
# CAR-T and Other Engineered Immune Cells: Panel Discussion

## Panelist Introductions:

**Mark J. Gilbert, M.D.** is the founding Chief Medical Officer at Juno Therapeutics, where he joined in March 2014. Prior to joining Juno, Dr. Gilbert served as an interim chief medical officer and consultant in strategic drug development and portfolio management in medical oncology for several U.S. biotechnology and pharmaceutical companies. Prior to his executive positions in biotech and oncology companies, Dr. Gilbert was a faculty member at the Fred Hutchinson Cancer Research Center and the University of Washington in Seattle and trained in the laboratory of Dr. Phil Greenberg, one of Juno's scientific co-founders.

**Dr. Chris Heery** is the Chief Medical Officer at Arcellx. Dr. Heery has developed significant expertise in cellular therapies through his time at Precision BioSciences and the National Cancer Institute (NCI) where he led numerous programs through clinical trials. As the CMO at Precision BioSciences he oversaw the clinical development of one of the first allogeneic CAR-T cell platforms and provided clinical insight into efforts for their gene editing therapeutics. Previously, Dr. Heery was the CMO of Bavarian Nordic where he oversaw clinical development programs for their immune-oncology and infectious disease vaccine portfolio.

**Dr. Mike Nicholson** spent nearly 13 years at Precision BioSciences where he held several leadership roles, including Executive Director of Scientific Operations, Vice President of R&D, and Senior Vice President of Research. Dr. Nicholson played a key role in developing Precision's novel gene editing platform and led research teams focused on allogeneic CAR T therapies and gene editing-based gene therapies.

**Moderator: Right now, CAR-T has 5 approved products, we know they are all in the hem-onc malignancies, when will we see a CAR-T have a breakthrough in solid tumors, and what is the expectation around that? Or will there be another different modality that is going to offer impact in solid tumor?**

**Mark Gilbert:** The timing of when this will occur, I think is a little bit challenging to pinpoint. I would step back and make the analogy with monoclonal antibody therapy, obviously if you just look at the timeline of the development of monoclonal antibodies, different entities, the real shift to having agents that target solid tumors came probably about 7 or 8 years after the approval for Toximab. There is one exception to that and that's Herceptin that was approved around the same time. In hematology we can target a specific target which ended up being very fortuitous that that was effective. We're kind of using that exact same approach with solid tumors right now at least in many of the clinical studies that are being done. The challenge is two-fold, one being that it doesn't really address the complexity of the solid tumor environment or the heterogeneity of these tumors relative to hemalogical malignancies and the other is that we have to pay attention to what the off-tumor toxicity represents when we select those targets within a setting because it's not just for example a b-cell that we're knocking out. But as we move forward, I think there's several avenues that may bear fruit in this arena beyond the anecdotal responses that we've seen so far in solid tumor. One of those is that we are looking at different type of effectors and we're looking at mismatched, meaning immunological mismatched effector cells, Chris can speak far more about allogeneic approaches than I can, but the other is we haven't yet done what the monoclonal antibody field did which is they went after targeting much more of the checkpoint and the tumor microenvironment, angiogenic targets and so forth. They were targeting things around the tumor to change that environment and so how we move forward within that may be actually looking at more than just what those tumor antigens are but more how we might be able to target some of those other mechanisms that we know are in play within this setting. As far as the exact timing, I would suggest that it is still a good 4 to 5 years before we are going to see more than just incremental changes and the field is very young in this space. I do think myself that it may come through a different effector cells than T-Cells, simply because the mechanisms for those cells are less susceptible to a microenvironment.

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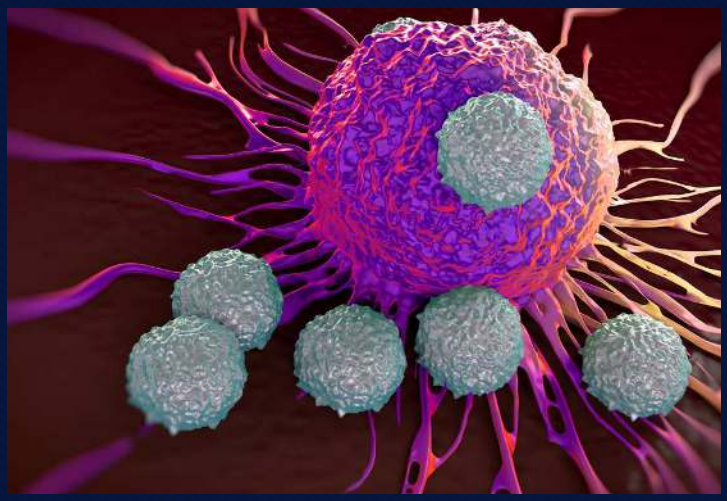

**Christopher Heery**: We have the complexity of which target to go after and how best to attack that target, is it a CAR or is it a TCR, and I think that is a pretty basic question that's on top of a lot of people's minds. We are seeing evidence that a TCR can have therapeutic impact in a very specific tumor already. It's reassuring to know that there is not something that is intrinsic to all solid tumors that is going to prevent any particular effector cell from eliminating a cancer cell in that setting, but what it does tell us is that if we could just skip over the hardest problem which is what the target is. We skip over that problem, addressing the tumor microenvironment, is probably something we have the tools to start to address more efficiently today than we did when cell therapy was pretty new. What I mean by that is the ability to modify the expression of certain genes in the T-Cell or whatever other effector cell you want to use actually affords you the ability to account for the microenvironments that it will have to live in. But one of the things that is really interesting is that that microenvironment issue may be specific to the given tumor type or even in some cases a subset of that tumor type in patients. One brief example is if we look at colorectal cancer, we can look at gene expression profiles within colorectal cancer and see that there are four different gene expression profiles by RNA Seq, but a lot of that has not been implemented in clinical practice. The question that people ask me is why are we not testing that? And the answer to that is that we don't know what to do with the information. But in theory if you were able to use that same type of method like RNA Seq, you might make your cell product specific to those microenvironmental issues so that it can survive or maybe even thrive in that environment, and that's something that's really only in the context of gene editing and gene engineering can we really take on. So, I think that is one really cool thing, because that allows us to think about if we solve a problem with a cell therapy can we work on how to solve it with other off the shelf therapeutics as well, but I think cell therapies offer a unique opportunity for proof of concept around some of those things very rapidly, but there is a lot of trial and error that is going to be involved. I would only push back one last thing on the question which is when are we going to see a breakthrough? I think with Adaptimmune's data we are seeing evidence that cell therapies can be effective in solid tumors, now it's a matter of solving it for not one specific sarcoma, but bigger, more difficult tumors to tackle.

**Mike Nicholson**: What we have seen in NT-CAR is that a mono directed mono cell therapy can be effective, and I don't think we're going to see that in solid tumors broadly speaking. Part of the challenge is we cant put aside the tumor antigen and solve this one problem. We have to address a much more complex set of questions all simultaneously all that are wildly different in a different tumor type, there are definitely more questions than answers at this point. We're seeing chinks in the armor, and I think we're asking better questions, Mark to your point even different effector cell types, that's still relatively new as we think about the relative timeline of CAR-T, and certainly success has been recent, but it is not a new technology. So, as we think about some of the other modalities, I think we are still in the very early stages there and equipping ourselves to ask questions we couldn't even ask a few years ago. I also can't name the precise date, but I feel like it's going to be a very steep curve in the couple of years, hopefully.

**Moderator: There is a lot of promise around allogeneic CAR-T therapies and a lot of interest moving forward. At this point we don't have an approved product, but there are companies that are working in this space, a lot of promising work that's being done in trials. Which companies are having the most promising results in trials? And what are some of the lessons we have learned thus far with allogeneic CAR-T's in this space?**

**Christopher Heery**: I probably have too many opinions and too much bias on this, but I am obviously a pretty big fan of what my former employer Precision BioSciences is doing because I think there was a step-wise approach to understanding what are the factors that are going to limit the activity of a first-generation cell if any. How can we characterize them, how can we characterize when those things occur, what can we do to address them within a group of patients with that first generation of cell. And then based on that information make the best inference you can about how to go to the next generation of cell. And I think that is a very thoughtful approach to a very complicated problem. Just a little bit of context just three years ago when people talked about allogeneic cell therapies, I would say about 80 percent of people I spoke with said this would never happen; they said this will be rejected so fast, you won't even see responses, it is a waste of time. I would say if we put allogeneic cell therapies through that lens, we are now the other way. I would say its only about 20 percent of people that I talk to in the academic space that say allogeneic cell therapies will never get there. What their question is now, is sort of a how, and I think most people I have spoken with are of the opinion that the best way to get there is to modify the cells to prevent rejection as much as you can, and that's what I really appreciate about this next generation of cells coming from Precision. It's not too different from what CRISPR Therapeutics has done with their first generation of cells, and it'll be really interesting to see what that first generation of cells does in a larger number of patients, you know the first disclosure was just ten patients. I think a lot of us are anxiously awaiting to see what that looks like because the difference between the two is that CRISPR Therapeutics knocked out beta 2 microglobulin which runs the risk of NK rejection, and we don't know the timelines for that exactly in patients. Precision knocked it down with the hope of avoiding both T and NK rejection so it's going to be fascinating over the next year if both of those work or one works better than the other, but I am a believer that one of them will likely get us very close to what autologous cell therapies have achieved with CD19 targeting. I think once that happens it opens up an entire new way of thinking about cell therapy which is really more focused on what patients need, which is to be able to get therapy when they need it and not wait four to six weeks to get treated.

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**Mark Gilbert**: I think in the early days of auto CAR-T we emphasized the issue of persistence to having the largest correlation with the reduction or minimalization of relapse, and for some diseases that may indeed be true. But what has been striking, and Chris mentioned this briefly, is how a number of Allo approaches are having shorter, at least in the peripheral blood compartment, are having shorter and shorter levels of persistence and yet they're still having durable responses. You can take everything from alpha beta T-Cell allogeneic approaches and I can't speak for Precision or CRISPR, but Allogene has at least published their updated results in hem malignancies and again they're starting to get close. There's a lot of manipulation not only the cell but then off the patient as well with the lymphodepletion that's used, but I have been not only struck but really amazed in the allogeneic field when you use cells other than alpha beta T-Cells and they may survive only days, and somehow, they're resetting this process. I really think that the success that comes with Allo is that this may be a space that we actually understand less about and there may be surprises coming through on breakthroughs. It's really a question to me of how simple you can go versus how complex do you need to make those gene edits that Chris was talking about. I don't have an answer for it right away, but it is an open question right now in the field that some of the early clinical data is coming out and I think it's going to be very intriguing. Chris did not say this, but I think he believes it, I think in the future that we're going to be in some Allo setting, because with Allo you can make this look much more like a drug then what Id classify as a cell therapy, and that is what I think is going to be the critical paradigm to actually see a lot of investment to this area.

**Christopher Heery**: To me that is the hook, that is what it has to be. I should have said it in the beginning but I'm a little bit biased towards those approaches that are a little bit simpler. That simplicity often is one of the biggest drivers of uptake in the therapeutic market, so physicians need to have something they can use and not put them in a position of having to manage an enormous amount of complicated toxicity, so the simpler it appears for the end user experience, being the patient and the physician, the more likelihood it has being a realistic drug candidate.

**Mike Nicholson**: **As we think about simplicity and gene editing trying to make the Allo approach more like a drug, one thing that's been on my mind recently as we're getting more sophisticated ways of dealing single cells and Allo cells, we're getting a better appreciation of the need for a heterogenous population. As we're looking at clonal or polyclonal expansion do we run the risk of oversimplifying it and eliminating some of that heterogony and polyclonality that we actually think we need in CAR-T to be effective and is that going to be more of an issue in solid tumors.**

> "So, we in general, want a product, specifically a commercial product to have some amount of homogeneity, it should be the same thing every time. Now that is impossible if you're making each product from a different donor because it's an autologous product, and it's even more difficult when you think about that with till. Because in fact what you're trying to do is harvest cells that are uniquely suited to the tumor you are trying to address."

**Mark Gilbert**: There's two pieces of general data I would bring in on this conversation, the first has to do with the success I'll claim on TIL therapy and the association with heterogeneity, more heterogeneous responses and TIL being more likely to have a favorable outcome. Some heterogeneity may be a good thing, if not the responses themselves, the cell types, what have you. The second piece is that as we learn more about engineering, for example iPSC's and trying to conceptually make this a homogeneous phenotype or cell type. What you begin to realize is our assay techniques are sensitive enough we can measure heterogeneity in all of these products. The real question is which of them matter within that, and that needs clinical experience in order to determine that, and quite frankly I don't feel like we're there yet for sure, but there are end roads being made to better understand what may be the critical pieces to be more consistent versus allowing heterogeneity, not so much on specifications but on product attributes within that.

**Christopher Heery**: Mark actually keyed in on something that does directly go to your question which is the TIL experience. You have a bit of a conflict right now in the world of cell therapy from a regulatory standpoint. So, in general, we want a product, specifically a commercial product to have some amount of homogeneity, it should be the same thing every time. Now that is impossible if you're making each product from a different donor because it's an autologous product, and it's even more difficult when you think about that with TIL. Because in fact what you're trying to do is harvest cells that are uniquely suited to the tumor you are trying to address. By definition they should be different from each other, so that heterogeneity between patients but also between the cells. I think that is enormously complicated, and my biggest concern right now is, we all heard Iovance is going to have this delay in the review process. I think there needs to be a broader strategic conversation with FDA and sponsors about what is actually the best, and probably KOLs in the field and treating physicians about, what are we actually trying to achieve and does this always have to be the same, and does a potency assay really tell us the answer to that when we know that the potency assay with the CAR-Ts don't really predict outcomes on a one to one patient basis that well. I think that those are all really important questions that unless we want to take them head on we are not going to get these therapies as to as many patients as could benefit from them as quickly as we could. But to answer your question if you made the same cell every single time like an iPSC and you made them all exactly the same I think you'd probably lose something overall, but how much I don't know yet and I don't think anyone knows the answer to that.

**Moderator: As you move from autologous over to allogeneic, the potentials, the economies of scale that you get from manufacturing, the number of doses that have to be produced, how much you can get out of a single donor. What are the benefits you gain from being able to produce from a single donor? Do you lose some of that in the effectiveness of the therapeutic itself? It sounds like there are some tradeoffs there that you are talking about.**

**Christopher Heery**: Well if you can solve the allogeneic rejection problem I think that there's a very good chance that the efficacy will be almost identical, and like Mark said, I didn't want to get into this level of complexity but we don't know how long those cells need to persist, could it be six weeks or eight weeks, and if it is I think we're right on the doorstep of that with allogenic cell therapies, and today I think we're right there, we're very close. But to answer the question, it is at least an order of magnitudes in terms of cost of goods. But as we think about the other things that could be done at greater scale once you really invest in process development on manufacturing, that could be two orders of magnitude difference in terms of cost of goods, it probably will be.


...So it is an enormous difference, and people sometimes say why, isn't it the same manufacturing? It's because for an autologous you're making each product for each patient and it's not just the manufacturing, which is expensive but not as expensive as you may think. The real cost is owning all that supply chain, keeping all of the resources that you need to make that thing up to quality control metrics making sure those are uniform. And then on the back end doing all those release assays for each product, that drives an enormous amount of cost. And it's not because the assays are expensive necessarily, it's because the assays need to be done in a highly validated controlled fashion and you're trying to do them in an assay that you otherwise might be able to do over the course of a few weeks and write a report over another few weeks. You are trying to do them all in like seven days, and you're asking a group of people who do that work waiting around, so they're charging you for all that time while they're waiting around so the scale really comes from combining the efforts of the manufacturing and the release and it makes a huge difference in cost. It is the pressure created by that timeline.

**Mark Gilbert**: For me there's also an additional layer, so part of it is, let's say you're going to go Allo, I don't think anyone's going to deny that there is a scale of economy from the autologous to Allo but then among the different Allo approaches, how do those splay out? And I have to say this is a harder piece to come by, in very recent days it has struck me there, this almost depends what disease you are trying to target or what situation you are trying to target. If I'm trying to target b cell malignancies, there is already clinical evidence, I don't have to do a lot of manipulation. There are cell types I could get, maybe not cell lines, but I could get it from a healthy donor, or cord blood and I can get sufficient cells and culturing techniques are there to bring that forward, maybe not a master cell bank but at least something that's a working cell bank that permits huge levels of scale, if that's all we're trying to solve for. But the other side of it is, when you're gene engineering and your objective is not just trying to make it scalable and less costly, but you're actually trying to use this platform to improve efficacy. So now back in the oncology setting, the economics are completely different in that setting in my mind. And it's worth taking the more, I'll call it complex, but let's say the complex and sophisticated approach that would allow you to actually target that tumor or indication to the best of your ability. So I see there's really two different ways that Allo can help one is that yes it can be made scalable and less expensive. I'm not going to make these elaborate genetic edits and do all this genetic engineering in an autologous product, that would be prohibitively time consuming and expensive. I cannot even come close to fathoming what it would be like in a regulatory environment to get something approved in that context, so it really provides that foundation for that as well.

**Moderator: We have proof of concept for CAR-NK and we also know that the first patient was dosed with CAR Macrophage trial earlier this year. From CAR-T moving into CAR-NK moving into CAR Macrophage, how does that compare, what is the benefits, the thoughts around moving into CAR-NK, moving into car macrophage, versus where we are with CAR-T?**

**Mike Nicholson:** So I'll start with the CAR Macrophage approach just because I feel like CAR-NK is certainly not CAR-T but perhaps a little bit closer than a CAR M. I'm personally very excited about CAR Macrophage just because I feel like it allows us to ask an entirely different set of questions because it works fundamentally from a very different mechanism. The idea of still using a CAR or some sort of targeting molecule to specify the engulfment you might get from an engineered Macrophage, and of course there are a couple of reasons to do this. Number one if you can specifically target your Macrophages to engulf specific tumor types that's good but then we also expect that we'll see antigen presentation and then activation of the immune system, it's almost an amplification signal. I was talking to Chris at one point and it's kind of like combining a CAR-T with a vaccine strategy, almost a cancer vaccine. So, I think on the one hand, what a great approach, because we can potentially attack tumors from two angles, on the other side that now doubles the complexity because we have several things we are trying to model and understand. Not to mention we still, as much as we understand how CARs work and CAR-Ts and to a lesser degree CAR-NKs. I think it's very exciting just because it is such a different effector cell to use, and opens up some mechanistic questions we can't address with CAR-T. But it also is just full of more complexities, but I'm very excited to see what happens in this first trial and follow ups.

**Mark Gilbert:** Maybe to talk a little bit about CAR-NK, while there aren't pivotal studies that are under way yet, I think work out of Anderson with Dr. Rezvani has demonstrated that you can produce and deliver CAR modified NK cells from cord blood and get these responses with an allogeneic cell product that's NK that mirror the effectiveness of currently approved CAR-T products. I think that there are a number of big questions out there right now, one is that we tend to treat the NK field as if it's all one cell and I don't believe that that is necessarily the case. Obviously, we have some companies that are working on classical NK cells, they aren't defined memory NK cells, NK T-Cells, and then gamma delta T-Cells, there are some similarities between those classes, and we tend to lump them all together, but it may be more of a continuum then a distinguishable strong difference between them. But it is possible to modify them, what signals we give a NK cell, because classical CAR construct are giving T-Cell signals to NK cells, and that appears to work but we haven't yet characterized what is the actual phenotype as those cells move forward and have we actually altered them in some specific way once they get in the body. So, I do think that CAR-NK is an approach, I think that there are some real technical hurdles in using true NK cells because of the freeze thaw sensitivity of those cells that may be challenging for that field. But it really is an interesting approach in using these other cell types within the field and they seem to match up with CAR-T, at least in homological malignancies, whether there are differences in solid tumor the jury's still out.

**Christopher Heery:** I would just emphasize that one point about CAR Macrophage, what is really interesting about that idea is the ability for antigen cascade, and multi specific antigen response. I think when we look at the question of when we will see a breakthrough in solid tumors, one of the first questions is how do we account for the heterogeneity of expression in solid tumors? So, that does offer a really interesting opportunity to help account for that problem. I think there's a lot of learning that would have to happen there to get it just right, but I think it's a really compelling idea to be able to generate a multi specific immune response while...

...also breaking down the tumor size initially with a highly effective other cell therapy, or maybe with that cell therapy product inserted directly into that tumor for instance. Just one other comment on Marks comments on CAR-NK, we should not also forget that there's generic activated NKs and those are also intended to help solve this problem of multi specific mini tumor antigens, its actually the problem that Arcellx is trying to work on. Could we take one universal CAR-T cell with mini potential target tags, and I think the highly activated NK cells we're actually seeing some interesting responses with those in combination with already known IGG1 monoclonal antibodies, so I think that's also a really interesting field. But it certainly suggests that NK cells are efficient killers, and they certainly could be just as good, but again it took 20+ years for CAR-T cells to get to where they are today, and I think we should expect that any new cell product or new approach is going to take a while for us to get it totally right, but it is exciting to see that there are these opportunities out there.

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**Moderator: We've kind of focused around this idea of how to appropriately leverage CAR into these different areas. I know you brought up NK without CAR, but are there other modalities in this space that are showing promise in what they are and what we might see moving forward separate from CAR?**

**Mark Gilbert:** I would just reiterate what Chris was talking about, whether you are using Allo NK with soluble antibody as a therapeutic, we are getting very close to having full-on proof of concept that can work in hemalogical malignancies, I think it really opens up a lot of prospects around this. As most here and on the call probably know, if you do not have to genetically modify cell, it changes certainly the post study follow up significantly, the costs are significantly lower just from a development standpoint within that.

**Christopher Heery:** One other thing I see in the chat, there was a question about the recent deaths with Tmunity, I thought it would be useful because there was some really interesting conversation between some really smart people on twitter, and looking at some of these old papers, that knocking out TGF beta might have caused this uncontrolled cell expansion and that uncontrolled cell expansion is typically the thing that is going to drive neurotoxicity. So, the question is in the chat is are their other agents that might control neurotoxicity? And the answer is yes there are some things in development, but I'm more interested in the idea that maybe the smarter approach is to have more control over the expansion characteristics of your cells, and it's not necessarily a kill switch but understanding the things that lead to the dynamics of the cell expansion. One of the problems we face in cell therapy is getting the effector to tumor cell ratio correct, but there's this assumption you need to do that immediately for that to occur and historically that has been true, because basically the cells are going to go in and peak expansion is your best metric of whether they encounter their antigen and expanded as much as they could. But if you could control that engagement you...

...might slow down the exhaustion phenotype of those cells and you might also get the same total area under the curve that you achieve with a super high expansion on a given day, because that peak expansion is usually directly related to the toxicity that patient is going to experience. So instead of focusing on managing a problem that we created perhaps we could figure out how to not create the problem and I think that's where things will evolve.

**Mark Gilbert:** Or as you said modulate it, and I absolutely agree with you, in fact many companies right now are focusing on these add-ons. You mentioned the TGF beta r2 and taking that whether it's a break or regulate, whatever it is on expansion. We'll see this come again with all the different probing's that are going on once they get in the clinic, because animal models aren't going to tell us the answer, so I definitely agree with you Chris we have to be thoughtful in that setting. I just wanted to comment on one piece, typically in this setting and Chris said it, its uncontrolled expansion or unbridled expansion that's occurring in this. The lack of response to Tocilizumab has actually been demonstrated in other settings as well, you have to stop the growth of the cells, Tocilizumab does not touch that, it's just blocking aisle six effects. We now know for neurotoxicity once you breach that blood brain barrier, those T-Cell's when they get in, there's PSMA expressed in the brain, and it's not called PSMA it's called by a different name but it's the exact same protein or an isoform of the protein. And within that it actually can be problematic, and I don't know as much about Poseidas PSMA but I know they also had reported a death at some point in their development. And I honestly do not remember if it was their auto or Allo program so I don't have more information on that, but it could be that the target also matters in this setting to some degree, but fully agree with Chris' assessment on that.

**Moderator: I just wanted to give each one of you a minute or two, what are some final thoughts and key takeaways or insights that you'd like to share with the group as far as what's happening in CAR-T these other modified cells, and just a couple key statements you want to share about this area of CAR-T and other engineered immune cells?**

**Mark Gilbert:** I'll start but it's going to be very simple. So, Chris was talking about being a believer in certain things and as I mentioned when I introduced myself I've been a believer of immune cell therapy from the beginning of my professional career and I absolutely believe we are now making the transition to seeing that as a reality and I think many people would agree with that statement. There's so much more to come, I think the biggest thing is being able to keep your finger on the pulse of the new findings that we will have with all of the different approaches that are being explored right now and so I think there's a great reason to see promise not only in these approaches and hope for patients thankfully. But it really is going to be an interesting period of the next five to ten years as these different therapies are reading out in the clinic more frequently.

**Mike Nicholson**: I was thinking the same thing Mark, right now it is moving so fast on so many fronts. There was a paper a couple months ago, I think there are over 500 CAR-T clinical trials worldwide now. So, I think one of the challenges in the field is not only to work on what we are working on but to keep track of what everybody else is too, because again I don't think anyone is going to have the sole answer or find the key question. I think it will really be this combination of understanding, none of these things are in a vacuum, you can't address the TME in a vacuum, you can't address targeting in a vacuum, you can't address cell type or effector type in a vacuum...

...I think as a field, as an industry, we have to keep our eyes open and recognize, not to belabor the point but a monotargeted monocell therapy is likely not going to be the answer. So, we all need to focus on what we need to focus on in our own programs but also make sure we're paying attention, collaborating when we can, trying new ideas, making sure that we're not missing out on everything that's happening right now.

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**Christopher Heery**: I would echo those thoughts, I think both answers remind us that there was 30 years of work in academic labs on these problems before it really got to the point where an industry partner was willing to put the money behind it to get it going, and we really have to give a lot of credit to those companies that blazed those trails, including Marks. The thing is now we have a quorum, we have so many companies working on so many different problems, that I believe what will happen is there will be, just like in most therapeutics, a convergence of all of these different questions into sort of an ultimate, ideal product, and I still think is 5 or 6 years away. But you're going to find yes there will still be winners in the allogeneic space that understand how to manipulate cells, there are going to be winners in how to control the expansion characteristics, how to find the best targets, all of those things. And they will converge into the best of the best products and then there will most likely be 4 or 5 of the best big companies that buy up little bits of that until they can own these. I think we needed this, it's almost like social media, it really doesn't work unless everyone's on it. And now here we are, it's happening, and it's just a matter of time now with this many smart people working on each problem until it really starts to crack the problems for more patients.