PS-OC Program Quarterly Publication Highlights: September 2014

Broken nuclei – lamins, nuclear mechanics, and disease. Davidson PM, Lammerding J. *Trends Cell Biol* 2014. **24(4):** 247-256.
This review provides a comprehensive overview of the role of nuclear mechanics, i.e., stiffness and stability, in a variety of crucial cellular functions, and how mutations or altered expression of nuclear envelope proteins such as lamins, emerin, and nesprin can contribute to the devastating phenotypes of various human diseases, including cancer.

Nuclear deformability constitutes a rate-limiting step during cell migration in 3-D environments. Davidson PM, Denais C, Bakshi MC, Lammerding J. *Cell Mol Bioeng* 2014. **7(3):** 293-306.
In this publication, Davidson et al. demonstrate the deformability of the cell nucleus can limit the ability of cells to migrate through narrow constrictions and that cells with reduced levels of the nuclear envelope proteins lamin A/C, which have more deformable nuclei, are able to pass faster through constrictions smaller than the size of the nucleus. These findings are highly relevant for the 3-D migration and perfusion behavior of cells with altered nuclear envelope composition, as seen in many cancer cells and neutrophils.

How multi-organ microdevices can help foster drug development. Esch MB, Smith AS, Prot JM, Oleaga C, Hickman JJ, Shuler ML. *Ad. Drug Deliv Rev* 2014. **69-70:** 158-169.
We review studies in which multi-organ microdevices have been developed and used in ways that demonstrate how the devices' capabilities can present unique opportunities for the study of drug action.

An adaptive algorithm for tracking 3D bead displacements: application in biological experiments. Feng X, Hall MS, Wu M, Hui C. *Meas Sci Technol* 2014. **25**.
This is a technical paper in which we developed a particle tracking algorithm for the development of a 3D traction microscope to measure traction force of single migrating cells in 3D.

NAD(+) and SIRT3 control microtubule dynamics and reduce susceptibility to antimicrotubule agents. Harkcom WT, Ghosh AK, Sung MS, Matov A, Brown KD, Giannakakou P, Jaffrey SR. *Proc Natl Acad Sci U S A* 2014. **111(24):** E2443-E2452.
Role of NAD and SIRT2 in the modulation of microtubule dynamics with implications for their response to microtubule agents.

Glioblastoma stem cells are regulated by interleukin-8 signaling in a tumoral perivascular niche. Infanger DW, Cho Y, Lopez BS, Mohanan S, Liu SC, Gursel D, Boockvar JA, Fischbach C. *Cancer Res* 2013. **73(23):** 7079-7089.
Glioblastoma multiforme (GBM) contains a subpopulation of cancer stem-like cells (CSCs) whose malignant behavior is closely linked to interactions with the vasculature. This study utilized a tissue-engineered model system to demonstrate that vascular assembly induces CSC maintenance and growth in vitro and accelerates tumor growth in vivo through paracrine IL-8 signaling.

RABbing cancer the wrong way. Khade PK, Giannakakou P. *Proc Natl Acad Sci U S A* 2014. **111(31):** 11230-11231.
Role of hypoxia and tumor metastasis in breast cancer via RAB mediated micro vesicle release.

Review: R28 retinal precursor cells: The first 20 years. Seigel GM. *Mol Vis* 2014. **20:** 301-306.

Retinal precursor cells have played an important role in retinal cell biology. This is a review of the work involving the R28 retinal precursor cell line over the past 20 years.

In vitro models of tumor vessels and matrix: Engineering approaches to investigate transport limitations and drug delivery in cancer. Seo BR, DelNero P, Fischbach C. *Adv Drug Deliv Rev* 2014. **69:** 205-216.
Tumor-stroma interactions have emerged as critical determinants of drug efficacy; however, the biological and physicochemical mechanisms by which the microenvironment regulates therapeutic response remain unclear. This article reviews engineering approaches to study drug delivery as a function of tumor-associated changes of the vasculature and extracellular matrix and highlights challenges and future directions of the field that may ultimately improve anti-cancer therapies.

Androgen receptor splice variants determine taxane sensitivity in prostate cancer. Thadani-Mulero M, Portella L, Sun S, Sung M, Matov A, Vessella RL, Corey E, Nanus DM, Plymate SR, Giannakakou P. *Cancer Res* 2014. **74(8):** 2270-2282.
We report that two clinically relevant androgen receptor splice variants, ARv567 and ARv7, differentially associate with microtubules and dynein motor protein, thereby resulting in differential taxane sensitivity in vitro and in vivo. Androgen receptor variants that accumulate in CRPC cells utilize distinct pathways of nuclear import that affect the antitumor efficacy of taxanes, suggesting a mechanistic rationale to customize treatments for patients with CRPC, which might improve outcomes.

Understanding drug resistance in breast cancer with mathematical oncology. Brocato T, Dogra P, Koay EJ, Day A, Chuang YL, Wang Z, Cristini V. *Curr Breast Cancer Rep* 2014. **6(2):** 110-120.
An integrated approach of mathematical modeling and experimental investigation has been widely used to understand drug resistance mechanisms, predict chemotherapy efficacy, and identify novel treatment approaches. This paper reviews recent modeling work for understanding cancer drug resistance through the use of computer simulations of molecular signaling networks and cancerous tissues, with a particular focus on breast cancer.

Simulating cancer growth with multiscale agent-based modeling. Wang Z, Butner JD, Kerketta R, Cristini V, Deisboeck TS. *Semin Cancer Biol* 2014. ePub ahead of print.
Agent-based modeling has become a powerful modeling method widely used by computational cancer researchers. This paper introduces some of the most recent agent-based models that have provided insight into the understanding of cancer growth and invasion, spanning multiple biological scales in time and space.

The effect of interstitial pressure on therapeutic agent transport: coupling with the tumor blood and lymphatic vascular systems. Wu M, Frieboes HB, Chaplain MA, McDougall SR, Cristini V, Lowengrub JS. *J Theor Biol* 2014. **355:** 194-207.
We apply our recently developed vascular tumor growth model which couples a continuous growth component with a discrete angiogenesis model to study the hydrodynamic effects of fluid flow within the tumor interstitium on the transport of small molecules.

Transport properties of pancreatic cancer describe gemcitabine delivery and response. Koay EJ, Truty MJ, Cristini V, Thomas RM, Chen R, Chatterjee D, Kang Y, Bhosale PR, Tamm EP, Crane CH, Javle M, Katz MH, Gottumukkala VN, Rozner MA, Shen H, Lee JE, Wang H, Chen Y, Plunkett W, Abbruzzese JL, Wolff RA, Varadhachary GR, Ferrari M, Fleming JB. *J Clin Invest* 2014. **124(4):** 1525-1536.
This paper demonstrates how mass transport properties of human pancreatic cancer can be derived from routine imaging, and the findings support the Transport Oncophysics view that multi-scale transport

phenomena are critical to fully describing drug delivery. Furthermore, these transport properties correlate with multiple clinically-relevant endpoints including overall survival, indicating that these measurements of transport may eventually be used as biomarkers to guide treatment and improve outcomes for patients with this deadly disease.

Capillary-wall collagen as a biophysical marker of nanotherapeutic permeability into the tumor microenvironment. Yokoi K, Kojic M, Milosevic M, Tanei T, Ferrari M, Ziemys A. *Cancer Res* 2014. **74(16):** 4239-4246.
Collagen in the capillary wall is the major biological barrier for nanotherapeutics injected intra-venously to enter tumor tissue. Using computational model and in vivo experiments, we found a direct correlation between the collagen content around tumor vessels with the vascular permeability to liposomes, providing deeper view regarding the balance between biological and physical aspects of drug delivery.

Serum biomarkers for personalization of nanotherapeutics-based therapy in different tumor and organ microenvironments. Yokoi K, Tanei T, Godin B, van de Ven AL, Hanibuchi M, Matsunoki A, Alexander J, Ferrari M. *Cancer Lett* 2014. **345(1):** 48-55.
Surrogate biomarkers for the EPR effect will aid in selecting patients who will accumulate higher amounts of nanotherapeutics and show better therapeutic efficacy. Our data suggest that the differences in the vascularpermeability and pegylated liposomal doxorubicin (PLD) accumulation are tumor type as well as organ-specific and significantly correlated with the relative ratio of MMP-9 to TIMP-1 in the circulation, supporting development of these molecules as biomarkers for the personalization of nanoparticle-based therapy.

Bone marrow endothelium-targeted therapeutics for metastatic breast cancer. Mai J, Huang Y, Mu C, Zhang G, Xu R, Guo X, Xia X, Volk DE, Lokesh GL, Thiviyanathan V, Gorenstein DG, Liu X, Ferrari M, Shen H. *J Control Release* 2014. **187:** 22-29.
Bone is a major organ for breast cancer metastasis. There is currently no effective treatment for breast cancer bone metastasis due to lack of effective drug accumulation in the bone marrow. An innovative approach was described in this study to enrich cancer therapeutics to the tumor-bearing bone marrow taking advantage of differential expression pattern of the bone marrow endothelia between normal and disease tissues.

Multifunctional gold nanorods for siRNA gene silencing and photothermal therapy. Shen J, Kim HC, Mu C, Gentile E, Mai J, Wolfram J, Ji LN, Ferrari M, Mao ZW, Shen H. *Adv Healthc Mater* 2014. ePub ahead of print.
A layer-by-layer assembly approach was applied to synthesize polyethylenimine on the surface of gold nanorods for effective siRNA delivery. The resulting gold nanorods possess a high siRNA-binding capacity while retaining thermal ablation capability. Thus, cancer cells can be effectively killed by suppression of key gene expression from siRNA in combination with near infrared-triggered heat generation from nanorods.

Polyarginine induces an antitumor immune response through binding to toll-like receptor 4. Yang Y, Wolfram J, Fang X, Shen H, Ferrari M. *Small* 2014. **10(7):** 1250-1254.
A new mechanism for polyarginine on anti-tumor immunity was described in this study. Polyarginine binds to toll-like receptor 4 and activates down-stream signaling. Subcutaneous administration of polyarginine effectively inhibited tumor growth in a murine model of melanoma.

Scaling behaviour for the water transport in nanoconfined geometries. Chiavazzo E, Fasano M, Asinari P, Decuzzi P. *Nat Commun* 2014. **5:** 4565.
The coefficient of water diffusion D in confined geometries (meso/nano-pores, around nanoparticles and molecules) is found to scale linearly with a sole parameter ϑ, which is primarily influenced by geometry and represents the ratio between the confined and total water volumes Through the parameter ϑ, D can be expressed directly as a linear function of DB and DC, being the bulk and totally confined diffusion of water, respectively.

Lipid-polymer nanoparticles encapsulating curcumin for modulating the vascular deposition of breast cancer cells. Palange AL, Di Mascolo D, Carallo C, Gnasso A, Decuzzi P. *Nanomedicine* 2014. **10(5):** 991-1002.
The delivery of nanoparticles (NANOCurc) encapsulating moderate amounts of curcumin – a natural anti-inflammatory molecule – towards inflamed endothelial cells can reduce the vascular adhesion of circulating tumor cells by ~70%. This suggests that NANOCurc could be used to modulate and prevent metastasis formation.

Vascular deposition patterns for nanoparticles in an inflamed patient-specific arterial tree. Hossain SS, Hughes TJ, Decuzzi P. *Biomech Model Mechanobiol* 2014. **13(3):** 585-597.
Computational modeling of the vascular transport and adhesion of nanoparticles (NPs) is employed to demonstrate that uniform vascular distribution of NPs can be achieved by encaging simultaneously two or more targeting moieties (multivalent vascular targeting).

Quantifying uncertainties in the microvascular transport of nanoparticles. Lee TR, Greene MS, Jiang Z, Kopacz AM, Decuzzi P, Chen W, Liu WK. *Biomech Model Mechanobiol* 2014. **(3):** 515-526.
A computational method that considers uncertainty in the blood vessel diameter is developed to predict nanoparticle transport and distribution characteristics in the microvasculature. The results show that nanoparticle transport is highly sensitive to microvasculature geometrical features such as blood vessel size.

Red blood cell tracking using optical flow methods. Guo D, van de Ven AL, Zhou X. *IEEE J Biomed Health Inform* 2014. **18(3)**: 991-998.
Optical flow method uses Intravital Microscopy to track red blood cell microcirculation information, such as flow velocity and vessel density, in order to monitor human conditions and develop effective therapies of certain diseases.

Employing ProteoWizard to Convert Raw Mass Spectrometry Data. Holman JD, Tabb DL, Mallick P. *Curr Protoc Bioinformatics* 2014. **46:** 13.24. 1-9.
LC-MS/MS instruments collect data into binary files that are not easily read or manipulated. Here we describe the use of ProteoWizard to enable easy translation of these raw data to a variety of formats.

MYC through miR-17-92 suppresses specific target genes to maintain survival, autonomous proliferation and a neoplastic state. Li Y, Choi PS, Casey SC, Dill DL, Felsher DW. *Cancer Cell* 2014. **26(2):** 262-272.
We find that MYC, through the expression of miR-17-92, suppresses specific target genes to maintain a neoplastic state. This finding provides mechanistic explanations to the phenomena of MYC oncogene addiction.

Addiction to multiple oncogenes can be exploited to prevent the emergence of therapeutic resistance. Choi PS, Li Y, Felsher DW. *Proc Natl Acad Sci U S A* 2014. **111(32):** E3316-E3324.

We demonstrate that combined inhibition of both MYC and beta-catenin oncogene addiction pathways results in sustained lymphoma regression. Our results suggest clinical outcomes can be dramatically improved through the simultaneous inhibition of multiple oncogenic addiction pathways.

Cyclin-dependent kinases regulate lysosomal degradation of hypoxia-inducible factor 1α to promote cell-cycle progression. Hubbi ME, Gilkes DM, Hu H, Shitiz K, Ahmed I, Semenza GL. *Proc Natl Acad Sci U S A* 2014. **111(32):** E3325-3334.
Hypoxia-inducible factor 1 (HIF-1) is a transcription factor that mediates adaptive responses to oxygen deprivation. Here we report that HIF-1α physically and functionally interacts with cyclin-dependent kinase 1 (Cdk1) and Cdk2.

Harnessing developmental processes for vascular engineering and regeneration. Park KM, Gerecht S. *Development* 2014. **141(14):** 2760-2769.
The formation of vasculature is essential for tissue maintenance and regeneration. In this Review, we will discuss how the process of vascular development can be used to guide approaches to engineering vasculature, specifically on some of the recently reported approaches to stimulate therapeutic angiogenesis.

Bioengineering paradigms for cell migration in confined microenvironments. Stroka KM, Gu Z, Sun SX, Konstantopoulos K. *Curr Opin Cell Biol* 2014. **30C:** 41-50.
A better understanding of cell migration requires a multi-disciplinary approach through integration of in vivo and in vitro studies, along with sophisticated bioengineering techniques and mathematical modeling. Here, we highlight such an approach that has led to discovery of a new model for cell migration in confined microenvironments (i.e., the Osmotic Engine Model).

Hydrogels to model 3D in vitro microenvironment of tumor vascularization. Song HH, Park KM, Gerecht S. *Adv Drug Deliv Rev* 2014. ePub ahead of print.
In this review, we explore current use of hydrogels and their design parameters to engineer vasculogenesis and angiogenesis and to evaluate the angiogenic capability of cancerous cells and tissues. By coupling these hydrogels with other technologies such as lithography and three-dimensional printing, one can create an advanced microvessel model as microfluidic channels to more accurately capture the native angiogenesis process.

Mechanochemical regulation of oscillatory follicle cell dynamics in the developing Drosophila egg chamber. Koride S, He L, Xiong LP, Lan G, Montell DJ, Sun SX. *Mol Biol Cell* 2014. ePub ahead of print.
During tissue elongation from stage 9 to stage 10 in Drosophila oogenesis, the egg chamber increases in length by ~1.7 fold while increasing in volume by eightfold. Here, we use a combination of quantitative modeling and experimental perturbation to show that mechanochemical interactions are sufficient to generate oscillations of myosin contractile activity in the observed spatiotemporal pattern. We propose that follicle cells in the epithelial layer contract against pressure in the expanding egg chamber.

Defining differences among perivascular cells derived from human pluripotent stem cells. Wanjare M, Kusuma S, Gerecht S. *Stem Cell Reports* 2014. **2(5):** 561-575.
Distinguishing between perivascular cell types remains a hurdle in vascular biology due to overlapping marker expressions and similar functionalities. Using in vitro cultures, we show unique cell morphology, subcellular organelle organization (namely endoplasmic reticulum, mitochondria, and stress fibers), and expression of smooth muscle myosin heavy chain and elastin for each cell type.

Hypoxia-inducible hydrogels. Park KM, Gerecht S. *Nat Commun* 2014. **5:** 4075.
Oxygen acts as a signalling molecule regulating cellular activities, while hypoxia, which occurs when the partial pressure of oxygen falls below 5%, plays a pivotal role during development, regeneration and cancer. Here we report a novel hypoxia-inducible (HI) hydrogel composed of gelatin and ferulic acid that can form hydrogel networks via oxygen consumption in a laccase-mediated reaction.

Hypoxia and the extracellular matrix: drivers of tumour metastasis. Gilkes DM, Semenza GL, Wirtz D. *Nat Rev Cancer* 2014. **14(6):** 430-439.
Emerging data indicate that hypoxia and the extracellular matrix (ECM) might have crucial roles in metastasis. Originally thought of as independent contributors to metastatic spread, recent studies have established a direct link between hypoxia and the composition and the organization of the ECM, which suggests a new model in which multiple microenvironmental signals might converge to synergistically influence metastatic outcome.

Hyaluronic acid hydrogel stiffness and oxygen tension affect cancer cell fate and endothelial sprouting. Shen YI, Abaci HE, Krupsi Y, Weng LC, Burdick JA, Gerecht S. *Biomater Sci* 2014. **2(5):** 655-665.
Three-dimensional (3D) tissue culture models may recapitulate aspects of the tumorigenic microenvironment in vivo, enabling the study of cancer progression in vitro. Both hypoxia and matrix stiffness are known to regulate tumor growth. We observed that increased matrix stiffness reduced endothelial sprouting and invasion in atmospheric conditions; however, we observed increased endothelial sprouting and invasion under hypoxia at all levels of matrix stiffness with the upregulation of vascular endothelial growth factor (VEGF) and angiopoeitin-1 (ANG-1).

Water permeation drives tumor cell migration in confined microenvironments. Stroka KM, Jiang H, Chen SH, Tong Z, Wirtz D, Sun SX, Konstantopoulos K. *Cell* 2014. **157(3):** 611-623.
Here, we present an integrated experimental and theoretical approach ("Osmotic Engine Model") and demonstrate that directed water permeation is a major mechanism of cell migration in confined microenvironments. Using microfluidic and imaging techniques along with mathematical modeling, we show that tumor cells confined in a narrow channel establish a polarized distribution of Na+/H+ pumps and aquaporins in the cell membrane, which creates a net inflow of water and ions at the cell leading edge and a net outflow of water and ions at the trailing edge, leading to net cell displacement.

Local mechanical response of cells to the controlled rotation of magnetic nanorods. Castillo M, Ebensperger R, Wirtz D, Walczak M, Hurtado DE, Celedon A. *J Biomed Mater Res B Appl Biomater* 2014. ePub ahead of print.
The mechanical response of the cytoplasm was investigated by the intracellular implantation of magnetic nanorods and exposure to low-frequency rotatory magnetic fields. Our results demonstrate that nanorods under magnetic fields are an effective tool to mechanically probe the intracellular environment. We envision that our findings may contribute to the noninvasive and direct mechanical characterization of the cytoplasm.

Tight coupling between nucleus and cell migration through the perinuclear actin cap. Kim DH, Cho S, Wirtz D. *J Cell Sci* 2014. **127(Pt 11):** 2528-2541.
Although eukaryotic cells are known to alternate between 'advancing' episodes of fast and persistent movement and 'hesitation' episodes of low speed and low persistence, the molecular mechanism that controls the dynamic changes in morphology, speed and persistence of eukaryotic migratory cells remains unclear. Here, we show that the movement of the interphase nucleus during random cell migration switches intermittently between two distinct modes - rotation and translocation - that follow

with high fidelity the sequential rounded and elongated morphologies of the nucleus and cell body, respectively.

Low oxygen tension enhances endothelial fate of human pluripotent stem cells. Kusuma S, Peijnenburg E, Patel P, Gerecht S. *Arterioscler Thromb Vasc Biol* 2014. **34(4):** 913-920.
We used a feeder-free, 2-dimensional differentiation system in which we could monitor accurately dissolved oxygen levels during human pluripotent stem cell differentiation toward early vascular cells (EVCs). Low oxygen tension during early stages of EVC derivation induces endothelial commitment and maturation through the accumulation of reactive oxygen species, highlighting the importance of regulating oxygen tensions during human pluripotent stem cell-vascular differentiation.

Dynamic transcription factor activity profiles reveal key regulatory interactions during megakaryocytic and erythroid differentiation. Duncan MT, Shin S, Wu JJ, Mays Z, Weng S, Bagheri N, Miller WM, Shea LD. *Biotechnol Bioeng* 2014. **111(10):** 2082-2094.
The directed differentiation toward erythroid (E) or megakaryocytic (MK) lineages by the MK-E progenitor (MEP) could enhance the ex vivo generation of red blood cells and platelets for therapeutic transfusions.

α-Catenin is an inhibitor of transcription. Daugherty RL, Serebryannyy L, Yemelyanov A, Flozak AS, Yu HJ, Kosak ST, deLanerolle P, Gottardi CJ. *Proc Natl Acad Sci U S A* 2014. **111(14):** 5260-5265.
We demonstrate that α-catenin limits expression of both β-catenin/TCF-dependent and -independent promoters in a manner that depends on both dimerization and actin-binding regions ofα-catenin.

Single cell nucleosome mapping reveals the molecular basis of gene expression heterogeneity. Small EC, Xi L, Wang JP, Widom J, Licht JD. *Proc Natl Acad Sci USA* 2014. **111(24):** E2462–E2471.
Nucleosomes limit access to DNA, which antagonizes gene expression and prevents recruitment of transcription factors that cannot bind DNA wrapped around the histone octamer. Numerous studies using large cell populations determined that active genes promoters tend to be nucleosome-depleted. We developed a method to examine nucleosome positioning in single cells and revealed significant heterogeneity of nucleosome configurations within a population.

Molecular Pathways: Deregulation of Histone 3 Lysine 27 Methylation in Cancer-Different Paths, Same Destination. Ezponda T, Licht JD. *Clin Cancer Res* 2014. ePub ahead of print.
The significance of mutations altering H3K27me is underscored by the fact that many tumors harboring such lesions often have a poor clinical outcome. Understanding the biological consequences and gene expression pathways affected by aberrant H3K27 methylation may also lead to other new therapeutic strategies.

Nodal signaling promotes a tumorigenic phenotype in human breast cancer. Kirsammer G, Strizzi L, Margaryan NV, Gilgur A, Hyser M, Atkinson J, Kirschmann DA, Seftor EA, Hendrix MJ. *Semin Cancer Biol* 2014. ePub ahead of print.
We have previously shown that a secreted TGF-β family signaling ligand, Nodal, is expressed in breast cancer in correlation with disease progression. Here we highlight key findings demonstrating that Nodal is required in aggressive human breast cancer cells to activate ERK signaling and downstream tumorigenic phenotypes both in vitro and in vivo.

Vascular measurements correlate with estrogen receptor status. Lloyd MC, Alfarouk KO, Verduzco D, Bui MM, Gillies RJ, Ibrahim ME, Brown JS, Gatenby. *RABMC Cancer* 2014 **14:** 279.

We conclude that ER expression can be understood as a Darwinian process and linked to variations in estrogen delivery by temporal and spatial heterogeneity in blood flow. This correlation suggests strategies to promote intratumoral blood flow or a cyclic introduction of estrogen in the treatment schedule could be explored as a counter-intuitive approach to increase the efficacy of anti-estrogen drugs.

Invasion and proliferation kinetics in enhancing gliomas predict IDH1 mutation status. Baldock AL, Yagle K, Born DE, Ahn S, Trister AD, Neal M, Johnston SK, Bridge CA, Basanta D, Scott J, Malone H, Sonabend AM, Canoll P, Mrugala MM, Rockhill JK, Rockne RC, Swanson KR. *Neuro Oncol* 2014. **16(6):** 779-786.
The strong correlation between IDH1 mutation status and the MRI-based invasion profile suggests that use of our tumor growth model may lead to noninvasive clinical detection of IDH1 mutation status and thus lead to better treatment planning, particularly prior to surgical resection, for contrast-enhancing gliomas.

Separation of metabolic supply and demand: aerobic glycolysis as a normal physiological response to fluctuating energetic demands in the membrane. Epstein T, Xu L, Gillies RJ, Gatenby RA. *Cancer Metab* 2014. **2:** 7.
Normal and cancer cells derive energy (ATP) from glucose metabolism. By far, the greatest amount of ATP is obtained when cells are metabolized with oxygen (oxidative phosphorylation). However, glucose can also be metabolized without oxygen (glycolysis) but the efficiency is low (2ATP/glucose compared to 36ATP/glucose for oxidative metabolism). For over 100 years biologists have assumed that oxygen controls the method of glucose metabolism so that oxidative phsophorylation is the default metabolism and glycolysis is an emergency back-up to be used only when oxygen is depleted. About 80 years ago Warburg noticed that cancer cells use glycolysis even when oxygen is present (the "Warburg effect") – a puzzle that remains unexplained but is generally assumed to be caused by some metabolic defect in cancer cells. We find that glucose metabolism without oxygen actually plays a crucial role for cell function even in normal conditions because it can very quickly supply the energy necessary to deal with sudden spikes in demand, particularly in the membrane. We propose that the "Warburg effect" is actually due to increased fluctuations of energy demand in the membrane that results from typical cancer cell functions such as invasion and proliferation.

Gene therapy enhances chemotherapy tolerance and efficacy in glioblastoma patients. Adair JE, Johnston SK, Mrugala MM, Beard BC, Guyman LA, Baldock AL, Bridge CA, Hawkins-Daarud A, Gori JL, Born DE, Gonzalez-Cuyar LF, Silbergeld DL, Rockne RC, Storer BE, Rockhill JK, Swanson KR, Kiem HP. *J Clin Invest* 2014. Epub ahead of print.
The current manuscript uniquely combines patient-specific bio-mathematical models with a novel Phase I/II clinical trial for hematopoietic stem cell gene therapy in poor prognosis glioblastomas. Specifically, this article documents the first application of patient-specific precision biomathematical modeling to analyze therapeutic benefit comparing model-predicted tumor growth with actual tumor measurements in poor-prognosis brain tumor patients who received temozolomide chemotherapy combined with the chemotherapy sensitizer, O^6-benzylguanine (O6BG) in the setting of hematopoietic stem cell gene therapy to protect from severe myelosuppression. While providing compelling supporting evidence for treatment efficacy in this particular low N early phase clinical trial, we believe that this manuscript also illustrates a broader and potentially field-defining development of new tools for early identification of treatment efficacy that would not be amenable using routine statistical analysis. There are two major ways of assessing therapeutic benefit in clinical trials: 1) comparison of progression-free and overall survival curves between treatment and control arms, if available, and 2) analyzing

(imageable) response metrics as predictors of therapeutic benefit. Both of these approaches are challenging in most early phase clinical trials of glioma. First, typical early phase, low N studies are very challenged in their ability to assess statistical differences between historic survival curves and those of the study as they are typically underpowered for such analysis. Second, this challenge is particularly compounded in gliomas as current clinical response metrics fail to reliably connect measures of imageable treatment response to prognosis for each patient. The current manuscript uses patient-specific mathematical models to assess response in this clinical trial to uniquely overcome both of these hurdles.

Targeting cancer's weaknesses (not its strengths): therapeutic strategies suggested by the atavistic model. Lineweaver CH, Davies PC, Vincent MD. *Bioessays* 2014. **36(9):** 827-835.
In the atavistic model of cancer progression, tumor cell dedifferentiation is interpreted as a reversion to phylogenetically earlier capabilities. The more recently evolved capabilities are compromised first during cancer progression. This suggests a therapeutic strategy for targeting cancer: design challenges to cancer that can only be met by the recently evolved capabilities no longer functional in cancer cells. We describe several examples of this target-the-weakness strategy. Our most detailed example involves the immune system. The absence of adaptive immunity in immunosuppressed tumor environments is an irreversible weakness of cancer that can be exploited by creating a challenge that only the presence of adaptive immunity can meet. This leaves tumor cells more vulnerable than healthy tissue to pathogenic attack. Such a target-the-weakness therapeutic strategy has broad applications, and contrasts with current therapies that target the main strength of cancer: cell proliferation.

Differences in DNA methylation signatures reveal multiple pathways of progression from adenoma to colorectal cancer. Luo Y, Wong CJ, Kaz AM, Dzieciatkowski S, Carter KT, Morris SM, Wang J, Willis JE, Makar KW, Ulrich CM, Lutterbaugh JD, Shrubsole MJ, Zheng W, Markowitz SD, Grady WM. Gastroenterology 2014. **147(2):** 418-429.
Genetic and epigenetic alterations contribute to the pathogenesis of colorectal cancer (CRC). There is considerable molecular heterogeneity among colorectal tumors, which appears to arise as polyps progress to cancer. This heterogeneity results in different pathways to tumorigenesis. Although epigenetic and genetic alterations have been detected in conventional tubular adenomas, little is known about how these affect progression to CRC. We compared methylomes of normal colon mucosa, tubular adenomas, and colorectal cancers to determine how epigenetic alterations might contribute to cancer formation.

Selective detection of target proteins by peptide-enabled graphene biosensor. Khatayevich D, Page T, Gresswell C, Hayamizu Y, Grady W, Sarikaya M. *Small* 2014. **10(8):** 1505-1513.
Direct molecular detection of biomarkers is a promising approach for diagnosis and monitoring of numerous diseases, as well as a cornerstone of modern molecular medicine and drug discovery. Currently, clinical applications of biomarkers are limited by the sensitivity, complexity and low selectivity of available indirect detection methods. Electronic 1D and 2D nano-materials such as carbon nanotubes and graphene, respectively, offer unique advantages as sensing substrates for simple, fast and ultrasensitive detection of biomolecular binding. Versatile methods, however, have yet to be developed for simultaneous functionalization and passivation of the sensor surface to allow for enhanced detection and selectivity of the device. Herein, we demonstrate selective detection of a model protein against a background of serum protein using a graphene sensor functionalized via self-assembling multifunctional short peptides. The two peptides are engineered to bind to graphene and undergo co-assembly in the form of an ordered monomolecular film on the substrate. While the probe peptide displays the bioactive molecule, the passivating peptide prevents non-specific protein adsorption onto the device surface,

ensuring target selectivity. In particular, we demonstrate a graphene field effect transistor (gFET) biosensor which can detect streptavidin against a background of serum bovine albumin at less than 50 ng/ml. Our nano-sensor design, allows us to restore the graphene surface and utilize each sensor in multiple experiments. The peptide-enabled gFET device has great potential to address a variety of bio-sensing problems, such as studying ligand-receptor interactions, or detection of biomarkers in a clinical setting.

Design and in vitro evaluation of layer by layer siRNA nanovectors targeting breast tumor initiating cells. Jaganathan H, Mitra S, Srinivasan S, Dave B, Godin B. *PLoS One* 2014. **9(4):** e91986.

Internalization of red blood cell-mimicking hydrogel capsules with pH-triggered shape responses. Kozlovskaya V, Alexander JF, Wang Y, Kuncewicz T, Liu X, Godin B, Kharlampieva E. *ACS Nano* 2014. **8(6):** 5725-5737.

Introduction: Beyond evolution: game theory and the progression of cancer. Austin RH. *Interface Focus* 2014. **4(4):** 20140044.

Game theory in the death galaxy: interaction of cancer and stromal cells in tumour microenvironment. Wu A, Liao D, Tlsty TD, Sturm JC, Austin RH. *Interface Focus* 2014. **4(4):** 20140028.

Bacteria and game theory: the rise and fall of cooperation in spatially heterogeneous environments. Lambert G, Vyawahare S, Austin RH. *Interface Focus* 2014. **4(4):** 20140029.

Resistance to chemotherapy: patient variability and cellular heterogeneity. Kessler DA, Austin RH, Levine H. *Cancer Res* 2014. **74:** 4663-4670.

Mechanisms of buffer therapy resistance. Bailey KM, Wojtkowiak JW, Cornnell HH, Ribeiro MC, Balagurunathan Y, Hashim AI, Gillies RJ. *Neoplasia* 2014. **16(4):** 354-364.

Inhibition of autophagy enhances the effects of the AKT inhibitor MK-2206 when combined with paclitaxel and carboplatin in BRAF wild-type melanoma. Rebecca VW, Massaro RR, Fedorenko IV, Sondak VK, Anderson AR, Kim E, Amaravadi RK, Maria-Engler SS, Messina JL, Gibney GT, Kudchadkar RR, Smalley KS. *Pigment Cell Melanoma Res* 2014. **27(3):** 465-478.

Histone modifications are associated with transcript isoform diversity in normal and cancer cells. Podlaha O, de S, Gonen M, Michor F. *PLoS Comput Biol* 2014. **10(6):** e1003611.

Non-cell-autonomous driving of tumor growth supports sub-clonal heterogeneity. Marusyk A, Tabassum DP, Altrock PM, Almendro V, Michor F, Polyak K. *Nature* 2014. ePub ahead of print.

Clonal evolution in breast cancer revealed by single nucleus genome sequencing. Wang Y, Waters J, Leung ML, Unruh A, Roh W, Shi X, Chen K, Scheet P, Vattathil S, Liang H, Multani A, Zhang H, Zhao R, Michor F, Meric-Bernstam F, Navin NE. *Nature* 2014. **512(7513):** 155-160.

Most human non-GCIMP glioblastoma subtypes evolve from a common proneural-like precursor glioma. Ozawa T, Riester M, Cheng YK, Huse JT, Squatrito M, Helmy K, Charles N, Michor F, Holland EC. *Cancer Cell* 2014. **26(2):** 288-300.

Genetic and phenotypic diversity in breast tumor metastases. Almendro V, Kim HJ, Cheng YK, Gönen M, Itzkovitz S, Argani P, van Oudenaarden A, Sukumar S, Michor F, Polyak K. *Cancer Res* 2014. **74(5):** 1338-1348.

Carboxymethylcellulose hydrogels support central nervous system-derived tumor-cell chemotactic migration: Comparison with conventional extracellular matrix macromolecules. Singh T, Kothapalli C, Varma D, Nicoll SB, Vazquez M. *J Biomater Appl* 2014. **29(3):** 433-441.

FGFR3 expression in primary and metastatic urothelial carcinoma of the bladder. Guancial EA, Werner L, Bellmunt J, Bamias A, Choueiri TK, Ross R, Schutz FA, Park RS, O'Brien RJ, Hirsch MS, Barletta JA, Berman DM, Lis R, Loda M, Stack EC, Garraway LA, Riester M, Michor F, Kantoff PW, Rosenberg JE. *Cancer Med* 2014. **3(4):** 835-844.

Risk prediction for late-stage ovarian cancer by meta-analysis of 1525 patient samples. Riester M, Wei W, Waldron L, Culhane AC, Trippa L, Oliva E, Kim SH, Michor F, Huttenhower C, Parmigiani G, Birrer MJ. *J Natl Cancer Inst* 2014. **106(5)**.

Nonstochastic reprogramming from a privileged somatic cell state. Guo S, Zi X, Schulz VP, Cheng J, Zhong M, Koochaki SH, Megyola CM, Pan X, Heydari K, Weissman SM, Gallagher PG, Krause DS, Fan R, Lu J. *Cell* 2014. **156(4):** 649-662.

Nanowire array chips for molecular typing of rare trafficking leukocytes with application to neurodegenerative pathology. Kwak M, Kim DJ, Lee MR, Wu Y, Han L, Lee SK, Fan R. *Nanoscale* 2014. **6(12):** 6537-6550.

A microchip platform for interrogating tumor-macrophage paracrine signaling at the single-cell level. Elitas M, Brower K, Lu Y, Chen JJ, Fan R. *Lab Chip* 2014. **14(18):** 3582-3588.