

Course Syllabus
Department of Biochemistry and Molecular Biology
Advanced Cardiovascular Biochemistry
BIOC 5309- Fall Term 2016

Instructor(s): Dr. Thomas Pulinilkunnil & Dr. Petra Kienesberger

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Dalhousie Medicine New Brunswick- Room 136

Lectures: Tuesday and Thursdays (11.30 am -1.00 pm) will be video-conferenced to Halifax
Location at either sites: Halifax: Tupper Complex C223; Saint John: DMNB Room 266

Laboratories: 0

Tutorials: 0

Course Description

Advanced Cardiovascular Biochemistry is a specialized area for students pursuing graduate and postgraduate program in cardiovascular sciences. The course material for BIOCXXX is presented in two 90 min lectures per week and is a 3 credit course. There will be 25 lecture sessions.

Course Prerequisites

The students must have gained fundamental knowledge of biochemistry, cell and molecular biology in the prerequisite classes. A basic knowledge on cardiovascular physiology will be desirable.

Course Objectives/Learning Outcomes

1. **Understand** cardiac anatomy with specifically structure of the heart, blood vessel and cardiomyocyte
2. **Describe** cardiac cycle and Frank Starling Law
3. **Describe** cardiac electrocardiogram and explain biochemical basis of cardiac action potential.
4. **Understand** the established principles of cardiogenesis and cell cycling pathways.
5. **Describe** molecular elements of cardiac contractile apparatus with emphasis on sarcoplasmic reticulum mediated calcium sensing and signaling.
6. **Explain** the vasoactive signaling of endothelial cells and EC cross talk with cardiomyocyte.
7. **Discuss** the necessity of protein folding turnover within the cardiac tissue by appreciating pathways of protein modification, synthesis, and degradation.
8. **Recalling** mechanisms of cytoskeletal signaling in the heart.
9. **Illustrate** biochemistry of substrate utilization in the heart. **Understand** the established principles of glucose, fatty acid and amino acid metabolism. **Decipher** the biological importance of mitochondrial metabolism and function.
10. **Apply** the knowledge of cardiac metabolism to understand the biochemistry of metabolic disorders in obesity and diabetes.
11. **Describe** the molecular basis for coronary artery disease and atherosclerosis.
12. **Depict** the mechanisms of myocardial inflammation and cell death.
13. **Distinguish** between physiological and pathological forms of hypertrophy.
14. **Comprehend** the mechanisms of various types of receptor signaling that govern heart failure.
15. **Assimilate** and **integrate** the knowledge on the pathogenesis of congenital heart disease.
16. **Apply** the knowledge garnered from methods and models of cardiovascular system to disease outcomes. **Understand** cardiovascular application of gene therapy.
17. **Organize** an effective literature search and **apply** it to **formulate** a mini review and **conceive** an idea for a potential grant application.

Course Materials

Those with limited knowledge of cellular biochemistry are urged to review appropriate sections of an introductory biochemistry textbook such as *Biochemistry* (5th Edition). Harper, 2004 or *Principles of Biochemistry* (5th Edition) Lehninger, 2005. This course will be beyond the scope of these texts. The textbooks recommended for this course are

- Molecular Mechanisms of Cardiac Hypertrophy and Failure- Edited by Richard Walsh
- Cardiac Energy Metabolism in Health and Disease- Edited by Lopaschuk & Dhalla
- Heart Physiology and Pathology by Eugene Braunwald
- Heart Failure-Bench to Bedside Jose Marin Garcia

Course Assessment

Review article writing and developing grant proposal directly test the ability of the student to apply the knowledge gained from cardiovascular biochemistry to the field and also further their career prospects in this discipline. Therefore students will be expected to write 1 mini review (2 pages, Font 12, single spaced, one separate page of figure/table allowed) and a three page grant (3 pages, Font 12, single spaced, two separate page of figure/table allowed) for a given topic during the term. Review article submission is on November 08 2016. Instructors will provide the topics for review and grant to each student. Review should attempt to summarize major findings in the last three years, and discuss outstanding questions in the field. Three page grant in either CIHR or HSFC format must be written on a research area that is at arm's length from student's graduate thesis work. Students will need to make a 10 min presentation (not more than 5 slides) on their proposed grant and defend the proposal similar to that expected of a qualifying exam.

To directly test the students' knowledge on the delivered course content, students will be given two written assignments (first assignment due on October 10 2016 and second due on Nov 25 2016). Specifically, in these assignments a research question based on unpublished or published manuscript data will be provided and student will be asked a series of questions around this experimental finding directly testing their ability to interpret concepts and data. It is expected that students complete these assignments in a timely manner. For any non-communicated deferral, 10% marks will be for every week after the deadline. University regulations on plagiarism will be strictly adhered to in this course. Details on guidelines and policies around plagiarism are available on the following URL: (<http://www.registrar.dal.ca/calendar/ug/UREG.htm#12>).

Class assessment and Grades

The final grade for this course will be determined based on the following:

Review Article	25%
Grant Proposal –Write Up	30%
Grant Proposal –Presentation	20%
Written Assignment	25%

Students with permanent or temporary disabilities who would like to discuss classroom or exam accommodations should contact course instructors. Conversion of numerical grades to Final Letter Grades follows the Dalhousie Common Grade Scale. **NOTE: An exemption is required if you are not planning to hold a final exam scheduled by the Registrar's Office for the final exam period. Submit your syllabus along with your request (**and reason for the request**) to the Assistant Dean (scieasst@dal.ca) at least 2 weeks prior to the start of classes.**

Course Content

<u>Date</u>		<u>LECTURE TOPIC</u>	<u>INSTRUCTOR</u>
Sep 06 2016	1.	Introduction: Basics of Cardiac Anatomy and Blood Flow	Pulinilkunnil T
Sep 08 2016	2.	Cardiovascular Growth: Cardiogenesis and Cell Cycle	Pulinilkunnil T
Sep 13 2016	3.	Cardiac Action Potential and Conduction	Pulinilkunnil T
Sep 15 2016	4.	Molecular Structure of Cardiomyocytes	Kienesberger P
Sep 20 2016	5.	Contractile Apparatus and Sarcolemmal Transport System	Kienesberger P
Sep 22 2016	6.	Pathways of Cardiac Calcium Sensing and Signaling	Kienesberger P
Sep 27 2016	7.	Endothelial-Vascular Smooth Muscle Signaling in the Heart	Pulinilkunnil T
Sep 29 2016	8.	Biological role of Vasoactive Signaling in the Heart	Kienesberger P
Oct 04 2016	9.	Cytoskeletal Signaling: Protein folding, trafficking and secretion	Pulinilkunnil T
Oct 06 2016	10.	Pathways and Players of Protein Synthesis and Degradation	Pulinilkunnil T
Oct 11 2016	11	Introduction to Cardiac Energy Metabolism	Pulinilkunnil T
Oct 13 2016	12.	Cardiac Glucose utilization: Role of Insulin and Contractility	Pulinilkunnil T
Oct 18 2016	13.	Cardiac Lipid Metabolism	Kienesberger P
Oct 20 2016	14.	Cardiac Lipoprotein Metabolism and Cholesterol Regulation	Kienesberger P
Oct 25 2016	15.	Cardiac Amino Acid Utilization: Branch Chain Amino Acid	Pulinilkunnil T
Oct 27 2016	16.	Mitochondrial Metabolism of Substrates: Randle's Hypothesis	Pulinilkunnil T
Nov 01 2016	17.	Metabolic Heart Disease-Part 1	Pulinilkunnil T
Nov 03 2016	18.	Metabolic Heart Disease-Part 2	Kienesberger P
Nov 08 2016		Study Break	
Nov 10 2016		Study Break- Review Article Submission Deadline	
Nov 15 2016	19	Coronary Artery Disease and Vascular Disease	Kienesberger P
Nov 17 2016	20.	Mechanisms of Myocardial Inflammation and Cell Death	Kienesberger P
Nov 22 2016	21.	Signal Transduction of Physiological and Pathological Hypertrophy	Pulinilkunnil T
Nov 24 2016	22.	Receptor Signaling Pathways in Heart Failure	Kienesberger P
Nov 29 2016	23.	Congenital Heart Disease	Pulinilkunnil T
Dec 01 2016	24.	Genetics of Cardiovascular Disease: Use of Gene Therapy	Kienesberger P
Dec 06 2016	25.	Grant Proposal Presentation and Submission	
Dec 13 2016		Final Grades will be posted	

Details of Lecture Topics**Lecture 1. Introduction: Basics of Cardiac Anatomy and Blood Flow**

Structure and organization of cardiac muscle and blood vessels
Myocardium ultrastructure
Cardiac Cycle
Frank Starling Law

Lecture 2. Cardiovascular Growth: cardiogenesis and cell cycle

Embryonic Cardiac Development
Heart Tube and Looping Effect
Atria/Ventricular Formation
Myocardial Compaction and Vasculoseptal Development
Development of Conduction System
Morphogenesis of Cardiovascular System
The mammalian cell cycle
Monitoring cardiomyocyte cell cycle activity in the heart
Cardiomyocyte cell cycle activity during normal development

Lecture 3. Cardiac Action Potential and Conduction

Ionic Basis for Cardiac Action Potential
SA Node Potential and Ventricular Action Potential
Cardiac Ion Channels and Currents
Biology of Sodium, Calcium and Potassium Channel
Biochemistry of Sodium Proton and Sodium Calcium Exchangers

Lecture 4. Molecular Structure of Cardiomyocytes

Sarcolemma, intercalated disks, transverse (T)-tubules, myofibrils, myofilaments, sarcomeres, sarcoplasmic reticulum, and terminal cisternae
Composition of thick and thin myofilaments in cardiac myocytes
Significance of a functional syncytium within the heart

Lecture 5. Cardiac Contractile Apparatus and Sarcolemmal Transport System

Steps of excitation–contraction coupling,
Role of T tubules, Ltype calcium channels, trigger calcium, terminal cisternae, ryanodine receptors (calcium release channels), troponin-C (TN-C), troponin-I (TN-I), troponin-T (TN-T), actin, myosin heads, adenosine triphosphate (ATP) hydrolysis,

Lecture 6. Pathways of Cardiac Calcium Sensing and Signaling

Function of sarco-endoplasmic reticulum calcium adenosine triphosphatase (SERCA) pump
Ryanodine Receptor and Phospholamban Biology
Mechanisms involved in the regulation of cardiac inotropy and lusitropy.
Calcium-induced calcium release

Lecture 7. Endothelial-Vascular Smooth Muscle Signaling in the Heart

location and primary function of vascular SMCs in blood vessels Ca²⁺-handling in SMCs
Organization of actin and myosin in vascular smooth muscle mechanisms that induce contraction/relaxation in SMCs

Mechanism of vascular smooth muscle contraction and include descriptions of the roles of calcium, calmodulin, and myosin light chain kinase. Discuss the effects of inositol triphosphate (IP3) and cyclic adenosine monophosphate (cAMP) signal transduction pathways on the contraction of cardiac muscle and vascular smooth muscle.

Lecture 8. *Biological role of Vasoactive Signaling in the Heart- Part 1*

Adrenergic Signaling Pathway
Cholinergic Signaling Pathway
Renin Angiotensin signaling pathway
GPCR Signaling
Small G Proteins
Phospholipases C and D Signal transduction
Protein Kinases

Lecture 9. *Cardiac Cytoskeletal Signaling: Protein Trafficking and Secretion*

Sarcomeric Cytoskeleton; Thin Filaments, Thick Filaments, Titin, Myomesins, Nebulette Z Disc
Extra Sarcomeric Cytoskeleton; Desmin Filaments, Actin Filaments, Microtubules
Dystrophin Glycoprotein Complex, Focal Adhesion Complex, Spectrin Complex
Nuclear Cytoskeleton
ER-Golgi Complex protein trafficking:

Lecture 10. *Pathways of Cardiac Protein Folding and Degradation*

ER Function
Protein Quality Control
Post Translational Modification
Proteasomal Protein Degradation
Lysosomal Autophagy

Lecture 11. *Introduction to Cardiac Energy Metabolism*

Whole body metabolism
Cardiomyocyte Metabolism
Substrate Classification

Lecture 12. *Cardiac Glucose Metabolism*

Whole body metabolism
Glucose Uptake: Regulation of Cardiac GLUTs
Insulin Signaling Pathway
Hexokinase Regulation
Glycolysis Pathway
Pyruvate Metabolism: Role of PDH and LDH

Lecture 13. *Cardiac Lipid Metabolism*

Lipid metabolism
LPL Regulation
Fatty acid transporters
FA Acylation

Beta and Omega Oxidation of FA
FA Storage
Triglyceride biosynthesis and mobilization in cardiac tissue
Kennedy Pathway
Extracellular and Intracellular TAG hydrolases

Lecture 14. *Cardiac Lipoprotein Metabolism*

Lipoprotein Uptake and Export: Role of MTP protein
Cholesterol Sensing, Uptake and Export: Role of ABCA proteins
Extracellular and Intracellular Lipases

Lecture 15. *Cardiac Amino Acid Utilization: Role of Branch Chain Amino Acid*

Whole body amino acid metabolism
Leucine, Valine and Isoleucine Metabolism
BCAT, BCKDH and BCKDK Regulation

Lecture 16. *Mitochondrial Metabolism of Substrates*

TCA Cycle
Anaplerosis and Malate-Aspartate Shuttle
Randle's Hypothesis; AMPK-ACC-Malonyl CoA Axis
Electron Transport Chain
Mitochondrial DNA
Transcriptional regulators of Mitochondrial Metabolism

Lecture 17. *Metabolic Heart Disease-Part 1*

Lipotoxic Cardiomyopathy
Obesity and Diabetic Heart Disease

Lecture 18. *Metabolic Heart Disease-Part 2*

Signaling Pathways in Hypertrophic Cardiomyopathy
Ischemic Heart Disease: Abnormal mitochondrial and ER signaling
Reperfusion Injury: RISK pathway, Anti-oxidant Signaling
Mitochondrial Cardiomyopathy

Lecture 19. *Coronary Artery Disease and Vascular Disease*

Mechanisms regulation Coronary blood flow (Nitric Oxide, EDHF, Prostacyclin)
Angiogenesis Pathways
Atherosclerosis
Vascular Remodeling: Signaling proteins

Lecture 20. *Mechanisms of Myocardial Inflammation and Cell Death*

Pro-inflammatory Mediators for Cell Death
Inflammasome Complex
Cyclooxygenase and lipoxygenase Pathway: Role of Arachidonic Acid
TLR4 Pathway
Difference between Apoptosis and Necrosis
Extrinsic and Intrinsic Pathway in Apoptotic Cell Death
PARP Signaling
Caspase Signaling

Lecture 21. *Signal Transduction of Physiological and Pathological Hypertrophy*

Overview of signaling pathways implicated for the development of cardiac hypertrophy

Mechano-transduction Mechanisms in Hypertrophy: Role of cytoskeletal proteins and stretch receptors

Extracellular Matrix Remodeling

G Proteins, PLC/PKC Pathway, MAPK Pathway, Calcium Signaling, JAK STAT, PI3K

Transcription Factor Regulating hypertrophic cell growth: Calcineurin, NFAT, CaMKK

Translation Pathways and Protein Synthesis: mTOR Signaling

Lecture 22. *Receptor Signaling Pathways in Heart Failure*

GPCR Signaling in heart failure: Adrenergic system, Angiotensin, Endothelin, GPCR

Kinases, Receptor Tyrosine Kinase Biology

Cytokines in Heart Failure

Transgenic mouse models of heart failure

Mitochondrial Oxidative Stress in Heart Failure

Mechanisms of Congestive Heart Failure

Lecture 23. *Congenital Heart Disease*

Atrial and Ventricular Defects during Heart Development: Role of transcription factors HAND & MEF2

Valvular Defects: Dows Syndrome- Role of SMAD proteins and TGF-beta signaling pathway

Cardiac Looping Phenomena

Cardiomyocyte Specification and Dedifferentiation: Role of PITX2 & NKX2.5

Ventricular septal defect (VSD), Atrial septal defect (ASD), Aortic stenosis (AS),

Pulmonic stenosis (PS), Coarctation of the aorta (COA), Tetralogy of Fallot (TOF),

Transposition of the great arteries (TGA)

Lecture 24. *Genetics of Cardiovascular Disease: Use of Gene Therapy*

Computerized databases of genes, cDNA, and proteins, bioinformatics—predicting genes from genomic sequences

Mapping and identifying genes through database sequence analysis

Determining gene function from single gene disorders

Predicting protein structure from computational genomics

Gene Therapy: Principles, Vector Delivery, Targeting areas, Diseases

Course Policies

POLICY ON MISSED EXAMINATIONS/MID-TERMS AND ASSIGNMENTS

A student who misses an examination (midterm test etc.) due to exceptional circumstances must notify the course coordinator or department office within 48 h. If there was a medical reason for not appearing for the exam then provide a valid medical certificate (see Dalhousie Calendar section 18.8). Special "make-up" examinations will normally be written within 7 calendar days after the missed examination. Absence for non-medical reasons is not ordinarily acceptable unless prearranged with the professor. A missed examination for which no satisfactory arrangement has been made will be given a mark of zero.

ACCOMMODATION POLICY FOR STUDENTS

Students may request accommodation as a result of barriers related to disability, religious obligation, or any characteristic protected under Canadian Human Rights legislation. The full text of Dalhousie's Student Accommodation Policy can be accessed here:

http://www.dal.ca/dept/university_secretariat/policies/academic/student-accommodation-policy-wef-sep--1--2014.html. Students who require accommodation for classroom participation or the writing of tests and exams should make their request to the **Advising and Access Services Centre (AASC)** prior to or at the outset of the regular academic year. More information and the **Request for Accommodation** form are available at www.dal.ca/access.

ACADEMIC INTEGRITY

Academic integrity, with its embodied values, is seen as a foundation of Dalhousie University. It is the responsibility of all students to be familiar with behaviours and practices associated with academic integrity. Instructors are required to forward any suspected cases of plagiarism or other forms of academic cheating to the Academic Integrity Officer for their Faculty. The Academic Integrity website (<http://academicintegrity.dal.ca>) provides students and faculty with information on plagiarism and other forms of academic dishonesty, and has resources to help students succeed honestly. The full text of Dalhousie's **Policy on Intellectual Honesty** and **Faculty Discipline Procedures** is available here:

http://www.dal.ca/dept/university_secretariat/academic-integrity/academic-policies.html

STUDENT CODE OF CONDUCT

Dalhousie University has a student code of conduct, and it is expected that students will adhere to the code during their participation in lectures and other activities associated with this course. In general: "The University treats students as adults free to organize their own personal lives, behaviour and associations subject only to the law, and to University regulations that are necessary to protect

- the integrity and proper functioning of the academic and non – academic programs and activities of the University or its faculties, schools or departments;
- the peaceful and safe enjoyment of University facilities by other members of the University and the public;
- the freedom of members of the University to participate reasonably in the programs of the University and in activities on the University's premises;
- the property of the University or its members."

The full text of the code can be found here:

http://www.dal.ca/dept/university_secretariat/policies/student-life/code-of-student-conduct.html

SERVICES AVAILABLE TO STUDENTS

The following campus services are available to help students develop skills in library research, scientific writing, and effective study habits. The services are available to all Dalhousie students and, unless noted otherwise, are free.

Service	Support Provided	Location	Contact
General Academic Advising	Help with <ul style="list-style-type: none"> - understanding degree requirements and academic regulations - choosing your major - achieving your educational or career goals - dealing with academic or other difficulties 	Killam Library Ground floor Rm G28 Bissett Centre for Academic Success	In person: Killam Library Rm G28 By appointment: <ul style="list-style-type: none"> - e-mail: advising@dal.ca - Phone: (902) 494-3077 - Book online through MyDal
Dalhousie Libraries	Help to find books and articles for assignments Help with citing sources in the text of your paper and preparation of bibliography	Killam Library Ground floor DMNB Site- UNBSJ Library Librarian offices	In person: Service Point (Ground floor). By appointment: Identify your subject librarian (URL below) and contact by email or phone to arrange a time: http://dal.beta.libguides.com/sb.php?subject_id=34328 Jackie Phinney; 506-648-5693 Room 209, Hans W. Klohn Commons University of New Brunswick, Saint John Campus
Studying for Success (SFS)	Help to develop essential study skills through small group workshops or one-on-one coaching sessions Match to a tutor for help in course-specific content (for a reasonable fee)	Killam Library 3rd floor Coordinator Rm 3104 Study Coaches Rm 3103	To make an appointment: <ul style="list-style-type: none"> - Visit main office (Killam Library main floor, Rm G28) - Call (902) 494-3077 - email Coordinator at: sfs@dal.ca or - Simply drop in to see us during posted office hours All information can be found on our website: www.dal.ca/sfs
Writing Centre	Meet with coach/tutor to discuss writing assignments (e.g., lab report, research paper, thesis, poster) <ul style="list-style-type: none"> - Learn to integrate source material into your own work appropriately - Learn about disciplinary writing from a peer or staff member in your field 	Killam Library Ground floor Learning Commons & Rm G25	To make an appointment: <ul style="list-style-type: none"> - Visit the Centre (Rm G25) and book an appointment - Call (902) 494-1963 - email writingcentre@dal.ca - Book online through MyDal We are open six days a week See our website: writingcentre.dal.ca