

## Attaining fluency in bioinformatics—the gremlins are coming!

David F. Albertini

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In the field of human ARTs, searching for reliable sentinels of “good” embryo or gamete health has not come easily. While the “looks are deceiving” argument has been expounded upon in the likes of *JARG*, *Fertility and Sterility*, and many companion journals, the quest for quantifiable and practical measures used for predicting embryo implantation and term gestation resembles more a litany of lost causes than one of crowning achievements. Moving beyond the realm of the subjective, which has punctuated the history of human IVF from the mid-1980s (How does your cumulus look? What was your embryo score?), through the 1990s, when ICSI took hold (How does your sperm look?)—to the present, when the reality of obtaining a running account of embryo behavior from fertilization to transfer now falls under the purview of those clinics who believe in (and can afford) the value of time-lapse imaging to make a coherent and repeatable decision that will benefit the patient. Such are the markings and marketings of morphological assessments brought into the fourth dimension-time!

As frustrating as these approaches have been, the language of morphology that is used to describe the appearances of gametes and embryos, as we know them today, is much the same as it was in the heyday of mammalian embryology, when microscopes first availed pioneers like Corner and Streeter the fundamental insights into preimplantation primate embryo development. Their lead, at the

Carnegie Institute of Embryology, etched forever the classical studies of Hertig and Rock, provided most of us with our first glimpse at the stages of early human development. Our fluency on this subject was carved out unceremoniously by those trend-setting and discriminating observationalists, and we have used their language dutifully to bring the evaluation of the human conceptus to the translationally significant standards upon which good clinical practice is based today. But looks are not enough! Enter the age of bioinformatics.

Armed with the ability to detect and measure quantities of more biologicals than could have been imagined at the dawning of human ARTs, the information load that we now bear in biomedical science has been afforded its own discipline in the form of bioinformatics. Whether a mutated gene, a subclass of RNA, a secreted protein, or an all-too-familiar metabolite (that you banished from your synaptic circuitry when you finished taking biochemistry), your favorite molecule is likely sitting in the depths of a supercomputer, awaiting revitalization in the context of some aspect of reproduction that you consider important enough to pursue at the next level.

Enter gremlins. According to Webster’s dictionary, gremlins are “impish, foot-high gnomes that tend to clog up the works.” One might consider them “non-specific irritants” (as the late Judah Folkman referred to ambitious young students who had all the answers to the most intractable of hypotheses). But in this case, we have a name ascribed to a cumulus gene product that was among the first to be implicated as a potential sentinel of oocyte quality. And further to our quest for fluency in the new world of bioinformatics comes the apparent paradox of what a name like gremlin means in the context of human ARTs.

Linguistically, it means nothing. Practically speaking, there is now an indication that the expression of gremlin is

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*Capsule* From single gene products to microbial complexity in the reproductive tract, bioinformatics is driving the field of human ARTs from a descriptive to an analytical endeavor that is likely to change the way infertility is treated in the not too distant future.

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D. F. Albertini (✉)  
University of Kansas Medical Center,  
Kansas City, KS 66103, USA  
e-mail: dalbertini@kumc.edu

tied to fecundity in females exhibiting diminished ovarian reserves (DOR). Preliminary studies coming from the Jindal group report in this issue of JARG that women with documented DOR express lower levels of mRNA for Gremlin in granulosa cells when expression is compared to granulosa cells of women with age-matched ovarian reserves. The significance of these findings rests firmly on the well accepted notion that oocyte-specific gene products such as GDF-9 and BMP-15, as immediate biomarkers of oocyte health, regulate many of the follicle cell genes that ensure survival, growth, and differentiation at multiple stages of folliculogenesis. Thus, this and related studies reinforce the power of bioinformatics that awaits application to the treatment of infertility treatments.

But bioinformatics is bringing much more to the forefront of research in ARTs. An elegant example of this is provided in this issue by work from the Giudice laboratory, in which the microbiome of the female reproductive tract in women undergoing infertility treatment is first described. Besides identifying a level of complexity for the kinds of bacterial organisms found in vaginal washings, this work draws attention to an aspect of reproductive tract fitness that is shown to influence patient outcome.

We hope our readership will follow these developments closely, and thereby obtain a fluency in our reproductive medicine knowledge base, as it transitions from the language of anatomy to the language of bioinformatics. Just remember, gremlins are not all that bad!