Preisträger:innen 2023

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Silent brain infarcts impact on cognitive function in atrial fibrillation

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It has long been known that patients with atrial fibrillation (AF) have increased risks for clinical brain infarcts and cognitive decline, but underlying mechanisms were incompletely understood. The research team of Philipp Krisai and Michael Kühne could previously observe in a cross-sectional study that one in five AF patients had clinically silent brain infarcts – despite a high rate of anticoagulation – and that these silent infarcts are associated with cognitive dysfunction similar to clinical infarcts. These results offered a potential explanation for the association between AF and cognitive decline in patients without a previous stroke, but prospective data were lacking.

To further investigate this association, the scientists followed 1227 AF patients prospectively in a multi-center study across Switzerland. The participants underwent brain magnetic resonance imaging (MRI) at the beginning of the study and after two years to investigate the occurrence of new ischemic brain infarcts, white matter lesions and microbleeds. Clinically silent infarcts were assessed in patients without a clinical stroke or ischemic attack during follow-up. Additionally, cognitive performance was analyzed with different neurocognitive tests.

The results after two years were as following: After two years, new ischemic brain infarcts were found in 5.5%, new white matter lesions in 18.7%, and new microbleeds in 11.4% of the patients. Nearly 9 out of 10 ischemic brain infarcts occurred in anticoagulated patients. Although most of the brain infarcts were clinically silent, they had similar associations with cognitive decline as clinically overt brain infarcts. By contrast, white matter lesions and microbleeds were not associated with cognitive decline.

The data of Philipp Krisai and his team are relevant for a growing population of AF patients at risk for cognitive decline. They suggest that anticoagulation alone may not be sufficient to prevent progressive brain damage in all AF patients and other preventive measures are needed. In summary, this study prospectively assessed the occurrence of clinically silent and overt brain lesions and their association with cognitive decline in patients with atrial fibrillation.


* Contributed equally
Cardiac troponin T (cTnT) and cardiac troponin I (cTnI), two blood proteins, stemming from the heart are commonly used to diagnose an acute myocardial infarction (AMI). Up to now, both isoforms have been considered equivalently accurate and cardiac-specific diagnostic tools. However, concentrations of cTnT but not cTnI were recently found to be elevated in patients who had skeletal muscle diseases but did not show any cardiac involvement. Therefore, elevated cTnT could potentially lead to erroneous diagnoses of heart attacks in those patients.

Based on these observations, the research group with Jeanne du Fay de Lavallaz and Alexandra Prepoudis aimed to examine the clinical validity of assessing cTnT or cTnI concentrations in patients with skeletal muscle diseases. They asked how often unexpected elevations of cTnT were seen in patients with skeletal muscle diseases and tried to uncover the underlying pathophysiology.

For this, the scientists enrolled patients with various active chronic muscle diseases and compared their blood concentration of cTnT and cTnI to the ones of patients with healthy hearts and no muscle problems. Furthermore, genes that might be responsible for the expression of cTnT in the patients’ skeletal muscles were investigated.

In patients with skeletal muscle diseases, cTnT levels were significantly more elevated than cTnI levels, even in patients with a healthy heart. The elevated cTnT levels could originate from the skeletal muscle, where the cTnT genes appeared more active than the cTnI genes. These results imply that special care needs to be taken when assessing a patient with skeletal muscle problems for a heart attack: In patients with noninflammatory myopathy and myositis, elevated cTnT might lead to erroneous diagnoses of heart attacks. The awardees suggest that in these patients, an alternative test looking at the cardiac Troponin I levels should be measured for an accurate diagnosis of heart attacks.

These findings represent a considerable progress in the pathophysiological understanding of troponin molecules.


* Contributed equally
Every athlete knows that magnesium (Mg2+) is important for well-functioning muscles. However, Mg2+ also plays an important role in cellular immunology, a fact which was largely unknown, just until recently. Mg2+ deficiency is the most underdiagnosed electrolyte abnormality and has been associated with a variety of diseases including infections and cancer. Therefore, the research team with Jonas Lötscher aimed to investigate the biological relevance of extracellular magnesium for immune cells.

In experimental tumor mouse models, the awardee has shown that CD8+ T cells – a specialized type of immune cells – require an Mg2+ -rich environment for activation and efficient elimination of cancer cells. Specifically, Mg2+ is important for the function of LFA-1. This cell surface molecule acts as a docking site and plays a key role in T cell activation. Mg2+ application into the tumors also resulted in an increased efficacy of so-called checkpoint inhibitors. These therapeutic agents support the immune system in attacking cancer cells. Based on these results, the young scientist retrospectively assessed the relation between serum Mg2+ levels and therapeutic outcomes in patients with lung cancer as well as B cell lymphoma who participated in a clinical trial with immune checkpoint inhibitors or CAR T cell therapy respectively. The retrospective analysis of both patient groups showed that the survival of patients was significantly reduced when they exhibited low serum Mg2+ levels.

The observation that Mg2+ is essential for efficient T cell function may be highly relevant in the context of modern cancer immunotherapies. The results offer the opportunity to develop novel preventive or therapeutic strategies in the battle against infections and cancer. The findings of Jonas Lötscher and colleagues have potential to be translated directly into clinical practice and clinical trials are planned.
Infektiologie, Rheumatologie und Immunologie

Immunity to common coronaviruses may promote rapid development of SARS-CoV-2-specific immunity

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Different human coronaviruses (HCoV) caused colds and other diseases in humans long before the COVID-19 pandemic outbreak. Could pre-existing immune responses to closely related circulating human coronaviruses cross-react with SARS-CoV-2? Irene Abela, Chloé Pasin and Magdalena Schwarzmüller investigated this question and aimed to find out if pre-existing HCoV immunity can protect against an infection with SARS-CoV-2 or against severe disease.

The three awardees developed a novel serology assay to evaluate the diversity of antibody responses to SARS-CoV-2 and HCoV. Utilizing a computational framework, they identified past and current SARS-CoV-2 infections. Based on the evaluation of antibody responses in over 1200 pre-pandemic and pandemic samples they developed a statistical strategy to predict whether an individual has neutralizing plasma antibodies that can prevent an infection with SARS-CoV-2. Furthermore, the scientists investigated whether pre-existing HCoV antibodies influence the development of SARS-CoV-2 antibodies and impact disease severity.

In an interdisciplinary approach, they found that individuals with high pre-existing immunity to HCoV are more likely to develop stronger SARS-CoV-2 specific antibody responses upon SARS-CoV-2 infection. In addition, individuals with high levels of antibodies against HCoV were less likely to require hospitalization. The young scientists demonstrated how prior immunity to circulating HCoV can protect against SARS-CoV-2 acquisition, promote the development of specific antibodies to SARS-CoV-2, and influence disease severity.

In conclusion, these results suggest that immunity to HCoV may promote the rapid development of SARS-CoV-2-specific immunity, thereby emphasizing the importance of exploring cross-protective responses for comprehensive coronavirus prevention.


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Eyes wide shut, brain wide awake

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During rapid eye movement (REM) sleep emotional memories are consolidated in the prefrontal cortex. Although this front part of the cerebral cortex plays a key role in discriminating between positive versus negatives emotions during wakefulness, it appears paradoxically quiescent during REM sleep. The processes involved, namely the underlying neocortical circuits, remain unclear.

Mattia Aime, a researcher in the team led by Prof. Adamantidis, aimed at understanding the role of the prefrontal cortex during REM and the underlying cellular mechanisms responsible for emotional processing during this phase of sleep. The researchers first conditioned mice to recognize auditory stimuli associated with safety or danger. They consequently recorded the neuronal response to these stimuli in the mice's brains during sleep-wake cycles and mapped the activity to different parts of the neurons.

They found that, during REM sleep, the dendrites (finest neuronal ramifications) of prefrontal neurons are highly activated while the cell bodies are kept silent. The scientists found that this decoupling plays an important role in emotional control. On the one hand, the strong activity of the dendrites allows discrimination of positive and negative emotions. On the other hand, the cell bodies remain silent and do not transmit signals during REM sleep, which could help avoiding over-reaction to emotions. In other words, the brain favors the distinction between safety and danger in the dendrites during REM sleep.

This study identified the neuronal mechanisms by which the brain distinguishes positive from negative emotions during sleep. The results provide a better understanding of how emotions are processed during sleep and open new perspectives for therapeutic targets of affective disorders, including Post-Traumatic Stress Disorder (PTSD).

Neurowissenschaften und Erkrankungen des Nervensystems

Identical twin study reveals non-heritable immune perturbations in multiple sclerosis

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Multiple sclerosis (MS) is the most common cause of neurological deficits in young adults. In Switzerland, more than 10'000 people are currently living with this disease. Both, genetic risk factors and environmental triggers, contribute to the immune-mediated destruction of the patients’ own central nervous system. However, it remains unknown how specifically heritable and non-heritable influences shape the immune system to ultimately elicit MS.

The aim of the study of Florian Ingelfinger and his colleagues was to dissect how genetic and environmental risk factors affect the immune system in MS patients and facilitate the immune-mediated disability. The scientists analyzed circulating immune cells of 61 genetically identical twin pairs, in which one twin was affected by MS and the other twin did not show any signs of the disease despite having the same genetic risk for MS.

Florian Ingelfinger and his team used state-of-the-art technology to describe the immune profiles of the twin pairs. They exerted a combination of mass cytometry and modern methods in genetics paired with artificial intelligence to uncover characteristic proteins in the immune cells of the sick twins. Moreover, they identified all the genes that were activated in these cells. The most pronounced differences in the immune profiles of twins affected by MS were found regarding intercellular communication: The scientists observed an increased sensitivity to certain cytokines (molecules that are used by the immune system for intercellular communication) that was associated with a stronger activation of T cells in the blood of patients with MS. These T cells were more likely to migrate into the central nervous system of patients and cause damage there.

The findings of this study with identical twins indicate that environmental stimuli cause an imbalance in the communication circuits of leukocytes during the development of MS. In combination with a genetic predisposition in patients, this imbalance could lead to the activation of pathogenic T cells and thus to the development of MS. These insights are fundamental to understand how genetics and environmental factors predispose to MS and can contribute to the development of novel therapeutic approaches.


* Contributed equally
Onkologie

Gut bacteria may fuel prostate cancer

Castration-resistant prostate cancer (CRPC) is usually treated with androgen deprivation therapy to reduce circulating androgens, slowing tumor growth. However, after an initial response, tumors can develop various mechanisms of resistance, resulting in bad prognoses. The human gastrointestinal tract hosts a wide range of bacteria that live in close contact with the host, usually with mutual benefit. Perturbations of this equilibrium can occur under pathological conditions, including cancer. So far, only a limited number of studies have investigated the role of the gut microbiota in prostate cancer initiation and progression.

The aim of Arianna Calcinotto, Nicolò Pernigoni, and Elena Zagato was to understand the role of gut microbiota in CRPC. Specifically, they investigated whether a disbalance of gut microbiota promotes CRPC progression and whether this effect can be counteracted through therapeutic intervention via microbiota manipulations. The researchers performed microbiota elimination experiments using broad-spectrum antibiotics in laboratory mouse strains which are susceptible to the development of CRPC. Moreover, through fecal transplantation experiments, they investigated, whether a new gut microbiota could accelerate or control tumor growth in mice and patients.

In fact, the intestinal microbiota of CRPC-bearing mice and patients is enriched with specific bacterial species, capable of producing androgens, hence fueling tumor growth even under androgen deprivation therapy. The researchers showed that gut microbiota from both mice and humans with CRCP accelerated CRPC progression, enriching androgen-producing bacterial species in the hosts. In contrast, under antibiotic therapy, a delay in CRPC emergence could be observed in mice. The researchers identified a “favorable” bacterial signature, associated with a better prognosis, and an “unfavorable” bacterial signature, associated with poor clinical outcome.

The discovery that bacteria can contribute significantly to circulating androgens paves the way to potential adjuvant therapeutic strategies. Moreover, intestinal microbiota signatures might predict prostate cancer outcome. Clinical studies are required to examine these strategies.


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Onkologie

Improving cancer immunotherapy with engineered probiotic bacteria

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Immunotherapies specifically support or activate the body’s own immune cells to seek out and attack cancer cells. For example, so-called checkpoint inhibitors are used, which specifically target “brakes” in the immune system. The efficacy of checkpoint inhibitor therapies, such as the one targeting the PD-1/PD-L1 pathway, relies on the ability to generate specific T cell activity. However, in order to be as effective as possible, such anti-PD-L1 therapies require a special microenvironment. Therefore, the availability of a large amount of the amino acid L-arginine in tumors is a key determinant of an efficient anti-tumor T cell response.

The goal of Camilla Basso, Fernando Pablo Canale and Roger Geiger was to develop effective means to locally increase L-arginine concentrations in tumors to improve cancer therapy. For this they modified genetically a non-pathogenic strain of the bacteria E. coli to produce continuously high local concentrations of arginine in the tumour. The injections of these bacteria in the tumors and the colonization of tumors with the microbes raised the arginine concentrations, increased the number of tumor-infiltrating T cells and had marked synergistic effects with PD-L1 blocking antibodies in the destruction of tumors.

In this study, the researchers showed a first example of how the metabolic milieu in tumors can be effectively and continuously modulated in favor of an effective anti-tumor T cell response. This bacteria-based therapy might be suitable for the development of human therapeutics.


* Contributed equally.
A novel genomic tool can rescue a genetic metabolic disease in mice

Monogenic diseases are caused by a mutation in a single gene, which can have severe implications for the development and health of patients over their lifetime. One such disease is the metabolic liver disorder phenylketonuria (PKU), which can cause neurological deficits in infants when left untreated. Could such serious diseases be treated or even cured on the genetic level?

Desirée Böck, Tanja Rothgangl and Lukas Villiger used a novel gene editing technology, called «prime editing», which has the potential to directly repair disease-causing mutations in monogenic diseases, such as PKU. The scientists optimized and applied prime editing to cure PKU in a respective mouse model. They first reduced the size of the prime editor (a fusion protein of Cas9 and a reverse transcriptase) in order to facilitate in vivo delivery to newborn and adult animals in a second step. The observed editing rates were dose-dependent and sufficient to cure the disease in animals permanently.

The three awardees could show that the prime editing technology is functional and highly precise in the mouse liver. In conclusion, this study demonstrates the potential of this novel tool in vivo. Further studies are required to examine if this technology could be used in the future to help patients suffering from various monogenic diseases.
Pollen exposure increases risk of respiratory symptoms in infancy

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Pollen has been identified as a risk factor for allergic and non-allergic respiratory symptoms in older age groups. However, there is no study on the impact of pollen for the first year of life, a particularly vulnerable period for lung development. A better understanding of the effects of pollen on the respiratory system in infancy may help improve respiratory health in the short and long term.

Amanda Gisler and colleagues wanted to assess whether exposure to grass and tree pollen in the first year of life is associated with an increased risk of respiratory symptoms (cough, wheezing, respiratory symptoms). In addition, they tried to evaluate whether a maternal predisposition to allergic reactions, male sex, or air pollution increased the susceptibility to pollen. For this the scientists used the data (ca.14,800 observations) from 401 infants from the Basel Bern Infant Lung Development (BILD) cohort. In the analysis period (January through September) they recorded weekly the symptoms of the children in telephone interviews. The pollen exposure for the corresponding week was estimated for each infant using data from the nearest monitoring station. Advanced statistical models were applied to examine whether there was a significant association between individual pollen exposure and respiratory symptoms and whether other factors, such as air pollution, exacerbated the effects of pollen.

In this longitudinal study Amanda Gisler and her team could show that exposure to tree and grass pollen is associated with an increased risk of respiratory symptoms already in the first year of life. They found this association even in healthy term-born infants. An allergic reaction or pollen-induced suppression of the immune response could be possible mechanisms linking pollen exposure and respiratory symptoms. Furthermore, they found that the effect of pollen did not depend on maternal predisposition to allergic reactions or the infant’s sex. However, they found a complex interaction effect of pollen and air pollution on respiratory symptoms.

This study shows that exposure to grass and tree pollen increases the risk of respiratory symptoms even as early as during the first year of life. This finding is significant because virtually every child is exposed to pollen and infancy is a particularly sensitive period for lung development. The better understanding of the effects of pollen during this sensitive period may serve as a starting point for future studies to elucidate the association between pollen and respiratory symptoms.

Pollen exposure is associated with risk of respiratory symptoms during the first year of life. Amanda Gisler, Marloes Eeftens, Kees de Hoogh, Danielle Vienneau, Yasmin Salem, Sophie Yamine, Julian Jakob, Olga Gorlanova, Fabienne Decrue, Regula Gehrig, Urs Frey, Philipp Latzin, Oliver Fuchs, Jakob Usemann, BILD study group. Allergy. 2022;00:1–11.
High antibiotic exposure among children in low- and middle-income countries

Appropriate antibiotic treatment for children with infections prevents mortality and severe illness. On the other hand, antibiotics increase the risk of allergic, inflammatory and metabolic disorders and widespread antibiotic use has contributed to rising antimicrobial resistance. Few estimates of total antibiotic exposure among children in low- and middle-income countries (LMICs) are available.

The goal of the study of Gillian A. Levine and Julia A. Bielicki was to estimate the total number of antibiotic treatments among children in LMICs in the first five years of life. They aimed to describe antibiotic treatment patterns by age, illness, and country. Moreover, they characterized antibiotic use practices in medical care settings and due to self-medication. To estimate the average number of antibiotic treatments children received in the first five years of life in 45 LMICs (countries from Africa, Asia, Central America, Caribbean), the researchers analyzed Demographic and Health Survey (DHS) data. They determined the two-week prevalence of fever, diarrhea or cough and antibiotic treatment rates for these illnesses in children aged 0 to 59 months and modeled the cumulative antibiotic treatment over the first five years of life for each country.

The two scientists identified large differences between countries in terms of antibiotic use: The proportion of illness episodes treated with antibiotics ranged from 10% (Niger) to 72% (Jordan). A mean of 42.7% of fever cases and 32.9% of illness episodes without fever received antibiotics. The researchers estimated that children in LMICs received a median of 18.5 antibiotic treatments during their first five years of life. The average number of antibiotic treatments in the first five years of life ranged from 3.7 in Niger to 38.6 in DR Congo. An average of 9% of antibiotic treatments was attributable to informal care and 17% to self-medication.

The study shows a high and, in some cases likely unjustified, use of antibiotics in young children in LMICs. These observations are concerning since antibiotic resistance is increasing while access to life-saving antibiotics still appears limited in some LMICs. Therefore, specific policies and tools are needed – both to reduce the inappropriate use of antibiotics, and to improve access to appropriate treatment.