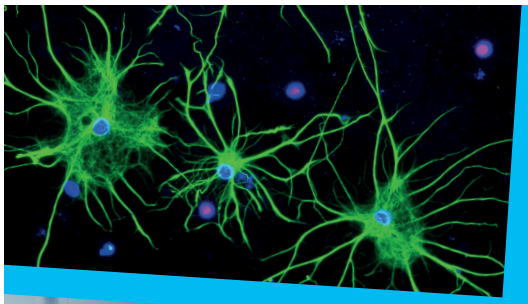
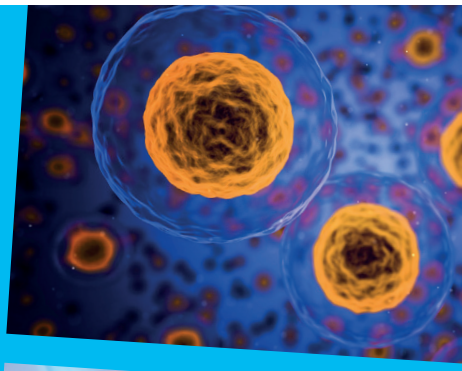
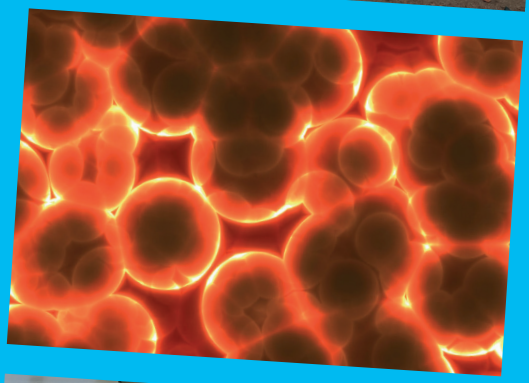
FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG
MEDIZINISCHE FAKULTÄT

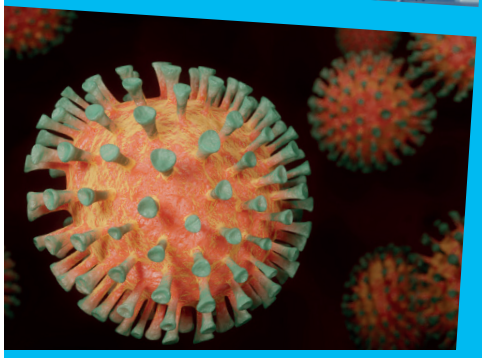
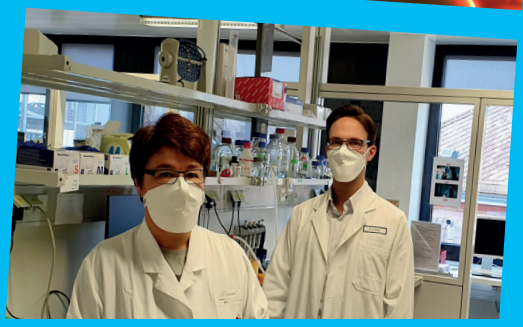
Universitätsklinikum
Erlangen

IZKF Erlangen 2020








interdisciplinary
Center for
Clinical Research

www.med.fau.de

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EDITORIAL

Dear Friends and Members of the IZKF,
Dear Readers,

Please find on the following pages the Annual Report 2020 of the IZKF Erlangen.

As you will notice, the format of our report has undergone substantial changes. Based on your feedback, we tried to modernize layout and increase usefulness as a reference source by focusing on the most important information, facts and figures of our programmes. Further information is available on our homepage: www.izkf.med.fau.de.

In deep mourning we had to say goodbye to Prof. Joachim Kalden, who passed away on February 6, 2021 at the age of 83. For many years, Joachim Kalden was the Spiritus Rector of the IZKF. He helped to launch it as a BMBF-funded institution in 1996 and led its fortunes as spokesman for more than 10 years. His enthusiasm for clinical research and his drive were coupled with joie de vivre, humor and human warmth. He had a lasting impact on the research atmosphere in Erlangen and the IZKF and will not be forgotten by those who knew him and had the privilege to work with him.

In 2020, the SARS-CoV-2 coronavirus changed all our lives. It also influenced research activities within the IZKF and caused delays in the start of new projects, interruptions in already funded projects and laboratory rotations, reduced congress participations and guest scientist invitations, but also a rise in web-based formats, for instance for the Postgraduate Workshop of the IZKF Research Training Group. The effects of the pandemic will still be felt in 2021. For that reason, we decided to postpone our biennial IZKF symposium in Kloster Banz (originally planned for June 2021) to June 09 - 11, 2022.

Despite the pandemic, interest in our funding schemes remained high so that in May we were able to approve funding for 7 new junior projects out of 17 applications and to admit three new participants to the Advanced Module of our Clinician Scientist Programme that has itself firmly established by now.

Prof. Zweier, who headed the Clinician Scientist programme and its committee, took up her new position as Chief Physician and Director of the University Clinic for Human Genetics at the University Hospital Bern on September 1, 2020. In her place, Prof. Berking joined the committee. We thank Prof. Zweier for her commitment and warmly welcome Prof. Berking.

During 2020, our current junior research groups headed by Prof. Ceppi and Prof. Dulin performed very well. Both group leaders have already moved upwards on their career ladder and taken up new positions as professors at University of Southern Denmark in Odense (Denmark) and VU Amsterdam (Netherlands), currently on a part-time basis until their IZKF position expires in mid-2021 and mid-2022, respectively.

In trying to further optimize the junior research group programme and maintain its attractiveness for the future, Managing Board and Scientific Advisory Board decided to slightly shift the funding focus and tailor the programme for provision of generous start-up funding for newly appointed colleagues on tenured W1 or W2 professorships. In the first round of applications, Prof. Günther, Prof. Müller-Deile, Prof. Karow and Prof. Zunke succeeded and will head the new IZKF junior research groups starting 2021.

There is also good news for the graduate students of the IZKF Research Training Group. From 2020 onwards, funding will be at 65% E13 right from the start. Furthermore, graduate students will no longer have to use paper-based study books, but can now rely on a new online system for registration, documentation of their structured training, and support measures such as automated reminders and annual account statements.

In closing, I thank all members of the IZKF Administrative Office for their strong commitment and excellent work. A big thanks to all of you as well for your interest and support. Wishing you an enjoyable and informative read.

Prof. Dr. Michael Wegner
Chairman

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THE IZKF IN NUMBERS

31 Advanced Projects

17 Immunology and Infection
7 Oncology
4 Neurosciences
3 Renal and Vascular Research

8 tandem projects between departments and institutes
42 project leaders

6 Junior Research Groups

4 Groups approved in 2020, starting 2021

24 Junior Projects

10 Immunology and Infection
4 Oncology
2 Neurosciences
4 Renal and Vascular Research
1 Medical Engineering
3 Others
thereof **9** projects completed in 2020

4 Appointments of IZKF project leaders to W2/ W3 - positions

40 Institutions with running projects 2020

4,434 K€ total expenditures in 2020

353 Members of Life@FAU 2020

35 SFB 1181
2 SFB 1350
32 GRK 2162
12 GRK 1962
14 GRK 2504
21 GRK 1660
11 TRR 130
9 TRR 221
14 TRR 241
9 TRR 225
172 IZKF
86 Dr. med.
86 Dr. rer. nat.
22 participants outside RTG

44 Pilot Projects

15 Newly granted in 2020
20 Projects completed in 2020

51 Ongoing Scientific Theses in 2020

9 Master theses
40 Doctoral theses
2 Habilitations

40 Publications

Cumulative Impact Factor **332.643**
Average Impact Factor per publication **8.316**
Average publications per project **0,8***
10 publication with an IF more than 10

*Based on advanced projects, junior research groups and junior projects

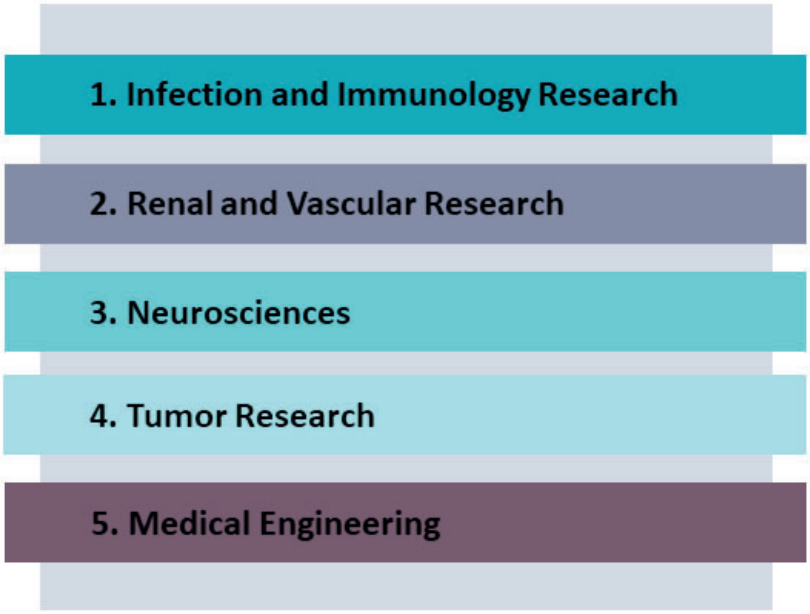
125 Employees of the IZKF

72 Doctoral fellows, Post-Docs and laboratory rotations
53 Non-scientists

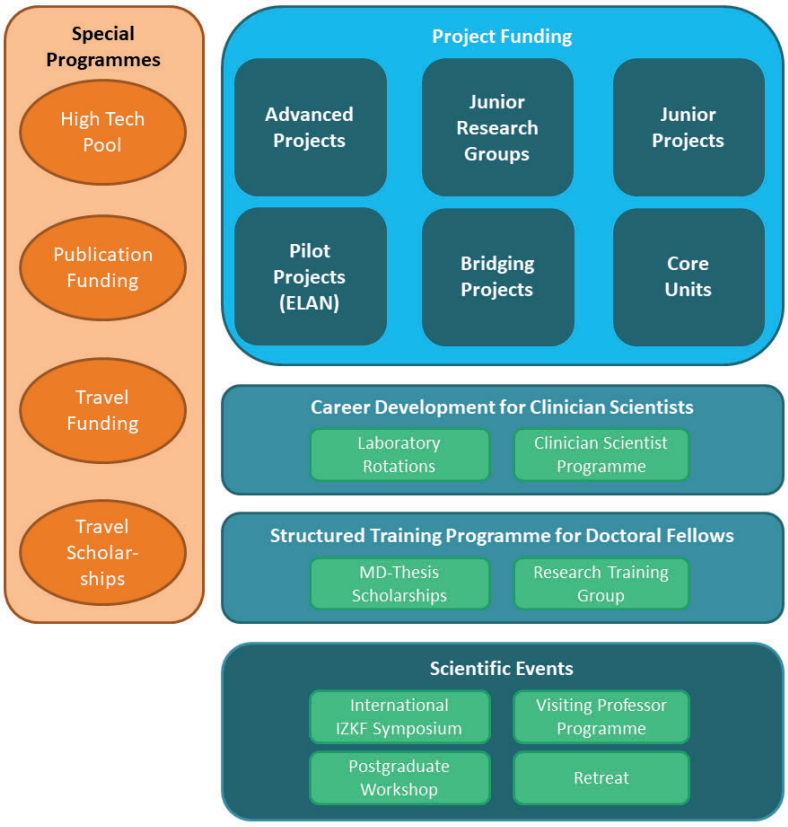
PROGRAMMES

The IZKF is the central structure of research development of the Faculty of Medicine. Its mission is to improve the overall quality of clinical research, to stimulate interdisciplinary research, to advance the careers of young scientists and to foster the acquisition of extramural funds. In order to achieve these goals, the IZKF supports projects in all research areas of the Faculty of Medicine on a strictly time-limited basis. The selection of projects is based exclusively on quality aspects. The various programmes are aimed at physicians and scientists at different stages of their scientific careers. Equipped with its own budget and own management structures, the IZKF continuously develops its own funding programmes in line with the needs of the Faculty of Medicine. In addition, the Faculty of Medicine also uses the structures established in the IZKF for the allocation and management of funds and avoids the creation of parallel structures.

The IZKF has created more transparency about research activities in the various areas and strengthened cooperation between clinics and institutes, but also between different clinics. The IZKF enables research funding beyond budget boundaries and also supports risk projects.



Main research areas of the Faculty of Medicine



Programmes and supporting activities of the IZKF for scientists at all carrier levels

The IZKF offers research grants in all main research areas of the Faculty of Medicine, i.e. immunology and infection research, renal and vascular research, neurosciences, tumor research and medical engineering.

Advanced projects are assigned to one of the five main research areas of the Faculty, which is also encoded in the project number. Junior projects and pilot projects are also assigned to these five main research areas. However, there are some junior and pilot projects that cannot be directly allocated to one of the main research areas. These are grouped under “others”. The project reports in the hind part of this report are initially grouped by funding line, and additionally sorted by research areas.

In all project lines with age restrictions childcare is taken into account. Periods of childcare are granted on a lump-sum basis without proof of actual periods of absence with two years per child for women and one year per child for men. Upon presentation of proof, additional periods of absence may be taken into account for both men and women. In junior projects the IZKF even offers additional project funding under certain circumstances.

The SARS-CoV2 pandemic also had an impact on approved projects. Some asked for a later start due to problems in recruiting staff. The IZKF made it therefore possible to start a project a maximum of one year after assessment. 26 projects could start on time. At the end, only 5 projects had a delayed start.

Advanced Projects

As already mentioned the IZKF supports clinically relevant projects on all main research areas of the Faculty of Medicine. The project duration is 30 months. After a single funding period projects should be transferred to extramural funding. If the application for extramural funding was filed (as listed below) within the duration of the IZKF project, the duration of the project will be extended for another 6 months. In case of a two-stage review process for third-party research proposals the full application is required for the extension of IZKF funding.

Project funding is allocated after a stringent peer-review process based solely on scientific criteria. Research grants are approved after a two-stage review process. In an initial step, draft proposals are subject to an internal review by the Management Board, members of the ELAN-Commission and the Junior Scientists Committee as well as other recognized scientists of the Faculty of Medicine based on a written proposal and public presentation. Decisions are reached after internal assessment and are communicated immediately afterwards. Successful proposals are presented in the second stage to the Scientific Advisory Board and peer-reviewed during on-site visits. Projects must start within six months (Exceptions during the Corona Pandemic). Over the years funding rates were about 30 - 40%.

Applicants are expected to have an active publication record and own external funding. Preliminary results should promise a successful transfer of the project into external funding after the 30-months term. Within this period an application for funding should be submitted to one of the listed funding institutions. Innovative and original ideas and concepts are especially valued as well as clinical relevance and interdisciplinary approaches. Applicants from all clinics, departments and institutes of the Faculty of Medicine and co-applicants from other faculties are entitled with no age limit.

Call for proposals	every 2 or 3 years
Eligibilty	active publication record and own external funding no age limit
Staff	Single projects: graduate student or technical assistant (one position) Tandem projects: graduate student(s) and/or technical assistant (two positions)
Consumables	Single projects: EUR 15,000 p.a. Tandem projects: EUR 25,000 p.a.
Others	Participation in Travel, Publication and High Tech Pool
Duration	30 + 6 months

LOM weighted 4-fold

- DFG
- BMBF
- Other Federal and State Ministries
- EU
- NIH-Grants

LOM weighted 2-fold

- Bayerisches Staatsministerium für Wissenschaft und Kunst
- Bayerische Forschungsstiftung/ Bayerische Landesstiftung
- Wilhelm Sander-Stiftung
- Volkswagen Stiftung
- Deutsche Stiftung für Herzforschung
- Humboldt-Stiftung
- Thyssen-Stiftung
- German-Israelian-Foundation (GIF)
- Mildred-Scheel-Stiftung/ Deutsche Krebshilfe
- Else Kröner Fresenius Stiftung
- José-Carreras-Stiftung
- Bill Gates Stiftung
- DAAD
- Deutsche Kinderkrebsstiftung/ HIT Deutsche Kinderkrebsstiftung
- Hertie-Stiftung
- Herman und Lilly Schilling-Stiftung

Junior Research Groups

Jochen-Kalden-funding programme

In honor of the founder and former IZKF chairman this programme has been renamed as the Jochen-Kalden-funding programme.

The junior research groups represent a central funding instrument of the IZKF. As the currently funded groups of Prof. Dr. Ceppi (Junior Research Group 1) and Prof. Dr. Dulin (Junior Research Group 2) expire in mid-2021 and 2022, the Management Board established a new concept for the junior research groups. Funding volume and application requirements have been redefined. Every year, two new junior research groups have now the possibility to benefit from this attractive career development programme.

Call for proposals	annually
Eligibility	Newly appointed W1 / integrated W2 professors with tenure track doctorate 10 years ago (medical doctorate) or 8 years ago (other doctorates, e.g. life sciences, engineering) no significant other funding for a junior research group
Staff	Graduate student Technical assistant
Consumables	EUR 40,000 p.a.
Others	Participation in Travel, Publication and High Tech Pool Possibility of providing laboratory space for shared use
Duration	24 + 12 months

The review takes place in a one-step process performed by the IZKF Management Board, members of the ELAN-Commission and the Junior Scientists Committee with the participation of the speakers for the research areas of the Faculty of Medicine as well as the Scientific Advisory Board.

Over a period of 2 years, each junior research group receives funding equivalent to one graduate student and one technical assistant and consumables in the amount of € 40,000 p.a. as flexible funding. If an application for extramural funding is submitted to a third-party agency that is at least LOM-weighted 2-fold a further project year is granted.

Junior Projects

For scientists starting their independent career, obtaining their first extramural research funding is an important step. To aid in this process, the IZKF offers starting grants to young postdoctoral physicians and scientists up to 35 years of age without previous significant external funding. Candidates should have a visible publication record and projects should be based on an original idea with first tangible results.

After this time it is expected that successful candidates submit an external grant application. If the application is filed within duration of the junior project, the spending period will be extended by another 6 months.

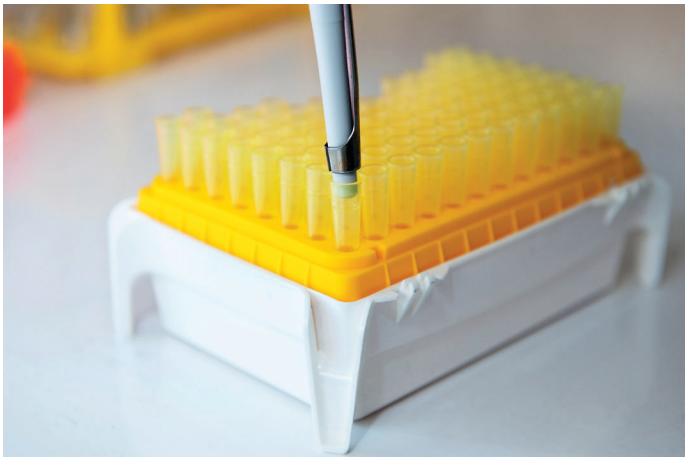
Junior projects are subject to a one-stage internal review only. Full proposals are reviewed by the Management Board, members of the ELAN-Commission and Junior Scientists Committee based on a written proposal and public presentation. Decisions are reached after internal deliberation and are then communicated immediately afterwards to the proponents.

The IZKF expects that at least 25% of the position of the applicant is financed from the budget of the applying institution. The contract should last at least as long as the project runs.

Call for proposals	annually
Eligibilty	for postdoctoral physicians/ scientists up to 35 years of age without previous external funding
Staff	Technical assistant or graduate student
Consumables	EUR 15,000 p.a.
Others	Participation in Travel, Publication and High Tech Pool IZKF laboratory rotations for physicians
Duration	30 months

Pilot Projects (ELAN)

The aim of the ELAN programme is to support scientific projects at a very early stage and help prepare them for successful application for external funding (start-up projects), to support newly established working groups, to develop new innovative ideas (pilot projects) or act as interim funding if temporary gaps arise between individual extramural funding periods. Young scientists until the age of 39 (i.e. before the 39th birthday) at the time of application are supported with a maximum of € 60,000 for a period of up to 12 months.



Call for proposals	continuously
Eligibilty	for young scientists until the age of 39 (i.e. before the 39th birthday) at the time of application with a doctoral degree, newly appointed (W2)-Professors can submit their application regardless of age position of the applicant is financed partly from the budget of the institution
Staff	only one position
Consumables	max. EUR 20,000
Total funding	max. EUR 60,000
Others	Participation in Publication Pool and Travel Pool
Duration	max. 12 months

In addition, newly appointed professors can submit their application regardless of age. A total of two ELAN projects can be applied for over the course of a scientific career, provided that a publication or a third-party funded project has arisen from the previous funding. The IZKF expects that at least 10% of the position of the applicant is financed from the budget of the applying institution.

Bridging Projects

The programme allows independent scientists (usually with a permanent employment contract) to bridge a precarious situation and continue their research. The prerequisite is a recently rejected application for third-party funding to a granting agency that is at least LOM-weighted 2-fold which has narrowly failed and which, after revision, can be submitted promptly.

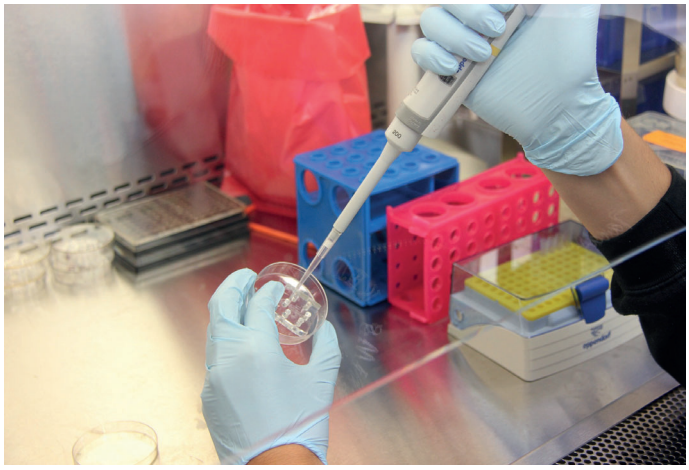
Other third-party or intramural funding must not currently exist, but in the past a corresponding external funding (at least LOM-weighted 2-fold) must already have been available. A repeated use of the programme is only possible if the previous funding was successful, i.e. the resubmitted application for third-party funding was finally granted. Applications can be submitted at any time promptly after the precarious situation has occurred. The amount of funding is up to € 50,000 for a period of 6 months. The evaluation is carried out by the ELAN-Commission. A member of the ELAN-Commission coordinates the evaluation and integrates a member of the External Scientific Advisory Board of the IZKF as an external expert.

Call for proposals	continuously
Eligibilty	for independent scientists to bridge a precarious situation no age limit
Staff and consumables	max. EUR 50,000 (the recruitment of new staff, especially of doctoral students is not intended)
Others	the use of central funds from the travel-, publication- and high-tech pool of the IZKF is not possible
Duration	about 6 months

Core Units

Modern molecular technologies, such as genomics, proteomics and advanced molecular imaging, require very expensive and complicated instrumentation and are methodologically very demanding. Thus it is often not scientifically worthwhile or cost-effective to establish and maintain these techniques in parallel in different groups. Core facilities or units are centralised methodological platforms that offer access to these modern methods and technologies to a broad user spectrum. This enables access to modern technologies to smaller groups and also to those with other main methodological interests. Also, it allows students to be directly exposed to these modern developments.

Core facilities are operated under the leadership of a scientific group with demonstrated excellence and interest in developing the methodology. In return for institutional support, it is expected that the operating group assists other groups with their know-how in accessing this technology. The support provided by the IZKF and the Faculty usually includes the initial investment for the instrumentation of the platform, the cost for setting up the operation as well as its continued technological development. IZKF pioneers the development of core facilities in Erlangen and usually supports them for an initial start-up phase of up to 6 years. Once established and successfully working, long-term support is provided directly by the Faculty.



Services and costs are to be made transparent and equal access has to be ensured. Core facilities are regularly evaluated for their effective operation, scientific excellence and timeliness.

The IZKF offers the possibility for developing new core units. Nearly all core units of the Faculty of Medicine have received a start-up funding by the IZKF.

Career development for Clinician Scientists

Release from clinical work for research

Access to protected research time is essential for young clinicians developing their projects. The laboratory rotation positions enable young scientists, who completed their doctorate, to fully devote themselves to a research project.

In the IZKF 8 rotation positions are financed continuously and are available as follows. Physicians, who apply for a rotation position in the first applicant programme, have the opportunity to apply for a rotation position for 12 months full-time or 24 months part-time directly as part of the project application. Within the Clinician Scientists Programme physicans can apply for the Advanced Modul that offers rotation positions for 12 months full-time or 24 months part-time.

In addition to these two programmes, there are rotation positions for flexible use. The positions are available for a period of 6 months full-time or 12 months part-time, an extension is not possible. Support of up to 4 rotation projects per year is possible.

Applications may be submitted at any time. There is no age limit, but the planned rotation position must make a suitable contribution to the scientific development of the applicant.

Junior Projects	Clinician Scientists Programme Advanced Modul	Laboratory Rotations
3 positions 12 months full-time or 24 months part-time	3 positions 12 months full-time or 24 months part-time	4 positions 6 months full-time or 12 months part-time

Available laboratory rotations according to programme

Clinician Scientist Programme

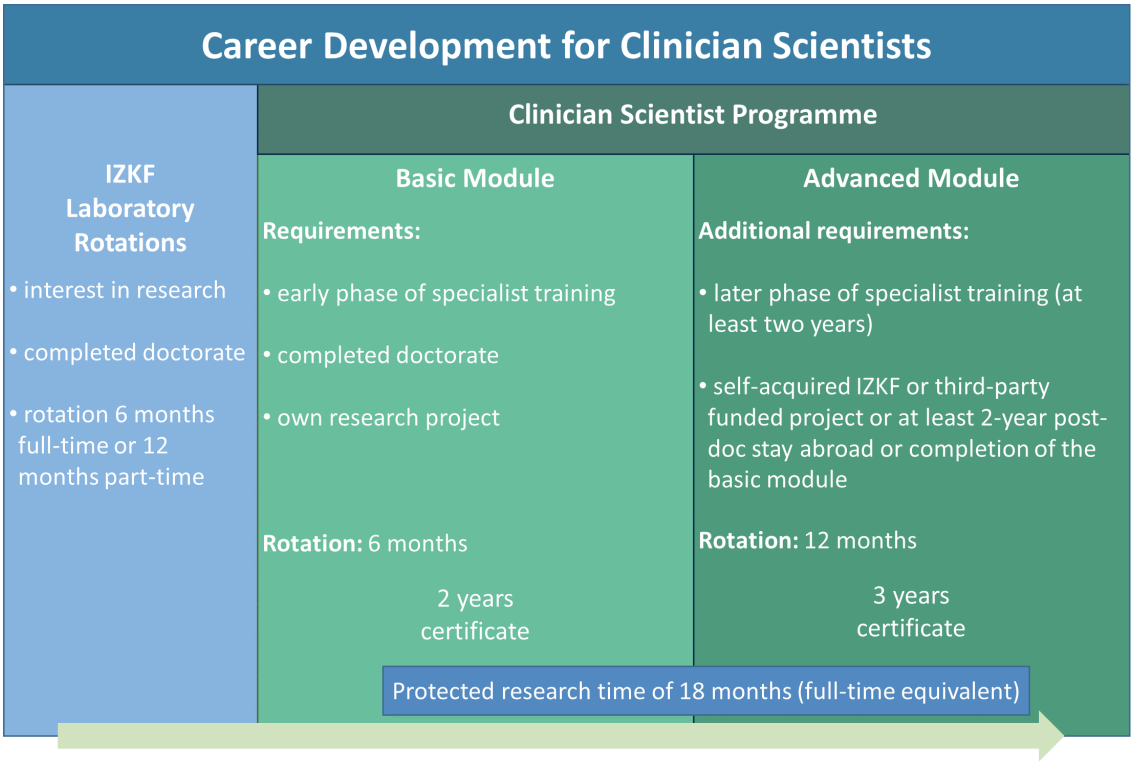
The Clinician Scientist Programme (CSP) is aimed at physicians who are in their specialist training, would like to conduct their own research project and to continue their scientific education within the frame-work of a structured training programme.

The aim of the CSP is to establish a new career path and promotion for Clinician Scientists and to create a structured scientific qualification programme for physicians performing clinical research. The focus is also on strengthening translational research by creating time for scientific work and the preparation for habilitation. The CSP includes professional as well as interdisciplinary further education, mentoring, retreats and regular meetings. At the same time, the physicians conduct their own research project.

The programme at the IZKF has a two-stage structure and is divided into a basic and an advanced module. The basic module lasts 2 years and requires a proof of the completed doctorate and enrolment in specialist training (already started at the time of joining the CSP).

The advanced module (duration 3 years) is aimed at physicians who have already successfully acquired a funding from the IZKF or a third party. The admission requirement for the advanced module is also fulfilled when having completed a post doctoral stay abroad of at least 2 years and at least 2 years of specialist training or with a successfully completed basic module. The leave of absence is 12 months full-time or equivalent part-time via rotation positions. An early change from the basic to the advanced module is possible by application under the following conditions: at least 2 years of specialist training and personally obtained IZKF- or third party funding. However, candidates who have been in the habilitation process for more than 2 years or who have already undergone an interim evaluation by the Fachmentorat cannot be accepted. In principle an early change into the advanced module is subject to a case-by-case examination and decision.

Applications for admission to the CSP may be submitted any time. Coincident with the application deadlines for the Junior Projects, a rotation position for participation in the CSP (advanced module) can be applied for at the IZKF on an annual basis.



Overview of career programmes for clinician scientists

Structured Training Programmes For Doctoral Fellows At The IZKF

Life@FAU

The Graduate School for Life Sciences (Life@FAU) was launched following an initiative of the IZKF to offer an interdisciplinary structured training programme for doctoral students at the Faculty of Medicine and the Department of Biology. The Faculty of Medicine and the Department of Biology at the Faculty of Sciences are involved on equal footing. All research training groups of both faculties are members of Life@FAU including the IZKF Research Training Group. The objectives of Life@FAU are to enhance structured training programmes for doctoral candidates at FAU, to create uniform standards in postgraduate education in the field of life sciences and to ensure the provision of structured training programmes.

MD-Thesis Scholarships

This programme was initiated to arouse interest for science in motivated medical students early on in their career. Medical students are supported in performing an experimental thesis.

Now up to 23 grants for 8 months each are available for medical students with outstanding performance and commitment in studies. The participants have to work full-time in the laboratory and a scholarship is offered during their research activity. Furthermore, the doctoral fellows have to complete defined training modules during their studies. Training modules including guest speaker seminars, soft skills courses and the continuous supervision by a mentoring committee should continue throughout and until completion of the doctorate. Every participant of the MD-Thesis Scholarship Programme automatically becomes a member of the IZKF Research Training Group and the Graduate School of Life Sciences at FAU (Life@FAU). Thus, the doctoral students can benefit from a structured, interdisciplinary training programme.

Research Training Group

The IZKF runs a research training group for all doctoral fellows and MD-students of the IZKF. Participation is mandatory for all IZKF-funded doctoral candidates in sciences and medicine who are not involved in an alternative structured training programme of the Faculty/ University. Other students may also associate with the research training group.

Aims of the IZKF Research Training Group include fostering networking and scientific self-organisation, methodological competence and soft skills as well as offering insights into other scientific fields and career opportunities. A structured seminar programme, courses in basic methods, in scientific writing and presentation are organised by the IZKF. In addition, the participants of the research training group have to attend guest speaker seminars and to participate in the annual internal retreat. Participation in external congresses and in seminars organised by the doctoral fellows are mandatory.

The research training group also offers a mentoring programme for all doctoral fellows. Each doctoral fellow selects three mentors. At least one annual meeting of the doctoral student and the mentoring committee is expected.

The IZKF Research Training Group is divided into four research areas: Jour Fixe Ink (Immunology/infection/renal and vascular research), Jour Fixe Neuro (Neuroscience), Jour Fixe Onko (Oncology) and the Jour Fixe DigIT (Digital information technology).

Course “Intellectual Property Rights” given on 24th May 2018.

Special Programmes

The following special programmes provide additional funding for IZKF projects:

High Tech Pool

The IZKF actively encourages the use of modern "omics" technologies in the projects, such as those provided by the Core Unit Next Generation Sequencing. Since these experiments are generally expensive and consumables within IZKF advanced and junior projects are restricted, additional support is necessary. Costs for consumables can therefore be supported upon request with up to € 10,000 per project, provided that the project itself contributes at least 30% of the total sum.

Travel Scholarships

Travel scholarships allow IZKF's young researchers to spend time in other laboratories in Germany or abroad to conduct important experiments or learn the latest techniques and methods. The programme also allows doctoral candidates to intensify existing collaborations or establish new ones. Travel grants include transportation and accommodation for up to 3 months. An extension of the travel scholarship for another 3 months is possible.

Travel Funding

To enable IZKF members to present their results to the academic community, the IZKF supports their participation in international conferences. All applicants are expected to give a lecture or present a poster. The subject matter of the event must be related to the IZKF project in order to receive funding. The financial contribution of the IZKF is limited to € 500 for conferences in Germany, € 1,000 in Europe, and up to € 1,500 for conferences outside Europe.

Due to the current pandemic, the IZKF temporarily covers the costs of web-based events up to € 500. A project-related active participation is required and an application in advance is necessary.

Publication Funding

The publication of results obtained in IZKF projects in scientific journals is actively supported. It is expected that the IZKF funding of the project is acknowledged and the affiliation is Erlangen. IZKF also supports open access publications.

If the IZKF is the only sponsor and the total costs of the publication are up to € 3,000, IZKF can cover up to € 1,500. If the total costs are more than € 3,000 a financial contribution of € 2,000 is given by the IZKF.

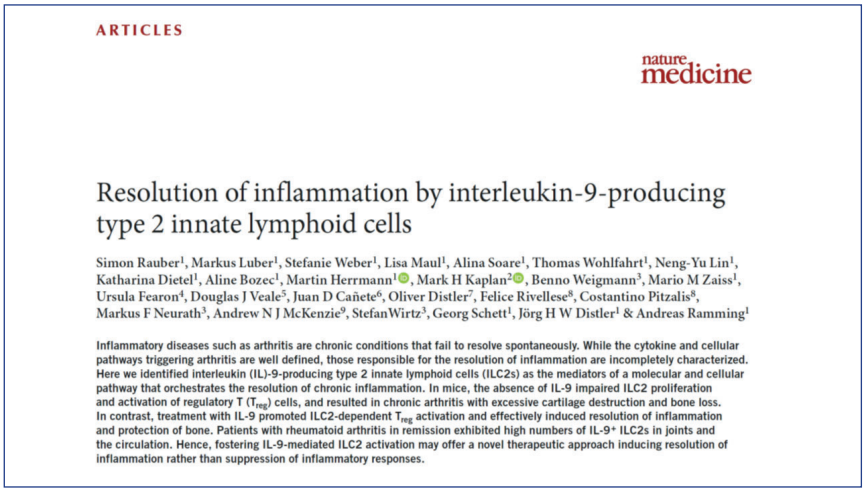
For publications in which the IZKF as well as other sponsors are mentioned, the IZKF contribution is € 500 lower.

IZKF Visiting Professor Programme

To encourage cooperation and to foster the exchange of ideas, IZKF promotes visits of external scientists. Every year approx. 10 scientists from abroad but also from other places in Germany can be invited for a stay of 2 days - 4 months. The programme covers an amount of up to € 3,000 for travel and accommodation costs for visiting researchers. Application is restricted to IZKF members and the invited researcher's subject must be related to the IZKF.

Prof. Ramanuj DasGupta, IZKF Symposium 2019

Availability of the special programmes in the various funding lines is summarized on the next page.



ARTICLES

nature medicine

Resolution of inflammation by interleukin-9-producing type 2 innate lymphoid cells

Simon Rauber[1], Markus Luber[1], Stefanie Weber[1], Lisa Maul[1], Alina Soare[1], Thomas Wohlfahrt[1], Neng-Yu Lin[1], Katharina Dietel[1], Aline Bozec[1], Martin Herrmann[1], Mark H Kaplan[2], Benno Weigmann[3], Mario M Zaiss[1], Ursula Fearon[4], Douglas J Veale[5], Juan D Cañete[6], Oliver Distler[7], Felice Rivellese[8], Costantino Pitzalis[8], Markus F Neurath[3], Andrew N J McKenzie[9], StefanWirtz[3], Georg Schett[1], Jörg H W Distler[1] & Andreas Ramming[1]

Inflammatory diseases such as arthritis are chronic conditions that fail to resolve spontaneously. While the cytokine and cellular pathways triggering arthritis are well defined, those responsible for the resolution of inflammation are incompletely characterized. Here we identified interleukin (IL)-9-producing type 2 innate lymphoid cells (ILC2s) as the mediators of a molecular and cellular pathway that orchestrates the resolution of chronic inflammation. In mice, the absence of IL-9 impaired ILC2 proliferation and activation of regulatory T (T_{reg}) cells, and resulted in chronic arthritis with excessive cartilage destruction and bone loss. In contrast, treatment with IL-9 promoted ILC2-dependent T_{reg} activation and effectively induced resolution of inflammation and protection of bone. Patients with rheumatoid arthritis in remission exhibited high numbers of IL-9$^+$ ILC2s in joints and the circulation. Hence, fostering IL-9-mediated ILC2 activation may offer a novel therapeutic approach inducing resolution of inflammation rather than suppression of inflammatory responses.

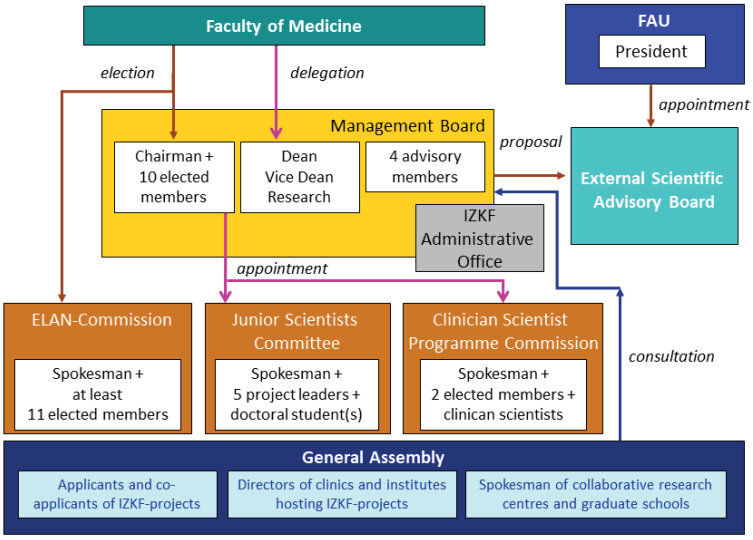
	High Tech Pool	Travel Pool	Publication Pool
Advanced Projects (Project leaders and scientific staff financed by project)	✓	✓	✓
Junior Projects (Project leaders and scientific staff financed by project)	✓	✓	✓
Pilot Projects (Project leaders and scientific staff financed by project)	✗	✓	✓
Bridging Projects	✗	✗	✗
Junior Research Groups (Project leaders and scientific staff financed by project)	✓	✓	✓
Clinician Scientists Programme (IZKF laboratory rotations)	✗	✓	✓
Clinician Scientists Programme (other funding)	✗	✗	✗
Other IZKF laboratory rotations	✗	✓	✓
MD-Thesis Scholarships	✗	✓	✓
Time frame	only within project period	6 months after the end of the project (MD: 12 months after the end of the scholarship)	12 months after the end of the project
The **Travel Scholarships** are available for young scientists (project leaders of Junior Projects, participants CSP, participants IZKF-laboratory rotation, doctoral students of all IZKF projects) only within the project period.			

The table shows which programmes of IZKF are eligible for using special programmes.

GOVERNANCE

The IZKF is a self-organised structure within the Faculty of Medicine. The IZKF has a set of written rules and regulations approved by the Faculty of Medicine. All rules and regulations are continuously reviewed and revised, if necessary. The Statutes of the IZKF regulate the status, tasks and objectives of the IZKF as well as the competence and composition of the committees. The Rules of Procedure specify the application procedure, the funding and duration of the projects as well as the decision-making process between the Chairman, the Management Board and the External Scientific Advisory Board. Finally, the Advisory Board regulations regulate the IZKF's cooperation with the Advisory Board in detail. All regulations are available on the IZKF Homepage.

Governing bodies include the Management Board, the External Scientific Advisory Board, the ELAN-Commission, the Junior Scientists Committee, the Clinician Scientist Programme Commission and the General Assembly.



Governance of the IZKF

The Management Board is the general steering commission of the IZKF. It is responsible for developing the scientific programme, controlling the financial framework and allocating resources to projects and ensures that results are reported. Five annual meetings are held and decisions are taken by simple qualified majority. Elected members include the Chairman who is responsible for daily operations with the support of the Administrative Office. Re-election is possible for all members of the Board.

Programmes and the financial framework are reviewed and approved by the External Scientific Advisory Board. This body meets on site every two or three years to oversee the general development of the IZKF and the proposed projects. The Board consists of at least 10 internationally recognized scientists from universities and research institutes led by an elected chairperson.

The ELAN-Commission is responsible for reviewing pilot and bridging projects and its members assist in the selection of advanced and junior projects. It consists of the spokesman for pilot projects (ELAN) and at least 11 further members all elected by the Faculty of Medicine for a period of three years.

The Junior Scientists Committee supports the Management Board in establishing and supervising career development programmes for young scientists. It selects the recipients of the MD-Thesis scholarships and organizes the IZKF Research Training Group. In addition, its members participate in the internal review process for project funding and for laboratory rotations.

The most recent committee of the IZKF is the Clinician Scientist Programme Commission (CSP-Commission). This commission accompanies the Clinician Scientist Programme of the IZKF in terms of organisation and content and makes recommendations regarding the admission of new applicants to the Clinician Scientist Programme.

The General Assembly convenes once a year to discuss the annual report of the chairman and the further development of the IZKF. Its members are all project leaders, the directors of clinics and institutes receiving funding, and the speakers of all local collaborative research centers and research training groups.

External Advisory Board (from left to right): Prof. Seufferlein, Prof. Siebert, Prof. Busch, Prof. Sendtner, Prof. Katschinski, Prof. Kalinke, Prof. Tiegs, Prof. Pavenstädt, Prof. Sorokin, Prof. Hengel, Prof. Rieß, Prof. Prinz

Management Board

Chairman

Prof. Dr. Michael Wegner, Institute of Biochemistry

Deputy Chairman

Prof. Dr. Aline Bozec, Department of Medicine 3


Prof. Dr. Wegner


Prof. Dr. Bozec

Members

Prof. Dr. Christoph Becker, Department of Medicine 1
Prof. Dr. Christian Bogdan, Institute of Clinical Microbiology, Immunology and Hygiene
Prof. Dr. Anja Bosserhoff, Institute of Biochemistry
Prof. Dr. Thomas Brabletz, Chair of Experimental Medicine I
Prof. Dr. Johann Helmut Brandstätter, Division of Animal Physiology
Prof. Dr. Dr. Raymund Horch, Department of Plastic and Hand Surgery
Prof. Dr. Dimitrios Mougiakakos, Department of Medicine 5
Prof. Dr. Markus Neurath, Department of Medicine 1
Prof. Dr. André Reis, Institute of Human Genetics
Prof. Dr. Mario Schiffer, Department of Medicine 4
Prof. Dr. Jürgen Winkler, Division of Molecular Neurology

Consultative Members

Prof. Dr. Joachim Hornegger, President of the FAU
Christian Zens, Head of Administration of the FAU
Prof. Dr. Dr. Heinrich Iro, Medical Director of the University Hospital Erlangen
Dr. Albrecht Bender, Head of Administration of the University Hospital Erlangen


Prof. Dr. Becker

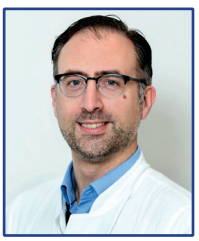

Prof. Dr. Bogdan


Prof. Dr. Bosserhoff


Prof. Dr. Brabletz


Prof. Dr. Brandstätter


Prof. Dr. Dr. Horch


Prof. Dr. Mougiakakos


Prof. Dr. Dr. Neurath


Prof. Dr. Reis


Prof. Dr. Schiffer


Prof. Dr. Winkler


Prof. Dr. Hornegger


Zens


Prof. Dr. Dr. Iro


Dr. Bender

Current members of the Management Board

External Scientific Advisory Board

Chairman

Prof. Dr. Thomas Seufferlein,
University Hospital Ulm - Internal Medicine I

Deputy Chairman

Prof. Dr. Tanja Kuhlmann,
University Hospital Münster, Institute of Neuropathology


Prof. Dr. Seufferlein


Prof. Dr. Kuhlmann

Members

Prof. Dr. Dirk Busch, Technical University of Munich, Institute for Medical Microbiology, Immunology and Hygiene

Prof. Dr. Ulf Dittmer, University Hospital Essen - Institute of Virology (since 22.02.2021)

Prof. Dr. Hartmut Hengel, Freiburg University Hospital - Department of Virology (until 31.12.2020)

Prof. Dr. Ulrich Kalinke, TWINCORE, Centre for Experimental and Clinical Infection Research

Prof. Dr. Thomas Kamradt, Jena University Hospital, Institute of Immunology

Prof. Dr. Dörthe Katschinski, Göttingen University Medical Center - Department of Cardiovascular Physiology

Prof. Dr. Peter R. Mertens, University Hospital Magdeburg - Clinic for Renal and Hypertension Diseases, Diabetology and Endocrinology (since 22.02.2021)

Prof. Dr. Holger Moch, University Hospital Zurich, Institute of Pathology and Molecular Pathology

Prof. Dr. Hermann Pavenstädt, Münster University Hospital - Internal Medicine, Department of Nephrology and Rheumatology (until 31.12.2020)

Prof. Dr. Jörg Prinz, LMU München, Department of Dermatology and Allergology

Prof. Dr. Olaf Rieß, University of Tübingen - Institute of Human Genetics

Prof. Dr. Jörg B. Schulz, University Hospital Aachen - Department of Neurology

Prof. Dr. Reiner Siebert, University Hospital Ulm, Institute of Human Genetics

Prof. Dr. Lydia Sorokin, University of Münster, Institute of Physiological Chemistry and Pathobiochemistry

Prof. Dr. Gisa Tiegs, Hamburg-Eppendorf University Medical Center - Institute of Experimental Immunology and Hepatology

Prof. Dr. Konstanze F. Winklhofer, Ruhr-University Bochum - Institute of Biochemistry and Pathobiochemistry (since 22.02.2021)


Prof. Dr. Busch


Prof. Dr. Hengel


Prof. Dr. Kalinke


Prof. Dr. Kamradt


Prof. Dr. Katschinski


Prof. Dr. Moch


Prof. Dr. Pavenstädt


Prof. Dr. Prinz


Prof. Dr. Rieß


Prof. Dr. Schulz


Prof. Dr. Siebert


Prof. Dr. Sorokin


Prof. Dr. Tiegs

External Scientific Advisory Board
(as of 31st December 2020)

ELAN-COMMISSION

Spokesman for pilot projects (ELAN)

Prof. Dr. André Reis, Institute of Human Genetics

Prof. Dr. Reis

Members

Prof. Dr. Tobias Bäuerle, Institute of Radiology
Prof. Dr. Jürgen Behrens, Chair of Experimental Medicine II
Prof. Dr. Felix Engel, Department of Nephropathology
Prof. Dr. Yesim Erim, Department of Psychosomatic Medicine and Psychotherapy
Prof. Dr. Anna Fejtova, Department Psychiatry and Psychotherapy
Prof. Dr. Martin Fromm, Chair of Clinical Pharmacology and Clinical Toxicology
Prof. Dr. Claus Hellerbrand, Institute of Biochemistry
Prof. Dr. Gerhard Krönke, Department of Medicine 3
Prof. Dr. Christian Pilarsky, Department of Surgery
Prof. Dr. Alexander Steinkasserer, Department of Immune Modulation
Prof. Dr. Maximilian Waldner, Department of Medicine 1
Prof. Dr. Beate Winner, Department of Stem Cell Biology

Prof. Dr. Bäuerle

Prof. Dr. Behrens

Prof. Dr. Engel

Prof. Dr. Erim

Prof. Dr. Fejtova

Prof. Dr. Fromm

Prof. Dr. Hellerbrand

Prof. Dr. Krönke

Prof. Dr. Pilarsky

Prof. Dr. Steinkasserer

Prof. Dr. Waldner

Prof. Dr. Winner

Current members of the ELAN-Commission

Junior Scientists Committee

Spokesman for career development programmes

Prof. Dr. Christoph Becker, Department of Medicine 1

Prof. Dr. Becker

Members

Prof. Dr. David Dulin, IZKF Junior Research Group 2

Prof. Dr. Felix Engel, Division of Nephropathology

Colin Griesbach, Department of Medical Informatics, Biometry and Epidemiology

Prof. Dr. Janina Müller-Deile, Department of Medicine 4

Dr. Christiane Krystelle Nganou Makamdop, Institute of Clinical and Molecular Virology

Tatjana Seitz, Institute of Biochemistry

Prof. Dr. Katharina Zimmermann, Department of Anaesthesiology

Dr. Dulin

Prof. Dr. Engel

Griesbach

Prof. Dr. Müller-Deile

Dr. Nganou Makamdop

Seitz

Prof. Dr. Zimmermann

Current members of the Junior Scientists Committee

Clinician Scientist Programme Commission

Spokesman for Clinician Scientist Programme

Prof. Dr. Dr. Christiane Zweier, Institute of Human Genetics (until 08/2020)

Prof. Dr. Jürgen Winkler, Department of Molecular Neurology (since 09/2020)

Members

Prof. Dr. Carola Berking, Department of Dermatology (since 09/2020)

Prof. Dr. Dimitrios Mougiakakos, Department of Medicine 5

Dr. Ferdinand Knieling, Department of Pediatric and Adolescent Medicine (since 02/2021)

Dr. Eva Maier, Department of Oral and Cranio-Maxillofacial Surgery (since 02/2021)

Prof. Dr. Berking

Prof. Dr. Mougiakakos

Prof. Dr. Winkler

Dr. Knieling

Dr. Maier

Current members of the CSP-Commission

Finances

Since 2004, the IZKF has been fully supported by intramural funds. The main financial contribution is given by the Faculty of Medicine. Additional contributions are received from the FAU.

Part of the expenditures of 2020 were financed from residual funds of the previous years.

Revenues	
Support of the Medical Faculty	5,497 K€
Support of the University	364 K€
Other revenues	10 k€
Total revenues 2020	**5,871 K€**

Expenditures	
Advanced projects	1,141 K€
Pilot projects	830 K€
Career development	2,183 K€
thereof junior research groups	558 K€
thereof junior projects	984 K€
thereof laboratory rotations	412 K€
thereof clinician scientist programme	5 K€
thereof MD-thesis scholarships	166 K€
thereof research training groups	58 K€
Central projects	47 K€
Administration	233 K€
Total expenditures 2020	**4,434 K€**

Revenues and expenditures 2020

Output and Evaluation

Various parameters are used to assess compliance with the mission of the IZKF in advancing clinically oriented research at the Faculty. Scientific publications and academic success of young scientists are the most obvious and straightforward ones. Additionally, the acquisition of extramural funding is an explicit objective of the IZKF. Other important parameters for the IZKF are the number of different institutions and scientists, who are involved in the IZKF, the number of interdisciplinary projects as well as the number of joint publications.

In the reporting period 86 scientific projects were actively running: 29 advanced projects, 20 junior projects, 35 pilot projects and 2 junior research groups. Another 2 advanced projects started in 2021. In addition, 7 junior projects started their work in 2020 (4) or in the beginning of 2021 (3). 4 new junior research groups will start in 2021.

29 advanced, 20 junior projects and 2 junior research groups published 40 original articles in 2020 resulting in an average of 0.8 publications per project. The cumulative impact factor (IF) was 332.643, averaging 8.316 per publication. The high quality of many of these publications is reflected in 10 publications with an IF of more than 10. Being part of the IZKF allows intensive networking and direct access to collaborations, which can be seen in 4 publications that were generated in a cooperation of multiple projects. Additional articles of finalised projects are in preparation, submitted or accepted. Publications that have already been accepted are listed in the corresponding final reports.

Intense academic activity within the IZKF advanced and junior projects is reflected in 9 master theses, 40 doctoral theses and 2 habilitations that were in progress or finalised in 2020. Four professorships to IZKF project leaders were offered. A total of 63 project leaders and 37 employed scientists (PhDs and Post-Docs) are involved in 51 scientific projects (running advanced projects, junior research groups and junior projects 2020) funded by the IZKF.

In many instances funding by the IZKF starts at an early phase of the project, thus it must be considered as a high risk funding programme. It is nevertheless reassuring that most of the projects are successful and many of them are continued after the termination of intramural funding. On the following pages the output of the IZKF-projects is given, supported by figures and results of a detailed survey of acquired third-party funding by the IZKF-projects.

In the following, the output of individual funding lines is presented.

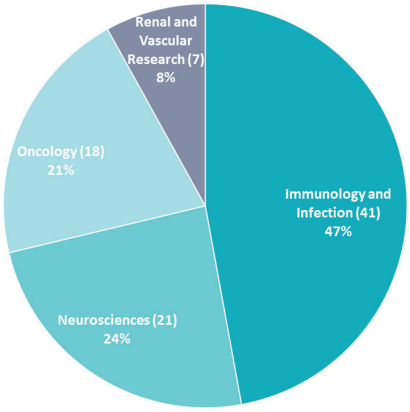
The following table shows all institutions with a running Advanced, Junior or Pilot Project in 2020 and their association to the main research areas of the Faculty. In addition, it can be seen which institution was funded with rotation positions (without assignment to a research area):

Institute	Advanced Projects	Junior Projects	Pilot Projects	Laboratory Rotation
Chair of Anatomy II			O	
Chair of Experimental Medicine I			O	
Chair of Experimental Medicine II	O		O	
Department of Anaesthesiology		N		X
Department of Dermatology	I		I	
Department of Medical Informatics, Biometry and Epidemiology		S		
Department of Medicine 1	I, O	I, O	I	X
Department of Medicine 3	I, O	I	I	X
Department of Medicine 4	O, R	R	R	X
Department of Medicine 5	O	I, O	I, O	X
Department of Nephropathology	I	M	R	
Department of Neurology			N	
Department of Neurosurgery			N	
Department of Nuclear Medicine			O	
Department of Obstetrics and Gynecology	O		O	
Department of Operative Dentistry and Periodontology				X
Department of Oral and Cranio-Maxillofacial Surgery			O	
Department of Orthodontics and Orofacial Orthopedics	N			
Department of Otorhinolaryngology - Head and Neck Surgery			O	
Department of Pediatrics and Adolescent Medicine	O	M	M	X
Department of Plastic and Hand Surgery			I, O	
Department of Psychiatry and Psychotherapy		S	I	
Department of Radiation Oncology				X
Department of Surgery	O	O		
Department of Urology			O	
Division of Immune Modulation	I		I	
Division of Molecular Neurology	N		N	
Division of Molecular Pneumology	I			
Division of Neuroradiology			M	
Division of Palliative Medicine	I		S	
Division of Stem Cell Biology	N	N	N	X
Institute of Biochemistry	I, N, O, R		N	
Institute of Cellular and Molecular Physiology	R	R	N	
Institute of Clinical and Molecular Virology	I	I	I, O	
Institute of Clinical Microbiology, Immunology and Hygiene	I	I		
Institute of Human Genetics	I, N		N	
Institute of Pathology			O	X
Institute of Radiology			I	
Institute of the History of Medicine and Medical Ethics			S	
Intitute of Neuropathology		M		

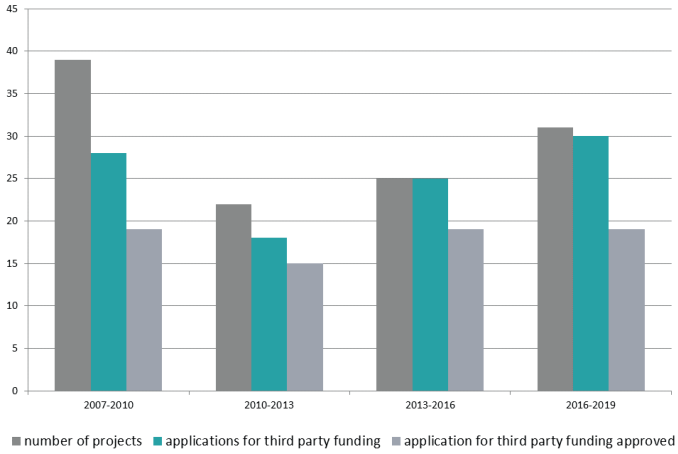
I - Infection and Immunology, N - Neurosciences, O - Oncology, R - Renal and Vascular Research, M - Medical Engineering, S - Others, X - Funding of a rotation position, without assignment to a research area

Advanced Projects

The 42 project leaders of the current funding period come from 23 different institutions. 12 (29%) of the project managers are women, 30 (71%) men. Project leaders include 19 (45%) natural scientists and 23 (55%) clinician scientists.



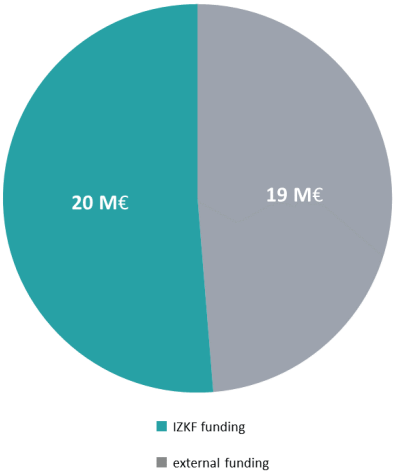
Distribution of advanced projects as per main research area between 2013 and 2020



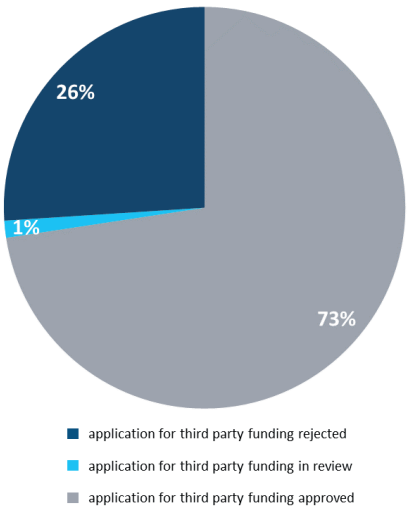
This column graph compares the number of advanced projects with the number of the submitted and approved applications for external funding in each funding period.

The projects started with the filling of the approved positions or with the first disposition. Due to the current pandemic, the projects had the possibility to start at the latest by January, 1 2021. Tandem projects have the option of filling their positions time shifted and thus do not lose any approved months of staff. Beginning with the funding period of 2010-2013, grants were awarded for a period of 30 months with an extension by 6 months, if these projects are submitted for external funding. Within the funding period of 2013-2016 all projects submitted third party funds applications and therefore received the 6 months funding extension. Of the 31 projects from the 2016-2019 funding period, 30 (97%) have applied for project extensions.

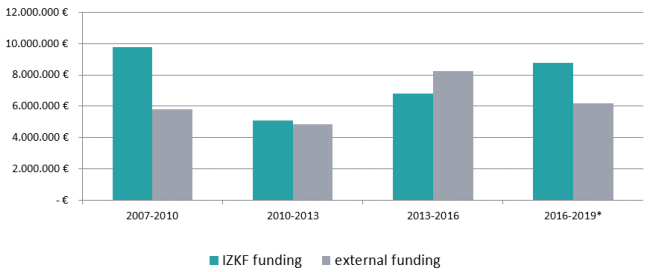
When considering the last three funding periods (2010-2019), 78 projects were funded by the IZKF of which 73 (94%) submitted third party funding applications. 53 of these projects (73%) were granted extramural funding, only 19 (26%) were not funded and 1 (1%) is still in review.



External funding received from advanced projects between 2010 and 2019



Approved applications for third-party funding of advanced projects between 2010 and 2020



External funding received from advanced projects between 2007 and 2019

Junior Research Groups

In 2020 there were two junior research groups running. One group (N1) is housed in the Nikolaus Fiebiger Center for Molecular Medicine with its attractive scientific environment and diverse activities; the other (N2) is located at the South-Campus in a new scientific building within the Optical Imaging Center Erlangen (OICE), where the group has modern laboratories and offices with excellent equipment at its disposal.

Since August 2019, Prof. Dr. Ceppi is Associate Professor in the Department of Biochemistry and Molecular Biology at the University of Southern Denmark in Odense. For the rest of the term, he will continue to run his junior research group in Erlangen.

Prof. Dr. Dulin accepted a new position as an Assistant Professor at VU Amsterdam (Netherlands), starting in January 2021, currently on a part-time basis until his junior research group in Erlangen will expire in September 2022.

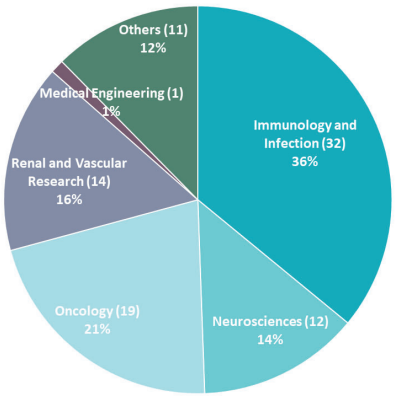
After the concept for junior research group funding had been revised, the call for the programme was announced in autumn 2020. The deadline for submitting applications was November 16, 2020. 7 applications were submitted. 5 applicants presented themselves and their projects on December 11, 2020 as part of a colloquium. As a result of the assessment, four new junior research groups have been established in the funding programme and will begin in 2021.

Junior Projects

The first call for junior projects was in 2009. Proposals are accepted every year. Overall 89 junior projects were selected for funding between 2009 and 2020. In this period, 36 (40%) physicians received funding and 53 (60%) scientists. 23 (64%) of the physicians requested a laboratory rotation, thereof 7 (30%) were women and 16 (70%) men. Over the entire funding period, men and women were almost equally supported:

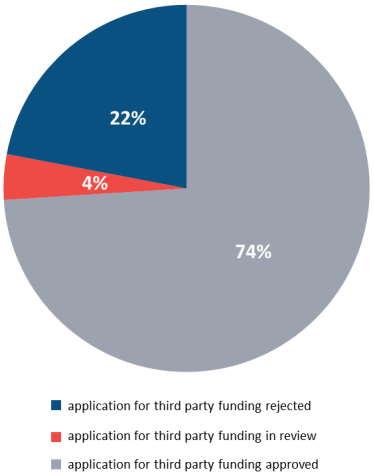
42 successful applicants were women and 47 men. The median age was 32 at the time of application, for both women and men. All main research areas of the Faculty are represented with immunology and infection (36%) and oncology (21%) being the most successful over the years. Overall candidates from 25 different institutions within the Faculty of Medicine were successful.

In 2020, 17 proposals were reviewed and 7 (41%) of them were selected for funding. The approved projects cover the main research areas immunology and infection, neurosciences and medical engineering. The successful applicants work in 5 different institutions within the Faculty of Medicine. In total, 3 (43%) are physicians and 4 (57%) are scientists; 5 (71%) of the successful applicants are men and 2 (29%) are women. The median age was 34 years.

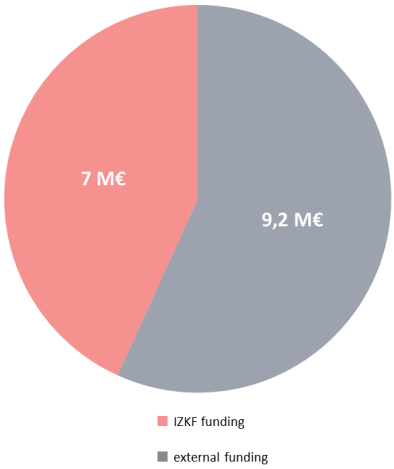


Distribution of junior projects as per main research area of the Faculty of Medicine between 2009 and 2020

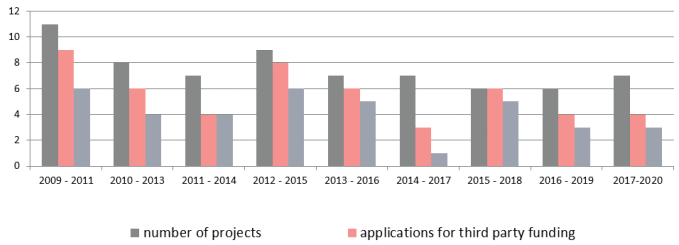
The Junior Projects also perform very well in raising third-party funding. 74% from the projects that started between 2009 and 2017 applied for third-party funding to an external funding agency. This development has been stable over the entire duration of the programme.



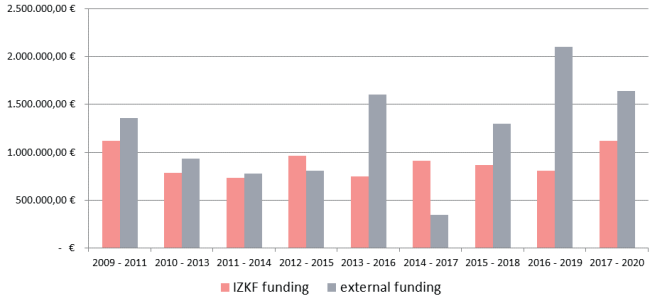
Approved applications for third-party funding of junior projects (projects initiated between 2009 and 2017)



External funding received from junior projects between 2010 and 2020



Success-rate of junior projects initiated between 2009-2017



External funding received from junior projects between 2007 and 2020

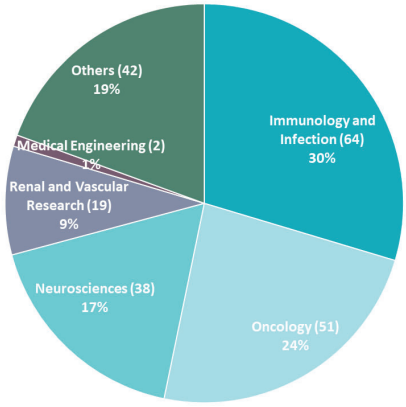
Pilot Projects (ELAN)

Pilot projects are intended to support scientists at an early stage.

In the reporting period of 2020, 22 proposals were assessed during the meetings of the ELAN-Commission, an internal reviewer was assigned to 26 projects. Of the 22 proposals evaluated in the meetings, 15 (68%) received funding. The approved projects cover nearly all the main research areas of the Faculty of Medicine: oncology 3, immunology and infection 4, neurosciences 6, medical engineering 1 and 1 without an allocation to a research area. In 2020, applicants were from 23 different institutions. In total, 11 (73%) of the successful applicants were men and 4 (27%) women. The median age was 35 for all project leaders.

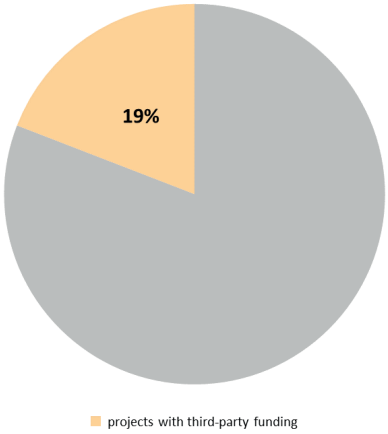
Applications for pilot projects can be submitted at any time. Since 2012 an electronic application using the ELAN-Tool is expected. The ELAN-Commission meets 5-6 times a year and selects projects for funding. The evaluation procedure includes external expertise. Between 2012 and 2020 a total of 309 proposals for pilot projects were reviewed by the ELAN-Commission. Overall, 216 (70%) projects were granted for funding. Between 2012 and 2020 in total 96 women (44%) and 120 men (56%) applied successfully for pilot projects. The median age was 34 years.

All main research areas of the Faculty are represented; with immunology and infection (30%) and oncology (24%) being the most successful over the years.

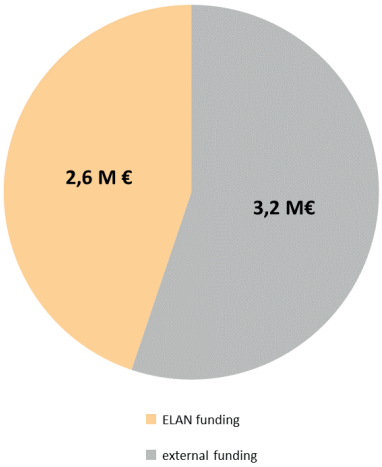


Distribution of pilot projects as per main research area between 2012 and 2020

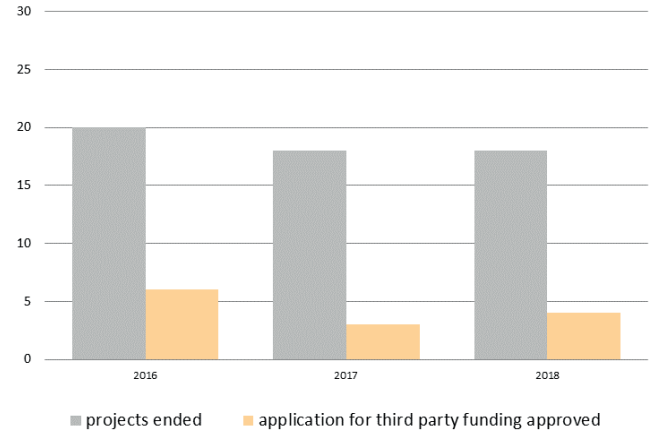
In the following, the success rate of acquiring third-party funding is shown graphically.



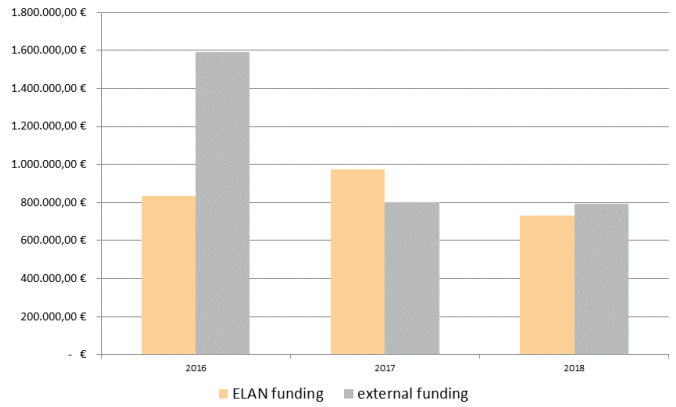
Pilot projects with third-party funding (projects completed between 2016 and 2019)



External funding received from all pilot projects completed between 2016 and 2018



Distribution of pilot projects as per main research area between 2012 and 2020



Distribution of pilot projects as per main research area between 2012 and 2020

Laboratory Rotations

In 2020, 18 physicians were funded with a rotation position. In addition to pure laboratory rotations, positions are also open to junior project leaders and participants in the Advanced Module of the Clinician Scientist Programme.

Rotations

- PD Dr. Anita Kremer, Department of Medicine 5, 10/2019-06/2020, 100%
- Dr. Eva Maier, Department of Medicine 5, 11/2020-10/2021, 50%
- Dr. Lisa Meintker, Department of Medicine 5, 07/2020-01/2021, 50%
- Dr. Stephanie Naas, Department of Medicine 4, 05/2019-03/2020, 06/2020-06/2020, 50%
- Dr. Florian Putz, Department of Radiation Oncology, 09/2019-08/2020, 50%
- Dr. Andrej Stoll, Department of Medicine 5, 10/2019-06/2020, 100%

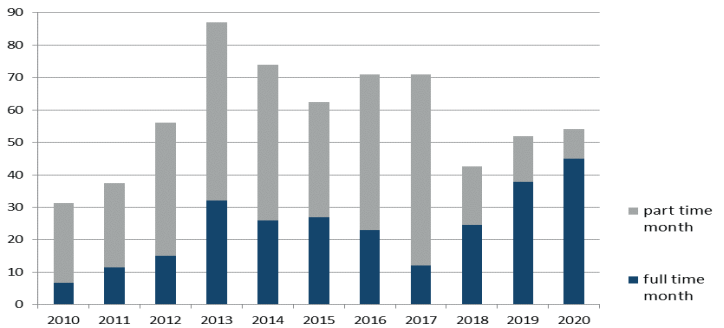
Rotations of Junior Project Leaders

- Dr. Steffen Grampp, Department of Medicine 4, 04/2019-03/2020, 07/2020-11/2020, 100%
- PD Dr. Regina Jitschin, Department of Medicine 5, 03/2020-02/2021, 50%
- Dr. Tilman Jobst-Schwan, Department of Medicine 4, 10/2018-03/2020, 08/2020-01/2021, 50%
- Dr. Adrian Regensburger, Department of Pediatrics and Adolescent Medicine, 01/2021-05/2021, 50%
- Prof. Dr. Stefan Uderhardt, Department of Medicine 3, 07/2020-11/2020, 100%

Rotations of Clinician Scientists

- Dr. Christina Bergmann, Department of Medicine 3, 01/2021-12/2021, 100%
- Dr. Esther Eberhardt, Department of Anaesthesiology, 07/2018-03/2020, 06/2020-08/2020, 50%
- Dr. Markus Eckstein, Institute of Pathology, 07/2020-06/2022, 50%
- PD Dr. Andreas Kremer, Department of Medicine 1, 01/2019-12/2020, 50%
- Dr. Markus Schüler, Department of Medicine 4, 01/2019-04/2020 50%
- Dr. Martin Regensburger, Division of Stem Cell Biology, 08/2020-12/2021, 50%

Laboratory rotations 2020 with name, institute, funding period und scope of position



The table shows the claimed months related to full time for each year. Due to the former duration of 12-24 months, the rotations usually last over a period of 2-3 calendar years.

Clinician Scientist Programme

During the funding period, altogether 25 physicians took part in the CSP. With the same deadline as for the junior projects, a rotation position within in the CSP (Advanced Module) can be applied for on an annual basis. The deadline for the submission of applications was March 16, 2020. Five applications were submitted. The interviews with the applicants took place on May 14. Four of the applicants were accepted for the advanced module and received funding for laboratory rotations. One applicant was admitted to the basic module.

The Clinician Scientist Programme RECORD has been funded by the Else Kröner-Fresenius Foundation since January 1, 2020 and is associated to the Clinician Scientist Programme.

The following physicians participated in the Clinician Scientist Programme in 2020:

Basic Module

- Dr. Eva Maier, Department of Operative Dentistry and Periodontology
- Dr. Harriet Morf, Department of Medicine 3
- Dr. Stephanie Naas, Department of Medicine 4
- Dr. Maria Gabriella Raimondo, Department of Medicine 3
- Dr. Christina Regensburger, Department of Pediatrics and Adolescent Medicine (RECORD)
- Dr. Andrej Stoll, Department of Medicine 5
- Dr. Patrick Süß, Division of Molecular Neurology
- Dr. Raluca Ursu, Department of Medicine 4 (RECORD)
- Dr. Alexander Zorob, Department of Medicine 4 (RECORD)

Advanced Module

- Dr. Christina Bergmann, Department of Medicine 3
- Dr. Markus Eckstein, Institute of Pathology
- Dr. Esther Eberhardt, Department of Anaesthesiology
- Dr. Ramona Erber, Institute of Pathology
- Dr. Ingo Ganzleben, Department of Medicine 1
- Dr. Steffen Grampp, Department of Medicine 4
- Dr. Tilman Jobst-Schwan, Department of Medicine 4
- Dr. Ferdinand Knieling, Department of Pediatrics and Adolescent Medicine
- PD Dr. Andreas E. Kremer, Department of Medicine 1
- Dr. Franz Marxreiter, Division of Molecular Neurology
- Dr. Adrian Regensburger, Department of Pediatrics and Adolescent Medicine
- Dr. Martin Regensburger, Department of Stem Cell Biology
- Dr. Markus Schüler, Department of Medicine 4
- Dr. David Simon, Department of Medicine 3
- Prof. Dr. Stefan Uderhardt, Department of Medicine 3
- Dr. Sebastian Zundler, Department of Medicine 1

Participants CSP 2020

Life@FAU as structured training programme for doctoral fellows

In 2020, the number of doctoral fellows participating in Life@FAU increased significantly compared to the previous year. In 2019, 273 doctoral fellows took part, in the reporting year there were already 353. The doctoral fellows are distributed among the participating networks as follows:

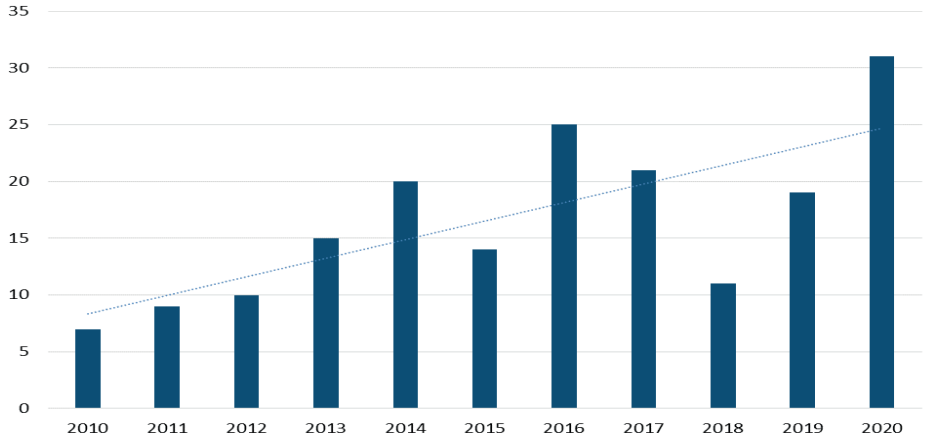
Programme/ Research Training Group	Registered participants	thereof Dr. rer. nat. and others	thereof Dr. med. / dent.
SFB 1181	35	25	10
SFB 1350	2	2	0
GRK 2162	32	26	6
GRK 1962	12	12	0
GRK 2504	14	14	0
GRK 1660	21	13	8
TRR 130	11	11	0
TRR 221	9	8	1
TRR 241	14	9	5
TRR 225	9	9	0
IZKF	28	28	0
IZKF associated	64	58	6
IZKF MD	80	0	80
no connection to RTG	22	21	1
total	**353**	**236**	**117**

Research Training Groups participating in Life@FAU, indicating the number of participants as of 31st December 2020

MD-Thesis Scholarships

In 2020, a total of 43 medical doctoral students from 19 institutions were funded. Due to the fact that some scholarships granted in 2019 ended in 2020, the number of funded doctoral students is higher than the number of scholarships available. Overall, 33 applications for the MD-Thesis scholarship programme have been received in 2020. The Junior Scientists Committee approved 31 applications (94%), 17 (55%) of the successful applicants were females and 14 (45%) males. The median age was 23 years. Three scholarships were canceled or not completed.

Since its inception in 2007, the IZKF supported a total of 224 medical students with a scholarship. Medical students often initiate experimental work on their doctoral thesis during their studies. They will finish the thesis frequently several years after they graduate. By the end of 2020, 73 (33%) students had already completed their doctoral thesis. Interestingly, 26 students (36%) obtained the highest degree possible, summa cum laude. This compares very favourably to the average 5% of all MD-Theses presented and is testimony to the excellent quality of MD-Theses performed within this programme.



Participants CSP 31/12/2020

The following overview shows all participants of the MD-Thesis scholarship programme with their name, institution and funding period, who had an ongoing scholarship in 2020.

Department of Medicine 1

- Appel, Majken (10/2020 – 07/2021)
- Knittel, Selina (12/2020 – 07/2021)
- Schmidt, Nina-Maria (02/2020 – 09/2020)

Department of Medicine 3

- Bierling, Theresa (12/2020 – 07/2021)
- Gimpel, Anne (10/2020 – 05/2021)
- Koch, Julia (07/2019 – 02/2020)

Department of Medicine 4

- Popanda, Carmen (05/2020 – 12/2020)
- Rehrl, Sonja (05/2020 – 12/2020)
- Rhode, Louis (12/2020 – 07/2021)
- Wopperer, Florian (12/2020 – 07/2021)

Institute of Cellular and Molecular Physiology

- Geiges, Linda (03/2020 – 10/2020)
- Schmidt, Maximilian (04/2020 – 11/2020)
- Sommer, Sophie (02/2020 – 09/2020)

Institute of Pathology

- Kullmann, Friederike (02/2020 – 09/2020)
- Pastorino, Gil Alessio (03/2020 – 10/2020)
- Prechtel, Philipp (08/2020 – 03/2021)

Institute of Biochemistry

- Herr, Felix (03/2020 – 10/2020)
- Lichtblau, Adrian (06/2019 – 01/2020)
- Stüfchen, Isabel (03/2020 – 10/2020)
- Weigel, Johannes (09/2020 – 04/2021)

Institute of Microbiology – Clinical Microbiology, Immunology and Hygiene

- Bailer, Moritz (03/2020 – 10/2020)
- Blaha, Niklas (08/2020 – 03/2021)
- Grundler, Magdalena (12/2020 – 07/2021)
- John, Dominik (09/2020 – 04/2021)
- Röger, Ole (09/2020 – 04/2021)
- Sommer, Julius (02/2020 – 09/2020)
- Zankl, Jeremias (03/2020 – 10/2020)

Others

- Albrecht, Leonie, **Department of Dermatology** (12/2020 – 07/2021)
- Auth, Janina, **Institute of Clinical and Molecular Virology** (12/2019 – 07/2020)
- Balaj, Viola, **Institute of Neuropathology** (03/2020 – 10/2020)
- Daume, Luisa, **Department of Nephropathology** (12/2020 – 07/2021)
- Fröba, Maria Carolin, **Institute of Clinical and Molecular Virology** (09/2020 – 04/2021)
- George, Rebekka, **Department of Medicine 5** (10/2019 – 05/2020)
- Gregoric, Gaspar, **Institute of Radiology** (09/2019 – 04/2020)
- Höke, Kathleen, **Department of Psychiatry and Psychotherapy** (12/2020 – 07/2021)
- Holtzhausen, Christian, **Institute of Neuropathology** (12/2020 – 07/2021)
- Kutz, Chiara-Sophie, **Department of Plastic and Hand Surgery** (10/2020 – 05/2021)
- Meier, Lukas, **Chair of Clinical Pharmacology and Clinical Toxicology** (05/2020 – 12/2020)
- Noack, Rosa, **Department of Medicine 5** (12/2019 – 07/2020)
- Seebauer, Lukas, **Division of Molecular Neurology** (03/2020 – 10/2020)
- Stehr, Antonia, **Department of Surgery** (09/2020 – 04/2021)
- Stürzenberger, Sophia, **Institute of Physiology and Pathophysiology** (12/2020 – 07/2021)
- Thoenissen, Tim, **Department of Surgery** (05/2020 – 12/2020)

Training courses in the IZKF

The IZKF Research Training Group again offered numerous courses in 2020. The effects of the pandemic can also be seen here. Almost all courses were offered as a virtual workshop.

Course	Course days	Offers 2020	Lecturer
Scientific Writing 1 An introduction to scientific writing	2,5	2	Dr. Deborah Bennett Bennett English Training for Academics
Scientific Writing 2 Writing research articles	2,5	1	Dr. Deborah Bennett Bennett English Training for Academics
Scientific Writing 3 Writing a PhD Thesis: Streamlining the writing process	2,5	2	Dr. Deborah Bennett Bennett English Training for Academics
An introduction to presentation skills	2,5	2	Dr. Deborah Bennett Bennett English Training for Academics
Application related statistics	1	1	Dr. Matthias Englbrecht Healthcare Data Scientist & Career Coach
Data analysis for medical students (SPSS)	2	1	Dr. Heiko Gaßner Department of Molecular Neurology
Basic Scientific Imaging	2,5	2	Dr. Ralph Palmisano OICE
Good Scientific Practice	2	3	Dr. Julia Verse (external)/ Dr. Anne Hamker (external)
Entrepreneurship & Intellectual Property Rights	1	1	Prof. Dr. Christian Pilarsky Department of Surgery + several internal and external speakers

Soft skill- and statistic courses given in 2020

The retreat planned for April at the Fraunhofer Research Campus in Waischenfeld unfortunately had to be canceled in 2020. A retreat/ postgraduate workshop took place on October 5 and 6 to enable networking and the fulfillment of the training modules. The doctoral students presented their projects in three parallel sessions.

The event was completed by three guest speakers:
Prof. Dr. Uderhardt (Department of Medicine 3, Erlangen), Prof. Dr. Greten (Institute of Tumor Biology and Experimental Therapy, Frankfurt) and Prof. Dr. Gilsbach (Institute of Cardiovascular Physiology, Frankfurt) presented their research in interesting lectures.

IZKF Retreat 2019 at Fraunhofer Research Campus in Waischenfeld

Organisation of the IZKF Research Training Group

All members regularly participate in the Jour Fixe (JF) once a month. Due to the broad thematic range of the doctoral theses at the IZKF, several Jour Fixes are held, which are at the moment

- Immunology, infection, kidney and vascular research (Ink)
- Neurology (Neuro)
- Oncology (Onco) and
- Digital information technology (DigIT)

Each JF is supervised by one to two spokespersons from the doctoral students who are elected by the participants for a period of 2-3 years. Usually, a new election takes place at the end of the doctoral thesis of the respective spokesperson. In addition to the spokespersons, each established JF has an appointed professor as scientific head.

Jour Fixe Ink

Scientific Head
Prof. Dr. Christoph Becker, Department of Medicine 1

Spokespersons
Myriam Jeninga, Institute of Microbiology

Katrin Peckert, Department of Immune Modulation

At the Jour Fixe INK, doctoral fellows working in the areas of immunology, infection, renal and vascular research will present the progress and results of their respective doctoral projects. The seminar is held in English and takes place once a month. It promotes both the transfer of knowledge between doctoral fellows in the different fields and the presentation and discussion skills in front of an audience.

Jour Fixe Neuro

Scientific Head
Prof. Dr. Dieter Chichung Lie, Institute of Biochemistry

Spokespersons
Judith Stemick, Department of Molecular Neurology

Mona Seifert, IZKF Junior Research Group 2

The neuroscientific doctoral fellows of the FAU Erlangen-Nuremberg meet monthly for the Jour Fixe „Neuroscience“, at which the doctoral fellows discuss new methods and technologies in addition to their respective doctoral projects. The programme of the Jour Fixe is solely organised by the doctoral students.

Jour Fixe Onco

Scientific Head
Prof. Dr. Anja Bosserhoff, Institute of Biochemistry

Spokespersons
Tatjana Seitz, Institute of Biochemistry

Kerstin Hübner, Institute of Pathology

In the Oncology Jour Fixe, doctoral fellows focusing on research in different fields of oncology discuss ongoing work as well as new approaches. Every participant presents her/his own project once a year in the form of a progress report. The topics of this seminar range from basic research in various cancer entities to clinical studies and targeted therapies.

Jour Fixe DigIT

Scientific Head
Prof. Dr. Olaf Gefeller, Institute of Medical Informatics, Biometry and Epidemiology

Spokespersons
Colin Griesbach, Institute of Medical Informatics, Biometry and Epidemiology

Anja Rappl, Institute of Medical Informatics, Biometry and Epidemiology

The JF DigIT is aimed at doctoral students with a data-analytical methodical approach. All participating institutions assign their self-conception to life sciences on the basis of their research orientation, even if in some doctoral projects there are clear references to other fields of science such as mathematics/ statistics, computer science, physics and electrical engineering.

Scientific Reports

Role of Gasdermin C in Gut Barrier Defence

Prof. Dr. Becker

A76 02/2020 - 07/2022

Prof. Dr. Christoph Becker, Department of Medicine 1

e-mail: christoph.becker@uk-erlangen.de

Abstract

We have discovered Gasdermin C as a gene induced by type 2 immunity in the gut. Little is known about the regulation and function of Gasdermin C. We hypothesize that GSDM C is induced and released in IEC by proinflammatory cytokines to promote host defence. Using newly-generated Gasdermin C knockout mice to determine the impact of GSDMC on host defense and antibodies for its detection, we aim to elucidate the expression, regulation and function of Gasdermin C in the gut.

Publications

no project-specific publications so far

Important results

- Successful establishment and validation of a mouse line deficient for Gasdermin C
- Generation and validation of specific antibodies for the immunohistochemical characterization of Gasdermin C
- In depth characterization of STAT-6 dependent Gasdermin C expression in the intestinal epithelium

Special methods

Organoid technology: human and murine intestinal organoids, 2D and 3D, organoid microinjection, live staining, imaging, etc.

HIF expression in B cells regulates bone loss

Prof. Dr. Bozec

A77 12/2020 - 06/2023

Prof. Dr. Aline Bozec, Department of Medicine 3

e-mail: aline.bozec@uk-erlangen.de

recently started

Abstract

While the influence of T cells on bone homeostasis has been well characterized, less is known about the role of B cells. Despite that B cells are able to produce RANKL, the major cytokine regulating osteoclast differentiation, its regulation of expression remains unclear. B cells reside in the low oxygen concentrations bone niche, and adapt to the environment through the expression of HIFs. I therefore hypothesize that HIF expression in B cells could influence the development of osteoporosis.

Special methods

- Ovariectomy induced bone loss in mice is assessed by micro-CT.
- Metabolic parameters are determined by Seahorse XF technology in in vitro wildtype, and mutant pro- and pre-B cells cultured under normoxic or hypoxic conditions
- Molecular mechanisms are determined by mRNA sequencing of isolated B cells from ovariectomized mice

Smurf2-IFN axis in IBD and mucosal healing


Dr. Dr. Chiriac


Prof. Dr. Neurath

A78 01/2021 - 06/2023

Dr. Dr. Mircea Chiriac, Department of Medicine 1
e-mail: mircea.chiriac@uk-erlangen.de

Prof. Dr. Markus Neurath, Department of Medicine 1
e-mail: markus.neurath@uk-erlangen.de

recently started

Abstract

To understand the role played by ubiquitination of type I interferon in the pathogenesis of inflammatory bowel disease we intend to induce DSS colitis in two newly generated conditional mouse strains i.e. Stat2 and Smurf2 in experimental colitis models. CRISPR/Cas, three dimensional organoids coupled with Nanostring and RNA-Seq/GO analysis will be used to understand molecular mechanisms underlying DSS findings. Data will be validated using samples from IBD patients and controls.

Special methods

1. Experimental colitis models: DSS-, oxazolone- or TNBS -induced colitis is assessed by mini-endoscopy and IVIS;
2. Wound healing: wound healing assays in vitro (Ibidi, xCelligence) and in vivo (forceps-biopsy wounds in mice);
3. Organoids: small and large intestine mouse and human organoids used to interrogate the molecular basis of our findings.

TR4 in tissue fibrosis


Prof. Dr. Distler

A79 01/2021 - 06/2023

Prof. Dr. Jörg Distler, Department of Medicine 3
e-mail: joerg.distler@uk-erlangen.de

recently started

Abstract

Fibrotic diseases are characterized by excessive accumulation of extracellular matrix. Activated fibroblasts are key effector cells in fibrotic diseases. The molecular mechanisms underlying their uncontrolled activation remain largely unknown. TR4 (testicular receptor 4, NR2C2) is member of the superfamily of nuclear receptors. TR4 is an orphan nuclear receptor that is active in the absence of an endogenous ligand. Deregulation of TR4 has been linked to the pathogenesis of cancer and metabolic disturbances. However, its role in tissue remodeling is currently unknown.

Special methods

- Bulk RNA sequencing and ChIP sequencing with subsequent integrated biostatistical evaluation (in cooperation with Meik Kunz; Medical bioinformatics)
- Different mouse models of fibrotic tissue remodeling
- Tools to analyze a potential epigenetic regulation of TR4 including DNA methylation, histone acetylation and H3K27 histone methylation

Inflammasomes in primary dendritic cells

Prof. Dr. Dudziak

A80 01/2020 - 06/2022

Prof. Dr. Diana Dudziak, Department of Dermatology

e-mail: diana.dudziak@uk-erlangen.de

Abstract

Inflammasomes play a pivotal role in the immune response. Our preliminary data suggest that select inflammasome ligands activate the inflammasome in human primary DCs without inducing cell death. We hypothesize that dysregulation of inflammasome activation in DCs might lead to a prolonged survival of DCs and consequently to continuous T cell activation. Understanding the role of DCs in inflammasome activation will help to find new therapies for the treatment of acute and inflammatory diseases.

Important results

To understand the role of inflammasome activation in primary DCs in human blood we analyzed the expression of inflammasome components in steady state and inflammation. We found a DC subset specific expression pattern of inflammasome subunits with an increased - but DC subset fixed - expression upon stimulation with TLR ligands.

Special methods

Our laboratory has established cell isolation and culturing methods for analysis of DC subpopulations from peripheral blood but also human lymphoid and non-lymphoid tissues. We use RNA seq and Nanostring analyses to identify transcriptional changes in primary cell populations including DCs, monocytes, macrophages and T cells.

Publications

Lühr JJ, Alex N, Amon L, Kräter M, Kubánková M, Sezgin E, Lehmann CHK, Heger L, Heidkamp GF, Smith AS, Zaburdaev V, Böckmann RA, Levental I, Dustin ML, Eggeling C, Guck J, Dudziak D. (2020) Maturation of Monocyte-Derived DCs Leads to Increased Cellular Stiffness, Higher Membrane Fluidity, and Changed Lipid Composition. Front Immunol. 11:590121.

Mühlberger M, Unterweger H, Band J, Lehmann C, Heger L, Dudziak D, Alexiou C, Lee G, Janko C. (2020) Loading of Primary Human T Lymphocytes with Citrate-Coated Superparamagnetic Iron Oxide Nanoparticles Does Not Impair Their Activation after Polyclonal Stimulation. Cells. 9(2):342.

Receptor and neuropathogenicity of Bornavirus

Prof. Dr. Ensser

A81 01/2020 - 12/2022

Prof. Dr. Armin Ensser, Institute of Clinical and Molecular Virology

e-mail: armin.ensser@fau.de

*The project was interrupted from July-Dec 2020 due to staff diagnostic obligations during the ongoing SARS-CoV2 pandemic.

Abstract

Borna disease virus (BoDV-1) was detected by us and others as the cause of human fatal encephalitis. Previous studies addressed the immune response and viral replication, but the host cell receptor of BoDV-1 remains unknown. We use an unique BoDV-1 patient isolate to search for this receptor, and we will address the possible direct, non-immune related neuropathogenic potential of BoDV-1, as well as an viral (chemo)therapeutic options, in IPSC derived human neuronal 3D organoid cultures.

Important results

We cloned a fusion protein of extracellular BoDV-1 G to immunoglobulin Fc (Bo-G-Fc); we further made domain swap constructs of the extracellular domains of BoDV-1 G proteins fused to the Vesicular Stomatitis Virus (VSV) glycoprotein stem, tested their expression of fusion proteins and generated of BODV1-G/VSV-G pseudotyped lentiviral particles.

Special methods

Lentiviral pseudotyping and p24 assays; viral infection under BSL2 and BSL3 conditions; wide-field fluorescence microscopy in BSL3.

Publications

no project-specific publications so far

Role of RANTES in the resolution of asthma

Prof. Dr. Neurath-Finotto

A82 02/2020 - 07/2022

Prof. Dr. Susetta Neurath-Finotto, Department of Molecular Pneumology

e-mail: susetta.neurath-finotto@uk-erlangen.de

Abstract

In this project we aim at investigating the role of RANTES and its receptors, CCR1, CCR3 and CCR5, in murine models and human allergic asthma by using rRANTES and RANTES, CCR3 and CCR5 deficient mice. Here we found that RANTES inhibited effector Th2 cells and inflammatory Eosinophils and induced immunosuppressive T cells and rEosinophils suggesting that RANTES is involved in the resolution of allergic asthma. In our human studies Predicta we analyse RANTES in healthy controls and asthmatic subjects.

Publications

no project-specific publications so far

Important results

- We observed reduced RANTES levels in PBMCs from asthmatic children with RV infection in their upper airways.
- Mice treated with rRantes resolved allergic asthma.
- CCR3 KO mice show a defect in inflammatory eosinophils (iEos) which contribute to asthma and induction of asthma resolving resident Eosinophils (rEos).

Special methods

no project-specific special methods so far

The role of SAMHD1 in CMV/ HIV coinfections

Prof. Dr. Gramberg

A83 01/2020 - 06/2022

Prof. Dr. Thomas Gramberg, Institute of Clinical and Molecular Virology

e-mail: thomas.gramberg@fau.de

Abstract

HIV patients coinfected with CMV show increased morbidity and mortality, even on therapy. Despite high coinfection rates, surprisingly little is known about molecular interactions of CMV and HIV. We found that CMV blocks the HIV restriction factor SAMHD1 to facilitate its own replication. This finding finally provides a handle to explain how CMV enhances HIV replication in the host. Thus, we will address the working hypothesis that CMV infection boosts HIV replication by inactivating the SAMHD1.

Publications

no project-specific publications so far

Important results

- enhanced HIV infectivity in primary macrophages and myeloid cells lines upon coinfection with CMV
- the increase in HIV infectivity depends on the presence of SAMHD1
- enhanced HIV infectivity correlates with CMV-mediated SAMHD1 phosphorylation

Special methods

- HIV and CMV reporter virus infection of monocyte-derived macrophages and various cell lines
- Kinase activity assays
- Cytokine release assays

Tissue-resident memory T cells in GvHD


Prof. Dr. Hildner


Dr. Zundler


Prof. Dr. Büttner-Herold

A84 05/2020 - 11/2022

Prof. Dr. Kai Hildner, Department of Medicine 1
e-mail: kai.hildner@uk-erlangen.de

Dr. Sebastian Zundler, Department of Medicine 1
e-mail: sebastian.zundler@uk-erlangen.de

Prof. Dr. Maike Büttner-Herold, Department of Nephropathology
e-mail: maike.buettner-herold@uk-erlangen.de

Abstract

Graft-versus-Host-Disease (GvHD) is a serious complication after allogenic hematopoietic stem cell transplantation caused by donor T cells recognizing the host tissue as foreign. To investigate the role of so-called tissue-resident memory T cells (Trm) in GvHD, we are employing both murine studies, as well as immunohistochemical stainings of human biopsies. Currently, we are also focusing on investigating allogenic responses in vitro.

Publications

no project-specific publications so far

Important results

Employing an in vitro intestinal epithelial cell (organoids) / intraepithelial lymphocytes (IEL) co-culture system we established a method for quantification of cell death within organoids. Here, we detected increased cell death in the presence of allogenic compared to the syngeneic IELs, which was accompanied by enhanced secretion of IFNγ.

Special methods

1. Quantification of intestinal epithelial cell death within organoids by staining and measurement in a microplate reader
2. In vitro co-culture of intestinal organoids with IELs suitable to discriminate allogenic and syngeneic IEL activation and function
3. Serial immunohistochemical stainings of human tissue for Trm cell markers

The pathophysiology of SAPHO syndrome


Prof. Dr. Hüffmeier

A85 06/2020 - 11/2022

Prof. Dr. Ulrike Hüffmeier, Institute of Human Genetics
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Abstract

Analysis of *PLXNA1*'s coding sequence in further SAPHO syndrome patients revealed one intronic variant not predicted to affect splicing and a further missense variant, predicted to be pathogenic. Mutagenesis of a vector comprising the cDNA of *PLXNA1* was successful for four missense variants. An analysis of coding variants in *MPO*, a gene identified to be causal in another pustular psoriasis form, did not reveal association with SAPHO syndrome (Haskamp et al., J Invest Dermatol accepted 2021).

Publications

no project-specific publications so far

Important results

- One further SAPHO syndrome patient identified with a 4th *PLXNA1* missense variant predicted to be pathogenic.
- Successful mutagenesis of 4 missense variants in a vector and transfection of HEK293 cells.
- Genotyping of SAPHO syndrome patients for rare coding variants in *MPO*, no evidence for association (Haskamp et al., J Invest Dermatol accepted).

Special methods

- Genotyping of genetic variants in larger patients groups
- Analysis of whole exome sequencing in single patients/ families

Characterization of synovial macrophage subsets

Prof. Dr. Krönke

A86 06/2020 - 12/2022

Prof. Dr. Gerhard Krönke, Department of Medicine 3

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Abstract

Our previous data identified several subpopulations of tissue-resident macrophages within the synovial tissue surrounding the joints. In the ongoing project, we are currently dissecting their role during homeostasis and arthritis. Using data derived from single cell RNA and ATAC sequencing we plan to identify central signaling pathways and transcriptional regulators that determine their differentiation and function.

Publications

no project-specific publications so far

Important results

Our current data has identified IL-4 as central regulator of the differentiation of several synovial macrophage subpopulations. We are currently studying the effects exerted by this cytokine in more details.

Special methods

- scRNAsequencing
- preclinical arthritis models
- light-sheet microscopy

DC subsets and natural antibodies in leishmaniasis

Dr. Lehmann

PD Dr. Schleicher

A87 07/2020 - 05/2023

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PD Dr. Ulrike Schleicher, Institute of Microbiology

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Abstract

The course of cutaneous leishmaniasis ranges from self-healing skin lesions to chronic ulcers. The clinical phenotype is determined by the Leishmania species and the elicited T and NK cell responses that are both instructed by dendritic cells (DCs). This project aims to clarify whether differences in the targeting and functional properties of DC subsets and natural antibodies are crucially involved in the outcome of self-healing L. major and chronic non-healing L. mexicana infection in mice.

Publications

no project-specific publications so far

Important results

Multicolor flow cytometry analysis for different DC subsets and other immune cell populations in the ear skin and draining lymph node of naïve and Leishmania-infected mice was established. A specific DC subpopulation and several other myeloid cell types could be identified as host cells of L. major and L. mexicana in the skin within the first three days upon infection.

Special methods

Fluorescently labeled Leishmania were used for infection. Cellular composition as well as infected cell types in the skin and draining lymph nodes at various time points after infection were analyzed with help of multicolor flow cytometry.

Cyclin interaction with a CDK-like viral kinase


Prof. Dr. Marschall


Prof. Dr. Sticht

A88 02/2020 - 01/2023

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Abstract

Cytomegalovirus replication is characterized by viral CDK-cyclin interaction. The CDK-like viral kinase pUL97 interacts with human cyclins. CycB1 is phosphorylated upon the interaction, dependent on pUL97 activity, whereas cycT1/H interaction stimulates pUL97 activity and substrate phosphorylation. Regions for cyclin interaction and antiviral drug resistance show overlaps in pUL97, so that this correlation is elucidated in terms of viral fitness for the development of a novel antiviral strategy.

Important results

1. Verification of cyclin B1 interaction patterns of mutant pUL97 kinases (drug-resistant HCMVs)
2. Demonstration of functional relevance of pUL97-cyclin T1 interaction (recombinant HCMVs carrying deletions in cyclin T1 binding site)
3. Computational assessment of drug resistance mutations in clinical HCMV ORF-UL97 (impact on pUL97-cyclin binding)

Special methods

1. Whole genome sequencing (Agilent SureSelect XT Community Design CMV) of clinical isolates of HCMV
2. BACmid-based genetic engineering of recombinant HCMVs
3. Structural bioinformatics (modeling, molecular dynamics)

Publications

Hamilton, S.T., Marschall, M. & Rawlinson, W.D. (2020). Investigational antiviral therapy models for the prevention and treatment of congenital cytomegalovirus infection during pregnancy. Antimicrob. Agents Chemother. AAC.01627-20, doi 10.1128/AAC.01627-20.

Schütz, M., Thomas, M., Wangen, C., Wagner, S., Rauschert, L., Errerd, T., Kießling, M., Sticht, H., Milbradt, J. & Marschall, M. (2020). The peptidyl-prolyl cis/trans isomerase Pin1 interacts with three early regulatory proteins of human cytomegalovirus. Virus Res. 285: 198023, doi: 10.1016/j.virusres.2020.198023.

Couté, Y., Kraut, A., Zimmermann, C., Büscher, N., Hesse, A.M., Bruley, C., De Andrea, M., Wangen, C., Hahn, F., Marschall, M. & Plachter, B. (2020). Mass spectrometry-based characterization of the virion proteome, phosphoproteome, and associated kinase activity of human cytomegalovirus. Microorganisms 8: 820, doi: 10.3390/microorganisms8060820

CD83 regulates homeostasis and inflammation


Prof. Dr. Steinkasserer

A89 07/2020 - 12/2022

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Abstract

Inflammation within the CNS can directly affect neuronal structures. Thus, molecules controlling inflammatory responses are of upmost importance. The immune-regulatory CD83 molecule is highly expressed by microglia and tissue-resident macrophages and thus represents a crucial factor for microglial activation and the neuro-immune cross-talk. Since its regulation and function in these cells has not been elucidated, we will investigate this during immune homeostasis and neuro-inflammation.

Publications

no project-specific publications so far

Important results

Using immunohistochemistry, we analyzed the different microglial subpopulations throughout the CNS regarding CD83 expression in situ. We detected significantly increased Cd83 expression signals in caudal regions of the CNS, i.e. in microglia originating from the cerebellum, brain stem and spinal cord as compared to cortex and hippocampus.

Special methods

We established an IHC staining protocol to analyze microglia subpopulations throughout the CNS. A tamoxifen-inducible CX3CR1-CreERT2 system was established to analyze the influence of a microglia-specific CD83 KO during neuro-inflammation (EAE). We used flow cytometry to analyze the phenotype of microglia and infiltrating monocytes within the CNS.

The fate of lung-resident memory T-cells

Prof. Dr. Tenbusch

A90 01/2020 - 12/2022

Prof. Dr. Matthias Tenbusch, Institute of Clinical and Molecular Virology

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*The project was interrupted from June-Nov 2020 due to staff diagnostic obligations during the ongoing SARS-CoV2 pandemic.

Abstract

Tissue-resident memory T-cells (T_{RM}) in the lung play an important role for the control of viral respiratory tract infections. In this project, we will address the fate of antigen-specific T_{RM} induced by a natural influenza infection or a mucosal adenoviral vector immunization. The impact of secondary events, like unrelated viral or bacterial infections, on T_{RM} longevity and their protective capacity will be analyzed in phenotypic, functional and histological analyses.

Publications

no project-specific publications so far

Important results

In a longitudinal comparison, T_{RM} induced by natural infection declined more rapidly than T_{RM} induced adenoviral vector immunization. The long-lived T_{RM} population is characterized by a strong expression of CD103. Further, our newly established in situ pentamer staining suggest differential organization of the T_{RM} population within the lung tissue.

Special methods

- Viral respiratory infection models in mice (Influenza, RSV)
- characterization of virus-specific lung T_{RM} by flow cytometry
- In situ pentamer staining in lung tissue

Interfering with HTLV-1 persistence

Dr. Thoma-Kreß

A91 03/2020 - 09/2022

Dr. Andrea Thoma-Kreß, Institute of Clinical and Molecular Virology

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Abstract

The highly oncogenic retrovirus Human T-cell leukemia virus type 1 (HTLV-1) causes incurable neoplastic or inflammatory diseases. The viral accessory protein p8, which is proteolytically cleaved from the pre-cursor p12 and transported to target cells prior to infection, is important for establishing persistent infections in vivo. Here, we aim to identify the protease cleaving p12 into p8, to inhibit this protease, and to assess the impact of blocking of p12/p8 processing on viral persistence.

Important results

- Generation of several stable cell lines expressing p8 and its precursor p12 by retroviral transducion
- Establishment of a new staining protocol to detect p8, which localizes in lipid rafts, by flow cytometry
- Identification of host factors and proteases that interact with p12, but not with p8 by mass spectrometry

Special methods

- Genome Editing (CRISPR/Cas9, shRNA) and retroviral transduction
- Transfection of primary cells (4D-Nucleofector ™)
- Experimental work in biosafety level 3 laboratories

Publications

Donhauser N, Socher E, Millen S, Heym S, Sticht H, Thoma-Kress AK (2020) Transfer of HTLV-1 p8 and Gag to target T-cells depends on VASP, a novel interaction partner of p8. PLoS Pathogens, 16(9):e1008879. doi: 10.1371/journal.ppat.1008879.

FRCs and immune tolerance induction

Prof. Dr. Zaiss

A92 09/2020 - 02/2023

Prof. Dr. Mario Zaiss, Department of Medicine 3
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recently started

Abstract

As lymphatics in the inflamed joint in rheumatoid Arthritis drain specifically the popliteal lymph node (pLN) where the adaptive immune response is initiated, we investigated a population of stromal cells in the pLN, namely the fibroblastic reticular cells (FRC). Our preliminary data show a significant immunomodulatory potential of pLN FRCs in inflammatory arthritis mouse models. Therefore, we hypothesize that specifically pLN stromal FRCs play a so far neglected role in the early onset of RA.

Special methods

- pre-clinical arthitis models
- Bulk mRNA isolated FRCs
- single cell RNA sequencing of FRC depleted lymph nodes
- light-sheet microscopy
- Metabolic parameters are determined by Seahorse XF technology

Axin at microtubuli

Prof. Dr. Behrens

Dr. Bernkopf

D30 03/2020 - 08/2022

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Abstract

Axin is a key negative regulator of the oncogenic Wnt/β-catenin pathway scaffolding the β-catenin destruction complex. We have evidence that anchoring of the destruction complex to microtubules (MTs) via a newly identified MT binding site in axin is of functional importance for regulating Wnt signaling. We analyse the dynamics and biochemical basis of axin association with MTs and define its mechanistic role in Wnt signaling.

Important results

Axin puncta were shown to behave as biocondensates via newly defined domains prone to liquid-liquid phase separation. Microtubule interaction of axin seems to alter/disrupt these biocondensates.

Special methods

Density gradient centrifugation of proteins

Publications

no project-specific publications so far

Modulation of oncogene-induced senescence

Prof. Dr. Bosserhoff

D31 03/2020 - 09/2022

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Abstract

Oncogene-induced senescence (OIS) was recently introduced as a strong tumor suppressive mechanism. The development of nevi out of melanocytes after BRAF V600 mutation is one prominent example for OIS. Melanoma cells obviously can overcome these limiting mechanisms; however, the molecular process is largely unknown. Here, we follow the hypothesis that senescence is modulated by cell-matrix contacts and aim to understand the role of mechanotransduction in induction and overcoming OIS.

Important results

In the first 7 months of the project, we could already demonstrate that changes in cell matrix adhesion (e.g. by modulating integrin expression, modulation RNA-binding molecules like HuR) modulates senescence induction in melanocytes. Further, a direct impact of wnt signal on YAP transcription factor activity in melanoma cells was revealed.

Special methods

Reporter gene assays, OIS induction via lentiviral transfection, analyses of senescence marker

Publications

Liebig JK, Kuphal S, Bosserhoff AK. (2020) HuRdling Senescence: HuR Breaks BRAF-Induced Senescence in Melanocytes and Supports Melanoma Growth.Cancers (Basel). 12(5):1299.

NPY in chemo-resistance and immune-escape in HCC

PD Dr. Dietrich

D32 03/2020 - 08/2022

PD Dr. Peter Dietrich, Department of Medicine 1

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Abstract

Neuropeptide Y (NPY) and its receptors represent a highly conserved system which is involved in cancer-related hallmarks. We found that NPY5-receptor (Y5R) is upregulated in sorafenib resistant HCC cells. Moreover, NPY and its receptors could modulate immune escape in HCC which is completely unknown. The aims of this study are to (i) unravel the role of Y5R-NPY-crosstalk in chemoresistance, and to (ii) analyze the role of the NPY-system as a potential major determinant of immune-escape in HCC.

Important results

1. NPY-5-receptor (Y5R) was found to be induced by treatment with first-line tyrosine receptor inhibitors (i.e., sorafenib, lenvatinib) in HCC cells
2. Y5R-inhibition prevented HCC cells to gain sorafenib-resistance in vitro
3. Infiltrating HCC cells were found to highly co-express immune-checkpoints (i.e. PD-L1) and Y5R

Special methods

1. Murine liver cancer models (e.g., orthotopic HCC model, DEN-induced HCC, STAM-induced HCC)
2. RTK-inhibitor-resistant cell lines
3. RNAi-methods, including siRNAs, microRNAs

Publications

Dietrich P, Wormser L, Fritz V, Seitz T, De Maria M, Schambony A, Kremer AE, Günther C, Itzel T, Thasler WE, Teufel A, Trebicka J, Hartmann A, Neurath MF, von Hörsten S, Bosserhoff A, Hellerbrand C. (2020) Molecular cross-talk between Y5-receptor and neuropeptide Y drives liver cancer. J Clin Invest. 1;130(5):2509-2526.

Linck-Paulus L, Hellerbrand C, Bosserhoff AK, Dietrich P. (2020)Dissimilar Appearances Are Deceptive-Common microRNAs and Therapeutic Strategies in Liver Cancer and Melanoma. Cells. 2;9(1).

Immunometabolism in CML


Prof. Dr. Metzler


Prof. Dr. Mougiakakos

D33 05/2020 - 12/2022

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Abstract

Tyrosine kinase inhibitors (TKIs) targeting the BCR/ABL1 fusion protein are widely used for the treatment of CML but there are still patients suffering from resistances, relapses, and side effects. This project focusses on a) the metabolic impact of different TKIs (imatinib (ima), dasatinib, nilotinib, and asciminib (asci)) on CML cell lines and intervention strategies derived from that and b) the influence on T cell metabolism and therefore function and immunosurveillance.

Publications

no project-specific publications so far

Important results

- Ima reduced expression of activation- and surface markers of activated T cells while asci had no effect
- Both TKIs attenuated T cell proliferation and had so far no effect on metabolic parameters of T cells
- TKIs rendered CML cells more susceptible towards oligomycin and led to reduced metabolic activity

Special methods

- Expression analysis of different CML cell lines and T cell proteins by FACS
- RNA-expression examination of metabolic enzymes by qPCR
- Metabolic flux analysis for the assessment of various mitochondrial and glycolytic parameters

Fibroblast polarization in colorectal carcinoma


PD Dr. Ramming


Prof. Dr. Stürzl

D34 05/2020 - 01/2023

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Abstract

The tumor microenvironment (TME) is of key importance in the development and progression of colorectal carcinoma (CRC). It is generally accepted that cancer-associated fibroblasts (CAFs) exert important functions in tumorigenesis. In own previous studies we could demonstrate an important role of differential fibroblast polarization in tissue fibrosis and identified the transcription factor PU.1 as a key regulatory molecule. As yet the role of fibroblast polarization in CRC is unknown. Accordingly, we will address the impact of differential fibroblast polarization on tumorigenesis in vitro, in experimental animal models, and validate the results in human tissues of CRC patients.

Special methods

In a first step TME-dependent fibroblast heterogeneity in CRC has been analyzed. To this goal tumor fibroblast cultures were established from CRC with and without a Th1-like TME and respective tumor free control tissues (n = 3 each). Transcriptomes were compared by RNA-Seq. Significant differences in gene expression were detected. These results are presently validated at the protein level.

Special methods

- RNA-Seq
- CRC fibroblast isolation and culture

Publications

no project-specific publications so far

Interactions of DPF3 and hypoxia in renal cancer

PD Dr. Schödel

D35 07/2020 - 12/2022

PD Dr. Johannes Schödel, Department of Medicine 4
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Abstract

The development of renal cell cancer depends on dysregulation of hypoxia pathways. The intronic variant rs4903064 in the DPF3 gene, coding for a chromatin remodeller, permits HIF-DNA interactions at this enhancer and promotes upregulation of DPF3 expression in renal cells. Increased DPF3 levels may contribute to global chromatin changes observed in renal cancer. The resulting epigenetic setting may modify transcription factor DNA-binding to critical regulatory elements and promote tumour growth.

Publications

no project-specific publications so far

Important results

We could determine a striking genotype-expression correlation of rs4903064 and DPF3 in a large cohort of RCC patients. We have established ATAC-seq experiments in renal tubular and cancer cells and observe differential chromatin configuration at the DPF3 HIF-binding site depending on the underlying rs4903064 genotype in tubular cells.

Special methods

We have established ATAC-seq experiments in primary cells to identify open chromatin and regulatory DNA-elements on a genome-wide scale. We further use chromatin immunoprecipitation to characterize DNA interactions of various transcription factors and histone marks. We use CRISPR activator and inhibitors to functionally test regulatory elements.

Endogenous retroviruses drive tumor inflammation

Prof. Dr. Strick

Prof. Dr. Hartmann

D36 03/2020 - 11/2022

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Abstract

Endogenous retroviral (ERV) genes are part of the human genome and silenced via epigenetic regulation, but become activated in a variety of tumors. After activation strong associations of ERV dsRNA and RNA/DNA intermediates with tumor inflammation have been shown. We focus on the molecular basis of ERVs and tumor inflammation of two different cancers; Bladder and ovarian cancer. Patient immune signatures with ERV RNA-DNA products using primary tumors, cell lines and tumoroids will be determined.

Publications

no project-specific publications so far

Important results

- DsRNA and RNA/DNA intermediates induce specific cellular genes.
- RNA/DNA intermediates are synthesized in cells via ERV coded reverse transcriptases.
- A general signature of ERV expression in bladder and ovarian carcinoma are generated using cloned genes, ERV specific poly-A transcript characterization and a custom-made Affymetrix chip.

Special methods

- Synthesis and transfection of various dsRNA and RNA/DNA intermediates.
- Novel method for a TAG-aided poly-A transcript isolation.
- Use of a custom-made Affymetrix chip for ERV, repetitive and reference genes with a total of 327,976 gene elements.

Neural Crest Regulators In Orofacial Clefting


Prof. Dr. Gölz


Prof. Dr. Wegner

E28 07/2020 - 01/2023

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Abstract

Orofacial clefts are frequent congenital malformations. Etiology is complex, poorly understood and involves environmental and genetic factors. We could identify several cranial neural crest transcription factors and chromatin remodelers as key regulators of palatal development. We will use genome-edited cell lines and mouse mutants to determine the exact function and relationship of these factors in their regulatory network and thus better understand palatal development and orofacial clefting.

Important results

We established protocols for efficient transfection of cleft-relevant cell lines and the in vitro differentiation of a cranial neural crest cell line (O9-1) into cleft-relevant cell types. CRISPR/Cas9-mediated gene knockout was successfully employed to inactivate key regulators of palatal development in cranial neural crest cells.

Special methods

- CRISPR/Cas9-mediated gene knockout
- In vitro neural crest differentiation

Publications

Weider M, Schröder A, Docheva D, Rodrian G, Enderle I, Seidel CL, Andreev D, Wegner M, Bozec A, Deschner J, Kirschneck C, Proff P, Gölz L (2020) A Human Periodontal Ligament Fibroblast Cell Line as a New Model to Study Periodontal Stress. International journal of molecular sciences 21(21): 7961

Lysosome dysfunction in stem cell ageing


Prof. Dr. Lie

E29 07/2020 - 01/2023

Prof. Dr. Dieter Chichung Lie, Institute of Biochemistry
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Abstract

Adult neural stem cell dysfunction and the resulting impairment in adult hippocampal neurogenesis are considered significant contributors to cognitive deficits in human ageing and neurodegenerative diseases. The mechanisms underlying ageing-associated neural stem cell dysfunction are largely unknown. This project investigates the hypothesis that dysfunction of lysosome-dependent degradation pathways is a major contributor for hippocampal neural stem cell dysfunction during ageing.

Important results

We have successfully generated transgenic mice, which conditionally overexpress the transcriptional master regulator of lysosomal biogenesis TFEB in adult neural stem cells. Activation of the TFEB transgene restricts stem cell activation in the hippocampus of young adult mice.

Special methods

Measurement of autophagic-lysosomal flux via biochemistry and imaging. Neural stem cell cultures. Retroviral vectors. Stereotactic injections (mouse).

Publications

no project-specific publications so far

Impact of the immune system on Parkinson‘s disease


Prof. Dr. Winner


Prof. Dr. Winkler

E30 04/2020 - 09/2022

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Abstract

Parkinson’s disease (PD) is characterized by the progressive loss of dopaminergic midbrain neurons and intercellular inclusions of a-synuclein aggregates. Altered gut microbiota may trigger or even accelerate a-synuclein aggregation in the enteric nervous system of PD patients. We investigated gut microbiota by sequencing the V3-V4 regions of the bacterial 16S ribosomal RNA gene in fecal samples. The present study suggests that altered microbiota may modify the clinical course in PD.

Important results

- Disease duration and stage had a major impact on microbiome composition.
- L-dopa equivalent dosage influenced the correlation of taxa with disease duration.
- After propensity score matching to control for non-motor symptoms such as constipation, *Faecalibacterium* and *Ruminococcus* were reduced in PD patients.

Special methods

- Development of standardized modelst o generate IPSC-derived dopaminergic midbrain neurons (mDANs)
- Autologous co-culture system of mDANS with myeloid cells

Publications

Cosma-Grigorov A, Meixner H, Mrochen A, Wirtz S, Winkler J, Marxreiter F (2020) Changes in Gastrointestinal Microbiome Composition in PD: A Pivotal Role of Covariates. Front Neurosci 11:1041

Proteasomal degradation in intellectual disability


Prof. Dr. Zweier

E31 01/2020 - 08/2021

Prof. Dr. Christiane Zweier, Institute of Human Genetics (till 08/2020)
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Abstract

Neurodevelopmental disorders (NDDs) are extremely heterogeneous but converge on a number of common molecular processes, such as the ubiquitin-proteasome system (UPS), in which mutations in several components are implicated in NDDs. Treatment options are limited so far. We investigate if manipulation of proteasome activity by two substances can ameliorate phenotypes in *Drosophila* and/or cell based models of UPS-associated NDDs and thus will gain insights into potential interventional options.

Important results

- siRNA based knockdown of nine UPS and NDD associated genes in HEK293 cells results in altered proteasome activity, used as a readout for subsequent rescue experiments.
- Knockdown of *Drosophila* orthologues resulted in altered activity and/or multiple dendrite neuron morphology. Proteasome modulating substances in the fly food ameliorate some phenotypes.

Special methods

- *Drosophila melanogaster* as a model for NDDs (knockdown or overexpression of genes of interest with the UAS/GAL4 system)
- iPSC based cell models for NDDs (CRISPR/Cas9 induced knockout of genes of interest)

Publications

Fliedner A, Kirchner P, Wiesener A, van de Beek I, Wasifisz Q, van Haelst M, Scott DA, Lalani SR, Rosenfeld JA, Azamian MS, Xia F, Dutra-Clarke M, Martinez-Agosto JA, Lee H, UCLA, Noh GJ, Lippa N, Alkelai A, Aggarwal V, Agre KE, Gavrilova R, Mirzaa GM, Straussberg R, Cohen R, Horist B, Krishnamurthy V, McWalter K, Juusola J, Davis-Keppen L, Ohden L, van Slegtenhorst M, de Man SA, Ekici AB, Gregor A, van de Laar I, Zweier C (2020) Variants in SCAF4 cause a neurodevelopmental disorder and are associated with impaired mRNA processing. Am J Hum Genet 107(3): 544-554

Gpr126 in kidney development and disease

Prof. Dr. Engel

F7 05/2020 - 10/2022

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Abstract

Chronic kidney disease represents the fastest growing pathology worldwide. Elucidating new regulators of kidney development and disease will promote the development of strategies for kidney repair. Here we propose to identify how the adhesion G protein-coupling receptor Gpr126 regulates kidney development and which diseases are associated with altered Gpr126 expression in order to design in the future experiments to determine whether Gpr126 inhibition or activation can improve kidney function.

Publications

no project-specific publications so far

Important results

- Gpr126 is expressed in collecting duct cells in the developing as well as tubular and some interstitial cells in the adult zebrafish and human kidney.
- Gpr126 is expressed in lung metastatic cells invading the human kidney
- Gpr126 is expressed during different kidney diseases in the proximal tubulus.

Special methods

- Zebrafish (wide variety of technologies)
- RNAscope technology (cells, tissues, mouse, rat, human)
- CRISPR/Cas technologies

Ion channel function of polycystin-2 in ADPKD

Prof Dr. Korbmacher

F8 02/2020 - 07/2022

Prof. Dr. Christoph Korbmacher, Institute of Cellular and Molecular Physiology

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Abstract

In about 15% of affected patients ADPKD (autosomal dominant polycystic kidney disease) is caused by mutations in the PKD2 gene coding polycystin-2 (PC2). Altered ion channel properties of PC2 may contribute to the pathophysiology of ADPKD. This project uses a novel experimental strategy to study the electrophysiological properties of PC2 and mutant PC2 channels in combination with molecular modelling. Its aim is to improve our understanding of PC2 ion channel function in health and disease.

Publications

no project-specific publications so far

Important results

Replacing the pore region of PC2 with that of the related channel PC2L1 leads to cyst formation in mice and alters PC2 ion selectivity. Channel function is preserved in PC2 with a mutated Ca^{2+} binding site in its EF-hand domain. Channel properties of PC2 are altered by co-expressing polycystin-1 (PC1) consistent with a heteromeric channel structure.

Special methods

Human PC2 channels expressed in *Xenopus laevis* oocytes are studied with the two-electrode voltage-clamp (TEVC) and patch-clamp technique to record whole-cell and single-channel currents, respectively. Different PC2 mutant channels are generated by site-directed mutagenesis. Electrophysiological studies are complemented by molecular modeling of PC2.

Generation of novel glomerular 3D culture systems


Prof. Dr. Müller-Deile


Prof. Dr. Schiffer

F9 06/2020 - 12/2022

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Prof. Dr. Mario Schiffer, Department of Medicine 4
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Abstract

The aim of this project is to generate 3D glomerular-like structures by co-culturing different glomerular cell types ex vivo to study glomerular functions and cell-cell interactions in physiological and pathophysiological conditions. Using podocytes derived from patients with podocyte mutations in the co-culture systems will allow us to characterise renal disease on a personalised level and enable us to study therapeutic responses ex vivo. Implementation of the 3D cultures in an av-loop vascularization model in rats will be performed to optimize glomerular cell assembly due to vascularization.

Publications

no project-specific publications so far

Important results

Human glomerular endothelial cells, podocytes and mesangial cells were co-cultured three-dimensionally to form self-organizing spheroids that produce their endogenous extracellular matrix. We were able to generate iPSCs from skin biopsies from patients with podocyte mutations and controls that we differentiate back into podocytes at the moment.

Special methods

- Three-dimensional co-culture
- Generation of iPSCs from skin biopsies
- Vascularization in an av-loop rat model

Understanding the plasticity of cancer cells

Prof. Dr. Ceppi

Prof. Dr. Paolo Ceppi

N1 08/2015 - 07/2021

Prof. Dr. Paolo Ceppi

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Summary

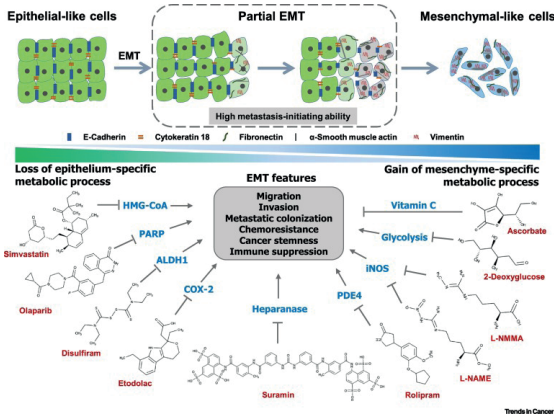
The group focuses on the identification of novel fundamental mechanisms of cancer biology using several cell and molecular biology techniques, mouse models, high-throughput approaches and the analysis of human samples. We aim at discovering novel genes and molecular pathways that regulate the plasticity and the aggressiveness of cancer cells and at studying the association between cancer differentiation and sensitivity to chemotherapy, with a special attention on metabolism genes. The final goal is the development of more effective drugs and therapeutic strategies.

Important results

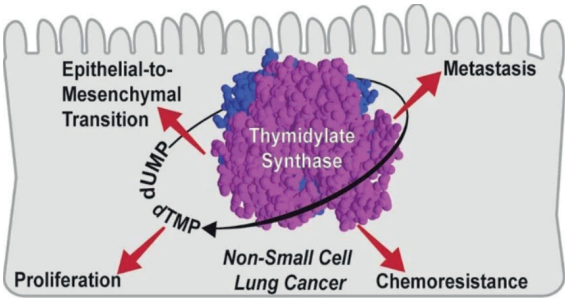
1. Publication on the British Journal of Cancer on the role of Thymidylate synthase as a driver of malignancy in NSCLC regulating proliferation, cellular differentiation and metastasis.
2. Opinion article on Trends in Cancer proposing the possibility of using repurposed metabolic inhibitors for suppressing the metastatic spread and the chemoresistance of solid cancers.

Special methods

1. Metastasis formation assay of cancer cells in mice
2. Incucyte real-time cell imaging (including for red and green fluorescence applications)
3. Bioinformatics on cancer datasets



The potential role of repurposed metabolic inhibitors in repressing the aggressive features of epithelial to mesenchymal transition (EMT). From Ramesh et al. Trends in Cancer 2020.



The role of thymidylate synthase as a driver of malignancy in non-small cell lung cancers, integrating epithelial to mesenchymal transition (EMT), metastasis formation and cellular proliferation, as identified in Siddiqui et al. British Journal of Cancer 2020.

Publications (selection of)

Siddiqui A, Gollavilli P, Ramesh V, Parma B, Schwab A, Vazakidou MA, Natesan R, Saatci O, Rapa I, Bironzo P, Schuhwerk H, Asangani I, Sahin O, Volante M, Ceppi P (2020). Thymidylate synthase drives the phenotypes of epithelial-to-mesenchymal transition in non-small cell lung cancer. British Journal of Cancer, Oct 7. doi: 10.1038/s41416-020-01095-x.

Ramesh V, Brabletz T, Ceppi P (2020). Targeting EMT in Cancer with Repurposed Metabolic Inhibitors. Trends in Cancer 2020 Nov;6(11):942-950.

Siddiqui A, Gollavilli P, Schwab A, Vazakidou ME, Ersan PG, Ramakrishnan M, Pluim D, Coggins SA, Saatci O, Annaratone L, Schellens JHM, Kim B, Asangani IA, Rasheed SAK, Marchiò C, Sahin O, Ceppi P (2019). Thymidylate synthase maintains the de-differentiated state of aggressive breast cancers. Cell Death and Differentiation. Nov;26(11):2223-2236.

Schwab A, Siddiqui A, Vazakidou ME, Napoli F, Böttcher M, Menchicchi B, Raza U, Saatci Ö, Krebs AM, Ferrazzi F, Rapa I, Dettmer-Wilde K, Waldner MJ, Ekici AB, Rasheed SAK, Mougiakakos D, Oefner PJ, Sahin Ö, Volante M, Greten FR, Brabletz T, Ceppi P (2018) Polyol pathway links glucose metabolism to the aggressiveness of cancer cells. Cancer Research. 78:1604-1618.

Siddiqui A, Vazakidou ME, Schwab A, Napoli F, Fernandez-Molina C, Rapa I, Stemmler MP, Volante M, Brabletz T, Ceppi P (2017) Thymidylate synthase is functionally associated with ZEB1 and contributes to the epithelial-to-mesenchymal transition of cancer cells. The Journal of Pathology; 242:221-233.

Research Focus

Despite the progresses made in the last years with the development of novel molecularly targeted agents, cancer is still a very deadly disease. This could be attributable in part to the fact that only a minority of selected patients benefit from the novel compounds (such as those targeting oncogenic drivers like EGFR, BRAF, HER2 and many others), while poor therapeutical options are available for the vast majority of the patients in which a targetable driving oncogenic mutation is undetermined. Moreover, the pathway redundancy and the very frequent occurrence of mutations limit the efficacy of these novel drugs even in initially responding patients. There is therefore an urgent need for the identification of novel fundamental mechanisms of cancer biology and of relevant determinants of chemoresistance in order to develop more effective drugs and therapeutic strategies.

The discovery of epithelial-to-mesenchymal transition (EMT), cancer stem cells (CSCs) and of their functional association and interdependence represent some of the most promising advances in the last two decades of cancer research. CSCs are defined as a subpopulation of undifferentiated cancer cells with stem-like features responsible for tumors' heterogeneity and for some of the most lethal features of cancers: tumorigenicity, metastatic spread, relapse and chemoresistance. The inter-conversion between CSCs and non-CSCs has been recently reported and the EMT clearly functionally involved. The EMT is a de-differentiation process frequently observed in cancers with increased invasive potential and drug resistance. A recently emerging concept is that the plasticity of cancers is greater than what initially hypothesized, and therefore a better understanding of the mechanisms behind the inter-conversion of cancer cells between differentiation stages may have many therapeutic implications. Moreover, cancers, and the CSC population in particular, are highly dependent on aerobic glycolysis, which they use as a major pathway for biosynthesis. The enhanced rate of glycolysis occurs largely because of the increased demand of a transformed cell for macromolecule components (the so-called Warburg effect). The connection between increased glycolytic rate, EMT and CSCs has recently started to emerge in the literature, but the molecular determinants involved are still undefined.

The Junior Group aims at discovering fundamental druggable mechanisms and molecular determinants that regulate the plasticity and the aggressiveness of cancer cells, and at studying the association between cancer differentiation and sensitivity to chemotherapy. By high-throughput approaches we have identified a number of potential EMT/CSC-regulating metabolic mechanisms, which we aim to validate by the analysis of human samples and functionally investigate by the use of cell and molecular biology techniques. This approach may ultimately lead to the identifications of novel targets for therapeutic intervention.

Top row from the left: Vignesh Ramesh, Paradesi Naidu Gollavilli, Aarif Siddiqui, Heike Wagner Bottom row from the left: Annemarie Schwab, Beatrice Parma, Sabine Marschall, Paolo Ceppi

Third-party funding

Paolo Ceppi, 2020 – Independent Research Fund Denmark, Molecular characterization and targeting of NSCLC with high thymidylate synthase levels, 0134-00012B (2020-2023).

Paolo Ceppi, German Cancer Aid Research Grant, Determination of the role of aldose reductase AKR1B1 and associated pathways in epithelial-to-mesenchymal transition and cancer stem cells, 33436004 (2017-2020).

Paolo Ceppi, International Association for the Study of Lung Cancer. The role of thymidylate synthase in epithelial-to-mesenchymal transition in NSCLC (2017-2018).

Paolo Ceppi, DFG Research Grant. Whole-genome CRISPR/Cas9 mediated identification of miR-200 repressors, DFG CE 281/5-1 (2018-2021).

Paolo Ceppi, DFG Research Grant. Deciphering and targeting the metabolic control of lung cancer de-differentiation DFG CE 281/6-1 (2019-2022).

Prof. Dr. Dulin

Prof. Dr. David Dulin

N2 09/2016 - 08/2022

e-mail: david.dulin@uk-erlangen.de, d.dulin@vu.nl

Summary

We aim at elucidating how directional transcription termination is mediated by MTERF1 in human mitochondria, the cell power plant. To this end, we developed a biophysical approach to mechanically probe whether MTERF1 senses the transcription direction of the mitochondrial RNA polymerase and terminate only the ones coming from one direction. RNA polymerase I (Pol I) is the RNA polymerase responsible for transcribing all the ribosomal RNA (rRNA) in eukaryotic cell, and its activity is therefore essential for growing cells and in cancer. The rate-limiting step in rRNA synthesis is the initiation phase, which is performed through multiple successive steps. The determinants and dynamics of Pol I initiation are poorly known because of their intrinsic stochasticity. Using a single molecule approach, we will characterize the different steps and determine the rate limiting one as their role to form an elongating complex. Finally, the last project aims at assembling a functional SARS-CoV-2 replisome to determine the role of each viral protein, to probe the efficacy and mechanism of action of antiviral drugs.

Important results

- The direction of transcription is directly sensed by transcription terminators through directional DNA unwinding.
- We developed a new platform to evaluate antiviral nucleotide analogues efficacy against SARS-CoV-2 replicase, demonstrating the real mechanism of action of Remdesivir.
- We developed a new high throughput magnetic tweezers-fluorescence microscopy platform.

Special methods

- We use bespoke high throughput magnetic tweezers assays to characterize the mechanochemical properties of protein nucleic acid interactions
- We have developed a combined fluorescence-magnetic tweezers set up to image and mechanically probe the protein nucleic acid complex.

Publications (selection of)

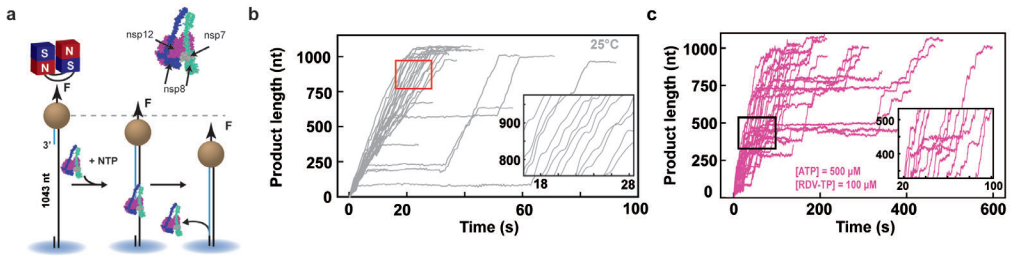
Seifert M, van Nies P, Papini FS, Arnold, JJ, Poranen MM, Cameron CE, Depken M, Dulin D (2020) Temperature controlled high-throughput magnetic tweezers show striking difference in activation energies of replicating viral RNA-dependent RNA polymerases. Nucleic Acids Research, 48:10, 5591-5602

Ostrofet E, Papini FS, Dulin D (2020) Microscopy-spectroscopy SI: High spatiotemporal resolution data from a custom magnetic tweezers instrument. Data in Brief, 30:105397. doi: 10.1016/j.dib.2020.105397

Papini FS, Seifert M, Dulin D (2019) High-yield fabrication of DNA and RNA constructs for single molecule force and torque spectroscopy experiments. Nucleic Acids Research, 47(22):e144. doi: 10.1093/nar/gkz851

Ostrofet E, Papini FS, Dulin D (2018) Correction-free force calibration for magnetic tweezers experiments. Scientific Reports 8:15920

Dulin D, Bauer DLV, Malinen AM, Bakermans JJW, Kaller M, Morichaud Z, Petushkov I, Depken M, Brodolin K, Kulbachinskiy A and Kapanidis AN (2018) Pausing controls branching between productive and non-productive pathways during initial transcription in bacteria. Nature Communications 9:1478



A magnetic tweezers assay to monitor nucleotide analogues efficacy against SARS-CoV-2 replicase. (a) Schematic of the magnetic tweezers assay. We monitor the position of the magnetic bead in 3D and real-time, which relates on the position and the dynamics of the replicase along the template. (b) SARS-CoV-2 replicase product length as a function of time with 500 µM NTPs. Most replicases synthesize the ~1 kbp product in ~25 s. (c) Same as (b), adding 100 µM Remdesivir-TP (RDV-TP), which induces pauses during synthesis, effectively slowing down the replicase.

Research Focus

The Dulin lab aims at understanding the fundamental processes involved in the central dogma of molecular biology, i.e. replication, transcription and translation, using high-end microscopy. Each step in gene expression involves complex molecular motors, e.g. DNA polymerase, RNA polymerase (RNAP) and ribosome. Much has been learned related to these motors using standard ensemble biochemical assay, but their detailed kinetic characterization remains elusive. Indeed, these enzymes do not progress linearly along their template, but rather through burst of successive catalytic reactions interrupted by pauses of various origins, e.g. co-factors binding, misincorporation, template sequence, which makes gene expression highly stochastic, and impacts the organism phenotype. By giving access to enzymatic processes at the single molecule level, and not to the ensemble population, single-molecule biophysics has changed our view on biology, offering an understanding of the rare, transient and stochastic — but important — events that interrupt enzymatic activity. Our lab develops high-end microscopy techniques, such as magnetic tweezers and single-molecule fluorescence microscopy, to describe in great details (1) how SARS-CoV-2 replicates its genome and (2) how bacteria and eukaryotic cells transcribe their genomes.

1- RNA virus replication mechanism

RNA viruses represent an important class of human and animal pathogens. We are currently living through the third and largest coronavirus pandemic in the 21st century, i.e. SARS-CoV-2, which greatly damages our economy and way of life. While vaccines now exist, an efficient drug with little side effect is still lacking to cure infected patients and to act swiftly against future outbreak. Our lab is interested in interrogating how SARS-CoV-2 replicates its genome, as the coronavirus replisome is the main target for antiviral drugs. The replisome is a complex multiprotein machinery of which little is known in terms of kinetics and biochemistry, limiting the development of drugs. Using single molecule biophysics technique, e.g. magnetic tweezers and single-molecule fluorescence microscopy, the role of each viral factors in the replication and transcription of the large coronavirus genome.

2- Cellular transcription

Transcription is at the heart of gene expression and maintenance any every organism. Our lab works on three different transcription systems: Escherichia coli (E. coli) bacteria, human mitochondria and yeast RNA polymerase I (Pol I). Bacterial transcription is the model system of cellular transcription and its most representative enzyme, E. coli RNA polymerase (RNAP), has been therefore intensively studied. We use the E. coli bacteria RNAP to benchmark our assays, and investigate the mechanisms of bacterial transcription initiation. Mitochondria are the powerhouse of the eukaryotic cell, and therefore, due to its importance in many cellular processes, abnormal mitochondria activity is linked to several disorders. Understanding the basis of mitochondria transcription, the first step in gene expression, will shed light on the biochemistry of this essential organelle. Pol I is responsible for synthesizing most of the ribosomal RNA, and is the rate limiting step in ribosome biogenesis. Because of its importance in ribosome production, thus on protein production, Pol I activity has become an attractive target for anti-cancer drugs. Using magnetic tweezers and single-molecule FRET assays, we investigate how these different RNA polymerases perform their transcription activity.

From the left: David Dulin, Ibrahim Obulqasim, Flavia Stal-Papini, Mona Seifert, Eugen Ostrofet, Subas Chandra Bera.

Third-party funding

DFG DU1872/3-1, Revealing the mechanism of directional transcription termination at the single-molecule level for the human mitochondrial transcription complex, 30 months from February 2020. Principal investigator.

DFG DU1872/4-1, Revealing the mechanism of nucleotide selection, addition and proofreading of the SARS-CoV-1 replication transcription complex at the single molecule level, 24 months, to be started. Principal investigator.

DFG DU1872/5-1, Determinants and dynamics of RNA polymerase I transcription initiation, 30 months, to be started. Principal investigator.

NIH R01, Coronavirus replication. Starting April 1st, 2021. Co-applicant.

Organ crosstalk in IMIDs

Prof. Dr. Günther

N5 24 months

Prof. Dr. Claudia Günther, Department of Medicine 1
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project start in 2021

Abstract

Both host environmental components as well as host cells release Extracellular vesicles (EVs) who are increasingly recognized for their immune-stimulatory properties and their potential role as biological shuttle system for inter-kingdom communication. Within this project, we will elucidate the role of extracellular vesicles as communication system and the impact of such vesicles on the pathogenesis of immune-mediated inflammatory diseases.

Special methods

The Günther Lab has a long lasting scientific expertise on preclinical ex vivo organ culture models, spanning the spectrum from organoids derived from various tissues (e.g., GI tract, liver, biliary tract, pancreas) as well as neoplastic tissues and associated technologies (genome editing, freezing, microinjection, co-culturing, functional assays)

Rare glomerular diseases

Prof. Dr. Müller-Deile

N6 01.04.2021 – 31.03.2023

Prof. Dr. Janina Müller-Deile, Department of Medicine 4
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project start in 2021

Abstract

I investigate rare glomerular diseases with different cell culture models, transgenic zebrafish models, podocyte specific knockout models, innovative techniques, interdisciplinary collaborations and patient material to cover multidimensional aspects of the disease in a patient centered manner. Cell-cell signaling through miRs, exosomes, autophagy and circulating factors are investigated to learn more about pathomechanisms of rare glomerular diseases that might translate into novel therapeutic targets in the future.

Special methods

- Analysis of cell-cell signalling via exosomes, microRNAs and autophagy
- Personalized assay for early detection of soluble factors in zebrafish
- Generation of podocytes with patient mutations from skin biopsies

Forging neural cell identity

Prof. Dr. Karow

N7 24 months

Prof. Dr. Marisa Karow, Institute of Biochemistry
e-mail: marisa.karow@fau.de

project start in 2021

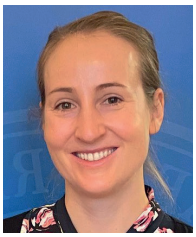
Abstract

This IZKF grant will be essential to realize my vision of using direct lineage reprogramming for the identification of novel regulators of human neurogenesis. My data provide evidence for the exciting opportunity to identify new potential molecular targets to enhance and navigate human neurogenesis for improving reprogramming and understanding developmental neurogenesis. We will study putative new neurogenesis key players during direct lineage reprogramming and early human brain development.

Special methods

- Stem cell-based 2D and 3D model systems to study human neuron formation
- Direct lineage reprogramming of somatic cells into induced neurons
- scRNA sequencing

Lysosomes & glial cells



Prof. Dr. Zunke

N8 16.02.2021 – 15.02.2023

Prof. Dr. Friederike Zunke, Department of Molecular Neurology
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recently started

Abstract

Recent studies suggest that glial dysfunction significantly contributes to neurodegeneration in Parkinson's disease (PD). Since lysosomal degradation is important for glial cell function, we aim to analyse the molecular consequences of lysosomal dysfunction within different glial cell lines. A better understanding of glial regulation and lysosomal turnover will help to unravel molecular mechanisms in PD and might facilitate the identification of novel therapeutic strategies in PD.

Special methods

1. Lysosomal assays: pH measurements; live-cell lysosomal enzyme activity assays: e.g. Cathepsin D, B, L, β-Glucocerebrosidase
2. Induced pluripotent stem cells & neuronal differentiation protocols
3. Analysis of amyloid protein structures; Protein missfolding cyclic amplification assay (PMCA): amplification of misfolded protein (e.g. Synuclein) from lysate or tissue

Neutrophils in rheumatoid arthritis

Prof. Dr. Grüneboom

J62 08/2017 - 01/2020

IMMUNOLOGY AND INFECTION

Prof. Dr. Anika Grüneboom, Department of Medicine 3 (till 10/2020)

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Abstract

Neutrophil play a key role during acute infections and tissue injury-induced inflammation as they are the first leukocytes recruited to inflammatory sites. Neutrophils are also highly abundant in the inflamed joints of rheumatoid arthritis (RA) patients, but their exact contribution to initiation, propagation and resolution of this autoimmune disease is poorly understood. This project focusses on the role of neutrophils in the onset of RA and their interaction with tissue resident macrophages.

Important results

- Neutrophil granulocytes display a bi-phasic recruitment into inflamed joints
- Synovial lining integrity is not disintegrated by invading neutrophils but immune complexes
- Synovial lining macrophages are suited as therapeutic targets in RA

Publications

no project-specific publications

IL-3 in inflammatory bowel disease

Dr. Zundler

J63 12/2017 - 05/2020

IMMUNOLOGY AND INFECTION

Dr. Sebastian Zundler, Department of Medicine 1

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Abstract

In this project, we elucidated the role of interleukin-3 (IL-3) in the pathogenesis of inflammatory bowel diseases (IBD). The data generated during the funding period support a protective role of IL-3 in experimental colitis, which seems to be associated with altered T cell mechanics and trafficking. These data provide novel insights into intestinal inflammation, pave the way towards further promising investigations and suggest that IL-3 might be an interesting therapeutic target in IBD.

Important results

- IL-3-deficiency aggravates intestinal inflammation in the T cell transfer and the oxazolon colitis model.
- IL-3 is substantially upregulated in severe ulcerative colitis and associated with short flare-free survival.
- IL-3 increases the stiffness of CD4+ T cells, which is associated with decreased transmigration and tissue homing.

Special methods

- Dynamic rolling and adhesion assays
- (Humanized) adoptive transfer model of cell trafficking to the inflamed gut
- Lightsheet microscopy and 3D reconstruction of gut samples

Publications

Schleier L, Wiendl M, Heidbreder K, Binder M-T, Atreya R, Rath T, [...] and Zundler S. (2020) Non-classical monocyte homing to the gut via α4β7 integrin mediates macrophage-dependent intestinal wound healing. Gut. 69(2):252–63

Zundler S, Becker E, Schulze LL, Neurath MF. (2020) Immune cell trafficking and retention in inflammatory bowel disease: mechanistic insights and therapeutic advances. Gut. 68(9):1688–700

Zundler S, Becker E, Spocinska M, Slawik M, Parga-Vidal L, Stark R, et al. (2019) Hobit- and Blimp-1-driven CD4+ tissue-resident memory T cells control chronic intestinal inflammation. Nat Immunol. 20(3):288–300.

Nephroprotection by HIF-hydroxylase inhibitors

Dr. Grampp

J64 10/2017 - 08/2020*

Dr. Steffen Grampp, Department of Medicine 4
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RENAL AND VASCULAR RESEARCH

*the project was interrupted from 10/2018 - 2/2019

Abstract

In Acute Kidney Injury (AKI) restricted blood flow and oxygen supply lead to tissue hypoxia and ultimately to cell death. Pre-conditional stabilization of hypoxia-inducible factors (HIFs) in renal tubular epithelial cells leads to an improved kidney function in AKI. My results from in vitro models of AKI using human primary tubular cells suggest that the additional activation of HIFs by inhibition of factor inhibiting HIF (FIH) further protects from AKI and provides a novel option for tissue protection.

Important results

FIH inhibition increases the hypoxic gene induction in vitro and in vivo

In primary human tubular cells (hPTEC) and C57BL/6 mice, simultaneous inhibition of PHD and FIH enzymes resulted in increased induction of HIF target genes.

Preconditional HIF-Stabilization protects hPETC in an in vitro AKI model

Simultaneous inhibition of PHD and FIH displayed the strongest reduction of apoptosis in hPTEC.

Special methods

Pirmary human tubular cells

Healthy cortical kidney tissue is used for generation of hPTEC from patients undergoing a tumornephrectomy.

ChIP-, RNA-, FAIRE-Seq:

Genome-wide methods for open chromatin (FAIRE-), transcription factor binding (ChIP-) and gene regulation (RNA-Seq) are used to characterize the effects of the PHD- and FIH-inhibition in hPTEC.

Publications

Safi W, Kraus A, Grampp S, Schödel J, Buchholz B. (2020) Macrophage migration inhibitory factor is regulated by HIF-1α and cAMP and promotes renal cyst cell proliferation in a macrophage-independent manner. J Mol Med (Berl). doi: 10.1007/s00109-020-01964-1. Online ahead of print.

Lauer V, Grampp S, Platt J, Lafleur V, Lombardi O, Choudhry H, Kranz F, Hartmann A, Wullich B, Yamamoto A, Coleman ML, Ratcliffe PJ, Mole DR, Schödel J. (2020) Hypoxia drives glucose transporter 3 expression through HIF-mediated induction of the long non-coding RNA NICI. Biol Chem 295(13):4065-4078. doi: 10.1074/jbc.RA119.009827. Epub

T-System Regulation by Glucocorticoids

PD Dr. Seidel

J65 11/2017 - 04/2020

PD Dr. Thomas Seidel, Institute of Cellular and Molecular Physiology
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RENAL AND VASCULAR RESEARCH

Abstract

The transverse tubular system (t-system), a specialized system of membrane invaginations in cardiac myocytes, facilitates cardiac excitation-contraction coupling. In heart failure, the t-system undergoes severe remodeling, which impairs cardiac contraction, adds to heart failure progression and prevents recovery. In this project we investigate mechanisms underlying t-system remodeling in heart failure with the ultimate goal to identify strategies for preventing and reversing heart failure.

Important results

1. Glucocorticoids preserve the t-system and excitation-contraction coupling in cardiomyocytes by upregulation of autophagic flux
2. Junctional coupling and t-system density is decreased in glucocorticoid receptor knockout mice
3. Glucocorticoids improve contractility in long-term culture of human myocardial slices

Special methods

1. Automated three-dimensional image segmentation and quantitative analysis
2. Isolation and cultivation of adult human cardiomyocytes and human myocardium
3. Live-cell confocal calcium imaging

Publications

D. J. Fiegle, M. Schöber, S. Dittrich, R. Cesnjevar, K. Klingel, T. Volk, M. Alkassar, T. Seidel (2021) Severe t-system remodeling in pediatric viral myocarditis. Frontiers in Cardiovascular Medicine. doi: 10.3389/fcvm.2020.624776

D. J. Fiegle, T. Volk, T. Seidel (2020) Isolation of human ventricular cardiomyocytes from vibratome-cut myocardial slices. Journal of Visual Experiments (159) doi: 10.3791/61167

M. Abu-Khousa, D. J. Fiegle, S. T. Sommer, G. Minabari, H. Milting, C. Heim, M. Weyand, R. Tomasi, A. Dendorfer, T. Volk, T. Seidel (2020) The degree of t-system remodeling predicts negative force-frequency relationship and prolonged relaxation time in failing human myocardium. Frontiers in Physiology 11:182

T. Seidel, D. J. Fiegle, T. J. Baur, A. Ritzer, S. Nay, C. Heim, M. Weyand, H. Milting, R. H. Oakley, J. A. Cidlowski, T. Volk (2019) Glucocorticoids preserve the t-tubular system in ventricular cardiomyocytes by upregulation of autophagic flux. Basic Research in Cardiology 114(6):47

β subunits: adding pieces to the puzzle of pain

Dr. Eberhardt

J66 01/2018 - 08/2020

NEUROSCIENCES

Dr. Esther Eberhardt, Department of Anaesthesiology (till 08/2020)

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Abstract

Stem cell derived sensory neurons of patients with hereditary pain syndromes caused by mutations in voltage-gated sodium channels (Navs) have recently improved our understanding of the pathophysiology of pain. The aim of this study is to use human induced pluripotent stem cells (hiPSCs) of patients with rare variants in Nav accessory proteins to elucidate the contribution of these β subunits to action potential generation and neuronal excitability in patient derived sensory neurons.

Important results

Patient derived sensory neurons of a patient suffering from erythromelalgia carrying the mutation β3 p.L10P exhibit higher spontaneous activity in patch-clamp and multi electrode array (MEA) recordings compared to neurons of healthy donors. This neuronal hyperexcitability seems to be caused by a higher proportion of tonically firing neurons.

Special methods

Our research group has specialised on the differentiation of hiPSCs to human sensory neurons. The focus is on electrophysiological characterisation of these neurons with patch-clamp and MEA recordings combined with pharmacological approaches to understand basic mechanisms of neuronal hyperexcitability and to deciper novel targets in chronic pain.

Publications

Lampert A, Bennett DL, McDermott LA, Neureiter A, Eberhardt E, Winner B, Zenke M (2020) Human sensory neurons derived from pluripotent stem cells for disease modelling and personalized medicine. Neurobiol Pain. 8: 100055

Namer B, Schmidt D, Eberhardt E, Maroni M, Dorfmeister E, Kleggetveit IP, Kaluza L, Meents J, Gerlach A, Lin Z, Winterpacht A, Dragicevic E, Kohl Z, Schüttler J, Kurth I, Warncke T, Jorum E, Winner B, Lampert A (2019) Pain relief in a neuropathy patient by lacosamide: Proof of principle of clinical translation from patient-specific iPS cell-derived nociceptors. EBioMedicine 39:401-408

Sommer A, Maxreiter F, Krach F, Fadler T, Grosch J, Maroni M, Graef D, Eberhardt E, Riemenschneider MJ, Yeo GW, Kohl Z, Xiang W, Gage FH, Winkler J, Prots I, Winner B (2018) Th17 Lymphocytes Induce Neuronal Cell Death in a Human iPSC-Based Model of Parkinson's Disease. Cell Stem Cell 23: 123–13

Metabolic reprogramming of AML MDSCs

PD Dr. Jitschin

J67 01/2018 - 06/2021

ONCOLOGY

PD Dr. Regina Jitschin, Department of Medicine 5

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Abstract

Acute myeloid leukemia (AML) is the most common acute leukemia amongst adults. Emerging evidence suggests that immune alterations favor leukemogenesis and relapse. Myeloid derived suppressor cells (MDSCs) have gained momentum as mediators of immune escape. We aim to decipher interconnections between metabolic reprogramming and MDSC abundance and to unravel the role of AML-derived exosomes in this context. Understanding those mechanisms is key for improving immune-based therapeutic approaches.

Important results

1. Monocytic CD14+ MDSCs accumulate in newly diagnosed AML patients and suppress T-cell responses in an IDO-dependent manner.
2. AML MDSCs can be targeted by autologous T-cells using CD3/CD33 bispecific antibodies.
3. Palmitoylated proteins on AML-derived extracellular vesicles promote the induction of MDSCs establishing a link to lipid metabolism.

Special methods

Isolation and imaging of extracellular vesicles; Seahorse-based metabolic flux analyses; FACS-based analysis of protein-palmitoylation.

Publications

Tohumeken S, Baur R, Böttcher M, Stoll A, Loschinski R, Panagiotidis K, Braun M, Saul D, Völkl S, Baur AS, Bruns H, Mackensen A, Jitschin R*, Mougiakakos D* (2020). Palmitoylated Proteins on AML-Derived Extracellular Vesicles Promote Myeloid-Derived Suppressor Cell Differentiation via TLR2/Akt/mTOR Signaling. Cancer Research 17: 3663-3676

Jitschin R, Böttcher M, Saul D, Lukassen S, Bruns H, Loschinski R, Ekici AB, Reis A, Mackensen A, Mougiakakos D (2019). Inflammation-induced glycolytic switch controls suppressivity of mesenchymal stem cells via STAT1 glycosylation. Leukemia 33: 1783-1796

Jitschin R, Saul D, Braun M, Tohumeken S, Völkl S, Kischel R, Lutteropp M, Dos Santos C, Mackensen A, Mougiakakos D (2018) CD33/CD3-bispecific T-cell engaging (BiTE®) antibody construct targets monocytic AML myeloid-derived suppressor cells. J Immunother Cancer 2018 Nov 5;6(1):116. doi: 10.1186/s40425-018-0432-9

Role of GATA4 in Intestinal Inflammation & Cancer

Dr. Patankar

J68 10/2017 - 03/2020

ONCOLOGY

Dr. Jay V. Patankar, Department of Medicine 1

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Abstract

Transcription factor GATA4 controls the differentiation of intestinal epithelial cells (IECs) and simultaneously acts as a tumor suppressor. We have previously shown that mice, which lack GATA4 specifically in the IECs experience a reduction in the absorptive functions, have an improved gut-liver cross-talk influenced by microbiota-derived products. We now show that immune cell-derived IL-22 mediated IEC growth, permeability, and mucous production depend on GATA4.

Important results

- We dedicated a sizeable proportion of the previous year to COVID research. We found that Crohn's disease patients have reduced levels of the SARS-CoV-2 receptors. We found specific regulation of the receptors via microbial and cytokine signaling.
- GATA4 drives metabolic repression seen as result of immune activation, specifically downstream of IL-22

Special methods

- Growing and maintaining 3D intestinal and colonic organoids and quantification of organoid lipid flux.
- Culturing 2D monolayers of intestinal epithelial cells derived from 3D organoids for wound closure, EMT, infection, co/culture and mucous and AMP release assays.
- Comparative Transcriptomic analyses.

Publications

Patankar JV, Chiriac M, Lehmann M, Kühl AA, Atreya R, Becker C (2020) Severe Acute Respiratory Syndrome Coronavirus 2 Attachment Receptor Angiotensin-Converting Enzyme 2 Is Decreased in Crohn's Disease and Regulated By Microbial and Inflammatory Signaling. Gastroenterology. 2020 Oct 17 (ahead of print)

Gößwein S, Lindemann A, Mahajan A, Maueröder C, Martini E, Patankar JV, Schett G, Becker C, Wirtz S, Naumann-Bartsch N, Bianchi ME, Greer PA, Lochnit G, Herrmann M, Neurath MF, Leppkes M (2019) Citrullination licenses calpain to decondense nuclei in neutrophil extracellular trap formation. Frontiers in immunology 10: 2481

Effect of HIV on pre-existing vaccine immunity

Dr. Nganou Makamdop

J69 09/2018 - 02/2021*

IMMUNOLOGY AND INFECTION

Dr. Christiane Krystelle Nganou Makamdop, Institute of Clinical and Molecular Virology

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* additional project funding from 05/2021-08/2021 du to parental leave

Abstract

This project studies the quality of antigen-specific responses in HIV-infected persons on antiretroviral therapy (ART). Following recruitment of HIV-uninfected and ART-treated HIV-infected participants with prior vaccinations against measles virus (MV) and tetanus toxoid (TT), markers of inflammation and peripheral recall T cell responses to MV and TT were assessed. Obtained results highlight the effect of HIV infection on the maintenance of vaccine-induced immunity.

Publications

no project-specific publications so far

Important results

Preliminary work showing significantly elevated T cell activation and inflammation confirms the persistence of immune dysfunctions despite ART. Importantly, inflammation associates with reduced MV and TT-specific T cell responses in HIV infection. To clarify underlying mechanisms, transcriptome analysis of antigen-specific cells is ongoing.

Special methods

no project-specific methods so far

Gene discovery in kidney disease


Dr. Jobst-Schwan

J70 10/2018 - 03/2021

Dr. Tilman Jobst-Schwan, Department of Medicine 4

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RENAL AND VASCULAR RESEARCH

Abstract

The genetic background of chronic kidney disease (CKD) in adults is insufficiently investigated. We perform genetic testing on local adult patients with CKD to identify novel monogenic causes of CKD. To prove deleteriousness of mutations identified, functional studies including RNA-Seq are conducted in primary skin fibroblasts or human urinary primary tubular cells of the patients. Candidate genes are further investigated, inter alia, in a zebrafish loss-of-function animal model.

Publications

no project-specific publications so far

Important results

- Identification of a novel *MYH9* variant in a family with Epstein-Fechtner syndrome
- Functional data excluded an obligatory splice site variant of the gene *KIF21A* as disease causing in a family with steroid resistant nephrotic syndrome. RNA-seq revealed complex dysregulation of cell cycle related pathways corresponding to slow proliferation of the index patient`s fibroblasts

Special methods

- Cell culture of primary skin fibroblasts and human urinary primary tubular cells
- Whole exome sequencing analysis
- Zebrafish knock-down models

P2Y2R-dependent cyst growth in ADPKD


Dr. Kraus

J71 01/2019 - 06/2021

Dr. Andre Kraus, Department of Medicine 4

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RENAL AND VASCULAR RESEARCH

Abstract

The main aim of our project is to descramble the precise role of the ATP-activated purinergic receptor P2Y2R in the context of Ca^{2+}-dependent Cl^--secretion as a main course of cyst growth in Autosomal Dominant Polycystic Kidney Disease. We are analysing the effect of Suramin (P2R inhibitor) as a potential drug and the impact of genetic deletion of P2Y2R in a PKD1-KO mouse model. In addition we test for ATP-dependent effects by performing micropuncture experiments in an in vitro cyst model.

Important results

1. Embryo transfer of P2Y2R fl mice and crossing with KSP-Cre PKD1 KO successful. First mice induced.
2. PKD1 KO mice were treated with Suramin and they trend towards an ameliorated cystic phenotype
3. Establishment of a micro puncture technique of in vitro cysts lacking PKD1. Currently injection of ATP luminally with subsequent live cell imaging.

Special methods

1. Micro puncture technique of in vitro cysts including micro grinding of capillaries
2. Life cell imaging of in vitro cyst growth
3. Phenotypic characterization of polycystic kidney disease

Publications

Ines Cabrita*, Andre Kraus*, Julia Katharina Scholz, Kathrin Skoczynski, Rainer Schreiber, Karl Kunzelmann, Björn Buchholz (2020) Cyst growth in ADPKD is prevented by pharmacological and genetic inhibition of TMEM16A in vivo. Nat Commun. 11(1):4320 *shared first

Safi W*, Kraus A*, Grampp S, Schödel J, Buchholz B. (2020) Macrophage migration inhibitory factor is regulated by HIF-1α and cAMP and promotes renal cyst cell proliferation in a macrophage-independent manner. J Mol Med (Berl). doi: 10.1007/s00109-020-01964-1 *shared first

Kraus A, Peters DJ, Klanke B, Weidemann A, Willam C, Schley G, Kunzelmann K, Eckardt KU, Buchholz B (2018) HIF-1α promotes cyst progression in a mouse model for autosomal dominant polycystic kidney disease. Kidney Int. 2018 Nov;94(5):887-899

Intracellular signaling by SPARCL1 in colon cancer

ONCOLOGY

Dr. Tenkerian

J73 09/2018 - 06/2020

Dr. Clara Tenkerian, Department of Surgery (till 06/2020)

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Abstract

The tumor microenvironment (TME) plays a pivotal role in tumorigenesis, prognosis and therapy. SPARCL1 is a vascular derived anti-tumorigenic factor that counteracts CRC tumorigenesis in a TME-dependent manner. Preliminary results indicate that SPARCL1 regulates ERK phosphorylation and subcellular localization in endothelial and CRC cells. This project aims to elucidate the signaling pathways by which SPARCL1 transmits its anti-proliferative and anti-angiogenic functions.

Important results

- Analysis of CRC data from the TCGA database shows a positive correlation in the expression of SPARCL1 and several modulators of the TGFβ and MAPK pathways.
- SPARCL1 regulates ERK by preferentially activating its cytoplasmic substrates.
- SPARCL1 differentially regulates the TGFβ pathway, depending on the presence or absence of its receptor Endoglin.

Publications

Regensburger D, Tenkerian C, Pürzer V, Schmid B, Wohlfahrt T, Stolzer I, López-Posadas R, Günther C, Waldner MJ, Becker C, Sticht H, Petter K, Flierl C, Gass T, Thoenissen T, Geppert CI, Britzen-Laurent N, Méniel VS, Ramming A, Stürzl M, Naschberger E (2021) Matricellular Protein SPARCL1 Regulates Blood Vessel Integrity and Antagonizes Inflammatory Bowel Disease. Inflamm Bowel Dis. 4:izaa346.

Klingler A, Regensburger D, Tenkerian C, Britzen-Laurent N, Hartmann A, Stürzl M, Naschberger E (2020) Species-, organ- and cell-type-dependent expression of SPARCL1 in human and mouse tissues. PLoS One. 15(5):e0233422.

CtBP1 and neuronal excitability

OTHERS

Dr. Salar

J74 02/2019 - 07/2021

Dr. Seda Salar, Department of Psychiatry and Psychotherapy

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Abstract

As a transcriptional corepressor of neuroplasticity-related genes, C-terminal binding protein 1 (CtBP1) modulates activity-dependent gene expression in a metabolic state-dependent manner. To elucidate the role of CtBP1 in hippocampal neuroplasticity, we employed acute hippocampal slices from CtBP1 knock-out (KO) mice. The basal synaptic transmission was unaltered, but neuroplasticity induced by strong physiological stimulation or upon metabolic stress was impaired in the absence of CtBP1.

Important results

Acute hippocampal slices from CtBP1 KO mice showed

1. impaired long-term potentiation,
2. faster suppression of neurotransmission and a higher failure of recovery following glycolytic stress
3. lower mitochondrial respiratory activity.

Our results indicate a role of CtBP1 in the metabolic regulation of neurotransmission.

Special methods

In Vitro electrophysiology: extracellular field potential and whole-cell patch clamp recordings in cortico-hippocampal acute brain slices

Pharmacological dissection of metabolic pathways in hippocampal slices and cultured neurons

Publications

Salar S, Guhathakurta D, Marx Hoffmann L (2019) Differential contribution of pyramidal cells and interneurons to activity-dependent gene transcription changes. J Neurophysiol. 122(6):2203-2205. Doi: 10.1152/jn.00089.2019

Statistical Analysis of Infectious Disease Spread

Dr. Meyer

J75 10/2018 - 04/2021

OTHERS

Dr. Sebastian Meyer, Department of Medical Informatics, Biometry and Epidemiology

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Abstract

Epidemic models can be used to evaluate socio-demographic and environmental factors, and to generate probabilistic forecasts of infectious disease spread. This project extends the epidemiologist's statistical toolbox for the analysis of time series from infectious disease surveillance. The first part of the project extends the well-established HHH model to proportion data and the second part handles count data with excessive zeros. All methods are implemented in open-source software.

Important results

We propose an endemic-epidemic beta model for time series of infectious disease proportions. Our approach accommodates the asymmetric shape and heteroskedasticity of proportion distributions, is easy to implement, and produces competitive forecasts of flu activity a few weeks ahead. A multivariate formulation accounts for spatio-temporal effects.

Special methods

Our model generates probabilistic forecasts to communicate uncertainty of predictions. Proper scoring rules are used to measure predictive performance including calibration and sharpness. All methods are implemented in the statistical programming environment R with core packages "betareg" and "surveillance".

Publications

Lu J, Meyer S (2020) Forecasting Flu Activity in the United States: Benchmarking an Endemic-Epidemic Beta Model. International Journal of Environmental Research and Public Health 17(4):1381

The role of itaconate in osteoclasts

Dr. Kachler

J76 10/2019 - 04/2022

IMMUNOLOGY AND INFECTION

Dr. Katerina Kachler, Department of Medicine 3

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Abstract

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease of the joints, causing damage to cartilage and bone. The bone erosion results from excessive maturation or activation of osteoclasts. The maturation capacity and function of osteoclasts might in turn depend on their metabolic state. A possible regulator of metabolic reprogramming in osteoclasts is the TCA intermediate, itaconate. In this project, we analyze the itaconate-dependent effects on osteoclast metabolism in RA.

Publications

no project-specific publications so far

Important results

Human and murine osteoclasts undergo a metabolic switch towards glycolysis during differentiation. The itaconate-derivative, 4-octyl-itaconate (4-OI) suppresses glycolytic activity and inhibits osteoclast differentiation in vitro. Accordingly, itaconate-deficiency enhances bone erosion in a murine model of K/BxN serum induced arthritis (SIA).

Special methods

To evaluate bone erosion, inflammation and osteoclast numbers in the K/BxN SIA model, we perform histological staining on tissue sections as well as micro-computed tomography for three-dimensional bone structure. To examine the metabolic state of in vitro cultured osteoclasts, we use extracellular flux analyses (Agilent Seahorse XF Analyzer).

Characterization of autoreactive B cells during RA


Dr. Pfeifle

J77 11/2019 - 04/2022

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IMMUNOLOGY AND INFECTION

Abstract

Rheumatoid arthritis (RA) is one of the most prevalent autoimmune diseases. Autoreactive B cells and autoantibodies are crucial drivers of RA pathogenesis. However, transcriptional changes in ACPA-specific B cells leading to the onset of RA are only sparsely understood. Here, we plan to use flow-cytometry and single cell sequencing approaches to analyze phenotypical and transcriptional changes of autoreactive B cells during the transition of asymptomatic autoimmunity into RA.

Important results

We validated the identification of ACPA+ B cells by fluorescence-activated cell sorting and subsequent activation of antibody-secretion in vitro and established the identification of tetanus-toxoid fragment C positive B cells from PBMCs. Secondly; we established the identification of B cells responsive to other RA-associated autoantigens.

Special methods

Flow-cytometry-based characterization of antigen-specific B cells.

Publications

no project-specific publications so far

Role of ferroptosis during microbial infection


Dr. Ruder

J78 01/2019 - 03/2022

Dr. Barbara Ruder, Department of Medicine 1
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IMMUNOLOGY AND INFECTION

Abstract

In this project, we aimed to investigate the role of the Glutathione peroxidase GPX4 and ferroptosis in macrophages under steady state conditions and during acute Salmonella infection. We hypothesize that GPX4-regulated ferroptotic cell death plays an important role during Salmonella infection and might display a new therapeutic target for treatment of acute infections. In the first part of this project, we analyzed ferroptosis and GPX4 activity in different experimental settings.

Important results

In a first set of experiments, we observed that macrophages undergo ferroptosis if GPX4 is blocked by the GPX4 inhibitor RSL3. Surprisingly, these experiments revealed that stimulation with Erastin, another known ferroptosis inducer, did not lead to ferroptosis in these cells, suggesting different mechanisms of ferroptosis induction in macrophages.

Special methods

In order to measure expression levels of important ferroptosis genes, we performed qPCR analysis. LDH assay, Flow cytometry and microscopy were used to analyze cell death in macrophages.

Publications

Ruder B, Günther C, Stürzl M, Neurath MF, Cesarman E, Ballon G et al. (2020) Viral Flip blocks Caspase-8 driven apoptosis in the gut in vivo. PLoS One 15(1): e0228441

PD-L1 function during obesity and dysbiosis

Dr. Schwartz

J79 09/2019 - 02/2022

IMMUNOLOGY AND INFECTION

Dr. Christian Schwartz, Institute of Clinical Microbiology, Immunology and Hygiene

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Abstract

Obesity has become one of the biggest challenges for global health. Obesity not only alters metabolic function but also impairs immune function and changes microbial composition. Using mouse models of diet-induced obesity and samples of patients undergoing bariatric surgery, we discovered a critical role for PD-L1 in the regulation of homeostasis in adipose tissue. In our ongoing studies, we characterise the cellular and molecular mechanisms that govern obesity-induced immune dysfunction.

Important results

PD-L1 regulates tissue homeostasis, Th2 and regulatory T cell responses, and delays obesity

Conditional deletion of PD-L1 reveals cell-specific functions of PD-L1 during obesity

Intervention with immune checkpoint inhibitors accelerates weight loss in obese mice

Special methods

Flow cytometry, cell sorting and ex vivo culture of mouse and human ILC2

Animal model of diet-induced obesity

Conditional deletion of PD-L1 on various immune cell populations

Publications

Saunders SP, Floudas A, Moran T, Byrne CM, Rooney MD, Fahy CMR, Geoghegan JA, Iwakura Y, Fallon PG, Schwartz C (2020) Dysregulated skin barrier function in Tmem79 mutant mice promotes IL-17A-dependent spontaneous skin and lung inflammation. Allergy 75:3216–3227

Psen1 in colorectal cancer

Dr. Mahapatro

J80 05/2020 - 12/2020

ONCOLOGY

Dr. Mousumi Mahapatro, Department of Medicine 1 (till 12/2020)

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Abstract

Presenilin1 (Psen1) is a transmembrane protease that plays an important role in generation of amyloid beta in Alzheimer's disease. Little is known about its expression and function in the gut epithelium. We aimed to characterize Psen1 at a functional level and evaluate its ability to initiate and promote intestinal tumor development. We could observe that Psen1 not only drives tumor development but also increases EGFR signaling by activating the COX-2-PGE2 pathway. Hence, Psen1 inhibition could be a useful strategy in treatment of colorectal cancer.

Publications

no project-specific publications

Important results

1. $Psen1^{\Delta IEC}$ mice developed smaller tumors when induced by carcinogen AOM
2. Tumor organoids derived from $Psen1^{\Delta IECAPCmin/+}$ mice exhibited reduced proliferation.
3. Gene expression analyses from Psen1 deficient tumors revealed a diminished expression of the EGFR and COX-2 and the aforementioned phenotype was partially reversed by administration of PGE2.

Special methods

1. $Psen1^{\Delta IEC}$ mice were subjected to chemically (AOM/DSS) and genetically (Apcmin/+) induced models of colorectal cancer.
2. CRISPR/Cas9-mediated Psen1 deletion in human colorectal cancer cells were studied in a xenograft tumor model
3. Tumor derived organoids were analyzed for growth and RNASeq was performed to identify major pathways.

Web based Brain Tumor Image Classifier (WeB-TIC)

Prof. Dr. Jabari

J81 01/2020 - 06/2022

MEDICAL ENGINEERING

Prof. Dr. Samir Jabari, Institute of Neuropathology
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Abstract

Low-grade epilepsy-associated brain tumors (LEAT) are difficult to diagnose at the microscope. Also, the genotype-phenotype classification developed by WHO in 2016 cannot be applied to LEAT. However, bioinformatics ‚deep learning' programs can detect genotype-phenotype correlations directly from the histological section. Our research project pursues this pioneering approach to develop imaging biomarkers for neuropathological diagnosis for the first time.

Publications

no project-specific publications so far

Important results

The automated filtering of image data to distinguish between background and tissue using established scores was reworked due to poor results and a new filtering system was developed (so-called Hanny score). The automated image data of gangliogliomas obtained in this way were analyzed using unsupervised clustering.

Special methods

Previous methods evaluate image data converted to grayscale as background if an absolute amount of pixel values does not exceed a certain threshold (e.g. OTSU method). Our newly developed method now puts these pixel values in topographic relation to the image and achieves much better results.

O-GlcNAcylation regulates osteoclastogenesis

Dr. Chen

J82 01/2020 - 12/2020

OTHERS

Dr. Chih-Wei Chen, Department of Medicine 3 (till 12/2020)
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Abstract

In rheumatoid arthritis (RA), increased osteoclast differentiation results in progressive bone loss. We demonstrate that increase O-GlcNAcylation (OG) promotes osteoclast differentiation during early stages of osteoclastogenesis, whereas its downregulation is required for osteoclast maturation. Inactivation of OG transferase (OGT) or O-GlcNacase (OGA) arrests osteoclastogenesis during early differentiation and late maturation, respectively. These findings may offer potential to therapeutically interfere with pathologic bone resorption.

Publications

no project-specific publications so far

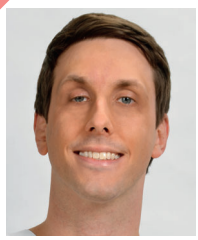
Important results

- OG increases during the early differentiation phase of osteoclastogenesis and decreases during the maturation process.
- Inhibition of OGT and OGA arrests osteoclastogenesis at early stages of differentiation and inhibition of impairs osteoclast maturation.
- OGT and OGA inhibition blocks the transcription of genes required for different stages of osteoclastogenesis.

Special methods

1. **CX5**
   Images and cellomics data were acquired by using a CellInsight CX5 High Content Screening Platform with SpotDetector. V4 BioApplication (Thermo Scientific, Darmstadt, Germany).
2. **WES**
   Capillary western blot was performed and analyzed by using a Western Wes system (ProteinSimple, Wiesbaden, Germany)
3. **In vitro and in vivo models of osteoclastogenesis and inflammatory bone resorption**

Role of ferroptosis in inflammatory lung diseases


Dr. Ganzleben

J83 10/2020 - 03/2023

Dr. Ingo Ganzleben, Department of Medicine 1
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IMMUNOLOGY AND INFECTION

recently started

Abstract

Ferroptosis is a novel form of regulated cell death with major importance in inflammatory conditions. The proposed study will elucidate the functional role of ferroptosis and its main regulator GPX4 in the lung under steady-state conditions and in the pathophysiology of the inflammatory lung disease of bronchial asthma. By characterizing the molecular pathways involved, we aim to lay the foundation for the development of new therapeutic avenues in the treatment of this frequent disease.

Special methods

- Murine disease models of bronchial asthma
- Micro computed tomography (µCT)
- Real-time cell death assays

Direct vs. indirect class II antigen presentation


Dr. Kretschmann

J84 11/2020 - 04/2023

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IMMUNOLOGY AND INFECTION

recently started

Abstract

Surface presentation of HLA class II-antigens can occur directly by the host cell or after intercellular transfer of the antigen to surrounding antigen presenting cells. We hypothesize that prior to surface presentation endogenously expressed class II-restricted antigens travel in different compartments as compared to exogenous antigens and therefore undergo differential processing. These processing steps which are critical for presentation, are characterized by antigen specific properties.

Special methods

- Cloning of wildtype and mutant antigen-libraries and retroviral transduction into cell lines
- Culture and re-stimulation of primary and antigen-specific CD4+ T-cell clones
- Antigen presentation assays and confocal microscopy

Cell-type-specific roles of IL36 in the Intestine

Dr. Scheibe

J85 11/2020 - 05/2023

Dr. Kristina Scheibe, Department of Medicine 1

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IMMUNOLOGY AND INFECTION

recently started

Abstract

Intestinal fibrosis is a common complication in IBD and has limited therapeutic options. IL36R ligands are upregulated in CD and UC patients as well as CD patients with stenosis. The systemic blockade of IL36R signaling reduces intestinal inflammation and fibrosis in vivo. Deciphering the cell-type-specific roles of IL36 via the newly generated IL36Rfl/f mouse strain will help to understand the mode of action of a neutralizing IL36R antibody in humans.

Special methods

- Detection of fibrotic remodeling in chronic mouse models of colitis by multiphoton microscopy and lightsheet microscopy
- Quantitative (Sirius Red assay) and qualitative (mass spectrometry) measurement of ECM remodeling in vitro
- Coculture of intestinal organoids with colonic fibroblasts derived from murine and human tissue

Virome/macrophage interaction in Crohn's disease

Dr. Schmitt

J86 01/2021 - 09/2022

Dr. Heike Schmitt, Department of Medicine 1

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IMMUNOLOGY AND INFECTION

recently started

Abstract

We aim to investigate the composition of the gut virome as a marker for resistance against anti-TNF therapy in Crohn's disease patients. We will functionally characterize the interaction of identified viruses with mucosal CD14+ macrophages. In particular, we will analyze mechanisms of increased mucosal IL23R expression and IL-23 production that mediate molecular resistance to anti-TNF therapy in Crohn's disease, to finally elucidate a signaling pathway that determine non-response to therapy.

Special methods

- In vitro culture with human intestinal organoids
- Organ culture of human intestinal biopsies

Network Communication in Inflammation

Prof. Dr. Uderhardt

J87 01/2021 - 06/2022

Prof. Dr. Stefan Uderhardt, Department of Medicine 3

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IMMUNOLOGY AND INFECTION

recently started

Abstract

I could previously identify resident tissue macrophages (RTM) as anti-inflammatory protectors of stromal integrity. The molecular mechanisms that regulate this tissue-protective function, however, are unknown. My preliminary work strongly suggests that within stromal tissues exist extensive, heterocellular communication networks. I hypothesize that functional network communication between stromal fibroblasts and RTM coordinate biological behavior of tissues and facilitate RTM functionality.

Special methods

1. Intravital Two-Photon Imaging
2. In vivo Cell and Tissue Biology
3. Histocytometric Image Analysis

New RNA-binding proteins in sporadic ALS

Dr. Krach

J88 11/2020 - 05/2023

Dr. Florian Krach, Department of Stem Cell Biology

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NEUROSCIENCES

recently started

Abstract

sALS is a motor neuron disease where pathological insoluble states of TDP-43, an alternative splicing (AS) factor are found. Dysregulated AS is detected, but it is unknown whether TDP-43 aggregation is causative for this. We develped an iPSC-derived model of sALS where AS changes in this system are not dependent on TDP-43. We propose to investigate pathological mechanisms of new AS factors in sALS using proteomics and NGS approaches and subsequent validation in sALS post mortem tissue.

Special methods

- Culture and differentiation of induced pluripotent stem cells into neuronal derivatives
- CRISPR/Cas9 genome editing
- Computational analyses in functional transcriptomics of RNA-binding protein

MSOT imaging of strictures in Crohn's disease

Dr. Regensburger

J89 01/2021 - 06/2023

MEDICAL ENGINEERING

Dr. Adrian Regensburger, Department of Pediatrics and Adolescent Medicine
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recently started

Abstract

Intestinal strictures are a major disease burden in Crohn's disease. Conventional cross-sectional imaging modalities are currently not able to differentiate between inflammatory and fibrotic components of strictures. This would be essential for the initiation of the appropriate therapy. In a translational approach we want to investigate whether optoacoustic imaging can be used to quantify hemoglobin as a sign of inflammation and collagen as a sign of fibrosis in murine and human intestine.

Special methods

Raster-scanning optoacoustic Mesoscopy (RSOM) allows raster scanning over a FOV of 12x12x3 mm (axial resolution 10µm) for the visualisation of murine vasculature.

Multispectral optoacoustic Tomography (MSOT) allows cross-sectional (spatial resolution of <150µm) quantification of single WLs and different unmixed MSOT parameters (e.g. hemoglobin).

Funded ELAN projects in 2020:

No.	Name	Institution		Project title
P034	Prof. Dr. Harald Schuhwerk	Experimental Medicine I	S	Myeloid ZEB1 in colorectal cancer
P035	Dr. Anne Gregor	Human Genetics	S	Role of FBXO11 in intellectual disability
P036	Dr. Maria Heckel	Palliative Medicine	S	Physicians' opinions on continuous sedation
P037	Dr. Jochen Sembill	Neurology	S	Prognostication in intracerebral hemorrhage
P038	Dr. Danijel Sikic	Urology	S	Molecular markers in stage T1 bladder cancer
P039	Dr. David Simon	Medicine 3	I	Bone characterization in early RA autoimmunity
P040	Dr. Iris Schäffner	Biochemistry	N	FoxO-dependent mitophagy in stem cell function
P041	Dr. Maria Leone	Department of Nephropathology	R	Polyploid cardiomyocytes for cardiac repair
P042	Dr. Dr. Gesche Frohwitter	Oral and Cranio-Maxillofacial Surgery	S	Immunology of NMSC of the head and neck
P043	PD Dr. Annika Kengelbach-Weigand	Plastic and Hand Surgery	S	The autotaxin-LPA axis in breast cancer
P044	Dr. Xianyi Meng	Medicine 3	I	HIF-1a in IgA class switching
P045	Dr. Linda Popella (Grosche)	Immune Modulation	I	HSV-1 modulates the IL-6 signaling pathway in mDCs
P046	Dr. Matthias Balk	Otorhinolaryngology - Head and Neck Surgery	S	Magnetic Drug Targeting for head and neck cancer
P047	Dr. Anna Maslarova	Neurosurgery	N	Synaptic plasticity in the human hippocampus
P048	Dr. Andrea Thoma-Kreß	Clin. and Mol. Virology	I	Collagen IV during retrovirus transmission
P049	Dr. Maria Raimondo	Medicine 3	I	Inflammation from skin to joint
P050	Dr. Dennis Kannenkeril	Medicine 4	R	Vascular, renal parameters in living kidney donors
P051	Dr. Silvia Spörl	Medicine 5	S	T follicular helper cells, transplantation
P052	Dr. Christian Schmidkonz	Nuclear Medicine	S	Treatment Response in EwS by PET/CT and ctDNA
P053	Dr. Sascha Kretschmann	Medicine 5	I	The influence of serotonin on antigen presentation
P054	Dr. Florian Krach	Stemm Cell Biology	N	Agrin and the neuromuscular junction in ALS
P055	Dr. Adrian Regensburger	Pediatrics and Adolescent Medicine	M	MSOT-imaging in spinal muscular atrophy
P056	Prof. Dr. Claudia Günther	Medicine 1	I	Host-microbial interaction in the Liver
P057	Dr. Maximilian Hessenauer	Plastic and Hand Surgery	I	Intravital microcopy in the AV-loop model
P058	Dr. Dominic Bernkopf	Experimental Medicine II	S	Wnt inhibitory peptide
P059	Dr. Patrick Süß	Molecular Neurology	N	Regional neuroinflammation in RA
P060	Dr. Markus Eckstein	Pathology	S	ERVs in the tumorigenesis of MIBC
P061	Prof. Dr. Mario Zaiss	Medicine 3	I	Gut-joint axis
P062	Dr. Andreas Wild	Immune Modulation	I	Role of CD83 on macrophages in tissue homeostasis
P063	Prof. Dr. Thomas Kinfe	Neurosurgery	N	Assay of neuroinflammation in chronic pain
P064	Dr. Vanessa Popp	Radiology	I	Molecular ultrasound of DSS induced colitis
P065	Dr. Alexandru-Emil Matei	Medicine 3	I	Engrailed-1 mediates skin fibrosis
P066	Dr. Claudia von Zimmermann	Psychiatry and Psychotherapy	I	Immune Regulation in the treatment of Depression
P067	Dr. Marius Wunderle	Obstetrics and Gynaecology	S	Immune-oncology in breast cancer
P068	Prof. Dr. Marisa Karow	Biochemistry	N	Direct reprogramming within brain organoids
P069	PD Dr. Nadine Metzger	History of Medicine and Medical Ethics	S	Reception of hippocratic On the Sacred Disease
P070	Prof. Dr. Alexey Ponomarenko	Physiology and Pathophysiology	N	Encoding of behaviours in the hypothalamus
P071	Dr. Dennis Lapuente	Clin. and Mol. Virology	S	Tissue-resident memory T cells against lung cancer
P072	Prof. Dr. Moritz Zaiss	Neuroradiology	M	Non-invasive Metabolic MR Fingerprinting
P073	Dr. Maximilian Sprügel	Neurology	N	Role of pericytes in intracerebral hemorrhage
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Bone characterization in early RA autoimmunity

P039 06/2019 - 05/2020

Dr. David Simon, Department of Medicine 3

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Abstract

To better understand the influence of the early phase of autoimmunity of rheumatoid arthritis (RA) on joint structure, longitudinal observations of pre-RA patients are necessary. High-resolution CT is used to investigate how bone density and structure and biomechanical properties of pre-RA patients develop over time, what influence different biomarker profiles have and what bone characteristics patients developing clinical RA have.

HIF-1a in IgA class switching

P044 08/2019 - 08/2020

Dr. Xianyi Meng, Department of Medicine 3

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Abstract

Germinal center (GC) has been described to contain hypoxic regions linked to B cell class switching. In this project, we will delineate molecular mechanism between HIF-1a-dependent glycolysis and epigenetic modification on IgA class switching region. By studying the IgA response following the C. rodentium infection, we aim to identify the link between the HIF-1a-dependent glycolytic metabolic shift and IgA class switching during microbial infection.

HSV-1 modulates the IL-6 signaling pathway in mDCs

P045 06/2019 - 06/2020

Dr. Linda Popella (Grosche), Divison of Immune Modulation

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Abstract

The focus of the present project is the investigation of Herpes simplex virus type-1 (HSV-1)-mediated modulations of the IL-6 signaling pathway in mature dendritic cells (mDCs). In particular, the underlying molecular mechanisms of reduced IL-6R?, gp130 and STAT3 expression will be analyzed on directly-infected versus uninfected bystander mDCs. Moreover, we will elucidate whether non-infectious L-particles, released from HSV-1-infected cells, are essential/sufficient to induce these modulations.

Collagen IV during retrovirus transmission

P048 05/2019 - 03/2020

Dr. Andrea Thoma-Kreß, Institute of Clinical and Molecular Virology

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Abstract

The oncogenic retrovirus Human T-cell leukemia virus type 1 transmits via cell-cell contacts and viral biofilms seem to constitute a major route of virus transmission. In viral biofilms, extracellular concentrated viral particles are embedded in cocoon-like structures containing collagens (COL) of unknown composition. Here, we hypothesize that the viral transactivator Tax-1 selectively induces expression of COL4 and that COL4 is important for biofilm formation and HTLV-1 transmission.

Inflammation from skin to joint

P049 10/2019 - 10/2020

Dr. Maria Raimondo, Department of Medicine 3
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Abstract
To date, it is still obscure why in some patients with psoriasis the autoimmune process is restrained to the skin, whereas in other it extends to the joints. We will take advantage of models resembling psoriatic arthritis, with the aim of studying the joint involvement secondary to skin inflammation. The understanding and characterization of the underlying mechanisms involved in the "skin-joint axis" is pivotal for a better comprehension of the link between physical barriers and autoimmunity

The influence of serotonin on antigen presentation

P053 10/2019 - 03/2020

Dr. Sascha Kretschmann, Department of Medicine 5
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Abstract
Non-classical HLA class II molecule HLA-DO largely influences the presented peptide repertoire in HLA class II. HLA-DO expression was shown to play a role in type 1 diabetes, in the generation of neutralizing antibodies to viral infections and in immune responses after allogeneic stem cell transplantation. However, the regulation of HLA-DO is distinct from other class II molecules and remains elusive. We here hypothesize that serotonin receptor signaling plays a role in the regulation of HLA-DO.

Host-microbial interaction in the Liver

P056 04/2020 - 03/2021

Prof. Dr. Claudia Günther, Department of Medicine 1
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Abstract
Liver biology and liver diseases are difficult to study using current in vitro models. We developed a new method to isolate and expand self-renewing liver organoids from the embryonic liver. Within this project we aim to understand how microbiome-associated signaling pathways influence maturation, injury and regeneration of the liver by using these organoids. Thus this project will provide new insights in the critical role of liver-gut communication and potentially hepatic disease development.

Intravital microcopy in the AV-loop model

P057 11/2019 - 03/2021

Dr. Maximilian Hessenauer, Department of Plastic and Hand Surgery
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Abstract
Tissue engineering in reconstructive surgery seeks to generate bioartifical tissue substitutes. The AV-loop allows generation of axially vascularized tissue. Cellular mechanisms of this process are largely unclear. Therefor the proposed project aims to evaluate leukocyte mediated processes in this context. Using intravital microscopy, the role of different leukocyte subsets is going to be evaluated. This is aimed to provide novel understanding of these processes for therapeutic application.

Gut-joint axis

P061 04/2020 - 03/2021

Prof. Dr. Mario Zaiss, Department of Medicine 3
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Abstract
In RA the degree of inflammation and autoantibody positivity are important initiators of bone destruction. Interestingly, among IBD patients with chronic gut inflammations about 45% were positive for at least one arthritis antibody. However, despite the reported higher incidence of bone destruction in IBD patients, it remains elusive whether and how local gut antibody production and their different posttranslational modifications during gut inflammations directly contribute to RA.

Role of CD83 on macrophages in tissue homeostasis

P062 01/2020 - 01/2021

Dr. Andreas Wild, Division of Immune Modulation
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Abstract
Tissue-resident macrophages (tirMΦ) contribute to steady state physiology in tissues but also modulate and terminate inflammatory processes. Gene expression data revealed that CD83, a molecule with potent immunoregulatory properties, is highly expressed in tirMΦ. However, the biological relevance of CD83 expression by macrophages is poorly understood. Thus, this project aims to elucidate the role and regulation of CD83 in tirMΦ and in macrophages under pro- and anti-inflammatory conditions.

Molecular ultrasound of DSS induced colitis

P064 09/2020 - 12/2021

Dr. Vanessa Popp, Institute of Radiology
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Abstract
Molecular ultrasound of inflammatory bowel disease has not yet been established. We want to exploit the essential role of endothelial cell adhesion molecules in the development of colitis and establish CAM (cell adhesion molecule)-specific ultrasound contrast agents in DSS-induced murine colitis for the analysis of colonic inflammation. This will facilitate both, assessment of disease progression and treatment response monitoring.

Engrailed-1 mediates skin fibrosis

P065 05/2020 - 04/2021

Dr. Alexandru-Emil Matei, Department of Medicine 3
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Abstract
Systemic sclerosis (SSc) is a prototypic fibrotic disease, with TGF-beta as a key mediator of fibroblast activation. Engrailed-1 (EN1) identifies a fibroblast lineage with intrinsic fibrogenic potential. We showed that EN1 was upregulated in fibrotic skin by TGF-beta, and that EN1 knockout partially prevented fibroblast activation and fibrosis. Next, we aim to study EN2 in fibrosis, to evaluate how EN1 is upregulated and to provide further evidence for the role of EN1 in fibroblast activation.

Immune Regulation in the treatment of Depression

P066 12 months

Dr. Claudia von Zimmermann, Department of Psychiatry and Psychotherapy
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Abstract
One third of the depressed patients do not respond adequately to conventional treatment. This seems to be associated with increased production of proinflammatory cytokines such as TNF-a and IL-1, as well as dysregulation of cortisol levels. This project aims to investigate the impact of the new psychotherapeutic method TaKeTiNa on serum lipids, cortisol Levels, and the production of proinflammatory cytokines.

Modulation of human osteoclasts by sCD83

P077 12 months

Dr. Dmytro Royzman, Division of Immune Modulation
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Abstract
Osteoclasts are the bone-resorbing cells of the body, which lead to severe damage of the musculoskeletal system under pathological conditions (such as RA). Treatment with soluble CD83 inhibited bone destruction in the murine arthritis model. Aim of this proposal is the translation of the murine data into the human system, which represents the next important step towards future therapeutic applications.

Myeloid ZEB1 in colorectal cancer

P034 01/2019 - 01/2020

Prof. Dr. Harald Schuhwerk, Chair of Experimental Medicine I
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Abstract
In colorectal cancer (CRC), the transcription factor ZEB1 is upregulated in tumor cells and tumor-associated macrophages. As only its tumor-promoting role in tumor cells is known, we are analyzing myeloid-specific ZEB1 knockout mice. Our preliminary data suggest that ZEB1 plays a role in macrophage polarization, intestinal inflammation and CRC growth. Here, we will explore novel functions of ZEB1 in immune homeostasis, macrophage plasticity, immune-modulation in CRC and colitis-associated CRC.

Molecular markers in stage T1 bladder cancer

P038 04/2019 - 03/2020

Dr. Danijel Sikic, Department of Urology
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Abstract
Previous studies demonstrated a prognostic relevance of several molecular markers in stage T1 bladder cancer. These might optimize risk stratification and decision making with regard to immediate cystectomy or bladder sparing approach. However, these findings have not been validated yet. The goal of the current study is to validate the association of the mRNA expression of these molecular markers with clinical and survival data in a new cohort consisting of stage T1 bladder cancer.

Immunology of NMSC of the head and neck

P042 09/2019 - 12/2021

Dr. Dr. Gesche Frohwitter, Department of Oral and Cranio-Maxillofacial Surgery

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Abstract

The facial skin is most frequently affected by non-melanoma skin cancer (NMSC). However, the immunological profile of these tumors is still poorly understood. The anticipated ELAN project aims to address this problem by immunohistochemical investigations and may anticipate the establishment of an immunoscore which supplements the TNM classification in prognostic information and therapeutic decision making.

The autotaxin-LPA axis in breast cancer

P043 07/2019 - 02/2021

PD Dr. Annika Kengelbach-Weigand, Department of Plastic and Hand Surgery

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Abstract

Breast cancer is the most common cancer in women worldwide. It is hypothesized that in a vicious cycle autotaxin (ATX) secreted by fat tissue influences breast cancer cells in behavior and leads to secretion of inflammatory cytokines which in turn stimulate ATX secretion of fat tissue. Radiotherapy could lead to an amplification of this effect. It is the aim of this study to evaluate the significance of the ATX/LPA-axis and the effect of radiotherapy in different breast cancer subtypes.

Magnetic Drug Targeting for head and neck cancer

P046 11/2019 - 10/2020

Dr. Matthias Balk, Department of Otorhinolaryngology - Head and Neck Surgery

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Abstract

The main goal in this project is to evaluate the effect of supramagnetic iron oxide nanoparticles for the treatment of head and neck cancer. At first, we will investigate the effects of specific supramagnetic iron oxide nanoparticles on head and neck cancer cell lines. Subsequently, the oncologic potential of supramagnetic iron oxide nanoparticles loaded with chemotheraputics will be analyzed on the various generated cell lines.

T follicular helper cells, transplantation

P051 01/2020 - 12/2020

Dr. Silvia Spörl, Department of Medicine 5

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Abstract

T cells play a major role in complications after allogeneic stem cell transplantation (allo-HSCT). In this projekt we will examine characteristics of T follicular helper cells in patients at different timepoints before and after allo-HSCT and we will correlate them with severe complications (e.g. EBV reactivation or GvHD). With this study, we aim to get more insight in phenotypes and function of Tfh- especially in the context of allo-HSCT.

Treatment Response in EwS by PET/CT and ctDNA

P052 10/2019 - 09/2020

Dr. Christian Schmidkonz, Department of Nuclear Medicine

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Abstract

18F-FDG PET/CT is a promising tool for determining treatment response in Ewing Sarcoma (EwS). Standardized uptake values as marker for metabolic tumor activity can be determined in serial scans to determine response to therapy. EwS is characetrised by circulating tumor DNA (ctDNA) that can be quantified from patients' plasma. We intend to use 18F-FDG-PET/CT and ctDNA to determine treatment response in 20 children and adolescents suffering from EwS.

Wnt inhibitory peptide

P058 04/2019 - 04/2021

Dr. Dominic Bernkopf, Chair of Experimental Medicine II

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Abstract

A synthetic peptide inhibits Wnt/ß-catenin signalling and growth of colorectal cancer cells by augmenting conductin-mediated ß-catenin degradation. Here, we want to improve peptide activity by optimising its functional and its cell permeability-providing parts. Then, cell penetration kinetics, cellular distribution and stability will be characterised, and the optimised peptide will be functionally compared to the old version to verify improvement of our peptide towards therapeutic applicability.

ERVs in the tumorigenesis of MIBC

P060 06/2020 - 05/2021

Dr. Markus Eckstein, Institute of Pathology

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Abstract

To investigate if high amounts of tumor cell dsRNA derived from ERVs regulate the tumor immune microenvironment by activating the 'viral alarm' or IFN response leading to high anti-tumor lymphocyte infiltration including establishment of tertiary lymphoid structures as well as adaptive responses (immune checkpoints, negative regulatory immune cells and ECM production) already in early precursor stages of muscle-invasive bladder cancer and how they might evade the immunosurveillance.

Immune-oncology in breast cancer

P067 12/2020 - 11/2021

Dr. Marius Wunderle, Department of Obstetrics and Gynaecology

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Abstract

DNA damage repair deficiency is common in triple-negative breast cancer, especially in the presence of BRCA1/2 mutations, and is associated with a higher mutational load and immunogenicity. In this project, multi-spectral imaging will be used to investigate the spatial distribution of different immune cells in specimens of triple-negative tumors (BRCA1+, BRCA2+, WT) and their influence on clinical parameters.

Tissue-resident memory T cells against lung cancer

P071 02/2021 - 01/2022

Dr. Dennis Lapuente, Institute of Clinical and Molecular Virology

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Abstract

Lung cancer is the most prevalent and deadly type of cancer. Although immunotherapy with checkpoint inhibitors can improve the clinical outcome, only a minority of patients responds to this treatment. Recent studies suggest that tissue-resident memory T cells (TRM) in the tumour mass correlate positively with prognosis and are essential for efficacy of immunotherapy. In the present study, a novel mucosal vaccination strategy will be employed to induce lung TRM against defined tumour antigens.

CD109 and cellular functions

P075 12 months

Dr. Philipp Arnold, Chair of Anatomy II

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Abstract

Cluster of Differentiation 109 (CD109) is a cell surface protein that is GPI anchored in the cell membrane. It belongs to the α2-macroglobulin, C3, C4, C5 protein family and is expressed on keratinocytes, platelets, immune stem cells as well as CD4 and CD8 positive T cells. In recent years CD109 was also described as risk factor for several tumour entities. In this project we will elucidate the interactome of CD109 on the cell surface and evaluate resulting cell- type specific changes.

Role of FBXO11 in intellectual disability

P035 01/2019 - 01/2020

Dr. Anne Gregor, Institute of Human Genetics

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Abstract

Recently we identified de novo variants in FBXO11, encoding a subunit of an E3-ubiquitin ligase complex, as causative for a neurodevelopmental disorder (NDD). The goal of this grant is to characterize the role of FBXO11 in NDDs. With the model organism Drosophila melanogaster anatomical studies of synapses and behavioral assays will be performed. Additionally effects of patient mutations will be tested in cell-based assays and target proteins of FBXO11 will be identified using AP-MS.

Prognostication in intracerebral hemorrhage

P037 07/2019 - 06/2020

Dr. Jochen Sembill, Department of Neurology

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Abstract

Prognostication in intracerebral hemorrhage (ICH) is biased by self-fulfilling prophecy. We will 1) validate the max-ICH Score, pooling patient data from i) single-center study from Massachusetts General Hospital (Harvard), ii) single-center UKER study, iii) multicenter RETRACE study. We will 2) conduct a prospective multicentre study with randomized controlled prognostic score usage to evaluate physician's prognostic variability & accuracy, optimal prognostic timing, improved outcome measures.

FoxO-dependent mitophagy in stem cell function

P040 09/2019 - 08/2020

Dr. Iris Schäffner, Institute of Biochemistry

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Abstract

Mitochondrial function is crucial for maintenance of the adult neural stem/progenitor cell (NSPC) pool. I found that loss of FoxO transcription factors leads to hyperproliferation and depletion of NSPCs and impairs autophagy-lysosome pathway activity. Moreover, loss of FoxOs is associated with mitochondrial dysfunction. I propose to investigate mitochondria as targets of FoxO-dependent autophago-lysosomal degradation, to establish a FoxO-mitophagy axis in the control of adult NSPC function.

Synaptic plasticity in the human hippocampus

P047 06/2019 - 12/2020

Dr. Anna Maslarova, Department of Neurosurgery

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Abstract

Synaptic plasticity refers to activity-dependent strengthening or weakening of synaptic transmission and underlies memory formation. It can be investigated in-vitro by repetitive network stimulation. In patients with temporal lobe epilepsy, affecting the memory-related hippocampal formation, deficits in memory can occur. We aim to investigate the link between synaptic plasticity and memory impairment by in-vitro field potential recordings from human hippocampus removed during epilepsy surgery.

Agrin and the neuromuscular junction in ALS

P054 10/2019 - 03/2020

Dr. Florian Krach, Department of Stemm Cell Biology

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Abstract

ALS is a neurological disorder molecularly manifesting in pathological aggregation of the splicing regulator TDP-43 and altered splicing in neurons (N). I aim to investigate an identified exon inclusion event in the neuromuscular junction inducer Agrin in a stem cell-based model of ALS. I use a microfluidics co-culture system of Ns and myoblasts. Additionally, in the same system, I analyze the effects of exon exclusion as seen in ALS post mortem tissue.

Regional neuroinflammation in RA

P059 03/2020 - 08/2021

Dr. Patrick Süß, Department of Molecular Neurology

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Abstract

Rheumatoid arthritis (RA) is linked to neuropsychiatric comorbidity like depression due to inflammatory brain involvement. This project aims to investigate the influence of chronic peripheral inflammation on the blood brain-barrier and macrophages in different brain regions in an RA mouse model and human post mortem tissue. Thereby, local factors promoting inflammatory susceptibility or resilience may be identified as therapeutic targets for the CNS involvement in RA.

Assay of neuroinflammation in chronic pain

P63 09/2020 - 08/2021

Prof. Dr. Thomas Kinfe, Department of Neurosurgery

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Abstract

Clinical and animal studies implicate neuroinflammatory features (interleukines, chemokines, adipokines, oxytocin, alarmins) as part of the pathophysiology. BurstDR-SCS and DRG-SCS stimulation present a paradigm shift in current neurostimulation to address the treatment of CPSP-associated pain. Such molecular analysis may underpin the emerging role of CPSP-related molecular patterns as potential biomarkers to reliably reproduce spinal stimulation effects.

Direct reprogramming within brain organoids

P68 06/2020 - 05/2021

Prof. Dr. Marisa Karow, Institute of Biochemistry

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Abstract

We have shown that pericytes derived from the adult human brain can be reprogrammed into induced neurons (iNs) by overexpressing the transcription factors Ascl1 and Sox2. A major challenge to further assess functionality of iNs is posed by the lack of human model systems to study whether iNs adopt properties of human bona fide neurons. In the present proposal we therefore aim at assessing the impact of the cellular microenvironment provided by brain organoids on the reprogramming outcome.

Encoding of behaviours in the hypothalamus

P70 06/2021 - 06/2022

Prof. Dr. Alexey Ponomarenko, Institute of Physiology and Pathophysiology

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Abstract

Functional organisation of brain circuits supporting adaptive behaviours has informed development of novel therapeutic interventions. In this interdisciplinary proposal we will combine artificial intelligence approaches with innovative electrophysiological recordings in behaving mice to decipher neural representations of innate behaviours in the hypothalamus. The results will enable new insights into the function of a blueprint circuit for behavioural command.

Role of pericytes in intracerebral hemorrhage

P73 12 months

Dr. Maximilian Sprügel, Department of Neurology

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Abstract

Pericytes are small cells around brain capillaries and play a major role in maintenance of the blood brain barrier. In intracerebral hemorrhage (ICH), blood products induce complex processes leading to dysfunction of pericytes, impairment of the blood brain barrier and perihemorrhagic edema (PHE) formation. Aim of this study is to identify the blood metabolites triggering pericyte dysfunction to develop treatment strategies against PHE formation and to improve functional outcome of ICH patients.

NEUROSCIENCES

Molecular control of neural stem cell decisions

P074 01/2021 - 12/2021

Dr. Sven Falk, Institute of Biochemistry

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Abstract

During development a small starting population of neural stem cells (NSCs) give rise to all neurons and macroglia cells in the mature central nervous system. Hence, controlling NSC decisions is crucial for the accurate production of the right amount of the desired cell types at the right time and place. Here we aim at determining cellular features that allow a prospective identification of lineage choices and thus will facilitate to reveal the molecular logic of decision-taking processes.

MRI based diagnosis of Multiple System Atrophy

P076 12 months

Dr. Franz Marxreiter, Department of Molecular Neurology

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Abstract

Diagnosis of the rare neurodegenerative disease multisystem atrophy (MSA) is hampered by a lack of biomarkers. We could show that in an MSA mouse model, a myelin deficit can be visualized by quant. susceptibility mapping (QSM)on MRI. Our preliminary clinical data show similar results. The aim is now to comprehensively assess QSM imaging as a biomarker for the differential diagnosis of neurodegenerative diseases.

RENAL AND VASCULAR RESEARCH

Polyploid cardiomyocytes for cardiac repair

P041 09/2019 - 08/2020

Dr. Maria Leone, Department of Nephropathology (till 01.03.2020)

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Abstract

Humans are incapable to regenerate their heart. Cardiac injury results in cardiomyocyte loss due to hypoxia and a changed mechanical micro-environment. Here we propose to determine the potential of polyploid cardiomyocytes, the majority in the adult heart, to contribute to heart repair. We propose to clarify if polyploid cardiomyocytes can be induced to proliferate or whether diploid and polyploid cardiomyocytes differ in regards to stress resistance, cell size, and mechanical properties.

Vascular, renal parameters in living kidney donors

P050 01/2020 - 12/2020

Dr. Dennis Kannenkeril, Department of Medicine 4

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Abstract

In this study our goal is to analyze to what extend renal and vascular parameters correlate with histological kidney changes, especially in a population with eGFR rate of more than 60 mL/min/1.73 m². Our crossectional analysis focus on the association of abnormal vascular and renal parameters with histological renal changes. Our longitudinal analysis focus on the association of histological with renal and/or vascular parameters at baseline, with the renal outcome after kidney donation.

MSOT-imaging in spinal muscular atrophy

P055 10/2019 - 10/2020

Dr. Adrian Regensburger, Department of Pediatrics and Adolescent Medicine
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Abstract
New non-invasive imaging biomarkers for childhood muscular diseases are not yet established. Using multispectral optoacoustic tomography (MSOT), we were already able to detect collagen as a potential biomarker for disease progression monitoring of patients with Duchenne muscular dystrophy. In this experimentell study, we will investigate, which specific optoacoustic spectrum could serve as a biomarker in patients with spinal muscular atrophy.

Non-invasive Metabolic MR Fingerprinting

P072 12 months

Prof. Dr. Moritz Zaiss, Division of Neuroradiology
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Abstract
The scientific aim of this work is to further develop the metabolic chemical exchange saturation transer MR fingerprinting (CEST MRF) and to translate it from previous animal experiments to human MRI scanners at 3T and 7T. This will enable accelerated quantitative CEST imaging that forms a metabolic MR fingerprinting approach, which can then be evaluated for its potential clinical benefit for tumor diagnosis and stroke prognosis at University Clinic Erlangen.

Physicians' opinions on continuous sedation

P036 04/2019 - 03/2020

Dr. Maria Heckel, Division of Palliative Medicine
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Abstract
Physicians' practice and opinions regarding continuous sedation until death are to be collected internationally. The German subproject aims to gain a comprehensive overview of the opinions of German palliative physicians by online survey and to link them to their professional background and experiences. The crosscultural comparison might contribute to an internationally binding definition and a more uniform treatment practice.

Reception of hippocratic On the Sacred Disease

P069 10/2020 - 10/2021

PD Dr. Nadine Metzger, Institute of the History of Medicine and Medical Ethics
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Abstract
Since the early 20th century, the hippocratic treatise On the Sacred Disease is renowned for its rejection of supernatural causes of disease, thus establishing the `rational' core of the Western medical tradition. How did scholars and physicians of the 19th and 20th century perceive On the Sacred Disease and worked towards its continuous rise? A DFG project proposal is in preparation.

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