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Stand Up To Cancer Announces $11M Collaborative, Multi-disciplinary Research Program; Microsoft Will Bring Power of AI to Investigate Immune System Response to Cancers

"Convergence" Teams of Life Scientists, Bioengineers and Microsoft Machine Learning Experts to Investigate New Cancer Therapies

Lustgarten Foundation and Society for Immunotherapy of Cancer (SITC) Provide Key Support

Santa Monica, CA (January 30, 2018) — Stand Up To Cancer (SU2C) announces today a "Convergence 2.0" research initiative that awards $11 million to seven multi-disciplinary research teams to investigate immune system response to cancers. The multi-institutional teams being announced today at SU2C's Scientific Summit draw from the nation's top academic research centers and will have access to Microsoft Research's experts in machine learning and artificial intelligence.

Each team will be comprised of experts in life sciences, physical sciences, mathematics and engineering and will have the opportunity to work collaboratively with Microsoft's machine learning experts to discover key aspects of the interaction between cancer and the immune system that can lead to the development of new treatments.

In addition to the significant support from Microsoft, the Lustgarten Foundation for Pancreatic Cancer Research committed $1.76 million in funding, and the Society for Immunotherapy of Cancer (SITC) will provide $1 million to support post-doctoral fellows on five of the seven teams, providing an opportunity for early-career scientists to work with leading researchers.

"It's an exciting new time in cancer research. Investigation of the human genome and individual tumor genetics is producing mammoth amounts of data that need to be interpreted in order to deliver the best possible cancer care," said Phillip A. Sharp, PhD, chairman of the SU2C Scientific Advisory Committee and institute professor at the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology. In 2011, Dr. Sharp co-authored the seminal MIT white paper, "*The Third Revolution: The Convergence of the Life Sciences, Physical Sciences, and Engineering*."

"Our first convergence research cohort, announced in 2016, established the effectiveness of a broad multidisciplinary approach for creating models for how cancer grows and reacts to treatment," said Arnold J. Levine, PhD, chair of the SU2C Convergence Initiative, co-vice chairman of the SU2C Scientific Advisory Committee and Professor emeritus, Institute for Advanced Study. Through the collaboration with Microsoft and using well characterized, de-identified patient data, we will look at how individuals

vary in their immune responses to an array of therapies. And we will create standardized measurement protocols that may speed the development of cancer therapies and ultimately save lives."

Working with Microsoft machine learning experts, SU2C researchers will be able to study terabytes of data derived from multiple data sets, including information on the patient's genome, imaging studies, medical and medication records, among other data. Over the course of three years, the Stand Up To Cancer Convergence 2.0 Research Teams will explore a host of factors that may contribute to a patient's response to a specific regimen, including: DNA mismatch repair, tumor-specific proteins from mutated genes, cytokine function and natural killer cells. These therapies will be studied both when they do work, and when they don't, to inform medical practice.

"We're thrilled to collaborate with Stand Up To Cancer on this amazing opportunity to merge Microsoft's state-of-the-art machine learning expertise, our work with the intelligent cloud, and our world-class research capabilities with their network of renowned researchers and clinicians – all to accelerate progress in cancer immunotherapy. Ultimately, we aim to provide patients with targeted therapies which control cancer with less damage than current therapies," said Dr. Jennifer Chayes, Technical Fellow & Managing Director, Microsoft Research New England, New York, Montreal. "All of us at Microsoft Research want to empower cancer researchers and ultimately cancer patients. Our goal is for patients to have more effective and less damaging therapies available, which will increase both their longevity as well as their quality of life."

Dr. Levine will announce the seven teams that are receiving the awards at the eighth annual Scientific Summit, organized by the American Association for Cancer Research (AACR) in its capacity as the Scientific Partner of SU2C.

The teams chosen by the Convergence 2.0 Selection Committee and SU2C Scientific Advisory Committee are:

- **Computational deconstruction of neoantigen-TCR degeneracy for cancer immunotherapy**
  Additional Support: Lustgarten Foundation; SITC
  Team Leaders: Benjamin Greenbaum, PhD, at the Icahn School of Medicine at Mount Sinai Hospital; Vinod Balachandran, MD, Memorial Sloan Kettering Cancer Center
  Team Members: Marta Łuksza, PhD, Icahn School of Medicine at Mount Sinai; Eileen M. O'Reilly, MD, David M. Rubenstein Center for Pancreatic Cancer Research; Jedd Wolchok, MD, PhD, Memorial Sloan Kettering Cancer Center
  Collaborators: Nina Bhardwaj, MD, PhD, Icahn School of Medicine at Mount Sinai; Curtis Callan, PhD, Princeton University; Timothy Chan, MD, PhD, Memorial Sloan Kettering Cancer Center; Simona Cocco, PhD, Ecole Normale Supérieure; Jeffrey Drebin, MD, PhD, Memorial Sloan Kettering Cancer Center; Anthony Gill, MD, Professor of Surgical Pathology, University of Sydney; Christine Iacobuzio-Donahue, MD, PhD, Memorial Sloan Kettering Cancer Center; Dmitry Krotov, PhD, Member, Institute for Advanced Study; Taha Merghoub, PhD, Memorial Sloan Kettering Cancer Center; Rémi Monasson, PhD, Centre National de la Recherche Scientifique; Thierry Mora, Ecole Normale Supérieure; Aleksandra Walczak, PhD, Ecole Normale Supérieure

Project Summary: The team will build on the work started under a Convergence 1.0 grant but further explore the underpinnings that constitute pancreatic survivorship. By looking at the few individuals who survive pancreatic cancer for long periods of time, the team identified an initial set of high-quality neoantigens, or protein tags, on cancer cells that the immune system recognizes. This project will continue the work to understand what makes a high-quality neoantigen and how the microbiome influences how the immune system recognizes it, with the goal of developing a method for creating vaccines to treat pancreatic cancers. This research will have a significant impact on understanding neoantigen-T cell immunobiology and could improve the treatment prospects of pancreatic cancer patients.

- **Single-Cell Functional Multi-Omics to Characterize and Monitor CAR T Therapy**
  Additional Support: SITC
  Team Leader: Rong Fan, PhD, Yale University;
  Team Members: Stephanie Halene, MD, PhD, Yale School of Medicine and Yale University; Carl H. June, MD, University of Pennsylvania Perelman School of Medicine; Pablo G. Cámara, PhD, University of Pennsylvania Perelman School of Medicine; J. Joseph ("Jos") Melenhorst, University of Pennsylvania Perelman School of Medicine
  Project Summary: Immunotoxicity and autoimmune-like response is a significant problem hindering widespread use of cancer immunotherapies. Major players in the immune response are cytokines, which are substances secreted by some immune cells to affect other cells in response to a signal, e.g., recognition of a foreign body. To understand this response, the full spectrum of cytokine functions in a pre-infusion setting will be assessed and matched with patient responses to treatment with the chimeric antigen receptor (CAR) T therapy. Afterward, the function of the infused CAR T cells will be assessed to determine the mechanisms of efficacy and/or immune toxicity. The team also proposes identifying molecular characteristics underlying therapeutic efficacy and toxicity of CAR T therapy, and biomarker discovery by using computational models and machine learning that look at the data. If successful, this will create a "tool" that clinicians can use to mitigate patient risk associated with CAR T therapies while improving the chances of therapeutic success.

- **Integrating Experimental and Computational Pipelines to Develop Biomarkers of Tumor Cell Resistance to NK Cells**
  Team Leader: Constantine Mitsiades, MD, PhD, Dana-Farber Cancer Institute
  Team Members: Michal Sheffer, PhD, Dana-Farber Cancer Institute; Ricardo de Matos Simoes, PhD, Dana-Farber Cancer Institute; Aedin Culhane, PhD, Dana-Farber Cancer Institute; Todd Golub, MD, Broad Institute of MIT and Harvard; Aviad Tsherniak, MSc, Broad Institute of MIT and Harvard; Christopher Mader, PhD; Broad Institute of MIT and Harvard; Jennifer Roth, MSc, MBA, Broad Institute of MIT and Harvard
  Collaborators: Jacob Laubach, MD, Dana-Farber Cancer Institute; Paul G. Richardson, MD, Dana-Farber Cancer Institute; Rizwan Romee, MD, Washington University School of Medicine in St.

Louis; Jerome Ritz, MD, Dana-Farber Cancer Institute; Lotte Wieten, PhD, Maastricht University Medical Center, Netherlands; Richard Groen, PhD, VU Medical Center, Amsterdam, Netherlands
Project Summary: Natural killer (NK) cells, white blood cells that play a role in viral response, have potent anti-tumor cell killing properties. Moreover, NK cells are not inhibited by many of the strategies cancer cells use to evade the immune system. This team hypothesizes that the genetic make-up of a tumor may serve as a basis to target its destruction by NK cells. To identify biomarkers that are responsible for tumor cell sensitivity or resistance to NK cells, the team will use computational approaches. The team members will also explore novel interaction patterns based on NK responses by using tools such as CRISPR screens. Finally, these biomarkers will be validated on different experimental platforms such as patient-derived organoids and high-throughput systems to quantify tumor cell responses to immune effector cells. Results from this research could have an impact on models used to study a wide range of cancers.

- **Correlating Immunological Health to Cancer Susceptibility**
  Additional Support: SITC
  Team Leader: Mark Davis, PhD, Stanford University
  Team Members: Stephen Quake, PhD, Stanford University; Thomas Montine, MD, PhD, Stanford University; Kari Nadeau, MD, PhD, Stanford University; David Furman, PhD, University of Buenos Aires, Argentina
  Project Summary: A preliminary analysis of over 450 adults showed that the immune response to influenza vaccine may be correlated with cancer susceptibility. In a small subset of elderly subjects who received the influenza vaccine, subjects with less robust immune response were more likely to develop and succumb to cancer. This team will correlate the varying immune cell (T- and B-cell populations) repertoires in individual patients with cancer susceptibility, comparing the results to a separate cohort of patients who are immune deficient. Even partial success could lead to testable signatures for cancer prediction.

- **Connecting Immune Health and Tumor Biology in Gynecologic Cancers**
  Additional Support: SITC
  Team Leader: John Wherry, PhD, University of Pennsylvania
  Team Members: Claire Friedman, MD, Memorial Sloan Kettering Cancer Center; Robert Burger, MD, FACOG, FACS, The Hospital of the University of Pennsylvania; Daniel Powell, PhD, University of Pennsylvania; Shelley Berger, PhD, Perelman School of Medicine University of Pennsylvania; Erica Carpenter, MBA, PhD, Perelman School of Medicine University of Pennsylvania; Dana Pe'er, PhD, Memorial Sloan Kettering Cancer Center; Dmitriy Zamarin, MD, PhD, Memorial Sloan Kettering Cancer Center; Travis Hollman, MD, PhD, Memorial Sloan Kettering Cancer Center
  Collaborators: Benjamin Greenbaum, PhD, Icahn School of Medicine at Mount Sinai; David Ting, MD, Massachusetts General Hospital/Harvard Medical School; Ernest Fraenkel, PhD, Massachusetts Institute of Technology

Project Summary: Mismatch repair (MMR)-deficiency, the inability to repair base pairing within the DNA helix, can give rise to a weakened DNA structure, which leads to the accumulation of mutations. The response to immune checkpoint inhibitors has been varied in gynecologic cancers, possibly due to the number of mutations carried by each tumor cell (mutational burden). The team hypothesizes that the tumors with a high mutational burden fail to respond to checkpoint inhibition because of an immune dysfunction that is based on the mechanism for the MMR deficiency. The team plans to initiate two clinical trials that will test whether a) tumor-intrinsic factors affect the response to checkpoint inhibition; b) baseline immune function and quality affects response to checkpoint inhibition; and c) on-treatment blood markers may reflect the tumor-immune interaction. Understanding the mechanism that leads to this phenomenon has the potential to dramatically affect those patients who do not respond to current treatments.

- **Responders and Non-responders to Endometrial Cancers with Mismatch Repair**
  Team Leader: Alessandro Santin, MD, Yale University School of Medicine
  Team Members: Ludmil Alexandrov, PhD, University of California San Diego; Akiko Iwasaki, PhD, Yale University School of Medicine; and Stefania Bellone, PhD, Yale University
  Collaborator: Richard Lifton, MD, PhD, President of Rockefeller University
  Project Summary: Researchers do not know why only about one-half of all patients with mismatch repair deficient, MSI-high(h) metastatic/recurrent tumors respond to anti-PD1 treatment. The team will develop and validate a novel computational method to assess DNA damage and tumor mutational burden using next-generation sequencing data. Once validated, the approach will be applied to an ongoing trial for patients with endometrial cancer treated with Pembrolizumab. The team hopes to be able to predict the patients who will have side effects to checkpoint therapies, predict antigens from T cell receptor sequences, and determine neoantigens that are expressed by tumors that are recognized by the immune system in an HLA-dependent fashion. Identification of the patients who will have side effects will allow for modification of treatment to mitigate the adverse effects.

- **Using Artificial Intelligence to predict molecular pathways and clinical outcomes**
  Additional Support: SITC
  Team Leader: Ernest Fraenkel, PhD, Massachusetts Institute of Technology
  Team Member: Regina Barzilay, PhD, Massachusetts Institute of Technology
  Collaborators: John Wherry, PhD, University of Pennsylvania; Claire Friedman, MD, Memorial Sloan Kettering Cancer Center; Constantine Mitsiades, MD, PhD, Dana-Farber Cancer Institute; Todd Golub, MD, Broad Institute of MIT and Harvard; Jerome Ritz, MD, Dana-Farber Cancer Institute
  Project Summary: Recent successes in cancer immunotherapy have raised high hopes that these approaches can be expanded to more cancer types and to more patients. However, there are many unmet challenges ahead that will require dramatically new approaches. For example, determining which patients are most likely to benefit from a particular immunotherapy may require integrating diverse types of data (such as lab values) or observational data that are captured in the text of an electronic medical record. As there are no established methods for such complex challenges, this

team will develop innovative solutions based on approaches integrating deep, multi-omic data, machine learning, and natural language processing.

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About Stand Up to Cancer

Stand Up To Cancer (SU2C) raises funds to accelerate the pace of research to get new therapies to patients quickly and save lives now. SU2C, a division of the Entertainment Industry Foundation (EIF), a 501(c)(3) charitable organization, was established in 2008 by film and media leaders who utilize the industry's resources to engage the public in supporting a new, collaborative model of cancer research, and to increase awareness about cancer prevention as well as progress being made in the fight against the disease. As SU2C's scientific partner, the American Association for Cancer Research (AACR) and a Scientific Advisory Committee led by Nobel Laureate Phillip A. Sharp, PhD, conduct rigorous, competitive review processes to identify the best research proposals to recommend for funding, oversee grants administration, and provide expert review of the research progress.

Current members of the SU2C Council of Founders and Advisors (CFA) include Katie Couric, Sherry Lansing, Lisa Paulsen, Rusty Robertson, Sue Schwartz, Pamela Oas Williams, Ellen Ziffren, and Kathleen Lobb. The late Laura Ziskin and the late Noreen Fraser are also co-founders. Sung Poblete, PhD, RN, has served as SU2C's president since 2011. For more information on Stand Up To Cancer, visit www.standuptocancer.org

About the Lustgarten Foundation

The Lustgarten Foundation is America's largest private foundation dedicated to funding pancreatic cancer research. Based in Woodbury, N.Y., the Foundation supports research to find a cure for pancreatic cancer, facilitates dialogue within the medical and scientific community, and educates the public about the disease through awareness campaigns and fundraising events. Since its inception, the Lustgarten Foundation has directed $154 million to research and assembled the best scientific minds with the hope that one day, a cure can be found. Thanks to private funding, 100 percent of every dollar donated to the Foundation goes directly to pancreatic cancer research. For more information, please visit www.lustgarten.org

About the Society for Immunotherapy of Cancer

The Society for Immunotherapy of Cancer (SITC) is the world's leading member-driven organization specifically dedicated to improving cancer patient outcomes by advancing the science and application of cancer immunotherapy. Established in 1984, SITC, a 501(c)(3) not-for-profit organization, serves scientists, clinicians, academicians, patients, patient advocates, government representatives and industry leaders from around the world. Through educational programs that foster scientific exchange and collaboration, SITC aims to one day make the word cure a reality for cancer patients everywhere. To learn more, visit www.sitcancer.org

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