4th Freiburg Pediatric Research Day

29. November 2022

Research Group Profiles

Research group leaders would be glad to talk to anyone interested in joining or working with their group – for example, for a masters or doctoral project or for post-doctoral work. Feel free to approach them during the breaks or after the Research Day!

This booklet contains short profiles for several research group leaders have put together short profiles of their work; for more information, including about other research groups, please visit www.research-for-children.de/research or https://www.uniklinik-freiburg.de/kinderklinik/forschung-und-klinische-studien.html.

Prof. Dr. Stephan Ehl

Human T cell immunodeficiencies

Human genetic diseases provide a fascinating window to understand T cell immunity and its relevance for the control of infectious diseases as well as for diseases of immune dysregulation. We study three immunodeficiency states representing models for different aspects of T cell immunity:

- T cell effector functions: Hemophagocytic Lymphohistiocytosis (HLH)
- T cell development and activation: Profound Combined Immunodeficiencies (P-CID)
- T cell differentiation and homeostasis: Autoimmune-lymphoproliferative primary immunodeficiencies (AL-PID)

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is one of the most dramatic and life-threatening human inflammatory diseases. Patients with HLH offer a unique opportunity to study the molecular regulation of lymphocyte cytotoxicity and intracellular vesicle trafficking. We characterize the uncontrolled T cell response in HLH to better understand the pathophysiological basis of the disease. Patients without a genetic diagnosis are evaluated by whole exome sequencing in search of novel genetic causes. We coordinate a world-wide international registry and a clinical study platform for experimental treatment studies on HLH (TREAT-HLH). We are using observations in human patients and in MUNC13 deficient mice to prepare gene therapy for human patients with FHL3.

Autoimmune-lymphoproliferative primary immunodeficiencies

Benign lymphoproliferation and autoimmunity, in particular autoimmune cytopenia, is observed in a number of primary immunodeficiencies (AL-PID)**.** The most prevalent disorder is autoimmune lymphoproliferative syndrome (ALPS), which is mostly associated with germline or somatic mutations in CD95. We investigate the pathophysiological basis of impaired T cell homeostasis in human ALPS by a combination of

genetic, phenotypic and functional investigations. In the last years, we have contributed to the discovery of several new diseases associated with lymphoproliferation and autoimmunity have been discovered. A number of these conditions affect signalling pathways and metabolic programming of T cells, offering interesting insights into human T cell biology and attractive options for novel therapies.

Combined immunodeficiencies

Combined immunodeficiencies (CID) present with a wide range of infectious diseases and manifestations of impaired immune regulation such as autoimmunity. The common immunological abnormality is a gentic impairment of T cell immunity. The study of CID offers a unique opportunity to understand the limiting factors of protective T cell immunity. We approach this problem by the study of individual patients, patient cohorts and mouse models. A prospective clinical study has been initiated to better define the threshold when stem cell transplantation should be performed in affected patients. In the laboratory, we combine genome analysis with functional assays to elucidate novel genetic causes for CID. These findings are related to the particular clinical phenotypes to better understand infection control and immune regulation in humans. The overall goal is to understand how human T cell immunity works under limiting conditions.

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PD Dr. Miriam Erlacher

Hematopoiesis, bone marrow failure and leukemia

Our research focuses on the hematopoietic system. We investigate how stress signals and developmental cues influence blood formation, with focus on **apoptosis** regulated by BCL-2 proteins. In addition, we have a strong research focus in the fields of **bone marrow failure**, genetic **predisposition to leukemia** and **juvenile myelomonocytic leukemia**. To study disease-causing mechanisms, we are using different preclinical model systems such as mouse models (i.e. for Gata2 deficiency, dyskeratosis congenita and Noonan syndrome) and lentivirally manipulated human hematopoietic stem and progenitor cells.

Examples of projects and publications

BCL-2 proteins regulate hematopoiesis - this can be used therapeutically

Anti-apoptotic BCL-2 proteins are essential for survival of human hematopoietic stem and progenitor cells. In contrast, pro-apoptotic BCL-2 proteins are crucial for stress response. We identified two pro-apoptotic BCL-2 proteins, BIM and BMF, as main killer genes responsible for apoptosis of donor stem cells. Their transient inhibition improves the outcome of stem cell transplantation without leading to side effects.

- Bohler et al, Inhibition of the anti-apoptotic protein MCL-1 severely suppresses human hematopoiesis, *Haematologica*, 2021
- Afreen et al, BCL-XL expression is essential for human erythropoiesis and engraftment of hematopoietic stem cells, C*ell Death Dis,* 2020
- Transient apoptosis inhibition in donor stem cells improves hematopoietic stem cell transplantation, *J Exp Med*, 2017
- Labi et al, Haematopoietic stem cell survival and transplantation efficacy is limited by the BH3-only proteins Bim and Bmf, *EMBO Mol Med*, 2013

Inhibition of apoptosis prevents bone marrow failure in a mouse model of dyskeratosis congenita (DC)

DC is a disease characterized by premature telomere shortening. We show that cells with critically short telomeres undergo p53- and PUMA-dependent apoptosis, which results in loss of hematopoietic stem and progenitor cells and bone marrow failure. Inhibition of PUMA is sufficient to prevent bone marrow failure while genomic stability is maintained.	• Molnar et al, PUMA-induced apoptosis drives bone marrow failure and genomic instability in dyskeratosis congenita, under revision
GATA2 deficiency leads to bone marrow failure and secondary leukemia	
GATA2 deficiency is a syndrome associated with high risk leukemia risk. In a newly developed mouse model, we show that GATA2 deficiency first leads to bone marrow failure and that leukemogenesis is a secondary event caused by aberrant chromosomal segregation.	• Manuscript in preparation
Juvenile myeloid leukemia: apoptosis resistance and immune escape molecules drive leukemogenesis and leukemia relapse	
JMML is an aggressive leukemia of early childhood. In genetically modified mice and patient-derived xenograft mice, we show that apoptosis resistance caused by BCL-XL over-expression as well as various immune escape molecules are responsible for leukemogenesis and leukemia relapse.	• Krombholz et al, Azacitidine is effective for targeting leukemia-initiating cells in juvenile myelomonocytic leukemia, *Leukemia*, 2019 • Krombholz et al, Long-term serial xenotransplantation of juvenile myelomonocytic leukemia recapitulates human disease in Rag2-/-γc-/- mice, *Haematologica*, 2016

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Dr. Karsten Häffner

Pediatric Nephrology Research

Our main focus is on complement system mediated disorders especially in renal disease in children. We also explore new therapeutic strategies for these patients. In particular we are focused on:

- Analysis of physiological and pathophysiological mechanisms in pediatric renal diseases (aHUS, C3G, ANCA-GN, IgAN, PSHN, …)
- Identification of new proteins involved in complement mediated diseases
- Development of new therapeutic strategies for complement mediated diseases
- Improving therapeutic long term applications in animal models

In our research we are elucidating mechanisms involved in complement regulation to better understand pathophysiological mechanisms. With this knowledge we are able to analyze and design new therapeutics for these diseases, with a special focus on physiological complement regulating proteins.

Examples of projects and publications

Revealing complement regulatory functions of Thrombospondin-1

TSP-1 is a major compound of α-granules in platelets and present in Weibel-Palade bodies of endothelial cells. The identification of its complement regulation potential might play a role in vasculitis or thrombotic events.

Konwar, Tschongov, et al & **Häffner**

in preparation (see poster)

Development and preclinical investigation of recombinant moos derived Factor H. *Cooperation with eleva GmbH, Freiburg*

Together with eleva GmbH we are developing recombinant FH for therapeutic applications. In preclinical *in vitro* and *in vivo* analyzes we are preparing a phase I clinical trial.

To optimize long term applications of therapeutic proteins in mouse models we developed a method preventing antibody formation.

Michelfelder, et al & **Häffner**. Moss-Produced, Glycosylation-Optimized Human Factor H for Therapeutic Application in Complement Disorders *JASN. 2017*

Development of physiological fusion proteins for complement mediated diseases

To optimize functionality and treatment options in complement mediated diseases we're developing fusion proteins to combine physiological functions for complement regulation.

Michelfelder, et al & **Häffner**. MFHR1 is a novel synthetic multi-target complement inhibitor with therapeutic potential *JASN. 2018*

Ruiz-Molina, et al & **Häffner**. *Communication Biology 2022*

Analyses for treatments indications

Medical treatment for aHUS patients is cost intensive and burdens families and young patients. In a retrospective study we analyzed necessity and treatment efficacy in MCP related aHUS patients.

Klämbt, et al. & **Häffner** Different approaches to long-term treatment of aHUS due to MCP mutations: a multicenter analysis. *Pediatr Nephrol. 2021*

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Prof. Dr. Simone Hettmer

Pediatric sarcoma research

We investigate pediatric sarcomas. Our research is directed at identifying causes of disease, establishing targets for rational treatments and estimating risk of adverse outcomes. Projects in the lab address the following questions:

- Interaction of *TP53* and MAPK signaling in rhabdomyosarcoma
- Epicycle: Confirmatory preclinical study of BRD4 and CDK9 inhibitors in PAX3:FOXO1 + rhabdomyosarcoma
- Plasticity/ intratumoral heterogenity of PAX3:FOXO1+ rhabdomyosarcoma
- Anti-tumor effects of azacitidine and trametinib in NRAS-mutated pediatric cancers
- Genetic sarcoma susceptibility
- Detection of bone marrow disease in rhabdomyosarcoma by FDG-PET/ CT
- Prognostic value of the fusion partner in FOXO1-rearranged rhabdomyosarcoma
- Reduction of bias in preclinical research

The goal of our research is to improve the outcomes of children, adolescents and young adults diagnosed with sarcomas through a deeper understanding of disease biology.

Examples of projects and publications

Plasticity/ intratumoral heterogenity of PAX3:FOXO1+ RMS.	
Understanding cell-to-cell heterogeneity in in PAX3:FOXO1 + rhabdomyosarcoma using a genetically engineered mouse model.	Regina, Hamed,…, Hettmer. Negative correlation of single-cell PAX3:FOXO1 expression with tumorigenicity in rhabdomyosarcoma. *Life Science Alliance 202*1

Therapeutic targeting of the asparagine dependence of sarcomas.	
Exploring metabolic vulnerabilities and their cellular outcomes in sarcoma cells with the goal of establishing anti-sarcoma combinations of antimetabolites	Bauer, Regina,…, Kammerer, Hettmer. Lack of electron acceptors contributes to redox stress and growth arrest in asparagine-starved sarcoma cells.*Cancers, 2021*
Azacitidine and trametinib in NRAS-mutated pediatric tumors.	
Clinical report of an exceptional response to treatment and preclinical studies to suggest that azacitidine may prevent trametinib resistance.	Hanft, Hamed, ... Niemeyer, Hettmer. Combinatorial effects of azacitidine and trametinib on NRAS-mutated melanoma.*PBC, 2022*
Genetic sarcoma susceptibility.	
Understanding individual susceptibility to develop soft-tissue sarcomas and establishing tools to recognize sarcoma patients who are likely carriers of cancer-predisposing germline variants	Uckunkaya,..., Hettmer. Patterns of prior and second malignant neoplasms in children and adolescents with soft-tissue sarcoma. *J Pediatr Hematol Oncol, 2020*
Diversity across the rahbdomyosarcoma spectrum	
PAX:FOXO1 neg. rhabdomyo-sarcomas are clinically and biologically diverse. A better understaning of diversity is a prerequisite for refined stratification of risk and tailoring of treatment intensity.	Teot, ..., Hettmer. Clinical and mutational spectrum of highly differentiated rhabdomyosarcoma. *Cancer, 2018*

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Dr. Friedrich Kapp

Understanding Vascular Anomalies

We investigate the genetic basis of vascular anomalies, such as lymphatic, venous, and arteriovenous malformations. Our research approach is broad and utilizes retrospective analyses of patient data, prospective clinical studies and registries, as well as basic laboratory research. However, the focus lies on translational science ("bedside to bench and back") utilizing the zebrafish model to model vascular anomalies, and on clinical trials to find effective treatments and interventions for patients with these rare diseases. Our group focuses on the following main thematic areas:

- Zebrafish model
    - Characterization of novel genes and variants of unknown significance implicated in vascular anomalies
    - Molecular effect of RAS pathway mutations on vascular development
    - Life-imaging of the development of vascular anomalies
    - Drug treatments to remodel vascular anomalies
- Clinical research
    - Clinical trials (e.g. sirolimus or alpelisib in patients with overgrowth / vascular anomalies)
    - Establishing a registry for vascular anomalies
    - Building networks of expert centers to improve patient care

The goal of our research is to better understand vascular anomalies to identify better and safer treatment approaches for patients with these diseases.

Examples of projects and publications

Functional Characterization of Genetic Variants in the Zebrafish	
We developed a pipeline for rapid assessment of novel mutations in vascular anomalies. Interestingly, mutations found in venous malformation lead to venous malformations in the zebrafish.	Bell, … , **Kapp**. Functional assessment of two variants of unknown significance in *TEK* by endothelium-specific expression in zebrafish embryos. Hum Mol Genet, 2021.
Use of Sirolimus in a Subset of Patients with very severe Disease	
We retrospectively looked at a subset of our cohort of patients with vascular and assessed efficacy of sirolimus in the setting of a life-threatening lymphatic malformations.	Holm, … , **Kapp**. Efficacy of Sirolimus in Patients Requiring Tracheostomy for Life-Threatening Lymphatic Malformation of the Head and Neck: A Report From the European Reference Network. *Front. Pediatr,* 2021
The SIPA-SOS and the EPIK-P2 Clinical Trials	
In these trials, we treat patients with vascular malformations and overgrowth to determine the efficacy of sirolimus (SIPA-SOS) and alpelisib (EPIK-P2) in shrinking the affected tissue.	

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Dr. Hannah Kappler

Congenital Heart Defect Research

In a combined experimental and clinical approach, we investigate the relationship of structural and functional remodeling of the right ventricle with clinical phenotypes and outcomes, especially arrhythmias. Here, we mainly focus on:

- Cellular electrophysiological alterations and pro-arrhythmic propensities in the myocardium of patients with congenital heart defects
- Fibrotic remodeling of the right ventricle
- Hetero-cellular coupling associated with fibrosis
- The influence of age, medical treatment and invasive procedures on the myocardium
- Possible predictive values of experimental myocardial findings in a clinical setting

The goal of our research is to identify underlying pro-arrhythmogenic substrates in congenital heart defect patients, and, by linking these myocardium-based findings to indicators of clinical phenotype and disease severity, to ultimately improve earlier identification of those patients at risk in the future.

All of our experimental research is done in collaboration with the Freiburg CardioVascular BioBank (CVBB) at the Institute of Experimental Cardiovascular Medicine (https://www.uniklinik-freiburg.de/experimentelle-kardiovaskulaere-medizin.html).

Examples of projects and publications

Structural and functional myocardial remodeling in patients with congenital heart defects	
Characterization of action potential shape, pro-arrhythmic perturbations, and fibrotic remodeling of right ventricular myocardium from patients	Wülfers, […], Rog-Zielinska, Fürniss (2021) Quantitative collagen assessment in right ventricular myectomies from patients with tetralogy of

with congenital heart defects and their relationship to clinical findings.	Fallot. *EP Europace* 2021 4:i38-i47. doi: 10.1093/europace/euaa389 Study ongoing.
Right ventricular fibrosis measured by cardiac MRI in patients with tetralogy of Fallot	
Appearance and time course of MRI-based indicators of myocardial fibrosis in repaired tetralogy of Fallot patients and influence of fibrosis on parameters of right ventricular function, e.g. contractility.	Study ongoing.

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Dr. Alexandra Klotz

Pediatric Epilepsy Research

The pediatric epilepsy research group focusses on clinical and translational research in pediatric epilepsies. The main themes include:

- High frequency oscillations in EEG
- Novel treatment options in pharmacoresistant epilepsies, regarding efficacy and tolerance as well as patients' and caregivers expectations and perception
- Comorbidities in pharmacoresistant epilepsies
- Epileptic networks in hypothalamic hamartomas
- Anxiety and effects of early intervention on anxiety in patients with a first unprovoked seizure or febrile seizures and their families
- Telehealth in pediatric epilepsy care

The goal of our research is to provide evidence in how to improve diagnostics and treatment in pediatric epilepsies. Most studies are tailored to improve the life of children with refractory epilepsies, but we are also interested in early diagnostics and interventions in patients at risk of developing seizures.

Examples of projects and publications

High frequency oscillations as biomarkers of epilepsy disorders as well as physiological brain processes

Improving the understanding of the difference between physiological and pathological high frequency oscillations, their role in brain maturation and cognitive development and in prediction of disease onset.

Klotz, Sag, Schönberger & Jacobs. Scalp ripples can predict development of epilepsy after first unprovoked seizure in childhood. *Annals of Neurol, 2020*.

Epileptic vs. physiologic high-frequency oscillations: Characterization of a single-neuron fingerprint

We aim to dissect high-frequency oscillations at the single-neuron level, and to reveal specific mechanisms of epileptic and physiologic high-frequency oscillations.	Guth, Kunz, Brandt, Dümpelmann, **Klotz**, Reinacher, Schulze-Bonhage, Jacobs, Schönberger. Interictal spikes with and without high-frequency oscillation have different single-neuron correlates. *Brain,* 2021

Cannabidiol as a new treatment option in severe epilepsies in childhood

The Freiburg Cannabidiol Program includes an open label study of efficacy and tolerance of synthetic cannabidiol in pharmakoresistant epilepsies and studies of effects of cannabidiol on cognition, comorbidities and EEG activity. In addition, we explored expectations and perceptions of this new treatment option among caregivers and medical professionals.	**Klotz**, Grob, Schönberger, Nakamura, Metternich, Schulze-Bonhage, Jacobs. Effect of Cannabidiol on Interictal Epileptiform Activity and Sleep Architecture in Children with Intractable Epilepsy: A Prospective Open-Label Study. *Front. Pediatr,* 2021

Epileptic networks in patients with hypothalamic hamartoma as an example of secondary epileptogenesis

Epileptic hamartoma can be used to study network changes during secondary epileptogenesis. We want to better understand the changes of networks over time and their relation to disease severity.	Metzger, Jacobs, Scheerer, Reinacher, Schulze-Bonhage, Wagner, Schönberger & **Klotz**. Ictal epileptic networks in 34 patients with hypothalamic hamartoma: A scalp EEG study. *AES annual meeting 2021*

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PD Dr. Rouven Kubicki

Pediatric Cardiology Research

We investigate new diagnostic tools and novel treatment strategies in newborn, children, adolescents and adults with congenital heart defects and acquired heart disease. Our research group focuses on the following main thematic areas:

- Participation in registry and drug studies
- Terminal heart failure and mechanical circulatory assist device
- Imaging in congenital heart defects
- Innovative cardiac catheter interventions

The goal of our research is to optimize treatment strategies in terms of efficiency and safety and to improve the long-term outcome as well as the quality of life for our vulnerable patients.

Examples of projects and publications

Management of rare and complex congenital heart defects

Transposition of the great arteries with ventricular septal defect (VSD) and left ventricular outflow tract obstruction is a rare malformation. We report on management and results of the cohort with non-committed VSD from a national registry for congenital heart disease.

Kari AF, Uzdenov M, Kroll J, Bohnens H, Stiller B, Bauer U, **Kubicki R**

Transposition of great arteries with left outflow tract obstruction and non-committed VSD: surgical management and late results

Eur J Cardiothorac Surg 2022

Integrity analysis of patch-like Gore devices

We describe our mid- to long-term experience with the Gore Septal Occluder for ASD closure in a pediatric cohort focusing on the device's mechanical durability.

Kubicki R, Fingerhut K, Uhl M, et al.

Wire-frame integrity of patch-like Gore devices following atrial septal defect closure.

Cath Cardiovasc Interv 2019

A novel catheter strategy	
To assess the potential occupational radiation reduction and technical feasibility in patients rotated 180° (upside-down) when requiring neck access for transcervical or trans-subclavian catheterisation.	**Kubicki R**, Hummel J, Höhn R, et al. Catheter strategy to ease the procedure and reduce radiation exposure when requiring neck access *Open Heart, 2020*
Acquired von Willebrand syndrome during mechanical circulatory support	
Bleeding signs can become life-threatening complications in patients on mechanical circulatory support. We conducted coagulation analyses and determined von Willebrand factor parameters in a pediatric cohort on temporary ECLS, ECMO or long-term ventricular assist device support.	**Kubicki R**, Stiller B, Kroll J, et al. Acquired von Willebrand syndrome in paediatric patients during mechanical circulatory support. *Eur J Cardiothorac Surg 2019*
Weaning from Extracorporeal Life Support (ECSL)	
ECLS weaning is a complex inter-disciplinary process with no clear guidelines. A standard protocol might optimize weaning results unbiased by on-site teams' clinical experiences and preferences. We developed such a protocol in order to adjust the weaning strategy to patients' hemo-dynamics in standardized way.	**Kubicki R**, Grohmann J, Höhn R, et al. Implementing and Assessing a Standardized Protocol for Weaning Children Successfully From Extracorporeal Life Support. *Artif Organs 2018*

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Dr. Dr. Anke Schumann

Basic research

Our research focusses on pathomechanisms driving kidney disease in different metabolic diseases (e.g. organic acidurias, Fabry's disease) using human model systems. Our special interest lies on the crosstalk between different organelles and cellular compartments. We also aim at the identification of potentially targetable mechanisms to modify affected pathways and the evaluation of specific compounds on renal cellular (energy) metabolism.

Examples of projects and publications

Mitochondrial damage in renal epithelial cells is potentiated by protein exposure in propionic aciduria	
In this study, we investigated which factors might be of importance for the progression of chronic kidney disease in propionic aciduria. Amino acid and high protein exposure aggravated changes in renal mitochondrial morphology and function. The metabolic stressors impacted on mitochondrial energy metabolism and quality control. Disease-specific metabolite profiles changed and accumulating potentially toxic metabolites seemed to prevent activation of protective mechanisms.	Schumann A, Belche V, Schaller K, Grünert SC, Kaech A, Baumgartner MR, Kölker S, Hannibal L, Spiekerkoetter U. Mitochondrial damage in renal epithelial cells is potentiated by protein exposure in propionic aciduria. *J Inherit Metab Dis.* 2021. doi10.1002/jimd.12419

Defective lysosomal storage in Fabry Disease modifies mitochondrial structure, metabolism and turnover in renal epithelial cells.	
In this study we provide evidence, that renal tubular epithelial cells are involved in the pathogenesis of chronic	Schumann A, Schaller K, Belche V, Cybulla M, Grünert SC, Moers N, Sass JO,

kidney disease (CKD) in Fabry disease. We shed light on how a lysosomal storage disorder modifies mitochondrial energy metabolism and homeostasis in the kidney and investigate which compensatory mechanisms might be used to prevent CKD progression.	Kaech A, Hannibal L, Spiekerkoetter U. Defective lysosomal storage in Fabry Disease modifies mitochondrial structure, metabolism and turnover in renal epithelial cells. *J Inherit Metab Dis.* 2021. DOI: 10.1002/jimd.12373

Impaired mitophagy links mitochondrial disease to epithelial stress in methylmalonyl-CoA mutase deficiency	
We combined genetic and pharmacological approaches to demonstrate that Methylmalonyl-CoA mutase (MMUT) deficiency induces metabolic and mitochondrial alterations leading to abnormalities in PINK1/Parkin–mediated mitophagy. Accumulation of dysfunctional mitochondria trigger epithelial stress and ultimately cell damage. These results obtained on a multisystem level suggest a link between primary MMUT deficiency, dysfunctional mitochondria, dysfunctional mitophagy and epithelial stress. They point at potential therapeutic targets for MMUT patient treatment.	Schumann A*, Luciani A*,.. Baumgartner MR, Devuyst O. Impaired mitophagy links mitochondrial disease to epithelial stress in methylmalonyl-CoA mutase deficiency. *Nat Commun.* 2020

We are currently testing the effect of pharmacological compounds on the identified altered pathways in the different disease models.

Helping hands are very welcome!

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