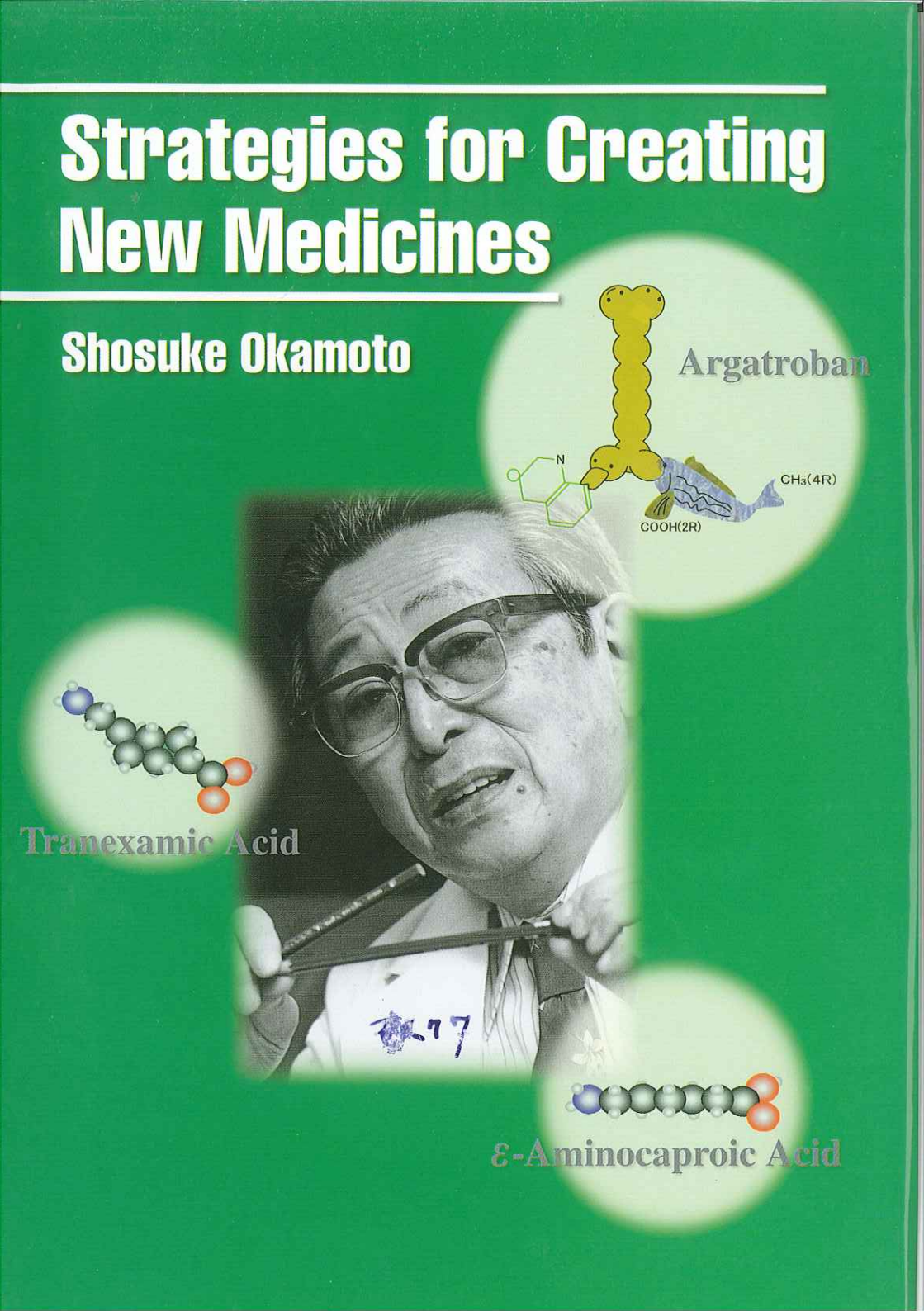
Strategies for Creating New Medicines

Shosuke Okamoto



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Professor Per Udden on a truck when the "Stone" was sent from Sweden to Japan in 1965. (page 30)

The STONE
First Over the Pole

By Per Uddén

Has the stone a soul? I don't know. Perhaps it's better to say: "If man has a soul, stones also have." You don't think so? Well, listen to this story.

(1964)

Last September, I took part in the International Hematologic Congress in Stockholm. At the opening party I greeted and welcomed many foreign guests, among them a young-looking Japanese on whose breast I read the name "Okamoto". I remembered that there was a Professor Okamoto who had succeeded in finding new principles of stopping bleedings after deliveries and gynecological operations. Where before young women were dying away despite of all imaginable efforts including blood transfusions during hours and days, we now give a little dose of epsilon-amino-capronic acid and the bleeding immediately comes to a standstill. This "epsicapron" was invented in Japan and it was Prof. Okamoto who found it and made it available to doctors all over the world. This, however, took many years, not at the least due to the existing scepticism towards medicine in Asian countries. Thanks to a Swedish Physician, Dr. Inga-Marie Nilsson from Malmö and the Kabi Pharmaceutical Company Stockholm, who were first in the Western world to produce and use epsicapron, Japan and Sweden established a very thorough medical contact. In fact, epsicapron is the only pharmaceutical development of any significance from a country outside of the Western world.

So, on welcoming him I asked: "Are you a relative to the great Okamoto?" And, showing that he knew Western sense of humour, he answered: "No, Sir, I am the great Okamoto." That was the start of a friendship between a young, unknown Swedish physician and a world famous Japanese scientist. This friendship was deepened in the archipelago of Stockholm where we spent the week-end in the Summer residence of my brother, the Architect Gösta Uddén. In the mild air the boat took us over to the island, where Swedish wood schnaps, raw herrings and just out of the earth potatoes were served as entrée, while a sheep leg was grilling on the open fire. Next morning, Prof. Okamoto went for a walk in the surroundings and came back very enthusiastic about the old oak-trees. We, too, admired them. But he went on telling us excitedly: "Everywhere I am looking you have stones, such wonderful stones. You see, stones are extraordinary things in Japan. In our old traditions they are living creatures with souls. Nobody believes such things today, but you know ...." - While he was speaking he transmitted to us a glimpse of the Japanese soul. At that moment I decided to send a stone of friendship to Prof. Okamoto.

Back in my wilderness district of approx. 1500 square miles (3000 km^2), where I am a combination of medical officer, general practitioner and hospital chief, I was serching for that special stone. Most of it should be grey as Swedish stones are, but as it should be sent by SAS via Northpole I wanted a stone with white quartz, and since Prof. Okamoto's research was related to blood, it also should contain some red.

I found here and there stones I liked, but never had that special feeling until, one day I was out "hunting" after mecingococc bacterias during an epidemic. Suddenly I saw from the car the STONE. He was superb, just of the right size (75 kgs) and shaped like the sugar peak in Rio de Janeiro. I marked the Stone and went home as happy as when, in old days, I met a pretty girl. The night thereafter, the year's frist snow fell covering everything. I had found my Stone in the very last minute.

Some days later I got a book on Japanese gardening. Five basic rock shapes were shown which are frequently used in Japanese garden arrangements. One of them was my Stone.

At that moment I felt that this very Stone had a soul. Hence, I could not place him in an ordinary box. I had to make something special out of good Swedish wood. Something open so the Stone would not feel emprisoned. The construction of this box took much time and only in Spring this year we could transport the Stone to Stockholm by air.

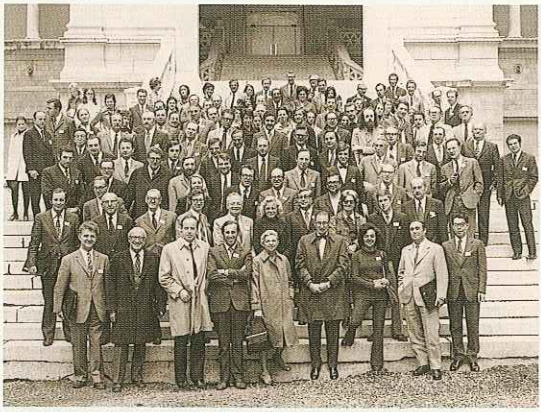
My friend, Dr. Virgin, Superintendent at the East-Asian museum, opened wide the doors admitting the Stone into his museum. There, for the first time, the Stone had the opportunity to get familiar with Japanese environment. There he also met with a Japanese Architect. They both liked each other.

Of course, we took the Stone to the Little Japanese Teahouse in Stockholm. After that visit we were convinced that the Stone would enjoy life in Japan for thousands and thousands of years to come. So it is now decided that this Stone will go to Japan by SAS via Northpole as a gesture of friendship not only from me to Prof. Okamoto, but also from the Swedish physicians to their Japanese colleagues and the Swedish people to the Japanese people.

This should have been the end of the story if not a Swedish priest, Eric Lindgren in Borgsvattnet, had written to me sending me a book en titled "Meditationen ueber Fernoestliche Symbole". In this interesting book I found that stones have different personalities: a "taimenseki" speaks with men and gives them consolation; the "ninjin-seki" is a guardian of a shrine or a temple and receives rice and wine. There are stones of calmness, of pleasure, of the wild waves and the flying goose. There is, too, "shobo-seki" the stone of life and death and, of course, my first thought was that my stone was a "shobo-seki" which brings life to the young women instead of death. Its red and white colour confirmed me in this belief. I also thought the Stone could be a "fuki-ishi", one who brings hapiness. But wasn't that presuming? So I felt and then, these very last days, I feel in my heart that the Stone is a "fude-ishi". He has given me so much inspiration, so much insight in a world I ignored before. As Goethe said: "Stones are silent teachers; they silence the looker-on and the best they teach, cannot be told."

So I am glad that the first stone flying over the Pole will be a "fude-ishi". I hope, that you, Professor Shosuke Okamoto, will be inspired by it to further investigations for the benefit of the sick.

The Conferment of Honorary Doctorate in Medicine in Lund University, in 1966



The International Committee of Thrombosis and Heamostasis, in 1972

With Prof. Nilsson at the International Committee of Thrombosis and Heamostasis, in 1970's (Currently, Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis)

With my wife, Utako Okamoto, at the Commemorative Ceremony for Retirement, in 1980

With Dr. Kikumoto of Mitsubishi (left) and Mr. Kanbara of Daiichi (right) at Okochi Memorial Award for Technology, on March 11, 1992

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Shosuke Okamoto

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Dedication

To my dear wife, Utako

歌子さんに捧ぐ

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Preface

On November 13, 2000, I received a fax from the United States. It was sent by the Department of Public Affairs at SmithKline Beecham (now known as GlaxoSmithKline), one of the world's top-tier multinational pharmaceutical enterprises. The fax announced that argatroban, which we long devoted ourselves to developing, was approved by the US Food and Drug Administration (FDA) to be marketed by SmithKline Beecham. This was our third major international debut; for the third time, a drug we developed would compete on a global basis.

Our study group sent at least three novel drugs of two therapeutic fields to the international drug market. The first of the three drugs was ε-aminocaproic acid (EACA, launched in Japan in 1954), a plasmin inhibitor. The second, more potent than the first one, was tranexamic acid (launched in Japan in 1965). As the third big hitter, argatroban was a synthetic direct thrombin inhibitor (launched in Japan in 1990).

In 1947, we initiated our challenging project on drug innovation despite the fact that most of the Japanese citizens were suffering in the desperate postwar ruins. Since then, we have steadfastly employed a unique style of industry-academia collaboration for more than 50 years, never hesitating to proclaim the highest summit as the solid anchor for our mission.

We designated three major objectives as our top priorities of the research principle. First, we committed ourselves to exceeding global standards. Second, we sought to place ourselves in a position avoiding current trends in research. Third, we dedicated ourselves to exploring

drugs that would benefit medical treatments that were awaited by patients. This third task directed all our researchers to a new chart for the subsequent voyage that resulted in a series of successes in the development of a plasmin inhibitor (hemostatic agent) and a thrombin inhibitor (antithrombotic agent). These achievements constituted impressive motivation to cultivate previously untouched therapeutic fields. I dare say that the implicit rhetoric included therein is a hint about uniquely informative, even ideal ways for problems of industrial-academia collaboration across varied situations. I relish the articles that contain my message in this book.

In addition, I am happy to delineate, in a separate chapter, the influence of patent matters in facilitating our developments in which the procedures of "Japan-originated" patent applications empowered PR capacity from the very beginning of the project.

For example, it was a major accomplishment in 1960 when the Conference of the International Society on Hematology met in Japan and we displayed a large wall banner illustrating EACA's patent documents acquired in Great Britain. This strategic visual demonstration attracted the audience much more effectively than a verbal presentation during the session. With respect to tranexamic acid, we were swamped with aggressive offers of the further development from more than 20 companies outside Japan. This happy shock made us open our eyes to new possibilities of promoting "research conduct" in Japan.

To our surprise, more than 200 energetic researchers from overseas visited us in Kobe or Tokyo to collect more detailed information about

our new drugs. We all plunged enthusiastically into overnight debates. Reconsidering and building on these experiences, we became convinced that the project itself greatly exceeded the mainstream of global standards and was of great value in terms of global presence.

At this juncture, the Japanese pharmaceutical industry took a 180-degree turn from an emphasis on "imported knowledge" to a new emphasis on "original knowledge." It was a historical revolution in drug discovery and development for those who had previously focused on "follow-up" of foreign studies.

My own long history of endeavors in medical and medicinal research prompted me to write this book introducing notable episodes in the process of the drug revolution. To substantiate the revolution, I wished to emphasize the formidable combination between medical and pharmaceutical sectors, so promising for the future. Moreover, I believed that the strong tie and cooperation between industry and academia were essential factors to richly benefit the drug development progress. In facilitating the extensively organized industry-academia collaboration, it is inevitable to establish "reciprocal understanding between two segments," which bridges diverse specialties. Nevertheless, it deems to be much easier said than done.

Shosuke Okamoto
Professor emeritus, Kobe University

Chapter 1. My Endeavor Begins

Imagination in a Scorched Land

In 1945, Tokyo was devastatingly scorched by air attacks during World War II. The neighborhood of Keio University School of Medicine, located in the vicinity of Shinjuku station in a city, was so demolished and scarcely anything was left in view. I still see pictures in my mind of the poor Japanese struggling daily with the miserable circumstances of their almost ruined habitat. Despite such a situation, I recklessly attempted to initiate our project on plasmin inhibitors.

As regards the organizational structure of the research project, the Hayashi Research Institute and then Mitsubishi Chemical Industries, Ltd. Research Center started this joint project at the research laboratory.

At that time, I was a lecturer at Keio University School of Medicine and also researcher of the Hayashi Research Institute, and joined the project as a representative of the above institute. Fujio Nagasawa, then deputy general manager of Mitsubishi Chemical Industries, Ltd. (now known as Mitsubishi Chemical Corporation) Research Center, served on behalf of Mitsubishi. Two fellows were in charge of the project's research plans and operations, and several other staff members joined us. Utako Okamoto, then assistant at Keio University School of Medicine took part in experiments as a scientist of the Hayashi Research Institute. Takashi Hayashi, then assistant professor at Keio University School of Medicine, Takaaki Miyagi then professor of Chiba University Faculty of Pharmaceutical Sciences and scientist of the Hayashi

Research Institute served the project and were members of the research committee.

The Hayashi Research Institute was a private research body founded and fully sponsored by Takashi Hayashi, a prominent novelist and winner of Naoki Prize - a famous Japanese prize - for his writing. From 1939 to 1945, the Hayashi group aggressively, and with excellent results, investigated the effects of a wide repertoire of chemical libraries (mainly glutamic acid and aspartic acid derivatives) on the Central Nervous System. This research satellite showed unique presence working even during wartime and postwar chaos. The aforementioned Takaaki Miyagi and many other talented colleagues developed their outstanding expertise at this small but vigorously active workshop. The uniquely free, interdisciplinary atmosphere of this institute afforded me, an immature doctor just 30 years old, the opportunity to engage in the challenging joint project with Mitsubishi group on behalf of Hayashi Research Institute. Preliminary discussions began in the summer of 1947 with Nagasawa's specific proposals as follows.

- First, our research themes should surpass "global standards" regardless of projected success or failure.
- Second, our research targets should lie in unprecedented areas previously unchallenged.
- Third, our research results should contribute to drug developments benefiting effective treatment of diseases.

In Japan's postwar chaos after losing the war, establishing a

"genuinely creative theme" was inevitable for the goal of outperforming global standards. In particular, one-of-a-kind research was desirable. In those days, studies of antibiotics (e.g., sulfones and penicillins) and antihistamine drugs formed the mainstream in drug innovation. Nagasawa's radical proposals, however, were not bound by attention to the mainstream. At that time, Nagasawa's goals seemed far beyond our capacity. Nevertheless, even today, his viewpoints remain illuminating enough to be highly appreciated. I assume that words, "the creativity of research themes much superior to global standards" might have probably been suggested by Miyagi, a superb contributor to this joint project. Whatever the case, this concept reflected very well Nagasawa's long-held philosophy.

Besides the creative presence in global research community, I would like to comment briefly on the personality of Takaaki Miyagi. Miyagi and Nagasawa have been dearest colleagues since they entered the University of Tokyo Faculty of Pharmaceutical Sciences. Miyagi was an outstanding pharmacologist, distinguished in his own specialty, being well versed in medical sciences. He was also extremely sensible in his sharp insights into the diverse issues arising from pharma-medical joint projects. It is not too much to say that studies on plasmin inhibitors could not have existed without his commitment.

In the many years since the joint project's inception, we have continuously walked this path until today with the explicit objective of drug innovation that remained at the core of our joint research throughout the history. Eventually, an enduring belief in this objective enabled us to appoint the most eligible staff to the project team.

Column 1 :

The Success Rate of Novel Drug Discovery

(Omitted the first half) This is the history of the development of isoniazid, an antituberculosis drug.

First, a discovery team screened 8,000 chemical compounds and thereafter approximately 5,000 of these compounds were entered into a tubercle bacilli-resistance study. Then, 1,000 leads were sent to the next pharmacological study after the above two screenings. Pharmacological study selected only 40 candidates were further entered into the clinical investigations to verify the potency for further clinical studies.

As a result of the above preliminary procedures, we yielded a single potent entity to serve as an antituberculosis drug, called isoniazid. Isoniazid prevailed against astonishing odds - 1 to 8,000 at the time of the exploratory screening.

By Takaaki Miyagi (A 15-year History of Antiplasmin Therapy, issued in 1968)

The Success Rate of Plasmin Inhibitors

Discovering a single substance that may promise superior potency in a field of 8,000 initial candidates was the result of extensive screening. When we screened for the potent lead compounds for plasmin inhibitors, some literatures were already available. Jobling et al. had reported that unsaturated (double-bonded) fatty acid indicated certain inhibitory effects on protease. There were other research results as well regarding the SH compounds.Kay et al. revealed that a protease suppressant existing in blood (likely to have been significantly high molecular weight) showed inflammatory effect. In the cases of antiinflammatory or antithrombotic drugs we developed, we discovered the only 1 promising lead entity out of approximately 200 to 300 candidates.

By Shosuke Okamoto

The Way of Novel Drug Discovery

After many discussions arising from Nagasawa's proposals, I put forth a candidate for a potential theme. The theme was "Plasmin inhibitors." As it captured Nagasawa's attention, he fully concurred with my idea and gave it the green light. The work began soon after that. Plasmin inhibitors were not known anywhere in the world, nor was its conceptual framework acknowledged. This fibrin-degradating component in blood, which used to be called "fibrinolysine," is a specific enzyme. The study was initiated immediately after a British hematology expert RG MacFarlane had given the fibrinolysine the new name, "plasmin."

Research on plasmin inhibitors evolved into a new research venture, a study on synthetic thrombin inhibitors. Along the way, there were vigorous discussions of the pros and cons before a final decision was made on a concrete theme.

One of the different views was to investigate actions of each of more than 50,000 organic compounds. I was unwilling to accept this proposal because of its endless tasks requiring several decades to finish. It seemed to me to involve a risky game without much chance of success. I conceived that the satisfactory percentage of research achievement deemed to be less possible. Therefore, I raised the alternative proposal to develop anticholinesterase drugs as enzyme inhibitors. A few days later, Nagasawa rejected my proposal. Studies on anticholinesterase drugs had already gained so many researchers' attention and he was quite reluctant to start in this area because scanning all the relevant research literature would be very time-consuming endeavor.

With step-by-step manner, through these processes, the breadth of our joint research became clearer and we all concurred with 3 key concepts that our research theme must be 1) superior to global standards, 2) original, regardless of major trends, and 3) full of potential for innovating epoch-making drugs.

What Nagasawa emphasized most was if we were able to select target themes which allowed us to prioritize highly efficient *in vitro* experiments, rather than animal experiments.

Column 2 :

Seeking an Excellent Role Model

I would like to offer some advice, which, by the way, is exactly the same as we discussed with my senior researchers who strived to devote themselves in drug innovation at the laboratory almost 50 years ago. The message I can advise young researchers is, "Select a competent predecessor as a role model all over the world." Never hesitate to contact notable predecessor(s) no matter how prominent he or she may be. Keep several points in your mind when studying their research papers or literature whether or not 1) the context is logically consistent, 2) the author envisions the future-driven perspective in his/her theme, and 3) their theory of the theme has been proven retrospectively.

Through such efforts, your research theme(s) will be able to ensure internationally accepted significance.

Chapter 2. Hemostasis and Anti-inflammatory Drugs

Hints in Textbooks

At the dawn of my life in research, I was lucky to be endowed rich networks consisting of not only seasoned veterans in the field but also many aspiring critics within the younger generation.

The fresh critics were graduate students in their 20s attending the immunobiology seminars and the hematophysiology lectures (in spite of early morning sessions) that I offered at Keio University. These young people were keenly interested in the newly emerging field of molecular pathology.

The topic I mainly taught in these classes was the "mechanism of protease and inflammation." The lecture title was otherwise cited only with small letters in a corner of Carl J Wiggers's physiology textbook. According to his theory, the aggravation of inflammation was attributable to the increased activation of in vivo proteolysis as a definite factor.

While investigating areas related with this concern, I realized that little attention within the research circle had been paid to the broad range of etiological/biochemistry studies conducted by JW Jobling and W Peterson as to the features of protease.

Studies by Jobling et al. explicitly indicated that protease activation in blood was markedly elevated due to acute inflammation, chronic inflammation, and allergic reactions. On the other hand, they also pointed out that antiinflammatory effect increased when the elevation was suppressed. However, the study on enzymatic activation itself was

not persuasive enough to capture academicians' attention at that time. I guessed this might be a reason why their studies could not demonstrate powerful impact.

In 1946, RG MacFarlane and R Biggs of Oxford University reported the striking results for a certain type of protease that they had identified in their observation. They reported that the protease selectively and readily degraded fibrinogen, coagulant protein in blood. In addition, they verified that the velocity of degradation was rapid enough to degrade all the fibrins completely within 2 or 3 minutes. In their report, they proposed to name this protein, so called plasmin. As soon as this surprising news reached the international audience, it made us begin to focus on the uniqueness in the profile and naming of plasmin. Despite this surged attention within the community, the precise meanings of plasmin remained unexplained.

What was the dissimilarity between protease investigated by Jobling et al. and plasmin named by MacFarlane? This question formed a maze from which we had to escape. To elucidate these unknown features, we needed to probe the specific characteristics of plasmin as well as inhibitory substances against plasmin. Meanwhile, another fact appeared supporting studies on the treatment with plasmin inhibitors. E Mashmann et al. in Germany announced that a sulfur group possessing different chemical structures showed weak but selective inhibition against a protease which worked as a digestive enzyme.

Lysine (an Amino Acid) Inhibits Plasmin Action

Initial members of this project team were Nagasawa, Mikio Yokoi and Masatsune Sato (who were chemists from Mitsubishi Chemical Industries, Ltd.), Utako Okamoto, and Shosuke Okamoto. In addition, a new graduate from Keio University School of Medicine Yasuzo Tsukada and Eiichi Takagi from Mitsubishi Chemical Industries, Ltd. joined us later.

Actually, the fact that a sulfur group (SH) which inhibited actions of plasmin guided our subsequent study. We began by scrutinizing the profiles of the libraries of sulfur group, and thereafter we fortunately identified that thioaspirin inhibited plasmin actions. Thioaspirin was a substance of which the oxygen in aspirin was simply replaced by sulfur. This substance somehow played a significant role in inhibiting plasmin, and was found less toxic and appropriate even for use in animal models. Eventually, the successful outcome attained after challenging several syntheses played a pivotal role in encouraging the subsequent long process of our study.

As a whole, the team believed that an optimistic, future-oriented perspective was essential to facilitating the study's progress and to finding additional clues to justify the study continuance. Despite the weak inhibitory effect of thioaspirin on plasmin, this fact in which we had elucidated was a precious finding, and also a great encouragement in this early stage of our endeavor. I very much appreciate enthusiastic supports at this stage that came from reliable scientists such as Takagi who was also a strong theoretician, Sato, and others.

Through the repeated syntheses, we obtained a wide variety of new

chemical entities, including thiosalicylic acid, one of the sulfur analogues. Unfortunately, this group did not provide us any satisfactory evidence of a suppressant showing significantly potent inhibition of plasmin action. The only fact we actually enjoyed after the experiments was a peculiar odor - a typical characteristic of the sulfurs - spilling out all over the neighborhood of the laboratory like the distinctive smell of a hot spring town.

In reality, we struggled with the unfavorable outcomes that most of thiosalicylic acid-related compounds showed weak inhibition and had a chemically unstable structure, which was a big impediment to overcome. Nevertheless, we were happy to have the energetic support of chemists who contributed to the successful accomplishment of the synthetic approaches.

At the same time we began to cover a broad range of screening targets to determine which low molecular entities were available. As a result, I began to have certain suspicions. Both glutamic acid and aspartic acid appeared to promote plasmin action, though not at a significant level. By contrast, we detected that arginine and histidine inhibited plasmin action. Our interest here was that, in most cases, glutamic acid and aspartic acid were composed of negatively charged molecules, while arginine and histidine were composed of positively charged molecules. Considering these two results, we began to focus on lysine containing positively charged amino acid. Unfortunately, in the poverty of the postwar era, it was almost impossible to obtain amino acids such as lysine. After a long wait, however, eventually lysine became available and we started examining its mechanism of actions.

One summer afternoon, Sumie Serata, a research assistant on our

team coming from the Hayashi Research Institute exclaimed, "Please have a look this, Dr Okamoto! Lysine is inhibiting plasmin action at a very low concentration." Immediately I jumped into this exciting discovery and repeated the experiments. At length, I confirmed a beautiful inhibition of plasmin action at very low concentration of lysine, and the group escaped from its long dilemma.

Column 3 :

Identification of Antiplasmin Activity

Here is a brief description of the procedural steps how we examined antiplasmin action.

First, note that features of protease vary in each animal model. Following painstaking examinations, we used blood samples obtained from horses because fresh horse blood was easily available from a meat-processing factory near our laboratory. Prior to the experiment, we eliminated erythrocytes from the whole blood to use only the liquid portion of the blood (plasma) as a starting material for extracting plasmin.

When the plasma was diluted 20-fold with water to make weak acid (pH 5.18), we yielded a precipitate showing plasmin action. We added the precipitate to fibrin solution to determine plasmin activation by measuring the velocity of fibrinolysis. Thereafter we measured the magnitude of inhibition of the test substance seen in plasmin activation. The magnitude of inhibition measured was regarded as an index for antiplasmin action.

Thanks to the considerable number of theories about the molecular charge suggested by synthesis experts, we soon were able to design a molecular model of EACA. In this model structure, in a sense, we hypothesized that 5 carbon groups combined positively charged amino acids with a negatively charged carboxyl group. Based on our hypothesis, we continued active discussions regarding matters such as a substitution of 5 carbon groups for other cyclic compounds.

The World's First Plasmin Inhibitor

It was also lucky for the project that we could encounter the breakthrough when antiplasmin action was confirmed in lysine (one of the amino acids as a bioelement). In general, we recognize that amino acids have favorable margin of safety in in vivo assay. From this new knowledge, we began to expect a candidate substance, which was safe and potent in plasmin-inhibiting by partially modifying its chemical structure one by one. Lysine constitutes amino groups at α-position and ε-position structured on caproic acid skeleton. EACA was obtained after we removed the amino group connecting with α-position (Figure 1). The antiplasmin action shown in EACA was 10 times greater than that of lysine and this was a safe and well-tolerated substance.

That is the story of the world's brand-new plasmin inhibitor, now called "Ipsilon®, Amicar®, etc."

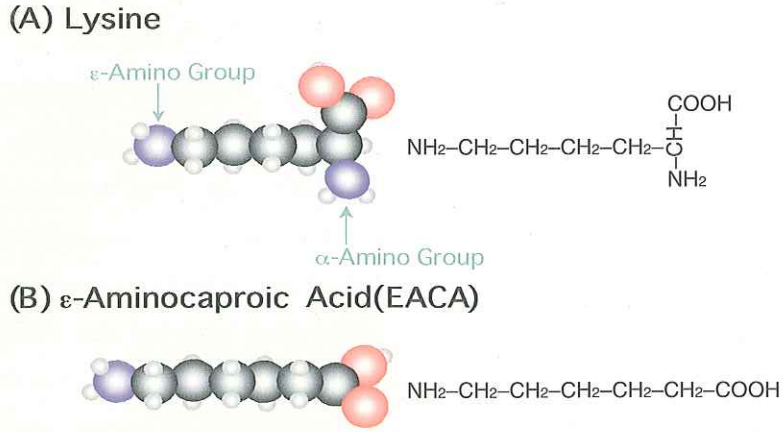


Figure 1. Lysine and ε-Aminocaproic Acid
EACA is obtained by detaching α-amino group from lysine. The antiplasmin action of EACA is 10 times greater than that of lysine.

We first attempted to announce our EACA's breakthrough at a Japanese Symposium for Enzyme Chemistry. We were, however, discouraged when our proposal was rejected by the committee for the selection of research themes. This harsh experience was the first time we began to doubt the authority of the committee, and to suspect that the judgment criteria of the scientific community were not necessarily insightful.

Thus we determined to go our own way under the conviction that no matter how our activities were underestimated or misinterpreted, as long as we believed our research results were virtually true. I conceived that this enduring belief provided essential momentum which would permit us to strive for innovating epoch-making drugs. Needless to say, we knew that the exercise of extreme caution and discretion were necessary while tenaciously conducting experiments to underpin the authenticity of the outcomes.

Companionship

Although then researcher of Keio University Faculty of Pathology Genju Ohneda had already revealed the non-toxic profiles of EACA, we were all still unaware of the appropriate usage of this drug because of its distinctively categorized characteristics. The only aspect we understood clearly was that plasmin increased when allergic reactions or menometrorrhagia occurred. Some researchers reported that plasmin could be a certain factor in causing allergic reaction; however, this opinion was regarded as just a trivial one among several hypotheses.

Some time during this period, my friends Gizo Itoga of Keio's Department of Pediatrics and Shoichi Sato of Department of Obstetrics and Gynecology reported the results of the first clinical trial using EACA. Itoga examined the effect on allergic and chronic eczema in pediatric subjects and Sato examined the effect on hyperemesis gravidarum. Afterward, Sato also confirmed the effect of EACA on hypermenorrhea and menometrorrhagia. Thanks to these supportive investigations conducted by the above two experts, we saw a launch of EACA in the Japanese market.

For the next stage of the study, the further development of our joint investigation was transferred to the clinical development section of Daiichi Pharmaceutical Corporation. The operation of patent issues remained in Mitsubishi Chemical Industries, Ltd. as before. One day, we received a claim from the US Patent and Trademark Office in connection with the fundamental matters of EACA's patent application which was under review in the United States. In a nutshell, they

requested a thorough reevaluation of results of both non-clinical studies in animals and clinical studies in humans.

It seemed an absolutely difficult task to undertake. In those days, the conventional procedures of Japanese drug development did not require us to take such complicated steps. What this requirement meant to us was, namely, a toe-to-toe objection to the validity of our research maneuvers. Their answer was, "Your application is not acceptable here. We conceive this theoretical hypothesis unfortunately does not deserve a patent grant." The reason for the rejection was that additional conducts of clinical and non-clinical studies were necessary to prove the fact that aggravation of symptoms was induced by the increase of plasmin in blood. The reality of the matter was: tremendously hard predicament to overcome.

Disparity Between Japan and Global Criteria

In the past, the determinant factor of success or failure on the New Drug Approval (NDA) was mainly "safety." Usually, new drugs were approved if very few adverse events had been observed during the clinical trial period in more than ten or a few hundred cases. The efficacy of investigational drugs was judged at the discretion of investigators. In addition, the importance of statistical analyses was not fully acknowledged in those days.

It seemed reasonable that even the US Patent and Trademark Office required us to reevaluate thoroughly the effect of plasmin inhibitors. It was a mandate that the patent applicant had to submit a package of dossiers signed by investigators if they were responsible for clinical judgments at their discretion, and if necessary, they had to swear to the

truth of the study conduct by means of an oath administered by an official of the United States government (for example, a counsel or diplomat). If flaws were found in the dossiers submitted, we could be charged with perjury and prosecuted.

These were reasonable requests from the United States and other western countries, so we were obliged to accept the claim of the US Patent Office after all.

Organizational Network

Accommodating the countermeasures against the claim of US Patent Office entailed onerous energy-consuming tasks. To overcome this hardship, we decided to mobilize more than half of our faculty researchers at Keio University.

Accordingly, a large-scale antiplasmin project was organized within Keio. The project team represented a broad range of expertise and consisted of interdisciplinary professionals such as Yoshio Kusama, then dean of the School of Medicine and chairman to take the helm of the project. Sato, Itoga and other newly joined leading specialists from their respective fields were responsible for conducting clinical investigations, and I myself supervised the primary and overall project schemes.

From the industrial sector, the Department of Intellectual Property and Patent at Mitsubishi Chemical Industries, Ltd. energetically garnered useful information about international patent issues. Their commitment worked as a mighty propellant for the project team in this respect. Hideo Shinojima, then president of Mitsubishi Chemical

Industries, Ltd., joined this project and showed great leadership through top-management meetings with Dr. Kusama. It was almost ideal that unanimous consensus of all levels drove this dream team in the same direction.

Daiichi Pharmaceutical Corporation was also committed to providing enthusiastic support for our project. Yasumitsu Takeya, who was then manager of Medical Affairs Department, confessed recently, "It was a high-risk bet in which we invested almost 70% of the total budget of our department into this project by designating the official grants of the university. We were on the verge of a "go-for-broke decision."

I was deeply impressed by his words and attitude in expressing Daiichi's passion for the project.

The enthusiasm of the team was contagious and strengthened the resolve of all staff at Keio University from top to bottom. We absolutely concurred with the aggressive effort of making a world-class challenge as such a small nation and loser of a major war.

At the beginning, I had recommended choosing foreign partners to work with because the project scale was too enormous for Japan alone. However, leaders of both parties shared the same view: "We consider it meaningful to achieve this goal under the name of Japan."

In 1959, the final result of our effort and commitment was published in a 13-chapter research paper translated into English. Official documents were sent to the US authority under researchers' oath. The antiplasmin drug was subsequently approved by the US government, and a big wave of "plasmin" ignited a noticeable worldwide boom.

Next Approach to a Newer Plasmin Inhibitor

With the advancement in studies on plasmin inhibitor and in the wake of the drug's approval, many related studies were undertaken in the United States, Sweden, France, Switzerland, and Belgium. EACA was gaining high status in the global community of plasmin research. EACA worked as a sufficient evidence to explain my first hypothesis suggesting that inhibition of plasmin could lead to an effective treatment for the disease.

On the other hand, EACA did not work effectively in cases of major bleeding during pulmonary surgery or serious plasmin-associated bleeding due to increased plasmin action. In Sweden and France, a super-large dose of EACA (30 to 60 g/day) was administered for the treatment of these bleedings. Such an extremely large dose was no longer so much "taking medicine," as "eating a nasty meal." No matter how much less toxic a profile of EACA had, the occurrence of adverse events such as diarrhea, anorexia, or vertigo could not be eliminated when the higher dose was administered to patients.

Clearly, a more therapeutically useful modality in dosing plasmin inhibitor needed to be developed.

Column 4 :

Persistent Bleeding (Oozing)

In the early period of the study, streptokinase (SK), a toxin derived from *Streptococcus,* was well known to be plasmin-activating. SK was also known to have activated only human plasmin; nevertheless, the similar activation was hardly observed in other experiments using animal models, such as rabbits and dogs.

Fortunately, our study group happened to know that susceptibility to SK activation was abruptly enhanced when a significantly small volume of human blood was added to blood samples of dogs and rabbits in advance. We carried out a wide variety of animal experiments during the preliminary stage prior to the subsequent studies on plasmin. These experiments taught us that outcomes were heavily dependent on the species of animal models being tested. Then, we administered SK to dogs and rabbits after dosing a small volume of human blood. What we confirmed was that plasmin activation in animal blood increased markedly after the dose of human blood.

As plasmin activation increased, bleeding began to occur at wound sites of animal models. Tetsuo Nakajima of Keio University Department of Surgery who helped our animal experiments recognized this evidence and noted, "This type of bleeding must be *oozing* about which so many surgeons complain."

When plasmin inhibitors such as EACA were administered intravenously, the oozing stopped. Plasmin values in blood also decreased. We continuously repeated the series of animal experiments many times and sent the results to the United States Trademark and Patent Office (USTPO). Of course, we also furnished with a comprehensive data package, which contained the clinical results showing that plasmin inhibitors stopped oozing, for example, evidences obtained from the clinical application of plasmin inhibitors as a hemostatic intervention for bleeding in patients with leukemia (Yahito Hasegawa et al.). Before long, the USTPO granted a patent to EACA.

The Asahi Shimbun, a major newspaper in Japan, introduced our research results in fine its arts and literature columns. This scientific news release triggered a surge of nationwide attention to our plasmin inhibitors.

(Note: Oozing is a type of bleeding in which blood seeps from vascular walls. Few effective hemostatic treatments have been available for this bleeding because of the unidentified wound sites.)

How? A hint was present in EACA itself. Let me remind you that the chemical structure of EACA is characterized by a composition of 1) amino group (NH2), 2) carboxyl group (COOH), and 3) hydrocarbon containing 5 carbon atoms between amino and carboxyl groups. Theoretically, this means that the ends are positively (amino position) and negatively (carboxyl position) charged respectively, and setting approximately 5 angstrom of in-between distance from one end to the opposite end allows plasmin molecules to become susceptible to the binding; accordingly, inhibition of plasmin action takes place (Figure 2).

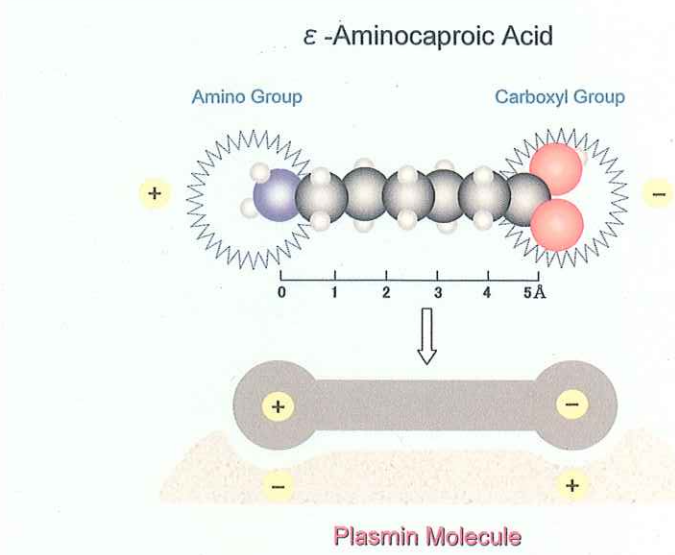


Figure 2. Interaction between EACA and plasmin molecule
By binding positive and negative charges at ends of EACA and the oppositely charged sites of plasmin molecule, plasmin action is inhibited. The length between positive and negative ends is 5 angstrom.

To stabilize the length between the positive and negative charges at each end, we tried to convert a chained hydrocarbon into the cyclized one (benzene or cyclohexane) after the above procedure. We finally found a precursor of tranexamic acid, amino-methyl-cyclohexane-carboxylic acid (AMCHA). That was in 1950.

Here, another problem rose. There were stereoisomers of AMCHA (cis and trans forms). As shown in Figure 3, a fragment of cyclohexane in AMCHA transformed either cis form or trans form. According to the results from similar studies conducted in Japan, a chair-conformation cyclohexane (trans form) showed significantly greater plasmin action; whereas that of a boat-conformation cyclohexane (cis form) was negligible.

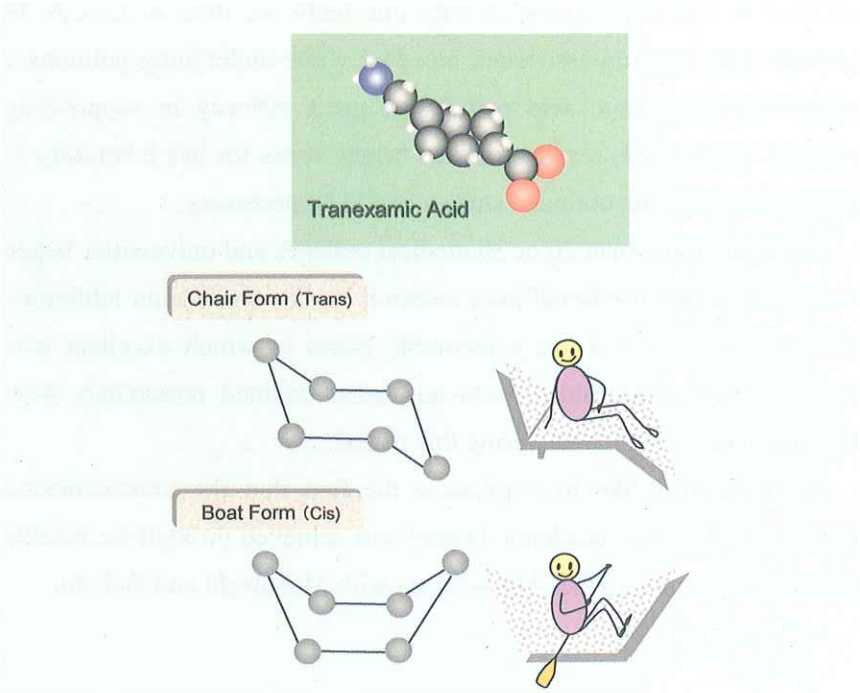


Figure 3. Stereoisomers of cyclohexane

During the study period, it was not easy to isolate isomers from the parent entity to identify their features. Through concentrated efforts, Masao Shimizu of the Daiichi Research Center succeeded in isolating the isomers. After a full discussion on this result, we confirmed that trans form met our objective. To our surprise, the potency of action was over 10 times greater than that of EACA. Eventually, through many ventures, tranexamic acid - a powerful plasmin inhibitor - was launched.

Non-clinical and clinical studies had been conducted by the antiplasmin project at Keio University since the AMCHA stage. Until that time, patients had been administered 20 g/day or above of EACA. However, we realized significant advantages in that tranexamic acid showed its efficacy in dose at only one tenth the dose of EACA. In patients with plasmin-associated bleeding while undergoing pulmonary operation, tranexamic acid manifested great efficacy in suppressing plasmin action. This result promised bright vistas for our laboratory in the future although continued studies would be necessary.

In Japan, more than 20 or 30 medical colleges and universities began to undertake organizational joint research studies on plasmin inhibitors. Fortunately, we could see a favorable boom in which excellent new leaders, such as Masahiro Maki and other talented researchers were making noteworthy marks during this period.

I would also like to emphasize the fact that the unprecedented progress in Japanese academic history was achieved through the notable industry-academia partnership working with Mitsubishi and Daiichi.

In Global Trends

In the United States, Sol Sherry was most influential in the area of plasmin research. Sherry was convinced that a *Streptococcus*-derived enzyme worked effectively for the treatment of thrombosis. This enzyme was a plasminogen-activating enzyme called streptokinase (hereinafter SK) and converted plasminogen to plasmin *in vivo*. Furthermore, this enzyme was absorbed via buccal but not via oral route. SK gained the attention of a major firm in New York and was to be positioned as one of the potential drugs to treat patients with thrombosis.

When I visited the Cancer Institute in New York, I was surprised to learn that the majority of American researchers believed that SK was effective for preventive treatments of cancerous metastases, and the metastases of cancer itself was caused by multi-organ thrombosis. However, the effectiveness of SK therapy for the treatment of cancerous metastases was completely denied later by a Danish researcher. In Europe, there was a different view. As mentioned above, MacFarlane and Biggs of Oxford University in Great Britain focused on a protease existing in blood. They focused on this enzyme, which selectively decomposed fibrins in particular, and they also named this enzyme "plasmin."

Presumably, widespread use of the term "plasmin" appeared to have depended on the PR strategy promoted by Oxford University: i.e., a capability to submit research papers consisting of well-organized and easy-to-understand contents to peer-reviewed journals.

Conferences on International Society of Hematology were held in Tokyo in 1960 and in Mexico in 1962. As a matter of fact, participation in the latter one was a crucial turning point for the watershed of the forthcoming advancement in antiplasmin research in the world.

Coincidentally, the person who chaired the conference in Mexico was JP Soulier, president of the Institute of Blood Transfusion located in Paris, and he had once reported plasmin-associated bleeding cases. Soulier was delighted with my report that administrations of plasmin inhibitors showed substantial effect on cancerous bleeding, and he gave us some 20 minutes for extra discussion after I finished my presentation. I was grateful for this unusual prestige. I realized the audience unanimously agreed with the fact I pointed out that increased plasmin induced bleeding; whereas, plasmin inhibitors had certain hemostatic effect on bleeding. Positive reactions among participants made me happy to enjoy a sightseeing tour after the conference in a suburb of Mexico which included a look at a huge pyramid.

In 1970, the International Committee was held in Bath, not so far from Oxford, proposed by Biggs. This committee was later named the International Committee for Thrombosis and Hemostasis. I took part in this committee's meetings held in Bath to make a presentation on EACA. What made me feel much more grateful than expected was that more than a few clinical studies on EACA were being followed, and half of the 70 topics addressed during the committee touched upon the use of EACA to identify the profiles of plasmin action.

I had innumerable opportunities to meet foreign scholars and scientists during the years the EACA's project was gradually gaining international popularity.

During a conversation with MacFarlane when I visited his laboratory, he suddenly asked me, "Now we have a new super-computer. Do you want me to show you from now?" A super-computer then a brand-new apparatus attractive for anyone, but I replied, "Well, I'd love to talk about hematology with you today."

We started a frank discussion in his office and I asked, "What kind of results would you expect if you continue intravenous administrations of EACA in rabbits?" He responded, "Let me see. Perhaps, fibrinogen must keep increasing up to a significantly lethal level and rabbits are going to die." At that period, their predominant prediction was that fibrinogen in blood was routinely metabolized because they overestimated the role of plasmin. I pointed out their misinterpretation by showing my figure illustrating the results of animal experiments. Obviously, these figures clearly depicted that no increase of fibrinogen occurred even after i.v. administration to rabbits. I explained to him, "This outcome means that plasmin does not work regularly, but it does only under particular circumstances." My explanation continued, "Some risks you may anticipate will not occur in the case of EACA injection." After our discussion, he completely concurred with my idea and asked me to provide the same explanation to his staff.

From then on, I widely introduced my idea to his staff wherever I visited in England. Thanks to such tenacious efforts, and through introductions to international patent and other international conferences, EACA gradually grew into an internationally appreciated drug.

MacFarlane's agreement, in particular, had a significant impact on global recognition of EACA. In my humble opinion, I began to scale up my research capacity as a hematology specialist and my good knowledge was mounting step by step to the level of worldwide class.

Tranexamic Acid Goes to World Stage

In the early 1960s, my research focus turned from EACA to AMCHA, a precursor of tranexamic acid.

One day, the president of a Japanese pharmaceutical company visited the president of KABI, a Swedish pharmaceutical company. They enjoyed playing golf and talking about AMCHA. When I next visited Sweden, I received a heartfelt welcome from the vice president of KABI, Mr. Hellstrom. He kindly arranged various opportunities to have me meet with Swedish scientists. This episode began my reciprocal relationship with Sweden that endured through 40 years of joint research, and eventually resulted in the launch of tranexamic acid in the world market.

Malmo is a peaceful town about an hour's flight south from Stockholm.

On the next day of my visit to Hellstrom, I met Lady Inger Mary Nilsson, professor of the Lund University Faculty of Medicine, and Lennert Anderssen, lecturer of Lund University and later professor at the Karolinska Institute. I knew they had been doing research on plasmin and they showed great interest in plasmin inhibitors. They soon agreed to help my work.

Column 5 :

BLODETS HEMLIGHET FÖREWAR SVERIGE OCH JAPAN 1965

In 1964, when the International Congress of Hematology was held in Stockholm, Dr. Per Udden and I met for the first time, at the welcome party of the Congress. The first question from him was "Can I have your name?" When I answered my name as S.Okamoto, he asked me again, "You are the great Okamoto?" I laughed and said, "Yes, I am!" This very curious meeting was the beginning of our long-lasting friendship of nearly 40 years.

Cooperative studies with Prof. I.M. Nilsson, Malmö, and very stimulating meetings with Prof. Birger Blombäck and Prof. Margareta Blombäck from Stockholm, have made it necessary for us to visit Sweden frequently. Surprisingly, during almost every visit to this country, Dr. Per Uddėn would be waiting for me at the hotel in Stockholm and we enjoyed discussions many times.

Another surprise to me was a large stone, weighing 300-400 kg, which was brought to Japan from Sweden, courtesy of Per Uddėn. The transport of the stone was also supported by Scandinavian Air System (SAS). The stone is now placed in a corner of the traditional Japanese-style garden at the International House of Japan, Tokyo. Behind this stone, a stainless steel plate was affixed, upon which the words "Hematology binds Sweden to Japan" are securely and permanently recorded.

Our amicable companionship lasted for more than 40 years. Swedish doctors believe that the plasmin inhibitor was nurtured by Father Okamoto and Mother Nilsson. (Although the plasmin inhibitor was originally created in Japan, it is widely known as a Swedish drug in the United States because of the strong distribution network of KABI in the US domestic market.) I started exchanging information about plasmin inhibitors with Fritz Koller, professor of University of Basel, Switzerland, several research groups in Paris, Oxford, and New York in the wake of the joint research with my Swedish partner.

Chapter 3. Inspiration for Thrombin Inhibitors

"Thrombosis is the worst enemy of mankind."

These are not my words. This is how Koller concluded his speech at the final session of the first conference of the International Society on Thrombosis and Hemostasis (ISTH) in 1970.

The emergence of plasmin inhibitors fueled the subsequent development of plasmin research. Medical professionals became increasingly interested in antiplasmin treatment and research focused on establishing new therapeutic options in hematology in clinical settings. The cross-field research commitments including medicine and pharmaceuticals gradually grew in number and scope. It was believed that new knowledge of thrombin inhibitors would widen a therapeutic window for patients with thrombosis. In a sense, one earnestly might have wished for "a dream coming true again."

Thrombosis is Major in the West, Minor in the East

In Japan, thrombosis was not positioned as a major disease as it was in Europe and the United States a few decades ago. Japanese hematologists considered other hemorrhagic diseases more critical. They struggled with the various outcomes of discrepancies in viewpoints between the West and Japan as to the status of this disease.

With respect to the frequency of disease onset, there was a sharp contrast in occurrence of thrombosis in the two regions. A higher ratio of mobility was observed in Europe and the United States than in Asia. Comparisons of this kind often raise different diagnostic criteria for thrombosis. One of my friends, Phumara Talalak who is a Thai

pathologist, pointed out that based on her pathological investigations, the proportion of patients with thrombosis was 8 times greater in Germany than that in Thailand. This result implied that the differing eating habits in both regions had affected a latent trigger that led to the dissimilarity in the onset rate. Figure 4 shows a significant decrease in mortality caused by thrombosis during the time of World War II food shortages. A main factor was reduction of fat intake during the war. The results of a Norwegian survey suggested that thrombosis-caused mortality began to increase again as food shortages disappeared after the war.

When I visited Munich, Germany, I stayed in a hotel (the Arabella House) that had an affiliated hospital in the same site. When I visited the hospital, I heard physicians expressing astonishment over bizarre cases in which cardiovascular thrombosis were complicated by surgery for appendicitis that was usually considered very easy and safe in Japan; so the German information surprised me.

While working as a member of the International Committee on Thrombosis and Hemostasis since 1969, I had been deepening my acquaintance with seasoned foreign scholars and doctors who brimmed with sage instructions. Through our communication, I began to realize that thrombosis was the most life-threatening disease that killed a huge number of patients throughout the world.

In general, hemorrhage and thrombosis are likely to be clinically paradoxical findings. Nevertheless, the fundamental mechanism seen in both symptoms is intrinsically akin to each other. As previously mentioned, a fortunate event resulted in the successful development of EACA and tranexamic acid that inhibited plasmin activities. In the wake of these two achievements, we gradually began to wonder if we could possibly develop thrombin inhibitors that worked as a suppressant with antithrombotic actions.

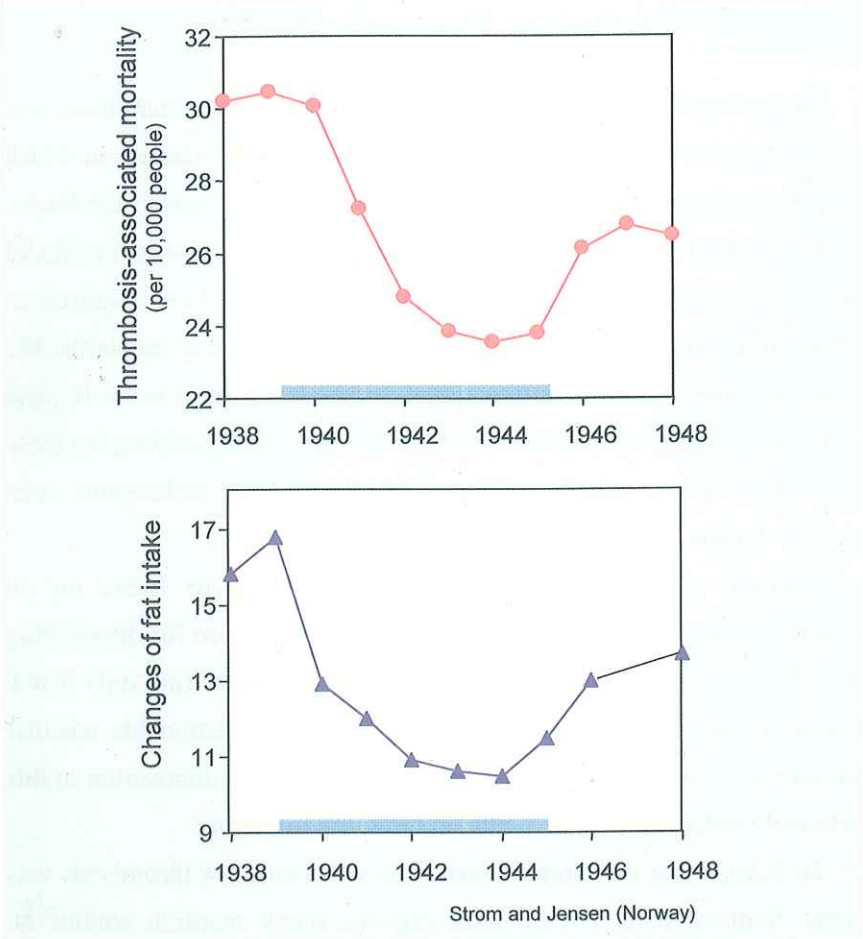


Figure 4. Thrombosis-associated mortality (per 10,000 people) during World War II
Norwegian survey indicated a correlation between the fat intake under food shortages and the mortality rate of thrombosis (per 10,000 people) during the wartime. As the fat intake increased in the postwar period, the mortality rate of thrombosis increased. In Japan, Kyushu University Faculty of Medicine also reported a similar result. The correlation between the onset of thrombosis and the amount of fat intake in diet should carefully be investigated not based on its direct "cause-and-effect" but lifestyle-related factors.

Selection of Creative Research Themes

Regarding the research and development of thrombin inhibitors, you may remember the episode I described in the previous chapter in which Nagasawa proposed on the initiation of studies on plasmin inhibitors. Hence, I had a new mission to ensure that Nagasawa's insightful proposal contained significant meanings. First, we were required to concentrate on the core principle of outperforming global standards. We must now merely follow international trends, but instead to far beyond it. In other words, we had to do much more than merely adding Japanese decorations to an existing pillar of the magnificent architecture seen outside Japan.

Second, along with Nagasawa's requirement to focus on an untouched theme, we needed to draw a strategic picture for discovering novel drugs in this unfamiliar area in which we could find only a few research publications on this theme. It was quite questionable whether or not we could find the right direction for future drug innovation in this relatively unknown area of synthetic thrombin inhibitors.

In Europe and the United States where the onset of thrombosis was more frequent than that in other regions, many research studies on potential treatments for thrombosis were being conducted. The most common studies involved treatments with heparin and warfarin to prevent thrombi generation, or streptokinase (SK) therapy to reduce blood clotting (fibrinolysis) in vessels. Given the frequency of this fatal disease, Europe and the United States were eager to develop antithrombotic drugs, and researchers in these countries in those days were the frontrunners in antithrombotic treatment. Our catching up and

taking the lead entailed an extremely hard battle against giant competitors who were extremely difficult to beat.

In that period, Koller et al. and the Roche group were enthusiastically undertaking studies on heparin therapy. Although antithrombin therapy using anticoagulant activities of endogenous heparin was reasonable, heparin exposure-associated adverse events (especially bleeding) were serious, even life-threatening. The most critical issue was the unstable optimal dosage. Heparin's effects heavily depend on the individual patient and his/her disease condition because heparin activities were significantly associated with the amounts of heparin cofactor (antithrombin factor III). Adverse events observed in heparin-treated patients posed a serious obstacle to recommending the use of heparin as a standard of care for patients with thrombosis. Heparin-induced thrombocytopenia (HIT), approved for an indication of argatroban in the United States, is one of serious adverse events of heparin exposure. Unfortunately, in the early days, HIT was not well recognized as a serious adverse drug reaction (ADR) caused by heparin administration. Coumarin derivatives including warfarin were used as an effective oral agent for prevention of thrombosis. Unfortunately, these derivatives exerted only delayed effects on anticoagulation treatment and the optimal dose level varied depending on each patient's condition just as seen in heparin therapy. Fibrinolytic interventions with streptokinase (SK) were considered inappropriate due to its antigenicity since SK was an exotoxin derived from *Streptococci*. Another factor working against SK therapy was its immature stage of the development to be confirmed in that SK therapy was deemed to be hardly possible to control the activation of plasmin system.

Considering the actual circumstances of antithrombotic therapy, I assumed that optional antithrombotic drugs must have been prepared or the use of antithrombotic drugs would need secondary therapeutic interventions as seen in treatments with antibiotics. So far as I knew, very few studies on synthetic thrombin inhibitors (low molecule) had been performed when I initiated the thrombin inhibitor project in the 1970's.

One day, Masatsune Sato of Mitsubishi Chemical Industries, Ltd. visited our laboratory in Kobe. He was one of the charter members of the antiplasmin research project. We have been close companions enjoying unbroken friendship and trust ever since. Our discussion in Kobe was too interesting to stop, and we shared the same perspective of research on thrombin inhibitors as a promising theme in the coming age.

After much debate and consultations with experts, a joint project on thrombin inhibitors was undertaken within the framework of industry-academia collaboration with which the core staff came from Kobe University and the scientific team from Mitsubishi's Research Center. Both parties were already strongly allied through the successful achievement of our challenging project on the plasmin inhibitor previously introduced.

Two Loaches Under a Willow Tree (Good Luck Can Repeat?)

The 1960s marked the dawn of molecular biology. One day when I was living in Tokyo, I received a phone call from a gentleman staying at a hotel near Tokyo station. The caller was Per Edman who was visiting from Australia. We soon agreed to have lunch together.

At lunch, I met Birger Blomback who came from Stockholm. Edman was a scientist who had developed an apparatus that could automatically determine and analyze the amino acid sequence of protein. In those days, he was investigating the amino acid sequence in fibrinogen in cooperation with Blomback. They verified that plasmin cut C-terminal of lysine and thrombin did C-terminal of arginine, respectively. Figure 5 illustrates the structure. (As you know, thrombin converts fibrinogen into fibrin. Plasmin possesses fibrinolytic action and dissolves fibrin.)

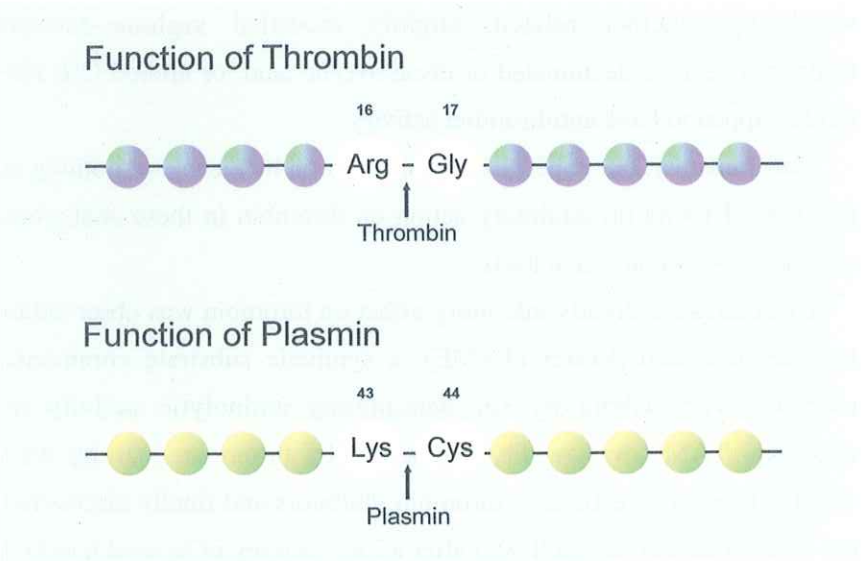


Figure 5. The function of thrombin at low molecular level
The cutting sites of fiblinogen in thrombin and plasmin.
Thrombin cuts C-terminal of arginine and plasmin cuts C-terminal of lysine mainly.

Although "good luck" is said to come only once, like catching a loach under a willow tree (a Japanese proverb), I started this thrombin inhibitor project with great optimism, just in case good luck could happen more than once. I introduced synthetic thrombin inhibitors for the first time at the Hematology Conference in Kyoto by beginning with the above proverb. Plasmin recognizes and hydrolyzes the site of C-terminal side of lysine in the amino acid sequence of fibrin. By simple modifications, we found we could derive plasmin inhibitors, such as EACA from lysine. On the other hand, C-terminal side of arginine in the amino acid sequence was hydrolyzed by thrombin. Then I found myself wondering whether related, slightly modified arginine-derived analogues such as deaminated or decarboxylic acid, or altered CH_2 site might happen to have antithrombin activity.

Unfortunately, our expectation of more good luck came to nothing at that time. I found no inhibitory action on thrombin in these analogous substances - even arginine itself.

By contrast, a slightly inhibitory effect on thrombin was observed in tosyl-argnine-methyl-ester (TAME), a synthetic substrate commonly used in every laboratory for determining aminolytic activity of thrombin. TAME was readily degradated by thrombin. Starting with TAME, I began investigating thrombin inhibitors and finally discovered my lucky loach. As a result, and after a long journey of several hundred modifications in syntheses to reach a potential chemical structure, I was eventually able to develop argatroban as a satisfactory synthetic thrombin inhibitor. Thus, I spent a great many years of utmost efforts to earn this "luck."

Here I would like to raise two subjects associated with the main

message, "Development of drugs." The first subject is aspects of molecular biology with great focus; the second is another approach from organic chemistry. From the perspective of molecular biology, thrombin cleaves C-terminal site of arginine. This arginine, one of the amino acids, was positively charged and markedly protruded from the structure of protein molecules as shown in Figure 6(b). This protrusion site binds to the thrombin. Figure 6 (c) shows the binding mode of action.

Our project studying synthetic thrombin inhibitors primarily focused on modifying chemical structures using techniques of organic chemistry and most of the compounds we developed had arginine-based structure. This point is consistent with the principles of molecular biology.

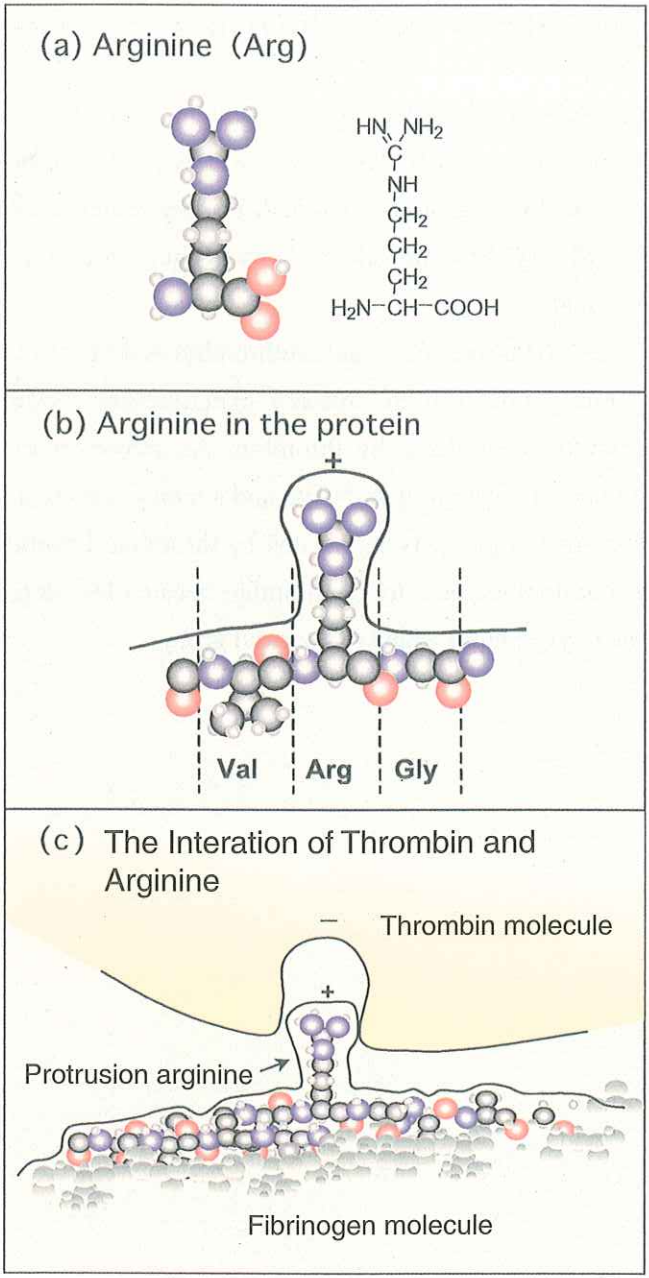


Figure 6. Arginine–one of amino acids

The Way to the Launch of Argatroban

The use of TAME as a reagent in many laboratories has a long history. In the 1940s, TAME was widely used for protease activity assay such as thrombin and plasmin. A leading researcher in plasmin studies, Sol Sherry first introduced this reagent into the theory of blood coagulation.

TAME possesses weak antithrombin activity. However, this activity is rarely observed in ordinary experimental condition because it is promptly degradated by thrombin. As shown in Figure 7(a), TAME contains a tosyl group at N-site and a methyl group at C-site of arginine. This methyl group is degradated by thrombin. I found it interesting that this amidolytic activity of thrombin became less degradable when only one oxygen atom added to the tosyl group.

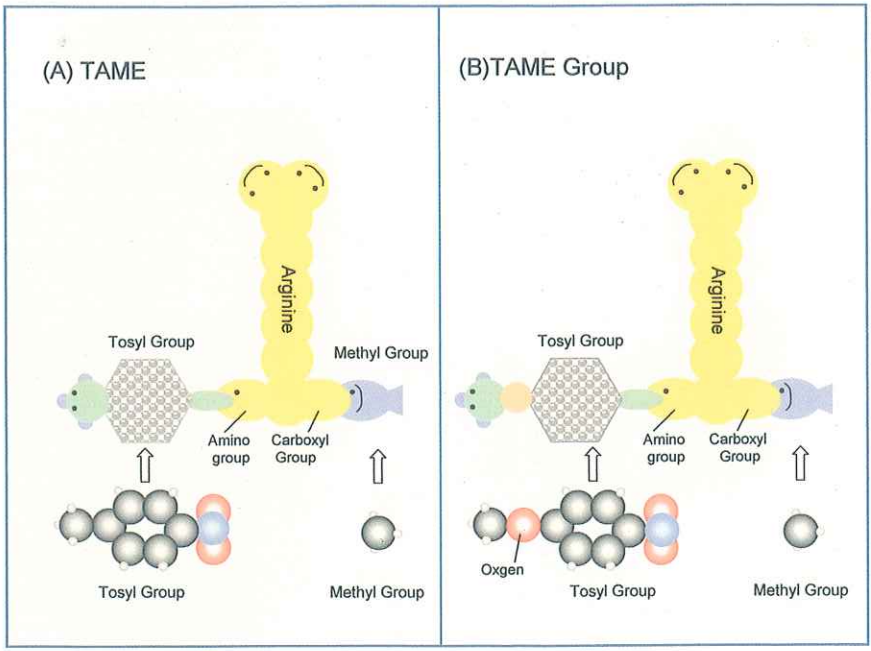
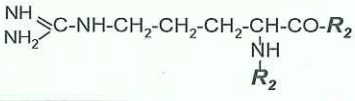


Figure 7. TAME and TAME group
(A) is tosyl-arginine-methyl-ester and (B) is its oxide. The weak but clear antithrombin action is confirmed.

It is important to note here that the mode of action on thrombin varies significantly due to (perhaps) very slight alteration of a tosyl group regardless of its arginine-based structure. This fact indicates the possibility acting as a thrombin inhibitor. In practice, we may be able to suggest that TAME containing an oxygen atom could possibly be a genuine prototype of argatroban.

Whatever the case, through the meandering process of our syntheses, we can say that it was a long journey to the success of argatroban initiated from the synthesis of TAME.

The next challenge we tackled was to alter R_1 and R_2 bound to C- and N-terminals of arginine, respectively. Table 1 depicts the outcome we obtained from this alterlation. I found this outcome amazing. The antithrombin activity in the substance obtained showed nearly 500 times greater than that of the first one in the course of innumerable syntheses beginning from TAME.



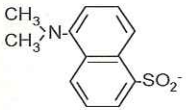
R_1	R_2	IC_{50}(μM)
	-O-CH_3	1,000
	-O-CH_3	20
	-O-CH_2-CH_3	20
	-O-CH_2- CH_2-CH_3	2
	-O-CH_2- CH_2- CH_2-CH_3	2
	-O-CH_2- CH_2- CH_2- CH_2-CH_3	50
	-NH-CH_2-CH_3	100
	-NH-CH_2- CH_2-CH_3	5
	-NH-CH_2- CH_2- CH_2- CH_2-CH_3	3
	-NH-CH_2- CH_2- CH_2-CH_3	150

Table 1. Thrombin inhibitors: substitution of C-terminal of arginine

When I made a presentation to introduce this noteworthy result of our hot topic at the Conference on Hematology in Kyoto, my presentation perfectly caught the keen interest of the audience.

No. 805 Argatroban

As mentioned above, our study group investigating the latent antithrombin activity of TAME challenged more than 800 syntheses of a broad spectrum of arginine derivatives. Finally, with the 805th synthesis, we successfully produced the most promising substance, argatroban.

Argatroban was thereby codenamed No.805 in recognition of the long period of its development. The reason we kept using the code name "No. 805" for argatroban was because I strongly felt we deserved to honor the endless effort that led to its discovery. Figure 8 shows the chemical structure of argatroban.

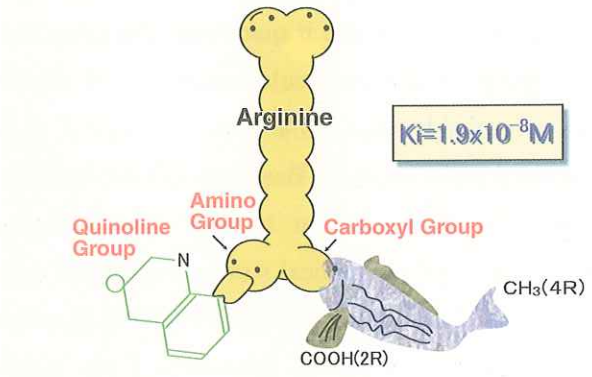


Figure 8. Chemical structure of argatroban
Alike a real fish?

Now, consider whether the chemical structure of argatroban was first implied from the molecular design model of thrombin, or whether, conversely, the structure of argatroban implied the details of the activated site of thrombin. This is a critical issue for further elucidations. Recently, our challenges were to identify potential suppressants based on the molecular structures of enzymes. The pivotal structure of activated sites of enzymes could be inferred from the structure of the suppressant.

Staffan Magunusson, the eminent Danish researcher as well as expert in thrombin, kindly accepted an invitation to visit my home in Kobe. Together we scrutinized the facts obtained and shared the same conclusion, which seemed quite reasonable. We agreed that the features of argatroban indicated the precise molecular structure of the active site of thrombin.

Biochemical perspectives make it mandatory for drug innovators to pay careful attention to the molecular structure of enzymes. It is possible, or even probable, that some pharmacological findings may precede biochemists' understanding. Based on this recognition, the most up-to-date knowledge in molecular biology is not necessarily the determinant for designing the chemical structure of potent drugs. On the other hand, we can read in-depth molecular structures of enzymes based on the chemical structure of potent inhibitors. I am convinced that studies of the mechanisms of actions in EACA and argatroban constituted typical examples of this notion. This is a noteworthy episode of which I can be proud.

Platelet and Argatroban

The year 2000 was a hectic period for argatroban, which achieved much attention in the media. Our group had already obtained remarkable preliminary results regarding interactive interferences among argatroban, platelet count, and thrombin. Study results revealed more than a thousand thrombin receptors existed in every single platelet. The University of San Francisco School of Medicine also obtained interesting results in connection with a correlation between thrombin and platelet counts.

Meanwhile, our group received another significant result from Takefumi Matsuo, president of Hyogo Prefectural Awaji Hospital in Sumoto, Awaji Island, Japan. Matsuo's report showed that argatroban was highly effective for heparin-treated patients who complicated heparin-induced thrombocytopenia (HIT) due to heparin exposure in clinical settings.

Similar information about heparin therapy was also reported in the United States. According to a survey conducted by the FDA, 1.2 million patients receive heparin therapy in the United States every year and 3 to 10 % of those patients suffered from HIT. Thus, these data suggested that argatroban be effective in treating patients with HIT complicated in heparin exposure.

In response to the proactive stand by the FDA, then SmithKline Beecham (presently known as Glaxo SmithKline), a world-class pharmaceutical company headquartered in Philadelphia, released the news that they would begin to market argatroban in November 2000 and to start the education program for the dissemination of this drug for

clinical and medical professionals.

Note :

Streptokinase (SK) is known to increase plasmin and degrades fibrins when administering to humans. Accordingly, around 1960, SK therapy was dominantly prescribed based on the belief that SK was useful for treating thrombosis. Excessively large doses of SK were used based on the idea that plasminogen should be converted to plasmin and the administered SK should show its action locally at blood clotting sites. It was concluded that SK was effective only for the early stage of thrombosis (within 12 hours after the onset of thrombosis). Most physicians, however, faced problematic complications for systemic subcutaneous bleeding occurred in almost all patients treated with SK. Physicians confessed to me that they really hated SK therapy. Coincidentally, another therapeutic option using a plasmin inhibitor we had developed was introduced in Europe and the United States during the same period. Ironically, the newly recommended treatment with our plasmin inhibitor became an easily accepted alternative to conventional, unsatisfactory SK, especially among physicians who had strongly insisted the necessity of SK therapy before.

Column 6 :

Humanized Dogs (Transformed to Human-like Models)

Large-scale clinical investigations were underway in the United States based on a premise that *Streptococci*-derived streptokinase (SK) seemed to be useful for antithrombin treatment by activating plasmin to reduce thrombi in blood vessels. However, it was interesting to see that SK was effective only in human and an exceedingly large dose was otherwise needed when administering to animal models. In animal experiments, the required dose of SK was a several tens of thousands or above compared with the dose for human; the experimental cost was therefore estimated extremely expensive. Meanwhile, we had already identified fractionated protein (SK reaction factor) in human blood that was sensitive to SK and significantly augmented the action of SK. Then, we isolated the fraction of protein to administer to animal models intravenously. Then, we successfully produced "humanized models" that had sensitivity to SK like human.

As far as a scope of the relationship between SK and plasmin is concerned, dogs could be humanized. Accordingly, we succeeded in developing animal models where plasmin could be strongly activated.

Chapter 4. Beyond the Trend

Research Themes and Trends

Sometimes a boom abruptly spotlights a research area long eclipsed. Some striking discovery opens a closed door; a technological innovation presents radical theory and expedites research advancement. Researchers swarm to work in the emerging area. Conference venues dealing with the tip of the trend are packed with attendees. Debates heat up.

This phenomenon in medical research is called a ***trend***. Meanwhile, the depth of the meaning is unexpectedly infinite.

I made this remark in my research paper, "About the trend in medicine," published in April, 1971 in the Japanese medical journal, Seitai no Kagaku. In 1938, John Desmond Bernal, a scientific ideologist and biologist in Great Britain, pointed out that scientific research in Japan tended to center too much on the popular topic. The 21st century marks a new era characterized by the embrace of the information technology revolution and genome-based drug discovery. The implications of the Japanese propensity in scientific research still hover over Japan.

A recent survey conducted by Keiko Nakamura, then research scientist at Mitsubishi Kasei Institute of Life Sciences (now known as Mitsubishi Kagaku Institute of Life Sciences), found that a trend quickly appears and quickly dissipates in the United States. By contrast, a trend emerges slowly and then lingers in Japan. One of my dear friends,

a biologist Dr. S. once confessed to me, "I feel somewhat insecure unless I stick to the mainstream in current research." This is understandable, for mainstream research is much comfortable. Students can easily become familiar with mainstream topics. We experience less stress. Actually, someone should be involved in popular areas, chasing and keeping apace with the latest trend in research. It may be true that this propels medical advancement considered from the bird eye's view. However, considering from a different angle, it is necessary to question whether or not a trend can serve as the powerhouse of practical science essential for developing novel drugs to strengthen global competitiveness.

Trends and Patents

Research studies arising from a trend may be placed in the category "foreign origin" if patent exclusivity is strictly prioritized first when disputes arise about intellectual property rights. The follow-up studies conducted in Japan are preempted by proprietary patent rights originating overseas.

On this subject, Takio Shimamoto of the Tokyo Medical and Dental University made a radical suggestion: "Faculty professors in Japan should receive monthly compensation from the Ministry of Foreign Affairs of the Japanese government since their main job is translating scientific literature."

In some respects, this opinion hits the nail right on the head as to the status quo currently prevailing in Japanese research circles. Whatever their reasons, Japanese scientists tend to stick to popular and

mainstream research; thus, we cannot deny that Japanese science can be interpreted as imported science with its origins overseas, such as countries like the United States. When patent conflicts arise over the licensure and intellectual property rights, Japan is perceived as the follower, not the originator. This implication is ominous because we cannot ignore the importance of the patent to the competitiveness of Japanese enterprises. Survival is at stake.

Beyond the issue of competition in the global drug market is the fact that the problems can not be solved merely by chasing trends. Instead, we really need to create our own trend. This creative activity is the pertinent suggestion for procedures and methods that we need for developing new drugs.

It bears repeating: so long as Japanese researchers are bound by mainstream trends, we will be capable of neither cultivating original research nor developing pro-patent new drugs.

Column 7 :

How Can Trend Research Survive?

It is not easy for the Japanese researchers to become fully knowledgeable in trend research areas originated overseas. Naturally, a trend's originator is always 1 or 2 years ahead of the trend's followers. As regards the research competitiveness, I presume that only a limited number of study teams armed with highly competent researchers can catch up with, and perhaps, can outstrip the top runner. This is the reason why choosing a research subject in the mainstream may not be advisable in this respect.

On the other hand, if these trend themes are selected, it sometimes allows industry sectors to enjoy much advantage when research projects are undertaken on technology alliance basis. Taking advantage of the sophisticated knowledge or know-how learned from the mainstream research, drug developers can accelerate the study processes from the early stage to the manufacturing stage. The more up-tempo progress of R&D can be attained. The expedited research advancement can also promise the remarkable reduction of the total expenditure on drug development. It is worthwhile and may well justify the vast investment for the trend-minded project. In addition, we may be able to apprehend some difficulty as a negative facet behind the gorgeous excellence in conducting trend research at the same time.

The Way to Drug Innovation

While we were developing plasmin inhibitors, Fujio Nagasawa, then deputy general manager of Mitsubishi Kasei Research Center, defined the prime condition for choosing potential themes: "There must be few or very few research papers published on the process." At first, I found this idea disturbingly unique. However, I respect his policy because his insightful direction led us to the wisest choice. Nagasawa's insistence

that "research themes to be selected must avoid a popular trend" was pinpointing the strategic drug innovation when we considered business climate the company faced.

The warning to avoid the mere following of trends made me ensure our industry-academia collaboration for several decades. To this end, we repeatedly and enthusiastically discussed the developmental process of argatroban, an antithrombin drug. Along these lines, I note that for many years, even international bodies, such as the Conference on Thrombosis and Hemostasis and the Committee for Thrombosis and Hemostasis tried to avoid the duplication of ongoing research activities.

I strongly believe that it is very important to establish the fundamental chemical structure of a new drug candidate at an earlier stage of the study to ask for supportive cooperation from chemists. In the case of synthetic plasmin inhibitors, the fundamental structures were sulfer group and lysine; arginine for synthetic thrombin inhibitors. It is also necessary to demonstrate the process by which chemical compounds screened are going to become a finished drug. Furthermore, not only screening procedures but also methodology for developing subsequent process should be clearly framed.

Many obstacles hampered the establishment of the screening method because we had very little know-how in an unfamiliar area. We struggled for nearly 2 years to establish the perfect design of a stable enzyme system. I cite here the summary of characteristics of plasmin inhibitor's development introduced by Takaaki Miyagi.

Note :

The members of this committee for Thrombosis and Hemostasis

consisted of 24 elected representatives from more than 12 countries. The main task of the committee is to eliminate duplicated research themes and unnecessary confusion. The committee performed valuable tasks and contributed substantially for more than 20 years, especially in dissemination of information. I chaired the committee and the vice chairman was Margareta Blomback from the Karolinska Institute in Sweden.

Column 8 :
The Path to Drug Discovery

I would like to mention a couple of distinct characteristics of studies on plasmin inhibitors. By focusing physiological and pathological significance of plasmin, we should evaluate the insight into the control of enzymatic activities. The relationship between inflammation and fibrinolysis, promotion of fibrinolysis by exposure of an exotoxin of *hemolytic streptococci*, promotion of fibrinolysis due to surgical invasions, and enhancement of fibrinolysis (as a hemorrhagic diathesis) were of great value in investigating the mechanism of plasmin itself. These aspects led us to demonstration of the therapeutic significance of enzymatic control and uncannily anticipated the emergence of today's new category, now called enzyme inhibitors.

Our new approach permitted us to establish a new method of designing an optimal study, namely pertinent screenings. Biochemical procedures were set forth first, and potential substances able to control specifically plasmin system were selected. It was very difficult to identify the chemical structures of those substances. In the absence of precedent models, it was like a trip through a labyrinth without a map.

Researchers performed systematic syntheses of thiol carboxylic acid and amino acid to prepare basic libraries. I was very much impressed with the cutting-edge technologies in organic syntheses conducted by chemists from mitsubishi Chemical Industries, Ltd. who diligently contributed to our industry-academia joint project. I have no doubt their excellence and persistence expedited this project.

By Takaaki Miyagi (A 15-year history, Antiplasmin therapy, issued in 1968)

Future Picture of Industry-Academia Collaboration

If I am asked, "Is it difficult to facilitate joint research projects under the auspices of both industry and university sectors?" I do not hesitate to answer, "Yes. It is much more difficult than you expect." I would add, "The history of industry-academia collaboration in Japan is much shorter than the European history."

After all, as the basic concept, "science" is intrinsically different at research centers run by universities than at centers run by private companies. Conceptual disparity can, however, be reconciled by reaching consensus by means of discussions. In general, I made it a rule to establish basic understanding between a corporation and my side upon initiating the project. This understanding meant that when any disagreement was revealed, both parties would work to reach resolution by mutual consent. This was a gentlemen's agreement.

In most cases, it was possible to gain consensus between two parties. However, sometimes head-on confrontation would occur in the course of the study. To resolve these difficulties, we always returned in spirit to our gentlemen's agreement, holding its principle in great esteem and repeating a long-time discussion. In many cases, a transparent perspective toward the furtherance of research activities was a decisive factor to solve to the problems. As a result, I am proud to say that our 50-year joint project has been underpinned by good faith.

I must add that a robust backbone of joint research lies in the awareness of equality inherent in the proclamation, proclaimed by the founder of Keio University Yukichi Fukuzawa. It is said in his conviction, "Heaven dose not create one man above or below another

man." I would say that success or failure of joint research projects definitely depends on the humanity as well as whole-heartedness of the team members and ends with a high degree of faith. As I write this, I remember fondly the exceptionally good teamwork of university scholars and pharmaceutical professionals in Switzerland, France, Sweden, and other countries.

We have heard that more than a few researchers in Great Britain have criticized their bitter experience of delay in clinical applications of penicillin. Even though penicillin had been discovered in Great Britain, critical time had been wasted before appropriate actions were taken for joint collaboration and thus they lagged behind the competition.

Today a nearly ideal style of industry-academia joint research is seen in Europe. The subsequent development of aspirin was promoted by industry and academic sectors for more than a century. Even in the time when administration of aspirin was considered a risk factor for causing bleeding, both pharmaceutical professionals and academic experts were committed to working harmoniously to consistently support aspirin as a useful treatment for patients with thrombosis. In this instance, Belgian researchers in hematology made a great contribution by collecting a huge amount of clinical findings to assure the benefit of aspirin.

Companies Unable to Develop Novel Drugs

Some say that a pharmaceutical company unable to develop genuinely effective drugs no longer deserves to exist. Others disagree. In the real world, the silent consensus among the pharmaceutical and bio-related industry is that only 2 or 3 major companies can survive

in the fierce competition of the drug innovation.

I spoke with one manager who agreed. "What about your company?" I asked him. "To be honest, our company may be on the verge of the safe zone," he replied.

When I was involved in the development of plasmin inhibitors, I was visited by a third party who offered me co-development of a drug that was still under development. After we elaborated the market share, we found that the market share of this company could occupy below 10 or 20 % compared with that of competitors which were also studying plasmin inhibitors for many years. It was obvious that the net profit might shrink to the minimal level. It may be true that companies will not survive unless they can afford to send a new drug to the market successfully.

I wonder if there is an ultimately best strategy for innovating new drugs for drug developers.

To answer this question, we need profound understanding. I will not be able to give you a satisfactory explanation about this point even if I use the whole page.

As I wrote in Chapter 1, original works in research were emphasized at the military research center. Although some radical ideas were raised, they were not persuasive enough to meet the concept of reasonable and matured originality. Pierre Curie once said, "A truth is naturally here as an inkpot is there." The innovation of novel drugs may be tantamount to his word.

Intellectual Property Rights (Patents)

In this chapter, I would like to discuss patent issues, especially as regards the United States. My knowledge in this area comes from advice and information learned from Mr. B, a patent attorney in New York, from valuable experience from many discussions with patent experts, and from consultations on intellectual property rights (i.e. patent) with the US Patent and Trademark Office (USPTO) in Washington, D.C.

Table 2 illustrates the conditions or terms of patent application procedures. As I will explain later, criteria for patent grants are as demanding as those for the Nobel Prize.

Table 2. Three key concepts for patent grant in the United States

- Novelty
- Unexpectability
- Usage

Proposed by Mr. B and his group (Patent attorney in New York)

One patent criterion requires determination of whether or not there is "unexpectability" in the item proposed for a patent. This criterion does not parallel a requisite for the Nobel Prize. The concept "unexpectability" requires clarification. Take, for example, a cleaning agent developed for the purpose of polishing the surface of glasses. If this agent can also

wash off the exterior walls of old buildings, the extra use does not represent an unexpected uniqueness.

By contrast, consider the case of EACA. In my previous studies, EACA was found to be useful in preserving vitamin B solution. Then there was an unexpected discovery that EACA also possessed hemostatic effect. The US Patent and Trademark Office granted patent rights to EACA based on the concept of "unexpectability." Originally, EACA's patent was not granted as product patent for the previously known product. While, EACA was the first patent granted by the United States Patent Office as patent for its usage.

In items proposed for patent, "novelty" is rigorously examined. If a similar discovery has already been patented, the subsequent item may be suspected as a free-ride patent (piracy) or unfortunately a stigma as so-called "the stolen invention" is often used.

"Patentability" is an inevitable issue for all Japanese companies negotiating with foreign companies. Business negotiations on an equal basis with foreign counter-partners are out of the question for Japanese companies lacking internationally acknowledged patent rights with originality belonging to Japan. Our study team had to be thoroughly prepared in this regard whenever we sat down at the negotiating table with our productivity-minded (cost versus performance) Swedish partners.

Column 9 :

Queen Elizabeth and Our Patent

An unforgettable event took place at the International Conference on Hematology in Tokyo in 1960. I made a morning presentation as to clinical application of plasmin inhibitors. The reaction of the audience was almost nothing in the sleepy morning. The next day, a mischievous co-presenter decided to play a trick using a wall banner hanging inside the venue. He attached to the banner a newly released document on our findings, written in English. Immediately after this, 22 pharmaceutical company representatives from Europe and the United States rushed up to me, inquiring about the details of the paper. Some world-famous companies even offered a plam to co-develop plasmin inhibitors with our study group.

The document which had suddenly captured all this public attention was a patent document imprinted with a red-wax seal bearing the honorable signature of Queen Elizabeth. We were indeed overwhelmed with the symbolic power of the British royal family under the name of Her Majesty Queen Elizabeth.

Productivity (Cost versus Performance)

In Sweden, it was pleasant to see a stranger on the street during my evening strolls, and it made me nostalgic about humane companionship. Even in a big city like Stockholm, it was rare to encounter people walking outside at night. Although Sweden is almost the same size as Japan, Sweden's total population is about the same as the population of Hyogo prefecture in Japan, only a few million citizens. With such a small population, it is difficult to recruit sufficient labor for Sweden's workplace. There are incentives, however. For example, there is an excellent social security system and it is one of the points in

advertisements targeted at labor. Because a work force is absolutely essential, a city of such low density must be optimal for developing good medicines with high productivity.

Imagine how many value-added products we can send to market made from a single kilogram of iron prepared for production. This example demonstrates a scale of productivity or cost/performance ratio. In industry, productivity is crucial aspect to strategic planning. Swedish pharmaceutical companies strongly emphasize this point. Now what does our business society need to enhance productivity? The answer is: we must be capable of strengthening "Science and Technology" to underpin better productivity. Not only that, all we must be at the leading edge in matters of internationally appreciated "Science and Technology." In questions of productivity, the field of drug innovation can enjoy very high priority.

Of course, we must develop good tactics for achieving this high productivity. Again, think how many valuable products could be made from 1 kilogram of iron. Surely, we might expect an inestimable figure.

Nomination Criteria for the Nobel Prize in Physiology and Medicine

In the early 1960s, streptokinase (SK) therapy was dominantly employed in treating patients with thrombosis. Soon, however, physicians faced a therapeutic dilemma. SK therapy caused serious bleeding as a critical adverse event. As discussed in an earlier chapter, Nilsson and her team conducted a series of studies using EACA to investigate hemostatic effect of EACA and obtained a favorable result. For almost 40 years after that, the Nilson group has taken the initiative

in Europe in clinical studies on plasmin inhibitors, EACA, and tranexamic acid. Non-clinical studies using animal models were also conducted at Nilsson's laboratory.

Under these circumstances, I began to make frequent visits to Lund University to lecture at the graduate school. In 1966, Lund University conferred upon me the honorable title, professor emeritus. To my surprise, the name of Sweden's king was imprinted in the prestigious certificate - and it was much bigger than the imprint of my name.

Swedish people love to celebrate. At receptions and ceremonies, the main topic is, of course, the Nobel Prize. According to the explanation of Per Udden, a famous medical critic in Sweden and onetime scientist of the Kalorinska Institute, a Nobel nominee must fulfill all the prerequisites. The three main requisite conditions are: first, to be **theoretically new**; second, to be **at the forefront of the new wave standing on the new theory**; and third, to **contribute to the well-being of mankind** using the theory as much as possible. In addition to these three conditions are two more. It is stipulated that Swedish research themes should not be shown favoritism in the nomination process, and that the final decision must be made by the Karolinska Institute Nobel Assembly in Stockholm, consisting of elected professors of the Institute.

The most stringent of these award criteria is that nothing is more important than "theoretically new."

A "new" theory must endure a number of follow-up studies performed by many researchers and maintain its status as the front-runner leading the trend. It is an extremely tough requirement to satisfy. A Nobel Prize laureate must fulfills the prize requirements not by being a trend follower, but by creating a trend in research activity.

The third major condition, "contribution to the well-being of mankind" received less attention in the past. However, new emphasis has been placed on this point. The study of PAS (antituberculosis agent), an antituberculosis treatment, conducted by the Swedish researcher Goteborg, was a Prize nominee in 1960.

As explained so far, the Nobel Prize selection criteria are very strict. They are both similar and dissimilar to the requirements for granting intellectual property rights. Namely, The Nobel Prize resides on the high-level spectrum of standardized sense; patentability is established only something far surpassed the standard in terms of its use. So far as I am concerned, creativity is a key factor needed for obtaining patent rights.

Corporate Researchers and the Nobel Prize

In the 1970's, two of my acquaintances in Japan unexpectedly received a strange correspondence. The correspondence explained that Shosuke Okamoto had been nominated for one of the Nobel Prize laureates, and asked them to submit a recommendation letter. Later, I learned the story of why such correspondence reached them.

At that time, the University of Paris intended to recommend a candidate for the prize. As usual, recommenders screened eligible candidates from their own university and selected two finalists for the nomination. Then a problem developed. The professors split evenly into two factions, one for each candidate. In this delicate situation, a decision could not be reached by the majority rule. At last, one of professors broke the deadlock with a proposal. "It is high time we broaden our

Column 10 :

Bound for Europe Even by Siberia Train

"Hi Jin, is it possible for you to arrange a courtesy visit for me to Dr. Shosuke Okamoto during my next stay in Japan?" This was an e-mail sent by Dr. Jawed Fareed, professor of Loyola University in Chicago to our colleague, Mr. Shiomura. Typical of his energetic transcontinental activities, Dr. Fareed is a leading authority in hematology not only in the United States but also in Europe.

We were relatively accustomed to receiving inquiries about visits to Dr. Okamoto as we had already hosted Dr. H Suzy Hassouna, professor of Michigan State University. We answered Dr.Fareed, "We will be pleased to do it for you, but I wonder if you have enough time to visit Kobe city. It is far from Hamamatsu city, the venue for the conference." He replied, "I was wondering if I might disturb him." "We don't think so," we responded. "You should know Dr. Okamoto is a man who welcomes with great respect any guests coming from far away." Even though Dr.Fareed is a respected, tenured professor with stature equivalent to Dean at a Japanese University, he sounded a little hesitant.

One sunny day in May, we escorted Dr.Fareed to meet Dr. Okamoto at his home in Kobe, a traditional Japanese residence overlooking a beautiful panorama of Akashi Bridge. Even though it was a breezy day, Dr.Fareed was perspiring. My heart was warmed by the contrast between Dr. Okamoto's dignified style of English as well as Mrs. Okamoto's gracious smile on the one hand, and on the other hand, Dr.Fareed's pressured manner as if he had been a young student meeting a famous star. To be honest, we used to have absolutely the same impression when Dr. H Suzy Hassouna coming from Michigan State University visited the famous Dr. Okamoto.

As the meeting drew to a close, Dr. Okamoto gently took down a Noh mask displayed on the wall and gave it to his guest. "This is a gift for your memory of today, Dr.Fareed. I am happy if you accept my sincere friendship."

scope of selection. Let me say that we should recommend a researcher outside France. Personally, I would pick out a Japanese study on plasmin inhibitor which has long been conducted by Dr. Shosuke Okamoto." I heard this story much, much later from the professor who recommended me. I think the authenticity of this story may be trusted, even though its details may not be perfectly accurate. Upon receiving the recommendation from the University of Paris, the Nobel Prize Assembly contacted my friends to request a letter recommending me.

By the way, I would like you all to imagine the reaction of the two guys when they received the announcement letter from Sweden. Gee! One of them threw the letter into a trashcan, thinking it was just a malicious prank.

I humbly introduce this episode in the present context to emphasize that it would not be a strange happening for anyone in a research field to become a nominee for even such an unparalleled honor as the Nobel Prize.

In fact, there are other examples of corporate researchers working for pharmaceutical companies who were recommended for the Nobel Prize. They were excellent scientists at F. Hoffmann-La Roche, Bayer, SmithKline Beecham, and others. I believe that top-notch scientists at pharmaceutical companies can reasonably target the Nobel Prize in the future.

(At the very least, do not be too modest and never think you are being teased with malicious mischief if you suddenly find a letter from Sweden in your mailbox.)

Standing beside the tall scholar, who still looked more or less tense, I was deeply impressed with Dr. Okamoto's naturalness and gentlemanliness as he eschewed any hint of haughtiness and paid profound respect to his visitor. On our way back to Tokyo, Dr.Fareed told me, "Oh, what a worthwhile visit I had today. I very much appreciate the considerate arrangement two of you made for me." Having witnessed this occasion, we became to recognize that this was so called "Go to Okamoto Worship on visiting Japan," a well-known reputation among hematological professionals all over the world.

Time flies. In July of 2001, the first symposium of the 21st century of the Conference on the International Society on Thrombosis and Hemostasis was held in Paris. It was also the very first opportunity for introducing argatroban, thrombin inhibitor, as the third drug developed with great and loving care by Dr. Okamoto. Dr.Fareed chaired the symposium.

Although Dr. Okamoto was indeed anxious to attend this symposium by any means even by Siberian Train, his recently suffered pulmonary edema, perhaps due to many years of smoking, did not permit the long flight to France. The young-minded professor insisted he would travel even by way of Suez Canal or some other ground routes. Unfortunately, he had to give up attending the conference after all.

In the absence of Dr. and Mrs. Okamoto, a huge picture of them was displayed on the screen at the convention hall. A unanimous ovation was given to this couple who tenaciously rendered distinguished services to the evolution of hematological research by developing EACA (a plasmin inhibitor known by brand name of Amicar), tranexamic acid (the second generation plasmin inhibitor), and Argatroban (thrombin inhibitor) benefiting global medicine. In this way, all the present members showed their great appreciation to these two great contributors of Hematology.

By Hidenobu Ikoma
Jin Shiomura

Personal History

Shosuke Okamoto, M.D., Ph. D.

(PROFESSIONAL CAREER)

1917 Born in Tokyo, Japan
1941 Graduated from Keio University School of Medicine
1956 Associate professor of Keio University School of Medicine
1959 Professor of Kobe University
1966 Received honorary degree of Ph. D. in medicine from Lund University (Sweden)
1975 Dean of Kobe University Faculty of Medicine (served 2 terms for 4 years)
1980 Retired from Kobe University (a snapshot with Mrs. Okamoto at the retirement ceremony)
1980 Representative of Kobe Research Project on Thrombosis and Hemostasis-present continued

(AWARD & PRIZE)

1969 Frey Commemorative Medal (from the former West Germany)
1970 Okochi Memorial Award (research on the development of plasmin inhibitors)
1985 Testimonal for the distinguished services (from International Society on Thrombin and Hemostasis)
1992 Okochi Memorial Award for Technology (research on the development of argatroban as a synthetic thrombin inhibitor)
1993 The Order of the Rising Sun, Gold Rays with Neck Ribbon (from the Japanese Emperor)
1996 Penner Award for the contribution to research on blood coagulation-presentFocusing on the subsequent research for developing the third-generation thrombin inhibitor following the previous launch of argatroban