Virtual Workshop on Systemic Immunogenicity Considerations for AAV-Mediated Gene Therapy

November 30–December 1, 2020

Day 1 — Monday, November 30

9:30 a.m. **Workshop Overview**

Anne Pariser, M.D. — Director, Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)

9:40 a.m. **Welcome Remarks**

Christopher Austin, M.D. — Director, NCATS, NIH

9:50 a.m. **Introductory Remarks**

Peter Marks, M.D., Ph.D. — Director, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA)

10:00 a.m. **Session 1: Immunogenicity on the Cellular Level**

How do the adaptive immune system and innate immune system (including the complement system) respond to systemically administered AAV gene therapies and contribute to immune response symptoms? Which responses are transgene related and which responses are related to the AAV capsid? How do cellular responses vary in response to CpG sequences? This session will feature in-depth background on the immunological processes underlying innate and adaptive immunity to AAV gene therapies.

Moderator: *Sonja Best, Ph.D.* — Chief, Innate Immunity and Pathogenesis Section, National Institute of Allergy and Infectious Diseases (NIAID), NIH

Panelists: *Roland Herzog, Ph.D.* — Riley Children's Foundation Professor of Immunology; Professor of Pediatrics; Professor of Microbiology and Immunology; Director, Gene and Cell Therapy Program, Indiana University School of Medicine

Percy Knolle, M.D. — Professor, Molecular Immunology, Technische Universität München; Director, Institute of Molecular Immunology and Director, Institut of Experimental Oncology, University Hospital München rechts der Isar, Technische Universität München; Director, Institute of Molecular Immunology and Experimental Immunology Faculty Weihenstephan, Technische Universität München

Olaf Stuve, M.D., Ph.D. — Professor, Department of Neurology and Neurotherapeutics, University of Texas (UT) Southwestern Medical Center; Chief, Neurology, VA North Texas Health Care System/Dallas VA Medical Center

Arthur Krieg, M.D. — Founder, Checkmate Pharmaceuticals

Louise Rodino-Klapac, Ph.D. — Senior Vice President, Gene Therapy, Sarepta Therapeutics

12:00 noon **Lunch Break**

12:30 p.m. **Session 2: Clinical Manifestations of Immunogenicity**

This session will provide an overview of immunogenic responses to systemically and locally administered AAV gene therapies. What is the spectrum of response symptoms across organ systems? How do innate and adaptive immune responses to the AAV capsid and transgene impact the short-term and long-term efficacy of gene therapies? What is the impact of patients null or mutation in transgene and CRIM status on the immune response (examples from hemophilia)?

Moderator: *J. Fraser Wright, Ph.D.* — Professor, Pediatrics, Center for Definitive and Curative Medicine, Stanford University School of Medicine

Panelists: *Carsten Bönnemann, M.D.* — National Institute of Neurological Disorders and Stroke (NINDS), NIH

Christian Mueller, Ph.D., M.Sc. — Vice President; Global Head, Genomic Medicine, Sanofi

Petra Kaufmann, M.D. — Senior Vice President, Translational Medicine and Clinical Development, Novartis Gene Therapies

Sarah Cramer, D.V.M., DACVP, Ph.D.— Senior Pathologist, StageBio

Brian Long, Ph.D. — Associate Director, Translational Sciences and Immunogenicity Assessment, BioMarin Pharmaceutical Inc.

Michael Binks, M.D. — Vice President, Clinical Research, Rare Diseases Research Unit, Pfizer

3:00 p.m. **Break**

3:10 p.m. **Session 3: Monitoring Patients Who Receive AAV-mediated Gene Therapies**

Best practices for assays in immunomonitoring pre-and post-treatment, e.g., monitoring anti-drug-antibodies (ADA) and neutralizing antibodies (nAb), correlation between binding and nAb, identifying neutralizing factors in the serum that are not ADA related, and methods to monitor cellular immune responses.

Moderator: *Roberto Calcedo, Ph.D.* — Vice President, Preclinical and Immunology, Affinia Therapeutics

Panelists: *Michael Betts, Ph.D.* — Professor, Microbiology, Perelman School of Medicine, University of Pennsylvania

Jeremy Rupon — Global Product Development, Rare Disease, Pfizer

Diana X. Bharucha-Goebel, M.D. — Clinical Research Collaborator, NINDS, NIH; Assistant Professor, Neurology, Children's National Hospital

Dimah Saade, M.D. — Clinical Research Fellow, NINDS, NIH; Child Neurologist, University of Iowa Children's Hospital

Soumi Gupta, Ph.D. — Senior Director, Head of Immunogenicity, BioMarin Pharmaceutical Inc.

4:30 p.m. **Day 1 Adjournment**

Day 2 — Tuesday, December 1

9:30 a.m. **Welcome**

9:35 a.m. **Session 4: The Impact of Varying Empty-to-Full Ratios**

This fireside chat will bring together regulatory, academic, and industry perspectives to focus on inconsistent empty-to-full ratios across the field and the resultant complications for clinical research. Discussion will probe the potential issues, their drivers, and prospects for resolution or amelioration.

Moderator: *Christian Mueller, Ph.D., M.Sc.* — Vice President, Global Head of Genomic Medicine, Sanofi

Discussants: *Zenobia Taraporewala, Ph.D.* — Acting Team Lead, Chemistry, Manufacturing and Controls (CMC), Division of Cellular and Gene Therapies (DCGT), CBER, FDA

J. Fraser Wright, Ph.D. — Professor, Pediatrics, Center for Definitive and Curative Medicine, Stanford University School of Medicine

Federico Mingozzi, Ph.D. — Chief Scientific Officer, Spark Therapeutics

10:15 a.m. **Session 5: Acquired Immunity to AAV and Clinical Trial Eligibility**

Currently, patients who develop AAV antibodies above certain thresholds are effectively excluded from receiving AAV-mediated gene therapies. Further, patients who receive AAV gene therapies may shed the virus for a period following administration. This session will review the implications of those facts for patients, patient communities, and the researchers who design gene therapy clinical trials. Topics will include preclinical best practices related to determining antibody thresholds, the likelihood of acquiring AAV immunity over the course of daily life, whether that likelihood could increase with the growing number of AAV gene therapy products, what prospective consumers of a future gene therapy can and should do to protect against acquisition of AAV antibodies, the role of patient organizations in educational efforts on this subject, and the challenges and opportunities of implementing sibling protocols.

Moderator: *Annie Kennedy* — Chief, Policy and Advocacy, Everylife Foundation

Panelists: *Cara O'Neill, M.D.* — Co-Founder and Chief Science Officer, Cure Sanfilippo Foundation

Glenn O'Neill — Co-Founder and President, Cure Sanfilippo Foundation

Pat Furlong, B.S.N. — Founding President and Chief Executive Officer, Parent Project Muscular Dystrophy

Catherine Zander, Ph.D. — Technical Program Manager, Standards Coordinating Body

Lesha D. Shah, M.D. — Co-Chair, Pediatric Gene Therapy & Medical Ethics Working Group, New York University; Assistant Professor and Medical Director of Child, Adolescent and Family Services, Icahn School of Medicine at Mount Sinai

Lei Xu, M.D., Ph.D. — Chief, General Medicine Branch 2, Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT), Office of Tissue and Advanced Therapies (OTAT), CBER, FDA

12:00 noon **Lunch Break**

12:30 p.m. **Session 6: Circumventing Immunogenic Response to AAV Vectors**

Less immunogenic AAV gene therapies would be desirable for many reasons, including simpler and safer clinical management and the ability to redose patients. This session will feature a selection of technologies and methods to prevent or reduce adaptive and/or innate immune responses to systemically administered AAV gene therapies. This session also will feature discussion of the adequacy of preclinical models to support innovation in this space.

Moderator: *Nicole Paulk, Ph.D.* — Assistant Professor, Gene Therapy, University of California San Francisco

Panelists: *Federico Mingozzi, Ph.D.* — Chief Scientific Officer, Spark Therapeutics

Kei Kishimoto, Ph.D. — Chief Scientific Officer, Selecta Biosciences

Barry Byrne, M.D., Ph.D. — Director, University of Florida Powell Gene Therapy Center; Professor, Pediatrics and Molecular Genetics and Microbiology, UF Health

2:00 p.m. **Session 7: Circumventing Immunogenic Response to Transgene Product and Transgene Tolerizing Strategies**

Non-immunogenic transgene would be desirable for many reasons, including preventing autoimmunity, simpler and safer clinical management, and the ability to redose patients. This session will feature a selection of technologies and methods to prevent or reduce adaptive and/or innate immune responses to systemically administered AAV gene therapies. This session also will feature discussion of the adequacy of preclinical models to support innovation in this space.

Moderator: *Roland Herzog, Ph.D.* — Riley Children's Foundation Professor of Immunology; Professor of Pediatrics; Professor of Microbiology and Immunology; Director, Gene and Cell Therapy Program, Indiana University School of Medicine

Panelists: *Lindsey George, M.D.* — Physician, Division of Hematology, Children's Hospital of Philadelphia (CHOP); Tenured Assistant Professor, Pediatrics, Perelman School of Medicine at the University of Pennsylvania

Guangping Gao, Ph.D. — Past President, ASGCT; Professor, Microbiology and Physiological Systems; Penelope Booth Rockwell Professor in Biomedical Research; Co-Director, Li Weibo Institute for Rare Diseases; Research Director, Horae Gene Therapy Center and Vector Core; Scientific Director, UMass Medical School (UMMS)

David Markusic, Ph.D. — Assistant Research Professor, Pediatrics, Indiana University School of Medicine

Juliette Hordeaux, D.V.M., Ph.D., DECVP — Senior Director, Translational Research, Gene Therapy Program, Perelman School of Medicine, University of Pennsylvania

3:30 p.m. **Break**

3:45 p.m. **Organizing Committee Roundtable: Workshop Themes and Opportunities**

4:30 p.m. **Adjournment**