BIOGRAPHICAL SKETCH

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NAME: Wasmuth, Elizabeth V.

eRA COMMONS USER NAME: WASMUTHE

POSITION TITLE: Research Scholar, Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Cornell University, Ithaca, NY	B.S.	12/2006	Animal Science; Development Sociology
Gerstner Sloan Kettering Graduate School of Biomedical Sciences, New York, NY	Ph.D.	3/2016	Structural biology; biochemistry
Memorial Sloan Kettering Cancer Center/The Rockefeller University, New York, NY	Postdoctoral	3/2016-Ongoing	Cancer biology; Structural biology

A. Personal Statement

My long-term career goal is to run an independent research laboratory that focuses on the basic mechanism of nucleic acid bindings proteins and their regulation in disease from the dual lens of a structural and cancer biologist. As an undergraduate Animal Science major, I appreciated the value in studying biology from the standpoint of an intact organism. However, a summer undergraduate internship in the laboratory of Dr. Mair Churchill, an x-ray crystallographer studying transcription factor biology at the University of Colorado Health Sciences Center, taught me to value biological phenomena on the molecular level. At that point, I realized that tackling important biological questions required a multidisciplinary approach. I saw there was a dearth of investigators who could couple structural understanding with human malignancies, due to the limited crosstalk between basic and translational scientists. At that point, I set up a training plan to fill this underrepresented niche. I subsequently spent a year at the NIH working in a genetics lab, then chose the Sloan Kettering for its diverse graduate training program, exposing students to principles of molecular biology to clinical trials. My broader perspective greatly enabled my productivity during my PhD as I dissected the function of the large multisubunit exoribonuclease complex, the RNA exosome, from structural, biochemical, and genetic angles in the laboratory of Dr. Chris Lima. I then chose Dr. Charles Sawyers as my post-doctoral mentor, a world expert in cancer biology known for his development of two targeted therapies and use of multidisciplinary and collaborative approaches. As a post-doc in the Sawyers lab, I am at the nexus between biochemistry, structural and cancer biology, and have developed into a scientist uniquely equipped to think about long-standing problems in androgen receptor (AR) biology, with relevance to normal prostate biology, cancer and other diseases. I have focused on two distinct angles of AR regulation: 1) intra- and intermolecular modulation of AR activity through biochemical and structural approaches, and 2) uncovering a novel role for loss-of-function alterations of the RNA exosome subunit, DIS3, in AR activation. My structural background has also allowed me to uniquely contribute to several colleagues' projects. The skillsets I am developing in the Sawyers lab will allow me to accomplish my career goal of running a successful and collaborative academic research group.

B. Positions and Honors

Positions and Employment

2006 Summer Undergraduate Research Fellow, Dr. Mair Churchill laboratory, Department of Pharmacology, University of Colorado Health Sciences Center (Aurora, CO)

2007 Research technician, Dr. Xingen Lei laboratory, Department of Animal Science, Cornell University (Ithaca, NY)

2007-2008 Post-baccalaureate Intramural Research Training Award Fellow, Dr. Forbes Porter laboratory, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (Bethesda, MD)

Other Experience

2008-2014 Cornell Alumni Admissions Ambassador Network
2011-2016 McNair Academic High School, Jersey City, alumni/science outreach

Honors

2010-2015 Ruth Kirschstein NRSA F31 Diversity Recipient (F31 GM097910)
2012 Selected talk, FASEB Post-Transcriptional Control of Gene Expression: mRNA Decay Conference
2013 Selected talk, 18th Annual Meeting of the RNA Society
2013 Selected talk, New York Structural Biology Discussion Group
2014 NSMB Poster Prize in Biophysics & Structural Biology, 19th Annual Meeting of the RNA Society
2014 Invited speaker, MUSC MCBP External Seminar Series, Charleston, SC
2014 Selected course participant, Cold Spring Harbor Laboratory X-ray Methods in Structural Biology
2015 Louis V. Gerstner Chairman's Prize Recipient
2018-2020 Department of Defense Early Investigator Research Award Recipient - "Structural and functional studies of the androgen receptor and its cofactors"
2019 Poster Prize, Geoffrey Beene Retreat Cancer Research Center Annual Retreat

C. Contributions to Science

1. Early career

While a research technician in the lab of Dr. Xingen Lei at Cornell University (January 2007 - July 2007), I assisted a master's student in completing his thesis work by designing experiments to assay transcriptional and protein alterations within the guts of anemic pigs as a result of dietary supplementation of the prebiotic, inulin. This work found that our observed increase in iron bioavailability was likely a consequence of suppressing genes associated with inflammation and increasing those related to iron storage and sequestration. Subsequent studies suggest inulin alters the gut microenvironment, which may be the basis for the increased iron bioavailability and nutrient absorption observed previously. Inulin is now a component of golden rice, a crop variant designed to feed malnourished populations in developing countries.

a) Yasuda K, Dawson HD, **Wasmuth EV**, Roneker CA, Chen C, Urban JF, Welch RM, Miller DD, Lei XG. Supplementary dietary inulin influences expression of iron and inflammation related genes in young pigs. *Journal of Nutrition*. 2009 Nov; 139 (11): 2018-23. PMCID: 19776179.

As a post-baccalaureate IRTA at the NIH (July 2007 – July 2008), I worked in the lab of physician-scientist, Dr. Forbes Porter who studies Smith-Lemli-Opitz syndrome (SLOS), an inborn genetic disorder of cholesterol biosynthesis. Treatment typically involves postnatal cholesterol supplementation, which does not address developmental abnormalities. My project focused on studying promoter effects and cellular localization of DHCR7 mutants in SLOS- and WT-derived human fibroblasts, and the transcriptional hallmarks of SLOS and a similar disorder of cholesterol biosynthesis, lathosterolosis. I also contributed to a study that identified the ABCA1 transporter in mice as a potential in utero target to upregulate maternal cholesterol transport to developing fetuses, and provided evidence that alteration of placental cholesterol transport may be a viable strategy for in utero therapy for SLOS. Maternal ABCA1 status has subsequently been shown to significantly correlate with SLOS severity in humans.

b) Lindegaard ML, Wassif CA, Vaisman B, Amar M, **Wasmuth EV**, Shamburek R, Nielsen LB, Remaley AT, Porter FD. Characterization of placental cholesterol transport: ABCA1 is a potential target for *in utero* therapy of Smith-Lemli-Opitz syndrome. *Human Molecular Genetics*. 2008 Dec 1; 17(23):3806-13. PMCID: 18775956.

2. Structural and functional characterization of Dis3/Rrp44- and Rrp6-containing exosomes

During my PhD, I studied biochemical, structural and genetic mechanisms of RNA decay by the eukaryotic RNA exosome, the major 3' to 5' exoribonuclease activity that processes and degrades virtually every class of RNA. The exosome is composed of an essential non-catalytic core of 9 distinct subunits (Exo9) and associates with two ribonucleases - Rrp44 (Dis3) in the cytoplasm and nucleus, and Rrp6 in the nucleus and nucleolus. At the start of my PhD, little was known about the mechanism of RNA decay by the RNA exosome, or if its

activities were coordinated. Wasmuth and Lima, *Mol Cell*, 2012 is the first example of rigorous biochemical analyses of the exosome – specifically, that the catalytically inert 9-subunit core (Exo9) allosterically modulated the activities of Rrp44 and Rrp6; that Rrp6 enhanced Rrp44 activity in a Exo9-dependent fashion; and that both enzymes' activities were somehow dependent on the conserved Exo9 central channel. Finally, experiments in yeast confirmed channel essentiality. I later designed the crystallization strategy and established the biochemical assay that identified the RNA exosome's alternative channel-independent, "direct access" path to Rrp44, which is utilized to degrade structured RNAs and those too short to span the Exo9 central channel (Zinder et al, *Mol Cell*, 2016). Finally, I structurally and biochemically reconciled how the nuclear protein cofactors of the exosome, Mpp6 and Rrp47, cooperatively stimulate the Rrp6 and/or Dis3 ribonuclease activities of the nuclear exosome via association with Rrp6 through partially overlapping yet distinct mechanisms, and how these cofactors recruit the essential RNA helicase, Mtr4 (Wasmuth et al., *eLife*, 2017).

a. **Wasmuth EV**, Lima CD. The exo- and endoribonucleolytic activities of yeast cytoplasmic and nuclear RNA exosomes are dependent on the non-catalytic core and central channel. *Molecular Cell.* 2012 Oct 12; 48(1):133-44. PMCID: 22902556.
b. **Wasmuth EV**, Lima CD. Structure and activities of the eukaryotic RNA exosome. *The Enzymes – Eukaryotic RNases and their Partners in RNA Degradation and Biogenesis.* 2012; 31:53-75. PMCID: 27166440.
c. Zinder JC, **Wasmuth EV**, Lima CD. Nuclear RNA exosome at 3.1 Å reveals substrate specificities, RNA paths, and allosteric inhibition of Rrp44. *Molecular Cell*. 2016 Nov 17; 64(4):734-45. PMCID: 27818140.
d. **Wasmuth EV**, Zinder JC, Zattas D, Das M, Lima CD. Structure and reconstitution of yeast Mpp6-nuclear exosome complexes reveals that Mpp6 stimulates RNA decay and recruits the Mtr4 helicase. *eLife*. 2017 Jul 25;6. pii: e29062. PMCID: 28742025.

3. Probing the exosome-dependent and independent mechanism of distributive 3' to 5' RNA decay by the exoribonuclease Rrp6

Following my discovery that yeast Rrp6 did not require Dis3 for exosome association and exosome-dependent activity (Wasmuth and Lima, Mol Cell, 2012), I crystallized and solved the structure of a catalytically dead variant of a Rrp6-bound 400 kDa exosome engaged with polyA RNA, a known substrate for the nuclear exosome, and performed structure-guided mutagenesis to validate this newly identified RNA path (Wasmuth et al., *Nature*, 2014). This study validated the biochemical and genetic findings from the Wasmuth and Lima 2012 study demonstrating previously unappreciated Rrp6 dependency on the central channel, and revealed how a RNase D family member interacts with RNA. Specifically, Rrp6 is observed resting atop the Exo9 channel, on the end opposite to where Rrp44 was known to bind. In a separate study (Wasmuth and Lima, *Nucleic Acids Res*, 2017), I identified a basic region in the Rrp6 C-terminal domain that was disordered in our crystal structure, yet biophysically conserved. Through biochemical and genetic (yeast) characterization, I found that that this region was mostly responsible for Rrp6 allosteric activation of Rrp44 through its RNA binding activities, thus dubbing it the Rrp6 "lasso." As a collaborator, I contributed essential reagents for an elegant biochemical study documenting Rrp6 kinetics at single nucleotide resolution (Axhemi et al, *PNAS*, 2019), which revealed intrinsic mechanisms for substrate specificity dictated by RNA sequence, and additionally corroborated many of our earlier structural and biochemical findings regarding Rrp6 mechanism in and out of the exosome (Wasmuth et al., *Nature*, 2014; Wasmuth and Lima, *Nucleic Acids Res*, 2017).

a. **Wasmuth EV,** Januszyk K, Lima CD. Structure of an Rrp6-RNA exosome complex bound to polyA RNA. *Nature*. 2014 Jul 24; 511(7510):435-9. PMCID: 25043052.
b. **Wasmuth EV**, Lima CD. The Rrp6 C-terminal domain binds RNA and activates the nuclear RNA exosome. *Nucleic Acids Research*. 2017 Jan 25; 45(2):846-60. PMCID: 27899565.
c. Axhemi A, **Wasmuth EV**, Lima CD, Jankowsky E. Substrate selectivity by the exonuclease Rrp6p. *Proceedings of the National Academy of Sciences*. 2019. Dec 26. pii: 201913236. PMCID: 31879344.

4. Postdoctoral career – modes of androgen receptor transcriptional regulation

My focus during my post-doctoral training in Dr. Charles Sawyers' laboratory is on modes of regulation of androgen receptor (AR) activity. AR is a type I nuclear hormone receptor normally critical for development and maintenance of male reproductive tissues and phenotype; however, its misregulation is commonly associated with castration resistant prostate cancer (CRPC), androgen insensitivity syndrome, and Kennedy's disease. Although AR targeting drugs, including anti-androgens, have long served as the backbone of CRPC therapy, resistance inevitably occurs, simply through AR amplification in 50% of cases. A major bottleneck in designing

better AR targeting drugs is that mechanistic understanding of AR is limited due to inherent difficulties isolating and stabilizing the protein. Using recombinant proteins, I have established a system to purify and stabilize active and anti-androgen inhibited AR using protein cofactors known to be important in prostate cancer in the lab of Dr. Sebastian Klinge at The Rockefeller University, an expert in nucleic acid and protein structural biology. This technical breakthrough has allowed us to write the first biochemical study describing how AR binds DNA, the contributions of its various domains to intramolecular regulation, and modulation of its DNA binding activity through direct interaction with the ETS transcription factor, ERG (**Wasmuth et al, *PNAS*, *in press***). I showed that the ERG/AR interaction has possible implications for other related ETS factors such as ERF, whose oncogenic loss-of-function mutations I previously identified were structurally destabilizing (Bose et al, *Nature*, 2017). Furthermore, I have reconstituted an agonist-bound ternary complex between multidomain AR, ERG, and DNA which has allowed us to perform structural studies via single particle cryo-electron microscopy to illuminate the molecular contacts required for AR DNA binding activity and cofactor interaction. The resulting model will have implications for other type I nuclear receptors that have been similarly recalcitrant to structural studies, as well as providing a platform for the design of more potent next-generation anti-androgens.

In addition to understanding how protein cofactors modulate AR activity, I have identified a new mode of AR activation through reoccurring loss-of-function alterations of the nuclear RNA exosome subunit DIS3 in prostate cancer (PCa). Several DIS3 hotspot mutations have previously been reported in multiple myeloma and promote disease through a mechanism that remains unclear. I have identified an expanded repertoire of DIS3 genomic alterations in PCa that stratify into distinct classes with variable penetrance. Stable introduction of these alterations into human prostate cells results in selective upregulation of AR transcriptional targets, certain coding and regulatory non-coding RNAs, and the DNA damage response, and is dependent on DIS3 catalytic activity. Further characterization of these alterations, whole transcriptome identification of their accumulated RNA substrates, and uncovering how they promote AR activation will be key to understanding how loss of this essential gene contributes to disease pathogenesis.

a. Bose R, Karthaus WR, Armenia J, Abida W, Iaquinta PJ, Zhang Z, Wongvipat J, **Wasmuth EV,** Shah N, Sullivan PS, Doran MG, Wang P, Patruno A, International SU2C/PCF Prostate Cancer Dream Team, Zheng D, Schultz N, Sawyers CL. Loss of Function Mutations in ETS2 Repressor Factor (ERF) Reveal a Balance Between Positive and Negative ETS Factors Controlling Prostate Oncogenesis. *Nature*. 2017 Jun 29; 546(7660):671-5. PMCID: 28614298.
b. **Wasmuth EV**, Hoover EA, Antar A, Klinge S, Chen Y, Sawyers CL. Modulation of androgen receptor DNA binding activity through direct interaction with the ETS transcription factor ERG. *Proceedings of the National Academy of Sciences, in press*.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/elizabeth.wasmuth.1/bibliography/43774796/public/

D. Research Support

Ongoing Research Support

W81XWH-17-PCRP-EIRA (PI: Wasmuth) 5/15/2018 – 5/14/2020
PCRP Early Investigator Research Award
Department of Defense
Structural and Functional Studies of Androgen Receptor and Its Cofactors
Role: PI

Completed Research Support

F31GM097910 (PI: Wasmuth) 8/11/2011 – 8/10/2015
F31 Ruth Kirschstein Diversity Award / NIH / NIGMS
Structural and Biochemical Characterization of the *S. cerevisiae* RNA Exosome
Role: PI

Functional Genomics Initiative – Rapid Response Grant 11/2018 – 11/2019
Memorial Sloan Kettering Cancer Center
Mechanisms of oncogenicity caused by loss of function mutations in the DIS3 RNA exosome subunit
Role: Co-PI (with Dr. Charles Sawyers)

BIOGRAPHICAL SKETCH

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NAME: Sawyers, Charles L.

eRA COMMONS USER NAME (credential, e.g., agency login): SAWYERS2

POSITION TITLE: Chairman, Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center; Investigator, Howard Hughes Medical 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
Princeton University, Princeton, NJ	B.A.	06/1981	History of Science
Johns Hopkins School of Medicine, Baltimore, MD	M.D.	06/1985	Medicine
University of California, San Francisco	Residency	06/1988	Internal Medicine
David Geffen School of Medicine at University of California, Los Angeles (UCLA)	Fellowship	06/1991	Hematology / Oncology
David Geffen School of Medicine at UCLA	Postdoc	06/1993	Molecular Biology

A. Personal Statement

I am an HHMI Investigator and Chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center (MSK). My research focuses on understanding abnormal cell signaling in cancer and strategies for therapeutic targeting. Previously, I studied BCR-ABL tyrosine kinase function in chronic myeloid leukemia (CML), and codeveloped the kinase inhibitor imatinib (Gleevec®) as primary therapy for CML. We then discovered that BCR-ABL kinase domain mutations confer imatinib resistance, and developed the second generation Abl kinase inhibitor dasatinib (Sprycel®) that overcomes imatinib resistance (Gorre et al. *Science*, 2001; Shah et al. *Science*, 2004; Talpaz et al. *NEJM*, 2006). I next turned my attention to a related problem, resistance to hormone therapy in prostate cancer. We determined that increased androgen receptor (AR) expression was both necessary and sufficient to confer this resistance (Chen et al. *Nat Med*, 2004). We then discovered a potent antiandrogen called enzalutamide, FDA-approved in 2012 for the treatment of castration resistant prostate cancer based on impressive clinical responses and improved survival (Scher et al., *Lancet*, 2010; Scher et al. *NEJM*, 2012). We are now examining mechanisms of resistance to enzalutamide by dissecting signaling pathway crosstalk between AR and other molecular lesions e.g. PTEN loss, how the *TMPRSS2-ERG* gene fusion causes prostate cancer, and prostate cell state plasticity (Balbas et al. *eLife*, 2013; Arora et al. *Cell*, 2013; Mu et al. *Science*, 2017). As department Chair, I have recruited and oversee ~24 physicians and scientists who bring molecularly targeted approaches and molecularly based patient stratification to clinical trials and patient treatment. I am committed to rigor and unbiased experimental design, methodology, analysis, interpretation and reporting of results as demonstrated by my service on the editorial boards of several leading journals (*Cell*, *eLife*) and many leadership roles at the national level, include past presidency of the AACR. I am committed to scientific transparency, both my own and of faculty and trainees in our department, who undergo MSK's Responsible Conduct of Research course in their initial training phase, and who receive formal mentorship at all career stages. My colleagues and I are conscious of the need to improve diversity of early career biomedical faculty and have hired and promoted 5 female HOPP faculty over the past 2 years, and we offer a tenure-pause for extenuating life events. As primary mentor to >65 graduate students and fellows over my career, I recognize the need to provide trainees with laboratory skills and resources that are tailored to their individual experience and career goals while balancing the need to complete training in a timely fashion. As evidence of my success in balancing these needs, I have been gratified to see many (>45) of my trainees continue their careers in science or medicine.

B. Positions and Honors

Positions and Employment

1993–2006	Assistant to Full Professor of Medicine, Division of Hematology-Oncology, UCLA School of Medicine; joint appointments in Pharmacology and Urology
2002–2006	Investigator, Howard Hughes Medical Institute (Los Angeles, CA)
2008–	Investigator, Howard Hughes Medical Institute (New York, NY)
2006–	Chair, Human Oncology and Pathogenesis, MSK, New York, NY

Honors

1981	Summa Cum Laude-History of Science Department, Princeton University
1994	Cheryl Whitlock Prize for Leukemia Research
1995–2000	Leukemia Society of America Scholar Award
2001	Doris Duke Distinguished Clinical Scientist Award
2003	Nature Medicine Translational Medicine Award, University of California, San Diego
2003	Bristol-Myers Squibb Biomedical Research Cancer Grant Recipient
2005	Richard and Hinda Rosenthal Foundation Award (AACR)
2005	David A. Karnofsky Memorial Award (ASCO)
2007–2008	President, American Society of Clinical Investigation (ASCI)
2007	Emil J. Freireich Award
2008	Member, Institute of Medicine (National Academy of Medicine)
2009	Dorothy P. Landon-AACR Prize for Translational Cancer Research
2009	Lasker-DeBakey Clinical Medical Research Award
2010	Member, National Academy of Sciences
2011	Stanley J. Korsmeyer Award
2013	Taubman Prize for Excellence in Translational Medical Science
2013	Breakthrough Prize in Life Sciences
2013-2014	President, American Association of Cancer Research (AACR)
2014	Hope Funds for Cancer Research Honoree
2014	Member, American Academy of Arts and Sciences
2015	Banco Bilbao Vizcaya Argentaria (BBVA) Foundation Frontiers of Knowledge Award
2017	American Cancer Society (ACS) Medal of Honor for Clinical Research
2017	The Scheele Award, Swedish Academy of Pharmaceutical Sciences

C. Contribution to Science

1. Kinase inhibitors for chronic myeloid leukemia

My laboratory has a long history of expertise BCR-ABL kinase signal transduction, dating back to my postdoctoral training with Owen Witte. As a clinician investigator in chronic myeloid leukemia (CML), I co-led the phase I and phase II clinical trials of imatinib (with Brian Druker and Moshe Talpaz) culminating in its FDA approval in 2001 (Druker, et al., *NEJM*, 2001). My laboratory subsequently discovered mutations in the BCR-ABL kinase domain as the primary mechanism of resistance to imatinib (Gorre, et al., *Science*, 2001), then collaborated with John Kuriyan to show that these mutations impaired drug binding through steric hindrance (in some cases) or through altered conformation of the kinase domain (more commonly) (Shah, et al., *Cancer Cell*, 2002). Based on predictions from the "altered conformation" hypothesis, we identified dasatinib as a second generation ABL inhibitor that can overcome nearly all forms of imatinib resistance (Shah, et al., *Science*, 2004). I then co-led the phase I and phase II clinical trials of dasatinib that resulted in its approval by the FDA in 2006 (Talpaz, et al., *NEJM*, 2006).

a. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, **Sawyers CL**. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *NEJM* 2001; 344:1031–1037. PMID: 11287972.
b. Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, **Sawyers CL**. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science* 2001; 293:876–880. PMID: 11423618.
c. Shah NP, Nicoll JM, Nagar B, Gorre ME, Paquette RL, Kuriyan J, **Sawyers CL**. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. *Cancer Cell* 2002;2: 117–125. PMID: 12204532.

d. Shah NP, Tran C, Lee FY, Chen P, Norris D, **Sawyers CL**. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science* 2004; 305: 399–401. PMID: 15256671.

2. Antiandrogen therapy for prostate cancer

Building on our success in elucidating mechanisms of resistance to kinase inhibitors in CML, we turned our attention to the problem of resistance to hormone therapy in prostate cancer. In 2004 we reported that increased expression of the AR was consistently observed in the castration resistant sublines of 7 different isogenic pairs of prostate cancer xenograft models. Furthermore, this increased expression conferred resistance to bicalutamide by converting the cellular response from antagonism to agonism (Chen et al, Nat Med, 2004). This observation led us to search for new antiandrogens that could overcome this resistance, which resulted in the discovery of enzalutamide, in collaboration with Michael Jung at UCLA (Tran et al, Science, 2009; Scher et al, Lancet 2010). Enzalutamide is now approved for castration-resistant prostate cancer.

a. Chen CD, Welsbie DS, Tran C, Baek SH, Chen R, Vessella R, Rosenfeld MG, **Sawyers CL**. Molecular determinants of resistance to antiandrogen therapy. Nat Med 2004;10:33–39. PMID: 14702632.
b. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, Smith-Jones PM, Yoo D, Kwon A, Wasielewska T, Welsbie D, Chen C, Higano CS, Beer TM, Hung DT, Scher HI, Jung M **Sawyers CL**. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009;324:787–790. PMCID: PMC2981508.
c. Scher HI, Beer TM, Higano C, Anand A, Taplin M-E, Efstathiou E, Rathkopf D, Shelkey J, Yu E, Alumkal J, Hung D, Hirmand M, Seely L, Morris MJ, Danila DC, Humm J, Larson S, Fleisher M, **Sawyers CL**. Antitumor Activity of MDV3100 in a Phase 1-2 Study of Castration-Resistant Prostate Cancer. Lancet, 2010, 375:1437-46. Epub 2010 Apr 14. PMCID: PMC5013546

3. Mechanisms of resistance to antiandrogen therapy

Although enzalutamide improves survival of men with metastatic prostate cancer, resistance eventually develops. We have recently reported three distinct mechanisms of resistance to enzalutamide– AR mutation, upregulation of the glucocorticoid receptor (bypass), and lineage plasticity caused by SOX2. We are currently exploring other potential resistance mechanisms as well as exploring various combination therapies to prevent resistance based on these mechanistic insights (Balbas et al, eLife, 2013; Arora et al, Cell, 2014; Mu et al, Science, 2017; Ku et al Science, 2017).

a. Arora VK, Schenkein E, Murali R, Subudhi SK, Wongvipat J, Balbas MD, Shah N, Cai L, Efstathiou E, Logothetis C, Zheng D, **Sawyers CL**. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. *Cell* 2013;155:1309–1322. PMCID: PMC3932525.
b. Mu P, Zhang Z, Benelli M, Karthaus WR, Hoover E, Chen CC, Wongvipat J, Ku SY, Gao D, Cao Z, Shah N, Adams EJ, Abida W, Watson PA, Prandi D, Huang CH, de Stanchina E, Lowe SW, Ellis L, Beltran H, Rubin MA, Goodrich DW, Demichelis F, **Sawyers CL**. SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer. Science. 2017 Jan 6;355(6320):84-88. PubMed PMID: 28059768; PubMed Central PMCID: PMC5247742.
c. Ku SY, Rosario S, Wang Y, Mu P, Seshadri M, Goodrich ZW, Goodrich MM, Labbé DP, Gomez EC, Wang J, Long HW, Xu B, Brown M, Loda M, **Sawyers CL**, Ellis L, Goodrich DW. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science. 2017 Jan 6;355(6320):78-83. PubMed PMID: 28059767. PMCID: PMC5367887.
d. Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, Cieslik M, Benelli M, Robinson D, Van Allen EM, Sboner A, Fedrizzi T, Mosquera JM, Robinson BD, De Sarkar N, Kunju LP, Tomlins S, Wu YM, Rodrigues DN, Loda M, Gopalan A, Reuter VE, Pritchard CC, Mate J, Bianchini D, Miranda S, Carreira S, Rescigno P, Filipenko J, Vinson J, Montgomery R, Beltran H, Heath EI, Scher HI, Kantoff P, Taplin ME, Schultz N, DeBono JS, Demichelis F, Nelson PS, Rubin MA, Chinnaiyan AM, **Sawyers CL**. Genomic correlates of clinical outcome in advanced prostate cancer, PNAS, 2019 116(23):11428-11436. doi: 10.1073/pnas.1902651116. Epub 2019 May 6. PMCID: PMC6561293.

4. Mechanisms of prostate cancer initiation and progression

In addition to our studies of cancer drug resistance, my group has developed and characterized several laboratory models to study prostate cancer initiation and progression. These include the establishment of new patient-derived xenograft models and organoid lines (Klein, et al., *Nat Med*, 1997; Karthaus, et al.,

Cell, 2014; Gao, et al., *Cell*, 2014) as well as genetically engineered mouse prostate cancer models for driver oncogenes such as MYC and ERG (Ellwood-Yen, et al., *Cancer Cell* 2002; Chen, et al., *Nat Med*, 2013). We have also co-led several comprehensive genomic landscape studies of primary and metastatic prostate cancer, including a commitment to make these genomic datasets available to the research community through the user-friendly data visualization tool cBioPortal (Taylor, et al., *Cancer Cell*, 2010; Robinson et al Cell 2015).

a. Karthaus WR, Iaquinta PJ, Drost J, Gracanin A, van Boxtel R, Wongvipat J, Dowling CM, Gao D, Begthel H, Sachs N, Vries RG, Cuppen E, Chen Y, **Sawyers CL**, Clevers HC. Identification of multipotent luminal progenitor cells in human prostate organoid cultures. *Cell* 2014;159:163–175. PMID: 25201529. PMCID: PMC4772677.
b. Robinson D, Van Allen EM, Wu YM, Schultz N, ….de Bono JS, Rubin MA, Nelson PS, Garraway LA, **Sawyers CL**, Chinnaiyan AM. Integrative clinical genomics of advanced prostate cancer. Cell. 2015;161(5):1215-28. PMCID: PMC4484602.
c. Bose R, Karthaus WR, Armenia J, Abida W, Iaquinta PJ, Zhang Z, Wongvipat J, Wasmuth EV, Shah N, Sullivan PS, Doran MG, Wang P, Patruno A, Zhao Y; International SU2C/PCF Prostate Cancer Dream Team, Zheng D, Schultz N, **Sawyers CL**. ERF mutations reveal a balance of ETS factors controlling prostate oncogenesis. Nature 2017 546(7660):671-675. PMID: 28614298; PMCID: PMC5576182.
d. Adams EJ, Karthaus WR, Hoover E, Liu D, Gruet A, Zhang Z, Cho H, DiLoreto R, Chhangawala S, Liu Y, Watson PA, Davicioni E, Sboner A, Barbieri CE, Bose R, Leslie CS, **Sawyers CL**. FOXA1 mutations alter pioneering activity, differentiation, and prostate cancer phenotypes. Nature. 2019 571(7765):408-412. doi: 10.1038/s41586-019-1318-9. Epub 2019 Jun 26. PMID: 31243370; PMCID: PMC6661172.

5. PI3-kinase signaling in prostate cancer

The high frequency of PTEN loss in prostate cancer led us to initiate a number of studies of PI3-kinase signaling. We discovered reciprocal negative feedback between PI3-kinase and androgen receptor signaling in prostate cancers with PTEN loss (Carver et al, Cancer Cell 2011) and, with Neal Rosen, therapeutic strategies with combinations of alpha- and beta-specific inhibitors that delay drug resistance (Schwartz et al, Cancer Cell 2015). In addition, we discovered an oncogenic role for the vesicular trafficking protein RAB35 in a screen for novel regulators of PI3-kinase activation (Wheeler et al, Science 2015).

a. Carver BS, Chapinski C, Wongvipat J, Hieronymus H, Chen Y, Chandarlapaty S, Arora VK, Le C, Koutcher J, Scher H, Scardino PT, Rosen N, **Sawyers CL**. Reciprocal Feedback Regulation of PI3K and Androgen Receptor Signaling in PTEN-Deficient Prostate Cancer. Cancer Cell. 2011 May 17;19(5):575-86. PMCID: PMC3142785.
b. Schwartz S, Wongvipat J, Trigwell CB, Hancox U, Carver BS, Rodrik-Outmezguine V, Will M, Yellen P, de Stanchina E, Baselga J, Scher HI, Barry ST, **Sawyers CL**, Chandarlapaty S, Rosen N. Feedback suppression of PI3Kalpha signaling in PTEN-mutated tumors is relieved by selective inhibition of PI3Kbeta. Cancer Cell. 2015;27(1):109-22. PMCID: PMC4293347.
c. Wheeler DB, Zoncu R, Root DE, Sabatini DM, **Sawyers CL**. Identification of an oncogenic RAB protein. Science. 2015 Oct 9;350(6257):211-7. PMCID: PMC4600465.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Sawyers%2C+Charles

D. Research Support

ACTIVE

Howard Hughes Medical Institute (PI: Sawyers) 01/16/2008 - 08/31/2025
Patient oriented research into molecularly targeted therapy of cancer

5 R01 CA193837-04 (PI: Sawyers) 04/01/2015 - 03/31/2020
NCI
Defining the Role of ERG in Modulating the AR Cistrome and Antiandrogen Sensitivity
This project will shed light on the molecular mechanisms by which ERG causes prostate cancer and the impact of ERG on response to therapies directed against the androgen receptor, the common form of treatment for metastatic prostate cancer.

2 T32 CA160001-08 (PI: Sawyers) 08/01/2016 - 07/31/2021
NCI

Translational Research in Oncology Training Program
The training program for translational cancer research will provide opportunities to postdoctoral PhD trainees to learn about human oncology and pathogenesis, and work collaboratively with clinicians to advance the treatment of cancer patients. The goals are: to help basic scientists to develop a strong clinical background so that they may effectively bring discoveries from bench to bedside; and to foster interdisciplinary research and collaboration. The funds cover stipends for fellows.

2 P50 CA092629-18 (PI: Scher) 09/01/2016 - 08/31/2022
NCI
SPORE in Prostate Cancer
Major Goals of this Project: This allocation is split between three projects: Project 3, Project 4, Development Research Program, and Core F. As a public health concern, prostate cancer is the second deadliest cancer in men. The translational research projects in this program aim to use knowledge of animal and human prostate cancer biology to develop and test interventions related to the prevention, early detection, diagnosis, prognosis, and treatment of prostate cancer in men. Dr Sawyers' portion is focused on glucocorticoid receptor and TP53 and RB1 loss.

1 U54 CA224079-02 (PI: Sawyers) 09/01/2017 - 08/31/2022
NCI
The MSKCC-UW/Fred Hutch Prostate Cancer Drug Resistance and Sensitivity Center (Project -001, Project-002, Admin Core)
The overarching goal of this DRSC proposal is to evaluate EZH2 and BET inhibitors across a unique set of preclinical organoid and patient-derived xenograft (PDX) models, and to catalyze the initiation of clinical studies in patients most likely to benefit based on appropriate biomarker profiles.

2 R01 CA155169-07 (PI: Sawyers) 01/01/2018 - 12/31/2022
NCI
Understanding Resistance to Next Generation Antiandrogens
This application will generate novel mechanistic insight into lineage plasticity in prostate cancer due to TP53 and RB1 loss, with obvious implications for the clinical challenge of drug resistance. The findings are also likely to have relevance for other epithelial tumor types such as lung cancer, breast cancer and melanoma where evidence implicating lineage plasticity as a cause of drug resistance has also emerged.

I12 0007 (PI: Sawyers) 01/01/2019 - 12/31/2020
Starr Cancer Consortium
Defining prostate cancer cells of origin through single cell profiling
This proposal is focused exclusively on genetically engineered mouse models (GEMMs) and fits the RFA category of "Disease Applications" because it applies the relatively new molecular technology of single cell RNA sequencing (scRNA seq) to the study of prostate cancer.

1 P01 CA228696 01A1 (PI: Kantoff) 09/01/2019 - 08/31/2024
NCI
The Impact of DNA Damage Repair Abnormalities in Prostate Cancer (RP3: Functional Evaluation and Interpre tation of DNA Damage Response Variants in Prostate Cancer)
Alterations in genes that help repair damaged DNA are seen in 25% of men with metastatic castration resistant prostate cancer, the lethal form of prostate cancer.
Role: Project Leader

Completed Research Support (Past 3 years)
I10-0062 (PI: Sawyers) 1/1/2017 - 12/31/2018
Starr Cancer Consortium
Transcriptional Reprogramming Drives Cancer Cell Heterogeneity and Drug Resistance
To elucidate the transcriptional regulators of lineage plasticity across a broader range of molecular contexts of tumor suppressor loss of function (PTEN, RB1).