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A four-dimensional view of breast cancer treatment

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Dr. Joe Gray, director of the Oregon Health & Science University Center for Spatial Systems Biomedicine, addressed a capacity crowd at the Environmental Molecular Sciences Laboratory Auditorium at Pacific Northwest National Laboratory on April 18 regarding his research involving a systems approach to breast cancer. Gray was at PNNL as part of the ongoing Frontiers in Biological Sciences Seminar series, which features academic, government, and industrial leaders who discuss novel ideas and scientific advances in biological sciences.

According to Gray, there is a need to identify a better group of drugs that will respond to metastatic breast cancer. Currently, early analysis can result in as much as a 98 percent survival rate, while survival rates for metastatic breast cancer hover near 25 percent and have remained unchanged for many years.

"Hundreds of compounds are approved or well along in the development pipeline," Gray said. "There is nearly $20 billion in annual investment. However, each drug has specificity, and the heterogeneity between tumors is different. We need to determine the recurrent features that are attackable and respond to therapies."

Gray, who until recently served as an Associate Laboratory Director for Biosciences at Lawrence Berkeley National Laboratory and professor at the University of California, Berkeley, explained how diverse support from a multi-member consortium, with membership spanning public government and academic institutions to the private sector, fuels the

systemic research to match treatments to "omes," which he fully expects will involve future collaborations using EMSL's user capabilities as well as PNNL and EMSL staff.

Gray's discussion focused on two targeted therapies—subtype-specific and ErbB2, or erythroblastic leukemia viral oncogene homolog 2—as well as his spatial systems approach of integrating data derived from multiple research areas to generate a higher-order understanding of cancers.

Beyond cataloging, Gray explained how understanding the manifestation of the 'omic time-dependent phenomenon is something that needs to be studied. What happens at receptors and within the microenvironment in metastatic cancer and how they influence responses will only become clearer as source information and models improve to account for composition and functional variations over time and space.

"To take the next steps in research, you have to understand more than the histopathology and genomics, you have to understand how these systems work in four dimensions—three-dimensional space and time," he said.

Getting Specific

Two well-organized international cancer genomics efforts are defining cancer subtypes.

The Cancer Genome Atlas is cataloguing genetic mutations responsible for cancer using high-throughput genome analysis techniques. Already, there are 500 breast cancers available. Data concerning the abnormalities composing these cancers are contributing to Gray's systemic matching of the "ome" and response. The well-characterized cancer cell lines are used to model molecular diversity of primary tumors. Gray's group has

tested 100 therapeutic compounds in more than 50 breast cancer cell lines to identify molecular response predictors. Half of all compounds show subtype specificity.

"Using these 100 cell lines as a model of diversity of agents that target or drive genomic aberrations is proving effective," he said.

Gray's group also uses the University of California, Santa Cruz (UCSC) Cancer Genomics Browser that allows users to click and sort data to identify molecular features. Per Gray, It has the potential to pull together all the data in the world on cancer. Pathway Recognition Algorithm using Data Integration on Genomic Models, or PARADIGM, allows researchers to take multiple aspects of genomic data and calculate pathway activity, which is crucial in generating connections between molecular markers and outcome.

Gray used a basal breast cancer example to show how analyzing subtype-specific activated pathways can show drug interaction/responses and individual DNA changes within cancer cells. By analyzing cancer cell DNA, specific cell aspects can be targeted and killed. Ultimately, these efforts will allow researchers to take some integrated molecular data (such as the DNA damage network in breast cancer), test it in model systems, and move these into clinical trials with confidence that there will be responses.

"One of the real advantages of this multiscale and tissue science is that it will more fully define what the cancers are at different interfaces," Gray added. "For the first time in history, we have the measurement technology to do this in a way to understand the cells and tissues across time and space domains."

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