Editorial

Myth versus mutant: Story of *o*

The story of the axolotl *o* mutant is ultimately heartbreaking. RR Humphrey discovered the mutant among the progeny from a cross between a pair of Mexican axolotl sibs. As the progeny larvae grew crowded in the laboratory glass bowl, they began to 'chew each other's legs off' (this vivid description is from Roy A Tassava and Barbara A Stover 1978 *Axolotl Newletter* pp 17–22; I thank Laura Muzinic, Ambystoma Genetic Stock Center, University of Kentucky, for sending me the article). Humphrey isolated these larvae and noticed that 25% of them failed to properly regenerate the chewed legs. When the poor regenerators were grown to maturity and mated, the males were found to be sterile, and the females were found to produce oocytes that arrested development at gastrulation, even if they had been fertilized by wild-type sperm. Humphrey (1966 *Dev. Biol.* **13** 57–76) hypothesized that the original brother–sister pair was heterozygous (o^+/o) for a recessive mutation in a gene he called *o* (*ova deficient*), and that the 25% non-regenerator female progeny were homozygous *o*/*o*, which failed to make a maternally active gene product required for oocytes to develop into gastrulae. This requirement cannot be fulfilled by the paternal o^+ allele. Later, R Briggs (1972 *J. Expt. Zool.* **181** 271–280) showed that the developmental defect of the o^+/o and *o/o* zygotes from *o/o* females was correctable by the injection of germinal vesicle (GV) sap from oocytes of $o^+/\ o^+$ or o^+/o females. Injected zygotes responded equally at first and developed to an advanced embryonic stage, at which time 50% of the embryos (*o/o*) stopped, and the other 50% (o^+/o) continued to develop. This indicated that the zygotic o^+ gene does not function in early development, but begins to do so in advanced embryos. Remarkably, even the GV sap of frog oocytes worked. Tragically, the *o* mutant is now lost, and the wonderful papers it engendered have been reduced to insubstantial myths. Real regenerative biologists would be ready to part with an arm for a chance to lay their stumps on *o*. To the dismal list of our disappearing heritage (e.g. Lonesome George, died 24 June 2012; Bamiyan Buddhas, destroyed March 2001; Babri Masjid, destroyed 6 December 1992), add 'fascinating mutants discovered by geneticists past'.

In 2001, invited to write a book review of the just published *Neurospora Compendium*, I came upon the unique phenotype of the *Neurospora* mutant *female and male fertility-1* (*fmf-1*). The *fmf-1* × *fmf-1*$^+$ cross arrests in sexual development regardless of whether the mutant serves as the male or female parent, unless the mutant nucleus is from an [*fmf-1* + *fmf-1*$^+$] heterokaryon. Crosses with heterokaryons produce two kinds of progeny, from *fmf-1* × *fmf-1*$^+$ ('signal'), and from *fmf-1*$^+$ × *fmf-1*$^+$ ('noise'). Possibly due to this complication, *fmf-1* was 'localized' only to between *mat* and *cr-1* (Johnson TE 1979 *Genetics* **92** 1107–1120), an interval now known to contain 3.7 Mbp and about 850 genes. No papers appeared on *fmf-1* in the next 25 years, proof of its passage into oblivion. In 2004, Srividhya Iyer joined my lab for doctoral research and, egged on by me, agreed to resurrect the mapping of *fmf-1*. The old strains were preserved at the Fungal Genetics Stock Center (fortunately, *Neurospora* strains are easier to maintain than axolotls). *Neurospora* genetics also had progressed: the genome sequence made duplication-mapping more precise, a new '*helper*' strain helped eliminate 'noise' from crosses with heterokaryons, and auxotrophic mutants could be generated in wild-isolated chromosomes without the loss of flanking sequence polymorphisms. Not only did we nail the mutant phenotype to a point mutation in the NCU 09387 gene, we even demonstrated a post-fertilization ascus-autonomous role for *fmf-1*$^+$, and used the *fmf-1* gene to devise a strategy to enrich for RIP-defective mutants (hint for RIP aficionados: *Dp(fmf-1)* × *fmf-1*, where *Dp(fmf-1)* is a linked duplication of *fmf-1* created by targeted integration). As John Wayne (1907–1979) might have put it, a mutant's gotta do what a mutant's gotta do – *instigate* research.

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