HOW TO DEVISE A CELL THERAPY CLINICAL DEVELOPMENT PLAN

Laboratory assessments — FROM PRECLINICAL RESEARCH THROUGH POST-MARKETING SURVEILLANCE — determine whether a cell-based therapy for cancer succeeds or fails.

Between 2010 and 2023, the US Food and Drug Administration (FDA) approved 34 cell and gene therapies[1]. This may seem small, given the thousands of drugs that enter clinical trials. Many of these cell and gene therapies, such as chimeric antigen receptor (CAR) T-cell therapies — in which a cancer patient's immune cells are genetically modified to fight the disease[2] — must go through an array of complex lab assessments to complement, or supplement, clinical data: from preclinical research, through clinical trials, to post-market surveillance. Surviving the rigorous process of regulatory approval and beyond is no easy feat, and there will be many more assessments to do because hundreds of CAR T-cell therapies were in clinical trials in 2023[3].

"Every developer out there advancing CAR T-cell therapy is required by regulators worldwide to provide data on its biodistribution, persistence, immunogenicity, and specific biomarkers to help estimate safety and efficacy," says Diego Correa, vice president & global head, Cell & Gene Therapy Center of Excellence at IQVIA — an international provider of advanced analytics, technology solutions, and clinical research services.

Although regulators mandate lab assessments for the approval of any cell therapy, the developer benefits as well. "Development programmes require lab data, for example, proof of mechanism, for internal decision making," explains Alan Wookey, global head of companion diagnostics at Q² Solutions, a clinical laboratory services organization that is part of IQVIA. Developing such cell treatments is expensive. Early results can help a sponsor, the company, institution, or organization who is responsible for the initiation, management, and financing of a clinical trial, decide whether it will move ahead with a specific project. "It's important for a pharma to see data that can give them confidence or some level of surety that they've got a good path for their clinical development," Wookey notes. So, how can developers make these decisions as early as possible? And if progressing, how can they give these therapies the best chance of avoiding obstacles along regulatory road?

▲ Diego Correa (IQVIA) and Alan Wookey (Q2 Solutions)

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PREPARING A PLAN

Typically, a sponsor enlists a contract research organization (CRO) to create a clinical development plan, which includes study protocols and lab assessments. For a cell-based therapy, these assessments include pseudo-pharmacokinetics — the process of estimating how a therapy behaves in the body, such as by determining vector levels, and pharmacodynamics, how the therapy impacts the body. These plans also involve developing expensive, bespoke assays that can be used from preclinical studies through clinical trials and beyond. Q² Solutions and IQVIA help a new therapy developer plan, design, and perform these complex assessments more efficiently and effectively.

In many cases, a CRO uses a central lab to run the tests. By doing all the assessments in one place, the resulting economies of scale can ease the financial burden and smooth the execution of clinical trials. To make lab assessments even more efficient, a complete plan, including selecting the best biomarkers and technologies to use along the entire development path, should be created even before the first preclinical studies. Q² Solutions and IQVIA work together, forming a team with the drug developer, to ensure that such integrated clinical and laboratory development plans provide all the information that regulators require to produce the highest quality product. And such collaborations can reduce the likelihood of missing key components.

A new therapy development plan also includes a timetable for performing lab assessments. Smaller sponsors may lack the experience and expertise required to develop such a collection of assays with appropriate timepoints. "Not having them all available and properly validated could compromise any submission or any subsequent approval," Wookey says.

KEY TECHNOLOGIES

For assessing each potential cell therapy, Q² Solutions and IQVIA must develop therapy-specific assays. "Cell therapies are unique in that the genetic sequences of the vectors are different," Wookey explains. "So, each assay needs to be validated utilizing a cell therapy's particular gene sequence."

To fight cancer, a CAR T-cell therapy must bind to a target on the tumour. "If we don't have a target, we don't have a therapy," Wookey says. In immunohistochemistry, scientists use a labelled antibody to measure a specific antigen — a cell therapy's target. Although this information is not usually requested by regulators, the developer of a cell therapy can still make use of the data. For example, this target identification could be used to develop a companion diagnostic: a test that can help to ensure that patients have the right target, such as an expressed protein on the surface of a tumour's cells.

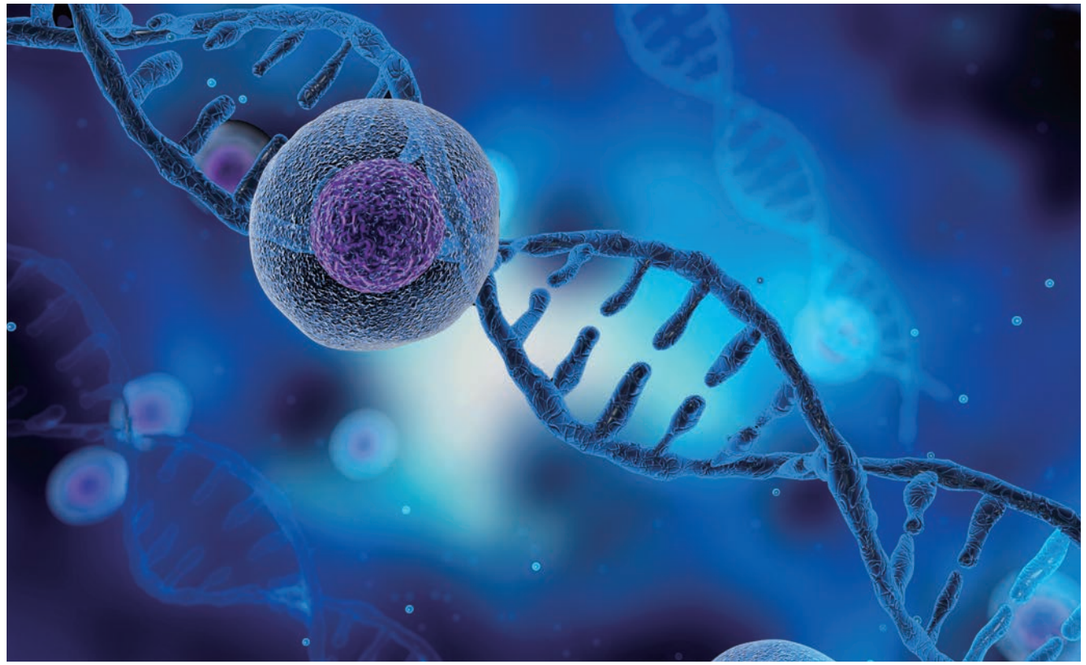
The engineered CAR T cells also divide in the patient's body, and it's important to know where these cells end up and how long they stay there. This biodistribution and clearance, respectively, is typically studied with digital droplet polymerase chain reaction (ddPCR), which quantifies the nucleic acids in a sample. "In a CAR T-cell therapy, we use ddPCR to monitor cell expansion and persistence, as well as any shuffling of the transgene in cells," Wookey says.

Lab assessments must be completed, often repeated, throughout the development of a new therapy. "Lots of assessments need to be done from preclinical research and manufacturing steps through clinical trials and commercial release of the therapy," Correa says. These tests must ensure that, throughout the process, nothing in a treatment triggers unwanted immune responses in patients.

COMBINING FORCES

Keeping track of all the information collected by a CRO and a central lab can be challenging, but IQVIA and Q² Solutions work closely to keep the process as smooth as possible. "Correlations between clinical and lab findings are key to demonstrate that there is a biological effect," Wookey explains, "and that there is a greater confidence that what we're seeing in clinical data is supported by laboratory data." Companies like IQVIA and Q² Solutions work with a therapy's developer to ensure the harmonized integration of that information.

"Through early engagement, we help plan out and perform assessments throughout the entire process," Correa concludes. Only then can a safe and efficacious cell-based therapy reach the patients that need it. ■



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▲ By early 2023, over 100 approved gene, cell, and RNA therapies existed worldwide, with more than 3,700 in development.

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