HHS Public Access

Author manuscript

Cancer Res. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Cancer Res. 2016 December 1; 76(23): 6774–6777. doi:10.1158/0008-5472.CAN-16-1580.

Systems Approaches to Cancer Biology

Tenley C. Archer[1], **Elana J. Fertig**[2], **Sara J.C. Gosline**[3], **Marc Hafner**[4], **Shannon K. Hughes**[5], **Brian A. Joughin**[6], **Aaron S. Meyer**[6,§], **Stephen R. Piccolo**[7], and **Ayesha N. Shajahan-Haq**[8]

[1]Department of Neurology, Boston Children's Hospital, Boston, MA 02115

[2]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD 21205

[3]Sage Bionetworks, Seattle, WA 98109

[4]Department of Systems Biology, Harvard Medical School, Boston, MA 02115

[5]Division of Cancer Biology, National Cancer Institute of the National Institutes of Health, Rockville, MD 20850

[6]Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139

[7]Department of Biology, Brigham Young University, Provo, UT 84602

[8]Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC 20057

Abstract

Cancer systems biology aims to understand cancer as an integrated system of genes, networks, and interactions rather than an entity of isolated molecular and cellular components. The inaugural Systems Approaches to Cancer Biology conference, co-sponsored by the Association of Early Career Cancer Systems Biologists and the National Cancer Institute of the NIH, focused on the interdisciplinary field of cancer systems biology and the challenging cancer questions that are best addressed through the combination of experimental and computational analysis. Attendees found that elucidating the many molecular features of cancer inevitably reveals new forms of complexity, and concluded that ensuring the reproducibility and impact of cancer systems biology studies will require widespread method and data sharing and, ultimately, the translation of important findings to the clinic.

Introduction

Cancer Systems Biology (CSB) recognizes that many individual disciplines and data types can be usefully brought to bear, alone or in combination, to systematically study cancer. The diversity of interactions among cancer systems biologists, who come from fields such as cancer biology, biochemistry, bioinformatics, engineering, mathematics, physics and computer science, can lead to novel approaches to the fundamental challenges within the

[§]Correspondence should be addressed to A.S.M. (ameyer@asmlab.org).

[+]Authors arranged alphabetically and contributed equally.

field of cancer research. The inaugural Systems Approaches to Cancer Biology conference highlighted the important biological insights gained through these synergistic interactions and discussed the unique challenges faced by those who are multidisciplinary. The meeting was organized and purposefully populated by mostly early career tenure-track and junior investigators in training, offering a unique perspective on the emerging field of cancer systems biology. The conference was held in Woods Hole, MA (USA) on April 3–6, 2016, and was chaired by field pioneers Elaine Mardis (Washington U.), Joe Gray (Oregon Health Sciences U.), and Douglas Lauffenburger (MIT).

Central to the meeting was the question of what exactly constitutes CSB, especially in comparison to quantitative or computational work within other fields. Through the diversity of approaches discussed, it became clear that the field is not defined by a particular set of methods, nor simply by the application of computational methods to cancer data. Rather, the field is defined by a recognition that cancer is a dynamic, multifactorial, and complex process that must be understood using both experimental methods and analytical approaches that bridge traditional disciplinary boundaries to directly address these concomitant challenges.

Embracing Cancer's Complexity

In his opening remarks to the meeting, Douglas Lauffenburger made the observation that CSB is a field for those who actively embrace the complexity of biology. A central component of this complexity, the heterogeneity of cancer within and across patients, is undeniably a barrier to accurate diagnosis and treatment. CSB is uniquely poised to address this heterogeneity through application of computational analyses that glean insights from pre-clinical and clinical data sets. For example, Andrea Bild (U. of Utah) presented on the striking temporal evolution of tumor heterogeneity measured by whole genome sequencing in individual breast cancer patients during the course of their various treatment regimens. Her study underscored the necessity of understanding sub-clonal evolution within a single patient and how this might influence treatment options and decisions. In a related longitudinal genomic and transcriptomic analysis of glioblastoma patients, Jiguang Wang (Columbia U.), reported that upon treatment many patients experience a loss of the dominant driver mutation but gain many novel mutations at relapse that change their disease subtype. Wendy Fantl (Stanford U.) showed that intra- and inter-tumoral heterogeneity is also reflected at the protein level and that increased tumor cell diversity measured with mass cytometry (CyTOF) is related to aggressive disease in ovarian cancer. As this and other single-cell studies are finding, the persistence of intratumor heterogeneity makes it important to develop analytical and experimental tools that can predict the best treatment options. John Paul Shen (U.C. San Diego) demonstrated that yeast can be used as a model system for identifying synthetic lethalities between inactivated tumor suppressor genes and genes that encode druggable proteins. Laura Heiser compared 'omics data from a panel of breast cancer cell lines against publicly available molecular profiling data from primary tumors in The Cancer Genome Atlas to identify conserved pathways and gene sets recurrently aberrant in different breast cancer subtypes. She described how the cell lines recapitulate major subtypes of breast cancer and can be used to identify distinct therapeutic vulnerabilities across subsets of the cell lines (1,2). Coupling the knowledge gained from profiling tumor

heterogeneity with an arsenal of computationally predicted treatment options may lead to the realization of precision cancer treatments.

CSB is driving numerous technological developments to better study the complex and dynamic nature of cancer. Frank Stegmeier (KSQ Therapeutics) compared large-scale shRNA-mediated knockdown to CRISPR-CAS9 knock-out technology, highlighting the benefits and drawbacks of both approaches. CRISPR-based knockout screens identified more synthetic lethal genes compared to RNAi across a panel of cancer cell lines, implying that the identification of cellular dependencies may require full gene inactivation. On a related topic, Kevin Janes (U. of Virginia) presented an elegant mathematical model illustrating that the network perturbation effects of gene knock-down versus chemical inhibition of protein activity encoded by the same gene can be vastly different. The difference in effect depended intimately on the network context of the molecule and was non-linearly related to the extent of gene knockdown (3). New experimental systems were described by Yvonne Chen (U.C. Los Angeles), who described the systems-level design and synthetic biology implementation of an ‘OR-gate’ T-cell receptor intended to target heterogeneous tumor populations and prevent drug resistance caused by tumor cell antigen loss (4), and Shelly Peyton (U. of Massachusetts, Amherst), who presented an *in vitro* biomaterial platform that enabled systematic comparison of various microenvironments as sites for potential metastases (5). These novel experimental approaches will fuel the collection of robust and reproducible data sets that can then be coupled with computational analysis to provide an essential step forward towards systems-level understanding of the complex tumor ecosystem.

Computational tools can aid in understanding the complexity of cancer by integrating new datasets with prior knowledge. Ben Raphael (Brown U.) described the HotNet2 algorithm, which integrates cancer mutational data with known protein interactions (6). Their analysis demonstrated that while there are only a relatively small number of *bona fide* cancer driver mutations, many lower incidence mutations cluster within signaling pathways that may provide mechanistic insight to their role in progression. Indeed, the phenotypic consequence of most detectable mutations is unknown. To this end, Pau Creixell (MIT) suggested that, in the case of protein kinases, our understanding of individual cancers might be aided by understanding the specific functional consequences of somatic mutations. By analyzing the exomes and phospho-proteomes of ovarian cancer cell lines using the ReKINect computational platform, he demonstrated that individual kinase mutations in cancer variously affect the activity and specificity of important mutated kinases (7). Taken together, the Raphael and Creixell studies suggested that integrating protein-level data with mutational information can be a powerful approach but that caution must be taken when assuming the consequence of a mutation with respect to protein activity. For example, in both studies, mutations were identified that were neither recurrent nor simply activating/inactivating, yet were functional through their network effects.

Reproducibility & Data Sharing

In some cases, the scale and complexity of systems-level studies make reproducibility a challenge, especially when connecting preclinical and clinical research (8). Executing

reproducible research requires the ability to recapitulate data analysis and laboratory protocols. The development of software protocols has provided the means to automatically document analyses for purposes of reproducibility (9). For example, Ben Raphael showcased his network algorithms by providing direct links to the source code, available on GitHub, and making all data available on Synapse (10). Trey Ideker (U.C. San Diego) described NDEx, a new resource to facilitate the sharing of networks derived from biological data to make these studies more reproducible (11). Data sharing is an essential part of recapitulating and building on prior work, and thus is a critical aspect of reproducible research. Building new models from existing data can additionally lead to novel findings, as showcased in the meeting by Stacey Finley (U. of Southern California), who presented a mathematical model to predict levels of angiogenic factors during tumor treatment, and Jorge Zanudo (Penn State U.) who presented a mathematical model to predict activated signaling pathways during the epithelial-to-mesenchymal transition in cancer. Each of these models relied on parameters from open data in publications that span years of research, scientific disciplines, and experimental systems (12–14). Many of the present works took advantage of open-access datasets such as ICGC or TCGA as well as more modestly-sized datasets collected through collaborations or gleaned from the literature tailored to their studies. With this in mind, closing keynote speaker Gordon Mills dubbed the conference community the “Society for Data Parasites” in support of data sharing as a means to accelerate the study of cancer.

Clinical Translation & Collaborative Science

During his opening comments, Douglas Lauffenburger pointed out that the results of CSB must ultimately improve patient care. Toward this goal, the Systems Approaches to Cancer Biology meeting included a number of studies with a strong translational focus. Galit Lahav (Harvard Medical School), the opening keynote speaker, showed how oscillating behavior in p53, a key tumor suppressor, can give rise to dynamic transcriptional and phenotypic behavior at the single cell level that is often masked in bulk-population analyses (15). This has directly led to recommendations for timing of treatments involving DNA damaging therapies such as cisplatin (16) and radiation (15). Jiyang Yu (Pfizer) used an shRNA screen to identify HDAC6 as a potential target for inflammatory breast cancer (IBC) (17). HDAC6 is not itself an oncogene in IBC, but Yu identified it as a key regulator of other genes involved in IBC proliferation. Mohammed Shahrok Espahani (Stanford U.) described Cancer Personalized Profiling by deep Sequencing (CAPP-seq), a method for targeted sequencing of circulating tumor DNA (ctDNA) that may enable “liquid biopsies” to track cancer progression. Raghu Kalluri (U. of Texas) showed that exosomes in fact can contain DNA, and can provide circulating tumor DNA with reduced contamination from non-tumor cells. The systems approaches taken in these studies yield clinical impact that go beyond what traditional studies based on single genomic mutations or amplification events can uncover.

Progress in translational research often depends on collecting multiple types of molecular data from the same tumor samples to enable comprehensive, systems-level studies. Early efforts to understand breast cancer at a systems level applied hierarchical clustering methods to gene expression data to identify clinically relevant subtypes (18). Anne-Lise Børresen-Dale (Oslo U.) described her team’s efforts to extend this work, which went beyond clustering of transcriptomic data to also include other types of molecular data and to provide

additional biological insights about these breast cancer subtypes (19). Interestingly, this analysis identified different subtypes, depending on the measurement (e.g. mRNA levels, somatic mutations, etc.) used in the analysis. This observation that subtype clusters are not uniquely defined was further supported by Kevin Brennan (Stanford U.), who found that DNA methylation profiles segregate head and neck squamous cell carcinoma by etiological factors.

To collect, analyze, and interpret multi-dimensional datasets, multi-institutional collaborations are often crucial. Over the past several decades, Børresen-Dale has helped to assemble a large group of international collaborators to derive insights about the interplay between genomic, transcriptomic, proteomic, and metabolomic features in breast cancer. For example, they examined the transcriptional consequences of somatic mutations and found that tumor cells express these mutations more actively than stromal cells and that this relationship depends on estrogen receptor status (20). As noted by Gordon Mills, greater collaboration across institutions and between academia and industry should help accelerate clinical translation of CSB studies.

Conclusion

There has been significant progress in characterizing the genetics of cancer and the contributions of individual intracellular pathways to tumor initiation and progression. Future progress in understanding fundamental cancer biology will continue to extend the range of hallmarks available for systems-level interrogation. For example, Isaac Harris (Harvard Medical School) described efforts to identify therapeutic sensitivities tied to the altered redox and metabolic state of breast carcinoma cells. The challenges faced when interpreting single parameter studies highlight the need to understand cancer as an integrated system. The emerging success, and limitations, of cancer immunotherapy illustrate this point well, where simultaneous understanding of the communication networks within and between cell types in the tumor microenvironment will be essential for extending the success of this treatment modality. As an example of how to begin addressing this multi-factorial environment, Molly Carroll (U. of Wisconsin-Madison) applied machine learning to identify ovarian cancer-released cytokines that modulate macrophage M1/M2 phenotype. On the other hand, Annelien Zweemer (MIT) showed that factors such as apoptotic cell debris can act as microenvironmental cues through TAM receptor signaling. Clearly, the complexity of cancer requires a multi-pronged approach that may only be fully realized when bringing together disparate academic disciplines as is common in systems biology.

At the same time, technological and methodological advancements will place systems-level approaches at the forefront of translating these for clinical benefit. Single cell technologies are providing ever-finer quantitation of tumor heterogeneity demanding improved and alternative methods to visualize and therapeutically address this complexity. On the scale of individuals, genome- and proteome-scale clinical diagnostic capabilities are presenting new challenges to prognostically identify effective therapies for individual patients. Realizing this goal, beginning to be addressed clinically through precision trials such as NCI-MATCH and ASCO TAPUR, will require new approaches integrating outside data and knowledge as well as new data such as more longitudinal measurements. The spirited discussions about the

scientific challenges in cancer, the importance of building and maintaining strong collaborations, how to improve data access, and the importance of reproducibility in systems analysis that occurred at the Systems Approaches to Cancer Biology meeting made it clear that participants in the interdisciplinary field of cancer systems biology are well-poised to improve our understanding of cancer and how to overcome it.

References

1. Goodspeed A, Heiser LM, Gray JW, Costello JC. Tumor-Derived Cell Lines as Molecular Models of Cancer Pharmacogenomics. Molecular Cancer Research. 2016; 14:3–13. [PubMed: 26248648]
2. Heiser LM, Sadanandam A, Kuo W-L, Benz SC, Goldstein TC, Ng S, et al. Subtype and pathway specific responses to anticancer compounds in breast cancer. Proc Natl Acad Sci USA National Acad Sciences. 2012; 109:2724–9.
3. Jensen KJ, Moyer CB, Janes KA. Network Architecture Predisposes an Enzyme to Either Pharmacologic or Genetic Targeting. Cell Syst Elsevier Inc. 2016; 2:112–21.
4. Zah E, Lin MY, Silva-Benedict A. T cells expressing CD19/CD20 bi-specific chimeric antigen receptors prevent antigen escape by malignant B cells. Cancer immunology …. 2016
5. Barney LE, Dandley EC, Jansen LE, Reich NG, Mercurio AM, Peyton SR. A cell-ECM screening method to predict breast cancer metastasis. Integr Biol. 2015; 7:198–212.
6. Leiserson MDM, Vandin F, Wu H-T, Dobson JR, Eldridge JV, Thomas JL, et al. Pan-cancer network analysis identifies combinations of rare somatic mutations across pathways and protein complexes. Nat Genet Nature Research. 2015; 47:106–14.
7. Creixell P, Schoof EM, Simpson CD, Longden J, Miller CJ, Lou HJ, et al. Kinome-wide Decoding of Network-Attacking Mutations Rewiring Cancer Signaling. Cell The Authors. 2015; 163:1–30.
8. Begley CG, Ioannidis JPA. Reproducibility in science: improving the standard for basic and preclinical research. Circulation Research. 2015; 116:116–26. [PubMed: 25552691]
9. Peng RD. Reproducible research in computational science. Science. 2011
10. Omberg L, Ellrott K, Yuan Y, Kandoth C, Wong C, Kellen MR, et al. Enabling transparent and collaborative computational analysis of 12 tumor types within The Cancer Genome Atlas. Nat Genet. 2013; 45:1121–6. [PubMed: 24071850]
11. Pratt D, Chen J, Welker D, Rivas R, Pillich R, Rynkov V, et al. NDEx, the Network Data Exchange. Cell Syst Elsevier. 2015; 1:302–5.
12. Steinway SN, Zañudo JGT, Ding W, Rountree CB, Feith DJ, Loughran TP, et al. Network modeling of TGFβ signaling in hepatocellular carcinoma epithelial-to-mesenchymal transition reveals joint sonic hedgehog and Wnt pathway activation. Cancer Res. 2014; 74:5963–77. [PubMed: 25189528]
13. Creixell P, Palmeri A, Miller CJ, Lou HJ, Santini CC, Nielsen M, et al. Unmasking Determinants of Specificity in the Human Kinome. Cell The Authors. 2015; 163:1–28.
14. Finley SD, Popel AS. Effect of tumor microenvironment on tumor VEGF during anti-VEGF treatment: systems biology predictions. J Natl Cancer Inst. 2013; 105:802–11. [PubMed: 23670728]
15. Chen S-H, Forrester W, Lahav G. Schedule-dependent interaction between anticancer treatments. Science American Association for the Advancement of Science. 2016; 351:1204–8.
16. Paek, AL.; Liu, JC.; Loewer, A.; Forrester, WC.; Lahav, G. Cell. Elsevier Inc; 2016. Cell-to-Cell Variation in p53 Dynamics Leads to Fractional Killing; p. 1-22.
17. Putcha P, Yu J, Rodriguez-Barrueco R, Saucedo-Cuevas L, Villagrasa P, Murga-Penas E, et al. HDAC6 activity is a non-oncogene addiction hub for inflammatory breast cancers. Breast Cancer Res BioMed Central. 2015; 17:149.
18. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA National Acad Sciences. 2001; 98:10869–74.

19. Curtis C, Shah SP, Chin S-F, Turashvili G, Rueda OM, Dunning MJ, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012; 486:346–52. [PubMed: 22522925]

20. Shlien A, Raine K, Fuligni F, Arnold R, Nik-Zainal S, Dronov S, et al. Direct Transcriptional Consequences of Somatic Mutation in Breast Cancer. Cell Reports. 2016; 16:2032–46. [PubMed: 27498871]

Appendix

The program committee consisted of the co-chairs Joe Gray (Oregon Health Sciences U.), Douglas Lauffenburger (MIT), and Elaine Mardis (Washington U.). The meeting planning committee of the Association of Early Career Cancer Systems Biologists (AECCSB) organized the SACB meeting and included Sara Gosline (Sage Bionetworks), Marc Hafner (Harvard Medical School), Shannon Hughes (NCI, NIH), Brian Joughin (MIT), Aaron Meyer (MIT), Stephen Piccolo (Brigham Young U.), and Erin Wetzel (NCI, NIH). In addition to the program committee members, invited participants included Andrea Bild (U. of Utah), Anne-Lise Børresen-Dale (Oslo University), Yvonne Chen (U.C. Los Angeles), Dan Gallahan (NCI, NIH), Trey Ideker (U.C. San Diego), Kevin Janes (U. of Virginia), Raghu Kalluri (U. of Texas), Galit Lahav (Harvard Medical School), Gordon B. Mills (U. of Texas), Shelly Peyton (U. of Massachusetts, Amherst), Ben Raphael (Brown U.), Frank Stegmeier (KSQ Therapeutics).