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EDITOR'S COMMENTARY

Renaissance, reinvention, or rhetoric: mitochondria in reproductive medicine 2017

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Move over, Dolly! Reproductive biology and medicine have over the past year displaced your ovine roots with those of driven hominids. Announced with fanfare some 20 years ago, the sheep cloned from a breast cell at the Roslin Institute outside Edinburgh established a milestone in contemporary science [1]. In the wake of her comings and goings, Dolly spawned careers (some of which were tragically truncated in the case of Keith Campbell, a colleague and JARG Board member); legitimized the deployment of somatic cell nuclear transfer (SCNT) in agriculture and stem cell propagation; and elicited a resounding spate of rhetoric from soothsayers preaching eternity of their cloned selves that was silenced faster than the staccato of calcium pulses that got the show on the road (*sic* egg activation) in the first place. Why?

Dolly opened a door to what has become a new dimension of reproductive medicine. And the range of publications appearing during 2017 that has built upon an existing post-Dolly human ART landscape is nothing short of remarkable. For many, these pronouncements expand our imaginations towards the possibilities of engineering gametes, embryos, or tissue equivalents providing a rationale for progress aimed at understanding fundamental developmental processes. For others, the recent technological *tour de force* for which 2017 will be long remembered casts a dark shadow on the potential uses likely to unfold from the marriage of business and medicine. In this context, but under very different conditions, Richard Feyman's insight seems ever so timely once again:

> *It is our responsibility not to give the answer today as to what it is all about, to drive everybody down in that direction and to say: 'This is a solution to it all.' Because we will be chained then to the limits of our present imagination. We will only be able to do those things that we think today are the things to do. Whereas, if we leave always some room for doubt, some room for discussion, and proceed in a way analogous to the sciences, then this difficulty will not arise.*
> (https://www.brainpickings.org/2012/08/27/richard-feynman-on-the-role-of-scientific-culture-in-modern-society/)

Recalling the milestones from 2017 could focus on any number of topics in reproductive medicine, ranging from gametes to stem cells to the two-headed scepter of gene editing for curative [2] or basic science explorations [3], and onto variations on the gene-editing theme that may already signal safety and effectiveness minimizing side effects that has attracted the attention of many poised to advance this field [4]. To think that only a year ago, the stage was set for this fledgling union between CRISPR/Cas9ism and human zygotes—with clear indications of obstacles to overcome including mosaic expression patterns and off-target editing consequences [5]. Ironically, many of those same obstacles confronting the pioneers of SCNT and the production of Dolly and other mammalian clones find their basis in matters of cell cycle status and the mystery of the egg-to-embryo transition. Stay tuned as gene editing continues to capture headlines designed for professional and public consumption.

Yet another subject dominating the field of reproductive medicine in 2017 was that of the mitochondrion.

To this end, JARG features several articles spanning various aspects of the mitochondrial madness (or merriment) so prevalent today. Our coverage includes commentaries on "Genetic affinity and the right to 'three-parent IVF'", (https://doi.org/10.1007/s10815-017-1046-8) and "At the dawn of personalized reproductive medicine: opportunities and challenges with incorporating multigene panel testing into fertility care", (https://doi.org/10.1007/s10815-017-1068). Given the ongoing debate with regard to the utility of mtDNA sampling in human embryos, we welcome the contribution of Tao and colleagues, a multi-institutional effort that begins to take a close look at the strengths and weaknesses of technological underpinnings in validation studies using an animal

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model ("Mitochondrial DNA content is associated with ploidy status, maternal age, and oocyte maturation methods in mouse blastocysts", https://doi.org/10.1007/s10815-017-1070). Finally, Viotti and colleagues provide a review on the mtDNA papers that have appeared over the past year, a viewpoint that is not shared by others working in this field, in "Is mitochondrial DNA quantitation in blastocyst trophectoderm cells predictive of developmental competence and outcome in clinical IVF?" (https://doi.org/10.1007/s10815-017-1072-6).

Looming large in the discourse over embryo selection broadly, and with respect to specific interventions that consumers are expected to finance on their own, is the specificity and sensitivity of techniques that require sampling of cultured human embryos. Complementing measures of mtDNA with parallel assessments of mitochondrial activity is a rarity amongst the papers attempting to resolve the ongoing controversy (having a distinctly molecular-centric rather than physiological content, with rare exceptions) [6].

Interested followers, and potential deployers of such technology clinically, are encouraged to follow the most recent work of Fragouli and her colleagues to obtain a balanced treatment of the subject at hand [7, 8]. Importantly, their most recent publication segues into the arena of clinical utility [9] with outcome measures that are eagerly anticipated from this and other groups bearing the burden of proof necessary before clinical implementation.

Contesting the value of the proof in hand has thus far focused on differences of opinion with respect to variations in technique and data analysis, a not uncommon quandary afflicting branches of medicine well outside of human reproduction. Burdening patients with the expense associated with tests requiring further scrutiny seems an unfair course of action, at least until a consensus can be reached on platforms for discovery that satisfy standards of genetic testing accepted by the broader medical communities around the world [10].

In many ways, what distinguishes our hopeful efforts to offer patients an array of genetic tests that could inform embryo selection practices and improve pregnancy outcomes from other domains are the limited source materials (pushing amplification technology to the limits) and an air of certainty that our methodologies are secure, reliable, and telling with respect to the biology we are trying to understand. Against a background of accomplishments in 2017 that are opening new avenues for research, it is fitting as we look forward to 2018 to face the inadequacies and limitations inherent in our approach to reproductive science, lest we contribute to the growing and worrisome problem of translating discovery of clinical import for the physicians and patients waiting for answers [11]. As Feynman said:

> *In order to make progress, one must leave the door to the unknown ajar — ajar only.*

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