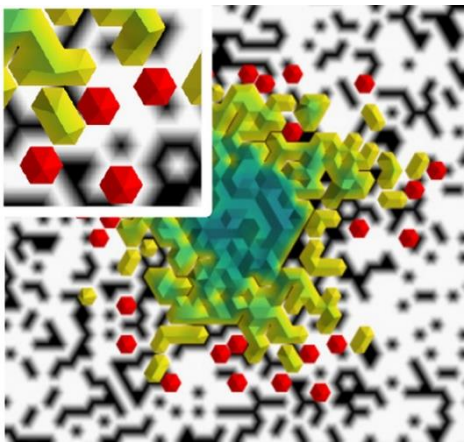
Virtual Seminar on Modeling Biocomplexity: Cancer Invasion and Progression

Abstracts



Schedule

One talk (45 min + 30 min discussion) on **every Wednesday** at **5 pm CEST** (corresponding to 4 pm BST, 8 am PDT, 10 am CDT, 11 am EDT, 8.30 pm IST, and 1 am AEST).

Date	Speaker	Topic
10/6	**Thomas Hillen** (University of Alberta, Edmonton, Canada)	The immune-mediated theory of metastasis
17/6	**Klaus Pantel** (University Medical Center Hamburg-Eppendorf, Germany)	Liquid biopsy: tracing of tumor cell dissemination in cancer patients at the single cell level
24/6	**Rob Noble** (ETHZ, Basel, Switzerland)	Characterizing and forecasting tumor evolution
1/7	**Simone Niclou** (Luxembourg Institute of Health)	Studying cancer cell invasion in Glioblastoma
8/7	**Natalia Komarova** (University of California, Irvine)	Mathematical modeling of cancer evolution
15/7	**Marek Kimmel** (Rice University, Houston, Texas)	Site frequency spectra and related statistics, and inference of tumor evolution
22/7	**Bob Gatenby** (Moffitt Cancer Centre, Tampa, Florida)	Evolution-based models to control and cure metastatic cancers

The immune-mediated theory of metastasis

Thomas Hillen (University of Alberta, Edmonton, Canada), 10/6/20

Accumulating experimental and clinical evidence suggests that the immune response to cancer is not exclusively anti-tumor. In fact, several pro-tumor effects of the immune system have been identified, such as production of growth factors, establishment of angiogenesis, inhibition of immune response, initiation of cell movement and metastasis, and establishment of metastatic niches.

Based on experimental data, we develop a mathematical model for the immune-mediated theory of metastasis, which includes anti- and pro-tumor effects of the immune system. The immune-mediated theory of metastasis can explain dormancy of metastasis and metastatic blow-up after resection of the primary tumor. It can explain increased metastasis at sites of injury, and the relatively poor performance of Immunotherapies, due to pro-tumor effects of the immune system.

Our results suggest that further work is warranted to fully elucidate and control the pro-tumor effects of the immune system in metastatic cancer. (with Adam Rhodes)

Liquid biopsy: tracing of tumor cell dissemination in cancer patients at the single cell level

Klaus Pantel (Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Germany), 17/6/20

“Liquid biopsy” was introduced as a new diagnostic concept in 2010 for the analysis of circulating tumor cells (CTCs) and has been now extended to material (in particular DNA) released by tumor cells in the peripheral blood of cancer patients. Over the past decade, various methods have been developed to detect CTCs and ctDNA in the peripheral blood of cancer patients. While reliable information can be easily obtained in patients with advanced disease, early stage cancer patients usually present with very low concentrations of CTCs and ctDNA. At present, most CTC assays rely on epithelial markers and the majority of CTCs detected are single isolated cells. The clinical relevance of ‘mesenchymal’ CTCs lacking any epithelial markers as well as CTC clusters are still under investigation. Although most published studies have been performed on patients with carcinomas and melanomas, CTCs have been also detected in the peripheral blood of patients with primary brain tumors (glioblastomas) despite the blood-brain barrier.

Liquid biopsy assays are currently being validated for early detection of cancer, which is supposed to reduce cancer related mortality. Despite remarkable progress, liquid biopsy-based detection of early stages of cancer remains a challenge, in particular in breast cancer. New blood-based biomarkers for early detection currently validated in clinical trials include miRNAs, exosomes and tumor-educated platelets.

In patients with diagnosed cancer, CTCs and ctDNA analyses can obtain independent information on prognosis in early and advanced stages of disease. In particular, CTC counts at initial diagnosis are able to refine the current risk stratification by TNM staging in early stage breast cancer. Moreover, early detection of relapse by sequential ctDNA (or CTCs) analysis of blood samples obtained post-surgery during the follow up is possible and may be used in future trials to stratify patients to “post-adjuvant” therapies.

Another key application of liquid biopsy is to identify therapeutic targets or mechanisms of resistance of metastatic cells in individual patients. While the analysis of ctDNA focuses on mutations relevant for

cancer therapy (e.g., EGFR, KRAS or ESR1 mutations), CTCs offer a wide spectrum of analyses at the DNA, RNA and protein levels. Metastatic cells might have unique characteristics that can differ from the bulk of cancer cells in the primary tumor currently used for stratification of patients to systemic therapy. Moreover, monitoring of CTCs and ctDNA before, during and after systemic therapy (e.g., chemotherapy, hormonal therapy, antibody therapy) might provide unique information for the future clinical management of the individual cancer patient and might serve as surrogate marker for response to therapy. In the context of recent success in antibody-mediated blockade of immune checkpoint control molecules, expression of the PD-L1 on CTCs might be of interest as potential predictive marker. Moreover, the expression of androgen receptor variant 7 in CTCs may predict resistance to anti-androgen therapy in prostate cancer, while mutations in the estrogen receptor gene (ESR1) provides information on resistance to hormone therapy in breast cancer. Additional therapeutic targets detected on CTCs in cancer patients include the estrogen receptor and HER-2 oncogene. Single cell RNAseq analysis of CTCs may provide more comprehensive information on relevant pathways.

For functional analysis of CTCs, the development of *in vitro* and *in vivo* test systems has started, which might also serve as models for drug testing. In particular, the development of cell lines and xenografts derived from CTCs can provide novel insights into the biology of tumor cell dissemination and may be used to discover new pathways to target specifically metastatic cells.

Besides CTCs and ctDNA the analysis of circulating microRNAs, exosomes or tumor-educated platelets may provide complementary information as "liquid biopsy". E.g., the integrin composition of exosomes seems to determine the organ site of metastatic niches and the RNA expression pattern of blood platelets reveals information on tumors in cancer patients.

Sensitive methods have been also developed to capture disseminated tumor cells (DTCs) in the bone marrow in cancer patients, which provide new insights into the process of "cancer dormancy". The nature of dormant breast cancer cells and the mechanisms leading to their outgrowth are poorly understood. Efforts to unravel the nature of cancer dormancy have been hampered by the lack of sensitive methods to detect dormant cells in cancer patients. The development of novel therapies designed to kill dormant residual tumor cells, or maintain them in a quiescent state, represents a highly attractive approach to prevent late recurrence. Such an approach, however, would require a far more detailed understanding of tumor dormancy and recurrence than exists today, as well as biomarkers to enable monitoring of this process and predict recurrence. Analysis of DTCs leads to the discovery of new molecules relevant to the biology of metastasis such as the putative metastasis-suppressor RAI2.

In conclusion, liquid biopsy analysis can be used to obtain new insights into metastasis biology, and as companion diagnostics to improve the stratification of therapies and to obtain insights into therapy-induced selection of cancer cells. Different approaches such as CTC or ctDNA analysis will provide complementary information. Technical and clinical assay validation is very important and can be achieved in international consortia such as the European Liquid Biopsy Society (ELBS) network (www.elbs.eu).

Characterizing and forecasting tumor evolution

Rob Noble (ETHZ, Basel, Switzerland), 24/6/20

Characterizing the mode – the way, manner, or pattern – of evolution in tumours is important for clinical forecasting and optimizing cancer treatment. DNA sequencing studies have inferred various modes, including branching, punctuated and neutral evolution, but it is unclear why a particular pattern predominates in any given tumour. I will argue that differences in tumour architecture can explain the variety of observed genetic patterns. I will present results of spatially explicit population

genetic models showing that, within biologically relevant parameter ranges, human tumours are expected to exhibit four distinct onco-evolutionary modes (oncoevotypes), governed by the mode of cell dispersal and the range of cell-cell interaction. New quantitative indices will be introduced for describing and classifying these oncoevotypes. I will further present an investigation of when, why and how intratumour heterogeneity can be used to forecast tumour growth rate and progression-free survival. I will thus provide explanations – grounded in evolutionary theory – for empirical findings in various cancers. This work informs the search for new prognostic biomarkers and contributes to the development of predictive oncology.

Studying cancer cell invasion in Glioblastoma

Simone Niclou (Luxembourg Institute of Health), 1/7/20

Diffuse gliomas are malignant tumors of the brain that are characterized, as the name implies, by extensive tumor cell infiltration throughout the brain. They include different types of tumors of glial origin or resemblance, including Glioblastoma (GBM), the most aggressive primary brain tumor in adults. The excessive invasion represents a major challenge in clinical disease management because it precludes complete tumor cell removal at the invasive front through surgical resection thus constituting a major source of tumor recurrence. Furthermore, invasive glioma cells represent a difficult therapeutic target since they are localized within normal functional brain areas with an intact blood brain barrier (BBB), thereby excluding most systemic drug treatments. The lecture will provide an overview of the various paths and modes of glioma cell invasion with a focus on the specific aspects of the brain microenvironment. We highlight recent insight into tumor microtubes, neuro-glioma synapses and tumor metabolism which can regulate invasion processes. Unpublished data on a genome-wide shRNA screen identifying potential novel regulators of GBM invasion will be presented. Finally, we will critically assess the challenges and opportunities for therapeutically targeting glioma cell invasion.

Mathematical modeling of cancer evolution

Natalia Komarova (University of California, Irvine), 8/7/20

Evolutionary dynamics is at the core of carcinogenesis. Mathematical methods can be used to study evolutionary processes, such as selection, mutation, and drift, and to shed light into cancer origins, progression, and mechanisms of treatment. I will present two very general types of evolutionary patterns, loss-of-function and gain-of-function mutations and discuss scenarios of population dynamics -- including stochastic tunneling and calculating the rate of evolution. Applications include origins of cancer, passenger and driver mutations, and how aspirin might help prevent cancer. I will also talk about evolution in random environments. The presence of temporal or spatial randomness significantly affects the competition dynamics in populations and gives rise to some counterintuitive observations. I will present some recent results on the evolutionary dynamics in systems where spatial and temporal randomness affects division and/or death parameters of cells. Of particular interest are the dynamics of non-selected mutants, which exhibit counterintuitive properties.

Site frequency spectra and related statistics, and inference of tumor evolution

Marek Kimmel (Rice University, Houston, Texas), 15/7/20

Site frequency spectrum (SFS) is the histogram of the number of mutations represented in k out of n cells in a sample. Under a variety of population genetics models, SFS can help estimate parameters of

cell evolution such as self-renewal rate, death or differentiation rate and mutation rate. Composite SFS obtained via tumor sequencing can be very informative of the past history of tumors. There is a serious difference between SFS obtained by different sequencing processes. Bulk sequencing is usually accompanied with elaborate variant censoring ("calling") schemes which distort the intrinsic contents of SFS. Single-cell sequencing allows bypassing some of the censoring but it has its own caveats. We will explore mathematical models such as the Moran model and birth and death process as well as more complex models. Examples of SFS based on different types of tumors will be examined and discussed in the context of clinical and laboratory evidence.

Evolution-based models to control and cure metastatic cancers

Bob Gatenby (Moffitt Cancer Center, Tampa, Florida), 22/7/20

An increasing number of treatment agents and strategies have extended the lives of patients with metastatic cancer. However, evolution of resistance to systemic therapies is virtually inevitable and remains a major barrier to durable responses and long-term survival. While cancer therapy remains focused on new drug discovery, the Cancer Biology and Evolution Program at Moffitt has developed strategies to integrate evolutionary dynamics into treatment protocols using existing agents to increase the probability of control and cure.