

BIOGRAPHICAL SKETCH

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NAME: Andrew Stern

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

POSITION TITLE: Director of Novel Therapeutics, University of Pittsburgh Drug Discovery Institute

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
State University of New York at Stony Brook	B.S.	1971	Chemistry
University of California, Los Angeles (UCLA)	Ph.D	1977	Biological Chemistry
Brandeis University	Postdoctoral Fellow	1980	Biochemistry

A. Personal Statement

My primary objective and passion is to determine mechanisms of disease progression and, based on the knowledge gained, identify biomarkers and develop novel therapies. I have a long-standing collaboration with Dr. Taylor, the PI on this UG3/UH3 application entitled "Human Microphysiology Systems Disease Model of Type 2 Diabetes Starting with Liver and Pancreatic Islets". We have developed and implemented a broadly applicable Quantitative Systems Pharmacology (QSP) platform to understand fundamental underpinnings of breast and colon cancer metastasis, Huntington's Disease, and liver diseases. We have extended this QSP approach to Type 2 Diabetes. My goal as Director of Novel Therapeutics of the Drug Discovery Institute of University of Pittsburgh School of Medicine is to provide team-oriented therapeutics-focused scientific leadership to help guide highly collaborative multidisciplinary drug and biomarker discovery teams comprised of experienced professionals, fellows and graduate students. I have experience leading drug discovery teams in both the academic and industrial communities from an early discovery stage through clinical development and approval. Prior to joining the University of Pittsburgh, I served as the Associate Director, Novel Therapeutics at the Broad Institute of Harvard and MIT. I co-led 5 cancer-related projects (please see corresponding publications below), served as a consultant to the Stanley Center for Psychiatric Research and was responsible for designing and implementing several phenotypic screens and animal model studies in conjunction with integrative approaches to target identification. As one example we demonstrated that AURKA kinase was an essential negative regulator of polyploidization in acute megakaryocytic leukemia and through a novel target identification approach have been able to repurpose a clinical candidate for this specific indication. This study inspired the development of the Quantitative Systems Pharmacology approach used in the current proposal. As another example, we developed an extensive pharmacogenomic database involving the Cancer Cell Line Encyclopedia (CCLE) with potential impact for patient stratification that associated activating mutations in beta catenin with sensitivity to navitoclax, a BCL2 family antagonist. In addition I co-led the effort to establish the Broad Institute as a MLPCN Core Screening Center. Before joining the Broad, I spent 17 years in the pharmaceutical industry with Merck and then DuPont/Merck Pharmaceuticals where I served as the Executive Director, Chemical Enzymology. In addition to playing a key role in the discovery, development, and approval of the nonnucleoside reverse transcriptase inhibitor for HIV, Sustiva, my team identified presenilin as the pharmacologic target of gamma-secretase inhibitors that led to clinical candidates for Alzheimer's disease and oncology indication. In addition to experience developing drugs, I led the effort at Merck/DuPont that elucidated the mechanism of drug-induced thrombocytopenia by a class of fibrinogen receptor antagonists. Based upon these studies, we then developed a diagnostic test for predicting those individual patients at risk for developing thrombocytopenia thereby reducing the incidence from 2-5% to <0.1%. I believe my 30 years of experience in drug and biomarker discovery and development, target identification, and physiologically relevant assay design will enable me to help our highly collaborative multidisciplinary team

develop physiologically relevant human models to elucidate mechanisms underlying Type 2 Diabetes to identify biomarkers mechanistically linked to the pathophysiology and inform novel therapeutic strategies

Five references that align with this proposal:

- a. Jia S, Miedel MT, Ngo M, Hassenius R, Chen N, Wang P, Bahreini A, Li Z, Ding Z, Shun TY, Zuckerman DM, Taylor DL, Puhalla SL, Lee AV, Oesterreich S, Stern AM. Clinically Observed Estrogen Receptor Alpha Mutations within the Ligand-Binding Domain Confer Distinguishable Phenotypes. *Oncology* 2018 Jan 6;94(3):176-89. PubMed PMID: 29306943. Epub 2018/01/08.
- b. Spagnolo DM, Al-Kofahi Y, Zhu P, Lezon TR, Gough A, Stern AM, Lee AV, Ginty F, Sarachan B, Taylor DL, Chennubhotla SC. Platform for Quantitative Evaluation of Spatial Intratumoral Heterogeneity in Multiplexed Fluorescence Images. *Cancer research* 2017 Nov 1;77(21):e71-e4. PubMed PMID: 29092944. Pubmed Central PMCID: PMC5683175. Epub 2017/11/03.
- c. Gough A, Stern AM, Maier J, Lezon T, Shun TY, Chennubhotla C, Schurdak ME, Haney SA, Taylor DL. Biologically Relevant Heterogeneity: Metrics and Practical Insights. *SLAS discovery: advancing life sciences R & D* 2017 Mar;22(3):213-37. PubMed PMID: 28231035. Pubmed Central PMCID: PMC5464733. Epub 2017/02/24.
- d. Wen Q, Goldenson B, Silver SJ, Schenone M, Dancik V, Zan Huang, Wang L-Z, Lewis TA, An WF, Xiaoyu L, Bray M-A, Thiollier C, Diebold L, Vokes MS, Moore CB, Bliss-Moreau M, VerPlank L, Tolliday NJ, Mishra R, Vemula S, Shi J, Wei L, Kapur R, Lopez C, Gerby B, Ballerini P, Pflumio F, Gilliland GD, Goldberg L, Birger Y, Izraeli S, Gamis AS, Smith FO, Woods WG, Scherer CA, Bradner J, Goh B-C, Mercher T, Carpenter AE, Gould RJ, Clemons PA, Carr SA, Root DA, Schreiber SL, Stern AM, Crispino JD. Identification of regulators of polyploidization presents therapeutic targets for treatment of AMKL. *Cell*. 2012 Aug 3;150(3):575-89. PMID: 22863010; PMCID: PMC3613864.
- e. Basu Amrita, Bodycombe NE, Cheah JH, Price EV, Liu K, Schaefer GI, Ebright RY, Stewart ML, Ito D, Wang S, Bracha AL, Liefeld T, Wawer M, Gilbert JC, Wilson AJ, Stransky N, Kryukov GV, Dancik V, Barretina J, Garraway LA, Hon CSY, Munoz B, Bittker JA, Stockwell BR, Khabele D, Stern AM, Clemons PA, Shamji AF, Schreiber SL. An interactive resource to identify cancer genetic and lineage dependencies targeted by small molecules. *Cell*. 2013 Aug 29;154(5): 1151-61. PMID: 23993102; PMCID: PMC3954635.

B. Positions and Honors

Positions and Employment

1981 – 1983	Research Associate, Graduate Department of Biochemistry, Brandeis University, Waltham, MA
1984 – 1985	Instructor and Assistant, Massachusetts General Hospital, Endocrine Unit, Harvard Medical School, Boston, MA
1986 – 1990	Research Fellow, Merck Research Laboratories, West Point, PA
1990 – 1996	Senior Research Fellow, Merck Research Laboratories, West Point, PA
1997 – 1998	Director, Chemical Enzymology, DuPont Merck Pharmaceuticals Company
1998 – 2000	Senior Director, Chemical Enzymology, DuPont Pharmaceuticals Company
2000 – 2001	Executive Director, Chemical Enzymology, DuPont Pharmaceuticals Company
2002	Group Director, Chemical Enzymology, Bristol-Myers Squibb Company/ DuPont Pharmaceuticals Company
2003 – 2004	Vice President, Molecular and Cell Biology, Infinity Pharmaceuticals, Inc., Cambridge, MA
2005 – 2007	Vice President, Biology, Ensemble Discovery Corporation, Cambridge, MA
2007 – 2012	Associate Director, Novel Therapeutics, Broad Institute of Harvard and MIT, Cambridge, MA
2012 – present	Associate Professor, Drug Discovery Institute, University of Pittsburgh, Pittsburgh, PA
2012 – present	Director of Novel Therapeutics, Drug Discovery Institute, University of Pittsburgh, Pittsburgh, PA

Other Experience and Professional Memberships

Honors

1970	Queens General Hospital Volunteer's Distinguished Service Award
1967 – 1971	New York State Regents Scholarship

1971 – 1972	Chancellor's Fellowship, University of California at Los Angeles
1977 – 1980	NRSA Individual Postdoctoral Fellowship, National Cancer Institute
1982 – 1984	Leukemia Society of America Fellow
1991	Merck Research Management Council Award (for key contributions leading to the development of non-nucleoside HIV-1 reverse transcriptase inhibitors)
1999	Summit Award, DuPont Pharmaceuticals Company (for elucidating the mechanism of roxifiban-induced thrombocytopenia and developing an assay to identify patients at risk)

C. Contribution to Science

1. Discovery and development of Sustiva (Efavirenz), nonnucleoside HIV-1 reverse transcriptase inhibitor: As a Research Fellow at Merck, played a key role in the discovery of a novel class of HIV-1 reverse transcriptase inhibitors that served as the progenitor to Sustiva, an essential medicine (WHO) for the treatment of HIV-1 infected patients. As a mainstay in highly active antiretroviral therapy (HAART) for more than 10 years, Sustiva has helped transform a fatal disease into a manageable disease saving > 1 million lives. Received the Merck Research Management Council Award for conducting critical mechanistic studies and for scientific insights leading to the development of this class of drugs.

- a. Goldman ME, Nunberg JH, O'Brien JA, Quintero JC, Schleif WA, Freund KF, Gaul SL, Saari WS, Wai JS, Hoffman JM, Anderson PS, Hupe DJ, Emini EA, Stern AM. Pyridinone derivatives: specific human immunodeficiency virus type 1 reverse transcriptase inhibitors with antiviral activity. *Proc Natl Acad Sci USA*. 1991 Aug 1;88(15):6863-7. PMID: 1713693; PMCID: PMC52189.
- b. Saari WS, Hoffman JM, Wai JS, Fisher TE, Rooney CS, Smith AM, Thomas CM, Goldman ME, O'Brien JA, Nunberg JH, Uintero JC, Schleif WA, Emini EA, Stern AM, Anderson PS. 2-Pyridone derivatives: a new class of nonnucleoside, HIV-1-specific reverse transcriptase inhibitors. *J Med Chem*. 1991 Sep;34(9):2922-5. PMID: 1716683.
- c. Stern AM. The development of human immunodeficiency virus type 1 reverse transcriptase inhibitors. In *Chemical and Structural Approaches to Rational Drug Design* (Chapter 2), Ed. W. Williams, D. Weiner CRC Press. 1994.

2. Identification of a novel differentiation therapy for acute megakaryoblastic leukemia (AMKL), a rare and fatal disease: As the Associate Director of Novel Therapeutics at the Broad Institute and in collaboration with Professor John Crispino from Northwestern University School of Medicine, we devised a strategy to identify small molecules that could enable AMKL blasts to bypass the blockade that would ordinarily prevent them from exiting a highly proliferative cycle and thus induce their differentiation. This strategy involved the development of a phenotypic screen and a novel multi-pronged target identification platform involving chemical proteomics and RNAi screening. Our studies identified AURKA both as a negative regulator of differentiation specific to the megakaryocyte lineage, and as a unique targetable dependency for AMKL blasts. Identifying this mechanism with an intrinsically high therapeutic index enabled the repurposing of Alisertib already in clinical trials for another indication. Clinical trial for AMKL patients is ongoing and if successful will provide these patients with their only therapeutic option.

- a. Wen Q, Goldenson B, Silver SJ, Schenone M, Dancik V, Zan Huang, Wang L-Z, Lewis TA, An WF, Xiaoyu L, Bray M-A, Thiollier C, Diebold L, Vokes MS, Moore CB, Bliss-Moreau M, VerPlank L, Tolliday NJ, Mishra R, Vemula S, Shi J, Wei L, Kapur R, Lopez C, Gerby B, Ballerini P, Pflumio F, Gilliland GD, Goldberg L, Birger Y, Izraeli S, Gamis AS, Smith FO, Woods WG, Scherer CA, Bradner J, Goh B-C, Mercher T, Carpenter AE, Gould RJ, Clemons PA, Carr SA, Root DA, Schreiber SL, Stern AM, Crispino JD. Identification of regulators of polyploidization presents therapeutic targets for treatment of AMKL. *Cell*. 2012 Aug 3;150(3):575-89. PMID: 22863010; PMCID: PMC3613864.

3. Determined the mechanism of drug-induced thrombocytopenia and designed and implemented a test to identify those patients at risk for developing thrombocytopenia while taking oral fibrinogen receptor antagonists: As the Executive Director of Chemical Enzymology, DuPont-Merck Pharmaceuticals Company, led a multidisciplinary team focused on determining the mechanism of thrombocytopenia that prevented the initiation of a Phase III clinical trial with the oral fibrinogen receptor antagonist, Roxifiban, for a peripheral

arterial disease indication. We determined that the drug induced a conformational change to the fibrinogen receptor exposing a neo-epitope that in ~3% of patients elicited an immune reaction resulting in antibody-mediated rapid clearance of platelets. Using patient samples, we were able to recapitulate in vitro the critical step in the mechanism: antibody binding to the fibrinogen receptor only in the presence of drug and accordingly we were able to develop an ELISA to identify those patients at risk. The Phase III drug trial was initiated in conjunction with the test. The test proved successful reducing the incidence 10-fold in this prospective study. In recognition of this work my colleagues and I received the DuPont Pharmaceuticals Company Summit Award for these studies that represented an early example of personalized medicine and the co-development of a drug and companion diagnostic.

- a. Billheimer JT, Dicker IB, Wynn R, Bradley JD, Cromley DA, Godonis HE, Grimminger LC, He B, Kieras CJ, Pedicord DL, Spitz SM, Thomas BE, Zolotarjova NI, Gorko MA, Hollis GF, Daly RN, Stern AM, Seiffert DA. Evidence that thrombocytopenia observed in humans treated with orally bioavailable glycoprotein IIb/IIIa antagonists is immune mediated. *Blood*. 2002 May 15; 99(10):3540-6. PMID: 11986205.
- b. Seiffert D, Stern AM, Ebling W, Rossi RJ, Barrett YC, Wynn R, Hollis GF, He B, Kieras CJ, Pedicord DL, Cromley DA, Hua TA, Stein RB, Daly RN, Sferruzza A, Pieniaszek HJ, Billheimer JT. Prospective testing for drug-dependent antibodies reduces the incidence of thrombocytopenia observed with the small molecule glycoprotein IIb/IIIa antagonist Roxifiban: implications for the etiology of thrombocytopenia. *Blood*. 2003 Jan 1;101(1):58-63. PMID: 12393571.

4. Identification of Presenilin-1 and 2 as the pharmacologic targets of gamma secretase inhibitors: As the Executive Director of Chemical Enzymology, DuPont-Merck Pharmaceuticals Company, led a multidisciplinary team focused on determining the pharmacologic targets of gamma secretase inhibition. This was an important part of our efforts to develop gamma secretase inhibitors initially for an Alzheimer's Disease indication and subsequently for oncology indications. My contribution was to devise the research strategy based on photoaffinity labeling and, in conjunction, the use of a set of competitive ligands with a known structure activity relationship to define the specific labeling of protein bands on a gel. These results contributed to the development of three gamma secretase inhibitors that entered clinical trials and also addressed a fundamental biomedical research question mechanistically linking presenilin with beta amyloid precursor and Notch processing.

- a. Seiffert D, Bradley JD, Rominger CM, Rominger DH, Yang F, Meredith Jr. JE, Wang Q, Roach AH, Thompson LA, Spitz SM, Higaki JN, Prakash SR, Combs AP, Copeland RA, Arneric SP, Hartig PR, Robertson DW, Cordell B, Stern AM, Olson RE, Zaczek R. Presenilin-1 and -2 are molecular targets for γ -secretase inhibitors. *J Biol Chem*. 2000 Nov 3;275(44):34086-91. PMID: 10915801.

5. Discovery of chemical nucleases: Working with David Sigman, I sought to understand the catalytic role of the putative Zn⁺⁺ in DNA polymerases. Contrary to the published literature my work showed no evidence for a role of Zn⁺⁺ in DNA polymerases but demonstrated that the heavy metal chelating agent, orthophenanthroline, inhibited DNA polymerases by interacting directly with the template-primer (not the polymerase) and in the presence of adventitious copper ion and reducing agent rapidly cleaved DNA through a Fenton-like reaction. The resulting DNA cleavage products were, in turn, potent binders and competitive inhibitors of the polymerase. These studies were seminal in the emerging field of chemical biology paving the way for the development of chemical nucleases and understanding mechanistic details of bleomycin mode-of-action.

- a. Sigman DS, Graham SR, D'Aurora V, Stern AM. Oxygen-dependent cleavage of DNA by the 1,10-phenanthroline-cuprous complex. Inhibition of *E. coli* DNA polymerase 1. *J Biol Chem*. 1979 Dec 25;254(24):12269-72. PMID: 387784.

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1fG71nOfKbxkd/bibliography/48062884/public/?sort=date&direction=descending>

D. Research Support

Ongoing Research Support

SAP#4100068731

Stern (PI)

01/01/2015-12/31/2018

PA Department of Health

Determining mechanisms of disease progression using Quantitative Systems Pharmacology (QSP)

A major goal is to demonstrate the broad applicability of QSP; accordingly, we aim to determine the value of QSP to enable the development of novel therapeutic strategies in a set of diverse diseases.

Role: Principal Investigator

Completed Research Support

Internal Funding

Stern (PI)

01/01/2014 – 12/31/2014

University of Pittsburgh Brain Institute

QSP Approach to Huntington's Disease

The goal of the project is to complete a comprehensive molecular and cellular characterization of Huntington's

Disease progression and selective neuronal cell vulnerability and determine the critical steps mechanistically linked to disease progression and identify and validate small molecule probes to their respective targets that alone and in combination may block disease progression.

Role: Principal Investigator

Internal Funding

Stern (PI)

06/01/2013 – 9/30/2014

UPMC/UPCI

Identification small-molecules that selectively kill HPV-associated tumor cells

Implement a cost-effective screening strategy to identify known drugs or small molecules that selectively kill HPV-dependent tumor cells; confirm mode-of-action and determine in vivo efficacy of prioritized compounds; use the data generated to support a grant proposal focused upon identifying novel compounds that selectively kill HPV(16)+ dependent tumors.

Role: Principal Investigator