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 25 – Apr 25
Location	BRB 1301

Course Director

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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 select from faculty selected primary research papers, with each student co-leading between 2 and 4 Journal Clubs, depending on the number of enrolled students. Student co-leads will collaboratively prepare slides covering background and paper figures. They will each cover a portion of the article result section with corresponding figure (-s). 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 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 given student contributing in aggregate to the student grade (50%).

Lectures: 3-4 lectures are 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.

- *In vivo macrophage engineering reshapes the tumor microenvironment leading to eradication of liver metastases. Kerzel et al., Cancer Cell 2023;* **PMID: 37863068**
- *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.

- *IL-1 and IL-1ra are key regulators of the inflammatory response to RNA vaccines;* **PMID: 35332327**
- *Modified mRNA Vaccines Protect against Zika Virus Infection;* **PMID: 28222903**
- *mRNA A phase 1 trial of lipid-encapsulated mRNA encoding a monoclonal antibody with neutralizing activity against Chikungunya virus;* **PMID: 34887572**
- *Biocompatible, Purified VEGF-A mRNA Improves Cardiac Function after Intracardiac Injection 1 Week Post-myocardial Infarction in Swine*; **PMID: 30038937**
- *CAR T cells produced in vivo to treat cardiac injury*; **PMID: 34990237**

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

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

- CRISPR-Cas9 Editing of the *HBG1* and *HBG2* Promoters to Treat Sickle Cell Disease*;* **PMID: 37646679**
- Engineered arylsulfatase A with increased activity, stability and brain delivery for therapy of metachromatic leukodystrophy; **PMID: 37644722**
- *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**
- Fertility-preserving myeloablative conditioning using single-dose CD117 antibody-drug conjugate in a rhesus gene therapy model*;* **PMID: 37828021**

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)

Industry perspective- Spark Therapeutics
Speakers: Katherine High
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.