Review

Intellectual property strategies for university spinoffs in the development of new drugs

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ABSTRACT: We will explain a new business model for university spinoffs involving the development of two types of products. The first are highly innovative, such as new drugs, while the second are typically less difficult to develop, such as functional foods. It is our belief that development of the second type of product can help solve the financial problems and stabilize management of Academic Start-ups. The key to development of several different types of products is accumulation of knowledge consisting not only of technical know-how, *e.g.* tips for use in injection, but also ideas obtained by researchers with the potential for future applications. Examination of the features of venture enterprises which have arisen from universities suggests that inventors, who are also professors, should participate in such start-ups.

Keywords: University spinoff, new drug, financial problem, second product

1. Introduction

We of Genome Pharmaceuticals Institute aim to develop new drugs and functional health foods using the silkworm as an experimental animal. We are a bio-venture company featuring cooperation between industry and academia that was established by Nobukazu Sekimizu, MBA, LLM, MOT and Dr. Kazuhisa Sekimizu, Professor of The University of Tokyo, in December 2000. The goal of our company is commercialization of the results of Professor Sekimizu's studies. Our unique feature is use of the silkworm as an experimental animal for the development of new drugs and health foods (*1-4*). We will explain the advantages of this technology.

There are two purposes of this paper. First, we will introduce advantages of the silkworm model for the study of bacterial infection and antibiotics. We will also show other results of our recent studies using silkworm models (*5*). Second, we will discuss an academic start-up model useful for overcoming funding problems and passing through the so-called "Valley of Death".

2. Assumption

Here, we explain the need for animal models in the development of new drugs, using as examples "Chemical A" and "Pathogenic bacteria B". Here, in the test tube (*in vitro*), "Chemical A" is effective against "Pathogenic bacteria B". However, if Chemical A is not stable in the animal body (*in vivo*), it will never exhibit therapeutic effects. A good drug should always be stable in the body. The stability of chemicals in the animal body is determined by 4 factors: Absorption, Distribution, Metabolism, and Excretion (ADME; Figure 1). Usually, medicines taken by mouth are absorbed through the intestine, enter the blood, and are distributed to the various organs of the body. They are mainly metabolized in the liver, and finally excreted. So, even when a chemical compound is for theoretical reasons considered likely to be effective, there are many cases in which it will be excreted without being absorbed or converted to new compounds called metabolites which do not exhibit medical effects. In

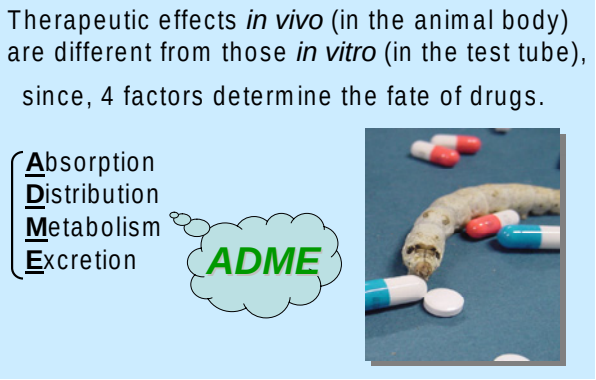

Figure 1. Need for animal models in development of new drugs.

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such cases, the compound will not be medically useful. It is therefore necessary to determine how medicines behave in the body in pharmacokinetic studies involving ADME.

Silkworms are, despite their appearance, biologically similar to humans in many respects, such as possessing analogous tissues or organs, having similar sensitivities to pathogens, and exhibiting comparable drug effects (*3*).

Here we show the advantages of the silkworm as an animal model (Figure 2). The first is cost which is much lower than with mice. The second is ethical problems. It is difficult to use mammals given the various issues related to animal protection. With silkworms, however, there are few ethical problems and no biohazards. In addition, it is easy to inject samples into their body fluids and gut accurately since they move little.

3. Technical aspects

3.1. *Silkworm models of infection for antibiotic screening*

We now consider technical aspects, as related to antibiotics (*1,2*). There are many candidate compounds for development as antibiotics. This makes searching for antibiotics among them extremely difficult. This challenging area is an ideal opportunity for establishing a company.

This study is based on a model of bacterial infection (*2*). As shown in Figure 3, Left is the control which

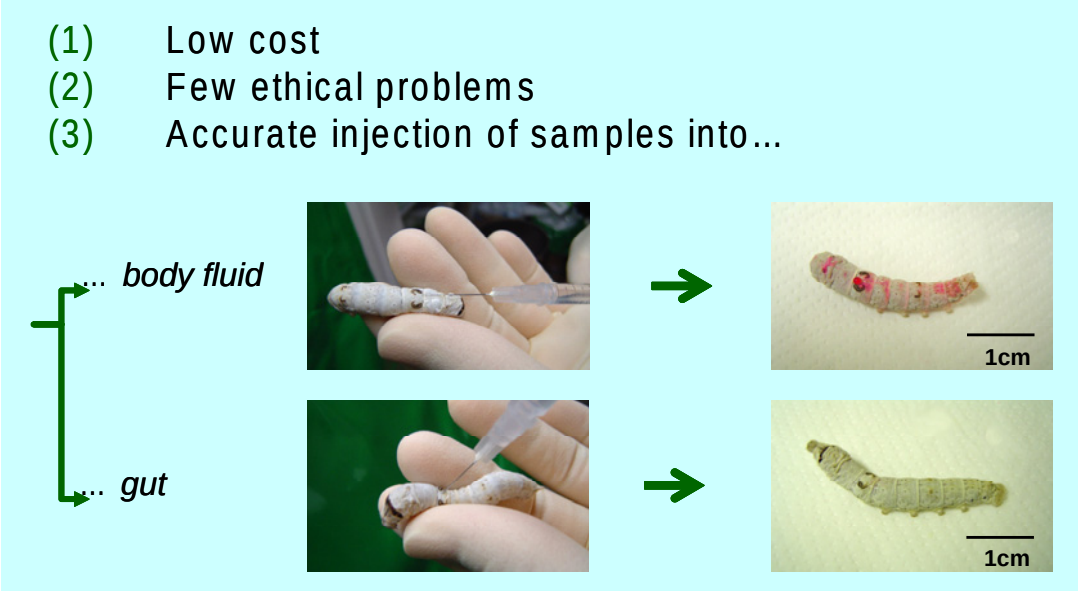
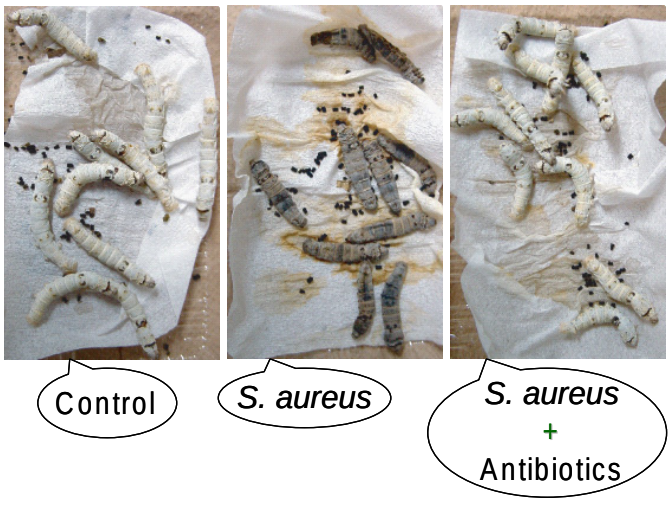


Figure 2. Advantages of the silkworm as an animal model.



Drugs	ED_{50}(μg/g · animal) [Strain · · · *S.aureus*]	
	silkworm	Mouse (reference)
teicoplanin	0.3	0.1
vancomycin	0.3	1
minocycline	3.9	1
flomoxef	0.2	0.3
linezolid	9	4

ED_{50}s of antibiotics

Figure 3. Therapeutic effects of antibiotics.

exhibits normal growth. The Center shows the condition in which bacteria (*Staphylococcus aureus*) were injected into silkworms which died. However, with treatment with appropriate antibiotics, they are still alive, at Right. Thus, although bacteria can kill silkworms, the infected silkworms can be successfully treated with antibiotics. Based on these findings, we are confident that this model will be very useful for searching for antibiotics, since the Effective Dose is the median dose that produces the desired pharmacological effect of a drug. In this experiment, the ED_{50} is the dosage in which half of the silkworms are cured and the others die.

Traditional methods of screening for antibiotics are shown in Figure 4. Normally, among many candidates, antibacterial activity is first examined in the test tube (*in vitro*); such tests may offer many discouraging attempts and finally yield candidate compounds. However, when compounds with antibacterial activity are injected into animals, in many cases there may be no therapeutic effects, depending on ADME, as already noted. Efficiency in screening candidates is thus of crucial importance to developing antibiotics. By comparison, the silkworm can be treated quickly and easily, at low cost, making it possible to experiment with a large number of candidates at once. This makes the silkworm an ideal tool for this type of study.

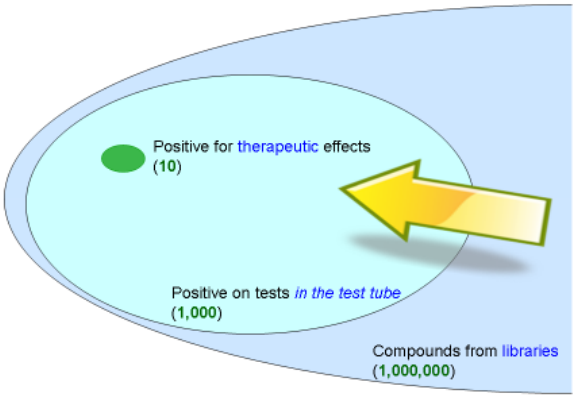


Figure 4. Traditional method for screening of antibiotics.

3.2. *Screening for stimulants of natural immunity*

We next consider screening for stimulants of innate immunity using the silkworm. There are two different systems of protection in mammals: acquired immunity, which depends on antibodies, and innate immunity, which is independent of them. Stimulation of innate immunity is useful for killing cancer cells, since this system is able to recognize them. Research can therefore be performed to determine the types of foods or agricultural products that can stimulate innate immunity.

For this purpose, we use silkworm muscle contraction as an index (*4*). If a sample stimulates innate immunity, then the silkworm muscle contracts.

This is a unique phenomenon, in which the muscle of the silkworm contracts and the silkworm's length gradually decreases (Figure 5). When stimulants of innate immunity activate immune cells, reactive oxygen species (ROS) are released. These act on serine proteases, which activate BmPP (Bombyx mori paralytic peptide), which in turn induces muscle

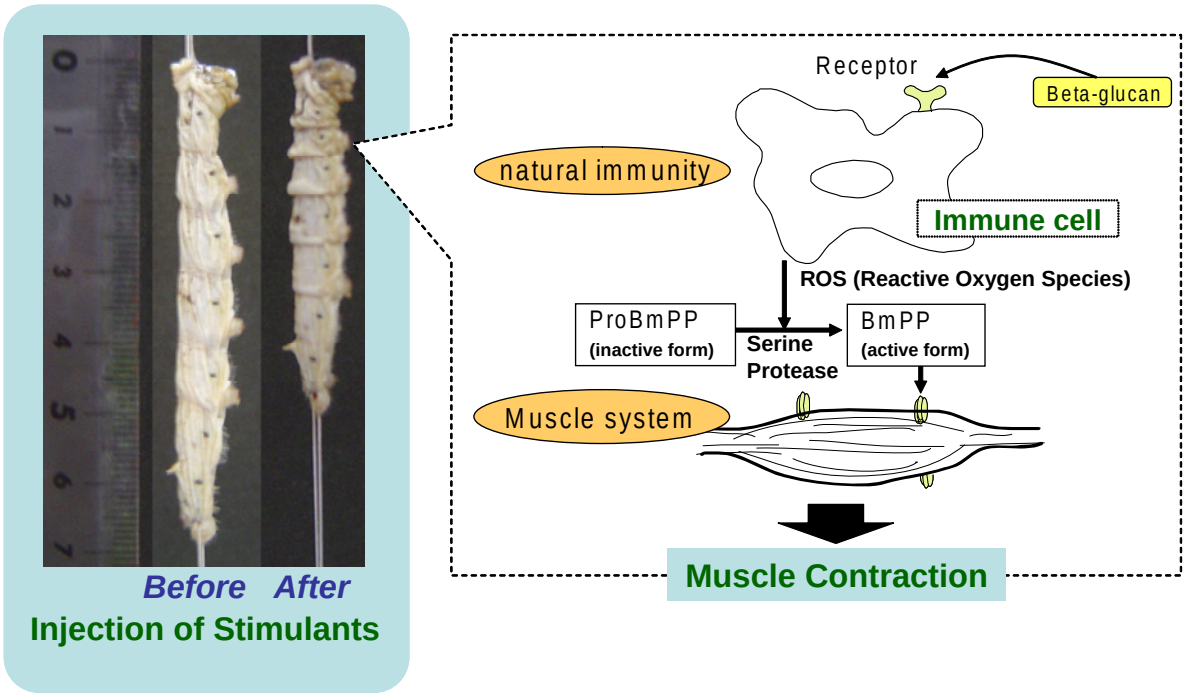


Figure 5. Muscle contraction of silkworms induced by stimulation of innate immunity.

contraction. Therefore, by observing the circumstances of muscle contraction valuable stimulants of innate immunity can be discovered.

Stimulation of innate immunity by some agricultural products and foods using this method is shown in Figure 6. In this way, we have developed effective food products, and have also developed a method for increasing specific activity.

3.3. *Other models and tests*

We have proposed safety tests for agricultural products, foods, and environmental agents using silkworms. Usually, in searching for poisonous materials in food, one chemical technique is required for each type of poison. However, testing for all substances that may be poisonous is not possible with this method. Silkworms, on the other hand, can function as a low-cost barometer for whether certain foods are dangerous for humans. The silkworm can thus function as a sort of "coal-mine canary" in such testing.

4. A proposed business model for academic start-ups

We have thus far considered some technical features of our work. We now consider a proposal for a new business model for academic start-ups. We will begin with aspects of academic start-ups in Japan. Then, based on our experience, we will propose a new model useful for overcoming problems with funding.

The numbers of new academic start-ups are shown in Figure 7. The horizontal axis shows years while the vertical axis shows the annual number of new academic start-ups. These data are based on the report "Plan for Improvement of Initial Conditions of Academic Start-Ups" (*6*).

Looking at changes over time, it can be seen that the number of Japanese start-ups has increased to a fair extent, and approached that of the U.S. However, it is still only half that of the U.S.

Cumulative numbers of Academic Start-Ups in Japan are shown in Figure 8 (*6*). The Japanese Government initiated the "1,000 Academic Start-Ups Plan" in 2001. The target was met in 2004 with several types of support from the Government. It should, however, be noted that the number of Start-Ups has recently been decreasing, due to decreases in government support and a decline in investment by venture capital.

We now consider some financial aspects (Figure 9). Funding is especially important for start-ups.

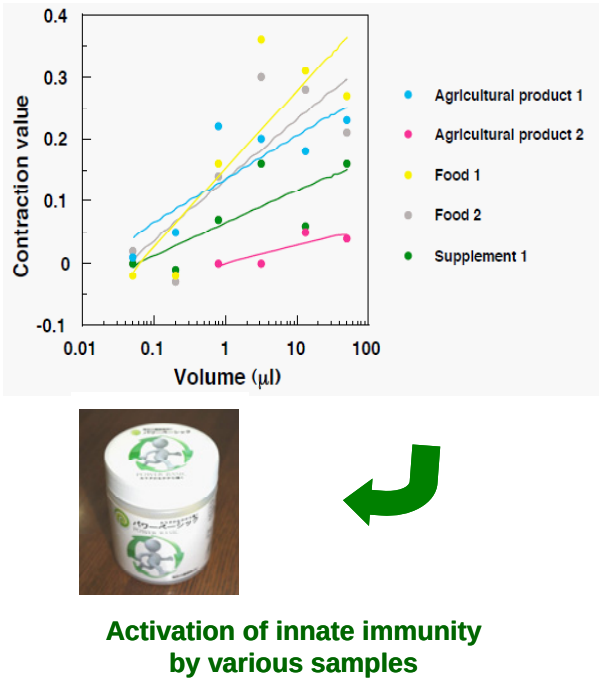


Figure 6. Induction of muscle contraction by activation of innate immunity.

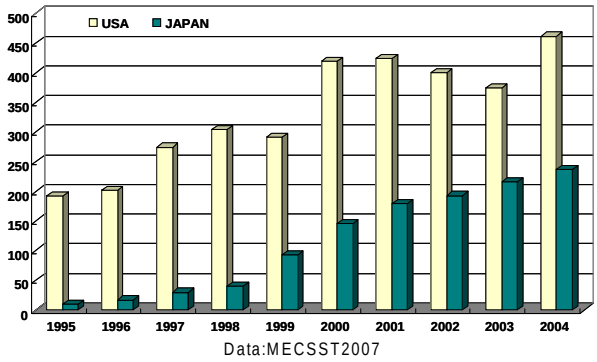


Figure 7. Number of new academic start-ups.

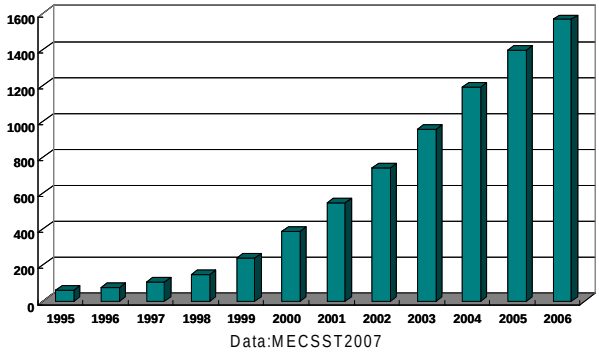


Figure 8. Cumulative numbers of academic start-ups in Japan.

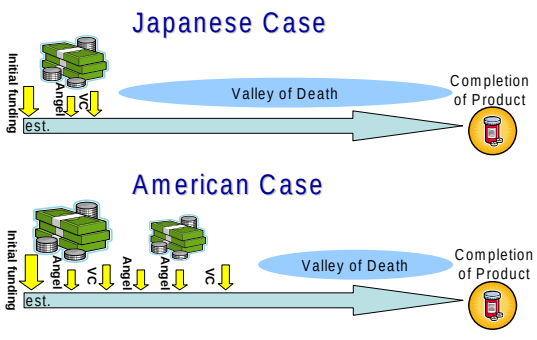


Figure 9. Model of funding for start-ups.

However, many venture enterprises have difficulty obtaining adequate research funds. They may eventually fall into the so-called "Valley of Death" and may go bankrupt. Here, the "Valley of Death" is the period until products are developed, after funding from venture capitalists, the "Angels". In Japan, since we do not have enough "Angels", or venture capitalists, the length of the "Valley of Death" is longer than in the U.S. (Figure 9).

We believe that the development of "second products" is one of the solutions to this problem. Quick development of such products can improve financial problems and stabilize management.

Next, we explain the key to the creation of second products. We believe that it involves the accumulation of knowledge consisting not only of technical know-how, *e.g.* tips for use in injection, but also ideas obtained by researchers with the potential for future applications. Since this type of knowledge is not usually able to receive patent protection, its real value is often unappreciated. We therefore simply call this type of knowledge "Know-How" here.

Examination of the features of venture enterprises which have arisen from universities suggests that inventors who are also professors have often participated in such start-ups (Figure 10). We also believe that this participation is of two types: cases in which the technology has been moved to a new enterprise by a TLO or something similar to that, and cases in which a professor continues to participate in a venture *as it is*.

In the former case, the model at Upper panel in Figure 10, since only the transfer of technology is involved, product development is limited to that closely related to the transferred technology. For example, during the development of health foods for humans, high-performance food for animals was also fortunately developed.

The latter case applies to Genome Pharmaceuticals Institute. In this case, the model at Lower panel in this figure, both "Know-How" and technology are involved in obtaining patentable products. It is thus possible to develop a wide variety of products using a Professor's new ideas along with "Know-How". This means that we can also develop second products unrelated to the technology used for first products.

Does any change occur with the existence of second products? We consider what happens. We can choose technologies which are easy to commercialize after taking marketing research into consideration, and sell the associated products. This will then provide funding for other products more difficult to develop.

In venture enterprises, especially those characterized by advanced technology, it is vital to company survival that funding continue until completion of the first main product (Figure 11). The development of second products should shorten the Valley of Death and make the venture enterprise viable.

We will now introduce our business model in greater detail (Figure 12). In the context of the model presented, in our company the first products are antibiotics and the second products are functional health foods. Although these products share use of the silkworm in their development, they are unrelated as regards to the technologies involved in their production. Notably, the second products are market-oriented and

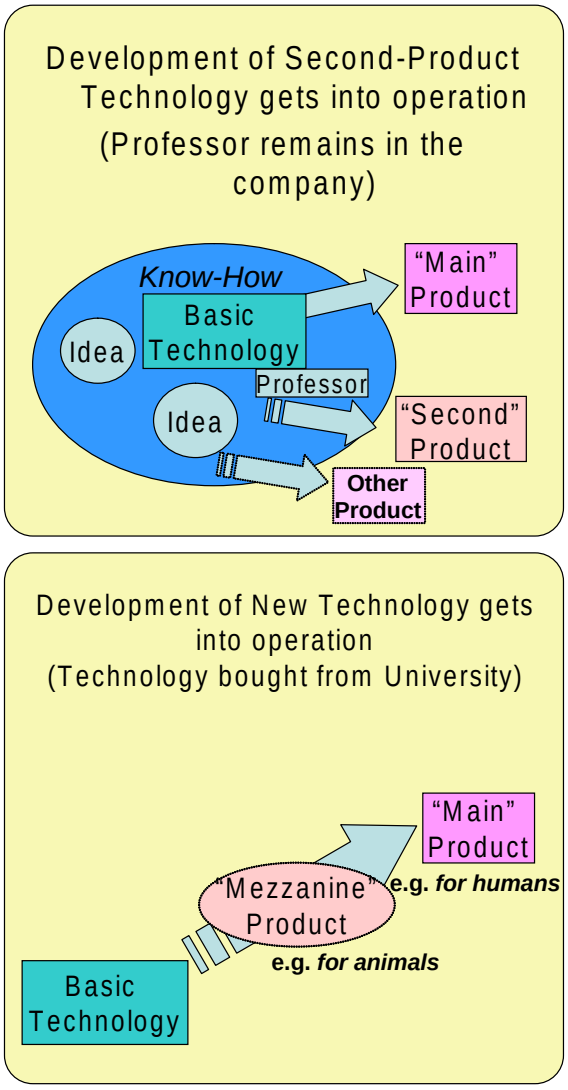


Figure 10. Intellectual property strategies for academic start-ups.

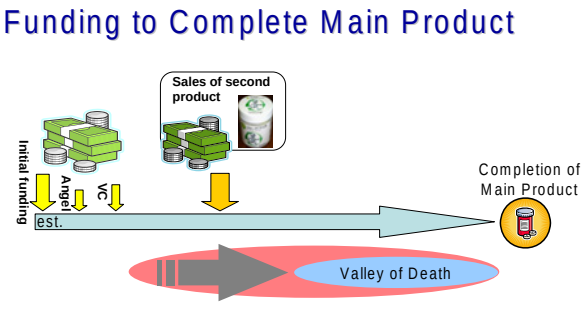


Figure 11. A proposed funding model.

tend to be closer to consumers.

This scheme is very attractive to our collaborating companies, and of course to us, since we usually need the cooperation of other pharmaceutical companies which have production lines enabling commercialization of products. It can be seen in this figure that this cooperation yields a variety of options.

We therefore believe that these various sources of financing assist cash flow in our company and enable continued development of antibiotics.

Data in Figure 13 is based on the "Basic report of academic start-ups" prepared by the Japanese Ministry of Economy, Trade, and Industry (*7*). According to this report, 13.8% of Academic Japanese start-ups develop second products. Of course, it might be thought that venture enterprises without sufficient funding would be unable to develop more than one product, and thus these data mean that few venture enterprises are able to develop second products. However, though they are few in number, they do exist.

Let us briefly consider the research situation in the United States. According to research by Scott Shane, development of general-purpose technology has good effects on cash-flow management. Such technology has many commercial applications and is close to consumers. Thus, this general-purpose technology and

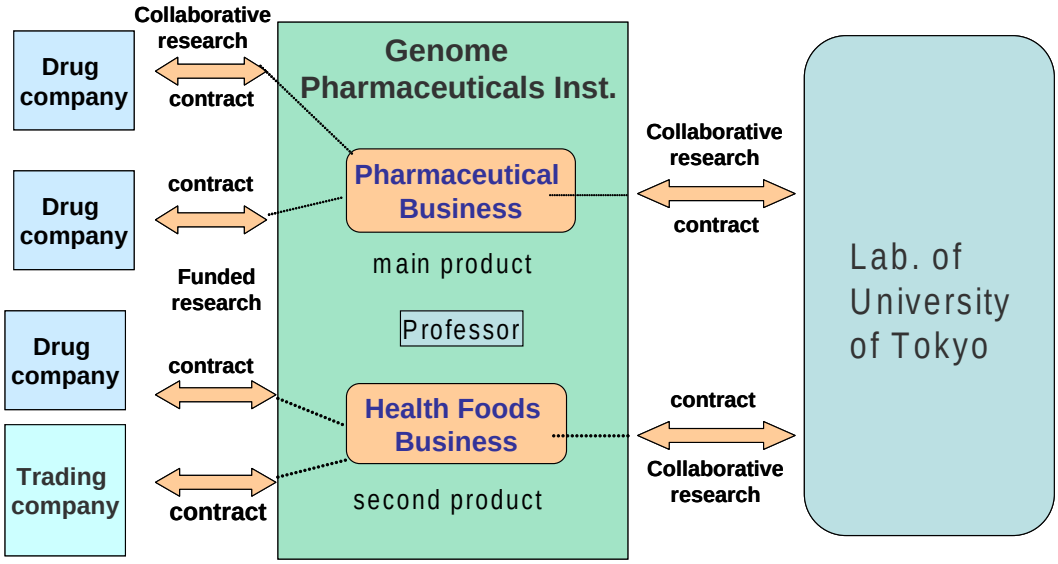


Figure 12. Our business model.

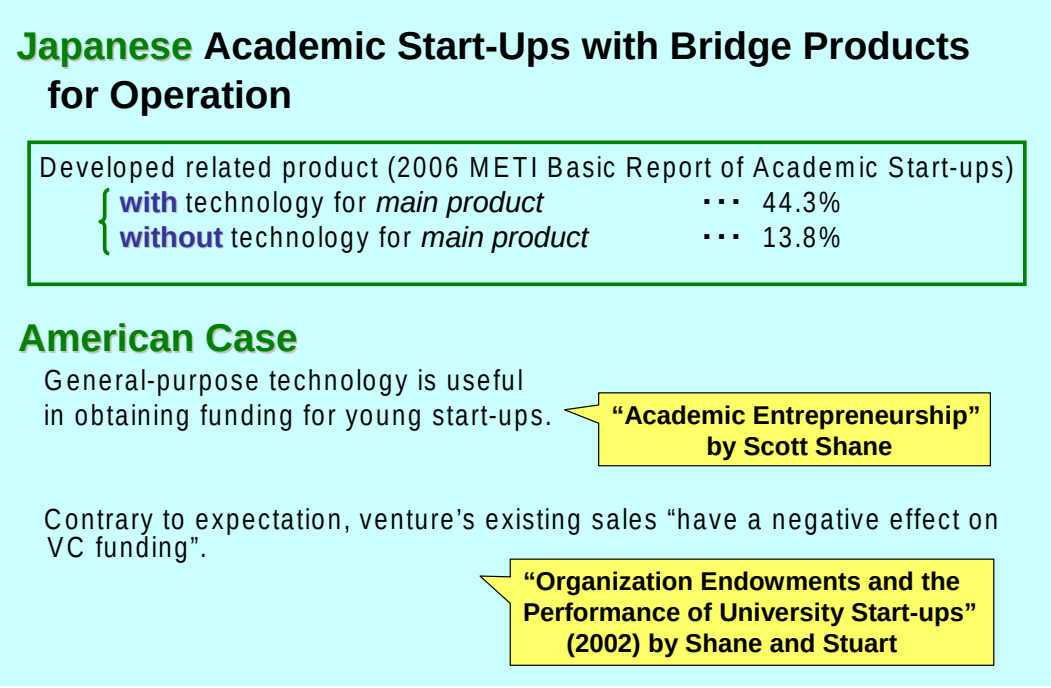


Figure 13. Obtaining sufficient funding for main products.

the second products we have explained are similar, and various sources of financing derived from product development are quite useful (*8*).

Shane also studied 134 ventures born at MIT, and concluded that, "Contrary to expectation, venture's existing sales have a negative effect on VC funding". He found the likely explanation for this result to be that "firms with substantial sales that have not yet received VC funding may not be actively looking for funding from venture capitalists because they are able to support their operations with internally generated cash flows" (*9*). We are confident that these findings support the importance of developing second products at an early stage of venture enterprises.

The overall conclusions of this paper are that, in the case of Academic Start-Ups: 1) professors *who invented* the original technology should, to the extent possible, continue to participate after the establishment of a start-up, 2) start-ups should obtain "Know-How" technology, and 3) start-ups should develop two or more products as a deliberate management strategy. This will enable passing through the Valley of Death and the development of very ambitious technology.

Acknowledgments

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