New screening method could pave the way for future cancer drug discoveries

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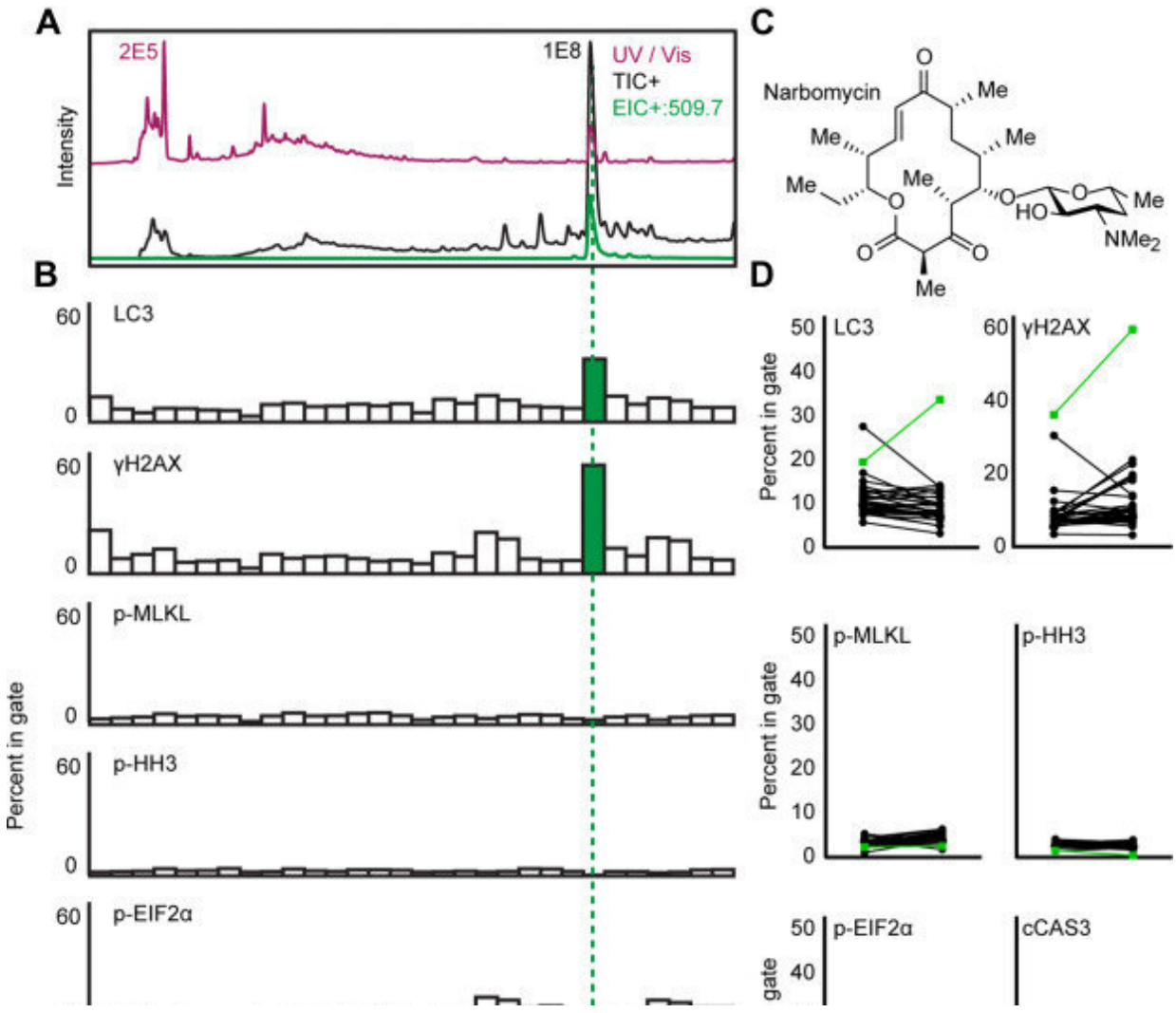

Multiplexed activity metabolomics informs isolation of secondary metabolites by injury signatures. A, KPBlue17 crude extract was fractioned by reverse phase, split flow HPLC/UV/MS with polarity switching mass scanning to associate

metabolite spectral data to well eluates by retention time. UV/Vis absorbance spectra is shown in purple, total positive ion current is shown in black, and positive extracted ion is shown in green (m/z 509.7 $[M + H]^+$). B, percent positive cells for each injury signal was aligned to chromatograms to identify spectral regions with a bioactive component. Green bars indicate a hit for the respective marker. C, chemical structure of the isolated active component, narbomycin. D, biological response to metabolomic challenge increased from 24 to 48 h in wells containing narbomycin (green 24). All other wells identified in black, 1 to 30, were negative for biological signal. Credit: *Journal of Biological Chemistry* (2022). DOI: 10.1016/j.jbc.2022.102300

The laboratories of Brian Bachmann, professor of chemistry, biochemistry and pharmacology, and Jonathan Irish, associate professor of cell and developmental biology and pathology, microbiology and immunology, have developed a method to discover new small molecules that may kill cancer cells by working through the body's immune system.

The method is the first of its kind, to the authors' knowledge, that combines a single-cell screen with metabolomics, the large-scale study of small molecules. Their study was published in the *Journal of Biological Chemistry*.

Cancer drugs contain molecules that target and kill cancer cells, though their effectiveness can depend on how they work. For example, some cancer drugs involve the immune system, which routinely stands guard against outside attackers. However, the immune system can also be used to respond to inside invaders, such as cancer cells, in a process known as "immunogenic cell death."

After coming in contact with cancer-targeting small molecules, cancer cells release tumor-specific antigens—molecules that trigger an immune response to defend the body. Once trained to recognize cancer cells, the

immune system can be primed to remove any future cancer cells, much as it is trained by vaccines to recognize and remove viruses.

Despite their effectiveness, cancer drugs that activate the immune system have only ever been determined by chance, after they have already entered the clinic. To discover more effective cancer drugs before clinical trials, the Bachmann and Irish labs tested a large quantity of small molecules on living cells to detect which ones could initiate long-lasting immune responses against cancer. To do this, they looked at markers for cell injury and stress in the treated cells, which indicate when the immune system is activated and when a small molecule has a significant effect.

"We will use this method to discover the next generation of cancer drugs that kill cancer cells more efficiently and recruit the immune system to make cures last longer," Bachmann said.

The authors hope that this method for determining new immunogenic cancer drugs will lead to more efficient treatments. Ultimately, these potential drug discoveries may lead to new tools to treat cancer and improve patient outcomes.

The paper, "An immunogenic cell injury module for the single-cell multiplexed activity metabolomics platform to identify promising anti-cancer natural products," was published in the *Journal of Biological Chemistry*.

More information: Joseph A. Balsamo et al, An immunogenic cell injury module for the single-cell multiplexed activity metabolomics platform to identify promising anti-cancer natural products, *Journal of Biological Chemistry* (2022). DOI: 10.1016/j.jbc.2022.102300

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