BIOGRAPHICAL SKETCH

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NAME: Christopher Benner

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

POSITION TITLE: Assistant Professor of Medicine

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, San Diego	B.S.	06/2002	Bioengineering
University of California, San Diego	Ph.D.	01/2009	Bioinformatics
University of California, San Diego	Postdoctoral	03/2011	Bioinformatics

A. Personal Statement

My background and expertise is in bioinformatics and data integration as it relates to the study of transcriptional and epigenetic regulation throughout the genome. For the past 10 years, I have been developing analysis methodology and software tools to streamline the interrogation of large-scale quantitative next-generation sequencing (NGS) projects. Many of the projects focused on the use of cutting-edge technologies, such as nascent RNA profiling (GRO-Seq) and 3D chromatin structure (Hi-C), requiring novel analysis methods and close collaboration with a wide range of experimental collaborators. I previously served as the director of the Integrative Genomics and Bioinformatics Core at the Salk Institute, where I worked with dozens of laboratories to advance their research. As a result, I have extensive experience analyzing different types of genomics data in fields spanning cancer, cellular development, the immune system, and evolution. My new laboratory focuses on developing experimental and computational techniques to elucidate mechanisms underlying enhancer function and gene regulation, which also encompasses the analysis of enhancer transcription, epigenetic changes, and genome structure. Using these approaches, we model how transcriptional networks in the immune system respond to foreign pathogens and the impact that non-coding genetic variation plays in perturbing transcriptional responses. We are also interested in studying the evolution of eukaryotic transcription by applying advanced NGS techniques across a large number of non-model organisms. Software produced from previous projects has been bundled into a software suite of tools for analyzing genomics sequencing data that is open source and has been cited over 1500 times (HOMER, http://homer.ucsd.edu/homer/).

B. Positions and Honors

Positions and Employment

2016-present Assistant Professor, University of California, San Diego, CA
2012-2015 Director of the Integrative Genomics and Bioinformatics Core, Salk Institute for Biological Studies, San Diego, CA
2011-2012 Assistant Project Scientist, Center for Cellular and Molecular Medicine, University of California, San Diego, CA
2009-2011 Postdoctoral Fellow, Department of Bioengineering, University of California, San Diego, CA
2002-2008 Graduate Research Scientist, Center for Cellular and Molecular Medicine, University of California, San Diego, CA
2001-2002 Cheminformatics/Bioinformatics Research Intern, Genomic Institute of the Novartis Research Foundation (GNF), La Jolla, California

C. Contribution to Science

1. Advances in NGS technology and rapid innovation in NGS assay development have resulted in a great need for computational analysis tools capable of both processing data and integrating results toward biologically meaningful conclusions. I have spent the last decade developing HOMER (http://homer.ucsd.edu/homer), a suite of software programs for the analysis and annotation of quantitative NGS data, including RNA-Seq and ChIP-Seq. HOMER is unique for its focus on cutting-edge NGS methods including analysis tools for nascent RNA (GRO-Seq) and chromatin structure (Hi-C). HOMER also includes a powerful *de novo* motif discovery algorithm and associated routines to integrate regulatory motif information with quantitative NGS results. Each of the following studies were accompanied by major developments in the HOMER software to enable each discovery:
    a. Heinz S, Benner C, Spann N, Bertolino E, Lin YC, Laslo P, Cheng JX, Murre C, Singh H, Glass CK. Simple combinations of lineage-determining transcription factors prime cis-regulatory elements required for macrophage and B cell identities. Mol Cell. 2010 May 28. PMCID: PMC2898526
    b. Wang D, Garcia-Bassets I, Benner C, Li W, Su X, Zhou Y, Qiu J, Liu W, Kaikkonen MU, Ohgi KA, Glass CK, Rosenfeld MG, Fu XD. Reprogramming transcription by distinct classes of enhancers functionally defined by eRNA. Nature. 2011 May 15. PMCID: PMC3117022
    c. Lin YC, Benner C, Mansson R, Heinz S, Miyazaki K, Miyazaki M, Chandra V, Bossen C, Glass CK, Murre C. Global changes in nuclear positioning of genes and intra- and inter-domain genomic interactions that orchestrate B cell fate. Nat Immunol. 2012 Oct 14. PMCID: PMC3501570
    d. Hah N, Benner C, Chong LW, Yu RT, Downes M, Evans RM. Inflammation-sensitive super enhancers form domains of coordinately regulated enhancer RNAs. Proc Natl Acad Sci USA. 2015 Jan 6. PMCID: PMC4311831
2. Cell-type and stimulus specific gene expression is modulated by promoter-distal enhancer elements, but the exact mechanisms by which these regulatory features function and influence gene expression is poorly understood. I have been a key contributor to a series of studies focusing on the role that transcription plays at enhancers. Nascent RNA sequencing (GRO-Seq) can be used to accurately measure unstable RNAs at enhancer elements to study their interplay between transcription factor recruitment, epigenetic modifications, and genome structure. I proposed a modification to GRO-Seq termed 5'GRO-Seq, which selectively sequences 5' capped nascent RNA, thus allowing the mapping of initiation sites of enhancer RNAs (eRNAs) at single nucleotide resolution (Lam et al.), and have developed a large body of analysis software that is used to study eRNA regulation.
    a. Wang D, Garcia-Bassets I, Benner C, Li W, Su X, Zhou Y, Qiu J, Liu W, Kaikkonen MU, Ohgi KA, Glass CK, Rosenfeld MG, Fu XD. Reprogramming transcription by distinct classes of enhancers functionally defined by eRNA. Nature. 2011 May 15. PMID: 21572438, PMCID: PMC3117022
    b. Lam MT, Cho H, Lesch HP, Gosselin D, Heinz S, Tanaka-Oishi Y, Benner C, Kaikkonen MU, Kim AS, Kosaka M, Lee CY, Watt A, Grossman TR, Rosenfeld MG, Evans RM, Glass CK. Rev-Erbs repress macrophage gene expression by inhibiting enhancer-directed transcription. Nature. 2013 Jun 27. PMCID: PMC3839578
    c. Kaikkonen MU, Spann NJ, Heinz S, Romanoski CE, Allison KA, Stender JD, Chun HB, Tough DF, Prinjha RK, Benner C, Glass CK. Remodeling of the enhancer landscape during macrophage activation Is coupled to enhancer transcription. Mol Cell. 2013 Aug 8. PMCID: PMC3779836
    d. Heinz S, Romanoski CE, Benner C, Allison KA, Kaikkonen MU, Orozco LD, Glass CK. Effect of natural genetic variation on enhancer selection and function. Nature. 2013 Oct 13. PMCID: PMC3994126
3. The structural configuration of nuclear chromatin plays an important role in regulating gene expression. I have spent the last 5 years developing software and innovative approaches to analyze Hi-C data and integrate it with transcriptome and epigenetic data. The genome structure underlying the adaptive immune system must not only orchestrate tightly controlled patterns of gene expression, but must also facilitate the functional recombination of antigen receptor loci. A deep understanding of these processes is important to understand B and T cell function and how Ig and Tcr loci are capable of generating diverse repertoires of receptors to combat disease. I have worked with several groups to elucidate developmental networks in lymphocytes by integrating multiple genomics technologies including RNA-Seq, ChIP-Seq, GRO-Seq, and Hi-C to improve the functional interpretation of lymphocyte genomes.

a. Lin YC, Benner C, Mansson R, Heinz S, Miyazaki K, Miyazaki M, Chandra V, Bossen C, Glass CK, Murre C. Global changes in nuclear positioning of genes and intra- and inter-domain genomic interactions that orchestrate B cell fate. Nat Immunol. 2012 Oct 14. PMCID: PMC3501570
b. Li X, Liang Y, LeBlanc M, Benner C, Zheng Y. Function of a Foxp3 cis-element in protecting regulatory T cell identity. Cell. 2014 Aug 14. PMCID: PMC4151505
c. Qian J, Wang Q, Dose M, Pruett N, Kieffer-Kwon KR, Resch W, Liang G, Tang Z, Mathé E, Benner C, Dubois W, Nelson S, Vian L, Oliveira TY, Jankovic M, Hakim O, Gazumyan A, Pavri R, Awasthi P, Song B, Liu G, Chen L, Zhu S, Feigenbaum L, Staudt L, Murre C, Ruan Y, Robbiani DF, Pan-Hammarström Q, Nussenzweig MC, Casellas R. B cell super-enhancers and regulatory clusters recruit AID tumorigenic activity. Cell. 2014 Dec 3. PMCID: PMC4272762
d. Benner C, Isoda T, Murre C. New roles for DNA cytosine modification, eRNA, anchors, and superanchors in developing B cell progenitors. Proc Natl Acad Sci U S A. 2015 Oct 13. PMCID: PMC4611620

4. Cellular differentiation follows a carefully orchestrated program of gene expression in which key transcription factors and epigenetic modifications interact with the chromatin landscape to produce lineage-restricted programs of gene expression. While it is widely acknowledged that promoter-distal regulatory elements are major contributors to developmental gene expression, the mechanisms driving their activation and organization have been difficult to work out. I served as a lead author in a study that discovered how master transcription factors cooperate at genome-wide scales to establish cell-type specific enhancers and patterns of histone methylation in macrophages (Heinz et al.). Much of this work was made possible by innovative approaches to regulatory motif analysis, including the HOMER *de novo* discovery algorithm I wrote to conduct this research. We then applied this framework to several studies focusing on different aspects of myeloid development, elucidating key differences in microglia and human macrophage development.
    a. Heinz S, Benner C, Spann N, Bertolino E, Lin YC, Laslo P, Cheng JX, Murre C, Singh H, Glass CK. Simple combinations of lineage-determining transcription factors prime cis-regulatory elements required for macrophage and B cell identities. Mol Cell. 2010 May 28. PMCID: PMC2898526
    b. Pham TH, Benner C, Lichtinger M, Schwarzfischer L, Hu Y, Andreesen R, Chen W, Rehli M. Dynamic epigenetic enhancer signatures reveal key transcription factors associated with monocytic differentiation states. Blood. 2012 Jun 14. PMID: 22550342
    c. Pham TH, Minderjahn J, Schmidl C, Hoffmeister H, Schmidhofer S, Chen W, Längst G, Benner C, Rehli M. Mechanisms of in vivo binding site selection of the hematopoietic master transcription factor PU.1. Nucleic Acids Res. 2013 Jul. PMCID: PMC3711439
    d. Crotti A, Benner C, Kerman BE, Gosselin D, Lagier-Tourenne C, Zuccato C, Cattaneo E, Gage FH, Cleveland DW, Glass CK. Mutant huntingtin promotes autonomous microglia activation via myeloid lineage-determining factors. Nat Neurosci. 2014 Apr. PMCID: PMC4113004
5. I have participated in multiple projects studying innate immunity, leveraging genome-wide technologies and bioinformatics analysis to better understand transcriptional networks regulated by Toll-like receptors and anti-viral pathways. My earlier worked focused on the regulation of inflammation in macrophages, including mechanisms of nuclear receptor mediated anti-inflammatory small molecules and the interactions between key transcription factors (e.g., NFkB, IRFs) and transcriptional co-repressors. I led the first analysis of RNA polymerase II proximal-promoter pausing in macrophage activation using GRO-Seq, and have since started studying the transcriptional mechanisms underlying the interferon response and its attenuation by infectious agents, including influenza.
    a. Ogawa S, Lozach J, Benner C, Pascual G, Tangirala RK, Westin S, Hoffmann A, Subramaniam S, David M, Rosenfeld MG, Glass CK. Molecular determinants of crosstalk between nuclear receptors and toll-like receptors. Cell. 2005 Sep 9. PMCID: PMC1430687
    b. Barish GD, Yu RT, Karunasiri M, Ocampo CB, Dixon J, Benner C, Dent AL, Tangirala RK, Evans RM. Bcl-6 and NF-kappaB cistromes mediate opposing regulation of the innate immune response. Genes Dev. 2010 Nov 24. PMCID: PMC3003193
    c. Escoubet-Lozach L, Benner C, Kaikkonen MU, Lozach J, Heinz S, Spann NJ, Crotti A, Stender J, Ghisletti S, Reichart D, Cheng CS, Luna R, Ludka C, Sasik R, Garcia-Bassets I, Hoffmann A, Subramaniam S, Hardiman G, Rosenfeld MG, Glass CK. Mechanisms establishing TLR4-

responsive activation states of inflammatory response genes. PLoS Genet. 2011 Dec. PMCID: PMC3234212

d. Rialdi A, Campisi L, Zhao N, Lagda AC, Pietzsch C, Ho JS, Martinez-Gil L, Fenouil R, Chen X, Edwards M, Metreveli G, Jordan S, Peralta Z, Munoz-Fontela C, Bouvier N, Merad M, Jin J, Weirauch M, Heinz S, Benner C, van Bakel H, Basler C, García-Sastre A, Bukreyev A, Marazzi I. Topoisomerase 1 inhibition suppresses inflammatory genes and protects from death by inflammation. Science. 2016 May 27. PMID: 27127234

List of Published Work (excluding abstracts and book chapters) in MyBibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/1dkgaabgby5Ag/bibliography/44516551/public/?sort=date&direction=descending

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

Ongoing Research Support

U19 AI106754 (Garcia-Sastre) 06/01/2013 - 05/31/2018
NIH / NIAID
Multiscale Analysis of Influenza Host-Pathogen Interactions: Fluomics
The major goal of this project is to use an –omics integrated systems biology approach to identify and validate novel host targets for therapeutic intervention during influenza A infections. The goal of the Genomics Core (C. Benner, Core PI) is to provide a central resource that will facilitate high-throughput measurements of the transcriptome and the epigenome in influenza virus-infected cells.
Role: Core PI

Completed Research Support

5 U19 AI106754 (sub-award/pilot) (Garcia-Sastre/Heinz) 06/01/2014-05/31/2015
NIH / NIAID
Influenza virus-induced changes in host 3D genome architecture
The major goal of this pilot project was to characterize changes in the three-dimensional configuration of the host genome in response to influenza virus infection to establish how long-range chromatin interactions contribute to regulation of the virus-host transcriptional network.
Role: Co-PI

P30 CA014195-42 (Hunter) 12/01/2014-11/30/2018
NIH / NCI
Cancer Center Support Grant
The major goal of this project is to understand the fundamental aspects of biology related to cancer, with the ultimate goal of reducing cancer incidents, morbidity, and mortality.
Role: Bioinformatics Core Director

Salk Innovation Grant (Benner) 09/01/14-10/31/15
Salk Institute for Biological Studies
Identifying disease-associated regulatory SNPs in humans by monitoring nascent transcription initiation genome-wide
The goal of this project was to apply 5'-global run-on sequencing (5'-GRO-Seq) to directly map the effects that regulatory genetic variants have on both local and global transcription patterns.
Role: Co-PI

Salk Innovation Grant (O'Shea) 09/01/14-02/29/2016
Salk Institute for Biological Studies
Transcriptional and genome 3D architecture dynamics of adenovirus infection
The goals of this project were to identify the location of the adenoviral genome relative to the host cell genome during adenoviral infection, and to test the hypothesis that the host genome nuclear 3D structure affects the viral transcription program, viral replication, and cellular tropism.
Role: Co-PI