PERSONALIZED MEDICINE IN ONCOLOGY
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A New Approach to Cell Culturing

An Interview with James Lim, PhD, of Xcell Biosciences

Interview with the Innovators


James Lim, PhD,

The drug discovery process has long been characterized by very low success rates in moving compounds from early-stage studies to clinically proven therapeutics. A confounding factor in the process is the inability to conduct high-throughput screening in an environment that truly mirrors human physiology. These early-stage tests are typically performed on cell lines that have been maintained and expanded over many years under conditions that rarely reflect in vivo settings. The cell culture incubators housing cell lines cannot fully reproduce the native conditions of the cells, and even small environmental changes can significantly alter the cells' gene and protein expression signatures that contribute to changes in

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To address these issues, Xcell Biosciences created the Avatar system to help drug discovery researchers generate more physiologically relevant data to identify and advance the best candidates to clinical trials. This innovative culturing system improves on current incubators by incorporating important biological traits—hypoxia and pressure—as fully customizable settings. Their studies have shown that this approach more closely mimics the native microenvironment of cells, allowing them to function as they would in vivo. By testing compounds on cells stored this way, the drug discovery and development process could become more efficient and effective by requiring fewer guesses to select a functional and safe compound.

Xcell Biosciences recently conducted a study for a large pharmaceutical company to compare results of drug compounds on cell lines stored in traditional incubators with those stored in the Avatar system with customized hypoxia and pressure levels. The study was performed with a class of drugs known as immunotherapies, a potentially transformative approach to cancer treatment that involves stimulating a patient's immune system to kill tumors with minimal side effects.

Immunotheapeutic approaches are quite promising for cancer treatment, but testing them in traditional drug discovery pipelines has been difficult. Mouse models must have their immune systems wiped out before a human-derived tumor can be implanted. However, immunotherapy methods rely on activating the native immune system that is typically repressed or absent in animal models. If results from cell line screening can be made more

accurate, it may be possible to eliminate animal testing and accelerate the development of immunotherapies that are most likely to be effective in people.

For this study, patient-derived CD8+ T cells were cultured with a lung carcinoma cell line under 2 conditions: a traditional incubator set at the standard 37°C and 5% CO_2 , and the Avatar system with the same CO_2 and temperature settings as well as 2% oxygen and a pressure level of 2 psi (210 mm Hg). Cells were then treated with 1 of 3 immune checkpoint inhibitor drugs—1 FDA-approved therapeutic and 2 investigational compounds—and monitored for 72 hours.

Tailored hypoxia and pressure levels not only produced different results, but because they allowed cells to live longer at optimal fitness, it was possible to monitor longer-lasting effects of the drugs. That turned out to be particularly important for revealing effects that took longer to occur and may help rescue drug candidates that take some time to gain momentum.

The FDA-approved immunotherapeutic showed a strong effect in the first 24 hours, but then rapidly lost effectiveness. Among patients who use this treatment, nearly half have a positive initial response followed by a severe relapse.

The 2 investigational drugs also showed unexpected results. One showed a decrease in efficacy in the Avatar system compared with the traditional incubator, suggesting that the drug may not be as effective in humans as preclinical results have indicated. The other drug showed little activity at first, becoming more effective over time, with peak activity in the Avatar system occurring hours

after the traditional cell culture study would have ended in a typical discovery pipeline.

One observation from the study was particularly noteworthy for its potential in activating the immune system. T-cell activity in the Avatar system outperformed those cultured in traditional incubators, which would suggest that only a small fraction of patient-derived T cells would work to kill cancer cells when injected back into the patient. If T-cell activity is diminished during bioproduction in traditional incubators, it is possible that the cells restored to the patient are no longer robust enough to battle a tumor. Culturing T cells under low oxygen and higher pressure in the Avatar system, however, appears to maintain optimal fitness, which may make the cells far more effective cancer killers when reintroduced to patients.

This study offers compelling data that improving culturing conditions may lead to better selection and advancement of drug candidates through the discovery and development process. The results indicate that oxygen and pressure levels are indeed influential in the behavior and function of cells and support the idea that incorporating them into cell culture may make results more physiologically relevant.

The Avatar system could have significant benefit for drug discovery pipelines by improving the quality of early-stage screening results and giving scientists better ability to choose candidates most likely to be successful in human trials. Looking ahead, Xcell Biosciences will conduct additional validation studies to further elucidate how the Avatar system could have an impact on drug discovery.

The publishers of *PMO* had the pleasure of speaking with the Chief Scientific Officer and Cofounder of Xcell Biosciences (xcellbio.com), James Lim, PhD, about the Avatar system, the current cell culturing environment, and company goals.

PMO Good morning, Dr Lim. We'd like to begin by having you introduce yourself and your company.

Dr Lim I'm one of the cofounders and Chief Scientific Officer of Xcell Biosciences. In brief, Xcellbio is developing next-generation cell culturing products, from bioreactors to culture media, enabling researchers to grow a variety of primary cell types obtained directly from a donor or patient that is not possible with traditional culturing methods.

PMO Can you provide your definition of what personalized medicine is and address how the Avatar system plays into this?

Dr Lim We believe that personalized medicine entails the investigation and research performed at the cellular level. Our Avatar system has provided a great service to the research community, and I think we're at the point within our development cycle where we can start looking at patient samples in an unprecedented way. The data generated suggest that my cells and your cells are similar, yet also very different.

PMO Can you talk about traditional culturing tools and how your system improves upon drug discovery capability?

Dr Lim If you take a close look at some of the commercially available cell culturing tools, they

haven't really evolved all that much in the past 60 years or so. In response to this fact, we have created a suite of products that takes the expertise and the advancements that scientists and researchers have reported in the academic literature and integrated them into a commercial platform that is then made available to the masses.

We examined the "gold standards" for drug discovery and basic scientific research and decided to focus on improving the traditional CO_2 incubator—which is a storage and cultivation apparatus for maintaining a variety of different cell types.

We decided to improve this incubator by integrating precise control of very important physiologic factors like oxygen and pressure. In addition, we've created a specialized culture media that's only composed of recombinant human proteins. These proteins are found in the human body, and our media is devoid of any animal products; nonhuman animal products, typically bovine, are present in a majority of culture media used for human cancer cell propagation.

PMO You are describing the Avatar system. Can you talk about the end benefit of this system over older technology?

Dr Lim We think the end benefit is that we enable scientists and researchers to start generating data that may be closer to what's happening within the human body. In the past, we relied on model cell systems maintained under conditions that our bodies typically don't present. This has led to years of data generation that may not reflect what's happening in vivo but is currently being used not only for drug development but also for target

discovery. By controlling these environmental factors and controlling the impact of what a cell feels, we think this could generate more meaningful data sets that can enable and enhance the drug discovery process.

PMO Xcell recently conducted a study comparing the Avatar system to traditional drug discovery systems. Can you talk about study goals?

Dr Lim About 1 in 10 drugs entering into human clinical trials are approved by the FDA. In oncology, the success rates for a given drug to receive approval is about 1 in 15. The problem is that millions of dollars and countless hours are spent in preclinical research from target discovery to drug development only to enter into human trials and have a success rate that's less than 10%.

It's our belief that some of these poor success rates can be attributed to the limitations of the tool sets themselves that are being used to identify drugs for human trials. The preclinical research tools are the traditional CO_2 incubator, animal serum–based culture media, and immortalized cancer cell lines and mouse models that are permanent fixtures in the drug discovery process, which we feel could benefit from improvement.

To improve on these tools, we've added precise control over oxygen and pressure levels in addition to CO_2 control in your classic incubator. We've created a chemically defined media so you know exactly what's going into the bottle that's comprised only of human growth factors and hormones that are relevant and free of animal serum.

When we combine all of these new tools, we can actually start to create protocols that allow pharma

researchers to not only maintain and propagate patient samples and cultures, but we can actually start to generate new classes of drugs based on patient samples. Our hope is that our innovative tool sets can challenge your classic mouse and animal models for identifying novel drugs that will ultimately be used in human trials.

PMO Can you elaborate on the way in which the Avatar system mimics the cellular microenvironment?

Dr Lim The Avatar system enables the culturing of various primary cell types. We can accomplish this by mimicking the microenvironments found within the body—from the brain to the bone marrow to the lungs. We achieve this by incorporating low oxygen culturing conditions that replicate the hypoxic state of tissues and organs when compared with the ambient oxygen levels found in the atmosphere. We can also tune it for pressure levels.

You can think of human beings as large pressurized sacks, and our organs are exactly the same, but smaller: they're pressurized and they're contained. When we take patient cells and culture them correctly in the Avatar bioreactor, we begin to see gene and protein expression patterns that are observed in vivo.

The important point here is that when you examine cells that have been cultured using traditional approaches, the gene and protein expression signatures look completely different than those found in the body. When we take these cells into our Avatar system, we can produce very similar gene and protein expression patterns by tuning the system to the proper oxygen and pressure setting of the organ or tissue of study.

For example, you can use the Avatar system to test a variety of different drugs on a patient's immune cells and cancer cells in different microenvironments found in the body to predict treatment response.

PMO Why did Xcellbio decide to focus its study in the field of immuno-oncology?

Dr Lim Immunotherapy has been transformative in the places where it has worked. A simple example is President Jimmy Carter. He received an experimental drug, an immunotherapeutic drug from Merck called Keytruda, and within a few cycles of treatment, his advanced melanoma that had spread to his brain was in remission.

In the past, patients with this disease would have succumbed within a few months. But Jimmy Carter, having had access to this drug, is alive and well.

Immunotherapies work not by targeting a mutation, but rather by targeting the proteins on the surface of both immune cells and cancer cells. These proteins are actually native proteins, meaning that they're found in a lot of different cell types but seem to be overexpressed or increased in some of these patient cells.

The study is really trying to figure out why the presentation of these drug targets vary between patients while also trying to figure out where the cells that express this target exist within the body.

PMO That's where the ability to mimic those microenvironments comes into play?

Dr Lim That's correct. This is really important for the simple fact that a patient's immune cells and cancer cells behave very differently depending on

where they're located. You can imagine a cancer that starts in the breast and migrates to the lungs is going to appear and behave differently, and that's partially owed to the fact that they're in a different microenvironment.

We're trying to test the simple idea that immunotherapy that works very well for the primary tumor may not work very well once the cancer has metastasized to a different microenvironment. The studies show that at least in a subset of these patients where the drug target was highly expressed in an environment that was reflective of the primary tumor, once we took the same cancer cells and put them in an environment that resembled the metastatic niche, they no longer expressed the drug target.

What we saw was that the patients' cells no longer responded to the drug because the target was no longer present.

The real potential here is that patients will vary in terms of their presentation of a drug target. The thought is that patients who do not respond initially may respond very well to these immunotherapies once the cancer has metastasized. So although it might not be used as a frontline treatment, it might be used in a subset of these patients and could potentially have a powerful impact once the cancer has metastasized.

This is very important, because a lot of our drugs that are currently approved by the FDA don't typically work very well for metastatic late-stage tumors.

PMO What have you gleaned from these initial insights, and how will it impact future studies?

Dr Lim These initial insights were again all done on a petri dish, so outside the human body. We generated some very interesting insights. But ultimately, I think from a patient perspective, you really want to know if the observations we've made in the lab could actually translate into clinical success. The additional plans based on our early observations were to then apply these same principles on patients who are currently enrolled in clinical trials for immunotherapy.

We just launched a small pilot study with UCSF [University of California San Francisco] in which we're examining patients with kidney cancer being treated with nivolumab, again an immunotherapeutic drug from Bristol-Myers Squibb, where we're basically taking a patient's cells that are undergoing treatment, putting them in the Avatar system and analyzing them to predict response to treatment.

If our observations hold true and if our approach works, we can ultimately create a diagnostic tool in which a medical oncologist can start treating patients more effectively and at the right time, because a patient who initially didn't show any presentation of the drug target may ultimately show the presentation of the drug target once the cancer is metastasizing. So initially they would be a noncandidate for the drug, but later on they may be, as assessed through a simple blood test.

PMO The Avatar system has 2 distinct applications. There's a research application in generating the right cell cultures for drug discovery, and there's also a clinical utility application to identify patients who may benefit from a targeted drug. Where are most of your customers using this system?

Dr Lim Right now we have some of our early beta systems that have been deployed to key research labs. We have customers at the National Cancer Institute at the NIH. We have folks at the UCSF Helen Diller Cancer Center. We also have had a lot of traction in the United Kingdom, specifically at Cancer Research UK. We'll be generating more early beta systems that will be deployed all across the United States at all the major institutions.

PMO Are the Avatar systems located at Xcell or onsite at research facilities?

Dr Lim We initially started out with doing a culturing service for a number of pharma partners as well as clinicians. We designed a complete workflow that would then be shipped out so it can be housed in a local lab, with the idea we believe our products in the hands of thousands of researchers will enable a lot of beneficial data generation across the spectrum of disease types that researchers are interested in studying.

PMO What are the long-term goals for Xcell?

Dr Lim I think our goal has always been to improve basic science. We believe by generating a new line of products we could start to integrate some of the findings that are reported in the literature that may not ultimately be commercialized, and we want to take the very best scientific results and findings, tricks and protocols, that have been developed over the years and incorporate them into a commercial entity that's focused on the culture of patient samples. Again, that could be their tumor cells, immune cells, neuronal cells. Rather than relying on canonical cancer cell line models, we really are interested in focusing on patient samples we're able to obtain through surgeries or through a

simple blood draw.

PMO Thank you very much for your time today, and continued success to you and Xcell Biosciences.

Dr Lim Thank you very much.

Dr Lim is the Chief Scientific Officer and Cofounder of Xcell Biosciences. He holds degrees from McGill University and the Scripps Research Institute, and completed his postdoctoral work at Harvard Medical School and Lawrence Berkeley National Laboratory.

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