

# Promotionsprojekt (ID = 5407\_2)



<b>Thema/Titel des Projekts</b> (max. 200 Zeichen)	
Investigating Mitochondrial Dysfunction and Metabolic Reprogramming in Hirschsprung Disease Intestinal Organoids under Proinflammatory Conditions	
<b>Art des Projekts / des Vorhabens</b>	
<input checked="" type="checkbox"/> experimentell <input checked="" type="checkbox"/> experimentell- grundlagenwissenschaftlich <input type="checkbox"/> experimentell-tierexperimentell <input type="checkbox"/> klinisch <input type="checkbox"/> klinisch – experimentell	<input type="checkbox"/> patientenorientiert <input type="checkbox"/> statistisch <input type="checkbox"/> statistisch-theoretisch <input type="checkbox"/> theoretisch <input type="checkbox"/>
<b>Fachgebiet</b>	
Kinderchirurgie	Fachgebiet 3
<b>Forschungsschwerpunkt</b>	
Forschungsschwerpunkt	Forschungsschwerpunkt
<b>Graduiertenkolleg / School</b>	
Graduiertenkolleg / School	Graduiertenkolleg / School
<b>Durchführungsort (Zentrum, Institut/Klinik )</b>	
Klinik und Poliklinik für Kinderchirurgie	
<b>Beschreibung und Zielsetzung des Forschungsprojekts</b>	
<p>Hirschsprung disease (HSCR) is characterized by the absence of enteric ganglia in the distal intestine, resulting in impaired motility, intestinal obstruction, and chronic inflammation. While genetic mutations are recognized as key drivers of neuronal deficits in Hirschsprung disease (HSCR), emerging evidence strongly suggests that metabolic dysregulation and mitochondrial dysfunction also play pivotal roles in the epithelial pathophysiology of this condition. Given the increased susceptibility of HSCR patients to inflammatory bowel disease (IBD), it is particularly important to investigate whether these two diseases share common metabolic and mitochondrial pathways that may underlie their inflammatory and pathological profiles. Organoids derived from intestinal stem cells have emerged as powerful tools to model such disorders, capturing both genetic and functional complexities of patient-derived tissue.</p> <p>Objectives: This project aims to investigate mitochondrial dysfunction and associated metabolic reprogramming mechanisms in HSCR organoids during proinflammatory stimulation. Specifically, we aim to:</p>	

1. Characterize mitochondrial respiratory function and metabolic flux in HSCR organoids vs. controls upon inflammatory stimulation.
2. Isolate and analyze mitochondria from HSCR and control organoids to pinpoint specific mitochondrial respiratory chain alterations, enzymatic dysfunctions, and structural abnormalities.
3. Identify metabolic and proteomic signatures linked to enhanced respiration, potentially revealing novel biomarkers

### Aufgaben und Methoden

Intestinal organoids derived from HSCR patients and matched healthy controls will be cultured and treated with proinflammatory cytokines to mimic inflammatory stress conditions relevant to clinical HSCR. Metabolic function will be initially assessed using Seahorse extracellular flux analysis, which allows real-time measurement of oxygen consumption rates (OCR) and extracellular acidification rates (ECAR). Given our preliminary findings, we hypothesize that increased mitochondrial respiration observed in HSCR organoids indicates a compensatory metabolic response or mitochondrial stress adaptation. To further dissect mitochondrial-specific changes, mitochondria will be isolated using an optimized differential centrifugation protocol adapted for intestinal organoids. Functional integrity of isolated mitochondria will be assessed through respiratory control ratios (RCR), ATP production assays, and measurement of membrane potential (JC-1 staining). Ultrastructural mitochondrial analysis via electron microscopy will provide morphological insights into potential

### Anforderung an die Bewerber:innen:

Scientific curiosity and the love for big data, coding, or analyzing.

12 months full-time lab

Voraussichtlicher Beginn:	01/10/2025
Voraussichtliche Dauer des Projekts (in Monaten):	18
Davon in Vollzeit:	12
Einbindung in Forschungsbesprechungen, Vortrags- und Seminarreihen:	JC Kinderchirurgie, JC Basic Science Kinderchirurgie
Finanzielle Fördermöglichkeit:	
Betreuer:in des Promotionsvorhabens:	Christian Tomuschat
Co-Betreuer:in:	Anna Romanova
Ansprechperson:	Christian Tomuschat
E-Mail-Adresse(n):	c.tomuschat@uke.de
Instituts- oder Klinikwebseite:	
Gewünschte Bewerbungsunterlagen:	
Bewerbungsfrist:	30/05/2025