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ISCT Committee Paper

Cell and gene therapy investment: evolution and future outlook on investor perspectives

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ABSTRACT

Background aims: To better understand the attitudes and behaviors of investors involved in funding cell and gene therapy (CGT) businesses, the Business Development and Finance) subcommittee of International Society for Cell and Gene Therapy, in collaboration with Truist Securities, conducted a broad survey of the investment community in late 2021.
Methods: This survey follows a similar study that this group executed in 2018, and the longitudinal comparisons between the two time periods provide insights into how investor behavior in the CGT field has evolved.
Results: The vast majority of investor respondents are specialist biotech investors who are primarily active in deploying capital in North America and Europe. There was a notable increase in the proportion of investors actively deploying capital in China and Japan between 2018 and 2021. The percentage of respondents' portfolios dedicated to CGT companies has also increased in this period, reflecting a noteworthy trend in the therapeutic landscape.
Conclusions: Clinically significant data remain the dominant force behind investment decisions, whereas competition from other drug modalities has now emerged as the most-cited barrier to making a CGT investment, eclipsing safety concerns as the most significant barrier to investment in 2018. Concerns around manufacturing and scale-up have also increased in prominence amongst the investment community. Gene-editing technologies are attracting investors as the most compelling new CGT technology. This survey also revealed that most investors expect to increase their level of investment in allogeneic technologies relative to autologous products in the coming years.

Introduction

The International Society for Cell and Gene Therapy (ISCT) is a global professional society dedicated to the translational development of cell and gene therapies (CGTs) for patients with significant unmet medical needs. The membership base of ISCT is primarily composed of academic scientists and clinicians, government stakeholders, biopharmaceutical industry representatives from smaller biotechnology companies and larger pharmaceutical companies and tools and technology providers that help enable CGT product development. In 2018, ISCT introduced the Investigators to Investors program, commonly referred to as "i to i," to foster greater involvement of the investment community as a new stakeholder for ISCT.

Recognizing the significant implications for the progress of the field of the interplay between investors and investigators, ISCT's Business Development and Finance (BD&F) subcommittee conducted, in 2018, an initial survey to query investors on their current perceptions and behaviors regarding CGT product development companies and technologies. The outcomes of the 2018 survey were subsequently published in the journal *Cytotherapy* [1], providing valuable insights into which areas within the field of CGT investors were most interested in deploying capital and what they perceived to be the most significant barriers to investing in a CGT opportunity. Empowered by these insights, ISCT's BD&F subcommittee crafted, through the "i to i"

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program, educational content aimed at deepening investors' comprehension of the intricate landscape of CGT, with the ultimate goal of bolstering investments in CGT-focused organizations.

Building on previous initiatives, the "i to i" program continued its commitment to understanding investor behaviors and perceptions within the realm of CGT companies, culminating in another survey conducted in late 2021 in collaboration with Truist Securities. The findings of this survey, along with their comparison with those of the 2018 survey, are detailed in this article and reveal a shift in investors' priorities and concerns from 2018. These insights into the evolving behavior of CGT investors offer a unique opportunity for investigators to leverage this information to their advantage, allowing them to enhance their interactions with investors when developing or seeking funding and support for their projects.

Methodology

The design and implementation of the survey was a joint effort between ISCT and Truist Securities. The survey consisted of 14 questions, including multiple choice and open response, and was streamlined to take 5–7 minutes to complete. The survey was constructed and hosted on SurveyMonkey, enabling responses to be gathered without duplicity and, importantly, enabling the data to be anonymized. Given the sensitivity of exposing specific positions and strategies, response anonymity was key in encouraging investor participation.

A key success factor for the previous survey was the incentive provided to participants, and this was a strategy incorporated in this iteration. Similarly, respondents received exclusive access to a live webinar where a panel of experts serving on ISCT's leadership team discussed topics of interest in CGT.

The survey was published to the Truist Securities health care research distribution list, which at the time included more than 4500 e-mail addresses. Three caveats need to be appreciated with this distribution: (i) This number includes investors, corporates and Truist Securities employees, and although it is more heavily weighted towards investors, some e-mail addresses may be redundant or obsolete; (ii) the rate at which a single e-mail is opened is low, typically less than 20% and (iii) investors can be reluctant to share insights to their investments or prohibited to do so by their respective company policies. Taking these three caveats together, the response rate to an investor survey can appear low. In our experience, a sample of 100 or more responses is generally quite robust.

Recipients were primarily based in North America, in contrast to the previous iteration of the survey, where responders were mixed between the European Union and the USA. We believe this is because the Truist Securities recipient list had more extensive North American representation, given the bank's geographic focus. Responses were collected over 2 weeks ending June 29, 2021, coinciding with the webinar. A new validation layer for responder authenticity and survey completeness was an essential enhancement to this survey iteration. Responders were required at the end of the survey to provide a corporate e-mail address to receive the invitation to join the webinar. These e-mail addresses were cross-referenced with known investor domain names before anonymization. Further, each survey question required an answer, and only feedback from responders completing all questions was included in the analysis. Although this impacted the number of responses collected, the quality and completeness of the answers were improved.

Respondent Demographics

An increase in specialist investor representation

In total, 110 individual investors completed the survey; 90% self-identified as specialist health care investors, whereas 8% of respondents were generalist investors, who tend to be more interested in broader markets and evaluate investments across a wide range of industries (Figure 1). This distribution denotes a 12% increase in the relative representation of specialist health care investors from the 2018 survey. The minor reduction in generalist investor participation potentially reflects a decrease in focus on the biotechnology industry at-large for these investors at the time of the 2021 survey rather than being specific for CGT companies.

Specialist health care investors tend to be scientifically savvy, with many having degrees in medicine or life sciences. It is unsurprising to us that both the 2018 and 2021 surveys attracted predominantly specialist health care investors, given that the more technical nature of CGT is more likely to attract this investor phenotype.

Responder population is more heavily tilted toward investment in public companies

Although 95% of investors who responded to the survey invest in public companies, only 58% invest in private companies (Figure 2).

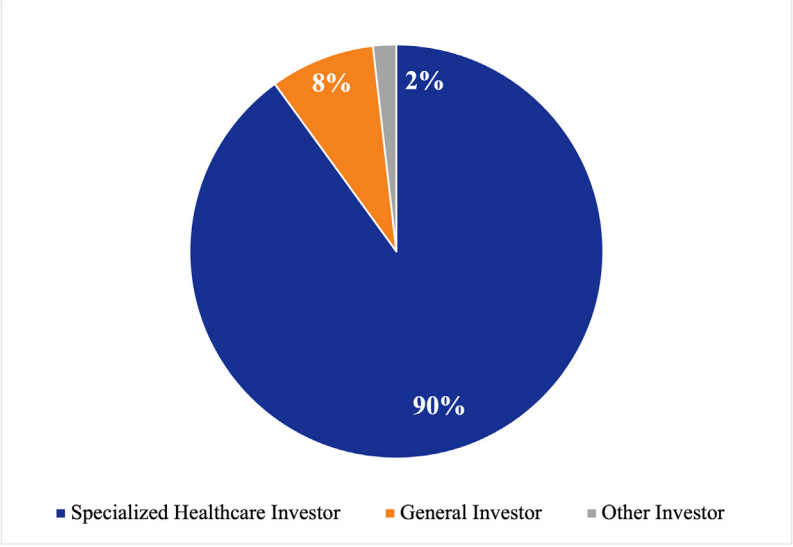

Figure 1. Survey respondent demographics by investor type.

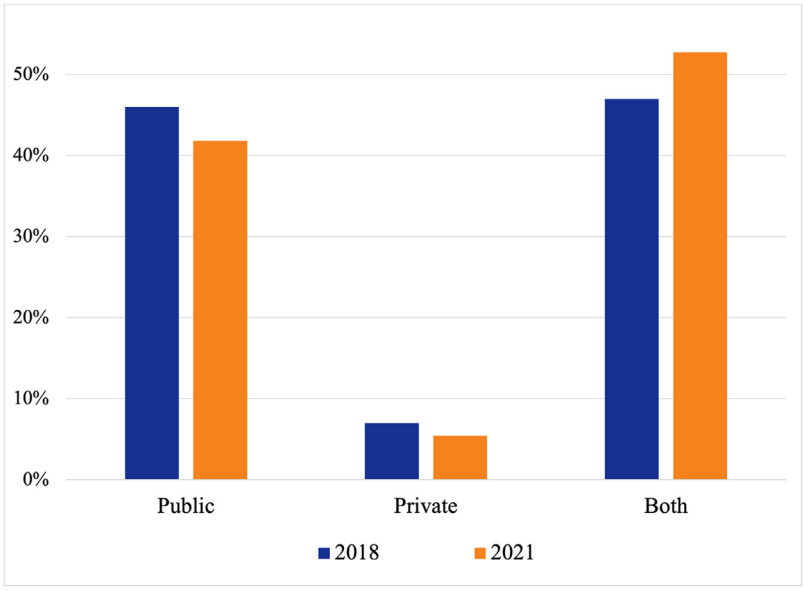

Figure 2. Survey respondent demographics based on investment focus on public and/or private companies.

Only 5% of those surveyed invest exclusively in private companies. These preferences are similar to those seen in 2018, when public and private investment accounted for 93% and 54% of answers, respectively. The skew toward public-focused funds likely reflects the channels used to distribute the survey to the investment community, namely Bloomberg and Truist Securities, which feature more hedge funds and mutual funds as clients. Investors from venture capital firms dedicated to earlier-stage companies are less likely to access market content from these information sources.

Increasing geographic diversity of investor respondents

As was the case in 2018, North America (97%) and Europe (76%) were the geographies in which responders were most likely to invest capital (Figure 3). Of note, the investors who were surveyed in 2021 expressed significant growth in investment in other territories relative to the previous iteration of the survey, with Japan (32% representation, 87% increase from 2018) and China (37% representation, 78% increase from 2018) experiencing the most significant growth. This survey also captured more enthusiasm for investment in Australian (22%), Asian (14%) and South American (9%) companies, which reflects the worldwide expansion of the biotechnology field and the willingness of investors to explore opportunities outside of their home geography.

Despite the significant investment focus in North America and Europe, it does not precisely correlate with the share of CGT companies in these regions, which accounted for just 49% and 18% of all the gene, cell and tissue-based therapeutic developers in 2021 [2], respectively, as many responders are likely to be active in multiple geographies. This gap may also explain the greater company valuations seen in North America and, to some extent, Europe and why many startups from other less-funded geographies choose to relocate in search of better access to investor capital. The growth in the field

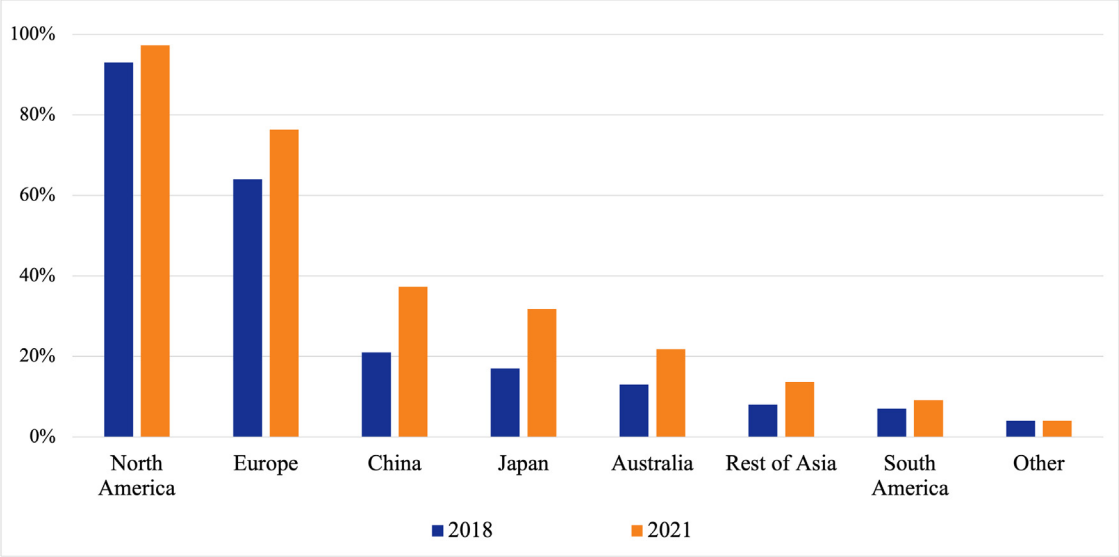

Figure 3. Geographies where surveyed investors deploy capital.

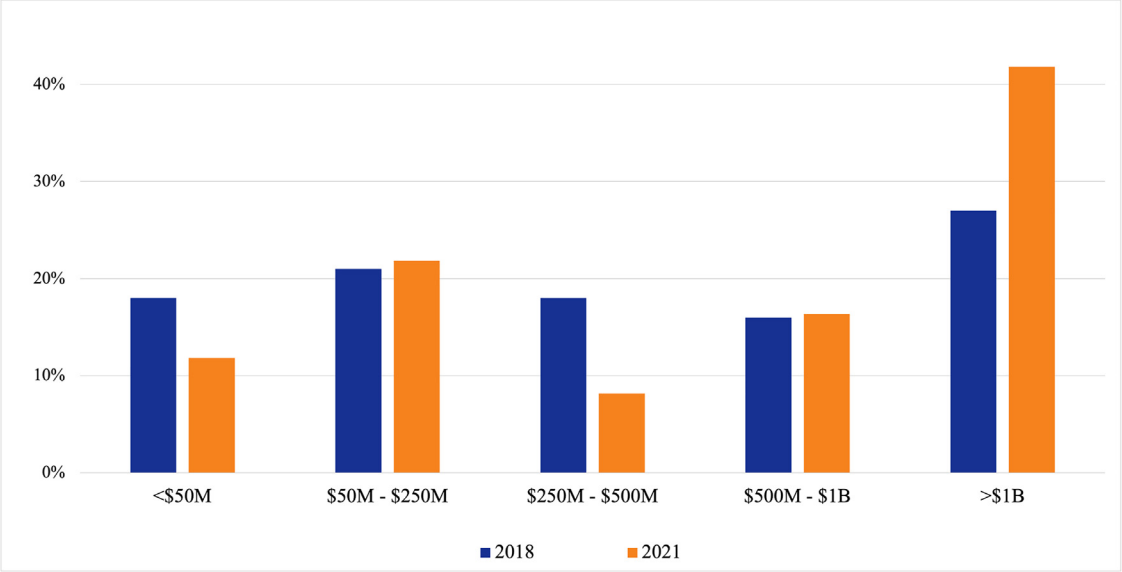

Figure 4. Health care fund size of survey respondents.

is global, but the respondents' investment in this survey is still biased toward North America and Europe.

Increasing size of investment funds involved in capitalizing health care innovation

The distribution of the size of health care funds also shifted notably in the 3 years between surveys. In 2018, funds were more evenly spread across small (<$50 million), mid-sized ($50-$500 million) and large funds (>$500 million), while in 2021, the proportion of small- and mid-sized funds decreased in favor of larger ones (Figure 4). Remarkably, funds exceeding $1 billion in assets increased by 55%. This significant increase in the asset base for a broad spectrum of health care funds suggests that many funds successfully raised fresh capital in this period while likely also generating positive returns on their health care portfolios. Of course, the onset of the global COVID-19 pandemic occurred in this period, which did attract record amounts of capital to the biotechnology field during 2020 and early 2021 [2].

Allocation of CGT investments within broader health care portfolios

One of the most important goals of this study was to understand the current level of CGT investment and how it may have changed

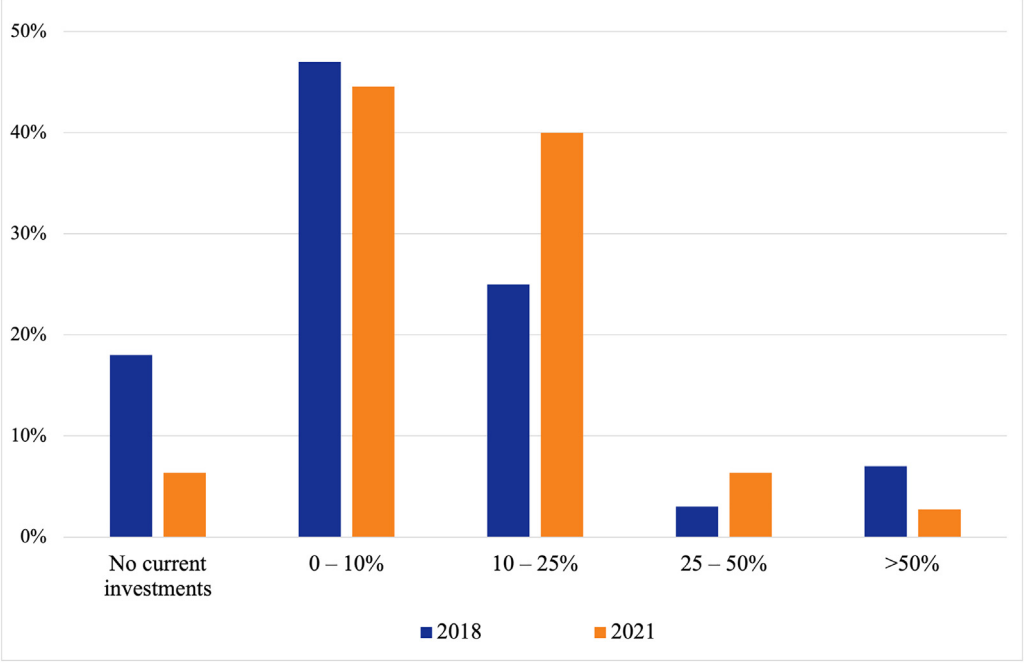

Figure 5. Respondents' level of investment in CGT companies as a percentage of their total health care portfolio.

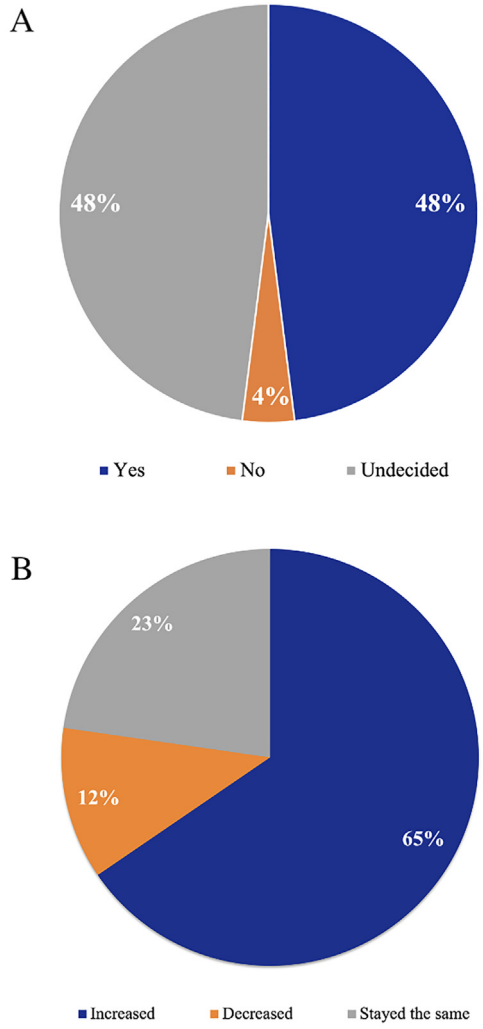

Figure 6. (A) Share of 2018-survey respondents who planned to increase their investment in CGT after 2018. (B) Change in 2021-survey respondents' level of investment in CGT in the 2019-2021 period.

since 2018. In this regard, the sharp decline, from 18% to 6%, in the share of investors not currently investing in CGT companies may be one of the most valuable facts confirmed by this survey regarding demographic data (Figure 5). Although a similar percentage of investors had between 0 and 10% of their capital allocated to CGT companies, 40% of respondents reported CGT exposure ranging from 10% to 25% of their portfolios, a 60% increase in the last 3 years. Very few funds have more than 25% of their portfolios invested in CGT companies in either survey iteration. However, this should not be surprising, given the relative immaturity of this field compared with more traditional drug modalities. CGT now represents a significant and growing proportion of the investment portfolios of the responders to this survey.

Investment Decision Factors

Future CGT investment was larger than predicted in 2018

When investors were asked in 2018 if they planned to increase their level of investment in CGT companies in the following 2 years, less than half of them replied yes (Figure 6a). Interestingly, this number was underestimated, as 66% of the 2021 respondents declared that their level of investment in CGT companies increased relative to total health care investment in the last 2 years (Figure 6b). It appears

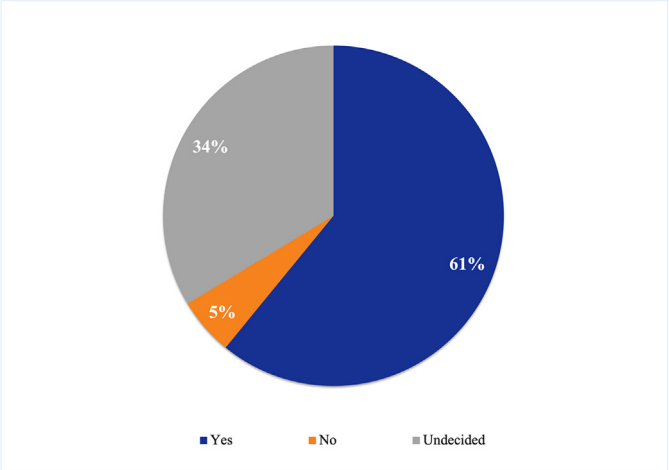

Figure 7. Share of 2021 survey respondents who expect to increase their investment in CGT after 2021.

that the landscape of opportunities to invest in CGT companies was more attractive to health care investors than they had initially anticipated several years ago.

Given ISCT's interest in continuing to analyze the sector's growth trajectory, the same question posed in 2018 about respondents' CGT investment plans in the future was included in the 2021 survey. Expansion of the field is likely to persist, as 61% of investors expect their investment level in CGT technologies will increase in the next 3 years (Figure 7). Notably, 75% of investors who reported their investment in CGT had risen in the last 2 years believed their investment in the area would continue to increase. This favorable momentum highlights the confidence in CGT's investment potential, especially among funds that have already raised their exposure in this field.

Gene-editing technologies are compelling for investors

The survey requested investors to select and rank the top three CGT technologies they considered most attractive. Among the listed choices, gene-editing technologies (18%), induced pluripotent stem cell–derived cell therapies (16%) and engineered natural killer cells (14%) received the greatest percentage of first-place votes from investors as the most compelling technology to influence their level of CGT investment positively (Figure 8a). When aggregating votes for technologies selected in the top three, the same technologies were favored, albeit in a slightly different order (Figure 8b).

Gene-editing technologies have notably captured the investment community's attention in recent years, which is reflected in the amount of capital raised by these companies. Natural killer cells have also emerged as an appealing alternative to T-cell–based cell therapies, with several exciting programs generating early-stage clinical data. It is also worth noting the technologies investors find least compelling, with *ex vivo* gene-modified cell therapies ranking at the bottom of the list of available choices. This may reflect the commercial challenges these products face, with therapies such as Strimvelis and Zynteglo achieving regulatory approval but still needing to produce superior commercial traction to remain viable products for their sponsors. A lower level of enthusiasm for chimeric antigen receptor (CAR-T) products for solid tumors may reflect the limited clinical success achieved in recent years for these programs.

Autologous versus allogeneic cell therapies

In both the 2018 and 2021 iterations of the investor survey, it was a primary goal to understand the investment community's relative

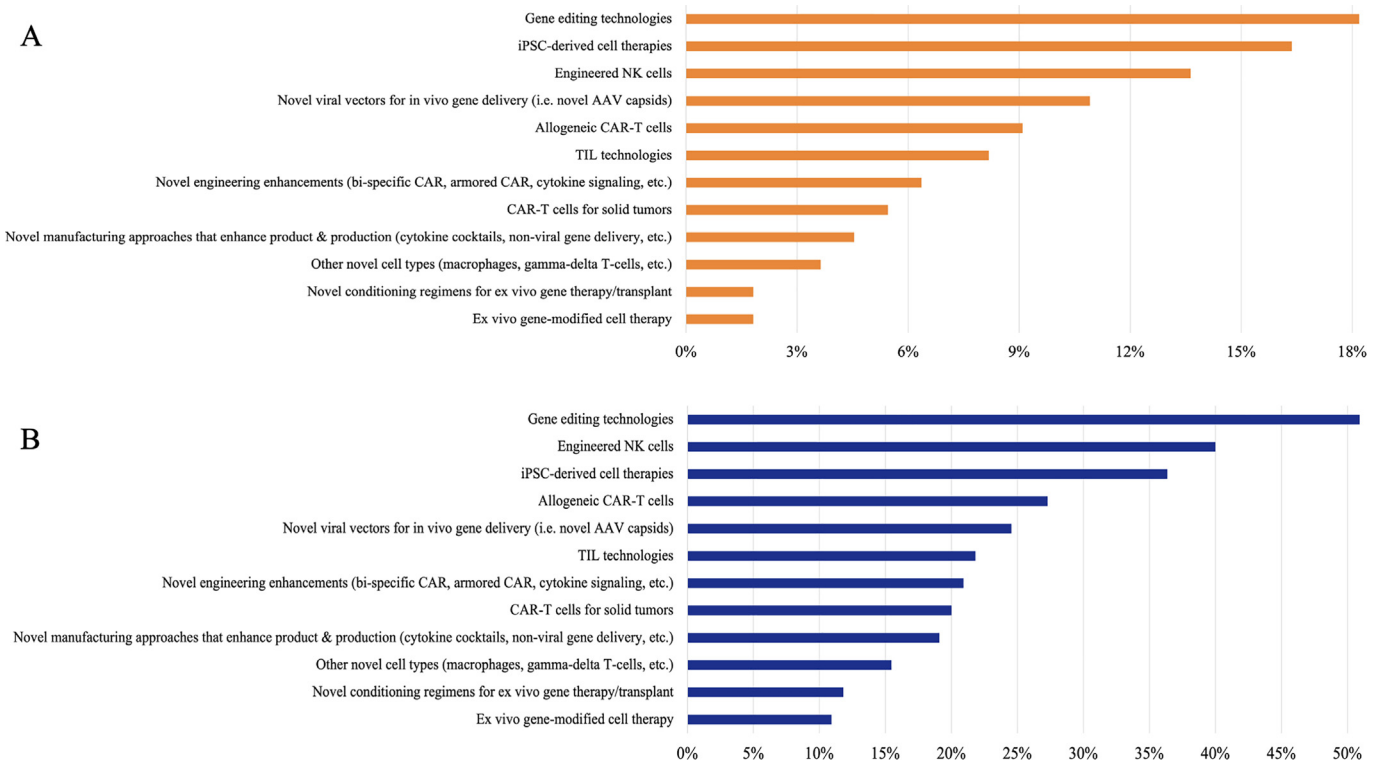

Figure 8. (A) Rank of technologies selected as first-place for most compelling to increase respondents' investment in CGT. (B) Rank of technologies selected in the top 3 for most compelling to increase respondents' investment in CGT. TIL, Tumor-infiltrating lymphocytes.

appetite for autologous versus allogeneic CGT products. The complexity and high cost of manufacturing patient-derived products have manifested in commercial challenges for recently approved cell therapies, and thus, the BD&F subcommittee of ISCT sought to ascertain the balance between the efficacy of autologous products compared with the benefits of cost and logistics of allogeneic products in terms of investor perception. This survey helped unveil that clinical data reported in the preceding two years had increased the perceived value of allogeneic cell therapies for most investors (Figure 9). In total, 23% of investors believed that the value of allogeneic products had decreased in this period, whereas 18% found the value unchanged.

A majority of investors (54%) also affirmed that their appetite for allogeneic cell therapies would likely increase over autologous approaches in the next 3 years (Figure 10). Only 7% indicated they were likely to increase their exposure to autologous cell therapy relative to allogeneic. In comparison, 39% expect the relative balance of their investments between the two to remain the same. These results indicate consistency with the preliminary questions regarding the most compelling CGT technologies, all of which essentially represent allogeneic product strategies. Despite autologous cell therapies' more substantiated clinical efficacy, the significant ongoing work, early clinical promise, and innovative potential of allogeneic products are capturing a greater share of investor attention.

Clinically significant data remain the top driver for CGT investment

When asked to select and rank the top three factors that were most likely to influence their decision- making process for investing in a CGT company, clinically significant data emerged as the most prevalent factor, consistent with the results from the 2018 survey. Nearly 60% of respondents chose "Clinically Significant Data" as their top choice (Figure 11a), and more than 75% selected this factor among their top three influences (Figure 11b). "Platform Technology" was the only other factor chosen by more than 10% of investors as the most influential company characteristic. These results highlight that impactful clinical data remains the driving force behind most investors' interest in any particular CGT company.

There were several notable changes in the most prominent factors influencing investment decisions between the 2018 and

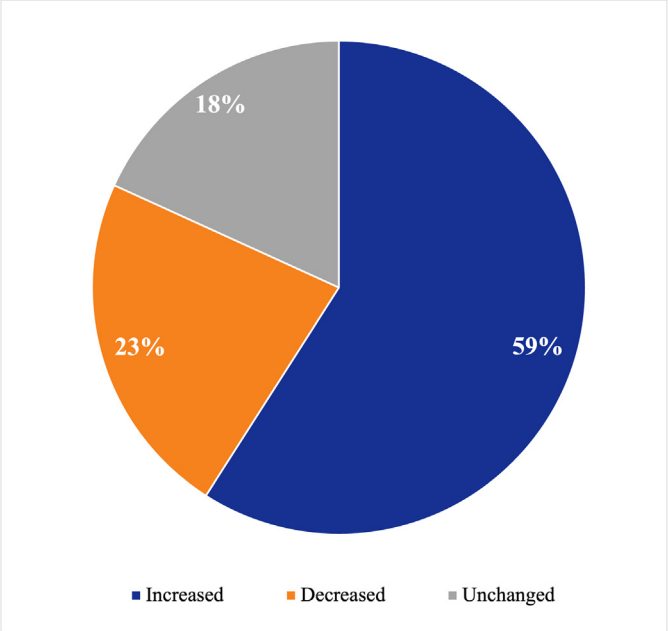

Figure 9. Impact of clinical data on investors' perception of the value of allogeneic cell therapies in the last 2 years.

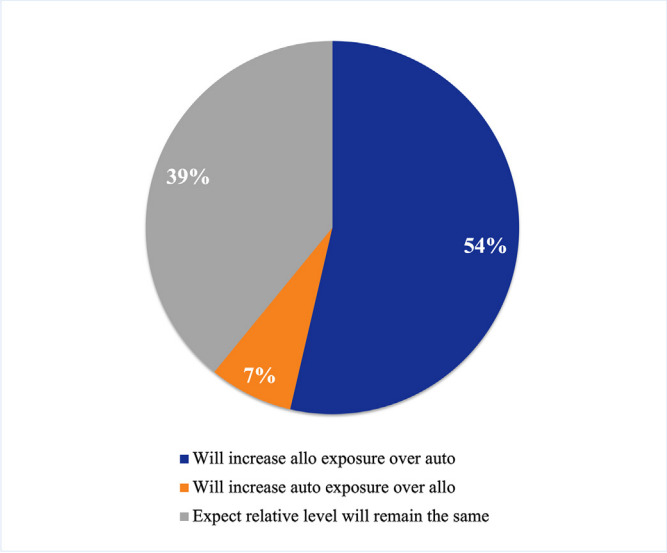

Figure 10. Expected change in the level of investment in allogeneic cell therapies versus autologous cell therapies in the next 3 years.

2021 surveys. "Manufacturing and Scale-up" was only chosen as a top-three factor by 37% of respondents in 2018. That proportion increased to 48% in 2021, suggesting that awareness of the challenges in cGMP manufacturing of CGT products is rising within the investment community. The number of investors selecting "Management Experience" as a major influence also increased significantly in the 3 years between surveys, rising from 17% to 40%. Interestingly, "Company Valuation" became a less-critical selection factor for investors between 2018 and 2021, dropping from 33% of top-three selections down to 19%. Taking all of these changes together, it appears that investors became more focused on the overall quality of the company as an investment and less focused on simply finding the best price.

Barriers to investing in a CGT company

Investors also were asked to select and rank the top-three factors that would dissuade them from investing in a CGT opportunity. The available choices remained consistent between the 2018 and 2021 surveys, allowing for a longitudinal evaluation of investors' perceived challenges in this space. In the 2021 survey, the most frequently selected barrier to investment was "Competition from other drug modalities," featuring in the top-three selections for 66% of respondents (Figure 12). "Manufacturing/scale-up challenges" and "Clinical development complexity" were close behind, garnering top-three votes from 63% and 60% of investors, respectively. In 2018 "Safety concerns" was the most frequently cited barrier to investment. This factor dropped to fourth place in the 2021 survey, indicating that investors are becoming more comfortable with the safety profiles of CGT products as the field gains more clinical and commercial experience. A notable example is the management of cytokine release syndrome and neurotoxicity of CAR-T products.

The significant increase in the number of investors highlighting competition from other drug modalities as an investment barrier is an impactful data point when comparing the two time periods. Bispecific antibodies have emerged as a primary challenger to many cell therapy products, particularly for treating hematological malignancies. This emergence will have to be addressed when CGT product developers are looking to raise equity capital in the coming years. More success in late-stage development for allogeneic cell therapies may help to address this concern, as the perceived advantages of bispecific antibodies as lower-cost, off-the-shelf products would be mitigated in the case of allogeneic cells.

Recommendations to Investigators

In this study, the BD&F group aimed to understand how the attitudes and behaviors of investors in the CGT field have evolved since the previous survey in 2018. By comparing the results of the two surveys, we identified substantial changes that inform how investigators should interact with investors and how this information might be used to increase access to investor capital.

First, the survey reveals important insights into investor demographics and their impact on the field. There has been an increase in the proportion of investors actively deploying capital in China and Japan, reflecting the global expansion of the biotechnology field. There are several private equity and venture capital firms that are located in traditional geographies (USA, European Union) but invest in nontraditional ones, and vice versa. Investigators should consider engaging with investors in other regions to expand their network and increase their chances of getting funded. Furthermore, the growing size of funds involved in health care innovation and the larger share of capital being deployed to CGT suggest increased investment opportunities for CGT companies. Many funds invest in CGT companies targeting certain therapeutic areas or of a certain level of maturity. Investigators should identify the optimal investment opportunity that matches their business strategy, therapeutic area, and level of development to increase their chances of securing funding and support for their projects.

Another notable finding is the increasing preference for allogeneic cell therapies. The perceived value of allogeneic products has increased from 2018 to 2021, and investors expect to intensify their investment in allogeneic technologies relative to autologous products in the coming years. Nonetheless, recent safety concerns regarding allogeneic CAR-T cell therapy products and the action of the Food and Drug Administration to halt trials indicate that many of the inherent challenges of some allogeneic therapies have not been fully addressed by developers. Investigators advancing allogeneic cell therapy pipelines should consider these pitfalls when interacting with investors. Investigators should clearly convey to investors how they are addressing safety as much as the manufacturing and scale-up challenges of their allogeneic products. Investigators developing autologous CGT products must convince potential investors that they have effective solutions for concerns around scalable manufacturing and reimbursement strategies.

The perceived barriers to investing in CGT companies have shifted since the previous survey. Although safety concerns were the most frequently cited barrier in 2018, competition from other drug modalities emerged as the most significant hurdle in the 2021 survey. This shift suggests that investors are becoming more comfortable with the safety profiles of CGT products as the field gains more clinical and commercial experience. Investigators should clearly articulate how their CGT product or platform generates a competitive advantage against other drug modalities in order to address the most frequently cited barrier to investment.

One way of demonstrating superiority over the competition is by backing claims with clinically significant data. Many companies fail to replicate successful preclinical results in human studies, which may be why clinically significant data remains the most influential factor driving investment decisions. Investors heavily rely on robust clinical evidence supporting the efficacy and safety of CGT products. Investigators should focus as much available resource as possible on generating high-quality clinical data to gain investor confidence and support for subsequent product development efforts.

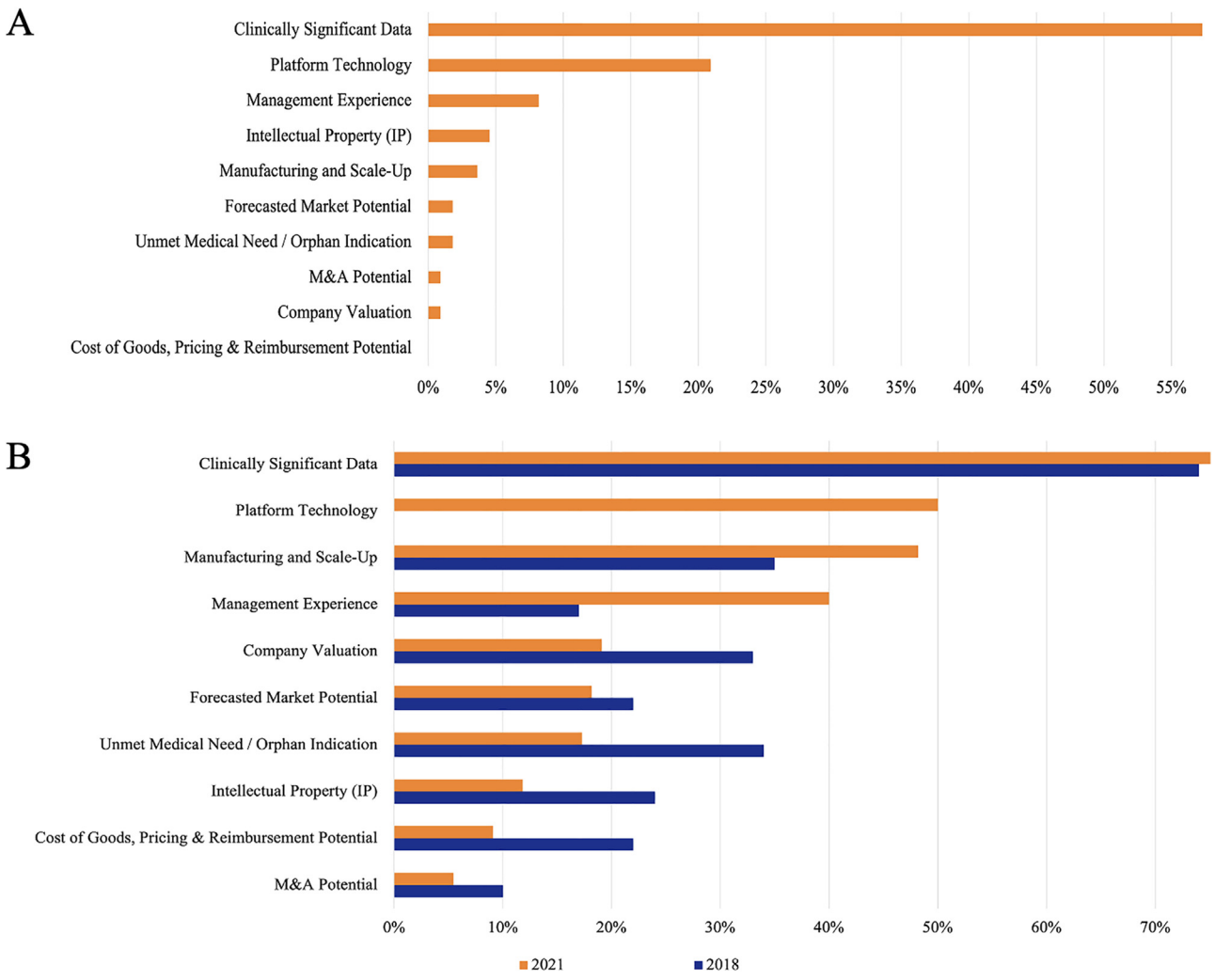

Figure 11. (A) Rank of factors selected as first-place for most influential in decision-making to invest in a CGT product development opportunity. (B) Rank of factors selected in the top three for most influential in decision-making to invest in a CGT product development opportunity. M&A, mergers and acquisitions.

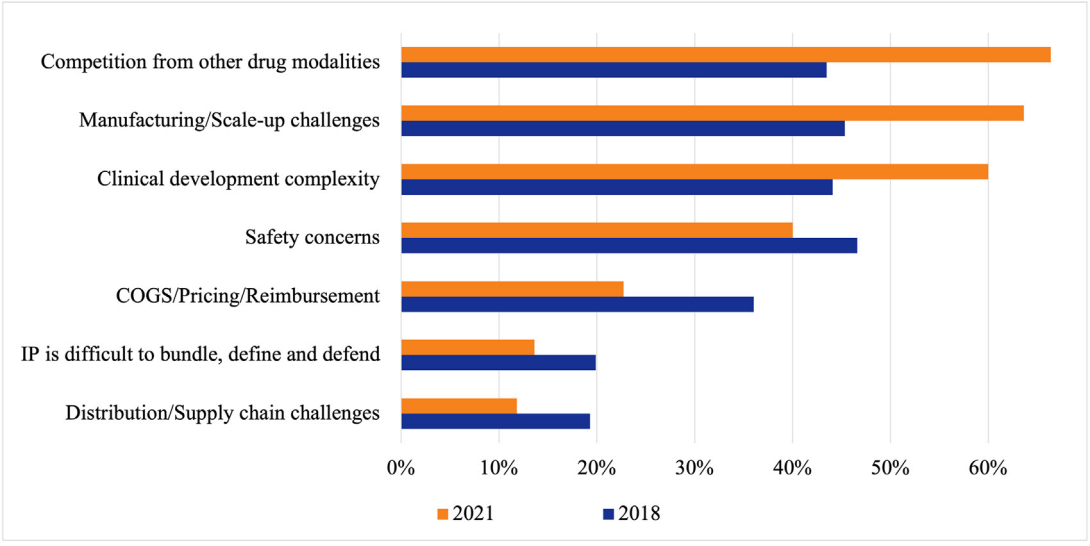

Figure 12. Rank of factors selected in the top three for greatest barriers in decision-making to invest in a CGT product development opportunity. COGS, cost of goods sold.

Conclusions

The initial investor survey executed by ISCT in September of 2018 helped to lay the foundation for ISCT's "i to i" program by providing a framework to understand which factors regarding CGT product development would have the greatest influence on the willingness to invest. Moreover, it provided valuable knowledge on how investigators should interact with investors in the CGT field, considering their technological preferences, demographics, and perceived barriers. The more recent survey administered in 2021 builds on this foundation by reassessing these critical factors and evaluating how they have evolved with the growth of the CGT field in recent years.

The 2021 survey reveals substantial changes in investor preferences and challenges within the CGT field since the first survey in 2018. Investors are increasingly interested in CGT investments and have shown a preference for allogeneic products. This interest is driven by manufacturing challenges and the perceived value of recent clinical data. The updated insights presented form the basis for future content generated by ISCT, both in service of educating investors and educating CGT product developers on the critical focus areas in the investment community.

Moving forward, investigators should leverage these survey findings to refine their communication strategies and prioritize their research and development efforts. By aligning their approach with investors' interests, addressing key manufacturing and management concerns, and focusing on generating robust preclinical and clinical data packages, investigators can position themselves for success in the evolving landscape of CGT investment.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

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Author Contributions

Conception and design of the study: PR, AG, SK. Acquisition of data: AG. Analysis and interpretation of data: MKK, ST, PR, AG, SK. Drafting or revising the manuscript: MKK. All authors have approved the final article.

References

[1] Moody J, Milligan WD, St Onge M, et al. Cell and gene therapy: a snapshot of investor perspectives. Cytotherapy 2021;23(3):256–60.
[2] Alliance for Regenerative Medicine 2021 Annual Report. Titled Regenerative Medicine: Disrupting the Status Quo 2022. < https://alliancerm.org/sector-report/2021-annual-report/ >[accessed 04.20.2023].