October 5, 2015

John J. Reilly, MD
Richard D. Krugman Endowed Professor
Dean, School of Medicine

Dear Dean Reilly,

This is a letter of intent for an application for Transformational Research Program Funding. The proposal will be entitled “Harnessing the Site-specific Genome Editing Revolution for Discovery, Treatment and Cure.”

Background

In just the past few years, an extraordinary set of scientific advances has fundamentally changed the prospects for therapeutic genetic engineering and for precise testing of genetic hypotheses in laboratory experiments. Core technology advances include engineered zinc finger nucleases (ZFNs), which were followed rapidly by the more readily engineered and accessible TAL effector nuclease (TALENs) and CRISPR/Cas9 systems. This site-specific gene editing field is still developing rapidly. Opportunities to make major basic and clinical advances remain enormous. For example, a novel CRISPR system (Cpf1) was reported in the journal Cell just this week (Zetsche et al., PMID: 26422227) and it is likely that numerous others will be forthcoming. Surprises are to be expected.

The science behind these breakthrough technologies is deeply elegant. The engineered CRISPR and TALEN systems use exquisitely specific DNA targeting systems that bacteria have evolved to modulate eukaryotic host species transcriptomes (TALEs) or defend their own genomes from viruses (CRISPR). The science is at the same time practically powerful and translatable because it enables precise genome microsurgery, in any gene or genetic regulatory element, using just a few components that are highly experimentally tractable. Designed changes can as small as a single base pair or can encompass many kilobases. Segments of therapeutic DNA can be inserted precisely into “safe harbor” locations in the genome, or downstream of highly transcriptionally active endogenous promoters (the albumin promoter in the liver, for example). Epigenetic changes can even be introduced, and transcriptional control can be adjusted. We are in the early stages of a revolution that is markedly improving prospects for harnessing the still minimally realized promise of the complete sequencing and annotation of the human genome.
The therapeutic landscape has thus shifted dramatically. Formerly, “gene therapy” was largely a set of techniques for transiently expressing proteins or RNAs or for invading the human genome by introducing, at random loci, segments of DNA compiled according to the best available knowledge, containing cDNAs, promoter/enhancer elements and other sequences. These methods generate many, many concerns for unintended consequences such as oncogenesis and poor efficacy due to inability to capture the exquisitely complex regulation of endogenous gene loci. The emerging technologies fundamentally address these issues, while raising new ones that require focused investigation.

Focus of the Proposal in One Paragraph

The University of Colorado School of Medicine should become an organic, participative, clinically translating part of this revolution. We must be recognized as (a) committed and (b) innovative. We must aim for research that spans bench to bedside. Our goals should be to make new discoveries in this this cutting edge, emerging, transformational field, and carry out clinical trials. The medical school cannot afford to sit on the sidelines, and the time to commit and invest with substantial funding is now, not a few years from now. We will use the funding to build an integrated, multi-disciplinary cell and gene-based therapies program that incorporates these and other genetic technologies, and leverages the discoveries into major extramural funding streams. The impact will be campus-wide, and involve basic scientists, clinical investigators and practicing physicians. The impact on the medical school's reputation and reality as a tier one medical school and a destination medical center that does cutting edge work will be substantial. Lead PIs will be Eric Poeschla MD and Craig Jordan PhD but numerous individuals in but not limited to the Departments of Medicine (including notably the Division of Bioinformatics and Personalized Medicine), Immunology and Microbiology, Biochemistry and Molecular Genetics, Ophthalmology, Surgery, Obstetrics and Gynecology, Psychiatry, Cell and Developmental Biology, and Neurology will be participants and will stand to benefit in concrete ways with new projects and new funding streams that result.

Impact and Multidisciplinary Nature; Example of a Translational Project.

The proposal will propose specific, achievable, ambitious deliverables. For example, an anchor project will be to achieve a cure for HIV-1 infection. The project will be led collaboratively by members of the Infectious Diseases Division and the Hematology Division. It will target HIV dependency factors (such as CCR5, LEDGF and others) in hematopoietic stem cells delivered to minimally pre-conditioned HIV-1 patients. The effort will involve Drs. Eric Poeschla, Craig Jordan, Thomas Campbell, Clayton Smith, post-doctoral scientists, and numerous others. This project has demonstrable feasibility and is modeled after the cure of one patient (Timothy Brown, “the Berlin Patient”) by allogeneic bone marrow transplantation from a CCR5 homozygous-negative donor.

The project also has top relevance and top downstream extramural funding potential. Receiving this award will hugely boost our chances of gaining an NIH-funded Center for AIDS Research (CFAR) as cure is one of the two declared major NIH/NIAID goals for this virus that now infects 35 million people (the other being an effective vaccine).
We are well-positioned for this project. We have a large, well-managed HIV patient population (> 2,000 individuals) and top clinical research infrastructure. Our faculty possess leading experience gained over three decades in clinical trials for HIV-1 disease (there is an active, productive AIDS Clinical Trials Unit led by Dr. Campbell). We have excellent collective hematopoietic stem cell transplantation expertise and animal modeling capability. Dr. Poeschla and his coworkers are expert in existing TALEN and CRISPR/Cas9 technologies and have used them to knock out several viral dependency factors. He is a virologist and gene vectorologist with expertise and two current R01 grants in cellular factors involved in viral replication and was a founding member of the Gene and Virus Therapy Program at Mayo Clinic for 12 years. He has been Chair of the American Society of Cell and Gene Therapy’s Infectious Diseases and Vaccines Committee for the past two years. He co-mentors a recently funded K08 award in the HIV cure field at Mayo Clinic (PI is his former fellow, Dr. H. Fadel; Title: “Engineering an HIV-resistant Immune system for HIV Cure.” Term of this K08 award is 2015-2020). Thus, this translational project will capitalize on fundamental experience sets and strengths and at the same time push the Divisions and Departments involved in transformational new directions that require close collaboration between molecular biologists and clinically-focused HIV researchers.

Importantly, HIV cure is an example of a focused bench-to-bedside project, but it is only one example of a specific deliverable. In the full proposal, substantial other basic science goals, potential clinical applications, and multi-disciplinary efforts in fields other than infectious diseases will be explained. We have identified numerous AMC investigators working with or seeking to work with site-specific gene editing tools and are carrying out systematic interviews to determine needs and directions. We wish to provide core services and expertise across the campus. While we have avoided use of the word “Center” at this point because of the specific University requirements that attach to centers, we are open to pursuing that model if so advised before the December 2015 submission. The initiative will also provide mentorship, training and career development for junior faculty, fellows and students. It will build and sustain a pipeline of new investigators by recruiting junior and key senior faculty, as well as Ph.D. and M.D. fellows, and medical and graduate students who will develop basic and clinical research in genetic therapies. It will support applications for program project grants that coordinate basic and clinical research teams.

We thank you for considering our submission.

Sincerely,

Eric M. Poeschla
Professor of Medicine
Tim Gill Endowed Chair in HIV Research
Chief, Division of Infectious Diseases
University of Colorado School of Medicine