http://www.broadinstitute.org/science/programs/cancer/icbp/broad-institute-icbp

PURPOSE

The Broad CCSB has the overall goal of developing computational models that predict genome-wide essentiality based on the molecular characteristics of the tumor. A critical goal in cancer research is to accurately predict essential genes/proteins across a diversity of tumor subtypes. Such a capability would allow for i) the elucidation of the molecular targets against which therapeutics should be developed, and ii) the identification of specific patient populations likely to respond to such targeted interventions. Accomplishing this goal will require developing a deep understanding of the cellular circuitry of tumor cells — the details of which are increasingly recognized to depend on the genetic subtype of the tumor. A single set of network dependencies is unlikely to explain the diversity of even a single tumor type (e.g., whereas EGFR mutation in lung adenocarcinoma signals EGFR essentiality in some patients, those also harboring KRAS mutation are EGFR-independent. Similarly, EGFR mutations do not appear to confer EGFR essentiality in glioblastoma, where more complex oncogenic and feedback mechanisms appear to be at play). A way to tie functional dependencies to genetic diversity is therefore needed.

Technical

A number of technology developments over the past several years are now making it possible to seriously take on this goal. For example, the ability to perform genome-wide RNAi screens now makes it possible to systematically perturb the cancer genome, thereby identifying those genes that are essential in a given experimental system. In addition, it is becoming increasingly possible to perform extensive molecular characterization of tumor samples and model systems — including the patterns of gene copy number, gene expression, somatic mutation, tyrosine phosphorylation, etc., which might serve as predictive features of essentiality.

Major obstacles currently prevent rapid progress toward the goal of predicting essentiality: First, there is a lack of data of sufficient scope (i.e., genome-wide RNAi screening data and extensive molecular characterization) and scale (i.e., data spanning large numbers of cell lines that adequately represent the true genetic diversity of cancer). Second, there is a lack of a computational framework proven to be successful for the integrative challenge of generating predictive models of cellular phenotypes based on molecular features of the cell.

Our Center aims to overcome these obstacles, with the ultimate goal of developing predictive models that accurately identify the "Achilles' heels" of tumors of different genotypes. We are focusing on lung cancer and melanoma because i) there is great unmet medical need, ii) there exist appropriate experimental systems, iii) there is commitment of the investigators to these diseases, and iv) the focus on two cancer types will allow us to determine to what extent the predictive "rules" that govern the behavior of one tumor type are applicable to the other.

KEYWORDS

Cancer vulnerabilities, genome-wide, cancer cell lines, molecular profiling, predictive modeling, precision medicine, dependencies, synthetic lethality, Achilles heels, RNAi.

RESOURCES

Broad Institute Cancer Program website: <u>www.broadinstitute.org/cancer</u>.

*Note: at our Program website, you can find the link for the Cancer Program Resource Gateway. At the Gateway, links to all data sets and tools developed by the Broad CCSB and Broad Cancer Program can be found. One can also find the link (on the right hand side) to the Broad ICBP website.

Publications

1. Barbie, D.A., *et al.* Systematic RNA interference reveals that oncogenic KRAS-driven cancers require TBK1. *Nature* 462, 108-112 (2009).

- 2. Barretina, J., *et al.* The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature* 483, 603-607 (2012).
- Cheung, H.W., et al. Systematic investigation of genetic vulnerabilities across cancer cell lines reveals lineage-specific dependencies in ovarian cancer. Proc Natl Acad Sci U S A 108, 12372-12377 (2011).
- 4. Garnett, M.J., *et al.* Systematic identification of genomic markers of drug sensitivity in cancer cells. *Nature* 483, 570-575 (2012).
- 5. Johannessen, C.M., *et al.* COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. *Nature* 468, 968-972 (2010).
- 6. Luo, B., *et al.* Highly parallel identification of essential genes in cancer cells. *Proc Natl Acad Sci U S A* 105, 20380-20385 (2008).
- 7. Nijhawan, D., et al. Cancer vulnerabilities unveiled by genomic loss. Cell 150, 842-854 (2012).
- 8. Rosenbluh, J., *et al.* beta-Catenin-driven cancers require a YAP1 transcriptional complex for survival and tumorigenesis. *Cell* 151, 1457-1473 (2012).
- 9. Shao, D.D., *et al.* ATARiS: computational quantification of gene suppression phenotypes from multisample RNAi screens. *Genome Res* 23, 665-678 (2013).
- 10. Straussman, R., *et al.* Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature* 487, 500-504 (2012).

Videos/Materials

Set of three introductory videos (go to blossoms.mit.edu, search for "Broad Cancer")

- 1. From teenage to old age: how cancer develops over time
- 2. Making it personal: using DNA to tailor cancer treatments
- 3. How scientific teams develop new anti-cancer drugs

Broad Blog: basic concepts in biology (<u>http://www.broadinstitute.org/blog_roll</u>) Broad Education page: <u>http://www.broadinstitute.org/partnerships/education/education</u> (see Midsummer Night's Science video series).

<u>Key tools and datasets</u> (related to the Broad CCSB - see links in Resource Gateway): Cancer Cell Line Encyclopedia: Comprehensive genomic characterization on 1000 cancer cell lines. Project Achilles: RNAi screening data on hundreds of cancer cell lines. Integrative Genomics Viewer: User friendly visualization tool for genomic data Molecular Signatures Database (MSigDB): Expansive database of gene expression signatures Gene Set Enrichment Analysis (GSEA): Tool for determining overlap between gene sets.

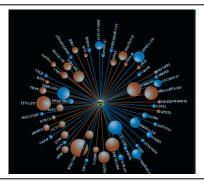
CONTACT

Jesse Boehm, PhD Assistant Director of Cancer Program Broad Institute boehm@broadinstitute.org THE COLUMBIA UNIVERSITY: CENTER FOR CANCER SYSTEMS BIOLOGY. MAGNet Center (Center for Multi-scale Analysis of Genomic and Cellular Networks) under the auspices of the Department of Systems Biology http://magnet.c2b2.columbia.edu/

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PURPOSE

The intellectual goal of systems biology is to infer the mechanism of biological processes from comprehensive experimental characterization of the quantities and states of biological molecules



and to use this information to quantitatively predict the behavior of biological systems on molecular, cellular, and phenotypic levels. The practical goal of systems biology is to apply systematic models of biological processes to diagnosis, prognosis, and treatment of disease on a personalized level. Systems biology methods are necessary to understand and treat cancer because the genomic reprogramming accompanying the disease is not susceptible to single-gene or few-gene approaches, but rather requires a system-wise approach.

Emphasis of Center:

- 1. Inference of genomic and cellular networks from experimental data.
- 2. Prediction of protein-DNA and protein-protein interactions based on structure.
- 3. Elucidation of transcriptional control mechanisms.
- 4. Characterization and understanding of genotype-phenotype relationships.
- 5. Application of systems biology methods to translational and clinical research.

KEYWORDS

Network inference, protein-protein networks, protein-DNA interactions, transcriptional networks, genotype-phenotype inference.

RESOURCES

Publications

- Floratos A, Honig B, Pe'er D, and Califano, A. Using systems and structure biology tools to dissect cellular phenotypes. J Am Med Inform Assoc 2012;19:171-5. <u>http://www.ncbi.nlm.nih.gov/pubmed/?term=22081223</u>
- Margolin AA, Nemenman I, Basso K, Wiggins C, Stolovitzky G, Dalla Favera R, and Califano A.ARACNE: an algorithm for the reconstruction of gene regulatory networks in a mammalian cellular context. BMC Bioinformatics 2006;7 Suppl 1:S7. http://www.ncbi.nlm.nih.gov/pubmed/16723010
- 3. Zhang QC, Petrey D, Garzon JI, Deng, L and Honig B. PrePPI: a structure-informed database of protein-protein interactions. Nucleic Acids Res 2013;41:D828-33.
- 4. http://www.ncbi.nlm.nih.gov/pubmed/23193263
- Gilman SR, Iossifov I, Levy D, Ronemus, M., Wigler, M., and Vitkup, D.Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses. Neuron 2011;70:898-907. <u>http://www.ncbi.nlm.nih.gov/pubmed/21658583</u>
- Cheng WY, Ou Yang TH, Anastassiou D. Development of a prognostic model for breast cancer survival in an open challenge environment. Sci Transl Med 2013;5:181ra50. http://www.ncbi.nlm.nih.gov/pubmed/23596202
- Floratos A, Smith K, Ji Z, Watkinson J and Califano A geWorkbench: an open source platform for integrative genomics. Bioinformatics 2010;26:1779-80. http://www.ncbi.nlm.nih.gov/pubmed/?term=20511363

Useful Books for Bioinformaticists (not an exhaustive list)

- 1. Zvelebil M, Baum J. Understanding Bioinformatics Garland Science, 2007.
- 2. Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell: Reference Edition

- Garland Scientific, 2007. (Note the Reference Edition is 1728 pages long. The student edition is 1392 pages long and has the last 5 chapters on PDF. If you don't mind this get the student edition. If not, get the Reference Edition).
- 4. Zar J. Biostatistical Analysis: Pearson, 1998 or 2009. 4th or 5th edition.
- 5. Crawley M. The R book: Wiley, 2007 or 2013.1st or 2nd edition.

Some Great Bioinformatics Papers not from this Center

- 1. Altschul SF. Amino acid substitution matrices from an information theoretic perspective. J Mol Biol 1991;219:555-65. <u>http://www.ncbi.nlm.nih.gov/pubmed/2051488</u>
- Irizarry RA, Hobbs B, Collin F, Beazer-Barclay YD, Antonellis KJ, Scherf U, and Speed TP. Exploration, normalization, and summaries of high density oligonucleotide array probe level data. Biostatistics 2003;4:249-64. <u>http://www.ncbi.nlm.nih.gov/pubmed/12925520</u>
- Smyth GK. Linear models and empirical bayes methods for assessing differential expression in microarray experiments. Stat Appl Genet Mol Biol 2004;3: Article3. http://www.ncbi.nlm.nih.gov/pubmed/?term=16646809

A Few Useful Web-sites

- 1. ISAAC Internet Sequence Analysis Algorithm Checkist A compendium of Bioinformatics web sites: http://friedman.c2b2.columbia.edu/isaac.html
- ROSIE Really Organized Sites for informatics Education A little sister to the Isaac page. http://friedman.c2b2.columbia.edu/rosie.html
- 3. NCBI- National Center for Biotechnology Information Blast plus just about everything else.
- 4. <u>http://www.ncbi.nlm.nih.gov/</u>
- 5. CRAN <u>http://cran.us.r-project.org/</u> The resource site for the free R statistical programming environment.
- Bioconductor <u>http://www.bioconductor.org/</u> The resource site for the free Bioconducor suite of Biology software (written in R).
- 7. Pathway Commons http://www.pathwaycommons.org/pc/ Central collection of pathway databases.
- 8. Ontotools <u>http://vortex.cs.wayne.edu/projects.htm</u> Tools for the functional analysis of gene expression data.

CONTACTS

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http://lombardi.georgetown.edu/BreastCancer/CCSB/about/ind ex.html

TITLE: Integration of Endocrine Resistant-related Signaling in Breast Cancer

PURPOSE

Scientific approaches that focus on a single gene or pathway cannot fully address the complex molecular makeup of breast cancer, nor can they adequately address why some tumors fail to respond to therapy. Our goal is to use a multi-disciplinary



approach to solve the problems associated with drug resistance in breast cancer.

Technical

The central focus of our center is to build integrated computational and mathematical models of endocrine resistance in estrogen receptor-positive (ER+) breast cancer, particularly how the unfolded protein response (UPR) regulates apoptosis and autophagy pathways to determine cell fate decisions. Our three central projects focus on: endocrine responsiveness, novel targets, and life-time exposure to estrogenic factors in contributing to endocrine resistance. Together these projects generate and integrate data from the genome, epigenome, metabolome, methylome, and transcriptome to build *in silico* models. These models predict how ER regulates molecular signaling and regulates cellular functions to affect the risk of neoplastic transformation in the normal breast, and responsiveness to endocrine therapies in breast cancer.

KEYWORDS

Breast cancer cells, endocrine resistance, antiestrogens, apoptosis, autophagy, unfolded protein response, pathway cross-talk, mathematical models, targeted therapeutics

RESOURCES

Publications

- 1. Gusev Y, Riggins RB, Bhuvaneshwar K, Gauba R, Sheahan L, Clarke R, and Madhavan S. In silico discovery of mitosis regulation networks associated with early distant metastases in estrogen receptor positive breast cancers. *Cancer Informatics* 12:31-51. (2013)
- Clarke R, Cook KL, Hu R, Facey CO, Tavassoly I, Schwartz JL, Baumann WT, Tyson JJ, Xuan J, Wang Y, Wärri A, Shajahan AN. Endoplasmic reticulum stress, the unfolded protein response, autophagy, and the integrated regulation of breast cancer cell fate. Cancer Res. 72(6):1321-31. (2012)
- de Assis S, Warri A, Cruz MI, Laja O, Tian Y, Zhang B, Wang Y, Huang TH, Hilakivi-Clarke L.High-fat or ethinyl-oestradiol intake during pregnancy increases mammary cancer risk in several generations of offspring. Nat Commun. 3:1053.
- (2012)Madhavan S, Gusev Y, Harris M, Tanenbaum DM, Gauba R, Bhuvaneshwar K, Shinohara A, Rosso K, Carabet L, Song L, Riggins RB, Dakshanamurthy S, Wang Y, Byers SW, Clarke R, Weiner LM. G-DOC®: A Systems Medicine Platform for Personalized Oncology. Neoplasia 13:9. (2011)
- 5. Tyson, J.J., Baumann, W.T., Chen, C., Verdugo, A., Tavassoly, I., Wang, Y., Weiner, L.M. & Clarke, R. "Dynamic models of estrogen signaling and cell fate in breast cancer cells." *Nature Rev Cancer*, 11: 523. (2011)

The purpose of G-DOC is to facilitate systems medicine by providing easy identification of trends and patterns in these integrated datasets that ultimately result in better targeted and personalized therapies for cancer and other diseases.

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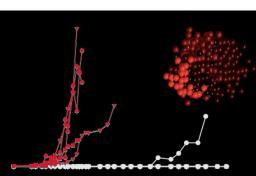
GENESYS RESEARCH INSTITUTE/TUFTS UNIVERSITY

SCHOOL OF MEDICINE: CENTER FOR CANCER SYSTEMS BIOLOGY

http://cancer-systems-biology.org

TITLE: Intercellular Interactions Modulate Carcinogenesis Course: A Dynamic System Study

PURPOSE



The Center of Cancer Systems Biology (CCSB) brings together diverse researchers from biological, mathematical, physical, and clinical backgrounds to better understand the molecular, tissue, and systems-level events underlying cancer progression and development (carcinogenesis). Because carcinogenesis evolves over multiple scales ranging from molecular signaling to cellular and tissue interactions, it is crucial to integrate the information from each level in order to gain an understanding of the entire process. By discovering and examining the underlying processes and interactions at the various levels, the GRI/Tufts CCSB aims to gain predictive insight into the development and evolution of cancer, as well as to identify key population-level dynamics and intercellular interactions that modulate carcinogenic transformation, tumor progression, or dormancy (a period of non-growth). In addition to laboratory investigations, we use mathematics and computer models to examine the influence of three essential determinants of tumor growth: interactions between cancer cells and normal cells; tumor heterogeneity, including the role of "cancer stem cells" (those cancer cells capable of initiating and sustaining tumor growth); and the capacity of the host to support cancer expansion e.g. tumor stimulation of blood vessel formation (angiogenesis). We additionally investigate the role of the body's immune system in modulating cancer development. Taking into account these underlying regulatory interactions, we construct theoretical and computational models to predict the evolutionary course of cancers. As part of the ICBP network, our efforts add to the current understanding of carcinogenesis and identify how interactions between cells in a tumor, as well as interactions between the tumor and the host affect disease development and progression.

Technical

The goal of our multi-disciplinary team is to gain predictive insight into the development and evolution of cancer, as well as to identify key population-level dynamics and intercellular interactions that modulate carcinogenic transformation, tumor progression, or dormancy. By incorporating interactions at the cellular, tissue and system levels, our aim is to gain multi-scale predictive insight into an augmented carcinogenesis paradigm that incorporates not only the well-established oncogene dysregulations known to drive individual cancer cell behavior, but also identifies key population-level dynamics, including intercellular interactions, that can contribute to carcinogenic transformation, cancer self-renewal, and tumor progression. Our tightly knit and highly interactive team incorporates a broad range of scientific expertise, in cellular, molecular and radio-biology, oncology, mathematics, bioinformatics, physics, and engineering, allowing us to be flexible in our strategy to improve the understanding of carcinogenesis dynamics for optimizing cancer treatment.

KEYWORDS

Carcinogenesis, cancer progression, heterogeneity, cancer stem cells, angiogenesis, tumor dormancy, mathematical and computer models, microenvironment, cell-cell interactions, multi-scale.

RESOURCES

Publications

1. Center of Cancer Systems Biology Second Annual Workshop--Tumor Metronomics: Timing and Dose Level Dynamics. Hahnfeldt P, Hlatky L, Klement GL. Cancer Res. 73(10):2949-54, 2013.

2. <u>Mathematical models of immune-induced cancer dormancy and the emergence of immune</u>

- evasion. Wilkie KP, Hahnfeldt P. Interface Focus. 2013;3(4):20130010. Epub 2013 Jun 25.
- Biological effects of proton radiation: what we know and don't know. Girdhani S., Sachs R. Hlatky L. Radiat Res 179(3): 257-72, 2013.
- 4. The emerging "hallmarks" of metabolic reprogramming and immune evasion: distinct or linked? Kareva I, Hahnfeldt P. Cancer Res. May 1;73(9):2737-42, 2013.
- 5. Tumor-immune dynamics regulated in the microenvironment inform the transient nature of immune-induced tumor dormancy. Wilkie KP, Hahnfeldt P. Cancer Res. 2013 Mar 27.
- 6. Cancer stem cells: a minor cancer subpopulation that redefines global cancer features. Enderling H, Hlatky L, Hahnfeldt P. Front Oncol. 2013 Apr 15;3:76.
- 7. The host support niche as a control point for tumor dormancy: implications for tumor development and beyond. Hahnfeldt P. Adv Exp Med Biol. 2013;734:19-35.
- 8. Molecular signaling network complexity is correlated with cancer patient survivability. Breitkreutz D, Hlatky L, Rietman E, Tuszynski JA. Proc Natl Acad Sci U S A. 2012 Jun 5;109(23):9209-12.
- Prospective identification of glioblastoma cells generating dormant tumors. Satchi-Fainaro R, Ferber S, Segal E, Ma L, Dixit N, Ijaz A, Hlatky L, Abdollahi A, Almog N. PLoS One. 2012;7(9):e44395.
- 10. Systems biology of tumor dormancy: linking biology and mathematics on multiple scales to improve cancer therapy. Enderling H, Hahnfeldt P, Hlatky L, Almog N. Cancer Res. 2012 May 1;72(9):2172-5.
- 11. Double-strand break motions shift radiation risk notions? Hlatky, L. Proc Natl Acad Sci USA 109(2):3511, 2012.
- 12. Proton irradiation suppresses angiogenic genes and impairs cell invasion and tumor growth. Girdhani S, Lamont C, Hahnfeldt P, Abdollahi A, Hlatky L. Radiat Res 178: 33-45, 2012.
- Immunoediting: evidence of the multifaceted role of the immune system in self-metastatic tumor growth. Enderling H, Hlatky L, Hahnfeldt P. Theor Biol Med Model. 2012 Jul 28;9:31.
- 14. A multicellular basis for the origination of blast crisis in chronic myeloid leukemia. Sachs RK, Johnsson K, Hahnfeldt P, Luo J, Chen A, Hlatky L. Cancer Res. 2011 Apr 15; (8):2838-47.

Wet Lab

- Full range of *in vitro* experimental assays, including function assays, (e.g. angiogenesis, invasion/migration, proliferation capacity, etc.) to investigate "hallmarks" of cancer.
- Full range of *in vivo* models of tumor growth and metastasis, including pathology and histological expertise.

Mathematical Modeling

- Intra-tumor Heterogenity: Tumor population composition models, e.g. cancer stem cells.
- Cell-to-Tissue Scale: Dynamic analytic models that predict how cell-cell signaling interactions modulate tumor growth and treatment response: e.g. Angiogenesis signaling, tumor-immune interactions.
- Organism to Tumor Population Scale: PMath models using patient tumor CT scan data to understand tumor growth over long-times (years) to inform therapy Analytic tools.
- Logistic Dynamic Carrying Capacity Analysis
- Network topology analysis for prognosis and therapeutic targeting
- Computational Modeling
 - o Agent-based methods for examining tumor growth in heterogeneous cellular environments
 - Radiation action: DNA damage kinetics
 - Drug dosing bolus vs metronomics -- principles of action and targets



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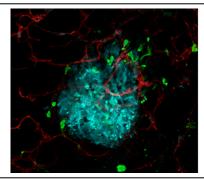
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THE METHODIST HOSPITAL RESEARCH INSTITUTE, BAYLOR COLLEGE OF MEDICINE, UNIVERSITY OF NEW MEXICO, CENTER FOR MODELING CANCER DEVELOPMENT: CENTER FOR CANCER SYSTEMS BIOLOGY http://www.methodisthealth.com/cmcd

TITLE: The Center for Modeling Cancer Development

PURPOSE

Breast cancer originates from a single cell, a tumor-initiating cell that



has acquired changes in its genetic makeup that allows it to divide more rapidly than normal cells, and to survive when normal cells would die. However, tumor-initiating cancer cells do not function on their own in the body and must interact not only with other cancer cells, but also with normal cells such as blood vessels, fat cells, fibroblasts, and cells in the immune system. Our center seeks to discover how tumor-initiating cancer cells are controlled by interactions with cancerous and normal cells, and how better to target tumor-initiating cells in treatment.

<u>Technical</u>

Our center has developed a series of fluorescent lentiviral vectors that report on the activity of signaling networks known to regulate the function of tumor-initiating breast cancer cells. Using these vectors, we can identify, and enrich for, tumor-initiating activity, localize such cells relative to other cells in the tumor microenvironment, and evaluate the response of these cells to treatment. We can also use these reporters as visual readouts for genetic (shRNA) and pharmacological manipulations of key regulatory pathways functioning in these cells. Resulting experimental data can be modeled computationally to understand how tumors develop as a community of cancer cells and normal cells, and model their regulation.

KEYWORDS

Cancer cells, proliferation, cell cycle, targeted therapeutics, microenvironment, dynamics, fluorescent lentiviral reporters, tumor microenvironment, mathematical models

RESOURCES

Publications

- Kessler JD, Kahle KT, Sun T, Meerbrey KL, Schlabach MR, Schmitt EM, Skinner SO, Xu Q, Li MZ, Hartman ZC, Rao M, Yu P, Dominguez-Vidana R, Liang AC, Solimini NL, Bernardi RJ, Yu B, Hsu T, Golding I, Luo J, Osborne CK, Creighton CJ, Hilsenbeck SG, Schiff R, Shaw CA, Elledge SJ, Westbrook TF. A SUMOylation-dependent transcriptional subprogram is required for Mycdriven tumorigenesis. *Science.* 2012 Jan 20;335(6066):348-53. Pubmed ID: 22157079.
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- Macklin P, Edgerton ME, Thompson AM, Cristini V. Patient-calibrated agent-based modelling of ductal carcinoma in situ (DCIS): from microscopic measurements to macroscopic predictions of clinical progression. J Theor Biol. 2012 May 21;301:122-40. Pubmed ID: <u>22342935.</u>

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INTEGRATIVE CANCER BIOLOGY PROGRAM @ MIT: TUMOR CELL NETWORKS CENTER: CENTER FOR CANCER SYSTEMS BIOLOGY

http://web.mit.edu/icbp/

TITLE: Regulatory Networks in Cancer Initiation and Progression

PURPOSE

Cancer is not a disease characterized by gene dysregulation alone. Integration of additional layers of biological data, including information about protein activity and energy



requirements, are critical to the understanding of how particular tumor cells respond to cues directing them to either proliferate, migrate, or die. The MIT ICBP center aims to build predictive mathematical models that incorporate protein information, including modifications, activity levels, and localization, with underlying genetic signatures to predict treatments and/or metastatic outcomes. Our center focuses on modeling the intracellular signaling networks of three key cell behaviors; mitogenesis (proliferation), migration (invasion/metastasis), and the DNA damage response. We combine hypothesis and data-driven experimental approaches to build predictive models that can be used to investigate tumor responses to conventional and targeted cancer therapies.

Technical

A central thread integrating our experimental and modeling efforts is a paradigmatic 'cue-signalresponse' framework for probing and modeling the regulation of tumor cell phenotypes. We seek to understand the convolution of genotype and environment in controlling molecular networks and consequent phenotypes. Environmental factors comprise the 'cue' category, including biochemical ligands (cytokines, extracellular matrix, inhibitory drugs) and physical inputs (DNA damaging agents, such as radiation and chemical toxins). Intracellular regulatory states conferred by these cues are cast in the 'signal' category; these primarily involve protein signaling and gene expression pathways in our work. Resulting phenotypic behaviors, such as cell death, proliferation, and migration, comprise the 'response' category, as measured by cytoskeletal, metabolic, and transcription/translation experiments.

Construction and testing of these predictive models is currently underway and linked to three important problems in cancer biology and therapy: (a) cancer progression via dysregulation of mitogenic signaling pathways downstream of receptor tyrosine kinases (with particular focus on the ErbB receptor system); (b) cancer progression via inappropriate cell migration that promotes invasive and metastatic behaviors; and (c) cancer treatment via molecular pharmaceuticals, including chemotherapeutics and targeted inhibitors (small molecules and antibodies). We believe that there are no "one size fits all" experimental or modeling approaches specifically suited to analyzing, interpreting, and/or predicting all types of questions in the realm of cancer biology. Thus, we employ a wide array of experimental methodologies, including techniques for identifying and analyzing correlative relationships (e.g., partial least-squares regression), network topologies (e.g., the prize-collecting Steiner forest algorithm), probabilistic influences between components (e.g., Boolean and fuzzy logic models, Bayesian networks), and physicochemical mechanisms (differential equations), to study cancer biology.

KEYWORDS

Mitogenesis, metastasis, gene regulatory network, protein signaling network, statistical modeling, DNA damage, Bayesian networks

RESOURCES

Publications

- 1. Kreeger, P.K. and D.A. Lauffenburger. Cancer systems biology: A network modeling perspective. Carcinogenesis 31, 2-8 (2010).
- Lee MJ, Ye AS, Gardino AK, Heijink AM, Sorger PK, MacBeath G, Yaffe MB. Sequential application of anticancer drugs enhances cell death by rewiring apoptotic signaling networks. Cell 2012 May 11;149(4):780-94.

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- 6. Pritchard JR, Bruno PM, Hemann MT, Lauffenburger DA. **Predicting cancer drug mechanisms** of action using molecular network signatures. Mol BioSyst. 2013. Ahead of print 20 Dec 2012.
- Huang SS, Clarke DC, Gosline SJ, Labadorf A, Chouinard CR, Gordon W, Lauffenburger DA, Fraenkel E. Linking Proteomic and Transcriptional Data through the Interactome and Epigenome Reveals a Map of Oncogene-induced Signaling. PLoS Comput Biol. 2013 Feb;9(2):e1002887.

Videos

Mike Hemann and Luke Gilbert discuss chemoresistance: <u>http://www.youtube.com/watch?v=vUNcswCZcSI</u> *Frank Gertler discusses Mena as a potential biomarker:*

http://www.youtube.com/watch?v=4fHywHv-I24

Websites

Data and models of the MIT ICBP center: <u>http://web.mit.edu/icbp/data/index.html</u> Computational and Systems Biology at MIT: <u>http://csbi.mit.edu/</u>

CONTACT

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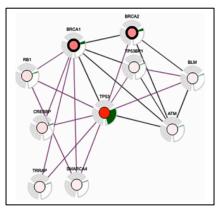
MEMORIAL SLOAN-KETTERING CANCER CENTER: CENTER FOR CANCER SYSTEMS BIOLOGY

http://cbio.mskcc.org/

TITLE: Systems Biology of Diversity in Cancer

PURPOSE

Memorial Sloan-Kettering Cancer Center's (MSKCC's) Center for Cancer Systems Biology comprises research groups with both computational and experimental expertise that apply a systems biology approach to studying cancer. Its faculty is also tightly involved in multiple collaborations with data generating groups who engage in



translational medicine projects with clinical data. By applying a systems biology framework, our Center studies diversity in cancer at multiple levels: within a monogenic population of cells, between cancer cells and host tissue, and between patients.

Technical

Recent advances in cancer biology and cancer genomics support the need to develop customized therapies for patients. We are investigating tumor cell heterogeneity both within tumors and among patients to gain insight needed for the development of subtype-specific and patient-specific therapies. We aim to understand cellular dynamics during oncogenesis and treatment, taking into account the heterogeneous distribution of tumor cells on a uniform genetic background. Additionally, we are dissecting and modeling communication between tumor cells and the host microenvironment to determine how these complex interactions contribute to cancer progression and invasion. We are also investigating differences in regulatory processes leading to patient-patient heterogeneity for a given cancer, such as differences in regulatory information flow due to alterations in cell signaling networks that establish cancer subtypes or differences in expression levels of key signaling regulators that underlie functional heterogeneity in a population of malignant cells.

KEYWORDS

Cancer genomics, machine learning, drug perturbations, agent-based modeling

RESOURCES

Publications

- 1. Jesse W. Cotari, Guillaume Voisinne, Orly Even Dar, Volkan Karabacak, and Grégoire Altan-Bonnet. "Cell-to-Cell Variability Analysis Dissects the Plasticity of Signaling of Common 7 Chain Cytokines in T Cells". 12 March 2013: ra17. *Science Signaling.*
- Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, Antipin Y, Reva B, Goldberg AP, Sander C, Schultz N. "The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data". 2012 May;2(5):401-4. doi: 10.1158/2159-8290.CD-12-0095. Cancer Discov.
- Setty M, Helmy K, Khan AA, Silber J, Arvey A, Neezen F, Agius P, Huse JT, Holland EC, Leslie CS. "Inferring transcriptional and microRNA-mediated regulatory programs in glioblastoma". 2012;8:605. doi: 10.1038/msb.2012.37. Mol Syst Biol.

Web Tools

http://cbio.mskcc.org/tools/index.html Cancer Genomics (Cancer Genomics Data Portal, Mutation Assessor, Cancer Genes) Clinical Data Repositories Handheld Devices (BioGene) microRNAs (MicroRNA.org, miRanda)



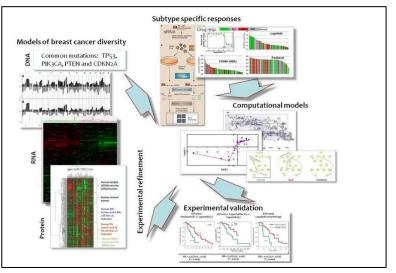
Pathways & Networks (BioPAX, Pathway Commons, Cytoscape) iHOP – Information Hyperlinked over Proteins MEMo (method for identifying mutually exclusive driver networks in cancer) NetBox (network analysis on human interaction networks)

CONTACT

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TITLE: Model-based Predictions of Responses to RTK Pathway Therapies

The Oregon Health and Science University ICBP Center focuses on developing a stronger understanding of the responses of ductal breast cancers to therapeutic agents that target aspects of aberrant receptor tyrosine kinase (RTK) signaling. Receptor Tyrosine Kinases are protein receptors on the surfaces of cells that bind, with high affinity, to signaling agents like hormones, cytokines, or other growth factors. When these signaling agents bind to an RTK, a



phosphate group attached to a tyrosine residue on the RTK may change from phosphorylated to unphosphorylated or vice versa, and this state change is used as an important switch in many signaling networks. We attempt to understand the reactions of these networks to therapies by designing models that predict the behavior of the signaling networks when treated with individual RTK-targeting drugs as well as combinations of such drugs. Our emphasis is on HER-family RTKs and their downstream targets in the PI3K and MAPK networks, where HER stands for Human Epidermal growth Receptor. The HER family of RTKs is a set of four genetically related and structurally similar RTKs that are often overexpressed in cancers and have to do with cell proliferation. The HER family is sometimes also referred to as the EGFR family or the ErbB family.

A recent report from the pharmaceutical industry suggests that over 800 new therapeutic agents are now under development or in early clinical trials with the majority targeting RTKs or their signaling networks. However, optimal deployment of agents has not yet been achieved in clinical trial and response varies substantially between patients, with most responses being short term. The central premise of our project is that development of optimal RTK network targeted drug combinations will require experimentally validated, computational models of the diverse resistance and response mechanisms that are specific to breast cancer subtypes and that allow drug combinations to be tested *in silico* so that the most promising can be prioritized for clinical evaluation in subsets of patients most likely to benefit.

PURPOSE

We want to better understand why some breast cancers respond to drugs that target their signaling networks, while some do not. We want to understand the best combinations of drugs to pursue for those that do not. Because the signaling networks involve many components, feedback loops, and changes over time, it is difficult to intuit the behavior of the network in response to a single drug or combination of drugs. It is not enough to simply know that a drug inhibits a particular protein in an isolated cell line experiment. Treatment regimes may need to vary the proportion of drugs in the "cocktail" given to the patient, as well as the timing of the doses. These treatment regimes, with their different ratios and schedules, are referred to as drug combinations. The interplay between the signaling networks and the drug combinations is a major factor in the long term efficacies of the different combinations. Experimentally validated mathematical models of the signaling network help us understand the dynamic behavior of the network, and allow us to try out different drugs in simulation before we try them out in cell lines.

Technical

We have previously demonstrated that, in the case of breast cancer, HER2-family RTK network function differs substantially between breast cancer subtypes. In ductal breast cancer, three subtypes are now well accepted; estrogen receptor positive (ER+), HER2 amplified (HER2+) and triple-negative (TNBC; ER negative (ER-), progesterone receptor negative (PR-) and not amplified for HER2). Our project includes: assessing specific connectivity models in all breast cancer subtypes; developing a unified model of MEK signal transduction networks in claudin-low TNBC; developing dynamic models of response to HER family inhibitors in tumors in which HER2 is amplified that encompasses both fast, phosphorylation-based events and slower transcriptional and epigenomic processes; modeling the regulatory connectivity in the PI3K signaling network in a panel of luminal breast tumor cell lines: and development of models of nutrient uptake and utilization associated with PI3K signaling. We have developed methods for inferring the signaling networks using Bayesian methods, convex optimization, and methods derived from new optimization methods which take advantage of network sparsity. Our Center has also developed the recent DREAM challenge: crowdsourcing network inference methods to try to come up with the network which most closely represents the data. Once we infer a network model, we develop experimentally validated differential equation models for this network which attempt to describe the dynamics of the signaling networks in both time and space.

KEYWORDS

Receptor tyrosine kinase (RTK) signaling; HER receptor family; HER2 positive breast cancer; Bayesian models; Ordinary Differential Equation (ODE) models in cancer; Bayesian modeling; compressive sensing methods in network identification.

RESOURCES

Publications

- 1. L. M. Heiser et al., "Subtype and pathway specific responses to anticancer compounds in breast cancer", October 14, 2011, doi: 10.1073/pnas.1018854108.
- 2. S. M. Hill et al., "Bayesian inference of signaling network topology in a cancer cell line", Bioinformatics 28(21):2804-10, November 2012. doi: 10.1093/bioinformatics/bts514.
- 3. Y. H. Chang, J. W. Gray, and C. J. Tomlin, "Optimization-based Inference for Temporally Evolving Networks with Applications in Biology", *Journal of Computational Biology*. 19(12): 1307-1323, 2012.

<u>Reviews</u>

J. Korkola and J. W. Gray, "Breast cancer genomes – form and function", Curr Opin Genet Dev. 2010 February; 20(1):4-14. doi:10.1016/j.gde.2009.11.005.

Special issues

http://rsfs.royalsocietypublishing.org/content/3/4/20130023.full

Favorite book

An Introduction to Systems Biology: Design Principles of Biological Circuits. Uri Alon, 2007 Chapman & Hall/CRC Press.

Training courses

MD Anderson Program in Biostatistics, Bioinformatics, and Systems Biology: http://www.mdanderson.org/education-and-research/education-and-training/schools-andprograms/research-training/programs-and-courses/program-of-biostatistics-bioinformatics-andsystems-biology/index.html

OHSU Biomedicine in 4D: <u>http://www.ohsu.edu/xd/education/schools/school-of-</u> medicine/departments/basic-science-departments/biomedical-engineering/spatial-systemsbiomedicine/conference.cfm

Websites related to HER-family RTK signaling networks, mathematical modeling of signaling networks:

- 1. Our project website: http://sysbio.banatao.berkeley.edu/
- 2. HPN DREAM network inference challenge: http://www.the-dream-project.org/challenges/hpndream-breast-cancer-network-inference-challenge
- 3. HER Signaling: http://www.biooncology.com/biological-pathways/her-signaling
- 4. UC Berkeley BIO301, Receptor Tyrosine Kinase Signaling: http://www.youtube.com/watch?v=G16ewh5iN9U
- 5. HER2 Positive Breast Cancer: http://www.mayoclinic.com/health/breast-cancer/AN00495; http://www.ucsf.edu/news/2010/03/5979/her2-breast-cancer-clinical-trial-based-research-advance
- Personalized medicine, AACR podcast interview with Gordon Mills: <u>http://www.youtube.com/watch?v=kS8dsrY0_3c</u>
- 7. Classification of breast cancers: <u>http://www.webmd.com/breast-cancer/breast-cancer-types-er-positive-her2-positive</u>

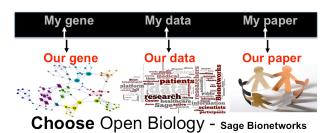
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PURPOSE

Sage Bionetworks is a non-profit research organization that provides the tools and environment to conduct dynamic, large-scale collaborative



to conduct dynamic, large-scale collaborative biomedical research. We believe in the importance of iteratively generating and testing novel hypotheses transparently and collaboratively. Our goal is to improve access to knowledge and accelerate the pace of research through interdisciplinary teams and to translate these research

At Sage Bionetworks, we believe that successful biomedical research requires active participation from all stakeholders. We are reimagining the role of citizens in the research process and are building tools to empower them to contribute both their data and expertise as they see fit. We are also engaging the community to crowd-source solutions to complex biomedical questions through targeted DREAM challenges.

results into actionable discoveries that can ultimately be used to improve patient care.

We have developed a technology platform for large-scale data analysis, sharing, and reuse. This open source platform, <u>Synapse</u>, enables researchers to seamlessly and transparently conduct, track and share their ongoing work – building up living research projects in real-time. Synapse also contains a rich collection of diverse molecular data that can be communally leveraged for building models of disease.

Cancer is a complex and heterogeneous disease and understanding its mechanisms of action can only be done by treating the human body as an elaborate and interconnected system. Our efforts in cancer research bring together clinical oncologists, computational scientists, and professional software engineers whose diverse backgrounds allow for critical assessment of working hypotheses. Our interdisciplinary teams work together to develop predictive disease models using large multi-layer data. We study the relationships between different molecular profiles and clinical outcomes to understand the molecular underpinnings that characterize and drive the tumorigenic process. We utilize a variety of statistical and machine learning techniques to develop predictive models in cell lines and primary tumor data and apply network and pathway analysis to integrate data and move toward evaluating biology at a system-wide level.

KEYWORDS

Data sharing, governance, challenges, open science, predictive modeling, machine learning, Bayesian methods, cell lines, drug sensitivity, driver genes, network analysis, Portable Legal Consent, Bridge, DREAM, Synapse

RESOURCES

Publications

- 1. Margolin A et al. "Systematic Analysis of Challenge-Driven Improvements in Molecular Prognostic Models for Breast Cancer".
- 2. Friend S and Norman TC "Metcalfe's law and the biology information commons".
- 3. Hanahan D and Weinberg RA. "Hallmarks of Cancer: the next generation".
- 4. For most up-to-date publications list: <u>http://sagebase.org/publications/</u>.

Online Resources

• Synapse: a platform to support open, collaborative data analysis for clear, reproducible science

- Description (<u>http://sagebase.org/synapse-overview/</u>)
- Main portal: (<u>https://www.synapse.org/</u>)
- Dialogue on Reverse Engineering Assessment and Methods (DREAM): project to run challenges that activate collaborative teams of scientists to work on biological and translational medicine discoveries
 - Description (<u>http://sagebase.org/dream/</u>)
 - Main portal (<u>http://www.the-dream-project.org/</u>)
- Consent to Research (<u>http://weconsent.us/</u>)
- BRIDGE (<u>http://sagebridge.org/</u>)
- Portable Legal Consent Ted talk (<u>http://weconsent.us/portable-legal-consent-ted-talk-online/</u>)
- Sage Bionetworks on GitHub (<u>https://github.com/Sage-Bionetworks</u>)
- R Bioconductor: Open source software for bioinformatics (http://www.bioconductor.org/)
- The Cancer Genome Atlas (TCGA):
 - TCGA Symposium, Lead Talk
 - The Link Between TCGA and Personalized Cancer Therapies (http://www.youtube.com/watch?v=epsZjJ_A1y4)
 - Peter W. Laird IDH and oncometabolite (http://www.youtube.com/watch?v=Xt3G6-ycv8Q)
- Sage Bionetworks Congress: "The Truth of Personalized Medicine: Our Commons Future" (http://fora.tv/conference/sage bionetworks commons congress 2013)
- Coursera: Online classes (<u>https://www.coursera.org/</u>)

CONTACTS

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Christine Suver, PhD christine.suver@sagebase.org STANFORD UNIVERSITY: CENTER FOR CANCER SYSTEMS BIOLOGY

http://ccsb.stanford.edu/

TITLE: Modeling the Role of Differentiation in Cancer Progression

PURPOSE

The Stanford Center for Systems Biology of Cancer (CCSB) aims to



discover molecular mechanisms underlying cancer progression by studying cancer as a complex biological system that is driven, in part, by impaired differentiation. Increasing evidence indicates that many cancers, like normal tissue, are composed of a hierarchy of cells at different stages of differentiation, and that the disease is maintained by a self-renewing subpopulation. Our goal is to provide a better understanding of the self-renewing properties of cancer that will enable us to identify molecular therapeutic targets and strategies to eradicate this disease, or to maintain it in a nonlethal state. Our biological projects are integrated with novel computational techniques, designed to dissect processes and causal factors underlying impaired differentiation as a driver of cancer progression in several blood cancers.

Technical

In order to identify mechanistic underpinnings of cancer progression, a network-based and multi-scale viewpoint is mandatory. Increasingly, diseases such as cancer are recognized as resulting from disruption in the coordinated performance of a complex biological system. This systems biology viewpoint necessitates the incorporation of high throughput, high dimensional data, and development of computational methods specifically geared to its analysis. We are developing essential and interlocking methods for a comprehensive systems analysis of cancer. First, powerful methods will be developed to infer molecular regulatory networks that drive phenotypic processes such as differentiation. Second, computational approaches will be developed that can identify and isolate underlying patterns of progression in cancer, which can then be related to underlying regulatory networks. Third, executable models will be developed so that it is possible to pose hypothetical "what if questions to predict how, for example, a targeted intervention might affect the subsequent course of disease. These computational approaches will be applied to the study of differentiation in AML. Follicular Lymphoma and T-ALL. In AML, we will identify regulatory networks driving leukemic stem cells. In Follicular Lymphoma, we will analyze the relationship between BCR-sensitive and BCRinsensitive subpopulations. In T-ALL, we will study the self-renewing properties of MYC in a transgenic mouse model. Our integrative approach will enable us to ascertain differences between these hematologic malignancies, and commonalities, which may generalize to other cancers.

KEYWORDS

Follicular lymphoma, T-cell acute lymphoblastic leukemia, acute myeloid leukemia, hematologic neoplasms, modeling, mouse model, network-based modeling, next generation sequencing, self-renewal, stem cells, systems biology, transgenic mice, tumor progression, topological analysis.

RESOURCES

Publications

- 1. Hierarchy in somatic mutations arising during genomic evolution and progression of follicular lymphoma. Green MR, Gentles AJ, Alizadeh AA, et al. Blood. 2013.
- Multiplexed mass cytometry profiling of cellular states perturbed by small-molecule regulators. Bendall SC, Nolan GP, et al. Nature biotechnology. 2012 Sep, 30 (9):858-67.

Extracting a cellular hierarchy from high-dimensional cytometry data with SPADE. Qiu P, Simonds EF, Bendall SC, Gibbs KD, Bruggner RV, Linderman MD, Sachs K, Nolan GP, Plevritis SK. Nat Biotechnol. 2011, 29 (10): 886-91.

- Topology based data analysis identifies a subgroup of breast cancers with a unique mutational profile and excellent survival. Nicolau M, Levine AJ, Carlsson G. Proc Natl Acad Sci U S A. 2011 Apr.
- B-cell signaling networks reveal a negative prognostic human lymphoma cell subset that emerges during tumor progression. Irish JM, Myklebust JH, Alizadeh AA, Houot R, Sharman JP, Czerwinski DK, Nolan GP, Levy R. Proc Natl Acad Sci U S A. 2010, Jul 20,107(29):12747-54.

Videos and presentations

Annual symposium videos http://ccsb.stanford.edu/events/video_gallery.html

Next generation sequencing workshop slides <u>http://ccsb.stanford.edu/education/ngs2012.html</u>

Principles in Cancer Systems Biology Slides http://ccsb.stanford.edu/education/cbio243course.html

<u>Software</u>

Program	Description	Contact	Implementation
<u>Correlate</u>	Performs sparse canonical correlation analysis.	Rob Tibshirani, PhD	Excel plug-in
<u>Cytobank</u>	Manage, analyze and share flow cytometry data over the web	info@cytobank.org	Web Platform
<u>DPM</u>	A nonlinear method based on modeling the joint distribution of response and covariates using the Dirichlet process mixtures of linear models.	Babak Shahbaba, PhD	Matlab
<u>FastPairMI</u>	Fast calculation of pairwise mutual information from gene expression microarrays for network reconstruction.	Peng Qiu, PhD	Matlab
Lirnet	Performs module network reconstruction.	Daphne Koller, PhD	Matlab
<u>Mapper</u>	A computational method for extracting simple descriptions of high dimensional data sets in the form of simplicial complexes.	Gunnar Carlsson, PhD	Matlab
<u>MethylMix</u>	A computational algorithm based on a Gaussian mixture modeling to identify DNA methylation states relative to normal tissue.	Olivier Gevaert, PhD	Matlab
PMA	Performs penalized multivariate analysis.	Daniela Witten, PhD	R
SPACC	A classifier that can perform both class discovery and classification.	Peng Qiu, PhD	Matlab
SPADE	An analytical tool for single-cell cytometry data analysis.	Peng Qiu, PhD	Matlab
<u>SPD</u>	A computational approach to discover patterns of biological progression underlying a microarray dataset.	Peng Qiu, PhD	Matlab

Program	Description	Contact	Implementation
<u>StepMiner</u>	Method to infer stepwise progression across ordered genomic data	Debashis Sahoo, PhD	Java
<u>MidReg</u>	A method of mining developmentally regulated genes using Boolean implications	Debashis Sahoo, PhD	
BGSA	Bayesian gene set analysis	Babak Shahbaba, PhD	R

CONTACTS

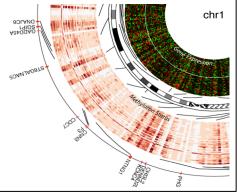
Anita Samantaray Program Manager anitas1@stanford.edu Andrew Gentles, PhD Scientific Program Manager andrewg@stanford.edu

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO-INDIANA UNIVERSITY: CENTER FOR CANCER SYSTEMS BIOLOGY

http://icbp.uthscsa.edu

TITLE: Cancer Epigenomics as a Path to Diagnose and Treat Tumors

The University of Texas Health Science Center at San Antonio and Indiana University ICBP sites (SA-IU CCSB) are focused on understanding the epigenomic changes associated with hormone resistant cancers and the development of therapies for tumor resistance, recurrence and metastasis. We hypothesize that DNA methylation signatures can be used for predictive prognostic testing in order to better tailor patient treatments.



Our centers assemble an integrated team of scientists to uncover how the epigenome interacts with the genome in the genesis and the progression of human cancers, at both the global level and the single gene level, to provide opportunities for personalized medicine in cancer prevention and recurrence. The centers use cutting-edge next generation sequencing technologies coupled with novel bioinformatics and computational approaches to unravel the role of epigenetic alternations in human cancers and their microenvironment in the dysregulated cellular and molecular functions observed in solid cancers. Our team of scientists systematically collects information on the cancer epigenome and provides informatics tools to the ICBP and research community using visualization of data through web portals to facilitate viewing and data mining.

PURPOSE

Genetic and epigenetic changes in tumor genomes are important predictors of patient outcomes. The environment tumors develop in also affects tumor growth and metastatic potential. Factors expressed by the host including cytokines and hormones alter the carcinogenesis process. One cellular modification known to be different between tumor and normal tissues and influenced by the host environment is DNA methylation.

Technical

The SA-IU CCSB focuses on studying epigenomic changes leading to carcinogenesis primarily using DNA methylation profiling (Methyl Binding Domain Capture Sequencing, MBDcap-seq, in particular). In analyzing retrospectively collected tumor and tissue samples collected through biobanks will associated prognostic data are used to identify Differentially Methylated Genes (DMGs) and Differentially Methylated Regions (DMRs) when comparing patients with good versus poor outcomes. Over 500 tissue samples (including from tumor, normal adjacent and non-cancer sources) have been profiled using MBDcap-seq and many datasets are available for browsing through the methylome browser (http://cbbiweb.uthscsa.edu/KMethylomes). By providing access to these data through an integrated browser based visualization tool you can easily choose areas of interest including differentially methylated regions or search for your genes of interest to analyze their DNA methylation status in several tumor types.

A second focus area is in hormone dependent cancers including ovarian, breast, endometrial and prostate cancer. A number of techniques are used in order to assess how hormone signaling affects genomic changes in tumors. Chromosome conformation capture (3C-seq) allows for the analysis of DNA structures formed by looping through protein-protein interactions including those of transcription factors and co-factors. This method has been used to profile genomic interactions of estrogen receptor with its enhancers in normal tissues and tumors.



KEYWORDS

Epigenomics, DNA methylation (5mC), Methyl binding domain capture sequencing (MBDcap-seq), Bioinformatics, pathway analysis, data visualization, tumor heterogeneity, genomic DNA methylation biomarkers, hormone dependence.

RESOURCES

<u>Review</u>

Next-generation sequencing in breast cancer: first take home messages. Desmedt et al. (2012).

Favorite book

The Transforming Principle: Discovering that Genes Are Made of DNA

Training courses

CS1173 (Kay Robbins, Professor, UTSA): <u>http://www.cs.utsa.edu/~cs1173</u> Yunlong Liu, Associate Professor, IUPUI: <u>http://www.youtube.com/playlist?list=PL1D0F3DA630CFBF70</u> The slides for this course can be requested.

Next generation sequencing tools

A bioinformatics tool set for next generation sequencing data analysis: (<u>http://www.ngsutils.org</u>), including: bamutils, bedutils, fastqutils and gtfutils.

Websites related to genomics, epigenomics and DNA methylation:

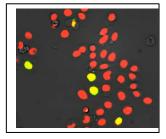
- 1. http://cbbiweb.uthscsa.edu/KMethylomes/
- 2. <u>http://www.dnaftb.org</u> Avery's experiment: http://www.dnaftb.org/17/index.html
- 3. More biochemical, for scientists: http://www.youtube.com/watch?v=7WEHoCA1hpo
- 4. DNA Methylation Animation EpiXplore[™] Methylated DNA Enrichment Kit: http://www.youtube.com/watch?v=4ZEWsjW4AZA
- 5. http://www.youtube.com/watch?v=4dkzG-Kr IQ
- 6. Epigenetics Overview: <u>http://www.youtube.com/watch?v=Tj_6DcUTRnM</u>
- Next-Generation Sequencing Technologies Elaine Mardis (2012) comparison of different sequencing chemistries: <u>http://www.youtube.com/watch?v=PMIF6zUeKko</u>
- 8. Regulatory and Epigenetic Landscapes of Mammalian Genomes Laura Elnitski (2012): http://www.youtube.com/watch?v=ycRcLqscnuQ&feature=relmfu
- 9. Science 101 for Parents: How Epigenetics is Revolutionizing the Understanding of Heredity: http://www.youtube.com/watch?v=NOsWY4Q_4IU
- 10. Epigenetic Cancer Treatments: http://www.youtube.com/watch?v=-KLAafIITBY
- 11. The Epigenome at a Glance: http://www.youtube.com/watch?v=s7dDd1bvNfA
- 12. Epigenetics: What Makes Us Who We Are? Begin Before Birth: http://www.youtube.com/watch?v=9AfBsTAQ8zs

CONTACTS

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http://ccsb.vanderbilt.edu/ccsb/

TITLE: Quantifying Variability of Treatment Response to Inform Predictions of Relapse and Tumor Progression



PURPOSE

Cancer is primarily a disease of uncontrolled cellular proliferation. It is now understood that even with the same genetic background (i.e., mutations) cancer cells can respond differently (variability or heterogeneity) to the same stimulus (treatment and microenvironment) yet little is known about how individual cells make decisions to progress through the cell cycle even during treatment.

Technical

Recent technological advances have now made it possible to obtain information about cell cycle progression at the single cell level and these rich data sets are providing a wealth of new information about how benign and cancerous cells make decisions such as survival and death. In our Center, we use fluorescent time-lapse microscopic imaging of human cancer cell lines to investigate population dynamics of cell cycle progression in response to drug treatment. Cells with fluorescent tags are imaged at high-resolution intervals to extract cell age and cell cycle states using novel computational software. The data is then fitted to one or more mathematical/computational models to help understand the underlying biology as well as make predictions of response and relapse.

KEYWORDS

Cancer cells, proliferation, cell cycle, targeted therapeutics, oncogenes, microenvironment, dynamics, non-linear responses, real-time imaging, single cell data, mathematical models, growth rates

RESOURCES

Publications

- 1. Tyson, D. R. & Quaranta, V. Personalized cancer treatment beyond genetics: Assessing dynamics and heterogeneity of tumor responses. Personalized Medicine (2013).
- 2. Tyson, D. R., Garbett, S. P., Frick, P. L. & Quaranta, V. Fractional proliferation: a method to deconvolve cell population dynamics from single-cell data. Nat Methods 9, 923–928 (2012).
- 3. Garraway, L. A. & Jänne, P. A. Circumventing cancer drug resistance in the era of personalized medicine. Cancer Discov 2, 214–226 (2012).
- 4. Georgescu, W., Wikswo, J. P. & Quaranta, V. Cell Animation: an open source MATLAB framework for microscopy assays. Bioinformatics 28, 138–139 (2012).
- 5. Anderson, A. R. A. & Quaranta, V. Integrative mathematical oncology. Nat Rev Cancer 8, 227– 234 (2008).

Videos/Materials

Cell Cycle:

Cancer: Unregulated Cell Division - http://www.youtube.com/watch?v=leUANxFVXKc The Cell Cycle and Cancer - http://videolectures.net/mitworld_amon_ccc/ Cancer Cell Cycle and Oncogene Addiction http://www.springerreference.com/docs/html/chapterdbid/306073.html

Growth and Rates:

Are Humans Smarter Than Yeast? - http://www.youtube.com/watch?v=hM1x4RljmnE Exponential Growth Wikipedia - http://en.wikipedia.org/wiki/Exponential_growth

Exponential Growth / Population Growth Problem - https://www.youtube.com/watch?v=63udRYh04sY The Logistic Equation and Models for Population - https://www.youtube.com/watch?v=MIOj-W-jY-k

Targeted Therapeutics: Defining the Spectrum of Resistance to be Targeted Anti-Cancer Therapeutics http://www.youtube.com/watch?v=Yoo0x2cMkxc Targeting critical oncogenic pathways in cancer - http://www.youtube.com/watch?v=JqNgKZ8AA60

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