CURA PLACIDA

CHILDREN'S CANCER RESEARCH FOUNDATION

10 YEARS OF CURA PLACIDA

Dr. med. Tatiana Prinzessin von Bayern

Dear Friends and Supporters of the Cura Placida Foundation,

Since 2020, at the request of Dr. Yvonne Princess of Croÿ, COO of Cura Placida Children's Cancer Research Foundation, and Professor Stefan Burdach, I have taken on the patronage of the Cura Placida Foundation. Why Cura Placida, and how did it come about?

In 2009, Professor Stefan Burdach's research group published the paper „EZH2 is a mediator of EWS/FLI1 driven tumor growth and metastasis blocking endothelial and neuro-ectodermal differentiation" in the PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. This study was groundbreaking: it showed that eternal youth carries the risk of malignant transformation: Forever Young is no free lunch.

For this significant work, he and his colleagues received the Kind Philipp Prize from the Society for Pediatric Oncology and Hematology. He used his prize money to establish Cura Placida as a non-profit foundation. The primary goal of the foundation is to promote the development of targeted, individualized therapies (Curative Targeted Therapies) for children with cancer, with a particular focus on placid treatment methods and the prevention of undesirable long-term effects associated with conventional treatments.

Through conventional cancer therapies, survivors often suffer from disfigurement, radiation damage, and long-term consequences of chemotherapy: The vulnerable organisms of children are particularly affected by the mutagenic effects of untargeted toxic therapies. Secondary tumors and reduced life expectancy due to increased mortality from non-malignant diseases are the price of curing cancer. However, modern high-throughput technologies at the two Munich universities and other leading research institutions today promise the development of targeted therapies that attack tumor cells while sparing the healthy cells of the growing body.

New and targeted treatments can be developed only through research. Childhood cancer is rare, and affected children belong to the most vulnerable members of society. In public research funding, voter interests often take precedence. Additionally, the pharmaceutical industry has only limited interest in developing new therapies due to understandable reasons of limited profitability. That is why research for children needs private charity.

The foundation supports national and international research projects. Unlike many other initiatives, the focus here is not primarily on individual medical assistance but on elucidating the mechanisms of childhood cancers to enable targeted and thus less toxic therapies.

Dr. med. Tatiana Prinzessin von Bayern

PATRON

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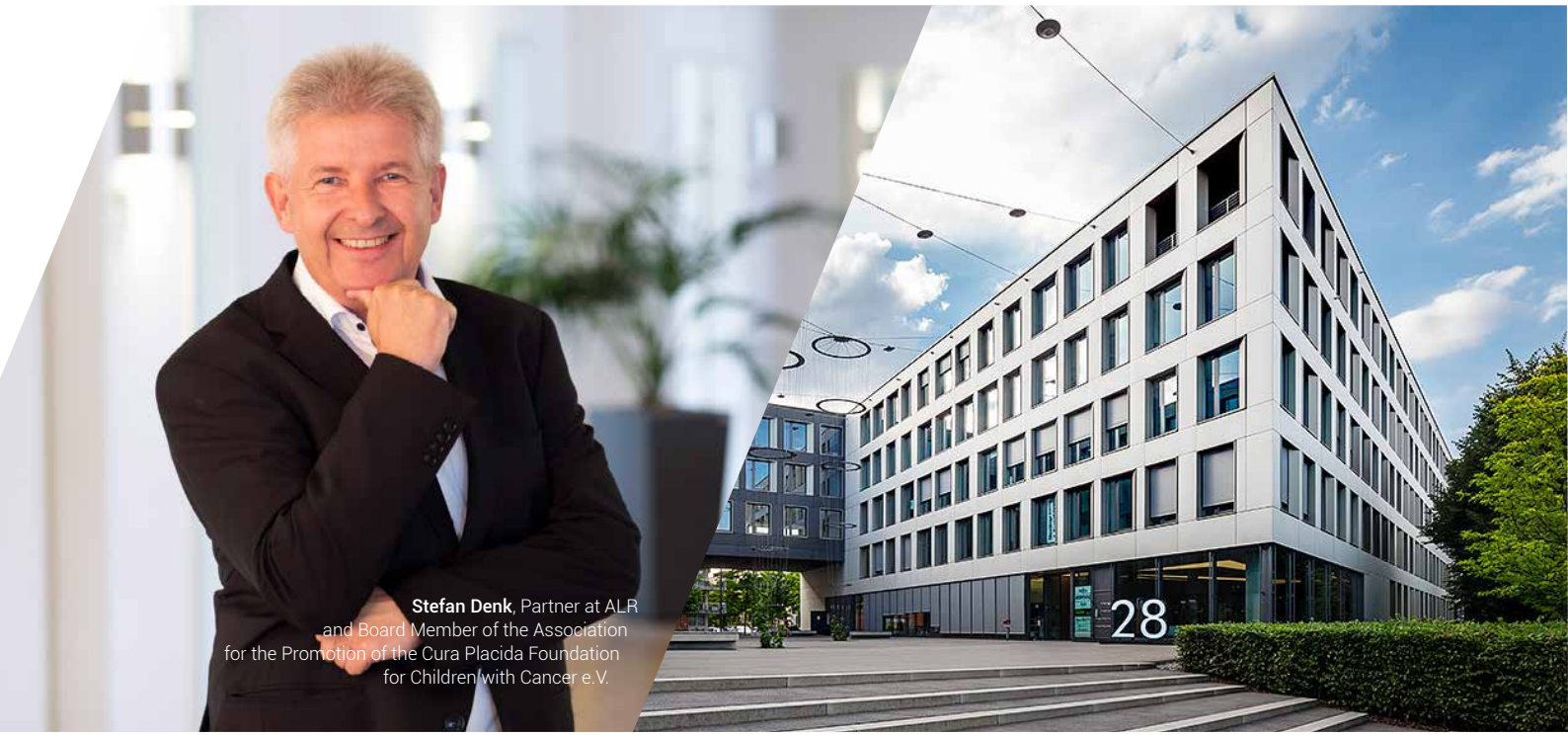

Stefan Denk, Partner at ALR and Board Member of the Association for the Promotion of the Cura Placida Foundation for Children with Cancer e.V.

TOGETHER FOR RESEARCH.

We have been supporting the research initiatives launched by Prof. Dr. Stefan Burdach and funded by the Cura Placida Foundation since 2007 to advance treatments for childhood cancer.

Who We Are: We are a team of approximately 120 dedicated and motivated auditors, tax consultants, and employees. From our headquarters in Munich and our branch office in Leipzig, we advise and audit renowned medium-sized companies across Germany.

We provide individualized support to our clients. What do our clients particularly appreciate about us as a partner-led auditing and tax consulting firm? We align ourselves with their specific needs. We are not an anonymous organization—each client is assigned a dedicated point of contact. This personal, long-term support, combined with our in-depth knowledge of the business environment, allows us to develop tailor-made solutions and recommendations. This approach is convincing, which is why we continue to grow.

For fifteen years, we have also been deeply committed to supporting research in the fight against childhood cancer. We regularly visit the pediatric oncology ward at the children's hospital and speak with young patients who, despite enduring challenging conventional treatments, continue to display resilience, joy, and optimism.

Experiencing the strength of these children, their hope, and their unwavering optimism is always a deeply moving experience. Every lost battle against childhood cancer is one too many. That is why, since its foundation, we have supported the Cura Placida Foundation, including through regular donations generated from charity events such as golf tournaments.

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Prof. Dr. med. Stefan Burdach

Ten years of support for the research of targeted therapies against cancer in children: a success story.

Discovering Treatment Methods That Spare the Vulnerable Organism of the Growing Child and Specifically Target Their Cancer – This Is the Funding Goal of the Foundation.

For this purpose, you, dear friends and supporters of the Cura Placida Foundation, have shown remarkable commitment over the past decade.

We present to you five biomedical projects, along with our social chess initiative. The findings and progress achieved in these projects are outstanding examples of the foundation's successful project funding.

Alexandra Sipol (Munich) discovered how leukemia cells protect themselves from the metabolic stress of uncontrolled growth. The discovery of this anti-burnout mechanism provides new approaches for targeted interventions in the metabolism of leukemia cells, thereby avoiding the undesirable effects of non-specific genetic alterations caused by many existing leukemia therapies.

Uwe Thiel (Munich) and Poul Sorensen (Vancouver, Canada) genetically enhanced immune cells to specifically prevent the spread of cancer cells (metastasis) in children with cancer. This is invaluable for the prospects of cure since cancer patients, especially children, typically do not die from the primary tumor itself but from metastases.

Hendrik Gaßmann (Munich) and Valentina Evdokimova (Toronto, Canada) uncovered how the tumor influences its immediate environment, the immune system, and even distant sites in the body to promote its spread (metastasis). They demonstrated that the tumor activates retroviral gene fragments in its genome to prepare the ground for metastasis. These fragments have accumulated in our genome over millions of years through evolution and are usually silent but can be activated under special growth conditions, such as pregnancy or cancer.

Sebastian Schober (Munich), together with Per Sonne Holm (Innsbruck), optimized immunotherapy for childhood cancer (see Project Thiel/Sorensen) using oncolytic viruses. Oncolytic viruses selectively replicate in cancer cells. The researchers developed a virus that destroys the cancer cell as soon as it begins to metastasize.

Michaela Nathrath (Kassel/Munich) deciphered the genetic instability characteristic of the most common bone cancer in childhood. This instability leads to highly variable changes, which is why a „one size fits all" therapy is not promising.

All these advancements for children with cancer would not have been possible without your help. With this booklet, we want to inform you about what has been achieved with your contribution. We sincerely thank you for your tremendous support.

Prof. Dr. med. Stefan Burdach

CHAIRMAN
BOARD OF GOVERNORS

Dr. med. Gerhard A. Brandl

Dr. phil. Yvonne Prinzessin von Croÿ

Message from the Executive Board

Over more than ten years since its founding, the Cura Placida Foundation has achieved significant advancements in improving therapies for children with cancer through the research it supports.

Science often requires patience, especially when aiming for well-founded and forward-looking results. Even though intermediate steps in medical research may sometimes seem small at first, the end results, as reflected in numerous high-profile scientific publications over recent years, have repeatedly demonstrated the substantial progress made, not least through projects supported by Cura Placida.

However, this philosophy of small but consistent forward steps applies not only to research itself but also within the foundation. Run entirely on a voluntary basis, Cura Placida relies on continuity and personal commitment in leadership and teamwork rather than on costly organized manpower.

As the board, we are responsible for Cura Placida's fundraising. The foundation fulfills its purpose primarily through donations from you, our benefactors. Many of our supporters have been closely associated with Cura Placida for a long time, continuously helping the foundation set new, forward-looking milestones in childhood cancer therapy.

"Private charity", i.e., financial support from private donors, is becoming increasingly important for us as well, given that public funding and occasional contributions from the industry are increasingly limited, not least due to the current political priorities.

We, therefore, see it as a particularly important part of our mission—supported by the expertise of many medical specialists and complemented by our own research within our network—to make highly responsible and goal-oriented decisions about the allocation of funds and the selection of projects to be funded. In addition to this duty of care, we also report regularly to governmental supervisory authorities, ensuring compliance with legal requirements.

In line with the foundation's philosophy of voluntary engagement, we can guarantee that your donations are almost entirely used to support research funding.

Finally, on behalf of all employees of the foundation and all beneficiaries, we would like to sincerely thank you, our supporters, donors, and sponsors, for your generous contributions. We would be delighted if you continued to support the foundation in the future.

At the same time, we would like to take this opportunity to invite new supporters and donors to join us in further improving cancer therapies for affected children—because children are not only beloved family members and an important, though often silent, part of our society, but also the future of us all!

Dr. med. Gerhard A. Brandl, MBA (INSEAD)
EXCECUTIVE BOARD, CEO

Dr. phil. Yvonne Prinzessin von Croÿ
EXCECUTIVE BOARD, COO

REPORTS

Alexandra Sipol, MD, PhD
Munich, Germany

Targeted Leukemia Therapy

The treatment of childhood leukemia is a good example of scientific success in cancer therapy.

Leukemia is no longer a fatal disease, thanks to the introduction of intensive chemotherapeutic treatments. However, despite the high efficacy of chemotherapy, the toxicity of the treatment and its long-term effects pose significant challenges. There is also a critical medical need to identify the mechanism that makes leukemia cells resistant. Like many other cancer cells, leukemia cells are characterized by an increased metabolism. At the same time, malignant cells possess a remarkable ability to withstand the stress associated with high metabolic activity and to escape the toxic effects of the resulting metabolic byproducts.

In this context, we observed that in the most common type of childhood leukemia, the MondoA protein is significantly elevated. We discovered that this protein acts as a sensor that makes leukemia cells resistant to the toxic effects of oncogenes.

By blocking the function of MondoA with a chemical compound or through genetic interventions, we demonstrate that leukemia becomes easier to combat.

Our findings could contribute to the development of future cancer therapies that are more effective and, at the same time, have fewer side effects.

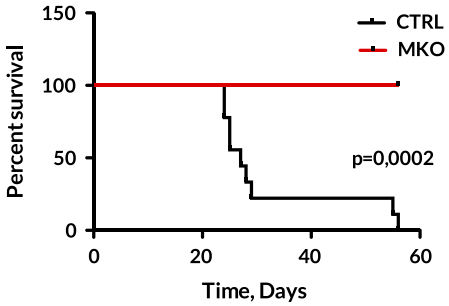
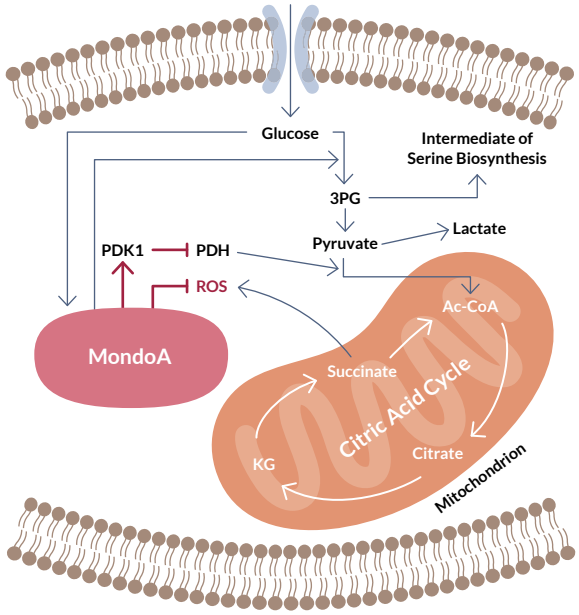


Figure 1: Genetic inactivation of MondoA (MKO, red curve) results in 100% survival from leukemia (Y-axis: Percent survival; X-axis: Time, Days).
*** Probability of error <1%.



Graphical Summary: MondoA blocks the uptake of pyruvate (the end product of glucose metabolism) into the mitochondria (the powerhouses of the cell) and also promotes the biosynthesis of cellular building blocks, such as the amino acid serine (top right), from the glucose metabolism intermediate 3-phosphoglycerate (3PG).
By slowing down the citric acid cycle (Krebs cycle) and the energy metabolism, the production of toxic amounts of reactive oxygen species (ROS) is limited. Additionally, MondoA directly inhibits ROS production. In the absence of MondoA, uncontrolled growth causes toxic stress for the leukemia cell, primarily due to the accumulation of ROS. MondoA alleviates this reaction by reducing the levels of ROS.

Publications of Cura Placida-funded research projects involving Alexandra Sipol, MD, PhD:

Sipol A, Hameister E, Xue B, Hofstetter J, Barenboim M, Öllinger R, Jain G, Prexler C, Rubio RA, Baldauf MC, Franchina DG, Petry A, Schmäh J, Thiel U, Gorlach A, Cario G, Brenner D, Richter G, Grünewald TGP, Rad R, Wolf E, Ruland J, Sorensen PH, Burdach SEG. MondoA Drives B-ALL Malignancy through Enhanced Adaptation to Metabolic Stress. Blood. 2021 Apr 28:blood.2020007932. doi: 10.1182/blood.2020007932. Epub ahead of print. PMID: 33908607.

Schulte V, Sipol A, Burdach S, Rieger-Fackeldey E. The Truncated Splice Variant of the Granulocyte-Macrophage-Colony-Stimulating Factor Receptor β- Chain in Peripheral Blood Serves as Severity Biomarker of Respiratory Failure in Newborns. Neonatology. 2021;118(2):187-193. doi: 10.1159/000513356. Epub 2021 Mar 30. PMID: 33784678.

Weidenbusch B, Richter GHS, Kesper MS, Guggemoos M, Gall K, Prexler C, Kazantsev I, Sipol A, Lindner L, Nathrath M, Witt O, Specht K, Beitinger F, Knebel C, Hosie S, von Eisenhardt-Rothe R, Weichert W, Luettichau IT, Burdach S. Transcriptome based individualized therapy of refractory pediatric sarcomas: feasibility, tolerability and efficacy. Oncotarget. 2018 Apr 17;9(29):20747-20760. doi: 10.18632/oncotarget.25087. PMID: 29755686; PMCID: PMC5945512.

PD Dr. med. Uwe Thiel
Munich, Germany

Prof. Dr. Poul Sorensen
Vancouver, Canada

Immunotherapy for Children with Metastatic Cancers

Ewing Sarcoma (ES) is a malignant bone tumor affecting children and adolescents. Currently, there is no curative therapy for most advanced ES patients as such with bone marrow metastases. Due to the extremely poor survival rates of children with advanced ES under existing therapies, it is essential to develop new, specific therapeutic strategies.

The transfer of specialized immune cells, known as cytotoxic (CD8+) T cells, which target specific structures essential for the tumor's survival, represents a promising immunotherapeutic approach. We were able to isolate and expand exactly these immune cells from the blood of healthy donors, triggering specific anti-tumor responses both in vitro and in animal models.

We identified an ES-specific T-cell receptor (TCR) and successfully introduced it into immune cells using gene transfer, enabling them to become tumor-specific. These T cells could be produced in large quantities and were capable of specifically targeting and combating ES cell lines.

Moreover, in individual compassionate use clinical applications, these T cells already demonstrated excellent tolerance and induced partial tumor regression in at least one of three treated ES patients. This approach can potentially be applied to other types of cancer as well.

The goal of our research group is to identify and implement new (immuno-) therapeutic approaches for the curative treatment of children with metastatic cancers who currently face poor prognoses.

Publications of Cura Placida-funded research projects involving PD Dr. med. Uwe Thiel and Prof. Dr. Poul Sorensen:

Thiel U, Schober SJ, Ranft A, Gassmann H, Jabar S, Gall K, von Lüttichau I, Wawer A, Koscielniak E, Diaz MA, Ussowicz M, Kazantsev I, Afanasyev B, Merker M, Klingebiel T, Prete A, Gruhn B, Bader P, Jürgens H, Dirksen U, Handgretinger R, Burdach S, Lang P. No difference in survival after HLA mismatched versus HLA matched allogeneic stem cell transplantation in Ewing sarcoma patients with advanced disease. Bone Marrow Transplant. 2021 Jul;56(7):1550-1557. doi: 10.1038/s41409-020-01200-x. Epub 2021 Jan 29. PMID: 33514918; PMCID: PMC8263340.

Thiel U, Schober SJ, Einspieler I, Kirschner A, Thiede M, Schirmer D, Gall K, Blaeschke F, Schmidt O, Jabar S, Ranft A, Alba Rubío R, Dirksen U, Grunewald TGP, Sorensen PH, Richter GHS, von Lüttichau IT, Busch DH, Burdach SEG. Ewing sarcoma partial regression without GvHD by chondromodulin-I/HLA-A*02:01-specific allorestricted T cell receptor transgenic T cells. Oncoimmunology. 2017 Apr 12;6(5):e1312239. doi: 10.1080/2162402X.2017.1312239. PMID: 28638739; PMCID: PMC5467994.

Kirschner A, Thiede M, Grünewald TG, Alba Rubio R, Richter GH, Kirchner T, Busch DH, Burdach S, Thiel U. Pappalysin-1 T cell receptor transgenic allo-restricted T cells kill Ewing sarcoma in vitro and in vivo. Oncoimmunology. 2017 Jan 17;6(2):e1273301. doi: 10.1080/2162402X.2016.1273301. PMID: 28344885; PMCID: PMC5353903.

Thiel U, Pirson S, Müller-Spahn C, Conrad H, Busch DH, Bernhard H, Burdach S, Richter GH. Specific recognition and inhibition of Ewing tumour growth by antigen-specific allo-restricted cytotoxic T cells. Br J Cancer. 2011 Mar 15;104(6):948-56. doi: 10.1038/bjc.2011.54. Erratum in: Br J Cancer. 2011 Aug 9;105(4):596. PMID: 21407224; PMCID: PMC3065285.

Dr. med. Hendrik Gaßmann
PhD-Kandidat
Munich, Germany

Valentina Evdokimova, PhD
Toronto, Canada

Tumor Microenvironment – The Influence of the Tumor on Its Cellular Surroundings, the Immune System, and the Body

Successful new immunotherapeutic approaches for the curative treatment of children with metastatic cancers require an understanding of how the tumor influences its immediate environment, the immune system, and distant sites in the body to its advantage and how it defends itself against therapy.

The release of signaling molecules (cytokines) and tiny nanoparticles known as exosomes by the tumor are fundamental mechanisms by which the tumor manipulates the patient's immune system. These exosomes are delivered to specific target cells of the immune system, similar to the concept of the Trojan horse, to alter the healthy host cell in favor of the tumor.

In international collaboration with the Ontario Institute for Cancer Research in Toronto, we recently succeeded in detecting these exosomes in Ewing sarcoma patients using a tumor-specific marker. Further studies on these exosomes will determine whether they can be established as potential early detection and progression markers for Ewing sarcoma.

Additionally, we demonstrated that upon uptake of these exosomes, the normally immune-supporting cells known as macrophages are misled into releasing a variety of signaling molecules that support tumor growth and potentially deactivate other immune cells (see Figures 1 and 2).

Measuring these signaling molecules in patients with Ewing sarcoma will provide important insights into the tumor's behavior.

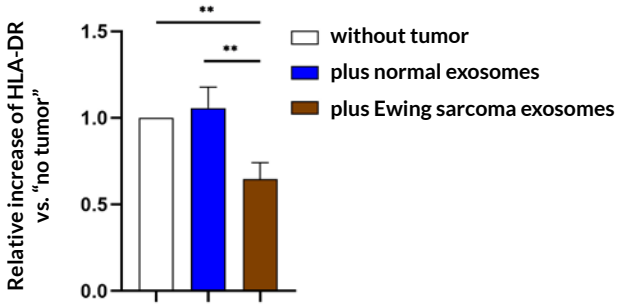


Figure 1: Exosomes from Ewing Sarcoma downregulate the activating HLA-DR molecule on macrophages.

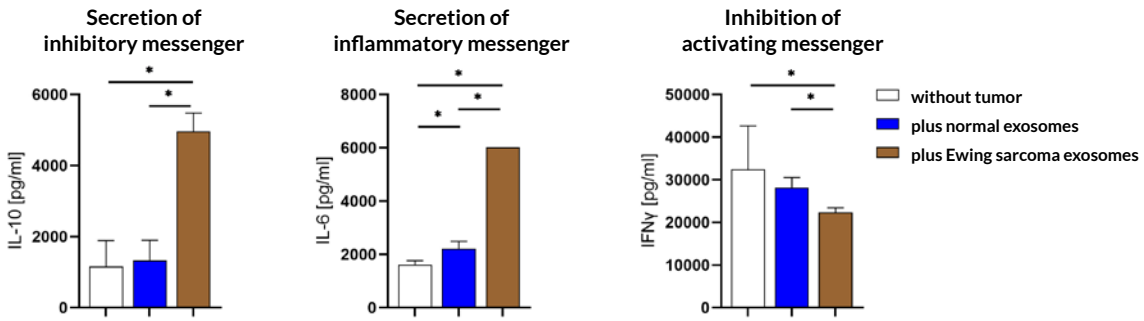
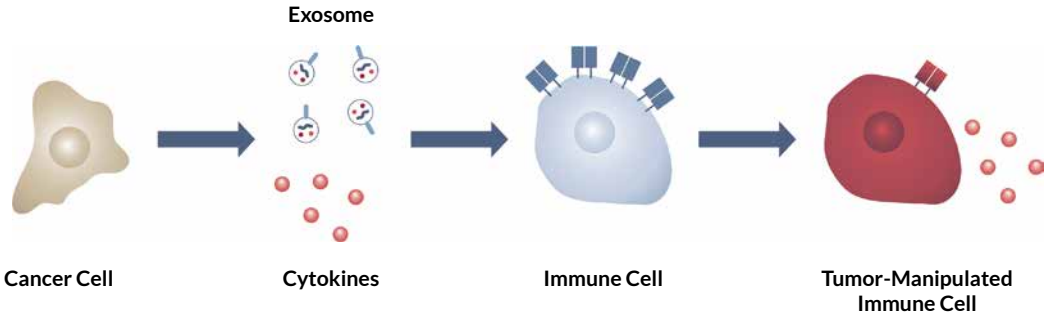


Figure 2: After exposure to Ewing Sarcoma exosomes, macrophages release inflammatory as well as immunosuppressive signaling molecules and inhibit the release of the activating cytokine IFN from cells of the adaptive immune system.



Graphical Summary: Tumor cells release tiny signaling molecules such as cytokines and exosomes. The exosomes are taken up by macrophages of the immune system, reprogramming them and causing them to lose the ability to activate the adaptive immune system. Thus, Ewing Sarcoma blocks the immune system via exosomes and prevents the elimination of the tumor.

Publications of Cura Placida-funded research projects involving Dr. med. Hendrik Gaßmann and Valentina Evdokimova:

Valentina Evdokimova, Peter Ruzanov, Hendrik Gassmann, Syed H. Zaidi, Vanya Peltekova, Lawrence E. Heisler, John D. McPherson, Marija Orlic-Milacic, Katja Specht, Katja Steiger, Sebastian J. Schober Uwe Thiel Trevor D. McKee, Mark Zaidi, Christopher M. Spring, Eve Lapouble, Olivier Delattre, Stefan Burdach, Lincoln D. Stein and Poul H. Sorensen. Exosomes transmit retroelement RNAs to drive inflammation and immunosuppression in Ewing Sarcoma. bioRxiv preprint first posted online Oct. 16, 2019; doi: http://dx.doi.org/10.1101/806851.

Gassmann, H.; Schneider, K.; Evdokimova, V.; Ruzanov, P.; Schober, S.J.; Xue, B.; von Heyking, K.; Thiede, M.; Richter, G.H.S.; Pfaffl, M.W.; Noessner, E.; Stein, L.D.; Sorensen, P.H.; Burdach, S.E.G.; Thiel, U. Ewing Sarcoma-Derived Extracellular Vesicles Impair Dendritic Cell Maturation and Function. Cells 2021, 10, 2081. https://doi.org/10.3390/cells10082081

Dr. med. Sebastian Schober, PhD
Munich, Germany

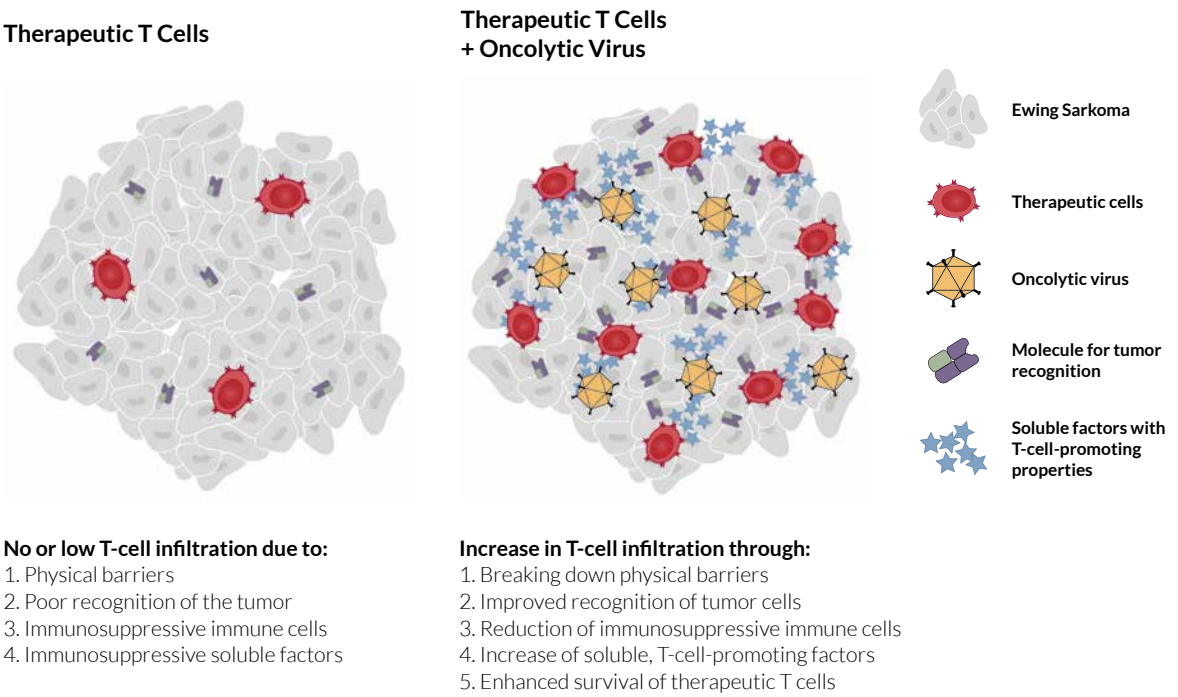
T-Cell Immunotherapy for Sarcomas in Children and Its Optimization Using Oncolytic Viruses

T-cell-based immunotherapies represent novel treatments that enable the targeted recognition and destruction of tumor cells through genetically modified immune cells.

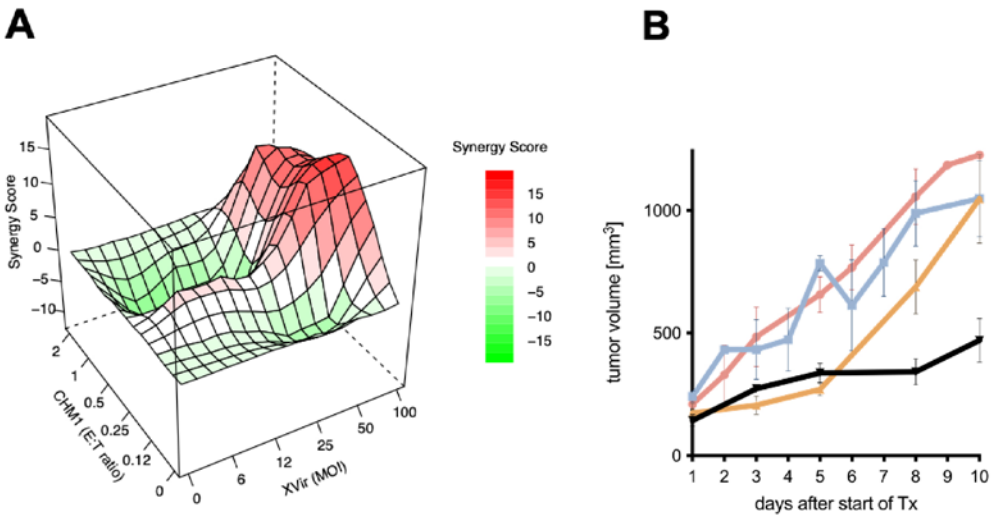
In the treatment of leukemia, such T-cell immunotherapies are already partially established in clinical practice. However, in the treatment of solid tumors, such as sarcomas, these cellular therapeutics have not yet achieved the desired clinical effect. Possible explanations for this include a T-cell-hostile microenvironment within the tumor, physical barriers, and other cellular and soluble immunosuppressive factors in circulation.

To understand and overcome these limiting factors, we investigated the role of genetically modified, tumor-specific cytotoxic T cells and T helper cells both individually and in combination. We found that the helper cells play a crucial role in controlling local tumor growth but are not able to reduce the metastatic potential.

To further optimize T-cell-based immunotherapy against sarcomas, we collaborated with Professor Per Sonne Holm (Medical University of Innsbruck) to investigate the immunostimulatory effect of an oncolytic adenovirus (XVir-N-31) combined with specific T cells (CHM1 T cells, see project Thiel/Sorensen: Immunotherapy for Children with Metastatic Cancers) against Ewing Sarcoma. Numerous positive mechanisms of this combination therapy were identified, which synergistically destroy tumor cells and significantly prolonged the survival of mice in a preclinical mouse model.



Synergistic Properties of CHM1 T Cells and Oncolytic Adenovirus XVir-N-31 – Model: On the left, the infiltration and thus control of the sarcoma are hindered by various T-cell-hostile factors. On the right, the combination with XVir-N-31 partially overcomes these hostile factors, leading to improved T-cell infiltration into the tumor and thereby increasing the therapeutic effect.



The combination of therapeutic (CHM1) T cells and the oncolytic virus (XVir-N-31) exhibits synergistic properties in the destruction of Ewing sarcoma cells.

(A) The ZIP synergy score shows particularly strong synergistic effects at 50-100 infectious virus particles per tumor cell (MOI = multiplicity of infection) and an effector-to-target ratio of therapeutic T cells to tumor cells of 0.5-1 (measured 48 hours after infection and 24 hours after T-cell application). The higher the peaks and the deeper the red coloring of their summits, the greater the synergy between T cells and the virus in tumor elimination.

(B) Inhibition of local tumor growth in a Ewing sarcoma mouse model through combination therapy (black line, single administration of both T cells and virus), resulting in a significant improvement in therapeutic response compared to monotherapies (red = no treatment, blue = T cells, yellow = virus). Data shown for days 1-10 after the start of treatment (Tx = therapy). (Unpublished, manuscript in preparation.)

Publications of Cura Placida-funded research projects involving Dr. med. S. Schober:

Schober SJ, Thiede M, Gassmann H, Prexler C, Xue B, Schirmer D, Wohlleber D, Stein S, Grünewald TGP, Busch DH, Richter GHS, Burdach SEG, Thiel U. MHC Class I-Restricted TCR-Transgenic CD4+ T Cells Against STEAP1 Mediate Local Tumor Control of Ewing Sarcoma In Vivo. Cells. 2020 Jun 29;9(7):1581. doi: 10.3390/cells9071581. PMID: 32610710; PMCID: PMC7408051.

Schober SJ, von Luettichau I, Wawer A, Steinhauser M, Salat C, Schwinger W, Ussowicz M, Antunovic P, Castagna L, Kolb HJ, Burdach SEG, Thiel U. Donor lymphocyte infusions in adolescents and young adults for control of advanced pediatric sarcoma. Oncotarget. 2018 Apr 27;9(32):22741-22748. doi: 10.18632/oncotarget.25228. PMID: 29854312; PMCID: PMC5978262.

Prof. Dr. Michaela Nathrath
Kassel, Germany / Munich, Germany

Identification of Therapeutically Relevant Targets in Osteosarcoma

Osteosarcoma is a rare malignant bone tumor in children and adolescents. Over the past 30 years, there have been no significant advances in its treatment. Patients who do not respond well to chemotherapy have a poor prognosis. Even worse is the chance of survival for patients who develop tumor cell dissemination—metastasis—during the course of their disease; the majority of these patients succumb to their illness. This tragic reality has remained largely unchanged for over 30 years despite numerous national and international studies.

New therapeutic strategies are urgently needed to improve the survival of these predominantly young patients. To achieve this goal, a deeper understanding of the disease's biology is essential. Osteosarcoma exhibits a unique characteristic: unlike many other childhood tumors, this malignant bone tumor does not arise from a single or a few mutations in the genetic sequence—so-called driver mutations—responsible for tumor formation. Instead, it involves numerous, highly complex, and „chaotic" genetic alterations.

In recent years, we have characterized many of these changes, including individual mutations found in small patient subgroups, such as mutations in the RET, NTREK, and IGF tumor genes, as well as the genome-wide pattern characteristic of osteosarcoma known as BRCAness, a DNA repair deficiency. As part of the nationwide INFORM study (Individualized Therapy for Relapsed Malignancies in Childhood), we conducted molecular genetic analysis of tumor samples from over 60 patients with relapsed osteosarcoma, focusing particularly on identifying therapeutically relevant targets.

We have come significantly closer to our goal of improving therapy. In relapsed osteosarcoma, we observe the involvement of various well-known tumor genes

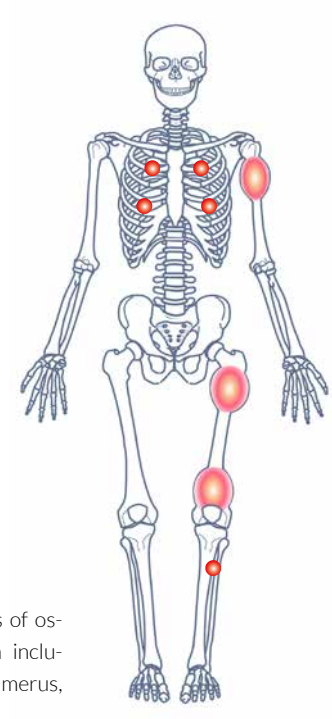


Figure 1 – Preferred sites of osteosarcoma manifestation include the knee region, the humerus, and the lungs.

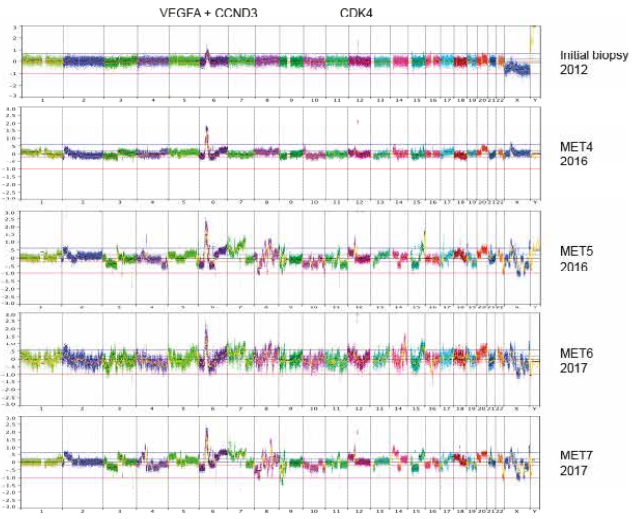


Figure 2 – Analysis of tumor samples from a patient at different stages of the disease: some of the initially present alterations (such as VEGFA, CCND3, and CDK4) are also found later in the metastases (MET 4-7) and therefore represent potential therapeutic targets.

with a high degree of heterogeneity and few recurring genomic alterations. We can demonstrate that the earliest and thus most therapeutically promising mutations affect the part of the cell cycle regulated by specific cell cycle genes—Cyclin D3 and E1, as well as the cyclin-dependent kinases 2, 4, and 6. Furthermore, we can calculate that these alterations occur in the majority of patients long before the clinical diagnosis of the tumor.

Based on these findings, we conclude that a „one size fits all" treatment strategy for patients with relapsed osteosarcoma is unlikely to be effective. Instead, different genomic alterations must be addressed with distinct therapeutic approaches to improve survival outcomes in these high-risk patients.

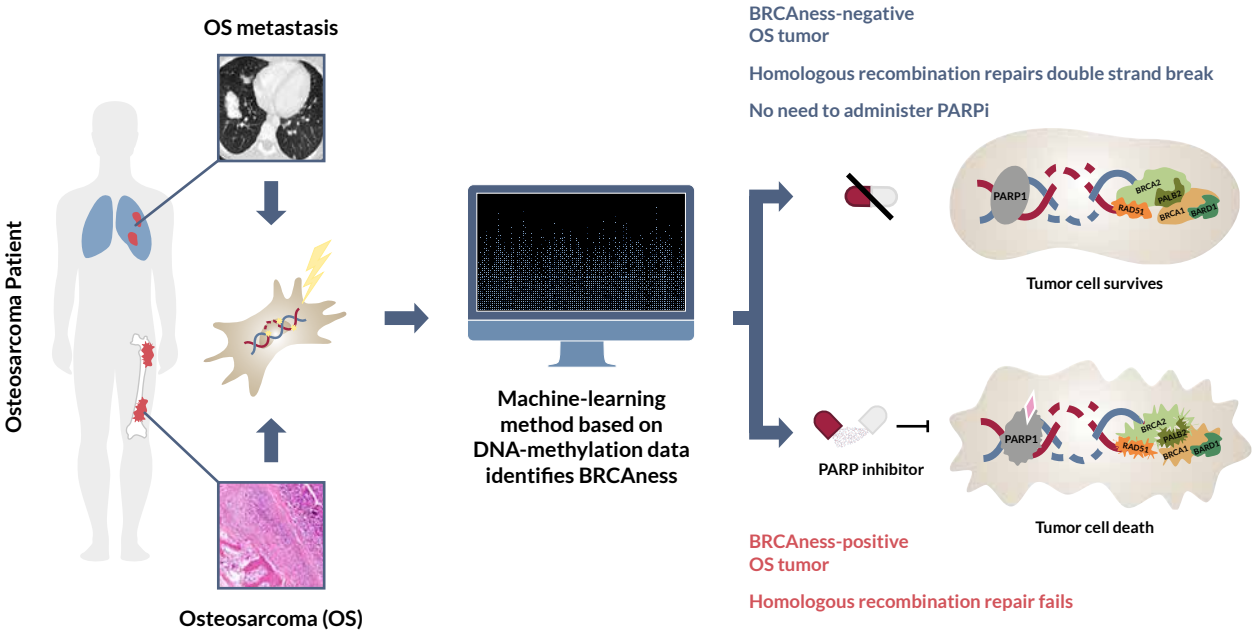


Figure 3 – Using a computer algorithm based on DNA methylation, BRCAness—a DNA repair deficiency characteristic of osteosarcoma—can be identified, enabling the development of an individualized therapy proposal aimed at inducing tumor cell death.

Publications of Cura Placida-funded research projects involving Prof. Dr. Michaela Nathrath:

[1] Michal Kovac, Sebastian Ribi, Claudia Blattmann, Eva Roth, Monika Kovacova, Andreas Kulozik, Wolfgang Hartmann, Stefan Bielack, David Thomas, Michaela Nathrath, Karl Heinimann, and Daniel Baumhoer. RET Germline Mutations and Susceptibility to Osteosarcoma. Med Genet. 2020 Mar

[2] Maxim Barenboim, Michal Kovac, Baptiste Ameline, David T. W. Jones, Olaf Witt, Stefan Bielack, Stefan Burdach, Daniel Baumhoer, Michaela Nathrath (2021) DNA methylation-based classifier and gene expression signatures detect BRCAness in osteosarcoma. PLoS Comput Biol 17(11): e1009562.

[3] Baptiste Ameline, Michal Kovac, Michaela Nathrath, Maxim Barenboim, Olaf Witt, Andreas H Krieg, Daniel Baumhoer. Overactivation of the IGF signaling pathway in osteosarcoma: a potential therapeutic target? J Pathol Clin Res. 2021 Mar;7(2):165-172.

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Recovering with Chess: Thanks to tablets donated by the Munich law and tax firm RDS, young cancer patients at the Children's Hospital Munich Schwabing can participate in the chess support program of the Munich Chess Foundation.
Pictured (from left to right) are chess trainer Dino Dehmel, foundation chairman Stefan Kindermann, foundation board member Dijana Dengler, PD Dr. Dr. Irene Teichert-von Lüttichau, Dr. Yvonne Princess of Croÿ, and lawyer and tax consultant Bernhard Schmid, who personally handed over the tablets.
(Photo: RDS Kanzlei)

Checkmate Cancer at the Children's Hospital Munich Schwabing

Chess Helps in the Fight Against Cancer – this is leap of faith at the Children's Hospital Munich Schwabing and the initiators of the project, the Cura Placida Foundation and the Munich Chess Foundation. With this initiative, the Munich Chess Foundation aims to set a new milestone. The chess project for children and adolescents with cancer, launched at the end of March 2017, is designed to significantly improve the quality of life for young cancer patients.

Chess provides a welcome distraction from the daily hospital routine, allowing children with cancer to a forget their illness. It also has long-term benefits. Many children and adolescents suffer from lasting health issues years after their cancer treatment. For this reason, chess training is also intended to stimulate the brain, helping to prevent neurological and neurocognitive damage—including concentration difficulties, psychological disorders, fine motor skill impairments, and other related conditions—as much as possible during cancer therapy.

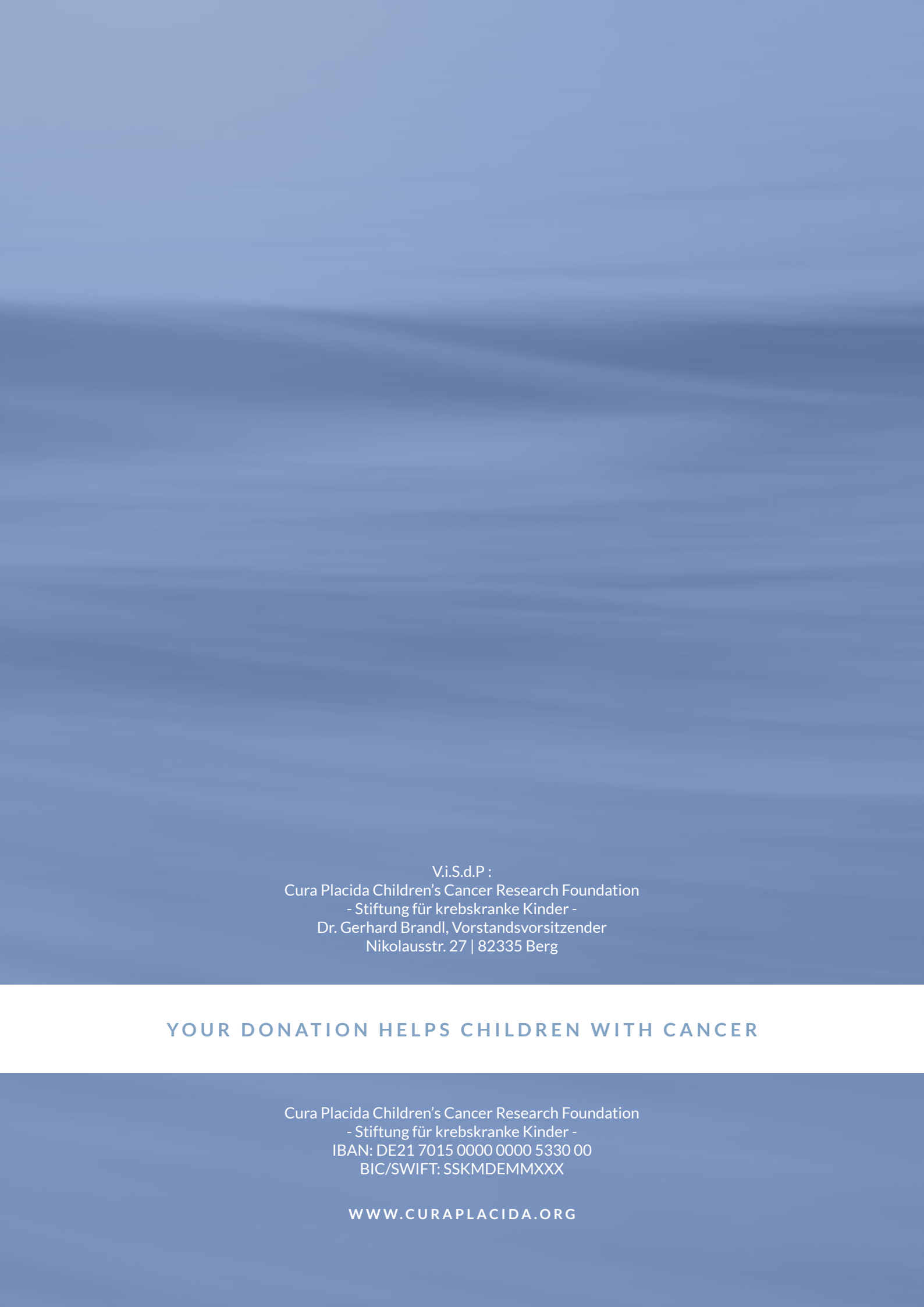
At the heart of this support program is a weekly chess instruction, conducted by chess trainer Dino Dehmel, who was specially trained for this task at the Munich Chess Academy. The sessions are coordinated with psychologists and doctors at the Children's Hospital Munich Schwabing. "Children and parents are enthusiastic about the program, and the demand is high. On average, two to three children play chess per working day. The duration of each session depends heavily on the child's health. I always check in every 30 minutes to see if they want to continue or stop. Overall, there is a strong interest in chess support, with many young patients and their parents wishing for even more flexible training sessions. I am more than happy to provide more intensive and long-term coaching," says chess trainer Dino Dehmel.

Tablet-Based Support Enhances Chess Training in the Hospital

When it comes to individual and sustainable support, technology plays a key role. In summer 2017, the Munich law and tax firm RDS financed four iPads for the project. These iPads come preloaded with carefully selected, child-friendly chess programs, allowing children to engage with chess independently outside of their scheduled training sessions and benefit from its cognitive advantages.

"Checkmate Cancer" is a joint project of the Munich Chess Foundation, led by board member Dijana Dengler and chairman Stefan Kindermann, the oncology department of the Children's Hospital Munich Schwabing, represented by Prof. Dr. Dr. Irene Teichert-von Lüttichau, and Dipl.-Psych. Walther Stamm, as well as the Cura Placida Foundation, represented by Dr. Yvonne Princess of Croÿ and Dr. Gerhard Brandl. The project was initiated by Dr. Yvonne Princess of Croÿ, in collaboration with the Munich Chess Foundation and the Children's Hospital Munich Schwabing.

We extend our sincere gratitude to foundation founder Roman Krulich, who has supported the project from the very beginning with strong financial commitment. Special thanks also go to RDS Law Firm for their generous donation of the tablets.



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- Stiftung für krebskranke Kinder -
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