



TOP TEN CLINICAL RESEARCH  
ACHIEVEMENT  
AWARDS

**Clinical Research Forum's  
Top Ten Clinical  
Research Achievement Awards**

## Advancing the Welfare of Patients through Clinical Research

A single idea can transform lives. Thanks to inspired researchers and their forward-thinking supporters, new medical breakthroughs are reshaping our future. The Top 10 Clinical Research Achievement Awards honor their groundbreaking achievements.

Herbert Pardes Clinical  
Research Excellence  
Award

*Systolic Blood Pressure Intervention  
Trial (SPRINT)*

Distinguished Clinical  
Research Achievement  
Award

*A Randomized Controlled Trial of  
Cavity Shave Margins in Breast  
Cancer*

Distinguished Clinical  
Research Achievement  
Award

*Overdiagnosis of Clostridium difficile  
Infection in the Molecular Test Era*

### Clinical Research Achievement Awards

*Tetanus Toxoid  
and CCL3  
Improve Dendritic  
Cell Vaccines in  
Mice and  
Glioblastoma  
Patients*

*Lenalidomide  
plus Rituximab  
as Initial  
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*Association of  
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Use with Risk of  
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According to  
Genetic  
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*Novel  
Recurrently  
Mutated Genes  
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### Clinical Research Achievement Awards

*Topical  
Resiquimod Can  
Induce Disease  
Regression and  
Enhance T-cell  
Effector Functions  
in Cutaneous T-cell  
Lymphoma*

*NY-ESO-1–  
specific TCR–  
engineered T  
cells Mediate  
Sustained  
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*Emergency  
Department–  
Initiated  
Buprenorphine/  
Naloxone  
Treatment  
for Opioid  
Dependence*

## About the Top 10 Clinical Research Achievement Awards

The Top 10 Clinical Research Achievements Awards recognize outstanding accomplishments in clinical research that identify major advances resulting from the nation's investment in research to benefit the health and welfare of its citizens. The Top 10 Awards are a signature program of the Clinical Research Forum, a leading organization committed to promoting understanding and support for clinical research and its impact on health and healthcare. For more information, visit [www.clinicalresearchforum.org/top10](http://www.clinicalresearchforum.org/top10).



## About the Clinical Research Forum

The Clinical Research Forum convenes annually to allow industry leaders to discuss issues facing the field, best practices, and promote understanding and support for clinical research and its impact on health and healthcare. Through its activities, the Forum has increasingly played a national advocacy role in supporting broader interests and needs of clinical research. For more information, visit [www.clinicalresearchforum.org](http://www.clinicalresearchforum.org). If you are interested in joining Clinical Research Forum, please email [admin@clinicalresearchforum.org](mailto:admin@clinicalresearchforum.org) or call (202) 367-1176.



## Herbert Pardes Award for Clinical Research Excellence

**Project Title:** Systolic Blood Pressure Intervention Trial (SPRINT)

**Publication:** *SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015;373(22):2103-2116*

**Summary:** Prior to SPRINT, definitive data evaluating the treatment of systolic blood pressure (SBP) to levels below 150 mmHg were unavailable. This prevented consensus on a recommended SBP treatment goal. In response, an expert panel convened by the National Heart Lung and Blood Institute recommended a clinical trial in non-diabetic patients to determine whether a lower SBP goal reduces hypertension-related complications more than lowering SBP to a standard goal. Thus, SPRINT enrolled 9,361 individuals and randomized them to a SBP target of less than 120 mmHg (Intensive) or one less than 140 mmHg (Standard). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, and cardiovascular death.

The intervention was stopped early after a median follow-up of 3.26 years due to a 25% lower rate of the primary composite outcome in the Intensive group (hazard ratio (HR) (95% confidence interval (CI) was 0.75: 0.64 to 0.89,  $P < 0.001$ ) and 27% reduction in all-cause mortality (HR: 0.73: 0.60 to 0.90,  $p = 0.003$ ). Overall serious adverse events (SAEs) did not differ between groups (Intensive: 38.3% compared to Standard: 37.1%,  $p = 0.25$ ), but small yet significantly increased rates of SAEs were noted due to hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure. Thus, SPRINT demonstrated that targeting a SBP of less than 120 mmHg vs. one less than 140 mmHg, reduced fatal and nonfatal major cardiovascular events, and death from any cause. Despite significant increases in some adverse effects, the overall benefits of the Intensive strategy exceeded the harms.

**Authors:** Jackson T. Wright, Jr., Jeff D. Williamson, Paul K. Whelton, Joni K. Snyder, Kaycee M. Sink, Michael V. Rocco, David M. Reboussin, Mahboob Rahman, Suzanne Oparil, Cora E. Lewis, Paul L. Kimmell, Karen C. Johnson, David C. Goff, Jr., Lawrence J. Fine, Jeffrey A. Cutler, William C. Cushman, Alfred K. Cheung, Walter T. Ambrosius.



**Institutions:** Division of Nephrology and Hypertension, University Hospitals Case Medical Center, Case Western Reserve University (JTW, MR), and Division of Nephrology and Hypertension, Louis Stokes Cleveland Veterans Affairs (VA) Medical Center (MR), Cleveland; Sticht Center on Aging (JDW, KMS), Section on Nephrology (MVR), and Department of Biostatistical Sciences (DMR, WTA), Wake Forest School of Medicine, Winston-Salem, NC; Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans (PKW); Clinical Applications and Prevention Branch, National Heart, Lung, and Blood Institute (JKS, LJF., JAC), and Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (PLK), Bethesda, MD; Divisions of Cardiovascular Diseases (SO) and Preventive Medicine (CEL), University of Alabama at Birmingham, Birmingham; Department of Preventive Medicine, University of Tennessee Health Science Center (KCJ), and the Preventive Medicine Section, VA Medical Center (WCC), Memphis; School of Public Health, University of Colorado, Aurora (DCG); and Division of Nephrology and Hypertension, University of Utah, Salt Lake City (AKC)

**Funding:** The Systolic Blood Pressure Intervention Trial is funded with Federal funds from the National Institutes of Health (NIH), including the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA), and the National Institute of Neurological Disorders and Stroke (NINDS), under Contract Numbers HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, HHSN268200900049C, and Inter-Agency Agreement Number A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. The SPRINT investigators acknowledge the contribution of study medications (azilsartan and azilsartan combined with chlorthalidone) from Takeda Pharmaceuticals International, Inc. All components of the SPRINT study protocol were designed and implemented by the investigators. The investigative team collected, analyzed, and interpreted the data. All aspects of manuscript writing and revision were carried out by the coauthors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the U.S. Department of Veterans Affairs, or the United States Government. For a full list of contributors to SPRINT, please see the supplementary acknowledgement list: ClinicalTrials.gov Identifier: NCT01206062.

Acknowledgement of the support from the following CTSA's funded by NCATS:  
CWRU: UL1TR000439, OSU: UL1RR025755, U Penn: UL1RR024134& UL1TR000003, Boston: UL1RR025771, Stanford: UL1TR000093, Tufts: UL1RR025752, UL1TR000073 & UL1TR001064, University of Illinois: UL1TR000050, University of Pittsburgh: UL1TR000005, UT Southwestern: 9U54TR000017-06, University of Utah: UL1TR000105-05, Vanderbilt University: UL1 TR000445, George Washington University: UL1TR000075, University of CA, Davis: UL1 TR000002, University of Florida: UL1 TR000064, University of Michigan: UL1TR000433, Tulane University: P30GM103337 COBRE Award NIGMS.

## Distinguished Clinical Research Achievement Award

**Project Title:** A Randomized Controlled Trial of Cavity Shave Margins in Breast Cancer

**Publication:** *N Engl J Med.* 2015; 373:503-510.

**Summary:** Every year, roughly 300,000 women in the United States are diagnosed with breast cancer; most at an early stage when breast conserving surgery is the mainstay of management. Yet, despite surgeons' best efforts, 20-40% of these patients will have positive margins (i.e., cancer cells abutting the edge of the resection specimen). As positive margins correlate with increased locoregional recurrence, these women often return to the operating room to have further tissue excised. This is a harrowing experience for patients, and one that results in higher costs and longer time to adjuvant therapy.

Various modalities have been explored to decrease re-excision rates. No technique was perfect, but retrospective studies, evaluating the concept of cavity shave margins (i.e., taking a small rim of tissue around the cavity during initial resection), had shown promising results. Critics argued that these studies were intrinsically flawed, that selectively removing tissue where the cancer approached the edge based on intraoperative imaging and gross evaluation may yield equivalent results, and that taking additional tissue circumferentially would adversely affect cosmetic outcome. What was needed was a simple randomized controlled trial.

We asked surgeons to do the operation as they normally would, taking more tissue in selective areas as they saw fit, until they were ready to close. Then, a sealed envelope was opened in the operating room, randomizing patients to either have a little more tissue taken all the way around the cavity ("shave"), or for the surgeon to close ("no shave"). We evaluated margin positivity, re-operation rates, patient-reported cosmetic outcomes, complication rates, intraoperative time, and are following patients for five years to evaluate long-term locoregional recurrence rates.

Our finding that this simple technique, that takes only 10 minutes to perform, cut the positive margin and re-excision rate in half without increasing complication rate or worsening patient-reported cosmetic outcome was published in the *New England Journal of Medicine*, lauded as one of ASCO's key clinical advances for 2016, been included in the "Toolbox" of recommendations by the American Society of Breast Surgeons to reduce re-excision rates, and has spurred a larger multicenter randomized controlled trial to prove external generalizability. This truly may become practice-changing for many surgeons worldwide.

**Authors:** Anees B. Chagpar, Brigid K. Killelea, Theodore N. Tsangaris, Meghan Butler, Karen Stavris, Fangyong Li, Xiaopan Yao, Veerle Bossuyt, Malini Harigopal, Donald R. Lannin, Lajos Pusztai, D.Phil., and Nina R. Horowitz.

**Institutions:** Yale University School of Medicine, Yale Cancer Center, Thomas Jefferson University

**Funding:** Yale Cancer Center



*Anees B. Chagpar, M.D., M.P.H*

## Distinguished Clinical Research Achievement Award

**Project Title:** Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era

**Publication:** *JAMA. Intern Med.* 2015 175(11):1792-801.

**Summary:** In 2009-2010, as more and more hospitals reported dramatic increases in the numbers of *C difficile* infections diagnosed by PCR, we recognized an urgent need to investigate the clinical significance of positive PCR results when conventional toxin tests were negative. We assembled a multidisciplinary team of clinical microbiologists, infectious diseases physicians, epidemiologists, biostatisticians, and health services research experts to answer this question. In preparation, we performed a retrospective study to evaluate the frequency and duration of symptoms and adverse events in previous patients tested for *C difficile* at our institution and validate the data collection methods and outcome measures to be used in the prospective study. The retrospective study also provided important evidence that toxin tests had not missed significant cases of *C difficile* infection at our institution during the prior five years. We then designed and conducted a prospective cohort study of nearly 1500 hospitalized patients tested for *C difficile* including prospective symptom verification and measurement of all relevant *C difficile*-related treatment and outcomes. This study showed conclusively that *C difficile*-related complications are rare among hospitalized most patients with positive PCR results and negative toxin tests and most patients in this group had outcomes similar to negative control patients without treatment. The impact of this research has been that UC Davis has continued using toxin tests as the primary method of diagnosing *C difficile* infection and other hospitals nationally are reconsidering and revising their diagnostic approach to *C difficile* infection in an effort to reduce PCR-related overdiagnosis.

**Authors:** Christopher R. Polage, Clare E. Gyorke, Michael A. Kennedy, Jhansi L. Leslie, David L. Chin, Susan Wang, Hien H. Nguyen, Bin Huang, Yi-Wei Tang, Lenora W. Lee, Kyoungmi Kim, Sandra Taylor, Patrick S. Romano, Edward A. Panacek, Parker B. Goodell, Jay V. Solnick, Stuart H. Cohen.

**Institutions:** University of California, Davis School of Medicine, Memorial Sloan Kettering Cancer Center, Weill Medical College of Cornell University



*Christopher R. Polage, M.D., M.A.S*

**Funding:** This study was supported by grant number UL1 RR024146 and TL1 RR024145-06 from the National Center for Research Resources (CRP); grant number UL1TR000002 and linked award TL1TR000133 from the National Center for Advancing Translational Sciences (DLC); and grant number T32HS022236 from the Agency for Healthcare Research and Quality (AHRQ) through the Quality Safety Comparative Effectiveness Research Training (QSCERT) Program (DLC). *C. difficile* diagnostic test kits and reagents were received from Cepheid, Meridian Biosciences, TechLab, and Alere.

## Top 10 Clinical Research Achievement Award Recipient

**Project Title:** Tetanus Toxoid and CCL3 Improve Dendritic Cell Vaccines in Mice and Glioblastoma Patients.

**Publications:** *Nature*. 2015;519(7543):366-9.

**Summary:** Dendritic cells (DCs), upon activation, migrate to draining lymph nodes and present acquired antigens to the lymphocytes of the immune system to elicit a coordinated adaptive immune response. DCs loaded with tumor antigens have been used as cellular vaccines in patients with advanced cancers, including glioblastoma (GBM), in attempts to boost antitumor immunity. Since the migration of DCs to vaccine-site draining lymph nodes was known to be limited from prior human and murine studies, Drs. Duane A. Mitchell, Kristen A. Batich, and John H. Sampson explored whether migration to lymph nodes could be enhanced by prior administration of the common tetanus-diphtheria (Td) vaccine or unpulsed mature DCs at the immunization site. Patients with newly-diagnosed GBM were randomized, in a blinded fashion, to receive Td-priming or unpulsed autologous DCs unilaterally prior to vaccination with human cytomegalovirus pp65 RNA-pulsed DCs. We and other laboratories have shown that pp65 is frequently expressed in GBM tumors and not surrounding normal brain, offering potential to co-opt this viral protein as a tumor-specific target. Td-priming significantly enhanced DC trafficking to regional lymph nodes bilaterally and significantly improved progression-free survival (>27.0 months vs 10.8 months) and overall survival (>36.6 months vs 18.5 months). These studies demonstrated that CMV pp65 may serve as a novel target for immunotherapy in patients with GBM and that DC migration to vaccine-site draining lymph nodes is a major axis for intervention to improve DC-based immunotherapy. A randomized phase 2 clinical trial is underway to confirm these results (clinicaltrials.gov protocol NCT02465268).



*Duane A. Mitchell, M.D. Ph.D.*

**Authors:** Duane A. Mitchell, Kristen A. Batich, Michael D. Gunn, Min-Nung Huang, Louis Sanchez-Perez, Smita K. Nair, Kendra L. Congdon, Elizabeth A. Reap, Gary E. Archer, Annick Desjardins, Alan H. Friedman, Henry S. Friedman, James E. Herndon II, April Coan, Roger E. McLendon, David A. Reardon, James J. Vredenburgh, Darell D. Bigner, John H. Sampson

**Institutions:** University of Florida and Duke University

**Funding:** Career development awards supporting foundation studies of this work include the Accelerate Brain Cancer Cure (ABC2) Young Investigator's Award (D.A.M.) and Duke University SPORE in Brain Cancer Career Development Award (D.A.M). This work was supported by grants from the National Institutes of Health National Institute of Neurological Disorders and Stroke Specialized Program of Research Excellence in brain cancer (P50CA108786; D.D.B. and J.H.S.) and SRC on Primary and Metastatic Tumors of the CNS (P50-NS20023, D.D.B. and J.H.S.) as well as NIH RO1 (R01-CA177476-01, J.H.S.; R01-NS067037, D.A.M.), P01 (P01-CA154291-01A1, D.D.B. and J.H.S.), and P50 (P50-NS020023-30, D.D.B. and J.H.S.) funding sources. Additional support is from the National Brain Tumor Society (D.A.M. and J.H.S.), the American Brain Tumor Association (D.A.M. and J.H.S), The Kinetics Foundation, (J.H.S) Ben and Catherine Ivy Foundation (J.H.S.), and in part by Duke University's Clinical & Translational Science Awards grant 1UL2 RR024128-01 from the National Institutes of Health National Center for Research Resources.



## Top 10 Clinical Research Achievement Award Recipient

**Project Title:** Lenalidomide plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma

**Publication:** *N Engl J Med.* 2015;373:1835-44.

**Summary:** Optimal treatment for MCL remains a clinical challenge and unmet need. Conventional, intensive treatment may be out of reach or undesirable for many MCL patients, who often receive less intensive or palliative care that is of limited benefit. Patients who do qualify for chemotherapy and undergo treatment frequently relapse, underscoring the need for treatment alternatives. We hypothesized that the biologic combination of lenalidomide and rituximab, which targets both the tumor cells and the microenvironment, could lead to high responses as initial therapy without the need of chemotherapy. We conducted a multi-center phase 2 single arm study to test the hypothesis. The results of this study demonstrate that this outpatient treatment regimen is highly active and well tolerated for patients with previously untreated mantle-cell lymphoma. The lenalidomide plus rituximab combination is potentially applicable to a broad-range of patients with MCL, particularly those who are not candidates for or wish to avoid intensive chemotherapy and stem cell transplant. This study provides an innovative treatment framework for future studies that could be either combined with other active biologic agents, or compared to conventional chemotherapy.

**Authors:**

Jia Ruan, Peter Martin, Bijal Shah, Stephen J. Schuster, Sonali M. Smith, Richard R. Furman, Paul Christos, Amelyn Rodriguez, Jakub Svoboda, Jessica Lewis, Orel Katz, Morton Coleman, and John P. Leonard.

**Institutions:** Meyer Cancer Center, Weill Cornell Medical College and New York-Presbyterian Hospital, Moffitt Cancer Center, University of Pennsylvania Abramson Cancer Center, University of Chicago Medical Center

**Funding:** Supported in part by Celgene Corporation and a Weill Cornell Medical College Clinical Translational Science Center grant (UL1-TR000457-06).



*Jia Ruan M.D., Ph.D.*

## Top 10 Clinical Research Achievement Award Recipient

**Project Title:** Association of Aspirin and NSAID Use with Risk of Colorectal Cancer According to Genetic Variants

**Publication:** *JAMA*. 2015;313(11):1133-1142

**Summary:** In the past decade years, genome-wide association studies (GWAS) have rapidly expanded our knowledge of the genetic architecture of colorectal cancer, identifying over 35 common germline variants associated with the disease. Despite this progress in characterizing genetic susceptibility, it is clear that lifestyle and environmental risk factors remain important predictors of an individual's risk of developing colorectal cancer. In particular, regular aspirin use has been consistently shown to reduce the risk of colorectal cancer. Gene-environment interactions are situations in which the association of a genetic variant with a complex disease such as colorectal cancer is modified by the presence or absence of a particular lifestyle or environmental factor. The proper study of gene-environment interactions requires large number of participants for adequate statistical power, preferably within well-characterized epidemiological studies that have collected detailed data on lifestyle risk factors for colorectal cancer. Thus, in 2009, we assembled the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and the Colon Cancer Family Registry (CCFR), which encompasses 18 cohort and population-based case-control studies across North America, Australia, and Europe that have been characterized extensively according to germline genetic, clinical, and established environmental risk factors, including aspirin use. Through this consortium, we sought to discover novel genome-wide significant interactions between germline variants and lifestyle factors such as regular aspirin use and risk of colorectal cancer. Ultimately, the goal of this work is to develop strategies in which genetic information can be used for more precise prevention strategies for colorectal cancer.

**Authors:** Hongmei Nan, Carolyn M. Hutter, Yi Lin, Eric J. Jacobs, Cornelia M. Ulrich, Emily White, John A. Baron, Sonja I. Berndt, Hermann Brenner, Katja Butterbach, Bette J. Caan, Peter T. Campbell, Christopher S. Carlson, Graham Casey, Jenny Chang-Claude, Stephen J. Chanock, Michelle Cotterchio, David Duggan, Jane C. Figueiredo, Charles S. Fuchs, Edward L. Giovannucci, Jian Gong, Robert W. Haile, Tabitha A. Harrison, Richard B. Hayes, Michael Hoffmeister, John L. Hopper, Thomas J. Hudson, Mark A. Jenkins, Shuo Jiao, Noralane M. Lindor, Mathieu Lemire, Loic Le Marchand, Polly A. Newcomb, Shuji Ogino, Bethann M. Pflugeisen, John D. Potter, Conghui Qu, Stephanie A. Rosse, Anja Rudolph, Robert E. Schoen, Fredrick R. Schumacher, Daniela Seminara, Martha L. Slattery, Stephen N. Thibodeau, Fridtjof Thomas, Mark Thornquist, Greg S. Warnick; Brent W. Zanke, W. James Gauderman, Ulrike Peters, Li Hsu, Andrew T. Chan.

**Institutions:** Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis; National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; Epidemiology Research Program, American Cancer Society, Atlanta, Georgia; Huntsman Cancer Institute, University of Utah, Salt Lake City; Department of Epidemiology, University of Washington School of Public Health, Seattle; Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine, Chapel Hill; Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany; German Cancer Consortium, Heidelberg, Germany; Division of Research, Kaiser Permanente Medical Care Program of Northern California, Oakland; Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles; Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany; Prevention and Cancer Control, Cancer Care Ontario, Toronto, Ontario, Canada; Genetic Basis of Human Disease Division, Translational Genomics Research Institute (TGen), Phoenix, Arizona; Department of Medical Oncology, Dana Farber Cancer Institute, Boston, Massachusetts; Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; Division of Epidemiology, Department of Population Health, New York University School of Medicine, New York, New York; Melbourne School of Population Health, University of Melbourne, Victoria, Australia; Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; Ontario Institute for Cancer Research, Toronto, Ontario, Canada; Department of Health Sciences Research, Mayo Clinic, Scottsdale, Arizona (Lindor); Epidemiology Program, University of Hawaii Cancer Center, Honolulu; Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts (Ogino); Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; Centre for Public Health Research, Massey University, Wellington, New Zealand; Department of Medicine and Epidemiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Department of Internal Medicine, University of Utah Health Sciences Center, Salt Lake City; Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota; Department of Medical Genetics, Mayo Clinic, Rochester, Minnesota; Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis; Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; Department of Biostatistics, University of Washington, Seattle; Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

**Funding:** U01 CA137178, R01 CA137178, K24 DK098311. The principal investigator also acknowledges career previous support as a Damon Runyon Cancer Research Foundation Clinical Investigator.





## Top 10 Clinical Research Achievement Award Recipient

**Project Title:** Topical Resiquimod Can Induce Disease Regression and Enhance T-cell Effector Functions in Cutaneous T-cell Lymphoma

**Publication:** *Blood*. 2015; 126(12):1452-146.

**Summary:** The principal investigator brought together a large research team with unique research skills to study the effects of potentially activating the innate immune response with the Toll-like receptor (TLR) agonist Resiquimod on the progress of tumor lesions among patients with cutaneous T-cell lymphoma (CTCL). Presently, the only known cure for CTCL, which is a lymphoma of skin trafficking T-cells, is allogeneic stem cell transplantation. However, our laboratory based research had suggested that Resiquimod, which is a TLR 7/8 agonist, could broadly activate the immune response of patients with advanced forms of CTCL. With provision of the drug from Spirig Pharma in Switzerland, and funding from the National Cancer Institute and the Division of Orphan Products, FDA, a phase I trial was conducted. Resiquimod was applied as a gel to a maximum of only 4 skin plaques and tumors. Eleven of 12 patients significantly improved, including two patients with highly refractory and active disease for more than 10 years, each of whom experienced complete remission which has been sustained more than two years beyond treatment discontinuation. We were able to demonstrate that malignant T-cells could be eradicated from treated lesions. Uniquely, even untreated distant lesions regressed indicating that Resiquimod could be well absorbed through the skin and could activate the systemic antitumor immune response. We did confirm that circulating dendritic cells and NK cells were activated.

Thus, Resiquimod produced exceptionally high response rates, induced regression of even untreated lesions, eradicated malignant cells from treated lesions and activated circulating immune cells. The implications of these observations are significant for other skin malignancies including malignant melanoma, squamous cell carcinoma and Merkel cell carcinoma.

**Authors:** Alain H. Rook, Joel M. Gelfand, Maria Wysocka, Andrea B. Troxel, Bernice Benoit, Christian Surber, Rosalie Elenitsas, Marie A. Buchanan, Deborah S. Leahy, Rei Watanabe, Ilan R. Kirsch, Ellen J. Kim, and Rachael A. Clark

**Institutions:** Department of Dermatology and the Center for Clinical Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Department of Dermatology, University Hospitals Basel and Zürich, Switzerland, Department of Dermatology, University of Tokyo, Japan, Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Adaptive Biotechnologies, Dana-Farber/Brigham and Women's Cancer Center



*Alain H. Rook M.D.*

**Funding:** R01-CA122569 NCI/NIH (Rook PI) Toll Receptor Ligand Therapy in Cutaneous T-Cell Lymphoma, FD-RO1-04092-01-A1 FDA Orphan Products (Rook P.I.) Phase 1 Study of Resiquimod Gel Therapy for the Treatment of Cutaneous T-Cell Lymphoma, 6177-10 Leukemia and Lymphoma Society (Rook PI) TLR Agonists synergize with interferon gamma: Relevance to T-cell lymphoma.

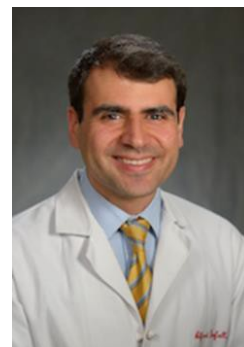
## Top 10 Clinical Research Achievement Award Recipient

**Project Title:** NY-ESO-1–specific TCR–engineered T cells Mediate Sustained Antigen-specific Antitumor Effects in Myeloma

**Publication:** *Nature Medicine*. 2015; 21:914-921

**Summary:** This study grew from a long-standing collaboration between Dr. June and Dr. Stadtmauer to test new immunotherapy strategies for multiple myeloma and collaborations between Dr. June and other clinical investigators at Penn to test anti-CD19 CAR T cells in B cell malignancies; these trials showed that anti-CD19 CAR T cells are very effective at eliminating both cancerous B cells and their normal counterparts. Based on these results and previously published studies suggesting that rare CD19-expressing B cells may have myeloma stem-cell activity, Drs. Garfall and Maus, junior investigators working with Drs. June and Stadtmauer, collaboratively designed a clinical trial testing anti-CD19 CAR T cells in multiple myeloma. The study combined high-dose melphalan (a standard myeloma therapy) to deplete myeloma plasma cells and added anti-CD19 CAR T cells to target the suspected myeloma stem-cell population. The first patient who received this therapy experienced a >1-year complete response despite experiencing only a six-month partial response to a prior cycle high-dose melphalan earlier in her disease course. One other subject on this pilot study experienced a similar response. These results are promising given the treatment-refractory state of these patients' cancers when they enrolled on this study. Our results suggest that the general concept of specifically targeting minor cancer stem-cell populations with potent immunotherapies may be a promising strategy for treating cancer. We are currently undertaking additional studies to substantiate our initial results. We predict that anti-CD19 CAR T cells may synergize with other anti-myeloma therapies, including other CAR T cell therapies.

**Authors:** Aaron P Rapoport, Edward A Stadtmauer, Gwendolyn K Binder-Scholl, Olga Goloubeva, Dan T Vogl, Simon F Lacey, Ashraf Z Badros, Alfred Garfall, Brendan Weiss, Jeffrey Finklestein, Irina Kulikovskaya, Sanjoy K Sinha, Shari Kronsberg, Minnal Gupta, Sarah Bond, Luca Melchiori, Joanna E Brewer, Alan D Bennett, Andrew B Gerry, Nicholas J Pumphrey, Daniel Williams, Helen K Tayton- Martin, Lilliam Ribeiro, Tom Holdich, Saul Yanovich, Nancy Hardy, Jean Yared, Naseem Kerr, Sunita Philip, Sandra Westphal, Don L Siegel, Bruce L Levine, Bent K Jakobsen, Michael Kalos, and Carl H June.



Alfred L. Garfall M.D.

**Institution:** The Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, Maryland, USA. Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA. Adaptimmune Ltd, Oxford, UK. Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland, USA. Department of Pathology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA. School of Mathematics and Statistics, Carleton University, Ottawa, Ontario, Canada, Cambridge Biomedical, Cambridge, Massachusetts, USA.

**Funding:** Funding support was provided by Novartis and an NIH grant to Dr. June (5R01CA165206). This research was also supported by career development grants from the National Institutes of Health to Dr. Garfall (K12CA076931 and T32CA009615) and Dr. Maus (K08CA166039). Additional support was provided by grants from the International Society for Advancement of Cytometry (to Dr. Mahnke), and the University of Pennsylvania Institute for Translational Medicine and Therapeutics (to Dr. Garfall); and a Conquer Cancer Foundation Young Investigator Award (to Dr. Maus).

## Top 10 Clinical Research Achievement Award Recipient

**Project Title:** Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence

**Publication:** *JAMA. 2015;313(16):1636-1644.*

**Summary:** This was the first known randomized clinical trial comparing three treatment strategies for opioid-dependent patients receiving emergency care. Researchers conducted a randomized trial of more than 300 opioid-dependent individuals in an urban teaching hospital. After initial screening in the emergency department (ED), study participants were randomized into three groups: a referral group that received a list of addiction treatment services in the area; a brief intervention group that received a brief motivational consultation and was directly linked to treatment services; and a medication initiation group that received a brief intervention and treatment with buprenorphine/naloxone, a treatment for opioid use disorder that decreases withdrawal, cravings, and opioid use.

Patients receiving ED-initiated buprenorphine were significantly more likely to be engaged in addiction treatment after 30 days (78% versus 37% for the referral group and 45% in the brief intervention group). This group also had reduced self-reported illicit opioid use and decreased use of inpatient addiction treatment services, which suggests more efficient and less costly use of resources. This study provides evidence that ED-initiated buprenorphine with community follow-up should help increase access to treatment options for opioid use disorder, a chronic and relapsing medical condition that is increasingly prevalent and linked to an increasing toll of overdose deaths.

**Authors:** Gail D’Onofrio, M.D., M.S., Patrick G. O’Connor, M.D., M.P.H, Michael V. Pantalon, Ph.D., Marek C. Chawarski, Ph.D., Susan H. Busch, Ph.D., Patricia H. Owens, M.S., Steven L. Bernstein, M.D., David A. Fiellin, M.D.

**Institution:** Yale University

**Funding:** The study was supported by grant 5R01DA025991 from the National Institute on Drug Abuse (NIDA), and Reckitt-Benckiser Pharmaceuticals provided buprenorphine through NIDA



*Gail D’Onofrio M.D., M.S.*