**BIOGRAPHICAL SKETCH**

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NAME: Wasmuth, Elizabeth V.

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

POSITION TITLE: Research fellow, 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 | 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 misregulation of nucleic acid bindings proteins in cancer 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 disease, 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 graduate school for its heavy exposure to cancer research ranging from 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. Christopher 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 structural and cancer biology, and have developed into a scientist uniquely equipped to think about long-standing problems in prostate cancer. I have focused on two projects: 1) structural and functional understanding of the androgen receptor in prostate cancer, and 2) probing how alterations of the RNA exosome subunit, DIS3, contribute to disease. 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)

**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. Contribution to Science**

**1. Early career (2007-2008)**

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. Graduate career (2008-2016)**

RNA levels are maintained by a balance of synthesis and decay. While much is understood about transcription, less is known about decay. I studied the RNA exosome, the major 3' to 5' eukaryotic exoribonuclease, which acts on virtually every class of RNA. An essential noncatalytic core of 9 distinct subunits (Exo9) 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 went on to crystallize and perform structure-guided mutagenesis on a RNA-bound exosome (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 first reveals how a RNase D family member interacts with RNA. Specifically, this work describes the crystal structure of a yeast 400 kilodalton Rrp6-associated exosome bound to polyA RNA, a known substrate of the nuclear exosome. Rrp6 is observed resting atop the Exo9 channel, on the end opposite to where Rrp44 was known to bind. RNA contacts within the Rrp6 active site and Exo9 are identified and confirmed biochemically. In a separate study, I identified a previously unappreciated region in the Rrp6 C-terminal domain that was disordered in our crystal structure, yet mostly responsible for Rrp6 allosteric activation of Rrp44 through its RNA binding activities, thus dubbing it the Rrp6 "lasso". Wasmuth and Lima, *Nucleic Acids Res*, 2017 represents the biochemical and genetic characterization of this conserved, disordered region. Finally, I structurally and biochemically reconciled how the nuclear protein cofactors of the exosome, Mpp6 and Rrp47, cooperatively stimulate the exoribonuclease activities of the nuclear exosome via Rrp6 through partially overlapping yet distinct mechanisms, and how these cofactors recruit the essential RNA helicase, Mtr4 (Wasmuth et al., *eLife*, 2017). In addition to the studies I led, I contributed to structural and biochemical understanding of 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).

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. **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.
d. 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.
e. **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.
f. **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.
g. 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.

**3. Postdoctoral career (2016-present)**

My primary project focuses on structural and functional studies of the androgen receptor (AR), the nuclear hormone receptor critical for development and maintenance of normal prostate tissue, and driver of advanced prostate cancer (PCa). Although AR targeting drugs have long served as the backbone of prostate cancer 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 inhibited AR using protein cofactors known to be important in prostate cancer. This technical breakthrough has allowed us to write the first biochemical study describing how AR binds DNA and its auto-regulation and modulation by protein cofactors, and to perform structural studies via cryo-electron microscopy and x-ray crystallography to illuminate the molecular contacts required for AR function and

cofactor interaction. This research will provide a platform for designing more potent next-generation anti-androgens to treat castration-resistant prostate cancer.

Building on my expertise in RNA exosome biology, I have initiated studies of how reoccurring alterations in DIS3, a catalytic component of the nuclear exosome, contribute to cancer. Several DIS3 hotspot mutations have been reported in multiple myeloma through a mechanism that remains unclear. I have identified an expanded repertoire of DIS3 genomic alterations that occur in PCa and in over a dozen other cancers that stratify into distinct classes with variable penetrance. My initial studies in PCa cells suggest these alterations activate AR transcription, certain coding and regulatory non-coding RNAs, and the DNA damage response. Characterization of these alterations and their accumulated substrates 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 revision*.

**Complete List of Published Work in MyBibliography:**
**https://www.ncbi.nlm.nih.gov/sites/myncbi/elizabeth.wasmuth.1/bibliography/43774796/public/?sort=date&direction=ascending**

### 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
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**

Provide the following information for the Senior/key personnel and other significant contributors.
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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

My laboratory is working on the general question of how prostate cancers progress to castration resistance. Our first breakthrough came from studies of isogenic castration-sensitive and castration-resistant xenografts, where we found that increased androgen receptor (AR) expression was both necessary and sufficient to confer resistance (Chen et al Nat Med, 2004). Based on this finding, we conducted a cell-based screen for novel antiandrogens that retain activity prostate cells expression high levels of AR (and hence resistant to current AR pathway inhibitors). We discovered a potent compound called enzalutamide that is highly active against several castration-resistant xenograft models and entered clinical development in 2007 (Tran et al, Science, 2009). In 2012, enzalutamide received FDA approval for the treatment of castration resistant prostate cancer based on clinical results showing impressive responses and improved survival (Scher et al, Lancet, 2010; Scher et al NEJM, 2012). We are now examining mechanisms of resistance to enzalutamide (Balbas et al eLife, 2013; Arora et al Cell, 2013; Mu et al Science, 2017). Previously my group tackled similar questions surrounding resistance to the ABL kinase inhibitor imatinib (Gleevec®) in chronic myeloid leukemia, which led to the discovery of BCR-ABL mutations and the development of the second generation ABL inhibitor dasatinib (Sprycel®) that overcomes imatinib resistance (Gorre et al, Science, 2001; Shah et al Science, 2004; Talpaz et al NEJM, 2006). As Chairman of the Human Oncology and Pathogenesis Program (HOPP) at Memorial Sloan Kettering Cancer Center (MSKCC), I work to bring molecularly targeted approaches and molecularly based patient stratification to clinical trials and patient treatment.

## 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)
2005-2006 Vice Chair, University of California, Los Angeles Department of Molecular & Medical Pharmacology

2006– Attending, Memorial Hospital for Cancer and Allied Diseases, Leukemia Service, Department of Medicine, 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
2000 Stohlman Scholar, Leukemia and Lymphoma Society
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 American Association of Cancer Research (AACR) Richard and Hinda Rosenthal Foundation Award
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 Giants of Cancer Care Award
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.

**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. Balbas MD, Evans MJ, Hosfield DJ, Wongvipat J, Arora VK, Watson PA, Chen Y, Greene GL, Shen Y, **Sawyers CL**. Overcoming mutation-based resistance to anti-androgens with rational drug design. *Elife* 2013;2:e00499. PMCID: PMC3622181.
c. 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. doi: 10.1126/science.aah4307. PubMed PMID: 28059768; PubMed Central PMCID: PMC5247742.
d. 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. Doi: 10.1126/science.aah4199. PubMed PMID: 28059767.

**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. Gao D, Vela I, Sboner A, Iaquinta PJ, Karthaus WR, Gopalan A, Dowling C, Wanjala JN, Undvall EA, Arora VK, Wongvipat J, Kossai M, Ramazanoglu S, Barboza LP, Di W, Cao Z, Zhang QF, Sirota I, Ran L, MacDonald TY, Beltran H, Mosquera JM, Touijer KA, Scardino PT, Laudone VP, Curtis KR, Rathkopf DE, Morris MJ, Danila DC, Slovin SF, Solomon SB, Eastham JA, Chi P, Carver B, Rubin MA, Scher HI, Clevers H, **Sawyers CL**, Chen Y. Organoid cultures derived from patients with advanced prostate cancer. *Cell* 2014;159:176–187. PMCID: PMC4237931.

c. Chen Y, Chi P, Rockowitz S, Laquinta PJ, Shamu T, Shukla S, Gao D, Sirota I, Carver BS, Wongvipat J, Scher HI, Zheng D, **Sawyers CL**. ETS factors reprogram the androgen receptor cistrome and prime prostate tumorigenesis in response to PTEN loss. *Nat Med*, 2013 Aug;19(8):1023-9. Epub 2013 Jun 30. PMCID: PMC3737318.

d. 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.

**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**

**Ongoing Research Support**

Howard Hughes Medical Institute (PI: Sawyers) 1/16/2008 – 8/31/2018
Patient oriented research into molecularly targeted therapy of cancer
Role: PI

5 R01 CA193837-02 (PI: Sawyers) 4/1/2015 – 3/31/2020
NIH/NCI
Defining the Role of ERG in Modulating the AR Cistrome and Antiandrogen Sensitivity
Specific aims: This project will shed light on the molecular mechanism 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.
Role: PI

2 T32 CA160001-06 (PI: Sawyers) 8/1/2016 – 7/31/2021
NIH/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: 1) to help basic scientists to develop a strong clinical backgrounds so that they may effectively bring discoveries from bench to bedside and 2) to foster interdisciplinary research and collaboration. These funds support the institution.
Role: PI

5 P30 CA008748-51 (PI: Thompson) 1/1/2014 – 12/31/2018
NIH/NCI
Cancer Center Support Grant (CCSG)
The CCSG supports MSK's research infrastructure. These shared resources facilitate the research activities of the clinical, translational and laboratory programs at the Cancer Center. These funds support the institution.
Role: Program Director

2 P50 CA092629-16 (PI: Scher) 9/1/2011 – 8/31/2021
National Institutes of Health
MSK Spore in Prostate Cancer
Our program will allow us to better distinguish between aggressive and slow-growing cancer, better predict which drugs will work for which patients, better assess if the treatments patients are receiving are working, and develop new therapies for men with advanced disease who are not helped by available treatments.
Role: Co-Leader of Project 3 and 4, Developmental Research Program and Admin Core

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).
Role: PI

**Completed Research Support (Past 3 years)**
Stand up to Cancer Dream Team Award (PI: Chinnaiyan) 8/1/2012 – 7/31/2016
SU2C/AACR-DT0712
Precision Therapy of Advanced Prostate Cancer
The goal of this project is to establish a precision medicine paradigm for castration-resistant prostate cancer. This proposal primarily funds the collection of clinical trial biopsies, sequencing and computational analysis.
Role: MSK Co-PI

5 R01 CA155169-05 (PI: Sawyers) 5/1/2012 – 3/31/2017
NIH/NCI
Understanding Resistance to Next Generation Antiandrogens
To explore the molecular basis by which GR selectively activates certain AR target genes (Aim 1), the functional role of GR, AR and the GR/AR target gene SGK1 in maintaining drug resistance (Aim 2), and the clinical relevance of these findings in circulating tumor cells obtained from patients at treatment start and at relapse (Aim 3).
Role: PI

Experimental Therapeutics Center (PI: Heller/Sawyers) 2/1/2017 – 12/31/2017
Memorial Sloan Kettering Cancer Center
Nanoparticle Delivery of Antiandrogen Therapy in Prostate Cancer
Role: Co-PI

Dr. Sawyers has an extensive list of completed grants from both federal and non-federal sponsors.