C. elegans Automated Imaging Platform:

De-risking drug candidates ahead of rodent studies with a non-mammalian model for ageing, neurodegeneration and the microbiome.

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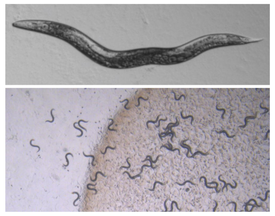
COVID-19 restrictions are slowing research productivity when drug development is needed most. Using the non-mammalian animal model *C. elegans*, Magnitude Biosciences is a UK-based CRO that can de-risk promising drug candidates before rodent testing.

Why Worms?

Relevant
- ~ 40% genes have human orthologs
- Track record in ageing, neurodegeneration, cancer, metabolism
- Transgenics as models of inherited diseases
- Indicator species for pesticide toxicity with good concordance for known toxicity in mammals

Efficient
- Small : 1-2mm worms grown in Petri dishes
- Fast: development and 2-3 weeks lifespan
- Nematode: No regulatory restrictions
- Ethical: Reduces mammalian testing



Top: *C. elegans* worm, showing internal organs. Bottom: Worm population maintained on bacterial lawn in standard Petri dishes. Phase contrast microscopy.

Versatile
- Nervous system, muscle, intestine, epidermis and reproductive system
- Transparent body: easy live visualisation of eg. GFP-tagged targets
- Amenable to transgenics, from strain banks or customised in-house.
- Assays for developmental toxicity or life-long intervention effects

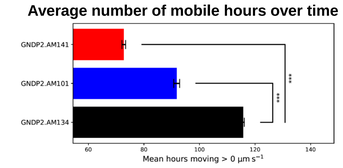
Magnitude Biosciences

C. elegans Research Services

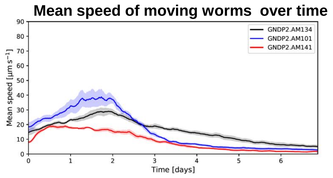
Case Study: Neurodegeneration

C. elegans' amenability to genetic modifications makes it a versatile model for inherited diseases, especially those with mobility or age-related symptoms. Complex data analysis also allows for the detection of trade-off effects between duration and speed.

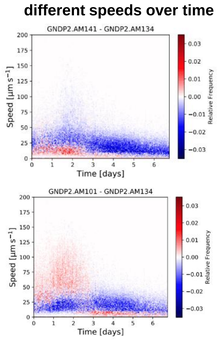
Average number of mobile hours over time



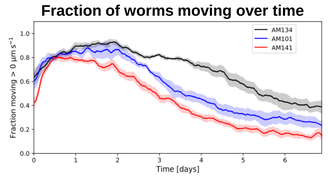
Mean speed of moving worms over time



Gain or Loss of worms at different speeds over time



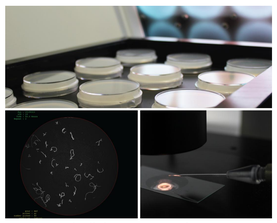
Fraction of worms moving over time



Multiple data analysis from a common dataset for **Huntington disease** model worms (PolyQ, 40 repeats): AM134 (control), AM 101(neuron expression), AM141 (muscle expression). Compared to controls, the muscle-expressing worms move the least often and are slowest throughout, while the neuron-expressing worms move less often but faster at early timepoints.

Revolutionary Technology

- Up to 32 Petri dishes at a time automatically tracked by separate small cameras each controlled by a single board computer.
- Near-continuously movement tracking: images taken every 0.8 seconds for 160 seconds, repeated every 5 minutes, for up to 10 days of worm adulthood.
- Non-invasive: no mechanical disruption, no abrupt changes in lighting or temperature.
- Multiple mobility parameters : worm speed, position, percentage moving, population fragmentation by speed, speed decline over time, chemotaxis, exploration, paralysis, increases in population size in fertile worms.
- Standardised reagents, protocols and schedules for manual worm maintenance prior to automated assays
- Assays monitored remotely.

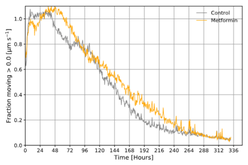


Top: Petri dish array set for illumination and image acquisition. Bottom Left: Representation worm tracks recording. Bottom Right: Micro-injection needle for transgenic strain generation.

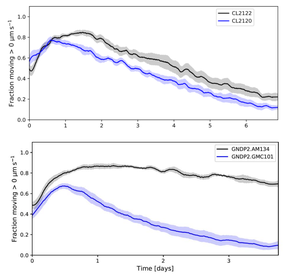
Case Study: Ageing

C. elegans' short lifespan allows its use as a natural model of ageing, wherein mobility decline can be recorded to assess the effectiveness of anti-ageing candidates, or track the progression of age-related diseases.

Metformin
- Type 2 diabetes drug Involved in AMPK and mTORC1 regulation
- Improves lifespan in *C. elegans* and mice
- Improves cognitive function in humans (observed in diabetes trials)



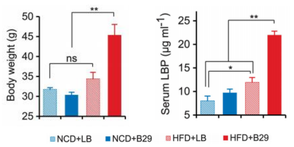
Percentage moving adult worms over 14 days imaging, showing a slower mobility decline over time in 50 mM metformin-treated worms.



Alzheimer's disease model strains in blue, showing more drastic mobility decline over time in the human-relevant muscle-expressing Aβ1-42 strain (GMC101, bottom) compared to muscle-expressing Aβ 3-42 strain (CL2120, top). black - Control strains

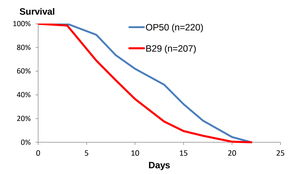
Case Study: Microbiome

C. elegans is routinely maintained on a bacterial lawn, which makes it ideal for studying host-bacteria interactions, either by direct co-culture with compatible strains, or by addition of bacterial extracts .

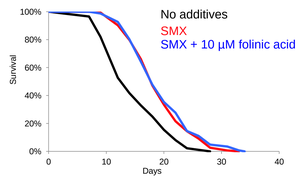


***Enterobacter cloacae* strain (B29), isolated from a morbidly obese human volunteer**, causes obesity in mice fed on a high-fate diet (HFD), but not in mice fed a normal chow diet (NCD). This correlates with an increase in serum LPS-binding protein (LBP), ,i.e. bacterial toxicity.

Data 16-weeks after inoculation.,- Advisor Board Member Liping Zhao Lab, (Fei & Zhao, 2013.).



C. elegans fed on B29 have a decreased lifespan compared to worms fed *on E. coli* (OP50). Data collected over 3 weeks. Data from Weinkove lab in collaboration with the Zhao lab.



SMX (sulfamethoxazole): Antibiotic disrupt excessive bacterial folate synthesis in OP50 *E. coli* and prevents likely mild toxicity by host-associated microbes (Virk *et al*., 2012 and 2016)

We believe that adoption of our C. elegans research services will boost drug pipeline productivity between *in vitro* and rodent studies, and strengthen the resilience of the biotech/pharma sector in these challenging times. For more info, www.magnitudebiosciences.com or email info@magnitudebiosciences.com