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Hemophilia A is a sex-linked disease caused by coagulation factor VIII (FVIII) deficiency. Patients with hemophilia A suffer from recurrent spontaneous bleedings into major joints and soft tissues. The current standard of care for hemophilia A is not prophylactic and patients with severe disease become crippled as a result of recurrent bleeding to the major joints.

Somatic gene therapy is expected to provide a 'final cure' for hemophilia A by providing sustained expression of therapeutic levels of FVIII (5% of normal). Adeno-associated virus (AAV) has been proven capable of providing long-term transgene expression. However, delivery of the large FVIII gene and the necessary regulatory elements to achieve therapeutic expression of FVIII is challenging when using AAV.

We recently reported repair of the mutant FVIII mRNAs and consequential hemophilia A phenotype correction in FVIII knockout mice using spliceosome-mediated RNA trans-splicing

## Spliceosome-mediated RNA trans-splicing for hemophilia A gene therapy

(SMaRT) technology. SMaRT obviates the need to deliver the entire coding sequence of FVIII gene and thereby circumvents the potential inefficiency of delivering the large FVIII gene. However, questions remain unanswered concerning the specificity of the SMaRT mediated FVIII mRNA repair, and the feasibility of achieving persistent hemophilia A phenotype correction. Novel AAV serotype vectors were recently explored with significantly enhanced gene transfer efficiency. Integration of SMaRT technology and AAV serotype vector for hemophilia A gene therapy remains to be tested.

The objective of this proposal is to develop SMaRT for hemophilia A gene therapy. The central hypothesis of this proposal is that specific and persistent FVIII gene repair can be achieved by using SMaRT technology. Our hypothesis is formulated based on the strong preliminary data generated in our laboratory. We have an extended track record of publications and expertise in hemophilia gene therapy, and are thus well-prepared to complete this project. We propose to investigate the specificity of SMaRT mediated FVIII mRNA repair and to explore sustained hemophilia A phenotype correction by SMaRT mediated FVIII mRNA repair in this proposal. Completion of this project will promote development of successful approaches for hemophilia A gene therapy.

The applicant's laboratory is on the 24th floor of the Annenberg building in the Mount Sinai Campus. Investigators of the Hemophilia and

Thrombosis Center, Divisions of Hematology/Oncology, and the Cardiovascular Research Institute share this floor. The laboratory consists of four wet bench spaces, tissue culture facilities and general laboratory equipment. A Windows-based computer in the laboratory is equipped with word-processing software, and connected to the Department of Medicine server, the Institutional server and the World Wide Web. A state-of-the-art animal facility is located in the East Building, adjacent to the Annenberg Building in the Mount Sinai campus. The animal facility supports a full time, in-house veterinarian and a complete veterinary staff. The facility ensures that all research complies with the federal and Medical School policies.

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*The central hypothesis of this proposal is that specific and persistent FVIII gene repair can be achieved using spliceosome-mediated RNA trans-splicing (SMaRT) technology*

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