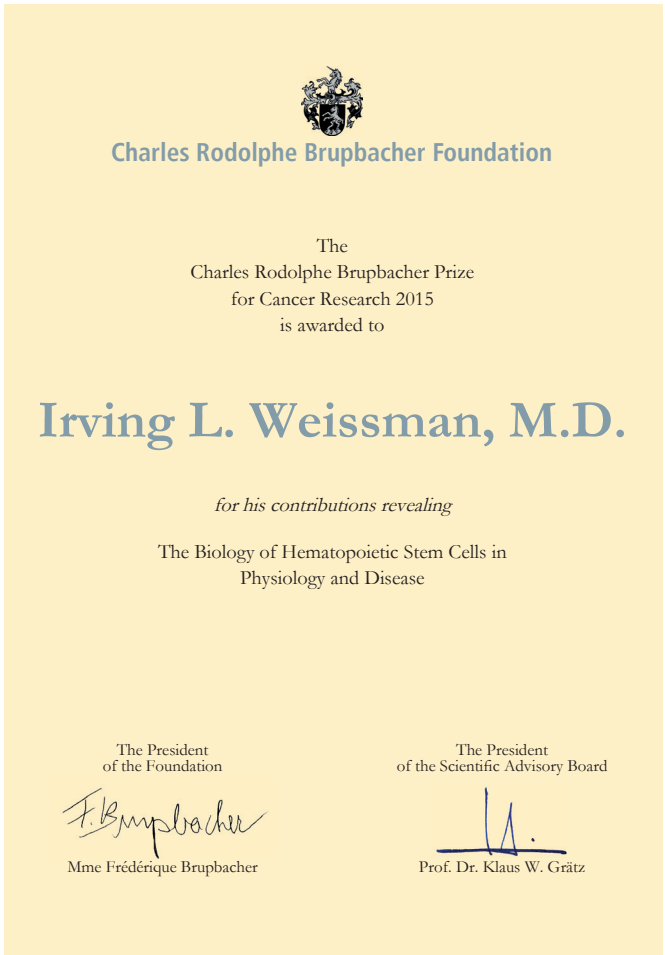

Laudatio

Markus G. Manz

When I met Irving Weissman almost twenty years ago, I walked in his tiny office at Stanford, packed with paper and magazines, and only realized him when he peeked over a pile, giving me a huge smile and then shouting "Now, who's that?". With my European-trained manners towards medical school authority, this was a first, somewhat shocking confrontation with his joyful curiosity that generically characterizes him. He already was a super-star in both immunology and hematology research, and I was thrilled that he then accepted me as a postdoctoral fellow in his laboratory.

Irving Weissman was born and raised in Great Falls, Montana, did zoology studies at Dartmouth College in Hanover, New Hampshire, pre-med studies at Montana State University in Bozeman, and then studied medicine at Stanford, where, with the exemption of a short stay in Oxford England, he continues to work. After a postdoctoral fellowship with Henry Kaplan at Radiology, he became professor of pathology with subsequently multiple additional appointments (details are listed in the program) and is now leading the Stanford Institute for Stem Cell Biology and Regenerative Medicine as well as the Stanford Ludwig Center for Cancer Stem Cell Research and Medicine. He is recipient of multiple awards (listed in the program) and member of the US American National Academy of Sciences.

Dr. Weissman is publishing since 1957, when he was still a teen-ager (by now over 800 publications of which over 80 appeared in the "big three", Cell, Nature and Science). He is one of the rare species with a very broad interest and the capacity to integrate different fields. While first focusing on transplantation tolerance and lymphoid system development, he then extended his research to hemato-lymphoid cell migration (including metastasis formation) and to stem cells in hematopoiesis, neurogenesis and cancer. Although working mostly on mammals, he also developed a research program in Monterey, California, on Botryllus schlosseri, the beautiful golden star tunicate that grows in saltwater environments, a research leading to bench-mark discoveries of their fascinating model immune system that teaches about self and non-self, and natural transplantation reactions. Also, he is an entrepreneur who founded several companies with the intention to bring scientific achievement to patients. These companies again published great science, however, Irv also discovered that (I cite from a Nat Biotech Interview in 2011) the "…. dilemma, when the medical school want to save lives, and the companies want to make a profit.." needs some new approach, a road he is currently taking with the California Institute for Regenerative Medicine.

Charles Weissmann, a scientist and former Zürich professor known to most of us and tightly connected to the Brupbacher Foundation, at this spot said that "for a professor it is more rewarding to educate students than to write papers because the half-live of papers is about three years while that of students is 30 years". Even if you see him rarely while working with him, Irv Weissman inspires and supports his pupils with his enormous generosity (including an annual lab-retreat on his ranch in Montana). Many of them have accomplished superb own careers in science and medicine and became mentors themselves. In fact, if you

go to international hematopoiesis, stem cell or immunology meetings, you always will find multiple former lab-members being prominently present, and ready for an ad hoc lab-meeting.

To laude Irv Weissman's achievements relevant for the here given award, I try to sketch hemato-lymphopoiesis in a nutshell: The hemato-lymphatic system is a paradigmatic, somatic stem-cell supported organ that serves as a "role-model" for both deciphering physiology and pathophysiology, as well as applying radically new therapeutic approaches. Hematopoietic stem cells (HSCs) are a very rare population of cells in the bone marrow that self-renew, and, through a series of differentiation and expansion steps, can give rise to all mature blood cells throughout the life of an individual. The hematopoietic system is one of the organs of the body with the highest proliferative activity. Amazingly, blood production seems rarely limited by HSC function, at least in young and middle-aged individuals. Indeed, HSCs can be transferred from donors to recipients, and, although only a small fraction of donor HSCs are used, they can expand in the recipient to reach similar homeostatic pool-sizes. However, once HSCs are compromised by either not producing enough offspring (leading to aplasia) or by proliferating uncontrolled (leading to leukemia), the consequences for the individual are massive.

Irv Weissman's groundbreaking identification and isolation of HSCs first in mice in 1988 and subsequently in humans in 1992, followed by deciphering the earliest developmental steps toward lympho- and myelopoieis in both species, his discoveries on aging in stem-cell systems, and finally his contributions to understanding pathways of stem cell to cancer transitions, and the ways the innate immune system might control these neoplastic cells, set the foundation for an enormous, lasting eruption of research and knowledge in the field.

All this and the continuous energy to translate science into better medicine make Irv Weissman a role-model and scientific giant. Congratulations Irv, today this is rewarded with the Charles Rodolphe Brupbacher Foundation Prize for Cancer Research!

Irving L. Weissman

Summary Curriculum vitae

Appointment Institute for Stem Cell Biology and Regenerative Medicine
Stanford University

Address 265 Campus Drive West, Room G3167
Stanford, CA 94305-5461

Stanford University Directorships/Professorships

Director, Stanford Institute for Stem Cell Biology and Regenerative Medicine
Director, Stanford Ludwig Center for Cancer Stem Cell Research and Medicine
Virginia and D. K. Ludwig Professor for Clinical Investigation in Cancer Research
Professor of Pathology, Developmental Biology, and, by courtesy, Biological Sciences and Neurosurgery
Director, Stanford Cancer Center (2005–2008)
Chairman, Stanford University Immunology Program (degree-granting), 1986 – 2001

Education

Stanford University, Stanford - California (Postdoctoral Fellow, H.S. Kaplan)	6/65 – 6/67
Oxford University, Oxford - England (Experimental Pathology)	5/64 – 12/64
Stanford University, Stanford - California (Medicine), M.D., 1965	9/60 – 6/65
Montana State University, Bozeman - Montana (Pre-Med), B.S., 1961	9/59 – 6/60
Dartmouth College, Hanover - New Hampshire (Zoology)	9/57 – 6/59

Fellowships

- Faculty Research Awardee, American Cancer Society (National), 1974 – 1978
- Josiah Macy Foundation Scholar, 1974 – 1975
- Senior Dernham Fellow, California Division of the American Cancer Society (National), 1969 – 1973
- NIH Postdoctoral Fellowship, Department of Radiology, Stanford University School of Medicine, 1965 – 1967
- NIH Student Traineeship, Cellular Immunology Research Unit, MRC, Sir William Dunn School of Pathology, Oxford University, Oxford, England, under Professor J.L. Gowans, F.R.S., Director of Unit, 1964
- NIH Student Traineeship, Department of Radiology, Stanford University School of Medicine, under Dr. Henry S. Kaplan, Professor and Chairman of the Department of Radiology, 1961 – 1964
- Montana Cancer Society Student Research Fellow at the Laboratory for Experimental Medicine, Montana Deaconess Hospital, Great Falls, Montana, under Dr. E. J. Eichwald, Director of Laboratories, Chief Editor, Transplantation Bulletin (now Transplantation), 1956 – 1961

Awards & Honors

2014 Elected, Fellow, American Association for Cancer Research, Philadelphia, Pennsylvania
2013 Award of Honor, The Radiological Society of North America, Chicago, Illinois
2013 Charles Rodolphe Brupbacher Prize for Cancer Research, Charles Rodolphe Brupbacher Foundation, Zurich, Switzerland (notified in 2013 that this will be awarded in 2015)
2013 Alumni Achievement Award, College of Letters & Science, Montana State University, Bozeman, Montana
2013 Agency for Science, Technology and Research (A*Star) National Day Award, The Public Service Medal (Friends of Singapore), A*Star, Republic of Singapore
2013 Max Delbruck Medal of the Max Delbruck Center, Berlin, for research that has a fundamental biomedical impact and a broad interdisciplinary perspective
2012 Hall of Fame, Montana BioScience Alliance, Montana
2012 Bennett J. Cohen Award, University of Michigan, Ann Arbor, Michigan
2011 National Academy of Sciences Council, National Academy of Sciences, Washington, DC
2011 Commencement speaker, PhD graduates, University of Southern California Medical School
2010 President, International Society for Stem Cell Research
2010 Simon M. Shubitz Award for Excellence in the Field of Cancer Research, University of Chicago, Chicago, Illinois
2010 Honorary Investigator, State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Disease Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, China
2010 Honorary Professor, Peking Union Medical College, China
2009 Honorary Director of the Center for Biotech and BioMedicine and the Shenzhen Key Lab of Gene & Antibody Therapy, Graduate School of Shenzhen, Tsinghau Universit, China
2009 The Cockrell Foundation Award in Clinical or Translational Research, The Methodist Hospital Research Institute, Houston, Texas

2009 Rosenstiel Award, Brandies University, Waltham, Massachusetts (shared with Shinya Yamanaka and John Gurdon)
2009 Passano Award, The Passano Foundation, Baltimore, Maryland
2008 Elected to American Philosophical Society, Philadelphia, Pennsylvania
2008 Fellow, American Association for the Advancement of Sciences, Chicago, Illinois
2008 Robert Koch Award, Koch Foundation, Berlin, Germany (shared with Shinya Yamanaka and Hans Scholer)
2007 Honoree of the Arthritis Foundation of Northern California Chapter's 2007 Tribute Dinner
2007 I. & H. Wachter Award, I. & H. Wachter Foundation
2007 Doctor of Science (Honoris Causa), Mount Sinai School of Medicine, New York City, New York
2006 John Scott Award, City of Philadelphia, Philadelphia, Pennsylvania
2006 American-Italian Cancer Foundation Prize for Scientific Excellence in Medicine, New York City, New York
2006 Honorary Doctorate, Columbia University, New York City, New York
2006 The Commonwealth Club of California 18th Annual Distinguished Citizen Award
2005 Jeffrey Modell "Dare to Dream" Award, Jeffrey Modell Foundation
2005 The Linus Pauling Medal for Outstanding Contributions to Science, Stanford University
2004 New York Academy of Medicine Medal for Distinguished Contributions to Biomedical Research
2004 Alan Cranston Awardee, Alliance for Aging Research
2004 Jessie Stevenson Kovalenko Medal, National Academy of Sciences Council
2004 Rabbi Shai Shacknai Memorial Prize in Immunology and Cancer Research, The Lautenberg Center for General and Tumor Immunology
2003 J. Allyn Taylor International Prize in Medicine
2003 Commencement Speaker to Ph.D. Graduates in Molecular and Cell Biology, University of California, Berkeley
2003 Society of Neurological Surgeons Bass Award
2003 American Diabetes Association Elliott Proctor Joslin Medal
2002 Commencement Speaker to all Graduates (MS, MD, PhD), Stanford University School of Medicine
2002 Election to the Institute of Medicine of the National Academy of Sciences
2002 Basic Cell Research Award by the American Society of Cytopathology
2002 Van Bekkum Stem Cell Award
2002 Association of American Cancer Institutes 2002 Distinguished Scientist Award
2002 California Scientist of the Year
2001 Ellen Browning Scripps Society Medal
2001 Irvington Institute Immunologist of the Year
1999 E. Donnall Thomas Prize to recognize pioneering research achievements in hematology, American Society of Hematology
1999 Leukemia Society of America de Villier's International Achievement Award
1997 Election to the American Academy of Microbiology
1995 Elected Honorary Member, Israel Immunological Society
1994 President, American Association of Immunologists
1994 Montana Conservationist of the Year Award
1993 Selected Top 100 Alumni of Montana State University
1992 Election to the California Academy of Medicine
1992 Honorary Doctor of Science Degree from Montana State University
1990 Election as a Fellow of the American Association for the Advancement of Science
1990 Election to the American Academy of Arts and Sciences
1989 Pasarow Award for Outstanding Contribution to Cancer Biology
1989 The Harvey Lecture
1989 Election to the National Academy of Sciences
1987 Karel and Avice Beekhuis Professor of Cancer Biology
1987 Kaiser Award for Excellence in Preclinical Teaching
1986 Outstanding Investigator Award, National Institutes of Health

Main Research Interests

- Leukemia and cancer stem cells; programmed cell removal pathways
- Hematopoietic stem and progenitor cells
- Central nervous system stem and progenitor cells
- Lymphocyte differentiation
- Homing receptors
- Normal and neoplastic hematolymphoid development
- Phylogeny of stem cells and alloreactivity in protochordates

Research & Professional Experience

- Director, Stanford Institute for Stem Cell Biology and Regenerative Medicine, 2002 – present
- Director, Stanford Ludwig Center for Cancer Stem Cell Research and Medicine, 2007 – present
- Professor, Department of Neurosurgery, Department of Medicine, Stanford University Medical Center, 2004 – present (by courtesy)
- Director, Institute of Cancer/Stem Cell Biology and Regenerative Medicine, 2003 – 2006
- Director Stanford Cancer Center, 2006 – 2010
- Professor, Department of Biology, Stanford University, 1990 – present (by courtesy)
- Professor, Department of Developmental Biology, Stanford University, 1989 – present
- Karel E. Beekhuis Professor of Cancer Biology, 1987 – 2005
- Chairman, Stanford University Immunology Program (degree-granting), 1986 – 2001
- Professor, Department of Pathology, Stanford University, 1981 – present
- Investigator, Howard Hughes Medical Institute, Stanford University, 1990 – 1992
- Associate Professor, Department of Pathology, Stanford University, 1974 – 1981
- Assistant Professor, Department of Pathology, Stanford University, 1969 – 1974
- Research Associate, Department of Radiology, Stanford University, 1967 – 1968
- Elected Member, Steering Committee, Stanford Medical School Faculty Senate
- Elected Member, Stanford University Faculty Senate – President's Office
- Elected Member, Steering Committee [Committee of Five], Stanford University Faculty Senate – President's Office
- Premed Advisor All Chicano and Native American Premeds, Academic Affairs Office, 1968 – 1988
- Member, Stanford Medical Scientist Training Program
- Director, Stanford Medical Scientist Training Program
- Executive Committee, Stanford Medical School

Biotechnology Boards

- Founder and Director, Cellerant, Inc., 2000 – 2010
- Scientific Advisory Board, Fate Therapeutics, 2009–2010
- Co-founder, Stem Cells, Inc., Director, Chair of SAB, 1998 – present
- Member, Board of Directors, SyStemix, 1988 – 1997
- Chairman, Scientific Advisory Board, SyStemix, 1988 – 1997
- Co-founder, SyStemix, 1988
- Scientific Advisory Board, (Founding) T Cell Sciences, 1988 – 1992
- Scientific Advisory Board, (Founding) DNAX, 1981 – 1992
- Scientific Advisory Board (Founding), Amgen, 1981 – 1989

The view from stem cell land: Stem cell biology in regeneration and cancer

Irving Weissman

In 1961 as a first year medical student at Stanford University, enrolled in a medical school that provided nearly 40% of our time during all 5 years of medical school to pursue scholarly and scientific research, I bumped into Henry Kaplan, a leading physician-scientist who had provided me with a lab and the example of how to translate discoveries to medical advances. He showed me a paper written by James Till and Ernest McCulloch in the journal Radiation Research that demonstrated that bone marrow transplants at limiting numbers into lethally irradiated mice led to a cell dose-dependent formation of donor cell colonies, each of which had several cells in the monocyte, granulocyte, megakaryocytic, and erythroid lineages. While Till and McCulloch were cautious at that time not to call the colony forming cells blood-forming, or hematopoietic stem cells [HSC], that was the beginning of the field of stem cell biology.

Over 25 years later my group developed the method that isolated blood-forming stem cells in mice and humans, and then began the process to identify and isolate each stage of development from stem cell to blood cell. In our earliest experiments we showed that mouse HSC were the only active cells in bone marrow transplants that led to rapid and sustained regeneration of the blood forming system in irradiated mice. Human HSC, as we isolated them were the only cells in the tube, and therefore were essentially free of the contaminating cancer cells found in blood forming tissues of people with metastatic breast cancers or aggressive lymphomas.

We therefore moved rapidly at a company I co-founded, SyStemix, to test whether cancer-free HSC taken from a patient could be used to regenerate the blood forming system of patients receiving potentially lethal doses of combination chemotherapy, the higher doses given to eliminate even more cancer cells in the body. Although even our early results in progression-free survival of these patients were much better than restoring patients with the unmodified bone marrow or mobilized blood that was the standard of care at the time, the large pharma that bought SyStemix decided to close down the program mid-trial. . When a decade and a half later, years after the trial was complete we checked the results from women with stage IV metastatic breast cancer treated at Stanford with either cancer-free HSC or cancer-contaminated mobilized blood, at 12-15 years post-transplant 33% of the patients receiving cancer-free HSC were alive vs only 7% of those receiving mobilized blood.

The closure of the program by the pharma also brought to a halt the regenerative medicine program we had established in SyStemix, to use pure donor HSC, free of contaminating donor T cells, to regenerate the system of recipients without causing a graft vs host disease from the immunocompetent T cells in the donor graft. We planned to replace the host defective hematopoietic cells that were the cause of deficiency diseases such as severe combined immune deficiency [SCID], sickle cell and Mediterranean anemias, and genetic autoimmune disorders such as lupus, type 1 diabetes, and multiple sclerosis. We had already shown in mice that the pure HSC, lacking T cells, engrafted but did not cause graft vs host disease, the constant side affect of such transplants that causes morbidity and mortality and is countered only by lifelong immunosuppression. We had also shown that any organ or tissue graft from the HSC donor was accepted with no requirement for immunosuppression other than for conditioning of the host to accept the HSC. We had also shown that HSC from donor mice cured SCID, and if given early enough from donors lacking the genetic predilection for autoimmune diseases, prevented progression to type 1 diabetes, or to death by renal failure in lupus mice. Late stage diabetic NOD mice could be cured with a co-transplant of HSC and insulin-producing cells from the HSC donor.

One problem with HSC transplants for regenerative medicine is the necessity, currently, to take the patients close to mortality by the drugs and irradiation used to make space for new HSC, and to eliminate the immune reactive T cells and NK cells that reject allografts. In the past 15 years we have found antibodies to T cells, and in mice to NK cells, that remove the need for the immunosuppressive properties of these conditioning regimens. Recently we have found antibodies that selectively deplete HSC and their early progenitors, and these enable mice with SCID to be saved with T cell free healthy MHC matched HSC. We have found an antibody counterpart for humans, and have current funding to carry out T cell free HSC transplants into SCID children [who have lost their grafts or have no suitable donor] with antibody conditioning. This line of investigation could lead to a new era of regenerative medicine in which patients are conditioned with antibodies, probably in the outpatient setting, and transplanted with HSC from a living donor who could also be an organ donor, or in the more distant future when both HSC and tissue stem cells derived from

the same pluripotent stem cell line [ES or iPS] could be co-transplanted into HLA matched patients.

When we had finally identified and isolated mouse HSC and the cells that made up the progenitors for blood, it became clear that only HSC of all of these cells could self-renew. This came at a time when we and others were finding oncogenes or cancer-enabling or promoting genes that could not endow self-renewal. John Dick has proposed that in human acute myelogenous leukemias [AML] a leukemia stem cell [LSC] existed that shared properties with HSC, and he suggested could be HSC. That would allow genes that don't cause self-renewal to accumulate in HSC that were in transit to becoming LSC. However, in the late 1990s we found that mouse AML LSCs were at the granulocyte-macrophage progenitor [GMP] stage, and that LSC from a particular kind of human AML were at the multipotent progenitor [MPP] stage, one or a few stages below HSC, cells that usually can't self-renew and that fail in bone marrow transplants. So how did the genes that don't cause self-renewal appear in human AMLs? The clue came from finding a particular genetic change, called a chromosomal translocation wherein two different chromosomes break apart, and can re-join with the wrong partner chromosome. The joining point can make an oncogene, such as bcr to abl in chronic myelogenous leukemia, or in our case, with the leukemias we studied, joining aml1 to eto to make a fusion gene, aml1-eto. While the particular unique translocation [which had to begin in a single cell] was found in every MPP LSC in the patient, the same translocation was in a small percent of normal HSC, and these cells were normal in making all kinds of blood without making leukemias. We proposed that the mutations or inherited changes in gene expression that play roles in cancer development, here leukemia development, but did not encode the property of self-renwal, had to occur in a 'clone' of HSC derived from the first mutation in a single HSC, that could accrue the other mutations or altered gene expressions one at a time over a very long time interval. By identifying all of the mutations in the leukemia cells of a particular patient, we could prepare DNA probes specific for each mutation in that patient. We then isolated from the patient HSC, and put one HSC per well in a culture dish. We could then give factors to the HSC that make it grow and differentiate to MPP and GMP and the other progenitors, and then test each 'clone' with the entire set of DNA probes. We found that we could find many HSC with no mutations, some with only mutation 1, others with mutations w and 2 [but none with 2 alone], and others with 1 and 2 and 3, etc. We had shown the order of mutations for each leukemia, that the mutations established a clone of HSC that self-renew and gradually acquire more mutations, and that the entire process except for the last mutation occurred in HSC –like self renewing cells. The last mutation occurred in the MPP stage for several independent AMLs, and the mutations, e.g. flte internal tandem repeat or K-ras give massive proliferative capacity to the clone, hence, leukemia. We found that in chronic myelogenous leukemia [CML] the early mutation, translocation of bcr to abl, occurs in HSC, causing a very slowly progressive proliferative disorder. When the CML abruptly takes off and will kill the patient in weeks, the HSC clone with bcr-abl gave rise to a GMP that had turned on a highly proliferative gene called beta-catenin, a gene whose activity drives HSC and brain stem cells and intestinal stem cells, to name a few. So in CML progression, as in AML, early mutations prepare the cell to survive proliferation and host surveillance, and later mutations drive the cell to proliferate massively and overgrow the original organ in which the cells reside. But what about host surveillance to guard against cancer development?

This answer came from a parallel set of studies we made with blood cells. In the 1980s it became apparent the programmed cell death [PCD] of aberrant of infected cells was a property that cancer cells somehow evaded. A cell death pathway, in fact several cell death pathways were revealed; e.g., aberrant cells can signal through p53, a protein that is turned on by many alterations within a cell that could compromise the cell's functions. Complete loss of p53 expression is a hallmark of many cancers, and so we now call p53 a tumor suppressor gene. Other cells can gain expression of bcl2 or related genes, whose function is to block PCD in cells that need it, but which can be a positive stimulus to cancer, and is called an oncogene or protooncogene. To study bcl2 in the blood forming system we made mice that overexpressed bcl2 only in the GMP and its progeny white blood cells. One type of white cell, the neutrophile, normally had a 1-2 day lifespan in the body, and that didn't increase with bcl2 expression, even though these cells didn't die over many days in a test tube by themselves. But in the body they disappeared at a rate that their numbers never increased in the blood or tissues. We then found that both about to die neutrophiles [about 12 hours old from their birthdate]and the deathless bcl2 neutrophiles put on their surface 'eat me' signals for roaming scavenger cells called macrophages. So bcl2 blocked PCD, but didn't block programmed cell removal [PrCR]. The property of PrCr in dying cells allows them to finish the dying process inside of macrophages instead of out in the tissues, where their death would cause inflammation[coined as 'death induced inflammation' by a

former Brupbacher awardee, Michael Karin]. PrCR therefore appeared to be a process to prevent death induced inflammation. This all became clearer when in 1998 David Traver and I looked at genes expressed in mouse LSC but not normal mouse GMP; of the many overexpresses genes , the highest change was in a gene called CD47. In 2000 Oldenberg and Lindberg published that CD47 was an age marker on mouse red blood cells, working by acting as a ligand for a macrophage receptor called Sirp.a. Binding CD47 to Sirp.a temporarily paralyzes the macrophage so that it can't eat the cell to which it is attached as it scans blood and tissues for cells with eat me signals. So a 'don't eat me' signal comes up in all mouse leukemias. When we found that human AMLs also selectively expressed more CD47 than normal MPPs or HSCs, it was time to see how 'don't eat me' plays a role in cancer development. In a large series of experiments using patient primary solid tumors or AML or lymphomas we could show that all overexpressed CD47, that the leukemias and lymphomas at least co-expressed a protein on their surface called calreticulin, which is an 'eat me ' signal for macrophages, and that blocking CD47 with antibodies caused macrophages to eat the leukemia cells, and blocking both CD47 and calretiulin on the same cell with antibodies resulted in no eating of the leukemia cells by macrophages. The anti-CD47 blocking antibody enabled all human cancer cells to be eaten in a petri dish by human macrophages, and we therefore wondered if it could be a cancer therapeutic. We found that all human solid tumors, leukemias, lymphomas, etc. that transplant into mice that lack the T cell, B cells, and natural killer cells that would reject human tissues in mice could grow until the mouse was infused with the anti-human CD47 blocking antibody; the antibody led to massive tumor phagocytosis and death inside macrophages, sometime curing the mouse, sometimes just slowing the tumor down, but in all cases eliminating the seeds of tumors at distant sites called metastases. The antibodies that block the don't eat me CD47 synergized with other anticancer antibodies that improve phagocytosis, so that anti-CD47 plus rituximab cures most malignant lymphomas growing in mice, that anti-CD47 plus Herceptin synergizes to eliminate the most aggressive her2+ breast cancers growing in immune deficient mice, etc. With the help of funding from the Ludwig Institute and from the California Institute of Regenerative Medicine our university team has made and 'humanized' our best anti-CD47 blocking antibody, done the types of toxicity testing and antibody dosing that usually happens in biotechs or pharma, and we have submitted an IND application to the US Federal Drug Administration, were approved to begin clinical trials, and they have begun at Stanford.

This is where we are, largely, in tracking stem cells and cancer stem cells, leaving out other work the lab does. We have brought together strands of data and observation on stemness, stem cell self-renewal, precancerous progression in tissue stem cells, and the phenomenon of PrCR and its blockade in all cancers to clinical translation, and we are trying to keep it in the university long enough so that no pharma or biotech licensee can close it down as the less favorable commercial opportunity.

References:

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Lagasse E, Weissman IL (1994): bcl-2 inhibits apoptosis of neutrophils but not their engulfment by macrophages. J Exp Med 179:1047–52.

Weissman IL (2000): Translating stem and progenitor cell biology to the clinic: barriers and opportunities. Science. 287:1442–6.

Uchida N et al (2000): Direct isolation of human central nervous system stem cells. Proc Natl Acad Sci U S A. 97:14720–5.

Reya T et al (2001): Stem cells, cancer, and cancer stem cells. Nature. 414:105–11.

Weissman IL (2002): Stem cells − scientific, medical, and political issues. N Engl J Med 346:1576–9.

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Chao MP et al (2011): Programmed cell removal: a new obstacle in the road to developing cancer. Nat Rev Cancer 12:58–67.

Jan M, TM Snyder, MR Corces-Zimmerman, P Vyas, IL Weissman*, SR Quake*, and R Majeti* (2012): Clonal evolution of preleukemic hematopoietic stem cells precedes human acute myeloid leukemia. Sci Transl Med. 4:149ra18 *co-senior authors.

Muller AM et al (2012): Long-term outcome of patients with metastatic breast cancer treated with high-dose chemotherapy and transplantation of purified autologous hematopoietic stem cells. Biol Blood Marrow Transplant 18:125–33.

Willingham SB et al (2012): The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci U S A. 109:6662–7.

Tseng D et al (2013): Anti-CD47 antibody-mediated phagocytosis of cancer by macrophages primes an effective antitumor T-cell response. Proc Natl Acad Sci U S A. 110:11103–8.