Podcast interview: Rita Fior


In cancer treatment, time is of the essence. Finding the most effective chemotherapy for an individual’s cancer can be a trial and error approach. Each ineffective trial takes up valuable time and introduces unnecessary toxicity. There is a way, however, to test several chemotherapies at once to determine the best one. It’s called an avatar. A mouse avatar, for example, is a mouse that has been incubated with a person’s cancer cells so that doctors can test drug effectiveness on the mouse tumor first. With several avatars, doctors can test several treatments. But obtaining a tumor assay from a mouse avatar could take months. And people fighting cancer don’t have months.

Rita Fior is a developmental biologist at Champalimaud Centre for the Unknown in Lisbon, Portugal. In a recent PNAS paper, Fior and her colleagues reported that they had successfully created human cancer avatars in zebrafish. Although they were not the first to attempt zebrafish avatars, their results show the viability of these avatars in aiding cancer treatment. The tumors in the zebrafish were ready to be assayed in just four days. I spoke with her recently about this study.

Fior: We wanted an in vivo model. Because before people have tried to do in vitro, but cells in vitro just die in the Petri dish or they get too much selected, so assays in vitro were not predictive of human response, of patient response, so really the state of the art is the in vitro mouse model. We needed an in vivo model, and we wanted a vertebrate model. That’s why zebrafish. It’s a vertebrate, and you can do high throughput screening.

PNAS: The researchers collaborated with gastrointestinal surgeons and implanted human colorectal cancer cells into zebrafish larvae. The process is called a patient-derived xenograft. They first wanted to verify that the human cells would proliferate in the fish. They also needed to verify that xenografts from different cell lines would behave differently from each other, and even that two cell lines that differed by only a single gene would display different characteristics.

Fior: If you put every human cell into the zebrafish and it behaves the same, you don’t have a good model. The big problem in cancer is really this heterogeneity and how to tackle this and to have a good assay. We went through the guidelines of chemotherapy for colorectal cancer. We went through from first to third-line treatments, and we could see differences in response to these treatments until the third line.

PNAS: The treatment guidelines include testing people for a mutation in a gene called KRAS. If the person does not have the mutation, then their chemotherapy is usually combined with Cetuximab, an antibody that blocks growth factor receptors on cancer cells. People who have a mutation in KRAS typically do not respond to Cetuximab. The zebrafish avatar, however, yielded a surprising result.
**Fior:** We had two cell lines. One is KRAS mutant and one is KRAS wild-type. These patients are sequenced and if they are KRAS wild type they can get Cetuximab. So we thought we had the perfect scenario to test this. But then what happened is that our cells that were KRAS mutant also responded. This shouldn't be happening. Then I went to the literature and I found that patients with this specific mutation can respond to Cetuximab. So then we were really happy. We can see also these sensitivities even in these mutations. And then we had to do the control for the G12 mutation, and then we didn’t see the response to Cetuximab.

**PNAS:** The team compared the results from the zebrafish avatars to similar mouse avatars, since mouse avatars are currently the primary method of personalized cancer screening.

**Fior:** We had the zebrafish results, right? And then we wanted to compare with the mouse. So we sent the results to the mouse pathologist, then we got an email saying, “Well, I don't remember what you got in zebrafish, but this cell line is resistant and the other is highly sensitive to both drugs.” And we were really happy because she did an unbiased analysis and got exactly the same results as the zebrafish.

**PNAS:** In the final part of the study, the team introduced xenografts from five surgically removed tumors to test whether the post-operative treatment outcomes would be the same in both the people with cancer and the zebrafish avatars. Their results showed that the zebrafish avatar correctly predicted relapse potential in four out of the five tumors. Fior and her colleagues are continuing to test the predictability of the zebrafish avatar. They are now conducting studies with both colorectal and breast cancer cells.

**Fior:** If that goes good, so if we really prove this can be predictive of the patient repose, then we think this will be very important for cancer treatments because we will be avoiding trial and error approaches, we will be reducing toxicity for patients and of course we will improve quality of life because then you’re not giving something that’s only giving toxicity and not doing anything to the tumor, and then changing treatment, and that takes time and it’s not good for patients.

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