SYLLABUS **Spring 2024**

CAMB 633 – *Advanced Seminar in Cell and Gene Therapy*

Perelman SCHOOL OF MEDICINE
University of Pennsylvania

Time	Thursdays 3.30 PM – 5.00 PM
Dates	2024, Jan 18 – Apr 25
Location	BRB 1301

Course Director

Peter Kurre, MD | Department of Pediatrics, Division of Hematology)
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Co-Directors

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Course Coordinator
Anna Kline | CAMB/GTV
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COURSE GOALS:

The course provides students with a conceptual framework for the critical appraisal of current cell and gene therapy landscape through review of the literature and seminar presentations. The course will critically review select articles from the scientific literature, exploring key aspects of experimental design and data interpretation, scientific rigor and reproducibility. There are several specific goals for this course. One is to introduce students to current approaches in the field of gene therapy, with emphasis on key techniques for delivery as well as laboratory and translational endpoint metrics. A second goal is to review the relevant disease physiology and translational challenges in matching treatment approach and disease context. Throughout, students will learn to consider both technical limitations and ethical boundaries of these novel approaches. A final goal is to convene with experts to better understand the role of intellectual property protection, industry partnerships and the requirements to bring a novel drug to the FDA for approval. These goals will be achieved through paper reviews, lectures and class discussions.

COURSE DESCRIPTION:

Prerequisites: CAMB 633 is open to students at all levels, but students will benefit from foundational knowledge in the molecular basis of gene therapy and basic immunology.

Structure of the course: The course comprises a mix of student-led Journal Club classes and Expert Seminar lectures.

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Class: Students will be responsible for leading a group discussion of assigned scientific manuscripts in the field of cell and gene therapy selected by course faculty. At the beginning of the course, students and faculty will assign primary research papers with the number of assignments varying (between 2 and 4) depending on the number of enrolled students. The assigned student to lead a given class will prepare slides covering background and paper figures. They will also assign other students to cover a portion of the article result section with corresponding article figure (-s) in order to promote interaction and participation. Emphasis in review will be placed on technical rigor and reproducibility, as well as the broader scientific context and disease pathophysiology. Each class will last 60-90 minutes, including presentation and discussion of the manuscripts with Q&A. Each class will cover one manuscript, with all paper presentations led by a student contributing in aggregate to the student grade (50%).

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

Evaluation:

Students are expected to actively participate in all aspects of the course and come prepared for class. Together, the lead student and faculty will guide and moderate the discussion of papers, their impacts on the field of gene therapy, including potential future outcomes. Class grades will be based on: 50% on paper presentations and 50% on discussion participation (in class and seminars). Absences should be cleared with course directors ahead of time. More than two absences will impact the attendance grade portion.

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, August 2023)

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- Spark Therapeutics
Speakers: Jeff Marrazzo
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.

Gene Therapy 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.