André Choulika – Chairman & CEO, Cellectis, France



Cellectis is working to develop the concept of off-the-shelf, gene edited UCART cells – universal CAR-T

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André Choulika, Chairman and CEO of Cellectis, discusses how UCART will revolutionize cell therapy as a universal gene-edited solution as opposed to the current therapies on the market which uses a patient's own re-engineered T-cells. Choulika goes on to share how the company is positioning itself for its anticipated commercialization and offers insights on key topics such as manufacturing, reimbursement, and regulatory frameworks.

What are the points of differentiation between TALEN® engineered UCART and existing therapies already on the market and what will ultimately make your technology more competitive?

CAR-T has been a paradigm shift in oncology treatment, transforming the way patients face the disease. However, we see the difficulties today of trying to bring these products to market. Even on the patient end, some individuals cannot be treated with CAR-T therapy because they do not have the raw materials in their body – the T-cells. In addition, the pricing of these therapies is also a barrier. Nevertheless, I believe CAR-T is a transformative innovation that will revolutionize oncology in the future to come.

Our goal is to shift the CAR-T therapies available today on the market into real frozen pharmaceutical products by harvesting T-cells from healthy donors, which can be gathered from the leftovers of blood donation, and engineering them into cancer-fighting cells. Cellectis is working

to develop this concept of off-the-shelf, gene edited UCART cells – universal CAR-T. These cells could become a standardized treatment for all patients in the same way that a traditional pharmaceutical drug is used.

What challenges are you facing in the development of UCART products?

The main challenge for these types of therapies is manufacturing – in gene therapies, 85 percent of the product is the process. We have been investing heavily into this area and we have been able to overcome many of the barriers by having a robust process. The product in a batch of UCART made today could be the same as the product you will produce and give to a patient three years from now. High efficacy and batch to batch consistency help create a low-cost process for Cellectis to offer a better price point while still having a sustainable margin. Many other players have negative margins and are losing money in their trials.

What lessons have you learned from the commercialization of existing CAR-T therapies and to what extent are you integrating them in the development of your own products?

From the products already on the market, we can learn from the examples of therapeutic methodology and application. The clinical treatment road of CAR-T has been paved by many KOLs, but this is not applicable to manufacturing. There have been constraints of time and raw materials faced by the first CAR-T producers, and furthermore, our component of gene editing has not been done within this field before.

We are expecting our UCART22 product candidate will soon enter the clinic. We have recently announced the construction of a manufacturing facility to commercially produce UCART in Raleigh, North Carolina. The 82,000 square foot facility project is called IMPACT and will be an extension of our fabrication activity here in Paris as we internalize and scale-up Cellectis' capabilities. Our facility here in Paris works on our SMART project and will produce the raw materials and nucleic acids which will be delivered to our facility in the US for processing.

Marketed CAR-T therapies have come at a staggering price. We understand as an "off-the-shelf" product, UCART could be more affordable – is this the case?

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UCART will absolutely be a more affordable option compared to the treatments that are currently on the market today. This is not a personalized therapy, so we are able to produce hundreds of dosages at a time to treat a wide patient base. Furthermore, Cellectis is providing a high quality, GMP-compliant product which is not the case of today's CAR-T therapies. Today's manufacturers have to deal with the resources they have and create treatments on individual bases – this costs hundreds of thousands and they can only market for half the price. Of course, we cannot offer a generic price, but we expect to be able to deliver a price point that is in line with the standard of other oncology treatments.

What reimbursement structure do you ultimately have in mind for the products you are developing?

Gene therapy treatments today are essentially autologous and classified as personalized medicine. On the other hand, UCART is a gene therapy for all patients that hospitals all over the world can keep in their inventories and utilize like a normal pharmaceutical. Yes, the therapy will be more expensive than some other drug options, but it will fit into the traditional reimbursement scheme. Due to its universal benefits and cost saving, I believe UCART can still be affordable to healthcare systems despite being priced slightly higher than current solutions on the market. For example, if the death toll in the US.can be reduced by one percent, the savings potential for the entire healthcare system would be close to USD 350 billion.

Cellectis has planned to establish commercial manufacturing capabilities in the US Do you envision developing such capabilities in France?

The difficulty in France is to find the skilled personnel needed to manage this type of operation. There is a high level of talent in France, but a lack of experience in these types of manufacturing processes. In the US it is easier to find workers already familiar with these processes, especially in the Research Triangle Park located in Raleigh-Durham, NC.

Secondly, it is much quicker and rational to deal with the FDA in the US than the ANSM in France. We cannot afford to fund ourselves through the lengthy delays that are commonplace here in

France. For example, applying for our clinical trial approval for UCART19 in the US took only a few months whereas here we had to wait 18 months before clearance. The Macron administration has taken a strong stance on this issue and has made some changes to reduce the time, but the fundamental constraints still exist.

The ANSM is a great organization, but it is entirely understaffed. The administration has not invested enough resources and energy into fortifying the ANSM into the same organizational scale as the FDA. For example, the strict restraints on KOLs having a conflict of interest make finding expertise and applicable knowledge very difficult as the most qualified scientists often interact with the pharma industry. Agnès Buzyn is working to improve this but a revolution cannot be completed in one day.

In parallel to the development of licensed development programs, your ambition is to have your own portfolio of products hitting the market – a path that very few biotech companies outside the US have successfully followed. What do you see as the main success factors to embrace in the coming years?

For a small company like Cellectis, we have a very important portfolio of product candidates. Within the next 12 months, we will have four different UCART molecules in clinical trials in several oncology areas. We see the performance of our products and UCART19 may even be more effective than the current autologous CAR-T therapies on the market today. We are now focused on the proof-of-concept for clinical performance and once we have a clear performance over a standard of care, the products can move very quickly to registration trials. We are aiming to reach this milestone within the next two to three years.

It has already been a 20-year ride at Cellectis being at the forefront of innovation in a highly competitive field, where you also have to manage shareholder expectations on top of the inherent uncertainty of innovative drug developments. Where do you take your stamina from?

Every day in biotech has its load of problems, so eventually, you have to learn to enjoy the journey overall. Determination and persistence are key. Furthermore, it is very rewarding to work with such a dedicated team every day. There are people who have been with Cellectis for nearly twenty years and we have built a company and reached milestones together while still having a clear view

of where we are going in the future.

Having a purpose in our work and creating solutions to better treat patients is a strong motivational force. Being able to see a patient return to their family makes all the hard work and challenges worth the fight.

What final message would you like to deliver to our audience about cell and gene therapies?

Cell therapy linked to gene editing is a profound paradigm shift in molecular medicine. This approach will absolutely revolutionize the way cancer is treated today. The gate is being opened to a new era which is unprecedented in the entire history of modern medicine. This is a thrilling turning point for medicine and I am excited to see what will come.

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