Module 3: Cancer

Overview:

Introduction: The cancer module consists of ten class sessions with faculty leaders and two scheduled TA sessions. TAs also participated in on-line Q&A in support of work on problem sets. The faculty-led sessions integrate important core cell and molecular topics, which include cell cycle, apoptosis, additional aspects of genetics and genetic screens, and signaling pathways that have roles in both development and cancer, and an introduction to additional aspects of human histology/physiology as different tissues, the vascular system and the lymphatic system enter discussions. These topics are highlighted in discrete sessions and integrated in other presentations that provide clinical and research perspectives on cancer biology. Epidemiological aspects of cancer and design of epidemiological research studies are presented as a capstone to the module. In this module, only one session, *Class 7*, is fully devoted to a journal club. One or more journal articles are assigned for most of the other sessions and students are called upon in class to comment on information from those articles that is relevant to the class discussion.

Module Flow:

Class 1: The Cancer Module presents core cell biological and signaling information in a context that highlights its relationship to cancer before clinician-scientists provide clinical perspectives that draw upon this information. The module starts with a session on defects in cell cycle regulation that builds upon an introduction to cell cycle that the topic of a class session in Introductory Module 1. Here, greater detail about the cell cycle is presented in order to explicate the direct and indirect contributions of cell cycle defects to oncogenesis. Among the topics that are part of this class are: the basis for association of particular gene/cycle component defects with particular cancers discussed; an outline of necrosis and apoptosis in normal physiology and in the pathobiology of cancer; DNA damage and repair/tumor suppressor genes.

Class 2: The material from *Class* 1 and the Tyson cell cycle model [Tyson, J.J. (1991). Modeling the cell division cycle: cdc2 and cyclin interactions. Proc. Natl. Acad. Sci. USA 88:7328-7332] are the basis of *Class 2.* This session includes a didactic piece that is followed by a workshop. The students are introduced to systems of ordinary differential equations (ODEs) and how to solve ODEs using Matlab. They review the principles of the cell cycle in the context of the Tyson model and then implement the model on their own computers, having been earlier provided with the Matlab program.

Class 3: The tissue origin, % of cancer diagnoses, and general characteristics are presented for carcinomas, sarcomas, leukemias/lymphomas and neuroectodermnal tumors. The epithelial origin of most cancers (carcinomas) is noted, with an introduction to the types of epithelium (e.g. simple squamous, stratified squamous, cuboidal and columnar types, etc) and categories of carcinomas. Genes or combinations of genes that whose dysfunction/dysregulation are associated with particular cancers are discussed. There follows an introduction of six of the signaling pathways that are associated with aspects of cell cycle and/or development and also with cancer: Hedgehog; TGFβ-SMAD; Wnt; Notch; EGF/FGF; and RTK-P13K pathways. In the next iteration of the schedule we will introduce a workshop in which these pathways are introduced by short presentations of student groups before the faculty-led class so that students will be more fully prepared for the subsequent discussion of the ways in which activation of signaling occurs in cancer settings, e.g. mutation, amplification and gene fusion. Overall, molecular steps of tumor formation and progression to metastasis are

introduced here, before more clinical presentations and greater detail on steps in this progression in later class sessions.

Class 4: This class session introduces students to animal models that are used in cancer research and some that are not used heavily now but had important historical roles in cancer research. The introduction encompasses the importance uses of animal models as well as the criteria used to evaluation the pros and cons of particular animal models for specific types of experimental goals. Reverse genetics and forward genetics approaches are defined and illustrated. Cancer-related examples of screens that search for modifiers, for suppressors (e.g. of apoptosis), genome-wide RNAi based screens and screen using mosaic tissue are presented. The use of animal model systems for cell migration and metastasis is illustrated as an avenue for testing possible drug targets or candidate drugs.

Class 5: The presentation of cancer from a clinical point of view focuses on prostate cancer and several other urological cancers, i.e. a renal mass, a testicular mass (Sertoli cell tumor), a familial Von Hippel Lindau Syndrome brain tumor, bladder cancer. The introduction reviews criteria for cancer, risk factors, the Knudsen“two-hit”theory, stage and grade terminology, principles of radiographic staging. Case presentations include radiological, pathological findings that lead to diagnosis, staging (prognosis) and development of treatment plans. Each case presentation leads the students through the analyses that lead to a diagnosis and issues involved in deciding whether to perform biopsies and involved in reaching the treatment decision. The presentation then focuses on prostate cancer screening via the PSA diagnostic test, data on specificity and sensitivity of the PSA test with respect to detection of prostate cancer. Data from the NCI Prostate Cancer Detection Trial are reviewed and critical issues are discussed, e.g. potential “overdiagnosis”, whether treatment of localized prostate cancer prolongs survival, when to recommend “active surveillance”.

Class 6: The class devoted to cancer genetics starts with an introduction that starts with an expansion of cancer nomenclature and a description of progression from mutation(s) to cancer from the points of view of monogenic disease with germline mutations in a single gene versus the complex disease involving changes in multiple genes interacting with environmental factors. Cancer nomenclature is expanded further. The discussion then moves to: examples of different type of genetic and epigenetic changes; the relative contribution of genetic susceptibility versus other etiologic factors (e.g. tobacco, diet, occupation etc); and risk of different cancers in different countries. Oncogenes are then discussed, first their original identification in RNA tumor viruses (*myc, abl, sis, ras*), and then the understanding that the corresponding human genes encode proteins that are important in cell cycle progression, division and differentiation. Mechanisms of oncogene activation are presented. There follow discussions of several examples of the genetics and molecular pathogenesis of sporadic and hereditary cancers, including: chronic myelogenous leukemia, the fused *bcr* and *abl* genes in the Philadelphia chromosome, and the development of efficacious tyrosine kinase inhibitors; mutations in the *p53* tumor suppressor gene that result in elevated risk for diverse tumors; and a monogenic osteosarcoma syndrome and its modifiers. The rest of the discussion focuses on the fundamentals, impact and further potential of SNP analyses, genome-wide screening and systems approaches to better definition of the molecular events, identification of targets and therapeutic strategies.

Class 7: This journal club session focuses on: Alizadhe et al. (2000) Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature **403**:503-511. In fall 2009, the students prepared this paper, referring back to material from a session in Module 1 in which the methodology, analyses and pitfalls of microarray analyses of the transcriptome were

studied. The expert faculty leader of the session provided historical notes to the study in the paper, engaged the students in presenting the goals and strategy of the study, the findings in each of the figures. There was a lively discussion of how the experimental approach would be different now and what has been learned about the molecular pathogenesis of this cancer since 2000.

Class 8: This second clinically oriented presentation focuses on strategies on cancer therapy. It is introduced with a review of: characteristics of benign and malignant tumors; public health data on the overall incidence of cancer in the USA for men and women; the annual estimate of total cases of different types of cancer; trends in cancer incidence between 1950-2008; trends in mortality rates; and a brief introduction to the history of cancer treatment and the significant leap in approach between the 20^{th} and 21^{st} centuries. General principles of cancer pharmacology are then presented in the contexts of: chemotherapy; monoclonal antibody therapy; immunotherapy; molecularly targeted therapy; hormonal therapy; and stem cell therapy. Examples of each of these types are presented with their mechanisms of action and the settings in which they are used. Principles of pharmacokinetics, pharmacodynamics, bioavailability, and problems of toxicity are presented with examples. The problem of treatment resistance and its mechanisms are presented along with strategies for overcoming it (e.g. combination therapy with drugs mutually non-cross-resistant drugs, sequential chemotherapy). Pipeline ideas are discussed.

Class 9: This class focuses on cancer metastasis --- lymphatic, hematogenous and direct seeding. The students are introduced to the lymphatic system and lymphangiogenesis, to the vasculature and angiogenesis and several types of cell-cell communication. There is a focus on the microenvironments involved and the cell biological/tissue re-modeling processes involved in metastasis. The steps from the primary cancer to a metastasis are first presented along with observation that different primary cancers have different patterns with respect to the most common metastatic sites and then different models of the metastatic process are considered. The growth factors, chemokines and potential therapeutic targets and marker with prognostic value are considered as part of the discussion of strategies to prevent, minimize or treat metastatic cancer.

Class 10: The module closes with a class focusing on cancer epidemiology. The goals of the session are to provide the students with a sufficient introduction to cancer epidemiology so that they are better able to critically evaluate a journal article in this area, can calculate and interpret an odds ratio and 95% confidence interval and have worked through different types of epidemiological studies and their pros and cons as the approach chosen for a particular question. Design principles for case-control and cohort studies are examined. Measures of association, odds ratio and relative risk are demonstrated in the context of particular studies. The factors determining choice of study populations, e.g. “population-based” or “hospital-based”, are considered together with the challenges of recruiting and retaining the population. Examples of data analysis are presented and an in-class hypothetical study is used as a vehicle to enhance the students’ engagement and understanding of the major principles, including odds ratio calculation, 2 X2 tables and calculation of 95% confidence interval.

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

Examples of Integration within the Cancer Module (Module 3): The class sessions within this module are integrated with one another through points of overlap that are built into the module planning and through integrating connections made during class and through problems. Examples of integration include:

- The principles and "parts list" of the cell cycle and of key signaling pathways are elaborated in an iterative and expanding manner throughout the module, culminating in the therapeutics session.
- The cell biology and physiology of different types of cell types and of metastasis is developed across classes.
- The TAs and module/course directors draw parallels between the molecular pathobiology involved in oncogenesis of the cancers discussed in the clinical cancer class 6, the genetics presented in class 5 and the therapeutics discussed in class 8.
- Tests of efficacy are more central to more of the class discussions in this module than in module 2 and are also tied to the systemic and systems properties of cancer physiology.

Integration with other modules:

- Transcriptome studies and genome-wide-association studies are, respectively introduced in Modules 1 and 2 and are further developed in the cancer module Class 5 on genetics and in the Journal Club session 7.
- The genetics principles in the cancer module, recapitulate and extend the pedigrees and gene-hunting discussed in the diabetes module. In this module, drug discovery, target validation, systems analyses and association studies are high-throughput experiments with a major computational components.
- The cell biology of polarized epithelial cells provides a framework for the cell biology of adhesion, matrix interactions and the numerous functional aspects of polarized epithelial cells of renal tissue in Module 4 (Renal Diseases).
- Growth control, the Warburg effect and recent insights into the reliance of many cancer cells on a fermentative pattern of central metabolism in which a major increase in overall, fermentable energy sources are used to fuel a rapid cell growth. Fuel consumption must be sufficient to sustain the protein, lipid, structural carbohydrate and nucleic acid syntheses needed to support rapid growth. This pattern is contrasted with the normal patterns of metabolism studied in detail in the introductory module 1 and diabetes module.

Note of special integration: During the cancer genetics session in 2009, the faculty leader presented the finding from "an unbiased genomic analysis" that glioblastoma multiforme, the most common and lethal brain cancer, had a high incidence of mutations in IDH1, the Krebs cycle isocitrate dehydrogenase (Parsons *et al.* 2008, **321**:1807-1812). Later, after the end of the course, the students were sent a paper by Zhao *et al.* (2008, Science, **324**:261-265), showing that the IDH1 mutations inhibit wild-type IDH1 by leading to production of inactive heterodimers that have impaired substrate affinity. In turn, this reduces production of α-ketoglutarate production which normally suppresses elevation of HIF-1α, the hypoxia-induced transcription factor that promotes tumorigenesis.