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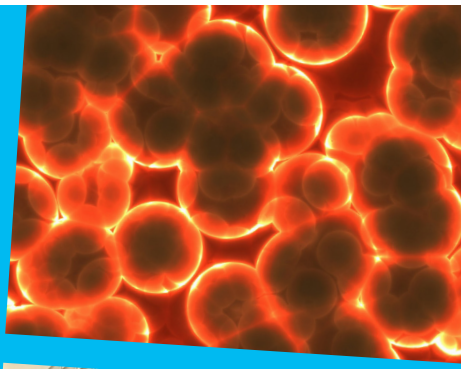
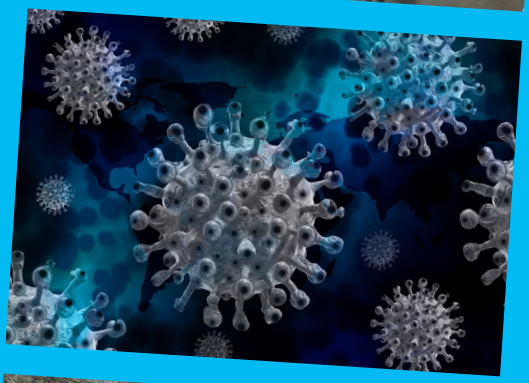
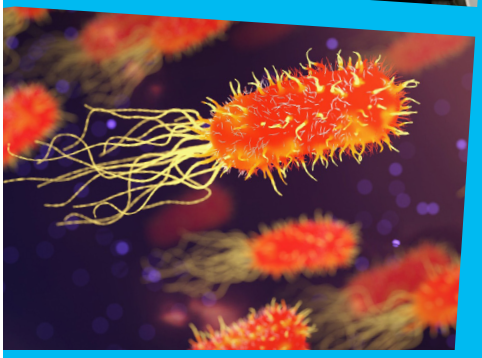
Universitätsklinikum
Erlangen

IZKF Erlangen 2021





interdisciplinary
Center for
Clinical Research

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EDITORIAL

Dear Friends and Members of the IZKF,

Dear Readers,

Please find on the following pages the Annual Report 2021 with an overview of the activities, recent developments and funded projects of the IZKF Erlangen. This publication complements the IZKF newsletter that has been released last year for the first time and from now on provides up-to-date information twice a year on various topics such as the 8 newly selected junior projects in 2021, current program calls or adjustments to our funding schemes and application guidelines. All information is also available on our homepage: www.izkf.med.fau.de.

Last year was still very much affected by the SARS-CoV-2 pandemic. Many meetings and congresses continued to take place as online events, including our own retreat of the IZKF Research Training Group. Fortunately, the 1st Clinician Scientist retreat and the IZKF postgraduate workshop could be held in person. At the workshop, the IZFK Publication Award was awarded to Dr. Kaveh Roshanbinfar from the Department of Nephropathology for his work on „Nanofibrous Composite with Tailorable Electrical and Mechanical Properties for Cardiac Tissue Engineering“.

In 2021, Dr. Paolo Ceppi has shut down his Junior Research Group after 6 successful years in Erlangen to continue his research as Professor at to the University of Southern Denmark in Odense/Denmark. We wish Prof. Ceppi every success for his future career.

On another note, Prof. Dr. Dimitrios Mougiakakos has accepted the chair of Hematology, Oncology and Stem Cell Transplantation at the University Magdeburg. As a consequence, he has retired from the IZKF Management Board and the Clinician Scientist Program (CSP) committee. Prof. Waldner was appointed as successor for the CSP committee. We thank Prof. Mougiakakos for his longtime commitment and warmly welcome Prof. Waldner.

As per IZKF statutes, most members of the Junior Scientist Committee had to be replaced in 2021. A big thank goes to to Prof. Dr. David Dulin, Prof. Dr. Felix Engel, Colin Griesbach, Dr. Christiane Krystelle Nganou Makamdop, Tatjana Seitz and Prof. Dr. Katharina Zimmermann for their participation over the last years and to Prof. Dr. Diana Dudziak, Prof. Dr. Claudia Günther, Prof. Dr. Chichung Lie, Dr. Adrian Regensburger as well as Sebastian Gehlen-Breitbach and Myriam Jeninga for their willingness to serve as newly appointed members on the Junior Scientist Committee.

The year 2021 has also seen our first graduates from the Clinician Scientist Program. Our congratulations go to PD Dr. Ferdinand Knieling (Department of Pediatrics and Adolescent Medicine), Prof. Dr. Andreas Kremer (Department of Medicine 1) and PD Dr. Franz Marxreiter (Department of Molecular Neurology).

Currently, we are preparing for the biennial IZKF symposium from June 09 - 11, 2022. We are hopeful that the event after its postponement by one year can take place in Kloster Banz in the same format as in previous years.

In 2022, the activities of the IZKF will once again be reviewed by the external scientific advisory board during its on-site visit on November 21 and 22. At this date, the scientific advisory board will also select a new set of Advanced Projects from the applications that succeeded in the internal colloquium and ensuing screening process on July 18 and 19.

As always, kudos to the IZKF Administrative Office for their unfailing support and commitment. Thank you very much for your interest in the IZKF. Enjoy the read!

Prof. Dr. Michael Wegner
Chairman

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IMPRINT

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 started in 2021

21 Junior Projects

10 Immunology and Infection
2 Oncology
4 Neurosciences
2 Renal and Vascular Research
2 Medical Engineering
1 Others
thereof **8** projects completed in 2021

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

34 Institutions with running projects 2021

5,308 K€ total expenditures in 2021

405 Members of Life@FAU 2021

31 SFB 1181
2 SFB 1350
29 GRK 2162
10 GRK 1962
21 GRK 2504
12 GRK 1660
5 TRR 130
11 TRR 221
17 TRR 241
11 TRR 225
2 TRR 305
214 IZKF
109 Dr. med.
105 Dr. rer. nat./ Dr. rer. biol. hum.
39 participants outside RTG

42 Pilot Projects

23 Newly granted in 2021
19 Projects completed in 2021

64 Ongoing Scientific Theses in 2021

9 Master theses
51 Doctoral theses
4 Habilitations

40 Publications

Cumulative Impact Factor **290.835**
Average Impact Factor per publication **7.270**
Average publications per project **0,7***
4 publication with an IF more than 10

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

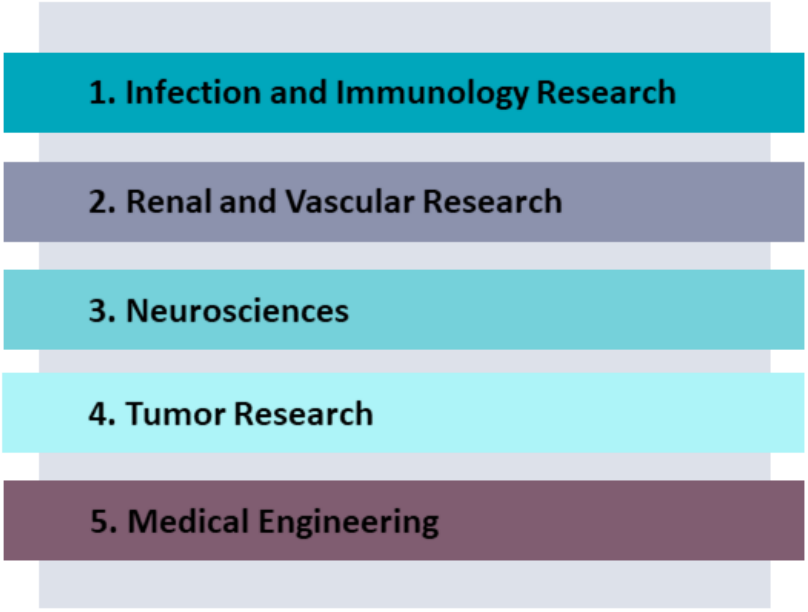
130 Employees of the IZKF

66 Doctoral fellows, Post-Docs and laboratory rotations
64 Non-scientists

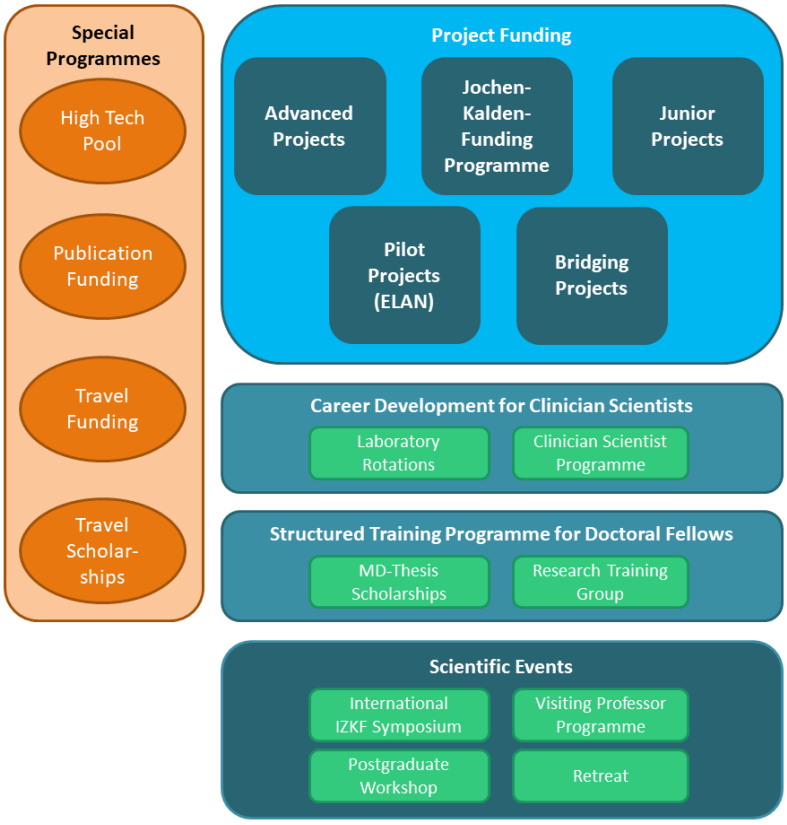
PROGRAMMES

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 project numbers.

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. The successful participation of doctoral fellows funded in Advanced Projects will also be included as a further criterion for a project extension. 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 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 35,000 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

Jochen-Kalden-Funding Programme

In honor of the founder and former IZKF chairman the Junior Research Groups have been renamed as the Jochen-Kalden-Funding Programme.

The junior research groups represent a central funding instrument of the IZKF. As the group of Prof. Dr. Ceppi (Junior Research Group 1) expired in mid-2021 and Prof. Dr. Dulin (Junior Research Group 2) will end in 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), based on the application deadline for professorship 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. The successful participation of doctoral fellows funded in Junior Projects will also be included as a further criterion for the additional spending period.

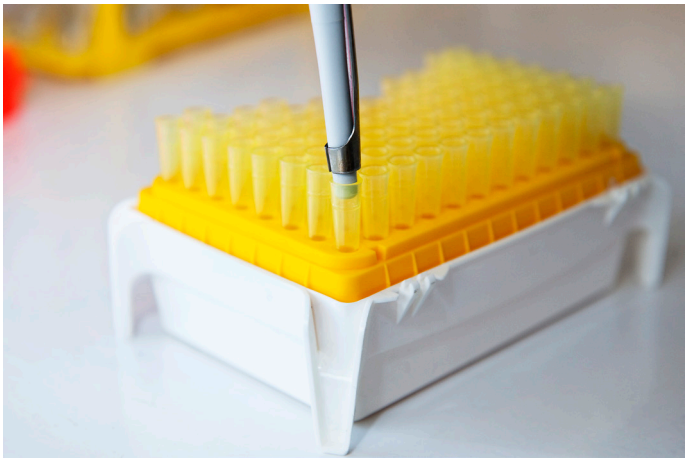
Junior projects are subject to a one-stage internal review only. Full proposals are reviewed by the Management Board, members of the ELAN-Commission and Junior Scientists Committee based on a written proposal and public presentation. Decisions are reached after internal deliberation and are then communicated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

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

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.

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 for a period of up to 12 months. In addition, newly appointed professors can submit their application regardless of age. If a funding application is submitted to an external funding agency within the project period, a bonus will be granted.



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 15,000
Others	Participation in Travel, Publication and High Tech Pool IZKF laboratory rotations for physicians
Duration	max. 12 months

The bonus comprises one third of the amount approved, up to a maximum of €20,000. The funds are to be spent within 6 months of the end of the project.

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.

From now on, the IZKF Administrative Office will be responsible for coordinating and supervising pilot projects.

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.

There is currently discussion about including the bridging projects as an integral part of the pilot projects.

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

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 physicians can apply for the Module Step 2 (former advanced module) 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 Module Step 2	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.

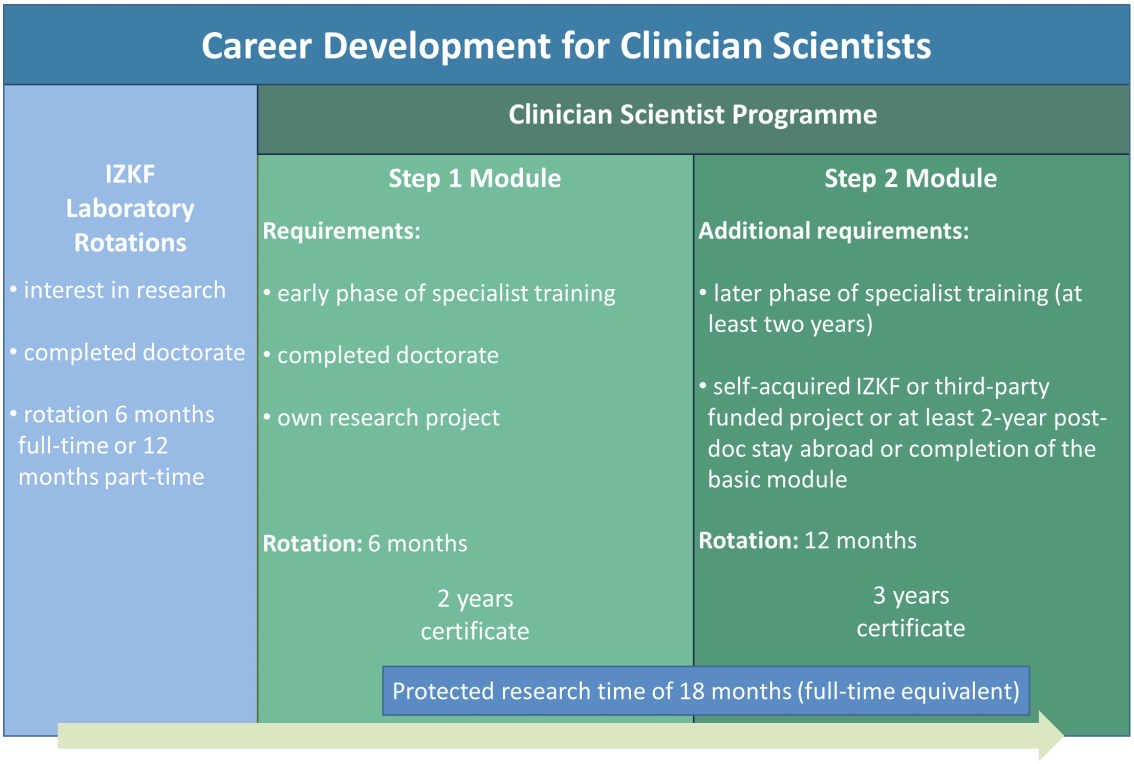
The aim of the CSP is to establish a new career path and promotion for Clinician Scientists and to create a structured scientific qualification programme for physicians performing clinical research. The focus is also on strengthening translational research by creating time for scientific work and the 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 Step 1 (former basic) and a Step 2 (former advanced module). Since a BMBF-financed Advanced Clinician Scientist program was acquired at the site, the two modules were renamed. The Step 1 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 Step 2 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 step 2 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 Step 1 module. The leave of absence is 12 months full-time or equivalent part-time via rotation positions. In order to obtain the certificate for the Step 2 module, a leave of absence of a total of 18 months is mandatory, even if the Step 2 was started directly. The department must agree to an additional 6 months of release, unless the IZKF (laboratory rotation or Step 1) or other funders have provided funding. The maximum laboratory rotations financed by the IZKF over the entire scientific career is limited to 18 months.

An early change from the Step 1 to the Step 2 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 Step 2 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 (Step 2 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 the 12 months after start of the fellowship. 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 five research areas: Jour Fixe Ink (Immunology/infection/renal and vascular research), Jour Fixe Neuro (Neuroscience), Jour Fixe Onko (Oncology), Jour Fixe DigIT (Digital information technology) and the Jour Fixe MedTech (Medical and healthcare 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.

The High Tech Pool is also available to active participants of the CSP Step 2 Module

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 finacial 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.

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 young scientists 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.

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.

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

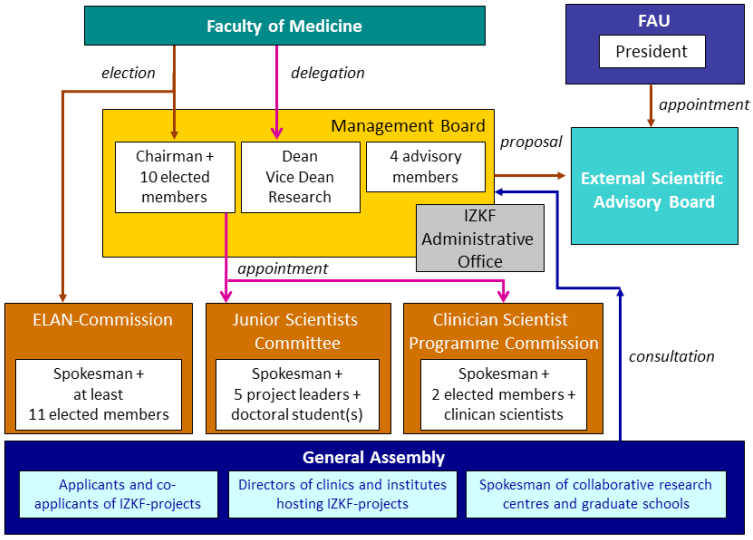
	High Tech Pool	Travel Pool	Publication Pool	Travel Scholarships
Advanced Projects (Project leaders and scientific staff financed by project)	✓	✓	✓	✓ (only for doctoral students)
Junior Projects (Project leaders and scientific staff financed by project)	✓	✓	✓	✓
Pilot Projects (Project leaders and scientific staff financed by project)	✗	✓	✓	✓
Bridging Projects	✗	✗	✗	✗
Jochen-Kalden Funding Programm **(former Junior Research Groups)** (Project leaders and scientific staff financed by project)	✓	✓	✓	✓ (only for doctoral students)
Clinician Scientists Programme (active members)	✓ (only for Step 2)	✓	✓	✓
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	only within 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, Department of Animal Physiology
Prof. Dr. Dr. Raymund Horch, Department of Plastic and Hand Surgery
Prof. Dr. Dimitrios Mougiakakos, Department of Medicine 5 (until 09/2021)
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, Department 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. 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

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

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

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

Prof. Dr. Olaf Rieß, University of Tübingen - Institute of Human Genetics (until 08/2021)

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

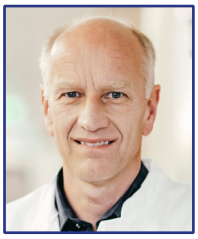
Prof. Dr. Reiner Siebert, University Hospital Ulm, Institute of Human Genetics

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


Prof. Dr. Busch


Prof. Dr. Dittmer


Prof. Dr. Kalinke


Prof. Dr. Kamradt


Prof. Dr. Katschinski


Prof. Dr. Mertens


Prof. Dr. Moch


Prof. Dr. Prinz


Prof. Dr. Schulz


Prof. Dr. Siebert


Prof. Dr. Sorokin


Prof. Dr. Tiegs


Prof. Dr. Winklhofer

External Scientific Advisory Board
(as of 31st December 2021)

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. Diana Dudziak, Department of Dermatology (since 10/2021)
Sebastian Gehlen-Breitbach, Institute of Biochemistry (since 10/2021)
Prof. Dr. Claudia Günther, Department of Medicine 1 (since 10/2021)
Myriam Jeninga, Institute of Clinical Microbiology, Immunology and Hygiene (since 10/2021)
Prof. Dr. Chichung Lie, Institute of Biochemistry (since 10/2021)
Prof. Dr. Janina Müller-Deile, Department of Medicine 4
Dr. Adrian Regensburger, Department of Pediatrics and Adolescent Medicine (since 10/2021)

Prof. Dr. David Dulin, IZKF Junior Research Group 2 (until 09/2021)
Prof. Dr. Felix Engel, Department of Nephropathology (until 09/2021)
Colin Griesbach, Department of Medical Informatics, Biometry and Epidemiology (until 09/2021)
Dr. Christiane Krystelle Nganou Makamdop, Institute of Clinical and Molecular Virology (until 09/2021)
Tatjana Seitz, Institute of Biochemistry (until 09/2021)
Prof. Dr. Katharina Zimmermann, Department of Anaesthesiology (until 09/2021)

Prof. Dr. Dudziak

Gehlen-Breitbach

Prof. Dr. Günther

Jeninga

Prof. Dr. Lie

Prof. Dr. Müller-Deile

Dr. Regensburger

Current members of the Junior Scientists Committee

Clinician Scientist Programme Commission

Spokesman for Clinician Scientist Programme

Prof. Dr. Jürgen Winkler, Department of Molecular Neurology

Prof. Dr. Winkler

Members

Prof. Dr. Carola Berking, Department of Dermatology

Dr. Markus Eckstein, Institute of Pathology (since 06/2021)

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

Prof. Dr. Maximilian Waldner, Department of Medicine 1 (since 10/2021)

Dr. Ferdinand Knieling, Department of Pediatric and Adolescent Medicine (until 06/2021)

Prof. Dr. Dimitrios Mougiakakos, Department of Medicine 5 (until 09/2021)

Prof. Dr. Berking

Dr. Eckstein

Dr. Maier

Dr. Waldner

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 2021 were financed from residual funds of the previous years.

Revenues	
Support of the Medical Faculty	5,346 K€
Support of the University	364 K€
Other revenues	39 k€
Total revenues 2021	**5,749 K€**

Expenditures	
Advanced projects	2,059 K€
Pilot projects	693 K€
Career development	2,233 K€
thereof junior research groups	580 K€
thereof junior projects	962 K€
thereof laboratory rotations	400 K€
thereof clinician scientist programme	10 K€
thereof MD-thesis scholarships	250 K€
thereof research training groups	31 K€
Central projects	53 K€
Administration	270 K€
Total expenditures 2021	**5,308 K€**

Revenues and expenditures 2021

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 103 scientific projects were actively running: 31 advanced projects, 18 junior projects, 48 pilot projects and 6 junior research groups. In addition, 8 junior projects started their work in 2021 (4) or in the beginning of 2022 (4).

31 advanced, 18 junior projects and 6 junior research groups published 40 original articles in 2021 resulting in an average of 0.7 publications per project. The cumulative impact factor (IF) was 290.835, averaging 7.270 per publication. 4 publications have an IF of more than 10. 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, 51 doctoral theses and 4 habilitations that were in progress or finalised in 2021. Two professorships to IZKF project leaders were offered. A total of 70 project leaders and 44 employed scientists (PhDs and Post-Docs) are involved in 55 scientific projects (running advanced projects, junior research groups and junior projects 2021) 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.

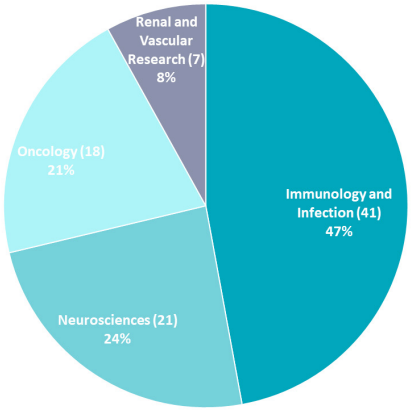
The following table shows all institutions with a running Advanced, Junior or Pilot Project in 2021 and their association to the main research areas of the Faculty. In addition, it can be seen which institution was funded with rotation positions (without assignment to a research area):

Institute	Advanced Projects	Junior Projects	Pilot Projects	Laboratory Rotation
Chair of Anatomy II			S	
Chair of Clinical Pharmacology and Clinical Toxicology			I	
Chair of Experimental Medicine II	O		S	
Department of Dermatology	I			
Department of Immune Modulation	I		I	
Department of Medical Informatics, Biometry and Epidemiology		S		
Department of Medicine 1	I, O	I, O	I, O	X
Department of Medicine 3	I, O	I	I	X
Department of Medicine 4	O, R	R		X
Department of Medicine 5	O	I, O	O	X
Department of Molecular Neurology	N	N	N	X
Department of Molecular Pneumology	I			
Department of Nephropathology	I, R		M	
Department of Neurology			N	X
Department of Neurosurgery			N	
Department of Obstetrics and Gynecology	O		O, S	
Department of Oral and Cranio-Maxillofacial Surgery			I, S	
Department of Orthodontics and Orofacial Orthopedics	N		I	X
Department of Pediatrics and Adolescent Medicine	O	M	M , S	X
Department of Plastic and Hand Surgery			I, S	
Department of Psychiatry and Psychotherapy		N, S	I	X
Department of Psychosomatic Medicine and Psychotherapy			S	
Department of Stem Cell Biology	N	N	N	X
Department of Surgery	O		I, R	
Institute of Biochemistry	I, N, O	N	N, O, M	
Institute of Cellular and Molecular Physiology	R			
Institute of Clinical and Molecular Virology	I	I	S	
Institute of Clinical Microbiology, Immunology and Hygiene	I	I	I	
Institute of Human Genetics	I, N			
Institute of Neuropathology		M		
Institute of Pathology	O		S	X
Institute of Physiology and Pathophysiology			N	
Institute of Radiology			I	
Institute of the History of Medicine and Medical Ethics			S	

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.

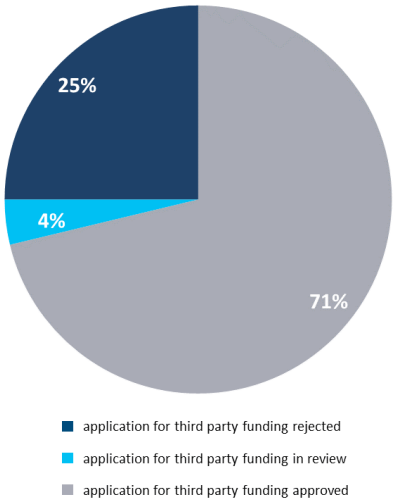


Distribution of advanced projects as per main research area between 2013 and 2021

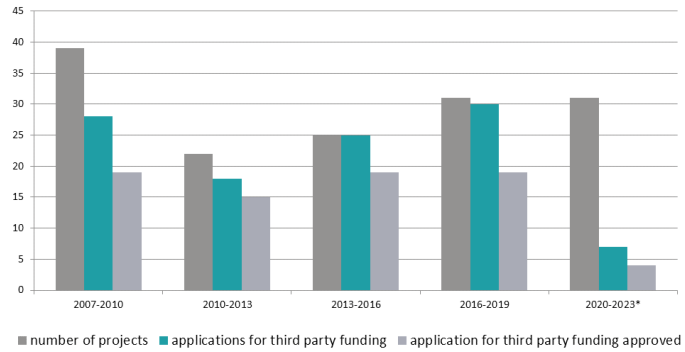
The projects started with the filling of the approved positions or with the first disposition. Due to the current pandemic, the projects had the possibility to start at the latest by January, 1 2021. Tandem projects have the option of filling their positions time shifted and thus do not lose any approved 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. From the current cohort (2020-2023), 7 (23%) of the 31 projects have already successfully applied for an extension.

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, 20 (27%) were not funded.

If you take a look at the projects currently running, you can see that 4 (57%) of the 7 projects, which applied for external grants, already received funding approvals.

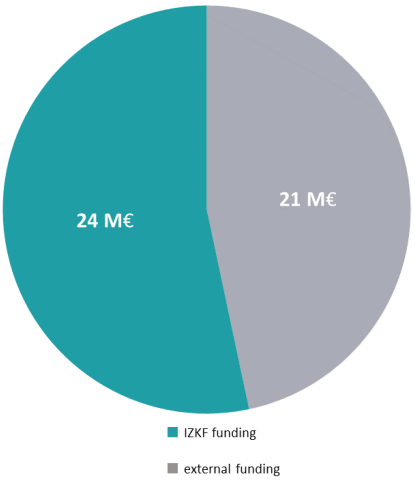


Approved applications for third-party funding of advanced projects between 2010 and 2021

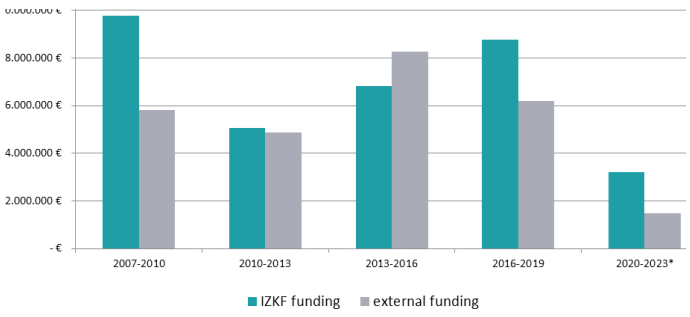


This column graph compares the number of advanced projects with the number of the submitted and approved applications for external funding in each funding period.

* Current funding period. Further applications to external third-party agencies are planned.



External funding received from advanced projects between 2010 and 2021



External funding received from advanced projects between 2007 and 2021

* Current funding period. Further applications to external third-party agencies are planned.

Junior Research Groups

Jochen-Kalden-Funding Programme

In 2021 there were 6 junior research groups running.

The junior research group of Prof. Dr. Ceppi (N1) run out in July 2022 and was placed in the Nikolaus Fiebiger Center for Molecular Medicine. 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 continued to run his junior research group in Erlangen. We wish Mr. Ceppi continued success with his research and thank him for his commitment.

Prof. Dr. Dulin started his new position as an Assistant Professor at VU Amsterdam (Netherlands) in January 2021, currently on a part-time basis until his junior research group in Erlangen will expire in September 2022. His junior research group N2 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.

In 2020, the concept for junior research group funding had been revised. The first call for proposals in autumn 2020 resulted in 4 new groups in the Jochen Kalden funding program. In the first round of applications, Prof. Claudia Günther, Prof. Dr. Janina Müller-Deile, Prof. Dr. Marisa Karow and Prof. Dr. Friederike Zunke succeeded. Three of the groups took over Prof. Ceppi's laboratories in the Nikolaus Fiebiger Center with its attractive scientific environment and diverse activities.

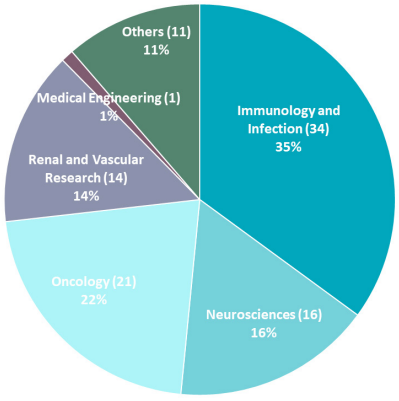
The last call for proposals for the Jochen-Kalden-Funding Programme was published on October 19, 2021. No applications were received, as applicants did not meet the requirements. However, in 2020, twice as many projects as planned were included in the Jochen Kalden funding program. In addition, numerous new appointments are currently being prepared.

Junior Projects

The first call for junior projects was in 2009. Proposals are accepted every year. Overall 97 junior projects were selected for funding between 2009 and 2021. In this period, 38 (39%) physicians received funding and 59 (61%) scientists. 25 (66%) of the physicians requested a laboratory rotation, thereof 7 (28%) were women and 18 (78%) men. Over the entire funding period, men and women were almost equally supported:

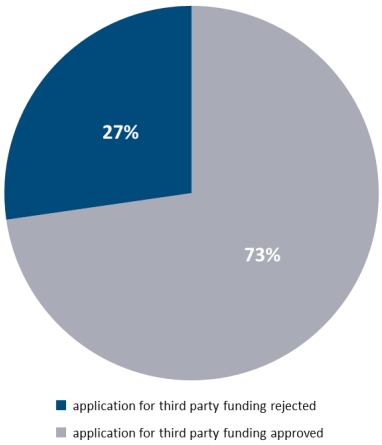
47 successful applicants were women and 50 men. The median age was 32 at the time of application, for both women and men. All main research areas of the Faculty are represented with immunology and infection (35%) and oncology (22%) being the most successful over the years. Overall candidates from 25 different institutions within the Faculty of Medicine were successful.

In 2021, 17 proposals were reviewed and 8 (47%) of them were selected for funding. The approved projects cover the main research areas neurosciences, oncology as well as immunology and infection. The successful applicants work in 6 different institutions within the Faculty of Medicine. In total, 2 (25%) are physicians and 6 (75%) are scientists; 3 (38%) of the successful applicants are men and 5 (62%) are women. The median age was 31 years.

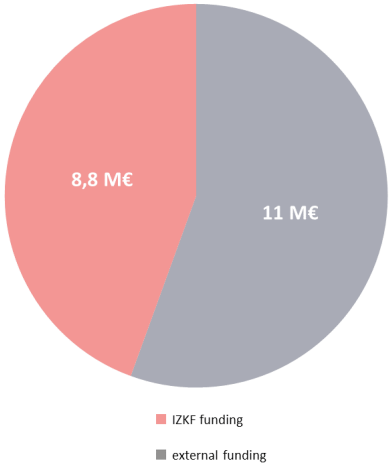


Distribution of junior projects as per main research area of the Faculty of Medicine between 2009 and 2021

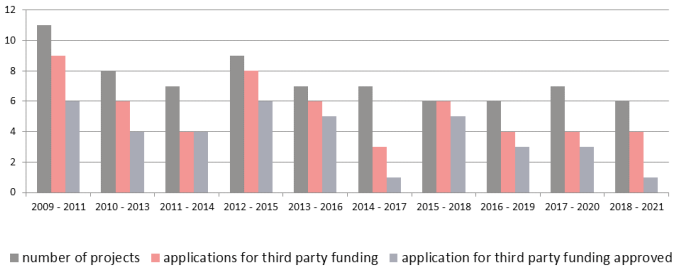
The Junior Projects also perform very well in raising third-party funding. 74% from the projects that started between 2009 and 2018 applied for third-party funding to an external funding agency. This development has been stable over the entire duration of the programme.



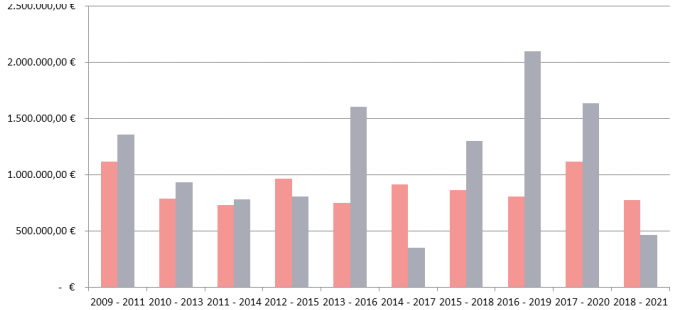
Approved applications for third-party funding of junior projects (projects initiated between 2009 and 2018)



External funding received from junior projects between 2010 and 2021



Success-rate of junior projects initiated between 2009-2018



External funding received from junior projects between 2007 and 2021

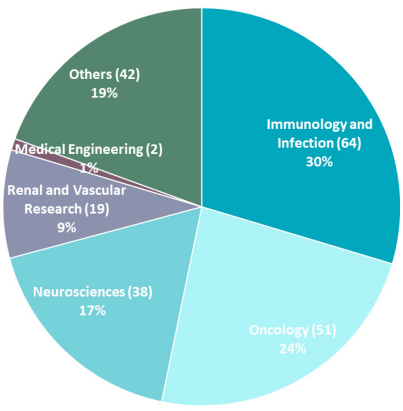
Pilot Projects (ELAN)

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

In the reporting period of 2021, 23 proposals were assessed during the meetings of the ELAN-Commission, an internal reviewer was assigned to 32 projects. Of the 23 proposals evaluated in the meetings, 100% received funding. One application was cancelled before meeting of the commission. The approved projects cover nearly all the main research areas of the Faculty of Medicine: immunology and infection 11, oncology 4, renal and vascular research 2, neurosciences 1, medical engineering 1 and 4 without an allocation to a research area. In 2021, applicants were from 17 different institutions. In total, 9 (39%) of the successful applicants were men and 14 (61%) women. The median age was 33, 34 for men and 33 for women.

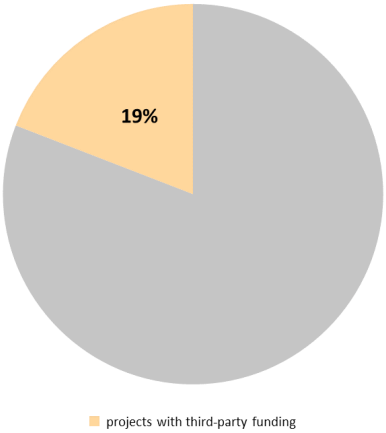
Applications for pilot projects can be submitted at any time. Since 2012 an electronic application using the ELAN-Tool is expected. The ELAN-Commission meets 4-5 times a year and selects projects for funding. The evaluation procedure includes external expertise. Between 2012 and 2021 a total of 332 proposals for pilot projects were reviewed by the ELAN-Commission. Overall, 239 (72%) projects were granted for funding. Between 2012 and 2021 in total 110 women (46%) and 129 men (54%) applied successfully for pilot projects. The median age was 34 years.

All main research areas of the Faculty are represented; with immunology and infection (31%) and oncology (23%) being the most successful over the years.

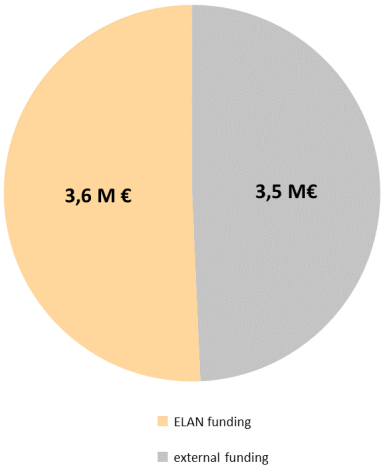


Distribution of pilot projects as per main research area between 2012 and 2021

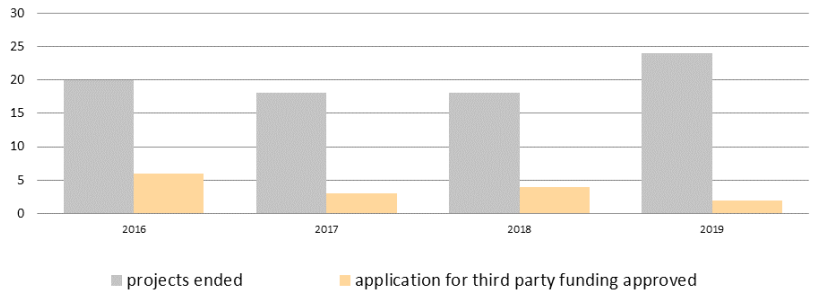
In the following, the success rate of acquiring third-party funding is shown graphically.



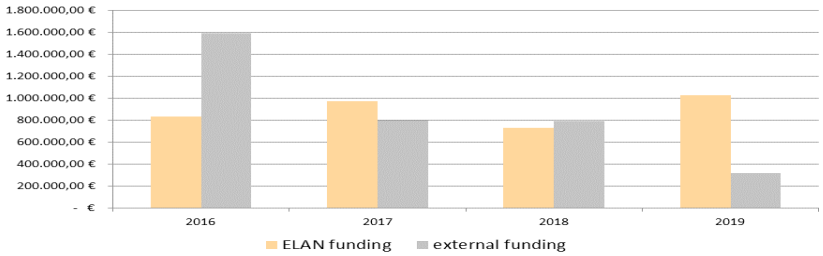
Pilot projects with third-party funding (completed projects with approval years between 2016 and 2019)



External funding received from all completed pilot projects (year of approval between 2016 and 2019)



Success-rate of pilot projects. Further applications of projects, initiated in 2019, are planned.



External funding from completed pilot projects started between 2016 and 2019

Laboratory Rotations

In 2021, 10 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 Module Step 1 of the Clinician Scientist Programme.

Rotations

- 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. Miriam Düll, Department of Medicine 1, 01/2021-12/2021, 50%

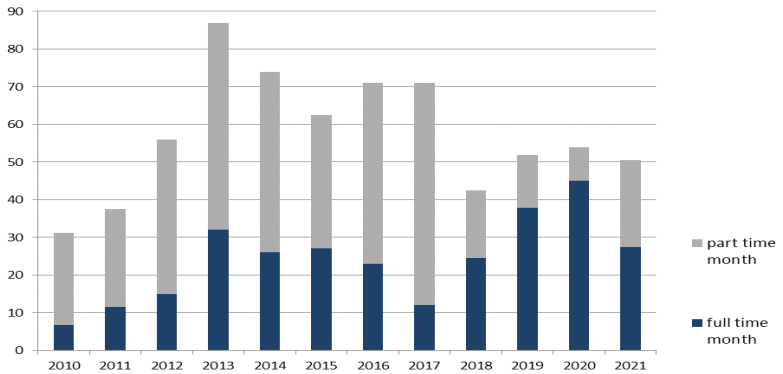
Rotations of Junior Project Leaders

- 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%

Rotations of Clinician Scientists

- Dr. Christina Bergmann, Department of Medicine 3, 01/2021-12/2021, 100%
- Dr. Markus Eckstein, Institute of Pathology, 07/2020-06/2022, 50%
- PD Dr. Ramona Erber, Institute of Pathology, 12/2020-11/2021, 100%
- Dr. Martin Regensburger, Department of Stem Cell Biology, 08/2020-12/2021, 50%

Laboratory rotations 2021 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 31 physicians took part in the CSP. With the same deadline as for the junior projects, a rotation position within in the CSP (Module Step 2) can be applied for on an annual basis.

The deadline for the submission of applications was March 15, 2021. Two applications were submitted. The interviews with the applicants took place on May 17. Unfortunately, the applicants in the Clinician Scientist programme did not receive any funding.

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 2021:

Module Step 1

- Dr. Razvan Marius Brazdis, Department of Psychiatry and Psychotherapy (S)
- Dr. Miriam Düll, Department of Medicine 1 (S)
- Dr. Marwin Gröner, Department of Medicine 4 (S, C)
- Dr. Alina Hilger, Department of Pediatrics and Adolescent Medicine (S)
- Dr. Benedikt Jacobs, Department of Medicine 5 (S)
- Dr. Eva Maier, Department of Operative Dentistry and Periodontology
- Dr. Harriet Morf, Department of Medicine 3
- Dr. Stephanie Naas, Department of Medicine 4 (C)
- Dr. Maria Gabriella Raimondo, Department of Medicine 3
- Dr. Christina Regensburger, Department of Pediatrics and Adolescent Medicine (RECORD)
- Dr. Jan Schaefer, Department of Pediatrics and Adolescent Medicine (S)
- Dr. Alexander Schnell, Department of Pediatrics and Adolescent Medicine (S)
- Dr. Andrej Stoll, Department of Medicine 5
- Dr. Raluca Ursu, Department of Medicine 4 (RECORD)
- Dr. Lisette Warkentin, Institute of General Practice (S)
- Dr. Alexander Zorob, Department of Medicine 4 (RECORD)

Module Step 2

- Dr. Christina Bergmann, Department of Medicine 3
- Dr. Markus Eckstein, Institute of Pathology
- PD 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
- PD Dr. Ferdinand Knieling, Department of Pediatrics and Adolescent Medicine (C)
- PD Dr. Andreas E. Kremer, Department of Medicine 1 (C)
- PD Dr. Franz Marxreiter, Division of Molecular Neurology (C)
- Dr. Adrian Regensburger, Department of Pediatrics and Adolescent Medicine
- Dr. Martin Regensburger, Department of Stem Cell Biology
- PD Dr. David Simon, Department of Medicine 3
- Prof. Dr. Stefan Uderhardt, Department of Medicine 3 (C)
- Dr. Patrick Süß, Division of Molecular Neurology
- PD Dr. Sebastian Zundler, Department of Medicine 1 (C)

Participants CSP 2021

(S) started in 2021

(C) completed in 2021

13 participants of the CSP went to Waischenfeld on the 18th of June 2021. They met for their first retreat at the Fraunhofer Forschungscampus. The two CSP speakers, Dr. Eva Maier and Dr. Ferdinand Knieling, were able to organize a programme with excellent guest speakers. The programme of the retreat was complemented with presentations by the CSP participants. A team event held at the end of the retreat provided ample opportunities for networking.

Lecture Hall CSP-Retreat 2021

We are very pleased to have our first CSP-graduates. PD Dr. Ferdinand Knieling is the first participant who completed the Clinician Scientist Programme. He is a physician from the Department of Pediatrics and Adolescent Medicine and enrolled in the CSP since July 2018 (Advanced Module, Step 2). As the programme's speaker and member of the CSP commission, he was committed to the interests of all programme participants. At the CSP retreat, Prof. Winkler, head of the CSP commission, presented him with his certificate. Besides PD Dr. Knieling, three additional graduates Prof. Dr. Andreas Kremer (Department of Medicine 1), PD Dr. Franz Marxreiter (Department of Molecular Neurology) and PD Dr. Sebastian Zundler (Department of Medicine 1) successfully graduated the CSP Step 2 Module in 2021. Dr. Stephanie Naas (Department of Medicine 4) was the first participant to successfully complete Module Step 1. We warmly congratulate all our graduates on their successful participation! Dr. Markus Eckstein was appointed as successor of PD Dr. Knieling and represents all participants in the committee.

First CSP-graduate PD Dr. Ferdinand Knieling (right) with Prof. Dr. Jürgen Winkler (left)

Course	Lecturer
Meet the expert – series "Aufbau einer GMP-Einheit"	Dr. Michael Aigner (Department of Medicine 5)
Kommunikation und Rhetorik	Gerhard Kranz (external)
Good Scientific Practice	Dr. Anne Hamker (external)
Grant Proposal Writing	Dr. Sabine Preusse (external)

Courses given in 2021 for participants of the CSP

Life@FAU as structured training programme for doctoral fellows

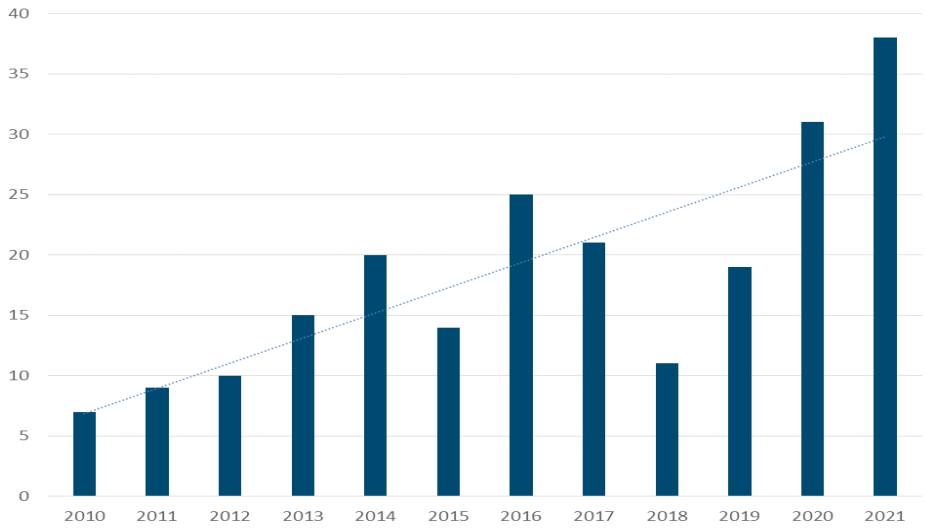
In 2021, the number of doctoral fellows participating in Life@FAU increased significantly compared to the previous year. In 2020, 353 doctoral fellows took part, in the reporting year there were already 405. The doctoral fellows are distributed among the participating networks as follows:

Programme/ Research Training Group	Registered participants	thereof Dr. rer. nat. and others	thereof Dr. med. / dent.
SFB 1181	31	22	9
SFB 1350	2	2	0
GRK 2162	29	18	11
GRK 2504	21	17	4
GRK 2599	1	1	0
TRR 221	11	8	3
TRR 241	17	9	8
TRR 225	11	11	0
TRR 305	2	2	0
IZKF	27	27	0
IZKF associated	78	68	10
IZKF MD	109	0	109
no connection to RTG	39	36	3
Ongoing	378	221	157
GRK 1962	**10**	**10**	**0**
GRK 1660	**12**	**6**	**6**
TRR 130	**5**	**5**	**0**
Expired	**27**	**21**	**6**
total	**405**	**242**	**163**

Research Training Groups participating in Life@FAU, indicating the number of participants as of 31st December 2021

MD-Thesis Scholarships

In 2021, a total of 59 medical doctoral students from 24 institutions were funded. Due to the fact that some scholarships granted in 2020 ended in 2021, the number of funded doctoral students is higher than the number of scholarships available. Overall, 41 applications for the MD-Thesis scholarship programme have been received in 2021. The Junior Scientists Committee approved 38 applications (93%), 22 (58%) of the successful applicants were females and 16 (42%) males. The median age was 24 years. Two scholarships were canceled or not completed. Since its inception in 2007, the IZKF supported a total of 262 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 2021, 82 (31%) students had already completed their doctoral thesis. Interestingly, 27 students (33%) 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 31/12/2021

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 2021.

Department of Medicine 1

- Besendorf, Laura (03/2021 - 10/2021)
- Dorner, Heidrun (08/2021 - 03/2022)
- Kaminski, Sophie (02/2021 - 09/2021)
- Knittel, Selina (12/2020 - 07/2021)
- Leikam, Stefanie (05/2021 - 12/2021)
- Leupold, Jannik (05/2021 - 12/2021)
- Lucius, Helena (03/2021 - 10/2021)
- Rhode, Louis (12/2020 - 07/2021)
- Appel, Majken (10/2020 - 05/2021)

Department of Medicine 3

- Bierling, Theresa (12/2020 - 07/2021)
- Gimpel, Anna (10/2020 - 05/2021)
- Hendel, Anna (11/2021 - 06/2022)

Department of Molecular Neurology

- Färber, Franziska (12/2021 - 07/2022)
- Gauer, Carina (02/2021 - 10/2021)
- Schmitt, Verena (05/2021 - 12/2021)
- Seisenberger, Juliana (12/2021 - 07/2022)
- Weiß, Alexander (12/2021 - 07/2022)

Department of Nephropathology

- Bleich, Erik (05/2021 - 12/2021)
- Daume, Luisa (12/2020 - 07/2021)
- Kösters, Peter (08/2021 - 03/2022)

Department of Paediatrics and Adolescent Medicine

- Paulus, Lars-Philip (02/2021 - 09/2021)
- Schielein, Sophie (09/2021 - 04/2022)
- Seiser, Esra (12/2021 - 07/2022)

Department of Psychiatry and Psychotherapy

- Höke, Cathleen (12/2020 - 07/2021)
- Neurath, Nicole (12/2021 - 07/2022)
- Wicht, Simon (12/2021 - 07/2022)

Department of Radiation Oncology

- Alomo, Jannik (04/2021 - 11/2021)
- Gehre, Simon (04/2021 - 11/2021)
- Siegert, Juliane (12/2021 - 07/2022)

Institute of Biochemistry

- Peschl, Vanessa (02/2021 - 09/2021)
- Weigel, Johannes (09/2020 - 04/2021)
- Lampersberger, Hanna (12/2021 - 07/2022)

Department of Surgery

- Hansen, Frederik (/03/2021 - 10/2021)
- König, Clara Maria (12/2021 - 07/2022)
- Stehr, Antonia (09/2020 - 04/2021)

Institute of Microbiology

- Blaha, Niklas (08/2020 - 03/2021)
- Hustadt, Samuel (10/2021 - 05/2022)
- John, Dominik (09/2020 - 04/2021)
- Röger, Ole (08/2020 - 03/2021)

Institute of Physiology and Pathophysiology

- Bülow, Nicolas (11/2021 - 30/06/2022
- Möhwald, Alexander (12/2021 - 07/2022)
- Stockinger, Florian (02/2021 - 09/2021)
- Stürzenberger, Sophia (12/2020 - 07/2021)

Others

- Albrecht, Leonie, Department of Dermatology (12/2020 - 07/2021)
- Fröba, Maria, Institute of Clinical and Molecular Virology (09/2020 - 04/2021)
- Gehring, Annemarie, Institute of Pathology (05/2021 - 12/2021)
- Grottker, Fridolin, Institute of Radiology (05/2021 - 12/2021)
- Grundler, Magdalena, Institute of Clinical Microbiology, Immunology and Hygiene (12/2020 - 07/2021)
- Holtzhausen, Christian, Institute of Neuropathology (12/2020 - 07/2021)
- Kutz, Chiara, Department of Plastic and Hand Surgery (10/2020 - 05/2021)
- Leupold, Lukas, Department of Stem Cell Biology (08/2021 - 03/2022)
- Lippler, Susanne, Department of Medicine 4 (08/2021 - 03/2022)
- Mitländer, Hannah, Department of Molecular Pneumology (02/2021 - 09/2021)
- Prechtel, Philipp, Institute of Pathology (08/2020 - 03/2021)
- Sankina, Polina, Department of Anesthesiology (08/2021 - 03/2022)
- Schomburg, Simon, Chair of Functional and Clinical Anatomy (08/2021 - 03/2022)
- Theil, Frank, Department of Paediatric Cardiac Surgery (02/2021 - 09/2021)
- Weinhold, Claire, Department of Plastic and Hand Surgery (08/2021 - 03/2022)
- Wopperer, Florian, Department of Medicine 4 (12/2020 - 07/2021)

Training courses in the IZKF

The IZKF Research Training Group again offered numerous courses in 2021. The effects of the pandemic can also be seen here. Almost all courses were offered as a virtual workshop.

Course	Course days	Offers 2021	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	2	Dr. Deborah Bennett Bennett English Training for Academics
Scientific Writing 3 Writing a PhD Thesis: Streamlining the writing process	2,5	1	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	1	Dr. Ralph Palmisano (OICE)
Good Scientific Practice	1	1	Dr. Anne Hamker (external)
Poster Workshop	1,5	2	Dr. Deborah Bennett Bennett English Training for Academics
Kommunikation und Rhetorik	2	1	Gerhard Kranz (external)
Fundamentals of bioinformatics analysis of functional genomics data	5	1	Dr. Fulvia Ferrazzi Department of Nephropathology
Project/ Time and Self Management	1	1	Dr. Alexander Egeling (external)
Grant Writing	5	1	Prof. Dr. Christoph Becker (Department of Medicine 1) Prof. Dr. Katharina Zimmermann (Department of Anesthesiology) Prof. Dr. Felix Engel (Department of Nephropathology)
Career Planning	1	1	Dr. Martin E. van de Sand (external)

Soft skill- and statistic courses given in 2021

Due to pandemic the IZKF Retreat in 2021 took place via Zoom again. The Retreat was devided in 3 parallel sessions (Oncology, Immunology, Further).

The two-part keynote session was led by Prof. Olaf Gefeller (Chair of Medical Biometry and Epidemiology). In addition to the lecture of Prof. Gefeller the movie “Paywall: The Business of Scholarships” was provided. Each doctoral students was involved with an own contribution of ten minutes. Besides that, all participants had an active role as moderator in addition to the presentation. A total of 95 doctoral students participated.

IZKF Retreat 2019 at Fraunhofer Research Campus in Waischenfeld

On October 21, 2021 the IZKF Postgraduate Workshop took place in the lecture halls of medicine. In a two-hour poster session, 36 posters were exhibited and reviewed. From these posters, 6 doctoral students were selected to immediately present their project in the plenary session. The poster committee finally awarded the IZKF poster prize to:

- Iris Stolzer (Department of Medicine 1 and IZKF Junior Research Group 5) with the poster title: Bone alterations in a mouse model of Crohn‘s disease are associated with altered tryptophan metabolism.
- Cora Kim (Department of Neurosurgery) with the poster title: Emotional pictures modulate annoyance of tinnitus-like sounds via alpha/beta band visual-auditory network

The review panel explicitly emphasized that they saw many excellent posters that day and were very impressed with the quality of all flash talks.

In the supporting programme, the doctoral students also heard lectures by Ms Makamdop (Institute of Clinical and Molecular Virology) and by Mr Bishnoi (National Agri-Food Biotechnology Institute).

In addition, the IZKF Publication Award was handed out. Dr. Kaveh Roshanbinfar from the Division of Nephropathology was selected from 22 applications by the Junior Scientist Committee for his publication „Nanofibrous Composite with Tailorable Electrical and Mechanical Properties for Cardiac Tissue Engineering“. The awardee presented his award-winning work and recent data based on it.

IZKF Postgraduate Workshop 2021

Prize winners at the IZKF-Postgraduate Workshop (from the left: Prof. Dr. Christoph Becker, Dr. Kaveh Roshanbinfar, Cora Kim and Iris Stolzer)

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

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

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 DigIT

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

Spokespersons
Isabel Galicia Ernst, Institute of Biomedicine of Aging

Pia Scheufele, Institute of General Practice

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.

Jour Fixe Ink

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

Spokespersons
Myriam Jeninga, Institute of Microbiology
Pia Langguth, 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 MedTech

Scientific Head
Prof. Dr. Christoph Bert, Department of Radiation Oncology

Spokespersons
Andre Karius, Department of Radiation Oncology
Sascha Daniel, Institute of Radiology

The Jour Fixe MedTech is aimed at all doctoral students with a medical-technical/-physical/-biological connection and/or background. Of course, the Jour Fixe is also open to all other interested parties, whom are warmly welcomed as new participants. The focal points of the Jour Fixes are questions from medical physics (radiation therapy, MR physics, audiology), radiation biology and radiology. Members of the Jour Fixe meet monthly. One project presentation per doctoral student is planned every year.

Jour Fixe Neuro

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

Spokespersons
Sebastian-Gehlen Breitbach, Institute of Biochemistry
Maria Strunz, Department of Ophthalmology

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
Lucia Haller, Institute of Biochemistry
Viola Kluge, Institute of Biochemistry

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.

Scientific Reports

Funded Advanced projects in 2021:

No.	Name	Institution	Project title
A76	Prof. Dr. Christoph Becker	Department of Medicine 1	Role of Gasdermin C in Gut Barrier Defence
A77	Prof. Dr. Aline Bozec	Department of Medicine 3	HIF expression in B cells regulates bone loss
A78	Dr. Dr. Mircea Chiriac, Prof. Dr. Markus Neurath	Department of Medicine 1	Smurf2-IFN axis in IBD and mucosal healing
A79	Prof. Dr. Jörg Distler	Department of Medicine 3	TR4 in tissue fibrosis
A80	Prof. Dr. Diana Dudziak	Department of Dermatology	Inflammasomes in primary dendritic cells
A81	Prof. Dr. Armin Ensser	Institute of Clin. and Mol. Virology	Receptor and neuropathogenicity of Bornavirus
A82	Prof. Dr. Susetta Neurath-Finotto	Department of Molecular Pneumology	Role of RANTES in the resolution of asthma
A83	Prof. Dr. Thomas Gramberg	Institute of Clin. and Mol. Virology	The role of SAMHD1 in CMV/ HIV coinfections
A84	Prof. Dr. Kai Hildner, PD Dr. Sebastian Zundler, Prof. Dr. Maike Büttner-Herold	Department of Medicine 1, Department of Medicine 1, Department of Nephropathology	Tissue-resident memory T cells in GvHD
A85	Prof. Dr. Ulrike Hüffmeier	Institute of Human Genetics	The pathophysiology of SAPHO syndrome
A86	Prof. Dr. Gerhard Krönke	Department of Medicine 3	Characterization of synovial macrophage subsets
A87	Dr. Christian Lehmann, PD Dr. Ulrike Schleicher	Department of Dermatology Institute of Microbiology	DC subsets and natural antibodies in leishmaniasis
A88	Prof. Dr. Manfred Marschall, Prof. Dr. Heinrich Sticht	Institute of Clin. and Mol. Virology Institute of Biochemistry	Cyclin interaction with a CDK-like viral kinase
A89	Prof. Dr. Alexander Steinkasserer	Department of Immune Modulation	CD83 regulates homeostasis and inflammation
A90	Prof. Dr. Matthias Tenbusch	Institute of Clin. and Mol. Virology	The fate of lung-resident memory T-cells
A91	PD Dr. Dr. Andrea Thoma-Kreß	Institute of Clin. and Mol. Virology	Interfering with HTLV-1 persistence
A92	Prof. Dr. Mario Zaiss	Department of Medicine 3	FRCs and immune tolerance induction
D30	Prof. Dr. Jürgen Behrens, Dr. Dominic Bernkopf	Chair of Experimental II – Molecular Oncology	Axin at microtubuli
D31	Prof. Dr. Anja Bosserhoff	Institute of Biochemistry	Modulation of oncogene-induced senescence
D32	PD Dr. Peter Dietrich	Department of Medicine 1	NPY in chemo-resistance and immune-escape in HCC
D33	Prof. Dr. Markus Metzler, Prof. Dr. Dimitrios Mougiakakos	Department of Pediatric and Adolescent Medicine, Department of Medicine 5	Immunometabolism in CML
D34	PD Dr. Andreas Ramming, Prof. Dr. Michael Stürzl	Department of Medicine 3, Department of Surgery	Fibroblast polarization in colorectal carcinoma
D35	PD Dr. Johannes Schödel	Department of Medicine 4	Interactions of DPF3 and hypoxia in renal cancer
D36	Prof. Dr. Reiner Strick, Prof. Dr. Arndt Hartmann	Department of Obstetrics and Gynaecology, Institute of Pathology	Endogenous retroviruses drive tumor inflammation
E28	Prof. Dr. Lina Gölz, Prof. Dr. Michael Wegner	Department of Orthodontics and Orofacial Orthopedics, Institute of Biochemistry	Neural Crest Regulators In Orofacial Clefting
E29	Prof. Dr. Dieter Chichung Lie	Institute of Biochemistry	Lysosome dysfunction in stem cell ageing
E30	Prof. Dr. Beate Winner, Prof. Dr. Jürgen Winkler	Department of Stem Cell Biology, Department of Molecular Neurology	Impact of the immune system on Parkinson‘s disease
E31	Prof. Dr. Christiane Zweier	Institute of Human Genetics	Proteasomal degradation in intellectual disability
F7	Prof. Dr. Felix Engel	Department of Nephropathology	Gpr126 in kidney development and disease
F8	Prof. Dr. Christoph Korbmacher	Institute of Cell. and Mol. Physiology	Ion channel function of polycystin-2 in ADPKD
F9	Prof. Dr. Janina Müller-Deile, Prof. Dr. Mario Schiffer	Department of Medicine 4	Generation of novel glomerular 3D culture systems

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 protein strongly induced in the gut following infectious and inflammatory challenges. We demonstrate that Gasdermin C is released by IL-4 and IL-13 via STAT6 signaling. Our data imply that gasdermin C contributes to intestinal barrier defense. We continue to investigate the regulation, molecular mechanism of action, and functional role of gasdermin C in vivo using newly generated gasdermin C knockout mice.

Important results

- Gasdermin C is induced by type 2 immunity in various models of infection and inflammation
- Gasdermin C is expressed in intestinal epithelial cells upon IL-4 and IL-13 signaling via IL4Ra and STAT6.

Special methods

- Intestinal organoid techniques
- Conditional gene targeting in the gut

Publications

Gonzalez Acera M., J.V. Patankar, L. Diemand, M.F. Neurath, S. Wirtz, C. Becker. (2021) Comparative transcriptomics of IBD patients indicates induction of type 2 immunity irrespective of the disease ideotype. Frontiers in Medicine. 8:664045.

Patankar J.V., M.Gonzalez-Acera, M. Chiriac, M. Lehmann, A.A. Kühl, R. Atreya, C. Becker. (2021) The SARS-CoV-2 attachment receptor ACE2 is decreased in Crohn's disease and regulated by microbial and inflammatory signaling. Gastroenterology. 160(3):925-928.e4.

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

Abstract

In our project, we demonstrated that prolonged HIF-1α signaling in B cells leads to enhanced RANKL production and osteoclast formation using genetically modified mice and high-throughput analyses. Deletion of HIF-1α in B cells prevents estrogen deficiency-induced bone loss. Mechanistically, estrogen controls HIF-1α protein stabilization through HSP70-mediated degradation. We have identified that the HSP70/HIF-1α axis may serve as a new therapeutic target for osteoporosis.

Publications

no project-specific publications so far

Important results

1. HIF-1α expression was upregulated in bone marrow B cells after ovariectomy (OVX)
2. HIF-1α protein stability regulated by estrogen is in HSP70-dependent manner
3. Treatment with Geranylgeranylacetone (GGA), HSP70 inducer, attenuated the OVX-induced osteopenia, increasing BV/TV and trabecular numbers in the tibia

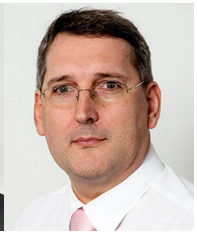
Special methods

In our project we used:

1. Murine model of Ovariectomy
2. Bone Micro-CT imaging and Bone histomorphometry
3. ChIP sequencing and data analysis

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

Abstract

We aim to understand the role of Smurf2, an ubiquitin E3 ligase family member that has been initially described in the context of TGF-β signaling but was recently reported to modulate interferon production, in the pathogenesis of inflammatory bowel disease (IBD). We will mainly focus on animal models of experimental IBD in both general and conditional KO mice, CRISPR/Cas9 modulated 3D organoid cultures and will try to confirm our findings using fresh samples from human IBD patients and controls.

Publications

no project-specific publications so far

Important results

Over 5000 genes were differentially expressed between *Smurf2KO* and WT mice in DSS colitis. Levels of inflammatory cytokines *(Il19, Il6)* and chemokines *(Ccl2, Ccl7)* as well as other proinflammatory markers *(Ptx3, Saa)* were tens to hundreds times higher in *Smurf2KO* than in WT whereas those of protective factors *(Muc2, Muc3, Tff3)* were downregulated.

Special methods

1. Generation of *Smurf2KO* and *Stat2KO* cell lines by CRISPR/Cas9;
2. Generation of human colonic organoids from well characterized IBD patients;
3. Comprehensive analysis (proteomics, RNA-seq and GO etc.) of *Smurf2KO* and WT mice in DSS colitis and generation of $Smurf2^{\Delta ICE}$ and $Stat2^{\Delta ICE}$ (CRISPR/Cas9) mice with intestinal epithelial cell-specific KO.

TR4 in tissue fibrosis


Prof. Dr. Distler

A79 01/2021 - 06/2023

Prof. Dr. Jörg Distler, Department of Medicine 3
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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.

Important results

- TR4 is upregulated in SSc fibroblasts in a TGFβ-dependent manner
- Overexpression of TR4 promotes fibroblast activation by Gα12/ROCK-dependent cytoskeletal reorganization, whereas knockout of TR4 inhibits TGFβ-driven fibroblast activation
- Fibroblast-specific knockout of TR4 protects from experimental fibrosis in different mouse models of SSc and full-thickness skin grafts

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
- multicellular cell culture models for human skin

Publications

Györfi A-H, Matei A-E, Fuchs M, Liang C, Rius-Rigau A, Hong Z, Zhu H, Luber M, Bergmann C, Dees C, Ludolph I, Horch RE, Distler O, Wang J, Bengsch B, Schett G, Kunz M, Distler JHW. (2021) Engrailed 1 coordinates cytoskeletal organization to promote myofibroblast differentiation and fibrotic tissue remodeling. J Exp Med, 2021 Sep 6;218(9):e20201916.

Zehender A, Li Y-N, Lin N-Y, Nüchel J, Stefanica A, Chen C-W, Hsu H-H, Zhu H, Ding X, Huang J, Györfi A-H, Soare A, Rauber S, Bergmann C, Ramming A, Plomann M, Eckes B, Schett G, Distler JHW (2021) TGFβ promotes fibrosis by MYST1-dependent epigenetic regulation of autophagy. Nat Commun., Jul 20;12(1):4404.

Zhang Y, Shen L, Dreißigacker K, Zhu H, Trinh-Minh T, Meng X, Tran-Manh C, Dees C, Matei A-E, Chen C-W, Ditschkowski M, Krauss S, Winkler J, Wolff D, Ziemer M, Beilhack A, Karrer S, Herr W, Mackensen A, Schett G, Spriewald BM, Distler JHW (2021) Targeting of canonical WNT signaling ameliorates experimental sclerodermatous chronic graft-versus-host disease. Blood, Apr 29;137(17):2403-2416.

Inflammasomes in primary dendritic cells

Prof. Dr. Dudziak

A80 01/2020 - 06/2022

Prof. Dr. Diana Dudziak, Department of Dermatology

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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

Analyzing the expression of inflammasomes 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. Mainly human cDC2 activated the inflammasome and induced stronger Th1/Th17 responses upon hyperactivation.

Special methods

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

Publications

Hatscher L, Lehmann CHK, Purbojo A, Onderka C, Liang C, Hartmann A, Cesnjevar R, Bruns H, Gross O, Nimmerjahn F, Ivanovic-Burmazovic I, Kunz M, Heger L*, Dudziak D*. (2021) Select hyperactivating NLRP3 ligands enhance the TH1- and TH17-inducing potential of human type 2 conventional dendritic cells. Sci. Signal. 14, eabe1757

Receptor and neuropathogenicity of Bornavirus

Prof. Dr. Ensser

A81 01/2020 - 12/2022

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

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*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 antiviral (chemo) therapeutic options, in IPSC derived human neuronal 3D organoid cultures.

Publications

Großkopf AK, Schlagowski S, Fricke T, Ensser A, Desrosiers RC, Hahn AS (2021) Plxdc family members are novel receptors for the rhesus monkey rhadinovirus (RRV). PLoS Pathog 17(3): e1008979

Important results

Domain swap constructs of the extracellular domains of BoDV-1 G proteins fused to the Vesicular Stomatitis Virus (VSV) glycoprotein stem were cloned. Fusion proteins were expressed. However, BoDV1-G incorporation lentiviral particles was inefficient, despite various attempts and modifications, and a VSV-based pseudovirus system is established.

Special methods

Lentiviral pseudotyping and p24 assays; viral infection under BSL2 and BSL3 conditions.

Wide-field fluorescence microscopy in BSL3 and Wide field high content imaging under BSL2 conditions.

Recombinant Vesicular Stomatitis Virus pseudotyping.

Role of RANTES in the resolution of asthma

Prof. Dr. Neurath-Finotto

A82 02/2020 - 01/2023

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

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Abstract

RANTES is a chemokine found in allergic asthma and in T cell-dependent clearance of infection. It is produced by T cells and binds to the receptors CCR1, CCR3 and CCR5. Here we found increased RANTES in the BALF and in antiviral TLR7/8 agonist treated PBMCS of asthmatic children. Moreover, Rhinovirus decreased RANTES in PBMCs of asthmatics. Consistently, treatment with rRANTES inhibited allergic asthma in mice, indicating that RANTES is involved in processes that resolve asthma exacerbations.

Important results

- RANTES levels were found reduced 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 an induction of asthma resolving resident Eosinophils (rEos).

Special methods

- Whole body plethysmography
- Invasive lung function measurement

Publications

Li N, Mirzakhani H, Kiefer A, Koelle J, Vuorinen T, Rauh M, Yang Z, Krammer S, Xepapadaki P, Lewandowska-Polak A, Lukkarinen H, Zhang N, Stanic B, Zimmermann T, Kowalski ML, Jartti T, Bachert C, Akdis M, Papadopoulos NG, Raby BA, Weiss ST, Finotto S (2021) Regulated on Activation, NormalT cell Expressed and Secreted (RANTES) drives the resolution of allergic asthma. iScience. 25;24(10):103163. doi: 10.1016/j.isci.2021.103163. PMID: 34693221; PMCID: PMC8511896.

The role of SAMHD1 in CMV/ HIV coinfections

Prof. Dr. Gramberg

A83 01/2020 - 12/2022

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

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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. Understanding this interaction might provide novel treatment options.

Publications

no project-specific publications so far

Important results

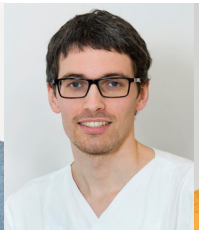
- HCMV coinfection enhances HIV infectivity on primary Macrophages, DCs, and monocytic cell lines
- Enhancement depends on inactivation of the restriction factor SAMHD1
- Inhibition of viral Kinase UL97 with kinase inhibitor abrogates enhancement.

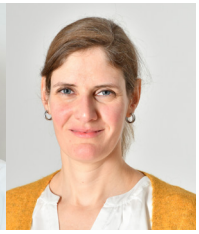
Special methods

- 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


PD Dr. Zundler


Prof. Dr. Büttner-Herold

A84 05/2020 - 05/2023

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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 unravel the role of so-called tissue-resident memory T cells (Trm) in murine and human GvHD, we are employing novel IEL-IEC co-culture model systems, novel imaging technologies and multicolor immunofluorescence stainings.

Special methods

1. In vitro co-culture of intestinal organoids and IELs to discriminate allogenic vs. syngeneic T cell functionality and migration behavior by live imaging
2. Multicolor immunofluorescence stainings of human intestinal biopsies for Trm cell markers
3. In vivo cell trafficking assays and intravital microscopy in humanized mice to study T cell circuits

Publications

Vonbrunn E, Ries T, Söllner S, Müller-Deile J, Büttner-Herold M, Amann K, Daniel C (2021) Multiplex gene analysis reveals T-cell and antibody-mediated rejection-specific upregulation of complement in renal transplants. Sci Rep.;11(1):15464. doi: 10.1038/s41598-021-94954-3.

Enderle K, Dinkel M, Spath EM, Schmid B, Zundler S, Tripal P, Neurath MF, Hildner K, Neufert C (2021) Dynamic Imaging of IEL-IEC Co-Cultures Allows for Quantification of CD103-Dependent T Cell Migration. Int J Mol Sci.;22(10):5148. doi: 10.3390/ijms22105148.

Müller TM, Becker E, Wiendl M, Schulze LL, Voskens C, Völkl S, Kremer AE, Neurath MF, Zundler S (2021) Circulating Adaptive Immune Cells Expressing the Gut Homing Marker α4β7 Integrin Are Decreased in COVID-19. Front Immunol 12:639329.

Important results

Employing an *in vitro* intestinal epithelial cell/ intraepithelial lymphocytes (IEL) co-culture system, we established novel live imaging tools to functionally study migration of allo-reactive T cells within epithelia *ex vivo.* In addition, we established multicolor immuno-fluorescence stainings for the detection of Trm in human intestinal tissue.

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

Vectors encoding Plexin-A1 or its interaction partners TREM2 and DAP12 were successfully used for cotransfection of HEK293T cells. Immunfluorescence staining revealed overlapping subcellular localizations of Plexin-A1 and TREM2 at plasma membrane and Golgi complex and of Plexin-A1 and DAP12 at plasma membrane. A targeted analysis of common functional variants in two candidate genes (TLR1, TLR2) conferring susceptibility to mycobacterial infections did not provide evidence for association.

Publications

no project-specific publications so far

Important results

- Study on MPO variants in SAPHO syndrome by Haskamp et al. published
- Successful immunofluorescence staining and subcellular localization of Plexin-A1, TREM2 and DAP12 in HEK293T cells
- Genotyping of SAPHO syndrome patients for common functional coding variants in two susceptibility genes for mycobacterial infections, no evidence for association

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 - 06/2023

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.

Special methods

- scRNAsequencing
- preclinical arthritis models
- light-sheet microscopy

Important results

Using scRNAseq we generated a dynamic dataset of the mRNA expression profile of synovial macrophage and synovial fibroblast subsets. These datasets allowed the construction of a ligand-receptor interaction map that shows various heterologous signaling circuits between these cells during homeostasis, as well as during onset and resolution of inflammation. Key findings are the role of fibroblast as source of MCSF acting on a distinct population of sublining macrophages that proliferate and maintain the pool of synovial macrophages as well as a central role of metabolic rewiring of macrophages that contributes to the differentiation of alternatively-activated macrophages and the resolution of inflammation.

Publications

no project-specific publications so far

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 versus chronic non-healing L. mexicana infection in mice.

Publications

no project-specific publications so far

Important results

Within the DC population a specific subset of skin DCs could be identified as main host cell of L. major and L. mexicana within the first days of infection. Ongoing studies focus on the functional relevance of this DC subset for the outcome of infection. Bioinformatic analysis of infected vs non-infected skin cells by scRNA sequencing was established.

Special methods

- Leishmania infection models in mice (L. major, L. mexicana, L. infantum)
- Characterization of DC subpopulations
- 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. Demonstration of functional relevance of pUL97-cyclin T1 interaction using HCMVs carrying deletions in cyclin T1 binding site
2. Generation of a panel of BACmid reporter viruses carrying drug-resistance mutations in pUL97 kinase
3. Computational assessment of pUL97-cyclin binding interfaces and drug resistance mutations in pUL97 of clinical HCMVs

Special methods

1. Molecular characterization of HCMV mutants: qPCR kinetics, confocal imaging, CoIP, in vitro kinase assays
2. Whole genome sequencing of clinical isolates of HCMV and BACmid-based genetic engineering of recombinant HCMVs
3. Bioinformatics: sequence-based investigation, molecular modeling and molecular dynamics simulations

Publications

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, PMID: 32428517

Schütz M, Steingruber M, Socher E, Müller R, Wagner S, Kögel M, Sticht H, Marschall M (2021) Functional relevance of the interaction between human cyclins and the cytomegalovirus-encoded CDK-like protein kinase pUL97. Viruses 13: 1248, doi.org/10.3390/v13071248, PMID: 34198986

CD83 regulates homeostasis and inflammation


Prof. Dr. Steinkasserer

A89 07/2020 - 12/2022

Prof. Dr. Alexander Steinkasserer, Department of Immune Modulation
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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 crosstalk. Since its regulation and function in these cells has not yet been elucidated, we aim to investigate this during immune homeostasis and neuro-inflammation.

Publications

no project-specific publications so far

Important results

Using the CRISPR/Cas technique, we generated cell specific KO mice, lacking CD83 expression only in microglia cells. In vitro as well as in vivo analyses of these mice revealed an over-activated microglia phenotype, leading to exaggerated neuro-inflammation, strongly enhanced paralyses in the MS-model Experimental-Autoimmune-Encephalomyelitis (EAE) and to an impaired resolution of inflammation. Thus, these results strongly support the important role of CD83 in the context of neuro-inflammatory autoimmune disorders.

Special methods

- Flow cytometry protocols to analyze microglia and infiltrating monocytes in the CNS
- IHC staining to analyze microglia subpopulations within the CNS.
- Tamoxifen-inducible CX3CR1-CreERT2 system to analyze the influence of a microglia-specific CD83 KO during neuro-inflammation.
- RNAseq analyses to identify CD83-induced transcriptional changes.

The fate of lung-resident memory T-cells

Prof. Dr. Tenbusch

A90 01/2020 - 12/2022

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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

T_{RM} induced by natural infection initially clustered in iBALT structures and declined more rapidly than T_{RM} induced by adenoviral vector immunization. T_{RM} recognizing their cognate antigen readily expand and provide protection against secondary IAV infection. In case of non-related RSV infections, no replacement of pre-existing T_{RM} was observed.

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

PD Dr. Dr. Thoma-Kreß

A91 03/2020 - 09/2022

PD Dr. 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

- Characterization of p8 transfer in several stable p8-/p12- expressing T-cell lines
- Production of p8- and p12-constructs fused to a biotin ligase, allowing identification of transiently interacting proteins
- Identification of a signal peptide in p12

Special methods

- Genome Editing (CRISPR/Cas9, shRNA) and retroviral transduction
- Transfection of primary cells (4D-Nucleofector TM)
- 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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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.

Publications

no project-specific publications so far

Important results

1. Local and temporary depletion of pLN CCL19-positive FRC ameliorates symptoms in collagen-induced arthritis (CIA) and decreased collagen-specific IgG.
2. FRC depleted CIA mice show alterations in immune cell composition.
3. FRC lose their ability to suppress T-cell activation and proliferation during the CIA time course.

Axin at microtubuli

Prof. Dr. Behrens

Dr. Bernkopf

D30 03/2020 - 08/2022

Prof. Dr. Jürgen Behrens, Chair of Experimental II – Molecular Oncology

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Dr. Dominic Bernkopf, Chair of Experimental II – Molecular Oncology

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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

The microtubule binding site (MTB) of axin was shown to depend on a cluster of arginine and lysine residues. It could be functionally replaced by the MTB of the known MT interactor tau. Efficient decoration of MT by axin requires both MT interaction and axin polymerization via its DIX domain.

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

Prof. Dr. Anja Bosserhoff, Institute of Biochemistry

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Abstract

Oncogene-induced senescence (OIS) is known to be 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

We could demonstrate that changes in cell matrix adhesion (e.g. by modulating integrin expression, modulation RNA-binding molecules like HuR) modulates induction of senescence in melanocytes (using BRAFmut expression). RNA-Seq was performed to understand the molecular changes in detail. Further, a direct impact of Wnt signal on breaking of senescence in melanoma cells was revealed.

Special methods

Analyses of senescence marker, reporter gene assays for analyses of transcription factors, OIS induction via lentiviral transfection

Publications

Pommer M, Kuphal S, Bosserhoff AK (2021) Amphiregulin Regulates Melanocytic Senescence. Cells, 10, 326

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

Böhme I, Bosserhoff A (2020) Extracellular acidosis triggers a senescence-like phenotype in human melanoma cells. Pigment Cell Melanoma Res. 33(1):41-51.

NPY in chemo-resistance and immune-escape in HCC

PD Dr. Dietrich

D32 03/2020 - 02/2023

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. The aims of this study are to (i) unravel the role of Y5R-NPY-crosstalk in chemoresistance, to (ii) analyze the role of the NPY-system as a potential major determinant of immune-escape in HCC and to (iii) determine the potential role of novel microRNA-target gene interactions 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. Molecular cross-talk between Y5-receptor and neuropeptide Y drives liver cancer. J Clin Invest.2020 May 1;130(5):2509-2526.

Gaza A, Fritz V, Malek L, Wormser L, Treiber N, Danner J, Kremer AE, Thasler WE, Siebler J, Meister G, Neurath MF, Hellerbrand C, Bosserhoff AK, Dietrich P. Identification of novel targets of miR-622 in hepatocellular carcinoma reveals common regulation of cooperating genes and outlines the oncogenic role of zinc finger CCHC-type containing 11. Neoplasia. 23(5):502-514. doi: 10.1016/j.neo.2021.04.001

Fritz V, Malek L, Gaza A, Wormser L, Appel M, Kremer AE, Thasler WE, Siebler J, Neurath MF, Hellerbrand C, Bosserhoff AK, Dietrich P. Combined de-repression of chemoresistance associated mitogen-activated protein kinase 14 and activating transcription factor 2 by loss of microRNA-622 in hepatocellular carcinoma. Cancers. 2021 Mar 9;13(5):1183.

Immunometabolism in CML


Prof. Dr. Metzler


Prof. Dr. Mougiakakos

D33 05/2020 - 06/2023

Prof. Dr. Markus Metzler, Department of Pediatric and Adolescent Medicine
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Prof. Dr. Dimitrios Mougiakakos, Department of Medicine 5 (until 09/2021)
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Abstract

Tyrosine kinase inhibitors (TKI) targeting the BCR/ABL1 fusion protein are generally highly effective for the treatment of chronic myeloid leukemia (CML). However, a considerable proportion of patients experiences significant side effects and resistance to treatment. Here we focus on the immunometabolic impact of the TKI imatinib, dasatinib, nilotinib and the first-in-class BCR-ABL1 inhibitor Specifically Targeting the ABL Myristoyl Pocket (STAMP) asciminib on T cell function and CML cells to investigate the different dimensions of treatment effects and to discover new targets for optimized combination therapy.

Publications

no project-specific publications so far

Important results

- T cell function is less severely disturbed by asciminib compared to established TKIs
- Glycolytic reserve and respiratory capacity were increased by TKI while glucose uptake and lactate production were inhibited in T cells
- CML cell lines showed reduced glycolytic activity and metabolic enzyme expression by TKI and were more susceptible to oligomycin and rotenone
- Unfolded protein response is a potentially important factor to be investigated in combination therapy.

Special methods

- Measurement of protein expression (e.g. surface marker) via flow cytometry
- Metabolic flux analysis for measurement of parameters concerning oxidative phosphorylation and glycolysis
- Untargeted metabolomics for detailed assessment of metabolic profile

Fibroblast polarization in colorectal carcinoma


PD Dr. Ramming


Prof. Dr. Stürzl

D34 05/2020 - 01/2023

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Abstract

The tumor microenvironment is of key importance in the development and progression of colorectal cancer (CRC). It is accepted that cancer-associated fibroblasts exert important functions in tumorigenesis. As yet, the role of fibroblast polarization in CRC is unknown. 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.

Important results

Transcriptome analyses revealed significant differences in gene expression between fibroblasts isolated from CRC with different microenvironments and from healthy colon. These results could be confirmed at the RNA and protein level and single cell RNAseq identified different subpopulations in fibroblasts derived from CRC and healthy colon tissues.

Special methods

- RNA-Seq
- scRNA-Seq
- CRC fibroblast isolation and culture

Publications

Stehr AM, Wang G, Demmler R, Stemmler MP, Straube J, Tripal P, Schmid B, Geppert CI, Hartmann A, Muñoz LE, Schoen J, Völkl S, Merkel S, Becker C, Schett G, Grützmann R, Naschberger E, Herrmann M, Stürzl M (2021) Neutrophil extracellular traps drive epithelial-mesenchymal transition of human colon cancer. Journal of Pathology, doi.org/10.1002/path.5860

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., 27(9): 1491-1502

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: e0233422

Interactions of DPF3 and hypoxia in renal cancer

PD Dr. Schödel

D35 07/2020 - 12/2022

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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 primary renal tubular cells and a large RCC cohort. We have established ATAC-seq experiments in primary renal tubular cells and observe differential chromatin configuration at the DPF3 HIF binding site in cells from individuals with different rs4903064 genotypes. Depletion of DPF3 in renal tubular cells leads to reduced proliferation of these cells in 2D and 3D experiments.

Special methods

We have established ATAC-seq experiments in primary renal cells. This method allows identification of open chromatin and regulatory DNA-elements on a genome-wide scale. We use CRISPR activator and inhibitors to functionally test these 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 integrated into the human genome during evolution and are epigenetically silenced. ERV become activated in cancers and generate dsRNA and RNA:DNA intermediates linked with inflammation. Activation of ERV families correlated with tumor inflammation in bladder and ovarian cancer using qPCR, Affymetrix chips and immunohistochemistry. DsRNA and RNA:DNA hybrids in cell culture correlated with different inflammation pathways (e.g. IFN, IL6) and innate immunity.

Publications

no project-specific publications so far

Important results

- Different ERV genes / proteins and inflammation signatures of bladder and ovarian tumors correlate with patient survival.
- dsRNA and RNA:DNA intermediates lead to specific immune gene activations.
- Custom made Affymetrix chips for the overall ERV and immune gene expression analyses of bladder cancer samples result in novel expression signatures.

Special methods

- Synthesis and transfection of dsRNA and RNA:DNA in human cells.
- Custom made Affymetrix chip with a total of 327,976 gene elements including ERVs, other repetitive elements and immune genes with RNA from FFPE tissues.
- In vitro transcription and cell transfection of functional ERV pol mRNA via jetMESSENGER® following reverse transcription assays.

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

- CRISPR/Cas9-mediated gene knockout was achieved for all 7 studied regulators in a cranial neural crest cell line.
- RNAseq was performed to determine the differentially regulated genes for each regulator.
- The Ep400/Tip60 remodeler primarily affects neural crest metabolism and proliferation.

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. We now found that increased activity of TFEB decreases stem cell activation in young adult mice and promotes longterm maintenance of the stem cell pool.

Special methods

Measurement of autophagic-lysosomal flux via biochemistry and imaging. Biochemical measurement of lysosome activity. 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

Atypical Parkinson’s disease (aPD) is characterized by the progressive dopaminergic loss and intercellular a-synuclein aggregates in oligodendroglial cytoplasmic inclusions (GCIs). We investigated the role of glial cells in regard to neuroinflammatory processes in aPD characterized by severe cerebellar degeneration and investigated oligodendrocytes in transgenic mice and post mortem tissue. We delineate an important role of glial cells for a-synuclein associated neuroinflammation.

Important results

- Post morten cerebellum from aPD patients, besides Purkinje cell loss, has prototypical GCI pathology and microgliosis.
- In the cerebellum of an aPD mouse model (MBP29-hα-syn mice) a severe myelin deficit, increased oligodendrocytes and myeloid cells are present early on, combined with the cerebellar specific motor impairment: cerebellar ataxia.

Special methods

- Development of standardized models to generate IPSC-derivedopaminergic midbrain neurons and brain organoids
- Autologous co-culture system of iPSC derived neurons with immune 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 Neurol, 11, 1041.

Meszaros, L., Riemenschneider, M. J., Gassner, H., Marxreiter, F., von Horsten, S., Hoffmann, A., & Winkler, J. (2021). Human alpha-synuclein overexpressing MBP29 mice mimic functional and structural hallmarks of the cerebellar subtype of multiple system atrophy. Acta Neuropathol Commun, 9(1), 68.

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

- Unaltered global proteasome activity upon siRNA based knockdown of UPS and NDD associated genes in HEK293 cells points to a pathomechanism more specific to its substrate proteins.
- Knockdown of *Drosophila* orthologues resulted in altered activity and/or multiple dendrite neuron morphology. Proteasome modulating substances in the fly food ameliorates several 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-coupled 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 mainly expressed in epithelial cell types of the urinary collecting system and its expression varies during development and upon disease.
- The induced deletion of Gpr126 in developing kidneys ex vivo results in impaired ureteric bud morphogenesis.
- Aldosterone enhances the GPR126 expression in a mouse cortical collecting duct cell line.

Special methods

- RNAscope® in situ hybridization technology
- Zebrafish as a model of kidney disease
- CRISPR/Cas technologies

Ion channel function of polycystin-2 in ADPKD

Prof Dr. Korbmacher

F8 02/2020 - 07/2022

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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.

Important results

- ADPKD causing mutations in the PC2 pore region alter PC2 ion channel function.
- Coexpression of polycystin-1 (PC1) modifies PC2 ion channel properties supporting the concept of a heteromeric channel structure.
- Several sites in the PC1 pore region were identified that appear to be critical for the function of the PC1-PC2-complex.

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.

Publications

Grosch M, Brunner K, Ilyaskin AV, Schober M, Staudner T, Schmied D, Stumpp T, Schmidt KN, Madej MG, Pessoa TD, Othmen H, Kubitza M, Osten L, de Vries U, Mair MM, Somlo S, Moser M, Kunzelmann K, Ziegler C, Haerteis S, Korbmacher C, Witzgall R (2021) A polycystin-2 protein with modified channel properties leads to an increased diameter of renal tubules and to renal cysts. J Cell Sci. 2021 Aug 15;134(16):jcs259013. doi: 10.1242/jcs.259013.

Generation of novel glomerular 3D culture systems


Prof. Dr. Müller-Deile


Prof. Dr. Schiffer

F9 06/2020 - 06/2023

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Abstract

Primary focal segmental glomerulosclerosis (FSGS) due to podocye mutations is very variable in response to treatment and often resistant for immunosuppression. In the search for better glomerular ex vivo models, we studied 3D co-cultures and an artificial glomerular basement membrane. We generated a protocol for personalized podocytes in cell culture that keep the patients' mutations and treated them with different substances used in the clinic to foresee individual response to treatment.

Publications

no project-specific publications so far

Important results

- 3D glomerular co-culture leads to differential expression in genes involved in differentiation, cell adhesion and vesical transportation.
- Generation of podocytes by reprogrammation of skin biopsy derived fibroblasts into iPSCs followed by cell type specific differentiation allows personalized podocyte characterization and treatment ex vivo.

Special methods

- 3D spheroidal glomerular cell culture
- Generation of an artificial glomerular basement membrane with glomerular endothial cells and podocytes growing on different sides of an artificial basement membrane.
- Generation of iPSC derived personalized human podocytes that keep the patients' mutation

Funded research groups in 2021:

No.	Name	Institution	Project title
N1	Prof. Dr. Paolo Ceppi	IZKF-NW 1	Understanding the plasticity of cancer cells
N2	Prof. Dr. David Dulin	IZKF-NW 2	Physics and Medicine
N5	Prof.Dr. Claudia Günther	Department of Medicine 1	Organ crosstalk in IMIDs
N6	Prof. Dr. Janina Müller-Deile	Department of Medicine 4	Rare glomerular diseases
N7	Prof. Dr. Marisa Karow	Institute of Biochemistry	Forging neural cell identity
N8	Prof. Dr. Friederike Zunke	Department of Molecular Neurology	Lysosomes & glial cells

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

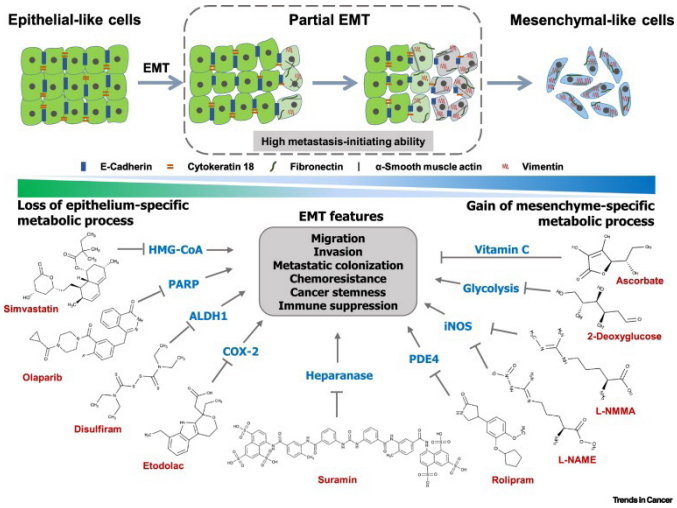
The group focuses on the identification of novel fundamental mechanisms of cancer biology using several cell and molecular biology techniques, mouse models, high-throughput approaches and the analysis of human samples. We aim at discovering novel genes and molecular pathways that regulate the plasticity 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

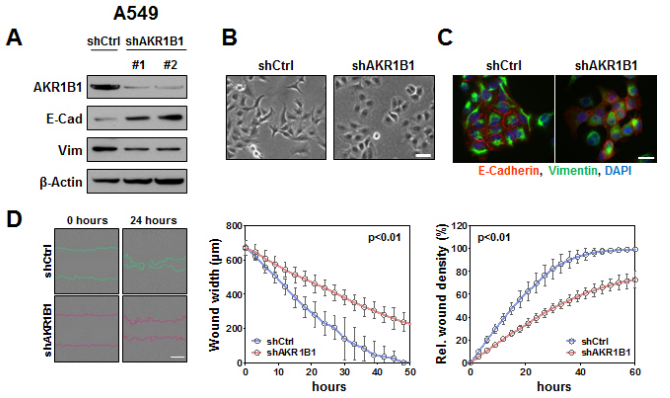
1. Cancer Research (IF=12.7) paper on the role of AKR1B1 as a driver of EMT in cancer.
2. Cell Death and Differentiation (IF=15.8) paper on the role of thymidylate synthase in maintaining the EMT/CSC phenotype
3. Oncogene (IF=9.8) paper on the role of miRNA-200b/c in balancing proliferation and differentiation

Special methods

1. miRNA activity reporter in living cells
2. Incucyte ZOOM real-time cell imaging
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.



AKR1B1 suppression inhibits EMT. A) Western blot, B) microscopic pictures C) immunofluorescence of E-Cadherin and Vimentin, and D) migration assay in A549 infected with shRNA targeting AKR1B1 vs. control cells (Schwab et al. Cancer Research 2018).

Publications (selection of)

Parma B, Ramesh V, Gollavilli PN, Siddiqui AM, Pinna L, Schwab A, Marshall S, Zhang S, Pilarsky C, Napoli F, Volante M, Urbanczyk M, Mielenz D, Schroeder HD, Stemmler M, Wurdak H, Ceppi P (2021) Metabolic impairment of non-small cell lung cancers by mitochondrial HSPD1 targeting. Journal of Experimental and Clinical Cancer Research, 40(1):248. doi: 10.1186/s13046-021-02049-8.

Gollavilli PN, Parma B, Siddiqui A, Yang H, Ramesh V, Napoli F, Schwab A, Natesan R, Mielenz D, Asangani IA, Brabletz T, Pilarsky T, Ceppi P (2021). The role of miR-200b/c in balancing EMT and proliferation revealed by an activity reporter. Oncogene;40(12):2309-2322.

Ramesh V, Brabletz T, Ceppi P (2020). Targeting EMT in Cancer with Repurposed Metabolic Inhibitors. Trends in Cancer;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.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.

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, 2021 - Health Insurance Company "Danmark", The role of nutrition on lung tumorigenesis and progression, 2021-0009 (2022-2025).

Paolo Ceppi, 2021 – Novo Nordisk Foundation, Hallas-Møller Emerging Investigator grant, Understanding and targeting the polyol pathway and fructose dependency of non-small-cell lung carcinoma, 0066909 (2021-2026).

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

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

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

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, 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).

Prof. Dr. Dulin

Prof. Dr. David Dulin

N2 09/2016 - 08/2022

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Summary

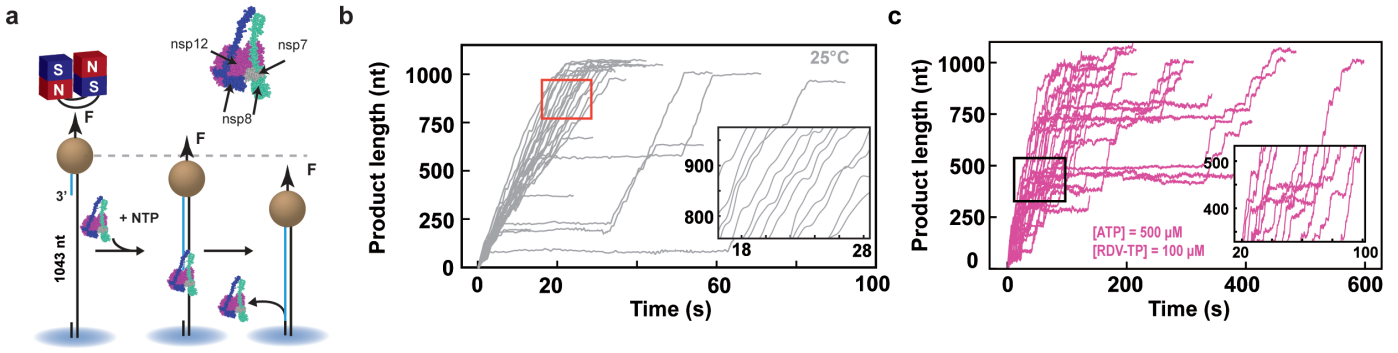
We aim at elucidating how directional transcription termination is mediated by MTERF1 in human mitochondria, the cell power plant. To this end, we developed a biophysical approach to mechanically probe whether MTERF1 senses the transcription direction of the mitochondrial RNA polymerase and terminate 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

- We developed a new assay to monitor the SARS-CoV-2 replication-transcription complex (RTC, the main antiviral drug target against coronaviruses) at near single nucleotide resolution, revealing its nucleotide addition cycle (Bera, Seifert, et al. Cell Rep. 2021).
- We applied this assay to evaluate the mechanism of action of several antiviral nucleotide analogs on SARS-CoV-2 RTC, discovering the real mechanism of action of Remdesivir (Bera, Seifert, et al., eLife 2021).

Special methods

- We developed and apply custom high-throughput and high-resolution magnetic tweezers assays to characterize the mechano-chemical properties of protein nucleic acid interactions, such as the non-structural protein of SARS-CoV-2 involved in viral genome replication.
- We have developed a combined fluorescence-magnetic tweezers assay to image and mechanically probe the protein-nucleic acid complex, but also to perform flow-stretching experiments.



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.

Publications (selection of)

Seifert M, Bera SC, van Nies P, Kirchdoerfer RN, Shannon A, Le TTN, Meng X, Xia H, Wood JM, Harris LD, Papini FS, Arnold JJ, Almo SC, Grove TL, Shi P-Y, Xiang Y, Canard B, Depken M, Cameron CE, Dulin D (2021) Inhibition of SARS-CoV-2 polymerase by nucleotide analogs: a single molecule perspective. eLife, 10 :e70968

Bera SC, Seifert M, Kirchdoerfer RN, van Nies P, Wubulikasimu Y, Quack S, Papini FS, Arnold JJ, Canard B, Cameron CE, Depken M and Dulin D (2021) The nucleotide addition cycle of the SARS-CoV-2 polymerase. Cell Reports. 36 (10). 109650

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, gkaa233.

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. 16;47(22):e144

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

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.

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, started 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, started August 2021. Principal investigator.

DFG DU1872/5-1, Determinants and dynamics of RNA polymerase I transcription initiation, 30 months, started July 2021. Principal investigator.

NIH R01AI161841-01, Coronavirus replication. 5 years duration, started April 1st, 2021. Co-applicant.

Organ crosstalk in IMIDs

Prof. Dr. Günther

N5 07/2021 – 06/2024

Prof. Dr. Claudia Günther, Department of Medicine 1

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Abstract

A substantial fraction of IMID patients does not sufficiently respond to current therapeutic approaches, whereas others require life-long and cost-intensive treatments. Therefore, both technological as well as scientific progress is urgently needed to allow innovative patient-centred precision medicine. Within the next 5 years, we will establish novel preclinical models to better understand disease mechanisms, to identify novel therapeutic approaches and to allow high throughput drug screening. This will be achieved by combining immunological research with stem cell biology, biophysical approaches and artificial intelligence.

Important results

Current research has attributed the powerful microbial impact on the host organism to bacterial-derived biomolecules transferred to mammalian host cells. We recently uncovered that outer-membrane vesicles (OMVs) released by microbes can serve as a communication tool to maintain and modulate microbe-host interaction in the gut and far beyond.

Special methods

- Human/murine organoid cultures (intestinal, biliary)
- host-microbe communication via extracellular vesicles (EVs) (bacterial vesicle isolation)
- mouse models for cholestatic liver diseases

Publications

Bittel M, Reichert P, Sarfati I, Dressel A, Leikam S, Uderhardt S, Stolzer I, Phu TA, Ng M, Vu NK, Tenzer S, Distler U, Wirtz S, Rothhammer V, Neurath MF, Raffai RL*, Günther* C, Momma S* (2021) Visualizing Transfer of Microbial biomolecules by Outer Membrane Vesicles in Microbe-Host-Communication in vivo. J Extracell Vesicles doi: 10.1002/jev2.12159. shared senior authorship

Rare glomerular diseases

Prof. Dr. Müller-Deile

N6 04/2021 – 03/2023

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

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Abstract

We investigate the role of cell-cell communication through miR containing exosomes and circulating factors in rare glomerular diseases. We use a 3D glomerular co-culture, the zebrafish model and mice model to investigate this research question. We speculate that autophagy and exosome secretion are linked by endolysosomal pathways and are dysregulated in membranous glomerulonephritis. We use Raman spectroscopy to get a molecular fingerprint in primary FSGS caused by unknown circulating factors.

Important results

- MiRNA containing endothelial cell derived exosomes induce podocyte cytoskeleton rearrangement.
- Podocyte NPNT is important for proper glomerular function and is regulated by endothelial cell derived miR-192 in membranous glomerulonephritis.
- Changed lipid metabolome profiles associate with primary FSGS that might reflect a new disease subtype.

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

Publications

Müller-Deile J, Sopel N, Ohs A, et al. Glomerular Endothelial Cell-Derived microRNA-192 Regulates Nephronectin Expression in Idiopathic Membranous Glomerulonephritis. J Am Soc Nephrol. 2021;32(11):2777-2794. (IF 10,1)

Forging neural cell identity

Prof. Dr. Karow

N7 07/2021 – 06/2023

Prof. Dr. Marisa Karow, Institute of Biochemistry

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Abstract

Based on our previous work on direct lineage reprogramming of adult human brain pericytes into induced neurons (iNs), we are here following the hypothesis that amongst the genes allowing fate switch of postmitotic pericytes into iNs, novel regulators of human neurogenesis can be identified. We are therefore dissecting the molecular framework underlying successful pericyte-to-iN conversion by performing single cell RNA-sequencing as well as continuous live-imaging.

Publications

no project-specific publications so far

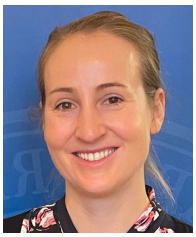
Important results

- Construction of reprogramming vectors carrying direct fusions of transcription factors (Ascl1, Sox2, Neurog2) with fluorescent reporters
- Establishment of nuclei isolation from pericytes undergoing reprogramming into iNs for simultaneous single cell ATAC-sequencing and single cell RNA-sequencing using the Multiome approach (10x Genomics)

Special methods

- Continuous live-imaging of fluorescently labelled pericytes undergoing reprogramming iNs for long period of time (up to 2 weeks)
- scATAC-/scRNA-seq using 10xGenomics platform (using the chromium controller) including library construction

Lysosomes & glial cells



Prof. Dr. Zunke

N8 02/2021 – 02/2024

Prof. Dr. Friederike Zunke, Department of Molecular Neurology

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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 analyze 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.

Publications

no project-specific publications so far

Important results

1. We were able to establish and differentiate oligodendroglial cell lines overexpressing PD-associated protein a-synuclein.
2. First results indicate impaired lysosomal function in oligodendrocytes harboring high a-synuclein level.
3. Rescue experiments in order to decrease a-synuclein burden were started.

Special methods

1. Live-cell lysosomal enzyme activity assays: e.g. Cathepsin B, L, b-Glucocerebrosidase
2. Induced pluripotent stem cells & differentiation protocols (neuronal, oligodendroglial)
3. Protein missfolding cyclic amplification assay (PMCA): amplification of misfolded protein (e.g. a-synuclein) from lysate or human tissue

Funded junior projects in 2021:

No.	Name	Institution		Project title
J67	PD Dr. Regina Jitschin	Department of Medicine 5	O	Metabolic reprogramming of AML MDSCs
J69	Dr. Christiane Krystelle Nganou Makamdop	Clin. and Mol. Virology	I	Effect of HIV on pre-existing vaccine immunity
J70	Dr. Tilman Jobst-Schwan	Department of Medicine 4	R	Gene discovery in kidney disease
J71	Dr. Andre Kraus	Department of Medicine 4	R	P2Y2R-dependent cyst growth in ADPKD
J74	Dr. Seda Salar	Department of Psychiatry and Psychotherapy	N	CtBP1 and neuronal excitability
J75	Dr. Sebastian Meyer	Biometry and Epidemiology	S	Statistical Analysis of Infectious Disease Spread
J76	Dr. Katerina Kachler	Department of Medicine 3	I	The role of itaconate in osteoclasts
J77	Dr. René Pfleifle	Department of Medicine 3	I	Characterization of autoreactive B cells during RA
J78	Dr. Barbara Ruder	Department of Medicine 1	I	Role of ferroptosis during microbial infection
J79	Dr. Christian Schwartz	Clin. Microbiology, Immunology and Hygiene	I	PD-L1 function during obesity and dysbiosis
J81	Prof. Dr. Samir Jabari	Institute of Neuropathology	M	Web based Brain Tumor Image Classifier (WeB-TIC)
J83	Dr. Ingo Ganzleben	Department of Medicine 1	I	Role of ferroptosis in inflammatory lung diseases
J84	Dr. Sascha Kretschmann	Department of Medicine 5	I	Direct vs. indirect class II antigen presentation
J85	Dr. Kristina Scheibe	Department of Medicine 1	I	Cell-type-specific roles of IL36 in the Intestine
J86	Dr. Heike Knott	Department of Medicine 1	I	Virome/macrophage interaction in Crohn's disease
J87	Prof. Dr. Stefan Uderhardt	Department of Medicine 3	I	Network Communication in Inflammation
J88	Dr. Florian Krach	Department of Stem Cell Biology	N	New RNA-binding proteins in sporadic ALS
J89	Dr. Adrian Regensburger	Department of Pediatrics and Adolescent Medicine	M	MSOT imaging of strictures in Crohn's disease
J90	Dr. Darja Andreev	Department of Medicine 3	I	The impact of Eos on bone loss
J91	Dr. Jean-Philippe Auger	Department of Medicine 3	I	Glucocorticoid-induced macrophage reprogramming
J92	Dr. Alana Hoffmann	Department of Molecular Neurology	N	Neuron-microglia interaction in MSA
J93	Dr. Liubov Kalinichenko	Department of Psychiatry and Psychotherapy	N	Lipids and Serotonin in drug instrumentalization
J94	Dr. Patrick Süß	Department of Molecular Neurology	N	Neuroinflammation and synucleinopathy in IBD
J95	Dr. Franziska Thiele	Institute of Biochemistry	N	Role of Tip60 in the PNS
J96	Dr. Maria de los Reyes Gamez Belmonte	Department of Medicine 1	S	Bace1/Bace2 in colorectal cancer development
J97	Dr. Benedikt Jacobs	Department of Medicine 5	S	Immune-metabolic dysfunction of NK cells

I - Infection and Immunology, N - Neurosciences, O - Oncology, R - Renal and Vascular Research, M - Medical Engineering, S - Others

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 (MDSC) have gained momentum as mediators of immune escape. We have aimed 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+ MDSC accumulate in newly diagnosed AML patients and suppress T-cell responses in an IDO-dependent manner.
2. AML MDSC can be targeted by autologous T-cells using CD3/CD33 bispecific antibodies.
3. Palmitoylated proteins on AML-derived extracellular vesicles promote the induction of MDSC 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 *shared senior authorship

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. IF: 12.791

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. IF: 11.37

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 6(1):116. doi: 10.1186/s40425-018-0432-9. IF: 13.751

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 due to parental leave

Abstract

This project studied the quality of antigen-specific T cell responses in HIV-infected persons on antiretroviral therapy and with prior vaccinations against measles virus (MV) and tetanus toxoid (TT). Markers of inflammation and immune activation, recall T cell responses to MV and TT as well as transcriptome analysis of sorted antigen-specific T cells was assessed. Obtained results highlight deleterious effects of HIV infection on the maintenance of vaccine-induced immunity.

Publications

no project-specific publications so far

Important results

- Our work shows blunted recall T cell responses associating with persistent inflammation and immune activation in HIV infection.
- Transcriptome analysis shows distinct gene signatures in comparison to uninfected persons, with unique gene expression profile of antigen-specific T cells and numerous pathways discriminating responses between groups.

Special methods

We have established methods to assess antigen-specific T cell responses (proliferation and cytokine production) as well as a workflow for flow cytometry sort of CD4 and CD8 antigen-specific T cells based on the expression of cell surface markers.

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
- Identification of a novel ACTN4 variant in a patient with SRNS
- Functional data excluded splice site variant of KIF21A as disease causing in a family with SRNS. RNA-seq revealed 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 aim of our project was to descramble the 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 (ADPKD). We have successfully analyzed 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 tested for ATP-dependent effects via micropuncture experiments in an in vitro cyst model.

Important results

1. Injection of ATP into in vitro cysts leads to increased cyst growth.
2. ATP application is accompanied by an increased Ca^{2+}-dependent Cl^- conductance.
3. Treatment with Suramin trends towards an ameliorated cystic phenotype in an ADPKD mouse model.
4. Deletion of P2Y2R significantly reduces cyst growth in vivo.

Special methods

1. Micro puncture technique of in vitro cysts using custom-built micro grinded glass capillaries.
2. Life cell imaging of micro-punctured in vitro cysts.
3. Genotype-phenotype correlation of in vitro and in vivo findings upon deletion of the Pkd1 gene.

Publications

Cabrita I*, Kraus A*, Scholz J, Skoczynski K, Schreiber R, Kunzelmann K, Buchholz B (2020) Cyst growth in ADPKD is prevented by pharmacological and genetic inhibition of TMEM16A in vivo Nat Commun. 11(1):4320. PMID: 32859916. *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. PMID: 32885302. *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. 94(5):887-899, PMID: 30173898

CtBP1 and neuronal excitability

NEUROSCIENCES

Dr. Salar

J74 02/2019 - 07/2021

Dr. Seda Salar, Department of Psychiatry and Psychotherapy

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Abstract

We aimed to reveal the role of C-terminal binding protein 1 (CtBP1) in the hippocampus by employing acute brain slices from CtBP1 knock-out (KO) mice. While basal synaptic transmission was intact, neurotransmission was impaired under glycolytic stress and irreversibly reduced under combined glycolytic-mitochondrial stress. In addition, the expression of mitochondrial genes and mitochondrial function were altered indicating the contribution of CtBP1 in neurotransmission via metabolic regulation.

Important results

We characterized for the first time in acute hippocampal slices from CtBP1 KO mice that,

1) the synaptic plasticity was impaired in the presence of intact basal excitatory synaptic transmission.
2) the resilience of neurotransmission was diminished under glycolytic and mitochondrial stress.
3) the mitochondrial function and gene expression were altered.

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

Anni D, Weiss EM, Guhathakurta D, Akdas EY, Klueva J, Zeitler S, Andres-Alonso M, Huth T, Fejtova A (2021) Aβ1-16 controls synaptic vesicle pools at excitatory synapses via cholinergic modulation of synapsin phosphorylation. Cell Mol Life Sci. 78(11):4973-4992. doi: 10.1007/s00018-021-03835-5

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

OTHERS

Dr. Meyer

J75 10/2018 - 04/2021

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

Endemic-epidemic models can be extended to time series of proportions or counts with excessive zeros. Likelihood-based inference is straightforward provided that numerical optimization uses analytical derivatives. In comparison with the existing SARIMA and HHH models, the proposed models improve both the goodness-of-fit and short-term forecast.

Special methods

Both models generate simulation-based probabilistic forecasts to communicate uncertainty. Proper scoring rules are used to measure predictive performance including calibration and sharpness. All estimation 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

Lu J, Meyer S (2022) An endemic-epidemic beta model for time series of infectious disease proportions. Journal of Applied Statistics, doi:10.1080/02664763.2021.1962264

The role of itaconate in osteoclasts

Dr. Kachler

J76 10/2019 - 04/2022

Dr. Katerina Kachler, Department of Medicine 3

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IMMUNOLOGY AND INFECTION

Abstract

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease of the joints that is associated with excessive osteoclast activity and consequently, bone degradation. Recent studies indicate that the maturation capacity and function of osteoclasts might 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

- Osteoclasts, derived from PBMCs of RA patients show increased glycolytic activity.
- Itaconate suppresses osteoclastogenesis by inhibiting glycolysis in a Hif1α-dependent manner.
- Itaconate-deficiency enhances bone erosion in a K/BxN serum induced arthritis model, while in vivo treatment with the itaconate-derivative 4-OI ameliorates the disease.

Special methods

- In vitro cell differentiation of murine osteoclasts form bone marrow-derived monocytes and human osteoclasts from peripheral blood mononuclear cells.
- Analysis of the metabolic state of in vitro cultured osteoclasts using extracellular flux assays (Agilent Seahorse XF Analyzer).
- CRISPR/Cas9-mediated gene editing in in vitro cultured osteoclasts.

Characterization of autoreactive B cells during RA

Dr. Pfeifle

J77 11/2019 - 04/2022

Dr. René Pfleifle, Department of Medicine 3

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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 healthy individuals (HI) asymptomatic autoimmunity (pre-RA) into RA.

Publications

no project-specific publications so far

Important results

We detected ACPA-specific B cells in active RA, pre-RA, and healthy individuals (HI) using flow cytometry. All ACPA+ B cells were memory B cells. However, while ACPA+ cells derived from RA patients and pre-RA individuals were class-switched to IgG, ACPA+ B cells in healthy controls were less abundant and all from the IgM isotype, suggesting that not the emergence of ACPA+ B cells in the periphery, but the evolution into a pathogenic phenotype is crucial for RA pathogenesis. Therefore, we established a protocol for isolating and analyzing ACPA+ B cells using single-cell sequencing to analyze these transcriptomic changes in HI, pre-RA, and RA.

Special methods

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

Role of ferroptosis during microbial infection


Dr. Ruder

J78 01/2019 - 02/2022

IMMUNOLOGY AND INFECTION

Dr. Barbara Ruder, Department of Medicine 1

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Abstract

In this project, we aim to investigate the role of the Gluthathione 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 bacterial infection and might display a new therapeutic target for treatment of acute infections. In this part of the project, we analyzed ferroptosis and GPX4 activity in different experimental settings.

Important results

In this part of the project, we identified inhibitors, which were able to block ferroptosis in macrophages in vitro. Moreover, we observed that reduction of the GPX4 activity during maturation of macrophages influenced the activation profile of these cells. In addition, we established an experimental setting to detect ferroptosis by flow cytometry.

Special methods

Flow cytometry, LDH-assay, mouse infection models

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

Bardenbacher M, Ruder B, Britzen-Laurent N, Naschberger E, Becker C, Palmisano R et al. (2020) Investigating Intestinal Barrier Breakdown in Living Organoids. J Vis Exp 26;(157)

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 on dendritic cells reduces Th1 polarization and limits adipose tissue inflammation
- Intervention with immune checkpoint inhibitors during obesity aggravates weight gain

Special methods

- Flow cytometry, cell sorting and ex vivo culture of mouse and human ILC2
- Animal model of diet-induced obesity and analysis of human adipose tissue
- 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

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

Malformations of cortical development (MCD) comprise a broad spectrum of epilepsy- associated structural brain lesions. Disease diagnosis remain challenging. Molecular classification of histopathological entities may help rationalize the diagnostic process. Additionally we developed an open-source library dealing with tasks in the processing of whole-slide images (WSI) and helping with the training and evaluation of neuronal networks as processing WSI can be intricate and labor intensive.

Important results

DNA methylation-based MCD classification is suitable across major histopathological entities amenable to epilepsy surgery and will help establish an integrated diagnostic classification scheme for epilepsy-associated MCD.

We developed a library enabling users to perform deep learning without the burden of managing WSI-associated overhead.

Special methods

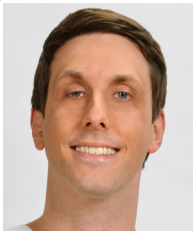
We present a retrospective, multi-center analysis of genome-wide DNA methylation from human brain specimens obtained from epilepsy surgery using a self written library for EPIC 850 K BeadChip array analysis open to the public.

We developed a whole-Slide Image Managing Library Based on Fastai for Deep Learning in the Context of Histopathology.

Publications

Wirries A, Geiger F, Hammad A, Redder A, Oberkircher L, Ruchholtz S, Bluemcke I, Jabari S. Combined Artificial Intelligence Approaches Analyzing 1000 Conservative Patients with Back Pain-A Methodological Pathway to Predicting Treatment Efficacy and Diagnostic Groups. Diagnostics (Basel). 2021 Oct 20;11(11):1934. doi: 10.3390/diagnostics11111934. PMID: 34829286; PMCID: PMC8619195.

Role of ferroptosis in inflammatory lung diseases



Dr. Ganzleben

J83 10/2020 - 11/2021

IMMUNOLOGY AND INFECTION

Dr. Ingo Ganzleben, Department of Medicine 1

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Abstract

Ferroptosis is a novel form of regulated cell death with major importance in inflammatory conditions. The current project's aim was to elucidate the functional role of ferroptosis and its main regulator GPX4 in the pathophysiology of the inflammatory lung disease bronchial asthma. Our preliminary results suggest an important role for GPX4 in bronchial asthma and ferroptosis inhibition as a potential treatment avenue based on our preclinical disease model.

Publications

no project-specific publications so far

Important results

Our preliminary results suggest that 1) Ferroptosis plays a role in the pathogenesis of bronchial asthma, 2) GPX4 plays an important role in the bronchial epithelium in allergic asthma, and 3) Pharmacologic inhibition of ferroptosis alleviates bronchial asthma.

Special methods

1. Murine disease model of bronchial asthma
2. Micro computed tomography (µCT)
3. 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

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 class II-restricted antigens travel in distinct compartments and therefore undergo differential processing. These processing steps which are critical for presentation, are characterized by antigen-specific properties.

Publications

no project-specific publications so far

Important results

- Currently, two proteins are fused, each of which with different properties in antigen presentation
- Successful cloning of genes and retroviral transduction of cell lines to establish cell culture assays
- Identification of sequence sections with putative roles in trans-Golgi sorting or HSC70-mediated cargo sorting

Special methods

- Culture and re-stimulation of primary and antigen-specific CD4+ T-cell clones
- Invention and usage of an accelerated antigen presentation screen assay
- Cloning techniques, e.g. a two-step PCR technique to fuse proteins

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

Abstract

IL36R signaling is known to be critically involved in intestinal inflammation and fibrosis, but the cell-type-specific functions of IL36R signaling in this context have to be further investigated. In our project, we will compare intestinal epithelial and fibroblast-specific IL36R ko in acute and chronic intestinal inflammation in vivo. We will further analyze the quality and quantity of ECM production by primary colon fibroblasts also upon co-culture with intestinal epithelial organoids.

Publications

no project-specific publications so far

Important results

- Mice with defective IL36R signaling in intestinal epithelial cells and fibroblasts are more sensitive to DSS in an acute setup compared to littermate controls
- In chronic DSS, IL36RΔIEC and IL36RΔfibro showed a protected phenotype regarding fibrotic remodeling compared to IL36Rfl mice
- The results fit to former results of universal IL36R-/- animals

Special methods

As an untargeted approach, we analyzed the secretome of primary fibroblasts upon IL36R activation by liquid chromatography-mass spectrometry in cooperation with the Chair of Food Chemistry (Dep. of Chemistry and Pharmacy). Bioinformatic evaluation of the data detected (proof-of-concept) the secretion of various proteins like keratins and collagens.

Virome/macrophage interaction in Crohn's disease


Dr. Schmitt

J86 01/2021 - 09/2022

Dr. Heike Knott, Department of Medicine 1
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IMMUNOLOGY AND INFECTION

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 IL23 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

Publications

no project-specific publications so far

Important results

1. Different identified viruses are able to induce IL23 expression in CD anti-TNF non-responders
2. The release of IL23 is TLR9 dependent and increases the expression of IL23R on intestinal macrophages from CD anti-TNF non-responders
3. IL23R expression is upregulated during in vitro generation of intestinal macrophages after IL23 stimulation

Special methods

1. Growing and maintaining of 3D human intestinal and colonic organoids
2. Characterization of human intestinal macrophages
3. Viral metagenomics analysis

Network Communication in Inflammation


Prof. Dr. Uderhardt

J87 01/2021 - 06/2023

Prof. Dr. Stefan Uderhardt, Department of Medicine 3
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IMMUNOLOGY AND INFECTION

Abstract

Inflammation has evolved to protect us from the outside world. While the mechanisms that govern inflammation once ongoing are well defined, we lack basic knowledge of the processes that regulate its actual onset in vivo. Here, we describe hard-wired communication mechanisms and synergies that allow macrophage-stroma networks to operate as a functional syncytium, a hitherto unknown operating system that coordinates stress responses and actively prevents the onset of inflammation.

Publications

no project-specific publications so far

Important results

- Stroma cells and macrophages express gap junction proteins that be visualized in 3d within intact tissue environments
- Pharmacological inhibition of gap junctions disrupts macrophage damage response in vivo.
- Pharmacological inhibition of gap junctions does not affect neutrophil swarming dynamics in vivo.

Special methods

- Intravital imaging
- Whole mount tissue imaging
- 3D-reconstruction and quantitative histocytometry

New RNA-binding proteins in sporadic ALS


Dr. Krach

J88 11/2020 - 05/2023

NEUROSCIENCES

Dr. Florian Krach, Department of Stem Cell Biology
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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 developed 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.

Publications

no project-specific publications so far

Important results

We overexpressed neuron-enriched RNA binding proteins in iPSC-derived motor neurons. We aim analyze alternative splicing using RNA-seq thereof. Additionally, we differentiated patient and control iPSC-lines into motor neurons, biochemically fractioned the insoluble protein parts and aim to analyze the ALS insoluble proteome by mass spectrometry.

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 proteins

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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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.

Important results

Raster-scanning optoacoustic Mesoscopy (RSOM) allows visualization of murine intestine.

A pilot-trial for assessing pediatric inflammatory bowel disease with Multispectral optoacoustic Tomography (MSOT) started recruiting 03/2021. A further study for noninvasive characterization of postprandial intestinal blood flow using MSOT started 11/2021.

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) quantfication of single WLs and different unmixed MSOT parameters (e.g. hemoglobin).

Publications

Aguilar C*, Regensburger AP*, Knieling F, Wagner AL, Siebenlist G, Woelfle J, Koehler H, Hoerning A, Jüngert J. (2021) Pediatric Buried Bumper Syndrome: Diagnostic Validity of Transabdominal Ultrasound and Artificial Intelligence. Ultraschall Med. doi: 10.1055/a-1471-3039. Epub ahead of print. PMID: 34034349.

Wagner AL, Danko V, Federle A, Klett D, Simon D, Heiss R, Jüngert J, Uder M, Schett G, Neurath MF, Woelfle J, Waldner MJ, Trollmann R, Regensburger AP*, Knieling F*. (2020) Precision of handheld multispectral optoacoustic tomography for muscle imaging. Photoacoustics. 11;21:100220. doi: 10.1016/j.pacs.2020.100220. PMID: 33318928; PMCID: PMC7723806.

The impact of Eos on bone loss


Dr. Andreev

J90 01/2022 - 06/2024

Dr. Darja Andreev, Department of Medicine 3
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IMMUNOLOGY AND INFECTION

recently started

Abstract

A healthy skeleton relies on a balance between bone-forming osteoblasts and bone-resorbing osteoclasts. A shift towards increased osteoclast activity can therefore lead to bone loss. The immune system strongly affects osteoclast biology, usually promoting osteoclast development. Interestingly, we demonstrated that eosinophils negatively regulate osteoclast formation and activity. Thus, it is of high relevance to unveil the molecular mechanisms underlying this regulatory function of eosinophils.

Special methods

- In vitro cell differentiation of murine osteoclasts from bone marrow-derived monocytes and human osteoclasts from peripheral blood mononuclear cells.
- Murine models of postmenopausal osteoporosis and inflammatory arthritis.
- Single-cell RNA sequencing with sorted eosinophils and RNA sequencing with in vitro osteoclasts.

Publications

no project-specific publications so far

Glucocorticoid-induced macrophage reprogramming


Dr. Auger

J91 01/2022 - 06/2024

Dr. Jean-Philippe Auger, Department of Medicine 3
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IMMUNOLOGY AND INFECTION

recently started

Abstract

Glucocorticoids are amongst the most important anti-inflammatory drugs, promoting inflammatory resolution via the functional reprogramming of macrophages, a process that promotes itaconate production. Though itaconate is a metabolite participating in immune-metabolic rewiring, its role and effects, as with the underlying mechanisms involved in its production, on immunometabolism and inflammatory resolution remain unknown, yet could contribute to further optimizing glucocorticoid treatment.

Special methods

- Primary murine and human macrophage cultures
- Evaluation of the metabolic state of cultured cells using extracellular flux analyses (Seahorse XF Analyzer)
- Murine models of acute lipopolysaccharide-induced lung injury and autoimmune K/BxN serum transfer arthritis

Publications

no project-specific publications so far

Neuron-microglia interaction in MSA

NEUROSCIENCES

Dr. Hoffmann

J92 07/2021 - 12/2021

Dr. Alana Hoffmann, Department of Molecular Neurology
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Abstract

Multiple system atrophy (MSA) is characterized by neurodegeneration and neuroinflammatory response of myeloid cells. The goal of this project is to decipher the role of microglia in disease mechanisms of MSA. Depletion of microglia results in improved survival, however, also in behavioural motor deficits in a MSA mouse model. Structural, biochemical and transcriptional approaches will be used to characterize changes in neuronal connectivity and synaptic networks upon microglia depletion in MSA.

Publications

no project-specific publications so far

Lipids and Serotonin in drug instrumentalization

NEUROSCIENCES

Dr. Kalinichenko

J93 01/2022 - 06/2024

Dr. Liubov Kalinichenko, Department of Psychiatry and Psychotherapy
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recently started

Abstract

Alcoholism and depression are highly comorbid disorders. Neutral sphingomyelinase (NSM) is suggested as a missing link between emotional status and alcohol consumption due to the downstream effects on the serotoninergic system. A new line of mice with NSM gene knockout specifically in the brain serotoninergic system was created to investigate if the interaction between NSM and the brain serotoninergic system determines the comorbidity between negative emotional state and alcohol consumption.

Special methods

The following methods are used in the project: behavioral testing of animals for evaluation of anxiety/depression-like behavior; in-vivo microdialysis allowing to analyze the response of brain monoaminergic systems to drug administration; intracranial administration of substances to certain brain structures with following behavioral testing.

Publications

no project-specific publications so far

Neuroinflammation and synucleinopathy in IBD


Dr. Süß

J94 12/2021 - 05/2024

Dr. Patrick Süß, Department of Molecular Neurology

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NEUROSCIENCES

recently started

Abstract

Inflammatory bowel disease (IBD) predisposes for synucleinopathies like Parkinson Disease. This is putatively caused by propagation of chronic inflammation into the brain. The hypothesis of this project is that chronic inflammation in IBD activates microglia in distinct brain regions, thereby mediating neuronal pathology and aggravating synucleinopathy. This hypothesis will be tested in post mortem brain tissue of IBD patients and mice with colitis.

Special methods

- Tracing and gene targeting of microglia using a novel and highly specific reporter mouse model based on the microglial marker gene Hexb
- Confocal microscopy of CNS immune cells and their interaction with synapses
- RNA sequencing of dissected brain regions and FACS-sorted CNS myeloid cells

Publications

no project-specific publications so far

Role of Tip60 in the PNS


Dr. Thiele

J95 01/2022 - 06/2024

Dr. Franziska Thiele, Institute of Biochemistry

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NEUROSCIENCES

recently started

Abstract

Proper Schwann cell development and myelination are essential for a functional peripheral nervous system and regulated by networks of chromatin modifiers and transcription factors. Here I plan to study the role of the acetyltransferase Tip60 as part of the Tip60/Ep400 chromatin remodeling complex in lineage progression and myelination by characterizing its target genes and interaction with transcription factor Sox10. Results may help to better understand peripheral neuropathies.

Special methods

- Phenotypic characterization of a Schwann cell- specific Tip60 mouse mutant using i.a. immunohistochemical staining
- Isolation and subsequent cultivation of primary rat Schwann cells under the influence of Tip60-inhibitors to perform RNA-Seq and ChIP-Seq
- Co-immunoprecipitations to validate physical interactions of Tip60

Publications

no project-specific publications so far

Bace1/Bace2 in colorectal cancer development


Dr. Gamez Belmonte

J96 10/2021 - 03/2024

Dr. Maria de los Reyes Gamez Belmonte, Department of Medicine 1
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ONCOLOGY

recently started

Abstract

The β-secretases (Bace1 and Bace2) are proteases involved in the pathogenesis of Alzheimer's disease (AD). However, Bace1/2 can be found in tissues other than the brain, suggesting that their role goes well beyond AD. Interestingly, our preliminary data reveal that the expression of Bace1/2 is modulated in response to intestinal inflammation and during cancer development. We hypothesize that the β-secretases might have regulatory functions in the gut and the pathophysiology of colorectal cancer

Special methods

- Intestinal (small intestine and colon) and tumor organoids culture
- Experimental induction of inflammation and colorectal cancer (DSS and AOM/DSS)
- Generation of knockout cell lines using CRISPR-Cas9 technology

Publications

no project-specific publications so far

Immune-metabolic dysfunction of NK cells


Dr. Jacobs

J97 01/2022 - 06/2024

Dr. Benedikt Jacobs, Department of Medicine 5
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ONCOLOGY

recently started

Abstract

The metabolism of reconstituting NK cells upon autologous SCT is altered in lymphoma patients who experience an early relapse upon transplantation. We intend to decipher the underlying cellular and molecular mechanism to identify factors leading to the increased relapse risk and to reveal potential opportunities to modify them. This will lay the foundation for further projects investigating NK cell reconstitution upon allogeneic SCT and CAR-transfected NK cell expansion in tumor patients.

Special method

Our group is specialized in the analysis of phenotypical, immune-metabolic and functional properties of NK cells from healthy donor and patient samples using multicolor flow cytometry techniques. Moreover, in order to optimize staining quality and reduce false antibody pipetting, we apply live- and fixed-cell fluorescent cell barcoding techniques.

Publications

no project-specific publications so far

Funded ELAN projects in 2021:

No.	Name	Institution		Project title
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
P054	Dr. Florian Krach	Stemm Cell Biology	N	Agrin and the neuromuscular junction in ALS
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	Dr. Moritz Zaiss	Neuroradiology	M	Non-invasive Metabolic MR Fingerprinting
P073	Dr. Maximilian Sprügel	Neurology	N	Role of pericytes in intracerebral hemorrhage
P074	Dr. Sven Falk	Biochemistry	N	Molecular control of neural stem cell decisions
P075	Dr. Philipp Arnold	Anatomy II	S	CD109 and cellular functions
P076	PD Dr. Franz Marxreiter	Molecular Neurology	N	MRI based diagnosis of Multiple System Atrophy
P077	Dr. Dmytro Royzman	Immune Modulation	I	Modulation of human osteoclasts by sCD83
P078	Dr. Eva Schäflein	Psychosomatic Medicine a. Psychotherapy	S	Self-perception in trauma-related disorders
P079	Dr. Ulrich Rother	Surgery	R	MSOT PAD
P080	Dr. Arne Gessner	Clin. Pharmacology and Clin. Toxicology	I	Tryptophan metabolites and rheumatoid arthritis
P081	Dr. Ines Böhme	Biochemistry	O	SNAT1/SLC38A1 in human melanoma
P082	Dr. Sabine Britting	Institute for Biomedicine of Aging	S	Safer Cycling in Older Age – Impact on Stress
P083	PD Dr. Rocío López Posadas	Medicine 1	I	Epithelial Rho GTPases and type2 immunity
P084	PD Dr. Kilian Schober	Clin. Microbiology, Immunology a. Hygiene	I	TCR repertoires after SARS-CoV-2 vaccination
P085	Dr. Fabian Müller	Medicine 5	O	Duotoxins for the treatment of cancer
P086	Dr. Corinna Lesley Seidel	Orthodontics and Orofascial Orthopedics	I	Oral symbiosis and dysbiosis
P087	Dr. Lisa Klotz	Biochemistry	N	Protective function of mGluR7 in the cochlea
P088	Prof. Dr. Miriam Kalbitz	Surgery	I	IL-18 dependent Cx43 translocation after trauma
P089	Dr. Harriet Morf	Medicine 3	I	Effect of Yoga on Spine Flexibility in SpA
P090	Dr. Katharina Gerlach	Medicine 1	I	Analysis of NFATc3 in intestinal inflammation

I - Infection and Immunology, N - Neurosciences, O - Oncology, R - Renal and Vascular Research, M - Medical Engineering, S - Others

No.	Name	Institution		Project title
P091	Dr. Mayte Buchbender	Oral and Cranio-Maxillofacial Surgery	I	Association between P and IBD
P092	Dr. Tanja Müller	Medicine 1	O	Role of GPR15L in colorectal cancer
P093	Dr. Kaveh Roshanbinfar	Nephropathology	M	Vascularization of an ECM-mimicking hydrogel
P094	Dr. Wibke Müller-Seubert	Plastic and Hand Surgery	S	Influence of stem cells on irradiated flaps
P095	Dr. Frederik Stübs	Obsterics and Gynecology	O	PD-L1 expression in vulvar cancer
P096	Dr. Andrea-Hermina Györfi	Medicine 3	I	DAX-1 mediates fibroblast activation and fibrosis
P097	Dr. Ulrike Steffen	Medicine 3	I	Anti-osteoporotic effects of metoprolol
P098	Dr. Vugar Azizov	Medicine 3	I	Acetate adversely affects T cell migration
P099	Dr. Krystelle Nganou	Clin. and Mol. Virology	I	Interplay between TCR and microbiome
P100	Dr. Simon Lévy	Radiology	M	Dynamic MR pulse design for fat suppression
P101	Prof. Dr. Heiko Reutter	Pediatrics and Adolescent Medicine	S	Exome and zebrafish analyses on VATER/VACTERL

I - Infection and Immunology, N - Neurosciences, O - Oncology, R - Renal and Vascular Research, M - Medical Engineering, S - Others

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.

I	Infection and Immunology
N	Neurosciences
O	Oncology
R	Renal and Vascular Research
M	Medical Engineering
S	Others

Agrin and the neuromuscular junction in ALS

P054 10/2019 - 03/2021

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.

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.

Wnt inhibitory peptide

P058 04/2020 - 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.

Regional neuroinflammation in RA

P059 03/2020 - 11/2021

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.

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.

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, Department 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.

I	Infection and Immunology
N	Neurosciences
O	Oncology
R	Renal and Vascular Research
M	Medical Engineering
S	Others

Assay of neuroinflammation in chronic pain

P063 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.

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.

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.

Direct reprogramming within brain organoids

P068 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.

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.

Encoding of behaviours in the hypothalamus

P070 06/2021 - 05/2022

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.

I	Infection and Immunology
N	Neurosciences
O	Oncology
R	Renal and Vascular Research
M	Medical Engineering
S	Others

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.

Non-invasive Metabolic MR Fingerprinting

P072 06/2021 - 05/2022

Prof. Dr. Moritz Zaiss, Department 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.

Role of pericytes in intracerebral hemorrhage

P73 05/2021 - 05/2022

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.

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.

CD109 and cellular functions

P075 04/2021 - 04/2022

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.

MRI based diagnosis of Multiple System Atrophy

P076 06/2021 - 11/2022

PD 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.

Modulation of human osteoclasts by sCD83

P077 07/2021 - 06/2022

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.

Self-perception in trauma-related disorders

P078 09/2021 - 08/2022

Dr. Eva Schäflein, Department of Psychosomatic Medicine and Psychotherapy

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Abstract

Severe dissociative disorders are characterized by distinct self-perception-related stress accompanied by autonomic blunting. The aim of the current study is to investigate self-reported, psychophysiological and biological stress reactions upon an experimental self-perception paradigm in patients suffering from diverse post-traumatic conditions with different levels of dissociation, to elucidate potential associations between dissociation intensity and the aversiveness of self-perception.

I	Infection and Immunology
N	Neurosciences
O	Oncology
R	Renal and Vascular Research
M	Medical Engineering
S	Others

MSOT PAD

P079 03/2021 - 02/2022

PD Dr. Ulrich Rother, Department of Surgery

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Abstract

Aim of the proposed study is the definition of an independent parameter for the diagnostic evaluation of the perfusion situation of the calf muscle based on MSOT-method in a cross-sectional collective of healthy volunteers and patients with different stages of PAD (study group 1). The validation of the results will be performed by an independent validation group (study group 2).

Tryptophan metabolites and rheumatoid arthritis

P080 06/2021 - 05/2022

Dr. Arne Gessner, Chair of Clinical Pharmacology and Clinical Toxicology

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Abstract

Intestinal barrier integrity is an important checkpoint in translating autoimmunity to inflammation in rheumatoid arthritis (RA). Microbial metabolites of tryptophan were shown to reduce intestinal permeability and inflammation. However, it is unknown if this translates to a favourable impact on RA. Furthermore, it is unknown how the metabolites are intestinally resorbed. These questions should be adressed in cell models of intestinal epithelium and in human serum samples.

SNAT1/SLC38A1 in human melanoma

P081 02/2023 - 01/2024

Dr. Ines Böhme, Institute of Biochemistry

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Abstract

SNAT1 mediates the transport of neutral amino acids into the cell. Preliminary data show a significant overexpression of SNAT1 in human melanoma cells compared to melanocytes. Transient downregulation of SNAT1 resulted in significant reduction of the cellular proliferation and cell cycle progression. With this project we aim to analyze the functional importance of SNAT1, an attractive therapeutic target, in human melanoma.

Safer Cycling in Older Age – Impact on Stress

P082 09/2021 - 08/2022

Dr. Sabine Britting, Institute for Biomedicine of Aging

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Abstract

SiFAr-Stress investigates the impact of cycling on stress level in older adults. Uncertainty due to change to motorized bicycle or fear of falling can be perceived as stressors for cyclists. Stress activates different physiological signal cascades and stimulate for their part low-grade inflammation, which – in the long-term – can be associated with negative health outcomes. The aim is to analyse inflammatory processes as well as the activity of stress systems.

Epithelial Rho GTPases and type2 immunity

P083 10/2021 - 09/2022

PD Dr. Rocío López Posadas, Department of Medicine 1

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Abstract

Basic research focusing on Tuft Cells (TCs) differentiation might contribute to the understanding of pleiotropic immune functions of the intestinal epithelium, which can be exploited in the context of immunomodulation. Our preliminary data support an interplay between type2 cytokines and Rac1/RhoA function within Intestinal Epithelial Cells (IECs) playing a role in the differentiation of IECs towards a TCs fate. Our aim is then to decipher the molecular mechanisms operating behind intrinsic/extrinsic control of Tuft cell fate decision.

TCR repertoires after SARS-CoV-2 vaccination

P084 07/2021 - 07/2022

PD Dr. Kilian Schober, Institute of Clinical Microbiology, Immunology and Hygiene

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Abstract

T cells are an integral part of adaptive immunity, which forms the basis of protection from infections after vaccination. While B cell and antibody responses are well understood, little is known about which antigen-reactive T cells are recruited after primary and booster vaccination, as well as into long-lasting resting memory. In this project, we will investigate these questions in SARS-CoV-2 vaccinees by state-of-the-art T cell receptor repertoire profiling and functionality assessments.

Duotoxins for the treatment of cancer

P085 07/2021 - 06/2022

Dr. Fabian Müller, Department of Medicine 5

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Abstract

We found immunotoxins - fusion proteins of toxins and antibodies - synergistically enhanced 100-fold by Paclitaxel. We developed Duotoxins combining Paclitaxel-like DM1 and immunotoxins on one antibody. But, conventional immunotoxins cannot be conjugated efficiently. After switching to full-length antibodies, an active Duotoxin was generated. Here, we aim to use novel technology to extend the concept to other targets before applying for an extension of current DFG grant.

Oral symbiosis and dysbiosis

P086 10/2021 - 09/2022

Dr. Corinna Lesley Seidel, Department of Orthodontics and Orofascial Orthopedics

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Abstract

In patients with periodontitis, orofacial clefts and partly also during orthodontic treatment an oral dysbiosis and an increase of inflammation markers have been observed. Here, for the first time a systematic analysis of the oral microbiome and local inflammation in oral niches will be carried out using 16S rDNA sequencing and multiplex immuno assay, which will be correlated with determinants such as gingivitis/periodontitis, age, orofacial clefts, exogeneous factors and orthodontic treatment.

I	Infection and Immunology
N	Neurosciences
O	Oncology
R	Renal and Vascular Research
M	Medical Engineering
S	Others

Protective function of mGluR7 in the cochlea

P087 09/2021 - 08/2021

Dr. Lisa Klotz, Institute of Biochemistry

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Abstract

MGluR7 has been correlated with hearing deficits and low glutamate affinity. Dimeric mGluRs can build inhibitory feedback loops thereby protecting the pre-synapse from toxic stimuli. Besides pre-synaptic localization of mGluR7 also mGluR4 & 8 were described pre-synaptically at IHC ribbon synapses. Heterodimeric mGluRs have unique properties, therefore it is essential to analyse if mGluR7 is present as homo- or heterodimer to analyse the function using electrophysiological techniques.

IL-18 dependent Cx43 translocation after trauma

P088 10/2021 - 09/2022

Prof. Dr. Miriam Kalbitz, Department of Surgery

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Abstract

Trauma is the leading cause of death in humans aged below 45. Trauma can affect everyone, everywhere at any time. Blunt cardiac injury is associated with increased mortality after trauma. Redistribution of the gap junction protein Connexin43 is associated with cardiac dysfunction. In the present project, important new molecular insights into the regulation of Cx43 in the heart after trauma will be revealed and may identify therapeutic targets for preservation of cellular coupling.

Effect of Yoga on Spine Flexibility in SpA

P089 02/2022 - 01/2023

Dr. Harriet Morf, Department of Medicine 3

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Abstract

Spondylarthritis can lead to stiffness of the spine and consequently to impaired function. Therefore, it is important to promote daily exercises in Spondylarthritis (SpA) patients. The objective of this study is to assess the feasibility of Yoga to affect spine mobility and disease activity in SpA patients. By measuring the mobility and improving spine flexibility, patients feel better with their disease and learn how important daily exercising is.

Analysis of NFATc3 in intestinal inflammation

P090 02/2022 - 01/2023

Dr. Katharina Gerlach, Department of Medicine 1

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Abstract

The transcription factor NFATc3 is important for regulating T cells. Patients with inflammatory bowel disease had high numbers of NFATc3+ cells in the lamina propria indicating an involvement of NFATc3 in mucosal inflammation. To investigate NFATc3 and colitis we will use specific knockout mice in experimental colitis models and analyse its molecular function. The results should clarify the role of NFATc3 in intestinal inflammation and provide a basis for NFATc3 as a new therapeutic concept.

Association between P and IBD

P091 08/2021 - 07/2022

Dr. Mayte Buchbender, Department of Oral and Cranio-Maxillofacial Surgery

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Abstract

Inflammatory bowel diseases (IBD) include two major subtypes: Crohn's disease (CD) and ulcerative colitis (UC) with immunological dysfunction underlying its development. Changes in the oral mucosa and changes in the periodontium can also be observed. Periodontitis (P) is defined as a dysbiotic inflammatory disease, however, the relationship between the incidence and severity of periodontitis and cytokine expression in IBD patients remains unclear.

Role of GPR15L in colorectal cancer

P092 10/2021 - 09/2022

Dr. Tanja Müller, Department of Medicine 1

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Abstract

In this project, the role of GPR15L in the formation and development of colorectal carcinoma will be investigated. For GPR15L anti-proliferative effects on tumor cell growth have already been shown in vitro and our aim is to also confirm these effects in a mouse model in vivo. In addition, we want to investigate the influence of GPR15L on the intestinal microbiome in relation to the development and progression of colorectal carcinoma in vitro and in vivo.

Vascularization of an ECM-mimicking hydrogel

P093 09/2021 - 08/2022

Dr. Kaveh Roshanbinfar, Department of Nephropathology

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Abstract

We aim at generating multicellular engineered tissues based on hiPSC-derived endothelial cells and cardiomyocytes in a collagen-based hydrogel mimicking the fibrous structure of the native cardiac matrix. We will determine whether such hydrogels provide a proper environment to enhance pre-vascularization utilizing hiPSC-derived endothelial cells and whether cardiomyocyte maturation as well as pre-vascularization is enhanced in 3D engineered multicellular cardiac tissues.

Influence of stem cells on irradiated flaps

P094 12 months

Dr. Wibke Müller-Seubert, Department of Plastic and Hand Surgery

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Abstract

Defect reconstruction in plastic surgery using tissue transfer, so called flaps, is a standard procedure, for example after Tumor resection. The proposed study evaluates the effect of topically stem cell or growth factor application on the size of the necrotic area of irradiated and post-ischemic random pattern flaps in an in-vivo model.

I	Infection and Immunology
N	Neurosciences
O	Oncology
R	Renal and Vascular Research
M	Medical Engineering
S	Others

PD-L1 expression in vulvar cancer

P095 12 months

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Abstract

Vulvar cancer is a rare gynecologic tumor with increasing incidence. New therapeutic strategies include the use of checkpointinhibitors, but clinical data is limited and contradictory. In this project we aim to assess the expression of PD-L1 in vulvar cancer. The expression will be assessed independently in primary, recurrent and lymph node metastasis. The expression will be compared to the clinical status such as TNM, L-,V-,Pn-infiltration.

DAX-1 mediates fibroblast activation and fibrosis

P096 12 months

Dr. Andrea-Hermina Györfi, Department of Medicine 3

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Abstract

SSc is the systemic rheumatic disease with the highest disease-related mortality. We identified DAX-1 as a mediator of fibroblast activation. We showed that DAX-1 is upregulated in fibrotic skin and that knockdown of Dax-1 ameliorates skin fibrosis. We plan to further characterize the mechanism of DAX-1 upregulation and study its potential transcriptional role in fibroblast activation as well as its potential antifibrotic role in 3D skin models and precision cut tissue slices from SSc skin.

Anti-osteoporotic effects of metoprolol

P097 04/2022 - 03/2023

Dr. Ulrike Steffen, Department of Medicine 3

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Abstract

Aberrant activation of bone resorbing osteoclasts causes osteoporosis. We found that the β-blocker metoprolol inhibits osteoclast development and resorption activity and increases bone mass in mice. In this project, we aim to investigate the mechanisms how metoprolol inhibits osteoclasts, focusing on its dependency on β-adrenergic receptor signaling and its effects on osteoclast fusion, motility and resorption. The long-term goal is to find new treatment strategies against osteoporosis.

Acetate adversely affects T cell migration

P098 04/2022 - 03/2023

Dr. Vugar Azizov, Department of Medicine 3

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Abstract

Epidemiological studies showed that alcohol intake reduces the incidence of RA. We published that alcohol sourced acetate prevents Tfh:B cell conjugates, crucial for antibody secretion. Here, we provide data showing that acetylation of cytoskeletal proteins by acetate reduces T cell motility. We propose to study if increased acetate levels favor cytoskeletal protein acetylation impacting cell motility and migration with direct consequences on the onset of autoimmunity and vaccination efficacies.

Interplay between TCR and microbiome

P099 04/2022 - 04/2023

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Abstract

Changes in the T cell receptor (TCR) repertoire can directly impact on the breath and magnitude of antigen-specific T cell responses. During treated HIV infection, dysfunctional T cell responses associate with inflammation that is at least in part driven by microbial translocation. Therefore, we aim to investigate the relationship between the translocated microbiome, the TCR repertoire and T cell functionality, with emphasis on vaccine-induced antigen-specific responses.

Dynamic MR pulse design for fat suppression

P100 01/2022 - 06/2022

Dr. Simon Lévy, Institute of Radiology

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Abstract

Chemical Exchange Saturation Transfer (CEST) MRI at 7T can provide high-quality metabolic maps for research in knee osteoarthritis, with a potential to replace the biopsy. Heterogeneity of the main magnetic field and constraints of the Specific Absorption Rate (SAR) make the fat suppression and the metabolite quantification challenging. This project aims to implement a routine for dynamic fat suppression pulse calculation including fields inhomogeneities and SAR limits specific to the subject.

Exome and zebrafish analyses on VATER/VACTERL

P101 01/2022 - 01/2023

Prof. Dr. Heiko Reutter, Department of Pediatrics and Adolescent Medicine

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Abstract

The VATER/VACTERL association describes the co-occurrence of malformations of the vertebral bodies, anorectum, heart, esophagus, kidneys, and limbs. The proposed study aims to identify new candidate genes and characterize the candidate gene FZD7 by morpholino knockdown and expression analysis in developing zebrafish larvae. In doing so, we hope to better understand the molecular mechanisms leading to this multisystem malformation.

I	Infection and Immunology
N	Neurosciences
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R	Renal and Vascular Research
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