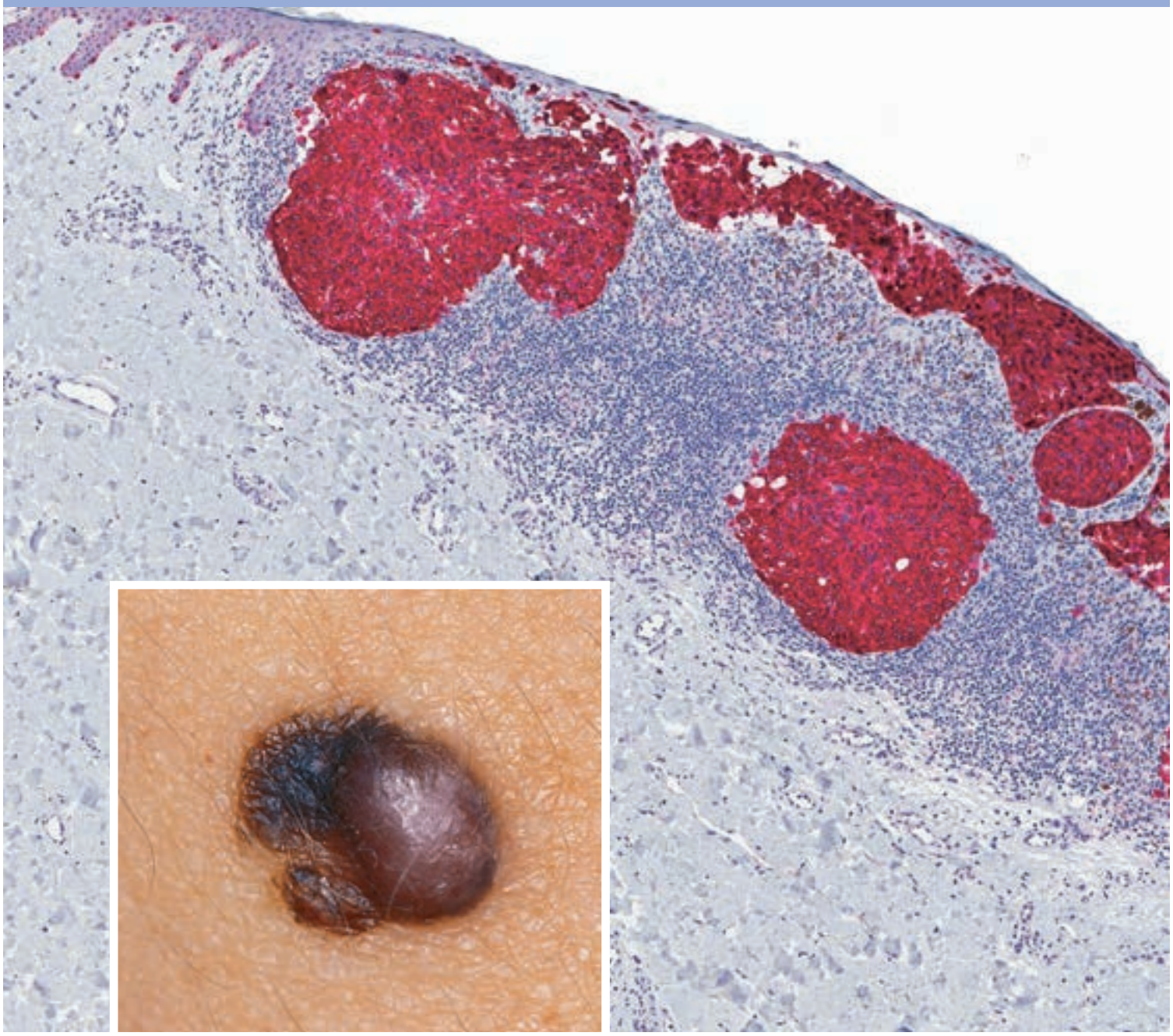
Universität Zürich[UZH]

UniversitätsSpital Zürich

University Research Priority Project (URPP)

Translational Cancer Research

Biennial Report 2013/2014



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Preface

Dear readers,

it is a pleasure for us as director and vice-director of the University Research Priority Program (URPP) Translational Cancer Research to present on behalf of the University of Zürich and a devoted team of physicians and scientists our first biennial report to you.

Cancer remains the second cause of death in most developed countries, accounting for nearly one of four deaths. Thanks to significant developments in research, prevention and therapy, age-adjusted cancer death rates are finally decreasing for certain types of cancer including lung, colon, prostate, breast and uterus. Despite this encouraging development, too many people still suffer from the major effects of being diagnosed with cancer, from an important reduction in the quality of life and often still from a reduced life expectancy.

Both the University and the University Hospital of Zurich have inscribed cancer research and oncology – the branch of medicine that deals with cancer – amongst its top priorities. The funding of our URPP Translational Cancer Research clearly underscores the commitment of our University to promoting innovative cancer research and translation of the latter to the clinic through high quality science.

The URPP Translational Cancer Research is unique and original in that it unites an exceptional team of internationally recognized scientists and physician-scientists in the field of oncology and cancer research, and is determined to bridge the unfortunate gap in communication and collaboration between physicians and basic scientists to bring cancer research a step closer to translation into the clinic. Our young postdoctoral fellows, who can be financed thanks to this URPP, have an essential bridging function between our different clinical and fundamental cancer research groups, and hopefully also represent future talents and leaders in cancer research of tomorrow.

It is no secret that clinical and basic scientists have different research cultures and use distinct research approaches. By installing research positions in the clinical environment and by enforcing collaborations between clinical and basic research groups, our URPP brings these two scientific cultures together. This has proven beneficial for both sides so far: Basic researchers gain first-hand insights into the intricate processes of cancer and can dedicate research efforts towards it, while physicians benefit from the enthusiastic and structured approaches to scientific problems typical for natural scientists. Furthermore, this close collaboration and exchange is essential for the validation of discoveries made in model systems on patient's samples, which is the first step of translational research. Therefore, this concept is key to our URPP.

We hope that our biennial report will give you a good impression of how young Postdocs, senior scientists and physicians are now actively collaborating in different constellations, thereby promoting exchange of knowhow, innovation and ultimately a step in the direction of translation.

With these introductory words, we cordially invite you, also on behalf of the entire URPP consortium, to find out more about our URPP in the pages following and wish you interesting and pleasant reading.

Enjoy!

Prof. Dr Lars E. French

Prof. Dr Konrad Basler

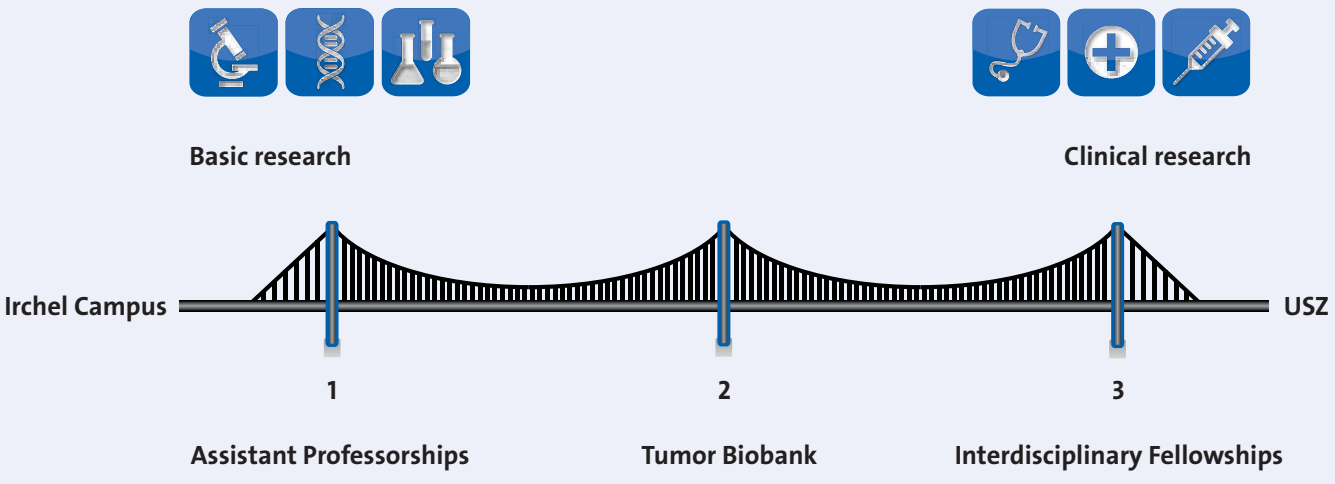
1. Our Mission

Cancer is caused by genetic, epigenetic and microenvironmental changes that facilitate the survival and proliferation of tumor cells and their ability to acquire invasive properties. The plasticity of human tumor cells generally replicates normal molecular processes occurring during development and tissue repair. In humans, cancer progression is also shaped by host immune responses that edit the final tumor-host interactions. The genetic complexity and extreme variability of human cancers means a multidisciplinary integrative approach is needed to understand the interactions between the genetic background of the host, the tumor and its microenvironment, and the impact of these on the immune system. It is becoming evident that successful anti-tumor strategies need to encompass a multimodal approach to avoid tumor escape or relapse, combining agents able to block essential signal transduction pathways with immunotherapy. To this end, experts on cancer pathways and tumor immunology both from basic and clinical disciplines need to engage in a close collaborative program to identify and test the most promising approaches, leading to tailored therapies, including personalized approaches.

The main motivation for this URPP is to foster collaboration between the best clinical and basic researchers at the UZH in the fields of clinical oncology, hemato-oncology, immunology, pathology, and molecular and developmental biology. Our aim is to accelerate the translation of knowledge generated by basic research labs into preclinical efficacy and safety assessments in relevant animal models and evaluation on human samples, followed by early clinical testing. Moreover, this URPP will motivate basic scientists to investigate questions of direct clinical relevance and thus promote a closer cooperation between basic and clinical scientists.

The research in the URPP Translational Cancer Research specifically focuses on the following four subprojects:

1. Oncogenic signal transduction pathways as targets for personalized tumor therapy
2. The interaction between cancer and the immune system
3. Tumor biopsy and live tumor cell biobank linked with clinical outcome data
4. Translation from bench to bedside and back



2. Introduction of the Consortium

The main incentive for this URPP is to foster collaboration between the best clinical and basic researchers at the University and the University Hospital of Zurich to accelerate the development of new therapeutic approaches.
The consortium of the URPP "Translational Cancer Research" consists of following scientists:

- Konrad Basler (Institute of Molecular Life Sciences, UZH)
- Burkhard Becher (Institute of Experimental Immunology, UZH)
- Onur Boyman (Clinic for Immunology, USZ)
- Reinhard Dummer (Department of Dermatology, USZ)
- Lars French (Department of Dermatology, USZ)
- Alex Hajnal (Institute of Molecular Life Sciences, UZH)
- Michael Hottiger (Institute of Veterinary Biochemistry and Molecular Biology, UZH)
- Markus Manz (Division of Hematology, USZ)
- Holger Moch (Department of Pathology, USZ)
- Lukas Sommer (Institute of Anatomy, UZH)
- Maries van den Broek (Institute of Experimental Immunology, UZH)

The board of the URPP is composed of Lars French and Konrad Basler, who function as co-directors, and Maries van den Broek, who is responsible for the scientific coordination. The board meets at least once every three months.
The Scientific Advisory Board is a neutral committee that oversees the performance of the consortium and reports back to the University of Zurich. It contains following members:

- Michel Aguet (School of Life Sciences Ecole Polytechnique Fédérale Lausanne, Switzerland)
- Marcus Groettrup (IDepartment of Immunology, University of Constance, Germany)
- Beat Imhof (Centre Médical Universitaire, University of Geneva, Switzerland)

3. The Current Team of Lead Investigators

Prof. Dr Konrad Basler
Institute of Molecular Life Sciences,
University of Zurich

Prof Dr Lars E. French
Department of Dermatology,
University Hospital Zurich

Prof. Dr Holger Moch, MD
Institute of Surgical Pathology
University Hospital Zurich

Prof. Dr Burkhard Becher
Institute of Experimental Immunology,
University of Zurich

Prof. Dr Alex Hajnal
Institute of Molecular Life Sciences,
University of Zurich

Prof. Dr Lukas Sommer
Division Cell and Developmental Biology, Institute of Anatomy, University of Zurich

Prof. Dr Onur Boyman
Department of Immunology,
University Hospital Zurich

Prof. Dr Dr Michael O. Hottiger
Institute of Veterinary
Biochemistry and Molecular Biology,
University of Zurich

Prof. Dr Maries van den Broek
Institute of Experimental Immunology, University of Zurich

Prof. Dr Reinhard Dummer
Department of Dermatology,
University Hospital Zurich

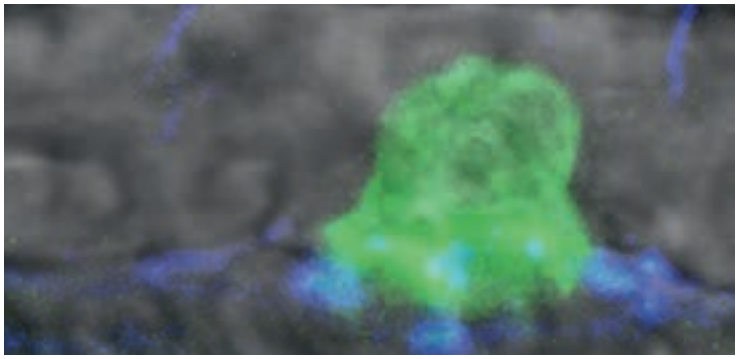
Prof. Dr Markus G. Manz
Division of Hematology
University Hospital Zurich,&
Chair Cancer Network Zurich

4. Description of Research Projects

1. Oncogenic Signal Transduction Pathways as Targets for Personalized Tumor Therapy.

Cancer research and developmental biology address similar questions: How do genes control cell proliferation, how is the formation of three-dimensional structures in organs achieved, how are superfluous cells eliminated by the organism, and how can specific molecular alterations modify the behavior of individual cells? The same signal transduction pathways that control the development of multicellular organisms and the proliferation of stem cells are frequently mutated and thereby deregulated in human cancers. Therefore, research on simple animal model organisms such as *C. elegans* (roundworm) or Drosophila melanogaster (fruit fly) can significantly contribute to the understanding of genetic and biochemical events leading to cancer formation in humans. Research in mammalian models can extend the elucidated concepts and provide further insights into the role of the host including the complex tumor microenvironment.

Tumor cell invasion is a prominent example to illustrate the integrative approach taken by this URPP. Most cancer-related deaths are not caused by the primary tumor but rather by metastases that have spread to distant sites. An initiating event in the conversion of primary tumor cells into metastatic cells is an epithelial-to-mesenchymal transition that generates a population of invasive cells that are capable of crossing the basal lamina delineating compartment boundaries and entering blood or lymphatic vessels, ultimately leading to the dissemination of malignant cells. The genetic and epigenetic factors underlying this "invasive switch" in individual tumor cells are therefore under intense investigation.



Cell invasion in the Nematode C. elegans.
The anchor cell (labelled in green) secretes the extracellular matrix protein HIM-4 (labelled in blue) and invades the underlying epithelium.
(courtesy of Matthias Morf)

Studies in developmental biology demonstrated that cell invasion also occurs in a strictly regulated fashion during normal development, e.g. in neural crest stem cells. The molecular pathways activating the developmental cell invasion program are being identified and studied in animal model organisms where cell invasion can be easily observed. Importantly, recent evidence indicates that the very same signaling pathways activating cell invasion during normal development, when deregulated in tumors, such as in melanoma, lead to the formation of invasive cancer cells.

By bringing together researchers studying oncogenic signaling pathways in the context of normal animal development with clinical scientists studying the related pathways in human tumor cells, this URPP will generate vital synergies for both clinical and basic research. Rather than focusing on individual signaling pathways to understand the complex cellular responses to extrinsic signals, we will characterize the entire signaling networks formed by the crosstalk of individual pathways. This will allow us, for example, to investigate compensatory mechanisms underlying tumor escape to a previously efficacious drug and predict the outcome of alternative or combined therapeutic interventions at the molecular level; this is key for the development of next generation (personalized) anti-cancer strategies. The members of this network will use a variety of methods, depending on the model system investigated, including but not limited to siRNA screens and pharmacological studies of specific inhibitors in cultured tumor cells, forward genetic screens in model organisms, genetic association studies in humans, systems genetics in animals, and deep sequencing in well-defined human tumor samples linked to clinical outcome data.

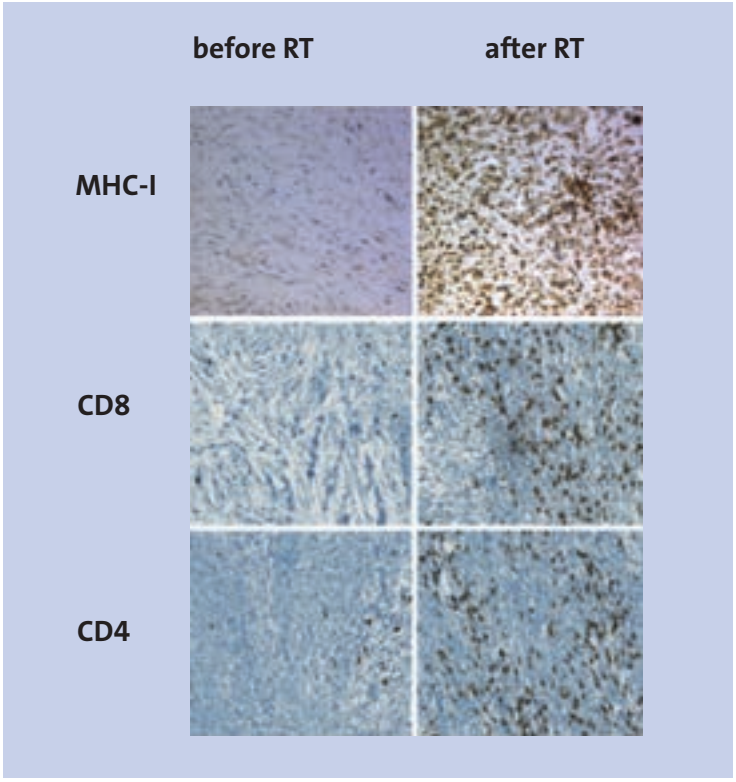
Our specific aims are:

1. Identification of molecular pathways relevant to tumor cell biology with a special emphasis on developmental biology, stem cell biology and tumor-host interactions (tumor angiogenesis, plasticity, invasion and metastasis).
2. Validation of the implicated signaling pathways using cultured primary tumor cells best suited for therapeutic intervention.
3. Initial development of novel therapeutic approaches, including innovative tools for drug delivery, advanced antibody technology and novel, innovative small molecule inhibitors.

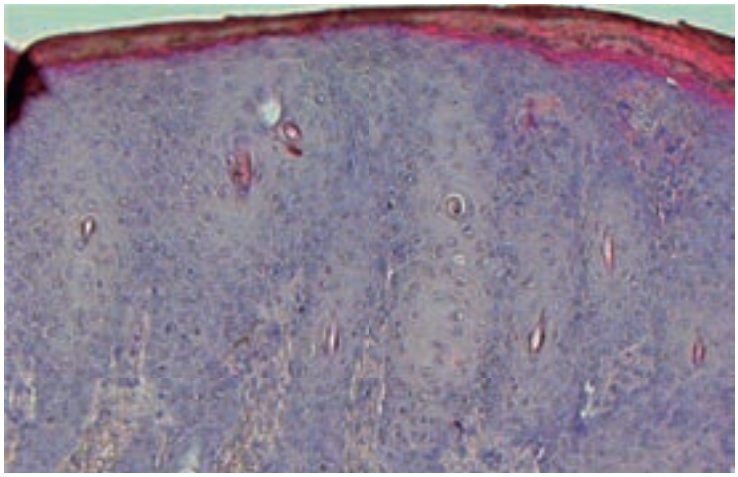
2. Tumor Immunology.

There is clear evidence from patients and preclinical cancer models that the adaptive arm of the immune system is involved in controlling the development of malignancies, a process termed tumor immune surveillance. Hence, immunosuppression or – deficiency leads to an increased cancer risk, both in humans and animals. Moreover, spontaneous tumor-specific immunity can be detected in cancer patients and in tumor-bearing mice. However, such anti-tumor immune responses are usually subverted by tumors allowing "uncontrolled" tumor growth. Recent evidence suggests that the immune system not only fails to eliminate established tumors and their metastases but it actually creates a niche enabling a pre-malignant lesion to develop into a tumor which has "learned" to evade immune surveillance. This kind of "natural selection" leads to the formation of a tumor which actively employs various pathways to block anti-tumor immunity.

The concept of utilizing and manipulating the immune system to control or eliminate tumors is a promising therapeutic option. Over the past ten years, advances have been made in anti-cancer strategies, including the use of immunotherapies and vaccination, with some considerable recent success. However, despite inducing strong systemic anti-tumor immunity, immunotherapies were frequently unable to breach the local barrier created by solid tumors and their microenvironment. Past failures in the translation from preclinical observations towards cancer care in patients are widely held to be due to the fact that the cooperation between basic sciences and clinical medicine was suboptimal. Little attention has been paid to the assessment of multimodal approaches combining the inhibition of key tumor signaling pathways and selective immunotherapy. Thus, a better understanding of the interactions between the tumor, its microenvironment, and the immune system, as well as a better usage of synergies between basic and clinical research – as proposed in this URPP – should strengthen our ability to design new therapeutic strategies focusing on combined regimens and personalized approaches.



Radiotherapy promotes tumor-specific immunity. Immunohistochemistryfor CD4, CD8 and MHC class I (brown) of paired human sarcomas before and after radiotherapy. Sharma A. et al., Clinical Cancer Res. 2013.



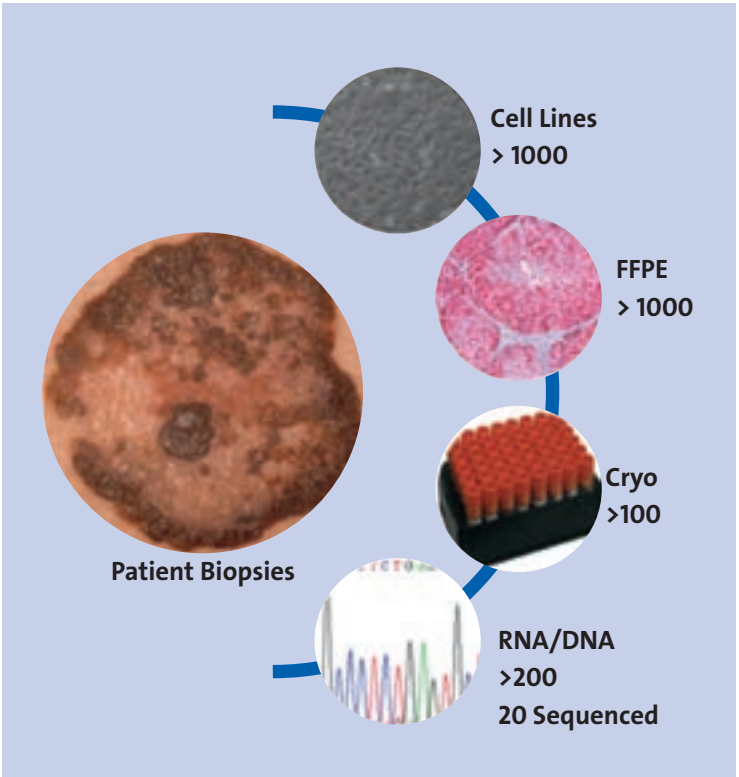
H&E staining of HPV8-E6 tumour 3 weeks after induction by UV irradiation of a K14-HPV8E6 FVB mouse (magnification 40X)

Our specific aims are:

1. Evaluation of selected signaling pathways in the tumor microenvironment relevant for tumor immune subversion and their targeting in conjunction with immunotherapy.
2. Assessment of the impact of tumors on their microenvironment and the immune system, leading to immune evasion.
3. Assessment of combination therapies to eliminate autochthonous or established tumors.

3. Tumor Biopsy and Live Tumor Cell Biobank linked with Clinical Data.

Tumor tissue biobanks typically include formalin-fixed tumor biopsies or frozen human material, which is suitable for molecular high-throughput analysis. However, such biobanks do not allow any *in vitro* or *in vivo* functional investigations. One strategy to overcome this limitation is the establishment of patient-derived tumor cell cultures, e.g. from surplus surgical materials. The Dermatology Clinic at the University Hospital Zürich has extensive experience in establishing melanoma cell cultures from primary and metastatic tumors originating from various organs including liver, lung, brain, skin and lymph nodes. Notably, when grafted onto immunodeficient mice, these cell lines reliably form new tumors. Similarly, we have expertise in propagating primary human hematopoietic neoplasias *in vitro* and in new *in vivo* models. Moreover, a series of tumor tissue microarrays and more than ten thousand frozen tissue samples are stored in the centralized biobank for research and diagnostic purposes at the Institute of Surgical Pathology of the University Hospital Zürich. The longitudinal collection of tumor biopsies and the respective cell cultures will allow us to characterize tumor cell evolution and development of resistance mechanisms arising from conventional and novel targeted therapies. Furthermore, RNA expression microarrays and whole-exome sequences of selected cell lines also exist.



I think that the most urgent challenges in the field of translational cancer research are...

Make personalized tumour treatment not just be a vision, but happen – to the level of individual patients.

A well-characterized biopsy and live-cell biobank of human tumor samples in addition to tumor tissue and cell line microarrays is essential for translational studies and personalized cancer therapy and thus is a central resource for this URPP. We will establish a live cell biobank not only for melanoma but also for colorectal, lung, breast, pancreatic, oropharyngeal, and renal cancer, depending on sample availability. A live cell biobank combined with the corresponding frozen tissue and clinical data will not only improve characterization of these biopsies and cell lines (e.g. by whole genome sequencing, proteome and transcriptome analyses) but it will also be instrumental for functional *in vivo* studies aimed at assessing antitumor responses of novel drug and/or immunotherapeutic approaches. Notably, these cell cultures will be linked to clinical patient data such as therapeutic response and patient outcome.

Our specific aims are:

1. Establishment and professional management of a high-quality patient tumor biopsy and live tumor cell biobank linked with detailed, completely anonymous patient and clinical outcome data.
2. Detailed characterization of the cell lines of this biobank for their *in vitro* and *in vivo* growth properties, in addition to clinical data acquisition.
3. Development of novel pre-clinical animal models carrying tumor cell lines or primary tumors in addition to immune cells from the same patient to assess *in vivo* anti-tumor responses to pre-clinical drugs.

4. Translation from Bench to Bedside and back.

A combined treatment using multimodal anti-tumor approaches, including immunotherapy and the blocking of signaling pathways, will very likely provide improved possibilities to attack tumor cells. However, parallel to increasing the efficacy of anti-tumor treatment it is crucial to control for adverse effects in order to avoid major drawbacks in clinical trials.

Adverse effects might occur as a result of a potent anti-tumor immune response, affecting organs such as lungs and liver (e.g. following cytokine immunotherapy), or they might result following targeted inhibition of a specific signaling pathway that dysfunctions in tumors (e.g. inhibitors of epidermal growth factor receptor in epithelial tumors or MEKK inhibitors in melanoma leading to severe cutaneous side effects). Both types of side effects limit the dose and/or duration of the treatment, thus jeopardizing successful treatment of the tumor. Knowledge on the mechanisms of these effects will allow us to establish strategies to avoid or dampen them.

Moreover, combined treatments might help reduce such unwanted effects while showing much improved anti-tumor properties. The early stage clinical testing of ipilimumab (an antibody to Cytotoxic TLymphocyte Antigen 4, CTLA-4) plus the B-Raf kinase inhibitor vemurafenib and the use of interleukin 2/antiinterleukin 2 antibody complexes are some examples of innovative multimodal early clinical trials ready to be tested in patients (investigator-initiated trials).

In focusing on the translation of basic research discoveries to clinical testing and back, this URPP aims at assessing and improving the beneficial effects of novel single or combined treatment strategies and simultaneously minimizing the adverse effects.

I became a scientist, because...

I was always interested in biological networks. As a clinical scientist I have to integrate basic research knowledge into patient care. This approach helps me to understand the peculiar clinical presentations of my patients and helps me to choose the best possible treatment option.

Our specific aims are:

1. Assessment of efficacy and adverse effects of novel single or combined treatment strategies using relevant (humanized) pre-clinical animal models.
2. Realization of novel investigator-initiated phase I/II clinical trials using lead (combination) regimens.
3. Investigation of the signaling pathways involved during serious adverse effects to established and novel treatment strategies.

I think that the most urgent challenges in the field of translational cancer research are...

How to translate results from mouse to humans (bridge the gap)!

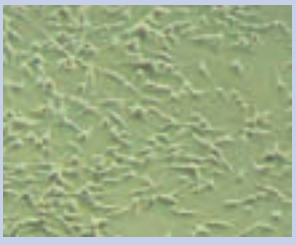
5. Biobank

Under the management of Prof. Mitch Levesque (Department of Dermatology at the USZ), the biobanking efforts of the URPP have established new cell culturing methods, generated early passage cultures from multiple cancer types and reference tissues, and begun morphological and molecular characterization of many of these samples. In this year, the biobank has made 196 new heterogeneous early passage cancer cell cultures from a wide variety of biopsy samples from consenting patients at the USZ. These include 157 confirmed primary cultures from melanoma tumors, 11 cultures from normal skin, and 28 primary cancer cultures from other tissues in the Department of Pathology (i.e. including Renal, Lung, Prostate, Ovarian, Larnyx, Adrenal, Testis, Breast, Lung, Tongue, Uterus). All melanoma cultures now undergo rigorous morphological and molecular quality control procedures, and a core set of 12 melanoma cultures has undergone more extensive molecular analysis such as whole-exome sequencing to provide a better understanding of the genetic heterogeneity present in the collection. These well characterized core lines, and the availability of reference material and anonymized clinical data from the relevant patients, will be a powerful resource for the URPP, as well as other researchers across Switzerland and the world.

Under the mamagement of Prof. Peter Schraml (Institute of Surgical Pathology at the USZ) a live cell biobank with cell cultures of malignant tumors is being established as an integrative platform of the tissue biobank at the Institute of Surgical Pathology. This project runs in parallel to the cell biobank at the Department of Dermatology where a resource for melanoma already exists. In a testing phase, which started in 2013, and in collaboration with Dermatology, we used protocols optimized for melanoma. Cell cultures from 11 tumor samples (non-small cell lung (4), breast (2), endometrial (1), head and neck (1), metastasis of uterus (1), metastasis of colorectal (1) and skin histiocytoma (1)) obtained from our histology laboratory were analyzed for cell growth properties and fibroblast contamination. Cells of all tumors were growing but had high fibroblast contamination. Cultures were harvested at 80% confluency after P1-P2 and stored in liquid N2. In a second phase of the project (2014) we tested a series of additional protocols aiming at significantly reducing the fibroblast cell growth. Based on the results we selected 3 different media and 3 differently coated culture dishes optimally suited for routinely establishing cell cultures independent of the tumor type. Currently, cell cultures from a further 29 tumors (kidney (9), prostate (8), lung (6), ovary (1), adrenal Gland (1), larynx (1), testis (1), urinary bladder (1), soft tissue (1)) are stored in the biobank. Cell growth characteristics, tissue and patient data are documented. Additional quality controls concerning epithelial origin (PanCK-IHC) and gene mutation analysis according to histology reports are permanently performed.

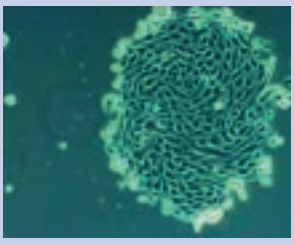
Validation Techniques

Morphology



Melanoma

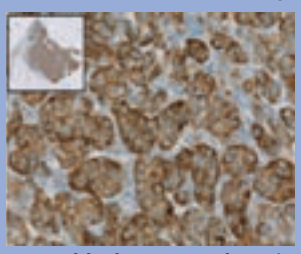
Clear cell RCC 1



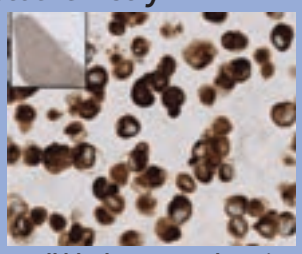
Clear cell RCC 2

Germ-cell tumor testis

Immunohistochemistry

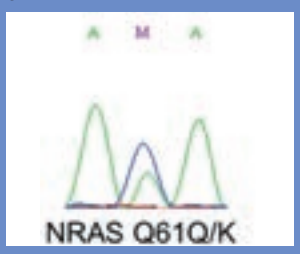


Tumor block: Pan Cytokeratin



Cell block: Pan Cytokeratin

Molecular



6. Latest Results

1. The role of β-catenin in basal and squamous cell carcinoma of the skin.

Tomas Valenta, Virginia Cecconi, Maries van den Broek, Konrad Basler

Squamous and basal cell carcinoma (SCC, BCC) are frequent skin cancers. Wnt signaling is one of the few known molecular pathways regulating SCC initiation and progression. However, Wnt signaling is an also important regulator of normal skin homeostasis. The key downstream molecule of Wnt pathway is β-catenin, which attracts – via its N- and C-terminus – specific transcriptional co-activators to Wnt-responsive elements and thus activates Wnt-mediated transcription. In addition, β-catenin is an important component of adherens junctions. Such a structural role might be important to maintain the integrity of skin epidermis.

Our focus is to determine the contribution of signaling versus structural roles of β-catenin in development and homeostasis of normal skin and skin cancer. Because this dual function complicates studying its role in both normal development and cancer, we have generated mutant mice with altered or deleted signaling but normal adherens function and established a genetic, UV-induced SCC murine model (K14-HPV8E6). We observed elevated levels of Wnt/β-catenin transcription in this SCC model indicating important role for β-catenin signaling in progression of SCC. Interestingly we also observed reduced β-catenin associated with adherens junctions, one of classical hallmarks of epithelial-mesenchymal transition. Currently we combine these SCC models with mutant strains expressing β-catenin, which is fully functional in adherens junctions but is compromised (or completely missing) in signaling outputs. Our first results indicate that in adult skin epidermis the structural role of β-catenin does not play significant role, whereas signaling outputs are essential for maintenance of hair follicles and regulating the thickness of the epidermis. Moreover, N-terminal β-catenin transcriptional co-activators are dispensable for normal development of skin and hairs, the role of C-terminal co-activators is under investigation.

We are establishing a new genetic model BCC, based on keratinocyte-specific deletion of the *Ptch1* gene (K5Cre*PR1/Ptch1$^{fl/fl}$), because biallelic deletion of *Ptch1* in mouse epidermis results in lesions closely resembling human BCCs. BCC are thought to be caused by uncontrolled activation of the hedgehog (Hh) signaling pathway. In the majority of cases, this is due to inactivating mutations in the Hh receptor and tumor suppressor gene *Ptch1*. Once established, we will use this model to investigate the contribution of signaling versus structural roles of β-catenin in tumor development and progression.

We think our results may lead to development of tools that target β-catenin such that tumor progression is inhibited but leaving skin integrity intact.

2. Role of T-cell derived cytokines in the pathogenesis of graft versus host disease (GvHD) and graft versus leukemia (GVL).

Sonia Tugues, Burkhard Becher, Michael Hottiger, Markus Manz, Maries van den Broek

Allogeneic hematopoietic cell transplantation is an effective treatment for hematological malignancies. This is achieved by mature T cells from the graft, which promote hematopoietic engraftment and mediate a potent anti-tumor response. Unfortunately, donor T cells can also target host tissues and cause GvHD, a complication associated with significant morbidity and mortality. Even though the role of the different T cell subsets in GvHD and GVL is slowly being characterized, the mechanisms by which they mediate these processes are still ill defined. Our aim is to systematically analyze the impact of individual T cell populations and cytokines in inducing a potent GVL response while limiting GvHD.

Using two different models of GVHD, we found that alloreactive T cells produce primarily GM-CSF and IFNg. By transferring T cells from the respective cytokine-gene deficient mice, we could show that GM-CSF was critical for disease development, whereas IFNg appeared to be protective. Interestingly, the use of GM-CSF receptor deficient mice revealed that the lack of GM-CSF signaling in cells from recipient origin was sufficient to ameliorate the course of the disease. We are currently investigating how the lack of GM-CSF affects the resident myeloid cell compartment in target organs during GvHD, and the consequences on effector T cells. We will also determine the contribution of this T-cell-derived cytokine in mediating GVL by testing the therapeutic efficacy of blocking this cytokine in two newly developed experimental models of leukemia.

3. New Therapies: Translation from Bench to Bedside and back.

Carsten Krieg, Onur Boyman, Burkhard Becher, Maries van den Broek, Lars French

Recent clinical trials underline the necessity of combining different therapies to fight cancer. In this project we want to use novel combination therapeutics, i.e. cytokines and blocking checkpoint inhibitors, for the immunotherapy of melanoma, glioblastoma and leukemia. We observed that in the absence of GM-CSF the immunotherapy of subcutaneously injected B16 melanoma with IL-2/anti-IL-2 complex is more efficient. Further we are testing IL-12 plus IL-2/anti-IL-2 complex in the immunotherapy of spontaneous melanoma models such as Tyr::N-Ras^{Q61K} INK4a$^{-/-}$ and Tyr::Cre^{ERT} PTen Braf$^{CA/+}$, both already established within the consortium. In addition, we are testing the efficacy of combining IL-2 or IL-12 with anti-CTLA-4 for the treatment of glioblastoma.

Beside the identification of successful combination immunotherapies by using the above mentioned mouse model of cancer, we are also using mass cytometry as a new technology to characterize immunologic fingerprints during the immunotherapy of cancer. To this aim, we started examining samples from melanoma patients and myeloperoliferative leukemia patients.

Being part of the URPP influences me, because...

I start to think more deeply about translational aspects of my research, especially if and how some of my scientific observations can be changed to therapeutic approaches. Simply the contact with clinical researchers affected my view to my own research.

4. Macrophages and innate lymphoid type 2 cells promote metastasis via IL-1β and thymic stromal lymphopoietin in malignant melanoma.

Emmanuel Contassot, Lars French

The molecular mechanisms regulating melanoma metastasis are still poorly characterized. We observed that the pleiotropic pro-inflammatory cytokine interleukin-1β (IL-1β) is highly expressed in human melanoma metastases. To investigate mechanisms through which IL-1β may promote metastasis, we generated murine B16 melanoma cells that overexpress and secrete active IL-1b. Overexpressed IL-1b promoted metastasis in tumor-draining lymph nodes and lungs. Cytokine expression analysis during primary tumor growth revealed that IL-1b promotes a Th2-biased cytokine environment in tumors and tumor infiltration by M2-macrophages. Analysis of fibroblasts revealed that IL-1b induces the expression of thymic stromal lymphopoietin (TSLP). Ablation of the TSLP-receptor in mice resulted in reduced Th2 cytokine expression, macrophage recruitment to tumors, and metastasis. Furthermore, *in vivo* depletion of macrophages resulted in a reduction of metastasis in mice. Given that innate lymphoid type 2 cells (ILC2s) can sustain M2 macrophage infiltration, the presence of ILC2 was analyzed. In IL-1b-producing B16 tumors and human melanoma metastases, increased numbers of ILC2s were detected. *In vivo* depletion of ILCs resulted in reduced intratumoral Th2 cytokines, M2-marker expression and lymph-node metastases indicating that ILC2 promote tumor enrichment with M2 macrophages and tumor metastasis. We demonstrated that the IL-1b-TSLP axis is essential for tumor infiltration by M2 macrophages and ILC2s that promote melanoma metastasis.

5. Complement is a central mediator of radiotherapy-induced tumor-specific immunity and clinical response

Laura Surace, Maries van den Broek

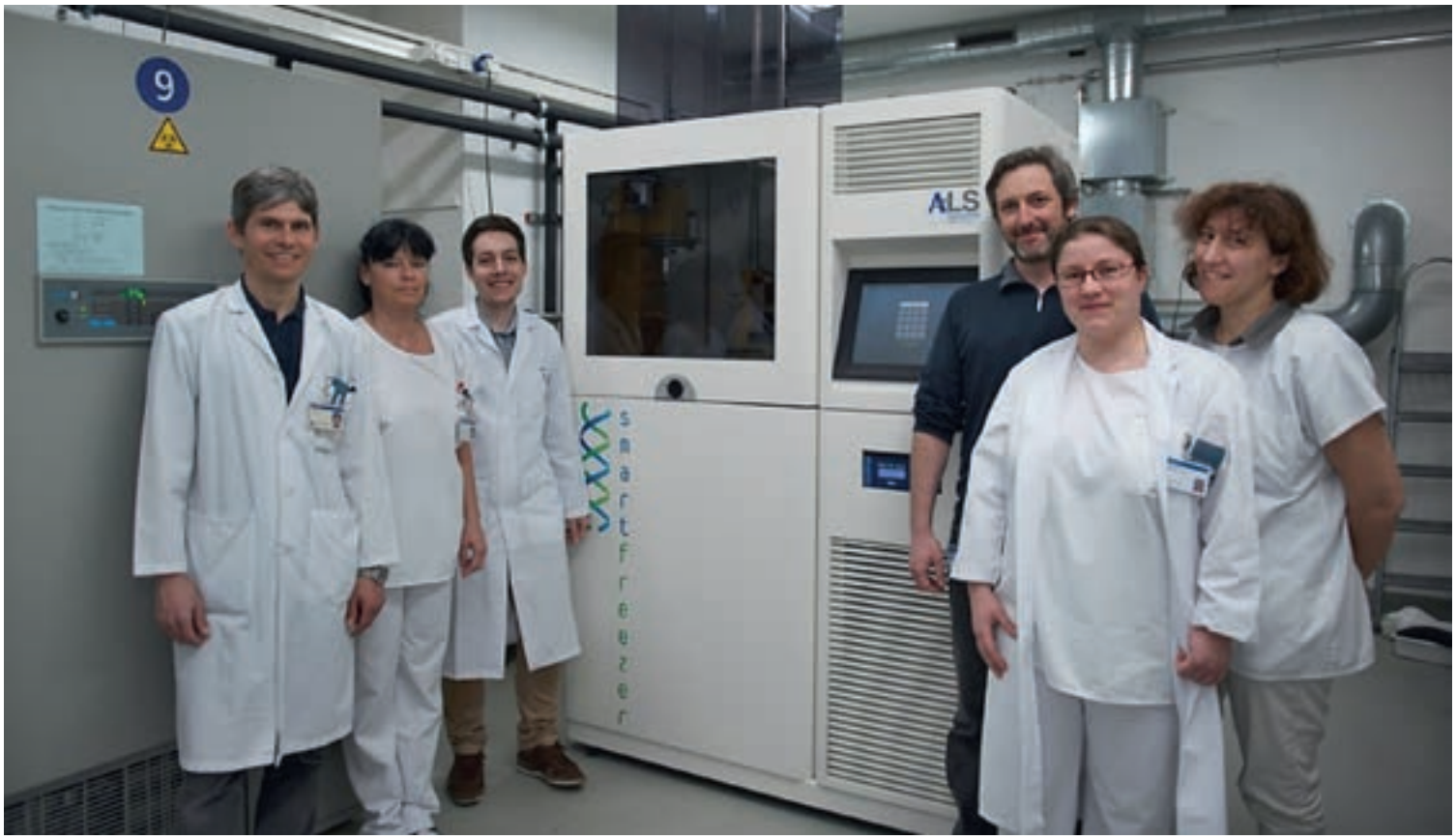
Radiotherapy induces irreversible DNA damage, but recent data suggest that concomitant immune stimulation is an integral part of the therapeutic action of ionizing radiation. It is insufficiently understood how radiotherapy supports tumor-specific immunity, although several pathways were suggested to play a role. We found that tumor cell death resulting from radiotherapy activated complement transiently in murine and human tumors. Moreover, local production of pro-inflammatory anaphylatoxins C3a and C5a was crucial to the tumor response to radiotherapy and concomitant stimulation of tumor-specific immunity. Dexamethasone, frequently given during radiotherapy treatment, limits complement activation and its effectiveness. Overall, our findings indicate that anaphylatoxins are key players in radiotherapy-induced tumor-specific immunity and clinical response.

6. The role of neural crest stem cell factors in melanoma progression.

Sandra Varum, Reinhard Dummer and Lukas Sommer

Melanoma, the most aggressive skin cancer, results from transformation of pigment cells that during development arise from neural crest (NC) cells. The NC is a multipotent stem cell population in vertebrate embryos that gives rise to a wide range of cell types. Abnormal NC biology is not only at the onset of many congenital diseases, but has also been associated with melanoma. For instance, reduction of the NC stem cell (NCSC) factor Sox10 is sufficient to prevent melanoma formation in a melanoma mouse model[1]. The objective of this URPP project is to reveal further factors that both modulate NCSC maintenance and play a role in melanoma biology. Based on microarray analyses, we identified several transcription factors as putative NCSC regulators. Conditional ablation of one of these transcription factors in mouse NCSCs resulted in agenesis or hypoplasia of various NC derivatives. Likewise, ablation of the same transcription factor in a genetic mouse model of melanoma led to decreased primary tumor formation and increased invasion in a level-dependent manner. Thus, our experiments led to the identification of cues that are important for NCSC homeostasis and also control melanoma formation and progression. Currently, we are studying the mechanisms of action of such factors and their implication in the human disease.

1. Shakhova O, Zingg D, Schaefer SM, Hari L, Civenni G, Blunschi J, Claudinot S, Okoniewski M, Beermann F, Mihic-Probst D, Moch H, Wegner M, Dummer R, Barrandon Y, Cinelli P, Sommer L. (2012). Sox10 promotes the formation and maintenance of giant congenital naevi and melanoma. Nature Cell Biology, 14: 882-890



The URPP Biobank team

7. Orthologues of genes, whose expression correlates with invasiveness in melanoma and neural crest cells, are required for efficient BM breaching during anchor cell invasion in *Caenorhabditis elegans*.

Evelyn Lattmann, Alex Hajnal, Mitch Levesque, Reinhard Dummer

Previously, the group of Prof. Dummer and Prof. Levesque have performed microarray analysis to address expression profiles of invasive vs. non-invasive melanoma and neural crest cells (Fig. 1A). In order to distinguish between genes directly involved in cell invasion and genes, whose expression just correlates with invasion, we used the model organism *C. elegans*. During *C. elegans* larval development, the invasive process of a specialized cell, called anchor cell (AC), can easily be observed *in vivo*. To this end, *C. elegans* orthologues of selected human candidate genes (Fig. 1A) were knocked-down by RNAi, and basement membrane (BM) breaching was assessed in worms expressing GFP-labeled laminin. Among the 92 genes analyzed (61 orthologues and 31 paralogues), 11 showed a delay in BM breaching during AC invasion (Fig. 1B). RNAi of cyclin D (called *cyd-1* in *C. elegans*) showed a pronounced BM breaching defect (Fig. 1B). Since cyclin D (CCND1 in humans) was upregulated by TGF-β stimulation in the microarrays (Fig. 1A), we measured the induction of CCND1 upon TGF-β stimulation in three different melanoma cell lines (M010817, M000921 and M000907) by quantitative real time PCR. CCND1 expression was increased upon TGF-β addition in the three analyzed melanoma cell lines and thus confirmed the microarray results (Fig. 1C). It has previously been shown that BM breaching by the anchor cell is triggered by an invasive cue that is secreted from the primary-fated vulval precursor cells (1° VPCs) [1].

In order to test whether Cyclin D acts cell-autonomously in the AC or in the 1° VPC by regulating the production of the invasive cue, we blocked the cell division of the 1° VPC by expressing the cell cycle inhibitor CKI (*cki-1*) under the 1°–fate specific promoter *egl-17* [2]. The presence of timely BM breaching in this background indicated that cell division of the 1° VPCs is not required for AC invasion (Fig. 1 D). This result points at a cell-autonomous role of Cyclin D in cell invasion. However, at this stage it cannot be excluded that Cyclin D has a cell-cycle independent function in the 1° VPCs or the AC. We are currently testing if knock down of CCND1 in melanoma cells reduces their invasive phenotype.

I think that the most urgent challenges in the field of translational cancer research are...

I would say metastases are an important clinical problem, together with tumor relapse after drug treatment.

[1] D.R. Sherwood, P.W. Sternberg, Anchor cell invasion into the vulval epithelium in *C. elegans*, Dev Cell 2003; 5, pp. 21–31
[2] Nusser-Stein S, Beyer A, Rimann I, Adamczyk M, Piterman N, Hajnal A, Fisher J. Cell-cycle regulation of NOTCH signaling during *C. elegans* vulval development. Mol Syst Biol 2012; 8

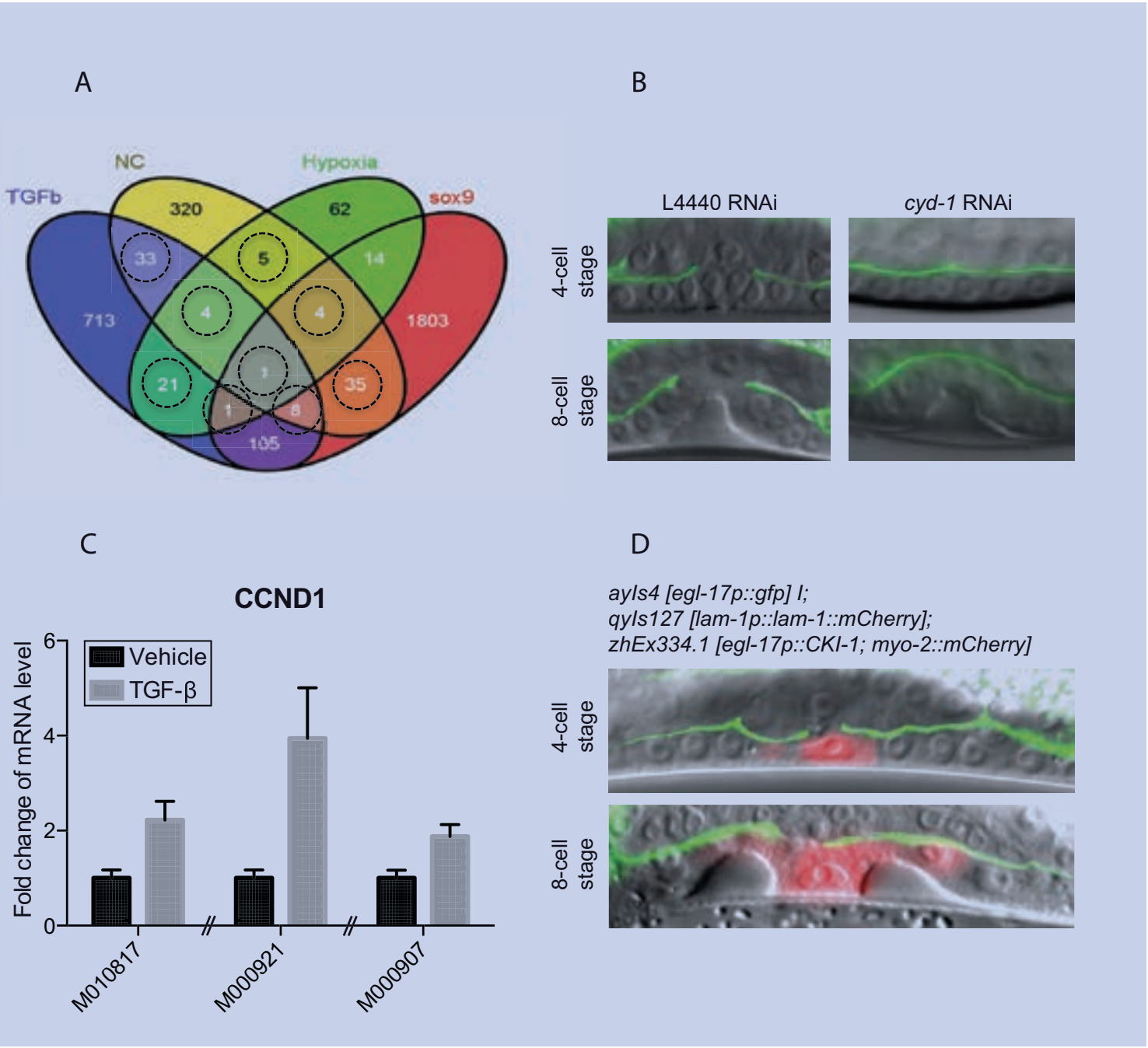


Fig. 1 Orthologues of genes, which are upregulated upon stimuli that induce invasivness in melanoma cells, compromise BM breaching during AC invasion in *C. elegans* A) Venn diagram of genes, which are upregulated in melanoma cells upon invasivness stimuli (TGFb, SOX9 overexpression, hypoxia) and/or are induced in neural crest cells that undergo EMT. Encircled genes were chosen for functional studies in *C. elegans.* B) BM breaching defects upon empty vector control (left panel) and *cyd-1* RNAi (right panel) in worms expressing *lam-1::GFP.* C) Quantitative real-time PCR of CCND1, the human homologue of *cyd-1* (Cyclin D) in the melanoma cell lines M010817, M000921 and M000907 after addition of 5 ng/ml TGF-β (+) during 56 hours. Note that CCND1 is induced upon TGFb stimulation. D) BM breaching of worms with the followng genotype: *ayIs4 [egl-17p::gfp] I; qyIs127 [lam-1p::lam-1::mCherry]; zhEx334.1 [egl-17p::CKI-1; myo-2::mCherry].* Note that AC invasion is not affected by a cell cycle arrest of the primary VPCs.

7. Collaboration USZ / UZH / Cancer Center

Prof. Dr med. Markus Manz, Chairman of the Department of Hematology, University Hospital Zurich.

I became a scientist, because...
I have always enjoyed nature and finding out how things work. It seemed that becoming a biologist was the best option to combine those interests.

Being part of the URPP influences me, because...
Being part of URPP brought me into a totally new field (Wnt and development) and I learned how to apply basic research to more translational questions.

The CNZ is a "bottom-up" network founded in 2001 that connects all active cancer researchers at the UZH and ETHZ and the associated institutions, including the University Hospital Zurich, the Children's Hospital Zurich and Balgrist. The CNZ is an integral part of Life Sciences Zurich, a joint venture of the University of Zurich and the ETH Zurich that also harbors the Cancer Biology PhD program.
The Mission of the Cancer Network Zurich (CNZ) is to facilitate communication between clinicians, research scientists and the public at large in matters concerning fundamental and translational research, diagnosis, prognosis, therapy and prevention of cancer. The CNZ is also instrumental in the organization of courses of further education for both clinicians and basic research scientists at postgraduate level, as well as in the organization of workshops, retreats and seminars that serve to increase the awareness of the latest developments in cancer-related fields.
The CNZ and URPP are tightly connected via the clinicians and scientists active in both communities and via the monthly "Joint Cancer Meetings" (JCM) where each 3 groups report on progress in clinical, preclinical and basic research.
Also, the URPP is active and holds a dedicated symposium at the CNZ biennial retreats, with the 6th CNZ retreat scheduled for April 12–14 2015.
Both the JCM and the CNZ retreat are financially supported by the URPP.

CNZ Retreat in Grindelwald (April 2013)

Prof. Dr med. Roger Stupp, Director of the Department of Oncology, University Hospital Zurich; Director of the Cancer Center at the University Hospital Zurich.

1. Which is/are the most urgent scientific question(s) in the field of translational cancer research in your opinion?
The theme of the time is personalised medicine. For this we need to be able to characterise each and every patient's tumor and molecular host characteristics. We have been treating cancer for over 50 years with surgery, irradiation and drugs (chemotherapy). However, these treatments are not specific, and the surprise is not that treatments often do not work, the surprise is that they do occasionally work and cure cancer. It is only now with modern understanding of cancer and molecular biology that we start to understand some of the reasons for our successes and failures. If we match the right treatment to the right patient, the individual success rate will immediately be much greater.
The current trend of over-regulation, medicine by guidelines and rules rather than innovation and implementation of scientific advancement is an increasing challenge. Tissue collection and tissue banking is a must and not only an option, crosstalk between bench scientists, molecular biologists, bioinformatics and clinicians is needed for progress and implementation of knowledge. We need new and better methodology in applied cancer research. In principle every patient receiving state of the art cancer treatment should contribute to the advancement of knowledge. Laws on data protection, excessive individualism and the general assumption that research is performed to the researchers glory and the patients detriment needs to be revisited. Big data is a topic also in applied cancer research, and it requires adequate and quality controlled data collection, verification and a large expertise in bioinformatics.

2. What do you think about the quality of cancer-related research in Zurich, its weaknesses, its strengths?
Zurich University has numerous excellent and world-class research groups, and the greater Zurich area including ETH, several university or university-affiliated hospitals are bringing together a unique composition of brain power, research infrastructure and expertise. The Schlieren campus aims at increasing the interaction with industry and translation of ideas and targets into drugs or products.
Our overall (in international standards) small size is both a weakness but also a strength. It allows for easy collaboration and communication, it allows for innovative transdisciplinary initiatives, rapid implementation and bringing questions not only from the lab to the clinic, but also from the bed to the bench. Our fragmentation however into numerous departments and affiliations with different universities and schools, the local competition for the same resources rather than collaboration and having the competition internationally leads to a lack of common identity and mission. For the public we are thus not sufficiently visible, and in the clinical arena there is fierce competition with the private sector at the detriment of science, research and expertise.

3. How do you think the URPP could or should contribute to cancer research in Zurich?
The URPP is a first step towards a strategic focus in cancer research in Zurich. It allows to recruit young investigators and new blood. This or future URPPs and other initiatives need to be integrated in an overall interactive network and structure. The Zurich Cancer Center in gestation will need to set priorities, recognise unique talent as well as opportunities and niches for research.

4. If you had one wish for cancer research in Zurich, which would this be?
Creation of a truly comprehensive cancer center, beyond limitations of affiliation, structure, and departments. If we want to make a difference rapidly (and that is what is needed) we need a generous sponsor who is willing to share our views, is willing to bring entrepreneurial expertise (we could name the cancer center after him or her). We can and need to advance rapidly, even when the ultimately needed new common building and research campus is not realistic in the very near future.
It is all about vision,and the ambition to advance science and cancer care. The Zurich cancer community has the expertise, diversity and motivation to advance, and then there is clearly enthusiasm towards collaboration, vision for a greater common objective and willingness to interact and exchange ideas. We cannot wait, we owe our impatience to our many patients waiting for better treatments.

8. Fostering Young Scientists

The URPP offers a supportive environment to 6 young and talented scientists, who profit from the interactive environment and scientific excellence and diversity of the consortium. These postdoctoral fellows work in the different URPP institutes and often play a bridging function between clinical and fundamental research partners. Following postdoctoral fellows are supported by the URPP:
Virginia Cecconi, Carsten Krieg, Evelyn Lattmann, Sonia Tugues, Tomas Valenta and Sandra Varum.

Being part of the URPP influences me, because...
Being part of the URPP allows me to broaden my horizon and to see scientific questions from a different perspective. I enjoy to work with top clinical and basic researchers and thanks to this collaboration I am constantly evolving scientifically and personally.

In 2014, the URPP launched two calls for research projects specifically addressing PhD students and young PostDocs. The project proposals were judged by two independent reviewers outside of Switzerland.
Following applicants received support through the first call:
Alexa Burger, Hassan Chaachouay, Anurag Gupta, and Antonia Müller.
Following applicants were supported through the second call:
Bahar Degirmenci, Dario Zimmerli, Christian Gentili, Virginia Cecconi, Phil Cheng, Mario Leutert, Karina Silina, Vanessa Pierroz, Verena Paulitschke, Larisa Kovtunyuk, Hella Bolck, Guiseppe de Gregorio, Karin Prummel.

I think that the most urgent challenges in the field of translational cancer research are...
To really understand the consequences of the mutual interaction between cancer and the immune system, so we can exploit the latter in a logical and controlled fashion to fight human cancer.

9. Report of the 2nd URPP Scientific Meeting

The second URPP scientific meeting took place on 17 September 2014 at the University Hospital Zurich. The Dean of the Faculty of Medicine, Prof. Dr Klaus Grätz, opened the meeting and stressed the importance of collaboration between clinical and basic researchers.

During this meeting, we had the pleasure to listen to two excellent keynote speakers, Prof. Dr Roger Stupp (Director of the Clinic for Oncology and Tumor Center, USZ) and Prof. Dr Robert Schreiber (Washington University Medical School of Pathology and Immunology, USA). In addition, two PIs from the consortium (Reinhard Dummer and Maries van den Broek) present current research data and all fellows presented their progress and outlook (further information in section 5 of this report). Mitchell Levesque presented the Dermatology Biobank including a newly developed online tool to correlate gene expression with survival data. More information can be found in section 4 of this report. Because translational research profits from regular exchange between academia and industry, we were very happy that Gerd Maas (Roche-UZH-ETHZ Translational Research Hub) presented his vision about how to substantiate this exchange.

Roger Stupp ("Academic research in Europe – Opportunities and risks") gave a stimulating overview of what we can learn from clinical trials if clinical and basic researchers closely collaborate. He made many important suggestions how this collaboration can be further improved.

Robert Schreiber ("Using genomics to personalize cancer immunotherapy") showed that T cells recognize mutated proteins expressed by cancer cells. Immune recognition of such cancer cells resulted in outgrowth of clones that lacked the expression of those mutated proteins. These important results demonstrate that the strong immunogenicity of an unedited tumour can be ascribed to expression of highly antigenic mutant proteins and show that outgrowth of tumour cells that lack these strong antigens via a T-cell-dependent immunoselection process represents one mechanism of cancer immunoediting.

Reinhard Dummer ("The central role of the interface between targeted and immunotherapy in skin cancers") presented results of clinical trials performed in melanoma using on kinase-inhibitors and checkpoint blockade (anti-CTLA-4) and suggested that both modalities synergize, which may result in improved clinical responses.

Maries van den Broek ("Using standard therapies to support tumour-specific immunity") showed that a standard therapy for cancer – radiotherapy – stimulates tumor-specific immunity and that, in fact, the latter is an integral part of the therapeutic response. Her group recently found that radiotherapy induced local complement activation, which is essential for immune stimulation and efficacy. These results suggest that the use of high-dose corticosteroids in the context of radiotherapy negatively impacts on therapeutic efficacy.

Without exception, the presentations were followed by lively and interesting discussions, which provided more food for thought and future plans. The lunch and coffee break were excellent opportunities to discuss and many of our fellows took the chance to interact with both keynote speakers.

Summarizing, our consortium has developed during the past two years into a well-functioning network with many synergistic collaborations. It is a pleasure to see how well the fellows are integrated, became an essential part of our consortium and fuelled our research projects with new and original ideas.

10. List of Honors and Prizes

Maries van den Broek: Dr Ernst Th. Jucker-Prize for cancer research (2013).

Onur Boyman: 13 November 2013, LEO Pharma Research Foundation Gold Prize (Copenhagen, Denmark): for research on the function of T cell subsets and different cytokines in the pathogenesis of psoriasis and other immune-mediated diseases and the treatment of melanoma.

I became a scientist, because...
I was driven by curiosity about things you cannot find in textbooks.

11. List of Publications form the Consortium

2013

Albers J, Rajski M, Schonenberger D, Harlander S, Schraml P, von Teichman A, et al. Combined mutation of Vhl and Trp53 causes renal cysts and tumours in mice. EMBO molecular medicine. 2013;5:949-64.

Ascierto PA, Schadendorf D, Berking C, Agarwala SS, van Herpen CM, Queirolo P, Blank CU, Hauschild A, Beck JT, St-Pierre A, Niazi F, Wandel S, Peters M, Zubel A, Dummer R. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. Lancet Oncol 2013;14:249-5

Barysch MJ, Weibel L, Neuhaus K, Subotic U, Schärer L, Donghi D, Hafner J, Braun R, Läuchli S, Dummer R, Schiestl C. Dermatofibrosarcoma protuberans in childhood treated with slow Mohs micrographic surgery. Pediatric Dermatology 2013;30:462-8

Bluwstein A, Kumar N, Léger K, Traenkle J, Oostrum Jv, Rehrauer H, Baudis M, Hottiger MO. PKC signaling prevents irradiation-induced apoptosis of primary human fibroblasts. Cell Death Dis. 2013 Feb 14;4:e498.

Boi M, Rinaldi A, Kwee I, Bonetti P, Todaro M, Tabbò F, Piva R, Rancoita PM, Matolcsy A, Timar B, Tousseyn T, Rodríguez-Pinilla SM, Piris MA, Beà S, Campo E, Bhagat G, Swerdlow SH, Rosenwald A, Ponzoni M, Young KH, Piccaluga PP, Dummer R, Pileri S, Zucca E, Inghirami G, Bertoni F. PRDM1/BLIMP1 is commonly inactivated in anaplasticlarge T-cell lymphoma. Blood 2013;122:2683-93

Boos LA, Dettmer M, Schmitt A, Rudolph T, Steinert H, Moch H, et al. Diagnostic and prognostic implications of the PAX8-PPARgamma translocation in thyroid carcinomas-a TMA-based study of 226 cases. Histopathology. 2013;63:234-41.

Braumüller H, Wieder T, Fischer S, Brenner E, Hahn M, Alkhaled M, Schilbach K, Essmann F, Kneilling M, Griessinger C, Ranta F, Ullrich S, Mocikat R, Braungart K, Mehra T, Fehrenbacher B, van den Broek M, Häring HU, Handgretinger R, Quintanilla-Martinez L, Fend F, Schaller M, Schulze-Osthoff K, Röcken M. 2013. TH1 Cell Cytokines Drive Cancer into Senescence. Nature, 494:361-365.

Broglie MA, Soltermann A, Rohrbach D, Haile SR, Pawlita M, Studer G, et al. Impact of p16, p53, smoking, and alcohol on survival in patients with oropharyngeal squamous cell carcinoma treated with primary intensity-modulated chemoradiation. Head & neck. 2013;35:1698-706.

Casagrande S, Ruf M, Rechsteiner M, Morra L, Brun-Schmid S, von Teichman A, et al. The protein tyrosine phosphatase receptor type J is regulated by the pVHL-HIF axis in clear cell renal cell carcinoma. The Journal of pathology. 2013;229:525-34.

Cronin JC, Watkins-Chow DE, Incao A, Hasskamp JH, Schönewolf N, Aoude LG, Hayward NK, Bastian BC, Dummer R, Loftus SK, Pavan WJ. SOX10 Ablation Arrests Cell Cycle, Induces Senescence, and Suppresses Melanomagenesis. Cancer Res 2013;73:5709-18

Dannenmann S, Hermanns T, Bransi A, von Boehmer L, Matter C, Stevanovic S, Schraml P, Moch H, Knuth A, van den Broek M. 2013. Spontaneous peripheral T cell responses towards the tumor-associated antigen Cyclin D1 in patients with clear cell renal cell carcinoma. Cancer Immunology Res. 1:288-295.

Dannenmann S, Thielicke J, Stöckli M, Matter C, von Boehmer L, Cecconi V, Hermanns T, Hefermehl L, Schraml P, Moch H, Knuth A, van den Broek M. 2013. Myeloid cells promote progression of clear cell renal cell carcinoma. OncoImmunology, 2: eLocation ID: e23429.

Das Thakur M, Salangsang F, Landman AS, Sellers WR, Pryer NK, Levesque MP, Dummer R, McMahon M, Stuart DD. Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance. Nature. 2013;494:251-5

Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. The American journal of surgical pathology. 2013;37:1490-504.

Dettmer M, Perren A, Moch H, Komminoth P, Nikiforov YE, Nikiforova MN. Comprehensive MicroRNA expression profiling identifies novel markers in follicular variant of papillary thyroid carcinoma. Thyroid : official journal of the American Thyroid Association. 2013;23:1383-9.

Dettmer M, Vogetseder A, Durso MB, Moch H, Komminoth P, Perren A, et al. MicroRNA expression array identifies novel diagnostic markers for conventional and oncocytic follicular thyroid carcinomas. The Journal of clinical endocrinology and metabolism. 2013;98:E1-7.

Dreier J, Felderer L, Barysch M, Rozati S, Dummer R. Basal cell carcinoma: a paradigm for targeted therapies. Expert Opin Pharmacother 2013;14:1307-18

Dummer R, Mangana M. Carboplatin, paclitaxel and sorafenib in advanced melanoma – what have we learned? Transl Cancer Res 2013;2:46-47

Dummer R, Rozati S, Guenova E, Cozzio A. Less can be more: the impact of chemotherapy on cutaneous T-cell lymphomas. Future Oncol. 2013;9:1061-4

Dummer R, Treating basal-cell carcinoma in a real life setting. Lancet Oncol 2013;14:572-573

Eichelberg C, Chun FK, Bedke J, Heuer R, Adam M, Moch H, et al. Epithelial cell adhesion molecule is an independent prognostic marker in clear cell renal carcinoma. International journal of cancer Journal international du cancer. 2013;132:2948-55.

Eichelberg C, Minner S, Isbarn H, Burandt E, Terracciano L, Moch H, et al. Prognostic value of alpha-methyl CoA racemase (AMACR) expression in renal cell carcinoma. World journal of urology. 2013;31:847-53.

Feldmeyer L, Shojaati G, Spanaus KS, Navarini A, Theler B, Donghi D, Urosevic-Maiwald M, Glatz M, Imhof L, Barysch MJ, Dummer R, Roos M, French LE, Surber C, Hofbauer GF. Phototherapy with UVB narrowband, UVA/UVBnb, and UVA1 differentially impacts serum 25-hydroxyvitamin-D3. J Am Acad Dermatol 2013;69:530-6

Goldinger SM, Zimmer L, Schulz C, Ugurel S, Hoeller Ch, Kaehler KC, Schadendorf D, Hassel JC, Becker J, Hauschild A, Dummer R on behalf of Dermatology Cooperative Oncology Group (DeCOG). Upstream mitogen-activated protein kinase (MAPK) pathway inhibition: MEK inhibitor followed by a BRAF inhibitor in advanced melanoma patients. Eur J Cancer 2013;50:406-10

Gupta A, Nuber N, Esslinger E, Wittenbrink M, Treder M, Landshammer A, Noguchi T, Kelly M, Gnjatic S, Ritter E, von Boehmer L, Nishikawa H, Shiku H, Old L, Ritter G, Knuth A, van den Broek M. 2013. A novel human-derived monoclonal antibody against NY-ESO-1 improves the efficacy of chemotherapy. Cancer Immunity, 13:3-11.

Harris ML, Buac K, Shakhova O, Hakami RM, Wegner M, Sommer L, Pavan WJ. (2013). A dual role for SOX10 in the maintenance of the postnatal melanocyte lineage and the differentiation of melanocyte stem cell progenitors. PLoS Genetics, 9(7):e1003644. doi: 10.1371/journal.pgen.1003644. Epub 2013 Jul 25.

Jakka G, Schuberth P, Thiel M, Held G, Stenner F, van den Broek M, Renner C, Mischo A, Petrausch U. 2013. Antigen-specific *in vitro* expansion of functional redirected NY-ESI-1-specific human CD8+ T cells in a cell-free system. Anticancer Res. 33:4189-4201.

Jungmichel S, Rosenthal F, Altmeyer M, Lukas J, Hottiger MO, Nielsen ML. Proteome-wide identification of poly(ADP-Ribosyl)ation targets in different genotoxic stress responses. Mol Cell. 2013 Oct 24;52(2):272-85.

Kassner I, Andersson A, Fey M, Tomas M, Ferrando-May E, Hottiger MO. SET7/9-dependent methylation of ARTD1 at K508 stimulates poly-ADP-ribose formation after oxidative stress. Open Biol. 2013 Oct 2;3(10):120173.

Lenggenhager D, Maggio EM, Moch H, Rossle M. HBME-1 expression in hyalinizing trabecular tumours of the thyroid gland. Histopathology. 2013;62:1092-7.

Lindgren AE, Karlberg T, Thorsell AG, Hesse M, Spjut S, Ekblad T, Andersson CD, Pinto AF, Weigelt J, Hottiger MO, Linusson A, Elofsson M, Schüler H. PARP inhibitor with selectivity toward ADP-ribosyltransferase ARTD3/PARP3. ACS Chem Biol. 2013 Aug 16;8(8):1698-703.

Moch H. An overview of renal cell cancer: pathology and genetics. Seminars in cancer biology. 2013;23:3-9.

Nuber N, Curioni-Fontecedro A, Dannenmann SR, Matter C, von Boehmer L, Atanakovic D, Knuth A, van den Broek M. 2013. MAGE-C1/CT7 spontaneously triggers a CD4+ T-cell response in multiple myeloma patients. Leukemia 27: 1767-1769.

Pawlowski R, Muhl SM, Sulser T, Krek W, Moch H, Schraml P. Loss of PBRM1 expression is associated with renal cell carcinoma progression. International journal of cancer Journal international du cancer. 2013;132:E11-7.

Perner S, Rupp NJ, Braun M, Rubin MA, Moch H, Dietel M, et al. Loss of SLC45A3 protein (prostein) expression in prostate cancer is associated with SLC45A3-ERG gene rearrangement and an unfavorable clinical course. International journal of cancer Journal international du cancer. 2013;132:807-12.

Pflueger D, Sboner A, Storz M, Roth J, Comperat E, Bruder E, et al. Identification of molecular tumor markers in renal cell carcinomas with TFE3 protein expression by RNA sequencing. Neoplasia. 2013;15:1231-40.

Raaijmakers MI, Rozati S, Goldinger SM, Widmer DS, Dummer R, Levesque MP. Melanoma immunotherapy: historical precedents, recent successes and future prospects. Immunotherapy. 2013;5:169-82

Rechsteiner M, von Teichman A, Ruschoff JH, Fankhauser N, Pestalozzi B, Schraml P, et al. KRAS, BRAF, and TP53 deep sequencing for colorectal carcinoma patient diagnostics. The Journal of molecular diagnostics : JMD. 2013;15:299-311.

Rechsteiner M, Zimmermann AK, Wild PJ, Caduff R, von Teichman A, Fink D, et al. TP53 mutations are common in all subtypes of epithelial ovarian cancer and occur concomitantly with KRAS mutations in the mucinous type. Experimental and molecular pathology. 2013;95:235-41.

Reiner CS, Roessle M, Thiesler T, Eberli D, Klotz E, Frauenfelder T, et al. Computed tomography perfusion imaging of renal cell carcinoma: systematic comparison with histopathological angiogenic and prognostic markers. Investigative radiology. 2013;48:183-91.

Rinderknecht JD, Goldinger SM, Rozati S, Kamarashev J, Kerl K, French LF, Dummer R, Belloni B. RASopathic Skin Eruptions during Vemurafenib Therapy. Plos One 2013;3:e58721

Robert C, Dummer C, Gutzmer R, Lorigan P, Kim KB, Nyakas M, Arance A, Liszkay G, Schadendorf D, Cantarini M, Spencer St, Middleton MR. Lancet Oncol 2013;14:733-40

Rolfs F, Huber M, Gruber F, Bohm F, Pfister HJ, Bochkov VN, Tschachler E, Dummer R, Hohl D, Schafer M, Werner S. Dual role of the antioxidant enzyme peroxiredoxin 6 in skin carcinogenesis. Cancer Res 2013;73:3460-9

Rosenthal F, Feijs KL, Frugier E, Bonalli M, Forst AH, Imhof R, Winkler HC, Fischer D, Caflisch A, Hassa PO, Lüscher B, Hottiger MO. Macrodomain-containing proteins are new mono-ADP-ribosylhydrolases. Nat Struct Mol Biol. 2013 Apr;20(4):502-7.

Rossle M, Sigg M, Ruschoff JH, Wild PJ, Moch H, Weber A, et al. Ultra-deep sequencing confirms immunohistochemistry as a highly sensitive and specific method for detecting BRAF V600E mutations in colorectal carcinoma. Virchows Archiv : an international journal of pathology. 2013;463:623-31.

Rossle M, Weber CS, Zullig L, Graf N, Jochum W, Stockli SJ, et al. EGFR expression and copy number changes in low T-stage oral squamous cell carcinomas. Histopathology. 2013;63:271-8.

Roth P, Silginer M, Goodman SL, Hasenbach K, Thies S, Maurer G, et al. Integrin control of the transforming growth factor-beta pathway in glioblastoma. Brain : a journal of neurology. 2013;136:564-76.

Sanjmyatav J, Hartmann A, Moch H, Hauke S, Gajda M, Meyer B, et al. Reply to Jerome Verine, Christophe Leboeuf and Philippe Ratajczak›s letter to the editor re: Jimsgene Sanjmyatav, Sven Hauke, Mieczyslaw Gajda, et al. Establishment of a multicolour fluorescence in situ hybridisation-based assay for subtyping of renal cell tumours. Eur Urol 2013;64:689-91. European urology. 2014;65:e71-2.

Sanjmyatav J, Hauke S, Gajda M, Hartmann A, Moch H, Meyer B, et al. Establishment of a multicolour fluorescence in situ hybridisation-based assay for subtyping of renal cell tumours. European urology. 2013;64:689-91.

Schuberth P, Hagedorn C, Jensen S, Gulati P, van den Broek M, Mischo A, Soltermann A, Jüngel A, Maaroquin Belaunzaran O, Stahel R, Renner C, Petrausch U. 2013. Treatment of malignant pleural mesothelioma by fibroblast activation protein-specific re-directed T cells. J. Transl. Med. 11:187-197.

Shakhova O. and Sommer L. (2013). Testing the cancer stem cell hypothesis in melanoma: the clinics will tell. Cancer Lett. 338(1):74-81.

Sharma A, Bode B, Studer G, Moch H, Okoniewski M, Knuth A, von Boehmer L, van den Broek M. 2013. Radiotherapy of human sarcoma promotes an intratumoral immune effector signature. Clin. Cancer Res. 19:4843-4853.

Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. The American journal of surgical pathology. 2013;37:1469-89.

Stadler R, Assaf C, Klemke CD, Nashan D, Weichenthal M, Dummer R, Sterry W. Brief S2k guidelines-Cutaneous lymphomas. J Dtsch Dermatol Ges. 2013;11 Suppl 3:19-28, 20-30

Tan PH, Cheng L, Rioux-Leclercq N, Merino MJ, Netto G, Reuter VE, et al. Renal tumors: diagnostic and prognostic biomarkers. The American journal of surgical pathology. 2013;37:1518-31.

Teleki I, Krenacs T, Szasz MA, Kulka J, Wichmann B, Leo C, et al. The potential prognostic value of connexin 26 and 46 expression in neoadjuvant-treated breast cancer. BMC cancer. 2013;13:50.

Tordella L, Koch S, Salter V, Pagotto A, Doondeea JB, Feller SM, et al. ASPP2 suppresses squamous cell carcinoma via RelA/p65-mediated repression of p63. Proceedings of the National Academy of Sciences of the United States of America. 2013;110:17969-74.

Varga Z, Noske A, Ramach C, Padberg B, Moch H. Assessment of HER2 status in breast cancer: overall positivity rate and accuracy by fluorescence in situ hybridization and immunohistochemistry in a single institution over 12 years: a quality control study. BMC cancer. 2013;13:615.

Varga Z, Sinn P, Fritzsche F, von Hochstetter A, Noske A, Schraml P, et al. Comparison of EndoPredict and Oncotype DX test results in hormone receptor positive invasive breast cancer. PloS one. 2013;8:e58483.

Vogetseder A, Thies S, Ingold B, Roth P, Weller M, Schraml P, et al. alphav-Integrin isoform expression in primary human tumors and brain metastases. International journal of cancer Journal international du cancer. 2013;133:2362-71.

Vom Berg J, Vrohlings M, Haller S, Haimovici A, Kulig P, Sledzinska A, Weller M, Becher B. 2013. Intratumoral IL-12 combined with CTLA-4 blockade elicits T cell-mediated glioma rejection. J Exp Med 210:2803-11.

von Boehmer L, Landshammer A, Bode P, Nuber N, Ritter G, Old L, Moch H, Jäger E, Knuth A, van den Broek M. 2013. NY-ESO-1-specific immunological pressure and escape in a patient with metastatic melanoma. Cancer Immunity 13:12-18.

Voskens CJ, Goldinger SM, Loquai C, Robert C, Kaehler KC, Berking C, Bergmann T, Bockmeyer CL, Eigentler T, Fluck M, Garbe C, Gutzmer R, Grabbe S, Hauschild A, Hein R, Hundorfean G, Justich A, Keller U, Klein C, Mateus C, Mohr P, Paetzold S, Satzger I, Schadendorf D, Schlaeppi M, Schuler G, Schuler-Thurner B, Trefzer U, Ulrich J, Vaubel J, von Moos R, Weder P, Wilhelm T, Göppner D, Dummer R, Heinzerling LM. The Price of Tumor Control: An Analysis of Rare Side Effects of Anti-CTLA-4 Therapy in Metastatic Melanoma from the Ipilimumab Network. PLoS One 2013;8:e53745

Walter A, Schäfer M, Matter C, Urosevic-Maiwald M, Belloni B, Schönewolf N, Cecconi V, Kulig P, Dummer R, Bloch W, Werner S, Beer HD, Knuth A, van den Broek M. 2013. Aldara activates two independent immune defense pathways. Nat. Commun. 4:1560 doi: 10.1038/ncomms2566.

Weber FA, Bartolomei G, Hottiger MO, Cinelli P. Artd1/Parp1 regulates reprogramming by transcriptional regulation of Fgf4 via Sox2 ADP-ribosylation. Stem Cells. 2013 Nov;31(11):2364-73.

Weber JS, Dummer R, de Pril V, Lebbé C, Hodi FS; MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: Detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 2013;119:1675-82

Widmer DS, Hoek KS, Cheng PF, Eichhoff OM, Biedermann T, Raaijmakers MI, Hemmi S, Dummer R, Levesque MP. Hypoxia Contributes to Melanoma Heterogeneity by Triggering HIF1α-Dependent Phenotype Switching. J Invest Dermatol 2013;133:2436-43

Zeh N, Wild PJ, Bode PK, Kristiansen G, Moch H, Sulser T, et al. Retroperitoneal teratoma with somatic malignant transformation: a papillary renal cell carcinoma in a testicular germ cell tumour metastasis following platinum-based chemotherapy. BMC urology. 2013;13:9.

Zimmermann AK, Imig J, Klar A, Renner C, Korol D, Fink D, et al. Expression of MAGE-C1/CT7 and selected cancer/testis antigens in ovarian borderline tumours and primary and recurrent ovarian carcinomas. Virchows Archiv : an international journal of pathology. 2013;462:565-74.

Zullig L, Roessle M, Weber C, Graf N, Haerle SK, Jochum W, et al. High sex determining region Y-box 2 expression is a negative predictor of occult lymph node metastasis in early squamous cell carcinomas of the oral cavity. European journal of cancer. 2013;49:1915-22.

2014

Amin MB, Smith SC, Agaimy A, Argani P, Comperat EM, Delahunt B, et al. Collecting duct carcinoma versus renal medullary carcinoma: an appeal for nosologic and biological clarity. The American journal of surgical pathology. 2014;38:871-4.

Barysch MJ, Levesque MP, Cheng P, Karpova MB, Mihic-Probst D, Civenni G, Shakova O, Sommer L, Biedermann T, Scheistl C, Dummer R. Coexpression of SOX10/CD271 (p75NTR) and β-Galactosidase in Large to Giant Congenital Melanocytic Nevi of Pediatric Patients. Dermatopathology 2014;1:35-46

Bitanihirwe BK, Meerang M, Friess M, Soltermann A, Frischknecht L, Thies S, et al. PI3K/mTOR signaling in mesothelioma patients treated with induction chemotherapy followed by extrapleural pneumonectomy. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2014;9:239-47.

Blattner M, Lee DJ, O›Reilly C, Park K, MacDonald TY, Khani F, et al. SPOP mutations in prostate cancer across demographically diverse patient cohorts. Neoplasia. 2014;16:14-20.

Bode PK, Thielken A, Brandt S, Barghorn A, Lohe B, Knuth A, et al. Cancer testis antigen expression in testicular germ cell tumorigenesis. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2014;27:899-905.

Curioni-Fontecedro A, Martin V, Vogetseder A, Knuth A, Moch H, Soldini D, et al. Chromosomal aberrations of cancer-testis antigens in myeloma patients. Hematological oncology. 2014.

Dettmer MS, Perren A, Moch H, Komminoth P, Nikiforov YE, Nikiforova MN. MicroRNA profile of poorly differentiated thyroid carcinomas: new diagnostic and prognostic insights. Journal of molecular endocrinology. 2014;52:181-9.

Dreier J, Cheng PF, Bogdan Alleman I, Gugger A, Hafner J, Tschopp A, Goldinger SM, Levesque MP, Dummer R. Basal cell carcinomas in a tertiary referral centre- a systematic analysis. Br J Dermatol 2014 [Epub ahead of print]

Dreier J, Dummer R, Felderer L, Nägeli M, Gobbi S, Kunstfeld R. Emerging drugs andcombination strategies for basal cell carcinoma. Expert Opin Emerg Drugs. 2014 Apr 29 [Epubahead of print]

Dreno B, Urosevic-Maiwald M, Kim Y, Guitart J, Duvic M, Dereure O, Khammari A, Knol AC, Derbij A, Lusky M, Didillon I, Santoni AM, Acres B, Bataille V, Chenard MP, Bleuzen P, Limacher JM, Dummer R. TG1042 (Adenovirus-interferon-γ) in Primary Cutaneous B-cell Lymphomas: A Phase II Clinical Trial. PLoS One 2014;9:e83670

Dummer R, Duvic M, Scarisbrick J, Olsen EA, Rozati S, Eggmann N, Goldinger SM, Hutchinson K, Geskin L, Illidge TM, Giuliano E, Elder J, Kim YH. Final results of a multicenter phase II study of the purine nucleoside phosphorylase (PNP) inhibitor forodesine in patients with advanced cutaneous T-cell lymphomas (CTCL) (Mycosis fungoides and Sézary Syndrome). Ann Oncol 2014 [Epub ahead of print]

Dummer R, Goldinger SM, Turtschi CP, Eggmann NB, Michielin O, Mitchell L, Veronese L, Hilfiker PR, Felderer L, Rinderknecht JD. Vemurafenib in patients with BRAFV600 mutationpositive melanoma with symptomatic brain metastases: Final results of an open-label pilot study. Eur J Cancer 2014;50:611-21

Dummer R, Goldinger SM, Widmer D, Dreier J, Levesque MP. To B-(RAF) or Not to Be. J Invest Dermatol 2014;134:1200-1

Dummer R. Precision medicine and skin cancer therapy: dealing with a moving target. Editorial. Curr Opin Oncol 2014;26:182-183

Engeli L, Moergeli H, Binder M, Drabe N, Meier C, Buechi S, Dummer R, Jenewein J. Resilience in patients and spouses faced with malignant melanoma. A qualitative longitudinal study. Eur J Cancer Care (Engl) 2014 [Epub ahead of print]

Espinosa E, Grob JJ, Dummer R, Rutkowski P, Robert C, Gogas H, Kefford R, Eggermont AM, Martin Algarra S, Hauschild A, Schadendorf D. Treatment Algorithms in Stage IV Melanoma. Am J Ther. 2014 Jan 9. [Epub ahead of print]

Flaherty KT, Hennig M, Lee SJ, Ascierto PA, Dummer R, Eggermont AM, Hauschild A, Kefford R, Kirkwood JM, Long GV, Lorigan P, Mackensen A, McArthur G, O›Day S, Patel PM, Robert C, Schadendorf D. Surrogate endpoints for overall survival in metastatic melanoma: a meta-analysis of randomised controlled trials. Lancet Oncol. 2014 Jan 30. pii: S1470-2045(14)70007-5 [Epub ahead of print]

Friemel J, Rechsteiner MP, Frick L, Boehm F, Struckmann K, Sigg M, et al. Intratumor heterogeneity in hepatocellular carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2014.

Gehrke S, Otsuka A, Huber R, Meier B, Kistowska M, Fenini G, Cheng P, Dummer R, Kerl K, Contassot E, French LE. Metastatic melanoma cell lines do not secrete IL-1β but promote IL-1β production from macrophages. J Dermatol Sci 2014;74:167-9

Guenova E, Hoetzenecker W, Rozati S, Levesque MP, Dummer R, Cozzio A. Novel therapies for cutaneous T-cell lymphoma: what does the future hold? Expert Opin Investig Drugs. 2014 Jan 8. [Epub ahead of print]

Guenova E, Schanz S, Hoetzenecker W, Desimone JA, Mehra T, Voykov B, Urosevic- Maiwald M, Berneburg M, Dummer R, French LE, Kerl K, Kamarachev J, Fierlbeck G, Cozzio A. Systemic corticosteroids for subcutaneous panniculitis-like T-cell lymphoma. Br J Dermatol. 2014 [Epub ahead of print]

Hell MP, Duda M, Weber TC, Moch H, Krek W. Tumor suppressor VHL functions in the control of mitotic fidelity. Cancer research. 2014;74:2422-31.

Ikenberg K, Valtcheva N, Brandt S, Zhong Q, Wong CE, Noske A, et al. KPNA2 is overexpressed in human and mouse endometrial cancers and promotes cellular proliferation. The Journal of pathology. 2014;234:239-52.

Kempf W, Kazakov DV, Rütten A, Rupec RA, Talarcik P, Ballová V, Kerl K, Dummer R, Lautenschlager S, Zimmermann DR, Tinguely M. Primary cutaneous follicle center lymphoma with diffuse CD30 expression: A report of 4 cases of a rare variant. J Am Acad Dermatol 2014 [Epub ahead of print]

Koppensteiner R, Samartzis EP, Noske A, von Teichman A, Dedes I, Gwerder M, et al. Effect of MRE11 loss on PARP-inhibitor sensitivity in endometrial cancer *in vitro*. PloS one. 2014;9:e100041.

Léger K, Bär D, Savić N, Santoro R, Hottiger MO. ARTD2 activity is stimulated by RNA. Nucleic Acids Res. 2014 Apr;42(8):5072-82.

Lenggenhager D, Curioni-Fontecedro A, Storz M, Shakhova O, Sommer L, Widmer DS, Seifert B, Moch H, Dummer R, Mihic-Probst D. An Aggressive Hypoxia Related Subpopulation of Melanoma Cells is TRP-2 Negative. Transl Oncol. 2014 [Epub ahead of print]

Lenggenhager D, Curioni-Fontecedro A, Storz M, Shakhova O, Sommer L, Widmer DS, et al. An Aggressive Hypoxia Related Subpopulation of Melanoma Cells is TRP-2 Negative. Translational oncology. 2014;7:206-12.

Lenggenhager D., Curioni-Fontecedro A., Storz M., Shakhova O., Sommer L., Seifert B., Moch H., Dummer R., Mihic-Probst D. (2014). An aggressive hypoxia related subpopulation of melanoma cells is TRP-2 negative. Translational Oncology, 7(2):206-12.

Lohri C, Hutzli Schaltegger C, van den Broek M, Wenger R, Ruegg C, Fink D, Fehr M, Knuth A, Zweifel M. 2014. Neutrophil expression of ICAM1, CXCR1, and VEGFR1 in patients with breast cancer before and after adjuvant chemotherapy. Anticancer Res. 34:4693-4700.

McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, Ribas A, Hogg D, Hamid O, Ascierto PA, Garbe C, Testori A, Maio M, Lorigan P, Lebbé C, Jouary T, Schadendorf D, O›Day SJ, Kirkwood JM, Eggermont AM, Dréno B, Sosman JA, Flaherty KT, Yin M, Caro I, Cheng S, Trunzer K, Hauschild A.Safety and efficacy of vemurafenib in BRAFV600E and BRAFV600K mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014 [Epub ahead of print]

McCusker M, Basset-Seguin N, Dummer R, Lewis K, Schadendorf D, Sekulic A, Hou J, Wang L, Yue H, Hauschild A. Metastatic basal cell carcinoma: Prognosis dependent on anatomic site and spread of disease. Eur J Cancer 2014;50:774-783

Mehra T, Ikenberg K, Moos RM, Benz R, Nair G, Schanz U, Haralambieva E, Hoetzenecker W, Dummer R, French

LE, Guenova E, Cozzio A. Brentuximab as a Treatment for CD30+ Mycosis Fungoides and Sézary Syndrome. JAMA Dermatol. 2014 Oct 8

Meller S, Bicker A, Montani M, Ikenberg K, Rostamzadeh B, Sailer V, et al. Myoglobin expression in prostate cancer is correlated to androgen receptor expression and markers of tumor hypoxia. Virchows Archiv : an international journal of pathology. 2014;465:419-27.

Moch H, Lukamowicz-Rajska M. miR-30c-2-3p and miR-30a-3p: new pieces of the jigsaw puzzle in HIF2alpha regulation. Cancer discovery. 2014;4:22-4.

Moch H, Srigley J, Delahunt B, Montironi R, Egevad L, Tan PH. Biomarkers in renal cancer. Virchows Archiv : an international journal of pathology. 2014;464:359-65.

Montavon G, Jauquier N, Coulon A, Peuchmaur M, Flahaut M, Bourloud KB, Yan P, Delattre O, Sommer L, Joseph JM, Janoueix-Lerosey I, Gross N, Mühlethaler-Mottet A. (2014). Wild-type ALK and activating ALK-R1275Q and ALK-F1174L mutations upregulate Myc and initiate tumor formation in murine neural crest progenitor cells. Oncotarget. 5(12):4452-66.

Nägeli MC, Dummer R. Vismodegib (Erivedge®). Schweiz Med Forum 2014;14:284-286

Poyet C, Jentsch B, Hermanns T, Schweckendiek D, Seifert HH, Schmidtpeter M, et al. Expression of histone deacetylases 1, 2 and 3 in urothelial bladder cancer. BMC clinical pathology. 2014;14:10.

Rechsteiner M, Muller R, Reineke T, Goede J, Bohnert A, Zhong Q, et al. Modelling of a genetically diverse evolution of Systemic Mastocytosis with Chronic Myelomonocytic Leukemia (SM-CMML) by Next Generation Sequencing. Experimental hematology & oncology. 2014;3:18.

Rechsteiner M, Wild P, Kiessling MK, Bohnert A, Zhong Q, Stahel RA, et al. A novel germline mutation of PDGFR-beta might be associated with clinical response of colorectal cancer to regorafenib. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2014.

Rodon J, Tawbi HA, Thomas AL, Stoller R, Turtschi CP, Baselga J, Sarantopoulos J, Mahalingam D, Shou Y, Moles MA, Yang L, Granvil C, Hurh E, Rose KL, Amakye DD, Dummer R, Mita AC. A Phase 1, Multicenter, Open-Label, First-in-Human, Dose-Escalation Study of the Oral Hedgehog Inhibitor Sonidegib (LDE225) in Patients With Advanced Solid Tumors. Clin Cancer Res 2014;20:1900-1909

Rosenthal F, Hottiger MO. Identification of ADP-ribosylated peptides and ADP-ribose acceptor sites. Front Biosci (Landmark Ed). 2014 Jun 1;19:1041-56.

Rozati S, Kempf W, Ostheeren-Michaelis S, Bode-Lesniewska B, Zimmermann DR,Dummer R, Cozzio A. Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type, With Bilateral Intraocular Involvement and Infiltration to the CNS. J Clin Oncol 2014 Sep 29. [Epub ahead of print]

Ruf M, Mittmann C, Hartmann A, Hermanns T, Poyet C, van den Broek M, Sulser T, Moch H, Schraml P. 2014. pVHL/HIF-regulated CD70 expression is associated with infiltration of CD27+ lymphocytes and increased serum levels of soluble CD27 in clear cell renal cell carcinoma. Clin. Cancer Res. in press.

Schadendorf D, Amonkar MM, Milhem M, Grotzinger K, Demidov LV, Rutkowski P, Garbe C, Dummer R, Hassel JC, Wolter P, Mohr P, Trefzer U, Lefeuvre-Plesse C,

Rutten A, Steven N, Ullenhag G, Sherman L, Wu FS, Patel K, Casey M, Robert C. Functional and symptom impact of trametinib versus chemotherapy in BRAF V600E advanced or metastatic melanoma: quality-of-life analyses of the METRIC study. Ann Oncol 2014;25:700-6

Schoenewolf NL, Belloni B, Simcock M, Tonolla S, Vogt P, Scherrer E, Holzmann D, Dummer R. Clinical implications of distinct metastasizing preferences of different melanoma subtypes. Eur J Dermatol 2014;24:236-41

Sommer L. (2014). Open questions: development of tumor cell heterogeneity and its implications for cancer treatment. BMC Biol, 5;12:15. doi: 10.1186/1741-7007-12-15.

Theurillat JP, Udeshi ND, Errington WJ, Svinkina T, Baca SC, Pop M, et al. Prostate cancer. Ubiquitylome analysis identifies dysregulation of effector substrates in SPOP-mutant prostate cancer. Science. 2014;346:85-9.

Tugues S, Burkhard SH, Ohs I, Vrohlings M, Nussbaum K, Vom Berg J, Kulig P, Becher B. New insights into IL-12-mediated tumor suppression. 2014. Cell Death Differ. In press.

Urner-Bloch U, Urner M, Stieger P, Galliker N, Winterton N, Zubel A, Moutouh-de Parseval L, Dummer R, Goldinger SM. Transient MEK inhibitor-associated retinopathy in metastatic melanoma. Ann Oncol 2014;25:1437-41

Varga Z, Tubbs RR, Moch H. Concomitant detection of HER2 protein and gene alterations by immunohistochemistry (IHC) and silver enhanced in situ hybridization (SISH) identifies HER2 positive breast cancer with and without gene amplification. PloS one. 2014;9:e105961.

Venturelli S, Sinnberg TW, Berger A, Noor S, Levesque MP, Böcker A, Niessner H, Lauer UM, Bitzer M, Garbe C, Busch C. Fr in Onc 2014:4;227.

Wang Y, Bu F, Royer C, Serres S, Larkin JR, Soto MS, et al. ASPP2 controls epithelial plasticity and inhibits metastasis through beta-catenin-dependent regulation of ZEB1. Nature cell biology. 2014.

Wolf MJ, Adili A, Piotrowitz K, Abdullah Z, Boege Y, Stemmer K, et al. Metabolic Activation of Intrahepatic CD8(+) T Cells and NKT Cells Causes Nonalcoholic Steatohepatitis and Liver Cancer via Cross-Talk with Hepatocytes. Cancer Cell. 2014;26:549-64.

Wyler L, Napoli CU, Ingold B, Sulser T, Heikenwalder M, Schraml P, et al. Brain metastasis in renal cancer patients: metastatic pattern, tumour-associated macrophages and chemokine/chemoreceptor expression. British journal of cancer. 2014;110:686-94

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