
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.


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.


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.


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.


Role of NAD and SIRT2 in the modulation of microtubule dynamics with implications for their response to microtubule agents.


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.


Role of hypoxia and tumor metastasis in breast cancer via RAB mediated micro vesicle release.

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.


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.

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.


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.


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 vascular permeability 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 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.


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.


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.

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 $\theta$, which is primarily influenced by geometry and represents the ratio between the confined and total water volumes. Through the parameter $\theta$, $D$ can be expressed directly as a linear function of $D_B$ and $D_C$, being the bulk and totally confined diffusion of water, respectively.


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.


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).


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.


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.


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.


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.

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.
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.

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.

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 angiopoietin-1 (ANG-1).

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.

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.

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.


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.


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.


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 of α-catenin.


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.


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.


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.

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.


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 phosphorylation 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.


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, O6-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.


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.


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.


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 biosensing problems, such as studying ligand-receptor interactions, or detection of biomarkers in a clinical setting.


