ELSEVIER

Induced pluripotent stem cells technology acts as an in vitro clinical trial and, therefore, is an opportunity for the drug discovery process to recapitulate human disease pathology without the need for animal models.

A low-cost, high-quality new drug discovery process using patient-derived induced pluripotent stem cells

Shibashish Giri and Augustinus Bader

Centre for Biotechnology and Biomedicine, Department of Cell Techniques and Applied Stem Cell Biology, Medical Faculty of University of Leipzig, Deutscher Platz 5, 04103 Leipzig, Germany

Knockout, knock-in and conditional mutant gene-targeted mice are routinely used for disease modeling in the drug discovery process, but the human response is often difficult to predict from these models. It is believed that patient-derived induced pluripotent stem cells (iPSCs) could replace millions of animals currently sacrificed in preclinical testing and provide a route to new safer pharmaceutical products. In this review, we discuss the use of IPSCs in the drug discovery process. We highlight how they can be used to assess the toxicity and clinical efficacy of drug candidates before the latter are moved into costly and lengthy preclinical and clinical trials.

Introduction

The drug attrition rate is high during both the preclinical and clinical stages (Phase I = 56%; Phase II = 82%; Phase III = 50%) of clinical drug developments. A cumulative estimate suggests that the attrition rate of drug candidates is 96% [1], representing a significant risk in terms of the capital invested in drug candidate development [2]. Only 25 small molecules and two biologics were approved by the US Food and Drug Administration (FDA) in 2013 [3]. Drug candidates that are passed as being safe in the preclinical stage often show toxic effects or are ineffective during the clinical stages, eventually failing their clinical trials. Post-marketing withdrawals and block-box warnings of current approved market drugs show that fundamental information is missing from the preclinical and clinical phases of drug discovery and the development pipeline, which results in a barrier to the production of safer, effective drugs. Biotechnology and pharmaceutical companies are facing heavy losses both financial and in terms of their reputation as a result of high drug attrition during the post-marketing period. After preclinical screening in an animal model, preclinical drug candidates are evaluated and their safety and efficacy are tested in healthy volunteers; however, this can result in adverse drug reactions or even death. It estimated that 2644 people died during clinical trials for 475 new drugs between 2005 and 2012 (http://www.thehindu.com/sci-tech/health/policy-and-issues/clinical-trial-of-untested-drugs-must-be-regulated–sc/article4956386.ece). The same article also reported that between January and June 2012 alone, 211 people were affected by serious adverse events and died during the trial. Cinacalcet was approved by the FDA in 2004 for treatment of parathyroid carcinoma in adults;

Corresponding author: Giri, S. (shibashish.giri@bbz.uni-leipzig.de)

Shibashish Giri earned his BSc in 1998 from Rairangpur College, Utkal University, and his MPhil in zoology from the University of Delhi, in 2003. He also received an MSc in zoology with specialization in cytogenetics from North Orissa University in 2001. After completing his PhD thesis, he joined the Biomedical and Biotechnological Center (BBZ) as a deputy head of applied stem cell biology and cell technology. He has 11 years of research experience with hepatocyte culture models. He is currently working on epigenetic targets for liver disease, hepatic differentiation from human-induced pluripotent stem cells, boosting factors for biotrachea construction, scarless healing mechanisms, and non-materials for stem cell research under the Augustinus Bader at the Centre for Biotechnology and Biomedicine, University of Leipzig. He has published 20 peer-reviewed papers on bioreactor-based hepatocyte culture models and is a member of the World Federation & World Virtual Institute of Preventive & Regenerative Medicine.

Augustinus Bader is a German physician and biomedical scientist and one of the leading experts in the field of stem cell research. He currently oversees a group at BBZ, where he has been the chair of cell techniques and applied stem cell biology since 2003. He is the founder of the International World Congress on Regenerative Medicine in Leipzig and president of the World Federation & World Virtual Institute of Preventive & Regenerative Medicine. Bader has given more than 450 lectures at national and international conferences, including more than 300 invited, plenary, or keynote lectures. He has contributed to more than 160 peer-reviewed papers and book contributions. His clinically most relevant inventions include a biological process that imitates bionic principles for stem cell activation and tissue regeneration. Most of his patents have a global coverage and there are 27 currently active patent families with more than 200 international filings. In 2010, Bader received the highest European scientific price (Cicatrix Price) organized by a patient organization for the development of a therapeutic method to prevent scar formation following severe thermal injuries (burns). He is also a member of the Scientific Advisory Committee of the umbilical-cord stem cell bloodbank.

1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2014.10.011

Please cite this article in press as: Giri, S., Bader, A. A low-cost, high-quality new drug discovery process using patient-derived induced pluripotent stem cells, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.10.011

however, its use was stopped by the FDA in February 2013 following the death of a 14-year-old patient (http://www.fda.gov/Drugs/DrugSafety/ucm340551.htm).

Conventional drug discovery and development rely on traditional, expensive, nonhuman animal models, such as mice, rat, pig and monkey. However, such models rarely mirror human disease pathological mechanisms. For example, stroke remains the second leading cause of death globally. Rapid loss of brain function because of inefficient blood supply to the brain has been developed as a stroke research model. However, nonhuman stroke models have been used during the preclinical stage but failed to predict the responses in humans [4]. Thus, animal models alone are unreliable for understanding human diseases and for screening drug candidates. Up until 2013, 85 HIV/AIDS vaccines had successfully passed preclinical trials and had been shown to effective in nonhuman primate models; however, all failed clinical trials in humans [5]. Similar failures have been reported in the use of nonhuman models in the development of antidepressant drugs, recently reviewed in [6]. As a result, many drug companies have reduced their research efforts towards treatments for neuropsychiatric disorders [7].

Mice have been extensively used in the drug development process because of their close genetic similarity with humans. However, the mouse drug development model for multiple sclerosis (MS) was found to be unreliable and dissimilar with the course of MS in humans [8]. Seok *et al.* [9] analyzed 4918 inflammation response genes in humans and mouse models to compare the similarly of three inflammatory diseases and concluded that the genomic responses in the mouse models poorly mimicked those in humans. This study highlights the dissimilarity between gene responses at the genome level in humans and mice. In addition, during the development of TGN1412, which is a humanized monoclonal antibody, researchers were unable to predict its toxicity profile in mice and cynomolgus monkeys [10]. However, when this antibody was tested on six healthy volunteers, multiple organ failure occurred [11–13].

Despite the negative points above, animal models do have some use in the drug development process and are reliable for basic research, some of which has resulted in Nobel Prize-winning discoveries [14–16]. Embryonic stem cells (ESCs) were first discovered in mouse embryos and then in human embryos. Following their discovery, mouse iPSC were created in mouse fibroblasts and then were found to work successfully in human fibroblasts, resulting in additional iPSCs. Since their discovery, much work has focused on the development of iPSC technology for use in the drug discovery process. In particular, this technology could be used to overcome the existing limitations in the prediction of a range of toxic effects, such as cardiovascular toxicity, hepatotoxicity, and renal toxicity. It was previously thought that iPSCs were genetically unstable, similar to other immortalized cell lines; however, it was recently shown that this was not the case and that these cells are stable [17]. Thus, here we discuss how the use of iPSCs could revolutionize the drug discovery pipeline and result in safer, more efficacious drugs.

Current post-marketing failures of approved market drugs and future risk

Post-marketing failures and block-box warnings of approved market drugs are currently of significant concern to the pharmaceutical industry and beyond. Although most of the marketed drugs available can cause hepatotoxicity, cardiovascular toxicity, adverse drug reactions and other harmful effects, there are some that have resulted in such adverse outcomes that their future is in doubt. For example, more than 1000 drugs are known to cause liver problems [18], and cardiovascular toxicity of non-cardiovascular drugs has also occurred [19]. Cardiovascular toxicity is one of the main reasons for drug withdrawals, accounting for 45% of all drugs taken off the market between 1994 and 2006 [20]. Significant health risks were observed in a survey of 279 drugs approved in Europe between 1999 and 2011 [21]. Withdrawal of antibiotic drugs by the FDA was higher than other classes of drugs between 1980 and 2009 [22]. In France, of 97 new drugs evaluated, only four were found to provide therapeutic advantages [23]. The FDA approved 749 new molecular entities between 1980 and 2009, but one in seven has since been removed from the market [24]. In 2013, ten small-molecule tyrosine kinase inhibitors were approved for treatment of cancer. However, soon after their approval, five received a black-box warning because they resulted in hepatotoxicity [25].

There is an expanding list of drugs that have been withdrawn or black-boxed post-marketing. For example, A drug for the treatment of osteoporosis (calcitonin salmon) was withdrawn because of possible cancer risk [26], while carisoprodol, which is a muscle relaxant that has been used for acute lower back pain since 1959, was withdrawn from the market in 2008 because of increased risk of abuse or addiction [27]. In December 2012, ponatinib hydrochloride was approved for the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). However, because of the risk of life-threatening blood clots and severe narrowing of blood vessels, use of the drug was suspended by the FDA (http://www.cancer.gov/cancertopics/druginfo/fda-ponatinibhydrochloride%5C). Most of the patients treated with the drug experienced serious adverse vascular events, including fatal and life-threatening heart attacks and stroke. Some patients even experienced serious adverse events 14 days after ponatinib hydrochloride therapy was stopped. In another instance, an anticonvulsant drug, retigabine, was approved in 2011 for treatment for partial epilepsies; however, in 2013, it received a black-box warning because of an abnormal risk to the retina, possible vision loss and skin discoloration (http://www.fda. gov/drugs/drugsafety/ucm372774.htm). Bevacizumab was approved in 2008 for metastatic breast cancer, but withdrawn in 2011 because it was neither effective for the treatment breast cancer nor did it improve their quality of life (http://www.cancer.gov/cancertopics/druginfo/fda-bevacizumab). Lariam, an antimalaria drug, entered the market in 1989 but received a black-box warning in 2013 because of neurologic and psychiatric adverse effects (http://www.fda.gov/drugs/drugsafety/ucm362227.htm). Liraglutide, a glucagon-like peptide-1 (GLP-1) analog drug approved in 2009 for type 2 diabetics mellitus, was withdrawn in 2012 because of unexpected rates of pancreatitis, thyroid cancer and kidney failure [28]. Byetta is also another diabetic drug, approved in 2005 but pulled from the market in 2013 because of an increased risk of acute pancreatitis (http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm). Cough and cold medications were voluntarily withdrawn in 2007 when it was found that the medication was not ineffective

Please cite this article in press as: Giri, S., Bader, A. A low-cost, high-quality new drug discovery process using patient-derived induced pluripotent stem cells, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.10.011