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Reminder of the 13th International C. elegans Meeting

Paul Sternberg

HHMI and Division of Biology, 156-29, Caltech, Pasadena, CA 91125

The 13th International C. elegans Meeting will be held June 22-26, 2001 at The University of California, Los Angeles, which is located in the Westwood section of Los Angeles. Members of the Organizing Committee for this meeting are Paul Sternberg (chair), Susan Strome, Ralf Schnabel, Monica Driscoll, Jim Thomas, Jocelyn Shaw and Alex van der Bliek.

The format of the meeting will be different from that of previous C. elegans meetings to accommodate the growth of the field. The mornings will have two-hour parallel platform sessions and one-hour workshops. There will be afternoon poster sessions and evening plenary sessions. We plan to have four plenary sessions of oral presentations and three poster sessions. More people will be able to speak with this format.

A pamphlet describing meeting details and how to register, submit abstracts, and request financial aid will be emailed to all Worm Breeder's Gazette subscribers, and will be downloadable from WormBase (http://www.wormbase.org). Abstract submission will be handled electronically at http://elegans.swmed.edu (thanks to Leon Avery!).

Registration will be handled electronically at a site to be announced.

The deadline for registration, submission of abstracts, and sending financial aid requests is April 5, 2001.

2001 Genetic Map of *C. elegans* : Call for Data

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[2]The Sanger Centre, Wellcome Trust Genome Campus, Hinxton Hall, Hinxton, Cambridge CB10 1SA, UK

The deadline for new genetic map data to be incorporated into the 2001 Genetic Map of *Caenorhabditis elegans* (Printed Version) is **31 May 2001**. As usual, the 2001 Map will be distributed as the last issue of this volume (Volume 16) of the Worm Breeders Gazette. This will also include lists of registered laboratories, gene names, genes, rearrangements and balancers.

Genetic map data, as well as information on gene/sequence links, new loci, polymorphisms and rearrangements, and gene name proposals can be communicated to the CGC via the Sanger Centre website:

http://www.sanger.ac.uk/Projects/C_elegans/CGC/

In particular, please note that proposed new gene names should be registered with the CGC before publication. This helps to ensure conformity with standard nomenclature, to avoid duplicated, unnecessary or inappropriate gene names, and to update the relevant databases. A summary of current recommendations for genetic nomenclature in *Caenorhabditis elegans* can be found at: http://elegans.swmed.edu/Genome/nomen.html

Data can also be sent by e-mail to **cgc@mrc-lmb.cam.ac.uk**, or by fax or mail to J. Hodgkin. For large datasets, this may be a more convenient method of submission than the website. Standard forms for data submission are available by e-mail or fax on request to:

Jonathan Hodgkin

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PRACTICAL COURSE ANNOUNCEMENT: 31st WELLCOME TRUST ADVANCED COURSE

Jonathan Hodgkin[1], Alan Coulson[2], Patricia Kuwabara[2]

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A practical course on Molecular, Genetic and Informatic Methods for *C. elegans* will take place at the Sanger Centre, Wellcome Trust Genome Campus, Hinxton, Cambridge, England, from Monday 10th September -- Tuesday 18th September 2001. Course instructors will be Alan Coulson, Jonathan Hodgkin and Patricia Kuwabara.

The course will be similar in format and content to the 27th Wellcome Trust Advanced Course, which was held at the Sanger Centre in September 2000, with the same instructors. For further details, see the Wellcome Trust Courses website (http://www.wellcome.ac.uk/en/1/biosersss.html).

Application deadline: **22nd June 2001**

Ver midi IV

Nathalie Pujol[1], Jonathan Ewbank[2]

[1]IBDM, Marseille
[2]CIML, Marseille

La quatrième réunion annuelle

des équipes françaises ayant un intérêt pour *C. elegans*

se tiendra le

Vendredi 23 février 2001

à Luminy, Marseille.

Contact: pujol@ibdm.univ-mrs.fr ewbank@ciml.univ-mrs.fr

Center For *C. elegans* Anatomy Expands its Archives

David Hall

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We have recently received thousands of archival prints from the collections of the MRC-LMB in Cambridge and from the White lab in Madison. When added to the extensive collections we have received from the former Russell lab, and from our own files, we now have a staggering number of prints and negatives. Over the next few years we will scan selected prints from wild type and mutant animals into digital format, including the original annotations used in analysing and reconstructing the various tissues. We expect to make some digital data available to the community by the time of the International meeting in late June 2001. Due to bandwidth restrictions, we expect to write the data onto either CDs or DVDs for now, as the large file sizes required for the images will make it difficult to transfer files over the web. John White has retained archival prints covering the region of the vulva in Madison, but virtually all the rest of the MRC-LMB collection is now stored here in New York. We are very appreciative of the consideration of both John White and Jonathan Hodgkin in choosing us as the new repository for this collection.

We welcome visitors to visit our laboratory if they wish to view the data in the print archive. Directions on how to reach us are listed on our website. Please email, call or write us in advance, to know when to expect you.

http://www.aecom.yu.edu/wormem/

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Postdoctoral Position Available

Eli Y. Adashi

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The Laboratory of Reproductive Sciences of the Department of Obstetrics and Gynecology at the University of Utah Health Sciences Center is pleased to offer a position to qualified postdoctoral trainees with C.elegans experience who may wish to secure exposure to mammalian reproductive physiology while interfacing with the local C.elegans community. Funding for one position is available effective immediately. The purpose of this initiative, among other objectives, is to accelerate the pace of discovery (through the use of the C.elegans paradigm) of novel genes applicable to the mammalian reproductive axis. The laboratory in question for which the principal investigator is Dr. Eli Y. Adashi is focusing on the molecular endocrinology of the mammalian ovary, novel gene discovery and tissue-specific gene ablation technology. The Adashi Laboratory is currently comprised of postdocs (7), technical personnel, and administrative personnel for a total of 15 members. The C.elegans community at the University of Utah is a strong and vibrant one complimenting broad strength in developmental biology and in human genetics. Strong parallel programs in mouse and Zebrafish genetics are likewise available.

Please feel free to send any and all inquires to Eli Y. Adashi, M.D., Presidential Professor of Obstetrics and Gynecology, John A. Dixon Professor and Chair, Department of Obstetrics and Gynecology, University of Utah Health Sciences Center at eadashi@hsc.utah.edu.

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Improved survivorship of frozen *C. elegans* deletion mutant libraries

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Random deletion mutagenesis provides a powerful mechanism for knocking out gene function in *C. elegans*. A "library" of mutagenized worms is stored frozen at -80ºC and lysates of individual worm cultures are screened for deletion mutations in specific genes by PCR. Once a mutation is detected, cultures are thawed and worms harboring the mutation are identified by further PCR screening (*1*).

Because mutant alleles are present at very low frequency, high survivorship of frozen worms increases the likelihood of detection and isolation of mutant worm strains. It is widely known among *C. elegans* workers that the rate of cooling and freezing of worms is key to good survival (*2*). Here, we report improved survivorship of frozen *C. elegans* by modification of a standard freezing protocol. Worms are frozen in an insulated cooler designed originally by Ranganathan and Reddien (http://info.med.yale.edu/mbb/koelle/protocol_list_page.html). Typically, worms are frozen by direct placement of the cooler in a -80ºC freezer. However, as shown below, worm survival is increased by pre-cooling the worms at -30ºC.

Synchronized N2 Bristol L1 larvae were suspended in M9 buffer and diluted to a density of approximately 160 larvae/10 ml. Sixty microliters of this worm suspension were then mixed with an equal amount of standard freezing medium in a PCR tube. Ten of these PCR tubes were placed among a stack of six empty freezing plates inside a fully-assembled cooler that was then placed into a -30ºC freezer. Ten similar PCR tubes were placed in the -30ºC freezer on a rack without any insulation. Finally, a second cooler with ten more PCR tubes of larvae and freezing medium was placed at -80ºC. Five hours later, both the cooler and the non-insulated tubes at -30ºC were moved to the -80ºC freezer. The next day, all thirty tubes were thawed and the contents of each tube were plated onto a separate 60 mm NGM plate seeded with *E. coli* OP50. Two days later, the number of live worms on each plate was determined and the data were analyzed by one-way Model I ANOVA after square-root transformation.

Worms frozen in the special cooler at -30ºC for 5 h showed significantly higher survival than both the non-insulated -30ºC treatment and the worms in the cooler placed directly at -80ºC ($F = 16.99$; df = 2, 29; $P < 0.0001$; Figure). The combination of the insulating cooler and the 5 h treatment at -30ºC prior to moving to -80ºC increased survivorship 3.5-fold. We postulate that the improved survivorship is due to a reduced rate of cooling in the cooler maintained at -30ºC. Workers are urged to optimize empirically their own freezing protocols to account for variation among freezers and conditions in different laboratories.

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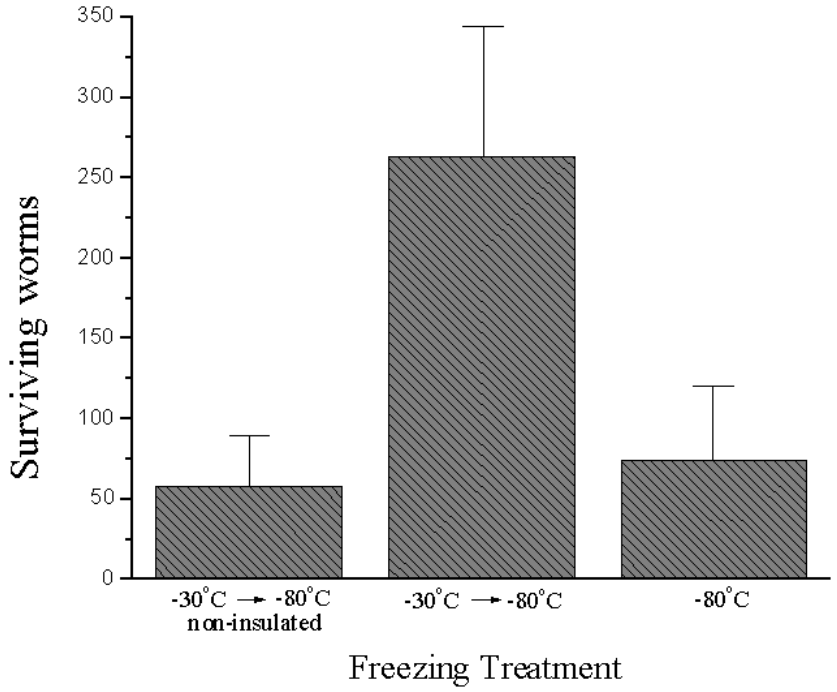

Figure. Number of worms surviving different freezing treatments: from left to right, non-insulated worms placed at –30°C for 5 h before moved to –80°C, worms insulated in a special styrofoam cooler placed at –30°C for 5 h before moved to –80°C, and worms insulated in a styrofoam cooler placed directly at –80°C. Error bars represent 95% confidence limits of the means.

Mapping useful GFP insertions; evidence for local suppression of recombination

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As pointed out by Mark Edgley et al. (WBG 15:5, p.20-21), chromosomes carrying integrated GFP transgenes are useful dominant chromosome markers. In the course of running the 24th and 27th Wellcome Trust Advanced Courses, on Methods for *C. elegans,* (held in November 1999 and September 2000), we made use of several different GFP insertions in order to demonstrate genetic mapping. The insertions were mapped using 3-factor mapping relative to established visible markers. The map positions of five insertions studied were confirmed, refined or corrected. Each of these has the useful properties of homozygous viability, good growth with no confounding phenotypes, male fertility and a strong GFP signal that can be easily scored using a dissecting microscope equipped with epifluorescence optics. Positions deduced were:

ccIs4251 LGI +4.0

ccIs9753 LGI +27.5

mIs13 LGI +27.5

mIs12 LGII +1.75

mIs11 LGIV +5.0

In the course of the mapping experiments, we made several incidental observations on these insertions:

1. *mIs13* and *ccIs9753* appear identical in map location, very close to the right end of LGI, and both also exhibit a weaker GFP signal than more central insertions of the same compound reporter at other locations. This might be the result of telomeric silencing or else of interference from the major rRNA cluster at this location.

2. *ccIs4251* males have been reported as unable to mate, but we found that they are occasionally fertile (a *him-8* strain, CB5600, has been deposited at the CGC). The males appear anatomically normal, and the reason for the low mating efficiency is not obvious.

3. The map position of *mIs12* has been problematic, with data suggesting linkage either to LGIII or to LGIV. We obtained the original strain for *mIs12 ,* DR2064, and found that the insertion in this strain is on neither of these chromosomes; instead, it has a convenient location close to *unc-4* on LGII.

4. In mapping *mIs11* on LGIV, we found that it exerts a significant suppression of recombination in its immediate neighbourhood. Map distance between the flanking markers *unc-5* and *dpy-20* was reduced from 3.3 cM to 1.3 cM. Local recombination suppression is not surprising, given that these insertions may consist of 100 kb or more of added DNA. However, such suppression may limit the usefulness of these inserts for detailed mapping. More extensive suppression of recombination may also result from rearrangement associated with insertion, as may have occurred in the case of *mIs10,* which suppresses recombination over a large part of LGV (Mark Edgley, pers. comm.)

Map data have been deposited in ACeDB. We encourage others to publish or deposit similar map data for inserted transgenes. Hitherto map data for only one GFP insertion has been published (*ayIs4,* Burdine et al. 1998) and none has been communicated to the CGC although many useful insertions have been constructed.

Participants in WTAC24 were: Patricia Berninsone, Marc Bickle, John Connolly, Rosane Curtis, Bill Gregory, Margorie Gurganus, Hisao Kondo, Dorota Kwasnika, Rowena Martin, Alison Motley, Rosa Estela Navarro, Karen Oegema, Tove Ostberg, Anastasia Papakonstantinopolou, Anna Salcini, Liora Shoshani, Anne Spang, Peter Tatnell.

Participants in WTAC27 were: Peter Askjaer, Alessandra Bodini, John Browne, Stefanos Christodoulou, David Clarke, Patrick Dekker, Maria Gravato-Nobre, David Lamb, Sara Mole, Patricia Murray, Sara Olson, Mark Petalcorin, Heike Schaurete, Stephen Stürzenbaum, Fiona Thompson, Jeremy Turnbull, Ross Waldrip.

We are grateful to the Wellcome Trust for supporting these courses, and to Leica Microsystems for lending MZII epifluorescence dissecting microscopes. Another course in this series will be taught in September 2001 (see announcement).

On the reproducibility of large-scale RNAi screens

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RNAi is being used routinely to determine loss-of-function phenotypes and recently large-scale RNAi analyses have been reported (1,2,3). Although there is no question about the value of this approach in functional genomics, there has been little opportunity to evaluate reproducibility of these results.

We are engaged in RNAi analysis of a set of 762 genes that are differentially expressed in the germline as compared to the soma (4 -- "Germline"), and have reached a point in our analysis that allows us to look at the issue of reproducibility. We have compared the RNAi results of genes in our set that were also analyzed by either Fraser et al. (1 -- Chromosome 1 set "C1") or Gonczy et al. (2 -- Chromosome 3 set "C3").

In making the comparison we have taken into account the different operational definition of "embryonic lethal" used by the three groups. In the C3 study, lethal was scored only if there were fewer than 10 surviving larva on the test plate, or roughly 90% lethal. In our screen and the C1 screen the percent survival was determined for each test. To minimize the contribution of false positives from our set, in our comparison with the C1 set we defined our genes as "embryonic lethal" if at least 30% of the embryos did not hatch, but included all lethals defined by Fraser et al. (> 10%). For our comparison with the C3 set, we used a more restrictive definition of "embryonic lethal" that required that 90% of the embryos did not hatch. (This means that in Table 1, five genes from our screen that gave lethality between 30-90% were included in the not lethal category; one of these was scored as lethal by Gonczy et al.).

We have analyzed 149 genes from the germline set that overlap with the C1 set and 132 genes that overlap with the C3 set. The table below shows the number of genes scored as embryonic lethal (EL) or not embryonic lethal (NL) in each study. (Note that these comparisons do not include data from our published collection of ovary-expressed cDNAs.)

Table 1. Comparing RNAi analysis of the same genes in different studies.

	Chromosome 1			Chromosome 3	
Germline	NL (117)	EL (32)	Germline	NL (97)	EL (35)
NL (104)	100	4	NL (89)	87	2
EL (45)	17	28	EL (43)	10	33

Overall, the degree of reproducibility is high. The concordance between our results and the published results was 86% with C1 (128/149 genes) and 90% with C3 (120/132).

However, we scored a larger number of genes as giving rise to embryonic lethal phenotypes than the other studies did. What does this mean? One possibility is that we are generating a large number of false positives (God forbid!). The other interpretation is that there is a fairly high frequency of false negatives in each screen (4-8% in our screen (2/45; 4/49); 22% in the C3 screen (10/45); and 35% (17/49) in the C1 screen).

It is no surprise that the different methods used by the three groups resulted in slightly different outcomes and we can only speculate on which methodological variation contributed most. In comparing our methods to those used in the C3 study we note that our two groups used different primer pairs for each gene; that we tested genes individually while they tested genes in pairs; and that the operational definition of "embryonic lethal" differed. Considering the latter two differences, we speculate that even with pools of two, the competition noted by Gonczy et al. in dsRNA pools could reduce levels of lethality below the 90% cutoff.

The major difference between our approach and the C1 approach is feeding vs. injection, raising the possibility that for some genes feeding may be a less effective means of administering dsRNA.

Whatever the basis for the difference, these comparisons indicate that genes scored as "non-lethal" in any single study may show an embryonic lethal RNAi phenotype when reanalyzed. It therefore seems useful to have more than one pass at analyzing C. elegans genes via RNAi.

We are indebted to P. Gonczy for very useful comments.

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N2 (ancestral) is a mutant with reduced fertility and longevity

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Genetic variation among different laboratory lines of N2 affects fertility and lifespan. A previous study found that median lifespans of different lines ranged from 12.0±0.8 to 17.0±0.6 days (20^{O}C)(1). To attempt to establish which of these best resembles the original N2 isolate, the lifespans of F1 hybrids between N2 variants, and those of seven *C. elegans* wild isolates, were examined (1). The results suggested that the N2 male stock currently distributed by the CGC (here designated CGCM), is most similar to the original N2 isolate. This strain is the longest-lived N2 variant.

An alternative approach to establish which variant best resembles wild type is to examine an N2 stock frozen at an early date. One such stock is N2 (ancestral), which is only 6 generations removed from a stock frozen in the Brenner lab in 1968. We compared the fertility and lifespan of N2 (ancestral) with 3 N2 variant lines: CGCM, CGCH (slightly short-lived) and JW (very short-lived). Our expectation was that it would most closely resemble CGCM.

Table 1: Longevity and fertility of N2 (ancestral) and other N2 lines

Strain	Median lifespan (days)	Maximum lifespan (days)	N*	Mean brood size	N*
N2 CGCM	20.5 ± 1.0	24.4 ± 0.7	5 (127)	292 ±11	1 (18)
N2 CGCH	18.3 ± 0.8	21.9 ± 0.7	7 (136)	270 ± 9	1 (18)
N2 JW	13.4 ± 1.0	23.1 ± 1.0	8 (194)	213 ± 9	1 (15)
N2 (ancestral)	13.6 ± 0.7	21.2 ± 1.0	10 (243)	260 ± 7	1 (19)
N2 CGCM/N2 (ancestral)	19.7 ± 0.3	25.7 ± 0.7	3 (53)	ND	-
N2 JW/N2 (ancestral)	15.0 ± 3.0	22.0 ± 0.0	2 (46)	ND	-

± Standard error. *Number of trials (number of animals scored).

To our surprise, the lifespan of N2 (ancestral) was significantly shorter than CGCM and CGCH (median 20^{O}C lifespan, $p < 0.001$ in each case)(Student's *t* test) (Table 1), yet indistinguishable from JW ($p > 0.1$). Furthermore, its fertility was significantly lower than that of CGCM ($p < 0.02$) but not CGCH ($p > 0.1$), but higher than that of JW ($p < 0.001$).

Does this mean that the longer-lived line CGCM is a mutant variant after all? We favour an alternative explanation: that as early as 1968 there existed a number of genetic variants of N2 in the Brenner lab (Cambridge), and N2 (ancestral) is a short-lived one. In 1975, when Don Riddle moved from Cambridge to Missouri, he took with him CGCH, CGCM and JW (obtained from John White), and froze them upon arrival. These three strains have different lifespans (1). Thus, by 1975 a number of variants certainly did exist.

One possibility is that N2 (ancestral) and JW are related. To test this, the lifespans of F1 hybrid hermaphrodites issuing from crosses between CGCM, JW and N2 (ancestral) were examined. The lifespan of CGCM/N2 (ancestral) was indistinguishable from that of CGCM, and significantly longer than that of N2 (ancestral) ($p < 0.001$). A reduction in median lifespan was seen in JW/N2 (ancestral) hybrids relative to CGCM/N2 (ancestral) hybrids, but due to the large standard error this did not reach significance. However, the maximum lifespan of JW/N2 (ancestral) was significantly reduced ($p < 0.02$). These preliminary results support the view that N2 (ancestral) and JW are related, short-lived mutant variants, and that the mutations concerned are recessive.

N2 (ancestral) thus appears to be another short-lived N2 variant, related to JW. We therefore advise that N2 (ancestral) not be used as wild type; instead, we recommend CGCM.

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Tight-seal whole-cell patch clamping of C. elegans neurons: erratum

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We regret to inform the C. elegans community that the published recipe for internal saline for whole-cell recordings[1,2] from neurons was incorrect. The published recipe was (in mM):

KGluconate 125, KCl 18, NaCl 0, CaCl2 0.7, MgCl2 1, HEPES 10, EGTA 10.

The recipe actually used was (in mM):

KGluconate 125, KCl 18, NaCl 4, CaCl2 0.6, MgCl2 1, HEPES 10, EGTA 10.

The main effect of this error resides in the difference in NaCl concentration. The correct saline will produce a predicted Na reversal potential of 90 mV with the published external saline, while the erroneous published saline has an undefined ENa. Because C. elegans lacks voltage-gated Na channels, this difference in salines may have little or no effect on recordings of voltage-gated currents. It may, however, affect measurements of currents carried by ligand-gated currents and currents carried by DEG/ENaC channels. We apologize for any inconvenience this error may have caused.

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Thiabendazole (with dimethyl sulfoxide and methylene blue) as a possible aid in the "limited contamination" culture of *Caenorhabditis elegans.*

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In the routine propagation of *C. elegans,* steam sterilization of the culture medium is standard practice, but in some circumstances it is inconvenient, impractical, or prone to error. In preliminary experiments in this lab, thiabendazole (TBZ) was added to *C. elegans* cultures in the expectation that the life cycle would be interrupted because of the well-known efficacy of the compound in preventing the development and hatching of nematode eggs. Surprisingly, the propagation of *C. elegans* appeared to be unaffected. Subsequent investigation showed that TBZ is without ovicidal efficacy against *C elegans* at concentrations that are fully effective against the eggs of the parasitic nematode *Haemonchus contortus* (Fasiuddin and Campbell, 2000). The qualitative observations here reported suggest the possibility of exploiting this finding to achieve a useful degree of microbial control in laboratory cultures.

TBZ was added to modified Nematode Growth Medium (Avery and Horowitz, 1990) at 20 µg/ml -- a concentration known to be ovicidal for nematodes (Egerton, 1969) and to have a broad spectrum of antifungal activity (Robinson et al., 1969). Methylene Blue, at 0.0002%, was added as a marker to prevent inadvertent mix-up in routine transfer operations (qualitative observations in this lab had indicated that such a concentration did not suppress the growth of the *Escherichia coli* seeded onto agar plates as food for *C. elegans*). The medium was boiled briefly to dissolve and clarify the agar, but it was not autoclaved. TBZ and Methylene Blue were added while the medium was still hot. TBZ was prepared as a solution of 10 mg/ml in 100% dimethyl sulfoxide and added to the medium so as to give a 500 fold dilution. An aqueous solution of Methylene Blue, 0.1%, was similarly added to give a 500 fold dilution. After dispensing the medium into 90-mm petri dishes, a suspension of *E. coli* (OP 50) was spread on the solidified medium and allowed to form a bacterial lawn in the usual way. Three days after the initial (October 8, 1999) preparation of the plates, 2 plates were inoculated with *C. elegans*; and single plates were inoculated with worms on day 28, 46, 55, 63 and 88. The plates were held in a humidity chamber at room temperature, without further addition of bacteria. Periodic microscopic examination of the dishes revealed prolific propagation of *C. elegans*, followed by the persistence of low numbers of motile worms (presumably dauer larvae) at intervals up to day 367 after inoculation of the first 2 plates. At that time, medium from each dish was transferred, without sterile technique, to conventional agar plates, resulting in abundant propagation of worms in all cases.

Another batch of 17 culture plates was prepared in a similar non-aseptic way, but without the addition of Methylene Blue. This batch has remained in a refrigerator for 9 months, during which time small compact colonies (presumably bacterial) have appeared, but there has been no trace of the mycelial fungal contaminants so commonly observed when sterilization and handling procedures have been imperfect.

The preparation of these two batches of non-sterilized culture plates was not accompanied by the simultaneous preparation of autoclaved plates, or plates with dimethyl sulfoxide or Methylene Blue as the only additive; but throughout the test period conventional plates, without additives, were being routinely made and used. Nor was any attempt made to expose the plates to known air-borne contaminants or to inoculate them with bacteria or fungi. Nevertheless, the absence of visible mycelial growth was in marked contrast to the degree of contamination customarily seen when sterility measures have been less than rigorous, and the year-long persistence of *C. elegans* was also striking.

If these findings can be confirmed in quantitative trials, supplementation of a medium with TBZ in a dimethyl sulfoxide vehicle (with an antibacterial adjunct) may provide a convenient "limited contamination" medium for the routine maintenance of C. *elegans*. Other antimycotic agents are available for use in culture systems. In the present context, the most useful characteristics of TBZ are its very long shelf life

at room temperature, its stability in media when boiled or even autoclaved, and the degree to which this otherwise antinematodal agent is tolerated by the nematode *C. elegans*. Methylene Blue has some degree of antibacterial efficacy and, at the concentration used here, was tolerated by both the worm and the bacterium on which it feeds. Other compounds with selective antibacterial activity may be more effectively combined with TBZ to suppress unwanted bacteria in *C. elegans* cultures.

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Using *Caenorhabditis elegans* as a model to study autophagy

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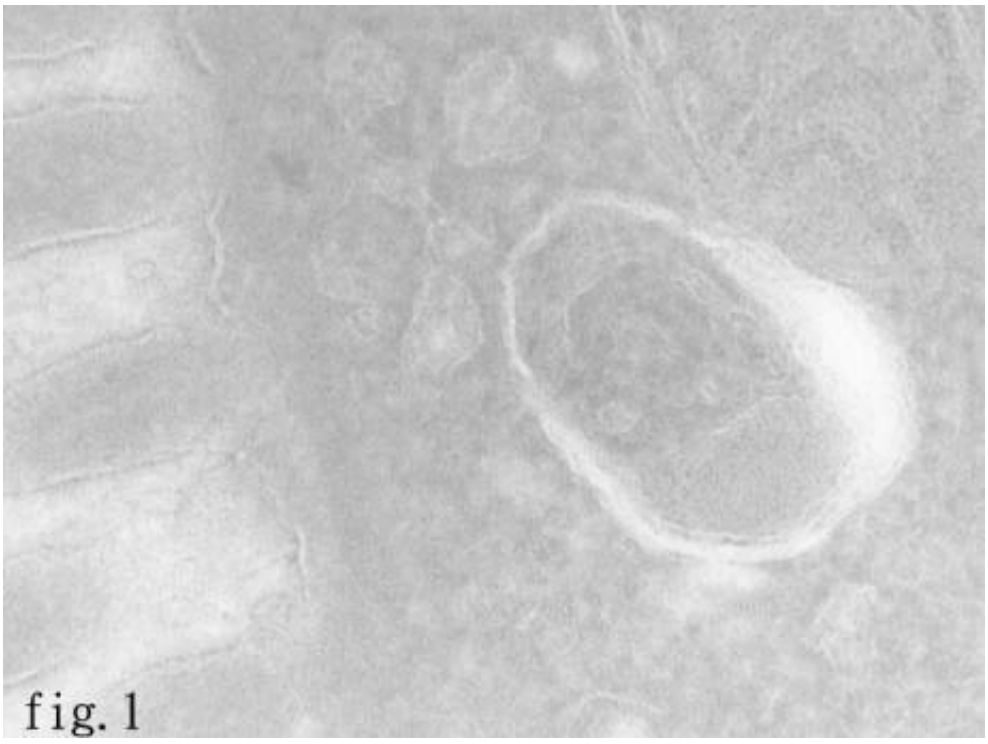
Autophagy is the bulk degradation of cytoplasmic components with the lysosomal enzymes. This physiological process can be upregulated by starvation and has been best studied in the liver. With the advent of molecular genetics, the autophagic pathway is now being dissected at the molecular level using yeast as a model system. Despite of exciting results, the use of yeast is not without its caveat for it is a single-cell organism and the data of which require prudent extrapolation to the mammalian cells in the light of complex physiological melieu of the multicellular organism. Furthermore, the fine structural features of autophagic vacuoles in yeast are, to a certain extent, different from those in the mammalian cells. For example, the sequestration apparatus of the nascent autophagic vacuoles, namely phagophore, found no counter part in the yeast.

By analogy to the ease of genetic manipulation and the complete genomic sequence now available in the yeast, I proposed another organism, the nematode *Caenorhabditis elegans*, as a model for the molecular dissection of the autophagic pathway. In this study I employed ultrathin cryosectioning method and demonstrated that the autophagic vacuoles - in all its likeness to that of the mammalian cells - indeed are present in the intestinal cells of the *C. elegans*. Figures 1, 2 and 3 shows the characteristic nascent autophagic vacuoles. They are isolated pieces of cytoplasm circumscribed by whorl-like membranous structure, namely phagophore. In an attempt to mark the autophagic vacuoles of later stages, i.e. degradative vacuoles, I then immunostained the ultrathin cryosections of the worms with antibodies against cathepsin D, a lysosomal enzyme. The result, shown in Figure 4, is somewhat surprising in that this hydrolytic enzyme is localized in the lumen of the gut in association with the bacteria being digested, instead of being intracellularly localized as in the case of human liver cells (Figure 5).

In conclusion, this study demonstrated for the first time the presence of autophagic vacuoles and the establishment of the ultracryomicrotomy technique in combination with immunoelectron microscopy in *C. elegans*. The significance of the extracellular localization of cathepsin D awaits further investigation.



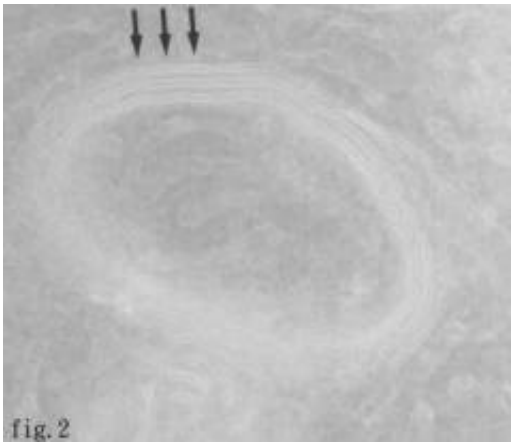


fig. 2

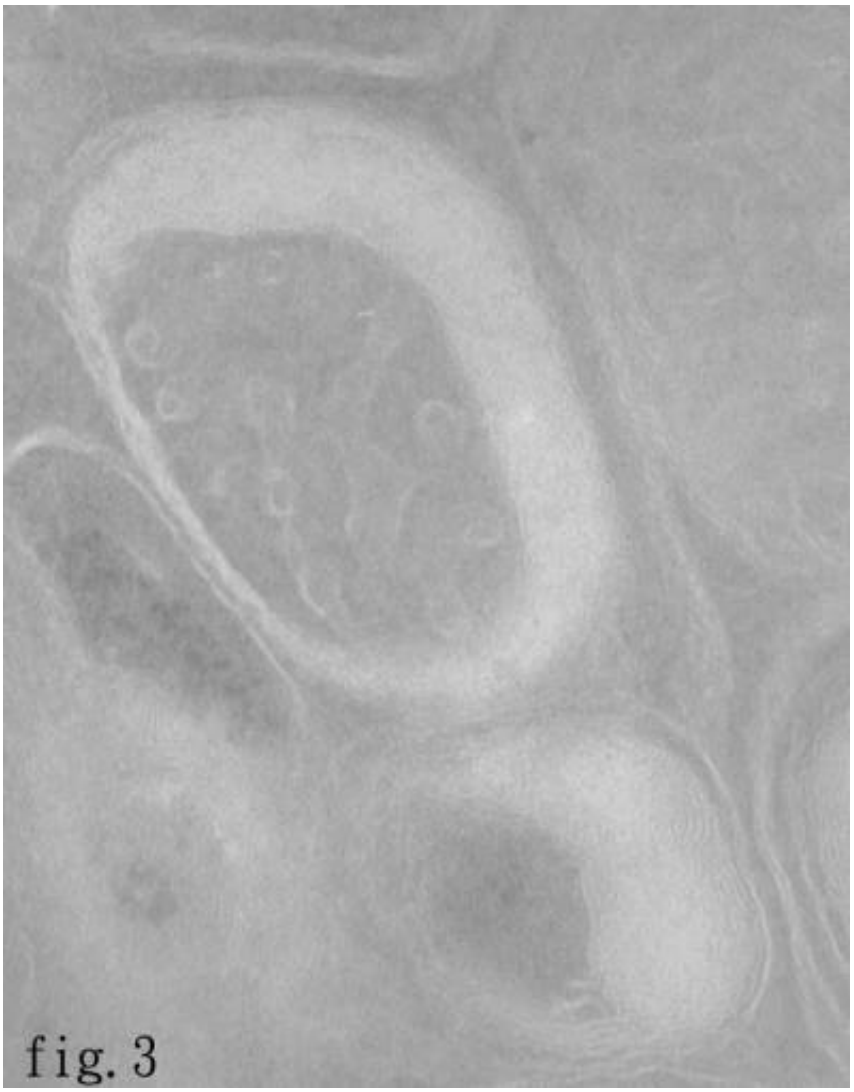


fig. 3

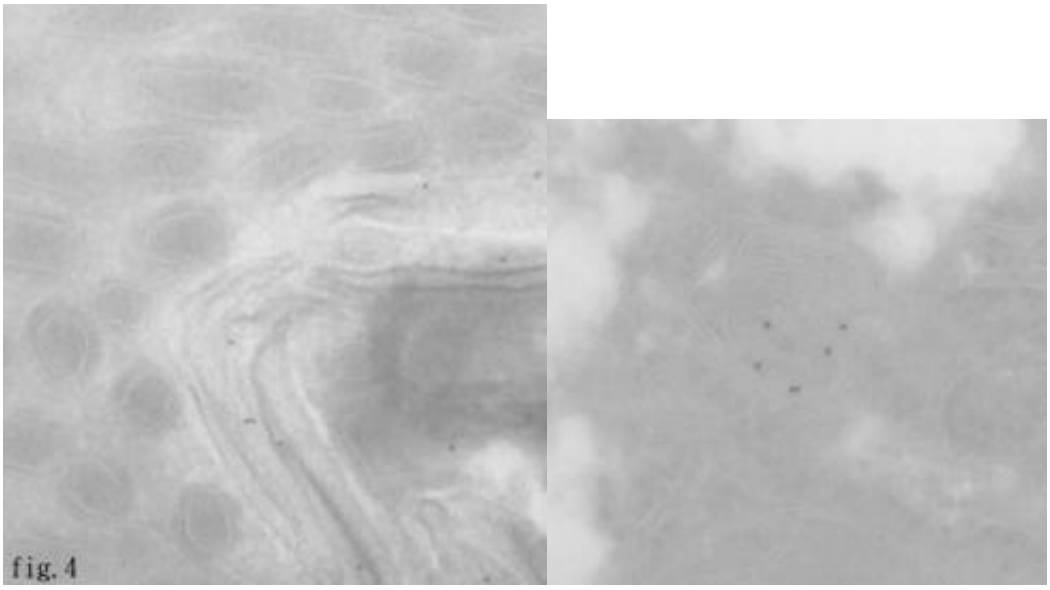


fig. 4

Characterization of rcn-1, a calcipressin homologue in C. elegans

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Calcipressins are a family of calcineurin regulating proteins conserved from fungi to yeast to man. They show binding, inhibiting, and even transcription regulation of the calcium/calmodulin phosphatase calcineurin, and also may play a role in Down Syndrome in humans. A calcipressin homologue, rcn-1, has been identified in C. elegans on chromosome III in cosmid F54E7.

A 3.1 kb upstream region of the genomic DNA of rcn-1 was cloned into a GFP vector and expression was seen in wild-type worms. Expression was seen mainly in pharyngeal muscle, excretory cells, vulval epithelial cells, ventral and dorsal nerve cords and commissures, head sensory neurons, nerve ring, pre-anal and tail neurons and to a lesser extent in hypodermal cells and intestine. High neuronal and pharyngeal muscle expression is consistent with highly expressed levels of the human homologue DSCR-1 (Down Syndrome Critical Region) in heart and brain in mammals.

Polyclonal antibodies were raised against the conserved region of DSCR-1 (Down Syndrome Critical Region), a human homologue of rcn-1 in rabbit, and immunostaining with these antibodies was performed in C. elegans. We were able to observe expression in excretory cells, vulval epithelial cells, ventral and dorsal nerve cords and commissures, head sensory neurons, nerve ring, tail neurons, and hypodermal cells. This expression not only confirms our previous GFP expression results, but also shows the conservation of calcipressins from humans to C. elegans. Preliminary data of calcineurin GFP and antibody expression from our laboratory has shown much overlap of expression between rcn-1 and calcineurin showing a possible relationship between the two proteins. We hope to further delineate this relationship by biochemical analysis of the two proteins. Currently, we are also preparing to raise antibodies against rcn-1 in rabbit.

Northern blot analysis has confirmed a low-level of expression of a 1.0 kb mRNA transcript. We are planning to conduct RNAi of rcn-1 and will try to obtain deletion mutants by UV-TMP mutagenesis to observe phenotypes.

Microevolution of vulval cell lineages within two nematode genera : *Caenorhabditis* and *Oscheius*.

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The cell lineage of *Caenorhabditis elegans* and some other nematodes is mostly invariant. Given this invariance, one can wonder how a cell lineage can evolve. We have started a microevolutionary approach by observing lineage variations of vulva precursor cells (VPCs) in different natural nematode populations : 13 strains of the *C. elegans* species and 5 different species in the *Caenorhabditis* genus, as well as 32 strains belonging to 3 different species of the *Oscheius/Dolichorhabditis* genus.

Our results show that, within both genera, lineage variations between species and even between strains of the same species occur mostly for VPCs that do not participate to the vulval invagination (VPCs with a 3° non-vulval fate). These cells are probably not under strong selection pressure and this could explain the large variations observed at a small evolutionary timescale.

In the reference strain *C. elegans* N2, the lineage of the P3.p cell is not invariant (Sulston and Horvitz, 1977). In 50% of N2 animals, P3.p is a true VPC : it is competent to form the vulva and divides once before fusing with the surrounding hypodermis. In the other 50%, P3.p is not competent, does not divide and fuses with the hypodermis. The percentage of occurrence of P3.p division varies between strains of the *C. elegans* species (from 10% to 60%) and between species of the *Caenorhabditis* genus (from 0% to 100%). In the *C. elegans* N2 strain, P3.p division is correlated with the competence of the cell. However, the correlation does not hold in the *C. elegans* strain CB4857, where P3.p divides in only 15% of the animals whereas it is competent in about 60% (as determined by ablation of P(4-8).p in the L1 stage). P3.p competence varies between *Caenorhabditis* species, suggesting that the size of the competence group (controlled by *lin-39* /*bar-1* / *lin-22* in *C. elegans* N2) has evolved between closely related species, but that the program of cell division can be affected even between strains of the same species.

Species of the *Oscheius* genus can be easily found in soil samples from around the world (much more easily than *Caenorhabditis* species). Thus, we have been able to compare a large variety of strains in this group. Variations mostly concern P4.p and P8.p lineages : these cells divide twice, once, or not at all, but are always competent to replace the vulval cells P(5-7).p. Variations observed between strains of the same species are larger in *Oscheius* sp.1 than in *C. elegans*. Therefore, we have undertaken a genetic analysis between two pairs of strains of *Oscheius* sp. 1 that show distinct P4.p and P8.p lineages. For each pair, at least three loci are involved in the phenotypic differences. We also find that variation at one locus has a relatively strong effect on the phenotype (instead of small additive effects of many genes).

Within both *Caenorhabditis* and *Oscheius*, a similar range of variations is found between strains of the same species and between closely related species of the same genus. Thus, cell lineage variations observed between species could be due to fixation of variants that segregate within species.

Promoter Dissection of *C. elegans* Hox Gene *egl-5*

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C. elegans Hox gene *egl-5* is involved in many cell-fate specification events in several tissues in the posterior body region. Jointly with Lisa Girard and Paul Sternberg, we have undertaken an *egl-5* promoter dissection in order to understand how the complex *egl-5* expression pattern is established. During male tail development, *egl-5* is activated in seam cell V6.ppp, which defines the fate of V6.ppp as the precursor of three sensory rays, rays 4, 5, and 6. In an *egl-5* null mutant, V6.ppp adopts the fate of its anterior counterpart V6.pap, which produces rays 2 and 3. Another Hox gene, *mab-5*, activates *egl-5* directly or indirectly. However, MAB-5 is present all through the V6 cell lineage in both hermaphrodites and males. Therefore, the temporally and spatially regulated, sex-specific expression pattern of *egl-5*in V6.ppp remains unaccounted for.

To study the mechanism of regulation underlying such a precise expression pattern, we decided to identify the regulatory sequence governing *egl-5*expression in the seam. We've compared the DNA sequences of the 30kb intergenic region upstream of *egl-5*gene in *C. elegans* and *C. briggasae* by blasting the two sequences against each other, and found that there are short stretches of noncoding sequences within the *egl-5*promoter region that are well conserved between the two species. We have somewhat arbitrarily numbered the longest of these conserved sequences 1-14 from distal to proximal. To assign the function of these conserved sequences, we've made deletion constructs using a PCR-based method with one of our *egl-5::gfp* reporters, EM#285, as template. Based upon the criterion that deletion of a lineage-specific enhancer will inactivate our *egl-5* reporter expression in that lineage, we've roughly mapped the enhancer of rectal epithelial cells to a region containing conserved sequences 7 and 8, and the enhancer of male tail hypodermal cells to a region containing conserved sequences 9 and 10.

We've also found that conserved sequences 11 and 12, which lie 3kb upstream of the translation initiation site, are not only necessary for the expression of our reporter in the V6 lineage, but also sufficient to replicate the expression pattern of *egl-5* in the V6 lineage when linked to a *Dpes-10::gfp* reporter. Sequences 11 and 12 lie right next to each other within a highly conserved 300bp region, which implies that they are likely to share the function of the V6 lineage enhancer. The same region from *C. briggasae* gives exactly the same expression pattern driving *Dpes-10::gfp*, further suggesting that the conserved sequences within this region represent the enhancer of the V6 lineage. We've found putative binding sites within the region for several transcription factors including TRA-1 (thanks to M. Sohrmann of the Sanger Center), POP-1 (TCF/LEF1 homolog), MAB-5/CEH-20 (Extradenticle homolog). Now we are making deletions and point mutations to eliminate the binding sites and looking for changes in the expression pattern of the reporter. Surprisingly, when we deleted the putative TRA-1 site, we got ectopic reporter expression in anterior seam cells, ventral cord neurons and head neurons in both male and hermaphrodite. We hypothesize that we have deleted another repressor binding site within or overlapping with this TRA-1 site, and now we are trying to identify this repressor.

egl-5 promoter analysis provides clues toward understanding anterior/posterior addressing at the cis-regulatory level

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The Hox genes encode a conserved set of transcription factors that are essential for anterior/posterior patterning in many animals and are expressed in a series of consecutive domains along this axis. These genes are almost always expressed in cells that are related by position rather than lineage and mutations in these genes often result in the transformation of one region to an adjacent one. Hox genes are typically found in clusters, with the order of the genes in the cluster colinear with their order of expression along the anterior/posterior axis, except for in C. elegans in which the order of two of the genes is inverted. In C. elegans, the Hox cluster contains a homolog of the anterior group genes, ceh-13, which is most similar to labial in the Drosophila HOM-C complex; two genes homologous to medial-group genes; lin-39 (sex-combs reduced, deformed, proboscipedia); mab-5 (Antennapedia) and a homolog of the posterior group, egl-5 (Abdominal-B)(1). Additionally, two more posterior homologs not contained within the quasi-cluster, nob-1 and php-3, have been characterized (2). The expression of Hox genes in positionally-related groups of cells raises interesting questions at the cis-regulatory level. Functional analysis of Hox gene promoters will help us understand how positional cues are read and interpreted resulting in correct anterior/posterior addressing along the body-length. C. elegans is ideal for such an analysis because fate-specification changes consequential to small perturbations in these promoters can be observed in individual cells, rather than the fields of cells as in many other organisms. To understand how cell-fate is specified in the posterior region of the hermaphrodite by the egl-5 Hox gene, we have undertaken, in a joint project with Yingqi Teng and Scott Emmons, a promoter analysis of this gene.

egl-5 is expressed in the hermaphrodite specific neuron (HSN), body wall muscle, posterior lateral microtubule neuron, PVC interneuron, M, V6, the rectal epithelial cells K, F, B, U and the P12 neuroectoblast cell (3). The experiments described here focus on our progress delineating cis-regulatory elements which direct expression in K, F, B, U and P12. egl-5 and its adjacent Hox gene mab-5 are divergently transcribed with approximately 30 kb between them. A gfp translational fusion containing approximately 13 kb of promoter was sufficient to direct expression in K, F, B, U, P12 while a second construct, containing the most proximal 7 kb of promoter was not, suggesting that the 6 kb differential fragment between the two may be sufficient to direct expression in these cell-types. We tested this 6 kb region fused to a heterologous pes-10 basal promoter driving gfp, and found that indeed it was sufficient. We then examined a series of egl-5 promoter truncations, with this 6 kb piece as a starting point and identified a 1.3 kb region within the 6 kb that is sufficient for expression. Within this 1.3 kb fragment we identified a 469 bp sub-fragment sufficient to drive gfp expression in B, but not K, F, U, P12 and a 446 bp piece sufficient to drive expression in K, but not F, B, U or P12. F, U and P12 elements have proven more difficult to define.

The 1.3 kb region sufficient to drive gfp expression in K, F, B, U, and P12 contains six sites (denoted here in distal to proximal order as 1-6) in the range of 20-30 bp each which are conserved between C. elegans and the closely related species C. briggsae. There are several notable consensus sites for trans-acting factors within these conserved regions including a binding site for SOX5 and FORKHEAD in site 3. The six sites are arranged in two quasi-clusters, with approximately 300 bp between the clusters. Specific deletions of either 1, 2 and 3 or 4, 5 and 6 abolishes expression in K, F, B, U and P12 suggesting that sequences in both clusters may be important for expression in these regions. One caveat of these types of experiments is that these deletions could alter spacing in the promoter, disturbing

enhancer-promoter interactions. However, constructs which specifically deleted 3, 4 and 5, removing a similar number of base pairs as the 1,2,3 and 4,5,6 constructs, and found that that expression in K, F, B, U and P12 was not affected, suggesting that the spacing in this region is not affected by deletions of this magnitude. These conserved regions are being further studied to assess their relative contributions to egl-5 expression in the rectal epithelial cells and P12. The study of the cis-regulation of egl-5 will reveal the natural taxonomy of differential anterior/posterior addressing within C. elegans.

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Reverse genetic approach to identify genes required for thermotaxis in *C. elegans*

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C. elegans can sense and memorize temperature, and change its temperature response, depending on the past experience. For example, after cultivation with sufficient food at 20 degree, *C. elegans* migrates to its cultivation temperature (i.e. 20 degree C) and then moves isothermally on a thermal gradient without food. In contrast, after cultivation without food for a few hours, *C. elegans* becomes to avoid its cultivation temperature. This behavior is called thermotaxis. It has been previously shown by laser ablation experiments that AFD thermosensory neurons, and their downstream neurons, AIY, AIZ and RIA interneurons, are required for execution of normal thermotaxis. For example, killing AFD thermosensory neurons results in athermotactic or cryophilic phenotype, and killing AIY or AIZ interneurons results in cryophylic or thermophilic phenotype, respectively. Several mutants defective in thermotaxis have been isolated. Of these, tax-4 and tax-2 show athermotactic phenotype, and both *tax-4* and *tax-2* gene were found to encode two different subunits of cyclic nucleotide-gated cation channel (CNG channel), which functions in several sensory neurons including AFD thermosensory neurons. The TAX-4/TAX-2 CNG channel shows higher affinity to cGMP than cAMP, suggesting that cGMP acts as a second messenger in thermosensory signal transduction. Thermotaxis must also require execution of some form of associative learning between temperature and food. Recently, our laboratory has been isolating mutants designated aho(abnormal hunger orientation), which are likely to be defective in mechanism of associative learning between temperature and food.

The completion of *C. elegans* genome project makes us possible to systematically analyze the function and development of the nervous system by reverse genetic approach. Among 19,000 genes that exist in the *C. elegans* genome, about 1,700 genes are thought to function in the nervous system. In order to dissect the molecular mechanism of thermotaxis, we have started to construct TMP/UV-induced deletion mutants for the genes that likely function in neurons required for thermotaxis. Since (1) cGMP could be a second messenger in thermosensation and (2) associative learning in thermotaxis can be established only in a few hours (0.5 ~ 4 hr), implicating the importance of change in neuronal activity, we focus on genes for (1) molecules related to cGMP signal transduction and (2) ion channels required for modulation of neuronal activity. For the first aim, we plan to knockout genes for guanylyl cyclase (GC), cyclic nucleotide phosphodiesterase (PDE), and cGMP dependent protein kinase (PKG). In *C. elegans,* there are at least 33 genes for GC, and at least two of these genes, *gcy-8* and *gcy-12*, are expressed in AFD thermosensory neurons. Also, there are several genes for PDE and a single gene for PKG. For the second aim, we are paying attention to the following genes; 6 genes for voltage-gated chloride channel, and 11 genes for transient receptor potential (TRP) ion channel. In any case, we first express GFP-tagged proteins encoded by these genes in wild type animals and look for genes that are expressed in neurons involved in thermotaxis circuit, before undertaking gene-knockout experiment. To date, we screened about 1,200,000 genomes and obtained deletion mutants for GCY-12 and TRP ion channel. These mutants showed nearly normal thermotaxis, but the gcy-12 mutant showed patial defect in chemotaxis to AWC-sensed isoamyl alcohol. Normal thermotaxis in the gcy-12 mutant would probably result from redundancy of gcy genes, which are expressed in AFD thermosensory neurons.

RNAi screen and functional analysis of genes required for germline development

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We are interested in germline development in *C. elegans*. In order to identify genes involved in germline development efficiently, we employed the Suppression Subtractive Hybridization (SSH) technique to generate subtractive cDNA pools either enriched for or deprived of the cDNAs from germline tissues. We then performed differential hybridization using these subtracted cDNA pools as probes on the high-density cDNA grid, on which about 7,600 non-overlapping EST clones were spotted, to identify a set of genes specifically expressed in the germline. One hundred and sixty-eight clones were then tested with the RNAi technique. Of these, fifteen clones showed sterility with a variety of defects in germline development, and other 21 clones showed embryonic and larval lethality.

We focused on two of the clones that showed the sterility phenotype. RNAi using one clone, yk445a8, caused sterility with underproliferative germ cells. This clone is derived from the T05G5.10 gene, which encodes a homologue of eIF5A. eIF5A was originally isolated as a candidate translation initiation factor, but recent studies have suggested a role in nuclear export of RNA. More recent studies show that it interacts with exportin 4 and has putative RNA binding domains, which suggests a function as an export adapter. *C. elegans* has another eIF5A homologue, F54C9.1. RNAi with a cDNA clone for this gene caused a larval arrest phenotype. *In situ* hybridization and Northern analysis showed the germline-specific expression pattern of T05G5.10 and the ubiquitous expression pattern of F54C9.1. We speculate that the germline specific eIF5A may recognize a set of mRNAs essential for the proliferation of germ nuclei and helps their export to the cytoplasm.

Another clone in which we are interested is yk519f1. It corresponds to the F35G12.10 gene, which encodes a homologue of the ATP synthase b subunit. The RNAi worms had many germ nuclei arrested at the pachytene stage and spermatocyte-like nuclei were often also observed. F35G12.10 shows a strong similarity with another *C. elegans* gene, F02E8.1. Northern analysis of staged worms shows that F35G12.10 is expressed in later larval stages and in adults and F02E8.1 is expressed at all stages. Now we intend to determine if the germline-specific ATP synthase b subunit regulates the function of mitochondria, which might in turn control the fates of germ nuclei.

Monoclonal Antibody MH33 Recognizes a Gut-specific Intermediate Filament

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The monoclonal antibody MH33 was produced by Francis and Waterston (1985) and detects a structure beneath the microvilli of intestinal cells, probably the terminal web. At the comma stage of embryogenesis, staining is both apical and cytoplasmic; apical staining becomes predominant in later stages up to the adult. The MH33 staining pattern differs from that produced by MH27, which recognizes a component of the adherens junction at the basolateral side of gut cells. To identify the MH33 antigen, we screened a C. elegans expression library (kindly provided by Dr. B. Barstead) by using MH33 antibody (kindly provided by Drs. Hresko and Waterson) and isolated 24 positive clone from ~ 100,000 plaques screened. A cross hybridization experiment indicated that these positive clones all encoded the same product. Several of the largest inserts were sequenced and identified gene F10C1.7, which encodes an intermediate filament. Dodement et al., (1994) had previously identified this protein as intermediate filament b2. Two observations suggest that we have indeed cloned the correct gene. (1) Westerns could easily detect a ~60kD band in extracts from twenty worms carrying a complete transgene; (Francis and Waterston (1991) originally reported that MH33 identifies bands at 62 and 64 kD, and Dodement et al. showed that alternative splicing gives rise to two forms of b2 that differ in size by ~ 2kD). (2) A five kb fragment from the F10C1.7 5!-flanking region, fused to pPD96.04, drives gut specific expression, starting at comma stage and continuing in all later stages. The MH33-detected gut-specific intermediate filament gene should be useful as a marker of early gut development (the gene is a potential direct target of elt-2, for example, and contains the usual suspiciously located WGATAR sites) and as a probe of intestinal cell structure, in particular the generation of apical-basal polarity during gut development.

Transcript specific RNAi phenocopies two classes of *mig-6* mutant

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In *C. elegans* hermaphrodites, the gonad acquires a U-shape by the directed migration of distal tip cells (DTCs). They start migration at late L2 stage from the ventral mid body of the animal, and by late L4 stage they finish migration. The first phase of DTC migration is longitudinal migration along the ventral muscle bands. The second phase is a circumferential migration, where DTCs migrate from ventral to dorsal along the epidermis, then finally they migrate retrogradely along the dorsal muscle band back to mid-body. Various mutants showing defects in different phases have been described. In *gon-1,* the first longitudinal phase is defective and the DTC stays there forming a very short gonad, which is sterile (1). *unc-5*, *unc-6*, *unc-40*, and *unc-130* have defects in the second phase. DTCs fail to migrate dorsally, resulting in ventral reflection of the gonad arms (2,3). In *mig-17*, both longitudinal and circumferential guidance are affected resulting in supernumerary turns of the DTC (4).

We have characterized two phenotypic classes of *mig-6* mutants. In conventional class 1 mutant, as described previously (5), the first longitudinal migration is defective, but ventral to dorsal migration is normal, which is partly similar to that of *gon-1*. By a large scale F1 screen for DTC migration mutants, we have obtained a new class of *mig-6* mutant (class 2). Heterozygotes of class 2 mutants display ventral reflection of DTCs that is similar to the defect in *unc-5*, *6*, *40*, and *130*. Interestingly, homozygotes of this class 2 are embryonic/early larval-lethal but escapers have DTCs that wander along both body axes, similar to *mig-17*. Thus, *mig-6* affects all of the three phases of DTC migration but separately.

Both classes of *mig-6* are rescued by a genomic fragment containing a single locus. There are two possible ORFs predicted by genome sequencing consortium and Yuji Kohara's EST clones. The two alternative transcripts, designated mig-6a and mig-6b, have the same exon structure down to exon 10 and have different 3' extensions. Northern blot analysis revealed two mRNA species, corresponding to the two predicted sizes. By designing dsRNA based on transcript specific 3' sequence, each transcript was disrupted independently or together. Quite surprisingly, it was shown that RNAi of mig-6b phenocopied the class 1 mutant, and RNAi of mig-6a alone or together with mig-6b phenocopied class 2 mutant recessive phenotype. All four class 1 alleles are nonsense mutations that affect just the mig-6b transcript. At least one of the class 2 mutations is a missense codon affecting both transcripts. Preliminary results suggest that expression of the two transcripts is under distinct regulation. Hence the expression patterns of the two transcripts, in addition to structural difference may define the class 1 and class 2 phenotypes.

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Identification of Genes Required for Ventralward Axon Guidance in *C. elegans*

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UNC-5 and UNC-40 receptors act together to mediate repulsive responses to the UNC-6 guidance cue. Attractive responses to UNC-6 also require UNC-40, but do not require UNC-5. Does UNC-40 require a co-receptor for attractive responses to UNC-6, the way it requires a co-recptor (namely UNC-5) to mediate repulsive responses to UNC-6? To look for mutations in such a hypothetical co-receptor for attraction or in mechanisms that act in parallel with UNC-6 and UNC-40, we searched for mutants specifically defective in ventralward guidance of the touch receptor axons AVM and PVM. The screen was carried out in a genetic background partially compromised for UNC-40 function. This screen yielded 12 mutations representing 6 genes. Two are *unc* genes previously identified as affecting axon guidance of a number of neurons (*unc-44* and *unc-51*), while mutations in the other 4 genes are not Unc and only appear to affect certain ventrally oriented axons. *avm-1* (allele *ev755*) is on LGIII, *avm-2* (allele *ev756*) is on LGI, *avm-3* (alleles *ev740*, *ev741*, *ev742*) is on LGX, and *avm-4* (alleles *ev750, ev751, ev752, ev753, ev754*) is on LGI. We have rescued *avm-3* with a fragment of cosmid C26G2 corresponding to the Slit gene (F40E10.4), which encodes an axon guidance ligand for the SAX-3 receptor. The laboratory of Dr. C. Bargmann (UCSF) is currently characterizing these mutations. We have also rescued *avm-4* mutations with overlapping cosmids F14B11 and F32A7, and further localized the rescuing region to a single open reading frame. We have found that *avm-4* mutations enhance AVM and PVM guidance defects of an *unc-6* null allele, suggesting that AVM-4 functions in an axon guidance pathway that acts in parallel with UNC-5, UNC-6, and UNC-40. We are currently determining in which cells this gene must function by expression and mosaic analyses. We are also cloning and characterizing *avm-1* and *avm-2*.

All available mutations in *flp-1* also delete *daf-10* sequences, confounding phenotype interpretation

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Based on the details explained below, several of the phenotypes previously attributed to *flp-1* mutants are more likely to be caused by loss of *daf-10*. These include defects in osmotic avoidance (Osm), thermal avoidance (Tav), nose-touch response (Not), wandering behavior, regulation of dauer formation, and possibly regulation of egg-laying behavior in response to food signals. Defects in these behaviors are characteristic of cilium-structure mutants, and could be easily accounted for by loss of *daf-10*.

In surveying a variety of behavioral mutants for a dauer phenotype at 27°, we found that both *flp-1* deletion mutants, *yn2* and *yn4*, have a moderate Daf-c phenotype at 27° and poor dauer recovery. Since many 27° Daf-c mutants are hypersensitive to dauer pheromone, we tested *flp-1(yn2)* for response to pheromone at 25°. Surprisingly, it formed no dauers in response to pheromone. Mutations in the *dyf* genes similarly lead to a Daf-d phenotype at 25° and a Daf-c phenotype at 27°. These mutants have defects in the structure of the ciliated endings of sensory neurons, a defect which can be assayed by the failure of these neurons to fill with fluorescent dyes. Thus, we performed FITC dye-filling assays on *flp-1(yn2*) and *flp-1(yn4)* and found that both mutants failed to exhibit dye-filling of any of the amphid or phasmid neurons.

flp-1 is not expressed in any of the amphid sensory neurons. Thus, we suspected that the *flp-1* Dyf phenotype was due to a background mutation present in both *flp-1* strains. The two alleles are not independent since they were isolated as deletions from the same parent strain which carries a Tc1 insertion just upstream of *flp-1*. We mapped the Dyf phenotype and found that it mapped to the right of *unc-5* and was not separable from *flp-1* (based on *flp-1* movement phenotypes). The only candidate *dyf* mutant in this region is *daf-10*. We found that *flp-1(yn2)* failed to complement *daf-10(e1387)* for the Dyf phenotype, indicating that the *flp-1* mutant strain also carries a mutation in *daf-10*. The *flp-1* strains exhibit a more severe dye-filling defect than *daf-10(e1387)*, indicating that they are stronger alleles.

daf-10 is encoded by F23B2.4 (Steve Stone and Jocelyn Shaw, personal communication), the gene immediately upstream of *flp-1*. Further inspection of the *flp-1* deletions indicates that *yn2* and *yn4* both delete the *daf-10* promoter and from two to four exons of the predicted *daf-10* coding sequence. The original Tc1 used to isolate the *flp-1* deletions appears to reside in the *daf-10* gene, and both *flp-1* deletion alleles are likely null for both genes.

Although several of the sensory phenotypes of *flp-1* mutants can be explained by loss of *daf-10*, it is likely that several other phenotypes previously ascribed to *flp-1* are bona fide *flp-1* phenotypes. Specifically, *flp-1* mutants have defects in movement and regulation of the active state of egg-laying that are not easily explained by loss of *daf-10*. Furthermore, both of these phenotypes were rescued by *flp-1(+)* transgenes.

GLC-3: A fipronil and BIDN-sensitive, but picrotoxinin-insensitive, L-glutamate-gated chloride channel subunit from Caenorhabditis elegans.

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Glutamate-gated chloride channels (GluCl) are a class of ligand-gated ion channel receptor found only in invertebrates, including nematodes. They are the targets of the avermectin/milbemycin anthelmintics, including ivermectin. Four C. elegans genes (glc-1, glc-2, avr-14 [which has also been called gbr-2] and avr-15) have been demonstrated to encode GluCl subunits. A further predicted C. elegans gene, ZC317.3, has high sequence identity to the GluCl genes. We have cloned and expressed the gene product and shown that it does indeed encode a further GluCl subunit. We have therefore named the gene glc-3.

Expression of glc-3 cRNA in Xenopus oocytes resulted in the formation of homo-oligomeric L-glutamate-gated chloride channels with robust and rapidly desensitising currents, an EC50 of 1.9mM and a Hill coefficient of 1.5. GABA, glycine, histamine and NMDA all failed to activate the GLC-3 homo-oligomer at concentrations of 1mM. Ivermectin directly and irreversibly activated the L-glutamate-gated channels with an EC50 of 0.4microM. The channels were selective for chloride ions, as shown by a shift in the reversal potential for L-glutamate-gated currents after the reduction of external Cl- from 107.6mM to 62.5mM. These properties are similar to those of other GluCl alpha subunits encoded by the avr-14 and avr-15 genes.

Picrotoxinin, a non-competitive antagonist of most other native and recombinant GluCl, failed to inhibit L-glutamate agonist responses at concentrations up to 1mM. However, the polycyclic dinitrile, 3,3-bis-trifluoromethyl-bicyclo[2,2,1]heptane-2,2-dicarbonitrile (BIDN), completely blocked L-glutamate-induced chloride currents recorded from oocytes expressing GLC-3 with an IC50 of 0.2microM. The phenylpyrazole insecticide, fipronil, reversibly inhibited L-glutamate-gated currents recorded from the GLC-3 receptor with an IC50 of 11.5microM. BIDN and fipronil have previously been reported to be specific blockers of GABA-gated channels. This antagonist pharmacology differs from that reported for the other GluCl alpha subunits.

VEGF-like Receptors in C. elegans

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We have previously described a C. elegans gene with significant similarity to VEGF-like growth factors from mammals (Tarsitano et al., WBG 16(2) page 36 (1999)).The next step was to look for potential VEGF-like receptors. A second motivation was that neuropilin, a cell surface glycoprotein that acts as a receptor for collapsin/semaphorin and is involved in axon guidance, also acts as a receptor for some members of the VEGF family of ligands. Popovici et al. (Genome Research (1999a) 9, 1026-1039) have collected some 28 sequences from the C. elegans genome that show significant similarity to receptor mammalian tyrosine kinase receptors. Among this collection, they point out four genes with similarity to mammalian VEGF receptors. Moreover, they have reported that one of these genes (T17A3.1) is expressed in head and tail neurons, including neurons of the amphid and phasmid (WBG 16(1) page 41 (1999b)).

We have focused on a tandem pair of VEGFR-like genes found on cosmid F59F3 (X chromosome). Sequence alignments (see also Popovici et al., 1999a) show anywhere from 22-33% amino acid identity (38-48% similarity) to VEGF Receptors 1 and 2, as well as to PDGF receptors A and B. Although presumably the result of a gene duplication event, the two genes (F59F3.5 and F59F3.1) show only 43% amino acid identity (59% similarity) to each other. Northern blots show that mRNAs have the size predicted from AceDB.

To determine expression pattern, we fused 4 or 5 kb of 5’-flanking region of each gene to one of Andy Fire’s GFP/lacZ reporter constructs and produced a number of transgenic strains. At least as monitored by GFP, the upstream gene (F59F3.5) is expressed intensely in the gut, beginning in the embryo, and in only a few cells outside of the gut. Expression of the downstream gene (F59F3.1), again as monitored by GFP, begins in the gut as early as the 4E-8E cell stage and expression remains intense in the gut of later stages. However, beginning roughly at the start of morphogenesis phase, high levels of expression are seen in many, possibly most, cells of the embryo; expression declines by hatching but in L1 larvae, expression can easily be detected in neurons and hypodermis along with many other cells. Expression declines rapidly thereafter (possibly complicated by reporter protein perdurance) but with gut expression remaining strong. The Kohara data base also reports strong gut expression. A developmental Northern also shows highest expression in embryos.

A probable knockout of the downstream gene (F59F3.1) has been isolated (deletion of exons 2,3 and part of 4, leading to loss of N-terminal immunoglobulin domains). The only obvious phenotype is an ectopic male ray 1 (anterior to the normal ray 1 position) and a short ray 3. The penetrance of these defects is roughly 30% and 10%, respectively. RNAi attempts only allow us to say that there is no obvious embryonic phenotype, despite the rather intense embryonic expression. A deletion that should remove the kinase domain of the upstream gene (F59F3.5) is in the last steps of sib-selection.

The future will include making antibodies, both to define expression patterns in more detail and to investigate localization within the expressing cells. Is there any reason to think that these receptors interact with the previously described VEGF-like ligand? What are the receptors doing in the early gut and why is there such a burst of widespread expression during morphogenesis? Finally, similar ray defects have been observed in mutants of semaphorin 1a and plexin 1a (Dalpe, Ginzburg, and Culotti, in preparation) and we plan to make and examine the appropriate double mutants with the latter genes.

smu-2 affects the alternative splicing of *unc-52* pre-mRNA and is homologous to a mammalian spliceosome-associated protein

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Mutations in *smu-2* were isolated as extragenic suppressors of the synthetic lethal phenotype of *mec-8 unc-52(viable)* double mutants. The *smu-2* mutations also suppress other phenes of *mec-8* mutants, such as mechanosensory and chemosensory defects, apparently by a bypass mechanism; *mec-8* encodes a putative RNA binding protein that affects the accumulation of certain alternatively-spliced transcripts of *unc-52* and other genes (Lundquist *et al.* Development 1996 **122:** 1601-1610). Finally, *smu-2* mutations suppress the uncoordination conferred by nonsense mutations in exon 17 but not exon 18 of *unc-52*. We hypothesized that *smu-2* encodes a factor that regulates the splicing of various target genes, at least some of which are also targets of splicing control by MEC-8. Indeed, our RT-PCR experiments indicate that mutation in *smu-2* leads to enhanced skipping of exon 17 but not exon 18 of *unc-52* pre-mRNA.

We identified *smu-2* by positional cloning and transformation rescue. We rescued the *smu-2* mutant phenotype (recessive suppression of *unc-52* and *mec-8*) with the YAC Y37F3 and with a long-range PCR product that contained the single gene Y49F6B.4. We also found that a construct containing 2 kb of the promoter region of Y49F6B.4 inserted 5' to a full length cDNA (YK563h8) rescued *smu-2(mn416)* and that a frameshift mutation introduced in the same construct abolished rescue. Finally, we identified sequence alterations in Y49F6B.4 associated with all three known *smu-2* mutations.

Database searches showed that *smu-2* is 37% identical to a mammalian nuclear protein called RED. The similarities between these proteins occur throughout their full extents. SMU-2 is the only protein with significant similarity to RED in the *C. elegans* genomic sequence database. Neubauer *et al.* (Nat. Genet. 1998 **20:** 46-50) identified RED in purified human splicesomes using mass spectrometry and peptide sequencing. The stringent conditions under which the spliceosomes were isolated--proteins transiently associated with spliceosomes were not isolated--suggest that RED is tightly associated with the spliceosome. RED was named after the most distinctive feature of the protein, a domain consisting of alternating basic (arginine) and acidic residues (aspartic and glutamic acid). RED domains are similar to RD domains that consist mainly of arginine and glutamic acid di-peptide repeats. RD domains have been found in a number of proteins that associate with the spliceosome. The human RED domain has diverged from SMU-2's RED domain--SMU-2 contains far more RD di-peptide repeats, and in addition it contains five serine residues. Surprisingly, *Drosophila* and *Arabidopsis* homologues do not contain a RED domain at all, although there is high conservation in regions outside this domain.

None of our three *smu-2* mutations is a molecular null. *mn416* is a 3' splice site mutation, *mn610* is a single base pair deletion in the last quarter of the protein, and *mn611* is a rearrangement with a breakpoint in the last quarter of the protein; thus, both *mn610* and *mn611* are predicted to make the N-terminal three-quarters of the protein, including the RED domain. We gained further evidence that these mutations are not null when we did transformation rescue experiments using long-range PCR products generated from mutant DNA templates: mutant DNA was able to rescue the *smu-2* phenotype, presumably as a consequence of overexpression. We did RNAi experiments to see if we could detect a more severe *smu-2* phenotype. When we injected *smu-2* dsRNA (including the RED domain) into *unc-52(ts)* mutants, we mimicked the *smu-2* mutant phenotype: over 98% suppression of *unc-52* and no embryonic lethality.

We have monitored expression of a rescuing *smu-2::gfp* reporter construct: the SMU-2::GFP is a nuclear protein that is ubiquitously expressed at all stages of development.

An attempt to slow aging in *C. elegans*. 18. No effect of sodium fusidine

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The purpose of this study was to investigate the effect of different concentrations of sodium fusidine in water solutions on nematode life span. In this experiment sodium fusidine was used in following dilutions: $1:10^3$,$1:10^4$,$1:10^5$,$1:10^6$,$1:10^7$ and $1:10^8$. Three adult animals (3 - 5 days old) were kept in microtitre wells containing 0,75 ml of liquid medium (with E. coli and without sodium fusidine) during 4 hours, then they were discarded and newborn larvae were transferred in next wells (with sodium fusidine 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 sodium fusidine	n	Longevity (days)	
		Mean±S.E.	Maximal
Control	36	9,47±0,76	21
$1:10^3$	36	10,03±0,81	23
$1:10^4$	36	9,44±0,88	25
$1:10^5$	36	8,72±0,51	18
$1:10^6$	36	9,86±0,94	26
$1:10^7$	36	8,86±0,73	24
$1:10^8$	36	8,86±0,73	15

Conclusion: If sodium fusidine solution was applied to C. elegans, it was not able to increase their mean as well as maximal 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.* 19. A positive effect of 1-butylbiguanide hydrochloride

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The purpose of this study was to investigate the effect of different concentrations of 1-butylbiguanide hydrochloride (this medicine is widely used for treatment of patients with diabetes mellitus) in water solutions on nematode life span. In this experiment 1-butylbiguanide hydrochloride was used in following dilutions: $1{:}10^3$,$1{:}10^4$,$1{:}10^5$,$1{:}10^6$,$1{:}10^7$ and $1{:}10^8$. Three adult animals (3 - 5 days old) were kept in microtitre wells containing 0,5 ml of liquid medium (with *E. coli* and without 1-butylbiguanide hydrochloride) during 4 hours, then they were discarded and newborn larvae were transferred in next wells (with 1-butylbiguanide hydrochloride 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 1-butylbiguanide hydrochloride	n	Longevity (days)	
		Mean±S.E.	Maximal
Control	12	14,25±1,30	23
$1{:}10^3$	12	13,08±0,70	22
$1{:}10^4$	12	17,58±1,01	29
$1{:}10^5$	12	15,75±0,86	24
$1{:}10^6$	12	15,58±0,91	23
$1{:}10^7$	12	15,33±0,89	24
$1{:}10^8$	12	14,00±0,62	23

Conclusion: If 1-butylbiguanide hydrochloride solution was applied to *C. elegans*, it was able to increase their mean (by 23,37%, $p<0,05$) 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.

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