Biologist advances cancer research with new data analysis techniques

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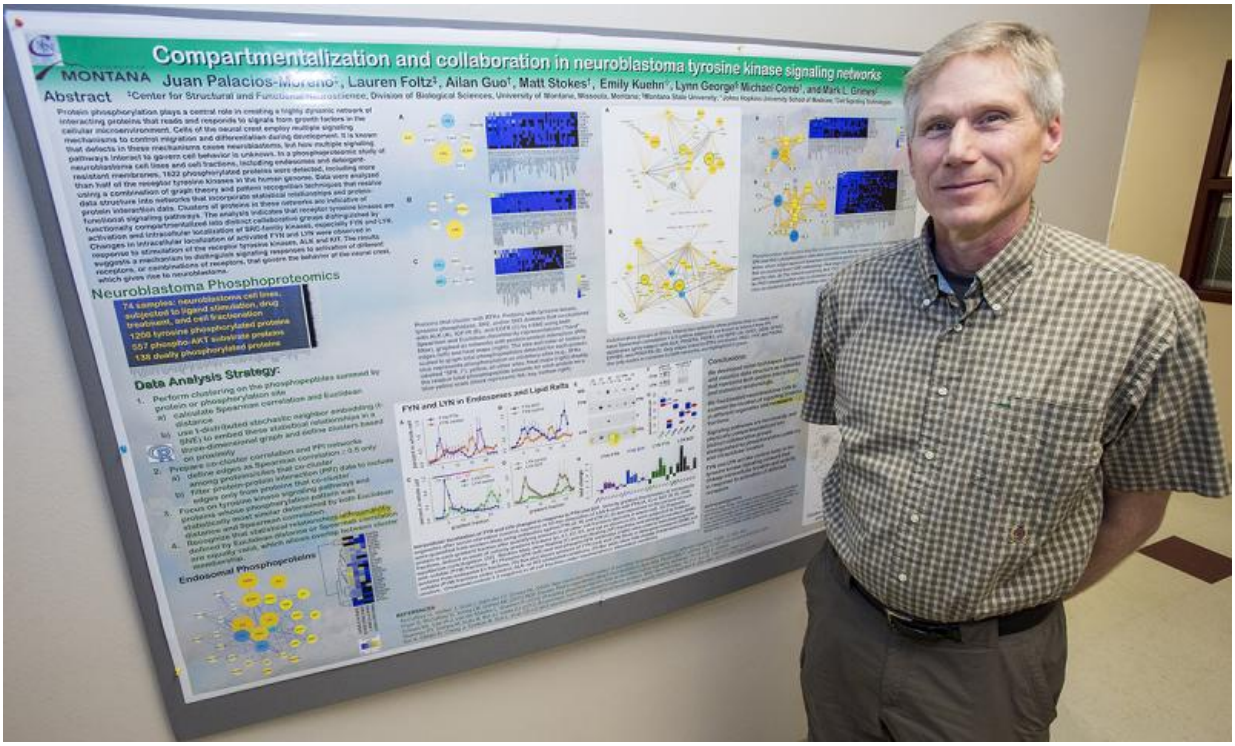

UM cell biologist Mark Grimes stands in front of a poster displaying the findings in his research paper. Credit: Todd Goodrich

Patience and persistence are beginning to pay off for University of Montana Professor Mark Grimes, whose research about the behavior of cell proteins in childhood cancer recently was published by the *Public Library of Science Computational Biology*.

In his quest to understand the childhood cancer called neuroblastoma - which is not the most common type of childhood cancer, but is the most lethal - Grimes started at the subcellular level, isolating organelles containing molecules that signal to cells to divide, die or differentiate. As a cell biologist, he wanted to understand why cancer cells behave differently than other cells.

Grimes laid the groundwork for his research by identifying a large number of signaling proteins using mass spectrometry in collaboration with Cell Signaling Technology, a company in Danvers, Massachusetts. He collected more data than he knew what to do with.

"I spent an embarrassingly long time staring at a spreadsheet trying to figure out what it all meant," Grimes said.

Perplexed, he set off on a five-year adventure in unknown territory: data analytics.

"I felt like Don Quixote for a while, wandering through the wilderness, because I'm really a cell biologist," Grimes said, "I'm not a statistician. I'm not a computer programmer."

So he sought out people who had those skills. He teamed up with Laurens van der Maaten, a pattern recognition specialist at Delft University of Technology in the Netherlands, and Paul Shannon, senior software engineer at the Fred Hutchison Cancer Research in Seattle, and started learning the skills himself.

"And after many trials and errors, I learned about a pattern-recognition technique that works really well and discovered a few new tricks that are actually pretty fundamental," he said. "Which is why I'm excited about this paper, because not only the results are interesting, but the way we analyze the data brings new tools to bear on these kinds of problems in

general."

By collaborating with people in the field of pattern recognition and bioinformatics, Grimes developed a way to calculate relationships in the data, even when that data contains a lot of missing information, as his did.

"I figured out a way to calculate relationships leaving the holes in there," he said, "because there are so many holes that if you put zeroes in there, the zeroes all correlate with each other and you get no information."

Grimes' new technique labels the zeroes as "data not available" rather than a numerical value, telling his algorithm only to analyze relationships among data that exists. Once he applied the new technique to the data he collected, the methods of sorting data into groups, called clustering, became more robust and the relationships became clearer: in cancer cells, the components that determine the cell's behavior - whether the cell will live, die, migrate or change identity (differentiate) - are functionally compartmentalized into distinct collaborative groups.

Therapeutic progress has been slow for neuroblastoma. Grimes and his research partners at Cell Signaling Technology analyzed a large number of neuroblastoma cells, dissecting them to find the specific location of their signaling proteins. The analysis found two related proteins act like central hubs that distinguish responses to the activation of different receptors.

Grimes hopes that by understanding the fundamentals of cell signaling, scientists eventually might be able to change the signals within cancer cells. For instance, they could trigger cancer cells to die rather than metastasize.

Since humans are born with more cells than we need to survive, many

cells in our bodies already are "programmed" to die. And by harnessing the same signals in those cells, Grimes said it just might be possible to tell cancer cells to do the same.

"If we can understand the fundamentals of signaling, then we can hope to manipulate these pathways and maybe apply it to neuroblastoma," he said. "If we can get them to march a little bit further in their differentiation, we could use that differentiation to make each cell susceptible to programmed cell death."

And if this signaling works for neuroblastoma cells, scientists possibly could use the same technology on all cancer cells.

"If we understand how different receptors elicit distinct cell responses," Grimes said, "we can devise strategies to manipulate cancer cells to cease proliferation, differentiate or commit cell suicide."

He said it's important to understand the highly dynamic network of interacting proteins and how they communicate inside the cellular environment to understand the cause of cancer.

"We've made tremendous progress on cancer, but we also have to acknowledge we've really just sampled a teaspoonful of an ocean full of things we need to do," he said. "We have a huge amount to do to increase the quality of life, survival and even lifespan. There's a lot to do on many fronts."

More information: Grimes' research paper, "Neuroblastoma Tyrosine Kinase Signaling Networks Involve FYN and LYN in Endosomes and Lipid Rafts" is available online at journals.plos.org/ploscompbiol … journal.pcbi.1004130

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