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Editorial

The Promise of Human Embryonic Stem Cell Research in Global Dentistry

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First isolated and reported by James Thomson in 1998 [1], human embryonic stem cells (hESCs) are self-renewing and undifferentiated cells that are pluripotential and capable of contributing to all tissues of the human body. Therefore, hESCs represent as an unprecedented *in vitro* human system for the study of human development, and the generation of differentiated somatic lineages for tissue regeneration [1-4]. Today, hESC research is revolutionizing human medical research by providing human-based platforms not only for studies of tissue development and formation, potential cell therapy for degenerative diseases and tissue injuries, but also for use in toxicity testing and drug development.

In dentistry, hESCs present the opportunities for: 1) the study of development and disease of the oral and craniofacial tissues and organs, 2) the development of predictive tools and platforms for toxicity testing of drugs and dental materials, and 3) derivation of clinically applicable cell types for craniofacial and dental tissue regeneration.

Craniofacial and dental abnormalities are the most common birth defects that occur in humans and mostly arise as a result of perturbations that affect the patterning, migration, proliferation, and differentiation of neural crest cells [5]. Much of our understanding of the neural crest development and specification has been based on *in vivo* studies utilizing model organisms such as xenopus, zebrafish, and mouse that have yet to be fully tested and validated in a human system [6]. In recent years, major efforts have been focused on delineating the gene and signalling networks regulating the neural crest development through directed differentiation of hESCs to neural crest and their derivatives [7]. Although much progress has been achieved in directing hESCs to neural crest cells, there is still very limited understanding of the transcription factors and signalling network that govern the specification to neural crest subpopulations including the cranial, trunk, vagal and sacral, and cardiac neural crest. Of note, cranial neural crest gives rise to the majority of bone and cartilage of the head and face, as well as to nerve ganglia, smooth muscle, dental and palatal mesenchyme [6]. At present, specific differentiation of hESCs to cranial neural crest and derivatives has yet to be achieved. Human ESC research of neural crest development and specification definitely holds promise for better understanding of human craniofacial/dental development and disease.

The application of ESCs in toxicology research is not new. It started in the early 1990s with the use of mouse ESCs for developmental toxicity testing, which was later validated as the embryonic stem cell test (EST) in 2004 by the European Center for the Validation of Alternative Methods (ECVAM) to predict embryo toxicity [8, 9]. Since then, EST has been one of the most studied *in vitro* alternatives for the developmental toxicity testing of compounds and materials including those for dental use [10]. With the successful isolation of hESCs, current research efforts have shifted to hESCs, which are likely to replace mouse ESCs as the next human-relevant platform for developmental toxicity testing. In recent years, human ESCs have also revolutionized drug discovery and toxicity screening by provision of organ-specific *in vitro* models for toxicity testing of drugs, compounds and materials. Although the core emphasis has been on the liver and kidney, the central nervous system, and the cardiovascular system, there is escalating effort in extending the research to cover other organ systems including the oral and craniofacial skeletal systems [11,12].

The application of hESCs in craniofacial and dental tissue regeneration is largely advanced through tissue engineering that encompasses the combination of stem cells, biomaterial scaffolds and growth factors [13]. Although several sources of adult mesenchymal stem cells including neural crest-derived dental stem cells have been identified and isolated in the last fifteen years [14], issues regarding the ease of isolation, cellular aging, and expandability still persist [15]. With the ability for differentiation to neural crest and derivatives, hESCs have the potential for development of an 'off-the-shelf' ready cell source for wide applications in craniofacial and dental tissue regeneration. Although directed differentiation of hESCs to neural crest derivatives still remains a challenge, recent advances in material science have developed biomaterials that are not only biocompatible and biodegradable, but also can incorporate certain micro environmental cues including mechanical cues through stiffness control of the material, and adhesive cues through surface engineering of adhesive ligands, to direct stem cell differentiation, in addition to biochemical cues provided by the addition of growth factors [16]. The field of tissue engineering

is fast-evolving and the techniques developed are likely to advance the translation of hESC research from the laboratory to the clinic.

The future advancement of hESC research in global dentistry will continuously focus on these key research areas as mentioned, with progression towards interdisciplinary collaboration among scientists, engineers and dentists to create new knowledge and innovative technologies that will improve the current dental practice and address the future needs of dental healthcare.

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