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BIOGRAPHICAL SKETCH

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NAME: Krummel, Matthew F.

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

POSITION TITLE: 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
University of California at Berkeley, Department of Molecular and Cell Biology	Ph.D.	06/1995	Immunology
University of Illinois, School of Liberal Arts and Sciences	B.S.	06/1989	Honors Biology and. Chemistry.
University College, London, England	Exchange Student	06/1988	Department of Chemistry
University of Illinois High School, Urbana, Illinois		06/1985	

A. Personal Statement

Matthew Krummel, PhD is the Chair of the UCSF ImmunoX Initiative (https://immunox.ucsf.edu/) and holds the Robert E. Smith Endowed Chair in Pathology. His lab (http://krummellab.com/) specializes in the discovery of archetypal collections of immune systems, notably those involving networks of cells built around T cell-myeloid interaction. His work spans scales from membrane organization, to cell biology, to entire immune systems.Dr. Krummel drives collaborative science: he founded a microscopy 'collaboratory' at UCSF which unites 'shared' technical personnel and he developed a novel industry consortium-funded project (http://immunoprofiler.org/) whichunites studies of over 15 cancer indications to understand the biology of individual patients. Together with other UCSF faculty, he co-founded the ImmunoX initiative, a radical collaboration platform focused on methods and data sharing as a means to accelerate discovery and cures. His initiative also emphasizes public outreach and interaction as a means to disseminate the value of science. Dr. Krummel's work has led to numerous clinical advances including co-discovering anti-CTLA-4 'checkpoint blockade' drugs (over 100,000 patients treated) and new next-generation therapies through Pionyr Immunotherapeutics, a biotechnology company that he founded. The aim of all of his research is to understand and apply the immune system to improve human health

B. Positions and Honors

Positions and Employment

2018-present Co-Founder and Inaugural Chair, ImmunoX Initiative, University of California at San Francisco
2012-present Professor, Department of Pathology, University of California at San Francisco
2006-present Faculty Director, Biological Imaging Development Center, University of California at San Francisco
2006-2011 Associate Professor, Department of Pathology, University of California at San Francisco
2001-2006 Assistant Professor, Department of Pathology, University of California at San Francisco
1997-2001 Postdoctoral Fellow, HHMI, Beckman Institute, Stanford University. Advisor: Dr. Mark M. Davis
1996-1997 Postdoctoral Fellow, Dendritic Cell Biology, Walter and Eliza Hall Institute, Melbourne Australia. Advisors: Dr. Bill Heath and Dr. Ken Shortman
1995-1996 Postdoctoral Fellow, MCB, UC Berkeley. Advisor: Dr. James P. Allison
1989-1995 Graduate Research Assistant, MCB, UC Berkeley. Advisor: Dr. James Allison
1988-1988 Stagiare (Technician), UGM, UGM, Institut Pasteur. Advisors: Dr. Julian Davies and Dr. Tom

Holt
1987-1987 HHMI Summer Fellow, Neurobiology, UTHSC Dallas. Advisor: Dr. Flora Katz

Other Experience and Professional Memberships

2002-present Ad hoc member of study sections, NIH: CMIA (formerly Aly), TTT
2003-present Ad hoc reviewer, Wellcome Trust
2004-present Ad hoc reviewer, US-Israeli Binational Science Foundation
2008-2009 Member: Board of Scientific Counselors, NIAID
2008-present Referee, European Research Council

Honors

2016 Robert E. Smith Endowed Chair in Experimental Pathology
2013 Pediatrics FLAG Mentorship Award, University of California, San Francisco
2009 Fellow of the American Asthma Foundation
2005 Leukemia and Lymphoma Foundation, Career Award
2004 Cancer Research Institute, Investigator Award
1997 NRSA Postdoctoral Fellowship, National Institutes of Health
1996 Postdoctoral Fellowship, Juvenile Diabetes Foundation International
1989 Luce scholars competition finalist, Henry Luce Foundation
1986 James scholar, University of Illinois
1985 Illinois State Scholar, National Merit scholar, Westinghouse Science Award

C. Contribution to Science

1. Direct Imaging of Immune Subversion in Solid Tumors and Identification of Immune Stimulatory Pathways and Antigen-presenting cells. My laboratory has developed mouse models through which to study the T cell-APC dynamics within spontaneous tumors in living animals. This has allowed us to track antigen-presentation pathways and to identify sites and APC subsets involved in immune subversion. Recently, we used this combined with 11-color flow cytometry to isolate a rare antigen-presenting cell that is required for T cell mediated tumor rejection and which is present in most tumors at very low levels.
   a) Broz M, Binnewies M, Boldajipour B, Nelson A, Pollock J, Erle DJ, Barczak A, Rosenblum M, Daud A, Barber DL, Amigorena S, van't Veer LJ, Sperling A, Wolf DM, Krummel MF: Dissecting the Tumor Myeloid Compartment Reveals A Rare Antigen Presenting Critical for T cell Immunity. Cancer Cell, 2014 26(5):638-52. PMC4254577
   b) Roberts, E.W., Broz, M.L., Binnewies, M., Headley, M.B., Nelson, A.E., Wolf, D.M., Kaisho, T., Bogunovic, D., Bhardwaj, N., and Krummel, M.F. 2016. Critical Role for CD103+/CD141+ Dendritic Cells bearing CCR7 for Tumor Antigen Trafficking and Priming of T cell Immunity in Melanoma. Cancer Cell. PMC5374862
   c) Barry KC, Hsu J, Broz ML, Cueto FJ, Binnewies M, Combes AJ, Nelson AE, Loo K, Kumar R, Rosenblum MD, Alvarado MD, Wolf DM, Bogunovic D, Bhardwaj N, Daud AI, Ha PK, Ryan WR, Pollack JL, Samad B, Asthana S, Chan V, Krummel MF. A natural killer-dendritic cell axis defines checkpoint therapy-responsive tumor microenvironments. Nat Med. 2018 Aug;24(8):1178-1191. doi: 10.1038/s41591-018-0085-8. Epub 2018 Jun 25. PMID: 29942093
   d) Binnewies M, Mujal AM, Pollack JL, Combes AJ, Hardison EA, Barry KC, Tsui J, Ruhland MK, Kersten K, Abushawish MA, Spasic M, Giurintano JP, Chan V, Daud AI, Ha P, Ye CJ, Roberts EW, Krummel MF. Unleashing Type-2 Dendritic Cells to Drive Protective Antitumor CD4+ T Cell Immunity. Cell. 2019 Apr 18; 177(3):556-571.e16. PMID: 30955881

2. Vital and Intravital Imaging of Immune Responses in the Lung. My laboratory has developed intravital imaging methods for assessment of immune responses directly in tissues. Using combinations of custom-built multiphoton microscopes and matched stabilization methods, we have been able to understand immune responses directly in fully ventilated lungs. This has permitted us to understand normal neutrophil surveillance and the early stages of lung injury. Additionally, it has permitted a direct study of dendritic cell functions in the lungs. This demonstrated direct antigen uptake, across the epithelium, by alveolar but not airway DC. Further, it allowed us to demonstrate that these DC cluster near the reactive airway and re-stimulate T cells there. We've applied this method to track myeloid cell differentiation in allergy and recently adapted this to track mast cell probing of vessels in the trachea. We've also applied this method to understand nematode interactions with the immune system in the lung.

a) Engelhardt, J.J., Boldajipour, B., Beemiller, P., Pandurangi, P., Sorensen, C., Werb, Z., Egeblad, M., Krummel, M.F. 2012. Marginating Dendritic Cells of the Tumor Microenvironment Cross-Present Tumor Antigens and Stably Engage Tumor-Specific T Cells. Cancer Cell 21, March 20; 402-417. PMC3311997.
b) Thornton, E.E., Looney M.R., Bose, O., Sen, D., Sheppard, D., Locksley, R., Huang, X., Krummel, M.F. 2012. Spatiotemporally Separated Antigen Uptake by Alveolar Dendritic Cells and Airway Presentation to T Cells in the Lung. J Exp Med., 209(6):1183-99. PMC3371730
c) Looney, M.R., Thornton, E.E., Sen, D., Lamm, W.J., Glenny, R.W., Krummel, M.F. 2010. Stabilized imaging of immune surveillance in the mouse lung. Nat Methods. 8(1):91-6. PMC3076005
d) Patnode,M.L., Bando, J.K., Krummel, M.F., Locksley, R.M., Rosen, S.D. Leukotriene B4 Amplifies Eosinophil Accumulation in Response to Nematodes. J. Exp.Med. 2014 Jun 30;211(7):1281-8. PMC4076593
e) Headley, M.R., Bins A., Nip A., Roberts E.W., Looney M., Gerard, A., Krummel,M.F. Visualization of Immediate Immune Responses to Pioneer Metastatic Cells in the Lung. Nature. March 24, 2016.

3. Dynamic Imaging of Immune Synapse Assembly in vitro and in vivo. I and my laboratory have defined the dynamics of immune synapse assembly, starting with the relationship of TCR and CD4 clustering and centralization to the onset of calcium signaling. We pioneered imaging of the TCR complex visualized in T cells within T cell-zones of vital lymph nodes by multiphoton microscopy. We defined how TCRs can signal while T cells are still moving across the APC surface. And,we've defined synaptic assembly between neighboring activating T cells, for the sharing of cytokine signals.
a) Cai, E., Marchuk, K., Beemiller, P., Beppler, C., Rubashkin, M.G., Weaver, V.M., Chen,B-C., Betzig,E., Bartumeus, F., Krummel, M.F. 2017Visualizing Dynamic Microvillar Search and Stabilization during Ligand Detection by T cells. Science 356(6338). pii: eaal3118. doi: 10.1126/science.aal3118.
b) Friedman, R.S., Beemiller, P., Sorensen, C.M., Jacobelli, J., Krummel, M.F. 2010 Nov 1. Real-time analysis of T cell receptors in naive cells in vitro and in vivo reveals flexibility in synapse and signaling dynamics. J Exp Med. 11(10):953-61. PMC2989766.
c) Beemiller, P., Jacobelli, J., Krummel, M.F., 2012. Integration of Signaling Microclusters Movement with Cellular Motility in Immunological Synapses. Nat Immunol. Jul 1. doi: 10.1038/ni.2364. PMC3902181.
d) Gérard, A., Khan, O., Beemiller, P., Oswald, E., Hu, J., Matloubian, M., Krummel, M.F. 2013. Secondary T cell-T cell synaptic interactions drive the differentiation of protective CD8+ T cells. Nat Immunol. 2013 14(4):356-63. PMC3962671

4. Identification of Key Cytoskeletal Regulators of T cell motility and arrest. My laboratory defined the key roles for Myosin IIA in facilitating optimal migration in T cells as well as its phosphorylation as part of the T cell 'stop' signal. We also identified the unconventional septin cytoskeleton as a key player in T cell shape and motility. Most recently, we demonstrated that the unconventional Myosin Myo1c is necessary for random turning and thereby provides optimal surveillance strategy for antigen-detection.
a) Jacobelli, J. Chmura, S.A., Buxton,D.B., Davis , M.M. and Krummel, M. F. 2004. Class II Myosin Heavy Chain 2A/MyH9 Is Involved in the T Cell Stop Signal but is not Required for Synapse Formation. Nature Immunology.5(5):531-8.
b) Jacobelli, J., Friedman, R.S., Conti, M.A., Lennon-Dumenil, A.-M., Piel, M., Sorensen, C.M., Adelstein, R.S., Krummel, M.F. 2010. Confinement-optimized three-dimensional T cell amoeboid motility is modulated via myosin IIA-regulated adhesions. Nat Immunol. 11, 953-961. PMC2943564
c) Gilden, J.K., Peck, S., Chen, Y.C.M., Krummel, M.F. 2012. The septin cytoskeleton facilitates membrane retraction during motility and blebbing. J Cell Biol. Jan 9;196(1):103-14. PMC3255977
d) Gérard, A., Patino-Lopez, G., Beemiller, P., Nambiar, R., Ben-Aissa, K., Liu, Y., Totah, F.J., Tyska, M.J., Shaw, S., Krummel, M.F. Detection of Rare Antigen-Presenting Cells through T Cell-Intrinsic Meandering Motility, Mediated by Myo1g. Cell. 2014 Jul 31;158(3):492-505. PMC4119593

5. Identification of CTLA-4 as an Inhibitor of T cell Responses and Modulation to Regulate Immunity In vivo. My work as a graduate student demonstrated that both CD4 and CD8 T cells express a homolog of the costimulatory molecule CD28, CTLA-4, after activation. I generated mouse antibodies to these and demonstrated that engagement of CTLA-4 by antibodies or by its ligand resulted in dampening of T cell responses. I subsequently injected this antibody into mice and demonstrated that this could be used to block this pathway and thus upregulate T cell responses in vivo. This served as a generalized method that we applied across multiple mouse models including augumenting anti-tumor immunity. This work was led to a patent for CTLA-4 blockade in cancer and immunization and has now become 'Checkpoint Blockade'

Therapy. The FDA approved anti-CTLA-4, also known as Yervoy or ipilulumab, the first FDA approved immunotherapeutic in cancer, in 2011.
a) Krummel, M.F. and Allison, J.P. 1995. CD28 and CTLA-4 deliver opposing signals which regulate the response of T cells to stimulation. J. Exp. Med. 182, 459-465.
b) Allison, J.P. and Krummel, M.F. 1995. The yin and yang of T cell costimulation. Science. 270,932-933.
c) Leach, D.R., Krummel, M.F. and Allison, J.P. 1996. Enhancement of antitumor immunity by CTLA-4 blockade. Science. 271, 1734-1736.
d) Krummel, M.F. and Allison, J.P. 1996. CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells. J. Exp. Med. 183, 2533-2540. PMC2192613.

Complete List of Published Work in MyBibliography:

Complete List of PubMed-indexed Published Work: http://www.ncbi.nlm.nih.gov/pubmed/?term=krummel+mf

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

On-going Research Support

R01 AI52116 Krummel (PI) 01/01/18-12/31/22
NIH, Spatiotemporal Control of T Cell Synapse Stabilization and Signaling
The major goals of this project are to analyze MyoIIA regulation during T cell motility and synapse formation. This includes mutational analyses as well as generation and analyses of knockout animals.
Role: PI

1R01CA197363 Krummel (PI) 03/15/17-02/28/22
NIH/NCI, Anti-Tumor Mechanisms of Intratumoral Stimulatory Dendritic Cells
The goal of this project is to study the generation and function of rare stimulatory dendritic cell populations in mouse and human tumors, with emphasis on determining the flow of antigens from tumors towards pathways that stimulate T cells.
Role: PI

U01CA217864 Balmain, Krummel, Weiss (PI) 08/17/17-07/31/22
NIH/NCI, Integrating targeted and immunotherapy to treat genetically heterogeneous cancers
The goal of this project is to perform crispr screens in monocytes and T cells to identify genes associated with tumor entry and function in two distinct tumor types. Will use genetic or pharmacological perturbation of newly generated candidate genes involved in metabolic stress and ros-induced DNA damage to increase mutation load and antigen abundance in a tumor-specific manner, leading to improved responses to IMT. Will also exploit gene expression networks to identify druggable targets and pathways that augment immune responses.
Role: Co PI

Consortia of Pharma Companies Krummel (PI) 01/1/20 - 12/31/22
UCSF Immunoprofiler (immunoprofiler.org)
This is funding of consortia of laboratories, initiated by Krummel Lab, for a project designed to profile the immune composition, localization, and gene-expression of hundreds of human tumors from multiple cancer indications. Funds largely drive a UCSF campus-wide clinical project designed to generate a common database of immune profiles.
Role: PI

3U19AI077439-13S1 Erle, Krummel (PI) 05/08/20-03/31/22
NIH-NIAID, UCSF COVID-19 extended immunophenotyping studies
The major goal of this emergency COVID-19 supplement is to apply key and cutting-edge immunophenotyping assays to patient samples derived from the Immunophenotyping assessment in a COVID-19 Cohort (IMPACC) study to understand the critical features that characterize hospitalized patients with COVID-19, a pandemic disease characterized by immune exacerbations of lung injury.
Role: Co PI

3U19AI077439-13S2 Erle, Krummel (PI) 05/07/20-03/31/22
NIH-NIAID, UCSF COVID-19 Immunophenotyping Clinical Study and Core Laboratories
The major goal of this emergency COVID-19 supplement is to develop and participate IMPACC multi-center longitudinal clinical study of hospitalized patients with COVID-19 and to immunophenotype participants using

shared immunological methods that will be designed an carried out by core laboratories at UCSF and at other participating institutions.
Role: Co PI

R01 AI052116 Krummel (PI) 05/27/20- 12/31/21
NIH/NIAID, COVID19 Admin Supplement to Rapidly Translate Immunobiology for Patient Benefit
This project will utilize a deep knowledge of T cell-myeloid biology to identify and rank immunotherapeutics that will be clinically useful to modulate the severity of catastrophic lung damage in the context of SARS-CoV-2.
Role: PI

Completed Research Support

R01 AI52116 Krummel (PI) 01/15/08-12/31/17
NIH, Myosin Motors in T cell Synapse Formation and Activation
The major goals of this project are to analyze MyoIIA regulation during T cell motility and synapse formation. This includes mutational analyses as well as generation and analyses of knockout animals.
Role: PI

2U19A1077439-06 Sheppard (PI) 04/01/08-03/31/18
NIH/NIAID, IL-13 and IL-17 Dynamics in the Asthmatic Airway
Project 3: Dynamic Imaging of IL13/IL17 Immune Infiltrates in Asthma
In conjunction with Projects 1 and 2, this project will directly analyze the unfolding of asthmatic responses in the context of the intact airway epithelium. It develops cutting-edge imaging technologies in mouse, applies them to human samples via the Clinical Subject and Biospecimen core and significantly develops reagents and methods that will advance our capacity to study living human biopsies at the subcellular level.
Role: Project 3 Leader

R21 CA196468-01 Krummel (PI) 09/01/15-08/31/18
NCI, Living Tumor Biopsies to Interrogate Immune Function and Response to Therapy
Here we seek to develop methodology to track immune populations in living biopsies.
Role: PI

1R01AI114787-01A1 Krummel (PI) 07/01/15-05/31/20
NIH/NIAID, Manipulating Ccollectivity and Niches for Developing CD8 Immunity
The goal of this project is to use advanced imaging methods to discover how we could take advantage of co-vaccination regimen to generate strong CD8 T cell immunity, systemically and in target tissue. This will have significant implications for protective immunizations to viruses.
Role: PI

Parker Institute Krummel (PI) 07/01/18-06/30/20
This program funds the development of a technology platform for spatial sequencing. Called ‘ZipSeq’ this platform permits the study of gene expression from single cells post live-imaging, with the ability to pinpoint which cells came from which regions.
Role: PI

UCSF ImmunoX Krummel (PI) 01/01/19 - 12/31/20
This program funds a comparative immunoprofiling project to compare mouse models of cancer against the common database of human immune profiles generated under immunoprofiler.org.
Role: PI

R01CA210561 Akhurst, Krummel (PI) 01/01/18–12/31/20
NIH/NCI, Advancing the translatability of mouse models for cancer immunotherapy
The major goals of this project are to investigate and credential the use of chemically induced SCC models for studying cancer immunotherapy. We will investigate translatability of testing standard of care, anti-PD-1 and a novel anti-TGF Beta drug, in syngeneic mouse models of transplantable tumors and in situ primary induced carcinoma with credentialing using biopsy material form HNSCC patients undergoing immunotherapy at UCSF.
Role: Co PI