SIAF

Swiss Institute of Allergy and Asthma Research

ANNUAL REPORT 2020

University of Zurich[UZH]

Index

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.

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

Das Schweizerische Institut für Allergie- und Asthmaforschung (SIAF) in seiner heutigen Form wurde 1988 von der Medizinischen Abteilung der Stiftung Schweizerisches Forschungsinstitut für Hochgebirgsklima und Medizin Davos (SFI) gegründet. Das SIAF ist seit 1996 der Universität Zürich angegliedert und seit 2008 Mitglied der Life Science Zurich Graduate School, einem gemeinsamen Ausbildungs-Projekt der Universität Zürich und der ETH Zürich. Diese Angliederung ermöglicht dem SIAF eine vollumfängliche PhD-Ausbidlung anzubieten. Darüber hinaus ist das SIAF aktives Mitglied der Academia Raetica und der Graduiertenschule des Kantons Graubünden.

Allergische Erkrankungen zeigten in den letzten Jahrzehnten einen epidemischen Anstieg und beeinträchtigen das Leben von mehr als einer Milliarde Menschen weltweit. Ihre Prävalenz nimmt in den Entwicklungsländern parallel zur Urbanisierung und Industrialisierung weiter zu. Es ist deshalb von enormer Wichtigkeit, den wissenschaftlichen Fragen nachzugehen, damit die Lösungsansätze direkt dem Patienten und den Angehörigen zu Gute kommen.

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. 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), in die Europäische Akademie für Allergologie und Klinische Immunologie (EAACI), in die Amerikanische Akademie für Allergie, Asthma und Immunologie (AAAAI) sowie in die World Allergy Organization (WAO) eingebunden. Die EAACI ist die weltgrösste Akademie für allergische Erkrankungen und übernimmt eine wichtige Rolle in Bezug auf Wissenschaft, Weiterbildung, Kommunikation und Öffentlichkeitsarbeit. Mit der Universität Stanford (Sean Parker Asthma and Allergy Center) besteht eine intensive Zusammenarbeit.

2020 wurden 119 wissenschaftliche Arbeiten in begutachteten internationalen Fachzeitschriften mit “Impact Factor” veröffentlicht oder sind noch in Druck. 2020 erreichte das SIAF einen Gesamtwert des “Impact Factors” von 882.682 und einen Durchschnitt von 7.609 Punkten pro Publikation. Die neusten Ergebnisse wurden zudem in 39 Abstracts an verschiedenen Fachtagungen mitgeteilt. Unsere Mitarbeitenden wurden zu 47 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 23 verschiedenen Sessionen hatten SIAF-Mitarbeitende den Vorsitz. Zusätzlich übernehmen SIAF-Mitarbeitende 54 wissenschaftliche Ämter in internationalen Gesellschaften und internationalen Zeitschriften. 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 2020 zum fünften Jahr in Folge von Thomson Reuters Clarivate in die Gruppe der meistzitierten Forscher aus allen wissenschaftlichen Fachbereichen weltweit aufgenommen. Das SIAF hat rund 1'440 Fachbeiträge veröffentlicht und gehört zu den meistzitierten Instituten weltweit. Die vom SIAF publizierten Artikel wurden 52‘530 Mal zitiert.

Mit der Eröffnung des Medizincampus Davos Wolfgang 2019 wurde ein Meilenstein gesetzt. Mit den eigenständigen Partnern CK-CARE AG, HGK, Davos BioSciences AG und Cardio Care AG besteht eine sehr enge Zusammenarbeit. Die zusammen erarbeiteten Resultate kommen direkt in Therapie und Klinik zur Anwendung. So profitieren die Patienten von der translationalen Allergie- und Kardio-Forschung auf dem Campus, da die Behandlung jederzeit auf dem aktuellsten Stand wissenschaftlicher Erkenntnis ist. Ebenfalls im Campus beheimatet ist die von der Kühne-Stiftung geförderte Stiftungsprofessur, mit der gleichermassen im Bereich der bildgebenden Methode zur Analyse von Oberflächenmarker von Zellen im Gewebe eng zusammen gearbeitet wird. Dank der Unterstützung durch die CK-CARE konnten seit 2009 mehr als 50 wissenschaftliche Mitarbeitende eingestellt und über 80 akademische Gäste im Austauschprogramm aufgenommen werden. Darüber hinaus wurden 250 Publikationen mit SIAF und CK-CARE Zugehörigkeit in namhaften Zeitschriften veröffentlicht.

Das Epithelgewebe – Schutzmauer oder Einfallstor für allergische Krankheiten und Immunerkrankungen

Allergische Krankheiten und Autoimmunerkrankungen haben stark zugenommen und epidemische Ausmasse angenommen, so dass mittlerweile mehr als eine Milliarde Menschen weltweit betroffen sind. In Industrieländern sind sie häufiger anzutreffen, aber ihre Prävalenz nimmt auch in den Entwicklungsländern parallel zur Urbanisierung und Industrialisierung weiter zu. Am SIAF Davos haben Forschende um Prof. Dr. Cezmi A. Akdis die Epithelbarriere-Hypothese aufgestellt, welche die Zunahme von Allergien, Autoimmunität und anderen chronischen Erkrankungen erklärt.

Intakte Haut- und Schleimhautbarrieren sind entscheidend für die Aufrechterhaltung des Gewebegleichgewichts, da sie das Wirtsgewebe vor Infektionen, Umweltgiften, Schadstoffen und Allergenen schützen. Eine defekte Epithelbarriere (das Epithel ist die oberste Zellschicht des Haut- und Schleimhautgewebes) wurde bei allergischen Krankheiten und Autoimmunerkrankungen wie Asthma, atopischer Dermatitis, allergischer Rhinitis, chronischer Rhinosinusitis, Zöliakie und entzündlichen Darmerkrankungen nachgewiesen. Darüber hinaus wird eine Undichtigkeit des Darmepithels auch bei systemischen Autoimmun- und Stoffwechselerkrankungen wie Diabetes, Adipositas, Multiple Sklerose, rheumatoide Arthritis und weitere Erkrankungen vermutet.

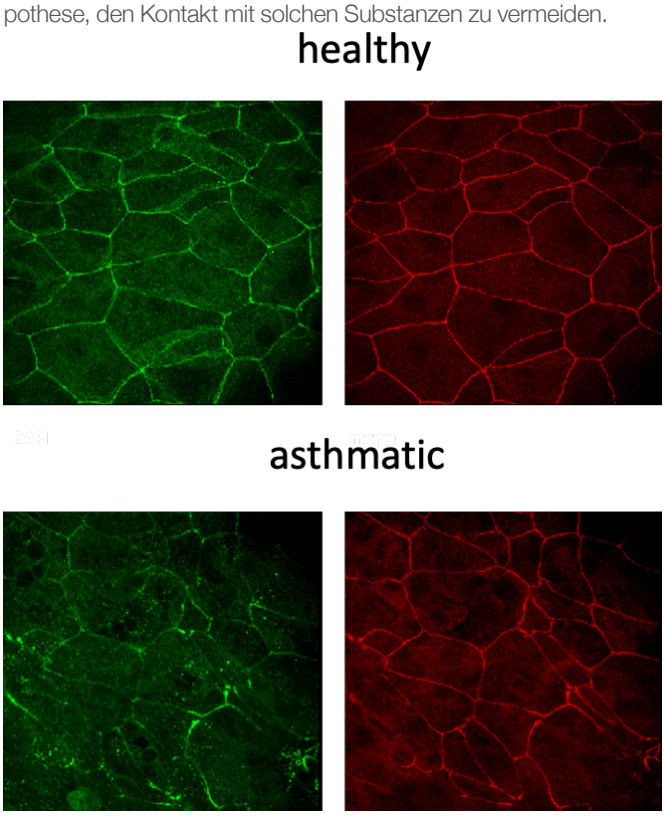
Die Erklärung für den Anstieg von Erkrankungen

In der sogenannten erweiterten Epithelbarriere-Hypothese, welche in einer der einflussreichsten Fachzeitschriften publiziert wurde, legen die Forschende vom SIAF nun nahe, dass die Zunahme von Epithelbarriere-schädigenden Substanzen, die mit der Industrialisierung, Urbanisierung und dem modernen Leben verbunden sind, zum Anstieg von allergischen, autoimmunen und anderen chroni-

schen Erkrankungen geführt haben könnte.

Schädliche Substanzen meiden

Die Barriere-Hypothese legt die Notwendigkeit der Vermeidung von Umweltauslösern nahe und rechtfertigt weitere Studien über Unbedenklichkeitsgrenze für potenziell schädliche Substanzen wie inhalierte und eingenommene Waschmittel, verarbeitete Lebensmitteln, die Emulgatoren enthalten, die Exposition gegenüber Feinstaub, Dieselabgasen, Mikroplastik und bestimmten Nanopartikeln. Die barriereschädigende Wirkung der meisten dieser Faktoren wurde durch das SIAF nachgewiesen. Wie bereits der Schweizer Heiler Paracelsus 1493 feststellte «sola dosis facit venenum» (Alles ist Gift, nichts ist Gift, alleine auf die Dosis kommt es an), empfiehlt die Hypothese, den Kontakt mit solchen Substanzen zu vermeiden.

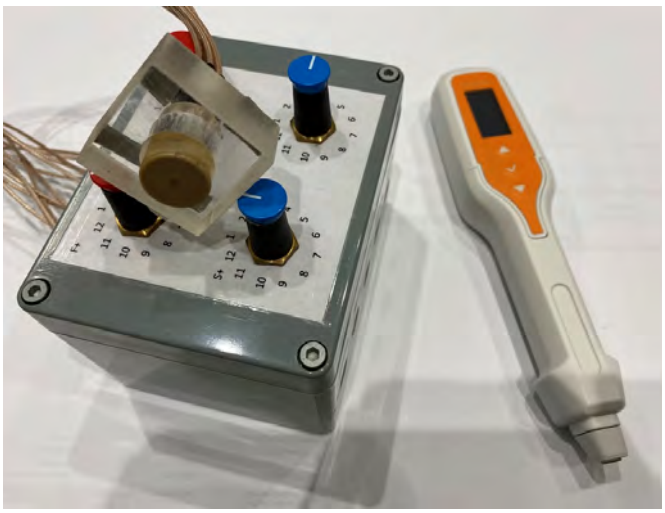


Auf den Bildern sind die Epithelzellen von Bronchien 400-fach vergrössert dargestellt. Oben sehen wir die geraden und klaren Linien der Epithelzellen in Bronchien bei einer gesunden Person. Und unten sind undichte und beschädigte Epithelzellen bei einer an Asthma erkrankten Person ersichtlich.

Frühintervention und neue therapeutische Ansätze

Basierend auf die Grundlage der neuen Erkenntnisse möchte das Forschungsteam um Prof. Akdis die Forschung der Epithelbarriere fortsetzen, um die Faktoren und molekularen Mechanismen einer "undichten Barrieren" besser zu verstehen. Hierfür sollen experimentelle Modelle entwickelt und validiert werden, um den Transport von Umweltschadstoffen durch die Haut und Schleimhaut noch genauer zu überwachen. Es ist auch wichtig, Personen mit undichter Hautbarriere zu identifizieren und zu diagnostizieren. Das SIAF hat ein Instrument zur Bestimmung der undichten Hautbarriere entwickelt und kürzlich veröffentlicht. Dadurch sollen neue Möglichkeiten zur Vorbeugung und frühzeitigen Therapie geschaffen werden und neue therapeutische Ansätze entwickelt werden.

Nevisens – vom Prototyp (links) zum marktreifen Messgerät (rechts).



COVID-19-Studien im SIAF

Unser Institut hat zu mehr als 30 COVID-19 und Sars-CoV-2 Publikationen beigetragen, die sehr zeitnah erschienen sind. Die klinischen Ergebnisse der COVID-19-Studien wurden in Zusammenarbeit mit Prof. Yadong Gao erstellt, einem SIAF-Mitglied der Universität Wuhan. Darüber hinaus haben wir wesentlich dazu beigetragen, wie man mit verschiedenen allergischen und asthmatischen Patienten während der Pandemien umgehen kann.

Wir waren die ersten, die in Zusammenarbeit mit der Universität Wuhan die erste Fallserie mit 140 COVID-19-Patienten veröffentlicht haben, lange bevor die Krankheit in Europa ausbrach. Es war die erste Studie, die den Kontakt von Mensch zu Mensch zeigte, da man zuvor dachte, dass sich die Krankheit vom Feinkost-Nassmarkt in Wuhan ausbreitete. Fortgeschrittenes Alter, Komorbiditäten wie Diabetes und Hypertonie wurden in dieser Studie erstmals als Risikofaktoren genannt, sowie die detaillierte Symptomatik, Lymphopenie und Eosinopenie und CT-Scan-Befunde der Lunge beschrieben. Veröffentlicht im Februar 2020.

Eine frühzeitige und zuverlässige Diagnose von COVID-19 war zu Beginn der Pandemie essentiell. Dieser Artikel konzentrierte sich besonders auf die falsch negativen Ergebnisse der PCR und zeigte, dass diese in 14% der Fälle auftreten. Dementsprechend sollte die Diagnose einer SARS-CoV-2-Infektion bei Patienten mit einem anfänglich negativen rRT-PCR-Ergebnis nicht ausgeschlossen werden, insbesondere wenn sie mit typischen klinischen Manifestationen vorgestellt werden. In Anbetracht dieser Ergebnisse empfehlen wir wiederholte rRT-PCR-Tests, um die Diagnose zu bestätigen und potenziell infizierte Personen zu identifizieren. Veröffentlicht im März 2020.

Wir haben elf verschiedene klinische Manifestationen von COVID-19 gezeigt, die im März 2020 erstmals veröffentlicht wurden.

Bericht des Direktors

Aufbau des Swiss Research Institute for Sports Medicine (SRISM)
Unser Forschungsteam und Dr. Beat Villiger, Dr. Walter Kistler, Dr. Michael Villiger und Dr. Debbie Maurer haben sich stark auf den Aufbau einer sportmedizinischen Forschungsgruppe innerhalb des SIAF und des Spitals Davos (SPIDA) mit den Schwerpunkten Sportmedizin, Immunologie und Stoffwechsel fokussiert, gefolgt vom Aufbau des Swiss Research Institute for Sports Medicine.
Die Patientenbetreuung und Kohortenentwicklung wird im Spital Davos durchgeführt. Molekulare Allergie-, Asthma-, Stoffwechsel- und Immunologieforschung wird im SIAF durchgeführt.
Eine Biobank, die Material von Sportkohorten und Kontrollen sammelt, wird im SIAF über die bestehende SIAF-Biobank entwickelt.
Ziel ist die Charakterisierung des Immunsystems bei Elitesportlern im Vergleich zu einer gesunden gleichaltrigen Kontrollgruppe (Amateursportler und Inaktive). Dazu gehören die Identifizierung der Ursachen der Empfindlichkeit für Infektionen und Allergien bei Elitesportlern, die Rolle von Stoffwechselveränderungen bei der Anfälligkeit für Infektionen und Allergien bei Elitesportlern, die Identifikation von molekularen Zielstrukturen und des Stoffwechsels der Infekt- und Allergieanfälligkeit und die Auswirkungen von intensivem Training auf die Immunantwort und den zellulären Stoffwechsel.

Einrichtung einer Sonderprofessur und eines Zentrums für Präzisions-Proteomics
Der Antrag im Profilfeld 5 Life Science zur Einrichtung der Sonderprofessur und einem Zentrum für Präzisions-Proteomics war am 15. November 2019 eingereicht worden. Daran angeknüpft war die Einrichtung einer non-tenured Assistenzprofessur an der Medizinischen Fakultät der Universität Zürich zur akademischen Anbindung der Sonderprofessur. Am 5. September 2020 hat die Regierung des Kantons Graubünden dann entschieden dem SIAF den Auftrag zu ersteilen, «...vom 1. August bis zum 31. Juli 2026 ein Zentrum für Proteomics mittels einer Sonderprofessur für das Profilfeld «Life Science» gemäss eingereichtem Konzept als «Leading House» ... aufzubauen und zu betreiben...». Prof. Cezmi Akdis und PD Dr. Katja Bärenfaller wurden für die interimistische Projektleitung bis zur Ernennung und Anstellung des/r Sonderprofessors/in auf der Non-Tenure-Track-Assistenzprofessur der Medizinischen Fakultät der Universität Zürich eingesetzt. Mit dem Entscheid des Kantons war gemäss eingereichtem Budget die Rest-Finanzierung für die Installation und der Betrieb des Orbitrap ECLIPSE Massenspektrometers gesichert. Das Orbitrap ECLIPSE Massenspektrometer ist seit Sommer 2020 nun voll funktionstüchtig und misst im Dauereinsatz diverse Proben. Diese stammen teils aus eigene SIAF-Projekte und teils aus nationalen und international en Projekten. Dies entspricht der in den Konzepten formulierten Forschungsausrichtung des Zentrums für Präzisions-Proteomics, das sich auf zwei Richtungen fokussieren soll. Erstens sollen in explorativen Studien experimentelle Methoden zu Massenspektrometer-Analysen von Proteinen im Kontext von Allergien und Asthma etabliert und angewendet werden. Zweitens ist vorgesehen, dass im Rahmen von Kollaborationen gezielte Experimente durchgeführt werden, die wichtige Daten zu den entsprechenden wissenschaftlichen Fragestellungen liefern. Damit soll einerseits längerfristig Expertise und eine Datenbasis aufgebaut werden, und andererseits rasch eine direkter Nutzen ersichtlich sein.

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.

Aufgrund der Pandemie und dem vom Bundesrat verhängten Veranstaltungsverbot musste die vierzehnte Durchführung des World Immune Regulation Meetings (WIRM) im Kongresszentrum Davos im März 2020 nur 4 Tage vor Beginn abgesagt werden. Der Kongress konnte vom 4. bis 7. Oktober 2020 nachgeholt werden, jedoch als komplett virtuelle Ausführung. Durch sehr gute Zusammenarbeit zwischen dem IT-Team des SIAF und der GroupConsulter AG konnte der erste virtuelle Kongress erfolgreich durchgeführt werden. Rund 450 Nachwuchsforscher sowie Senior Wissenschaftler aus über 40 verschiedenen Länder hielten 124 Vorträge und trugen 197 Abstracts vor, tauschten sich über die neuesten Erkenntnisse in der Immunologie und zum aktuellsten Thema „COVID-19“ aus.

Das WIRM bietet jährlich eine perfekte Plattform, um die besten Forscher im Gebiet zu versammeln und die neuesten Entwicklungen zu diskutieren. Dieser globale Austausch von hochwertigen aktuellen Erkenntnissen hilft, neue Behandlungen zu entwickeln und neue Lösungsansätze zu finden. Das international ausgeschriebene WIRM zählt mittlerweile in Europa zu einem der angesehensten Kongresse seiner Art.

Finanzielle Grundlage
Die Ausgaben und der finanzielle Ertrag des SIAF haben sich im Vergleich zu den vergangenen Jahren nur unwesentlich verändert. Eine Grundfinanzierung des Instituts ist durch die Hauptsponsoren gegenwärtig sichergestellt. Sie besteht vor allem aus einem Beitrag des Bundes (Forschungsförderungsgesetz Art. 15), Beiträge des Kantons Graubünden und der Gemeinde Davos, Beiträge der Universität Zürich, Beitrage des Schweizerischen Nationalfonds sowie Beiträge von Stiftungen, wie die PROMEDICA Stiftung und die Stiftung vormals Bündner Heilstätte Arosa, die Doktorandenprogram-

me fördern. Die zusätzlichen Ausgaben wurden aus Erträge von zusätzlichen kompetitiv erworbenen Drittmitteln und des WIRM-Kongresses gedeckt.

Dank

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

Insbesondere möchte ich hier unsere fruchtbare Zusammenarbeit mit der CK-CARE betonen, welche uns patientenorientierte Forschung 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 vergeben 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 Behörden, die sich unermüdlich für die Forschung des SIAF interessieren und das Institut in jeder Hinsicht fördern.

Davos, Mai 2021

Report of the director

Prof. Dr. med. Cezmi A. Akdis

The Swiss Institute of Allergy and Asthma Research (SIAF) in its present form was founded in 1988 by the Medical Department of the Swiss Research Institute for High Altitude Climate and Medicine Davos Foundation (SFI). SIAF has been affiliated with the University of Zurich since 1996 and a member of the Life Science Zurich Graduate School, a joint educational project of the University of Zurich and ETH Zurich, since 2008. This affiliation enables SIAF to offer a fully comprehensive PhD education. In addition, SIAF is an active member of Academia Raetica and the Graduate School of the Canton of Graubünden.

Allergic diseases have shown an epidemic increase in recent decades and affect the lives of more than one billion people worldwide. Their prevalence continues to increase in developing countries in parallel with urbanization and industrialization. It is therefore of enormous importance to pursue the scientific issues so that the solutions can directly benefit the patients and their families.

The research at SIAF focuses on patient-relevant translational research and investigation of the immunological basis of allergic and asthmatic diseases, which creates starting points for new preventive and curative treatments for the benefit of those affected. The research is designed for direct cooperation with the clinics in Davos, the University of Zurich and other specialized institutes. In addition, SIAF is involved in the European network of national centers of excellence (GA2LEN project: Global Allergy and Asthma European Network of Excellence), in the European Academy of Allergology and Clinical Immunology (EAACI), in the American Academy of Allergy, Asthma and Immunology (AAAAI), and in the World Allergy Organization (WAO). EAACI is the world's largest academy for allergic diseases and plays an important role in science, continuing education, communications, and outreach. There is an intensive collaboration with Stanford University (Sean Parker Asthma and Allergy Center).

The SIAF has published 1'440 research articles and is one of the most cited institutions of its size worldwide. The articles published by the SIAF have been cited 62'530 times. The institute with its approximately 45-50 employees is one of the highest 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 2020, 119 scientific papers were published or are still in press in peer-reviewed international journals with "Impact Factor". In 2020, SIAF achieved a total "Impact Factor" score of 882.682 and an average of 7.609 points per publication. The latest results were also shared in 39 abstracts at various professional meetings. Our employees were invited to 47 different seminars and lectures at national and international congresses. Such invitations are important for the dissemination of the results obtained and for the international acceptance of the Institute's research. SIAF staff members chaired 23 different sessions. In addition, SIAF staff members hold 54 scientific positions in international societies and international journals. In addition, Prof. C. A. Akdis holds the position of Editor-in-Chief of the journal Allergy since 2018. As a result of his internationally highly respected scientific publications, in 2020 Prof. Dr. C. A. Akdis was included by Thomson Reuters Clarivate in the group of the most cited researchers from all scientific disciplines worldwide for the fifth year in a row.

A milestone was set with the opening of the Davos Wolfgang Medicine Campus in 2019. There is very close cooperation with the independent partners CK-CARE AG, HGK, Davos Bioscience AG and Cardio Care AG. The results developed together are directly applied in therapy and clinic. Patients benefit from translational allergy and cardio research on the campus, as treatment is always based on the latest scientific findings. The campus is also home to the endowed professorship funded by the Kühne Foundation, with which close collaboration is equally being pursued in the field of imaging methods for analyzing surface markers of cells in tissue. Thanks to the support of CK-CARE, more than 50 scientific staff members have been hired since 2009 and more than 80 academic guests have been hosted in the exchange program. In addition, 250 publications with SIAF and CK-CARE affiliation have been published in high impact journals.

Our institute contributed to more than 30 COVID-19 and Sars-CoV-2 publications very timely. Clinical findings of COVID-19 studies were done in collaboration with Prof. Yadong Gao one of the SIAF members from Wuhan University. In addition, we have substantially contributed to how to handle different allergic and asthmatic patients during the pandemics.
We were the first ones to publish the first 140 case series In collaboration with Wuhan University, it was one of the first publications of the 140 COVID-19 patients, much before the disease started in Europe. It was the first study showing human to human contact, because before it was thought that the disease was spreading from the wetmarket in Wuhan. Older age, comorbiditis as diabetes and hypertension were mentioned for the first time as risk factors as well as the detailed symptoms, lymphopenia and eosinopenia and CT-Scan findings of the lungs were described in this study, published in February 2020.
Early and reliable diagnosis of COVID-19 was essential in the beginning of the pandemic and this article focused particularly on the false negative results of PCR and demonstrated that it occurs in 14% of the cases. Accordingly, the diagnosis of SARS-CoV-2 infection should not be excluded in patients with an initial negative rRT-PCR result, especially when presented with typical clinical manifestations. In view of these results, we recommend repeated rRT-PCR tests to confirm diagnosis and identify potentially infected individuals. Published in March 2020. In addition, we demonstrated eleven different clinical manifestations of COVID-19 for the first time published in March 2020. In May 2020, we published for the first time the detailed analysis of the expression of SARS-CoV-2 receptors across different human cells and tissues, in children and in adults as well as in patients with asthma, COPD, obesity, hypertension and risk factors for severe COVID-19.

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 tole-

rance; 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.

Defective Epithelial Barriers Linked to Two Billion Chronic Diseases

Humans are exposed to a variety of toxins and chemicals every day. According to the epithelial barrier hypothesis, exposure to many of these substances damages the epithelium, the thin layer of cells that covers the surface of our skin, lungs and intestine. Defective epithelial barriers have been linked to a rise in almost two billion allergic, autoimmune, neurodegenerative and psychiatric diseases.

Epithelial cells form the covering of most internal and external surfaces of the human body. This protective layer acts as a defense against invaders – including bacteria, viruses, environmental toxins, pollutants and allergens. If the skin and mucosal barriers are damaged or leaky, foreign agents such as bacteria can enter into the tissue and cause local, often chronic inflammation. This has both direct and indirect consequences.

Chronic diseases due to defective epithelial barriers

Cezmi Akdis, Director of the Swiss Institute of Allergy and Asthma Research (SIAF), which is associated with the University of Zurich (UZH), has now published a comprehensive review of the research on epithelial barrier damage in Nature Reviews Immunology. “The epithelial barrier hypothesis proposes that damages to the epithelial barrier are responsible for up to two billion chronic, non-infectious diseases,” Professor Akdis says. In the past 20 years, researchers at the SIAF alone published more than 60 articles on how various substances damage the epithelial cells of a number of organs.

Rise in allergic and autoimmune conditions

The epithelial barrier hypothesis provides an explanation as to why allergies and autoimmune diseases have been increasing for decades – they are linked to industrialization, urbanization and westernized lifestyle. Today many people are exposed to a wide range of toxins, such as ozone, nanoparticles, microplastics, household cleaning agents, pesticides, enzymes, emulsifiers, fine dust, exhaust fumes, cigarette smoke and countless chemicals in the air, food and water. “Next to global warming and viral pandemics such as COVID-19, these harmful substances represent one of the greatest threats to humankind,” emphasizes Akdis.

Asthma, Alzheimer’s et al.

Local epithelial damage to the skin and mucosal barriers lead to allergic conditions, inflammatory bowel disorders and celiac disease. But disruptions to the epithelial barrier can also be linked to many other diseases that are characterized by changes in the microbiome. Either the immune system erroneously attacks “good” bacteria in healthy bodies or it targets pathogenic – i.e. “bad” – invaders. In the gut, leaky epithelial barriers and microbial imbalance contribute to the onset or development of chronic autoimmune and metabolic diseases such as diabetes, obesity, rheumatoid arthritis, multiple sclerosis or ankylosing spondylitis. Moreover, defective epithelial barriers have also been linked to neurodegenerative and psychiatric diseases such as Parkinson’s disease, Alzheimer’s disease, autism spectrum disorders and chronic depression, which may be triggered or aggravated by distant inflammatory responses and changes in the gut’s microbiome.

Prevention, intervention – and more research

“There is a great need to continue research into the epithelial barrier to advance our understanding of molecular mechanisms and develop new approaches for prevention, early intervention and therapy,” says Akdis. Novel therapeutic approaches could focus on strengthening tissue-specific barriers, blocking bacteria or avoiding colonization by pathogens. Other strategies to reduce diseases may involve the microbiome, for example through targeted dietary measures. Last but not least, the focus must also be on avoiding and reducing exposure to harmful substances and developing fewer toxic products.

Development of Swiss Research Institute for Sports Medicine (SRISM)

Our team including Dr. Beat Villiger, Dr. Walter Kistler, Dr. Michael Villiger and Dr. Debbie Maurer have strongly focused on the development of a Sports Medicine Research Group within the SIAF and the Hospital of Davos (SPIDA) with the main focus on sport medicine, immunology and metabolism, followed by development of a Swiss Research Institute on Sports Medicine.
Patient care and cohort development is performed in Spital Davos. Molecular allergy, asthma, metabolism and immunology research is performed in SIAF.
A biobank that collects material from sports cohorts and controls is being developed in SIAF over the existing SIAF biobank.
We are aiming for the characterization of the Immune System in Elite Sport athletes compared with a healthy same age control group (amateur athletes & inactive persons), These includes the identification of the reasons of the sensitivity for infections & allergies in elite sports athletes, the role of metabolic changes in the sensibility for infections & allergies in Elite Sport athletes, the identification of molecular target structures and the metabolism of the sensibility for infections and allergies and the effects of intensive trainings on the immune response and the cellular metabolism.

Establishment of the special professorship and a center for precision proteomics

The application in profile field 5 Life Science for the establishment of the special professorship and a center for precision proteomics was submitted on November 15, 2019. This was followed by the establishment of a non-tenured assistant professorship at the Medical Faculty of the University of Zurich for the academic connection of the special professorship. On September 5, 2020, the government of the Canton of Graubünden then decided to award SIAF the contract to "...establish and operate a center for proteomics by means of a special professorship for the profile field "Life Science" as a "Leading House" ... from August 1 to July 31, 2026 according to the

submitted concept...". Prof. Cezmi Akdis and PD Dr. Katja Bärenfaller were appointed for the interim project management before the appointment and employment of the special professor in the non-tenure-track assistant professorship of the Medical Faculty of the University of Zurich. Thus, according to the submitted budget, the remaining funding for the installation and operation of the Orbitrap ECLIPSE mass spectrometer was secured. The Orbitrap ECLIPSE mass spectrometer is now fully functional since summer 2020 and measures various samples in continuous operation. These samples originate partly from our own SIAF projects and partly from national and international projects. This corresponds to the research orientation of the Center for Precision Proteomics formulated in the concepts, which is to focus on two directions. First, experimental methods for mass spectrometry analysis of proteins in the context of allergy and asthma will be established and applied in exploratory studies. Secondly, it is envisaged that targeted experiments will be carried out in collaborations that will provide important data on the relevant scientific questions. On the one hand, this is intended to build up expertise and a database in the longer term, and on the other hand, a direct benefit will quickly become apparent.

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. PD Dr. Katja Bärenfaller and Dr. Milena Sokolowska are members of the UZH teaching faculty and organise a 3-week block course on biomedical data mining within the framework of the Life Science Faculty of the University of Zurich.

Due to the pandemic and the event ban imposed by the Federal Council, the fourteenth staging of the World Immune Regulation Meeting (WIRM) at the Davos Congress Center in March 2020 had to be cancelled only 4 days before the start. The congress could be organized from 4th to 7th of October 2020, but as a completely virtual execution. Thanks to very good cooperation between the IT team of SIAF and GroupConsulter AG, the first virtual congress could be held successfully. About 450 young researchers as well as senior scientists from more than 40 different countries gave 124 lectures and presented 197 abstracts, exchanged information about the latest findings in immunology and about the most current topic "COVID-19".

The WIRM annually provides a perfect platform to gather the best researchers in the field and discuss the latest developments. This global exchange of high quality current knowledge helps to develop new treatments and find new approaches. The internationally announced WIRM is now one of the most prestigious congresses of its kind in Europe.

Financial basis

SIAF's expenses and financial income have changed only insignificantly compared to previous years. Basic funding of the Institute is currently ensured by the main sponsors. It consists mainly of a contribution from the federal government (Research Promotion Act Art. 15), contributions from the Canton of Graubünden and the municipality of Davos, contributions from the University of Zurich, contributions from the Swiss National Science Foundation, and contributions from foundations, such as the PROMEDICA Foundation and the Foundation formerly Bündner Heilstätte Arosa, which support doctoral programs. The additional expenses were covered by income from additional competitively acquired third-party funds and the WIRM congress.

Acknowledgements

I would like to sincerely thank all employees for their great work and the good working atmosphere at SIAF. At the same time, I would like to thank the Davos clinics, their chief physicians and their staff, as well as the University of Zurich for their constant and effective support of our institute.

In particular, I would like to emphasize our fruitful collaboration with CK-CARE, which enables us to conduct patient-oriented research in atopic dermatitis. I especially thank Mrs. and Mr. Kühne for their support, which enables our research to find sustainable solutions for better diagnoses and treatments of atopic dermatitis patients. Thanks to this support, many Master's degrees and PhD degrees have been obtained in the Institute.

Above all, my thanks also go to the Swiss Research Institute for High Altitude Climate and Medicine (SFI) Foundation, its Foundation Board and Foundation Board Committee for the support they have always provided. Last but not least, my thanks go to the authorities, who have taken a tireless interest in SIAF's research and have supported the Institute in every way.

Davos, May 2021

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Prof. Dr. Cezmi A. Akdis, MD

Studies on Epithelial Barrier Hypothesis

Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?

Akdis CA. Nat Rev Immunol. 2021. doi: 10.1038/s41577-021-00538-7.

The incidence of allergic asthma and atopic dermatitis started to grow to epidemic proportions after the 1960s. Since 2000, the prevalence of food allergy, eosinophilic esophagitis and drug-induced anaphylaxis has risen to epidemic proportions. In addition, a substantial increase in autoimmune and metabolic conditions, such as diabetes, obesity, rheumatoid arthritis, multiple sclerosis and celiac disease has been recorded in industrialized countries since the 1960s, and this trend is still continuing today. During the same period, a significant increase in the prevalence of specific IgG and IgE against allergens was observed. Allergen-specific IgG antibodies were rarely detected in the 1970 and 80s, whereas in 2018, milk and egg-specific IgG antibodies were detected in almost all babies tested at the age of one. Currently, allergen-specific IgE prevalence (to any allergen) exceeds 50% of the population in Europe, Northern America and Australia. Several recent studies in animals and humans suggest a connection between increased intestinal barrier leakiness and neurodegenerative and psychiatric disorders such as Parkinson's disease, Alzheimer's disease, autism-spectrum disorders and chronic depression. Although they require further evidence, these conditions have substantially increased in prevalence during the same time period as allergic and autoimmune diseases. "Epihelial Barrier Hypothesis" proposes that increased exposure to epithelial barrier damaging agents linked to industrialization, urbanization and modern life underlies the rise in allergic, autoimmune and other chronic conditions. It discusses whether the immune response to dysbiotic microbiota that cross the damaged barrier are involved in the development of these diseases. Almost two billion patients are affected with the epithelial barrier damaging agents. The development of leaky epithelial barriers then leads to microbial dysbiosis and the translocation of bacteria to interepithelial and subepithelial areas and the development of tissue microinflammation. These processes underlie not only the development of allergy and autoimmune conditions in barrier-damaged tissues but also a wide range of diseases in which an immune response to commensal bacteria and opportunistic pathogens occurs. A defective epithelial barrier has been demonstrated in allergic and autoimmune conditions such as asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, eosinophilic esophagitis, celiac disease, and inflammatory bowel disease. In addition, leakiness of the gut epithelium is also implicated in systemic autoimmune and metabolic conditions such as diabetes, obesity, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and autoimmune hepatitis. Finally, distant inflammatory responses due to a 'leaky gut' and microbiome changes are suspected in Alzheimer's disease, Parkinson's disease, chronic depression and autism spectrum disorders.

Box 1 | The increase in allergy and asthma, specific antibody responses to environmental antigens, and immune responses to *Staphylococcus aureus*

The beginning of the allergy and asthma epidemic in the 1960s

- Increase in incidence of asthma observed in Finnish army recruits in 1961 (REF.[185])
- Increase in patients of all ages with asthma observed in the UK in the early 1960s[186]
- Almost 10-fold increase in hospital admissions of children with asthma in Australia, the UK, New Zealand, Canada and the USA between 1965 to 1980 (REF.[187])
- Asthma prevalence doubled in Swedish army recruits (particularly those from urban areas) between 1971 and 1981 (REF.[188])
- Low prevalence of allergic diseases in East Germany in 1989, but it became comparable to that in West Germany after reunification[189,190]

Increased IgG and IgE responses against allergens from the 1970s until present

- Very rare or no IgG antibody response in healthy individuals to environmental antigens in the 1970s and 1980s[14,17]
- Increase in allergen-specific IgE and IgG against environmental antigens observed after the 1970s[14,35,191,192]
- Increased allergen-specific IgE in frozen serum samples from 1998 as compared to samples from 1990, when analysed with the same assay[192]
- 49.8% of Norwegian children aged between 10 and 16 years had IgE sensitization against at least one environmental allergenic protein in 2015 (REF.[193])
- IgG against grass pollen, olive/ash pollen, birch pollen or house dust mites in most adults in 2017 (REF.[194])
- IgG antibodies against milk and egg in almost all babies at the age of 1 year in 2018 (REF.[16])
- IgE against one of the allergens in a broad panel of 64 aeroallergen components were detected in more than 90% of individuals with rhinitis, conjunctivitis and asthma in 2019 (REF.[195])

Figure 1. The problem: Pandemic of many chronic noncommunicable diseases starting after 1960s and increasing after 2000s. The incidence of allergic asthma and atopic dermatitis started to grow to epidemic proportions after the 1960s (see also Box 1). Since 2000, the prevalence of food allergy, eosinophilic esophagitis and drug-induced anaphylaxis has risen to epidemic proportions. In addition, a substantial increase in autoimmune and metabolic conditions, such as diabetes, obesity, rheumatoid arthritis, multiple sclerosis and celiac disease has been recorded in industrialized countries since the 1960s, and this trend is still continuing today. During the same period, a significant increase in the prevalence of specific IgG and IgE against allergens was observed. Allergen-specific IgG antibodies were rarely detected in the 1970 and 80s, whereas in 2018, milk and egg-specific IgG antibodies were detected in almost all babies tested at the age of one. Currently, allergen-specific IgE prevalence (to any allergen) exceeds 50% of the population in Europe, Northern America and Australia. Several recent studies in animals and humans suggest a connection between increased intestinal barrier leakiness and neurodegenerative and psychiatric disorders such as Parkinson's disease, Alzheimer's disease, autism-spectrum disorders and chronic depression). Although they require further evidence, these conditions have substantially increased in prevalence during the same time period as allergic and autoimmune diseases.

A number of allergens, pathogens and environmental toxins can damage the epithelial barrier. These include allergens derived from dust mites, certain bacteria, fungi, viruses, toxins contained in laundry, dishwashing and household cleaning agents. Moreover,

surfactants, enzymes and emulsifiers in processed food, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles and microplastics have been shown to damage the epithelial barrier. A large number of these substances are encountered by humans as a consequence of industrialization, urbanization and modernization

Electrical impedance spectroscopy for the characterization of skin barrier in atopic dermatitis.

Rinaldi AO, Korsfeldt A, Ward S, Burla D, Dreher A, Gautschi M, Stolpe B, Tan G, Bersuch E, Melin D, Askary Lord N, Grant S, Svedenhag P, Tsekova K, Schmid-Grendelmeier P, Möhrenschlager M, Renner ED, Akdis CA. Allergy. 2021 Apr 8. doi: 10.1111/all.14842.

This study aimed to establish a method to directly assess the in vivo status of epithelial barrier using electrical impedance spectroscopy (EIS). Thirty-six patients with AD were followed during their 3-week hospitalization and compared with 28 controls. EIS and transepidermal water loss (TEWL) were measured in lesional and non-lesional skin. Targeted proteomics by proximity extension assay in serum and whole-genome sequence were performed. Electrical impedance spectroscopy was able to assess epithelial barrier integrity, differentiate between patients and controls without AD, and characterize lesional and non-lesional skin of patients. It showed a significant negative correlation with TEWL, but a higher sensitivity to discriminate non-lesional atopic skin from controls. During hospitalization, lesions reported a significant increase in EIS that correlated with healing, decreased SCORAD and itch scores. Additionally, EIS showed a significant inverse correlation with serum biomarkers associated with inflammatory pathways that may affect the epithelial barrier, particularly chemokines such as CCL13, CCL3, CCL7, and CXCL8 and other cytokines, such as IRAK1, IRAK4, and FG2, which were significantly high at admission. Furthermore, filaggrin copy numbers significantly correlated with EIS on non-lesional skin of patients. In conclusion, electric impedance spectroscopy can be a useful tool to detect skin barrier dysfunction in vivo, valuable for the assessment of AD severity, progression, and therapy efficacy.

Inhibition of CpG methylation improves the barrier integrity of bronchial epithelial cells in asthma.

Wawrzyniak P, Krawczyk K, Acharya S, Tan G, Wawrzyniak M, Karouzakis E, Dreher A, Jakiela B, Altunbulakli C, Sanak M, O'Mahony L, Nadeau K, Akdis CA. Allergy. 2020 Nov 19

Our group has published several key papers on the epigenetic regulation mechanisms of the epithelial barriers. This study demonstrates an increased global methylation level in human bronchial epithelial cells from asthmatic individuals. CpG methylation of specific genes is essential for the defect of epithelial barrier integrity, which is reversed upon DNA methyltransferase inhibition. The inversion of CpG methylation restores leakiness in the epithelium in asthma by increasing transepithelial resistance, decreasing paracellular flux and improves the structure of bronchial epithelial cells by increasing the expression of tight junction proteins.

Global warming, climate change, air pollution and allergies.

D'Amato G, Akdis CA. Allergy. 2020 Sep;75(9):2158-2160.

This editorial takes the attention to global warming and climate change in the world. The average global temperatures on our planet are increasing due to rising anthropogenic greenhouse gases in the atmosphere, in particular carbon dioxide (CO2). There is an urgent need to call for action on global warming, which is resulting in extreme weather and related catastrophes. The Earth's rising temperature is evidenced by warming of the oceans, melting glaciers, rising sea levels, and the diminished snow cover in the Northern Hemisphere. Climate-related factors can affect interactive atmospheric components (chemical and biological) and their interrelationship with human health.

Table 2 | **Epithelial barrier-damaging substances introduced by industrialization and urbanization that are linked with chronic inflammatory conditions**

Condition associated with damaged epithelial barrier	Substance	Evidence
Occupational asthma (employees in the detergent industry)	Cellulase and lipase enzymes	Allergic sensitization to enzymes in patients
Occupational asthma (employees in the detergent industry)	Amylase	Allergic and non-allergen-specific bronchial hyperreactivity in patients
Occupational asthma and chronic bronchitis (individuals working as domestic cleaners)	Bleach and other irritants	Case–control study
Occupational asthma (employees in modern detergent factory)	Different enzymes in laundry detergents	Investigation of 342 workers showed upper respiratory or chest symptoms in 19% and 16% of the workers, respectively
Asthma and rhinitis	*Bacillus subtilis* enzyme	Allergic and direct tissue-destructive activity observed in employees of detergent factory
Asthma	Different cleaning products	Evidence laid out in consensus document of the EAACI
Asthma	Medical disinfectants	4,102 nurses were included in the study; poor asthma control was observed in nurses exposed to medical disinfectants
Asthma	Proteases of *Alternaria alternata*	Air–liquid interface cultures from patients with asthma show increased barrier disruption
Chronic rhinosinusitis	*Staphylococcus aureus*	Human sinus biopsy explant cultures
Atopic dermatitis	*S. aureus*	Human skin biopsies

Table 3 | **Animal and in vitro models of barrier disruption**

Substance	Evidence
Polystyrene microplastic	Mouse models show effect of polystyrene microplastics on gut barrier
Ozone	Mouse models show respiratory barrier injury through ozone
Cigarette smoke	Mouse models show that cigarette smoke causes acute lung injury
Particulate matter	Ex vivo experiments with human and rat alveolar epithelial cells show that particulate matter affects the distribution of occludin and the alveolar barrier; PM2.5 causes defects in the nasal epithelial barrier in non-inflamed nasal biopsy samples of patients with sinusitis; PM10 stimulates myeloid dendritic cells to induce T_H17 cells with brain-homing property in vitro
Diesel exhaust particulates	Human and rat alveolar epithelial cells exposed to diesel exhaust particulates show low occludin expression and barrier leakiness
Nanoparticles	Human cell cultures show that nanoparticles disrupt intestinal barrier homeostasis
Anionic surfactants and commercial detergents	Human skin keratinocyte cultures show that anionic surfactants and commercial detergents decrease tight junction barrier integrity
Detergent residue	Human bronchial epithelial cell air–liquid interface cultures show that detergent residues disrupt tight junction barrier integrity in human bronchial epithelial cells even at low concentrations
Emulsifiers in processed food	Emulsifiers increased damage to the structure of hamster small intestine in vivo and the translocation of *Escherichia coli* across M-cells in vitro

PM2.5, particulate pollutant that is 2.5 μm or smaller in size; PM10, particulate pollutant that is 10 μm or smaller in size; T_H17, T helper 17.

Figure 2. Epithelial barrier damaging substances introduced by modern life linked to chronic inflammatory diseases.
A number of allergens, pathogens and environmental toxins can damage the epithelial barrier. These include allergens derived from dust mites, certain bacteria, fungi, viruses, toxins contained in laundry, dishwashing and household cleaning agents. Moreover, surfactants, enzymes and emulsifiers in processed food, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles and microplastics have been shown to damage the epithelial barrier (Table 2-Table3). A large number of these substances are encountered by humans as a consequence of industrialization, urbanization and modernization.

Environmental factors in epithelial barrier dysfunction.

Celebi Sözener Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA.J Allergy Clin Immunol. 2020 Jun;145(6):1517-1528.

This is an important review on environmental factors that affect epithelial barriers. The main interfaces controlling and attempting to homeostatically balance communications between the host and

the environment are the epithelial barriers of the skin, gastrointestinal system, and airways. The epithelial barrier constitutes the first line of physical, chemical, and immunologic defenses and provides a protective wall against environmental factors. Following the industrial revolution in the 19th century, urbanization and socioeconomic development have led to an increase in energy consumption, and waste discharge, leading to increased exposure to air pollution and chemical hazards. Particularly after the 1960s, biological and chemical insults from the surrounding environment-the exposome-have been disrupting the physical integrity of the barrier by degrading the intercellular barrier proteins at tight and adherens junctions, triggering epithelial alarmin cytokine responses such as IL-25, IL-33, and thymic stromal lymphopoietin, and increasing the epithelial barrier permeability. A typical type 2 immune response develops in affected organs in asthma, rhinitis, chronic rhinosinusitis, eosinophilic esophagitis, food allergy, and atopic dermatitis. This article discusses the effects of environmental factors such as protease enzymes of allergens, detergents, tobacco, ozone, particulate matter, diesel exhaust, nanoparticles, and microplastic on the integrity of the epithelial barriers in the context of epithelial barrier hypothesis.

Outside-in hypothesis revisited: The role of microbial, epithelial, and immune interactions.

Sugita K, Soyka MB, Wawrzyniak P, Rinaldi AO, Mitamura Y, Akdis M, Akdis CA. Ann Allergy Asthma Immunol. 2020 Nov;125(5):517-527. doi: 10.1016/j.anai.2020.05.016.

This review summarizes the recent advances in microbial, epithelial, and immune interactions in atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, and asthma. Dynamic crosstalk between the environmental factors and microbial, epithelial, and immune cells in the development of atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, and asthma underlies the pathogenesis of these diseases. There is substantial evidence in the literature suggesting that environmental factors directly affect barrier function of the epithelium. In addition, T-helper 2 (TH2) cells, type 2 innate lymphoid cells, and their cytokine interleukin 13 (IL-13) damage skin and lung barriers. The effects of environmental factors may at least in part be mediated by epigenetic mechanisms. Histone deacetylase activation by type 2 immune response has a major effect on leaky barriers and blocking of histone deacetylase activity corrects the defective barrier in human air-liquid interface cultures and mouse models of allergic asthma with rhinitis. We also present and discuss a novel device to detect and monitor skin barrier dysfunction, which provides an opportunity to rapidly and robustly assess disease severity.

COVID-19 and SARS-CoV-2

Our institute contributed to more than 30 COVID-19 and Sars-CoV-2 publications very timely. Clinical findings of COVID-19 studies were done in collabration with Prof. Yadong Gao one of the SIAF members from Wuhan University. In addtion we have substantially contributed to how to handle different allergic and asthmatic patients during the pandemics.

Allergic reactions to the first COVID-19 vaccine: a potential role of Polyethylene glycol?

Cabanillas B, Akdis CA, Novak N. Allergy. 2020 Dec 15.

This was the first article on immediate side effects of COVID-19 vaccines. The COVID-19 vaccine developed by Pfizer and BioNTech was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom (UK) on December 2nd 2020. On the second day of the vaccination program, the national health system in England informed that two healthcare workers experienced systemic adverse allergic symptoms shortly after receiving the vaccine. This article evaluates these cases and the vaccine incipients that may cause severe allergic reactions.

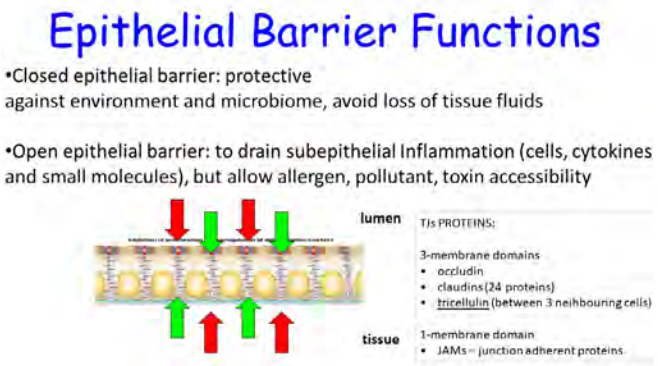


Figure 3: Epithelial barrier functions
The epithelial barrier in the airways, gastrointestional system and urogenital system consists of mucus, microbiota, surface liquids, and junctional complexes between adjacent epithelial cells that comprise tight junctions and adherens junctions. Interepithelial junction molecules bind through homotypic and heterotypic interactions, establish cell-cell contact and regulate the passage of molecules and small particles between cells. In the skin, the stratum corneum forms a physically stronger barrier compared to mucosal membranes due to the expression of proteins such as the filament-forming filaggrin and the structural protein loricrin, its interacting partner involucrin and the pro-fillagrin-like protein hornerin. Epithelial cells also play a role in innate immune responses by facilitating mucociliary clearance,producing antimicrobial peptides, cytokines and chemokines, activating intraepithelial and subepithelial cells, recruiting these to tissues and thereby supporting a physical, chemical and immunological barrier. The ability of the epithelium to control the balance of tissue damage and repair signals is essential to limit tissue injury and to control the resolution of inflammation during tissue repair. Studies performed on the gut, skin, esophagus, bronchus and sinus have demonstrated that inflammatory responses can be induced as a consequence of an opening of the epithelial barrier, leading to a vicious cycle where the subepithelial inflammation itself continues to keep the barriers damaged and open. Closed epithelial TJs in the mucosal epithelium protect against the exposome, such as allergens, pollutants, microbes and their enzymes and toxins. Open epithelial TJs in the mucosa help to drain immune cells and proinflammatory molecules from the subepithelial inflammation, but at the same time, allow the entrance of foreign substances to deeper tissues.

A compendium answering 150 questions on COVID-19 and SARS-CoV-2.

Riggioni C, Comberiati P, Giovannini M, Agache I, Akdis M, Alves-Correia M, Antó JM, Arcolaci A, Azkur AK, Azkur D, Beken B, Boccabella C, Bousquet J, Breiteneder H, Carvalho D, De Las Vecillas L, Diamant Z, Eguiluz-Gracia I, Eiwegger T, Eyerich S, Fokkens W, Gao YD, Hannachi F, Johnston SL, Jutel M, Karavelia A, Klimek L, Moya B, Nadeau KC, O'Hehir R, O'Mahony L, Pfaar O, Sanak M, Schwarze J, Sokolowska M, Torres MJ, van de Veen W, van Zelm MC, Wang Y, Zhang L, Jiménez-Saiz R, Akdis CA.Allergy. 2020 Oct;75(10):2503-2541.

As an efficient collaboration with the EAACI Junior Members this

paper answers pressing questions, formulated by young clinicians and scientists, on SARS-CoV-2, COVID-19, and allergy, focusing on the following topics: virology, immunology, diagnosis, management of patients with allergic disease and asthma, treatment, clinical trials, drug discovery, vaccine development, and epidemiology. A total of 150 questions were answered by experts in the field providing a comprehensive and practical overview of COVID-19 and allergic disease.

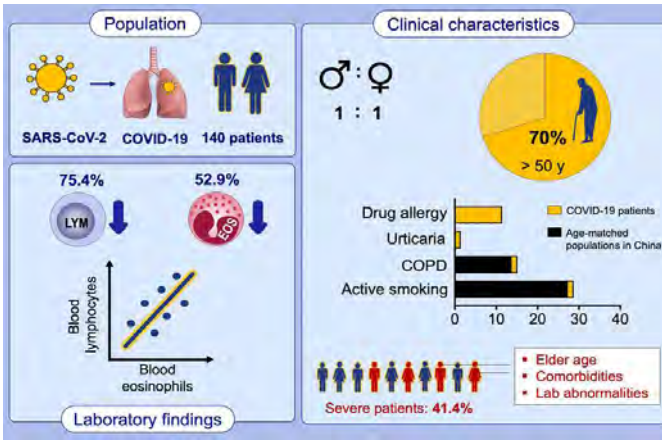


Figure 4. The Graphical Abstract of the first publication in the world on the COVID-19 pandemics published online on the 16th of Febrary 2020 much before the first cases in Europe, showing human to human contact for the first time, symptoms and diagnostic criteria (Cited more than 2'600 times and downloaded more than 200'000 times).

Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19.
Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Brüggen MC, O'Mahony L, Gao Y, Nadeau K, Akdis CA.Allergy. 2020 Jul;75(7):1564-1581.
Better understanding the immunological mechanisms of COVID-19 and this article was made available to public online within the first one and a half months of the pandemic. As a zoonotic disease that has already spread globally to several million human beings and possibly to domestic and wild animals, eradication of coronavirus disease 2019 (COVID-19) appears practically impossible. There is a pressing need to improve our understanding of the immunology of this disease to contain the pandemic by developing vaccines and medicines for the prevention and treatment of patients. In this review, we aim to improve our understanding on the immune response and immunopathological changes in patients linked to deteriorating clinical conditions such as cytokine storm, acute respiratory distress syndrome, autopsy findings and changes in acute-phase reactants, and serum biochemistry in COVID-19. Similar to many other viral infections, asymptomatic disease is present in a significant but currently unknown fraction of the affected individuals. In the majority of the patients, a 1-week, self-limiting viral respiratory disease typically occurs, which ends with the development of neutralizing antiviral T cell and antibody immunity. The IgM-, IgA-, and IgG-type virus-specific antibodies levels are important measurements to predict population immunity against this disease and whether cross-reactivity with other coronaviruses is taking place. High viral load during the first infection and repeated exposure to virus especially in healthcare workers can be an important factor for severity of disease. It should be noted that many aspects of severe patients are unique to COVID-19 and are rarely observed in other respiratory viral infections, such as severe lymphopenia and eosinopenia, extensive pneumonia and lung tissue damage, a cytokine storm leading to acute respiratory distress syndrome, and multiorgan failure. Lymphopenia causes a defect in antiviral and immune regulatory immunity. At the same time, a cytokine storm starts with extensive activation of cytokine-secreting cells with innate and adaptive immune mechanisms both of which contribute to a poor prognosis. Elevated levels of acute-phase reactants and lymphopenia are early predictors of high disease severity. Prevention of development to severe disease, cytokine storm, acute respiratory distress syndrome, and novel approaches to prevent their development will be main routes for future research areas. As we learn to live amidst the virus, understanding the immunology of the disease can assist in containing the pandemic and in developing vaccines and medicines to prevent and treat individual patients.

Distinct characteristics of COVID-19 patients with initial rRT-PCR-positive and rRT-PCR-negative results for SARS-CoV-2.
Zhang JJ, Cao YY, Dong X, Wang BC, Liao MY, Lin J, Yan YQ, Akdis CA, Gao YD. Allergy. 2020 Jul;75(7):1809-1812.
Early and reliable diagnosis of COVID-19 was essential in the beginning of the pandemic and this article focused particularly on the false negative results of PCR and demonstrated that it occurs in 14% of the cases. Accordingly, the diagnosis of SARS-CoV-2 infection should not be excluded in patients with an initial negative rRT-PCR result, especially when presented with typical clinical manifestations. In view of these results, we recommend repeated rRT-PCR tests to confirm diagnosis and identify potentially infected individuals.

Eleven faces of coronavirus disease 2019.
Dong X, Cao YY, Lu XX, Zhang JJ, Du H, Yan YQ, Akdis CA, Gao YD.Allergy. 2020 Jul;75(7):1699-1709.
Early in the beginnig of the pandemic in collaboration with Wuhan University we demonstrated eleven different clinical manifestations of COVID-19

Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China.
Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD.Allergy. 2020 Jul;75(7):1730-1741.
In collaboration with Wuhan University, this was one of the first publications of the 140 COVID-19 patients, much before the disease started in Europe. It was the first study showing human to human contact, because before it was thought that the disease was spreading from the wetmarket in Wuhan. Older age, comorbiditis as diabetes and hypertension were mentioned for the first time as risk factors as well as the detailed symptoms, lymphopenia and eosinopenia and CT-Scan findings of the lungs were described in this study.

Davos, May 2021

Prof. Dr. Mübeccel Akdis, MD, PhD

B Reg cells and their role in immune regulation

Initial reports that indicated immunoregulatory functions exerted by B cells date back to the 1970s. It was demonstrated that B cell-depleted splenocytes isolated from OVA-sensitized guinea pigs exerted a significantly reduced suppressive capacity on delayed-type hypersensitivity reactions in recipient animals compared to non-B cell-depleted splenocytes. The authors concluded that B cells and T cells are important in the homeostasis of T-cell functions and that the mechanisms of suppression could not be attributed to antibodies. In 1996 Wolf et al published a study that demonstrated an immunosuppressive role for B cells in experimental autoimmune encephalomyelitis (EAE), a murine model for multiple sclerosis. B cell-deficient (μMT) and Wild-type (WT) mice immunized with the myelin basic protein (MBP) peptide Ac1-11 in complete Freund's adjuvant (CFA), showed a similar onset and severity of disease symptoms. However, while WT mice spontaneously recovered, μMT mice failed to do so. The authors concluded that while B cells were not required to induce EAE, they play a role in protection against the autoimmune response in EAE. Several years later, Fillatreau et al provided some mechanistic insight into the immunosuppression exerted by B cells in EAE. They found that in mice with an interleukin-10 (IL-10) deficiency that was restricted to B cells, the pro-inflammatory type I immune response induced in the EAE model persisted and mice did not recover. Adoptive transfer of IL-10 proficient B cells isolated from WT mice that recovered from EAE could reduce the severity of EAE symptoms in recipient mice with a B cell contained IL-10 deficiency. These findings demonstrated that IL-10 secreted by B cells plays an important role in controlling autoimmune responses in the EAE mouse model. Around the same time, other studies reported that IL-10 producing B cells also exerted protective effects in other mouse models of chronic inflammation. Mauri et al found that activation of arthritogenic splenocytes with anti-CD40 and antigen resulted in high levels of IL-10 production by B cells. Adoptive transfer of these B cells into recipient mice in a collagen-induced arthritis (CIA) model prevented the development of arthritis and ameliorated established disease. Adoptive transfer of B cells isolated from IL-10 knockout mice, or WT B cells treated with anti-IL-10 or anti-IL-10R failed to confer protection against CIA. While these early studies were highly important in demonstrating that B cells can suppress inflammation through the production of IL-10, they provide limited insight into the origin and phenotype of these B cells. Moreover, as these studies were conducted solely in animal models, it remained unclear to what extent these findings could be translated to humans. The first indications that B cells may also exert immune regulatory functions in humans came from several case reports of patients treated with the anti-CD20 B cell-depleting antibody rituximab for a variety of indications. B cell depletion in these patients was associated with the development of psoriasis or exacerbation of ulcerative colitis. Similar findings have reported by other groups. Since then, the field of Breg research has taken a significant leap forward. Many studies have been published describing in-depth the phenotypic and functional characteristics of subsets of murine and human B cells with immune regulatory functions, either through IL-10 production or through other suppressive mechanisms. While many studies on Bregs primarily focused on their role in autoimmune diseases, potential immune regulatory roles for B cells have been reported in the context of allergy, parasite infections, bacterial infections, cancer and transplantation (Figure 1). Our work on Bregs has mainly been focused on their potential role in the induction and maintenance of tolerance to allergens. We saw that IL-10 expression was increased in B cells in response to bee venom AIT and reported this in 1998. It was not until 2013 that we published a more detailed analysis of IL-10 producing B cells in the context of allergen tolerance.

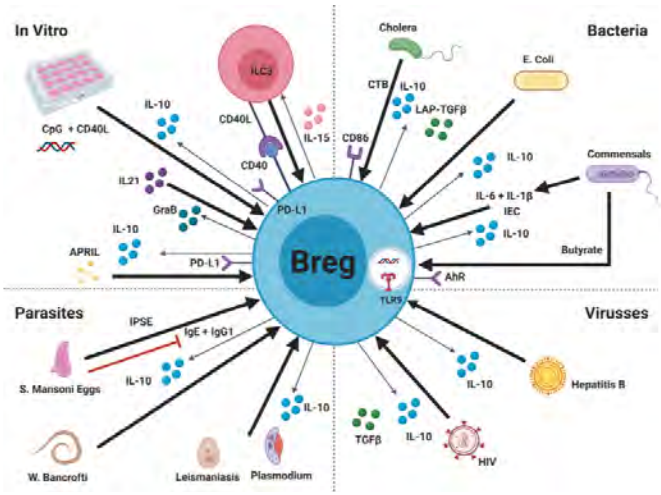


Figure 1: Induction of B regulatory cells.

Breg cells can be induced by many different stimuli. In vitro CpG, CD40L, IL-21 and APRIL have been shown to be able to induce Breg cells and the production of IL-10, GraB, IL-10 an PD-L1. Parasites such as S. Mansoni, W. Bancrofti, Leismaniasis and Plasmodium, Cholera, E.coli, all can induce Bregs cells and IL-10 production. Commensal bacteria or pathogenic bacteria such as Cholera can also induce IL-10 production in Bregs and TGFβ. Lastly viruses such as Hepatitis B and HIV are able to induce Bregs and IL-10 production.

Breaking of immune tolerance; Role of Rhinovirus infection

Rhinoviruses (RVs) are the most common cause of viral-induced respiratory diseases in humans, accounting for around 50% of the upper respiratory tract infections and 20% of the lower respiratory tract infections. RV infections can lead to a broad scope of clinical manifestations, from asymptomatic infections to severe lower respiratory illness. In addition, RV induced wheezing illness and RV associated bronchiolitis early in life are strongly associated with the development of asthma later in life. Additionally, RV is one of the major causes of exacerbations of asthma. In 60-90% of the asthma exacerbations in children RV can be detected. It is clear that there is a strong correlation between RV infections and asthma. However, how RV infections are linked to asthma development and exacerbations is not fully understood.

Most research thus far has been done on bronchial epithelial cells as the main site of infection and viral replication. In response to RV infection, bronchial epithelial cells can produce many different pro-inflammatory cytokines including type I and III interferons (IFN). Several studies have investigated the differences between epithelial responses to RV in asthmatic and healthy subjects. Some studies have reported a deficient production of type I and III interferons in asthmatic subjects, where this reduced IFN production may lead to a reduced anti-viral response and greater viral load and worsening of symptoms. In contrast, some studies suggest that there is not a deficiency, but rather a delayed anti-viral response in asthmatic subjects. Veerati et al showed that in healthy individuals anti-viral gene expression peaked at 48h post-infection, while in asthmatic subjects this happened 72-96 hours post-infection. However, in well-controlled asthma, there is no significant difference in RV replication or induction of type I or III IFNs. Differential expression of certain airway remodeling genes and immune response genes have been reported after RV infection in bronchial epithelial cells of asthmatic subjects. as well as differential susceptibility to cell death. Asthma is a heterogeneous disease with different endotypes that represent molecular pathways in the pathogenesis. Since a major endotype of asthma is characterized by T-helper 2 (Th2) responses, it is relevant to investigate which role these type 2 responses play in rhinovirus infections. One study showed that Th2 cytokines such as IL-4 and IL-13 can inhibit immune responses to RV via toll-like receptor 3 (TLR3) inhibition, and thereby increase the susceptibility to viral infections. While most research on RV has been focused on bronchial epithelial cells, it is highly relevant to assess the effect of RV on the immune system. Previous studies have shown RV interacts and activates immune system cells, such as dendritic cells, macrophages, mast cells, T cells and B cells. It has also been shown that RV can attach or enter CD4 and CD8 positive T cells and induce proliferation and the production of IL-4, IL-13, IFN-γ, TNF, and IL-10 in vitro. A study focused on virus-specific and allergen-specific T cells found that after experimental RV infection, asthmatic subjects mounted a stronger antiviral Th1 response compared to controls.

Treg cells are essential players of antigen-specific immune tolerance to allergens. So far there have been limited reports on mechanisms by which Treg cells may fail to induce and maintain allergen tolerance. It has been suggested that FOXP3+ Treg cells might lose their suppressive capacity under certain inflammatory conditions and adopt a phenotype of effector CD4+ T cells. We propose that viruses might affect this plasticity and their suppressive capacity. So far, some studies have looked into the effect of type I IFNs on Treg function, but the results are quite controversial. Therefore, this study aimed to identify if Treg cells could be modified by RV infection and if this could affect their immune regulatory function. We also wanted to investigate the differences in responses between asthmatic and healthy subjects during experimental RV16 infection (Figure 2). We have demonstrated that Treg cells are functionally disturbed by RV infection. We showed that Treg cells from the periphery can mount an antiviral response after RV challenge. This response seemed exaggerated in asthmatic subjects and less specific than in healthy controls. Furthermore, we showed that Treg cells loose part of their suppressive capacity after RV stimulation. Treg cells stimulated with RV were less capable of suppressing Th2 type cytokines (Figure 3). We identified several Treg cell function-related gene expressions differences that may explain these findings and hypothesized several mechanisms that could be involved in the loss of their suppressive capacity. Future studies have to elucidate which mechanisms are the most relevant. Further understanding of a loss of function of Treg cells after viral infections might not only be relevant for virus related asthma exacerbations, but might even provide further insight into virus-associated development of certain autoimmune diseases.

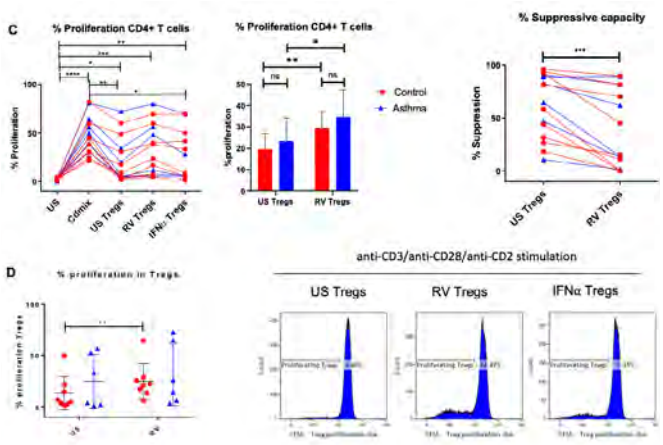


Figure 2. Suppressive capacity of Tregs is reduced after RV16 stimulation. (C) Cumulative data of all suppression assays combined indicating the amount of proliferation (left panel), the amount of proliferation for asthma and controls separately (middle panel) and suppression (right panel). (D) Percentage of proliferating Treg cells after anti-CD3/anti-CD28/anti-CD2 stimulation.

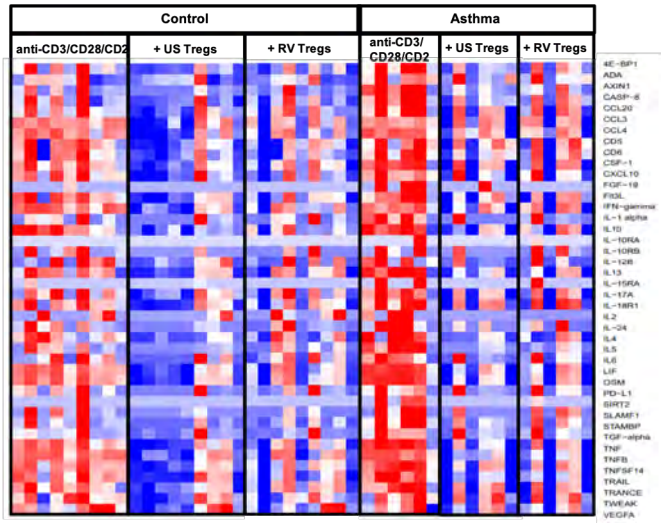
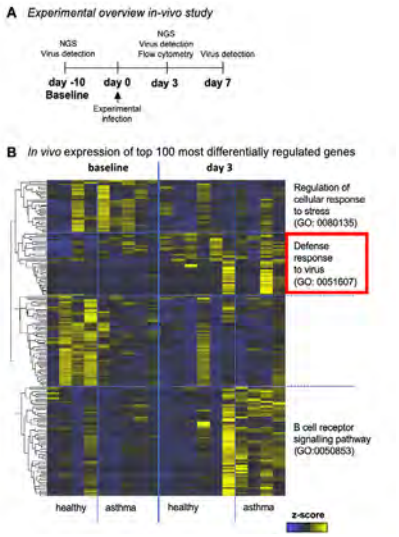


Figure 3. Treg cells stimulated with RV16 are less capable to suppress inflammatory cytokine production. Heatmap with all the significantly changed proteins from anti-CD3/CD28/CD2 stimulated CD4+ T cells compared to anti-CD3/CD28/CD2 stimulated CD4+ T cells + Unstimulated Tregs + RV16 stimulated Treg cells in full PBMC.

Given the frequent incidence of RV infections and the central role of B cells during antiviral responses, it is surprising that the cellular side of this response was not yet addressed in more detail. Therefore, this study aimed to identify the underlying gene regulatory networks driving the B cell response during RV infection in vivo; to define the external stimulating factors driving this response; to address whether B cells directly interact with RV in vivo; and to discover potential B cell functions in addition to well-known antibody production. Furthermore, since responses to RV were described as less efficient in patients with chronic respiratory diseases, we addressed possible dysregulation of circulating B cells in asthmatics. Here, we report early upregulation of an antiviral gene program, followed by subsequent upregulation of a pro-inflammatory response in B cells from experimentally infected human individuals. B cells carried viral RNA after RV infection in vivo, suggesting direct interactions of B cells with infecting virions. Asthmatic subjects showed an elevated antiviral response and broad upregulation of antibody genes in B cells (Figure 4).



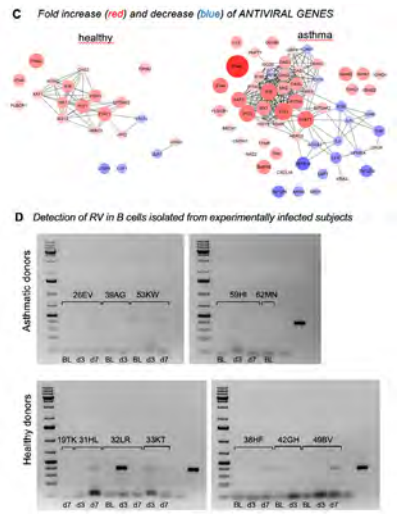


Figure 4. Extensive peripheral B cell response to RV infection in asthmatic individuals. (A) Experimental layout of experimental RV infection experiment. Gene expression of B cells sorted from experimentally RV infected human subjects was analyzed using RNA-sequencing. (B) Full RNA-sequencing from purified B cells at baseline and 72h after experimental infection. Top 100 genes most differentially expressed genes of healthy and asthmatics. Pathway enrichment shown for main clusters (day 3). (C) Satellite plot showing known interactions of upregulated gene families. (D) RV RNA was detected using a highly sensitive two-step pan-RV PCR. RV-A16 was used at MOI10, unless noted otherwise.

Dysregulated antiviral response of circulating B cells in experimental rhinovirus infection in asthma.

(Oliver F. Wirz et al. Allergy in press)

Rhinoviruses are the predominant cause of respiratory viral infections and are strongly associated with asthma exacerbations. While humoral immunity plays an important role during virus infections, cellular aspects of this response are not well understood. Here, we investigated the antiviral response of circulating B cells upon experimental rhinovirus infection in healthy individuals and asthmatic patients. We demonstrated that B cells from healthy subjects exhibited an anti-viral gene profile linked to IFN-alpha, carried viral RNA in vivo, and were transiently infected by rhinovirus in vitro. Importantly, B cells themselves lacked expression of interferons in response to rhinovirus exposure. Furthermore, IFN-alpha stimulated B cells upregulated pro-inflammatory cytokines in response to rhinovirus infection. Asthmatic individuals showed extensive upregulation and dysregulation of antiviral gene expression. This study contributes to the understanding of systemic effects of local rhinovirus infections on lymphocytes in the periphery and findings might also have implications during infection with other respiratory viruses.

Loss of regulatory capacity in T regulatory cells upon rhinovirus infection.

(Kirstin Jansen et al. JACI, in press)

Respiratory infections with rhinoviruses (RV) are strongly associated with the development and exacerbations of asthma and pose an additional health risk for allergic subjects. How RV infections and chronic allergic diseases are linked, and which role RV plays in the breaking of tolerance in T regulatory cells (Tregs) is unknown. Therefore, this study aims to investigate the effects of RV on Tregs.

Tregs were isolated from asthmatic subjects and controls after experimental infection with RV16 and were analyzed with next-generation sequencing. Additionally, suppression assays, qPCRs, and protein quantifications were performed with Tregs after in vitro RV16 infection. RV16 induced a strong antiviral response in Tregs from asthmatic subjects and controls, including the upregulation of IFI44L, MX1, ISG15, IRF7, and STAT1. In asthmatic subjects, the inflammatory response was exaggerated and showed a dysregulated immune response compared to controls. Furthermore, asthmatic subjects failed to upregulate several immunosuppressive molecules such as CTLA4 and CD69 and upregulated the inflammasome related genes PYCARD and AIM2. Additionally, RV16 reduced the suppressive capacity of Tregs of healthy and asthmatic subjects in vitro and increased Th2-type cytokine production. Tregs from healthy and asthmatic subjects displayed an anti-viral response after RV infection and showed reduced suppressive capacity. This data suggest that Treg function might be altered or impaired during RV infections, which might play an important role in the association between RV and the development of asthma and asthma exacerbations.

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

(van de Veen W et al. Sci Adv. 2020 May 13;6(20): eaaz3559.)

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 regulatory cells in allergy.

(Siyuan Ma et al. Immunol Rev. 2021 Jan;299(1):10-30.)

B cells have classically been recognized for their unique and indispensable role in the production of antibodies. Their potential as immunoregulatory cells with anti-inflammatory functions has received increasing attention during the last two decades. Herein, we highlight pioneering studies in the field of regulatory B cell (Breg) research. We will review the literature on Bregs with a particular focus on their role in the regulation of allergic inflammation.

Increased antiviral response in circulating lymphocytes from hypogammaglobulinemia patients.

(Oliver F Wirz et al. Allergy. 2020 Dec;75(12):3147-3158.)

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 2021

PD Dr. Katja Bärenfaller, PhD

Running the Orbitrap ECLIPSE: now we are cooking with gas
The installation of the Orbitrap ECLIPSE mass spectrometer required considerable effort mainly by Patrick Westermann. Furthermore, the laboratory methods and infrastructure needed to be set up to allow for mass spectrometer sample preparation. Finally, in July 2020 the Orbitrap ECLIPSE was measuring the first samples, and after some minor adjustments, was ready for operation. This allowed us to pursue our strategy to both start with own projects setting up experimental methods and doing exploratory studies and pilot projects, and establishing collaborative projects. The first collaboration was with Klemens Fröhlich from the group of Oliver Schilling at the University of Freiburg, Germany, who was very helpful in establishing methods, and whose measurements were included in the first manuscript including data from our new Orbitrap ECLIPSE mass spectrometer. PhD student Elena Barletta is currently doing mass spectrometry measurements in a variety of projects acquiring relevant expertise and interesting data. The first main project is the detection of food allergen proteins, for which she is setting up and using the Parallel Reaction Monitoring (PRM) method for which this type of instrument is ideally suited.

The molecular profile of T cell differentiation and activation
In the PhD project of Jana Koch funded by "Stiftung vormals Bündner Heilstätte Arosa" we investigate transcriptional and translational regulation in the differentiation of naïve CD4+ T cells into T helper cells and their activation. After the protocol for ribosome footprint sequencing in which only those stretches of RNAs are sequenced that are located inside elongating ribosomes had been established, it was now used in the Th1 differentiation and activation biological system. After some more experimental hurdles were overcome, the ribosome footprint and total RNA sequencing data have been acquired and are currently analyzed in depth.

DAViS Center (Center for Data Analytics, Visualization and Simulation)
In the DAViS Center established in 2019 at Fachhochschule Graubünden (FHGR) in Chur with SIAF as primary partner, MLM-SOS-ALL was the first joint project for which both the expertise and the required infrastructure and hardware were built up. However, while advancing in data analysis, we obtained laboratory data from the COVID-19 hospital in Zgierz, Poland, in a collaboration established by Milena Sokolowska, and a request for providing Machine Learning analyses. Due to the relevance and urgency of this project, we decided to prioritize the analysis of these data with the aim to use Machine Learning mainly by by Marco Schmid (FHGR) and PhD student Damir Zhakparov (SIAF), and produced very informative results summarized below:

Predicting infection of SARS-CoV-2 and mortality of COVID-19 using Machine Learning.
Strzynski F*, Zhakparov D*, Schmidt M*, Makowska J., Sokolowska M, Bärenfaller K. et al. In prep
* first co-authors
COVID-19 is an infectious disease caused by the SARS-CoV-2 virus that is spreading worldwide leading to many diseased patients and deaths. To limit its spread, it is critical to identify infected individuals as fast as possible. Therefore, it is for example important that potential positive patients can already be reliably identified at hospital admission. In addition, it is important that the course of the disease in COVID-19 patients is closely monitored and that the treatment is modified in a timely manner when the condition of the patient worsens. It is therefore important to identify a reliable set of features that can predict survival or death already at the beginning of the treatment, but also during the treatment based on the longitudinal changes of the laboratory values. In collaboration with the COVID-19 center at the Medical University of Lodz in Poland, we enrolled a big cohort of SARS-CoV-2 negative and positive patients, who were admitted to the hospital showing similar symptoms. After testing for SARS-CoV-2 infection, the disease course of the positive patients was monitored longitudinally during the hospitalization at several time points. The aims of our study were as follows: i) to build a robust prediction model of SARS-CoV-2 infection to identify patients with similar clinical symptoms, who should be prioritized in PCR testing at the entrance to the hospital; ii) to find the combination of laboratory parameters, comorbidities and previous medications predicting the survival or death in COVID-19 patients and iii) to define the alarming pattern of longitudinal changes in the laboratory parameters, predicting respiratory failure and death. Using the important features identified by 7 different Machine Learning algorithms, we successfully built a 3-step decision tree with which SARS-CoV-2 positive and negative patients can be distinguished based on counts of white blood cells and antibody-synthesizing cells, on monocyte/lymphocyte and platelets/neutrophil ratios, and on procalcitonin levels allowing for more than 70% accuracy in initial prediction of SARS-CoV-2 positivity (Figure decision tree). Considering initial laboratory values, comorbidities and pre-medications in the survival analysis, we found that Troponin I, procalcitonin and hemoglobin levels are the strongest initial predictors of COVID-19-related death, regardless of comorbidities or used medications. Finally, in the longitudinal analysis we found that discrete patterns of white blood cells and C-reactive protein fluctuations are strongly predicting survival or death during the disease progression and should constitute a valid warning, urging the intensification of treatment.
Altogether, our study can provide clinicians with valuable informati-

on on patient's possible status, based on which, they can proceed further with diagnosis and treatment modification.

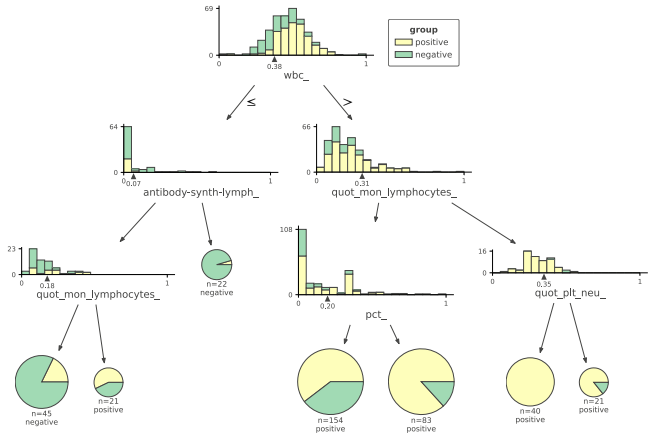


Figure Decision_Tree: A decision tree in three steps for assessing whether a patient might be SARS-CoV-2 negative or positive at hospital admission based on laboratory parameters.

Interesting insights from Particulate Matter measurements

The title of the Science Café in Davos planned for 27 August 2020 and organized by Naturforschende Gesellschaft Davos, Science City Davos and Academia Raetica was 'Feinstaub – Ursachen und Folgen' (Particulate Matter – Causes and Consequences). In preparation for this event, 8 particulate matter PM2.5 sensors from Dr. Födisch AG, provided by Jörg Kachelmann, were installed in Davos in January/February 2020. From these sensors, 5 were transmitting data, which by coincidence provided us with PM2.5 data before and after the COVID-19 lockdown measures put in place in Davos on 13 March 2020. Working together with Hanspeter Lötscher from the cantonal Office for Nature and Environment (ANU), we thus obtained data on the effect of the lockdown measures on nitrogen oxide and PM2.5 concentrations in Davos and St. Moritz. Analysis of the data has shown that the nitrogen oxide concentrations, which are a measure for combustion engine traffic, were considerably and significantly reduced in the three weeks after the lockdown as compared to the three weeks before (-48.8% NOx in Davos, -63.3% NOx in St. Moritz). In contrast, the particulate matter concentrations were increased after the lockdown (+43.3% PM2.5 in Davos, +39.2% PM2.5 in St. Moritz). The decrease in traffic was therefore not associated with a decrease in PM2.5 concentrations (Figure 1). These data were provided to the PAN ENVIRONMENT study in which data from 89 different studies from around the world were collected to assess the immediate impacts of changes in human activities on wildlife and environmental threats during the early lockdown months of 2020. Reports of unusual species observations suggested that animals quickly responded to the reduction in human presence. However, negative effects of lockdown on conservation also emerged, indicating that humans are important custodians of species and ecosystems. This highlights the dual role that humans play in threatening and protecting species and ecosystems.

Working with data on particulate matter concentrations, we also analyzed data measured on the night of New Year's Eve 2019/2020 by ANU and by the secondary school together with Salesforce. This showed that especially in the lower parts of Davos firework caused very high concentrations of PM2.5 during this night (up to 670 µg/m3). These data were published in the local newspaper in September 2020 beforehand a public vote on restricting the use of firework, which was accepted by 74%.

The measurements of PM2.5 at 3 positions in Davos are currently ongoing. The current measurements confirm that, in general, air quality is good with PM2.5 concentrations of 2-5 µg/m3. However, occasional peaks in PM2.5 concentrations at all positions do occur, and are caused by the burning of biomass in households (wood fires). In addition, we observed in 2021 several peaks caused by Sahara dust.

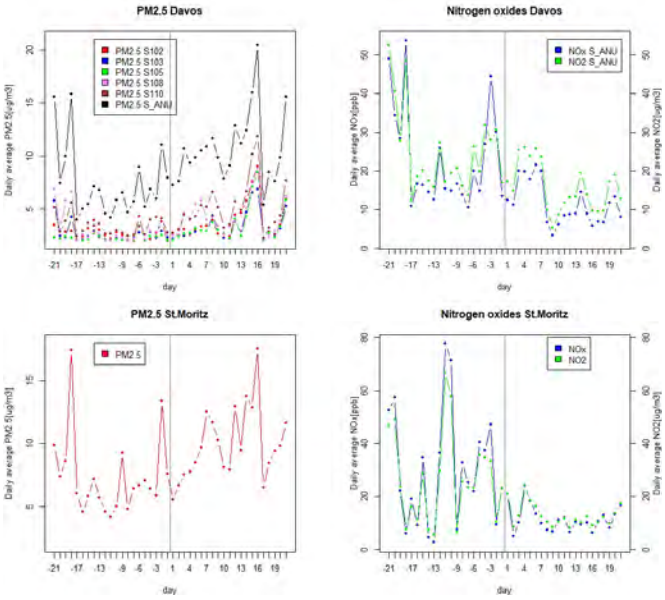


Figure 1: PM2.5 and nitrogen oxide concentrations measured in Davos and St. Moritz in the three weeks before and after the lockdown measures were put in place.

Impact of DJ-1 and Helix 8 on the Proteome and Degradome of Neuron-Like Cells.

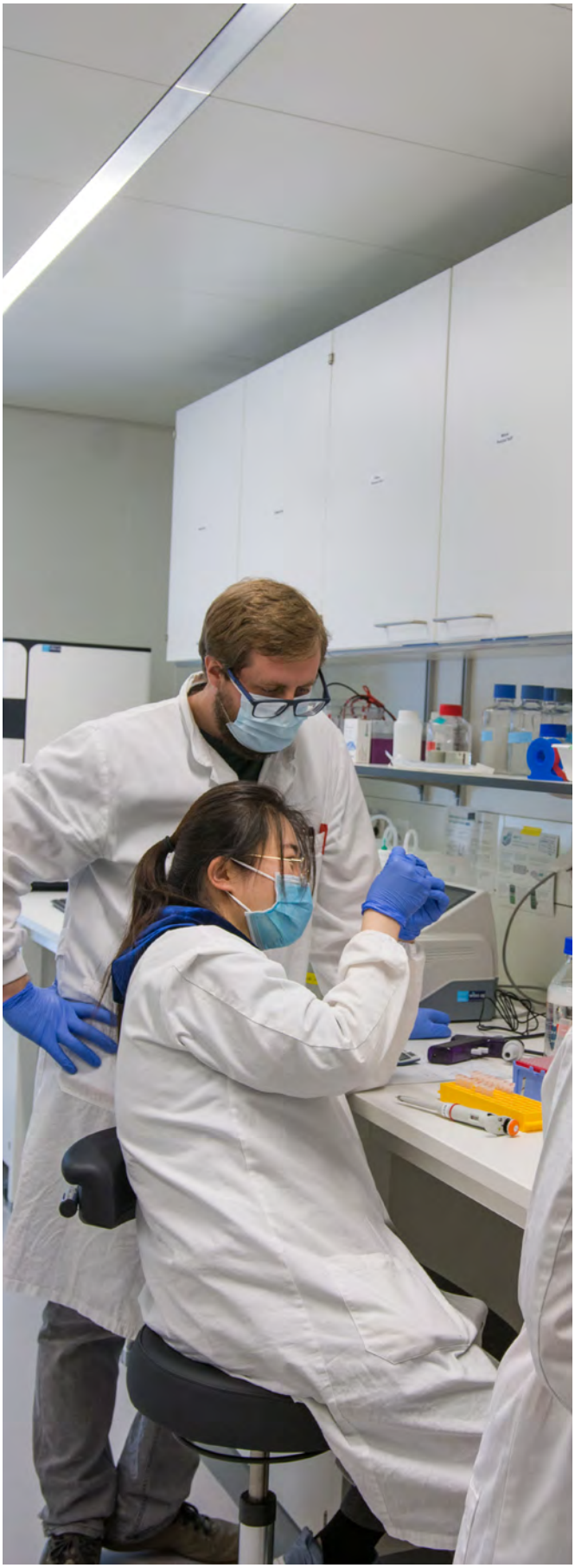
Kern U, Fröhlich K, Bedacht J, Schmidt N, Biniossek ML, Gensch N, Baerenfaller K, Schilling O. (2021) Cells, 10 (2): 404. doi. org/10.3390/cells10020404

DJ-1 is an abundant and ubiquitous component of cellular proteomes. DJ-1 supposedly exerts a wide variety of molecular functions, ranging from enzymatic activities as a deglycase, protease, and esterase to chaperone functions. However, a consensus perspective on its molecular function in the cellular context has not yet been reached. Structurally, the C-terminal helix 8 of DJ-1 has been proposed to constitute a propeptide whose proteolytic removal transforms a DJ-1 zymogen to an active hydrolase with potential proteolytic activity. To better understand the cell-contextual functionality of DJ-1 and the role of helix 8, we employed post-mitotically differentiated, neuron-like SH-SY5Y neuroblastoma cells with stable over-expression of full length DJ-1 or DJ-1 lacking helix 8 (ΔH8), either with a native catalytically active site (C106) or an inactive site (C106A active site mutation). Global proteome comparison of cells over-expressing DJ-1 ΔH8 with native or mutated active site cysteine indicated a strong impact on mitochondrial biology. N-ter-

minomic profiling however did not highlight direct protease substrate candidates for DJ-1 ΔH8, but linked DJ-1 to elevated levels of activated lysosomal proteases, albeit presumably in an indirect manner. Finally, we show that DJ-1 ΔH8 loses the deglycation activity of full length DJ-1. Our study further establishes DJ-1 as deglycation enzyme. Helix 8 is essential for the deglycation activity but dispensable for the impact on lysosomal and mitochondrial biology; further illustrating the pleiotropic nature of DJ-1.

Global COVID-19 lockdown highlights humans as both threats and custodians of the environment.
Bates, Primack, Duarte & PAN-Environment Working Group. Biological Conservation (in press)
The global lockdown to mitigate COVID-19 pandemic health risks has altered human interactions with nature. Here, we report immediate impacts of changes in human activities on wildlife and environmental threats during the early lockdown months of 2020, based on 877 qualitative reports and 332 quantitative assessments from 89 different studies. Hundreds of reports of unusual species observations from around the world suggest that animals quickly responded to the reductions in human presence. However, negative effects of lockdown on conservation also emerged, as confinement resulted in some park officials being unable to perform conservation, restoration and enforcement tasks, resulting in local increases in illegal activities such as hunting. Overall, there is a complex mixture of positive and negative effects of the pandemic lockdown on nature, all of which have the potential to lead to cascading responses which in turn impact wildlife and nature conservation. While the net effect of the lockdown will
need to be assessed over years as data becomes available and persistent effects emerge, immediate responses were detected across the world. Thus initial qualitative and quantitative data arising from this serendipitous global quasi-experimental perturbation highlights the dual role that humans play in threatening and protecting species and ecosystems. Pathways to favorably tilt this delicate balance include reducing impacts and increasing conservation effectiveness.

Davos, May 2021



Vaccine Development

Dr. Claudio Rhyner, PhD

Since the introduction of allergen immunotherapy (AIT) over 100 years ago, focus has been on standardization of allergen extracts, with reliable molecular composition of allergens receiving the highest attention. While adjuvants play a major role in European AIT, they have been less well studied. Immunomodulatory interventions play a key role in the treatment of infections and cancer as well as allergic diseases. Adjuvants such as micro- and nanoparticles are often added to immunomodulatory therapies to enhance the triggered immune response. We investigate the immunological assessment of novel and economically manufactured adjuvants, namely strontium-doped hydroxyapatite porous spheres (SHAS), which we suggest for the use as adjuvant and carrier in allergen-specific immunotherapy (ASIT).

Allergen-specific immunotherapy is currently the only treatment able to cure allergic diseases. For the majority of the patients, symptomatic treatments based on corticosteroids or other short-term-acting drugs remain as therapeutic treatment. Because the common hallmark of all allergic diseases is related to the production of allergen-specific IgE, approaches aimed at eliminating IgE responses, could be an optimal therapy for multi-sensitized patients or patients suffering from a hyper IgE syndrome. Both, poly-sensitization and hyper IgE syndrome can be considered as common diseases that are not causally treatable with the current therapeutic options. Our continuously developing vaccination system (modular antigen translocation) has been successfully proven in clinical studies to develop protective antibody responses in patients suffering from cat allergy. As a logical extension of these projects, we propose to develop an active prophylactic vaccination concept aimed at suppressing both the establishment of IgE expressing memory B cells and to target soluble Ig.

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.

Davos, May 2021

Dr. Milena Sokolowska, MD, PhD

Due to environmental and lifestyle changes, there is an increasing frequency of allergies and respiratory viral and bacterial infections. The current pandemics of COVID-19 is the most extreme demonstration of this trend. 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. Similarly, the it is unclear why some people are more susceptible to viral infections or for the development of more severe forms of respiratory diseases, leading sometimes to the respiratory failure and death. Several reasons are postulated, such as lack of proper microbiome stimulation early in life, recurrent viral infections and exposure to environmental pollutants. In addition, central metabolic disorders such as obesity or even an unbalanced diet itself also influence the proper function of immune responses. All of those factors impact the proper cross-talk 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. Our group applies high throughput transcriptomic, proteomic, metabolomic methods 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, asthma, immune tolerance, respiratory viral diseases and microbial dysbiosis.

Understanding COVID-19

Due to the rapid development of the COVID-19 pandemics, our group joined the global efforts in understanding the mechanisms of SARS-CoV-2 infection, the immunological outcomes of the disease, responses to vaccinations as well in establishing international COVID-19 patients cohorts. In addition, in close collaboration with the other experts from SIAF and from the European Academy of Allergy and Clinical Immunology (EAACI) we developed several international reports and guidelines to clarify the fast-changing evidence on COVID-19 and to provide validated source of information.

Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors.

Radzikowska U, Ding M, Tan G, Zhakparov D, Peng Y, Wawrzyniak P, Wang M, Li S, Morita H, Altunbulakli C, Reiger M, Neumann AU, Lunjani N, Traidl-Hoffmann C, Nadeau KC, O'Mahony L, Akdis CA, Sokolowska M. Allergy. 2020 Nov;75(11):2829-2845.

The aim of our study was to analyze the expression of known and potential SARS-CoV-2 receptors and related molecules in the extensive collection of primary human cells and tissues from healthy subjects of different age and from patients with risk factors and known comorbidities of COVID-19. We performed RNA sequencing and explored available RNA-Seq databases to study gene expression and co-expression of ACE2, CD147 (BSG), and CD26 (DPP4) and their direct and indirect molecular partners in primary human bronchial epithelial cells, bronchial and skin biopsies, bronchoalveolar lavage fluid, whole blood, peripheral blood mononuclear cells (PBMCs), monocytes, neutrophils, DCs, NK cells, ILC1, ILC2, ILC3, CD4+ and CD8+ T cells, B cells, and plasmablasts. We analyzed the material from healthy children and adults, and from adults in relation to their disease or COVID-19 risk factor status. We found that ACE2 and TMPRSS2 were coexpressed at the epithelial sites of the lung and skin, whereas CD147 (BSG), cyclophilins (PPIA andPPIB), CD26 (DPP4), and related molecules were expressed in both epithelium and in immune cells. We also observed a distinct age-related expression profile of these genes in the PBMCs and T cells from healthy children and adults.

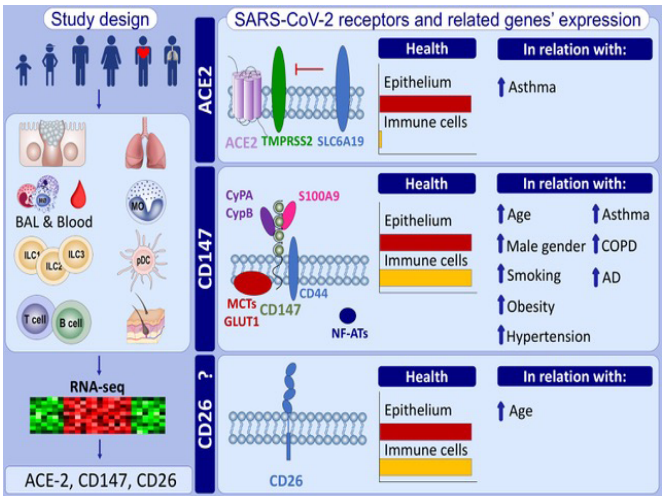


Figure 1. Graphical summary of Radzikowska and Ding et al. ACE2 and TMPRSS2 expression is unique for the epithelial barrier sites, whereas CD147, cyclophilins, and CD26 are expressed in both, epithelial and immune cells. Age is a factor associated with the differential expression profiles of ACE2-, CD147- and CD26-related genes in the PBMCs and naive CD4+ T cells from healthy children and adults. Asthma, COPD, hypertension, smoking, obesity, and male gender generally lead to the higher expression of ACE2- and CD147-related genes in the bronchial biopsy, BAL or blood.

Asthma, COPD, hypertension, smoking, obesity, and male gender status generally led to the higher expression of ACE2- and CD147-related genes in the bronchial biopsy, BAL, or blood. Additionally, CD147-related genes correlated positively with age and BMI. Interestingly, we also observed higher expression of CD147-related genes in the lesional skin of patients with atopic dermatitis. Our data suggest different receptor repertoire potentially involved in the SARS-CoV-2 infection at the epithelial barriers and in the immune cells. Altered expression of these receptors related to age, gender, obesity and smoking, as well as with the disease status, might contribute to COVID-19 morbidity and severity patterns. (Fig 1). We continue to determine the importance of various SARS-CoV-2 receptors in the airways an in the periphery.

Predicting infection of SARS-CoV-2 and mortality of COVID-19 using Machine Learning.
Strzynski F*, Zhakparov D*, Schmidt M* et al., Makowska J, Sokolowska M, Bärenfaller K. In preparation.* first co-authors
In collaboration with Katja Bärenfaller's group, DAViS Center and Joanna Makowska from the Medical University of Lodz, we developed robust models and algorithms predicting infection with SARS-CoV-2 and mortality of COVID-19.

Immunology of COVID-19: Mechanisms, clinical outcome, diagnostics, and perspectives-A report of the European Academy of Allergy and Clinical Immunology (EAACI).
Sokolowska M, Lukasik ZM, Agache I, Akdis CA, Akdis D, Akdis M, Barcik W, Brough HA, Eiwegger T, Eljaszewicz A, Eyerich S, Feleszko W, Gomez-Casado C, Hoffmann-Sommergruber K, Janda J, Jiménez-Saiz R, Jutel M, Knol EF, Kortekaas Krohn I, Kothari A, Makowska J, Moniuszko M, Morita H, O'Mahony L, Nadeau K, Ozdemir C, Pali-Schöll I, Palomares O, Papaleo F, Prunicki M, Schmidt-Weber CB, Sediva A, Schwarze J, Shamji MH, Tramper-Stranders GA, van de Veen W, Untersmayr E. Allergy. 2020 Oct;75(10):2445-2476.
We characterize here the differences between adequate innate and adaptive immune response in mild COVID-19 and the deep immune dysfunction in the severe multiorgan disease. The similarities of the human immune response to SARS-CoV-2 and the SARS-CoV and MERS-CoV are underlined. We also summarize known and potential SARS-CoV-2 receptors on epithelial barriers, immune cells, endothelium and clinically involved organs such as lung, gut, kidney, cardiovascular, and neuronal system. Finally, we discuss the known and potential mechanisms underlying the involvement of comorbidities, gender, and age in development of COVID-19. Consequently, we highlight the knowledge gaps and urgent research requirements to provide a quick roadmap for ongoing and needed COVID-19 studies.

Outsmarting SARS-CoV-2 by empowering a decoy ACE2.
Sokolowska M. Signal Transduct Target Ther. 2020 Nov 3;5(1):260.
Along with the current efforts to develop high-affinity neutralizing antibodies, researchers engineered the soluble variant of human ACE2 with enhanced binding to the spike protein, outranking the soluble wild type protein in blocking SARS-CoV-2 infection in vitro. In addition, the newly created soluble ACE2 is enzymatically active in cleaving angiotensin-2, increasing its therapeutic potential in COVID-19.

SARS-CoV-2 candidate vaccines - composition, mechanisms of action and stages of clinical development.
Rodriguez-Coira R, Sokolowska M. Allergy 2020 Dec 19.
We described here the approved COVID-19 vaccines and other candidates in the final stages of clinical trials. We explained briefly their modes of action, immunological mechanisms, as well as advantages and disadvantages of each type of vaccination platform.

EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines.
Sokolowska M, Eiwegger T, Ollert M, Torres MJ, Barber D, Del Giacco S, Jutel M, Nadeau KC, Palomares O, Rabin RL, Riggioni C, Vieths S, Agache I, Shamji MH. Allergy. 2021 Jan 16.
The first approved COVID-19 vaccines include Pfizer/BioNTech BNT162B2, Moderna mRNA-1273 and AstraZeneca recombinant adenoviral ChAdOx1-S. Soon after approval, severe allergic reactions to the mRNA-based vaccines that resolved after treatment were reported. Regulatory agencies from the European Union, Unites States and the United Kingdom agree that vaccinations are contraindicated only when there is an allergy to one of the vaccine components or if there was a severe allergic reaction to the first dose. This position paper of the European Academy of Allergy and Clinical Immunology (EAACI) agrees with these recommendations and clarifies that there is no contraindication to administer these vaccines to allergic patients who do not have a history of an allergic reaction to any of the vaccine components. Importantly, as is the case for any medication, anaphylaxis may occur after vaccination in the absence of a history of allergic disease. Therefore, we provide a simplified algorithm of prevention, diagnosis and treatment of severe allergic reactions and a list of recommended medications and equipment for vaccine centres. We also describe potentially allergenic/immunogenic components of the approved vaccines and propose a workup to identify the responsible allergen. Finally, we identify unmet research needs and propose a concerted international roadmap towards precision diagnosis and management to minimize the risk of allergic reactions to COVID-19 vaccines and to facilitate their broader and safer use.

Immune tolerance, allergy, asthma

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. J Allergy Clin Immunol 2020, 2020 Oct 9: S0091-6749(20)31396-8.
Despite the efficacy of allergen-specific immunotherapy (AIT), the role of trained immunity and tolerance in this process has not been elucidated. Here, we have performed a comprehensive longitudinal analysis of the systemic innate immune cell repertoire during the course of AIT. Patients with allergy received standard preseasonal

subcutaneous AIT with allergoids to birch and/or grass. Healthy controls were monitored without any intervention. Flow cytometry of innate lymphoid cell (ILC), natural killer cell, monocyte cell, and dendritic cell (DC) subsets was performed at baseline, 3 months (birch season), 6 months (grass seasons), and 12 months after the therapy in patients or at similar seasonal time points in controls. Additional analyses were performed in the third-year birch and grass season. We observed a durable decrease in group 2 ILCs and an increase of group 1 ILCs after AIT, with dynamic changes in their composition. We found that an expansion of CD127+CD25++ clusters caused observed shifts in the heterogeneity of group 1 ILCs. In addition, we observed development of CD127+CD25++c-Kit+ group 3 ILC clusters. Moreover, we found an increase in the number of intermediate monocytes in parallel with a reduction in nonclassical monocytes during the first year after AIT. Classical and intermediate monocytes presented significant heterogeneity in patients with allergy, but AIT reduced the HLA-DR++ clusters. Finally, an increase in plasmacytoid DCs and CD141+ myeloid DCs was observed in individuals with allergy, whereas the number of CD1c+ myeloid DCs was reduced during the first year of AIT. AIT induces changes in the composition and heterogeneity of circulating innate immune cells and brings them to the level observed in healthy individuals. Monitoring of ILCs, monocytes, and DCs during AIT might serve as a novel biomarker strategy.

T cell requirement and phenotype stability of house dust mite-induced neutrophil airway inflammation in mice.

Hagner S, Keller M, Raifer H, Tan HT, Akdis CA, Buch T, Sokolowska M, Garn H. Allergy. 2020 Nov;75(11):2970-2973.

In collaboration with the group of Holger Garn we established and verified an animal model of a neutrophil-dominated airway inflammation which represents major inflammatory of features of human neutrophil-driven asthma.

Immunometabolism of allergen-specific T cells: multi-omics approach.

Sokolowska M et al. In preparation

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. 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.

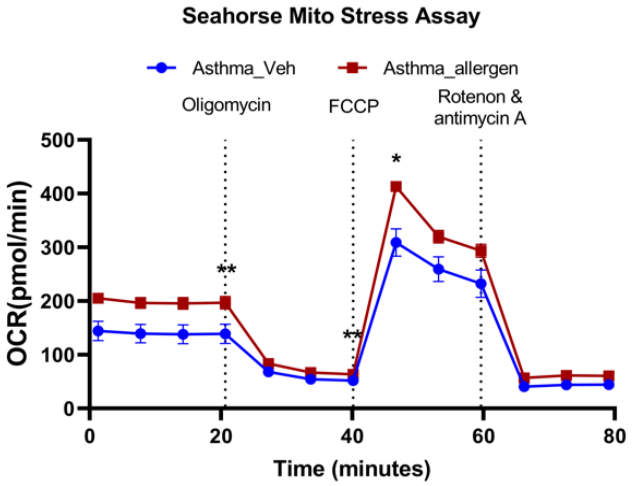


*Figure 2. Allergen exposure increases production of mitochondrial ATP in asthma. Oxygen consumption rate (OCR) of allergen-treated bronchial epithelial cells measured with Seahorse XFe96 Analyzer. Oligomycin, FCCP and Rotenon& antimycin A were injected sequentially marked by the vertical lines. *P < 0.05, **P < 0.01 are marked for asthma_allergen compared with asthma_veh group*

Distinct metabolome of regulatory T cells and T effector cells in health and allergic diseases.

Rodriguez-Coira R et al. In preparation

We performed a detailed untargeted and targeted metabolomic analysis of ex vivo sorted regulatory T cells and T effector cells from healthy subjects and in patients allergic to grass in collaboration with Domingo Barber's group. We found unique metabolites involved in the mitochondrial respiration and oxidative phosphorylation, responsible for regulatory and effector function and proliferative capacities of T cells. We also determined metabolites, which might be responsible for the skewed immunological phenotype of Tregs and T effectors in allergic patients.

Immunological markers of glucocorticosteroids insensitivity in patients with severe asthma.

Cardoso C, von Blumenthal T et al. In preparation.

The development of reproducible biomarkers, which can recognize the different phenotypes of severe asthma (SA) and the different underlying pathological mechanisms is one of the most challenging research needs in asthma. We developed a phenotyping approach based on the dynamic flow cytometry results of 142 patients with severe asthma before and after systemic glucocorticosteroids administration in order to reflect the pathophysiologic processes and disease heterogeneity in these patients. We identified two severe asthma clusters which differed in baseline cell frequencies, response to glucocorticoids and atopy status. This novel biomarker could improve clinical and research strategies, allowing the prediction of minimal steroid doses with maximal treatment success, the selection of patients who requires alternative therapies like disease-modifying biologics and the selection of biological therapy based on the underlying immunological response.

Current perspective on eicosanoids in asthma and allergic diseases - EAACI Task Force consensus report, part I.
Sokolowska M., Rovati G.E., Diamant Z., Untersmayr E., Schwarze J., Lukasik Z., Sava F., Angelina A., Palomares O., Akdis C., O'Mahony L., Sanak M., Dahlen S-E., Woszczek G. Allergy, 2020 Apr 12. doi: 10.1111/all.14295
This review, produced by an European Academy of Allergy and Clinical Immunology (EAACI) task force, highlights our current understanding of eicosanoid biology and its role in mediating human pathology, with a focus on new findings relevant for clinical practice, development of novel therapeutics, and future research opportunities.

Respiratory viral diseases and microbial dysbiosis

Rhinovirus-dependent RIG-I inflammasome activation in airway epithelium alters antiviral response in asthma.
Radzikowska U, Eljaszewicz A et al. In preparation
We determined the novel mechanism of action of the human rhinovirus in primary human airway epithelial cells, which might be partly responsible for the delayed antiviral responses in patients with asthma. In addition, we studied the effects of the combined rhinovirus and SARS-CoV-2 coinfection as well as the influence of allergens on the rate of infection.

Allergens and viral infections modify metabolic reprogramming of airway epithelium in asthma. Ding M, Huang M et al. In preparation
We aim to determine the effects of allergen exposure and human rhinovirus infection on mitochondrial respiration, oxidative phosphorylation and glycolysis in primary human epithelial cells and subsequent dysfunction of epithelium in asthma (Fig. 2).

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.
This review focuses on recently discovered connections between lung and gut microbiota, including bacteria, fungi, viruses, and archaea, and their influence on asthma.

Davos, May 2021

Dr. Willem van de Veen, PhD

B cells play a central role in the regulation of immune responses through the production of antibodies. In the context of allergies, B cells play a pivotal role in IgE-mediated allergies, as a result of their unique ability to produce allergen-specific IgE antibodies that sensitize mast cells and basophils by binding to their high affinity IgE receptors (FcεRI). Subsequent allergen crosslinking of FcεRI-bound IgE on mast cells and basophils initiates the release of pro-inflammatory mediators resulting in a type I hypersensitivity reaction. Immune regulatory functions of B cells, particularly regulatory B (Breg) cells, have also been described. Serological mechanisms of immune regulation by B cells include the prominent increase of IgG4 antibodies in serum observed in patients gaining immune tolerance, as seen during allergen-specific immunotherapy. Thus, B cells are fundamental in both induction of of allergies as well as developing tolerance to allergens.

Our lab is interested in the different aspects of B cell immunology in the context of allergies and other immune pathologies.

Regulatory B cells, A to Z.
Jansen K, Cevhertas L, Ma S, Satitsuksanoa P, Akdis M, van de Veen W.
Allergy. 2021 Feb 5. doi: 10.1111/all.14763. Online ahead of print.
B cells play a central role in the immune system through the production of antibodies. During the past two decades, it has become increasingly clear that B cells also have the capacity to regulate immune responses through mechanisms that extend beyond antibody production. Several types of human and murine regulatory B cells have been reported that suppress inflammatory responses in autoimmune disease, allergy, infection, transplantation, and cancer. Key suppressive molecules associated with regulatory B-cell function include the cytokines IL-10, IL-35, and TGF-β as well as cell membrane-bound molecules such as programmed death-ligand 1, CD39, CD73, and aryl hydrocarbon receptor. Regulatory B cells can be induced by a range of different stimuli, including microbial products such as TLR4 or TLR9 ligands, inflammatory cytokines such as IL-6, IL-1β, and IFN-α, as well as CD40 ligation. This review provides an overview of our current knowledge on regulatory B cells. We discuss different types of regulatory B cells, the mechanisms through which they exert their regulatory functions, factors that lead to induction of regulatory B cells and their role in the alteration of inflammatory responses in different diseases.

Biology and dynamics of B cells in the context of IgE-mediated food allergy.
Satitsuksanoa P, Daanje M, Akdis M, Boyd SD, van de Veen W.
Allergy. 2020 Dec 3. doi: 10.1111/all.14684. Online ahead of print.
An increasing number of people suffer from IgE-mediated food allergies. The immunological mechanisms that cause IgE-mediated food allergy have been extensively studied. B cells play a key role in the development of IgE-mediated food allergies through the production of allergen-specific antibodies. While this particular function of B cells has been known for many years, we still do not fully understand the mechanisms that regulate the induction and maintenance of allergen-specific IgE production. It is still not fully understood where in the body IgE class switch recombination of food allergen-specific B cells occurs, and what processes are involved in the immunological memory of allergen-specific IgE responses. B cells can also contribute to the regulation of allergen-specific immune responses through other mechanisms such as antigen presentation and cytokine production. Recent technological advances have enabled highly detailed analysis of small subsets of B cells down to the single-cell level. In this review, we provide an overview of the current knowledge on the biology of B cells in relation to IgE-mediated food allergies (Figure 1).

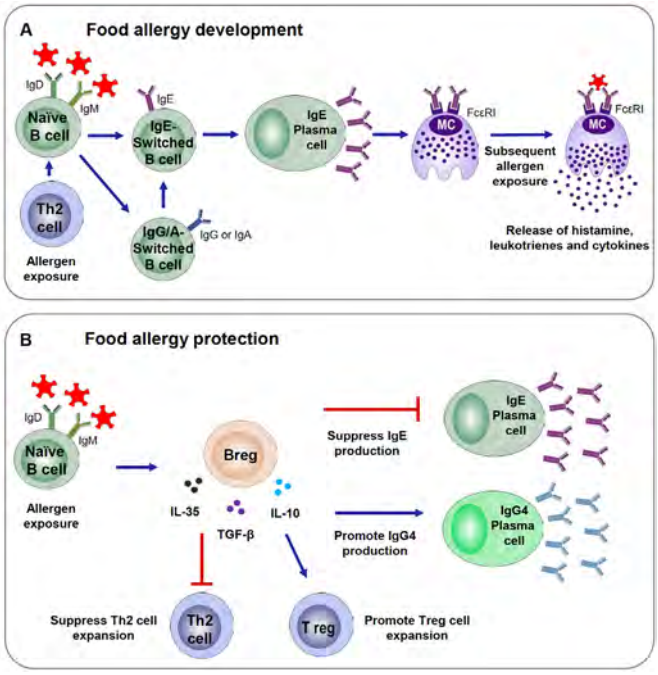


Figure 1. Role of B cells in food allergy.
(A) Food allergy development: A major role for B cells in the development of food allergies is related to their capacity to produce IgE. This occurs when B cells are exposed to food antigens with the help from Th2 cell. They undergo class switch recombination to IgE and memory B cells. Then, these cells are differentiated into IgE-producing plasma cells that produce IgE antibodies, which bind to the high affinity IgE receptor on mast cells and basophils. Upon subsequent exposure to the culprit allergen, these IgE antibodies crosslink FcεRI, thereby triggering mast cell and basophil degranulation. The release of histamine, leukotrienes and cytokines induces allergic inflammati-

on. (B) Food allergy protection: In contrast, B cells may also protect against food allergy. This process involves the induction of Breg cells, which produce suppressor cytokines such as IL-10, TGF-β, and IL-35. These anti-inflammatory molecules will suppress inflammation, promote IgG4 production and suppress IgE production. In addition, the IgG4 induction is also promoted by Tregs via the secretion of IL-10.
Abbreviations: FcεRI, Fc epsilon RI receptor; IgE, Immunoglobulin E; IgG4 Immunoglobulin G4; Th2, T helper 2; TGF-β, Transforming growth factor beta.

Immunological Outcomes of Allergen-specific Immunotherapy in Food Allergy.
Schoos AM, Bullens D, Chawes BL, Costa J, De Vlieger L, Dunn-Galvin A, Epstein MM, Garssen J, Hilger C, Knipping K, Kuehn A, Mijakoski D, Munblit D, Nekliudov NA, Ozdemir C, Patient K, Peroni D, Stoleski S, Stylianou E, Tukalj M, Verhoeckx K, Zidarn M, van de Veen W. On behalf of the Core Outcome Measures for Food Allergy (COMFA) consortium
Frontiers in Immunology. 2020 Nov 3;11:568598.
IgE-mediated food allergies are caused by adverse immunologic responses to food proteins. Allergic reactions may present locally in different tissues such as skin, gastrointestinal and respiratory tract and may result is systemic life-threatening reactions. During the last decades, the prevalence of food allergies has significantly increased throughout the world, and considerable efforts have been made to develop curative therapies. Food allergen immunotherapy is a promising therapeutic approach for food allergies that is based on the administration of increasing doses of culprit food extracts, or purified, and sometime modified food allergens. Different routes of administration for food allergen immunotherapy including oral, sublingual, epicutaneous and subcutaneous regimens are being evaluated. Although a wealth of data from clinical food allergen immunotherapy trials has been obtained, a lack of consistency in assessed clinical and immunological outcome measures presents a major hurdle for evaluating these new treatments. Coordinated efforts are needed to establish standardized outcome measures to be applied in food allergy immunotherapy studies, allowing for better harmonization of data and setting the standards for the future research. Several immunological parameters have been measured in food allergen immunotherapy, including allergen-specific immunoglobulin levels, basophil activation, cytokines, and other soluble biomarkers, T cell and B cell responses and skin prick tests. In this review we discuss different immunological parameters and assess their applicability as potential outcome measures for food allergen immunotherapy that may be included in such a standardized set of outcome measures.

In vivo dynamics of the allergen-specific B cell repertoire in a human model of high-dose allergen exposure.
Willem van de Veen*, Ramona A. Hoh*, Ji-Yeun Lee, David Mirer, Monique Daanje, Mirelle Kleuskens, Hergen Spits, Scott D. Boyd**, Mübeccel Akdis**. * /** Authors contributed equally
Manuscript in preparation
Understanding the mechanisms of tolerance induction to allergens is critical for the development of targeted therapies for the treatment of allergic disease. Beekeepers, who are frequently exposed to high-doses of bee venom allergens, represent a unique human in vivo model for studying these mechanisms. The aim of this study was to characterize the allergen-specific B cell repertoire in highly exposed healthy individuals and track its development over time. Blood samples were collected from 12 beekeepers before and during the beekeeping season over the course of up to 20 years. B cells specific for the major bee venom allergen phospholipase A2 (PLA) were identified through staining with fluorescently labeled PLA, and purified using fluorescence activated cell sorting. PLA-specific B cells were immortalized through transduction with BCL6 and BCL-XL, and expanded. Deep sequencing of the B cell repertoire was performed on expanded PLA-specific B cells as well as primary total B cells.

Frequencies of PLA-specific B cells were higher during the beekeeping season than before the season. PLA-specific clones were overrepresented within the IgE and IgG4 repertoire compared to other isotypes. Moreover, PLA-specific clonal lineages had increased V-gene mutations at the end of the season. Members of many PLA-specific clonal lineages were detected at multiple time points, which, in some individuals, were more than 20 years apart. PLA-specific clonal lineages contained members of different immunoglobulin heavy chain isotypes including IgG1, IgG2, IgG3, IgG4 and IgE. Within the clonal lineages that contained an IgE member, the members of other isotypes that showed the highest sequence similarity to the IgE member were most frequently IgG2 or IgG4 clones, indicating that IgE members may have undergone sequential class switch recombination through an IgG2 or IgG4 intermediate. Interestingly, clusters of PLA-specific clones with identical V and J gene usage and a CDR3 AA similarity of >90% were found in different beekeepers, indicating the existence of public antibody clonotypes against PLA.

Our study shows that allergen-specific clonal lineages in highly exposed non-allergic individuals persist for many years, are clonally expanded and show a large diversity. Moreover, allergen-specific clones expand and accumulate V-gene mutations in response to seasonal allergen exposure. PLA-specific IgE clones may develop through an IgG2 or 4 intermediate and public PLA-specific antibody clonotypes exist. It remains to be determined which features of the B cell repertoire are indicative of allergen tolerance. Comparative analysis of the allergen-specific B cell repertoire of allergic individuals before and after allergen-specific immunotherapy is currently underway and will potentially help to identify key differences between healthy and allergic B cell responses.

A novel pro-angiogenic B cell subset is increased in cancer and chronic inflammation.
Willem van de Veen, Anna Globinska, Kirstin Jansen, Alex Straumann, Terufumi Kubo, Daniëlle Verschoor, Oliver F. Wirz, Francesc Castro-Giner, Ge Tan, Beate Rückert, Urs Ochsner, Marietta Herrman, Barbara Stanić, Marloes van Splunter, Daan Huntjens, Alexandra Wallimann, Rodney J. Fonseca Guevara, Hergen Spits, Desislava Ignatova, Yun-Tsan Chang, Christina Fassnacht, Emmanuella Guenova, Lukas Flatz, Cezmi A. Akdis, Mübeccel Akdis
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Distinct functional B cell subsets have been identified on the basis of their cytokine production profiles. Immunosuppressive B regulatory (reg) cells and other potential B cell subsets, such as B effector 1 (Be1) and Be2 cells, as well as interleukin-17 (IL-17)–producing B cells, have been reported. B cells can secrete a wide range of cytokines and accumulate in chronic inflammatory areas and around tumor cells. Their interaction with tissue cells and tumor cells and their contribution to tissue remodeling remain largely open questions. Angiogenesis is an essential physiological process that occurs during embryogenesis, normal tissue development, and repair after injury. 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).

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 proangiogenic cytokines including VEGF, CYR61, ADM, FGF2, PDGFA, and MDK. We identified CD49b and CD73 as surface markers identifying proangiogenic B cells. IgG4+CD73+CD49b+ B cell clones produced a wide range of proangiogenic factors and facilitated endothelial tube formation. (Figure 2A-C). Circulating CD49b+CD73+ B cells showed significantly increased frequency in patients with melanoma and eosinophilic esophagitis (EoE), two diseases associated with angiogenesis (Figure 2D). In addition, tissue-infiltrating IgG4+CD49b+CD73+ B cells expressing proangiogenic cytokines were detected in patients with EoE and melanoma, two model diseases with a demonstrated link to IgG4 and angiogenesis. Together, our findings demonstrate a previously unidentified proangiogenic B cell subset characterized by the expression of CD49b and CD73.

In continuation of this project we have ongoing collaborations for several projects focused on the role of B cells in EoE (collaboration with Prof. Straumann from the university hospital in Zurich) and melanoma (collaboration with Prof. Flatz at the University of Tübingen & Cantonal hospital St. Gallen).

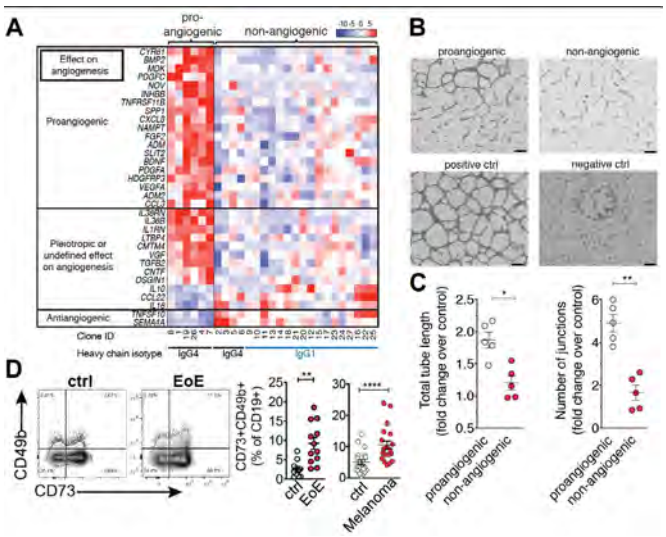

*Figure 2: A subset of B cells promotes angiogenesis and is increased in EoE and melanoma patients. A) Heat map showing gene-scaled (z score) log2 normalized counts of genes encoding secreted immunomodulatory proteins that are differentially expressed between proangiogenic B and nonangiogenic B cell clones (FDR < 0.01, log2 fold change > 0.5). The top box indicates genes with known proangiogenic effects, the middle box indicates genes with unknown or pleiotropic effects on angiogenesis, and the bottom box indicates genes with known anti-angiogenic effects. B) Representative images of HUVEC tube formation assay to quantify proangiogenic effect of B cell clones (scale bars, 400 µm). Negative control, IMDM +2% FCS; positive control, EGM medium with growth factors. C) Quantitative analysis of rate of HUVEC tube formation induced by supernatants of pro- and nonangiogenic B cell clones. D) Frequencies of circulating CD73+CD49b+ B cells in patients with melanoma or EoE compared to healthy controls (ctrl). (mean ± SEM). *P < 0.05 and **P < 0.01, Mann-Whitney test. Science advances 2020, van de Veen et al.*

IL-10 induces IgG4 production in NOD-scid Il2rgamma**nullmice humanized by engraftment of peripheral blood mononuclear cells.**

Lacin Cevhertas*, Siyuan Ma*, Barbara Stanic, Urs Ochsner, Kirstin Jansen, Ruth Ferstl, Remo Frei, Obinna, Chijoke,Christian Münz, Liam O'Mahony, Mübeccel Akdis, Willem van de Veen. * Authors contributed equally

Allergy, under revision

IgG4 antibodies are considered to have anti-inflammatory activity and may confer protection against anaphylaxis and allergic inflammation. The production of IgG4 by human B cells in vitro is strongly enhanced by IL-10. In vivo studies of the regulation of IgG4 have been handicapped by the fact that mice do not express this immunoglobulin isotype. The use of humanized mice allows the study of human immunoglobulin regulation including IgG4. Immunodeficient NOD-scid Il2rgammanull (NSG) mice lack murine lymphocytes, including T, B and NK cells.

This strain enables efficient engraftment of human hematopoietic progenitor cells (HPC) and peripheral blood mononuclear cells (PBMC). Here, we established a humanized mouse model to study the regulation of IgG4 production in vivo.

To determine optimal conditions for B cell engraftment in NSG mice, engraftment of human leucocytes after intraperitoneal (IP) and intravenous (IV) injections of 5x106 and 20x106 PBMC were analyzed after 14 and 21 days in spleen. Engraftment of human cells was determined by flow cytometry. Expression of human (hu)CD45 was used for gating of human leukocytes (Figure 3A). The highest level of engraftment of huCD45+ cells was observed 21 days after IV injection of 20x106 PBMC. Human B lineage cells (gated as huCD45+CD19+) were detectable at low levels on day 14 in the IV group and in both the IV and IP group on day 21 (Figure 3 E,F). Total CD19+ B lineage cells, CD19+CD138- B cells and CD138+ plasma cells showed a similar pattern in which the highest level of engraftment, both as a percentage of huCD45+ cells and in absolute engrafted cell numbers, was observed with IV injection of 5x106 PBMC. Therefore, we concluded that the IV route with 5x106 PBMC was optimal for B lineage cell engraftment.

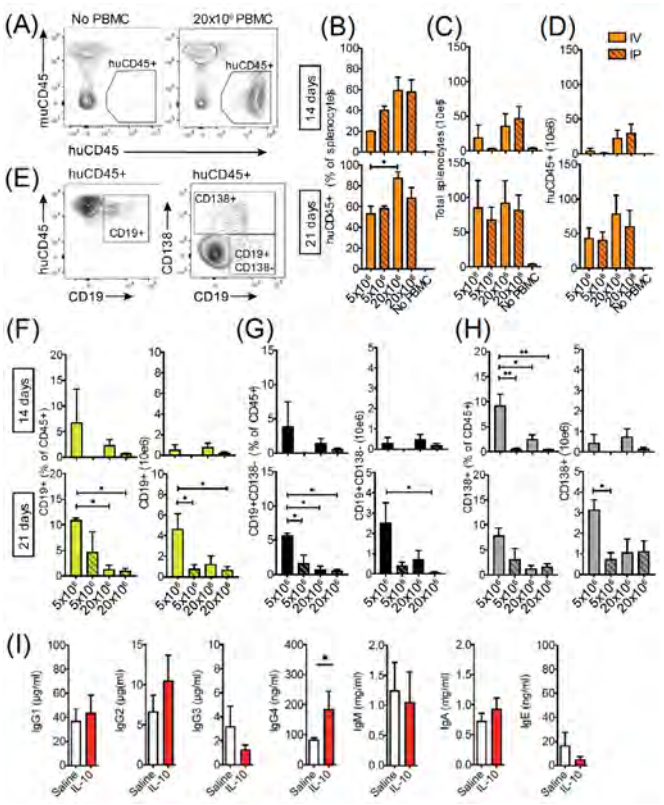

*Figure 3. Human lymphocyte engraftment in NSG mice and effect of IL-10 treatment on immunoglobulin production. (A) Representative dot plots showing muCD45 and huCD45 staining in splenocytes of a mouse that did not receive PBMC and a mouse that was engrafted with human PBMCs. (B) Frequencies of huCD45+ cells in splenocytes of NSG mice 14 and 21 days after injection of 5x106 or 20x106 PBMC through IV or IP injection. (C) Total cell counts per spleen. (D) Total number of engrafted huCD45+ cells. (E) Gating strategy for CD19+, CD19+CD138- and CD138+ cells. (F) Frequencies (left) and absolute numbers per spleen (right) of CD19+, (G) CD19+CD138-, (H) CD138+ cells. (I) Serum immunoglobulin levels measured 21 days after PBMC engraftment in mice treated with saline or IL-10. *P < .05, ** P < .01. Statistics were calculated using one-way ANOVA followed by Tukey's multiple comparison test (B-H) or Wilcoxon matched-pairs signed rank test (I).*

Next, we assessed the effect of IL-10 on the B cell compartment and immunoglobulin production. All human immunoglobulin isotypes were detectable in serum of saline and IL-10 treated mice (Figure 3G). Interestingly, IL-10 induced a significant increase in the serum level of IgG4, while no significant changes were observed for IgG1, 2, 3, IgM, IgA and IgE.

Our findings demonstrate that NSG mice can be utilized to study human B cell and immunoglobulin responses. 5X106 PBMC and application through IV injection were optimal for B cell and plasma cell engraftment. IL-10 stimulated the in vivo upregulation of IgG4 production.

The effect of measles on allergic sensitization in children

Measles remains a significant cause of childhood morbidity and mortality, and causes more than 100,000 deaths globally each year. Hallmark of the disease is a generalized immune suppression that can last for several weeks to months after resolution of measles virus (MV) infection, resulting in increased susceptibility to opportunistic bacterial and viral infections. At the same time measles is associated with immune activation and induces strong MV-specific immune responses that confer life-long immunity. This apparent contradiction is known as the 'measles paradox'. Measles-associated loss of memory T cells, B cells and plasma cells may contribute to immune amnesia. In fact, acute measles apparently results in a partial "reset" of the adaptive immune system. Although in the majority of cases such a reset will be detrimental to the host, there may be exceptions to this rule. Especially in children with allergic disease and atopic sensitization, an immunological reset could potentially be beneficial. The immune amnesia effect resulting from measles infection indicates a broad, and non-specific elimination of the immunological memory. Measles infection in children who are sensitized to allergens could lead to a depletion of allergen-specific B- and T-lymphocytes, plasma cells and IgE antibodies. This may result in a reduction of allergic sensitization and the risk of allergies. We are currently carrying out a study in which we will assess whether MV infection results in a reduction of allergic sensitization.

To this end, total and allergen-specific IgE antibody levels will be analysed in paired plasma samples previously collected from unvaccinated children before and after measles. This will demonstrate whether there is a direct relation between MV infections and allergic sensitization. This is a retrospective cohort study that involves the analysis of biobanked plasma samples obtained from unvaccinated children aged four to 17 years old that were collected for a previous observational cohort study that was recently published. This observational cohort study was performed during a measles outbreak in the Orthodox Protestant community in the Netherlands. This study is currently ongoing and results are expected this year.

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ABSTRACTS

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Cevhertas Lacin, Willem van de Veen, Öyku Uzulmez, Pattraporn Satitsuksanoa, Kirstin Jansen, Hergen Spits, Lukas Flatz, Mübeccel Akdis, CI-tedavili Melanoma Hastalarında Melanoma Farklılaşma Antijenlerine Özgü B-Hücrelerin Saptanması, 25th National Immunology Congress, Istanbul, Turkey 20-22 November 2020.

Koch Jana, Dreher Anita, Rückert Beate, Heider Anja, Baerenfaller Katja. Ribosome Profiling to Identify Differentially Regulated Translational Events in Differentiating Human T Cell Populations. EAACI Winter school 2020, Chamonix, 23-26 January 2020.

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Komlósi ZI, Kovács N, Peng Y, van de Veen W, Tan G, Yángüez E, Buzás E, Akdis C. Follicular helper innate lymphoid cells. Hungarian Society for Immunology, annual meeting 7-8 October 2020.

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Radzikowska Urszula. Novel tissue inflammatory mechanisms of rhinovirus in the presence of house dust mite. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

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Rinaldi AO. Electrical impedance spectroscopy as a safe and efficient tool for the evaluation of epithelial barrier. Gordon Research Conference (GRC), Ventura, CA, United States, 5-10 January 2020.

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for the characterization of epithelial barrier in patients with atopic dermatitis. EAACI Digital Congress 2020, 06 - 08 June 2020.

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Rodriguez-Coira, J. Severe olive allergic patients present a distinctive pro-inflammatory profile. EAACI conference 2020, Online, 6-8 June 2020.

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Satitsuksanoa P. B cells responses in allergic children during oral immunotherapy comparison to natural tolerance. Food Allergy Gordon Research Conference 2020, California, United States, 5-10 January 2020.

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Sokolowska M. Airway microbiota in health and disease - bacteria, viruses, fungi and archaea. JSA/WAO Joint World Allergy Congress 2020, Kyoto, Japan, 17-20 October 2020.

Sokolowska M. Modulation of immune responses by fatty acids. EAACI FAAM-EUROBAT Digital 2020; 16-17 October 2020.

Sokolowska M, Boonpiyathad T, Eljaszewicz A, Castro Giner F, Ruchti F, Globinska A, Ruckert B, Dreher A, Radzikowska U, Morita H, Jansen K, Rinaldi A, Gschwend A, Meyer N, Helbling A, Negoias S, Hool S-L, Borner U, Kwok W, Akdis M, Kahlert H, Berek N, Nandy A, Willers C, Akdis CA. Multi-omics analysis reveals local and systemic immunometabolic adaptations of allergen-specific T cells to allergen-specific immunotherapy. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

van de Veen W. In vivo dynamics of the allergen-specific B cell repertoire in a human model of high-dose allergen exposure. Gordon Research Conference on Food Allergy 2020, Ventura, United States, 5-10 January 2020.

SOS-ALL Consortium, Schmid M, Keller T, van Schie A, Roelke H, Baerenfaller K. MLM-SOS-ALL: With Machine Learning and Modelling in search of significant features in the SOS-ALL dataset. Graubünden forscht 2020, Digital, 23-24 September 2020.

van de Veen W. A novel pro-angiogenic B cell subset is increased in cancer and chronic inflammation. EAACI Congress 2020, London, United Kingdom, 6-10 June 2020.

Wallimann A, Thompson K, Moriarty TF, Akdis CA, O'Mahony L. The Influence of Microbial-Derived Metabolites on Bone Health. EAACI Winter School 2020, Chamonix, France, 23-26 January 2020.

Wallimann A, Thompson K, Moriarty TF, Akdis CA, O'Mahony. The Influence of Microbial-Derived Metabolites on Bone Health. Graubünden forscht Congress 2020, Davos (online), Switzerland, 23-24 September 2020.

Wallimann A, Thompson K, Pugliese B, Magrath W, Moriarty TF, Akdis CA, O'Mahony L. The influence of short-chain fatty acids on bone health. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

SEMINAR AND CONGRESS TALKS

Akdis CA. Epithelial barriers functions and food allergy. Gordon Research Conference (virtual), Ventura LA, USA, January 2020.

Akdis CA. Epithelial barriers and development of allergic diseases. Bern Immunology Club (virtual), , University of Bern, January 2020.

Akdis CA. Epithelial barriers in allergic diseases. EAACI Annual Meeting (virtual), 6-8 June 2020.

Akdis CA. The immunology of COVID-19 infection. EAACI Annual Meeting (virtual), 6-8 June 2020.

Akdis CA. Epithelial barrier hypothesis. Novartis Research Institute, Basel, Switzerland, 29 June 2020.

Akdis CA. Type 2 immune response and inflammation, Sanofi R&D Group, 28 July 2020.

Akdis CA. The epithelial barrier hypothesis for the development of allergic and autoimmune diseases. JSA/WAO Joint Congress, Kyoto, Japan (online), 18 September 2020.

Akdis CA. Symposium: Bronchial epithelium. JSA/WAO Joint Congress, Kyoto, Japan (online), 18 September 2020.

Akdis CA. The epithelial barrier hypothesis for the development of allergic and autoimmune diseases. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Akdis CA. Epithelial Barrier Hypothesis. National Immunology Congress, Turkey, 21 November 2020.

Akdis CA. What do editors expect – how to publish in high impact journals. National Immunology Congress, Turkey, 21 November 2020.

Akdis CA. The epithelial barrier hypothesis for the development of allergic and autoimmune diseases. 47th IMSUT founding commemorative symposium, Japan (online), 27 November 2020.

Akdis CA. Covid-19: immunology and pathogenesis. Academy of Pediatric Allergy and Asthma, Turkey, 18 November 2020.

Akdis CA. Epithelial barrier hypothesis in allergies and autoimmunity. Chinese Allergy Meeting, Hubei, 5 September 2020.

Akdis CA. How to review manuscripts for journals. PhD students education program at Helmholtz Centre Munich, October 2020.

Akdis CA. COVID-19 pathogenesis and risk factors. Uriach Symposium to Latin American Society, 11 December 2020.

Akdis M. The Role of B cells in allergen immunotherapy. Food Allergy Gordon Research Conference, Food Allergy Research in the Context of Mucosal Homeostasis and Immunity, Ventura, CA on 5-10 January 2020.

Akdis M. B cells tolerance: An essential mechanism for allergen immunotherapy in house dust mite allergy. EAACI Digital Congress 6-8 June 2020.

Akdis M. Novel B cell subsets and immune regulation. JSA/WAO XXVII World Allergy Congress (WAC 2020) conjoint with the APAAACI/APAPARI 2020 Congress, 17 – 20 September 2020.

Akdis M. Immune tolerance mechanisms in food allergy. 27. Ulusal Alerji ve Klinik İmmünoloji Kongresi, 24-25 Ekim 2020.

Akdis M. Regulatory immune mechanisms in tolerance to food allergy. AAAeIC -Argentine Association of Allergy, Asthma and Clinical Immunology-Annual Congress, 21-23 November 2020.

Akdis M. The mechanisms of breaking and inducing allergen-specific tolerance. 25. Ulusal İmmünoloji Kongresi, 20-22 November 2020.

Akdis M. The role of B cells in allergen tolerance. Izmir Biomedicine and Genome Center, 10 November 2020.

Baerenfaller K. Towards elucidating molecular mechanisms shaping proteotypes in health and disease. Seminars in Translational Immunology (STIMM), Zurich, Switzerland, 5 February 2020.

Baerenfaller K. Endophyte Infection and Alkaloid Detection in European Seed Mixtures. World Biodiversity Forum 2020, Davos, Switzerland, 23-28 February 2020.

Baerenfaller K. MLM-SOS-ALL: With Machine Learning and Modelling in search of significant features in the SOS-ALL dataset. Graubünden forscht 2020, Digital, 23-24 September 2020.

Cevhertas L. Characterization of B cell responses during checkpoint inhibitor therapy in Melanoma. 7th Conference, Graubünden forscht 2020, Davos, Switzerland 23-24 September 2020.

Fieten KB. Indoor allergen exposure of Swiss school children living at 1560 m altitude. EAACI digital congress, 6-8 June 2020.

Ma Siyuan, Cevhertas Lacin, Akdis Mübeccel, van de Veen Willem. Antigen-presenting capacity of B cells expressing different B cell receptor isotypes. Graubünden forscht– The Young Researchers Convention, online, 23-24 September 2020.

Mitamura Yasutaka. The characteristic of the effect of IL-13 on the keratinocyte. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Rodriguez-Coira J. Severe olive pollen allergic patients present a distinct T cells and innate lymphoid cells (ILCs) profile. Winter School 2020, Chamonix, France, 23-26 January 2020.

Rodriguez-Coira J. The impact of metabolic alterations on immune response in severe allergic disease. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Satitsuksanoa P.B cells responses in allergic children during oral immunotherapy comparison to natural tolerance. Food Allergy Gordon Research Conference 2020, California, United States, 5-10 January 2020.

Satitsuksanoa P. B Cells Responses in Allergic Children During Oral Immunotherapy Comparison to Natural Tolerance. EAACI winter school 2020, Chamonix, France, 23-26 January 2020.

Satitsuksanoa P. B cells responses during immunotherapy in allergic children compared to natural tolerance. EAACI 2020 Digital, London, United Kingdom. 6-8 June 2020.

Satitsuksanoa P. B cell responses to food allergy. 7th Conference Graubünden forscht (The Young Researchers Convention 2020) Davos, Switzerland. 23-24 September 2020.

Satitsuksanoa P.B cell responses to food allergy. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Sokolowska M. Understanding next generation sequencing through gene ontologies and user-friendly platforms. Winterschool,

Chamonix, France, January 2020.

Sokolowska M. Distribution of ACE2, CD147, CD26 and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension and COVID-19 risk factors, EAACI Digital Congress 2020, 6-8 June 2020.

Sokolowska M. Metabolic regulation of T cells during Allergen-Specific Immunotherapy, EAACI Digital Congress 2020, 6-8 June 2020.

Sokolowska M. Multi-omics analysis reveals local and systemic immunometabolic adaptations of allergen-specific T cells to allergen-specific immunotherapy. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Sokolowska M. Distribution of SARS-CoV-2 receptors and associated molecules in health and disease. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Sokolowska M. Modulation of immune responses by fatty acids, EAACI FAAM-EUROBAT Digital 2020; 16-17 October 2020.

Sokolowska M. Airway microbiota in health and disease - bacteria, viruses, fungi and archaea, JSA/WAO Joint World Allergy Congress 2020, Kyoto, Japan, 17-20 October 2020.

Sokolowska M. Distribution of SARS-CoV-2 receptors and associated molecules in health and disease, Biomarkers of Paris, Virtual Meeting, 25 November 2020.

van de Veen W. Identification of pro-angiogenic B cells and their potential role in cancer and chronic inflammation. EAACI Congress 2020, London, United Kingdom, 6-10 June 2020.

van de Veen W. Detection and characterization of antigen-specific B cells in allergy and cancer. 2nd Flow cytometry congress 2020, London, United Kingdom, 8-9 October 2020.

van de Veen W. In vivo dynamics of the allergen-specific B cell repertoire in a human model of high-dose allergen exposure. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Wallimann A.The Influence of Microbial-Derived Metabolites on Bone Health. Graubünden forscht Congress 2020, Davos (online), Switzerland, 23-24 September 2020

Wallimann A. The influence of short-chain fatty acids on bone health. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Zhakparov D. Introduction to Machine Learning in Life Science. DAViS Center Information Day, Davos, Switzerland, 26 November 2020.

CHAIRS AT CONGRESSES

Akdis CA. Plenary Session II. EAACI Annual Meeting (virtual), 6-8 June 2020.

Akdis CA. Immune response to Corona virus infection. EAACI Annual Meeting (virtual), 6-8 June 2020.

Akdis CA. Innate immune response and immune regulation. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Akdis CA. Special Covid Session. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.
Akdis CA. Severe Asthma. Meet the Experts 2.0 in Asthma, Severe Asthma, COPD and Rare Lung Diseases (webinar), Turin, Italy, 30-31 October 2020.

Akdis M. B cell immunology. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Baerenfaller K. Medicine & Health Session. SIB Days 2020, Digital, 9-10 June 2020.

Baerenfaller K. Medical/Life Sciences Session. Graubünden forscht 2020, Digital, 23-24 September 2020.

Baerenfaller K. Novel diagnosis and treatments of allergic diseases. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Gao YD. Special Covid Session; Poster Session 9: Covid-19, Allergy and Asthma III. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Komlósi ZI. Innate immunity and ILCs (Workshop). WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Komlósi ZI. T and B cell memory and immune regulation (Poster Session). WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Mitamura Yasutaka. Poster Session 5: Allergy and Asthma II and type 2 response. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Mitamura Yasutaka. Poster Session 7: Epithelial cells and other resident tissue cells and innate immunity. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Ogulur I. Epithelial cells, immune response and tolerance. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Radzikowska Urszula. Metabolism. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Rhyner Claudio. Novel diagnosis and treatments of allergic diseases. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Sokolowska M. Injury induced lung inflammation. EAACI Winter-

school, Chamonix, France, 23-26 January 2020.

Sokolowska M. Metabolism and Immune Regulation. Main symposium. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Sokolowska M. Metabolism Workshop. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

Sokolowska M. Diagnosis, Food Allergen, Molecular and cellular mechanisms. Poster Abstract Session 9. EAACI FAAM-EUROBAT Digital 2020; 16-17 October 2020.

van de Veen W. B cells and Immune regulation. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

van de Veen W. Mechanisms of disease development. WIRM-XIV, Davos, Switzerland (digital), 4-7 October 2020.

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.
BME351. Block course “Biomedical Data Mining”
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

Sokolowska M.
BME351. Block course “Biomedical Data Mining”

AWARDS

Akdis M., EAACI Paul Ehrlich Award for Experimental Research, June 2020.

Akdis CA. & Akdis M., Anerkennungspreis for Natural Sciences, Canton of Grisons, November 2020.

Akdis CA. & Akdis M., Honorary Professorship, University of Wuhan, China, September 2020

Gao YD., Distinguished Reviewer Award. Allergy 2020.

Mitamura Y., Molecular features of non-lesional skin in atopic dermatitis. FreeNovation 2020, Novartis Basel, Oktober 2020.

Radzikowska U., Free Registration for Asthma: New discoveries and therapies in the age of COVID - for abstract distribution of SARS-CoV-2 receptors and associated molecules in health and disease, Virtual KeyStone Symposia, December 2020.

Satitsuksanoa P., Outstanding Scientific Award. 7th Conference Graubünden forscht (The Young Researchers Convention 2020) in Davos, Switzerland. September 2020.

Sokolowska M., Distinguished Reviewer Award, Allergy 2020.

van de Veen W., Genetic basis and molecular mechanisms of acquiring allergies. FreeNovation 2020, Novartis Basel, October 2020.

Wallimann A., Outstanding Poster Presentation. The Influence of Microbial-Derived Metabolites on Bone Health. EAACI Winter School 2020, Chamonix, France, January 2020.

DEGREES

Burla D., Uptake and effect of microplastic in epithelial cells of the human lung. University of Zurich, SIAF, December 2020.

Komlósi ZI., Associate Professor, Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary, 15 March 2020.

Ma S., Rhinology (Venia Legendi, MD, PhD), Luo Zhang. Rhinology and immunology, Beijing TongRen Hospital, Capital Medical University, China, 2020.

Rinaldi AO., PhD defense: Skin Barrier Assessment Using Electrical Impedance Spectroscopy: Implications for Research and Clinical Practice. University of Zurich, SIAF, 18 December 2020.

2020

PUBLIC SEMINARS

04.03.2020
Peter B. Ernst: Control of Host Responses to Oxidative Stress

04.03.2020
Vladimir Zlateski: Visualization of low-level Gene Expression and Biomarker Localization within Tissue: Applications of RNAscope® and BaseScope™

04.03.2020
Mark Reudelsterz: CyTOF mass cytometry technology: a comprehensive solution for cell suspension and imaging applications

05.03.2020
Iain Comerford: The atypical chemokine receptor ACKR4 regulates soluble CCL21 bioavailability and dendritic cell egress from barrier sites

05.03.2020
Musa Khaitov: New antigen-specific strategies for prophylaxis and treatment of immune-mediated diseases

26.03.2020 (aufgrund der Pandemie abgesagt)
Agilent Seahorse Cell Analysis Seminar
Georg Kienzle & Lilly von Münchow: Agilent Seahorse Cell Analysis Seminar

03.06.2020 (aufgrund der Pandemie abgesagt)
Jeanne Duus Johansen: The epidemiology of contact allergy- and effect of interventions
Charlotte Menne Bonefeld: The role of local memory in allergic contact dermatitis
Sanne Steengaard Meisser: Allergic contact dermatitis to paraphenylenediamine and immune mechanisms

11.06.2020 (aufgrund der Pandemie abgesagt)
Kenji Izuhara: Periostin: From a key mediator in allergic inflammation to a promising biomarker for allergic diseases

12.06.2020 (online)
Francesco Papaleo: Perinatal Antinflammatory Oxytocin Effects Ameliorates Developmental Trajectories in 22q11.2 Deletion Syndrome

22.06.2020 (online)
Rudi Schläfli: From Single Cell to Spatial Transcriptomics with 10x Genomics

22.09.2020 (online)
Dieter Ulrich: New Bio-Sensors for continuous health monitoring

SIAF SCIENCE DAY (online)
16.12.2020
Allergy Team: You better watch out, you better not cry, ALLERGY is reaching sky high!

Juan Rodriguez: Who killed the regulation?

Jana Koch: Ribosome profiling of Th1 cells

Urszula Radzikowska: RIG-I: Grinch or merrymaker?

Alexandra Wallimann: The role of the microbiota in bone and cheese

Mengting Huang: Performing nasal swab microbiome research: A method to the madness

Siyuan Ma: The difference between IgG1 and IgG4 B cells in antigen presenting capacity

Pattraporn Satitsuksanoa: The roles of B cells in cow‘s milk allergy

Yasutaka Mitamura: Visium shed light on the pathogenesis of atopic dermatitis

Daniel Burla: Plasto’s Adventure

Ismail Ögülür: New generation trojan horse: Processed food with emulsifiers

Arturo Rinaldi: Household laundry detergents disrupt epidermal barrier integrity in mice

Winner of the SIAF Sciene Day 2020: Arturo Rinaldi

SCIENTIFIC POSTS AND EDITORIAL ACTIVITIES

Akdis CA.

Allergy, Editor in Chief

Current Opinion in 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

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) – Scientific Boardr

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

EAACI Research and Outreach Committee (ROC) Immunology Chair

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.

Principal Investigator-The Microbiology and Immunology PhD program, UZH-ETH

EAACI Research and Outreach Committee (ROC) Member

EAACI Food Allergy Guideline member

Member of Scientific Board of Sean Parker Allergy Center, Stanford

Member of Scientific Board of Leo Foundation Skin Immunology Research Center

Workpakcage Member of EU project CURE

Allergy, Editorial Board Member

Journal of Allergy and Clinical Immunology, Reviewer Board Member

SNF project reviewer

PAI, Reviewer Board Member

Science Foundation Ireland, Reviewer Board member

World Immune Regulation Meeting, Member of the scientific committee

Baerenfaller K.

Interim co-leader of the Center for Precision Proteomics at the Medical Campus Davos

Member of the SIB Board of Directors

Jury member for the SIB Best Graduate Paper Award

Group leader of the SIB

Board member of the EAACI WG Genomics&Proteomics

Member of the EAACI ROC Diagnostics group

Abstract Reviewer for the EAACI Congresses

Member of EAACI

Editor of a Frontiers in Immunology Research Topic

Part of the editorial board of the Frontiers in Allergy Allergens Section

Reviewer for a variety of journals

Grant reviewer for a variety of science foundations

Board member of Science City Davos

Member of LS2

Vice-President of the LS2 Bioinformatics intersection

World Immune Regulation Meeting, Member of the scientific com-

mittee

Rhyner C.
Allergy, member of the editorial board

JACI, Member of the reviewer board

Int Arch All, member of the editorial board

Frontiers in Allergy Therapies, Therapeutic targets and Mechanisms, Associated Editor

EAACI Interest Group „Clinical and veterinary allergology", member of the board

Member of Life Sciences Zurich Graduate School-Zurich

World Immune Regulation Meeting - Member of the organizing committee

Sokolowska M.
Principal Investigator-The Microbiology and Immunology PhD program, UZH-ETH

EAACI Immunology Section, Secretary

EAACI TF on Public Otreach, Secretary

EAACI TF on Eicosanoids, Secretary

EAACI TF on Immune Metabolism, Chair

EAACI Research and Outreach Committee (ROC) Member

Allergy, Editorial Board Member

Clinical and Molecular Allergy, Editorial Board member

Frontiers in Pharmacology, Reviewer Board Member

Frontiers in Allergy, Reviewer Board member

World Immune Regulation Meeting, Member of the scientific committee

van de Veen W.
Allergy, Editorial Board Member

Frontiers in Allergy, Reviewer Board Member

Journal of Allergy and Clinical Immunology (JACI), Reviewer Board Member

European Science Foundation (ESF), Member College of Expert Reviewers

The Microbiology and Immunology (MIM) PhD Program, UZH-ETH, Principal Investigator

COST action entitled: "The Core Outcome Measures for Food Allergy (COMFA)", management committee member and deputy lead Immmunological outcomes

The Graduate School Graubünden, Programme committee member

World Immune Regulation Meeting, Member of the scientific committee

National and international collaborations

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

Allergy & Pulmonology Depart., 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, (CH), Dr. S. Grad, Prof. M. Alini, Dr. F. Moriarty, Prof. R.G. Richards, 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, Dr. A. Alba Querencias

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

Erasmus MC, Rotterman (NL), Dr. R. de Swart, Prof. S. Pasmans, Dr. M. Schreurs

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

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, Dr. G. Tan

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

Hacettepe University, Ankara (TR), Prof. O. Kalayci, Prof. E. Birben, Prof. C. Karaaslan, Prof. Dr. B. Seker, Dr. P. Gür

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

Hochgebirgsklinik Davos Wolfgang (CH), Prof. H.W. Duchna, Dr. M. Möhrenschlager, Dr. A. Kalweit, Dr. C. Steiner, Dr. A. Kirsch

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

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

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

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

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

Nederlands Astmacentrum, Dr. D. Prins, Dr. M. Drijver

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

Scibase AG, Stockholm (SE), S. Grant, P. Svedenag, N. L. Askary, A. Karsfeld, D. Melin

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

Spital Davos, Dr. W. Kistler, Dr. M. Villiger, Dr. T. Rothe, Dr. A. Speiser

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

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

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

Tokyo University, Dept of Pediatrics (JP), Dr. H. Morita, Prof. K. Matsumoto, Prof. H. Saito

Tottori University, Faculty of Medicine, Yonago (JP), Division of Dermatology, Department of Medicine of Sensory and Motor Organs, Dr. K. Sugita

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

Universidad CEU San Pablo, Madrid (SP), Prof. Coral Barbas, Dr. D. Barber, Dr. M.M. Escribese

Universität Bern
-Dept. Clinical Vet. Medicine (CH), PD Dr. E. Marti, Prof. A. Zurbriggen
- Vetsuisse Faculty, Institute of Virology and Immunology, Prof. V. Thiel, Prof. Dr. C. Favrot, Dr. A. Rostaher

Universität Freiburg (D), Institut für Molekulare Medizin und Zellforschung, Prof. O. Schilling

Universität Graz (AT)
-Deptartement of Pediatrics, Dr. E.M. Varga
-Inst. Pharm. Chem., Prof. A. Kungl

Universität Zürich (CH)
-Biochemical Institute, Prof. M. Grütter, Dr. P Mittl
-Clinical Trial Center (CH), PD Dr. G. Senti

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

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

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

Universität Tübingen (DE), Prof. L. Flatz

Universitätsspital Bern (CH)
- Eggel Lab, Prof. A. Eggel
-Kinderklinik, Inselspital, Prof. R. Kraemer, Dr. C. Aebischer-Casaulta, Prof. M.H. Schöni
-Universitätsklinik für Rheumatologie, Immunologie und Allergologie, Inselspital, Prof. A. Helbling, Dr. A. Gschwend

-Universitätsklinik für Hals-, Nasen- und Ohrenkrankheiten, Kopf- und Halschirurgie, Dr. U. Borner, Dr. S. Negoias, Dr. S.-L. Hool

Universitätsspital Zürich (CH)
- Allergiestation, Dr. C. Cardoso
-Abteilung für Klinische Immunologie, Prof. Dr. O. Boyman
-Abteilung ENT, PD Dr. D. Holzmann, PD Dr. M. Soyka
-Abfteilung Pneumologie, Prof. Dr. M. Kohler, PD Dr. C. Clarenbach
-Abteilung Gastroenterologie, Prof. R. Gerhard
-Abteilung Kardiologie, Prof. F. Duru, Dr. D. Akdis
-Dermatologische Klinik, Prof. R. Dummer, PD Dr. Th. Kündig, Prof. Dr. P. Schmid-Grendelmeier, Prof. Dr. M.-C. Brüggen, PD Dr. E. Guenova, PD Dr. G. Hofbauer
- Swiss EoE Clinics and Research Network, Prof. Dr. A. Straumann, Dr. L. Biedermann, Dr. P. Schreiner

Universitäts-Kinderspital Zürich (CH), Prof. J. Reichenbach, Prof. R. Lauener, Dr. C. Roduit, Dr. A. Jung

Universitäts-Kinderspital Zürich (CH)
-Forschungszentrum für das Kind, Klinische Chemie und Biochemie, Dr. P. Wawrzyniak

University of Applied Sciences of the Grisons / Fachhochschule Graubünden (FHGR), DAViS Center (CH), Dr. Heiko Rölke, Marco Schmid, PD Dr. Ralf-Peter Mundani, Keller Thomas, Dr. Yves Staudt

University of Cape Town, Department of Dematology (ZA), Assoc Prof. M. Levin, Dr. C. Hlela

University College Cork, Alimentary Pharmabiotic Centre (IE), Prof. Dr. L. O'Mahony, Dr. N. Lunjani, Dr. D. Groeger, Dr. T. Tan

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

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

University of Manchester (UK), Prof. N.G. Papadopoulos

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

University of Szeged, Department of Dermatology and Allergology, Szeged (HU), Dr. N. Nagy, Prof. L. Kemeny

University of Tartu (EE), Dr. A. Rebane, Prof. P. Peterson, Prof. K. Kingo

University of Toronto, Pediatrics (CA), Prof. T. Eiwegger

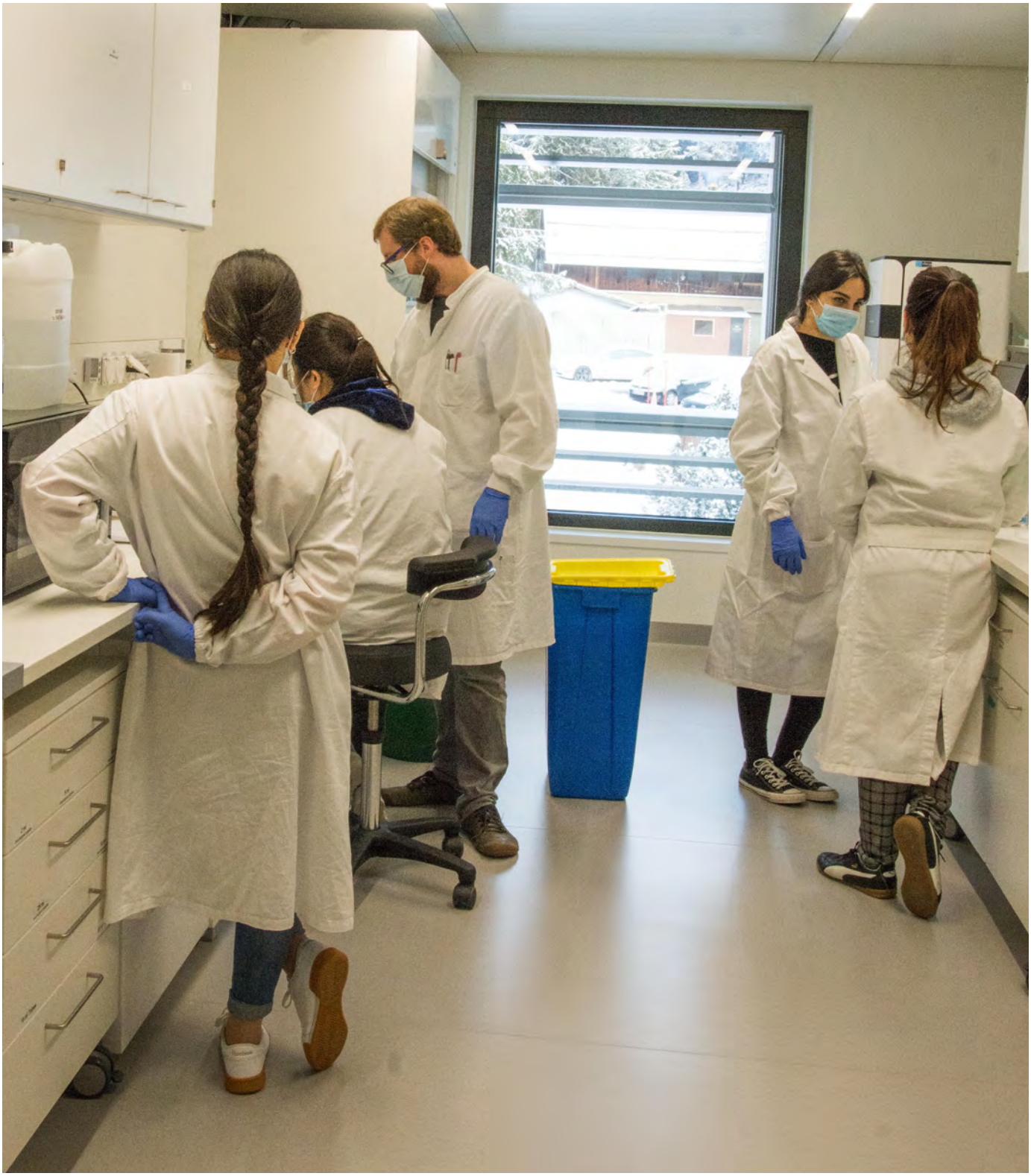
University of Turku, Paediatrics and Adolescent Medicine (FI), Prof. T. Jartti

University of Wisconsin-Madison (US), Prof. J. E. Gern

University of Würzburg (DE)
-Department of Animal Ecology and Tropical Biology, Prof. Jochen Krauss

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

Wroclaw Medical University, Wroclaw (PL), Prof. M. Jutel, Dr. S. Smolinska, Dr. P. Gajdanowicz



Schweizerisches Institut für Allergie- und Asthmaforschung

Bilanz per 31. Dezember 2020

(inklusive Drittmittel)

	31.12.2020	31.12.2010
	CHF	CHF
AKTIVEN		
Flüssige Mittel	1’650’477.13	1’186’895.64
Forderungen	285’434.77	856’269.24
Aktive Rechnungsabgrenzungen	250’850.18	191’914.02
	2’186’762.08	2’235’078.90
PASSIVEN		
Verbindlichkeiten	107’380.19	621’295.70
Bankverbindlichkeiten	14.20	0
Kontokorrent SFI Stiftung	36’919.05	28’967.50
Passive Rechnungsabgrenzungen	1’364’673.88	833’473.45
Rückstellungen	457’618.95	531’186.44
Eigenkapital	220’155.81	220’155.81
	2’186’762.08	2’235’078.90

Schweizerisches Institut für Allergie- und Asthmaforschung

Betriebsrechnung 2020

(inklusive Drittmittel)

	Rechnung 2020	Budget 2020	Rechnung 2019
	CHF	CHF	CHF
ERTRAG			
Beitrag Bund Forschungsgesetz Art. 15	835'200.00	835'200.00	848'300.00
Beitrag Kanton Graubünden	520'000.00	520'000.00	520'000.00
Beitrag Gemeinde Davos	524'560.00	524'560.00	474'560.00
Beitrag Universität Zürich	366'870.95	513'657.00	366'028.15
Beitrag Stiftung SFI Mietererlass	0	0	80'000.00
Finanzierungsbeitrag Universität Zürich	0	0	717'249.75
Beitrag Stiftung vormals Bündner Heilstätte Arosa	56'108.50	55'621.00	54'383.50
Beitrag Stiftungen/Drittmittel	75'608.80	70'000.00	256'149.89
Overheadbeiträge	55'458.00	49'900.00	68'247.00
Spenden	0	0	2'214'621.67
Übriger Ertrag	22'576.34	3'000.00	44'846.31
Finanzertrag	0	0	0.10
Ausserordentlicher Ertrag	23'687.69	50'000.00	22'468.14
Auflösung von Rückstellungen	73'567.49	0	437'492.74
WIRM-Kongress	131'459.01	300'000.00	340'994.93
Drittmittel	2'112'277.41	2'384'494.00	1'318'975.42
	4'797'374.19	5'306'432.00	7'764'317.60
AUFWAND			
Personalaufwand	2'420'977.20	2'803'382.00	2'463'567.53
Verbrauchsmaterial	991'107.41	1'085'350.00	563'487.14
Raumaufwand	325'973.77	335'000.00	242'188.90
Unterhalt/Reparaturen/Ersatz	113'766.72	210'500.00	109'698.18
Investitionen	397'189.30	150'000.00	3'667'162.16
Sachversicherungen/Abgaben	8'626.65	20'000.00	8'088.30
Energie- und Entsorgungsaufwand	139'350.36	130'000.00	95'787.34
Verwaltungsaufwand	89'225.61	103'000.00	136'153.48
Werbeaufwand	6'743.60	0	7'177.20
Reisespesen	41'595.35	50'000.00	75'723.80
WIRM-Kongress	133'813.35	300'000.00	254'551.87
Übriger Betriebsaufwand	6'654.09	12'000.00	121'977.95
Abschreibungen	105'200.00	105'200.00	0
Finanzaufwand	16'091.53	1'000.00	18'753.75
Ausserordentlicher Aufwand	1'059.25	1'000.00	0
	4'797'374.19	5'306'432.00	7'764'317.60
Ergebnis	0	0	0
	4'797'374.19	5'306'432.00	7'764'317.60

Swiss Institute of Allergy and Asthma Research (SIAF)
University of Zurich
Herman-Burchard-Strasse 9
CH-7265 Davos Wolfgang
T: +41 (0)81 410 08 48
siaf@siaf.uzh.ch
www.siaf.uzh.ch

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