Awardees 2024

The winners of these ten research projects were honoured with the Pfizer Research Prize in 2024.

Cardiovascular Medicine, Urology and Nephrology

Prof. Dr. med. Camilla Schinner
University of Basel

Dr. med. Matthias Diebold
University Hospital Basel

Infectious Diseases, Rheumatology and Immunology

Dr. Chen Wang, Dr. Coline Barnoud
University of Geneva

PD Dr. med. Aline Wolfensberger, Prof. Dr. Lauren Clack
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Neuroscience and Neurology

Dr. Florence Aellen, Prof. Dr. Athina Tzovara
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Dr. Barbara Swiatczak
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Oncology

Dr. Joanna Triscott
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Dr. Reza Naghavian
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Pediatrics

Dr. Sara Danielli
University Children's Hospital Zurich

Dr. Adina Epure
University of Fribourg

Cardiovascular Medicine, Urology and Nephrology

Loosing connection breaks the heart

Prof. Dr. med. Camilla Schinner
University of Basel

Arrhythmogenic Cardiomyopathy (ACM) is an inherited disease characterized by life-threatening abnormal heart rhythm (arrhythmias) up to sudden cardiac death especially in young athletes. The disease is mainly caused by genetic mutations in components of cell-cell junctions, which are important for the connection of cardiac muscle cells. Typical symptoms include palpitations, arrhythmic syncope and sudden cardiac arrest. Until today, the disease is not well understood, and therapeutic options are only limited to management of symptoms. Only by knowing more about the origin of the disease, it may be possible to develop an effective treatment one day. Therefore, Camilla Schinner and her team aimed to better understand the mechanisms leading to ACM to support the identification of new therapeutic targets.

In the Cell Adhesion lab at the DBM, University of Basel, they investigated the relevance of insufficient cell-cell connection for the development of the disease. To approach this, the research team introduced a specific gene mutation into a mouse model to disrupt the connection of cardiac muscle cells. Analyses of the diseased hearts revealed that disruption of the cell-cell connection leads to changes in the connection of cardiac muscle cells to the surrounding tissue. Importantly, this is contributing to cardiac scar formation. The resulting heart fibrosis could be prevented by blocking the identified pathway with a chemical compound.

This study shows that impaired cell-cell connection can lead to the development of symptoms characteristic to ACM. With the newly generated mouse model, Camilla Schinner and her team were able to identify a novel pathway promoting scar formation in the heart. This is important, as it helps to better understand the mechanisms causing the disease. Moreover, they tested a first approach to target these changes therapeutically. This highlights the high value of the new model to discern mechanisms of ACM to identify novel treatment strategies for this cardiac disorder.

Defective Desmosomal Adhesion Causes Arrhythmogenic Cardiomyopathy by Involving an Integrin-αVβ6/TGF-β Signaling Cascade. Camilla Schinner, Lifen Xu, Henriette Franz, Aude Zimmermann, Marie-Therès Wanuske, Maitreyi Rathod, Pauline Hanns, Florian Geier, Pawel Pelczar, Yan Liang, Vera Lorenz, Chiara Stüdle, Piotr I. Maly, Silke Kauferstein, Britt M. Beckmann, Farah Sheikh, Gabriela M. Kuster and Volker Spindler. Circulation. 2022 Nov 22;146(21):1610-1626

Cardiovascular Medicine, Urology and Nephrology

SARS-CoV-2 mRNA vaccination is not associated with an elevated risk for glomerulonephritis

Dr. med. Matthias Diebold
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The COVID-19 pandemic led to the development of mRNA-based vaccines and a worldwide vaccination campaign. Two of the most widely used mRNA-based vaccines (Pfizer-BioNTech, Moderna) demonstrated good safety profiles in large trials. However, soon after the start of the vaccination campaign, reports associating the vaccines with kidney diseases (glomerulonephritis) have emerged. What did that mean?

The goal of Matthias Diebold and his team was to investigate whether there was a causal relationship between the vaccines and the development of glomerulonephritis or just a temporal coincidence. The scientists analysed two connected studies. For the first study, they gathered data from all Swiss pathology institutes, which process kidney biopsies. By analysing the incidence data of four types of glomerulonephritis from 2015-2019, they calculated an expected incidence for the vaccination campaign 2021 and compared it with the observed incidence. For the second study, they included all patients who developed glomerulonephritis in 2021 and compared the risk to develop glomerulonephritis between vaccinated patients and those who were not vaccinated.

The observed incidence of the four types of glomerulonephritis during the vaccination campaign from January to August 2021 was not different from the expected incidence based on the years 2015 to 2019. Among the 111 patients with newly diagnosed glomerulonephritis between January and August 2021, the estimated risk for the development of new-onset biopsy-proven glomerulonephritis was not significantly different between vaccinated and unvaccinated individuals.

Asserting itself against the many myths spread about the SARS-CoV-2 vaccination, this important study was able to show that vaccination against SARS-CoV-2 was not associated with new-onset glomerulonephritis.

Incidence of new onset glomerulonephritis after SARS-CoV-2 mRNA vaccination is not increased. Matthias Diebold, Eleonore Locher, Philipp Boide, Annette Enzler-Tschudy, Anna Faivre, Ingeborg Fischer, Birgit Helmchen, Helmut Hopfer, Min Jeong Kim, Solange Moll, Giliane Nanchen, Samuel Rotman, Charalampos Saganas, Harald Seeger, Andreas D. Kistler. Kidney Int. 2022 Dec;102(6):1409-1419

Infectious Diseases, Rheumatology and Immunology

Circadian rhythms, a new player in the fight against cancer

Dr. Chen Wang
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Dr. Coline Barnoud
University of Geneva

Like sleeping and waking up, the immune system is under circadian control and exhibits a time-of-day dependent response to threat encounter. Cancer, which is caused by the capacity of abnormal cancer cells to escape the surveillance of our immune system, is such a threat. Until today, little was known about how day and night rhythms regulate the immune system in cancer. Therefore, the aim of Chen Wang, Coline Barnoud and their team was to learn more about the influence of the circadian rhythm on cancer immunosurveillance.

The scientists engrafted tumour cells of various tumour models into mice at different times of the day. They then quantified tumour growth as well as immune cells in the tumour and lymph nodes to determine the importance of different immune cell subsets. Finally, they performed chrono-immunotherapy experiments to evaluate the effect of anti-tumour vaccination in dependence of time-of day.

They demonstrated that the tumours grew faster when engrafted into mice during their active phase (in the night/dark period) compared to their resting phase (in the day/light period). This is true across different cancer types, including melanoma, breast cancer, and colon cancer. Specifically, more defence cells like dendritic cells and T-cells were present during the resting phase in the draining lymph nodes. Also, the molecule CD80 is controlled by the circadian rhythm, which further enhances the anti-tumour immune response. Lastly, in mice, vaccination in the resting phase can reduce tumour size by 50% compared to active phase vaccination. In humans, morning anti-tumour vaccination is 5-fold more efficient than afternoon vaccination in terms of triggering tumour-specific CD8 T-cell responses.

These remarkable results show for the first time that the response of the immune system to tumour challenges is under circadian control. Therefore, they highlight the importance of considering the time of day for the administration of treatments involving the activation of the immune system to improve the patients' clinical outcome.

Dendritic cells direct circadian anti-tumour immune responses. Chen Wang, Coline Barnoud, Mara Cenerenti, Mengzhu Sun, Irene Caffa, Burak Kizil, Ruben Bill, Yuanlong Liu, Robert Pick, Laure Garnier, Olga A. Gkountidi, Louise M. Ince, Stephan Holtkamp, Nadine Fournier, Olivier Michielin, Daniel E. Speiser, Stéphanie Hugues, Alessio Nencioni, Mikaël J. Pittet, Camilla Jandus, Christoph Scheiermann. Nature. 2023 Feb;614(7946):136-143

Infectious Diseases, Rheumatology and Immunology

A bundle of preventive measures reduces hospital-acquired pneumonia by one third

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Hospital-acquired pneumonia is one of the most common healthcare-associated infections and affects stationary patients who are not intubated. The implications for patients range from prolonged hospital stay to increased mortality. However, little is known about many aspects of this nosocomial infection.

The aim of Aline Wolfensberger, Lauren Clack and their team was to test a bundle of five specific measures to prevent such hospital-acquired pneumonia in non-ventilated patients (nvHAP). These measures included oral care, dysphagia screening and management, mobilisation, discontinuation of non-indicated proton-pump inhibitors, and respiratory therapy. The study was conducted in nine surgical and medical departments at the University Hospital Zurich over a period of 38 months.

The scientists showed that implementation of the nvHAP bundle effectively lowered the incidence rate of infections by 31%. Departments with higher implementation success (defined as high acceptability, appropriateness, fidelity, and sustainability) showed a higher reduction of new infections. The implementation success was associated with alignment of the prevention measures with the “core business” of the department, high perceived nvHAP risk, physical proximity of the different professions involved in nvHAP prevention, and favourable individual traits.

The finding that a bundle of preventive measures led to a reduction of hospital-acquired pneumonia is of great practical benefit, since nvHAP is a common, but so far little studied infection. The knowledge of the determinants of implementation success might help in upscaling nvHAP prevention.

Prevention of non-ventilator-associated hospital-acquired pneumonia in Switzerland: a type 2 hybrid effectiveness-implementation trial. Aline Wolfensberger*, Lauren Clack*, Stefanie von Felten, Mirjam Faes Hesse, Dirk Saleschus, Marie-Theres Meier, Katharina Kusejko, Roger Kouyos, Leonhard Held, Hugo Sax. Lancet Infect Dis. 2023 Jul;23(7):836-846
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Neuroscience and Neurology

Using artificial intelligence to predict chances of recovery from a coma

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Most survivors of cardiac arrest (CA) are initially in a coma. Currently used outcome prediction techniques mainly rely on expert assessment of clinical variables and physiological measurements such as electroencephalography (EEG). Assessing neural functions of coma patients and predicting chances for recovery still remain challenging. Notably, the existing markers for prognostication leave up to one third of patients with uncertain prognosis, in a 'grey zone'.

Therefore, Florence Aellen, Athina Tzovara, and their colleagues challenged the traditional approach for predicting coma outcome and used artificial intelligence to assess the integrity of neural functions in coma and chances of recovery. They utilized state-of-the-art deep learning algorithms applied to coma patients' EEG responses to sound stimuli.

During the first 24 hours of coma following cardiac arrest, 134 comatose patients in the intensive care units of four different Swiss hospitals were presented with sound stimuli via headphones. The researchers then trained deep learning algorithms to predict whether a given patient would survive the coma three months later based on EEG responses to the sounds.

The analysis showed that neural responses to sounds in combination with deep neural networks can indeed be used to predict a patient's chances of awakening from coma. Crucially, outcome prediction was at similar levels in a cohort of 48 'grey zone' patients, whose outcome would be indeterminate based on existing clinical tests. Moreover, the confidence of the neural network in predicting patients' outcome was reflecting interpretable properties of EEG signals.

The researchers show, for the first time, systematic evidence that a deep learning framework can disentangle auditory processing in coma patients and assist in prognosticating their chances to recover. This work not only provides novel insights on neural functions that are preserved without consciousness but may further have implications for the field of neuro-critical care and outcome prognostication.

Auditory stimulation and deep learning predict awakening from coma after cardiac arrest. Florence M. Aellen, Sigurd L Alnes, Fabian Loosli, Andrea O. Rossetti, Frédéric Zubler, Marzia De Lucia, Athina Tzovara. Brain. 2023 Feb 13;146(2):778-788

Neuroscience and Neurology

Why does the eye develop myopia?

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Myopia (near-sightedness) is the most common eye disorder in young people worldwide. The disease is characterized by eyeballs too long for their optical power which causes distant objects to be seen blurred or out of focus. Although myopia can be corrected by spectacles, contact lenses, or laser surgery, none of these interventions can stop further eyeball elongation leading to the development of high myopia which increases the risk of retinal complications.

In the process of eye growth and development children's eyes undergo adjustments to achieve the best possible image quality and sharp vision by matching eye length to its optical power (perfectly seeing eyes are called “emmetropic“). For Barbara Swiatczak and her colleague, one crucial question remained unanswered: Despite this tightly controlled mechanism of eye growth, why do some children develop myopia while others remain emmetropic? Why does the retina seem „to give up“ during myopia development?

They knew that the visible light contains blue, green and red light with different wavelengths. Green light focuses on the retina creating a sharp image while blue light is focused in front of the retina, and red light behind the retina, imposing blur. Since the myopic eye is too long, red light is in better focus than green light. On the other hand, the hyperopic eye (far-sightedness) which is too short sees blue light in better focus. The innovative approach of the scientists was to trick the retina by digital filtering of the separate colour channels in order to trigger changes in the eye length. They developed two digital filters: the “red in focus” filter which imitates the myopic eye, and the “blue in focus” filter which mimics a hyperopic eye. When young adults watched a movie with the “red in focus” filter, their retina triggered eye shortening. Conversely, the “blue in focus” filter induced eye elongation. Surprisingly, these changes were only observed in emmetropic but not myopic eyes.

The findings of this study resolve a long-standing ophthalmologic question. Apparently, the myopic retina no longer detects chromatic defocus and therefore can no longer generate growth-inhibiting signals, but instead triggers more eye elongation and myopia progression. The results also suggest a new non-invasive strategy to inhibit early myopia development: keeping the red image plane on a computer screen sharp but low pass filtering the blue.

Myopia: why the retina stops inhibiting eye growth. Barbara Swiatczak*, Frank Schaeffel*. Sci Rep. 2022 Dec 15;12(1):21704)
* contributed equally

Oncology

Lipid regulator exposes prostate cancer vulnerability

Dr. Joanna Triscott
University of Bern

An estimated one in seven men will develop prostate cancer by the age of 60. The dependence of this form of cancer on androgen hormone signalling for growth and development distinguishes it from other tissue types. New androgen targeted treatments have improved prostate cancer outcomes. However, some patients develop resistance to these therapies. Despite great scientific efforts, the whole network of biochemical changes that occur during prostate cancer progression has yet to be characterized.

The assumption of Joanna Triscott and her colleagues was that PI5P4Ks (Phosphatidylinositol 5-phosphate 4-kinases), a family of relatively understudied metabolic enzymes, plays an important role in prostate cancer biology. Therefore, they aimed to determine whether PI5P4Kα influences the ability of cancer cells to adapt to treatment stress, which might lead to the discovery of a potential vulnerability in cancer survival. To test whether PI5P4Kα has a relationship with androgen receptor (AR) hormone signalling, they queried patient datasets and used cell culture models to experimentally determine the impact of down regulation of PI5P4Kα. Additionally, they generated a prostate-specific PI5P4Kα-targeted mouse model to assess fundamental prostate biology.

The results show that expression of PI5P4Kα is increased in advanced prostate cancer cells and based on the mouse model, is localized to the lysosome. Data from *in vivo* and *in vitro* experiments further demonstrate that prostate cancer cells dramatically increase the volume of lysosomes under conditions of androgen receptor inhibition, and that PI5P4Kα may interact with androgen receptor signalling through a key pathway in cancer biology called mTORC1. Finally, the scientists could show *in vitro* that depletion of PI5P4Kα makes cancer cells less viable.

Joanna Triscott and her team shed light on the role of the lesser known lipid regulator PI5P4Kα in prostate cancer and its relationship with androgen hormone signalling, which promotes cancer cell survival. The study showed the importance of lipid regulation during metabolic stress adaptation in prostate cancer, particularly under androgen deprivation. This remarkable work suggests that targeting PI5P4Kα could disrupt the metabolic adaptation of prostate cancer as it progresses. This could make the enzyme a potential target for the development of new drugs against prostate cancer.

PI5P4Kα supports prostate cancer metabolism and exposes a survival vulnerability during androgen receptor inhibition. Joanna Triscott, Matthias Reist, Lukas Küng, Francielle C. Moselle, Marika Lehner, John Gallon, Archna Ravi, Gurpreet K. Arora, Simone de Brot, Mark Lundquist, Hector Gallart-Ayala, Julijana Ivanisevic, Salvatore Piscuoglio, Lewis C. Cantley, Brooke M. Emerling, Mark A. Rubin. Sci Adv. 2023 Feb 3;9(5):eade8641

Oncology

Microbial allies: bacterial antigens boost anti-tumour immune response

Dr. Reza Naghavian
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Microbial organisms play a key role in numerous physiological processes in the human body and have been shown to modify the immune response. In fact, there is evidence on tumour shrinkage during bacterial infection and that immunotherapies are more effective when specific bacteria are present in the patients' gut microbiome. This indicates that protective immune responses against bacteria may also target tumour tissue.

Reza Naghavian and his team addressed the role of microbial organisms and their potential involvement in immune reactivity against glioblastoma in the brain. The focus was on cancer-specific T cells as they are crucial for anti-tumour responses and successful immunotherapies. The researchers investigated T cell clones (TCCs), single T cell receptor, from tumour-infiltrating lymphocytes (TILs) in glioblastoma and investigated whether they recognize foreign antigens such as those from bacteria. They pursued several experimental paths to address if and how bacterial antigens contribute to immune reactivity against glioblastoma. For example, they established tumour-specific TCCs from TILs of a patient and examined their response to synthetically produced peptides derived from bacteria present in the tumour microenvironment.

The results are remarkable: The researchers showed that bacterial peptides in glioblastoma may be involved in tumoral immune responses through activation of certain TCCs. Through their broad antigen discovery approach, they subsequently defined a new set of peptides from pathogenic bacteria and gut microbiota that were strongly stimulatory for single TCCs and even bulk TILs. Finally, the data indicates that peripheral blood memory T cells stimulated and enriched with the newly identified bacterial antigens are capable of recognizing glioblastoma tumour cells.

The identification of bacteria, which have an active role in tumour defence mechanisms, and microbial peptides for T cell activation holds promise for strong anti-tumour responses. These important results pave the way for new personalized tumour vaccination approaches through synthetically produced bacterial peptides.

Microbial peptides activate tumour-infiltrating lymphocytes in glioblastoma. Reza Naghavian, Wolfgang Faigle, Pietro Oldrati, Jian Wang, Nora C. Toussaint, Yuhan Qiu, Gioele Medici, Marcel Wacker, Lena K. Freudenmann, Pierre-Emmanuel Bonté, Michael Weller, Luca Regli, Sebastian Amigorena, Hans-Georg Rammensee, Juliane S. Walz, Silvio D. Brugger, Malte Mohme, Yingdong Zhao, Mireia Sospedra Marian C. Neidert, Roland MartinNature. Nature. 2023 May;617(7962):807-817

Pediatrics

Hijacking tumour cells to bring them back onto the right track

Dr. Sara Danielli
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Rhabdomyosarcoma (RMS) is a tumour originating from the muscle lineage, and the most common soft tissue cancer in children and adolescents. Its most aggressive form alveolar RMS (aRMS) is refractory to surgery and treatments, and in critical need for effective therapeutic approaches. Traditionally, RMS cells have been characterized in bulk, which is limited to measuring only the average signal within a complex population. As one of the greatest barriers to successful anticancer treatment is intratumoral heterogeneity, understanding the composition of RMS tumours cell by cell could help identifying better treatments.

The goal of Sara Danielli and her team was to understand aRMS tumours at single-cell resolution. Her focus was on the identification of cellular subpopulations within the complex tumour, their dynamics during treatment, and novel targeting approaches. First, they studied several thousands of tumour cells from primary samples using single-cell technologies to identify the relevant tumour subpopulations. Next, they utilized computational and experimental tools to study the way different subpopulations change identity over time. They then applied chemotherapy on RMS cells (*in vitro*) as well as mouse models (*in vivo*) and investigated the composition of the surviving tumour cells. Finally, they screened for drugs that could shift the tumour cell composition towards ”more desired” populations.

The scientists showed that aRMS tumours contain a majority of aggressive cells resembling immature developing muscles, but also a minority of cells that resembles more mature and differentiated muscle fibres, i.e. cells that have lost their ability to proliferate. In patients with better outcomes, the differentiated ”good“ muscle-like cells were enriched. They therefore identified a combination of drugs that initiate cellular differentiation in aRMS tumours, and thereby inhibits the growth of the cancer cells.

Sara Danielli and her team, unraveled the single-cell composition of pediatric RMS. They devised a novel drug-based treatment approach that forces the tumour cells to differentiate and thereby slows down their growth. With other words: They discovered for the first time that alveolar RMS can be treated not only by chemotherapy, but also by directing their tumour circuit from aggressive subpopulations into less malignant differentiated cells using drugs that are already under clinical evaluation.

Single-cell profiling of alveolar rhabdomyosarcoma reveals RAS pathway inhibitors as cell-fate hijackers with therapeutic relevance. Sara G. Danielli, Ermelinda Porpiglia, Andrea J. De Micheli, Natalia Navarro, Michael J. Zellinger, Ingrid Bechtold, Samanta Kisele, Larissa Volken, Joana G. Marques, Stephanie Kasper, Peter K. Bode, Anton G. Henssen, Dennis Gürgen, Olivier Delattre, Didier Surdez, Josep Roma, Peter Bühlmann, Helen M. Blau, Marco Wachtel, Beat W. Schäfer. Sci Adv. 2023 Feb 10;9(6):eade9238

Pediatrics

Covering perinatal health-care costs improves newborn health

Dr. Adina Epure
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Low birthweight (<2500 g) and preterm birth (<37 weeks gestation) are key indicators of newborn health. Both are associated with an increased risk of death in the first year of life as well as chronic conditions during the life course. Therefore, reducing poor birth outcomes is a global public health priority and requires strategies to improve access to health services during pregnancy.

Previously, the existing evidence on this topic was limited to the United States and specific vulnerable subgroups such as low-income individuals or immigrants. Adina Epure and her team assessed the effect of a Swiss health policy that expanded coverage of healthcare costs during pregnancy on newborn health outcomes. For this they performed a nationwide study and included nearly all live births (about 509.000 children) in Switzerland between 2011 and 2019. The scientists implemented a quasi-experimental design that imitated a randomized experiment. They assessed the effect on birthweight, gestational age, and neonatal death of a 2014 Swiss policy expansion, which provided full coverage of mother participation to healthcare costs from 13 weeks of gestation through 8 weeks postpartum.

The results of the study showed that the policy expansion had a positive effect on newborn health at a population level, notably with respect to reducing the risk of low and very low birthweight births. For example, the predicted proportion of low birthweight births decreased by 0,81%. However, the risk of preterm births and neonatal deaths was not reduced in the population at risk of poverty.

This investigation showed that expanding coverage of healthcare costs during pregnancy had a positive effect on the health of babies born in Switzerland. But the policy did not reduce socioeconomic health inequalities. Therefore, strategies targeting both financial and non-financial barriers could be considered in the future to reduce socio-economic inequalities and to maximize maternal and child health.

Effect of covering perinatal health-care costs on neonatal outcomes in Switzerland: a quasi-experimental population-based study. Adina Mihaela Epure, Emilie Courtin, Philippe Wanner, Arnaud Chiolero, Stéphane Cullati, Cristian Carmeli. Lancet Public Health. 2023 Mar;8(3):e194-e2024

PP-UNP-CHE-0929 Dec 2023