Advanced therapies are ready to take centre stage: academia's involvement with regulation needs to raise its game

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EDITORIAL

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Several CAR-T cells-based therapies have been approved for the treatment of blood cancers.[1] Gene therapies are constantly maturing and are now targeting not only rare diseases but also more common ailments such as beta thalassemia. Although toxicity issues are by no means minor,[2] it marks the beginning of an era where gene therapies will become widely applied.

Clinical trials for advanced therapies (ATMPs, which comprise genetic and somatic cells therapies and tissue engineered products) have grown at a rapid pace, with a dramatic global increase in the number of clinical trials, but much less so in Europe than in other regions of the world.[3] This is despite a substantial influx of money from the European Commission (EC) and others in research programmes like Horizon 2020[4] and the Innovative Medicine Initiative (IMI).[5] Why have so few products emerged from these investments? No one doubts the quality of the institutions, the high level of scientific and research know-how and the level of experience of the many academic institutions in the EU. A stronger link is needed between the great advances at the basic research level and the path to market authorisation and patient access to these therapies.

The use of animal experimentation in the development of ATMPs is a remnant of traditional development of medicines that is currently being revisited for ATMPs. Van der Laan and colleagues set the stage for the reduction of the use of animal models: they see limited added value in the development of at least some of these therapies.[6] This should not be seen as an invitation to further reduce the amount of data provided to regulators in a type of therapies where uncertainty is already substantial. It should rather be taken as a call to break with the traditional approach and to explore and collect relevant evidence that helps with the identification of key issues: regulators need to assess the benefit risk balance of all therapies but are open to new approaches for innovative therapies.

Looking beyond the attainment of market approval, it is not only regulators that need to be satisfied. Access to the market is not synonymous with access to the patient for many advanced therapies, and economic considerations are becoming more and more important, as discussed in this issue.[7,8] Health Technology Assessment bodies (HTAs), insurance companies, governments, and the general public question the high prices of many of these therapies and criticise the lack of transparency in drug pricing policies, especially considering the amount of uncertainty they carry. As a result, some of the authorised ATMPs have hardly been used because a reimbursement strategy could not be agreed upon. A one-off treatment that "cures" a previously incurable disease is certainly an attractive proposition, but rarely more than 2 years of follow-up data are available to judge the "forever" claim. In these cases, a more sophisticated reimbursement system may be needed: new approaches that take long-term outcome data into account.

The unequal treatment of genetically modified organisms (GMO) in members states in the EU has been identified as one of the potential culprits of the slow growth of clinical trials for advanced therapies in Europe.[3,9] Although the problem is recognised, the application of the rules to deal with GMOs containing medicines varies widely across Europe.[10] Harmonisation efforts are ongoing, but it may take some time before we approach the full harmonisation that industry and academia are calling for. A radically different approach to solve this problem has arrived with the emergency measures taken by the EC for the COVID-19 pandemic, providing an exception for vaccines containing GMOs,[11] but the derogation applies only to operations necessary to conduct the clinical trial phase and for compassionate or emergency use in the context of COVID-19.

An interesting and related observation focuses on the relative lack of awareness and expertise of academic institutions regarding the path to registration of advanced therapies. Academic centres are primarily evaluated on scientific output and subsidies, and often lack specific expertise and infrastructure for complying with regulatory requirements. Regulatory obligations are sometimes even perceived as obstacles to rapid clinical translation. One example of this lack of awareness and understanding is the suboptimal use of available tools, such as regulatory scientific advice, by academic developers of ATMPs. Academic institutions generally have fewer early interactions with regulators and submit marketing authorisation dossiers that are less than ideal for a smooth and fast approval process. The benefits of early and frequent scientific advice with regulators are less commonly exploited by academic developers,[12] including the non-clinical aspects.[13] The success of academic ATMP development could be substantially advanced if it were appropriately acknowledged that seeking and following scientific advice from regulatory authorities results in a better chance of gaining marketing authorisation.[14]

Over the past decade, (basic) research from academic or not-for-profit institutes has increasingly contributed to the development of innovative new drugs, primarily related to the identification of druggable targets that are directly related to their mechanism of action, but also to biological drugs, including ATMPs. Publicly funded research has become a major driver of innovation. This has allowed pharma to reduce its internal research capacity, while their role in

manufacturing, testing, and distribution has remained crucial. At the same time, (public-private) partnerships or open innovation models between pharma and academia have become both stronger and earlier in the drug development chain, thereby promoting the clinical development of candidate drugs.[15] Some of these partnerships focus on the development of single drugs, but others extend to long-term collaborations and broader areas of research, such as stem cell biology.[15] This successful strategy has become instrumental in modern drug development. However, many other potential breakthroughs have been unable to progress to the development stage and we suspect that a substantial part of academic research remains unexploited. Better and earlier engagement between academic researchers, regulatory agencies, and biotech/pharma could help to fill this gap.[16] In addition, mechanisms to enhance returns of revenues into academic research could reduce this unused potential and could further advance the successful development of future innovative drugs.

If we are going to see the many advances originating in academic settings—not only medicines, but devices, diagnostic tests, and all types of innovative methodology—converting into clinical benefit, we will gain a lot from the engagement of the wide academic community already working on ATMPs with the realities of Public Health: full regulatory scrutiny is the path to safe and effective therapies. The active ATMP researching academic community can be more universal in acknowledging the necessity of proper regulation underpinning access to the market and the clinic and engaging with the regulatory network in a productive and collegial manner. The patients will be the winners.

COMPETING INTERESTS

There are no competing interests to declare.

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