MCB 5255

Cellular and Molecular Immunology

Inflammatory disease: Molecular mechanisms and therapeutic approaches to Type 1 Diabetes

**Course organization:** Readings will be from the recent primary literature.  Student participation will include both individual presentations, involvement in class discussions of the current literature, and the writing of an NIH-style grant proposal.

Meeting times: Wednesdays 4-6 pm

Instructor: Michael Lynes; 860-486-4350; [michael.lynes@uconn.edu](mailto:michael.lynes@uconn.edu)

**Course overview:** This course will explore the genetic, biochemical, and organismal mechanisms that are central to type 1 Diabetes (T1D) in both humans and in animal models, and the therapeutic interventions that may manipulate these mechanisms.

**Student responsibilities:** This graduate level course will focus not only on the informational content described above, and will involve student participation. Students will be responsible for (1) participation in discussions of the current primary literature, (2) a presentation of a specific research theme to the class, and (3) a written grant proposal. Some classroom discussion will review the organization and presentation of student proposals, and to the mechanisms associated with the writing and reviewing of an NIH style grant proposal.

**Student topic selection**: There is a list of potential student topics attached to this syllabus. These topics have been chosen for their relevance to the specific theme for the course. If a student has a specific topic in mind that is relevant to the course theme, they should consult with Dr. Lynes. Dates for presentations will be assigned based on the topics selected (to put them in a logical order).

**Written grant proposal format:**  The grant will follow the standard format designed for an NIH R03 proposal. The grant will be based on questions that arise from the findings reported in the two papers discussed in your presentation of your topic. A general outline of the required parts of the grant will be provided.

**Class schedule**

Jan 22 Introduction to the course, expectations, resources for the course

Origins of the course topic, and overview of my engagement in this topic

assigned reading for general discussion on 1/29 (send individual presentation topic choices ordered from 1-3 for most desired to third place desire)

Jan 29 Overview: autoimmune disease overview (ppt lecture)

Selection/Assignment of Student presentation topics

Feb 5 Diabetes molecular mechanisms overview (ppt lecture)

Group discussion of assigned papers

Feb 12 NO CLASS today; work on your presentations!

Feb 19 Grantsmanship: Who, What, When, How and Why

extra reading: "Sidestep These Application Missteps: Unfocused Hypothesis or Specific Aims" Discussion of what a specific aim is designed to express in a grant proposal

Group discussion of assigned papers

Feb 26 Group discussion of assigned papers

Mar 4 Specific aims discussion (come with your hypothesis and grant specific aim thought out and written down; email of this aim due to Dr Lynes by 5pm of March 1st

Mar 11 Student Presentation GWAS identification of T1D markers (Jen)

Mar. 15-21 Spring recess

Mar 25 Student presentation The Gut microbiome and T1D (Brandon)

April 1 Student presentation Environmental stressors and T1D (note PFAS controversy) (Jon)

April 8 Student presentation Macrophages, oxidative stress and T1D (Paige)

April 15 Student presentation Inflammation of the brain (Insulin signaling and T1D) (Didem)

April 22 Student presentation Pancreatitis vs Insulitis in T1D (Meghan)

April 29 Student presentation T1D therapeutic approaches (Kyle)

May 1 last day of spring semester classes; Grant proposal due at 5pm on May 1. Deliver hard copy to Dr. Lynes’ office AND email a digital version. Include an addressed envelope (campus or postal address) if you wish to have the hard copy returned with comments.

May 4-9 Examination period (There is no final examination in this course).

**Suggested student topics:**

1. Errors in insulin signaling that produce diabetes
   1. Solheim MH, Winnay JN, Batista TM, Molven A, Njølstad PR, Kahn CR. Mice Carrying a Dominant-Negative Human PI3K Mutation Are Protected From Obesity and Hepatic Steatosis but Not Diabetes. *Diabetes*. 2018 Jul;67(7):1297-1309. doi: 10.2337/db17-1509. Epub 2018 May 3. PMID: 29724723; PMCID: PMC6014554.
   2. García-Cuesta EM, Santiago CA, Vallejo-Díaz J, Juarranz Y, Rodríguez-Frade JM, Mellado M. The Role of the CXCL12/CXCR4/ACKR3 Axis in Autoimmune Diseases. *Front Endocrinol (Lausanne)*. 2019 Aug 27;10:585. doi: 10.3389/fendo.2019.00585. PMID: 31507535; PMCID: PMC6718456.
2. Environmental stressors and T1D susceptibility; the debate rages on
   1. <https://www.hindawi.com/journals/bmri/2015/208947/>
   2. Salo HM, Koponen J, Kiviranta H, Rantakokko P, Honkanen J, Härkönen T, Ilonen J, Virtanen SM, Tillmann V, Knip M, Vaarala O; DIABIMMUNE Study Group. No evidence of the role of early chemical exposure in the development of β-cell autoimmunity. *Environ Sci Pollut Res Int*. 2019 Jan;26(2):1370-1378. doi: 10.1007/s11356-018-3659-6. Epub 2018 Nov 13. PMID: 30426368; PMCID: PMC6331740.
   3. Bodin J, Groeng EC, Andreassen M, Dirven H, Nygaard UC. Exposure to perfluoroundecanoic acid (PFUnDA) accelerates insulitis development in a mouse model of type 1 diabetes. *Toxicol Rep*. 2016 Aug 29;3:664-672. doi: 10.1016/j.toxrep.2016.08.009. PMID: 28959590; PMCID: PMC5616085.
   4. Conway B, Innes KE, Long D. Perfluoroalkyl substances and beta cell deficient diabetes. *J Diabetes Complications*. 2016 Aug;30(6):993-8. doi: 10.1016/j.jdiacomp.2016.05.001. Epub 2016 May 4. PMID: 27311784; PMCID: PMC5556924.
   5. Bodin J, Stene LC, Nygaard UC. Can exposure to environmental chemicals increase the risk of diabetes type 1 development? *Biomed Res Int*. 2015;2015:208947. doi: 10.1155/2015/208947. Epub 2015 Mar 26. PMID: 25883945; PMCID: PMC4391693.
3. Abnormal pancreatic secretions and stress
   1. Lee MG, Ohana E, Park HW, Yang D, Muallem S. Molecular mechanism of pancreatic and salivary gland fluid and HCO3 secretion. *Physiol Rev*. 2012 Jan;92(1):39-74. doi: 10.1152/physrev.00011.2011. PMID: 22298651; PMCID: PMC3667394.
   2. Williams JA. Proteomics as a systems approach to pancreatitis. *Pancreas*. 2013 Aug;42(6):905-11. doi: 10.1097/MPA.0b013e31828fddc3. PMID: 23851428; PMCID: PMC3713413.
   3. Metallothionein is a component of exocrine pancreas secretion: implications for zinc homeostasis
      1. [R. C. De Lisle](https://www.physiology.org/doi/abs/10.1152/ajpcell.1996.271.4.C1103), [M. P. Sarras Jr](https://www.physiology.org/doi/abs/10.1152/ajpcell.1996.271.4.C1103), [J. Hidalgo](https://www.physiology.org/doi/abs/10.1152/ajpcell.1996.271.4.C1103), and [G. K. Andrews](https://www.physiology.org/doi/abs/10.1152/ajpcell.1996.271.4.C1103) OCT1996<https://doi.org/10.1152/ajpcell.1996.271.4.C1103>
   4. Danger signals and T1D
      1. Primary Human and Rat b-Cells Release the Intracellular Autoantigens GAD65, IA-2, and Proinsulin in Exosomes Together With Cytokine- Induced Enhancers of Immunity

Chiara Cianciaruso, Edward A. Phelps, Miriella Pasquier, Romain Hamelin, Davide Demurtas, Mohamed Alibashe Ahmed, Lorenzo Piemonti,Sachiko Hirosue, Melody A. Swartz, Michele De Palma, Jeffrey A. Hubbell, and Steinunn Baekkeskov Diabetes 2017;66:460–473 | DOI: 10.2337/db16-0671

* + 1. Morse ZJ, Horwitz MS. Innate Viral Receptor Signaling Determines Type 1 Diabetes Onset. Front Endocrinol (Lausanne). 2017 Sep 26;8:249. doi: 10.3389/fendo.2017.00249. PMID: 29018409; PMCID: PMC5623193.

1. Pancreatitis vs insulitis; is treating the inflammation enough?
   1. Su KH, Cuthbertson C, Christophi C. Review of experimental animal models of acute pancreatitis. *HPB (Oxford)*. 2006;8(4):264-86. doi: 10.1080/13651820500467358. PMID: 18333137; PMCID: PMC2023897.
   2. In't Veld P. Insulitis in human type 1 diabetes: a comparison between patients and animal models. *Semin Immunopathol*. 2014 Sep;36(5):569-79. doi: 10.1007/s00281-014-0438-4. Epub 2014 Jul 9. PMID: 25005747; PMCID: PMC4186970.
   3. Pakala SV, Kurrer MO, Katz JD. T helper 2 (Th2) T cells induce acute pancreatitis and diabetes in immune-compromised nonobese diabetic (NOD) mice. *J Exp Med*. 1997 Jul 21;186(2):299-306. doi: 10.1084/jem.186.2.299. PMID: 9221759; PMCID: PMC2198973.
   4. Pugliese A. Insulitis in the pathogenesis of type 1 diabetes. *Pediatr Diabetes*. 2016 Jul;17 Suppl 22(Suppl Suppl 22):31-6. doi: 10.1111/pedi.12388. PMID: 27411434; PMCID: PMC4948864.
   5. In't Veld P. Insulitis in human type 1 diabetes: The quest for an elusive lesion. *Islets*. 2011 Jul-Aug;3(4):131-8. doi: 10.4161/isl.3.4.15728. Epub 2011 Jul 1. PMID: 21606672; PMCID: PMC3154446.
2. Multiple roles for MT in diabetes
   1. Chen S, Han J, Liu Y. Dual Opposing Roles of Metallothionein Overexpression in C57BL/6J Mouse Pancreatic β-Cells. *PLoS One*. 2015 Sep 3;10(9):e0137583. doi: 10.1371/journal.pone.0137583. PMID: 26335571; PMCID: PMC4559390.
   2. Kadota Y, Toriuchi Y, Aki Y, Mizuno Y, Kawakami T, Nakaya T, Sato M, Suzuki S. Metallothioneins regulate the adipogenic differentiation of 3T3-L1 cells via the insulin signaling pathway. *PLoS One*. 2017 Apr 20;12(4):e0176070. doi: 10.1371/journal.pone.0176070. PMID: 28426713; PMCID: PMC5398611.
3. Oxidative stress and T1D
   1. Burg AR, Tse HM. Redox-Sensitive Innate Immune Pathways During Macrophage Activation in Type 1 Diabetes. *Antioxid Redox Signal*. 2018 Nov 10;29(14):1373-1398. doi: 10.1089/ars.2017.7243. Epub 2017 Nov 27. PMID: 29037052; PMCID: PMC6166692.
4. The role of the dendritic cell in T1D
   1. Hotta-Iwamura C, Tarbell KV. Type 1 diabetes genetic susceptibility and dendritic cell function: potential targets for treatment. *J Leukoc Biol*. 2016 Jul;100(1):65-80. doi: 10.1189/jlb.3MR1115-500R. Epub 2016 Jan 20. PMID: 26792821; PMCID: PMC4946618.
5. The role of the macrophage in T1D
   1. Korf H, Breser L, Van Hoeck J, Godoy J, Cook DP, Stijlemans B, De Smidt E, Moyson C, Monteiro Carvalho Mori Cunha JP, Rivero V, Gysemans C, Mathieu C. MIF inhibition interferes with the inflammatory and T cell-stimulatory capacity of NOD macrophages and delays autoimmune diabetes onset. *PLoS One*. 2017 Nov 2;12(11):e0187455. doi: 10.1371/journal.pone.0187455. PMID: 29095944; PMCID: PMC5667746.
   2. Parisi L, Gini E, Baci D, Tremolati M, Fanuli M, Bassani B, Farronato G, Bruno A, Mortara L. Macrophage Polarization in Chronic Inflammatory Diseases: Killers or Builders? *J Immunol Res*. 2018 Jan 14;2018:8917804. doi: 10.1155/2018/8917804. PMID: 29507865; PMCID: PMC5821995.
6. T1D therapeutic approaches
   1. Cabello-Olmo M, Araña M, Radichev I, Smith P, Huarte E, Barajas M. New Insights into Immunotherapy Strategies for Treating Autoimmune Diabetes. *Int J Mol Sci*. 2019 Sep 26;20(19):4789. doi: 10.3390/ijms20194789. PMID: 31561568; PMCID: PMC6801436.
   2. Bone RN, Evans-Molina C. Combination Immunotherapy for Type 1 Diabetes. *Curr Diab Rep*. 2017 Jul;17(7):50. doi: 10.1007/s11892-017-0878-z. PMID: 28534310; PMCID: PMC5774222.
   3. Aboumrad E, Madec AM, Thivolet C. The CXCR4/CXCL12 (SDF-1) signalling pathway protects non-obese diabetic mouse from autoimmune diabetes. *Clin Exp Immunol*. 2007 Jun;148(3):432-9. doi: 10.1111/j.1365-2249.2007.03370.x. Epub 2007 Mar 21. PMID: 17374136; PMCID: PMC1941939.
   4. Leng, Qibin & Nie, Yuchun & Zou, Yong-Rui. (2008). Elevated CXCL12 expression in the bone marrow of NOD mice is associated with altered T cell and stem cell trafficking and diabetes development. BMC immunology. 9. 51. 10.1186/1471-2172-9-51.
7. What does GWAS tell us about T1D?
   1. Pociot F. Type 1 diabetes genome-wide association studies: not to be lost in translation. *Clin Transl Immunology*. 2017 Dec 1;6(12):e162. doi: 10.1038/cti.2017.51. PMID: 29333267; PMCID: PMC5750451.
   2. Denis M. Nyaga, Mark H. Vickers, Craig Jefferies, Jo K. Perry, Justin M. O'Sullivan,The genetic architecture of type 1 diabetes mellitus,Molecular and Cellular Endocrinology,Volume 477,2018,Pages 70-80,ISSN 0303-207,https://doi.org/10.1016/j.mce.2018.06.002.(<http://www.sciencedirect.com/science/article/pii/S0303720718301886>)
8. How is the gut microbiome involved in onset or severity of T1D?
   1. Zheng P, Li Z, Zhou Z. Gut microbiome in type 1 diabetes: A comprehensive review. Diabetes Metab Res Rev. 2018;34:e3043 10.1002/dmrr.3043
      1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6220847/