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The path to successful commercialization of cell and gene therapies: empowering patient advocates

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Abstract

Often, novel gene and cell therapies provide hope for many people living with incurable diseases. To facilitate and accelerate a successful regulatory approval and commercialization path for effective, safe and affordable cell and gene therapies, the involvement of patient advocacy groups (PAGs) should be considered early in the development process. This report provides a thorough overview of the various roles PAGs play in the clinical translation of cell and gene therapies and how they can bring about positive changes in the regulatory process, infrastructure improvements and market stability.

Key Words: *affordability, cell and gene therapies, clinical trials commercialization, patient advocacy, regulation, reimbursement*

In recent years, cell and gene therapies, particularly immunotherapies for cancer and gene therapy applications for severe combined immunodeficiencies have crossed over from mere research procedures to highly valuable and effective therapies [1]. Most interestingly, personalized therapies, in which prevention, diagnosis and treatment modalities are tailored to target specific types of diseases based on individual patient variability using factors such as individual patient characteristics (health status, age, medical history), genetic profile and their environment, have received a lot of attention [2]. In light of all these developments, engaging patients and their families proactively in their care can positively affect treatment outcome. However, illness and the stress associated with caring for a loved one can impair judgment, and patients are in need of support so that they can effectively assess the benefits and risks of available novel therapies [3]. Patient advocacy groups (PAGs) are therefore particularly valuable and can play several critical roles in this process. PAGs are groups of stakeholders seeking to inform patients of their rights and providing them with requisite information for informed decisions that affect their health and health care choices; additionally, they can play an important role in translating scientific and medical information into a lay-friendly format. For cell and gene therapies, these groups have been lobbying research organizations and agencies to provide new therapeutic modalities, especially for rare diseases, and help patients and their families become involved in decision-making processes.

Researchers face pressure from the public to develop cell therapies that will reach the clinic within a short time period [4,5]. However, the field of cell and gene therapy research has been subject to significant commercialization challenges, for reasons related to high development costs, heterogeneity of reimbursement and volatile market conditions, among others [6]. Although for many cell and gene therapy–based innovations, the question of whether these technologies can be commercialized at reasonable costs is a major concern, there are also several other aspects that are often not discussed but can influence the successful commercialization of these products. Patient advocates can contribute greatly to addressing these issues and be catalysts in accelerating the commercialization of these products and their adoption into the market, particularly if few patients are affected, and profit-driven, mainstream product commercialization would not be easily achievable. The International Society for Cellular Therapy Commercialization Committee recently met with PAGs from around the world

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(Joseph P. Roberson Foundation, USA; Genetic Alliance UK, United Kingdom; Lung Foundation Australia) to discuss the several ways patient advocacy can influence the success of bringing cell and gene therapies to patients (Table I).

Capturing the power of big data

The amount of data available today in the biotechnology field is unprecedented. This has been triggered by significant technological advances, such as whole genome sequencing, the generation and sharing of large amounts of clinical trial data and the rise in patient numbers and registries [7]. Taking advantage of the rapidly advancing field of bioinformatics generating insights from these data, developers are increasingly able to transform the way cell and gene therapies, and other innovations, are discovered, developed and marketed [8]. Moreover, pricing strategies and shaping new business models [9] are types of efforts that have the potential to benefit from the analysis of large sets of data. It is therefore important that the trust of patients, who may be inherently reluctant to share their data and participate in clinical translational research, will be gained. Transparency and patient ownership of the data they contribute will be central to establishing this trust relationship. PAGs are best positioned to initiate discussions about data sharing and taking an active part in bringing both parties—patients and developers—closer to reaching common understanding and trust that will enable developers to capture the advantages of big data aimed toward improving the success rate of novel therapeutics. For instance, a program titled Big Data for Patients (BD4P) has been introduced by the Reagan-Udall Foundation to provide specialized training for patients and advocates in the imminent discipline of data science (www.reaganudall.org/our-work/bd4p). The program aims to equip PAGs with the knowledge and tools they need to effectively communicate with different stakeholders regarding the use of big data in health care. Such strategies will also enable drug manufacturers to incorporate patient-centered strategies into all stages of clinical research where targeted therapies are lacking.

Combating the threat of unauthorized cell-based interventions

PAGs can play a vital role in stopping unauthorized or even dangerous cell-based interventions [10], often found in "stem cell tourism," by stressing the need for strengthening appropriate and proportionate regulatory oversight and enforcement, and perhaps by helping develop a system of international governance that oversees clinical cell and gene therapy research and treatment. At the same time, it would be important to facilitate patient access to tested and authorized novel therapies in their own countries [11] and allow for the timely, equitable and sustainable reimbursement of safe and efficacious cellular therapies. Although several PAGs have raised concerns about the introduction of the REGROW Act in the United States, which could possibly weaken Food and Drug Administration (FDA) regulations and oversight of experimental stem cell therapies (www.michaeljfox.org/foundation/news-detail.php?mjff-signs-letter-opposing-the-regrow-act), patient advocates could play an important role in obtaining a balance between accessibility of therapies and regulatory oversight. PAGs could participate in discussions with the FDA, the European Medicines Agency (EMA) and other regulatory agencies worldwide to reach this balance. PAGs could also lead initiatives for increasing awareness of the potential risks associated with stem cell tourism and provide education to patients and the public about the harms of such practice and how to spot and report unauthorized stem cell clinics [12]. Most important, it is essential today, more than ever, for PAGs to help manage the therapeutic hopes and, at the same time, the psychological distress of patients suffering from the many diseases that cell and gene therapies are potentially able to treat. PAGs are trusted mediators and have largely remained immune from the criticism placed on industrial drug developers. The sharing of personal narratives from patients and families and ways they have found to handle and manage the mental, emotional and medical aspects of specific, often devastating diseases forms a new set of knowledge, different from what health professionals might be able to offer. Thus, PAGs become a trusted voice that could more effectively pass on the message that research demonstrating treatment safety and efficacy is needed, which could be facilitated and achieved by a well-thought-out regulatory system [13]. PAGs from a range of diseases, where cellular therapies may be effective treatment modalities, should therefore come together, deliberate and issue a joint statement explaining the need to reach a balance between accelerating the delivery of novel therapies to patients and having rigorous research and regulatory oversight in place. Greater coordination is needed to create a more powerful voice, if such a message is to be heard.

Influencing the translational process of novel therapeutic approaches

Taking advantage of the extraordinary reach of online medical information, patients today have more knowledge and influence in the drug development process than ever before. Because many cellular therapy approaches address rare diseases, patient engagement is critical to every step of a cellular drug's development for these applications. This includes filing

Table I. Roles PAGs can play to influence the success of bringing safe and effective cell and gene therapies to patients.

Roles of PAGs	Impact on clinical translation and commercialization of cell and gene therapies
Communicating the value of data sharing and the ethical use of big data among different stakeholders (patients, families, governments, registries, and developers)	• Derive clinically relevant conclusions • Discover potential diagnostic and therapeutic targets • Optimize cell therapy production strategies • Guide pricing strategies and shape new business models
Combating the threat of unauthorized cell based interventions by stressing the need for appropriate and proportionate regulatory oversight and educating patients	• Advance scientific discovery and drive research forward to target unmet medical needs • Elaborate on the nature of scientific evidence required for demonstrating treatment safety and efficacy • Improve regulatory enforcement and enhance national and global governance efforts • Provide patients' access to safe and effective treatments
Influencing the translational process of novel therapeutic approaches from securing regulatory approvals, getting patients diagnosed and recruited into clinical trials, and promoting adherence to follow-up	• Incorporate patients' perspectives in defining added-value, acceptable risk and efficacy of new therapies • Promote and promulgate good translational/clinical research practices • Accelerate the development of new therapies for rare diseases • Correlate real-world evidence with traditional clinical end points to ensure that the intended outcome is achieved
Advocating for affordability and accessibility of cell and gene therapies by helping to shape the pricing and reimbursement strategies for advanced therapies by mediating discussions between developers and payers	• Adapt the traditional health technology assessment methodologies to fit cell and gene therapies with usually insufficient clinical evidence at market launch • Facilitate timely patient access to lifesaving therapies • Control the often very high prices assigned to gene therapies
Enhancing awareness and support for clinical trials	• Increase recruitment of patients to cell and gene therapy clinical trials, particularly for rare diseases • Develop reliable patient-relevant outcome measures • Ensure long-term safety and efficacy of outcomes in patients receiving gene therapies
Addressing the ethics of using novel technologies, such as genome editing, by engaging professional organizations and other stakeholders in open discussions about an appropriate course of action	• Promote the ethical use of innovative technologies to correct life threatening genetic defects • Address the public fear on the use of gene editing techniques in clinical research
Integrating patient-specific cell and gene therapy products into clinical practice by offering support to patients and their families	• Improve overall patient care, especially for those patients dealing with life-threatening diseases • Introduce cell and gene therapies as standard of care to clinical practitioners • Offer new "models of care" for cell and gene therapy developers to adopt and improve access to therapies

investigational new drug applications and getting FDA approval (and the equivalents in other jurisdictions), getting patients diagnosed and recruited into clinical trials and as promoting adherence to follow-up. As a result, the patient perspective becomes critical in weighing the benefit-to-risk ratio of new medical interventions, and industry must incorporate its perspectives in defining added-value, acceptable risk and efficacy [14,15]. Patient-centered drug development is not new; the FDA has included the patient perspective during FDA advisory committee meetings since 1991 and also when conducting meetings with developers for the review of new medical products (www.fda.gov/ForPatients/PatientEngagement/default.htm). Moreover, the FDA Patient-Focused Drug Development initiative aggregates patients' perspectives earlier in the drug development process [14]. Similarly, the EMA has the dedicated Patients' and Consumers' Working Party, which has continuously been involved with patient advocacy groups and consumer organizations to ensure that the needs and concerns of a wide range of patients and consumers are represented via direct contact with the agency. Within the EMA, patient advocates also participate as members of other scientific committees and working parties with equal voting rights, such as in the Committee for Orphan Medicinal Products and the Committee for Advanced Therapies. These collaborative efforts aim to empower patients as active participants, and not leave them as passive recipients of care, particularly when devastating diseases with no available treatment options are being addressed.

PAGs may also be well positioned to address bias in research and act as educated peers to argue against scientific misconduct and promote proper conduct of translational/clinical research [15]. They have become integral partners in research-related activities, with their service on institutional review boards and other oversight committees. Unfortunately, such a major role is frequently underestimated and underutilized; patient advocates are often only invited to endorse a research activity after the fact, without their involvement from the very beginning. What should really be done is to bring in patients early in the process because patient advocates can make a genuine contribution to how investigators will actually design and implement a clinical trial and how to reach the appropriate patient population as quickly and efficiently as possible. Specifically, clinical trials designed to test personalized medicines such as cell and gene therapies will likely become much more dependent on the involvement of patients [16]. Finally, as greater volumes of patient reporting information will be captured and tracked for a long period of time, especially for gene therapies, PAGs can support developers in collecting and reviewing data and correlating real-world evidence with traditional clinical end points to ensure that the intended outcome is actually achieved. For instance, they can indicate what an improvement in a 6-minute walk test means for patients in real life and can rank, from the patient's perspective, the acceptability of risks and possible adverse events associated with a novel therapy.

Advocating for affordability and accessibility of cell and gene therapies

Many patients and patient advocates are concerned that cell and gene therapies may be too expensive for most health care systems, which are often dealing with significant financial constraints [5]. With new gene therapies being high priced when introduced to the market, most patients will face the inability to cover treatments using these therapies, particularly if health insurers refuse to reimburse them [17]. This is usually because reimbursement of these high-priced products requires value-based assessments to explore the added value of a novel therapy compared to existing therapeutic alternatives [18]. However, this method cannot be applied to cell and gene therapies targeting diseases with no available standard of care. Although decision-makers acknowledge that advanced therapies have the potential to be cost-saving options in the long run, they also expect that significant up-front capital investment in equipment and infrastructure is required, which most entities cannot easily afford. They also suspect that advanced therapies may lead to increased medical follow-up with added costs to detect any late toxicities. For developers, this creates additional challenges, beyond the regulatory approval process, both in terms of market forecasting and adoption of their products [6]. Patient advocates and academic researchers therefore fear that high prices will prevent patients from obtaining needed therapies, especially those that target rare diseases [19,20]. PAGs can play a critical role in early assessment and shaping of the pricing and reimbursement potential for advanced therapies by mediating the discussions between developers and payers, as well as participating in the development of new approaches for reimbursement. Another aspect to target is the need for legislation to address unrealistic prices for cell and gene therapies because many of the novel therapies have already used government funding for their development, and such development costs need not be taken into account for pricing [9]. Another avenue to consider might perhaps be the generation of special funds for therapies with orphan designation. PAGs might be able to help put these efforts on the agenda of politicians by joining forces with medical practitioners and other interested professional organizations.

Enhancing awareness and support for clinical trials

During the past 2 decades, patient advocates have been instrumental in raising funds for medical research and increasing recruitment of patients to clinical trials [21]. Patient advocates are therefore integral to enhancing awareness and support for clinical trials, which helps to increase accrual and contributes to the generation of reliable clinical trial data. They also offer support in many ways for patients during the conduct of a clinical trial and also afterward, an often much overlooked but vital activity. Although clinical trials may measure physical, physiological or biochemical patient functions, other extremely important data, such as complaints and opinions, can only be obtained from the patients by asking them directly. For this reason, there is increased recognition of the value of patient-reported outcomes (PRO) in clinical research, and such measurements should be included in treatment evaluations [22]. It is important to stress that disease survival often may not be the ultimate goal of the treatment; improvement in quality of life may be the most important outcome for patients. PAGs can help integrate PRO end points and guidance principles into cell and gene therapy development and clinical applications. One should always have patients' best interests in mind when faced with a decision to choose treatments that have shown modest benefits without extending life, and thus patients need to know what they can expect from the treatment and what improvements they will experience, if any. Enforcing the use of systematically collected PRO data can also help patients gain access to patient-reported anecdotes about perceived quality of life and benefits as well as potential adverse events. For this to be achieved in a reliable and reproducible fashion, there will be a need to develop a framework that can be recognized by regulators and will allow PROs to progress from "anecdote" to "trend" and finally to "evidence." As we move toward a "patient-centered" health care system, the concept of PROs can also be extended to "patient-relevant outcomes." PAGs could be instrumental in leading an initiative to bring stakeholders from industry, academia and regulators together to identify outcome measures relevant to patients' well-being that could be endorsed as acceptable by FDA or EMA for cell and gene therapy product labeling.

Addressing the ethics of using novel technologies

Recently, the field of genome engineering has become a of great significance in medical research with the development of powerful new gene editing platforms [23]. Genome engineering can now be achieved with unprecedented efficiency, and with this in mind, gene modification of germ cells has emerged as a possible concern. Although still far from being a practical reality, a conversation on such life-altering possibilities should already be initiated [24]. Including the perspectives of patient advocates would be essential because consideration should be paid to which research efforts need to be aligned with patient autonomy and social and ethical boundaries. Patient advocates could lead the discussion on the issue of germline genome editing and engage professional organizations such as the International Society for Cellular Therapy, the American Society of Gene and Cell Therapy, the European Society of Gene and Cell Therapy and the International Society for Stem Cell Research because these important organizations are best suited to facilitate such discussions.

Integrating patient-specific cell and gene therapy products into clinical practice

Cell and gene therapies are unique products in the way they are manufactured and administered to patients. Challenges in integrating these therapies into clinical practice, after securing reimbursement, are often associated with the need for prescriber awareness on their appropriate use, while addressing any patient-related concerns. Strong partnerships among patient advocates, the public sector (i.e., research institutes or academia) and the private sector (i.e., company) can be instrumental by combining their respective skills and systems in delivering these therapeutics to patients, while guiding them through the long journey from diagnosis to treatment and beyond, particularly for gene therapies with multistep manufacturing processes and long-term health monitoring plans. For instance, the recently European Union–approved *ex vivo* autologous stem cell gene therapy (Strimvelis, GlaxoSmithKline) for children with adenosine deaminase severe combined immunodeficiency (ADA-SCID) is currently only available at the specialist facility Ospedale San Raffaele in Milan, Italy. To receive the gene therapy, eligible children and their families need to relocate to Italy for approximately 3 to 4 months. GSK and their collaborative partners, Fondazione Telethon (Telethon) and OSR, are committed to providing support to patients and their families during this time. A care coordinator will provide personalized assistance, which includes information on the treatment, advice regarding logistics and travel arrangements, family support, counseling and addressing any questions that may arise. This model is facilitated by a "global patient advocacy" team at GlaxoSmithKline and is an excellent example of and academia and industry partnership. Moreover, innovative approaches to genetic counseling should also be considered for patients either being enrolled in stem cell and gene

therapy trials [25] or when receiving a commercial product. Such counselors serve as patient advocates and support patients and their families during follow-up and for further genetic evaluation and testing if needed.

Conclusions

Patient advocates can have a major impact in driving forward the commercialization of cell and gene therapies through efficient communication with medical and research specialists, policymakers and regulatory agencies, while reporting these communications to the patients in need of such treatments. To benefit from the opportunities that PAG engagement provides, there also needs to be greater investment for capacity building of PAGs, particularly for rare diseases. Many support groups are quite small, run largely by those affected or family members and caregivers. For them to participate effectively, appropriate support will need to be organized. Through these means, academia, industry, policymakers and regulatory agencies, working with patient advocates, can join forces to overcome current hurdles to bringing cell and gene therapies to the patients and the overall market.

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