feature

Development of cell therapy medicinal products by academic institutes

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In the rapidly evolving fields of cellular immunotherapy, gene therapy and regenerative medicine, a wide range of promising cell therapy medicinal products are in clinical development. Most products originate from academic research and are explored in early exploratory clinical trials. However, the success rate toward approval for regular patient care is disappointingly low. In this paper, we define strengths and hurdles applying to the development of cell therapy medicinal products in academic institutes, and analyze why only a few promising cell therapies have reached late-stage clinical development. Subsequently, we provide recommendations to stakeholders involved in development of cell therapies to exploit their potential clinical benefit.

Introduction

Increasing pathophysiological knowledge and technological advances should permit development of a variety of safe and effective innovative drugs. In particular, the field of cell and tissue therapies has been boosted by improved insights into immunology and disease biology, especially for regenerative and cancer medicines [1]. These therapies, particularly autologous ones, are technically challenging when compared with the manufacture of conventional pharmaceutical products but are akin to cell and organ transplant products making their development fit better with academic institutes than conventional manufacturers [2,3]. This explains why most cell therapy strategies originate from academic research groups across the EU and the USA. The development of these promising novel therapies results in high-impact scientific publication of preclinical and clinical data, but only very few cell therapies have obtained a marketing authorization (MA) (for regulatory background see Box 1) [4].

Many cell therapies are in development for (ultra-)orphan indications [5,6]; possibly because of the disease-specific mode of action, and because most cell therapies are 'tailored' for each patient. Cell therapies have been thought to be of limited commercial value owing to the challenging logistics that are associated with personalized manufacturing. In addition, commercial developers are more cautious in committing to high risk products in early development [7]. Only in recent years, a series of breakthrough results have persuaded companies to invest in academic cell therapies toward commercial development (Box 2).

Many of the academic cell therapies have been tested in multiple early-phase exploratory clinical trials, resulting in peer-reviewed publications [8]. However, in Europe 98% of clinical cell therapy trials have not contributed to development of licensed products yet [5]. Even successful early clinical trials were rarely followed up by well-designed (controlled) Phase II/III trials [5]. Thus, although academic product development receives medical ethical clinical trial approval, the collected data are not sufficient to build a dossier for MA. A possible explanation could be that academic drug developers are driven by novelty which does not fit with the requirement for registration and generally requires confirmatory trials. Therefore, it seems that promising innovative cell therapies remain in early clinical development.

Here, we discuss the strengths and hurdles of academic institutes in the development of innovative cell therapies and try to understand why only a few of the large number of cell therapies reach late-phase development and

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BOX 1

Regulatory framework for cell therapies in the USA and Europe

In Europe cell therapies belong to advanced therapy medicinal products (ATMPs), which are defined in EU regulation 1394/2007/EC, implemented on the 30th of December 2008. This implies that compliance with the full medicinal product regulatory framework is required. The ATMP regulation stipulates that an application for marketing authorization (MA) should be submitted by the centralized procedure at the European Medicines Agency (EMA). The Committee for Advanced Therapies (CAT) at the EMA is responsible for assessing the quality, safety and efficacy of ATMPs. The CAT is also responsible for ATMP classifications, and involved in scientific advice procedures on development of ATMPs [5,31].

In the USA the MA of cell therapies, defined as cellular therapy products, is coordinated by the FDA's Center for Biologics Evaluation and Research (CBER) via Title 21 Part 1271, Human Cells, Tissues and Cellular And Tissue-Based Products (HCT/P), in the Code of Federal Regulations [32].

The EMA and the FDA have defined distinctive features that distinguish the cell therapies from other cellular products, falling under the Tissue and Cells Directive (2004/23/EC) in the EU and the HCT/Ps in the USA. Cells that have been subjected to substantial[a] manipulation and/or cells that are used in a non-homologous fashion[a] are defined as cell therapy (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm427692.htm).

[a]The precise definitions 'non-homologous use' and 'substantial manipulation' are different for the USA and the EU.

even fewer have become standard patient care. Subsequently, we aim to provide recommendations to public stakeholders involved in development of cell therapies, to exploit their potential clinical benefit fully. The focus in this paper is on cell therapies in general, as defined by the EMA and FDA (Box 1). When more-specific subtypes are mentioned, this is to illustrate an example.

Cell therapies originate from academic research

The academic strengths can be identified by analyzing why cell therapies mainly originate from academic research.

Academic strength: disease-specific expertise

As tertiary referral centers, academic institutes have an inherent focus on complex and orphan diseases. Specialized clinicians and scientists

BOX 2

Commercial agreements between academic institutes and commercial companies

Table I
Examples of successful cell therapy commercial agreements

Product	Characteristic[a]	Indication	Academic origin	Commercial agreement	Year of agreement
Holoclar®	Human corneal epithelium	Severe cornea damage	University of Modena and Reggio Emilia	Holostem and Chiesi Farmaceutici	2008
CTL019	CAR-T	CLL	University of Pennsylvania	Novartis	2012
Multiple TCRs	TCR platform	Various tumors	Netherlands Cancer Institute	Kite Pharma	2015
GSK2696273	Lentiviral vector gene modified $CD34^+$ cells	ADA-SCID	Ospedale San Raffaelle, Fondazione Telethon	GSK	2015

[a]All from autologous origin.

Abbreviations: CTL, cytotoxic T lymphocyte; CAR-T, chimeric antigen receptor T cell; CLL, chronic lymphoblastic leukemia; ADA-SCID, adenosine deaminase deficiency – severe combined immunodeficiency; GSK, GlaxoSmithKline.

http://ir.kitepharma.com/releasedetail.cfm?releaseid=901985; http://www.pharmaworldmagazine.com/italy-leader-in-the-regenerative-medicine-field-with-holoclar/; http://www.uphs.upenn.edu/news/News_Releases/2014/12/ctl019/; https://www.gsk.com/en-gb/media/press-releases/2015/gsk-fondazione-telethon-and-ospedale-san-raffaele-announce-eu-regulatory-submission-for-gene-therapy-to-treat-rare-disease- ada-scid/.

Example of a commercial agreement: CTL019 (http://www.uphs.upenn.edu/news/News_Releases/2014/12/ctl019/)

- 2011: breakthrough results published by the University of Pennsylvania.
- 2012: global research and licensing agreement between the University of Pennsylvania and Novartis.
- 2014: CTL019 receives FDA Breakthrough Therapy Designation.

Agreement:

- Novartis receives a global license to the technologies for the specific patient group and CAR-based therapies.
- Investment in future research of the technology by Novartis.
- Additional payments to the University of Pennsylvania by Novartis.
- Building and investment of 'Center for Advanced Cellular Therapies' (CACT) on the University of Pennsylvania campus, for T cell immunotherapies:
  - o discovery,
  - o development,
  - o manufacturing.