Module 2: Diabetes

Overview:

Introduction: The diabetes module consists of ten class sessions with faculty leaders. In addition, there are three or more TA sessions in which students can receive group or individualized help with computational or other problems. The faculty-led sessions integrate important topics such as metabolism and the different metabolic programs and regulatory responses of different subsets of cells within particular organs, protein processing and secretion, with their clinically relevant implications to diabetes. They also encompass genome-wide screens and other genetic studies of diabetes and the insights provided by MODY (mono-genetic based Type 2 diabetes syndromes) into the major syndromes. Potential targets for new therapeutics and the modes of action of current therapeutics used to treat diabetes are also discussed throughout the module. A full session is devoted to nuts-and-bolts principles of developing new therapeutics, including the practical and regulatory hurdles along the way. Throughout the module, students develop quantitative skills through discussion of enzymatic kinetics and analysis of single nucleotide polymorphisms identified in genome wide association studies. The students also collaborate on multiple presentations of journal articles. The slide sets provided by the faculty for this module are often large, with only a sub-set of slides forming a class presentation while others are made available for students to use as resource as they prepare for class or work on problems. Some faculty leaders use their slides only as a resource for students and do not show them in class.

Module Flow:

Class 1: The Diabetes Module begins with a presentation by a physician-scientist that presents a clinical overview of Type 1 and Type 2 diabetes, their patho-physiological features and how some of these features relate to the biochemistry of different organs/tissues. Principles of the epidemiology of the disease are presented along with the growing burden of Type 2 diabetes and its relationship to obesity. Differences in presentation of diabetes and obesity in different genders and ethnic groups are described. This introduction to the disease context is followed by four classes that highlight the biochemistry, cell and molecular biology and genetic aspects of diabetes. Regulatory circuits and potential targets are noted but these topics are expanded and given much more of a systems biology context during the second half of the module.

Classes 2,3: The second and third classes focus on the tissue-specific metabolic pathways that account for the dysfunctions in insulin secretion and/or sensitivity and in glucose homeostasis. This provides a context in which the major metabolic pathways (especially for carbohydrate and fatty acid metabolism and central pathways) are studied along with specialized issues such as ketoacidosis. The discussion highlights the importance of tissue-specific isozymes and transporters with different kinetic/binding properties, tissue-specific hormonal responses and tissue-specific regulatory features that underpin their different fuel preferences and capacities and underpin the insulin-dependence of some tissues.

Class 4: The fourth class focuses on insulin secretion, introducing the crucial role of mitochondrial energetics as well as the channels and transporters (including transporters of NADH shuttles) that have roles in aspects of the overall process from glucose-sensing to insulin release. Principles of cell biology are introduced in the context of insulin secretion and trafficking of the GLUT4 type glucose transporters of insulin-dependent cells.

Class 5: The fifth class focuses on the genetics of diabetes, taking advantage of the substantial number of gene products that have already been introduced as playing roles in glucose homeostasis and related metabolic and hormonal pathways. Modes of inheritance are

reviewed in the context of Type 1 and Type 2 diabetes, and strategies of linkage and association studies are presented, with strengths and weaknesses. Genes that have been identified as having an impact upon the risk of developing diabetes are described. Discussion focuses on their failure to account for the observed genetic risk of diabetes and the contrast between Type 2 diabetes and MODY syndromes in this context.

Class 6: The second half of the module starts with the sixth class of the module, which focuses on details of insulin signaling, its multiple pathways and different effects in different tissue contexts. Selected receptor tyrosine kinases and phosphatases are discussed in detail while a broad picture of the larger network of relevant signaling entities is also introduced. Origins of insulin resistance are discussed and students are introduced to roles of stress (e.g. epinephrine), inflammation and free fatty acids as well as to proposed therapeutic approaches based on inhibition of the rennin-angiotensin system.

Class 7: The seventh class then follows with a discussion of ER (endoplasmic reticulum) stress and its important involvement in diabetes. The discussion provides the context for study of chaperone functions, the unfolded protein response and aspects of the ubiquitin/proteasome system and apoptosis.

Class 8: The eighth session is devoted to principles and steps of drug development, with diabetes and cancer (Module 3) as the major disease themes. The discussion includes systems analyses at various steps, including target identification (including GWAS, genome-wide association studies) and validation, as well as prediction of adverse effects.

Class 9: The ninth class focuses on the physiological systems arena with a focus on organ cross-talk in diabetes, with a review of the biochemical and patho-physiological concepts already introduced built into a new discussion of nutrient sensing, responses and resistance.

Class 10: The tenth and final class outlines current and potential future drug strategies (and other therapeutic strategies) to prevent or treat diabetes in a context that reviews and extends the concepts presented throughout the module, introducing the concept of personalized medicine and pipeline ideas that are currently being tested.

Class numbers highlighted in red are those in which a Journal Club, with students or groups of students assigned different papers or sections of a single paper, was built into the session. Sometimes the Journal Club was presented in one hour of a two-hour class session and sometime the Journal Club was integrated into the overall discussion in a variety of integrated ways. In a particularly effective use of the Journal Club component, *Class 9*, on organ cross-talk, includes a major segment in which the sub-sets of the class present a paper on the anticipated versus observed effects of an insulin receptor knock-out of a particular tissue in an animal model.

Examples of Points of Integration within this Module and between this Module and other Modules of Systems Biomedicine:

Integration with Module 1: The Diabetes Module (Module 2) is integrates much of the introductory information introduced with broad brush strokes in Module 1 into a more specific context. Examples include but are not limited to the following:

- An introductory MatLab unit of hands-on faculty-led sessions in Module 1 acquaints students with applications and a “how-to” introduction to this program. During the workshop that follows, the faculty leader and TAs guide students in applying these skills to enzyme kinetics problems that are based on enzymes/enzyme kinetics class-work in Module 1. In the Diabetes Module these applications are used for evaluating efficacy of glucokinase activators and for evaluating the basis whereby the high K_m values of GLUT2 and glucokinase underpin their roles in liver and pancreas.

- A Module 1 session on protein structure and motifs forms the basis for detailed discussions about G-protein coupled receptors (GCPRs) and receptor tyrosine kinases (RTKs) in Module 2.
- Module 1 introduces elements of transcriptional regulation, using CREB as one of the central examples. In the Diabetes Module, the regulation of liver PEPCK integrates principles presented in Module 1 with regulation this key enzyme in Hepatic Glucose Production. The complex regulation of PEPCK also is linked to transcription factors that turn up on the list of "diabetes genes".
- Module 1 contains an overview session on design principles of metabolic pathways, e.g. limiting pools of cofactors, strategic placement of irreversible reactions, the basis for tissue-specific metabolic repertoires, etc. All of these principles are illustrated in connection with key pathways involved in diabetes and the tissue-specific metabolic patterns that relate to different physiological roles.

Examples of Integration within the Diabetes Module (Module 2):

- Hepatic Glucose Production by both glycogenolysis and gluconeogenesis and the concept of "starvation in the midst of plenty" are pervasive themes. The biochemistry of the pathways (and the ancillary production of ketone bodies during gluconeogenesis) are presented from diverse viewpoints, including therapeutic intervention to diminish pathological HPG and therapeutic intervention to increase muscle consumption of elevated blood glucose.
- Insulin secretion and insulin resistance are presented in from multiple perspectives that are integrated as they arise, including the emerging importance of factors secreted by the gut (e.g. incretins) and by the adipose tissue (and the difference between different forms of fat tissue).
- Genes that were identified in GWAS and other diabetes gene-hunting efforts are noted throughout the module as their pathways, mechanisms of action are presented. There is also an ongoing integration of an important perspective of "diabetes genes do not fully determine destiny", which presents clinical evidence for the efficacy, even in individuals at significant genetic risk, of adding a rigorous diet-exercise regimen to strategies of prevention/treatment of Type 2 diabetes.
- Inflammatory stress and stress by direct generation of reactive oxygen species (ROS) are introduced several times in this Module, with integrative comments highlighting the mechanisms whereby these stresses arise and how they may be mitigated.

Integration with later modules:

- Organ cross-talk is cogently introduced in Module 2 and remains a major theme across later modules. The rennin-angiotensin system recurs in Module 4, Renal Diseases. These two modules are integrated at many levels since end-stage renal disease is often associated with diabetic nephropathy. In addition there is a proposed use of inhibitors of SGLT1 a renal transporter for glucose re-absorption in the kidney as a therapeutic agent in diabetes that must be evaluated vis a vis systems effects on kidney function.
- The cataloguing of different types of membrane transporters and channels begins with Module 2 but extends to every other module, in which quantitative concepts, mechanistic distinctions, and increasing structural information is presented throughout the course and must be integrated. Modules 4 (Renal Diseases) and Module 5 (Drug Abuse) together with Module 2 offer an opportunity to create an integrated picture of emerging

insights into both primary and secondary, active and facilitated membrane transporters and a diverse group of channel types.

- The adverse effects of therapeutics whose use is based on sound mechanistic reasoning is introduced in Module 2 and is a recurring theme in most of the modules, especially Module 5. These examples provide opportunities to discuss network analyses that can potentially predict and help avoid such effects, either broadly or in particular genetically susceptible sub-sets of individuals.