Memorial Sloan-Kettering
Cancer Center

Richard J. O'Reilly, M.D.

Chairman, Department of Pediatrics
Chief, Bone Marrow Transplantation Service
Claire L. Tow Chair in Pediatric Oncology Research

Dear Friends of the Max Cure Foundation,

On behalf of the Department of Pediatrics and the Adoptive Immune Cell Therapy Laboratory at Memorial Sloan Kettering Cancer Center, I want to thank you all for your extraordinary support of our research and clinical investigations on immune cell therapies for the treatment of lymphomas and leukemias in children. Much has transpired over the last year, and I wanted to provide you with an update on the progress that has been made.

Our studies of T-cells from the blood of healthy donors that have been immunized against the Epstein-Bar Virus (EBV) and grown in culture flasks for use in the treatment of EBV-associated cancers have progressed rapidly. We now have a bank of over 300 EBV immune T-cell lines from which we can select T-cells that are partially HLA-matched and can recognize and kill EBV+ lymphoma cells that can be used to treat over 98% of the patients that have been referred. Among patients who develop EBV+ lymphomas following marrow or organ solid transplant who have failed conventional treatment with Rituximab (a B-cell specific antibody) +/- chemotherapy, infusions of the EBV-immune T-cells have induced complete remissions and or durable longterm (>2 - >7 years) partial remissions in 68% of the patients. Based on these findings, the FDA has given us a Breakthrough Designation and we are now opening 4 multicenter national trials. A biotechnology company has licensed the bank and will support the trials with the intent of gaining FDA approval for this "off the shelf" cell therapy.

We have also extended the used of these EBV-immune T-cells to other EBV-associated malignancies, including EBV+ Hodgkins disease and EBV+ nasopharyngeal carcinoma (NPC). Initial promising results in the treatment of NPC will soon be presented at the American Society of Clinical Oncology meeting in June.

We have also recently extended our trial of EBV-specific T-cells, genetically engineered to express a chimeric antigen receptor that binds the CD19 protein on B cell leukemias and lymphomas, so as to be able to use EBV T-cell from our bank of healthy donors. CD19 CAR^+ T-cells from transplant donors and from patients themselves, have exhibited striking ability to induce longterm remissions in patients with chemotherapy resistant B-cell leukemias in children and adults. Use of third party donor derived EBVCTLs expressing a CAR could provide a minimally toxic, immediately accessible "off the shelf" cell therapy. Our initial patient was treated with third party donor derived EBVCTLs expressing a CD19 CAR for a relapse of an EBV negative Burkett's lymphoma that occurred early after a transplant. This patient achieved a complete remission that has lasted over 2 years. Because of this experience, we

1275 York Avenue | New York, NY 10065
Phone: 212-639-5957 | Fax: 212-717-3447
oreillyr@mskcc.org | www.mskcc.org

have now received FDA clearance for a trial of third party EBVCTLs expressing a CAR, for treatment of patients with B-cell lineage ALL or Non-Hodgkins lymphoma who relapse following a transplant.

We have also completed Phase I trial of transplant donor-derived T-cells that have been immunized against the Wilms Tumor protein, WT-1, as a treatment for $WT\text{-}1^{+}$ hematologic malignancies. This trial has demonstrated that these T-cells do not have toxic effects against normal tissues, but can suppress or eradicate populations of $WT\text{-}1^{+}$ acute myelogenous leukemia cells as well as $WT\text{-}1^{+}$ myelomas. At the higher doses that can now be administered, these WT-1 specific T-cells have been able to induce durable complete remissions in a proportion of patients who have relapsed after an allogeneic marrow transplant. Phase II trials to assess response rated with these doses are now in progress. Trials with 3^{0} party donor-derived T-cells are also being planned.

In summary, our banks of virus-specific and leukemia targeted T-cells have provided our "off the shelf" resource for immune cell therapies applicable to over 90% of patients referred. The results of our clinical trials have demonstrated the capacity of these T-cells to induce complete remissions of otherwise refractory leukemias and lymphomas in a high proportion of cases. As a result, we are soon to open multicenter trials of these immune T-cells, with the ultimate intent of obtaining FDA approval of these promising therapies.

Again, I want to thank the Max Cure Foundation and all who have supported its work, for the support you have provided to our program and to this promising new form of immune cell therapy.

My best to all,

Richard J. O'Reilly
Chairman, Department of Pediatrics