BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
James A. Wells	Professor
eRA COMMONS USER NAME	
JAMESAWELLS	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of California, Berkeley, CA	B.A.	1973	Biochemistry
Washington State University	Ph.D.	1979	Biochemistry
Washington State University	Postdoc	1979-1980	Chemistry
Stanford University Medical School	Postdoc	1980-1982	Biochemistry

A. Personal Statement

I am committed to fundamental mechanistic studies and technologies that can impact human health. I began my independent research career as a scientist at Genentech and a founding member of the Protein Engineering Department. We performed some of the first gain-of-function engineering experiments initially on a simple bacterial serine protease, subtilisin. Through structure-guided and selection-based screens, we were able to redesign the enzyme specificity, catalytic mechanism, and stability to heat, pH and oxidants. We next probed the receptor-binding mechanism of human growth hormone to discover how human growth hormone oligomerizes and activates the receptor, a paradigm for cytokine signaling. Using this information, we built receptor-selective hormone variants and antagonists that prevent effects of excess growth hormone in acromegalics. We developed a variety of technologies to facilitate the engineering of proteins such as cassette mutagenesis, alanine-scanning mutagenesis, and protein phage display. In 1998, I co-founded a company, Sunesis Pharmaceuticals, and developed a novel fragment-based discovery platform called Tethering, which we applied to ~30 different protein targets, including those that impact caspases. I managed a research group that supported numerous drug discovery programs and several that reached clinical stage.

Since joining UCSF in 2005, my lab has focused on developing engineered enzymes and small molecules to interrogate signaling pathways that drive regulated cell death. We study the activation mechanism and allostery of caspases, which are proteases that act as molecular demolition experts to dismantle the cell. We have developed a novel technology to study proteolysis in cells through N-terminal tagging using an enzyme called subtiligase that my group has engineered. Through this proteomics technology, we have identified some 1700 caspase targets, their rates of cleavage, and the cellular pathways that they impact. We have designed a small molecule activated protease called the SNIPer to cut and dissect the phenotypic consequences of individual targets. Recently, we have developed a catalytic tagging device called the NEDDylator to interrogate molecular binding partners in cellular pathways involving E3 ligases. We have discovered small molecules that allosterically activate kinases or inhibit caspases, using a site-directed fragment discovery approach called Tethering that my group has developed. I also founded the Small Molecule Discovery Center, which aids UCSF investigators in discovering chemical matter for biological targets or phenotypes of interest.

B. Positions and Honors

Positions & Employment

1982-1986 Scientist, Genentech, Inc., Dept. of Protein Engineering
1986-1989 Senior Scientist, Genentech, Inc., Dept. of Protein Engineering
1989-1998 Staff Scientist, Genentech, Inc., Dept. of Protein Engineering
1988-2005 Adjunct Assistant, Associate, and Full Professor, Dept of Pharmaceutical Chemistry, UCSF
1998-2005 President and Chief Scientific Officer, Sunesis Pharmaceuticals
2005-present Harry Wm. and Diana V. Hind Professor in Pharmaceutical Sciences, UCSF
2005-present Director, Small Molecule Discovery Center, UCSF
2008-present Chair, Dept of Pharmaceutical Chemistry, UCSF

Other Experience and Professional Memberships (Selected)

1994-2003	Organizer or Co-organizer of various scientific meetings (e.g., 2003 Keystone Drug Discovery Meeting; 2000 Protein Society meeting, 1999 ASBMB meeting, 1994 Peptides in Biology GRC)
1989-present	Editorial Board service on scientific journals (Proteins, Protein Engineering, Protein Science, Chemistry & Biology, Journal Molecular Biology, Trends in Biotechnology, PNAS)
1994-1998	Member of the Executive Council of Protein Society
2005-2007	Chair of NIH study section on Molecular Libraries Screening Centers Network (MLSCN)
2005-present	Member of the Executive Committee for QB3 at UCSF
2007-2010	Member of the Executive Council of ASBMB
2011-present	NIH Board of Scientific Counselors, Basic Science, NCI

Selected Honors

1979-1981	Damon M. Runyon - Walter Winchell Postdoctoral Fellowship
1990	Pfizer Award given by the American Chemical Society for achievements in enzyme chemistry
1998	Christian B. Anfinson Award presented by the Protein Society
1998	Vincent du Vignead Award given by the American Peptide Society
1999	Elected Member to the National Academy of Sciences
2003	Hans Neurath Award given by the Protein Society
2006	Perlman Lecture Award of the ACS Biotechnology Division
2006	Paul Janssen Prize in Adv. Biotech and Medicine
2007	Fred Richards Distinguished Lecture, Yale University
2008	Jane Darnell Distinguished Lecture, Rockefeller University
2009	Kossiakoff Lecture in Biophysics, Johns Hopkins University
2009	Herman S. Bloch Award given by the University of Chicago "for scientific excellence in industry"
2009	Weinhouse Lecture in Biochemistry, Thomas Jefferson University
2010	ASBMB Merck Award
2011	Smissman Award in Medicinal Chemistry given by the American Chemical Society
2011	Ada Doisy Lecture, University of Illinois
2011	Cori Lecture, Washington University in St. Louis
2011	Green Lecture, University of Wisconsin, Madison
2011	Burkholder Award Lecture, St Luke's, Boise ID
2012	Lubomir S. Hnilica Endowed Lecture, Vanderbilt University
2012	Gordon Lecture, University of Washington
2012	Keynote at Gladstone Scientific Retreat, San Francisco, CA

C. Selected publications (from a total of 162)

32. Cunningham, B.C. and Wells, J.A., (1989) *Science* 244, 1081-1085. "High-resolution epitope mapping of hGH-receptor interactions by alanine-scanning mutagenesis". PMID: 2471267
55. Fuh, G. Cunningham, B.C., Fukunaga, R., Nagata, S., Goeddel, D.V., and Wells, J.A. (1992) Science, 256, 1677-1680. "Rational Design of Potent Antagonists to the Human Growth Hormone Receptor". PMID: 1535167
62. Lowman, H.B. and Wells, J.A. (1993) J. Mol. Biol. 234, 564-578 "Affinity Maturation of Human Growth Hormone by Monovalent Phage Display". PMID: 8254660
75. Jackson, D.Y., Burnier, J., Quan, C., Stanley, M., Tom, J. and Wells, J.A. (1994) Science 266, 243-247. "A Designed Peptide Ligase for Total Synthesis of Ribonuclease A with Unnatural Catalytic Residues." PMID: 7939659
81. Clackson, T. and Wells, J.A. (1995) Science 267, 383-386. "A Hot Spot of Binding Energy in a Hormone-Receptor Interface". PMID: 7529940
104. Atwell, S., Ultsch, M., De Vos, A.M. and Wells, J.A. (1997) Science 278, 1124-1127 "Structural Plasticity in a Remodeled Protein-Protein Interface" PMID: 9353194
136. Thanos, C.T., Delano, W.D. and Wells, J.A. (2006) Proc. Natl. Acad. Sci. USA 103, 15422-15427. "Hot spot Mimicry of a Cytokine Receptor by a Small Molecule" (Covered in Nature (2006) 443,886 Research Highlights; also selected for coverage in Faculty of 1000 Biology: http://www.f1000biology.com/article/id/1097485/evaluation) PMCID: PMC1592646

140. Mahrus, M., Trinidad, J.C, Barkan, D.T., Sali, A., Burlingame, A.L., & Wells, J.A. (2008) Cell, 134, 866-876. “Global Sequencing of Proteolytic Cleavage Sites in Apoptosis by Specific Labeling of Protein N Termini”. PMCID: PMC2566540.
142. Wolan, D., Zorn, J., Gray, D. & Wells, J.A. (2009) Science 326, 853-858. “Small-molecule activators of a proenzyme”. PMCID: 2886848
148. Gray, D., Mahrus, S. & Wells, J.A. (2010) Cell 142, 637-646. “Activation of specific apoptotic caspases with an engineered small-molecule-activated protease”. PMID: 20723762
151. Sadowsky, J., Burlingame, M., Wolan, D., McClendon, C., Jacobson, M., & Wells, J.A. (2011) Proc. Natl. Acad. Sci. USA. Apr 12; 108(15): 6056-61. "Turning a protein kinase (PDK1) on or off from a single allosteric site via disulfide trapping". PMCID: PMC3076885153.
154. Agard, N.J., Mahrus, S., Trinidad, J.C., Lynn, A., Burlingame, A.L., & Wells, J.A. (2012) Proc Natl Acad Sci U S A. 109:1913-8. “Global kinetic analysis of proteolysis via quantitative targeted proteomics”. PMCID: PMC3277568
155. Shimbo K., Hsu G.W., Nguyen H., Mahrus S., Trinidad J.C., Burlingame A.L., and Wells J.A. (2012) Proc Natl Acad Sci U S A. 109:12432-7. "Quantitative profiling of caspase-cleaved substrates reveals different drug-induced and cell-type patterns in apoptosis" PMCID: PMC3412033
160. Zhuang, M., Guan, S., Wang, H., Burlingame, A.L., Wells, J.A. (2012) Mol Cell. 2012 Nov 28 [Epub ahead of print]. “Substrates of IAP ubiquitin ligases identified with a designed orthogonal E3 ligase, the NEDDylator”. PMID: 23201124
161. Crawford E.D., Seaman J.E., Agard N., Hsu G.W., Julien O., Mahrus S., Nguyen H., Shimbo K., Yoshihara H., Zhuang M., Chalkley R.J., Wells J.A. (2012) Mol. Cell. Proteomics. 2012 Dec 20 [Epub ahead of print]. "DegraBase: A Human α-aminome database" Mol. Cell. Proteomics". PMID: 23264352

D. Research Support (past 3 years)

Wells Laboratory Ongoing Research

R01 NIH/NIAID 3/1/07 – 2/28/13
“Site-specific Allosteric Inhibitors for Inflammatory Caspases”: The major goal of this project is to characterize the allosteric circuitry of inflammatory caspases and to develop selective small molecule allosteric inhibitors to probe the roles of these caspases in cellular inflammation.”
Role: Principal Investigator

R01 NIH/NIGMS 4/1/07 - 7/31/16
“Global analysis of Proteolysis in Apoptosis”: The long-term goal of the proposed work is to elucidate the process leading to programmed cell death by applying a new and general method we have developed for global proteomic profiling of proteolysis (“degradomics”).
Role: Principal Investigator

R01 NIH/NCI 12/5/08 - 11/30/13
“Direct Chemical Activators of Caspases”: The long-term goal of this proposal is to gain a fundamental understanding of the terminal process in cell death mediated by executioner caspases-3, -6, and -7.
Role: Principal Investigator

R01 NIH/NCI 2/1/11 – 1/31/15
“Approaches to discover and quantify apoptotic biomarkers for cancer treatment”: The long-term goal is to develop a novel, rapid, quantitative platform to monitor the proteolytic activity associated with apoptosis in patients undergoing chemotherapy for hematologic malignancies.
Role: Principal Investigator

R01 NIH/NIGMS 9/20/11 – 6/30/15
“Regulating proteolysis to dissect apoptosis”: The long-term goal of this project is to understand the role of specific caspase cleavage events in driving apoptosis. The immediate goal is to induce site-specific proteolysis of central nodes in the apoptotic web one target at a time.
Role: Principal Investigator

Wells Laboratory Completed Research

Individual Biomedical Research Award Hartwell Foundation 5/1/07 – 4/30/10
“Novel Drug Targets for Leukemias” : The major goals of this project are to use global profiling of proteolysis in a leukemia cell line and RNAi analysis to identify and validate new drug targets.
Role: Principal Investigator

Rogers Research Award Rogers Foundation 1/1/08 – 12/30/10
“Apoptotic Biomarkers for Hematologic Cancers”: The goal is to develop apoptotic biomarkers for hematologic cancers.

Role: Principal Investigator

R01-S1 NIH/NIGMS 9/1/10 – 8/31/11

"Global Analysis of Proteolysis in Apoptosis": Administrative Supplement for R01 GM081051 (see above)

Role: Principal Investigator

Small Molecule Discovery Center (SMDC, a core facility for which Jim Wells is director) Ongoing Research

P01 (Prusiner, Wells, Renslo) NIH/NIA 4/1/09 – 3/31/14

"Novel Therapeutics for Prion Diseases": Subproject involving medicinal chemistry to advance anti-prion compounds identified in screening at the SMDC.

Role: Principal Investigator on subproject

Collaborative Innovation Award (Peter Walter) HHMI 3/1/09 – 2/28/13

"Deciphering the Role of the Unfolded Protein Response in Disease": Subproject involving cell-based and biochemical high-throughput screening for each branch of the unfolded protein response.

Role: Principal Investigator on subproject

29XS133TO13 (Wells, Arkin) Chemical Biology Consortium/NCI/SAIC-F 4/1/11 - 3/31/13

"Optimization of Lead Small Molecule Inhibitors of Taspase1": The goal of this project is to develop validated pharmacodynamically optimized small molecules that selectively inhibit the threonine protease Taspase1. The iterative process of chemistry optimization and biological testing will lead to the discovery and validation of lead series ready for further development in the hit-to-candidate pipeline.

Role: Co- Principal Investigator

29XS133TO15 (Wells, Arkin) Chemical Biology Consortium/NCI/SAIC-F 4/1/11 – 3/31/13

"Development of Small Molecule Inhibitors of the AAA ATPase p97: The goal of this project is the development of small molecule inhibitors of the AAA ATPase p97. The SMDC will develop biophysical methods for hit characterization and lead validation.

Role: Co-Principal Investigator

U54 (Kossiakoff, Wells, Sidhu) NIH 9/26/11-8/31/16

Recombinant Antibody Network (RAN): Production of Affinity Reagents for Human Transcription Factors The RAN will be a consortium of three recombinant antibody production centers at UChicago, UToronto and UCSF. All three will contribute to generating antibodies to the ~1500 existing human transcription factors.

Role: Co-Principal Investigator

1S10 (Wells) NIH 5/15/12-5/14/13

"Automated System for High-Throughput In Vitro Selection of Recombinant Antibodies"

The high throughput automation for which we are requesting funds will be used for the *in vitro* selection and characterization of recombinant antibodies. The antibodies will be selected for affinity and specificity to serve as biological probes, biomarkers and potential therapeutics.

SMDC Completed Research

Sandler New Technologies Award Sandler Program in Basic Sciences 4/1/08 – 4/14/10

"Fragment-based Discovery Technology for Small Molecule Discovery": The goal is to establish fragment discovery at the SMDC.

Role: Principal Investigator

Promise Grant Susan G. Komen for the Cure Foundation 12/22/08 – 12/21/10

"An Integrated Approach Towards the Eradication of HER2-driven Breast Cancer": Subproject involving screening to identify small molecule inhibitors of HER2-HER3 dimerization being done at the SMDC.

Role: Co-Principal Investigator

ARRA GO Grant NIH/NIAMS 9/25/09 – 8/31/11

"An Allosteric Inhibitor of ZAP-70 as a Novel Therapeutic for Autoimmune Disease": Subproject involving screening in the SMDC for inhibitors of ZAP-70.

Role: Co-Principal Investigator

Drug Discovery Research Collaboration Genentech, Inc. 1/1/10 – 1/20/12

This collaboration with the SMDC involves small-molecule discovery and development for an undisclosed target implicated in neurodegenerative disease.

Role: Co-Principal Investigator