Agilent case study: AbbVie

Agilent helps researchers at Abbvie uncover potential target using CAR T therapeutics

Though the weapons used in the battle against cancer come from a wide range of disciplines and approaches, one fundamental goal has remained a constant in oncology: namely, the need to develop tools that recognize and selectively kill cancer cells.

One recent advance in cancer therapies involves the re-engineering of T cells – a class of white blood cells that serve as part of our body's natural defense system – to make them even more highly suited for this task. A host of new tools for altering T cell behavior have come online in recent years, and one that has shown particular promise is the production of CAR T cells, so named because they contain a surface receptor (a chimeric antigen receptor) that improves their ability to recognize, and therefore, bind to and kill, certain cancer cells. Once these CAR T cells are produced however, a primary challenge is assessing, understanding, and perhaps even predicting the functional behaviors of those newly engineered cells in the tumor microenvironment.

Albert Lo, a Senior Scientist II at the biopharmaceutical company AbbVie, sees cellular metabolism as a critical signpost on the road to developing new CAR T cell therapeutics. Cellular metabolism is a fundamental biological process that drives cellular behavior, fate, and function, and accurate assessment of cellular metabolic phenotype can provide extremely useful insight into the potential for engineered T cells as targets for further therapeutic development and predictor of performance.

Albert Lo

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"The term "validating targets" is very context-dependent; it can mean different things for people who are coming at the end goal of cancer therapeutics from different directions," Lo explains. "In our work, the optimal outcome is that the target we are actively pursuing is an agent that can lead to tumor inhibition."

"Beyond the primary question of whether a certain CAR T cell kills tumor cells *in vitro* and *in vivo*, understanding the mechanism of that effect is key. Of course, it's vital that the toxic effects of the engineered T cells are only directed at the target tumor cells – not at healthy host cells."

After extensive evaluation, Lo and co-workers selected Seahorse XF technology as a valuable platform for assessing the metabolic behavior of their CAR T cells.

"Metabolic fitness is critical for efficacy," Lo says. "There are tradeoffs that can be achieved between the potency and persistence of the therapeutic effect, and potency and persistence can be associated with quite different metabolic behaviors. Potency is typically higher in cells that exhibit a tendency toward glycolysis to satisfy their energy needs, while persistence is more often a feature of cells that tend to rely on oxidative phosphorylation."

"To really understand the metabolic fitness of a target, it isn't enough to simply evaluate phenotypic differences, which may not be clearly evident early in the cell's development," Lo continued. "We need to understand the full biology of these cells, and for that, we need to use Seahorse XF."

Faced with the multiple goals of selecting candidates for development and gaining deeper metabolic understanding of prospective targets, having access to a broad range of metabolic parameters is especially enabling. Lo uses these detailed metabolic profiles in combination with data from cyotoxicity assessment, cytokine production, and other quality attributes to assemble a deeper understanding of the drug candidates. The goal of Lo's research is to deliver as complete a picture as possible, not only of the biology of these cells, but also what that biology means – and how it impacts their stated therapeutic goals.

Challenges remain for researchers, especially in terms of establishing detailed correlations between metabolic data and cell function. These challenges are particularly important for researchers like Lo, who are pushing the application of Seahorse XF technology in new directions. Still, Lo expressed his appreciation for the efforts of the Agilent Seahorse team, both in terms of helping them understanding Seahorse XF technology, and in partnering with his team to apply it in a way that furthers their goals.

"Setting up novel assays can be intimidating, and there are so many considerations around workflows and skill development and scalability that have to be considered," he said. "Agilent has been very mindful of our desired outcome, and their recorded seminar series, as well as conversations and other resources, have been extremely helpful in furthering our understanding of what Seahorse XF can tell us."

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