

Programme Report Basel Research Centre for Child Health



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Executive Summary

The Postdoctoral Excellence Programme (PEP) was launched by the Basel Research Centre for Child Health (BRCCH) in October 2020 with the generous support of Fondation Botnar. The programme's main purpose was to foster the next generation of scientific leaders in paediatric digital health.

Five projects received funding to conduct interdisciplinary research to tackle the challenges associated with the designing of child-specific diagnostic tools and the development of innovative treatment options for the global paediatric population. The impact and outcomes of the projects conducted within the PEP initiative are relevant and wide-ranging; from the generation of paediatric medical devices for blood extraction and neonatal sepsis monitoring to computational and molecular approaches for improving the treatment of diffuse midline glioma and fragile X syndrome.

The scientific results and achievements of the PEP programme were presented during the "Future of Paediatric Health Spotlight Day," a symposium and networking event organized by the BRCCH to mark the end of the PEP initiative. This symposium attracted many national and international scientists working across various disciplines of paediatric health, providing a unique opportunity for the PEP fellows to present their findings while interacting with leading figures of the field.

An additional element of the PEP initiative was the Early Career Programme, a series of training workshops and lectures in which young researches had the opportunity to enhance their communication, leadership and entrepreneurial skills.



Overview of the Postdoctoral Excellence Programme

Programme Purpose and Aims

As part of its core mission, the BRCCH launched its Postdoctoral Excellence Programme in 2020. The main goal of this initiative was to foster the next generation of scientific leaders pursuing cutting-edge research to address the unmet medical needs of children and adolescents worldwide.

Research proposals, which were expected to be scientifically outstanding and highly translational, were submitted under one of the following research areas:









Paediatric Digital Health

Projects on innovative and scalable digital health interventions to improve paediatric healthcare delivery as well as big data-driven approaches to predict, manage and treat childhood and adolescence diseases.

Advance Bioengineering for Paediatric Medicine

Projects leveraging biotechnological and system biological approaches to create innovative diagnostic tools and treatment solutions for children.

Paediatric Medical Devices

Projects with an interest in developing new medical devices and technologies tailored to improve the diagnosis, treatment and management of paediatric diseases.

Ethics and Policy in Paediatric Health

Projects addressing outstanding ethical, regulatory and economic challenges associated with paediatric health interventions.

Application, selection and evaluation processes

The call for proposals was made on 14 October 2020 with a deadline of 12 February 2021. Principal investigators from the BRCCH's four partner institutions (ETH Zurich, University of Basel, University Children's Hospital Basel and the Swiss Tropical and Public Health Institute) who wished to bring to life a step-changing project in collaboration with a highly talented young researcher were invited to submit applications.

Fifteen applications were submitted; of those applications, six were submitted by a principal investigator (PI) based at ETH Zurich and nine by a PI based at the University of Basel or an associated institute. Proposals were submitted under all of the above research foci: three applications in the Paediatric Digital Health area, two in the Advanced Bioengineering of Paediatric Medicine area, six in the Paediatric Medical Devices area and two in the Ethics and Implementation research area. Each application was evaluated by at least two external reviewers specializing in the research field and five projects involving 12 researchers received financial support. Three of the successful postdoctoral researchers were affiliated with ETH Zurich, one with the University of Basel and one with the Swiss Tropical and Public Health Institute.

The PEP research grants were stipulated to be three years in duration with up to 350,000 CHF in funding per award. The grants covered postdoctoral researchers' salaries according to the regulations of their host institutions. The postdoctoral researchers were also endowed with additional funds to cover the operational costs associated with their research projects.



Bioinspired, Low-Cost Device for Minimally Invasive Blood Sampling

Blood tests are a cornerstone in medicine, as they help healthcare providers to diagnose infections and other diseases even before symptoms manifest. Yet blood sampling is not exempt from challenges, as conventional extraction methods such as venipuncture are often distressing for children and impose a heavy financial burden on healthcare systems, especially in lowand middle-income countries (LMICs). Hence, there is a pressing need to create a more child-friendly and efficient blood sampling procedure that remains financially accessible to LMICs.

To this aim, the researchers from this consortium developed an open-source, cost-effective and patient-friendly device that can extract a small blood volume suf-

ficient for testing in a few minutes. The development of this suction cup device started with its design, which drew its inspiration from the anatomy of sanguivorous leeches. These blood-sucking parasites possess three jaws, each with an array of teeth, with which they penetrate the host's skin while secreting an anticoagulant substance that prevents blood clotting. They use muscular suction to draw in large volumes of blood, creating negative pressure that ensures continuous blood flow.

The researchers in this consortium first selected the best biocompatible materials and geometry for the device (e.g., silicone

Image: Photograph showing the hidden microneedle patch after compression of the blood microsampling prototype. Credit: Nicole Zoratto.



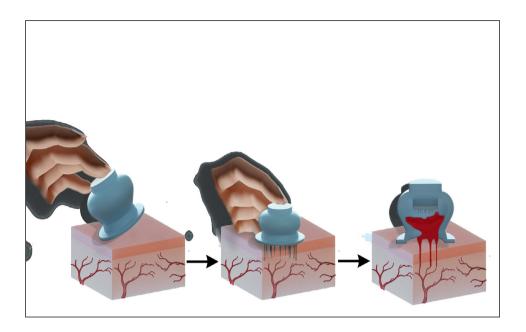


Nicole Zoratto ETH Zurich



Jean-Christophe Leroux ETH Zurich





hardness, wall thickness) to obtain an optimal negative pressure and skin adhesion. Stainless steel was chosen for the microneedle due to its excellent mechanical strength and low manufacturing costs, while silicone was used for the cylindrical dome. The amount and distribution of stress and strain energy exerted by the different devices was evaluated first via computational methods and subsequently through ex vivo experiments. These experiments yielded a final design featuring a circular array of 20 to 30 microneedles with a thickness of 75 µm and a tip angle of 20°. Moreover, the researchers inserted an anticoagulant substance into the storage compartment of the device, to prevent blood clotting. Furthermore, a tailor-made lid and adapter were developed to enable safe fluid transportation and/or integration with commercially available point-of-care systems, such as rapid testing kits for the detection of malaria or HIV.

Taken together, the proposed platform holds significant promise for enhancing healthcare in the paediatric population by potentially improving patient compliance via concealed microneedles. Most importantly, its cost-effective fabrication coupled with its user-friendly design, which does not need to be used by trained healthcare staff, makes this device an ideal blood sampling method in resource-constrained healthcare settings. While further experiments are required to validate the use of this prototype in humans, the team is currently working on the development of a fully biodegradable device which can reduce biohazardous waste and further mitigate the risk of infection after the device has been disposed of.

Image: Operating principle of the microsampling device. When compressed, the device deploys the microneedles, creating small punctures in the skin upon attachment. The release of the compression force creates negative pressure, drawing blood into the device. Credit: Nicole Zoratto.

Patch-IT: Multi-Sensor Nodes for Continuous Vital Sign Monitoring to Identify Novel Digital Biomarkers for Sepsis Detection in Neonatal Intensive Care

Sepsis is a life-threatening organ dysfunction that results from an extreme immune response to infection. It has a high death toll among preterm infants: over 2,000 neonates per 100,000 live-births develop neonatal sepsis every year, which accounts for a mortality rate of approximately 20%. Early detection followed by antibiotic therapy and fluid administration is crucial for survival, as a delay in medical treatment increases the risk of neurodevelopment impairment and death.

Sepsis manifests with a wide range of symptoms, including altered heart rate, fever and cardiorespiratory uncoupling. As there is no specific therapy for sepsis dysfunction, paediatricians rely on laboratory tests and monitoring the infant's physiology to detect infection and sepsis onset respectively. Although vital sign

monitoring is a cornerstone of clinical care in neonatal care units, the currently available monitoring devices attach multiple wires to the neonate's fragile skin, thus increasing the risk of skin laceration. Moreover, they impede skin-to-skin contact between parent and child, which has been demonstrated to be of therapeutic value.

To overcome these challenges, this consortium developed PATCH-IT, a wireless, battery-free multi-sensor electronic epidermal system that continuously monitors heart rate variability, respiratory rate, peripheral body temperature and oedema

Image: PATCH-IT integrated into an incubator in NICU. The base unit is placed below the mattress and the chest patch is placed on the neonate's chest, while the foot patch is placed on the neonate's foot. Credit: Kanika Dheman.

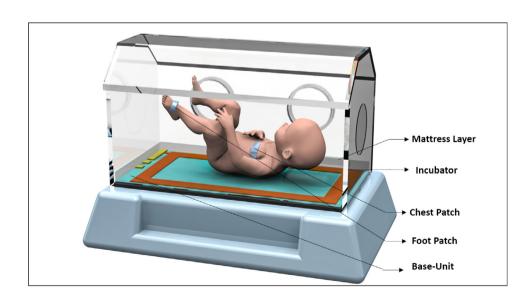


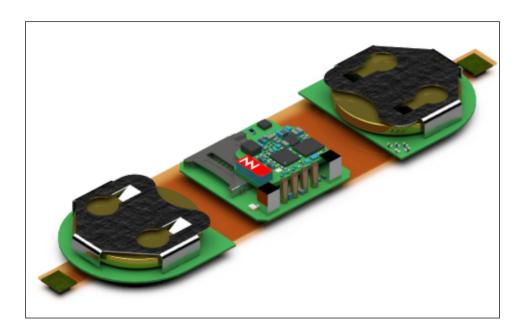


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Michele Magno ETH Zurich





activity, among other vital signs. In addition, the research team embedded a mathematical algorithm based on a sepsis-prognosis model into the device's single-chip computer, the so-called microcontroller unit. Unlike previous models, the neural network developed by the team can detect sepsis threat based only on changes in the vital sign pattern without laboratory tests. Hence, PATCH-IT's continuous assessment of the baby's vital signs can alert clinicians to deterioration in the baby's health, enabling their early treatment.

Presently, the researchers of this team are closely working with clinicians at University Hospital Zürich to assess this monitoring device in adult healthy patients, a step that precedes the validation and implementation of medical devices in the paediatric clinical setting.

The potential impact of PATCH-IT in neonatal care is manifold; as antibiotic overuse is detrimental to child health, this wireless device will reliably alert clinicians when they need to prescribe antimicrobial therapy. In addition, the battery-free nature of PATCH-IT coupled with a vital sign-based alert system renders this device suitable for resource-constrained healthcare systems, where laboratory tests often remain highly expensive and inaccessible.

Image: First prototype of PATCH-IT, a wearable sensor whose aim is to enable the effective detection of sepsis in neonates. Credit: Kanika Dheman.

Developing Novel Drug Strategies for the Treatment of Fragile X Syndrome by Functional Screening of Human Pluripotent Stem Cell Models

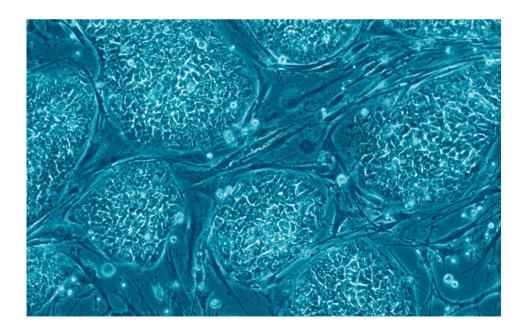
Fragile X syndrome (FXS) is an inherited genetic disorder that causes learning and intellectual disabilities, including autism and attention-deficit/hyperactivity disorder. This condition is caused by the abnormally reduced expression of the FRAGILE X MESSENGER RIBONUCLEOPROTEIN 1 (FMR1) gene, whose function is partially required for the normal development of synapses and the delivery of nerve impulses.

Unfortunately, most existing drugs for FXS are neither very effective nor curative, as they fail to revert FMR1 expression to normal levels. As FXS drugs need to be taken throughout an individual's life, they often pose a financial burden on patients and

their families. Hence, there is a pressing need to identify and test new drugs to resolve the molecular factors underlying FXS

To restore FMR1 expression, and in turn, reverse FXS symptoms, the research team focused on reverting gene hypermethylation, the root cause of FMR1 silencing. Unfortunately, mice models mimicking FMR1 hypermethylation remain unavailable to date, hindering the screening of potential therapeutical molecules in in vivo condi-

Image: An image displaying embryonic stem cell cultures, which can be modified into organoids to study human diseases and drug screening. Credit: Prof Nissim Benvenisty's research group.



Lead Researchers



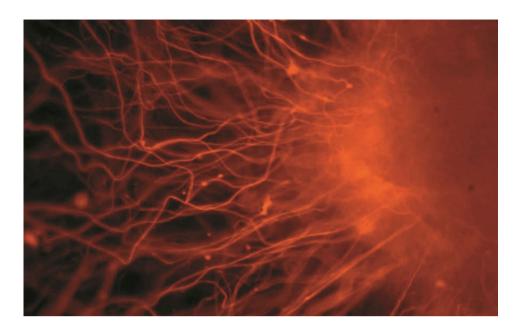
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tions. To overcome this challenge, this consortium successfully established patient-derived brain organoids, small self-assembled aggregates whose cell types and architecture resemble those of the embryonic human brain. From a molecular and morphological perspective, FXS organoids feature many of the neurodevelopmental defects observed in human FXS patients, including the dysregulation of several genes controlling synaptic development alongside disorganized, improperly formed neural structures.

The tour de force generation of FXS organoids enabled this research team to investigate the potential therapeutic effect of a wide plethora of compounds for reverting FMR1 expression. Notably, they identified ascorbic acid, a dietary factor also known as vitamin C, as a suppressor of FMR1 hy-

permethylation in brain organoids. Ascorbic acid application to FXS organoids not only increased FMR1 expression, but also restored the aberrant morphology of FXS neural structures.

In contrast to most prescribed drugs for FXS patients, which are designed to alleviate disease symptoms, ascorbic acid can counteract FXS's root cause. While the potential positive effect of ascorbic acid in reverting the neurodevelopmental defects of FXS patients requires further investigation, the compelling evidence presented by this project opens new avenues for more cost-effective treatments.

Image: These neurons, which are derived in vitro from human embryonic stem cells, can be used to study how the human brain develops and to model neurological disorders. Credit: Prof Nissim Benvenisty's research group.

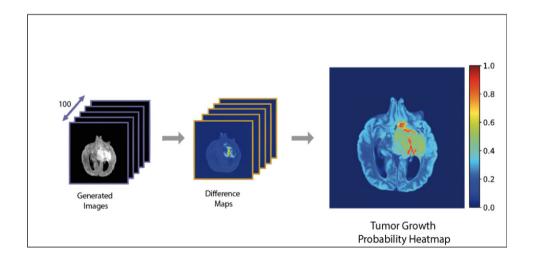
Harnessing Machine Learning and Mechanistic Modelling for Personalized Radiotherapy of Paediatric Diffuse Midline Glioma

Brain tumours remain the leading cause of cancer-related childhood mortality, with diffuse midline glioma accounting for the highest mortality rates and worst prognoses among paediatric brain tumours. Diffuse midline glioma tumours are often found in delicate brain regions, which control essential vital functions and are difficult to operate on. There is currently no curative treatment for these young patients, who rely on radiotherapy for symptom relief and prolonged survival. However, not every child and tumour responds equally well to radiotherapy, highlighting the need to personalize radiotherapy treatment for each child.

Radiotherapy planning for children accounts for the current tumour location

but could possibly benefit from predicting tumour growth and response to treatmentfor target adaptation. One additional challenge in the treatment of sick children is that the current one-size-fits-all therapy is mostly based on clinical experience in adults. Therefore, to improve radiotherapy treatment (i.e., dosage and schedule) for the paediatric population, this consortium created a machine learning-based method predicting tumour volume growth based on magnetic resonance imaging scans.

Image: Generation of tumour growth heatmap prediction based on generated magnetic resonance images of brain tumours. Credit: Sarah Brüningk.



Lead Researchers



Sarah Brüningk ETH Zurich



Catherine Jutzeler ETH Zurich



Karsten Borgwardt Max Planck Institute of Biochemistry, Germany



Javad Nazarian University Children's Hospital Zürich



To generate this prognostic model, the research team collected more than 1,000 scans from over 300 patients worldwide. First, they validated an AI algorithm to detect tumour presence in imaging scans, creating an automated segmentation pipeline that can be translated into real-world scenarios and, more importantly, applied to paediatric tumours. Next, they recreated the tumour's volume expansion based on two-dimensional (2D) images acquired at different time points, which is an essential component for predicting where a tumour is most likely to progress and whether it has already infiltrated the healthy brain at a level that is invisible on an image. Importantly, their predictive model not only accurately forecasts tumour volume, but also predicts its spatial 3D distribution, delineating the brain area suitable for radiotherapy treatment.

In addition, the team developed a digital pathology framework that accurately predicts several proteomic markers in data from paediatric midline diffuse glioma tissue from standard histopathology slides. As such, they make high-end assessments, such as spatial proteomics, available at a much larger scale for sam-

ples acquired in clinical practice. With this approach, we can now assess a much larger set of patient samples in order to learn about patterns of drug response and resistance in relation to the tumour's molecular profiles. The ultimate goal of this approach is to generate digital markers that can be used to help clinicians to predict tumour response to drugs based solely on imaging-derived information.

The findings of this project highlight how in the near future, it will be possible to integrate computational methods into the clinical care of paediatric oncology patients. The methodologies developed by this research team will support clinicians and parents to select an optimal radiotherapy and pharmacological treatment that best fulfils the individual needs of children suffering from diffuse midline glioma.

Image: The combination of machine learning and the modelling of tumour growth with differential equations will enable the creation of a digital health tool that will improve the quality of life of children diagnosed with diffuse midline glioma. Credit: Ryzhi/Shutterstock.

Electronic Clinical Decision Algorithms and Machine Learning to Improve Quality of Care and Clinical Outcomes for Sick Young Infants in Resource-Limited Countries

Sick young infants under two months of age require appropriate clinical care from highly trained healthcare workers, who often rely on laboratory tests to provide an accurate diagnosis. Unfortunately, healthcare workers who are trained in the care of sick young infants and specialized diagnostic services are rarely available in the primary healthcare services of lowand middle-income countries (LMICs), forcing healthcare providers to base their diagnosis and disease management on patients' history and symptoms, using paper-based empiric treatment guidelines. However, quideline adherence is often poor, leading to inappropriate and ineffective management

The implementation of evidence-based, electric clinical decision support algorithms (eCDSAs) in clinical settings LMICs may offer a solution, as they guide health-care-workers in the evaluation and man-

agement of young patients using evidence-based treatment approaches and can integrate results from simple point-of-care diagnostics. In spite of the benefits associated with the use of eCDSAs for older children and endorsement by the World Health Organization, few such tools have been validated for managing sick young infants in outpatient care settings.

The main objectives of this research consortium were to develop an eCDSA module for sick young infants in primary care settings, test its acceptability and its effect on clinical practice and determine barriers and facilitating factors for implementation among healthcare workers in Kenya, Tanzania, Senegal and India.

Image: Health workers in Senegal test the electronic clinical decision support tool to manage sick young infants. Credit: Gillian Levine.





Gillian Levine Swiss TPH



Tracy Glass Swiss TPH





The team observed that in regions such as Kenya or Tanzania, where healthcare workers were not used to routinely using paper-based evidence-based guidelines for managing sick young infants, the integration of the eCDSA into clinical practice improved adherence to guidelines. Higher rates of conducting recommended assessments including measuring temperature, respiratory rate and weight were observed after eCDSA implementation. Health workers reported that with the eCDSA, the clinical consultation became simplified and more comprehensive, helping them to deliver a better diagnosis and treatment alongside optimal medication prescription and dosing. However, in Senegal, where guideline adherence was higher before the eCDSA was introduced, substantial improvements in clinical practice were not observed. In India, where the average clinical consultation times at the research sites were extremely short, it was decided during pilot testing that implementing the eCDSA would not be feasible without adaptations to clinical care systems and processes.

The research team also evaluated the frequency with which sick young infants were referred to a higher level of medical care for managing severe illness, as they hypothesized that the tool would help healthcare workers identify and re-

fer severe illness cases. Contrary to the researchers' hypothesis, eCDSA implementation did not translate into a higher likelihood of referral to a higher level of care, despite the healthcare workers' reported high confidence and trust in the accuracy of clinical recommendations from the tool, including recommendations to refer. Healthcare worker and caregiver preferences, as well as barriers to referral acceptance and feasibility in the health system, may constrain uptake of referral in such settings.

The main barrier to eCDSA implementation encountered by healthcare workers was the additional time needed to conduct a complete clinical consultation with the tool, as the time allocated per consultation is very short in some healthcare settings due to high patient volumes and staff shortages.

The project results will be used by policy-makers and the Ministries of Health in each country to take informed decisions regarding approaches to upscaling eCD-SA use in healthcare facilities.

Image: Clinical consultation room in a health facility where paper-based guidelines are posted, prior to the eCDSA intervention. Credit: Gillian Levine.

Research Outputs and Communications

Over the course of the PEP programme, the five talented postdoctoral researchers regularly shared their research findings with the academic community at international and national conferences as well as with the public at numerous events. In addition, PEP researchers engaged with stakeholders across a wide variety of settings and have contributed to capacity building in resource-constrained areas.



Additional Activities

Conference:

Future of Paediatric Health Research Spotlight Day

On 19 April 2024, the BRCCH hosted the "Future of Paediatric Health Research Spotlight Day" in Basel. This one-day symposium and networking event brought together researchers across disciplines and institutions with a common focus on improving child and adolescent health.

Over the course of the day, the PEP fellows had the opportunity to present their research objectives and their main project outcomes. In addition, each fellow invited an international expert, whose complementary views on the research topic were provided in their keynote lectures. Recordings of these lectures are available via our website and can be viewed on our <u>YouTube</u> channel.

Image: A PEP fellow presents her work on digital support systems to improve child health and development in low-income settings.during the Future of Paediatric Health Research Spotlight Day. Credit: BRCCH Management Office.



Early Career Programme

Starting in Autumn 2021, the BRCCH launched a lecture and workshop series where young researchers could improve their skills in effective communication and leadership alongside gaining new insights into how to establish fair partnerships and protect their intellectual ideas.

2021

14 October

"How to Communicate Effectively in Multi-Cultural Settings," an online seminar delivered by the communication coach Mark Moser. The participants were taught how to adapt their verbal and non-verbal communication to different audiences.

Image: Zoom screenshot of Mark Moser's presentation. Credit: BRCCH Management Office.



2022

10 February

"How to Establish Fair and Equitable Global Research Partnerships," an in-person workshop delivered by Dr. Fabian Kässer and Jonas Karlström (Commission for Research Partnerships with Developing Countries and UNICEF, respectively). The main topics covered during this session were the importance of generating context-specific solutions and tackling inequalities and preconceptions while establishing cross-border collaborations.

24 May

"Understanding Key Needs in Global Child Health," a lecture delivered by Prof. Yvonne Maldonado discussing the challenges and big gaps in medical care and health in the paediatric population.

2023

14 March

"Importance of Sponsorship and Mentorship," an in-person workshop delivered by Petra Wüst, a personal-branding and leadership consultant. The session was complemented by presentations from Patricia Zweifel and Patricia Heuberger, who introduced the mentoring programmes available at the time at their respective institutions (i.e., University of Basel and ETH Zurich, respectively).

Image: Petra Wüst at the workshop. Credit: BRCCH Management Office.



24 May

"Science Communication I: Communicating Science with Impact," an in-person workshop in which the keynote speaker Jo Filshie Browning helped the attendees to bring their science to the general public by using alternative communication channels. In addition, the participants learnt how to communicate their research to the general public in an impactful fashion.

14 September

"Scientific Communication II: Smartphone Science Storytelling," a workshop delivered by Dr. Samer Angelone on how to leverage filmmaking and story-telling formats to deliver research messages to the lay public. During this hands-on workshop, the participants had a chance to use a free software application to create and edit a short video summarizing their research projects.

2024

15 February

"Defining and Growing your Personal Brand: Effective Strategies for Researchers," an interactive workshop delivered by the marketing and branding expert Dr. Alex Mari. Over the course of three hours, the participants learnt the best practices of brand management and digital marketing to build a distinctive personal brand as researchers in digital media.

Image: Workshop flyer. Credit: BRCCH Management Office.



11 March

"A Guide to Scientific Translation: From Discovery to Market," a course delivered by two experts from the University of Basel's Innovation Office, Dr. Anna-Elina Pekonen and Dr. Alice Freton. The speakers walked the participants through the current challenges and opportunities underlying the generation of spin-off companies stemming from their research projects.

19 April

"Leadership and Nurturing Research Teams," an interactive workshop delivered by Dr. Maddalena Fumigal-li. Leveraging her expertise in behavioural science and research experience, the speaker presented the advantages and limitations of different leadership styles while challenging the participants with practical and self-reflecting activities.

7 November

"Fundamentals of Intellectual Property," a two-hour session delivered by Dr. Cornelia Fürstenberger and Dr. Patrick Sticher (Unitectra). In this lecture, the researchers received a stepwise guide to the processes required to legally protect their research ideas, obtain national and international patents and grant licenses.

Image: Patrick Sticher at the workshop presentation. Credit: BRCCH Management Office



PEP Fellows Highlights



Dr Sarah Brüningk has been appointed as an Assistant Professor at the <u>University of Bern</u>, where she will continue her research work on developing new machine learning-based tools for the diagnosis of paediatric brain tumors.

Dr Gillian Levine has supported the World Health Organization in the development of a global <u>Digital Adaptation Kit (DAK)</u> for the care of sick infants. She has also assisted the Ministries of Health in Cameroon and Iraq in the piloting of DAK implementation in real-world settings.





Dr Kanika Dheman has been awarded a <u>SNF BRIDGE fellowship</u> to translate her recently developed neonatal monitoring systems into daily practice in neonatal clinical units.

Dr Keith Gunapala is the corresponding author of a recent <u>Stem Cell Reports</u> publication on chromosome Y loss in embryonic cells and its implication for Turner syndrome, a condition that affects girls from birth onwards.





Dr Nicole Zoratto has been appointed as an Assistant Professor at <u>Tor Vergara University of Rome</u>, where she will continue her research work.

Finances

Institution	Principal Investigator and Postdoctoral Researcher	Department	Project Title	Grant obtained
ETHZ	Prof Leroux Dr Zoratto	D-CHAB	Bioinspired, Low–Cost Device for Minimally Invasive Blood Sampling	CHF 313,612.61
	Prof Jutzeler/ Prof Borgwardt Dr Brüningk	D-HEST	Harnessing Machine Learning and Mechanistic Modelling for Personalized Radiotherapy of Paediatric Diffuse Midline Glioma	CHF 354,891.31
	Prof Magno Dr Dheman	D-ITET	Patch-IT: Multi-Sensor Nodes for Continuous Vital Sign Monitoring to Identify Novel Digital Biomarkers for Sepsis Detection in Neonatal Intensive Care	CHF 353,349.5
	Total			CHF 1,021,853.42
UniBas	Prof Taylor Dr Gunapala	DBM	Developing Novel Drug Strategies for the Treatment of Fragile X Syndrome by Functional Screening of Human Pluripotent Stem Cell Models	CHF 336,989.91
	Prof Glass Dr Levine	Swiss TPH	Electronic Clinical Decision Algorithms and Machine Learning to Improve Quality of Care and Clinical Outcomes for Sick Young Infants in Resource-Limited Countries	CHF 347,971.92
	Total			CHF 684,961.83
Programme Grants Total				CHF 1,706,815.25

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