Device allows evaluation of the efficacy, toxicity of drugs metabolized through the liver

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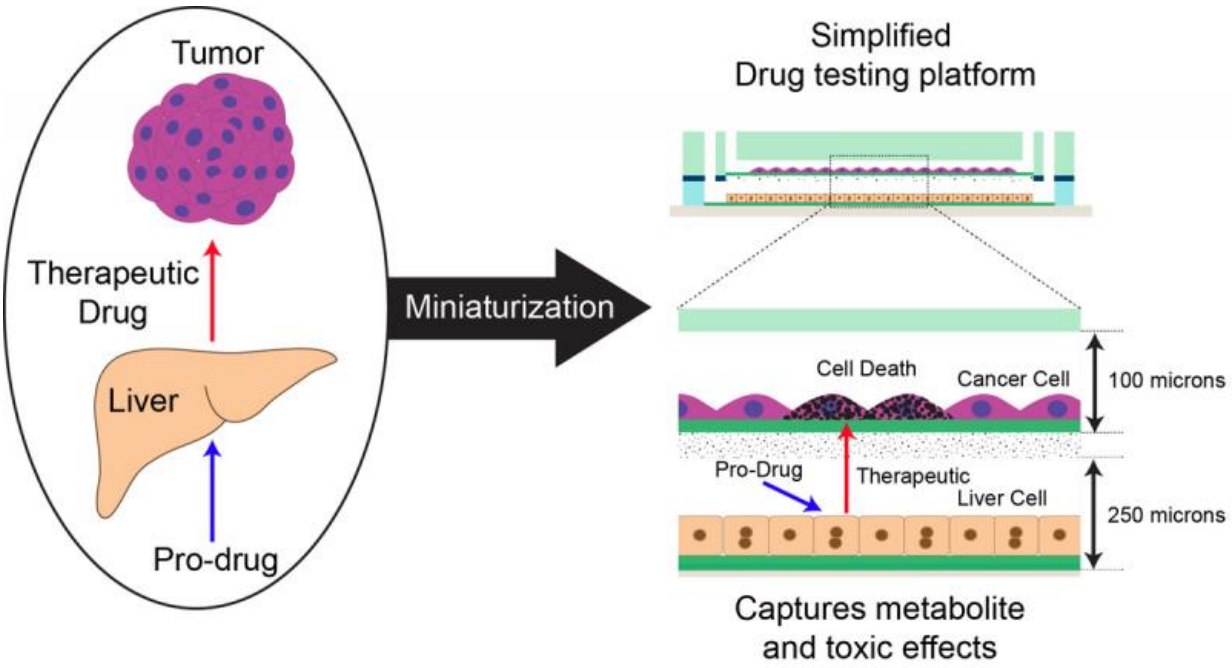

A microfabricated device developed by the Massachusetts General Hospital Center for Engineering in Medicine is able to analyze the effects of pro-drugs -- substances transformed within the liver into therapeutic agents -- on cancer cells. The two-chamber microscale platform enables the culture of liver cells called hepatocytes and tumor cells in close proximity and in small amounts of supportive media. The microscale environment leads to the rapid accumulation of greater quantities of the desired metabolite and detection of its toxic effect on cancer cells. Credit: Shyam Sundhar Bale, Massachusetts General Hospital Center for Engineering in Medicine

A team of researchers from the Massachusetts General Hospital Center for Engineering in Medicine (MGH-CEM) has developed a novel approach that dramatically simplifies the evaluation of the liver's drug-metabolizing activity and the potential toxic effects of the products of that activity on other organs. Their report appears in the June issue of the journal *Technology*.

'The liver plays a central role in drug metabolism, a process that has been exploited in the development of pro-drugs that are transformed by the liver into the ultimate therapeutic agent,' says Martin Yarmush, M.D., Ph.D., director of the MGH-CEM and the paper's senior author. 'Currently, there is a large effort underway to create systems that enable evaluation of organ-to-organ interaction in the context of drug efficacy and toxicity. Most investigators in this field use approaches that rely on the flow of fluids between organs to achieve this interaction. But these systems can be cumbersome, with limitations in speed and undesirable excessive dilution. Our approach relies on capturing organ-to-organ interactions in a simple, static system that overcomes these limitations.'

The authors describe development of a microfabricated device that enables the separate culture of primary liver cells and cancer cells. The device contains two microchambers separated by a tissue-culture membrane allowing very small amounts of the two different cell types to be cultured within the same device. The team demonstrated the efficacy of the system by analyzing the metabolic conversion in liver cells of Tegafur, a chemotherapeutic pro-drug, into the toxic metabolite 5-fluorouracil and its subsequent effect on cancer cells. The simplified platform eliminates the need for pumping and tubing connections and provides a novel, easy-to-use platform for studying drug metabolism, toxicity and interactions between multi-tissue systems, serving as a robust, valuable tool for screening drugs for toxic effects.

'This work is significant because many commercially available 'organ-on-

a-chip' devices are not truly microscale, and therefore can totally miss important biological and toxicological phenomena simply because sample volumes and dimensions are too large. This paper clearly demonstrates that critical, subtle interactions can be detected if the device is designed and fabricated properly,' says Shyam Sundhar Bale, Ph.D., a research fellow in the MGH-CEM and lead author of the paper. 'Our method takes advantage of a microenvironment in which the cells can be cultured in much smaller quantities of supportive media than in traditional culture methods, enabling the accumulation of higher concentrations of the metabolized product. This methodology is particularly attractive in cases where in the toxic metabolite that is formed is either short lived or is processed further into other, non-toxic components.'

Co-senior author Rohit Jindal, Ph.D., of MGH-CEM, adds, 'The microfabrication methods applied in this study are readily amenable to designing a device in which multiple two-chamber wells could be operated at the same time, dramatically increasing processing speed, that would be no larger than a standard, 96-well culture plate.' Jindal is an instructor in Surgery at Harvard Medical School.

Provided by Massachusetts General Hospital