ST. ANNA CHILDREN'S CANCER RESEARCH INSTITUTE SCIENCE REPORT 2023

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INTRODUCTION

THE POWER OF COLLABORATION AND INNOVATION

As we look towards the horizon of scientific progress, it is with great anticipation and a deep sense of purpose that I introduce this report and our efforts to combat childhood cancer. Our journey is driven by a collective vision: to harness the full potential of modern research and bring about transformative change for the children and families who place their hopes in our hands.

The field of childhood cancer research is at a pivotal moment. Advances in technology and our deepening understanding of the disease have opened new avenues for exploration. Yet, it is not just the tools and knowledge we possess that will drive progress – it is the unwavering dedication and innovative spirit of our researchers, the steadfast commitment of our staff and the collaborative efforts of our international partners. The exchange of knowledge and resources across borders enriches our research and brings us closer to our shared goal. Together, we form a global network of excellence, demonstrating that through unity and cooperation, we can achieve what once seemed impossible.

Collaboration pulses through the very heart of our institute, woven into our fabric by the extraordinary partnership with St. Anna Children's Hospital. This synergy sets us apart, making us a beacon of hope and innovation as one of the few institutes dedicated to childhood cancer research in Central Europe. Our mission is nothing short of transformative: to delve deeply into the biology of cancer, unraveling its mysteries at the genetic and epigenomic levels. By understanding cancer's very essence, we strive to pioneer treatments that are not only more effective but also gentler and tailored to each child's unique needs. Together, we are not just advancing science; we are aiming to ignite a revolution in pediatric oncology, fueled by passion, precision, and an unyielding commitment to change. We aim to get better at understanding childhood cancer, we will unravel the mysteries of disease recurrence and resistance, and we will not stop our mission before we have been able to find efficient – and sometimes targeted – treatment for these challenging diseases. We dream even further – if we were able to identify patients with specific predisposition to childhood cancer efficiently, we could aim at preventing occurrence of cancer in the first place. This would be my personal dream for the next years to come.

To further strengthen our cross-institutional networks and expand both national but also international research collaborations, St. Anna CCRI hosted two important international conferences in 2023: EuSARC and the first-ever Scientific Days by the Innovative Therapies for Children with Cancer (ITCC). EuSARC facilitated critical connections between leading experts such as Kimberly Stegmaier from Dana-Farber Cancer Institute and Harvard Medical School to integrate basic and clinical research in sarcoma. Meanwhile, in partnership with the Department of Pediatric Neuro-Oncology at the Medical University of Vienna and the St. Anna Children's Hospital, the ITCC has brought together experts such as Sir Mike Stratton (Sanger Institute, UK), Soheil Meshinchi (Fred Hutch Cancer Center, US), Mariella Filbin (Dana-Farber Cancer Institute and Boston Children's Hospital) and Sam Behjati (Sanger Institute and University of Cambridge, UK) to advance early clinical trials in leukemia, solid tumors and brain tumors.

I am also pleased that last year, we were able to recruit two new Principal Investigators at our institute who fit very much into the collaborative, future-looking mindset at St. Anna CCRI:

Florian Grebien, an expert in leukemia genetics who now has a dedicated research group in pediatric leukemias at St. Anna CCRI in addition to maintaining his role as Professor and Institute Head at the University of Veterinary Medicine, and George Cresswell, an aspiring computational biologist specializing in childhood cancers who previously worked at the Institute of Cancer Research in London. Their hiring significantly enhances our research capabilities and fosters collaborations that cross traditional boundaries.

The excellence of research at St. Anna CCRI is visible through both high-impact scientific publi-cations but also through successful applications for competitive third-party funding. As such, one of the highlights last year was that Eleni Tomazou received an ERC Consolidator Grant for her work in epigenome-based precision medicine for Ewing's sarcoma. These accomplish-ments underscore our institute's leadership in pediatric oncology, as confirmed by the 2023 Scientific Advisory Board. They recognize our robust scientific capabilities, strategic foresight, and collaborative spirit with esteemed partners such as the Research Center for Molecular Medicine of the Austrian Academy of Sciences (CeMM) and the Medical University of Vienna. Together, we are embarking on a journey of mutual inspiration, poised to redefine the frontiers of medical re-search. All of these achievements mentioned above are only possible in collaboration with innovative people and institutions.

In closing, I would like to express my sincere gratitude to all those who contribute to this vital work. Our achievements to date would not have been possible without the steadfast commitment of our colleagues and the collaborative efforts of our international partners. In this global fight against childhood cancer, we are united by a common goal. By working together, sharing insights, and combining our strengths, we create a synergistic force that accelerates the pace of discovery and amplifies the impact of our work.

Kaan Boztug
Scientific Director & Managing Director

UNFOLDING POTENTIAL

For more than 35 years, the St. Anna Children's Cancer Research Institute has been tirelessly dedicated to its goal of making cancer curable for children. On our journey we have achieved remarkable milestones in our work with leading research institutions and clinics.

At St. Anna CCRI, we believe that scientific advancement is not only a solitary pursuit but much more a collective endeavor combining outstanding talent, intellectual curiosity, engagement, and dedication to explore new frontiers in science.

The last year has been outstanding in various aspects, not only if we count the traditional metrics for scientific performance, focus on prestigious grants acquired by research groups, or share international recognition for scientific achievements. The Scientific Advisory Board during its recent evaluation of St. Anna CCRI explicitly congratulated the institute on its groups and scientists have made tremendous progress.

For the last years, it has been our mission to provide high-caliber scientists with the best environment, infrastructure and services so that they can fully concentrate on excelling in their scientific work and unfold their potential. Dedicated people "behind the scenes", who contributed in diverse areas to the development of the institute, are sometimes not visible.

The remarkable acquisition of high-caliber grants, the highly professional management of grant execution and administration today are a key strength of St. Anna CCRI Research Management Office, Accounting & Controlling and Human Resources have developed a unique, highly productive collaboration for which we are admired by our cooperation partners and the scientific community. There have been significant developments and improvements driven by the Human Resources Department in the past to actively manage the employee life cycle that clearly contribute to the impressive increase in scientific output of the last years. Various efforts of the FM&P department resulted in a more efficient use of our resources and managing risks in all areas of infrastructure more effectively. Our IT infrastructure and services were developed to a state-of-the-art level, while in the last year we prioritized all relevant IT-security aspects due to the increasing threats and exposures.

Our science report will provide you with more in-depth information about some of the exciting achievements of the research institute. Establishing specialized diagnostics for pediatric cancer patients was and is also one of the cornerstones of St. Anna CCRI, which due to its early success in providing specialized diagnostic test and analysis for pediatric patients resulted in the foundation of the Labdia Labordiagnostik, which was a pioneer in these area in its early years, established a remarkable treasure of knowledge in different areas of pediatric cancer diagnostic and dedication to our overall purpose.

In the last year, the Labdia Labordiagnostik achieved important key milestones in its further development, demonstrating that collaboration across all departments reaching for a common goal had a successful outcome.

The implementation of a state-of-the-art diagnostic laboratory ERP system was successfully achieved during the beginning of the last year, which was an important step within the accreditation process,

started two years earlier, guided and managed by the quality management team of the general administration of St. Anna CCRI. With the very successful passing of the accreditation audit at the end of last year, the Labdia Labordiagnostik is one of the first diagnostic provider to achieve this European quality standard, which underlines the company-wide high standards of the organization, diagnostic methods and procedures, and qualification and expertise of diagnostic specialists in all areas. With the formal accreditation confirmation, issued by the ministry and expected in mid-2024, the Labdia Labordiagnostik will strengthen its position as a reference expertise diagnostic laboratory for its diagnostic analysis portfolio and achieve one of the most important strategic objectives of its strategic plan. With Katharina Rötzer-Londgin joining at the beginning of last year as the head of human genetics at Labdia, this important area of expertise at Labdia took a dynamic development through her leadership, with a promising outlook for future development, and intensified the collaboration with St. Anna CCRI research groups.

Our world today has become a yet more exciting place where change has become a constant factor that we have to accept. Science has always been dominated by exploring unknown ground with curiosity, optimism, and engagement. Our achievements of the past shouldbe an inspiration to move forward with more optimism and engagement. Success today is determined by collaborative approaches, value diversity for better decision, and taking different approaches.

For the last year, I would like to express my sincere gratitude to a great team in the general administration and all who contributed to our vital work and the major achievements we accomplished together. However, the journey in science to further develop, explore new grounds, stay curious and excited has never an end point. Working together with trust, anticipate future challenges and meet them with optimism has been a key strength in the past and will guide us into a prosperous future.

Jörg Bürger
CFO & Managing Director

FROM BENCH TO BEDSIDE

A bridge connects the St. Anna Children's Cancer Research Institute and St. Anna Children's Hospital. It enables clinicians to access the institute's laboratories and scientists to take a direct route to the clinic.

As Head of St. Anna CCRI, a particular task is to facilitate the cooperation between researchers on the one hand and clinicians on the other, who both have the same vision – to provide better care for children with cancer and cancer predisposition syndromes (CPSs). This includes enabling opportunities for an exchange of ideas and experiences as well as creating an environment that promotes the establishment of friendships, a major driving force for successful cooperation. PhD programs at St. Anna CCRI for MDs from the St. Anna Children's Hospital are in place, and three colleagues have already successfully entered such programs.

The bridge may also serve as a symbol; to connect the St. Anna CCRI to local partners like the Medical University of Vienna (MUW), the Research Center for Molecular Medicine (CeMM), the Institute for Molecular Pathology (IMP), and other national as well as international cooperative clinical study groups and their related research groups. Such cooperation is especially essential to improve outcomes in children and adolescents who suffer from highly aggressive cancers, with poor outcomes, like osteosarcomas. In osteosarcoma, the most common malignant bone tumor in children and adolescents, about 4/10 patients with localized disease will suffer a relapse of disease within 5-years from diagnosis. As intensification of chemotherapy failed to improve systemic tumor control in osteosarcoma, novel therapies have to be developed. Researchers from St. Anna CCRI are also among the international leaders in the field to develop programs for coordinated analyses to detect cancer particles in the peripheral blood (liquid biopsies) in sarcomas, neuroblastoma and other pediatric malignancies. Moreover, in vitro 3-D models of the lung are in development to study the mechanism of lung metastases in different solid tumors.

In order to facilitate cooperation, international meetings are an important prerequisite, and the St. Anna CCRI was involved in the organization of two such meetings in Vienna, namely EuSARC 2023 and ITCC Scientific Days.

One important emerging field in pediatric oncology is cancer predisposition. That is, some children carry an inborn higher risk for cancer development because they have pathogenic variants in so-called cancer predisposition genes (CPGs). On the other hand, about 1/10 children with cancer carry such a pathogenic variant in a CPG. Moreover, some patients with inborn hematological diseases (like inherited bone marrow failure syndromes) and immunological disorders (e.g., X-Men disease) have a higher risk to develop certain malignancies.

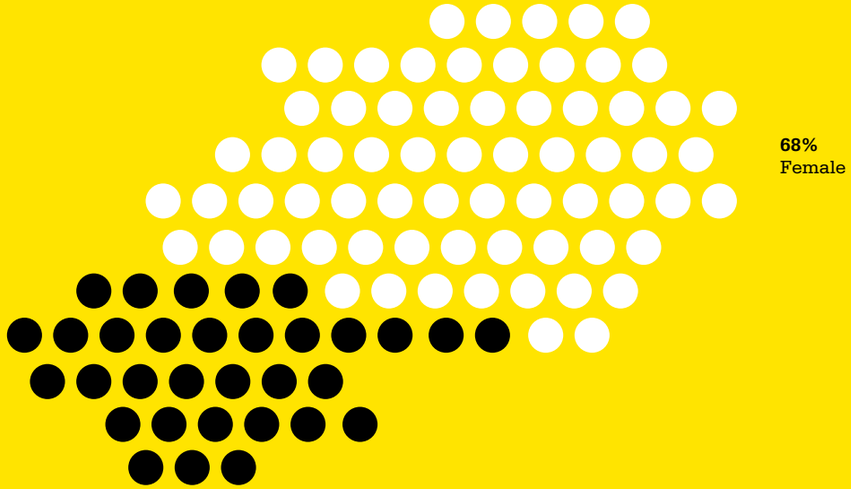
In order to address this issues, a Cancer Predisposition Outpatient Clinic at St. Anna Children's Hospital has been established, which is embedded in the Hematology, Oncology & Immunology Outpatient Clinic. Specialists in pediatric hematology, oncology and immunology work together with scientists from St. Anna CCRI and Labdia Labordiagnostik GmbH, the laboratory diagnostics subsidiary of St. Anna CCRI, to apply state-of-the-art diagnos-tics to identify and manage children with cancer predisposition syndromes. Currently we care for more than 100 children with such syndromes. At the St. Anna CCRI, several research groups use computational genomic approaches to study the aberrant development in pediatric cancers, in order to decipher the mechanisms that give rise to cancer development in children with CPS. Once such mechanisms are discovered, one can develop strategies to counteract cancer development – so the ultimate goal is the prevention of cancer.

"High achievement always takes place in the framework of high expectation" [Charles Kettering], and based on the success in 2023 one can have high expectations that the research groups at St. Anna CCRI in collaboration with clinicians at St. Anna Children's Hospital together will achieve further improvements for children with cancer and CPS.

Leo Kager
Head of the Institute

FACTS & FIGURES

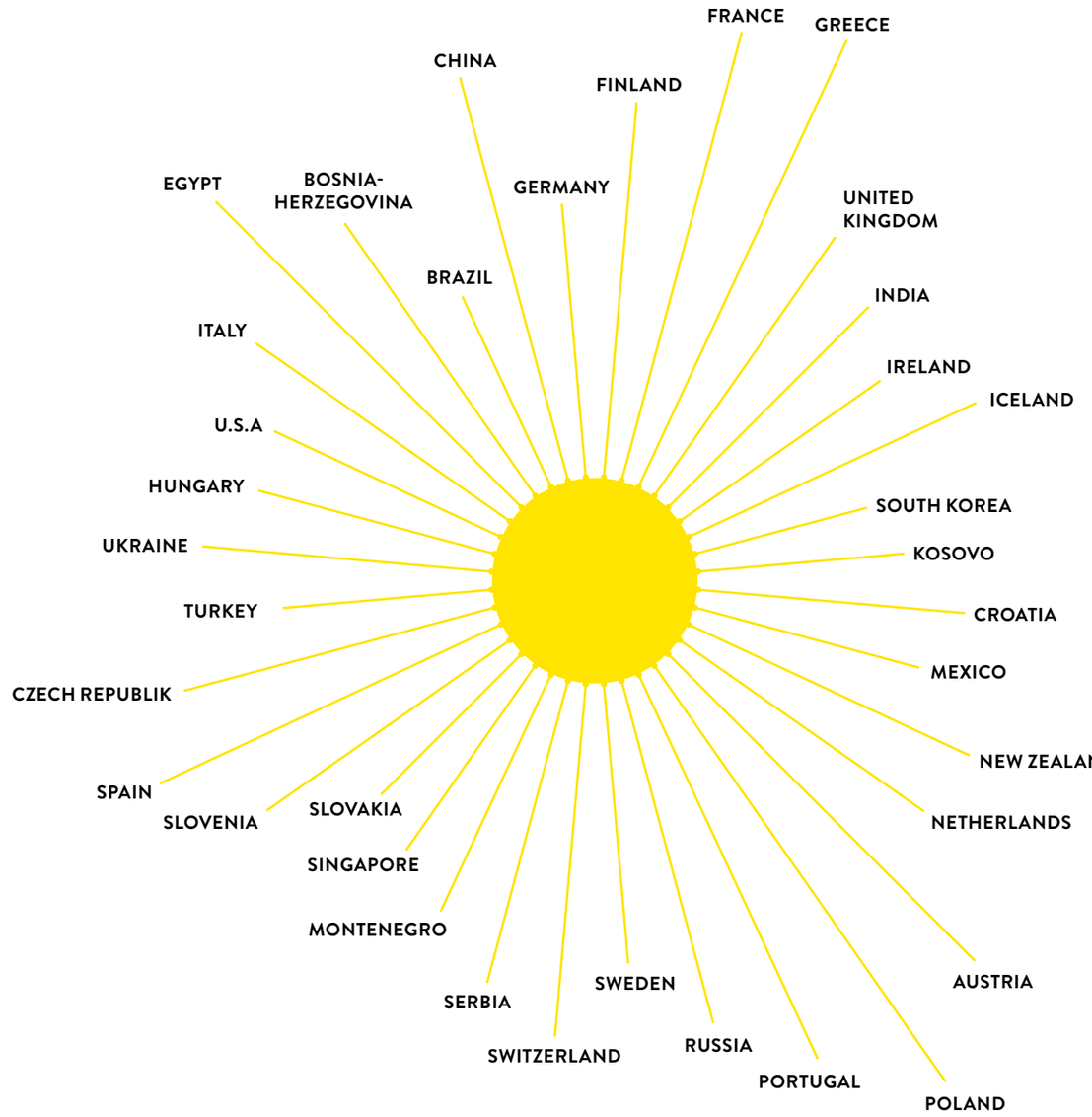
STAFF COMPOSITION



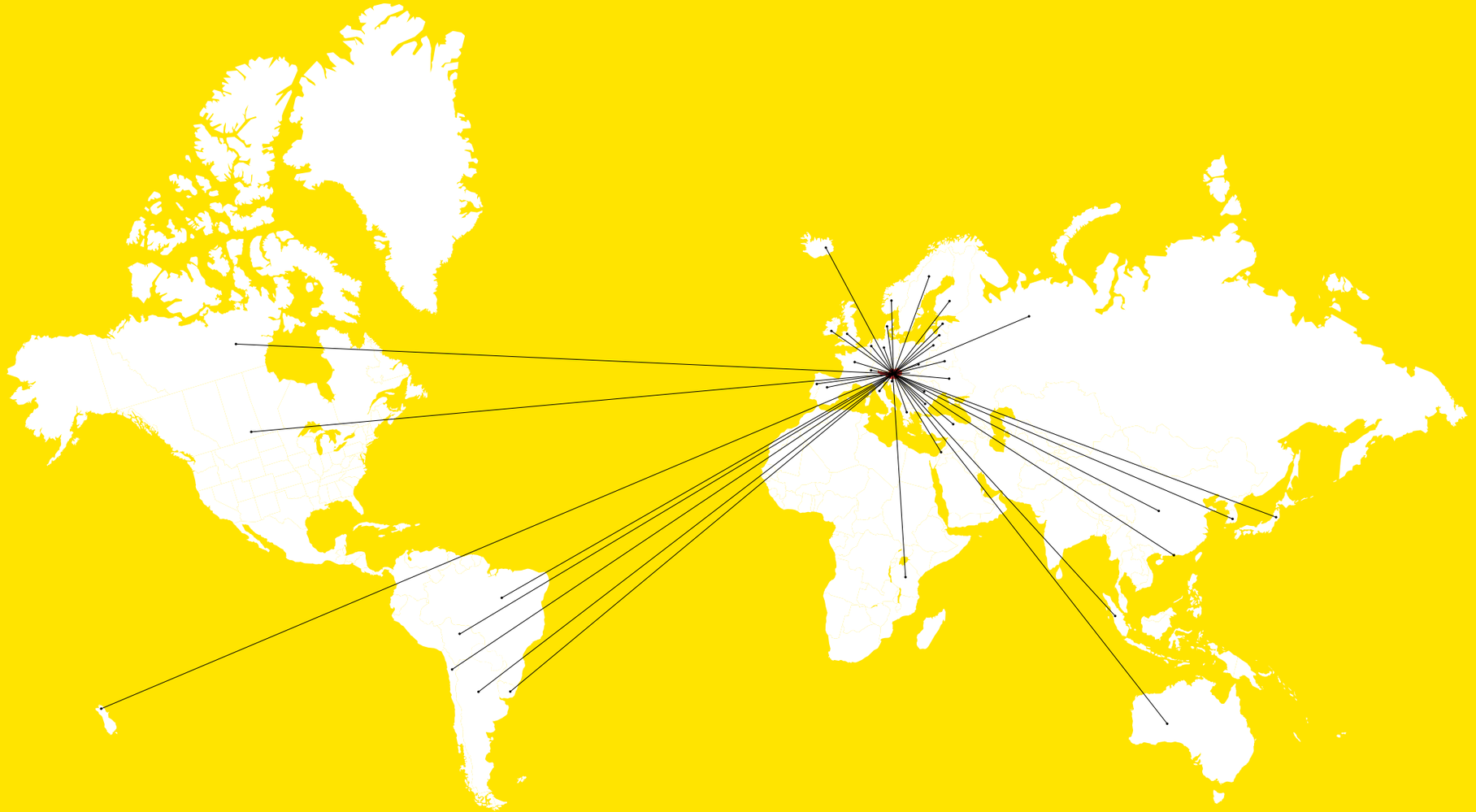
68%
Female

32%
Male

NATIONS



RESEARCH NETWORK



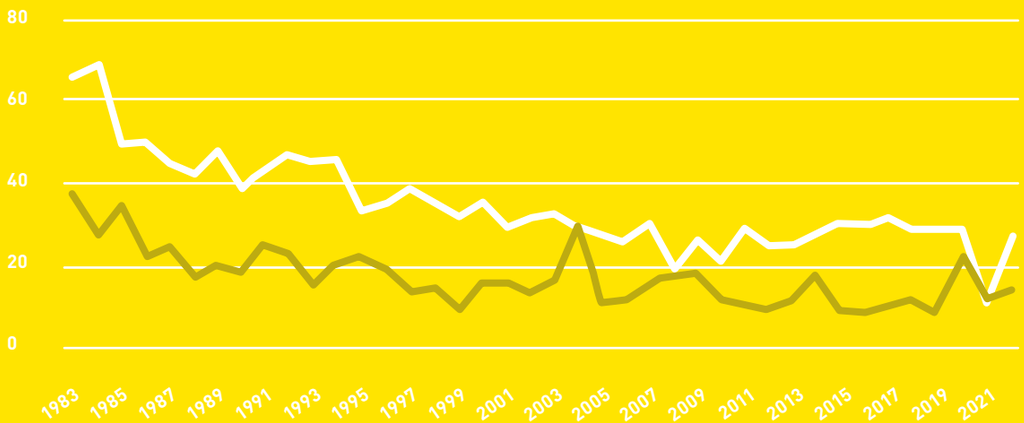
ALBANIA
ARGENTINA
AUSTRALIA
AUSTRIA
BELGIUM
BOSNIA AND HERZEGOVINA
BRAZIL
BULGARIA
CANADA
CHILE
CHINA
COLOMBIA
CROATIA
CZECH REPUBLIC
DENMARK
FINLAND
FRANCE
GERMANY
GREECE
HONG KONG
HUNGARY
INDIA
IRAN
IRELAND
ISRAEL
ITALY
JAPAN
JORDAN
KUWAIT
LITHUANIA
MEXICO
NETHERLANDS,
NORWAY
PAKISTAN
POLAND
PORTUGAL
ROMANIA
RUSSIA
SERBIA
SLOVAKIA
SLOVENIA
SPAIN
SWEDEN
SWITZERLAND
TANZANIA
TURKEY
UKRAINE
UNITED KINGDOM
URUGUAY
U.S.A.

COLLABORATION IS KEY

In 2022, around 150 children under 14 and almost 100 adolescents between the ages of 15 and 19 developed cancer in Austria.
Accordingly, childhood cancer is considered "rare" as compared to other diseases. Although the number of new cases has hardly changed over the decades, the number of cancer deaths has seen a significant decline.

This is mainly thanks to cooperation between research institutes, medical professionals, parents, and the community. Through improved coordination and the intensive exchange of knowledge, innovative therapeutic approaches have been developed and successfully implemented. These achievements not only help to reduce the number of deaths, but also significantly improve the quality of life of affected children.

CANCER DEATHS



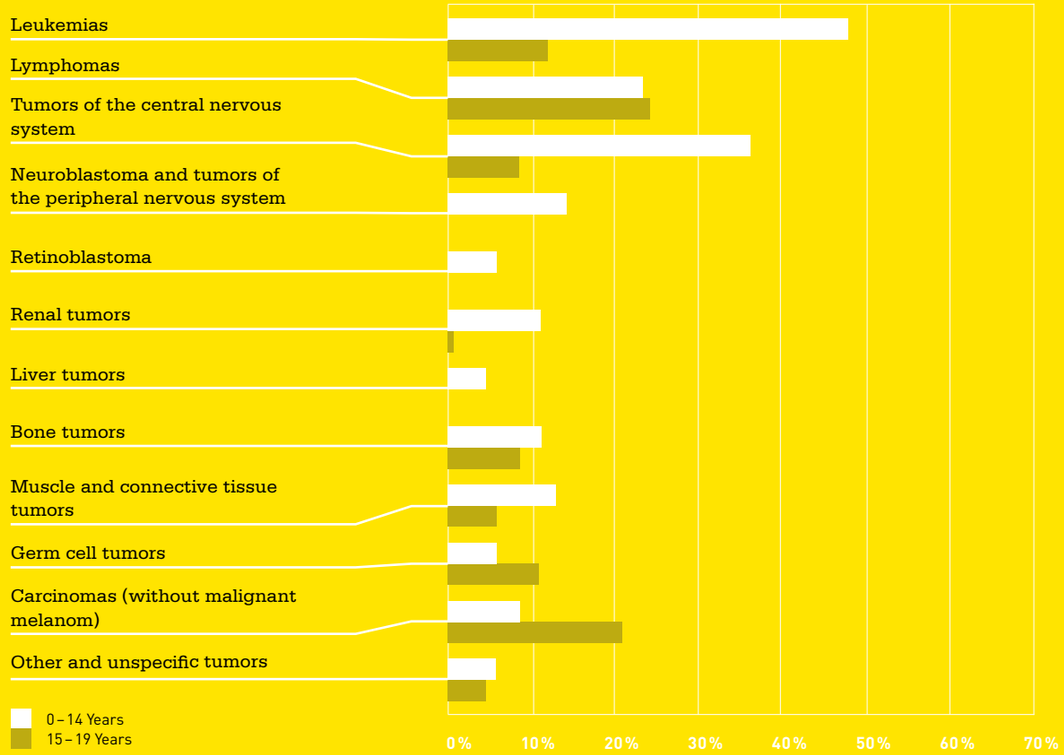
STATISTIK AUSTRIA, Österreichisches Krebsregister (Stand 09.01.2024) und Todesursachenstatistik.

LOW CASE NUMBERS REQUIRE INTERNATIONAL NETWORKING

The four most frequently diagnosed cancers in children in Austria are leukemias (57 cases), tumors of the central nervous system (36 cases), lymphomas (23 cases) as well as neuroblastomas and tumors of the peripheral nerves (14 cases). Considering the small number of cases, the treatment of children with these rare tumors essentially requires international cooperation, since conducting representative studies on a purely national level is simply impossible.

This makes international cooperation a crucial element in enabling comprehensive and meaningful studies. St. Anna CCRI is committed to deepening the understanding of rare tumors through joint efforts, thereby developing new therapeutic approaches in order to sustainably improve the life prospects of affected children.

TUMOR LOCALIZATION ANNUAL AVERAGE (2013-2022)



STATISTIK AUSTRIA, Österreichisches Krebsregister (Stand 09.01.2024) und Todesursachenstatistik.-1) Internationale Klassifikation von Kinderkrebserkrankungen, ICCC-3.

NEW LEADERSHIP OF CLINICAL GENETICS: KATHARINA RÖTZER-LONDGIN

In February 2023, Katharina Rötzer-Londgin, MD, PhD, assumed the medical leadership position of Clinical Genetics at Labdia Labordiagnostik GmbH, a subsidiary of St. Anna CCRI. She brings extensive experience in medical genetics and the determination to set new standards in genetic diagnostics.

Katharina Rötzer-Londgin completed her training as a specialist in medical genetics and as a general practitioner. Prior to her current role, she was a senior physician and deputy head at the Centre for Medical Genetics at Hanusch Hospital in Vienna. Her career has particularly been marked by a commitment to genetic counseling and diagnostics, first and foremost in the area of rare and hereditary tumor diseases.

SPECIALIZED GENETIC PRACTICE IN VIENNA

In her private practice in Vienna's 13th district, Rötzer-Londgin offers comprehensive genetic consultations with a special focus on hereditary tumor predispositions syndromes (e.g., hereditary breast and ovarian cancer) as well as connective tissue disorders and couples struggling to conceive. "At Medical Genetics, we make a point of ensuring low-threshold access in order to provide straight-forward counseling and diagnostics for all affected individuals," she explains.

EXPANSION AND INNOVATION AT CLINICAL GENETICS AT LABDIA/ST. ANNA CCRI

As the head of the Department of Clinical Genetics – Human Genetics, Rötzer-Londgin oversees a broad spectrum of molecular genetics and molecular cytogenetic diagnostics. The department stands out with its innovative approach to genetic research and patient care, placing a major focus on the continuous development of diagnostic methods designed to deepen the understanding of genetic factors in malignant and non-malignant diseases. Diagnostic emphases include mutation analyses and detection of gene deletions and duplications by use of advanced techniques such as Whole Exome Sequencing and SNP Arrays.

"Becoming head of Clinical Genetics at Labdia was a very exciting step for me. As a clinical geneticist, I have a deep interest in orphan diseases, including children's cancer. The tight cooperation between Labdia and St. Anna CCRI is very special and inspiring, and we plan to intensify our relationship as we believe this to be the best way to make major progress achievable."

FUTURE-ORIENTED VISION AND RESEARCH

Rötzer-Londgin intends to further expand the genetic counseling and diagnostic services with particular emphasis on integrating the latest research findings and technologies, including the use of artificial intelligence in genetic diagnostics. The extensive experience of St. Anna CCRI in bioinformatics, together with the profound diagnostic knowledge of Labdia, offers the chance to decipher new and complex genetic causes. Furthermore, the functional evaluation of variants of unknown significance in cooperation with St. Anna CCRI is a future way both to enhance the accuracy and impact of diagnostic results and to gain deeper insight into the pathomechanism of certain rare diseases. Rötzer-Londgin's vision also encompasses the advancement of personalized medicine as a prerequisite for more precise and effective treatment strategies for hereditary diseases. The results of her diagnostic work not only form the basis for personalized treatment approaches but also significantly contribute to research supported by St. Anna CCRI.

NEW PRINCIPAL INVESTIGATOR: FLORIAN GREBIEN

Eager to understand why some childhood leukemias show poor treatment response and how this can be tackled, professor Florian Grebien, PhD, is now establishing his own team at St. Anna CCRI.

Florian Grebien is the head of the Institute of Medical Biochemistry at the University of Veterinary Medicine, Vienna, where he will continue to be active in research and teaching. Previously, he led a group at the Vienna-based Ludwig Boltzmann Institute for Cancer Research (LBI-CR). He also won one of the highly prestigious Starting Grants of the European Research Council (ERC) to study how blood cancers develop and progress using cutting-edge technologies. Florian Grebien has published his findings in renowned journals such as Blood, Nature Structural & Molecular Biology, and Genome Biology.

EXPLOITING NATURE'S EXPERIMENTS

"What makes St. Anna CCRI the ideal place for my research ambitions is the fact that it covers the topics that interest me most," says Florian Grebien. In particular seeking to find new therapeutic targets for acute leukemias in children, Grebien investigates so-called fusion proteins, which result from chromosomes reassembled incorrectly after breakage. "Such 'misguided experiments' of nature often have devastating consequences in that some of these fusion proteins trigger cancer." While some fusion proteins have been known for a long time, for many it is still unclear whether, and if so how, they cause malignancies. "There is a lot of potential for therapeutic intervention because fusion proteins can be attractive targets for new therapies. They do not occur in normal cells. So, if you can find a way to turn them off, you can target cancer very specifically."

IMPROVING TREATMENT FOR LEUKEMIA

In his new role, Florian Grebien plans to work on pressing questions related to the treatment of pediatric leukemias to improve children's chances of survival. "The close proximity to physicians was an important motivation for me to join St. Anna CCRI." In addition, he wants to assume a bridging function to the University of Veterinary Medicine and take advantage of potential synergies between the two institutions. Kaan Boztug states that he is "very happy that we were able to win Florian Grebien – a scientist who has been repeatedly rewarded – for our institute. I am sure that his research will open up new perspectives for the institute and for the clinical application of new findings, thus actively supporting the mission of St. Anna CCRI."

NEW PRINCIPAL INVESTIGATOR: GEORGE CRESSWELL

British bioinformatician George Cresswell has been exploring various forms of childhood cancer, especially nephroblastoma, since his student days. As Principal Investigator at St. Anna CCRI, he will turn his attention to the evolutionary biology of cancer cells in an attempt to better understand and perhaps even predict their development.

Since genome sequencing has become part of everyday life in the biological sciences and has revolutionized medical research, bioinformaticians have become an indispensable part of research institutes. Experts in reading big data in biology are in great demand today – including at St. Anna CCRI, where a core unit staffed with bioinformaticians already exists. Now the institute has brought to Vienna a young bioinformatician who is setting up his own group as Principal Investigator: George Cresswell. Raised in Crewe, a town in the county of Cheshire in the northwest of England, the scientist studied biochemistry at the University of Manchester.

Amid an initial boom in genome sequencing applications, Cresswell learned quite quickly how the technology worked. Even then, collecting high-throughput genetic data was considered a major advance in understanding processes important to cell development as they provide an amazing insight into the cell's DNA and its composition. As part of an exchange program, he first made his way to Vienna for 13 months in 2011 – to the Boehringer-Ingelheim Regional Center. „I learned a lot back then." When a biomathematician convinced him that with bioinformatics he would learn exactly the technique that would allow him to interpret the data obtained in the best possible way, the next step on his educational path was set: Cresswell graduated with a degree in biochemistry from Manchester and moved on to the Francis Crick Institute in London to complete his PhD.

RESEARCH FOCUS ON KIDNEY CANCER

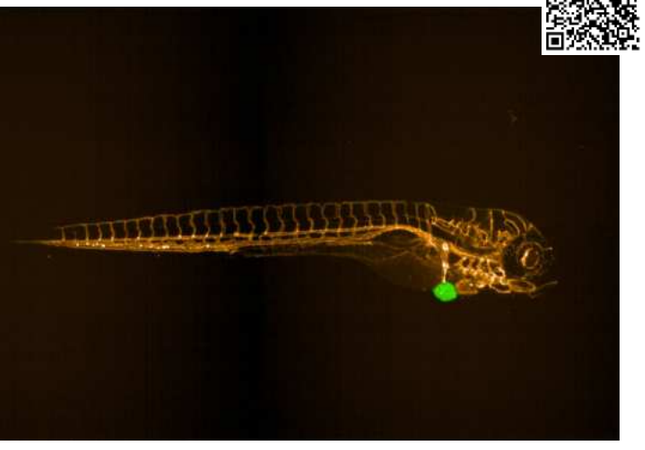
Even then, the scientist focused on cancer research, more specifically on research into kidney tumors (nephroblastoma) in children. The third most common tumor disease in children, it has seen a dramatical improvement of 5-year survival rates: Occurring mostly in patients aged one to five, today up to 90% survive, compared with about 50% in the 1960s. Particularly interested in the evolutionary biology of tumor cells, Cresswell explores which factors play a supporting role, how metastasis occurs and what leads to relapse. His expertise in searching for single nucleotide variations, a type of mutation, is highly valued, as is his understanding of chromosomal instability in whole genome sequencing data.

ELENI TOMAZOU WINS ERC CONSOLIDATOR GRANT

Eleni Tomazou has been awarded a European Research Council Consolidator Grant to research pediatric sarcomas. Funded with a total of 2 million euros, this project will develop models to understand these cancers' origins so as to advance drug discovery and precision medicine. Tomazou's innovative approach could significantly impact the treatment of pediatric sarcomas.

TWO FWF STAND-ALONE PROJECTS APPROVED!

Kaan Boztug and Irinka Castanon secured funding from the Austrian Science Fund FWF for two projects on immune system rare diseases. The first project explores the roles of non-ribosomal proteins in ribosome function, which could impact immune diseases. The second examines the regulation of non-coding RNA in immune function and diseases by RNA-binding proteins with a view to identifying new cellular processes contributing to immune deficiency.

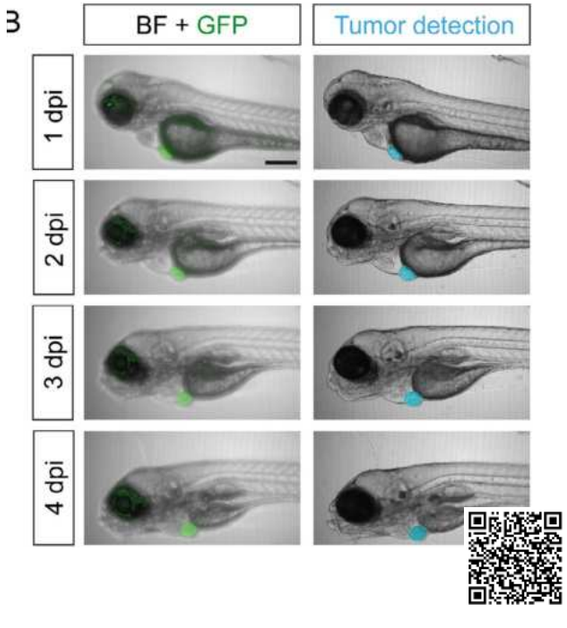


AUTOMATED TESTING OF PEDIATRIC CANCER THERAPIES

A method called High-Throughput Screening that allows testing multiple drugs at once to determine their effectiveness helps researchers to quickly find out which drugs work against specific types of tumors. The study provides first instructions on how to apply this technique to test drug effectiveness on childhood tumors using zebrafish models, which could speed up the discovery of new treatments for these cancers. Read more in the chapter *Core Units & Platforms*.

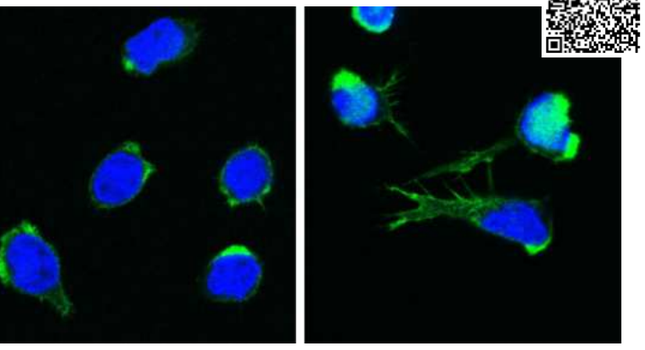
NEUROBLASTOMA FOLLOW-UP PROJECT FUNDED BY WWTF "NEXT"

Sabine Taschner-Mandl's lab at St. Anna CCRI is part of a WWTF-funded project dedicated to the advancement of neuroblastoma research. Having developed a test to identify genetic changes associated with high-risk neuroblastoma, the project seeks to enable diagnostic labs to conduct the test independently using a web-based app in order to improve the diagnosis and treatment of this severe cancer affecting children.



DRUG COMBINATION SHRINKS CHILDHOOD CANCER IN ZEBRAFISH

Researchers from St. Anna CCRI have devised a combination therapy that, when tested in zebrafish larvae, effectively shrinks or eliminates childhood bone cancer. Using these small, transparent fish, which develop tumors within 24 hours, allows for rapid and simultaneous observation of tumor response to treatments. The study established a semi-automated method to test up to twelve different therapies in just one week, with the research team discovering three combinations of drugs that were particularly effective at reducing or eradicating the tumors. It will take some time, though, before these treatments can be used in children. Read more about this publication in the chapter *Core Units & Platforms*.

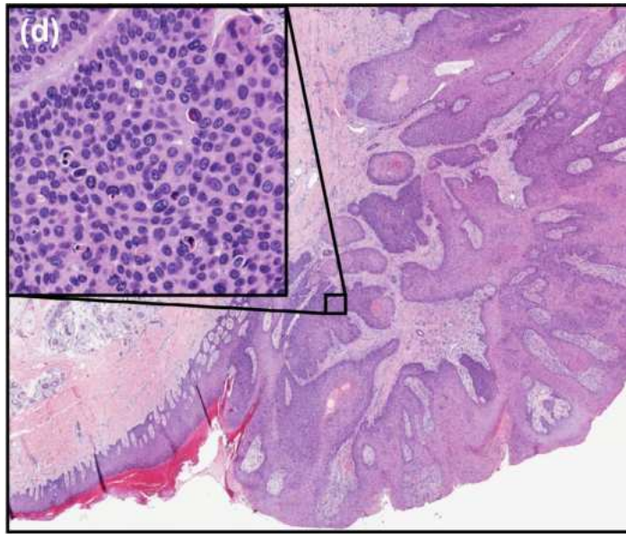


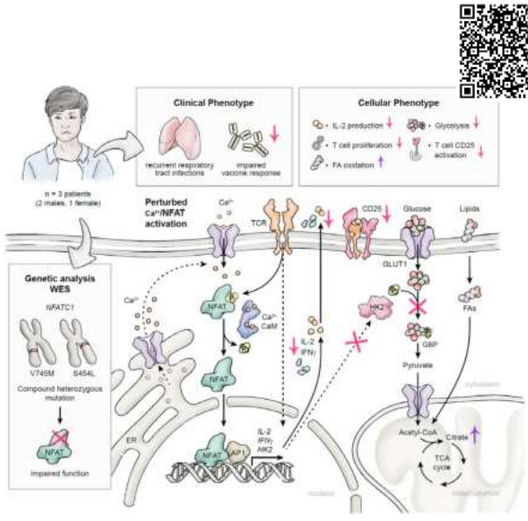
NEWLY DISCOVERED GENETIC DEFECT DISRUPTS BLOOD FORMATION AND IMMUNE SYSTEM

In the quest to find the origin of symptoms in four children, researchers from St. Anna CCRI, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, and the Medical University of Vienna discovered a genetic defect in *DOCK11* linking disruptions of blood formation, the immune system, and inflammation. This link has not been described before, nor has it even been assumed. In any case, this discovery provides the basis for a better understanding of similar diseases. Read more about the publication in the chapter *Immunology, Hematology, Immunotherapy.*

POLYMERASE-δ DEFICIENCY AND SYNDROMIC COMBINED IMMUNODEFICIENCY

A recent discovery has been made by researchers from St. Anna CCRI, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, and the Department of Dermatology of the Medical University of Vienna: The team found a new connection between a lack of the enzyme polymerase-δ, a type of enzyme that helps cells copy their DNA accurately when dividing, and a rare type of immune deficiency that affects multiple aspects of the immune system. This finding has generated a lot of interest and excitement among medical researchers.
Read more about this publication in the chapter *Immunology, Hematology, Immunotherapy.*



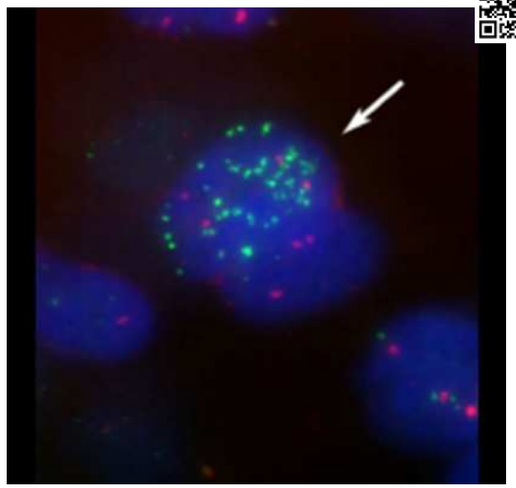


ANTI-DIABETES DRUGS MAKE IMMUNE CELLS MORE EFFECTIVE AGAIN

A team of scientists led by St. Anna CCRI and Marmara University Istanbul has been able to show for the first time that a mutation of the transcription factor NFATc1, which is important for the activation of T cells, causes a previously unknown inborn immune defect: The affected patients suffer from recurrent infections and inflammations. Read more about the publication in the chapter *Immunology, Hematology, Immunotherapy.*

IMMUNOTHERAPY AND STEM CELL TRANSPLANTATION IMPROVE NEUROBLASTOMA SURVIVAL RATES

Results from a new study by St. Anna CCRI and the Eberhard Karls University Tuebingen show that immunotherapy administered after a specific type of bone marrow transplant from parents has greatly increased the survival rates for children with neuroblastoma. The survival rate five years after treatment has gone up to 53%. This improvement is largely due to a treatment with dinutuximab beta, which boosts the activity of natural killer cells, immune cells which play a crucial role in fighting cancer. Read more about this publication in the chapter *Clinical Studies*.

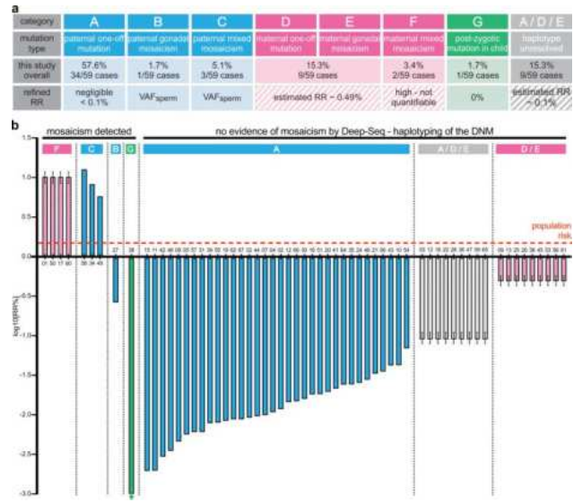


13TH BIENNIAL CHILDHOOD LEUKEMIA AND LYMPHOMA SYMPOSIUM IN VALENCIA

The 13th Biennial Childhood Leukemia and Lymphoma Symposium in Valencia showcased significant advancements in leukemia and lymphoma research, among them contributions from St. Anna CCRI, Labdia, and St. Anna Children's Hospital. Key topics included various aspects of acute lymphoblastic leukemia, non-Hodgkin's lymphoma, cellular therapies, and international collaborative efforts aimed at shaping future clinical trials, particularly in developing countries.

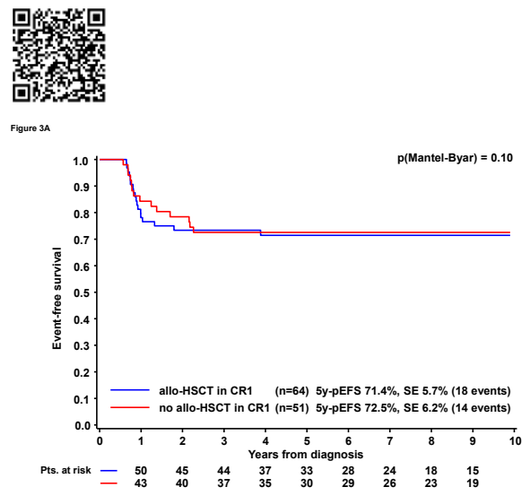
PREGCARE STUDY PROMISES PERSONALIZED RECURRENCE RISK ASSESSMENT FOR FAMILIES

To a healthy couple with no family history of diseases, the birth of a child with a serious health condition will come as a major shock. Until recently, there was no clear way for doctors to predict whether future children could be similarly affected. Now, a scientist from St. Anna CCRI together with her former colleagues from University of Oxford has developed a new method to provide families with a clear understanding, helping them make informed decisions about their future. Read more about this publication in the chapter *Solid Tumors*.



EXPLORING IMPROVED TREATMENTS FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

In a big collaborative effort, researchers from St. Anna Children's Hospital and St. Anna CCRI, Medical University of Vienna, Medical School Hannover, Christian-Albrechts-University Kiel and University Medical Center Schleswig-Holstein, and the Leukaemia Research Cytogenetics Group at Newcastle University are advancing treatment options for a specific type of acute lymphoblastic leukemia (ALL) with 11q23/*KMT2A* gene rearrangements. A study published in the Journal of Clinical Oncology focuses on identifying key prognostic factors and assessing the effectiveness of allogeneic hematopoietic stem-cell transplantation. This research aims to improve outcomes for patients with this particular genetic form of leukemia. Read more about this publication in the chapter *Affiliated Clinicians*.



Credit: Heinz Stephan Tesarek

ST. ANNA CCRI HOSTS EUSARC IN VIENNA

St. Anna CCRI hosted the EuSARC 2023 meeting that took place from May 18th to 20th, welcoming scientists and physicians from all over the world to address the critical need for novel therapies in sarcomas.

EuSARC, an annual assembly of European scientists, strives to fill the research gaps in sarcomas, a group of poorly explored bone and soft tissue tumors. Particularly understudied and lethal, pediatric sarcomas demand collaborative efforts to propel advancements and improve patient outcomes.

FOSTERING INTERNATIONAL COLLABORATION: EUSARC 2023 HIGHLIGHTS

Eleni Tomazou, a Principal Investigator at St. Anna CCRI and EuSARC Scientific Committee member, emphasizes the significance of gatherings like EuSARC: "Given the fact that they are rare, they get less attention, which makes meetings like EuSARC so important." Collaboration becomes pivotal in advancing understanding and exploring new therapeutic avenues.

"Pediatric sarcomas are understudied and deadly cancers, with limited new therapies and very little improvement of patient outcomes. Bringing together the best scientists and fostering international collaboration is crucial for discussing new findings and ways of how to move forward," Kaan Boztug, Scientific Director of St. Anna CCRI, adds.

POTENTIAL NEW TARGET FOR EWING SARCOMA

At the conference, keynote speaker Kimberly Stegmaier from Dana-Farber Cancer Institute delved into new discoveries related to Ewing sarcoma.

"This tumor is driven by a fusion oncoprotein, most commonly the EWS-FLI1 fusion, which has proven to be a difficult drug target. From our studies we have learned that Ewing sarcoma tumors require a precise amount of the EWS-FLI1 fusion, a so-called 'Goldilocks' phenomenon," Kim Stegmaier explains. She also pointed out the delicate balance required for optimal therapeutic impact, with either too little or too much of the fusion being deleterious to the Ewing sarcoma cells.

LOCAL CONTRIBUTIONS

The conference also featured talks from St. Anna CCRI researchers. Guest speaker Florian Grebien expounded on the oncogenic mechanisms of fusion proteins in pediatric cancer, enriching the event with insights into molecular processes driving pediatric cancers.

Martin Distel provided valuable contributions to the sarcoma research landscape by sharing findings on cPLA2 expression and its correlation with enhanced invasion of osteosarcoma cells in vivo.

ARTEM KALINICHENKO GIVES BEST TALK AT API CONFERENCE

At the API conference in Germany, Artem Kalinichenko won the best talk prize for his presentation on a genome-wide CRISPR screening approach to study key factors in human lymphocyte function. His research offers new insights into immune cell regulation, potentially advancing the understanding and treatment of immunological diseases.

SIGNIFICANT PRESENTATIONS AT ADVANCES IN NEUROBLASTOMA MEETING

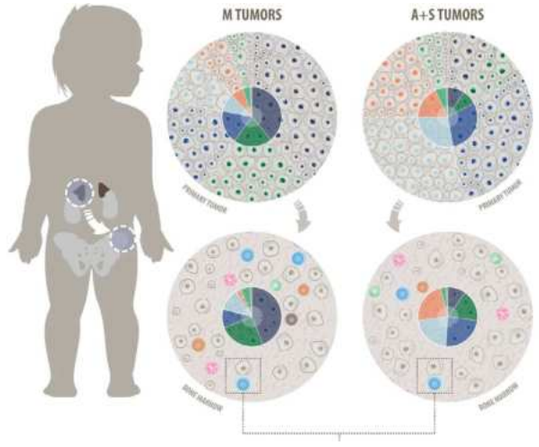
Researchers from St. Anna CCRI, including Florian Halbritter and Sabine Taschner-Mandl, presented their studies on neuroblastoma research at the Advances in Neuroblastoma Research Association meeting, also dwelling on collaborative spirit and the dedication to neuroblastoma research.

POSTDOC FELLOWSHIP FROM ENGELHORN FOUNDATION

Cheryl van de Wetering (Boztug Group) received a postdoc fellowship to carry out a study on a novel inborn error of immunity linked to severe immune disorders and potential cancer predisposition. Her research focuses on understanding the role of the mutated gene in immune deficiency to develop personalized diagnosis and treatment strategies. The research could offer new insights into the molecular and cellular mechanisms underpinning severe immune deficiencies.

IMMUNE RESPONSE VULNERABILITIES IN NEUROBLASTOMA BONE MARROW METASTASES

For the first time, researchers from St. Anna CCRI and the Paris Lodron University of Salzburg have studied cancer spread to the bone marrow from brain-related cancers in children using a detailed method that looks at individual cells. What they found was that cancer cells can manipulate monocytes, making this type of immune cell help the cancer grow instead of fighting it. The manipulation involves changes in how cells communicate. This discovery could contribute to finding new ways of treating this type of cancer. Read more about this publication in the chapter *Solid Tumors*.



Credit: Heinz Stephan Tesarek

ITCC BROUGHT TOGETHER LEADING INTERNATIONAL EXPERTS AND RESEARCHERS

The Innovative Therapies for Children with Cancer (ITCC) Scientific Days, organized by St. Anna CCRI, St. Anna Children's Hospital, and the Medical University of Vienna, brought together leading international experts and researchers in pediatric oncology to discuss the latest advancements, challenges, and opportunities in understanding and treating pediatric cancers.

Exciting breakthroughs were discussed, including a novel treatment approach for high-grade gliomas that leverages specific signaling pathways such as PDGFRA. Another promising avenue highlighted was the targeting of driving epigenetic alterations using cutting-edge anticancer agents that might trigger more precise and targeted attacks on cancer cells.

AN EXCITED ORGANIZING COMMITTEE

Kaan Boztug, Michael Dworzak (St. Anna Children's Hospital), and Johannes Gojo (Medical University of Vienna) shared their enthusiasm about the exceptional quality of speakers as well as the attendees' overall satisfaction with the engaging program in a video (available through the QR Code).

BRIDGING MINDS IN ONCOLOGY

In his opening comment, Kaan Boztug, referring to the incredible potential for networking and knowledge exchange, expressed his hope that every scientist would leave the conference with at least one new collaboration. This resonated deeply with the participants, including the distinguished keynote speaker Mike Stratton who is renowned for his groundbreaking work in genomics.

In an exclusive interview, Stratton pointed out that forming collaborations does not always happen on the spot but can emerge naturally over time. “Regard it as an opportunity that these people have been exposed to the same sort of ideas as you have been, and contact them later, when things come to you,” he said.

GLOBAL EXPERTISE

The conference not only facilitated fruitful discussions among European institutes but also welcomed non-ITCC participants, particularly young scientists, thus initiating a broader scientific dialogue. The overwhelming positive feedback from attendees attests to the success of this remarkable event. A heartfelt thank you to everyone who contributed to making the Scientific Days of ITCC an unforgettable experience!

NATURAL KILLER CELL SYMPOSIUM IN KREMS

The crucial role of natural killer cells in cancer immunotherapy was at the centre of the NK Cell Symposium convened in Krems. Researchers, including from St. Anna CCRI, shared insights on NK cells' potential to fight cancer and discussed the development of new therapeutic strategies, emphasizing the need for collaborative research and translational science to advance cancer treatment.

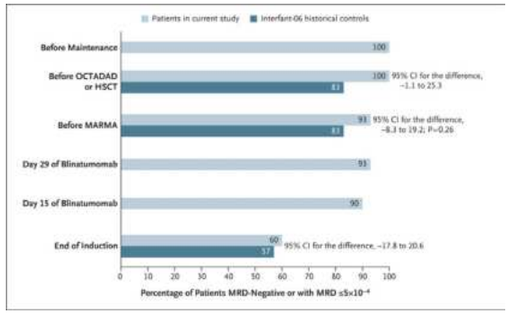
ERN PAEDCAN GENERAL ASSEMBLY IN VIENNA

The ERN PaedCan General Assembly, jointly organized by St. Anna CCRI and SIOP Europe, reviewed five years of achievements in pediatric oncology. Discussions focused on patient communication, educational initiatives, and the integration of digital tools to enhance research and treatment of rare pediatric cancers, setting the stage for future collaborative efforts within the ERN community.

INSTAND-NGS4P GENERAL ASSEMBLY IN VIENNA

The St. Anna CCRI team participated in the INSTAND-NGS4P General Assembly meeting in Vienna that focused on enhancing cancer diagnosis through Next Generation Sequencing. This EU co-funded project aims to develop a standardized diagnostic workflow, combining genetic data with drug-genome interactions, to improve patient treatment decisions. The initiative is set to continue its research and development until mid-2025.

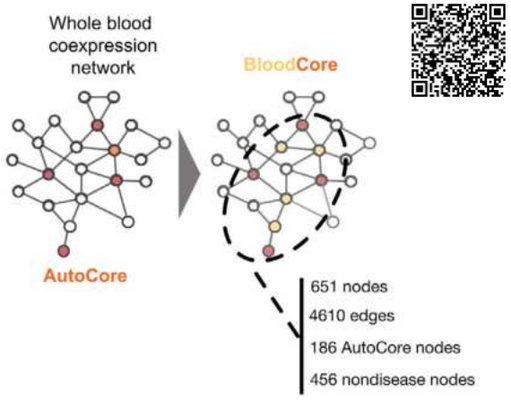
ADDITIONAL BLINATUMOMAB THERAPY FOR INFANTS WITH *KMT2A*-REARRANGED ALL

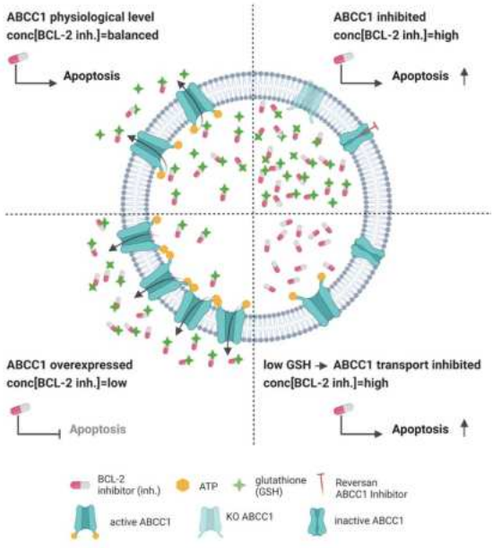


Infants with a specific type of acute lymphoblastic leukemia (ALL) involving a gene rearrangement called *KMT2A* have historically had low survival rates, with only 36% living without events such as relapse for six years. Despite intensive chemotherapy, half of these infants experience a relapse within two years, and stem-cell transplants have not improved survival over the last two decades. Now, a recent study by the Princess Máxima Center for Pediatric Oncology with support from St. Anna CCRI and St. Anna Children's Hospital explored new treatment options with a drug called Blinatumomab. The drug could significantly improve outcomes for the young patients with this aggressive form of leukemia. Read more about this publication in the chapter *Affiliated Clinicians*.

NETWORK-BASED STRATEGIES IN CLASSIFYING AND TREATING RARE DISEASESS

By analyzing how closely different molecular interactions are connected, researchers from CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Max Perutz Labs, and St. Anna CCRI discovered new similarities between rare immune system disorders, which led them to reclassify some of these disorders. As a comparison of their findings with patient data revealed, patients with diseases of the same classification group responded well to the same treatments. This discovery could improve both diagnosis and treatment of these diseases, making therapy more effective. Read more about this publication in the chapter *Immunology, Hematology, Immunotherapy.*



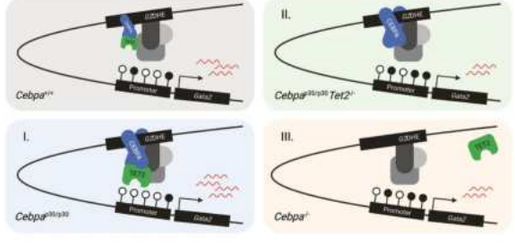


NEW AVENUES IN AML TREATMENT

Treatments for acute myeloid leukemia (AML), a type of blood cancer, are often challenged by resistance and relapse. Venetoclax, a drug known to kill leukemia cells, while working well for many patients, does not lead to long-lasting recovery in about a third of cases. Researchers from St. Anna CCRI, the University of Veterinary Medicine, Vienna, and the Vienna BioCenter investigated the role of certain proteins called ATP-binding cassette (ABC) transporters and the ways they affect the ability of Venetoclax to fight AML. Elucidating the reasons why the drug fails to work for some patients, the research may help to devise better treatment strategies. Read more in the chapter *Leukemias & Lymphomas, Molecular Microbiology.*

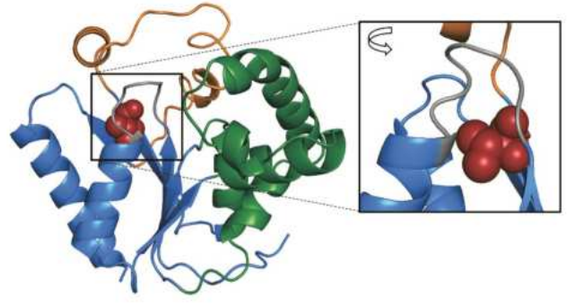
DRIVERS OF AML AGGRESSIVENESS

Researchers from St. Anna CCRI, the University of Veterinary Medicine, Vienna, and the University of Copenhagen studied how certain genetic changes, specifically *TET2* mutations, can make a type of blood cancer called acute myeloid leukemia (AML) more severe. These mutations affect the ways another gene, *GATA2*, works, which is important for the development and function of blood cells. The team's findings help us understand why this cancer can be more aggressive in some people and point to new possible ways to treat it. Read more about the publication in the chapter Leukemias & *Lymphomas, Molecular Microbiology.*



PMVK DEFICIENCY: A NEW TYPE OF AUTOINFLAMMATORY METABOLIC DISORDER

St. Anna CCRI and the Medical University of Innsbruck have identified a new autoinflammatory disorder called Phosphomevalonate Kinase Deficiency (PMKD). This study was able to help a five-years-old girl who suffered from recurring bouts of fever and inflammation. Read more about the publication in the chapter *Immunology, Hematology, Immunotherapy.*



Credit: St. Anna CCRI

CHILDHOOD CANCER AWARENESS MONTH 2023

Throughout the year, we are committed to raising awareness about childhood cancer, which fundamentally differs from adult cancer. Every September, during Childhood Cancer Awareness Month, we think of something special to go the extra mile. This year we interviewed our young researchers, delving deeper into the personal and professional challenges they face in their work to highlight the critical importance of their contributions.

WHAT HAS AFFECTED YOU EMOTIONALLY DURING WORK?

Maud: It is really difficult for me to look at clinical data tables, even though they are anonymized of course. My blood always freezes when I read patients' ages at the time of diagnosis or relapse and so on.

Martha: Sometimes we work with patient-derived material, in particular tumor tissues. This, in essence, contributes a lot to my research. So it's very important to reach my goals and to select some findings. On the other hand, however, it's always very emotional knowing that this actually affects many people, children, and families.

George: I think sometimes you can get caught up in the excitement of researching and discovering new things. But sometimes when you look back on patient histories and what they have been through and some of the outcomes it can certainly affect you.

WHAT IS THE BIGGEST CHALLENGE YOU FACE IN YOUR RESEARCH?

Magdalena: I think in my research the biggest challenge is to set up a good model. Neuroblastoma, the cancer I am working on, is a really complex disease and extremely heterogeneous. And having good models to test your hypothesis is crucial in order to have answers that can actually help the kids to be healthy again.

Lena: Doing my master thesis here, I am still at a very early stage. Almost everything I do, I do for the first time. So in the beginning everything I do is a challenge. But I'm just trying to observe as much of the information I can get and learn from mistakes. Gaining confidence is yet another challenge.

Theresa: Coming up with new ideas and alternate paths is always a great challenge. I think especially as a researcher it is very important to not have a tunnel vision but to always be open to new ideas and suggestions. Talking to fellow researchers and colleagues can always be a great enrichment.

WHAT DO YOU DO WHEN AN EXPERIMENT GOES WRONG?

Leonie: It is always troubleshoot, repeat, fail. Troubleshoot, repeat, fail. Repeat, don't troubleshoot, succeed!

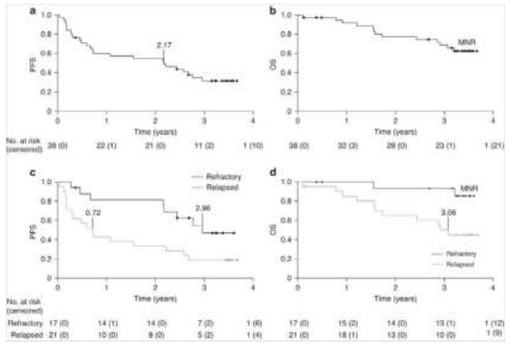
Wouter: Basically just repeat the experiment. Talk with your colleagues and your supervisor. Think about what went wrong and then repeat it and try to alter some of the steps in the protocol.

3RD SCHOOL OF MALIGNANT LYMPHOMAS IN LJUBLJANA

Researchers and scientists from St. Anna CCRI attended the 3rd School of Malignant Lymphomas in Ljubljana to share their expertise in workshops on flow-cytometry. Among them was Michael Dworzak who delivered an insightful lecture on ALL treatment and flow cytometric analyses.

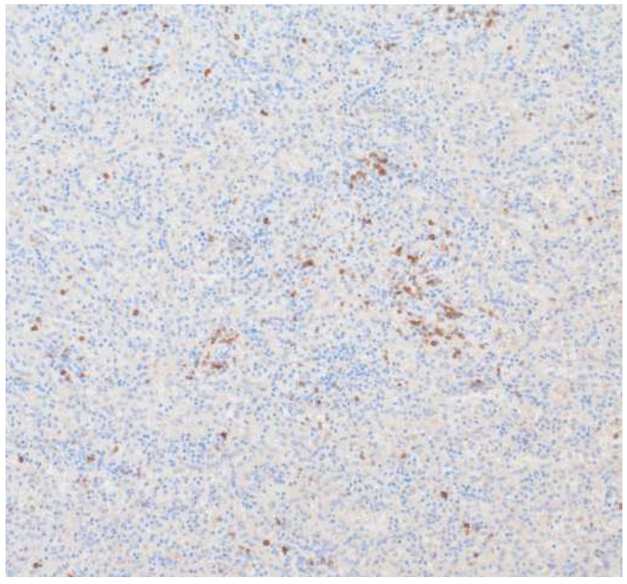
EVOLUTIONARY TREATMENT FOR HIGH-RISK NEUROBLASTOMA INTRODUCED

A new drug could significantly enhance the treatment of high-risk neuroblastoma, a serious cancer primarily affecting young children. The study details how the continuous infusion of dinutuximab beta yields remarkable results for patients whose cancer has returned or resisted previous treatments. This approach not only improves survival chances but also reduces the side effects associated with aggressive cancer therapies. Read more about this publication in the chapter *Clinical Studies*.



TREL: A VISIT FROM VULSK

In a move towards enhancing the EU-funded TREL project, St. Anna CCRI welcomed specialists from VUL Santaros Klinikos for a secondment. The visit focused on exchanging knowledge and training in clinical trials with a view to improving childhood solid tumor research and treatment in Lithuania.



INSIGHTS INTO THE PATHO-GENESIS OF MULTILINEAGE CYTOPENIAS

A study by scientists from St. Anna CCRI, the Medical University of Vienna, the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, and St. Anna Children's Hospital has uncovered new genetic causes of Evans Syndrome, a condition that sees patients suffer from low levels of multiple blood cell types due to immune system problems. Using advanced genetic testing on a patient with this syndrome, the researchers found a new genetic mutation, which helps explain why the immune system attacks the body's own cells. Read more about this publication in the chapter *Immunology, Hematology, Immunotherapy*.

CLOSER LEUKEMIA GENERAL ASSEMBLY

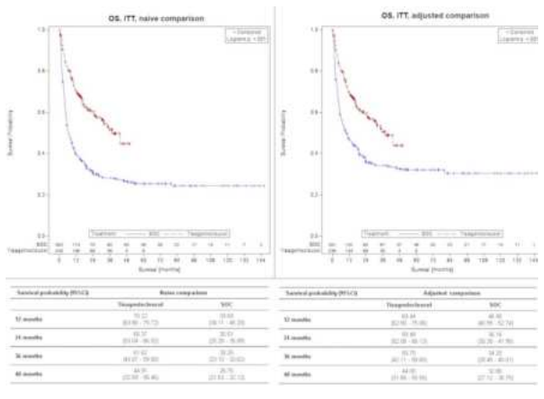
St. Anna CCRI's Sabine Strehl was among the contributors to discussions held at the CLOSER Leukemia General Assembly in Santiago de Chile on improving childhood leukemia diagnostics in Latin America. The assembly underscored the importance of collaborative efforts to equalize survival rates and enhance diagnostic procedures across continents.

JOINT CONFERENCE: EJPRD AND ERICA

The joint conference, held in Amsterdam, brought together the EJPRD and ERICA initiatives dedicated to enhance rare diseases research and diagnosis. St. Anna CCRI played a key role, showcasing the collaboration between projects to bolster European Reference Networks' research capabilities.

FIRST INTERNATIONAL INNOVATIVE MODELS FOR NEUROBLASTOMA WORKSHOP

St. Anna CCRI hosted the International Workshop on Innovative Models for Neuroblastoma Research, gathering global experts to discuss the latest advancements in neuroblastoma research. The event provided a forum for dialogue on developing effective models to advance the understanding and treatment of neuroblastoma.



TISAGENLECLEUCEL VS. STANDARD CARE IN PEDIATRIC RELAPSED B-CELL ALL

In this study, researchers from the Charité University Hospital Berlin, St. Anna CCRI, and St. Anna Children's Hospital investigated a new immune cell therapy called tisagenlecleucel. The team compared its effectiveness against the usual treatments for a tough form of leukemia, known as relapsed or refractory acute lymphoblastic leukemia (r/r ALL), which has not responded well to previous treatments. This therapy involves the modification of a patient's own immune cells to better fight the cancer. The goal was to see if this innovative approach could improve outcomes for young patients facing this challenging disease. Read more about this publication in the chapter *Affiliated Clinicians.*

Copyright: Kurier

KAAN BOZTUG FEATURED ON “SPONTAN GEFRAGT”

Kaan Boztug, Scientific Director of St. Anna CCRI, featured on "Spontan gefragt" on Kurier.TV, where he discussed the unique aspects of pediatric medicine and research. The program highlighted the importance of tailored approaches to diagnosis and treatment in pediatric medicine, providing insights into the challenges and successes encountered in the field.

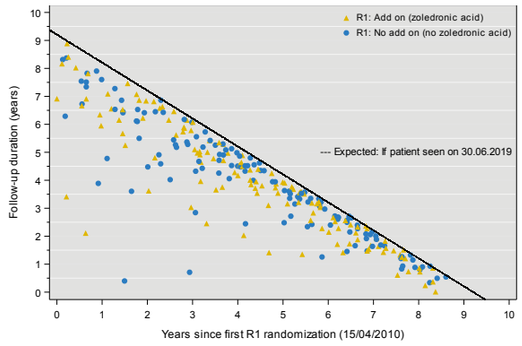
ST. ANNA CCRI - CEMM COLLABORATION AGREEMENT

As both parties are dedicated to support biomedical research and training, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and St. Anna CCRI agreed to enter into a collaboration agreement. Several common projects of strategic importance have already been established between CeMM and St. Anna CCRI over the past years, forming a highly productive partnership between the two institutes. Another centerpiece of the CeMM - St. Anna CCRI collaboration is the joint Adjunct PI Program to broaden scientific competence and to complement the current faculty in institute-wide matters.


Credit: © Bubu Dujmicd

AN ADD-ON THERAPY FOR EWING SARCOMA PATIENTS

A study published in a collaborative effort by St. Anna CCRI, the University of Muenster, and Princess Máxima Center for Pediatric Oncology looks into a new way to treat Ewing sarcoma, a type of cancer that usually affects young people. The study tests whether adding a medicine called zoledronic acid to the usual treatment helps patients live longer without the cancer getting worse, and whether it improves their overall survival chances. The focus is on seeing how this addition could make a difference in their treatment outcomes. Read more about this publication in the chapter *Clinical Studies*.



Credit: Leila Winkler

35 YEARS OF PIONEERING PEDIATRIC CANCER RESEARCH

St. Anna CCRI celebrates 35 years at the forefront of scientific efforts against pediatric cancer. On this significant anniversary, the institute granted rare insights into its laboratories, showcasing the cutting-edge research that is conducted there.

EXCLUSIVE INSIGHTS INTO LEADING-EDGE LABORATORIES

During an exclusive lab tour, selected journalists had the opportunity to visit the laboratories of Heinrich Kovar and Sabine Taschner-Mandl. These labs are at the forefront of research in molecular oncology and the biology of high-risk neuroblastoma. The tour provided an overview of advanced technologies and innovative research approaches engendering the development of new treatment methods.

COMMEMORATIVE PUBLICATION UNVEILED: AN EVENING WITH STARS AND PIONEERS

The highlight of the evening was the presentation of the commemorative publication, a testament to the achievements and stories that have shaped the institute over the past 35 years. Among the guests were friends and long-standing companions of the institute and, of course, our excellent researchers. Their presence underscored the connection between research and the broader public, emphasizing the importance of community support for progress in pediatric cancer research.

A LOOK TO THE FUTURE

As the institute reflects on over three decades of groundbreaking research, it steadfastly looks to the future. The event was not just a celebration of the past but also a commitment to continuous dedication to science and the tireless pursuit of improving the lives of children with cancer worldwide.

SCIENCE REPORT

SOLID TUMORS

CAROLINE HUTTER

I do not think that any research can be successful without interdisciplinary collaboration and knowledge exchange. Both are imperative. Networking happens constantly – it may take place next to the coffee machine, when waiting for a seminar to start, or in a more structured way during meetings. There are indeed plenty of opportunities and people, as a rule, are very friendly. My advice for young researchers, who are just starting to build a network is:

Just talk to them!

This advice becomes even more pertinent when considering the evolving landscape of scientific inquiry. The amount and complexity of data generated using new approaches such as single cell analyses and high-throughput imaging have changed considerably – a simple experiment now often requires input from both cell biologists and people trained in bioinformatics, for instance.

HUTTER GROUP

Langerhans Cell Histiocytosis Biology

We work to better understand the biology of Langerhans Cell Histiocytosis (LCH) in order to devise new treatment approaches to this disease.

PRINCIPAL INVESTIGATOR
Caroline Hutter

STAFF SCIENTIST
Raphaela Schwentner

TECHNICAL ASSISTANT
Philipp Ben Soussia-Weiss

POSTDOCTORAL FELLOW
Giulio Abagnale

PHD STUDENT
Wouter van Midden

ASSOCIATED CLINICIAN, BIOINFORMATICIAN
Sebastian Eder

HEINRICH KOVAR

Interdisciplinary intellectual exchange and dispute are at the core of scientific work. The close interaction with other research groups both at St. Anna CCRI and outside, combining complementary expertise to mutual benefit, is a mainstay and strength of our research in a

highly inspiring and friendly atmosphere.

In addition to the collaboration on site, it is international collaboration that is crucial. Given that childhood cancers are rare diseases, collaboration on an international scale is warranted to obtain statistically valid results when studying childhood cancers such as bone sarcomas. Beyond multicentric sample and data collection, international collaboration greatly expands the spectrum of available technologies and models for us to successfully complete our studies. Moreover, it provides a versatile platform for discussion and exchange of opinions, knowledge, and expertise.

KOVAR GROUP

Molecular Biology of Solid Tumors

Our studies focus on the influence of tissue origin, cellular and molecular context, and driver gene biology at the basis of bone sarcoma plasticity and metastasis.

PRINCIPAL INVESTIGATOR
Heinrich Kovar

POSTDOCTORAL FELLOWS
Valerie Fock
Sarah Grissenberger
Utkarsh Kapoor

TECHNICAL ASSISTANT
Karin Mühlbacher

PHD STUDENTS
Veveeyan Suresh
Martha Magdalena Zylka

ASSOCIATED POSTDOCTORAL FELLOW
Branka Radic-Sarikas

SABINE TASCHNER-MANDL

In the past ten years, technologies have developed from the analysis of single markers to integrated approaches generating high-dimensional datasets on different levels and scales, e.g., DNA, protein, cells, and tissues. In many aspects of data analysis we now use artificial intelligence (AI) and this requires the involvement of data scientists and informatics specialists in addition to international clinical trial groups, oncologists, and statistics, which remain important collaborations.
My research aims at better understanding how solid tumors in children, specifically neuroblastoma, develop and spread and how we can leverage this

knowledge to design

new innovative treatment approaches. In this endeavor, we work closely together to bridge basic, translational, computational, and precision oncology aspects.

TASCHNER-MANDL GROUP

Tumor Biology

We tackle unresolved questions of neuroblastoma pathogenesis and develop new diagnostic and therapeutic approaches to facilitate precision medicine for children with malignant tumors.

TUMOR BIOLOGY

PRINCIPAL INVESTIGATOR
Sabine Taschner-Mandl

SENIOR POSTDOCTORAL FELLOW
Irfete Fetahu (until 08/2023)

POSTDOCTORAL FELLOWS
Polyxeni Bozatzi (until 01/2023)
Sara Wernig Zorc

PHD STUDENTS
Simon Gutwein
Daria Lazic
Polina Perepelkina (until 09/2023)
Magdalena Rados

MASTER STUDENTS
Maaike Bos (until 08/2023)
Viktoria Humhal (until 03/2023)

SOFTWARE DEVELOPER
Matthias Kellner

TUMOR BIOLOGY DIAGNOSTICS

SENIOR STAFF SCIENTIST & TEAM LEADER TUMOR BIOLOGY DIAGNOSTICS
Marie Bernkopf

STAFF SCIENTISTS
Fikret Rifatbegovic (until 05/2023)
Eva Bozsaky

TECHNICAL ASSISTANTS (PRECISION ONCOLOGY PROGRAM)*
Anna Hurt (since 02/2023)
Romana Sickha
Julia Schrammel
Zoltan Spiro (until 07/2023)
Peter Zöscher**

* coordinated jointly with Kaan Boztug

** Bioinformatics Core Unit

ELENI TOMAZOU

In today's scientific landscape, collaboration has become indispensable given the vast expanse of knowledge and the complexity of modern research challenges. From its establishment, my group has embarked on a multidisciplinary research agenda incorporating a wide array of methodologies and expertise.

Of particular importance to the success of our research group are international collaborations. We engage in highly collaborative and interdisciplinary research spanning cell biology, epigenomics, proteomics, single-cell technologies, genetic screening, and bioinformatics. Our projects often have translational potential, necessitating access to patient material and clinical data.

Collaboration is essential in advancing such multi-faceted projects as otherwise many of these tasks would pose

significantly greater challenges to accomplish.

TOMAZOU GROUP

Epigenome-Based Precision Medicine

We study how fusion oncoproteins rewire healthy cells for malignancy with the perspective of exploiting the relevant findings towards precision medicine for pediatric sarcomas.

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PUBLICATIONS

IMMUNE RESPONSE VULNERABILITIES IN NEUROBLASTOMA BONE MARROW METASTASES

For the first time, researchers from St. Anna CCRI and the Paris Lodron University of Salzburg analyzed bone marrow metastases from childhood tumors of the nervous system using modern single-cell sequencing analysis and with the focus on different genetic subtypes. In doing so, they discovered that metastatic tumor cells manipulate monocytes, promoting tumor growth rather than suppression. This manipulation involves altered signaling pathways, particularly regulated by MK and MIF proteins, which suggests new therapeutic targets.

Neuroblastoma is the most common solid tumor in infants and young children. Despite constantly improving therapy options, more than half of patients with a very aggressive form (high-risk neuroblastoma) experience relapses. Because recurrences often originate in the bone marrow, the researchers specifically studied bone marrow metastases. The tumor cells seem to manipulate their environment so that it supports their growth instead of fighting them.

HOW CANCER CELLS MANIPULATE THEIR NEIGHBORING CELLS

The study therefore examined the cell architecture and cell-cell communication of neuroblastoma metastases of two major genetic subtypes (*MYCN* amplification or *ATRX* mutations) and those without such changes using single-cell transcriptomics and epigenomics. Until now, studies have focused in such detail only on primary tumors, but not on neuroblastoma metastases.
Examining more closely the interaction of metastatic tumor cells with healthy bone marrow cells, the team developed algorithms enabling the analysis of different cells in the bone marrow as well as new models of their interactions. As further analysis has shown, monocytes react to unwanted invaders and in the process foster growth processes, releasing cytokines that stimulate tumor growth. Furthermore, investigations at the epigenetic level have revealed that monocytes in the tumor microenvironment, although activated to attack cancer cells, fail to respond appropriately to these signals and hence are no longer able to fight the tumor.

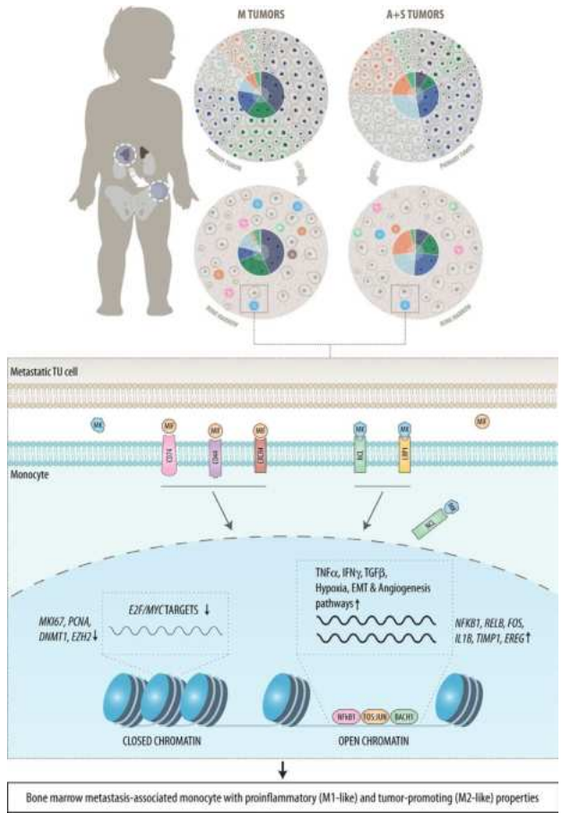
INTERFERENCE WITH PATHOLOGICAL IMMUNE CELL STATES

The communication between neuroblastoma cells and bone marrow or monocytes is to a large extent regulated by the proteins MK (midkine), MIF (macrophage migration inhibitory factor), and associated molecules. Signaling pathways controlled by these proteins are upregulated in immune cells. This pathological interaction is disrupted by drugs targeting MK and MIF, which are currently under investigation. It seems possible that through selective inhibition these pathologically altered monocytes can be returned to their original state.

METASTASES ACT DIFFERENTLY

The scientists also found that cellular plasticity, i.e. the ability of cells to change depending on environmental influences, is retained during metastasis. In addition, the gene expression of metastatic tumor cells depends on the neuroblastoma genetic subtype. For example, neuroblastoma cells that have a *MYCN* amplification change only slightly when metastasizing from the primary tumor to the bone marrow, whereas tumor cells with *ATRX* mutation show pronounced differences upon metastasis.

The genetics of the tumor lead to characteristic signals and thus very specific changes in the microenvironment of the bone marrow, which is expressed in individual signatures. This could explain why neuroblastoma patients with *ATRX* mutations often respond poorly to therapy.



Credit: Fetahu et al., Nat Commun 2023, Creative Commons CC BY 4.0 license

The figure depicts interactions between NB and myeloid cells in the bone marrow compartment, which are mediated through the Macrophage Migration Inhibitory Factor (MIF) and Midkine (MK) pathways.

M, *MYCN* amplified; A, *ATRX* mutated; S, sporadic.

PUBLICATION

Fetahu IS#,*, Esser-Skala W#, Dnyansagar R#, Sindelar S, **Rifatbegovic F**, Bileck A, Skos L, **Bozsaky E**, **Lazic D**, Shaw L, **Tötzl M, Tarlungeanu D, Bernkopf M, Rados M**, Weninger W, **Tomazou EM**, Bock C, Gerner C, **Ladenstein R**, Farlik M, Fortelny N*,§, **Taschner-Mandl S***,§. Single-cell transcriptomics and epigenomics unravel the role of monocytes in neuroblastoma bone marrow metastasis. *Nature Comms*, 2023 Jun, 14(1):3620.

doi: 10.1038/s41467-023-39210-0.

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PREGCARE STUDY PROMISES PERSONALIZED RECURRENCE RISK ASSESSMENT FOR FAMILIES

Until recently, there was no systematic approach to assessing the recurrence risk of dominant disorders caused by apparent de novo mutations. A scientist from St. Anna CCRI together with her former colleagues from University of Oxford have now pioneered a transformative approach, offering families facing serious developmental disorders newfound hope and personalized guidance.

To a healthy couple with no previous family history, the birth of a child with a serious clinical disorder is a life-changing event. Beyond the immediate challenges associated with caring for the child, anxiety looms over the prospect of future children facing similar issues. This study provides a first systematic approach to addressing the recurrence risk of dominant disorders caused by apparent de novo mutations (DNMs).
DNMs are defined as changes in the DNA sequence of a gene in an individual appearing for the first time. Occurring rarely, these mutations can take place during sperm or oocyte development, or post-zygotically in the child, leading to mosaic genotypes. If occurring in the parents, post-zygotic mutations can be the cause of increased recurrence risk due to undetected parental gonadal or mixed mosaicism.

GUIDANCE FOR FAMILIES AFFECTED BY DNMS

The PREcision Genetic Counselling And REproduction study, abbreviated as PREGCARE, involved 60 couples with children diagnosed with serious developmental disorders caused by apparent DNMs, who were seeking individualized reproductive counseling about recurrence risk in future pregnancies. Using deep sequencing and haplotping techniques, the research team examined up to 14 biological samples per family to detect low-level mosaicism in the parents, an underlying postzygotic mutation in the child and to trace the parent-of-origin of the DNM.

PERSONALIZED RECURRENCE RISK ASSESSMENT

At the heart of the PREGCARE strategy lies its ability to categorize couples into discrete risk groups based on the origin of DNMs. Such personalized approach ensures that couples receive individualized recurrence risk assessments tailored to their unique situation. The study aims to provide reassurance to the majority of couples with low or negligible risks while focusing attention on those with heightened recurrence risks.

ADVANCING DIAGNOSTICS WITH ONT PLATFORM

The study introduces locus-specific long-read sequencing on the MinION platform from Oxford Nanopore Technologies (ONT) as a tool to determine the origin of the mutations and with that refine the risk in non-mosaic families. Although harder to scale and process than traditional methods, ONT has demonstrated its potential for diagnostics. Despite technical considerations and a 15% minority of unresolved cases, the method – through which the researchers achieved a nuanced understanding of the complexities surrounding DNMs and their parental origins – might lead to significant strides in risk refinement.

CHALLENGES IN MATERNAL CASES AND FUTURE PREGNANCY CONSIDERATIONS

The study showed that 54/59 DNMs had reduced risk compared to the population baseline risk, while the mixed mosaics – which made up 5/59 DNMs – had increased risk (see figure). However, the authors acknowledge several barriers that have to be considered prior to clinical translation of this work. On the one hand, cases of maternal origin or haplotype-unresolved cases presented certain challenges, emphasizing the need for cautious interpretation. The detection of mixed mosaicism in maternal tissues warrants caution in future pregnancies, with note of potential complications in diagnostic options due to the unsuitability of non-invasive prenatal testing.

TECHNICAL HURDLES AND INNOVATIVE SOLUTIONS

On the other hand, the technical challenge of implementing individualized recurrence risk measurement necessitates robust laboratory methods. In this respect, the study proposes a solution involving targeted Deep-NGS of key tissues that are readily achievable in clinical settings and reduce the risk of mosaicism presentation for the remaining couples to approximately 0.1%.

TRANSFORMING GENETIC COUNSELING PRACTICES

The ability of PREGCARE to provide pre-conception recurrence risk assessments for couples with a child affected by a DNM promises a major shift in genetic counseling. Armed with evidence-based estimations of actual risk, couples can now be prioritized for further investigations and support – and thus empowered to make informed choices about available diagnostic options.

PUBLICATION

Bernkopf M#, Abdullah UB#, Bush SJ, Wood KA, Ghaffari S, Giannoulatou E, Koelling N, Maher GJ, Thibaut LM, Williams J, Blair EM, Kelly FB, Bloss A, Burkitt-Wright E, Canham N, Deng AT, Dixit A, Eason J, Elmslie F, Gardham A, Hay E, Holder M, Homfray T, Hurst JA, Johnson D, Jones WD, Kini U, Kivuva E, Kumar A, Lees MM, Leitch HG, Morton JEV, Németh AH, Ramachandrappa S, Saunders K, Shears DJ, Side L, Splitt M, Stewart A, Stewart H, Suri M, Clouston P, Davies RW, Wilkie AOM§, Goriely A§,*. Personalized recurrence risk assessment following the birth of a child with a pathogenic de novo mutation. *Nat Commun*, 2023 Feb, 14(1):853. doi: 10.1038/s41467-023-36606-w.

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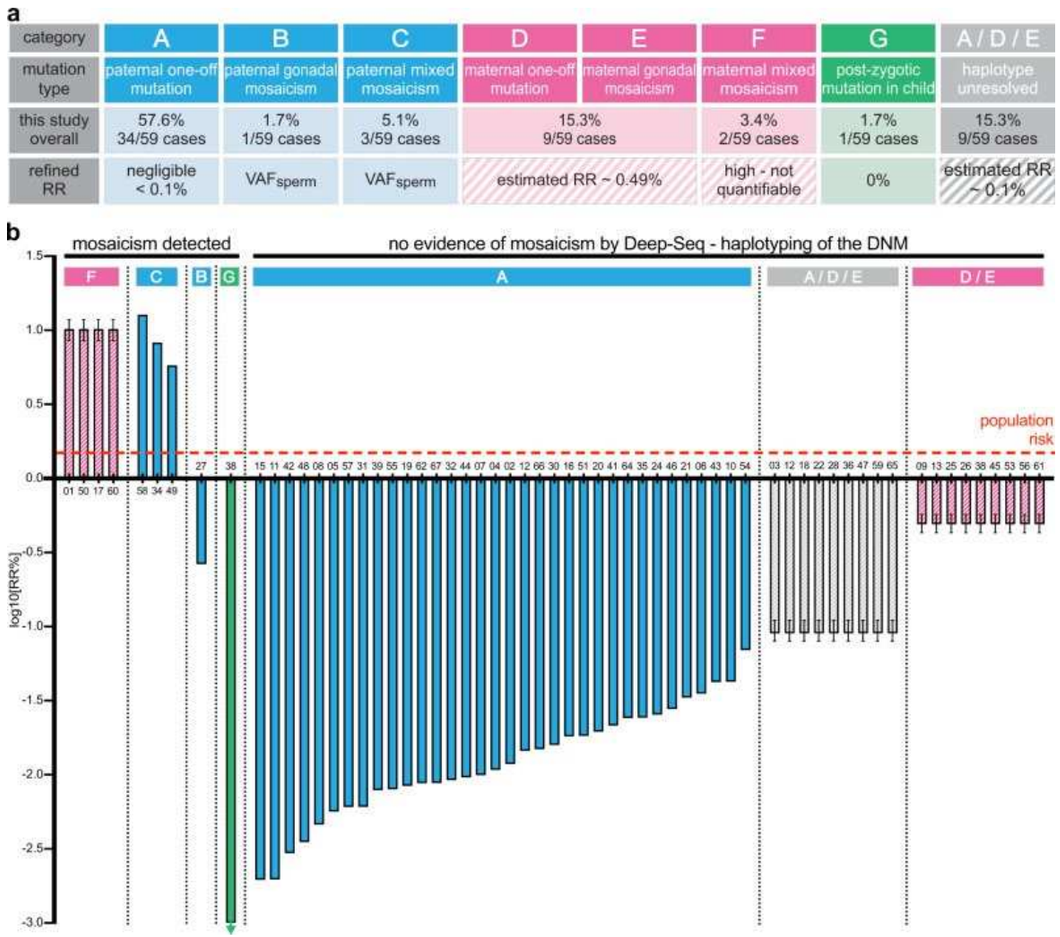

a. PREGCARE results for the 59 analyzed DNMs and overview of the refined recurrence risk (RR). b. Personalized recurrence risk (RR%) estimates for each of the 60 PREGCARE study families (61 DNMs); individual family numbers are on the x-axis and the red dotted line shows the generic population RR for couples having a child with a DNM (~1.5%).

RUTH LADENSTEIN

S²IRP acts as an important link between respective laboratory research activities, holding data from more than 16,000 patients from national and international pediatric clinical trials. At St. Anna CCRI, we work closely together with different groups on a variety of topics.
In rare disease settings like pediatric oncology, sufficient patient numbers are key, hence the need for international cooperations, the latter being

a factor of success.

Scientific communications and interactions are pivotal and inspiring for the field to maintain the innovation pathways and creation of new international standards.
S²IRP plays a crucial role in this regard, as we coordinate clinical trials and registries, both nationally and internationally, facilitating the development of new treatment strategies and international care standards. Our collaborations ensure access to vast patient data, enabling critical research and publications that drive innovation and set new international benchmarks in the field.

LADENSTEIN GROUP

Studies & Statistics for Integrated Research and Projects (S^2IRP)

Networking is key to improve cancer care in children and adolescents.

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PUBLICATIONS

SCIENCE REPORTS

IMMUNOTHERAPY AND STEM CELL TRANSPLANTATION IMPROVE NEUROBLASTOMA SURVIVAL RATES

Immunotherapy after parental stem cell transplantation has markedly improved survival in high-risk neuroblastoma patients, with a study by St. Anna CCRI and the Eberhard Karls University Tuebingen demonstrating a five-year survival rate increase to 53%. Enhanced natural killer cell function through dinutuximab beta immunotherapy plays a key role in this improved outcome.

Neuroblastomas are associated with an unfavorable prognosis if the tumor is classified as a high-risk type. The chances are particularly poor for patients in the relapsed stage. In this case, immunotherapy following stem cell transplantation is now associated with long-term survival in a substantial proportion of the patients included in a recent study. Compared to an earlier study, the survival rate was increased. patients responding well to previous treatments exhibited markedly better survival rates.

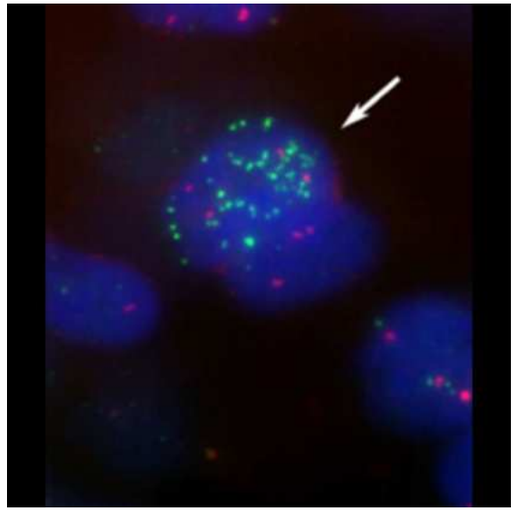
LONG-TERM SURVIVAL EXCEEDS 50 PERCENT

The use of dinutuximab beta immunotherapy after matched family donor stem cell transplantation has shown significant benefits, particularly for patients who had achieved at least a partial response to previous treatments. The study observed no unexpected side effects and a low frequency of graft-versus-host disease.
This approach enhances the immune response following stem cell transplantation from a parent, significantly improving patient outcomes. Following a median eight-year observation period, over half of the patients (53%) achieved a five-year survival rate, a substantial increase compared to the 23% five-year survival rate in a prior study without post-transplantation immunotherapy. Notably,

BOOSTING NATURAL KILLER CELLS

Dinutuximab beta, an antibody that binds to the GD2 molecule on tumor cells, marks these cells for destruction by the immune system, particularly by natural killer cells. However, prior chemotherapies may impair certain abilities of natural killer cells. Here, a transplantation of intact natural killer cells from matched family donors before administering immunotherapy is considered a viable strategy to counteract this, allowing the newly transplanted natural killer cells to more efficiently target tumor cells through an antibody-dependent reaction.

Further studies are crucial to determine the individual components of the therapeutic approaches. Recent advances have seen conventional chemotherapy paired with immunotherapy early in the treatment strategy, resulting in similarly improved response rates. The innovative concept of rejuvenating the immune system via healthy parental stem cells, coupled with the transplantation method, holds promise for enhancing survival rates. This approach aims to provide more robust and enduring tumor control. In order to validate the potential benefits of this novel immune system strategy in relapse therapy, a randomized study would be essential.



MYCN-amplified neuroblastoma cells

Credit: Taschner-Mandl group / St. Anna CCRI

PUBLICATION

Flaadt T*, #, **Ladenstein RL#**, Ebinger M, Lode HN, Björk Arnardóttir H, **Pötschger U**, Schwinger W, Meisel R, Schuster FR, Döring M, **Ambros PF**, Queudeville M, Fuchs J, Warmann SW, Schäfer J, Seitz C, Schlegel P, Brecht IB, Holzer U, Feuchtinger T, Simon T, Schulte JH, Eggert A, Teltschik HM, Illhardt T, Handgretinger R*; Lang P*. Anti-GD2 Antibody Dinutuximab Beta and Low-Dose Interleukin 2 After Haploidentical Stem-Cell Transplantation in Patients With Relapsed Neuroblastoma: A Multicenter, Phase I/II Trial. *J Clin Oncol*, 2023 Jun, 41(17):3135-3148. doi: 10.1200/JCO.22.01630.

# T.F. and R.L.L. equally contributed as first authors

R.H. and P.L share senior authorship

* corresponding author

AN ADD-ON THERAPY FOR EWING SARCOMA PATIENTS

The Ewing 2008R1 trial, published in a collaborative effort by St. Anna CCRI, the University of Muenster, and Princess Máxima Center for Pediatric Oncology, explores a critical issue in the treatment of standard-risk Ewing sarcoma (EWS) patients. This study investigates the efficacy of adding zoledronic acid (ZOL) to the standard treatment regimen, focusing on its impact on event-free survival (EFS) and overall survival (OS).

Ewing sarcoma, a devastating bone cancer, predominantly affects children and young adults. Despite advancements in chemotherapy and localized treatments, the prognosis for standard-risk EWS patients remains challenging. Positioning itself at the forefront of this ongoing battle, the Ewing 2008R1 trial seeks to establish whether ZOL can be of significant benefit in enhancing patient outcomes, thereby addressing a vital gap in current research.

RESEARCH DESIGN

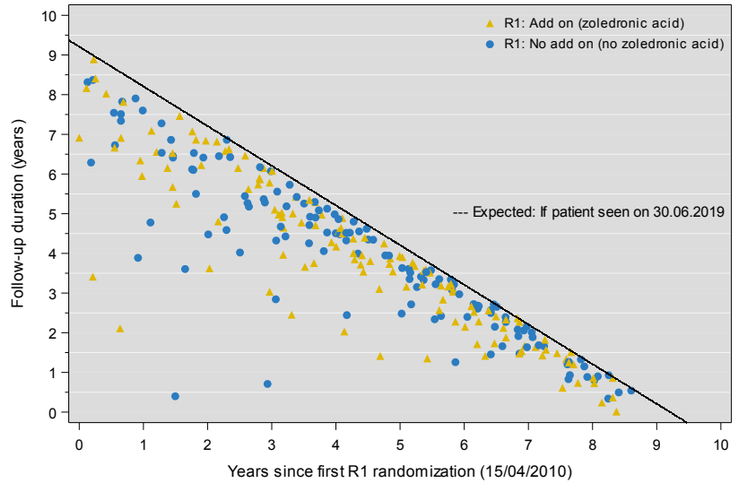
The trial involved patients with localized EWS who had either responded well to induction chemotherapy or had smaller tumors (<200 mL). They underwent a rigorous treatment regime, including six cycles of VIDE induction and subsequent consolidation with VAI or VAC, depending on gender. ZOL treatment commenced alongside the sixth consolidation cycle, the aim being to explore its potential as a maintenance therapy. A robust phase III, open-label, prospective, multicenter, randomized design was employed, involving participants from 12 countries. The trial's adaptive design was intended to ensure precision and reliability of the results and included a planned sample size of 448 patients to achieve substantial statistical power.

EFFICACY OF ZOLEDRONIC ACID

After a median follow-up of 3.9 years, the study did not find a significant difference in EFS between the ZOL group and the control group. Neither did overall survival rates show a notable difference, challenging the hypothesis that ZOL could provide a substantial benefit in the maintenance treatment of EWS. An important aspect of the trial was the observation of increased renal, neurologic, and gastrointestinal toxicities in the ZOL group, highlighting the necessity of weighing potential benefits against the risks of additional toxicities in treatment decisions.

BALANCING THERAPEUTIC EFFICACY

The Ewing 2008R1 trial contributes significantly to the body of knowledge surrounding EWS treatment in that it confirms that while ZOL does not enhance event-free or overall survival for standard-risk patients, it is crucial to continue exploring other potential therapeutic strategies. Underscoring the importance of balancing therapeutic efficacy with potential side effects, the findings from the trial will guide future research directions in EWS treatment.



Follow-up duration among patients still alive at last follow-up, according to the date of randomization

PUBLICATION:

Koch R*, Haveman L*, **Ladenstein R***, Brichard B, Jürgens H, Cyprova S, van den Berg H, Hassenpflug W, Raciborska A, Ek T, Baumhoer D, Egerer G, Kager L, Renard M, Hauser P, Burdach S, Bovee JVMG, Hong AM, Reichardt P, Kruseova J, Streitbürger A, Kühne T, Kessler T, **Bernkopf M**, Butterfaß-Bahloul T, Dhooge C, Bauer S, Kiss J, Paulussen M, Bonar F, Ranft A, Timmermann B, Rascon J, Vieth V, Kanerva J, Faldum A, Hartmann W, Hjorth L, Bhadri VA, Metzler M*, Gelderblom H*, Dirksen U*. Zoledronic Acid Add-on Therapy for Standard-Risk Ewing Sarcoma Patients in the Ewing 2008R1 Trial. *Clin Cancer Res*, 2023 Dec, 29(24):5057-5068.

doi: 10.1158/1078-0432.CCR-23-1966.

* contributed equally

REVOLUTIONARY TREATMENT FOR HIGH-RISK NEUROBLASTOMA INTRODUCED

A new drug could significantly enhance the treatment of high-risk neuroblastoma. Scientists from St. Anna CCRI presented the results in a study published in the journal *British Journal of Cancer*.

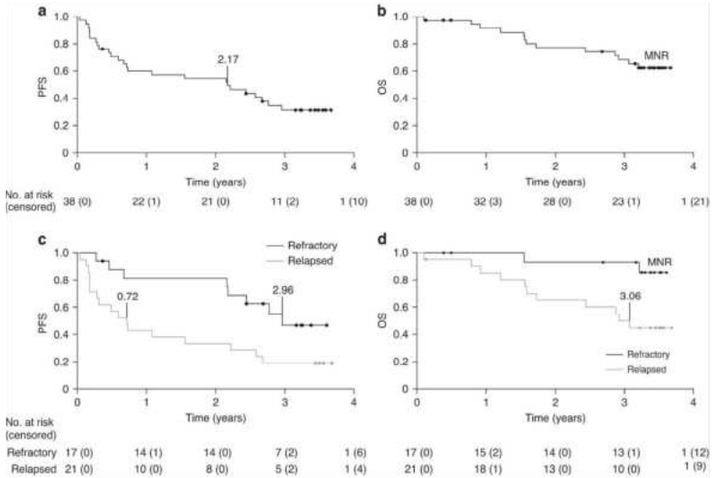
Representing a landmark achievement for pediatric oncology, a groundbreaking study has unveiled a transformative treatment approach for high-risk neuroblastoma (HR-NB), a malignant tumor of the peripheral nervous system. Neuroblastoma mainly affects toddlers and young children, with 1,500 new cases per year occurring in the EU region. The innovative therapy, which is based on continuous infusion of dinutuximab beta, shows remarkable efficacy in patients with relapsed or refractory HR-NB, offering new hope in the fight against this aggressive disease. The bench-to-bedside academic development of dinutuximab beta was driven by Ruth Ladenstein (St. Anna CCRI and St. Anna Children's Hospital) and Holger Lode (University of Medicine Greifswald) in collaboration with SIOPEN (International Society of Paediatric Oncology European Neuroblastoma Group) and Apeiron / EUSA as industrial partners, which in 2017 achieved EMA licensure approval for this immunotherapy.

TRANSFORMING PEDIATRIC CANCER CARE

High-risk neuroblastoma presents complex treatment challenges often necessitating aggressive therapies with significant side effects. However, the findings from this pioneering study, which highlight the potential of precision medicine to revolutionize treatment strategies and improve outcomes for children battling HR-NB, herald a new era in pediatric cancer care.

EMPOWERING PATIENTS AND FAMILIES

The introduction of a tailored treatment regimen utilizing dinutuximab beta not only enhances therapeutic efficacy but also prioritizes patient comfort by minimizing the burden of treatment-related side effects. It thus reflects the importance of effective treatment and supportive care interventions to achieve better outcomes and improve quality of life for young cancer patients and their families.



Credit: Lode et al., Br J Cancer 2023, Creative Commons CC BY 4.0 License

Kaplan–Meier estimates for progression-free survival (a), overall survival (OS) (b), progression-free survival (PFS) by disease status (c), and overall survival by disease status (d). MNR median not reached.

PUBLICATION:

Lode HN*, Ehlert K, Huber S, Troschke-Meurer S, Siebert N, Zumpe M, Loibner H, **Ladenstein R**. Long-term, continuous infusion of single-agent dinutuximab beta for relapsed/refractory neuroblastoma: an open-label, single-arm, Phase 2 study. *Br J Cancer,* 2023 Nov, 129(11):1780-1786. doi: 10.1038/s41416-023-02457-x

* corresponding authors

IMMUNOLOGY, HEMATOLOGY & IMMUNOTHERAPY

KAAN BOZTUG

In a world where cancer remains one of the biggest challenges in medicine, national and international scientific collaboration is paramount. By joining forces, we can better understand the mechanisms of genetic defects that lead to cancer and develop more effective therapies. In 2023, our collaborative efforts have yielded significant results which we were able to publish in leading scientific journals such as *The New England Journal of Medicine* and *Blood*. By working together, researchers, physicians, and physician-scientists can make breakthroughs that can lead to prevention and cures. Some of the most innovative and surprising new findings come about when scientists collaborate across traditional boundaries and disciplines, and this is something we are trying to foster in particular at St. Anna CCRI. For childhood cancer in particular, the observation that these diseases are rare and peculiar, and that the fact that we cannot simply extrapolate data from adult cancer since the biology of these diseases is fundamentally different, we need to be more collaborative and more innovative than ever before –

now is the time to join forces

and build a future where the fight against cancer is finally won.

BOZTUG GROUP

Immune Deficiency, Cancer Predisposition & Precision Oncology

Working at the interface of inborn immune disorders and inherited predisposition to childhood tumors, our group aims to understand fundamental mechanisms of immune surveillance relevant to pediatric oncology and immunotherapy approaches.

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* coordinated jointly with Sabine Taschner-Mandl and Marie Bernkopf

MANFRED LEHNER

Interdisciplinary collaboration and knowledge exchange

play an essential role

in pediatric cancer research. In my case, it is additional expertise in protein engineering that is crucial, which is ensured through my cooperation with Michael Traxlmayr (BOKU) within the CDL. I also have had and am still having intra- and extramural exchange both with chemists and pharmacologists over the selection of our drugs and their chemical coupling to biotin as well as with computational biology in order to identify tumor antigens we could target with our CAR T cells and to simulate the expected specificity improvement by different strategies for combinatorial antigen recognition. It is indeed a very broad range that my collaboration with our company partner Miltenyi Biotec and the pertinent scientific contacts covers.

CHRISTIAN DOPPLER LABORATORY FOR NEXT GENERATION CAR T CELLS

Head: Manfred Lehner

We focus on the development of therapeutic strategies based on T cells modified with chimeric antigen receptors (CARs). The goal of this CD Laboratory is to generate novel molecular tools to minimize the destruction of healthy tissue and to be able to reversibly control CAR T cell activity in the patient.

ST. ANNA CCRI – CAR BIOLOGY

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PUBLICATIONS

UNRAVELING THE MYSTERY: POLYMERASE-δ DEFICIENCY AND SYNDROMIC COMBINED IMMUNODEFICIENCY

In this study, researchers from St. Anna CCRI, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, and the Departments of Dermatology of the Medical University of Vienna shed light on the intricate link between polymerase-δ deficiency and a novel form of syndromic combined immunodeficiency, sparking curiosity and interest within the medical community.

In 2019, two patients were observed with a unique form of syndromic combined immunodeficiency. Patient 2, particularly noteworthy, exhibited a constellation of symptoms including short stature, microcephaly, lymphopenia, and skin warts, suggesting an underlying molecularly defined cancer predisposition syndrome.

At 27 years old, Patient 2 presented with a striking array of symptoms, including widespread pityriasis versicolor-like hypopigmented macules on the torso and numerous plane warts on the lower extremities reminiscent of epidermodysplasia verruciformis (EV). Further investigation unveiled the presence of EV-associated δ-HPV5 DNA, giving proof of the intricate relationship between polymerase-δ deficiency and HPV infection.

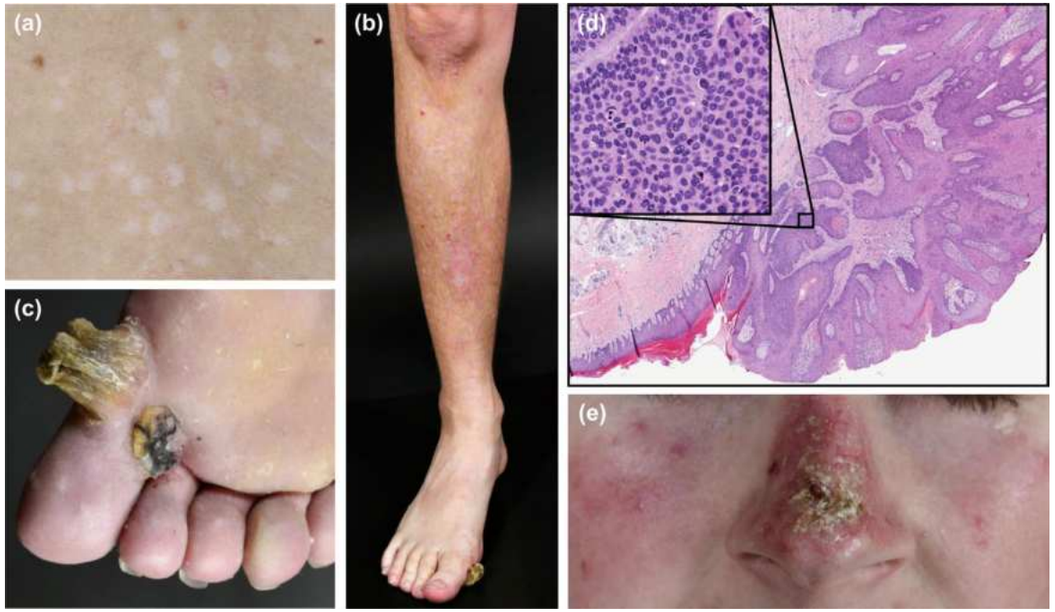
NEED OF INNOVATIVE TREATMENT STRATEGIES

Despite treatment efforts, including ablation using a carbon dioxide laser and topical imiquimod therapy, Patient 2 experienced recurrence of lesions, attesting to the challenges present in managing this complex condition. The incomplete clinical response underscored the pressing need for innovative treatment strategies tailored to the unique immunological profile of patients with polymerase-δ deficiency.

An analysis of serum reactivity to HPV5 provided crucial insights into the immune response to viral infection that will pave the way for potential immunization strategies aimed at bolstering immunity against oncogenic viruses in vulnerable populations. This groundbreaking research not only deepens our understanding of polymerase-δ deficiency but also stresses its implications for cancer predisposition and immune dysfunction.

OPENING NEW AVENUES

Moving forward, the study's findings will have profound ramifications for patient care, as they emphasize the importance of tailored interventions and proactive monitoring in individuals with polymerase-δ deficiency. Continued research aimed at unravelling the mysteries surrounding this condition holds the promise of opening new avenues for understanding and intervention in syndromic combined immunodeficiency associated with polymerase-δ deficiency.



Credit: Strobl et al., Br J Dermatol 2023, Creative Commons CC BY license

A patient with polymerase-δ deficiency presented with (a) HPV5-positive hypopigmented maculae, (b) disseminated plane verrucae, and (c) HPV1-positive plantar mosaic warts, a cutaneous horn, and HPV63-positive verrucous squamous cell carcinoma at 27 years, with (d) histopathological confirmation of verrucous SCC on the foot. Follow-up at 29 years revealed (e) lesions on the nose and face.

PUBLICATION:

Strobl J, Huber B, Heredia RJ, Kirnbauer R, **Boztug K***, Stary G*. Polymerase-δ-deficiency as a novel cause of inborn cancer predisposition associated with human papillomavirus infection. *Br J Dermatol*, 2023 Apr, 188(5):684-685. doi: 10.1093/bjd/ljad021

* contributed equally

NEWLY DISCOVERED GENETIC DEFECT DISRUPTS BLOOD FORMATION AND IMMUNE SYSTEM

In the quest to find the origin of symptoms in four children, researchers from St. Anna CCRI, the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, and the Medical University of Vienna have discovered a genetic defect in DOCK11 linking disruptions of blood formation, the immune system, and inflammation. This discovery provides the basis for a better understanding of similar diseases.

DOCK11 belongs to a family of proteins that are integral to the dynamics of the actin cytoskeleton, influencing cell shape, migration, and intercellular communication – which is vital for the proper functioning of immune cells. Despite its established role in animal models, the specific functions of DOCK11 in human immune and hematopoietic systems remain underexplored. This research addresses this gap by investigating how DOCK11 mutations influence human health, with a particular focus on immune system regulation and blood cell formation.

CLINICAL SPECTRUM OF DOCK11-ASSOCIATED DISEASE

The research focused on four male patients, each with a distinct familial background, with unique yet overlapping symptoms. Notable manifestations included diverse forms of anemia and varied platelet counts, the latter indicating thrombocytopenia or thrombocytosis. They also shared common inflammatory symptoms such as recurrent fever, skin inflammation, and organ-specific issues like splenomegaly and Crohn's disease. Moreover, they suffered from frequent respiratory infections and other health complications ranging from hernias to developmental delays.

DOCK11 CONTROLS BLOOD FORMATION

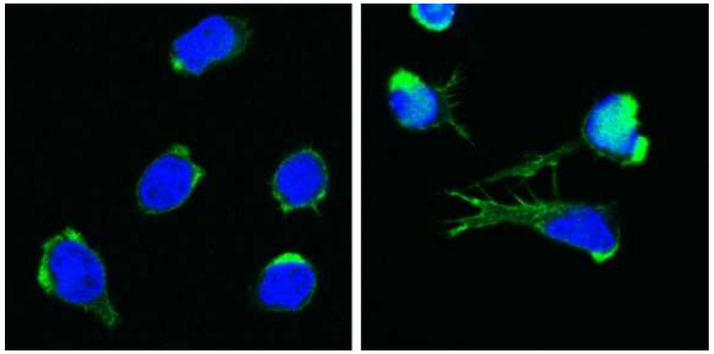
One of the patients suffered from a significantly reduced number of red blood cells and required regular blood transfusions. Anemia often occurs with immune deficiencies, and in many cases a person's red blood cells are destroyed by autoantibodies targeting their own blood cells. However, no such autoantibodies were found by the study. The cause of the decreased number of red blood cells was clarified by the researchers with the help of a zebrafish model. The DOCK11 defect resulted in impaired blood cell formation that led to a novel mechanism for anemia, a deficiency of red blood cells.

DOCK11 KEEPS T CELLS IN CHECK

Previous studies had shown the importance of the protein for the development of B cells in mouse models, whereas in humans the role of DOCK11 until recently had remained unexplored. As the researchers now have revealed, in humans with DOCK11 deficiency B cells do not, to a certain extent, develop properly either, and at the same time T lymphocytes are overactivated. Hence, DOCK11 appears to play a role in keeping the activation of T cells within a certain range. A connection between T cell defects and predisposition to tumor diseases is observed in other immune deficiencies and cannot be ruled out in the case of DOCK11 deficiency.

STEM CELL TRANSPLANTATION AS A POSSIBLE TREATMENT

Although not all details of DOCK11's function are yet understood, the researchers suggest transplantation of blood-forming stem cells as a possible cure for the disease. It is also conceivable that DOCK11 deficiency could be treated through gene therapy.



Healthy and DOCK11-deficient T cells with visible nucleus (blue) and actin cytoskeleton (green)

Credit: St. Anna CCRI

PUBLICATION:

Block J, Rashkova C#, Castanon I#, Zoghi S, Platon J, **Ardy RC**, Fujiwara M, Chaves B, Schoppmeyer R, van der Made CI, **Jimenez Heredia R**, Harms FL, Alavi S, Alsina L, Sanchez Moreno P, Avila Polo R, Cabrera-Perez **R, Kostel Bal S**, Pfajfer L, **Ransmayr B**, Mautner AK, Kondo R, Tinnacher A, Caldera M, Schuster M, Dominguez Conde C, Platzer R, **Salzer E**, Boyer T, Brunner HG, Nooitgedagt-Frons JE, Iglesias Jimenez E, Deya-Martinez A, Camacho Lovillo M, Menche J, Bock C, Huppa JB, Pickl WF, **Distel M**, Yoder JA, Traver D, Engelhardt KR, Linden T, **Kager L**, Hannich JT, Hoischen A, Hambleton S, Illsinger S, Da Costa L, Kutsche K, Chavoshzadeh Z, van Buul JD, Anton J, Calzada-Hernandez J, Neth O, Viaud J, Nishikimi A, Dupre L, **Boztug K***. Systemic inflammation and normocytic anemia in DOCK11 deficiency. *N Engl J Med*, 2023 Aug, 389(6):527-539, doi: 10.1056/NEJMoa2210054.

# contributed equally to this work

* corresponding author

ANTI-DIABETES DRUGS MAKE IMMUNE CELLS MORE EFFECTIVE AGAIN

A team of scientists led by St. Anna CCRI and Marmara University Istanbul has been able to show for the first time that a mutation of the transcription factor NFATc1, which is important for the activation of T cells, causes a previously unknown inborn immune defect making affected patients suffer from recurrent infections and inflammations.

T cells are highly adaptable and can change their roles according to signals from their environment. This adaptability, which is crucial for their various functions in the immune system, is achieved by integrating signals, gene activity, and metabolism. Understanding how T cells adjust their metabolism is a key area of research, especially in the context of human diseases.

NFATC1 REGULATES T CELLS

The NFAT family is essential in controlling how T cells grow, survive, and function. NFATc1, in particular, plays a central role in T cell metabolism by regulating the transition from oxidative phosphorylation to glycolysis during T cell activation. Glycolysis is a faster way to generate energy and is especially important when T cells need to be activated and proliferate quickly.

NFATC1 MUTATION DELAY T CELL ACTIVATION

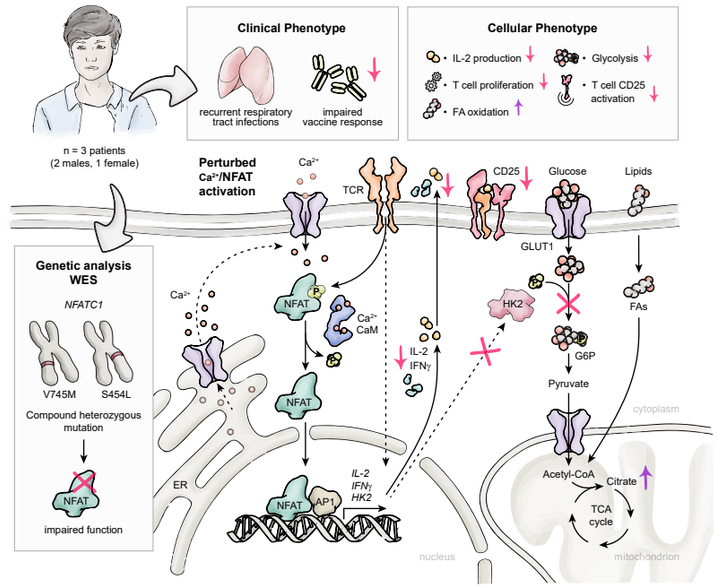
In this study, two mutations in *NFATC1* were identified that lead to a new type of immune disorder. These mutations impair the stability of NFATc1 and its ability to interact with DNA and other proteins, which has far-reaching effects on the maturation and functionality of T cells.

Interestingly, when NFATc1 malfunctions, T cells demonstrate a remarkable ability to adapt by turning to fats as alternative energy sources instead of using their usual energy sources. This adaptability opens up new treatment possibilities: With drugs such as metformin and rosiglitazone showing the potential to modify these energy pathways, they may offer a new therapeutic approach to improve the efficacy of T cells in the presence of *NFATC1* mutations.

Nevertheless, mutations in NFATc1 result in a delayed activation of the defensive responses of T cells.

A GLIMPSE INTO THE MOLECULAR WORLD OF NFATC1

The study also analyzes *NFATC1*-mutant lymphocytes, revealing signs of ongoing inflammation and a shift towards a more senescent state. This suggests a broader impact of NFATc1 on immune health. Moreover, changes in the chromatin landscape indicate a fundamental alteration in how these cells access their genetic blueprints, impacting their function and identity.



Germline mutation of *NFATC1* in a novel inborn error of immunity

Credit: The American Society of Hematology

PUBLICATION

Köstel Bal S, Giuliani S, Block J, Repiscak P, **Hafemeister C, Shahin T**, Nurhan K, **Ransmayr B, Miao Y, van de Wetering C, Frohne A, Jimenez Heredia R**, Schuster M, Zoghi S, Hertlein V, Thian M, **Bykov A**, Babayeva R, Bilgic Eltan S, Karakoc-Aydiner E, Shaw LE, Chowdhury I, Varjosalo M, Argüello RJ, Farlik M, Ozen A, Serfling E, Loïc Dupré L, Bock C, **Halbritter F**, Hannich JT, **Castanon I, Kraakman MJ**, Baris S#, **Boztug K#**. Biallelic NFATC1 mutations cause an inborn error of immunity with impaired CD8+ T-cell function and perturbed glycolysis. *Blood,* 2023 Aug, 142(9):827-845. doi: 10.1182/blood.2022018303.

# contributed equally

NETWORK-BASED STRATEGIES IN CLASSIFYING AND TREATING RARE DISEASES

A significant advancement in the research of rare immune system disorders has been achieved by scientists from CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Max Perutz Labs, and St. Anna CCRI who, through a network-based approach, have reclassified approximately 200 rare diseases. The study has been published in *Science Advances*.

Examining the high degree of interconnectedness of molecular interactions, this study successfully identified new molecular and mechanistic similarities between rare immune system disorders, which also entailed their reclassification. By comparing their results to clinical data, the researchers demonstrated that patients with diseases falling within a certain classification group also responded to the same medications.

NEW CLASSIFICATION ENABLES MORE TARGETED THERAPIES

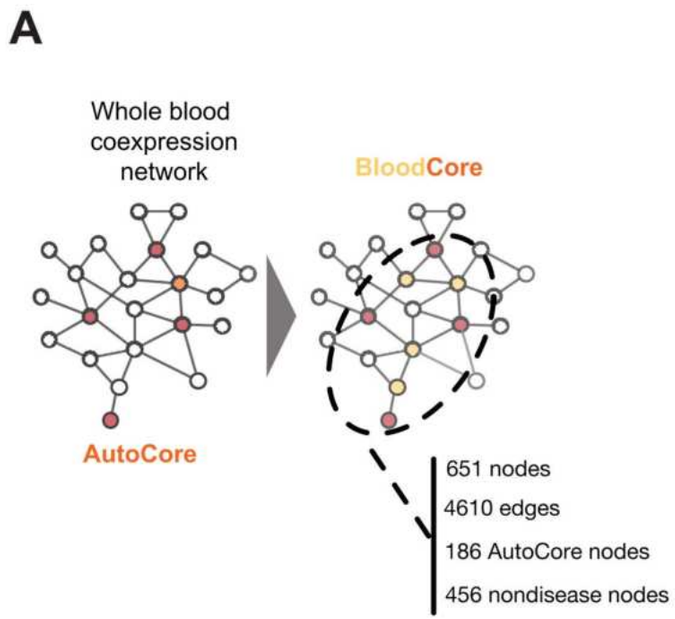
In an examination of 200 rare immune system disorders, the scientists employed network-based analysis to reveal shared molecular mechanisms, which resulted in disease reclassification and the identification of optimal therapies. As co-study leader Kaan Boztug has pointed out, this new classification system improves therapy prediction, demonstrating the effectiveness of network biology in understanding immune system diseases and enabling personalized treatment approaches.

SIMILAR PATTERNS IN AUTOIMMUNE AND AUTOINFLAMMATORY DISEASES

The results also indicate a close linkage between numerous autoimmune and autoinflammatory diseases such as chronic inflammatory disorders, multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes. The scientists were able to identify a group of key genes and their interaction partners that are central to homeostasis, which they refer to as 'AutoCore.' In autoimmune and autoinflammatory diseases, the AutoCore resides right at the center of the associated genes. Additionally, 19 other subgroups that are believed to provide better insights into homeostasis and immune system deregulation were identified.

TAKING A BROADER PERSPECTIVE

While conventional approaches often categorize immune system disorders according to specific body regions and, accordingly, view them in isolation, a systemic approach aims to offer a more detailed picture of underlying mechanisms. There is increasing recognition of the conceptual and practical limitations of the traditional paradigm of 'one gene, one disease' in the research of rare diseases as it hinders the understanding of the complex molecular network through which the components of the immune system are orchestrated. So for the purpose of visualization, the scientists developed a multidimensional network that depicts all currently known monogenic immune defects underlying autoimmunity and autoinflammation as well as their molecular interactions. As a result, it can be seen how closely genes are interconnected in rare diseases. The data acquired also serves as a crucial foundation for identifying better treatment options for specific groups of disorders.



The approach: Expanding the AutoCore on the blood coexpression network to obtain the "BloodCore" network.

PUBLICATION

Guthrie J, **Köstel Bal S**, Lombardo SD, Müller F, Sin C, Hütter CVR, Menche J*, **Boztug K***. AutoCore: A network-based definition of the core module of human autoimmunity and autoinflammation. *Sci Adv*, 2023 Sep, 9(35):eadg6375. doi: 10.1126/sciadv.adg6375.

* corresponding author

PMVK DEFICIENCY: A NEW TYPE OF AUTOINFLAMMATORY METABOLIC DISORDER

St. Anna CCRI and the Medical University of Innsbruck have identified a new autoinflammatory disorder called Phosphomevalonate Kinase Deficiency (PMKD) – a discovery that helped treat a five-years-old girl who suffered from recurring bouts of fever and inflammation. The results of the study have been published in the *Journal of Allergy and Clinical Immunology*.

The patient, a five-year-old girl of Turkish descent, showed a worrying clinical picture made up by recurring hyperinflammatory episodes characterized by fever, arthritis, aphthous stomatitis, and maculopapular rash. Laboratory findings revealed elevated inflammatory parameters, severe normochromic, microcytic anemia, thrombocytopenia, and granulocytopenia. Whole-exome sequencing identified a homozygous missense variant in PMVK, resulting in markedly reduced PMVK enzyme activity and confirming PMVK deficiency, a newly reported autoinflammatory disease characterized by recurrent fevers, arthritis, and cytopenia.

Clinically, the patient showed various similarities as well as distinct features compared to patients with MVK deficiency (an increased concentration of mevalonic acid in the urine) and responded well to therapeutic IL-1 inhibition. Nevertheless, the suspicion that this could be the already known disease MKD (mevalonate kinase deficiency), whose genetic cause lies in the MVK gene, was not confirmed.

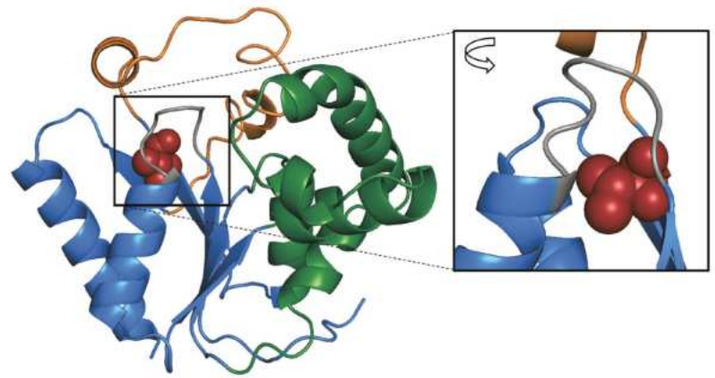
EXOME SEQUENCING

In the course of subsequent exome sequencing, a defect in the gene of the downstream enzyme of mevalonate kinase (MVK), phosphomevalonate kinase (PMVK) was found. As an additional enzyme analysis at the University of Amsterdam revealed, PMVK – in contrast to MVK – is not produced at all in the girl.

Genetic analyses of the healthy family members revealed that the genetic change was heterozygous (present on only one chromosome) in both parents and the siblings, but homozygous (present on both chromosomes) in the young patient – which was what caused the symptoms. Pathogenicity was supported by genetic algorithms and modeling analysis and confirmed in patient cells.

A NEW THERAPY

The mystery was solved when after one and a half years of research a new autoinflammatory disorder was identified: Phosphomevalonate Kinase Deficiency (PMKD). Accordingly, the girl – now five years old – receives a monthly injection of the interleukin-1 antagonist canakinumab to block the inflammation. Thanks to the close international networking in the field of rare diseases, in the meantime two more children – in Germany and Turkey – have been identified to be affected by PMKD.



Shown are the three domains of the PMVK Proteins:
core region (blue),
acceptor substrate binding region (green),
lid region (orange).
The p-loop, a core element with a crucial role in phosphate binding, is shown in gray.

PUBLICATION

Berner J, van de Wetering C, Jimenez Heredia R, Rashkova C, Ferdinandusse S, Koster J, Weiss JG, **Frohne A, Giuliani S,** Waterham HR, **Castanon I**, Brunner J*, **Boztug K***. Phosphomevalonate kinase deficiency expands the genetic spectrum of systemic autoinflammatory diseases. *J Allergy Clin Immunol*, 2023 Oct, 152(4):1025-1031.e2. doi: 10.1016/j.jaci.2023.06.013.

* joint senior authors

KB is corresponding author

INSIGHTS INTO THE PATHOGENESIS OF MULTILINEAGE CYTOPENIAS

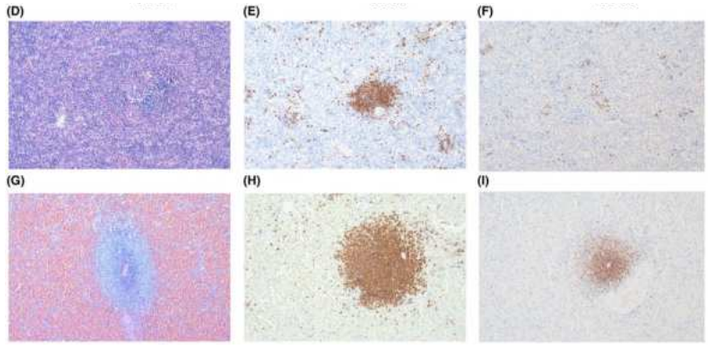
A study of Evans Syndrome reveals novel inborn errors of immunity: The paper by scientists from St. Anna CCRI, the Medical University of Vienna, the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, and St. Anna Children's Hospital was published in the *British Journal of Haematology*.

Revealing a potential link to inborn errors of immunity (IEI) characterized by immune dysregulation, this study sheds light on the complex landscape of multilineage cytopenias, commonly known as Evans syndrome (ES). Characterized by concurrent autoimmune haemolytic anemia and immune thrombocytopenia, multilineage cytopenias represent a clinical conundrum that requires deeper molecular understanding. Conducting an in-depth analysis of a patient presenting with ES by means of cutting-edge genomic technologies, the researchers revealed a pathogenic germline mutation in SASH3. This mutation, which was identified for the first time in this context, signifies a pivotal milestone in delineating the genetic underpinnings of IEI-related autoimmune cytopenias. Post-splenectomy immunohistochemistry studies uncovered pronounced hypoplasia/absence of germinal centers, which are indicative of profound disruptions in adaptive immune responses. Further immunophenotypic characterization unveiled a distinct profile marked by an augmented subset, concomitant with diminished regulatory T cell populations and compromised T cell proliferation kinetics. Notably, an exacerbation of T cell exhaustion markers underscored the intricate immunological dysregulation observed in ES.

CLINICAL MANIFESTATION OF SASH3 DEFICIENCY

The study also elucidated the heterogeneous clinical manifestations of SASH3 deficiency exemplified by the asymptomatic younger sibling harboring the identical SASH3 mutation. Testifying to the multifaceted nature of IEIs, this phenotypic variability stresses the imperative for nuanced diagnostic approaches tailored to individual genetic profiles.

This groundbreaking research not only advances our comprehension of autoimmune cytopenias but also underscores the pivotal role of genomic analyses in unraveling the complexities of immune dysregulation. Elucidating the intricate molecular cascades underpinning autoimmune cytopenias, this study holds promise for the development of targeted therapeutics tailored to individual genetic susceptibilities.



Credit: Novak et al., Br J Haematol 2023, Creative Commons CC BY-NC 4.0 license

Immunohistochemistry and histopathology of spleen tissue in patient P1 and a comparison with hereditary spherocytosis. (D–F) In patient's spleen, few lymphocytes and B cells are present with absent follicular organization; (G–I) contrastingly, normal follicular structure with clear mantle zones is evident in a patient with hereditary spherocytosis.

PUBLICATION

Novak W#, **Berner J#, Svaton M#, Jimenez-Heredia R, Segarra-Roca A, Frohne A, Guiliani S**, Rouhani D, Eder SK, Rottal A, Trapin D, Scheuchenstuhl A, Pickl WF, Simonitsch-Klupp I, **Kager L***, **Boztug K***. Evans syndrome caused by a deleterious mutation affecting the adaptor protein SASH3. *Br J Haematol*, 2023 Nov, 203(4):678-683. doi: 10.1111/bjh.19061.

# equally contributed as first authors

* equally contributed to this work

LEUKEMIAS & LYMPHOMAS, MOLECULAR MICROBIOLOGY

MICHAEL DWORZAK

Interdisciplinary collaboration and knowledge exchange are the be-all and end-all – in other words, you simply can't do without them. You can hardly handle everything required for complex research topics in a single laboratory. This is why we have established a joint R&D focus on acute myeloid leukemia in children and adolescents. We are concerned with

excellence at the highest international level

regarding both in-depth research into driver changes and vulnerabilities as well as next-generation diagnostics (MRD, drug response) and treatment (precision medicine, cellular immunotherapy). Working together with other groups at St. Anna CCRI is immensely enriching, because, after all, only together can we pursue our goals and ultimately be successful.

DWORZAK GROUP

Immunological Diagnostics

We use flow cytometry immunophenotyping to develop new diagnostic methods for children and adolescents with leukemia and lymphomas.

PRINCIPAL INVESTIGATOR
Michael Dworzak

STAFF SCIENTIST
Margarita Maurer-Granofszky

PROJECT TEAM MEMBERS (PART TIME)
Dominik Emminger
Evdoxia Gounari
Michael Reiter
Lisa Weijler (since 07/2023)

PROJECT TEAM MEMBERS (EXTERNAL)
Florian Kleber (TU Vienna)
Doris Kroiss (St. Anna Children's Hospital)
Melanie Lux (St. Anna Children's Hospital, until 09/2023)
Elpiniki Lygizou (TU Vienna)
Matthias Wödlinger (TU Vienna)

TECHNICAL ASSISTANT
Romana Sickha (since 10/2023)

FLORIAN GREBIEN

The most important advice I have for young researchers is to actively approach other scientists.

Every researcher loves to talk

about their work. So instead of waiting for your PI or anyone else to establish a connection, do it yourself! Do not be shy! At St. Anna CCRI, there are several opportunities to do so – especially given that the building is small, which makes interactions easier.
This culture of open communication and collaboration is reflective of the broader ethos at St. Anna CCRI where every PI shares the dedication and enthusiasm it takes to contribute to a deeper understanding of pediatric cancer as the prerequisite for generating better therapies in the future. Moreover, the translational/clinical background of some of the CCRI groups is a source of inspiration for me to identify novel problems that are worth tackling.

GREBIEN GROUP

Biology of Pediatric Leukemia Oncoproteins

We study the molecular mechanisms of leukemia development and progression in order to identify novel vulnerabilities of pediatric cancers.

PRINCIPAL INVESTIGATOR
Florian Grebien

PHD STUDENT
Christina Horstmann (since 09/2023)

THOMAS LION

Interdisciplinary collaboration and exchange of knowledge have always been integral parts of our research. These activities include(d) both clinicians from various fields and scientists working in related or different areas. Thus, one of our ongoing projects is based on close collaboration with physicists who provide important technical support for our work. St. Anna CCRI has from the beginning been involved in many national and international networks, fostering collaborations in all areas of its research activities. It is this which makes St. Anna CCRI an attractive institution for young researchers

seeking collaboration

and trying to establish an inspiring and supporting professional network.

LION GROUP

Molecular Microbiology

We focus on the complexity of viral, fungal, and bacterial infections in immunocompromised patients as well as the subclonal architecture of Ph-positive leukemias.

PRINCIPAL INVESTIGATOR
Thomas Lion

POSTDOCTORAL FELLOWS
Tamires Bitencourt
Klara Obrova (until 02/2023)
Julia Senkiv (since 05/2023)

TECHNICAL ASSISTANTS
Anna-Maria Bandian (until 12/2023)
Michaela Fortschegger
Paola Fürhacker (until 02/2023)
Chantal Lucini (since 04/2023)
Sandra Preuner
Isabella Sponseiler

DAVIDE SERUGGIA

International collaborations are highly important, and this is why my group is involved in a large consortium focused on gene regulation through which we have access to state-of-the-art science and technology of the field all over the world. Although sometimes we have to adjust our schedule and align with time differences, it is absolutely worth the effort. If you can resort to both your own expertise and that of collaborators, whether they work in the same building or across the globe, collaboration indeed multiplies research output,

yielding faster and more precise answers

to scientific questions. Moreover, collaboration forces us to take a more rigorous approach to our science.
This collaborative spirit is rooted in curiosity, generosity and communication. To ignite the engine of collaborative work, one must first offer help to a colleague, e.g., by sharing an idea or a technology you master from which they might benefit. And next time, help may spontaneously come to your door.

SERUGGIA GROUP

Pediatric Leukemia Biology

We focus on non-coding regulatory elements, chromatin modifiers, and other epigenetic factors to understand how pediatric leukemia develops and to find new targets of therapy.

PRINCIPAL INVESTIGATOR
Davide Seruggia

POSTDOCTORAL FELLOWS
Paul Batty (since 09/2023)
Ana Kutschat
Maciej Piotr Zaczek (until 06/2023)

PHD STUDENTS
Hannah Beneder (since 09/2023)
Leonie Lehmayer
Robert Paxton (until 09/2023)
Sandra Wittibschlager (since 09/2023)

TECHNICAL ASSISTANT
Sophie Müller
Sandra Wittibschlager (from 01-06/2023)

SABINE STREHL

Joint brainstorming and bouncing ideas are both creative and fun. The

beauty of collaboration

with other groups lies in the interaction with people coming from various disciplinary backgrounds and in looking at scientific questions from different angles, which broadens the horizon and increases the chances of success.
Participation in national and international meetings provides a great opportunity to present your work and receive feedback from experts in the field even at an early stage of career development and at the same time to personally get to know the peers of the scientific community. At St. Anna CCRI, attendance of internal seminars and lectures of invited speakers are key to getting acquainted with scientific questions and the ways they are addressed by different research groups. Last but not least, you don't need to be best friends with everybody, but personally knowing each other does facilitate communication. So attending social events and going out for dinner or a drink with colleagues once in a while will also foster scientific collaborations.

STREHL GROUP

Genetics of Leukemias

We focus on the detection and characterization of genetic alterations involved in the pathogenesis and progression of leukemia.

PRINCIPAL INVESTIGATOR
Sabine Strehl

STAFF SCIENTIST
Klaus Fortschegger

BIOINFORMATICS DATA ANALYST
Dagmar Schinnerl

MASTER STUDENT
Edwin Rzepa (until 08/2023)

TECHNICAL ASSISTANT
Marion Riebler

PUBLICATIONS

NEW AVENUES IN AML TREATMENT: THE INTERPLAY OF ABCC1 AND GLUTATHIONE METABOLISM WITH BCL2 INHIBITORS

Acute myeloid leukemia (AML) treatments often encounter hurdles, resulting in resistance and subsequent relapse. Venetoclax, known for its ability to trigger leukemia cell death, proves effective for many, yet fails to bring about durable remissions in a third of patients. Delving into the role of ATP-binding cassette (ABC) transporters, a study by St. Anna CCRI, the University of Veterinary Medicine, Vienna, and the Vienna BioCenter explores their influence on the effectiveness of Venetoclax in combating AML.

Acute myeloid leukemia (AML) is a type of cancer affecting the blood and bone marrow that is characterized by the rapid increase of abnormal white blood cells. Despite advancements in treatment, challenges such as toxicity and resistance persist, underscoring the need for more targeted and effective therapies. Addressing this gap, this study provides insights into potential strategies to enhance treatment outcomes.

TARGETING THE SURVIVAL MECHANISM OF CANCER CELLS

One of the critical players in the survival of cancer cells, the protein BCL-2 is often found in excess in various cancers, including AML. Venetoclax, a drug approved by FDA for certain cases, promotes apoptosis of leukemia cells by blocking this protein.

MORE THAN 30% DO NOT RESPOND TO TREATMENT

Contrary to promises, about a third of patients do not respond to Venetoclax, with resistance often developing within one year of treatment. Understanding how changes in the cell affect the drug's behavior and its accumulation in leukemic target cells would be crucial, however, this question requires further exploration.

ZOOMING IN ON ABC TRANSPORTERS

Being vital in moving substances across cell membranes, ATP-binding cassette (ABC) transporters play key roles in processes like detoxification and signaling. The research investigates these transporters, particularly ABCC1, whose high levels are linked to poor disease-free survival. Through the use of advanced CRISPR/Cas9 technology, the study probes how these transporters affect the response to Venetoclax.

ABCC1: A KEY TO ENHANCING DRUG SENSITIVITY

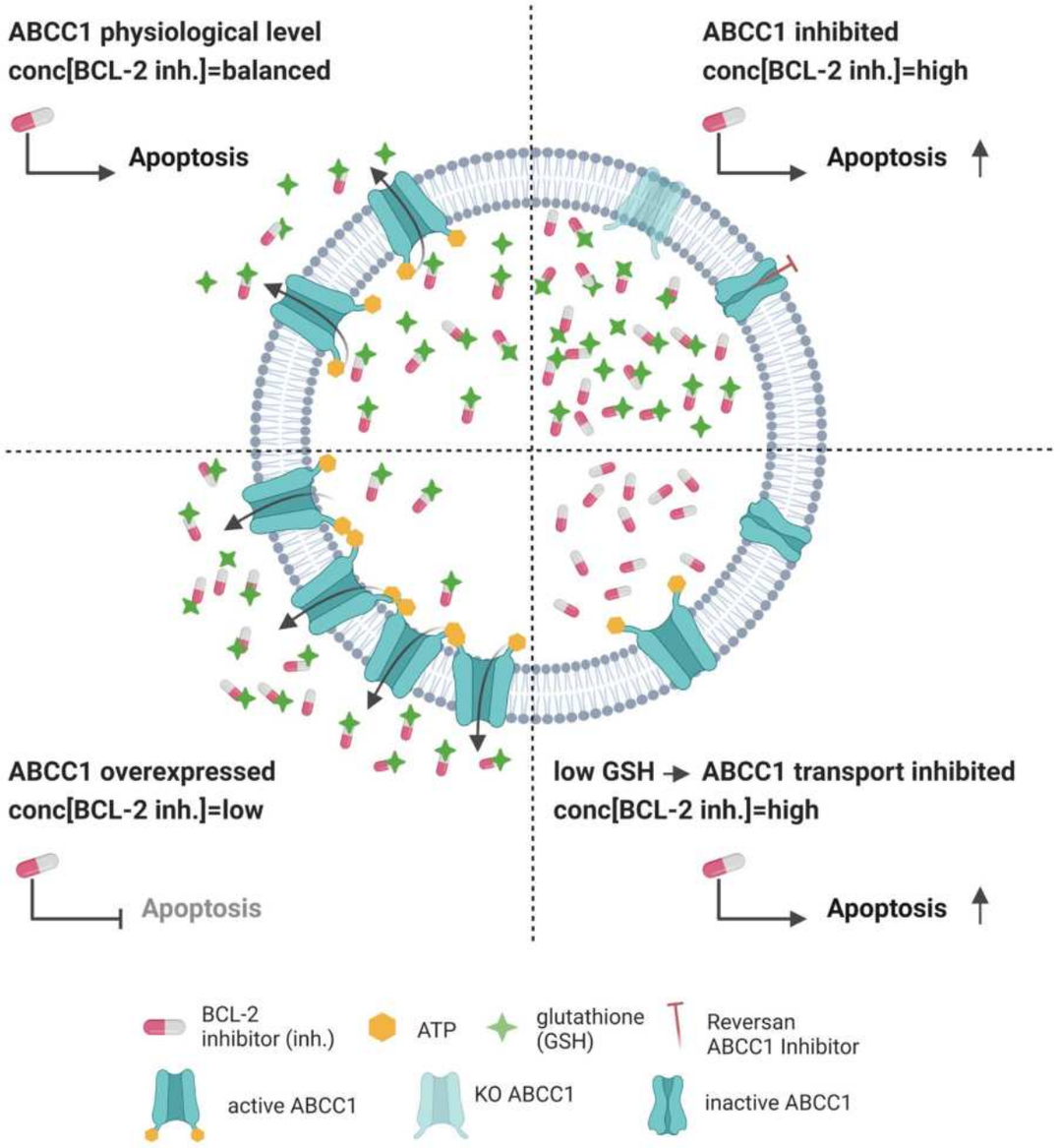
The research revealed that inhibiting or genetically inactivating ABCC1 increases AML cells' vulnerability to Venetoclax. This finding offers a potential strategy to counteract resistance in that it shows that reducing ABCC1's function can re-sensitize Venetoclax-resistant leukemia cells to the drug. Moreover, it underscores the significance of ABCC1 in the cellular mechanisms that influence the success of the treatment, suggesting that ABCC1 could serve as a biomarker to predict how AML patients will respond to Venetoclax.

THE IMPACT OF GLUTATHIONE METABOLISM

Beyond ABCC1, the study shines a light on the crucial role of glutathione metabolism in shaping drug response. Glutathione, a key antioxidant, is involved in detoxifying harmful compounds within cells via the ABCC1 transporter. The research indicates that when glutathione synthesis or its ability to bind to drugs is hindered, AML cells become more sensitive to BCL-2 inhibitors like Venetoclax. This discovery suggests that the interplay between glutathione metabolism and ABCC1 could be a target for enhancing the effectiveness of leukemia treatments, offering a dual approach to overcome resistance and improve patient outcomes.

POTENTIAL PATHS FORWARD

Although integrating ABCC1 inhibitors with BH3 mimetics is not yet an option, the study paves the way for innovative strategies such as developing new inhibitors or targeting glutathione metabolism to improve drug efficacy. These findings not only propose ABCC1 as a biomarker for treatment response but also highlight the potential of targeting such mechanisms to overcome drug resistance in AML.



PUBLICATION

Ebner J#, Schmoellerl J#, Piontek M, Manhart G, Troester S, Carter BZ, Neubauer H, Moriggl R, Szakács G, Zuber J, Köcher T, Andreeff M, Sperr WR, Valent P, **Grebien F***. ABCC1 and glutathione metabolism limit the efficacy of BCL-2 inhibitors in acute myeloid leukemia. *Nat Commun*, 2023 Sep, 14(1):5709. doi: 10.1038/s41467-023-41229-2

# equally contributed as first authors

* corresponding author

Schematic model of the effects of ABCC1 levels on intracellular levels of BCL2 inhibitors. Low expression of ABCC1 causes reduced drug efflux and increased drug activity, while high ABCC levels lead to reduced intracellular drug concentration and resistance.

Credit: St. Anna CCRI

ENHANCING AGGRESSIVENESS IN AML: THE INTERACTION BETWEEN TET2 AND CEBPA

Through exploring how *Tet2* mutations influence the severity of *Cebpa*-mutant acute myeloid leukemia (AML) by affecting *Gata2* expression, researchers from St. Anna CCRI, the University of Veterinary Medicine, Vienna, and the University of Copenhagen have provided insights into potential therapeutic targets.

AML is characterized by genetic alterations leading to the unchecked growth of immature blood cells. Studies have shown that certain genetic changes like mutations in *CEBPA*, *GATA2*, and *TET2* tend to occur together in AML, suggesting they might work in tandem to drive the disease. The specifics of how these changes interact, however, are not yet fully understood. This study combines various advanced techniques to compare AML cells with and without *Tet2* mutations alongside the *Cebpa* mutations. Such approach helps uncover a complex interaction where the loss of TET2 function, together with *CEBPA* mutations, brings about changes in the expression of the *GATA2* gene, which in turn contributes to the aggressiveness of leukemia.

MASTER TRANSCRIPTION FACTOR CEBPA

CEBPA is a gene that acts as a master regulator for the development of myeloid blood cells via the direct activation and repression of transcriptional changes. When mutated, CEBPA causes the development of AML. These mutations lead to the production of an abnormal version of the CEBPA protein, which can disrupt normal blood cell development. Patients with *CEBPA* mutations often have additional mutations in genes like *TET2* and *GATA2*, which also regulate gene expression and blood cell growth.

TET2 AND DISEASE AGGRESSIVENESS

The loss of TET2 function in *CEBPA*-mutant AML leads to a more severe disease by affecting GATA2 levels, which are critical for blood cell development. *TET2* mutations increase DNA methylation at specific sites, influencing GATA2 expression and, consequently, the behavior of leukemia cells.

TET2-CEBPA COMUTATIONS REDUCE GATA2 LEVELS

The interaction between mutant CEBPA and TET2 in reducing GATA2 levels was consistent across various experimental models and patient data, highlighting a critical pathway where TET2 mutations exert their influence in the context of *CEBPA* mutations.

THE ROLE AND REGULATORY MECHANISMS OF GATA2

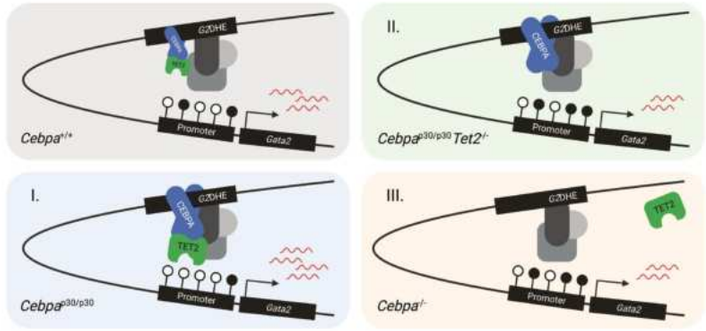
GATA2 regulation is central to CEBPA-mutant AML. The study highlights how elevated CEBPA levels, particularly the p30 variant that is only produced in cells with specific CEBPA mutations, influence GATA2 expression. This interplay between mutant CEBPA and TET2, and their effect on GATA2, provides a clearer picture of the molecular dynamics driving AML progression.

POTENTIAL TREATMENT INSIGHTS

The study suggests the potential benefit of treating *CEBPA* and *TET2* co-mutated AML with demethylating agents like 5-Azacytidine. These treatments target the methylation changes caused by *TET2* loss, potentially reversing the aggressive nature of leukemia.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Underscoring the importance of GATA2 in the context of *CEBPA*-mutant AML, the findings suggest that an understanding of these mutational interactions can guide more effective treatment strategies. The observation that TET2 deficiency sensitizes leukemia cells to certain treatments opens up new avenues to targeted therapy for AML patients with specific genetic profiles.



Model of differential *Gata2* expression as a consequence of (I) elevated CEBPA p30 due to the hypermorphic effect of CEBPA N-terminal mutations, (II) TET2 deficiency together with CEBPA p30 expression, (III) CEBPA deficiency.

Credit: Heyes et al., Nat Commun 2023, Creative Commons CC BY 4.0 license

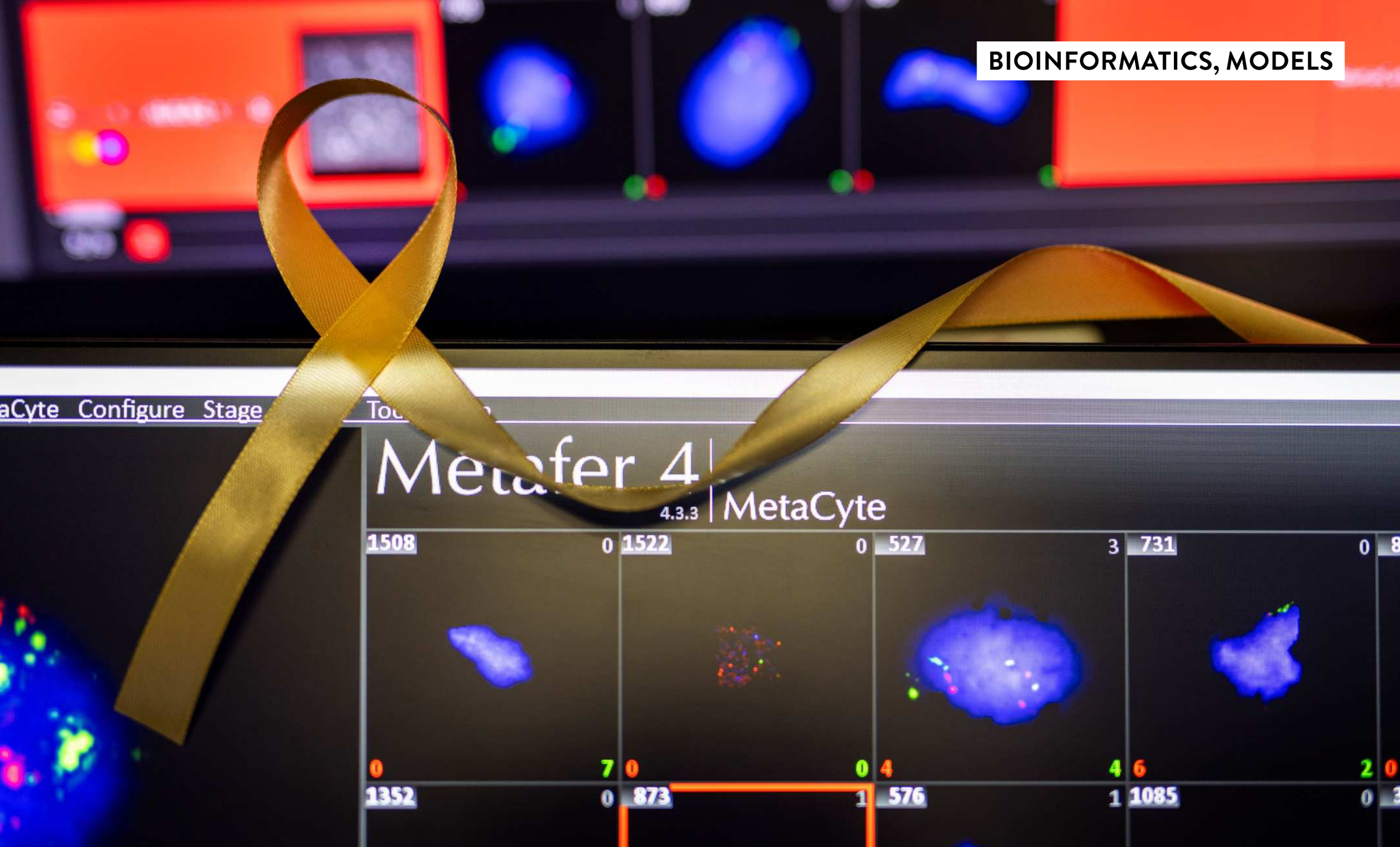
PUBLICATION

Heyes E#, Wilhelmson AS#, Wenzel A, Manhart G, Eder T, Schuster MB, Rzepa E, Pundhir S, D'Altri T, Frank AK, Gentil C, Woessmann J, Schoof EM, Meggendorfer M, Schwaller J, Haferlach T, **Grebien F**§,*, Porse BT§,*. TET2 lesions enhance the aggressiveness of CEBPA-mutant acute myeloid leukemia by rebalancing GATA2 expression. *Nat Commun*, 2023 Oct, 14(1):6185. doi: 10.1038/s41467-023-41927-x

# contributed equally

§ jointly supervised this work

* corresponding authors


aCyte Configure Stage
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FLORIAN HALBRITTER

Throughout my career, I've always found myself as a kind of oddball and newcomer:
as a computer scientist among stem cell researchers, as a stem cell researcher among epigeneticists and immunologists, and now as an epigeneticist among cancer researchers. I have learnt to be comfortable in this role and try to

approach new topics with curiosity and humility.

Working with other research groups who are experts in completely different fields allows us to efficiently dive into these new topics and to make new discoveries together.
Interdisciplinarity is essentially built into our approach. As bioinformaticians, we operate at the interface of biology, medicine, statistics, and computer science – the very fields from which my colleagues and collaboration partners hail. Our daily exchange fosters fresh perspectives and makes research even more exciting.

HALBRITTER GROUP

Developmental Cancer Genomics

We study aberrant development in pediatric cancers using computational genomics with the aim to achieve a mechanistic understanding of the underlying biology in order to inspire diagnostics and treatments.

PRINCIPAL INVESTIGATOR
Florian Halbritter

POSTDOCTORAL FELLOWS
Christoph Hafemeister
Luis F. Montano-Gutierrez
Maud Plaschka

PHD STUDENT
Mohamed R. Shoeb

GEORGE CRESSWELL

As a Computational Biology team we thrive on collaboration and knowledge exchange, particularly with 'wet lab' teams that generate new data in laboratories. This collaboration enriches our perspective on cancer biology and the intricacies of technical experiments, creating a valuable feedback loop where our analysis and their experiments inform each other. In the same way, we are dependent on similar knowledge exchange with clinicians to help focus our research on clinical questions and to tailor our results to best help patients.
In this context of continuous learning and collaboration, my advice to young researchers is to seize every opportunity to engage with the broader scientific community. Attend conferences and meetings even if you feel like you have no time. Approach people and talk about science, and if you find something interesting about someone's research, tell them.

Don´t be afraid

to reach out to people regardless of their 'status' and don't be discouraged if it doesn't go anywhere.

CRESSWELL GROUP

Cancer Evolution and Genomics

We study the evolution and mutational processes of pediatric cancers to understand why patients respond differently to treatment.

PRINCIPAL INVESTIGATOR
George D. Cresswell

INTERN
Isabella Kraus (from 10-12/2023)

CORE UNITS & PLATFORMS

CLINICAL CELL BIOLOGY & FACS CORE UNIT

In view of the continuously growing importance of cell diagnostics in the fight against cancer, in 1989 the FACS Core Unit was founded, which is closely linked to the Clinical Cell Biology Research Laboratory.

Headed by Wolfgang Paster, the FACS Core Unit offers state-of-the-art instrumentation and services for flow cytometric cell analysis and cell sorting for diagnostics for St. Anna Children's Hospital but also supports other St. Anna CCRI laboratories as well as external hospitals and research institutes.

The unique strength of flow cytometry lies in the rapid multi-parameter assessment of cells or particles in suspension. Heterogenous samples can be analyzed in detail at single cell level. The FACS Core Unit is currently running four flow cytometers for 14 to 30 parameter measurements and offers flow cytometric analysis of multicolor samples and sorting of up to 4 target populations simultaneously from a single sample.

The experienced staff provides practical and theoretical support on all issues related to the acquisition and analysis of flow cytometric data, helps with experimental design, the choice of control samples, sample preparation techniques, multicolor panel design, the choice of fluorochromes and compensation setup, instrument setup, and troubleshooting.

DEPARTMENT HEADS
René Geyergegger (until 01/2023)
Milos Hejtman (since 11/2023)
Wolfgang Paster (until 12/2023)

TECHNICIANS
Laura Hall
Anna Maria Husa (since 02/2023)
Svea Pfefferkorn
Dieter Printz
Daniela Scharner
Laura Senk (maternity leave)
Dijana Trbojevic
Elke Zipperer

BIOINFORMATICS CORE UNIT

The primary aim of the Bioinformatics Core Unit is to support research groups at St. Anna CCRI in gaining insights from complex biological data. The bioinformatics team gives support at various levels, including the development of pipelines for data processing, raw data processing with an already existing tool kit, assistance in data analysis and visualization, or a combination of these services. Each member of the unit has a specific set of skills, and together they can analyze almost any type of biological data, including:

- variant analyses in genomics data (structural variants, copy number variants, small variants, fusions in whole genome sequencing (WGS), whole exome sequencing (WES), low-coverage WGS, targeted sequencing, etc.)
- transcriptomics (RNA-Seq and single cell RNA-Seq)
- epigenomics (ChIP-Seq, ATAC-Seq, whole genome bisulfite sequencing (WGBS))
- mass spec-omics (lipidomics, metabolomics, and proteomics)
- CRISPR screens
- deep learning for high-throughput image analyses
- functional genomics (integrated analyses of the above)

Frequent discussions and knowledge exchange with research groups at St. Anna CCRI, especially the computational groups of Florian Halbritter and George Cresswell, are important aspects of the unit's work. Through sharing expertise, best practices, and resources, the bioinformaticians ensure that these collaborations are able to tackle complex biological questions and stay up to date with the standards in the bioinformatics field. In addition, the team is closely involved in maintaining their computations infrastructure, working in collaboration with the IT department.

Involvement in large-scale projects extending beyond collaboration with single groups is yet another point of pride. Participation includes programs like SUNRISE – St. Anna CCRI's children's precision oncology program. Moreover, some of the members are engaged in the European Union-wide Pre-Procurement Project – INSTAND-NGS4P. Both projects aim to improve personalized therapy for cancer patients by developing integrated and standardized workflows.

BIOINFORMATICIANS
Aleksandr Bykov (since 03/2023)
Chloe Anne Lara Casey
Celine Prakash
Maximilian von der Linde
Peter Zöscher*

* also works within POP Workframe

INNOVATIVE CANCER MODELS AND ZANDR

To study pediatric cancer, the Innovative Cancer Models group & the Zebrafish Platform Austria for preclinical drug screening (ZANDR) focuses on using the advanced imaging and drug screening capabilities of zebrafish. Zebrafish are a versatile vertebrate model organism offering remarkable live imaging abilities that allow researchers to observe cancer cells within an intact organism and monitor their interactions with other cell types in great detail. By employing genetic modeling and xeno-transplantation strategies, the facility observes tumor cell behavior at the subcellular level and investigates interactions with the tumor micro-environment. The goal is to uncover the underlying mechanisms of pediatric cancers such as Ewing sarcoma and osteosarcoma and to identify novel therapeutic strategies through innovative research and drug screening.

Collaboration is integral to ZANDR's mission. The facility works closely with research groups, industry, and institutions to enhance the under-standing of pediatric cancer and improve treatment options. Zebrafish models are particularly valuable in these collaborative efforts due to their suitability for in vivo drug screens, which facilitate the rapid testing of potential treatments in a natural bio-logical context.

The ZANDR platform is designed to screen small compounds on zebrafish disease models in an automated fashion, which significantly speeds up the research process. Recent screenings have identified promising compounds and combinations effective against Ewing sarcoma cells. The work-flows and cutting-edge technologies of ZANDR are also utilized in collaborative efforts to identify effective compounds for other tumor entities and are vital to ZANDR's success in developing inno-vative solutions for pediatric cancer patients.

HEAD OF INNOVATIVE CANCER MODELS AND ZANDR
Martin Distel

INNOVATIVE CANCER MODELS

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POSTDOCTORAL FELLOW
Hugo Poplimont (until 02/2023)

PHD STUDENTS
Sarah Grissenberger (until 02/2023)
Adam Varady

ZANDR

ZANDR OPERATOR
Caterina Sturtzel

AQUATIC TECHNICIAN
Benjamin Natha

FREELANCERS
Alexander Kaptejna
Ekin Dogan

GUEST
Fatemeh Hefzolsehhe (until 10/2023)

PUBLICATIONS

AUTOMATED TESTING OF PEDIATRIC CANCER THERAPIES

A novel high-throughput screening method allows for simultaneous testing of the efficacy of numerous drugs, enabling researchers to quickly and efficiently assess which substances are effective against certain tumors. This study provides the first guide on how to use this method for testing the sensitivity of childhood tumors to different drugs in zebrafish models.

Zebrafish xenotransplantation models, particularly through larval xenografts, are increasingly used for high-throughput phenotypic drug screening in complex in vivo environments to identify small molecules for precision oncology. In this study and in collaboration with renowned laboratories around the world, the researchers have established a previously missing standardized workflow to unlock the zebrafish xenograft's full potential.

NOVEL COMPOUND TESTING IN ZEBRAFISH MODEL

It was a collaboration with Slovenian chemists that led to the testing of a new compound in a zebrafish model for sarcomas. These tests showed that the new compound, an inhibitor of certain heat-shock proteins, works slightly better than its predecessors. Based on this finding, the researchers will now further fine-tune the compound in a planned follow-up project.

FOUNDATION OF ZEBRAFISH TUMOR MODELS

At the core of this research lies the transplantation of human tumor cells into zebrafish larvae to test cancer drugs. The transparent nature of zebrafish larvae allows for direct monitoring of tumor development, which occurs rapidly over just a few days. The precision of the transplantation process is vital for the success of tumor growth.

IMPORTANCE OF PRECISION IN TUMOR CELL TRANSPLANTATION

Due to its significant impact on tumor growth, the transplantation site within zebrafish larvae is of crucial importance. The study highlights the role of specific microenvironments, suggesting that factors conducive to tumor growth are localized to particular anatomical sites within the zebrafish.

RELIABLE ANALYSIS AT THE PUSH OF A BUTTON

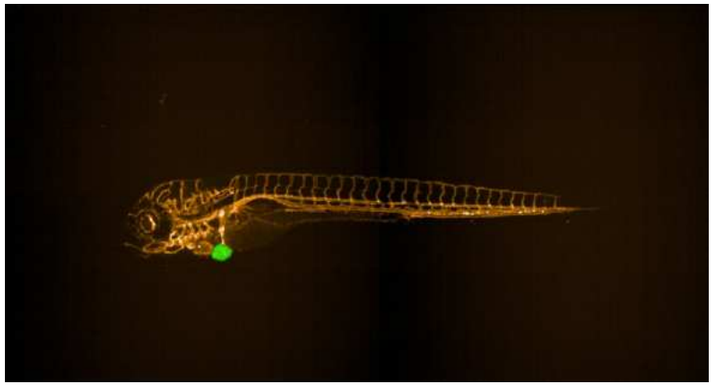
In addition to leukemias, certain soft tissue, bone, and brain tumors, the team also focused on childhood neuroblastomas. Unlike other tumors like Ewing sarcomas, neuroblastomas don't always grow equally well, so in order to assess growth, the researchers have to compare each tumor on day 1 and day 3. To this end, they have programmed an analysis workflow that detects the tumor and performs this comparison between day 1 and day 3 in an automated way. This process has been implemented for the first time worldwide by a high-content imager called Operetta CLS.

NEUROBLASTOMA RESPONSE VARIABILITY TO DRUG TESTING

Varying responses to ceritinib and temozolomide were observed across different neuroblastoma types. This underscores the value of employing zebrafish models for the rapid testing of drug combinations, particularly when other animal models are unsuitable for certain genetic types of neuroblastoma.

OPTIMIZING TUMOR CELL VISUALIZATION FOR ACCURATE RESULTS

In addressing the issue of cell staining for imaging, an initial dye was found to incorrectly mark non-cancerous cells, simulating metastasis. A subsequent adaptation to a different dye has since enabled accurate and reliable visualization of tumor cells, which is crucial for precise assessment of drug responses.



Imaging of xenotransplanted zebrafish larvae

Credit: St. Anna CCRI

PUBLICATION

Sturtzel C #, Grissenberger S #, Bozatzi P, Scheuringer E, Wenninger-Weinzierl A, Zajec Z, Dernovšek J, **Pascoal S, Gehl V**, Kutsch A, Granig A, **Rifatbegovic F**, Carre M, Lang A, Valtingojer I, Moll J, Lötsch D, Erhart F, Widhalm G, Surdez D, Delattre O, André N, Stampfl J, Tomašič T, **Taschner-Mandl S*, Distel M***. Refined high-content imaging-based phenotypic drug screening in zebrafish xenografts. *NPJ Precis Oncol*, 2023 May, 7(1):44. doi: 10.1038/s41698-023-00386-

# contributed equally

* corresponding authors

DRUG COMBINATION SHRINKS CHILDHOOD CANCER IN ZEBRAFISH

A combination therapy against childhood bone cancer has proved efficient in living organisms: When transplanted into fish larvae and treated with certain drugs, the tumor shrinks significantly or disappears completely.

Zebrafish larvae facilitate the search for drugs against aggressive childhood bone and soft tissue tumors, so-called Ewing sarcomas, as tumor development in fish larvae takes only 24 hours and can be followed simultaneously in the transparent organisms. Scientists from St. Anna CCRI have now developed a workflow that allows the semi-automated testing of up to 12 (combination) therapies against tumor cells in just one week. Three drug combinations were found to eradicate or at least significantly shrink the tumor.

ACTIVATING CELL DEATH IN TUMOR CELLS

The simultaneous treatment of fish larvae with two agents reactivating apoptosis in tumor cells proved to be highly effective: This approach leverages the inherent cellular mechanism of programmed cell death, which tumor cells often deactivate to ensure their survival. This apoptotic pathway is reactivated with the help of a specific drug combination, including an MCL-1 and a BCL-XL inhibitor. Previously tested only in cell cultures, this potent combination has now yielded compelling results in a living organism, leading to the complete disappearance of tumors in fish larvae. The study also introduces the first testing of two other combination therapies, each pairing an MCL-1 or BCL-XL inhibitor with irinotecan, which have induced significant reductions in tumor size.

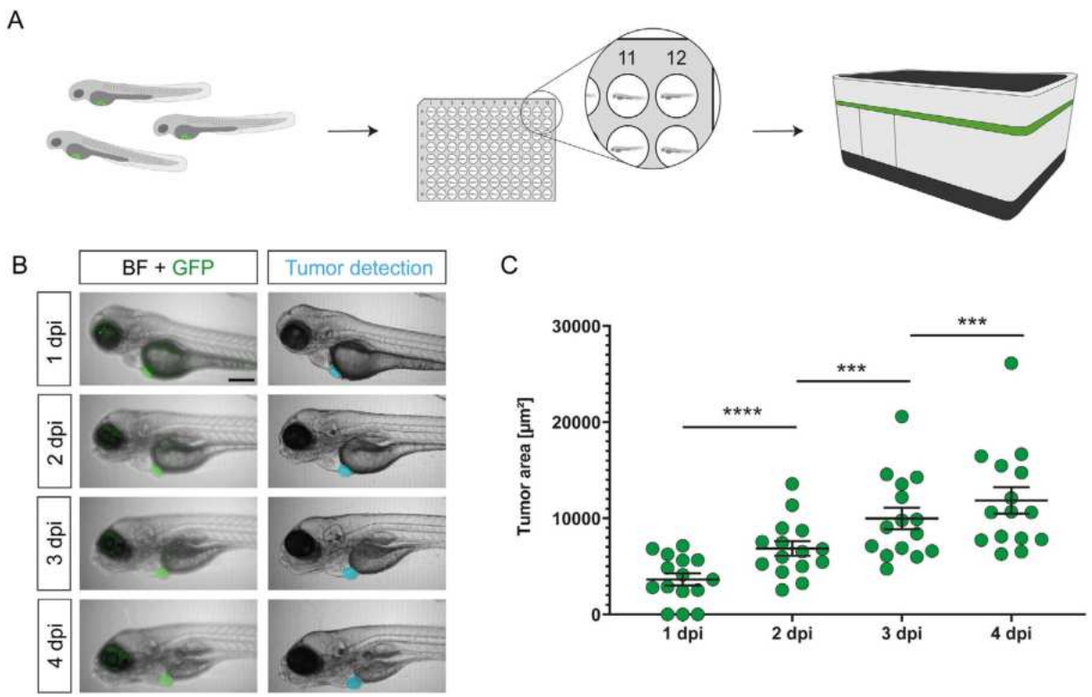
BALANCING EFFICACY AND SIDE EFFECTS

As demonstrated in further experiments, the highly effective treatment is associated with side effects. Administering the drugs sequentially was found to improve tolerance but this came at the expense of reduced efficacy. Still, there are various options to mitigate these side effects thanks to the availability of different compounds with the same mechanism of action. Drug development is a protracted process, and while intensive work is ongoing to understand the basic mechanisms, substantial progress and time are required before such treatments can be applied in pediatric settings.

FIRST STEP TOWARD NEW TREATMENT

The possibility to test numerous drugs within a living organism in such a short period is a significant step forward, however, the capacity to conduct such screenings is limited to a few laboratories worldwide. The process begins with the introduction of tumor cells, either from patients or cell lines, into fish larvae. Within 24 hours, a tumor develops, which is treated immediately. After another two days, the effects of this treatment are clearly visible.

Thanks to this rapid screening process, potential new therapies can be narrowed down at an early point, which significantly saves time.



Automated imaging workflow for xenotransplanted zebrafish larvae, including tumor detection and size quantification over four days using Operetta high-content imager

PUBLICATION

Grissenberger S, Sturtzel C, Wenninger-Weinzierl A, Radic-Sarikas B, Scheuringer E, Bierbaumer L, Etienne V, Némati F, **Pascoal S, Tötzl M, Tomazou EM**, Metzelder M, **Putz EM**, Decaudin D, Delattre O, Surdez D, **Kovar H, Halbritter F, Distel M***. High-content drug screening in zebrafish xenografts reveals high efficacy of dual MCL-1/BCL-XL inhibition against Ewing sarcoma. *Cancer Lett*, 2023 Feb, 554:216028. doi: 10.1016/j.canlet.2022.216028

* corresponding author

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Kaan Boztug, MD

Burak Caliskan, MD

Anna Cvrtak, MD

Christofer Diakos, MD

Michael Dworzak, MD

Sebastian Eder, MD

Markus Egger-Matiqi, MD

Gernot Engstler, MD

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Caroline Hutter, MD

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Christina Peters, MD

Herbert Pichler, MD

Fiona Poyer, MD

Leila Ronceray, MD

Monika Schneider, MD

Daniel Üblagger, MD

Hannah von Mersi, MD

Volker Witt, MD

Natalia Zubarovskaya, MD

PUBLICATIONS

ADDITIONAL BLINATUMOMAB THERAPY FOR INFANTS WITH *KMT2A*-REARRANGED ALL

Infants with KMT2A-rearranged acute lymphoblastic leukemia (ALL) have historically faced survival rates below 40%. A groundbreaking study by the Princess Máxima Center for Pediatric Oncology with support from St. Anna CCRI and St. Anna Children's Hospital offers hope with Blinatumomab, potentially transforming patient outcomes.

Infant acute lymphoblastic leukemia (ALL), characterized by *KMT2A* (formerly known as *MLL*) gene rearrangements and myeloid markers presence, poses a tough challenge: Only 36% of these infants live free of event for six years. Despite more intense chemotherapy, the relapse rate within two years is alarmingly high at 50%. Despite intensification of chemotherapy, outcomes have not improved in recent decades, which emphasizes the need for new therapeutic strategies regarding this aggressive form of leukemia.

FINDING THE TARGET

KMT2A is crucial in gene regulation, which, when altered, can contribute to leukemia development by controlling gene activity and hence also cell growth. In infant ALL, leukemic cells are identified as CD19+ B-cells, i.e., B-cells which express the protein CD19. By targeting exactly this protein, Blinatumomab, a drug that has proven safe and effective in prior studies, offers a focused approach to combat this cancer type.

ADDING ON TO AN ESTABLISHED PROTOCOL

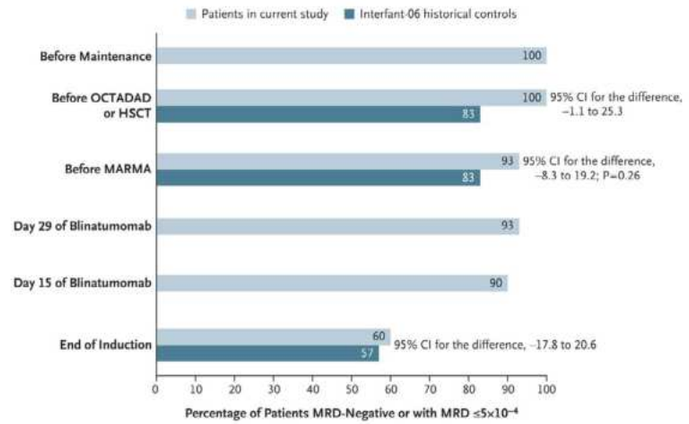
In this study, the investigators proposed a novel approach, namely, administering a sole Blinatumomab course alongside standard chemotherapy to infants with KMT2A-rearranged ALL. The trial, which included 30 participants in 20 countries, adhered to the Interfant-06 chemotherapy protocol but incorporated an extra Blinatumomab treatment course. The 28-day continuous infusion of Blinatumomab, dosed at 15 µg/m²/day, aimed to evaluate its added benefits in this specific patient cohort.

HIGHER LEVEL OF ANTILEUKEMIC ACTIVITY

All 30 children completed the Blinatumomab treatment without serious side effects. Impressively, 93% showed very low or no signs of leukemia after the treatment. The chance of staying free from leukemia for two years was 81.6%, i.e., considerably higher than the 49.4% in the previous Interfant-06 trial. Also, the overall survival rate after two years was 93.3%, significantly exceeding the earlier 65.8% seen in the prior study, thus indicating the treatment's potential benefit (Fig. 1).

LIMITATIONS DUE TO THE DISEASE'S RARITY

This study acknowledges some limitations such as the brief follow-up period. Due to the disease's rarity, and ethical concerns about withholding a potentially beneficial treatment, a traditional control group was not feasible. Instead, Blinatumomab was added to the existing Interfant-06 protocol in a single-arm design. This approach underscores the necessity for collaborative efforts in researching rare diseases, in particuar for collective action beyond individual institutions to advance understanding and treatment options.



MRD assessed using PCR targeting KMT2A and immunoglobulin/TCR gene rearrangements, comparing MRD negativity or levels below 5x10^-4 in study participants versus historical Interfant-06 controls, with 95% CIs and Fisher's exact test results for MRD response evaluation at various study time points.

PUBLICATION

Van der Sluis IM*, de Lorenzo P, Kotecha RS, **Attarbaschi A**, Escherich G, Nysom K, Stary J, Ferster A, Brethon B, Locatelli F, Schrappe M, Scholte-van Houtem PE, Valsecchi MG, Pieters R. Blinatumomab Added to Chemotherapy in Infant Lymphoblastic Leukemia. *N Engl J Med*, 2023 Apr, 388(17):1572-1581. doi: 10.1056/NEJMoa2214171

* corresponding author

EXPLORING IMPROVED TREATMENTS FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

In a big collaborative effort, researchers from St. Anna Children's Hospital and St. Anna CCRI, Medical University of Vienna, Medical School Hannover, Christian-Albrechts-University Kiel and University Medical Center Schleswig-Holstein, and the Leukaemia Research Cytogenetics Group at Newcastle University are in the pursuit of advancing treatment for noninfant acute lymphoblastic leukemia (ALL) with 11q23/*KMT2A* rearrangements. Their study investigates key prognostic factors and the efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Modern therapies have significantly enhanced survival rates in childhood ALL, but challenges remain, particularly for cases with 11q23/*KMT2A* rearrangements. This study aims to clarify the prognostic implications of these rearrangements and to assess the potential benefits of allo-HSCT in first remission, offering a new angle on treatment strategies for this subgroup of ALL patients.

DATA OF 629 YOUNG PATIENTS ANALYZED

The study collected data from 17 international groups, focusing on patients aged 1-18 years and treated between 1995 and 2010. Through detailed analysis, researchers sought to understand the impact of 11q23/*KMT2A* rearrangements on treatment outcomes and to explore how allo-HSCT might influence these patients' survival and relapse rates.

LOWER MRD LEVELS COME WITH BETTER PROGNOSIS

The research demonstrated that minimal residual disease (MRD) levels at the end of induction therapy are a crucial prognostic factor. Patients with lower MRD levels showed better event-free survival, which highlights the importance of early response to treatment in predicting long-term outcomes.

NO ONE-SIZE-FITS-ALL APPROACH

Interestingly, the study found no significant improvement in event-free survival or overall survival with the use of allo-HSCT in first remission compared to chemotherapy alone. Thus suggesting that allo-HSCT might not be universally beneficial for all patients with 11q23/*KMT2A* rearranged ALL, the finding emphasizes the need for tailored treatment approaches. The results had direct consequences for the upcoming ALL protocols as patients with *KMT2A-AFF1*+ ALL, if they respond well to induction therapy, will no longer have an indication for allo-HSCT in first remission.

Figure 3A

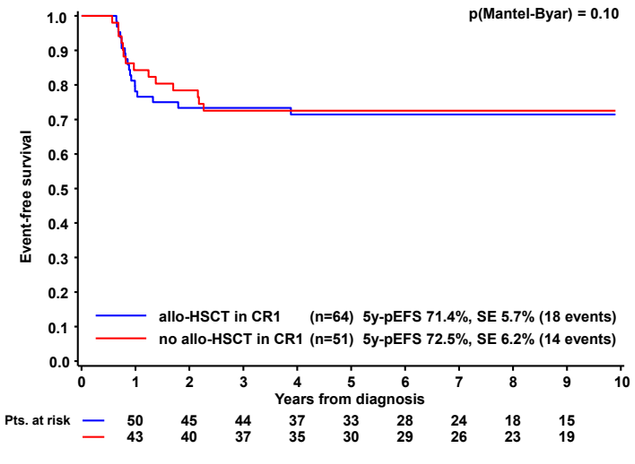


Illustration of the impact of MRD levels at the end of induction on the 5-year event-free survival and overall survival for patients with 11q23/*KMT2A*-rearranged T-ALL and B-ALL, emphasizing the prognostic value of early treatment response.

Credit: St. Anna CCRI

PUBLICATION

Attarbaschi A#,*, Möricke A#, Harrison CJ#, Mann G, Baruchel A, De Moerloose B, Conter V, Devidas M, Elitzur S, Escherich G, Hunger SP, Horibe K, Manabe A, Loh ML, Pieters R, Schmiegelow K, Silverman LB, Stary J, Vora A, Pui CH, Schrappe M*, Zimmermann M*; Ponte-di-Legno Childhood Acute Lymphoblastic Leukemia Working Group. Outcomes of Childhood Noninfant Acute Lymphoblastic Leukemia With 11q23/KMT2A Rearrangements in a Modern Therapy Era: A Retrospective International Study. *J Clin Oncol*, 2023 Mar, 41(7):1404-1422. doi: 10.1200/JCO.22.01297

# A.A., A.M. C.J.H. contributed equally as first authors

# M.S. and M.Z. contributed equally as last authors

* corresponding author

TISAGENLECLEUCEL VS. STANDARD CARE IN PEDIATRIC RELAPSED B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

In this study, researchers from Charité University Hospital Berlin, St. Anna CCRI, and St. Anna Children's Hospital have compared the efficacy of tisagenlecleucel, a chimeric antigen receptor T cell therapy, with historical standard of care (SOC) in pediatric and young adult patients suffering from relapsed or refractory acute lymphoblastic leukemia (r/r ALL).

The absence of randomized controlled trials (RCTs) comparing tisagenlecleucel with standard of care (SOC) prompted researchers to conduct a comprehensive analysis using patient-level data from three tisagenlecleucel studies and three disease registries in Germany and Austria. The data analysis, which used sophisticated statistical methods to adjust for relevant confounders, revealed favorable outcomes for tisagenlecleucel across all examined endpoints, including overall survival (OS) and overall response rate (ORR). Acute lymphoblastic leukemia (ALL) poses significant challenges, particularly for patients with relapsed or refractory disease. While contemporary chemotherapy regimens and allogeneic stem cell transplantation yield improved overall survival rates, a subset of patients face a dismal prognosis necessitating innovative treatment strategies.

A GLIMMER OF HOPE

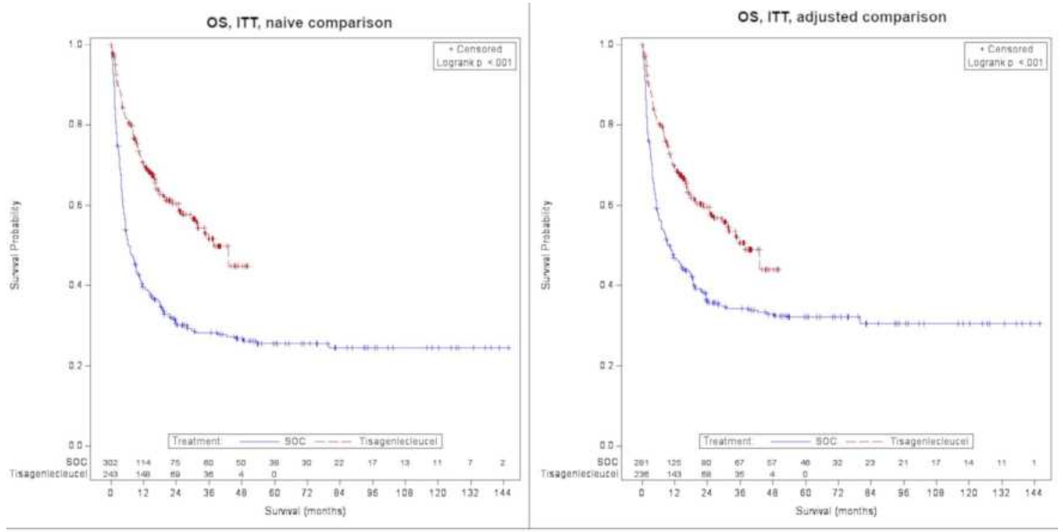
The approval of tisagenlecleucel in 2018 provided a glimmer of hope for patients with r/r ALL, which are those patients with refractory disease or advanced relapse. The pivotal ELIANA trial, along with supportive open-label trials, demonstrated promising results for this novel therapy, paving the way for its adoption in clinical practice.

Despite the lack of comparative evidence from RCTs due to the rarity and severity of the disease, this study utilized real-world data from registries to conduct a rigorous comparative analysis. By applying patient-level adjustment and sophisticated statistical techniques, researchers were able to demonstrate the superiority of tisagenlecleucel over historical SOC in terms of OS and ORR, offering new insights into the treatment landscape for r/r ALL.

THE VALUE OF LEVERAGING REAL WORLD DATA

As personalized medicine continues to evolve, the importance of non-randomized comparative studies is becoming increasingly apparent, particularly in the context of rare diseases where conducting RCTs presents ethical and logistical challenges. This study underscores the value of using real-world data to inform treatment decisions and improve outcomes for patients with life-threatening conditions.

Moving forward, these findings, highlighting the potential of tisagenlecleucel as a transformative therapy for pediatric and young adult patients with r/r ALL, have significant implications for clinicians, regulators, and healthcare policymakers. As research in this field progresses, the quest for innovative treatments and improved outcomes for patients with hematologic malignancies remains a top priority.



Survival probability (95%CI)	Naive comparison	
	Tisagenlecleucel	SOC
12 months	70.22 (63.80 - 75.72)	39.69 (34.11 - 45.20)
24 months	60.37 (53.04 - 66.92)	30.51 (25.28 - 35.88)
36 months	51.62 (43.07 - 59.50)	28.25 (23.10 - 33.62)
48 months	44.91 (32.59 - 56.46)	26.75 (21.63 - 32.12)

Survival probability (95%CI)	Adjusted comparison	
	Tisagenlecleucel	SOC
12 months	69.44 (62.90 - 75.06)	46.96 (40.95 - 52.74)
24 months	59.49 (52.08 - 66.13)	36.16 (30.38 - 41.95)
36 months	50.70 (42.11 - 58.65)	34.20 (28.45 - 40.01)
48 months	44.05 (31.88 - 55.56)	32.86 (27.12 - 38.70)

Credit: Stacklberg et al., Leukemia 2023, Creative Commons CC BY 4.0 license

The figure shows the outcome of different approaches.

PUBLICATION

V Stackelberg A, Jäschke K, Jousseaume E, Templin C, Jeratsch U, Kosmides D, Steffen I, Gökbuget N*, **Peters C***. Tisagenlecleucel vs. historical standard of care in children and young adult patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. *Leukemia*, 2023 Dec, 37(12):2346-2355. doi: 10.1038/s41375-023-02042-4.

* contributed equally

FINANCIAL REPORT

GUIDELINES FOR THE USE OF DONATIONS

St. Anna Children's Cancer Research Institute is mainly financed by private donations. For the operation of the research institute; more than ten million euros are required annually, whereas the association has no basic funding from the public sector. Additional funds are acquired through competitive project grants from recognized national and international agencies.

We are committed to our donors to use the funds entrusted economically and efficiently. The annual financial statement is prepared in accordance with the provisions of § 22 of the Federal Act on Associations. As a large association, the financial management as well as the annual financial statements of the association are audited by a public accountant who provides an independent auditor's certificate. Thus, proper and appropriate handling and allocation of the donations in alignment with the statutes can be assured.

SEAL OF APPROVAL FOR DONATIONS AND TAX DEDUCTIBILITY

Since 2002, St. Anna Children's Cancer Research Institute has been one of the first organizations in Austria to receive the seal of approval for donations from the Chamber of Public Accountants and Tax Advisors. For the annual re-awarding, an auditor carries out an additional audit to the one already provided for the annual accounts, scrutinizing for transparency and proper use of funds in accordance with the strict guidelines of the Donation Quality Certificate. On the basis of a notice (Bescheid) issued by the Federal Ministry of Finance, St. Anna Children's Cancer Research Institute is classed as a tax-privileged group of recipients, so donations are tax-deductible from either private or corporate income tax.

QUALITY ASSURANCE OF SCIENTIFIC WORK

The research institute has a Scientific Advisory Board – a committee of external experts – with the task of continuously evaluating the scientific work and advising the Institute's management. In addition, new scientific projects are regularly submitted to renowned national and international research funding bodies and research results are published in internationally recognized scientific journals. In addition, an objective assessment of the scientific performance by recognized external experts in the field takes place at regular intervals.

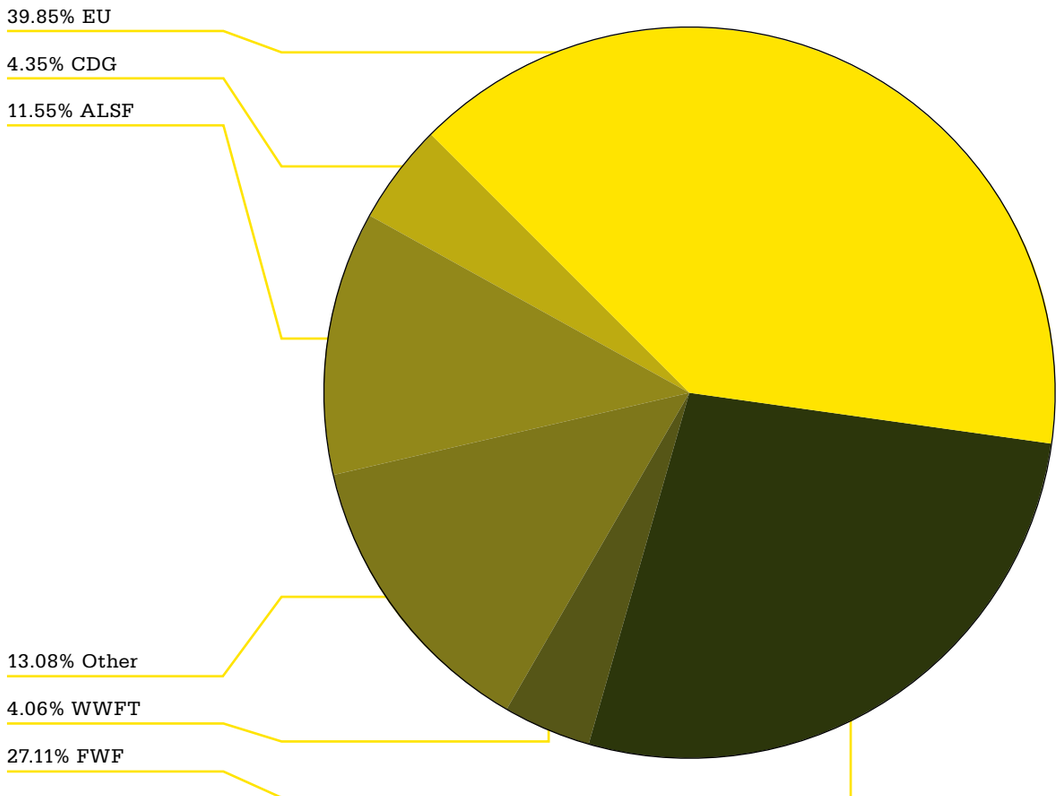
SOURCE OF FUNDS

		2022	2023
I.	Donations		
	a) undedicated donations	€ 0.00	€ 0.00
	b) dedicated donations	€ 15,034,720.61	€ 11,357,359.07
II.	Membership fees	€ 660.00	€ 660.00
III.	Operating income		
	a) operating income from public funds	€ 0.00	€ 0.00
	b) other operating income	€ 1,268,316.01	€ 1,647,800.81
IV.	Public subventions and subsidies	€ 0.00	€ 0.00
V.	Other income		
	a) asset management	€ 1,313.86	€ 8,601.66
	b) other income not included in positions I to IV	€ 0.00	€ 0.00
VI.	Revenue from release of donations and subsidies not yet used for the intended purpose	€ 0.00	€ 2,003,579.52
VII.	Release of reserves	€ 0.00	€ 0.00
VIII.	Annual loss	€ 0.00	€ 0.00
TOTAL		**€ 16,305,010.48**	**€ 15,018,001.06**

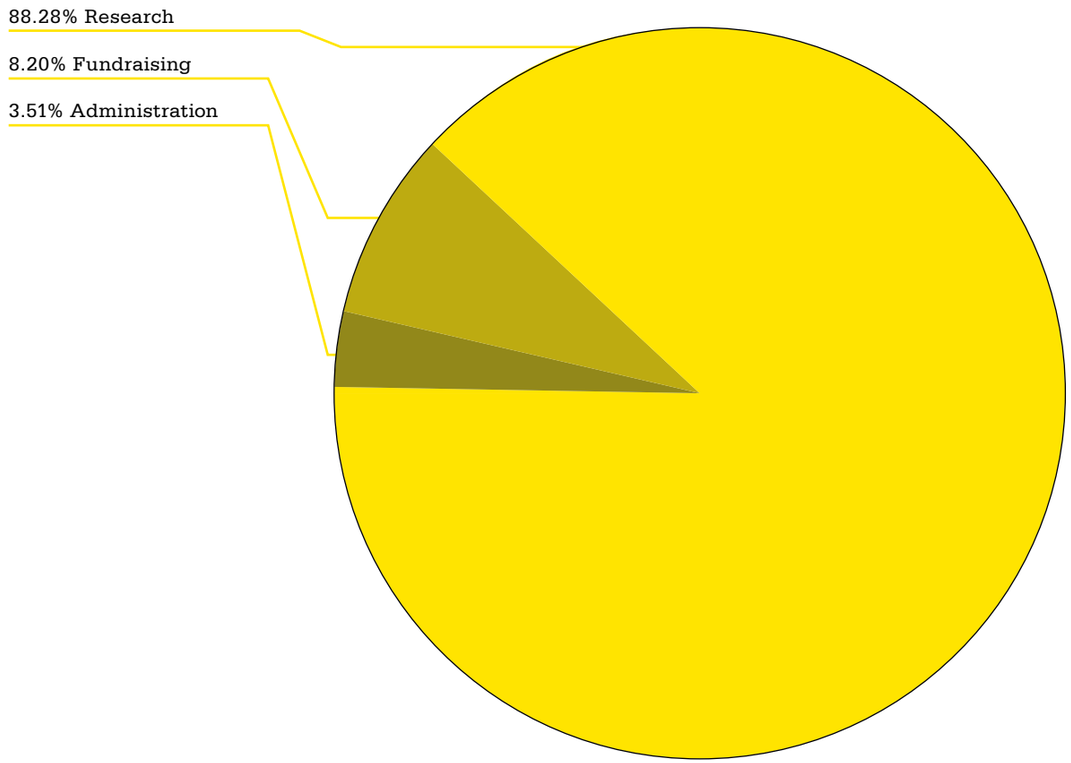
USE OF FUNDS

		2022	2023
I.	Expenditures for statutorily defined purposes	€ 12,354,262.31	€ 13,257,849.14
II.	Fundraising	€ 1,163,672.22	€ 1,232,115.14
III.	Administration	€ 575,372.57	€ 527,336.67
IV.	Other expenditures not included in posititons I to III	€ 286,215.00	€ 700.11
V.	Donations and subsidies not yet used for the intended purpose (allocation to liabilities)	€ 1,925,488.38	€ 0.00
VI.	Allocation of funds to reserves	€ 0.00	€ 0.00
VII.	Annual profit	€ 0.00	€ 0.00
TOTAL		**€ 16,305,010.48**	**€ 15,018,001.06**

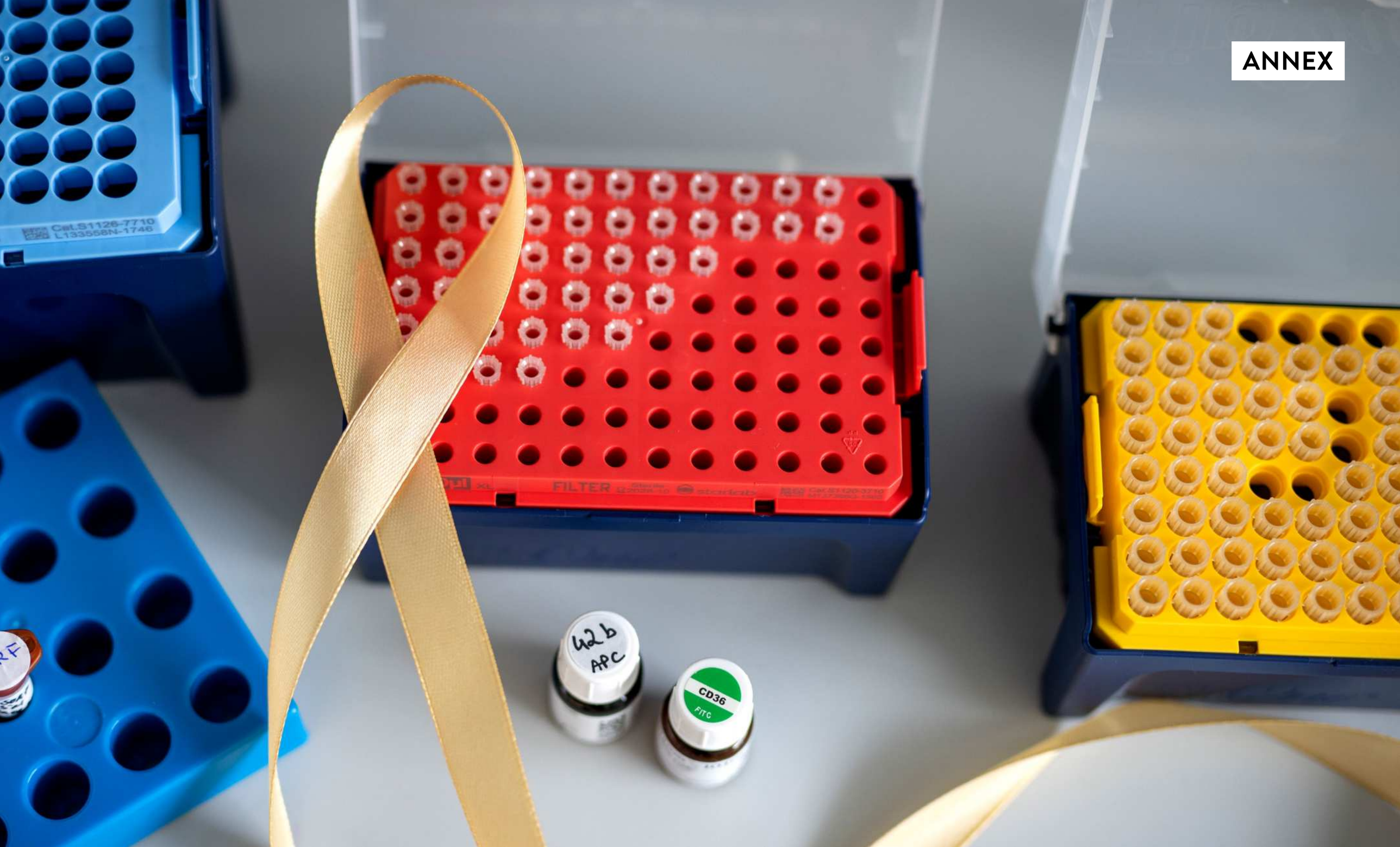
COMPETITIVE RESEARCH GRANTS 2023



ALLOCATION OF FUNDS 2023



ANNEX



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Executive Assistant: Theresa Kröswagn

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Stephanie Weber (since 07/2023)

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Milos Hejtman (Deputy)
Commercial & Managing Director
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Marie Christin Meta
Julia Richter
* Heading Clinical Genetcs at Labdia (Fachärztin für Humangenetik)

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Sabrina Haslinger
Andrea Inthal
Margit König
Soren Mai
Bettina Nocker
Maya Plank
Michaela Pregesbauer
Eva Winkler*
Sven Wohlmacher*

* work in both groups

SCIENTIFIC ADVISORY BOARD

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Shai Izraeli:
Director, Department of Pediatric Hematology / Oncology Schneider Children's Medical Center, Israel

Scientific Advisory Board Meeting 2023

INTERNATIONAL AND NATIONAL GRANTS 2023

INTERNATIONAL GRANTS 2023

European Reference Network on Paediatric Oncology Y7-Y10 (ERN-PaedCan)
CCRI responsible Principal Investigator and Coordinator: Ruth Ladenstein
Grant from the European Union, EU4Health Work Programme, ID – 101155946
Duration: 01/10/2023 - 30/09/2027

Developmentally programmed pediatric sarcomas: a versatile platform for drug discovery and molecular precision medicine (SARCOMAkids)
CCRI responsible Principal Investigator and Awardee: Eleni Tomazou
Grant from the European Commission, European Research Council Consolidator Grant (ERC-CoG), ID - 101087883
Duration: 01/09/2023 - 31/08/2028

International Study for Treatment of Childhood Relapsed ALL 2020 (IntReALL 2020)
CCRI responsible Principal Investigator: Ruth Ladenstein
Additional CCRI-linked Collaborators: Andishe Attarbaschi (SAK)
Coordinator: Arend von Stackelberg (Charité, Germany)
Grant from the European Commission, Horizon Europe, ID – 101104582
Duration: 01/05/2023 - 30/04/2028

Cancer Survivor Smart Card
CCRI responsible Principal Investigator: Ruth Ladenstein
Coordinator: European Cancer Organisation (Belgium)
Grant from the EU4Health Programme 2021-2027, ID – 101080048
Duration: 01/01/2023 - 31/12/2024

Molecular dissection of the role of an RNA-binding protein in human immune homeostasis
CCRI responsible researcher and Awardee: Cheryl van de Wetering (Supervisor: Kaan Bozutg)
Grant from the Peter und Traudl Engelhorn-Stiftung
Duration: 01/01/2023 – 31/12/2024

High-resolution dissection of non-coding determinants of disease (B-ALLeles)
CCRI responsible researcher and Awardee: Ana Patricia Kutschat (Supervisor: Davide Seruggia)
Grant from the European Union, HE- Marie Sklodowska-Curie Action Postdoctoral Fellowship, ID – 101061151
Duration: 01/11/2022 - 31/10/2024

The immunopeptidome of paediatric high-grade osteosarcoma
CCRI responsible Head of Facility: Wolfgang Paster
Grant from the Medical Research Charity - Myrovlytis Trust, ID - MT22_1
Duration: 01/08/2022 – 31/07/2023

Towards an UNIque approach for artificial intelligence data-driven solutions to fight Childhood cAncer FOR Europe (UNICA4EU)
CCRI responsible Principal Investigator: Ruth Ladenstein
Coordinator: SIOPE, Belgium
Grant from the European Union, Pilot Projects and Preparatory Actions (PPPA), ID – LC-01815952 / 101052609
Duration: 01/07/2022 to 29/02/2024

European Reference Network on Paediatric Oncology – Year 6&7
CCRI responsible Principal Investigator and Coordinator: Ruth Ladenstein
Grant from the European Union, EU4Health Work Programme, ID – 101085543
Duration: 01/03/2022 - 31/08/2023

Modeling Langerhans Cell Histiocytosis with patient derived iPSCs
CCRI responsible researcher and Awardee: Giulio Abagnale (Supervisor: Caroline Hutter)
Grant from the Histiocytosis Association (USA)
Duration: 01/01/2022 – 31/12/2023

European Reference Network on Paediatric Cancer Connecting Facility-3
CCRI responsible Principal Investigator: Ruth Ladenstein
Grant from the European Union, CEF Grant Agreement ID – INEA/CEF/ICT/A2020/2393583
Duration: 01/09/2021 to 31/08/2023

Functional Interrogation of Non-coding DNA Sequences in leukemia development and drug resistance (FIND-seq)
CCRI responsible Principal Investigator and Awardee: Davide Seruggia
Grant from the European Union, H2020 ERC Starting Grant, ID - 947803
Duration: 01/03/2021 - 28/02/2026

Tracking Ewing sarcoma origin by developmental and trans-species genomics (ORIGIN)
CCRI responsible Principal Investigator and Coordinator: Heinrich Kovar
Additional CCRI Collaborators: Martin Distel, Florian Halbritter
Grant from Alex's Lemonade Stand Foundation (ALSF), Crazy 8 Initiative Award Program
Duration: 01/03/2021 - 28/02/2025

European Rare Disease Research Coordination and Support Action (ERICA)
CCRI responsible Principal Investigator: Ruth Ladenstein
Coordinator: Alberto Pereira (Leiden University Medical Center, the Netherlands)
Grant from the European Union, H2020 Grant Agreement ID – 964908
Duration: 01/03/2021 to 28/02/2025

PanCare studies of the scale-up and implementation of the digital Survivorship Passport to improve people-centred care for childhood cancer survivors (PanCareSurPass)
CCRI responsible Principal Investigator: Ruth Ladenstein
Coordinator: Desiree Grabow (Universitätsmedizin Mainz, Germany)
Grant from the European Union, H2020, ID – 899999
Duration: 01/03/2021 to 28/02/2025

Twinning research and education to improve survival in childhood solid tumors in Lithuania (TREL)
CCRI responsible Principal Investigator: Ruth Ladenstein
Additional CCRI Collaborator: Sabine Taschner-Mandl
Coordinator: Jelena Rascon (Vilnius University Hospital Santaros Klinikos, Lithuania)
H2020 Grant Agreement ID – 952438
Duration: 01/01/2021 - 31/12/2023

Validation of Actionable Genomic Aberrations in a Paediatric Oncology Network for Doctorate students (VAGABOND)
CCRI responsible Principal Investigator: Heinrich Kovar
Coordinator: Jan Molenaar (Prinses Máxima Centrum, the Netherlands)
Grant from the European Union, H2020 - MSCA Innovative Training Networks, ID – 956285
Duration: 01/12/2020 - 30/11/2024

Integrated and standardized NGS workflows for Personalised therapy (INSTAND-NGS4P)
CCRI responsible Principal Investigators: Ruth Ladenstein and Kaan Boztug
Coordinator: Kurt Zatloukal (Medical University Graz)
Grant from the European Union, H2020 – Innovation Procurement, ID – 874719
Duration: 01/01/2020 - 31/05/2025

Charting key molecules and mechanisms of human immune Dysregulation (iDysChart)
CCRI responsible Principal Investigator and Awardee: Kaan Boztug
Grant from the European Commission, European Research Council Consolidator Grant (ERC-CoG), ID - 820074
Duration: 01/06/2019 – 31/05/2025

Childhood Leukemia: Overcoming distance between South America and Europe Regions (CLOSER)
CCRI responsible Principal Investigator: Sabine Strehl
Coordinator: Mireia Camos (Hospital Sant Joan de Déu de Barcelona, Spain)
Grant from the European Union, H2020, ID – 825749
Duration: 01/01/2019 - 31/03/2024

European Joint Programme on Rare Diseases (EJP RD)
CCRI responsible Principal Investigator: Ruth Ladenstein
Coordinator: Daria Julkowska (Inserm, France)
Grant from the European Union, H2020, ID – 825575
Duration: 01/01/2019 – 31/08/2024

Comprehensive heatmap for TKI-resistance of mutations in BCR-ABL1 kinase domain
CCRI responsible Principal Investigator: Thomas Lion
Investigator initiated research grant from Incyte Inc.
Duration: 11/03/2019 – 2026

PRedictive In-silico Multiscale Analytics (PRIMAGE)
CCRI responsible Principal Investigator: Ruth Ladenstein
Coordinator: Luis Martí-Bonmatí (HULAFE, Spain)
Grant from the European Union, H2020, ID – 826494
Duration: 01/12/2018 to 31/05/2023

ITCC Pediatric Preclinical POC Platform (ITCCP4)
CCRI responsible Principal Investigator: Heinrich Kovar
Coordinator: Stefan Pfister (Deutsches Krebsforschungszentrum DKFZ, Germany)
Grant from the Innovative Medicines Initiative (IMI), ID – 116064
Duration: 01/01/2017 to 31/12/2023

NATIONAL GRANTS 2023

PROMISE – Proteostasis, Metabolism and a Novel Immunodeficiency Syndrome
CCRI responsible Project Lead: Michael Kraakman (Kaan Boztug group)
Grant from the Austrian Science Fund (FWF), Principal Investigator Project
DOI: 10.55776/PAT4663523
Duration: 01/12/2023 – 30/11/2026

Artificial intelligence for diagnostics of ALT-positive cancer (AI4CAN)
CCRI responsible Principal Investigator: Sabine Taschner-Mandl
Grant from the Vienna Science and Technology Fund (WWTF), NEXT 2022, ID – NXT22-009
Duration: 01/09/2023 – 28/02/2025

Disease-associated variants at ARID5B
CCRI responsible Principal Investigator: Davide Seruggia
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P36302
Duration: 01/09/2023 – 31/08/2026

RiboPOP
CCRI responsible Project Lead: Irinka Castanon (Kaan Boztug group)
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P36334
Duration 01/02/2023 – 31/01/2026

Lost in translation
CCRI responsible Principal Investigator: Kaan Boztug
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P36548
Duration 01/02/2023 – 31/01/2026

Iterative programming of blood cells (ML2Cell)
CCRI responsible Principal Investigator: Florian Halbritter
Grant from the Austrian Science Fund (FWF), TAI-1000 Ideas Program
DOI: 10.55776/TAI732
Duration: 01/01/2023 – 31/07/2024

Harnessing vulnerabilities at SAGA in MYC-driven cancer
CCRI responsible Principal Investigator: Davide Seruggia
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P36069
Duration: 01/01/2023 – 31/12/2025

Development of Hsp90 C-terminal domain inhibitors for the treatment of pediatric sarcomas
CCRI responsible Head of Facility and Coordinator: Martin Distel
Grant from the Austria's Agency for Education and Internationalisation (OEAD), ID – SI 29/2023
Duration: 01/01/2023 – 31/12/2024

Targeting Tumor Metabolism (TATUM)
CCRI responsible Project Lead: Artem Kalinichenko (Kaan Boztug group)
Grant from the Austrian Science Fund (FWF), TAI-1000 Ideas Program
DOI: 10.55776/TAI815
Duration: 01/11/2022 – 31/10/2024

Linking ex-vivo chemosensitivity, treatment and pathway activations for a deeper understanding of pediatric AML (ExTrAct-AML)
CCRI responsible Principal Investigator and Coordinator: Kaan Boztug
Additional project partners: Giulio Superti-Furga (CeMM) and Michael Dworzak (CCRI)
Grant from the Austrian Science Fund (FWF), Programme Clinical Research
DOI: 10.55776/KLI1056
Duration: 01/10/2022 – 30/09/2024

Regulating CAR T cells with a safe and naturally occurring drug
CCRI responsible researcher and Awardee: Elise Sylvander (Supervisor: Manfred Lehner)
Grant from the Austria Academy of Sciences (ÖAW), DOC fellowship, ID – 26323
Duration: 01/07/2022 to 01/07/2024

Exploration of lung metastases in pediatric cancer through single-cell analysis and 3d modelling (MetLung)
CCRI responsible Principal Investigator and Coordinator: Heinrich Kovar
Additional CCRI Collaborator: Florian Halbritter
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P35353
Duration: 02/05/2022 – 01/05/2025

MAPMET – Mapping metastatic cancer by multi-modal imaging
CCRI responsible Principal Investigator: Sabine Taschner-Mandl
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P35841
Duration: 01/05/2022 – 30/04/2026

Cracking the ribosome code of drug resistance in sarcomas
CCRI responsible Principal Investigator: Eleni Tomazou
Grant from the Austrian Science Fund (FWF), TAI-1000 Ideas Program
DOI: 10.55776/TAI592
Duration: 01/01/2022 to 31/12/2024

Interplay of fusion genes and cellular context in sarcoma
CCRI responsible Principal Investigator: Eleni Tomazou
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P34958
Duration: 01/10/2021 – 31/03/2025

Comprehensive cell contact tracing (C3T)
CCRI responsible Principal Investigator: Florian Halbritter
Additional CCRI Principal Investigators: Martin Distel
Grant from the Austrian Science Fund (FWF), TAI-1000 Ideas Program, ID – TAI 454
Duration: 01/09/2021 to 31/12/2022

Validation of a liquid biopsy based molecular diagnostic toolkit for pediatric sarcomas
CCRI responsible Principal Investigator: Eleni Tomazou
Grant from the Vienna Science and Technology Fund (WWTF), Life Sciences 2020, ID – LS20-045
Duration: 01/09/2021 – 31/08/2025

Characterization of bacterial-fungal interactions: a basis for discovery of microbial markers (BacFun)
CCRI responsible Principal Investigator: Thomas Lion
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P34152
Duration: 01/08/2021 – 31/07/2024

How do leukemic cells escape natural killer cell-mediated surveillance?
CCRI responsible researcher and Awardee: Michelle Buri (Supervisor: Eva König)
Grant from the Austria Academy of Sciences (ÖAW), DOC fellowship, ID – 25905
Duration: 01/08/2021 to 31/08/2024

Establishing light-mediated clonal cancer models to investigate tumor initiation
CCRI responsible researcher and Awardee: Adam Varady (Supervisor: Martin Distel)
Grant from the Austria Academy of Sciences (ÖAW), DOC fellowship, ID – 25931
Duration: 01/08/2021 to 31/01/2024

Identification of a key molecular coordinator of the exocytosis machinery and cytoskeletal dynamics essential for human lymphocyte cytotoxicity
CCRI responsible Principal Investigator: Kaan Boztug
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P34834
Duration 01/07/2021 – 30/06/2024

EWS-FLI1 fluctuation in Ewing sarcome
CCRI responsible Principal Investigator: Heinrich Kovar
Grant from the Austrian Science Fund (FWF), Stand-Alone Project
DOI: 10.55776/P34341
Duration 01/04/2021 – 31/03/2025

Decontamination of sensitive materials using cold atmospheric plasma technology
CCRI responsible Principal Investigator: Thomas Lion
Grant from the Austrian Science Fund (FWF), CEUS
DOI: 10.55776/I5293
Duration: 01/04/2021 – 30/09/2024

Crossroads of immunometabolism and human deficiency
CCRI responsible researcher and Awardee: Michael Kraakman (Supervisor: Kaan Boztug)
Grant from the Austrian Science Fund (FWF), Lise Meitner Program, ID - M 3013
Duration: 01/01/2021 to 28/02/2023

Automated minimal residual disease assessment in childhood acute myeloid leukemia
CCRI responsible researcher: Margarita Maurer-Granofszky (Supervisor: Michael Dworzak)
Grant from the Vienna Business Agency, Call Science to Products 2019, ID – 2841342
Duration: 15/03/2020 – 30/09/2024

CD Laboratory for "Next generation CAR-T cells"
Head of CD Laboratory and Coordinator: Manfred Lehner
Grant from the Christian Doppler Association, Christian Doppler Lab, ID – 345
Duration: 01/11/2019 to 31/10/2026

Find tumor immune evasion strategies by cellular barcoding
CCRI responsible Principal Investigator: Eva König
Grant from the Austrian Science Fund (FWF), Stand Alone Project, ID - P 32001
Duration: 15/03/2019 to 14/09/2023

Ultra-high-risk pediatric cancer – combinatorial drivers and therapeutic targets for precision medicine
CCRI responsible Principal Investigator and Coordinator: Sabine Taschner-Mandl
Additional CCRI Collaborators: Ruth Ladenstein and Martin Distel
Grant from the Vienna Science and Technology Fund (WWTF), Life Sciences 2018, ID – LS18-111
Duration: 01/03/2019 – 28/02/2024

Characterizing and targeting the Ewing sarcoma microenvironment to overcome resistance to therapy
CCRI responsible Principal Investigator and Coordinator: Eleni Tomazou
Grant from the Vienna Science and Technology Fund (WWTF), Life Sciences 2018, ID – LS18-049
Duration: 01/03/2019 to 28/02/2023

ACKNOWLEDGEMENTS

- Abbott Österreich GmbH / Abbott Austria GmbH
- Alex's Lemonade Stand Foundation for Childhood Cancer
- Alle der St. Anna Kinderkrebsforschung nahestehenden Institutionen, Verbände und Vereine / All institutions, associations and societies related to St. Anna Children's Cancer Research Institute
- Alle Direktionen und alle Mitarbeiter:innen des St. Anna Kinderspitals / All heads and employees of St. Anna Children's Hospital
- Bezirksorganisation Alsergrund / District Organisation Alsergrund
- Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz / Federal Ministry of Social Affairs, Health, Care and Consumer Protection
- Bundesministerium für Bildung, Wissenschaft und Forschung (BMBWF) / Federal Ministry of Education, Science and Research (BMBWF)
- Bundesministerium für Frauen, Familie, Integration und Medien / Federal Ministry for Federal Ministry for Women, Family, Integration and Media
- Bundesministerium für Inneres / Federal Ministry of the Interior
- CeMM Forschungsinstitut für Molekulare Medizin der Österreichischen Akademie der Wissenschaften / CeMM – Research Center for Molecular Medicine of the Austrian Academy of Sciences
- Christian Doppler Forschungsgesellschaft / Christian Doppler Research Association (CDG)
- Dachverband der Österreichischen Kinderkrebshilfe / Umbrella Organisation of the Austrian Children's Cancer Charity
- Deutsches Krebsregister, Universität Mainz / German Cancer Registry, University of Mainz
- EBMT Europäische Gruppe für Blut- und Knochenmarktransplantation / EBMT European Society for Blood and Marrow Transplantation
- Ethikkommission der Medizinischen Universität Wien / Ethics Commission of the Medical University of Vienna
- European Commission / Europäischen Kommission (HE, H2020, ERC, EU4Health, MCSA, 3HP, HaDEA)
- Fellinger Krebsforschung / Fellinger Cancer Research
- Fonds der Stadt Wien für innovative interdisziplinäre Krebsforschung / City of Vienna Fund for Innovative, Interdisciplinary Cancer Research
- Fonds zur Förderung der wissenschaftlichen Forschung (FWF) / Austrian Science Fund (FWF)
- Forschungsrahmenprogramme der Europäischen Kommission / Research and Innovation Programmes of the European Commission
- Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) / Society for Paediatric Oncology and Haematology
- Gigax Privatstiftung FL / Gigax Private Trust FL
- Herzfeldersche Familienstiftung / Herzfeldersche Family Foundation
- Histiocytosis Association
- Incyte Corporation
- Ingrid Shaker Nessmann Krebsforschungsvereinigung / Ingrid Shaker Nessmann Cancer Research Association
- Innovative Medicines Initiative (IMI)
- Kapsch AG
- Kinder-Krebs-Hilfe, Elterninitiative für krebskranke Kinder / Kinder-Krebs-Hilfe, Parents' initiative for children with cancer
- Liddy Shriver Sarkom Initiative / The Liddy Shriver Sarcoma Initiative
- Medizinische Universität Wien / Medical University of Vienna
- Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Stadt Wien / Medical-Scientific Fund of the Mayor of the City of Vienna
- Mitglieder des Ehrenkomitees der St. Anna Kinderkrebsforschung / Members of the St. Anna Children's Cancer Research Institute Honorary Committee
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- Österreichische Agentur für Bildung und Internationalisierung (OeAD) / Austria's Agency for Education and Internationalisation (OeAD)
- Österreichische Akademie der Wissenschaften (ÖAW) / Austrian Academy of Sciences (ÖAW)
- Österreichische Forschungsförderungsgesellschaft (FFG) / Austrian Research Promotion Agency (FFG)
- Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie (ÖGHO) / Austrian Society of Haematology and Oncology (ASHO)
- Österreichische Gesellschaft für Kinder- und Jugendheilkunde (ÖGKJ) / Austrian Society for Paediatric Medicine (ÖGKJ)
- Österreichische Nationalbank (OeNB) / Austrian National Bank (OeNB)
- Österreichisches Rotes Kreuz, Landesverband Wien / Austrian Red Cross, Vienna Regional Association
- Österreichisches Stammzell-Register / Austrian Stem Cell Register
- Peter und Traudl Engelhorn Stiftung / Peter and Traudl Engelhorn Foundation
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- Wiener Wissenschafts-, Forschungs- und Technologiefonds (WWTF) / Vienna Science and Technology Fund (WWTF)
- Wirtschaftsagentur Wien / Vienna Business Agency
- Alle Mitarbeiter:innen der St. Anna Kinderkrebsforschung / All employees of the St. Anna Children's Cancer Research Institute
- Alle Vereins- und Vorstandsmitglieder / All association and board members

BACHELOR, MASTER (DIPLOMA) AND PHD THESES

GRADUATED IN 2023

DANIEL MAYR
Germline gain-of-function mutations in SYK are associated with inborn errors of immunity and immune dysregulation
> Supervised by Kaan Boztug
Diploma thesis

SANDRA HOLZINGER
Erhöhung der Sensitivität und Genauigkeit der Oxford Nanopore Sequenziertechnologie für den Nachweis und die Quantifizierung von Single und Compound Mutationen in der BCR::ABL1-Tyrosinkinasedomänea
> Supervised by Sandra Preuner
MSc thesis

PATRICK GANO
Optimization of the AvidCAR platform for the use in T cell-based cancer immunotherapy.
> Supervised by Manfred Lehner
MSc thesis

SANDRA WITTIBSCHLAGER
Non-coding elements controlling immune evasion in neuroblastoma
> Supervised by Davide Seruggia
MSc thesis

SOPHIE CHARLOTTE LIEGENFELD (née Knoll)
Establishment and characterization of RBM15::MRTFA+ and GATA2::HOXA9+ human induced pluripotent stem cell lines.
> Supervised by Klaus Fortschegger and Sabine Strehl
MSc thesis

VIKTORIA HUMHAL
Establishing a multimodal tissue preparation and imaging workflow to study tumor heterogeneity in neuroblastoma
> Supervised by Sabine Taschner-Mandl
MSc thesis

MAAIKE BOS
The role of ALCAM and CD6 cell interaction in ATRX-mutated neuroblastoma: implications for natural killer cell function and tumor immune microenvironment
> Supervised by Sabine Taschner-Mandl
BSc thesis

JOHANNES TEMME
Classification of tumor cells in childhood cancer using automated microscopy and deep learning
> Supervised by Sabine Taschner-Mandl
MSc thesis

DONYA ESMAEILIGOUDARZI
Identification of new vulnerabilities in high-risk neuroblastoma
> Supervised by Sabine Taschner-Mandl
MSc thesis

PUBLICATIONS

2023

1. Block, J., Rashkova, C., Castanon, I., Zoghi, S., Platon, J., Ardy, R. C., Fujiwara, M., Chaves, B., Schoppmeyer, R., van der Made, C. I., Jimenez Heredia, R., Harms, F. L., Alavi, S., Alsina, L., Sanchez Moreno, P., Avila Polo, R., Cabrera-Perez, R., Kostel Bal, S., Pfajfer, L., Ransmayr, B., Mautner, A. K., Kondo, R., Tinnacher, A., Caldera, M., Schuster, M., Dominguez Conde, C., Platzer, R., Salzer, E., Boyer, T., Brunner, H. G., Nooitgedagt-Frons, J. E., Iglesias, E., Deya-Martinez, A., Camacho-Lovillo, M., Menche, J., Bock, C., Huppa, J. B., Pickl, W. F., Distel, M., Yoder, J. A., Traver, D., Engelhardt, K. R., Linden, T., Kager, L., Hannich, J. T., Hoischen, A., Hambleton, S., Illsinger, S., Da Costa, L., Kutsche, K., Chavoshzadeh, Z., van Buul, J. D., Anton, J., Calzada-Hernandez, J., Neth, O., Viaud, J., Nishikimi, A., Dupre, L., & Boztug, K. (2023). Systemic Inflammation and Normocytic Anemia in DOCK11 Deficiency. N Engl J Med, PMID: 37342957 https://doi.org/10.1056/NEJMoa2210054

2. Strobl, J., Huber, B., Heredia, R. J., Kirnbauer, R. #, Boztug, K. #, & Stary, G. # (2023). Polymerase-delta-deficiency as a novel cause of inborn cancer predisposition associated with human papillomavirus infection. Br J Dermatol, PMID: 36787285 https://doi.org/10.1093/bjd/ljad021 # Shared senior authorship

3. Berner, J., van de Wetering, C., Jimenez Heredia, R., Rashkova, C., Ferdinandusse, S., Koster, J., Weiss, J. G., Frohne, A., Giuliani, S., Waterham, H. R., Castanon, I., Brunner, J., # & Boztug, K. # (2023). Phosphomevalonate kinase deficiency expands the genetic spectrum of systemic autoinflammatory diseases. J Allergy Clin Immunol, PMID: 37364720 https://doi.org/10.1016/j.jaci.2023.06.013 # Shared senior authorship

4. Kostel Bal, S., Giuliani, S., Block, J., Repiscak, P., Hafemeister, C., Shahin, T., Kasap, N., Ransmayr, B., Miao, Y., van de Wetering, C., Frohne, A., Jimenez-Heredia, R., Schuster, M. K., Zoghi, S., Hertlein, V., Thian, M., Bykov, A., Babayeva, R., Bilgic Eltan, S., Karakoc-Aydiner, E., Shaw, L. E., Chowdury, I., Varjosalo, M., Arguello, R. J., Farlik, M., Ozen, A., Serfling, E. A. E., Dupre, L., Bock, C., Halbritter, F., Hannich, J. T., Castanon, I., Kraakman, M. J., Baris, S., & Boztug, K. (2023). Biallelic NFATC1 mutations cause an inborn error of immunity with impaired CD8+ T-cell function and perturbed glycolysis. Blood, PMID: 37249233 https://doi.org/10.1182/blood.2022018303

5. Guthrie, J., Bal, S., Lombardo, S., Müller, F., Sin, C., Hütter, C., Menche, J.#, & Boztug, K#. (2023). AutoCore: A network-based definition of the core module of human autoimmunity and autoinflammation. Sci Adv, 9(35), eadg6375, PMID: 37656781 https://doi.org/10.1126/sciadv.adg6375 # Shared senior and corresponding authorship

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