

Alliance for Regenerative Medicine Conference, October 2016: White Paper

Immuno-Oncology

This document contains a chapter from Datamonitor Healthcare's Immuno-Oncology

Ref Code: DMKC0165545

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Report reference: DMKC0165545

Published on: 14/10/2016

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CONTENTS

5 **ARM'S 6TH ANNUAL MEETING HIGHLIGHTS DEVELOPMENT, COMMERCIALIZATION, AND REIMBURSEMENT CHALLENGES**

5 **BIBLIOGRAPHY**

6 **CELL-BASED IMMUNO-ONCOLOGY**

6 The cell-based immuno-oncology field has "lifted the plateau" in treatment

6 First CAR-T therapy approvals could happen in the next couple years, followed by combinations

6 Gene editing has applications with cell-based immunotherapy

7 There are challenges to using cell-based immuno-oncology in solid tumors

7 Multiple commercialization challenges remain, but some progress has been made

7 Advice to start-ups includes building on knowledge already generated

8 There is still a long road toward personalized treatment

8 Bibliography

8 **GENE EDITING**

8 Gene editing potential is limitless, but proceed with caution

9 Off-target effects and safety in gene editing are big issues

9 To advance gene editing, collaboration between industry and academia will help

9 Patient advocacy groups are also expected to help advance gene editing

10 Gene editing presents global regulatory challenges

10 Bibliography

11 **CELL AND GENE THERAPY PRICING AND REIMBURSEMENT**

11 Cell and gene therapies are a new and challenging class for payers

12 Pay-for-performance methods in the US would be difficult to execute

12 Accelerated pathways for cell/gene therapy take on significant meaning to payers

13 "Adverse selection" is a big threat to payers

13 Panelists differed on whether patients can afford the out-of-pocket expense of cell and gene therapies

13 Cell and gene therapy developers need to start discussions with payers early

14 Bibliography

14 **FINANCING CLIMATE FOR CELL AND GENE THERAPY COMPANIES**

14 The financing environment for cell and gene therapy is a small proportion of overall biotech financing

14 Investors are looking for low-risk companies and experienced management

15 Big Pharma validation is a nice-to-have, not a necessity

15 Cell and gene therapy companies should not be afraid to ask for sufficient capital to create value

15 Forging partnerships with their investors can give cell and gene therapy developers many advantages

16	Bibliography
16	COMMERCIAL CONSIDERATIONS FOR CELL AND GENE THERAPY
16	Value recognition in cell and gene therapy focuses on patient first, price second
17	Insights behind GlaxoSmithKline's Strimvelis strategy
18	Cell and gene therapy will change the care pathway
18	Educating stakeholders is key
18	Manufacturing is among the unique capabilities needed to commercialize a gene or cell therapy product
19	Bibliography

Datamonitor Healthcare attended the 6th annual meeting/partnering forum of the Alliance for Regenerative Medicine (ARM), held between 5–6 October 2016. ARM is a critical advocate in the US for pressing and significant issues affecting the cell and gene therapy field, including clinical, regulatory, commercial, industrial, and reimbursement.

The following conference highlights are discussed in this white paper:

- cell-based immuno-oncology
- gene editing
- cell and gene therapy pricing and reimbursement
- financing of cell and gene therapy companies
- commercialization of cell and gene therapies.

ARM's 6th annual meeting highlights development, commercialization, and reimbursement challenges

The Alliance for Regenerative Medicine held its 6th annual meeting/partnering forum between 5–6 October 2016. ARM is a critical advocate in the US for pressing and significant issues affecting the cell and gene therapy field, including clinical, regulatory, commercial, industrial, and reimbursement. ARM's membership includes a wide range of organizations, encompassing cell and gene therapy companies, large pharmaceutical and biotech firms, life sciences companies, disease philanthropy organizations, foundations, and academia. ARM has recently embarked on a new initiative, announced by managing director Morrie Ruffin at the annual meeting, to further support its membership by creating the non-profit ARM Foundation, which will provide additional educational efforts and awareness of cell and gene therapy to the public and key stakeholders.

From a regulatory standpoint, the cell and gene therapy field is growing rapidly. Celia Witten, the deputy director of the Center for Biologics Evaluation and Research, reported that there has been an explosion of investigational new drug (IND) applications submitted to the Office of Cellular, Tissue, and Gene Therapies (OCTGT) over the last couple years, including over 200 filings in both 2014 and 2015 (Office of Cellular, Tissue, and Gene Therapies, 2016). Of the IND applications submitted for breakthrough therapy designation, 11 in total have been granted, seven of which are oncology therapies. The OCTGT has recently been reorganized and will become part of the new Office of Tissues and Advanced Therapies.

Over the course of the two days, several important issues affecting the cell and gene therapy field were discussed during panels at the conference. This paper presents some of the key highlights from various panel discussions on cell-based immuno-oncology, gene editing, pricing and reimbursement, financing, and commercialization.

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Cell-Based Immuno-Oncology

Panel name: Measuring progress in cell-based immuno-oncology: how close are we?

Participants:

- Stewart Abbot, chief development officer, Fate Therapeutics
- David Chang, chief medical officer and executive vice president of research and development, Kite Pharma
- Thomas Farrell, president and chief executive officer, Bellicum Pharmaceuticals
- Christian Homsy, chief executive officer, Celyad.

THE CELL-BASED IMMUNO-ONCOLOGY FIELD HAS "LIFTED THE PLATEAU" IN TREATMENT

In a discussion on where cellular immunotherapy has made the most progress, the panelists highlighted that the major achievement in this area lies in the significant improvement that has been made over standard oncology treatment. Kite Pharma's chief medical officer and executive vice president of research and development, David Chang, pointed out that historically, chemotherapy provided an incremental benefit. Cell therapy has now lifted that plateau, where some patients in studies have progressed without recurrence of disease. Celyad's chief executive officer Christian Homsy agreed, saying there is a real impact of cell-based immunotherapy on patients' lives in terms of overall survival.

FIRST CAR-T THERAPY APPROVALS COULD HAPPEN IN THE NEXT COUPLE YEARS, FOLLOWED BY COMBINATIONS

Fate Therapeutics' Stewart Abbot, chief development officer, highlighted how quickly players such as Juno Therapeutics and Novartis have moved in the chimeric antigen receptor T (CAR-T) cell therapy field, and he anticipates that the first approvals in this area will occur over the next two-to-three years, followed by more progress with and potentially approvals of combination therapies. On the reality of combinations, Kite's Chang believes there is rationality for combining cell therapy with drugs that have proven efficacy. He gave the example of his company's KTE-C19 combined with a programmed death-ligand 1-targeted treatment (Kite is testing such a combination with Roche/Genentech's Tecentriq [atezolizumab] [Business Wire, 2016]). Chang also spoke about another dimension of combinations that would include packaging small molecules onto T cells during ex vivo manufacturing to make the T cells more effective.

GENE EDITING HAS APPLICATIONS WITH CELL-BASED IMMUNOTHERAPY

The use of gene editing is still very much in its infancy, but was brought up in terms of its use with cell therapy as an enabling technology. The panel agreed it is still early days for gene editing, and that there has been a rush to invest in innovations in the field, but that it was important to take a pause and be mindful of what companies are doing with this technology now. There are several potential synergies between cell-based immunotherapy and gene editing. Kite's Chang says gene editing may be used to knock out checkpoints, or to help cells expand more effectively. Fate's Abbot cautioned that what happens to these edited cells once they go into the body is critical and needs to be monitored. Abbot said it is difficult to apply multi-gene editing tools and that it is critical to be able to edit cells on a stable platform, using the analogy of trying to cook dinner on a yacht in a storm.

THERE ARE CHALLENGES TO USING CELL-BASED IMMUNO-ONCOLOGY IN SOLID TUMORS

In contrast to the potential for an unprecedented impact on hematological cancers such as diffuse large B-cell lymphoma and chronic lymphocytic leukemia, the treatment of solid tumors with cell-based immunotherapy presents challenges. Celyad's Homsy believes it will require an approach building on what has been previously done in researching cell therapy, and adding to that. The key considerations include how to deprive the tumor of oxygen, managing tumor toxicity, and creating an adaptive mechanism. Bellicum Pharmaceuticals' president and chief executive officer Thomas Farrell pointed out further challenges, including the fact that T cells take too long to get to the tumor. He stressed the importance of managing the cell population and its proliferation through the course of treatment. Farrell also questioned how to keep the T cells in the body, and what becomes of them in terms of managing downstream toxicity.

MULTIPLE COMMERCIALIZATION CHALLENGES REMAIN, BUT SOME PROGRESS HAS BEEN MADE

The panel believes that to advance cell-based immuno-oncology, there must be a translation of treatment from single institutions to more multi-center trials. This is the next step that gets the field closer to the reality of commercialization. In addition to translation of cell-based immuno-oncology studies to multiple centers, the panel also had some ideas for making cell immunotherapy commercialization a reality. Celyad's Homsy said there is still some skepticism on the part of Big Pharma and top biotech companies, which could speed up efforts toward commercialization via partnering due to their regulatory and commercial expertise. Bellicum's Farrell pointed out that advancements in cryopreservation have been a big positive and will play an important role in managing logistics once cell-based immunotherapies come to market. Kite's Chang believes some challenges still need to be addressed, such as handling the manufacturing of the cells.

ADVICE TO START-UPS INCLUDES BUILDING ON KNOWLEDGE ALREADY GENERATED

The panel was asked to give advice to start-up companies working in cell-based immuno-oncology. The early pioneers of the field had the luxury of time, said Bellicum's Farrell. That is not the case anymore, with so much investment being put into the field. Start-ups have a challenge managing this, and it is critical not to underestimate the challenge. Kite's Chang suggests starting with a foundation platform and getting the best people to work on it, including those who are "smarter than you" and who have a vision of what the field will look like. Having a strong focus on clinical development is

important too, said Fate's Abbot, who stressed that there is a risk of missed opportunities.

THERE IS STILL A LONG ROAD TOWARD PERSONALIZED TREATMENT

On the idea of personalizing cell-based immunotherapy, the panel agreed that this will take time. Kite's Chang said the field is in a transition phase now and clinical feedback is still needed. Until then, researchers will not know if personalized treatment or "one-size-fits-all" will be the best approach. Chang believes that autologous cell therapies will carry the field for the near-term future, but in time a universal cell approach will come. The difficulty in personalized cell-based immunotherapy is that consistency, as with other therapeutic modalities, is nearly impossible. Fate's Abbot said that waiting on a consistent outcome with so many variables – patient variation and cell variation, for example – is laughable.

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Gene Editing

Panel name: Gene editing interview

Participants:

- Alexandra Glucksmann, chief operating officer, Editas Medicine
- Sandy Macrae, president and chief executive officer, Sangamo BioSciences
- Prashant Mali, assistant professor, Department of Bioengineering, University of California, San Diego.

GENE EDITING POTENTIAL IS IIMITLESS, BUT PROCEED WITH CAUTION

Gene editing – the process by which various molecular tools are used to cut genes and either modify, remove, or replace them – has the means to treat or potentially cure diseases. Since 2014, the amount of venture funding for companies involved in gene editing techniques such as clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 or transcription activator-like effector nucleases (TALEN) has reached over \$600m, and three such companies have completed initial public offerings (Strategic Transactions, 2016). Sandy Macrae, president and chief executive officer of Sangamo BioSciences, which focuses on another type of gene editing via the zinc finger DNA-binding protein, says there is a need to put out a safe and effective gene editing solution that is patient-focused. He urged those working in gene editing to step back from the hype, understand the promises, come to some consensus on what are the necessary on-target and off-target responses, and work closely with the US Food and Drug Administration. Eventually, said Macrae, gene editing will be used for a wide

number of diseases, but for now, it is being applied to those conditions for which there is no other alternative.

OFF-TARGET EFFECTS AND SAFETY IN GENE EDITING ARE BIG ISSUES

The panel stressed the importance of considering off-target effects in gene editing. In addition to coming to consensus on off-target responses, there were other concerns voiced. Prashant Mali, an assistant professor in the Department of Bioengineering at the University of California, San Diego, said that the efficacy of the gene editing tool needs to be considered to help define the on-target/off-target responses. He also stated that the field itself has not yet defined what a reasonable off-target response is. Editas Medicines' chief operating officer Alexandra Glucksmann cautioned, however, that there needs to be a separation of the safety issue from off-target responses. Many of the off-target effects can lead to safety issues, but safety in terms of gene editing is linked more to the individual indication being treated, as opposed to the off-target response of the gene editing technology as a whole (Innovative Genomics Initiative, 2016). Sangamo's Macrae stressed that with gene editing, it is important to go very cautiously into patients, because the consequences of "getting it wrong" are dangerous, and that it is not the same as stopping treatment with a small molecule, for example. Gene editing drug developers have the responsibility of communicating the risks and benefits to patients, and tracking them for the duration of treatment and for the long term. To enable such long-term tracking and ensure proper data collection, which Macrae says will also help drive future plans, it is necessary to form relationships with investigators and patients themselves, and to produce some kind of database to store the information. Medpace's Blythe Thomson, senior director of medical affairs, hematology and oncology, who moderated the panel, added that contract research organizations could play a critical role here, and that there are novel technologies capable of that long-term tracking.

In September 2016, the US Defense Advanced Research Projects Agency (DARPA) proposed a funding program called Safe Genes that would finance an estimated \$50–100m in gene editing safety research. Specifically, Safe Genes would focus on three key areas to ensure safety measures for gene editing. They include techniques for on- and off-switches once gene editing is being performed inside the body; drug development focused on blocking or reducing the actions of gene editing; and tools that clean up leftover gene editing in the body (Xconomy, 2016)

TO ADVANCE GENE EDITING, COLLABORATION BETWEEN INDUSTRY AND ACADEMIA WILL HELP

There is a need for close ties between academia and industry, said UC San Diego's Mali, to help advance gene editing. Mali pointed out that this kind of collaboration is great advertising for the pharmaceutical industry. However, Mali cautions that trade secrets are something that could halt the field. Editas' Glucksmann cited her company's work with the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) in Milan, the same institute that worked with GlaxoSmithKline to develop the ex vivo gene therapy Strimvelis. Editas and SR-TIGET are working on genome-edited hematopoietic stem cell and T-cell therapies for rare diseases (FierceBiotech, 2016). Glucksmann said deals like this take some time, but that doing these types of alliances in a targeted way is important.

PATIENT ADVOCACY GROUPS ARE ALSO EXPECTED TO HELP ADVANCE GENE EDITING

The role of patient advocacy groups has increased in importance and impact, especially as a result of the recent approval of Sarepta Therapeutics' Exondys 51 (eteplirsen), which had strong support from patient advocates (Pink Sheet, 2016a). The panel discussed patient advocacy influence in gene editing. Sangamo's Macrae pointed out that these are vulnerable patients, and doubted that anyone on the panel or in the room at the meeting would not be out there advocating too if they were a parent. He said that companies need to be prepared for requests for compassionate use if and when successful clinical trial results are announced, especially in oncology. Editas' Glucksmann receives emails from parents; because of a collaboration with the Foundation Fighting Blindness (one of the areas Editas is working in), she can refer patients to that organization. Glucksmann says that gene editing companies have an obligation to educate patients about their technology. The education component goes both ways. To create better relationships with pharmaceutical firms, patient advocacy groups want to be involved in educational and awareness efforts, in terms of providing information about the diseases they represent, early in the development process. Pharmaceutical companies can also benefit from partnering with patient advocacy groups to use the patient registries for clinical trial enrollment and outreach (inVentiv Health, 2015).

GENE EDITING PRESENTS GLOBAL REGULATORY CHALLENGES

Much of gene editing development has been concentrated in the US, but because many rare disease patients live outside the US, said Sangamo's Macrae, there will eventually be a need for international harmonization of regulations since gene editing will be a global effort. The most established regulations to date are in the US and Europe, and this is largely because it has not been beneficial to go to less-developed regulatory environments. Macrae pointed out that there are good investigators in China, for example, that the US gene editing industry should be working with. However, agreement on international regulations for gene editing is likely a long way off. Editas' Glucksmann stated that it would be challenging to have regulations harmonized worldwide. There are some policies being drafted by various governments to advise on human genome editing, but the regulations are vague for many reasons, including the fact that certain definitions related to gene editing are not consistent (BioIT World, 2016). The language used in these regulations also needs to be careful so as to acknowledge the ethical issues while also avoiding a stunt in gene editing research. In the absence of harmonized regulations, Glucksmann suggested gene editing companies be as transparent as possible, and that doing so would not present a threat to business. She pointed out that even with bad news, transparency does not necessarily halt a field, citing Juno Therapeutics' disclosure in mid-2016 of patient deaths in its Phase II ROCKET trial for CAR-T therapy JCAR015 (Pink Sheet, 2016b).

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Cell and Gene Therapy Pricing and Reimbursement

Panel name: The impact of a new healthcare model: what do payers think of gene therapies?

Participants:

- Nick Crabb, program director, scientific affairs, Centre for Health Technology Evaluation, National Institute for Health and Care Excellence
- Michael Fine, medical director, Health Net
- Mark Trusheim, founder and president, Co-Bio Consulting; visiting scientist, MIT Sloan School of Management.

CELL AND GENE THERAPIES ARE A NEW AND CHALLENGING CLASS FOR PAYERS

During a panel on the impact of cell and gene therapies as a new healthcare model for payers, the panelists agreed that gene therapies represent uncharted territory. Payers lack the evidence base in cell and gene therapy to help make reimbursement decisions, and said that issues and solutions will evolve over time. Payers also need to be thoughtful regarding how cell and gene therapy will fit into clinical pathways.

NICE'S HYPOTHETICAL CASE FOR CAR-T THERAPIES FINDS ITS METHODS WOULD WORK

The UK National Institute for Health and Care Excellence's (NICE) Nick Crabb, program director of

scientific affairs at the Centre for Health Technology Evaluation, discussed a hypothetical case that NICE ran for CAR-T therapies. Results were disclosed in March 2016. The organization tested whether or not it could use its existing health economic approaches in reviewing advanced regenerative medicine therapies, such as cell therapies. The test case involved a CAR-T therapy that provided up to 10 additional quality-adjusted life years and cost more than £500,000 per patient. The study concluded that NICE could use the same decision-making methods it already uses for these kinds of drugs, which would represent major advances. NICE's Crabb stressed, however, that it is important not to forget real pricing and what healthcare systems can afford. The NICE study suggested that healthcare systems will need to create new methods to make these products financially stable, proposing a "lifetime leasing" model that would replace the up-front costs with monthly payments (PharmaPhorum, 2016).

PAY-FOR-PERFORMANCE METHODS IN THE US WOULD BE DIFFICULT TO EXECUTE

Besides the monthly payment plans that have been suggested, including annuity type payments or the "lifetime leasing" model from NICE, another innovative mechanism for paying for cell and gene therapies is based on pay for performance. While theoretically a pay-for-performance model sounds ideally suited for cell and gene therapies, the panel believed implementation would be difficult. Michael Fine, medical director at the commercial insurer Health Net, said the problem is that patients are mobile, and move from plan to plan. This means there is no easy way to track them and their clinical outcomes. The issue of patient records also makes this model difficult. Fine pointed out that in the past, a patient's medical record would consist of five pages of illegible handwriting; now it is 200 pages of typed information from an electronic medical record (EMR), but payers do not know what to look for within that. There are multiple formats for EMRs, but no way for them to communicate. Sven Kili, GlaxoSmithKline's vice president and head of cell and gene therapy development, who spoke on a separate panel on commercialization, stated that there is interest from payers in innovative models, but no one has the appetite to do it yet. GlaxoSmithKline itself has pledged to refund the entirety of the cost of its ex vivo gene therapy Strimvelis, which will have an initial cost of \$665,000, if the drug does not work (MIT Technology Review, 2016). Kili also stated that GlaxoSmithKline is committed to 15-year follow-up on patients. In terms of setting and justifying prices, Health Net's Fine suggested cell and gene therapy drug developers be transparent about the inputs: how much the research and development costs were, what the manufacturing cost will be, and how much profit the company wants to make.

ACCELERATED PATHWAYS FOR CELL/GENE THERAPY TAKE ON SIGNIFICANT MEANING TO PAYERS

The grant of an accelerated pathway, such as breakthrough therapy designation (BTD) status in the US, for a cell or gene therapy takes on an important meaning for value demonstration to payers. For a cell or gene therapy company, the grant of BTD can be beneficial for sponsors because it forces them to think through their development plans early on, and with input from the US Food and Drug Administration (FDA), according to Celia Witten, who spoke on a separate panel focused on regulatory processes. Sponsors with BTD are required to have a communication plan and an outline of important milestones. The agency works with the companies and provides advice on what is needed at different stages of development. Witten said the Office of Cellular, Tissue, and Gene Therapies has granted BTD

to 11 cell and gene therapies to date, including seven oncology products and four non-oncology products.

In their discussion, the panel implied that more drugs might be put on accelerated pathways, such as BTB, than should be. NICE's Crabb said there needs to be a consensus on what transformational need is, and that would probably lead to a smaller number of products on these accelerated pathways. "Breakthrough really has to be breakthrough," said Health Net's Fine, otherwise this can cause trouble for payers down the road. He gave the example of Avastin (bevacizumab; Genentech/Roche/Chugai), which was approved in the US through an accelerated pathway in February 2008 for breast cancer. The drug was eventually shown to be ineffective for breast cancer, and in November 2011, the FDA revoked approval (Biomedtracker, 2016). Fine, however, pointed out that it was a battle to get physicians and patients to stop using the drug in that indication. He says in the US there needs to be a mechanism by which payers do not need to pay for a drug if it does not work, even if it was granted accelerated approval.

"ADVERSE SELECTION" IS A BIG THREAT TO PAYERS

A major threat to payers, according to Health Net's Fine, when it comes to cell and gene therapies, is what he called "adverse selection." It is a risk to be the payer that is the first to cover a novel cell or gene therapy for a rare disease, for example, because that payer will automatically attract all of the patients with that rare disease and be responsible for paying for them. It is inevitable, said Fine, that all patients would be attracted to the one and only plan covering a transformative therapy.

PANELISTS DIFFERED ON WHETHER PATIENTS CAN AFFORD THE OUT-OF-POCKET EXPENSE OF CELL AND GENE THERAPIES

There was a difference in opinion between Health Net's Fine and Mark Trusheim of the MIT Sloan School of Management on whether or not patients can bear the potentially large expenses of cell and gene therapies. Fine said that in the US, the Affordable Care Act has largely removed patient participation in expensive drugs; this would apply to cell and gene therapies. There is a patient cap at \$6,250. Fine believes that if a patient will be cured by such a therapy, that cost is not a lot, so patients will not refuse them. Trusheim countered that argument, saying that 35% of personal bankruptcy is due to medical costs, specifically because of out-of-pocket expenses that do not get covered. Therefore, according to Trusheim, cell and gene therapy will present a real patient burden. He says that \$6,000 is a huge cost to someone with an annual salary of \$40,000–50,000, which is the national average in the US.

CELL AND GENE THERAPY DEVELOPERS NEED TO START DISCUSSIONS WITH PAYERS EARLY

The panelists all urged cell and gene therapy drug developers to meet with payers and health technology assessment (HTA) organizations to pressure test their clinical trial designs. MIT's Trusheim believes that it is key for developers to understand how to create the evidence they will need, in an adaptive approach, before going to market. Health Net's Fine said it is important for companies to get feedback on the evidence they will need for a long-term therapy, for example, that they say will work in 10 years. Most importantly, the panelists agreed these discussions should happen early on so that

cell and gene therapy developers can understand the outcomes that payers and providers want from their products. On the flip side, payers and HTA bodies, according to NICE's Crabb, should get better at horizon scanning and thinking more about innovative payment mechanisms.

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Financing Climate for Cell and Gene Therapy Companies

Panel name: Financing gene and cell therapy companies: the investors' perspective

Participants:

- Raquel Bracken, vice president, Venrock
- Rowan Chapman, head of healthcare investing, GE Ventures
- David Kabakoff, executive partner, Sofinnova Ventures
- Deval Lashkari, senior partner, Telegraph Hill Partners
- Joseph Sum, director of research, EcoR1 Capital.

THE FINANCING ENVIRONMENT FOR CELL AND GENE THERAPY IS A SMALL PROPORTION OF OVERALL BIOTECH FINANCING

In the first six months of 2016, financing for the entire biotech industry totaled \$27bn (Medtrack, 2016). The regenerative medicine market only represented a small share of that, reaching \$2bn in financing (including initial public offerings, follow-on public offerings, venture capital, private investments in public equity, and private equity deals) for cell and gene therapy and tissue engineering companies (Alliance for Regenerative Medicine, 2016).

INVESTORS ARE LOOKING FOR LOW-RISK COMPANIES AND EXPERIENCED MANAGEMENT

A panel made up of industry investors from Venrock, GE Ventures, Sofinnova Ventures, Telegraph Hill Partners, and EcoR1 Capital discussed several aspects for financing cell and gene therapy companies. The diversity of the panel in terms of investing style varied, but there was consensus on mitigating as much risk in their investments as possible, and looking for management teams with broad experience. Venrock, for example, focuses on earlier-stage companies, while Sofinnova is interested in those that

are in the clinic with their drugs. GE Ventures, the corporate venture arm of General Electric, only invests in life sciences tools and not therapeutics. EcoR1 was the sole crossover investor on the panel; crossovers are those that usually back public companies, but may also finance private companies prior to them going public, and may theoretically provide a smoother transition to public status. EcoR1's Joseph Sum, director of research, Telegraph Hill Partners' Deval Lashkari, senior partner, and Venrock's Raquel Bracken, vice president, said their firms are not willing to take certain risks in their portfolios, such as financing, development, and commercial risks. In terms of management, EcoR1's Sum stressed it is important that leaders are experienced in the industry, especially in times of crisis which can often occur for a start-up. Venrock's Bracken said the typical timeline for an average investment is seven to 10 years, so it is critical to build a good management team, especially if that team needs to pivot over that time period.

BIG PHARMA VALIDATION IS A NICE-TO-HAVE, NOT A NECESSITY

When asked how important it is for a cell and gene therapy company to have validation from a Big Pharma partner, both EcoR1's Sum and Telegraph's Lashkari stressed that this was not important or essential. According to Sofinnova's executive partner David Kabakoff, Big Pharma involvement via a corporate venture arm can be a mixed bag, and sometimes can cap the upside. He said that he does like co-investing with a strategic partner, where both parties can bring unique skills. However, Kabakoff also prefers when the start-up can control its own destiny.

CELL AND GENE THERAPY COMPANIES SHOULD NOT BE AFRAID TO ASK FOR SUFFICIENT CAPITAL TO CREATE VALUE

The question came up regarding how much money is enough for a cell and gene therapy company to sustain operations, and whether the financing is usually sufficient for the company to make it to commercialization, or only to a certain phase of development, for example. Venrock's Bracken stressed the importance of milestone-driven financing, saying that milestones, such as when a company meets proof-of-concept in trials, are a way to create value. Sofinnova's Kabakoff pointed out some challenges with funding by phase, including the fact that start-ups need to be mindful of time in terms of their intellectual property. According to Kabakoff, "the clock is ticking," and simultaneously a company is losing patent life, but it also needs to be getting ready for the next phase. Kabakoff, like Bracken, stressed value creation, suggesting that companies should request as much capital as they need to reach certain inflection points, and not be timid when asking. He said that competition for investment has driven up terms. GE Ventures' head of healthcare investing, Rowan Chapman, advised start-ups to think about the expected outcome of their company, and then to ask themselves how much capital would it take to get there.

FORGING PARTNERSHIPS WITH THEIR INVESTORS CAN GIVE CELL AND GENE THERAPY DEVELOPERS MANY ADVANTAGES

Besides the actual financing investors supply, the panel pointed out several other benefits they can provide to cell and gene therapy companies. EcoR1's Sum said there is opportunity for introductions to contacts within the investor's network to forge relationships in the industry. Venrock's Bracken agreed that there is potential for contacts for recruiting or transactions, for example. She also

emphasized the advantage some investors have as an incubator, especially in providing office space that may be shared with other newly formed companies – "lots of synergies happen there." The investor and the start-up should be partners, according to Telegraph Hill Partners' Lashkari, and the investor can be a good advisor to help avoid pitfalls and to be an advocate for the company, especially during deal negotiations or difficult times.

Start-ups may also take advantage of the in-house expertise of investors' management. Kabakoff said Sofinnova is active in its portfolio companies and usually has board seats. This allows for the company to benefit from a broad range of regulatory and business development experience. As a corporate venture fund, GE Ventures can provide access to various General Electric business units, according to Chapman, to help build partnerships and intellectual property. GE Ventures offers the Edge Fellowship, which allows a General Electric employee to go on secondment to one of the portfolio companies to further encourage collaboration.

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Commercial Considerations for Cell and Gene Therapy

Panel name: Gene therapy: commercializing a therapeutic product

Participants:

- Andrea Hunt, vice president, new product therapeutic area lead gene therapy, neuroscience and ophthalmology, Shire
- Sven Kili, vice present and head of cell and gene therapy development, GlaxoSmithKline
- Matthew Patterson, president and chief executive officer, Audentes Therapeutics
- Sue Washer, president and chief executive officer, Applied Genetic Technologies
- Elizabeth White, assistant vice president, early commercial planning, rare disease and gene therapy, Pfizer Innovative Health.

VALUE RECOGNITION IN CELL AND GENE THERAPY FOCUSES ON PATIENT FIRST, PRICE SECOND

"Commercialization is more than just pricing." This quote, from president and chief executive officer of Applied Genetic Technologies Sue Washer, represented the overarching theme of the commercial panel discussion. Washer acknowledged that, understandably, cell and gene therapy drug developers want to see a return after working on the development of a product for years. However, the real focus

should be on the patient and the societal benefit. She said it is important that through the clinical development plan, the company gets the data it needs for not only regulatory approval but for other stakeholders to show value to the patient and society. Sven Kili, vice president and head of cell and gene therapy development at GlaxoSmithKline, agreed that at the forefront is creating value for patients, parents, and stakeholders; what the company charges and gets reimbursement for comes at the end.

In a discussion on value challenges, the panelists pointed out that cell and gene therapy is a unique case study. Elizabeth White, the assistant vice president for early commercial planning in rare disease and gene therapy at Pfizer Innovative Health, said that these therapies are designed to last for a long time, but the ability to show that in clinical trials is limited. GlaxoSmithKline's Kili further backed up that point, admitting that the field is uncharted territory. Companies just do not know yet what will happen to patients receiving cell or gene therapy 30, 60, or 90 years down the road, for example.

The panelists discussed what needs to be done early on in development to demonstrate the value of cell and gene therapies. Matthew Patterson, president and chief executive officer of Audentes Therapeutics, stressed the importance of building in a collection of data that are robust enough to satisfy regulatory authorities and payers. For the latter group, it is equally important to add in quality of life measurements. He also said that early dialogue with external stakeholders, such as patient organizations, key opinion leaders, and payers, would help. On the topic of interacting with payers early on in development, Applied Genetic Technologies' Washer pointed out that this is especially critical for those working in rare diseases where payers may not have much or any experience. She gave the example of rare blinding diseases, in which her company is involved, saying that payers are not yet experienced with reimbursing for any products that cure blindness. Therefore, it is the developer's job to produce the primary data on health economics and to do that early.

INSIGHTS BEHIND GLAXOSMITHKLINE'S STRIMVELIS STRATEGY

GlaxoSmithKline's Strimvelis was the most recent cell and gene therapy to be approved worldwide. The European Commission granted marketing authorization on 27 May 2016 for the ex vivo stem cell gene therapy in severe combined immunodeficiency due to adenosine deaminase deficiency, a rare disease affecting the immune system (GlaxoSmithKline, 2016). On the panel, GlaxoSmithKline's Kili provided insight behind the company's strategy with Strimvelis. He said GlaxoSmithKline will not make a profit on this first indication for the drug (the company exercised options from its licensors Fondazione Telethon (Telethon) and Ospedale San Raffaele to also develop programs in metachromatic leukodystrophy and Wiskott-Aldrich syndrome [GlaxoSmithKline, 2015]). Strimvelis is expected to cost \$665,000, and Kili says the price is appropriate, not ridiculous (Kili also cited GlaxoSmithKline's pledge not to price a drug more than 14% of the R&D costs). In working with the Italian Medicines Agency (Strimvelis may only be administered in one clinic in Milan), GlaxoSmithKline has committed to a money-back guarantee, agreeing to refund the cost if the drug does not work. In terms of not making a profit initially on Strimvelis, GlaxoSmithKline has stated that its goal with the launch is to help patients and get experience with cell and gene therapies (MIT Technology Review, 2016).

In marketing a cell-based gene therapy, Kili stressed GlaxoSmithKline's various responsibilities to its

patients. He said it is critical to find ways to follow up with patients, and that GlaxoSmithKline is committed to do this for at least 15 years. Kili also mentioned the importance of logistics in ex vivo therapy, saying companies in this area need to put together logistical pathways so that the sponsor is always in control of and responsible for those cells on behalf of the clinicians and patients. He believes there needs to be complete comfort with who is handling the cells throughout the entire process. For Strimvelis specifically with a limited half-life of the transduced cells, Kili said the logistics of patients having to travel to Milan for therapy is a key consideration for GlaxoSmithKline. The company is trying to make the drug available for patients closer to home, and is looking for hubs where more patients can be treated.

CELL AND GENE THERAPY WILL CHANGE THE CARE PATHWAY

The introduction of cell and gene therapy into disease management has the potential to disrupt the clinical care pathway. Pfizer's White talked about this in terms of hemophilia, which is an area where her company is developing through a deal with Spark Therapeutics (Strategic Transactions, 2014). There are already effective agents available for hemophilia. For example, severe patients are stable on prophylactic coagulation factor therapy on a regular basis, and payers have certainty around how much they are paying for these drugs. When cell and gene therapies come into the mix, they are expected to alter the care pathway, especially if they provide a one-time treatment for patients and clinicians who no longer need to manage their disease. White stressed that there will be a need to follow patients over time to build the evidence base. Andrea Hunt, the vice president of new product therapeutic area lead gene therapy for neuroscience and ophthalmology at Shire, agreed that the care pathway will change, but not all clinicians will adopt cell and gene therapy. In the hemophilia example, she said some patients will still need to take factor therapies, and that the old and new models will have to co-exist. This will further complicate value demonstration to payers, given the uncertainty around future factor consumption for patients that have received gene therapy.

EDUCATING STAKEHOLDERS IS KEY

Educating various stakeholders on cell and gene therapy was a key consideration on the commercial panel. Shire's Hunt, in talking about the disruption to the clinical care pathway, says that clinicians will require education for adopting these therapies. Clinicians will also need education to ensure the products are applied appropriately, so that patients will get good results, and the patients themselves have to understand the therapy and its shortcomings. GlaxoSmithKline's Kili pointed out that patients will get nervous, based on the fact that what is happening could be a permanent change to their genome. Education is also important for outreach to parents of pediatric patients on cell and gene therapy. Kili told a story of a father who would not allow his dying child to take gene therapy out of fear, based on headlines in the media about gene therapy causing cancer. Examples like this, said Kili, are why parents need to be educated too, since they are in control of their child's health.

MANUFACTURING IS AMONG THE UNIQUE CAPABILITIES NEEDED TO COMMERCIALIZE A GENE OR CELL THERAPY PRODUCT

In a discussion on the unique capabilities required to bring a cell or gene therapy to market, the consensus was that manufacturing is critical. Audentes' Patterson, whose company is investing in

manufacturing to build out its own capabilities, said that because manufacturing in this field is still in its infancy, and the science is complex, it is difficult to manufacture at a large scale. Applied Genetic Technologies' Washer agreed that manufacturing was an important consideration. She also said that analytics will be critical too, stressing that regulatory agencies care about the robustness of the data and characterization standards.

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