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ON THE ROLE OF PATIENT ASSOCIATIONS IN THE IMPLEMENTATION OF APPROACHES TO TREAT RARE DISEASES

# Patient power

IN the previous two editions of Pan European Networks: Science & Technology, we focused on the overall vision necessary for developing cutting-edge therapeutics and the individual constituents that form them – currently a focus for the Endostem and Biodesign project partners.

In this article, we shift our focus to clinical applications and patient needs, as well as the importance of patient associations in the drug development process. We note that unlocking therapeutic insights into rare diseases with regenerative therapeutics will not only benefit those patients directly affected, but will open up the application of these therapies to other areas.

## Low prevalence

Rare diseases are those with a low prevalence of patients. In the European community, this term is defined as fewer than one in 2,000 people. Low prevalence is associated with difficulty in gaining a deep understanding of all pathogenic aspects of the diseases and their natural history. This invariably leads to difficulties in the design of effective therapeutic approaches and the evaluation of drug effectiveness through appropriate outcome measures and/or significant endpoints.

Therapies for rare diseases have, until recently, been a neglected field, occasionally attracting small and medium-size biotech companies, but mainly receiving attention from academic research rather than the pharmaceutical industry.

Things have changed in the last decade and rare diseases are attracting an increasing amount of interest, including from big pharmaceutical companies. This is due to a series of factors, the most relevant of which include the advantages granted by regulatory agencies (the EMA and FDA) to drugs for rare diseases (known as orphan drug designation), including speed to market authorisation.

There has also been a change in global public opinion, which has become increasingly sensitive to issues surrounding rare diseases, prompted in part by the high-profile campaigns carried out at all levels by well-organised patient associations.

## Repositioning

An additional aspect concerns how therapies developed for rare diseases can be repositioned for more common injuries. In most cases, therapies for rare diseases are designed to resolve the underlying genetic defect. There are essentially two strategies behind this: gene therapies and enzyme replacement therapies in which the defective gene/protein is substituted with a new one, or the part of it which is dysfunctional because the mutation is removed from the protein.

Therapeutics in this class are hard to reposition for more common diseases as they target a very specific molecule. However, they still provide an advantage to pharmaceutical companies in that they yield useful and transferrable information on the carriers/vehicles needed to facilitate absorption and distribution to the proper target of these drugs, which differs significantly from the small molecules used in traditional pharmacology.

Traditional pharmacology is also used alongside these approaches; these classical pharmacological strategies are designed to slow/halt disease progression rather than heal it. In general, these strategies target one or more of those pathological events responsible for the progression of the disease. These events include pathological features that are also found in several common diseases such as tumours and degenerative diseases. Classical examples of these pathological features include chronic inflammation, fibrosis, tissue death by apoptosis/necrosis, uncontrolled angiogenesis, or atrophy. Therapies designed to target these pathogenic events in rare diseases may be rapidly transferred to common diseases, thereby exploiting the advantage offered by the orphan drug designation in terms of the costs of the trials.

As we have indicated in previous editorials in this series, this is specifically pertinent in the context of therapeutic approaches that focus on regenerative medicine, and which target both disease alleviation and restoration of tissue functionality. Targeting stem cells – either in the tissue directly with bioactive materials, biotherapies and pharmacologicals, or through the introduction of bioactive materials with exogenous stem cells – permits the validation of the therapy for one disease, which, following secondary fine tuning, repurposes the therapy for a wider spectrum of diseases.

## Patient organisations

These drug development strategies are also gaining momentum because of the active role played in rare disease therapies by patient organisations. In particular, one role they have carved for themselves is to help overcome critical issues inherent to orphan drug development that are not eliminated by the orphan drug designation.

Pharmaceutical companies and clinicians are coming to realise the importance of having close interactions with patient associations to develop proven and effective therapies, as well as the need to maintain links with patients and care providers.

Because of the small number of patients involved, the return on investment for orphan drugs is at risk; this often discourages their commercial development by the pharmaceutical industry, despite the advantage provided by the orphan drug designation. However, lobbying at governmental level and a stirring of public opinion have, both in the past and currently, been successful in enhancing awareness on these diseases. As a consequence, investments in research by charitable funds and governments have increased steadily over the last decade. In addition, the associations themselves are often able to play an active role in fundraising and money seeding.

Patient associations and caregivers are fundamental in integrating knowledge about rare diseases, as annually they spend thousands of hours with patients, dealing with their needs on a daily basis. This puts them in a unique position to observe and emphasise details that are frequently overlooked by clinicians and researchers.

In certain situations, as in the case of Parent Project that manages the patient registry for Duchenne and Becker Muscular Dystrophies, the associations are essential in the early phases/design of new studies, in the organisation of clinical trials, and in the recruitment of patients for these trials. This facilitates the process and furnishes clinicians with well-characterised study groups, which reduces the risks of drop-outs.

## Translation

This is a very promising landscape, and a significant change from the past. Yet, many things still need to be improved. One critical issue concerns the steps necessary for the clinical translation of innovative therapies, such as combination approaches, and how they can be simplified by the authorities for the benefit of patients.

In Europe and the USA, there is now an on-going debate about the opportunity to request the publication and dissemination of data from clinical trials, including of those with negative results. We believe that anything that encourages the sharing of data and promotes a better knowledge of the mechanisms is crucial in rare diseases and would tremendously enhance the chances of designing effective drugs and bringing them rapidly to the market.

Indeed, this is critical in the context of rare diseases in the global setting, particularly when it is taken into account that, in countries where access to healthcare and correct diagnosis is hindered or restricted, rare diseases are still treated as oddities and there is no comprehensive strategy for patient support or treatment.

Patient associations are pioneering support for these patient groups and are extensively lobbying the relevant national governments to provide infrastructure for better care. There is also a significant economic consideration to this, which may result in global innovation in healthcare and drug development processes, irrespective of drug complexity. That is, these countries have a very high demand for cost-effective therapeutics which are geographically mobile, and which the governments are willing to pay for. As such, the costs have to be low and the impacts high, with a major focus on long-term functional restoration.

If it is possible to supply therapies to such low-income countries, then it stands to reason that this supply should also be possible in richer countries, and patient associations are integral to such a strategy, federalising patient need and focusing on cures.

The commercial characteristics and ethical constraints of this aspect will be addressed in the series' final editorial in the next edition of Pan European Networks: Science & Technology.

There is no universal recipe for promoting clinical translation, but a common element that is always useful is the presence of patient associations and patient advocates whenever the fate of the patient is discussed, and not only with regard to clinical trials. As the motto states: *Nihil de nobis, sine nobis* ('Nothing about us, without us').

Patients reinvigorated and placated by the involvement of patient organisations in the drug development process is a guarantee of better compliance and of the success of trials. The regulatory authority should recognise this aspect and help in its implementation.

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