Nervous systems are generally bilaterally symmetric in morphology, but in many animals there are subtle left/right asymmetries in function. The processes that lead to the establishment and maintenance of bilateral asymmetry in the nervous system are not well understood. The nematode *C. elegans*, with its simple and well-defined nervous system, has provided a model for identifying genes important for normal lateralization of the nervous system (reviewed in Klein et al 2005, Hobert 2006).

*C. elegans* has only 302 identified neurons; most of the 32 presumed chemosensory neurons consistent of laterally symmetric pairs of neurons with similar dendritic and axonal morphology and similar postsynaptic partners (Bargmann 2006). However, early genomics studies of the expression patterns of putative receptor guanylyl cyclases found reproducible difference in expression in the paired neurons ASE left (ASEL) vs. ASE right (ASER) (Yu et al. 1997). ASEL and ASER are also different in their sensitivity to chemicals (Pierce-Shimomura et al. 2001). In the past several years, many of the genes important for establishing and maintaining the differences between ASEL and ASER have been identified and characterized in the laboratory of Dr. Oliver Hobert (Hobert 2006).

The first gene identified as important for the chemosensory differences between ASEL and ASER was, not surprisingly, a homeobox gene, *lim-6* (Pierce-Shimomura et al. 2001). A large-scale screen was done using marked transgenic strains (with guanylyl cyclase promoters driving expression of green fluorescent protein (GFP) in only ASEL or ASER). This screen identified several additional transcription factors as important for lateralization (Chang et al. 2003), as well as a small ‘gene’ called *lsy-6* (Johnson and Hobert 2005). Mutation analyses and rescue experiments were consistent with *lsy-6* encoding a conserved microRNA with a putative 23-nucleotide hairpin. This microRNA had significant complementation with the 3'-UTR of *cog-1*, one of the transcription factors identified as important for ASE development. Characterization of mutants has identified additional transcription factors (*die-1* and *lsy-6*) and an additional microRNA (*mir-273*) that are important for lateralization (Chang et al. 2004, Johnston and Hobert 2005). More recently, epistasis experiments were done using combinations of mutants in these and other genes in the putative cell fate decision pathway. Hobert et al. constructed numerous transgenic strains expressing GFP under the control of putative promoters for each gene in the hypothesized cell fate pathway; they also assayed chemical sensitivity of some of the resultant double mutants. Their results led to the hypothesis that several transcription factors and at least two regulatory micro RNAs act in a single pathway with a ‘double-negative feedback loop’ to create bi-stable states representing ASER or ASEL (Johnston et al. 2005). More recently, they have expanded their studies to look at the initiation of the bilateral differences, using cell ablation experiments in early embryos. Their results suggested that early cell autonomous changes in the precursors of ASEL and ASER were important for establishing bilateral differences (Poole and Hobert 2006).

I will discuss the strength of the evidence in support of the hypothesis of Hobert et al. that a relatively simple pathway with negative feedback controls a bi-stable state that is established very early in development.
REFERENCES


