BIOGRAPHICAL SKETCH

NAME: LINSLEY, PETER S.

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

POSITION TITLE: Associate Member and Director, Systems Immunology

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Auburn University	BS	06/1973	Biology
University of California, Los Angeles (UCLA) Advisor: C. Fred Fox	PhD	06/1980	Molecular Biology (EGF Receptor)
University of Toronto, Hospital for Sick Children, Department of Genetics, Advisor: Louis Siminovitch	Post-doc	09/1983	Somatic Cell Genetics

Personal Statement

My career has largely been spent in the pharmaceutical and biotechnology industries, where I developed my current research interest in Systems Approaches to biomarker and target identification for immune diseases and therapies. To pursue this interest, I left industry in 2012 and joined the Systems Immunology Division at Benaroya Research Institute (BRI). Since joining BRI, I have developed several RNAseq profiling projects, including: full transcriptome molecular profiling of individual antigen-specific cells; identifying whole blood molecular signatures characterizing successful treatment of T1D subjects; and modular transcriptome approaches to analyzing immune surveillance in solid tumors.

My industry career has provided me with unique research experience, especially in immunology and cancer. My experience in these areas began at Oncogen/Bristol-Myers Squibb, and continued at Rosetta Informatics/Merck where I also transitioned into Systems Biology studies. At Rosetta, we pioneered molecular profiling approaches with primary tumors to classify and predict prognosis of breast cancer (van't Veer et al, 2002) and guide pathway analysis (Ivanovska et al and Burchard et al). A common thread to all of this work was a careful and rigorous application of molecular profiling to significant biological problems.

1. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, **Linsley PS**, Bernards R, Friend SH. Gene expression profiling predicts clinical outcome of breast cancer. **Nature**. 2002;415(6871):530-6.
2. Ivanovska I, Ball AS, Diaz RL, Magnus JF, Kibukawa M, Schelter JM, Kobayashi SV, Lim L, Burchard J, Jackson AL, **Linsley PS**, Cleary MA. MicroRNAs in the miR-106b family regulate p21/CDKN1A and promote cell cycle progression. **Mol Cell Biol**. 2008;28(7):2167-74. PMCID: PMC2268421.
3. Burchard J, Jackson AL, Malkov V, Needham RH, Tan Y, Bartz SR, Dai H, Sachs AB, **Linsley PS**. MicroRNA-like off-target transcript regulation by siRNAs is species specific. **RNA**. 2009;15(2):308-15. PMCID: PMC2648714.

B. Positions and Honors

Professional Experience:

1973-1980	Graduate student, Molecular Biology Institute, Univ. of California, Los Angeles, CA
1980-1983	Postdoctoral Fellow, Dept. of Genetics, Hospital for Sick Children, Toronto, Ontario
1983-1996	Senior Scientist, Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA
1996-1997	Director, Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA

1997-1999	Director, Mammalian Team, Rosetta Inpharmatics, Kirkland, WA
1999-2001	Sr. Director, Research & Development, Rosetta Inpharmatics, Kirkland, WA
2001	Vice President, Research & Development, Rosetta Inpharmatics, Kirkland, WA
2001-2008	Executive Director, Cancer Biology, Merck/Rosetta Inpharmatics, Seattle, WA
2008-2010	Chief Scientific Officer, Regulus Therapeutics, San Diego, CA
2011-2012	Chief Scientific Officer, AVI BioPharma, Bothell, WA
2012-2013	Visiting Scientist, Benaroya Research Institute, Seattle, WA
2013-present	Research Associate Member, Benaroya Research Institute, Seattle, WA
2014-present	Director, Systems Immunology Division, Benaroya Research Institute, Seattle, WA

Fellowships and Awards:

1972-Alpha	Epsilon Delta Pre-Medical Honorary Society
1973-1978	Chancellor's Intern Fellow, UCLA 1973 Phi Kappa Phi Scholastic Honorary Society
1978-1980	Traineeship, National Cancer Institute
1979-1980	Fellowship, Jonsson Comprehensive Cancer, UCLA
1980-1983	Postdoctoral Fellowship, Medical Research Council of Canada
1990-1994	Identified by The Scientist as one of the top 20 most highly cited immunology research scientists
2007	Oncology Enablement Award, Merck Research Laboratories
2013	Jerry Award for “exceptional contributions in the field of autoimmunity”, Autoimmune Advocacy Society

Study Sections and Boards:

1994-present	Many Ad Hoc assignments
1995-1997	Arthritis Foundation Study Section
2011-present	Research Advisory Committee, Oncofactor Corp., Seattle, WA
2012-present	Reviewer, Life Sciences Discovery Fund, Seattle, WA
2012-present	Medical Advisory Committee, Children’s Turner Foundation, New York, NY
2013-present	Scientific Advisor, Eos Corp., Los Angeles, CA

Editorial Positions:

1994-1997	Editorial Board, Therapeutic Immunology
1996	Editor Immunological Techniques, Current Opinion in Immunology
1999	Co-editor, Lymphocyte activation and effector functions, Current Opinion in Immunology
2002-2006	Assistant Editor, Journal of Immunology
2010-present	Associate Editor, BMC Immunology

C. Contributions to Science

1. ***I discovered the B7/CD28/CTLA-4 T cell costimulatory axis.*** In the late1980s, it was unclear how T cell surface molecules, other than the antigen receptor, might function in regulating T cell proliferation. One molecule on T cells, CD28, was of interest because anti-CD28 monoclonal antibodies (mAbs) triggered T cell proliferation. While I was a group leader at Bristol-Myers Squibb (BMS), my collaborators and I postulated that this proliferation occurred because anti-CD28 mAbs mimicked activity of a then undiscovered natural ligand for CD28 expressed on other immune cells. To test this hypothesis, I developed a novel CD28-mediated cell adhesion assay that I then used to identify a natural ligand for CD28. The ligand I identified was the B7/BB-1 antigen, now known as CD80 or B7-1, and now widely accepted as a counter receptor for CD28 expressed at sited antigen-presenting cell activation. Our subsequent studies (see below) showed that T cell receptor CTLA-4 was also a receptor for the B7/BB-1 antigen. This discovery set the stage for development of a new class of immunomodulatory therapies that modulate “second” signals (T cell costimulation) during T cell activation. To date, the Food and Drug Administration (FDA) has approved three therapeutics targeting the B7/CD28/CTLA-4 T cell costimulation axis (Abatacept, Belatacept and Ipilumimab).
    a. **Linsley PS**, Clark EA, Ledbetter JA. Pillars article: T-cell antigen CD28 mediates adhesion with B cells by interacting with activation antigen B7/BB-1. 1990. **Proc. Natl. Acad. Sci. USA** 87: 5031-5035. PMCID: PMC54255. **J Immunol**. 2009;182(5):2559-63.

b. **Linsley PS**, Brady W, Grosmaire L, Aruffo A, Damle NK, Ledbetter JA. Binding of the B cell activation antigen B7 to CD28 costimulates T cell proliferation and interleukin 2 mRNA accumulation. **J Exp Med**. 1991;173(3):721-30. PMCID: PMC2118836.
c. Chen L, Ashe S, Brady WA, Hellstrom I, Hellstrom KE, Ledbetter JA, McGowan P, **Linsley PS**. Costimulation of antitumor immunity by the B7 counterreceptor for the T lymphocyte molecules CD28 and CTLA-4. **Cell**. 1992;71(7):1093-102.
d. Tan P, Anasetti C, Hansen JA, Melrose J, Brunvand M, Bradshaw J, Ledbetter JA, **Linsley PS**. Induction of alloantigen-specific hyporesponsiveness in human T lymphocytes by blocking interaction of CD28 with its natural ligand B7/BB1. **J Exp Med**. 1993 Jan 1;177(1):165-73. PMCID: PMC2190874.

2. ***I discovered the immunosuppressants, Abatacept and Belatacept.*** During our efforts to elucidate the B7/CD28/CTLA-4 T cell costimulation axis, I designed a soluble recombinant immunoglobulin Fc domain fusion with the extracellular region of CTLA-4 (CTLA4Ig). We discovered that this molecule binds B7 family molecules with high affinity and can be used to block CD28/B7 T cell costimulation in vitro and in vivo. We then showed that administration of CTLA4Ig was therapeutic for animal models and human subjects with autoimmune diseases, and had an extremely favorable safety profile. The same CTLA4Ig molecule I designed was developed by BMS, approved by the FDA, and is now marketed as a therapeutic for Rheumatoid Arthritis (Abatacept). My research group also engineered a recombinant form of CTLA4Ig with higher binding affinity for B7 molecules (LEA29Y), which was developed and approved by the FDA for treatment of kidney transplantation (Belatacept).
    a. **Linsley PS**, Brady W, Urnes M, Grosmaire LS, Damle NK, Ledbetter JA. CTLA-4 is a second receptor for the B cell activation antigen B7. **J Exp Med**. 1991;174(3):561-9. PMCID: PMC2118936
    b. **Linsley PS**, Wallace PM, Johnson J, Gibson MG, Greene JL, Ledbetter JA, Singh C, Tepper MA. Immunosuppression in vivo by a soluble form of the CTLA-4 T cell activation molecule. **Science**. 1992;257(5071):792-5.
    c. Abrams JR, Lebwohl MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, Menter A, Lowe NJ, Krueger G, Brown MJ, Weiner RS, Birkhofer MJ, Warner GL, Berry KK, **Linsley PS**, Krueger JG, Ochs HD, Kelley SL, Kang S. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. **J Clin Invest**. 1999;103(9):1243-52. PMCID: PMC408469.
    d. Larsen CP, Pearson TC, Adams AB, Tso P, Shirasugi N, Strobert E, Anderson D, Cowan S, Price K, Naemura J, Emswiler J, Greene J, Turk LA, Bajorath J, Townsend R, Hagerty D, **Linsley PS**, Peach RJ. Rational development of LEA29Y (belatacept), a high-affinity variant of CTLA4-Ig with potent immunosuppressive properties. **Am J Transplant**. 2005;5(3):443-53.

3. ***I pioneered the use molecular profiling techniques for improving drug discovery.*** With the emergence of genomics and molecular profiling technologies in the early 2000s, we became interested in using these technologies in the drug discovery process. While a Senior/Executive Director at Merck Research Laboratories, I was part of interdisciplinary teams that developed new applications for molecular profiling and genomics techniques in drug discovery. Our efforts included the use of profiling technologies to identify patients most likely to benefit from therapies (Responder ID); the use of genome-scale in vitro genetic screens with human cells to identify new drug targets by synthetic lethality (Target ID); and the development of microRNAs as a new class of drug targets (Pathway ID). Today, there is a commercial product based on our initial work in Responder ID (MammaPrint) and numerous efforts are underway to use synthetic lethality for the selective targeting of cancer and to target microRNAs therapeutically.
    a. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, **Linsley PS**, Bernards R, Friend SH. Gene expression profiling predicts clinical outcome of breast cancer. **Nature**. 2002;415(6871):530-6.
    b. Radich JP, Dai H, Mao M, Oehler V, Schelter J, Druker B, Sawyers C, Shah N, Stock W, Willman CL, Friend S, **Linsley PS**. Gene expression changes associated with progression and response in chronic myeloid leukemia. **Proc Natl Acad Sci U S A**. 2006;103(8):2794-9. PMCID: PMC1413797.
    c. Bartz SR, Zhang Z, Burchard J, Imakura M, Martin M, Palmieri A, Needham R, Guo J, Gordon M, Chung N, Warrener P, Jackson AL, Carleton M, Oatley M, Locco L, Santini F, Smith T, Kunapuli P, Ferrer M, Strulovici B, Friend SH, **Linsley PS**. Small interfering RNA screens reveal enhanced

cisplatin cytotoxicity in tumor cells having both BRCA network and TP53 disruptions. **Mol Cell Biol**. 2006;26(24):9377-86. PMCID: PMC1698535.

d. He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, Xue W, Zender L, Magnus J, Ridzon D, Jackson AL, **Linsley PS**, Chen C, Lowe SW, Cleary MA, Hannon GJ. A microRNA component of the p53 tumour suppressor network. **Nature**. 2007;447(7148):1130-4.

4. ***I led efforts demonstrating that siRNAs and microRNAs target multiple mRNAs***. During our work to use molecular profiling efforts to improve drug discovery, we initiated efforts to combine the use of molecular profiling with recently discovered siRNA genetic disruptions for Pathway ID. While siRNAs were then believed to be exquisitely specific in their silencing of selected mRNAs, my research group used microarrays to make the unexpected discovery that siRNAs actually regulated numerous off-target transcripts. We demonstrated that this off-target silencing was sequence-specific, and mediated by short (6-8 nucleotide) sequence matches between the seed region of siRNAs and the 3'UTR of mRNAs, similar to how microRNAs were known to recognize targets. Our discovery of off-target transcript recognition by siRNAs then led directly to the seminal discovery that mammalian microRNAs regulate many mRNA targets. While our findings were at first controversial, it is now widely recognized that an inherent feature of siRNAs and microRNAs is that they regulate levels of dozens or hundreds of mRNAs through seed matched recognition.
    a. Jackson AL, Bartz SR, Schelter J, Kobayashi SV, Burchard J, Mao M, Li B, Cavet G, **Linsley PS**. Expression profiling reveals off-target gene regulation by RNAi. **Nat Biotechnol**. 2003;21(6):635-7.
    b. Burchard J, Jackson AL, Malkov V, Needham RH, Tan Y, Bartz SR, Dai H, Sachs AB, **Linsley PS**. MicroRNA-like off-target transcript regulation by siRNAs is species specific. **RNA**. 2009; 15(2):308-315. PMCID: PMC2648714.
    c. Jackson AL, Burchard J, Schelter J, Chau BN, Cleary M, Lim L, **Linsley PS**. Widespread siRNA "off-target" transcript silencing mediated by seed region sequence complementarity. **RNA**. 2006;12(7):1179-87. PMCID: PMC1484447.
    d. Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, **Linsley PS**, Johnson JM. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. **Nature**. 2005;433(7027):769-73.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/14Kkjxody-lku/bibliograpahy/40305576/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

DP3 DK104465 Linsley (PI) 09/25/14 – 08/31/16
Determining the molecular basis for different rates of T1D progression
Our goal is to identify molecular and/or cellular signatures in whole blood that characterize non-progressor responses to different therapies and during natural history, and to determine whether these signatures are unique or treatment-specific. From these signatures, we anticipate discovering unique, data-driven insights into immunological aspects of T1D progression.
Role: PI

U01 AI082110 Linsley (PI) 08/18/09 – 06/31/16
Blood transcriptional biomarker profiles for category B pathogens
The major goals of this project are to identify and validate molecular biomarker signatures for category B pathogens by creating a consortium of worldwide investigators working in areas where pathogens are causing substantial morbidity and mortality. Former PI: Damien Chaussabel
Role: PI

R01 AI108839 Wambre (PI) 07/01/14 – 06/30/19
Induction and signature of pathogenic T cells in allergy
We aim to identify a $CD4^+$ T cell signature for allergic diseases resulting from a comprehensive understanding of the mechanisms associated with the pathogenesis of allergic disease and peripheral tolerance to allergens.
Role: Co-Investigator

PO1 DE021954 Rose (PI) 05/01/13 – 04/30/16
Oral Pathogenesis and Host Interactions of KSHV Infection - *Supplement*
Dr. Linsley will be responsible for overseeing the RNAseq analysis of KSHV-infected patient samples. He will participate in the analysis of RNAseq experiments,help direct the activities of Bioinformaticians needed for advanced statistical analysis, and in systems analysis.
Role: Co-Investigator

3-SRA-2014-315-M-R James (PI) 09/01/14 – 08/31/17
Immune effector and regulatory balance as a predictor for preserved beta cell function in subjects with established T1D
This project will investigate the central hypothesis that T cell effector and regulatory balance represents a key mechanism that determines the persistence of C-peptide in established T1D.
Role: Faculty Collaborator

W81XWH-15-1-003 Buckner (PI) 12/10/14 – 09/29/17
In Depth Analysis of Citrulline-specific CD4 T Cells in Rheumatoid Arthritis
To test the hypothesis that cit-specific CD4 T cells present in RA patients exhibit a distinct cell surface phenotype and transcriptional signature that could be used to predict disease, response to therapy and identify novel therapeutic targets for the treatment of RA.
Role: Co-Investigator

UH2 AR067681 Holers (PI) 09/24/14 – 05/31/16
Evolving Adaptive and Effector Mechanisms from Pre-RA through Established Disease
The central hypothesis of this Clinical and Technology Research Site proposal focuses on Rheumatoid Arthritis (RA) is that novel disease stage-and cell lineage-specific therapeutic targets can be identified through the comprehensive evaluation of the linked adaptive and effector arms of the immune system as the disease sequentially progresses from its earliest origins through to a fully established destructive arthritis.
Role: Co-Investigator

R01 DK101062 Ziegler/Bettelli (PIs) 04/01/15 – 03/31/20
Molecular mechanism of Th17-induced inflammation
The purpose of this project is to determine the molecular mechanisms of Th17 regulation during inflammatory responses and autoimmune disease development.
Role: Other Significant Contributor (no measurable effort)

201302819 Nepom, J (PI) 04/28/15 – 03/31/17
Profiling immune subsets for biomarker assessments
There is a critical need to predict, at the time of diagnosis of T1D, the rate of decline in beta cell function that will occur in the first few years of disease. The goal of this study to define blood transcriptome signatures from blood samples collected within six months of enrollment in recent onset T1D clinical trials that will predict the change in MMTT-stimulated c-peptide production at 2 years compared to baseline. Our primary aim is to define which sets of transcripts, either by their baseline level or as they change over time, correlate with rate of c-peptide decline.
Role-Co-Investigator

DP3 DK106909 Kwok, W (PI) 09/01/15–08/31/18
Phenotypic Analysis of Islet Antigen-specific Effector T cells in Pre-diabetic Subjects
The aims are to test the following hypotheses: 1. that an increase in the frequency of recently activated auto-reactive CD4+ and CD8+ T cells precedes the onset of clinical diabetes; 2. that prediabetic subjects that progress to T1D acquire an expanded TCR repertoire of islet antigen specific T cells and that those T cells exhibit a distinct transcript signature; and 3. that progression toward T1D is accompanied by an imbalance between Treg function and effector T cell responsiveness and by periods of active beta cell destruction.
Role: Co-Investigator

<u>Completed Research Support</u>

There are 8 completed grants which could not be listed due to space constraints.