The advent of immuno-oncology is currently shaking up the pharma world both clinically and commercially, spearheaded by the successful launch and clinical expansion of checkpoint inhibitors (PD-[L]1 and CTLA-4). Players that did not have the vision (or luck) to develop such an asset in their pipeline are spending big money on competitor’s programmes to partner or to in-license.

Another modality that has created breakthrough designation-like data and has stirred up significant industry, but also public interest, are Chimeric Antigen Receptor T-cells (CAR-T). In spite of front-runner programmes producing early but stellar clinical response data in B-cell malignancies, several open questions regarding their applicability remain to be addressed.

However, investors, both return-oriented and strategic from the biopharma industry understand that they might be dealing with another potential game-changer, driving up valuations of leading players such as Juno Therapeutics or Kite Pharma into the multi-billion dollar range and deals are announced almost on a weekly basis.

Whether these investments will pay-off in a few years depends on many unpredictable factors – so crystal ball gazing or gut feelings often dominate the discussions.

Systematic historical analysis of the clinical and commercial adoption of novel therapeutic modalities can lead to a number of relevant insights for the CAR-T investment case. To do so, Catenion, a boutique consultancy focused on biopharma strategy, has adopted the boom and bust cycle of novel technologies that was popularised in the IT field by the Gartner Group as the ‘hype cycle’, to the adoption of therapeutic modalities and novel scientific approaches in the biopharma world.

Not surprisingly, a similar boom and bust cycle was observed. Even though it should not be perceived as a strictly predictive pattern, the ‘hype cycle’ approach appears to be a valuable tool when discussing the prospects of novel modalities, technologies and approaches, before making investment or partnering decisions.

An interesting example is that of monoclonal antibodies that are hugely successful today (approximately $75 billion global sales in 2014 and forecasted $125 billion by 2020), characteristics of a ‘Plateau of Productivity’ phase in the ‘hype cycle’. Between being ‘hyped’ as ‘magic cancer bullets’ severe toxicities in trials and disappointing sales lead the field into a depression and the first commercially successful antibodies (rituximab and infliximab 1997/98) were launched years after first approved muronomab (1985).

A similar pattern can be observed for almost all newly introduced technologies/drug formats with the caveat that the timelines may be different (Catenion has reviewed 13 technologies so far, data not shown).

The hot field of CAR-T in immuno-oncology

While CAR-Ts have already demonstrated convincing efficacy in a specific setting, the jury is still out on whether they are a ‘game-changer’ for oncology as a whole and can justify current valuations and investor interest.

By Christoph Oldenburg, Dr Markus Thunecke and Dr John Herrmann
provides an excellent case study of an evolving hype cycle, but before exploring this in more detail let us quickly review a few fundamentals.

The use of T-cells to fight cancer is by no means a new concept, but rather the evolutionary development of clinical applications that have been applied and fine-tuned for decades.

Edward Donnall Thomas received his Nobel Prize in 1990 for his work on allogeneic hematopoietic stem cell transplantation (allo-HSCT) dating back to the 1950s. Its application is based on a two-fold rationale: (1) the implant of stem cells into a patient after lympho-depleting chemotherapy, and (2) the anti-leukaemic effect of T-cells that are co-infused with the stem cells. As these T-cells are allogeneic, they can recognise and fight leukaemic cells in the patient. Efficacy is usually a trade-off against safety since the graft-versus-leukaemia effect only the positive side of the medal that is sometimes counterbalanced by regularly-fatal graft-versus-host reactions.

The concept became more sophisticated around the end of the 1980s when Dr Steven Rosenberg and his colleagues at the National Cancer Institute (NCI) experimented with the direct introduction of Tumor Infiltrating Lymphocyte (TILs) isolated directly from a patient’s tumour. Rosenberg’s team expanded TIL's ex vivo then reinfused into the same patient often with recombinant human Interleukin-2 (IL-2), a potent cytokine that modulated T-cell proliferation and cytolytic activation. In principal, this approach, while cumbersome, allowed more specific targeting of patient-unique tumour associated antigens (TAAs), possibly including ‘neoantigens’ expressed exclusively by certain malignant cells.

Around the same time, Dr Eshar Zelig and his colleagues at the Weizmann Institute in Israel raised the T-cell therapy game to the next level. Not only were T-cells chosen for antigen specificity that they had developed naturally, but the specificity was manipulated artificially by introducing antibody variable fragments (scFv) into alpha and beta chains of their T-cell receptors (TCR).

Not much later, around 1993, these constructs were simplified into single-chain antibody fragments that were linked to the zeta-chains of a T-cell receptor – the first reported generation of a functional CAR-T. The lack of efficacy of these cells was overcome by introduction of an additional co-stimulatory domain that improved their activity. These constructs – the second generation – are the same that are in the clinic today (most advanced product is Novartis’ CTL019 with an estimated launch date of 2017).

Despite having been applied in the clinic for many years already, no trials applying CAR-T before circa 2009 have produced truly exciting data. In all these years – until 2009 – no specialised biotech was founded and industry practically neglected the topic. Instead different academic institutions continued to drive the scientific work.

Then, in 2012, newswires announced a newly-formed collaboration between Novartis and Dr Carl June’s research team at the University of Pennsylvania that Novartis proudly announced could revolutionise the treatment of certain cancers. At the time the research collaboration was signed a ‘chimeric antigen receptor’ (CAR) T-cell therapy targeting the CD19 antigen had only been used in three patients with advanced leukaemia.
With that deal, the field exploded, with novel advances and biotech/pharma alliances being announced almost on a weekly basis. Arguably, the hype also heated-up.

The first evidence of media frenzy was a cover story entitled “Will this man cure cancer?” about Novartis CEO Joe Jimenez, appearing in Forbes Magazine in June 2014.

Backed by excited investors, biotechs were built based on programmes of various academic research institutions – such as Juno Therapeutics/SCRI, MSKCC and Fred Hutch, Kite/NCI. Other companies licensed in academic CAR-T programmes – such as Bluebird Bio and Intrexon – and biotechs with relevant capabilities such as gene editing announced and started programmes such as Celllectis and Transposagen. Following this inflow of talent and capital, several large pharma companies – namely Pfizer, Merck KGaA, Celgene and Amgen – also joined the CAR-T partnering arms race.

The resulting CAR-T hype is reflected by the first two capital rounds of Juno summing up to $310 million as well as the IPO valuations and steep increases in market caps of the major CAR-T focused biotechs (Juno, Kite, Celllectis and others) within the past 24 months.

Based on Catenion’s consulting in support of clients, we believe there is no boardroom or executive committee overseeing major oncology business units with R&D efforts that has not grappled with the question of whether or not to invest in this technology. And, if so — ‘how?’ in respect of how rapidly the field is evolving.

Typical for a developing hype is the influx of ‘naïve money’ that drives up valuations. Superheated valuations can often create conditions that increase the risk of over-reactions to any new data (whether supportive or negative) sometimes leading to wild fluctuations in share prices.

Naïve in this context means that some investors will not understand the difference between a genetically modified T-cell product and an antibody and the slogan ‘harnessing the power of the immune system to fight cancer’ that circulates may be enough to convince some that they know enough to spot a winner. Similarly, these investors remain naïve to competitive pressures of similar technologies applied to the same target. For example, many naïve investors are unlikely to be capable of discerning which companies are among the handful of front-runners with CAR-T’s platforms directed to CD19+ B-cell malignancies and which will be both clinically and commercially successful.

Even though the complexity of what Zelig Eshar had first achieved – replacing parts of endogenous

Table 1: Technological developments in different dimensions that will define future waves of products

<table>
<thead>
<tr>
<th>DIMENSION</th>
<th>TODAY</th>
<th>NEAR FUTURE</th>
<th>REMOTE FUTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell type</td>
<td>• Autologous</td>
<td>• Allogeneic (TCR+)</td>
<td>• Universal donor</td>
</tr>
<tr>
<td></td>
<td>• Allogeneic (TCR+)</td>
<td>• Selection for certain ratios of subtypes of CD4/CD8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Haeme tumours: CD19, CD22, NK2DG</td>
<td>• Haeme tumours: CD123, CD44v6</td>
<td>• Neoantigens</td>
</tr>
<tr>
<td></td>
<td>• Solid tumours: L1CAM, EGFRvIII, GD2, c-Met, mesothelin, HER2</td>
<td>• Solid tumours: ROR-1, MUC-16, CD38, CS1, PSMA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Targeting HLA-presented antigens</td>
<td>• Targeting HLA-presented antigens</td>
<td></td>
</tr>
<tr>
<td>Transfection</td>
<td>• Viral (expensive)</td>
<td>• Gene editing</td>
<td>• Viral (cheap)</td>
</tr>
<tr>
<td></td>
<td>• Non-viral (inefficient)</td>
<td>• Non-viral (efficient)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DNA/RNA</td>
<td>• Virus editing</td>
<td></td>
</tr>
<tr>
<td>Construct</td>
<td>• Type and # of costimulatory domains</td>
<td>• Armoured CAR-Ts</td>
<td>• Multi-specific CARs (either-or)</td>
</tr>
<tr>
<td></td>
<td>• Suicide switches</td>
<td>• Safety switches (induce, titratable)</td>
<td>• Bi-specific CAR-Ts (and, not-if)</td>
</tr>
<tr>
<td></td>
<td>• Modular CAR-Ts</td>
<td>• Safety switches (cont. progress)</td>
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</tr>
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TCRs with scFvs of antibodies – was already substantial and laid the foundation even for today’s clinical programmes, this is merely the beginning compared to the complexity of what is envisioned by scientists who are continuously pushing the boundaries of cell engineering.

During the first 25 years of development of this class of products, the major structural change within CAR-T constructs was the introduction of a ‘costimulatory domain’ – that differentiated the first from the second generation. The third generation products incorporating two costimulatory domains have been tested clinically already, but the additional activity has caused lethal toxicities. Currently, it seems that the type and number of costimulatory domains is not the major differentiator for future products.

Instead, the characteristics (and thereby the success) of future CAR-T products will be determined by a large number of factors that each still have to prove their relevance and practicability. In order to keep track of the vast variety of approaches, we have introduced the concept of ‘dimensions’ to group the most important features such as cell type or target antigen (see Table 1).

While CAR-Ts have already demonstrated convicing efficacy in a specific setting, the jury on CAR-T as a game-changer for oncology as a whole – that would justify the current valuations and investor interest – is still out. So far, several trials have created strong positive response data in CD19-positive hematological malignancies, mostly in the true salvage setting – and as a bridge to allo-HSCT-settings. Unprecedented efficacy has been demonstrated in Acute Lymphocytic Leukemia (ALL), and to a lesser degree also in Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin’s Lymphoma (NHL). The initial salvage setting is certainly suitable to demonstrate a strong proof of concept (PoC) in an area of very high unmet need, but it is commercially somewhat limited, as there are only approximately 5,000 incident patients per year in the seven major markets (7MM) and virtually all advanced products target this segment. Commercial success will depend on expansion into earlier lines of therapy, but this requires an acceptable safety profile, as patients still have other therapeutic options. The major safety challenge at the moment is the almost inevitable cytokine storm, an on-target effect of CAR-T. Although this can be managed with anti-IL6, it might still limit application in less advanced and sick patients. Even more interesting both clinically and commercially will be the expansion beyond the CD19 antigen. Is CD19 just a special case or are there other suitable target antigens for CAR-Ts that will produce equally convincing clinical data?

The ultimate challenge and biggest prize for CAR-T lies in the area of solid tumours. Here, in contrast to replaceable B-cells, lineage-specific antigens cannot be targeted, while tumour-specific testis antigens that are truly unique to the tumour are rare. Since the occurrence of a fatal toxicity in a colon cancer patient that was treated with a third generation anti-HER2 CAR-T (on-target, off tissue toxicity due to low expression levels of HER2 in the lung), only very low doses of CAR-T are used in clinical trials that are solely powered for safety (the mantra is ‘dose low, go slow’). Hence, the real verdict is still out on the potential of CAR-T in
solid tumours. Solid tumour targeting is where TCR-engineered T-cells may demonstrate some advantages. TCRs (T-cell receptors), while HLA-restricted, are capable of redirecting T-cells to highly tumour specific neoantigens. Numerous biotechs are advancing platforms to design and evaluate TCR-engineered T-cells.

The evolving field of neoantigens may hold lots of promise both for antibodies but also cellular products such as CAR-T, but this may require even more ‘personalisation’ due to patient-specific expression patterns. Such a degree of personalisation may pose additional logistical challenges for cellular products, and overall this area may be best tackled through easy-to-manufacture vaccines.

A way to overcome the antigen-related safety issues is to engineer control circuitry into CAR-Ts through the activation or silencing of the introduced genes of interest. So called ‘safety switches’ that are in the clinic today already allow clinicians to kill off CAR-T as soon as dangerous toxicities occur. The natural next step will be to induce CAR gene expression \textit{in vivo} and thereby allow for modulation of intensity of activity.

One exciting development will be the introduction of multi-antigen recognition. The aim would not be to simply expand the scope of antigens that a cell will target, but to allow programmed decision-making. That is, activation only if two antigens are recognised or recognition of one but not another. Although this is currently only a concept, and clinical applicability is still far down the road, it would open up a whole new area of tumours that do not present unique antigens.

The immune-suppressive tumour microenvironment, that has rendered many immuno-oncology therapies ineffective, will most likely also dampen the efficacy of CAR-T in solid tumour indications. Also for this challenge, an exciting mix-and-match approach is already tested in the labs of several CAR-T pioneers, eg the introduction of cytokine release functions into CAR-Ts (Juno) – they are termed armoured CAR-Ts or TRUCKs.

The significant complexity of the involved cell engineering and required capabilities are often not covered by a single company. As a consequence, interesting partnership networks of different players – such as oncology biopharma leaders, cell therapy specialist, gene editing pioneers and others – have emerged.

From a scientist’s point of view, these are truly fascinating and have nearly limitless possibilities. For regulatory functions and authorities, on the other hand, these advances pose significant challenges. Already the basic question of what to
define as active pharmaceutical ingredient (API) in such a ‘cyborg cell’ is a matter of much debate, and could lead to some sleepless nights in regulatory agencies.

Imagine what you would have thought 15 years ago – shortly after the tragic death of patient Jesse Gelsinger in a trial for gene therapy – if someone confronted you with the concept of a cell product with a number of genetic mutations in order to enable T-cells to make decisions based on the composition of arbitrary antigens on human tissue ‘armoured’ with a cytokine release function, all of which is modifiable in vivo by administration of an oral drug. “The times they are a-changing!”

Another important stakeholder group, that may not share the unlimited enthusiasm about the prospects of CAR-T, are payers. They will certainly appreciate the clinical benefits for patients (especially in those hard-to-treat salvage settings), but the cost of therapy could easily turn out to be a major issue, if CAR-T therapies were successfully expanded into much broader groups. The costs of goods sold (COGS) has been one of the neck-breakers for the first cellular therapeutic that has been approved in the US, Dendreon’s much-disputed sipuleucel-T, could turn out to be a ‘Sword of Damocles’ for T-cell-based approaches. Of course, the expertise and technologies have improved since 2010 when sipuleucel-T was approved by the FDA and it is no coincidence that Dendreon’s COO, Hans Bishop, is now CEO of Juno, and Novartis acquired Dendreon’s manufacturing plant. But the first estimates point to a COGS problem, and the leader in this field, Paris-based Cellectis, aims at COGS of $10,000 per patient.

Another complication for the manufacturers is that the high envisioned list prices of CAR-T are due to actual COGS (explained by significant process complexity and supply chain), unlike for some other premium-priced drugs that justify their prices only on health-economic grounds. Hence, only limited negotiation headroom for patient access schemes or rebates may be available.

CAR-T is not the only approach that aims at redirecting T-cells to tumour tissues, another competing therapeutic modality are bispecific T-cell engaging antibodies (essentially sharing the same MoA as CAR-T, leading to T-cell redirection). Like other antibodies, bispecifics can be produced much easier and hence cheaper than cellular therapeutics.

Approval of blinatumomab, Amgen’s anti-CD19/CD3 bispecific, by the FDA in December 2014 was based on a Phase II 32% complete response rate (CR) and 31% minimum residual disease negative (MRD-) CRs with a safety profile that was dictated mainly by on-target effects – the typical cytokine storm. Using the early data that has been published from various trials for comparison, CAR-T has a very similar safety profile, but the response rates are much higher – regularly 90-100% CRs and MRD- CRs and also in blinatumomab refractory patients. Even if this quantitative difference was replicated in larger head-to-head studies, many questions regarding the relative merits of the two competing T-cell engaging approaches will still remain:

- Will bispecifics be preferred by clinicians due to the greater convenience and existing experience with the modality?
- Will next generations of bispecifics – the BITE platform that blinatumomab is based on suffers from extremely short half-lives – overcome its limitations and improve efficacy? Is the short half-life, and therefore controllability, preferable over uncontrollable cellular products, especially in indications that can only be targeted via antigens that are shared by healthy tissues?
- How will the suicide switches of cellular therapies change the safety situation and perception by clinicians? Will the termination of activity set in fast enough?
- Will programmable CAR-T that can recognise antigen compositions on cells make it from the concept stage into clinical reality?
- The price question may well have an influence on the clinical application – will potentially more expensive cellular products only be applied in bispecific-refractory patients?

Trying to give answers to most of these questions today would be a speculative exercise.

While bispecific antibodies are the closest competitors to CAR-Ts in terms of MoA, there are several more modalities and approaches in immune oncology such as TCR therapeutics (cellular and non-cellular), vaccination approaches (especially in combination with checkpoint inhibitors) and – underlined by the recent approval of T-Vec – oncolytic viruses.

Coming back to the original question of how to assess the future perspectives of CAR-T in the light of its own scientific maturity as well as the significant competition that we outlined above, it seems that one requires a very large crystal ball to take
into account the various influencing factors. An alternative is to review what can be learned from the adoption of other novel modalities over the last 20 years (our hype cycle analysis).

Technologies usually suffer from setbacks after initial hypes and first-generation products so far have always disappointed before a second-generation roughly 10 years later finally overcome initial limitations and fulfilled the initial promises. Considering all the different factors (as well as the many more that were not explicitly discussed in this paper) we have simplified the option space and created two dominant scenarios for the future of CAR-T.

While approval in the commercially-limited salvage CD19 settings seems very likely based on the demonstrated efficacies, the expansion to broader patient segments will be decisive for commercial success.

In the positive scenario, the use of CAR-T can be expanded to earlier lines of treatment and further to solid tumours quickly as technological advances in additional dimensions that are about to enter the clinics can already overcome the limitations in safety and applicability of the first wave of products already in pivotal trials.

While in the negative scenario use will be confined to the initial segments and it will require the usual time for follow-up products (up to 10 years), the result being a slide into depression in the meantime. CD19 CAR-Ts would be the muronomab-equivalent first approvals – they may bring significant clinical benefit, but they will be of limited impact commercially.

While the learnings from antibodies and other technologies make the latter scenario seem more likely and private investors may be better off sticking to Sir John Templeton’s famous advice: The four most dangerous words in investing are: “this time it’s different”, industry investors have the advantage of ‘riding the hype cycle’. The trick will be to avoid an overcorrection, as soon as first scientific/clinical setbacks scare away the naive investors, such a situation can be turned into a scientific leadership position for companies with unique insights/capabilities and perseverant management.

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