Creating Transgenic *C. elegans* Models For Clinical Variants of Unknown Significance

Customer Story

InVivo Biosystems

> ***There's no excuse to stay in your silo in today's science. There's no such thing as a cell biologist or geneticist. These categories are all merging now, maybe under some greater molecular biology or something. But you have to be flexible and be able to move between things — move to the system that's easiest to study your question. And if you have a collaborator down the hall, great. But if you don't, there's companies like [InVivo Biosystems] that can collaborate really well with you.***
>
> -Dr. Dan Starr

Overview

Dr. Dan Starr, a professor at UC Davis, often uses a multimodal approach to his research, which focuses on nuclear positioning in cell and developmental biology. One of his research projects required him to establish and functionally characterize two potential disease-causing variants, LMNA and KLC4.

Challenge

Genomic data is now widely accessible to clinicians, consequently, there has been a rise in variant discovery. However, the role that these variants play in disease processes is unknown. The Starr & Luxton Labs decided to use C. elegans models to study the two components of the LINC complex, LMNA and KLC4, which are two potential disease-causing variants.

Solution

As an officially licensed CRISPR solutions provider, InVivo Biosystems is able to create the gold standard of human disease models using *C. elegans* for Dr. Starr's project. InVivo Biosystems used CRISPR/Cas9 to replace the worm's gene with its human ortholog, and to introduce the potentially pathogenic variants into the humanized models.

Benefits

Using the models provided by InVivo Biosystems, the Starr & Luxton Labs were able to focus their efforts on understanding and evaluating the variants and complete their project in a timely manner.

Dr. Dan Starr has spent the last 20 years studying nuclear migration in *C. elegans.* Nuclear migration can be used to study basic biological processes as well as disease processes like cancer metastasis, and *C. elegans* are an excellent model for this research because many of the fundamental cellular processes that Starr's Lab studies are conserved between *C. elegans* and humans.

Dr. Starr ascribes to a multimodal approach to research, an approach whose benefits are becoming more widely recognized. For instance, Dr. Starr explained that, while his lab also uses induced pluripotent stem cells (iPSCs) in their research, it is important for them to utilize multiple model systems. One of the main reasons Dr. Starr believes this is because tissue cells have limitations due to their 2D environment that *C.elegans* do not exhibit thanks to their 3D structure. Dr. Starr said that, "in the worms, everything has got these neighboring tissues. And we find many differences in behaviors of the nuclei and stuff just because they're in a three-dimensional tissue and throughout development." For Dr. Starr, using a combination of models means he can bypass the structural limitations of certain models, and therefore shorten the timeline of studies. This approach also means that more simplistic models can be tested prior to the traditional mammalian models, making it particularly useful for rare disease research.

Dr. Starr approached InVivo Biosystems to help build worm models for possible disease variants (LMNA and KLC4) that are components in the system they study (the LINC complex). To build these models, we utilized our proven genome editing techniques using CRISPR/Cas9 to humanize the worm models. InVivo Biosystems offers two types of humanization services: whole gene humanization and point mutation humanization. You can learn more about the differences between the two types of humanizations here.

"The gold standard for these human disease models is replacing the worm's endogenous gene with the human version at the endogenous locus, so InVivo Biosystems went ahead and replaced the worm klc-2 with KLC4. This process was also repeated with LMNA" explained Ellen Gregory, a PhD student in Starr's lab. At times, however, point mutations are the best option for a project, like in this case, as "unfortunately the humanized LMNA worm was inviable. But nonetheless, InVivo [Biosystems] created strains that introduced the variants of interest at the endogenous *C.elegans* locus." InVivo Biosystems adapted to the needs of this project, and in doing so, "acted as a temporary post-doc, to speed this project along much faster than we [the Starr Luxton Labs] could have done in the lab ourselves," said Gregory.

When asked why Dr. Starr chose InVivo Biosystems, he said that InVivo Biosystems "can crank the transgenics out faster than we [the Starr & Luxton Labs] can." He explained how working together was a collaborative endeavor that allowed his team to focus on what they do best, and that after IVB delivered the models, "then we can use our skills to analyze it in our assays of

nuclear movements and things like that." Our technology and expertise makes genome editing straightforward for us, and by providing these services we can take pressure off of labs.

The importance of collaboration in science is something that Starr feels passionately about. Recently, Dr. Starr was awarded the coveted Allen Distinguished Investigator award, and largely attributes this success to it being a joint application with his colleague Dr. Gant Luxton.

Reflecting on this award Dr. Starr advised that, "students and faculty, students and labs — they shouldn't be afraid of [a collaborative, highly integrative approach]...so, if you want to move into a place where you're using *C. elegans* as a transgenic model, you find a collaborator. And if you have a collaborator down the hall, great. But if you don't, there's companies like [InVivo Biosystems] that can collaborate really well with you."

The collaboration between Dr. Starr and InVivo Biosystems has been a very collaborative, on-going process, "we've been working very closely with [InVivo Biosystems] for the last couple of years, and moved some of our projects forward during this pandemic. And when we can't hire fast enough - it's been great working with you." Starr concluded saying, "it's been a really fruitful collaboration."

About InVivo Biosystems

Founded in Eugene, Oregon in 2011, InVivo Biosystems is working to accelerate deep in-vivo insights into human biology and enable researchers to develop and deliver solutions that improve human health. An expert in CRISPR genome editing, InVivo Biosystems provides a unique capability for creating custom genome edited zebrafish and *C. elegans* that enable therapeutic research on genetic models of aging, developmental, and neurodegenerative disease, uncovering potential cures. The company's *in vivo* analytical testing platforms and technologies provide faster, cost-effective investigations that focus on proof-of-principle experiments for rapid go/no go decision making so that biopharma and nutraceutical companies around the world can better understand aging and aging related diseases and explore potential treatments.

All our projects include on-call project status updates, as well as regularly scheduled communication. We also provide on-call consulting and interpretation with our Ph.D. level, subject-matter experts.

What we do:

- Deliver scientific data on test results in less than 5 months.
- Produce the best outcome measures for anti-aging products.
- Provide information about mechanisms of action (MoA).
- Support your Marketing and IP claims with real science.

Contact us to start a conversation about how our services can support your innovation.


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