Curt I. Civin M.D.

Academic Title: Professor
Primary Appointment: Pediatrics
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Personal History:

Curt Civin MD serves as Associate Dean for Research, Director of the Center for Stem Cell Biology & Regenerative Medicine, and Professor of Pediatrics and Physiology in the University of Maryland School of Medicine. Civin discovered CD34+ lympho-hematopoietic stem-progenitor cells, opening entirely new directions in stem cell, leukemia, immunology and transplantation research. He developed the first successful stem cell therapy emanating from basic research, as proved in his own patients. CD34 was the first and is still the best marker for hematopoietic stem-progenitor cells.

Identification and isolation of CD34+ blood-forming stem-progenitor cells dramatically improved stem cell research and led to improved stem cell transplantation for thousands of patients. Dr. Civin studies the cell and molecular biology of the stem and progenitor cells that form the normal blood and immune systems, and the malignant counterparts of these stem-progenitor cells, the leukemias. Currently, Dr. Civin's lab seeks to understand how the survival, proliferation, and differentiation of normal and malignant stem-progenitor cells are regulated. In basic studies, the Civin lab has comprehensively described protein-coding genes and microRNAs that are active in human hematopoietic stem-progenitor cells, using microarrays and amplification strategies. The lab's mission is to translate the resulting understanding and tools to clinical use.

In 1984, Curt Civin made the CD34 monoclonal antibody and identified CD34+ lympho-hematopoietic stem-progenitor cells, immediately opening entirely new directions in stem cell, leukemia, and transplantation research (Civin *et al.*, *J Immunol,* 1984; Leary *et al.*, *J Clin Invest*, 1984). His work led to the first successful approach emanating from basic molecular research into stem cell therapy, as Civin proved in his own patients. Civin then went on to immunophenotypically characterize most major stages and lineages of human blood and immune cell development from CD34+ progenitors (*e.g.* Loken *et al., Blood*, 1987), determine diagnostic-prognostic subtypes of leukemias (*e.g.* the CD34+CD38- subset which is highly enriched in engrafting human hematopoietic stem cells [Civin *et al., Blood*, 1996]), and discover key stem cell molecules (*e.g.* FLT3 receptor [Small *et al., PNAS*, 1994], KLF4 [Alder *et al.*, *J Immunol*, 2008), microRNAs [Georgantas *et al.*, *PNAS*, 2007], TTP [Kaplan *et al.*, *J Immunol*, 2011]).

CD34 was the first and is still the best marker for identification of hematopoietic stem-progenitor cells, as well as endothelial cells and their progenitors. The CD34 monoclonal antibodies Civin developed have provided a highly efficient technology to immunoaffinity-purify these key cells. Over 25,000 scientific articles have been published involving CD34, and thousands of patients have received CD34+ cell transplants. The direct clinical impact of CD34 also includes many thousands of patients whose leukemias have been sub-classified using monoclonal antibody immunophenotyping panels and whose cytokine-mobilized peripheral blood stem cell harvests have been assessed for numbers of CD34+ hematopoietic stem-progenitor cells. These discoveries continue to guide the field of hematopoietic stem cell research and to provide a lasting impact on patient care.

Meanwhile in his own laboratory, Civin has gone on to further study the biology of the hematopoietic stem-progenitor cells he identified. Recently, the Civin laboratory profiled mRNA and microRNA expression in primary human CD34+ hematopoietic stem-progenitor cells and proposed (Georgantas *et al.*, *PNAS*, 2007) a model wherein many of the mRNAs that specify hematopoietic differentiation are transcribed by hematopoietic stem-progenitor cells, but hematopoietic stem-progenitor cell differentiation is held in check post-

transcriptionally by microRNAs. They also investigated microRNAs that they found downregulated in many leukemias, as compared to normal hematopoietic stem-progenitor cells or more mature hematopoietic cell types. (Re)expressing these downregulated microRNAs in leukemias led to reduced cell proliferation and increased apoptosis (Scheibner *et al.*, *PLOS ONE* 2012). Indeed, the Civin lab and others have identified many microRNAs differentially expressed in normal *versus* leukemic cells, in the hopes of targeting such differences to selectively kill leukemic cells while sparing normal cells. However, expression analysis alone cannot distinguish the microRNAs driving leukemia from those associated with leukemia. Thus, the Civin lab developed a functional genomic screen to identify microRNAs with tumor suppressor activity (Cheng *et al., BioTechniques, 2013*).

As they considered the potential of these and other tumor suppressive microRNAs for antileukemic therapy, Civin realized that there is still no clearly effective means to deliver a variety of miRs to cancer cells at all sanctuary sites in the body and microRNAs are considered to be undruggable targets. Therefore, they attempted to discover small molecule compounds that selectively alter the levels of specific microRNAs in human cells. MiR-34, a paradigm tumor suppressor microRNA, is a key effector of the DNA damage response, and overexpression of miR-34a inhibits proliferation and survival of multiple cancers including leukemias. The Civin lab conducted an innovative high-throughput screen to identify clinically approved drugs that selectively upregulate miR-34 in a p53-negative leukemia cell line, with the goal of repurposing the best such drugs as leukemia therapeutics. Via this drug screen, they have found a set of drugs that selectively upregulate miR-34 and have been used in humans. This drug set includes the Artemisinins, a (low cost) drug class used widely for severe malaria with broad anti-cancer activity in preclinical studies. Artesunate has low clinical toxicity and is active against leukemia cell lines and primary human leukemia cases at low micromolar concentrations. The Civin lab very recently determined structure-activity relationships for 20 new dimeric Artemisinin analogs on growth of human acute leukemia cell lines, and they have found a highly potent analog called ART-838 that inhibits leukemia cell growth at nanomolar concentrations (Mott *et al.*, *Bioorg Med Chem,*2013) and has a high therapeutic index. In addition, they have found that mice tolerate high doses of ART-838, and that Artemisinins synergize with existing antileukemic drugs. The Civin lab is in the midst of experiments *in vitro* and in their primary xenograft model to determine predicted therapeutic indices for Artesunate and ART-838. Based on their preclinical results, they will design Phase I/II clinical trials to repurpose Artesunate and ART-838 for adult and childhood leukemia treatment and plan future Artemisinin-based successor clinical trials. They are also determining the mechanistic role of leukemia mutations, reactive oxygen species, and miR-34 in Artemisinin sensitivity in basic research studies. They hypothesize that Artesunate and ART-838 both have sufficient antileukemic potential to justify Phase I/II clinical trials in acute leukemias, and they further predict that Artesunate and/or ART-838, eventually in combination with current antileukemic drugs or other lead candidates from their screens, will improve the treatment of at least some subtypes of leukemia, and potentially other cancers. The clinical success of their research would validate the idea of discovering drugs that upregulate tumor suppressor microRNAs as an effective new strategy for antineoplastic drug development.

Discoveries are just one category of product of Civin's >30 year cancer research career. Civin has also built outstanding programs (Johns Hopkins Division of Pediatric Oncology, University of Maryland Center for Stem Cell Biology & Regenerative Medicine), and via these programs, he has inspired many highly talented trainees in cancer and stem cell research and served as a direct laboratory research mentor to several leading cancer researchers (*e.g.* Professors Kastan, Small, Gore, Mirro, Schwartz, Wiley, Friedman, Leung). In recognition of the exceptional training and career guidance he had provided for others, Civin received the 2015 American Society of Hematology Mentor Award.

Civin has also been a tireless and highly effective public advocate for childhood cancer, cancer/leukemia, transplantation, stem cell and regenerative medicine research, and translational biomedical research. His testimony on the importance of human embryonic stem cell research in the US Senate and Maryland House of Delegates is always scholarly but clear and to-the-point. His advocacy efforts led to the thriving Stem Cell Research Fund in the State of Maryland. Civin is both an inventor and chaired for a decade the Johns Hopkins Committee on Conflicts of Interest, and has spoken on the difficult regulation of these related areas. Similarly, he weaves together medicine and science and exemplifies the physician-scientist. Over his long career, Civin has led in every aspect of academic biomedicine, and he brings his abundant talents to academic missions enthusiastically.

Other Information

- Associate Dean for Research, University of Maryland School of Medicine
- Director, Center for Stem Cell Biology & Regenerative Medicine, UMSOM
- Professor, Departments of Pediatrics and Physiology, UMSOM
- Member, UM Greenebaum Cancer Center

- Member, UM Center for Biologic Therapies

Principal Previous Positions Held:

- Investigator, Pediatric Oncology Branch, National Cancer Institute/NIH, 1978-1979
- Assistant Professor, Associate Professor, Professor, King Fahd Professor, Herman & Walter Samuelson Professor; Depts of Oncology & Pediatrics, Johns Hopkins University School of Medicine, 1979-2009 (Adjunct Professor, 2009-pres)
- Director, Pediatric Oncology Division, JHUSM, 1984-2000
- Co-Director, Immunology & Hematopoiesis Division, JHUSM, 2000-2009
- Adjunct Senior Investigator, Pediatric Oncology Branch, Division of Clinical Sciences, National Cancer Institute, 2000-pres

Education:

- BA, magna cum laude, Biology/Independent Study, Amherst College, Amherst, MA, 1966-70
- MD, cum laude, Harvard Medical School, Boston, MA, 1970-74
- Pediatric Residency, Children's Hospital Medical Center, Boston, MA, 1974-76
- Fellowship in Pediatric Hematology-Oncology, National Cancer Institute, Bethesda, MD, 1976-79
- ScD (honorary), Amherst College, Amherst, MA, 2001

National Leadership Positions:

- Editorial Boards: *Experimental Hematology,* 1986-89; *Hematologic Pathology*, 1987-96; *Blood*, 1988-92; Editorial Board, *Journal of Hematotherapy,* 1992-99; *Oncology News International,* 1992-2004; *Communications in Clinical Cytometry,* 1993-98; *Clinical Cancer Research*, 1994-2001; *Cell Transplantation,* 1995-98; *Stem Cells,* 1994-96, 1998-2008 (Assoc Editor, 1998-2000; Editor-in-Chief, 2000-08)
- Young Investigators Award Selection Committee, American Society of Clinical Oncology, 1989-93 (1991-92, Chair)
- Program Committees: Multiple, including American Society of Hematology, American Society of Clinical Oncology, American Association for Cancer Research
- Medical/Scientific Advisory Boards (national, nonprofit): Sidney Kimmel Foundation for Cancer Research, 1996-pres; Gabrielle's Angels (formerly G&P Charitable Foundation For Cancer Research), 1999-pres; Leukemia Lymphoma Society, 1999-pres (Co-Chair, 2010-pres)
- Member, Subcommittee D (Translational Studies), National Cancer Institute Initial Review Group, 2005-2007
- Chair, Career Development Program, Clinical Scholar & Fellow Awards, Leukemia & Lymphoma Society, 2007-2010
- Member, National Cancer Institute Board of Scientific Advisors (BSA), 2007-2015
- Member, National Cancer Institute Clinical Trials Advisory Committee (CTAC), 2008-2015

Honors And Awards

- 1966: National Honor Society Scholarship, Amherst College
- 1970: Oscar E. Schotte Award and Scholarship in Biology, Amherst College
- 1970: Magna cum Laude, Amherst College
- 1970: Phi Beta Kappa, Amherst College
- 1970: Sigma Xi, Amherst College
- 1974: Cum Laude, Harvard Medical School
- 1974: Soma Weiss Award, Harvard Medical School
- 1980-1983: American Cancer Society Junior Clinical Faculty Fellow
- 1984-1989: Scholar Award, Leukemia Society of America
- 1986: Dr. Frederick Stohlman Award, Leukemia Society of America
- 1989: Distinguished Service Award for Leukemia Research, Leukemia Society of America National Capital Chapter
- Multiple yrs: Best Doctors in Baltimore, *Baltimore* Magazine
- 1993-2000: King Fahd Chair in Pediatric Oncology, Johns Hopkins University

- Multiple yrs: Best Doctors in America, Woodward/White Inc.
- 1999: Hope Award, Leukemia Society of America, MD Chapter (award for extraordinary achievement)
- 1999: National Inventor of the Year Award, Intellectual Property Owners Association
- 2000-2009: Samuelson Chair in Cancer Research, Johns Hopkins University
- 2001: Innovator of the Year, The Leukemia Lymphoma Society of America, MD Chapter
- 2001-Present: America's Top Doctors, Castle Connolly Medical Ltd
- 2001: Doctor of Science (honorary), Amherst College, Amherst, MA
- 2004: Return of the Child Award, Leukemia Lymphoma Society, Washington, DC (the Society's highest honor)
- 2008: David G. Marsh Genetics of Asthma and Allergic Diseases Award and Lecture
- 2009: Karl Landsteiner Memorial Award & Lectureship (American Association of Blood Banks)
- 2009: Influential Marylanders, *The Daily Record*, Baltimore, MD
- 2011: A "Top Doctor," *US News and World Report*
- 2011: The John L. Kellerman III Memorial Lecture (2011 Keynote), Maryland Stem Cell Research Fund Annual Meeting
- 2013: 2013 Baltimore Jewish Hall of Fame, Gordon Jewish Community Center, Baltimore, MD
- 2015: 2015 American Society of Hematology Mentor Award

Research Interests:

Curt Civin's breakthrough discovery of the CD34 lympho-hematopoietic stem cell antigen and monoclonal antibody has facilitated basic research in stem cell biology and leukemia and has led to improved stem cell transplantation for thousands of patients. These discoveries have led to multiple honors for Civin, including the 1999 National Inventor of the Year Award and the 2009 Karl Landsteiner Award. Civin built a leading Pediatric Oncology division at Johns Hopkins and inspired an exceptional number of talented trainees to pursue careers in translational research. While now expanding his impact on the next generation of physician-scientists at the University of Maryland School of Medicine Center for Stem Cell Biology & Regenerative Medicine, Civin's own research focuses on the roles of key molecules, especially microRNAs, in normal and leukemic stem-progenitor cells.

Research Support:

Ongoing Research Support

TRP#285855 **Leukemia & Lymphoma Society** Civin (PI) 10/1/13-09/30/16

Translational Research Award: Artemisinins for treatment of acute leukemias

Compare Artesunate vs Artemisinin-derived-dimer-838 for effects on growth of primary human acute myeloid leukemia cases and normal hematopoietic stem-progenitor cells, using in vitro and in vivo assays.

No number **National Foundation for Cancer Research** Civin (PI) 01/01/14 - 12/31/16

NFCR Fellow Award

Support general laboratory infrastructure and specific research not specifically funded by any other source.

No Number **William Lawrence & Blanche Hughes Foundation** Chen (PI) 12/1/13 - 11/30/14

Preclinical development of Artemisinins for treatment of childhood acute lymphoblastic leukemias

Determine the efficacy of Artesunate and the potent ART-838 analog against childhood acute lymphoblastic

leukemias in vitro and in vivo, as well as toxicity to normal human hematopoietic stem-progenitor cells. Role: Investigator

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2010-MSCRFII-0065 **MSCRF/TEDCO** Civin (PI) 06/30/10-06/29/15

Hematopoietic stem cell-enriched microRNAs in human stem cell differentiation and self-renewal

Understand the effects of Hematopoietic Expressed-miRs in early hematopoiesis.

R41HL110574 **NIH/NHLBI** Civin/Sturm (Multi-PI/PD) 08/01/12-04/30/14

STTR: High Efficiency Microfluidic Purification of Stem Cells to Improve Transplants

Effectively deplete erythrocytes and recover leukocytes from cord blood via microfluidic chips.

R41CA174121 **NIH/NCI** Civin/Sturm (Multi-PI/PD) 09/24/12-08/31/14

STTR: Microfluidic Processing of Leukocytes for Molecular Diagnostic Testing

Modify deterministic lateral displacement microfluidic technology to replace Wash/Concentrate Steps in leukocyte processing.

2012-MSCRFE-0272 **MSCRF/TEDCO** Kingsbury (PI) 06/30/12-06/29/14

MicroRNAs and control of quiescence and pluripotency

Identify microRNAs whose enforced expression reduces hematopoietic stem-progenitor cell ROS. Role: Investigator

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2012-MSCRFE-0244 **MSCRF/TEDCO** Scheibner (PI) 06/30/12-06/29/14

Regulation of DNA double strand break repair in human hematopoietic stem cells by microRNAs

Identify specific miRs regulated by radiation, and to determine if radiation-regulated miRs regulate DSB repair in hHSPCs. Role: Investigator

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T32CA154274 **NIH/NCI** Antalis/Civin (Multi-PI/PD) 07/01/11-06/30/16

Training Grant in Cancer Biology

Create a new program in Integrative Cancer Biology to train post-doctoral and pre-doctoral trainees committed to careers in cancer research.

U01FD004320 **FDA** Bentley/Polli (Multi-PI/PD) 09/15/11-09/14/14

University of Maryland Center of Excellence in Regulatory Science and Innovation

Supports a Collaborating Center of Excellence in Regulatory Science and Innovation (CERSI) in the national capital region. Role: Investigator

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2012-MSCRFE-0081 **MSCRF/TEDCO** Zhan (PI) 06/30/12-06/29/14

Modulation of homing and engraftment of hematopoietic stem cells by I-BAR proteins
Characterize the role of MIM gene in human HSPC homing, engraftment and mobilization, and develop small molecules targeting MIM dimerization. Role: Investigator

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K08HL097069 **NIH/NHLBI** Kaushal (PI) 09/1/09-5/31/14

Mentored Clinical Scientist Development Award: Characterization of Cell-Based Therapy for Congenital Heart Patients
Characterize endogenous cardiac stem cells from the mouse and congenital heart patients to recover a doxorubicin induced cardiomyopathy model. Role: Mentor

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2013-MSCRFII-0158 **MSCRF-TEDCO** Kaushal (PI) 06/01/13–05/30/16

Characterization of Cardiac Stem Cells in Neonates
Characterize endogenous cardiac stem cells from neonates. Role: Investigator

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R01 HL118491 **NIH/NHLBI** Kaushal (PI) 04/1/14 - 03/31/19

Biological Characterization of Cardiac Stem Cells
Better understand mechanisms by which resident cardiac stem cells exert their functional activity.
Role: Investigator

K08HL93207 **NIH/NHLBI** Banerjee (PI) 09/1/10–5/31/15

Mentored Clinical Scientist Development Award: Transcriptional Regulation of CD8+ T Cell Differentiation
Determine the roles of T-bet and Eomesodermin in CD8+ T cell subset differentiation during anti-tumor immune responses. Role: Mentor

Publications:

Key Publications:

Fox J.M., Moynihan J.R., Mott B.T., Mazzone J.R., Anders N.M., Brown P.A., Rudek M.A., Liu J.O., Arav-Boger R., Posner G.H., **Civin C. I.**, Chen X. Artemisinin-Derived Dimer ART-838 Potently Inhibited Human Acute Leukemias, Persisted in Vivo, and Synergized with Antileukemic Drugs. Oncotarget 7:7268-7279, 2016. PMID: 26771236

Heiser D., Tan Y.S., Kaplan I., Godsey B., Morisot S., Cheng W.C., Small D., **Civin C.I.** Correlated miR-mRNA expression signatures of mouse hematopoietic stem and progenitor cell subsets predict “stemness” and “myeloid” interaction networks. PLoS One 9:e94852,

2014. PMID: 24747944 PMCID: PMC3991639

Kim M.J., Tan Y.S., Cheng W.C., Kingsbury T.J., Heimfeld S., **Civin C.I.** MiR-144 and miR-451 regulate human erythropoiesis via RAB14. Br J Haematol 168:583-597, 2015. PMID: 25312678; PMCID: PMC4314389

Tan Y.S., Kim M.J., Kingsbury T.J., **Civin C.I**., Cheng W.C. Regulation of RAB5C is important for the growth inhibitory effects of miR-509 in human precursor-B acute lymphoblastic leukemia. PLoS One 9:e111777, 2014. PMID: 25368993 PMCID: PMC4219775

Alder JK, Georgantas RW, Hildreth RL, Kaplan IM, Morisot S, Yu X, McDevitt M, **Civin CI**. Kruppel-like factor 4 is essential for inflammatory monocyte differentiation *in vivo*. J Immunol 2008;180:5645-5652.

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Cheng WC, Kingsbury TJ, Wheelan SJ, **Civin CI.** A simple high-throughput technology enables gain-of-function screening of human microRNAs. BioTechniques 2013;54:77-86.

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Civin CI, Trischmann T, Kadan NS, Davis J, Noga S, Cohen K, Duffy B, Groenewegen I, Wiley J, Law P, Hardwick A, Oldham F, Gee A. Highly Purified CD34+ Cells Reconstitute Hematopoiesis. J Clin Oncol 1996;14:2224-2233.

Civin CI, Almeida-Porada G, Lee M-J, Olweus J, Terstappen LWMM, Zanjani ED. Sustained, retransplantable, multilineage engraftment of highly purified adult human bone marrow stem cells *in vivo*. Blood 1996;88:4102-4109.

Georgantas RW, Tanavde V, Malehorn M, Heimfeld S, Chen C, Carr L, Murillo F, Riggins G, **Civin CI**. Microarray and SAGE analyses identify known and novel transcripts over-expressed in hematopoietic stem cells. Cancer Res 2004;64:4434-4441.

Cramer K., Nieborowska-Skorska M., Scheibner K., Padget M., Irvine D., Sliwinski T., Haas K., Lee J., Roy D., Slupianek A., Waski M., Childers W., Copland M., Muschen M., **Civin C.I.**, Skorski T. Personalized Synthetic Lethality Induced by Targeting RAD52 in Leukemias Identified by Gene Mutation and Expression Profile. Blood 122:1293-304, 2013. PMID: 23836560 PMCID: PMC3744994

Georgantas RW, Hildreth R, Morisot S, Alder J, Liu CG, Heimfeld S, Calin GA, Croce CM, **Civin CI**. CD34+ hematopoietic stem-progenitor cell microRNA expression and function. A circuit diagram of differentiation control. Proc Natl Acad Sci 2007;104:2750-2755.

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Loken MR, Shah VO, Dattilio KL, **Civin, CI.** Flow Cytometric Analysis of Human Bone Marrow. II. Normal B Lymphocyte Development. Blood 1987;70:1316-1324.

Morisot S, Wayne AS, Bohana-Kashtan O, Kaplan IM, Gocke CD, Hildreth R, Stetler-Stevenson M, Walker RL, Davis S, Meltzer PS, Wheelan SJ, Brown P, Jones RJ, Shultz LD, **Civin CI**. High Frequencies of Leukemia Stem Cells in Poor Outcome Childhood Precursor B Acute Lymphoblastic Leukemias. Leukemia 2010;11:1859-1866.

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Sharkis SJ, Jones RJ, **Civin CI**, Jang YY. Pluripotent Stem Cell-Based Cancer Therapy: Promise and Challenges. Sci Transl Med 2012; 4:127.

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Zambidis ET, Peault B, Park TS, Bunz F, **Civin CI**. Hematopoietic differentiation of human embryonic stem cells progresses through sequential hemato-endothelial, primitive, and definitive stages resembling human yolk sac development. Blood 2005;206:860-870.

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