NUS Graduate School for Integrative Sciences and Engineering
Research Project Write-up

Title of Project: Creation of novel and efficient model of hESC derived cell-tissue for wide application in health science, dentistry, medicine and biotechnology

Name of Supervisor: CAO Tong

Contact Details: omscaot@nus.edu.sg

Short Description

As one of global pioneers in this innovation, our work demonstrated the great potential of human embryonic stem cell for this purpose. The human embryonic stem cell lines are of single clonal origin, have been demonstrated to be genetically healthy and stable, possess unlimited proliferative capacity, and can potentially serve as an unlimited and permanent source of human cells for various clinical and non-clinical applications.

Government authorities, universities, research institutes and the industries of health, pharmaceutical, food and environment are presently hindered by a lack of functional human cell systems, and predominantly use cells of low clinical relevance in addition to costly live animal models. Existing models of live animals or on immortalized cell lines of either animal or human origin, often poorly reflect human physiology. Primary human cell cultures are difficult to procure in sufficient quantity and can be prone to much inter-batch variability, depending on the cell source. By contrast, self-renewable human embryonic stem cells exhibit enhanced biological relevance and predictivity over its more expansive counterparts [2]. Based on our work on human embryonic stem cell differentiation, we have developed various differentiated progenitor and somatic lineages from human embryonic stem cells for industrial and health applications.

Hence, we endeavour to develop a technically-simple, cost-effective and replicable system of generating differentiated human embryonic stem cell progenies. These will then be applied to the bio-functional studies and biocompatibility/safety studies of cytotoxicity, genotoxicity, carcinogenicity and mutogenicity specified by the International Organization for Standardization (ISO) and the Organization for Economic Co-operation and Development (OECD) guidelines. The human embryonic stem cells and progenies will also be compared with established cell lines and primary cultures, to determine whether these provide a better cellular model for the studies.

Peers

Europe and United States have recently initiated the similar strategy. EU Embryonic Stem cell-based Novel Alternative Testing Strategies (ESNATS, EU) has since 2008 been developing a novel toxicity test platform based on hESC to accelerate drug development, reduce related R&D costs and propose a powerful alternative to animal tests. In 2007, The UK Government decided to establish a public-private partnership to develop predictive toxicology
tools for stem cell lines. Department of Health UK has started the program of Stem Cells for Safer Medicines (SC4SM) to enable the creation of a bank of stem cells, open protocols and standardised systems in stem cell technology that will enable consistent differentiation of stem cells into stable homogenous populations of particular cell types, with physiologically relevant phenotypes suitable for toxicology testing in high throughput platforms. In 2009, GE Health and Geron in US have jointly initiated the strategy to develop and commercialize cellular assay products derived from hESCs for use in drug discovery, development and toxicity screening.

**Challenges**

‘Worldwide it is estimated that the number of vertebrate animals—from zebrafish to non-human primates—ranges from the tens of millions to more than 100 million used annually [3]. Invertebrates, mice, rats, birds, fish, frogs, and animals not yet weaned are not included in the figures; one estimate of mice and rats used in the United States alone in 2001 was 80 million [4]. Government funded animal testing costs U.S. taxpayers over $12 billion annually [5].

Despite the supposed stringency of animal tests on drugs deemed safe for human consumption and released onto the market, two million Americans become seriously ill and approximately 100,000 people die every year because of reactions to medicines they were prescribed [6]. This figure exceeds the number of deaths from all illegal drugs combined, at an annual cost to the public of more than US$136 billion in health care expenses [7]. In England, an estimated 70,000 deaths and cases of severe disability occur each year because of adverse reactions to prescription drugs, making this the third most common cause of death (after heart attack and stroke) [8]. The drug company Ciba-Geigy has estimated that only five per cent of chemicals found safe and effective in animal tests actually reach the market as prescription drugs [9]. Even so, during 1976 to 1985 the US Food and Drug Administration (FDA) approved 209 new compounds-102 of which were either withdrawn or relabeled because of severe unpredicted side-effects including heart attacks, kidney failure, liver failure and stroke [10]. The fact that months or years of human studies are also required suggests health authorities do not trust the results. In 2004, the FDA reported that 92 out of every 100 drugs that successfully had passed animal trials subsequently failed human trials [11].’

**Reference**

11. Harding, A. More compounds failing phase I. The Scientist, August 6th 2004