Future trends in commercial cell and gene therapy: the investor’s perspective

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Q: What are your chief considerations when you evaluate a potential company or technology? And have these criteria changed at all over recent years?

GB: Our diligence criteria for investments are similar to other folks in the biotech space. The top few criteria are always technology,
regulatory pathway, team, intellectual property portfolio and then commercialisation considerations. For us, technology is the driver. For us, technology is the driver. First and foremost, we're interested in identifying technologies that will drive sea changes in the field. Typically, we're not looking at technologies that would make an incremental improvement over an existing technology, but something that will fundamentally change the approach. The promise of regenerative medicine, cell and gene therapies, has always been that they would fundamentally alter the approach to healthcare. The good news is that in the last 10 years, that promise has been realised.

One of the other key criteria for us is looking at the regulatory strategy and path. How long will it take to get approval? How rapidly can a company build human data demonstrating their technology works? One of the hallmarks of investing these days is the ability to get early data to get a go/no-go decision sooner rather than later. Fundamentally, valuation in biotech is a relatively straightforward process. Value is built in biotech by moving your technology through the regulatory path. What that means, at a very fundamental level, is demonstrating in humans that your technology works and provides significant therapeutic value. Human data is the key driver of value in biotech companies across the board; certainly in cell and gene therapies.

We also look at the intellectual property portfolio. We want to make sure the company is capable of protecting its IP so that if we put money into developing a technology, there will be an opportunity to commercialise that technology without folks coming in and copying it.

We also look at the management team, of course. That's important because these are fundamentally business decisions. As much as technology plays a dominant role, you still have to execute on the business plan.

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Then last, but certainly not least, is the ability to commercialise technology and move from your clinical programme into a successful commercial launch. That means having a manufacturing strategy that allows you to optimise your manufacturing process and the ability to go from a process in which you’re producing relatively small volumes into full scale commercial manufacturing. This is an important issue, as manufacturing challenges have proven to be a real problem for a number of companies. Going back 10-15 years, Advanced Tissue Sciences raised a ton of money, went public, had a big valuation, then found they couldn’t manufacture their product. Dendreon is another company that had immunotherapy technology, raised a ton of money, had a big valuation, but ultimately could not manufacture their product on a cost-efficient, commercially viable basis.

We’re very pleased to see the dramatic results coming out of clinical trials but this hasn’t changed our diligence criteria or investment criteria. We have focused more than we have in the past on manufacturing. If you look at where we are now in terms of clinical phases, there’s a significant amount of activity now in late-stage clinical trials. Companies garnering big valuations and significant investment dollars are now in late phase 2 or in phase 3. Manufacturing has become a much more significant issue for us in our diligence than in the past. There is a significant shortfall in underlying manufacturing capability, both at the cell level and even more acutely, at the viral level. My understanding that the time delay to get a viral vector produced is in the order of 12-18 months, such that production of the vector ends up being a rate limiting step, whether you’re working on a pure gene therapy or an engineered cell like a CART.

Q Will the recent trend for very high levels of private investment and public company valuations in cell and gene therapy be maintained, or even grow further?

GB: I think it will continue. The valuations are very high by historic terms for biotech, but the clinical data justify that, quite honestly. Immunotherapy is the technology area that has really garnered the attention and started this wave of new investment in the field, largely because they were demonstrating really dramatic results in their clinical studies. Some immunotherapies have been showing 70, 80, 90% response rates in their trials – and that’s previously unheard of.

The field as a whole is maturing. As I mentioned earlier, we’re seeing many more technologies in late-stage clinical development and on the verge of commercial launch. Again, these are companies bringing forward
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technologies that fundamentally change the approach to treatment of disease. They’re looking to cure the disease, not simply manage it, and they’re showing dramatic results.

If you believe, as I do, that value is created in biotech by demonstrating your product has therapeutic value, the greater that therapeutic effect, the more significant the value of the company should be. The sooner you can demonstrate that therapeutic effect, the more investor interest you will attract. As a result, we’ve seen some very high valuations in the field following release of robust clinical data. Then, on the gene therapy side, we’ve seen people come in for monogenic disorders, such as lysosomal storage disorders, correct a single gene defect and demonstrate that it can effectively cure the patient of the disease. So, I’m not surprised that we’ve got these large valuations.

Another factor in the rate of investment is that there’s been a huge flood of money into the field. It seems like almost every year we’re hitting new heights in this regard.

On the other side of the coin, you’re also seeing that the field itself has matured on the infrastructure side. Manufacturing is still a challenge, but there’s a significant amount of manufacturing infrastructure in place now that did not exist 10 years ago and more is being built all the time. All these things come together to generate investor enthusiasm and explain the large valuations that are coming into play.

Do I expect that to continue? I expect it to continue for companies that are able to demonstrate that they can provide that significant therapeutic value. The good news is you’re getting big valuations and lots of money is coming in through venture and public markets. But along with that, the bar has been raised significantly for companies wanting to come into the field. If you want to attract these large rounds of financing and hope to get a large number in your IPO, you’re going to have to demonstrate at least 60, 70, 80% response rate in your clinical trials. Valuation numbers are up, but so are expectations. If you look at what happened to some of the companies that went public and then met difficulties in their clinical programme – not necessarily that the programme failed, but that it didn’t meet lofty expectations – their stock got crushed. That’s not a new phenomenon – historically in biotech, if you don’t do well in clinical trials, your stock gets crushed. But the standards in terms of what it takes to succeed are now higher.
Regarding the rare disease space in particular, how does one justify high biotech valuations and how do you expect that scenario to play out?

GB: It’s a somewhat new phenomenon in the field that rare disease and ultra-rare disease models are garnering a lot of investor interest and valuations. Why do people go after rare and ultra-rare disease? It’s a variation in theme on the orphan drug strategy that’s been applied by pharma and biotech for many years. The notion is if you’re looking at an orphan disease or a rare or ultra-rare disease, you are able to get into your clinical trials and generate data more rapidly – the clinical path to approval is accelerated.

The reason people have gone into those indications, particularly in gene therapy, is there is this convergence of two models that can produce dramatic results on a relatively easy path. What you’re seeing in the rare and ultra-rare disease area, at least on the gene therapy side, is companies looking at monogenic disorders. These are single gene defects that can be cured with a single gene manipulation. I’m not trying to underestimate or minimise the challenges facing these companies in any way, or their underlying technology, but they’re ‘easy’ because you only have to modify one gene. The other thing is, once you modify that gene, it’s binary: it either works or it doesn’t, so you tend to get your results relatively quickly.

Owing to the fact that the diseases are ultra-rare and orphan, because there aren’t other treatments available for them, the regulatory path is fairly straightforward. The FDA, EMA and other agencies around the world are providing straightforward paths into trials and approval pathways that are much shorter than if you’re looking at other disease models.

That explains why people are going into it. Does it explain the lofty valuations attached to these companies? I’m not sure it does entirely. I think there will be some reality testing once we have a few more companies approved and in full commercial launch, where they’re being measured by the amount of revenue they generate rather than success in clinical trials. There

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will have to be some very lofty reimbursement codes for these technologies in order to justify the significant expense that went into developing them, and I wonder whether the system can support those kinds of codes.

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Q  Which specific disease and technology areas will come to the fore in commercial terms and drive the field forward over the short- to mid-term?

GB: We’re going to continue seeing the majority of clinical trials in gene therapy or gene modified cells – CAR-T or other engineered cells. The third category would be primary cells. Tissue engineering has relatively few clinical trials underway. The majority of therapeutics being developed 5 years from now will be engineered cells of some kind. The technology is too compelling for it not to go this way. If you can engineer a mesenchymal cell and optimise its anti-inflammatory effects, why wouldn’t you do that and have the cell provide 5 or 10 times more therapeutic value?

We will also see continued growth in gene therapy. Gene insertion technologies, such as CRISPR and others, are getting better – there appears to be a whole new generation of gene insertion technologies coming that will enable more gene therapies and solve some of the problems we have with viral vectors. I think we’re going to see some growth and activity that might replace viral vectors, and that will continue to enable gene therapies and engineered cells.

At some point, genetic engineering of cells will reach a level of sophistication where the sector can begin to take on more complex diseases. I wish I could give you a timeframe for that, but I can’t. It will happen eventually, but in the near term, you’ll see activity continue to expand in monogenic disorders and the number of disorders being addressed will continue to increase. What will happen is we’ll end up with people bringing forward new insertion technologies and more targeted technologies to minimise some of the off-target effects and toxicity related to viral vectors in general.

Longer term, we will start to see some dramatic results in cancer. Right now, we have seen dramatic results in hematologic malignancies, but it has been more challenging to bring these immunotherapies in to solid tumours. I do think we’re beginning to see some progress being made there, though, and that will continue.
Q What specific trends do you expect to see in geographical terms moving forward, given the tremendous market potential in regions beyond North America and Europe?

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GB: This is one of the more interesting developments in the field in the last 24 months. What has happened is that Asia has emerged as a key player in the cell and gene therapy field – not simply because carrying out a clinical trial in China may be cheaper and faster, but because there has now emerged a whole group of investors. The momentum started to build in Asia when the Japanese PMDA introduced their new regulations around regenerative medicine technologies. They were the first legitimate jurisdiction to adopt a regulatory framework that accelerated the approval process specifically for cell and gene therapies. Because that happened in Japan, and not in the United States or Europe, that started people looking at the Asian market. It also garnered some investment activity and money flowing into Japanese companies, or other companies utilising the PMDA’s accelerated process to bring their products to market.

China is growing as an economic force worldwide, but there have been concerns about IP protection, the legitimacy of their regulatory programmes and around the infrastructure in China. The Chinese Government has adopted some progressive and aggressive programmes to develop the biotech infrastructure, and it’s now starting to bear fruit. In 2017 there were almost 40 billion dollars raised in biotech funds focused on China. That was almost a threefold growth over the 2 years prior. In terms of venture investment in Chinese biotech, in 2017 there was almost US$12 billion invested – that’s 5 times the amount invested in 2016. And in 2018, that trend continued, according to PwC data.

We’re seeing the Asian market emerge as a legitimate, reliable player in the field – both in terms of the fundamental ability to do clinical trials there, but also because there are large patient populations, so being able to enrol patients in trials is not as much of a challenge as it can be in the West. Now you have infrastructure being built and funding being provided. Those are the pillars on which biotech is built. North America had been the centre of power for healthcare, and for biotech in particular, for 40-50 years, but I think the Asian market is emerging as a legitimate challenger in
the field with internal, indigenous funding, technology and infrastructure – both clinical and manufacturing infrastructure – that will allow people to bring their technologies forward.

Q Finally, can you highlight some of the most critical specific elements of the ‘begin with the end in mind’ mantra, as far as investors are concerned?

GB: The notion of beginning with the end in mind actually applies with the greatest force in IT. The problems emerging companies face in IT are largely engineering problems, not fundamental science. If you have a clear vision of where you want to go and enough dollars, you can always engineer your way out of a problem or to a solution. In biotech, clinical trials are in essence a scientific endeavour. You’re still testing the science, still testing the technology, and often you are making advances in the underlying science while bringing your technology forward. It’s not an engineering challenge through the clinical trials phases, but once you launch, it does become an engineering challenge.

So I’m not sure that maxim applies as much to biotech as a whole, but the comments I made earlier around manufacturing do apply with tremendous force here. Given the maturation of the field, the amount of money being invested and where we are in terms of clinical trials, manufacturing and the ability to successfully launch on a commercial scale has now become a very, very important issue.

Traditionally, when you’re in phase 1 or 2, you’re typically at least 3-5 years from a commercial launch and historically, management teams in those companies haven’t spent a huge amount of time on manufacturing issues at that stage. But today, with the way things are moving much more rapidly, I think it is incumbent on any biotech company management team to have mapped out and tested its manufacturing strategy by that stage. You need to identify your manufacturing partners, decide whether you’ll do it on your own or outsource, and optimise your manufacturing process.

The sooner you can address those issues and optimise your manufacturing process, the better off you will be. To succeed, cell and gene therapy companies need to think long and hard about their manufacturing strategy and do it sooner rather than later.

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