SIAF

ANNUAL REPORT 2012

University of Zurich[UZH]

Schweizerisches Institut für Allergie- und Asthmaforschung SIAF

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

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

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Bericht des Direktors

Prof. Dr. med. Cezmi A. Akdis

In weniger als einem halben Jahrhundert sind Allergien und Asthma (früher waren diese Erkrankungen eher rar) epidemisch angestiegen und wurden zu einem grossen Gesundheitsproblem der Weltbevölkerung. Heute beeinträchtigen sie die Leben von über einer Milliarde Menschen weltweit. Die Verbreitung dieser Erkrankungen und deren Auswirkungen sind die Folge der Zunahme der Urbanisierung und der Globalisierung, verbunden mit dem ökologischen Wandel und der Lebensstiländerung. Nebst dem individuellen Leid stellen diese Erkrankungen eine sehr hohe sozio-ökonomische Belastung für das Gesundheitssystem und die Familien dar. Zudem sind in vielen Entwicklungsländern die Patientenbetreuung und der Zugang zu Behandlungsmöglichkeiten mangelhaft. Um diese Lücke auf globaler, regionaler und nationaler Ebene zu schliessen, bedarf es wirksamer Massnahmen und Strategieentwicklungen.

Die Anstrengungen, um diese unerfüllten Bedürfnisse zu überwinden, können in vier Richtungen gruppiert werden.
- Forschung und Entwicklung müssen effektiver zusammenarbeiten um Forschungsergebnisse zu Prävention, Biomarker, anti-virale Impfungen und Entwicklung von neuen Medikamenten voranzutreiben und umzusetzen. Im Speziellen soll aus dieser Zusammenarbeit eine Behandlung für die schweren Formen dieser Erkrankungen resultieren.

- Für eine verbesserte Patientenbetreuung auf globaler Ebene wird ein weltweiter Ansatz benötigt, um die Barrieren in Bezug auf Prävention und Behandlungsmöglichkeiten zu überwinden. Zu diesem Ansatz gehören die Erstellung von Allergie- und Asthma-Registern, die Erstellung von zeitgemässen Richtlinien, die Verbesserung der Zugänglichkeit zu Diagnose und medizinischer Versorgung in Entwicklungsländer, die Durchführung von Massnahmen zum Umweltschutz, direkte und routinemässige psychologische Betreuung und lückenlose Aufklärung von Patienten, aber auch die Ausbildung.von Allgemeinmedizinern und medizinischem Personal in jeglichen Aspekten.

-Um das Bewusstsein der Öffentlichkeit zu erweitern, müssen allergische Erkrankungen und Asthma als eines der wichtigsten Ursachen für eine hohe chronische Erkrankungsrate der Bevölkerung anerkannt werden, welche eine hohe Belastung für die Gesundheitskosten mit sich ziehen.. Die Gründung patientenorientierte Organisationen für Allergien und Asthma weltweit ist von grosser Dringlichkeit.

Politiker sind nun gefordert zu reagieren, denn die Anzahl erkrankter Personen und Familien ist enorm hoch und die Gesundheitskosten aufgrund allergischer Erkrankungen und Asthma belastet das Budget der Gesundheitssysteme aller Länder.

Eine weltweite Strategie gegen allergische Erkrankungen und Asthma sollte entwickelt werden:
- Es sollte ein interdisziplinärer Ansatz mit Einbezug von Spezialisten, Allgemeinmedizinern, Krankenschwestern, Ernährungswissenschaftler, Psychologen, Apothekern, Patientenorganisationen, Ausbildnern, Industrie und Politik verfolgt werden.

- Weltweites Management von Allergien und Asthma sollte in das Konzept von „One Health“ (Global Risk Forum, Davos), das Systemzusammenhänge von Mensch, Tier, Gesundheit und Umwelt mit Lebensmittelsicherheit berücksichtigt, eingebunden werden. In einer Zeit von Klimaveränderung, Ressourcenabbau, Verarmung der Böden, Ernährungsunsicherheit und Entwicklungsänderungen ist ein integrativer Ansatz zu nachhaltigen Gewährleistung von Gesundheit erforderlich.

- Das Erstellen von neuen zeitgemässen Richtlinien für Allergien, Asthma und allergische Begleiterkrankungen wird dringend benötigt. Diese detaillierten Richtlinien sollen dazu dienen vor Ort, auch unter Berücksichtigung von kulturellen Unterschieden, strukturiert die optimale Patientenbetreuung zu garantieren.

- Die Gründung eines „World Allergy and Asthma Center“ mit einem hervorragend verknüpften Netzwerk zu allen nationalen Allergie- und Asthmazentren und anderen Netzwerken, Bündnissen, Gesellschaften und Akademien, die alle die Förderung der weltweiten Überwachung, der Strategieentwicklung und der Edukation zum Ziel haben. In den Vereinten Nationen, der WHO und nationalen politischen Agenden, wo weitere chronische nicht-übertragbare Krankheiten bereits heute als Priorität gelten, werden Allergien und Asthma besonders berücksichtigt. Ein Management von Asthma zusammen mit weiteren Atemwegserkrankungen und chronischen nicht-übertragbaren Krankheiten innerhalb dieser Organisationen könnte in der Frühphase dienlich sein. Um

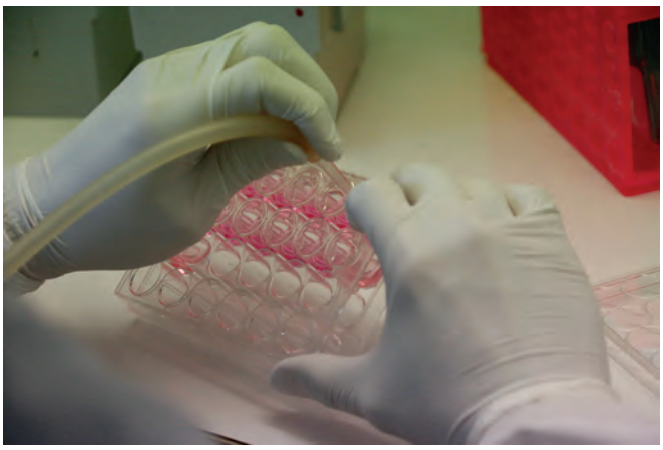
einen Langzeiterfolg zu erzielen sollte die komplette Aufmerksamkeit dem Asthma gewidmet werden. Mit Hilfe von Krankheitsregistern, pharmakoökonomischer Bewertung und umfangreichen Biobanken sollte ein weltweites und integriertes Überwachungsnetzwerk für Allergien und Asthma errichtet werden.

- Gesundheitsökonomische Allergie- und Asthmastudien und Studien von anderen lebenslangen chronischen Erkrankungen zeigen, dass durch Prävention und kurativen Behandlungen die Kosten massiv gesenkt werden können. Besonders die Prävention in Bezug auf Entwicklung von Asthma und Allergien und die Verschlechterung zu schweren Formen dieser Krankheiten haben enorme Auswirkungen auf die Kosten im Gesundheitswesen. Es wäre nun an der Zeit, dass Krankenversicherungssysteme und andere Finanzierungsmodelle im Gesundheitswesen in die Forschung und Edukation für Primär- und Sekundärprävention und kurativen Behandlungsmöglichkeiten investieren würden.

- Ein multidisziplinärer wissenschaftlicher Ansatz ist unerlässlich. Ein erster Vorstoss in diese Richtung wurde am 17. – 20. Juli 2011 anlässlich des Global Allergy Forum, das unter dem Patronat der Christine-Kühne Stiftung – Center for Allergy Research und Education (CK-CARE AG) steht, gemacht. 40 Wissenschaftler und Ärzte aus aller Welt versammelten sich in Davos und erstellten die „Davos Deklaration“, welche 2012 in der Fachzeitschrift „Allergy“ erschien.

Die Allergieforschung am SIAF konzentriert sich auf die Untersuchung der immunologischen Grundlagen allergischer und asthmatischer Erkrankungen. 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. Des Weiteren 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. Das SIAF ist ausserdem der Academia Raetica angeschlossen, welche unter anderem zum Ziel hat, die interdisziplinäre Zusammenarbeit und die wissenschaftliche Tätigkeit der angeschlossenen Institutionen zu fördern.

Die EAACI ist die weltgrösste Akademie für allergische Erkrankungen und übernimmt eine wichtige Rolle in Bezug auf Wissenschaft, Weiterbildung, Kommunikation und Öffentlichkeitsarbeit. Im Jahr 2012 stand der jährlich stattfindende Kongress mit rund 7‘000 Teilnehmern in Genf auf dem Programm. 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. 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 4 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 spielt in der CK-CARE eine tragende Rolle.

Bericht des Direktors

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 Krankheitssymptomen führen. Es 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 mehr als 20 wissenschaftliche Mitarbeiter eingestellt und zehn akademische Gäste im Austauschprogramm aufgenommen werden, die an den folgenden Projekten gearbeitet und 45 Publikationen in namhaften Zeitschriften veröffentlicht haben.

- Allergische Erkrankungen entstehen aus einem Ungleichgewicht von regulatorischen Zellen und Effektor-Zellen. 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 dritten Jahr und soll, angesichts der Aktualität dieses Forschungszweiges, effizient weiterentwickelt werden. Im letzten Jahr sind zu diesem Projekt zwei Artikel in namhaften Fachzeitschriften erschienen.

- Defekte in der Ausbildung der Zell-Zellbarrieren (Tight Junctions) und Zelltodaktivierung von bronchialen Epithelzellen und Keratinozyten bei allergischen Erkrankungen: Das Lungenepithel von Asthmatikern und die Haut von Patienten mit Neurodermitis zeigen eine abnorm hohe Durchlässigkeit zwischen den Zellen, da die Ausbildung der Tight Junctions defekt sind. Zu diesem Thema konnten im letzten Jahr zwei Artikel publiziert werden.

- Der krankheitsbedingte Umbau der zellulären Bronchienstruckturen (Remodellierung) in Asthma, die eine Konsequenz von übermässiger Reparaturprozesse sein könnte, führen zu einer Verdickung der Muskelschichten und des Bindegewebes und zu vermehrter Mukusproduktion.. Dadurch wird das Lungenvolumen stark reduziert und das Atmen erschwert. Die Wissenschaftler am SIAF erforschen Mechanismen zum besseren Verständnis der Atemwegsremodellierung und entwickeln Strategien, um Gewebezerstörungen und die Remodellierung bei Asthma und Neurodermitis zu behandeln.

Die folgenden Forschungsgebiete werden aktuell am SIAF bearbeitet und durch den Schweizerischen Nationalfonds, MeDALL, PREDICTA, ALLFUN, NANOASIT, das Swiss-Polish Cooperation Programme, Marie Curie, Müller-Gierok Stiftung, die Kommission für Technologie und Innovation KTI 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 allergischer Entzündungen in den betroffenen Organen.

- 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.

- Die Arbeitsgruppe Molekulare Immunologie macht grosse Fortschritte bei der Entdeckung neuer Wechselwirkungen zwischen dem Mensch und Bakterium. Diese Wechselwirkung 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-Zel-

len, 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. MeDALL 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. 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 aufgenommen 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 nicht-allergischen Immunreaktion wird untersucht. Zudem werden die biochemischen Signale, welche die Aktivierung der regulatorischen Zellen steuern, erforscht. 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.

- 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 Treg handelt. Es ist auch klar, dass Th17 und Th22 eine wesentliche Funktion in der Pathogenese von Athma und atopischem Ekzem 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? Welche Infektionserreger werden von den Th17 Zellen bekämpft? Ausser IL-17 produzieren die Th17-Zellen eine Reihe weiterer Zytokine (TNF-alpha, 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 Projektes PREDICTA besteht darin, dass wiederholte akute Vireninfektionen die angeborene, adaptive und/oder regulatorische Immunantwort so verändern, dass ein chronisches Entzündungsmuster entstehen kann. Diese Studie untersucht die Regulierung von Entzündungen durch akute Infektionen in Patientenkohorten. Es sollen Strategien entwickelt werden, um die Progredienz/Persistenz von Krankheiten zu verzögern und/oder zu verhindern, indem man sich auf ursächliche oder spezifische Elemente von Entzündungsabläufen fokussiert.

- Die allergen-spezifische Immunotherapie (SIT) wird seit mehr als einem Jahrhundert als desensibilisierende Therapie für allergische Krankheiten eingesetzt und ist die einzige kurative Behandlungsmethode. Durch die Untersuchung von verabreichten Allergenextrakten 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. Um den Erfolg der SIT im einzelnen Patienten zu beobachten, konzentriert sich unser KTI-Projekt in Zusammenarbeit mit zwei Industriepartnern auf ein neues diagnostisches Verfahren, das mittels Biomarker den Erfolg der SIT dokumtentiert. 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, welche ein nach wie vor ungelöstes Problem darstellen. 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.

Das vergleichsweise kleine SIAF hat über 760 Fachbeiträge veröffentlicht und gehört zu den meistzitierten Instituten weltweit. Die vom SIAF publizierten Artikel wurden über 30‘000 Mal zitiert. Das Institut gehört mit seinen rund 45 Mitarbeitern (im Vergleich zu Universitäten mit Tausenden von Forschern) weltweit zu den Besten bezüglich Anzahl Mitarbeiter oder Zitierung geteilt durch Budget. In den letzten Jahren konnte eine signifikante Erhöhung der Anzahl Zitierungen erreicht werden. Es ist eine international bekannte Ausbildungsstätte für Doktoranden und Habilitanden.

Im vergangenen Jahr wurden insgesamt 66 wissenschaftliche Arbeiten (ohne Abstracts) publiziert. 54 wurden in begutachteten internationalen Fachzeitschriften veröffentlicht. Der durchschnittliche “Impact-Factor” betrug 9.317 Punkte. 2012 erreichte das SIAF einen Gesamtwert des “Impact Factors” von 428.600. Die neusten Ergebnisse wurden zudem in 36 Kurzfassungen (Abstracts) an verschiedenen Fachtagungen mitgeteilt. Mitarbeiter des SIAF wurden zu 82 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 42 verschiedenen Sessionen hatten SIAF Mitarbeiter den Vorsitz. Zusätzlich werden 40 wissenschaftliche Ämter in internationalen Gesellschaften durch Wissenschaftler des SIAFs besetzt. Des Weiteren 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. Im Jahr 2012 wurden insgesamt 39 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 der Hochgebirgsklinik Davos-Wolfgang durchgeführt. Das SIAF bietet als einziges Institut im gesamten Kanton Graubünden Davoser und allen weiteren interessierten Kliniken und praktizierenden Ärzten spezielle zelluläre immunologische Untersuchungen an. Für die Durchführung dieser Untersuchungen besitzt das SIAF eine vom Gesundheitsamt Graubünden ausgestellte Bewilligung zum Betreiben eines „Immunologischen Laboratoriums“ und ein vom Schweizerischen Zentrum für Qualitätskontrolle (CSCQ) 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. Prof. C. Akdis Fakultätsmitglied der Medizinischen Fakultät der Universität Zürich mit Promotionsrecht in der Mathematischen und Naturwissenschaftlichen Fakultät und Honorarprofessor an der Bezmialem Universität Istanbul. Prof. C. Akdis und PD Dr. M. Akdis

haben zudem eine Honorarprofessur am Tungren Spital der Peking-Universität.

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.

World Immune Regulation Meeting-VII 2013

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 13. bis 16. März 2013 fand zum siebten Mal das WIR-Meeting im Kongresszentrum Davos statt. Rund 650 Wissenschaftler aus 40 verschiedenen Länder trafen sich zu diesem viertägigen Kongress, um sich über die neuesten Erkenntnisse in der Immunologie auszutauschen und trugen 114 Vorträge und 265 Abstracts vorgestellt. 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 Posteraustellung 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 40 zu den wissenschaftlichen Angestellten. Derzeit führen am SIAF 13 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-Polish Research Cooperation, das schweizerische Förderungsprogramm Scientific Exchange Programme NMS-CH sowie die European Respiratory Society (ERS) ermöglichten wiederum Forschern Weiterbildungsaufenthalte am SIAF. Insgesamt 18 Wissenschaftler 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. Die zusätzlichen Ausgaben wurden aus Erträge des WIRM Kongresses und zusätzlichen Drittmitteln gedeckt.

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 Institutes.

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 2013

Report of the director

Prof. Dr. med. Cezmi A. Akdis

In less than half a century, allergies and asthma, originally rare diseases, showed an epidemic increase, and had become a major public health problem. Today, they are affecting the lives of more than 1 billon people worldwide. Their prevalence and impact are particularly on the rise in urbanizing regions and globalizing World associated with environmental and lifestyle changes. Apart from individual suffering of patients, they present a very high socioeconomic burden to health care systems and families. In addition, patient care and access to treatment is inadequate in many developing regions and countries. Effective policies and strategy development are needed to fill this gap at the global, regional, national level.

The efforts to overcome high numbers of unmet needs can be grouped in four directions.

A) Research and development should be synergized and prioritized in order to achieve sustainable results on prevention, biomarkers, anti-viral vaccines, and novel drug development particularly for the treatment of severe forms of these diseases.

B) Better patient care at the global level requires a worldwide approach to identify barriers for prevention and cure; develop allergy and asthma registries; develop next generation guidelines; improve accessibility to diagnosis and essential drugs in low income countries; implement full environment control; realize psychological help directly and routinely without any need for consultation; implement every aspect of education of patients, primary care physicians and allied health personal.

C) To increase the public awareness, it is now essential to position allergic diseases and asthma as one of the most important causes of chronic morbidity and health care burden. Allergy and asthma focused patient organizations should be immediately established in all countries.

D) It is not possible for the politicians to remain silent at this stage, because the number of affected individuals and families are huge, and health care burden of allergic diseases asthma is forcing the budgets of health systems in all countries.

A worldwide strategy to fight and manage allergic diseases and asthma should be developed.

A) A multisectorial approach including specialists, primary care physicians, nurses, dieticians, psychologists, pharmacists, patient organizations, educators, industry, and policy makers should be taken.

B) Worldwide allergy and asthma management should be integrated with the “One Health” (Global Risk Forum, Davos) concept that acknowledges the systemic interconnections of human, animal and environmental health in close relationship with food safety and security. In an era of climate change, resource depletion, land degradation, food insecurity and development challenges, an integrative approach is needed to ensure sustainable health.

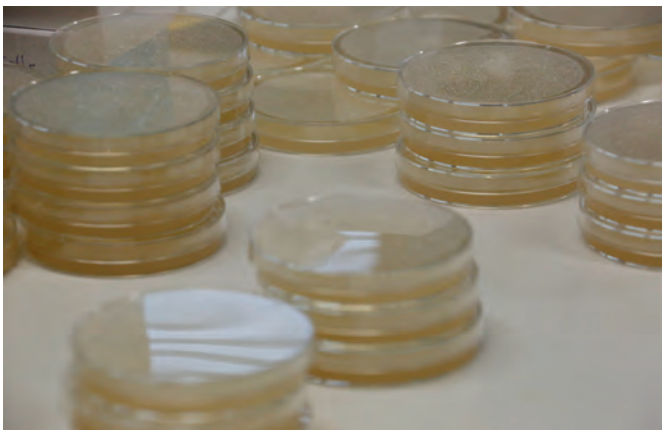
C) Next generation guidelines should be implemented in allergic diseases and asthma and co-morbidities to provide structured, multidisciplinary, region and environment-oriented, individual patient-focused, considerate on differences across cultures and detailed patient care guidelines.

D) A World Allergy and Asthma Center should be established with a fully integrated network to all national allergy and asthma centers and already established networks, alliances, societies, academies aiming at worldwide asthma surveillance, strategy development and education. Prioritization of allergies and asthma is going to take place more and more in United Nations, WHO and national political agendas, where chronic noncommunicable diseases are being prioritized nowadays. Management of asthma together with other respiratory diseases and other chronic noncommunicable diseases in these organizations may help to economize efforts in the early stage, however, full and only focus to asthma is inevitable for the success in the long run. A worldwide and integrated allergy and asthma surveillance network, using disease registries, pharmacoeconomic evaluation, as well as large biobanks should be developed.

E) Health economics studies in asthma and other life-long lasting chronic diseases demonstrate a huge financial benefit of prevention and curative treatments. Particularly, prevention of severe asthma development and exacerbations have an immense effect on healthcare costs. It now very appropriate that health insurance systems and other health-care financing models invest on research and education for primary and secondary prevention and curative treatments.

F) A multidisciplinary scientific approach is essential. A group of 40 scientists and clinicians from all around the world and all fields of allergy, asthma and related disciplines gathered under the sponsorship of the Christine-Kühne Center of Allergy Research and Education (CK-CARE) AG for the first ‘Global Allergy Forum’. Under the topic “Barriers to Cure” and developed the Davos Declaration, published in Allergy.

Our CK-CARE research focused on the identification of molecular and cellular mechanisms that play a role in severity of asthma. Most asthmatic patients can be adequately managed according to practice guidelines, however, there is a minority group of patients with so called severe and refractory asthma, who remain poorly controlled despite high-dose treatment with inhaled glucocorticoids and beta2-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. So far we have published 45 articles in the area with the support of CK-CARE. We could engage more than 20 scientific co-workers and in the short term exchange programme there were 21 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 and this mechanism is responsible for the polarization of naïve lymphocytes into regulatory T cells. In addition, we have discovered that certain microbes secrete histamine and microbial-derived histamine modulates TLR signaling pathways in host dendritic cells. Histamine decreases the pro-inflammatory response to microbial ligands via the histamine 2 receptor.

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 is continuously generating 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.

Report of the director

The 7th frame work EU research PREDICTA is that repeated, acute rhinovirus infection-mediated events may reprogram the innate, adaptive and/or regulatory immune responses to predispose towards a chronic inflammation pattern. This study 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. For this project SIAF will investigate the chemical structure and biochemical properties 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 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.

The Swiss-Polish research collaboration will continue to investigate whether there is correlation between the type of airway inflammation, and the concentration of cytokines of Th1/Th2 or Treg/Th17 axis 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.

In 2012, SIAF generated 66 scientific publications (exclusive abstracts), of which 54 appeared in peer-reviewed international journals. The total average of impact factor is 9.317. In 2012, SIAF reached a total impact factor amounting to 428.600 and 36 abstracts were presented at different congresses. Members of SIAF were invited to 82 different seminars or lectures at international congresses, universities and other research institutions and chaired 42 sessions.
SIAF is involved in GA2LEN, in EAACI as well as in AAAAI and is associated to the Academia Raetica.

World Immune Regulation Meeting-VII 2013
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 seventh time this successful international meeting from 13-16 March 2013 at the Kongresszentrum Davos. The congress was focused on "Innate and Adaptive Immune Response and Role of Tissues in Immune Regulation" with approximately 650 participants from over 40 countries with 114 presentations and 265 abstracts.

Davos, May 2013

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RESEARCH

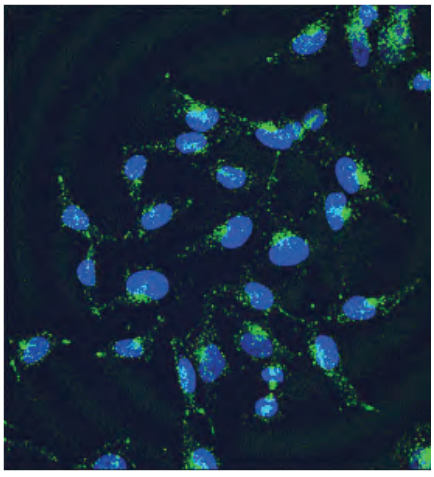
Molecular Allergology

Prof. Reto Crameri

The main activities of the Molecular Allergology Division at SIAF were focused on the Swiss National Science Foundation project "Route of application and mode of action of modular antigen transporter (MAT) vaccines" and with the continuation of the two projects "ALLFUN" and EURONANOMED" supported by the European Union. All three projects are thematically focused around the development of novel diagnostic and vaccination strategies for allergic diseases which cause steadily increasing health burdens to modern societies. IgE-mediated diseases such as rhinitis, atopic eczema and allergic asthma have reached a pandemic dimension affecting up to 25-30% of the population in industrialized countries. Although relevant progress has been made in developing therapeutic intervention aimed at controlling the symptoms of these diseases, the only treatment able to cure atopic diseases is allergen specific immunotherapy.

As previously, reported the clinical efficacy of the MAT-Fel d 1 vaccine against cat allergy has been demonstrated in a double blind, placebo controlled study Phase I/IIa dose finding and safety clinical trial conducted in collaboration with the University of Zürich. The study involving twenty cat dander allergic patients randomized either to a verum group of 12 patients receiving three intralymphatic (ILIT) injections with MAT-Fel d 1 absorbed to alum (1 µg, 3 µg and 10 µg), or to the placebo group (8 patients) including follow up one year after treatment has now been completed. Three injections of MAT–Fel d 1 induced a 5.66-fold increase of cat dander–specific IgG4 titers paralleled by a relevant increase of the IL-10 levels both within the range of what has been reported after 3 years of conventional high-dose SIT with cat dander. The short term therapy increased nasal tolerance to cat dander extract by a factor 74, however, in absence of boosting IgE levels, an unwanted phenomenon frequently observed in patients undergoing conventional SIT.

Although ILIT with MAT–Fel d 1 proved readily feasible, safe, and effective, there are limitations to the interpretation of these results. We used a novel molecule delivered through a novel route of application, and therefore the clinical data do not allow us to distinguish which aspect contributed more to the positive results. The contribution of MAT would have to be investigated in a superiority study comparing ILIT with MAT–Fel d 1 versus rFel d 1, whereas the contribution of ILIT would have to be examined by comparing subcutaneous versus intralymphatic administration of MAT–Fel d 1. We could not formally investigate this in a clinical trial. However, in preclinical murine models ILIT enhanced the immunogenicity of both Fel d 1 and MAT–Fel d 1 by orders of magnitude compared with subcutaneous administration (i.e., subcutaneous immunotherapy required approximately 104-fold higher allergen doses than ILIT to induce comparable IgG2a titers). Furthermore, ILIT with MAT–Fel d 1 was significantly more effective than ILIT with rFel d 1. 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 and this is the first clinical trial where patients can be cured from (cat) allergy in a short time. Unfortunately ImVisioN Therapeutics, the company which took over the rights for development and commercialization of MAT vaccines was not able to close the third round of financing and, therefore, all developments of this highly promising therapeutic concept are presently put on hold.



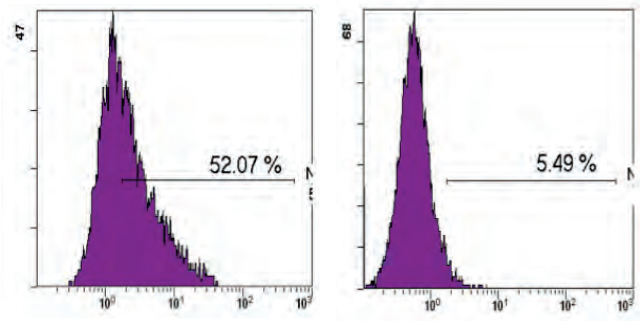


Figure 1) Intracellular localization of pep3-green fluorescent protein fusion (blue panel), (%) uptake of GFP (left panel) and pep-3-GFP by dendriWtic cells (right panel).

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 aiming a direct targeting of the MHC class II antigen presentation pathway in dendritic cells, the most potent antigen presenting cells.

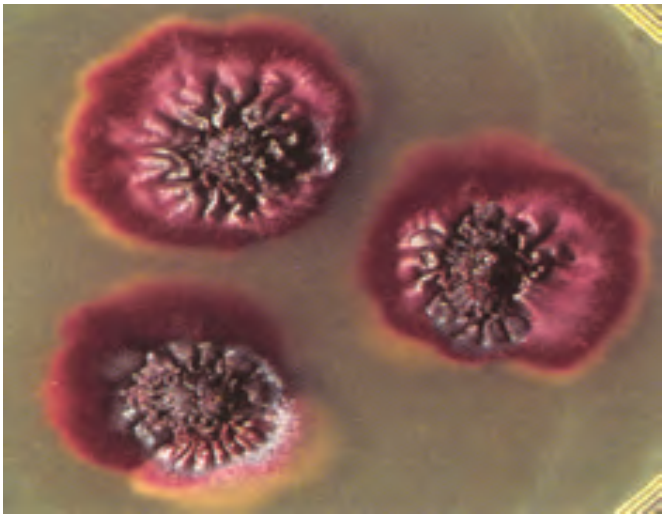


Figure 2) Tricophytum ruben, an example of an allergenic fungus.

A successful development of such vaccines would allow a drastic reduction of the allergen dose required for an efficient presentation. Reduced allergen doses in turn avoids severe side effects and an increased MHC class-II mediated presentation favors the development of protective immune responses and a cytokine shift from a Th2 to a Th1/Treg profile, as demonstrated by the application of MAT vaccines. As an extension of the MAT-vaccine concept we have engineered a whole array of candidate dendritic cell targeting vaccines by combinatorial assembly of different genetic elements potentially eliminating the disadvantages of the first MAT-vaccine generation. MAT vaccines are efficiently internalized in every cell and are therefore not able to specifically target antigen presenting cells, they have a tendence to translocate to the nucleus and probably need to be injected into the lymp node for full efficacy. We aim now to create a new generation of vaccines where the TAT peptide is substituted or supplemented by newly discovered peptides lacking nuclear localization sequence and/or able to specifically target dendritic cells, the most potent antigen presenting cells. These improvements should allow transcutaneous application of the vaccines using leaser-assisted microporation and therefore eliminate the need for injection.

Using Green Fluorescent Protein fusions we were able to confirm specific targeting of dendritic cells by the DC-specific peptide pep3 both by confocal microscopy and flow cytometry (Figure 1). Pep3 bound to DCs, but not other cell types like CaCo-2 and THP1. Currently the efficacy of the modified versions of the MAT vaccines is being tested in vivo in mouse models of allergy.

Most cases of fungal allergy are associated with severe asthma or, if sensitization is induced by yeasts, to atopic dermatitis. Depending on the definition, about 10-20% of these patients might be classified as subjects suffering from severe asthma and in this group 30-70% can be expected to be sensitized to at least one fungal species. Extrapolating this figure to the industrialized countries we have to assume that several million asthmatic patients are affected by fungal allergy. The aim of the ALLFUN project supported by the EU is to define the cellular and molecular mechanisms by which ubiquitous airborne or commensal fungi contribute to immune homeostasis and its deregulation leading to inflammatory diseases. The role of SIAF as leader of work package 2 within ALLFUN is the identification, cloning, purification and characterization of common immunogenic fungal molecules including proteins, cell wall polysaccharides and lipids. These molecules will serve as a basis to study their immunogenicity in serology and to develop diagnostic kits based on multiplexed highly sensitive biosensor technology. For this purpose, 19 and 10 allergens from A. fumigatus and M. sympodialis, respectively, have been cloned and expressed in E. coli. Additionally 8 allergens from Tricophytum ruben (Figure 2) and the 9 most important allergens of A. fumigatus have been cloned and expressed using a newly developed cloning system to

express proteins in Aspergillus niger. This was necessary because some proteins do not fold correctly if expressed in E. coli resulting in allergens lacking IgE-binding capacity. Additionally a whole array of cross-reactive allergens from different fungal species including Coprinus comatus, Candida boidiini, Candida albicans, Alternaria alternata and Cladosporium herbarum have been cloned and expressed in different heterologous expression systems and are now ready for serological analyses. In parallel the human proteins cyclopilin A and B, ribosomal P2 protein, thioredoxin (Figure 3) and manganese dependant superoxide dismutase belonging to the families of phylogenetically highly conserved proteins showing IgE-cross reactivity to fungal allergens have been expressed and purified to homogeneicity. All the allergens, cross reactive structures, and human IgE-binding proteins are currently under investigation for their diagnostic value and will be used in a later stage to develop highly sensitive multiplexed chips for the diagnosis of fungal allergy.

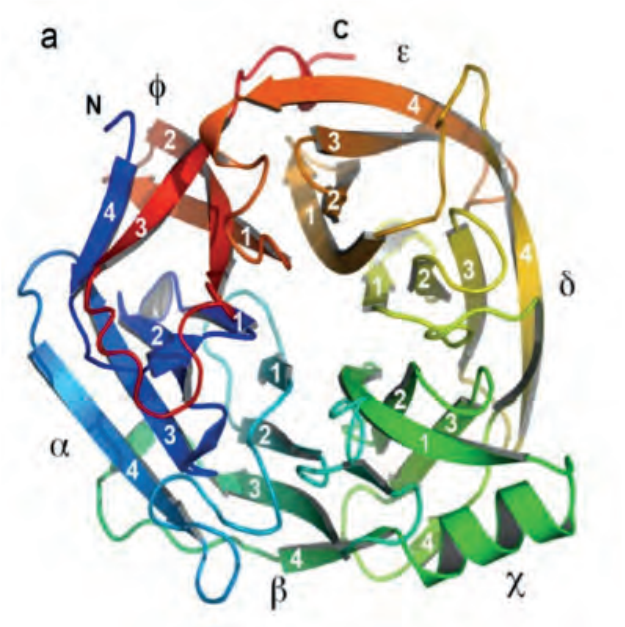


Figure 3) Crystal structures the major Malassezia sympodialis allergen Mala s 1.

Immunoglobulin E-binding autoantigens: biochemical characterization and clinical relevance

Crameri R.

Clin Exp Allergy. 2012; 42, 343-351.

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 FcRIepsylon 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.

Microbiota and dietary interactions - an update to the hygiene hypothesis?

Frei R, Lauener RP, Crameri R, O'Mahony L.

Allergy 2012; 67, 451-461.

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, micro-organisms, 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.

Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections

Senti G, Crameri R, Johansen P, Martinez-Gomez JM, Graf N, Steiner M, Hothorn LA, Grönlund H, Tivig C, Zaleska A, Soyer O, van Hage M, Akdis CA, Akdis M, Rose H, Kündig TM.

J Allergy Clin Immunol. 2012, 129, 1290-1296.

Background: Subcutaneous allergen-specific immunotherapy frequently causes allergic side effects and requires 30 to 80 injections over 3 to 5 years.
Objective: We sought to improve immunotherapy by using intralymphatic allergen administration (intralymphatic immunotherapy [ILIT]) and by targeting allergen to the MHC class II pathway.
Methods: 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).
Results: 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 ($P < .001$).
Conclusion: In a first-in-human clinical study ILIT with MAT-Fel d 1 was safe and induced allergen tolerance after 3 injections.

Selection of mimotopes mimicking the extracellular membrane-proximal domain (EMPD) of mIgE

Feichtner S, Crameri R, Achatz G.

In: Proc. 28th CIA Symposium. Marone, G. Triggiani, M. Genovese, A. (eds). pp. 215-218. Pacini Editore, Pisa, 2012.

Background: Allergen-specific immunotherapy (SIT) is the only therapy able to cure allergic diseases which, however, suffers from a low patient's compliance related to the long treatment time ranging from 3 to 5 years. We aimes at enhancing SIT by targeting the allergen to the MHC classII presentation pathway and direct intralymphatic administration of the vaccine.
Methods: The modular antigen translocation vaccine (MAT) for Fel d 1, the major cat dander allergen, was engineered by fusing a protein translocation peptide to a truncated invariable chain able to target the MHC class II antigen presentation pathway. Twenty cat dander allergic patients were randomized into two groups: 12 received three intralymphatic injections with MAT-Fel d 1 adsorbed to alum (1 mg, 3 mg and 10 mg) at four weeks intervals and 8 received alum adsorbed placebo. Efficacy was assessed by nasal provocation testing, skin tests, serological and T cell analyses.
Results: MAT vaccination was well tolerated and no drug related adverse events were observed. Three low dose intralymphatic MAT-Fel d 1 injections resulted in an increased IgG4 and IL-10 production within 12 weeks. Clinically, verum treated patients showed a markedly increased tolerance to nasal provocation with cat extract, and a reduced skin prick- and intradermal test reactivity to cat dander challenges.
Conclusions: Intralymphatic administration of MAT-Fel d 1 vaccine confers protection to the offending allergen after only three injections, administrated at four week intervals, thus dramatically reducing SIT treatment time. If the MAT therapy is able to induce a long lasting protection is currently under evaluation.

Targeting the MHC-class II antigen presentation pathway as a novel vaccination strategy for allergy

Crameri R.

In: Proc. 28th CIA Symposium. Marone, G. Triggiani, M. Ge-

novese, A. (eds). pp. 355-357. Pacini Editore, Pisa, 2012.

Background: In our current manuscript we suggest an alternative strategy of anti-IgE therapy. In contrast to conventional anti-IgE therapy, which addresses free serum IgE antibodies, we focus on membrane-bound IgE to inhibit IgE synthesis systematically. The extracellular membrane-proximal domain (EMPD) of mIgE, which is part of the transmembrane domain and therefore exclusively expressed on the membrane-bound form, allows a specific targeting of mIgE bearing B cells.
Methods: In order to isolate peptides that successfully mimic the EMPD region, a mimotope phage library was screened with our previously generated monoclonal anti-EMPD antibody (mAbA9). DNA sequences of positively screened mimotopes were used for peptide synthesis. Affinities of these peptides were measured with BIACORE X device.
Results: After four rounds of biopanning, we were able to isolate two peptides that were recognized by our mAbA9 after BIACORE affinity measurement. Interestingly, a clear difference in the binding affinity between these two peptides was observed. This difference was not only reflected in the kinetics of analyte binding, but also in the amount needed for measurable interaction.
Conclusion: By means of mimicking EMPD epitopes, we should be able to actively induce anti-EMPD specific antibodies. Mice immunised with mimotopes mimicking the EMPD region of membrane-bound IgE should generate anti-mIgE antibodies in vivo. Crosslinking mIgE receptors with anti-EMPD antibodies without further T cell help should then trigger direct clonal deletion of mIgE+ B cells.

Mechanisms of peripheral tolerance to allergens

Soyer OU, Akdis M, Ring J, Behrendt H, Crameri R, Lauener R, Akdis CA.
Allergy. 2013;68:161-70.

The immune system is regulated to protect the host from exaggerated stimulatory signals establishing a state of tolerance in healthy individuals. The disequilibrium in immune regulatory vs. effector mechanisms results in allergic or autoimmune disorders in genetically predisposed subjects under certain environmental conditions. As demonstrated in allergen-specific immunotherapy and in the healthy immune response to high-dose allergen exposure models in humans, T regulatory cells are essential in the suppression of Th2-mediated inflammation, maintenance of immune tolerance, induction of the two suppressive cytokines interleukin-10 and transforming growth factor-b, inhibition of allergen-specific IgE, and enhancement of IgG4 and IgA. Also, suppression of dendritic cells, mast cells, and eosinophils contributes to the construction of peripheral tolerance to allergens. This review focuses on mechanisms of peripheral tolerance to allergens with special emphasis on recent developments in the area of immune regulation.

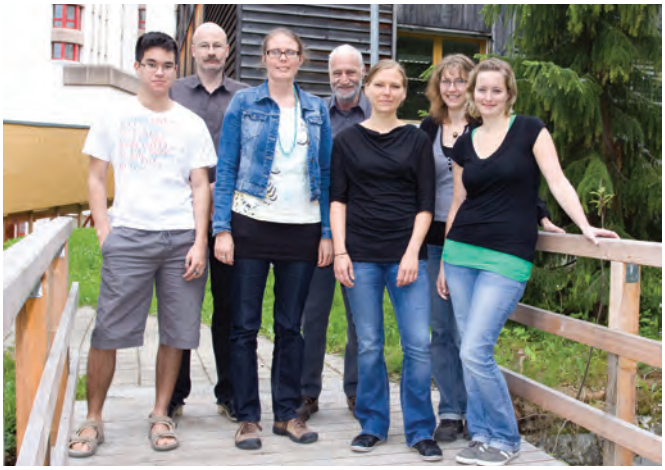
A Th17-/Th2-skewed cytokine profile in Cystic Fibrosis lungs represents a potential risk factor for Pseudomonas aeruginosa infection

Tiringer K, Treis A, P, Gona M, Gruber S, Renner S, Dehlink E, Nachbaur E, Horak F, Jaksch P, Döring G, Crameri R, Jung A, Rochat MK, Hörmann M, Spittler A, Klepetko W, Akdis CA, Szépfalusi Z, Frischer T, Eiwegger T.
Am J Respir Crit Care Med 2013; (in press)

Rationale: Cystic Fibrosis (CF) is characterized by progressive pulmonary inflammation that is infection-triggered. P. aeruginosa represents a risk factor for deterioration of lung function and reduced life expectancy. Objectives: To assess T-cell cytokine/chemokine production in clinically stable
children with CF and evaluate the association between T-cell subtypes and susceptibility for infection with P. aeruginosa.
Methods: T-cell cytokine/chemokine profiles were measured in bronchoalveolar lavage fluid (BALF) from children with CF (n=57; 6.1±5.9y) and non-CF controls (n=9; 5.9±4.3y;). Memory responses to A. fumigatus and P. aeruginosa were monitored. HR-CT-based Helbich-score was assessed. In a prospective observational trial the association between BALF cytokine/chemokine profiles and subsequent infection
with P. aeruginosa was studied.
Results: Th1 (INF-gamma), Th2 (IL5, IL13), Th17 (IL17A) and Th17-related cytokines (IL1beta, IL6) were significantly upregulated in airways of CF patients. IL17A, IL13 and IL5 were significantly higher in BALF of symptomatic as compared to clinically
asymptomatic CF patients. IL17A and IL5 correlated with the percentage of neutrophils in BALF ($r=0.41$, $p<0.05$ and $r=0.46$, $p<0.05$, respectively). Th17- (IL17A, IL6, IL1beta, IL8)

and Th2-associated cytokines/chemokines (IL5, IL13, TARC/CCL17), but not IFNgamma levels, significantly correlated with HR-CT-changes (Helbich-score; $p<0.05$). P. aeruginosa- and A. fumigatus-specific T-cells from CF patients displayed significantly higher IL5 and IL17A mRNA expression. IL17A and TARC/CCL17 were significantly augmented in patients that developed P. aeruginosa infection within 24 months.
Conclusion: We propose a role for Th17 and Th2 T-cells in chronic inflammation in lungs of CF patients. High concentrations of these cytokines/chemokines in CF airways precede infection with P. aeruginosa.

Davos , May 2013



(f.l.t.r. M. Wieland, C. Rhyner, C. Huitema, R. Crameri, J. Olzhausen, M. Kenk, K. Romer; not present: M. Prati, M. Garbani, M. Schwaller, M. Wiki)

RESEARCH

Cellular Allergy / Immunology

Prof. Dr. med. Cezmi A. Akdis

Allergic or atopic patients have an altered state of reactivity to common environmental and food antigens that do not cause clinical symptoms in non allergic individuals. Patients with clinical allergy produce immunoglobulin (Ig) E antibodies to the antigens that trigger their illness. The term allergy represents the clinical expression of IgE-mediated allergic diseases that manifest as hyperresponsiveness in target organs such as the lung, skin, gastrointestinal tract, and nose. There has been a significant increase in the prevalence of allergic diseases during the last few decades. This increase is attributed to changes in environmental factors (exposure to tobacco smoke, air pollution, indoor and outdoor allergens, respiratory viruses, obesity).

Everyone is exposed to potential allergens. Atopic individuals respond to allergen exposure with rapid expansion of T helper type 2 (Th2) cells that secrete cytokines, such as interleukins IL-4, IL-5, and IL-13, favoring IgE synthesis and eosinophilia. Allergen-specific IgE antibodies associated with atopic response are detectable by serum testing or positive immediate reactions to allergen extracts on prick skin testing. The Th2 cytokines IL-4 and IL-13 play a key role in immunoglobulin isotype switching to IgE. IL-5 and IL-9 are important in differentiation and development of eosinophils. The combination of IL-3, IL-4, and IL-9 contributes to mast cell activation. Th2 cytokines are important effector molecules in the pathogenesis of asthma and allergic diseases; acute allergic reactions are characterized by infiltration of Th2 cells into affected tissues. In addition, IL-25, IL-33 and TSLP contribute to Th2 response and eosinophilia.

A fraction of the immune response to allergen results in proliferation of T helper type 1 (Th1) cells. Th1 cells are typically involved in the eradication of intracellular organisms, such as mycobacteria, because of the ability of Th1 cytokines to activate phagocytes and promote the production of opsonizing and complement-fixing antibodies. The Th1 component of allergen-specific immune response contributes to chronicity and the effector phase in allergic disease. Activation and apoptosis of epithelial cells induced by Th1 cell–secreted interferon-gamma (IFN-gamma), tumor necrosis factor-alpha (TNF-alpha), and Fas-ligand constitute an essential pathogenetic event for the formation of eczematous lesions in atopic dermatitis and bronchial epithelial cell shedding in asthma.

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 turn into a lymphatic organ like organization, where professional dendritic cells, T cells, B cells and innate lymphoid cells contact each other and a second step of antigen-presentation, activation and inflammation takes place in the inflamed tissue.

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. Airway eosinophilia and angiogenesis were also observed in asthmatic children and atopic children who did not develop clinical asthma, suggesting that pathologic changes occur early in asthma The efforts of the immune system, epithelial cells and lung fibroblasts to increase lami-

na reticularis thickness might be indeed aiming to make a mechanical barrier between the allergens (mites and pollens) and the submucosal immune system.

Proposed roles of tissues in immune regulation and chronicity in asthma, atopic dermatitis and chronic rhinosinusitis

- Continuous low level of tissue inflammation takes place during remissions, which increases during exacerbations
- Prevention of basal epithelial cell death from apoptosis (full epithelial recovery occurs, when submucosal inflammation is suppressed)
- Apoptototic cell death of highly activated suprabasal epithelial cells is the mechanism of eczema/spongiosis and epithelial shedding
- Drainage of inflammation to mucosal lumen by opening of tight junctions
- Drainage of inflammation by lymphatic vessels
- Suppression of submucosal inflammation by various regulatory cell subsets, Treg cells, Breg cells, regulatory DC, regulatory NK cells etc.
- Continuous angiogenesis and remodeling of tissue cells
- Basement membrane [*Lamina reticularis*] tickening takes place in asthma to make a physical barrier between disease-inducing factors (allergens/environment) and cells of the immune system
- ILCs exist in mucosal surfaces and may play an essential role not only in immune effector processes, but also in regulation of tissue responses

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 release of chemokines and pro-inflammatory cytokines take place (pro-inflammatory stage). This is followed by eventual death of keratinocytes and bronchial and sinus 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. Basal epithelial cells are protected from epithelial apoptosis in asthma and atopic dermatitis, full recovery occurs.

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 Tight junctions (TJ) consist of different transmembrane and scaffold adaptor proteins and form the most apical intercellular junction between epithelial cells. Epithelial barrier function of keratinocytes in the skin of atopic dermatitis patients, bronchial epithelial cells in the asthmatic lung and sinus epithelial cells in the sinus tissue of chronic rhinosinusitis patients 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. 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 (two manuscripts in preparation). In conclusion, the balance between inflammation inducing factors, keep away factors, wash away factors and suppression factors plays a decisive role in the remission, exacerbation and chronicity of allergic inflammation.

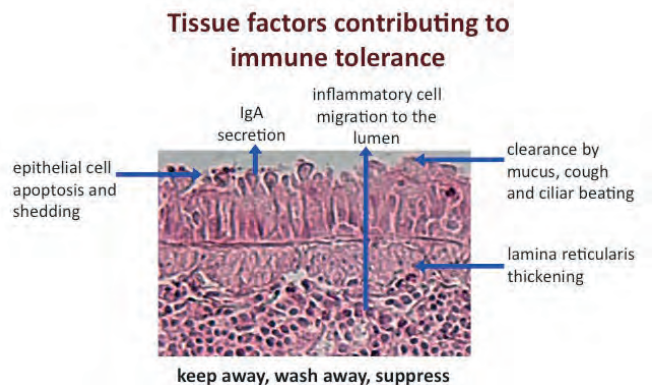


Figure 1) There is an essential role for tissue factors that may play a role in down-regulation of asthmatic inflammation. Similar mechanisms also play a role in chronic rhinosinusitis and atopic dermatitis. i. allergen ignorance related factors: increased basement membrane thickness that acts as a physical barrier between allergens and the immune system cells, mucosal IgA production against allergens, mucus production in physiological quantities, cough and ciliary movement. ii. inflammatory cell and cytokine

clearance related factors: clearance of airway tissue inflammatory cells by migration towards lumen and bronchial epithelial cell apoptosis and shedding.

Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN-gamma and IL-4

Soyka MB, Wawrzyniak P, Eiwegger T, Holzmann D, Treis A, Wanke K, Kast JI, Akdis CA.

J Allergy Clin Immunol. 2012;130:1087-1096.

Chronic rhinosinusitis (CRS) is a common disease with still unclear pathophysiologic mechanisms. Epithelial tight junctions (TJs) have been shown to be involved in different chronic disorders, including bronchial asthma, inflammatory bowel diseases, and skin disorders. The regulation of epithelial barrier function and TJ expression has not been extensively studied in patients with CRS and in the paranasal sinus epithelium thus far. Trans-tissue resistance was measured in biopsy specimens from healthy control subjects and patients with CRS with and without nasal polyps. TJ protein expression was determined by using immunofluorescence, Western blotting, and real-time PCR. Primary epithelial cell cultures from patients with CRS and control subjects were used in air-liquid interface (ALI) cultures for the measurement of transepithelial resistance (TER) and TJ expression. The effect of IFN-gamma, IL-4, and IL-17 on ALI cultures was assessed.A decreased trans-tissue resistance was found in biopsy specimens from patients with CRS with nasal polyps along with an irregular, patchy, and decreased expression of the TJ molecules occludin and zonula occludens 1. TER was reduced in ALI cultures from patients with CRS with nasal polyps. The cytokines IFN-gamma and IL-4 decreased TER, whereas IL-17 did not have any influence on epithelial integrity. In conclusion, a defective epithelial barrier was found in patients with CRS with nasal polyps along with a decreased expression of TJ proteins. The disruption of epithelial integrity by IFN-gamma and IL-4 in vitro indicates a possible role for these proinflammatory cytokines in the pathogenesis of patients with CRS.

The broad spectrum of interepithelial junctions in skin and lung

Kast JI, Wanke K, Soyka MB, Wawrzyniak P, Akdis D, Kingo K, Rebane A, Akdis CA.

J Allergy Clin Immunol. 2012;130:544-7.

To perform a fully detailed analyses of interepithelial junction expression, we developed a Low Density Array Micro Fluidic Card (Applied Biosystems) containing all known junctional and associated proteins that are expressed in the epidermis and epithelia. In addition to TJs proteins, desmosomes, gap junctions and adherens junction genes were included into the analysis (methods in the Online Repository). We analyzed lung and skin biopsies, primary keratinocytes (KCs) and normal human bronchial epithelial (NHBE) cells either grown as monolayers or in air-liquid interphase (ALI) cultures7 for the expression of junctional proteins. After performing the detailed expression analyses of interepithelial barrier molecules, we realized that it is essential to study the TJs in a broader way. Although some are dominantly expressed, the determination of one or two junctional molecules; especially TJs may not represent the whole picture. There are distinct and overlapping patterns of tight junctions and other cell-cell adhesion molecules expressed in the skin and lung epithelia, which implicate a highly regulated and complex pattern. Each cell type shows its own, unique expression profile reflecting their specialization related to their function within the organism. In addition, we have to take into account that TJs are not uniquely expressed in epithelial cells, but are also found and regulated in other cells, especially in endothelium. Furthermore, other mesenchymal tissues also express them as we have recently observed in smooth muscle cells in asthma. The number of different junctional proteins, which are expressed, interact in multiple ways in every cell type to form appropriate cell-cell contacts and tissue integrity. Our data demonstrated in this study suggest that the picture of the junctional apparatus in each cell type and tissue is distinct, and the regulation of epithelial integrity might be more complex than being considered so far.

Early suppression of basophil activation during allergen-specific immunotherapy by histamine receptor 2

Novak N, Mete N, Bussmann C, Maintz L, Bieber T, Akdis M, Zumkehr J, Jutel M, Akdis C.

J Allergy Clin Immunol. 2012;130:1153-1158.

Early desensitization of FcepsylonRI-bearing mast cells and basophils has been demonstrated in allergen-specific im-

munotherapy and drug desensitization. However, its mechanisms have not been elucidated in detail. Histamine is one of the main mediators released on FcepsylonRI triggering of basophils and mast cells, and it exerts its functions through histamine receptors (HRs). We investigated HR expression on basophils of patients undergoing venom immunotherapy (VIT) and its effect on allergen, IgE, and FcepsylonRI cross-linking-mediated basophil function and mediator release. Basophils were purified from the peripheral blood of patients undergoing VIT and control subjects and were studied functionally by using real-time PCR, flow cytometry and ELISA assays. We demonstrated that rapid upregulation of H2R within the first 6 hours of the build-up phase of VIT was observed. H2R strongly suppressed FcepsylonRI-induced activation and mediator release of basophils, including histamine and sulfidoleukotrienes, as well as cytokine production in vitro. In conclusion, immunosilencing of FcepsylonRI-activated basophils by means of selective suppression mediated by H2R might be highly relevant for the very early induction of allergen tolerance and the so-called desensitization effect of VIT.

Therapies for allergic inflammation: refining strategies to induce tolerance

Akdis CA.

Nat Med. 2012;18:736-49.

Current therapies for asthma and allergy are relatively safe and effective at controlling symptoms but do not change the chronic course of disease. There is no established method to prevent asthma and allergy, and major unmet needs in this area include the better control of the severe forms of these diseases and the developments of curative therapies. Two major therapeutic strategies for asthma and allergy are currently being developed, and I here discuss the advances and challenges for future therapeutic development in these two areas. The first approach, allergen-specific immunotherapy, aims to induce specific immune tolerance and has a long-term disease-modifying effect. The second approach is the use of biological immune response modifiers to decrease pathological immune responses. Combination strategies using both of these approaches may also provide a route for addressing the unmet clinical needs in allergic diseases.

Mechanisms of IFN-gamma-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-gamma-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-gamma 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-gamma responses in skin of patients with AD and suggest involvement of multiple new apoptosis- and inflammation-related factors in the development of AD.

IgE class switching and cellular memory

Akdis M, Akdis CA.

Nat Immunol. 2012;13:312-4 (Editorial).

Immunoglobulin E (IgE) antibodies are involved in type 1 hypersensitivity reactions and allergen capture via their high affinity and low affinity Fc receptors, and in the pathogenesis of allergic disease and host defense mechanisms against helminthic infections. B cell isotype class switch to an IgE-producing cell is a tightly regulated process, but the location and kinetics of IgE memory B cell and IgE plasma cell responses has been rather enigmatic. In large part the difficulty of studying IgE+ B cells has been a consequence of their vanishingly small numbers under physiological conditions. This editorial was written to highlight a study by Talay et al. Nat Immunol. 2012;13:396-404.

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;129:964-73.

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. 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-gamma, TNF-alpha, Th1 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-gamma, TNF-alpha, Th1 cells, and rhinovirus in bronchial epithelial cells. It inhibits angiogenesis, and its serum levels are associated with a good treatment response in asthmatic patients.

Davos declaration: allergy as a global problem.

Ring J, Akdis C, Behrendt H, Lauener RP, Schäppi G, Akdis M, et al.

Allergy. 2012;67:141-3.

A group of 40 scientists and clinicians from all around the world and all fields of allergy, asthma and related disciplines gathered under the sponsorship of the Christine-Kühne Center of Allergy Research and Education (CK-CARE) in Davos, Switzerland from 17 to 20 July 2011 for the first 'Global Allergy Forum'. Under the topic "Barriers to Cure" and developed the Davos Declaration.

Davos Declaration: Research Needs

- The causes of the epidemic increase in allergic diseases are unknown. Environmental exposures that appear to be critical factors include factors as diverse as air quality, diet and nutrition, climate, UV radiation, and direct skin contact as well as psycho-social interactions. Moreover, when genetic predisposition is taken into account, environment can provide either risk or protection.
- The effects of changes in climate, urbanization, etc. have to be anticipated. Better ways to assess spatial and temporal environmental exposure at population and individual levels are much needed and should be related to the ssessment of individual genetic susceptibility.
- The interactions between microbes, pollutants, and the immune system are marginally understood.
- There is inadequate understanding of the natural mechanisms that limit acute vs. chronic disease or spontaneous resolution.
- There is a need for better subclassification of allergic disor-

ders based on pathobiology.
- There is a need for new agents acting on specific pathways in pathogenesis with regard to new therapeutic approaches.
- There is a need for better preclinical models for translational research.
- There is a need to develop better tools for complex data analysis.
- There is a need for efficient strategies for primary and secondary allergy prevention.
- There is a need for better approaches in diagnosis and prediction of treatment responses and the monitoring of therapeutic effectiveness.

Davos Declaration: Needs for Education and Awareness.
- Apart from true lack of information, there is a tremendous gap between actual existing knowledge and its effective application for the millions of people in need.
- There is a shortage of well-trained specialists in most countries.
- Education and training efforts should also be directed toward medical students at the curricular level and extended to primary care physicians, who have to be involved in a strategy for diagnosing and managing allergic diseases with such high prevalence rates of 20% of the population.
- Awareness campaigns for targeted public groups should be performed. Allied health professionals, such as nurses, school teachers, etc., should be included. Better and more effective tools to spread the available information should be developed.
- Close cooperation with patient organizations is highly recommended.
-Decision makers involved in developing and approving health policies and administration must be made more aware of the problem.

FcepsylonRI stimulation promotes the differentiation of histamine receptor 1-expressing inflammatory macrophages

Novak N, Peng WM, Bieber T, Akdis C.

Allergy. 2013;68:454-61

Monocyte differentiation into dendritic cells or macrophages and recruitment to peripheral organs in chronic inflammatory diseases are directed by allergen challenge via FcepsylonRI as well as the nature of soluble factors in the microenvironment. High-affinity receptor for IgE stimulation of effector cells results in the release of histamine, which acts on various histamine receptors (HR) 1-4, expressed by immune cells. We examined the effect of FcepsylonRI stimulation of human monocytes on H1R expression and function of differentiating cells. The mRNA levels of H1R, H2R and histidine decarboxylase of differentiating cells were detected by quantitative real-time PCR. Expression of CD1c, CD11c, CD68 and CD163 was detected by flow cytometry. Amount of histamine, IL-6 and IL-12p70 in the cell culture was measured with the help of cytometric bead arrays or ELISA assays. Numbers of H1R-expressing macrophages were evaluated by immunofluorescence double staining of CD68 and H1R on human skin sections. We demonstrated that FcepsylonRI stimulation promotes the generation of H1R-expressing macrophage-like cells with enhanced histamine biosynthesis and H1R-mediated proinflammatory properties. Supporting our in vitro findings, high numbers of H1R-expressing CD68(pos) macrophages were detected in the dermis of atopic dermatitis skin lesions. In conclusion, our observations point to a close histamine-/HR-mediated activation of dermal macrophages, leading to modified cell differentiation and responsiveness via H1R, which might contribute to the aggravation of allergic skin inflammation.

Davos, May 2013

(f.l.t.r. P. Wawrzyniak, C.A. Akdis, B. Rückert, T. Kubo, J. Kast, C. Agache, K. Wanke, A. Wegrzyn, H. Morita, R. Costa, K. Sugita, A. Rebane, C. Altunbulakli)

RESEARCH

Immunodermatology

PD Dr. Mübeccel Akdis

Allergy is one of the immune tolerance-related diseases that arises as a direct consequence of a dysregulated immune response. Currently, allergen-specific immunotherapy (allergen-SIT) by the administration of increasing doses of allergen extracts remains the single curative approach to allergic diseases with the potential to modify its course.

Mechanisms of peripheral tolerance during the successful immunotherapy

It is generally accepted that allergen-specific peripheral T-cell tolerance is characterized mainly by generation of allergen-specific Treg cells and initiated by IL-10, which is increasingly produced by the antigen-specific Treg cells. Subsets of Treg cells with distinct phenotypes and mechanisms of action include the CD4+ CD25+ FoxP3+ Treg cells, and the CD4+ IL-10-producing Tr1 cells. Different studies show roles for both subsets, suggesting an overlap particularly in the inducible subsets of Treg cells in human subjects. It has been shown that CD4+ CD25+ Treg cells from atopic donors have a reduced capability to suppress the proliferation of CD4+CD25- T cells. The presence of local FOXP3+ CD25+ CD3+ cells in the nasal mucosa, their increased numbers after immunotherapy, and their association with clinical efficacy and suppression of seasonal allergic inflammation strengthen the concept of allergen tolerance based on Treg cells in human subjects25. In addition to conventional immunotherapy, peptide immunotherapy in patients with allergic asthma generates IL-10–dependent immunologic tolerance associated with linked epitope suppression.

Similar to IL-10-secreting Tr1 cells, we have demonstrated that a distinct small fraction of NK cells with regulatory functions exist in humans. Although T-cell tolerance is the key event, peripheral tolerance also includes other suppressive cells, suppressive cytokines, and regulatory APCs. Different phenotypes of diseases show different patterns of cytokines and different inflammation patterns and therefore may require other mechanisms to suppress the inflammation. Any deviation in the immune mechanisms listed above may result in a loss of tolerance and a state of atopy. The role of Treg cells is particularly irreplaceable in tolerance induction. Allergen-SIT is a desensitizing therapy and acts as a model to induce a natural-like tolerance to allergens because it aims to upregulate Treg cells both in number and function in individuals with atopic diseases. Still, current allergen-SIT approaches have inadequacies in terms of potential side effects, long duration, patient compliance, and insufficient outcomes in some patients. Further developments in the field of mechanisms of peripheral tolerance to allergens will guide future treatment options in allergic diseases

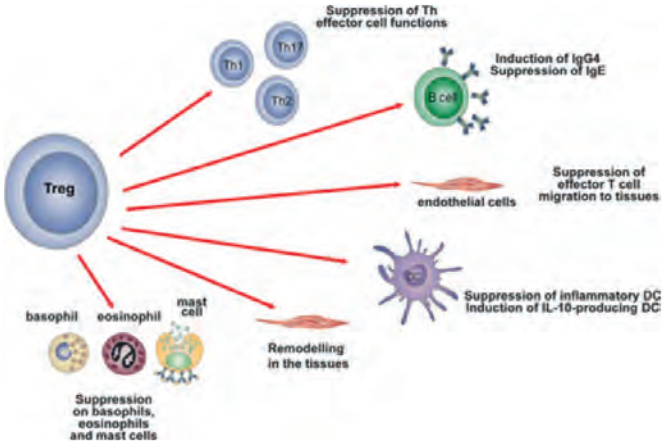


Figure 1) Immunoregulatory functions of Treg cells: suppression of Th cell effector functions; suppression of allergen-specific IgE; induction of IgG4; inhibition of migration of effector T-cell migration to tissues; suppression of inflammatory dendritic cells (DCs); interference with remodeling; and suppression of basophils, eosinophils, and mast cells.

Induction of allergen-specific IgG4 is a hallmark of successful peripheral tolerance induction, as observed in allergen SIT. Our findings demonstrate that PLA-specific B cells from beekeepers mainly express IgG4. PLA-specific and non–PLA-specific B cells were isolated from peripheral blood and directly analyzed without in vitro culture. The increased IgG4 expression in PLA-specific B cells indicates that these cells mainly represent circulating IgG4-switched PLA-specific memory B cells. Interestingly, IL-10 mRNA expression was also significantly higher in these cells, suggesting that in vivo cir-

culating PLA-specific B cells in beekeepers have increased IL-10 production. Furthermore, when stimulated in vitro with TLR9-L, PLA-specific cells showed higher IL-10 secretion than non–PLA-specific B cells. This increased frequency of IL-10+ cells among PLA-specific B cells was not observed in patients with bee venom allergy. However, after SIT, the frequency of PLA-specific IL-10+ B cells significantly increased to the same level seen in beekeepers. PLA-specific IgG4 was detected at high concentrations in sera of nonallergic beekeepers, which showed greater than 1000 times lower PLA-specific IgE/IgG4 ratios than sera from allergic subjects. Allergen SIT and high-dose allergen tolerance has been linked to increased serum IgG4 and IL-10 production from T cells. Here we demonstrate that allergen-specific B-cell IL-10 production is increased during allergen SIT. Our data demonstrate that particularly CD27–IL-10+ B cells are precursors of IgG4-producing cells. In addition, the ongoing immune response of memory B cells contributes to IgG4 production. We found increased IgG4 expression and an increased frequency of IL-10+ cells among PLA-specific B cells in bee venom–tolerant subjects. This suggests that in these subjects there exists a PLA-specific IgG4-switched memory B-cell compartment that retains high IL-10 expression and might play a role in maintenance of tolerance. Whether these cells derive from BR1 cells requires further investigation.

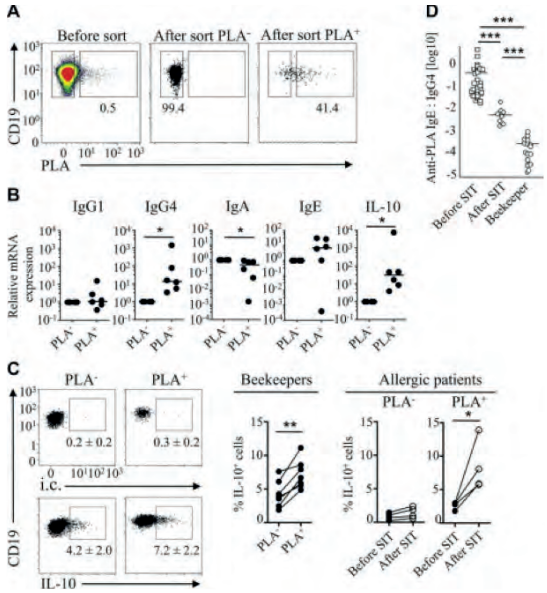


Figure 2) Allergen-specific B cells from tolerant subjects upregulate IL-10 and IgG4. A, Enrichment of PLA-specific B cells from beekeeper-derived peripheral CD19+ cells. B, Direct ex vivo analysis of immunoglobulin and IL-10 mRNA expression (relative to PLA– cells). C, IL-10 and PLA staining in B cells from beekeepers or patients with bee venom allergy after 3 days of TLR9-L stimulation. D, PLA-specific serum IgE/IgG4 ratio.
This article is published in J Allergy Clin Immunol. by van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Akdis DG, Rückert B, Akdis CA, Akdis M. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. 2013 Apr;131(4):1204-12.

IL-22 and Th22 cells

Upon encounter with their cognate antigen, naive CD4+ T cells differentiate into a number of different subsets, which are defined by their biological functions, and production of characteristic effector cytokines. Th1, Th2, Th17, T follicular helper cells (Tfh) and T regulatory cells (Treg) are phenotypically classified by their production of INF-gamma, IL-4, IL-17, IL-21 and IL-10/TGF-beta, respectively. A unique cytokine signature has been used for the classification of new Th subsets such as, Th9 cells expressing IL-9 and in humans, Th22 cells producing IL-22 but not IL-17 or INF-gamma.

IL-22 was first described in 2000 by Renauld et.al. The similarities between IL-22 and IL-10 with respect to their primary sequence resulted in the IL-22`s initial designation as "IL-10 related T cell-derived inducible factor. In addition to IL-22 and IL-10, IL-19, IL-20, IL-24, IL-26 is included to IL-10 cytokine family. IL-10 family cytokines have essential functions in maintaining the integrity and homeostasis of tissue epithelial layers. IL-22 mediates the crosstalk between leukocytes and tissue epithelia with its receptor being expressed mainly on epithelial cells. By eliciting various innate defensive mechanisms from tissue epithelial cells, IL-22 is essential for host defense against infections of extracellular pathogens, such as bacteria and yeasts. Cells of both innate and adaptive immune system mainly Th cells, NK cells and lymphoid tissue inducer cells produce IL-22.

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

precise molecular mechanisms by which these factors regulate IL-22 expression are largely unknown in human.

As a first step in the characterization of these different T cell populations, we are currently sorting IL-22+ and IL22- cells and perform a whole genome microarray expression analysis. This will provide insight in the mechanisms underlying the differential regulation of IL-22 production. We will search for transcription factors specifically expressed in IL-22-producing T cells. Furthermore, we will look into the mechanisms responsible for the distinct response to certain common gamma chain cytokines that affect T cell IL-22 production. Freshly purified IL-22 positive T cells will be characterized for their surface molecules, other cytokines that they release, help to B cells for Ig production, and their interaction with epithelial cells in co-cultures. All of these experiments will be performed by human tonsil T cells and differentiated peripheral blood naïve T cells so that direct in vivo expression of IL-22 will be studied in comparison with in vitro differentiated cells.

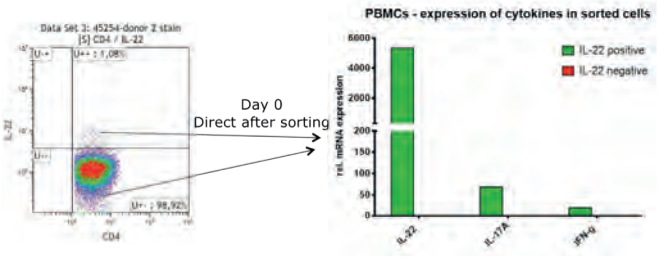


Figure 3) IL-22 secretion assay

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. We demonstrate how peripheral T-cell tolerance to major environmental allergens can be broken by triggering of TLR4 or TLR8 and by the pro-inflammatory cytokines IL-1beta or IL-6 in human tonsils and peripheral blood. We also show that relatively low numbers of matured mDCs, but not pDCs, are able to induce proliferation of tolerized allergen-specific CD4+ T cells and that this DC subset mediates these effects through mechanisms that partially depend on the upregulation of HLA-DR and the costimulatory molecules OX40L and CD80.

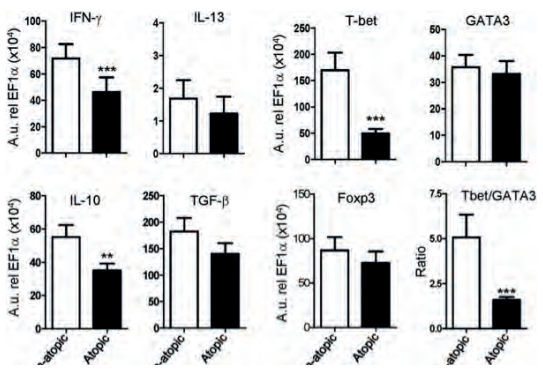


Figure 4) In vivo mRNA expression levels of cytokines or T-cell transcription factors in tonsils. The mRNA expression in palatine tonsils of 24 atopic and 24 nonatopic subjects was determined by using quantitative real-time RT-PCR. The T-bet/GATA3 ratio is also shown.

This article is published in J Allergy Clin Immunol. by Kücükse-

zer UC, Palomares O, Rückert B, Jartti T, Puhakka T, Nandy A, Gemicioğlu B, Fahrner HB, Jung A, Deniz G, Akdis CA, Akdis M. Triggering of specific Toll-like receptors and proinflammatory cytokines breaks allergen-specific T-cell tolerance in human tonsils and peripheral blood. 2013 Mar;131(3):875-885.

Regulatory B cells

B cells contribute to immune responses essentially through antigen presentation to T cells, secretion of cytokines, and production of antibodies after differentiation to plasma cells. When they receive the right survival signals, plasma cells can reside for many years in dedicated niches in the bone marrow and continuously produce antibodies independent of antigen exposure. On activation, IgM+IgD+ naive B cells can undergo class-switch recombination, leading to the expression of IgA, IgG, or IgE antibodies. Human B cells express several Toll-like receptors (TLRs), including TLR1, TLR6, TLR7, TLR8, TLR9, and TLR10. TLR7 (activated by single-stranded RNA) and TLR9 (activated by hypomethylated CpG DNA) are the most highly expressed TLRs on B cells.

Despite accumulating data describing immunoregulatory functions of IL-10–producing B-cell subsets in murine models, there is still little known about the function and phenotype of human Breg cells. There are indications that distinct B-cell subsets have immunoregulatory functions in human subjects. Human CD24hiCD38hi B cells were shown to suppress the differentiation of TH1 cells through provision of IL-10 and possibly also through CD80- and CD86-mediated signaling. In another study a CD24hiCD27+ human B-cell subset was identified that contained a majority of IL-10–producing B cells and was found at higher frequencies in patients with autoimmune disease compared with healthy control subjects. The current findings demonstrate an essential role for B cells in the induction and maintenance of immunologic tolerance. Our recent findings demonstrate 2 ways to directly purify and analyze these cells in human subjects according to IL-10 secretion and surface CD25, CD71high, and CD73low expression. By analyzing CD27, it was observed that both naive and memory subsets of BR1 cells can express IL-10 on TLR9-L stimulation. BR1 cells act on T-cell responses by interfering with CD4+ T-cell activation, and they contribute to peripheral tolerance through production of noninflammatory IgG4 antibodies. We demonstrated significant in vivo regulation of these cells by isolating major allergen-specific BR1 cells in high-dose allergen-exposed beekeepers, as well as in vivo induction of these cells after allergen SIT of subjects with bee venom allergy. Therefore BR1 cells bring together 2 important arms of immune tolerance, namely playing a role as suppressive cells and directing the humoral response toward IgG4, which together characterize a healthy immune response to allergens.

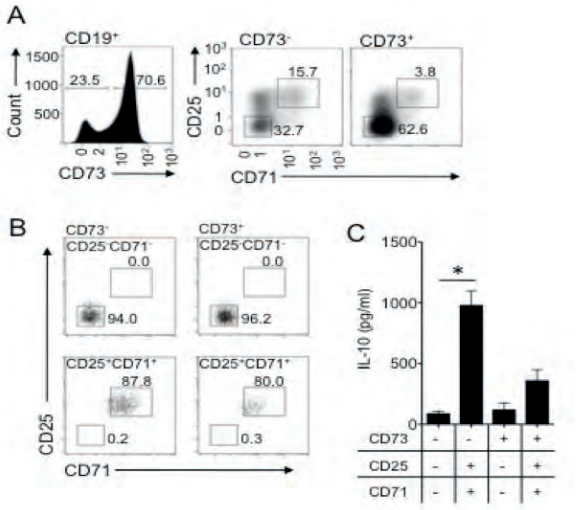


Figure 5) Sorting of cell populations from resting B cells based on expression of CD73, CD25, and CD71. A, Staining of CD25 and CD71 on CD73– and CD73+ B cells. B, Sorted B-cell populations were reanalyzed to assess purity. C, Sorted B-cell populations were stimulated for 48 hours, and IL-10 levels were measured in supernatants.This article is published in J Allergy Clin Immunol. by van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Akdis DG, Rückert B, Akdis CA, Akdis M. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. 2013 Apr;131(4):1204-12.

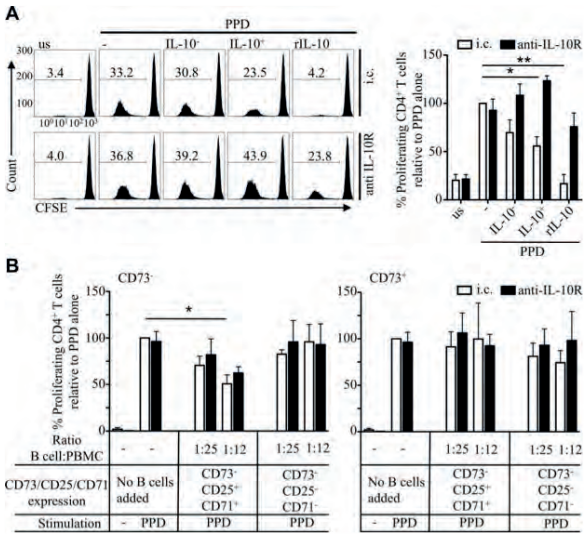


Figure 6) BR1 cells suppress antigen-specific proliferation. A, Cocultures of carboxyfluorescein succinimidyl ester (CFSE)–labeled PBMCs with IL-10+ or IL-10- B cells (ratio, 1 B cell to 25 PBMCs)

with blocking anti– IL-10R or isotype control (i.c.) mAbs. rIL-10 was used as a control. Numbers indicate the percentage dividing CD4+ cells. B, Cocultures of PBMCs with CD73, CD25, and CD71+/- B cells.
This article is published in J Allergy Clin Immunol. by van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Akdis DG, Rückert B, Akdis CA, Akdis M. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. 2013 Apr;131(4):1204-12.

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 travel grant and invited student grant to IFReC/SigN Winter School, Japan.

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

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.
J Allergy Clin Immunol. 2013;131:875-85.
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.

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 TM, Akdis CA, Crameri R, Akdis M.

J Clin. Invest. Submitted

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.

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 CA, Akdis M.

J Allergy Clin Immunol. 2013;131:1204-12.

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.

Suppression of B-cell activation and IgE, IgA, IgG1 and IgG4 production by mammalian telomeric oligonucleotides

Sackesen C, van de Veen W, Akdis M, Soyer O, Zumkehr J, Ruckert B, Stanic B, Kalaycı O, Alkan SS, Gursel I, Akdis CA. Allergy. 2013;68:593-603.

The fine balance of immunoglobulins (Ig) E, IgG1, IgG4 and IgA in healthy production is maintained by the interaction of B cells with adaptive and innate immune response. The regulation of toll-like receptors (TLRs)-driven innate and adaptive immune effector B-cell response and the role of mammalian telomeric TTAGGG repeat elements represent an important research area. Human PBMC and purified naive and memory B cells were stimulated with specific ligands for TLR2, TLR3, TLR4, TLR5, TLR7, TLR8 and TLR9 in the presence or absence of telomeric oligonucleotides. B-cell proliferation, differentiation and antibody production were determined.TLR9 ligand directly activates naive and memory B cells, whereas TLR7 can stimulate them in the presence of plasmacytoid dendritic cells. Human B cells proliferate and turn into antibody-secreting cells in response to TLR3, TLR7 and TLR9, but not to TLR2, TLR4, TLR5 and TLR8 ligands. Stimulation of B cells with intracellular TLR3, TLR7 and TLR9 induced an activation cascade leading to memory B-cell generation and particularly IgG1, but also IgA, IgG4 and very low levels of IgE production. Mammalian telomeric oligodeoxynucleotide (ODN) significantly inhibited all features of TLR ligand-induced events in B cells including B-cell proliferation, IgE, IgG1, IgG4, IgA production, class switch recombination, plasma cell differentiation induced by TLR3, TLR7 and TLR9 ligands. B cells require specific TLR stimulation, T-cell and plasmacytoid dendritic cell help for distinct activation and Ig production profiles. Host-derived telomeric ODN suppress B-cell activation and antibody production demonstrating a natural mechanism for the control of overexuberant B-cell activation, antibody production and generation of memory.

Human IL-10-overexpressing B cells exibit complex immunoregulatory phenotype and possess extensive regulatory capacity toward both innate and adoptive arm of immune response

Stanic B, van de Veen W, Wirz O, Rückert B, Söllner S, Akdis CA, Akdis M. Submitted.

Distinct human IL-10-producing B cells with immunoregulatory properties demonstrated in vivo were described. However, the broader spectrum of their direct cellular targets and mechanisms of suppression have not yet been extensively reported, particularly in the light of direct and indirect solely IL-10 mediated functions. To characterize regulatory phenotype and, based on solely IL-10 intrinsic properties, to assess the immunosuppressive capacity of IL-10 producing cells on TLR- stimulated innate responses in PBMC, maturation of dendritic cells and antigen specific proliferation using in vitro model of IL-10-overexpressing normal human B cells. Highly purified IL-10-overexpressing B cells were phenotypically characterized in terms of their profile of cytokine and immunoglobulin production (using specific ELISA, beads-based multiplex cytokine and isotyping measurement), antigen presentation and co-stimulation capacity, transcription factors signature, and chemokine receptor profile (by quantitative PCR and flow cytometry). Effects of IL-10-overexpresing B cells on PBMC and MDDC were addressed in co-cultures with autologous cells under stimulatory conditions. Cytokine release from TLR2- and TLR4-triggered PBMCs, cytokine production and co-stimulatory molecules expression from TLR4-L stimulated maturation of MDDC and antigen-specific stimulation of PBMC were assessed (by beads-based multiplex cytokine measurement, flow cytometry and by incorporation of 3H-thymidine). Our data show that under IL-10 overexpression normal human B cell are quickly able to acquire prominent immunoregulatory profile with reduced activation (CD19loCD27lo) that comprise enhanced expression

of surface GARP and transcription factor HELIOS, molecules expressed on regulatory T cells, and intracellular SOCS3 probably responsible for reduced production of TNF-a, IL-8 and MIP-1a, and enhanced secretion of IL-1RA and VEGF. IL-10 overexpression was found associated with decrease in co-stimulatory potential retaining antigen presentation. Furthermore, IL-10-overexpressing cells induce IRF-4 and XBP-1 transcription factors and CD38 and CD138 surface markers, which depict reduced activated B cell transition to antibody secreting plasmablasts with no significantly skewed isotype secretion. When co-cultured with autologous PBMC IL-10-overexpressing B cells potently reduce the secretion of proinflamatory cytokines induced by TLR2 and TLR4 stimulation, cause shift of MDDC to less differentiated stage and remarkably downregulate their co-stimulatory capacity by reducing expression of CD80, CD86 and CD83, while inducing expression of PD-L1 molecule important for induction of regulatory T cells. IL-10-overexpressing B cells substantially inhibit antigen specific proliferation of PBMC. Our data demonstrate prominent IL-10 role in inducing complex immunoregulatory phenotype of B cells capable to exert substantial anti-inflammatory functions as well as to significantly contribute immunomodulation of immune response providing tolerance-inducing environment.

TH17 and TH22 cells: a confusion of antimicrobial response with tissue inflammation versus protection

Akdis M, Palomares O, van de Veen W, van Splunter M, Akdis CA.

J Allergy Clin Immunol. 2012;129:1438-49.

Substantial progress in understanding mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumors, organ transplantation, chronic infections, and pregnancy is in an exciting developmental phase that might lead to a variety of targeted therapeutic approaches. Recent progress in the interaction between immune/inflammatory cell subsets through cytokines, particularly the extension of the knowledge on reciprocal regulation and counterbalance between subsets of T(H)1, T(H)2, T(H)9, T(H)17, T(H)22, T follicular helper cells and different subsets of regulatory T cells, as well as corresponding and co-orchestrating B-cell, natural killer cell, dendritic cell, and innate lymphoid cell subsets, offers new possibilities for immune intervention. Studies on new subsets confirm the important role of T cells in the instruction of tissue cells and also demonstrate the important role of feedback regulation for the polarization toward distinct T-cell subsets. T(H)17 and T(H)22 cells are 2 emerging T(H) cell subsets that link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both cytokines play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. This review focuses on current knowledge on T(H)17 and T(H)22 cells and their role in inflammation, with special focus on the mechanisms of their generation and driving and effector cytokines, as well as their role in host defense, autoimmunity, and allergic diseases.

Davos, May 2013

(f.l.t.r. W. van de Veen, M. Akdis. A. Aab. T. Kubo, U. Ochsner, H. Morita, M. Wawrzyniak, B. Stanic; not present: O. Wirz)

RESEARCH

Molecular Immunology

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.

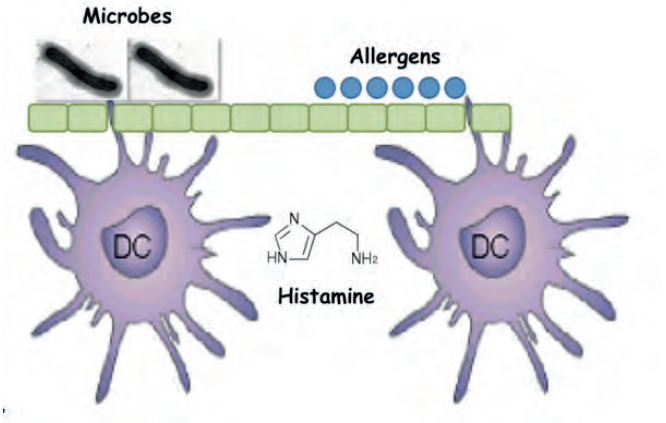


Figure 1) Microbes, allergens and metabolites (e.g. histamine) directly influence DC maturation, activation and lymphocyte polarization.

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. histamine or retinoic acid). DCs shape the functional differentiation of the dividing T cells into Th1, Th2, Th9, Th17 and Treg responses by producing cytokines such as IL-1b, IL-12, IL-18, IL-23, IL-11, IL-10 or TGF-b. 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-b to commensal microbes while pathogens stimulate TNF-a and IL-12 secretion. Certain intracellular pathways have been well described (e.g. TLR-4 activation by LPS) while others are still being explored. However, in vivo, multiple dendritic cell PRRs are simultaneously activated and the co-operation or competition between the resultant signaling cascades is not well understood. The specificity of these responses is achieved through the activation of a particular mosaic of PRRs, that is determined by the available PAMPs and the innate immune cells involved. pDCs preferentially express TLR-7, TLR-9 and DCIR while mDCs express TLR-1, TLR-2, TLR-4, TLR-5, TLR-8, DC-SIGN and Dectin 1. A number of regulatory mechanisms have been described which prevent PRR over-activation. These include intracellular inhibitors, such as IRAK-M and TAG, and other cell types, such as T regulatory cells, which can dampen PRR activation and prevent inflammatory damage to the host.

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

at mucosal sites; (iii) determine the role of G protein-coupled receptors (GPCRs) in regulating the immune response in asthma patients.

(i) Histamine is a biogenic amine with extensive effects on many cell types including important immunological cells such as antigen-presenting cells (APCs), Natural Killer (NK) cells, epithelial cells, T lymphocytes and B lymphocytes. Histamine and its four receptors (H1R – H4R) represent a complex system of immunoregulation with distinct effects dependent on receptor subtypes and their differential expression. These are influenced by the stage of cell differentiation as well as micro-environmental influences, leading to the selective recruitment of effector cells into tissue sites accompanied by effects on cellular maturation, activation, polarization and effector functions leading to tolerogenic or pro-inflammatory responses. H1R, H2R, and H4R are expressed by many cell types of the innate and adaptive immune system, including DCs, while expression of H3R is largely limited to the central nervous system. Histamine has diverse effects depending on the cell type and the repertoire of histamine receptors that are expressed. For example, Th1 cells predominantly express H1R while Th2 cells express H2R and activation of the H2R can suppress activation of both T cell lineages. H2R activation of human pDCs leads to a significant downregulation of IFN-a and TNF-a release following CpG stimulation. H4R has been shown to mediate mast cell, eosinophil, and dendritic cell chemotaxis and can modulate cytokine production from dendritic cells and T cells. H4R has also been shown to be upregulated on human T cells under Th2 polarizing conditions in vitro. H4R-/- mice and wild-type mice treated with a selective H4R antagonist display reduced disease activity following induction of airway inflammation. In contrast, H4R activation mediated by a selective agonist, delivered intratracheally, mitigated airway hyper-reactivity and inflammation. This effect was associated with a potent Foxp3+ T regulatory cell response in the lung. Thus, it is clear that histamine and its receptors play an important role in linking innate and adaptive immune responses.

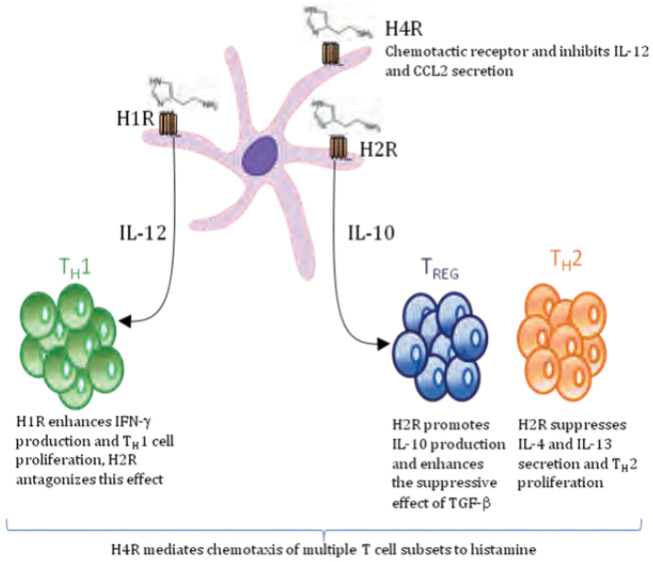


Figure 2) Histamine influences DCs and lymphocytes via their expression of different histamine receptors.

As described in previous reports, histamine signaling through the H2R significantly alters the human dendritic cell immune response to bacterial ligands (such as TLR ligands). In addition, ovalbumin sensitized mice were co-treated with Famitodine (H2R antagonist) or Dimaprit (H2R agonist), resulting in a more severe allergic phenotype or protection from allergic sensitization, respectively. Furthermore, we have also demonstrated in H2R knock-out animals, that loss of this receptor results in more exaggerated allergic responses within the lung. This is characterized by enhanced recruitment of eosinophils and elevated cytokine release from tissue cells. Interestingly, the balance between regulatory cells and effector cells within the lung is severely disrupted, even prior to allergen sensitization and challenge. In particular, CD1d expressing DC numbers are increased in the lung, while invariant natural killer T cells (iNKT) are also increased. Stimulation of iNKT cells within the lungs of H2R knock-out animals resulted in more severe respiratory inflammation, characterized by an enhanced TH17 response and recruitment of neutrophils. Our group is currently dissecting these cellular interactions in order to further define the molecular basis for this defect in immunoregulation. Thus, our results to date suggest that histamine signaling via H2R suppresses 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.

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. In addition, the protective effect of this microbe on colitis induction in the murine DSS model is lost when retinoic acid signaling is inhibited. These molecular mechanisms highlight an important link between diet (e.g. vitamin A, which is required for DC metabolism to retinoic acid), composition of the gastrointestinal microbiota and regulation of intestinal immune responses. 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. Current collaborations with Prof Lauener, Dr Frei and Dr Roduit are examining the role for novel dietary components in managing allergic disorders. In addition, the identification of novel immunoregulatory polysaccharide structures is ongoing and preliminary results suggest that these bacterial-derived molecules exert protective effects. A clearer understanding of the mechanisms employed in vivo for the induction of oral tolerance by the microbiota will likely result in rational strategies to manipulate both T regulatory and effector cells, thereby influencing inflammatory disorders such as allergy and asthma. In addition, the identification of bacterial-derived components or metabolites which selectively activate the immune regulatory program will lead to the rationale design of new drugs for in vivo assessment.

(iii) The incidence of obesity has risen dramatically during the last decades and obesity has been correlated with significant public health implications, including a well established link with an increased risk of developing diabetes, coronary artery disease and non-alcoholic steatohepatitis. More recent epidemiologic studies have demonstrated an increased risk of asthma associated with increasing obesity. The effect of obesity on the occurrence of asthma seems to be more prominent in women and non-allergic individuals, while there is a dose response effect of increasing body mass index (BMI) on asthma incidence. Interestingly, the interaction between obesity and asthma is not mediated by classical TH2 inflammation as suggested by cytokine profiling and exhaled nitric oxide studies. It is becoming increasingly evident that obesity is associated with a unique asthma phenotype that is characterized by more severe disease with variable response to conventional asthma therapies. Metabolic factors, such

as free fatty acids (FFA) could also play a role in the increased risk for developing asthma. FFA can be derived from host metabolism or also from microbiota-associated metabolic processes. FFAs play important physiological roles in many tissues as an energy source and as signaling molecules in various cellular processes. We are currently evaluating the immunological and clinical importance of these FFAs in asthma patients.

Immunomodulation by Bifidobacterium infantis 35624 in the Murine Lamina Propria Requires Retinoic Acid-Dependent and Independent Mechanisms.

Konieczna P, Ferstl R, Ziegler M, Frei R, Nehrbass D, Lauener RP, Akdis CA, O'Mahony L.

PLoS One. 2013 May 21;8(5):e62617.

Appropriate dendritic cell processing of the microbiota promotes intestinal homeostasis and protects against aberrant inflammatory responses. Mucosal CD103(+) dendritic cells are able to produce retinoic acid from retinal, however their role in vivo and how they are influenced by specific microbial species has been poorly described. Bifidobacterium infantis 35624 (B. infantis) feeding to mice resulted in increased numbers of CD103(+)retinaldehyde dehydrogenase (RALDH)(+) dendritic cells within the lamina propria (LP). Foxp3(+) lymphocytes were also increased in the LP, while TH1 and TH17 subsets were decreased. 3,7-dimethyl-2,6-octadienal (citral) treatment of mice blocked the increase in CD103(+) RALDH(+) dendritic cells and the decrease in TH1 and TH17 lymphocytes, but not the increase in Foxp3(+) lymphocytes. B. infantis reduced the severity of DSS-induced colitis, associated with decreased TH1 and TH17 cells within the LP. Citral treatment confirmed that these effects were RALDH mediated. RALDH(+) dendritic cells decreased within the LP of control inflamed animals, while RALDH(+) dendritic cells numbers were maintained in the LP of B. infantis-fed mice. Thus, CD103(+)RALDH(+) LP dendritic cells are important cellular targets for microbiota-associated effects on mucosal immunoregulation.

Bifidobacterium infantis suppression of Peyer's patch MIP-1α and MIP-1β secretion during Salmonella infection correlates with increased local CD4+CD25+ T cell numbers.

Scully P, Macsharry J, O'Mahony D, Lyons A, O'Brien F, Murphy S, Shanahan F, O'Mahony L.

Cell Immunol. 2013 Feb;281(2):134-40.

The outcome following infection depends on the generation of an immune response that results in control of the pathogenic microorganism, while limiting inflammatory collateral damage to the host. Bifidobacterium infantis 35624 was shown to be protective against Salmonella associated host injury via a Treg-dependent mechanism. In this study, we further examined the mechanisms by which B. infantis-induced Tregs protect against Salmonella-associated inflammation. B. infantis 35624 feeding to Salmonella-infected mice significantly reduced Peyer's patch MIP-1alpha and MIP-1beta secretion. Chemokine secretion was significantly inversely correlated with Peyer's patch CD4+CD25+ cell numbers. In vitro, CD25+ T cells, but not CD25- T cells, specifically inhibited TNF-alpha and IFN-gamma secretion. However, both CD25+ and CD25- T cells suppressed MIP-1alpha and MIP-1beta secretion to the same extent. This study suggests that although B. infantis 35624-induced Tregs correlate with inhibition of chemokine secretion within the mucosa of pathogen infected animals, indirect cellular mechanisms may play a role.

Histamine receptor 2 modifies dendritic cell responses to microbial ligands.

Frei R, Ferstl R, Konieczna P, Ziegler M, Simon T, Rugeles TM, Mailand S, Watanabe T, Lauener R, Akdis CA, O'Mahony L.

J Allergy Clin Immunol. 2013 Mar 1.

The induction of tolerance and protective immunity to microbes is significantly influenced by host- and microbiota-derived metabolites, such as histamine.

We sought to identify the molecular mechanisms for histamine-mediated modulation of pattern recognition receptor signaling.

Human monocyte-derived dendritic cells (MDDCs), myeloid dendritic cells, and plasmacytoid dendritic cells were examined. Cytokine secretion, gene expression, and transcription factor activation were measured after stimulation with microbial ligands and histamine. Histamine receptor 2 (H2R)-deficient mice, histamine receptors, and their signaling pathways were investigated.

Histamine suppressed MDDC chemokine and proinflammatory cytokine secretion, nuclear factor kB and activator protein 1 activation, mitogen-activated protein kinase phosphorylation, and TH1 polarization of naive lymphocytes, whereas IL-10 secretion was enhanced in response to LPS and Pam-3Cys. Histamine also suppressed LPS-induced myeloid dendritic cell TNF-alpha secretion and suppressed CpG-induced plasmacytoid dendritic cell IFN-alpha gene expression. H2R signaling through cyclic AMP and exchange protein directly activated by cyclic AMP was required for the histamine effect on LPS-induced MDDC responses. Lactobacillus rhamnosus, which secretes histamine, significantly suppressed Peyer patch IL-2, IL-4, IL-5, IL-12, TNF-alpha, and GM-CSF secretion in wild-type but not H2R-deficient animals.
Both host- and microbiota-derived histamine significantly alter the innate immune response to microbes through H2R.

Bifidobacterium infantis 35624 protects against salmonella-induced reductions in digestive enzyme activity in mice by attenuation of the host inflammatory response.

Symonds EL, O'Mahony C, Lapthorne S, O'Mahony D, Sharry JM, O'Mahony L, Shanahan F.

Clin Transl Gastroenterol. 2012 May 10;3:e15.

Salmonella-induced damage to the small intestine may decrease the villi-associated enzyme activity, causing malabsorption of nutrients and diarrhea, and thus contribute to the symptoms of infection. The objective of this study was to determine the mechanism by which different doses and durations of Salmonella infection and lipopolysaccharide (LPS) affect brush border enzyme activity in the mouse, and to determine if the probiotic Bifidobacterium longum subspecies infantis 35624 could attenuate the intestinal damage.

BALB/c mice were challenged with Salmonella enterica serovar Typhimurium UK1 at various doses (10(2)-10(8) colony-forming unit (CFU)) and durations (10(6) CFU for 1-6 days). Mice were also treated with B. longum subsp. infantis 35624 for 2 weeks before and during a 6-day S. Typhimurium challenge (10(6) CFU), or before injection of LPS. The small intestine was assessed for morphological changes, mRNA expression of cytokines, and activity of the brush border enzymes sucrase-isomaltase, maltase, and alkaline phosphatase.
S. Typhimurium infection significantly reduced the activity of all brush border enzymes in a dose- and time-dependent manner ($P<0.05$). This also occurred following injection of LPS. Pre-treatment with B. longum subsp. infantis 35624 prevented weight loss, protected brush border enzyme activity, reduced the small intestinal damage, and inhibited the increase in interleukin (IL)-10 and IL-8 expression due to Salmonella challenge.
Salmonella infection reduces the small intestinal brush border enzyme activity in mice, with the level of reduction and associated weight loss increasing with dose and duration of infection. B. longum subsp. infantis 35624 treatment attenuated the effect of Salmonella infection on brush border enzyme activity and weight loss, which may be due to modulation of the host immune response.

Portrait of an immunoregulatory Bifidobacterium.

Konieczna P, Akdis CA, Quigley E, Shanahan F, O'Mahony L.

Gut Microbes. 2012 May-Jun;3(3):261-6.

There is increasing interest in the administration of microbes or microbial metabolites for the prevention and treatment of aberrant inflammatory activity. The protective effects associated with these microbes are mediated by multiple mechanisms involving epithelial cells, DCs and T cells, but most data are derived from animal models. In this addendum, we summarize our recent data, showing that oral consumption of Bifidobacterium infantis 35624 is associated with enhanced IL-10 secretion and Foxp3 expression in human peripheral blood. In addition, we discuss the potential DC subset-specific mechanisms, which could contribute to DC(REG) and T(REG) programming by specific gut microbes.

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, micro-organisms, 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.

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.

Intestinal homoeostasis is dependent on immunological tolerance to the microbiota.
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.
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.
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.
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.

Davos, May 2013

(f.l.t.r. M. Sabatebresco, E. Schiavi, N. Rodriguez, M. Ziegler, L. O'Mahony, R. Ferstl; not present: R. Frei)

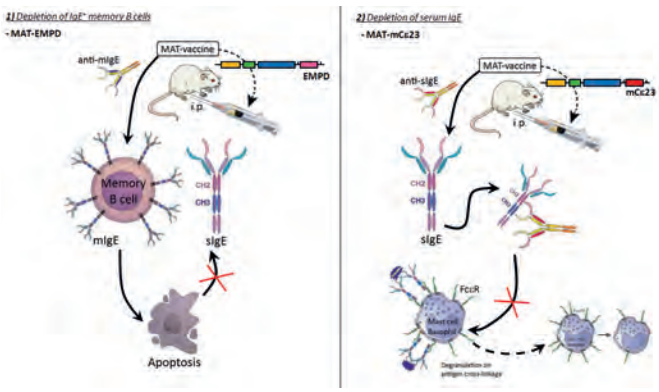
RESEARCH

Vaccine Development

Dr. Claudio Rhyner

The activities of the new SIAF Division Vaccine Development during the timeframe of reporting were mainly focused on two projects. The Swiss National Science Foundation Project "Targeted elimination of IgE memory B cells and serum IgE through active vaccination" 310030_138251/1 and a Commission of Technology and Innovation (CTI) granted project "SIT-MONITOR". The first project is performing research in the development and application of our MAT Vaccine technology to address two of the key players in allergic reactions, IgE positive B cells and serum IgE. The latter one is a CTI granted project requesting for the collaboration of industry and academia, where Davos Diagnostics and Hamilton figured as the industry part and the Vaccine Development Group as the academic partner.

Background: Allergic diseases have reached a pandemic dimension where up to 25-30% of the population is suffering from allergic rhinoconjunctivitis, allergic asthma or atopic dermatitis/eczema. Allergen-specific immunotherapy is currently the only treatment able to cure allergic diseases. For the majority of the patients, symptomatic treatments based on corticosteroids or other short-term-acting drugs remain as therapeutic treatment. Because the common hallmark of all allergic diseases is related to the production of allergen-specific IgE, approaches aimed at eliminating IgE responses, could be an optimal therapy for multi-sensitized patients or patients suffering from a hyper IgE syndrome. Both, multi-sensitization and hyper IgE syndrome can be considered as common diseases that are not causally treatable with the current therapeutic options. We investigated the possibility to develop a broad applicable vaccination therapy based on the targeted elimination of B cells responsible for the establishment of IgE memory immune responses (subproject A) and targeted IgE directly by a vaccination against the receptor binding site (subproject B). We showed that passive immunization with antibodies specific for the extracellular proximal domain of membrane bound IgE (EMPD) on the surface of B cells can suppress the establishment of an allergen-specific IgE response in naïve mice. Our continuously developing vaccination system (modular antigen translocation) has been successfully proven in clinical studies to develop protective antibody responses in patients suffering from cat allergy. As a logical extension of these projects, we developed an active prophylactic vaccination concept aimed at suppressing both the establishment of IgE expressing memory B cells and to target soluble IgE. Experimental design: (A) We engineered EMPD isotype-specific proteins, immunized naïve mice with novel MAT-constructs of these proteins and investigated the effects of the active vaccination on the development of memory B cell and IgE responses and characterized the biological rational of MAT vaccines by elucidating the underlying mechanisms on a serological and cellular level and in vivo in mice. Since long-living plasma cells do not express membrane bound IgE, and are therefore not targetable with anti-EMPD antibodies, we plan to target IgE in serum (B), we produced polypeptides encompassing the IgE region responsible for the binding of IgE to its receptors. We used the novel MAT construct proteins with new engineered targeting peptides. A protective immune response raised against derivatives of the Fc 3 domain of IgE should decrease the serum IgE levels resulting in a persistent suppression of allergic symptoms. The final goal is to heckle the key player of allergic diseases, IgE, by targeting its production site (B cells) and IgE itself by a combined vaccination strategy (see Figure 1).



Additionally we plan to use the developed monoclonal anti EMPD antibodies to isolate IgE+ memory B cells and to produce Fab fragments to be used for co-crystallization with allergen. Expected value: The cure of IgE-mediated diseases is a so far insufficiently addressed medical need with relevant socio-economic impact. Both active immunization strategies targeting IgE+ memory B cells and serum IgE using our MAT system, have the potential to control complex allergic diseases not yet treatable with conventional therapeutic interventions. We started with mouse models of allergy to elucidate the potential of active immunization procedures to prevent and control IgE production. This proposal fits perfectly into the work we are currently performing in our institute and is driven by established methods and knowledge. Furthermore, it extends MAT-vaccination technology in a novel and more generalized direction. The proposed approach has the potential to be developed into a universal treatment of allergic disease, since it is completely independent of any allergen, and represents a novel and promising immunotherapeutic approach to target dysfunctions of the immune system, with the potential to be extended to other diseases with prominent role of B cells.

A complementary and more practical approach to cure allergy is specific immunotherapy (SIT). In this field we are developing diagnostic tests to monitor the progress and success of SIT. Although introduced 100 years ago, SIT still faces several problems related to side effects and limited efficacy. In addition, low patient adherence due to very long duration (3 to 5 years) with frequent injections every couple of weeks and high average costs of 1500€/SIT patient are essential problems. Currently, allergen-SIT is performed with vaccines based on allergen extracts. Administration of allergen extracts can cause severe, some times even life threatening, anaphylactic reactions as well as new IgE sensitization to other antigens in the extract. In addition, many extracts derived from natural materials contain innate immune response triggering substances. An increasing number of patients undergoing SIT are raising the rapidly growing demand of monitoring tools to check the suitability of a patient to initiate SIT, and to early monitor the successful development of the therapy. Furthermore, many novel therapeutics for SIT are entering clinical trials, raising a high demand of the trial centers for appropriate, fast and easy analyses of the important parameters to monitor SIT. Efficient monitoring of SIT will not only allow tracing the success of a therapy, but also adapt or stop in an early stage inefficient therapies to avoid unwanted side effects and reduce costs. This project proposal aims to develop and realize tools, protocols and diagnostic assay kits for the detection of the important parameters for monitoring SIT, e.g. allergen specific IgE, allergen specific IgG4, IL-10, TGF-beta, CTLA-4, PD-1, histamine receptor (HR) 2 and FoxP3-protein. For the readout of these immunological parameters we will use biosensor tests based on evanescent field technology, which will enable cost effective, highly sensitive measurements based on laser excited fluorescence and – most important - without any washing steps. A diagnostic test for the four to eight most important parameters of SIT will have a targeted end-user price of ~10-40 Euros per test. This diagnostic system will be available in two different formats, either as a single patient point-of-care (POC) test for the allergologist or as a 96/384 well high-throughput diagnostic assay system for analytical laboratories in a later phase. In the first step, we are developing the assays to measure four parameters, specific IgE, specific IgG4, IL-10, and FoxP3, for each single patient in 10 min in a POC device. This clinical on-site SIT monitoring test will be possible during the patient visit at the allergologist and will allow the initiation of patient-tailored specific therapy, because the time for testing is less than the average doctors visiting time of a patient. In a later phase, high-throughput assays for specialized analytical laboratories and large clinical trial centers will be developed. This project is in close collaboration with our industrial partners for support in test development.

Equine insect bite hypersensitivity: what do we know?
Schaffartzik A, Hamza E, Janda J, Crameri R, Marti E, Rhyner C.
Vet Immunol Immunopathol. 2012;147, 113-126.

Insect bite hypersensitivity (IBH) is an allergic dermatitis of the horse caused by bites of insects of the genus Culicoides and is currently the best characterized allergic disease of horses. This article reviews knowledge of the immunopathogenesis of IBH, with a particular focus on the causative allergens. Whereas so far hardly any research has been done on the role of antigen presenting cells in the pathogenesis of IBH, recent studies suggest that IBH is characterized by an imbalance between a T helper 2 (Th2) and regulatory T

cell (T(reg)) immune response, as shown both locally in the skin and with stimulated peripheral blood mononuclear cells. Various studies have shown IBH to be associated with IgE-mediated reactions against salivary antigens from Culicoides spp. However, until recently, the causative allergens had not been characterized at the molecular level. A major advance has now been made, as 11 Culicoides salivary gland proteins have been identified as relevant allergens for IBH. Currently, there is no satisfactory treatment of IBH. Characterization of the main allergens for IBH and understanding what mechanisms induce a healthy or allergic immune response towards these allergens may help to develop new treatment strategies, such as immunotherapy.

Research needs in allergy: an EAACI position paper, in collaboration with EFA

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In less than half a century, allergy, originally perceived as a rare disease, has become a major public health threat, today affecting the lives of more than 60 million people in Europe, and probably close to one billion worldwide, thereby heavily impacting the budgets of public health systems. More disturbingly, its prevalence and impact are on the rise, a development that has been associated with environmental and lifestyle changes accompanying the continuous process of urbanization and globalization. Therefore, there is an urgent need to prioritize and concert research efforts in the field of allergy, in order to achieve sustainable results on prevention, diagnosis and treatment of this most prevalent chronic disease of the 21st century.The European Academy of Allergy and Clinical Immunology (EAACI) is the leading professional organization in the field of allergy, promoting excellence in clinical care, education, training and basic and translational research, all with the ultimate goal of improving the health of allergic patients. The European Federation of Allergy and Airways Diseases Patients' Associations (EFA) is a non-profit network of allergy, asthma and Chronic Obstructive Pulmonary Disorder (COPD) patients' organizations. In support of their missions, the present EAACI Position Paper, in collaboration with EFA, highlights the most important research needs in the field of allergy to serve as key recommendations for future research funding at the national and European levels.Although allergies may involve almost every organ of the body and an array of diverse external factors act as triggers, there are several common themes that need to be prioritized in research efforts. As in many other chronic diseases, effective prevention, curative treatment and accurate, rapid diagnosis represent major unmet needs. Detailed phenotyping/endotyping stands out as widely required in order to arrange or re-categorize clinical syndromes into more coherent, uniform and treatment-responsive groups. Research efforts to unveil the basic pathophysiologic pathways and mechanisms, thus leading to the comprehension and resolution of the pathophysiologic complexity of allergies will allow for the design of novel patient-oriented diagnostic and treatment protocols. Several allergic diseases require well-controlled epidemiological description and surveillance, using disease registries, pharmacoeconomic evaluation, as well as large biobanks. Additionally, there is a need for extensive studies to bring promising new biotechnological innovations, such as

biological agents, vaccines of modified allergen molecules and engineered components for allergy diagnosis, closer to clinical practice. Finally, particular attention should be paid to the difficult-to-manage, precarious and costly severe disease forms and/or exacerbations. Nonetheless, currently arising treatments, mainly in the fields of immunotherapy and biologicals, hold great promise for targeted and causal management of allergic conditions. Active involvement of all stakeholders, including Patient Organizations and policy makers are necessary to achieve the aims emphasized herein.

Davos, May 2013

(f.l.t.r. M. Wieland, C. Rhyner, C. Huitema, R. Crameri, J. Olzhausen, M. Kenk, K. Romer; not present: M. Prati, M. Garbani, M. Schwaller, M. Wiki)

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ABSTRACTS

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Akdis CA.
Pathophysiologic and clinical features of allergic disorders.
CIA meeting, Jeju, South Korea, October 2012.

Akdis CA.
XIX. National Allergy and Clinical Immunology Congress, Antalya, Turkey, November 2012.

Akdis CA.
Regulations and guidelines – optimal allergy treatment.
Allergy School, Specific Allergy and Immunotherapy, Madrid, Spain, November 2012.

Akdis CA.
Molecular allergy.
FASIT Workshop 2012, Hamburg, Germany, November 2012.

Akdis CA.
Milan 2013: Immune effector mechanisms and immune tolerance in allergic disease.
WAO International Scientific Conference, Hyderabad, India, December 2012.

Akdis M.
Asthma.
Allergy School, From Skin to Lung – from Theory to Patients.
Davos, Switzerland, March 2012.

Akdis M.
Oral Abstract Session 17 - Allergen-specific immune responses .
EAACI 2012, Geneva, Switzerland, June 2012.

Akdis M.
Late breaking Oral Abstract Session 1 - Regulatory pathways in allergy and inflammation.
Introductory lecture title: Regulatory pathways in allergy and inflammation.
EAACI 2012, Geneva, Switzerland, June 2012.

Akdis M.
Poster session 43- Immune deviations in allergic disease.
EAACI 2012, Geneva, Switzerland, June 2012.

Akdis M.
SSAI Basic Science Symposium - From innate immunity to allergy.
EAACI 2012, Geneva, Switzerland, June 2012.

Akdis M.
Novel T cell subsets
World Immune Regulation Meeting (WIRM) - VI, Davos, Switzerland, March 2012.

Akdis M.
Empathy – sympathy, namely tolerance.
Molecular Immunology & Immunogenetics Congress, Tur-

key, April 2012.

Crameri R.
World Immune Regulation Meeting (WIRM) - VI, Davos, Switzerland, March 2012.

Crameri R.
Symposium 4: Immunobiology of allergy.
International Congress on adjuvants & allergen vaccines 2012, Varadero, Cuba, May 2012.

Crameri R.
Plenary Session 13: Fungal allergy.
18th Congress of the "International Society for Human and Animal Mycology" (ISHAM) Berlin, Germany, June 2012.

Crameri R.
Clinical mycology session 17: Environmental mycology/ fungal allergy/mycotoxins.
18th Congress of the "International Society for Human and Animal Mycology" (ISHAM) Berlin, June 2012.

Crameri R.
Late breaking oral abstract session.
4. EAACI Meeting, Geneva, Switzerland, June 2012.

Crameri R.
Poster Session 15: Extracts and molecules for allergy diagnosis.
4. EAACI Meeting, Geneva, Switzerland, June 2012.

Crameri R.
Oral presentations: Medical science.
Graubünden Forscht: Young Scientists in Contest" Academia Raetica Symposium, September 2012.

Crameri R.
ALLFUN WP2, State of the art.
Borgo Scopeto, Italy, October 2012.

Ferstl R.
Poster session late breaking abstracts: Immune regulation
World Immune Regulation Meeting (WIRM) - VI, Davos, Switzerland, March 2012.

Frei R.
Th subsets and T- and B-cell memory.
World Immune Regulation Meeting (WIRM) - VI, Davos, Switzerland, March 2012.

O'Mahony L.
World Immune Regulation Meeting (WIRM) - VI, Davos, Switzerland, March 2012.

O'Mahony L.
4. EAACI Meeting, Geneva, Switzerland, June 2012.

O'Mahony L.
EMBRN-COST International Mast Cell and Basophil Meeting, Berlin, Germany, November 2012.

Palomares O.
Modulating allergic immune responses.
XXXI EAACI Congress, Geneva, Switzerland, June 2012.

Palomares O.
Development of effector and regulatory T cells.
World Immune Regulation Meeting (WIRM) - VI, Davos, Switzerland, March 2012.

Rebane A.
The role of microRNAs in immune regulation and effector functions.
World Immune Regulation Meeting (WIRM) - VI, Davos, Switzerland, March 2012.

Rhyner C.
Workshop.
World Immune Regulation Meeting (WIRM) - VI, Davos, Switzerland, March 2012.

Rhyner C.
Symposium 4: Immunobiology of allergy.
International Congress on adjuvants & allergen vaccines 2012, Varadero, Cuba, May 2012.

Rhyner C.
Poster Session - Clinical and experimental applications of molecular allergology.
EAACI Congress Geneva, Switzerland, June 2012.

CHAIR AT CONGRESSES

2012

Rhyner C.
Symposium - Molecular profiling of allergy and inflammation.
4. EAACI Meeting, Geneva, Switzerland, June 2012.

van de Veen W.
Poster session 5 – Hygiene hypothesis in immune regulation
World Immune Regulation Meeting (WIRM) - VI, Davos, Switzerland, March 2012.

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 and Honors

Akdis CA.
Cluster Lecture, Borstel Research Center, Borstel, Germany

Akdis CA.
BUSIAD Prize, Bursa, Turkey

Akdis M.
Keynote lecture, Breg symposium, Leiden University Medical Center in Leiden, The Netherlands, January 2012.

Ferstl R.
Travel Grant: EAACI Congress 2012, Geneva, Switzerland, 16-20 June 2012.

Ferstl R.
Travel Grant: EAACI Winter School, Pichl, Austria, 27-30 January 2013.

Garbani M.
Abstract Prize, EAACI Congress 2012, Geneva, Switzerland, 16-20 June 2012.

Palomares O.
The 12th Allergopharma award 2012.
XXXI EAACI Congress, Geneva, Switzerland, June 2012.

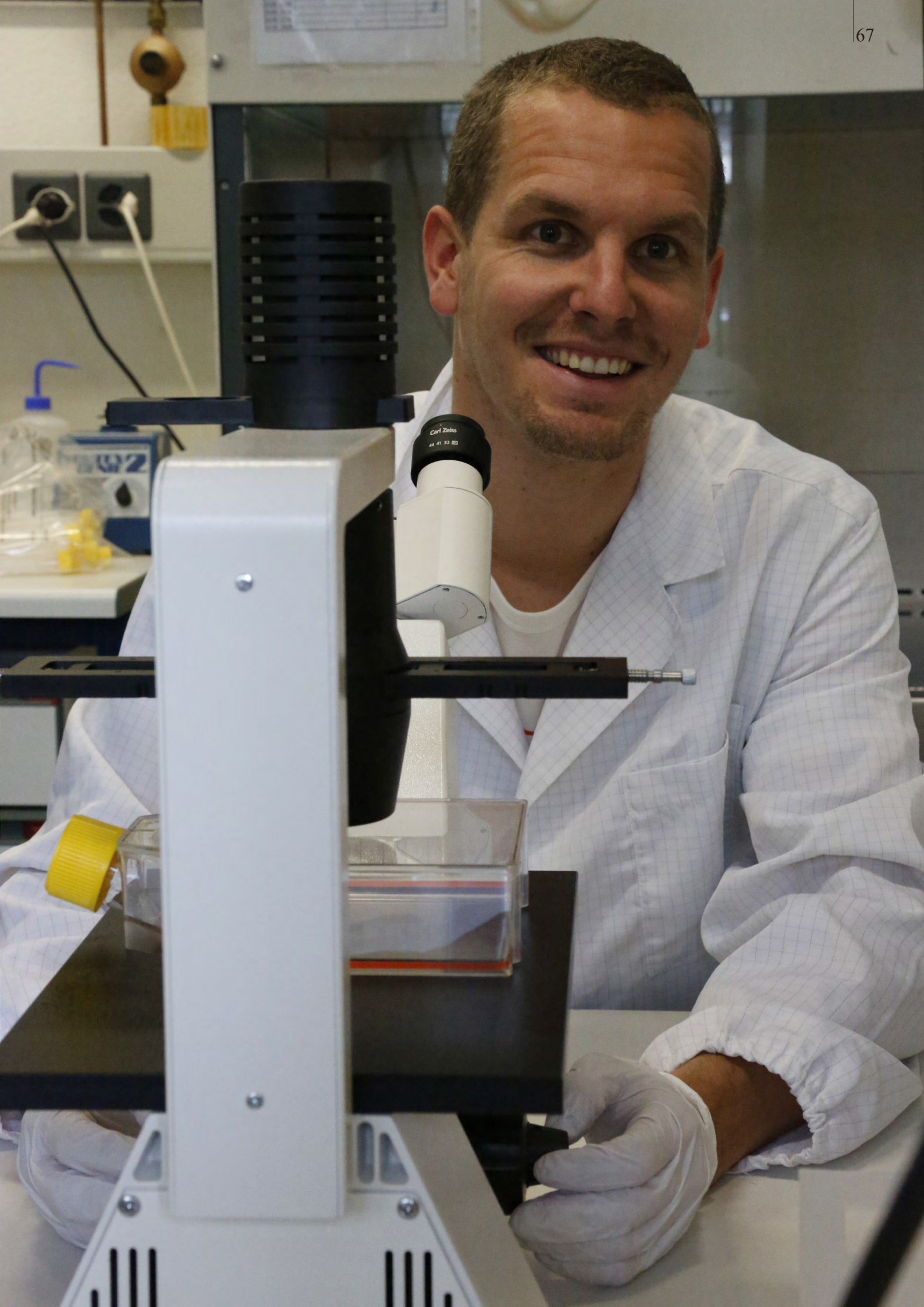
Rhyner C.
"Miembro de Honor". Cuban Society of Immunology.

Schiavi E.
EAACI Research Fellowship Award 2012.

van de Veen W.
Travel grant and free registration.
1st iFReC SIgN Winter School 2012, Awaji Island, Japan.

Academic Degrees

Kast Jl., MSc.
University of Zurich, Faculty of Science, Department of Molecular and Cell Biology
Thesis: „The Expression Pattern of Tight Junctions in Various Tissues and Epithelial Cells, Their Regulation by Cytokines and Cloning of Murine IL-35“, March 2012.


Carl Zeiss

PUBLIC SEMINARS AND EVENTS

Public Seminars at SIAF

Public Seminars

5.1.2012
Prof. Dr. Giorgio Walter Canonica
Allergy & Respiratory Diseases Clinic, DIMI Dept. Internal Medicine, IRCSS S. Martino, University of Genova, Italy.Allergy & Asthma Treatment: from blockbusters to biosimilars.

13.3.2012
Dr. Marina Ulanova Marina Ulanova, MD, PhDMarina Ulanova, MD, PhDMa
Division of Medical Sciences, Northern Ontario School of Medicine, Lakehead University (CAN).
Mechanisms of immune response to encapsulated bacterial pathogens.

16.3.2012
Prof. Dr. Peter Kast
Laboratory of Organic Chemistry, ETH Zurich.Mycobacterium tuberculosis enzymes dissected by directed evolution.

29.3.2012
Davos – HEALTH and MARIE CURIE.
Dr. Sasha Hugentobler, National Contact Point HEALTH, Euresearch Head Office.
Petra Hertkorn-Betz, Euresearch Regional Office St. Gallen.

10.5.2012
Dr. Tom Boileau
Health and Nutrition Innovation Entrepreneur, Bell Institute of Health and Nutrition, General Mills Inc., Minneapolis, USA. Diet, gastrointestinal health and immune function.

3.9.2012
Prof. Massimo Triggiani
Division of Allergy and Clinical Immunology, University of Salerno, Italy.
The role of beta-glucuronidase in inflammation and macrophage activation.

Angela Treis
Swiss Institute of Allergy and Asthma Research, Davos, Switzerland.
A novel gene in human core duplicons regulates cell survival.
Dr. Can Alkan
Bilkent University, Ankara, Turkey.
Next-generation sequence characterization of complex genome structural variation.

4.9.2012
Prof. Marek Sanak
Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland.
Eicosanoids and their biosynthesis by respiratory epithelia.

3.10.2012
Prof. Antonella Muraro
Head of the Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, Treasurer of the European Academy of Allergy and Clinical Immunology (EAACI), Department of Pediatrics, University of Padua, Italy.
A to Z of food allergy.

23.10.2012
Dr. Terufumi Kubo
Department of Pathology, Graduate School of Medicine, Sapporo Medical University, Japan.
A novel autocrine-paracrine loop of TSLP in atopic dermatitis is mediated by p63.

7.11.2012
Dr. Christoph Reymond
Chief Scientific Officer (CSO), Angergis SA, Epalinges, Switzerland
Allergy vaccines based on Contiguous Overlapping Peptides (COPs): from low IgE binding to sustained immunological response in human.

20.12.2012
Prof. Dr. Hergen Spits
Department of Cell Biology and Histology, Amsterdam Medical Center, University of Amsterdam, The Netherlands.
Spectrum of human innate lymphoid cells.

21.12.2012
Dr. Kazunari Sugita
Department of Dermatology, Kyoto University School of Medicine, Japan.
Prostaglandin E2-EP2/EP4 signaling mediates the development of niacin-deficiency-induced photosensitivity.

World Immune Regulation Meeting-VII 2013

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 seventh time this successful international meeting from 13-16 March 2013 at the Kongresszentrum Davos. The congress was focused on "Innate and Adaptive Immune Response and Role of Tissues in Immune Regulation" with approximately 650 participants from over 40 countries with 114 presentations and 265 abstracts.

SIAF Science Day

Prof. Spits H.
Opening talk: Spectrum of human innate lymphoid cells.

Komlosi Z.
IL-15 dependent innate lymphoid cells with regulatory potential.

Kovacs N.
Visualization of the innate lymphoid cells in tonsil tissue.

Wawrzyniak M.
Isolation and characterization of human Th22 cells.

van de Veen W.
Characterization of human allergen-specific B cell subsets.

Prati M.
Characterization of preventive/therapeutic vaccines in a murine model of asthma.

Stanic B.
The regulatory capacity of IL-10 – overexpressing B cells.

Ferstl R.
Role of NKT-cells in H2R-/- mice during allergic airway inflammation.

Konieczna P.
Histamine production in response to microbes.
Garbani M.
Dentritic cells targeting in immunotherapy

Frei R.
Exposure to the sialic acid Neu5Gc is associated with less allergic disease in humans and mice.

Olzhausen J.
Development of diagnostic assays for the detection of important parameters for monitoring SIT.

Huitema C.
IgE quantification using an evanescent biosensor.
Treis A.
Characterization and functional analysis of SMA, a novel gene in human core duplicons.

Wawrzyniak P.
Role of Th2 cells in the regulation of tight junctions in bronchial epithelial cells in asthma.

Wanke K.
Bronchial epithelium integrity and tight junctions are regulated by T regulatory cells and TGFbeta.

Aab A.
Mononuclear cells response to rhinovirus infection.

Winners:
Huitema C.
1st price for "Best presentation award".

Komlosi Z.
2nd price for "Best presentation award".

Wawrzyniak M.
3rd price for "Best presentation award".

SCIENTIFIC POSTS AND EDITORIAL ACTIVITIES

Scientific Posts

Scientific Posts

Akdis C.A.
Allergopharma Award
Committee member

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)
Board of directors

COST Action BM0806
Recent advances in histamine receptor H4 research member

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

European Academy of Allergy Clinical Immunology (EAACI)
Executive Committee Member (2003-)
Vice President 2007-2011
President 2011-2013
Congress President Geneva Congress 2012
Congress President Milan Congress 2013

Global Allergy and Asthma European Network GA2LEN
Executive Committee Member

PHARF (Phadia Allergy Research Forum) Award
Committee member

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)

Member of evaluation board for PhD exam of Lars Bloom, University of Copenhagen, 20th September, 2012.

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

European Academy Allergy Clinical Immunology
Immunology Section Board Member

World Immune Regulation Meeting
Member of the organizing committee

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

European Union Research, Predicta
Steering board member
Work package leader

Crameri R.
Academia Raetica
Co-founder and vice president

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

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

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

7th Framework Program "ALLFUN"
Steering board member

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

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

Naturforschende Gesellschaft Davos,
Advisory board member and treasurer

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

World Immune Regulation Meeting
Member of the organizing committee

O'Mahony L.
EAACI Immunology Section Board Member 2011-2013
EAACI Food Allergy and Anaphylaxis Guidelines Group member
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

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

Academia Raetica
Member

British Biochemical Society
Member

World Immune Regulation Meeting (WIRM), Davos
Organizing committee member

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

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
Clinical Translational Allergy, associate editor
Nature Scientific Reports, editorial board member
Genes and Immunity (Nature) Editorial board member
Annals of Allergy, Asthma & Immunology, Editoial 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. A. Nandy, Dr. S. Klysner)

Bilkent University, Ankara (TR), (Prof. I. Gürsel, Dr. C. Alkan, Dr. O. Tastan)

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, Dr. O. Soyer)

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 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)

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 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, Dr. M. Soyka)

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 Research-group (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)


G630
Deflection
Plates

Swiss National Science Foundation

Regulation of allergen-specific immune response
Akdis M.
CHF 337'000.-
01.04.2012 - 31.03.2014
(2012: 170'000; 2013: 97'000; 2014: 70'000)

T cell interaction with tissue cells in allergic inflammation
Akdis C.A.
CHF 537'000.-
01.10.2010 – 31.09.2012
(2010: 214'800; 2011: 187'950; 2012: 134'250)

Microbiota-Derived Histamine – Relevance to Mucosal Immune Homeostasis
O'Mahony L.
CHF 471'500.-
01.11.2012 – 31.10.2014
(2012: 261'500; 2013: 105'000; 2014: 105'000)

Targeted elimination of IgE memory B cells and serum IgE through active vaccination
Rhyner C.
CHF 269'110.-
(2012: 87'920.-; 2013: 90'370.-; 2014: 90'820.-)

SNF Overhead 2012
CHF 42'383.-

Staatssekretariat für Bildung und Forschung (SBF)
CHF 807'000.-

Stiftung vormals Bündner Heilstätte Arosa
CHF 75'000.-

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.-

Alimentary Health Ldt
O'Mahony Liam
EUR 90'000.-

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

Marie-Curie
O'Mahony L.
for 2 years
CHF 180'000.-

Kommission für Technologie und Innovation KTI
Rhyner C.
CHF 402'521.-

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.-

Bilanz per 31. Dezember 2012

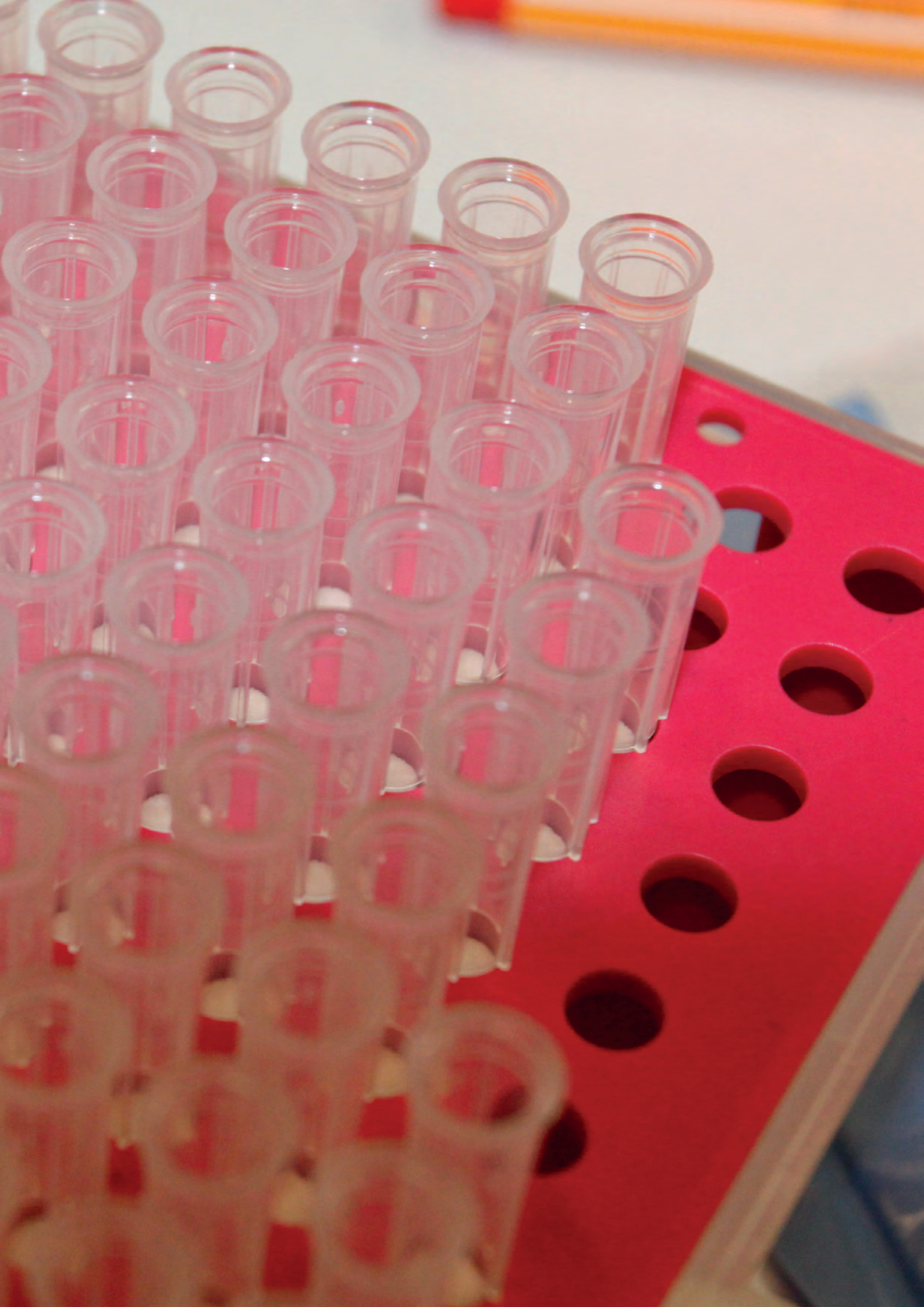
(inklusive Drittmittel)

	31.12.2012	31.12.2011
	CHF	CHF
AKTIVEN		
Flüssige Mittel	1'226'943.47	1'163'051.34
Forderungen	12'422.12	80'034.72
Aktive Rechnungsabgrenzung	179'550.22	137'240.81
	1'418'915.81	1'380'326.87
PASSIVEN		
Verbindlichkeiten	65'628.58	105'428.54
Bankverbindlichkeiten	25.49	14'225.70
Kontokorrent SFI Stiftung	57'817.90	24'038.65
Passive Rechnungsabgrenzung	1'075'987.35	1'017'177.49
Eigenkapital	219'456.49	219'456.49
	1'418'915.81	1'380'326.87

Betriebsrechnung 2012

(inklusive Drittmittel)

	Rechnung 2012	Budget 2012	Rechnung 2011
	CHF	CHF	CHF
ERTRAG			
Beitrag Bund Forschungsgesetz Art. 16	807'000.00	807'000.00	795'000.00
Beitrag Kanton Graubünden	146'050.00	146'050.00	137'187.05
Beitrag Gemeinde Davos	424'560.00	424'560.00	402'400.00
Beitrag Universität Zürich	299'523.00	299'600.00	298'345.00
Beitrag Stiftung SFI Villa Fontana	100'000.00	100'000.00	100'000.00
Beitrag Stiftung vormals Bündner Heilstätte Arosa	50'000.00	50'000.00	50'000.00
Beitrag Stiftungen/Drittmittel	338'913.35	0	400'000.00
Overheadbeiträge	70'242.91	88'000.00	130'438.00
Ertrag aus Dienstleistung Asthmaforschung	10'715.48	20'000.00	18'069.46
Übriger Ertrag	3'047.06	4'000.00	2'396.54
Finanzertrag	119.76	0	780.79
Ausserordentlicher Ertrag	0	0	6'949.70
WIRM-Kongress	433'974.33	450'000.00	430'598.51
Drittmittel	2'408'789.04	2'314'931.00	2'071'763.61
	5'092'934.93	4'704'141.00	4'843'928.66
AUFWAND			
Personalaufwand	2'980'633.11	2'855'600.00	2'442'824.71
Verbrauchsmaterial	1'054'806.90	987'000.00	1'442'194.00
Raumaufwand	17'660.65	25'000.00	20'952.60
Unterhalt/Reparaturen/Ersatz	109'032.53	125'000.00	106'909.58
Investitionen	205'167.95	96'800.00	98'915.02
Sachversicherungen/Abgaben	7'688.60	7'000.00	7'271.20
Energie- und Entsorgungsaufwand	76'113.80	70'000.00	68'016.80
Verwaltungsaufwand	153'721.12	133'000.00	147'902.30
Reisespesen	84'046.31	73'700.00	77'314.00
WIRM-Kongress	390'444.32	329'000.00	398'229.82
Übriger Betriebsaufwand	3'708.80	1'000.00	2'519.00
Finanzaufwand	4'433.55	1'000.00	6'352.65
Ausserordentlicher Aufwand	5'477.29	0	24'526.61
	5'092'934.93	4'704'100.00	4'843'928.29
Ergebnis	0	41.00	0.37
	5'092'934.93	4'704'141.00	4'843'928.66



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