Worm Breeder's Gazette 17(1)

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C. elegans Researcher Directory

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Please remember to add or confirm your information in the *C. elegans* Researcher Directory. Even if your information has not changed you still need to confirm your listing. All listings which are not confirmed before March 2002 will be deleted in order to remove those people who are no longer in the *C. elegans* field.

It's a quick and easy process. Just go to **http://elegans.swmed.edu/CeRD** and find your listing. Make changes, if necessary, and then click "Submit Changes". This will cause an email message to be sent to you. (This step prevents others from changing your information without your knowledge.) Click on the link contained in the email message. Just by following this link you are confirming the information; no need to do anything else unless you want to make changes. That's it!

Technician/Research Assistant position available at Yale University

Frank Slack

Dept of Molecular, Cellular and Developmental Biology, Yale University

A technician/research assistant position is currently available in my laboratory in the Department of Molecular, Cellular and Developmental Biology, at Yale University. Our research focuses on an analysis of developmental timing, using the nematode *C. elegans* as an experimental organism (see http://www.yale.edu/slack). The research involves a variety of different procedures including: PCR amplification, DNA sequencing, isolation and blot analysis of RNA and DNA, preparation of cosmid DNA, plasmid subcloning, microscopy, animal anatomy, genetic analysis, generation of transgenic animals, cytological analysis, immunostaining. Apart from routine operations, the successful applicant will be actively participating in ongoing research projects in the lab. The specific research project will depend on skills and experience of the candidate hired. Duties also include responsibility for overseeing frozen strain collection, and general laboratory organization. Requires B.S./B.A. degree in applicable science field, with a strong academic record. One year prior experience in either molecular biology or *C. elegans* genetics preferred. Excellent organizational and record-keeping skills, ability to work independently and troubleshoot are essential prerequisites. Experienced Research Assistants as well as recent graduates who are interested in gaining research experience, are encouraged to apply. The lab is seeking an energetic and highly motivated individual. The successful applicant will work in a very stimulating academic and cultural environment.

Interested persons should send their resume and the names of three references to:

Frank Slack, Dept of MCDB, Yale University, PO Box 208103, New Haven, CT, 06520-8103.
email: frank.slack@yale.edu

Post-Doctoral Research Opportunity: Functional Genomics Studies in Aging

Marco Marra

601 West 10 Ave. Vancouver, B.C., Canada V5Z 4E6

Functional Genomics: Studies in Aging.

To participate in a funded collaboration with Dr. Don Riddle, University of Missouri (Columbia), Dr. Marco Marra and Dr. Steven Jones at the British Columbia Cancer Agency Genome Sequence Centre (www.bcgsc.bc.ca) seek a post-doctoral researcher to participate in high-throughput functional genomic studies in C. elegans, focussing on genes involved in aging and dauer biology. Previous experience in standard C. elegans procedures, including germ line transformation, is an asset. The study, funded by the National Institute of Aging, will concentrate on identification and validation of genes targetted through a combination of gene expression studies and bioinformatic approaches. The position would suit a candidate possessing some familiarity with the bioinformatic tools available for C. elegans and who wishes to develop additional bioinformatic skills. The successful applicant would be located at the Genome Sequence Centre in Vancouver, British Columbia. Please send applications by email to jobs@bcgsc.bc.ca using the subject heading "C. elegans".

Position at Caltech, CA

Paul Sternberg

Division of Biology, 156-29, California Institute of Technology, Pasadena, CA, 91125

CURATOR. Will annotate gene functions in *C. elegans*, using Gene Ontology (Nature Genetics [2000], vol. 25, pp. 25-29). Duties include: analysing gene functions in the primary literature; judging the optimal description of these functions in Gene Ontology, inventing new terms for Gene Ontology where necessary; and incorporating these descriptions into Wormbase. A Ph.D. in some area of biology and substantial *C. elegans* experience are required. The successful job candidate will have broad scientific erudition, verbal articulacy, and creative intelligence as well as patience and a willingness to work hard. Computer literacy in UNIX or Linux is a plus, but is not required. Direct inquiries to Paul Sternberg (pws@its.caltech.edu).

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Theresa Stiernagle, Bob Herman

University of Minnesota, 250 Biological Sciences Center, 1445 Gortner Avenue, St. Paul, MN 55108-1095

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WormBase Update

WormBase Consortium

www.wormbase.org

Release schedule

One of the most important improvements to WormBase over the past 12 months has been a drastic increase in the frequency of database updates. WormBase is built in two stages. In the first stage, a complete database (ACeDB) is built incorporating changes and additions from all WormBase sites. This is done weekly, and unless there is a major problem, can be downloaded weekly. The version of the database is listed on the WormBase homepage as WS#, e.g., WS56 for the September 28, 2001 update to WormBase site. In the second stage, the database is configured to support the wormbase.org website. This is now done about every two weeks.

We are close to having mirror sites at the Sanger Centre and Caltech; see the WormBase homepage for details.

User Interface

The WormBase user interface is still very much evolving. Some of the changes are:

Genome Browser. The genome browser Genome Hunter has been updated to show predicted and confirmed genes, the precise endpoints of cosmids and YACs, ESTs aligned by BLAT (see below), the regions of genomic sequence corresponding to genes defined by the Worm Transcriptome Project's analysis of Y. Kohara's ESTs, regions of homology to C. briggsae, regions with Prosite domains, the oligos and regions they amplify that have been used in some microarray and RNAi experiments, ESTs, among other features. These features are color-coded in the display. You can check boxes to specify the features you would like to see.

BLAT is a sequence alignment program written by W.J. Kent at UC Santa Cruz. It efficiently scans a pair of DNA sequences for small regions of high identity: those 40 or more bases long with 95% identity, or perfect sequence matches down to 33 bases in length. It is highly useful for aligning cDNAs to genomic DNA, or small genomic fragments to a genome draft.

Genetic Map Viewer. The new genetic map viewer that became available this past spring is Java-based and still not compatible with Macintoshs. We therefore enhanced the classic acedb graphic map display to make it easier to navigate. A new more web-friendly viewer is under development.

Search pages

Genetic Interval Search. A new genetic Interval Search page takes advantage of the interpolation of genetic and physical maps at the resolution of individual clones. This search allows you to specify a range by map position, gene name, or clone, and returns a list of genes in that region. After determining the range, this script lists all mapped mutants within the range as well as predicted genes on clones that have been interpolated into the range. Of course, since not all genetic loci are mapped relative to one another, the order of genetic loci presented in chromosomal coordinates may not actually reflect the physical order of these genes.

RNAi Phenotype Search. An RNAi search page allows you to search for genes for which RNAi experiments have been done. Most of these are from the large scale projects published in the past year, and an increasing set from individual papers. Negative data from all but the EMBL screen are included.

New data

RNAi. In addition to the 147 movies from RNAi experiments from the Ahringer laboratory (Zipperlen et al., 2001) are now included in WormBase.

Expression patterns from papers. We are focusing on extracting gene expression patterns from the 4630 papers in the CGC bibliography. We almost half done, and now have with 1297Expr patterns representing about 518 genes. In general, each experiment or cluster of related experiments is described in one Expr object. For example, if a gene's expression has been analyzed by GFP fusions and by antibodies, there will be two Expr objects in wormbase

WTP genes. The regions corresponding to over 10,000 genes from the Worm Transcriptome Project's analysis of EST sequences have been added this summer. The Thierry-Mieg's might have additional information on splicing patterns of individual genes, and you should email them for more information.

WormPep. WormPep is a set of current best inferences about proteins encoded in the C. elegans genome. Since WormPep is now revised weekly, you can obtain the data for previous versions at http://www.sanger.ac.uk/Projects/C_elegans/wormpep/.

Coming Soon

SNPs. The positions of the Washington University SNPs will be included in the Genome Viewer.

Deletions from the C. elegans Knockout Consortium will be indicated in the genome viewer and on the Gene report pages.

***C. briggsae* data.** The assembled genomic sequence from C. briggsae generated by 10x coverage shotgun sequencing at the Sanger Centre and at the Washington University Genome Sequence Center should be in WormBase this Fall.

Microarray data. We have started with Stuart Kim's global analysis of gene expression that clusters genes over about 500 experiments. Other data will be added in the near future.

Gene Ontology Consortium

WormBase has joined the Gene Ontology (GO) Consortium. GO is a structured vocabulary allowing the biological functions of gene products to be described with arbitrarily high levels of detail, and compared between diverse organisms in a way independent of sequence similarity or idiosyncrasies of a given model system. More details are available at http://www.geneontology.org.

We have begun incorporating GO terms into Wormbase. The first step was to automatically generate annotations based on the Interpro repository of protein sequence motifs, which has become the standard for computational annotation of protein-encoding portions of whole genomes (e.g., the Arabidopsis and human genomes). A second step, currently underway, is to automatically map GO terms onto ~800 genes with mass-produced RNAi phenotypes. This is being done in collaboration with the WormPD database at Proteome, Inc. The longer term and most important phase is to manually annotate each gene with GO terms. During all of this, it is continually necessary to invent new GO terms specifically fitted to the biology of C. elegans. Another basic requirement is to develop a logical scheme (ontology) relating parts of the anatomy; this is being done in collaboration with David Hall and Zeynep Altun of the Worm Atlas Project.

Gene Knockout Methods Available Online

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The Vancouver node of the *C. elegans* gene knockout consortium has made information on the gene knockout process available on the web (http://ko.cigenomics.bc.ca/protocols.html) for researchers who wish to perform gene knockout experiments in their own labs. The time-line and methods for the gene knockout process is described, from mutagenesis to isolation of individual mutations. The information also includes a detailed description and experimental protocols for PCR screening of mutagenized libraries using the "poison primer" technique. Our library construction methods are modeled after the Moulder and Barstead protocol (http://www.mutantfactory.ouhsc.edu/protocols.asp), while our mutagenesis protocol is modified from the method developed by Shohei Mitani.

We have also released an updated version of a web-accessible program that uses information in ACeDB to design PCR primers for gene knockout experiments (http://ko.cigenomics.bc.ca/oligos.shtml) and a searchable database of pre-designed knockout primer sets for standard and "poison primer" PCR screening (http://ko.cigenomics.bc.ca/oligodb.shtml).

Using *spe-26* as an alternative marker for rescue by biolistic transformation

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One of the limitations of *C. elegans* transgene studies has been the difficulty in obtaining stable (i.e., integrated), low copy number lines. Praitis et al. (*Genetics* 2001, 157:1217-26) have adapted biolistic transformation (bombardment with DNA-coated gold microparticles) to worms for this purpose by selecting for rescue of *unc-119(ed3)* lethality on starved plates. The identification of selectable markers in addition to *unc-119(ed3)*would facilitate the construction of lines with multiple integrated transgenes. In a pilot experiment, we attempted to rescue the temperature-sensitive, sperm-specific sterility (Spe) of the *spe-26(hc138ts)* mutation via biolistic transformation. We used the *spe-26* plasmid pJV145, which, by microinjection, complements the Spe phenotype. Synchronized populations of *spe-26(hc138ts)* were grown at 15 degrees until young adulthood, subjected to bombardment, allowed to recover for two hours, transferred to new plates, then shifted to 25 degrees. Otherwise, conditions for bombardment were identical to the published protocol. The large number of worms quickly depleted the available OP50, so we added an OP50 "soup" (1ml of a centrifuged culture containing ~50% bacteria by volume) every day or two as needed to prevent dauer arrest. F1 progeny of the bombarded worms should be sterile unless rescued. We obtained four independent fertile lines from 20 bombardments. PCR screening of single fertile worms with plasmid-specific primers confirmed its presence in all four lines. In three of the lines, the high frequency of sterility in subsequent generations suggested extrachromosomal maintenance; those lines were not characterized further. The fourth line exhibited stable maintenance of fertility, and Southern blot analysis confirmed the integration of a single copy of the transgene. Current efforts include testing of a different *spe-26* allele (*it112ts*) and different bombardment parameters to increase the efficiency of integrated rescue.

RNAi feeding to produce males

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Heat-shock has traditionally been used as a means to obtain males, but particular worm strains will not tolerate this process. This problem may be overcome through genetic means by introducing a *him* mutation but this involves additional steps and may complicate later experiments. In an effort to obtain males from strains that are not amenable to heat-shock, we turned to RNA mediated interference as an approach.

We made and tested a *him-14* feeding construct (many thanks to Yuji Kohara for the *him-14* cDNA and Lisa Timmons and Andy Fire for the L4440 vector) to see if males could be generated. Hermaphrodites that consume HT115(DE3) bacteria producing *him-14* dsRNA consistently produce a low but significant number of males. Interestingly, the males appear among the progeny at the end of the brood. We typically see 5-7% males in the last 100 progeny from three pooled hermaphrodites at 20ºC. Our best results are obtained by feeding L4 hermaphrodites for about 50-55 hours and then transferring these worms to a fresh RNAi plate and inspecting the progeny from the end of the brood for males. We did not observe an increase in the percentage of males if the RNAi feeding was carried over additional generations. To test if the effect persists once worms are removed from the dsRNA-producing bacteria, hermaphrodite siblings of RNAi-induced males were transferred to OP50 bacterial lawns. These animals threw fewer than 1% males (from a pooled total of 12 bulk-inspected hermaphrodite broods) in the first generation and none in the subsequent generation. We have also confirmed that males produced by *him-14* RNAi can sire cross progeny. Finally, we did not see evidence of embryonic or larval lethality.

We stress that feeding *him-14* dsRNA to produce males is effective and reversible, but not efficient. We have not successfully obtained sufficient numbers of males from strains that are somewhat unhealthy or that have a reduced brood size. Since males appear at the end of a normal brood, low brood size may hinder the production of males by this approach. Furthermore, we found that the bacteria used to produce males must be freshly grown from a healthy plate colony and used immediately. Ultimately, other genes may be more useful for this purpose. Indeed, large scale RNAi screens have identified many genes that give Him phenotypes when targeted by RNAi (e.g., Fraser *et al*., 2000).

Theresa Stiernagle kindly agreed to distribute GC363, the HT115 (DE3) bacterial strain carrying pGC8 [*him-14* partial cDNA in the Fire L4440 vector]. Many thanks to David Greenstein for discussions that led to this experiment. These results were also described in a March, 2001 note to the *C. elegans* newsgroup.

A skim milk-supplemented axenic medium to support development and reproduction of *C. elegans*

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The Reproductive Hazards Laboratory is engaged in efforts to assess effects of environmental chemicals on *C. elegans*. Incubations using liquid culture media containing *E. coli* have shown that the bacteria alone are capable of catabolizing organic compounds rapidly. Also, previously-available axenic media for liquid culture of *C. elegans,* as described by Sayre, Hansen, Vanfleteren and others, have produced relatively long generation intervals and have been found in our laboratory to contain enzymatic activity that can produce breakdown of chemicals. Either approach produces unacceptable confounding effects when applied to evaluation of toxicologic effects on worms from exposures to organic compounds. To circumvent this problem, a new axenic medium has been developed. This medium, the *C. elegans* Habitation and Reproduction (CeHR) medium, uses a base medium similar to previously published axenic media such as CbMM, but substitutes ultrahigh-temperature pasteurized skim milk at 20% of the medium volume for ingredients such as heated liver extract. The skim milk is obtained from grocery stores and is handled using sterile technique. Each batch of milk is checked thoroughly for sterility prior to use in the medium. The completed medium also is tested for sterility prior to use, and the worms added to the medium are either from existing microbiologically sterile cultures or from bleached embryos. The formula and directions for preparing CeHR medium may be accessed at http://usacehr.detrick.army.mil/clegglab.html. This medium has been used very successfully for liquid culture of N2 *C. elegans*. Beginning with synchronized cultures of L1 larvae, the interval to production of the next generation of L1 larvae is approximately 3.5 days. Worm motion is vigorous, and the medium supports high densities of worms. The CeHR medium is being used in the Reproductive Hazards Laboratory for multigenerational exposure experiments.

A rapid, PCR-based protocol to create GFP fusions

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Due to recurrence of requests, I describe here a protol to create gfp fusion constructs ready for injection within one day. The protocol entails a simple fusion PCR, which fuses two primary PCR products with a set of nested primers, schematically outlined in the Figure. In two separate PCR reactions, the promoter (or the complete gene) and the gfp coding sequence + unc-54UTR are amplified; the former from genomic DNA (or a cosmid prep), the latter from the standard Fire vector pPD95.75. The 3 primer for the promoter/gene, termed B, has a 24nt overhang to the gfp vector pPD95.75 (see Fig for details). In older versions of the protocol the 5primer for the gfp coding sequence, termed C, also had an overlap to the promoter sequence (thus making it the reverse complement of primer B), which increased the total overlap of the 2 primary PCR products by a factor of two; however, this was found not to be necessary; a 24nt overlap of the 2 PCR products created by the B primer is entirely sufficient to give a fused PCR product. The obvious advantage of this is that the C primer is no longer promoter/gene specific and can thus be used for different reactions.

An important, though enigmatic trick is NOT to purify (by whatever gel-elution method) the 2 PCR products. Just run them on a gel, eye-ball the concentration, dilute an aliquot of the PCR reaction with water to roughly 10-50 ng/ul of each product (in case the yield of the PCR product is low, it can also be used undiluted; I have encountered cases where the first PCR product was invisible on a gel and nevertheless got a fusion product) and then use 1 ul of each diluted PCR reaction in the fused PCR reaction. For the fusion reaction, nested primers must be used (A* and D*; see Figure).

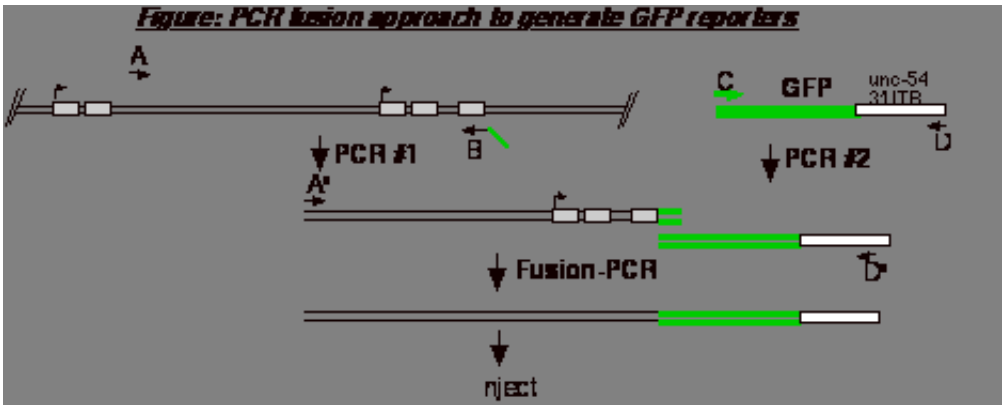
Although in most cases one will get a single band from the fusion PCR reaction, one can occasionally see another band, possibly some sort of a GFP-dimer; sometimes this additional band may even be much stronger than the fusion PCR product. It can be ignored and considered as some sort of carrier DNA for the injection. The concentration of the fusion-PCR is eye-balled on a gel and the DNA, again NON-purified, injected into worms at a final concentration of rougly 20-50ng/ul. As injection marker, rol-6 in N2 and pBX into pha-1 has been used successfully. Note that neither of these injection markers has any sort of sequence overlap to the co-injected PCR product, yet co-segration of the injected DNAs has virtually always been found.

We typically use 4 kb of promoter; other people used this protocol successfully with pieces of >10 kb. For the PCR reaction, I had best luck with Boehringers Expand Long Template PCR system using their buffer #2 and a PCR program that they recommend in the datasheet (which adds extension time for every cycle).

Provided that PCR #1 worked (in those few cases it did not work initially, shifting the A and/or A* primer usually eliminated the problem), the fusion PCR never failed. In my exprierence with more than 50 constructs so far, I also never had problems getting lines and in >90% of cases got clearly discernably gfp expression.

A slightly less optimized version of the protocol is hidden in the Method section of Hobert et al., 1999, *J.Cell Biol.*144, 45-57.

Thanks to Stephen Nurrish for an initial inspiration.



Primers:

A= 5 upstream, approx.20-25 nt

A* = nested to A (3-10 bp away from A

B = spanning 20-24 nt of end of gene to fuse + 24 nt of gfp-vector pPD95.75 (= sequence of the PLUS strand: 5-AGCTTGCATGCCTGCAGGTCGACT-3). Example: If the 3end of the gene/promoter has the plus strand sequence 5-agagagagagagagagagagag-3, the whole primer B would be: 5- AGTCGACCTGCAGGCATGCAAGCTctctctctctctctctctct-3

C = polylinker beginning of pPD95.75: 5-AGCTTGCATGCCTGCAGGTCGACT-3

D=at the end of unc-54 3UTR: 5AAGGGCCCGTACGGCCGACTAGTAGG-3

D*= immediately nested to D: 5-GGAAACAGTTATGTTTGGTATATTGGG-3

A vector for pan-neuronal smg-1-dependent transgene expression.

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We have previously described construction of strains with *smg-1*-dependent muscle-specific expression of human beta amyloid peptide (Abeta) [see WBG 16(1) p33] using the expression system devised in Andy Fire's lab (see Fire lab '97 vector kit). We have now brewed up a new vector that has allowed us to similarly generate strains with *smg-1* dependent pan-neuronal expression of Abeta and other neurodegenerative disease-associated proteins. We amplified and cloned a 3kb promoter fragment of the *snb-1* gene into Fire vector pPD118.74, a promoterless GFP construct with an abnormally long (i.e., *smg-1* dependent) 3' UTR. (Thanks to Chris Li for info on using this promoter fragment.) The GFP portion was then replaced with a newly designed multiple cloning site cassette containing a small intron (stolen from a previous Fire lab vector-based construct) upstream of the MCS, resulting in pCL35. A GFP coding cassette was re-inserted into this expression vector, and the resulting plasmid was used to transform *smg-1(cc546ts)* animals. Analysis of an integrated line (CL1234) containing this construct at 16 and 25 degrees C showed strong temperature-dependent induction of neuronal GFP. As previously reported in the original *snb-1* paper (Nonet et al, 1998), we also see GFP expression in the spermatheca. As observed for our previous *myo-3* driven *smg-1* dependent constructs, the temperature induction is not absolute, and weak GFP expression (only visible under a compound epifluorescence scope) can be seen in transgenic animals raised at 16 degrees C.

We inserted an Abeta-coding minigene cassette into pCL35 and established integrated lines in a *smg-1(546ts)* background. These lines also show temperature background-dependent expression of Abeta. We are particularly happy about this, because we have had surprising difficulty getting lines with good pan-neuronal Abeta expression, and have had a long series of failures with *unc-119* promoter-based constructs. We suspect (but have no direct evidence) that inclusion of the 5' UTR intron may have been important for getting good neuronal expression. Although including an intron is apparently not essential for *myo-3* based constructs (our *smg-1*- dependent *myo-3* driven lines do not contain an intron), this may be important for neuronal expression or expression with weaker promoters.

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Overexpression of UNC-40 in the touch neurons results in misdirection of the ALM axon.

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Ectopic expression of UNC-5 in the touch neurons leads to reorientation of their axons toward the dorsal side in an *unc-6* dependent manner (1). Therefore, the expression of UNC-5 changes their responsiveness to the UNC-6 signal from attraction to repulsion in the case of the AVM and PVM, and from non-responsiveness to repulsion in the case of the ALM. The latter suggests that the ALM contains the necessary machinery to respond to the UNC-6 signal, but is refractory to UNC-6 and sends a process longitudinally rather than ventrally. Several reasons might account for this, including that UNC-40, which is expressed in the ALM, is tightly regulated and therefore is prevented from responding to the UNC-6 ventral signal or that the forces that drive the ALM process longitudinally are dominant over the UNC-6 ventral cue. We have overexpressed an UNC-40gfp fusion protein in the touch neurons by using the *mec-7* promoter. The overexpression of UNC-40 in the ALM results in a variety of axon reorientations which we intend to pursue further. The most common phenotype we observe is that the ALM process, which normally migrates longitudinally, reorients itself towards the ventral cord before it reaches the nerve ring, suggesting that it became responsive to the proximal UNC-6 signal expressed by the axon tracts entering the nerve ring. This finding suggests that the overexpression of UNC-40 in the ALM increases its sensitivity to UNC-6 and prompted us to initiate a screen to look for mutants in which the ALM sends a process ventrally at an earlier stage. Such further increase in the sensitivity to UNC-6 may result from mutations in genes that function either in the regulation of UNC-40 or in the opposing forces that prevent the ALM from sending its process ventrally .

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Identifying male fertility genes by recombinant inbred mapping

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We have found that the Hawaiian race CB4856 exhibits much higher male fertility than N2 Bristol. We initially observed that a CB4856 mating plate can be maintained indefinitely by repeated chunking, while an N2 mating plate becomes dominated by hermaphrodites after a few generations. Since CB4856 hermaphrodites are not Him (1), the sustained presence of males must be due to more efficient mating.

Increased mating efficiency is a property of CB4856 males rather than hermaphrodites. We tested the four possible matings between males and hermaphrodites of both races. Single L4 males were mated to three adult hermaphrodites and transferred daily to new hermaphrodites, and successful matings were scored by the presence of males. Strikingly, by the fourth day of mating N2 males were almost completely sterile (1/19 successful) while CB4856 males mated well (10/15 successful). The race of the hermaphrodite played no role in increased mating. Moreover, when we tested heterozygous males, CB4856 male fertility was dominant to N2 infertility.

The *npr-1* locus is a source of behavioral differences between N2 and CB4856 (2). Thus, we tested N2 males that carry the EMS-induced *npr-1(n1353)* allele. *npr-1(n1353)*animals, like CB4856, border and clump on bacterial lawns. However, *npr-1(n1353)* males did not have increased fertility compared to N2, suggesting that the *npr-1* pathway does not control male fertility.

Hodgkin and Doniach (1) described extended male fertility in the Stanford race CB4855. The increase in fertility was dominant over N2, and loci on LGIV, LGX, and possibly LGV contributed to this behavior. Our data suggest that at least some of the loci governing male fertility are similar in the Hawaiian and Stanford races.

To determine the molecular basis of this difference in male fertility we are cloning the relevant genes. As a first step in cloning, we are using recombinant inbred mapping to locate the genes that determine male fertility differences between N2 and CB4856. In recombinant inbred mapping a large number of self-progeny are cloned from a heterozygote between the two strains of interest. Single self-progeny are cloned from each animal, and this is repeated for 10 generations. Each line thus generated is homozygous for a random sample of parental alleles, approximately half of each. The phenotype and genotype of each line is then determined. Recombinant inbred mapping is ideal for potentially complex phenotypes because it can identify multiple genes simultaneously, including modifiers.

We have generated a large number of inbred lines from N2/CB4856 heterozygotes and are currently characterizing them for male fertility and genotype. Thanks to the very large number of SNP markers between N2 and CB4856 (3), we will be able to quickly construct maps for each strain. In addition to male mating, these lines are useful for mapping any other phenotypic difference between the N2 and the Hawaiian race.

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Natural variation in egg-laying behavior

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N2 wild-type worms lay most of their eggs at the mid-to-late gastrulation stage of embryogenesis. N2 animals typically carry between 15 and 20 eggs in the first day of adulthood when grown at 20°. However, this pattern of egg-laying is not conserved among all *C. elegans* natural isolates. We examined the egg-laying behavior of 20 other *C. elegans* natural isolates by assaying the stage of eggs laid and the number of eggs carried in the gonad 24 hours after the L4 stage. By these assays, the strains can be divided into two broad groups. Five other strains laid eggs at a similar stage as N2: CB3191, CB4507, CB4555, TR388 and TR389. Fifteen strains laid eggs at earlier stages than N2 and retained fewer eggs in their gonad: AB1, AB3, CB4852-CB4858, CB4932, KR314, LSJ1, PB303, PB306, and RC301. CB4856, for example, laid 100% of its eggs earlier than mid-late gastrulation, compared to 6% for N2. Furthermore, 48% of the eggs laid by CB4856 had four cells or fewer; N2 never laid eggs at such early stages. CB4856 adults typically carried four or five eggs in their gonad.

The fifteen strains that lay eggs at early stages all show clumping behavior, whereas the six strains that lay eggs at later stages are not clumpy. Clumping behavior in these strains is determined by a polymorphism in the *npr-1* gene. We looked at the egg-laying behavior of *npr-1(ad609)* animals; *npr-1(ad609)* is a mutation in the N2 background that causes clumping by this strain. However, *npr-1(ad609)* animals do not lay early eggs (4% eggs laid before mid-late gastrulation). Thus, it is likely that clumping and egg-laying are partially independent, though it remains possible that the *npr-1(g320)* allele found in the wild strains leads to early egg-laying.

We began a genetic investigation of early egg-laying in strain CB4856. CB4856 F1 hybrids with N2 laid 33% of their eggs before mid-late gastrulation, and only 2% with four cells or fewer. This suggests that early egg-laying is a semi-dominant phenotype. Preliminary mapping of the early egg-laying phenotype of CB4856 suggested weak linkage to *lon-2* on the X chromosome. *npr-1* is tightly linked to *lon-2*.

Many questions are raised by these observations. Is early egg-laying in different natural strains determined by the same genetic polymorphism(s)? Why is there a strong correlation between early egg-laying and clumping? And perhaps the most interesting question: why is there variation in the stage of eggs laid?

Understanding the function of egl-38 and lin-48 using heat shock promoters hsp16-2 and hsp16-41

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In *C.elegans* studies of hindgut development indicate the EGL-38 Pax transcription factor directly regulates *lin-48*, a gene encoding an Ovo related zinc finger transcription factor. To better understand the function of these two genes, we have made clones that include a heat shock promoter (*hsp 16-2* and *hsp 16-41*) and cDNA for each gene. These clones will allow us to test the effect of ectopic expression for each gene.

Since egl-38 and *lin-48* are initially expressed in embryos, we wanted to test the effect of heat shock on embryos. In preliminary experiments, we observed embryos are very sensitive to the commonly used conditions of 33 ºC for 1+ hours. Consequently, we wanted to identify a heat shock (HS) condition that could both induce heat shock expression and minimize lethality. To identify a good heat shock condition, a *gfp* cDNA was cloned into the *hsp16-2* and hsp *16-41* promoter vectors. After the injection of the animals and the production of transgenic lines, the animals were heat shocked under various conditions (Table 1.1). We found the greatest *gfp* expression with minimum amount of lethality due to the heat shock was observed when the animals were incubated at 35 º C for half an hour. The above heat shock conditions were also not too detrimental for the animals if they were heat shocked everyday for 24 hours through out their developing life.

HS conditions	Clone	% lethality after HS	% lethality w/out HS	gfp expression
33 ºC for 1 hour	*hsp16-2::gfp*	7%	6%	+/-
33 ºC for 1 hour	*hsp16-41::gfp*	9%	5%	+/-
35 ºC for 1 hour	*hsp16-2::gfp*	39%	7%	+
35 ºC for 1 hour	*hsp16-41::gfp*	55%	0%	+
35 ºC for ½ hour	*hsp16-2::gfp*	9%	1%	+
35 ºC for ½ hour	*hsp16-41::gfp*	6%	5%	+

Table 1.1

These conditions were then used on transgenic animals carrying a clone with *hsp16-2::egl-38*, and animals with *hsp16-41::lin-48*. Although we found neither transgene significantly affected embryonic variability, both affected adult male spicule development (Table 1.2), *hsp16-2::egl-38* also affects larvae viability. Genetic results indicate that *lin-48* plays an inhibitory role in the development of the male spicules because *lin-48* mutant males have ectopic spicule-like structures. The similarity in effect for *egl-38* and *lin-48* is most likely due to the fact that *egl-38* is a transcription factor for lin-48. Therefore, over expressing *egl-38* results in an over expression of *lin-48,* and there by yielding the deformed or absent male spicule phenotype.

Clone	% abnormal males after HS	% abnormal males w/out HS
hsp16-2::lin-48	59%	1.6%
Control	3%	0%

Table 1.2

Suppressor Screen of *egl-38* egg-laying defect to study the vulva to uterus signalling pathway

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Communication between tissues in an organ system during their development is vital to ensure that they function as a unit. The egg-laying system in *Caenorhabditis elegans* offers a good model system to study this paradigm. Here the reciprocal interactions from the AC to the vulva and from the vulva to the uterus coordinate development between these tissues. The AC initially induces 3 of 6 multipotential Vulval Precursor Cells (VPCs) to form the vulval cells by the LIN-3-LET-23 mediated signalling pathway. Then the 1° vulval cells reciprocally signal to the uterine cells to induce uv 1 cell formation via LIN-3 again. Some genes important for the AC to vulva signal also mediate the vulva to uterus signal, whereas others function in only one or the other developmental pathway. For example, only the vulval transcription of *lin-3* requires EGL-38, a PAX transcription factors while the earlier AC expression is EGL-38- independent (1). Although the AC to vulva signal pathway has been studied in detail, the vulva to uterus pathway is less well characterized.

To identify additional genes in the reciprocal pathway from the vulva to the uterus, we have devised a mutagenesis screen for temperature sensitive supressors using *egl-38(n578*) animals. These animals are egg-laying defective (2,3). We reasoned that mutations in genes that act as negative regulators of the reciprocal pathway may supress the egg-laying defect. Identification and characterization of these suppressor genes would enable us to better understand at a molecular level, the signalling pathway occuring between tissues during their development to form an organ system.

We have carried out two genetic screens using EMS as a mutagen wherein the mutagenized animals are subjected to different temperatures during their development. To identify mutations in genes that may have essential additional functions one screen incorporates a temperature shift during the egg-laying system development:

1.Screen 1: Mutagenized worms allowed to grow at 15° C throughout their development 18,783 gametes were screened and eight candidate supressors were recovered. Two supress at all temperatures, five are cold sensitive and one supresses at 20° C.

2.Screen 2: Mutagenized worms allowed to grow at 15° C at all stages but exposed t 25° C during vulval development.12,375 gametes were screened, wherein five candidate supressors were isolated.Two have been verified to be strong supressors at 15° C while two more are weaker. One candidate seems to require exposure to both 15° C and 25° C during development to exhibit supressor phenotype.Results from screening another 12,408 gametes are still awaited.

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Comparative study of the *ovo*-related gene *lin-48* provides evidence for the evolution of transcriptional regulation

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Comparative analysis shows that proteins can be conserved entities throughout the animal kingdom, but their regulation can change during the evolutionary process. Therefore, a meaningful investigation of the molecular changes underlying gene evolution can be provided by comparison of noncoding regulatory regions from closely related species. Previous studies have characterized the *C.elegans ovo*-related gene *lin-48* as a downstream gene of the Pax factor EGL-38, and showed *lin-48* functions with *egl-38* in the development of hindgut (1). *In C. elegans*, *lin-48* encodes a C2H2 zinc finger protein. It is expressed in head sensory neuron support cells and excretory duct cell as well as hindgut cells. In preliminary studies, we showed that in *C. briggsae*, the *C. elegans lin-48* (*Ce-lin-48*) promoter was able to drive *gfp* (green fluorescent protein) expression in the same hindgut cells and neuron support cells as it does in *C. elegans*. However, expression in the excretory duct cell was essentially eliminated. This result indicated that there is a difference between *C. elegans* and *C. briggsae* in either the function or regulation of *lin-48*.

To investigate the molecular nature of this difference, we have isolated the *C. briggsae lin-48* gene (*Cb-lin-48*) from a fosmid clone. A *C. briggsae* 6.2kb *Sal I* subclone containing the *lin-48* gene could rescue the hindgut and male spicule defects in *C. elegans lin-48*(*sa469*) mutants. To test the fuction of *lin-48* in *C. briggsae*, we used RNAi. RNAi treated animals from both species showed low but reproducible levels of lethality, which is similar to *C. elegans lin-48* chromosomal mutations (2).

We constructed *gfp* reporter transgenes to investigate the expression pattern of *Cb-lin-48. Cb-lin-48::gfp* is expressed only in hindgut cells and neuronal support cells in *C. briggsae* animals, as was observed for the *C. elegans* gene. This result suggests the expression pattern of *lin-48* is different between *C. elegans* and *C. briggsae*. *Cb-lin-48::gfp* in *C. elegans* animal is likewise expressed only in hindgut cells and neuronal support cells. Thus, at least part of the difference between *lin-48* in *C. elegans* and *C. briggsae* results from differences in the regulatory sequences. To narrow down the sequences that are critical for the regulation differences between the two species, we did a series of swapping tests. The basic idea behind this is that if any sequences within the regulatory region are important for the regulation differences, the swapping of *C.elegans* sequences into *C.briggsae lin-48* should recover the expression in the excretory duct cell. One swapping clone made up of *C.briggsae* distal region and *C.elegans* proximal region showed high excretory duct cell expression. To further narrow down the proximal region, we constructed another swapping clone including 2.4kb *C. briggsae* distal and about 500bp proximal *C. elegans* sequence. This clone is able to drive expression of *gfp* in the excretory duct cell, indicating that this 500bp piece of *C. elegans* sequence is sufficient for *lin-48* transcriptional regulation in this cell. Currently, we are performing a deletion analysis of the *C. elegans* sequences in this clone. With deletion clones, it is our hope that we will be able to pinpoint the sequence changes that are responsive for the evolutionary changes in gene transcriptional regulation.

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qui-1 has been molecularly identified and corresponds to Y45F10B.10

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We have previously described the isolation, after EMS mutagenesis, of a series of mutants that have lost the ability to avoid the water soluble repellent quinine hydrocloride (*qui* mutants=QUInine non-avoiders).

Five mutants presented an unaltered response to light touch and a wild-type structure of the sensory cilia when stained with the fluorescent dye DiO. One of them, *qui-1* (*gb 404*) showed very low avoidance of quinine and SDS although its avoidance responses to high osmotic strength and Cu^{++} appear unchanged. We cloned *qui-1* using the SNPs mapping strategy (Wicks et al. 2001). Initially, we positioned *qui-1* in a small interval on the LG IV of about 120 kb, between the two SNPs Y45F10A and C08F11A. Then, we rescued the quinine avoidance mutant phenotype by injecting long wild-type PCR products in the *qui-1* (*gb404*) strain. The smallest rescuing fragment was 11 kb and contained a single gene Y45F10B.10, predicted by the *C.elegans* genome-sequencing consortium. We then sequenced the complete Y45F10B.10 gene in the *qui-1* (*gb404)* strain and found a CAA to TAA transition that generates a stop codon in the first exon. The locus can in principle produce a truncated protein of only 76 aa which presumably has no function. The results obtained in the rescue experiments and those of the sequence of the *qui-1* (*gb404*) indicate that *qui-1* corresponds to Y45F10B.10.

BLAST search results revealed that QUI-1 is a novel protein of unknown function that contains four WD 40 domains described as functional modules for protein-protein interaction. However the cellular function of QUI-1 cannot, at present, be inferred from its amino acid sequence.

Using different GFP fusion constructs we discovered that qui-1 is expressed in a subset of the sensory neurons of the amphid including ASH, ADL that have been previously identified as water soluble avoidance neurons. Using GFP constructs with the entire gene we found that the localization of the protein is not confined to the sensory cilia instead the GFP is diffuse in the cell body, the dendrite, sensory cilia and axon.

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Common imprinting for temperature and odor memories

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The AFD neurone and its postsynaptic interneurons AIY and AIZ have been identified as responsible for thermotaxis in C. elegans. It has been shown by the group of Ikue Mori that nematodes are able to learn and memorise temperature (A. Mohri et al., JWM 2000), as they display preference for and move along isotherms corresponding to their breeding temperature. This experience-dependent behavior called isothermal tracking (IT) suggest that sensory inputs present in the environment during early development can influence adult sensory properties. Genetic analysis involved several molecules in this learning process, including recently the neurone specific calcium-sensor 1 (NCS-1) expressed in the AIY interneurone (Gomez et al., Neuron 2001 Apr; 30(1): 241-8). We already suggested that olfactory imprinting (or odor memory) could exist in nematodes (Remy J.J., EWM 2000). More experiments confirmed now that adults worms can be sensitized to odorant molecules that are present during a short period of their early development. For N2 as well as for a number of other of C. elegans strains, we were able to define a critical period during which worms can learn and memorize short odor inputs. Chemotactic assays performed on adults showed that early exposure to an attractive molecule such as beta-citronellol or benzaldehyde, does sensitize worms to these attractants, but sensitization is restricted to the breeding concentration. Moreover, as for temperature memory, this behaviour is dependent on the presence of food and starved worms showed no odor learning ability. Thus olfactory imprinting and temperature memory seem to share at least three common features : short inputs during early development are efficient, memory of the "intensity" of sensory stimulation (heat level or odor concentration), and food-dependence. It is known that the thermosensory AFD and the chemosensory neurones responsible for attraction to volatil attractants, AWA and AWC, cosynapse the same interneurone AIY, suggesting the possibility of common integration of the two sensations. If this is true, then all mutations affecting temperature memory would also affect olfactive memory. We found for instance that the two alleles ot-22 and ks-5 of the thermotaxis mutant ttx-3, a LIM homeobox exclusively expressed in AIY (Hobert O et al., Neuron 1997, 19:345-357), although not affected in their chemotaxis behaviour, are affected in olfactory learning. These observations reinforce and provide new experimental support to the idea of cointegration of thermo and chemosensory inputs in C. elegans (Pierce-Shimomura, IWM 2001).

The *C. elegans* gastronome: differential palates for *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*

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It has been observed that certain strains of *Pseudomonas aeroginosa*, when served as the only food source, are lethal to the nematode worm *Caenorhabiditis elegans*. This observation has led to the use of *C. elegans* for the expeditious screening of virulence factors of *P. aeroginosa*, based on lethality. Importantly, this screen has allowed identification of *P. aeuroginosa* factors that proved essential for virulence in plant and mice. We have initiated studies to test the suitability of the use of *C. elegans* to screen for virulence factors in *Mycobacterium tuberculosis*.

The relatively avirulent, rapid-growing *M. smegmatis* (MC^2155) was initially used to examine the behavior of the nematode when offered mycobacteria as the sole food source. Preliminary studies revealed that *C. elegans* readily consumes *M. smegmatis*. Some worms, however, migrated away from the *M. smagmatis* lawn in the initial period following transfer to the center of the lawn, only to return later. This temporary avoidance was not observed on the *Escherichia coli* (OP50) lawn. Interestingly, though not quantified, enhanced sexual activities were observed in worms fed *M. smegmatis* as the sole diet, as assessed by the increased tendency of pairing of males and hermaphrodites. This apparent enhancement in sexual activities could be the result of aggregative behavior induced by mycobacterial noxious stimuli.

The aversion displayed by *C. elegans* to *M. smegmatis* was confirmed in another set of experiments. In these studies, eggs derived from bleach-treated gravid worms, deposited on a bacteria-free region of an agar plate seeded with the organism of interest (*E. coli*, *M. smegmatis*, or *M. tuberculosis*), were allowed to hatch and the migration of young larvae to the bacterial lawn monitored. While virtually all hatched larvae migrated to the *E. coli* lawn within 24 h, those seeded next to the virulent *M. tuberculosis* lawn avoided the tubercle bacillus completely. Trafficking of the larvae to the relatively avirulent *M. smegmatis* was apparent, although a significant number of worms still failed to reach the MC^2155 lawn at the end of 48h.

Young larvae obtained by the method described above were also followed to evaluate the effects of different diets on overall *C. elegans* development and reproduction. On *M. smegmatis* plates, the ability of young larvae to develop and reproduce appeared to be comparable to those fed *E. coli*, although the number of eggs produced was not enumerated. In addition, as described above, *C. elegans* readily feeds on MC^2155. By contrast, on *M. tuberculosis* plates, development was markedly stunted: the larvae remained small and moved sluggishly. This specific developmental pattern of *M. tuberculosis*-fed *C. elegans* is most likely due to the worm's aversion to the tubercle bacillus as a diet, and hence starvation.

In summary, the degree of shunning of *C. elegans* from the relatively avirulent *M. smegmatis* and the virulent *M. tuberculosis* differs significantly, as assessed by migration toward the food source, consumption of the specific mycobacterial species, and development. It is also noteworthy that C*. elegans* mating activities are enhanced when *M. smegmatis* is offered as the sole food source. Thus, although the *C. elegans* virulence screen may not be an expeditious or a suitable system for the study of *M. tuberculosis* pathogenesis, the species-specific effects of mycobacteria on some behaviors of *C. elegans* as complex as sexual activities and food consumption, and on the developmental process may deserve further investigation.

Arrhythmicity of the defecation oscillator in *lin-42* mutants

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Part of the heterochronic gene *lin-42* (1) shows significant similarity to the *Drosophila* and vertebrate *per* circadian clock genes. This encompasses the PAS domain (and adjacent PAC domain) found in many clock genes. One of most interesting aspect of the *Drosophila per* gene is that mutations affect not only the circadian clock but also two other timing processes, temperature-dependent development and a temperature-compensated ultradian clock modulating the male's courtship song (2).

The defecation oscillator of *C. elegans* L4 larvae is characterised by a remarkable regularity of the period under a given set of conditions while being highly dependent on temperature and nutritional status. Because of its regularity, it is possible to distinguish between effects on period length and cycle variability in mutants. For example, the period in the *clk-1 (qm30)* mutant is 50% longer whereas the regularity remains close to that of the wild type. Since defecation is a permanently recurring process, it may be difficult to decide when a mutant is 'arrhythmic'. However, we found that in a presumptive *lin-42* null mutant (*mg152* [a gift of Ann Rougvie]), regularity was completely lost, with an increase in the mean coefficient of variation for the 15 cycles of a single L4 from 3.5% to 23.1%. It seems justified to call this arrhythmicity. When we looked at a second *lin-42* allele (*n1089* [from the CGC]), we found it to be temperature-sensitive for the oscillator phenotype. At 20ºC, period regularity of larvae was close to wild type. At 25ºC, the strain became similar to the null mutant. The LIN-42 protein thus appears to play a crucial role in conferring to the defecation oscillator its remarkable regularity.

We have recently described a circadian clock in *C. elegans* (3) and our preliminary investigation indicates that the two alleles behave similarly with respect to the circadian clock, *i.e.* arrhythmicity in the null mutant and the ts strain at 25ºC but close to normal circadian rhythms in the ts strain at 20ºC. Like the *Drosophila per* gene, *lin-42* thus appears to be involved in at least 3 different timing processes on different time scales and with different characteristics. Its role in the ultradian and circadian rhythms is now under closer investigation.

(1) Jeon M *et al* (1999) Similarity of the *C. elegans* developmental timing protein *LIN-42* to circadian rhythm proteins. Science 286:1141-1146. (2) Kyriacou CP & Hall JC (1994) Genetic and molecular analysis of *Drosophila* behavior. Adv. Genet. 31:139-186. (3) Kippert F, Saunders DS & Blaxter ML (2001) *C. elegans* has a circadian clock. Curr. Biol., in press

Strain (30 L4 each)	Temperature (°C)	Period (sec)	Shortest mean (sec)	Longest mean (sec)	Shortest cycle (sec)	Longest cycle (sec)
N2	20°C	49.4	46.2	53.5	44	58
N2	25°C	38.2	35.9	42.2	34	44
clk-1 (qm30)	20°C	77.5	70.8	86.5	66	92
lin-42 (n1089)	20°C	52.8	46.7	58.4	43	65
lin-42 (n1089)	25°C	50.5	36.0	62.5	24	91
lin-42 (mg152)	20°C	53.3	43.1	71.4	22	118
Strain (30 L4 each)	Temperature (°C)	Standard deviation	Coefficient of variation (%)	Mean of CVs (%)	Lowest CV (%)	Highest CV (%)
N2	20°C	2.2	4.5	3.5	1.7	5.5
N2	25°C	1.9	5.0	3.7	2.8	5.6
clk-1 (qm30)	20°C	5.3	6.8	4.6	2.3	6.1
lin-42 (n1089)	20°C	3.6	6.8	4.2	2.3	7.6
lin-42 (n1089)	25°C	6.7	13.3	14.1	7.2	27.8
lin-42 (mg152)	20°C	7.6	14.2	23.1	10.6	46.2

Towards a *Pristionchus* genome map- I *P. pacificus* BAC Library construction and end sequencing of BAC clones

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In order to facilitate the easier cloning of genes in the satellite model system *Pristionchus pacificus*, we have initiated a genomic approach by constructing genetic and physical maps of *Pristionchus pacificus*. An essential prerequisite for a good genomics approach is the availability of a good genomic library with large insert sizes.

We constructed a BAC library of *Pristionchus pacificus*. The library contained 13, 440 clones in total and was a result of 4 different ligations. The average insert size of the clones is 128 kb. Insert sizes ranged between 100-180kb. We estimate the genome coverage of the library to be approximately 8 times. End sequencing of the BAC clones was done at the Genome Centre of the MPI Tübingen. Uptil now 6000 BAC clones have been end sequenced. On an average approximately 600 bp were read from each BAC end. The sequence was checked for quality using the PHRED/PHREP protocol. The total length of the BAC ends sequenced was approximately 10 Mb. The GC content of the sequence was 47%. From the 11271 ends sequenced, 8232 BAC ends gave no hits and 1129 gave hits to the non-redundant NCBI database.

Towards a *Pristionchus* genome map II Microevolutionary analysis of the nematode genus *Pristionchus*

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We describe the molecular characterization of laboratory strains of the nematode genus *Pristionchus*, which lays a foundation for microevolutionary analyses of vulva development. We isolated 13 laboratory strains of the *Pristionchus* genus that are derived from natural isolates from around the world. Mating experiments and ITS sequence analysis indicated that these 13 strains represent four different species; the gonochoristic species *P. lheritieri* and three hermaphroditic species, *P. pacificus*, *P. maupasi* and an as yet undescribed species *Pristionchus* sp., respectively.

P. pacificus is represented by five different strains isolated from California, Washington, Hawaii, Ontario and Poland. Our working ´wild type´ strain is the California strain. Since polymorphisms are becoming an important tool in modern day genomic analysis, which facilitate cloning of mutations, we decided to search for polymorphisms in the various *Pristionchus pacificus* strains. We performed amplified restriction fragment length polymorphism (AFLP) analyses of the different *P. pacificus* strains and found that the American strains are highly polymorphic (Srinivasan et al., 2001). We observed the largest genetic variation between the strain from California on the one hand and Washington and Hawaii on the other hand. In contrast, the developmentally distinct strain from Poland is identical to the Californian strain. Hence, we chose the Washington strain as our polymorphic strain for future experiments. These results provide us a framework for further studies on microevolution in developmental processes.

Reference: Srinivasan, J., Pires-daSilva, A.; Gutierrez, A.; Jungblut, B.; Zheng, M.; Witte, H.; Schlak., I. & Ralf J. Sommer, *Evolution & Development* (2001) **3**: 229-240.

Towards a *Pristionchus* genome map III SNP searches and analyses in *Pristionchus pacificus*

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The availability of polymorphic strains of *P. pacificus* and a genomic BAC library of *Pristionchus pacificus* with large insert sizes encouraged us to use a BAC end based strategy to achieve our goal of constructing genetic and physical maps of the satellite model system *Pristionchus pacificus*. We looked for polymorphisms in the sequenced BAC ends using the SSCP (single stranded conformation polymorphism) technique. The BAC end sequences were obtained from our Genome Centre at the institute and primers were designed to amplify 180-250 bp amplicons within these BAC end sequences. We used an inhouse program Prime Array 3.0 to design the primers. These primers were used to amplify both California and Washington DNA´s and the resulting PCR products were run on an agarose gel to check for the presence or absence of bands. Later they were run on an SSCP gel to check for mobility differences. We found a total 131 SNP´s . BAC ends that showed mobility differerences were then rechecked by sequencing the Washington PCR product and compared to the already available California sequence. Sequence comparison was done on a commercially available program Sequencher3.0. We found that the percentage of insertions and deletions in *Pristionchus pacificus* was more than in *C.elegans* (data from Wicks *et al*) However the single base pair substitutions were lesser than in *C.elegans*. This result indicates that insertion and deletion events are more common in *Pristionchus pacificus* than single base pair substitution events.

Towards a *Pristionchus* genome map IV A genetic linkage map of *Pristionchus pacificus*

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In order to construct a genetic linkage map of *Pristionchus pacificus*, we generated a meiotic mapping panel of 46 animals. These animals were randomly picked in the F2 generation of a cross between a California phenotypic marker and Washington strain. Each SNP gives a certain segregation pattern with these 46 animals and the segregation patterns can then be fed into a computer program(Map Manager written by Stanford University) which then generates a genetic linkage map. We tested 131 SNPs on the mapping panel by SSCP analysis to construct a genetic linkage map of *P.pacificus*. Out of these 131 SNPs, 38 of them were ESTs and genes and the rest were BAC ends.

129 of the 131 SNPs assign to six linkage groups, the two remaining SNPs are unlinked to one another and to any other linkage group. We only considered markers that showed a recombination distance of less than 22 cM. The average genetic distance per linkage group is around 78 cM and the total genetic distance is 469 cM. The number of SNPs per chromosome and the distribution of the SNPs on a chromosome varies in accordance with genetic linkage maps of other organisms. We have selected two SNPs per chromosome for mapping *P. pacificus* vulva defective mutants. California derived mutant hermaphrodites were crossed to Washington males and 21 clones of mutant F2 animals were tested with the respective SNP markers for each chromosome by SSCP analysis. Unlinked markers are expected to be represented equally, whereas linked markers should give a predominant segregation of the Californian pattern. To demonstrate the utility of this method, we mapped *Ppa-unc-1*, the *P. pacificus* homolog of *Cel -unc-22*.

Simulation of bacterial transport in the pharynx

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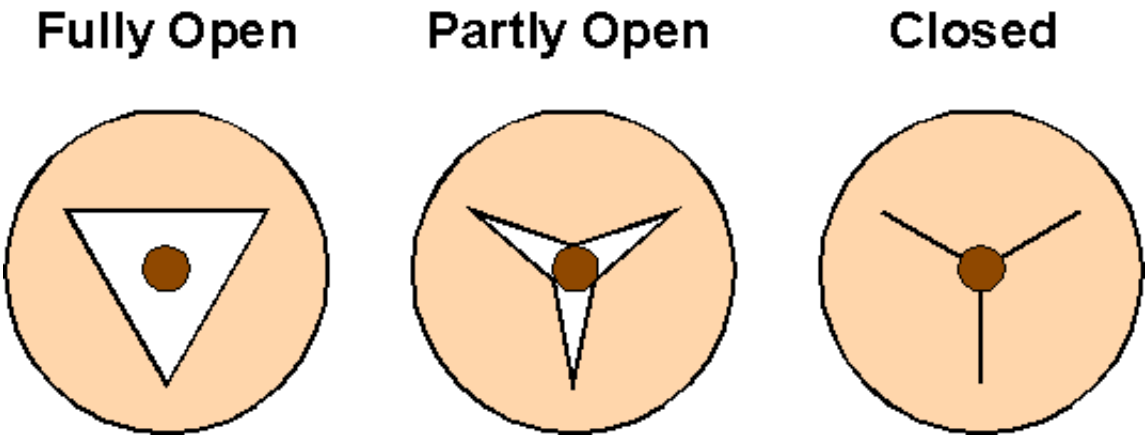
C elegans is a filter-feeder: it takes in liquid with suspended particles (bacteria), then spits out the liquid, while trapping the particles. However, the pharynx lacks any obvious filter. When one analyzes videotaped motions of bacteria in the pharyngeal lumen, they seem to move backward with the liquid during the pharyngeal contraction, as you would expect. However, when the muscle relaxes, the liquid rushes forward and out the mouth, while the bacteria seem to remain where they are. Unfortunately, the relaxation is very fast, only a few milliseconds, so that the detailed motions can't be seen. One can imagine exotic mechanisms by which bacteria are trapped during muscle relaxation (one that seminar audiences often come up with is differential adhesion of bacteria to the walls of the pharyngeal lumen depending on membrane potential). However, I decided to test whether I could simulate the trapping of bacteria by simple hydrodynamic mechanisms.

The simulation incorporates three assumptions. Two are not controversial:

1. When the diameter of the pharyngeal lumen is less than the diameter of the bacterium, the bacterium is held in place by the lumen walls.

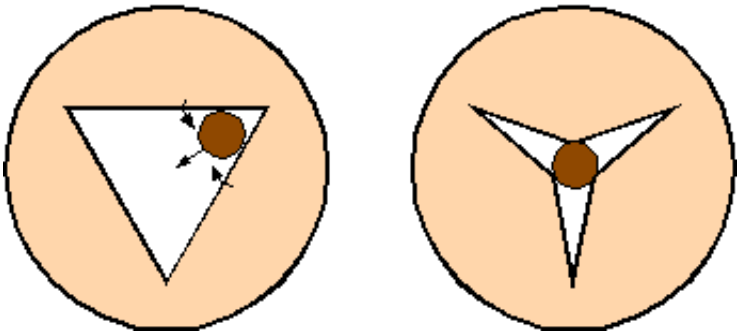
2. When the diameter of the lumen is greater than the diameter of the bacterium, the bacterium moves with the fluid.



Under these assumptions, there would be no net transport of bacteria if the pharynx contracted simultaneously along its entire length and the relaxation were a simple reverse of the contraction. This is actually a very general result: in a system as small as the nematode pharynx, inertial forces can be ignored, and fluid motions are linearly related to the forces that generate them. Such a system can generate no net change if its motions are described by a single degree of freedom. In fact, analysis of videotapes shows that pharyngeal motions are not synchronized along the entire length of the pharynx: the anterior isthmus begins its contraction and relaxation slightly after the corresponding motions of the corpus. When this slight delay is included in the simulation, bacteria assumed to move at the mean fluid velocity are trapped and transported, but very inefficiently. The volume of the anterior isthmus is much less than that of the corpus, so that its influence is small.

The last assumption that went into the simulation is less obvious, but is plausible given the triradiate shape of the pharyngeal lumen (figure above):

3. Bacteria are pushed to the center of the pharyngeal lumen when it closes (figure below).



Fluid moves faster than the mean velocity at the center of a tube, because motion near the walls is slowed by friction. The ratio of center to mean flow velocities can be determined by solving the Poisson equation. Solving Poisson's equation for the pharyngeal lumen predicts that the center flow velocity should range from 2.2 to 3.2 times mean velocity, depending on the extent to which the lumen is open. Thus, the third assumption predicts that bacteria will at move 2-3x mean velocity. This increased velocity, it turns out, greatly magnifies the effect of the delayed isthmus motions. The simulated pharynx transports bacteria posteriorly with an efficiency that looks like the real thing.

The simulation, along with a more detailed explanation, is available as a Java applet at http://eatworms.swmed.edu/~leon/pharynx_sim/.

These results suggest that simple hydrodynamics are indeed sufficient to explain the trapping and transport of bacteria within the pharynx. The most direct way to test whether this mechanism is correct would be high-speed videotapes of the motions of particles in the pharyngeal lumen, which, although technically difficult, is probably possible. Until that can be done, there are other predictions that are simpler to test. First, the model predicts that the changes in anterior isthmus motions should have large effects on the transport of bacteria within the corpus. Second, it predicts that the relative timing of the motions of the corpus and anterior isthmus should be critical. (We have had evidence for this for many years: M3, which control the timing of relaxation, is important for efficient transport of bacteria.) Third, it predicts that asymmetric motions of the pharyngeal muscles, which would tend to drive the bacteria off-center, should decrease the efficiency of bacterial transport.

Dye transport and the *bright* screen

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In an attempt to label embryos, we injected distal gonad arms with fluorescent dyes. To our surprise, the labeling failed, because the dyes were rapidly transported from the gonad to the intestine. We tried three dyes that differ in charge: hydroxypyrenetrisulfonic acid (HPTS), which, with three sulfonic acid groups, is always highly charged at neutral pH, carboxyfluorescein (CF), which has a single carboxylic acid group and therefore will carry a single negative charge most of the time and be neutral about 0.1% of the time, and rhodamine B (RB), which has a neutral resonance form at neutral pH. HPTS was in the gonad immediately after injection, but four hours later was entirely in the intestine. RB moved from gonad to intestine incredibly fast: by the time we injected the second gonad arm of a worm, most of the dye injected into the first arm had already moved into the intestine. CF moved from gonad to intestine at an intermediate rate. Injected dyes were rapidly eliminated when the worm was placed on a seeded plate lacking dye. In one RB-injected worm the anus was disrupted by clumsy injection technique. This worm became constipated and remained highly fluorescent, suggesting that dyes are pumped into the intestinal lumen and then defecated.

Since injection is too labor-intensive a way to label large numbers of worms, we tested whether we could label them by soaking. HPTS was not taken up by worms soaked in it, but worms soaked for 20 hours in high concentrations of RB or CF became brightly fluorescent throughout their bodies (including the gonad). Bacteria in the suspension improved the uptake of dye, presumably by stimulating pharyngeal pumping. When these labeled worms were placed on a seeded plate without dye, fluorescence rapidly moved to the intestine, and most was eliminated in an hour.

The dyes do not merely equilibrate between the gonad and the intestine - they move quantitatively from the gonad to the intestine. This suggests an active process for pumping dyes out of the gonad. The efficient elimination of HPTS, which should not be able to cross membranes passively (and didn't get in by soaking), also suggests an active process. The P-glycoproteins are an obvious candidate for the pumps. However, those P-glycoproteins that have been studied in the Plasterk lab are expressed in the intestine. Thus, although they are candidates for eliminating dyes from the intestine, they probably don't explain transport from gonad to intestine. Consistent with this, when we tested *pgp* and *mrp* mutants by soaking in CF then allowing them to feed in the absence of dye, we found that they efficiently concentrated dye in the intestine, but that the intestine remained fluorescent far longer than in wild-type.

By soaking the F_2 progeny of mutagenized worms in CF, then allowing them to feed on unlabeled bacteria and screening for worms that remained fluorescent, we have isolated two *bright* mutants. One of them looks like the *pgp* mutants: it concentrates CF in the intestine but is slow to eliminate it. The other retains dye in the gonad.

Many chemicals are ineffective on intact worms, even though they can be shown to be effective if they somehow can be gotten to their targets in the animal. For instance, 1 μM serotonin produces a maximal stimulation of pumping in a dissected pharynx, but 10 mM is required to maximally stimulate an intact worm. Jim Lewis showed many years ago that levamisol is more effective on cut worms than intact. That worms would have defenses against foreign chemicals is not surprising. We suspect that these defenses are more complex than the simple passive defense of a relatively impermeable cuticle. Active metabolism of foreign

chemicals by the worm’s array of cytochrome P450’s, and elimination through the intestine by the mechanisms we describe here, could also serve as chemical defenses.

The MAP kinase phosphatase LIP-1 is required for the meiotic cell-cycle arrest in developing oocytes

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The RAS/MAP kinase signaling pathway plays an essential role at two steps during hermaphrodite germline development. First, RAS/MAP kinase (MPK-1) signaling is required for the progression of germ cells through the pachytene stage of meiotic prophase I (Lee *et al.* 2001, IWM abstract 991). After pachytene exit, MPK-1 is rapidly inactivated and the developing oocytes arrest in the diakinesis stage of meiotic prophase I. As the oocytes approach the spermatheca, the secreted sperm signal MSP causes the re-activation of MPK-1, which induces oocyte maturation and allows the meiotic cell cycle to progress (Miller *et al.* 2001).

We have previously shown that the dual specificity phosphatase LIP-1 acts as a negative regulator of MPK-1 during vulval induction (Berset *et al.* 2001). Here, we report an important role for LIP-1 in regulating MPK-1 activity during germline development. A *lip-1* loss-of function-mutation (*zh15*) suppresses the pachytene arrest caused by reduction-of-function mutations in *mpk-1* (*oz140* or *ga111*). Consistent with this genetic interaction, we detected anti-LIP-1 antibody staining in pachytene stage germ cells but no staining at other stages of germline development. Furthermore, the proximal gonads of *lip-1(zh15)*mutants contain more but smaller oocytes than wild-type gonads (12.3±4.1 oocytes in *lip-1(zh15)* as opposed to 7.9±1.6 in wild-type gonads). The rate of oocyte maturation, on the other hand, is unchanged. Thus, germ cells in *lip-1(zh15)* mutants exit the pachytene stage at an increased rate, resulting in an overall acceleration of oocyte development. Moreover, by staining gonads with an antibody specific for the diphosphorylated, activated form of MAP kinase (anti-DP-ERK) we found that MPK-1 fails to be inactivated after germ cells exit the pachytene stage in *lip-1(zh15)*mutants. The increased levels of activated MPK-1 persist throughout the diakinesis stage until fertilization occurs. Interestingly, in 9% of *lip-1(zh15)* single mutants a few (< 5) unfertilized oocytes per gonad arm display an endomitotic (Emo) phenotype, they start multiple mitotic cell cycles without undergoing cytokinesis. This Emo phenotype is more penetrant (>80%) and stronger (usually >20 mitotic nuclei per gonad arm) in feminized (*fem-2* or *fog-1*) *lip-1(zh15)* mutants that produce no sperm. Thus, unfertilized oocytes in *lip-1(zh15)* mutants often fail to arrest the meiotic cell-cycle.

Taken together, our results indicate that LIP-1 is responsible for the inactivation of MPK-1 after germ cells exit the pachytene stage. The inactivation of MPK-1 by LIP-1 is critical to allow the developing oocytes to arrest the meiotic cell cycle in the diakinesis stage until oocyte maturation is induced.

EGL-15 promotes protein degradation in muscle by activating the Ras-MAPK pathway

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· We reported earlier that activation of LET-60 Ras provokes the degradation of a soluble, enzymatically active unc-54::lacZ fusion protein in body-wall and vulval muscles [1]. Specifically, animals homozygous for the temperature-activated Ras allele ga89 shifted to 25°C as adults had a time-dependent loss of lacZ activity and of reporter protein. We also reported [2] that lin-45(sy96), mek-2(ku114), or mpk-1(n2521) suppressed degradation in let-60(ga89) animals. Using animals homozygous for gaIs37 (Ef1a::Dmek hs::mpk-1+) [3] we were able to acutely activate MPK-1 in adults and observed degradation of reporter protein. Thus, the Raf-MAPK cascade is necessary and sufficient to elicit muscle protein degradation in response to Ras.

We also reported that clr-1(e1745) animals, like let-60(ga89) animals, catabolized lacZ reporter at 25°C but not at 16°C. Degradation in clr-1(e1745) animals was suppressed by a reduction-of-function mutation in egl-15(n1783), which encodes a fibroblast growth factor receptor homologue. In clr-1(e1745), like let-60(ga89) animals, cycloheximide treatment from the time of temperature shift does not prevent protein breakdown, implying that in both cases protein catabolism does not depend upon induced gene expression, but rather uses pre-existing signaling pathways and proteases.

Since activation of EGL-15 (via clr-1 reduction-of-function), LET-60, or MPK-1 (gaIs37 animals) leads to both a "clear" phenotype and protein degradation, and egl-15(n1783) fails to suppress protein degradation in let-60(ga89) animals, we have performed epistasis experiments to determine if EGL-15 is signaling protein degradation via the Ras-MAPK pathway. A strong reduction-of-function mutation in let-60(n2021) was previously reported [4] not to suppress the "clear" phenotype of clr-1(e1745) and similarly fails to suppress protein degradation. However, treatment of these animals (but not clr-1(e1745)) with the Ras farnesyltransferase inhibitor manumycin [5] from the time of temperature shift does result in suppression of protein degradation and to a lesser extent the "clear" phenotype. Protein degradation in clr-1(e1745) animals is suppressed by lin-45(sy96), mek-2(ku114), or mpk-1(n2521). Both lin-45(sy96) and mek-2(ku114) also suppress the "clear" phenotype of these animals. Mutations in genes whose products have a role in Ras signaling and which are known to suppress the "clear" phenotype [sem-5(n1619), sem-5(n1779), soc-2(n1774), or sur-8(ku167)] also suppress protein degradation in clr-1(e1745) animals. The finding that both LET-60 and MPK-1 are necessary for protein degradation in clr-1(e1745) animals, coupled with the observation that activation of either LET-60 or MPK-1 is sufficient to provoke protein degradation, implies that EGL-15 signals protein degradation via SEM-5 and the Ras-MAPK pathway.

In contrast to our previous results on muscle protein degradation in response to starvation, loss of cholinergic input, or Ras activation, there is no precedent in mammals for FGFR activation leading to protein degradation. However, it is attractive to speculate that FGF-induced protein degradation may be important for muscle remodeling or myoblast migration. Currently we are attempting to determine how EGL-15 induced protein degradation is opposed by signal from another receptor tyrosine kinase known to be involved in protein catabolism in mammals, and if these signals are acting in muscle cells.

(Many thanks to Stuart Kim, Dave Eisenmann, Min Han and the CGC for strains.)

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Isolation and characterization of suppressors of the ryanodine receptor gene *unc-68* mutants

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unc-68 encodes the *Caenorhabditis elegans* ryanodine receptor consisting 5,071 amino acid residues. Most of deletion mutants move slower than the wild-type N2. Only one missense *unc-68*(*kh30*) mutant is isolated as a ketamine-response abnormal (Kra) showing convulsions with intermittent paralysis in 30 mM ketamine. The *unc-68*(*kh30*) worm produced a full-sized protein having an amino acid substitution at Ser1,444 to Asn which is a putative phosphorylation site of a protein kinase C (Sakube *et al*., J. Mol. Biol., **267**, 849-864, 1997).

To investigate molecules interacting with the ryanodine receptor, we isolated revertants from *unc-68*(*e540*) and *unc-68*(*kh30*) animals. Seven revertants were isolated from *unc-68*(*e540*), a nonsense mutant having splicing defect, by choosing faster moving animals. Although the motility of these animals was recovered, the brood size was not. Wild-type N2 bred 330 +/- 49 eggs and 99 % was hatched while *unc-68*(*e540*) bred 102 +/- 12 eggs and 87.6 % was hatched. The brood size of revertants was similar to that of *unc-68*(*e540*) and hatching rate was about 70 % of the wild-type. We also determined the egg laying rate and defecation cycle. Egg laying rate of the wild-type and *unc-68*(*e540*) animals were 7.3 and 1.4 per hour respectively. Egg laying rate in each revertant was two to three times higher than that of *unc-68*(*e540*). Although we have not analyzed more details about these *unc-68*(*e540*) revertants, these results suggest that in *C. elegans*, only one ryanodine receptor has different function in body-wall and vulval muscles. On the other hand, five revertants were isolated from *unc-68*(*kh30*) by choosing a paralyzed phenotype in 30 mM ketamine like as the wild-type. We tested responses of revertants against some drugs. From the sensitivities to 50 mM caffeine which induces ryanodine receptors to the open-state, five revertants assigned to three groups; the first had high sensitivity, the second had lower sensitivity than the *unc-68*(*kh30*), and the last had medium sensitivity between wild-type and *unc-68*(*kh30*). We also observed sensitivity to ryanodine; open the channel of ryanodine receptors, levamisole; agonist of acetylcholine receptor, and ouabain; N^+, K^+-ATPase blocker. We assume that the revertants showing lower sensitivity to drugs have abnormal Ca^{2+} control, and one of them showing slow movement and high sensitivity to drugs may be very low Ca^{2+} concentration in body-wall muscle. The suppressor gene of the latter was mapped to X chromosome. Using three-factor analysis and cosmid rescuing, this gene was mapped to the region of 0.5 map unit neighbor of *lin-15*.

Sodium-dependent Neurotransmitter Transporter (*snf*) Genes in *C. elegans*.

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Sodium-dependent neurotransmitter transporters are required for efficient clearance of neurotransmitters (and other bioactive molecules) from synaptic clefts. These proteins typically have 12 transmembrane domains and transport activity is dependent on Na^+ and Cl^-. Several of these transporters have well-established roles in behavior and/or neurological disorders; however, for many, the endogenous substrate and/or cellular functions are unknown. These transporters are generically designated as members of the **S**odium:**N**eurotransmitter symporter **F**amily, with the Pfam entry "SNF". There are at least 18 members of the SNF family in humans and 14 each in *D. melanogaster* and *C. elegans*. Sequence comparisons suggest that humans, fruitflies, and nematodes share a core set of SNF proteins, which include the dopamine, serotonin, and GABA transporters. In addition, each species has a unique set of SNF proteins. There are already two characterized members in *C. elegans*: *dat-1* (T23G5.5) encodes the dopamine transporter (Duerr *et al*. 2001; Nass *et al*. 2001) and *mod-5* (Y54E10BR.7) encodes the serotonin transporter (Ranganathan *et al*., 2000). By our analysis, there are 12 additional family members in the worm genome. We propose the *C. elegans* gene designation *snf*, consistent with the Pfam designation. The gene names are listed below in order of LG and map position. There are at least three additional genes that turn up in database searches, but have significantly lower BLAST scores and have not been given the *snf* designation. These include Y43D4A.1 (CE21874), F56F4.3 (CE11264), and C09E8.1 (CE19347). We now have knockouts of F55H12.1 (*snf-2*), T13B5.1 (*snf-3*), C49C3.1 (*snf-9*), Y32F6A.2 (*snf-10*), T03F7.1 (*snf-11*), and T25B6.7 (*snf-12*). Together with *dat-1* and *mod-5*, there are now knockouts of 8 of the 14 gene family members (isolated by the Barstead and Mitani divisions of the Gene Knockout Consortium). Based on the subtlety of the phenotypes thus far, we think it is unlikely that any of these mutants will turn out to represent previously identified loci.

Proposed Name	Cosmid ORF	LG	Map Position	Wormpep
snf-1	W03G9.1	I	-0.46	CE14554
snf-2	F55H12.1	I	3.19	CE11206
snf-3	T13B5.1	II	-13.5	CE13605
snf-4	Y46G5A.25	II	9.05	CE24297
snf-5	Y46G5A.30	II	9.05	CE24301
snf-6	M01G5.5	III	-22.75	CE19539
snf-7	ZK1010.9	III	20.01	CE23490
snf-8	ZK829.10	IV	5.43	CE24742
snf-9	C49C3.1	IV	29.36	CE18554
snf-10	Y32F6A.2	V	2.57	CE16609
snf-11	T03F7.1	V	3.1	CE06344
snf-12	T25B6.7	X	0.31	CE14176

The serotonin-synthetic AAADC *bas-1* gene is C05D2.4

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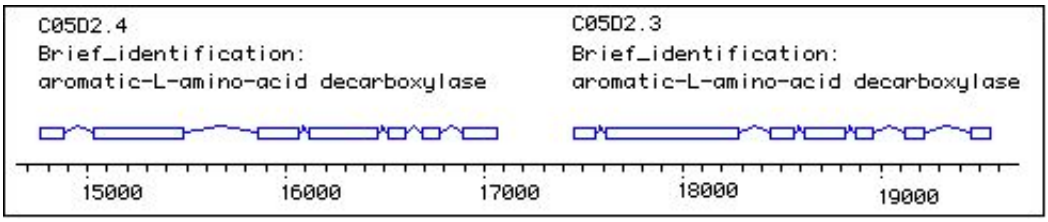
We are characterizing genes used by the serotonergic neurons in *C. elegans* to learn how they are regulated; among these is the *bas-1* gene, which encodes a serotonin- and dopamine-synthetic aromatic amino acid decarboxylase (AAADC). Mutants in *bas-1* are serotonin- and dopamine-deficient. Wildtype serotonin immunoreactivity (IR) can be restored by application of exogenous serotonin, but not its immediate precursor 5-HTP; this phenotype is consistent with the loss of serotonin-synthetic aromatic amino acid decarboxylase activity. Wildtype serotonin-IR is rescued in *bas-1* mutants by injection of the cosmid C05D2 and various subclones containing two adjacent AAADC genes called C05D2.4 and C05D2.3 (see figure below). We now show that the first predicted gene, C05D2.4, is required for rescue of *bas-1* and encodes the serotonin-synthetic AAADC activity in *C. elegans*.

We have identified the mutations in four *bas-1* mutant alleles (*ad446*, *pa4*, *n2948*, *n3008*); a fifth allele (*tm351*) was recently generated by the *C. elegans* Gene Knockout Consortium with a large deletion of C05D2.4 coding sequence (thanks!). Both the *tm351* homozygote and *tm351*/*ad446* are serotonin-(-IR)-deficient. The alleles *pa4*, *n2948* and *n3008* contain point mutations in C05D2.4 coding sequence resulting in premature stop codons. The original *bas-1* allele, *ad446*, contains a 4268 bp deletion from the second exon of C05D2.4 to the final intron of C05D2.3, so is a knockout of both predicted genes. [Vexing question: why do *ad446* worms have residual serotonin-IR?] Our results are consistent with the hypothesis that mutations in C05D2.4 cause the Bas phenotype. We have also determined that a construct mutated in C05D2.4 (frameshift creating a premature stop codon) does not restore serotonin-IR to *bas-1* mutants (2 independent lines) whereas constructs mutated in C05D2.3 do rescue *bas-1* (frameshift creating a premature stop codon - 1 line; GFP insert into coding region - 2 lines). The smallest subclone we have tested to date that rescues *bas-1* mutants has 8.8 kb containing both genes intact, with 2.6 kb upstream of the C05D2.4 start.

C05D2.4/*bas-1* cDNAs are trans-spliced to SL1. We have isolated *bas-1* cDNAs with RT-PCR; we have received other cDNAs from the EST project (thanks to Y. Kohara et al.) and the ORFeome project (thanks to J. Reboule et al.). Two YK clones came from the 'full-length' capped library, and each has an SL1 leader and poly-A tail, but both contained internal deletions (overall abnormality of these clones reported at ~5% - J. Thierry-Mieg et al., 2001 IWM Abstract 231). We have cloned two splice variants different from the Genefinder-predicted cDNA (the predominant form); to date we have found one of these also among ORFeome project-derived clones (also predominantly the predicted form). In one variant, a 27 bp microexon is spliced in between predicted exons 2 and 3. A second variant uses an alternative splice acceptor 60 bp upstream of the usual splice site for exon 3; this alternate splice introduces a premature stop codon in the coding sequence. It remains unclear what functional significance these splice variants may have.

The predicted genes C05D2.4 and C05D2.3 are very close together -- only 369 bp apart from predicted stop of C05D2.4 to predicted start of C05D2.3 (figure). This could indicate the two genes are transcribed together as an operon. To date, however, there is no evidence that the genes are transcribed together. Although there is an EST project partial cDNA, and we have sequenced a partial cDNA for C05D2.3, we have not yet isolated an SL1 or SL2-spliced cDNA using RT-PCR. Furthermore, C05D2.4 and C05D2.3 are not among genes identified as likely operons by microarray expression analysis (T. Blumenthal, personal communication). The function of C05D2.3 remains a mystery. Intriguingly, one of C05D2.3's 15 "nearest neighbors" in the gene expression map using the "Worm Proximity Analyzer"

(http://workhorse.stanford.edu/cgi-bin/murray/nneighbors.cgi) is F12A10.3 - one of the other AAADC genes in *C. elegans*.



Cloning of the *ceh-13/labial/hox1* ortholog from *C. remanei*

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The *C. elegans labial/Hox1* type gene *ceh-13* , in contrast to some other members of the *C. elegans* Hox cluster, is required for viability, in particular for proper organization of anterior structures during embryogenesis[1]. Since spaciotemporal *ceh-13* expression appears to be controlled at the level of transcription[1,2] we have undertaken a deletional and mutational promoter analysis[3]. In order to complement these earlier studies we have cloned and preliminarily sequenced the *ceh-13* ortholog from *C. remanei* (*Cr-ceh-13*) and compared its sequence with *Ce-ceh-13* and with *ceh-13* from *C. briggsae* (*Cb-ceh-13*) that has recently been sequenced by the *C. briggsae* sequencing consortium. The intron exon structure of *ceh-13* is conserved in all three species. At the amino acid level the overall identities / similarities are 77% / 80% for *Ce-ceh-13* and *Cb-ceh-13*, 81% / 87% for *Ce-ceh-13* and *Cr-ceh-13* and 83% / 86% for *Cb-ceh-13* and *Cr-ceh-13* (Fig. 1). Not surprisingly the homeodomain is 100% conserved between the three species.

A *Ce-ceh-13:: gfp* reporter construct (pMF1[2]) that reflects *ceh-13* expression very well at all developmental stages tested, appears to be correctly controlled also in *C. briggsae*. Therefore we expected to find conserved elements also in non-coding regions.

Indeed, in a preliminary analysis we found short conserved stretches that might be regulatory elements. Interestingly, the three most obvious ones are located in regions that had previously been shown to be important for the control of *Ce-ceh-13* expression. A first element with 26 bp that are identical in all three species is located in a region of 400bp that is sufficient to confer *ceh-13* like expression to GFP in, among other places, the male tail. A second element with 15 bp out of 16 bp that are identical in all three species lies within a fragment of 740bp that is sufficient to drive correct early embryonic *ceh-13*expression[3]. Finally there is a stretch of 15 identical bp that resides within intron 1. From earlier studies we suspect that intron 1 is required to prevent *ceh-13* expression in adult body wall muscles[4]. We are currently performing mutational analyses to test the significance of these findings.

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C.briggsae: HSSAECYGAPPPNYYSDW-TTPSYYAGAAPSYSPINHHHHPADIWAAHPSNYALGGTGSN
C.remanei:  HSSAECYGAPP-NYYSDW-STPPYYASAAPSYSPINHH--PSDIWAAHPSNYVLGGT---
C.elegans:  HSSTECYGAPPHNYYQDWPTTHSYYPSVPSSYSPLNHH--PADIWAAHPSNYIMG----N

C.briggsae: GTISPPAP--GANARGSPSSNSSVEMPAGVTASQHNTYKWHHTKRVQRPVVPKKKVIDEN
C.remanei:  GTMSPPASKVSPN-RSSNSSAASADLPVGVTASQHNTYKWHHTKRVQRPAVPKKKVVDEN
C.elegans:  GHVSPPATASGLSPPASRSSNSSAELPTGVTASQHNTYKWHHTKRSQRPAAPKKKVIDEN

C.briggsae: GTNRTNFTTHQLTELEKEFHTAKYVNRTRRTEIASNLKLQEAQVKIWFQNRRMKEKKREK
C.remanei:  GTNRTNFTTHQLTELEKEFHTAKYVNRTRRTEIASNLKLQEAQVKIWFQNRRMKEKKREK
C.elegans:  GTNRTNFTTHQLTELEKEFHTAKYVNRTRRTEIASNLKLQEAQVKIWFQNRRMKEKKREK

C.briggsae: EKAFLARNSWDSASP-GSV--EDCKGFK 202aa
C.remanei:  EKAFLARNSWDSNSP-GSCSGEDVKNFK 199aa
C.elegans:  EKAFLARNTWESNSPTSSCSGEDVKNFK 202aa
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Fig. 1: Comparison of the predicted CEH-13 amino acid sequences from the three *Caenorhabditis* species. The 100% conserved homeodomain is underlined; amino acids that are identical in all three species are in bold.

1) Brunschwig et al. (1999) Development 126:1537-1546
2) Wittmann et al. (1997) Development 124:4193-41200
3) Streit et al. submitted
4) Reto Kohler (1999) Ph.D. thesis, University of Fribourg.

ceh-44, a Cut-like gene in *C. elegans*

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The Cut homeobox gene in Drosophila is required for the specification of neuronal identity in the external sensory organs of the peripheral nervous system. It is also involved in dorsoventral patterning of the wing margin and the formation of Malpighian tubule, tracheal system and some structure in the central nervous system. Two murine homologues of Cut, named Cux-1 and Cux-2 have been cloned. While Cux-1 is expressed in most tissue during development, Cux-2 expression is restricted to the nervous system. Interestingly, ectopic expression of Cux-1 in the fly was shown to rescue the wing scalloping phenotype in a *cut* mutant. This suggests at least partial conservation of Cut function between invertebrates and mammals (review 1).

The sequencing of the *C. elegans* genome has recently revealed the presence of a Cut-like gene, Y54F10AM.4a, which we call *ceh-44*. Several Y. Kohara cDNAs confirm the existence of a *ceh-44* transcript. It has the same structure as other members of the Cut gene family, consisting of three cut repeats upstream of a cut class homeodomain. Phylogenetic analysis shows that the three cut repeats of CEH-44 are the most divergent of the Cux family, but still cluster with the Cut family. The three cut repeats are 45% (69%), 62% (79%) and 35% (52%) identical (similar) to Drosophila Cut, respectively. The homeodomain of CEH-44 is more divergent and does not cluster significantly with any family, being only 39% identical with mouse Cux-2. The gene is predicted to be the second in an operon downstream of Y54F10AM.5, which has sequence similarity with a NADH-ubiquinone oxidoreductase.

Several Y. Kohara cDNAs reveal a spliced form containing the 5' end of the *ceh-44* gene, without the cut repeats and the homeodomain (the predicted Y54F10AM.4b form), linked to the predicted adjacent 3' gene Y54F10AM.3. This transcript encodes a protein similar to the vertebrate CASP proteins, the N-terminal part being shared with the vertebrate Cux proteins and CEH-44 (but not Drosophila Cut, which seems to have lost CASP). In the mouse, this protein also arises from alternative splicing of the Cux-1 transcript (2). However, the CASP protein is an evolutionarily old protein, also found in plants and fungi, where it is not associated with an homeobox gene. Thus CASP and an ancestral Cut gene must have merged in early animal evolution.

In situ experiments in Y. Kohara's database with yk394a11 (3), one of the cDNA corresponding to *ceh-44*, reveal an early embryonic expression, mostly anterior in the coma stage, as well as in the nerve ring in the larvae and in the gonad in the adult. Our future aim will be to test if *ceh-44* in *C. elegans* functions as a determinant of cell-type specification comparable to Cut in the fly. We will study in more details the *ceh-44* expression pattern with GFP fusions and plan to perform loss-of-function and gain-of-function studies.

1. Nepveu A. Gene 2001 2. Lievens P. et al. Gene 1997.

3. http://nematode.lab.nig.ac.jp/cgi-bin/db/ShowGeneInfo.sh?celk=CELK06251

An attempt to slow aging in *C. elegans*. 20. A positive effect of ascorbic acid

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The purpose of this study was to investigate the effect of different concentrations of ascorbic acid in water solutions on nematode life span. In this experiment ascorbic acid was used in following dilutions: $1:10^1$, $1:10^2$, $1:10^3$, $1:10^4$, $1:10^5$, $1:10^6$ and $1:10^7$. Three adult animals (3 5 days old) were kept in microtitre wells containing 0,5 ml of liquid medium (with *E. coli* and without ascorbic acid) during 4 hours, then they were discarded and newborn larvae were transferred in next wells (with ascorbic acid in any concentration) every day (one worm in one well) beginning from third day. This investigation was carried out in temperature $+21^0$C and in the darkness.

The obtained results are presented in the following table.

Concentration of ascorbic acid	n	Longevity (days)	
		Mean±S.E.	Maximal
Control	12	13,7±1,6	28
$1:10^1$	12	toxic	
$1:10^2$	12	15,4±1,3	23
$1:10^3$	12	17,9±1,6	22
$1:10^4$	12	22,0±0,7	29
$1:10^5$	12	18,6±1,3	30
$1:10^6$	12	19,3±1,3	30
$1:10^7$	12	16,3±1,1	27

Conclusion: If ascorbic acid solution was applied to *C. elegans*, it was able to increase their mean (by 61,0%, $p<0,001$) as well as maximal longevity in comparison with control in dilution of $1:10^4$.

Acknowledgment: The author wishes to express his thanks to CGC for providing C. elegans (Bristol, N2) and E. coli OP50.

An attempt to slow aging in *C. elegans*. 21. No positive effect of vitamin B_{12}

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The purpose of this study was to investigate the effect of different concentrations of vitamin B_{12} in water solutions on nematode life span. In this experiment vitamin B_{12} was used in following dilutions: $1:10^4$, $1:10^5$, $1:10^6$, $1:10^7$, $1:10^8$ and $1:10^9$. Three adult animals (3 5 days old) were kept in microtitre wells containing 0,5 ml of liquid medium (with *E. coli*and without vitamin B_{12}) during 4 hours, then they were discarded and newborn larvae were transferred in next wells (with vitamin B_{12} in any concentration) every day (one worm in one well) beginning from third day. This investigation was carried out in temperature $+21^0$C and in the darkness.

The obtained results are presented in the following table.

Concentration of vitamin B_{12}	n	Longevity (days)	
		Mean±S.E.	Maximal
Control	12	17,8±1,9	30
$1:10^4$	12	18,8±2,3	32
$1:10^5$	12	19,7±1,6	37
$1:10^6$	12	15,3±1,1	26
$1:10^7$	12	13,9±1,0	28
$1:10^8$	12	17,4±1,1	30
$1:10^9$	12	16,6±1,2	30

Conclusion: If vitamin B_{12} solution was applied to *C. elegans*, it was not able to increase significantly their mean longevity in comparison with control.

Acknowledgment: The author wishes to express his thanks to CGC for providing C. elegans (Bristol, N2) and E. coli OP50.

An attempt to slow aging in *C. elegans*. No positive effect of ascorbic acid in postreproductive period

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The purpose of this study was to investigate the effect of different concentrations of ascorbic acid in water solutions on the nematode life span in postreproductive period. In this experiment ascorbic acid was used in following dilutions: $1:10^1$, $1:10^2$, $1:10^3$, $1:10^4$, $1:10^5$, $1:10^6$ and $1:10^7$. Three adult animals (3 5 days old) were kept in microtitre wells containing 0,5 ml of liquid medium (with *E. coli* and without ascorbic acid) during 4 hours, then they were discarded and newborn larvae were transferred in next wells (without ascorbic acid in medium) every day (one worm in one well) beginning from third day. Then, beginning from 10th day, these worms were transferred every day in next wells containing medium with ascorbic acid in any concentration. This investigation was carried out in temperature +21° C and in the darkness.

The obtained results are presented in the following table.

Concentration of ascorbic acid	n	Longevity (days)	
		Mean±S.E.	Maximal
Control	12	19,9±1,0	24
$1:10^1$	12	toxic	
$1:10^2$	12	9,1±0,1	10
$1:10^3$	12	14,5±0,7	22
$1:10^4$	12	14,0±0,5	22
$1:10^5$	12	16,1±0,9	26
$1:10^6$	12	18,2±1,1	31
$1:10^7$	12	16,3±0,7	22

Conclusion: If ascorbic acid solution was applied to *C. elegans* in postreproductive period, it was not able to increase their mean longevity in comparison with control.

Acknowledgment: The author wishes to express his thanks to CGC for providing C. elegans(Bristol, N2) and E. coli OP50.

An attempt to slow aging in *C. elegans*. 23. No positive effect of ascorbic acid in reproductive period

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The purpose of this study was to investigate the effect of different concentrations of ascorbic acid in water solutions on the nematode life span in reproductive period. In this experiment ascorbic acid was used in following dilutions: $1:10^1$, $1:10^2$, $1:10^3$, $1:10^4$, $1:10^5$, $1:10^6$ and $1:10^7$. Three adult animals (3 - 5 days old) were kept in microtitre wells containing 0,5 ml of liquid medium (with *E. coli* and without ascorbic acid) during 4 hours, then they were discarded and newborn larvae were transferred in next wells (without ascorbic acid in medium) every day (one worm in one well) beginning from third day. Then, from 3th to 10th day, these worms were transferred every day in next wells containing medium with ascorbic acid in any concentration. This investigation was carried out in temperature +21°C and in the darkness.

The obtained results are presented in the following table.

Concentration of ascorbic acid	n	Longevity (days)	
		Mean±S.E.	Maximal
Control	12	12,8±1,1	18
$1:10^1$	12	toxic	
$1:10^2$	12	13,0±1,3	21
$1:10^3$	12	13,7±0,7	21
$1:10^4$	12	14,0±0,6	23
$1:10^5$	12	14,8±0,7	21
$1:10^6$	12	10,8±0,5	17
$1:10^7$	12	13,9±0,8	23

Conclusion: If ascorbic acid solution was applied to *C. elegans* in reproductive period, it was not able to increase their mean longevity in comparison with control.

Acknowledgment: The author wishes to express his thanks to CGC for providing C. elegans (Bristol, N2) and E. coli OP50.

Mitochondrial Metabolism in C. elegans

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We have been studying a mutation called gas-1 that was isolated in a screen for hypersensitivity to the volatile anesthetic isoflurane. This animal is hypersensitive to all the volatile anesthetics in which it has been tested, has a shortened lifespan, produces only 50 or so eggs at room temperature, and is basically a temperature sensitive lethal. gas-1 encodes a subunit of the first protein complex of the electron transport chain. We>have done a great deal of metabolic measurements to characterize the defect in this animal. The ability of mitochondria from gas-1 to metabolize complex I specific substrates like malate or glutamate is about 1/4 that of N2 mitochondria. Their ability to use succinate, a substrate specific for complex II, is greater than N2. gas-1 animals possess the same ratio of ATP to ADP + AMP as N2 when in air, but this ratio drops when they are immobilized in a volatile anesthetic. We are now mapping two suppressors of the anesthetic sensitive phenotype. These two mutations are dominant, with no clear phenotype of their own for mapping. The suppressors do extend the lifespan of gas-1, although they do not restore it to normal. This is also true for the ability of their mitochondria to metabolize malate or glutamate.

We have now produced an antibody to GAS-1 that is designed to distinguish it from another protein that may be expressed from a virtually identical cDNA that is contained on the cosmid T26A5.3. Although we know this sequence is expressed, we have not seen any signal via a GFP promoter, whereas a gas-1 construct apppears widely expressed. T26A5.3 does not rescue gas-1 unless the sequence is placed under the gas-1 promoter. We are also trying to identify the different complexes of the electron transport chain via a native gel in order to see the stoichiometry of the subunits of complex I in a gas-1 animal. Although we can estimate weights of each complex based on the predictions of genomic sequences of each subunit of each complex, commercial antibodies so far have not helped us distinguish Complex I from the other four major bands on gels. Another major effort on this project is the identification of the kinds of damage generated by defective mitochondria in gas-1 animals. Westerns that are probed with an antibody to products of lipid peroxidation and also gels using a kit that measures oxidative damage to proteins show that gas-1 mitochondria undergo more oxidative damage than N2. We are planning to identify the major proteins damaged in gas-1 mitochondria. Since we are anesthesiologists, we have also been interested in patients with mitochondiral myopathies. There have long been anecdotal reports of children with mitochondrial defects that are hypersensitive to anesthetics. We have some observations on children that have come to our operating room for either diagnosis or treatment of a mitochondrial disease, that would suggest that different defects may lead to different sensitivities to a volatile anesthetic. Only those few children we observed with a complex I defect were hypersensitive (4 children out of 16 patients). Children with defects in Complex II were not hypersensitive. We know that mev-1, a defect in Complex II in C. elegans, shares many phenotypes with gas-1, but is not hypersensitve to volatile anesthetics. It cannot use succinate as a substrate for oxygen consumption. Isolation of mitochondria, measurements of ATP, extraction of mitochondrial proteins, and attempts to age-match very large numbers of mutant worms have also absolutely demonstrated to us the reasons biochemistry is not much fun in C. elegans. Once in a while we do a nice mating just to satisfy a longing for the good old days.

Author index

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