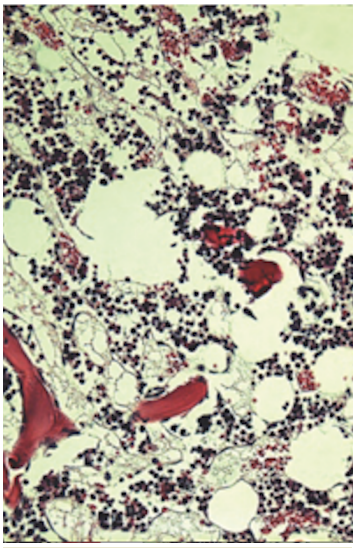
STANFORD BMT UPDATE
News About the Stanford BMT Program



After antibody treatment against c-Kit and CD47, the host hematopoietic stem cells were deleted, pending acceptance of allogeneic stem cells from a donor source (see Page 3 for story).

The Modern-Day Magic Missile: Arming the T-Cells with Cancer-Targeting Antibody

When Kohler and Milstein developed hybridoma technology in 1975, a monoclonal antibody was thought to be the "Magic Bullet" to treat cancer since it can go directly to the targeted cancer cells. Therapeutic monoclonal antibodies have come to fruition such as rituximab for lymphoma and herceptin for breast cancer. However, monoclonal antibody therapy alone did not fulfill its original promise. On the other hand, the cellular arm of the immune system has shown to be even more effective against cancer cells. One such example is allogeneic transplant where donor T-cells eliminate residual cancer cells, resulting in a cure in many different kinds of hematologic malignancies. However, this process is not precise and off-target killing occurs in the form of graft-versus-host disease (GVHD). One way to bring these two potentially powerful anti-cancer therapeutics together is by arming the T-cells with a monoclonal antibody that recognizes molecule(s) on the cancer cells. Thus far, the most successful approach is the chimeric antigen receptor (CAR) T-cells. In this strategy, the patient's own T-cells are genetically engineered to produce a hybrid molecule (the CAR) on these tumor-killing cells. The extracellular portion of the CAR molecule is composed of the antigen-recognizing part of a monoclonal antibody, while the intracellular portion contains the activating motifs of the T-cell receptor. When CAR T-cells are infused into the body, the antigen-recognizing part brings these cells to the targeted cancer cells and

THE HIGHLIGHTS

- **Patient's own T-cells are used to produce chimeric antigen receptor (CAR)**
- **CAR combines the targeting part of an antibody and signaling part of the T-cell receptor**

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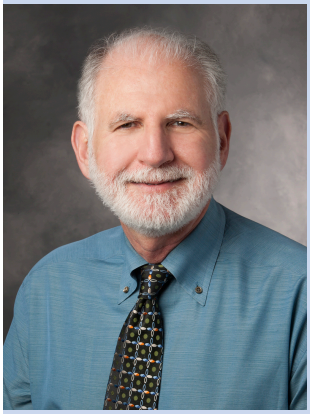
THE DIRECTOR FILE

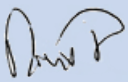


Welcome to the Division of Blood and Marrow Transplantation. We are very proud of the outstanding compassionate care that we provide our patients while conducting state of the art basic and translational science on stem cell biology, cellular immunology and transplantation biology. Our Program is focused on the comprehensive evaluation and care of patients with complex hematological malignancies and other bone marrow failure syndromes where blood and marrow transplantation can provide benefit.

Our program has provided transplantation services to over 5,800 patients. Our team based treatment approach involves faculty, fellows, residents, nurse practitioners, physician assistants, an expert nursing staff as well as other aligned staff who work together to provide the best possible care for our patients undergoing treatment at Stanford during this time of their greatest health challenge.

Our faculty performs cutting edge research exploring the basic biology of hematopoietic stem cells and effector T cells such as natural killer cells, regulatory T cells, cytotoxic T cells and B cells with the aim of exploring translational research opportunities wherever possible. We are supported by grants from the National Institutes of Health including a Program Project Grant now in the 25th year of funding as well as foundation support from institutions like the California Institute of Regenerative Medicine and the National Marrow Donor Program. The Division runs the Bone Marrow Transplant Cellular Therapeutics Facility where all clinical material is prepared for transplantation and where complex cell separation and expansion protocols can be accomplished. We pride ourselves in training physician scientists and performing translational research to find better approaches for the treatment of our patients and advancement of the field.

We welcome the opportunity to serve your patients and are always available for consultation and referral. Thank you for the opportunity and trust in providing the best possible care supported by the strongest science for your patients.



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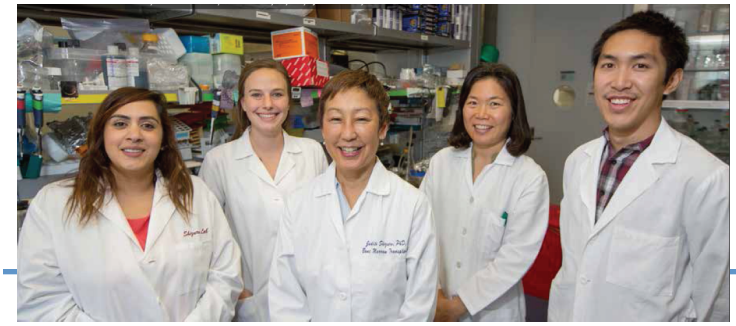


Disruptive Innovation:
Antibody-Only Allogeneic Transplantation

While allogeneic transplantation can be life saving for patients with hematologic malignancies, or inherited disorders such as several forms of immuno-deficiency, the transplant-related side effects and complications remain the biggest hurdles. One of the sources for side effect/complication is the conditioning regimen patients receive prior to the donor graft infusion. The conditioning regimen is usually composed of a combination of chemotherapies with or without radiation, and is designed to get rid of the hematopoietic cells in the recipient so the donor hematopoietic cells can take a hold (engraftment) after infusion. In addition, the donor grafts usually contain mature blood cells (T-cells, B-cells, NK cells), which are necessary to facilitate engraftment. However, these mature donor blood cells can also cause graft-versus-host disease (GVHD).

Ideally, transplants should be performed using a chemotherapy/radiation-free conditioning regimen with purified donor hematopoietic stem cells without mature blood cells. In this scenario, patients could avoid the toxicities brought by traditional conditioning and the GVHD caused by mature donor blood cells carried over in the standard graft. It turns out that this is not an easy task. For successful donor cell engraftment, two obstacles must be overcome. First, the recipient immune system has to be contained so it will not reject the incoming donor cells. Second, the donor hematopoietic cells must be able to enter the niche space in the recipient bone marrow. In Dr. Judith Shizuru's laboratory, efforts were devoted to finding antibodies that can deplete the recipient hematopoietic stem cells in the bone marrow to open the niche for the donor cells. After extensive testing of different molecules on the stem cells, they found that monoclonal antibodies against c-Kit (CD117) are able to achieve that goal. In an animal model, anti-c-Kit antibody alone was sufficient to promote successful engraftment of purified donor stem cells in immuno-compromised mice. In these animals, there were limited number of immune cells to reject the donor stem cells. However, as expected, anti-c-Kit treatment alone is not enough for stem cells engraftment in immune-competent mice due to the robust recipient immune cells. To overcome that challenge, Dr. Shizuru's team used an additional antibody against CD47 to enhance the effect of anti-c-Kit. With the combination of anti-c-Kit and anti-CD47, purified donor stem cells can successfully engraft in immuno-competent mice without any other treatment. In these animals, no GVHD was observed since no mature donor blood cells were infused.

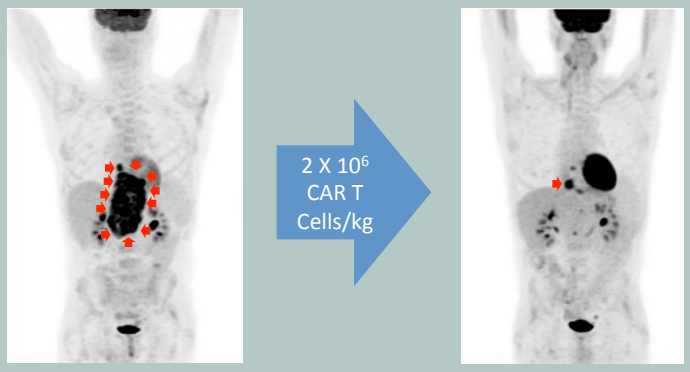
While this is only a pre-clinical study, the promise from this innovation is limitless. To bring this disruptive innovation to patient care, a phase I study has recently been opened to treat children with severe combined immunodeficiency (SCID) using anti-human-c-Kit antibody and purified donor hematopoietic stem cells. As Dr. Shizuru put it, "I want to make the transplantation procedure an order of magnitude safer, and to achieve the end-goal that cures cancer, immunodeficiency and autoimmune disease. ■

continued from cover

The Modern-Day Magic Missile

drives CAR-T cell proliferation. Upon contact with cancer cells, CAR T-cells will be activated to kill the targeted cancer cells. Since February 2016, 7 patients with refractory diffuse large B-cell have received CD19-CAR T-cells targeting the CD19 molecule on the lymphoma cells. While some experienced significant therapy-related side effects, all recovered fully with several patients achieving tremendous tumor shrinkage as demonstrated in one such example shown below.

To facilitate clinical trials employing cellular immunotherapies such as CAR T-cells, Dr. Crystal Mackall, director of the Stanford Cancer Immunotherapy Program, will work closely with faculty members in BMT to develop novel cancer cellular immunotherapies.



PET in one patient showed great tumor reduction 4 weeks after CD19-CAR T-cells infusion.

Dr. David Miklos leads the way introducing the clinical trials with CAR T-cell therapeutics at Stanford. While the initial study was for patients with lymphoma, this new technology can potentially benefit patients with a variety of hematologic malignancies and even solid tumors. Dr. Miklos will continue to work with Dr. Mackall to develop a robust clinical program.

SELECTED RECENT PUBLICATIONS

Hematopoietic stem cell transplantation in immunocompetent hosts without radiation or chemotherapy.
SCIENCE TRANSLATIONAL MEDICINE
A Chhabra, AM Ring, K Weishopf, PJ Schnorr, S Gordon, AC Le, H-S Kwon, NG Ring, J Volkmer, S Tseng, IL Weissman, **JA Shizuru**
2016; 8 (351): 351ra105

Presensitization to HY antigens in female donors prior to transplant is not associated with male recipient post-transplant HY antibody development nor with clinical outcomes.
HAEMATOLOGICA
H Nakasone, B Sahaf, L Tian, T Wang, MD Haagenson, K Schoenrock, S Perloff, CE Ryan, F Wu, SR Spellman, SJ Lee, J Ritz, **DB Miklos**, CIBMT
2016; 101 (1): e30-e33

Psychological morbidities in adolescent and young adult blood cancer patients during curative-intent therapy and early survivorship.
CANCER
LS Muffly, FJ Hlubocky, N Khan, K Wroblewski, K Breitenbach, J Gomez, JL McNeer, W Stock, CK Daugherty
2016: 122 (6): 954-961

A randomized phase II crossover study of imatinib or rituximab for cutaneous sclerosis after hematopoietic cell transplantation.
CLINICAL CANCER RESEARCH
S Arai, J Pidala, I Pusic, X Chai, S Jaglowski, N Khera, J Palmer, GL Chen, MH Jagasia, SA Mayer, WA Wood, M Green, TS Hyun, Y Inamoto, BE Storer, DB Miklos, HM Shulman, PJ Martin, S Sarantopoulos, SJ Lee, ME Flowers
2016; 22 (2): 319-327

Allogeneic hematopoietic cell transplant for normal karyotype AML: Indirect evidence of selection for adverse molecular profile.
BONE MARROW TRANSPLANTATION
ME Pervival, BC Medeiros, S Robeson, GG Laport, LJ Johnston, JA Shizuru, DB Miklos, S Arai, WK Weng, RS Negrin, **R Lowsky**
2015; 50 (7): 1004-1006

Third-party CD4+ invariant natural killer T cells protect from murine GVHD lethality.
BLOOD
D Schneidawind, J Baker, A Pierini, C Buechele, RH Luong, EH Meyer, **RS Negrin**
2015; 125 (22): 3491-3500

Risks and benefits of sex-mismatched hematopoietic cell transplantation differ according to conditioning strategy.
HAEMATOLOGICA
H Nakasone, M Remberger, L Tian, P Bordin, B Sahaf, F Wu, J Mattsson, R Lowsky, RS Negrin, DB Miklos, **EH Meyer**
2015; 100 (11): 1477-1485

Allogeneic hematopoietic cell transplantation after failed autologous transplant for lymphoma using TLI and anti-thymocyte globulin conditioning.
BONE MARROW TRANSPLANTATION
AR Rezvani, AS Kanate, B Efron, S Chhabra, HE Kohrt, JA Shizuru, GG Laport, DB Miklos, JE Benjamin, LJ Johnston, S Arai, WK Weng, RS Negrin,, S Strober, **R Lowsky**
2015; 50 (10): 1286-1292

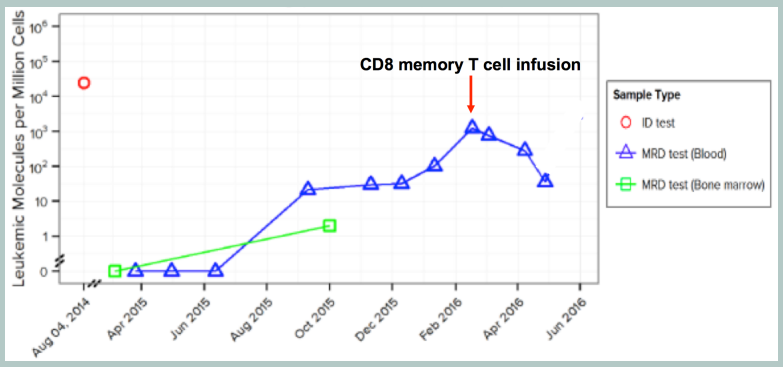
Cellular Therapeutics:

Harness the Power of the "Good" Cellular Component

While the graft-versus-tumor effect provided by the donor graft can be very powerful in controlling the disease, disease relapse is still the primary reason that patients do not do well after an allogeneic transplantation. Two strategies are commonly deployed in managing post-transplant relapses: reducing the tumor burden by appropriate means, and heightening the graft-versus-tumor effect. The former usually requires traditional chemotherapies, radiation or targeted therapies. However, there are several different ways to heighten the donor graft function. These include withdrawal of immunosuppression; immune stimulation with immunomodulators such as CpG, interferon or checkpoint inhibitors; and infusion of additional donor cells. At Stanford, we have a special interest in donor cellular therapeutics.

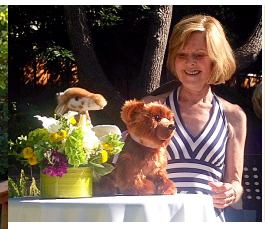
The use of donor lymphocyte infusions (DLI) has been pivotal in treating post-transplant relapse. The efficacy of DLI depends on the dose of the infused T cells. However, higher doses of DLI are also associated with higher incidence of graft-versus-host disease (GVHD). To dissect the role of different T cell populations, a pre-clinical mouse model was conducted at Dr. Samuel Strober's laboratory. In a seminal report (Blood 2011; 117:3230-3239), they found that $CD8^+$ memory T cells were the only population capable of eradicating cancer cells without inducing GVHD. Based on this critical observation, Dr. Robert Lowsky started a clinical trial using enriched $CD8^+$ memory T cells as an alternative to DLI in patients who relapsed after allogeneic transplant.

In this phase I trial, 15 patients with a variety of diseases (acute myeloid leukemia, lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, myeloma, and acute lymphoblastic leukemia) received $CD8^+$ memory T cell infusions at three dose levels. The goal is to infuse a high dose of donor $CD8^+$ memory T cells without triggering GVHD. Most of the patients (87%) received cytoreductive therapy prior to $CD8^+$ memory T cell infusion. Five patients received the highest planned $10x10^6$/kg dose. As expected, there were no severe adverse events after infusion, and no dose-limiting toxicities occurred. GVHD developed in only one patient, was limited to grade II involvement of the liver, and resolved following a course of steroids. Ten patients (67%) maintained or achieved response (7 complete response, 1 partial response, 2 stable disease) including one acute lymphoblastic leukemia patient who has responded to CD8+ memory T cells alone without any other therapy (see left).



Three log reduction of circulating leukemia burden after single donor CD8+ memory T cell infusion in a patient with relapsed acute lymphoblastic leukemia after allogeneic transplant.

This is one example of our tireless commitment to understanding the function of critical cellular components from the donor graft, and our efforts to translate our research into clinical practice to advance the quality of patient care. ■



(left) Robin with Sarah in Germany. *(right)* Robin with her "Chimera", the stuffed animal she had made to symbolize her story.

It Takes a World to Cure a Cancer

When Robin was first diagnosed with acute myeloid leukemia in December 2011, she knew that it would be a long journey for her fight against this cancer. Given the dysplastic changes in her bone marrow, standard chemotherapies were unlikely to give her a long-term remission or a cure. Her best chance was to receive an allogeneic (donor) transplant. However, neither of her siblings were a match to her. The only option was to find a suitable matched donor through the National Marrow Donor Program (NMDP). First, Robin had to undergo several rounds of chemotherapy prior to being considered for transplant. By June 2012, she went into clinical remission and learned that one (the only one) 10/10 fully matched donor had been identified through the NMDP.

Robin then received the conditioning regimen, followed by donor cell infusion in late July. At the time she received her life-saving cells, she only knew that they were from a young woman who lives in Europe. Even though she was still struggling with immediate post-transplant side effects, she managed to write thank-you notes in August, which she later found out did not reach her donor until December. Gradually, she recovered bit by bit and her leukemia was gone. Although she exchanged anonymous letters with her donor a few times, they were not allowed to reveal their private information until two years after transplant. By the end of 2014, Robin finally learned that her donor was a woman named Sarah from Northern Germany.

They started to exchange emails with personal information. However, the burden of translating English to German made it very difficult. After a few months of slow back-and-forth emails, Robin and Sarah declared their wish to meet in person, and of course, in Germany. Armed with a short course in German, Robin and her husband flew to Hamburg in the Fall of 2015, before driving to the small farm village where Sarah lived. The first meeting occurred at the hotel lobby where Robin stayed. Robin and Sarah looked at each other unbelievingly and then collapsed into a long embrace. The following days, Sarah hosted Robin and her husband in her family home. They spent time with Sarah's and her husband's families, toured neighboring villages and visited Sarah's favorite resort town on the Baltic Sea. To Robin, this trip also meant some answers. The first one was how Sarah decided to join the donor program. It turned out that there were two boys in the neighboring towns needing donors for transplant, which prompted donor drives in the preceding years. Unfortunately, neither boy found a suitable donor. Robin also wanted to know why Sarah decided to donate even though she was scared and the timing was not ideal. Sarah's answer was so matter-of-fact, "What else is there than to help another human?" After the four-day reunion of these two lives that had intertwined forever through this life-saving procedure, Robin returned home feeling peaceful and fulfilled. To this date, Robin and Sarah continue to communicate on a daily basis.

Each year, Stanford BMT program performs about 90-95 allogeneic transplants with hematopoietic stem cells from an unrelated donor just like Sarah. Having a suitable donor through the NMDP can mean a life-saving event. Currently, approximately 27 million potential donors are accessible either within the United States network or by International registry. If you are interested in becoming a potential donor, please visit NMDP website at http://BeTheMatch.org ■

STANFORD BMT WELCOMES 2016-2017 FELLOWS

Carlos Silva, MD

received his medical degree from the Health Science University Foundation in Colombia. He completed Internal Medicine residency at the State University of New York Downstate Medical Center and was rotating house staff at Memorial Sloan-Kettering Cancer Center in Hematological malignancies and Bone Marrow Transplant. He did his Hematology and Oncology fellowship at Case Western Reserve University/Case Comprehensive Cancer Center, where he served as Chief fellow. His clinical research interest has been focused on Lymphoid malignancies and transplantation. Some of his work was recently presented at the 2016 ASBMT annual meeting.

Nasheed Hossain, MD

received his medical degree from the Case Western Reserve University. He completed his Internal Medicine residency at the University of Chicago Medical Center and a Hematology/Oncology Fellowship at the Fox Chase Cancer Center/ Temple University Hospital. His research has primarily focused on epigenetic therapy in MDS/ AML and the evaluation of minimal residual disease in various hematologic malignancies. Through his participation in the American Society of Hematology Clinical Research Training Institute (ASH-CRTI) program he was developed a Phase IB/II trial at Fox Chase of a novel epigenetic drug combination therapy for elderly or unfit MDS/AML patients.

Saurabh Dahiya, MD

finished his medical school at Maulana Azad Medical College prior to coming to the U.S. He completed his Internal Medicine residency and Hematology/ Oncology fellowship at Baystate Medical Center/ Tufts University in Massachusetts. He has been very proliferative in publications including many first-authored papers covering topics from spontaneous coronary artery dissection to lymphoma. His interests outside of medicine are traveling, exploring various cuisines and amateur writing.

Amandeep Godara, MD

finished his medical school at Government Medical College at Maharashtra, India. During his medical school years, he was very active in volunteer works including organizing Polio Immunization Drive and Blood donation. He finished his Internal Medicine resident training at Wayne State University, Detroit. He is interested in pursuing a career focus on hematologic malignancy including myeloma, MDS and CML.

Kathryn Cappell, MD, PhD

did her undergraduate at University of Miami (as an inspiring marine biologist!). However, medicine charmed her into the MD/PhD program at University of North Carolina-Chapel Hill. Her PhD work (Pharmacology) focused on finding ways to increase cancer cells' sensitivity to paclitaxel chemotherapy using a synthetic lethal screening system. She then did her Internal Medicine residency at Stanford. She is very interested in hematology and wants to seek an academic career in this field.

STANFORD
BMT
BLOOD & MARROW TRANSPLANTATION

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OUR VISION

By working with faculty in other divisions within the School of Medicine and Stanford Cancer Institute along with the support of Stanford Hospital, the Stanford BMT program has built a new expanded Cellular Therapeutics Facility. With this new facility, the Stanford BMT program will develop life-saving treatments and implement novel clinical trials more efficiently in the coming years.

Precision Medicine with Technologies

The BMT Immuno-monitoring program will continue to apply state-of-art technologies such as High-Throughput Sequencing (HTS), and Mass Cytometry (CyTOF) to monitor the minimal residual disease and the changes of immune system in transplant patients.

Developing Novel Cellular Therapeutics

Just like memory CD8+ T cells, we will develop new cellular therapeutics using different cell populations. Examples include using regulatory T cells (Treg) to treat GVHD; utilization of virus-specific cytotoxic T cells in managing life-threaten-ing viral infections; engineering Chimeric Antigen Receptor (CAR) T cells to target different hematological malignancies and solid organ cancer.

Expanding Cellular Therapeutics to Other Diseases

We will apply novel approaches to treat patients with non-malignant conditions, such as the ongoing trial with purified stem cells in immuno-deficient patients. We will also use cellular therapeutics to modulate the immune system, for managing diseases such as autoimmune disease and solid organ transplantation.

How You Can Help

Participating in one of our clinical studies is one of the most precious gifts our patients can give. As a referring physician, encouraging your patients to work with our team would be a tremendous benefit. In addition, if you or someone you know would like to make a philanthropic donation to the BMT, please contact Michele Thompson at 650-725-1109 or visit our website: http://bmt.stanford.edu.

CLINICAL TRIAL HIGHLIGHTS

Post transplant infusion of **allogeneic CD8 memory T cells** as consolidation therapy after non-myeloablative allogeneic hematopoietic cell transplantation in patients with leukemia and lymphoma *(Robert Lowsky, MD)*

Phase I/II trial for patients undergoing myeloablative allogeneic HCT with a T cell depleted graft with simultaneous infusion of **conventional T cells and regulatory T cells** *(Everett Meyer, MD, PhD)*

A multi-center, phase III, randomized trial of reduced intensity conditioning and transplantation of **double unrelated umbilical cored blood** versus **HLA-haploidentical related bone marrow** *(Andrew Rezvani, MD)*

A randomized, multi-center, phase III trial of **calcineurin inhibitor-free interventions** for prevention of graft-versus-host disease *(Lori Muffly, MD, MS)*