Opportunities and challenges for the cellular immunotherapy sector: a global landscape of clinical trials

Global investments in cellular immunotherapies reflect their curative potential. Our landscape of clinical trials will aid developers, investors, adopters and payers in planning for adoption and implementation along realistic time horizons. Trend data enable stakeholders to adapt their business models and capacity to bring immunotherapies to the clinic. For cancer, trends suggest a shift from cancer vaccines to adoptive cellular transfer, alongside a focus on solid tumors. Academic centers, mainly in the USA, lead in early-phase clinical trials and target identification; but industry involvement has increased fourfold over the past two decades. Trends indicate an increasingly personalized approach to onco-immunology, which raises challenges for cost-effective manufacturing and delivery models. Overcoming these challenges provides opportunities for innovative biotechnology firms.

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Opportunities & challenges for cellular immunotherapy

Public and private sector investments in cancer immunotherapy recognize its curative potential. In 2013, *Science* hailed cancer immunotherapy as its breakthrough of the year [1], echoed by the American Society of Clinical Oncology in 2016 [2]. Reflecting its promise, immunotherapy took a central role in Vice President Joseph Biden's cancer moonshot [3]. In 2015, the largest portion – US\$1.5 billion – of private investment in biomedical biotechnology companies went to immunotherapy and vaccine companies, a 37% increase from 2014 to 2015 [4].

While the first suite of antibody immunotherapies has gained regulatory approvals, the translation of cellular immunotherapies will likely prove as challenging as for other cell therapies. It is timely, therefore, to evaluate translational activity and emerging global trends for cellular immunotherapies

across all approaches. Our objective is to aid developers, investors, clinical adopters and payers in planning for cellular immunotherapies along realistic time horizons. Armed with data on translational trends, stakeholders can adapt their business models and develop the relevant expertise and infrastructure required to bring immunotherapies to the clinic for the benefit of cancer patients.

The development of cancer immunotherapy over the past 20 years provides important lessons about trajectories for clinical translation of basic research [5]. Similar to cell-based regenerative medicine, immunotherapy exemplifies lengthy translational timelines; false starts, successes and the iterative nature of scientific inquiry; the respective roles of academic and industry researchers; the extent to which successful clinical translation requires multidisciplinary collaboration; and the pace of transition from clinical trials lead by academic

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centers to those sponsored by biotechnology and pharmaceutical companies.

Current translational activity is tied to a scientific lineage of immunological studies that span over 100 years [6]. The first monoclonal antibody for cancer, rituximab, was approved by the US FDA in 1997, based on production technologies developed in the 1970s; cytokine therapies became available between 1986 and 2000, 30 years after interferon was discovered, and the first PD-1 and PD-L1 checkpoint inhibitors were approved by the FDA in 2014 and 2016, respectively.

In contrast to antibodies, only one cellular immunotherapy has been approved by the FDA in 2010 and the EMA in 2013 for asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer: Dendreon's (WA, USA) Sipuleucel-T (Provenge) [7]. Three lessons may be learned from Dendreon's experience. First, effectiveness needs to be high to justify a correspondingly high price-tag; Dendreon's randomized, placebo-controlled trial demonstrated a 4.1-month improvement in median survival [8] at a cost of US\$93,000 for the product alone. Second, while regulatory approvals are a necessary first step, positive reimbursement decisions by payers determine commercial success [9]. Third, the logistic complexity of autologous therapies may drive-up costs and negatively impact uptake by clinicians [10]. Dendreon declared Chapter 11 bankruptcy in 2013, and its assets were purchased by Valeant Pharmaceuticals International, Inc. (MO, Canada) for US\$495 million.

Despite the experience of Dendreon, a plethora of cellular immunotherapies are currently in clinical development, using a variety of cell types, including cells of the innate immune system such as natural killer cells, dendritic cells (DCs), and macrophages and adaptive immune system cells such as polyclonal or antigen-specific T cells and lymphokine-activated killer cells [11]. Some approaches promise greater than the marginal improvements over standard of care achieved by many conventional drugs – the median gain in overall survival for new cancer drugs approved between 2002 and 2014 was only 2.5 months [12].

Because of promising clinical trial results, there has been considerable interest in the field of cellular immunotherapy from investors and industry [13], especially adoptive cell transfer (ACT), wherein a patient's circulating lymphocytes are isolated, genetically modified with retroviruses to recognize tumor cells, expanded and transfused into the patient. ACT uses tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor-modified T (CAR-T) cells or T-cell receptor (TCR) engineered T cells to mediate an effector function [14]. Most prominently, in 2014, a US clinical trial

of CAR-T cells in patients with relapsed acute lymphoblastic leukemia (ALL) reported complete remission in 27 out of 30 patients [15]. The CAR-T cells were engineered to express a receptor targeted to the tumor-associated antigen, CD19. Positive results with CAR-T cells have also been observed in relapsed refractory chronic lymphocytic leukemia [16], refractory multiple myeloma [17,18] and pediatric relapsed and refractory B-cell acute lymphocytic leukemia (B-ALL) [19]. Other cell-types have also shown promise in ACT clinical trials, including TCRs for metastatic melanoma [20], and multiple myeloma [21], TILs for metastatic melanoma [22–24], and *ex vivo* expanded T cells targeting viral antigens [25–27] or tumor-associated antigens [28].

With industry as a driver, CAR-T therapies like Novartis' (Basel, Switzerland) Tisagenlecleucel-T (previously CTL019) have received fast-track status from the FDA [29]. However, core challenges for clinical adoption of cellular immunotherapies remain. These include cost, with industry estimates as high as US\$150,000–500,000 per dose [30]. Contributing to the cost is the proposed business model for autologous therapies that requires patient-specific T-cells to be processed in a centralized current Good Manufacturing Practice (cGMP) facility and returned to the cancer center for infusion into the patient [31]. Indeed, Novartis purchased Dendreon's New Jersey manufacturing facility to support its personalized cancer immunotherapy program [10]. Cellular immunotherapy biotech companies, Kite Pharma and Juno Therapeutics, have similarly opened manufacturing facilities. Here we analyze global trends in industry-sponsored cellular immunotherapy clinical trials and discuss challenges for the successful clinical translation of these promising therapies.

Analysis of global trends in cellular immunotherapy clinical trials

We analyzed 1579 interventional clinical trials from global registries that measured at least one of: safety, tolerability or efficacy and modeled the factors that influenced industry sponsorship (See [Supplementary Methods](#), [Supplementary Table 1](#) & [Supplementary Figure 1](#) for our analytical approach). The USA dominated the global immunotherapy clinical trials landscape across 33 countries ([Figure 1](#)); it had six-times the number of trials ($n = 856$) as China ($n = 142$), see [Supplementary Figure 2](#). Japan ($n = 139$) and China lead European countries in number of trials, including the Netherlands ($n = 53$), Germany ($n = 41$) and the UK ($n = 39$). Nevertheless, the dominance of the USA has been challenged by increasing numbers of trials in east Asia and Europe since 2008 ([Figure 2](#)).

Figure 1. Global landscape of adoptive cellular immunotherapy clinical trials.

Figure 2. Percentage of 1560 clinical trials started per year from 1995–2015 by region (determined by location of principal investigator/trial chair).

The first clinical trial in our dataset started in 1976 (NCT00000581). This Phase III trial was sponsored by the National Heart, Lung and Blood Institute and used granulocyte transfusions as a prophylactic to prevent infections in chemotherapy patients. However, our focus is the 1560 (98.8%) clinical trials that started between 1995 and 2015, the last complete year of our study. During this period, the number of clinical trials increased, dominated by early-stage clinical trials sponsored by public research sector institutions (Figure 3). Nevertheless, there were 61 Phase III clinical trials in 17 countries (19 in the USA), and 378 completed trials (all phases) in 22 countries (Supplementary Figure 3). Other trials were active but not recruiting ($n = 328$), recruiting ($n = 550$), not yet recruiting ($n = 125$), suspended ($n = 9$), terminated ($n = 126$) or withdrawn ($n = 44$). In comparison to a more mature area of immunotherapy, 3021 cancer trials registered in clinicaltrials.gov that identified ‘antibody’ as an intervention 10% (310) were in Phase III and 36% (1080) were completed (search date: August 3, 2016).

Trends in conditions targeted by immunotherapies

While the number of clinical trials for cellular immunotherapies increased steadily from 1995 to

2015, the proportion of trials targeting the leukemias and other hematological malignancies has remained relatively constant over time (Figure 4). Since 2006, 45–60% of trials have targeted solid tumors. The most commonly targeted solid tumors were melanoma ($n = 185$) and brain/CNS cancer ($n = 81$), prostate ($n = 75$), lung cancers ($n = 58$), liver ($n = 51$), kidney ($n = 49$) and breast ($n = 48$). 83 trials included multiple topographically distinct solid tumors indications (see Supplementary Figure 4 for the percent of clinical trials from 1995 to 2015 that target specific cancers).

The likelihood of industry sponsorship of cellular immunotherapy clinical trials ($n = 329$) increased from 1995 to a plateau in 2014 (Figure 5). Compared with the reference year of 1999, clinical trials started in 2014 were four-times as likely to register industry sponsorship. Adjusting for other explanatory variables, including start year (Supplementary Table 2), trials in east Asia were more likely to be sponsored by industry ($n = 93$) than trials in the USA ($n = 156$) (odds ratio [OR]: 1.55; $p = 0.012$, see Supplementary Table 2). In east Asia, 70 of 93 industry sponsored trials investigated solid tumors, predominantly esophageal ($n = 8$), liver ($n = 15$) and gastric ($n = 7$) cancer, which have the second, third and sixth highest age-standardized incidence rates, respectively, of all cancers in China [32].

Figure 3. Number of 1560 clinical trials per year from 1995–2015 by type of funding sources.

Industry sponsored trials were less likely to use cells from autologous compared with allogeneic sources (OR: 0.62; $p = 0.030$) but more likely to use T lymphocytes (OR: 8.13; $p = 0.001$) or natural killer cells (OR: 11.18; $p < 0.001$) compared with dendritic cells, the most frequent cell type across all clinical trials (Supplementary Figure 5). Industry sponsored trials targeted solid tumors (61%), hematological cancers (23%), noncancerous diseases (10%), viral reactivation (5%) and either solid or hematological tumors (1%). Peptide pulsed/loaded antigen-presenting cells ($n = 320$) were the most commonly used manipulated cells in clinical trials, whether sponsored by industry or not (Supplementary Figure 6). Compared with this cell type, antigen primed effector cells (OR: 0.08; $p < 0.001$), CAR or TCR modified effector cells (OR: 0.05; $p < 0.001$), cytokine or lymphokine activated effector cells (OR: 0.12; $p = 0.001$) and effector cells selected *ex vivo* (OR: 0.09; $p < 0.001$), were less likely to be used in industry sponsored trials.

Over the past decade, there has been a shift in industry development area. From 2007 to 2012, there was growth in industry-sponsored cellular vaccine trials. Since 2013,

such trials have declined in number, while the number of trials for CAR/TCR transformed effector cells, antigen primed effector cells and effector cells selected *ex vivo* has increased. The rise in number of trials has been most marked for CAR/TCR modified effector cells.

Trends in target validation

Since 2006, 40 novel molecular targets for antigen-presenting cells and 37 new targets for effector cells have entered clinical trials (Figure 6). However, only a minority of novel targets (11 and five, respectively) were being validated in industry-sponsored trials. CD19 has been the dominant target since 2011 for effector cell clinical trials. Targets employed in antigen-presenting cell clinical trials were more numerous, however, PAP, an enzyme produced by the prostate, was the most widely studied target over the same time period (Supplementary Figure 7: top ten targets used in clinical trials for antigen presenting and effector cells).

Discussion of global trends

The historical development of cellular immunotherapy, from experiments that demonstrated proof

Figure 4. Percent of 1560 clinical trials started per year from 1995–2015 by category of condition.

Figure 5 (see facing page). Odds ratio of industry sponsorship compared to other funding sources for 1560 cellular immunotherapy clinical trials started between 1995 and 2015.

Figure 6. Number of novel targets in 1206 clinical trials using antigen-presenting and effector cells started from 2006 to 2015.

of concept to current promising clinical trial results, suggests “that scientists’ creativity and vision can outpace the more prosaic but critical factors necessary for clinical success” [33]. Exciting research into the human immune system and the molecular basis of disease must proceed in lock step with incremental methodological advances that enable clinical applications of cellular immunotherapies [34]. Here we discuss the extent to which the respective strengths of academe and industry are being harnessed to address regulatory and commercial challenges, as well as the needs of patients, health systems and payers for effective and affordable therapies. Our discussion focuses on immuno-oncology, which has dominated clinical research since 1995. We first contextualize the global trends identified by our analysis, predominantly the shift from cancer vaccines to ACT, and then discuss

the challenges and opportunities for successful clinical translation.

Our analysis is the first, to our knowledge, that provides a comprehensive global landscape across cellular immunotherapies in clinical development to understand emerging trends. Similar to other cell therapies [35,36], the majority of clinical trials are early phase, nonindustry funded and sponsored by academic centers. The NIH is the main funder, reflecting the number of trials in the USA. Our data demonstrate that academic researchers play a key role in target identification and validation. These first steps are similar to early drug discovery and commonly fall within the province of academic centers; target identification is based on peer-reviewed literature followed by early-phase trials to demonstrate safety and proof-of-concept in humans [37]. Identification of

appropriate targets has proven to be a major obstacle for treatment of solid tumors with ACT – the most promising form of cancer immunotherapy [38]. Most targets will prove to be neither safe nor efficacious, demonstrating the role of publicly funded, academic center trials in de-risking potential therapies prior to private sector investment. At present, only a handful of cancer antigens can safely be targeted by ACT [14].

Regulatory approvals and late-phase trials reflect the historic dominance of cancer vaccine clinical trials using DCs (1997–2013); many have published results [39], but, with the exception of Provenge, pivotal studies of cancer vaccines have generally failed to demonstrate efficacy, even though three products received regulatory approval in South Korea in 2007 [40]. DC vaccines have proven safe, but their personalized approach requires cells to be manipulated in centralized GMP-compliant facility [39,41]. DC cells, derived from a patient may be activated, loaded with tumor-associated antigens, and/or genetically modified prior to infusion into the patient.

Encouragingly, biotechnology companies in North America, Europe and east Asia are increasing their sponsorship of clinical trials, and many have forged collaborations with leading academic centers (Supplementary Table 2). Such collaborations are a sign of investment in the sector [4] and are a necessary step in the translation process [42]. While academic centers develop new targets and approaches, industry partners contribute expertise in scale-up for clinical delivery [42]. Investment and industry trends, suggest clinical translation is most anticipated for CAR-T cell therapies [13,43,44], first developed at the Weizman Institute of Science in the late 1980s and further advanced through collaborations with researchers at the NIH, National Cancer Institute (MD, USA) [45,46]. Nearly 40 years later, it is anticipated that CD19-specific CARs will receive regulatory approval for B-cell malignancies [47] based on clinical trial data that demonstrate impressive clinical responses in patients with refractory disease that had not responded to current therapies.

Further reflecting the maturation of the field are R&D partnerships with Big Pharma. Of the top 25 pharmaceutical companies by global sales, only Novartis is sponsoring Phase II clinical trials of its CAR-T cell therapy, Tisagenlecleucel-T, in ALL, CLL, diffuse large B-cell lymphoma, multiple myeloma and other non-Hodgkin's lymphomas. Pre-clinical work is also underway in breast, ovarian and pancreatic cancers and mesothelioma. Novartis exclusively licensed the technology from the University of Pennsylvania, where it was developed by researchers at the Perelman School of Medicine. In February

2016, the School opened the Center for Advanced Cellular Therapeutics, in part funded by the licensing deal with Novartis, enabling a continued R&D collaboration for novel CAR-T cell therapies [48]. However, in August 2016, Novartis announced that it would close its Cell and Gene Therapies Unit and integrate some activities into its wider organization, impacting some 120 jobs [49]. It intends to continue in its collaboration with the University of Pennsylvania to develop and seek regulatory approval for Tisagenlecleucel-T, but is additionally working on other noncell-based immuno-oncology approaches whose allogeneic application, mass production and delivery align more closely with its standard pharmaceutical business model.

Other Pharma companies were following Novartis' lead in CAR-T cell R&D, including Merck Serono, Amgen, Pfizer and GlaxoSmithKline, but it remains to be seen if this trend will continue in light of Novartis' actions. These companies have partnered with biotechnology companies Intrexon, Kite Pharmaceuticals, Cellectis and AdaptImmune, respectively. Of these biotechnology companies, only Kite Pharmaceuticals has advanced CAR-T cell therapies into Phase I/II clinical trials, both targeting EGFRvIII and DC19 in patients with refractory aggressive non-Hodgkin's lymphoma. In September 2016, the company reported 47% complete remission for patients with diffuse large B-cell lymphoma in its pivotal Phase II trial, data supportive of FDA approval [50].

In addition to advances in ACT for hematological malignancies, most clinical trials target solid tumors, where the greatest disease burden lies [51]. The most positive clinical outcomes for solid cancers have been seen in melanoma. ACT using TILs has been effective in inducing complete and durable regressions in patients with metastatic melanoma (55% of 194 patients treated at the National Cancer Institute showed an objective response to the therapy) [24]. Lion's lead product candidate is a ready-to-infuse autologous T-cell therapy utilizing TILs for the treatment of patients with stage IV metastatic melanoma and its Phase II study is recruiting (NCT02360579). In June 2016, the company announced US\$100 million in equity financing and it has filed applications with the FDA for additional clinical trials. However, the company will face many of the same challenges as Dendreon in commercializing an autologous therapy based on centralized cGMP manufacture.

Challenges become opportunities: toward solutions

The first challenge is the development of business models. Similar to trends in regenerative medicine,

we found that industry preferentially sponsors clinical trials of allogeneic therapies. Generic, ‘off-the-shelf’ allogeneic therapies (as opposed to the highly personalized donor-derived allogeneic therapies used in allogeneic stem cell transplantation) are more analogous to biopharmaceuticals and have advantages over their autologous counterparts. They have significant cost reductions associated with economies of scale in manufacture, quality control and release of a single batch that can treat multiple patients [52]. In contrast, autologous products have a more complex value chain, based on a service-business model. Clinicians and manufacturers must work closely together to isolate cells from the patient, transport these to a centralized cGMP facility for manipulation and expansion, and then return the engineered cells to the original patient, all within tightly controlled physical environments [52]. Brindley and Mason identify a major translation and gap for autologous therapies “*between discovery and the perceived safe phase in the development cycle to invest – the end of Phase II.*” While investment in cGMP facilities by companies like Novartis and Lion Biotechnologies may signal an acceptance of a new business model for autologous cellular immunotherapies, previous experience suggests that high-cost therapies much demonstrate correspondingly high efficacy [53]. To date, autologous therapies have demonstrated far greater efficacy than generic allogeneic products. This observation is coupled to another translational lesson – the trajectory of cellular immunotherapy from early-stage clinical trials to clinical adoption will require advances in gene engineering technologies and manufacturing systems that are compliant with regulatory requirements for cGMP [54]. The need for technological advances open additional opportunities for innovative biotechnology companies, such as Discovery Genomics, Inc.’s nonviral Sleeping Beauty Transposon System or Editas’ CRISPR/Cas9 gene editing systems [14,55]. Indeed, Juno Therapeutics and Editas have already announced an exclusive collaboration to generate CAR-T cells and TCR therapies [56]. Other researchers in both public and private sectors are working to automate selection and bioprocessing of therapeutic CAR-T cells to reduce labor costs and enhance product consistency and reduce operator errors [57].

Cellular immunotherapy also diverges from the pharmaceutical clinical development paradigms reviewed in Hoos [34]. Health and safety regulatory frameworks were developed for small molecule drugs, and regulatory uncertainty has been a disincentive for Big Pharma investment. Despite the lack of participation by this source of expertise in the regulatory approval process [58], regulatory agencies are proving

open to dialogue and adaptations recommended by the cell therapy clinical research community [53]. Adaptation, however, needs to be balanced against the significant safety concerns that accompany efficacy in ACT.

Cellular immunotherapies do not have the same correlative relationship between toxicity and efficacy as conventional oncology drugs [59]. For example, toxicities of CAR-T cell therapies for malignancies such as ALL include cytokine release syndrome which can be lethal [42]. B-cell aplasia (an on-target but off-cancer toxicity) in the case of CD19 CAR T-cell therapy requires immunoglobulin replacement [42].

However, our analysis demonstrates that clinical trials are increasingly directed to solid tumors, and “*the successful treatment of large numbers of people with solid cancers using [ACT] is unlikely to be straightforward*” [47]. Most solid tumors do not derive from nonessential or replaceable tissues, such as B cells. It may require innovative autologous therapies that target tumor-specific mutations (neoepitopes) to avoid severe on-target, off-tissue toxicities. Recent experience using affinity enhanced TCR modified T cells targeting weakly antigenic public tumor associated antigens can result in significant toxicities due to unforeseen off-target reactivity [60–62]. Our data demonstrate that academic centers are validating new targets in early-phase clinical trials, an approach that is supported by advances in high-throughput sequencing of unique tumor mutations. This approach will likely improve the precision of cellular immunotherapy, but is likely to lead to even more individualized therapeutic approaches since mutated neoepitopes vary between tumor cells and between patients.

It is important to note that toxicity management, requiring intensive care and treatment with expensive biologics, adds to the overall cost of cellular immunotherapies [63]. Unanticipated adverse events can negatively impact clinical development timelines and company valuation. When FDA ordered Juno Therapeutics to suspend the trial of its CAR-T cell, JCAR015 in ALL because three patients died from brain edema, the company lost approximately US\$1 billion [64]. The trial was restarted a week later when the company convinced the FDA that the deaths were caused by cytotoxic drugs used to precondition the patient for immunotherapy [65], however, further deaths prompted the company to halt development of JCAR015 to focus on a second product in its pipeline, JCAR017 for relapsed/refractory diffuse large B-cell lymphoma. Biotechnology-sector media have speculated that the Juno experience may have played a factor in Novartis’ decision to reduce its investments in cellular immunotherapy. Toxicity management therefore opens further opportunities for partnerships between academic

centers and innovative biotechnology companies in overcoming some of the safety issues associated with ACT. For example, Bellicum Pharmaceuticals (TX, USA) is developing molecular switch technology that leads to programmed cell death of CAR-T or similar cells based on modified signaling proteins that may be triggered in a patient by way of infusion with rimiducid [66]. Similarly, Bluebird Bio (MA, USA) is attempting to mute CAR-T cell therapy associated adverse events, such as cytokine release syndrome.

Finally, underpinning the clinical translation of cellular immunotherapy approaches is intellectual property rights associated with products, such as CAR-T cell constructs and vectors, and associated methods. The field has already been marred by litigation over CARs between the University of Pennsylvania and St. Jude's Children's Research Hospital, which was partly driven by their commercial partners, Novartis and Juno Therapeutics, respectively. At its heart was a Material Transfer Agreement between the two academic centers over the use of a lentiviral chimeric T-cell receptor construct originating from St. Jude's and St. Jude's US Patent 8,399,645 title 'Chimeric Receptors with 4-1BB Stimulatory Signaling Domain' [67]. While the litigation was settled in April 2015 in favor of St. Jude's and Juno for a sum of US\$12.25 million plus future milestone payments and royalties, it is evidence of potential for litigation in a complex intellectual property environment, with likely overlapping claims over key aspects of this therapeutic approach. Intellectual property uncertainty serves as a disincentive for investment and may inhibit the development of combinatorial approaches that require the aggregation of intellectual property and which are viewed as the future of oncology.

Conclusion

Cellular immunotherapy represents a burgeoning translational field that promises advanced therapies for cancer patients. Clinical translation is global and increasingly attracting private sector involvement, although the majority of early-stage clinical trials remain in academic centers. Its trajectory has been very similar to cell-based regenerative medicines. The key role for partnerships between public and private sectors is apparent, with biotechnology companies increasingly engaged in ACT for solid tumors. Trends suggest that academic centers continue in their traditional role of identification of targets with research into tumor neoepitopes. This trend presages an increasingly personalized approach to onco-immunology, which compounds concerns over the field's manufacturing and delivery models and cost-effectiveness. Advances in more efficient methods for genetic manipulation of

immune cells, bioprocessing and the management of adverse events will address the concerns of regulators and potential investors and provide opportunities for innovative biotechnology companies.

Future perspective

Public and private sector investments in cancer immunotherapy research and development recognize its curative potential. Trends indicate that many of the current challenges facing the field will be addressed in 5–10 years. The key role for collaborations between academic centers and the private sector is apparent, with biotechnology companies increasingly engaged in adoptive cell therapy for solid tumors. Trends suggest that academic centers continue in their traditional role of identification of targets with research into tumor neoepitopes. This trend presages an increasingly personalized approach to onco-immunology, which compounds concerns over the field's manufacturing and delivery models and cost-effectiveness. Advances in more efficient methods for genetic manipulation of immune cells, bioprocessing and the management of adverse events will address the concerns of regulators and potential investors and provide opportunities for innovative biotechnology companies.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/rme-2017-0031

Author contributions

K Bonter, JS Delisle, S Lachance and T Bubela designed the research questions, and, with Z Breckenridge, developed the final clinical trial coding frame. K Bonter and Z Breckenridge coded the clinical trials. T Bubela and K Bonter (with assistance from a consulting biostatistician) analyzed the data. JS Delisle and S Lachance, assisted in data interpretation. T Bubela drafted the manuscript and all authors provided input and approved the final version for publication.

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Executive summary

Opportunities & challenges for cellular immunotherapy

- Public and private sector investments in cancer immunotherapy research and development recognize its curative potential. Clinical translation in this field will likely prove as challenging as for other cell therapies.
- We analyze global trends in industry-sponsored cellular immunotherapy clinical trials and discuss challenges for the successful clinical translation of these promising therapies.

Analysis of global trends in cellular immunotherapy clinical trials

- We analyzed 1579 interventional clinical trials from global registries that measured at least one of: safety, tolerability, or efficacy and modeled the factors that influenced industry sponsorship.
- The USA dominated the global immunotherapy clinical trials landscape across 33 countries. The number of clinical trials for cellular immunotherapies increased steadily from 1995 to 2015. Since 2006, 45–60% of trials have targeted solid tumors.
- The likelihood of industry sponsorship of cellular immunotherapy clinical trials ($n = 329$) increased from 1995 to a plateau in 2014. Clinical trials started in 2014 were four-times as likely to register industry sponsorship than those started in 1999. Trials in east Asia were more likely to be sponsored by industry ($n = 93$) than trials in the USA ($n = 156$).
- Over the past decade, there has been a shift in industry development area. Since 2013, cellular vaccine trials have declined in number, while the number of trials for chimeric antigen receptor (CAR)/T-cell receptor (TCR) transformed effector cells, antigen primed effector cells, and effector cells selected *ex vivo* has increased. The rise in number of trials has been most marked for CAR/TCR modified effector cells.

Discussion of global trends

- We discuss the extent to which the respective strengths of academe and industry are being harnessed to address regulatory and commercial challenges as well as the needs of patients, health systems and payers for effective and affordable therapies.
- Similar to other cell therapies, the majority of clinical trials are early phase, nonindustry funded and sponsored by academic centers. The NIH is the main funder, reflecting the number of trials in the USA. Academic researchers play a key role in target identification and validation.
- Academic-industry collaborations are a sign of investment in the sector and are a necessary step in the translation process. While academic centers develop new targets and approaches, industry partners contribute expertise in scale-up for clinical delivery. Investment and industry trends suggest clinical translation is most anticipated for CAR-T cell therapies.

Challenges become opportunities: toward solutions

- The first challenge is the development of business models. Similar to trends in regenerative medicine, industry sponsors clinical trials of allogeneic over autologous therapies.
- The need for technological advances in cell processing and manufacturing and toxicity management open opportunities for innovative biotechnology companies.

Conclusion

- Cellular immunotherapy represents a burgeoning translational field that promises advanced therapies for cancer patients. Clinical translation is global and increasingly attracting private sector involvement, although the majority of early-stage clinical trials remain in academic centers.
- Advances in more efficient methods for genetic manipulation of immune cells, bioprocessing and the management of adverse events will address the concerns of regulators and potential investors and provide opportunities for innovative biotechnology companies.

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