3-D tumor models improve drug discovery success rate

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Imagine millions of cancer cells organized in thousands of small divots. Hit these cells with drugs and when some cells die, you have a candidate for a cancer drug. But a review published this week in the journal *Expert Opinion on Drug Discovery* argues that these 2D models in fact offer very little information about a potential drug's effects in the body and may often give researchers misleading results.

"Up until the 1980s animal models were the standard for cancer drug discovery. However, with the increase in the number of compounds available for testing and the advent of high-throughput screening (HTS), the use of animals to discover cancer drugs became too costly and unethical. Consequently, 2D cell culture models have become the mainstay for drug discovery or to explore a drug's mechanism of action," says Dan LaBarbera, PhD, investigator at the University of Colorado Cancer Center and the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences. LaBarbera is principal investigator of the recent review, on which he collaborated with Skaggs colleagues Brian Reid, PhD, and Byong Hoon Yoo, PhD.

LaBarbera cites the gap between results in 2D cells and effects in tumors themselves as a contributing factor for the declining rate of drugs passing FDA approval. In particular, only 5 percent of investigational new drugs targeting cancer make it through clinical trials, at a cost of about $800 million per drug. When you factor in the inevitable failures at various points in development, each approved drug costs an average $1.5 billion.

To increase the drug success rate, LaBarbera suggests something called the multicellular tumor spheroid (MCTS) model. In these models, instead of 2D monolayers, cancer cells are cultured as 3D spheroids. One of the advantages of the MCTS model is that when spheroids reach a critical diameter, they begin to form an outer proliferating zone, an inner quiescent zone, and a central necrotic core – more faithfully mimicking the microenvironments of human tumors. Additionally, spheroids can be grown in the presence of compounds that mimic extra cellular matrix – the environment that surrounds and very much affects the growth and behaviors of human tumors.

Instead of indiscriminately killing cells, modern cancer drugs tend to target cells with very specific genetic mutations that turn on and off very specific growth and survival mechanisms that in turn very frequently depend on everything else going on in and around the cells. Using MCTS models, researchers can ask questions about how a drug will penetrate a tumor's heterogeneous 3D structure and how a drug will interact with the environment surrounding these tiny tumors.

"Though these MCTS models have been around since the 1970s, only recently has technology made it possible to use them in place of 2D models for the high-throughput screening used in drug discovery," LaBarbera says.

Remember those millions of cancer cells organized in independent divots that researchers hit with drugs? We're fairly tied to the technology that reads the results of these divots. But micro-technologies now allow multicellular tumor spheroids to be cultured in place of 2D cell cultures using high-throughput micro-well plates – we can use the same drug testing machinery on these new models. Likewise, materials science technology now exists to grow cells within semipermeable membranes, helping researchers define the shape of the eventual spheres. And as futuristic as it undoubtedly sounds, magnetic cell levitation can help

alleviate the problem of cells sticking to the plastic well surface, which limits spheroid growth.

The recent practicality of high-throughput MCTS screening leads LaBarbera to call today a "renaissance" for the technique.

Of course, this 3D testing is initially more expensive and more challenging. "A lot of researchers try to get cost down to pennies per well – you can see how screening millions of compounds equals millions of dollars – but this often leads to a higher cost down the road due to a lower success rate. Yes, it may cost more to do HTS with 3D models, but in the long run it may lead to higher success rates and so decreased costs," LaBarbera says.

LaBarbera suggests that another use of the systems biology approach made possible by 3D models like MCTS is to bridge the gap between high-volume, low-accuracy screens and more involved testing in animal models.

"We envision a future in which MCTS arrays enable a convergence of systems biology and chemical biology, improving the success rate of drugs in the pipeline of discovery," LaBarbera says.

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