Analysis of metastatic prostate cancers suggests treatment options

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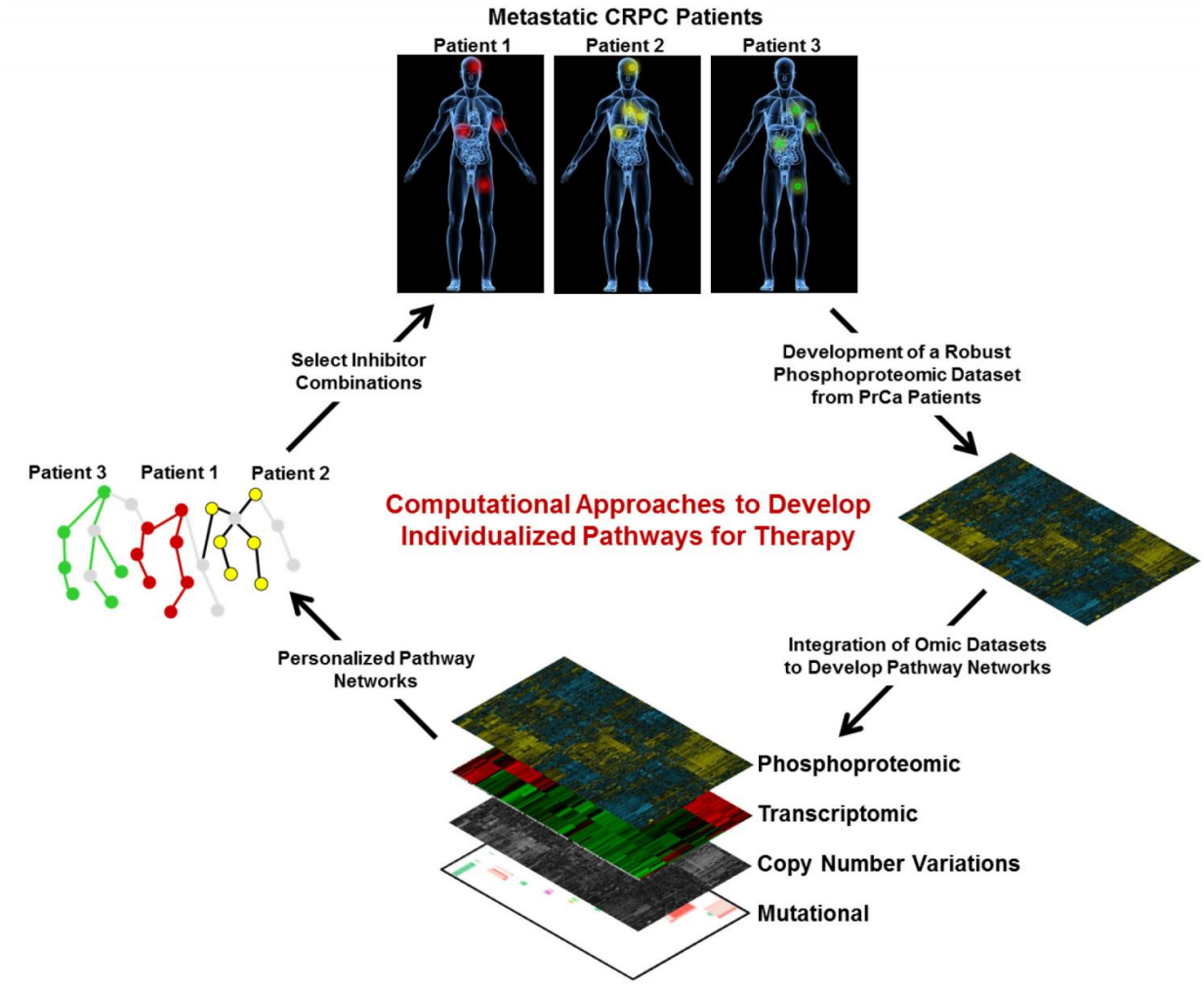

Drake et al. developed a systematic computational approach to incorporate gene expression and new phosphoproteomic information that has been generated from the analysis of clinical prostate cancer tissues. This analysis revealed the most

comprehensive network of activated kinases and transcription factors to date in this disease. Personalized pathway diagrams constructed using phosphoproteome information for six individual CRPC patients reveal common and distinct signaling mechanisms whose details suggest targets for therapeutic consideration. Credit: Drake et al., Cell, 2016

Cancer researchers have applied a comprehensive set of analytical tools to lethal cases of metastatic prostate cancer, yielding a detailed map of the complex networks of interactions among genes and proteins that enable prostate cancer cells to proliferate and evade treatment. The team also developed a computational approach for analyzing patient-specific data to help doctors choose the most effective drugs for individual patients.

The study, published August 4 in *Cell*, was a collaborative effort involving research teams at UC Santa Cruz and UCLA. They began with clinical tissue samples obtained at autopsy from patients with lethal metastatic prostate cancer, then performed a range of sophisticated analyses to characterize the cancer cells from each patient in unprecedented detail. A novel computational analysis of the resulting datasets produced personalized diagrams of signaling pathways in the cancer cells of each patient, the details of which suggest potential targets for therapy.

"It's like having a blueprint for each tumor. This is our dream for personalized cancer therapy, so we're not just guessing any more about which drugs will work but can choose drug targets based on what's driving that patient's cancer," said Josh Stuart, the Baskin professor of biomolecular engineering at UC Santa Cruz, director of cancer and stem cell genomics at the UCSC Genomics Institute, and a senior corresponding author of the paper.

"Therapies for metastatic prostate cancer are urgently needed," said Dr. Owen Witte, founding director of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, university professor of microbiology, immunology and molecular genetics at the UCLA David Geffen School of Medicine, and a senior author of the paper. "This type of interdisciplinary research is critical as we seek to pinpoint the cellular changes occurring in aggressive prostate cancer and cross new boundaries in understanding the disease."

Cancer genomics promises to enable personalized cancer treatment by revealing the genetic mutations driving an individual patient's tumor cells. But interpreting the genomic data remains a challenge. The effects of mutations and other genetic changes in cancer cells play out in the complex networks of molecular interactions or "signaling pathways" involved in cell growth, proliferation, and other hallmarks of cancer biology. By mapping the key pathways active in prostate cancer cells, the researchers were able to identify the "master switches" in those pathways that could be targeted with drugs to disrupt the disease.

A key step in many signaling pathways is "phosphorylation," the activation or deactivation of a protein by adding a phosphate group at certain sites on the protein. The enzymes that phosphorylate proteins are called kinases, and many new cancer drugs are kinase inhibitors. A major component of the study was a comprehensive analysis of the "phosphoproteome" of prostate cancer tumors and cells, revealing changes in the phosphorylation states of cellular proteins.

Justin Drake, a postdoctoral researcher in Witte's lab at UCLA (now an assistant professor at Rutgers Cancer Institute of New Jersey), led the phosphoproteomics work, producing a new encyclopedia of protein phosphorylation in prostate cancer cells and tissues. Evan Paull, a graduate student in Stuart's lab at UC Santa Cruz (now at Columbia University), led the computational analyses, which involved integrating

the phosphoproteomic data with genomic and gene expression datasets to provide a unified view of the activated signaling pathways in late stage prostate cancer. Drake and Paull are co-first authors of the paper.

"Having the phosphoproteomics data in addition to the traditional genomics and transcriptomics enabled us to get a more comprehensive view of aberrant signaling in this disease," Paull said. "We developed a method to integrate these multiple large datasets to understand what's driving the disease in individual patients."

Prostate cancer is the third most commonly diagnosed cancer in the United States. The main treatment for advanced cases is androgen deprivation, because the male sex hormones (androgens, including testosterone) stimulate prostate cancer growth. Anti-androgen therapies target either androgen synthesis or the androgen receptor. Eventually, however, most cases of metastatic prostate cancer become resistant to these therapies.

The new study revealed some of the mechanisms behind the resistance to anti-androgen therapies. According to Stuart, in many cases a mutation results in changes to the androgen receptor protein. In other cases, alternative kinase signaling pathways allow the cancer cells to keep growing even though androgen-receptor signaling is blocked.

Individual profiles based on the analysis of each patient's tumor cells revealed clinically relevant information that could be used to prioritize the drugs most likely to be effective in these cases. The tool used to generate these individual profiles goes by the acronym pCHIPS, and the researchers created an online pCHIPS resource that allows users to make patient-specific network predictions based on their own data and visualize the results using the pCHIPS methodology.

Applying these methods to prostate cancer cell lines, the researchers

found that accurate predictions of drug sensitivity could be achieved using either genomics data or phosphoproteomics data alone. That's important because the comprehensive set of analyses performed on clinical samples in this study is unlikely to be available to most patients. Clinical use of genomics, however, is growing.

Stuart explained that the integrated datasets from multiple analyses enabled the researchers to build a generic model of the signaling networks involved in metastatic prostate cancer. The pCHIPS tool uses that generic model and refines it based on patient-specific data, such as the genetic mutations in a patient's cancer cells.

"For now it's a research tool, but the hope is to have a strategy like this to use in the clinic," Stuart said. "These mutations in the genome create a lot of havoc in the cell, and trying to interpret the genomic information can be overwhelming. You need the computer to help you make sense of it and find the Achilles heel in the network that you can hit with a drug."

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