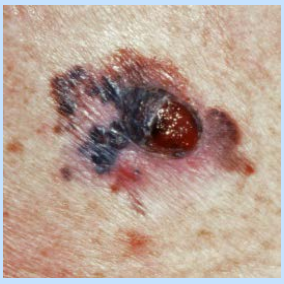
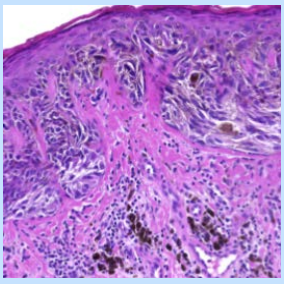
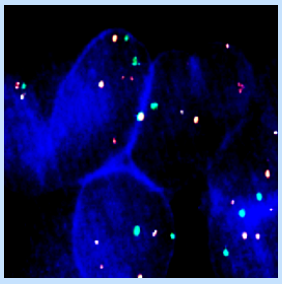
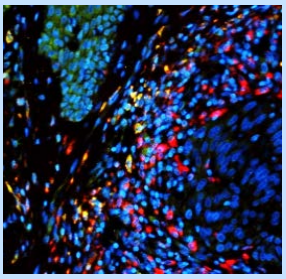
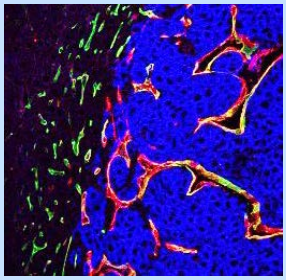
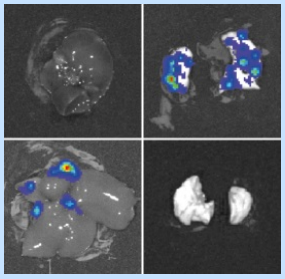
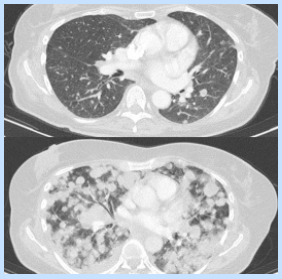
UNIVERSITÄT HEIDELBERG
ZUKUNFT SEIT 1386

DEUTSCHES KREBSFORSCHUNGSZENTRUM
IN DER HELMHOLTZ-GEMEINSCHAFT

Final Report | RTG 2099/1-2

HALLMARKS OF SKIN CANCER
RTG 2099

Tumor Microenvironment
Melanoma Immunity

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DKFZ Heidelberg

Speaker: Prof. Dr. S. Goerdt
Vice-Speakers: Prof. Dr. J. Utikal,
Prof. Dr. C. Géraud
London Coordinator: Prof. Dr. A. Hayday

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Table of Contents

1. General Information

1.1. General Information

1.1.1. DFG Reference Number

GRK 2099/1-2

1.1.2. Project Number

259332240

1.1.3. Title in German and English

Hallmarks of Skin Cancer: Tumor Microenvironment and Melanoma Immunity

Hallmarks of Skin Cancer: Tumor-Mikromilieu und Melanom-Immunologie

1.1.4. Name of Applicant University

Heidelberg University and DKFZ Heidelberg

1.1.5. Foreign Partner Institution

King's College London and further Colleges of the University of London

1.1.6. Spokespersons of RTG 2099

Speaker

Prof. Dr. Sergij Goerdt, Dept. Dermatology Mannheim, Heidelberg University

Vice-Speakers

Prof. Dr. Jochen Utikal, Dept. Dermatology Mannheim, Heidelberg University; Clinical Cooperation Unit Dermato-Oncology, German Cancer Research Center Heidelberg (since May 2015)

Prof. Dr. Cyrill Géraud, Dept. Dermatology Mannheim, Heidelberg University (since June 2018)

1.1.7. Official Address

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1.1.8. Reporting Period

01.04.2015 – 31.03.2024 (31.12.2024)

1.2. Participating Researchers

TABLE 1: PARTICIPATING RESEARCHERS

PRINCIPAL INVESTIGATORS OF THE RTG IN BOTH FUNDING PERIODS		
FIRST / LAST NAME, TITLE, AFFILIATION[1]	PERIOD	RESEARCH AREA
Prof. Dr. Peter Angel, DKFZ	2015-2024	Signal Transduction in Cancer
Prof. Dr. Hellmut Augustin, ECAS/MFM; DKFZ	2015-2024	Vascular Oncology
Prof. Dr. Michael Boutros, MFM/MFHD; DKFZ	2015-2024	Functional Genomics
Prof. Dr. Adelheid Cerwenka, MI3/MFM	2015-2024	Innate and Tumor Immunity
Prof. Dr. Moritz Felcht, Dermatology/MFM	2015-2022	Dermatology, Vascular Biology
Prof. Dr. Maria Gaiser, Dermatology/MFM	2015-2023	Dermato-Oncology

Prof. Dr. Cyrill Géraud, Dermatology/MFM	2015-2024	Dermatology, Vascular Biology
Prof. Dr. Sergij Goerdt, Dermatology/MFM	2015-2024	Dermatology, Vascular Biology
Prof. Dr. Philipp-Sebastian Reiners-Koch, Dermatology/MFM	2015-2024	Dermatology, Vascular Biology
Prof. Dr. Astrid Schmieder, Dermatology/MFM[2]	2015-2021	Dermatology, Immunology
Prof. Dr. Jonathan Sleeman, ECAS/MFM	2015-2024	Vascular Biology, Metastasis
Prof. Dr. Viktor Umansky, Dermatology/MFM	2015-2024	Innate and Tumor Immunity
Prof. Dr. Jochen Utikal, Dermatology/MFM; DKFZ	2015-2024	Dermato-Oncology
Prof. Dr. Frank Winkler, Neuro-Oncology, MFHD	2015-2024	Neurology, Brain Metastasis
PRINCIPAL INVESTIGATORS OF THE RTG ONLY IN THE SECOND FUNDING PERIOD		
Dr. Theresa Bunse, Neurology/MFM	2019-2024	Neuro-Immunology
Prof. Dr. Guoliang Cui, DKFZ[3]	2019-2023	T-Cell Metabolism in Cancer
Prof. Dr. Jessica Hassel, Dermatology/MFHD	2019-2024	Dermato-Oncology
Dr. Matthia Andrea Karreman, DKFZ	2019-2024	Neurology, Brain Metastasis
PD Dr. Victor Olsavszky, Dermatology/MFM	2022-2024	Dermatology, Vascular Biology
Dr. Jens Pahl, MI3/MFM[4]	2019	Innate andTumor Immunity
Prof. Dr. Michael Platten, Neurology/MFM; DKFZ	2019-2024	Neurology, Neuro-Oncology, Neuro-Immunology
Prof. Dr. Carmen Ruiz de Almodovar Egea, ECAS/MFM[5]	2019-2022	Neuro-Vascular Biology
Dr. Sebastian Wohlfeil, Dermatology/MFM	2019-2024	Dermatology, Vascular Biology
PRINCIPAL INVESTIGATORS OF THE RTG ONLY IN THE FIRST FUNDING PERIOD		
Prof. Dr. Iris Augustin, DKFZ[6]	2015-2016	Molecular Cell Biology
Prof. Dr. Alexander Enk, Dermatology/MFM	2015-2019	Dermatology, Immunology
PD Dr. Peter Geserick, Dermatology/MFM[7]	2015-2016	Molecular Biology, Apoptosis
Prof. Dr. Martin Leverkus†, Dermatology/MFM[8]	2015	Dermatology, Apoptosis
PD Dr. Anke Lonsdorf, Dermatology/MFHD	2015-2019	Dermatology, Immunology
Prof. Dr. Knut Schäkel, Dermatology, MFHD	2015-2019	Dermatology, Immunology
Prof. Dr. Stefan Schneider, Dermatology/MFM[9]	2015-2016	Dermatology, Vascular Biology
LONDON COLLABORATORS OF THE RTG IN BOTH FUNDING PERIODS		
Dr. Dimitrios Anastasiou, Crick	2019-2024	Cancer Metabolism
Prof. Dr. Buzz Baum, UCL	2015-2024	Biology of Morphogenesis
Prof. Dr. Anthony Dorling, KCL	2015-2019	Vascular Inflammation
Dr. Andrew Furness, The Royal Marsden	2015-2019	Solid Tumor Cell Therapy
Dr. Pierre Guermonprez, KCL	2019-2024	Immunobiology
Prof. Dr. Adrian Hayday, KCL; Crick	2015-2024	γ, δ-T-cells, Immunotherapy
Dr. Caroline Hill, Crick	2015-2024	Intercellular Communication
Prof. Dr. Kairbaan Hodivala-Dilke, QMUL	2015-2024	Vascular Oncology

Prof. Dr. James Larkin, The Royal Marsden	2019-2024	Melanoma Immunotherapy
Prof. Dr. Toby Lawrence, KCL	2019-2024	Cancer Immunology
Prof. Dr. Pascal Meier, ICU	2015-2019	Cell Death and Immunity
Prof. Dr. Tony Ng, KCL	2019-2024	Cancer Cell Biology, Imaging
Prof. Dr. Sergio Quezada, UCL	2015-2024	Cancer Immunology
Prof. Dr. Anna Randi, NHIL	2015-2024	Vascular Biology
Dr. Erik Sahai, Crick	2015-2024	Mechanisms of Metastasis
Prof. Dr. Henning Walczak, UCL[10]	2015-2019	Immunology, Apoptosis
Prof. Dr. Fiona Watt, KCL; EMBL	2015-2019	Skin Stem Cell Development

[1]MFM = Medical Faculty Mannheim, Heidelberg University; MFHD = Medical Faculty Heidelberg, Heidelberg University; DKFZ = Deutsches Krebsforschungszentrum / German Cancer Research Center; ECAS = European Center of Angioscience (MFM); MI3 = Mannheim Institute of Innate Immunoscience; Crick: The Francis Crick Institute London; UCL = University College London; KCL = King's College London; The Royal Marsden = The Royal Marsden NHS Foundation Trust; QMUL = Queen Mary University of London; ICU = The Institute of Cancer Research London; NHLI = The National Heart and Lung Institute, Imperial College, London; EMBL = European Molecular Biology Laboratory; [2]Present address: Dept. Dermatology, University of Würzburg; [3]Present address: National Science Center, Hefei, China; [4]Present address: Affimed, Mannheim; [5]Present address: Institute of Neurovascular Biology, University of Bonn; [6]Present address: University of Applied Sciences Weihenstephan; [7]Present address: Max Rubner Center (MRC) für kardiovaskuläre-metabolische-renale Forschung, Charité, Berlin; [8]Former Chairman, Dept. of Dermatology, RWTH Aachen; [9]Present address: Dept. Dermatology, University Medical Center Hamburg-Eppendorf; [10]Present Address: Biochemie-Zentrum, Universität zu Köln

During the funding periods, 7 PIs of the RTG (I. Augustin, G. Cui, C. Géraud, M. Leverkus, C. Ruiz de Almodovar Egea, A. Schmieder, S.W. Schneider) were offered professorial positions at other universities. 5 junior PIs obtained their "Habilitation" (Felcht, Lonsdorf, Reiners-Koch, Schmieder, Wohlfeil) and 5 obtained an extra-ordinary professorial title (Felcht, Gaiser, Géraud, Hassel, Reiners-Koch, Schmieder). Due to the support by Prof. Adrian Hayday, the London Coordinator of RTG 2099, the established ties of the members of RTG 2099 to their collaboration partners of the London Faculty of RTG 2099 were preserved despite the pandemic during the second funding period. Unfortunately, due to the unexpected retirement of former Director General of the Institut Gustave Roussy, Prof. Dr. Alexander Eggermont, and the upcoming pandemic, the collaboration with the diverse departments of the Institut Gustave Roussy in Paris could not be realized as planned.

1.3. Number of doctoral researchers, doctoral researchers in medicine, postdoctoral researchers, qualifying fellows and student assistants (Table 2)

Individuals funded through the Research Training Group	**Number**
Doctoral Researchers (position with 65% of full-time hours)	43
Doctoral Researchers in medicine (fellowship MFM)	39
Postdoctoral Researchers	-
Qualifying fellows	1
Student assistants	8
Individuals funded from other sources	
Doctoral researchers	21
Doctoral researchers in medicine	-
Postdoctoral researchers	-

2. Summary

2.1. Summary in English

Despite the incredible progress in the development of effective therapies for metastatic malignant melanoma, therapy resistance is a major obstacle to long-term survival. Therefore, RTG2099 focused on deciphering context-dependent mechanisms of melanoma metastasis and on identifying strategies to overcome resistance to immune checkpoint inhibitor therapy (ICI). Melanoma-derived signaling mechanisms as well as organotropic mechanisms of metastasis were analyzed in the different ecosystems of the primary tumor, the vascular system and at the major distant sites, i.e. brain and liver, and potential targets to prevent and treat melanoma metastasis were identified. Regarding resistance to ICI therapy, the inhibitory effects of tumor-associated macrophages and myeloid-derived suppressor cells on antitumor immunity of tumor-infiltrating T-cells and NK cells were analyzed to identify strategies to unleash their immunotherapeutic potential. In addition, the PhD and MD doctoral researchers were trained in a broad range of research and managerial skills to finally be able to self-confidently develop their own research agenda and to become successful applicants in the job market. Finally, the RTG has tremendously profited from the close collaboration with outstanding experts at King's College, of further institutes of the University of London and of the Francis Crick Institute.

2.2. Summary in German

Trotz der beträchtlichen Fortschritte bei der Entwicklung effektiver Therapien stellt die Therapieresistenz weiterhin ein großes Hindernis für das langfristige Überleben bei metastasiertem malignem Melanom dar. Daher lag der Schwerpunkt des RTG2099 auf der Entschlüsselung kontextabhängiger Mechanismen der Melanommetastasierung und auf der Identifizierung von Strategien zur Überwindung der Resistenz gegen Immun-Checkpoint-Inhibitoren (ICI). Signalwege und Mechanismen organotroper Metastasierung wurden in den verschiedenen Ökosystemen des Primärtumors, im vaskulären Kompartiment und in den wichtigsten Organen der Fernmetastasierung, d.h. Gehirn und Leber, analysiert, und es wurden Zielstrukturen zur Verhinderung und Behandlung der Metastasierung identifiziert. Im Hinblick auf die Resistenz gegen die ICI-Therapie wurden die inhibitorischen Effekte von Tumor-assoziierten Makrophagen und myeloid-derived suppressor cells auf die Antitumor-Immunität von Tumor-infiltrierenden T-Zellen und NK-Zellen untersucht und Strategien zur Freisetzung ihres immuntherapeutischen Potenzials erforscht. Darüber hinaus wurden die Promovenden in einem breiten Spektrum von Forschungs- und Managementfähigkeiten geschult, damit sie selbstbewusst ihre eigene Forschungsagenda entwickeln und sich erfolgreich auf dem Arbeitsmarkt bewerben können. Darüber hinaus hat das RTG ganz beträchtlich von der Zusammenarbeit mit herausragenden Forschern am King's College, weiteren Instituten der University of London und des Francis-Crick-Instituts in London profitiert.

3. Scientific Progress Report

Due to the high capacity to metastasize, malignant melanoma counts among the deadliest cancer types with a rising incidence of newly diagnosed patients every year. The development of highly effective targeted and immunotherapies for metastatic malignant melanoma has been an unprecedented success story during the last two decades that will soon be outperformed regarding overall survival by adjuvant and neoadjuvant treatment regimens. Despite this incredible progress, therapy resistance is a major obstacle to long-term survival of high risk primary as well as metastatic melanoma. Resistance to immune checkpoint inhibitor therapy (ICI) is a multifaceted challenge, primary resistance being especially strong in malignant melanoma metastasizing to brain and liver. Therefore, RTG2099 focused on A) deciphering context-dependent mechanisms of melanoma growth and distant melanoma metastasis especially to brain and liver as well as on B) identifying mechanisms of and developing strategies to overcome resistance to ICI.

For aim A, melanoma-derived autocrine and paracrine signaling mechanisms as well as organotropic mechanisms of metastasis were analyzed in the different ecosystems of the primary tumor, the circulatory and vascular compartment and at the major distant sites. Wnt (Project [P] 1), Bmp (P3), Angpt(l) (P4), and VEGF (P6) signaling pathways were scrutinized. While Wnt factors and Angpt2[1] acted directly in an autocrine fashion, Bmp family members used matrix assistance to improve their efficacy. Paracrine VEGF promoted tumor angiogenesis in endothelial cells in the tumor microenvironment via induction of a Stat3/Yap/TAZ signaling cascade[2] co-activated by protein phosphatase A2 and by physical matrix properties, i.e. matrix stiffness. Notably, Angptl4 exerted context-dependent effects. While full-length Angptl4 and its c-terminal fragment were primarily found in the primary tumor and supported tumor growth and metastasis, the n-terminal fragment (nAngptl4) predominated in the systemic circulation, inhibited melanoma metastasis by interfering with Wnt signaling and reducing vascularity, and inversely correlated with disease progression. Therefore, nAngptl4 may serve as a novel substance to prevent and treat melanoma metastasis[3]. Regarding organotropic mechanisms of melanoma metastasis, the work of P7 discovered 3 novel organ-specific mechanisms of melanoma brain metastasis. Highly metastatic melanoma cells turned out to be ensheathed by a blood clot formation of which was induced by melanoma cell-derived thrombin followed by cancer cell arrest in the brain microvasculature[4]. Subsequent extravasation of melanoma cells is mediated by melanoma cell-derived matrix metalloproteinase (MMP)-9 and growth of metastatic melanoma seed in the brain is supported by the unexpected formation of direct excitatory synapses between melanoma cells and neurons[5]. To study the hepatic vascular niche and especially its endothelial component, liver sinusoidal endothelial cells (LSEC), and its transformation into a premetastatic vascular niche in the liver, P5 generated novel Cre driver mice to be used for

[1] Abdul Pari AA et al, Cancer Res 2020, 65:2586-2598; [2] Shen Y et al, Sci Signal 2021, 14, eabj8393; [3] Hübers C et al, J Exp Med 2023, e20202595; [4] Feinauer ML et al, Blood 2021, 137:1219-1232; [5] Venkatamarani V et al, bioRxiv 2024.01.08.574608; doi: https:// doi.org/10.1101/2024.01.08.574608

establishing liver sinusoidal endothelial cell (LSEC)-specific knockout mice[1,2,3,4]. In the liver, P5 and P8 identified the Notch pathway as an important signaling pathway in liver sinusoidal endothelial cells (LSEC) to control hepatic melanoma metastasis via regulation of melanoma cell adhesion mediated by ICAM1[4]. As metabolic-associated fatty liver disease (MAFLD) and metabolic-associated steatohepatitis (MASH) have become a pandemic, P5 investigated whether MAFLD/MASH transforms the hepatic vascular niche into a pre-metastatic niche. Notably, MAFLD/MASH strongly enhanced organotropic melanoma metastasis to the liver mediated by upregulation of melanoma cell adhesion via ICAM1 and by a profibrotic angiocrine switch in LSEC differentiation orchestrated by down-regulation of transcription factor Gata4 in LSEC[5]. Therefore, in the future, life style changes and development of organ-specific angiotargeted therapies for the liver may open up new avenues for preventing and treating hepatic melanoma metastasis.

For aim B, the inhibitory effects of the close companions, i.e. tumor-associated macrophages (TAM) and myeloid-derived suppressor cells (MDSC), on antitumor immunity as well as the resistance mechanisms of tumor-infiltrating T-cells and NK cells to ICI were analyzed to identify strategies unleashing their immunotherapeutic potential in malignant melanoma. In P10, TAM were extensively characterized in vivo and in vitro and shown to express TAM marker proteins such as Stabilin1, Lyve1, MS4A8A inducible by stimulation with glucocorticoids and/or the Th2 cytokine interleukin (IL)-4. In addition, P10 identified the purinergic receptors P2Y12 and P2Y14 as highly expressed by TAM; functionally, P2Y12 fuels a feedforward cycle secreting chemokines that recruit further TAM to hypoxic areas of the tumor rich in ADP further activating P2Y12[6]. As TAM are exposed to systemic as well as locally secreted glucocorticoids, a mouse line was generated with a myeloid-specific deficiency of the glucocorticoid receptor ($GR^{TAM\text{-}KO}$). $GR^{TAM\text{-}KO}$ mice showed reduced melanoma growth, an effect that was further enhanced by PD1 ICI. As proof of principle for future therapeutic approaches, mifepristone-containing nanoparticles were developed and elicited a similarly robust response to ICI as seen in the $GR^{TAM\text{-}KO}$ mice. When studying melanoma brain metastasis, P14 found that radiotherapy induced type I interferons down-regulating transcription factor Cebp/b in TAM and converting them into proinflammatory macrophages exhibiting enhanced T-cell stimulatory capacity[7]. Regarding MDSC, results of P11 and P15 were complex. P11 showed that melanoma-derived extracellular vesicles induced monocyte-to-MDSC differentiation via activation of TLR4 by HSP90α and S100A9 accompanied by up-regulation of PD-L1 and T-cell inhibition. These effects were counter-acted by TLR4 antagonist resatorvid[8,9,10]. Conversely, P15 discovered in immunometabolic studies that sphinganine generated by serine-palmitoyltransferase long chain subunit 2 (Sptlc2) is

[1] Géraud C et al, J Clin Invest 2017, 127:1099-1114; [2] Heil J et al, Nat Commun 2021, 12: 6963; [3] Wohlfeil SA et al, Cancer Res 2019, 79:598-610; [4] Schmid C et al, Hepatolog 2023, 77: 1211–1227; [5] Winkler M et al, J Hepatol 2021, 74:380-393; [6] Kloss L et al, Cell Death Dis 2019, 10:760; [7] Gellert J et al, Cancer Res Commun 2024, 10.1158/2767-9764-CRC-24-0024; [8] Fleming V et al, Cancer Res 2019, 79: 4715-28; [9] Arkhypov I et al, J Immunother Cancer 2022, 10:e005551; [10]Özbay Kurt F et al, J Immunother Cancer 2024

indispensable to maintain basic antitumor immune functions of bone marrow-derived macrophage-like MDSC by recruiting TLR4 adaptors and activating the TLR4 signaling pathway[1]. At present, this paradox is not easy to reconcile, but may be resolved due to the different sources of MDSC derived from either monocytes or bone marrow stem cells. Regarding resistance to ICI, several experimental approaches were selected. P7 and P14 focused on brain metastases. P7 discovered that circulating T-cells preferably adhered and extravasated at a distinct type of venous blood vessel in the tumor vicinity, i.e. peritumoral venous vessels (PVV) whose endothelial cells highly expressed ICAM1. ICI increased T-cell motility in the brain facilitating the route from the PVV to the metastasis and inhibiting intracranial tumor growth[2]. P14 developed a method to capture frequent T-cell clones from ICI-responsive tumors using scRNASeq and to perform TCR identification for future adoptive T-cell therapeutic approaches[3]. P13 further elaborated on the concept of adoptive cell therapies developing functionally active hiPSC-derived single positive CD8 T-cells with tumor antigen-specific TCR or CAR. Finally, P9 studied melanoma resistance to NK cell treatment. They discovered a feedforward cycle driven by NK cell-derived IFN-γ inducing HLA-E and classical MHC-I molecules, thereby paralyzing the surrounding NK cells. This resistance mechanism could be overcome by using a cocktail of three antibodies blocking inhibitory NK cdell receptors NKG2A, KIR2, and DX9.

The results achieved in the projects of the RTG open up new avenues towards improved treatment options for metastatic and therapy-resistant melanoma. The new options will also contribute to improve adjuvant and neoadjuvant therapies for high risk melanomas that are only recently being developed and introduced into clinical studies (Long GV et al, Nat Med 2024, 10.1038/s41591-024-03077-5), but still bear a high risk of treatment failure as well as of development of severe adverse reactions.

3.1. Scientific Outcome / Publication Metrics

Table 3: Publications authored or co-authored by doctoral researchers

Doctoral Researchers	Article Category	Numbers	Cumulative Impact Factor[2]
Doctoral Researchers funded by the RTG	Original Articles	116	1220,30
	Review Articles	19	219,10
Associate Doctoral Researchers	Original Articles	12	103,30
	Review Articles	5	26,50
Total[1]		152	1.569,20

[1]See also complete list of publications of the RTG in Part 5 “Project Results / Publications” of this report
[2]Regardless of the publication dates of the articles, the 2022 impact factors were used

[1] Hering M et al, Nat Commun 2024, 15:6067; [2] Messmer JM et al, Immunity 2024, 10.1016/j.immuni.2024.09.003; [3] Tan CL et al, Nat Biotechnol 2024, 10.1038/s41587-024-02161-y

4. Qualification, Supervision, and Partnerships

Qualification Program. The special approach of the qualification program of RTG 2099 intended to educate junior clinical researchers and junior natural scientists together, as mutual understanding of clinical medicine and basic science is required both for the development of clinically relevant basic research projects and for the translation of discoveries in basic science back into clinical practice. Therefore, the RTG set up a highly successful multi-disciplinary approach to teach cancer biology and dermato-oncology. To this end, the RTG closely collaborated with the Graduate Schools of the Medical and Life Science Faculties of Heidelberg University, i.e. HBIGS, and of the DKFZ, i.e. HIGS, providing a broad range of excellent teaching offers in general and tumor biology. *Vice versa*, the RTG provided additional teaching in a broad range of topics covering clinical and experimental dermato-oncology. Incorporation into the two preexistent Graduate Schools was very well received by the students. Altogether, the teaching program of the RTG comprised regular seminars, laboratory (hands-on) courses, workshops, and clinical rounds as well as summer schools that were offered in a structured sequence. The seminars focused on general aspects of oncology (HIGS) and special aspects of dermato-oncology (RTG), while the course/workshop program offered training in general techniques in cell/molecular biology (HBIGS, HIGS) and special techniques in skin cancer research (RTG). The courses and workshops were modular and could be freely chosen by the students. Soft skill training was also part of the program offered by both HBIGS and HIGS. Courses on the rules of good scientific practice, on research involving animal experiments, and on data handling were carried out in a mandatory manner during the RTG kick-off meeting for each novel cohort of PhD students. In general, the teaching progam of the RTG was positively evaluated by the students using the evaluation tool provided by the Medical Faculty Mannheim. As a result of the evaluation by the students who demanded to establish higher connectivity between the scientific projects in a structured way, the RTG set up a seminar series held without PIs in which two students working on a similar topic presented their projects. In addition, to better integrate clinical dermatology into the teaching offers, the RTG implemented clinical rounds to expose the students to real-life clinical medicine. This was well received by the students and improved their understanding for unmet clinical needs. For better integration of the MD students, the membership period of MD students was prolonged from 1 yr to 2 yrs in the 2nd funding period.

Additional Qualification: Collaboration with the London Partners. As science is international, one of the aims of the RTG was to stimulate the students to engage in international scientific collaboration. To this end, the RTG set up an inter-institutional scientific faculty in London comprising high-ranking scientists of King's College and other Colleges of the University of London as well as of the Francis Crick Institute, who collectively offered an outstanding expertise across the spectrum of relevant basic, translational, and clinical science (see Table 1). Under the guidance of Prof. Adrian Hayday, a great immunologist and mentor, the London project partners hosted PhD/MD students for a lab visit either to conduct part of the experiments for their thesis projects or to learn new techniques. These lab visits were positively evaluated by the students; however, the duration of the stay had to

be shortened as especially preclinical experiments cannot easily be transferred from one lab to another. Still, due to the pandemic and better digital communication platforms, collaborative ties were more easily perpetuated to promote collaborative publications. During the 3-4-yr course of a PhD student's life in the RTG, the RTG organized a yearly "Anglo-German Workshop on Skin Cancer Biology" in which also part of the London project partners actively participated. In the 1st year of a PhD student, this Workshop was held in Mannheim as a kick-off meeting with plenary lectures from London partners, project presentations by the students and the introductory courses on good scientific practice, animal experiments and research data management. In each 2nd year (with omissions during the pandemic), these Workshops were organized as Summer Schools in London. Prof. Hayday always put a very attractive program together that included interactions with professionals from pharmaceutical and start-up companies, funding agencies, and publishing houses to prepare the students for the job market. In their 3rd year, the students independently organized the international "Hallmarks of Skin Cancer" conference (HoSC), exposing them to fundamentally different professional requirements than met in their daily lab life.

Supervison and Career Development. The RTG offered the doctoral researchers a structured and individualized supervision concept as well as further support for career development. Judged by the fact that a high number of RTG students completed their doctoral studies with great success, this RTG concept comprehensively fulfilled its intended purposes. At the beginning of a student's career, all rights and liabilities of the doctoral researcher and of the RTG were fixed in a contract. The supervision concept included elements of daily/weekly PI supervision with the active contribution of graduate students in weekly group seminars to develop presentation skills and scientific discussion abilities. The supervisors regularly met at least once a month with each student for intense exchange and project-specific discussions. Each student chose a co-supervisor from the RTG to discuss the project progress at least annually, preferentially during a thesis advisory committee (TAC) meeting. To continuously evaluate the progress of the student, the RTG implemented a credit point system. Altogether, the graduate students had to earn at least 180 ECP during their 3-year thesis work. Of these, 50 ECP per year were given for the continuous experimental work, while 10 ECP had to be collected annually by participation in the educational program. Considering the feedback provided by the students, the amount of events in the educational program was reduced to 7-10% of the working time during the 2nd year of funding. Caused by the pandemic, most teaching events were offered as digital or hybrid courses, reducing the time for commuting. MD students had to earn 60 ECP, preferentially during the full experimental phase, while they were exempt from collecting ECP during the preparatory and finalizing phases. Due to these measures, the adjusted program was well accepted by the doctoral researchers and the necessary ECPs were earned by the students without problems.

Scientific Independence. One of the major goals of the RTG was to support early scientific independence of its doctoral researchers. Formal requirements were obtained by the obligatory introductory courses ("Conducting Animal Studies", "Research Data Management" and "Good

Scientific Practice") and by regular presentations and discussions of the project outlines during the Anglo-German Workshops and the TAC meetings. For all students, and in particular for the organizing team consisting of 4-5 students, the organization of the HoSC Conference during their 3rd year was a major experience. The students gained professional independence working in various subteams and successfully scoped with all obstacles that occured; the HoSC conference 2020 had to be fully digital due to the Corona pandemic – a special challenge, but well mastered by the student organizing team. In addition, the graduate students were encouraged and financially supported to participate in other scientific conferences to present their data.

Gender Equality. To balance the relation between male and female researchers and to support the compatibility of work and family, the RTG facilitated access to all measures offered by Heidelberg University including the Medical Faculty Mannheim and the DKFZ. As only few doctoral students became pregnant or had children during the RTG funding periods, the focus of the RTG's equality program were the "Gender Workshops" and "Female Expert in Science" meetings. The Gender Workshops had a strong inspiring, motivating and mentoring effect on our female doctoral researchers. The "Female Expert in Science" meetings provided the opportunity for female students to get directly in touch with leading international female scientists who could serve as role models for the students. For the needs of our parental couples among the PIs, the RTG mainly offered child care and measures to enhance the compatibility of study, research and family by offering student assistance to working parents, a parent-child room and free parking spaces in Mannheim and Heidelberg as well as support by technical assistance in case of long parental leaves.

Influence of the RTG on Doctoral Programs at the Applicant University. Encouraged by the success of the several RTGs supported by the DFG at the Medical Faculty Mannheim, the Medical Faculty Mannheim has developed a multilevel structured program for pre- and postgraduate education which is organized within the School of Translational Medicine Mannheim (STMM). The STMM comprises a structured program especially for medical students, but also for students in other medicine-related master and bachelor courses including the degree Dr. sc.hum. For highly talented and science-oriented medical students, the STMM offers a scientific master class program to prepare them for an experimental MD thesis. For MD students committed to at least 6 months of MD thesis work, the STMM offers a competitive fellowship grant. To further support an MD student's decision to continue a career in medical research, a clinician scientist program is part of the STMM.

Table 4: Doctoral Record of the Doctoral Researchers Financed by the RTG					
Number of Doctoral Researchers (PhD and MD students)	**Completed Doctorates**	**Theses that Have Only Been Submitted to Date**	**Average Duration of Doctorates in Months**	**Number of Interruptions of Doctoral Studies due to Illness, Maternity or Parental Leave, asf. (>3 months)**	**Promotion Dropouts**
82	**42**	**9**	**59 (52 PhD, 74 MD)**	**2**	**4**

5. Project Results/Publications

5.1. Project Results achieved by the doctoral researchers and (where applicable) postdoctoral researchers

5.1.1. Project Results achieved by the doctoral researchers and (where applicable) postdoctoral researchers (financed from RTG funds): regular PhD and regular MD students of the RTG. Open access publicatons are designated by "OA"

5.1.1.1. Publications with Scientific Quality Assurance

2015

1. Geserick P, Wang J, **Schilling R, Horn S,** Harris PA, Bertin J, Gough PJ, Feoktistova M, Leverkus M. Absence of RIPK3 predicts necroptosis resistance in malignant melanoma. **Cell Death Dis.** 2015 Sep 10;6:e1884. doi:10.1038/cddis.2015.240. **OA.**

2016

2. Goertz L*, Schneider SW*, Desch A, Mayer FT, **Koett J,** Nowak K, Karampinis I, Bohlmann MK, Umansky V, Bauer AT. Heparins that block VEGF-A-mediated von Willebrand factor fiber generation are potent inhibitors of hematogenous but not lymphatic metastasis. **Oncotarget.** 2016 Oct 18;7(42):68527–68545. doi:10.18632/oncotarget.11832. **OA.**

3. Hughes MA, Powley IR, Jukes-Jones R, **Horn S,** Feoktistova M, Fairall L, Schwabe JWR, Leverkus M, Cain K, MacFarlane M. Co-operative and Hierarchical Binding of c-FLIP and Caspase-8: A Unified Model Defines How c-FLIP Isoforms Differentially Control Cell Fate. **Mol Cell.** 2016 Mar 17;61(6):834–49. doi:10.1016/j.molcel.2016.02.023. **OA.**

4. Kather JN, Weis CA, Bianconi F, **Melchers SM,** Schad LR, Gaiser T, Marx A, Zöllner FG. Multi-class texture analysis in colorectal cancer histology. **Sci Rep.** 2016 Jun 16:6:27988. doi:10.1038/srep27988. **OA.**

5. Krachulec JM, **Sedlmeier G,** Thiele W, Sleeman JP. Footprintless disruption of prosurvival genes in aneuploid cancer cells using CRISPR/Cas9 technology. **Biochem Cell Biol.** 2016 Jun;94(3):289–96. doi:10.1139/bcb-2015-0150. Epub 2016 Jun 2.

6. Weina K*, **Wu H*,** Knappe N, Orouji E, Novak D, Bernhardt M, **Hüser L,** Larribère L, Umansky V, Gebhardt C, Utikal J. TGF-β induces SOX2 expression in a time-dependent manner in human melanoma cells. **Pigment Cell Melanoma Res.** 2016 Jul;29(4):453–8. doi:10.1111/pcmr.12483.

2017

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8. Géraud C*, Koch PS*, **Zierow J*,** Klapproth K, Busch K, Olsavszky V, **Leibing T,** Demory A, Ulbrich F, Diett M, Singh S, Sticht C, Breitkopf-Heinlein K, Richter K, Karppinen S, Pihlajaniemi T, Arnold B, Rodewald H, Augustin HG, Schledzewski K, Goerdt S. GATA4-dependent organ-specific endothelial differentiation controls liver development and embryonic hematopoiesis. **J Clin Invest.** 2017 Mar 1;127(3):1099-1114. doi: 10.1172/JCI90086. Epub 2017 Feb 20. **OA.**

9. **Horn S,** Hughes MA, **Schilling R,** Sticht C, Tenev T, Ploesser M, Sprick MR, Meier P, MacFarlane M, Leverkus M. Caspase-10 Negatively Regulates Caspase-8- Mediated Cell Death, Switching the Response to CD95L in Favor of NF- kB Activation and Cell Survival. **Cell Rep.** 2017 Apr 25;19(4):785–797. doi: 10.1016/j.celrep.2017.04.010. **OA.**

10. Kather JN, Zöllner FG, Schad LR, **Melchers SM,** Sinn HP, Marx A, Gaiser T, Weis CA. Identification of a characteristic vascular belt zone in human colorectal cancer [published correction appears in PLoS One. 2017 May 8;12 (5):e0177586]. **PLoS One.** 2017 Mar 2;12(3):e0171378. doi: 10.1371/journal.pone.0171378. eCollection 2017. **OA.**

11. Koch PS*, Olsavszky V*, Ulbrich F, Sticht C, Demory A, **Leibing T**, Henzler T, Meyer M, **Zierow J,** Schneider S, Breitkopf-Heinlein K, Gaitantzi H, Spencer-Dene B, Arnold B, Klapproth K, Schledzewski K, Goerdt S, Géraud C. Angiocrine Bmp2 signaling in murine liver controls normal iron homeostasis. **Blood.** 2017 Jan 26;129(4):415–419. doi: 10.1182/blood-2016-07-729822. Epub 2016 Nov 30. **OA.**

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13. Sachindra, Larribère L, Novak D, **Wu H, Hüser L, Granados K,** Orouji E, Utikal J. New role of ID3 in melanoma adaptive drug-resistance. **Oncotarget.** 2017 Nov 27;8(66):110166–110175. doi: 10.18632/oncotarget.22698. eCollection 2017 Dec 15. **OA.**

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2018

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2019

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2020

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2021

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129. **Messmer JM, Thommek C, Piechutta M,** Venkataramani V, Wehner R, Westphal D, Schubert M, Mayer CD, Effern M, Berghoff AS, Hinze D, Helfrich I, Schadendorf D, Wick W, Hölzel M, Karreman MA*, Winkler F*. T lymphocyte recruitment to melanoma brain tumors depends on distinct venous vessels. **Immunity.** 2024 Sep 28:S1074-7613(24)00447-3. doi: 10.1016/j.immuni.2024.09.003. Online ahead of print. **OA.**

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132. Schlieper-Scherf S, **Hebach N,** Hausmann D, Azorín DD, Hoffmann DC, Horschitz S, Maier E, Koch P, Karreman MA, Etminan N, Ratliff M. Disrupting glioblastoma networks with tumor treating fields (TTFields) in in vitro models. **J. Neurooncol.** 2024 Oct;170(1):139-151. doi: 10.1007/s11060-024-04786-0. Epub 2024 Aug 1. **OA.**

133. Streibel Y, Breckwoldt MO, Hunger J, Pan C, Fischer M, Turco V, Boztepe B, Fels-Palesandro H, Scheck JG, Sturm V, Karimian-Jazi K, **Agardy DA,** Annio G, Mustapha R, Soni SS, Alasa A, Weidenfeld I, Rodell CB, Wick W, Heiland S, Winkler F, Platten M, Bendszus M, Sinkus R, Schregel K. Tumor biomechanics as a novel imaging biomarker to assess response to immunotherapy in a murine glioma model. **Sci Rep.** 2024 Jul 6;14(1):15613. doi: 10.1038/s41598-024-66519-7. **OA.**

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138. Strobel SB, **Machiraju D, Wiecken M,** Richter J, Klein JAF, Berger A, Hassel JC. CMV IgG in the blood is not associated with hepatitis but correlates with poor outcomes in immunotherapy treated melanoma patients. **Cancer Immunology, Immunotherapy.** *in press*

5.1.1.2. Other Publications and Published Results

2019

139. **Hüser L,** Altevogt P, Utikal J. Role of STAT3 dependent SOX2 and CD24 expression in melanoma cell adaptive resistance towards targeted therapies. **Oncotarget.** 2019 Mar 1;10(18):1662-1663. doi: 10.18632/oncotarget.26718. (Editorial). **OA.**

2020

140. **Simon SCS**, Utikal J. Fortschritte im Kampf gegen den Hautkrebs – neue therapeutische Strategien. **Kompendium Dermatologie** 2020; 16:1–8

141. **Patent:** Augustin HG, Hübers C, Pari AA, Petkov M, Felcht M. INHIBITION OF METASTASIS DEVELOPMENT BY NANGPTL-4. EP 20190190563.

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142. **Groth C, Weber R,** Utikal J, Umansky V. Depletion and Maturation of Myeloid-Derived Suppressor Cells in Murine Cancer Models. **Methods Mol Biol.** 2021:2236:67-75. doi: 10.1007/978-1-0716-1060-2_7. (Protocol, part of book series)

143. **Simon SCS**, Utikal J. Adjuvante Therapie des Hochrisikomelanoms. **Best Practice Onkologie** 2021; 7-8:308-314

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144. **Patent:** Augustin HG, Grieshober D, Hübers C, Pari AA, Felcht M. NANGPTL-4 AS MARKER FOR DISEASE PROGRESSION. EP20210156649.

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145. **Patent:** Sleeman J, **Sedlmeier G,** Jung N, Bräse S, Grässle S. CHEMICAL INHIBITORS OF ID PROTEINS FOR THE TREATMENT OF CANCER AND OTHER DISEASES. PCT/EP2020/066097. Patent granted and covers USA, Japan and Europe.

146. Venkataramani V*, Karreman MA*****, Nguyen LC, **Tehranian C, Hebach N,** Mayer CD, Meyer L, Mughal SS, Reifenberger R, Felsberg J, Köhrer K, Schubert MC, Westphal D, Breckwoldt MO, Brors B, Wick W, Kuner T#, Winkler F#. Direct excitatory synapses between neurons and tumor cells drive brain metastatic seeding of breast cancer and melanoma. bioRxiv 2024.01.08.574608; doi: https://doi.org/10.1101/2024.01.08.574608

5.1.1.3. Completed Theses that have not yet been published

n.a.

5.1.2. Project Results achieved by the doctoral researchers and (where applicable) postdoctoral researchers (financed from other sources): associated PhD and associated MD students of the RTG. Open access publicatons are designated by "OA"

5.1.2.1. Publications with Scientific Quality Assurance

2016

1. **Fehrenbach S**, Novak D, Bernhardt M, Larribere L, Boukamp P, Umansky V, Utikal J. 2016. Loss of tumorigenic potential upon transdifferentiation from keratinocytic into melanocytic lineage. **Sci. Rep**. 2016 Jul 8;6:28891. doi:10.1038/srep28891. **OA.**

2. Sharbi-Yunger A, **Grees M,** Tzehoval E, Utikal J, Umansky V, Eisenbach L. mRNA-based dendritic cell immunization improves survival in ret transgenic mouse melanoma model. **Oncoimmunology.** 2016 Apr 22;5(6):e1160183. doi: 10.1080/2162402X.2016.1160183. eCollection 2016 Jun. **OA.**

3. Tähtinen S, **Blattner C,** Vähä-Koskela M, Saha D, Siurala M, Parviainen S, Utikal J, Kanerva A, Umansky V, Hemminki A. 2016. T-Cell Therapy Enabling Adenoviruses Coding for IL2 and TNFα Induce Systemic Immunomodulation in Mice With Spontaneous Melanoma. **J Immunother.** 2016 Nov/Dec;39(9):343-354. doi: 10.1097/CJI.0000000000000144.

4. Umansky, V, **Blattner, C**, Gebhardt, C, Utikal, J. The Role of Myeloid-Derived Suppressor Cells (MDSC) in Cancer Progression. **Vaccines (Basel).** 2016 Nov 3;4(4):36. doi: 10.3390/vaccines4040036. (Review) **OA.**

2017

5. Hawila E, Razon H, Wildbaum G, **Blattner C,** Sapir Y, Shaked Y, Umansky V, Karin N. CCR5 Directs the Mobilization of $CD11b_{+}Gr1_{+}Ly6C_{low}$ Polymorphonuclear Myeloid Cells from the Bone Marrow to the Blood to Support Tumor Development. **Cell Rep.** 2017 Nov 21;21(8):2212-2222. doi: 10.1016/j.celrep.2017.10.104. **OA.**

6. Umansky V, **Blattner C, Fleming V, Hu X,** Gebhard C, Altevogt P, Utikal J. Myeloid-derived suppressor cells and tumor escape from immune surveillance. **Semin. Immunopathol.** 2017 Apr;39(3):295-305. doi: 10.1007/s00281-016-0597-6. Epub 2016 Oct 27. (Review)

7. Umansky V, **Blattner C,** Gebhardt C, Utikal J. 2017. CCR5 in recruitment and activation of myeloid-derived suppressor cells in melanoma. **Cancer Immunol Immunother.** 2017 Aug;66(8):1015-1023. doi: 10.1007/s00262-017-1988-9. Epub 2017 Apr 5 (Review)

2018

8. **Grees M,** Sharbi-Yunger A, Evangelou C, Baumann D, Cafri G, Tzehoval E, Eichmüller SB, Offringa R, Utikal J, Eisenbach L, Umansky V. Optimized dendritic cell vaccination induces potent CD8 T cell responses and anti-tumor effects in transgenic mouse melanoma models. **Oncoimmunology.** 2018 Mar 26;7(7):e1445457. doi: 10.1080/2162402X.2018.1445457. eCollection 2018. **OA.**

9. Huber V, Vallacchi V, **Fleming V, Hu X,** Cova A, Dugo M, Shahaj E, Sulsenti R, Vergani E, Filipazzi P, De Laurentiis A, Lalli L, Di Guardo L, Patuzzo R, Vergani B, Casiraghi E, Gualeni A, Bollati V, Arienti F, Mariani L, Villa A, Altevogt P, Umansky V, Rodolfo M, Rivoltini L. Tumor-derived microRNAs induce myeloid suppressor cells and predict immunotherapy resistance in melanoma. **J Clin Invest.** 2018 Dec 3;128(12):5505-5516. doi: 10.1172/JCI98060. Epub 2018 Nov 5. **OA.**

10. **Wu H,** Huang J. Drug-Induced Nephrotoxicity: Pathogenic Mechanisms, Biomarkers and Prevention Strategies. **Curr Drug Metab.** 2018;19(7):559-567. doi: 10.2174/1389200218666171108154419. (Review)

11. **Wu H,** Huang J. Optimization of Protein and Peptide Drugs Based on the Mechanisms of Kidney Clearance. **Protein Pept Lett.** 2018;25(6):514-521. doi: 10.2174/0929866525666180530122835. (Review).

12. **Wu H,** Larribère L, Sun Q, Novak D, Sachindra S, **Granados K,** Umansky V, Utikal J. Loss of neural crest-associated gene FOXD1 impairs melanoma invasion and migration via RAC1B downregulation. **Int J Cancer.** 2018 Dec 1;143(11):2962-2972. doi: 10.1002/ijc.31799. Epub 2018 Sep 29.

13. Yamauchi Y, Safi S, **Blattner C,** Rathinasamy A, Umansky L, Juenger S, Warth A, Eichhorn M, Muley T, Herth FJF, Dienemann H, Platten M, Beckhove P, Utikal J, Hoffmann H, Umansky V. 2018. Circulating and Tumor Myeloid-derived Suppressor Cells in Resectable Non-small-cell Lung Cancer. **Am J Respir Crit Care Med.** 2018 Sep 15;198(6):777-787. doi: 10.1164/rccm.201708-1707OC. **OA.**

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14. Jäger K*, Larribère L*, **Wu H,** Weiss C, Gebhardt C, Utikal J. Expression of Neural Crest Markers GLDC and ERRFI1 is Correlated with Melanoma Prognosis. **Cancers (Basel).** 2019 Jan 11;11(1):76. doi: 10.3390/cancers11010076. **OA.**

15. Sharbi-Yunger A, **Grees M,** Gal C, Bassan D, Eichmüller SB, Tzehoval E, Utikal J, Umansky V, Eisenbach L. A universal anti-cancer vaccine: Chimeric invariant chain potentiates the inhibition of melanoma progression and the improvement of survival. **Int J Cancer.** 2019 Feb 15;144(4):909-921. doi: 10.1002/ijc.31795. Epub 2018 Dec 5.

16. Umansky V, Adema GJ, Baran J, Brandau S, Van Ginderachter JA, **Hu X,** Jablonska J, Mojsilovic S, Papadaki HA, Pico de Coaña Y, Santegoets KCM, Santibanez JF, Serre K, Si Y, Sieminska I, Velegraki M, Fridlender ZG. Interactions among myeloid regulatory cells in cancer. **Cancer Immunol Immunother.** 2019 Apr;68(4):645-660. doi: 10.1007/s00262-018-2200-6. Epub 2018 Jul 12. (Review).

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17. Shevchenko I, Mathes A, **Groth C,** Karakhanova S, Müller V, Utikal J, Werner J, Bazhin AV, Umansky V. Enhanced expression of CD39 and CD73 on T cells in the regulation of anti-tumor immune responses. **Oncoimmunology.** 2020 Apr 9;9(1):1744946. doi: 10.1080/2162402X.2020.1744946. **OA.**

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18. Shen Y*, Wang X*, Liu Y, Singhal M, **Gürkaslar C,** Freire Valls A, Lei Y, Hu W, Schermann G, Adler H, Yu FX, Fischer T, Zhu Y, Augustin HG, Schmidt T, Ruiz de Almodovar C. STAT3-YAP/TAZ signaling in endothelial cells promotes tumor angiogenesis. **Sci Signal.** 2021 Dec7;14(712):eabj8393. doi: 10.1126/scisignal.abj8393. Epub 2021 Dec 7. **OA.**

5.1.2.2. Other Publications and Published Results

19. **Fleming V,** Umansky V. Two MDSC faces in obesity: Correcting metabolic dysfunctions but promoting tumor development. **J Leukoc Biol.** 2018 Mar;103(3):373-375. doi: 10.1002/JLB.3CE1017-416R. Epub 2017 Dec 15. (Editorial)

5.1.2.3. Completed Theses that have not yet been published

n.a.

5.2. Project Results Generated by the RTG (List of the 20 most important publications of the RTG since 2015). Open access publicatons are designated by "OA"

1. **Messmer JM, Thommek C, Piechutta M,** Venkataramani V, Wehner R, Westphal D, Schubert M, Mayer CD, Effern M, Berghoff AS, Hinze D, Helfrich I, Schadendorf D, Wick W, Hölzel M, **Karreman MA*, Winkler F*.** T lymphocyte recruitment to melanoma brain tumors depends on distinct venous vessels. **Immunity.** 2024 Sep 28:S1074-7613(24)00447-3. doi: 10.1016/j.immuni.2024.09.003. Online ahead of print. **OA.**

2. Ma S*, Sandhoff R*, Luo X*, Shang F*, Shi Q, Li Z, Wu J, Ming Y, Schwarz F, Madi A, Weisshaar N, Mieg A, **Hering M,** Yan X, Mohr K, ten Bosch N, Li Z, Poschet G, Rodewald HR, Papavasiliou N, Wang X, Gao P, **Cui G.** 2024. Serine enrichment in tumors promotes regulatory T cell accumulation through sphinganine-mediated regulation of c-Fos. **Sci Immunol.** 2024 Apr 19;9(94):eadg8817. doi: 10.1126/sciimmunol.adg8817. Epub 2024 Apr 19.

3. Tan CL, Lindner K, Boschert T, Meng Z, Rodriguez Ehrenfried A, De Roia A, Haltenhof G, Faenza A, Imperatore F, Bunse L, Lindner JM, Harbottle RP, Ratliff M, Offringa R, Poschke I, **Platten M*,** Green EW*. Prediction of tumor-reactive T cell receptors from scRNA-seq data for personalized T cell therapy. **Nat Biotechnol.** 2024 Mar 7. doi: 10.1038/s41587-024-02161-y. Online ahead of print. (*equal contribution). **OA.**

4. Hausmann D, Hoffmann DC, Venkataramani V, Jung E, Horschitz S, Tetzlaff SK, Jabali A, Hai L, Kessler T, Azoŕin DD, Weil S, Kourtesakis A, Sievers P, Habel A, Breckwoldt MO, **Karreman MA,** Ratliff M, **Messmer JM,** Yang Y, Reyhan E, Wendler S, Löb C, Mayer C, Figarella K, Osswald M, Solecki G, Sahm F, Garaschuk O, Kuner T, Koch P, Schlesner M, Wick W, **Winkler F.** Autonomous rhythmic activity in glioma networks drives brain tumour growth. **Nature.** 2023 Jan;613(7942):179-186. doi: 10.1038/s41586-022-05520-4. Epub 2022 Dec 14.

5. Hübers C, **Abdul Pari AA, Grieshober D,** Petkov M, Schmidt A, **Messmer T,** Heyer CM, Schölch S, Kapel SS, Gengenbacher N, Singhal M, Schieb B, Fricke C, Will R, Remans K, **Utikal JS,** Reissfelder C, Schlesner M, Hodivala-Dilke KM, Kersten S, **Goerdt S, Augustin HG*, Felcht M*.** Primary tumor-derived systemic nANGPTL4 inhibits metastasis. **J Exp Med.** 2023 Jan 2; 220(1):e20202595. doi: 10.1084/jem.20202595. Epub 2022 Oct 21. (*equally contributing senior authors). **OA.**

6. **Schmid CD*; Olsavszky V*,** Reinhart M*, Weyer V, Trogisch FA, Sticht C, Winkler M, **Kürschner SW, Hoffmann J,** Ola R, Staniczek T, Heineke J, Straub BK, Mittler J, Schledzewski K, Ten Dijke P, Richter K, Dooley S, **Géraud C, Goerdt S*, Koch PS*.** ALK1 Controls Hepatic Vessel Formation, Angiodiversity, and Angiocrine Functions in Hereditary Hemorrhagic Telangiectasia of the Liver. **Hepatology.** 2023 Apr 1;77(4):1211-1227. doi: 10.1002/hep.32641. Epub 2022 Jul 17. (*equal contribution). **OA.**

7. Weisshaar N, Ma S, Ming Y, Madi A, Mieg A, **Hering M,** Zettl F, Mohr K, ten Bosch N, Stichling D, Buettner M, Poschet G, Klinke G, Schulz M, Kunze-Rohrbach N, Kerber C, Klein IM, Wu J, Wang X, **Cui G.** The malate shuttle detoxifies ammonia in exhausted T cells by producing 2-ketoglutarate. **Nat Immunol.** 2023 Nov;24(11): 1921-1932. doi:10.1038/s41590-023-01636-5. Epub 2023 Oct 9. **OA.**

8. Manta CP*, **Leibing T*,** Friedrich M, Nolte H, Adrian M, Schledzewski K, Krzistetzko J, **Kirkamm C, Schmid CD,** Xi Y, Stojanovic A, Tonack S, de la Torre C, Hammad S, Offermanns S, Krüger M, **Cerwenka A, Platten M, Goerdt S*, Géraud C*.** 2022. Targeting of Scavenger Receptors Stabilin-1 and Stabilin-2 Ameliorates Atherosclerosis by a Plasma Proteome Switch Mediating Monocyte/Macrophage Suppression. **Circulation.** 2022 Dec 6;146(23):1783-1799. doi: 10.1161/CIRCULATIONAHA.121.058615. Epub 2022 Nov 3. (*equal contribution) **OA.**

9. **Feinauer MJ, Schneider SW,** Berghoff AS, **Robador JR, Tehranian C, Karreman MA,** Venkataramani V, Solecki G, Grosch JK, Gunkel K, **Kovalchuk B,** Mayer FT, Fischer M,

Breckwoldt MO, Brune M, Schwab Y, Wick W, Bauer AT, **Winkler F.** 2021. Local blood coagulation drives cancer cell arrest and brain metastasis in a mouse model. **Blood.** 2021 Mar 4;137(9):1219-1232. doi: 10.1182/blood.2020005710. **OA.**

10. Gengenbacher N*, Singhal M*, Mogler C, Hai L, Milde L, **Abdul Pari AA,** Besemfelder E, Fricke C, Baumann D, Gehrs S, **Utikal J, Felcht M,** Hu J, Schlesner M, Offringa R, Chintharlapalli SR, **Augustin HG.** 2021. Timed Ang2-targeted therapy identifies the Angiopoietin-Tie pathway as key regulator of fatal lymphogenous metastasis. **Cancer Discov.** 2021 Feb;11(2):424-445. doi: 10.1158/2159-8290.CD-20-0122. Epub 2020 Oct 26. **OA.**

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