyner C. Evanescent field-based fast measurements of allergen specific antibodies during SIT. Allergy School e-PAD: EAACI Practical Allergy Diagnosis, Moscow, Russia, 27-29 August 2015.

Rhyner C. New biotechnologies in allergy diagnosis. ISMA, Lisbon, Portugal, 19-21 November 2015.

Sokolowska M. Prostaglandin E2 inhibits NLRP3 inflammasome activation through EP4 receptor and intracellular cAMP in human macrophages. 9th World Immune Regulation Meeting, Davos, Switzerland, 18 - 21 March 2015.

Sokolowska M. Prostaglandin E2 inhibits NLRP3 inflammasome activation through EP4 receptor and intracellular cAMP in human macrophages. European Respiratory Society International Congress, Amsterdam, Netherlands, 26-30 September 2015.

van de Veen W. Year in review: B cells. EAACI Congress, Barcelona, Spain, 6 – 10 June 2015.

Wawrzyniak P. Regulation of leaky epithelial barrier and tight junctions in asthma. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Wawrzyniak P. Dendritic and epithelial cells as the first responders. EAACI, Barcelona, 6-10 June 2015.

Chair at congresses

Akdis CA. The IgE microarray: MeDALL results so far and how to analyze data available from the birth cohorts. MeDALL meeting, Paris, France, 5-6 February 2015.

Akdis CA. EAACI: Bringing molecular diagnosis and treatment closer to the bedside: European Trials. AAAAI Annual Meeting, Houston, Texas, USA, 20-24 February 2015.

Akdis CA. EAACI ENT Section – One airway one disease. Rhino Camp, Bodrum, Turkey, 27-31 May 2015.

Akdis CA. Novel regulatory mechanisms in allergic diseases. EAACI Congress, Barcelona, Spain, 6-10 June 2015.

Akdis CA. Discussion – The future of immune tolerance research in allergy. National Institute of Allergy and Infectious Diseases, Rockville, USA, 18 June 2015.

Akdis CA. Atopic Dermatitis/Eczema – Challenges and Opportunities. Global Allergy Forum, Davos, Switzerland, 28 June – 1 July 2015.

Akdis CA. Immune deviation. Global Allergy Forum, Davos, Switzerland, 28 June – 1 July 2015.

Akdis CA. Final Plenary Session. Global Allergy Forum, Davos, Switzerland, 28 June – 1 July 2015.

Akdis CA. Critical novel molecules for allergic diseases. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Akdis CA. Development of allergy: lessons from the birth cohort study. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Akdis M. EAACI ENT Section – One airway one disease. Rhino Camp, Bodrum, Turkey, 27-31 May 2015.

Akdis M. Innate immune responses. EAACI Congress, Barcelona, Spain, 6-10 June 2015.

Akdis M. T and B cells BOTH regulate allergic responses. EAACI Congress, Barcelona, Spain, 6-10 June 2015.

Akdis M. Intervention & Therapy of Allergy – Part 1. European Congress of Immunology (ECI), Vienna, Austria, 6-9 September 2015.

Akdis M. Atopic dermatitis: a comprehensive update. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Akdis M. Immunology. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Akdis M. Update on the mechanism of asthma and airway inflammation. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Akdis M. Patient education and adherence in allergy and atopic dermatitis. XXIV World Allergy Congress, Seoul, Korea, 14-17 October 2015.

Crameri R. Vaccine development. Nanoasit II meeting, Davos, Switzerland, 17 March 2015.

Crameri R. Regulation of immune response and immune pathology. World Immune Regulation Meeting IX, Davos, Switzerland, 18-21 March 2015.

Crameri, R. RaptaDIAG WP2: Evanescence biosensors, overview of the progress. 5th Project Meeting, Madrid, Spain, 22-24 April 2015.

Morita H. Innate lymphoid cells 2. World Immune Regulation Meeting, Davos, Switzerland, March 2015.

Neumann AU. Workshop: Development of effector and regulatory T cells. World Immune Regulation Meeting, Davos, Switzerland, March 2015.

Neumann AU. Hepatitis C epidemiology. ISVHLD, June 26 2015.

Neumann AU. Symfonia grant review panel. National Science Foundation (NCN), Krakow, Poland, July 20 2015.

O'Mahony L. MIM Introductory Course, Zurich, Switzerland, January 2015.

O'Mahony L. European Academy of Allergy and Clinical Immunology Winter School, Les Arcs, France, February 2015.

O'Mahony L. World Immune Regulation Meeting, Davos, Switzerland, March 2015.

O'Mahony L. European Academy of Allergy and Clinical Immunology Congress, Barcelona, Spain, June 2015.

O'Mahony L. Imparas Meeting, Madrid, Spain, September 2015.

O'Mahony L. Pediatric Allergy and Asthma Meeting (PAAM), Berlin, Germany, October 2015.

Rhyner C. Severity of allergy at a glance: EVAnescence measurement, advanced provocation testing. Practical session. Allergy School e-PAD: EAACI Practical Allergy Diagnosis, Moscow, Russia, 27-29 August 2015.

Rhyner C. Biologicals. World Immune Regulation Meeting, Davos, Switzerland, March 2015.

Sokolowska M. Infection and immunity-poster session 2. 13th European Respiratory Society Lung Science Conference, Estoril, Portugal, 13-15 March 2015.

Sokolowska M. Immune system interaction with tissue cells. 9th World Immune Regulation Meeting, Davos, Switzerland, 18 - 21 March 2015.

Sokolowska M. Immune aspects of asthma and other airway diseases. European Respiratory Society International Congress, Amsterdam, Netherlands, 26-30 September 2015.

Sokolowska M. Asthma and lung immunology. European Respiratory Society International Congress, Amsterdam, Netherlands, 26-30 September 2015.

van de Veen W. Animal studies in asthma research. EAACI Congress, Barcelona, Spain, 6 – 10 June 2015.

van de Veen W. Immunology mechanisms. EAACI Congress, Barcelona, Spain, 6 – 10 June 2015.

van de Veen W. T and B cell subsets. World Immune Regulation Meeting, Davos, Switzerland, 18 – 21 March 2015.

Wawrzyniak P. Dendritic and epithelial cells as the first responders. EAACI Congress, Barcelona, Spain, 6–10 June 2015.

2015

Lectures

Lectures at University of Zurich

Akdis CA. HS 2015 Nr. 1180. Klinisch-experimentelle Konferenz zur Allergologie
Akdis CA. HS 2015 Nr. 1215 e. Mechanisms of Allergic Diseases
Akdis CA. HS 2015 Nr. BCH301.1. Vorlesung Molekulare Zellbiologie
Akdis M. HS 2015 Nr. 1180. Klinisch-experimentelle Konferenz zur Allergologie
Akdis M. HS 2015 Nr. 1215 e. Mechanisms of Allergic Diseases
Akdis M. HS 2015 Nr. BCH301.1. Vorlesung Molekulare Zellbiologie
Crameri R. HS 2015 Nr. 1180. Klinisch-experimentelle Konferenz zur Allergologie
Crameri R. HS 2015 Nr. 1215 e. Mechanisms of Allergic Diseases
Crameri R. HS 2015 Nr. BCH301.1. Vorlesung Molekulare Zellbiologie

Lectures at University of Salzburg

Crameri R. SS 2015: MOD.259. Mastermodul.: Molekulare Zellbiologie als Analyseplattform in Medizin und Industrie.
Crameri R. SS 2015: Nr. 439.006. Molekulare Zellbiologie in der Medikamentenentwicklung.
Crameri R. SS 2015: Nr. 439.007. Molekulare Interaktionen als Target für therapeutische Interventionen.

Degrees

Akdis M., Prof., University of Zurich, Switzerland

O'Mahony L., PD, University of Zurich, Switzerland

Garbani M. Evaluation of peptide mediated Dendritic Cell targeting and particulate adjuvants for immunotherapy. PhD Thesis ETH No. 22698 defended 30.04.2015, Zurich, Switzerland.

Wawrzyniak M. PhD Thesis: "Isolation and characterization of human IL-22-producing T cells". University of Zurich, Microbiology and Immunology PhD Program, November 2015.

Awards

Sokolowska M. Long-term Fellowship travel grant. 13th European Respiratory Society Lung Science Conference, Estoril, Portugal, 13-15 March 2015.

Sokolowska M. Best oral presentation. 9th World Immune Regulation Meeting, Davos, Switzerland, 18 - 21 March 2015.

Sugita K. EAACI Examination in Allergology/Clinical Immunology.
Sugita K. EAACI abstract award winner.

Wawrzyniak P. Workshop prize "Epigenetic regulation of immune response" WIRM, March 2015.
Wawrzyniak P. GA2LEN Junior Travel Grant winner for EAACI Barcelona 2015.

Public Seminars

19.01.2015: Walch M. Cytotoxic immune proteases in antibacterial immunity. Institute of Anatomy, Department of Medicine University of Fribourg, Switzerland.

03.02.2015: Schlegel J. Chipcytometry: Getting out more information from your valuable cell or tissue samples with a great new technology enabling exciting applications. VP Research at Zellkraftwerk GmbH, Hannover, Germany

03.03.2015: Garn H. Endotypes of asthma – From models to novel treatments. Philipps University of Marburg, Center for Tumor- and Immunobiology, Institute of Laboratory Medicine and Pathobiochemistry Marburg, Germany

25.&26.03.2016: Kornfeld C. Seminar and Workshop on CytoFlex Cytometer, Beckman Coulter, Switzerland

14.04.2015: SIAF – AO Exchange Meeting, Stoddart M. Inflammation and MSC differentiation into osteoblast., Hermann M. Vessel formation and inflammatory cytokines., Grad S. Inflammatory pathway and disc degeneration., Rhyner C. Biotechnology and the discovery, design and detection of molecules of the immune system., Crameri R. Substituting ELISA with Evanescence-based technology., O'Mahony L. Immune responses to microbial components and metabolites., Akdis M. Human rhinovirus infections and immune response., Akdis C. Epithelial barrier and two faces of inflammation.

04.05.2015: Ebisawa M. Recent advances in food allergy. Clinical Research Center for Allergology and Rheumatology, Sagamihara National Hospital, Kanagawa, Japan

09.06.2015: Strasser C. LSM 780 and Confocal Microscopy – an Introduction. Carl Zeiss Schweiz AG

11.06.2015: Infoevent on HORIZON 2020 HEALTH – new calls 2016-2017, Damjanovic M. Euresearch, National Contact Point (NCP) Health. Hertkorn-Betz P. Euresearch Regional Office St. Gallen

25.06.2015: Schwarz E. The Osteoimmunology of Bone Infection and Development of a Passive Immunization for MRSA Osteomyelitis. University of Rochester Medical Center, Rochester (NY), USA

09.07.2015: Karouzakis E. Epigenetic regulation of immune responses within inflamed tissue. Center of Experimental Rheumatology, University Hospital Zurich and University of Zurich, Switzerland

10.08.2015: Moniuszko M. Monocytes: neglected players in allergy and allergen immunotherapy. Department of Regenerative Medicine and Immune Regulation and Department of Allergology and Internal Medicine Medical University of Bialystok, Poland

13.08.2015: Bostanci N. Salivary proteome: A gateway to periodontal health., Belibasakis G. Transcriptomic and proteomic profiling of host-biofilm interactions. Division of Oral Microbiology and Immunology, Institute of Oral Biology, Center of Dental Medicine, University of Zürich, Switzerland

19.10.2015: Mantel P-Y. Cellular communication mediated by extracellular vesicles during malaria. Department of Medicine, Unit of Anatomy University of Fribourg, Switzerland

04.12.2015: Virchow C. How to optimize your scientific presentation. Department of Pneumology, University of Rostock, Germany

SIAF Science Day

17.12.2015

Altunbulakli C. Regulation of skin junctional complexes in atopic dermatitis.

Barcik W. Understanding of microbiota-derived histamine will heal the world.

Boonpiyathad T. Mechanism of AIT and allergen-specific T and B cells.

Eljaszewicz A. Novel class of pattern recognition receptors in airway epithelium.

Frei R. Early-life exposure to food components protects mice against the development of asthma.

Groeger D. Bifidobacterium infantis 35624 & Lactobacillus rhamnosus JB-1 Fractions modulate MDDC response to rhinovirus.

Morita H. Retinoic acid controls homeostasis by converting ILC2 into regulatory phenotype.

Morita H. Role of Interleukin-33 in innate type immune cells in allergy.

Olzhausen J. Quantitative measurements Using the EVA technology.

Sabate Bresco M. Immune responses in an implant-associated infection model.

Sokolowska M. Beginning of Tolerance in Allergen Specific Immunotherapy.

Sugita K. Group 2 innate lymphoid cells regulate bronchial epithelial cell tight junctions and promote airway inflammation.

van de Veen W. Identification of novel human effector B cell subsets.

Wawrzyniak M. Transcriptomic characterization of human IL-22-producing T cells by next generation RNA sequencing.

Wawrzyniak P. Regulation of bronchial epithelial barrier integrity by

type 2 cytokines and histone deacetylases in asthma.

Wirz O. Rhinovirus - B cell interactions.

Winner of the SIAF Science Day 2015: Hideaki Morita

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

Graduate School Graubünden - Co-founder and vice president

Euronanomed Program “NANOASIT II” - Steering board member

Euronanomed Program “NANOASIT II” - Work package leader

Eurostars Projekt 8599 DIAPET - Steering board member

Eurostars Projekt 8599 DIAPET - Work package leader

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

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

Global Allergy Forum Davos - Member

Naturforschende Gesellschaft Davos - Advisory board member and treasurer

World Immune Regulation Meeting - Member of the organizing committee

Davos Diagnostics AG – CEO

O’Mahony L.
EAACI Immunology Section Secretary 2013-2015.

EAACI Immunology Section Chair 2015-2017.

EAACI Executive Committee Member 2015-2017.

Management Committee Member to EU COST Action FA1402 – Improving Risk Assessment Strategies for Food Allergens (Impa-ras).

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

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

Scientific program committee member for the annual EAACI meeting, Barcelona 2015.

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

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

Academia Raetica - Member

British Biochemical Society - Member

World Immune Regulation Meeting - Member of the organizing committee

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

European Journal of Immunology, editorial board member

Expert Opinion on Emerging Drugs, editorial board member

International Reviews of Immunology, editorial board member

Journal of Allergy and Clinical Immunology, 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

Mycoses, deputy editor

The open Immunology Journal, editorial advisory board member

O'Mahony L.
Allergy. Member of the editorial board

Rhyner C.
Allergy. Member of the editorial board

Collaborations with the Clinics of Davos

AO Research Institute Davos (ARI), (Prof. M Alini, Dr. F. Moriaty, Dr. D. Nehrbass)

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

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

Spital Davos (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)

Alimentary Health Ltd, Cork (IE), (Dr. J. Roper, Dr. B. Kiely)

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, Dr. H. Kahlert, Dr. N. Karschuk)

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)

Catalan Institute for Research and Advanced Studies (ICREA), Barcelona Biomedical Research Park, Barcelona (ESP), (Prof. A. Cerutti)

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

Centre Hospitalier Universitaire Vaudois (CHUV), Faculty of Biology and Medicine, University of Lausanne, Service de Pneumologie, Lausanne, (Dr. B. Marsland)

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

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

Complutense University Madrid (ESP), (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. O. Holst)

GSK, London (UK), (Dr E. Hessel, Dr. D. Michalovich)

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

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

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

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

Inselspital Bern, Universitätsklinik für Rheumatologie, Immunologie und Allergologie, Bern (CH), (Prof. Dr. A. Helbling, Dr. N. Meyer, Dr. A. Gschwend)

Inselspital Bern, HNO Universitätsklinik, Bern (CH), (Dr. U. Borner, Dr. S. Negoias, Dr. S-L. Hool)

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, Prof. H. Grönlund, Prof. O. Rasool, Prof. A. Scheynius, Prof. M. van Hage, Dr. S. Thunberg, Prof. G Nilsson, Dr. J. Mjösberg)

Klinikum rechts der Isar, Institut für Umweltmedizin, Technische Universität München (D), (Prof. C. Traidl-Hoffmann)

McMaster Brain-Body Institute, Hamilton (CA), (Prof. J. Bienenstock)

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

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, Department of Immunology, Rheumatology and Allergy Lodz (P), (Prof. M. Kowalski)

Medical University of Vienna, Au, Department of Pediatrics, Vienna (A), (Prof. Z. Szepfalusi)

Medizinische Hochschule Hannover, Klinik für Dermatologie, Allergologie und Venerologie, Hannover (DE), (Prof. T. Werfel)

National Research Institute for Child Health and Development, Tokyo (JP), (Prof. H Saito, Dr. K Matsumoto)

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

Odense Universitetshospital (DK), (Dr. Bindslev-Jensen, Dr. E. Eller)

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

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

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

Philipps-Universität Marburg, Institut für Laboratoriumsmedizin und

Pathobiochemie, Molekulare Diagnostik (DE), (Dr. D.P. Potaczek)

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. K. Nadeau)

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

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)

The Hospital for Sick Children, Cancer and Blood Research Program, Toronto (CAN), (Dr. T. Eiwegger, 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 (Prof. E. Marti, Prof. A. Zurbriggen)

Universität Bern, Dept, Clinical Research (Dr. W Hofstetter)

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

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

Universitätsklinikum Erlangen, Abteilung Molekulare Pneumologie (D), (Prof. Dr. Dr. S. Finotto)

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

University of Manchester, Centre for Paediatrics and Child Health, Institute of Human Development (UK), (Prof. N.G. Papadopoulos)

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

University of Tokyo (JP), (Prof. S Nakae)
Universität Zürich, Clinical Trials Center, Zürich (CH), (PD Dr. G. Senti)

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

Universitätsspital Bern, Kinderklinik, Inselspital, Bern (CH), (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), (Prof. M. Kohler)

Universitätsspital Zürich, Abteilung Gastroenterologie, Zürich (CH), (Prof. G. Rogler)

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

University Hospital Ghent, Upper Airways Research Laboratory (BEL), (Prof Dr. Dr. h.c. C. Bachert)

University of Natural Resources and Life Sciences, Vienna (AT), (Prof. F. Altmann)

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 Marseille (F), (Prof. B. Malissen)

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

University of Oslo (S), (Prof. K. T. Smerud)

University of Turku (FIN), (Dr. T. Jartti)

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)

University of Uppsala, Uppsala ((S), Prof. E. Hakan, Dr. X. Wei)

University Children's Hospital, Dr. von Haunersches Kinderspital, LMU Munich (D), (PD Dr. E. Renner)

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

Zentrums für Rhinologie und Allergologie, Wiesbaden (D), (Prof. L. Klimek)

Schweizerisches Institut für Allergie- und Asthmaforschung

Bilanz per 31. Dezember 2015

(inklusive Drittmittel)

	31.12.2015	31.12.2014
	CHF	CHF
AKTIVEN		
Flüssige Mittel	1'976'206.35	1'615'787.49
Forderungen	170'272.04	23'796.55
Aktive Rechnungsabgrenzungen	368'924.84	259'880.36
	2'515'403.23	1'899'464.40
PASSIVEN		
Verbindlichkeiten	226'343.83	113'780.47
Kontokorrent SFI Stiftung	77'486.25	212'756.40
Passive Rechnungsabgrenzungen	1'634'936.85	1'215'523.20
Rückstellungen	357'179.81	137'947.84
Eigenkapital	219'456.49	219'456.49
	2'515'403.23	1'899'464.40

Schweizerisches Institut für Allergie- und Asthmaforschung

Betriebsrechnung 2015

(inklusive Drittmittel)

	Rechnung 2015	Budget 2015	Rechnung 2014
	CHF	CHF	CHF
ERTRAG			
Beitrag Bund Forschungsgesetz Art. 16	843'000.00	852'500.00	840'000.00
Beitrag Kanton Graubünden	290'000.00	146'050.00	146'050.00
Beitrag Gemeinde Davos	424'560.00	425'000.00	424'560.00
Beitrag Universität Zürich	657'078.70	630'000.00	326'180.90
Beitrag Stiftung SFI Villa Fontana	100'000.00	100'000.00	100'000.00
Beitrag Stiftung SFI Mieterlass	160'000.00	160'000.00	0
Beitrag Stiftung vormals Bündner Heilstätte Arosa	75'000.00	75'000.00	75'000.00
Beitrag Stiftungen/Drittmittel	233'000.00	0	0
Overheadbeiträge	99'767.00	201'930.00	90'693.00
Ertrag aus Dienstleistung Asthmaforschung	- 400.00	5'000.00	2'721.04
Übriger Ertrag	55'428.57	3'000.00	32'500.80
Finanzertrag	41.35	0	84.28
WIRM-Kongress	351'235.26	450'000.00	401'363.93
Drittmittel	2'468'864.36	2'164'392.00	2'755'376.25
	5'757'575.24	5'212'872.00	5'194'530.20
AUFWAND			
Personalaufwand	2'997'068.68	2'804'352.00	3'079'722.59
Verbrauchsmaterial	1'131'649.61	1'174'020.00	997'574.51
Raumaufwand	170'077.70	165'000.00	17'521.41
Unterhalt/Reparaturen/Ersatz	109'144.02	115'500.00	138'319.02
Investitionen	737'402.41	300'000.00	327'880.76
Sachversicherungen/Abgaben	8'162.85	7'500.00	7'358.70
Energie- und Entsorgungsaufwand	67'537.40	83'000.00	66'110.95
Verwaltungsaufwand	142'932.14	171'500.00	118'403.61
Reisespesen	103'456.52	75'000.00	119'939.86
WIRM-Kongress	268'146.18	306'500.00	299'853.88
Übriger Betriebsaufwand	14'394.50	4'000.00	4'933.45
Finanzaufwand	3'006.15	1'000.00	2'092.87
Ausserordentlicher Aufwand	4'597.08	5'500.00	14'818.59
	5'757'575.24	5'212'872.00	5'194'530.20
Ergebnis	0	0	0
	5'757'575.24	5'212'872.00	5'194'530.20

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