Wandering-and wondering-about the pharmacological management of human infertility

David F. Albertini

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The medical management of human health disorders has taken some interesting twists in direction over the past decade. Cell based therapies have gained traction in the aspiring field of regenerative medicine. Therapeutic correction of genetic defects- through the tinkering efforts of molecular biologists- continue to be hotly pursued despite some alarming setbacks. And in the business of drug development-investments in R and D at the production end of things, coupled with the disturbingly increased financial strains imposed on consumers- a call for creative solutions has led to the generation of several options, many of which will impact the practice of reproductive medicine. So what is looming on the horizon with respect to the next iteration of drugs for managing human infertility-or fertility-for that matter?

Ironically, the halcyon days of recombinant gonadotropins are yielding to mounting pressures to reduce excessive COH where in appropriate situations patients will likely begin to reap benefits at both the pharmacy desk and their pocketbooks. Meanwhile, natural products like HMG continue to be a mainstay in human ARTs as do drugs like clomid and GnRH agonists and antagonists. Therapeutic pharmacology is aggressively taking aim at “small molecules”, which will hopefully bear the fruits of new therapeutic agents based on the massive small molecule library screening activities ongoing within academic institutions and the pharmacological industry. So far, at least to my knowledge, no breakthroughs are in evidence.

An additional tack in the quest for “new” treatments has involved the repurposing and revitalization of drugs that

already have FDA approval for what one might call an “on-target” malady. Some signs that this could be the case in the reproductive medicine field are emerging. In the same vein, we should also be mindful of the fact that not all track records are unsoiled given the reputation of DES. But in some cases, sordid mistakes from the past do reveal themselves in a redeeming light as has been the case for thalidomide and the treatment of certain cancers.

One example of this approach has emerged from the Meirow group in Israel, work that appeared earlier this year in *Science Translational Medicine* (Kalich-Philosoph *et al.*, *Sci Transl Med.* 2013 May 15;5(185):185ra62. doi: 10.1126/scitranslmed.3005402). In seeking a pathway to protect the ovarian reserve in patients undergoing ovotoxic therapies like cyclophosphamide, they demonstrated that when the drug AS101(an immunomodulator) was given concurrently to mice receiving cyclophosphamide, a significant proportion of the primordial follicle pool was retained that would have otherwise undergone premature activation and degeneration. The prospect raised by these intriguing results is that agents being developed and approved for use in treating chronic immune disorders may have a parallel application for patients whose fertility is likely to be compromised as a result of having survived ovary damaging therapies. Of course, there is a long road to haul before the utility of agents like AS101 acquire the status of a disease fighting and yet ovary-friendly drug reaches a clinical setting. But, in principle, there is every reason to believe that empirical testing in animal models is an initial step in the right direction. Importantly, and as stated repeatedly by leaders in the field of fertility preservation, having safe and efficient multi-purpose drugs that can act in a systemic was is a more direct and non-invasive approach-*sic* rational- than many of the in vitro approaches being proposed for protection of the ovarian reserve.

The reality, however, is that in the daily practice of human ARTs, working with gametes and embryos in an ex vivo context remains the norm rather than the exception and is

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Capsule The changing landscape in drug development will alter the options and strategies used in human ARTs in the future. Two examples of how novel or “repurposed” drugs are gaining traction in reproductive medicine are discussed.

D. F. Albertini (✉)
University of Kansas Medical Center, Kansas City, KS 66160, USA
e-mail: dalbertini@kumc.edu

likely to remain this way for years to come. In this light, it is interesting to note how the development of new drugs is being harnessed to manipulate gamete or embryo quality. The use of embryo culture media sets an appropriate backdrop for this kind of venture. One need step no further back than to consider the many formulations, additives, and supplements (typically not disclosed) that grace the litany of media choices purchased and adopted by embryology laboratories around the world. While not exemplifying the use of drugs per se, the deployment of human ARTs has necessarily depended on the successful marketing and development of media that in the end provide for pregnancies and healthy offspring.

A somewhat different tack, and one much more in tune with the topic of drug development, is creeping into the ART scene in the form of patentable “factors” that might be used for making some of those less than optimal oocytes much better-suited for infertility treatment.

A good example of this was recently published in the *Proceedings of the National Academy of Science* (Peng *et al.* www.pnas.org/cgi/doi/10.1073/pnas.1218020110). This cleverly crafted study builds on the nearly 20 year old discovery that mammalian oocytes synthesize, process, and secrete proteins belonging to the TGFbeta/BMP family of ligands, a large family of biologically active factors generally thought to act in a local or paracrine fashion. The authors take the reader on a journey through their own exercises in genetic engineering, resulting in the production of a recombinant GDF9:BMP15 “heterodimer”, and culminating in a series of experiments resolving an ongoing discourse over how and why these oocyte generated factors play such a prominent role in the regulation of fertility in mammals. To be fair, there is an appreciable measure of thoroughness and analysis obtained by characterization of the biological activ-

ities for the array of ligands tested. And if you are a fan of playing the evolution card, then you will enjoy and appreciate the arguments supporting why and how these molecules came to be and persisted as central characters in ovarian physiology.

But the real punchline of this work is that, with patent pending, the GDF9:BMP15 “heterodimer” will become a key additive for promoting oocyte developmental competence in human IVF. That an arena for such factors is alive and well in the field of human ARTs is not surprising. After all, there remains much momentum for using IVF and, to date, there is much discussion about what the correct conditions will be to generate high quality oocytes. The interested reader is encouraged to follow this story and the concerns that have been raised by Mottershead and colleagues (www.pnas.org/cgi/doi/10.1073/pnas.1303459110).

In the end, wandering around the literature in these fast and furious days of drug development and discovery should prompt our curiosity about how the management of infertility will look in years to come. Stay tuned for what will undoubtedly be a defining dimension in the future of human ARTs.

In closing, I would like to alert our readership to several important changes that have taken place in the editorial management of JARG. We welcome Ann Avouris as the new managing editor at Springer and thank Samantha Lewis for her key contributions to JARG over the past year. Ann is a 9 year veteran at Springer and brings a wealth of experience to us and a keen interest in publishing ethics and scientific misconduct. Two of our Editorial Board members are now serving as Associate Editors. Both Raj Kumar and Nathan Treff have served JARG over the years and respectively bring their expertises of reproductive genetics and PGD to the forefront of our mission. Finally, our newest Board members are Francesca Duncan and Paolo Taitson-welcome aboard!