Building likenesses of human blastocysts: friend or folly

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The early days of embryonic stem cells and regenerative medicine research commenced in the twilight years of the last century, and with attendant fanfare for possible disease diagnosis and treatments. Founded primarily on harnessing the differentiative potential of human embryonic stem cells (ESCs), the optimistic forecast for novel therapies encompassed organ replacement or repair strategies and single cell therapies, and perhaps models for drug screening, revolutionizing the practice of medicine. Fast forward to 2021.

Along the road most traveled through the promise of stem cell-mediated therapies has appeared the discovery of factors and conditions that could make even a mere mortal fibroblast take on potentialities thought to have been reserved for ESCs, hence the Nobel prize winning arrival of induced pluripotent stem cells (iPSCs). And while the introduction of iPSCs provided alternatives to the troublesome case of destroying embryos to make new ESC lines, the stone left unturned would become how, given the fragile and fickle nature of human embryos, would the origins of so many developmental disorders ever become tractable experimentally without access to appropriate models of early human embryos?

That ESCs and iPSCs have been coaxed into assuming the identities of a variety of organs, generating any number of so-called organoid models is now commonplace. The ever-expanding repertoire of “oids” steadily sustains the biomedical research enterprises’ quest into the origins of developmental disorders and disease. And, as a bonus, these stem cell-derived organ models offer an important alternative to animal use in research by providing a more hominin-centric platform for testing newly developed drugs (1).

Within the realm of reproductive biology and medicine, we have seen the coming—and sometimes passing—of research claiming to recapitulate the propagation of gametes, male and female, in vitro from embryonic or induced pluripotent stem

cells (ESCs or iPSCs, respectively). The journey from gametes to adult “oids” via stem cells of one kind or another nearly completes the life cycle with one exception—the earliest stages of human development bridging the gap between zygote and epiblast have yet to be demonstrated even though several years ago work was published on the generation of what appeared to be the other side of the implantation ledger—true placental organoids (2)! Missing along the developmental pathway of “oidish” entities, enabled by the transformative potential of human stem cells, has been the blastocyst—at least until now!

Two recent papers published in *Nature* (and more in the queue), taking very different approaches, have managed to produce structures resembling human blastocysts. The paper by Liu and colleagues reports the production of blastocyst-like structures from re-programmed human fibroblasts under culture conditions requiring imposition of a three-dimensional environment (3). Referred to as iBlastoids, this model bears the molecular signatures and morphological features of many players expected to be involved with blastocyst development and implantation.

The paper by Yu and co-workers took a slightly different tact but also managed to produce iBlastoids bearing great similarity to those described above (4). In both cases, cultures required some 6–8 days before the blastocyst-like structures began to emerge, and notably, the efficiency remains low under their collective but different culture conditions. In this case, sequential and distinct media changes resulted in the generation of trophectoderm and hypoblast, a strategy that has been invoked in many other stem cell systems to propagate differentiated cell lines from ESC or iPSC for all of the embryonic germ layers.

Well intentioned as they are in sidestepping the restrictive limitations imposed on human embryo research, dating back to the so-called 14-day rule, the search for strong resemblances at least for blastocysts comes down to the question of - is what you see what you get? In other words, the inherent plasticity of stem cells and what they become is not only a matter of manipulating the environment from a physical and compositional point of view but enabling the self-organizing

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principles that govern so much of early development as was shown some years ago with two-dimensional cultures of human blastocysts (5, 6).

Whether these new publications on human iBlastoids (and those currently in process) will withstand the test of time as useful models for the human condition remains to be seen. There are many outstanding questions that could be addressed should the likenesses of being a blastocyst hold true. For example, how do human embryos deal with and adjust their genetic composition? Could culture conditions and medium components be defined that might minimize genetic and epigenetic susceptibilities known to exist under current practice patterns? Answers to these and related questions would greatly add to our expanding foundation of clinical knowledge along with the insights into basic cellular and molecular principles governing early human development.

We welcome Frederick Luccardi to our editorial board this month and would like to alert our readership to upcoming special issues of JARG on artificial intelligence and human ARTs and the promising prospects for IVM of human oocytes.

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