OVERVIEW AND SYLLABUS (REVISED 12/20/22)
CAMB 633 – Advanced Seminar in Gene Therapy

Spring 2023

IN PERSON: ROOM: BRB 1301

Weekday (Jan 19 – Apr 27); Thursday 3.30 PM – 5.00 PM

COURSE GOALS:

The course will provide students with a conceptual framework for the critical appraisal of the literature and seminar presentations. There are several specific goals for this course. One is to introduce students to current approaches in the field of gene therapy and ask them to clearly and criticallyreview select articles from the literature. Emphasis is on evaluation of a specific hypothesis through experimental design and data interpretation, with emphasis on scientific rigor and reproducibility in this field. A second goal is to challenge students' understanding of the spectrum of potential applications of gene and cell therapy technologies, but also to critically consider the ethical boundaries of these novel approaches. A third goal is to discuss how, some of these novel therapies, are utilized to create partnerships with industry or launch a novel biotech company. A fourth goal is to investigate the requirements to bring a novel drug to the FDA for its approval. These goals will be achieved through paper reviews, lectures and class discussions.

COURSE DESCRIPTION:

Prerequisites: CAMB 633 does not attempt to cover all aspects of gene therapy and is therefore not intended for students seeking a lecture course that provides a comprehensive survey of the field. Suggested prior courses are: CAMB 610 (Molecular Basis of Gene Therapy); Basic immunology.

Structure of the course: Each student will be responsible to lead a group discussion of several scientific manuscripts. The number of papers will be defined by the number of students enrolled in this class.

This class will give priority to GTV students, followed by CB, and MVP students, but also accept other students with the required prerequisites. Enrollment is capped at 12 students, but can be increased based on student interest.

Class: Each class will involve a review of a manuscript in the field of gene therapy selected by course faculty (Drs. Kurre, Pardi, Rivella, Ahrens-Niklas). At the beginning of the course students and faculty will assign primary research papers and potentially review articles that provide relevant background to the students. The assigned student will prepare slides covering background and paper figures and is encouraged to meet with the faculty moderator for a given class date ahead of time. Two faculty are typically present for each class. Students volunteer to each cover a portion of the result section and corresponding article figure (-s) in order to promote discussion, interaction and participation. The student leader will introduce the paper and coordinate those figure assignments. Emphasis will be placed on technical rigor and reproducibility as well as the broader scientific context. Each session will last 60-90 minutes,

including presentation of the manuscripts and Q&A. Each session will cover one manuscript on a weekly base. Each presentation will be utilized to grade the students (50%).

Lectures: 3-4 lectures will be spread throughout the semester. During each lecture, a faculty or external speakers will lecture for ~45-60 minutes followed by ~30 minute discussion. Student s are expected to ask questions during or at the end of the lecture. Course faculty will moderate lecture and discussion.

COURSE GRADE:

Grades will be based on participation in class preparation and discussion. The course grade will be based on: 50% on paper presentation and 50% on discussion participation. Participation will be evaluated by attendance, engagement in prompted and/or unprompted discussions. The faculty will guide and coordinate the conversation during the presentation. The presentation will last ~45 minutes. During the remainder of the time (15-45 minutes), the students will be encouraged to discuss if and how this paper impacts the field of gene therapy, including potential future outcomes. The presentations will be graded, and the participating faculty and/or course director should provide feedback at the end of class.

COURSE DIRECTOR: Peter Kurre
CO-DIRECTORS: Stefano Rivella, Norbert Pardi, Rebecca Ahrens-Nicklas

SELECTION OF ARTICLES BY FACULTY

Peter Kurre (Perelman SOM, Department of Pediatrics, Division of Hematology)

Dr. Kurre will focus on aspects of Gene Therapy that relate to the unique biology of the Hematopoietic Stem Cells (HSC) commonly targeted for genetic correction in monogenic diseases. The papers explore the importance of disease specific phenotypes that are central to the overall translational strategy and successful clinical outcomes. Foundational aspects of HSC biology, access, targeting, conditioning, *in vivo* selection and stem cell clonality will be covered.

- *Lifelong multilineage contribution by embryonic-born blood progenitors*. Patel et al., Nature 2022; **PMID 35705805**
- *Successful engraftment of gene-corrected hematopoietic stem cells in non-conditioned patients with Fanconi anemia*. Rio et al., Nat Medicine 2019; **PMID 31501599**
- *Modest Declines in Proteome Quality Impair Hematopoietic Stem Cell Self-Renewal*; Hidalgo San Jose et al., Cell Rep 2020; **PMID 31914399**
- *Enhanced liver gene transfer and evasion of preexisting humoral immunity with exosome-enveloped AAV vectors*; Meliani et al., Blood Adv. 2017. **PMID 29296848**

Norbert Pardi (Perelman SOM, Department of Medicine, Division of Infectious Diseases)

Dr. Pardi will focus on the use of antibodies and RNA molecules for immunological but also gene editing therapies.

- *Protective efficacy of in vitro synthesized, specific mRNA vaccines against influenza A virus infection;* Petsch et al., Nat Biotechnol. 2012; **PMID: 23159882**
- *IL-1 and IL-1ra are key regulators of the inflammatory response to RNA vaccines*; Tahtinen et al., Nat Immunol 2022; **PMID: 35332327**

- *mRNA Delivery for Therapeutic Anti-HER2 Antibody Expression In Vivo;* Rybakova et al., Mol. Ther. 2019; **PMID: 31160223**
- *Biocompatible, Purified VEGF-A mRNA Improves Cardiac Function after Intracardiac Injection 1 Week Post-myocardial Infarction in Swine.* Carlsson et al., Mol Ther Methods Clin Dev; **PMID: 30038937**
- *CAR T cells produced in vivo to treat cardiac injury.* Rurik et al. Science 2022; **PMID: 34990237**

Stefano Rivella (Perelman SOM, Department of Pediatrics, Division of Hematology)

Dr. Rivella will focus on stem cell directed gene therapy for hemoglobinopathies

- *Lentiviral globin gene therapy with reduced-intensity conditioning in adults with β-thalassemia: a phase 1 trial;* Boulad et al., Nat. Med. 2022; **PMID: 34980909**
- *Betibeglogene Autotemcel Gene Therapy for Non-β0/β0 Genotype β-Thalassemia;* Locatelli et al. NEJM 2021; **PMID: 34891223**
- *CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia*; Frangoul et al. NEJM 2021; **PMID: 33283989**
- *Intracerebral lentiviral ABCD1 gene therapy in an early disease onset ALD mouse model; Gong et al.* Gene Ther., 2022; **PMID: 35790794**
- *Approaches for Systemic Delivery of Dystrophin Antisense Peptide Nucleic Acid in the mdx Mouse Model; Brolin et al., Nucleic Acid Ther;* **PMID: 32678992**

Rebecca Ahrens-Nicklas (Perelman SOM, Department of Pediatrics, Division of Human Genetics and Metabolism)

Dr. Ahrens-Nicklas review seminal mouse and human papers detailing major approaches to gene therapy for genetic / metabolic disorders.

- *Gene therapy augments the efficacy of hematopoietic cell transplantation and fully corrects mucopolysaccharidosis type I phenotype in the mouse model;* Visigali et al., Blood 2010; **PMID 20847202**
- *Hematopoietic Stem- and Progenitor-Cell Gene Therapy for Hurler Syndrome;* Gentner et al., NEJM 2021; **PMID 34788506**
- *Early heart failure in the SMNDelta7 model of spinal muscular atrophy and correction by postnatal scAAV9-SMN delivery;* Bevan et al., Hum MolGenet 2010; **PMID 20639395**
- *Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy;* Mendell et al., NEJM 2017; **PMID 29091557**

LECTURES (Provisional, Dec 2022)

Approaching industry
Speaker: Dana Hammill

The purpose of conducting research is to seek truth and expand knowledge for the benefit of social development. Oftentimes, new technologies can be patented and licensed to an outside party for commercialization purposes, which allows the public access to the new technology on the market. This lecture explores the options available to researchers at an academic institution

to disclose inventions, patent and license with the intention of forming start-up or a strategic alliance with a start-up, biotech, or pharma company. Types of strategic alliances will be explored with examples of each. The lecture will close with deep dive into the largest, most successful academic-pharma alliance between UPenn and Novartis for the commercialization of Kymriah™, the first FDA-approved gene therapy in the United States.

Industry perspective-1 Spark
Speakers: Katherine High, Chief Scientific Officer of Spark
Dr. High will discuss how do you create an integrated gene therapy company, from discoveries in an academic environment to production of gene therapy drugs.

GT and Ethical Issues
Speaker: Kiran Musunuru
Recently, the birth of twin girls whose genomes were altered before birth using CRISPR gene-editing techniques was announced. The feat wasn't necessarily a technical breakthrough, but raised ethics and scientific concerns about the application of this technology. Dr. Musunuru will discuss the potential applications of this technology, but also the potential abuses in absences of clear guidelines.

Going to the FDA: From Bench to Bedside: Regulatory Pathway to IND Submission for Cell and Gene Therapy products.
Speaker: Nancy Robinson Garvin
The lecture will discuss the FDA governing body for cell and gene therapy products (CBER), the various types of FDA meetings available to researchers (INTERACT, Type A, Type B (Pre-IND), or Type C) and how to request each meeting type, data needed to support the request, and timeline from submission to approval/clinical trial. The lecture will also review the various types of FDA applications (IND, NDA, ANDA, OTC, BLA, DMF, EUA) focusing primarily on the IND submission. Providing a framework for the preclinical, pharm/tox studies, and CMC data needed to support an IND submission as well as distinguish the various types of IND (standard, Emergency Use, and Treatment IND) and when each is applicable as well as the difference requirements for commercial vs research IND. The lecture will conclude with a discussion of the new four distinct FDA approaches (Priority Review, Breakthrough Therapy, Accelerated Approval, & Fast Track) for new breakthrough/first in human therapies and how this can apply to novel cell and gene therapy drug products and the timelines for each, etc.