CENTER *for* APPLIED MOLECULAR MEDICINE

University of Southern California Physical Sciences in Oncology Center

Monthly Seminar Series

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"Leveraging integrative genomics and tumor evolutionary dynamics to infer mechanisms of disease progression"

FRIDAY, SEPTEMBER 27, 2013

NOON - 1:00 P.M.

Q & A to follow

(Pizza and beverages will be served for attendees at 11:45 a.m.)

HARKNESS AUDITORIUM

HSC - Clinical Sciences Building, **2nd Floor**
2250 Alcazar Street, Los Angeles, CA

ABSTRACT:

Although the direct observation of human tumor progression is impractical, the ancestral relationships between cancer cells are recorded in the form of mutations acquired during somatic cell division. As such, the dynamics of tumor growth can be inferred from genomic signatures found in the present day tumor. We have developed an experimental and computational framework that leverages these principles to delineate mechanisms of disease progression. For example, by employing a multiple sampling scheme and computational genomic inference framework in colorectal cancer, we find that tumors grow predominantly as a single expansion from the initial transformed cell into a large number of heterogeneous subclones in a *Big Bang* fashion. In this model, rapid expansion determines that most observable intra-tumor heterogeneity originates well before the neoplasm is detectable, irrespective of microenvironmental effects or subclone fitness changes. Hence, patterns of intra-tumor heterogeneity provide a looking glass into the primordial tumor, revealing early events that influence genomic and phenotypic outputs. In related work, we have demonstrated that it is possible to measure clinically relevant patient-specific parameters, including the cancer stem cell fraction, (a) symmetric cell division rate, mutation rate, and tumor age from genomic data. We are applying these approaches to clinically annotated colorectal cancer cohorts in order to discriminate between alternate models of metastatic dissemination. Similarly, we are developing tools to model therapeutic resistance to anti-HER2 agents in breast cancer. Our findings suggest that a quantitative understanding of tumor evolutionary dynamics will have significant implications for cancer diagnosis and prognosis, and ultimately for preventing resistance.

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