

Nathan O. Siemers, Ph.D.

904 Beauford Place, Pacific Grove, California 93950 | +1 609 731-8472 | siemerscv@fiveprime.org

Current Position: Director, R&D, Translational Medicine Bristol-Myers Squibb (BMS)

Profile: Investigator and Scientific Manager across biotech/pharma discovery, translational, and clinical domains, with current focus on Immuno-Oncology • In-depth experience in oncology, genomics, data science, immunology, medical/industrial diagnostics, protein engineering, and chemistry • Leader of laboratory Genomics and Bioinformatics/Data Science teams • Discovery portfolio management across multiple therapeutic areas in pharmaceutical R&D

Goals: Lead effort in a premier oncology R&D organization to: **1** Exploit cancer molecular profiles to infer immune dynamics and relationship to therapeutic response in immuno-oncology **2** Identify markers and diagnostics for patient response to oncology therapy in clinical trials and clinical practice **3** Advance the next generation of genomic methods and tools to advance our understanding of tissue micro-environments **4** Use the knowledge gained to create the next generation of successful oncology therapeutics.

Professional Experience

BMS TRANSLATIONAL MEDICINE (TM), REDWOOD CITY, CALIFORNIA 2014-
Director, R&D

- Initiate bioinformatics and translational medicine support of BMS' Immuno-Oncology research site
- Discovery: Identify and validate immuno-oncology targets from *in-silico* mining of public, alliance, and internal cancer databases
- Translational Research: Identify disease indications and patient stratification for multiple exploratory clinical agents in immuno-oncology
- Clinical: As TM lead analyst for gastric-esophageal cancer, identify and validate/invalidate predictive markers of response to nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) therapies from clinical studies; Influence biomarker strategy and support regulatory filings in US, Europe, and Japan
- Platforms: Design and create next-generation omics analytical platforms focused on the study of tumor/tissue micro-environments via single-cell genomic data
- Governance: core member of Oncology and Immuno-Oncology discovery target management groups

BMS GENOMICS, HOPEWELL, NEW JERSEY 2004-2013
Director, R&D

- Lead Bioinformatics, Bioinformatics Platforms, and Proteomics groups responsible for genomics support across BMS preclinical and clinical R&D via:
 - Target identification and validation
 - Analysis of drug efficacy, specificity and safety with advanced genomic methods
 - Identification of relevant animal model species and systems
 - Discovery and validation of pre-clinical and clinical biomarkers of pharmacodynamics, safety, efficacy, and resistance
 - Regulatory submissions (genomic elements)
 - Defense of drug label

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- The teams made major contributions to the development of Orenicia® (abatacept), Nulogix® (belatacept), Reyataz® (atazanavir), Erbitux® (cetuximab), Onglyza® (saxagliptin), FARXIGA® (dapagliflozin), Daklinza® (daclatasvir), Sunvepra® (Asunaprevir), and beclabuvir.
- Governance: core member of Oncology, Immunology, Immuno-Oncology, Cardiovascular, and Metabolic Disease discovery target management groups
- Alliances and Budgets: Manage department operating and capital budgets; Identify and establish strategic alliances (Sanger Centre, UCLA, Moffitt Cancer Center), data sources, technology platforms, and reagents to support genomics in R&D

BMS BIOINFORMATICS, HOPEWELL, NEW JERSEY 1998-2004

Group Leader/Associate Director

- Lead Bioinformatics Platforms group responsible for delivering genomic tools to pre-clinical and clinical research groups
- Co-design and establish the high-performance computing platform for BMS genomic research from supercomputing and commodity components

WHITEHEAD INSTITUTE/MIT, CAMBRIDGE, MASSACHUSETTS 1997-1998

Visiting Scientist, Functional Genomics Consortium (Eric Lander/Todd Golub)

- Initiate RNA profiling laboratory and bioinformatics capabilities for Bristol-Myers Squibb
- Create the first “large” RNA profiling database of cancer cell lines (NCI-60) on the Affymetrix platform
- Demonstrate that gene regulatory networks can be reconstructed from libraries of RNA profiles
- Study in-vivo pharmacodynamics and selectivity of the statin class of cholesterol-reducing drugs

BMS APPLIED BIOTECHNOLOGY, PRINCETON, NJ 1996-1997

Research Investigator

- Establish high-throughput DNA sequencing group at BMS
- Cofounder of Bioinformatics department; Identify and validate novel targets via *in-silico* mining of expressed sequence tag (EST) libraries.

BMS (ONCOGEN/GENETIC SYSTEMS), SEATTLE, WASHINGTON 1993-1996

Post-Doctoral Fellow (Peter Senter/Dale Yelton)

- Apply molecular biology/immunology methods (antibody cloning, library mutagenesis, phage-display technology) to create antibody-based cancer therapeutics; Clone and characterize L49, a high-affinity antibody to the tumor antigen p97/melanotransferrin
- Antibody engineering: design, create, test, and produce (pilot scale) L49-sfv-bL, an antibody single-chain β -lactamase fusion protein for use in cancer therapy (development rights to L49-sfv-bL were acquired by Seattle Genetics)

CRYSTAL DIAGNOSTICS, WOBURN, MASSACHUSETTS 1985-1988

Research Scientist

- Develop diagnostic methods and devices for medical (cholesterol testing, therapeutic drug monitoring) and OSHA-approved (occupational exposure) testing

Education

CORNELL UNIVERSITY, ITHACA, NEW YORK 1988-1993

Ph.D. Chemistry (John E. McMurry)

MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, MASSACHUSETTS 1982-1985

B.S. Chemistry

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Selected Publications *(Full bibliography: [Google Scholar](#))*

Siemers NO, Holloway JL, Chang H, Chasalow SD, Ross-MacDonald PB, Voliva CF, et al. Genome-wide association analysis identifies genetic correlates of immune infiltrates in solid tumors. *PloS one. Public Library of Science*; 2017;12: e0179726.

Ji R-R, Chasalow SD, Wang L, Hamid O, Schmidt H, Cogswell J, et al. An immune-active tumor microenvironment favors clinical response to ipilimumab. *Cancer Immunology, Immunotherapy*. Springer-Verlag; 2012;61: 1019–1031.

Ji R-R, Siemers NO, Lei M, Schweizer L, Bruccoleri RE. SDRS—an algorithm for analyzing large-scale dose-response data. *Bioinformatics*. Oxford University Press; 2011;27: 2921–2923.

Bennett BJ, Farber CR, Orozco L, Kang HM, Ghazalpour A, Siemers N, et al. A high-resolution association mapping panel for the dissection of complex traits in mice. *Genome research*. Cold Spring Harbor Lab; 2010;20: 281–290.

Ji R-R, Silva H de, Jin Y, Bruccoleri RE, Cao J, He A, et al. Transcriptional profiling of the dose response: A more powerful approach for characterizing drug activities. *PLoS computational biology*. Public Library of Science; 2009;5: e1000512.

Ucar D, Neuhaus I, Ross-MacDonald P, Tilford C, Parthasarathy S, Siemers N, et al. Construction of a reference gene association network from multiple profiling data: Application to data analysis. *Bioinformatics*. Oxford University Press; 2007;23: 2716–2724.

Huttenhower C, Flamholz AI, Landis JN, Sahi S, Myers CL, Olszewski KL, et al. Nearest neighbor networks: Clustering expression data based on gene neighborhoods. *BMC bioinformatics*. BioMed Central; 2007;8: 250.

Kerr DE, Vrudhula VM, Svensson HP, Siemers NO, Senter PD. Comparison of recombinant and synthetically formed monoclonal antibody- β -lactamase conjugates for anticancer prodrug activation. *Bioconjugate chemistry*. ACS Publications; 1999;10: 1084–1089.

Siemers NO, Kerr DE, Yarnold S, Stebbins MR, Vrudhula VM, Hellström I, et al. Construction, expression, and activities of I49-sFv- β -lactamase, a single-chain antibody fusion protein for anticancer prodrug activation. *Bioconjugate chemistry*. ACS Publications; 1997;8: 510–519.

Siemers NO, Yelton DE, Bajorath J, Senter PD. Modifying the specificity and activity of the enterobacter cloacae p99 β -lactamase by mutagenesis within an m13 phage vector. *Biochemistry*. ACS Publications; 1996;35: 2104–2111.

McMurry JE, Siemers NO. Periplanone total synthesis via intramolecular pinacol coupling. *Tetrahedron letters*. Elsevier; 1994;35: 4505–4508.

McMurry JE, Siemers NO. On the stereochemistry of the titanium-induced intramolecular pinacol coupling reaction. *Tetrahedron letters*. Elsevier; 1993;34: 7891–7894.

Patents: 16 published US applications, 4 granted ([link](#))

Published Analytics Platforms

FAUXFLOW: ANALYSIS OF SINGLE-CELL RNA-SEQ DATA IN A FLOW-CYTOMETRY PARADIGM

- [Single Cell Melanoma](#) (Tirosh et al.)
- [Single Cell Hepatocellular Carcinoma](#) (Zheng et al.)
- [Single Cell Blood Derived Monocytes and Dendritic Cells](#) (Villani et al.)

CANCER MINING (USING THE R/SHINY FRAMEWORK)

[TCGA-GTEX-TARGET Miner](#)

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HIVEMINER.COM: IMAGE SEARCH

[Flickr Hive Mind](#) This early experiment in internet web services and folksonomy mining, dating from the 2000s, is visited by 13 million people per year.

Professional Associations

Grant Review Panel Member: National Science Foundation; National Genome Research Network (Germany); Network Centres of Excellence Program (Canada)

Manuscript Review: *Bioconjugate Chemistry* and *Bioinformatics*

Member: American Association for Cancer Research, New York Academy of Sciences, American Chemical Society, American Society of Mass Spectroscopy

Selected Awards

Academic: Campbell Scholar (Whitman College); Mattin Research Fellow (Cornell University); United States Department of Education Fellow (Cornell); John James Blackmore Prize (Cornell)

Internal industry awards: US and European regulatory submissions for OPDIVO® (nivolumab); Japan NDA regulatory submission for Farxiga® (dapagliflozin); Metabonomics in Toxicology; Statin (HMG-CoA reductase inhibitor) Pharmacodynamics and Selectivity; Target Validation via Bioinformatics.

Selected Speaking Invitations

Stanford University (Biomedin 206 Course): Informatics in Industry (2018)

University of California – Santa Cruz Department of Biomolecular Engineering: “The interactions of cancer genetics with immune state” (2016)

European Bioinformatics Institute (Industry Programme): “Genome-wide association analysis identifies genetic correlates of immune infiltrates in solid tumors” (2016)

SRI International Bioscience Division: “Immuno-phenotyping of tumors using next-generation sequencing and immune pathway tracers” (2015)

Broad Institute (LINCS consortium): “Systems pharmacology to understand drug mechanism, activity, and resistance” (2013)

George Jackson Academy (elementary/middle school for underserved boys in New York): “Human genetics and your personal genome” (2013)