Tales of a spermatological variety—finding master right

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Reflecting on what has been an amazing year of discovery in the biology of sperm, especially from an ART perspective, brings pause to the process and promise of selecting the very best candidate for incipient IVF or ICSI patients anxiously waiting with eggs in hand. The matter of sperm selection stands firmly as a challenge for urologists, andrologists and embryologists alike whether working up the plethora of likely suitors residing in a normal ejaculate or desperately seeking the scarce spermatozoa looming within a TESA sample. With selection strategies moving well beyond the tell-tale signs of normality accorded traditional semen analysis, the search for “Master Right” is acquiring a technological cloak that is unmasking the deep and dark truths buried within the process of spermatogenesis. Consistent with the dawning of new technologies for sperm selection are a series of papers in this issue of JARG that both portend and preview a world of spermatological wonder that will come to play a greater and greater role in the practice of human ARTs.

From the discovery of novel sperm gene products linked to motility and improved treatment outcomes reported by Hinduja and colleagues, to the systematic review and meta-analysis of magnetic activated cell sorting (MACS) for sperm selection by Gil and colleagues, our readership will find some hope for the future in this field alongside a series of reality checks. Among the many sources of frustration attendant to the process of sperm selection is the need to identify assayable biomarkers that will begin to limit the

subjectivity accorded by many of our current methods while sparing viability for postdiagnostic use in IVF or ICSI. What choices have we? Again the answers are emerging in the context of specific diagnoses for male subfertility or infertility where the means may not always justify the ways to an end.

Take for example what has been looming on the front of “good looks.” The debate has continued over the ability of so-called “high magnification” microscopy to differentiate between the good, bad or indifferent members of an ejaculate with respect to the genetic integrity of master right on the way to ICSI. Vialard and colleagues evaluated the utility of this approach with patients heterozygous for reciprocal translocations finding in the process of their studies that high magnification sperm selection did not reduce the incidence of aneuploidy in this population. Whether the risk factor is increased for the range of genetic reasons attributable to inherited disorders, environmental exposures, or age, there is little escaping the inherent limitations of gauging outward appearances for what are likely to be subtle but significant alterations in our genomes within.

When sperm are not of limited quantity, and the riches of a “normal” ejaculate populate the andrology lab, choosing master right becomes less of a challenge in the case of IVF unless ICSI is indicated or preferred, in which case the “many are called but few(are) are chosen” doctrine prevails. In either case, IVF or ICSI, concerns over genetic or genomic integrity are exacerbated when the very *modus operandi* of sperm—their motility—assumes front and center importance as an immediate reflection of gametic competence. As motility properties retain a mainstream role in the assessment of sperm quality, prompting enquiry as to the mechanisms befitting of those sperm designated as swift, swifter or swiftest falls well within the purview of contemporary research. Such appears to be the case in two of the studies reported herein. For example, Lin and colleagues (“*Characterization of 3-hydroxyisobutyrate dehydrogenase-HIBADH—as a sperm-motility marker*”) expand our

Capsule The challenges of sperm selection are slowly dissipating as new and old methodologies conspire to reveal the deepest and darkest secrets of our male gametes.

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horizons on the front of energy metabolism in their identification of a previously unsuspecting enzymatic candidate with which tractable assays could be developed. And, in gracing this month's cover image, the work coming from the Hinduja laboratory extends their previous efforts to hone in on relevant physiological indicators of sperm quality in the likes of Tektin 2 and CatSper2. In relating expression levels of these biomarkers to embryo quality and pregnancy rate, we see one of the first indications of how a sperm profile linked to clinical outcomes can begin to shed light on mechanistic explanations for the wide variety of results that typically linger in the many cases of infertility falling into the "unexplained" category.

Curiously, Tektins are emerging as one of those family of gene products that keep rearing their heads in the context of human reproduction. Discovered over 20 years ago by a friend and colleague of mine, Dick Linck now at the University of Minnesota, Tektins were then and continue to be recognized as fundamental building blocks in the sperm axoneme. As a foundational component of the motility apparatus in all sperm so far studied—and hence their likelihood of

being an evolutionarily conserved piece of the motility puzzle—the discovery of a clinical association with a key protein at the heart of motility behavior should resonate in the eyes of many seeking to optimize the task of sperm selection in the future. While the reverse genetic approach of associating a phenotype with candidate genes remains a long, arduous, costly, and admittedly indirect approach at best, possibilities are arising in the arena of single cell genome analysis.

Consider among these the efforts reported last summer by Quake and colleagues on the use of this technology to monitor mutation rates in human sperm (Wang et al. 2012 *Cell* 150:402–412; <http://dx.doi.org/10.1016/j.cell.2012.06.030>). There can be little doubt that the tales of a spermatological variety in forthcoming issues will be extended in verse and chapter to a level of sophistication afforded by single cell whole genome sequencing—revealing in the process the core and content sought after to explain the variable and fascinating biology of this cell.