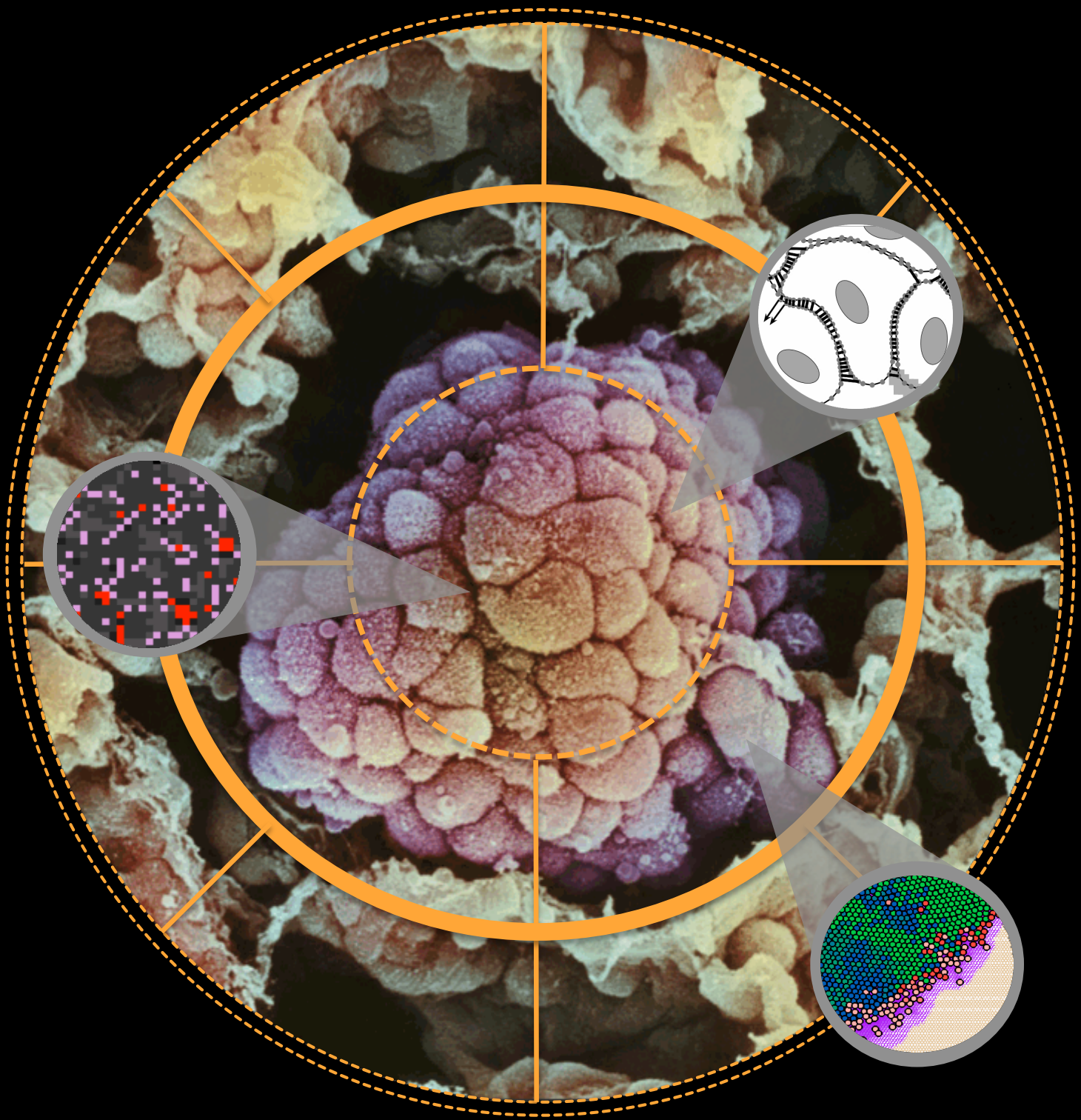
IMO WORKSHOP 1

December 5th - 9th 2011



TARGETING THERAPY

On behalf of the department of Integrated Mathematical Oncology we welcome you to the 1st annual workshop, "Targeting Therapy". The complexity of cancer requires the application of innovative tools to integrate and interrogate the data that is being produced at different biological scales both experimentally and clinically. Mathematical and computational models are an ideal tool to facilitate this integration. The theme for this 1st workshop is targeting therapy - we specifically chose targeting because this is precisely where we believe that mathematical models can facilitate better treatment. Obvious areas in which we can aid treatment are in terms of drug scheduling, dosing, combination and less obvious surgical resection, adaptive therapy, metastatic regulation and stromally directed treatments.

This workshop is designed exclusively for Moffitt, to motivate and facilitate hands-on modeling experience focused around treating four different cancers (lung, melanoma, breast and sarcoma). The workshop is comprised of both an educational event and competition. The workshop will divide into four teams (one for each cancer) integrating clinical, experimental and theoretical members that will integrate their energies to develop and implement a mathematical model focused on cancer treatment. The colour of the dot on your badge indicates the team that you have been allocated:

● Breast ● Lung ● Melanoma ● Sarcoma

The primary goals of each team are to (i) Cultivate interdisciplinary collaboration to promote the exchange of ideas and develop novel approaches to the treatment of cancer (ii) Focus on a specific treatment question (iii) Develop a mathematical/computational model to facilitate answering this question and (iv) Utilize this model in a practical manner. Critical to the success of each team and the workshop as a whole is participation, so please attend as much of the meeting as possible, the teams cannot function otherwise.

Remember this is a competition and we have four eminent judges who will view your closing presentation: William Dalton, Julie Djeu, Jack Pledger and Tom Sellers. Every active team member (as defined by the team leaders) of the winning team will receive a $100 Amazon gift voucher. Judges will be looking at several criteria, including (i) Importance of the question, (ii) Degree if integration, (iii) Degree of success, (iv) Quality of presentation.

We hope you enjoy this intense experience and learn to communicate across disciplines, provide tools and skills required to approach the complexities of cancer with broader perspectives, and create a truly integrated and collaborative environment for all out investigators involved in the study of cancer.

Good luck and happy model building!

Sandy Anderson.

AGENDA
MONDAY

45 Minutes	8:30 am – 9:15 am	Registration/Breakfast	SRB, Ferman
30 Minutes	9.15 am – 9:45 am	Welcome Remarks/Introduction	SRB, Ferman

Session I (Lung)

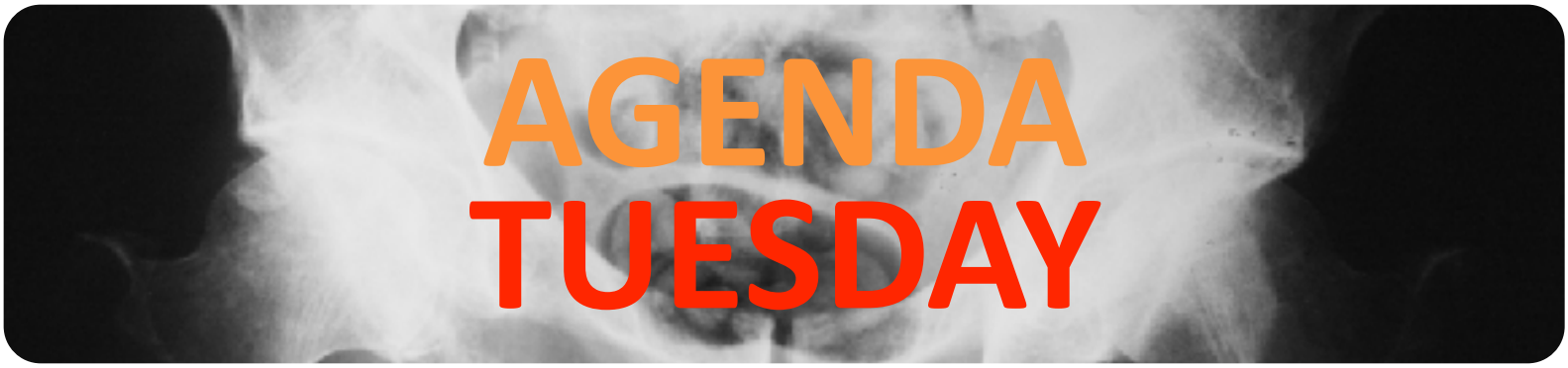
40 Minutes	9:45 am – 10:25 am	**Clinical:** Javier Torres Roca, MD	SRB, Ferman
40 Minutes	10:25 am – 11:05 am	**Experimental:** Eric B. Haura, MD	SRB, Ferman
40 Minutes	11:05 am – 11:45 pm	**Modeling:** David Basanta, Ph.D.	SRB, Ferman
	12:00 pm – 1.00 pm	**Lunch**	SRB, Atrium

Session II (Breast)

40 Minutes	1:00 pm – 1:40 pm	**Clinical:** Robert A. Gatenby, MD	SRB, Ferman
40 Minutes	1:40 pm – 2:20 pm	**Experimental:** Mark Lloyd	SRB, Ferman
40 Minutes	2:20 pm – 3:00 pm	**Modeling:** Sandy Anderson, Ph.D.	SRB, Ferman
30 Minutes	3:00 pm – 3:15 pm	**Break**	

Working Group Session I

Open	3:15 pm	Breast Team	SRB Ferman
	3:15 pm	Lung Team	SRB D. Murphey
	3:15 pm	Melanoma Team	SRB Atrium 2
	3:15 pm	Sarcoma Team	SRB Atrium 4



AGENDA
TUESDAY

30 Minutes	8:30 am – 9:15 am	Breakfast	SRB, Ferman
		Session III (Melanoma)	
40 Minutes	8:30 am – 9:10 am	**Clinical:** Vernon K. Sondak, MD	SRB, Ferman
40 Minutes	9:10 am – 9:50 am	**Experimental:** James Mulé, Ph.D.	SRB, Ferman
40 Minutes	9:50am – 10:30 am	**Modeling:** Ariosto Silva, Ph.D.	SRB, Ferman
15 Minutes	10.30 am – 10:45 am	**Break**	
		Session IV (Sarcoma)	
40 Minutes	10:45 am – 11:25 am	**Clinical:** Damon Reed, MD	SRB, Ferman
40 Minutes	11:25 am – 12:05 pm	**Experimental:** Damon Reed, MD/Dan Sullivan, MD	SRB, Ferman
40 Minutes	12:05 pm – 12:45 pm	**Modeling:** Kasia Rejniak, Ph.D.	SRB, Ferman
	12:45 pm – 1.45 pm	**Lunch**	SRB, Atrium
	1:45 pm - 5.00 pm	**Working Group Session II**	
		Breast Team	SRB Atrium 4
		Lung Team	SRB Atrium 2
		Melanoma Team	SRB D. Murphey
		Sarcoma Team	SRB Ferman
	5:00 pm - 6.30 pm	**Dinner Break**	
	6:30 pm - 9.00 pm	**Working Group Session III**	
		Breast Team	SRB Atrium 4
		Lung Team	SRB Atrium 2
		Melanoma Team	SRB D. Murphey
		Sarcoma Team	SRB Ferman

AGENDA
WEDNESDAY

45 Minutes	8:30 am – 9:15 am	**Breakfast**	Foyer
30 Minutes	9.15 am – 9:45 am	**Selected Talk I: John Koomen**	Preserve I
	9:45 am – 12:15 am	**Working Group Session IV**	
		Breast Team	Preserve I
		Lung Team	Boardroom
		Melanoma Team	Garden
		Sarcoma Team	Temple Terrace I & II
	12:15 pm – 1.30 pm	**Lunch**	
	1:30 am – 3:30 am	**Working Group Session V**	
		Breast Team	Preserve I
		Lung Team	Boardroom
		Melanoma Team	Garden
		Sarcoma Team	Temple Terrace I & II
15 Minutes	3.30 pm – 3:45 pm	**Selected Talk II: Jonathan Wojtkowiak**	Preserve I
15 Minutes	3.45 pm – 4:00 pm	**Selected Talk III: Ann Chen**	Preserve I
	4:00 pm – 6:00 pm	**Working Group Session VI**	
		Breast Team	Preserve I
		Lung Team	Boardroom
		Melanoma Team	Garden
		Sarcoma Team	Temple Terrace I & II
	6:00 pm - 7.30 pm	**Dinner Break**	
	7:30 pm - 9.00 pm	**Working Group Session VII**	
		Breast Team	Preserve I
		Lung Team	Boardroom
		Melanoma Team	Garden
		Sarcoma Team	Temple Terrace I & II

AGENDA
THURSDAY

45 Minutes	8:30 am – 9:15 am	**Breakfast**	Foyer
30 Minutes	9.15 am – 9:45 am	**Selected Talk IV: Conor Lynch**	Preserve I
	9:45 am – 12:15 am	**Working Group Session VIII**	
		Breast Team	Preserve I
		Lung Team	Boardroom
		Melanoma Team	Garden
		Sarcoma Team	Temple Terrace I & II
	12:15 pm – 1.30 pm	**Lunch**	
	1:30 am – 3:30 am	**Working Group Session IX**	
		Breast Team	Preserve I
		Lung Team	Boardroom
		Melanoma Team	Garden
		Sarcoma Team	Temple Terrace I & II
15 Minutes	3.30 pm – 3:45 pm	**Selected Talk V: Dansheng Song**	Preserve I
15 Minutes	3.45 pm – 4:00 pm	**Selected Talk VI: Tamir Epstein**	Preserve I
	4:00 pm – 6:00 pm	**Working Group Session X**	
		Breast Team	Preserve I
		Lung Team	Boardroom
		Melanoma Team	Garden
		Sarcoma Team	Temple Terrace I & II
	6:00 pm - 7.30 pm	**Dinner Break**	
	7:30 pm - 9.00 pm	**Working Group Session XI**	
		Breast Team	Preserve I
		Lung Team	Boardroom
		Melanoma Team	Garden
		Sarcoma Team	Temple Terrace I & II

45 Minutes	8:00 am – 8:45 am	Breakfast	SRB, Ferman
15 Minutes	8.45 am – 9:00 am	Introduction/Recap	SRB, Ferman
		Final Presentation to Judges	
35 Minutes	9:00 am – 9:35 am	**Lung Team Presentation**	SRB, Ferman
35 Minutes	9:35 am – 10:10 am	**Breast Team Presentation**	SRB, Ferman
35 Minutes	10:10 am – 10:45 pm	**Melanoma Team Presentation**	SRB, Ferman
35 Minutes	10:45 am – 11.20 am	**Sarcoma Team Presentation**	SRB, Ferman
	11:20 am – 11.35 am	**Break/Judge Discussion**	SRB, Ferman
	11:35 am - 12:00 pm	**Closing Remarks & Award Presentation**	SRB, Ferman
	12:00 pm – 1:30 pm	**Lunch**	SRB, Atrium

A Gene Expression Model of Tumor Intrinsic Radiosensitivity

Javier Torres-Rocca

The development of a predictive biomarker of tumor intrinsic radiosensitivity (biologically-determined) has been a central focus of radiation biology research for several decades. A predictive biomarker of radiosensitivity would have significant impact in clinical practice, potentially opening the door to biologically-based radiation dose individualization. In addition, it can lead to the identification of biological pathways associated with clinical failure after RT. In recent studies we have developed RSI (Radiosensitivity Index), a genomic-based model exclusively developed as a biomarker of radiosensitivity. RSI is based on the expression of 10 specific genes and a linear regression algorithm. Importantly, RSI has been clinically-validated in five independent datasets in four different disease sites (breast, rectum, esophagus, head and neck) in a total of 621 patients. Further, we have shown that in breast cancer, RSI is RT-specific i.e. a predictive biomarker, as it predicts outcome only in patients treated with RT. RSI represents to our knowledge the first of this type of biomarker in radiation oncology (disease site-independent and RT-specific).

LUNG
ERIC HAURA

Network models in oncogene addicted lung cancer

Jiannong Li, Guolin Zhang, Jae-Young Kim, Lanxi Song, Yun Bai, Takeshi Yoshida, Bin Fang, Steven Eschrich, Anne Chen, John Koomen, Eric Haura

Lung cancer is a devastating world wide disease yet enthusiasm exists for treatment of subsets of the disease with molecularly targeted agents. Mutations in the epidermal growth factor receptor (EGFR) or translocation of echinoderm microtubule associated protein like 4 – anaplastic lymphoma kinase (EML4-ALK) define two unique subsets of lung cancer characterized by sensitivity to tyrosine kinase inhibitors (TKI). Despite striking results with TKI, not all patients respond, the drugs are non-curative, and resistance is universal. Mutations in KRAS also define a group of patients awaiting therapeutic opportunities.

We are characterizing signaling networks using tandem affinity purification (TAP) and liquid chromatography-mass spectrometry (LC-MS/MS) to map protein-protein interactions (PPI) and anti-phosphotyrosine immunoprecipitation coupled with LC-MS/MS to map tyrosine phosphorylation. In PC9 cells with mutated EGFR, we characterized a physical EGFR network consisting of 266 proteins by integrating both TAP and pTyr MS data. In H3122 cells harboring EML4-ALK, we identified a PPI network consisting of 113 proteins and using pTyr MS identified changes in tyrosine phosphorylation in 120 proteins (58 decreased, 62 increased) following exposure to ALK tyrosine kinase inhibitor. Functional proteins are being discovered from these networks using siRNA and inhibitor screens. In KRAS mutant lung cancer, we have used SILAC and IMAC to identify global changes in phosphorylation following loss of TBK1, an essential kinase in KRAS in lung cancer cells. Using various proteomic pathway profiling approaches (SH2 domain binding, phosphotyrosine based mass spectrometry), oncogene addicted cell lines (EGFR, EML4-ALK, and KRAS), and kinase inhibition strategies (tyrosine kinase inhibitors (TKI), RNAi), we have observed proteins whose phosphorylation is elevated.

Similar events have been observed in yeast where kinase loss can result in increased levels of phosphorylation in some substrates. We interpret these results to mean that genetically determined 'system states' dynamically respond to kinase inhibitors allowing robust responses that protect cells in some cases against loss of kinases. We propose that cells with mutant oncogenes disrupt these robust mechanisms thereby preventing compensatory pathways from responding in a timely way to prevent cell death. We propose that adaptor proteins can remodel complexes in a dynamic fashion and timing of feedback loops is critical for cells response to loss of oncogenic kinases. Could adaptor proteins move across complexes and 're-purpose' existing or re-activated kinases (reactivated as a result of loss of another oncogenic kinase) as compensatory mechanisms? Could models of robustness be produced that can be tested and validated with mass spectrometry-based proteomics to examine compensatory mechanisms that explain robustness (or lack thereof) in subtypes of cancers as an explanation for 'oncogene addiction' and hypersensitivity of some cells to kinase inhibitors?

It is not just who you are: why cell interactions matter in the understanding of cancer progression

David Basanta

There is growing evidence suggesting that tumour progression is the result of Darwinian evolutionary dynamics. These dynamics result from the interactions between a heterogeneous collection of tumour cells, the stromal cells and the stroma itself. Understanding these interactions is key if we want to treat cancer and avoid the emergence of resistance. This goal will require an integrated approach combining mathematical models, biological experimentation and clinical validation. In this presentation I will discuss these aspects from the perspective of an evolutionary theoretician.

The central interest of Dr. Torres-Roca's laboratory is in the development of a systems level understanding of the biological networks that regulate radiosensitivity. We apply and integrate engineering principles and mathematical modeling along with experimental cellular and molecular biology in an effort to elucidate the topology and function of the radiosensitivity network. In collaboration with ET members (Eschrich SA and Chen DT) his group has developed a mathematical approach to integrate genomics, genotype, tissue type and biological pathway interactions to identify radiation-specific biomarkers in a large dataset of cancer cell lines. This strategy has resulted in the identification of a novel and highly redundant genetic free-scale network with 10 central nodes that we have proposed as central in the determination of radiophenotype. We applied this knowledge by developing in cell lines a gene expression linear regression model of cellular radiosensitivity based on the expression of the ten central network hubs. This model was subsequently independently validated as a predictor of response and prognosis in 621 patients in four different disease sites (breast, head and neck, rectal, esophagus), thus providing critical clinical validation for this approach. An NCI-sponsored prospective clinical trial is currently underway at Moffitt to further test the systems-based gene expression model as a predictor of clinical response in rectal and esophageal cancer patients treated with preoperative concurrent chemoradiation. A major implication of this work is that mathematical modeling of cellular systems can lead to the development of technologies that can impact the clinic. Current efforts in the laboratory are aimed at integrating experimentally quantified cellular and clonogenic heterogeneity into computer-based models of the clonogenic assay.

I am a medical oncologist with expertise and training in signal transduction pathways and experimental therapeutics. My translational research interests include signaling pathways and novel drugs that target signaling pathways in lung cancer. My lab has had long standing interest in STAT (Signal Transducer and Activators of Transcription) pathways. This includes studies examining STAT pathway activation in cells and human tumors, effects of STAT pathway inhibitors on lung cancer growth and survival, and upstream/downstream pathways of STAT proteins. Another focus of our lab is Src proteins and Src kinase inhibitors. This work includes detailed understanding of mechanism of action of Src inhibitors using chemical and phosphoproteomics, combination therapy approaches with Src inhibitors, and patient based translational studies of Src inhibitors. Our lab also has emerging interest and expertise in proteomic approaches to studying kinase signaling pathways. This includes chemical proteomics, phosphoproteomics, and mapping of protein-protein interaction networks.

Degree in Computer Science (Oviedo, Spain) and PhD in Evolutionary Computing (London, UK). Interested in the use of mathematical and computational models to understand how the interactions between different tumour cells and the tumour microenvironment explains the Darwinian dynamics behind Cancer progression towards malignancy.

The Future of Melanoma Research and Treatment

Vernon K. Sondak

Until recently, the past three to four decades have been marked by improvements in the early detection of localized melanoma and advances in the identification and management of microscopic nodal metastasis, but there has been little or no impact on survival from advanced melanoma. The median survival for patients with metastatic melanoma had been under 1 year, and was unchanged for decades. Traditional cytotoxic drugs are largely ineffective against melanoma, but anecdotal reports of spontaneous regressions and dramatic responses to immune-modulating agents resulted in many immunomodulatory strategies, particularly vaccines, being evaluated. Interleukin-2 (IL-2) and interferon-α were approved by the FDA as melanoma immunotherapies in the 1990s; both are only effective in small subsets of patients and are associated with significant toxicity. The past 2 years, however, saw a dramatic turnaround in the treatment of metastatic melanoma, with multiple phase III trials documenting significant improvements in outcome compared with conventional therapy. Recently published phase III trials involving interleukin-2, ipilimumab and vemurafenib redefine 'standard-of-care' for metastatic melanoma. All three agents are potential first-line options for patients with metastatic melanoma, with optimal treatment strategies evolving based on tumor mutation status, disease burden, performance status and comorbidities.

Key points

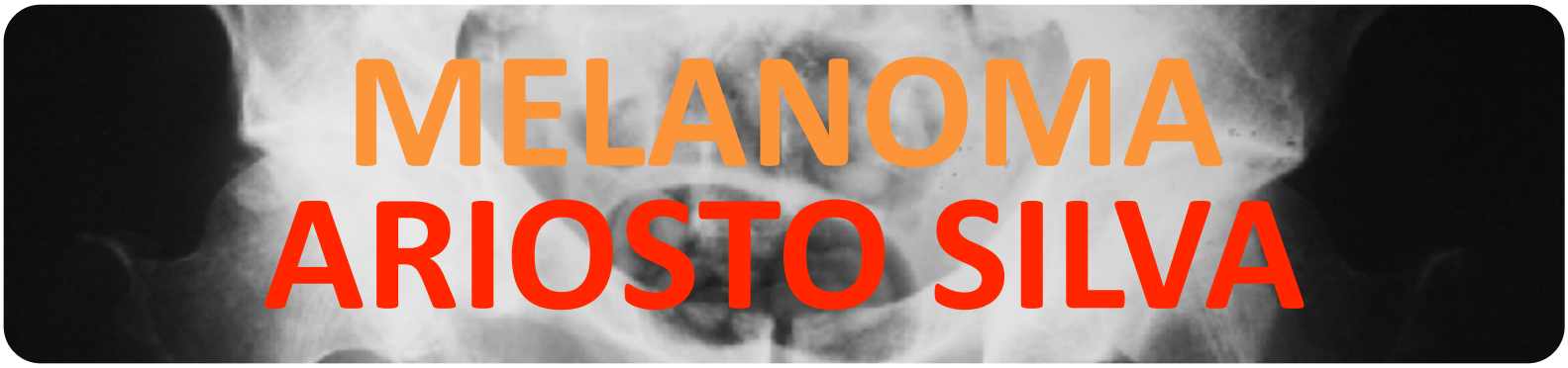
- Immunotherapy with ipilimumab or interleukin-2 is associated with low response rates, but responses are frequently of long duration
- Approximately 50% of stage IV melanomas harbor activating mutations in codon 600 of the BRAF gene; selective inhibitors of the resultant mutant BRAF protein, such as vemurafenib and dabrafenib, are associated with high response rates (50-60%) even in patients with extensive disease, but resistance emerges in most patients within months
- Even with recent advances, patients with metastatic melanoma should still be considered for participation in clinical trials

Excerpted and modified from: Sondak VK, Flaherty LE: Improved outcomes for patients with metastatic melanoma. Nature Reviews in Clinical Oncology 2011;8:513–515.

Creating ‘Designer Lymph Nodes’ for Melanoma Therapy

James Mule

The experimental platform is based on the improvement, manipulation, and stimulation of the patient’s own immune system. It uses a specialized, antigen-presenting cell (i.e. dendritic cell), produced from the patient’s blood, which is then tumor antigen-pulsed and genetically-manipulated to express highly selected chemokine (i.e. chemotactic cytokines) genes prior to injection into cancer patients. This gene-modified, tumor antigen-loaded cell “design builds” a functioning ‘lymph node’ on its own at any injection site that then produces a pre-planned immunologic response against cancer cells (depending on the antigen(s) selected) locally and then throughout the patient’s body. The technology includes the option of injecting like gene-modified cells at multiple, independent sites to create multiple, independent ‘lymph nodes’ of the same function and specificity concurrently. The injections can also be staggered to create additional new structures over time. Moreover, these structures could potentially act independently of each other, creating completely different functioning ‘lymph nodes’ in the same person by injecting pools of different gene-modified cells. The resulting benefit from these ‘designer lymph nodes’ is that they can be utilized by patients to provide an enhanced, unified or diversified immune system to fight cancer. In addition, the technology extends into the area of gene profiling and personalized medicine. A molecular chemokine gene signatures has now been identified that predicts the presence of unique, ectopic lymph node-like structures within human solid tumor masses that are associated with better patient prognosis (survival), and, importantly, are independent of tumor staging and treatment received. This molecular chemokine gene signature has not only provided gene leads for constructing ‘designer lymph nodes’ in mice but may also be used for preselecting melanoma patients for immunotherapy interventions by identifying the presence of tumor-localized, ectopic lymph node-like structures without any supervision.



Reverse Engineering Multiple Myeloma

Robert Gatenby, Zayar Khin, Ariosto Silva

We propose an innovative approach to build predictive computational models of chemotherapy response for multiple myeloma (MM) patients. The innovation of this work resides in the use of microfluidics to establish gradients to mimic the heterogeneity of the tumor microenvironment (bone marrow, BM) and detailed computational models to map the cancer cells response into the geometry of the BM.

MM is a complex hematologic malignancy, where a phenotypically heterogeneous population of malignant plasma cells proliferates uncontrollably throughout the environmentally heterogeneous microenvironment of the BM. It is known that the BM microenvironment confers opportunities for MM cells to survive treatment by soluble factors or adhesion and that these are among the main causes of minimal residual disease and patient relapse.

In this work we explore a combination of microfluidics and computational models to characterize the response of chemo-sensitive and chemoresistant human MM cell lines (HMCL) to different drug combinations and protocols in the microenvironment of the BM. First we cultured fluorescent HMCLs in microfluidics under stable gradients of chemotherapy, oxygen, glucose and pH, in single cell suspension or in co-culture with stromal cell lines. Using live imaging we quantified replication and death in two dimensions (time of exposure and drug concentration). We built cell-line specific computational models of dose response based on the extracellular cues, and integrated these models into a previously published spatial computational model of the BM. We used these models to simulate the growth and response to different drug combinations in hypothetical patients.

To our knowledge, this is the first time that a high-throughput model of assessment of drug response in a controlled reconstruction of the tumor microenvironment is proposed for MM. Our in vitro experiments allowed the quantization of cell death, quiescence and proliferation across time, which is not possible in regular dose response assays. The use of a stable drug gradient also allowed us to observe migration of live cells from areas of low to high drug concentration, being a putative mechanism for evolution of drug resistance.

The computational model built from the in vitro multi-dimensional data was capable of reproducing different levels of therapy response, ranging from complete to refractory, with a complex signature of minimum residual disease combining phenotypic and environmental resistance. Our simulations also proposed optimum regimens of drug combination which will be explored in pre-clinical models.

This proof of principle, that such approach may be used to build models of therapy in complex microenvironments with unprecedented levels of details, has the potential of becoming a translational tool for individual patient response. Each experimental assay required ~18K cells, making this approach feasible for MM patient cell aspirates.

VERN

DR SONDAK is Chair of the Department of Cutaneous Oncology and Director of Surgical Education at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida. He is also a Professor in the Departments of Oncologic Sciences and Surgery at the University of South Florida, College of Medicine. His research interests include surgical treatment of malignant melanoma in adults and children; surgical treatment of Merkel cell carcinoma and soft-tissue sarcomas, including dermatofibrosarcoma protuberans, angiosarcoma, gastrointestinal stromal tumors, and desmoid tumors; adjuvant therapy of melanoma; and evaluation of vaccine treatments for patients with localized or disseminated melanoma. Dr. Sondak has also been a leader in studies of surgical treatment of melanoma and other cutaneous malignancies, particularly in the application of sentinel lymph node biopsy to the staging of melanomas, sarcomas and non-melanoma skin cancers. He is actively involved in ongoing analyses to determine which patients with thin melanoma are most likely to benefit from sentinel node biopsy, as well as which patients with sentinel node metastases are most likely to have further metastases identified in other regional lymph nodes.

Dr Sondak is the author or coauthor of over 260 articles in peer-reviewed publications, 146 abstracts, and 8 books and 66 book chapters.

JAMES

Dr. Mulé received his post-graduate degrees from the University of Washington and the Fred Hutchinson Cancer Research Center. He then received his formal post-graduate training at the Division of Cancer Treatment, NCI, NIH, and soon became a Senior Investigator there at the Surgery Branch. Dr. Mulé took an 18-month leave as an Adjunct Visiting Professor at Dept of Surgery, Stanford University, where he also helped to launch the biotechnology companies SyStemix and Progenesys. He then moved to Michigan as the Director of the Tumor Immunology and Immunotherapy Program at the University of Michigan Cancer Center. He was also Founding Director of the Immunology Graduate Program, the Maude T. Lane Endowed Professor of Surgery, Dept of Surgery, and he was Prof in the Dept of Internal Medicine as well. Dr. Mulé is now EVP and ACD for Translational Research and the Michael McGillicuddy Endowed Chair for Melanoma Research and Treatment at Moffitt. He serves on the Board of Directors of Medicine in Need, and is a member of the Scientific/ Medical Advisory Board of Aura Biosciences; both selected as 2011 Technology Pioneers by the World Economic Forum, Davos). He currently serves on the advisory boards of several NCI-designated Cancer Centers and was a member of the NCI Director's Board of Scientific Counselors. Dr. Mulé's research group is involved in vaccine strategies and other approaches (e.g., gene therapy) to stimulate the immune system to recognize and destroy tumors. The work in these areas has helped to develop new treatments for advanced cancer patients. Dr. Mulé has published nearly 200 articles in cancer immunotherapy, and is an NCI-NIH funded investigator continuously for nearly 20 years.

ARIOSTO

Undergraduate degree of Computer Engineering (Instituto Tecnologico de Aeronautica, ITA, Sao Paulo, Brazil), after a short passage of 4 years in the Industry (Accenture, Portugal Telecom and SchlumbergerSema), received a PhD in Genetics and Molecular Biology (University of Campinas, UNICAMP, Campinas, Brazil). Ever since has studied cancer progression and evolution of drug resistance using computational models built with clinical data and microfluidics in vitro assays.

SARCOMA
DAMON REED

Modelling Metastatic behavior, Response to therapy, and Patterns of Recurrence in Sarcomas

Jiannong Li, Damon Reed

Sarcomas are mesenchymal neoplasms which can occur at many sites and at any age. They represent about 10% of pediatric cancers, 8% of adolescent and young adult cancers, and 1% of cancers in patients over 40 years of age. There are over 60 type of sarcoma and these are typically divided between soft tissue and bone sarcomas. The histologic types peak at well defined age ranges with rhabdomyosarcoma being common in young children, bone sarcomas being relatively common in adolescents and young adults, and soft tissue sarcomas being the most common in older adults.

For bone sarcomas, histologic subtype, and stage at presentation affect treatment and prognosis. Three quarters of patients present with localized disease while the remainder have metastatic disease at presentation. Treatment is often multimodal with neoadjuvant chemotherapy (VDC/IE for Ewing sarcoma, and MAP for osteosarcoma) given for 10-12 weeks. Surgery is typically required for local control and cure and radiation is used at times for Ewing sarcoma and inoperable lesions. Histologic response to neoadjuvant chemotherapy based on tumor necrosis is predictive of outcome, particularly in osteosarcoma with >90% necrosis portending a better prognosis (~80%) than tumor with responses <90% necrosis (~50% prognosis). Furthermore, location also matters with pelvic locations having an inferior prognosis in comparison to extremity primaries. Metastatic patients have poor outcomes which correlate to sites of metastasis and disease burden in both Ewing sarcoma and Osteosarcoma. There is currently no validated radiographic or chemical test to predict the behavior of these tumors. Chondrosarcoma is another form of bone sarcoma which is not responsive to chemotherapy and treated with surgical resection for cure and radiation for palliation.

For soft tissue sarcomas, which number 40-50 diagnoses, tumor grade, histologic subtype, and stage at presentation affect treatment and prognosis. Tumor grade is based on a French system which incorporates tumor necrosis at baseline, mitotic rate, and histologic subtype/degree of differentiation. We have developed a standardized clinical pathway for the treatment of many types of extremity soft tissue sarcomas. There is by no means a national standard and most institutions have wide variation of opinions of sarcoma therapy within departments. Treatment is often multimodal with surgery is typically required for local control and cure and radiation used for most high grade tumors. Low grade tumors are treated by surgical resection with radiation reserved for recurrent masses or unresectable masses. Small (<5cm), intermediate or high grade tumors are typically treated with neoadjuvant chemotherapy or radiation followed by resection. Adjuvant radiation is recommend for local control if not given before surgery, whereas there is less evidence that adjuvant chemotherapy is helpful (though is may have benefit for high grade, deep, tumors in younger individuals). Chemotherapy thus is employed in certain histologic subtypes routinely and in other subtypes reserved for tumors with metastases or a size above 5cm. Radiographic responses to chemotherapy range between subtypes though often tumor density changes with chemotherapy and varying degrees of necrosis can be seen after resection.

SARCOMA
KASIA REJNIAK

In silico Analogues of Clinical and Laboratory Experiments

Kasia Rejniak

Various in silico models that recreate and complement both 2D & 3D in vitro, as well as certain aspects of in vivo experiments and clinical data sampling will be presented, and their use application to cancer related questions discussed.

I am a pediatric oncologist with interests in improving cancer care for children and young adults with sarcoma. To this end, I work with a local foundation to create early phase trials for children with solid tumors, serve as the principal investigator for sarcoma chemotherapy trials at Moffitt, and am developing an Adolescent and Young Adult Center between Moffitt and All Children's to improve care to this population. I am interested in understanding models to help predict sarcoma behavior in terms of metastases, responses to chemotherapy, and patterns of recurrence. I believe that sarcomas may be an ideal tumor type to model as some behaviors seem very logical. I am also very aware of the difficulties in studying a rare tumor, particularly when the rare tumor has 70 subtypes.

Daniel Sullivan, MD, is the overall PI of the Southeast Phase 2 Consortium (SEP2C) and received an MD degree and MS (Biochemistry) from the University of Louisville School of Medicine, which was followed by residency training in internal medicine and a fellowship in hematology/oncology at the University of Florida. He is board certified in Internal Medicine and Medical Oncology and is currently a Senior Member of the Moffitt, and a member of Moffitt's Blood and Marrow Transplant Dept. Dr. Sullivan is the Associate Center Director and Executive Vice President for Clinical Investigations at Moffitt, serves on the Moffitt Scientific Review Committee, is the leader of the Phase I Program.

PhD in Applied Mathematics from Tulane University in New Orleans, MSc in Mathematics and Computer Science from Gdansk University in Poland. Several years of experience in biomathematical modeling in close collaboration with experimentalists.

BREAST
BOB GATENBY

Evolutionary games in cancer therapy

Robert Gatenby

A number of successful systemic therapies are available for treatment of disseminated cancers. However, tumor response to these treatments is almost invariably transient and therapy fails due to emergence of resistant populations. The latter reflects the temporal and spatial heterogeneity of the tumor microenvironment as well as the evolutionary capacity of cancer phenotypes to adapt to therapeutic perturbations. Interestingly, although cancers are highly dynamic systems, cancer therapy is typically administered according to a fixed, linear protocol. Treatment is changed only when the tumor progresses but successful tumor adaptation begins immediately upon administration of the first dose. Applying evolutionary models to cancer therapy demonstrate the potential advantage of using more dynamic, strategic approaches that focus not just on the initial cytotoxic effects of treatment but also on the evolved mechanisms of cancer cell resistance and the associated phenotypic costs. The goal of evolutionary therapy is to prevent or exploit emergence of adaptive tumor strategies. Examples of this approach include adaptive therapy and double bind therapy. The former continuously alters therapy to maintain a stable tumor volume using a persistent population of therapy-sensitive cells to suppress proliferation of resistant phenotypes. The latter uses the cytotoxic effects of an initial therapy to promote phenotypic adaptations that are then exploited using follow-on treatment.

Quantitative Evaluation of the Morphological Heterogeneity in Breast Cancer Progression

Mark Lloyd

Cancer cell heterogeneity has long been accepted to be a factor of cancer progression and resistance to therapeutic intervention. To gain quantitative insights in tumor heterogeneity, many studies have been carried out at the molecular and genetic scale. However, there is little information on tumor heterogeneity at the cellular scale, i.e., the variability of individual cells with respect to phenotypic core traits like proliferation, survival, morphology, and metabolism. While genetics and signaling networks are the basis of core traits; cell variability with respect to their ability to perform core trait functions under diverse conditions within the physical microenvironment is what may decide trends in tumor growth dynamics.

Methods:

Twelve (12) retrospectively selected lobular and ductal breast carcinoma excision samples were identified and multiple serial sections were collected. An H&E was used to diagnose the Nottingham grade, and used to computationally investigate the morphological features of cancer cells throughout each tissue. 10 additional biomarkers were stained for to interrogate molecular expression levels. Complex computer algorithms were developed to segment cancerous regions from the tumor's microenvironment and other non-malignant tissue structures. Every cancer cell was also segmented individually (~1.5-3million/sample depending on the tumor size) and 5 morphological features were extracted from each cell (nuc size, n:c, nuc intensity, cyto intensity and Haralick texture). This expansive data set was parsed and interrogated using co-variant analyses to indicate if subpopulations of cells at the leading edge of invasive cancers were morphologically identifiable.

Results:

Using a single morphological parameter was useful in identifying subpopulaitons of cells spatially related to the invasive edge of GIII breast cancer samples, which were not significantly present in GI samples. A multiparametric analysis of morphological features and molecular expression in the same sample indicated 2.6% (n=264) of the total cancer cell population within 50µm of the invasive edge of GI tumors compared to 14.7% (n=1,338) in GII and 21.7% (19,584) in GIII. This represents a GI<GII 5fold increase and GII<GIII 15fold increase in identifiable subpopulations of aggressive cells.

Conclusions:

If cells can be identified as potentially aggressive in early stages of breast cancer (DCIS) then it may be possible to use H&Es and simple IHC stains in combination with computational feature analysis algorithms to predict which patients are most likely to progress or respond to specific therapy options. varying degrees of necrosis can be seen after resection.

How Do Interactions Modulate Heterogeneity In Cancer Progression and Drug Resistance?

Sandy Anderson

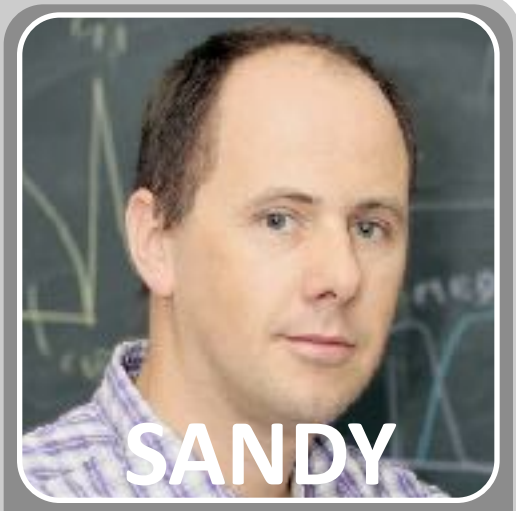
Heterogeneity in cancer is an observed fact, both genetically and phenotypically. Cell-cell variation is seen in almost all aspects of cancer from early development all the way through to invasion and subsequent metastasis. Our current understanding of this heterogeneity has mainly focussed at the genetic scale with little information on how this variation translates to actual changes in cell phenotypic behavior. Given that many genotypes can lead to the same cellular phenotype, it is important that we quantify the range and scope of this heterogeneity at the phenotypic scale as ultimately this variability will dictate the aggressiveness of the tumor and its treatability. Central to our understanding of this heterogeneity is how the tumor cells interact with each other and with their microenvironment. Cell behavior can be described in terms of phenotypic traits e.g. proliferation, apoptosis and migration rates. Given that these traits are varying across a heterogeneous tumor population a useful way to represent them is in terms of distributions e.g. a distribution of proliferation rates. The manner that traits are passed on as cells divide and compete for space and resources obviously affects how the subpopulations grow, within the tumor, relative to one another. We will discuss how different inheritance schemes give rise to populations with new phenotypic trait distributions and the role that the microenvironment plays in their modulation. Using an integrated experimental/theoretical approach we will investigate how these subpopulations can drive cancer initiation, progression and treatment resistance.

BOB

Robert A. Gatenby, MD is the Chairman of the departments of Radiology and co-director of the Integrated Mathematical Oncology at H. Lee Moffitt Cancer Center. He joined Moffitt in 2008 from the University of Arizona where he was Professor, Department Radiology and Professor, Department of Applied Mathematics since 2000. He received a B.S.E. in Bioengineering and Mechanical Sciences from Princeton University and an M.D. from the University of Pennsylvania in 1977. He completed his residency in radiology at the University of Pennsylvania where he served as chief resident. Bob remains an active clinical radiologist specializing in body imaging. While working at the Fox Chase Cancer Center after residency, Bob perceived that cancer biology and oncology were awash in data but lacked coherent frameworks of understanding to organize this information and integrate new results. Since 1990, most of Bob's research has focused on exploring mathematical methods to generate theoretical models for cancer biology and oncology. His current modeling interests include: 1. Tumor microenvironment and its role in tumor biology. 2. Evolutionary dynamics in carcinogenesis, tumor progression and therapy. 3. Information flow in living systems and its role in maintaining thermodynamic stability.

MARK

Mark Lloyd has been employed by the Moffitt Cancer Center for over 8 years and has served the last 5 years as staff scientist and supervisor of the Analytic Microscopy Core facility. He has over 10 years of advanced microscopy experience and training, and is co-author on multiple publications regarding digital pathology and advanced image analysis techniques. He participates on a national level in a leadership role within the Digital Pathology Association as a Selection Program Member, and represents Moffitt's digital pathology initiative as platform presenter at several annual professional meetings. Mark's past research interests are funded to investigate progression of breast cancer using morphological and immunohistochemical single cell segmentation and feature analysis of human histology samples. His current research builds on the foundation of digital images and feature analysis to investigate our specific hypothesis that single cell features will distinguish subpopulations of cells, both in the tumor and the PME, which will correlate with clues of somatic evolution including phenotypic variation, heritable changes and niche partitioning and parameterization. This novel approach has the potential to link the observation of tumor progression with its underlying evolutionary explanation. Furthermore, it is an opportunity to evaluate the translation of multiparametric feature analysis to the pathologist's toolbox, which could directly affect precision medicine.



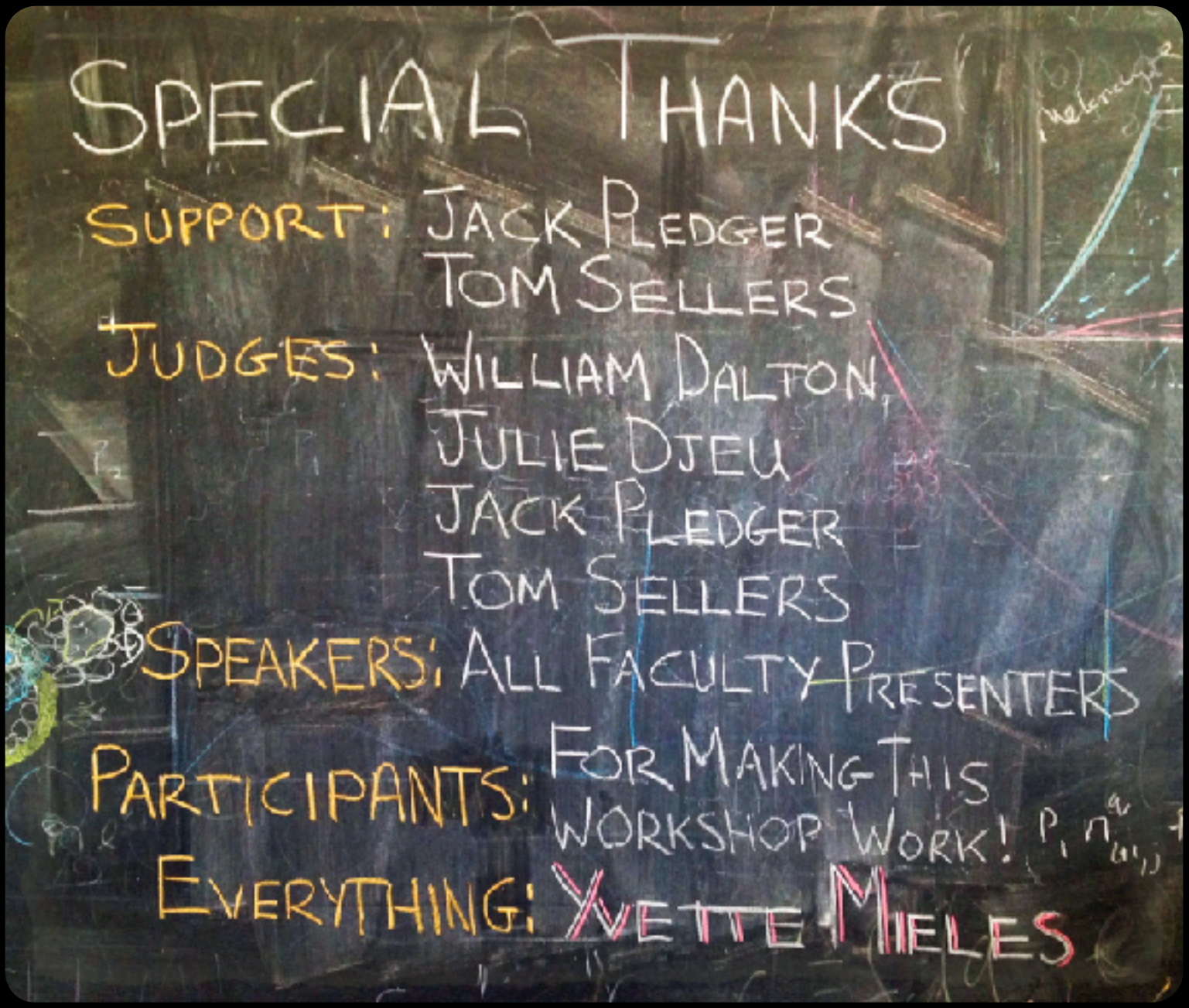
SANDY

Alexander R. A. Anderson, Ph.D. is Co-Director of Integrated Mathematical Oncology (IMO). His lab is focused on developing organ specific models of tumor initiation and progression that examine the key role of the microenvironment as a selective force in the growth and evolution of cancer. A common theme of these organ specific models is the importance of understanding normal organ form and function particularly in relation to homeostasis. During the last seven years he has closely collaborated with biologists to develop truly integrated models, this has both changed the way biologists do experiments but also the way in which models are developed. Building models that can generate testable hypothesis and utilizing experimental data to parameterize them is a key component of his research.

Dr. Anderson performed his doctoral work on hybrid mathematical models of nematode movement in heterogeneous environments at the Scottish Crop Research Institute in Dundee, UK. His postdoctoral work was on hybrid models of tumor-induced angiogenesis with Prof. Mark Chaplain at Bath University, UK. He moved back to Dundee in 1996 where he worked for the next 12 years on developing mathematical models of many different aspects of tumor progression and treatment, including anti-angiogenesis, radiotherapy, tumor invasion, evolution of aggressive phenotypes and the role of the microenvironment. He is widely recognized as one of only a handful of mathematical oncologists that develop truly integrative models that directly impact biological experimentation.

IMO WORKSHOP 1

December 5th - 9th 2011



TARGETING THERAPY