New chemistry technology promises more effective prescription drug therapies

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(PhysOrg.com) -- Scientists at the University of Toronto and Stanford and Columbia Universities have developed a way to measure the action and function of candidate prescription drugs on human cells, including the response of individual cells, more quickly and on a larger scale than ever before.

The researchers say their mass cytometry technology has the potential to transform the understanding of a variety of diseases and biologic actions and will provide a better tool to understand how a healthy cell becomes diseased. Clarifying the underlying biochemistry of cells may enable earlier detection of illness and ultimately advance personalized medicine, notably for cancer and HIV treatments, by offering more and less aggressive options for treatment.

“We’ve shown that drug response is specific to certain sub-populations of cells and gained insight into the signalling cascade that defines that response” said Professor Scott Tanner of the Department of Chemistry, who led the development of the technology used in research to be published this week in Science. “We’ve also shown that a drug can activate or suppress multiple response pathways simultaneously, and that these responses are modified when a combination of drugs are administered.”

“Together, this suggests that the technology will be of significant value in the development and validation of rational drugs to target particular pathogens - a quantum step towards the provision of personalized

medicine," said Tanner.

Mass cytometry allows simultaneous measurement of as many as 100 biomarkers - specific physical traits of cells used to measure or indicate the effects or progress of a disease, illness or condition - in single cells, at 1,000 cells per second. It applies the analytical capabilities of atomic mass spectrometry - used to measure the number and type of atoms that comprise a sample - to the technique of flow cytometry, which is a method of examining thousands of microscopic particles per second by suspending them in a stream of fluid or gas and passing them through an electronic detection apparatus. The two very disparate disciplines previously had no reason to be combined.

The U of T scientists developed the chemistry and methods of attaching the metal atoms necessary for the detection of the vanishingly rare biomolecules of interest at the individual cell level, where personal therapeutic response is defined. They also developed a unique instrument to simultaneously measure a large number of these diagnostic signals for individual cells at a high analysis rate. Garry Nolan, a professor of microbiology and immunology at Stanford University and lead investigator of the research presented in this paper, adapted and expanded his earlier work in flow cytometry to take advantage of the much higher power that mass cytometry provides.

Nolan and his colleagues at Stanford, with collaborators at Columbia, used the U of T technology to monitor 34 different substances found inside and on the surface of different cell types produced in human bone marrow, the place where all immune and blood cells, as well as blood disorders such as leukemia, originate. They were able not only to correctly categorize over a dozen different immune cell types but, at the same time, to peer inside the cells and learn how various internal processes differed from one cell type to the next. "We can tell not only what kind of cell it is but what it's thinking, and what it may become,"

says Nolan.

The findings are presented in a paper titled 'Single-Cell Mass Cytometry of Differential Immune and Drug Responses Across a Human Hematopoietic Continuum', published May 6 in *Science*. The technology developed by Tanner and his associates is being brought to market by DVS Sciences Inc., a U of T spin-off of which Tanner is president and CEO.

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ABSTRACT
Flow cytometry is an essential tool for dissecting the functional complexity of hematopoiesis. We used single-cell “mass cytometry” to examine healthy human bone marrow, measuring 34 parameters simultaneously in single cells (binding of 31 antibodies, viability, DNA content, and relative cell size). The signaling behavior of cell subsets spanning a defined hematopoietic hierarchy was monitored with 18 simultaneous markers of functional signaling states perturbed by a set of ex vivo stimuli and inhibitors. The data set allowed for an algorithmically driven assembly of related cell types defined by surface antigen expression, providing a superimposable map of cell signaling responses in combination with drug inhibition. Visualized in this manner, the analysis revealed previously unappreciated instances of both precise signaling responses that were bounded within conventionally defined cell subsets and more continuous phosphorylation responses that crossed cell population boundaries in unexpected manners yet tracked closely with cellular phenotype. Collectively, such single-cell analyses provide system-wide views of immune signaling in healthy human hematopoiesis, against which drug action and disease can be compared for mechanistic studies and pharmacologic intervention.

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