OMB No. 0925-0001 and 0925-0002 (Rev. 03/2020 Approved Through 02-28-2023)

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 (http://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 systemsDr. 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/) which unites studies of over 15 cancer indications to understand the biology of individual patients. His resulting work on archetypes in COVID-19 has implicated antibodies, binding through CD32 FcR in mediating the loss of interferon pathways in severe 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

2020 Dial Fellow, Emerson Collective
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 therapyresponsive 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 custombuilt 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

restimulate 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.

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

On-going Research Support

R01 AI52116 Krummel (PI) 01/01/18-12/31/22
NIH/NIAID, 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

3U19AI077439-13S1 Erle, Krummel (PI) 05/08/22-03/31/22
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

3U19AI0774309-13S2 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 particiate IMPACC multi-center longitudinal clincial study of hospitalized patients with COVID-19 and to immunophenotype participants using shared immunological methods that will be designed and carried out by core laboratories at UCSF and at other participating institution.
Role: Co-PI

R01 AI052116 Krummel (PI) 05/27/20-12/31/21
NIH/NIAID, COVID19 Admin Supplement to Rapidly Translate Immunobiology for Patient Belief
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 int he context of SARS-CoV-2.
Role: PI

R35CA242447 Weaver, Krummel (PI) 09/01/20-08/31/27
NIH/NCI, Tissue mechanics reprograms the tissue to malignancy and metastasis
The major goals of this project to identify conserved mechanical reinforcement circuits that drive malignant transformation and progression focusing on inflammation and mitochondrial stress.
Role: Co-PI

Completed Research Support

1S10RR029266-01 Krummel (PI) 06/05/11-06/04/13
NIH/NCRR
Multiphoton Instrumentation for Translational Assays from Human Tissue Biopsies
This equipment grant is to purchase a state-of-the art multiphoton microscope specifically configured and situated to accommodate a portfolio of translational imaging approaches and further dedicated to extension of two-photon technology to human biopsy tissues.
Role: PI

1R21CA167601 Krummel (PI) 04/01/12-03/31/14
NIH/NCI
Defining the First Hours of Lung metastasis using Intravital Live-Imaging
This proposal will apply novel intravital imaging of the lung to define the first hours following the arrival of metastatic cells into the mouse lung. As we know very little about why metastatic tumor cells survive in this environment, this represents a major undertaking in determining how to decrease their success.
Role: PI

1U01CA141451 Krummel (PI) 09/01/09-08/31/14
NIH
Collaborative Innate-Adaptive Immune Regulation of Tumor Progression
The major goals of this project are;
Goal 1: Visualize the progression in crosstalk between the innate and adaptive immune response during tumor development using mouse models of luminal and basal breast cancer.
Goal 2: Define the specific attractants that regulate immune cell-cell interactions in the tumor.
Goal 3: Use mouse models to determine mechanisms of existing and putative immuno- and cytotoxic anti-cancer regimens and to design and test combinatorial therapies based upon this information.
Role: PI

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

PO1 HL024136 Caughey (PI) 05/01/10-03/31/14
NIH/NHLBI
Evolving Microenvironments in Airway Inflammation
The aims of this proposal are to identify shifts in antigen-trafficking into APC, the temporal pairing of specific APC with T cell subsets, and the effects of Mycoplasma-mediated inflammation and mast-cell-mediated regulation upon T cell-APC pairing in lung microenvironments.
Role: P2 PI

PO1 HL024136-CoreB Caughey (PI) 05/01/10-03/31/14
NIH/NHLBI
Core B: This core supports the basic activities of the PPG
Role: Co-PI

U54 CA163123-01 (Coussens, Krummel, Van't Veer: multi-PI) Coussens (PI) 09/01/11-08/30/16
NIH/NCI
Leukocyte Biomarkers for Predicting Human Breast Cancer Outcome
The goal of this project is to identify predictive biomarkers in human breast cancer, using genomic profiling of mouse and human breast cancer infiltrates and correlated analyses of outcome.
Role: PI (MPI)

1U01HL111054-01
(Chapman, Chuang, Krummel, multi-PI) (co-PI) Chapman (PI) 12/01/11-11/30/16
NHLBI
Epithelial Progenitor Cells in Lung Repair and Regeneration
This project will analyze the stem cells and events that take place during lung repair.
Role: co PI

2U19A1077439-06 Sheppard (PI) 04/01/08-03/31/18
NIH/NIAID
Program: 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

R21CA191428 Krummel (PI) 01/01/15-12/31/16
NIH/NCI
Cutting Edge Lineage Tracking of Tumor-Educated Immune Cells
The goal of this project is to devise novel lineage-tracking tools, taking advantage of photoconvertable tamoxifen derivatives and high resolution intravital imaging.
Role: PI

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) 07/01/15-06/30/20
NIH/NIAID
Manipulating Collectivity 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