Drug Screening and Safety Test Using Silkworm as Model Animal

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In spite of its appearance, silkworm takes after human in lots of ways such as analogous tissues or organs, similar sensitivities to pathogens and comparable effects of drugs, and it is low in cost, in little conflict with ethical problem and in no danger of biohazard. Therefore, silkworm is excellent tool for drug screening and safety test.

I. Test systems

(1) Disease model therapeutic effect test

We previously constructed various disease silkworm models including **bacterial** or **virus infection**, **hepatopathy (liver injury)**, **diabetes (hyperglycemia)** and so on.

(2) Natural immunity stimulation test

Silkworm lacks acquired immunity but instead protects itself through innate immunity. We found that muscle of silkworm is contracted by stimulation of innate immunity.

(3) Safety (Toxicity and pathogenicity) test

Pathogenic bacteria can be detected by their silkworm killing activity. Since lethal doses per animal weight in silkworm are consistent with those in mammals, poison of about 1/100,000 of lethal dose in human can be detected.

(4) Drug kinetics test

Gastrointestinal absorbability of compounds can be examined by removed midgut.

(1) Low in cost

Silkworm is in low cost compared to mouse.

(2) Little conflict with ethical problem

It is harder than ever to use mammals for experiments because of kindness to animals.

(3) Rapid and convenient assay

We can obtain data rapidly and conveniently with small doses of samples.

(4) Injection into not only hemolymph but also midgut

Silkworm can be injected into not only hemolymph but also midgut. Each corresponds to intravenous injection or peroral administration. (**Fig. 1**)。

(5) No danger of biohazard

Silkworm is in no danger of biohazard because it is inescapable from laboratory.

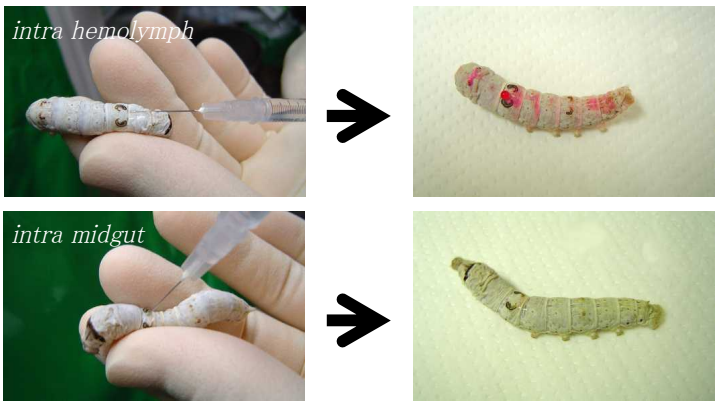


Fig. 1. Injection into hemolymph and midgut

When sting is shallow, red ink is injected into blood (**Upper**). On the other hands, when sting is deep, it is injected into midgut and silkworm is not stained (**Bellow**).

II. Advantage of silkworm as model animal

III. Principles and examples of test systems

(1) Disease model therapeutic effect test

A. Bacterial infection model

Silkworm is died after injection of pathogenic bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Vibrio cholera* and others but it is survived by injection of antibiotics including chloramphenicol (Kaito *et al*. 2002) (**Fig. 2**). Since 50% effective doses (ED_{50}) of antibiotics in silkworm are consistent with those in mammals (Hamamoto *et al.*, 2004) (**Table 1**), silkworm is useful for antibiotics screening.

Control **S. aureus** **S. aureus + Chloramphenicol**

Fig. 2. Cure of bacterial infection by antibiotics in silkworm

Table 1. ED_{50} of antibiotics in silkworm or mammals infected with *S. aureus*

Antibiotics	ED_{50} (mg/g•animal)[a]	
	Silkworm	Mouse
Teicoplanin	0.3	0.1
Vancomycin	0.3	1
Minocycline	4	1
Flomoxef	0.2	0.3
Linezolid	9	4

[a] 50% effective dose per gram animal

Conventional method of antibiotics screening is that antibacterial activities are examined and the positive substances are further subject to therapeutic effect test but almost are unstable *in vivo* because of problem for ADME (administration, distribution, metabolism and excretion). On the other hands, our method is that therapeutic effects are first examined and antibacterial activities are confirmed afterwards. Thus, low cost, rapid and convenient silkworm system allows high efficient screening.

B. Fungi infection model

Silkworm is also died by fungi such as *Candida albicans*, *Candida tropicalis*, *Cryptococcus neoformans* and *Aspergillus fumigantes* and it is cured by antifungals including fluconazole.

C. Virus infection model

Nuclear polyhedrosis virus (baculovirus) kills silkworm and ganciclovir or foscarnet that is the antiviral agent used in the treatment of human herpesvirus or cytomegalovirus infection (Orihara *et al*., 2008). Thus, we can search for antiviral agents using baculovirus as a model virus (**Example 1**).

Example 1: Purification of antiviral agents from herbal medicines

Using the infection model, the antiviral activity of herbal medicines was screened and it was found that the Japanese traditional medicine Mao-to had a therapeutic effect (**Fig. 1A**). Based upon the therapeutic activity, an antiviral substance, cinnzelanine, was purified (**Fig. 1B**).

It is actually the rare case that any active substances are purified on the basis of therapeutic effects of individual animals. The clear index of life or death, simple and rapid measurement of the activity and small doses of materials enough to be injected into silkworm allow the purification.

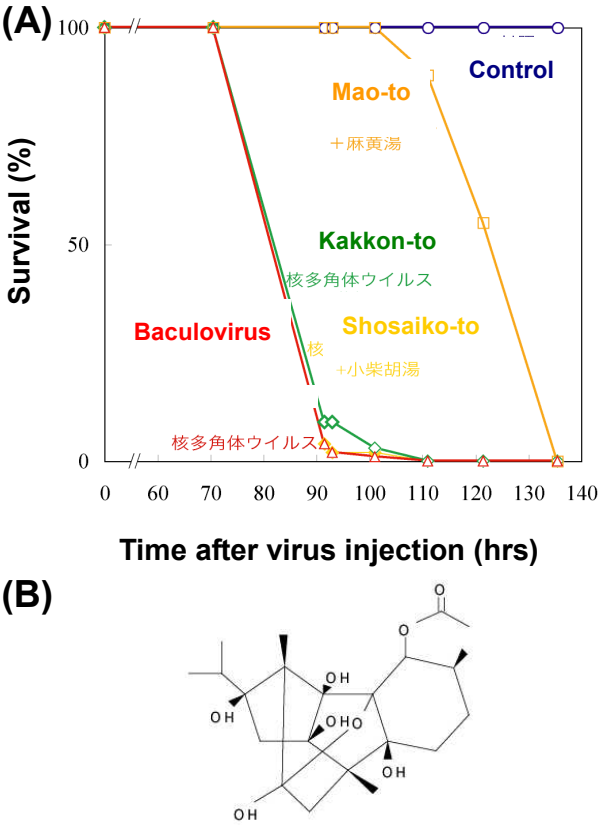


Fig. 1. Therapeutic activities of herbal medicines (A) and the purified antiviral agent (B)

D. Diabetes (hyperglycemia) model

Blood sugar is increased by feeding of glucose in silkworm and suppressed by injection of human insulin (**Fig. 3**). In accordance with this result, growth of silkworm is inhibited by glucose diet and canceled by insulin (**Fig. 4**). Therefore, we can search for hypoglycemic agent using this model (**Example 2**).

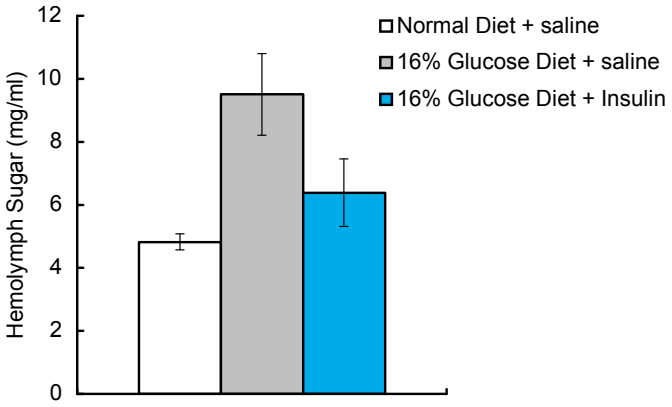


Fig. 3. Increase in blood sugar by feeding of glucose in silkworm and suppression by human insulin

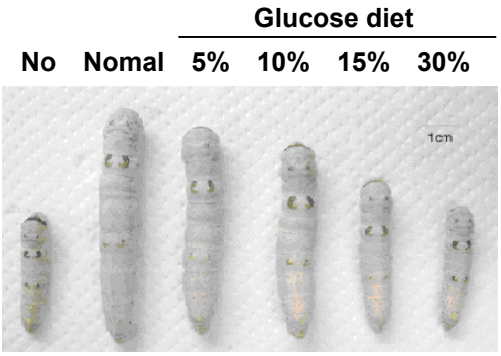


Fig. 4. Growth inhibition of silkworm by glucose diet

It seems likely that human insulin may bind to insulin-like hormone bombyxin receptor. We now investigate the molecular mechanism thorough which insulin transduces the signal responsible for decrease in blood sugar to other cellular factors in silkworm.

Hyperglycemia in silkworm can be also improved by metformin, a drug for insulin resistant, type II diabetes (**Fig. 5**).

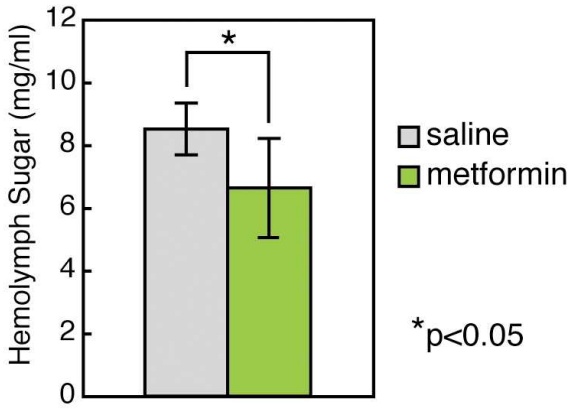


Fig. 5. Decrease in blood sugar by metformin

We previously succeeded in purification of a hypoglycemic agent on the basis of therapeutic activity of hyperglycemia silkworm and we now investigate its effectiveness in mammals.

Example 2: Diabetes therapeutic activity of a food

We attempted to search for agricultural products or foods of diabetes therapeutic activity and found that blood sugar is decreased by injection of the extract from a food (**Fig. 1**).

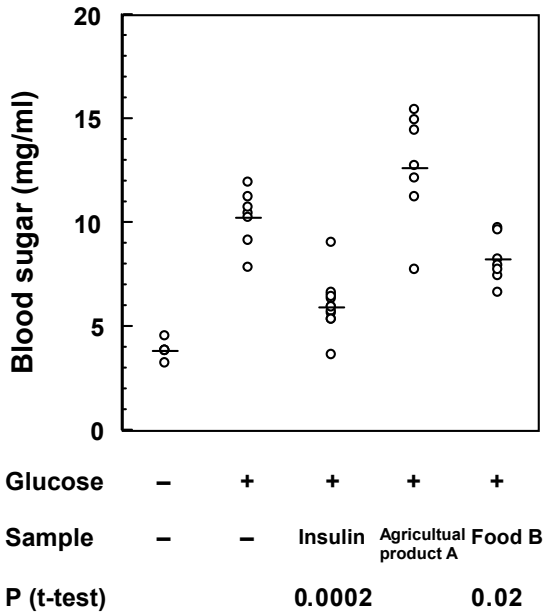


Fig. 1. Evaluation of anti-diabetic activity of agricultural products or foods

E. Hepatopathy (liver injury) model

Liver is what we called "silent organ" and it is too late to show jaundice. Using hepatopathy model, liver toxicity and therapeutic effect can be examined (**Example 3**). A liver injury marker alanine aminotransferase (ALT) is increased by injection of carbon tetrachloride (CCl_4) and suppressed by a radical scavenger *N*-acetyl L-cysteine (NALC) (**Fig. 6**).

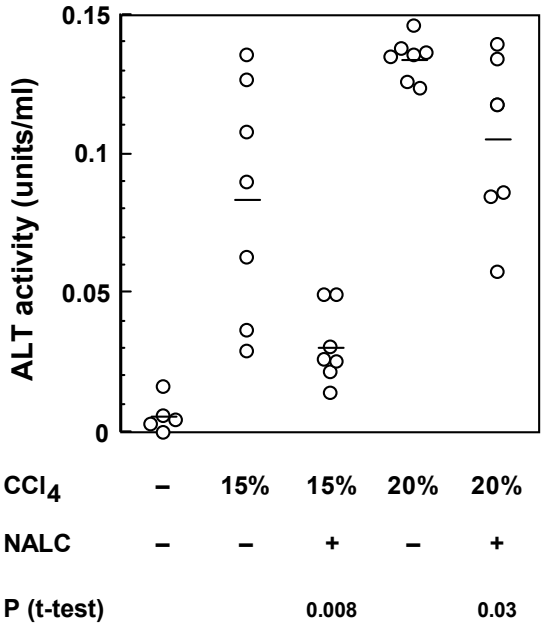


Fig. 6. Increase in ALT (GPT) by injection of CCl_4 and suppression by NALC

Fig. 7 indicates a proposed mechanism of liver injury in silkworm by analogy of mammals; CCl_4 is metabolized by P450 and trichlororadical (CH_3•) that is scavenged by NALC is produced. Fat body and/or gut are (is) injured because ALT is localized in these tissue and organ. ALT is finally released to blood.

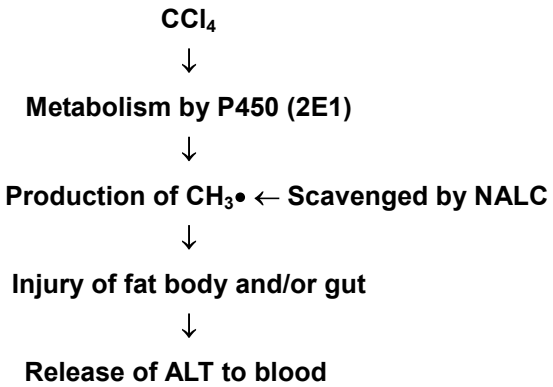


Fig. 7. A proposed mechanism of liver injury in silkworm

Example 3: Hepatopathy therapeutic activity of a plant

ALT is decreased by injection of the extract from a plant (**Fig. 1**). In accordance with this result, ALT is not increased in the silkworm that fed the plant (**Fig. 1**). We now attempt to purify this factor on the basis of hepatopathy therapeutic activity.

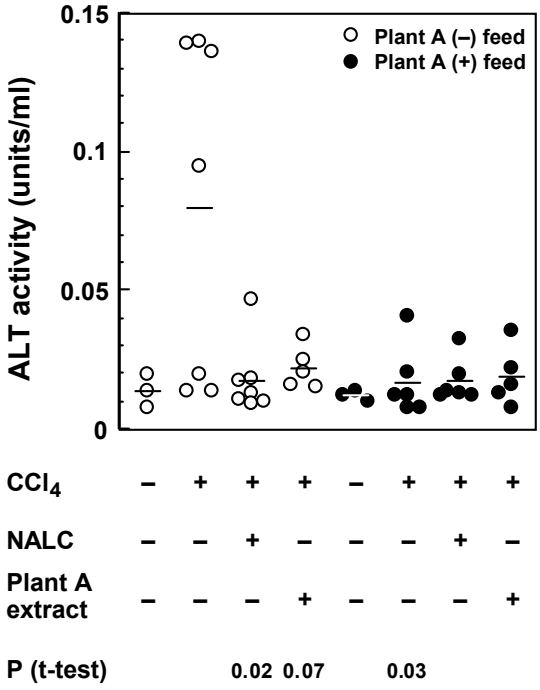


Fig. 1. Evaluation of anti-hepatopathy activity of a plant

F. Periodontal disease model

Silkworm is died after injection of periodontal bacteria *Porphyromonas gingivalis* but it is not cured by tetracycline in contrast to the case of *S. aureus*, although the antibiotics limits the proliferation of the bacterium *in vitro*. It seems likely that *P. gingivalis* excessively stimulates the innate immunity of silkworm and results in the death.

G. Hay fever model

Cedar pollen also causes the excessive stimulation of innate immunity in silkworm and leads to its lethality. Therefore, immunosuppressive agents might be effective in periodontal disease and/or hay fever.

Stimulation of innate immunity of silkworm was measured by the muscle contraction assay (Ishii *et al.*, 2008) (**(2) Natural immunity stimulation test**).

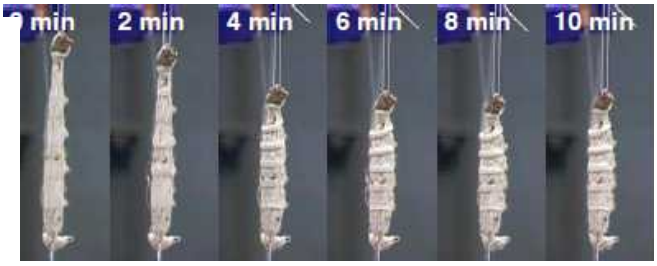
(2) Natural immunity stimulation test

Silkworm lacks acquired immunity but instead protects itself through innate immunity. We found that muscle of silkworm is contracted by stimulation of innate immunity (Ishii *et al*., 2008) (**Figs. 8 and 9**). On the basis of the muscle contraction, we can search for immunostimulatory agents (**Example 4**).

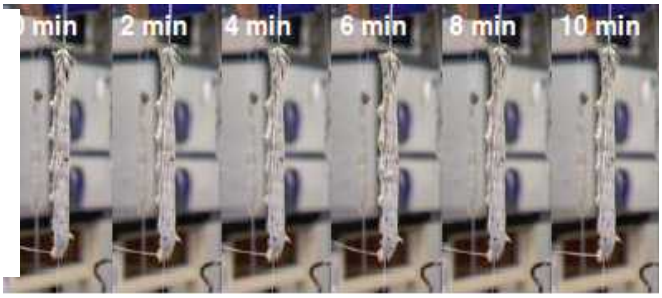
Since the muscle contraction does not respond to lipopolysaccharide (LPS), this assay is able to avoid false positive by the contaminated bacteria in the test samples as opposed to the conventional method of cytokine induction in mammal lymphocytes.

(A)

(i) Innate immunity stimulation factor



(ii) Saline



(B)

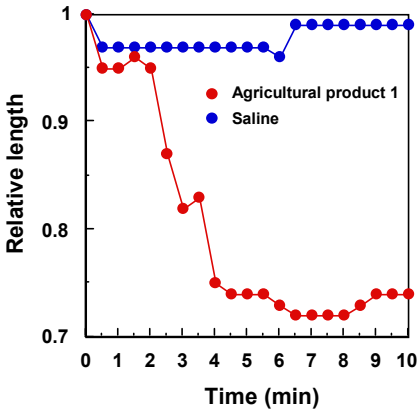


Fig. 8. Muscle contraction by stimulation of innate immunity in silkworm

Head and midgut of silkworm are removed and the muscle specimen is hung (**A**). Injection of innate immunity stimulation factor leads to muscle contraction within 10 minutes (**A** and **B**).

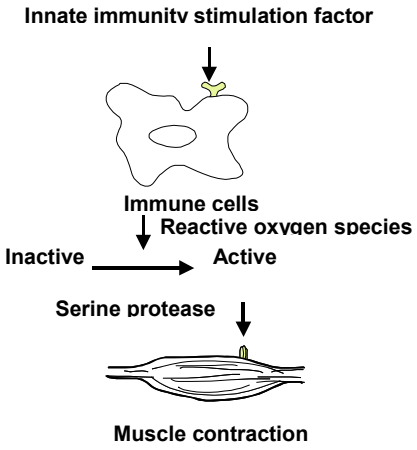


Fig. 9. A mechanism of muscle contraction by innate immunity stimulation.

Immune cells produce reactive oxygen species and serine protease activates paralytic peptide that paralyzes muscle.

Example 4: Natural immunity stimulation activities of agricultural products and foods

Using the muscle contraction assay, we aim to develop "evidence-based" functional foods or supplements that activate natural immunity. The activity of an agricultural product and a food are higher than that of well-known fucoidan (**Fig. 1**) and we confirmed that they stimulate cytokine induction in human lymphocyte. In accordance with these results, they indicated antiviral activities (**Table 1**).

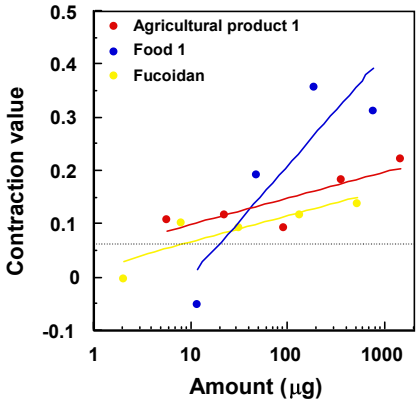


Fig. 1. Natural immunity stimulation activities of agricultural products and foods

Table 1. Natural immunity stimulation and antiviral activities of an agricultural product and a food

Sample	Specific activity[a] (units/mg)	Antiviral activity[b]
Agricultural product 1	10	++
Food 1	20	++
Fucoidan	2	+

[a] Activity of the freeze-dried extract from the sample

[b] Survival for 6 – 12hours (+) or > 12hours (++) compared to control

(3) Safety test

A. Pathogenicity test

Since pathogenic bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Vibrio cholera* and others kill silkworm (**Fig. 2,** p2) but *Escherichia coli* laboratory strain does not, they can be detected by their killing activity (**Example 5**).

Silkworm is died after injection of pathogenic bacteria within one or two day(s) and the bacteria that cause food poisoning and in-hospital infection could be immediately detected.

Example 5: Detection of pathogenic bacteria from environment

Pathogenic bacteria were isolated from oil well water and the extents of killing activities in silkworm correlate with those in mammals (**Table 1** and **Fig. 1**).

Table 1. Pathogenicity of bacteria isolated from oil well water in silkworm and mammals

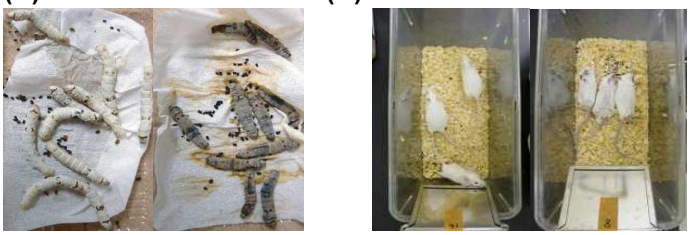
Strain[a]	Killing activity	
	Silkworm[b]	Mouse[c]
#1	+	–
#2	+	–
#3	+	–
#5	+	++
#6	++	+++
#7	+++	+
#8	++++	+++
#10	+	–
#13	+	–
S. aureus	+	+++
E. coli	–	–

[a] Genus was determined by sequence of rRNA gene.

[b] Silkworm was died after injection of 1/1 (+), 1/10 (++), 1/100 (+++) or 1/1000 (++++) culture.

[c] Surviving fraction after injection of 1/1 culture is 2/3 (+), 1/3 (++) or 0/3 (+++)

(A) Silkworm **(B) Mouse**



Control Pathogen Control Pathogen

Fig. 1. A pathogenic bacterium that kills silkworm also kills mouse.

B. Toxicity test

Not only ED_{50} of antibiotics (**Table 1**, p2) but also 50% lethal doses (LD_{50}) of poisons (**Table 2**) in silkworm are consistent with those in mammals (Hamamoto *et al.*, 2008). Taking into consideration that lethal doses per animal weight are comparable, about 1/100,000 of lethal dose in human could be detected (**Example 6**).

Table 2. LD_{50} of poisons in silkworm and mammals

Poison	LD_{50} (μg/g・animal)[a]	
	Silkworm	Mouse / Rat
Ethanol	9500	10000
Methanol	2100	2130
DMSO	33000	12000
DMF	16000	2800
Phenol	310 - 3100	310
m-cresol	0.63	2
NaCl	9100	4000
$FuSO_4$	220	1500
$CuSO_4$	310	960
Sodium azide	380	45
KCN	115	8.7

[a] 50% lethal dose per gram animal

Physical and chemical methods are commonly used for the detection of poisons but it seems to be impossible that all of detecting tests could be applied to one sample. We propose safety test of agricultural products, foods and environments such as water and soil using silkworm as "coal mine canaries."

Example 6: Detection of agricultural chemicals

We detected methamidophos that is involved in a massive food-poisoning scandal caused by Chinese wrapling (**Fig. 1A**) and residual agricultural chemicals from an agricultural product (**Fig. 1B**).

(A) Methamidophos **(B) Agricultural chemicals**

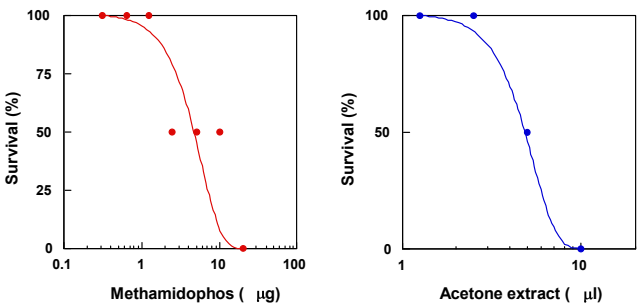


Fig. 1. Detection of purified methamidophos and residual agricultural chemicals

(4) Drug kinetics test (Gastrointestinal absorbability test)

It is because drug kinetics in silkworm and mammals are similar to each other that ED_{50} of antibiotics (**Table 1,** p2) and LD_{50} of poisons (**Table 2,** p6) are consistent between these animals; silkworm possess drug-metabolizing enzymes that are identical to those in mammals and their gastrointestinal absorbability of drug is also comparable to each other. In silkworm, vancomycin is low in gastrointestinal absorbability and it is not effective through peroral administration as well as the case in mammals (Hamamoto *et al*., 2004) (**Table 3**, **Fig. 10**).

Table 3. Effect of difference in the administration method on ED_{50} of antibiotics in silkworm

Antibiotics	ED_{50} (μg/g･animal)[a]		
	i. h.[b]	*i. m.*[c]	Peroral
Chloramphenicol	9	11	40
Tetracycline	0.4	1	8
Vancomycin	0.3	> 700	> 400
Kanamycin	3	> 700	> 500

[a] 50% effective dose per gram animal

[b] *intra hemolymph*

[c] *intra midgut*

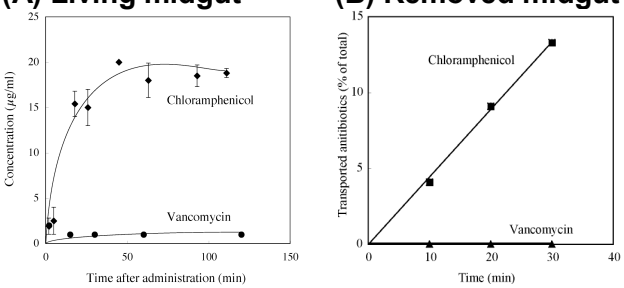


Fig. 10 Gastrointestinal absorbability of antibiotics in living (A) or removed (B) midgut of silkworm

Gastrointestinal absorbability test can be carried out *in vitro* using removed midgut of silkworm (**Fig. 11**).

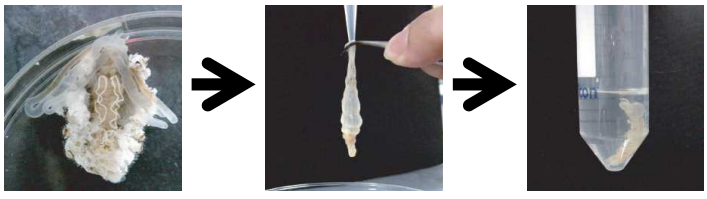


Fig. 11 Gastrointestinal absorbability test *in vitro* using removed midgut of silkworm

IV. Publication

1. Sekimizu, N., Paudel, A., Hamamoto, H. (2012) Animal welfare and use of silkworm as a model animal. *Drug Discov Ther* 6, 226-229

2. Fujiyuki, T., Hamamoto, H., Ishii, K., Urai, M., Kataoka, K., Takeda, T., Shibata, S., Sekimizu, K. (2012) Evaluation of innate immune stimulating activity of polysaccharaides using a silkworm (Bombyx mori) muscle contraction assay. *Drug Discov Ther* 6, 88-93.

3. Dhital, S., Hamamoto, H., Urai, M., Ishii, K. & Sekimizu, K. (2011) Purification of innate immunostimulant from green tea using a silkworm muscle contraction assay. *Drug Discov Ther* 5, 18-25.

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6. Fujiyuki, T., Imamura, K., Hamamoto, H., Sekimizu, K. (2010) Evaluation of therapeutic effects and pharmacokinetics of antibacterial chromogenic agents in a silkworm model of Staphylococcus aureus infection. Drug Discov Ther 4, 349-354.

7. Ishii K, Hamamoto H, Imamura K, Adachi T, Shoji M, Nakayama K, Sekimizu K. Porphyromonas gingivalis peptidoglycans induce excessive activation of the innate immune system in silkworm larvae. *J Biol Chem*.285(43): 33338-47, (2010)

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10. Ishii, K., Hamamoto, H., Kamimura, M. and Sekimizu, K. (2008) Activation of the silkworm cytokine by bacterial and fungal cell wall components via a reactive oxygen species-triggered mechanism. *J. Biol. Chem.,* **283,** 2185-2191.

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12. Hamamoto, H., Kamura, K., Razanajatovo, I. M., Murakami, K., Santa, T. and Sekimizu, K. (2005) Effects of molecular mass and hydrophobicity on transport rates through non-specific pathways of the silkworm larva midgut. *Int. J. Antimicrob. Agents* **26,** 38-42.

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V. Patent

1. Genome Pharmaceuticals Institute Co., Ltd. and The University of Tokyo, “Hepatopathy model animal and method for screening drug or food material to ameliorate or prevent hepatopathy by using the animal” Japan Patent No. 5161718, Dec 21, 2012 (**Hepatopathy model**).

2. Genome Pharmaceuticals Institute Co., Ltd., "Method for evaluating degree of contamination caused by pathogenic microorganism of test specimen" Japan Patent Application No. 2008-063817, Mar 13, 2008 (**Pathogenicity test**).

3. Genome Pharmaceuticals Institute Co., Ltd., "Toxicity testing method" Japan Patent No. 5260915, May 2, 2013 (**Toxicity and drug kinetics tests**).

4. Genome Pharmaceuticals Institute Co., Ltd., "Evaluating method, screening method, and manufacturing method of matter for lowering blood sugar level" Japan Patent Application No.5303209, Jun 28, 2013 (**Diabetes model**).

5. Genome Pharmaceuticals Institute Co., Ltd., the University of Tokyo and Imagine Global Care Corporation, "Evaluation method and screening method for substance having action of activating/suppressing innate immunity, agent and food product for activating/suppressing innate immune mechanism and method for producing the same" US 8313779, Nov 20, 2012, Japan Patent No. 5394233, Oct 25, 2013 (**Natural immunity stimulation test**).

6. Genome Pharmaceuticals Institute Co., Ltd., "Method of screening sample having antiviral activity against virus with ability to infect organism exhibiting acquired immune mechanism by use of individual organism, or its cultured cell, exhibiting natural immune mechanism only, and method of estimating the antiviral activity by use of individual organism, or its cultured" Patent No. 4668900, Jan 21, 2011 (**Virus infection model**).

7. Genome Pharmaceuticals Institute Co., Ltd., "Method for screening compound having antimicrobial activity to pathogenic microbe infecting living thing having acquired immunologic mechanism by utilizing living thing having only natural immunologic mechanism, and method for evaluating antimicrobial activity by utilizing living thing having only natural immunologic mechanism" Japan Patent No. 4733080, Apr 28, 2011 (**Bacterial and fungi infection models**).

8. Genome Pharmaceuticals Institute Co., Ltd., "Method of screening compound having antimicrobial activity on

pathogenic microorganism infecting organism having acquired immune mechanism by using larva of insect having only natural immune mechanism, and method of evaluating antimicrobial activity by using larva of insect having only natural immune mechanism" Japan Patent No. 5103491 Oct 5, 2012 (**Bacterial and fungi infection models**).

9. Genome Pharmaceuticals Institute Co., Ltd., The University of Tokyo, "Medicine for preventing or treating infectious disease, and method for producing the same and evaluation method and screening method for the same and method for evaluating pathogenesis of pathogenic bacterium and method for detecting infectious disease" Japan Patent No. 4914200, Jan 27, 2012 (**Pathogenic bacteria model**)

10. Genome Pharmaceuticals Institute Co., Ltd., The University of Tokyo, "Novel cyclic peptide compound and method for producing the same, as well as anti-infective agent" Japan Patent Application No. 2011-116485, May 25, 2011 (**Manufacturing method of novel cyclic peptide compound and its anti-infective drug**)

11. Genome Pharmaceuticals Institute Co., Ltd., The University of Tokyo, "Hypoglycemic agent, and food or beverage for prevention of diabetes or amelioration of condition of diabetes comprising same" Japan Patent Application No. 2008-178450, Jul 8, 2008 (**Hypoglycemic agent, Galactose**)

12. Genome Pharmaceuticals Institute Co., Ltd., The University of Tokyo, Nobelpharma Co., Ltd., "Method for evaluating and screening substance having activity for alleviating side effect of a medicine and side effect alleviating agent containing substance identified by these methods as effective component" Japan Patent No. 5219013, Mar 15, 2013

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March, 2014,

Genome Pharmaceuticals Institute Co. Ltd.

Genome Pharmaceuticals Institute Co. Ltd. is the bio-venture company of cooperation between industry and academia that is established to rely on Prof. Sekimizu's research to put into practical use. We aim to develop novel drugs using silkworm as experimental animal. We previously constructed various disease silkworm models including bacterial or virus infection, diabetes and so on.

In spite of its appearance, silkworm takes after human in lots of ways such as analogous tissues or organs, similar sensitivities to pathogens and comparable effects of drugs, and it is low in cost, in little conflict with ethical problem and in no danger of biohazard. In addition, silkworm can be injected into not only hemolymph but also midgut. Therefore, silkworm is excellent tool for drug discovery and therapeutics.

We recently search for antibiotics using bacterial infection model (This work is supported by funds from National Institute of Biomedical Innovation of Japan (NIBIO)) and develop "evidence-based" functional foods or supplements using silkworm, especially that activate natural immunity using muscle contraction assay. Moreover, we propose safety test of agricultural products, foods and environments using silkworm as "coal mine canaries" (This work is supported by funds from Japan Science and Technology Agency (JST)).

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