Jahresbericht 2011
Annual Report 2011

Schweizerisches Institut für Allergie- und Asthmaforschung (SIAF)

Abteilung der Stiftung Schweizerisches Forschungsinstitut für Hochgebirgsklima und Medizin Davos (SFI)

A Department of the Foundation Swiss Research Institute for High Altitude Climate and Medicine Davos (SFI)

Philosophie
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

Universität Zürich[UZH]

Schweizerisches Institut für Allergie- und Asthmaforschung (SIAF)

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JAHRESBERICHT 2011

Bericht des Direktors

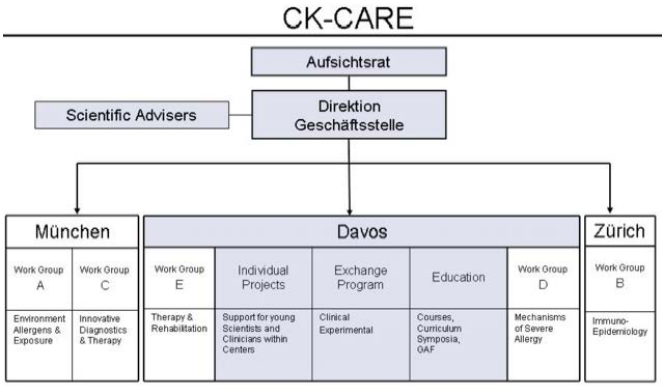
Prof. Dr. med. Cezmi A. Akdis

Allergische Erkrankungen sind eines der Hauptprobleme im Gesundheitswesen, weshalb die EU im November 2011 entschieden hat , chronische Atemwegserkrankungen (vor allem Asthma) bei Kindern als Priorität im Gesundheitswesen anzuerkennen. Allergien sind klassische Umweltkrankheiten, die durch eine fehlgeleitete Auseinandersetzung des individuellen Organismus mit Stoffen aus der Umwelt hervorgerufen werden. Allergien gehören zu den grossen globalen gesundheitspolitischen Herausforderungen unserer Zeit. Sie haben in den letzten 3 - 4 Jahrzehnten – insbesondere in den Industrienationen – dramatisch an Häufigkeit zugenommen, ohne dass die Ursachen hierfür eindeutig geklärt wären. Allergische Erkrankungen sind durch ihren chronischen Verlauf und ihr teilweise lebensbedrohliches Erscheinungsbild nicht nur für die Betroffenen ein schweres Schicksal. Sie stellen auch eine erhebliche sozio-ökonomische Belastung für die Volkswirtschaft dar. Allergien sind eine der grossen gesundheitspolitischen Herausforderungen in fast allen Ländern der Welt.

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. Zusätzlich wird die Forschung von den europäischen FP7-Programmen MeDALL, PREDICTA, ALLFUN, EURONANOMED und Marie-Curie unterstützt.

Die EAACI ist die weltgrösste Akademie für allergische Erkrankungen und übernimmt eine wichtige Rolle in Bezug auf Wissenschaft, Weiterbildung, Kommunikation und Öffentlichkeitsarbeit. Dieses Jahr steht der jährlich stattfindende Kongress in Genf auf dem Programm mit rund 7‘000 erwarteten Teilnehmern. Zudem organisiert die EAACI in Zusammenarbeit mit dem SIAF und der CK-CARE AG die in Davos jährlich stattfindenden EAACI Davos Schools mit rund 100 jungen Teilnehmern. Prof. C. Akdis war in den Jahren 2008-2011 als Vizepräsident der EAACI für die Sektion Immunologie tätig. 2011 wurde er zum Präsidenten der Akademie gewählt. Seine Amtsperiode dauert von 2011 - 2013. Dr. L. O‘Mahony ist Vorstandsmitglieder der Sektion Immunologie. PD Dr. M. Akdis ist Mitglied des Herausgebergremius und Prof. R. Crameri Associate Editor von Allergy, Hauptjournal der EAACI.

In den letzten 2 Jahren haben sich beachtliche Fortschritte in der Aufklärung der grundlegenden Mechanismen, welche zu allergischen Erkrankungen führen, erzielen lassen. Nach wie vor besteht allerdings eine grosse Kluft zwischen theoretischem Wissen und Alltagserfahrung der Betroffenen und ihres Umfeldes. Die Kühne-Stiftung weitet deshalb ihre Förderaktivitäten auf das Gebiet der Allergologie aus und hat das Allergieforschungsprojekt „CK-CARE Christine Kühne – Center for Allergy Research and Education“ ins Leben gerufen mit dem Ziel, Forschung, Weiterbildung und Prävention auf dem Gebiet der Allergien zu fördern und die Umsetzung der Forschungsergebnisse in die klinische Versorgung zugunsten der betroffenen Patienten zu verbessern. Das SIAF in der CK-CARE eine tragende Rolle.



In unserem Arbeitsbereich in der CK-CARE werden diejenigen Mechanismen erforscht, welche bei schweren Allergikern und Asthmatikern, die trotz therapeutische Behandlung nach dem modernsten Stand der Wissenschaft zur Entwicklung von Krankheitsymptomen führen. Zwischen 2010 und 2011 wurden neue Moleküle identifiziert, welche die Funktion von einer speziellen Zelle steuern, die letztlich über die Entstehung und den Schweregrad einer Allergie entscheidet. Deren genauere Charakterisierung wird in Zukunft möglicherweise zu neuen Behandlungstherapien führen. Es wurde auch gezeigt, dass die abnorm hohe Durchlässigkeit der Epithelien bei Asthmatikern auf Störungen von Zell-Zell-Kontakten beruht. Diese sind mit Entzündungsprozessen verbunden, die zu Umbauvorgängen im darunter liegenden Bindegewebe führen. Zudem hat die CK-CARE spezifische Projekte auf dem Gebiet von Asthma und schwerer Allergie sowie Immuntoleranz gegenüber Allergenen am SIAF unterstützt.

Dank der Unterstützung durch die CK-CARE konnten seit 2011 elf wissenschaftliche Mitarbeiter eingestellt und zehn akademische Gäste im Austauschprogramm aufgenommen werden, die an den folgenden Projekten gearbeitet und 23 Publikationen in namhaften Zeitschriften veröffentlicht haben.

- Allergische Erkrankungen entstehen aus einem Ungleichgewicht zwischen Allergen-induzierter Aktivierung von regulatorischen Zellen und Effektor-Zellen. Allergen-spezifische T-Zell-Toleranz beruht auf der Unterdrückung von pathologischen, zellvermittelten und humoralen Antworten sowie auf der Unterdrückung von gestörten Interaktionen zwischen Immun- und Gewebszellen. Die Identifikation von Molekülen, die entscheidend für die Funktion oder Dysfunktion der regulatorischen Zellen sind und somit zur Entstehung dieser Krankheitsbilder beitragen, kann zur Entwicklung neuer Behandlungstherapien führen.

- Human-regulatorische B-Zellen: Dieses Projekt befindet sich im zweiten Jahr und soll, angesichts der Aktualität dieses Forschungszweiges, effizient weiterentwickelt werden. Treg- und Breg-Zellen befinden sich in menschlichen Tonsillen, die eine zentrale Organe der Immuntoleranz darstellen. Die vorläufigen Ergebnisse deuten darauf hin, dass dieses Projekt effizient dazu beitragen kann, die Mechanismen der Immunregulation besser zu verstehen.

- Defekte in der Ausbildung von Tight Junctions sowie der Aktivierung und Apoptose von bronchialen Epithelzellen und Keratinozyten bei allergischen Erkrankungen: Das Epithel von Asthmatikern und Patienten mit Neurodermitis zeigt eine abnorm hohe Durchlässigkeit durch Defekte in der Ausbildung von Tight Junctions und ist in der Lage, Zytokine und Wachstumsfaktoren zu produzieren, die den Entzündungsprozess und die Umbauvorgänge unterhalb der Basalmembran beeinflussen.

- Die Remodellierung im Asthma, die eine Konsequenz der übermäßigen Reparaturprozesse sein könnte, führt zur Ablagerung von verschiedenen extrazellulären Matrixproteinen in der Basalmembran und der bronchialen Mukosa sowie zu einer Erhöhung der glatten Atemwegsmuskulaturmasse, Becherzell-Hyperplasie und zu neuer Blutgefässbildung. Infolgedessen ist die asthmatische Atemwegwand verdickt und die Luftzufuhr reduziert. Die Wissenschafter am SIAF erforschen Mechanismen zum besseren Verständnis der Atemwegsremodellierung und entwickeln Strategien, um Gewebezerstörungen und die Remodellierung bei Asthma und Neurodermitis zu behandeln. Die Gewebezerstörung durch aktiven Zelltod der Epithelzellen in der Haut, der Lungen- und der nasalen Epithelzellen sowie der glatten Muskelzellen der Lunge, zusammen mit den involvierten Vermittlern und Empfänger, stellt ein Forschungsschwerpunkt am SIAF dar.

- Die Rolle zirkulierenden Fibrozyten bei Neurodermitis und allergischem Asthma: Dieses Forschungsprojekt beschäftigt sich mit der Rolle von zirkulierenden Fibrozyten in der Pathogenese von Neurodermitis und allergischem Asthma.

Die Forschungsaktivitäten am SIAF fokussieren sich auf die immun-pathologischen Mechanismen von allergischen Erkrankungen und Asthma. Geforscht werden die zellulären und molekularen Mechanismen, welche die Gesundheit und die allergische Reaktion auf allergene Stoffe regulieren sowie die Auswirkungen der aktivierten Immunzellen auf die Gewebszellen der betroffenen Organe. Es werden neue Zielvorgaben für die Arzneimittelentwicklung untersucht und neue Impfungstoffe für die allergenspezifische Immunotherapie entwickelt. Schwerpunkt unserer Studien ist die humane *in vivo*-Forschung mit direkter Untersuchung von humanen Biopsieproben, Körperflüssigkeiten und peripherem Blut.

Die folgenden Forschungsgebiete werden aktuell am SIAF bearbeitet und durch den Schweizerischen Nationalfonds, die CK-CARE AG, MeDALL, PREDICTA, ALLFUN, NANOASIT, Marie Curie, Müller-Gierok Stiftung sowie durch andere private Stiftungen und Firmen gefördert:

- Die zellulären und molekularen Grundlagen bei der Auswanderung spezifischer T-Lymphozyten in das Gewebe und ihre Wirkung bei der Entstehung aller-

gischer Entzündungen in den betroffenen Organen. Letztendlich finden die allergischen Entzündungen im Gewebe und in verschiedenen Organen statt. Gewebe-selektive Rezeptoren steuern zusammen mit verschiedenen Chemokinen die Auswanderung der Entzündungszellen in Haut und Lunge.

- Überschiessende Antworten von Fibroblasten und glatten Muskelzellen auf Reize bei Neurodermitis und allergischem Asthma: Forschungsansatz: Persistierende entzündliche Verhältnisse führen zu einer veränderten Expression und/oder Funktion einer grossen Anzahl von pro-inflammatorischen Zytokinen, und dies führt zur Dysregulation der Differenzierung, Proliferation und Apoptose von glatten Muskelzellen, Schädigungen des Epithels, Verdickung der sub-epithelialen Basalmembran und Zellinfiltration.

- Asthma Patienten reagieren auf harmlose Stoffe (Allergene) mit einer Entzündung anstatt mit Toleranz, was die normale Reaktion von gesunden Personen wäre. Die Hiluslymphknoten – die zentralen Organe des Immunsystems bei Erkrankungen der Lunge – werden während der Entwicklung von Asthma umorganisiert. Lymphoides Gewebe induzierende Zellen (lymphoid tissue inducer cells, LTi-Zellen) sind die „Architekten" der lymphoiden Organe. Sie haben eine fundamentale Rolle in der Bestimmung von Struktur und Funktion von lymphoidem Gewebe. Unsere Hypothese lautet, dass diese LTi-Zellen in die Entwicklung und das Andauern einer Asthma-Erkrankung involviert sind.

- Das menschliches Mikrobiom enthält eine enorme Vielfalt verschiedener Bakterienstämme mit einer ebenso erstaunlich grossen Anzahl an Genen mit einer Reihe metabolischer Funktionen, welche die immunregulatorischen Mechanismen des Menschen beeinflussen. Die Arbeitsgruppe Molekulare Immunologie macht signifikante Fortschritte bei der Entdeckung neuer Wechselwirkungen zwischen dem Wirt und den mikrobiellen Erregern. So haben wir herausgefunden, dass gewisse kommensale Mikroorganismen den Retinoidsäurehaushalt innerhalb menschlicher dendritischer Zellen über die Rezeptoren TLR-2 und DC-SIGN begünstigen. Dieser Mechanismus ist für die Polarisation von naiven Lymphozyten in Foxp3+ regulatorische T-Zellen verantwortlich. Zusätzlich haben wir entdeckt, dass gewisse Bakterien Histamin sekretieren und mikrobielles Histamin den TLR-Signalweg in den dendritischen Zellen des Wirts beeinflusst. Histamin senkt die entzündliche Reaktion gegenüber mikrobieller Liganden über den Histamin-2-Rezeptor. Bei Histamin-2-Rezeptor-Knockout-Mäusen konnten wir einen erhöhten Schweregrad von Atemwegsallergien und eine verstärkte Entzündungsaktivität als Folge von veränderter Aktivitäten verschiedener Zelltypen beobachten, zu denen auch regulatorische T-Zellen, B-Zellen, dendritische Zellen und iNKT-Zellen gehören.

- Das Projekt MeDALL „Mechanismen der Entstehung von Allergien" hat zum Ziel, die Gründe für die Allergie-Epidemie zu verstehen, damit der Gesundheitszustand der europäischen Bevölkerung verbessert werden kann und soll bahnbrechende Erkenntnisse betreffend Ursachen und Mechanismen von allergischen Erkrankungen (einschliesslich Asthma, allergische Rhinitis, atopische Dermatitis und Nahrungsmittelallergie, insbesondere bei Kindern) eröffnen. Haben Umweltfaktoren Einfluss auf die Entwicklung von Allergien? Wenn ja, inwiefern tragen diese Faktoren zur globalen Allergie-Epidemie bei?

- NANOASIT (Novel drug delivery routes mediated via nanotechnology: targeting allergy vaccination) ist ein vom Schweizerischen Nationalfonds zur Förderung der wissenschaftlichen Forschung im Rahmen der Europäischen Initiative EuroNanoMed unterstütztes Forschungsprojekt. Ziel des Projektes ist die Entwicklung neuartiger Vakzinierungskonzepte zur Behandlung allergischer Erkrankungen basierend auf Nano-Partikeln. Das SIAF hat bereits mehrere Ansätze für die Entwicklung von spezifischen Vakzinen ausgearbeitet, die direkt auf den MHC Klasse II Präsentationsweg zielen. Diese neuartigen Vakzine wurden bereits erfolgreich in einer Phase I/IIa klinischen Studie getestet. Für das NANOASIT-Projekt werden wir, basierend auf unserer Erfahrung in Klonierung und Produktion rekombinanter Allergene, neuartiger Vakzine entwickeln, welche die Fähigkeit besitzen, selektiv von dendritischen Zellen (DC) aufgenommen zu werden. Dazu werden wir aus Peptidbibliotheken, welche auf der Oberfläche von filamentösen Phagen exprimiert werden, solche Peptide, isolieren die von dendritischen Zellen spezifisch aufge-

nommen werden. Die gentechnologische Fusion dieser Peptide mit rekombinanten Allergenen wird es erlauben, DC-spezifische Vakzine zu entwickeln. Diese sollen nach chemischer Kopplung mit Nano-Partikeln subkutan injiziert werden, um einen lang anhaltenden Depot-Effekt zu erzielen.

- Die Bedeutung aktivierter regulatorischer T-Zellen für die Entwicklung einer nichtallergischen Immunreaktion und die biochemischen Signale, welche die Aktivierung der regulatorischen Zellen steuern. Die Entwicklung einer genügenden Anzahl regulatorischer T-Lymphozyten, die das Allergen erkennen und die allergische Immunabwehr unterdrücken, ist entscheidend für die Entstehung einer normalen Immunreaktion. Bei Allergien sind diese regulatorischen Zellen zu wenig ausgeprägt, um die allergische Immunantwort zu unterdrücken. Diese neuen Erkenntnisse über Vorgänge, die zur Vermehrung dieser regulatorischen Zellen führen, dienen nicht nur dem grundlegenden Verständnis allergischer Krankheiten, sie sind auch eine Voraussetzung für die Entwicklung verbesserter Therapien.

- In den letzten Jahren wurde herausgefunden, dass es sich bei den Th9, Th17 und Th22 Zellen um einen eigenen Differenzierungsweg, zusätzlich zu Th1, Th2 oder T_{reg} handelt. Es ist auch klar, dass Th17 und Th22 eine wesentliche Funktion in der Pathogenese von Autoimmunkrankheiten und Chronizität spielen. Unbekannt sind noch die Stabilität und Plastizität dieser Zellen im Menschen: Kann die Differenzierung zu Th9, Th22 und Th17 Zellen verhindert oder rückgängig gemacht werden? Für die Bekämpfung welcher Infektionserreger sind Th17-Zellen unabdingbar? Ausser IL-17 produzieren die Th17-Zellen eine Reihe weiterer Zytokine (TNF-α, GM-CSF, IL-6, IL-22). Wir können sicher sein, auch in den nächsten Jahren neues von den Th-Zellen zu hören, die Unterteilung der Th-Zellen in Th1 und Th2 gehört der Vergangenheit an.

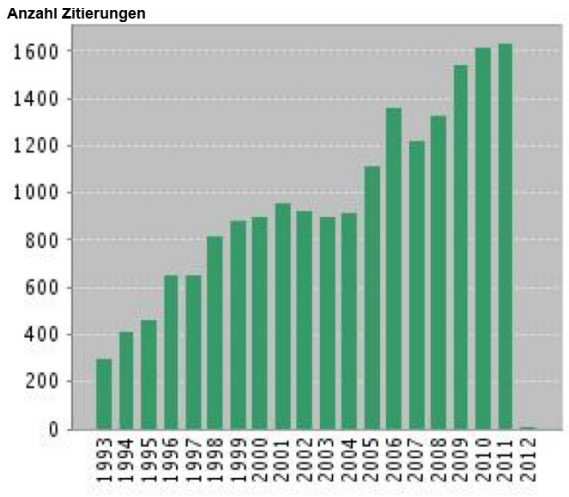
- Die Hauptthese des Programms PREDICTA besteht darin, dass wiederholte akute Infektionen die angeborene, adaptive und/oder regulatorische Immunantwort so verändern, dass ein chronisches Entzündungsmuster entstehen kann. Diese Studie untersucht die Regulierung von Entzündungen durch akute Infektionen in Patientenkohorten, Mausmodellen und experimentellen *in-vitro*-Systemen. Durch die Ermittlung von spezifischen Wirkelementen sollen innovative Möglichkeiten zur Diagnostik von Chronizität entwickelt werden. Es sollen Strategien entwickelt werden, um die Progredienz/Persistenz von Krankheiten zu verzögern und/oder zu verhindern, indem man sich auf ursächliche oder spezifische Elemente von Entzündungsabläufen fokussiert.

- Die allergen-spezifische Immunotherapie (SIT) wird seit fast einem Jahrhundert als desensibilisierende Therapie für allergische Krankheiten eingesetzt und ist die einzige kurative Behandlungsmethode. Durch die Verabreichung von Allergenextrakten in steigender Konzentration konnte gezeigt werden, dass eine reproduzierbare Wirkung erzielt wird, wenn die Patienten sorgfältig ausgewählt werden. Jedoch tragen die derzeitigen Allergen-SIT-Impfstoffe und die Behandlungsprotokolle Nachteile mit sich. Diese beziehen sich auf den Inhalt des Impfstoffs, des Anwendungswegs, die lange Behandlungsdauer, Nebenwirkungen und zum Teil auf eine eingeschränkte Wirksamkeit. Es sind einige Strategien entwickelt worden, um diese Kernprobleme anzugehen und es wurde möglich, rekombinante Allergen-SIT-Impfstoffe mit verringerten Nebenwirkungen zu entwickeln. Die Rolle immunmodulatorischer und antigen-spezifischer Adjuvantien in der Schleimhaut-SIT wird intensiv erforscht und wertvolle Erkenntnisse konnten veröffentlicht werden. Das gegenwärtige Verständnis von immunologischen Mechanismen der Allergen-SIT, besonders der Rolle der regulatorischen T-Zellen in der allergen-spezifischen peripheren Toleranz, ermöglicht es, neue Behandlungstrategien zu entwickeln. Mit Hilfe neuester Erkenntnisse und Methoden werden am SIAF verbesserte und sicherere Ansätze für die zukünftige Prävention und Heilung allergischer Erkrankungen erarbeitet.

- Seit dem Anfang beschäftigt sich das SIAF mit Pilzallergien, ein nach wie vor ungelöstes Problem. Im Rahmen des 7th Framework Programms hat jetzt die Europäische Kommission das Problem erkannt und ein Grossprojekt unter dem Titel „Fungi in the setting of inflammation, allergy and autoimmune diseases: Translating basic science to clinical practices“ bewilligt. In diesem Forschungsprojekt nimmt das SIAF eine führende Rolle ein und das wird uns erlauben, während der nächsten Jahre diese Forschungsrichtung zu verstärken.

- Die Untersuchung der chemischen Struktur und biochemischen Eigenschaften von Allergenen sowie deren Herstellung in reiner Form mittels Genklonierung. Die rekombinant hergestellten Allergene finden vor allem in der klinischen Feindiagnostik allergischer Krankheiten Verwendung. Sie führen zu einem besseren Verständnis der molekularen Grundlagen der Allergenizität und Kreuzreaktivität zwischen Allergene von unterschiedlicher Herkunft und aus unterschiedlichen Spezies.

Das vergleichsweise kleine SIAF hat über 760 Fachbeiträge veröffentlicht und gehört zu den meistzitierten Instituten weltweit. Die vom SIAF publizierten Artikel wurden über 25'000 Mal zitiert. Das Institut gehört mit seinen rund 40 Mitarbeitern (im Vergleich zu Universitäten mit Tausenden von Forschern) weltweit zu den Besten bezüglich Anzahl Mitarbeiter oder Zitierung geteilt durch Budget. In den letzten 6 Jahren konnte eine signifikante Erhöhung der Anzahl Zitierungen erreicht werden. Es ist eine international bekannte Ausbildungsstätte für Doktoranden und Habilitanden.



Im vergangenen Jahr wurden insgesamt 76 wissenschaftliche Arbeiten (ohne Abstracts) publiziert. 72 wurden in begutachteten internationalen Fachzeitschriften mit "Impact Factor" veröffentlicht. Davon sind 23 Artikel dank der Unterstützung der CK-CARE AG publiziert worden. Der durchschnittliche "Impact-Factor" betrug 6.80 Punkte. 2011 erreichte das SIAF einen Gesamtwert des "Impact Factors" von 462.446. Die neusten Ergebnisse wurden zudem in 35 Kurzfassungen (Abstracts) an verschiedenen Fachtagungen mitgeteilt. Mitarbeiter des SIAF wurden zu 65 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 35 verschiedenen Sessionen hatten SIAF Mitarbeiter den Vorsitz. Zusätzlich werden 37 wissenschaftliche Ämter in internationalen Gesellschaften durch Wissenschaftler des SIAFs besetzt. Desweiteren sind die Forscher des SIAF bei insgesamt 20 internationalen Zeitschriften als Mitglieder der redaktionellen Komitees tätig.

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. Die Daten werden ausgewertet und die Befunde unter Berücksichtigung der klinischen Symptome und Verdachtsdiagnosen den Kliniken und Ärzten in übersichtlicher Form mitgeteilt. Mit Hilfe der Immunphänotypisierung ist es möglich, Lungenerkrankungen, Asthma und chronische Entzündungen, Immundefekte sowie lymphoproliferative Erkrankungen zu diagnostizieren und in ihrem Verlauf zu kontrollieren. Ausserdem wird dieses Verfahren zur Beurteilung der Reaktivität des Immunsystems und zum Erfassen von Nebenwirkungen bei immunsuppressiver Therapie herangezogen. Das SIAF besitzt die Bewilligung zur Durchführung dieser Untersuchungen, die auch mit einer regelmässigen Kontrolle durch ein anerkanntes, externes Kontrollinstitut verbunden ist. Im Jahr 2011 wurden insgesamt 73 Blut- oder BAL-Analysen durchgeführt.

Die klinische Dienstleistung am SIAF wurde unter der Leitung von Prof. Dr. Cezmi A. Akdis, dem technischen Personal des SIAF und in Zusammenarbeit mit Dr. Anna Kirsch und Dr. Norbert Meyer von der Hochgebirgsklinik Davos-Wolfgang, durchgeführt.

Das SIAF bietet als einziges Institut im gesamten Kanton

Prof. Dr. med. Cezmi A. Akdis

Graubündenden 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) erteiltem Zertifikat, das auch mit einer regelmässigen Kontrolle durch ein anerkanntes, externes Kontrollinstitut (UK-NEQAS for Immunophenotyping, Sheffield, UK) verbunden ist.

Ausbildung und Lehrverpflichtungen
Eine wichtige Aufgabe erfüllt das SIAF in der Ausbildung von Studenten und Studentinnen 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 R. Crameri an der Blockvorlesung „Molekulargenetische Grundlagen der Immunologie“ der Universität Salzburg beteiligt.

Nebst zahlreichen Seminaren mit eingeladenen Referenten führt das SIAF gemeinsam mit den Kliniken klinische Fallbesprechungen, verbunden mit Forschungsergebnissen, durch. Diese 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. Zudem organisiert das SIAF mit der EAACI und der CK-CARE die Winter School mit.

Prof. C. Akdis und PD Dr. M. Akdis haben eine Honorarprofessur am Tungren Spital der Peking-Universität. Zudem ist Prof. C. Akdis Fakultätsmitglied der Medizinischen Fakultät der Universität Zürich mit Promotionsrecht in der Mathematischen und Naturwissenschaftlichen Fakultät.

Kongressorganisation 2012
Das international ausgeschriebene World Immune Regulation Meeting (WIRM) zählt mittlerweile in Europa zum angesehensten Kongress seiner Art und zieht hochkarätige Senior-Wissenschaftler sowie Nachwuchsforscher an. Vom 18. bis 21. März 2012 fand zum sechsten Mal das WIR-Meeting im Kongresszentrum Davos statt. Rund 750 Wissenschaftler aus aller Welt trafen sich zu diesem viertägigen Kongress, um sich über die neuesten Erkenntnisse in der Immunologie auszutauschen und es wurden 115 Vorträge und 394 Abstracts vorgestellt.

Dabei trafen sich erfahrene Experten und talentierte Nachwuchsforscher. WIRM ist gross genug, um von anderen zu lernen und klein genug, um die Experten persönlich zu treffen. Dieser globale Austausch von hochwertigen aktuellen Erkenntnissen hilft, neue Behandlungstherapien zu entwickeln und neue Lösungsansätze für Patienten zu finden.

Zudem bietet das WIRM eine perfekte Plattform, um die besten Forscher im Gebiet zu versammeln und auf höchstem Niveau die neuesten Entwicklungen in der Immunologie zu diskutieren.

Die Besucher des World Immune Regulation Meetings nehmen tagsüber an hochkarätigen wissenschaftlichen Vorträgen teil. Die Abende im Kongresszentrum sind reserviert, um in ungezwungener Atmosphäre wissenschaftliche Projekte in Form einer Posterausstellung zu präsentieren und dabei kulinarisch verwöhnt zu werden. Der Kongress generiert jährlich etwa 4’000 Übernachtungen in den Davoser Hotels und in den Ferienwohnungen.

Personal
Gegenwärtig beschäftigt das SIAF 45 Mitarbeiter. Davon zählen 38 zu den wissenschaftlichen Angestellten. Derzeit führen am SIAF 11 Doktoranden eine naturwissenschaftliche Doktorarbeit durch. Die Europäische Akademie für Allergologie und Klinische Immunologie (EAACI), das europäische FP7-Förderungsprogramm Marie-Curie, die Müller-Gierok Stiftung, die Swiss-

Bericht des Direktors

Polish Research Cooperation, das schweizerische Förderungsprogramm Scientific Exchange Programme NMS-CH sowie die European Respiratory Society (ERS) ermöglichten wiederum Forschern Weiterbildungsaufenthalte am SIAF. Insgesamt 11 Wissenschafter aus verschiedensten Ländern waren im letzten Jahr zu Gast im SIAF. Eine Direktionsassistentin sowie eine Kongressassistentin, eine 80%- und eine Halbtagesstelle für den Unterhalt und die Reinigung des Gebäudes vervollständigen das Personal. Die Buchhaltung und Lohnauszahlungen werden durch das Treuhandbüro Wälti Treuhand und Revisionen AG in Bad Ragaz erledigt.

Finanzielle Grundlage

Die Ausgaben und der finanzielle Ertrag des SIAF haben sich im Vergleich zu den vergangenen Jahren nur unwesentlich verändert. Eine Grundfinanzierung des Instituts ist durch die Hauptsponsoren gegenwärtig sichergestellt. Sie besteht vor allem aus einem Beitrag des Bundes (Forschungsförderungsgesetz Art.16), Beiträge des Kantons Graubünden und der Gemeinde Davos, Beiträge der CK-CARE AG, des Förderungsprogramms Sciex, der Müller-Gierok Stiftung sowie einem Beitrag der Stiftung Ehem. Bündner Heilstätte. Von spezieller Bedeutung waren bis jetzt die Beiträge der Hochgebirgsklinik Davos Wolfgang an das SIAF. Die zusätzlichen Ausgaben wurden aus Erträge des WIRM Kongresses und zusätzlichen Drittmitteln gedeckt. Für das Jahr 2011 stehen dem Ertrag inkl. der eingeworbenen Drittmittel von Fr. 4‘843‘928.- Ausgaben in Höhe von Fr. 4‘843‘928.- gegenüber. Die direkt eingebrachten Drittmittel belaufen sich auf total Fr. 2‘069‘150.-.

Dank

Für die grosse geleistete Arbeit und die gute Arbeitsatmosphäre im SIAF danke ich allen Mitarbeiterinnen und Mitarbeitern herzlich. Gleichzeitig danke ich den Davoser Kliniken, ihren Chefärzten und deren Mitarbeitern und Mitarbeiterinnen sowie allen Mitarbeiterinnen und Mitarbeitern der Allergiestation der Universität Zürich für die ständige, wirkungsvolle und problemlose Unterstützung unserer Projekte.

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, Mai 2012

Report of the Director

Prof. Dr. med. Cezmi A. Akdis

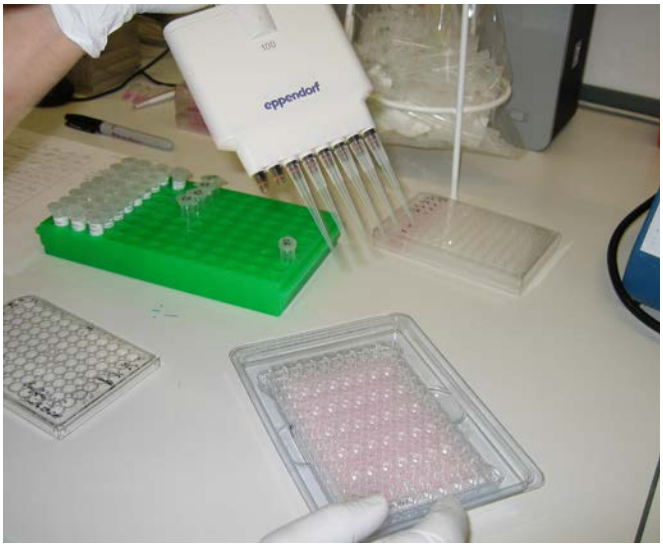
Allergic diseases are one of the most relevant public health problems and EU has decided to accept childhood chronic respiratory diseases (mainly asthma) as the number one public health priority in November 2011. Currently, allergy and asthma are the highest prevalent childhood chronic disease in the industrialized world. The main focus of SIAF has been to find ways for long-term cure and prevention of allergic diseases. This is only possible by induction of immune tolerance to allergens as observed in healthy individuals, who are exposed to high doses of allergens. Allergen-specific immune tolerance is based on suppression of pathological, cell-mediated and humoral responses, and on the suppression of defective interactions between Immune cells and tissue cells.

The development of a of regulatory T and B lymphocyte response, which recognize the allergen and suppress the immune response, is defining a key mechanism for the development of a normal immune defense. Allergen-specific immunotherapy (SIT) has been used for almost a century as a desensitizing therapy for allergic diseases and represents the only curative and specific way of treatment. Administration of appropriate concentrations of allergen extracts has been shown to be reproducibly effective when patients are carefully selected. However, current allergen-SIT vaccines and treatment protocols have several disadvantages related to the content of the vaccine, type of adjuvant, route of application, long duration of treatment, side effects, and sometimes limited efficacy. Several strategies have been developed to tackle these issues and it became possible to produce recombinant allergen-SIT vaccines with reduced allergenic activity. The use of immunomodulatory and antigen-directing adjuvants and mucosal SIT routes are being intensely investigated and fruitful results have been reported. Current understanding of immunological mechanisms of allergen-SIT, particularly the role of T regulatory cells (Treg) in allergen-specific peripheral tolerance, is an essential way for the development of novel treatment strategies. By the application of the recent knowledge, more rational and safer approaches are being investigated at SIAF for the future of prevention and cure of allergic diseases. Starting from the beginning of January 2012, Claudio Rhyner, PhD, is going to develop his own research, particularly on developing efficient vaccines to induce clinical allergen tolerance.

Our CK-CARE research focus has been the identification of molecular and cellular mechanisms that play a role in severity of asthma. Most asthmatic patients can be adequately managed according to practice guidelines, however, there is a minority group of patients with so called severe and refractory asthma, who remain poorly controlled despite high-dose treatment with inhaled glucocorticoids and β2-mimetics. Apart from classifications based on asthma severity and control, a number of clinical and pathological asthma phenotypes have also been distinguished. Remodeling in asthma, which might be the consequence of excessive repair processes following repeated airway injury, includes increased deposition of several extracellular matrix proteins in the reticular basement membrane and bronchial mucosa, as well as increases in airway smooth muscle mass, goblet-cell hyperplasia and new blood vessel formation. Consequently, the airway wall in asthma is usually characterized by increased thickness and markedly and permanently reduced airway caliber. SIAF investigates mechanisms of better understanding of airway remodeling and develops strategies to overcome tissue destruction and remodeling in asthma and atopic dermatitis skin related to disease severity. The epithelium of asthmatics and patients with atopic dermatitis shows an abnormally high permeability through defects in the formation of tight junctions and is capable of cytokines and to produce growth factors, the inflammatory process and the conversion processes influence below the basement membrane. We had and will have series of publications in the area with the support of CK-CARE. So far 23 articles were published supported by CK-CARE. We could engage 11 scientific co-workers and in the short term exchange programme there were 10 academic guests working on the specific projects of CK-CARE. Better understanding of asthma phenotypes and endotypes to address the complexities of the disease related to severity is very important and distinguishing phenotypes with regard to the severity or duration of the disease is essential. An asthma phenotype covers the clinically relevant properties of the disease, but does not show the direct relationship to the pathophysiology. Different pathogenetic mechanisms are addressed by the term ‚endotype'. Classification of asthma based on endotypes provides advantages for epidemiological, genetic,

and drug particularly recent biologicals-related studies. A successful definition of endotypes and identification of corresponding molecular biomarkers for individual pathogenic mechanism underlying subgroups within a phenotype is essentially important. Thus, our research on better understanding asthma endotypes and their relationship to phenotypes will be more and more important in the future for clinical practice.

The human microbiome contains an enormous diversity of different bacterial strains, with an equally astonishing number of genes conferring an array of metabolic functions, that influence immunoregulatory mechanisms of the host. The Molecular Immunology group has made significant progress in discovering novel microbial-host immunoregulatory interactions. We have identified that certain commensal microbes promote retinoic acid metabolism within human dendritic cells, via TLR-2 and DC-SIGN, and this mechanism is responsible for the polarization of naïve lymphocytes into Foxp3+ regulatory T cells. In addition, we have discovered that certain microbes secrete histamine and microbial-derived histamine modulates TLR signaling pathways in host dendritic cells. Histamine decreases the pro-inflammatory response to microbial ligands via the histamine 2 receptor. Using histamine 2 receptor KO mice, we have observed increased severity of respiratory allergy and inflammatory activity, which is due to altered activity of multiple cell types including T regulatory cells, B regulatory cells, dendritic cells and iNKT cells.



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The project MeDALL stands for “Mechanisms of the Development of ALLergy” and aims at improving the health of European citizens by understanding the causes of the allergy epidemic. MeDALL will generate groundbreaking knowledge on the causes and mechanisms of allergic diseases (including asthma, allergic rhinitis, atopic dermatitis, and food allergy, particularly in children). Do environmental factors influence the development of allergies? If so, how do these factors contribute to the global allergy epidemic? The first year has been finalized with fulfilling all the deliverables. There is more than 43’000 children involved in MeDALL cohorts and SIAF takes it as great advantage to work with these cohorts and lead this work package.

The central hypothesis of the program PREDICTA is that repeated, acute rhinovirus infection-mediated events may reprogram the innate, adaptive and/or regulatory immune responses to predispose towards a chronic inflammation pattern. This study will look into the modulation of inflammatory patterns by acute infections in patient cohorts, mouse models and experimental in vitro systems. The role of specific agents will be sought in order to develop innovative diagnostics for predicting disease chronicity, as well as intervention strategies that may delay and/or prevent disease progression/persistence, by targeting the causative agents and/or specific elements of these inflammatory pathways.

During the last two decades, SIAF has been investigating mechanisms and diagnosis of fungal allergies. Although we had significant developments, there is still unmet needs. Under the 7th Framework Program, the European Commission has now recognized the problem and a major project ALLFUN under the title “Fungi in the setting of inflammation, allergy and autoimmune diseases: Translating basic science to clinical practices has been approved. The grant involves the SIAF in a leading role and will enable us to strengthen this research during the next three years. For this project SIAF will investigate the chemical structure and biochemical proper-

ties of allergens and produce highly pure recombinant allergens through gene cloning and biotechnological methods. The production of recombinant allergens is required for the clinical characterization, definition and for a reliable patient-tailored diagnosis and clinical monitoring of allergic diseases. They are a prerequisite for a better understanding of the molecular basis of allergenicity and cross-reactivity among allergens of different species and origin.

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

Last year, we initiated a Swiss Polish research collaboration together with Professor Andrezej Szczeklik from Jagelonnian University, Krakow, Poland. Unfortunately, we lost Professor Szczeklik, just a few months ago. Professor Szczeklik was one of the main contributors to aspirin sensitive asthma, who identified the disease and within the research frame of his group, he enabled us to understand most of the pathomechanisms. We will continue the project with his team, particularly with Professor Marek Sanak and follow the path in the memories of Professor Szczeklik. In this project, we will investigate whether there is correlation between the type of airway inflammation, and the concentration of cytokines of Th1/Th2 or Treg/Th17 axis (in BALF and serum), and the abundance of T-cell differentiation-related markers in lymphocytes. We will analyze the exacerbation-related changes, and characterize the eicosanoid profile in the patients by measuring exhaled breath condensate concentrations of prostanoids, leukotrienes and lipoxins; and assess possible associations between rhinovirus infection and the immune and eicosanoid response in aspirin sensitive asthma.

The work at SIAF during the last year generated a total of 76 scientific publications (exclusive abstracts), of which 72 appeared in peer-reviewed international journals. The total average of impact factor is 6.8. In 2011 SIAF reached a total impact factor amounting to 462.446 and 35 abstracts were presented at different congresses. Members of SIAF were invited to 65 different seminars or lectures at international congresses, universities and other research institutions and chaired 35 sessions. In addition, SIAF members continued to take place in 37 scientific posts in international institutions and play a role in 20 editorial board and editorship activities. Several members of SIAF have teaching responsibilities at the Universities of Zurich and Salzburg.

Organization of WIRM-VI by SIAF

The international World Immune Regulation Meeting (WIRM) belongs to one of the most important meetings in its area in the Wolrld. 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 for the sixth time this successful international meeting in 18-21 March 2012 at the Kongresszentrum Davos. The congress was focused on “Innate and Adaptive Immune Response and Role of Tissues in Immune Regulation” with approximately 700 participants. There was record number of abstracts (394) this year with 115 presentations.

Davos, May 2012

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RESEARCH

Molecular Allergology

Prof. Reto Crameri

The Molecular Allergology Division at SIAF has been working for many years on the development of novel vaccination strategies for allergic diseases. During the past decades allergic diseases, including rhinitis, atopic eczema and allergic asthma have developed a pandemic dimension and about 25-30% of the population in industrialized countries suffers from allergies. Although some progress has been made in developing therapeutic interventions aimed at controlling the symptoms of these diseases, the only treatment able to eradicate and cure IgE-mediated diseases is allergen specific immunotherapy.

As mentioned in the last annual report, in collaboration with ImVisioN the first batch of GMP-grade MAT-Fel d 1 was produced and a Phase I/IIa dose finding and safety clinical trial was planned in collaboration with the University of Zürich. The double blind, placebo controlled study, including follow up, has been completed. This study involved twenty cat dander allergic patients randomized either to a verum group of 12 patients recieving three intralymphatic injections with MAT-Fel d 1 absorbed to alum (1 µg, 3 µg and 10 µg), or to the placebo group (8 patients) and the results are now in press in the Journal of Allergy and Clinical immunology. Clinical efficacy was evaluated by conjunctival and nasal provocation testing, titrated skin prick and intradermal testing and adverse events were recorded. All patients were assessed for the following immunologic parameters at baseline and 1 week after the last injection: T cell proliferation, Fel d 1-specific IgG, IgG4, IgE and cytokine secretion in supernatants of T cell cultures (IL-2, IL-4, IL-5, IL-13, INF-γ, IL-17). The vaccine was well tolerated, no drug related adverse events were observed and MAT-Fel d 1-treated patients tolerated much more Fel d 1 in challenge experiments than placebo-treated patients, indicating an efficient therapy. The follow up study one year after completion of therapy showed that three injections of MAT-Fel d 1 within two months rendered cat-allergic patients tolerant to nasally administered cat dander extract, and allergy symptoms remained reduced for at least one year. After only three intralymphatic injections, MAT-Fel d 1 stimulated allergen-specific regulatory T-cell responses, and IL-10 production correlated with Fel d 1-specific IgG4 responses, the typical outcome obtained also with classical immunotherapy. In conclusion, intralymphatic immunotherapy (ILIT) with the modular antigen transporter MAT-Fel d 1 was safe and induced tolerance with symptom amelioration in allergic patients after only three injections. This is a major improvement over conventional subcutaneous or sub-lingual immunotherapy which both require years of treatment. This vaccination approach therefore represents an attractive treatment-option, especially for all those allergic patients who are reluctant to undergo allergen-specific immunotherapy due to time constraints and risk of allergic side effects.

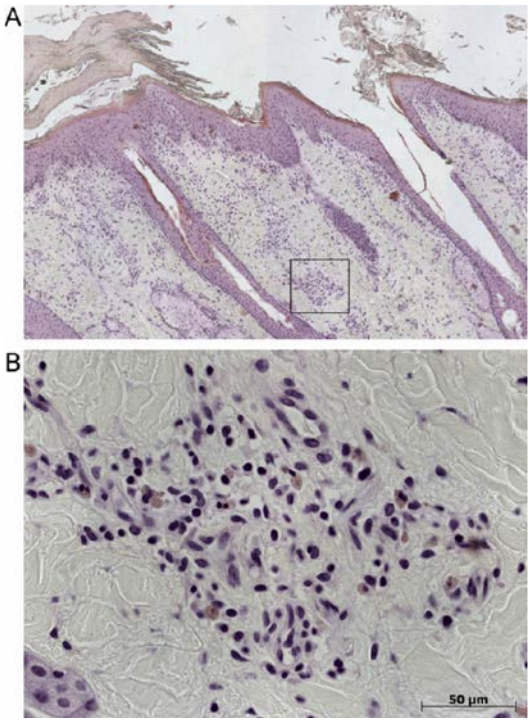


Fig. 1. HE-stained lesional skin biopsy of a horse with IBH. (A) shows hyperkeratosis and perivascular and interstitial dermatitis (original magnification 40×). (B) shows infiltration with eosinophils and mononuclear cells (original magnification 400×).

Great efforts were undertaken to understand the molecular mechanisms underlying the fast protection conferred by ILIT that was never observed by all other described allergen-specific immunotherapeutic applications. Development of specific immune responses requires antigen presentation to CD4+ T cells through APC-displayed MHC II-peptide complexes and interaction with the T cell receptor. It has been apparent for many years that T cell help is required for the production

of both IgE and IgG antibodies by B cells. The development of T cell subsets from naive T cells is decisive for the isotype switch of specific antibodies. There is clear evidence that low amounts of antigen, such as those encountered during natural exposure to most of the environmental allergens favor the switch of B cells towards IgE production, whereas higher doses of antigen given by allergen-SIT favors the development of protective IgG4 antibody responses. This can be traced back to the induction of IL-10 and IFN-γ in high antigen doses and Th2 cytokines in low antigen doses. Based on these observations, increased cellular uptake and efficient antigen-presentation through the MHC class-II antigen-presentation pathway provided the rational for the development of our efficient MAT vaccines. The therapeutic window for allergy vaccination is narrow because allergens are highly toxic for sensitized individuals and therefore cannot be applied at sufficiently high doses to directly induce a switch to protective IgG4 antibody responses. Moreover, every antigen has to reach the lymphatic organs and persist for a certain time at a certain concentration to elicit an immune response. If an antigen does not reach secondary lymphoid organs in minimum doses or for sufficiently long time periods, it is ignored by the immune system, while antigens reaching and persisting in the lymph nodes in excessive amounts for long periods of time delete primed T cells to avoid exaggerated immune responses. Thus dose- and time-dependent antigen presentation is most likely to be responsible for weak immune responses to allergens and not the potential of the immune system to mount strong immune responses. Direct injection of MAT vaccines targeting the MHC-II presentation pathway into lymph nodes, the place where they have to localize to elicit protective responses, provides a rational explanation for the efficacy of this novel vaccination concept.

Interestingly horses suffering from insect bite hypersensitivity (IBH) develop the so called summer eczema, a disease resembling atopic dermatitis in humans. This cronic relapsing disease develops during the summer months when midges are flying and disappears during the winter months due to the lack of exposure. We have now completed a larger study aimed at cloning, producing and characterizing salivary gland allergens from Culicoides nubeculosus, the midge assumed to be responsible for the disease. Western blot analyses of all ten recombinant allergens with a serum pool of IBH-affected horses showed their ability to specifically bind serum IgE of sensitized horses, and ELISA determinations yielded individual horse recognition patterns with a frequency of sensitization ranging from 13 to 57%, depending on the allergen tested. The in vivo relevance of eight of the recombinant allergens was demonstrated in intradermal skin testing. These allergens have the potential to provide a tool for better diagnosis of IBH which is to date based on ELISA and skin tests using C. nubeculosus extracts. In contrast to extracts which suffer from large batch to batch variations, recombinant allergens can be produced as highly pure standardized protein solutions without batch to batch variations for both diagnosis and therapy. In analogy to our work with allergens eliciting allergy in humans, we have started engineering and production of MAT-vaccines aimed at curing IBH. Due to the resemblance to atopic dermatitis, this horse disease might serve as a model to understand the cutaneuous changes induced by allergens and might therefore help to develop adequate curative treatments for atopic dermatitis, a yet unsolved medical need. The first horses have now been immunized in collaboration with the veterinary faculty of the University of Berne and during the next summer we will be able to evaluate if the horses are protected or not.

Although extremely successful, MAT vaccines still suffer from the fact that they need to be injected, and injection-based therapies strongly reduce the patient's compliance. Currently we are developing a second generation of improved vaccines which should directly target dendritic cells and we envisage direct cutaneous application of these vaccines using laser-based microporation.

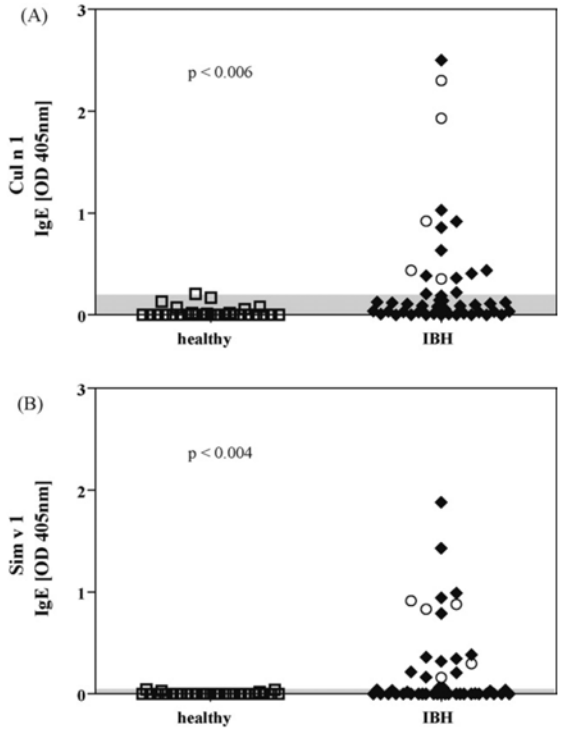


Fig. 2. Specific serum IgE against recombinant Cul n 1 (A), and Sim v 1 (B) determined by solid phase ELISA. Sera from 48 IBH-affected horses (♦) and 29 healthy control horses (□) were analyzed. The cut-off values for positive results are highlighted in gray and correspond to 3-fold the standard deviation +mean of the healthy control horses. IBH-affected horses indicated by open

circle (○) were chosen for intradermal skin test.

Selective cloning, characterization, and production of the Culicoides nubeculosus salivary gland allergen repertoire associated with equine insect bite hypersensitivity
Schaffartzik, A., Marti E, Torsteinsdottir S, Mellor PS, Crameri R, Rhyner C.
Vet Immunol Immunopathol. 139, 200-9, 2011.

Salivary gland proteins of Culicoides spp. have been suggested to be among the main allergens inducing IgE-mediated insect bite hypersensitivity (IBH), an allergic dermatitis of the horse. The aim of our study was to identify, produce and characterize IgE-binding salivary gland proteins of Culicoides nubeculosus relevant for IBH by phage surface display technology. A cDNA library constructed with mRNA derived from C. nubeculosus salivary glands was displayed on the surface of filamentous phage M13 and enriched for clones binding serum IgE of IBH-affected horses. Ten cDNA inserts encoding putative salivary gland allergens were isolated and termed Cul n 2 to Cul n 11. However, nine cDNA sequences coded for truncated proteins as determined by database searches. The cDNA sequences were amplified by PCR, subcloned into high level expression vectors and expressed as hexahistidine-tagged fusion proteins in Escherichia coli. Preliminary ELISA results obtained with these fusions confirmed the specific binding to serum IgE of affected horses. Therefore, the putative complete open reading frames derived from BLAST analyses were isolated by RACE-PCR and subcloned into expression vectors. The full length proteins expressed in Escherichia coli showed molecular masses in the range of 15.5-68.7 kDa in SDS-PAGE in good agreement with the masses calculated from the predicted protein sequences. Western blot analyses of all recombinant allergens with a serum pool of IBH-affected horses showed their ability to specifically bind serum IgE of sensitized horses, and ELISA determinations yielded individual horse recognition patterns with a frequency of sensitization ranging from 13 to 57%, depending on the allergen tested. The in vivo relevance of eight of the recombinant allergens was demonstrated in intradermal skin testing. For the two characterized allergens Cul n 6 and Cul n 11, sensitized horses were not available for intradermal tests. Control horses without clinical signs of IBH did not develop any relevant immediate hypersensitivity reactions to the recombinant allergens. The major contribution of this study was to provide a repertoire of recombinant salivary gland allergens repertoire from C. nubeculosus potentially involved in the pathogenesis of IBH as a starting basis for the development of a component-resolved serologic diagnosis of IBH and, perhaps, for the development of single horse tailored specific immunotherapy depending on their component-resolved sensitization patterns.

Fig. 3. (A) Female Culicoides (original magnification 6×, length of the wings corresponds to 2 mm). The arrow indicates where the salivary glands are situated.

MeDALL (Mechanisms of the Development of ALLergy): an integrated approach from phenotypes to systems medicine
Bousquet J, Anto J, Auffray C, Akdis M, Cambon-Thomsen A, Keil T, Haahtela T, Lambrecht BN, Postma DS, Sunyer J, Valenta R, Akdis CA, Annesi-Maesano I, Arno A, Bachert C, Ballester F, Basagana X, Baumgartner U, Bindslev-Jensen C, Brunekreef B, Carlsen KH, Chatzi L, Crameri R, Eveno E, Forastiere F, Garcia-Aymerich J, Guerra S, Hammad H, Heinrich J, Hirsch D, Jacquemin B, Kauffmann F, Kerkhof M, Kogevinas M, Koppelman GH, Kowalski ML, Lau S, Lodrup-Carlsen KC, Lopez-Botet M, Lotvall J, Lupinek C, Maier D, Makela MJ, Martinez FD, Mestres J, Momas I, Nawijn MC, Neubauer A, Oddie S, Palkonen S, Pin I, Pison C, Rancé F, Reitamo S, Rial-Sebbag E, Salapatas M, Siroux V, Smagghe D, Torrent M, Toskala E, van Cauwenberge P, van Oosterhout AJ, Varraso R, von Hertzen L, Wickman M, Wijmenga C, Worm M, Wright J, Zuberbier T.
Allergy 66, 596-604, 2011.

The origin of the epidemic of IgE-associated (allergic) diseases is unclear. MeDALL (Mechanisms of the Development of ALLergy), an FP7 European Union project (No. 264357), aims to generate novel knowledge on the mechanisms of initiation of allergy and to propose early diagnosis, prevention, and targets for

therapy. A novel phenotype definition and an integrative translational approach are needed to understand how a network of molecular and environmental factors can lead to complex allergic diseases. A novel, stepwise, large-scale, and integrative approach will be led by a network of complementary experts in allergy, epidemiology, allergen biochemistry, immunology, molecular biology, epigenetics, functional genomics, bioinformatics, computational and systems biology. The following steps are proposed: (i) Identification of 'classical' and 'novel' phenotypes in existing birth cohorts; (ii) Building discovery of the relevant mechanisms in IgE-associated allergic diseases in existing longitudinal birth cohorts and Karelian children; (iii) Validation and redefinition of classical and novel phenotypes of IgE-associated allergic diseases; and (iv) Translational integration of systems biology outcomes into health care, including societal aspects. MeDALL will lead to: (i) A better understanding of allergic phenotypes, thus expanding current knowledge of the genomic and environmental determinants of allergic diseases in an integrative way; (ii) Novel diagnostic tools for the early diagnosis of allergy, targets for the development of novel treatment modalities, and prevention of allergic diseases; (iii) Improving the health of European citizens as well as increasing the competitiveness and boosting the innovative capacity of Europe, while addressing global health issues and ethical issues.

Editorial: The problem of cross-reactivity in the diagnosis of fungal allergy
Crameri, R.
Clin. Exp. Allergy 41, 302-304, 2011.

HIV interferes with SOCS-1 and -3 expression levels driving immune activation
Miller, R. C., Schlaepfer, E., Baenziger, S., Crameri, R., Zeller, S., Byland, R., Audigé, A., Nadal, D., Speck, R. F.
Eur J Immunol. 41(4):1058-1069, 2011.

HIV infection is characterized by sustained immune activation, which is reflected by activated T cells and, in particular, by increased levels of phosphorylated STAT proteins. Here, we hypothesized that T-cell activation in HIV infection is partially due to the inability of SOCS-1 and SOCS-3 to control the JAK/STAT pathway. We found higher levels of SOCS-1/3 mRNA levels in CD4(+) T cells of HIV-infected patients than in healthy controls. However, SOCS protein levels were lower, explaining the lack of attenuation of the JAK/STAT pathway. Infection of CD4(+) T cells alone did not activate STATs, while ex vivo infection of PBMC did, indicating that non-T cells critical for shaping the immune response, e.g. DC were responsible for the STAT-1 activation. Supernatants from ex vivo-infected PBMC transferred to CD4(+) T cells induced JAK/STAT activation, pointing to a central role of soluble factors. Notably, over-expression of SOCS-1/3 in CD4(+) T cells prevented JAK/STAT activation. Thus, HIV infection interferes with SOCS-1/3 expression driving immune activation. Sustained immune activation disrupts the lymphoid system and favors HIV replication since HIV preferentially infects activated cells. We speculate that regulating SOCS may be a potential way to counteract immune activation in HIV disease

Auto-reactive IgE responses to acidic ribosomal P(2) protein in systemic lupus erythematosus
Rhyner, C., Daigle, I., Crameri, R.
Allergy. 66,1127-1129, 2011.

Malassezia sympodialis thioredoxin-specific T cells are highly cross-reactive to human thioredoxin in atopic dermatitis
Heratizadeh, A., Wichmann, K., Niebuhr, M., Crameri, R., Scheynius, A., Werfel, T.
J. Allergy Clin. Immunol. 128, 92-99.e4, 2011.

BACKGROUND: IgE-mediated cross-reactivity between fungal antigens and human proteins has been described in patients with atopic dermatitis (AD), but it remains to be elucidated whether there is also cross-reactivity at the T-cell level.
OBJECTIVE: We sought to explore cross-reactivity at the T-cell level between the fungal thioredoxin (Mala s 13) of the skin-colonizing yeast Malassezia sympodialis and its homologous human thioredoxin (hTrx).
METHODS: T-cell lines (TCLs) were generated in the presence of rMala s 13 from the peripheral blood and from skin biopsy specimens of positive patch test reactions of patients with AD sensitized to Mala s 13 and hTrx. Patients with AD not sensitized to Malassezia species, healthy subjects, and patients with psoriasis served as control subjects. Mala s 13-specific T-cell clones (TCCs) were generated from TCLs. TCCs were characterized by antigen specificity, phenotype, and cytokine secretion pattern. Human keratinocytes were stimulated with IFN-γ, TNF-α, and IL-4, and the release of hTrx was determined by means of ELISA.
RESULTS: Mala s 13-specific TCLs and TCCs from the blood and skin of patients with AD sensitized to Mala s 13 and hTrx were fully cross-reactive with hTrx. Mala s 13- and hTrx-specific TCCs could not be generated from control subjects. The majority of cross-reactive TCCs were CD4(+) and coexpressed cutaneous lymphocyte antigen. In addition to T(H)1 and T(H)2 TCCs, we could also identify TCCs secreting IL-17 and IL-22. After stimulation with IFN-γ and TNF-α, keratinocytes released substantial amounts of thioredoxin.

CONCLUSION: In patients with AD sensitized to Malassezia species, cross-reactivity at the T-cell level to Mala s 13 and the homologous hTrx is detectable. hTrx autoreactive skin-homing T cells might be relevant for cutaneous inflammation in patients with AD.

IgE-binding epitopes: a reappraisal
Crameri, R.
Allergy 66, 1261-1274, 2011.

Here, we discuss various questions related to IgE epitopes: What are the technical possibilities and pitfalls, what is currently known, how can we put this information into hypothetical frameworks and the unavoidable question: how useful is this information for patient care or allergenicity prediction? We discuss the information obtained by (i) 3D structures of allergen-antibody complexes; (ii) analysis of allergen analogues; (iii) mimics without obvious structural similarity; (iv) mAbs competing with IgE; (v) repertoire analysis of cloned IgEs, and other developments. Based on limited data, four suggestions are presented in the literature: (i) IgE might be more cross-reactive than IgG; (ii) IgE might be more often directed to immunologically 'uninviting' surfaces; (iii) IgE epitopes may tend to cluster and (iv) IgE paratopes might have a higher intrinsic flexibility. While these are not proven facts, they still can generate hypotheses for future research. The hypothesis is put forward that the IgE repertoire of switched B-cells is less influenced by positive selection, because positive selection might not be able to rescue IgE-switched B cells. While this might be of interest for the discussion about mechanisms leading to allergen-sensitization, we need to be modest in answering the 'clinical relevance' question. Current evidence indicates the IgE-epitope repertoire is too big to make specific IgE epitopes a realistic target for diagnosis, treatment or allergenicity prediction. In-depth analysis of a few selected IgE epitope-peptides or mimitopes derived from allergen-sequences and from random peptide libraries, respectively, might well prove rewarding in relation to diagnosis and prognosis of allergy, particularly food allergy.

In vitro evolution of allergy vaccine candidates, with maintained structure, but reduced B cell and T cell activation capacity.
Nilsson, O. B., Adedoyin, J., Rhyner, C., Neimert-Andersson, T., Grundström, J., Berndt, K. D., Crameri, R., Grönlund, H.
PLoS One. 6(9), e24558, 2011. Epub 2011 Sep 13.

Allergy and asthma to cat (Felis domesticus) affects about 10% of the population in affluent countries. Immediate allergic symptoms are primarily mediated via IgE antibodies binding to B cell epitopes, whereas late phase inflammatory reactions are mediated via activated T cell recognition of allergen-specific T cell epitopes. Allergen-specific immunotherapy relieves symptoms and is the only treatment inducing a long-lasting protection by induction of protective immune responses. The aim of this study was to produce an allergy vaccine designed with the combined features of attenuated T cell activation, reduced anaphylactic properties, retained molecular integrity and induction of efficient IgE blocking IgG antibodies for safer and efficacious treatment of patients with allergy and asthma to cat. The template gene coding for rFel d 1 was used to introduce random mutations, which was subsequently expressed in large phage libraries. Despite accumulated mutations by up to 7 rounds of iterative error-prone PCR and biopanning, surface topology and structure was essentially maintained using IgE-antibodies from cat allergic patients for phage enrichment. Four candidates were isolated, displaying similar or lower IgE binding, reduced anaphylactic activity as measured by their capacity to induce basophil degranulation and, importantly, a significantly lower T cell reactivity in lymphoproliferative assays compared to the original rFel d 1. In addition, all mutants showed ability to induce blocking antibodies in immunized mice.The approach presented here provides a straightforward procedure to generate a novel type of allergy vaccines for safer and efficacious treatment of allergic patients.

Immunoglobulin E-binding autoantigens: biochemical characterization and clinical relevance
Crameri, R.
Clin. Exp. Allergy. 2011 Oct 10. doi: 10.1111/j.1365-2222.2011.03878.x. [Epub ahead of print]

Although immediate-Type I skin reactions to human dander have been described six decades ago, only the recent application of molecular biology to allergology research allowed fast and detailed characterization of IgE-binding autoantigens. These can be functionally subdivided into three classes: (1) self-antigens with sequence homology to environmental allergens belonging to the class of phylogenetically conserved proteins, (2) self-antigens without sequence homology to known environmental allergens, and (3) chemically modified self-antigens deriving from workplace exposure. As environmental allergens, also IgE-binding autoantigens belong to different protein families without common structural features that would explain their IgE-binding capability. Many of the self-antigens showing sequence homology to environmental allergens, are phylogenetically conserved proteins like manganese dependent superoxide dismutase, thioredoxin or cyclopilin. Their IgE-binding capability can be explained by molecular mimicry resulting from shared B-cell epitopes. A common factor of IgE-binding self-

antigens without sequence homology to known environmental allergens is that they elicit IgE responses only in individuals suffering from long-lasting atopic diseases. In contrast, IgE-mediated reactions to modified self-antigens might be explained with the generation of novel B-cell epitopes. Chemically modified self-antigens are likely to be recognized as non-self by the immune system. The clinical relevance of IgE responses to self-antigens remains largely unclear. Well documented is their ability to induce immediate Type I skin reactions in vivo, and to induce mediator release from effector cells of sensitized individuals in vitro. Based on these observations it is reasonable to assume that IgE-mediated cross-linking of FcRIε receptors on effector cells can elicit the same symptoms as those induced by environmental allergens, and this could explain exacerbations of chronic allergic diseases in the absence of external exposure. However, because most of the described IgE-binding self-antigens are intracellular proteins normally not accessible for antigen-antibody interactions, local release of the antigens is required to explain the induction of symptoms.

(Group Molecular Allergology led by Prof. R. Crameri)

Microbiota and dietary interactions - an update to the hygiene hypothesis?
Frei, R., Lauener, R. P., Crameri, R.
Allergy. 2012 Jan 19. doi: 10.1111/j.1398-9995.2011.02783.x. [Epub ahead of print]

The dramatic increase in the incidence and severity of allergy and asthma has been proposed to be linked with an altered exposure to, and colonization by, microorganisms, particularly early in life. However, other lifestyle factors such as diet and physical activity are also thought to be important, and it is likely that multiple environmental factors with currently unrecognized interactions contribute to the atopic state. This review will focus on the potential role of microbial metabolites in immunoregulatory functions and highlights the known molecular mechanisms, which may mediate the interactions between diet, microbiota, and protection from allergy and asthma.

Davos, May 2012

RESEARCH

Cellular Allergy / Immunology

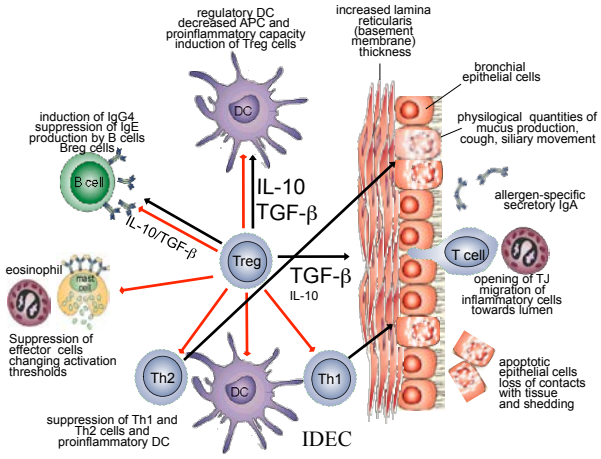
Prof. Dr. med. Cezmi A. Akdis

Immune system is a highly interactive networking, which makes its decisions on the basis of input from all tissues, infections, normal flora bacteria and many or even any environmental agents. General rules of immunity versus tolerance as well as co-evolutionary development applies to allergen-specific immune response, because rules for regulators and effectors has probably been developed in a co-evolutionary manner with helminths, mites, insect venoms, foods and other allergens.

In chronic allergic inflammation dermis in the atopic skin and submucosa in the asthmatic lung turns into a lymphatic organ like organization, where professional dendritic cells, T cells and B cells contact each other and a second step of antigen-presentation, activation and inflammation takes place in the inflamed tissue. The overall evaluation of the studies on T and B cell response against allergens suggest that immunological ignorance and active suppression are not entirely distinct, but rather, represent linked mechanisms of peripheral tolerance.

If a detectable immune response is mounted, allergen-specific T regulatory 1 (Tr1) cells represent the dominant T cell subset against allergens in healthy immune response and after allergen-specific immunotherapy (SIT). In healthy individuals, the antibody response against allergens varies between no response to IgG4- or IgG1- dominating allergen-specific antibodies in the presence or absence of low amounts of IgE. The induction of non inflammatory IgG4 and IgA type antibodies against allergens may represent an important allergen tolerance mechanisms. Tr1 cells do not only suppress allergen-specific immune response development, but also regulate B cells by induction of IgG4 by IL-10. In addition, antigen-specific secretory IgA displays a role in ignorance to food and aeroallergens.

Several essential tissue events play a role in immune tolerance to allergens. Basement membrane (lamina reticularis) thickening, allergen-specific secretory IgA can be listed as tissue events that try to keep the allergens away from submucosal immune system cells (keep away effects). There is clear evidence that lamina reticularis thickening starts very early in asthma, even at the time of first diagnosis, suggesting that a barrier between activated epithelium or mucosal allergens and inner tissues i.e. immune system cells occurs with the aim of down-regulation of the allergen-induced inflammatory response. The efforts of the immune system and lung fibroblasts to increase lamina reticularis thickness might be indeed aiming to make a mechanical barrier between the allergens (mites and pollens) and the submucosal immune system. These mechanisms resemble features of immune response to chronic helminth infections in order to decrease antigenic burden of the helminths and mechanically keep them away from tissues. For example, keeping them in fibrous sacks etc.



Immune suppression and allergen tolerance in asthma (keep away, wash away, suppress)

Epithelial-cell activation followed by apoptosis (activation-induced cell death) seems to be one of the hallmarks of visible pathology both in asthma and atopic dermatitis. It involves two stages. First, activation of epithelial cells and relase of chemokines and pro-inflammatory cytokines takes place (pro-inflammatory stage). This is followed by eventual death of keratinocytes and bronchial epithelial cells, which leads to desquamation of dead epithelial cells in asthma, spongiosis in eczema. However, it may play an anti-inflammatory role because the highly active and proinflammatory epithelial cell dies and it's contacts with the inner tissue is physically broken and its contribution to inflammation does not exist anymore. Bronchial epithelial cell shedding, mucus production, ciliary movements, cough represent mechanisms regulated by the immune system, which attempt to decrease the amount of allergen exposure (wash away effect) and may play a role in decreasing the allergen burden.

Epithelial barrier function of keratinocytes in the skin of atopic dermatitis patients and bronchial epithelial cells

in the asthmatic lung have been demonstrated to be defective. These studies suggest that tissue integrity is disturbed in patients and allergens, bacterial toxins and other particles are able to penetrate the epidermis and the lung epithelium, where they may activate the immune system leading to severe chronic inflammation in both diseases. Therefore, paracellular sealing of keratinocytes and bronchial epithelial cells appears to be very important to prevent the infiltration of the subepithelial tissues by factors that induce allergic inflammation. Epithelial Tight junctions (TJ) consist of different transmembrane and scaffold adaptor proteins and form the most apical intercellular junction between epithelial cells. They are responsible for the regulation of paracellular flux and epithelial impermeability. In addition, they prevent foreign particles, such as allergens, to enter into subepithelial layers. In contrast, opening of TJs can lead to drainage of inflammatory cells towards the lumen, supporting the resolution of phlogistic processes. Consequently, they can be considered as gatekeepers that could contribute both to aggravation of inflammation related tissue damage or resolution of inflammation via drainage. Treg cells and Th2 cells efficiently contribute to the opening/closing and regeneration of epithelial cells. In conclusion, our research demonstrate that the balance between inflammation inducing factors, keep away factors, wash away factors and suppression factors plays a decisive role in the remission, exacerbation and chronicity of allergic inflammation.

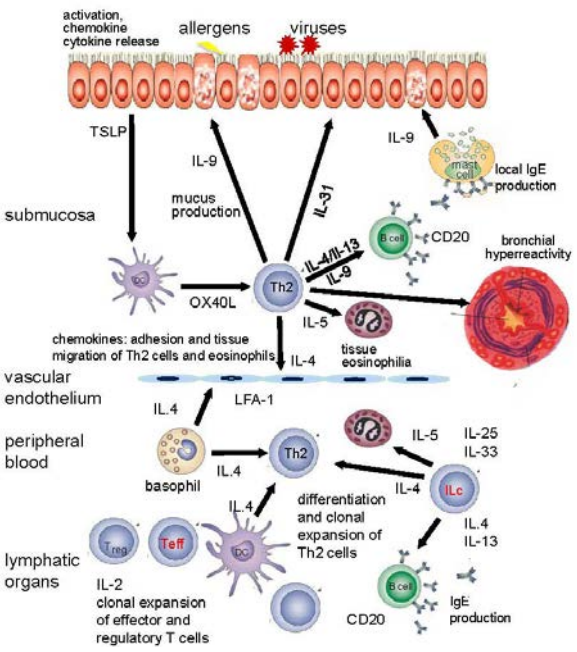


Figure 2: Mechanisms of Asthma and novel molecular targets for the treatment Epithelial cell activation and their proinflammatory cytokines and chemokine production that induces inflammation and contributes to Th2 response; epithelial apoptosis and shedding in eczema and asthma; Th2 response: IL-4, IL-5, IL-9, IL-13, IL-25, IL-33; eosinophilia: IL-5, IL-25, IL-33; local and systemic IgE production: IL-4, IL-13, CD20, IgE; cross-linking of IgE receptor FcεRI on the surface of mast cells and basophils and their degranulation; smooth muscle, myofibroblasts activation and bronchial hyperreactivity: IL-4, IL-9, IL-13, IL-25, IL-33; survival and reactivation of migrating inflammatory cells and their interaction with resident tissue cells and other inflammatory cells: IL-2, IL-4; cell migration and chemokines; other effector T cell subsets, such as Th9, Th17 and Th22 cells; type 2 lymphoid tissue inducer cells.

Mechanisms of IFN-γ-induced apoptosis of human skin keratinocytes in patients with atopic dermatitis
Rebane A, Zimmermann M, Aab A, Baurecht H, Koreck A, Karelson M, Abram K, Metsalu T, Pihlap M, Meyer N, Fölster-Holst R, Nagy N, Kemeny L, Kingo K, Vilo J, Illig T, Akdis M, Franke A, Novak N, Weidinger S, Akdis CA. J Allergy Clin Immunol. 2012;129:1297-306.

Enhanced apoptosis of keratinocytes is the main cause of eczema and spongiosis in patients with the common inflammatory skin disease atopic dermatitis (AD). The aim of this study was to investigate molecular mechanisms of AD-related apoptosis of keratinocytes. Primary keratinocytes isolated from patients with AD and healthy donors were used to study apoptosis by using annexin V/7-aminoactinomycin D staining. Illumina mRNA Expression BeadChips, quantitative RT-PCR, and immunofluorescence were used to study gene expression. In silico analysis of candidate genes was performed on genome-wide single nucleotide polymorphism data. We demonstrated that keratinocytes of patients with AD exhibit increased IFN-γ-induced apoptosis compared with keratinocytes from healthy subjects. Further mRNA expression analyses revealed differential expression of apoptosis-related genes in AD keratinocytes and skin and the upregulation of immune system-related genes in skin biopsy specimens of chronic AD lesions. Three apoptosis-related genes (NOD2, DUSP1, and ADM) and 8 genes overexpressed in AD skin lesions (CCDC109B, CCL5, CCL8, IFI35, LYN, RAB31, IFITM1, and IFITM2) were induced by IFN-γ in primary keratinocytes. The protein expression of IFITM1, CCL5, and CCL8 was verified in AD skin. In line with the functional studies and AD-related mRNA expression changes, in silico analysis of genome-wide single nucleotide polymorphism data revealed evidence of an association between AD and genetic markers close to or within the IFITM cluster or RAB31, DUSP1, and ADM genes. In conclusion, our results demonstrate increased IFN-γ responses in skin of patients with AD and suggest involvement of multiple

new apoptosis- and inflammation-related factors in the development of AD.

Inhibition of angiogenesis by IL-32: Possible role in asthma

Meyer N, Christoph J, Makrinioti H, Indermitte P, Rhyner C, Soyka M, Eiwegger T, Chalubinski M, Wanke K, Fujita H, Wawrzyniak P, Bürgler S, Zhang S, Akdis M, Menz G, Akdis C.

J Allergy Clin Immunol. 2012;129:964-973

IL-32 is a proinflammatory cytokine involved in various chronic inflammatory diseases. Chronic airway inflammation in asthmatic patients results in structural airway changes, including angiogenesis. Vascular endothelial growth factor (VEGF) is a key inducer of angiogenesis in the airways of asthmatic patients. The aim of the study was to investigate the expression and function of IL-32 in patients with angiogenesis and asthma. In this study, the expression and regulation of IL-32 in normal human bronchial epithelial (NHBE) cells was analyzed by using RT-PCR, ELISA, Western blotting, immunofluorescent staining, and flow cytometry. After knockdown of IL-32 in NHBE cells by small interfering RNA (siRNA) transfections, VEGF secretion was quantified by means of ELISA. New blood vessel formation was determined with human umbilical vein endothelial cells by culturing with supernatants from IL-32 siRNA-transfected NHBE cells. IL-32 was determined in serum and induced sputum samples of asthmatic patients and healthy control subjects by means of ELISA. We demonstrated that IL-32 is expressed in NHBE cells on stimulation with IFN-γ, TNF-α, T(H)1 cells, and rhinovirus. Inhibition of IL-32 expression resulted in significantly increased secretion of the proangiogenic factors VEGF and platelet-derived growth factor by NHBE cells. Human umbilical vein endothelial cells cultured in supernatants from IL-32 siRNA-transfected NHBE cells showed enhanced in vitro angiogenesis. IL-32 is detectable in induced sputum from asthmatic patients. IL-32 serum levels were significantly higher in asthmatic patients compared with those seen in healthy control subjects and correlated with response to asthma treatment. In conclusion, IL-32 is induced by IFN-γ, TNF-α, T(H)1 cells, and rhinovirus in bronchial epithelial cells. It inhibits angiogenesis, and its serum levels are associated with a good treatment response in asthmatic patients.

Induction and maintenance of allergen-specific FOXP3+ Treg cells in human tonsils as potential first-line organs of oral tolerance.

Palomares O, Rückert B, Jartti T, Kücüksezer UC, Puhakka T, Gomez E, Fahrner HB, Speiser A, Jung A, Kwok WW, Kalogjera L, Akdis M, Akdis CA.

J Allergy Clin Immunol. 2012;129:510-20

Tonsils are strategically located in the gateway of both alimentary and respiratory tracts representing the first contact point of food and aeroallergens with the immune system. Tonsillectomy removes only the palatine tonsils and sometimes adenoids. Lingual tonsil is anatomically big and remains lifelong intact. The aim of this study was to demonstrate cellular and molecular mechanisms of oral tolerance induction to food and aeroallergens in human tonsils. In this study, Tonsil allergen-specific FOXP3(+) regulatory T (Treg) cells, plasmacytoid dendritic cells (pDCs), and myeloid dendritic cells were characterized by flow cytometry and suppressive assays. Intracellular staining, [(3)H]-thymidine incorporation, and carboxyfluorescein succinimidyl ester dilution experiments were performed. Tonsil biopsies were analyzed by confocal microscopy. We demonstrated that CD4(+)FOXP3(+) Treg cells and pDCs constitute important T- and dendritic cell-compartments in palatine and lingual tonsils. Tonsil pDCs have the ability to generate functional CD4(+)CD25(+)CD127(-)FOXP3(+) Treg cells with suppressive property from naive T cells. CD4(+)FOXP3(+) Treg cells proliferate and colocalize with pDCs in vivo in T-cell areas of lingual and palatine tonsils. Tonsil T cells did not proliferate to common food and aeroallergens. Depletion of FOXP3(+) Treg cells enables the allergen-induced proliferation of tonsil T cells, indicating an active role of Treg cells in allergen-specific T-cell unresponsiveness. High numbers of major birch pollen allergen, Bet v 1-specific CD4(+)FOXP3(+) Treg cells, are identified in human tonsils compared with peripheral blood. A positive correlation between the percentages of FOXP3(+) Treg cells and pDCs is observed in tonsils from nonatopic individuals. In cocnclusion, functional allergen-specific Treg cells are identified both in lingual and in palatine tonsils.

T-cell and antibody responses to phospholipase A2 from different species show distinct cross-reactivity patterns

Sin BA, Akdis M, Zumkehr J, Bezzine S, Bekpen C, Lambeau G, Akdis CA.

Allergy. 2011;66:1513-21

Secreted phospholipases A2 (sPLA2) represent antigens to which humans may be rarely or frequently exposed. Thus, the investigation of humoral and cellular immune responses to sPLA2s from different species can provide a suitable model in the study of antibody and T-cell cross-reactivity. Specific IgE, IgG1, IgG4, and IgA antibodies were analyzed by ELISA against sPLA2s from pancreas of Bos taurus (BT), Apis mellifera (AM) bee venom, Daboia russellii (DR) and Naja mossambica (NM) snake venoms, and human group III (hGIII) sPLA2 using sera of nonallergic beekeep-

ers, AM-allergic patients, and healthy controls. T-cell cross-reactivity was investigated in PBMC, and T-cell clones (TCC) are generated against AM sPLA2. We demonstrated that hyperimmune and allergic individuals showed high levels of sPLA2-specific IgG4 and significant IgG4 cross-reactivity between BT, DR, and NM sPLA2s. Furthermore, IgE, IgA, and IgG1 cross-reactivities against BT, DR, and NM sPLA2s were also detectable in the range of 22.2-44.8%. Allergic patients showed significant T-cell proliferative response to NM sPLA2 together with increased IFN-γ and IL-13 production even though they had never been exposed to cobra venom. Although nonallergic healthy controls show no cross-reactivity at T-cell level, they did have low levels of IgG4 and IgA against BT, DR, and NM sPLA2s. Human TCC spanning three major T-cell epitopes of AM sPLA2 showed minor proliferative response to NM and hGIII sPLA2s. In conclusion, this study shows that T cells and antibodies may show cross-reactivity between different species without being naturally exposed to sPLA2s.

Claudin-1 expression in airway smooth muscle exacerbates airway remodeling in asthmatic subjects

Fujita H, Chalubinski M, Rhyner C, Indermitte P, Meyer N, Ferstl R, Treis A, Gomez E, Akkaya A, O'Mahony L, Akdis M, Akdis CA.
J Allergy Clin Immunol. 2011;127:1612-21.

Increased airway smooth muscle (ASM) mass is an essential component of airway remodeling and asthma development, and there is no medication specifically against it. Tight junction (TJ) proteins, which are expressed in endothelial and epithelial cells and affect tissue integrity, might exist in other types of cells and display additional functions in the asthmatic lung. The aim of this study was to investigate the existence, regulation, and function of TJ proteins in ASM in asthmatic patients. The expression and function of TJ proteins in primary ASM cell lines, human bronchial biopsy specimens, and a murine model of asthma were analyzed by means of RT-PCR, multispectral imaging flow cytometry, immunohistochemistry, Western blotting, 5-(and-6)-carboxyfluorescein diacetate succinimidyl ester staining, tritiated thymidine incorporation, wound-healing assay, and luminometric bead array. We demonstrated that increased claudin-1 expression was observed in ASM of asthmatic patients, as well as in a murine model of asthma-like airway inflammation. Whereas IL-1β and TNF-α upregulated claudin-1 expression, it was downregulated by the T(H)2 cytokines IL-4 and IL-13 in primary human ASM cells. Claudin-1 was localized to the nucleus and cytoplasm but not to the cell surface in ASM cells. Claudin-1 played a central role in ASM cell proliferation, as demonstrated by increased ASM cell proliferation seen with overexpression and decreased proliferation seen with small interfering RNA knockdown of claudin-1. Overexpression of claudin-1 induced vascular endothelial growth factor and downregulated IL-6, IL-8, and IFN-γ-induced protein 10 production by ASM cells. Claudin-1 upregulation by IL-1β or TNF-α was suppressed by dexamethasone but not by rapamycin, FK506, or salbutamol. In conclusion, these results demonstrate that claudin-1 might play a role in airway remodeling in asthmatic patients by means of regulation of ASM cell proliferation, angiogenesis, and inflammation.

TNF-like weak inducer of apoptosis (TWEAK) and TNF-α cooperate in the induction of keratinocyte apoptosis

Zimmermann M, Koreck A, Meyer N, Basinski T, Meiler F, Simone B, Woehrl S, Moritz K, Eiwegger T, Schmid-Grendelmeier P, Kemeny L, Akdis CA.
J Allergy Clin Immunol. 2011;127:200-7.

Activation of skin keratinocytes followed by their apoptotic death leads to eczema and spongiosis formations in patients with atopic dermatitis (AD). TNF-like weak inducer of apoptosis (TWEAK) binds to its receptor, fibroblast growth factor-inducible 14 (Fn14), and controls many cellular activities, including proliferation, migration, differentiation, apoptosis, angiogenesis, and inflammation. The aim of the study was to investigate the role of TWEAK and Fn14 in the formation of eczema in patients with AD. Primary keratinocytes were isolated from nonlesional skin from patients with AD and psoriasis and from normal skin of healthy donors. Apoptosis analysis was performed by using annexin V/7-aminoactinomycin D and terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling staining. The expression and regulation of TWEAK, TNF-α, Fn14, TNF receptor (TNFR) 1, and TNFR2 were measured by means of RT-PCR, flow cytometric analysis, and ELISA. TWEAK and Fn14 expression of lesional AD and psoriatic skin and normal control skin was analyzed by using immunohistochemistry and immunofluorescence. We demonstrated that TWEAK and TNF-α cooperate in the induction of apoptosis in primary keratinocytes obtained from patients with AD, patients with psoriasis, and healthy subjects and in artificial skin equivalents. TNFR1 and Fn14 were the main receptors involved. TWEAK upregulates TNF-α expression in primary keratinocytes, whereas TNF-α did not affect the expression of TWEAK and its receptors. High TWEAK expression was observed in AD lesions but not in psoriatic lesions or normal skin. Fn14 was highly expressed in the lesional skin of patients with AD and patients with psoriasis and in healthy control skin. In conclusion, the high expression of TWEAK in lesional AD skin contributes to the dif-

ference in keratinocyte apoptosis and lesional formation between AD and psoriasis.

Regulation and expression of IL-32 in chronic rhinosinusitis
Soyka MB, Treis A, Eiwegger T, Menz G, Zhang S, Holzmann D, Akdis CA, Meyer N.
Allergy. 2012;67:790-798.

Activated T lymphocytes and their interaction with resident tissue cells, particularly epithelium, play important roles in inflammatory processes in chronic rhinosinusitis (CRS). IL-32 is a recently described cytokine, which is expressed in a variety of tissue cells and involved in the pathogenesis of several chronic inflammatory diseases. In this study, human sinus epithelial cells were isolated from biopsies and stimulated with different cytokines, which play a role in the pathogenesis of CRS. IL-32 mRNA expression was analyzed using real-time-PCR, IL-32 protein was determined by Western blot and flow cytometry as well as immunofluorescent staining in primary sinus epithelial cells and nasal biopsies from patients with CRS and healthy controls. We demonstrated that IL-32 mRNA was upregulated by TNF-α and IFN-γ in primary sinus epithelial cells, whereas IL-1 β, IL-4, IL-13, and IL-17 did not influence IL-32 expression. IL-32 mRNA expression was significantly higher in human primary sinonasal epithelial cells (HSECs) cocultured with Th1 cells compared with HSECs cocultured with Th0 or Th2 cells. IL-32 mRNA expression was significantly higher in biopsies from sinus epithelial tissue of CRS patients with nasal polyps compared with healthy subjects (P = 0.01). IL-32 was detected in biopsies from patients with CRS, whereas it was scarcely present in control tissues. In conclusion, the induction of IL-32 by TNF-α, IFN-γ and Th1 cells as well as its increased expression in sinus tissues from CRS patients with nasal polyps demonstrated a potential role for IL-32 in the pathogenesis of CRS.

Davos, May 2012

(Group Cellular Allergy / Immunology led by Prof. C. A. Akdis)

Dr. Liam O'Mahony

The molecular Immunology group is primarily focused on cells of the innate immune system, which 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.

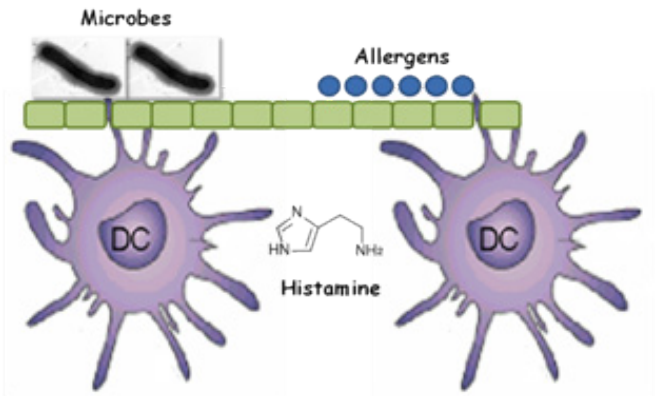


Figure 1. Microbes, allergens and metabolites (e.g. histamine) directly influence DC maturation, activation and lymphocyte polarization.

DC activation, maturation and polarization are largely influenced by local factors within their micro-environment such as microbial components, cytokines and metabolic products (e.g. 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 allergy; (ii) describe the PRR activation pattern and intracellular signaling cascades which govern commensal microbial activation of DCs leading to polarization of naïve T cells into functional regulatory cells.

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

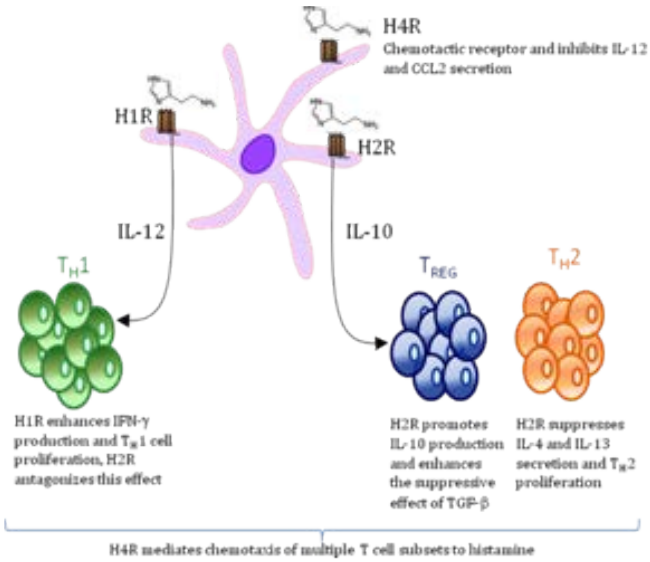


Figure 2. Histamine influences DCs and lymphocytes via their expression of different histamine receptors.

As described in previous reports, histamine signaling through the H2R significantly alters the human dendritic cell immune response to bacterial ligands (such as TLR ligands). In addition, ovalbumin sensitized mice were co-treated with Famitodine (H2R antagonist) or Dimaprit (H2R agonist), resulting in a more severe allergic phenotype or protection from allergic sensitization, respectively. Furthermore, we have now 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. Our group is currently dissecting these cellular interactions in order to identify the specific cell types responsible for this defect in immunoregulation. Thus, our results to date suggest that histamine signaling via H2R suppresses the pro-inflammatory response and may represent a novel intervention target in the treatment of allergy and asthma.

(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.

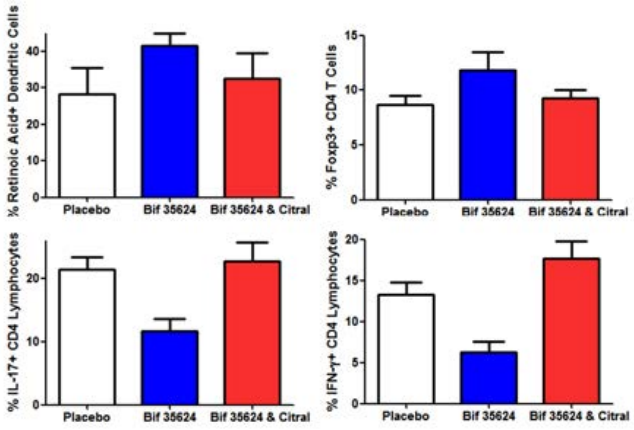


Figure 3. B. infantis-induced retinoic acid metabolism in mucosal dendritic cells is required for induction of Foxp3 expression and inhibition of IL-17 and IFN-γ production by mucosal lymphocytes. Citral is an inhibitor of retinoic acid metabolism.

Bifidobacterium infantis 35624 (B. infantis) is a commensal microbe originally isolated from the human gastrointestinal mucosa and has been extensively studied for its ability to regulate inflammatory responses, both in mice and humans. We selected this bacterium as a model Foxp3 inducing organism. B. infantis induction of regulatory cytokines, such as IL-10, is dependent on TLR-2 recognition by mDCs but TLR-9 is required for pDC activation. In addition to regulatory cytokines, DCs regulatory metabolic processes become activated, which are also required for the induction of Foxp3+ CD4 cells by B. infantis-stimulated mDCs and pDCs. However, the mechanisms of Foxp3 induction differ for mDCs and pDCs. Of particular interest, is the induction of retinoic acid metabolism by human mDCs. Thus, we have now performed mouse studies, which confirm that B. infantis directly induces retinoic acid metabolism in mucosal dendritic cells, associated with increased Foxp3 expression and diminished Th1 and Th17 cytokine expression (Figure 3). These molecular mechanisms highlight an important link between diet, composition of the gastrointestinal microbiota and regulation of intestinal immune responses. Interestingly, recent findings by other investigators on microbiota-derived short-chain fatty acids suggest that we may have previously underestimated the importance of the relationship between diet and the microbiota. Manipulation of T regulatory cell numbers or function is an exciting therapeutic target in a wide range of inflammatory diseases. 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.

Microbiota and dietary interactions: an update to the hygiene hypothesis?
Frei R, Lauener RP, Crameri R, O'Mahony L.
Allergy. 2012 Apr;67(4):451-61.

The dramatic increase in the incidence and severity of allergy and asthma has been proposed to be linked with an altered exposure to, and colonization by, microorganisms, particularly early in life. However, other lifestyle factors such as diet and physical activity are also thought to be important, and it is likely that multiple environmental factors with currently unrecognized interactions contribute to the atopic state. This review will focus on the potential role of microbial metabolites in immunoregulatory functions and highlights the known molecular mechanisms, which may mediate the interactions between diet, microbiota, and protection from allergy and asthma.

Histamine regulation of innate and adaptive immunity
Ferstl R, Akdis CA, O'Mahony L.
Front Biosci. 2012 Jan 1;17:40-53.

Histamine influences many cell types involved in the regulation of innate and adaptive immune responses including antigen-presenting cells (APCs), Natural Killer (NK) cells, epithelial cells, T lymphocytes and B lymphocytes. These cells express histamine receptors (HRs) and also secrete histamine, which can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization and effector functions leading to tolerogenic or pro-inflammatory responses. Histamine and its four receptors represent a complex system of immunoregulation with distinct effects of receptor subtypes and their differential expression, which changes according to the stage of cell differentiation as well as micro-environmental influences. In this review, we discuss histamine receptor expression and differential activation of cells within both the innate and adaptive immune response and the signal transduction mechanisms which influence their activity.

RESEARCH

Molecular Immunology

Bifidobacterium infantis 35624 administration induces Foxp3 T regulatory cells in human peripheral blood: potential role for myeloid and plasmacytoid dendritic cells
Konieczna P, Groeger D, Ziegler M, Frei R, Ferstl R, Shanahan F, Quigley EM, Kiely B, Akdis CA, O'Mahony L.
Gut. 2012 Mar;61(3):354-66.

BACKGROUND: Intestinal homoeostasis is dependent on immunological tolerance to the microbiota.
OBJECTIVE: To (1) determine if a probiotic could induce Foxp3 T cells in humans; (2) to elucidate the molecular mechanisms, which are involved in the induction of Foxp3 T cells by human dendritic cells.
DESIGN: Cytokine secretion and Foxp3 expression were assessed in human volunteers following Bifidobacterium infantis feeding. Monocyte-derived dendritic cells (MDDCs), myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs) were incubated in vitro with B. infantis and autologous lymphocytes. Transcription factor expression, costimulatory molecule expression, cytokine secretion, retinoic acid and tryptophan metabolism were analysed.
RESULTS: Volunteers fed B. infantis displayed a selective increase in secretion of interleukin (IL)-10 and enhanced Foxp3 expression in peripheral blood. In vitro, MDDCs, mDCs and pDCs expressed indoleamine 2,3-dioxygenase and secreted IL-10, but not IL-12p70, in response to B. infantis. MDDC and mDC IL-10 secretion was Toll-like receptor (TLR)-2/6 dependent, while pDC IL-10 secretion was TLR-9 dependent. In addition, MDDCs and mDCs expressed RALDH2, which was TLR-2 and DC-SIGN dependent. B. infantis-stimulated MDDCs, mDCs and pDCs induced T cell Foxp3 expression. TLR-2, DC-SIGN and retinoic acid were required for MDDC and mDC induction of Foxp3 T cells, while pDCs required indoleamine 2,3-dioxygenase.
CONCLUSIONS: B. infantis administration to humans selectively promotes immunoregulatory responses, suggesting that this microbe may have therapeutic utility in patients with inflammatory disease. Cross-talk between multiple pattern-recognition receptors and metabolic pathways determines the innate and subsequent T regulatory cell response to B. infantis. These findings link nutrition, microbiota and the induction of tolerance within the gastrointestinal mucosa.

Regulation of the immune response and inflammation by histamine and histamine receptors.
O'Mahony L, Akdis M, Akdis CA.
J Allergy Clin Immunol. 2011 Dec;128(6):1153-62.

Histamine is a biogenic amine with extensive effects on many cell types, including important immunologic cells, such as antigen-presenting cells, natural killer cells, epithelial cells, and T and B lymphocytes. Histamine and its 4 receptors 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 microenvironmental influences, leading to the selective recruitment of effector cells into tissue sites accompanied by effects on cellular maturation, activation, polarization, and effector functions, which lead to tolerogenic or proinflammatory responses. In this review we discuss the regulation of histamine secretion, receptor expression, and differential activation of cells within both the innate and adaptive immune responses. It is clear that the effects of histamine on immune homeostasis are dependent on the expression and activity of the 4 currently known histamine receptors, and we also recognize that 100 years after the original identification of this biogenic amine, we still do not fully understand the complex regulatory interactions between histamine and the host immune response to everyday microbial and environmental challenges.

CONCLUSION: These results demonstrate that claudin-1 might play a role in airway remodeling in asthmatic patients by means of regulation of ASM cell proliferation, angiogenesis, and inflammation.

Editorial:
The many routes of dendritic cells to ensure immune regulation
Palomares O, O'Mahony L, Akdis CA.
J Allergy Clin Immunol. 2011 Jun;127(6):1541-2.

Recombinant lactobacilli expressing linoleic acid isomerase can modulate the fatty acid composition of host adipose tissue in mice
Rosberg-Cody E, Stanton C, O'Mahony L, Wall R, Shanahan F, Quigley EM, Fitzgerald GF, Ross RP.
Microbiology. 2011 Feb;157(Pt 2):609-15.

We have previously demonstrated that oral administration of a metabolically active Bifidobacterium breve strain, with ability to form cis-9, trans-11 conjugated linoleic acid (CLA), resulted in modulation of the fatty acid composition of the host, including significantly elevated concentrations of c9, t11 CLA and omega-3 (n-3) fatty acids in liver and adipose tissue. In this study, we investigated whether a recombinant lactobacillus expressing linoleic acid isomerase (responsible for production of t10, c12 CLA) from Propionibacterium acnes (PAI) could influence the fatty acid composition of different tissues in a mouse model. Linoleic-acid-supplemented diets (2%, w/w) were fed in combination with either a recombinant

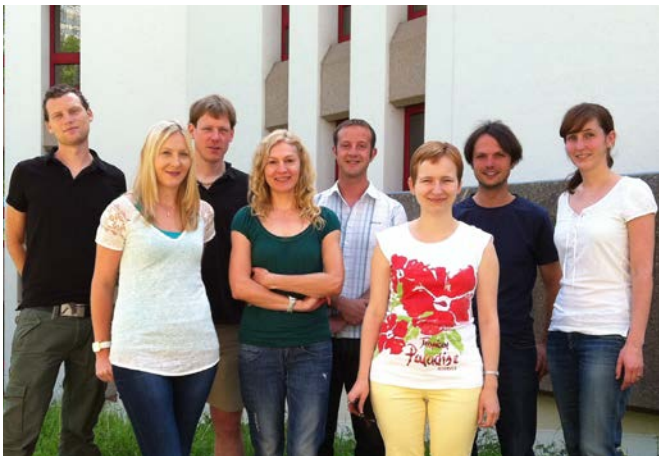
t10, c12 CLA-producing Lactobacillus paracasei NFBC 338 (Lb338), or an isogenic (vector-containing) control strain, to BALB/c mice for 8 weeks. A third group of mice received linoleic acid alone (2%, w/w). Tissue fatty acid composition was assessed by GLC at the end of the trial. Ingestion of the strain expressing linoleic acid isomerase was associated with a 4-fold increase (P<0.001) in t10, c12 CLA in adipose tissues of the mice when compared with mice that received the isogenic non-CLA-producing strain. The livers of the mice that received the recombinant CLA-producing Lb338 also contained a 2.5-fold (albeit not significantly) higher concentration of t10, c12 CLA, compared to the control group. These data demonstrate that a single gene (encoding linoleic acid isomerase) expressed in an intestinal microbe can influence the fatty acid composition of host fat.

Small intestinal bacterial overgrowth in nonalcoholic steatohepatitis: association with toll-like receptor 4 expression and plasma levels of interleukin 8

Shanab AA, Scully P, Crosbie O, Buckley M, O'Mahony L, Shanahan F, Gazareen S, Murphy E, Quigley EM.
Dig Dis Sci. 2011 May;56(5):1524-34.

BACKGROUND: Experimental and clinical studies suggest an association between small intestinal bacterial overgrowth (SIBO) and nonalcoholic steatohepatitis (NASH). Liver injury and fibrosis could be related to exposure to bacterial products of intestinal origin and, most notably, endotoxin, including lipopolysaccharide (LPS).
AIM: To compare the prevalence of SIBO and its relationships to LPS receptor levels and systemic cytokines in NASH patients and healthy control subjects.
METHODS: Eighteen NASH patients (eight males) and 16 age-matched and gender-matched healthy volunteers were studied. SIBO was assessed by the lactulose breath hydrogen test (LHBT), plasma lipopolysaccharide binding protein (LBP) levels by ELISA, and expression (as a percentage) of TLR-2 and 4 on CD14-positive cells by flow cytometry. Pro-inflammatory cytokines (IL-1β, IL-6, IL-8, and TNF-α) were measured in plasma.
RESULTS: SIBO was more common in NASH patients than control subjects (77.78% vs. 31.25%; P < 0.0001). LBP levels and TLR-2 expression were similar in both groups, TLR-4/MD-2 expression on CD14 positive cells was higher among NASH patients: expression, mean ± SEM, NASH vs. control: 20.95 ± 2.91% vs. 12.73 ± 2.29%, P < 0.05. Among the examined cytokines, only IL-8 levels were significantly higher in patients than control (P = 0.04) and correlated positively with TLR-4 expression (r = 0.5123, P = 0.036).
CONCLUSION: NASH patients have a higher prevalence of small intestinal bacterial overgrowth which is associated with enhanced expression of TLR-4 and release of IL-8. SIBO may have an important role in NASH through interactions with TLR-4 and induction of the pro-inflammatory cytokine, IL-8.

Davos, May 2012



(Group Molecular Immonolgy led by Dr. L. O'Mahony)

RESEARCH

Immunodermatology

PD Dr. Mübeccel Akdis

Allergic diseases and asthma affect almost one third of the European population, with a substantial social and economic impact on the society. Understanding the mechanisms of immune response that prevent disease occurrence in non-allergic individuals and evidence for treatment by healing of altered regulatory mechanisms in allergic diseases offers promises for new immune interventions.

Role of T regulatory cells during the successful immunotherapy.

Allergen-SIT represents the only curative approach in established allergic diseases. Studies on its mechanism of action have revealed modulation of the delicate and complex regulatory mechanisms including suppression of Th2 responses via IL-10-and TGF-b-producing Treg cells. Peripheral tolerance to allergens induced by allergen-SIT in allergic patients or healthy individuals, who are exposed to high doses of allergens involves control of allergen-specific immune response in multiple phases including specific T cell suppression, generation of non-inflammatory antibody isotypes such as IgG4 and IgA, suppression of IgE and type 1 hypersensitivity responses, suppression of late phase responses and mast cells, eosinophils and basophils (Figure 1). In healthy individuals, immune response to allergens have included unresponsiveness of T cells or active peripheral tolerance induction by subsets of Treg cell. PBMC of healthy subjects secrete higher levels of IL-10 and TGF-β after allergen stimulation leading to active suppression of specific T cell responses. Also, in non-atopic individuals, active suppression against allergens is mediated by Tr1 cells or CD4+ CD25+ Treg cells . Subsets of Treg cells with distinct phenotypes and mechanisms of action include the naturally occurring, thymic selected CD4+CD25+ Treg cells, and the inducible type 1 Treg cells (Tr1). Different studies show roles for both subsets suggesting an overlap in particularly the inducible subsets of Treg cells in humans. Their first effect is realized by suppression of allergen-specific Th2 and Th1 cells. The suppression by these cells could partially be blocked by the use of neutralizing antibodies against secreted or membrane-bound IL-10 and TGF-beta In coherence with this, 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 humans. These findings were coined by tracking specific T cells with allergen class-II tetramers: clinical tolerance induction in humans is associated with a marked loss of IL-4-producing T-cells and the acquisition of IL-10-producing and FOXP3-positive antigen-specific CD4+ T-cells. In addition to conventional immunotherapy, peptide immunotherapy in allergic asthma generates IL-10-dependent immunological tolerance associated with linked epitope suppression. Treatment with selected epitopes from a single allergen resulted in suppression of responses to other (“linked”) epitopes within the same molecule.

Similar to IL-10-secreting Tr1 cells, we have demonstrated that a distinct small fraction of NK cells with regulatory functions exist in humans. Taking the recent advances in the knowledge of peripheral tolerance mechanisms into account, developments of safer approaches and more efficient ways of allergen-SIT are soon awaiting. Molecular mechanisms of direct T cell suppression by IL-10 has been focused in recent studies. It was demonstrated the rapid inhibition of the CD28 or ICOS co-stimulatory pathways by SHP-1 represents a novel mechanism for direct T cell suppression by IL-10.

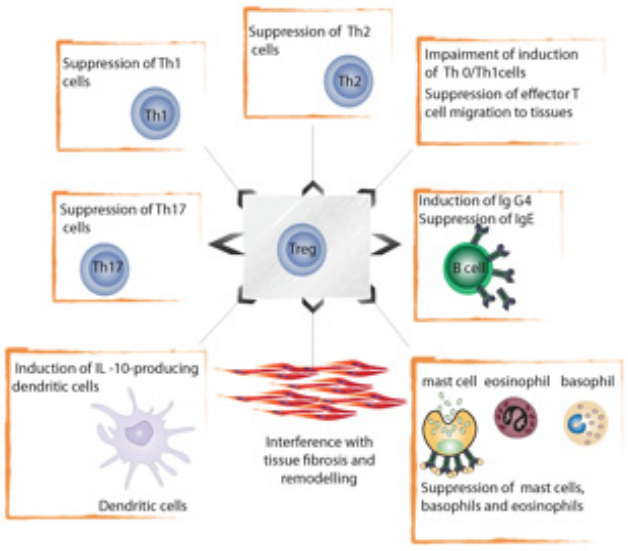


Figure 1: Treg cells in allergic immune response. Treg cells utilize multiple suppressor factors to regulate undesired activity of effector cells. IL-10 and TGF-b suppress IgE production and IL-10 induces non-inflammatory Ig

isotype IgG4 and TGF-b is a class switch factor for IgA. These two cytokines directly suppress allergic inflammation induced by effector cells such as mast cells, basophils and eosinophils. Treg cells influence the generation of DC and promote the development of IL-10-producing DC. In addition, Treg cells inhibit Th2 cells, which can no longer provide cytokines such as IL-3, IL-4, IL-5 and IL-9. These cytokines are required for the differentiation, survival and activity of mast cells, basophils, eosinophils and mucus producing cells, as well as for the tissue homing of Th2 cells. Moreover, suppression of the induction of Th0/Th1 cells abrogates tissue injury mechanisms, such as apoptosis of keratinocytes and bronchial epithelial cells, via IFN-g.

IL-22 and Th22 cells

IL-22 was identified in mice as a gene induced by IL-9 in T cells. It binds to a receptor complex built of IL-22R1 and IL-10R2. IL-22 is expressed by activated T cells and, at lower levels, by activated NK cells. More recently, IL-22 has been shown to be specifically produced by Th17 cells and by NK-22 cells. The IL-10R2 chain, which is shared with other cytokine receptors, is ubiquitously expressed. The IL-22R1 chain, in contrast is not detected on immune cells, but in organs like kidney, small intestine, liver, colon and lung, and particularly pancreas and skin. IL-22 has been shown to induce genes that are involved in the antimicrobial defense of keratinocytes. Upregulation of IL-22 consistently occurs in different bacterial infections and a major role for IL-22 has been shown in psoriasis and atopic dermatitis. Although IL-22 seems to be involved in inflammatory diseases, its role that has been sometimes suggested as beneficial or in some studies detrimental has not been clarified.

Investigations addressing the functions of IL-22 rapidly revealed that, despite the structural relationship, IL-22 is not functionally related to IL-10. Initial studies observed an up-regulated production of acute phase reactants and IL-10 in several cells lines, suggesting a functional role for IL-22 in inflammation. Reports analyzing immortalized cell lines give hints for a role of IL-22 in the acute phase of infections as well as in proliferation of certain cells. Further investigations using primary cells are required in this area. Consistent with the high expression of the IL-22 receptor on keratinocytes, IL-22 increases the antimicrobial defense of these cells by enhancing the expression of b-Defensin 2 and b-Defensin 3, psoriasin, calgranulin A, calgranulin B. IL-22 also contributes to skin immunity by synergizing with IL-17A and IL-17F in the induction of antimicrobial peptides in keratinocytes. A role of IL-22 in the defense of several bacteria has been found. IL-22 is important for the defense of Citrobacter rodentium, a bacterium that induces the appearance of IL-22-secreting NK (NK-22) cells in the lamina propria. Furthermore, IL-22 is increased upon infection with Mycobacterium tuberculosis and Klebsiella pneumoniae, suggesting a role for IL-22 in the defense of these bacteria. Finally, as chronic mucocutaneous candidiasis (CMC) was found to be associated by significantly lower IL-22 levels, the inability to clear Candida albicans might be due to a defect in IL-22 production. Taken together, these studies support an important role for IL-22 in the defense against different pathogens.

As keratinocytes are a major target for IL-22, its role in keratinocyte-associated diseases has been studied. Indeed, one study found an important role for IL-22 in psoriasis by mediating dermal inflammation and acanthosis. Consistently, in a mouse model of psoriasis, neutralization of IL-22 prevented development of the disease, reducing acanthosis (thickening of the skin), inflammatory infiltrates, and expression of Th17 cytokines. In humans, T cells isolated from psoriatic skin produced higher levels of IL-22, and supernatants of lesional psoriatic skin-infiltrating T cells induced an inflammatory response by normal human epidermal keratinocytes, resembling that observed in psoriatic lesions. Another study investigates the influence of two different drugs on IL-22 and finds that etanercept, but not acitretin is able to reduce IL-22 levels, accompanied by lower psoriasis area and severity index. To date, only few reports investigated the role of IL-22 in allergic diseases. Inflamed skin of nickel-challenged allergic individuals was observed to contain infiltrating cells expressing IL-22 and IL-22R. Another study reports that Th17 cells induce airway hyperresponsiveness in steroid-resistant asthma. It remains to be determined, whether this effect is due to IL-22 or due to other Th17 cytokines.

Tonsils as organs of immune tolerance and immune reactivity

Tonsils are strategically located in the gateway of both alimentary and respiratory tracts representing the first contact point of food and aeroallergens with the immune system. Tonsillectomy only removes palatine tonsils and sometimes adenoids. Lingual tonsil is anatomically big and remains life-long intact. CD4+FOXP3+ Treg cells and pDCs constitute major T and DC compartments in palatine and lingual tonsils. The subepithelial, lymphoid compartments of tonsils are formed by numerous secondary lymphoid follicles (B-cell areas), surrounded by interfollicular regions (T-cell areas). Tonsils possess several unique characteristics: unlike the spleen or the lymph nodes, they are not fully encapsulated; they do not possess afferent lymphatics; they are lymphoreticular and lymphoepithelial organs; and the tonsillar epithelium not only provides a protective surface cover, but also invaginates and lines the tonsillar crypts. Histologically, these structures consist of well-defined microcompartments which all participate in the immune response: the cryptepithelium, the follicular germinal center with the

mantle zone and interfollicular area. With the uptake of antigen by M-cells present in the cryptepithelium a process is initiated, which ultimately results in the generation and dissemination of antigen-specific memory and mainly dimeric IgA-producing effector B-lymphocytes. This process requires successful cognate interactions between antigen-presenting cells and lymphocytes and mutually between lymphocytes, which depend not only on antigen-specific signals, but also on the expression of various complementary adhesion and costimulatory molecules. Tonsil pDCs have the ability to generate functional CD4+CD25+CD127-FOXP3+ Treg cells with suppressive property from naïve T cells. CD4+FOXP3+ Treg cells proliferate and co-localize with pDCs in vivo in T cell areas of lingual and palatine tonsils. Tonsil T cells did not proliferate to common food and aeroallergens. Depletion of FOXP3+ Treg cells enables the allergen-induced proliferation of tonsil T cells, indicating an active role of Treg cells in allergen-specific T cell unresponsiveness. High numbers of major birch pollen allergen, Bet v 1-specific CD4+FOXP3+ Treg cells are identified in human tonsils compared to peripheral blood.

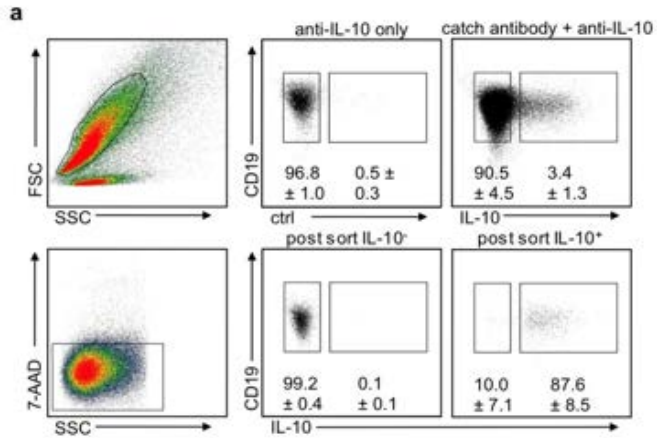


Figure 2: Purification of IL-10-producing B cells.

Regulatory B cells

Studies in mice indicate that IL-10-producing B cells play important roles in the suppression of autoimmune and inflammatory disease. During experimental autoimmune encephalomyelitis (EAE) in mice, IL-10-producing cells down regulate autoimmune disease.

Likewise, B-cell deficiency delays the emergence of regulatory T cells and IL-10 production in the central nervous system, resulting in worse disease. In humans, B-cell depletion using rituximab was recently suggested to exacerbate ulcerative colitis and trigger psoriasis, both conditions representing Th1-mediated autoimmune conditions. Hence, B-cell elimination may exacerbate disease in some autoimmune conditions. Development of IgE response to helminths has been commonly observed although there are no typically accompanying allergic diseases. IL-10-producing B cells were suggested as an underlying mechanism for the prevention of anaphylaxis during Schistosoma mansoni infection, suggesting the control of mast cell degranulation threshold by IL-10. Helminth infections are also accompanied by high levels of helminth-specific IgG4 as a link for IL-10, peripheral tolerance and suppression of allergic reactions. Human B cell regulatory (Breg) subsets remain to be elucidated in detail and tonsils provide a suitable model to study the in vivo existence and functions of Breg cells in humans.

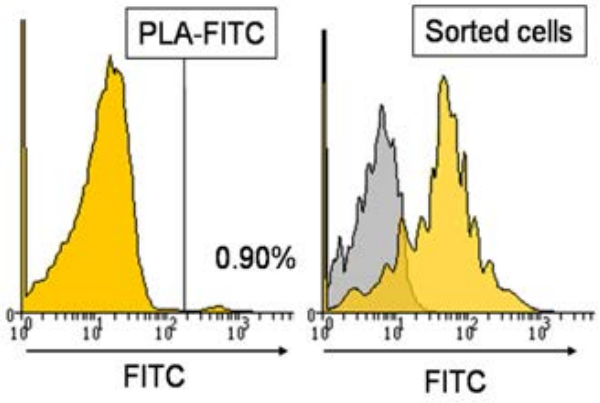


Figure 3: PLA-specific B cells isolated from B keepeers.

The immunodermatology group has granted in 2010-2011 two new EU projects from FW7 program as work package leader. The role of SIAF in MeDALL as WP9:

To better understand the immunologic mechanisms in the initiation of allergic diseases, molecular and cellular mechanisms leading to either a healthy or an allergic immune response will be investigated.
To investigate the mechanisms of allergen-specific T cell tolerance.
To define molecular mechanisms of allergen-specific T cell and B cell regulation. More specifically, we will investigate the following focused areas of research: a) the role of functional balance between Th2 cells and T regulatory cells and molecular mechanisms of allergen-specific T cell tolerance; b) demonstration of the role of B regulatory cells and molecular mechanisms in their development, and their role in allergen tolerance.
To investigate the interaction of epithelium and T cell subsets.

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

abate the epidemic.
Objectives
MeDALL (Mechanisms of the Development of ALLergy) aims to generate novel knowledge on the mechanisms of initiation of allergy from early childhood to young adulthood, in order to propose early diagnosis, prevention and targets for therapy. A novel definition of phenotypes of allergic diseases and an integrative translational approach are needed to understand how a network of molecular and environmental factors can lead to complex allergic phenotypes.
Dissemination activities of MeDALL
•Willem van de Veen won the SIAF science day best study and presentation and travel grant from EAACI for the Annual congress in Istanbul, 2011
•Willem van de Veen won travel grant and invited student grant to IFReC/SigN Winter School, Japan

Induction and maintenance of allergen-specific FOXP3(+) Treg cells in human tonsils as potential first-line organs of oral tolerance
Palomares O, Rückert B, Jartti T, Kücüksezer UC, Puhakka T, Gomez E, Fahrner HB, Speiser A, Jung A, Kwok WW, Kalogjera L, Akdis M, Akdis CA. J Allergy Clin Immunol. 2012 Feb;129(2):510-20, 2011 Nov 3.

Human B regulatory 1 cells suppress antigen-specific immune responses and develop IgG4-producing plasma cells
van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Rückert B, Akdis D, Akdis C and Akdis M. Submitted

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

Inhibition of angiogenesis by IL-32: Possible role in asthma
Meyer N, Christoph J, Makrinioti H, Indermitte P, Rhyner C, Soyka M, Eiwegger T, Chalubinski M, Wanke K, Fujita H, Wawrzyniak P, Bürgler S, Zhang S, Akdis M, Menz G, Akdis C.
J Allergy Clin Immunol. 2012 Feb 13.

Induction and maintenance of allergen-specific FOXP3(+) Treg cells in human tonsils as potential first-line organs of oral tolerance
Palomares O, Rückert B, Jartti T, Kücüksezer UC, Puhakka T, Gomez E, Fahrner HB, Speiser A, Jung A, Kwok WW, Kalogjera L, Akdis M, Akdis CA. J Allergy Clin Immunol. 2012 Feb;129(2):510-20, 2011 Nov 3.

Proinflammatory cytokines and triggering of specific Toll-like receptor break allergen-specific T cell tolerance in human peripheral blood and tonsil
Kucuksezer UC, Palomares O, Rückert B, Jartti T, Puhakka T, Nandy A, Gemicioglu B, Deniz G, Akdis CA, Akdis M. submitted.

The generation and maintenance of allergen-specific regulatory T (Treg) cells is a key step in healthy immune responses to allergens and successful allergen-specific immunotherapy. Factors and mechanisms involved in breaking peripheral tolerance to allergens are not completely understood. The aim of this study to identify agents able to break allergen-specific T cell tolerance in humans. Proliferative responses of mononuclear cells from peripheral blood and tonsils to allergens and different factors were measured by 3H-thymidine incorporation and carboxy-fluorescein succinimidyl ester (CFSE) dilution experiments. Cytokine levels in cell-free supernatants were quantified by cytometric bed array. mRNA expression of transcription factors (TFs) and cytokines in tonsil biopsies was analysed by quantitative PCR. Purified myeloid DCs (mDCs) were characterized by flow cytometry after stimulation. The proinflammatory cytokines IL-1b or IL-6 and triggering of TLR4 or TLR8 breaks allergen-specific T cell tolerance in human peripheral blood and tonsils. Tonsils are organs resembling patient's allergic status with low expression of Th1 cell-specific TFs and cytokines; T-bet, IFN-g as well as IL-10, thus representing very suitable in vivo models to assess mechanisms of breaking allergen-specific T cell tolerance. mDCs induced proliferation of allergen-specific CD4+ T cells and orchestrated the effects exerted by proinflammatory cytokines or TLR-Ls through mechanisms depending on the upregulation of HLA-DR and the costimulatory molecules OX40L and CD80. Danger signals or proinflammatory cytokines acting on mDCs breaks allergen-specific T cell tolerance in unresponsiveness subjects, suggesting that healthy individuals may develop allergic diseases after encountering

microbes or inflammatory conditions.

Histamine receptor H1 signaling on dendritic cells plays a key role in the IFN-g/IL-17 balance in T cell–mediated skin inflammation
Vanbervliet B, Akdis M, Vocanson M, Rozieres A, Benetiere J, Rouzaire P, Akdis CA, Nicolas JF and Hennino A.
J Allergy Clin Immunol 2011; 127:943-53.

The diverse effects of histamine on immune regulation are a result of the differential expression and regulation of 4 histamine receptors. Many of the immediate allergic and inflammatory actions of histamine are mediated via the type 1 receptor (H1R).
In this study it was hypothesized that H1R was involved in the fine tuning of the initiation of T cell–mediated skin pathology—that is, dermatitis. The impact of the H1R invalidation on the development of skin inflammation was analyzed in a mouse model of atopic dermatitis. It was shown that H1r –/– mice developed reduced allergen specific skin lesions. Lack of H1R expression on dendritic cells (DCs) led to diminished IL-12, upregulated IL-23, and IL-6 production upon allergen stimulation. H1R engagement on dendritic cells was necessary for DC activation and subsequent priming of effector IFN-g+CD8+ T cells. H1R blockade on DCs promotes generation of noneffector IL-17+CD8+ T cells that are unable to initiate the skin inflammation. Conclusion: This data identify that histamine signaling through the H1R on DCs is an important early event conditioning the quality of the skin effector immune response.

Immune regulation by intralymphatic immunotherapy with modular allergen translocation MAT vaccine
Zaleska A, Soyer O, Eiwegger T, Bassin C, Söllner S, Palomares O, Indermitte P, Senti G, Kündig M, Akdis CA, Crameri R, Akdis M

Allergen-specific immunotherapy (SIT) has been used as a desensitizing therapy for allergic diseases and may represent a curative and specific way of the treatment. However, current allergen-SIT has several disadvantages related to the content of the vaccine, type of adjuvant, route of application, long duration time, side effects, and sometimes limited efficacy. In the present study, direct vaccine administration into lymph nodes and targeting the MHC class II antigen presentation pathway has been hypothesized to increase the immunogenicity, efficacy and the safety of immunotherapy because of low allergen dose, however better presented to T cells. The major cat dander allergen Fel d 1 was fused to a TAT-derived protein translocation domain and to a truncated invariant chain (MAT-Fel d 1). This MAT-Fel d 1 vaccine is efficiently internalized by APCs and induces IL-10 and IFN-g dominated response, but low Th2 cytokines' production in PBMCs of allergic individuals. In a double-blind placebo-controlled clinical trial, MAT-Fel d 1 vaccine adsorbed to alum was administered by 3 intralymphatic injections in increasing dose (1 µg, 3 µg, 10 µg) into inguinal, subcutaneous lymph node within 2 months with 4 weeks intervals. Cat allergic patients became tolerant to nasal challenge with cat dander after only 3 injections. The blood for cell cultures have been taken before the therapy and twice after finishing the treatment: one week and one year respectively. Fel d 1-specific T cell tolerance was observed in the MAT-Fel d 1 group compared to placebo group after one year and the significant enhancement of IL-10 production measured in supernatants correlated with the rise of specific IgG4 in plasma samples. In addition, we observed tendency of increase in Fel d 1-specific CD3+CD4+FOXP3+ T cells' number in MAT-Fel d 1 treated patients using MHC class II peptide tetramers. Specific IgE production however rose during ILIT but it was contrary to the lack of drug related side effects. These data demonstrate that intralymphnode administration of MAT-Fel d 1 induces allergen-specific immune tolerance in cat allergic patients.

IgE class switching and cellular memory
Akdis M, Akdis CA.
Nat Immunol. 2012 Mar 19;13(4):312-4.

After class switching in naive B cells, memory B cells and plasma cells that produce immunoglobulin E (IgE+ cells) develop through a germinal-center IgE+ intermediate cell without an IgG1 phase. In addition, cellular IgE memory resides in IgE+ memory B cells, and IgG1+ memory B cells are not an important source of IgE memory.

Human IL-10-producing B cells suppress antigen-specific immune responses and produce IgG4
van de Veen W, Stanic B, Yaman G, Rückert B, Akdis D, Ferstl R, O'Mahony L, Chijioke O, Münz C, Akdis C, Akdis M

B cells are emerging as important regulators of immune responses. The lack or loss of regulatory B cells leads to exacerbated symptoms in experimental autoimmune encephalitis, chronic colitis, contact hypersensitivity, collagen-induced arthritis and non-obese diabetic mouse models. Another B cell-related immune regulatory response restricted to humans is induction of non-inflammatory IgG4 antibodies, which is characteristic for all high dose antigen tolerance models. We hypothesize that if a B cell plays an anti-inflammatory role, the antibody isotype produced by the plasma cell originating from this B cell should be anti-inflammatory. Therefore we want to characterize human IL-10-producing B cells

and determine whether these cells differentiate into IgG4-secreting plasma cells. TLR9 stimulation induced B cell proliferation and IL-10 production in human B cells. IL-10-producing B cells were purified and microarray analysis was performed. Several molecules including CD25 and PD-L1 were upregulated in IL-10-producing B cells, which was confirmed on protein level. IL-10-producing B cells suppressed antigen-specific T cell proliferation whereas other B cells did not. TLR9 stimulation of B cells induced production of IgG4 and this effect was strongly enhanced when cultures were supplemented with IL-10. Isolation of IL-10-producing B cells showed that these cells produce significantly higher levels of IgG4 than cells that do not secrete IL-10. Humanized NOD/SCID/gamma mice engrafted with fetal liver hematopoietic stem cells or peripheral blood mononuclear cells were used to study the in vivo regulation of IgG4. IL-10 treatment induced IgG4 production in these mice as well as CD25 upregulation on B cells. In addition, B cells specific for the major bee venom allergen phospholipase A2 were purified from beekeepers who developed strong T and B cell tolerance towards bee venom antigens. These cells expressed higher IgG4 compared to other B cells. Taken together, these data demonstrate that human suppressive B cells exist that produce mainly IgG4 after differentiation into plasma cells.

Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections
Senti G, Crameri R, Kuster D, Johansen P, Martinez-Gomez JM, Graf S, Steiner M, Hothorn LA, Grönlund H, Tivig C, Zaleska A, Soyer O, van Hage M, Akdis CA, Akdis M, Rose H, Kundig TM.
J Allergy Clin Immunol. 2012 May;129(5):1290-6.

Subcutaneous allergen-specific immunotherapy frequently causes allergic side effects and requires 30 to 80 injections over 3 to 5 years. Thea im of this study to improve immunotherapy by using intralymphatic allergen administration (intralymphatic immunotherapy [ILIT]) and by targeting allergen to the MHC class II pathway. Recombinant major cat dander allergen Fel d 1 was fused to a translocation sequence (TAT) and to part of the human invariant chain, generating a modular antigen transporter (MAT) vaccine (MAT-Fel d 1). In a randomized double-blind trial ILIT with MAT-Fel d 1 in alum was compared with ILIT with placebo (saline in alum) in allergic patients (ClinicalTrials.govNCT00718679). ILIT with MAT-Fel d 1 elicited no adverse events. After 3 placebo injections within 2 months, nasal tolerance increased less than 3-fold, whereas 3 intralymphatic injections with MAT-Fel d 1 increased nasal tolerance 74-fold (P < .001 vs placebo). ILIT with MAT-Fel d 1 stimulated regulatory T-cell responses (P = .026 vs placebo) and increased cat dander-specific IgG(4) levels by 5.66-fold (P = .003). The IgG(4) response positively correlated with IL-10 production (P < .001). In a first-in-human clinical study ILIT with MAT-Fel d 1 was safe and induced allergen tolerance after 3 injections.

Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases
Akdis M, Burgler S, Crameri R, Eiwegger T, Fujita H, Gomez E, Klunker S, Meyer N, O'Mahony L, Palomares O, Rhyner C, Ouaked N, Schaffartzik A, Van De Veen W, Zeller S, Zimmermann M, Akdis CA.
J Allergy Clin Immunol. 2011 Mar;127(3):701-21.e1-70.

Advancing our understanding of mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumor development, organ transplantation, and chronic infections could lead to effective and targeted therapies. Subsets of immune and inflammatory cells interact via ILs and IFNs; reciprocal regulation and counter balance among T(h) and regulatory T cells, as well as subsets of B cells, offer opportunities for immune interventions. Here, we review current knowledge about ILs 1 to 37 and IFN-γ. Our understanding of the effects of ILs has greatly increased since the discoveries of monocyte IL (called IL-1) and lymphocyte IL (called IL-2); more than 40 cytokines are now designated as ILs. Studies of transgenic or knockout mice with altered expression of these cytokines or their receptors and analyses of mutations and polymorphisms in human genes that encode these products have provided important information about IL and IFN functions. We discuss their signaling pathways, cellular sources, targets, roles in immune regulation and cellular networks, roles in allergy and asthma, and roles in defense against infections.

Davos, May 2012

(Group Immunodermatology led by PD Dr. M. Akdis)

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American Academy of Allergy, Asthma & Immunology: Annual Meeting, San Francisco, USA, March 2011

Akdis M.
The human cathelicidin LL-37; a modulator of inflammation and immunity
Advances in Immunology and Cancer Biology: Workshop, Istanbul, Turkey, April 2011

Akdis M.
Mechanisms of immunotherapie: Role of B cells
Immunology Congress, Marmaris, Turkey, April 2011

Akdis M.
New insight into the mechanisms of immunotherapy
EAACI annual congress, Istanbul, Turkey, June 2011

Akdis M.
Regulatory B cells and IgG4 production
EAACI annual congress, Istanbul, June 2011

Akdis M.
Immune regulation by human IL-10-producing B cells
EAACI annual congress, Istanbul, June 2011

Akdis M.
Mechanisms of immunotherapy and role of B regulatory cells
Austrian Society for Allergology and Immunology, Graz, September 2011

Akdis M.
Mechanisms of allergen tolerance
Graduate School of Immunology, Sandbjerg, Denmark, September 2011

Akdis M.
What can clinicians learn from the underlying immune mechanism?
EAACI, Pediatric Allergy & Asthma Meeting, Barcelona, October 2011

Akdis M.
Allergen immunotherapy: mechanisms and future strategy
Italian Association of Hospital and Territorial Allergists and Immunologists, National Meeting, October 2011

Akdis M.
Role of T and B regulatory cells in immune tolerance to allergens
Joint Swiss-Polish project meeting, Krakow, Poland, November 2011

Akdis M.
Inducing immune tolerance to allergens - implications for treatment
World Allergy Organization: XXII World Allergy Congress, Cancun, December 2011

Akdis M.
Immunologic response with venom immunotherapy
World Allergy Organization: XXII World Allergy Congress, Cancun, December 2011

Crameri R.
Malassezia, the skin, allergens and atopic dermatitis: an intriguing situation
Charité, Berlin, January 2011

Crameri R.
The ALLFUN Project: and introduction. Meeting of the work package 2 group “Fungi in the setting of inflammation, allergy and autoimmune diseases: Translating basic science into clinical practices, Davos, February 2011

Crameri R.
Tasks and goals of the ALLFUN Work package 2
Davos, February 2011

Crameri R.
Dendritic cell targeting vaccines
NANOASIT Meeting, Stockholm, April 2011

Crameri R.
Hyperantigen presentation. A novel way to divert immune response and induce allergen tolerance in allergen SIT
EAACI Meeting, Istanbul, June 2011

Crameri R.
Davos Diagnostics: Rapid and simple biosensor technology for diagnostic applications. Venture-Kick presentation, Zürich, July 2011

Crameri R.
Targeting dendritic cells for optimal allergy vaccination
NANOASIT Meeting, Marseille, August 2011

Crameri R.
Das Schweizerische Institut für Allergie- und Asthmaforschung
Veranstaltung der BDP Graubünden, Davos, September 2011

Crameri R.
Allergenic fungal cell wall proteins
The 2nd International Fungal Cell Wall Meeting, Giens, France, October 2011

Crameri R.
Davos Diagnostics: Rapid and simple diagnostics and point-of-care. Venture-Kick presentation
EPFL, Lausanne, November 2011

Crameri R.
Common immunogenic molecules and auto-antigens: Towards a universal diagnosis ALLFUN Meeting, Guadalupe, November 2011

Crameri, R.
Rapid and simple biosensor technology for diagnostic applications ALLFUN Meeting, Guadalupe, November 2011

Crameri R.
Das Schweizerische Institut für Allergie- und Asthmaforschung
Besuch Amt für Wirtschaft und Tourismus Graubünden, Davos, December 2011

Crameri R.
Engineering optimal allergy vaccines
NANOASIT Meeting, Uppsala, December 2011

Crameri R.
Rapid and easy to use Evasensor-based diagnostic technology
Immunotek, Madrid, December 2011

O'Mahony L.
Immune system in the intestine and mucosal inflammation
Food Allergy and Anaphylaxis Meeting, Venice, Italy, February 2011

O'Mahony L.
Dendritic cell regulation by microbes and metabolites
Seminar series of the Pharmacology Department, University of Bern, Switzerland, May 2011

O'Mahony L.
Mechanism of immune tolerance to foods
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, June 2011

O'Mahony L.
Toll-like and C-type Lectin receptors activation in dendritic cells by microbial components
Sociedad de Inmunologia de la Comunidad de Madrid, Spain, October 2011

O'Mahony L.
Therapeutic mining of the innate immune response to microbes
GlaxoSmithKline seminar series, London, UK, December 2011

Palomares O., Rückert B., Jartti T., Kücüksezer U., Puhakka T. Gomez E., Fahrner H. B., Speiser A., Jung A., Kwok W. W., Kalogjera L., Akdis M. and Akdis C.
Allergen tolerances is taking place in tonsils
World Immune Regulation Meeting WIRM-V, Davos, Switzerland, March 2011

Palomares O.
Dendritic cells in immune tolerance
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, June 2011

Palomares O., Rückert B., Jartti T., Kücüksezer U., Puhakka T. Gomez E., Fahrner H. B., Speiser A., Jung A., Kwok W. W., Kalogjera L., Akdis M., Akdis C.
Allergen tolerances is taking place in tonsils
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, June 2011

Rebane A.
MicroRNA expression profiles of human blood monocyte derived dendritic cells and macrophages reveal miR-511 as putative positive regulator of TLR4
World Immune Regulation Meeting WIRM-V, Davos, Switzerland, March 2011

Rhyner C.
Podium: Stammzellforschung – Brauchen wir sie?
Wissensstadt Davos, Davos, Switzerland, August 2011

Rhyner C.
Kinetics on cells-bridging the gap between traditional biosensor and cell based assay
European Antibody Congress, Geneva, Switzerland, December 2011

van de Veen W.
Human IL-10-producing B cells suppress antigen-specific immune responses and produce IgG4

CHAIR AT CONGRESSES

2011

World Immune Regulation Meeting WIRM-V, Davos, Switzerland, March 2011

van de Veen W.
Human IL-10-producing B cells negatively regulate immune responses and produce IgG4.
12th Meeting of the Swiss Immunology PhD students, Schloss Wolfsberg, Switzerland, March 2011

van de Veen W.
Human regulatory B cells suppress antigen-specific immune responses and give rise to IgG4-producing plasma cells.
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, June 2011

van de Veen W.
Human regulatory B cells mediateiImmunological tolerance
Istanbul University, Istanbul, Turkey, June 2011

van de Veen W.
Human regulatory B cells in allergic disease
Molecular Immunology and Microbiology (MIM)-Retreat, Chandolin, September 2011

van de Veen W.
Human regulatory B cells and their protective potential against allergic disease
University Medical Center (UMC), Utrecht, Netherlands, October 2011

Zaleska A.
Immune regulation by intralymphatic immunotherapy with mudlar allergen-translocation MAT vaccine
XXX Congress of the Euopean Academy of Allergy and Clinical Immunology, Istanbul, Turkes, 11th - 15th June 2011

Chair at congresses

Akdis C. A.
Hot topics in the treatment of food allergy
European Academy of Allergy and Clinical Immunolgoy: Food Allergy and Anaphylaxis Meeting, Venice, February 2011

Akdis C. A.
The 100th anniversary of the discovery of histamine
American Academy of Allergy, Asthma & Immunology: Annual Meeting,San Francisco, March 2011

Akdis C. A.
Regulatory T cells and allergen tolerance in humans
American Academy of Allergy, Asthma & Immunology: Annual Meeting,San Francisco, March 2011

Akdis C. A.
Human NK cells: Their impact in the therapy of high risk of leukemias
Immunology Congress, Marmaris, April 2011

Akdis C. A.
Protection from allergic disease by pathogens and commensals
Allergy School: Clinical impact and mechanisms of infections in Allergy, EAACI chair, Edinburgh, September 2011

Akdis C. A.
Rationale: Scientific evidence of the priority
Medical University of Warsaw: Prevention and control of childhood asthma and allergy in the EU from the public health point of view: urgent need to fill the gaps, Warsaw, September 2011

Akdis C. A.
The origins of childhood allergy
EAACI: Pediatric Allergy & Asthma Meeting, Barcelona, October 2011

Akdis C. A.
Endotypes and phenotypes of allergic disease
The American College of Allergy, Asthma and Immunology (ACAAI): Annual Scientific Meeting, Boston, November 2011

Akdis C. A.
European academy of allergy and clinical immunology: Phenotypes and endotypes of allergic disease
World Allergy Organization: XXII World Allergy Congress, Cancun, December 2011

Akdis C. A.
2013 EAACI-WAO World Allergy & Asthma Congress - Milan, Italy: Novel and emerging therapeutic strategies for allergy and asthma
World Allergy Organization: XXII World Allergy Congress, Cancun, December 2011

Akdis M.
Mechanisms of food allergy
European Academy of Allergy and Clinical Immunolgoy: Food Allergy and Anaphylaxis Meeting,Venice, February 2011

Akdis M.
Novel developments in allergen specific immunotherapy
American Academy of Allergy, Asthma & Immunology: Annual Meeting, San Francisco, March 2011

CHAIR AT CONGRESSES

2011

Akdis M.
Novel T cell subsets
World Immune Regulation Meeting WIRM-V, Davos, Switzerland, 24th - 27th March 2011

Akdis M.
JMA poster session – Basic immunology
EAACI Meeting, Istanbul, June 2011

Akdis M.
Oral abstract session 3 – Immunological updates on immunotherapy
Introductory lecture title: New insights into mechanisms of immunotherapy
EAACI Meeting, Istanbul, June 2011

Akdis M.
Poster session – Allergic inflammation and innate
EAACI Meeting, Istanbul, June 2011

Akdis M.
Plenary symposium 4 – Specific immunotherapy: basic mechanisms immunity
EAACI Meeting, Istanbul, June 2011

Akdis M.
Mechanisms of Allergic Inflammation
World Allergy Organization: XXII World Allergy Congress, Cancun, December 2011

Akdis M.
German society for allergology and clinical immunology: Microbes - friends or foes of allergic disease?
World Allergy Organization: XXII World Allergy Congress, Cancun, December 2011

Akdis M.
Hymenoptera Allergy
World Allergy Organization: XXII World Allergy Congress, Cancun, December 2011

Crameri R.
Meeting of the work package 2 ALLFUN “Fungi in the setting of inflammation, allergy and autoimmune diseases: Translating basic science into clinical practices
Davos, February 2011

Crameri R.
Workshop 4: Why do we need synthetic IgE antibodies?
EAACI Meeting, Istanbul, June 2011

Crameri R.
Graubünden forscht: Gemeinsam die Zukunft gestalten

O’Mahony L.
Innate immune responses
World Immune Regulation Meeting WIRM-V, Davos, Switzerland, 24th – 27th March 2011

O’Mahony L.
Year in Review 2 – Basic research in asthma and atopic dermatitis
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, 11th - 15th June 2011

O’Mahony L.
Poster Discussion Session 10 – Innate immune response in allergy
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, 11th - 15th June 2011

O’Mahony L.
Poster Session 43 – Novel mechanisms: what do mouse models tell us?
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, 11th - 15th June 2011

O’Mahony L.
Veterinary allergy in the 21st century – lessons from mouse and man
Gesellschaft Schweizer Tierärztinnen und Tierärzte: Vets 2011 Workshops, Davos, September 2011

Palomares O.
Dendritic cell subsets in immune regulation
World Immune Regulation Meeting WIRM-V, Davos, Switzerland, 24th – 27th March 2011

Prati M.
Cronobacter spp.(former Enterobacter sakazakii): environmental organism and opportunistic pathogen
5th Microbiology and Immunology Introductory Course, Zürich, June 2011

Rebane A.
miRNAs
World Immune Regulation Meeting WIRM-V, Davos, Switzerland, 24th – 27th March 2011

Rhyner C.
Development of novel vaccines and drugs
World Immune Regulation Meeting WIRM-V, Davos, Switzerland, 24th – 27th March 2011

Rhyner C.
Biological aspects of allergens for vaccination
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, 11th - 15th June 2011

LECTURES, AWARDS AND DEGREES

2011

van de Veen W.
B cell regulation and function
World Immune Regulation Meeting V, Davos, March 2011

Wanke K.
Control of bronchial epithelium integrity and tight junctions by regulatory T cells in asthma
4th MIM Retreat, Chandolin, Septermber 2011

Lectures at University of Zurich

Akdis C.A.
HS 2011 Nr. 1108
Mechanisms of Allergic Diseases

Akdis C.A.
HS 2011 Nr. 1078
Klinisch-experimentelle Konferenz zur Allergologie

Akdis C.A.
HS 2011 Nr. 3357
Vorlesung Molekulare Zellbiologie

Akdis M.
HS 2011 Nr. 1108
Mechanisms of Allergic Diseases

Akdis M.
HS 2011 Nr. 1078
Klinisch-experimentelle Konferenz zur Allergologie

Akdis M.
HS 2011 Nr. 3357
Vorlesung Molekulare Zellbiologie

Crameri R.
HS 2011 Nr. 1108
Mechanisms of Allergic Diseases

Crameri R.
HS 2011 Nr. 1078
Klinisch-experimentelle Konferenz zur Allergologie

Crameri R.
HS 2011 Nr. 3357
Vorlesung Molekulare Zellbiologie

O'Mahony L.
HS 2011 Nr. 1108
Mechanisms of Allergic Diseases

O'Mahony L.
HS 2011 Nr. 3357
Vorlesung Molekulare Zellbiologie

O'Mahony L.
HS 2011 Nr. 1078
Klinisch-experimentelle Konferenz zur Allergologie

Lectures at University of Salzburg

Crameri R.
FS 2011 Nr. 437.663
Einführung in die molekulare Immunologie

Scientific Awards

Akdis Cezmi
Appointment as honorary professor of
Beijing Institute of Otolaryngology

Akdis Mübeccel
Appointment as honorary professor of
Beijing Institute of Otolaryngology

Hiroyuki Fujita
Oral presentation abstract prize
Claudin-1 expression in airway smooth muscle exacerbates airway remodeling in asthma
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, 11th - 15th June 2011

Jung Andreas
Outstanding presentation award
Nasal NO measurement in pre-school children
7th Rhinocamp Winter, 6th – 8th February 2012, Davos, Switzerland

Soyka Michael
Outstanding presentation award
Epithelial barrier function in CRS
7th Rhinocamp Winter, 6th – 8th February 2012, Davos, Switzerland

van de Veen Willem
Travel grant winner
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, 11th - 15th June 2011

van de Veen Willem
Best presentation award
SIAF science day, Davos, Switzerland, 14th December 2011

Zaleska Anna
Travel grant winner
Workshop best presentation prize
XXX Congress of the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, 11th - 15th June 2011

Academic Degrees

Stanic Barbara, PhD
University of Zagreb, Faculty of Science, Department of Biology
Thesis: „Dibenzoazulenes- novel class of TNF-alpha inhibitors", September 2011

Public Seminars and Events

7.1.2011
Prof. Christian Münz
Institute of Experimental Immunology, University of Zurich "Human tumorvirus infection and immune control in vivo."

14.1.2011
Dr. Naja Jann, PhD
Infection Biology, Department of Biomedicine, University Hospital Basel "TLR2-mediated activation of innate and adaptive immunity by Staphylococcus aureus."

18.1.2011
Dr. Maurice Tangui, PhD
INSERM, University of Montpellier, France
"Alzheimer's Disease Models Based on Administration of Abeta25-35 Peptide: Scientific Rationale and Pharmacological Validation."

3.3.2011
Dr. Dieter Maier
Head of Project Management, Biomax Informatics AG, Planegg, Germany
"Knowledge Management in Systems Medicine."

11.3.2011
Dr. Natacha Ralainirina, PhD
Laboratory of Immunogenetics and Allergology, Centre de Recherche Public de la Santé, Luxembourg, Luxembourg
"The regulation of TrkA expression on NK cells."

15.3.2011
Dr. Stefan F. Martin, PhD
Allergy Research Group, Department of Dermatology, University Medical Center Freiburg, Germany
"Innate inflammatory signals in allergic contact dermatitis."

15.3.2011
Dr. Stefan F. Martin, PD
Forschergruppe Allergologie, Hautklinik, Universitätsklinikum Freiburg
"Neue Erkenntnisse über die Kontaktdermatitis."

Dr. Norbert Meyer, MD
Schweizerisches Institut für Allergie- und Asthmaforschung (SIAF) Davos
"IL-32 beeinflusst den strukturellen Atemwegsumbau beim Asthma bronchiale."

11.4.2011
Dr. Sasha Hugentobler, HEALTH
Veronique Sordet, Euresearch Head Office Bern
Petra Hertkorn-Betz, Euresearch Regional Office St. Gallen
FP7 FUNDING OPPORTUNITIES IN HEALTH & MARIE CURIE
„FP7 in a nutshell"
„Health in FP7 - The upcoming Health Call"
„The Innovative Medicine Initiative (IMI)"
„The PEOPLE programme: individual fellowships, training networks and industry-academia-partnerships"
„Grants of the European Research Council (ERC)"

13.5.2011
Dr. Carly Huitema
Ecole Polytechnique Fédérale de Lausanne, Switzerland
"Two Selection and Screening systems: A protease specificity screen and phage display of chemically modified peptides"

11.7.2011
Prof. Marco Idzko, MD
Emmy-Noether-Researchgroupleader, COPD & Asthma Researchgroup (CARG), Department of Pneumology, University Hospital Freiburg, Germany
"P2R-signalling in allergic airway disease."

16.7.2011
Prof. Donald Y. M. Leung
National Jewish Hospital, Department of Pediatrics, Denver, USA
„Mechanisms underlying infection in atopic dermatitis"
Prof. Ruby Pawankar, MD, PhD
President-elected, World Allergy Organization, Nippon Medical School, Tokyo, Japan
"Epithelial cell-immune cells cross-talk in allergic airway inflammation."

SIAF SCIENCE DAY

organized by SIAF

13.9.2011
Dr. Laurence Feldmeyer, PD
Dermatologische Klinik, Universitätsspital Zürich
“AGEP: Erworbene generalisierte exanthematische Pustulose - eine besondere Form der kutanen Arzneimittelreaktionen.”

Dr. Ana Rebane, PhD
Schweizerisches Institut für Allergie- und Asthmaforschung (SIAF) Davos
“MicroRNAs in atopic dermatitis.”

26.9.2011
Dr. David Bolton (Chip man technologies)
Dr. Christiane Klas (LabForce AG)
„Cell-IQ2 from Chip man technologies“

27.9.2011
Prof. Dr. Burkhard Ludewig, Dr. med. vet.
Head Institute for Immunobiology, Medinzinisches Forschungszentrum, Kantonsspital St. Gallen “Targeting lymphoid stromal cell in vivo.”
18.10.2011
David Bolton & Mika Remes (Chip man technologies)
Jane Klas (LabForce AG)
Live Cell Imaging Cell-IQ2, Chip man technologies
21.11.2011
Prof. Dr. med. Jürgen Schwarze, FRCPCH
Edward Clark Chair of Child Life and Health, Child Life and Health and Centre for Inflammation Research, The University of Edinburgh, Edinburgh, UK
Honorary paediatric consultant, Royal Hospital for Sick Children Edinburgh, NHS Lothian, UK
“Mechanisms at the interphase between innate and adaptive immunity in RSV bronchiolitis and subsequent allergic airways disease.”

22.11.2011
Dr. Pål Johansen, PhD
Department of Dermatology, University Hospital of Zurich “The Janus face of antihistamines.”

22.11.2011
PD Dr. med. Dominik Schaer
Klinik für Immunologie, Universitätsspital Zürich
“Neues Blut, altes Blut, gar kein Blut? - Von neuen Problemen mit der alten Bluttransfusion.”

Jeannette Kast, B.Sc.
Schweizerisches Institut für Allergie- und Asthmaforschung (SIAF) Davos
“Tight Junctions in Epithelzellen.”

2.12.2011
Dr. Hicham Bouabe, PhD
Max von Pettenkofer institut for Hygiene and Medical Microbiology, Munich (GER) “Cytokine Reporter Mice: The Special Case of IL-10”

16.12.2011
Dr. Krzysztof Pyrc, PhD
Department of Microbiology, Faculty of Biochemistry, Biophysics and Biotechnology,
Jagiellonian University, Krakow, Poland
“Novel molecular tools for virus discovery.”

SIAF Science Day 2011

Aab Alar
“The regulatory role of rhinoviruses in PBMC proliferation”

Ferstl Ruth
“Allergic airway inflammation in histamine 2 receptor knockout mice”

Fieten Karin
“Top care for children with severe topic dermatitis: a randomized pragmatic clinical trial”

Frei Remo
“Immune response of human leukocytes to the xenogenic molecule Neu5Gc”

Garbani Mattia
“Therapeutic targeting of dendritic cells in allergy”

Huitema Carly
“Quantification of antigen specific IgE antibodies”

Kast Jeannette
“Tight junctions in tonsil epithelial cells”

Komlosi Zsolt
“Lymphoid tissue inducer-like cells in asthma”

Konieczna Patrycja
“Bacterial-derived histamine: a pathogenic or commensal mechanism?”

Prati Moira
“Towards human allergen-specific monoclonal antibodies of the IgE isotype”

Treis Angela
“HCD, HCD, HCD or SMA, SMA, SMA”

van de Veen Willem
“Generation of phospholipase A2-specific, IgG4- and IgE-switched memory B cell lines”

Wanke Kerstin
“Control of bronchial epithelium integrity and tight junctions by regulatory T cells in asthma”

Wawrzyniak Marcin
“Characterization of Th22 cells in human palatine tonsils”

Wawrzyniak Paulina
“Role of Th2 cells in regulation of tight junction proteins in bronchial epithelial cells”

Winner: Willem van de Veen

Scientif posts

Akdis C.A.
American Academy of Allergy, Asthma & Immunology (AAAAI)
Eczema Section, Board 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

COST Action BM0806
Recent advances in histamine receptor H4 research member

European Academy Allergy Clinical Immunology
Executive Committee Member (2003-)

European Academy of Allergy Clinical Immunology
Vice President 2007-2011
President 2011-2013

Global Allergy and Asthma European Network GA2LEN
Executive Committee Member

Global Allergy and Asthma European Network GA2LEN
Assembly Member (Representative of Switzerland)

World Allergy Organization Research Council
Council Member

World Immune Regulation Meeting
Chairman

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

Collegium Internationale Allergologicum
Council Member (2006-2010)

European Academy Allergy Clinical Immunology
Immunology Section Board Member
Global Allergy and Asthma European Network GA2LEN
Work package member (2004-2008)

World Immune Regulation Meeting
Member of the organizing committee

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

European Union Research, Predicta
Steering board member
Work package leader

Crameri R.
Academia Raetica
Co-founder and vice president

Academia Raetica Symposium 2011
„Graubünden forscht: Young Scientists in Contest”
Member of organizing committee

Global Allergy and Asthma European Network GA2LEN
Intellectual property task force member

Global Allergy and Asthma European Network GA2LEN
Work package member (IgE sensitization an allergic diseases)

18th Congress of the “International Society for Human and Animal Mycology” (ISHAM), Berlin
Member of the organizing committee

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

7th Framework Program “ALLFUN”
Steering board member

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

Euronanomed Program “NANOASIT”

SCIENTIFIC POSTS AND EDITORIAL ACTIVITIES

Editorial activities 2011

Steering board member
Euronanomed Program “NANOASIT”
Work package leader (Engineering optimal allergy vaccines)

Naturforschende Gesellschaft Davos,
Advisory board member and treasurer

World Immune Regulation Meeting
Member of the organizing committee

O’Mahony L.
EAACI Immunology Section Board Member 2011-2013
Management Committee Member to EU COST Action BM0806 – Histamine H4 Receptor
Financial Rapporteur - COST BM0806
Organizing committee member of World Immune Regulation Meeting (WIRM), Davos
Local organizing committee member for the annual EAACI meeting, Geneva 2012

Jung A.
Chairman Modul “Case-Based-Learning”
ERS e-Learning-Programm (European Respiratory Society)

Vorstandsmitglied der Forschungsgemeinschaft Mukoviszidose (Mukoviszidose e.V.)

Mitglied der AWMF-Leitlinienkommission zur Diagnose der Cystischen Fibrose (Gesellschaft für Pädiatrische Pneumologie)

Mitglied der Forschungskommission der Swiss Working Group of Cystic Fibrosis

Medizinischer Leiter der Asthmaakademie Davos

Editorial Activities

Akdis C.A.
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 Clinical Immunology, associate editor (2007-)
Journal of Investigational Allergology and Clinical Immunology, editorial board member
Nature Reviews in Immunology, highlight advisor
Clinical Translational Allergy, associate editor
Nature Scientific Reports, editorial board member

Akdis M.
Allergy, editorial board member
International Archives of Allergy and Immunology, editorial board member
Recent patents in inflammation, allergy and drug discovery, editorial board member
Journal of Allergy Clinical Immunology, editorial board member

Crameri R.
Allergy, associate editor
Biochemical Journal**,** editorial board member
International Archives of Allergy and Immunology, editorial board member
Mycoses, deputy editor
The Open Allergy Journal, editorial board member
The Open Immunology Journal, editorial board member
The Open Mycology Journal, editorial board member

Collaborations with the Clinics of Davos

Hochgebirgsklinik Davos-Wolfgang (PD Dr. G. Menz, Prof. R. Lauener, Dr. C. Steiner, Dr. A. Kirsch)

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

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

Zürcher Höhenklinik Davos, Davos Clavadel (Dr. T. Rothe, Dr. S. Spiess, Dr. P. Risi)

Collaborations outside Davos

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

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

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)

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

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

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

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

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

Forschungszentrum Borstel, Borstel (D), (Dr. U. Jappe)

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

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

Institute of Medical Microbiology and Hygiene, University of Tübingen (D), (Prof. Gerd Döring)

Institut Pasteur, Paris (F), (Prof. J.P. Latgé, Dr. S. Paris)
Kantonsspital Basel, Abt. Dermatologie, Basel (CH), (Prof. A. Bircher)

Kantonsspital Chur, Department ENT, Chur (CH), (Heinz B. Fahrner)

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

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

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

Medical University of Wroclaw, (P), (Prof. M. Jutel)

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

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

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

Novartis Institutes for BioMedical Research, Horsham (UK), (Christoph Walker PhD,
Gerald Dubois PhD)

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

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

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

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

Skirball Institute of Biomolecular Medicine, New York University School of Medicine, New York (USA), (MD Dr. Dan R. Littman, Dr. Mark M.W. Chong)

Stallergenes SA (FR), (Dr. P. Moingeon, Dr. L. van Overtvelt, Dr. E. Wambre)

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. H. Behrendt, Dr. C. Traidl-Hoffmann)
The Hospital for Sick Children, Cancer and Blood Research Program, Toronto (CAN), (Dr. M. Letarte)

The Netherlands Cancer Institute, Divison of Cellular

SCIENTIFIC COLLABORATIONS

2011

Biochemistry, Amsterdam (NL), (Prof. P. ten Dijke, Dr. S. Itoh)

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

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

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

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

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

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

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

Universitätsspital Zürich, Abteilung für Pneumologie, Zürich (CH), (Prof. E. Russi)
Universitätsspital Zürich, Abteilung für Klinische Immunologie, Zürich (CH), (Dr. L. Bisset, Prof. A. Fontana)

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

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

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

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

Wroclaw Medical University, Wroclaw (PL), (Prof. M. Jutel, Dr. K. Solarewicz)

Center for Inflammation Research, University of Edinburgh (UK), (Prof. J. Schwartze)
Universitätsklinikum Freiburg D, COPD & Asthma Researchgroup (CARG), Abtl. für Pneumologie, Freiburg (D), (PD Dr. Marco Idzko)
Medical University of Vienna, Au, Department of Pediatrics, Vienna (A), (Dr. T. Eiwegger, Prof. Z. Scephaluzi)

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

Complutense University of Madrid, Department of Biochemistry and Molecular Biology, Chemistry School, Madrid (SP), (Dr. O. Palomares)

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

Swiss National Science Foundation
- Regulation of allergen-specific immune response
Akdis M.
CHF 93‘750.-
01.05.2009 - 31.03.2011
(2009: 150‘000; 2010: 131‘250; 2011: 93‘750)

- T cell interaction with tissue cells in allergic inflammation
Akdis C.A.
CHF 214‘800.-
01.10.2010 – 31.09.2012
(2010: 214‘800; 2011: 187’950; 2012: 134’250)

- Molecular interactions regulation innate, adaptive and regulatory responses in allergic diseases
Crameri R.
CHF 119’500.-
01.04.2010 – 31.03.2011

- Route of application and mode of action of modular antigen transporter (MAT) allergy vaccines
Crameri R.
CHF 93’750.-
01.10.2009 – 30.09.2012
(2009: 150’000; 2010: 131’250; 2011: 93’750)

- Dendritic cell-glycan interactions – key modulators of T cell function in allergy and asthma
O’Mahony L.
CHF 115‘850.-
01.12.2009 – 30.11.2011
(2009: 132‘400; 2010: 115‘850; 2011: 82‘750)

- Targeted elimination of IgE memory B cells and serum IgE through active vaccination
Rhyner C.
CHF 269‘110.-
(2011: 87‘920.-; 2012: 90‘370.-; 2013: 90‘820.-)

Staatssekretariat für Bildung und Forschung (SBF)
CHF 795‘000.-

Stanley Thomas, Johnson-Stiftung
R. Crameri
CHF 25‘000.-

Stiftung vormals Bündner Heilstätte Arosa
CHF 50‘000.-

Universität Zürich
Akdis C.A.
CHF 50‘000.-

EAACI
Akdis C.A. for President
EUR 20‘000.-

CK-CARE AG
Akdis C.A.
CHF 500‘000.-

Universitätsspital Zürich
Soyka M.
CHF 25‘000.-

Novartis Pharma AG
Akdis C.A.
CHF 60‘385.77

Alimentary Health Ltd
O’Mahony Liam
EUR 90‘000.-

Amalgen D.O.O.
Mercep M.
CHF 100‘000.-

Marie-Curie
O’Mahony L.
CHF 161‘658.30

MeDALL
Akdis M.
for 4 years
CHF 700‘024.64

Allfun
Crameri R.
for 3 years
CHF 374‘567.-

PreDicta
Akdis M.
for 5 years
CHF 769‘146.-

Euronanomed
Crameri R.
for 3 years
CHF 300‘000.-

TEAM-EPIC
O‘Mahony L.
for 3 years
EUR 276‘162.-

MARIE-CURIE
O‘Mahony L.
for 2 years
EUR 180‘000.-

Bilanz per 31. Dezember 2011

(inklusive Drittmittel)

	31.12.2011	31.12.2010
	CHF	CHF
AKTIVEN		
Flüssige Mittel	1'163'051.34	353'153.43
Forderungen	80'034.72	274'010.81
Aktive Rechnungsabgrenzung	137'240.81	292'345.26
	1'380'326.87	919'509.50
PASSIVEN		
Verbindlichkeiten	105'428.54	100'638.09
Bankverbindlichkeiten	14'225.70	73'539.19
Kontokorrent SFI Stiftung	24'038.65	84'090.00
Passive Rechnungsabgrenzung	1'017'177.49	441'786.10
Eigenkapital	219'456.49	219'456.12
	1'380'326.87	919'509.50

Betriebsrechnung 2011

(inklusive Drittmittel)

	Rechnung 2011	Budget 2011	Rechnung 2010
	CHF	CHF	CHF
ERTRAG			
Beitrag Bund Forschungsgesetz Art. 16	795'000.00	795'000.00	775'000.00
Beitrag Kanton Graubünden	137'187.05	137'600.00	138'013.00
Beitrag Gemeinde Davos	402'400.00	400'000.00	380'000.00
Beitrag Universität Zürich	298'345.00	298'300.00	50'000.00
Beitrag Stiftung SFI Villa Fontana	100'000.00	100'000.00	100'000.00
Beitrag Stiftung vormals Bündner Heilstätte Arosa	50'000.00	30'000.00	50'000.00
Beitrag Hochgebirgsklinik Davos	0	10'000.00	10'000.00
Beitrag Stiftungen/Drittmittel	400'000.00	0	486'311.64
Overheadbeiträge SNF	130'438.00	82'000.00	165'438.00
Ertrag aus Dienstleistung Asthmaforschung	18'069.46	20'000.00	15'122.52
Übriger Ertrag	2'396.54	4'000.00	10'195.06
Finanzertrag	780.79	0	625.06
Ausserordentlicher Ertrag	6'949.70	0	0
WIRM-Kongress	430'598.51	455'000.00	534'574.16
EAACI-Kongress	2'612.64	0	4'907.00
Drittmittel	2'069'150.97	2'082'160.00	2'087'403.02
	4'843'928.66	4'414'060.00	4'807'589.46
AUFWAND			
Personalaufwand	2'442'824.71	2'497'800.00	1'851'856.25
Verbrauchsmaterial	1'442'194.00	992'000.00	1'339'340.90
Raumaufwand	20'952.60	25'000.00	16'400.55
Unterhalt/Reparaturen/Ersatz	106'909.58	125'000.00	108'496.68
Investitionen	98'915.02	157'560.00	767'251.49
Sachversicherungen/Abgaben	7'271.20	9'000.00	6'851.20
Energie- und Entsorgungsaufwand	68'016.80	70'000.00	65'790.93
Verwaltungsaufwand	147'902.30	133'000.00	149'487.26
Reisespesen	74'758.90	73'700.00	91'022.50
WIRM-Kongress	398'229.82	329'000.00	392'302.94
EAACI-Kongress	2'555.10	0	5'459.60
Übriger Betriebsaufwand	2'519.00	1'000.00	1'871.46
Finanzaufwand	6'352.65	1'000.00	4'926.42
Ausserordentlicher Aufwand	24'526.61	0	5'841.77
	4'843'928.29	4'414'060.00	4'806'899.95
Ergebnis	0.37	0	689.51
	4'843'928.66	4'414'060.00	4'807'589.46

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