Balzan Postdoctoral Fellowship for Immunological Approaches in Cancer Therapy

James P. Allison and Robert D. Schreiber

2017 Balzan Prize for Immunological Approaches in Cancer Therapy

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Affiliated Institutions: University of Texas MD Anderson Cancer Center in Houston, Texas
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James P. Allison is Chairman of the Department of Immunology, Executive Director of the Immunotherapy Platform, and Director of the Parker Institute for Cancer Immunotherapy, University of Texas MD Anderson Cancer Center in Houston, Texas. Robert D. Schreiber currently holds several positions at the Washington University School of Medicine in St. Louis: the Andrew M. and Jane M. Bursky Distinguished Professor at the Department of Pathology and Immunology, Professor of Molecular Microbiology, Director at the Andrew M. and Jane M. Bursky Center for Human Immunology and Immunotherapy Programs and Program Co-Leader in Tumor Immunology at the Alvin J. Siteman Cancer Center.

A Research Project on Cancer Immunotherapy – James Allison

The field of cancer immunotherapy, the development for which Drs. Allison and Schreiber received the 2017 Balzan Prize, has radically changed the landscape of cancer treatment. The findings that paved the way to the birth of immune checkpoint inhibitor therapy, pioneered by Allison, are a result of basic research conducted over a period of two decades in his laboratory while seeking to understand the fundamental biology of T cell activation and regulation. The subsequent steps of translating Allison's vision of altering the regulation of tumor specific T cells through a protein called CTLA-4 and related molecules as a means of coaxing the immune system to attack tumors required a mammoth effort by a number of visionary scientists and clinicians. Since 2011, there have been eight approvals of immune checkpoint inhibitors by the US Food and Drug Administration for the treatment of advanced

melanoma, lung cancer, and metastatic kidney cancer, resulting in new treatment regimens that have saved of tens of thousands of lives.

While currently available anti-CTLA-4 therapy provides a long-term cure for about 20% of metastatic melanoma patients, it remains ineffective for the rest. Additionally, many other cancers termed "immunologic deserts" are resistant to immunotherapy. This situation is unacceptable, and current work seeks to find out why certain patients do not benefit from immunotherapy and how to extend its benefits to them. The pace of change toward immunological approaches to the treatment of cancers is accelerating, creating a shortage in the availability of scientists trained in the field that are required to build on these remarkable advances and clear the new hurdles that have arisen toward further expansion of immunotherapy to previously resistant disease.

With the research funds provided by the Balzan Prize, James Allison will establish a postdoctoral fellowship to recruit three outstanding young investigators to receive training in cancer immunotherapy research. This will serve as part of a continuing effort to train the next generation of researchers to advance cancer immunotherapy deeper on the basic science and translational level. Three career investigators who wish to learn about cancer immunotherapy translational research will be supported for one year each with this award mechanism, as basic scientists who conduct immunotherapy research studies on patient samples.

Research Plan

Applicants for the Balzan Postdoctoral Fellowship will submit proposals for the work they intend to carry out during the fellowship. All projects, to be reviewed by the internal review committee, should fall under one of the following areas of active research:

1. Identification of biomarkers that predict response to immunotherapy

Although immune checkpoint inhibitor therapies have proven to be effective as long-term cures to a subset of cancer patients, up to this point, it has proven difficult to select which patients are most likely to respond to a specific checkpoint inhibitor. In the short term, the ability to predict likely responders would allow oncologists to give checkpoint therapy only to those most likely to benefit, while preventing those most unlikely to benefit from suffering any side effects of increased immune activity. As more checkpoint inhibitors become available, the ability to predict which immune

therapies might be most beneficial will allow physicians to select the best treatment for a specific patient. Using pre- and post-treatment patient samples obtained by the IMT platform, immune and tumor cells will be isolated from tumors and profiled to find predictive markers of treatment response. Fellows will have access to flow cytometry, single cell sequencing, and CyTOF proteomics technology.

2. *Identification and validation of new targets for cancer immune checkpoint inhibitor therapy*

Transcriptional and proteomic profiling of tumor infiltrating T cells have revealed a number of gene transcripts and cell surface proteins specific to inactivated T cell populations. Further investigation in cultured cells continues to identify new immune checkpoint-related products. Using bioinformatics approaches on transcriptional profiling and proteomic data from patient-derived tumor-infiltrating lymphocytes, the highest ranked potential new immune checkpoint-related genes will be identified. The signalling activity and effect on T cell activation of these proteins will be examined in cultured cells. Finally the potential therapeutic role of manipulation of candidate genes will be determined in mouse models of human cancer either by genetic manipulation or blocking antibodies and monitoring the effect on tumor growth.

3. *Rational prediction of combination therapies involving cancer immune checkpoint inhibitors*

While a wealth of evidence shows that combinations of immune checkpoint inhibitors together or with other anti-cancer therapies drastically increases the response rate, selecting the best combinations for a particular patient and cancer remains difficult. There are currently over 1,300 clinical trials exploring the safety and efficacy of various immunotherapies and combinations, selected in a non-systematic manner, which makes it extremely difficult to accumulate enough patients for a given combination. Accurate and rational design of immunotherapy combinations would reduce the number of active cancer immunotherapy trials, and greatly accelerate the approval of more effective combinatorial treatments. Up to this point, prediction of immune checkpoint inhibitor combinations has been hindered by gaps in the knowledge of the specific T cell populations and the downstream molecular pathways involved. Using CyTOF proteomic profiling of circulation and tumor infiltrating T cells, we identify specific T cell populations affected by individual checkpoint blockers. Selecting checkpoint blockers that act on separate T cell populations has enriched candidate targets that may provide additive or even synergistic therapeutic value.

Involvement of Young Investigators

The Balzan Fellowships will involve young investigators at multiple levels. Most directly, the purpose of the fellowship is to selectively recruit and train the best possible young researchers for the field of cancer immunotherapy. Top candidates will be identified during the selection process, and young professors will be involved on the selection committee. The research progress of the selected fellows will be evaluated by the supervisors at the midpoint and end of the year of support provided by the Balzan Fellowship. Each fellow will provide a progress report of his or her own progress at or near the end of the one-year period. Those three individual reports plus a brief overall summary provided by Dr. Allison will form the report of the overall results of the program at or near the end of the three-year funding period.

Symposium and Publications

At the end of the three-year period, a half-day Balzan Symposium for Immunological Approaches in Cancer Therapy open to the public will be held at MD Anderson's south campus. Three first author publications are expected.