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## Gaps! Transgenesis, Model Organisms and Human Diseases

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It is certain that the evolutionary gaps are challenges in that they limit the interpretation of our exciting findings because it is difficult to translate them from model organisms into humans. On one hand, a gene product in a lower model organism might possibly have a larger function profile, possibly as a potential divergent function (2 or n)-in-1 homolog in mammalian systems; on the other hand, the tightly regulated gene expression and finely adjustable concentrations of physiological material in humans may exacerbate the difference by adding new complexity due to natural selection. However, many innovative methods of overcoming such gaps allow model organisms to contribute greatly to our knowledge of human health and the means of addressing human diseases [1-4]. We briefly review some recent studies and discuss some novel challenges to overcome.

Firstly, we summarize recent progress in humanized mice used for HIV, cancer, autoimmune diseases and infectious diseases; transgenic *Caenorhabditis elegans* models for neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, autism and Type 1 diabetes (an autoimmune disease); and transgenic fly *Drosophila melanogaster* for brain tumors (Table 1). Humanized mice (the NOG mouse, developed in Japan; the BRG mouse, developed in Switzerland; and the NSG mouse, developed and distributed by the Jackson Laboratory) are currently used for cancer co-clinic trials or the like, which is helpful for identifying which drugs a cancer is sensitive to and also for obtaining new targets very early before a patient's cancer develops resistance to standard treatment [2,5,6] (Table 1).

Particularly valued for its short life span, *C. elegans* has a well characterized nervous system and several genes that are homologous to the human genes implicated in AD, such as the amyloid-beta protein precursor, presenilins and tau. Additionally, human genes linked to AD, such as amyloid-beta or tau, can be expressed and studied in *C. elegans*. It lacks orthologs of the human disease-related genes *PARK1* and *LRRK2* for Parkinson's disease, but it allows transgenic expression of some human genes and permits us to study the impact on dopaminergic neurons.

For research, there is another type of gap: the natural features of animals and the approaches available to identify them. For such gaps, a creative idea and sometimes a little bit of luck is needed. For example, in the past, we faced the challenge of DAF-12, namely, its tendency prone to degrade. This hindered us capturing some of its important activities *in vivo*. However, we have been able to create an integrated transgenic DAF-12 worm with a few copies by means of DNA recombine ring and gene gun bombardment, which may replicate the natural regulatory settings, with no obvious compromise of the animal's natural functions. We conjecture that this transgenic organism may provide us with a potential counterbalance of DAF-12 protein prone to the degradation or un-stability during the harsh experimental process for a success of ChIP assays [3,7] and/or proteomics assays. Its endogenous protein cannot work well through the whole assay possibly due to its low abundance whatever.

Though the evolutionary gap exists, surprisingly, DAF-12/VDR target genes from screening based on *C. elegans* overlaps with many validated homologs identified in human VDR studies, so we are

hopeful that this finding should somehow to translate into the human context. Furthermore, since cell culture lacks organismal complexity, two different developmental stages of worms were pooled plus with whole animals rather than using focused mammalian cell lines, so our screening expected to cover VDR/DAF-12 target genes better (Zhang, Y., in preparation). Moreover, we consider that DAF-12/VDR could hold the secret that will unravel the common basis of autoimmune diseases and associated cancers (Zhang, Y., in preparation). Further efforts using ChIP-seq on other stages, as well as proteomics assays, will shed further light on this approach.

The model of germline tumor in C. elegans is relatively clear [17]. However, its model of somatic tumour remains to be established [19]. More or less like Drosophila, but C. elegans seems to lack any vestige of DNA methylation [2]. It is tempting to hypothesize that this may not cause a transplantable somatic tumor in C. elegans. Importantly, it also remains unclear how significant the adaptive immunity is in C. elegans, since we currently assume that it lacks adaptive immunity, and it may be an imperfect model of autoimmune diseases because it lacks or has no identifiable orthologs of the human disease-related genes for adaptive immunity. Despite this fact, the nematode could either provide some insights directly from this evolutionary gap in the adaptive immunity through comparative studies of model systems' or it could be improved as a good model, while it allows transgenic expression of these human genes and the study of its impact after model transformation on autoimmune diseases, similar to the creation of model of Parkinson's disease in C. elegans. Lastly, the humanized mice model of diabetes may help to decipher the development of type 1 diabetes in particular.

For experimental repeatability, along with cost-effectiveness, even if the key process can be conserved and the core pathway could be reproduced in lower model organisms, we can say that mice are relatively expensive for small labs, not to mention how difficult it is for a small lab to obtain human specimens. Consequently, *C. elegans* and *Drosophila* may be considered as alternatives. During last four decades, the nematode is a superstar that has shown many advantages that can be integrated with breakthroughs from other animal models and human research, and it might provide an unprecedented complementary experimental approach for the elucidation of the molecular mechanisms of complex diseases such as autoimmune diseases and associated cancers. So far, the meta-analysis has been used to address the limitations of case availability in human studies. Once we truly understand the gaps, we will profit from them.

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Diseases	Gap	Issues	Solution	How it works and the limitations	References
1. HIV	Differences in the viruses and different immune systems between humans and monkeys.	The rhesus monkey responds to its related virus. This limits insights to understanding HIV or to testing drugs and vaccines with the rhesus monkey for HIV research.	Humanized mice, which respond to HIV more like a human than a mouse	<ol> <li>(1). Disable the mouse immune system and equip it with a human immune system.</li> <li>(2). The mouse immune system behaves fully like a human system.</li> </ol>	[4,6]
2. Cancer	The cell lines are most likely different from those cells in the context of the patient.	Cancer relapses with no options, such as pancreatic cancer.	Humanized mice	<ol> <li>Some tumor types do not grow in the humanized mice, including breast cancer.</li> <li>It takes about half a year for mice to grow the tumors and to test how the cancers respond to treatment.</li> </ol>	[5,8]
		Cancer cells easily mutate. In some cases, anti-cancer drugs that seemed promising based on screenings in cell lines have failed in human clinical trials.			[9]
3. Infectious disease			Humanized mice		[6,10]
4. Autoimmune diseases	Dramatic differences between human and mouse immune systems.	Studying rheumatoid arthritis in mice probably does not give an accurate representation of how the disease functions in humans. Some rheumatoid arthritis drugs that seemed promising based on results in mice failed in human clinical trials	Humanized mice	Human stem cells (especially umbilical cord blood, including white blood cells, which regulate immunity) have been injected into mice.	[11]
5. Parkinson's disease	A lack of orthologs of the human disease-related genes <i>PARK1</i> and <i>LRRK2</i> for Parkinson's disease.		Transgenic C. elegans	Transgenic expression of some human Parkinson's disease-related genes so as to study the impact on dopaminergic neurons.	[12]
6. AD	<i>C. elegans</i> lacks a vascular system.		Various models, including the fruit fly <i>Drosophila</i> <i>melanogaster</i> and the mouse <i>Mus musculus</i> .		[13]
			The nematode <i>C.</i> <i>elegans</i> model in AD research.	<ol> <li>C. <i>elegans</i> features some genes that are homologous to the human genes implicated in AD.</li> <li>Human genes linked to AD, such as amyloid-beta or tau, can be expressed in <i>C. elegans</i>.</li> </ol>	[13]
7. Diabetes	<i>C. elegans</i> lacks a vascular system.		<i>C. elegans</i> model in diabetes.	<ol> <li>Advanced glycation endproducts</li> <li>(AGEs) accumulate in <i>C. elegans.</i></li> <li>Increased AGE-formation and mitochondrial AGE-modification are responsible for increased oxidative stress and limit the life span.</li> </ol>	[13]
8. Ageing	<i>mTORC1</i> and <i>mTORC2</i> in are found mammals; only <i>TOR</i> is found in <i>C. elegans.</i>		One of core ageing/ longevity pathways was revealed.	<i>mTORC1</i> is homologous to <i>TOR</i> .	[14,15]
9. Brain tumor	Vestiges of DNA methylation in the fly <i>Drosophila</i> <i>melanogaster</i> .		Studies on fly <i>L</i> (3) <i>mbt</i> brain tumor has shed light on the human brain tumor.		[2,16] [2,14,16-18]
Unresolved gaps	Likely lacking of transplanted somatic tumour growth niche in <i>C. elegans.</i>				[17,19,20]
	Likely lacking of adaptive immunity in <i>C. elegans.</i>	Autoimmune diseases			[3]
Genetically modified food safety	Difference in natural corn and non-natural corn.	Long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize.			[4,20]

Table 1: The gaps and their applications in human diseases.

As a final word of caution, we should take care with genetically modified foods until more is known [20].

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