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Bluestone, Jeffrey A
Tang, Qizhi

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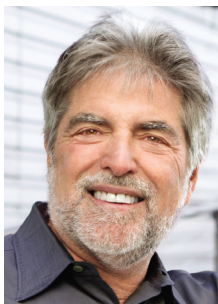
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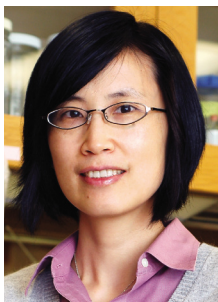
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PRECISION MEDICINE



Jeffrey A. Bluestone is Director, Hormone Research Institute, and holds the A. W. and Mary Margaret Clausen Distinguished Professorship in Metabolism and Endocrinology at the University of California, San Francisco, San Francisco, CA 94143, USA. E-mail: jeff.bluestone@ucsf.edu



Qizhi Tang is Associate Professor of Surgery and Director of the UCSF Transplantation Research Laboratory, University of California, San Francisco, San Francisco, CA 94143, USA.

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Immunotherapy: Making the case for precision medicine

IN HIS 2015 STATE OF THE UNION ADDRESS, U.S. PRESIDENT BARACK OBAMA announced the precision medicine initiative, which promises to profoundly transform biomedical research and clinical medicine (www.nih.gov/precisionmedicine). This framework envisions a world in which diseases are diagnosed not simply on the basis of a patient's symptoms but on a wealth of data that—when aggregated, integrated, and analyzed—unearth fundamental mechanistic bases of human diseases. Precision medicine has been equated with personalized medicine because both have the potential to provide individualized diagnoses and treatments for a wide range of diseases and syndromes. But the goal of precision medicine is much broader. By joining genomic, phenotypic, environmental, and societal data, precision medicine promises to reveal the connectivity in biological pathways among various diseases with diverse symptoms, leading to platform treatments of the shared targets of these diseases. This issue of *Science Translational Medicine* highlights comprehensive assessments of progress in the development of immunotherapy and other therapeutics in the areas of oncology, autoimmune and allergic diseases, and transplantation (1–5), providing a glimpse into the transformative power of precision medicine.

TARGETING IMMUNE REGULATION

Many diseases of the modern age result from a dysregulated immune system. The connection between the immune system and autoimmune diseases, allergies, and complications of transplantation is obvious; recently, the link between immune dysfunction and many nonimmune diseases has become more widely appreciated. Cancer, once thought to be simply the malignant growth of cells, is fueled by inflammation and localized immunosuppression. Similarly, type 2 diabetes, obesity, cardiovascular diseases, Alzheimer's disease, and depression all have the fingerprint of chronic inflammation and its associated disruption of tissue homeostasis and function. In fact, the components of the immune system do not simply reside in lymphoid organs but throughout various tissues, organs, and systems, poised to respond to stress and injury as well as infections. Thus, although the immune system mobilizes against pathogens that cause smallpox and polio, for which vaccination had led to almost complete eradication, immune processes also are involved more generally in maintaining mechanisms of homeostasis intended to limit organ damage and promote tissue repair. Therefore, it is not surprising that such a strong force against foreign invaders is laced with layers of counterregulatory mechanisms to prevent excessive collateral damage.

The discovery of immune self-regulation and acquired immune tolerance in the 1950s and the mapping of its cellular and molecular mechanisms that followed in the ensuing 70+ years form the biological foundations of today's emerging immunotherapies. In fact, state-of-the-art immunotherapies (1–5) tap into these physiological processes of immune regulation to shift immunity from destruction to protection or the reverse. These recent advances result from an increased specificity and selectivity of the drugs, adding power and precision to what has been largely an armamentarium of pan-immunosuppressive drugs that block or deplete large components of the immune system.

Take cancer, for example. This complex disease remains a top killer decades after the war on cancer was declared in the early 1970s. There has been a wealth of drugs and radiation treatment protocols developed to “poison” cancer cells and cause mass destruction of tumors. This approach has been highly successful in limited settings—for example, the discovery of Gleevec for the treatment of chronic myelogenous leukemia or rituximab for B cell lymphomas. But too often, cancers return because they carry mutations that bypass the drug-targeted pathways; even more often, the drugs cause debilitating off-target toxicities and, in some cases, even new malignancies. Only recently, with cancer genomics fueling the development of personalized cancer immunotherapy, have we seen signs of a decisive victory over certain cancers (6).

The path to this remarkable victory began in a seemingly unrelated quest to understand the molecular basis of immune activation, which revealed myriad T cell receptor

(TCR) subunits and TCR costimulatory and coinhibitory molecules. This intricate system of checks and balances is hijacked by cancer cells to evade immune rejection and, in reverse, is defective in autoinflammatory diseases that lead to the disruption of normal tissue functions. This deeper mechanistic understanding of the human immune system drove the discovery of a plethora of new drugs (several of which are U.S. Food and Drug Administration–approved) that target immune regulatory pathways. For example, the monoclonal antibody (mAb) ipilimumab (anti–CTLA-4 mAb) is an immune checkpoint–blockade therapy for the treatment of several different cancer types. Pembrolizumab and nivolumab, two mAbs that target the programmed cell death–1 receptor (PD-1) on activated T cells, remove the brakes imposed by coinhibitory molecules so that cancers can be recognized and destroyed by the immune system. In contrast, belatacept and abatacept, two CD28 costimulatory antagonists, have been approved for the treatment of organ transplantation and rheumatoid arthritis, respectively. These drugs and others described in the various reviews in this issue shift the balance from regulation to immunity or visa versa in subtle but effective ways. Such drugs will increase in specificity as researchers discover biomarkers that permit the identification of patients in which selected pathways drive the immune dysfunction.

T CELL THERAPIES

The pharmaceutical industry, long dominated by small-molecule drugs and biologics, now recognizes cell-based therapies as versatile therapeutic engines for treating a variety of diseases (7). But scientists and physicians in the transplantation field have recognized the therapeutic superiority of cells and organs for over 50 years. When living in bubbles combined with assortments of medications could not save the lives of children with severe combined immunodeficiency, bone marrow cell transplantation became the primary treatment of choice, with an 80% cure rate. Similar contrasts can be made between insulin injection and islet cell transplantation for diabetes or dialysis and kidney transplantation for renal failure.

Cells are superior options when therapeutic tasks are too complex to be performed by biologics and small-molecule drugs. Unlike conventional drugs, cells are smart drugs that traffic to the right place at the right time and respond to their environments to impart more specific and precise therapeutic outcomes. In the fields of cancer, infectious diseases, organ transplantation, and autoimmunity, a precise understanding of the target antigens on tumors and self tissues, an improved understanding of TCR signal transduction pathways, and tools to genetically modify cells have enabled the generation of therapeutic T cells with improved target precision. Genetically engineered TCRs or chimeric antigen receptors (CARs) direct killer T cells to virally infected cells or a specific tumor cell population; the modified T cells then destroy their target cells without large collateral damage (1). Such T cell therapies have achieved complete remission in patients with certain blood cancers that were untreatable using biologics and small-molecule drugs. The use of immune cells, both natural and engineered, is spreading beyond cancer, with increasing efforts in autoimmunity and transplantation by using immune-suppressive cells ranging from regulatory T cells, mesenchymal stem cells, and regulatory dendritic cells (2). The advent of new genetic editing tools such as CRISPR may lead to universal cell therapies for off-the-shelf use and designer cells with synthetic circuits so that their behaviors can be controlled with drugs.

TARGETING IMMUNE DEVIATION

In the treatment of autoimmune diseases, the traditional approach has been to classify a disorder on the basis of the affected organs and vague descriptive symptoms. For example, inflammatory bowel disease, arthritis, and psoriasis are managed by individual doctors in different subspecialties who use language that often obscures the relatedness of these diseases even though they are all products of tissue inflammation. Experimental human research and clinical trials have taught us that there are common molecular pathways that drive inflammation in various organs and that inflammation in a single organ can manifest through distinct mechanisms in different individuals. More importantly, a growing appreciation of various immune-cell subsets has given immunologists a deeper understanding of the heterogeneous nature of inflammation. Assays that more accurately define the nature of the immune response and new drugs that selectively target the molecular pathways responsible for the disease can quell inflammation while leaving the larger immune system intact.

In one example, the application of genomics to classify the autoimmune disease systemic onset juvenile idiopathic arthritis led to the identification of a single cytokine, interleukin-1 (IL-1), as the major source of disease pathogenesis. The administration of an IL-1 antagonist, Anakinra, yields a complete therapeutic response in a majority of the children whose disease is refractory to other therapies (8). Similarly, systems-biology approaches have improved our understanding of the heterogeneity of vaccine and autoimmune responses and promise to aid in the improvement of immunogenic and tolerogenic vaccine design (9).

Just last month, the Immune Tolerance Network (ITN) published an astonishing study based on the pioneering work of Billingham, Brent, and Medawar, which demonstrated that foreign antigens introduced during the neonatal period induce tolerance and prevent response to the same antigen later in life. In the ITN study, investigators evaluated the impact of peanut consumption during infancy on peanut-allergy incidence in young children (10) and found that allergy-prone infants (under 1 year of age) who were fed a peanut-containing snack exhibited a remarkable 70 to 86% protection against peanut allergy when measured at 5 years of age. The treatment induced tolerance in these subjects even after showing signs of peanut sensitization. The efficacy was most likely due to the deviation of the peanut-specific antibody response from a pathogenic immunoglobulin E (IgE)-dominated to a protective IgG4-dominated one. This result suggests that the current practice of peanut avoidance for allergy prevention not only has no scientific basis but also may have contributed to the sharp rise in the number of peanut allergies in recent years.

IMMUNE TOLERANCE

The induction and maintenance of immune tolerance has been the holy grail of immunotherapy because it would translate a short course of immunotherapy into long-term benefit while maintaining immune competency. An enhanced understanding of the mechanistic basis of immune tolerance has led to the development of new therapies that target specific tolerance defects. Approaches to achieve tolerance range from adoptive regulatory T cell and tolerogenic dendritic cell therapies to therapeutics that drive immune deviation toward a tolerant state. In this regard, it has become increasingly clear that tolerance can be achieved during liver transplantation by a combination of targeted immunotherapies and the tolerogenic potential of the liver tissue itself. Under some conditions, up to 75% of patients can maintain their liver allografts without immunosuppression, a process that is now becoming more predictable by the use of molecular biomarkers to guide immunosuppression withdrawal. New cancer immunotherapies are likely to be efficacious because of the drugs' ability to break down the same tolerogenic processes that we aim to engage in the autoimmune, allergy, and transplant settings.

NEXT-GENERATION HEALTH CARE

The past decade has witnessed a revolution in our understanding of the immune system and our ability to develop safer and more effective immunotherapies. Recent successes make the case that the future of clinical medicine lies in our ability to better define the molecular basis of human diseases by using the wealth of data that can now be achieved through highly sensitive technologies, bioinformatics methods, and the ability to interrogate the immune response before and after perturbation. Precision medicine is not a destination but an iterative process. Classification of diseases according to their biological underpinnings will guide more precise targeting of new therapies, and molecular characterization of therapeutic responses will allow a clearer understanding of human biology and provide direction for therapy improvement. Systems biology and interdisciplinary team science are needed to make precision medicine a reality. The next decade will witness breakthroughs in our understanding of human physiology and pathophysiology through therapeutic explorations that will propel the advance of health care for the next generation.

– Jeffrey A. Bluestone and Qizhi Tang

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Competing interests: J.A.B. is a scientific advisor for Juno Therapeutics; is a member of the scientific advisory boards of Flexus Biosciences, Kadmon Corp., Pfizer, and NeoStem (Athelos Division); is a shareholder in MacroGenics; and receives research support from Neostem.