BIOGRAPHICAL SKETCH

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NAME: Petritsch, Claudia Katharina

eRA COMMONS USER NAME (credential, e.g., agency login): petritschc

POSITION TITLE: Associate Professor - Neurosurgery

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Vienna, BioCenter, Vienna	B.S.	05/1989	Biology
University of Vienna, BioCenter, Vienna	M.S.	05/1990	Molecular Biology
Institute of Molecular Pathology, Vienna	Ph.D.	08/1996	Cell Biology and Biochemistry

A. Personal Statement

I am a neuroscientist and cancer biologist whose research focuses on glia and stem cells in brain homeostasis and cancer. The generation of in vivo models in transgenic mice and from human patient-derived specimen for brain tumors is an area of emphasis in my laboratory. My lab generated a model for BRAF mutant high-grade gliomas, including an adenovirus-induced transgenic and syngeneic engraftment model for BRAF V600E CDKN2A-deficient mouse gliomas (Huillard et al., 2014 *PNAS*; Grossauer et al., 2016 *Oncotarget*). We recently generated new murine and human patient-derived xenograft models for BRAF mutant tumors, that closely represent the human disease of low-grade gliomas. Together with these modeling studies, my team conducts preclinical studies to optimize the therapies for treatment of BRAF mutant brain tumors. We study the involvement of cancer stem cells in resistance to small molecule targeted inhibitors. My team has contributed preclinical data using one of the few existing human BRAF V600E mutant xenograft models, to demonstrate that there is considerable intra-tumoral heterogeneity in responses of small molecule BRAF inhibitors, including vemurafenib tool compound PLX4720, with non-stem like glioma cells but not stem cell-like glioma cells responding to the anti-proliferative effects of the drug (Lerner et al., 2015 *Cancer Res*). We also study how oncogenes and therapies affect cell fate determination of glial cells, in particular oligodendrocyte progenitor cells (Sugiarto et al., 2011 *Cancer Cell;* Persson et al., 2010 *Cancer Cell;* Daynac et al., 2018 *Nature Comm*). We use our knowledge to guide clinical treatment schedules aimed at overcoming lack of response and therapy resistance and approaching these questions, *brings my team closer to reach* our overarching goal, which is to optimize existing therapies for pediatric patients and to translate new therapeutic approaches for low-grade glioma patients to the clinic.

1) Huillard E.*, Hashizume, R.*, Phillips, J.J. Griveau, A., Ihrie, R. I., Aoki, Y., Nicolaides T., Perry, A., Waldman, T., McMahon, M., Weiss, W. A., **Petritsch, C.,** James, C. D., Rowitch, D. (2012) Cooperative interactions of BRAFV600E and CDKN2A deficiency in pediatric malignant astrocytoma as a basis for rational therapy. *PNAS* 109(22): 8710-5. PMID: 22586120 PMCID: PMC3365162
2) Lerner, R.G.*, Grossauer, S.*, Kadkhodaei, B., Meyers, I., Sidorov, M., Koeck, K., Hashizume, R., Ozawa, T., Phillips, J.J., Berger, M.S., Nicolaides, T., James, C.D., **Petritsch, C.K.** (2015). Targeting a Plk1-controlled polarity checkpoint in therapy-resistant glioblastoma-propagating cells. *Cancer Research* 75(24): 5355-66. *Equal contribution. PMID: 26573800 PMCID: PMC4698003.
3) Grossauer, S.*, Koeck, K.*, Murphy, N.E., Meyers, I.D., Daynac, M., Truffaux, N., Truong, A.Y., Nicolaides, T., McMahon, M., Berger, M.S., Phillips, J.J., James, C.D., **Petritsch, C.K.** (2016) Concurrent MEK targeted therapy prevents MAPK pathway reactivation during BRAFV600E-targeted

inhibition in a novel syngeneic, high-grade glioma model. *Oncotarget* 15;7(46): 75839-53. PMID: 27713119 PMCID: PMC5342782 *Equal contribution.

4) Daynac, M., Chouchane, M., Collins, H.Y., Murphy, N.E., Andor, N., Niu, J., Fancy, S.P., Stallcup, W., **Petritsch, C.K**. (2018). Lgl1 controls NG2 endocytic pathway to regulate oligodendrocyte differentiation and asymmetric cell division and gliomagenesis. *Nature Communications* 21;9(1): 2862. PMID: 30131568 PMCID: PMC6104045

B. Positions and Honors

Positions and Employment

1991-1996	Graduate Student at Institute of Molecular Pathology, Vienna, Austria
1996-1997	Research Scientist at Institute of Molecular Pathology, Vienna, Austria
1997-2002	Postdoctoral Fellow at Howard Hughes Medical Institute, University of California, San Francisco, San Francisco, CA
2002-2003	Postgraduate Researcher, Department of Physiology, University of California, San Francisco, San Francisco, CA
2003-2005	Lecturer; Gene Center and Dept. of Biochemistry, Ludwig-Maximilian-University Munich, Germany
2005-2008	Associate Research Biochemist, Dept. of Neurological Surgery, University of California, San Francisco, San Francisco, CA
2009-2014	Assistant Professor, Dept. of Neurological Surgery, University of California, San Francisco, San Francisco, CA
2014-2019	Associate Professor, Dept. of Neurological Surgery, University of California, San Francisco, San Francisco, CA
2019- present	Associate Professor, Dept. of Neurosurgery, Stanford University School of Medicine, Stanford, CA

Other Experience and Professional Memberships

2006-present	Ascina/Austrian Scientists and Scholars in North America, member
2007-present	Faculty, UCSF Eli and Edythe Broad Institute for Regeneration Medicine
2007-present	Society for Neuro-Oncology (SNO), member and abstract reviewer
2009-present	Member of the Helen Diller UCSF Comprehensive Cancer Center
2009-present	NIH Peer Review Committee: Stimulus grants, ad hoc reviewer
2010-present	Medical Research Council, UK, grant reviewer
2010-present	International Society for Stem Cell Research (ISSCR), member
2011-present	American Association for Cancer Research (AACR), member
2014-present	NIH Peer Review Committee: NCF/CNBT, ad hoc reviewer
2015-2019	Member of the Executive Vice Chancellor & Provost Office Review Committee
2016-2019	Bridge Curriculum UCSF Medical School, instructor

Honors

2005	Bavarian California Technology Award/BaCaTec, Munich, Germany
2006	CBRCP, IDEA Award, San Francisco, USA
2007/08	National Brain Tumor Foundation, Oligodendroglioma Award, San Francisco, USA
2007/08	Brain Tumor SPORE, Career Development Research Award, San Francisco, USA
2008	Academic Senate, Individual Investigator Award, San Francisco, USA
2008	Pilot Research Award, Research Allocation Program (REAC), San Francisco, USA
2009	American Cancer Society, Intramural Award, San Francisco, USA
2009	Stewart Trust Cancer Research Award, San Francisco, USA
2010	American Brain Tumor Association, Discovery Award, Des Plaines, USA
2011	Clinical and Translational Science Institute Opportunity Award, San Francisco, USA
2012	Voices Against Brain Cancer Award
2013	The Childhood Foundation for Brain Tumor Investigator Award

2014 Pilot Research Award, Research Allocation Program (REAC), San Francisco, USA
2015 RAP Award
2016 California Research Coordinating Committee – Investigator Award
2016 UCSF Research Allocation Program - Pilot Award for Junior Investigators

C. Contributions to Science

1. **Unraveling the mechanism for cell fate decisions in the adult brain.** Oligodendrocyte progenitor cells (OPC) in the adult brain face the decision of whether to differentiate or continue to proliferate as OPC throughout development and adulthood. The mechanism that governs these cell fate decisions is largely unknown. The extent to which OPC proliferate or differentiate is crucial for homeostasis. Only if we understand normal neural precursor cell differentiation, will we be able to determine how differentiation can be interrupted in favor of precursor cell expansion and associated tumorigenesis. As a faculty at UCSF, my lab discovered that oligodendrocyte progenitor cells undergo asymmetric cell division (ACD) to generate progeny of diverse fate. We demonstrated that normal OPC undergo asymmetric divisions by segregating the NG2 complex consisting of NG2, EGFR and PDGFRα to only one daughter cell during each division. We further showed that OPC, while undergoing asymmetric and symmetric divisions at equal rates in the normal murine and human brain, divide mostly symmetrical at the expense of asymmetric divisions and fail to differentiate, at premalignant stages of murine gliomagenesis, and in human glioma, suggesting that disrupted asymmetric divisions are an important step in neoplastic transformation (**Persson et al., Cancer Cell, 2010; Sugiarto et al., Cancer Cell, 2011)**. In continued studies into the mechanism of asymmetric cell division of OPC, we conducted loss of function analyses in transgenic mice, and established that decreased asymmetric division and differentiation synergizes with cell cycle deregulation due to loss of tumor suppressor CDKN2A in promoting neoplastic transformation and gliomagenesis **(Daynac et al., 2018**). *In making these discoveries, I provided rationale for testing regulators of asymmetric cell division as novel therapeutic targets for anti-glioma therapies. Additional studies of regulation of cell fate are needed and hold the promise to unravel novel points of susceptibility, to which more effective therapy against many cancer types, including gliomas can be targeted.*

1. Persson, A., **Petritsch, C.,** Itsara, M., Swartling, F., Goldenberg, D., Vandenberg, S., Ngyuen, K., Yakovenko, S., Thorne, C.A., Lee, E., Nishiyama, A., Stallcup, W., Berger, M.S., Goldman, S., Bergers, G., Weiss, W.A. (2010). Non-stem cell origin for oligodendondroglioma. *Cancer Cell* 14;18(6): 669-82. PMID: 21156288 PMCID: PMC3031116
2. Sugiarto, S., Persson, A., Gonzalez-Munoz, E., Waldhuber, M., Lamagna, C., Hanecker, P., Philips, J., Vandenberg, S., Berger, M. S., Stallcup, W., Bergers, G., Weiss, W. A., **Petritsch, C**. (2011). Asymmetry-defective oligodendrocyte progenitors as glioma precursors. *Cancer Cell* 13;20(3): 328-40. PMID: 21907924 PMCID: PMC3297490
3. Gomez-Lopez, S., Lerner, R., **Petritsch, C.,** (2014) Asymmetric Cell Division of Stem Cells and Progenitor cells during Homeostasis and in Cancer. *Cellular and Molecular Life Sciences* 71(4): 575-97. PMID: 23771628 PMCID: PMC3901929
4. Daynac, M., **Petritsch, C.K.** (2017). Regulation of asymmetric cell division in mammalian neural stem and cancer precursor cells. *Results Probl Cell Differ*. 61:375-99. PMID: 28409314 DOI: 10.1007/978-3-319-53150-2_17

2. **Targeting cancer stem cells in pediatric gliomas to overcome therapy resistance.** My team researches $BRAF^{V600E}$ pediatric gliomas with the broader goal of identifying novel therapies for this clinically challenging disease. We generated transgenic mouse models to faithfully recapitulate the genetic alterations found in a high-grade glioma subtype marked by $BRAF^{V600E}$ mutation and CDKN2A (p16) deletion and showed that these two alterations cooperate to generate tumors in **Huillard et al, 2012**. Our recent studies raise the concern that BRAF inhibitor monotherapy may not effectively eliminate the stem-like tumor-propagating cells (aka glioma stem cells), which may explain therapy resistance and tumor recurrence in patients treated with BRAF inhibitor monotherapy. **Lerner et al., 2015,** focused on proliferative, asymmetric cell division (ACD) vs. symmetric cell division, and inhibitor responses of two cell subpopulations in $BRAF^{V600}$-p16 null human tumor models. CD133+ tumor initiating cell subpopulations were determined as being less proliferative, more likely to undergo ACD, and less responsive to mutant BRAF or MEK inhibition than were NG2+ cells that are representative of the majority of bulk tumor. Polo-like-kinase-1 (PLK1) was determined to be a potential mediator of ACD in CD133+ cells and, in fact, its

small molecule inhibition was determined as being important in blocking CD133+ ACD and preventing maintenance of this tumor initiating cell population. These results are significant because they indicate a potential strategy for targeting a specific tumor cell subpopulation that is associated with therapy resistance and tumor recurrence. **Grossauer et al., 2016,** was based on the development and utilization of a $BRAF^{V600}$-p16 deficient syngeneic mouse glioma engraftment model. Treatment of $BRAF^{V600}$-p16 deficient tumor cells using a small molecule inhibitor against mutant BRAF revealed activation of MEK signaling that allowed tumor cells to minimize the effects of mutant BRAF inhibition. Knowledge of this tumor cell adaptive response was acted upon by co-treatment of tumor cells and derivative engrafted tumors with $BRAF^{V600}$ + MEK inhibitor combination therapy, which showed heightened anti-tumor activity (anti-proliferative and pro-apoptotic) in relation to either monotherapy. This study is significant because it identifies a potential therapeutic strategy for combatting $BRAF^{V600}$ therapeutic resistance. The development and characterization of the new syngeneic orthotopic mouse model of $BRAF^{V600E}$ mutated glioma is relevant as it is expected to help the search for effective combination therapies, including immune checkpoint blockade, as an effective strategy against $BRAF^{V600E}$-mutant glioma. *Additional preclinical experiments are needed to test the extent of which combined immune checkpoint and targeted therapy by MAPK pathway inhibition, will eliminate cancer stem cells and harness the power of the immune system to overcome therapy resistance.*

1. Huillard E.*, Hashizume, R.*, Phillips, J.J. Griveau, A., Ihrie, R. I., Aoki, Y., Nicolaides T., Perry, A., Waldman, T., McMahon, M., Weiss, W. A., **Petritsch, C.,** James, C. D., Rowitch, D. (2012) Cooperative interactions of BRAFV600E and CDKN2A deficiency in pediatric malignant astrocytoma as a basis for rational therapy. *PNAS* 109(22): 8710-5. PMID: 22586120 PMCID: PMC3365162
2. Lerner, R.G.*, Grossauer, S.*, Kadkhodaei, B., Meyers, I., Sidorov, M., Koeck, K., Hashizume, R., Ozawa, T., Phillips, J.J., Berger, M.S., Nicolaides, T., James, C.D., **Petritsch, C.K.** (2015). Targeting a Plk1-controlled polarity checkpoint in therapy-resistant glioblastoma-propagating cells. *Cancer Research* 75(24): 5355-66. *Equal contribution. PMID: 26573800 PMCID: PMC4698003.
3. Olow, A., Mueller, S., Yang, X., Hashizume, R., Meyerowitz, J., Weiss, W., Resnick, A.C., Waanders, A.J., Stalpers, L.J., Berger, M.S., Gupta, N., James, C.D., **Petritsch, C.K.,** Haas-Kogan, D.A. (2016). BRAF status in personalizing treatment approaches for pediatric gliomas. *Clin Cancer Res* 22, 5312-5321. PMCID: PMC5093033
4. Grossauer, S.*, Koeck, K.*, Murphy, N.E., Meyers, I.D., Daynac, M., Truffaux, N., Truong, A.Y., Nicolaides, T., McMahon, M., Berger, M.S., Phillips, J.J., James, C.D., **Petritsch, C.K.** (2016) Concurrent MEK targeted therapy prevents MAPK pathway reactivation during BRAFV600E-targeted inhibition in a novel syngeneic, high-grade glioma model. *Oncotarget* 15;7(46): 75839-53. PMID: 27713119 PMCID: PMC5342782 *Equal contribution.

3. **Brain tumor clonal evolution:** The underlying mechanism for the intra-tumoral heterogeneity found in many cancers can be explained by the clonal evolution model, whereby growth advantageous mutations cause the expansion of cancer cell subclones. The recurrent phenotype of many cancers may be a consequence of coexisting subpopulations responding unequally to therapies. To address cellular subpopulation dynamics within human tumors, a graduate student in my lab developed a bioinformatic method, EXPANDS. It estimates the proportion of cells harboring specific mutations in a tumor. By modeling cellular frequencies as probability distributions, EXPANDS predicts mutations that accumulate in a cell before its clonal expansion. More recently, we used the bioinformatics tools EXPANDS and PyClone to detect clones that are present at a ≥10% frequency in 1,165 exome sequences from many tumor types and showed that mortality risk declined when >4 clones coexisted in the sample, suggesting a trade-off between the costs and benefits of genomic instability. ITH and genomic instability thus have the potential to be useful measures that can universally be applied to all cancers.

1. Andor, N., Harness, J., Mewes, H. W., **Petritsch, C.** (2014) EXPANDS: Expanding Ploidy and Allele Frequency on Nested Subpopulations. *Bioinformatics* 30, 50-60. PMCID: PMC3866558
2. Andor, N., Graham, T.A., Jansen, M., Xia, L.C., Aktipis, C.A., **Petritsch, C.,** Ji, H.P.*, Maley, C.C.* (2016). Pan-cancer analysis of the extent and consequences of intra-tumor heterogeneity. *Nat Medicine* 22. 105-113. PMCID: PMC4830693.

Complete list of published works in MyBibliography
https://www.ncbi.nlm.nih.gov/myncbi/1hyR-65amDU5Z/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support

R21 NS099836 Petritsch (PI) 12/01/2016 - 11/30/2019
Investigating ASPM regulation of asymmetric division for therapeutic opportunities
The goal of this study is to investigate spindle-dependent functions of ASPM in proneural glioblastoma to overcome therapy resistance.
Role: PI

R01 CA201537 Bergers (PI) 08/01/2016 - 08/01/2020
Interregulatory function of immune-modulation and angiogenesis in cancer
The goal of this study is to gain mechanistic insights into synergy of anti-angiogenesis and immunosuppression therapy for the purpose of overcoming therapy resistance.
Role: Co-Investigator (ended 11/2019)

R01 CA171610 Pieper (PI) 02/01/2013 - 01/31/2018
Understanding the role of altered metabolism in gliomagenesis
The goal of the study is to improve therapy of glioma by better understanding the role altered metabolism plays in gliomagenesis.
Role: Co-Investigator

CRCC 38890 7504335 Petritsch (PI) 01/01/2017 – 06/30/2018
UC Cancer Research Coordinating Committee
Harnessing the immune system to eliminate glioma stem cells
The goal of the study is to investigate mechanisms to eliminate the most malignant cell subpopulations and to develop better anti-glioblastoma treatment. It will allow us to collect preliminary data for a larger grant application
Role: PI

R01 NS080619 James & Petritsch (Co-PI) 09/01/2012 – 08/31/2018
BRAF Mutation in Malignant Astrocytoma Origin, Evolution, and Response to Therapy
The goal of the study is to improve targeted therapy of malignant astrocytoma by defining the mechanisms of cellular transformation and recurrence in relation to BRAFV600E expression.
Role: Co-PI