Scientists Have Been Studying Cancers in a Very Strange Way for Decades

By growing cells in unrealistic liquids, they may have inadvertently skewed the results of their experiments.

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A fridge of culture media for growing cells in labs.Dan Kitwood / Getty

In 1959, an American physician named Harry Eagle mixed up one of the most pivotal cocktails in medical history—a red blend of sugar, salts, vitamins, and amino acids that allowed scientists to efficiently grow the cells of humans and other animals in laboratory beakers. This red elixir, known as Eagle's minimal essential medium (EMEM), became a bedrock of biological research. Sixty years later, the medium and its variants are still heavily used whenever researchers want to study animal cells, whether to investigate the viruses that infect us, or to work out what goes wrong when cells turn cancerous.

As its name suggests, EMEM was designed to be as simple as possible—it has everything a cell needs to grow and nothing more. And in recent years, scientists have started realizing that such pared-down concoctions might be skewing their results, by warping the ways in which cells process nutrients. It's as if they had spent decades studying the health of people who had only ever been given rations to eat.

Instead of using generic "culture media" like EMEM (or its more concentrated variant, Dulbecco's Modified Eagle's Medium, known as DMEM), it might be better to start creating concoctions that more accurately reflect the chemical profiles of our bodies. That's what Saverio Tardito did in 2012, when he joined the Cancer Research UK Beatson Institute in Glasgow. "Around 90 percent of the papers in cancer research are using the same two or three commercially available media," he says. "We researchers are aware that the medium you choose at the beginning of the experiment will affect the output, but it's too easy to open the door of the fridge and use what's there. I think we have been all been a bit too lazy."

Over several years, he fine-tuned a mixture called Plasmax, which contains around 60 nutrients and chemicals at the concentrations usually found in human blood. "It was a side project—just a way of obtaining a better tool to do better research," Tardito says. "But from the beginning, we noticed that the medium was making a difference."

His colleague Johan Vande Voorde realized that cancer cells, when grown in Plasmax, behave more like they would in actual tumors, without several weird behaviors that are triggered by commercially available media. For example, DMEM contains a substance called pyruvate at 10 times its normal concentration in blood. These abnormal levels force cancer cells to grow as if they were starved of oxygen, even when the gas is abundantly present. In DMEM, the cells act as if they were being choked. In Plasmax, they do not.

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Unlike DMEM, Plasmax also contains selenium, an essential mineral. By comparing the two media, Vande Voorde showed that when breast cancer cells are grown at low densities, they die in the absence of selenium, but flourish in its presence. That's a little worrying. Several researchers have tested selenium supplements as a way of preventing cancer, but despite many studies there's no strong evidence for a protective effect. Instead, Tardito wonders if such supplements could be risky: If selenium allows cancer cells to survive in sparse populations, it might make it easier for fragments of tumors to spread to other parts of the body. "We'll need to follow that up in animal studies," he says.

David Sabatini of the Whitehead Institute for Biomedical Research has also been mixing up his own culture medium that mimics the nutrient levels of human blood. In 2017, he showed that cancer cells grown in this mixture are much less sensitive to a chemotherapy drug called Adrucil.

These results come at an interesting time. In recent years, cancer biologists have been grappling with a possible reproducibility crisis, in which results from several experiments involving lab-grown cells can't be repeated by other teams. More broadly, researchers have struggled to translate the results of basic experiments involving such cells into new treatments that actually help cancer patients. Although there are many possible reasons for these problems, Tardito wonders whether he and his colleagues might get better results if they grow their cells in more realistic media.

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“Could these new media uncover vulnerabilities of cancer cells more robustly than before?” adds Chi Van Dang of the Wistar Institute, who also wants to know how immune cells might react under these more physiological conditions. “Could these media help us to understand immunotherapy better?”

“These studies are absolutely a step in the right direction,” says Gina DeNicola of the Moffitt Cancer Center. “For this approach to be applied more broadly, these types of media will need to be commercialized. While it’s possible to make these media in a lab, it’s very costly and time-consuming. Commercial media preparations are also more consistent and higher quality, which will help with reproducibility between labs.” (Indeed, that’s partly why researchers have been so slow to move beyond traditional media like DMEM.)

Commercial preparations would also help Sabatini and Tardito, whose teams have been laboriously making up stocks of their own artisanal media and shipping them to collaborators around the world. “I struggle to keep up with the requests,” Tardito says. Sabatini adds, “We are working with vendors, but it is not easy, as physiological media is more expensive and is likely to have a shorter half-life.”

For researchers looking to understand how cancers gobble up nutrients, “testing one’s finding in a medium such as Plasmax would, without any doubt, add unparalleled rigor, and hopefully become a more widespread practice,” says Natasha Pavlova of the Memorial Sloan Kettering Cancer Center.

But she notes that such media aren’t perfect. They’re still largely missing many important components of blood, including fats and proteins. They don’t capture the different chemical profiles that exist in other tissues and organs. They don’t reflect the chemical wastelands that exist at the heart of tumors, which grow so quickly that their blood supplies can’t provide them with enough nutrients. Just last month, Alexander Muir of the University of Chicago showed that the fluids *inside* a tumor, which circulate between its cancerous cells, contain different levels of nutrients to those in blood.

Perhaps most important, Pavlova says, many cancer researchers rely on lineages of tumor cells that were created decades ago. These lines have been grown in conventional media like DMEM ever since, and have likely adapted accordingly. If they were now dunked in Plasmax, would that get researchers *closer* to real-life biology, or further away? Would researchers have to create entirely new cell lines that are grown in Plasmax from the start?

Tardito acknowledges these issues. “There will never be a perfect medium that mimics the tumor environment beginning to end,” he says. “All we can do is try and minimize those imperfections as much as we can.”

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