



Maladaptations at  
Physiological Barriers:  
Insights and Outlooks  
Magdeburg, Germany 5-7 May 2025



Magdeburg May 5-7, 2025

# Maladaptation at Physiological Barriers: Insights and Outlooks

Symposium Schedule



MEDIZINISCHE  
FAKULTÄT



UNIVERSITÄTS MEDIZIN  
MAGDEBURG

## Additional Information



### Accommodation

Motel One Magdeburg  
Domplatz 5  
39104 Magdeburg  
Germany



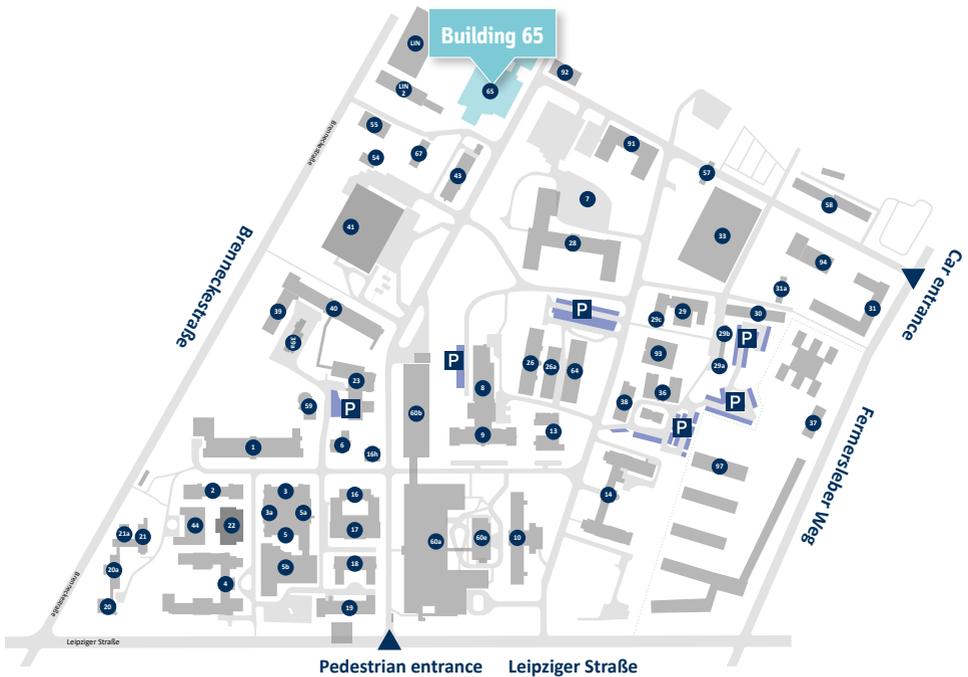
### Event Venue

UMMD Campus Building 65  
Leipziger Straße 44  
39120 Magdeburg  
Germany  
Building 65 is located on the campus.



### Welcome Dinner & Social Evening Venue

Festung Mark  
Hohefortewall 1  
39104 Magdeburg  
Germany



## Day 1. // 05.05.25

Time	Event	Talk
08:00 - 09:00	Registration	
09:00 - 09:45	Welcome	
09:45 - 10:35	Session 1	<b>Prof. Jonathan Pruneda</b> ( <i>Oregon Health &amp; Science University, USA</i> ) Pathogenic bacteria manipulate host ubiquitin signaling with surgical precision
10:35 - 11:25		<b>Prof. Romina Fiorotto</b> ( <i>Yale School of Medicine, USA</i> ) Innate immunity and the gut/liver axis in biliary diseases
11:25 - 12:30	Poster Presentation and Coffee Break	
12:30 - 13:30	Lunch Break	
13:30 - 14:20	Session 2	<b>Prof. Petya Apostolova</b> ( <i>University of Basel, Switzerland</i> ) Immunotherapy-related colitis - novel approaches to restore tissue homeostasis
14:20 - 15:10		<b>Prof. João T. Barata</b> ( <i>University of Lisbon, Portugal</i> ) IL-7 and IL-7R signaling gone wrong
15:10 - 18:00	City Walk	
18:30	Welcome Dinner	

## Day 2. // 06.05.25

Time	Event	Talk
09:15 - 10:05	Session 3	<b>Prof. Reiko Sugiura</b> ( <i>Kindai University, Japan</i> ) Novel regulatory mechanisms of ERK MAPK signaling and its application to cancer therapy
10:05 - 10:55		<b>Prof. Soman Abraham</b> ( <i>Duke University, USA</i> ) Mast cells in host defense: Benefits and detriments
10:55 - 11:25	Coffee Break	
11:25 - 12:05	Session 4	<b>Prof. Christina Zielinski</b> ( <i>Leibniz - HKI, Germany</i> ) Gasdermin E pore transfer - a new T cell cytotoxicity mechanism
12:05 - 12:55		<b>Prof. Daniel Dwyer</b> ( <i>Harvard Medical School, USA</i> ) TGF-beta regulation of MCT differentiation and effector function
13:00 - 15:30	Lunch Break	
15:30 - 16:20	Session 5	<b>Prof. Keiji Hirota</b> ( <i>University of Tokyo, Japan</i> ) Type 17 immunity in health and chronic inflammation
16:20 - 17:10		<b>Prof. Masanori Hatakeyama</b> ( <i>Institute of Microbial Chemistry, Japan</i> ) Direct and indirect roles of <i>Helicobacter pylori</i> CagA in gastric cancer development
18:30	Social Evening and Dinner	

## Day 3. // 07.05.25

Time	Event	Talk
09:15 - 10:05	Session 6	<b>Prof. Paul Elliott</b> ( <i>University of Oxford, UK</i> ) Molecular basis of IKK-dependent activation of A20 DUB activity
10:05 - 10:55		<b>Prof. Pierre-Louis Tharaux</b> ( <i>Paris-Cardiovascular Research Center, France</i> ) Epithelial metabolism at the crossroads with kidney inflammation and fibrosis
10:55 - 11:30	Coffee Break	
11:30 - 12:30	Panel Discussions   Invited speakers participate in a round of discussion	
12:30 - 13:30	Lunch and Closing Ceremony	

We are pleased to announce the following additional talk at short notice:

Prof. Thomas Worzfeld (University of Marburg, Germany):

Molecular mechanisms of epithelial (mal-)adaptation to organ damage

07.05.25 | 11:00 - 11:40

Jonathan Pruneda | Day 1. | 09:45 - 10:35

### **Pathogenic bacteria manipulate host ubiquitin signaling with surgical precision**

A healthy immune response to infection requires rapid and robust post-translational signaling following pathogen detection. At the heart of many immune signaling pathways is the essential regulatory modifier ubiquitin, which can signal for many different cellular outcomes including protein degradation or kinase activation. Some bacterial detection pathways even require three or four discrete types of ubiquitin modifications for proper signaling. Unfortunately, pathogenic bacteria have evolved secreted effector proteins that redirect, inhibit, or eliminate host ubiquitin signaling events in order to facilitate invasion, replication, and persistence. Although some families of these ubiquitin-targeted effectors are eukaryote-like in structure and mechanism, others are entirely distinct and likely reflect a strong evolutionary pressure that has led to convergence of function. Our research aims at identifying novel ubiquitin-targeted effectors among human pathogens, characterizing their target specificity and mechanism of action, and evaluating their contribution to infection and disease. I will present our latest findings that demonstrate the remarkable strategies employed by bacteria to subvert host signaling, and highlight how studying these effectors can shed light on both host and microbe biology.

---

Romina Fiorotto | Day 1. | 10:35 - 11:25

### **Innate immunity and the gut-liver axis in biliary diseases**

Chronic diseases of the biliary tree (cholangiopathies) represent a major unmet need in clinical hepatology. These disorders primarily target cholangiocytes, the epithelial cells lining the biliary ducts. Under homeostasis, cholangiocytes regulate bile composition, form a protective barrier, and contribute to innate immunity, inflammation, and tissue repair. However, disruption of homeostasis or persistent injury induces a reactive cholangiocyte phenotype characterized by secretion of pro-inflammatory cyto-chemokines, proliferation and reduced secretory function. Cystic fibrosis liver disease (CFLD), a genetic cholangiopathy caused by dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR), exemplifies this process.

CFTR deficiency in cholangiocytes disrupts TLR4-dependent innate immune regulation, rendering the biliary epithelium hypersensitive to endotoxins and triggering an exaggerated inflammatory response upon TLR4 activation. Simultaneously, CFTR deficiency in the gut alters microbiota composition, weakens the epithelial barrier, and creates a chronic inflammatory state. The translocation of bacteria and their products from the gut to the liver further amplifies biliary inflammation, as overreactive cholangiocytes fuel an immune response.

This gut-liver crosstalk in CFLD serves as a model for studying biliary innate immunity and the role of the microbiome in cholangiopathies.

Petya Apostolova | Day 1. | 13:30 - 14:20

### **Immunotherapy-related colitis - novel approaches to restore tissue homeostasis**

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) and immune checkpoint inhibitors are two of the most frequently used tumor immunotherapy modalities. While they have significantly improved patient outcomes, both approaches can lead to immune-mediated complications, such as graft-versus-host disease (GVHD) and immune-related adverse events (irAE). Maladaptations at epithelial barriers, such as the gastrointestinal tract, are at the core of these disorders, and restoring tissue homeostasis contributes to patient cure. Dr. Apostolova will discuss experimental and early clinical approaches to treat intestinal GVHD and immune checkpoint inhibitor-induced colitis. In the context of GVHD, the focus will lie on the role of bile acids in controlling epithelial cell fitness and immune cell activation. Furthermore, she will present novel data on the efficacy and molecular mechanism of extracorporeal photopheresis (ECP) as a potent treatment for irAE.

---

João T. Barata | Day 1. | 14:20 - 15:10

### **IL-7 and IL-7R signaling gone wrong**

IL-7 (a cytokine produced in the bone marrow, thymus and other organs) and IL-7R (the receptor for IL-7, which is expressed in lymphoid precursors) are essential for normal lymphoid development. However, excessive IL-7R-mediated signaling can promote leukemia. I will provide an overview of how the IL-7/IL-7R axis can contribute to acute lymphoblastic leukemia (ALL) initiation, progression and resistance to chemotherapy, and share some of our current studies on the idiosyncrasies of IL-7R signaling in leukemia, and on how aberrant IL-7R activation at different stages of hematopoietic development may lead to immunophenotypically similar yet transcriptionally distinct subsets of ALL.

Reiko Sugiura | Day 2. | 09:15 - 10:05

### **Novel regulatory mechanisms of ERK MAPK signaling and its application to cancer therapy**

Liquid-liquid phase separation (LLPS) has recently emerged as a new fundamental mechanism for the eukaryotic cellular organization via the formation of membrane-less intracellular organelles exemplified by RNA granules. RNA granules play important roles in various physiological and pathological processes, including regulation of gene expression, cellular stress responses, and signal transduction. Especially, recent studies have highlighted the importance of these biomolecular condensates in cancer signaling. Among them, SGs have attracted strong attention as a promising target for cancer treatment because of their involvement in various aspects of cancer progression, ranging from cancer formation to metastasis, as well as drug resistance. SGs regulate important signaling pathways, such as mTOR and MAPK via spatial recruitment of signaling molecules thus indicating that SGs constitute signaling hubs that can rewire signal transduction relevant to cancer. We have been studying MAPK signaling pathways using the fission yeast *Schizosaccharomyces pombe* as an excellent model system to unravel the fundamental principles of cell fate. In this presentation, I will discuss how SGs have a role as signaling hubs beyond serving as a repository for non-translated mRNAs during acute stress. Additionally, I will discuss our recent discovery of a novel compound to stimulate ERK-dependent apoptosis, thereby proposing a concept of ERK pathway agonism as a cancer therapy.

---

Soman Abraham | Day 2. | 10:05 - 10:55

### **Mast Cells in Host Defence: Benefits and Detriments**

Mast cells (MCs) are tissue-resident immune cells located at the host-environment interface, adjacent to blood vessels and nerves. Their capacity to release a large bolus of pre-stored inflammatory mediators upon activation makes MCs crucial for regulating initial immune responses to invading pathogens. In contrast to wild-type mice, MC-deficient mice show a reduced ability to recruit immune cells, leading to increased susceptibility to bacterial and viral infections.

While the roles of MCs are generally beneficial, they can also have detrimental effects. For example, in the bladder, which is prone to recurrent urinary tract infections (UTIs), MCs facilitate the rapid recruitment of neutrophils and monocytes to combat infection. However, these recruited cells also produce significant amounts of nerve growth factor (NGF), which can stimulate excessive nerve growth in the bladder. Thereafter, local MCs sustain bladder nerve growth through NGF release, long after the infection has resolved, leading to lingering pain, and frequent urination in UTI patients.

Another instance of harmful MC responses occurs when infections become systemic. In such cases, bacteria or viruses trigger simultaneous activation of MCs lying at the abluminal regions of blood vessels throughout the body, resulting in a cytokine storm and systemic immune dysregulation with severe consequences. While MCs play a vital protective role against infections, their repeated or simultaneous activation throughout the body can contribute to significant pathology.

Christina Zielinski | Day 2. | 11:25 - 12:05

### **Gasdermin E pore transfer - a new T cell cytotoxicity mechanism**

Cytotoxic T cells (CTLs) exert their killer functions by releasing cytotoxic molecules such as perforin and granzymes or by engaging the Fas-FasL pathway, which induce apoptosis in the target cells. Additionally, they can trigger cell death through the Fas-FasL pathway, a receptor-mediated mechanism that leads to programmed cell death. We report a new cytotoxic effector function, which is exerted via transfer of T cell derived gasdermin E membrane pores. These membrane pores get established temporarily on the plasma membrane upon T cell receptor activation. Despite pore formation, no evidence for T cell death was observed. This is mechanistically due to enhanced membrane repair through ESCRT, resulting in the release of extracellular vesicles (EVs) containing the gasdermin E pores. Interestingly, these EVs can enter other cells leading to gasdermin E transplantation and cell death by osmotic shock, whereas T cells remain protected due to TCR-induced membrane repair. This cytotoxic function was especially pronounced in T cells with high stemness. In sum, we suggest a novel T cell killer mechanism that integrates stemness and potent effector functions and might be harnessed for anti-tumor therapies in the future.

---

Daniel Dwyer | Day 2. | 12:05 - 12:55

### **TGF- $\beta$ regulation of MCT differentiation and effector function**

Human mast cells (MCs) fall into two main histochemically defined categories: MCs co-expressing the proteases tryptase and chymase (MCTCs) and MCs containing tryptase alone (MCTs). Of these, MCTs selectively expand within the mucosal epithelium during inflammation, yet little is known about the signals directing MCT differentiation or how their effector functions differ from MCTCs deeper within the tissue. We have used single-cell RNA sequencing as a tool to probe human MC heterogeneity, focusing on the expanded MC population found within human nasal polyps. Through this approach, we identified TGF- $\beta$  as a candidate driver of MCT differentiation. In vitro-differentiated MCs treated with TGF- $\beta$  after maturation took on an MCT-like transcriptional and cell surface phenotype, while exposure to TGF- $\beta$  signaling during differentiation inhibited granule incorporation of the hallmark MCTC proteases chymase and cathepsin G, allowing selective in vitro differentiation of MCTs for functional study. In vitro-derived MCTs exhibit a distinct effector phenotype, including elevated secretion of IL-5 but decreased IL-13 in response to activation and a striking elevation in pro-inflammatory eicosanoid production, recapitulating functional distinctions between MCT and MCTC in primary nasal polyps. Together, our findings support a role for TGF- $\beta$  in promoting human MCT differentiation and generate a powerful tool for further unraveling the role of MCT in mucosal inflammation.

Keiji Hirota | Day 2. | 15:30 - 16:20

### **Type 17 immunity in health and chronic inflammation**

The IL-23 signaling pathway in both innate and adaptive immune cells is vital for orchestrating type 17 immunity, which is marked by the secretion of signature cytokines such as IL-17, IL-22, and GM-CSF. These proinflammatory mediators play indispensable roles in maintaining intestinal immune equilibrium and mucosal host defense. However, their dysregulation contributes to the pathogenesis of chronic inflammatory conditions, such as inflammatory bowel diseases and autoimmunity.

In this presentation, I will explore the distinct sources of IL-23 under homeostatic versus inflammatory conditions. In the gut, EpCAM<sup>+</sup> DCIR2<sup>+</sup> conventional dendritic cells are the primary source of IL-23, playing a key role in maintaining intestinal barrier integrity. Conversely, IL-23-producing interfollicular epithelial cells are central to driving psoriatic skin inflammation.

I will also discuss the functional heterogeneity of pathogenic Th17 cells in the context of autoimmune arthritis. Single-cell RNA sequencing in conjunction with single-cell TCR-seq of joint-infiltrating CD4<sup>+</sup> T cells revealed three phenotypically distinct Th17 cell clusters, ranging from a CD103<sup>+</sup> Tcf1<sup>high</sup> IL-17F<sup>high</sup> IL-22<sup>high</sup> stem-like state to a CD200<sup>+</sup> Egr2<sup>high</sup> IL-17A<sup>high</sup> GM-CSF<sup>high</sup> highly pathogenic state. Together, these findings highlight the diverse cellular landscape of the IL-23–IL-17 axis and underscore its potential as a therapeutic target in inflammatory and autoimmune diseases.

---

Masanori Hatakeyama | Day 2. | 16:20 - 17:10

### **Direct and indirect roles of *Helicobacter pylori* CagA in gastric cancer development**

Infection with *Helicobacter pylori* cagA-positive strains is causally associated with the development of most, if not all, human gastric cancers. The Capital C. cagA-encoded CagA protein is injected into gastric epithelial cells via bacterial type IV secretion, where it undergoes tyrosine phosphorylation by host-cell kinases. Tyrosine-phosphorylated CagA binds to the pro-oncogenic tyrosine phosphatase SHP2, which aberrantly activates SHP2 and thereby elicits deregulated stimulation of the pro-mitogenic/pro-oncogenic RAS-ERK signaling pathway. In recipient host gastric cells, CagA also binds to and inhibits the polarity-regulating serine/threonine kinase PAR1b, inducing junctional and polarity defects. Furthermore, CagA-mediated PAR1b kinase inhibition impairs the cytoplasmic-to-nuclear translocation of the BRCA1 tumor suppressor by preventing PAR1b-mediated BRCA1 phosphorylation. Loss of BRCA1 in the nucleus provokes the cellular status known as „BRCAness“ that induces excess DNA double-strand breaks (DSBs), triggering the expansion of CagA-expressing cells with BRCAness-associated genomic instability, from which CagA-independent gastric cancer cells eventually emerge. Notably, *H. pylori* infection in carriers of BRCA1 pathogenic variants causes a dramatic increase in gastric cancer risk. These findings indicate that the induction of BRCAness by CagA–PAR1b interaction plays a crucial role in the development of gastric cancer by *H. pylori*.

Paul Elliott | Day 3. | 09:15 - 10:05

### **Molecular basis for IKK-dependent activation of A20 DUB activity**

The deubiquitinating enzyme A20 acts as a negative regulator of NF- $\kappa$ B signalling pathways, and mutations in the A20 gene (TNFAIP3) have been linked to various inflammatory disorders. Genetic studies in mice indicate that while A20's DUB activity is not essential for normal function, its capability to bind non-degradative Met1-linked ubiquitin chains is crucial for preventing inflammation-induced cell death. The purified catalytic domain of A20 displays low enzymatic activity compared to other DUBs and shows a preference for cleaving Lys48-linked ubiquitin chains, in contrast to the Lys63-linked chains regulated by A20 in cells. We have identified IKK, the master kinase of inflammatory signalling, as a kinase of A20, whereby phosphorylation enhances A20 DUB activity. Through a combination of structural studies and biochemical assays, we illustrate how IKK phosphorylation boosts A20 DUB activity and suggest a re-evaluation of the functional significance of A20 DUB activity.

---

Pierre-Louis Thauraux | Day 3. | 10:05 - 10:55

### **Epithelial Metabolism at the Crossroads with Kidney Inflammation and Fibrosis**

In the kidney, peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) regulates lipid metabolism in tubular epithelial cells (TECs) by facilitating the reabsorption and mitochondrial metabolism of free fatty acids (FFAs) from the glomerular filtrate.

We observed that PPAR $\gamma$  expression is markedly alleviated in TECs of kidney biopsies from patients with chronic kidney disease caused by crescentic glomerulonephritis (CGN) or HIV-associated nephropathy (HIVAN). Likewise, we observed PPAR $\gamma$  downregulation in TECs, and PUFAs (ligands of PPAR $\gamma$ ) were decreased in a mouse CGN model, suggesting a link between TEC metabolism and fibrosis.

Therefore, to investigate a potential causal role for PPAR $\gamma$  in CKD, we generated a model with conditional Pparg gene targeting in TECs (Pax8<sup>-</sup>LC1<sup>-</sup>Cre<sup>-</sup>PPAR $\gamma$ ) that developed accentuated kidney injury and fibrosis in a CGN, suggesting a cytoprotective role for PPAR $\gamma$ . The PPAR $\gamma$  agonist pioglitazone displayed a powerful anti-fibrotic action in CGN and HIVAN models and fully prevented epithelial profibrotic STAT3 and SMAD3 serine-phosphorylation in TECs. At last, we found that PPAR $\gamma$ , SMAD3 and STAT3 form a complex with a serine/threonine kinase. PPAR $\gamma$  and this kinase exhibit reciprocal actions, controlling fibrotic cascades.

**Otto-von-Guericke-Universität Magdeburg**

Medizinische Fakultät

Leipziger Str. 44

39120 Magdeburg

[mapbio@med.ovgu.de](mailto:mapbio@med.ovgu.de)

[sandro.gogia@med.ovgu.de](mailto:sandro.gogia@med.ovgu.de)

[arun.kanthasamy@med.ovgu.de](mailto:arun.kanthasamy@med.ovgu.de)

Funded by



Deutsche  
Forschungsgemeinschaft

German Research Foundation

