IMMUNE DEFICIENCY FOUNDATION

The National Patient Organization Dedicated to Advocacy, Education and Research for Primary Immunodeficiency Diseases

July 13, 2012

Jonathan Thomas, Ph.D., J.D.
Chair, Governing Board of the CIRM (ICOC)
210 King Street
San Francisco, CA 94107

RE: CIRM Disease Team Grant - DR2-05365
Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas,

I am writing this letter to convey to the CIRM governing board the Immune Deficiency Foundation's strongest support for the above proposal by Drs. Shizuru and Cowan to evaluate a monoclonal antibody that depletes stem cells in the bone marrow prior to bone marrow transplant. This approach has the potential to cure children with SCID or other immune deficiencies while eliminating the need for the toxic chemotherapy and radiation therapy that is often given to these young patients.

One of the greatest challenges faced by individuals diagnosed with primary immunodeficiency diseases is finding the right information and resources when they need it. With knowledge and foresight from their personal experience, the Immune Deficiency Foundation (IDF) was founded by families of children with primary immunodeficiency diseases and their physicians to help meet those needs. It is with the spirit and energy of this keen perspective that IDF exists today, thriving as an organization dedicated to individuals living with primary immunodeficiencies.

Since 1980, IDF has provided accurate and timely information for the nearly quarter-million Americans who have been diagnosed with a primary immunodeficiency disease. Governed by a Board of Trustees – and supported by a Medical Advisory Committee comprised of some of the world's leading clinical immunologists, as well as hundreds of grassroots volunteers and a compassionate, professional staff – IDF has provided individuals and their families with vital knowledge and made tremendous strides in:

- Helping the patient and medical community gain a broader understanding of primary immunodeficiency diseases through education and outreach efforts;

- Promoting, participating, and funding research that has helped characterize primary immunodeficiency diseases and given patients and physicians substantially improved treatment options;

- Addressing patient needs through public policy programs by focusing on issues such as insurance reimbursement, patient confidentiality, ensuring the safety and availability of immune globulin therapy, advocating for Newborn Screening for SCID, and maintaining and enhancing patient access to treatment options.

Today, thousands of individuals and families affected by primary immunodeficiency diseases depend on IDF for advocacy, education and empowerment.

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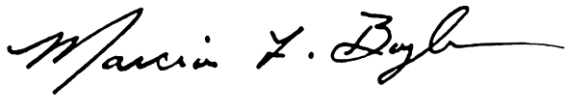
The IDF is a major patient advocacy group that supports the Primary Immune Deficiency Treatment Consortium (PIDTC) and its annual scientific workshop headed by Dr. Cowan. We are fortunate to have Dr. Cowan and his colleagues participate regularly in IDF regional patient meetings as well as the biennial national convention to update our patient and parent members of the progress in the field of transplantation and gene therapy for PID.

I know that the high dose chemotherapy that is currently essential to make space in the marrow prior to a bone marrow transplant, unfortunately, has both early and late effects on our children. A monoclonal antibody that might eliminate the need for chemotherapy would be a god-send for which we all are hoping. The positive impact that such a therapy would have on thousands of patients world-wide is too great to not pursue.

The application by Dr. Shizuru and Dr. Cowan addresses a very critical need for children with primary immunodeficiency that has been identified by the IDF and its patient representatives and we will do anything to support its approval by the CIRM Board. If there is anything more that I can do please let me know.

Sincerely yours,



Marcia Boyle
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July 16, 2012

Jonathan Thomas, Ph.D., J.D.
Chair
Governing Board of the CIRM (ICOC)
210 King Street
San Francisco, CA 94107

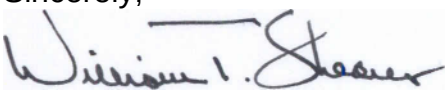
Dear Dr. Thomas,

I am writing in strong support of Dr. Judith Shizuru and Dr. Morton Cowan's application for a CIRM grant to fund human studies that will facilitate transplantation of allogeneic stem cells into children born with severe combined immunodeficiency (SCID). Their approach is novel and may lead to a better quality of life for children as they grow up. The novelty of Drs. Shizuru and Cowan's approach is that they propose the use of a monoclonal anti-C kit molecule found on human stem cells that will clear the bone marrow of the patient's stem cells so that the transplanted stem cells will find unoccupied niches in the bone marrow. This leads to accelerated immune reconstitution and without the toxicities associated with chemotherapy that are used to create space in the patient's bone marrow. This approach in humans is experimental, but Drs. Shizuru and Cowan have provided sufficient animal work to justify its extrapolation to humans. If successful, this approach would revolutionize how hematopoietic stem cell transplantation is performed in the entire world.

Drs. Shizuru and Cowan's credentials are impeccable as bone marrow transplanters with decades of experience. For example, among the top 15 pediatric immunologists who perform bone marrow stem cell transplantation in North America, Dr. Cowan was peer-selected to be the principal investigator of the Primary Immunodeficiency Transplant Consortium, a group of 13 major medical centers of excellence in restoring SCID infants to health with stem cell transplants. Dr. Shizuru is equally suited for this research. Their team and facilities necessary to carry out this new study are perfect. They have the enormous benefit of having Dr. Jennifer Puck as a collaborator at their institution. Dr. Puck is a world authority in the screening of infants by the T cell receptor excision circle assay. Drs. Shizuru and Cowan's program will have sufficient patients for their study with the SCID children identified by Dr. Puck.

I most strongly support the application of Dr. Judith Shizuru and Dr. Morton Cowan for CIRM for their exciting new study.

Sincerely,



William T. Shearer, M.D., Ph.D.
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WTS:jmh

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July 14, 2012

Jonathan Thomas, Ph.D., J.D.
Chair, Governing Board of the CIRM (ICOC)
California Institute of Regenerative Medicine
210 King Street
San Francisco, CA 94107

RE: CIRM Disease Team Grant - DR2-05365

Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas,

I am writing to strongly advocate for the application submitted to CIRM by Drs. Shizuru and Cowan which proposes to test a novel biologic agent aimed at depleting hematopoietic stem cells as a way to prepare children with severe combined immune deficiency (SCID). I have been very involved in the blood and marrow transplantation field since 1989 and am one of the leaders in pediatric blood and marrow transplantation in North America, I am the past chair of the Canadian Blood and Morrow Transplantation (CBMTG BMT) Group Clinical Trials Network (2000 – 2004), the past chair of the Pediatric Blood and Marrow Transplantation Consortium (PBMTC) (2004 – 2009), past member of the NHLBI funded Blood and Marrow Transplant Clinic Trials Network (BMT CTN) Steering committee (2004 – 2009), past co-chair of the BMT CTN Pediatric State of the Science Committee and past chair of the BMT CTN Special Populations Committee focused on the inclusion of children, women and vulnerable populations in transplantation research.

Currently, I am a member of the executive of the PBMTC and the CBMTG CTN, as well as a member of the Children's Oncology Group Hematopoietic Transplant Strategy Group and BMT CTN Biomarkers Committee, and chair of the Data Management, Clinical Trials, and Registry Core for the CIHR funded Canadian Transplant Research Network. As one of the principle leaders in pediatric BMT, I was one of the founders of the Primary Immune Deficiency Treatment Consortium (PIDTC). I am focused on expanding my efforts to network North America with Europe for pediatric BMT research and have organized the first pediatric BMT forum to be held in October 2012 in Frankfurt, Germany. Because of this background I believe I am well qualified to comment on this important work.

Since its inception over 50 years ago, the transplantation of blood and bone marrow (which contain rare stem cells) has involved the treatment of recipients with toxic agents such as radiation and chemotherapy in order to eliminate the recipient's own stem cells and permit the donor stem cells to take root and make blood. Tens of thousands of people world-wide are given these types of bone marrow transplants yearly. Of the patients treated by bone marrow transplants, the most vulnerable to the effects of radiation and chemotherapy are children and babies. Infants who are born with genetic disorders such as severe combined immune deficiency (SCID) will usually not live beyond 2 years unless they receive a transplant from a donor with a normal blood system. The idea that a biologic agent such as the one proposed in Drs. Shizuru's and Cowan's application (called anti-cKit) can target and specifically deplete recipient blood stem cells and permit engraftment of donor cells is transformative for our field. As a community of

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pediatric transplanters, we have looked forward to the possibility that such a biologic agent would be developed since the initial ground-breaking studies were published by Dr. Irving Weissman in 2007. Those studies showed that when mice with a disease analogous to human SCID were prepared with an anti-cKit antibody they had minimal toxic side effects and engrafted robustly with their donor's stem cells.

Our first hope is to be able to offer this treatment to our patients. However, we can also see that success in treating our patients with this biologic agent will have implications for many other diseases because it may replace the chemotherapy or radiation given to other patients that undergo transplant. We also foresee that in order for stem cell therapies to work for all other tissues, the defective stem cells present in a recipient will need to be depleted. Thus, the anti-cKit studies would be a first example that a biologic agent can be used for this purpose – a significant step forward for stem cell therapies.

Given the long lead time and expense that it takes new ideas to make it to clinic, I am concerned that if their application fails to receive funding, it will be many, many more years before this biologic reagent will reach patients. Thus, I hope that the CIRM Board will see fit to look favorably upon the petition when it comes up for consideration in the near future.

Sincerely,

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July 17, 2012

John Thomas, PhD, JD
Chair, Governing Board of the CIRM (ICOC)
210 King Street
San Francisco, CA 94107

RE: CIRM Disease Team Grant - DR2-05365

Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas,

It is my privilege to write a letter urging the CIRM to support a proposed study that will make what I consider one of the most important recent discoveries in the biology of hematopoietic stem cell biology into a clinical therapy that could change the way we perform transplants for many classes of patients.

I am the Chair of the Pediatric Blood and Marrow Transplant Consortium (PMBTC), the largest pediatric hematopoietic transplant research consortium in the world (77 of the top centers in the US, Canada, New Zealand, and Australia). I have a specific interest in transplantation of children with non-malignant disorders. Our major challenge with these children is that current approaches rely on toxic chemotherapeutic agents and total body irradiation in order to deplete a patient's own stem cells and immune suppress them sufficiently so that other elements of their immune system do not reject incoming transplanted cells. This results in high risks of organ damage, infection, infertility, and other long-term consequences, and is often unsuccessful (the new bone marrow grafts are rejected).

Drs. Shizuru and Weissman are world experts in the biology of bone marrow stem cells. Their elegant experiments in animal models show that the use of antibodies to c-Kit allow selective depletion of stem cells and repopulation by transplanted stem cells without these toxic approaches. They have a humanized monoclonal antibody to c-Kit (CD117) that is now ready to test in humans. They have very wisely partnered with Dr. Mort Cowan, an internationally recognized expert in immunodeficiency disorders and the PI of the NIAID-funded Pediatric Immune Deficiency Treatment Consortium (of which the PBMTC is a principal partner for transplant approaches to these children), and designed a study in the best population in which to begin testing this agent. Children with immune deficiencies can sometimes engraft T-cells with minimal approaches, but they often do not engraft stem cells, allowing full recovery of T-cell and B-cell populations, unless more intensive preparative regimens are used. Intensive transplant approaches in these

children are often very unsafe because they usually have multiple infections and organ damage prior to transplant therefore do not tolerate intensive therapy. Successful testing of this antibody in these patients would be a proof of principal that minimal intensity transplantation by selective depletion and repopulation of stem cell niches is possible.

If this approach works in humans the implications will be profound. Use of the antibody could allow marked reductions in the intensity of preparative regimens for over twenty non-malignant disorders including sickle cell disease, thalassemia, bone marrow failure disorders (aplastic anemia, Fanconi anemia), Hurler syndrome, other immune deficiencies, etc.. There may be further implications for the therapy of malignancies undergoing transplantation. There is evidence to suggest that leukemia "stem cells" are difficult to treat with standard chemotherapy due to quiescence, and if not eliminated will lead to relapse. Giving this agent could either kill leukemia stem cells or put them into circulation, out of the potential protection of the stem cell niche, and thus make them more susceptible to chemotherapy.

In summary, the preliminary data for this antibody shows it to be one of the most promising approaches to improving engraftment after bone marrow transplant seen in years. It has minimal toxicity, and if successful will change the non-malignant transplant field. It is a top priority for study in our consortium, as we hope to partner with the PIDTC to perform multi-institutional trials to further develop this agent if early studies show promise. This antibody is a potential game changer, and I urge you to support these critical early steps in its development.

Sincerely,

Michael A. Pulsipher, MD
Chair, Pediatric Blood and Marrow Transplant Consortium
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July 13, 2012

Jonathan Thomas, Ph.D., J.D.
Chair, Governing Board of the CIRM (ICOC)
210 King Street
San Francisco, CA 94107

RE: CIRM Disease Team Grant - DR2-05365
Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas:

I would like to support the application by Dr. Judy Shizuru to evaluate an anti-CD 117 antibody to improve hematopoietic stem cell (HSC) engraftment without the need for myeloablative chemotherapy. My enthusiasm is not just for its potential use in patients with Severe Combined Immune Deficiency (SCID), but more importantly its potential use generally in HSC transplantation (HSCT). The ability to achieve HSC engraftment without the need for myeloablative chemotherapy would reduce the toxicities associated with HSCT, especially in children with genetic diseases, who are especially sensitive to the toxic effects of myeloablative chemotherapy.

Besides being of particular importance for the HSCT of children, the successful use of the anti-CD117 antibody to achieve HSC engraftment would be a major advancement to the field of HSCT generally. I, therefore, wholeheartedly support Dr. Shizuru's grant application.

If you have any questions, please do not hesitate to contact me.

Sincerely,

Robertson Parkman, M.D.
Professor of Pediatrics, Molecular Microbiology and Immunology
Department of Pediatrics, USC Keck School of Medicine
Division of Research Immunology/BMT, and
The Saban Research Institute of Childrens Hospital Los Angeles

HARVARD MEDICAL SCHOOL

Luigi D. Notarangelo, M.D.
Jeffrey Modell Chair in Pediatric Immunology Research at Children's Hospital Boston
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Boston, July 13, 2012

Jonathan Thomas, Ph.D., J.D.
Chair, Governing Board of the CIRM (ICOC)
210 King Street
San Francisco, CA 94107

RE: CIRM Disease Team Grant - DR2-05365
Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas:

I am delighted to write this letter of enthusiastic support of Dr. Shizuru's and Dr. Cowan's application to the California Institute for Regenerative Medicine.
My name is Luigi D. Notarangelo, and I am Professor of Pediatrics and Pathology at the Harvard Medical School and Jeffrey Modell Chair of Pediatric Immunology Research at Children's Hospital Boston. I am also the chair of the International Union of Immunological Societies Committee on Primary Immunodeficiencies, and I have served as President of the European Society for Immune Deficiencies. I am also the co-PI of the Primary Immune Deficiency Network Consortium, an NIH-supported initiative that gathers 33 centers that are particularly active in the field of hematopoietic cell transplantation (HCT), enzyme replacement therapy and gene therapy for severe forms of primary immunodeficiency (PID) in North America Before moving to Boston, I have directed the center of HCT for PID in Brescia (Italy), one of the largest centers worldwide for the treatment of these disorders. In addition to contributing to the identification of the molecular and cellular bases of several immunodeficiency disorders, I have offered important contributions to the field of HCT in PID, in particular in regard to the use of HCT from alternative donors in Severe Combined Immunodeficiency Disease (SCID) and in the Wiskott-Aldrich syndrome (Mazzolari et al., J All Clin Immunol 2007; Moratto et al., Blood 2011). I have been active in this field for the past 20 years. I am giving this information solely to demonstrate that I can comment properly on the merit and significance of Dr. Shizuru's application.

Dr. Shizuru's application intends to pursue a novel, and potentially ground-breaking avenue to facilitate engraftment of donor stem cells in infants with SCID, and hopefully in other disorders. It is well known

that children with SCID have intrinsic limitations in the ability to reject donor-derived cells, because of the lack of functional T lymphocytes. In this sense, there is clear evidence that unconditioned HCT in SCID most often results in sustained long-term persistence of donor-derived T cells. However, this long-term reconstitution is typically achieved because of the engraftment of committed lymphoid progenitors to the thymus, without engraftment of hematopoietic stem cells (HSCs). Because of this, other compartments, and notably the B cell compartment, typically remain host-derived after unconditioned T cell-depleted HCT. We have demonstrated that failure to attain donor stem cell engraftment is associated with poor humoral immune reconstitution, especially in infants with SCID due to genetic defects that affect B cell function, such as X-linked SCID and JAK3 deficiency (Recher et al., Blood 2011). Moreover, there is also evidence that in recipients of unconditioned HCT, in the absence of true stem cell engraftment, the peripheral T cell compartment is progressively populated by memory/activated T cells that often show a restricted repertoire. Use of high-dose conditioning regimens has been advocated to overcome these intrinsic limitations, and is universally used for HCT from unrelated donors. While this approach yields a higher chance to engraft donor stem cells, it is associated with significant morbidity and mortality, both acutely and short-term. Furthermore, some forms of SCID with increased cellular radiosensitivity (Artemis, LIG4, and Cernunnos defects) are uniquely susceptible to the side effects of alkylating agents. Therefore, it is not surprising that no agreement has been reached yet in the scientific community on optimal approach to HCT for SCID patients who lack HAL-identical related donors. More in general, there is an urgent need to explore novel, safer and effective approaches to facilitate donor stem cell engraftment and sustain long-term immune reconstitution, without the risks associated with use of high-dose chemotherapy.

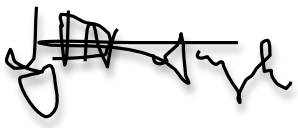
Dr. Shizuru's and Dr. Cowan's proposal is potentially ground-breaking. Also through an impressive network of stellar collaborators, including Dr. Irv Weissman, they have explored a novel approach that is based on use of HSC-depleting monoclonal antibody (mAb) to CD117 (c-kit), the stem cell factor (SCF) receptor. In a large set of preclinical experiments in immunodeficient mice, they have shown that injection of anti-CD117 mAb leads to dramatic depletion of autologous HSCs, thereby making space for the engraftment of donor-derived HSCs at very high (>90%) levels for prolonged period of time. This is a **conceptually highly innovative approach** based on targeting of the stem cell niche, without affecting other populations in the marrow or in other tissues, and thus overcoming the limitations inherent to the use of highly-toxic, non-HSC-specific chemotherapeutic regimens. There is an urgent need to translate these exciting observations into a Phase I/II clinical trial. Should the use of anti-CD117 mAb in humans prove to be safe and capable of mediating depletion of autologous HSCs, it would represent a novel, safe and effective approach that is expected to result in sustained multi-lineage engraftment of donor-derived cells in infants with SCID. I can immediately see several important applications of this technology. Newborn screening for SCID is now available in at least 8 States in this country, and is being considered in many others and in several other countries worldwide. This is a very powerful approach to allow early identification of babies with SCID, before they develop severe, potentially life-threatening infections. However, its is imperative that the early identification of babies with SCID be followed by prompt treatment with HCT, and yet even larger concerns apply to what is the best approach for these very young infants. For newborn screening to be really effective from a public health perspective, we need HCT to be highly efficacious, and unconditioned HCT may fall short of this. On the other hand, use of chemotherapeutic agents in newborns and very young infants is even more problematic and worrisome. Use of HSC-depleting anti-CD117 mAb may represent the ideal approach. **This hypothesis needs to be tested through a clinical trial**.

I also foresee application of this agent in gene therapy protocols for PIDs. I am currently the PI on a gene therapy protocol for X-linked SCID and the co-PI for a gene therapy protocol for the Wiskott-Aldrich

syndrome (WAS) at Children's Hospital Boston. Gene therapy for X-linked SCID is performed without conditioning, but previous trials have shown that engraftment of gene-corrected B cells is very inconsistent, and many patients continue to require intravenous immunoglobulins. Should we succeed to engraft a good number of gene-corrected HSCs, we might be able also to attain humoral reconstitution. Similarly, efficacy of gene therapy in WAS depends on multilineage engraftment of gene-corrected cells, and this requires stem cell engraftment. In current trials, this goal can only be achieved with use of chemotherapeutic agents, with significant potential toxicity. Use of anti-CD117 mAb might allow for robust engraftment of gene-corrected HSCs and thereby permit hematopoietic and immune reconstitution. I am also convinced that while SCID represents the ideal disease model to test safety and efficacy of anti-CD117-based HSC depletion for HCT in the human setting, this approach could be applied to other congenital and acquired disorders that are currently treated with HCT.

For these reasons, I consider Dr. Shizuru's and Dr. Cowan's application highly meritorious, and I enthusiastically support it for consideration by the CIRM. As co-PI of the PIDTC, I will be delighted to work at a multi-institutional trial that involves PIDTC centers, to explore further the safety and efficacy of this novel approach in the treatment of SCID and other disorders by HCT and gene therapy.

Sincerely,



Luigi D. Notarangelo, M.D.
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Jeffrey Modell Chair of Pediatric Immunology Research
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Neena Kapoor, M.D.
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Clinical Director, Research Immunology and Bone Marrow Transplantation
Director, HSCT Program at Children's Hospital Los Angeles
Division of Research Immunology & Bone Marrow Transplant
Children's Hospital Los Angeles

July 17, 2012

Jonathan Thomas, Ph.D., J.D.
Chair, Governing Board of the CIRM (ICOC)
210 King Street
San Francisco, CA 94107

Re: LOS for CIRM Disease Team Grant DR2-05365
Project title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants

Dear Dr. Thomas:

It is my pleasure to write a letter of support for Drs. Judith Ann Shizuru and Mort Cowan's for their application for CIRM Disease Team Grant for their project titled "monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants". This translational project is an application of information learned in immune deficient mice where transplant can be performed following conditioning with cKit monoclonal antibody conditioning to children with severe combined immune deficiency (SCID) disorder.

Since 1968, children with SCID have been treated with correction of their immune deficiency by undertaking allogeneic stem cell transplant. Since that time, transplants from histo-compatible sibling donors have been the gold standard. Such transplants could be undertaken without any pre-transplant conditioning of the patient. However, with such procedures, in many cases only T cell number and functional correction is accomplished. In other patients, B cell deficiency continues to be an ongoing problem thus; patient remained dependent on immunoglobin replacement therapy for life. In this type of transplant there is also concern that in many cases there may only be T progenitor cell engraftment and not stem cell engraftment thus limiting the T cell repertoire and rendering the patient vulnerable and incapable of mounting immune response to neo antigens. While non conditioned transplant does achieve T cell engraftment in sibling donor transplant setting, such procedure may not be successful when alternative donors are used.

To facilitate the complete T cell, B cell and antigen presenting cell engraftment (complete immunological correction) invariably pre-transplant conditioning of the patients with myelo-ablative doses of chemotherapy is used. While such treatment facilitates engraftment of stem cells and the progenitor cells, this also carries significant short and long term side effects. The acute toxicity is related to myeloablation leading to pancytopenia, mucositis, risk of infection and organ toxicity. In some cases these toxicities can lead to serious complication causing acute morbidity and mortality. There are also long term side effects of chemotherapy such as organ failure, secondary malignancy, etc. Therefore, with such conditioning regiment where we enhance the chances of full immunological correction, there is a risk of serious short and long term side effects.

Drs. Shizuru and Cowan's are proposing the use of anti-human CD117 mAb that binds to CD117, the receptor to stem cell factor (SCF) on hematopoietic stem cells (HSCs), thereby inhibiting SCF signaling and leading to depletion of >98% of host HSCs. In immune deficient mice, the conditioning with anti-CD117 mAb dramatically enhances donor HSC engraftment resulting in long term chimerism up to 90%. Their pre-clinical observation is quite promising and its translation into human application is very exciting. This project has the potential to give us the advantage of accomplishing myeloablation and facilitating engraftment without exposing young children to the toxic doses and associated risks of chemotherapy. There is an ongoing debate amongst clinicians and scientists involved with the care of children with SCID whether or not chemotherapy should be given in preparation for transplant. Both groups recognize the benefits and risks associated with their recommendation but have not been able to come to the agreement what is more acceptable for the patient in long term. I believe the above mentioned proposal, if successful, will provide the ultimate answers we are looking for.

I strongly support this proposal and highly recommend approval of the grant.

Thank you for your consideration.

Sincerely,

Neena Kapoor, M. D.
Professor of Pediatrics
Keck School of Medicine
University of Southern California
Clinical Director, Research Immunology and Bone Marrow Transplantation
Director, HSCT Program at Children's Hospital Los Angeles
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NK/rh

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July 16, 2012

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210 King Street
San Francisco, CA 94107

RE: CIRM Disease Team Grant - DR2-05365
Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas,

I am writing to express my support for Dr. Judith Shizuru's and Dr. Mort Cowan's CIRM Disease Team grant application.

As a pediatric hematologist and blood and marrow transplant physician, my career has focused on the development of methods for using gene therapy to treat children with primary immune deficiencies — diseases resulting from inherited mutations or deletions in genes required for the production or survival of specific immune cells (e.g., T, B, or NK lymphocytes, neutrophils, or antigen-producing cells). Hematopoietic stem cell (HSC) transplantation has been performed for many of the life-threatening PID, including severe combined immune deficiency (SCID), Wiskott-Aldrich syndrome (WAS), chronic granulomatous disease (CGD), leukocyte adhesion deficiency (LAD), X-linked hyper IgM syndrome (X-HIM, due to deficiency of the CD40 ligand CD154), hemophagocytic lymphohistiocytosis (HLH) and immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX), among others.

A critical barrier to widespread success of gene therapy for SCID and the other PID is the lack of minimally toxic conditioning regimens to ensure adequate engraftment of gene-modified hematopoietic stem cells. In many of the trials I have led, we have infused genetically modified autologous HSC with no or minimal pre-conditioning due to the fact that chemotherapy and radiotherapy have largely unacceptable long-term side effects when used in children, particularly those already compromised by opportunistic infections in the setting of SCID. Although we have advanced the technology of gene-transfer into HSC to ensure that a

substantial portion of the HSC administered are correctly modified to express the gene congenitally lacking in the patient, we unfortunately have experienced difficulty obtaining high level long-term engraftment of the gene-modified stem cells. We strongly believe that this is due to a need for clearance of the HSC niche prior to administering the gene-modified cells so that they encounter a microenvironment open and favorable to their long-term engraftment.

To address this problem, my pre-clinical and clinical research groups have investigated the use of low-dose chemotherapy (i.e., Busulfan). Although we have had some success with this approach in a subset of SCID patients, it has not proven to be a simple and widely applicable solution. Many of the SCID children unfortunately still lose a substantial portion of the gene-modified stem cells and ultimately have poor immune reconstitution and ongoing risk for life-threatening infections. We believe that this failure of long-term high-level engraftment of autologous gene-modified HSC is due, at least in part, to insufficient niche clearance using low dose Busulfan. Escalating the dose of Busulfan is not a favored alternative, again because of the significant toxicity in children with SCID.

When Dr. Irv Weissman's lab at Stanford published pre-clinical data showing that HSC niche clearance could be achieved in SCID mice using an anti-c-kit monoclonal antibody with subsequent high level engraftment of donor HSC, I immediately thought the ramifications of this approach would be profound for the field of autologous HSC gene therapy. Since that time, I have been eager to see this approach advance to clinical utility specifically for application in children with SCID, but also other immune deficiencies, hemoglobinopathies and storage disorders. I strongly believe this approach may be exactly what we need to dissolve the barriers to high level engraftment of genetically modified autologous HSC that we have encountered in all SCID gene therapy trials to date.

I am in full agreement with Dr. Shizuru, Dr. Mort Cowan, and their Disease Team that the pre-clinical data strongly support advancement of the available anti-humanized anti-c-kit antibody to a clinical trial in SCID children as soon as possible. The allotransplant trial proposed by the Shizuru Disease Team will provide critically important proof-of-principle for this approach of targeted stem cell replacement, and success will have broad implications. I unequivocally support funding the Stanford CIRM Disease Team grant led by Drs. Shizuru and Cowan, and I believe the Disease Team they have assembled will help revolutionize stem cell replacement with allogeneic or gene-modified autologous stem cells.

Sincerely,

Donald B. Kohn, M.D.
Professor, Microbiology, Immunology &
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July 13, 2012

Jonathan Thomas, Ph.D., J.D.
Chair, Governing Board of the CIRM (ICOC)
210 King Street
San Francisco, CA 94107

RE: **CIRM Disease Team Grant - DR2-05365**
Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas,

We are writing this letter to provide our most enthusiastic support for the proposal by Drs. Shizuru and Cowan to evaluate a monoclonal antibody that depletes stem cells in the bone marrow and might permit the avoidance of chemotherapy in treating children with SCID or other primary immune deficiencies (PID) with a bone marrow transplant or gene therapy.

So you might understand who we are, we established the Jeffrey Modell Foundation (JMF) in 1987, in memory of our son Jeffrey who died when he was 15 years old from a PID. The JMF is a global nonprofit organization dedicated to early diagnosis, meaningful treatments and, ultimately, cures through research, physician education, public awareness, advocacy, patient support and newborn screening. Just a few of our accomplishments include: Support for the establishment of newborn screening for SCID beginning in Wisconsin in 2008; establishment of more than 120 Jeffrey Modell Diagnostic and Research Centers (including Dr. Cowan's center at UCSF) and a referral network of 493 Expert Immunologists at 196 academic teaching hospitals and medical schools in 64 countries, 191 cities, spanning 6 continents; establishment of a $12 million funding and research collaboration with the NIH; and, the funding of a variety of research programs including endowed chairs in Pediatric Immunology Research, Post-doctoral fellowships, Prizes in Immunology, Scientist-of-the-Future Program, and a joint research collaboration with NIH and Affymetrix for Newborn Screening of SCID using microarray technology. This represents only a few of our many endeavors to promote research in the diagnosis, treatment and cure of all PID!

We are well aware of the major progress that Dr. Cowan and his colleagues have made in organizing the Primary Immune Deficiency Treatment Consortium (PIDTC) and we have helped to support their annual PIDTC Scientific Workshop where for the first time investigators from North America and Europe focused on PID are coming together to identify the most optimal approach to diagnosing and treating SCID and other PID. At the recent meeting in Boston which we attended Dr. Cowan made us aware of the potential use of this monoclonal antibody that

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could potentially replace the need for high dose chemotherapy prior to transplant or gene therapy for babies with severe immunodeficiencies who will die without this life-saving therapy. As parents whose child did die from PID and who talk every day with other parents from around the world about the transplant experiences of their children, the thought of one's child having to be treated with high doses of chemotherapy with its many known toxicities in order to be "saved" from their PID is heart wrenching. The possibility of having a monoclonal antibody that could eliminate the need for this toxic and dangerous treatment is a dream that we all have and that we absolutely must pursue!

Drs. Shizuru's and Cowan's application is unique and innovative, and the first one that we've seen that addresses a very critical need that could make a quantum leap in the care of not only children with SCID but children with many other diseases that can only be cured with a bone marrow transplant. The JMF has worked tirelessly to promote newborn screening for SCID in the United States and to think that there might be a way to safely cure these newborn babies with a transplant that would avoid chemotherapy is astounding to us. We only regret that we were not asked to comment on their application sooner but we are willing to do anything possible to move this highly critical and very exciting proposal forward.

Please feel free to contact us if you need further information as we are fully supportive of Drs. Shizuru's and Cowan's application.

Sincerely yours,

Vicki and Fred

Vicki and Fred Modell
Co-Founders
Jeffrey Modell Foundation

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

Université de Montréal

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To the attention of:
Jonathan Thomas, M.D., Ph.D.
Chair, Governing Board of the CIRM (ICOC)
California Institute of Regenerative Medicine
210 King Street
San Francisco, CA 94107

RE: CIRM Disease Team Grant -- DR2-05365

Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas,
I am writing this letter to you in order to strongly support the application referenced above. Simply stated, I consider that this trial could revolutionize haematopoietic stem cell transplantation (HSCT) used in the treatment of non-malignant and perhaps malignant disease as well. What we are facing here, from my point of view, is a possible major breakthrough, the kind that we usually only see once every 20 years in a given field. Also, I have to admit that given the potential importance of this trial, it is an opportunity that I would have jumped at in being able to set up in my own unit and assume the role of PI for it.

With this introduction, let me present myself and briefly explain why I feel that it is so urgent for me to write to you and express what makes me so enthusiastic about this trial.

My name is Elie Haddad, I am an MD, PhD, Senior Clinician Scientist, full Professor of Pediatrics at the University of Montreal, and I work at Ste-Justine Hospital in Montreal, QC, Canada, a tertiary care center pediatric hospital. In Ste-Justine Hospital, I am the Head of the "pole of excellence in Hematology-Immunology-Oncology" and I am responsible for all research-related immunological aspects of transplantation. With regard to the clinic, in addition to being the Head of the Immunology and Rheumatology Division, I am responsible for all HSCTs performed in patients with primary immunodeficiency (PID), which in our hospital we perform about 10 per year.

I have been involved in the study of HSCT for PID and particularly for severe combined immunodeficiency (SCID) since 1993. I previously spent 7 years as a Research Clinician in the Immunology Unit of Professor Alain Fischer in Paris, which was the first to perform gene therapy in SCID patients. My particular field of expertise is in immune reconstitution and the impact that various chemotherapies have on immune reconstitution in HSCT for the treatment of SCID. I have published several papers in Blood on this subject and my manuscript on immune reconstitution after HSCT in SCID, published

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Pour l'amour des enfants

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in 1995, is one of the most cited in this field. I moved from France to Canada in 2005, and I am a member of the Primary Immunodeficiency Treatment Consortium (PIDTC) since its inception in 2008. In the last meeting of the PIDTC in 2012, I was asked to participate in a controversial debate about the role of chemotherapy used in the conditioning regimen (CR) for B-cell reconstitution after HSCT for SCID, which involved a panel of experts debating the necessity and consequences of chemotherapy in these patients. Interestingly, in my last presentation slide, I concluded that future treatment strategies for SCID patients would involve ones that avoid chemotherapy and that the use of an anti-c-kit antibody would be the best option if someone could produce a monoclonal antibody that works in humans!

Indeed, all of the debate concerning SCID for many years has revolved around the issue of whether or not one should use a CR, and with which chemotherapeutic dose intensity? The reason for this debate is that CR induces a better engraftment and immune reconstitution, but can be accompanied by important short and long term adverse events, particularly relevant for SCID patients because they are transplanted at a very young age and in many cases, there is a defect in DNA repair. Also, CR induces more GvHD and unlike in malignant disease, GvHD is absolutely unwanted in SCID, as is responsible for morbidity and impaired immune reconstitution. On the other hand, in the absence of a CR, the rate of engraftment is much lower and T and B cell immune reconstitution is often incomplete requiring most patients to receive life long immunoglobulin replacement therapy.

In this trial, it is proposed that use of a humanized monoclonal anti-c-kit antibody will deplete the haematopoietic stem cells of the recipient and, thus will permit engraftment to take place. If this trial achieves its goal and the hypothesis is validated, it would then mean that we can "make some room" in the bone marrow niches, without the need for any radiotherapy or chemotherapy. This would be a major breakthrough in the field of HSCT, and it is interesting to point out that SCID disease is unique in the sense that various centres perform HSCTs with or without a CR. Therefore, SCID represents the perfect disease to test this approach on from both a scientific and ethical point of view. In addition, this option of depleting stem cells without chemotherapy could be considered in HSCT for other non-malignant diseases in which it would not be necessary to destroy any leukemic residual disease for example. Moreover, this kind of strategy could also be very useful in gene therapy in which autologous stem cells are replaced by genetically cured autologous stem cells. In this setting, it has been established in both humans and mice that depleting autologous stem cells by chemotherapy prior to gene therapy gives the best results. However, the toxicity associated with such a depletion that requires chemotherapy is a serious hurdle to overcome with respect to gene therapy. Having the possibility of doing stem cell depletion by means of a biologic would, therefore, also be a great advantage in this setting.

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In addition to all these points that explain why this clinical trial is so important and why SCID is the ideal clinical disease to test this new approach on, it is noteworthy to point out that in my opinion Dr. Mort Cowan is the ideal person to lead this trial. Indeed, Dr. Mort Cowan is internationally recognized in the transplant community as a leader in HSCT for children, particularly in the area of immunodeficiency disease. He is the co-founder of the PIDTC that is a very active group and he is a co-PI for a multicentre study on HSCT in SCID in North America. Over a number of years he has developed and tested many non-chemotherapy-based approaches in HSCT and he is the best person in North America and possibly the world to lead this clinical trial. The overall effort will be led by Judith Anne Shizuru and her colleagues who have expertise in HSCT and in the use of an anti-c-kit antibody. Altogether, this team is the ideal one to translate this basic research to the bedside.

For all of these reasons, it is not only a distinct pleasure but also a duty, as an MD involved in HSCT for PID, to send you this letter of unqualified support for this trial. I am convinced that this trial will take an important place in the history of HSCT and I profoundly hope that your Institute will give a positive recommendation for its funding.

Sincerely,

Elie Haddad MD, PhD

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

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July 12, 2012

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Jonathan Thomas, Ph.D., J.D.
Chair, Governing Board of the CIRM (ICOC)
210 King Street
San Francisco, CA 94107

RE: CIRM Disease Team Grant - DR2-05365
Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas,
I am writing in enthusiastic support of the CIRM proposal from Drs. Cowan and Shizuri, to develop the use of a humanized anit-CD117 mAb as a novel approach to deplete HSC in children with SCID prior to allogeneic transplantation. This antibody blocks the binding of a growth factor critical for hematopoietic stem cells (HSC). Their strategy is based on pre-clinical studies by Weissman and colleagues (Czechowicz et al Science 318; 2007), which showed that a murine CD117 mAb effectively reduced HSC content in immunodeficient mice, and enabled engraftment of syngeneic donor cells without any additional conditioning.

Depletion of endogenous HSC prior to transplantation is a critical step in facilitating engraftment of donor HSC in order to achieve robust reconstitution of all lymphocytes in SCID. Identifying more selective approaches for HSC cytoreduction that spare young children the global toxicity of chemotherapy- or irradiation-based regimens will greatly advance in the field. With my background in pediatric hematology-oncology, as well as an advisor to the Pediatric Immunodeficiency Treatment Consortium, I am well aware of these issues.

My own research is focused on developing gene therapy of the neutrophil immunodeficiency, chronic granulomatous disease, using transplantation of gene-corrected autologous HSC. While anti-CD117 mAb alone is not successful in efficiently depleting HSC in immunocompetent mice, we recently showed that anti-CD117 mAb treatment greatly synergized with low dose irradiation to facilitate syngenetic donor cell engraftment to level similar to intensive irradiation (Xue et al Blood 116; 2010). Thus, targeting CD117 has promise as a transplant conditioning regimen for many other patients with non-malignant diseases undergoing HSC transplantation or HSC gene therapy.

Mary C. Dinauer, MD, PhD
Fred M. Saigh Distinguished Chair of Pediatric Research
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RE: CIRM Disease Team Grant -- DR2-05365
Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy-free transplants

Dear Dr. Thomas:

I am writing in support of the above-named proposal to use an anti-human c-kit monoclonal antibody prior to bone marrow or other types of stem cell transplantation in infants with severe combined immunodeficiency (SCID) in an effort to open niches in the autologous marrow and facilitate donor stem cell engraftment. Such infants cannot survive beyond infancy unless they receive successful hematopoietic stem cell transplants (or, in rare instances, gene therapy or enzyme replacement) because they have no T cells. When such transplants are given SCID infants, many centers in the United States and abroad use toxic chemotherapy in an effort to open the host bone marrow niches in order to achieve donor B cell reconstitution. The side effects of pre-transplant conditioning are well known, including veno-occlusive disease, damage to the lungs, brain and endocrine organs and sterility. Centers that routinely use such agents have a higher mortality rate, because most such infants present with serious infections. Moreover, pre-transplant chemotherapy does not guarantee B cell function.

Because infants with SCID--no matter what the underlying molecular cause--have no T cells, they should not be able to reject a graft. Knowing that, I have transplanted 171 infants with SCID here at Duke over the past 30 years, and none of them were given pre-transplant chemotherapy prior to their initial transplants. Seventy-six percent of them are surviving, compared with much lower mortality rates at centers

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that use pre-transplant conditioning. B cell reconstitution has been more problematic, particularly in certain molecular types of SCID, and those who do not develop B cell function require immunoglobulin replacement therapy on an ongoing basis. Many of these infants are now young adults leading productive lives, and several of them have had children of their own. One of the most important things learned from our experience here (the largest in the world) is that the survival rate in the infants we transplanted in the first 3.5 months of life is 94%. This is most likely because the infants were not infected at the time of transplant. That information was key in gaining the approval for newborn screening for SCID.

Now that newborn screening for SCID has been initiated, babies identified with this condition will be much younger than the average age at presentation in the past (i.e. 6 months of age). If pre-transplant chemotherapy is given to neonates, the toxic effects will be even more severe. Therefore, the development of a treatment that will enable B cell development that lacks the toxic side effects of chemotherapy is highly desirable. If anti-human c-kit antibody is found to be useful in that regard, it is possible that it may be able to serve as the sole conditioning agent needed in other primary immunodeficiency diseases that require stem cell transplantation.

It is very important that a trial of this type take place soon. Therefore, I enthusiastically endorse this proposal.

Sincerely,

Rebecca H. Buckley, M.D.

Rebecca H. Buckley, M.D.
J. Buren Sidbury Professor of Pediatrics
Professor of Immunology