



# SFB/TR 209 LIVER CANCER

## New mechanistic and therapeutic concepts in a solid tumor model

### Dear SFB/TR 209 - colleagues,

After a very busy last year, a long grant application period and the virtual review of our SFB/TR 209 in February we are pleased to be able to share with you the latest developments in our SFB with this newsletter.

Please also keep us updated about the developments in your projects and achievements.

Yours,



P. Schirmacher



N. Malek



M. P. Manns

### SFB/TR 209 GRANT PROPOSAL AND REVIEW

The proposal for the second funding period of our SFB/TR 209 was finally finished and sent to the DFG on 30<sup>th</sup> December 2020.

In January and February, we prepared for a virtual review of the SFB, as it could not be held in presence due to the Corona-virus pandemic. All project members and the Universities' governing boards supported us very well. We had two preparatory meetings with all PIs and one preparatory technical session with the DFG to get comfortable with the format of the video conference. The virtual review of our SFB/TR 209 took place on 23<sup>rd</sup> February and all projects were well prepared and gave their best in the review process. The plenary session started on 4:45 pm with the presentation of the SFB/TR 209 by Peter Schirmacher.



Immediately afterwards Prof. Manns presented the Universities Heidelberg, Tübingen and Hannover, followed by a discussion about the SFB/TR 209. The breakout sessions took place between 6:30 pm and 8:30 pm. Every SFB-project had an individual video conference room. The members of the SFB discussed intensively the own project with the reviewers during this time. After the breakout sessions we met for a short internal, virtual meeting for exchange. Almost all SFB-PIs were satisfied with the review. In the evening of the 24<sup>th</sup> February the review ended with a final virtual meeting (participants: 3 members of the SFB, Universities' governing boards, representatives from the state ministries, rapporteurs, DFG Head Office staff) where we got informed about the recommendations of the review panel.

We have received very positive feedback from the reviewers and got a strong funding recommendation for a second period of our SFB. Unfortunately, two projects were not selected for further funding in case of a second funding period. The **final funding decision** of the SFB will be made in the meeting of the Grant Committee of the DFG, which will be held **on May 21<sup>st</sup>**. The DFG will inform us about the decision thereafter. As soon as we know it, we will inform you.

In case of a second funding of our SFB, the following changes will occur:

\* 9 new PIs would join our SFB:

*Manfred Claassen* (Tübingen; joint project A04 with Mathias Heikenwälder), *Heike Bantel* (MHH; project A07), *Sofia Weiler* (Heidelberg, project B03 together with Kai Breuhahn), *Stephan Singer* (Tübingen; project B09, former project B04) together with *Kerstin Singer*, *Nikita Popov* (Tübingen, project B10), *Norman Woller* (MHH; project C08) together with *Heiner Wedemeyer*, *Tanja Poth* (Heidelberg, INF-project together with Peter Schirmacher, Thomas Illig and Sven Nahnsen).

\* The following PIs will leave us in the upcoming funding period:

*Ramona Rudalska* (Tübingen; joint project A03 with Lars Zender). Project A03 will be continued by L. Zender as single PI. *Sergij Goerdts* (UMM, joint project C03 with Hellmut Augustin). The successful project C03 will be carried on by H. Augustin as single PI. *Ulrich Lauer* (Tübingen; project C07 together with Florian Kühnel) will leave the SFB/TR 209 and project C07 will be terminated by the end of the ongoing funding period. *Klaus Schulze-Osthoff* (Tübingen) and *Stephan Hailfinger* (Münster),



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both running project A06, will also leave the SFB/TR 209 and project A06 will be terminated by the end of the ongoing funding period. *M. P. Manns* will step down from his positions of Co-coordinator of the SFB/TR 209 and project Z01 as well as member of the Steering committee. His replacement will be decided immediately after the funding decision of the DFG in June 2021. The two non-funded projects B02 (Nordheim/Proikas-Cezanne) and C06 (Kühnel) will remain part of the SFB/TR 209 until the end of 2021.

We want to thank all SFB PIs and all members related to our SFB for your great support during the past few months! We really hope to be successful and look forward to continue our work in the SFB in July.

For now, we remain with our best regards, wishing you all health and hope to see you all in our Kick-off-meeting in June.

### SFB-KICK-OFF MEETING 2021

In case of positive review, we scheduled the **Kick-off meeting for June 29<sup>th</sup>**. We would like to hold it in presence in Heidelberg if the situation allows it and look forward to see you all on this day. So we ask all SFB PIs to reserve this date. It is also planned to hold our general assembly on this date.

### SFB-INTERNAL MEETING 2020

Unfortunately, our planned international HCC conference in July 2020 had to be postponed due to Corona restrictions. We hope to be able to hold the conference in 2022. We switched the cancelled HCC conference to a two days internal retreat (July 7-8<sup>th</sup>) in Heidelberg with reviewing and discussion of the projects for the follow-up application and discussion of the further strategy.



### GENDER ISSUES

Financial support can be given to **childcare support** for care of children of SFB/TR 209 personnel: additional slots and longer than regular opening hours as well as holiday care. Requests should be addressed to the scientific coordinator, M. Skunde, or the gender representative of the SFB, A. Saborowski.

With the purpose of career advancement of women in science, fees for coaching, mentoring programs, soft skill seminars, management trainings etc. can also be covered by the gender budget.

Currently we are happy to offer up to 5 online courses for the **FEMALE LEADERSHIP PROGRAM** by Vera Strauch. This five-week online course is primarily intended for female postdocs and PIs within the SFB who are looking to promote their career and asks questions such as: Do you wish for more clarity to find your way and are you ready to live your own confident style? Do you want to maximize your leadership effectiveness? Are you interested in how to better navigate challenges? Please find detailed information about the course here: <https://female-leadership-academy.de/programm>.

If you are interested in participating in the program please contact M. Skunde or A. Saborowski **until Thursday, May 20<sup>th</sup>** at the latest.

**FEMALE LEADERSHIP PROGRAMM**

Das Female Leadership Programm ist ein zweitägiger Online-Kurs für weibliche Führungskräfte und Arbeitskräfte. Durch die Kombination aus täglichem, digitalem Input und persönlichem Austausch werden die Teilnehmerinnen in ihrer Potenzialentwicklung und der Entwicklung wichtiger (Soft-) Führungsqualitäten unterstützt.

**FÜR WEN?**

- Weibliche (angehende) Führungskräfte
- mit mindestens zwei Jahren Berufserfahrung
- Insightful zur Arbeitswelt Ausschüßlichen
- Interdisziplinär durch Online-Formate

**ERGEBNISSE DES PROGRAMMS**

- Steigerung individueller Führungskompetenzen
- Verbesserte Fähigkeit zur Strukturierung und Organisation
- Erhöhtes Selbstbewusstsein
- Neue Perspektiven auf Verantwortung und Eigeninitiative
- Praktische Kommunikation
- Erhöhter Selbstbewusstsein
- Erfolgreiches Konfliktmanagement
- Verstärkte Synergie im Team

**KOMPETENZ-ENTWICKLUNG**

- Analyse eigener Motivation und Wünsche
- Visualisierung von Zielen
- Individuelle Rollenklärung
- Entwicklung individueller Rollen
- Erklärung verschiedener Rollenverständnisse
- Verknüpfung von Führungsrollen

**15 TAGE INPUT**

- Tägliche Videos und praktische Übungen für den Alltag
- 1 Live-Online-Seminar
- Gedrucktes Workbook und Online-Workshop
- Personlicher Austausch im Mentoring-Format
- Netzwerke in der Community
- Einige persönliche Begleitungen durch alle Academic Partner
- Außer-Grenze mit 5 Mentoringpartnern
- Regelmäßiger Support für eventuelle Begleitprobleme in den Phasen und Kommunikation

female-leadership-programm.de

### GEROK STIPENDS

Gerok stipends are in place at all three sites according to the regulations. The SFB-Gerok stipend position is now located in Heidelberg. Since April 2020 we had or have the following stipendiaries: F. Brinkmann – working in project B01 (Rössler), Dr. B. Köhler – cooperating with project A04 (Heikenwälder), H. Wiethoff – working in project B05 (Tschaharganeh), M. Tóth – working in project B03 (Breuhahn), T. Ritz – working in project B08 (Longerich) and A. Brobeil – supporting the INF-project.



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### MD-STIPENDIARIES

We are happy to introduce our new MD stipendiary who joined the SFB/TR 209 in October 1<sup>st</sup>, 2020: Mrs Y. Rasen is working for her experimental MD thesis on the project “Characterization of Fibroblast Growth Factor Receptor Substrate 2 (FRS2) Amplifications in intrahepatic Cholangiocarcinoma”, related to the project C02 (Dauch/Bitzer).

### SERVICE PROJECTS

INF-Data analysis: Access to TCGA data only for applying sites (TÜ and MHH) available; in HD the Institute of Pathology and DKFZ have access to raw data of TCGA; SOPs for application to access will be provided.

INF-Cell lines: The list of available cell lines can be downloaded from the internal part of the SFB/TR 209 homepage or requested from M. Skunde.

### UPCOMING CONFERENCES



digital meeting



virtual conference

Einladung zur Viszeralmedizin 2021

13. bis 18. September 2021 | Erst Online. Dann Leipzig.



### HOMEPAGE

The homepage of the SFB/TR 209 is available under [www.livercancer.de](http://www.livercancer.de). Please let us know your ideas and suggestions and keep us informed about any changes and announcements concerning your project on the homepage. The logo can be downloaded from the site. Please use it wherever possible.

### RECENT TOP PUBLICATIONS

Pfister D, Gonzalo Núñez N, Pinyol R, Govaere O, Pinter M, Szydłowska M, Gupta R, Qiu M, Deczkowska A, Weiner A, Müller F, Sinha A, Friebel E, Engleitner T, Lenggenger D, Heide D, Stirm K, Kosla J, Youssuf S, Dudek M, Kotsiliti E, Ramadori P, Yahoo N, Leone V, Inverso D, Singh I, Castet F, Montironi C, Haber PK, Tiniakos D, Bedossa P, Cockell S, Younes R, Vacca M, Marra F, Schattenberg JM, Allison M, Bugianesi E, Ratzu V, Pressiani T, D'Alessio A, Personeni N, Rimassa L, Daly AK, Scheiner B, Pomej K, Kirstein MM, **Vogel A**, Peck-Radosavljevic M, Hucke F, Finkelmeier F, Waidmann O, Trojan J, Schulze K, Wege H, Koch S, Weinmann A, Bueter M, Rössler F, Müllhaupt B, Siebenhüner A, De Dosso S, Jugold M, Luedde T, Schietinger A, **Schirmacher P**, **Augustin HG**, Billeter A, Müller-Stich B, Wolter K, **Zender L**, Mei HE, Schulz AR, Ringelhan M, **Malek N**, Spahn S, **Bitzer M**, Lujambio A, Rahbari N, Dufour JF, Marron TU, Kaseb A, Kudo M, Huang YH, Teijeiro A, Djouder N, Weber A, Marche PN, Pinato DJ, Decaens T, Macek Jilkova Z, Rad R, Mertens JC, Unger K, Meissner F, Roth S, **Claassen M**, Anstee QM, Amit I, Becher B, Knolle P, Llovet JM\*, **Heikenwalder M\*** (2021) NASH limits anti-tumor surveillance in immunotherapy-treated hepatocellular carcinoma. *Nature* 592:450-456. \*equal contribution. (A03, A04, B06, C01, C02, C03, INF)

Dudek M, Pfister D, Donakonda S, Filpe P, Schneider A, Laschinger M, Hartmann D, Hüser N, Meiser P, Bayerl F, Inverso D, Wigger J, Sebode M, Öllinger R, Rad R, Roth S, Hegenbarth S, Anton M, Guillot A, Bowman A, Heide D, Müller M, Garcia Caceres C, Gruber T, Seifert G, Kabat A, Malm JP, Effenberger R, Billeter A, Müller-Stich B, Pearce EJ, Koch-Nolte F, Käser R, Tilg H, Thimme R, Böttler T, Tacke F, Dufour JF, Haller D, Murray P, Heeren R, Zehn D, Böttcher J, **Heikenwalder M**, Knolle P (2021) CXCR6 PD-1hiCD8 T cells cause liver immune pathology after metabolic activation in non-alcoholic steatohepatitis. *Nature* 592:444-449. (A04)

Deczkowska A, David E, Ramadori P, Pfister D, Safran M, Li B, Giladi A, Jaitin DA, Barboy O, Cohen M, Yofe I, Gur C, Shlomi-Loubaton S, Henri S, Suhail Y, Qiu M, Kam S,



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Hermon H, Lahat E, Ben-Yakov G, Cohen-Ezra O, Davidov Y, Likhter M, Goitein D, Roth S, Weber A, Malissen B, Weiner A\*, Ben-Ari Z\*, **Heikenwalder M\***, Elinav E\*, Amit I\* (2021). XCR1+ type 1 conventional dendritic cells drive liver pathology in Non-Alcoholic Steatohepatitis. *Nat Med*, in press. \* Co-last, co-corresponding author. (A04)

Rappez L, Stadler M. **Heikenwalder M\***, Aelxandrov T\* (2021). SpaceM reveals metabolic states of single cells. *Nat Methods*, in press. \* Co-last, co-corresponding author. (A04)

Gengenbacher H, Singhal M, Mogler C, Hai L, Milde L, Abdul Pari AA, Besemfelder E, Fricke C, Baumann D, Gehrs S, Utikal J, Felcht M, Hu J, Schlesner M, Offringa R, Chintharlapalli SR, **Augustin HG** (2021) Timed Ang2-targeted therapy identifies the Angiopoietin-Tie pathway as key regulator of fatal lymphogenous metastasis. *Cancer Discov* 11:424-445. (C03)

Pinyol R, Torrecilla S, Wang H, Montironi C, Piqué-Gili M, Torres-Martin M, Wei-Qiang L, Willoughby CE, Ramadori P, Andreu-Oller C, Taik P, Lee Y, Moeini A, Peix J, Faure-Dupuy S, Riedl T, Schuehle S, Oliveira CP, Alves VA, Boffetta P, Lachenmayer A, **Roessler S**, Minguez B, **Schirmacher P**, Dufour JF, Thung SN, Reeves HL, Carrilho FJ, Chang C, Uzilov AV, **Heikenwalder M**, Sanyal A, Friedman SL, Sia D, Llovet JM (2021) Molecular characterization of hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. *J Hepatol*, accepted. (A04, B01, INF)

Winkler M, Staniczek T, Kürschner SW, Schmid CD, Schönhaber H, Cordero J, Kessler L, Mathes A, Sticht C, Neßling M, Uvarovskii A, Anders S, Zhang XJ, von Figura G, Hartmann D, Mogler C, Dobrova G, Schledzewski K, Géraud C, Koch PS, **Goerd S** (2021) Endothelial GATA4 controls liver fibrosis and regeneration by preventing a pathogenic switch in angiocrine signaling. *J Hepatol* 74:380-393. (C03)

**Roessler S**, Edeline J, **Schirmacher P\***, Coulouarn C\* (2021) Integrative genomics highlights opportunities for innovative therapies targeting the tumor microenvironment in gallbladder cancer. *J Hepatol* 74:1018-1020. \*equal contribution. (B01, INF)

Mohs A, Otto T, Schneider KM, Peltzer M, Boekschoten M, Holland CH, Hudert CA, Kalveram L, Wiegand S, Saez-Rodriguez J, **Longerich T**, Hengstler JG, Trautwein C (2021) Hepatocyte-specific NRF2 activation controls fibrogenesis and carcinogenesis in steatohepatitis. *J Hepatol* 74:638-648. (B08)

Goeppert B, Stichel D, Toth R, Fritzsche S, Loeffler MA, Schlitter AM, Neumann O, Assenov Y, Vogel MN, Mehrabi A, Hoffmann K, Köhler B, Springfield C, Weichenhan D, Plass C, Esposito I, **Schirmacher P**, von Deimling A, **Roessler S** (2021) Integrative analysis reveals early and distinct genetic and epigenetic changes in intrahepatic papillary and tubulopapillary cholangiocarcinogenesis. *Gut*. doi: 10.1136/gutjnl-2020-322983. (B01, INF)

Kendre G, Marhenke S, Lorz G, **Kühnel F**, **Woller N**, Reineke-Plaaß T, **Poth T**, Becker D, Marquardt JU, Wirtz RM, Bonin M, **Saborowski M**, **Vogel A\***, **Saborowski A\*** (2021). The co-mutational spectrum determines the therapeutic response in murine FGFR2 fusion - driven cholangiocarcinoma. *Hepatology*. doi: 10.1002/hep.31799. \*equal contribution. (B07, C01, C06, C07, C08, INF)

**Rudalska R**, Harbig J, Snaebjornsson MT, Klotz S, Zwirner S, Taranets L, Heinzmann F, Kronenberger T, Forster M, Cui W, d'Artista L, Einig E, Hinterleitner M, Schmitz W, Dylawerska A, Kang T-W, Poso A, T. Rosenfeldt MT, **Malek NP**, **Bitzer M**, Laufer S, Pichler B, **Popov N**, Schulze A, **Zender L\***, **Dauch D\*** (2021) LXR $\alpha$  activation and Raf inhibition trigger lethal lipotoxicity in liver cancer. *Nat Cancer* 2:201-217. \*equal contribution and shared last author. (A03, B06, B10, C02)

### NEWS AND ACCOMPLISHMENTS

**Noujan Ganjian**, PhD student in project B08 (Longerich/Pellegrino), was awarded with the poster prize (session "Tumors") of the 37th annual conference of the German Association of the Study of the Liver (GASL). The poster holds the title "Dissecting the molecular interplay between tumor cells and -stroma in primary liver cancer".



**R. Bartenschlager** (A02) received again a prestigious international award for his research on hepatitis C: The Beijerinck Virology Prize 2021 of the Royal Netherlands Academy of Arts and Sciences.



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**M. P. Manns** (President of Hannover Medical School) received the Paris Hepatology Conference Award 2020.

Last year, **R. Bartenschlager** (A02) and **M. Heikenwälder** (A04) appeared on the list of "Highly Cited Researchers" (acc. to Web of Science). R. Bartenschlager was one of the most cited scientists in the field of Microbiology, M. Heikenwälder was one of the most cited scientists in the Category Cross-Field.

**D. Dauch** (C02) has successfully completed his Tenure Track evaluation in the context of his junior research group at the Universitätsklinikum Tübingen and the Comprehensive Cancer Center Tübingen-Stuttgart.

The European Research Council (ERC) has awarded an ERC Starting Grant for the research project "CripsSCNAs-Dissecting the functional and therapeutic impact of somatic copy number alterations (SCNAs)" to **D. Tschaharganeh** (project B05), starting in January 2021.

### FINANCIAL ISSUES

#### Travel grants

According to the application and granting **each project has 2.000 €/year travel allowance** for travel costs related to scientific issues of the respective SFB/TR 209 project. At the moment almost all conferences are held in virtual format due to the Corona-virus pandemic. The SFB can also take over registration fees for conferences. For reimbursement of your travel expenses please complete the form which can be downloaded from the internal area of our homepage or provided by M. Skunde. **Send the original receipts** together with the signed form to our SFB/TR209 office (Dr. Skunde). In addition, we ask you to provide us with information to which conferences you have contributed by presentation and represented the SFB/TR 209 for announcement in the newsletters and on our homepage.

#### Publication funds

We have a common pool to support publications if the work published is related to the SFB/TR 209. Therefore, please always use the following phrase in your publications:  
„Gefördert durch die Deutsche Forschungsgemeinschaft (DFG) - **SFB/TRR 209 - 314905040**“ or „funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) - SFB/TRR 209 - 314905040“.

Please also here keep us updated about the latest publications also in advance for announcement in the newsletter and on our homepage.

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