

Meeting report

***Caenorhabditis elegans* comes of age**

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Published: 16 June 2008

Genome Biology 2008, **9**:312 (doi:10.1186/gb-2008-9-6-312)

The electronic version of this article is the complete one and can be found online at <http://genomebiology.com/2008/9/6/312>

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A report of the European *C. elegans* 2008 meeting, Seville, Spain, 29 March-2 April 2008.

In 1998, the publication of the genome sequence of *Caenorhabditis elegans* (a first for metazoans) and the discovery of RNA interference (RNAi) in this species provided a Big Bang for research using this model organism. What has happened since? Ten years later, scientists continue to squeeze the excellent experimental features of this animal to push the frontiers of knowledge forward in subjects as diverse as genomics, aging, behavior and development. Such breadth and variety was showcased at the recent European *C. elegans* conference [<http://www.upo.es/ewm2008>]. To take just one example, as evidenced at the meeting, genomic approaches often require validation that relies on genetics, and single-gene studies in return locate the gene of interest into larger functional networks. But the need to choose between the whole and the detail is long gone these days, because by now the 'wood' and the 'trees' are irreversibly connected.

Projects in the pipeline

High-throughput work was presented by Mihail Sarov (Max Planck Institute, Dresden, Germany), who showcased the TransgeneOme project, based on an alternative recombination method for protein tagging. The TransgeneOme aims to provide an open resource of tagged fosmid transgenes for *C. elegans* at a genome-wide scale. The project is rolling and is initially focusing on proteins involved in transcriptional regulation as part of an international network, the modENCODE project [<http://www.modENCODE.org>], that aims to identify all functional DNA sequence elements in the *C. elegans* genome. Importantly, the TransgeneOme project

is open for other protein sets from *C. elegans* to be included in their pipeline.

Mark Edgley (University of British Columbia, Vancouver, Canada) reported on progress from the *C. elegans* Gene Knockout Consortium in Canada and the USA. As a result of the combined efforts of the Consortium, Shohei Mitani's group in Japan and the research community worldwide, approximately one-quarter (around 5,000) of all *C. elegans* genes has been knocked out, all of which are publicly available via the *Caenorhabditis* Genetics Center website [<http://www.cbs.umn.edu/CGC>]. This is a significant milestone, and is a big step toward completing knockout coverage for the entire genome. Denis Dupuy (University of Bordeaux, France) explained the tasks that lie ahead for the *C. elegans* Localizome project [<http://localizome.dfci.harvard.edu>], which is based on expression-pattern studies in transgenic animals carrying gene promoter-green fluorescent protein (GFP) fusion constructs. The next big hurdle to overcome will be to expand the present-day small overlap between the interactome (1,541 proteins) and the localizome (1,610 gene promoters): only 48 gene/protein pairs are present in both datasets. RNAi-induced modification of expression patterns will be another way to expand the Localizome project.

Engineering the genome

Three presentations by members of Marcel Tijsterman's group (Hubrecht Institute, Utrecht, the Netherlands) presented different approaches to unraveling the mechanisms controlling DNA double-strand breakage (DSB) and repair in meiosis. Daphne Pontier described the generation of a double-transgenic strain that allows the induction of DSB at known genomic locations by controlling the expression of the rare-cutting DNA endonuclease *I-SceI* through heat

shock. This strain is being used to identify novel players in DSB repair/signaling pathways in genome-wide RNAi screens, as reported by Wouter Koole. In an effort to develop an efficient gene targeting method in *C. elegans*, Bennie Lemmens explained how they are taking advantage of *I-SceI* expressed in the germline in order to favor homologous recombination between a given locus in the genome and a transgenic DNA construct flanked by *I-SceI* target sites (located on an extrachromosomal array) that is homologous to the genome locus of interest. Marie Gendrel (Ecole Normale Supérieure, INSERM, Paris, France) presented a successful application of homologous recombination using the *Mos1* transposon. *Mos1*-based insertional mutagenesis led to identification of LEV-9 as a protein required for acetylcholine receptor clustering during signaling at the neuromuscular junction. Subsequently, she and her colleagues exploited *Mos1* using the *MosTIC* technique (*Mos1* excision induced transgene instructed gene conversion) to knock in a T7 tag at the amino terminus of LEV-9. This tag made immunostaining easier and helped locate LEV-9 at the neuromuscular junction.

Gene regulation in *C. elegans*

The recent completion of four genome sequences from different *Caenorhabditis* species is helping Frederick Partridge (University of Oxford, UK) to develop an intriguing project about translational frameshifting in *C. elegans*. This special regulatory mechanism of gene expression enables an alternative reading of the genetic code by moving the ribosome one base along the mRNA and thereby changing the frame of translation. By comparing the four *Caenorhabditis* genomes, Partridge has identified possible conserved frameshifting sites. The availability of multiple *Caenorhabditis* genomes also enables detailed analysis of *cis*-regulatory control regions. Using reporter gene analysis, Nuria Flames (Columbia University, New York, USA), has defined the phylogenetically conserved *cis*-regulatory logic of neuronal cell type specification. She defined a motif that is required and sufficient to determine gene expression in dopaminergic neurons and identified the ETS domain transcription factor AST-1 as an activator of this motif.

Andre Furger (University of Oxford, UK) highlighted the benefits of *C. elegans* to study transcription termination. The existence of operons facilitates the exploration of mechanisms that prevent premature transcription termination at the end of each gene within such a polycistronic unit. Analyzing the coupling of 3'-end formation and transcription termination at the end of transcription units, he and colleagues found that transcription can continue for up to 0.8 kb downstream of poly(A) sites before cleavage and transcription termination occurs. They also observed that after cleavage at poly(A) sites, low levels of transcription can continue to more than 1.5 kb downstream of the poly(A) site. Considering the compact *C. elegans* genome, these findings

imply the existence of previously unknown overlapping transcription units.

Helge Grosshans (Friedrich Miescher Institute, Basel, Switzerland) reported a novel nuclear export route for microRNAs (miRNAs). In vertebrates, Exportin-5 functions as an exporter of miRNAs from the nucleus to the cytoplasm. Grosshans described how the lack of an exportin-5 ortholog in *C. elegans* guided their work toward the identification of a new export complex in the nematode. Interestingly, by working with a human cell line they observed how this novel nuclear export route is conserved in vertebrates. Giana Angelo (Fred Hutchinson Cancer Research Center, Seattle, USA) shocked the audience by describing a hitherto unreported adult diapause state that will certainly be deeply studied in the following years. By using a different signaling pathway from the one responsible for dauer formation, adult worms are able to survive starvation for at least 30 days and recover a functional germline when returned to food. Angelo noted that entry into this adult diapause is dependent upon the nuclear receptor NHR-49.

An old classic never dies: the genetic screen

Genetic screens have been developed from the very beginning of *C. elegans* research. Still, the variety of strategies and questions to be addressed seems unlimited in the minds of worm scientists. Valeria Pavet (IGBMC, Strasbourg, France) reported the characterization of a transdifferentiation event, a process that directly transforms a rectal epithelial cell (Y) into a motor neuron (PDA) without involving cell division. She and colleagues have so far recovered 17 mutations from a screen for genes affecting this transdifferentiation process. Some of those mutants display a persistent Y cell that does not transdifferentiate, others a loss of a recognizable Y cell (as visualized with cell-type specific GFP fusions). This screen will be a gold mine for elucidating the intermediate cellular steps the Y cell goes through and for finding the molecules governing the processes of transdifferentiation and cell plasticity. As exemplified by Marie Silhankova (Hubrecht Institute), genome-wide RNAi screens are extremely powerful for uncovering gene function. She and colleagues screened for enhancers of the Q neuroblasts migration defect in mutants of the intracellular protein trafficking complex termed the retromer. Q neuroblast migration is regulated by the EGL-20/Wnt signaling pathway. From the results of this screen, Silhankova reported that members of the myotubularin family of lipid phosphatases are required to produce the Wnt signal involved in the migration of the neuroblasts. This role, uncovered using an RNAi approach, was then confirmed by using 'real' mutations.

A screen-in-waiting was presented by Philippa Mitchell (University of Southampton, UK), who talked about modeling alcohol dependence and tolerance, withdrawal and

relief from withdrawal behaviors in worms using ethanol concentrations that are equivalent to those with effects in humans. She and colleagues have dissected wild-type worm behaviors in great detail and are now ready to use this knowledge in screens to get at the genetics of behaviors affected by alcohol.

The early publication of a genome sequence, RNAi, and the efforts of public consortia generating powerful *C. elegans* research tools (plus tens of years of hard and gifted work beforehand) have transformed the worm into a 'top model' organism. Judging impact by the number of publications, the increasing number of *C. elegans* labs around the world and by the research presented at conferences like this one, the worm is here to stay for good - feeding biomedical research projects with vibrant and innovative ideas. It is humbling to realize though that quite a bit of the work described above was already envisaged by Sydney Brenner in the early 1960s, before both the authors of this report were born.