Building Cancer Drug Business Through Licensing

BY DR. GORDON MAXWELL*

Case history of search for successful anticancer drugs by Bristol-Myers

The discovery of new anticancer drugs is an extraordinarily difficult process. Despite massive national and international research investment, most new cancer drugs have been discovered serendipitously. Thus, we decided nearly twenty years ago to capture the results of this serendipity by licensing as many anticancer drugs as we could identify on a worldwide basis.

At the time we began, the conventional wisdom was that one could not create a significant business in the cancer field because no one had done it before.

Table 1 shows the conventional wisdom to have been in serious error.

1986 Worldwide Sales (IMS - $)	Bristol-Myers Cancer Drugs	Year of Marketing
2,900,000	Carboplatin - Michigan State	1986 - UK
39,200,000	Etoposide -Sandoz	1983
88,300,000	Cisplatin - Michigan State	1978
20,900,000	Bleomycin - Nippon Kayaku	1973
25,400,000	Mitomycin C - Kyowa Hakko	1974
4,700,000	Methotrexate - Monsanto Research	1979
710,000	CCNU - NIH	1976
2,300,000	BCNU - NIH	1977
400,000	Mitotane - Calbiochem	1970
300,000	Teniposide - Sandoz	1976 - Europe
23,500,000	Megestrol acetate - British Drug Houses	1971
25,700,000	Cytoxan - Asta Werke	1959

Total $234,310,000.

(The 1987 total was about $350 million, and security analysts suggest that the 1988 total will be over $400 million).

Table 1

During the early 1970s the Bristol and Mead Johnson Laboratories were operating independently, so there were two separate licensing efforts and we will discuss their efforts in turn. These activities were subsequently coordinated and then merged, as will be described later.

BLEOMYCIN

The licensing story at Bristol-Myers can be said to have begun with the role played by Dr. Amel Menotti in developing a relationship with Dr. Hamao Umezawa of the Microbial Chemistry Research Foundation in Tokyo. As a result of support of Dr. Umezawa by Bristol, we obtained marketing rights to drugs developed at the MCRF.

The first such compound was the antibiotic, kanamycin, and the second was the anticancer compound bleomycin. From a licensing point of view the situation was complicated by the fact that the MCRF worked through Japanese companies to develop and market the drugs in Japan. In the case of bleomycin the company was Nippon Kayaku.

Thus, although Bristol had rights to bleomycin for the United States through Dr. Umezawa, we effectively had to negotiate with Nippon Kayaku as well before Bristol could market bleomycin in the U.S. This discussion consumed more than a decade.

No time was lost in putting bleomycin on the U.S. market, because development of the drug continued here while negotiations were going on. Negotiations typically ran through the day and into the night, so we adjourned to a local restaurant. It came to be known as the "bleomycin restaurant," and today we cannot remember its true name. It's difficult now to identify why it took so long to reach agreement. No doubt the Japanese tradition of trying to reach internal consensus on every point led to much delay. It also seemed that every time we reached apparent agreement in one session and adjourned, upon resuming the next day or the next week or the next month we found that the demands had changed. These problems cannot be laid at the doorstep of a single Japanese company, because they were experienced in the case of mitomycin C and the Kyowa Hakko Company, as we will describe later.

During the 1960s and 1970s we developed widespread contacts with Japanese university professors that continue today. There is an organization called JARA, the Japan Antibiotics Research Association, which is a nonprofit volunteer association of companies, individuals, and universities who are interested in antibiotic research. Bristol gave research grants, and still does, to academic scientists through JARA. A professor in a Japanese national university is in effect a governemnt employee, and he or she can't accept money from industry. By feed-

Chairman and CEO, Lenti-Chemico Pharmaceutical Laboratory, Inc., Teaneck, New Jersey, subsidiary of Ajinomoto Co., Inc., Tokyo, Japan.

ing the money through a nonprofit organization the money is "laundered," so companies can then make grants to university professors. That was an important development.

MITOMYCIN C

Professor Toju Hata of Tokyo's Kitasato Institute discovered mitomycin C, a significant anticancer antibiotic under a JARA grant supported by the Bristol-Myers Company.

Mitomycin C was turned over to the Kyowa Hakko Company for development in Japan, so licensing discussions for the U.S. had to be carried out with both Professor Hata and with the Kyowa Hakko Company. The professor was no problem, but the Kyowa Hakko discussions went on for 14 years without reaching a conclusion. These discussions went on during the same period as the bleomycin negotiations noted above.

As with the bleomycin case, Bristol continued to work on the mitomycin C development in the U.S. while the negotiations were ongoing. Bristol filed a New Drug Application on mitomycin C, had it approved, and put it on the U.S. market without having reached an agreement. Since Kyowa Hakko would not agree that Bristol had rights, they would not accept royalties. Bristol paid the money into an escrow fund. Finally, we went to Tokyo with Mr. Jules Pericola, who was president of Bristol Laboratories, and hammered out an agreement on the basis that they had the patent on the compound and Bristol had the approved NDA. Neither of us could operate without the other.

Under the gun, so to speak, we did reach an equitable agreement. Bristol is still operating under that agreement, and the product is still growing. The U.S. sales of mitomycin C (called Mutamycin) have far exceeded those in the home country of Japan.

DIFFERENCES OF OPINION

We mentioned earlier that the conventional wisdom was that it was uneconomic to do cancer research in industry. It was more or less dismissed as a research objective. Several companies had been in cancer research very early. Lederle Laboratories, for example, had been in it the 1940s. Lederle worked intensively in the folic acid antagonist area and developed methotrexate, which is still marketed. Then the company pretty much abandoned the field for 40 years.

Hoffman-LaRoche had done some work early on and developed 5-fluorouracil (5-FU) in the 1950s. But it then left the field for quite a while. It was apparent to us that there was a therapeutic vacuum in cancer (and in many respects there still is), and we thought it was a promising area to work in.

A policy committee at Bristol-Myers periodically reviewed research areas, and typically one might see 39 votes against the cancer area and one vote for. But that vote was Dr. Herman Sokol's. Since he was chairman of the committee and President of the company, that vote carried. We hung on by slender threads with the cancer program for several years; everybody got on board when the wisdom of it was obvious.

The fascinating thing about licensing is that you get involved in the search for new products intellectually. You find that you must get ahead of the conventional wisdom. Otherwise you will be too late. As is well known, a revolution in molecular and cell biology is taking place, thanks to gene splicing and other techniques, and the field is moving faster than anyone could have dreamed. The jury is still out on who the new leaders in cancer chemotherapy will be, since the present conventional wisdom is that the cytotoxic drugs are still the hope of the future.

NITROSOUREAS

Going back to our history, the next compounds licensed came from the U.S. Government. They were the nitrosoureas CCNU, BCNU and methyl-CCNU, the first two of which have been marketed. This was a case where the compounds were discovered through government-supported research, so the government had title to them and was developing them in the clinic. The National Cancer Institute (NCI) understood that it was not in a position to market the compounds, so it decided to offer them for licensing to industry. Since there were no patents, what the NCI had to offer was exclusive use of the data under which we could register the compounds.

The NCI asked for bids from companies in which the bidder described its qualifications and stated why it should be selected as the developer and marketer of the compounds. We at Bristol said that we knew how to register cancer compounds because we had just done it, and that we had filed an NDA on Blenoxane. We enclosed a copy of the bleomycin NDA as proof of our competence. That worked. Bristol was awarded exclusive rights to these compounds. There were about six other companies that were competing for them, but the fact that we could point to recent experience in doing what the government wanted done was an important factor in Bristol being awarded the license.

For example, Lederle Laboratories had not had a cancer drug approved since 1948, so they could not point to very recent experience. Bristol also, at that time, had formed the first marketing force to sell anticancer drugs. It consisted of only six men, but that was six more than anyone else had. Bristol also had clinical oncologists on board who could do the drug evaluations, whereas no other company had even one fulltime oncologist.

USSR ADVENTURES

Our adventures in Russia were quite interesting, although nothing useful came out of them. To begin, the anticancer drug ftorafur excited our interest. This compound had been made at the Institute of Organic Synthesis in Riga, Latvia, now one of the Soviet Republics. Through an obscure chain of circumstances, ftorafur was licensed to the Japanese company, Taiho, in whose hands it became extraordinarily successful under the name

Futraful. It is still a major product in Japan a dozen years later.

Although ftorafur was a great commercial success in Japan, there was a question about its clinical efficacy. We wanted an agreement under which we would have an option to evaluate the compound clinically and then, hopefully, market it. We were competing with a number of U.S. companies that also had expressed interest in the compound. No doubt our background in having a half-dozen cancer drugs on the market persuaded the Russians that we were the logical people to develop ftorafur in the U.S. and in most of Europe.

We found the Russian negotiators very difficult to deal with, even more so than the Japanese. We have mentioned earlier the 14-year negotiation on mitomycin C. At one point in the Russian negotiations we were convinced we were going to spend that long in Russia, and life is too short for that prospect. Anyway, we did spend a total of several months during successive visits in negotiating the USSR agreements.

◄ Negotiations Difficult ►

The Russian negotiations were a difficult experience, in terms of the amenities, the hotels were terrible, the food was worse, and the people were inhospitable. We typically negotiated in one of the Medexport or Licensintorg offices. We would come in the morning and negotiate until noon. The first Soviet team would leave, a second team would come in to continue, and we wouldn't get any lunch. On a good day we would get some tea and cookies, which would have to carry us through the day. The meeting rooms were unheated, so we were uncomfortable as well as hungry. We are sure that must have been a purposeful negotiating tactic to wear us down. The Japanese also sometimes employ serial negotiating teams, but they kill you with kindness. They take you out to sumptuous lunches and dinners to try to melt your resistance.

In the Russian sessions we had a curious experience. We were dealing with one chief negotiator whom we will call Leon Trotsky, which was not his name. We were working with him through an interpreter, going back and forth for several days, with no indication that he knew English.

At the next series of negotiations, held in New York, we sat down with Trotsky and found that he spoke fluent English. He did not even bring an interpreter. Then the puzzle deepened. When we went back to Russian the next time, Trotsky had his interpreter. We couldn't understand Trotsky's tactics. He spoke English sometimes, and used an interpreter at other times in the same session. Finally, it dawned on us that, when he had good things to say, he would say them in English. When there were bad things to say, he would say them in Russian and let the translator become the bad guy. It was a curious experience.

◄ Reason ►

The reason we were putting up with all of this Russian discomfort was because the compound we were discussing was an anticancer agent called ftorafur. This was marketed by Taiho in Japan and had become a great commercial success, so we were interested in Western rights. The Japanese called it futraful, because that was the way they pronounced ftorafur. This compound did have anticancer activity in our laboratory animals, but this does not always predict clinical activity, as we will note later.

A major problem in the Russian negotiations for ftorafur, and for other compounds, is that there were multiple organizations involved. One was called Medexport, which was the export agency that we were negotiating with for the purchase of the supplies of the compound. Another organization was called Licensintorg, with whom we were negotiating for a license under the ftorafur patent application.

We had to have an agreement that was satisfactory to both Medexport and Licensintorg. But the organizations would not sit down together with us, because each reported to different ministries in the government. We negotiated with one group and then with the other, and we had to quote to the second group what the first group had told us. To make matters worse, they would say something at one meeting, and then retract it the next time, leaving us in a bad position with the other group with whom we had tried to build a scaffold of agreement based on the statements of the first group. That is why things took so long, and why they were so difficult to negotiate with. We felt like a ping-pong ball being batted back and forth between two agencies. With nearly infinite patience and fortitude we finally did reach a license/supply agreement on ftorafur.

Then came the problem of trying to make a drug of ftorafur in the U.S. We tried the injectable form first, since it was marketing in Japan, but at effective doses it turned out to be too toxic. It affected the central nervous system. Ftorafur is a variant of 5-FU (5-flourouracil) which was developed in the 1950s. Since ftorafur was supposed to be an improved form of 5-FU, and since the latter was an injectible drug, it was logical to try ftorafur in the injectable form first.

◄ Abandon Effort ►

As a result of the ftorafur injectable toxicity experience, we tried the oral form. We did a double blind comparison of 5-FU injectable with oral ftorafur, and we could not find an adequate level of activity in any of the human tumors. As a result, after six or seven years of work, we abandoned the compound. There was no hope of getting Food and Drug Administration approval with a 10% clinical response.

Another drug we negotiated rights to was carminomycin, an anticancer drug that was an analog of Adriamycin. We had to deal with yet another Soviet agency, the Institute of New Antibiotics in the Ministry of Science. Carminomycin was supposed to be less cardiotoxic than Adriamycin, but it was also less active. It is not difficult to find less toxic compounds that don't cure. Carminomycin was also given up, which more or less terminated our Russian Adventure.

A curious sidelight of our experiences in the Soviet Union was, as others have observed, that the Russians were very suspicious. They didn't like to speak freely to foreigners, especially about technical matters. As a result, we had difficulty talking with people in various organizations. On our first visit we were supposed to meet with a group of scientists. We arrived in Moscow and were told that the group was not ready to see us. So we went back to New York. On a subsequent visit we met the group and were asked what happened the first time. They said they had assembled as scheduled.

After the fiasco of our first visit we were advised to sign a protocol with the Central Committee of the Soviet Union, the one that has jurisdiction over all of the scientific academies. We, in effect, negotiated a treaty with the Russians. Gavin MacBain, who was then Chairman of the Board, flew to Russia with his wife, suffering a diversion to Kiev because of a snowstorm in Moscow. We had a ceremonial signing party. That was the only time we were fed by the Russians — once in four years.

We now had a specific Protocol signed by the Central Committee of the USSR, in both Russian and English. When we visited an institute, for example, the Institute of New Antibiotics, we would first say hello and pass the time of day. Then we would take out the Russian version of our Protocol and present it. They would say, "Ah, yes." They then felt free to talk, because we were "certified" as official friends of the Soviet Union.

◄ Welcome ►

After we got over the hurdle of the Protocol, individual scientists were quite professional and helpful in our discussions. Indeed, they welcomed the opportunity to break out of their scientific isolation. These discussions were in the mid-1970s, which was a period of relative detente, so things were friendlier than they would have been a few years later. The warming trend today in U.S.-Soviet relations might approximate what we experienced.

One great disadvantage to doing business in the Soviet Union was the total sense of isolation. The only broadcasts on radio and television were in Russian, as were all the newspapers and magazines. The only thing we could buy in English was the *Daily Worker*, and that was not edifying. A visitor really had to rely on his or her own resources.

A few things were pleasant in Moscow, however. We attended concerts at Tchaikovsky Hall, saw the circus, and rode the subways. Those were very good. But other than that, the isolation was terrible, especially since the amenities were so poor.

The food in Moscow was incredibly bad. Once we were at a hotel called the Metropole, which was quite famous in pre-war days. We found the food to be unimaginably bad. Later, when we came back to Moscow on another trip with a larger delegation, including our Executive Vice-President, we found that we were billeted at the Metropole for the first time. At that time you could not reserve a specific hotel. You reserved a hotel at a certain price, and when you landed in Moscow Intourist would tell you which hotel you would be in. You telexed back home to tell people where you were.

After having had a long flight to Moscow and delays in clearing customs we arrived at the Metropole at about eight or nine o'clock at night. Since we were tired and didn't want to start running around looking for restaurants, we said, "It can't be as bad as we remembered it. Let's eat here." Well, it was even worse than we remembered it. First, they refused to seat us, saying the kitchen was closed. We said it was only 8:30 p.m., so they relented and said we could have some soup. They brought out soup that tasted like dishwater. It was impossible to eat it. So we sent the soup back. Finally, we ended up with some tea and stale cookies. That was our dinner. It was no joy at all. On subsequent trips we carried two suitcases — a large on for food and a small one for clothes. It was the only way to survive.

◄ Culture Shock ►

The thing that made such an impression on our first trip to Moscow was that we were coming from Tokyo where we had been on business. What a culture shock! We came from one of the best tourist cities in the world to the worst. No one in the company volunteers to go to Russia, unless they have never been there. The novices figure it can't be as bad as the stories people tell about it.

PLATINOL (CISPLATIN)

The licensing of the anticancer drug Platinol has a very interesting history. The drug was discovered by Dr. Barnett Rosenberg of Michigan State University. He is, curiously enough, a biophysicist who was doing experiments on the effect of electrical fields on cell growth. Dr. Rosenberg noticed that his bacteria, instead of dividing normally into additional bacteria, grew into long strands like spaghetti. The cells grew, but they did not divide. So he made the mental leap that perhaps the solution inhibited cell division, and maybe the solution had antitumor properties. Dr. Rosenberg tested the substance isolated from his cell (which originally contained only sodium chloride solutions and platinum electrodes) and found that the isolate had antitumor properties in animals. It turned out that the platinum electrodes reacted with the sodium chloride under the influence of the electric field to produce cisplatin (cis-dichloro diamine platinum II).

Cisplatin was submitted to the National Cancer Institute (NCI), which confirmed its anti-tumor activity in animals and took the compound into clinical trial. However, cisplatin turned out to be very nephrotoxic, so at that point it looked as though it might never be a useful drug. However, a group at the Memorial Sloan-Kettering Cancer Center discovered that, if a patient is hydrated with saline before and during cisplatin infusion, there is marked attenuation of the nephrotoxicity. Thus, cisplatin became a practical reality as a cancer drug.

Originally, because of the nephrotoxicity, Michigan State was unable to find a licensee for cisplatin, so it was turned over to Research Corporation, a nonprofit licensing foundation. After the Sloan-Kettering discovery, competition developed for a license. Bidders were required to make presentations to Research Corporation as to why they should be selected to develop the drug. The licensing situation was complicated by the fact that the work of Dr. Rosenberg had been supported by two platinum companies, Johnson-Matthey (U.K.) and Engelhard Industries. He also had some minimal support from the U.S. Government, which meant that the government set the terms for and had to approve the license. Hence, we were involved in multiple-party negotiation.

◄ Turn of Events ►

Early in the cisplatin negotiation we thought we had convinced the U.S. branch of Johnson-Matthey, located in Malvern, Pennsylvania, that we should be licensed exclusively. We were on our way with serious negotiations when their superior came over from the U.K. We started talking with him and he started raising questions. We said we thought the decision had been made in our favor, but he said not as far as he was concerned. As a result, we had to take a team to Britain and make a presentation there. In a similar way we had to sell ourselves to a half-dozen groups. We called this period the nine-cats-in-a-bag period. When you are trying to collect nine cats in a bag, everytime you catch one another jumps out. This is the way our negotiations were going.

The main negotiating party was Research Corporation, then headquartered in New York and now in Tucson, Arizona, which held title to the patent. These negotiations started badly because Research Corporation had the idea of giving multiple licenses. We countered this by finally convincing Johnson-Matthey that it should give us a license. We then went to Research Corporation and pointed out that only Bristol could be given an exclusive license since we already had a license from Johnson-Matthey. We also pointed out that a higher royalty rate could be justified with an exclusive license. It amounted to a bit of arm-twisting, but it did work, and we got all the parties to agree and got the government to bless the agreement. It was one of the most complex negotiations we ever had and took two years to bring to fruition.

The following is a list of the parties at interest who had to be convinced:

— Dr. Barnett Rosenberg, inventor

— Michigan State University, the host institution

— Research Corporation, the licensing organization

— Matthey Bishop, the U.S. arm of Johnson-Matthey

— Johnson-Matthey of Sonning Common, U.K.

— Engelhard Industries

— NCI

— Department of Health and Human Services

— Bristol-Myers Company

Platinum Analogs

As part of the cisplatin negotiations we also discussed getting rights to cisplatin analogs. In this way we obtained an option to carboplatin from Research Corporation, now marketed in various countries as Paraplatin. We also obtained an agreement with Johnson-Matthey to look at its future compounds. The analog, iproplatin, came out of the Johnson-Matthey negotiation. It is interesting that there have been more than one thousand platinum analogs made by dozens of research groups around the world, yet the three best candidates to reach the clinic were all licensed by us. We did a fairly good job at picking the winners, although that was more luck than skill. We still do not know how to predict which analogs will be clinically useful based on animal data.

Podophyllotoxin Analogs

Two of the most interesting compounds we licensed were two semisynthetic analogs of podophyllotoxin (from the May apple) called etoposide and teniposide. The first, trademarked Vepesid, has become Bristol-Myers' largest-selling anticancer drug, leading to wry faces at the Sandoz Company in Basel, from whom the compounds were licensed. We had been talking with Sandoz about these compounds since the early 1970s. At every discussion, several times a year, the Sandoz people mentioned that they had two anticancer compounds and did not know what to do with them, although they had not decided to license them out. On every occasion we said they should license them to us because we knew how to develop them. After half a dozen years of talking with us, Sandoz decided that it had been spending money in the area for 10 or 12 years without much return. Finally, Sandoz decided it might be better off licensing the products to us. The decision has been mutually rewarding to both companies. As always, hindsight is very good.

Amsacrine

Amsacrine was an interesting story that added to our roster of unusual business destinations. This anticancer agent was synthesized originally by the New Zealand Cancer Research Laboratory in Auckland, and it was being studied by the NCI. We thought it was interesting at the time. We went over to New Zealand to negotiate, and managed to sign a letter of intent with the Institute. We even were invited to appear on New Zealand television to describe how we were going to develop this New Zealand-discovered product.

However, one of our competitors came along and reopened the bidding. We looked at the question carefully and decided we did not want to get involved in an auction on this product. We did not know where it would stop. Since amsacrine, a decade later, is still not a product in the U.S., we don't feel badly about having let that one get away.

We have on a few other occasions

elected not to stay in an auction for a license and have let other people take over certain compounds because the price was too high. Thus, our success has not been because we licensed everything in sight. We exercised a scientific and financial selectivity, and it has worked out reasonably well.

Ifosfamide

The origins of this alkylating agent go back to the Cytoxan (cyclophosphamide) story, which was licensed in the 1960s from Asta Werke in Germany by Dr. Ken Campbell of Mead Johnson, before it became part of Bristol-Myers. Ifosfamide, also from Asta Werke, has had a checkered history in the U.S. It was first developed by Bristol for non-small cell lung cancer. An NDA was filed and it even got as far as FDA Advisory Committee approval. However, before the FDA could act on this recommendation, a new committee rotated into being, and the new members of the committee did not believe the compound worked. Thus, the new committee reversed the original decision and withdrew the approval recommendation.

Ifosfamide was subsequently thought to have activity in pancreatic cancer, but insufficient data were available for an NDA. Finally, the drug was found to be very useful as third-line therapy in testicular cancer. Hopefully, by the time this article appears, the drug will finally reach the U.S. market, 20 years after it was discovered.

◄ Footnote ►

There is an interesting footnote to the licensing story. Given at adequate doses, ifosfamide causes damage to the kidney. This resembles the cisplatin story, but here hydration does not work. However, another compound called mesna, also from Asta Werke, was found to be uroprotective. Thus, if you give mesna together with ifosfamide one can obtain useful clinical results without nephrotoxicity. As a result, our colleagues went back to Asta Werke to get rights to mesna, because without it ifosfamide would not be approved by the FDA.

NEW DIRECTIONS

Having come this far in licensing of anticancer drugs of the cytotoxic type, it is time to think of new directions for the future. This brings us to the area of biological response modifiers or BRMs. This the category of the interleukins and the interferons. There is, as the reader may be aware, a great deal of controversy within the scientific community about the value of these alternative therapies in cancer. It is an ongoing debate.

Our position is that the cytotoxic compounds have reached a plateau in the 40% cure rate range. With the current rate of progress, with therapy for the major cancers of colon, lung and breast still eluding us, by the end of the century we would still be at only 50%. That means half the cancer patients will not be helped. This suggests a change of direction is warranted.

Fifteen years ago the conventional wisdom was that you could not build a drug business in the cancer field. That was wrong. At that time the cytotoxic drugs were underdeveloped and the wave of the future. Today, the conventional wisdom is that the cytotoxics are the preferred approach. In today's scientific environment, that is equally wrong. It reminds us of the old adage that the generals always fight the last war. People in cancer still tend to concentrate on the the last war. We think there should be more emphasis on BRMs.

People criticize interferon because a lot of expectations were raised for it that were not realized. But the opponents have to recognize that the reason the proponents had to make some noise was because the cytotoxic establishment was against the concept. If the proponents had not lobbied vigorously, they would never have gotten any funding from federal agencies. Making the noise did raise public expectations, which were not realized. However, there are certain tumors like renal cell carcinoma and hairy cell leukemia where alpha interferon has proved useful. It is hard to understand why scientists should expect that we will learn how to use the interferons instantly, when it has taken so long to learn how to use the cytotoxics. We described earlier the long gestation times for etoposide, cisplatin and ifosfamide. All of them were discovered 20-30 years ago, and we are still learning about them in the clinic.

The BRMs probably will be most useful in combinations, just like the cytotoxic agents are. The immune modulator Lentinan, from the Ajinomoto Company in Tokyo, looks to be interesting in combination with interleukin-2, with the cytotoxics, etc. One of the great advantages of the BRMs is that, if you give them in combination you do not get cumulation of toxicity, as you do with the cytotoxic chemotherapeutic agents. Hence, there is more latitude in treating the patient, and we feel the BRMs in combination are the wave of the future.

We have not mentioned monoclonal antibodies here. This is a vast area of research with both therapeutic and diagnostic potential. To cite just one example, the Wistar Institute in Philadelphia has found a monoclonal antibody, called 17-1A, which has been found to be clinically active in treating melanoma. There is an indication from animal work that a combination of 17-1A and the immune modulator, Lentinan, may be more effective than either compound alone. The group at Wistar is talking about a four-component combination of 17-1A, Lentinan, gamma-interferon and interleukin-2. That begins to sound more and more like the cytotoxic drug-use pattern that took so long to develop.

ACADEMIC RELATIONSHIPS

Academic relationships play a vital role in the discovery and licensing of new drugs. We mentioned earlier the role of the Japanese Microbial Chemistry Research Foundation in the discovery of bleomycin and that of the Kitasato Institute in the development of mitomycin C. However, at the more basic level we have cast a very wide net. Bristol-Myers has had an innovative program over the last dozen years in giving no-strings grants of $500,000 each to leading cancer research institutions. There were 21 of them at last count. We are pleased to have played a role in establishing and implementing this program, and to have had in-depth relationships with these premier organizations such as Stanford, Yale, Chicago, Hopkins, Baylor, Rockefeller, and Cold Spring Harbor, to name a few.

The academic institutions have not been immune to the great debate between the cytotoxic and non-cytotoxic drug proponents. Our frustration has been that Bristol-Myers, having been more-or-less at the cutting edge of the move into anticancer drugs, now seemed to be hung up there and was not giving enough priority of funds to the new areas. Now we see the pendulum swinging, and are more optimistic for the future.

Acknowledgement:

The author is indebted to the Bristol-Myers Company for the opportunity to engage in these fascinating and rewarding adventures. Special thanks are offered to Curtis C. Carlson, who participated in these licensing efforts in a central way.