PCCC CIRCULAR

HELMHOLTZ ASSOCIATION

Alliance - Preclinical Comprehensive Cancer Center (PCCC)

Newsletter of the Helmholtz Alliance Preclinical Comprehensive Cancer Center - No. 1

PCCC at a Glance

The Helmholtz Alliance Preclinical Comprehensive Cancer Center was inaugurated in March 2013. This consortium brings together leading German scientists in the field of preclinical mouse tumor model research. The consortium aims at developing new tumor models which better mimic the human pathology of cancer and to improve the translation of basic research into clinical application.

The limited availability of tumor models which truthfully mimic the pathology of different entities and subtypes of human cancer has emerged as one of the most critical and rate-limiting bottlenecks of preclinical drug and therapy development. Preclinical animal tumor models are not only rate-limiting for translational research but also for basic cancer research. PCCC scientists consequently joined forces for a concerted effort to remedy the current situation.

The nationwide PCCC consortium consists of 25 Principal Investigators in 20 research groups from five different institutions (three Helmholtz Centers [German Cancer Research Center, Heidelberg; Max-Delbrück Center, Berlin; Helmholtz Center Munich] and five universities [Charité, Berlin; Heidelberg University; University of Cologne; Technical University, Munich; Ulm University]). Given the translational mission, the PCCC includes four hospital departments. Likewise, 50 % of the PIs are physicians who see patients on a daily basis. The PCCC is in an unique position to bridge the gap between basic cancer research and its translation into clinical application. To fulfill its ambitious goals, the PCCC has establishd partnerships with four strong industry partners (BayerHealthcare, EliLilly, ProKinase, Taconic,) and four clinical study groups (German-Austrian AML Study Group, German CLL Study Group, Competence Network Malignant Lymphoma, German High Grade Non-Hodkin-Lymphoma Study Group).

The scientific program is mechanism- and process-oriented and focuses on three major tumor entities: gastrointestinal tumors, brain tumors and hematological malignancies. The prioritization on three tumor entities is based on a combination of scientific and strategic considerations, with prioritizing those tumor entities in which the consortium could earn a globally leading position in basic science-driven and translational-relevant bench-to bedside research.

Work pursued within the PCCC will have major impact on the translational program of the German Cancer Consortium (DKTK). This is reflected by a focus on the same tumor entities in both consortia. A close interaction within DKTK will be also be ensured by the fact that most PCCC investigators also serve as Principal Investigators within DKTK.

The ultimate goal of the PCCC is to advance preclinical basic cancer research with translational perspective and to establish a new global standard of preclinical tumor models.

Inside PCCC

Word from the Directorate

The PCCC Kickoff Meeting in March 2013 was a great success. The meeting has set the stage for the first year's work of the consortium. It is quite gratifying to see that all clusters are up and running and work productively.

The Heidelberg brain cluster meets every other month. Mathias Heikenwälder has organized a meeting of the GI cluster in Munich in September. The first work package reports have been filed. PCCC scientists have in 2013 published important mouse tumor model work in the best journals, which is a good sign of the lifelines and productivity of the PCCC.

Our next consortium meeting will take place in January 2014. We are excited to hear about the latest discoveries of the PCCC groups. We are also looking forward to the first International Meeting in Kloster Seeon, March 8-11, 2013, which promises to be very high profile. Several editors of high profile journals have applied to participate, which will surely stimulate all presenters of talks and posters to present their very latest and unpublished work.

We wish to thank all of you who made this first year of the PCCC such a great success! We are looking forward to the challenges of 2014 and wish all PCCC scientists and readers of the PCCCircular a happy, healthy, peaceful and successful new year!

With best wishes,

Hellmut Augustin, Heidelberg
Clemens Schmitt, Berlin
Ulrike Stein, Berlin

Directors of the PCCC

In this issue

German Israeli Co-operation in Cancer Research

The German-Israeli Cooperation in Cancer Research was founded in 1976 and is the longest lasting scientific cooperation between Germany and Israel. To date, 159 projects have been funded. Beyond this, the cooperation has fostered friendships between scientists of both countries and other partners (www.dkfz.de/israel).

The 6th German-Israeli Cancer Research School on *Mouse Models of Human Cancer* was supported by the Joint Scientific Program Committee of the Cooperation and was jointly organized by Hellmut Augustin and Eli Pikarsky. The aim of this school was to offer a platform for intense interactions between PhD students, young postdocs and principal investigators.

The first school was held in Pichl (Austria) in 2008 and was such a great success that the PhD students requested that the school be held

Poster prizes were awarded to Shlomi Finkin, Dharanija Madhavan and Ayelet Jerafi-Vider. Left to right: Eli Pikarsky, Peter Angel, Dharanija Madhavan, Ayelet Jerafi-Vider, Varda Rotter, Hellmut Augustin

every year. This was the start of a successful Cancer Research School alternating between Pichl and Israel.

The organization of this year's school incorporated two novel program points: Student speakers selected by the organizing team presented research short talks. A second novelty was a "grant writing competition". Students could choose between different topics which were proposed by the invited speakers. With support of their mentor, the students presented their

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Science and Desert Feelings

6th German-Israeli Cancer Research School on Mouse Models of Human Cancer

Science and desert feelings

The 6th German Israeli Cancer Research School on *Mouse Models of Human Cancer* focused on the most critical bottleneck in the advancement of basic tumor biology and translational research: the availability of suitable preclinical animal tumor models that better mimic the human pathology of cancer.

Eight speakers from Israel, six speakers from Germany, which are all members of the Helmholtz Alliance Preclinical Comprehensive Cancer Center (PCCC) and 26 young scientists (students and junior postdocs) met at Mitzpe Ramon in the middle of the Negev Desert for three intense and stimulating days of scientific exchange and development of new ideas. The participants highly appreciated that Otmar Wiestler, Chairman and Scientific Director of the German Cancer Research Center had joined the meeting for two days to learn first hand about the latest developments in this rapidly moving field of ongoing cancer research. He emphasized the importance and success of the German–Israeli Cooperation, which promotes intense scientific cooperation and friendship between cancer researchers of both countries.

The event provided the young scientists with the unique opportunity to meet some of the key opinion leaders in the field in the informal setting of a small workshop. Among others, the list of speakers included PCCC member Klaus Rajewsky, whose group has as early as 1994 established the feasibility and power of the Cre-lox recombination system for conditional gene targeting *in vivo* (Gu et al., Science). This technique has revolutionized preclinical mouse models and is nowadays used by hundreds of laboratories around the world.

The scientific program of the Cancer Research School focused on three tumor entities: gastrointestinal tumors, brain tumors and hematological malignancies and covered the cutting-edge research topics in the field. Tumors are now widely recognized not just as a clump of tumor cells, but as a neoplastically growing organ, consisting of tumor cells, host-derived stroma and recruited immune cells. This was reflected by the number of contributions covering the topic tumor microenvironment. Likewise, advanced models for deciphering the role of cancer stem cells and longevity in tumorigenesis were presented. Last but not least a plethora of preclinical mouse models for various therapy approaches were discussed.

A further highlight was the keynote lecture by Uri Alon, who is not only known as a very successful systems biologist, but also as an outstanding entertainer. Using simple flip chart lectures and his guitar, he spread his ideas about empathy in science to the upper echelons of scientific institutions around the world.

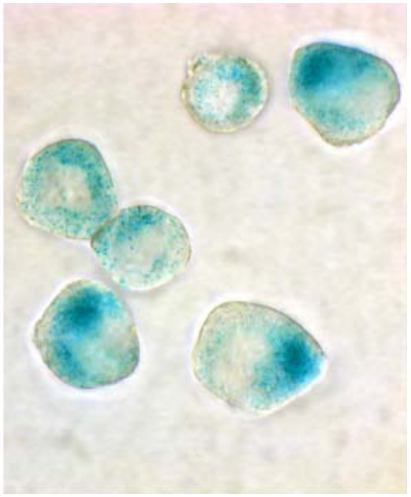
A birthday surprise for Klaus Rajewsky

Synthetic Lethality- New Avenues in Cancer

Two genes are synthetic lethal if the mutations of one gene is compatible with life, whereas mutations in both genes induce cell death. Therefore, targeting mutations, which are specifically synthetic lethal in cancer cells would only target tumor cells and spare normal cells. This is the basic concept for the development of highly specific anti-cancer drugs.

One of the most widely used therapeutic approaches in cancer treatment is chemotherapy. However, besides its severe side effects, chemotherapy does not kill all tumor cells. Some tumor cells escape chemotherapy by undergoing cellular senescence. Despite these cells stop growing, they are comparable to a "time bomb" - similar to cancer stem cells. First of all, senescent cells secret high levels of inflammatory proteins and secondly, they can be reactivated and cause tumor relapse. Scientists around PCCC Director Clemens Schmitt (Charité and Max Delbrück Center, Berlin) recognized that senescent lymphoma cells have an extremely high energy demand and heavily rely on glucose (Dörr et al., Nature, 2013). Moreover, they require an intact autophagy machinery to digest the excessive amount of toxic proteins they produce. By blocking either glucose utilization or autophagy, the tumor cells are selectively killed by apoptosis. The high metabolic demands are unique for tumor cells and therefore glucose deprivation or autophagy inhibition does not affect healthy body cells.

A further synthetic lethal approach was undertaken by the group of PCCC scientist Christian Reinhardt (University Hospital, Cologne). Cancer cells are capable to circumvent apoptosis in response to the accumulation of mutations. However, cancer cells also require a DNA repair mechanism for survival. DNA double strand break repair is guaranteed by homologous recombination (HR) and non-homologous end joining (NHEJ). These two processes are regulated by different signal transduction systems. HR requires ATM (Ataxia Telangiectasia Mutated) a serine threonine kinase, whereas NEHJ relies on DNA-PKcs (DNA-dependent protein kinase catalytic subunit). ATM is frequently mutated in tumor cells which thus cannot utilize this DNA repair mechanism. ATM-mutant cells solely rely on DNA-PKcs. Consequently, the use of DNA-PKcs inhibitors will induce apoptosis in ATM-mutant lymphoma cells and they undergo apoptosis by specifically blocking DNA-PKcs (Riabinska et al., Sci Trans Med, 2013).



Senescent Lymphoma cells post chemotherapy

Synthetic lethality has major translational implications. Whereas conventional therapies target single molecules, these two approaches target processes unique to cancer cells: Targeting DNA-PKcs has clinical relevance since it is hypothesized that ATM mutations accumulate in therapy-refractory CLL patients who have limited therapy options. Treating these patients with DNA-PKcs inhibitors could pave the way for new and efficient treatment of therapy-refractory CLL patients.

Synthetic lethal therapy approaches will have a great benefit for cancer patients not only by its increased efficacy but also by its reduced side effects. Synthetic lethal approaches are certainly at the cutting edge between preclinical and clinical research.

German Israeli Co-operation in Cancer Research

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proposal in a 10 min talk which was challenged and evaluated by a panel of reviewers. This educative game was not only a great challenge but also a lot of fun for all participants. The students and postdoc swere extremely curious, open to new challenges and the meeting

Winners of the „Grant Writing Competition". From left to right: Sami Stalin, Stefan Eser, Polina Weitzenfeld, Neta Erez, Yeal Ben-Nun, Deian Yuan

was a great think tank for scientific exchange and ideas.

Besides the intense scientific program, there was ample time to enjoy the social activities. The walk for the sunrise at the Makhtesh Ramon crater rim was as impressive, as the trip through the crater, where the group enjoyed an incredible sunset. The winter school in Mitzpe Ramon is a great example that such events are more than worthwhile. The organizers got an overwhelming feedback from junior and the senior participants. Notably, the selection of talks and the grant writing competition have been highly appreciated. I am sure The participants surely returned with a lot of new ideas and plenty of impressions from this exceptional winter school.

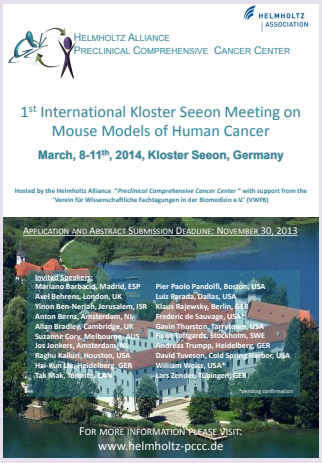
Recent PCCC - Publications

- Borsig et al: Inflammatory chemokines and metastasis-tracing the accessory. **Oncogene**, epub ahead of print, 2013.
- Vucur et al: RIP3 inhibits inflammatory hepatocarcinogenesis but promotes cholestasis by controlling Caspase-8- and JNK-dependent compensatory cell proliferation. **Cell Reports**, 4: 1-15,2013.
- Rad et al: A genetic progression model of Braf(V600E)-induced intetestinal tumorigenesis reveals targets for therapeutic intervention. **Cancer Cell**, 24:15-29, 2013.
- Eser et al: Selective requirement of PI3K/PDK1 signaling for Kras oncogene-driven pancrea tic cell plasticity and cancer. **Cancer Cell**, 18: 406-20, 2013.
- Riabinska et al: Therapeutic targeting of a robust non-oncogene addiction to PRKDC in ATM-defective tumors. **Sci Transl Med**, 5: 189ra78, 2013.
- Reinhardt and Yaffe: Phospho-Ser/Thr-binding domains: navigating the cell cycle and DNA da mage response. **Nat Rev Mol Cell Biol**, 14:563-80, 2013
- Huang et al: Intrahepatic myeloid-cell aggregates enable local proliferation of CD8+ T cells and successful immunotherapy against chronic viral liver infection. **Nat Immunol**, 14:574-83, 2013.
- Dörr et al: Synthetic lethal metabolic targeting of cellular senescence in cancer therapy. **Nature**, 501:421-5, 2013.

Awards for PCCC Scientists

Stefan Pfister has received the **Württembergische Cancer Award** and the **German Cancer Award** for his research on the molecular characteristics of pediatric brain tumors.

Upcoming PCCC Events



1st Consortium Meeting, January 30th - February 2nd,Lenggries Germany

1st International Kloster Seeon Meeting on Mouse Models of Human Cancer, March 8 - 11th, 2014, Kloster Seeon Germany

Impressum PCCCCircular

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IN THE HELMHOLTZ ASSOCIATION

50 Years – Research for A Life Without Cancer