The rapid progress in the fields of cell and gene therapy is being reflected in the scientific advances, breadth and scope of discovery and development programmes for new therapeutics, and new preclinical and clinical knowledge. Preclinical approaches for cell manipulations and processing have been steadily improving and new vectors for gene therapy have opened new directions. Moreover, cell and gene therapy clinical trials have been systematically increasing in multiple therapeutic areas and diseases. A search in clinicaltrials.gov (15 April 2019) using the terms “cell therapy” and “gene therapy” yielded 1,236 and 805 clinical studies (380 and 229 of which with status of recruiting patients, respectively). Progress to the clinical trial phase reflects the availability of preclinical data that support proceeding with further development.

In parallel, the regulatory environment has also been evolving.
Recognizing the rapidly advancing knowledge on cell and gene therapies, Health Authorities have responded with a sustained effort in providing feedback and updating guidances. In fact, during the last 12 months there have been multiple guidance updates or draft guidances focusing on helping developers in the cell and gene therapy fields with the design of development programmes [1–7].

These recent guidances have various objectives including multidisciplinary considerations and address diverse themes such as programmes for serious conditions in regenerative medicine therapies which include cell therapies [1]; simplification and streamline of regulatory requirements for combination device and cell or tissue products [2]; recommendations regarding gene therapy CM&C [3]; recommendations on the design of long-term follow-up observational studies for the collection of data on delayed adverse events following administration of a gene therapy product [4]; recommendations on the manufacturing, preclinical and clinical trial design issues for all phases of the clinical development program for human gene therapy products for the treatment of rare diseases (addressing issues of limited patient study population size, potential feasibility and safety issues, matters relating to the interpretability of bioactivity/efficacy outcomes that may be unique to rare diseases or to the nature of the gene therapy product itself) [5]; guidance on the structure and data requirements for a clinical trial application for exploratory (including first-in-human) and confirmatory trials with advanced therapy investigational medicinal products (gene therapy, somatic cell therapy medicinal products and tissue engineered products) [6]; and guidance for the development and evaluation (quality, nonclinical aspects and safety and efficacy requirements) of medicinal products containing genetically modified cells intended for use in humans [7]. The nonclinical section of this guidance includes updated information on nonclinical studies requirements including a specific section on the scientific principles and guidance for CAR-T cell and TCR products, induced pluripotent stem cell derived cell-based products and cell-based products derived from genome editing [7].

Moreover, advances in specific therapeutic areas have also generated new guidance documents that provide specific recommendations on product development for specific diseases; examples being the gene therapy draft guidance for hemophilia [8] and for retinal disorders [9].

Cell and gene therapy products are both diverse and unique in their characteristics and properties. Cell therapy products include stem cell-derived cell therapy products and functionally differentiated cell-derived cell therapy products, as well as combinations with scaffolds and other non-cellular components [10]. Significant differences in profiles may exist depending on the source of cells and the cellular genetic background (e.g., autologous, allogenic, etc.). Cell processing methods and the in vivo administration route can also greatly influence the biological properties and safety of a cell therapy product. Gene therapy products, on the other hand, comprise non-viral and viral (e.g., replication-deficient, replication competent, microbial) vectors [10], which also may present
Significant differences in efficacy, safety and benefit-risk.

Key aspects of the rapidly progressing scientific advances and the evolving regulatory environment for cell and gene therapy are the preclinical requirements. These requirements have multiple complementary dimensions from in vitro and in vivo studies to support a development programme (including pharmacology, biodistribution, safety and delivery) on a product-by-product basis as required by the uniqueness of each potential cell and gene therapy.

Preclinical studies that address the pharmacology and pharmacodynamic properties are essential to assess bioactivity, understand mechanistic aspects and to support proof-of-mechanism and/or proof-of-concept in the target disease. They are also necessary to characterize the cell (or genetically modified cell) properties, survival, differentiation, host integration and biological activity. For gene therapy, the host response to an expressed transgene and long-term expression sustainability of a transgene are two key readouts. A particular aspect of in vitro and in vivo models targeting characterization of cell and gene therapy products is the fact that standard models may not apply and depending on the case, specific tailored tests and animal species are required such as the use of knockouts or transgenic animals that may recapitulate (in particular for monogenic models) features of the intended disease condition (pathology, pathophysiology, clinical biochemistry and hematology, and/or behavioral manifestations).

At the same time, for cell and gene therapy products, in vitro studies (functional and biochemical assays, morphological and immunological evaluations, phenotypic and genotypic markers) can also be instrumental in providing very relevant data on biological activities and the mechanism(s) of action. In vitro and in vivo analyses of pharmacological and biological activities can also result in findings applicable to safety assessments.

In cell and gene therapies, preclinical ADME (absorption, distribution, metabolism and excretion), pharmacokinetics and biodistribution assessments need tailoring to a specific programme. The analysis of the fate of a cell or gene therapy product in anatomical sites (intended and not intended in organ[s], tissue[s] and cell[s]) is key to fulfil requirements and to assess profiles with implications for efficacy, safety, and for the design of clinical trials.

Biodistribution approaches using genetically modified cells expressing visualization labelling markers in histopathology, and the use of non-invasive imaging and molecular genetics, can be determinant in defining the cellular anatomical features and implications for further development (i.e., cell engraftment, proliferation, differentiation, local environment and host responses including pharmacological, immunoregulatory/inflammatory and tumorigenic).

In case of gene therapy, the analysis of a vector biodistribution also focuses in understanding the vector anatomical presence in the...
intended target organs/tissues and its detection (depending on the product) in the blood, urine, cerebrospinal fluid, ocular fluid, etc., as well as the impact on the intended gene expression, its magnitude and long-term persistence.

Furthermore, short- and long-term preclinical safety evaluations and GLP regulatory toxicology studies to identify potential target organs of toxicity, acute and chronic effects, and local and systemic reactions are of utmost importance [10]. Because each cell and gene therapy product may be unique, preclinical product specific approaches and safety assessments may need to be considered (including, as needed, reproductive, developmental and carcinogenicity studies).

Preclinical approaches integrating in vitro and in vivo systems are also essential in the optimization of existing therapeutics (enhancing efficacy and safety, and sustained effectiveness), in the design of emerging cell and gene therapies, and in cell or tissue-device combinations. To note is that preclinical animal model systems and validation studies of cell-based therapies and genetically modified cellular approaches have been enabling in progressing the field and also to link with manufacturing and translational sciences.

Overall, the preclinical data generated during a cell and/or gene therapy programme development provide an initial benefit-risk assessment in the target disease indication to be used in clinical trial designs. This would include the safety criteria to use including (as needed) specific enhanced monitoring such as immunogenicity. Preclinical data are also fundamental to define clinical endpoints and support the use of other parameters and measures/biomarkers (genetic, biochemical, hematological, physiological, developmental and morpho-pathological) in efficacy determination, preclinical-to-clinical translatability, patient population stratification, and in deducting biodistribution-pharmacodynamic relationships. Moreover, preclinical data (including data derived from modelling techniques) allow determination of first-in-human dosage, regimen of administration (single dose, acute, chronic), route of administration, and timing of administration concordant with the disease needs (i.e., prior or at appearance of disease signology and symptomatology or during disease progression stages).

Fulfilling preclinical requirements is not only a priority for advancing a development program, but also for the generation of new knowledge in research-to-patient translatability, in the clinical trial design in cell and gene therapy across therapeutic areas, and in the development of personalized and individualized treatments. An example are the inherited monogenic diseases where a therapy can be designed to treat the precise underlying pathophysiology of the medical condition.

Preclinical advances in cell and gene therapy have made possible the development of various therapeutics for significant unmet medical needs now available to patients. Examples are axicabtagene ciloleucel [11] and tisagenlecleucel [12] (CD19-directed genetically modified autologous T-cell immunotherapies) indicated for the treatment of various types of lymphoma; autologous cellular immunotherapy (sipuleucel-T) [13] indicated for
the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer; and voretigene neparvovec-rzyl [14], an adeno-associated virus vector gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.

The current ‘Spotlight’ edition on Preclinical Data Requirements for Cell & Gene Therapies is privileged to comprise a series of contributions on contemporary preclinically-focused themes by leaders in gene and cell therapy disciplines including: Paula Salmikangas et al. on immunogenicity of adeno-associated viral vectors; Gaya Hettiarachchi and Wei Liang with the US FDA perspective on cell and gene therapy preclinical considerations; Karen Kozarsky on gene therapy preclinical-clinical translation in CNS; Lucie Low on the development of tissue chips as novel in vitro tools; James McBlane on how to engage with regulatory authorities; David Morrow et al. on broadly applicable imaging platforms for optimising cell therapies in solid tumours; Danica Stanimirovic and Anna Jezierski on blood-brain barrier for preclinical assessment in CNS; Lincoln Tsang, on Good Laboratory Practice and assays; Darin Bloomberg, Scott McComb and Risini Weeratna on emerging high-throughput in vitro tools for CAR selection and optimization; and Charles River Laboratories on optimising preclinical study designs. I am grateful to each contributor for making this ‘Spotlight’ edition possible.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

The author is a full-time employee of Esteve Pharmaceuticals, S.A., a company with projects in gene therapy (www.esteve.com/global/researchdevelopment/pipeline).

No writing assistance was utilized in the production of this manuscript.

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