ASBMT
American Society for Blood and Marrow Transplantation

2008 Research Priorities

Based on recent clinical data and advances in understanding of the biology of hematopoietic stem cell transplantation (HSCT), the American Society for Blood and Marrow Transplantation (ASBMT) has identified research priorities in several areas of basic and clinical research:

- Advances in stem cell biology (inducible pluripotent stem cells and cancer stem cells)
- New cellular and molecular therapies for relapse in autologous and allogeneic HSCT (T cell transfer, combination with molecular targeting agents, chemoimmunotherapy)
- Emerging predominance of certain complications, especially chronic graft-versus-host disease (GVHD)
- Emerging technologies with prognostic and diagnostic uses (imaging, proteomics, genomics)
- Wider applications of HSCT for various disease states (solid organ transplantation, autoimmunity, potential regenerative applications, radioprotection in bioterrorism)
- Survivorship issues

All are important areas of interface between clinical experience and basic science. As described below, research in each of these areas can have direct and immediate clinical benefits.

STEM CELL BIOLOGY

The demonstration of inducible hematopoietic stem cells (HSCs) from progenitor cells has opened the door for stem cell approaches in various diseases. Understanding of the potential plasticity of HSCs has obvious implications but requires further research. We need a better understanding of the biology of stem cells and their sources (marrow, cord blood, and peripheral blood). More data on stem cell applications in disease, as well as the conditions allowing for optimal reconstitution and recovery, is another priority. Cancer stem cells, particularly the leukemia stem cell, may be critically important. Efforts toward achieving cancer "cures" must consider and target this cell population. Further preclinical and clinical studies of both inducible pluripotent stem cells and cancer stem cells are needed.

IMMUNE EFFECTOR POPULATIONS AND IMMUNOBIOLOGY OF ALLOGENEIC HSCT

Relapse from the cancer and occurrence of GVHD remain at the forefront of issues in allogeneic HSCT. Adoptive immunotherapy has been shown to play a role in attacking hematologic malignancies. Recent reports have described the successful use of adoptive T cell transfer after reduced-intensity conditioning in melanoma. In addition, T cells have been shown to play a central role not only in graft-versus-tumor (GVT) effects, but also in GVHD. Thus, more work is needed to understand the biology and application of immunomodulating agents or cellular therapies. Priorities include research on the trafficking of immune effector cells in GVHD and cancer, reconstitution of the T cell compartment after HSCT, cellular regulation of immune cell function and survival, and the development of preclinical models that better reflect the clinical scenario (eg, the aging patient).

Natural killer (NK) cells represent another effector arm that needs to be better characterized, not only as an antitumor effector, but also as immunodulatory cells that can affect outcome. Studies characterizing the immunomodulatory properties and cellular interactions of potentially useful cell products (regulatory T cells, NK/T cells, suppressive dendritic cell subsets, NK cells) in the context of HSCT are a priority. Finally, molecular targeting agents have the potential not only to exert immunomodulating effects, but also to augment the antitumor effects of allogeneic HSCT. Understanding pathways that can distinguish GVHD and GVT and the roles of the various immune cell populations continues to be of paramount importance for applying HSCT in cancer therapies.

CHRONIC GVHD

There is an urgent need to improve our understanding of the biology of chronic GVHD and to develop new ways of targeting it clinically. In addition to better preclinical models of chronic GVHD and better prognostic indicators, more efficacious treatments than continuous global immunosuppression are a top priority. The molecular targeting agents currently under assessment in acute GVHD also should be applied to preclinical and subsequent clinical chronic GVHD. Studies should assess the effects of age on chronic GVHD, as well as effects of the conditioning used in HSCT on the aged population. These studies should focus on immunologic recovery and chronic GVHD risk.

PROGNOSTIC INDICATORS AND MONITORING TOOLS

The advent of proteomics and genomics has increased the need to validate potential clinical markers in GVHD. Such markers have important implications for patient selection, prognosis, and treatment. Imaging techniques are needed not only to assess clinical efficacy and cellular therapy trafficking, but also to advance our basic understanding of disease processes. Using proteomics to determine correlative markers for GVHD progression and to identify high-risk patients is of considerable importance. Another critical area is the development of immune monitoring parameters that reflect immune competence and recovery, particularly with the increasing use of HSCT in older patients.

EXPANDING THE USE OF HSCT

Recent breakthrough studies indicate that HSCT may have applications in solid organ transplantation by the induction of immune tolerance. Expanded use of HSCT may be advantageous in other situations, including, but not limited to, regenerative medicine (heart disease and others), autoimmunity, and radioprotection in the advent of bioterrorism or a mass radiologic accident. For radioprotection/bioterrorism applications, we need to develop ways of applying HSCT to large populations, along with means of augmenting recovery. Preclinical and clinical studies of immune reconstitution, tolerance (including appropriate functional correlates), efficacy, and long-term effects will aid in understanding the applicability of HSCT in these conditions. Means of expanding the application of HSCT in solid cancers are an ongoing priority. We also need to define the optimal stem cell source (e.g. cord blood, ex vivo expanded stem cell populations, peripheral stem cells), banking, and typing, particularly as they relate to the treatment of specific diseases.

PREVENTION OF TUMOR RELAPSE

Relapse remains of paramount concern after autologous HSCT to treat hematologic malignancies. We need to understand the mechanisms by which cancer cells can resist cytotoxic therapies in autologous HSCT. Use of immune therapies, monoclonal antibodies, molecular targeted agents, and chemotherapeutics—alone and in combination—should be explored in the context of HSCT. This may also help in applying autologous HSCT to a wider spectrum of malignancies.

SURVIVORSHIP

HSCT is being used in a more elderly population. As more patients survive the initial period after transplantation, many are living free of recurrent malignancy. Currently, however, a substantial proportion of these patients develop late complications, including chronic GVHD, immune deficiency, endocrinologic failure, bone loss, and secondary malignancies. These events can adversely affect the quality of life for long-term transplantation survivors. Of high priority are investigating risk factors for late complications, developing more relevant preclinical models, designing interventional strategies, and developing better means of assessing quality of life in long-term survivors. In addition, the long period of immune deficiency that follows HSCT leaves this population at risk for opportunistic infections; therefore, development of means to promote immune reconstitution is a priority, particularly in the elderly.

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