

INTERVIEW

Realizing the potential of NK cell therapy



ALVIN SHIH joined Catamaran as President and CEO in February 2021. He is an experienced physician and biopharma executive with a track record of building and leading companies that develop therapeutics addressing significant unmet medical needs. Most recently, Alvin was CEO of Disarm Therapeutics, a private neuroscience company that was acquired by Eli Lilly in 2020. Prior to Disarm, Alvin was CEO of Enzyvant Therapeutics, a company developing cell/tissue-based regenerative medicines for rare diseases. He previously held senior leadership roles at Retrophin and Pfizer, where he was the Chief Operating Officer of the Pfizer Rare Disease Research Unit. Alvin began his career as a strategy consultant at McKinsey & Co. and LEK Consulting. He holds an MD from the University of Alabama, an MBA from the Kellogg School

of Management, and a BA from Vanderbilt University. Alvin completed his residency training in internal medicine at the Massachusetts General Hospital.

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Q What are you working on right now?

AS: We are working on building a company that is differentiated from the rest of the field in cell therapy, and that has a real chance of providing a transformative therapy for patients with solid tumors.

Q How would you sum up the story of NK cell therapy development to date?

AS: We know that cell therapy in general has come a long way in a short period of time and has been quite transformative for patients with hematologic malignancies in particular.

However, it's been a difficult transition to apply the learnings from hematologic malignancies to solid tumors. That is the next frontier that needs to be addressed for cell therapy to reach its full potential in treating tumors.

The other attractive feature of our platform is that NK cells play into the movement from autologous to allogeneic therapies. Autologous therapies (such as currently approved forms of CAR-T) are very useful but have been limited in uptake because of the logistical and technical challenges. If we can provide an allogeneic or off-the-shelf therapy, it will increase the reach of cell therapy in general.

Our engineered CAR-NK cells are allogeneic and have potent anti-tumor activity. From what we know about the biology and the early clinical experience, using NK cells may result in a cell therapy with a better safety profile than autologous CAR-T, at least with regard to severe outcomes like cytokine release syndrome (CRS), neurotoxicity, and graft vs. host disease (GvHD). It is a great chassis to be building on for this next generation of allogeneic therapies.

Q There are great expectations for further advancement in the field as we enter a new year, particularly in terms of applications in the solid tumor realm - what specifically is fuelling this optimism, for you?

AS: I am optimistic because of the great progress we've seen at Catamaran over a very short period of time, as well as progress in the cell therapy field overall. Cell

therapy in general has been a robust area for clinical exploration as well as investment, so I am optimistic that the technologies being developed right now are going to increase the armamentarium of approaches that doctors have to hand.

One of the things that has been nice to see is the early but growing body of clinical data on CAR-NKs. The initial data coming out of the MD Anderson experience has certainly fueled optimism around the potential for NKs to be transformative in cancer therapy.

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Q Tell us more about Catamaran's own platform & approach. What differentiates it in this increasingly busy space?

AS: We have two dimensions on which we differentiate – our strategy and our technology.

On the strategic side, we are targeting solid tumors by first intent, which is different to most companies out there who are looking to go first into hematologic malignancies and then into solid tumors. We hope that the approaches targeting hematologic malignancies work, but we think there is something to be said for aiming for solid tumors where the greatest degree of unmet need lies. We know that about 80% of cancer diagnoses are in solid tumors, so it is important that those patients have some therapeutic options.

On the technology side, our means of engineering is different to most others in the space. Many companies use viral vectors to make genetic edits to their cells, whether they be autologous or allogeneic. Our approach is to use a transposon-based system to edit NK cells. This allows us to insert larger payloads than a typical viral vector would allow, and also enables us to design and manufacture these cells in a more efficient and scalable way. The larger payload opportunity means we can get more creative in the way we think about editing these cells. For instance, we are able to design in synthetic receptors that help our CAR-NK cells evade the immunosuppressive tumor microenvironment. Being able to survive – or even thrive – in the harsh tumor microenvironment will be an important strategy for addressing solid tumors.

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Q What would you single out as the key challenges facing NK cell therapy developers such as yourselves moving forward & can you share some details of your plans to address them?

AS: One challenge that often gets raised is manufacturing. It does not matter how elegant your cell construct is if you cannot make it and get it into the hands of doctors who treat patients.

To manage this, we have invested very early on in building our own internal process development and manufacturing group, so we have ownership of the process and can more effectively manage the external vendors and collaborators we are working with. That is an important piece.

Another potential challenge is on the regulatory front. Regulations are constantly changing and especially with some of the recent reports of cell and gene therapies being placed on clinical hold by the FDA, it is quite possible that regulators will want tighter controls on cell therapies in the early stages of development moving forward. The mitigation strategy there is to have early and frequent engagement with regulators. We have certainly initiated that - we

have a scheduled interaction with the FDA in the early part of 2022 that will help inform the development pathway for our programs.

Q What are the likely next steps for the NK cell therapy field – for instance, in the combination therapy setting?

AS: We always think about possible combination approaches, and where a therapy like ours can be best applied. It's unclear what combinations will make sense, but we have the privilege of watching the rest of the field to see what sort of data emerges from approaches like antibodies, antibody drug conjugates, small molecules, and other cell therapies.

Each modality is going to play a role and add therapeutic options. I think combinations may ultimately extend the magnitude and durability of the clinical effects of individual therapies. It will be interesting to see if there is some combination of cell therapies that would make sense with each other. This will be enabled by an allogeneic approach making cell therapies more accessible and allowing a greater degree of experimentation with combination approaches.

Q Can you sum up some chief goals & priorities both for Catamaran over the next few years?

AS: It is going to be a really busy time ahead of us as we try to move our programs closer to the clinic in the most efficient way. We are prosecuting two programs in parallel. Our first program is targeting HER2 expressing solid tumors, specifically breast and gastric cancer. Our second program is targeting CD70 expressing tumors, such as renal cell carcinoma. Our priority over the next few years will be trying to get those moved along as quickly as possible so that we can get into the clinic and demonstrate that our platform has potential.

My own goal is to build the company to enable us to do that. Part of that is building the organization and hiring the best people who will allow us to move these programs forward and deliver therapies to patients.

AFFILIATION

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AUTHORSHIP & CONFLICT OF INTEREST

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