SIAF

Swiss Institute of Allergy and Asthma Research

# ANNUAL REPORT 2019

University of Zurich[UZH]

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## About us

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

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

## Bericht des Direktors

*Prof. Dr. med. Cezmi A. Akdis*

1988 wurde das Schweizerische Institut für Allergie- und Asthmaforschung (SIAF) in seiner heutigen Form von der Medizinischen Abteilung der Stiftung Schweizerisches Forschungsinstitut für Hochgebirgsklima und Medizin Davos (SFI) gegründet. Seit 1996 ist das Institut der Universität Zürich angegliedert und seit 2008 Mitglied der Life Science Zurich Graduate School, einem gemeinsamen Ausbildungs-Projekt der Universität Zürich und der ETH Zürich. Weiter ist das SIAF aktives Mitglied der Academia Raetica und der Graduate School Graubünden.

Die Forschung am SIAF konzentriert sich auf die patientenrelevante translationale Forschung und Untersuchung der immunologischen Grundlagen allergischer und asthmatischer Erkrankungen, die Ansatzpunkte für neue präventive und kurative Behandlungen zugunsten der Betroffenen schafft. Das SIAF setzt sich auch verstärkt für eine personalisierte Medizin ein, damit Behandlungsansätze entwickelt werden können, die besser auf den einzelnen Patienten zugeschnitten sind, und welche die individuelle Symptomausprägung des jeweiligen Patienten stärker berücksichtigt. Nicht nur massgeschneiderte Behandlungstherapien, sondern auch präzisere Diagnosen erhofft man sich von der personalisierten Medizin. Die Forschung ist auf eine direkte Kooperation mit den Kliniken in Davos, der Universität Zürich und weiteren spezialisierten Instituten ausgelegt. Ausserdem ist das SIAF in das europäische Netzwerk nationaler Kompetenzzentren (Projekt GA2LEN: Global Allergy and Asthma European Network of Excellence), der Europäischen Akademie für Allergologie und klinische Immunologie (EAACI) sowie der Amerikanischen Akademie für Allergie, Asthma und Immunologie (AAAAI) eingebunden. Mit der Universität Stanford (Sean Parker Asthma and Allergy Center) besteht eine intensive Zusammenarbeit.

Das SIAF hat über 1'320 Fachbeiträge veröffentlicht und gehört zu den meistzitierten Instituten weltweit. Die vom SIAF publizierten Artikel wurden 53'700 Mal zitiert. Das Institut gehört mit seinen rund 45-50 Mitarbeitern weltweit zu den Besten in Bezug auf seine Grösse. Es ist eine international bekannte Ausbildungsstätte für Doktoranden und Habilitanden.
2019 wurden 84 wissenschaftliche Arbeiten in begutachteten internationalen Fachzeitschriften mit “Impact Factor” veröffentlicht oder sind noch in Druck. 2019 erreichte das SIAF einen Gesamtwert des “Impact Factors” von 606.373 und einen Durchschnitt von 7.2 Punkten pro Publikation. Die neusten Ergebnisse wurden zudem in 26 Abstracts an verschiedenen Fachtagungen mitgeteilt. Unsere Mitarbeitenden wurden zu 62 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 27 verschiedenen Sessionen hatten SIAF-Mitarbeitende den Vorsitz. Zusätzlich werden 35 wissenschaftliche Ämter in internationalen Gesellschaften durch Wissenschaftler des SIAF besetzt. Des Weiteren sind die Forscher des SIAF bei insgesamt 16 internationalen Zeitschriften als Mitglieder der redaktionellen Komitees tätig. Zudem hält Prof. C. A. Akdis seit 2018 das Amt des Chefredaktors der Fachzeitschrift Allergy inne. Als Folge seiner international höchst angesehenen wissenschaftlichen Publikationen wurde Prof. Dr. C. A. Akdis 2019 zum vierten Jahr in Folge von Thomson Reuters in die Gruppe der 1‘000 meistzitierten Forscher aus allen wissenschaftlichen Fachbereichen weltweit aufgenommen.

Das SIAF und das Christine-Kühne Center for Allergy Research and Education (CK-CARE) in Davos-Wolfgang spielen in ihren Bereichen je eine international tragende Rolle. Die Hochgebirgsklinik Davos (HGK) konnte unter einem neuen Betriebskonzept neu ausgerichtet werden, mit dem Ziel eine der führenden Kliniken im Allergiebereich zu formen, nicht zuletzt dank der Nähe zur Forschung.
Das neue Campus Gebäude ist mit Labor- und Büroräumen 3’136m2 gross. Die Labore sind mit modernster Technologie ausgestattet. Das SIAF konnte Anfangs August seine Forschungstätigkeiten in den neuen Laboren aufnehmen.
Dank der Unterstützung durch die CK-CARE konnten seit 2009 mehr als 50 wissenschaftliche Mitarbeitende eingestellt und über 76 akademische Gäste im Austauschprogramm aufgenommen werden. Darüber hinaus wurden 208 Publikationen mit SIAF und CK-CARE Zugehörigkeit in namhaften Zeitschriften veröffentlicht.

**"Die Epithelbarriere-Hypothese" für die Entwicklung allergischer, autoimmuner und mikroinflammatorischer Erkrankungen**

Mit einem epidemischen Anstieg in den letzten 60 Jahren sind weltweit mehr als eine Milliarde Menschen von allergischen Erkrankungen und Autoimmunerkrankungen der Haut, der Schleimhäute und des tiefer liegenden Körpergewebes betroffen. Diese Krankheiten sind in Industrieländern häufiger anzutreffen und nehmen in Entwicklungsländern parallel zur Urbanisierung und Industrialisierung weiter zu. Intakte Haut- und Schleimhautbarrieren sind für die Aufrechterhaltung der Gewebehomöostase von entscheidender Bedeutung, da sie das umliegende Gewebe vor Infektionen, Umweltgiften, Schadstoffen und Allergenen schützen. Bei Asthma, atopischer Dermatitis, allergischer Rhinitis, chronischer Rhinosinusitis, eosinophiler Ösophagitis und entzündlichen Darmerkrankungen wurde eine defekte Epithelbarriere des betroffenen Gewebes nachgewiesen. Auch bei vielen anderen Erkrankungen mit Autoimmun- und Mikroinflammations-Ätiologie, wie Diabetes, Multiple Sklerose, Lupus, Zöliakie, Hepatitis, Parkinson-Krankheit und autistische Störungen wird eine Undichtigkeit des Darmepithels vermutet. Und genau hier können wir die von uns erstmals vorgeschlagene „Epithelbarriere-Hypothese“ als allgemeiner Begriff zur Erklärung der Ursachen nichtübertragbarer chronischer Erkrankungen vorstellen, welche in den letzten Jahrzehnten einen epidemischen Ausmass angenommen haben. Die Hypothese der Epithelbarriere beschreibt Defekte an Haut- und Schleimhautbarrieren, die durch die Exposition gegenüber Barriere-schädigende Substanzen verursacht werden, die mit der Industrialisierung, der Urbanisierung und dem modernen Leben verbunden sind. Eine undichte Epithelbarriere initiiert die Translokation des Mikrobioms von der Oberfläche der betroffenen Gewebes in interepitheliale und noch tiefere subepitheliale Bereiche. In Geweben mit einer defekten Epithelbarriere findet eine Besiedlung opportunistischer Krankheitserreger, eine verminderte Artenvielfalt in der Mikrobiota, eine gestörte subepitheliale Immunantwort, eine lokale Entzündung sowie eine inkorrekte Regeneration und Umbauprozesse statt. Die Migration entzündeter Zellen in andere betroffene Gewebsareale sowie die systemische Immunaktivierung und Mikroinflammation sind weitere Akteure, die bei der

Entwicklung und Verschlimmerung vieler chronisch-entzündlicher Erkrankungen eine Rolle spielen.

Derzeit liegen umfangreiche Daten vor, aus denen hervorgeht, dass Allergene wie Hausstaubmilben, bestimmte Bakterien, Pilze, Viren, Wasch- und Spülmittel, Haushaltsreiniger, Tenside, Enzyme und Emulgatoren in verarbeiteten Lebensmitteln, Zigarettenrauch, Feinstaub, Dieselabgas, Ozon und Nanopartikel und Mikroplastik die Epithelbarriere schädigen. Das Auftreten dieser Faktoren stieg parallel zur Industrialisierung, Urbanisierung und Modernisierung. Von all diesen Substanzen sind Waschmittel und Haushaltsreinigungsmittel die Giftstoffe, die das Epithel am stärksten angreift. Der vermehrte Einsatz von Waschmitteln im Allgemeinen und die Zugabe von Tensiden zu handelsüblichen Waschmitteln hat die tägliche Exposition der Menschen gegenüber gewebebarriereschädigenden Substanzen erheblich zugenommen. Eine zusätzliche Belastung für die Epithelbarriere begann mit der Einführung proteolytischer Enzyme im Waschpulver Mitte der 1960er Jahre, um deren Reinigungseffizienz zu erhöhen. Zahlreiche Studien zeigten epidemiologische Hinweise auf die Entwicklung von Asthma und AD bei direkter Exposition gegenüber Waschmitteln. Haushaltsreiniger und medizinische Desinfektionsmittel gehören zu den häufigsten mit Asthma verbundenen Reizstoffen. Berufsbedingtes Asthma konnte in Waschmittelfabriken in epidemischen Ausmassen nachgewiesen werden. Asthma beim Reinigungspersonal wurde mit dem Einsatz von Bleichmitteln und Reinigungsmitteln in Verbindung gebracht. Beim Reinigungspersonal wurde über berufsbedingtem Asthma und Ekzemen berichtet. Berufsasthma und Rhinitis wurden durch Exposition gegenüber Waschmittelenzymen wie Bacillus subtilis-Toxin, Amylase, Lipase und Cellulase verursacht. Eine systematische Überprüfung epidemiologischer Studien zeigte in vier Querschnitts-, Längsschnitt- und Fall-Kontroll-Studien einen Zusammenhang zwischen der Exposition gegenüber Reinigungsmitteln und Asthma. Berufsallergien und Asthma in der Waschmittelindustrie sind durch umfassende Massnahmen und die Entwicklung von Best-Practice-Richtlinien zur Expositionskontrolle in Produktionsanlagen erheblich zurückgegangen. Es wurden umfangreiche Untersuchungen zum Ersatz nicht biologisch abbaubarer Produkte durch umweltfreundlichere und sicherere Alternativen durchgeführt. Und trotzdem sind weiterhin viele Menschen täglichen gewebsbarriereschädigenden Dosen von Waschmitteln und Haushaltsreinigern ausgesetzt.

In zwei Studien wurde kürzlich über die durch Waschmittel auf der menschlichen Haut und den Bronchialepithelzellen verursachte Schädigung der Epithelbarriere berichtet. Selbst bei hohen Verdünnungen zerstört das Waschmittel die epitheliale Barrierefunktion der menschlichen Haut und der bronchialen Epithelzellen. Das RNA-Sequenztranskriptom von 1 bis 50'000-fach verdünnten Waschmittel-exponierten Bronchialepithelzellen zeigte hochregulierte Gene des Lipidstoffwechsels, des oxidativen Stresses und des Zellüberlebens, herunterregulierte Gene der Zelladhäsion, der extrazellulären Matrixorganisation und der Wundheilung zusammen mit einer erhöhten IL-33-Expression. Die beiden Haupttenside Natriumdodecylsulfat und Natriumdodecylbenzolsulfonat, die üblicherweise in Waschmitteln, Seifen, Shampoos und vielen Haushaltsreinigungsmitteln verwendet werden, zerstören die TJ-Barriere der Lunge und des Hautepithels in extrem hohen Verdünnungen wie 1 zu 100'000. Die Nachspülflüssigkeit, die am Ende des Waschvorganges aus den Handtüchern und der Kleidung gesammelt wurde, enthielt immer noch aktive Detergenzien und Tenside, welche die epitheliale TJ-Barriere beeinträchtigen können.

**Entdeckung neuartiger B-Zell-Untergruppen**

Es wurde lange angenommen, dass die Funktion von B-Zellen auf die Erzeugung von Immunglobulin-produzierenden Plasmazellen beschränkt ist. B-Zellen können jedoch einen vielfältigeren Bereich von Immuneffektor- und Regulationsfunktionen ausüben. Verschiedene funktionelle B-Zell-Untergruppen wurden basierend auf ihre Zytokinproduktionsprofile identifiziert. Es wurde bereits über immunsuppressive B-regulatorische (reg) Zellen und andere potenzielle B-Zell-Untergruppen wie B-Effektor (Be) 1- und Be2-Zellen sowie IL-17-produzierende B-Zellen berichtet. Die Angiogenese (Gefässneubildung) ist ein wesentlicher physiologischer Prozess, der während der Embryogenese (Embrionalentwicklung), der normalen Gewebeentwicklung und der Wiederherstellung nach einer Verletzung auftritt. Durch eine kontrollierte Reihe von Ereignissen ermöglicht die Angiogenese, dass neue Gefässe aus bereits vorhandenen Gefässen wachsen, um den physiologischen Bedürfnissen von Geweben gerecht zu werden. Im SIAF wurde eine neuartige Untergruppe angiogenetischer B-Zellen entdeckt. Die Angiogenese spielt auch eine Rolle beim Tumorwachstum und ist am Umbau des Gewebes bei chronisch entzündlichen Erkrankungen wie Asthma und eosinophiler Ösophagitis beteiligt. Eine breite Palette von sekretierten Molekülen fördert diesen Prozess durch direkte Wechselwirkung mit vaskulären Endothelzellen. Dazu gehören vaskuläre endotheliale Wachstumsfaktoren, Fibroblastenwachstumsfaktoren, von Blutplättchen abgeleitete Wachstumsfaktoren, Hepatozytenwachstumsfaktoren, Axonleitfaktoren und Angiopoietine.

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

Das DAViS-Zentrum wurde 2019 an der Fachhochschule Graubünden (FHGR) in Chur mit dem SIAF als Hauptpartner im Zusammenhang mit der Umsetzung der Forschungsstrategie des Kantons Graubünden im Profilfeld „Computational Science" gegründet. Im ersten gemeinsamen Life-Science-Projekt «MLM-SOS-ALL« versuchen wir mithilfe neuartiger Berechnungsmethoden Merkmale zu identifizieren, die für die Entwicklung und die zunehmende Verbreitung allergischer Erkrankungen verantwortlich sind. Bei den Daten in diesem Projekt handelt es sich um Transkriptsequenzierungsdaten, die zuvor mit 150 Kinder für die SOS-ALL-Studie in einem Konsortium, bestehend aus dem SIAF, der Universität Kapstadt und dem Kinderspital Zürich und der Klinik für Dermatologie des Universitätsspital Zürich gesammelt wurden. Ebenso wurden umfangreiche Daten mittels Fragebogen zur Lebens- und Gesundheitssituation der Kinder erfasst. Durch das hohe Volumen der Sequenzierungsdaten wurden die biostatistischen Analysen parallel zum Aufbau der erforderlichen Infrastruktur und Hardware durchgeführt. Weitere Analysen mit unterschiedlichen Ansätzen, einschliesslich Methoden des maschinellen Lernens, werden derzeit in enger Zusammenarbeit durchgeführt und die Ergebnisse auf ihre biomedizinische Relevanz hin bewertet.

## Bericht des Direktors

**Immunmetabolismus bei Allergien und Immuntoleranz: Ein Multiomics-Ansatz**

Auf der Suche nach neuen Mechanismen und Biomarkern für die allergenspezifische Immuntherapie ist die allergische Immunantwort in T-Zellen unter anderem durch eine erhöhte Sekretion entzündungsfördernder Mediatoren durch Th2-Effektorzellen gekennzeichnet. Die Hauptunterdrücker dieser Reaktion sind allergenspezifische regulatorische T-Zellen (Tregs). Es ist wenig über den Stoffwechselbedarf allergenspezifischer und unspezifischer Effektor-T-Zellen und Tregs zur Erfüllung ihrer Funktionen in-vivo bekannt. Ziel unserer Studien ist es, wesentliche Stoffwechselwege für regulatorische und Effektor-populationen allergenspezifischer und unspezifischer Gedächtnis-T-Zellen in-vivo beim Menschen, ihre möglichen Veränderungen bei allergischen Erkrankungen sowie ihre Veränderungen während der allergenspezifischen Immuntherapie zu identifizieren. Allergenspezifische T- und Treg-Zellen bei allergischen Patienten zeigen eine tiefgreifende Herunterregulierung der Immunantwort und der Zellaktivierungswege durch Gene und Proteine mit Ausnahme der Typ-2-Immunität, der TCR-Signalübertragung und des Fettsäure- und Prostaglandin-Metabolismus. Plasma und nasales, nicht zielgerichtetes und zielgerichtetes Proteom spiegeln die spezifische zelluläre Signatur wider, wobei die Hochregulierung von Proteinen zur Lymphozytenproliferation, T-Zell-Differenzierung und zum Fettsäurestoffwechsel sowie zur Herunterregulierung mehrerer entzündungshemmender Wege führt. Bemerkenswerterweise induziert AIT signifikante Veränderungen in zuvor dysregulierten Immun- und Stoffwechselwege und führt zur Induktion von Toleranzprogrammen in allergenspezifischen CD4+-T-Zellen und Treg-Zellen. Allergenspezifische Treg-Zellen in Non-Respondern auf AIT zeigten jedoch immer noch aberrante Typ-2-Gen-, Protein- und Stoffwechselprofile, gekoppelt mit dem entsprechenden Plasma- und Nasenentzündungsmilieu, parallel zu einer funktionellen Beeinträchtigung ihrer Unterdrückungskapazitäten. Insgesamt deuten unsere Daten darauf hin, dass bei Allergien eine systemische und lokale Aberration der Immun- und Stoffwechselsignale vorliegt, die zu einer gestörten metabolischen Reprogrammierung und einer anschliessenden funktionellen Beeinträchtigung allergenspezifischer Effektor- und regulatorischer T-Zellen führt.

**Klinische Dienstleistung**

Das SIAF bietet den Davoser und allen weiteren interessierten Kliniken und praktizierenden Ärzten spezielle zelluläre immunologische Untersuchungen an. Mit Hilfe der durchfluss-zytometrischen Analyse (FACS Analyse) von Blut, bronchoalveolären Lavagen (BAL), aber auch weiteren Gewebsflüssigkeiten, werden die verschiedenen Immunzellen und Subpopulationen in ihrer Entwicklung, ihren Mengenverhältnissen und ihrem Aktivierungszustand gemessen.

**Ausbildung, Lehrverpflichtungen, Kongress**

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

Bereits zum dreizehnten Mal fand vom 6. bis 9. April 2019 das international ausgeschriebene World Immune Regulation Meeting (WIRM) im Kongresszentrum Davos statt. Rund 600 Wissenschaftler aus 40 verschiedenen Länder trafen sich zu diesem Kongress, um sich über die neuesten Erkenntnisse in der Immunologie auszutauschen und trugen 120 Vorträge und 232 Abstracts vor. Tagsüber nahmen die Teilnehmer an hochkarätigen wissenschaftlichen Vorträgen teil. Die Abende im Kongresszentrum waren reserviert, um wissenschaftliche Projekte in Form einer Posterausstellung zu präsentieren. Der Kongress und weitere SIAF Aktivitäten generieren jährlich etwa 3'000 Übernachtungen in den Davoser Hotels und Ferienwohnungen.

**Finanzielle Grundlage**

Die Ausgaben und der finanzielle Ertrag des SIAF haben sich im Vergleich zu den vergangenen Jahren nur unwesentlich verändert. Eine Grundfinanzierung des Instituts ist durch die Hauptsponsoren gegenwärtig sichergestellt. Sie besteht vor allem aus einem Beitrag des Bundes (Forschungsförderungsgesetz Art. 15), Beiträge des Kantons Graubünden, der Gemeinde Davos und der Universität Zürich. Die zusätzlichen Ausgaben wurden aus Erträgen von zusätzlichen kompetitiv eingeworbenen Drittmitteln, dem Schweizerischen Nationalfonds, verschiedenen EU-Projekten und des WIRM-Kongresses gedeckt.

**Dank**

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

Ganz besonderer Dank gebührt dem inzwischen leider verstorbenen Herr Prof. Dr. Dr. H. Batliner und der Hans Gröber Stiftung für ihre äussert grosszügige Spende für die Modernisierung unserer Labore.

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

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

Davos, Mai 2020

# Report of the director

*Prof. Dr. med. Cezmi A. Akdis*

The Swiss Institute for Allergy and Asthma Research (SIAF) was founded in 1988 in its present form by the Medical Department of the Swiss Research Institute for High Altitude Climate and Medicine Davos (SFI). Since 1996, the institute has been affiliated with the University of Zurich and since 2008 it is a member of the Life Science Zurich Graduate School, a joint post graduate education project of the University of Zurich and the ETH Zurich. Furthermore, the SIAF is an active member of the Academia Raetica and the Graduate School of the Canton of Grisons.

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

Research at the SIAF focuses on patient-relevant translational research and the study of the immunological basis of allergic and asthmatic diseases, which provides a starting point for new preventative and curative treatments in favor of those affected. The SIAF is also increasing its commitment to personalized medicine projects to develop treatment approaches that are better tailored to each patient and that take greater account of each patient's individual symptom severity. The research in SIAF has been designed for direct cooperation with the clinics in Davos, the University of Zurich and other specialized institutes. The SIAF is also involved in the European Network of National Competence Centers (GA2LEN: Global Allergy and Asthma European Network of Excellence), the European Academy of Allergology and Clinical Immunology (EAACI) and the American Academy of Allergy, Asthma and Immunology (AAAAI). The EAACI is the world's largest academy for allergic diseases and plays an important role in science, education, communication and public relations. The collaboration with University of Stanford (Sean Parker Asthma and Allergy Center) is working intensively and several projects.

The SIAF has published over 1'320 research articles and is one of the most cited institutions of its size worldwide. The articles published by the SIAF have been cited 53'700 times. The institute with its approximately 45-50 employees is one of the best in terms of number of employees or citation divided by budget worldwide. In recent years, a significant increase in the number of citations has been achieved as an internationally renowned training center for doctoral students and post-doctoral candidates who join SIAF groups with their own country or institutional stipends.

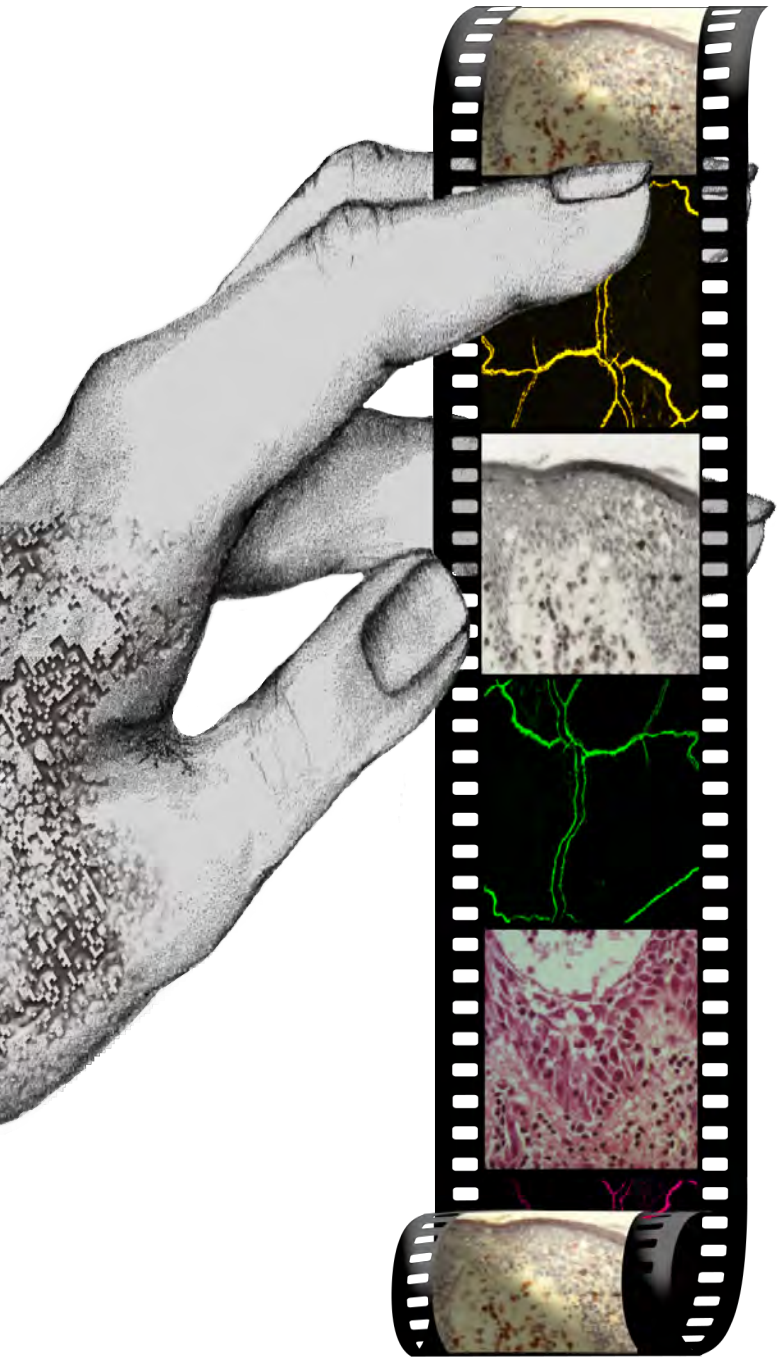
In 2019, 84 scientific papers were published in peer-reviewed international journals with "Impact Factor" or are still in print. The SIAF achieved a total value of the impact factor of 606.373 and an average of 7.2 points per publication. The latest results were also communicated in 26 abstracts at various symposia. Our employees were invited to 62 different seminars and lectures at national and international congresses. SIAF co-workers chaired 27 different international sessions. In addition, 35 scientific posts in international organizations are being occupied by scientists of the SIAF. Furthermore, the SIAF researchers are members of the editorial committees of a total of 16 international journals. In addition, Prof. C. A. Akdis holds the position of Editor-in-Chief of the Allergy journal.

The SIAF and the Christine-Kühne Center for Allergy Research and Education (CK-CARE) in Davos-Wolfgang each play an internationally leading role in their respective fields. The Hochgebirgsklinik Davos (HGK) was realigned under a new operating concept with the aim of becoming one of the leading clinics in the allergy, not least thanks to the proximity of the research. The new campus building in Davos Wolfgang has 3'136 m2 of laboratory and office space. Today the building is completed with extremely front laboratories and equipment including a biosafety level 3 lab. SIAF was able to run its research activities from the beginning of August 2019 on.
Thanks to the support of CK-CARE, more than 50 scientific staff have been recruited since 2009 and 76 academic guests have joined the exchange fellowship program. 208 publications were published in high impact journals.

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

**Discovery of Novel B cell subsets**
The function of B cells has long been thought to be limited to the generation of immunoglobulin-producing plasma cells. However, B cells can exert a more diverse range of immune-effector and regulatory functions. Distinct functional B cell subsets have been identified based on their cytokine production profiles. Immunosuppressive B regulatory (reg) cells and other potential B cell subsets such as B effector (Be) 1 and Be2 cells, as well as IL-17-producing B cells have been reported. Angiogenesis is an essential physiological process that occurs during embryogenesis, normal tissue development and repair after injury. Through a controlled series of events, angiogenesis allows new vessels to grow from pre-existing vessels in order to meet the physiological needs of tissues. A novel subset of Angiogenetic B cells have been disovered i SIAF Angiogenesis also plays a role in tumor growth and is involved in tissue remodeling in chronic inflammatory conditions such as asthma and eosinophilic esophagitis (EoE). A wide range of secreted molecules promotes this process through direct interaction with vascular endothelial cells. These include vascular endothelial growth factors (VGF, VEGF), fibroblast growth factors (FGF), platelet-derived growth factors (PDGF), hepatocyte growth factors, axon guidance factors and angiopoietins.

**DAViS Center (Center for Data Analytics, Visualization and Simulation)in action**
The DAViS Center has been established in 2019 at Fachhochschule Graubünden (FHGR) in Chur with SIAF as primary partner to implement the research strategy of canton Graubünden in profile field “Computational Science”. The first joint Life Science project in



which we attempt to use novel computational methods to identify features that are responsible for the development and the increasing prevalence of allergic diseases is MLM-SOS-ALL. The data in this project are transcript sequencing data, which were previously acquired for 150 children in the SOS-ALL study in a consortium consisting of SIAF, the University of Cape Town, the Children's Hospital in Zurich and the Department of Dermatology at the University Hospital Zurich, as well as extensive questionnaire data on the living and health situation of the children. Through the high volume of the sequencing data, the biostatistical analyses were performed in parallel to building up the required infrastructure and hardware. Further analyses with different approaches including Machine Learning methods are currently implemented in close collaboration, and the results are evaluated for their biomedical relevance.

**Immunometabolism in allergy and immune tolerance: multiomics approach. In search of novel mechanisms and biomarkers of allergen-specific immunotherapy**

Allergic immune response in T cells is characterized, among others, by increased secretion of pro-inflammatory mediators by Th2 effector cells. The main suppressors of this response are allergen-specific regulatory T cells (Tregs) as demonstrated in the steady state and in allergen-specific immunotherapy (AIT). Little is known about the metabolic requirements of allergen-specific and non-specific effector T cells and Tregs to carry out their functions in vivo. The aim of our studies is to identify essential metabolic pathways for regulatory and effector populations of allergen-specific and non-specific memory T cells in vivo in humans, their potential alterations in allergic disease, as well as their changes during allergen-specific immunotherapy. Allergen-specific T and Treg cells in allergic patients display profound gene and protein downregulation of immune response and cell activation pathways except type 2 immunity, TCR signaling, fatty acid and prostaglandin metabolism. Plasma and nasal untargeted and targeted proteome reflect specific cellular signature with upregulation of proteins leading to lymphocyte proliferation, T cell differentiation and fatty acid metabolism and downregulation of several anti-inflammatory pathways. Remarkably, AIT induces significant changes in previously dysregulated immune and metabolic pathways and leads to induction of tolerance programs in allergenspecific CD4+ T cells and Treg cells. However, allergen-specific Treg cells in non-responders to AIT still displayed aberrant type 2 gene, protein and metabolic profiles, coupled with the corresponding plasma and nasal inflammatory milieu, in parallel to functional impairment of their suppressive capacities. Altogether, our data suggest that in allergy there is a systemic and local aberration of immune and metabolic signaling, leading to dysfunctional metabolic reprogramming and subsequent functional impairment of allergenspecific effector and regulatory T cells.

**The Epithelial Barrier Hypothesis for the Development of Allergic, Autoimmune and other Microinflammatory Diseases**

One of the major contributions of SIAF was the proposal of the Epithelial Barrier Hypothesis that explains the Development of Allergic, Autoimmune and other Microinflammatory Diseases. Our "epithelial barrier hypothesis" explains the origins of chronic noncommunicable diseases, which have reached epidemic proportions during the last few decades. With more than 20 publications we reported

that there is a defective epithelial barrier of the affected tissues has been demonstrated in asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, eosinophilic esophagitis, and inflammatory bowel disease. In addition, to barrrier leakiness in skin and respiratory tract leakiness of the gut epithelium has been demonstrated. Evidence is developing that it can be linked to many other diseases with autoimmune and microinflammation etiology, such as diabetes, multiple sclerosis, systemic lupus erythematosus, celiac disease, hepatitis, Parkinson's disease, and autism spectrum disorder. We have demonstrated with many studies and now propose that epithelial barrier hypothesis describes defects in skin and mucosal tissue barriers caused by exposure to barrier damaging agents that are linked to industrialization, urbanization and modern life. As a major mechanism a leaky epithelial barrier initiates the translocation of the microbiome from the surface of affected tissues to interepithelial and even deeper subepithelial areas. In such affected tissues such as skin, lung and gut with a defective epithelial barrier, colonization of opportunistic pathogens, decreased biodiversity in the microbiota, dysregulated subepithelial immune response, local inflammation, and incorrect regeneration and remodelling takes place. Migration of inflamed cells to other affected tissues, and systemic low-level immune activation and microinflammation are additional players in the development and exacerbation of many chronic inflammatory diseases.This research area will be the main stream of future research throughout the whole world in the next decade to discover novel treatment and prevention modalities.

**Clinical service**

The SIAF offers to Davos and all other interested clinics and practicing physicians special cellular immunological diagnosis. By means of the flow cytometric analysis of blood, bronchoalveolar lavage (BAL), but also other tissue fluids, the different immune cells and subpopulations are measured in their development, their proportions and their activation state.

**Education, teaching, congresses**

An important task has been fulfilled by the SIAF in the education of PhD students as well as in postgraduate studies. At the same time, the SIAF fulfills teaching obligations at the University of Zurich. These consist of various lecture courses within the framework of biochemistry at the Biochemical Institute. Prof. C. A. Akdis is a faculty member of the Medical Faculty of the University of Zurich with promotion rights in the Faculty of Mathematics and Natural Sciences and honorary professor at the Bezmialem University of Istanbul. Prof. C. A. Akdis and Prof. M. Akdis also hold an honorary professorship at the Tungren Hospital of Beijing University.

From 6 to 9 April 2019, the internationally reknown World Immune Regulation Meeting (WIRM) took place for the thirteenth time in the Davos Congress Center. Around 600 scientists from 40 different countries came to this congress to discuss the latest findings in immunology and delivered 120 lectures and 232 abstracts. During the day participants took part in top-class scientific lectures. The evenings in the congress center were reserved to present scientific projects in the form of a poster exhibition. The congress and other SIAF activities generate around 3,000 overnight stays each year in the Davos hotels and holiday apartments.

**Financial basis**

The expenditures and the financial return of the SIAF have changed only insignificantly compared to the past years. A basic funding of the institute is currently ensured by the main sponsors. It mainly consists of a federal contribution (Forschungsförderungsgesetz Art. 15), contributions from the canton of Graubünden, the municipality of Davos and the University of Zurich. The additional expenses were covered by additional competitive third-party funding, the Swiss National Science Foundation, several EU projects and the WIRM Congress.

**Acknowledgements**

I cordially thank all our employees for the great work and the good working atmosphere in the SIAF. At the same time, I would like to thank the Davos-based clinics, their chief physicians and their employees. I am extremely honored with our continuous collaboration with the University of Zurich for the immense support of our institute.

A very special thank you goes to the sadly and regretfully deceased Prof. Dr. Dr. H. Batliner and the Hans Gröber foundation for their tremendous sponsorship for the modernization of our labs.

In particular, I would like to emphasize here our fruitful collaboration with CK-CARE, which enables patient-oriented atopic dermatitis research in our institute. I would particularly like to thank Ms. and Mr. Kühne for their support, which enables our research to find sustainable solutions for better diagnosis and treatment of atopic dermatitis patients. Thanks to this support, many master's degrees and PhD titles have been obtained at the institute and in Davos.

My thanks go especially to the Foundation Swiss Research Institute for Mountain Climate and Medicine (SFI), its Foundation Council and Foundation Committee for the continuous support. Finally, I would like to thank the authorities in Cantonal and Davos institutions, who tirelessly support SIAF in every respect.

Davos, May 2020

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## Cellular Allergy / Immunology

*Prof. Dr. Cezmi A. Akdis, MD*


**The Epithelial Barrier Hypothesis for the Development of Allergic, Autoimmune and other Microinflammatory Diseases**

With an epidemic rise during the last 60 years, allergic and autoimmune diseases of the skin, mucosas and deep tissues are affecting more than one billion people worldwide. These diseases are more common in industrialized countries and their prevalence continues to rise in developing countries in parallel to urbanization and industrialization. Intact skin and mucosal barriers are crucial for the maintenance of tissue homeostasis as they protect host tissues from infections, environmental toxins, pollutants and allergens. A defective epithelial barrier of the affected tissues has been demonstrated in asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, eosinophilic esophagitis, and inflammatory bowel disease. In addition, leakiness of the gut epithelium has been proposed in many other diseases with autoimmune and microinflammation etiology, such as diabetes, multiple sclerosis, systemic lupus erythematosus, celiac disease, hepatitis, Parkinson's disease, and autism spectrum disorder. The "epithelial barrier hypothesis" proposed here explains the origins of chronic noncommunicable diseases, which have reached epidemic proportions during the last few decades is presented. The epithelial barrier hypothesis describes defects in skin and mucosal tissue barriers caused by exposure to barrier damaging agents that are linked to industrialization, urbanization and modern life. A leaky epithelial barrier initiates the translocation of the microbiome from the surface of affected tissues to interepithelial and even deeper subepithelial areas. In tissues with a defective epithelial barrier, colonization of opportunistic pathogens, decreased biodiversity in the microbiota, dysregulated subepithelial immune response, local inflammation, and incorrect regeneration and remodelling takes place. Migration of inflamed cells to other affected tissues, and systemic low-level immune activation and microinflammation are additional players in the development and exacerbation of many chronic inflammatory diseases.

There is currently substantial data showing that allergens, such as dust mites, certain bacteria, fungus, viruses, laundry and dishwasher detergents, household cleaners, surfactants, enzymes and emulsifiers in processed food, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles and microplastic damage the epithelial barrier. The majority of these factors have entered human life in parallel to industrialization, urbanization and modernization. Within all of these substances, one of the most overwhelmingly exposed toxic one to epithelium are detergents and household cleaning substances. Increased usage of detergents in general and the addition of surfactants to commercial detergents has significantly increased the daily exposure of the public to tissue barrier damaging substances. An additional burden to epithelial barrier was the introduction of proteolytic enzymes in washing powders in the mid-1960s to improve their cleaning efficiency. Numerous studies demonstrated epidemiological evidence relating to the development of asthma and AD to direct detergent exposure. Household cleaning products and medical disinfectants have been among the most common irritants associated with asthma. Occupational asthma was demonstrated in epidemic proportions in detergent factories. Asthma in domestic cleaning workers was associated with exposure to bleaches and detergents. Occupational asthma and eczema were reported in household cleaners. Occupational asthma and rhinitis were caused by exposure to detergent enzymes, such as Bacillus subtilis toxin, amylase, lipase, and cellulase. A systematic review of epidemiological studies showed an association between exposure to cleaning products and asthma in four cross-sectional, longitudinal and case-control studies. Occupational allergies and asthma in the detergent industry have significantly decreased by adopting extensive measures and development of best practice guidelines focused on exposure control in production facilities. There has been extensive research on replacing nonbiodegradable products with more environmentally friendly and safer alternatives. However, daily exposure to tissue barrier destructing doses of laundry detergents and household cleaners continues today with the addition of household dishwashers and professional dishwashers.

The epithelial barrier damage caused by laundry detergents on human skin and bronchial epithelial cells has been recently reported in two studies. Even at high dilutions, exposure to laundry detergents disrupted the epithelial barrier function of human skin and bronchial epithelial cells. RNA sequence transcriptome of 1 to 50,000 times diluted laundry detergent-exposed bronchial epithelial cells demonstrated upregulated genes of lipid metabolism, oxidative stress and cell survival, downregulated genes of cell adhesion, extracellular matrix organization, and wound healing together with increased IL-33 expression. The two major surfactants, sodium dodecylsulfate and sodium dodecylbenzenesulphonate that are commonly used in laundry detergents, soaps, shampoos and many household cleaning products, injured the TJ barrier of the lung and skin epithelium in extremely high dilutions, such as 1 to 100,000. Post-rinse fluid collected at the end of the laundry from towels and clothes still contained active detergents and surfactants that can hamper the epithelial TJ barrier.

A better understanding of the barrier hypothesis is needed for the prevention, early intervention, and development of novel therapeutic approaches. Possible strategies to reduce diseases associated with a disrupted epithelial barrier include: avoidance and dose control of all of the above mentioned products; development of safer, less-toxic products; discovery of biomarkers for the identification of barrier leaky subjects; development of novel therapeutic approaches for tightening the tissue-specific barrier molecules; strengthe-

ning other components of the mucosal barrier; blocking bacterial translocation; avoiding the colonization of opportunistic pathogens; interventions through diet and microbiome, and many more novel approaches.

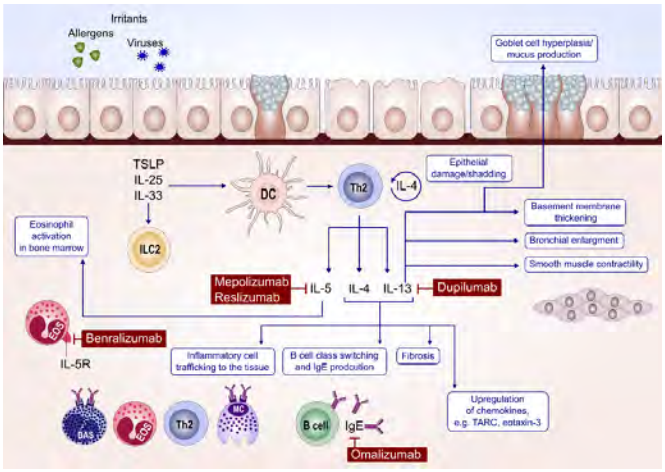



*Figure 1. Overview of currently used biologics in asthma and their molecular targets. Mepolizumab and reslizumab are anti-IL-5 antibodies. Benralizumab binds to the α chain of IL-5 receptor α. Omalizumab is an antibody against IgE. Dupilumab binds to the alpha subunit of the interleukin-4 receptor. Allergy 2020, Akdis et al.*

### Type 2 immunity in the skin and lungs

Akdis CA, Arkwright PD, Brüggen MC, Busse W, Gadina M, Guttman-Yassky E, Kabashima K, Mitamura Y, Vian L, Wu J, Palomares O. Allergy 2020

There has been extensive progress in understanding the cellular and molecular mechanisms of inflammation and immune regulation in allergic diseases of the skin and lungs during the last few years. Asthma and atopic dermatitis are typical diseases of type 2-immune responses. IL-25, IL-33 and TSLP are essential cytokines of epithelial cell that activation by allergens, pollutants, viruses, bacteria and toxins that derive type 2 responses. Th2 cells and innate lymphoid cells produce and secrete type 2 cytokines such as interleukin (IL)-4, IL-5, IL-9 and IL-13. IL-4 and IL-13 activate B cells to class switch to IgE and also play a role in T cell and eosinophil migration to allergic inflammatory tissues. IL-13 contributes to maturation, activation, nitric oxide production and differentiation of epithelia, production of mucus as well as smooth muscle contraction and extracellular matrix generation. IL-4 and IL-13 open tight junction barrier and cause barrier leakiness in the skin and lungs. IL-5 acts on activation, recruitment and survival of eosinophils. IL-9 contributes to general allergic phenotype by enhancing all of the aspects, such as IgE and eosinophilia. Type 2 innate lymphoid cells (ILC) contribute to inflammation in atopic dermatitis and asthma by enhancing the activity of Th2 cells, eosinophils and their cytokines. Currently five biologics are licensed to suppress type 2 inflammation via IgE, IL-5 and its receptor and IL-4 receptor alpha. Some patients with severe atopic disease have little evidence of type 2 hyperactivity and do not respond to biologics which target this pathway. Studies in responder and non-responder patients demonstrate the complexity of these diseases. In addition, primary immune deficiency diseases related to T cell maturation, regulatory T cell development, T cell signaling, such as Omenn syndrome, severe combined immune deficiencies, IPEX syndrome, DOCK8, STAT3 and CARD11 deficiencies help in our understanding of the importance and redundancy of various type 2 immune components. The present review aims to highlight recent advances in type 2 immunity and discuss the cellular sources, targets, and roles of type 2 mechanisms in asthma and atopic dermatitis.

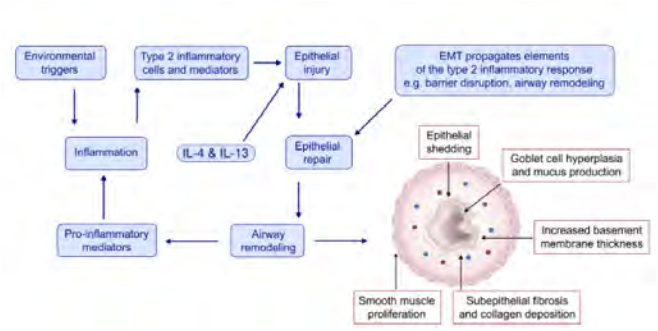



*Figure 2. The vicious cycle in the pathogenesis of type 2 inflamation. Exposure to environmental triggers can lead to airway damage and induce alarmin (IL-25, IL-33, TSLP) production, followed by type 2 inflammation. Impaired airway and its repair may go on to develop tissue remodeling and sustained inflammation. Increased activation of the epithelium leads to signaling to inflammatory cells and also activation of the underlying mesenchymal cells, such as smooth muscle cells and fibroblasts. It leads the epithelial-mesenchymal transition (EMT) propagation. Both structural and inflammatory cell produce growth factors, such as transforming growth factor (TGF)-superfamily, vascular endothelial growth factor (VEGF) and interleukin (IL)-13. Progressive structural changes include proliferation of fibroblasts and airway smooth muscle and vascular remodeling together with excessive and dysregulated extracellular matrix (ECM) deposition, which may lead to an airway hyperresponsiveness and airway obstruction. In turn, the pro-inflammatory environment generated by airway remodeling sustains the inflammatory response.*

### Skin barrier damage after exposure to paraphenylenediamine

Meisser SS, Altunbulakli C, Bandier J, Opstrup MS, Castro-Giner F, Akdis M, Bonefeld CM, Johansen JD, Akdis CA.

J Allergy Clin Immunol. 2019

P-Phenylenediamine (PPD) is a strong contact allergen used in hair dye that is known to cause allergic contact dermatitis (ACD). Both private and occupational exposure to PPD is frequent, but the effect of PPD exposure in nonallergic occupationally exposed subjects is unknown. We sought to investigate the effects of PPD exposure on the skin of occupationally exposed subjects with and without clinical symptoms. Skin biopsy specimens were collected from 4 patients with mild and 5 patients with severe PPD-related ACD and 7 hairdressers without contact dermatitis on day 4 after patch testing with 1% PPD in petrolatum. RNA sequencing and transcriptomics analyses were performed and confirmed by using quantitative RT-PCR. Protein expression was analyzed in skin from 4 hairdressers and 1 patient with ACD by using immunofluorescence staining. Reconstructed human epidermis was used to test the effects of PPD in vitro. RNA sequencing demonstrated downregulation of

tight junction and stratum corneum proteins in the skin of patients with severe ACD after PPD exposure. Claudin-1 (CLDN-1), CLDN8, CLDN11, CXADR-like membrane protein (CLMP), occludin (OCLN), membrane-associated guanylate kinase inverted 1 (MAGI1), and MAGI2 mRNA expression was downregulated in patients with severe ACD. CLDN1 and CLMP expression were downregulated in nonresponding hairdressers and patients with mild ACD. Filaggrin 1 (FLG1), FLG2, and loricrin (LOR) expression were downregulated in patients with ACD. Confocal microscopic images showed downregulation of CLDN-1, FLG-1, and FLG-2 expression. In contrast, 3-dimensional skin cultures showed upregulation of FLG-1 in response to PPD but downregulation of FLG-2. In conclusion, PPD-exposed skin is associated with extensive transcriptomic changes, including downregulation of tight junction and stratum corneum proteins, even in the absence of clinical symptoms.

**Particulate Matter 2.5 Causes Deficiency in Barrier Integrity in Human Nasal Epithelial Cells**

Xian M, Ma S, Wang K, Lou H, Wang Y, Zhang L, Wang C, Akdis CA.

Allergy Asthma Immunol Res. 2019

The effect of air pollution-related particulate matter (PM) on epithelial barrier function and tight junction (TJ) expression in human nasal mucosa has not been studied to date. This study therefore aimed to assess the direct impact of PM with an aerodynamic diameter less than 2.5 μ (PM2.5) on the barrier function and TJ molecular expression of human nasal epithelial cells. Air-liquid interface cultures were established with epithelial cells derived from noninflammatory nasal mucosal tissue collected from patients undergoing paranasal sinus surgery. Confluent cultures were exposed to 50 or 100 μg/mL PM2.5 for up to 72 hours, and assessed for 1) epithelial barrier integrity as measured by transepithelial resistance (TER) and permeability of fluorescein isothiocyanate (FITC) 4 kDa; 2) expression of TJs using real-time quantitative polymerase chain reaction and immunofluorescence staining, and 3) proinflammatory cytokines by luminometric bead array or enzyme-linked immunosorbent assay. Compared to control medium, 50 and/or 100 μg/mL PM2.5-treatment 1) significantly decreased TER and increased FITC permeability, which could not be restored by budesonide pretreatment; 2) significantly decreased the expression of claudin-1 messenger RNA, claudin-1, occludin and ZO-1 protein; and 3) significantly increased production of the cytokines interleukin-8, TIMP metallopeptidase inhibitor 1 and thymic stromal lymphopoietin. In coclusion, exposure to PM2.5 may lead to loss of barrier function in human nasal epithelium through decreased expression of TJ proteins and increased release of proinflammatory cytokines. These results suggest an important mechanism of susceptibility to rhinitis and rhinosinusitis in highly PM2.5-polluted areas.

**Human type 2 innate lymphoid cells disrupt skin keratinocyte tight junction barrier by IL-13**

Sugita K, Altunbulakli C, Morita H, Sugita A, Kubo T, Kimura R, Goto H, Yamamoto O, Rückert B, Akdis M, Akdis CA.

Allergy. 2019 Dec;74(12):2534-2537.

The largest organ of the human body is the epidermis, which consists mainly of keratinocytes (KCs) and serves as a physical barrier. Along with the stratum corneum, which is the outer surface of the epidermis, the tight junctions (TJs) located in the skin surface side of stratum granulosum are crucial for the integrity and function of the epidermal barrier. TJs form a network of molecules that ensures a nonpermeable intercellular adhesion and seal the paracellular space in the epithelium, thus protecting the body from the penetration of invading microorganisms, pollutants, environmental toxins, and allergens. Accordingly, skin KC TJ barrier dysfunctions permit the penetration of antigens, allergens, toxins, and pollutants through the surface of the epidermis to dermis and subdermal connective and fat tissues. Recent evidence suggests that TJ barrier dysfunction plays a key role not only in atopic dermatitis but also in asthma, allergic rhinitis, chronic rhinosinusitis, and colitis. In a recent study we demonstrated that ILC2s decreased trans epithelial resistance after coculture with human NHEKs and increased the paracellular permeability, suggesting a major role for ILCs.

**Induction of Human Regulatory Innate Lymphoid Cells From Group 2 Innate Lymphoid Cells by Retinoic Acid**

Hideaki Morita, Terufumi Kubo, Beate Rückert, Avinash Ravindran, Michael B Soyka, Arturo Ottavio Rinaldi, Kazunari Sugita, Marcin Wawrzyniak, Paulina Wawrzyniak, Kenichiro Motomura, Masato Tamari, Keisuke Orimo, Naoko Okada, Ken Arae, Kyoko Saito, Can Altunbulakli, Francesc Castro-Giner, Ge Tan, Avidan Neumann, Katsuko Sudo, Liam O'Mahony, Kenya Honda, Susumu Nakae, Hirohisa Saito, Jenny Mjösberg, Gunnar Nilsson, Kenji Matsumoto, Mübeccel Akdis, Cezmi A Akdis

J Allergy Clin Immunol. 2019 Jun;143(6):2190-2201.

Group 2 innate lymphoid cells (ILC2s) play critical roles in induction and exacerbation of allergic airway inflammation. Thus clarification of the mechanisms that underlie regulation of ILC2 activation has received significant attention. Although innate lymphoid cells are divided into 3 major subsets that mirror helper effector T-cell subsets, counterpart subsets of regulatory T cells have not been well characterized. We sought to determine the factors that induce regulatory innate lymphoid cells (ILCregs). IL-10+ ILCregs induced from ILC2s by using retinoic acid (RA) were analyzed with RNA-sequencing and flow cytometry. ILCregs were evaluated in human nasal tissue from healthy subjects and patients with chronic rhinosinusitis with nasal polyps and lung tissue from house dust mite- or saline-treated mice. We demonstrated that RA induced IL-10 secretion by human ILC2s but not type 2 cytokines. IL-10+ ILCregs, which were converted from ILC2s by means of RA stimulation, expressed a regulatory T cell-like signature with expression of IL-10, cytotoxic T lymphocyte-associated protein 4, and CD25, with downregulated effector type 2-related markers, such as chemoattractant receptor-homologous molecule on TH2 cells and ST2, and suppressed activation of CD4+ T cells and ILC2s. ILCregs were rarely detected in human nasal tissue from healthy subjects or lung tissue from saline-treated mice, but numbers were increased in nasal tissue from patients with chronic rhinosinusitis with nasal polyps and in lung tissue from house dust mite-treated mice. Enzymes for RA synthesis were upregulated in airway epithelial cells during type 2 inflammation in

vivo and by IL-13 in vitro. In conclusion we have identified a unique immune regulatory and anti-inflammatory pathway by which RA converts ILC2s to ILCregs. Interactions between airway epithelial cells and ILC2s play an important roles in the generation of ILCregs.

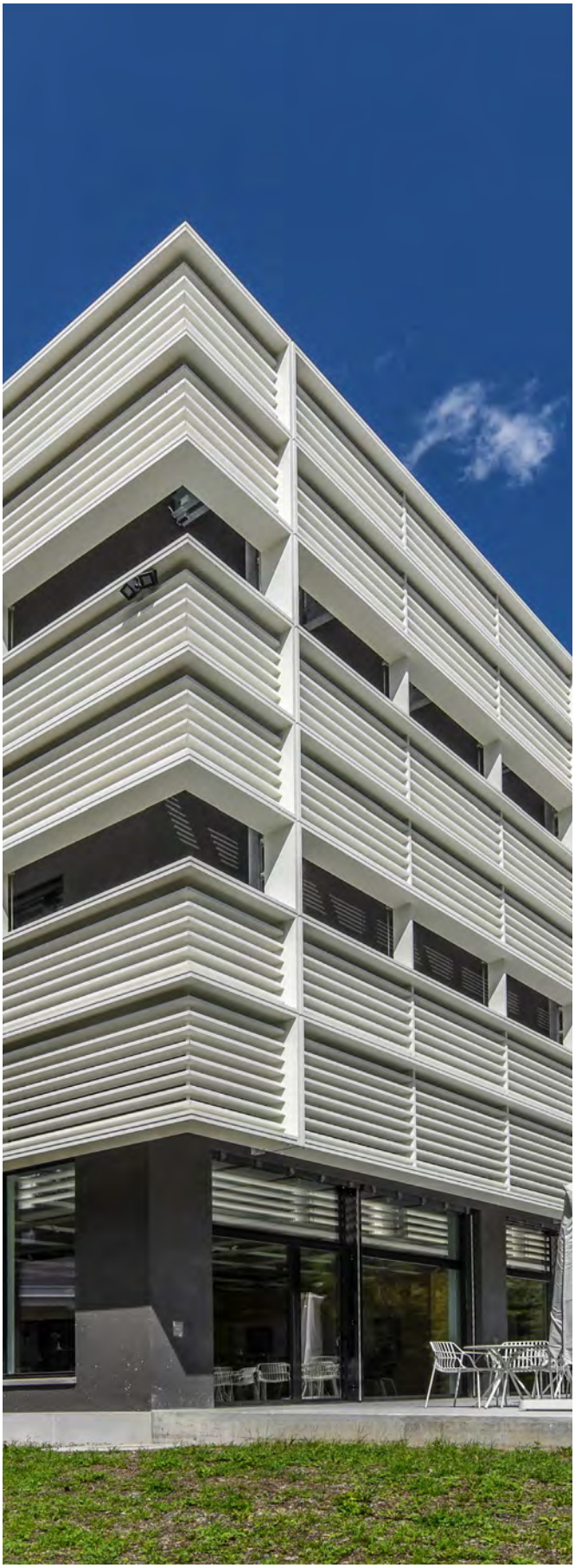
**Gene Expression Signatures of Circulating Human Type 1, 2, and 3 Innate Lymphoid Cells**

Shuo Li , Hideaki Morita , Milena Sokolowska , Ge Tan, Tadech Boonpiyathad, Lennart Opitz, Keisuke Orimo, Stuart K Archer, Kirstin Jansen, Mimi L K Tang, Damian Purcell, Magdalena Plebanski, Cezmi A Akdis

J Allergy Clin Immunol. 2019 Jun;143(6):2321-2325.

Innate lymphoid cells (ILCs) are a functionally and phenotyp-ically heterologous group of small lymphocytes that lackconventional linage markers but can become potent effector cellsupon appropriate stimulations thereby producing large amountsof cytokines. Some examples of ILCs include natural killer (NK)cells, lymphoid tissue-inducer cells, and helper-like ILCs. Thisstudy focuses on the helper-like ILCs. Although geneexpression profiles of ILCs have been studied in tissues, such ashuman tonsils, only limited information is available on humancirculating ILCs. Tissue-resident ILCs could be quite different from the ILCs in blood. To understand the distinct functions of the type 1, 2 and 3 ILC subsets, it is necessary to delineate both the overlapping and unique functional signatures of these cells.In this study we present one of the first whole-genome gene expressionstudies of the 3 ILC subsets from peripheral blood of healthy donors. In this study, we identified novel gene signatures of the 3 different ILC subsets, which might be further developed into ILC biomarkers. We also provide evidence for abnormal TCR expression in ILCs, which suggests a potentially new developmental link between ILCs and T cells.

Davos, May 2020



## Immune Regulation

*Prof. Dr. Mübeccel Akdis, MD, PhD*


### Novel B cell subsets

The function of B cells has long been thought to be limited to the generation of immunoglobulin-producing plasma cells. However, B cells can exert a more diverse range of immune-effector and regulatory functions. Distinct functional B cell subsets have been identified based on their cytokine production profiles. Immunosuppressive B regulatory (reg) cells and other potential B cell subsets such as B effector (Be) 1 and Be2 cells, as well as IL-17-producing B cells have been reported. Angiogenesis is an essential physiological process that occurs during embryogenesis, normal tissue development and repair after injury. Through a controlled series of events, angiogenesis allows new vessels to grow from pre-existing vessels in order to meet the physiological needs of tissues (Figure 1).

### A subset of B cells promotes angiogenesis

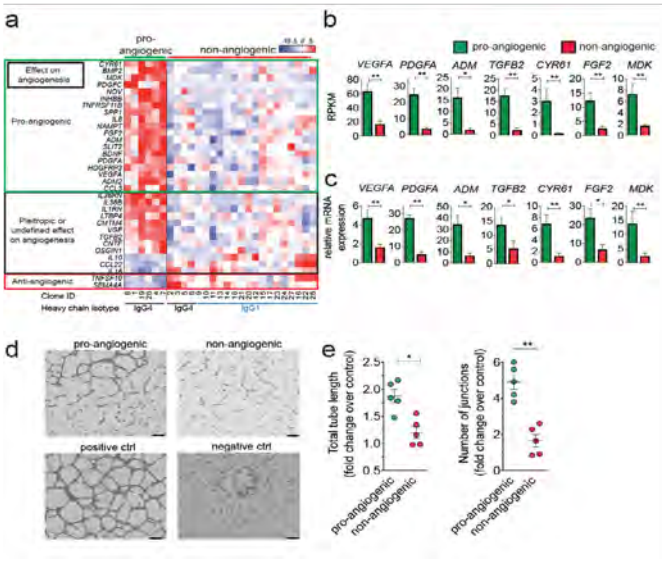



*Figure 1: A subset of B cells promotes angiogenesis. (a) Heat map showing gene-scaled (z-score) log2 normalized counts of cytokine-encoding genes that are differentially expressed between pro-angiogenic B and non-angiogenic B cell clones. (b) Reads Per Kilobase Million (RPKM) expression values from NGS data. (c) RT-qPCR gene expression after prolonged (> 3 weeks) in vitro expansion of pro-angiogenic (n=5) and non-angiogenic (n=5) clones. (d) Representative images of HUVEC tube formation assay to quantify pro-angiogenic effect of B cell clones e) Quantitative analysis of rate of HUVEC tube formation induced by supernatants of pro- and non-angiogenic B cell clones (mean +/- SEM). * P<0.05, ** P<0.01 Mann-Whitney test.*

Angiogenesis also plays a role in tumor growth and is involved in tissue remodeling in chronic inflammatory conditions such as asthma and eosinophilic esophagitis (EoE).

A wide range of secreted molecules promotes this process through direct interaction with vascular endothelial cells. These include vascular endothelial growth factors (VGF, VEGF), fibroblast growth factors (FGF), platelet-derived growth factors (PDGF), hepatocyte growth factors, axon guidance factors and angiopoietins. Other factors including cysteine-rich angiogenic inducer 61 (CYR61), andromedullin (ADM), midkine (MDK) have also been reported to promote angiogenesis. Free adenosine also promotes angiogenesis both through its direct mitogenic effects on endothelial cells as well as through induction of pro-angiogenic factors such as VEGF, IL- 8 and FGF from vascular and immune cells. Extracellular ATP levels are significantly elevated in inflamed and hypoxic tissues. This extracellular ATP can rapidly be hydrolized by ecto-nucleotidases. CD39 is an ecto-nucleoside triphosphate diphosphohydrolase and is the rate-limiting enzyme in the conversion of ATP and ADP into AMP. AMP is then converted to adenosine by ecto-5'-nucleotidase (NT5E), also known as CD73. CD39 is expressed on most peripheral (>90%) B cells and monocytes, and can be expressed on a subset of CD4+ T cells, cytotoxic T cells and NK cells while CD73 is expressed by 75% of the B cells, and a subset of CD8+ T cells, CD4+ T cells and NK cells. CD49b, also known as integrin subunit alpha 2 (ITGA2) is expressed as a part of the α2β1 integrin duplex on platelets, NK cells, T cells and fibroblasts. α2β1 functions as a collagen receptor. The β1 subunit (CD29) is expressed on the majority of hematopoietic and non-hematopoietic cells. CD49b and LAG3 co-expression has been reported as a signature of type 1 regulatory (Tr1) T cells. IgG4 can be regarded as an anti- inflammatory immunoglobulin isotype, because of its low affinity for binding to Fcγ receptors, its inability to fix complement and its functional monovalency, which results from its rearrangement of immunoglobulin heavy chains by a mechanism called Fab arm exchange. No murine antibody isotype exists that shares these characteristics with human IgG4, therefore mouse models are not suitable to study these immunological mechanisms associated with IgG4. IgG4 appears to play a role in the induction and maintenance of immune tolerance to allergens by blocking allergen-specific IgE and allergen-specific IgG4 antibodies are significantly increased during the course of allergen-specific immunotherapy and in high dose allergen exposed individuals, such as bee keepers and cat owners. We recently identified B cells that express IgG4 and produce pro angiogenic cytokines and have the capacity to promote angiogenesis. We further show that these cells are characterized by the expression of CD49b and CD73 (Figure 2).

### Pro-angiogenic B cells are characterized by expression of CD49b and CD73

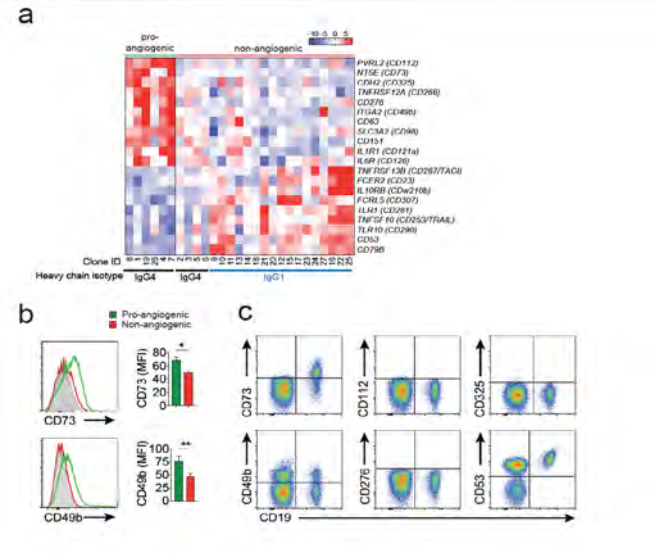



*Figure 2: Pro-angiogenic B cells are characterized by expression of CD49b and CD73. (a) Heat map showing gene-scaled (z-score) log2 normalized counts of CD marker-encoding genes that are differentially expressed between pro-angiogenic B and non-angiogenic B cell clones. (b) Flow cytometry analysis of CD73 and CD49b surface expression on pro-angiogenic (n=5) and non-angiogenic B cell clones (n=20) (c) Flow cytometry analysis of surface expression of CD73 and CD49b on freshly isolated peripheral blood B cells.*

Cells with this phenotype are elevated in circulation of EoE patients as well as melanoma patients and are present in affected tissues. Thus, our findings reveal a potential novel pro-angiogenic B cell subset that is associated with tissue remodeling in chronic inflammatory conditions and tumor angiogenesis.

### Mechanisms of immune tolerance to food allergens in cow's milk: Role of B regulatory cells

Food allergen-specific immunotherapy (food-AIT) is a developing treatment for food allergy. In addition, to reduce the symptoms of disease, food-AIT can change the course of food allergy and provide long-term efficacy by inducing food allergen-specific immune tolerance. Although not fully demonstrated, its mechanisms of action are expected to be similar to other AIT mechanisms, such as pollen and venom allergens, which include mast cell and basophil desensitization, increase in both T and B regulatory cells and decreased food allergen-specific IgE and increased IgG4 antibodies. In addition, decreased numbers and activation of mast cells and eosinophils in the affected tissues has been reported. Memory B cell responses appear to be extremely important, but due to technical limitations, this investigation has not been done so far. Here, we are proposing a novel technology, which will be for the first time used for the in depth characterization of allergen-specific human B cells. Better understanding of the mechanisms is needed in food-AIT to identify, prior to immunotherapy, responder versus non-responder patients; to follow the therapy response of patients during immunotherapy in order to modulate and adapt treatment schemes; to decide when to stop food-AIT with a high degree of confidence.

In this ongoing research, we aim to examine the role of B cells during tolerance induction to milk allergens in healthy individuals comparison to allergic patients. A recently developed technique enables to immortalize antigen-specific B cells and in depth investigate them. The food allergen-specific CD 19+ B cells were sorted by double-labeled allergen technique using the flow cytometry and transduced with a retroviral vector containing GFP, BCL6 and Bcl-xL to immortalize the cells. Both antigen-specific primary and immortalized B cells were analyzed by flow cytometry in terms of surface markers and cytokines. In addition, total RNA was isolated for RNA-seq to perform for transcriptome profiling. After purification of αS1-casein specific B cells and non-specific B cells, we measured the Ag-specific Ig profile to confirm their specificity. Specific IgE, IgG1, and IgG4 production from culture supernatants of αS1-casein positive B cells were significantly elevated compared to αS1-casein negative cells, while total IgE, IgG1, and IgG4 levels were comparable. The in-depth analysis of gene expression showed significantly different αS1-casein-specific B cells of allergic children before and after OIT compared to natural tolerance. The top 200 differentially expressed genes were shared between allergic children before and after OIT and natural tolerance. Within these shared significant genes, we identified roughly 30 tolerance-induced genes display similar gene expression patterns in allergic children after Food-AIT compared to natural tolerance. For examples, gut homing marker genes including CCR6 and CXCR5 are upregulated, immunoregulatory genes including IL10RB and IGHG4 are upregulated, and allergic asthma and atopic dermatitis-related genes including MAPK6, SMC6, DIMT1, CKAP2, AXL, and LHFPL2 are downregulated. After Food-AIT proinflammatory cytokine machinery was shut down and tolerance related genes were upregulated. Our data suggest that allergen-specific B cells in food allergic children compared to natural tolerance display clearly different gene signatures. Approximately 30 tolerance-induced genes were identified (Figure 3).

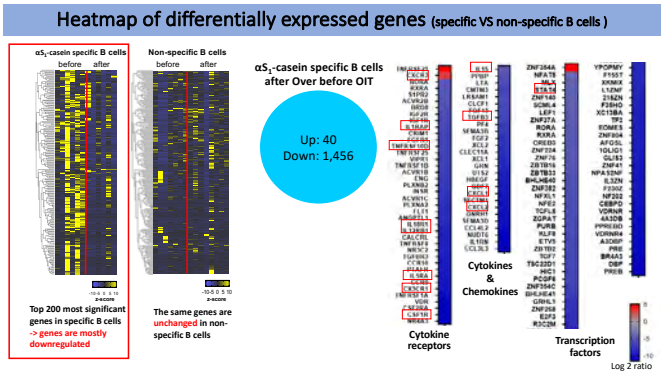



*Figure 3: The heatmap analysis of differentially expressed genes. αS1-casein specific B cells versus to non-specific B cells.*

The in-depth analysis of significant genes was suggesting the cells migrate to gut with the presence of immunoregulatory molecules and regulate the allergy-related genes. The extensive analyses of these antigen-specific B cells will lead us to have more knowledge on different B cell functions and the purification of antigen-specific antibodies for the better understanding of the mechanisms of food allergen specific immunotherapy.

**Breaking of immune tolerance; Role of Rhinovirus infection**

Around 50-70% of upper respiratory tract infections are caused by human rhinoviruses (RV), making them the most common cause of viral induced respiratory diseases and major health care burden. Most adults are infected at least once per year. RV infections are usually not life-threatening for healthy individuals and as much as 30% of infections can be asymptomatic. However, RV infections during early life are strongly associated with the development of asthma during later childhood. In addition, RV infections are the main cause of exacerbations in asthma. Early interferon response is an essential component of antiviral immunity. In asthmatics, higher virus load was seen in airway epithelial cells due to deficient early induction of type-I and type-III interferons (IFN). Increased risk for virus-induced asthma exacerbations could be a direct effect of impaired antiviral immune response found in the context of predominant IgE antibodies and type-2-inflammatory cytokines.

The primary site of RV replication are epithelial cells of the upper and lower respiratory tract. Upon infection, type-I and type-III IFNs and other proinflammatory cytokines such as interleukin-6 (IL-6), IL-8, IL-16 and RANTES are secreted. In response to RV infection of the airways, also phagocytes of the airways produce type-I-IFNs, especially IFN-α. These cytokines initiate an antiviral state in neighboring cells. In asthmatic patients, bronchial epithelial cells and phagocytes such as monocytes and macrophages show a deficient production of type-I and type-III interferons. While decreased early antiviral response seems to result in increased viral load and reduced apoptosis of epithelial cells, the overall effect on cells of the adaptive immune system in the periphery is not completely understood.

In peripheral blood, circulating immune cells are found contributing to all facets of hosts immune responses. Direct interactions of RV with several types of antigen presenting cells (APC) including monocytes, dendritic cells and macrophages were reported. Furthermore, infection of mast cells and T cells was shown, the lesser of which can be transiently infected, activated and produce inflammatory cytokines in response to RV-exposure.

We have previously reported that human B cells can bind, uptake and show proliferation in response to RV stimulation in vitro. B cells are constantly circulating through the body's tissues and are also present at the mucosal sites of the respiratory tract. B cell-mediated humoral immune response plays an important role in controlling RV infections. In addition, a crucial role for the transport of different lung-derived antigens to secondary lymphoid organs was proposed. Neutralizing serum IgG as well as secretory IgA in the mucosa can be detected one to two weeks after infection and can prevent re-infection with the same strain. Asthmatics tend to produce high concentrations of non-neutralizing antibodies in response to rhinovirus infection with levels that correlate to disease severity and may not be protective from reinfection. However, it is not well understood how the local inflammatory environment in the RV infected airway tissue can influence migrating B cells before they recirculate to the periphery. Also, it is not clear to which extend direct virus contact or inflammatory cytokine environment modulate B cell-mediated immune responses upon RV infection. Particularly, the cellular side of this response, altered cytokine milieu or antiviral gene expression programs were not studied in detail. Here, we describe the cellular response of B cells after in vitro and experimental in vivo RV infection of healthy and asthmatic subjects. We show that inflammatory cytokine milieu but not RV itself induces an antiviral response in B cells in vitro. IFN-α stimulation induces an inflammatory phenotype in RV infected B cells and reduces cellular virus load. Similarly, antiviral response is induced in circulating B cells after experimental infection and B cell carry RV particles after experimental infection that were collected from the airways (Figure 4).

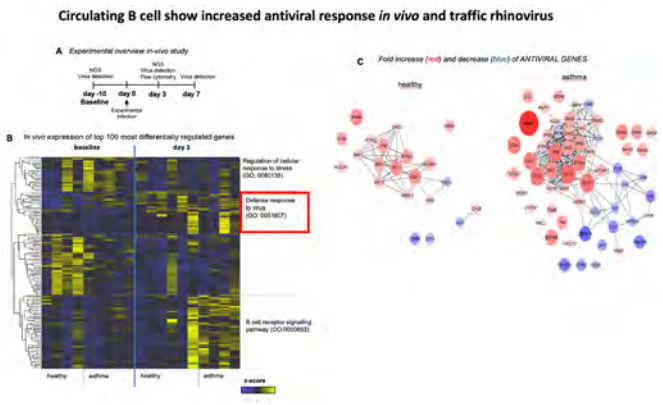



*Figure 4: Intranasal rhinovirus infection induces antiviral response in circulating B cells which is not deficient in B cells from asthmatic patients.*

Gene regulation in response to infection is dysregulated in asthmatic patients compared to healthy subjects. Collectively, we presented detailed analysis of cellular response of B cells to RV infecting humans. We were able to show dysregulated activation of circulating B cells upon infection in asthmatics. Also, for the first time we were able to provide evidence for direct interactions of B cells and RV in vivo, showing that RV was either infecting B cells or was transported by the B cells (Figure 5).

***Detection of RV in B cells isolated from experimentally infected subjects***

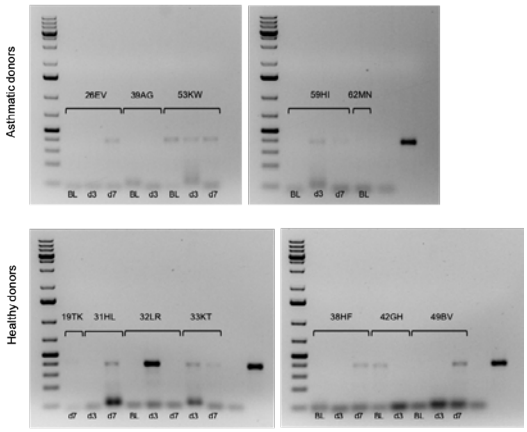



*Figure 5: Rhinovirus can be detected in circulating B cells of experimentally infected individuals.*

Also, we suggest a role for inflammatory B cells during an acute respiratory virus infection. The mechanisms suggested here are most probably not restricted to rhinovirus infections and this study opens a new window for further research on virus-induced B cell regulation in vivo in humans.

**A novel pro-angiogenic B cell subset is increased in cancer and chronic inflammation**

(van de Veen W et al. Science Advances, in press.)

B cells contribute to immune responses through the production of immunoglobulins, antigen-presentation and cytokine production. Several B cell subsets with distinct functions and polarized cytokine profiles have been reported. In this study we used transcriptomics analysis of immortalized B cell clones to identify an IgG4+ B cell subset with a unique function. These B cells are characterized by simultaneous expression of pro-angiogenic cytokines including VEGF, CYR61, ADM, FGF2, PDGFA and MDK. Consequently, supernatants from these clones efficiently promote endothelial cell tube formation. We identified CD49b and CD73 as surface markers identifying pro angiogenic B cells. Circulating CD49b+CD73+ B cells showed significantly increased frequency in melanoma and eosinophilic esophagitis patients, two diseases that are associated with angiogenesis. In addition, tissue-infiltrating IgG4+CD49b+CD73+ B cells expressing pro-angiogenic cytokines were detected in EoE and melanoma patients. Our results demonstrate a novel pro angiogenic B cell subset characterized by expression of CD49b, CD73 and pro-angiogenic cytokines.

**B-cell responses in allergen immunotherapy**

(Satitsuksanoa P et al. Curr Opin Allergy Clin Immunol. 2019 Dec;19(6):632-639.)

The establishment of long-term clinical tolerance in AIT requires the involvement of basophils, mast cells, allergen-specific regulatory T and B cells, downregulation of effector type 2 responses, and increase in production of specific IgG, particularly immunglobulin G4 (IgG4) antibodies. This review aims to provide an overview of the role of B cells in AIT, their mechanism of action, and their potential for improving AIT. In-depth research of B cells has paved the way for improved diagnosis and research on allergic diseases. B cells play a central role in allergy and allergen tolerance through the production of immunglobulin E (IgE)-blocking antibodies. However, an increasing body of evidence has emerged supporting a role for B cells in regulating immune responses that extends beyond the production of antibodies. Regulatory B cells play an important role in immunosuppression, mediated by secretion of anti-inflammatory cytokines. Successful AIT establishes the reinstatement of immune tolerance toward allergens, reduces allergic symptoms, and improves clinical treatments in patients. B cells play a central role in this process through antibody-independent immune regulatory processes in addition to the production of IgE-blocking antibodies.

**Increased antiviral response in circulating lymphocytes from hypogammaglobulinemia patients**

(Oliver F Wirz et al. Allergy, 2020,under revision)

Rhinovirus (RV) is the main cause of respiratory tract infections. B cells play a crucial role during these infections by production of virus neutralizing antibodies. Patients with hypogammaglubolinemia (HG) often have severely reduced levels of antibody producing B cells and suffer from prolonged virus infection. Here, we addressed whether antiviral response of B cells, T cells and monocytes from peripheral blood differs between in HG patients and healthy individuals during natural RV infection. Using fluorescence-activated cell sorting, CD19+ B cells, CD14+ monocytes and CD3+ T cells were isolated from frozen peripheral blood mononuclear cells (PBMC) from 11 RV-infected hypogammaglobulinemia patients, 7 RV-infected control subjects and 14 non-infected control subjects. Flow cytometry was used for detection of different B cell subsets and real-time PCR to study expression of antiviral genes. A pan-RV PCR was used to detect RV genome in all samples. In HG patients, total B cell numbers, as well as IgA- and IgG-switched memory B cells were reduced with RV infection. The number of naïve B cells was increased. A dominant T cell response with significantly increased numbers of CD3+ cells was observed in RV-infected HG patients, whereas the numbers of monocytes did not change. The expression of STAT1 was increased in HG patients compared to controls in all three lymphocyte subsets. The expression of antiviral genes IFITM1 and MX1 correlated with STAT1 expression in B cells and monocytes. RV RNA was found in 88.9 % of monocytes of infected HG patients, 85.7 % of monocytes of infected controls without HG and 7.1 % of monocytes of uninfected controls. We demonstrate an increased antiviral response in B cells and monocytes in HG patients and their correlation with STAT1 expression. Monocytes of infected HG patients and infected non-HG controls carry RV RNA.

Davos, May 2020

## Molecular Allergology

*PD Dr. Katja Bärenfaller, PhD*


### A perspective on Digital Biomarkers

Digital biomarkers are objective quantifiable, physiological, and behavioral measures that are collected by digital devices that are portable, wearable, implantable, or digestible. Digital devices have begun to be integrated into the medical landscape as they enable the measurement of digital biomarkers, which contribute new and unique features including longitudinal and continuous measurements. As digital biomarkers are an emerging field it is important to address rising possibilities and challenges and to define a standardized nomenclature and process. To address this need, a workshop was organized by BaselArea.Swiss and in a perspective we presented our findings on identifying similarities and differences between traditional and digital biomarkers and a discussion on how these fields could be further harmonized. For digital biomarker classification we propose a method that takes into account the digital measurement tool and clinical outcome assessment (Figure 1). Approved biomarkers are such that improve or accelerate generally accepted practices, such as digital biomarkers that consist of approved measurements such as heart rate, pulse, and known clinical outcomes such a cardiac risk. Original biomarkers are either a novel measurement with a known clinical outcome, or an approved measurement to describe a novel clinical outcome. An example for the latter would be measurements of heart rate to describe depression. Novel would be biomarkers in which novel measurements are connected to novel clinical outcomes. In this context, approved digital biomarkers are expected to be the first ones to be implemented, while those in the original and especially in the novel category will require rigorous testing and validation. Digital biomarkers with their novel ways of measuring health status can therefore provide observations and perspectives into diseases that were unavailable before. They can thereby supplement and enhance conclusions from traditional biomarkers and have the potential to redefine diagnosis and the medical classification of diseases.

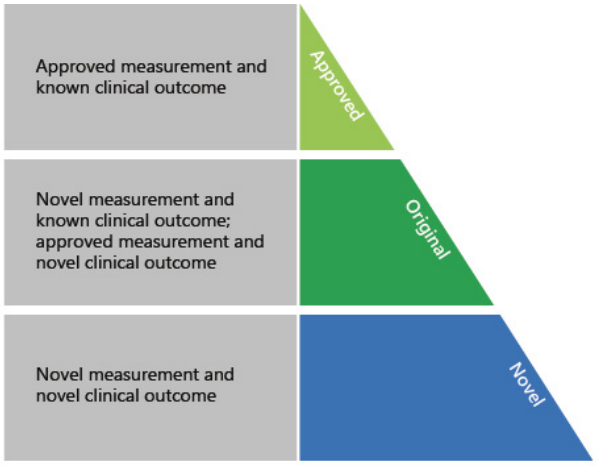



*Figure 1: As in Figure 3 of Babrak et al. (2019): Both traditional and digital biomarkers can be classified based on the status of a particular measurement to a particular clinical status or outcome. A digital biomarker either replaces a non-digital biomarker (Approved), opens a new field (Novel) or is a hybrid that on the one hand replaces and on the other hand opens a new field (Original).*

### DAViS Center (Center for Data Analytics, Visualization and Simulation) in action

The DAViS Center has been established in 2019 at Fachhochschule Graubünden (FHGR) in Chur with SIAF as primary partner to implement the research strategy of canton Graubünden in profile field “Computational Science”. The first joint Life Science project in which we attempt to use novel computational methods to identify features that are responsible for the development and the increasing prevalence of allergic diseases is MLM-SOS-ALL. The data in this project are transcript sequencing data, which were previously acquired for 150 children in the SOS-ALL study in a consortium consisting of SIAF, the University of Cape Town, the Children’s Hospital in Zurich and the Department of Dermatology at the University Hospital Zurich, as well as extensive questionnaire data on the living and health situation of the children. Through the high volume of the sequencing data, the biostatistical analyses were performed in parallel to building up the required infrastructure and hardware. Further analyses with different approaches including Machine Learning methods are currently implemented in close collaboration, and the results are evaluated for their biomedical relevance.

### The molecular profile of T cell differentiation and activation

The activation and differentiation of naïve CD4+ T cells into T helper cells are tightly regulated processes. In addition to transcriptional regulation through increased expression of master regulatory genes, translational processes such as changes in translational efficiency or translation of non protein-coding RNAs are expected to play a role in T cell differentiation. To elucidate this further, we currently investigate transcriptional and translational regulation in Th1 cell differentiation from naïve T cells in the PhD project of Jana Koch funded by “Stiftung vormals Bündner Heilstätte Arosa”. A critical milestone in this project was establishing the method for ribosome sequencing with an achievable number of cells. Ribosome sequencing describes the method in which only those stretches of RNAs are sequenced that are located inside elongating ribosomes, which

requires an elaborate protocol with many steps. With a working protocol in hand and all the reagents available, the experiments are currently ongoing.

**Endophyte Infection and Alkaloid Detection in European Seed Mixtures**

In a project in which we originally got involved because horse keepers suspected their horses to suffer from allergic diseases, we started looking at fungal endophyte infection of grasses, even though it became clear early on that it rather was a suspected intoxication effect. Fungal endophytes of the genus Epichloë live inside grass species and can enhance their resistance against environmental stressors such as drought, herbivores, and pathogens. As these beneficial traits can enhance yield, some fungal endophytes have intentionally been used in breeding efforts. Yet these endophytes often produce vertebrate toxic compounds that cause fescue toxicosis and ryegrass staggers, two severe intoxications in grazing animals including horses. Fescue toxicosis is caused by the ergot alkaloid ergovaline produced by Epichloë caenophiala that infects tall fescue, while ryegrass staggers are caused by lolitrem B that is produced by Epichloë festucae var. lolii infecting perennial ryegrass. Both perennial ryegrass and tall fescue are important grass species used for temperate grasslands and are often contained in forage grass or turfgrass seed mixtures. The distribution and toxicity of Epichloë endophytes have received quite some attention overseas, as grasslands there are often dominated by a single non-native grass species with high endophyte infection rates and intoxications are much more common compared to Europe. Despite the known toxicity of fungal alkaloids, European seed mixtures are rarely tested for Epichloë infection and their infection status is unknown for consumers. In collaboration with the University of Würzburg and the Noble Research Institute and sample analysis also in the Endophyte Service Laboratory in Oregon, we therefore conducted a study in a selection of 24 commercially available forage grass and turfgrass seed mixtures with the aim to provide an overview on Epichloë infection rates and the alkaloid content of European grass seed mixtures.

We found that four of the seed mixtures contained ergovaline and lolitrem B and therefore must have contained Epichloë infected seeds. These seed mixtures contained different varieties of perennial ryegrass, but no tall fescue varieties. Detection for the presence of Epichloë using PCR identified six E+ seed mixtures of which three were those for which we also found high levels of lolitrem B and ergovaline. As we investigated seeds we cannot conclude the alkaloid concentration and potential toxicity of the pastures after seeding the infected mixtures. Yet assuming the endophytes are viable after sowing, seeding E+ seeds introduces endophyte-infected plants into the environment. As Epichloë infected grass species have a selective advantage in hot and dry environmental conditions that are expected to increase due to climate change, their distribution may increase to a level that endophyte-infected plants could dominate grasslands and thereby increase cases of animal toxicity. Based on our results we therefore suggested a number of improvement measures, including the avoidance of Epichloë infected seed mixtures especially of those containing perennial ryegrass varieties, regular testing on Epichloë infection of the breeding and seed material by the seed companies and providing detailed information on the exact composition and Epichloë infection of the seed mixtures to consumers.

**Traditional and Digital Biomarkers: Two Worlds Apart?**

Babrak LM, Menetski J, Rebhan M, Nisato G, Zinggeler M, Brasier N, Baerenfaller K, Brenzikofer T, Baltzer L, Vogler C, Gschwind L, Schneider C, Streiff F, Groenen PMA, Miho E. Digital Biomarkers; 3(2), 92-102

The identification and application of biomarkers in the clinical and medical fields has an enormous impact on society. The increase of digital devices and the rise in popularity of health-related mobile apps has produced a new trove of biomarkers in large, diverse, and complex data. However, the unclear definition of digital biomarkers, population groups, and their intersection with traditional biomarkers hinders their discovery and validation. We have identified current issues in the field of digital biomarkers and put forth suggestions to address them during the DayOne Workshop with participants from academia and industry. We have found similarities and differences between traditional and digital biomarkers in order to synchronize semantics, define unique features, review current regulatory procedures, and describe novel applications that enable precision medicine.

**Epichloë Endophyte Infection Rates and Alkaloid Content in Commercially Available Grass Seed Mixtures in Europe**

Krauss J, Vikus V, Young CA, Krischke M, Mueller MJ, Baerenfaller K. Microorganisms. 2020; 8(4), 498

Fungal endophytes of the genus Epichloë live symbiotically in cool season grass species and can produce alkaloids toxic to insects and vertebrates, yet reports of intoxication of grazing animals have been rare in Europe in contrast to overseas. However, due to the beneficial resistance traits observed in Epichloë infected grasses, the inclusion of Epichloë in seed mixtures might become increasingly advantageous. Despite the toxicity of fungal alkaloids, European seed mixtures are rarely tested for Epichloë infection and their infection status is unknown for consumers. In this study, we tested 24 commercially available seed mixtures for their infection rates with Epichloë endophytes and measured the concentrations of the alkaloids ergovaline, lolitrem B, paxilline, and peramine. We detected Epichloë infections in six seed mixtures, and four contained vertebrate and insect toxic alkaloids typical for Epichloë festucae var. lolii infecting Lolium perenne. As Epichloë infected seed mixtures can harm livestock, when infected grasses become dominant in the seeded grasslands, we recommend seed producers to test and communicate Epichloë infection status or avoiding Epichloë infected seed mixtures.

Davos, May 2020

## Vaccine Development

*Dr. Claudio Rhyner, PhD*


Genetic, epidemiologic, and clinical evidence suggests that, in horses, as in other species, different manifestations of hypersensitivity occur concurrently. In humans, the “atopic march” manifests as a temporal sequence of hypersensitivities, with atopic dermatitis in the neonate preceding the development of allergic rhinitis and asthma. The atopic march and multiple allergies in humans can be associated with increased total serum immunoglobulin E (IgE), IgE cross-reactivity between different allergens, or both.

In horses, multiple hypersensitivities can manifest as the combined occurrence of equine asthma (EA), insect bite hypersensitivity (IBH), and chronic recurrent urticaria. Particularly, the prevalence of IBH is increased in recurrent airway obstruction (RAO)–affected horses and vice-versa. Although longitudinal studies in affected horses are lacking, the typical earlier onset of IBH compared to RAO suggests that as in humans with multiple hypersensitivity disorder, a dysfunctional skin barrier serves as the site of allergen sensitization, resulting in a systemic T-helper-2 immunity which is a predisposing factor for the development of respiratory allergies.

IBH is an allergic dermatitis provoked by *Culicoides* midge bites. Affected horses have intense pruritus, which results in typical skin lesions localized mainly along the dorsal midline and the base of the tail and the mane. The involvement of IgE-mediated reactions in the pathogenesis of this disease has been clearly established. The specific *Culicoides* allergens causing IBH have been identified at the molecular level and produced as pure recombinant (r) allergens. The use of these r-allergens compared to crude *Culicoides nubeculosus* whole-body extract improves the sensitivity and specificity of serologic IgE tests for IBH.

Allergen-specific serum IgE against the different r-allergens was determined by ELISA, as described previously. Because of the individual reaction patterns of the horses to the single r-allergens, the sum of IgE concentrations against all 8 tested r-*Culicoides* allergens were calculated for each horse and used for additional analyses. Accordingly, IgE concentrations to the mold or the mite allergens were also summed up for analysis. In conclusion, the study shows that r-*Culicoides*-specific serum IgE in IBH is not associated with concurrent severe EA. Thus, the clinically documented increased risk of IBH horses to develop severe EA does not seem to be influenced by a concomitant increase in total or allergen-specific IgE concentrations. Further studies using a larger panel of r-allergens, for example, by using an allergen chip array and larger numbers of horses to reduce type 2 errors are warranted. The results are published in J Vet Intern Med. 2019 Jan;33(1):266-274

Davos, May 2020

*Dr. Milena Sokolowska, MD, PhD*


Due to environmental and lifestyle changes, there is an increasing frequency of allergies and respiratory viral and bacterial infections. This further leads to an increase in the prevalence of asthma, rhinitis, food allergy and atopic dermatitis. It is still not well understood why the same substances are leading to the development of allergic inflammation in some people, while being well tolerated by others. Several reasons are postulated, such as lack of proper microbiome stimulation early in life, recurrent viral infections with common respiratory viruses and exposure to environmental pollutants. In addition, central metabolic disorders such as obesity or even an unhealthy diet itself also influence the proper regulation of immune responses. All of those factors impact the proper crosstalk between innate and the adaptive immunity responses on the metabolic level. Immune cell needs to engage in a wide array of energetically demanding intracellular processes in order to respond to external stimuli, such as allergen, virus or bacteria. These processes encompass changing the expression of a large number of genes, translating proteins, synthesis of lipids, activation of intracellular signaling cascades, altering cytoskeleton, and as a result production of cytokines, lipid mediators and proliferation or migration. To be competent to perform all those duties, the cell needs active metabolic processes, shifting nutrients into different pathways-a process called metabolic reprogramming.

**Figure 1**

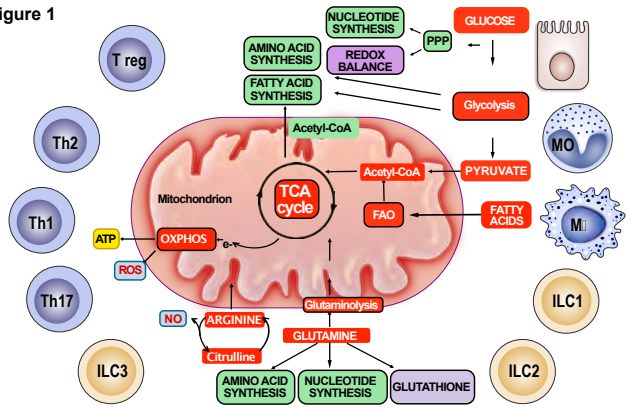



*Figure 1. Overview of the metabolism of the cells*

The role of immunometabolism in the development of allergy and asthma is not well understood. Therefore, our group applies high throughput transcriptomic, proteomic, metabolomic, coupled with gene editing, multi-color flow cytometry, confocal microscopy and live cell metabolic assays to understand immune and metabolic reprogramming of innate and adaptive immune cells. Our aim is to understand immune and metabolic crosstalk in allergy and immune tolerance, in response to allergen, respiratory viruses and microbial dysbiosis and different endotypes and phenotypes of asthma and other allergic diseases.

**Immunometabolism in allergy and immune tolerance: multi-omics approach. In search of novel mechanisms and biomarkers of allergen-specific immunotherapy**

Allergic immune response in T cells is characterized, among others, by increased secretion of pro-inflammatory mediators by Th2 effector cells. The main suppressors of this response are allergen-specific regulatory T cells (Tregs) as demonstrated in the steady state and in allergen-specific immunotherapy (AIT). Little is known about the metabolic requirements of allergen-specific and non-specific effector T cells and Tregs to carry out their functions in vivo. The aim of our studies is to identify essential metabolic pathways for regulatory and effector populations of allergen-specific and non-specific memory T cells in vivo in humans, their potential alterations in allergic disease, as well as their changes during allergen-specific immunotherapy. Allergen-specific T and Treg cells in allergic patients display profound gene and protein downregulation of immune response and cell activation pathways except type 2 immunity, TCR signaling, fatty acid and prostaglandin metabolism. Plasma and nasal untargeted and targeted proteome reflect specific cellular signature with upregulation of proteins leading to lymphocyte proliferation, T cell differentiation and fatty acid metabolism and downregulation of several anti-inflammatory pathways. Remarkably, AIT induces significant changes in previously dysregulated immune and metabolic pathways and leads to induction of tolerance programs in allergen-specific CD4+ T cells and Treg cells. However, allergen-specific Treg cells in non-responders to AIT still displayed aberrant type 2 gene, protein and metabolic profiles, coupled with the corresponding plasma and nasal inflammatory milieu, in parallel to functional impairment of their suppressive capacities. Altogether, our data suggest that in allergy there is a systemic and local aberration of immune and metabolic signaling, leading to dysfunctional metabolic reprogramming and subsequent functional impairment of allergen-specific effector and regulatory T cells.

**Trained immunity and tolerance in innate lymphoid cells, monocytes, and dendritic cells during allergen specific immunotherapy**

Eljaszewicz E., Ruchti F., Radzikowska U.; Globinska A., Boonpiyathad T.; Gschwend A., Morita H., Helbling A.; Arasi S.; Helga Kahlert, Berek N., Nandy A., Akdis M., Willers C., Moniuszko M., C.A. Akdis, Sokolowska M. *In revision.*

Background: Despite efficacy of allergen-specific immunotherapy (AIT), the role of innate immune mechanisms in this process has not been fully elucidated. Therefore, we performed a comprehen-

sive, longitudinal analysis of systemic innate immune cell repertoire in the course of AIT. Methods: Allergic patients received standard pre-seasonal subcutaneous AIT with allergoids to birch and/or grass. Healthy controls were monitored without any intervention. Flow cytometry of ILC, NK, monocyte, and DC subsets was performed at baseline, in birch and grass seasons, and 12 months after the therapy in patients or in similar seasonal time points in controls. Results: We observed a decrease of ILC2 and ILC3 and an increase of ILC1 during AIT with dynamic changes in their heterogeneity. We found that observed shifts in ILC1 composition were caused by an expansion of CD127++CD25++clusters. In addition, we observed development of CD127+CD25++c-Kit+ ILC3 clusters. Moreover, we found an increase in intermediate monocytes, in parallel to the reduction of non-classical monocytes during AIT. Classical and intermediate monocytes presented significant heterogeneity in allergic patients, but AIT reduced HLA-DR++clusters.

**Figure 2**

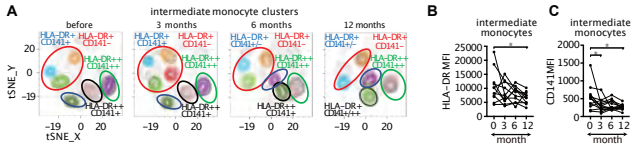



*Figure 2. Increase in anti-inflammatory phenotypes of intermediate monocytes in the course of AIT. Representative tSNE two-dimensional plots of changes in the complexity and clustering of CD14++CD16+ intermediate (J), monocytes subsets in each analyzed time point. Summary of HLA-DR and CD141 geometric mean intensity analyses of CD14++CD16+ intermediate (K and L, respectively) monocyte subsets in AIT patients.*

Finally, an increase in pDCs and mDC2s was observed in allergic individuals while mDC1s were reduced during AIT. Conclusion: Subcutaneous AIT induces time-dependent changes in the systemic cellular innate immune responses demonstrating an in vivo switch towards subsets playing a role in innate memory and tolerance induction. Monitoring of ILC, monocytes, and DCs during AIT might serve as a novel biomarker strategy.

**The Influence of Dietary Fatty Acids on Immune Responses**

Radzikowska U., Rinaldi AO., Çelebi Sözener Z., Karaguzel D, Wojcik M, Cypryk K, Akdis M, Akdis CA, Sokolowska M. Nutrients. 2019 Dec 6;11(12).

Diet-derived fatty acids (FAs) are essential sources of energy and fundamental structural components of cells. They also play important roles in the modulation of immune responses in health and disease. Saturated and unsaturated FAs influence the effector and regulatory functions of innate and adaptive immune cells by changing membrane composition and fluidity and by acting through specific receptors. Impaired balance of saturated/unsaturated FAs, as well as n-6/n-3 polyunsaturated FAs has significant consequences on immune system homeostasis, contributing to the development of many allergic, autoimmune, and metabolic diseases. In this paper, we discuss up-to-date knowledge and the clinical relevance of the influence of dietary FAs on the biology, homeostasis, and functions of epithelial cells, macrophages, dendritic cells, neutrophils, innate lymphoid cells, T cells and B cells. Additionally, we review the effects of dietary FAs on the pathogenesis of many diseases, including asthma, allergic rhinitis, food allergy, atopic dermatitis, rheumatoid arthritis, multiple sclerosis as well as type 1 and 2 diabetes.

**Allergen-specific immunotherapy: Power of adjuvants and novel predictive biomarkers**

Sokolowska M., Boonpiyathad T, Escribese MM., Barber D. Allergy. 2019 Nov;74(11):2061-2063.

In this invited editorial, we gave an informed review on the current adjuvants and biomarkers of AIT on the basis of novel papers published recently.

## Immunologic and metabolic responses to allergen, environmental pollutants, viruses and microbiota

**The Role of Lung and Gut Microbiota in the Pathology of Asthma**

Barcik W., Boutin RCT., Sokolowska M., Finlay BB. Immunity. 2020 Feb 18;52(2):241-255.

Asthma is a common chronic respiratory disease affecting more than 300 million people worldwide. Clinical features of asthma and its immunological and molecular etiology vary significantly among patients. An understanding of the complexities of asthma has evolved to the point where precision medicine approaches, including microbiome analysis, are being increasingly recognized as an important part of disease management. Lung and gut microbiota play several important roles in the development, regulation, and maintenance of healthy immune responses. Dysbiosis and subsequent dysregulation of microbiota-related immunological processes affect the onset of the disease, its clinical characteristics, and responses to treatment. Bacteria and viruses are the most extensively studied microorganisms relating to asthma pathogenesis, but other microbes, including fungi and even archaea, can potently influence airway inflammation. This review focuses on recently discovered connections between lung and gut microbiota, including bacteria, fungi, viruses, and archaea, and their influence on asthma.

*Figure 3. Project cover image was designed and created by Anna Globinska. Figures depicting the bacteriophage, fungus, bacterium, archaeon and virus (from the left) were created from plasticine by the members of our lab. Photograph was taken by Wojciech Lipowski.*

**Obesity and disease severity magnify disturbed microbiome-immune interactions in asthma patients**

Michalovich D., Rodriguez-Perez N., Smolinska S., Pirozynski M., Mayhew D., Uddin S., Van Horn S., Sokolowska M., Altunbulakli C., Eljaszewicz A., Pugin B., Barcik W., Kurnik-Lucka M., Saunders KA., Simpson KD., Schmid-Grendelmeier P., Ferstl R., Frei R., Sievi N., Kohler M., Gajdanowicz P., Graversen KB., Lindholm Bøgh K., Jutel M., Brown JR., Akdis CA, Hessel EM., O'Mahony L. Nat Commun. 2019 Dec 13;10(1):5711.

In order to improve targeted therapeutic approaches for asthma patients, insights into the molecular mechanisms that differentially contribute to disease phenotypes, such as obese asthmatics or severe asthmatics, are required. Here we report immunological and microbiome alterations in obese asthmatics (n=50, mean age=45), non-obese asthmatics (n=53, mean age=40), obese non-asthmatics (n=51, mean age=44) and their healthy counterparts (n=48, mean age=39). Obesity is associated with elevated proinflammatory signatures, which are enhanced in the presence of asthma. Similarly, obesity or asthma induced changes in the composition of the microbiota, while an additive effect is observed in obese asthma patients. Asthma disease severity is negatively correlated with fecal Akkermansia muciniphila levels. Administration of A. muciniphila to murine models significantly reduces airway hyper-reactivity and airway inflammation. Changes in immunological processes and microbiota composition are accentuated in obese asthma patients due to the additive effects of both disease states, while A. muciniphila may play a non-redundant role in patients with a severe asthma phenotype.

**House dust mite enhances rhinovirus-induced RIG I inflammasome activation and delayes antiviral response in asthma**

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

**Phenotypes and endotypes of asthma and chronic obstructive pulmonary disease**

Chronic airway diseases are amongst the most common causes of death worldwide. The prevalence of these diseases is increasing. Asthma and COPD are complex, heterogenous diseases and their treatment should be tailored specifically according to their various endotypes. Therefore, we are studying the heterogeneity of chronic respiratory diseases on the level of immune responses, metabolic changes and microbiome alterations in vivo in animal models, in vitro in primary cells and in clinical cohorts of patients with asthma and COPD.

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

Tan HT, Hagner S, Ruchti F, Radzikowska U, Tan G, Altunbulakli C, Eljaszewicz A, Moniuszko M, Akdis M, Akdis CA, Garn H, Sokolowska M. Allergy 2019 Feb;74(2):294-307.

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

Davos, May 2020

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Rinaldi AO. Electrical impedance spectroscopy is a safe and efficient tool for the evaluation of epidermal barrier integrity in atopic dermatitis. EAACI PAAM meeting 2019, Florence, Italy, 17 -19 October, 2019.

Satitsuksanoa P.Functional and phenotypic analysis of allergen-specific B cells in cow's milk allergy and tolerance. EAACI winter school 2019,Trysil, Norway, 24 - 27 January 2019.

Satitsuksanoa P. Characterization of food allergen-specific B cells in allergic children during oral immunotherapy and natural tolerance. Immune modulation in human and animal infections: impact on health, disease and therapy Eurolife Summer school 2019, Leiden, The Netherlands, 8 - 12 July 2019.

Satitsuksanoa P. Characterization of allergen-specific B cells in cow's milk allergy. Opening day of SIAF-CK care, Davos, Switzerland, 6 September 2019.

Satitsuksanoa P. Functional and phenotypic analysis of allergen-specific B cells in cow's milk allergy and tolerance. WIRM 2019, Davos, Switzerland, 6-9 April 2019.

Sokolowska M. Immunometabolic changes in allergen-specific CD4+T and regulatory T cells during allergen-specific immunotherapy.WIRM, Davos, Switzerland 6-9th April.

Üzülmez, Ö. A plant-based transient expression system for the production of nature-identical allergens. WIRM 2019, Davos, Switzerland, 6-9 April 2019.

Wallimann A. The influence of microbial-derived metabolites on bone health. WIRM 2019, Davos, Switzerland, 6-9 April 2019

Wallimann A. The influence of microbial-derived metabolites on bone health. SBMS Summer School 2019, Bern, Switzerland 16-17 May 2019

Wallimann A. The influence of microbial-derived metabolites on bone health. eCM conference 2019, Davos, Switzerland 26-28 June 2019

Wallimann A. The influence of microbial-derived metabolites on bone health. SSM Annual Meeting 2019, Zurich, Switzerland, 3-4 September 2019

Wirz OF. Experimental rhinovirus infection induces extensive antiviral response in circulating B cells from asthmatic patients. World Immune Regulation Meeting (WIRM) XIII, Davos, Switzerland, 6. - 9. April 2019.

## SEMINAR AND CONGRESS TALKS

Akdis CA. What is the target of AIT? Transcriptomic and proteomic profiles of allergen-specific CD4+T and regulatory T cells. FASIT Workshop 2019, Hamburg, Germany, 8-9 February 2019.

Akdis CA. Discussion leader. Detergents in allergic sensitization. AAAAI Annual Meeting, San Francisco, USA, 22-25 February 2019.

Akdis CA. Epithelial barrier hypothesis. Keystone Symposia, Tahoe, USA, 24-28 March 2019.

Akdis CA. Interaction between Fungi and the immune system. WISC 2019, Beirut, Lebanon, 4-6 April 2019.

Akdis CA. Chronic inflammatory diseases. WISC 2019, Beirut, Lebanon, 4-6 April 2019.

Akdis CA. The epithelial barrier hypothesis for the development of allergic diseases. National Otolaryngology Head and Neck Surgery Alliance Conference, Beijing, China, 12-13 April 2019.

Akdis CA. Pediatric Allergy Meeting Endotypes of Allergic Disease, 24-26 April 2019.

Akdis CA. Epithelial barrier hypothesis for the development of chronic inflammatory diseases. International molecular immunology and immunogenetics congress IV, Bursa, Turkey, 27-29 April 2019.

Akdis CA. The epithelial barrier hypothesis for the development of inflammatory diseases. Next Immune, International Scientific Retreat, Luxembourg, 7-9 May 2019.

Akdis CA. The epithelial barrier hypothesis and allergic skin and respiratory diseases. SIAF opening symposium. Davos, Switzerland, 27 September 2019.

Akdis CA. The epithelial barrier. AID Congress, 8-11 November 2019.

Akdis CA. How to make bst scientific presentations. AID Congress, 8-11 November 2019.

Akdis CA. How to present your data best fr a scientific talk or for a publication. 5th Annual Dr. Robert W. Goltz Dermatology International Lectureship, Minnesota, USA, 13 November 2019.

Akdis CA. Epithelial barrier hypothesis for allergic and inflammatory diseases. 5th Annual Dr. Robert W. Goltz Dermatology International Lectureship, Minnesota, USA, 13 November 2019.

Akdis CA. Epithelial barrier hypothesis of allergic and inflammatory diseases. 2nd Moscow Molecular Allergology Meeting, Moscow, Russia, 19 November 2019.

Akdis CA. Elithelial barrier hypothesis. Symposium on type 2 immunity and associated pathologies. Toulouse, 11 December 2019.

Akdis M. Novel mechanisms of allergen tolerance. Forschung und Translational Medicine am Campus Davos, Switzerland, 14 February 2019.

Akdis M. Current knowledge of allergen immunotherapy mechanisms. AAAAI Annual Meeting, San Francisco, USA, 22-25 February 2019.

Akdis M. B cell tolerance. European Rhinallergy Meeting RHINA, Eastbourne, UK, 21-23 March 2019.

Akdis M. Mechanisms and biomarkers. WISC 2019, Beirut, Lebanon, 4-6 April 2019.

Akdis M. Mechanisms of allergen tolerance. National Otolaryngology Head and Neck Surgery Alliance Conference, Beijing, China, 12-13 April 2019.

Akdis M. Novel B-cell subsets and immune tolerance. International molecular immunology and immunogenetics congress IV, Bursa, Turkey, 27-29 April 2019.

Akdis M. Regulatory and angiogenic novel B cell subsets. Next Immune, International Scientific Retreat, Luxembourg, 7-9 May 2019.

Akdis M. Novel insights into B cell memory responses in allergy. EAACI Annual congress, Lisbon, Portugal, 1-5 June 2019.

Akdis M. Regulatory B cells. 50 Years of Department of Immunology, University Zurich, Switzerland, 2 July 2019.

Akdis M. Novel B cell subsets and regulation of allergic inflammation. SSAI Annual meeting. Lugano, Switzerland, 5-7 September 2019.

Akdis M. B cells in immune tolerance and regulation of tissue responses. SIAF opening symposium. Davos, Switzerland, 27 September 2019.

Akdis M. Innate Lymphoid cells and B cell interaction. XXVI. Turkish Allergy and Clinical Immunology Congress. Antalya, Turkey, 9-13 November 2019.

Akdis M. Mechanisms of immune tolerance to allergens. 2nd Moscow Molecular Allergology Meeting, Moscow, Russia, 19 November 2019.

Frei R. Mechanisms by which microbes influence allergic sensitization. Physiologie et Pathologie des Barrières: Rôle du Microbiote sur l'Hôte, Nantes, France 2019.

Jansen K. The effect of human rhinovirus on T regulatory cells. EAACI winterschool 2019, Trysil, Norway, 24-27 January 2019.

# SEMINAR AND CONGRESS TALKS

## 2019

Jansen K. The effect of human rhinovirus on T regulatory cells. MIMIC IV, Bursa, Turkey, 27-29 April 2019
Jansen K. The effect of human rhinovirus on T regulatory cells. SIAF opening symposium, Davos Platz, Switzerland, 27th September 2019.

Meisser SS. Skin barrier changes upon exposure to p-phenylenediamine in hair dye allergic individuals and occupational exposed non-responding individuals. EACCI congress 2019. Lisabon, Portugal, 1-6 June 2019.

Radzikowska U. Rhinovirus.induced inflammasome activation is increased by house dust mite in asthmatic bronchial epithelium. NextImmune International Scientific Retreat, Luxembourg, Luxembourg, 07-09 May 2019.

Radzikowska U. Cell culture techniques and EVOS. AO-SIAF Meeting for Novel Technologies. Davos, Switzerland, 27 November 2019.

Radzikowska U. Novel tissue inflammatory mechanisms of rhinovirus in the presence of house dust mite. SIAF Opening Symposium. Davos, Switzerland, 27 September 2019.

Rodriguez-Coira J. Immunometabolism of human T regulatory and T effector cells.WIRM 13th, Davos, Switzerland, 5-9 April 2019.

Rodriguez-Coira J. T regulatory and T effector cells display distinct metabolic profiles in allergic patients. EAACI Congres 2019, Lisboa, Portugal, 1-5 June 2019.

Rinaldi AO. Electrical impedance spectroscopy as a safe and efficient tool for the characterization of epidermal barrier in atopic dermatitis. EAACI Congress 2019, Lisbon, Portugal, 1-5 June 2019.

Rinaldi AO. Electrical impedance spectroscopy is a safe and efficient tool for the evaluation of epidermal barrier integrity in atopic dermatitis. EAACI PAAM meeting 2019, Florence, Italy, 17 -19 October, 2019.

Satitsuksanoa P. Characterization of food allergen-specific B cells before and after oral immunotherapy. International Molecular Immunology & Immunogenetics Congress IV (MIMIC IV), Bursa, Turkey, 27-29 April 2019.

Satitsuksanoa P. Functional and phenotypic analysis of allergen-specific B cells in cow's milk allergy and tolerance.XXXI Meeting of the Swiss Immunology PhD students (Wolfberg meeting), Seepark, Thun, March 13 – March 15, 2019.

Satitsuksanoa P. B cell responses in food allergy and tolerance. OPENING SYMPOSIUM OF THE NEW CAMPUS BUILDING, Davos, Switzerland, 27 September 2019.

Sokolowska M. Microbiome and asthma" Molecular Diagnostics Symposium 2019, 28th February-1st March 2019.

Sokolowska M. Immunometabolic changes in allergen-specific CD4+T and regulatory T cells during allergen-specific immunotherapy. WIRM, Davos, Switzerland, 6-9th April 2019.

Sokolowska M. Crosstalk of innate and adaptive immunity on a metabolic level in asthma and allergy. Strategy of Excellence Project - the University of Research of the Future meeting, Bialystok, Poland, 29.05.2019.

Sokolowska M. Immunometabolism in asthma, allergy and immune tolerance. Bern Immunology Club, University of Bern, Bern, Switzerland, 25.09.2018.

Sokolowska M. Understanding next generation sequencing through gene ontologies and user-friendly platforms. EAACI Congress, Lisbon, Portugal, 01 - 05 June 2019.

Sokolowska M. Translating novel concepts in metabolomics into allergy interventions. EAACI Annual Congress, Lisbon, Portugal, 01 - 05 June 2019.

Sokolowska M. Avenues in immunomodulation-session roadmap. EAACI Congress; Lisbon, Portugal, 01 - 05 June 2019.

Sokolowska M. Allergen-specific T cell regulation and allergen tolerance during allergen-specific immunotherapy. SIAF opening symposium, Davos, Switzerland, 27.09.2019.

Sokolowska M. Next generation sequencing and single cell approaches. AO-SIAF meeting, Davos, Switzerland, 27.11.2019.

Üzülmez, Ö. A plant-based transient expression system for the production of nature-identical allergens. WIRM 2019, Davos, Switzerland, 6-9 April 2019.

van de Veen W. The Role of B Cells in the Regulation of Allergic Immune Responses. Keystone Symposium Origins of Allergic Disease: Microbial, Epithelial and Immune Interactions, Granlibakken, Tahoe City, CA, USA, 24-28 March 2019.

van de Veen W. Allergen-specific B cell responses in a human model of high-dose allergen exposure. International Molecular Immunology & Immunogenetics Congress (MIMIC) IV, Bursa, Turkey, 27-29 April 2019.

van de Veen W. The allergen-specific B cell repertoire in a human model of high-dose allergen exposure. World immune regulation meeting (WIRM) XIII, Davos, Switzerland, 6-9 April 2019.

van de Veen W. Immunological Mechanisms of Tolerance to Allergens, 33th Mediweek Davos, Davos, Switzerland, 1-5 July 2019.

van de Veen W. In vivo clonality of antigen-specific B cell responses, Scientific Opening Symposium SIAF, Davos, Switzerland, 27 September 2019.

Wallimann A. The influence of microbial-derived metabolites on bone health. SBMS Summer School 2019, Bern, Switzerland, 16-17 May 2019.

Wallimann A. The influence of microbial-derived metabolites on bone health. MIM retreat 2019, Grindelwald, Switzerland, 29-31 August 2019.

**CHAIRS**

Akdis CA. FASIT Workshop 2019, Hamburg, Germany, 8-9 February 2019.

Akdis CA. T cells in the pathogenesis and treatment of autoimmunity. World Immune Regulation Meeting (WIRM) XIII, Davos, Switzerland, 6. - 9. April 2019.

Akdis CA. Barrier dysfunction in allergic diseases. Origins of Allergic Disease: Microbial, Epithelial and Immune Interactions. Keystone Meeting, Tahoe City, USA, 24-27 March 2019.

Akdis CA. Oral Abstract Session 1. WISC 2019, Beirut, Lebanon, 4-6 April 2019.

Akdis CA. SIAF opening symposium. Davos, Switzerland, 27 September 2019.

Akdis CA. Poster Session. Next Immune, International Scientific Retreat, Luxembourg, 7-9 May 2019.

Akdis CA. Plenary session, EAACI Congress; Lisbon, Portugal, 01 - 05 June 2019.

Akdis CA. 2nd Moscow Molecular Allergology Meeting, Moscow, Russia, 19 November 2019.

Akdis M. Th2 high asthma: which biologic test suits your patients. WISC 2019, Beirut, Lebanon, 4-6 April 2019.

Akdis M. B cells in allergy and autoimmunity. World Immune Regulation Meeting (WIRM) XIII, Davos, Switzerland, 6. - 9. April 2019.

Akdis M. B-cell immunity: Recent discoveries and therapeutic approaches. International molecular immunology and immunogenetics congress IV, Bursa, Turkey, 27-29 April 2019.

Akdis M. Poster Session. Next Immune, International Scientific Retreat, Luxembourg, 7-9 May 2019.

Akdis M. Symposia chair, Current and future perspective on adjuvants for allergen immunotherapy, EAACI Annual congress, Lisbon, Portugal, 1-5 June 2019.

Akdis M. Workshop chair on Clinical Immunology and Allergology. SSAI Annual meeting. Lugano, Switzerland, 5-7 September 2019.

Baerenfaller K. Immune Activation, Effector Functionas and Immune Tolerance with a special focus on Autoimmunity. World Immune Regulation Meeting XIII (WIRM), Davos, Switzerland, 6-9 April 2019.

Baerenfaller K. SIAF Scientific Opening Symposium, Davos, Switzerland, 27 September 2019.

Sokolowska M. Regulatory T Cell Subversion as a Key Pathogenic Mechanism in Allergic Disorders. EAACI Winterschool 24- 27 January 2019.

Sokolowska M. Lymphocytes. EAACI Winterschool 24- 27 January 2019.

Sokolowska M. Metabolism and immunity. WIRM, Davos, Switzerland, 6-9th April 2019.

Sokolowska M. Forgotten and new players of immune responses: Lipid mediators. EAACI Congress; Lisbon, Portugal, 01 - 05 June 2019.

Sokolowska M. Year in Review: Basic and Clinical Immunology. EAACI Congress; Lisbon, Portugal, 01 - 05 June 2019.

Sokolowska M. Experimental studies in asthma. EAACI Congress; Lisbon, Portugal, 01 - 05 June 2019.

Sokolowska M. Access to allergy via innate immunity. EAACI Congress; Lisbon, Portugal, 01 - 05 June 2019.

Sokolowska M. Clinical immunology from autoimmunity to cancer. EAACI Congress; Lisbon, Portugal, 01 - 05 June 2019.

Sokolowska M. Avenues in immunomodulation. EAACI Congress; Lisbon, Portugal, 01 - 05 June 2019.

van de Veen W. Workshop 7, T and B cell memory and immune regulation. World immune regulation meeting (WIRM) XIII, Davos, Switzerland, 6-9 April 2019.

Wirz OF. Poster Session 10: Transcriptomics, lncRNAs, miRNAs. World Immune Regulation Meeting (WIRM) XIII, Davos, Switzerland, 6. - 9. April 2019.

# LECTURES, AWARDS AND DEGREES

## 2019

### LECTURES

**Lectures at University of Zurich**

Akdis CA.
BCH301. Introduction to immunology, Cells and organs of the immune system, Immune tolerance, Immune effector functions and tissue inflammation

Akdis M.
BCH301. Adaptive immune response, B cells and antibodies, T cells and T cell receptor

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

### AWARDS

Akdis CA. EAACI Fellowship

Akdis CA. SGAI Honorary Member

Akdis CA. EAACI Honorary Member

Akdis CA. Robert W. Goltz Lecture: Minneapolis University

Akdis M. International Distinguished Fellow Award of the American College of Allergy, Asthma & Immunology (ACAAI) in recognition of her valuable contributions to the field.

Morita H. PhARF Award, EAACI Annual Congress, Lisbon, Portugal, 01-06 June 2019.

Radzikowska U. Dailly poster winner. EAACI Annual Congress, Lisbon, Portugal, 01-06 June 2019.

Radzikowska U. Abstract prize winner. EAACI Annual Congress, Lisbon, Portugal, 01-06 June 2019.

Radzikowska U. BioLegend Best Presentation Award. World Immune Regulation Meeting, Davos, Switzerland, 06-09 April 2019.

### DEGREES

Meisser SS. PhD degree, Allergic contact dermatitis to pare-phenylenediamine and the immunology involved. Copenhagen University, Denmark

Prati M. PhD degree, Evaluation of strategies to suppress IgE mediated hypersensitivity reations. EHT Zurich, Switzerland

### SIAF SCIENCE DAY

**19.12.2019**

Akdis CA.: SIAF 1988-2020

Koch J.: Looking for ribosome footprints

Radzikowska U.: Will I learn how to swim?

Rinaldi A.: Electrical impedance spectroscopy as a safe and efficient tool for the evaluation of epithelial barrier

Liu C.: Allergen and Environment related endotypes of pediatric asthma

Gao Y.: PreDicta Cohort: Association of lung function and immune responses in preschool asthmatics

Satitsuksanoa P.: Characterization of allergen-specific B cells in cow's milk allergy

Cevhertas L.: Isolation of Melanoma Antigen Specific B Cells

Jansen K.: Tregs lost in the (common) cold

Westermann P.: DJ Detergent and MC Plastic in the mix

Mitamura Y.: Distinct molecular features of nonlesional and lesional skin of atopic dermatitis compared to healthy skin

Meisser SS.: Skin barrier and immune response in allergic contact dermatitis to hair dye PPD

Allergy Team: Allergy, together we make an impact

*Winner of the SIAF Sciene Day 2019: Arturo Rinaldi*

## PUBLIC SEMINARS

06.02.2019
Engelbert Precht: Moving from Bulk NGS to Precision Sequencing with Single-Cell Genomics: Resolving Heterogeneity in Blood and Solid Tumors

08.03.2019
Boyman-Akdis Lab Symposia
Lukas Heeb: The effects of dupilumab therapy in atopic dermatitis on human neutrophils
Arturo Rinaldi: Easy and rapid detection of skin barrier integrity and its implications in atopic dermatitis
Cecilie Egholm: High throughput assessment of neutrophil migration using microfluidics
Pattraporn Satitsuksanoa: Characterization of food allergen-specific B cells before and after oral immunotherapy
Maddalena Marconato: Circadian periodicity of human peripheral blood leukocytes
Milena Sokolowska: Transcriptomic and proteomic signature of systemic and local responses during allergen-specific immunotherapy
Sarah Adamo: Alternative strategies for selective IL-2 delivery to T regulatory cells
Kirstin Jansen: T-regulatory cells out of control after rhinovirus infection
Onur Boyman: Toward tolerance induction in immune pathologies

23.04.2019
Francois Pujol: Dead or Alive? How to assess your cell status and activity Flow Cytometry

31.07.2019
Oscar Palomares: Anti-inflammatory and immune regulatory roles of the cannabinoids and their receptors

02.09.2019
Cezmi A. Akdis: Epithelial barrier hypothesis
Ge Tan: Introduction to single cell RNA-Seq
Marie-Charlotte Brüggen: From adipose tissue to atopic dermatitis

09.10.2019
Alexander Eggel: Systemic Rejuvenation: Can eosinophils reset our aging clock

05.11.2019
Müge Akpinar: The microfluidic approach for genomic profiling

27.11.2019
AO - SIAF Meeting for Novel Technologies
Keith Thompson: Bone immunology
Zhen Li: TGFβ for cell differentiation and functional phenotype induction
Anja Heider: OLINK Targeted proteomics
Katja Bärenfaller: Orbitrap ECLIPSE mass spectrometer and high-throughput proteomics
Elena Della Bella: Non-coding RNA Biomarker and phenotype control
Martin Stoddart: Labelling mRNA in live cells
Milena Sokolowska: Next generation sequencing and single cell approaches
Urszula Radzikowska:Cell culture techniques and EVOS
Willem van de Veen: B cell immortalization technique and its applications
Geoff Richards: SEM Imaging / Confocal
Cezmi A. Akdis: BSL3 Lab
Tiziano Serra / Andrea Schwab: Cells and ECM assembly using biofabrication technologies
Arturo Rinaldi: Skin barrier detection with electric impedance

06.12.2019
Karsten Strauss: OLINK: Better understanding of health & disease using protein biomarker discovery

27.11.2019

## SCIENTIFIC POSTS

**Akdis CA.**

American Academy of Allergy, Asthma & Immunology (AAAAI) - Eczema Atopic Dermatitis Committee Member

American Academy of Allergy, Asthma & Immunology (AAAAI) - Cells and Mediators Committee, Board Member

Christine Kuehne - Center for Allergy Research and Education (CK-CARE) – Directorium member

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

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

European Academy of Allergy Clinical Immunology (EAACI) – Member of Biologicals Guidelines

European Academy of Allergy Clinical Immunology (EAACI) - Member of Allergen Immunotherapy Guidelines

European Asthma Research and Innovation Partnership (EARIP) - Member

Global Allergy and Asthma European Network GA2LEN - Member

World Immune Regulation Meeting - Chairman

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

**Akdis M.**

European Academy of Allergy Clinical Immunology (EAACI), Biologicals guideline committee

World Allergy Organization (WAO) Board Member

Leo foundation, Kopenhagen, Board Member of Dermatology Research Center

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

National Institute of Health, USA, Food allergy panel member and speaker

World Immune Regulation Meeting - Member of the organizing committee

**Baerenfaller K.**

Group leader of the Swiss Institute of Bioinformatics (SIB)

Jury member for the SIB Best Swiss Graduate Paper Award

Board member of the EAACI Working Group Genomics & Proteomics

World Immune Regulation Meeting - Member of the organizing committee

**Rhyner C.**

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

Member of Life Sciences Zurich Graduate School-Zurich

World Immune Regulation Meeting - Member of the organizing committee

**Sokolowska M.**

EAACI Basic and Clinical Immunology Section, Secretary (2019-2021)

Organizing committee chair of the EAACI Immuology Winter School (2020 & 2021)

Secretary of the EAACI Task Force on Public Outreach in Immunology (2019-2020)

Secreatry of the EAACI Task Force on Eicosanoids in the Treatment of Asthma and Allergic Diseases (2019-2020)

Member of the EAACI Task Force on Nutritional Factors in Immunomodulation (2019-2020)

Member of the EAACI Task Force on High Altitude Treatment in Asthma (2019-2020)

Member of the EAACI Task Force on Antibiotics (2019-2020)

World Immune Regulation Meeting - Member of the organizing committee

**van de Veen W.**

Management committee member and Deputy lead Immmunological outcomes on the COST action entitled: "The Core Outcome Measures for Food Allergy"

Programme committee member for the Graduate School Graubünden

Organizing committee member for the conference "Graubünden Forscht"

## EDITORIAL ACTIVITIES

**Akdis CA.**
Allergy, Editor in Chief

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 Investigational Allergology and Clinical Immunology, editorial board member

**Akdis M.**
Allergy, editorial board member

International Archives of Allergy and Immunology, editorial board member

European Journal of Immunology, editorial board member

**Rhyner C.**
Allergy, member of the editorial board

Int Arch All, member of the editorial board

**Sokolowska M.**
Allergy, Editorial Board Member

Clinical and Molecular Allergy,Editorial Board Member

Inflammation Pharmacology (specialty section of Frontiers in Immunology and Frontiers in Pharmacology) Editorial Board Member

**van de Veen W.**
Allergy, Editorial board member

Journal of Allergy and Clinical Immunology (JACI), Reviewer board member

**Collaborations with the Clinics of Davos**
-Hochgebirgsklinik Davos-Wolfgang, Prof. H.W. Duchna, Dr. M. Möhrenschlager, Dr. A. Kalweit, Prof. R. Lauener, Dr. C. Steiner, Dr. A. Kirsch
-Nederlands Astmacentrum, Dr. L.H.M. Rijssenbeek-Nouwens
-Spital Davos, Dr. T. Rothe, Dr. A. Speiser
-Zürcher Höhenklinik Davos Clavadel, Dr. C. Cardoso

**Collaborations outside Davos**
Amsterdam UMC, Location UMC, University of Amsterdam (NL)
-Department of Experimental Immunology, Prof. H. Spits
-Department of Pathology, Prof. C. van Noesel

Allergopharma GmbH & Co. KG., Reinbek (DE), Dr. A. Nandy, Dr. C. Willers, Dr. H. Kahlert, Dr. Nadine Berek

Allergy and Pulmonology Department, Postgraduate Center for Medical Education, Warsaw (PL), Prof. M. Pirozynski

Allgem. Krankenhaus (AKH) Wien (AT), Institut für Allgemeine und Experimentelle Pathologie, Prof. H. Breiteneder, Dr. P. Ebersteiner, Prof. E.-J. Jarolim, Dr. S. Natter, Prof. O. Scheiner, Prof. R. Valenta, Dr. S. Vrtala

AO Research Institute Davos, AO Foundation, Davos Platz (CH), Dr. S. Grad, Prof. M. Alini, Dr. F. Moriarty, Prof. R.G. Richards, Dr. B. Stanic, Dr. K. Thompson, Prof. M. Stoddart

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

Benaroya Research Institute at Virginia Mason; Department of Medicine, University of Washington (US), Dr. W. Kwok, I-Ting Chow

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

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

Centre Suisse d'Electronique et Microtechnique SA (CSEM) Landquart (CH), Dr. S. Generelli, Dr. D. Ulrich

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

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

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

Endophyte Service Laboratory in Corvallis (US), Dr. Jenni Duringer

ETH Zürich (CH)
-Computational Systems Biology Group, Prof. Jörg Stelling
-Departement Pharmazie, Prof. G. Folkers
-Department of Biotechnology, Prof. C. Lacroix

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

Functional Genomic Center Zurich (CH), Prof. Dr. R. Schlapbach, Dr. H. Rehrauer, Dr. C. Aquino, Dr. F. Castro Giner, Dr. W. Wolski, Dr. P. Nanni, Dr. C. Fortes

GlaxoSmithKline (GSK), Stevenage (UK), Dr. E. Hessel, Dr. D. Michalovich

Hacettepe University, Ankara (TR), Prof. O. Kalayci, Prof. E. Birben, Prof. C. Karaaslan

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

Immunologie et Neurogénétique Expérimentales et Moléculaires (INEM) UMR7355, Department of Molecular Immunology, Orleans (FR), Prof. B. Ryffel, Dr. D. Togbe

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

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

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

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

Kantonsspital Graubünden, Chur (CH), Dr. M. Kuhn, Prof. W. Reinhart, Prof. T. Fehr, Dr. E. Riedi, Dr. HB. Fahrner

Kantonsspital St. Gallen, Institute of Immunobiology (CH), Prof. L.Flatz

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

Ludwig Maximilians Universität, Department of Pathology, Munich (DE), PD Dr. J. Neumann

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

Medical University of Bialystok, Department of Regenerative Medicine and Immune Regulation (PL), Prof. M. Moniuszko, Dr. A. Eljaszewicz

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

Medical University of Lodz (PL), Prof. M. Kowalski, Prof. J. Makowska

Medical University of Vienna, Au, Department of Pediatrics, Vienna (AT), Prof. Z. Scephaluzi

Monash University, Department of Immunology, Melbourne (AU), Dr. M. van Zelm

Noble Research Institute LLC (US), Prof. Carolyn Young

Novartis, Basel (CH), Dr. C.H. Heusser
Office for Nature and Environment of the Grisons

Ostschweizer Kinderspital, St. Gallen (CH), Prof. R. Lauener, Dr. C. Roduit

Padua University Hospital, Italy (IT), Prof. A. Muraro

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

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

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

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

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

Stanford University, Department of Pathology (US), Dr. S. Boyd, Prof. S.J. Galli

Swiss EoE Research Network, Olten, (CH), Prof A. Straumann

Technische Universität München (DE)
-Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Prof. J. Ring
-Forschungszentrum für Umwelt und Gesundheit, Prof. C. Schmidt-Weber, Prof. Dr. E. Renner, Prof. Dr. C. Traidl-Hoffmann

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

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-Clinical Trial Center (CH), PD Dr. G. Senti

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-Department of Pharmaceutical Biology, Prof. Martin J. Müller

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## Schweizerisches Institut für Allergie- und Asthmaforschung

### Bilanz per 31. Dezember 2019

(inklusive Drittmittel)

| | 31.12.2019 | 31.12.2018 |
|---|---|---|
| | CHF | CHF |
| **AKTIVEN** | | |
| Flüssige Mittel | 1’186’895.64 | 1’416’724.04 |
| Forderungen | 856’269.24 | 152’238.32 |
| Kontokorrent SFI Stiftung | Passiv | 59’015.05 |
| Aktive Rechnungsabgrenzungen | 191’914.02 | 261’192.58 |
| | 2’235’078.90 | 1’889’169.99 |
| **PASSIVEN** | | |
| Verbindlichkeiten | 621’295.70 | 218’248.89 |
| Kontokorrent SFI Stiftung | 28’967.50 | Aktiv |
| Passive Rechnungsabgrenzungen | 833’473.45 | 767’464.44 |
| Rückstellungen | 531’186.44 | 683’300.85 |
| Eigenkapital | 220’155.81 | 220’155.81 |
| | 2’235’078.90 | 1’889’169.99 |

## Schweizerisches Institut für Allergie- und Asthmaforschung

### Betriebsrechnung 2019

(inklusive Drittmittel)

| | Rechnung 2019 | Budget 2019 | Rechnung 2018 |
|---|---|---|---|
| | CHF | CHF | CHF |
| **ERTRAG** | | | |
| Beitrag Bund Forschungsgesetz Art. 16 | 848'300.00 | 823'800.00 | 818'100.00 |
| Beitrag Kanton Graubünden | 520'000.00 | 520'000.00 | 520'000.00 |
| Beitrag Gemeinde Davos | 474'560.00 | 524'560.00 | 424'560.00 |
| Beitrag Universität Zürich | 366'028.15 | 359'799.00 | 361'629.20 |
| Beitrag Stiftung SFI Villa Fontana | 0 | 0 | 100'000.00 |
| Beitrag Stiftung SFI Mieterlass | 80'000.00 | 80'000.00 | 160'000.00 |
| Finanzierungsbeitrag Universität Zürich | 717'249.75 | 0 | 0 |
| Beitrag Stiftung vormals Bündner Heilstätte Arosa | 54'383.50 | 52'685.00 | 9'016.00 |
| Beitrag Stiftungen/Drittmittel | 256'149.89 | 0 | 52'480.95 |
| Overheadbeiträge | 68'247.00 | 100'000.00 | 86'981.00 |
| Spenden | 2'214'621.67 | 3'000'000.00 | 0 |
| Übriger Ertrag | 44'846.31 | 3'000.00 | 23'408.45 |
| Finanzertrag | 0.10 | 0 | 845.60 |
| Ausserordentlicher Ertrag | 22'468.14 | 0 | 17'680.07 |
| Auflösung von Rückstellungen | 437'492.74 | 0 | 0 |
| WIRM-Kongress | 340'994.93 | 350'000.00 | 319'892.70 |
| Drittmittel | 1'318'975.42 | 1'631'294.00 | 1'527'528.90 |
| | 7'764'317.60 | 7'445'138.00 | 4'422'122.87 |
| **AUFWAND** | | | |
| Personalaufwand | 2'463'567.53 | 2'436'532.00 | 2'580'916.95 |
| Verbrauchsmaterial | 563'487.14 | 783'921.00 | 504'068.59 |
| Raumaufwand | 242'188.90 | 305'260.00 | 183'071.38 |
| Unterhalt/Reparaturen/Ersatz | 109'698.18 | 130'500.00 | 124'702.99 |
| Investitionen | 3'667'162.16 | 3'083'526.00 | 19'148.63 |
| Sachversicherungen/Abgaben | 8'088.30 | 10'000.00 | 7'408.40 |
| Energie- und Entsorgungsaufwand | 95'787.34 | 87'000.00 | 65'948.35 |
| Verwaltungsaufwand | 136'153.48 | 249'500.00 | 132'645.06 |
| Werbeaufwand | 7'177.20 | 0 | 0 |
| Reiseaufwand | 75'723.80 | 74'899.00 | 88'041.22 |
| WIRM-Kongress | 254'551.87 | 300'000.00 | 254'627.70 |
| Übriger Betriebsaufwand | 121'977.95 | 12'000.00 | 12'799.78 |
| Finanzaufwand | 18'753.75 | 101'000.00 | 1'794.13 |
| Bildung von Rückstellungen | 0 | 0 | 446'949.69 |
| Ausserordentlicher Aufwand | 0 | 1'000.00 | 0 |
| | 7'764'317.60 | 7'575'138.00 | 4'422'122.87 |
| Ergebnis | 0 | - 130'000.00 | 0 |
| | 7'764'317.60 | 7'445'138.00 | 4'422'122.87 |

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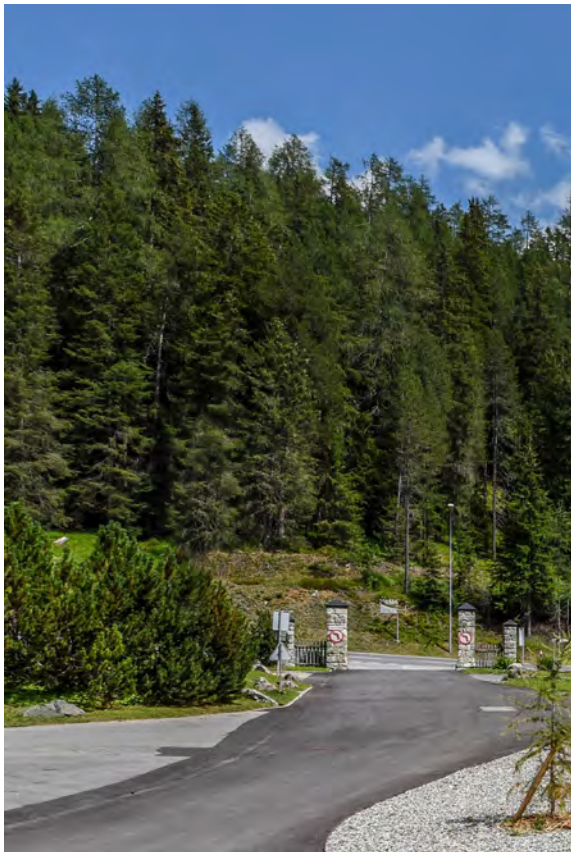

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