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Killer Cures: Industry Heavyweights Make Their Presence Felt In Cell And Gene Therapy

by Ashley Yeo

Cell and gene therapies, described as the most exciting developments in the life sciences industry, pick up more momentum with every passing month. The spiraling enthusiasm for an activity that will change how health care is delivered was captured by GE, GSK and other key industry players at a leading UK life sciences industry meeting in spring 2017.

- The tailwind behind cell and gene therapy, and regenerative medicine, blows ever stronger, with the larger companies now following the early lead taken by smaller innovators despite occasional clinical research setbacks seen in parts of the industry.
- Industry majors present at the 2017 BioWales conference included GSK and GE Healthcare, which both observed that while science is making the breakthroughs, payment models for this transformative field of medicine need to be addressed rapidly.
- With manufacturers wanting to play a leading role, Pfizer UK stresses that all health care system stakeholders must work together if the benefits of life sciences breakthroughs are to be maximized. The UK is seeking to do this in cell and gene therapy with a new manufacturing center.
- So what? As the bigger players take a bigger stake in the still-young cell and gene therapy industry, confidence in the viability of the therapies is growing, even if the payer scenario is a possible block on growth up ahead. But if the full potential is reached, and palliative care is supplanted by once-and-for-all curative solutions, purveyors of traditional pharma therapies will be watching their industry transform before their eyes.

There is perhaps no better place to highlight the benefits of regeneration than at Cardiff Bay in South Wales.

On stage at the Millennium Centre to officially open the 2017 *BioWales* life sciences conference, Wales' government business director Mick McGuire is recalling that 35 years ago, this 1,100-hectare area of the Welsh capital was desolate brownfields and derelict docklands. Today, besides the Millennium arts and conference center, it counts the modern National Assembly for Wales, TV studios and the Life Sciences Hub Wales (LSHW) among its stylish architectural statements, and is celebrated as an urban regeneration triumph.

Similarly, in health care, increasing numbers of innovators are pressing for their research in cell and gene therapy and regenerative medicine to demonstrate equally groundbreaking effects in the medicines and therapy sectors.

This year's *BioWales* showcased the progress being made in cell and gene therapy by some of the industry's heavyweights and key stakeholders – *GlaxoSmithKline PLC*, *GE Healthcare*and the non-profit UK Cell and Gene Therapy Catapult. Completing an impressive quartet of keynote speakers, *Pfizer Inc.*'s UK managing director Erik Nordkamp spoke of the need for forward-looking life sciences ecosystems to ensure that the benefits of life sciences breakthroughs are not squandered.

Unstoppable Momentum

While many of the basic questions regarding cell and gene therapy remain to be answered and companies are prone to gear changes, this industry sector's momentum is undeniable and unstoppable. (Also see "*Cell Therapy Manufacturing: Challenges Remain*" - In Vivo, 14 Dec, 2016.) (Also see "*Juno, Kite Stand By Their Products As Novartis's Shift Renews CAR-T Concerns*" - Scrip, 31 Aug, 2016.) *BioWales* speaker Mark Briggs, PhD, observed that the public is demanding access to these therapies because the results so far have been so compelling.

Briggs, who is the senior program and research manager of cell therapy technologies at GE Healthcare Cell Therapy, observed that enthusiasm for cell and gene therapy is at a record high. This is despite setbacks of the kind experienced by chimeric antigen receptor T-cell (CAR-T) and T-cell receptor (TCR) platform developer *Juno Therapeutics Inc.* In March, Juno ended development of its Phase II CD19-targeting CAR-T therapy JCAR015 for the treatment of acute lymphoblastic leukemia (ALL) because of patient deaths. (Also see "*Juno Ends JCAR015 Development In ALL, Cementing Third Place CAR-T Position*" - Scrip, 1 Mar, 2017.)

Bad news for that particular program, but not a hammer blow for the company or the wider industry; in fact, around the same time, another key player, *Kite Pharma Inc.*, was announcing encouraging safety and efficacy findings from Phase I trials of high disease burden patients treated with *KTE-C19* (the investigational name of Kite's lead product candidate, axicabtagene ciloleucel). Kite reported a death from cerebral edema in early May, but the company did not see that as limiting the therapy's use or its ability to win approvals. (Also see "*Too Sick For CAR-T? Kite Reports Cerebral Edema Death*" - Scrip, 8 May, 2017.) In fact, in late May, Kite announced

that its Biologics License Application (BLA) was accepted by the FDA with priority review.

And *Novartis AG*'s decision to consolidate its CAR-T therapy operations into its broader oncology business last August was seen as potentially a de-prioritization of that platform. But the company continues to say that it is an important part of its oncology strategy, which implies a commitment that readers might have missed in the stream of punchy story headlines at the time. Novartis in fact has a slight lead over Kite in getting a CAR-T therapy approved, although in a different indication. (Also see "*BLA Accepted: Novartis Inches Ahead In CAR-T Race With Kite*" - Scrip, 29 Mar, 2017.)

Measured Approach

The manner in which disappointing trial news tends to be received indicates both a maturing of attitudes toward and also heighted expectations of cell and gene therapy. Julie Kerby, of the UK Cell and Gene Therapy Catapult, and head of the manufacturing development team, observed that sporadic setbacks now tend to be viewed in a more measured fashion.

Speaking to *In Vivo* at *BioWales*, she said, "In the early days, such news would have been significant, but my feeling, now that the industry has been around for some years and is so large, is that people understand the risks with these novel therapies, especially in very ill patient populations."

For Kerby, cell and gene therapy manufacturing is a "game changer," given that it represents a complete shift in the way people are given medicine. "We are moving away from daily, weekly and monthly dosing regimes that treat symptoms, and toward a 'one-treatment-cure' approach," she said. "That is really quite amazing."

GSK's Approach To Cell And Gene Therapy

The next logical step for industry is to embrace the payer scenario. That is the view of Sven Kili, MD, vice-president, cell and gene and therapy development head at GlaxoSmithKline. GSK was a self-confessed "new boy on the block" as recently as early 2015, when the group revealed its commitment to cell and gene therapy, and later that year presented at the *London Alliance of Regenerative Medicine* meeting.

The GSK view then was that cell and gene therapy solutions clearly showed the potential for lasting innovation, although they would not provide immediate benefits. GSK describes its participation in the industry as a long-term strategic move, starting with ultra-orphan diseases where there is high unmet need. As understanding of the disease mechanisms grows, so does the potential for moving onto more common indications.

Kili advanced the story for delegates at *BioWales*. "We are finally rounding the corner with cell and gene therapy. We are now understanding the causes of disease, can manipulate cells and

genes, and can make a long-term difference to patients' lives," he said. Patients receiving therapy are being followed up for long periods to allow understanding of the effects of their therapy.

GSK started work in cell and gene therapy in 2010, on entering an alliance with *San Raffaele Telethon Institute for Gene Therapy* (Milan, Italy). *[See Deal]*It has oncology collaborations with *Adaptimmune Therapeutics PLC*, of Oxford, UK, an alliance that is looking at a number of T-cell receptor therapies. *[See Deal]*And in March 2016, GSK entered a partnership with cell processing specialist Miltenyi Biotec Ltd. (Surrey, UK).*[See Deal]* It continues to seek and develop new cell and gene therapies.

Kili stressed the importance of GSK keeping scale in all areas, including manufacturing, which was another reason for the agreement with Miltenyi Biotec. This industry is prone to rapid change. "The technologies we use now will probably not be those that we will be using in 10 years' time," he said.

GSK Projects Underway

In a snapshot of cell and gene therapy projects underway at GSK, Kili referenced *Strimvelis*, approved last year as a gene therapy for ADA-SCID, a very rare immunodeficiency syndrome that annually affects just 14 to 15 children in Europe and a similar number in the US. A minimum 15-year follow-up is performed for this one-time therapy that has so far showed 100% survival. "It's really exciting, but we're just at the beginning," he noted.

Another GSK project targets the rare cross-linked recessive disease Wiskott-Aldrich syndrome (WAS), in which boys are affected by bruising and bleeding diathesis caused by a *WAS* gene mutation. Following gene therapy, GSK has seen the number of severe bleeds and severe infections reduce substantially. "This therapy makes a massive difference to children's quality of life and can even allow them to have normal interactions at school," said Kili. It too has seen 100% survival, and no abnormal side effects.

A third GSK project highlighted by Kili targets metachromatic leukodystrophy, which affects one in 40,000 children in the UK and leads to death at age five to eight.

A recent horizon scan showed that there are some nine advanced therapies approved in the EU. They are not yet household names (*uniQure NV*'s *Glybera* aside – for its price tag possibly as much as its science) and are normally intended for very small niche indications.

But many new companies are being formed: figures quoted by Kili revealed over 735 companies focused on cell and gene therapy around the world at the end of 2016. The US is leading the way in terms of new companies being formed. A lot of money is following them: in the EU last year, close to €400 million ($432 million) was invested in these companies. Clinical trial numbers are increasing too, with over 800 underway globally (more of them in Phase I than Phase III,

understandably).

And now, in what remains a young industry, big pharma and the larger health care industry players are increasingly making their presence felt. "This is important, as it sends a very clear signal that these types of therapies are viable and can make a difference to people's lives. We see this as an area of exciting growth and development," said Kili.

Payment Models Vital To Get Right

But how are companies incentivized and rewarded for their efforts? The concept of a one-off treatment that has, say, 70 to 80 years of therapeutic effect, is difficult to factor in, Kili acknowledged. But industry has a responsibility: "We need to show value for money and to price responsibly, which means doing that in a way that payers and society can afford."

When companies eventually branch out into the big diseases such as heart failure and neuro diseases, for instance, the industry will certainly need to broach different methods of payment. "We have to take the long-term view – these therapies are expensive, and we as an industry need to find ways, including via more cost-effective manufacturing, to bring costs down," said Kili.

> *"You can't be in this for the short term. We are aware that we need to engage with payers early and often, but this is a long-term investment." – GSK's Sven Kili, MD*

But it's a balancing act, and manufacturers need the financial incentives to do the research and develop the therapies. "You can't be in this for the short term. We are aware that we need to engage with payers early and often, but this is a long-term investment, and we need to work with payers to develop new and unique ways of being reimbursed." (Also see "*Curative Regenerative Medicines: Preparing Health Care Systems For The Coming Wave*" - In Vivo, 15 Nov, 2016.)

Kili is confident of one thing: "As reimbursement comes, investors will see how worthwhile these therapies are. We need to see a reset from the VCs too." The VCs had been expecting Strimvelis to be priced at Glybera levels, "but we priced substantially lower," said Kili. He added, "We are right at the beginning – but this is an area of health care that we are committed to."

New UK Facility To Support Fast-Growing Cell And Gene Therapy Sector

UK Cell and Gene Therapy Catapult head of manufacturing development Julie Kerby agrees: she

says there is a "big conversation to be had" on payment models. One option is to pay annually for therapies over time to spread the burden, instead of using the one-off payment approach. "The industry is still very young, and right now, therapies look very expensive to make, but in the future, costs will come down," she said.

Kerby told *In Vivo* that of the 22 UK facilities licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, most were for small-scale processes. At present, the UK has six gene therapy manufacturers.

Some companies use CMOs, but this does not suit all players, especially those with a bespoke or unique process. Also, CMO capacity in the UK is becoming limited, and this is particularly a problem in the viral vector side.

The alternative is owner-operated businesses, but this too comes with its own issues: the need for investment, the need to recruit expertise, and the struggle to simply keep ahead of the game and factor in advances in this fastest-moving sector of the industry. Companies must think about how they "crystal-ball" their facilities, Kerby said.

So she suggests a third option: companies can take space at the new Cell and Gene Therapy Manufacturing Centre at Stevenage (Hertfordshire, UK). The center, owned and run by the Catapult, will offer cleanroom, quality, stability and product cryo-preservation services. The facility, which was nearing completion in spring 2017, will have batch-to-batch segregation to prevent cross contamination, and will hold users to GMP (good manufacturing practice) guidelines.

The Centre hopes to get an MHRA license by the end of 2017 and to be delivering clinical material in 2018. It will be able to house multi-users, with each company owning its manufacturing space and having its own Quality Management System (QMS). It will initially have six modules, and 12 when fully occupied. There is already a "huge amount of interest" – including from large companies and large pharma contract manufacturers, said Kerby, who added, "This is a way for them to test the water with us."

"It's a total risk-based approach," said Kerby, but it needs to be fit for purpose and to use lean solutions. "It was a bold decision by Innovate UK and the Catapult to initiate the center – it took a lot of far-sightedness, but that is the purpose of Catapults – to take risks and look into the future."

She added, "World-leading research is coming out of UK universities, and we want to ensure that it doesn't move away to the US or elsewhere." A lot of companies in the cell and gene therapy space are quite small, with just 30 to 40 members of staff, and need a lot of support. (*See box, "An Enhanced UK Role In Cell And Gene Therapy Post-Brexit."*)

It is foreseen that companies will stay at the center for two to three years at least, as these are "long-term endeavors." Companies need to generate clinical data to secure investment. Having to construct their own facility at the same time would slow them down. When the time comes for them to leave the facility, they can take an identical copy of their QMS with them.

Kerby acknowledges that cleanrooms are a very expensive part of the operation, and that in the future, the industry might be able to dispense with them. "We're still a way off that, but it's something to aspire to."

GE's Focus On Turnkey Solutions

GE Healthcare's senior program and research manager Mark Briggs shares the enthusiasm for cell and gene therapy on several levels. While results from drug discovery can take 15 to 20 years to come through, results in cell therapy can be seen almost immediately.

An Enhanced UK Role In Cell And Gene Therapy Post-Brexit

A consensus is growing that the Cell & Gene Therapy Catapult and the new Cell and Gene Manufacturing Centre can help the UK carve out a particular role for itself as the country gives up its membership of the EU. In the post-Brexit phase, especially, the UK is urged by MPs, the MHRA and the industry alike to capitalize on research expertise and be opportunistic – especially in these fields of ATMPs and cell and gene therapy. *BioWales* speaker Erik Nordkamp, managing director of Pfizer UK, supports this approach, but is wary about the increasingly competitive environment. He feels the UK needs to develop a better life sciences ecosystem, guard against an over-focus on cost containment, avoid bureaucracy, simplify systems, be pragmatic and realistic, and use up-to-date therapies in order to keep attracting the most modern therapies.

In addition, these therapies – "the antibiotics of the future" in Briggs' view – will help health care systems move from palliative to curative care, and as such will help lift some of the cost burden from the health care systems. But like Kili and Kerby, he acknowledges the challenges of reimbursement and notes the high costs associated with some therapies.

GE profiles itself as an integrator in the cell and gene therapy field, and aims to make the therapies robust, practical and viable. The group wants to help develop turnkey solutions and is building a suite of products that meet end-to-end workflow needs and allow cell manipulations to be done in a closed and safer manner.

During the past year, GE has announced: the acquisition of Biosafe SA, a supplier of integrated cell bioprocessing systems; a collaboration with *Mayo Clinic* – Vitruvian Networks – which provides cloud-based software systems and manufacturing services for cell and gene therapies; and a co-investment with the Canadian government in the BridGE@CCRM Cell Therapy Centre

of Excellence, to promote new technologies for the production of cellular therapies. (Also see "*GE Healthcare Embraces Solutions Role In Growing Regen Med Sector*" - In Vivo, 17 Jan, 2017.)

GE recently added to this with the acquisition of Asymptote Ltd, a specialist in cryochain technology for sensitive cellular therapies. This fills a critical gap in GE Healthcare's end-to-end ecosystem and will enable the industrialization of these therapies.

In Briggs' view, the industry still doesn't have the basic tools and processes in place. "What we have been doing is repurposing equipment, techniques and processes from adjacent industries and from the clinic, and simply trying to apply them to cellular therapy. It's an imperfect approach that won't deliver cost-effective practical solutions. But at least we know where the issues are and can start to deal with them."

> *"The apprentice model needs to give way to a scientific management approach, implying a rethink in the way teams work with each other." – GE's Mark Briggs*

He added, "Fundamentally, there needs to be a rethink in the way we approach this field: the academic or apprentice model, where an individual might see a process through to the end, needs to give way to a scientific management approach, implying a rethink in the way teams work with each other."

To make operations cheaper, the industry needs to move away from cleanrooms, he said. GE is also seeking to exploit the digital era, in simple areas such as connectivity between systems, data logging, data integrity, customization of processes and pulling it together to enable predictions. "We need smarter, more intelligent approaches," said Briggs.

The Pfizer View: Opportunities Must Be Taken In Competitive Health Care Sector

That view is echoed by Pfizer UK managing director Erik Nordkamp, but from the wider viewpoint of entire health care ecosystems. The UK, especially, faces competition from countries that have a "joined-up, holistic approach." Leaving the European Union additionally leaves the UK open to as-yet-unknown risks in the life sciences industries.

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"Creating a 21st century health care system requires all strands of the life sciences industry to work in collaboration and form new partnerships in fields like digital and medtech." –Pfizer UK's Erik Nordkamp

Creating a 21st century health care system requires all strands of the life sciences industry to work in collaboration and to form new partnerships, in fields like digital and medtech, that are truly transformative. The opportunities are there to be taken. But the UK, which in reality has a poor record in new medicines adoption, faces competition from countries that have a networked approach and have factored in future needs and opportunities – countries like Singapore, Israel and Belgium, for instance.

Taking the example of Belgium, Nordkamp observed that a continued and open dialogue between the government and industry is already making for enhanced transparency. Belgium has secured fully 10% of EU pharma R&D expenditure, the Pfizer executive noted. "They are punching far above their weight." Wales is another smaller country that has worked hard to develop effective health care networking. (*See Box, "Health Care Ecosystem Helps Wales Punch Above Its Weight."*)

Can the bigger countries take a leaf out of their book? "The UK needs to get the right people around the table. This doesn't always happen. There needs be a strategic-level dialogue about ecosystems, in order to build trust, and create new partnerships for new ways of working," said Nordkamp.

Science now requires such collaborative, networking approaches. Pfizer's Centers for Therapeutic Innovation (CTI) are examples of new ecosystems that focus on translating new areas of promising science into clinical candidates.

Press The Reset Button

In what should be read as a warning to

Health Care Ecosystem Helps Wales Punch Above Its Weight

Several elements combine to make Wales one of the global health care networking and ecosystem hot spots. The Millennium Centre has become the regular venue for *BioWales*, which has developed into one of the UK's leading life sciences events over the course of 15 annual conferences. The *MediWales* industry forum has played a big part in putting the local devices, diagnostics, digital and biotech industries on the global map. The new Life Sciences Hub Wales (LSHW) serves as the

health care stakeholders, Nordkamp said there is no room for complacency or a half-hearted approach. "The time to get this is right now. We need to press the reset button – the industry is under intense pressure to improve population health, and a holistic approach to health care is needed."

Turning back to the UK once more, Nordkamp said there is a real opportunity for the UK to take advantage of the upcoming opportunities in advanced therapy manufacturing, but he advised less bureaucracy, simplified and faster processes, and wrapping services around offerings to attract new investment.

life sciences' front door to Wales and as a forum for industry, academia, health care professionals, investors, entrepreneurs and inventors. And the £100 million ($130 million) Welsh Life Sciences Fund has so far made 11 investments, while the Life Science Bridging Fund has supported 26 projects during their most vulnerable phases.