Collaborative Research Centre/Transregio 240

– Platelets –
Molecular, cellular and systemic functions in health and disease

Julius-Maximilians-Universität Würzburg

Eberhard Karls Universität Tübingen

Final Report

2018/2 – 2023/1

FINAL REPORT

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– Platelets – Molecular, cellular and systemic functions in health and disease

Applicant university/universities: Julius-Maximilians-Universität Würzburg

Eberhard Karls Universität Tübingen

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1 Summary

Zusammenfassung

Thrombozyten sind von zentraler Bedeutung für die Hämostase, aber auch bei der Entstehung akuter thrombotischer Erkrankungen wie Herzinfarkt oder Schlaganfall. Darüber hinaus sind Thrombozyten aber auch vielseitige Effektorzellen von Entzündungsprozessen, der angeborenen Immunität, bei zellulären Abwehrmechanismen sowie bei der Aufrechterhaltung der Gefäß- und Organintegrität. Diese neuen, als *Thrombo-Inflammation* und *Immunothrombose* bezeichneten Funktionen haben im Rahmen der COVID-19 Pandemie große Aufmerksamkeit erlangt, da betroffene Patienten systemische Entzündungszustände in Verbindung mit thromboembolischen Komplikationen aufweisen, die oft auch tödlich verlaufen. Im SFB/TR 240 arbeitete ein interdisziplinäres Team von grundlagenorientierten, translationalen und klinischen Wissenschaftlern zusammen an der Erforschung dieser neuartigen Thrombozytenfunktionen mit dem Ziel, neue verbesserte Therapiemöglichkeiten für kardiovaskuläre, aber auch andere Erkrankungen zu entwickeln. Während der Förderphase haben wir i) die Mechanismen aufgeklärt, die in seltenen Fällen nach Impfung mit Adenovirus-basierten Vakzinen gegen Sars-CoV-2 zu lebensbedrohlichen thromboembolischen Komplikationen führten, ii) neue Funktionen und Regulationsmechanismen thrombozytärer Rezeptoren identifiziert, die Grundlage zur therapeutischen Intervention sein könnten und iii) neue Technologien entwickelt, die vertiefte Studien zur Biologie der Megakaryozyten, den Vorläuferzellen der Thrombozyten im Knochenmark, ermöglichen und den Weg zu einer gezielten Beeinflussung der Thrombozytenbiogenese und –funktion ebnen könnten. Die Projekte des TR 240 konzentrierten sich auf die folgenden komplementären Forschungsgebiete: **(A)** *Zellbiologie der Megakaryozyten und Thrombozyten* mit dem Ziel eines verbesserten Verständnisses der grundlegenden Funktionen beider Zelltypen und **(B)** *Thrombozyten als Modulatoren und Effektoren bei Erkrankungen*. Um dieses Ziel zu erreichen, wurde ein sehr umfassender Ansatz verfolgt, der sich von *in vitro* Systemen über Tiermodelle bis hin zur klinischen Forschung mit Biobanken und großen, prospektiven Patientenkohorten erstreckte. Der SFB/TR 240 konnte in der vergleichsweisen kurzen Zeit seiner Förderung grundlegend neue Erkenntnisse zu den Mechanismen der Thrombozytenbiogenese, Thrombozyten-Signaltransduktion und -Effektorfunktionen erarbeiten und neue MK/Thrombozyten-spezifische Angriffspunkte für Diagnose und Therapie thrombotischer, hämorrhagischer und thrombo-inflammatorischer Erkrankungen identifizieren.

Summary

Besides their central role in haemostasis and thrombosis, platelets are increasingly recognised as versatile effector cells in inflammation, the innate and adaptive immune response, extracellular matrix reorganisation and fibrosis, maintenance of barrier and organ integrity, and host response to pathogens. These platelet functions, referred to as thrombo-inflammation and immunothrombosis, have gained major attention in the COVID-19 pandemic, where patients develop an inflammatory

disease state with severe and life-threatening thromboembolic complications. In the CRC/TR 240, a highly interdisciplinary team of basic, translational and clinical scientists explored these emerging roles of platelets with the aim to develop novel treatment concepts for cardiovascular disorders and beyond. We have i) unravelled mechanisms leading to life-threatening thromboembolic complications following vaccination against SARS-CoV-2 with adenoviral vector-based vaccines, ii) identified unrecognised functions of platelet receptors and their regulation, offering new potential targets for pharmacological intervention and iii) developed new methodology to study the biology of megakaryocytes (MKs), the precursor cells of platelets in the bone marrow, which lay the foundation for the modulation of platelet biogenesis and function. The projects of the CRC/TR 240 built on the unique expertise of our research network and focussed on the following complementary fields: (**A**) *Cell biology of megakaryocytes and platelets* and (**B**) *Platelets as regulators and effectors in disease*. To achieve this aim, we followed a comprehensive approach starting out from *in vitro* systems and animal models to clinical research with large prospective patient cohorts and data-/biobanking. Despite the comparably short funding period the CRC/TR 240 discovered basic new mechanisms of platelet biogenesis, signal transduction and effector function and identified potential MK/platelet-specific molecular targets for diagnosis and therapy of thrombotic, haemorrhagic and thrombo-inflammatory disease states.

2 Published Results

2.1 Publications with scientific quality assurance

Becker, I. C., Z. Nagy, G. Manukjan, M. Haffner-Luntzer, M. Englert, T. Heib, T. Vogtle, C. Gross, R. Bharti, S. Dietrich, K. Mott, J. Heck, S. Stegmaier, A. Baranowsky, T. Schinke, N. Schlegel, T. Heckel, D. Stegner, I. Pleines, A. Ignatius, H. Schulze and B. Nieswandt (2022). "G6b-B regulates an essential step in megakaryocyte maturation." **Blood Adv** 6(10): 3155-61. DOI: 10.1182/bloodadvances.2021006151. OA (open access)

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2.2 Other publications and published results

Name	**Patent**
Greinacher	(Test) Risikobestimmung für eine prothrombotische Thrombozytopenie (DE Patent) DE-Patentanmeldung DE 10 2021 106 913.0 (Dok-Referenz 2021031919325400DE) Patentschrift: 20.03.2021/ Erteilung am 16.01.2023
Greinacher	Modifizierter SARS CoV 2 Impfstoff (DE Patent) DE- Patentanmeldung DE 10 2021 106 940.8 (Dok-Referenz 2021032112544200DE)
Greinacher	Modifizierter SARS CoV 2 Impfstoff – Erweiterung (DE Patent) DE- Patent-anmeldung DE 10 2021 106 940.8, DE 10 2021 107 085.6, (Dok-Referenz 2021032220550000DE)
Nieswandt/ Schuhmann/ Stegner/Stoll	Treatment and prevention of ischemic diseases and/or ischemic tissue damages. PCT/EP/2020/068464; WO 2021/001404A1, US 2022/0372159 A1.
Schulze	Novel biomarker allowing the early diagnosis of sepsis: EP 3772651A1 (EP19190817.7)

3 Overview of Projects

Project	Title	Research area	Project leaders, institute(s), location(s)	Duration indicated only in case of deviation from funding period
A01	Mechanisms of megakaryocyte polarisation and platelet biogenesis	Cell Biology, Haematopoiesis, Cardiovasc. Res.	**Irina Pleines,** Inst. of Exp. Biomed. I, UKW **Zoltan Nagy,** Inst. of Exp. Biomed. I, UKW **Bernhard Nieswandt** Inst. of Exp Biomed. I & RVZ, UKW / JMU	2018/7 – 2021/6 2021/7 – 2023/6
A02	Casein kinase dependent signalling in platelet activation and thrombopoiesis	Cell Biology, Haematopoiesis, Cardiovasc. Res.	**Oliver Borst** Internal Medicine III, UKT	
A03	Impact of the irradiated bone marrow niche on platelet biogenesis and function	Experimental Haematology, Haematopoiesis	**Harald Schulze,** Inst. of Exp. Biomedicine I, UKW **Süleyman Ergün,** Inst. Of Anatomy and Cell Biol. JMU **Tamara Girbl,** RVZ, JMU	2018/7 – 2022/6 2022/7 – 2023/6

A04	Optogenetic approaches to study platelet production and function	Optogenetics, Haematopoiesis	**Markus Bender,** Inst. of Exp. Biomed. I, UKW **Georg Nagel,** Inst. of Physiology - Neurophysiology, JMU **Shiqiang Gao** Inst. of Physiology - Neurophysiology, JMU	2022/7 – 2023/6
A05	Mechanosensitive cGMP signalling in platelets	Biochem., Cell Signalling, Mouse Gen.	**Robert Feil / Susanne Feil** Interfaculty Institute of Biochemistry, UT	
A06	The role of the platelet cytoskeleton in platelet mechanics	Platelet Biology, Mechanobiology, Biophysics	**Rhagavendra Palankar** Institute of Immunology and Transfusion Medicine, UMG **Oliver Otto,** Centre for Innov. Competence / Institute of Physics, UG **Markus Bender,** Inst. of Exp. Biomed. I, UKW	2018/7 – 2022/6
A07	Mechanisms of platelet receptor regulation and disintegration	Haemostaseology, Cell Biology, Cardiovasc. Res.	**Bernhard Nieswandt** Inst. of Exp. Biomedicine I & RVZ, UKW / JMU **Markus Sauer,** Biotech. & Biophysics, JMU	
A08	Regulation of the platelet lipidome and its implications in thrombo-inflammation	Platelet Biology, Lipidomics, Advanced Imaging	**Madhumita Chatterjee,** Internal Med.III, UKT **Michael Lämmerhofer,** Institute of Pharmaceutical Sciences, UT **Tilman Schäffer,** Inst. of Appl. Physics, UT	*Project A08* 2018/7 – 2022/6
A09	Relevance and molecular mechanisms of zinc homeostasis in megakaryopoiesis and platelet function	Haemostaseology, Platelet Biology, Thrombosis	**Attila Braun** Inst. of Exp. Biomed. I, UKW **Heike Hermanns** Department of Internal Medicine II, UKW	2018/7 - 2019/5 2018/7 – 2022/12
A11	The interplay between platelets and pathogenic bacteria	Infection, Microbiology, Transf. Med., Haemostasis, Immunology	**Sven Hammerschmidt,** Interfaculty Institute for Genetics and Funct. Genomics, UG **Andreas Greinacher,** Institute of Immunology and Transfusion Medicine, UMG	
B01	CXC chemokine receptors and regulation of platelet function, thrombo-inflammation and myocardial remodelling in I/R	Cardiovascular Research, Inflammation, Cell Signalling	**Harald Langer** Internal Medicine II, University Hospital Lübeck **Anne Katrin Rohlfing** Internal Medicine III, UKT **Meinrad Gawaz** Internal Medicine III, UKT	2018/7 – 2022/6 2022/7 – 2023/6
B02	Platelet-dependent injury and safeguard mechanisms in acute ischaemic stroke	Neurology, Neuroradiology, Neuroimmunology	**Guido Stoll,** Department of Neurology, UKW **Michael Schuhmann,** Department of Neurology, UKW **Mirko Pham** Inst of Diagn. & Intervent. Neuroradiol., UKW	2022/7 – 2023/6

B03	Platelet CyPA/RAGE as modulators of inflammation and immune responses during myocardial remodelling and aneurysm formation	Vascular and Myocardial Biology, Platelets	**Alma Zernecke-Madsen** Inst. of Exp. Biomedicine II, UKW **Peter Seizer** Internal Medicine III, UKT **David Heinzmann** Internal Medicine III, UKT	 2018/7 – 2019/9 2019/10 – 2023/6
B04	Role of platelets in tissue remodelling and functional recovery after experimental cerebral ischaemia	Mol. And Cellular Neurology, Thrombosis, Inflammation	**Harald Langer** Internal Medicine II, University Hospital Lübeck **Christoph Kleinschnitz** Department of Neurology, UK Essen	 *Project B04* 2018/7 – 2022/6
B05	The role of platelets in premetastatic niche formation and metastasis	Tumour immunology / Metastasis	**Lars Zender,** Med. Oncology & Pulmonology/IM VIII, UKT **Oliver Borst** Internal Medicine III, UKT	
B06	Platelets as modulators of neuro-inflammation in the ischaemic brain	Neurology, Bio-Imaging	**Katrin Heinze,** RVZ, JMU **Michael Schuhmann,** Dept. of Neurol., UKW **David Stegner,** Inst. of Exp. Biomed. I, UKW	
B07	The role of platelets in pulmonary inflammation during ARDS	Inflammation, Cardiovascular Research	**Peter Rosenberger** Dept. of Anesthesiol./ Intens. Care Med., UKT **Bernhard Nieswandt** Inst. of Exp Biomed. I & RVZ, UKW / JMU	
B08	Role of platelet-mediated resolution-regeneration programmes of bacterial-induced sepsis	Inflammation, Resolution of Inflammation, Regeneration	**Valbona Mirakaj** Dept. of Anesthesiol. and Intens. Care, UKT **David Stegner** Institute of Exp. Biomedicine I, UKW	2018/7 – 2022/1
B09	Platelet-derived inflammatory mediators in progressive aortic valve disease	Cardiovasc. Res., Inflammation, Cell Signal., Infection	**Stella Autenrieth** Internal Medicine II, UKT **Karin Müller /** **Meinrad Gawaz** Internal Medicine III, Dept. of Cardiology, UKT	2018/7 – 2020/9 2020/10 – 2023/6
B10	The impact of platelets on the maintenance of pancreatic β cell mass and development of diabetes	Immunology, Diabetes, Physiology	**Grzegorz Sumara** Rudolf Virchow Centre, JMU / Since 09/19: Nencki Institute for Experimental Biology, Warsaw Poland	 *Project B10* 2018/7 – 2022/6
Z01	Central tasks of the CRC	N/A	**Bernhard Nieswandt** Inst. of Exp Biomed. I & RVZ, UKW / JMU	
Z02	Platelet Proteomics Platform (PPP): combining proteomics, phosphoproteomics, lipidomics and bioinformatics	Proteomics, Systems biology	**Thomas Dandekar** Dept. of Bioinformatics, Biocenter, JMU **Michael Lämmerhofer** Institute of Pharmaceutical Sciences, UT **Albert Sickmann,** Leibniz-Inst. ISAS, Dortmund **Robert Ahrends,** Leibniz-Inst. ISAS, Dortmund	 2022/7 – 2023/6 2018/7 – 2019/12

Z03	Translational platform	Platelet Research, Clinical Studies	**Tobias Geisler** Internal Medicine III, UKT **Peter Heuschmann** Inst. of Clin. Epidemiol. and Biometry, JMU **Andreas Greinacher** Inst. of Immunology & Transfusion Med., UG **Hermann Neugebauer** Dept. of Neurology, UKW	2022/7 – 2023/6
Z04	Multiparametric *in vivo* imaging	Molecular Imaging	**Bernd Pichler / Barbara Schörg** Dept of Preclin. Imaging & Radiopharm., UKT	2022/7 – 2023/6
INF	The Virtual Platelet Platform ViPP: An Images and Systems Biology data repository and workbench	Bioinformatics, Data Science	**Thomas Dandekar** Dept of Bioinformatics, Biocenter, JMU **Katrin Heinze** Bio-Imaging-Centre, RVZ, JMU	

4 Research Achievements of the CRC

Research goals of the CRC/TR 240

The references (highlighted in blue) generated within the CRC/TR 240 and cited in the text are listed in chapter 2.1.

Blood platelets are small, anucleate cells that play a critical role in preventing excessive bleeding at sites of injury, a process known as haemostasis. Platelet activation also triggers blood clots within the diseased circulation (thrombosis), e.g. following rupture of inflammatory atherosclerotic lesions in the vessel wall, causing heart attack and stroke, two of the leading causes of death and severe disability worldwide representing an enormous socio-economic burden for modern societies. Basic, translational as well as clinical platelet research has advanced considerably in recent years. A deepened understanding of the role of platelets in cardio- and cerebrovascular diseases has led to significant improvements in therapy and reduced morbidity and mortality, but often at the expense of bleeding complications. In addition, recent evidence has indicated unexpected roles of platelets in (patho-)physiological conditions beyond thrombosis and haemostasis, such as thrombo-inflammation, innate immunity and host defence,

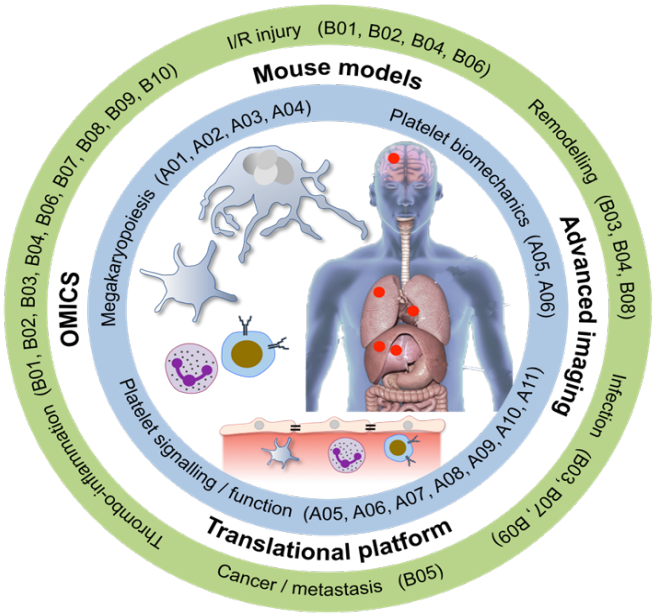

Figure 1. The projects to the CRC/TR 240.

maintenance of barrier and organ integrity, tissue regeneration, and proliferative diseases. However, the molecular mechanisms and therapeutic relevance of these novel platelet functions are largely unknown. Exploring these emerging platelet functions may finally lead to novel treatment concepts also beyond cardiovascular disorders. This ultimate goal requires a highly interdisciplinary approach relying on a combination of state-of-the-art mouse genetics, *in vivo* disease models, super-resolution microscopy and advanced *in vivo* imaging techniques, systems biology/*omics*, translational platforms, and clinical research expertise. To meet this challenge, the CRC/TR 240 was established in July 2018 by scientists of the Julius-Maximilians University Würzburg, the Eberhard Karls University Tübingen, the corresponding University hospitals, the University of Greifswald, the Leibnitz Institute for Analytical Sciences (ISAS) and the University of Duisburg-Essen, all of whom have demonstrated a long-standing commitment in the fields of platelet/megakaryocyte biology and thrombotic/thrombo-inflammatory disorders. The CRC/TR 240 built on two DFG-funded research consortia (CRC 688, CRU 274) establishing a unique network of basic, translational and clinical scientists that focused on the following complementary fields (**Fig. 1**): In **Project Area A** (*Cell biology of megakaryocytes and platelets*), and **Project Area B** (*Platelets as regulators and effectors in disease*), the aim was to study the pathophysiological significance of platelets in major disease settings with limited treatment options (*unmet need)*. Hereby, we concentrated our work on the increasingly recognised function of platelets as orchestrators of thrombo-inflammatory processes and tissue remodelling. The goal was to identify general as well as organ-specific pathways by which platelets modulate these pathologies while simultaneously maintaining vascular integrity and barrier function. To achieve this, the projects in Area B assessed and compared platelet functions in paradigmatic thrombo-inflammatory disease settings in major organs, notably heart and brain, but also lung, liver, and pancreas. Together, the projects of Area A and B aimed to provide new targets for disease and organ-specific treatment approaches based on manipulating platelets in patient-individualised protocols (precision medicine), building on a comprehensive strategy starting out from *in vitro* systems and animal models to clinical research with large prospective patient data-/biobanking (**Fig. 2**).

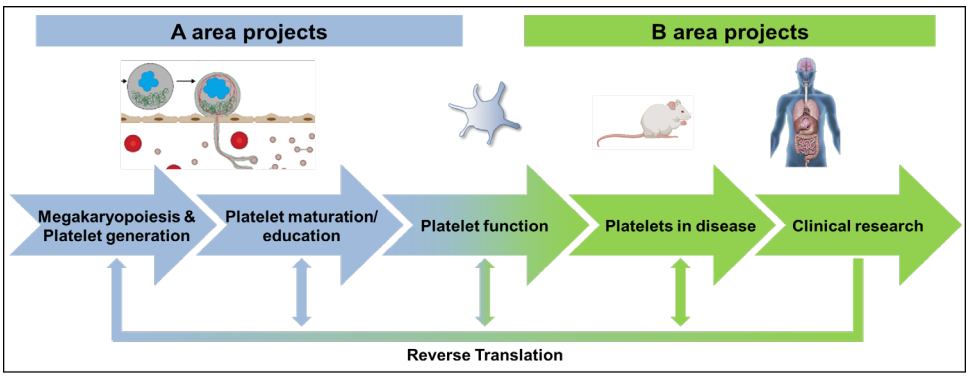

Figure 2. The project areas of the CRC/TR 240.

Achievements of the CRC/TR 240

In the first funding period, the CRC/TR 240 successfully established collaborative structures within and between the participating sites. The clinical **Z03** platform was very rapidly established as a key point to integrate human translational studies. Numerous projects (**B01**, **B02, B03**, **B09**) benefitted from standardised clinical protocols and joint SOPs to validate their experimental findings in the clinical setting. The technological achievements included, but were not limited to the following: first description of pial blood sampling and profiling in hyperacute stroke patients, super-resolution microscopy of platelets and MKs, scRNA-seq of primary MKs, optogenetics in MKs and platelets, in-depth lipidomic profiling of platelets (human/mouse), intravital microscopy and light sheet fluorescence microscopy (LSFM) techniques to study platelet/MK behaviour at subcellular resolution *in situ* in different organs in mice, including brain, liver, lung, pancreas, BM and spleen, generation of humanised and reporter mouse lines and establishment of real time deformation cytometry for high throughput biophysical assessment of platelets. Successful experiments investigating mouse models with genetic platelet defects and blood samples of patients with the corresponding hereditary platelet disorder within the same experimental setup in Würzburg and Greifswald, hereby overcoming distances and establishing the infrastructure for the following funding period. Successful remote auditing to improve quality management. The CRC/TR 240 established the Virtual Platelet Platform ViPP of INF, which allowed for large-scale data exchange and provides software pipelines and tailored analysis tools for all members of the CRC. In addition, the ViPClass teaching cloud provided video tutorials on methods and laboratory procedures, particularly for young researchers. ViPP and ViPClass were instrumental to foster collaborations, training, and teaching, especially during the pandemic. These structures will be maintained and further developed despite the ending of the CRC/TR 240.

Based on these structural and technological developments, our consortium uniquely generated a significant quantity of data on platelets/MKs, including in-depth transcriptomic, proteomic and lipidomic profiling as well as functional insights into major platelet/MK signalling cascades and their cellular interactions. We identified novel molecular interactions driving thrombo-inflammation and immunothrombosis in different organs and disease settings and could contribute to the current understanding of the pathomechanisms underlying severe COVID-19 and vaccine-induced immune thrombotic thrombocytopenia (VITT).

The CRC/TR 240 has contributed to 231 original research articles with a cumulative impact factor of 2,900. In addition, we have written 48 reviews/editorials. **Some examples illustrating our scientific productivity in the different areas of research are:**

We elucidated the relevance of the lipid metabolism for **platelet biogenesis** (Manke *et al.* Circ Res 2021 – A02, Z02, A01, B08, de Jonckheere *et al.* Nat Cardiovasc Res 2023 – A02, Z02, A03, B06) and identified the platelet receptor G6b-B as an essential modulator of megakaryocyte maturation (Geue *et al.* Blood 2019 – A02, A01, A03, B01, B08, Becker *et al.* Blood Adv 2022 – A01, A03, B08).

In addition, the interplay of CXCL12-abundant cells and megakaryocytes were studied in the context of thrombopoiesis (Wagner *et al.* Cells 2021 – A03, B06). Moreover, we were among the first to apply optogenetics to megakaryocytes, providing a more detailed understanding of phosphodiesterase activity in megakaryocytes (Zhang *et al.* Open Biol 2022 – A04, A05) and offering a technological platform to address previously untraceable questions on the spatio-temporal organisation of platelet biogenesis (e.g. MK polarisation, initiation of proplatelet formation).

We have unravelled principal **new signalling checkpoints/pathways in platelets** and MK, some of which might have translational potential for the modulation of platelet biogenesis and/or function (Geue *et al.* Blood 2019 – A02, A01, A03, B01, B08, Volz *et al.* J Clin Invest 2020 A09, B02, B06, INF, Z02). We established the first comprehensive quantitative lipidomic analysis in platelets (Peng *et al.* Blood 2018, Peng *et al.* Nat Commun 2020 B01, B05, Harm *et al.* Cardiovasc Res 2021). By using this quantitative lipidomics platform, we were able to identify critical regulators of platelet lipid metabolism and arachidonic acid (AA)-derived oxylipin generation upon GPVI-dependent platelet activation (Manke *et al.* Circ Res 2021 – A02, Z02, A01, B08). Likewise, we could show that platelet CXCR7 senses lipids and regulates thrombo-inflammation (Cebo *et al.* Blood 2022 - A08, B01, A02). We provided new insights into the relevance of mechanosensing for platelet function and how the platelet cytoskeleton (Scheller *et al.* Haematologica 2022 – A01, B08, A06) and cGMP signalling (Wen *et al.* Nat Commun 2018 - A05, B01, B04) contribute to it. It could also be shown that platelet lamellipodium formation is dispensable for thrombus formation (Schurr *et al.* Blood 2019 - A06, A07). Moreover, we could demonstrate that storage pool diseases affect Zinc homeostasis of platelets (Kiran Gotru *et al.* Sci Rep 2019 - A03, A09, A01, A11, Elgheznawy et al., A09, A01, A03, A07).

Thrombo-inflammation and regulation of **vascular integrity**: Platelets critically contribute to organ dysfunction beyond acute vessel occlusion by thrombo-inflammation, which has been demonstrated by the COVID-19 pandemic. The underlying pathomechanisms and how they differ between organs was a central research topic in our CRC/TR: We have demonstrated an unexpected role of platelets in the development of non-alcoholic steatohepatitis (NASH) and its progression to cirrhosis and hepatocellular carcinoma (HCC) (Malehmir *et al.* Nat Med 2019 - A02, A07, B01, B05, B08, Z03). We described previously unrecognised functions of platelet receptors and their regulation in cardio-/neurovascular thrombo-inflammation offering new potential targets for pharmacological intervention (Kohler *et al.* Nat Commun 2020 - B07, A07, B01, Z03, Rath *et al.* J Thromb Haemost 2020 - B03, Z03, B01, A02, Schuhmann *et al.* Circ Res 2020 - B06, A07, A09, B02, Z03, Weiss *et al.* Blood 2021 - A03, A07, Rohlfing *et al.* Nat Commun 2022 - B01, B04, A08, Burkard *et al.* Blood 2023 - B07, INF). We were the first to show that brain infarct progression under occlusion, i.e. before recanalisation, is amenable to anti-platelet treatment in mice and thrombo-inflammation is a driving force in hyperacute human stroke as assessed by pial blood sampling during thrombectomy (Essig *et al.* JAMA Neurol 2021 - B02, B06, Kollikowski *et al.* Transl Stroke Res 2021 - B02, B06, B07, Schuhmann *et al.* J Neuroinflammation 2021 - B02, A07, B06, INF). We revealed that platelet-derived lipids

promote insulin secretion of pancreatic β-cells (Karwen *et al.* EMBO Mol Med 2023 - B10, A07, B08, INF). We identified new molecular mechanisms how platelets might regulate metastatic niche formation (Hinterleitner *et al.* Nat Commun 2021 - B05, A02, Z04), haematogenous metastasis (Mammadova-Bach *et al.* Blood 2020 - A07, A09, B07, B08, INF) and tumour vascularisation (Volz *et al.* Blood 2019 - A03, A07, B03; Greinacher *et al.* N Engl J Med 2021).

Besides thrombo-inflammation, platelets and immune cells are also main drivers of a functionally distinct pathomechanism, referred to as **immunothrombosis**, where thrombotic obstruction / occlusion of vessels is triggered by pathogens and/or immune-related mechanisms. One example are the thrombotic events observed in some patients receiving adenovirus-based SARS-CoV-2 vaccines. We characterised the new entity of VITT and identified FcγRIIA dependent, platelet activating anti-PF4 antibodies as the underlying cause (Greinacher *et al.* Blood 2021, Greinacher *et al.* Blood 2021, Greinacher *et al.* N Engl J Med 2021 – A11, A06, Z03). In addition, we provided the first direct evidence that aberrant platelet activation –through a CLEC-2/integrin αIIbβ3-dependent pathway– induces foudroyant cerebral (sinus) vein thrombosis (CVT) in mice. This is the first described CVT model which now enables mechanistic studies and experimental intervention (Stegner *et al.* Nat Cardiovasc Res 2022 - B06, A07, A11, B02, B03, B07, INF, Z04). In this study, we benefited from our advanced fluorescence and PET imaging (Feil *et al.* Circ Res 2023 - A05, Z04) and transcranial fluorescence microscopy. We identified the role of platelet anaphylatoxin receptors C3aR and C5aR in linking innate immunity and arterial thrombosis as well as the impact of platelets on tissue remodelling and neovascularisation (Sauter *et al.* Circulation 2018, Nording *et al.* Nat Commun 2021 - B04, A02, B01, Z03).

As outlined above, the impact of platelet basic science on **translational medicine** is dependent on findings and validations in humans. To ensure a research focus with the highest relevance possible, we evaluated platelet phenotypes and thrombo-inflammatory markers, including *Omics* profiling in large prospective clinical studies and synchronised our data-/biomaterials banking and diagnostic tools at the participating research sites. Besides the project work within the CRC/TR 240, we have significantly contributed to international multicentre randomised trials of antiplatelet / antithrombotic therapy regimes in patients with structural, valvular and ischaemic heart disease, e.g. GALILEO trial (Dangas *et al.* N Engl J Med 2020), AUGUSTUS trial (Lopes *et al.* N Engl J Med 2019), GLOBAL-LEADERS trial (Vranckx *et al.* Lancet 2018 - A02, B01, Z03). PIs of the TR 240 started and accomplished an investigator initiated, randomised clinical trial that shows that platelet inhibition can be performed without enhancing risk of bleeding in coronary artery disease (ISAR-PLASTER Phase 2 trial – (Mayer *et al.* JAMA Cardiol 2021 - A02, B01)).

4.1 Scientific Event and Science Communication

Scientific events:

The COVID-19 pandemic had a major impact on the organisation of scientific events in of the CRC/TR 240. Due to several lockdowns, the 1st Student Symposium of our consortium, which was planned to be held in Greifswald (July, 21-22, 2020) had to be cancelled without replacement. The 4th Platelet Symposium, which was scheduled to take place in Würzburg (June 17-19, 2021) had to be postponed for the same reason and was finally held in 2022 (Würzburg, June 23-25). For more information, please see table below.

Titel	Date	Location	Speakers/Guests
3rd Symposium "Platelets"	October 24-26, 2019	Conference Center, Tübingen	40 invited speakers, among them Patricia Maguire (Dublin), Karlheinz Peter (Melbourne), Alastair Poole (Bristol), Matthew Rondina (Salt Lake City), Wolfram Ruf (Mainz)
(planned) 1st student symposium	July 20-24, 2020	Greifswald	*Cancellation due to COVID-19*
4th Symposium "Platelets"	June 23-25, 2022	Schloss Steinburg, Würzburg	30 invited speakers, among them Lawrence Brass (Philadelphia), Anna Planas (Barcelona), Steve Watson (Birmingham), Dietmar Vestweber (Münster)

Science communication:

Although the COVID-19 pandemic had a serious impact, particularly on any kind of outreach involving people coming together physically, a number of remarkable events and incidents of extensive media coverage have taken place to reach the academic community and the wider public.

For instance, Bernhard Nieswandt and Guido Stoll regularly gave public lectures on stroke and stroke research, members of the CRC/TR 240 contributed to the 6th Symposium on Stroke and doctoral researchers of the CRC/TR 240 took part in the organisation of the 14th EUREKA symposium. Further, the discovery of the signalling molecule CD84 by researchers of the CRC/TR 240 that plays a crucial role in linking platelet activity and T lymphocytes in inflammatory processes following acute stroke in 2020 had an extensive echo in the media including local print media as well as national media. A research team led by the CRC/TR 240 member Andreas Greinacher was at the forefront of mechanistically explaining the development of vaccine-induced immune thrombotic thrombocytopenia (VITT) in connection with the AstraZeneca COVID-19 vaccine, a highly pressing issue since

2021 with major reverberations in public debates on COVID-19 vaccination strategies. The findings by Greinacher *et al.* on the role of anti-PF4 antibodies in the development of rare, but potentially lethal cases of cerebral venous sinus thrombosis were widely reported in the media (leading national print and online media such as FAZ, ZEIT, but also in media addressing medical doctors and pharmacists such as “Ärzteblatt” and “Deutsche Apothekerzeitung”). The “Spiegel” news magazine in February 2021 published a photo documentation on what was happening behind the doors of a COVID-19 intensive care unit at the University Hospital Tübingen/Anaesthesia & Intensive Care headed by the Medical Director and CRC/TR 240 member Peter Rosenberger. The SWR provided information on the treatment of seriously ill COVID-19 patients at the University Hospital Tübingen and in other places across Germany on its website in November 2020.

The CRC/TR 240 website has been a central element of the communication strategy of the consortium and has provided information on research activities of the CRC/TR 240. The website has also been the gate to VIPPClass, the Virtual Platelet Class, which has a dedicated section on public relations intended to foster dialogue between the consortium and the wider public. Part of the communication strategy has been to publish news related to the CRC/TR 240 via a linked X/Twitter account (twitter handle: @TR_240). Public awareness about the research topics was further increased through outreach videos, such as an image movie on the YouTube website (https://www.youtube.com/watch?v=U6BWvhbE6M4).

The Public Science Center (PSC) of the RVZ as well as the press offices of the University of Würzburg and Tübingen supported the CRC/TR 240 for its public outreach activities. The PSC published a number of press releases covering research of the CRC/TR 240 and targeting both the university audience and a network of professional science communicators and journalists. Moreover, the PSC supported the consortium in its outreach activities via social media such as Facebook and Twitter. The PSC also collaborated with researchers of the CRC/TR 240 in the Campus Festival of the University of Würzburg in 2018, where a team of doctoral researchers introduced cardiovascular research to a broader university and non-university audience.

To foster academic exchange with the academic community, the University of Tübingen organised the 3rd international symposium on platelets in October 2019. In 2022, the 4th international symposium on platelets was held in Würzburg. At various national and international conferences, scientific talks by researchers (PIs, postdoctoral researchers, doctoral researchers) of the CRC/TR 240 were given either in-person or online (e.g. State-of-the-Art Lectures at the Congresses of the ISTH; GRCs, ASH Meetings etc.) many of our young researchers received prices (e.g. >25 Young Investigator Awards of the ISTH). We launched a CRC/TR 240 seminar series featuring presentations by members of our consortium as well as distinguished national and international invited speakers (among others Profs. Yotis Senis and Pierre Mangin from Strasbourg, Prof. Alice Assinger from Vienna, Prof. Wolfgang Bergmeier from Chapel Hill, Prof. Matthew Rondina from Utah, and Prof. Alastair Poole from Bristol).

4.2 National and international collaboration

National and international cooperation and networking

Investigators of this CRC have been working in multiple national and international collaborations and networks for many years. For example, PIs from Würzburg collaborated with partners from Maastricht, Birmingham and Reading in the European Training Network TAPAS (2018 – 2021) and with researchers from Boston (USA), Cambridge (UK), Strasbourg (France) and Vienna (Austria). PIs from Tübingen cooperated with researchers in Haifa (Israel), Dublin (Ireland), La Jolla, Baltimore and Boston (USA). PIs from Greifswald collaborate with partners in Hamilton (Canada), Tours (France), and Chapel Hill (USA). Furthermore, we have also built up and intensified excellent collaborations and an ongoing scientific exchange with “platelet research hot spots” in other parts of the world (e.g. University of Pennsylvania, USA; University of Toronto, Canada; McMaster University, Canada; University of Yamanashi, Japan; Monash University, Melbourne, Australia; University of Utah, USA).

We are part of the EUROPEAN PLATELET NETWORK (EUPLAN) with B. Nieswandt and M. Bender representing Germany and the groups of the CRC/TR 240 have long-standing collaborations with most of the contributing research sites all over Europe. We will host the **2025 EUPLAN Meeting** (Congress chairs: M. Bender, B. Nieswandt) which will be held in Würzburg. There have also been close interactions between the BRIDGE consortium (Cambridge, UK), with PIs in Würzburg (H. Schulze), and Greifswald (A. Greinacher) being members and others sharing multiple joint projects and publications with them. Despite the expiration of the CRC/TR 240, we will further strengthen these interactions to facilitate the further development of a European-wide platelet research platform. We are part of the International Clopidogrel Pharmacogenomic Consortium (ICPC) (M. Gawaz, T. Geisler) that concentrates on genome-wide and candidate gene approaches and pharmacogenomic polygenic response in patients treated with antiplatelet drugs.

We have been actively involved in clinical thrombosis and haemostasis as well as transfusion medicine networks (A. Greinacher), including international guideline groups responsible for therapeutic application of platelets or the ClinGen-based Hemostasis/Thrombosis Gene Curation Expert Panel Study, which further opens the translational transfer of basic findings derived from the CRC/TR 240 into clinical application We are also active in the Permanent Commission Pediatrics of the GTH where H. Schulze is a member of the Steering Committee of the GTH/GPOH-mandated THROMKIDplus Study Group on Inherited Platelet Disorders.

5 Impact on Research Priorities and International Visibility

5.1 Impact of the CRC on research priorities at the host institutions

Both the University of Würzburg and the University of Tübingen are strongly committed to research in the life sciences with numerous collaborative initiatives and research centres across disciplines, faculties and departments. By far the majority of grant-funded collaborative research projects at the University of Würzburg are part of the life sciences spectrum. In Tübingen, nearly half of the research profile areas of the university cover aspects of the life sciences, including two of three DFG-funded Clusters of Excellence and a large number of collaborative initiatives. Such initiatives with a cardiovascular research focus and emphasis on platelet biology and close interactions between basic science and clinical institutes have a long-standing tradition at both universities.

The most prominent examples of successful collaborative projects prior to the CRC/TR 240 (2018 – 2023) were the DFG-funded CRC 688 “Mechanisms and imaging of cardiovascular cell-cell interactions” (funding period: 2006-2017) in Würzburg and the CRU 274 “Platelets – molecular mechanisms and translational implications” (funding period: 2011-2019) in Tübingen. The underlying concept of the CRC/TR 240 was based upon the established networks and results by these two consortia and aimed to strengthen the cardiovascular research networks not only in Würzburg and Tübingen, but also to further support ongoing collaborations between the two major sites. Together with its cooperation partners at the Leibniz-Institut für Analytische Wissenschaften – ISAS in Dortmund, and the University of Greifswald and their long-standing commitment in the fields of platelet/megakaryocyte biology and thrombotic/thrombo-inflammatory disorders, the CRC/TR 240 managed to assemble a unique network of basic, translational and clinical scientists.

Throughout the funding period of the CRC/TR 240 from 2018 – 2023, cardiovascular research developed vividly not only in the consortium itself, but also within the larger life sciences community at the two universities due to new research initiatives, newly acquired research infrastructure and recruitment of excellent researchers.

<u>Würzburg</u>

The Faculty of Medicine defined its research profile with cardiovascular research being among the five top research foci. To transcend the traditional clinically oriented research areas, novel level-of-complexity-oriented research dimensions were identified ranging from the cellular and organ/tissue level to system/network diseases. The CRC/TR 240 exemplified this conceptual approach with its project area A (Cell biology of megakaryocytes and platelets) emphasising the cellular/tissue level and B (Platelets as regulators and effectors in disease) addressing pathological system level failure. During the funding period of the CRC/TR 240, several exciting developments have taken place in the life sciences community at the University of Würzburg. The UKW has provided a completely renovated building for the Institute of Experimental Biomedicine (Chair I: Bernhard Nieswandt; Chair

II: Alma Zernecke-Madsen) hosting the groups of A. Zernecke-Madsen, H. Schulze, M. Bender and Z. Nagy. In Würzburg, the RVZ and Institute of Experimental Biomedicine are located in the same research building, which allows the joint usage of state-of-the-art infrastructure in newly organised central facilities (e.g. sequencing core unit, imaging facility, flow cytometry and a modern animal facility). New devices have become available during the CRC/TR 240 funding period. For example, a new confocal Airyscan (fast) super-resolution microscope (ZEISS) was purchased from DFG and institutional funds as part of the W3 appointment for Katrin Heinze. This new microscope was particularly useful for high-resolution live cell imaging, where laser exposure of the sample must be kept to a minimum. Additionally, a ZEISS ELYRA Lattice SIM microscope has become available at the Chair of Biotechnology and Biophysics/Biocenter (Markus Sauer). More details are provided in chapter 6.4 Research Infrastructure. Excellent scientists with highly competitive imaging expertise have been recruited or have been appointed as professors: Katrin Heinze (W3, Würzburg). David Stegner (W2, Würzburg), Markus Bender (W2 Heisenberg, Würzburg), Oliver Borst (W2 Heisenberg, Tübingen) and Oliver Otto (W3, Greifswald). More information about newly attracted or promoted researchers can be found in chapter 6.1.

Over the funding period of the CRC/TR 240, the concept for another cardiovascular collaborative research centre at the University of Würzburg matured and the CRC 1525 “Cardio-Immune Interfaces” was finally funded from 2022 on. The research agenda of this consortium with a focus on immunological pathologies in the context of a failing heart would have been an ideal complementary partner to the CRC/TR 240.

A major recent development of the cardiovascular field in Würzburg beyond the cardiovascular CRCs has been the successful transformation of the Comprehensive Heart Failure Center/CHFC (DZHI – Deutsches Zentrum für Herzinsuffizienz) from a BMBF-funded initiative into a permanent research and treatment centre, largely sustained from institutional funds (Free State of Bavaria, Faculty of Medicine). The CHFC is an integrated centre for research and treatment, and it has catalysed major structural developments in the cardiovascular field in Würzburg. Its interdisciplinary concept of research, teaching and care for patients with heart failure is unique in Germany and probably worldwide. The CHFC performs basic science, imaging, epidemiology and clinical studies. The interdisciplinary approach to research is key to the success of this institution. The CHFC has access to clinical research facilities of the Medical Clinic I, supports a research professorship of Epidemiology of Heart Failure (Stefan Störk), the Department of Translational Research (Christoph Maack), a research professorship of Genetics of Heart Failure (Brenda Gerull) and the Department of Molecular and Cellular Imaging (Laura Schreiber). High-end imaging facilities, including a 7T MRT for human use, and state-of-the-art animal facilities for mice, rats, rabbits and pigs are also available. Shaping the CHFC has created an environment extraordinarily conducive to cardiovascular research in Würzburg, particularly for projects with a translational perspective.

EU funding to stimulate collaborations between academia and regional small and medium enterprises (SMEs) in the framework of the European Fund for Regional Development (EFRE) measures provided additional support for the CRC/TR 240. The “Translational Network for Research in Thrombo-Inflammatory Diseases/THROMBO-INFLAME” (until 08/2021) coordinated by Bernhard Nieswandt established fruitful collaborations with local partners, which, for example, contributed to projects of the CRC/TR 240 by developing project-specific antibodies.

Tübingen

The Faculty of Medicine of the University Tübingen has four broad research priorities: neurology, infectious diseases, immunology/oncology and cardiovascular medicine/diabetes. The CRC/TR 240 successfully integrated into and strengthened this existing research focus, which has had a successful history in Tübingen with particular strengths in both basic research and patient care.

Since Meinrad Gawaz took office at the Department of Cardiology in Tübingen in 2004, a basic, translational and clinical research programme focussing on platelets and their role in cardiovascular and thrombo-inflammatory diseases has been implemented. The CRC/TR 240 successfully built on previous research results from the CRU 274 and, as one of very few such collaborative programmes in Germany, integrated translational and clinically relevant aspects.

Over its funding period, the CRC/TR 240 interacted with a number of collaborative research activities beyond the cardiovascular field. These are the CRCs 685 (“Immunotherapy”) and 766 (“The Bacterial Cell Envelope: Structure, Function and Infection Interface”), the DFG Research Units 2314 (“Targeting therapeutic windows in essential cellular processes for tumour therapy”) and 2060 (“cGMP signalling in cell growth and survival”) as well as the CRC/TRs 156 (“The skin as sensor and effector organ orchestrating local and systemic immune responses”), 34 (“Pathophysiology of Staphylococci in the Post-genomic Era”) and, finally, the CRC/TR 209 ("New mechanistic and therapeutic concepts in a solid tumor model").

In 2020, Tübingen successfully established a nationally leading certified heart failure unit (HFU) of the German Society of Cardiology, which complements clinical cardiovascular research.

The widely visible cardiovascular research activities in Tübingen have only been possible because researchers have established close ties with projects in other areas of the life sciences. Various meetings have shaped a research network between the individual research groups. Examples are joint meetings and interdisciplinary doctoral seminars of the CRU 273, 274 and the Research Unit 2060 as well as symposia and conferences (International Platelet Meeting Tübingen, Heart Days Tübingen, Thrombosis Forum, the largest national scientific meeting). These joint activities have built an interdisciplinary cardiovascular network with a total of nine clinics, institutes and departments participating. A number of coordinated training programmes for young researchers are active in Tübingen. Several groups with a focus on platelet research participate in these programmes (PhD study programmes “Experimental Medicine”, “Preclinical Molecular Imaging”, IZKF doctoral programmes).

Over the last years, cardiovascular and particularly platelet research in Tübingen has also seen continuous growth because the University of Tübingen has attracted excellent scientists or has been able to retain them. The cardiovascular department of the University Hospital Tübingen has been recognised to be among the top centres of cardiovascular medicine nationally (Focus) and internationally (Newsweek). Furthermore, the blood platelet research in Tübingen ranks among the ten best research groups worldwide (Expertscape.com). Members of the CRC/TR 240 contributed to these successful developments.

Taken together, the CRC/TR2 240 made invaluable contributions to the area of cardiovascular research at both universities, by catalysing significant advancements in the field and strengthening the research priorities of the host institutions. Regrettably, the promising trajectory was halted by the discontinuation of funding, leaving a void in the vital work the CRC/TR 240 had initiated.

5.2 International visibility of the host institutions

The host institutions significantly enhanced their international visibility through the CRC/TR 240. This consortium has shown to be highly successful with more than 230 original research articles. Among them 47 articles were published in international journals on thrombosis and haemostasis in interdisciplinary high impact journals (IF >10) which mirror productivity and success (details see chapter 2.1). Members of the consortium actively participated in and presented their research findings at renowned international conferences and symposia (such as ISTH, ASH, GTH, Gordon conferences), some of them are listed in the table below.

Name	Year	Event	Location
Gawaz, Meinrad	09/2022	Inaugural Session “Platelets, thromboinflammation and COVID-19” 5th EUPLAN International Conference:	Milan, Italy
Greinacher, Andreas	10/2018	Plenary lecture: “From Bacterial Host Defense to a New Mechanism of Autoimmunity – Lessons Learned from HIT”; 2nd European Congress on Thrombosis and Haemostasis	Marseille, France
Greinacher, Andreas	02/2020	Plenary lecture: “Heparin-induced thrombocytopenia”, 64. Jahrestagung der Gesellschaft für Thrombose- und Hämostaseforschung	Bremen, Germany
Greinacher, Andreas	06/2021	Keynote-Speaker: “Vaccine associated thrombotic thrombocytopenia” EHA - ISLH Joint Symposium	virtual
Greinacher, Andreas	07/2021	State of the art: “Vaccine-Induced Thrombocytopenia and Thrombosis: Current Thoughts on Mechanism and Management”, ISTH	virtual
Greinacher, Andreas	07/2022	State of the art: “Thrombocytopenia and Thrombosis”, ISTH	London, UK
Heinze, Katrin	09/2023	Plenary lecture “Fluorescence imaging of platelet biology”, European Platelet Network (euPLAN)	Bristol, UK

Nieswandt, Bernhard	03/2023	Keynote Lecture GRC “Cell Biology of Megakaryocytes and Platelets”, Gordon Research Conference	Lucca, Italy
Schulze, Harald	02/2019	Invited Speaker GRC “Cell Biology of Megakaryocytes and Platelets”, Gordon Research Conference	Galveston, TX, USA
Stegner, David	06/2023	State-of-the-Art “Thrombo-neuro-inflammation” 31st Congress of the International Society on Thrombosis and Haemostasis, ISTH	Montréal, Canada
Stegner, David	02/2019	Invited speaker GRC “Thrombopoiesis is spatially regulated by the bone marrow vasculature”, Gordon Research Conference	Galveston, TX, USA

These platforms allowed us to disseminate our discoveries to a global audience, facilitating knowledge exchange and fostering international collaborations. The CRC/TR 240 also took the initiative to organize international conferences and seminars, inviting researchers and experts from around the world (see also chapters 4.1 and 4.2). This not only showcased their commitment to knowledge dissemination but also solidified their reputation as leaders in their respective fields.

Press releases and social media played a pivotal role in communicating the scientific achievements to the broader public, including the media and the scientific community, further amplifying the international recognition of our members of the consortium (see also chapter 4.2). In recognition of their outstanding contributions, the members of the CRC/TR 240 (PIs and students) received prestigious awards (see table below), underscoring their exceptional research impact.

Name	**Year**	**Award**
Bender, Markus	2020	Alexander-Schmidt Award (Basic Medical Research)
Dittrich, Kristina (Lämmerhofer Lab)	2023	Merckle Promotionspreis
Gawaz, Meinrad	2022	Paul-Morawitz-Award (German Cardiac Society (DGK))
Gawaz, Meinrad	2023	Rudolf Schönheimer-Medal (German Atherosclerosis Society - DGAF)
Göb, Vanessa (Stegner Lab)	2023	Doctoral Award of the Ernst and Hedda Wollheim Foundation
Greinacher, Andreas	2018	James Blundell Award, British Blood Transfusion Society
Greinacher, Andreas	2020	Esteemed Career Award of the ISTH
Greinacher, Andreas	2021	Virchow Award, Aktionsbündnis Thrombose
Greinacher, Andreas	2022	Preis für Biochemische Analytik der DGKL
Greinacher, Andreas	2023	Wallace H. Coulter Distinguished Lecture of the International Society for Laboratory Hematology (ISLH)
Greinacher, Andreas	2023	Ham-Wasserman Lecture of the American Society of Hematology ASH
Greinacher Andreas	2022	Preis der Deutschen Hochschulmedizin (Greinacher A., K. Selleng, T. Thiele, L. Schönborn, N. Endlich, U. Völker, T. Renné, F. Salih, J. Mayerle, B. Nieswandt)

Greinacher Group	2020	GTH 2020 Best Abstract Handtke S., Jahn K., Palankar R., Kohler T.P., Rohde M., Hammerschmidt S., Greinacher A. *Streptococcus pneumoniae* toxin Pneumolysin renders platelets non-functional
Greinacher Group	2021	GTH 2021 Best presentation S. Handtke, K. Jahn, R. Palankar, T. P. Kohler, J. Wesche, S. Hammerschmidt, A. Greinacher, Presenter: S. Handtke Antibodies protect platelet damage by pneumolysin
Kollikowski, Alexander	2021	Alexander M. Kollikowski – Interventional Award of the German Society of Neuroradiology
Kollikowski, Alexander	2022	Alexander M. Kollikowski – Hentschel Award for Stroke Research, Hentschel Foundation
Lämmerhofer, Michael	2019 and 2023	Selection into “The Power List” of the 100 most influential people in analytical sciences of “The Analytical Scientist”
Lämmerhofer, Michael	2021	Agilent Technologies Research Award
Lämmerhofer, Michael	2020	JFK Huber Lecture Award (Austrian Society of Analytical Chemistry)
Langnau, Carolin (Müller Lab)	2021	Abstract Preis 2021 (German Cardiac Society (DGK))
Nagel, Georg	2019	Rumford Prize of American Academy of Arts & Sciences, Cambridge MA,
Nagel, Georg	2020	The Shaw Prize in Life Science and Medicine
Nieswandt, Bernhard	2022	Preis der Deutschen Hochschulmedizin (Greinacher A., K. Selleng, T. Thiele, L. Schönborn, N. Endlich, U. Völker, T. Renné, F. Salih, J. Mayerle, B. Nieswandt)
Rohlfing, Anne-Katrin	2020	39. Animal Welfare Research Award (federal ministry of food and agriculture)
Rohlfing, Anne-Katrin	2023	Abstract Prize for clinical lipid research (German Cardiac Society (DGK))
Schönborn, Linda (Greinacher Lab)	2023	Bayer Thrombosis Research Award
Schönborn, Linda (Greinacher Lab)	2023	Global Research Award of the American Society of Hematology
Stehle, Daniel (Feil Lab)	2023	PhD award from the University of Tübingen
Zernecke-Madsen, Alma	2022-2023	Top Reviewer Award 2022-2023, Cardiovascular Research