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Review

Human cells: New platform for recombinant therapeutic protein production

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ABSTRACT

The demand for recombinant therapeutic proteins is significantly increasing. There is a constant need to improve the existing expression systems, and also developing novel approaches to face the therapeutic proteins demands. Human cell lines have emerged as a new and powerful alternative for the production of human therapeutic proteins because this expression system is expected to produce recombinant proteins with post translation modifications more similar to their natural counterpart and reduce the potential immunogenic reactions against nonhuman epitopes. Currently, little information about the cultivation of human cells for the production of biopharmaceuticals is available. These cells have shown efficient production in laboratory scale and represent an important tool for the pharmaceutical industry. This review presents the cell lines available for large-scale recombinant proteins production and evaluates critically the advantages of this expression system in comparison with other expression systems for recombinant therapeutic protein production.

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Contents

Introduction

Therapeutic proteins were initially extracted from human tissue or blood; for example, blood clotting factors and human serum albumin from plasma, insulin from pancreas, and glucocerebrosidase from placenta. However, the protein extraction from tissue (animal or human) has several disadvantages such as not having the biological material available in the quantity required for an industrial production and it can be contaminated by pathogens (viruses and/or prions contamination). Even when a protein could be obtained from human tissue in sufficient quantities, it can be much safer to use genetically engineered-derived products. In addition to safety issues, a major benefit of recombinant proteins

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Table 1
Biopharmaceuticals approved by FDA between 2008–2011 (adapted from Zhu, 2011 [2]).

Product	Indication	Expression system	Year approved	Manufacturer
Fibroblasts, autologous	Appearance of nasolabial fold wrinkles	Patient fibroblasts	2011	Fibrocell science
Belatacept (CTL4-Ig Fusion)	Prevention of acute rejection in adult kidney transplant patients	Mammalian	2011	BMS
Yervoy (Ipilimumab)	Metastatic melanoma	Mammalian	2011	BMS
Benlysta (Belimumab)	Systemic lupus erythematosus	Mammalian	2011	HGS
Prolia (Denosumab)	Osteoporosis	Mammalian	2010	Amgen
Pegloticase (Krytexxa)	Chronic refractory gout	Bacteria	2010	Savient
Victoza (Liraglutide)	Diabetes	Yeast	2010	Novo Nordisk
Pancreaze (Pancrelipase)	Exocrine pancreatic insufficiency	Tissue extraction	2010	J&J
Xeomin (Incobotulinumtoxin A)	Cervical dystonia, blepharospasm	Bacteria	2010	Merz
Vpriv (Velaglucerase)	Gaucher disease	Mammalian	2010	Shire
Menveo (Meningitis vaccine)	Prevention of invasive meningococcal disease	Bacteria	2010	Novartis
Provenge (Prostate cancer cellular vaccine)	Metastatic prostate cancer	Cancer cell	2010	Dendreon
Xiaflex (Collagenase)	Dupuytrenśs Disease	Bacteria	2010	Auxilium
Lumizyme (Alglucosidase alfa)	Pompe disease	Mammalian	2010	Genzyme
Prevnar 13	Pneumoniae	Bacteria	2010	Wyeth
Actemra (Tocilizamab)	Systemic juvenile idiopathic arthritis	Mammalian	2010	Genentech
Cervarix MEDI 501	Cervical cancer	Baculovirus	2009	GSK
Stelama (Ustekinumab)	Plaque Psoriasis	Mammalian	2009	Centocor/J&J
Arzerra (Ofatumumab)	Chronic lymphocytic leukemia	Mammalian	2009	Genmab
ATryn (rhATIII)	Blood clots	rTransgenic goat	2009	GTC (Genzyme)
Simponi (Golimumab)	Immune dysfunction-related artritis	Mammalian	2009	Centocor/J&J
Ilaris (Canakinumab)	Cryopyrin-associated periodic syndromes	Mammalian	2009	Novartis
Crtmzia (Certolizumab Pegol)	Crohńs disease	Bacteria	2008	UCB
Nplate (Romiplostim)	Chronic immune thrombocytopenia purpura	Bacteria	2008	Amgen
Arcalyst (Rilonacept)	CAPS and FCAS	Mammalian	2008	Regeneron
Rotarix (Rotavirus vaccine)	Rotavirus infestion	Virus	2008	GSK
Cinryze (C1 Inhibitor)	Angioedema attacks in with hereditary angioedema	Human plasma	2008	Lev

is that they serve as a platform for the development of more advanced products that are engineered for an improved therapeutic profile, such as enhanced safety, lower immunogenicity, increased half-life and improved bioavailability [1].

Recombinant therapeutic proteins have been traditionally produced in mammalian, insect cells, bacteria and yeast. Mammalian cells are the preferred expression systems to produce complex glycosylated proteins. Among the 27 lasted FDA approved biopharmaceuticals (2008–2011), 18 are proteins derived from cultivated cells, microorganisms or transgenic animals (Table 1). The other nine are vaccines and therapeutics manufactured from natural product sources. Considering the 18 recombinant products, 12 are produced using mammalian expression systems, three are produced in *Escherichia coli* and the others are produced in baculovirus, yeast and transgenic goat [2].

The preference for the mammalian expression system is due to their ability to synthesize proteins that are similar to those naturally occurring in human with respect to molecular structures and biochemical properties [2]. Mammalian cell lines have the basic machinery to express and secrete recombinant protein, and huge number of cell lines from various tissues and species with suitable growth properties is available. Two hamster cells lines, Chinese hamster cell ovary cells (CHO)[1] and BHK (Baby hamster kidney cells) and two mouse cell lines, NS0 (myeloma) and SP2-0 (hybridoma), supply most of the biopharmaceutical industry. Research and clinical studies have provided substantial safety information about the use of these cells [3].

Despite the safety and efficacy of recombinant protein expression in murine cells, the glycosylation pattern is of profound importance when considering their potential as expression systems for biosynthesis of human recombinant glycoproteins. Murine cells simply do not possess the "machinery" required for human-type glycosylation: specific glycosidases, glycosyltransferases and specific sugar donors are absent. These differences in glycosylation pattern may be highly immunogenic in humans, and/or may be rapidly cleared the recombinant protein from circulation [4].

In spite the great interest of human cell lines as a new production platform, currently, little information about the cultivation of human cells for the production of biopharmaceuticals are available. These cells have shown efficient production in laboratory scale, however the application for commercial manufacturing is still limited. The human cell lines that are been considered for recombinant proteins production are HEK293, HKB11, PER.C6 and CAP cells [5]. These cell lines will be further described in this review as well as the commercial recombinant products related.

It is worth highlighting that for many years, there was an issue regarding the use of human cell lines for recombinant therapeutic protein production: the regulatory hurdles. The lack of species barrier allowing easier transfer of adventitious agents was considered as a major limitation. Rose et al. [3] argue that infection with human pathogenic agents is likely to result in a full-blown pathogenic effect in human cells that is easy to detect, whereas the agent may be dormant in rodent cells. For all new cell lines, whether of animal or human origin, the risk of transmission of prion-based diseases is addressed with strict documentation requirements and the lack of contact with any potentially infected bovine material.

[1] *Abbreviations used:* CHO, Chinese hamster cell ovary cells; BHK, Baby hamster kidney cells; EBNA, Epstein-Barr virus nuclear antigen; CMV, cytomegalovirus; CAP, CEVEC's Amniocyte Production; MCB, master cell bank; PEG, polyethylene glycol; HKB, hybrid of kidney and B cells; IL, interleukin; Ig, immunoglobulin; Neu5Ac, *N*-acetylneuraminic acid; Neu5Gc, *N*-Glycolyineuraminic acid.

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