# *Caenorhabditis elegans* as a successful platform to develop new drugs: 4 encouraging examples.

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## Introduction

***Caenorhabditis elegans*** **is a tiny, transparent, free-living nematode that has been widely used as a model organism since its introduction by Sidney Brenner in the early 1970s. In addition to the key contribution to fundamental biology (three Nobel prizes awarded to researchers working with this organism), *C. elegans* has proven to be a powerful tool for drug discovery. This is because it is easy to grow; it has a short generation time; it has a small size, which allows testing with a large number of animals, and it is transparent, which allows the use of fluorescent markers to study biological processes in vivo. We can also model many different human diseases. For the development of drugs, it is interesting that the treatment is carried out in whole animals, with a cellular and tissue complexity that includes the nervous system, digestive system or muscle tissues, among others.**

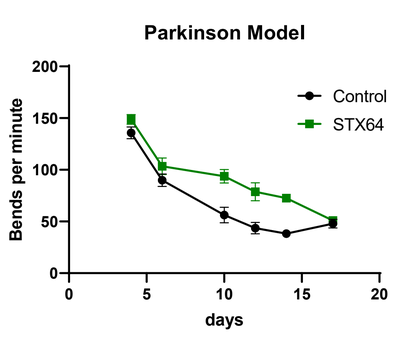
## Platform for drug and natural extracts validation

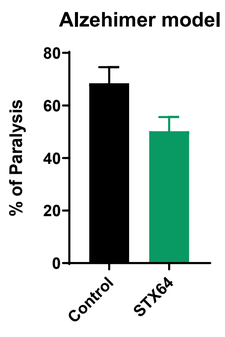
**With more than 20 years of experience with this nematode, we offer a platform for high-throughput drug screening for companies and research groups (https://www.upo.es/upotec/catalogo/salud/unidad-de-ensayos-validacion-actividad-biologica/). We routinary make assays on longevity, neurodegenerative models (Parkinson's, Alzheimer's, or Huntington's), metabolic diseases, like diabetes or obesity, whole animal toxicity, and infection, and also generate new models upon request. In addition to very experimented personnel, we have the equipment to do high throughput assays. We not only work for companies and research groups but also use the platform to identify our own compounds. All these are summarized in the following four examples.**

## Examples

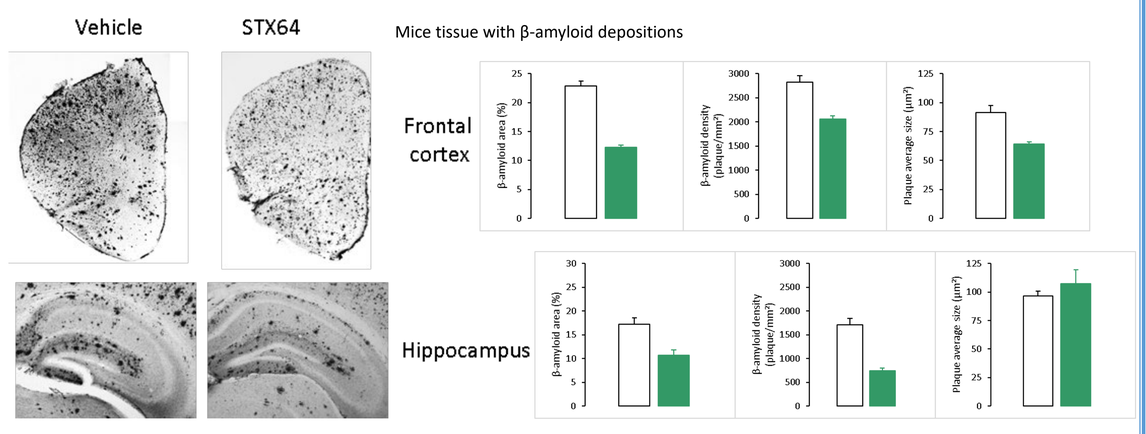
### STX64 is a new candidate for neurodegenerative disease treatment.

**STX64 is a potent, irreversible inhibitor of steroid sulfatase (STS). STS is the enzyme responsible for the hydrolysis of steroid sulfates. STX64 was previously postulated as a drug for hormone-dependent breast cancer treatment (1).**




**We used two *C. elegans* models for degenerative diseases, NL5901 for Parkinson's which overexpress human α-synuclein, and GMC101 for Alzheimer's which overexpress human β-amyloid peptide, in muscle cells in both cases. Those overexpressions cause paralysis with time. The use of STX64 ameliorates these paralysis problems in *C. elegans*.**




**We demonstrated that these findings in *C. elegans* can be extrapolated to mammals. STX64 administration ameliorates β-amyloid plaque formation, in number and in size, in a mouse Alzheimer's model, for example. STX64 also recovers β-amyloid dependent cognitive impairment (data not shown) (2). At this moment, there is a spin-off company (Olavide Neuron STX, https://onestx.bio/) managing the use of STX64 as a new treatment for neurodegenerative diseases.**

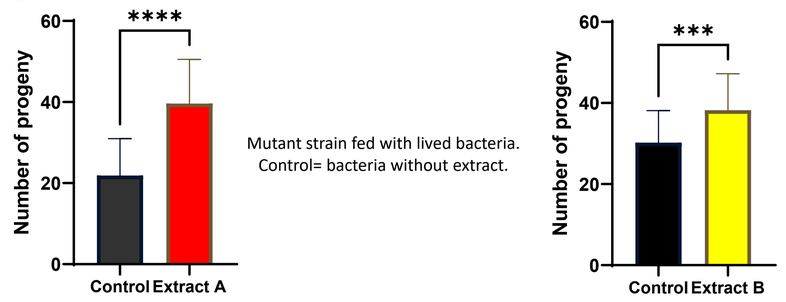
### Asaco_drug1 and Asaco_drug2 as a novel drug SMA treatment.

**Spinal Muscular Atrophy (SMA) is a progressive neuromuscular disease characterized by the loss of motor neurons and atrophy of skeletal muscles (3). SMA is caused by SMN1 gene recessive mutation. A second SMN gene, SMN2 is 5 nucleotides different from SMN 1, however, can produce 10% of functional mRNA like SMN1. The promoter sequences of both genes are identical. A therapeutic option may be to search for drugs that inhibit negative regulators of SMN expression. SMN1 has a homologous in *C. elegans*. We searched putative SMN1 negative regulators and then we focused on drugs described as inhibitors of those negative regulators.**

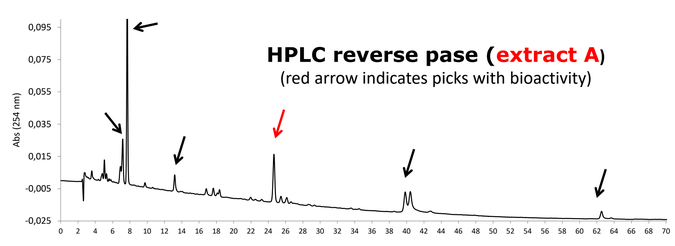

**We generated a model where the SMN homolog in *C. elegans* was labeled with a fluorescent reporter. Using our platform, we tested the drug pool and we found 2 that increased protein SMN1 abundance, asaco_drug1, and asaco_drug2. Data in human cell culture indicate that at least asaco_drug1 also increases levels of human SMN. We are in a process of patenting the drugs.**

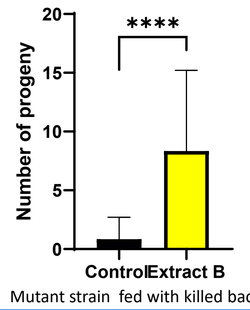
### Two natural extracts show beneficial effects on polycystic ovary syndrome(PCOS) model.

**There is a clear correlation between PCOS and diabetes (4). In *C. elegans*, several mutants with impaired insulin pathway function show a decrease in fertility. We have used one of these mutants as a model for infertility. Extract A and B can increase the number of progeny of this mutant.**




**Both extracts came from edible plants. In extract A, we already have done several steps of purification and isolation in collaboration with Fundación Medina. For extract B, we already used a quite purified extract, and we are on the way to demonstrating if the majority compound is responsible for the effect. We also know extract B fertility increase is not prebiotic, since it also works with killed bacteria as a unique source of food.**




## Conclusion

***C. elegans*** **is a wonderful tool for new drug development and natural extract bioactivity validation. Thanks to our expertise and years of hard work, we can offer a versatile, high throughput, and successful platform for in vivo drugs and extract testing. This platform has demonstrated its validity and power to help in the process to bring new drugs to the market. If you think that an in vivo test could boost your work, do not hesitate to contact us. mmunrui@upo.es jmmonmor@upo.es**

## References

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