XCell Biosciences Aims to Improve CTC Analysis, Biomarker Discovery With New Cell Culture Platform

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NEW YORK (GenomeWeb) – XCell Biosciences, a four-year-old startup firm and graduate of Illumina's business accelerator program, recently unveiled its novel platform for culturing and propagating a variety of cell types in an in vivo-like environment to yield more accurate and relevant results from downstream molecular analyses.

Xcell is now focused on getting its platform, called Avatar, into the hands of as many collaborators as possible in the hopes of establishing a commercial toehold, particularly in the area of circulating tumor cell analysis and biomarker discovery and validation, Co-founder and Chief Scientific Officer James Lim told GenomeWeb in a recent interview.

To that end, the company has already established two partnerships, both of which take advantage of the company's physical location in the San Francisco Mission Bay biosciences ecosystem.

In one project, researchers from XCell Bio and the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center are comparing gene and protein expression in circulating prostate cancer cells cultivated in the Avatar system with those obtained from traditional tumor biopsy to learn more about the underlying mechanisms of treatment response.

In a second project, researchers from XCell Bio and Bayer — in whose "CoLaborator" small business incubator XCell currently makes it home — are working on discovering biomarkers and validating drug targets in oncology.

XCell developed the Avatar system to address what it believes is a fundamental problem with ex vivo studies of cells: gold-standard culturing methods do not accurately represent the native microenvironment of most cells, and as such, results generated from studies of these cells do not accurately reflect their natural biology.

For example, as the company explains in a white paper published on its website, most traditional incubators maintain mammalian cells at 37° C with 5 percent CO2 and 85 percent humidity — a "one-size-fits-all approach that does not allow scientists to tailor certain factors that would more faithfully represent a cell's origin environment."

Meantime, studies have shown that cancer cells respond well to 1 percent oxygen and about 4 psi; while skin cells need around 20 percent oxygen and just 1 psi for ideal fitness. Even small changes in pressure or oxygen level can be enough to stress a cell, altering its gene expression in minutes.

The Avatar is a desktop incubator system that allow scientists to customize oxygen, pressure, temperature, and CO2 levels to recreate a cell's native environment. The platform also features an animal serum-free, collagen-based hydrogel that promotes cellular binding in a 3D matrix, which also helps better mimic cells' natural environment.

The end result of culturing cells in Avatar, according to Lim, is that they "act like cells would in the body," demonstrating "profound differences in gene expression and protein expression" as compared to traditionally cultured cells.

However, proving that cells cultured in the platform act like they would in the body is no small task. Plenty of published literature exists supporting the idea, and XCell has conducted its own internal work to demonstrate this, but the company's collaboration with the UCSF Helen Diller Family Comprehensive Cancer Center is also attempting to provide more evidence, among other goals.

"We're always looking, in the world of prostate cancer, of ways to interrogate the tumor without doing an invasive biopsy," Charles Ryan, professor of medicine and urology at the UCSF Helen Diller Comprehensive Cancer Center and lead investigator on the XCell project, told GenomeWeb. "One of the barriers to doing precision-guided therapy in prostate cancer is just getting to the tumor. From a prostate cancer perspective, I got attracted to [XCell] because of their ability to take CTCs and grow them … so that we can interrogate them not only once, but maybe serially. CTCs in prostate cancer have been found to be prognostic, but we're not quite at the point where we're using them as predictive biomarkers or doing much with them."

Furthermore, Ryan explained, as in most cancers cellular heterogeneity is a huge problem in prostate cancer research in that a biopsied sample may not capture cells that represent what's going on in different parts of a tumor. In addition, "cancer is more than just the tumor cell. In order for a cancer to be the lethal thing that it is, it has to deal with the immune system. It has to incorporate stromal elements or connective tissue elements. When we stick a needle right in the tumor and just take out the tumor cells and purify it, we may be missing something."

The potential of Avatar then, Ryan noted, is the aforementioned ability to propagate and serially interrogate CTCs, as well as the idea that "capturing cells from the circulating blood of the patient may represent a sort of soup made up of cancer elements coming from all different types of tumors so that the heterogeneity piece may be something we'll be able to account for with this technology."

In addition, Ryan said, "When we get these colonies to grow, and this is what got me really excited, we see not only tumor cells. We see immune cells, stromal cells, and we see that the CTCs are trying to make a tumor, and we can study that interaction."

In another white paper published on its website, XCell describes some early results from its work with Ryan and colleagues at UCSF. So far, the team has gathered CTCs from blood samples of patients with late-stage, castration-resistant prostate cancer and cultured them in Avatar with settings designed to recreate their native blood environment.

The cells, which typically do not grow in traditional incubators, were able to survive and propagate, and after a week the researchers studied the colonies using immunofluorescence imaging, real-time PCR, and mRNA sequencing.

About 25 percent of the colonies were identified as tumor cells based on various prostate cancer biomarkers. In addition, the researchers found that CTC colonies based on cells from the same patient showed differential gene expression, which indicated activity from multiple tumor clones. Some of the differentially expressed genes were associated with neuroendocrine-like signatures as well as biomarkers linked to stem cells and immuno-oncology activity, XCell noted.

In addition to expanding this work, Ryan and colleagues plan to conduct more downstream sequencing of Avatar-cultured circulating prostate cancer cells.

"Mutational analysis is something that can be done," Ryan said. "One of the recent developments in prostate cancer is that we think there are actually morphologic changes in the subtype of the cancer — so the cancer goes from being an adenocarcinoma to being more of a neuroendocrine carcinoma. One of our goals is to see if we can sequence neuroendocrine carcinoma as a separate entity from adenocarcinoma."

"And the other thing we could potentially do is look at androgen receptor variation," Ryan added. "It's still early, but one of the goals would be that we could do drug testing in vitro with these colonies as they grow, and be able to look at genomic changes in relation to drugs."

XCell Bio's Lim noted that all of the company's sequencing work so far has been optimized for Illumina instruments, but cells grown on the Avatar system could be interrogated with other sequencing instruments, as well as other types of technologies to examine gene and protein expression.

And though Avatar's potential for studying CTCs is large, XCell Bio is looking to push the technology into a number of other areas, such as stem cell growth and analysis and compound screening for drug discovery. At the same time, the company is also looking to broaden the types of research collaborations it is engaged in.

"There is also a tremendous opportunity outside of oncology," Lim said. "Initially, we started out providing very basic services to collaborators. … We quickly outgrew those kinds of relationships, and are now focused on … larger studies, and have begun placing instruments with a number of our collaborators who are doing this work internally with their own technicians and their own patient samples. And that's what we'll be focused on for the next year."

Besides the small amount of funding it received under the Illumina Accelerator program, XCell Bio also closed a small seed funding round for an undisclosed amount last year, Lim said. To support its endeavors in the coming year, Xcell Bio will look to raise Series A funding in the fall, he added.