Editorial

DOI: 10.5582/ddt.2016.01018

Using silkworms as a laboratory animal to evaluate medicines and foods

Kazuhisa Sekimizu*, Hiroshi Hamamoto

Laboratory of Microbiology, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan.

Summary **For this special issue, we, the Editors of Drug Discoveries & Therapeutics, have asked researchers who are using silkworms to actively develop drugs and study foods to summarize their recent work. Our profound hope is that this special issue encourages researchers who are helping to develop the new field of "using silkworms as a laboratory animal to evaluate medicines and foods".**

Keywords: Silkworm, *Bombyx mori,* animal model, antibiotics, drug discovery

Many countries are facing an aged population unlike that ever seen before. People fervently want better health and a longer lifespan. Therefore, medical care systems need to be developed in various fields. An important task for both medical and economic experts is to develop new medicines to treat various diseases. People also want evidence that foods can keep them healthy. The use of laboratory animals is a key issue in these situations involving the production of medicines and foods. Mammals like mice and rats have been used as laboratory animals, but sacrificing a large number of mammals poses a serious problem in terms of cost as well as in terms of animal welfare. A recent highlighting on animal welfare is seriously hampering the development of medicines in Europe, and countries in Asia will need to address this problem in the near future.

The use of invertebrates is a possible solution to the problems of high costs and ethical issues caused by the use of mammals. Studies have proposed that fruit flies (*Drosophila melanogaster*) and nematodes (*Caenorhabditis elegans*) could serve as laboratory animals in order to evaluate the therapeutic effects of drug candidates (*1,2*). A problem with the use of these invertebrates is that they are too small, making injection of precise volume of sample difficult. Techniques to inject animals as models need to be established in order to evaluate drug candidates.

Silkworms are the larvae of the silk moth, *Bombyx mori*. Methods of rearing silkworms have been established over a history of sericulture spanning more than five thousand years (*3*). Here, we would like to propose a new concept: "use of silkworms for drug development". Silkworms are akin to a silk-producing factory. Over the past few years, silkworms have been used to produce recombinant proteins (*4*). However, little attention has been paid to the usefulness of silkworms as laboratory animals in the field of medicine and pharmaceutical sciences. Therefore, "use of silkworms in drug development" is a novel idea substantiated by a long history of sericulture. Sericulture is still expanding in Asia. Hopefully, the concept of "using silkworms in drug development" will develop as a new industry.

Silkworms are useful at evaluating drug candidates (*5-8*) as well as foods (*9*). People are looking to food for nutrition and to supplements for substances that provide better health. Silkworms are particularly useful at evaluating food that may contain substances that activate innate immunity. Determining whether or not immunity is activated in humans and other mammals is usually difficult. We found that stimulating innate immunity in silkworms causes muscle contractions (*10,11*). Activation of cells responsible for innate immunity in silkworms leads to enhancement of immune cells that results in the activation of a cytokine that has the pharmacologic capacity to induce muscle contractions. We can easily use this phenomenon to screen food for substances that activate immunity. Beta-glucans in yeast cells and peptidoglycans in lactic acid bacteria have potent activity according to a silkworm muscle contraction assay (*10*).

**Address correspondence to:*
Dr. Kazuhisa Sekimizu, Laboratory of Microbiology, Graduate School of Pharmaceutical Sciences, The University of Tokyo Hongo 7-3-1, Bunkyo-ku, Tokyo 113-0033, Japan.
E-mail: sekimizu@mol.f.u-tokyo.ac.jp

Substances that cause innate activation were previously evaluated based on cytokine production by macrophages isolated from mammals, but lipopolysaccharides (LPS) derived from the outer structure of Gram-negative bacteria like *Escherichia coli* produce false positives at very low concentrations. The clear advantage of the silkworm muscle contraction assay is that it does not respond to LPS. Since we can easily develop models of various conditions like infections, diabetes, and cancer, silkworms should prove highly useful at evaluating the various functions of food components.

For this special issue, we, the Editors of Drug Discoveries & Therapeutics, have asked experts, who are using silkworms to actively develop drugs and study foods to summarize their recent results. Our profound hope is that this special issue encourages researchers who are helping to develop the new field of "using silkworms as a laboratory animal to evaluate medicines and foods".

References

1. Breger J, Fuchs B B, Aperis G, Moy T I, Ausubel F M, Mylonakis E, Antifungal chemical compounds identified using a *C. elegans* pathogenicity assay. PLoS Pathog. 2007; 3:e18.
2. Needham A J, Kibart M, Crossley H, Ingham P W, Foster S J, *Drosophila melanogaster* as a model host for *Staphylococcus aureus* infection. Microbiology. 2004; 150:2347-2355.
3. Goldsmith M R, Shimada T, Abe H, The genetics and genomics of the silkworm, Bombyx mori. Annu Rev Entomol. 2005; 50:71-100.
4. Banno Y, Shimada T, Kajiura Z, Sezutsu H, The silkworm-an attractive BioResource supplied by Japan. Experimental animals/Japanese Association for Laboratory Animal Science. 2010; 59:139-146.
5. Hamamoto H, Kurokawa K, Kaito C, Kamura K, Manitra Razanajatovo I, Kusuhara H, Santa T, Sekimizu K, Quantitative evaluation of the therapeutic effects of antibiotics using silkworms infected with human pathogenic microorganisms. Antimicrob Agents Chemother. 2004; 48:774-779.
6. Hamamoto H, Urai M, Ishii K, *et al*., Lysocin E is a new antibiotic that targets menaquinone in the bacterial membrane. Nature Chemical Biology. 2015; 11:127-133.
7. Uchida R, Hanai H, Matsui H, Hamamoto H, Sekimizu K, Iwatsuki M, Kim Y P, Tomoda H, *In vitro* and *in vivo* anti-MRSA activities of nosokomycins. Drug Discov Ther. 2014; 8:249-254.
8. Matsumoto Y, Sumiya E, Sugita T, Sekimizu K, An invertebrate hyperglycemic model for the identification of anti-diabetic drugs. PLoS One. 2011; 6:e18292.
9. Dhital S, Hamamoto H, Urai M, Ishii K, Sekimizu K, Purification of innate immunostimulant from green tea using a silkworm muscle contraction assay. Drug Discov Ther. 2011; 5:18-25.
10. Ishii K, Hamamoto H, Kamimura M, Sekimizu K, Activation of the silkworm cytokine by bacterial and fungal cell wall components *via* a reactive oxygen species-triggered mechanism. J Biol Chem. 2008; 283:2185-2191.
11. Ishii K, Hamamoto H, Sekimizu K, Paralytic Peptide: An insect cytokine that mediates innate immunity. Arch Insect Biochem Physiol. 2015; 88:18-30.

(Received February 11, 2016; Accepted February 25, 2016)