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Examining the Ethics and Efficacy of Model Organisms: perspective from Undergraduate Students

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A B S T R A C T

Focusing on selected studies, this article will review the applications of several model organisms in order of perceived cognition: yeast, nematodes or worms, fruit flies, and mice. The analysis in the main body sections are provided by 16 undergraduate students (13 female) currently enrolled in a Genetics course at the University of Houston-Victoria. The discussions provided are excerpts from reports they undertook as an assignment for said course and have been edited for length and content. It is the aim of this paper to provide a narrative on the applications and ethical implications behind the use of model organisms in genetics from the perspective of an undergraduate student.

Introduction

The value of a model organism to in a clinical or laboratory setting is in the extrapolation of data collected from that species to another species, usually humans (Kallio, et al., 2014). This is an established practice that has yielded many results, from modern-day organ transplants to the polio virus of Jonas Salk in the 1940's to our earliest understanding of anatomy from the dissection, vivisection and experimentation by the contemporaries of Aristotle (Botstein and Fink, 2011). The question of ethics and animal rights is a new challenge (Funk and Rainie, 2015).

From the Cartesian theory of the 1600's up until the mid-1970's animals were classified as automata, incapable of thought of feeling. The modern consensus is that animals exhibit responses to painful stimuli in highly similar ways as do humans. Current ethical discussion focuses on level of cognition, attempting to determine at what level of evolution an animal becomes conscious of self, which has resulted in the banning of high primates as test samples in many countries (Sullivan, et al., 2014). Many other animal rights activists will point out the

perceived hypocrisy in this model and believe that all animals deserve equal rights, regardless of sentience or "cuteness". Proposed alternatives mentioned include cell cultures, computer simulation, or at the very least refinement of the current animal model process in terms of managing distress and maintaining a close proximity to the animals psychological and physiological homeostasis. What cannot be argued is the results that have been borne from the use of animal models, as will be discussed at length in the body sections. These will begin with 3 lower-level microorganisms that have had great impacts in multiple disciplines on left: *E.Coli* strain containing plasmid pKJK10 expressing Green Florescent protein (GFP) and on right: plasmid RP437 expressing red fluorescent protein (dsRED)..

E. coli are bacteria that when detected may indicate the presence of fecal pollution. It develops in many strains but can be harmless, existing inside human or animal intestines; however it can sometimes cause serious illness (Zhang, et al., 2015). Our understanding of DNA replication, the genetic code, gene expression, and protein synthesis derives from the study of *E. coli* (Lederberg and Tatum, 1946). The first discovery of *E. coli* was in the 1800's by Theodore Escherich upon his investigation for the cause of infant deaths due to diarrhea (Botstein, et al., 1997). Joshua Lederberg was the first to use *E. coli* as a model organism when he founded bacterial conjugation in 1946 (Botstein and Fink, 2011). Years later in 1988, Richard Lenski conducted a study of asexually reproducing *E. coli* strains to better understand genetic mutations. In a study conducted by Dr. Susan Rosenberg, Ph.D., a Professor of Molecular and Human Genetics at Baylor College of Medicine, along with other researchers, a new technique was used that makes cells with DNA damage appear green (Merrianm-Webster, 2015). Their team developed the technology in *E. coli* by attaching a gene for green fluorescent protein to a gene that promotes the SOS DNA damage response (Merrianm-Webster, 2015). The SOS response is generated when the cell detects breaks in the double-strands of DNA (Merrianm-Webster, 2015). SOS is designed to repair these breaks and let the genome reproduce normally in new cells (Merrianm-Webster, 2015). The fluorescent protein caused cells to look green when SOS was activated (Merrianm-Webster, 2015). Recently, a team of researchers successfully made colonies of *Escherichia coli* to produce new forms of antibiotics. According to the research led by Blaine A. Pfeifer, a colony of *E. Coli* were engineered into producing new varieties of erythromycin, a popular antibiotic that is used to treat or prevent different types of infections caused by bacteria. The formation of the new-version of erythromycin involved different processes. *E.coli* was manipulated into producing all of the materials necessary for creating the new erythromycin which involved combining and manipulating chemical compounds through an assembly line-like process. The objective was to ideally tweak any part of this assembly line, using techniques to attach parts with structures that differ slightly from the original erythromycin. Enzymes were used to attach 16 different shapes of sugar molecules the 6-deoxyerythronolide B molecule which lead to more than 40 new versions of erythromycin (Zhang, et al., 2015). Three of the newly engineered varieties of erythromycin were capable of killing the bacteria species- *Bacillus subtilis* which were initially resistant to the original form of erythromycin. Also, *E.coli* has been genetically engineered to produce renewable propane which is used as bottled fuels. Researchers used *E.coli* to interrupt the biological process that turns fatty acids into

cell membranes by using enzymes to move the fatty acids on a different part, so that the bacteria made engine-ready renewable propane instead of cell membranes (Kallio, et al., 2014). Also, *E.coli* serves as a method for engineering human therapeutic glycoproteins which are proteins that are altered at specific amino acid "acceptor" sites with oligosaccharides. Glycosylation - the In the fight of cancer cells, *E.coli* has been a very helpful engineered motor vehicle that delivers natural *E.coli* molecules and recombinant molecules to kill tumors. In the research, that was conducted Panc-02 mice's were injected with invasive *E. coli*. When the mice's were treated with only invasive *E.coli* it was shown that the amount of tumor cells dwindled by about 50%. The research showed that *E.coli* serves the function of alerting the immune cells to the site of the tumor to kill the cancerous cells because the amount of white blood cells and macrophages at the site of the tumors in the Panc-02 mice's significantly increased.

Yeast *Saccharomyces cerevisiae*

Yeast is a sexual eukaryote and a domesticated microorganism. Yeasts are non-pathogenic and non-motile microorganisms that can be easily breed and manipulated with in the laboratory. The generation time of yeast is very short (roughly 90 minutes). An important theme of yeast biology is the use and study of homologous recombination, a process whereby broken piece of DNA uses homologous DNA template as a substrate for repair. This process is being used by yeast to fix DNA damage, switching mating types and segregate homologous chromosomes during meiosis. It is also used by researchers for genetic mapping and integrative transformation of DNA into specific locations of the genome. Yeast as a single celled eukaryote uses variations of the same mechanisms found in higher eukaryote to make developmental decisions and differentiate into different cell types. Much of what we have learned about in the field of cell and molecular biology has come from research on yeast. The genes and mechanisms that are involved in many cellular processes are highly conserved across eukaryotic taxa, so by studying the yeast we learn about the fundamental biology of all eukaryotes. Research on using the S. cerevisiae yeast as a model organism for studying different genetic and health issues such as mitochondrial mutations, cancer and Werner syndrome has been a great success (Karathia, et al., 2011). One of the first known applications of S. cerevisiae testing was by Boris Ephrussi and colleagues in 1956. In 2011, Hiren Karathia led research on finding out how S. cerevisiae would work as a model organism for 704 organisms. Their research found that humans, dogs, mice, cows, rats, and other mammals in general were good organisms to use the S. cerevisiae as a model organism. This was due to their similarities with S. cerevisiae in regards to proteins, remembering that genetic code is used by cells to produce proteins. Other similarities included cytoskeleton organization, transcription, anatomical structure morphogenesis, transposition, conjugation, cell budding, and protein modification process (Karathia, et al., 2011).

Yeast cells produce ATP through two mechanisms: through glycolysis when glucose is available or through oxidative phosphorylation (OXPHOS), when there are no fermentable carbon sources. Mutations that affect OXPHOS components are not harmful, they can be manipulated by changing culture conditions; making for a convenient selection of respirator defective mutants. Researchers use yeast to create models of mitochondrial diseases, because

of the similarities between yeast and human mitochondrial tRNA. They transformed the yeast mitochondria to have the mutations as those of human mitochondria to study the mitochondrial tRNAs and study pathological tRNA mutations. Because of the high degree of similarity between yeast and human mitochondrial, biogenesis and function makes *S. cerevisiae* an exceptional model for human mitochondrial physiopathology study. Yeast models of Huntington disease have been characterized and summarized in many disease phenotypes. The long history of yeast research has led to an enormous set of resources that are available to the scientific community. The genome is completely sequenced; a complete set of nonessential gene knockouts has been constructed; open reading frame (ORF) and genomic arrays are cheaply available; and robust and detailed databases on the budding yeast have been developed and are available online. These resources and the massive amount of accumulated data on the budding yeast have made it a central component of modern biological research.

Nematode *Caenorhabditis elegans*

In 1963, a man named Syndey Brenner introduced *Caenorhabditis elegans* (*C.elegans*) as a model organism for molecular biology (Donald, 1997). *C. elegans* were the first multicellular organisms to have their entire genome sequenced, and it was found that they are comparable to the human genome. This gave biologists a valuable tool that would open the door to experiment and learn how genomes function. By obtaining the genome sequence researchers can detect mutations and link to finding a solution on how to correct it by using proteins as discussed in the article. Disciplines that have used *C. elegans* to advance studies include immunology, genetics, toxicology, and neurology among others. Many studies involve infecting the organisms with some sort of pathogen or a manipulation of its genome to test its resistance or susceptibility (Horvitz, 1997). In previous studies and current studies researchers have found different methods to investigate aging, effects of diet, pathogens, immunity, genetic variations and genetic mutations. Nematode lipid droplets are stored for membrane synthesis and energy reservation very similar to the human body. The lipid and proteins are very similar to those located in other species with enriched fatty acids. By using *E. coli* as a dietary substance it will allow for the *C. elegans* to survive for a long period of time with the containment of the lipid droplets proteins. When the droplet is isolated from *daf*2 mutants it will show a less abundance of those droplets along with the proteome MDT28. In other uses of *C. elegans* the localization of certain organelles and the infection into the organelles could lead to a genome change which could cause the *C. elegans* to change by slowing the aging process or even shorten the lifespan of the organism. This study could later expand the aging process due to the effects of organelle and genome coding. It overall affects enrichment of the gene development, reproductive, and the homeostasis of the organisms. The purpose of the experiment was to confirm the localization of the acylCoA synthetase ACS4 to the surface of the lipid droplets. The lipid droplets and proteins were isolated and an RNAi was conducted to encode the genes that were most relatable to the lipid droplet protein that supported growth, development and reproduction so it can be regulated and stabilize. The article mentioned how different mutations can cause there to be smaller and larger lipids than the average lipids in the *C. elegans*. Another significant factor that was addressed was that *C.*

elegans contains a very low level of cholesterol which could have applications in heart disease (Wood, 1988). By distinguishing the genes that codes for low cholesterol could possibly cure diseases associated with cholesterol. In previous studies, as discussed in earlier section of the review, the use of *C. elegans* has been conveniently used. *Caenorhabditis. elegans* has proven to be a successful model organism. Since *Caenorhabditis elegans* genome and the human genome have so many similarities, the organism can be studied for ways to decrease cholesterol and lipid levels in humans. *C. elegans'* lipid droplets naturally have less cholesterol and cholesterol esters. If researchers and scientists can find a way to use the information from the study to do this, it would improve the quality of life for many people and possibly extend their lifespans. Other possibilities are that the study of *Caenorhabditis elegans* could also cure other diseases as well. The effects of drugs and diseases could be studied on this organism without having to use human subjects. The following 2 sections discuss the applications of 2 higher-order members of the animal kingdom, and with them we begin to see a heightened presence of ethical dilemmas coupled with a heightened transference of data pertinent to humans.

Fruit Fly *Drosophila melanogaster*

Drosophila Melanogaster is a fruit fly and for the last 100 years or so, has been a favorite organism for biological research, initially in the field of genetics, but later in the investigation of fundamental problems in biology from the fields of ecology to neurobiology. These flies are small and easily reared in the laboratory. They have a short life cycle: a new generation of adult flies can be produced every two weeks. They fecund; a female may lay hundreds of fertilized eggs during her brief life span. *D.melanogaster* has been a very useful tool for analyzing the broad range of human genetics. Viruses within the human body are potential variables that can be studied by using the *D.melanogaster*. For example, the known viruses like HIV and HPV would be good candidates because of the known strains within the virus. When taking a look at these strains inside the flies, researchers can compare what makes the different strains more violent than the others. This small, short-lived organism has the potential to cure many diseases such as Alzheimer's and Diabetes. *Drosophila* has a clear homolog of APP, APP-like protein (dAPPL). Fruit flies deficient for dAPPL exhibit behavioral abnormalities (phototaxis deficiency), which can be rescued by a human APP transgene, indicating a functional conservation between dAPPL and human APP. dAPPL is involved in synaptic differentiation; synaptic development and neurite arborization dAPPL overexpression causes axonal transport defects. Similarly, overexpression of human APP induces axonal transport defects and increases cell death in the larval fly brain.

Parkinson's disease and Alzheimer's are 2 areas in which flies can also be used as the key model to further investigate how the changes in the structure of the mitochondria can improve or cause damage in the disease. In addition, they could also provide additional help for detecting the basis for polygenic disorders. Researchers would not only be able to just analyze a single dispensable structure of the fly, but more than one which leads to multiple genetic combinations. *D.melanogaster* has already assisted in identifying some proteins that are involved in Alzheimer's. In the future, the complex disorders within the human body will continue to be studied in the flies'

genetics. The fly is the simplest organism that has a pumping heart tube. Therefore, flies' heart is can be experimentally manipulated and adhere to physiological testing.

Drosophila Melanogaster will also be able to provide opportunities for research into therapeutic interventions. With thorough study and research conducted, the *Drosophila* study complex has created a platform to study the "lysis" or breakdown of a protein within a gene. This concept makes the discovery for revealing protein encoding quite attainable and in fact, fascinating. The *Drosophila* genome as discussed before obtains six encoding proteins that are paralleled to mRNA cap binding proteins which expedites the discovery. Overall, understanding the significance of this organism is by far very telling of the future of replicated disease and their potential to cure those diseases with the *D. melanogaster* genome. With a great deal of RNA binding protein being exposed it is probable that the depth of comprehension of translationalregulation will proliferate drastically.

House Mouse: *Mus musculus*

Commonly known as the house mouse, *Mus musculus* is used as an organism for genetic research. It serves as a model that is closely related to humans. Experiments on *Mus musculus* can provide benefits for human health and many other treatment discoveries. Knowing that they are closely related to humans allows researchers to experiment different type of diseases and medicine that are used. Mice can have a relatively long life span and they can reproduce large litter. Being that mice are cheap and can multiply quickly gives scientists the ability to preform multiple experiments at once. Mice have a life span of 2 years with a new generation every 9 weeks. They have an estimated 3 billion base pairs of DNA and roughly 40,000 genes, similar to humans. Almost every gene has a counterpart in the mouse and some blocks of sequenced mouse DNA are proving impossible to tell apart from the human versions. The comparison that a mouse has to a human makes it easier to research on disease that the two share and find treatment. A rodent can also be created from specific genes for a specific experiment. The ability to create transgenic mouse is a big advantage in research for scientist and the experiments.

Accompanying the explosive growth of modern technology has been a shift in public perceptions (Goodman, et al., 2012). Within today's connected society, it is almost impossible to discuss the future of mice in research without considering public opinions on animal experimentation. A 2014 poll showed that 50% of Americans oppose using animals in research, 47% favor, and 3% were unsure. In 2014, an unprecedented case was presented in New York State to determine the rights of two chimps used in experiments at a research facility and whether their captivity should be deemed false imprisonment. While the case was dismissed a year later, it brings to light many important questions about our relationship with other animals and underlines the current climate of the ongoing debate. Fortunately, alternatives to animal testing are currently being developed at increasing pace. Non-profit organizations such as People For Ethical Treatment of Animals (PETA) are funding developers whose goals are to replace laboratory animals with software. Alliances between scientists within varied fields are yielding emerging technologies that promise to replace animals, and thus mice, in experimentation within the near future. One such technology is computer modeling of experiments. One type of model developed is animal dissection, which provides a

virtual workbench in place of live animals. These have gained popularity in public schools and universities as cost-effective, conflict-free, and engaging educational resources.

Oxford student Oliver Britton developed a computer model of cardiac electrophysiology that could "potentially identify drug compounds that could be toxic to the heart before animal studies are done". This award-winning model's unique feature is that it "includes individual variations in 'normal' heart properties that traditional models have tended to ignore". The model is now incorporated into a package called Virtual Assay which can reveal problems that may arise due to variability within the population later down the road in clinical trials.

Bacterium: *Escherichia coli*

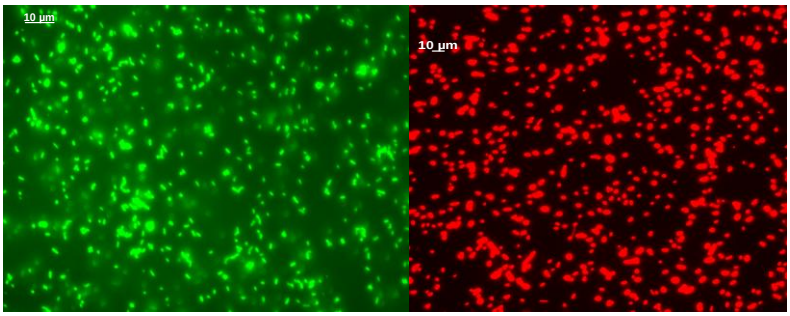

Figure.1 On left: *E.coli* strain containing plasmid pKJK10 expressing Green Florescent protein (GFP) and on right: plasmid RP437 expressing red fluorescent protein (dsRED)

Quantitative structural activity relationships (QSARs) have also proven to be invaluable computer tools for determining a chemical's toxicity before animal testing is done (Sullivan, et al., 2014). How a chemical will behave in an organism can be predicted by looking at its structure and using biomarkers. This strategy has "greatly reduced the reliance on laboratory animals for testing."

In 2015, the Wyss Institute of Harvard presented their "organs-on-chips", winning the Design of the Year by London's Design Museum. The chip is constructed of clear rubber with a network microchannels that house living organ cells. This innovative creation is expected to "significantly reduce the need for animal testing" by combining cost-efficiency, speed, and accuracy. An especially impressive feature is that multiple chips can be connected by "flowing human blood or nutrient-containing liquid" to model the human body. Emulate, Inc., the startup company that formed from the project, has teamed up with Johnson & Johnson to test the chip. Their work will investigate the mechanics of thrombosis and also liver toxicity, "a major cause of drug failures" in clinical trials.

Technologies like these may be a solution to this complex and divisive issue. These most recent scientific innovations are celebrated examples of creative solutions through interdisciplinary partnerships. The questions we have about animal rights will continue to deepen as scientists continue to learn more about animals and our relationships with them.

Conclusion

Having discussed the applications of 5 various species, the use of model organisms as a representation to outside phylogeny is a viable means of furthering the biological sciences. Though there remain questions about the extrapolation of data collected from these studies towards human trials even in higher-order subjects (e.g. cancer studies on lab rats to humans) the use of a simpler, idealized system makes for accessible and easily manipulated work for researchers. When choosing a model organism, it is important to select one with the most direct application. *E. coli's* ability to take up exogenous genetic material via DNA-mediated cell transformation has makes it a popular model for studies using recombinant DNA. The fruit fly is the most popular eukaryote for classroom study in the areas of heredity and Mendelian genetics. *C. elegans*' visible transparency and hermaphroditic nature make it perfect for studying genes of interest. Ultimately, model organisms are used for the testing of hypotheses that would not be ethical or practical to study on people. Combine this with their accessibility and ease of manipulation and the value surrounding the use of model organisms becomes all too clear.

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