BIOGRAPHICAL SKETCH

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NAME: Zakrzewski, Johannes L.

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

POSITION TITLE: Associate Member, Associate Professor

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
Friedrich-Alexander University	MD	04/2000	Medicine
University Hospital Hamburg-Eppendorf	Resident	05/2000	Pediatrics
Bone Marrow Transplantation Center Idar-Oberstein	Resident	08/2001	Pediatric Bone Marrow Transplantation
University Hospital of Essen	Resident	03/2004	Pediatrics
Memorial Sloan Kettering Cancer Center	Postdoctoral Research Fellow	06/2008	Immunology
SUNY Downstate Medical Center	Resident	06/2010	Pediatrics
Memorial Sloan Kettering Cancer Center	Clinical Fellow	06/30/2013	Pediatric Hematology/Oncology

A. Personal Statement

I am a clinician-scientist with extensive expertise in immunotherapy of hematologic malignancies, hematopoietic stem cell transplantation and transplantation immunology. I am an Associate Member of the HMH Center for Discovery and Innovation, directing a laboratory with focus on thymic CAR T cell development and the development of immunotherapies for the treatment of hematologic malignancies. I invented off-the-shelf tumor immunotherapy with allogeneic T cell precursors, developed intrathymic injection-based approaches for tumor immunosurveillance, and established inhibition of NF-kB DNA binding and cancer cell-selective induction of oxidative stress as safe and effective strategies for targeted cancer therapy. I am currently collaborating with several companies and academic centers on projects developing immune cell-based, small molecule-based, and nanomaterial-based approaches for targeted therapy of leukemias, lymphomas and multiple myeloma. My laboratory is routinely working with immunocompetent (syngeneic) mouse models of mouse blood cancers as well as cell line-based and patient-derived xenograft models of human blood cancers, conducting preclinical and translational studies laying the foundation for future clinical trials.

Ongoing projects that I would like to highlight include:
NCI 1R37CA250661
Zakrzewski, Johannes (PI)
02/01/2022 – 01/31/2027
Harnessing the thymus for long-term tumor control with hematopoietic stem cell-derived naive CAR T cells

Sponsored Research Agreement with NexImmune Inc.
Zakrzewski, Johannes (PI)
07/01/2022 – 06/30/2024
Title: Combination of bispecific antibody therapy with NexImmune's Artificial Immune Modulation (AIM) platform in acute myeloid leukemia

New Jersey Health Foundation Grant
Zakrzewski, Johannes (PI)
02/15/2023-02/14/2024
Title: Next generation precision medicine of hematologic malignancies with a nano-immuno-molecular therapeutic platform

B. Positions, Scientific Appointments, and Honors

2019 – Attending Physician, Pediatric Stem Cell Transplant, Hackensack University Medical Center
2019 – Associate Professor, Hackensack Meridian School of Medicine
2018 – Associate Professor, Georgetown University School of Medicine
2018 – Associate Member, Hackensack Meridian Center for Discovery and Innovation
2018 – Assistant Clinical Professor in Pediatrics, Weill Cornell Medical Center (courtesy appointment)
2014 – 2017 Instructor in Pediatrics, Weill Cornell Medical Center
2013 – 2017 Assistant Attending Pediatrician, Memorial Sloan Kettering Cancer Center
2007 – 2009 Adjunct Professor, NYU Polytechnic School of Engineering

Other Experience and Professional Memberships

2010 –	Member, COG
2012 –	Member, ASTCT
2013 –	Member, ASH
2014 –	Scientific Advisory Board, ImmuneTarget Inc.
2020 –	Ad Hoc member, NIH/CSR – cancer immunopathology and immunotherapy study section
2020 –	Member, NCI – subcommittee J – career development review committee

Honors

2005	Fellowship Award, German Research Foundation
2006	Fellowship Award, Lymphoma Research Foundation
2008	David G. Nathan Award in Hematology/Oncology, Society for Pediatric Research

Clinical Licensures and Board Certifications

New York Medical License	Inactive
New Jersey Medical License	Active

Board Certification: American Board of Pediatrics
Sub-Specialty Board: Pediatric Hematology/Oncology

C. Contributions to Science

1. Stem cell or T cell-based therapies have been used for decades to confer immunity and anti-tumor activity to T cell-deficient patients. However, these cell therapies are associated with a variety of limitations, in particular a limited availability of suitable cells: donor and recipient have to be either the same person, or donor and recipient have to be at least partially HLA matched. As a research fellow from 2004 to 2008 I pioneered a cell culture-based immunotherapy method for the treatment of T cell deficiency in cancer patients and HSCT recipients. This approach is based on adoptive transfer of in vitro generated T cell precursors using a co-culture system with a stromal cell line expressing the Notch 1 ligand DL1 to generate large numbers of T lineage committed precursor cells ex vivo. These T cell precursors can engraft in the thymus upon adoptive transfer into irradiated recipients and give rise to a single wave of T cell development resulting in enhanced T cell reconstitution and graft-versus-tumor activity in the absence of graft-versus-host disease (GVHD). Moreover, I demonstrated that precursor T cells that were genetically targeted to the CD19 antigen could mature in fully mismatched recipients and yield T cells with potent anti-lymphoma activity without causing GVHD in tumor-bearing mice. The cells have been shown to mature into functional T cells that are host MHC restricted and host tolerant, likely due to intrathymic selection and education, negating the need for HLA matching. This procedure is not only laborsaving and cost-effective (since virtually unlimited quantities of precursor cells can be generated and stored for “off-the-shelf” use), but it facilitates the application of gene transfer technology to generate antigen- specific or otherwise enhanced designer cells.

a) **Zakrzewski JL** et al. Adoptive transfer of T-cell precursors enhances T-cell reconstitution after allogeneic hematopoietic stem cell transplantation. Nat Med 2006; 12: 1039-1047. PMID: 16936725.
b) **Zakrzewski JL** et al. Tumor immunotherapy across MHC barriers using allogeneic T cell precursors. Nature Biotechnol 2008; 26: 453-461. PMCID: PMC2731996.
c) **Zakrzewski JL**, van den Brink MRM, Sadelain M. Methods for off-the-shelf tumor immunotherapy using allogeneic T-cell precursors. United States patent application 20110052554.

2. Injection of lymphoid organs has the potential to open up new exciting avenues for cell, drug, and gene therapy. Our current main focus is on the development of an approach for tumor immunosurveillance with thymus-derived naïve CAR T cells. In addition to manipulation of the thymic microenvironment, this research program explores bioengineering and nanotechnology methodology to develop strategies promoting thymus-independent T cell generation. These methods utilize molecularly tailored biomaterials, micro and nanofabrication techniques to create an artificial implantable hematopoietic niche providing the microarchitecture and signaling requirements for T cell development from HSCs.

   a) Tuckett AZ, Thornton RH, Shono Y, Smith OM, Levy E, Kreines F, van den Brink RM, **Zakrzewski JL**. Image-guided intrathymic injection of multipotent stem cells supports life-long T cell immunity and facilitates targeted immunotherapy. Blood 2014; 123: 2797-2805. PMID: 24652996.
   b) **Zakrzewski JL**, van den Brink MRM, Hubbell JA. Overcoming immunological barriers in regenerative medicine. Nat Biotechnol 2014; 32: 786-794. PMCID: PMC4409427.
   c) Tuckett, A.Z., Thornton, R.H., O'Reilly, R.J., van den Brink, M.R.M., **Zakrzewski, JL.** Intrathymic injection of hematopoietic progenitor cells establishes functional T cell development in a mouse model of severe combined immunodeficiency. Journal of Hematology & Oncology 2017; 10: 109. PMID: 28511686.

   d) McGuire M, Tuckett AZ, Faith M, **Zakrzewski JL**. A Minimally Invasive, Accurate and Efficient Technique for Intrathymic Injection in Mice. J Vis Exp 2022; 186. PMID: 36094273.

3. Separation of GVHD from anti-tumor activity is one of the most important challenges in the field of allogeneic HSCT, and even though a number of experimental approaches have been developed, none of them has been established in mainstream clinical practice. A potential molecular target for a strategy to separate GVHD from graft-versus-tumor (GVT) activity is the NF-kB family member c-Rel, a transcription factor that upon antigen receptor triggering regulates lymphocyte survival and proliferation and is known to play dominant roles in inflammation, autoimmune disease, as well as oncogenesis. Using high-throughput screening our team identified a small molecule that acts as a highly specific direct inhibitor of c-Rel activity. We discovered that inhibition of c-Rel diminishes alloactivation while preserving antigen-specific T-cell receptor activation, revealing redundancy of c-Rel in T-cell mediated anti-tumor activity of both mouse and human T cells. This study provides a highly innovative immunomodulatory approach with broad therapeutic implications including tolerance induction after HSCT and solid organ transplantation, as well as anti-tumor therapies.

   Shono Y, Tuckett AZ, Ouk S, Liou HS, Altan-Bonnet G, Tsai JJ, Oyler JE, Smith OM, West ML, Singer NV, Doubrovina E, Pankov D, Unhad CV, Murphy GF, Lezcano C, Liu C, O'Reilly RJ, van den Brink MRM, **Zakrzewski JL**. A small molecule c-Rel inhibitor reduces alloactivation of T cells without compromising anti-tumor activity. Cancer Discovery 2014; 4: 578-591. PMID: 24550032.

4. Over the past decade I have worked extensively on the potential of NF-kB and oxidative stress response pathways as targets for cancer therapy. NF-kB is a promising therapeutic target in its own right, but our recent work revealed that modulation of the redox homeostasis in cancer cells, including inhibition of NF-kB and Nrf2 dependent antioxidant responses, is safe and can be exploited for targeted cancer therapy. We anticipate that our work will produce drug candidates for clinical trials in the near future.
   a) Shono Y, Tuckett AZ, Liou HC, Doubrovina E, Derenzini E, Ouk S, Tsai JJ, Smith OM, Levy ER, Kreines F, Ziegler CGK, Scallion MI, Doubrovin M, Heller G, Younes A, O'Reilly RJ, van den Brink MRM, **Zakrzewski JL**. Characterization of a c-Rel inhibitor that mediates anticancer properties in hematologic malignancies by blocking NF-kappaB-controlled oxidative stress responses. Cancer Research 2016, 76: 377-389. PMID: 26744524.
   b) Liu HY, Tuckett AZ, Fennell M, Garippa R, **Zakrzewski JL**. Repurposing of the CDK inhibitor PHA-767491 as a NRF2 inhibitor drug candidate for cancer therapy via redox modulation. Invest New Drugs 2018; 36: 590-600. PIMD: 29297149.

c) Bariana M, Cassella E, Rateshwar J, Ouk S, Liou HC, Heller C, Colorado I, Feinman R, Makhdoom A, Siegel DS, Heller G, Tuckett A, Mondello P, **Zakrzewski JL**. Inhibition of NF-κB DNA binding suppresses myeloma growth via intracellular redox and tumor microenvironment modulation. Molecular Cancer Therapeutics 2022; 21(12):1798-1809. PMID: 36190955.
d) Manpreet Bariana, Beilu Zhang, Jingyu Sun, Weiwei Wang, Jinping Wang, Elena Cassella, Faith Myint, Shaina A. Anuncio, Samedy Ouk, Hsiou-Chi Liou, Ming Tan, Hongjun Wang, **Zakrzewski JL.** Targeted Lymphoma Therapy Using a Gold Nanoframework-based Drug Delivery System. ACS Applied Materials & Interfaces 2023; 15(5):6312-6325. PMID: 36701696.

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/johannes%20l..zakrzewski.1/bibliography/public/