BIOGRAPHICAL SKETCH

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NAME: Kaye, Jonathan G.

eRA COMMONS USER NAME (credential, e.g., agency login): jkaye1

POSITION TITLE: Vice Chair and Professor of Biomedical Sciences

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
California Institute of Technology, Pasadena, CA	B.S.	06/1976	Biology
Yale University, New Haven, CT	Ph.D.	12/1985	Biology (Immunology)
University of California, San Diego, La Jolla, CA	Postdoctoral	07/1990	Immunology

A. Personal Statement

My laboratory has a long-standing interest and expertise in T cell biology, with particular focus on the molecular regulation of cell fate decisions in the immune system. A major focus of our work is on the TOX nuclear protein family, first characterized in our laboratory. These proteins are DNA-binding factors of the HMG-box superfamily and regulators of gene expression, likely by modulation of chromatin. We have used varied approaches, from molecular to cellular, to determine the role of the founding member of this family, TOX, in T cell, and more recently, innate lymphoid cell development. In collaborative work, we have recently published a role for TOX in CD8 T cell effector autoimmunity, and another ongoing collaborative project involves a role for TOX in tumor mediated CD8 T cell exhaustion. In addition, we have solved the crystal structure of the TOX DNA-binding domain and are performing a number of structure-function analyses, both in normal cells and tumor cells. We have also demonstrated high-level expression of another family member, TOX3, in a subset of breast cancers and showed that TOX3 upregulates genes in breast cancer cells involved in cell cycle, DNA repair and cell migration, as well as estrogen-receptor target gene activation in the absence of estrogen and in the presence of tamoxifen. Most recently we are characterizing TOX3 knockout mice, where we find a severe block in brain development. Together, these data, and that from others, makes it clear that the TOX family of proteins plays very significant roles in a number of biological and disease contexts.

A second significant line of inquiry is effector cell development among type 2 innate lymphoid (ILC2) cells. This work has led to a recent publication in *Nature Communications*, for the first time describing $ILC2_{10}$ effector cells, a molecularly distinct subset of ILC2 cells which produce IL-10 and develop by an alternative activation pathway. Ongoing work seeks to identify human $ILC2_{10}$ cells

B. Positions and Honors

Positions and Employment

1985-1987 Cancer Research Institute Postdoctoral Fellow, University of California, San Diego, La Jolla, CA
1988-1990 American Cancer Society, California Division, Senior Fellow, University of California, San Diego, La Jolla, CA
1990-1996 Assistant Professor, Department of Immunology, The Scripps Research Institute, La Jolla, CA
1992-2009 Faculty Member, Graduate Programs in Chemical and Biological Sciences, The Scripps Research

Institute, La Jolla, CA
1996-2009 Associate Professor, Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA
2009-present Professor, Department of Biomedical Sciences and Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA
2009-present Professor in Residence, Department of Medicine, The David Geffen School of Medicine, University of California, Los Angeles, CA
2010-present Scientific Director, Cedars-Sinai Research Cores
2010-present Director, Research Division of Immunology, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA
2011-present Vice-Chair, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA
2013-June 2016 Program Leader, Center for Translational Technologies, UCLA Clinical and Translational Science Institute
July 2016-present Co-Leader of the Pilot program, UCLA Clinical and Translational Science Institute

Other Experience and Professional Memberships

1991-present Member, American Association of Immunologists
1991-1992 Ad hoc member, American Cancer Society, Scientific Advisory Committee on Developmental Biology
1993-94,1996-97 NIH, Immunobiology Study Section, Ad hoc member
1998-2001 NIH, Immunobiology Study Section, Member
1993-1999 Associate Editor, Journal of Immunology
2002-2003 NIH, Allergy and Immunology Study Section, Ad hoc member
2002-2005 NIH, Special Emphasis Panels, Member
2005 Site Visit Team Member, National Cancer Institute, Laboratory of Immune Cell Biology
2009 Member, NIH, Special Emphasis Panel, Primary Immunodeficiency Diseases
2009-2013 Section Editor, Journal of Immunology
2010-2017 NIH, Chair, Special Emphasis Panel, Primary Immunodeficiency Diseases
2017 NIH, Chair, Member Conflict Panel, Immune Mechanisms
2018 NIH, Chair, Special Emphasis Panel, NIAID Investigator Initiated Program Project Applications

Honors

1976 B.S. with Honors, California Institute of Technology
1985 John Nicholas Spangler Prize for Outstanding Doctoral Candidate in Experimental Zoology, Yale University
1985 Awarded Helen Hay Whitney Fellowship (not accepted)
1990 American Cancer Society Junior Faculty Award

C. Contributions to Science

1. As a graduate student with Dr. Charles Janeway, I was among the first to identify the T cell antigen receptor at the level of protein, using an agonist antibody. This was a highly contentious and speculative field at the time and understanding the molecular basis of T cell specificity of critical importance to immunology. Our work, first published in 1983, demonstrated that that an antibody directed against a clone-specific epitope on a novel cell surface disulfide-linked heterodimeric protein on a helper T cell line was a potent activator of the cells, strongly suggesting that this was the long-sought antigen receptor. Moreover, I subsequently demonstrated that this protein was required both for self-MHC plus foreign antigen peptide recognition and allogeneic MHC recognition, another oft-debated topic. My biochemistry was also essential in clarifying an erroneous early identification of the TCR α-chain by others, which instead turned out instead to be a component of the $\gamma\delta$TCR. I also demonstrated that the T cell clone used in this work (still available at ATCC) was highly sensitive to IL-1, and this became one of the earliest examples of a T_H2 T cell line.

a. **Kaye, J.**, Porcelli, S., Tite, J., Jones, B., Janeway, C.A. Jr. (1983) Both a monoclonal antibody and antisera specific for determinants unique to individual cloned helper T cell lines can substitute for antigen and antigen-presenting cells in the activation of T cells. *Journal of Experimental Medicine*, 158(3),836-856. PMCID: PMC2187090
b. **Kaye, J.**, Janeway, C.A. Jr. The Fab fragment of a directly activating monoclonal antibody that precipitates a disulfide-linked heterodimer from a helper T cell clone blocks activation by either allogeneic Ia or antigen and self-Ia. (1984) *Journal of Experimental Medicine* 159(5),1397-1412. PMCID: PMC218729
c. **Kaye, J.**, Gillis, S., Mizel, S.B., Shevach, E.M., Malek, T.R., Dinarello, C.A., Lachman, L.B., Janeway, C.A. Jr. Growth of a cloned helper T cell line induced by a monoclonal antibody specific for the antigen receptor: interleukin 1 is required for the expression of receptors for interleukin 2. (1984) *Journal of Immunology*, 133(3),1339-1345. PubMed PMID: 6235287
d. **Kaye, J.**, Janeway, C.A. Jr. The alpha- and beta-subunits of a murine T cell antigen/Ia receptor have a molecular weight of 31,000 in the absence of N-linked glycosylation. (1984) *Journal of Immunology*, 133(5),2291-2293. PubMed PMID: 6237148

2. My postdoctoral work with Dr. Stephen Hedrick followed directly from my earlier work, but in this case using, at the time, cutting-edge molecular approaches. Here too I made fundamental discoveries, including definitively mapping by gene transfer that the heterodimeric TCR encoded multiple specificities; for foreign antigen, alloantigen, and 'superantigen'. In addition, I created the AND-TCR transgenic strain of mice to demonstrate that TCR specificity regulated lineage commitment in the thymus, as well as investigated aspects of thymic negative selection. This animal model remains highly used today.
    a. **Kaye, J.**, Hedrick, S.M. Analysis of specificity for antigen, Mls, and allogeneic MHC by transfer of T-cell receptor alpha- and beta-chain genes. (1988) *Nature*, 336(6199),580-583. PubMed PMID: 2849059
    b. **Kaye, J.**, Hsu, M.L., Sauron, M.E., Jameson, S.C., Gascoigne, N.R., Hedrick, S.M. Selective development of CD4+ T cells in transgenic mice expressing a class II MHC-restricted antigen receptor. (1989) *Nature*, 341(6244):746-749. PubMed PMID: 2571940
    c. **Kaye, J.**, Vasquez, N.J., Hedrick, S.M. Involvement of the same region of the T cell antigen receptor in thymic selection and foreign peptide recognition. (1992) *Journal of Immunology*, 148(11),3342-3353. PubMed PMID: 1316916
3. In the role as an independent investigator, my laboratory continued to contribute to understanding the mechanism of T cell development in the thymus. We were able to create an *in vitro* model that could mimic important aspects of thymic positive selection, reducing a complex *in vivo* process to one of receptor-mediated cell differentiation. Moreover, we were able to show that thymic epithelial cells were unique in their ability to drive this process, while other antigen presenting cells required addition of cognate foreign antigen. We also contributed to an understanding of mitogen-activated protein kinase signaling during T cell development and identified one of the first downstream gene targets, *Egr1*, of this signaling pathway.
    a. **Kaye, J.**, Ellenberger, D.L. Differentiation of an immature T cell line: a model of thymic positive selection. (1992) *Cell*, 71(3),423-435. PubMed PMID: 1423605
    b. Poirier, G., Lo, D., Reilly, C.R., **Kaye, J**. Discrimination between thymic epithelial cells and peripheral antigen-presenting cells in the induction of immature T cell differentiation. (1994) *Immunity*, 1(5),385-391. PubMed PMID: 7882169
    c. Shao, H., Kono, D.H., Chen, L.Y., Rubin, E.M., **Kaye, J.** Induction of the early growth response (Egr) family of transcription factors during thymic selection. (1997) *Journal of Experimental Medicine*, 185(4),731-744. PMCID: PMC2196139
    d. Shao, H., Wilkinson, B., Lee, B., Han, P.C., **Kaye, J.** Slow accumulation of active mitogen-activated protein kinase during thymocyte differentiation regulates the temporal pattern of transcription factor gene expression. (1999) *Journal of Immunology* 163(2):603-610. PubMed PMID: 10395647
4. We, coincident with another group at the time, identified a novel coinhibitory protein expressed by T cells, subsequently named B and T lymphocyte attenuator (BTLA). Our unique contributions to the field were our functional studies, including the demonstration that this protein negatively regulated CD8 T cell memory responses.
    a. Krieg, C., Han, P., Stone, R., Goularte, O.D., **Kaye, J.** Functional analysis of B and T lymphocyte attenuator engagement on CD4+ and CD8+ T cells. (2005) *Journal of Immunology* 175(10),6420-6427. PubMed PMID: 16272294

   b. Krieg, C., Boyman, O., Fu, Y.X., **Kaye, J.** B and T lymphocyte attenuator regulates CD8+ T cell-intrinsic homeostasis and memory cell generation. (2007) *Nature Immunology*, 8(2),162-171. PubMed PMID: 17206146

5. Our most recent work has focused on the TOX-family of transcriptional regulators. We have performed pioneering work in this area. We have shown that the founding member of this family, TOX, is required for development of many T cell lineages in the thymus (conventional $CD4^+$ T, Treg, NKT), regulating cell differentiation at an early stage of positive selection. Most recently, we have demonstrated a key role for TOX in innate lymphoid cell lineage specification in the bone marrow. In this work, we performed whole transcriptome analysis of small numbers of TOX-deficient precursors, leading to new insights and identification of new 'players' in this cell fate determination process. We have also recently published the identification of a novel effector cell subset of ILC2 cells. In addition, it is worth noting that the importance of TOX goes beyond establishment and function of a working immune system, as TOX is also implicated in CD8 T cell exhaustion, CD8 T cell autoimmunity (in a collaborative project recently published in *Immunity*), cutaneous T cell lymphoma, T cell acute lymphocytic leukemia, and neurogenesis. We have also published on a role for family member TOX3 in the progression of breast cancer (BMC Cancer, 'Highly Accessed' publication). This protein may be a new prognostic biomarker for a subset of estrogen receptor positive disease with poor outcome.
   a. Aliahmad, P., **Kaye, J.** Development of all CD4 T lineages requires nuclear factor TOX. (2008) *Journal of Experimental Medicine*, 205(1),245-256. PubMed Central PMCID: PMC2234360
   b. Aliahmad, P., de la Torre, B., **Kaye, J.** Shared dependence on the DNA-binding factor TOX for the development of lymphoid tissue-inducer cell and NK cell lineages. (2010) *Nature Immunology* 11(10),945-952. PubMed Central PMCID: PMC2943551.
   c. Seehus, C.R., Aliahmad, P., de la Torre, B., Iliev, I.D., Spurka, L., Funari**,** V.A., **Kaye, J.** The development of innate lymphoid cells requires TOX-dependent generation of a common innate lymphoid cell progenitor. (2015). *Nature Immunology*, 16(6):599-608. PubMed Central PMCID: PMC4439271
   d. Seehus C.R., Kadavallore A., de la Torre B., Yeckes A., Wang, Y., Tang, J., and **Kaye, J.** Alternative activation generates IL-10-producing type-2 innate lymphoid cells. *Nature Communications* 8:1900 (2017). PubMed Central PMCID: PMC5711851

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