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SYMPOSIUM: FUTURES IN REPRODUCTION
REVIEW

A rapidly evolving revolution in stem cell biology and medicine

Alan Trounson

Californian Institute for Regenerative Medicine, 210 King Street, San Francisco, CA 94107, USA
E-mail address: atrounson@cirm.ca.gov.

Alan Trounson, PhD, FRCOG, FANZCOG and President of the California Institute for Regenerative Medicine (CIRM) is responsible for the management of the US$3 billion fund for stem cell research in California. Under his leadership, CIRM has constructed 12 new Californian Stem Cell Research Institutes, raising more than US$800 million in donor contributions. He has developed training programmes for new scientists entering stem cell science for a large number of MD–PhD and PhD researchers and university, college and high school students. He has overseen an extraordinary development of stem cell research which has led to more than 1000 peer-reviewed publications (24% in high impact factor journals) in the last 4 years. He has globalized the stem cell research programme and has led the translation of basic science discovery into clinical trials.

Abstract The developments arising from human IVF are remarkable. Embryos were studied for developmental patterns that have consequences for viability and fertility. Growing human blastocysts *in vitro* allowed further exploration of the differentiation of primitive embryonic cells, leading to the discovery of human embryonic stem cells (ESC). The availability of perhaps unlimited numbers of human ESC could inform the study of differentiation and also provide cells for therapies in human regenerative medicine. The developments in cell biology have been impressive, including the discovery of induced pluripotent stem cells — adult cells transduced by specific transcription factors to behave like human ESC. Key regulators of development such as activators or inhibitors of lineage progression have also been explored, particularly the fibroblast growth factor, Wnt and transforming growth factor β signalling pathways and miRNA. Such regulators can be utilized in algorithms to predict how cells differentiate *in vitro*. Using multistep differentiation protocols, many different cell types can be formed and matured into functionally effective cells, some of which are already in translational research for clinical applications. Possible future developments include destruction of cancer stem cells, reversal of type I diabetes, restoration of vision, repair of motor function, cure for HIV/AIDS and heart muscle regeneration.

KEYWORDS: blastocysts, differentiation, embryonic stem cells, gametes, germ stem cells, human embryos
VIDEO LINK: http://sms.cam.ac.uk/media/1401048

Introduction

Beginning in the late 1960s and early 1970s, human preimplantation embryos were first made by IVF techniques by the British cell biologist Robert Edwards and his colleagues (Edwards et al., 1970; Steptoe et al., 1971). Independently Carl Wood and his colleagues in Australia began research into human IVF in 1970 and they published on the first IVF pregnancy that lasted a very short time *in vivo* (De Kretzer et al., 1973). Work continued in both groups studying human IVF using fertility drugs and laparoscopic procedures to recover multiple mature oocytes for fertilization and trans-

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fer to infertile patients with some encouraging results (Steptoe and Edwards, 1976). Edwards and Steptoe in 1978 (Edwards et al., 1980; Steptoe et al., 1980) demonstrated that the mature oocyte recovered in the natural ovulatory cycle could be fertilized and that viable embryos developed using IVF could be returned to infertile patients for delivery of healthy babies. These developments were the basis for a well-deserved Nobel prize in Physiology or Medicine for Robert Edwards in 2010. The Australian group was the first to confirm independently that successful IVF could be performed in the natural ovulatory cycle of infertile women (Lopata et al., 1980). However, the method required careful tracking of the surge in the concentration of the preovulatory LH in the blood or urine from predicted days of probable ovulation. There was no control of the timing of ovulation (which could therefore occur at any time of the day or night) and there was usually only a single follicle with a maturing oocyte present. The low efficiency of single oocyte recovery and the inconvenience of untimed laparoscopic procedures made this natural cycle method difficult to sustain.

Using clomiphene for mild ovarian stimulation and the administration of human chorionic gonadotrophin to induce preovulatory oocyte maturation instead of the natural LH surge, Trounson et al. (1981) demonstrated for the first time multiple births and pregnancies using fertility drug controlled IVF. This was an effective way to recover multiple mature oocytes on a preplanned programme of laparoscopic surgery for infertile women. This method of superovulation, which evolved through clomiphene, clomiphene + human menopausal gonadotrophin to human menopausal gonadotrophin alone or FSH, became the basic procedure used for clinical IVF studies from then on. This method resulted in multiple embryos developing from a single cycle of superovulation and required the introduction of embryo freezing to preserve patients' embryos for future transfer if necessary (Trounson and Mohr, 1983; Zeilmaker et al., 1984). The fertility drug-based ovulatory control of IVF enabled the method to improve and increase its' efficiency and enabled human embryos to be produced for all stages of preimplantation development (Trounson et al., 1982) as the source for the development of human embryonic stem cells (ESC) (Reubinoff et al., 2000; Thomson et al., 1998). The recovery of multiple oocytes enabled oocyte and embryo donation (Lutjen et al., 1984; Trounson et al., 1983) and the development of embryo biopsy techniques for preimplantation genetic diagnosis of inherited genetic disease (Handyside et al., 1990; Verlinsky et al., 1990). These developments form a continuum on the timeline of developments that have evolved from IVF and continue to develop into the future (**Figure 1**).

Eggs, embryos and human ESC

The ability to cryopreserve human embryos that were donated for stem cell research, as excess to the patient's own needs, provided a source of human ESC for studying: the developmental processes during differentiation; the biology of stem cells and their developmental potential; possible cell products for therapeutic purposes in regenerative medicine; cells for tissue engineering; a source of cells for discovery of small molecules and biologics as new drugs for regenerative medicine; the understanding of disease pathology and cancer (cancer stem cells); and the manipulation of cell phenotype using transcription factors, small RNA and other key signalling molecules. Thus, this approach is likely to underpin a whole new revolution in cell biology and medicine.

What was the impetus for exploring human ESC? Firstly, the ability to develop human embryos *in vitro* to the blastocyst stage with properly formed inner cell mass (ICM) and trophectoderm (Mohr and Trounson, 1982), suggested that methods similar to those used in mouse embryology could

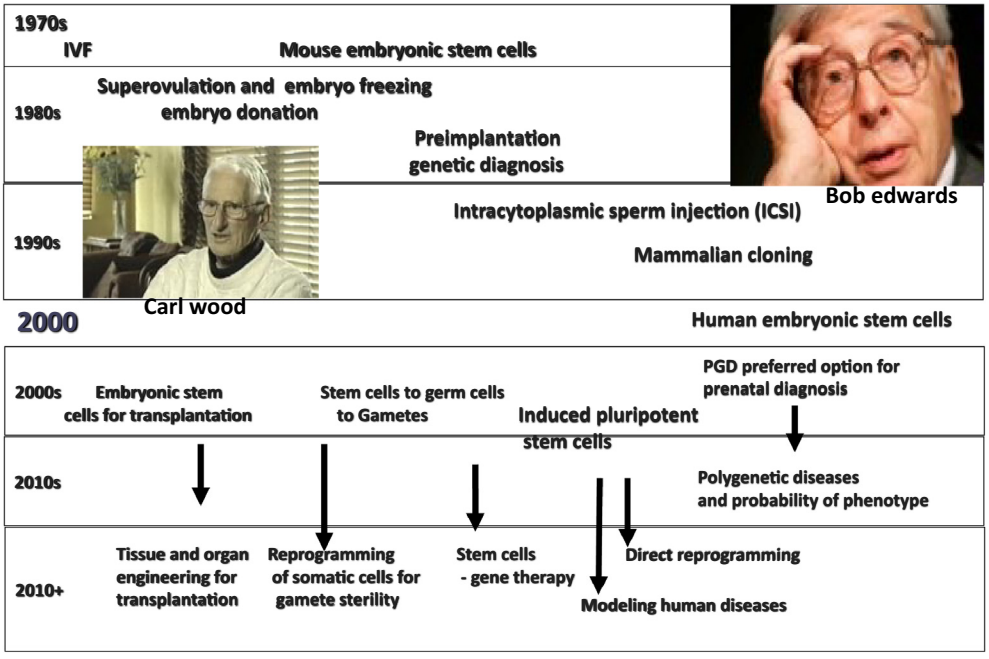

Figure 1 Timeline of human reproductive/stem cell discovery.