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ADOPTIVE CELL THERAPY IN SOLID TUMORS

Based on the web panel discussion of the same name on November 21, 2019

Adoptive cell therapy, cell transfer or cellular immunotherapy is a form of treatment using cells of the immune system to fight cancer. Some approaches involve directly isolating a patient's own immune cells or that of donors (or other sources) and expanding their numbers by reinfusing.

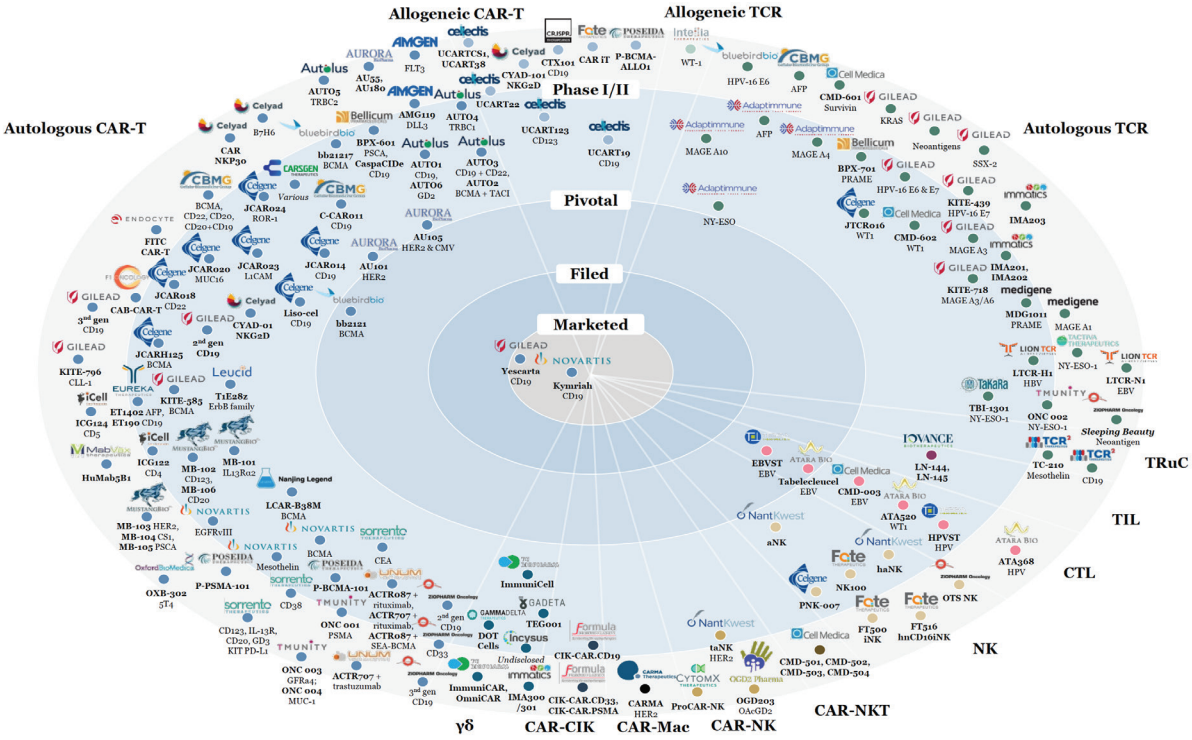
What's catalyzed the field most recently is the ability to engineer these cells in order to express or "knock down" different factors. Today, this is being done with a range of different cell types, T cells being perhaps the most common at present, but also rare T cell subtypes, NK cells, macrophages and a number of others.

There are currently a couple of commercial products already on the market with various targeting modalities, the most predominant being CAR and TCR T-cells. There are also discussions around endogenous TILs and cytotoxic T-lymphocytes and whether they can be directed against different antigens and whether these cells can, in fact, become truly off-the-shelf at some point.

One of the big questions in the field is whether, and to what extent, this cellular immunotherapy will be able to penetrate into solid tumors in a replicable manner.

To further explore this question, ShareVault, along with **Linda Pullan, PhD, of Pullan Consulting**, recently assembled a panel of experts to engage in a discussion regarding recent advances in Adoptive Cell Therapy and what it means for the treatment of solid tumors. The panel consisted of:

- **Joel Sandler, PhD, Associate Principal at Cello Health**
- **Mythili Koneru, MD, PhD, SVP of Clinical Development at Marker Therapeutics**
- **Ferran Prat, PhD, JD, SVP of Research, Admin & Ventures at MD Anderson**
- **Stewart Abbot, PhD, COO at Adicet Bio**



Source: WellsFargo Securities

As illustrated in this graphic we can see that there are a couple of marketed products in immuno-oncology cell therapy and a huge number of players at earlier stages.

BARRIERS TO SUCCESS IN SOLID TUMORS

Linda: There has been tremendous excitement about Adoptive Cell Therapy in liquid tumors, but what about solid tumors? What are the barriers to success in solid tumors and why are they so much more difficult to address than B-cell malignancies?

Mythili: Two of the major challenges facing cell therapy studies are poor T-cell fitness which can lead to a lack of proliferation or persistence of the T cells, and secondly, low antigen expression or antigen loss. That can be due to a variety of reasons, such as splice variants or mutations.

Additionally, many cellular therapies require lymphodepletion, which prevents the endogenous immune system from being engaged in the antitumor killing. So, without persistence and endogenous immune system recruitment, the durability of these responses can actually be compromised. This is noted in CD19 approved CARs where up to 50% of patients actually relapse. Most of those relapses occur in the first year of therapy.

On the other hand, there is tumor heterogeneity, which results in antigen negative or antigen-low tumor escape, which limits the ability to mount an appropriate response, particularly in solid tumors where target identification has already been challenging.

Using therapy targeting multiple antigens can be important in dealing with antigen loss. Multiple targeting is needed to deal with loss not just in one or two targets, but to deal with even greater heterogeneity between patients in a particular tumor type or even within a specific patient at different sites of metastases. This is going to be a critical feature for adoptive cell therapies.

So, some of the major barriers include: poor T-cell fitness, leading to lack of persistence, the inability to recruit the endogenous immune system, and then finding the appropriate target and not just focusing on one or two.

Regarding why solid tumors are more difficult to address with cellular therapy than B-cell malignancies:

We already touched on the issue of the lack of one specific antigen target and, of course, CD19 or BCMA and multiple myeloma are exceptions, but we also just discussed the issue of heterogeneity in the tumor or the density of the antigen expression being important factors. There are even more difficult issues to handle in solid tumors.

One is the issue of T-cell trafficking into the tissue itself. There are various barriers for T-cells to get to the correct destination, such as chemokine receptor mismatch. There could also be physical barriers, such as cancer-associated fibroblasts or casts. There could be abnormal vasculature to block the entry. These are just a few examples, but even if the T-cells can make it to the site of the tumor, then we have to deal with the inhibitory microenvironment. Things like PD-L1, myeloid-derived suppressor cells, and key regulatory cells, just to name a few.

The field of the tumor microenvironment itself has gotten very complicated. Before it used to be as simple as thinking of M1 and M2 macrophages. M1 being the good macrophages and M2 being the bad macrophages. Now, we have subtypes of M2, the bad macrophages, A through D. M2d is the worst in promoting tumors and angiogenesis. That's just one example of how complicated the tumor microenvironment and understanding it is, and how complicated all the inhibitory mechanisms that are at play have gotten in recent years.

In terms of how important cellular therapy is in solid tumors, I would say that it's actually quite important because a majority, perhaps 60%, of all tumor types are solid tumors, the foremost common being breast, colorectal, lung, and prostate. According to the American Cancer Society, only about 3% to 5% are leukemias, and so the incidence is quite low compared to solid tumors.

Penetration in solid tumors is going to be very important moving forward. Addressing all of these issues and barriers in solid tumors is going to be critical.

Linda: What kind of things favor adoptive cell therapy compared to targeted therapies and what will be deemed most important?

Stewart: It really depends on whom you ask as to what will be deemed to be most important, but most individuals agree that overcoming the immunosupressive tumor microenvironment is critically important to the success of adoptive cell therapies in solid tumor settings.

There are a number of factors. **Almost everything in a solid tumor microenvironment is out to inhibit T-cell function**, whether it's hypoxia, glucose, cytokine profiles, immunosuppressive enzyme metabolites, kynurenic and quinolinic acid et cetera. The challenges include radically diverse ranges in antigen presentations, especially if the adoptive cell therapies are targeting naturally-expressed surface molecules on the solid tumor cells, **there can be four log-order variation in the antigen density from tumor cell to tumor cell, which is an incredibly difficult challenge to overcome**.

However, there are quite a few things about adoptive cell therapies that make them particularly suitable to tackle solid tumors. In particular, it was noted earlier that poor T-cell fitness could be problematic. We have the opportunity to transfer cells of an individual, whether they have had their fitness improved by ex vivo culture and brought back into the patient or they're coming from a healthy donor and therefore have an inherent fitness advantage to begin with. That fitness advantage can be critical in overcoming some of the solid tumor challenges.

Along with fitness, we also have the capacity of the cells to actively distribute TIL fit and NK cells and other cell types that can actively distribute into solid tumors. So, to clear solid tumor in the solid tumor environment, the cell has to get there and the active trafficking with chemokines that mediate trafficking of many of these

cell types is a key advantage over other therapies that diffuse more passively to the tumor.

We've got a number of challenges to overcome with the microenvironment, but we've also got a number of features of fit cells from healthy donors or fit cells from manufacturing processes. We've got autologous products that can overcome many of these challenges. And, if the inherent properties of the cells don't overcome all of those challenges, then our ability to engineer cells, whether it be with chimeric antigen receptors or approaches to minimize the effects of TGF-beta or to maximize the effect of pro-inflammatory cytokines, many of these attributes can be enhanced relatively easily through genetic engineering and genetic editing approaches.

We're at a stage now where we have the tools to overcome many of the microenvironment challenges. What we need to figure out is which features of the microenvironment should be addressed first.

Ferran: I'm always concerned that for the T-cell approach we have seen on-target toxicities and it's not clear with the universe of targets available today which solid tumors will be compatible with the T-cell approach. There are two ways to go about it. First is to simply not use Alpha Beta T cells and use something else. Secondly, move towards HLA-restricted peptides as opposed to the typical protein expressed in the surface of the cell. But the universe of HLA-restricted peptides in solid tumors is barely understood. It's barely understood in heme, and much less so in solid tumors.

US/EU Clinical ACT TAAs by Lead Indication (n=15)	Breast	CRC	Endometrial/ Uterine	Gastric	GBM/Glioma	HCC	Mesothelioma	Neuroblastoma	NSCLC	Osteosarcoma	Ovarian	Pancreatic	Prostate	Sarcoma	SCLC	Metastasis	Cancer (Unspecified)	Solid tumor
CD171								1										
CEACAM5						1										1	1	
DLL3															1			
EGFR					1							1						
EGFRvIII					4													
FOLR1											2							
GD2					1			4						1				
HER-2	1				4					2				1		1	1	
IL13Ra2					1													
Mesothelin	1		1				2		2		3	2				1		
MUC16																	1	
NKG2D Ligands		1																1
PSCA				1								1	1					
PSMA													2					
ROR1																	2	

Note: Agents with >1 Lead Indication are double counted; Includes **ALL** cell therapies; Adis R&D Insight; Cortellis Clarivate Analytics; CHBC Analysis.

WHAT WILL SUCCEED FIRST?

Linda: The graphic above illustrates a number of targets and a number of tumor types in which they're being pursued. What are the targets that are going to be most important as we move forward?

Joel: The question of targets is a very interesting one and when you look at the different programs that are at the leading edge in the space. CAR-Ts, for example, are going after what are considered the more de-risked or validated targets. Things like mesothelin, EGFRvIII, and GD2. These are the target's that have exquisitely selective expression profiles in terms of on- versus off-tumor expression.

It makes perfect sense for them to be upfront. My concern about those targets is even if we do get wins, how scalable are the wins that we get from those when you get into other tumor types and other targets that are not expressed as cleanly. That's when you get into some of the more interesting questions and some of the more interesting modalities.

We know tumor-infiltrating lymphocytes work in solid tumors; we've known that since the late '80s when Dr. Rosenberg demonstrated as much in melanoma and cervical cancer. Now, Iovance is advancing those through the clinic. Atara Bio has EBV targeted cytotoxic T-lymphocytes. Beyond that is when it starts to get

really interesting. In addition to having a decent target, perhaps not a perfect target, the question becomes, What else is required? I think it's clear that looking beyond the target alone as a silver bullet is going to be critical in terms of achieving replicable success in solid tumors.

Linda: How far off do you think the first approval is and what solid tumor types will be successful first, and why?

Joel: If you look at what's in development, likely what we'll see first is Iovance's TILs, which I believe the company is looking for approval towards the end of next year. Atara is likely not to be far behind. Beyond that, it's a wide-open field with lots of players. Marker Therapeutics is developing a multi TAA approach for breast cancer. Companies like GSK and Adaptimmune are developing TCR redirecting T-cells against different subtypes of soft tissue sarcoma. Eureka and Adaptimmune are developing AFP targeted TCR T cells to address liver cancer.

There are also a lot of interesting things taking place behind the scenes, such as multiplexing. Tmunity just entered the clinic with their CRSPR triple modified cell that's been engineered to redirect the cell towards NY-ESO, which is a very cleanly expressed target on sarcomas and other tumor types. But they're also knocking down PD-1 in order to address the immunosuppressive microenvironment, one of the many components that ultimately are going to need to be addressed.

Then there are novel cell types such as gamma delta T-cells that Adicet Bio is developing. Carisma Therapeutics is developing CAR engineered macrophages. It's likely that we may get some initial wins in the next year or two. We may also see some high-profile failures, which is more or less inevitable, but this field really has legs in terms of all the creativity being brought to bear.

Stewart: It's important to note that with CD19 there is the possibility of tumor escape. With adoptive cell therapies targeting CD19, the targeted antigen can be lost in up to 30% of the patients. With that antigen loss there tends to be a relapse in those individuals. That's something we can learn from the hematologic malignancies applications and how we might overcome that in a solid tumor site. **Of the clinical stage targets, one could argue that 80% of those are targeting single antigens and will probably fail.**

It's a fairly provocative statement, but if you're in adoptive cell therapy, bearing a chimeric antigen receptor **targeting a single antigen puts incredibly powerful selective pressure on the**

tumor. That selective pressure will likely drive many of those tumors to down regulate antigens that are not essential for the survival of the tumor. Once they've been down regulated, there is likely to be a relapse.

Part of the reason that we're particularly interested in understanding gamma delta T cells and NK/T and NK cells is that gamma-deltas, NK and NK/T cells also express a range of natural cytotoxicity receptors. Those NCRs (natural cytotoxicity receptors) can recognize and address tumor antigens other than the chimeric antigen receptor that's generally introduced into the cells.

That's one way of targeting multiple targets in any given tumor type. Groups are developing combinations of antibodies and cell therapies to achieve the same aims. As we go forward, it will be essential to think about targeting tumors by more than one antigen, where those antigens are not effectively drivers of the ongoing tumor growth.

We're at a stage now where we like to think about these types individually. I think the field will rapidly evolve to thinking about multiple targeting, whether it be through combinations of CARs, combinations of CARs and antibodies, or combinations of different engineering approaches with natural cytotoxicity receptors and different cell populations.

Mythili: If you're working in solid tumors and you're going after one target, you have to use one target almost like a delivery system, almost like an armored car or armored T cell where you're using that target to allow the T cell to traffic to the tumor site, but then administering something to actually change the tumor microenvironment.

I worked on the MUC16 program in ovarian cancer. Basically, the concept was that there is going to be antigen loss or escape. If you use that specific target to bring some sort of payload, in the MUC16 program we worked with IL-12, in order to change the tumor milieu from an anti-inflammatory to a more pro-inflammatory microenvironment.

That's going to be important if your focus is on one specific target. On the other hand, there is this multi-antigen approach where you're not going after one target, you're actually going after multiple different targets in the tumor and dealing with the heterogeneity.

There you don't have the issue of tumor escape or antigen loss, especially if you have the ability to recruit the endogenous immune system and allow it to help deal with some of the heterogeneity inherent in tumors.

WHAT WILL BE THE MOST SUCCESSFUL MODALITIES?

Ferran: I'm always a lit bit conflicted on that topic because we do have certain technologies and we don't have others. At MD Anderson we believe that HER2 is very specific, and it is, but we have seen HER2 toxicities with T cells, it's just what it is. **If a target like HER2 could be problematic, let alone other targets or combination of targets, then I don't know if enough emphasis is being put on the toxicity aspect at all of these T cells. It seems like everybody's going there and I don't know if we're in for a rude awakening.**

SAFETY IMPROVEMENTS

Mythili: Safety and ways to improve safety is certainly going to be a very important factor moving forward. Dealing with the cytokine release syndrome, or CRS, which is essentially triggered by the activation of those T cells, which release cytokines and chemokines which eventually can lead to organ dysfunction, or neurotoxicity also associated with CAR T cells, where you can have things like CRES (CAR T cell related encephalopathy syndrome).

These are both going to be two major important issues to resolve. I bring up these two in particular because we have two approved agents on the market and dealing with the toxicities associated with those are going to be important. Depending on the severity, they're typically handled with steroids or tocilizumab, which is an IL-6 receptor antagonist and, of course, intensive support.

Often, these therapies are administered in patients who are in the ICU. Of course, people are exploring opportunities to administer these therapies more in an outpatient setting, but I don't think we're there yet. There are many approaches to deal with safety. One, for example, is adding a suicide gene or safety switch to the construct.

One example of the suicide gene that's often used is inducible Caspase-9. Basically it's a modified human Caspase-9 and it's fused to FK-605 binding protein. The idea is that you add a chemical inducer to dimerize these things and it leads to apoptosis.

Another example could be a safety switch. In previous therapies, I've done a truncated EGFR. There you use cetuximab and then when you administer it, it basically induces antibody dependent cellular cytotoxicity or EGFR mediated CAR T T death can actually be mediated by complement as well.

Essentially, safety is a definite concern really with the CAR T cells. There are different safety concerns with other cellular therapies, but with TIL therapies these are also

seen, and I think both of them require lymphodepletion. **With lymphodepletion, you're really depleting the host immune system to stop toxicities but that can result in infections and other complications as well. To make these products safer and more easily administrable outside of an ICU stay is going to be critical moving forward.**

Linda: I would think, until we do that, their sales will inherently be limited to certain centers and certain patients.

Mythili: Yes, absolutely. That's a barrier to administering these things.

Stewart: Right now, we are a bit challenged as a field because we're still in relatively early-stage studies for many of these therapies but we're treating relatively late-stage patients. Those late-stage patients are often quite frail. They're immunologically beaten up and they tend to have rapidly progressing tumors.

In general, we're trying to treat large tumor masses. This is one of those Catch-22s. If the safety can be improved in the background of that type of patient, then it may allow us to treat patients earlier in their disease progression. Treating patients earlier in the disease progression means they may be able to better tolerate therapy in the first place. There wouldn't be quite such large, rapidly growing tumors and therefore the tumor burden and the associated Cytokine Release Syndrome might not be as high.

If we can get over some basic aspects of safety concerns and treat patients earlier then we will undoubtedly actually improve safety just by virtue of treating patients earlier.

Mythili: Yes, I completely agree. Because of the safety issues, we really focus on later stage disease. **If cell therapy was actually deemed safer, then it's something that you could actually give in adjuvant setting, where the patient has no evidence of disease but is potentially waiting for recurrence.**

If you could administer something that almost looks like a maintenance therapy where those cells are actually constantly circulating and searching for micrometastases of tumor and can handle that and persist, that would be very revolutionary.

Linda: Does that require a controlled dose? One of the concepts in most of these is that the cells expand inside patients in a highly variable way. To get really safe, do you have to have control of dose?

Mythili: Yes. At Marker, we do work with the T cells in both an adjuvant and an active disease setting. So,

you're right. Dosing depends on the technology or the cellular therapy and how it works. Regarding the dosing with CAR T cells, they work a little bit differently and they persist; they proliferate better when there is a target there.

The dosing question ultimately depends on the technology and how it would work. It's hard to comment on all of them, but yes, that's going to be an important factor if you're looking at an adjuvant setting.

Stewart: Doses are a tricky thing to manage when you have a living drug that effectively has the potential to double its effective dose every 14 to 18 hours, if not faster. We know that there are inducible systems to modulate cell proliferation and cell activation that may be useful. We're also getting a better understanding of what the underlying mechanism of the safety issues are when most of our understanding at the moment is focused toward overcoming Cytokine Release Syndrome and Tumor Lysis Syndrome.

We're seeing promising improvements in the modulation of CRS, the interaction of T cells and NK cells with stromal elements and the liberation of IL-6 and TNF. I think as we get a better understanding of the basic mechanisms underpinning the Cytokine Release Syndrome and some severe adverse events, we'll have the tools mentioned earlier, whether it be engineering or other approaches to overcome some of these safety issues. Certainly it's going to get better.

To briefly address lymphodepletion: This, to me, is another one of these incredible double-edged swords. Arguably, one of the single best advances in the treatment of hematological malignancies with CTL-019, or what became KYMRIAH, was the inclusion of lymphodepletion in the overall treatment strategy.

Most recently we've seen products such as from Allogene where even lymphodepletion with CyFlu wasn't sufficient to bring about efficacy. The addition of a further lymphodepleting factor in the form of alemtuzumab, which arguably results in almost an immune desert in the individual, brought about the efficacy. The first four patients treated with CyFlu saw no efficacy. But CyFlu was administered with alemtuzumab and efficacy was noted.

Lymphodepletion seems to be required, but it's not ideal. We have immunologically active therapies that arguably require the interaction of different lymphocyte populations with one another and in lymphodepleting our patients we are effectively

depriving tour cell therapies with the opportunity to interact with other cell types.

As we go forward, I'd argue that we will definitely want to move away from lymphodepletion, not just because it's not particularly well tolerated by many patients, but that removing lymphocytes, from an immunologically active therapy and removing recipient lymphocytes from an immunologically active therapy is not a particularly good idea.

As we move forward, we might want to think more about the village that it might take to overcome some of these solid tumors where the village is the interaction of the different lymphocyte subpopulations, and that village may include the particular cell types that we're actively removing with lymphodepleting conditioning. It's an evolving field, and necessary, but not particularly helpful. If we can overcome the need for it, we will be in a better position to treat more patients more effectively.

Mythili: **It's not really clear why lymphodepletion is necessary.** Some postulate that it makes more space in the bone marrow for the cell therapy to expand. So, if you don't lymphodeplete, the cells that you infuse don't have the necessary room to continue to expand. Another theory is the concept of getting rid of the host key regulatory cells. So, why exactly lymphodepletion is necessary hasn't been proven, just that it seems to be important.

One of the limitations of lymphodepletion is that it prevents the endogenous immune system from participating in the anti-tumor killing.

It's almost like saying, "Your immune system is not working at all, so we're just going to give you these cells that are going to fix everything." That's not always the case. Sometimes you just need to boost the host immune system to do its job a little more effectively and to help it along. There can definitely be limitations of lymphodepletion. Some therapies seem to require it to be effective and some therapies don't. We know that without lymphdepletion we get a lot more epitope spreading and that seems to be important in showing that the endogenous immune system is able to participate.

Joel: If the role of lymphodepletion is to clear the T cell compartment, I assume that's going to be more relevant for the liquid tumors versus solid tumors where really what we're trying to do is address the host versus graft at the site of the tumor. There are more targeted means, potentially, to do so, including engineering if it's a T-cell that is non-responsive to the

PD-1, PDL-1 axis. By introducing a dominant negative PD-1, or introducing factors such as Max Mamonkin at Baylor College has spoken about to address the site of the tumor and address only the actively proliferating host immune cells that are likely to wipe out the graft, while preserving the rest of the compartment.

When you get into solid tumors, I don't know if you need to bring such a blunt instrument as lymphodepletion, although you do need to address the warfare that's going to be going on within the tumor microenvironment.

ROLE FOR NON-CURATIVE CELL THERAPY

Linda: What is the role for non-curative cell therapy?

Joel: This is such an important question. There are a couple ways to think about this. One is if you have a therapy that just generates some sort of temporary response and that's kind of the bridge to transplant approach. There are, potentially, niche roles for something like that, for example, leading up to hematopoietic stem cell transplant in AML patients.

The bigger question is, can we, and should we, as a field, expect solid tumor CAR Ts and adoptive cell therapy approaches to achieve greater than 50% complete response rates that we're getting with B-cell malignancies, or that that we're getting, at least seemingly, in myeloma patients with anti-BCMA CAR T.

I suspect, at least with some of the initial programs that are entering the clinic today, we're going to see more modest responses. There is still a barrier and a bar that needs to be achieved and when you look at PD-1, for example, and anti-PD-1 therapies. **If you're achieving durable remissions in 30% or 40% of melanoma patients, that's huge. The difference here is that you have a cell therapy that is a living therapy. It's very complicated, particularly when you're talking about autologous approaches. There's a complicated supply chain, with logistical hurdles and costs associated, and then there's the toxicity.**

When we're talking about what needs to be achieved from a target product profile with cell therapy, there has to be consideration of non-clinical factors, including cost, the ability to re-dose, and scalability. Ultimately, if we get to a place where we have off-the-shelf therapies like NK or modified T-cells that are truly off-the-shelf and able to be re-dosed, if such a thing is possible, then I think that lowers the bar in terms of what needs to be demonstrated with clinical performance.

At the same time, you can argue that some of those innovations are still a few years away and so as a field, I think everyone is kind of tracking these early mover solid tumor programs. We may see 30% response rates but the question is whether that is deemed clinically meaningful, meaningful from a regulatory standpoint, meaningful from a reimbursement standpoint and ultimately from a commercial adoption and patient uptake perspective.

Ferran: With very few exceptions, such as pancreatic, glioblastoma and a few others, I don't believe there is a role for non-curative cell therapy for autologous. Seeing the physicians around here and how stretched they are and the time demands on all the physicians, I just don't see it. I don't see them ordering autologous cell therapy on a non-curative setting.

ROLE OF ALLOGENEICS

Linda: What's the role of allogeneics? Are they going to be as effective or more effective in the setting of solid tumors compared to liquid tumors?

Stewart: That's certainly the hope. If we rewind the clock a few years, the initial attraction to move from autologous to allogeneic therapy was largely to reduce the high cost associated with patient-specific therapy or autologous therapy. Manufacturing costs for autologous therapy can be as high as $120,000 per patient. So, the ability to scale a therapy to be able to treat more than one patient from a given manufacturing batch using an allogeneic off-the-shelf approach appears to make allogeneic therapy a much more feasible approach to overcoming costs.

That's still a driver, but I would argue that one of the key reasons that we are interested in allogeneic therapy at this point is to get better consistency in our products. We know that patient-derived products are incredibly inconsistent. They can be incredibly effective, but they are highly variable, because every patient is different.

The goal now is to improve safety profiles and improve the ability to predict a therapeutic index of these types of drugs. In order to do that, we will have to have batch-to-batch consistency both in the production and different approaches to allow more predictable responses to be achieved. The hope is that with that batch-to-batch consistency we will achieve more predictable efficacy and safety profiles. Predictability is needed to move these

therapies out of specialized centers and to use them in non-specialized centers and with better safety outcomes for patients.

There are a couple of key considerations. One is the potential immunogenicity of the allogeneic cell when the host reacts to the donor cell. The other is the effect of the unrelated donor cell on the host; specifically alpha beta T-cell off-the-shelf therapies, with the potential for quite severe graft versus host disease induced by alpha beta T-cells recognizing recipients healthy cell antigens.

Those are the factors that need to be considered as we're thinking about how to best utilize and best develop off-the-shelf therapies and whether they can be more effective than autologous therapy.

Autologous therapies, in large part, do not suffer from the challenges of immunogenicity. They also don't necessarily suffer from the challenges of graft versus host disease. However, they are potentially highly inconsistent, and they are costly to produce.

COMPLEXITY AND COMBINATIONS

Linda: How many different things do we have to put together to really make this successful in solid tumors?

Mythili: Obviously, the therapeutics has gotten quite complex. If we look at the competitive landscape, we can see the various permutations and approaches that different companies are taking. However, I don't think that the most complex way to do it is necessarily going to be the correct way.

We need to design an approach that's going to deal with some of these barriers that we've talked about, such as the heterogeneity that's inherent in tumors and across patients. We also need to address ways of handling the prevailing issue of the tumor microenvironment and that can vary by the tumor site.

The same way to address the tumor microenvironment for one tumor is not necessarily what's going to work for another tumor type. We talked earlier about administering cytokines to polarize the tumor milieu to a more pro-inflammatory state and using the cell therapy as a way to hone the armored T cell and deliver something

to the site of the tumor to deal with the tumor microenvironment allowing improved recruitment there.

There are other approaches to this kind of armored CAR approach. People are exploring the ability to combine with PD-1 inhibitors, but we need to think about the ability to have the T cell engineered to actually secrete the PD1 inhibitor and have it be localized at the site of the tumor.

There are a lot of different ways to handle these specific barriers, but that doesn't necessarily mean you have to layer on more complexity. That's not necessarily the best approach. You have to be very specific with each change that you're making to deal with a specific issue.

Joel: It's very exciting and buzz-worthy to have a number of different types of modifications, but it's true, every step you take away from the endogenous biology of the cell, you add complexity. There are different companies and different platforms out there that are each leveraging the endogenous properties of different cell types. I don't think any one cell type is necessarily perfect, with the exception, possibly, being some of these rare subtypes like those being developed at Adicet, that are situated at the interface between the adaptive and innate immune interface.

For the most part, if you have T cells and you want to make them off-the-shelf, you have to knock down a number of different properties that make it less immunogenic-looking and to address the tumor microenvironment.

If you have NK cells, you have to knock in things that are going to address, potentially, limited in vivo or in situ persistence. In each case, you're talking about different means to address shortcomings and the inherent properties of the cell. That said, I think that there are a number of creative solutions out there.

There is a big expectation that these cells will be, to some extent, one-pot solutions. Whether that means positioning in tumor types where you're able to achieve durable remissions with a relatively simple cell type, or coming in with different multiplexing solutions using CRISPR and different gene-editing approaches to knock in targeting moieties and trafficking things that address the tumor microenvironment.

One area that I think we haven't talked about yet is induced pluripotent cells, which I think are attractive. Obviously, it's costly and the efficiency is somewhat low in terms of multiplexing and generating cells

that harbor different types of desired properties, but once the clone has been generated, then that clone lives on, presumably, and can be appended with a number of different additional properties that enable it to be positioned for tumor type X, Y, or Z.

I think that we are headed in that direction. At the same time, if you look at the adoptive cell therapy trials, a lot of them are being tested in combination with anti PD-1 and other components of the standard of care for given tumor types. I think we'll see a bit of both, but I think ultimately the expectation is that cells are going to be one-stop-shop.

Linda: Universal immune receptors, what about them?

Joel: There are a couple of companies like Fate with their CD16 expressing NK cells, UNUM with ACTR platform, Arcellx and others that are progressing the idea that you can have a single cell or single cell type, whether it's a T cell or an NK cell, that's infused in patients and activity of which is dependent upon co-infusion of an additional ligand or an antibody that redirects that universal cell to the tumor.

I think that's very attractive for a number of reasons. One being that you can control proliferation, and activity of the cell, and homing to the tumor tissue depending on how much ligand is being administered, so you have somewhat of a potential for rheostat-type control.

The other is the modularity afforded by it. You get flexibility with the same cell platform that could potentially be positioned to address a number of different tumor-types, depending on what the ligand is. The counterpoint to that is when you have two separate novel therapeutic candidates; that adds some complexity biologically, clinically and from a regulatory standpoint.

There are enough companies and enough different types of technologies being brought to bear to look at this that I think we will see it achieve success in the clinic and ultimately beyond.

Stewart: I think there's a temptation in the world that we live in now with sophisticated technologies to assume that there is a path to success via multiple edits of cells. While there is certainly positioning for gene editing and engineering of cells, I would suggest that we want to do as little as is necessary to modify the cell. Complexity and the knock-on consequences are poorly understood at this time. Case in point, knock out the TCR of an alpha beta T-cell and that cell suddenly becomes much, much more dependent on IL 7 and IL 15 for survival and proliferation than it was

prior to the TCR editing. We might want to edit out the TCR to avoid GVHD, but it's not a free lunch. Every time you modify something in the cell, there's a knock-on consequence. Some of those are useful, some of them not.

We and others have taken the approach that we try to start with the most useful cell-type. It doesn't have any risk of GVHD, has good potency for both solid and liquid tumors and to minimize the number of modifications that we make. I think time will tell how many are absolutely required. There are modifications that will need to be made to make these cells more applicable to tackling solid tumors but I would suggest that we ought to make as few edits as we can to ensure efficacy and safety.

PARTNERING

Linda: Let's switch gears and talk about licensing deals. With all these components, how big is the challenge of freedom to operate and royalty stacking?

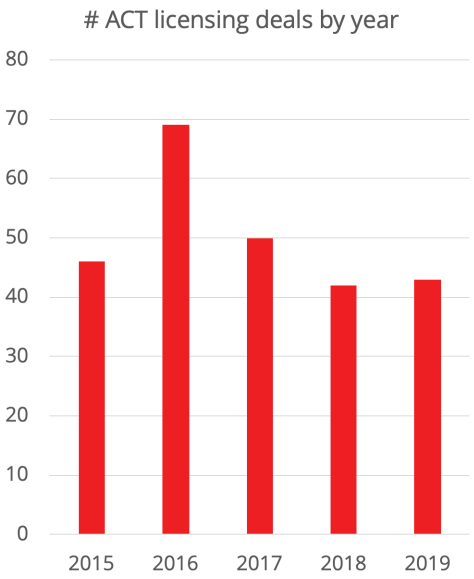
Ferran: Well, freedom to operate, period. I've done a lot of work licensing in the antibody field, which is not a walk in the park, but it's child's play compared to what we have experienced in cell therapy. I wouldn't say that it's a licensing nightmare because in a way, it's a dream. The complexity and the beauty of it, it really makes you feel like you're adding value, but on the other hand, it is outrageously complex.

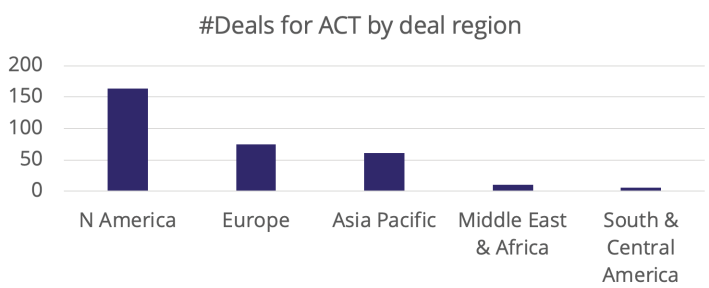
We have a current deal and the amount of diligence and the number of IP pieces that we've had to get from third parties is just remarkable. It took us more than a year just to assemble all those IP pieces, even before we started the partnering effort.

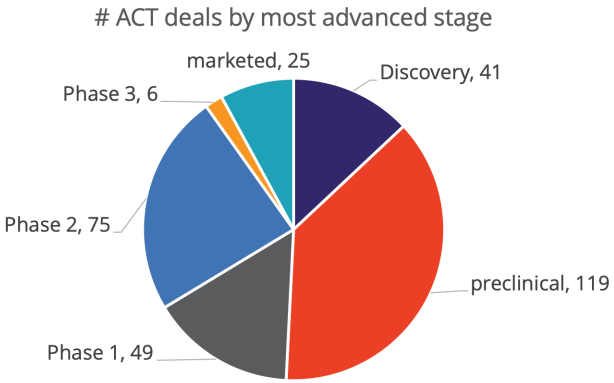
We've talked a lot about how much editing you want to do on the cells and, needless to say, the more editing you do, the more scientifically complex things get. But business-wise it gets even more complex because you have to deal with the freedom to operate for every single bell and whistle that you put into the construct. So, I would summarize it as absolutely fascinating, but not for the faint of heart.

Linda: What do potential partners and investors want to see as data before they will do a deal for ACT for solid tumors? Are they building collections and platforms or are they looking for an all-in-one product? What kind of data do they want to see?

Ferran: There is a lot of skepticism about cell therapy for solid tumors. The bar is fairly high. At MD Anderson, we are in no rush to license anything before the clinic, because our perception, and we could be wrong







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because it's just perception, but our perception is that the bar is very high, and we wouldn't get the appropriate value if we were to pursue a deal in solid tumors before the clinic. There is just too much skepticism.

STRATEGIC POSITIONING FOR ACT

Linda: In the PD1s, we see a few companies being really, really dominant and creating a platform upon which things are added. Do we expect anything similar in ACT; is size or first-mover advantage critical in adoptive cell therapy?

Joel: First-mover advantage doesn't exist here. If anything, it depends on how optimistic you are about the future of adoptive cell therapy. A lot of the platforms and value propositions that we're seeing from development stage or even preclinical stage platform companies are positioned around what are perceived to be the shortcomings of the first-movers, whether it's the fact that they're autologous or they're limited to relatively small and crowded indications.

The question of whether there's ultimately going to be several consolidators, versus more room for smaller players or multiple players in the space, I don't know. I think it depends how successful the consolidators, the Pharmas and the like, are at putting together all

the pieces. There are a number of pieces here. I think different platform companies, many of them bring something unique to the table and ultimately, many of these are going to get consolidated.

On the other hand, I think that there are some companies that are coming out today that are small or new, but they're launching with pretty big Series A rounds with the mindset of being able to bring all things to the field that don't exist.

Companies like Lyell Immunopharma who just came out with a big deal with GSK. Fate is a very interesting one. I think that they're taking iPSCs and really applying a number of different approaches with the iPSC with the mindset that they are going to be all things to the field. I think so far the portfolio that they have is very encouraging in that direction.

Ultimately we are going to see some consolidation in this field. We see a lot of the big front runners who are some of the big players or big stakeholders leaving those companies to go seed smaller companies with the hope and the mindset that they'll get licensing deals with the company that they left. I don't think that's inconceivable. Ultimately you do need the wherewithal and resources of Pharma to make commercialization a reality.

On the other hand, I think Pharma is very much in an education mode here and they're learning as much as the rest of us are. They're probably taking a number of different meetings with potential partners and ultimately figuring out all the different gaps that they need to plug and play and ultimately deliver solutions that are going to be comprehensive to the market.

CRYSTAL BALL: WHAT'S EXCITING ON THE HORIZON?

Linda: What do each of you see as the most exciting development in the field and why?

Mythili: It's a fast growing field. I think the two areas you can break it down into are the biological approaches versus the technical advances. In terms of the biological approach, right now it's multi-targeted strategies, including endogenous immune system. I think it's going to be important.

On a more technical level, the complexity of manufacturing is going to evolve and continue to evolve. Then ultimately, trying to think of appropriate combinations, whether it is another agent or even things to enhance in the actual cell therapy itself to deal with some of these barriers we talked about.

Ferran: I think point of care manufacturing and blurring the

division between autologous and allogeneic. If you have point of care manufacturing at the provider, then whether it's autologous or allogeneic, it doesn't matter that much. I think that the biggest breakthrough is going to come from that field. I mean this in terms of closed-loop manufacturing—sample in, product out. **A single machine typically at the stem cell transplantation department, we think that that could revolutionize the field.** We think that certain companies are well positioned to accomplish that.

Stewart: I remember back in 2010 I was trying to encourage a senior colleague in business development that the future of immuno-oncology was cell-based therapy and they were incredibly skeptical, and rightfully so.

However, fast-forward a couple of years to 2014 or so, we're having a similar discussion. They said, "Stewart, this will probably work." They went from a position of being incredibly skeptical to the position of, "Hey, this is probably going to work." I asked them, "Why did they think that? Why did they change their mind?" The simple answer was, "There's enough money in the field to make it work."

As we look at solid tumors now and the amount of investment that's gone into this field over the last few years, there's a lot of money in the field. From a patient perspective, these therapies will work. There may be some fits and starts along the way, but there are enough groups working on this with enough funding behind them to make cell therapy for solid tumors a reality.

Joel: I think to quote Wallace Shawn, "It's inconceivable" to believe that this field doesn't have legs. If you compare it to, for example, antibody-drug conjugates, which had plenty of money behind it, but it was a handful of players. Today we see these things working in a handful of settings.

In contrast here, there's money. **There are also so many different options that can be brought to bear in terms of cell-types, in terms of engineering, targeting and there's so much money and there's so much academic effort being thrown at this.** Many of the biggest breakthroughs are coming straight from academic labs. Every time you see a Nature paper, a week later it's a startup company being formed by that investigator.

ABOUT THE MODERATOR

Linda Pullan, PhD
Pullan Consulting

Linda and her team at Pullan Consulting offer biotech and pharmaceutical companies consulting in all aspects of partnering. Linda has a PhD in Biochemistry, a BS in Chemistry, and over twenty years of drug industry experience, including work on more than 75 deals.

ABOUT PULLAN CONSULTING

STRATEGY

Pullan Consulting can help you decide which studies will be more important for a partner or an investor. They can also help assess partnerability of new indications or programs.

OUTREACH

Pullan Consulting can mount an email partnering campaign, represent you at partnering meetings, and introduce you to investors. They have a very large database of industry contacts, along with notes on their interests, and they subscribe to databases to facilitate searches for companies in your space.

EVALUATIONS AND VALUATIONS

Pullan Consulting can assess differentiation from competition, both existing and in the pipeline. They can also model risk-adjusted discounted cash flow value of your drug candidate or of a deal.

NEGOTIATIONS

Pullan Consulting can help you prepare for a deal, both by considering the alternatives of deals and by evaluating your priorities. They can also lead negotiations for you or give advice on how to negotiate.

I think that there's a lot to learn and we have a long way to go. I think we're going to see some big breakthroughs.

ABOUT THE PANELISTS

Joel Sandler, PhD, Associate Principal at Cello Health

As an Associate Principal with Defined Health, now known as Cello Health BioConsulting, Joel provides insight to various life sciences industry clientele (biotechnology/pharmaceutical) on fundamental issues in drug development and partnering based on a comprehensive analysis of the key scientific, clinical, regulatory, and commercial questions relevant to the client's particular situation. In previous industry roles, Joel was instrumental in the scouting and evaluation of licensing and partnering opportunities for various oncology assets. Prior to his BD&L activities, Joel spent ten years focused on the discovery and characterization of bioactive compounds for cancer and infectious disease research at several leading academic institutions. His work has resulted in numerous grants, fellowships, patent filings, and peer-reviewed publications. He received his BA with honors from Cornell University, a PhD in Organic Chemistry from UCSD, and was a NIH Postdoctoral Fellow at The Rockefeller University.

Mythili Koneru, MD, PhD, SVP of Clinical Development at Marker Therapeutics

Mythili Koneru, MD, PhD joined Marker Therapeutics in February 2019. In her previous role as Associate Vice President of Immuno-Oncology at Eli Lilly and Company, Dr. Koneru designed early-stage clinical trials for hematologic and solid tumor malignancies and was instrumental in developing clinical trial protocols, serving as medical lead for trial conduct. She has also served as Senior Medical Director of Early Phase Clinical Development at Eli Lilly before she was promoted to her most recent position. Prior to Eli Lilly, Dr. Koneru was an Oncology Fellow in the laboratory of Dr. Renier Brentjens at Memorial Sloan-Kettering Cancer Center, where she developed adoptive T cell therapies in both leukemia and solid tumor malignancies in early phase clinical trials. Dr. Koneru earned a BA in Cellular and Molecular Biology from the University of Chicago, a PhD in Biomedical Research:

Tumor Immunology from New York University, and an MD from the Robert Wood Johnson Medical School.

Ferran Prat, PhD, JD,
SVP of Research, Admin & Ventures at MD Anderson

Prat helps the faculty and researchers at MD Anderson develop collaborative opportunities with pharmaceutical, biotech, diagnostics, imaging, laboratory medicine, and other industry partners. He is responsible for establishing a direct line of contact with pharmaceutical companies to understand their needs in terms of pre-clinical and Phase 1 activities, and internally convey them so that the researchers and clinicians at MD Anderson can follow-up and establish personal relationships with such companies.

Prior to joining MD Anderson, he worked at Alere Inc., an international firm dedicated to developing health management services and solutions, including diagnostic tools and tests. At Alere, Ferran led a business turnaround and integrated three businesses in São Paulo and Belo Horizonte, Brazil. He also served as the head of the Oncology and Women's Health Divisions in San Diego, where he was responsible for all pre-commercialization activities and post-launch product management.

Prior to Alere, Ferran held a number of industry and academic positions, including vice president for licensing at Biosite Inc., management consultant at McKinsey & Co., an engineer at Chromogenia-Units and researcher at the University of California – Los Angeles. In these roles, he in-licensed and out-licensed new technologies, led and executed strategic plans, coordinated intellectual property agreements among private and public sector entities, and conducted basic science research that led to multiple peer-reviewed articles.

Prat has a PhD in organic chemistry from the University of California – Los Angeles and a JD from the University of San Diego School of Law.

Stewart Abbot, PhD,
COO at Adicet Bio

Stewart Abbot is the Chief Operating Officer at Adicet Bio. He holds a BSc in Biological Sciences (Edinburgh), MSc in Biomedical Engineering (Glasgow) and PhD in Pathology (London). His academic career focused on basic and translational science initiatives in vascular biology, pharmacology and toxicology. He joined Amersham Biosciences in 2000 and developed Amersham's and, following the acquisition, General Electric's stem cell-based drug screening capabilities. He was head of the Molecular and Cellular Biology research laboratory at GE's Global Research Center from 2004-2007. In 2007 he joined Celgene to develop novel cell-based therapeutic candidates and subsequently the development of external cellular therapy R&D collaborations and alliances. In 2015 he joined Fate Therapeutics and held roles of VP translational research and chief development officer. He joined Adicet Bio in June 2018 and his current role oversees the development of novel genetically engineered gamma delta T cell-based therapies.

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