BIOGRAPHICAL SKETCH

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NAME: Weinacht, Katja Gabriele

eRA COMMONS USER NAME: K_Weinacht

POSITION TITLE: Assistant Professor, Department of Pediatrics, Division of Stem Cell Transplantation and Regenerative Medicine, Stanford School of Medicine

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
Technische Universitaet Muenchen, Munich, Germany	M.D.	11/2002	Medicine
Technische Universitaet Muenchen, Munich, Germany	Ph.D.	08/2004	Medicine (Microbiology)
Channing Laboratory, Boston, MA	Postdoctoral	06/2006	Microbiology/Immunology
Massachusetts General Hospital, Boston, MA	Residency	06/2009	Pediatrics
Boston Children's Hospital, Dana-Farber Cancer Institute, Boston, MA	Fellowship	06/2012	Pediatric Hematology/ Oncology

A. Personal Statement

I am a pediatric hematologist-oncologist with specialization in hematopoietic stem cell transplantation (HSCT), and a physician-scientist with clinical and research focus on the niche of diseases that intersect immunodeficiency and bone marrow failure. This interest is a natural extension of my training background. During my dissertation, I studied host-commensal interactions from the microbials' point of view. My fellowship research in the laboratory of Dr. Luigi Notarangelo focused on understanding the mechanistic basis of genetic immune defects using induced pluripotent stem cells (iPSCs). After relocating from Boston Children's Hospital to Stanford University, I started my own research group in 2017. My laboratory has two distinct areas of study.

(1) We focus on understanding the mechanisms underlying human thymic development. The thymus is an essential immune organ, critical for T-cell development and function. Thymic injury can be congenital or acquired, e.g. during HSCT. In addition, thymic function naturally declines with age (immune senescence). We have developed a differentiation platform to derive thymic epithelial progenitor cells from iPSCs. We use iPSCs from patients with gene defects in thymic development and function as a window into studying the mechanisms underlying thymic organogenesis. Our goal is to derive fully functional thymic epithelial organoids *in vitro* that can be transplanted into patients and serve as cell therapy to promote and accelerate immune reconstitution. In addition, regenerative thymic tissues could be engineered to modulate endogenous immune effector functions, e.g. to induce tolerance after solid organ transplantation. As such, regenerative thymic tissues could constitute a novel immunotherapy platform.

(2) We are interested in understanding the how derangements in hematopoietic stem cell metabolism lead to a failure in hematopoiesis. Specifically, we are studying a rare disease called Reticular Dysgenesis (RD), caused by defects in the mitochondrial enzyme Adenylate Kinase 2 (AK2). Patients with RD present with a combined differentiation arrest of the myeloid and lymphoid lineages. We have developed a novel biallelic CRISPR-knockout model of AK2 in primary human hematopoietic stem/progenitor cells to precisely mimic the failure of human myelopoiesis in culture. In this model, we have discovered that AK2-deficient myeloid progenitors exhibit reductive stress, severely decreased levels of aspartate and defects in purine, nucleotide and ribosome synthesis that are all caused by a depletion in nicotinamide adenine dinucleotide (NAD+) levels.

In my clinic, I follow patients with genetic immune defects, specifically patients with 22q11 Deletion Syndrome.

(1) Rissone A*, **Weinacht KG*,** la Marca G, Bishop K, Giocaliere E, Jagadeesh J, Felgentreff K, Dobbs K, Al-Herz W, Jones M, Chandrasekharappa S, Kirby M, Wincovitch S, Simon KL, Itan Y, DeVine A, Schlaeger T, Schambach A, Sood R, Notarangelo LD, Candotti F. Reticular dysgenesis-associated AK2 protects hematopoietic stem and progenitor cell development from oxidative stress. J Exp Med. 2015 July;212(8):1185-202. PMCID: PMC4516804 ***(*Co-first authors, contributed equally)***

(2) **Weinacht KG**, Charbonnier LM, Alroqi F, Plant A, Qiao Q, Wu H, Ma C, Torgerson TR, Rosenzweig SD, Fleisher TA, Notarangelo LD, Hanson IC1, Forbes LR1, Chatila TA. Ruxolitinib reverses dysregulated T helper cell responses and controls autoimmunity caused by a novel signal transducer and activator of transcription 1 (STAT1) gain-of-function mutation.J Allergy Clin Immunol. 2017 Jan 23. PMCID: PMC5482293

(3) Gernez Y, de Jesus AA, Alsaleem H, Macaubas C, Roy A, Lovell D, Jagadeesh KA, Alehashemi S, Erdman L, Grimley M, Talarico S, Bacchetta R, Lewis DB, Canna SW, Mellins ED, Goldbach-Mansky R, **Weinacht KG**. Severe autoinflammation in four patients with C-terminal variants in CDC42 successfully treated with IL-1beta inhibition. J Allergy Clin Immunol. 2019 Oct;144(4):1122-1125. PMCID: PMC31271789

B. Positions and Honors

Employment

2006-2009	Resident, Pediatrics, Massachusetts General Hospital, Harvard Medical School, Boston, MA
2009-2012	Fellow, Pediatric Hematology/Oncology, Boston Children's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
2012-2016	Instructor in Pediatrics, Boston Children's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
2016-	Assistant Professor, Department of Pediatrics, Division of Stem Cell Transplantation and Regenerative Medicine, Stanford School of Medicine, Stanford, CA

Professional Societies:

2002-	Member, German Medical Association
2003-	Member, German Pediatric Society
2009-	Fellow, American Academy of Pediatrics (FAAP)
2009-	Associate Member, American Society of Hematology (ASH)
2009-	Member, Children's Oncology Group (COG)
2009-	Member, American Society of Pediatric Hematology Oncology (ASPHO)
2011-	Member, American Society of Clinical Oncology (ASCO)
2012-	Member, American Society of Hematology (ASH)
2013-	Member, International Society of Stem Cell Research (ISSCR)
2013-	Primary Immunodeficiency Treatment Consortium (PIDTC), site PI for Stanford since 2018
2014-	Member, European Society of Gene and Cell Therapy (ESGCT)
2017-	Member, 22q11.2 Society

Awards and Honors:

1996-2002	Scholar of the German National Scholarship Foundation Cusanuswerk
2000-2001	Travel Research Stipend awarded by the German National Scholarship Foundation
2002	Graduation with highest honors, Technical University Munich Medical School, Munich Germany
2004	Dissertation summa cum laude, Technical University Munich Medical School, Munich, Germany
2007	Excellence-in-Teaching-Award as a resident, Massachusetts General Hospital for Children, Harvard Medical School
2008	Excellence-in-Teaching-Award as a resident, Massachusetts General Hospital for Children, Harvard Medical School
2009	Dan Heller Award for exceptional teaching throughout residency, Harvard Medical School
2012-2013	Amy-Potter Research Fellowship, Boston Children's Hospital, Harvard Medical School
2012-2014	Charles King Trust Research Fellowship Award, Charles King Foundation
2013-2014	Primary Immunodeficiency Treatment Consortium Research Award
2013-2014	Amy-Potter Research Fellowship, Boston Children's Hospital, Harvard Medical School
2016-2021	NIH NIAID, K08 Physician Scientist Career Development Award
2017	Baxter Faculty Scholar
2018-2020	California Institute of Regenerative Medicine Discovery Award

2019- endowed MCHRI Hamilton-Uytengsu Scholar Award

C. Contributions to Science

My most significant contributions to science in my career thus far are described below:

1. Discovered distinct DNA invertases dynamically control the surface architecture of a human commensal microorganism. My early publications, which stem from my dissertation as well as my time as postdoctoral research fellow in the group of Laurie E. Comstock, Ph.D., Professor at the Channing Laboratory of Brigham and Women's Hospital, Harvard Medical School, examined the intricate surface interactions between the human host and the commensal microbiota from the bacteria's point of view. In Dr. Comstock's laboratory, I participated in research showing that *Bacteroides fragilis,* a representative of the human intestinal microbiota with particularly high virulence in extra-intestinal sites, synthesizes 13 distinct capsular polysaccharides (CPS) that are expressed in a tightly regulated manner by inversion of their promoter regions. To identify the factors that promote inversion of the CPS promotor regions, we performed a hypothesis-driven screen for candidate genes. During my dissertation, I developed a system to assess the differential role of individual candidate genes in *B. fragilis'* dynamic polysaccharide expression and discovered that a single serine site-specific recombinase (SSR), later designated MPI (multi promotor invertase) globally regulates the expression of all 13 capsular polysaccharides by positioning the promoter region in the ON- or OFF-orientation. I generated a mutant strain, in which all CPSs are expressed simultaneously by locking their promoter regions in the ON-position. This strain produces a zwitter-ionic polysaccharide that was patented for potential use as a vaccine in inflammatory bowel disease. My work in Dr. Comstock's lab led to the authorship/co-authorship of 4 manuscripts published in Nature (cover story, 3rd author), PNAS (2nd author on two different publications) and Molecular Microbiology (first author). In *"Tyrosine site-specific recombinases mediate DNA inversions affecting the expression of outer surface proteins of Bacteroides fragilis"* (Weinacht *et al.*, Mol Micro, 2004), I described a different kindred of DNA invertases, designated Tyrosine site-specific recombinases (TSR), that regulates the expression of outer surface proteins in *B. fragilis*. Unlike MPI, which acts globally, TSRs act on the operon located immediately downstream. TSR deletion mutants with outer surface protein promoter regions locked in the ON-position display an autoaggreative/biofilm-forming phenotype, demonstrating that primary virulence factors in *B. fragilis* are regulated by means of invertible promoter elements and that DNA inversion represents an evolutionary conserved mechanism to modulate surface antigenicity in *B. fragilis*.

(1) Krinos CM, Coyne MJ, **Weinacht KG**, Tzianabos AO, Kasper DL, Comstock LE. Extensive surface diversity of a commensal microorganism by multiple DNA inversions. Nature. 2001 Nov 29;414(6863):555-8. (***Cover article***)

(2) Coyne MJ, **Weinacht KG**, Krinos CM, Comstock LE. MPI recombinase globally modulates the surface architecture of a human commensal bacterium. Proc Natl Acad Sci U S A. 2003 Sep 2;100(18):10446-51. PMCID: PMC193581

(3) **Weinacht KG**, Roche H, Krinos CM, Coyne MJ, Parkhill J, Comstock LE. Tyrosine site-specific recombinases mediate DNA inversions affecting the expression of outer surface proteins of Bacteroides fragilis. Mol Microbiol. 2004 Sep;53(5):1319-30.

(4) Chatzidaki-Livanis M, **Weinacht KG**, Comstock LE. Trans locus inhibitors limit concomitant polysaccharide synthesis in the human gut symbiont Bacteroides fragilis. Proc Natl Acad Sci U S A. 2010 Jun 29;107(26):11976-80. PMCID: PMC2900635

2. Determined Adenylate Kinase 2 (AK2) protects from oxidative stress during hematopoietic stem and progenitor cell development and hematopoietic differentiation. While completing my clinical training as pediatric hematology oncology fellow at Boston Children's Hospital/Dana Farber Cancer Institute, Harvard Medical School, I conducted my fellowship research in Dr. Luigi D. Notarangelo's research group in the division of immunology. Here, I used human induced pluripotent stem cells (hiPSCs) to study the molecular underpinnings of primary immunodeficiencies. At that time, I established the reprogramming technology for our laboratory and created a repository of iPSCs from patients with a wide range of primary immunodeficiency diseases. I have generated iPSCs from over 15 fibroblast lines with genetic defects underlying congenital immunodeficiency and have shared many of these lines with other investigators to achieve their research goals (Chen *et al.,* JACI, 2013; La Marca *et al*., JACI, 2014). Reticular Dysgenesis (RD) became the focus of my study; accordingly, I have developed a disease model for RD in iPSCs that recapitulated the maturation arrest of the myeloid lineage *in vitro*. Transcriptome analysis of RD iPSC-derived myeloid cells pointed to

derangements in oxidative phosphorylation; however, electron microscopy revealed no abnormalities in number, size or cristae morphology of AK2-mutant mitochondria, suggesting that AK2 deficiency manifests through functional/metabolic abnormalities, rather than by impacting the mitochondrial structure. We have analyzed the adenine nucleotide profile in AK2-deficient cells by tandem mass spectrometry, which demonstrated a severe decrease in ADP:ATP ratio compared to controls. Based on these findings, I hypothesized that AK2 deficiency impairs ATP-synthase activity by limiting its substrate ADP. Studies in isolated mitochondria have shown that ADP exhaustion not only impairs ATP synthase activity but leads to an increase in mitochondrial proton gradient, membrane potential, and production of reactive oxygen species (Liesa *et al.*, Cell Metabol, 2013). To examine if there is indeed a link between arrested hematopoiesis in RD and oxidative stress, I tested in parallel the effect of the antioxidant agent glutathione along with other compounds known to promote neutrophil differentiation in other conditions, i.e. G-CSF and all-trans-retinoic acid (ATRA). Antioxidant treatment with glutathione, but not with other compounds tested, led to a significant improvement of myeloid maturation in RD-iPSCs. Our collaborator Dr. F. Candotti has corroborated the effectiveness of antioxidants in rescuing hematopoietic defects in a zebrafish model of RD. These results in iPSC and zebrafish models of RD have been published jointly (Rissone/Weinacht *et al.*, J Exp Med, 2015).

(1) **Weinacht KG**, Brauer PM, Felgentreff K, Devine A, Gennery AR, Giliani S, Al-Herz W, Schambach A, Zúñiga-Pflücker JC, Notarangelo LD. Curr Opin Immunol. 2012 Oct;24(5):617-24. The role of induced pluripotent stem cells in research and therapy of primary immunodeficiencies. PMCID: PMC3478496

(2) Felgentreff K, Du L, **Weinacht KG**, Dobbs K, Bartish M, Giliani S, Schlaeger T, DeVine A, Schambach A, Woodbine LJ, Davies G, Baxi SN, van der Burg M, Bleesing J, Gennery A, Manis J, Pan-Hammarström Q, Notarangelo LD. Differential role of nonhomologous end joining factors in the generation, DNA damage response, and myeloid differentiation of human induced pluripotent stem cells. Proc Natl Acad Sci U S A. 2014 Jun 17;111(24):8889-94. PMCID: PMC4066476

(3) Rissone A*****, **Weinacht KG*,** la Marca G, Bishop K, Giocaliere E, Jagadeesh J, Felgentreff K, Dobbs K, Al-Herz W, Jones M, Chandrasekharappa S, Kirby M, Wincovitch S, Simon KL, Itan Y, DeVine A, Schlaeger T, Schambach A, Sood R, Notarangelo LD, Candotti F. Reticular dysgenesis-associated AK2 protects hematopoietic stem and progenitor cell development from oxidative stress. J Exp Med. 2015 July;212(8):1185-202. PMCID: PMC4516804 ***(*Co-first authors, contributed equally)***

3. Found Ruxolitinib reverses Dysregulated T Helper Cell Responses and controls Autoimmunity caused by a Novel *STAT1* Gain of Function Mutation. This work was inspired by a patient of mine in need of novel therapies beyond the standard of care. Gain-of-function (GOF) mutations in the human Signal Transducer and Activator of Transcription 1 (STAT1) manifest in immunodeficiency and autoimmunity with impaired T helper (T_H) 17 cell differentiation and exaggerated responsiveness to interferon. Allogeneic hematopoietic stem cell transplantation (HSCT) has been attempted in severely affected patients but outcomes have been poor. Due to lack of a suitable HSCT donor, we sought to define the effect of increased STAT1 activity on T helper cell polarization and to investigate the role of ruxolitinib in treating autoimmunity and immunodeficiency secondary to *STAT1* GOF. The child I report on had a novel mutation in the linker domain of STAT1 and suffered from life-threatening autoimmune cytopenias and chronic mucocutaneous candidiasis. Naïve patient lymphocytes displayed increased T_H1 and T follicular helper (T_{FH}) cell as well as suppressed T_H17 cell responses. Treatment with the Janus kinase (JAK) 1/2 inhibitor ruxolitinib reduced hyper-responsiveness to interferon, normalized T_H1 and T_{FH} cell responses, improved T_H17 differentiation, cured mucocutaneous candidiasis and maintained remission of immune mediated cytopenias. We found autoimmunity and infection due to STAT1 GOF mutations is caused by dysregulated T helper cell responses. JAK inhibitor therapy represents an effective targeted treatment for long-term disease control in severely affected patients for whom hematopoietic stem cell transplantation is not available.

(1) **Weinacht KG**, Charbonnier LM, Alroqi F, Plant A, Qiao Q, Wu H, Ma C, Torgerson TR, Rosenzweig SD, Fleisher TA, Notarangelo LD, Hanson IC, Forbes LR, Chatila TA. Ruxolitinib reverses dysregulated T helper cell responses and controls autoimmunity caused by a novel signal transducer and activator of transcription 1 (STAT1) gain-of-function mutation. J Allergy Clin Immunol. 2017 May;139(5):1629-1640. PMCID: PMC5482293

(2) Forbes LR, Vogel TP, Cooper MA, Castro-Wagner J, Schussler E, **Weinacht KG**, Plant AS, Su HC, Allenspach EJ, Slatter M, Abinun M, Cunningham-Rundles C, Olbrich P, Guillerman RP, Freeman AF, Holland SM, Szabolcs P, Gennery A, Torgerson TR, Milner JD, Leiding JW. Jakinibs for the treatment of

immune dysregulation in patients with gain-of-function signal transducer and activator of transcription 1 (STAT1) or STAT3 mutations. J Allergy Clin Immunol. 2018 Nov;142(5):1665-1669. PMCID: PMC6322659

4. Discovered Gain of Function Mutations in CDC42 activate the Inflammasome.
This work was inspired by 4 patients who presented with novel specific mutations in cell division control protein 42 homolog *(CDC42)*. *CDC42* encodes a small Rho family GTPase that regulates cell polarity, migration, actin polarization and cytoskeletal architecture. We found that activating mutations in CDC42 activate the inflammasome, leading to high IL-1b and IL-18 levels which clinically cause a debilitating autoinflammatory syndrome with failure to thrive, hepatomegaly, anemia, thrombocytopenia, severe joint pain and soft tissue swelling. We established that therapy with the IL1-receptor antagonist anakinra reversed the clinical symptoms of autoinflammation and has thus far afforded the affected patients a seemingly normal life.

(3) Gernez Y, de Jesus AA, Alsaleem H, Macaubas C, Roy A, Lovell D, Jagadeesh KA, Alehashemi S, Erdman L, Grimley M, Talarico S, Bacchetta R, Lewis DB, Canna SW, Mellins ED, Goldbach-Mansky R, **Weinacht KG**. Severe autoinflammation in four patients with C-terminal variants in CDC42 successfully treated with IL-1beta inhibition. J Allergy Clin Immunol. 2019 Oct;144(4):1122-1125. PMCID: PMC31271789

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/katja.weinacht.1/bibliography/47886608/public/?sort=date&direction=ascending

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

Grant Number: 7K08AI123571-02 ***Weinacht (PI)*** 04/14/2016 - 03/31/2021
The Role of Oxidative Stress in the Pathogenesis of Reticular Dysgenesis and The Therapeutic Potential of Antioxidants
The major goal of the award is to understand how the AK2-defect affects mitochondrial function.

Center for Definitive and Curative Therapies ***Weinacht (PI)*** 10/01/2016 - 08/31/2021
Stanford School of Medicine
Analysis of The Thymic Microenvironment in Patients with DiGeorge Syndrome
The major goal of this grant is to understand how defects in 22q11 or TBX1 impair the thymic microenvironment in patients with DiGeorge syndrome.

California Institute of Regenerative Medicine (CIRM) ***Sebastiano (PI)*** 11/01/2018 - 10/31/2020
Weinacht (PI, year 2)
Regenerative Thymic Tissues as Curative Cell Therapy for Patients with 22q11 Deletion Syndrome
The major goal of this grant is to derive fully functional thymic epithelial progenitor cells from pluripotent stem cells to generate a cell-based therapy for patients with congenital or acquired thymic defects.

Uytengsu-Hamilton Faculty Scholar Award ***Weinacht (PI)*** 07/09/2019 - Endowed
This is an endowed research scholarship award through the Stanford Maternal & Child Health Research Institute that supports basic research in the Weinacht laboratory.

Stanford ITI - Bill and Melinda Gates Foundation ***Weinacht (PI)*** 05/01/2020 05/312021
Differences between Adult and Pediatric T cell and Macrophage Responses in COVID-19
The major goal of this grant is to understand differential T cell and macrophage responses in patients with COVID-19 using adult and pediatric patient samples

Completed Research Support

Baxter Foundation ***Weinacht (PI)*** 04/01/2017 - 03/31/2018
iPSC-derived Thymic Epithelial Progenitor Cells as Cell-based Therapy to restore Thymic Function in Hematopoietic Stem Cell Transplant Recipients
The major goal of this grant is to derive fully functional thymic epithelial progenitor cells from iPSCs.