

PS-OC Quarterly Publication Highlights, December 2013

Biochemical heterogeneity and developmental varieties in T cell leukemia. Chakraborty AK, Roose JP. Cell Cycle. 2013; 12(10):1480-1481.

https://www.landesbioscience.com/article/24858/full_text/#load/info/all

This minireview describes the heterogeneous biochemical nature of leukemic signal transduction pathways and how this poses an obstacle for designing molecularly targeted therapies that are universally successful.

Biological techniques: Chromosomes captured one by one. Dekker J, Mirny L. Nature. 2013; 502(7469): 45–46.

<http://www.nature.com/nature/journal/v502/n7469/full/nature12691.html>

This is a News and Views article summarizing current understanding of functional features in chromosomal organizations and illuminating these features observed in a recent single-cell Hi-C experiment.

Cancer-stromal cell interactions mediated by hypoxia-inducible factors promote angiogenesis, lymphangiogenesis, and metastasis. Semenza GL. Oncogene. 2013; 32(35):4057-63.

<http://www.nature.com/onc/journal/v32/n35/full/onc2012578a.html>

Interactions between cancer cells and stromal cells, including blood vessel endothelial cells, lymphatic vessel endothelial cells, bone marrow-derived angiogenic cells and other bone marrow-derived cells play important roles in cancer progression. Intratumoral hypoxia, which affects both cancer and stromal cells, is associated with a significantly increased risk of metastasis and mortality in many human cancers.

Controlling the mechanical properties of three-dimensional matrices via nonenzymatic collagen glycation. Mason BN, Reinhart-King CA. Organogenesis. 2013; 9(2):70-75.

<https://www.landesbioscience.com/journals/organogenesis/article/24942/>

This commentary reviews some of the current methods that are being used to modulate matrix mechanics and discuss how our recent work using non-enzymatic collagen glycation can contribute to this field.

Exploring the three-dimensional organization of genomes: interpreting chromatin interaction data.

Dekker J, Marti-Renom MA, Mirny LA. Nat Rev Genet. 2013; 14(6):390–403.

<http://www.nature.com/nrg/journal/v14/n6/full/nrg3454.html>

This is a comprehensive review of chromosomal organization in human cells.

HIF-1 mediates metabolic responses to intratumoral hypoxia and oncogenic mutations. Semenza GL. J Clin Invest. 2013; 123(9):3664-71.

<http://www.jci.org/articles/view/67230>

Hypoxia occurs frequently in human cancers and induces adaptive changes in cell metabolism that include a switch from oxidative phosphorylation to glycolysis, increased glycogen synthesis, and a switch from glucose to glutamine as the major substrate for fatty acid synthesis. This broad metabolic

reprogramming is coordinated at the transcriptional level by HIF-1, which functions as a master regulator to balance oxygen supply and demand. HIF-1 is also activated in cancer cells by tumor suppressor (e.g., VHL) loss of function and oncogene gain of function (leading to PI3K/AKT/mTOR activity) and mediates metabolic alterations that drive cancer progression and resistance to therapy.

Implications of Read-Write genomics for cancer biology. Comment on "How life changes itself: The Read-Write (RW) genome" by James A. Shapiro. Davies PC. *Phys Life Rev.* 2013; 10(3):338-340.
<http://www.sciencedirect.com/science/article/pii/S1571064513001000>

The standard somatic theory of cancer assumes that mutations cause cancer. But maybe it is the other way around? A recent paper by geneticist James Shapiro summarizes many ways in which cells can re-engineer their genomes, not just by changing gene expression, but by changing DNA sequences too. My paper applies Shapiro's concept to cancer.

The need for integrative computational oncology: an illustrated example through MMP-mediated tissue degradation. Mumenthaler SM, D'Antonio G, Preziosi L, Macklin P. *Front Oncol.* 2013; 3:194.
<http://www.frontiersin.org/Journal/10.3389/fonc.2013.00194/full>

In this perspectives piece, which is part of a special issue in *Frontiers in Oncology* titled "Computational Models in Oncology: from Tumor Initiation to Progression to Treatment," we highlight the importance of integrative computational oncology, the fusion of novel experiments with mathematical and computational modeling. We focus on a widely used mathematical model of tissue degradation by matrix metalloproteinases to demonstrate the need for proper numerical techniques, applied to biologically relevant space and time scales, and experimental validation of mathematical model predictions in order to develop accurate models that can be used to simplify, analyze, and assess complex phenomena observed in cancer biology.

Oxygen sensing, hypoxia-inducible factors, and disease pathophysiology. Semenza GL. *Annu Rev Pathol.* 2013; ePub ahead of print.
<http://www.annualreviews.org/doi/pdf/10.1146/annurev-pathol-012513-104720>

Hypoxia-inducible factors (HIFs) are transcriptional activators that function as master regulators of oxygen homeostasis, which is disrupted in disorders affecting the circulatory system and in cancer. The role of HIFs in these diseases has been elucidated by clinical studies and by analyses of mouse models. HIFs play a protective role in the pathophysiology of myocardial ischemia due to coronary artery disease, limb ischemia due to peripheral arterial disease, pressure-overload heart failure, wound healing, and chronic rejection of organ transplants.

Porous silicon advances in drug delivery and immunotherapy. Savage DJ, Liu X, Curley SA, Ferrari M, Serda RE. *Curr Opin Pharmacol.* 2013; 13(5):834-41.
<http://www.sciencedirect.com/science/article/pii/S1471489213001161>

New silicon particle fabrication techniques, dynamics of cellular transport, advances in the multistage vector approach to drug delivery, and the use of porous silicon as immune adjuvants.

RasGRP Ras guanine nucleotide exchange factors in cancer. Ksionda O, Limnander A, Roose JP. *Front. Biol.* 2013; 8(5): 508-532.

<http://link.springer.com/article/10.1007%2Fs11515-013-1276-9>

This review summarizes the recent notion that RasGRP molecules play a significant role in several types of cancer.

Regulation of Ras exchange factors and cellular localization of Ras activation by lipid messengers in T cells. Jun JE, Rubio I, Roose JP. *Front. Immunol.* 2013; 4:239.

<http://www.frontiersin.org/Journal/10.3389/fimmu.2013.00239/full>

This review summarizes the recent findings in the field of Ras activation in normal lymphocytes.

Role of hypoxia-inducible factors in breast cancer metastasis. Gilkes DM, Semenza GL. *Future Oncol.* 2013; 9(11):1623-36.

<http://www.futuremedicine.com/doi/full/10.2217/fon.13.92>

Human breast tumors contain regions of hypoxia in which cells that are located far from a functional blood vessel have significantly reduced oxygen concentrations when compared with normal mammary tissue. Breast cancer cells adapt to hypoxic conditions by increasing levels of hypoxia-inducible factors (HIFs), which induce the expression of multiple genes involved in angiogenesis, glucose utilization, resistance to oxidative stress, cell proliferation, resistance to apoptosis, invasion and metastasis. Breast cancer patients with increased HIF expression levels in primary tumor biopsies are at increased risk of metastasis.

Toward single cell traction microscopy within 3D collagen matrices. Hall MS, Long R, Feng X, Huang Y, Hui CY, Wu M. *Exp Cell Res.* 2013; 319(16):2396-2408.

<http://www.sciencedirect.com/science/article/pii/S001448271300270X>

This article discusses the development of 3D cell traction microscopy, its current limitations, and perspectives on the future of this technology. Emphasis is placed on strategies for applying 3D cell traction microscopy to individual tumor cell migration within collagen gels.

Theme: Physical Biology in Cancer. 4. Physical cues guide tumor cell adhesion and migration. Stroka KM, Konstantopoulos K. *Am J Physiol Cell Physiol.* 2013. ePub ahead of print.

<http://ajpcell.physiology.org/content/ajpcell/early/2013/10/10/ajpcell.00289.2013.full.pdf>

In this review, we focus on the extravasation and invasion sections of the metastatic cascade. We first discuss the physical role of the endothelium during tumor cell extravasation and invasion, and how contractility of both endothelial and tumor cells contributes to the ability of tumor cells to exit the vasculature. Next, we examine how matrix dimensionality and stiffness co-regulate tumor cell adhesion and migration beyond the vasculature. Finally, we summarize how tumor cells translate and respond to physical cues through mechanotransduction.

Aspergillus fumigatus hyphal damage caused by noninvasive radiofrequency field-induced hyperthermia. Kaluarachchi WD, Cisneros BT, Corr SJ, Albert ND, Curley SA, Kontoyiannis DP. *Antimicrob Agents Chemother.* 2013; 57(9):4444-8.

<http://aac.asm.org/content/57/9/4444.long>

Keywords: *radiofrequency-induced hyperthermia, Aspergillus fumigatus, hyphae, mold infection, cell wall*

Dysregulated RasGRP1 responds to cytokine receptor-input in T cell leukemogenesis. Hartzell C, Ksionda O, Lemmens E, Coakley K, Yang M, Dail M, Harvey RC, Govern C, Bakker J, Lenstra TL, Ammon K, Boeter A, Winter SS, Loh M, Shannon K, Chakraborty AK, Wabl M, Roose JP. *Sci Signal*. 2013; 6(268):ra21.

<http://stke.sciencemag.org/cgi/content/full/sigtrans;6/268/ra21>

These studies describe how T cell leukemia can arise from two biochemically distinct Ras signals, either via somatic, oncogenic mutations in Ras or via overexpression of the Ras activator Rasgrp1. These studies also reveal how cytokine receptor signaling to Rasgrp1 plays a role in leukemogenesis.

An integrated computational/experimental model of lymphoma growth. Frieboes HB, Smith BR, Chuang YL, Ito K, Roettgers AM, Gambhir SS, Cristini V. *PLoS Comp Biol*. 2013; 9(3):e1003008.

<http://www.ploscompbiol.org/article/info%3Adoi%2F10.1371%2Fjournal.pcbi.1003008>

A critical element of molecular resistance in lymphoma has been traced to the loss of functionality in proteins such as the tumor suppressor p53. We investigate the tissue-scale physiologic effects of this loss by integrating in vivo and immunohistological data with computational modeling to study the spatiotemporal physical dynamics of lymphoma growth. We find that the transport phenomena within the lymphoma may contribute in nontrivial, complex ways to the difference in drug sensitivity between $\text{E}\mu\text{-myc Arf-/-}$ and $\text{E}\mu\text{-myc p53-/-}$ tumors, beyond what might be solely expected from loss of functionality at the molecular scale.

Intracellular water exchange for measuring the dry mass, water mass and changes in chemical composition of living cells. Feijó Delgado F, Cermak N, Hecht VC, Son S, Li Y, Knudsen SM, Olcum S, Higgins JM, Chen J, Grover WH, Manalis SR. *PLoS One*. 2013; 8(7):e67590.

<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0067590>

We present a method for direct non-optical quantification of dry mass, dry density and water mass of single living cells in suspension. Dry mass and dry density are obtained simultaneously by measuring a cell's buoyant mass sequentially in an H_2O -based fluid and a D_2O -based fluid. Rapid exchange of intracellular H_2O for D_2O renders the cell's water content neutrally buoyant in both measurements, and thus the paired measurements yield the mass and density of the cell's dry material alone.

Phosphatidylserine index as a marker of the procoagulant activity of acute myelogenous leukemia cells. Tormoen GW, Recht O, Gruber A, Levine RL, McCarty OJ. *Phys. Biol*. 2013; 10(5):056010.

<http://iopscience.iop.org/1478-3975/10/5/056010/article>

Patients with acute myelogenous leukemia (AML) are at risk for thrombotic complications. Risk to develop thrombosis is closely tied to leukemia subtype, and studies have shown an association between leukocytosis and thrombosis in AML M3. We evaluated the relative roles of cell count and the surface expression of tissue factor (TF) and phosphatidylserine (PS) in the procoagulant phenotype of AML cell lines. We propose that leukemia cell PS index may serve as a biomarker for procoagulant activity.

Realistic control of network dynamics. Cornelius SP, Kath WL, Motter AE. Nat Commun. 2013; 4:1942. <http://www.nature.com/ncomms/2013/130627/ncomms2939/full/ncomms2939.html>

Our approach accounts for the nonlinear dynamics inherent to real systems, and allows bringing the system to a desired target state even when this state is not directly accessible due to constraints that limit the allowed interventions. Applications show that this framework permits reprogramming a network to a desired task, as well as rescuing networks from the brink of failure—which we illustrate through the mitigation of cascading failures in a power-grid network and the identification of potential drug targets in a signaling network of human cancer.

Unexpected dissemination patterns in lymphoma progression revealed by serial imaging within a murine lymph node. Ito K*, Smith BR*, Parashurama N, Yoon JK, Song SY, Miething C, Mallick P, Lowe S, Gambhir SS. Cancer Res. 2012; 72(23):6111-8.

<http://cancerres.aacrjournals.org/content/72/23/6111.long>

Using a mouse model of this disease, we used multimodal imaging, including intravital microscopy (IVM) combined with bioluminescence, as a powerful tool to better elucidate NHL progression. Long-term observation inside a peripheral lymph node was enabled by a novel lymph node internal window chamber technique that allows chronic, sequential lymph node imaging under in vivo physiologic conditions. Unexpectedly, we detected a reproducible efflux of lymphoma cells from spleen and bone marrow, concomitant with a massive and synchronous influx of lymphoma cells into the ILN, several days after injection.

Human fucosyltransferase 6 enables prostate cancer metastasis to bone. Li J, Guillebon AD, Hsu JW, Barthel SR, Dimitroff CJ, Lee YF, King MR. Br J Cancer. 2013; ePub ahead of print.

<http://www.nature.com/bjc/journal/vaop/ncurrent/full/bjc2013690a.html>

The interaction between human prostate cancer cells and bone marrow endothelium follows a rolling-and-adhesion cascade mediated by E-selectin ligand (ESL): E-selectin. This adhesion is enabled by elevated expression of α -1,3-fucosyltransferases (FTs), enzymes responsible for ESL-mediated bone metastasis in humans. In contrast, the incidence of bone metastasis in mice is rare. We show that FT6 is a key mediator of prostate cancer cells trafficking to the bone marrow. It may serve as a viable drug target in preclinical tests of therapeutics for reduction of prostate cancer bone metastasis.

Probing cell traction forces in confined microenvironments. Raman PS, Paul CD, Stroka KM, Konstantopoulos K. Lab Chip. 2013; 13(23):4599-607.

<http://pubs.rsc.org/en/content/articlehtml/2013/lc/c3lc50802a>

Cells migrate in vivo within three-dimensional (3D) extracellular matrices as well as through 3D longitudinal channels formed between the connective tissue and the basement membrane of muscle, nerve, and epithelium. Although traction forces have been measured during 2D cell migration, no assay has been developed to probe forces during migration through confined microenvironments. We thus fabricated a novel microfluidic device consisting of deflectable PDMS microposts incorporated within microchannels of varying cross-sectional areas.

A contact line pinning based microfluidic platform for modelling physiological flows. Tung CK, Krupa O, Apaydin E, Liou JJ, Diaz-Santana A, Kim BJ, Wu M. Lab Chip. 2013; 13(19):3876-85.

<http://pubs.rsc.org/en/content/articlehtml/2013/lc/c3lc50489a>

This work introduces a contact line pinning based microfluidic platform for the generation of interstitial and intramural flows within a three dimensional (3D) microenvironment for cellular behavior studies. Using this device, we demonstrated that the breast tumor cells' (MDA-MB-231 cell line) morphology and motility were modulated by the interstitial flows, and the motility of a sub-population of the cells was enhanced by the presence of the flow. The presented microfluidic platform provides a basic framework for studies of cellular behavior including cell transmigration, growth, and adhesion under well controlled interstitial and intramural flows, and within a physiologically realistic 3D co-culture setting.

Cooperative roles of SDF-1 α and EGF gradients on tumor cell migration revealed by a robust 3D microfluidic model. Kim BJ, Hannanta-anan P, Chau M, Kim YS, Swartz MA, Wu M. PLoS One. 2013; 8(7):e68422.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0068422>

We studied tumor cell chemoinvasion in well-defined and stable chemical gradients using a robust 3D microfluidic model. We used CXCL12 (also known as SDF-1 α) and epidermal growth factor (EGF), two well-known extracellular signaling molecules that co-exist in the tumor microenvironment (e.g. lymph nodes or intravasation sites), and a malignant breast tumor cell line, MDA-MB-231, embedded in type I collagen. Interestingly, we found that the chemoinvasive behavior to SDF-1 α gradients was abrogated or even reversed in the presence of uniform concentrations of EGF; however, the presence of SDF-1 α and EGF together modulated tumor cell motility cooperatively. These findings demonstrate the capabilities of our microfluidic model in re-creating complex microenvironments for cells, and the importance of cooperative roles of multiple cytokine and growth factor gradients in regulating cell migration in 3D environments.

Differential drug responses of circulating tumor cells within patient blood. Hughes AD, Marshall JR, Keller E, Powderly JD, Greene BT, King MR. Cancer Lett. 2013; ePub ahead of print.

<http://www.sciencedirect.com/science/article/pii/S0304383513006010>

We present a proof of concept for predicting individualized drug response. Therapeutics were assessed on circulating tumor cells (CTC) directly in whole blood. Use of matched samples allows for detection of CTC depletion due to drug sensitivity. Sensitive CTC capture detected dose-dependent drug-induced depletions in CTC counts. Parallel drug trials afford ability to simultaneously test multiple therapeutics.

The effect of interstitial pressure on tumor growth: coupling with the blood and lymphatic vascular systems. Wu M, Frieboes HB, McDougall SR, Chaplain MA, Cristini V, Lowengrub J. J Theor Biol. 2013; 320:131-151.

<http://www.sciencedirect.com/science/article/pii/S0022519312006200>

We develop a vascular tumor growth model by coupling a continuous growth model with a discrete angiogenesis model. We include fluid/oxygen extravasation as well as a continuous lymphatic field, and study the micro-environmental fluid dynamics and their effect on tumor growth by accounting for blood flow, transcapillary fluid flux, interstitial fluid flow, and lymphatic drainage. We thus elucidate further

the non-trivial relationship between the key elements contributing to the effects of interstitial pressure in solid tumors.

Fibronectin conformation regulates the proangiogenic capability of tumor-associated adipogenic stromal cells. Wan AMD, Chandler EM, Madhavan M, Infanger D, Ober CK, Gourdon D, Malliaras GG, Fischbach C. *Biochim Biophys Acta*. 2013; 1830(9):4314-20.

<http://www.sciencedirect.com/science/article/pii/S030441651300127X>

Our findings suggest that tumor-associated partial unfolding of Fn decreases adhesion while enhancing VEGF secretion by breast cancer-associated adipogenic precursor cells, and that altered integrin specificity may underlie these changes. These results not only have important implications for our understanding of tumorigenesis, but also enhance knowledge of cell-ECM interactions that may be harnessed for other applications including advanced tissue engineering approaches.

High capacity nanoporous silicon carrier for systemic delivery of gene silencing therapeutics. Shen J, Xu R, Mai J, Kim HC, Guo X, Qin G, Yang Y, Wolfram J, Mu C, Xia X, Gu J, Liu X, Mao ZW, Ferrari M, Shen H. *ACS Nano*. 2013; 7(11):9867-80.

<http://pubs.acs.org/doi/full/10.1021/nn4035316>

Safe and effective delivery of high capacity polycation-functionalized nanoporous silicon (PCPS) platform comprised of nanoporous silicon microparticles functionalized with arginine-polyethyleneimine inside the nanopores for effective delivery of gene silencing agents in vivo and knockdown of gene expression in human breast cancer cells.

Impact of diffusion barriers to small cytotoxic molecules on the efficacy of immunotherapy in breast cancer. Das H, Wang Z, Niazi MK, Aggarwal R, Lu J, Kanji S, Das M, Joseph M, Gurcan M, Cristini V. *PLoS One*. 2013; 8(4):e61398.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0061398>

We hypothesize that underestimating the role of biophysical factors that impact the delivery of drugs or cytotoxic cells to the target sites (for associated preferential cytotoxicity or cell signaling modulation) may be responsible for poor clinical outcome. Our analysis shows that diffusion barriers of cytotoxic molecules conspire with $\gamma\delta$ T-cell scarcity in tissue to limit the inhibitory effects of $\gamma\delta$ T-cells on cancer cells. This may increase the necessary ratios of $\gamma\delta$ T-cells to cancer cells within tissue to unrealistic values for having an intended therapeutic effect, and decrease the effectiveness of the immunotherapeutic treatment.

Polycation-functionalized nanoporous silicon particles for gene silencing on breast cancer cells. Zhang M, Xu R, Xia X, Yang Y, Gu J, Qin G, Liu X, Ferrari M, Shen H. *Biomaterials*. 2014; 35(1):423-31.

<http://www.sciencedirect.com/science/article/pii/S0142961213011162>

Non-toxic delivery of nanoporous silicon particles (pSi) conjugated with polyethyleneimine (PEI) and siRNA payload effectively silenced the ataxia telangiectasia mutated (ATM) cancer gene in human breast cancer cells.

Sweeping lymph node micrometastases off their feet: an engineered model to evaluate natural killer cell mediated therapeutic intervention of circulating tumor cells that disseminate to the lymph nodes.

Chandrasekaran S, McGuire MJ, King MR. Lab Chip. 2013; 14(1):118-27.

<http://pubs.rsc.org/en/content/articlepdf/2014/LC/C3LC50584G>

This paper presents a cell culture platform termed microbubbles formed in polydimethylsiloxane (PDMS) from a microfabricated silicon wafer for mimicking lymph node micrometastases. We cultured lymph node seeking cancer cells in microbubbles to evaluate the efficacy of natural killer (NK) mediated therapy for targeting lymph node micrometastasis. We show that cancer cells cultured in microbubbles with therapeutic NK cells undergo apoptosis after 24 h in culture. Since lymph node metastases are prevalent across several types of cancer, this platform may be useful for developing improved cancer therapies for targeting lymph node micrometastases.

Glioblastoma stem cells are regulated by interleukin-8 signaling in a tumoral perivascular niche.

Infanger DW, Cho YJ, Lopez BS, Mohanan S, Liu SC, Gursel D, Boockvar JA, Fischbach C. Cancer Res. 2013; 73(23):7079-89.

<http://cancerres.aacrjournals.org/content/73/23/7079.full>

In this study, we engineered a scaffold-based culture system enabling brain endothelial cells to form vascular networks. Using this system, we showed that vascular assembly induces CSC maintenance and growth in vitro and accelerates tumor growth in vivo through paracrine interleukin (IL)-8 signaling. Relative to conventional monolayers, endothelial cells cultured in this three-dimensional system not only secreted enhanced levels of IL-8 but also induced CSCs to upregulate the IL-8 cognate receptors CXCR1 and CXCR2, which collectively enhanced CSC migration, growth, and stemness properties. CXCR2 silencing in CSCs abolished the tumor-promoting effects of endothelial cells in vivo, confirming a critical role for this signaling pathway in GMB pathogenesis. Together, our results reveal synergistic interactions between endothelial cells and CSCs that promote the malignant properties of CSCs in an IL-8-dependent manner.

Mechanistic patient-specific predictive correlation of tumor drug response with microenvironment and perfusion measurements. Pascal JA, Bearer EL, Wang Z, Koay EJ, Curley SA, Cristini V. Proc Natl Acad Sci U S A. 2013; 110(35):14266-71.

<http://www.pnas.org/content/110/35/14266.full>

We develop a mathematical model to predict the outcome of chemotherapy based on the physical laws of diffusion. Patient-specific data from either in vivo imaging or histopathology drives output of the model's formulas. Values obtained from standard clinical diagnostic measurements for each individual are entered into the model, producing accurate predictions of tumor kill after chemotherapy.

Altered RECQ helicase expression in sporadic primary colorectal cancers. Lao VV, Welsch P, Luo Y, Carter KT, Dzieciatkowski S, Dintzis S, Meza J, Sarvetnick NE, Monnat RJ, Loeb LA, Grady WM. Transl Oncol. 2013; 6(4):458-69.

<http://www.transonc.com/pdf/manuscript/v06i04/neo13238.pdf>

Determination of the expression of the RECQ helicase DNA repair proteins in colorectal cancer. Many of these proteins are abnormally expression in colorectal cancer, which may make the cancers susceptible to certain types of chemotherapy.

NTRK3 is a potential tumor suppressor gene commonly inactivated by epigenetic mechanisms in colorectal cancer. Luo Y, Kaz AM, Kanngurn S, Welsch P, Moris SM, Wang JP, Lutterbaugh JD, Markowitz SD, Grady WM. PLoS Genet. 2013; 9(7):e1003552.

<http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1003552>

NTRK3 is a receptor for a class of signaling proteins called neurotrophins. This study showed that NTRK3 can act as a tumor suppressor and is often inactivated in colorectal cancer by epigenetic alterations.

pH-responsive hydrogels with dispersed hydrophobic nanoparticles for the oral delivery of chemotherapeutics. Schoener CA, Hutson HN, Peppas NA. J Biomed Mater Res A. 2013; 101(8):2229-36.

<http://onlinelibrary.wiley.com/doi/10.1002/jbm.a.34532/full>

Keywords: hydrogels, pH-responsive, nanoparticles, doxorubicin, controlled release, oral delivery

Barrett's oesophagus: epidemiology, cancer risk and implications for management. de Jonge PJ, van Blankenstein M, Grady WM, Kuipers EJ. Gut. 2014; 63(1):191-202.

<http://gut.bmj.com/content/63/1/191.long>

A 256 pixel magnetoresistive biosensor microarray in 0.18 μ m CMOS. Hall DA, Gaster RS, Makinwa K, Wang SX, Murmann B. IEEE J Solid-State Circ. 2013; 48(5): 1290-1301.

<http://ieeexplore.ieee.org/xpls/icp.jsp?arnumber=6506131>

We report an integrated sensor interface for an array of 256 GMR SV biosensors designed in 0.18 μ m CMOS. Arranged like an imager, each of the 16 column level readout channels contains an analog front-end and a compact $\Sigma\Delta$ modulator with 84 dB of dynamic range. Performance is demonstrated through detection of an ovarian cancer biomarker, secretory leukocyte peptidase inhibitor (SLPI), spiked at concentrations as low as 10 fM.

Protocols for assessing radiofrequency interactions with gold nanoparticles and biological systems for non-invasive hyperthermia cancer therapy. Corr SJ, Cisneros BT, Green L, Raouf M, Curley SA. J Vis Exp. 2013; 78:e50480.

<http://www.jove.com/video/50480/protocols-for-assessing-radiofrequency-interactions-with-gold>

Detailed protocols assessing radiofrequency heating of gold nanoparticles colloids, in vitro nanoparticle-assisted RF-Induced hyperthermia, and in vivo nanoparticle-assisted RF-induced hyperthermia in ectopic hepatic cancer tumors.

Temsirolimus combined with sorafenib in hepatocellular carcinoma: a phase I dose-finding trial with pharmacokinetic and biomarker correlates. Kelley RK, Nimeiri HS, Munster Pn, Vergo MT, Huang Y, Li C-M, Hwang J, Mulcahy MF, Yeh BM, Kuhn P, Luttggen MS, Grabowsky JA, Stucky-Marshall L, Korn WM, Ko AH, Bergland EK, Benson III AB, Benook AP. Ann Oncol. 2013; 24(7):1900-7.

<http://annonc.oxfordjournals.org/content/24/7/1900.full>

Based upon preclinical evidence for improved antitumor activity in combination, this phase I study investigated the maximum-tolerated dose (MTD), safety, activity, pharmacokinetics (PK), and biomarkers of the mammalian target of rapamycin inhibitor, temsirolimus, combined with sorafenib in hepatocellular carcinoma (HCC). The MTD of sorafenib plus temsirolimus in HCC was lower than in other tumor types. HCC-specific phase I studies are necessary. The observed efficacy warrants further study.

Tumor selective hyperthermia induced by short-wave capacitively-coupled RF electric-fields. Raouf M, Cisneros BT, Corr SJ, Palalon F, Curley SA, Koshkina NV. PLoS One. 2013; 8(7):e68506.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0068506>

We investigated the heating behavior and dielectric properties of normal mouse tissues and orthotopically-implanted human hepatocellular and pancreatic carcinoma xenografts using high-intensity short wave capacitively-coupled radiofrequency (RF) electric-fields for nanoparticle-mediated tumor-targeted hyperthermia.

Characterizing deformability and surface friction of cancer cells. Byun S, Son S, Amodei D, Cermak N, Shaw J, Kang JH, Hecht VC, Winslow MM, Jacks T, Mallick P, Manalis SR. Proc Natl Acad Sci U S A. 2013; 110(19):7580-85.

<http://www.pnas.org/content/110/19/7580.long>

Metastasis requires the penetration of cancer cells through tight spaces, which is mediated by the physical properties of the cells as well as their interactions with the confined environment. We introduce a device that enables the precise measurement of (i) the size of a single cell, given by its buoyant mass, (ii) the velocity of the cell entering a constricted microchannel (entry velocity), and (iii) the velocity of the cell as it transits through the constriction (transit velocity). We find that some cell types with higher metastatic potential exhibit greater than expected changes in transit velocities, suggesting that not only the increased deformability but reduced friction may be a factor in enabling invasive cancer cells to efficiently squeeze through tight spaces.

An observational study of circulating tumor cells and F-FDG PET uptake in patients with treatment-naïve non-small cell lung cancer. Nair VS, Keu KV, Luttggen MS, Kolatkar A, Vasanawala M, Kuschner W, Bethel K, Lagaru AH, Hoh C, Shrager JB, Loo Jr BW, Bazhenova L, Nieva J, Gambhir SS, Kuhn P. PLoS. 2013; 8(7):e67733.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0067733>

We investigated the relationship of circulating tumor cells (CTCs) in non-small cell lung cancer (NSCLC) with tumor glucose metabolism as defined by 18F-fluorodeoxyglucose (FDG) uptake since both have been associated with patient prognosis. We conclude that CTCs are detected frequently in early-stage NSCLC using a non-EpCAM mediated approach with a wide range noted for a given level of FDG uptake or tumor size. Integrating potentially complementary biomarkers like these with traditional patient data may eventually enhance our understanding of clinical, in vivo tumor biology in the early stages of this deadly disease.

Mo1487 measurement of circulating tumor cell levels before and after endoscopic ultrasound-guided fine needle aspiration in patients with newly diagnosed pancreatic adenocarcinoma: interim analysis.

Hunt D, Kuhn P, Bethel K, Kuldau J, Luttggen MS, Coyle W. Gastro Endosc. 2013; 77(5):AB400-AB401.

<http://www.giejournal.org/article/S0016-5107%2813%2900450-1/fulltext>

Circulating tumor cells (CTCs) have been identified in a number of different malignancies, including pancreatic adenocarcinoma, and may be important markers of disease severity and prognosis.

Differential Tks5 isoform expression contributes to metastatic invasion of lung adenocarcinoma. Li CM, Chen G, Dayton TL, Kim-Kiselak C, Hoersch S, Whittaker CA, Bronson RT, Beer DG, Winslow MM, Jacks T. *Genes Dev.* 2013; 27(14):1557-67.

<http://genesdev.cshlp.org/content/27/14/1557.full>

Metastasis accounts for the vast majority of cancer-related deaths, yet the molecular mechanisms that drive metastatic spread remain poorly understood. Here we report that Tks5, which has been linked to the formation of proteolytic cellular protrusions known as invadopodia, undergoes an isoform switch during metastatic progression in a genetically engineered mouse model of lung adenocarcinoma. Characterization of these isoforms by knockdown and overexpression experiments demonstrated that Tks5long promoted invadopodia in vitro and increased metastasis in transplant models and an autochthonous model of lung adenocarcinoma. Conversely, Tks5short decreased invadopodia stability and proteolysis, acting as a natural dominant-negative inhibitor to Tks5long. Tipping the Tks5 isoform balance to a high Tks5long to Tks5short ratio promotes invadopodia-mediated invasion and metastasis.

A serial micropipette microfluidic device with applications to cancer cell repeated deformation studies. Mak M, Erickson D. *Integr Biol (Camb).* 2013; 5(11):1374-84.

<http://pubs.rsc.org/en/content/articlehtml/2013/ib/c3ib40128f>

We developed a highly adoptable, automated, serial micropipette device and assay usable in any existing cell biology lab without additional infrastructure. This platform minimizes the manual labor cost and peripheral instrumentation necessary in traditional cell deformability-related techniques, such as micropipette aspiration and atomic force microscopy. We applied our device and method to study multiple sequential deformations of individual cells at the subnuclear scale in a parallel manner, which offer insights beyond the more typical studies that sample cells at low strains and only once. This is especially relevant in phenomena such as cancer metastasis, which involves not simply a single deformation event but rather a multitude of deformations often at the subnuclear scale.

Formation of microvascular networks in vitro. Morgan JP, DelNero PF, Zheng Y, Verbridge SS, Chen J, Craven M, Choi NW, Diaz-Santana A, Kermani P, Hempstead B, López B, Corso TN, Fischbach C, Stroock AD. *Nat Protoc.* 2013; 8(9):1820-36.

<http://www.nature.com/nprot/journal/v8/n9/full/nprot.2013.110.html>

This protocol describes how to form a 3D cell culture with explicit, endothelialized microvessels. The approach leads to fully enclosed, perfusable vessels in a bioremodelable hydrogel (type I collagen). The platform enables real-time fluorescence imaging of living engineered tissues, in situ confocal fluorescence of fixed cultures and transmission electron microscopy (TEM) imaging of histological sections.

Immunoreactivity of pluripotent markers SSEA-5 and L1CAM in human tumors, teratomas and induced pluripotent stem cells. Cassidy L, Choi MR, Meyer J, Chang R, Seigel GM. *J Biomark.* 2013; (2013): Article ID 960862.

<http://www.hindawi.com/journals/jbm/2013/960862/>

Impact of deleterious passenger mutations on cancer progression. McFarland CD, Korolev KS, Kryukov GV, Sunyaev SR, Mirny LA. Proc Natl Acad Sci U S A. 2013; 110(8):2910-15.

<http://www.pnas.org/content/110/8/2910.full>

This work provides a computational model and genomic analysis of passenger mutations in cancer. Simulations demonstrate that mildly deleterious passenger mutations and chromosomal alterations can accumulate during cancer progression. Analysis of cancer genomics data shows that passenger mutations observed in sequenced clinical cancers can be deleterious to cancer cells. Finally, simulations are used to show that increasing deleterious effects of passengers can lead to cancer meltdown, thus suggesting a clinical approach to use the load of passenger mutations.

Nanosensor dosimetry of mouse blood proteins after exposure to ionizing radiation. Kim D, Marchetti F, Chen Z, Zaric S, Wilson RJ, Hall DA, Gaster RS, Lee JR, Wang J, Osterfeld SJ, Yu H, White RM, Blakely WF, Peterson LE, Bhatnagar S, Mannion B, Tseng S, Roth K, Coleman M, Snijders AM, Wyrobek AJ, Wang SX. Sci Rep. 2013; 3:2234.

<http://www.nature.com/srep/2013/130719/srep02234/full/srep02234.html>

Giant magnetoresistive (GMR) nanosensors provide a novel approach for measuring protein concentrations in blood for medical diagnosis. Using an in vivo mouse radiation model, we developed protocols for measuring Flt3 ligand (Flt3lg) and serum amyloid A1 (Saa1) in small amounts of blood collected during the first week after X-ray exposures of sham, 0.1, 1, 2, 3, or 6 Gy. A multiplex assay with both proteins showed improved dose classification accuracy. Our magneto-nanosensor assay demonstrates the dose and time responses, low-dose sensitivity, small volume requirements, and rapid speed that have important advantages in radiation triage biodosimetry.

Physicochemical regulation of endothelial sprouting in a 3D microfluidic angiogenesis model.

Verbridge SS, Chakrabarti A, DelNero P, Kwee B, Varner JD, Stroock AD, Fischbach C. J Biomed Mater Res. 2013; 101(10):2948-56.

<http://onlinelibrary.wiley.com/doi/10.1002/jbm.a.34587/pdf>

We present a biomaterials-based microfluidic 3D platform for analysis of endothelial sprouting in response to morphogen gradients. Gradients of vascular endothelial growth factor (VEGF) promoted sprouting, whereby endothelial cell responsiveness was markedly dependent on cell density and vessel geometry regardless of treatment conditions. These results point toward mechanical and/or autocrine mechanisms that may overwhelm pro-angiogenic paracrine signaling under certain conditions. To date, neither geometrical effects nor cell density have been considered critical determinants of angiogenesis in health and disease.

Structural analysis of autoinhibition in the Ras-specific exchange factor RasGRP1. Iwig JS, Vercoulen Y, Das R, Barros T, Limnander A, Che Y, Pelton JG, Wemmer DE, Roose JP, Kuriyan J. eLife. 2013; 2:e00813.

<http://elife.elifesciences.org/content/2/e00813>

These studies describe the crystal structure of the Ras activator RasGRP1. We uncovered that RasGRP1 resides in an autoinhibited state that is held in place by two distinct mechanisms. Receptor stimulation that generates the 2nd messengers calcium and diacylglycerol allows for the autoinhibited state to be unlocked.

Activation of extracellular signal-regulated kinase but not of p38 mitogen-activated protein kinase pathways in lymphocytes requires allosteric activation of SOS. Jun JE, Yang M, Chen H, Chakraborty AK, Roose JP. *Mol Cell Biol.* 2013; 33(12):2470-84.

<http://mcb.asm.org/content/33/12/2470.long>

These studies describe how the Ras activator SOS1 plays two distinct roles in lymphocyte signaling. Catalytic activity of SOS1 and SOS1's allosteric activation are critical for ERK MAPkinase activation with a digital nature. By contrast, activation of the P38 MAP kinase pathway does not require any catalytic activity from SOS1 but requires presence of SOS1 as an adapter.

Allele-specific detection of single mRNA molecules in situ. Hansen CH, van Oudenaarden A. *Nat Methods.* 2013; 10(9):869–71.

<http://www.nature.com/nmeth/journal/v10/n9/full/nmeth.2601.html>

We describe a method for fluorescence in situ identification of individual mRNA molecules, allowing for quantitative and accurate measurement in single cells of allele-specific transcripts that differ by only a few nucleotides. By using a combination of allele-specific and non-allele-specific probe libraries, we achieve >95% detection accuracy. We investigate the allele-specific stochastic expression of Nanog, which encodes a pluripotency factor, in murine embryonic stem cells.

Changes in cell morphology are coordinated with cell growth through the TORC1 pathway. Goranov AI, Gulati A, Dephoure N, Takahara T, Maeda T, Gygi SP, Manalis S, Amon A. *Curr Biol.* 2013; 23(14):1269-79.

<http://www.sciencedirect.com/science/article/pii/S0960982213006301>

Here we demonstrate that polarization of the actin cytoskeleton inhibits the highly conserved Target of Rapamycin Complex 1 (TORC1) pathway. Our results indicate that extended periods of polarized growth inhibit protein synthesis, mass accumulation, and the increase in cell size at least in part through inhibiting the TORC1 pathway. We speculate that this mechanism serves to coordinate the ability of cells to increase in size with their biosynthetic capacity.

Ciliated micropillars for the microfluidic-based isolation of nanoscale lipid vesicles. Wang Z, Wu HJ, Fine D, Schmulen J, Hu Y, Godin B, Zhang JX, Liu X. *Lab Chip.* 2013; 13(15):2879-82.

<http://pubs.rsc.org/en/content/articlehtml/2013/lc/c3lc41343h>

We fabricated a microfluidic device consisting of ciliated micropillars, forming a porous silicon nanowire-on-micropillar structure. We demonstrated that the prototype device can preferentially trap exosome-like lipid vesicles, while simultaneously filtering out proteins and cell debris. Trapped lipid vesicles can be recovered intact by dissolving the porous nanowires in PBS buffer.

Dampening of expression oscillations by synchronous regulation of a microRNA and its target. Kim DH, Gruen D, van Oudenaarden A. *Nat Genet.* 2013; 45(11):1337–44.

<http://www.nature.com/ng/journal/v45/n11/full/ng.2763.html>

The complexity of multicellular organisms requires precise spatiotemporal regulation of gene expression during development. We find that in the nematode *Caenorhabditis elegans* approximately 2,000 transcripts undergo expression oscillations synchronized with larval transitions while thousands of genes are expressed in temporal gradients, similar to known timing regulators. Our results demonstrate that

this insulation is optimal when pulsatile expression of the miRNA and its target is synchronous. We propose that such a miRNA-mediated incoherent feed-forward loop is a potent filter that prevents the propagation of potentially deleterious fluctuations in gene expression during the development of an organism.

Derivation and network formation of vascular cells from human pluripotent stem cells. Gerecht S. *Methods Mol Biol.* 2013; ePub ahead of print.

http://link.springer.com/protocol/10.1007%2F7651_2013_39/fulltext.html

We demonstrate methods to derive a bicellular population of early specialized vascular cells from human pluripotent stem cells, to differentiate these toward mature endothelial cells and pericytes, and to utilize a collagen scaffold to facilitate organization into vascular networks.

Distinct signaling mechanisms regulate migration in unconfined versus confined spaces. Hung WC, Chen SH, Paul CD, Stroka KM, Lo YC, Yang JT, Konstantopoulos K. *J Cell Biol.* 2013; 202(5):807-24.

<http://jcb.rupress.org/content/202/5/807.full>

Using a microchannel assay, we demonstrate that cells adopt distinct signaling strategies to modulate cell migration in different physical microenvironments. We studied $\alpha 4\beta 1$ integrin-mediated signaling, which regulates cell migration pertinent to embryonic development, leukocyte trafficking, and melanoma invasion. We show that $\alpha 4\beta 1$ integrin promotes cell migration through both unconfined and confined spaces.

Form-finding model shows how cytoskeleton network stiffness is realized. Gong J, Zhang D, Tseng Y, Li B, Wirtz D, Schafer BW. *PLoS One.* 2013; 8(10):e77417.

<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0077417>

In eukaryotic cells the actin-cytoskeletal network provides stiffness and the driving force that contributes to changes in cell shape and cell motility, but the elastic behavior of this network is not well understood. In this paper a two dimensional form-finding model is proposed to investigate the elasticity of the actin filament network.

High-resolution mapping of the spatial organization of a bacterial chromosome. Le TBK, Imakaev M, Mirny LA, Laub MT. *Science.* 2013; 342(6159):731-4.

<http://www.sciencemag.org/content/342/6159/731.full>

Combination of Hi-C experiments and polymer modeling allowed us to characterize chromosome organization in bacteria at unprecedented resolution and establish connections between gene expression and chromosome organization.

Poly(dA:dT)-rich DNAs are highly flexible in the context of DNA looping. Johnson S, Chen YJ, Phillips R. *PLoS One.* 2013; 8(10):e75799.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0075799>

In this work we explore the effect of sequence flexibility on transcription factor-mediated DNA looping by drawing on sequences identified in nucleosome formation and ligase-mediated cyclization assays as being especially favorable for or resistant to large deformations.

Replisome stall events have shaped the distribution of replication origins in the genomes of yeasts.

Newman TJ, Mamun MA, Nieduszynski CA, Blow JJ. Nucl. Acids Res. 2013; 41(21):9705-18.

<http://nar.oxfordjournals.org/content/early/2013/08/19/nar.gkt728.full>

A simple mathematical model was developed to describe the probability of replication failing due to the irreversible stalling of replication forks. The theory predicts that significantly larger genomes, such as those of mammals, will experience a much greater probability of replication failure genome-wide, and therefore will likely require additional compensatory mechanisms.

Self-organized vascular networks from human pluripotent stem cells in a synthetic matrix.

Kusuma S, Shen YI, Hanjaya-Putra D, Mali P, Cheng L, Gerecht S. Proc Natl Acad Sci U S A. 2013; 110(31):12601-6.

<http://www.pnas.org/content/110/31/12601.long>

The success of tissue regenerative therapies is contingent on functional and multicellular vasculature within the redeveloping tissue. Here we derived a bicellular vascular population from human pluripotent stem cells (hPSCs) that undergoes morphogenesis and assembly in a synthetic matrix. We found that hPSCs can be induced to codifferentiate into early vascular cells (EVCs) in a clinically relevant strategy amenable to multiple hPSC lines.

Single-cell analysis reveals that expression of nanog is biallelic and equally variable as that of other pluripotency factors in mouse ESCs.

Faddah DA, Wang H, Cheng AW, Katz Y, Buganim Y, Jaenisch R. Cell Stem Cell. 2013; 13(1):23-9.

<http://www.sciencedirect.com/science/article/pii/S1934590913001550>

The homeodomain transcription factor Nanog is a central part of the core pluripotency transcriptional network and plays a critical role in embryonic stem cell (ESC) self-renewal. Using single-cell gene expression analyses combined with different reporters for the two alleles of Nanog, we show that Nanog is biallelically expressed in ESCs independently of culture condition. We also show that the overall variation in endogenous Nanog expression in ESCs is very similar to that of several other pluripotency markers. Our analysis suggests that reporter-based studies of gene expression in pluripotent cells can be significantly influenced by the gene-targeting strategy and genetic background employed.

Single-molecule mRNA detection and counting in mammalian tissue.

Lyubimova A, Itzkovitz S, Junker JP, Fan ZP, Wu X, van Oudenaarden A. Nat Protoc. 2013; 8(9):1743-58.

<http://www.nature.com/nprot/journal/v8/n9/full/nprot.2013.109.html>

We present a protocol for visualizing and quantifying single mRNA molecules in mammalian (mouse and human) tissues. In the approach described here, sets of about 50 short oligonucleotides, each labeled with a single fluorophore, are hybridized to target mRNAs in tissue sections. Each set binds to a single mRNA molecule and can be detected by fluorescence microscopy as a diffraction-limited spot.

Stochastic cytokine expression induces mixed T helper cell states.

Fang M, Xie H, Dougan SK, Ploegh H, van Oudenaarden A. PLoS Biol 2013; 11(7): e1001618.

<http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1001618>

During eukaryotic development, the induction of a lineage-specific transcription factor typically drives differentiation of multipotent progenitor cells, while repressing that of alternative lineages. This process is often mediated by some extracellular signaling molecules, such as cytokines that can bind to cell

surface receptors, leading to activation and/or repression of transcription factors. We explored the early differentiation of naive CD4 T helper (Th) cells into Th1 versus Th2 states by counting single transcripts and quantifying immunofluorescence in individual cells. Contrary to mutually exclusive expression of antagonistic transcription factors, we observed their ubiquitous co-expression in individual cells at high levels that are distinct from basal-level co-expression during lineage priming.

Vascular deposition patterns for nanoparticles in an inflamed patient-specific arterial tree. Hossain SS, Hughes TJ, Decuzzi P. *Biomech Model Mechanobiol.* 2013; ePub ahead of print.

<http://link.springer.com/article/10.1007/s10237-013-0520-1/fulltext.html>

A computational model is developed to understand and predict the vascular deposition of blood-borne nanoparticles within an inflamed arterial tree using endothelial adhesion antibodies of intravascular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin. The surface density distribution of these particles depends on the local wall shear stress.