COURSE OUTLINE.

CALCIUM-DEPENDENT ARRHYTHMIAS AND THE ROLE OF RYANODINE RECEPTORS IN CARDIAC PHYSIOLOGY AND DISEASE.

Designed by:
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Target audience:
Our target student body consists of Masters and Doctoral students enrolled in several of the courses offered by the Université Paris Sud and other affiliate Universities. Given the breadth of our teaching programs throughout the Université Paris-Sud and other universities in the Paris area, we anticipate that a minimum of 30 students and as many as 50 students will enroll in the course. For the practical, hands-on aspects of the course, enrolment will be limited to 2 groups of ~10 students each, to access comfortably the equipment and research facilities available to this program.

Number of lectures:
30 interacting lectures on basic and specialized aspects of cardiovascular physiology and pathophysiology, followed by 30 to 40 hours of direct, hands-on practical lectures.

Duration:
Lectures will be concentrated in ~6 weeks, and practical sessions will be arranged at the beginning of the course according to the particular need of the students and participating faculty.

Dates:

I) Goals:
We will strive to reach an in-depth understanding of:

1) Normal function of the heart at the organ, cellular, and molecular level, and its coordinated physiological responses during basal and stress conditions.

2) Major cardiac pathologies, especially congenital cardiac arrhythmias and “channelopathies”, which are cardiac rhythm disturbances resulting by malfunction of ionic channels.
3) The structure-function relationship of **Ryanodine Receptors**, which are the calcium release channels of sarcoplasmic reticulum that provide the majority of Ca^{2+} ions that are needed for contraction of the heart, and whose dysfunction represents the most salient example of **calcium-dependent arrhythmias**.

II) Lectures:

Lectures are open to students, faculty, staff, and all interested parties. They will be 50 minutes long, with at least 10 minutes for discussion and questions. Expect in-class quizzes and “flash questions” on the current or past material. All questions and comments are welcome!

III) Paper Discussions:

There will be approximately 10 paper discussions on topics directly relevant to the lecture subject. Paper discussions will consist of reading assigned original research paper(s), and then writing a short (~1-page) summary of the paper (due in class on discussion day), and being prepared to discuss the paper in class.

The written summary should include the purpose/hypothesis of the paper, the key methods used, what information each figure/table conveys, and conclusions of the paper. A clear, concise written summary will be a useful tool during the class discussion.

In class, students will have time to discuss individual experiments or figures within a small group, and then may be called upon to share conclusions or explain a figure. For some papers, there may be questions about a particular figure/experiment for group discussion. To grab the essence of the article, students should come to class prepared to discuss any figure or the major conclusion. An advanced analysis would include the ability to discuss: limitations of the methods used, limitations of the conclusions made based on the evidence provided, ideas for future experiments or ways to improve the study.

Questions regarding the papers may appear on tests, so attendance and participation in important.

IV) Practical, hands-on sessions:

We will form 2 groups of ~10 students each, and invite one group at a time to join faculty to conduct experiments of direct relevance to the topic of the course. Sessions will last at least 2 hours and as many as ~5 hours, depending on the experiment, therefore, students should block the whole afternoon for these sessions. Group 1 and group 2 will participate in even and odd days of the month, respectively.

Students will not handle live animals, only tissues, cells and homogenates. They are required to wear appropriate attire, lab coat, and mandatory safety equipment (gloves,
goggles, etc). A written summary of activities describing salient learning points and overall impression of the techniques used will be required at the end of the sessions.

Practical sessions will be as described in the Host Invitation Letter, consisting of a) methods for isolation of sarcoplasmic reticulum and purification of RyRs, b) measurement of arrhythmogenic calcium waves in cells acutely isolated from mice harboring mutations in the RyRs (and models of CPVT).

V) Course Content:
A. The Cardiovascular System (3 lectures)
   1. The heart
   2. Heart volumes
   3. Vascular System
   4. Basic cardiovascular responses to physical activity/emotional stress

B. The Heart
   1. Myocytes (3 lectures)
      a) cell structure
      b) ionic basis of action potentials
      c) overview of excitation-contraction coupling
      c) metabolic activity
   2. Electrical activity of the heart (4 lectures)
      a) Intrinsic and extrinsic control of the cardiac cycle rate
      b) ionic basis of pacemaker activity
      c) normal and abnormal electrical flow
      d) introduction to axis
   3. Electrocardiography (2 lectures)
      a) Determination of rate and rhythm
      b) ST segment changes
      c) Measures of ventricular hypertrophy
      d) Main electrical disturbances: premature ventricular contractions, bi-directional ventricular tachycardia, A-V block, and bigeminy.

C. Excitation-contraction coupling and Calcium Signaling
   1. Cardiac E-C coupling (3 lectures)
      a) The Dihydropyridine Receptors – voltage sensors and Ca^{2+} entry
      b) Ryanodine Receptors – amplifiers of Ca^{2+} signals
      c) Accessory proteins of DHPR and RyRs – calsequestrin & junctin
d) E-C coupling gone awry: Timothy syndrome and CPVT

2. Skeletal E-C coupling (2 lecture)
   a) main similarities and differences
   b) malfunctions of skeletal e-c coupling: malignant hyperthermia and central core disease

D. Congenital arrhythmias and Channelopathies (4 lectures)
   1. Sodium channel malfunction: Long-QT syndrome, Brugada syndrome
   3. Ryanodine Receptor Channelopathies: Catecholaminergic Polymorphic Ventricular Tachycardia and Arrhythmogenic Right Ventricular Cardiomyopathy
   4. Molecular basis of heart failure – emphasis on deranged Ca$^{2+}$ Homeostasis

E. The Ryanodine Receptor in Health and Disease (9 lectures)
   1. Theoretical basis of techniques used to isolate skeletal and cardiac sarcoplasmic reticulum
   2. Physiological role of RyR in cardiac and skeletal muscle E-C coupling
   3. Techniques to study RyRs at the whole heart, cellular and molecular levels
   4. Regulation of RyRs by cytosolic and luminal Ca$^+$
   5. Accessory proteins of RyRs
   6. Modulation of RyRs by post-translational processes – phosphorylation
   7. Modulation of RyRs by post-translational processes – oxidation and nitrosylation
   8. Pathophysiological role of RyRs in arrhythmogenic syndromes
   9. Calcins as ligands of RyRs and anti-arrhythmic effect