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FOREWORD

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Ten years of CIBE Symposia, 1989–1998

On a cold day in January 1989, I was able to luckily convince my director of thirty years, dear Dr. Edward O. Stapley, to allow me to set up a special cycle of Symposia that would be organized and sponsored by CIBE. It would be carried out though with the collaboration of well-known national and international scientists who did not need to be professionally related to CIBE. This was the first and successful step in developing a novel idea that nobody could predict would be a success. Before going on to explain the development of the symposia over those ten years, let me briefly relate what CIBE is, and how and when it was set up. While doing this, I look back in joy at being able to show the role, relevance and development of research centers and companies in the Spanish framework since the middle of this century.

The beginnings

The first Spanish Center for the discovery of new compounds of therapeutical application produced by microbes was set up in Madrid in 1954. It was the result of a personal agreement between the management of Merck, Sharp & Dohme Research Laboratories (MRL), a division of Merck, Sharp and Dohme (MSD), in the United States, and Compañía Española de la Penicilina y de los Antibióticos (CEPA) in Spain. It would prove a very successful attempt to introduce a collaborative research program in Spain and, more importantly, to provide a few Spanish scientists with training in the latest, novel technologies. Those who participated in such a program were aware of the extraordinary possibilities opened for their own scientific development.

Twenty-five years later, MSD took full control of the program, and the center was called “Centro de Investigación Biológica de España” (CIBE, Spanish Center for Biological Research). The CIBE belongs to the MRL Natural Products Drugs Discovery (NPDD). Throughout these forty-four years, the Center’s main goal has been the discovery of new compounds with a potential to become new marketable drugs.

Until the early 1970s, the CIBE Program had mainly focused on the discovery of new antimicrobial agents. We must bear in mind that it was the period which corresponds to what Dr. Boyd Woodruff, one of the first Directors, called wisely “the antibiotic explosion”. I would add that it coincided with the golden age of antibiotics. In fact, most antibiotics were discovered in less than ten years, defeating the serious problem of infectious disease, and dramatically changing human life worldwide. As often happens in science, some antibiotics were discovered, simultaneously, by different researchers in different countries.

Since I started working for Dr. Stapley, biology in general, and medicine and pharmacology in particular, had gone under major changes. New tools to fight disease were developed, but new challenges had also arisen. In 1959 the search for new antibiotics was a major topic for research; twenty years after the discovery of the first deliberately-sought antibiotics, many bacteria had started to show resistance to such drugs, especially among people who recovered in hospitals. In that very year, 1959, Japanese scientists discovered that plasmids inside bacteria were carrying genes for drug resistance which could be passed on to other bacteria. Since then, we have learned a lot about the development of antibiotic-resistance. Currently, there is some support for the notion that the pool of antibiotic-resistant genes has a source in the antibiotic-producing bacteria themselves. It has been found that most antibiotic preparations contain contaminating DNA from the producing organism. This suggests that in the patient being treated, the infectious organism might easily be in contact with the DNA which encodes antibiotic resistance. Now we are also aware that plasmid DNA is not only able to withstand the environment in the blood system or the gastrointestinal tract but can also survive for several weeks in certain body tissues. Since 1959, other major discoveries have been made: pathogenic agents unknown before have been described, such as *Borrelia burgdorferi* and *Legionella pneumophila*, which cause Lyme disease and legionellosis respectively; the human immunodeficiency virus (HIV), causing agent of AIDS; and more recently, prions, the possible agents of the Creutzfeldt-Jakob disease and bovine spongiform encephalopathy. Besides, we have witnessed the re-emergence of classical infections that we thought we had overcome, such as tuberculosis and several sexually transmitted diseases. On the other hand, the search for new antibiotics, as well as investigations to discover the molecular mechanisms

for infection and resistance, have continued, and major advances in different scientific fields have taken place. In the mid 1970s, there was the launching of genetic engineering and the use of recombinant DNA. In 1989, when the first CIBE Symposium was held, the polymerase chain reaction (PCR) was still a novel technique, hardly more than a project, and not many people had realized its potential as a tool for research and diagnosis.

Following the innovative trend of the time, CIBE also had good opportunities to perform its work. The group had been lucky enough to discover three new families of antibiotics, which were inhibitors of the bacterial cell wall. The antibiotics met Merck's requirement not to produce any compound that could be toxic for humans. This was a critical condition that was necessary for any further study.

Achieving the goals

CIBE Spanish researchers felt very proud of the discovery of fosfomycin, the first true Spanish antibiotic. To make the story nicer, the microorganism that produced the compound had been selected from a soil sample taken in Eastern Spain. But getting the product into the market was an arduous task. Their sincere belief in its efficacy, however, made the participants consider those times among the most exciting in their professional careers. They happened to be pioneers in practically all the experiments they performed; they had to establish their own variables and controls. They had the opportunity of dealing with all the aspects that make a scientist's career so appealing.

Nor was it easy to go ahead with the two latest discoveries: cefoxitin and thienamicin. Before they were marketed not only did all Merck employees have to make great efforts, but they also spent a long time dealing with the deep disappointment and great expectations. Luckily, success was the outcome, and the satisfaction of getting two new compounds to save human lives made CIBE researchers forget previous bitter moments. When the research program was launched, the participants could never have imagined the dramatic forthcoming advances which were to occur in scientific knowledge and technology. Merck managers also took advantage of these times. They were now able to plan the type of substances they would like to discover, with higher chances of success. Science had also advanced dramatically in the knowledge of the specific mechanisms of antibiotics. For example, for compounds to be selected as "potentially interesting", it needed to be more than just an inhibitor of the cell wall formation; it had to be an inhibitor of a well-defined step in the cell wall formation. Since the mid 1970s, this has been their goal, which they aimed at and were fortunate enough to achieve.

In the 1970s the program also addressed the discovery of a broader group of compounds, not necessarily only antibiotics. As a result, a new compound, Mevacor, was put into the market. As is well known, Mevacor is a very effective cholesterol depressor, with major characteristics, with a well-established mechanism—the inhibition of the HMG-CoA (hydroxymethyl glutaryl-CoA) reductase—that was discovered through an assay to specifically detect compounds with such a mechanism. As had happened with the discovery of new antibiotics, the new drug helped decrease the risk of a very serious disease, in this case heart troubles.

In the 1980s, scientific expectations to discover new compounds had greatly increased. In that way, most of the CIBE assays were really very specific, with very well defined targets for the primary assays and effective counter screenings to select, specific compounds. As a consequence, a new family of antifungal compounds with a broad spectrum, pneumocandins, was discovered. The producer organism was the fungus *Glarea lozoyensis*, a new species isolated from a water sample from the Lozoya River, in the province of Madrid, in 1985 (see the cover of this issue).The major interest came from its antifungal spectrum, broader than any other compound ever found by MSD or by any other pharmaceutical company. The final product is now in clinical trials and the results are very promising. There is the possibility of placing the product in the market in the near future. Fourteen years have passed since the activity generated by the new microorganism, *Glarea lozoyensis*, producer of the pneumocandins family, was discovered and caused it to be selected as "new and interesting compound". But CIBE has still to wait to consider, for sure, that the new compound is safe to be used in humans. This is a simple indication as to show how slow research on pharmaceutical compounds proceeds, and how long it takes to make a new drug available for human use.

Many interesting compounds and microbiological samples are still in different phases of the various screenings they are going through. Some of them are brilliantly passing the strict controls. These new compounds and the continuous innovations regarding future research are among the most exciting and stimulating reasons to pursue this type of work. CIBE is now facing new technologies, new approaches, and new procedures not only to make the study of the large number of "non-cultivable cultures" available, but also to improve, chemically, the purity of the microbiological samples to be tested. As always happens in science, a broad spectrum of applications and new challenges will be open. CIBE people are aware of that and, as they have done before and will always do, they work together very hard, and with a high motivation to begin CIBE's new decade in the new millennium in the most fruitful way.

Drafting the CIBE Symposia

The idea behind the CIBE Symposia, when they were set up, was to create the opportunity for Spanish scientists to exchange information at a different level than the typical meetings organized by pharmaceutical industries at the time. We did not have any intention of limiting the presentors to specific

topics or lecturers, nor even of suggesting that the meeting should be held in our laboratory facilities. The scientific aspects of each Symposium were to be based only on the suggestions of participants. Nine years later, I believe that CIBE has succeeded in rigorously maintaining this principle of non-interference.

Dr. Stapley and I discussed how we could approach these Symposia. We did not want to bad them towards one specific type of research although Natural Products was our special interest. We wanted to make the scope of these meetings as broad as possible, covering many aspects of our microbiological surroundings. We were also interested in including topics on basic research, although they might not have seemed very close to our company interests. So, we were very cautious in choosing the general name for the series. "Current Topics in Biological Research" was the name we unanimously agreed upon. It seems to me that this title has been adequate for each particular topic.

Thanks to the collaboration of very good friends, the First Symposium was organized in a very short time and it had an exceptional chairperson, Julian Davies, who was then at the Institute Pasteur, in Paris. He and the other lecturers—Ricardo Amils, Fernando Baquero, Luis Carrasco and Antonio Jiménez—behaved like close friends, trusting and helping me at every moment. They were the main characters of the First Symposium, which took place in May 1989 in the School of Sciences of the Autonomous University of Madrid. This has been the same location chosen for the Tenth Symposium, to which we devote this issue of INTERNATIONAL MICROBIOLOGY. The First CIBE Symposium succeeded because the lecturers did an excellent job. Such a good job, in fact, that immediately new ideas for the Second Symposium came up. From then on, new lecturers, as excellent as those early pioneers, have been added to the list.

This year, 1998, we commemorate the Symposia's tenth anniversary. It is a great time for CIBE and especially for me. In fact, I must confess that first organizing and then attending these Symposia has been one of my favourite hobbies throughout this period of my scientific career. And I must say that I have had a lot of hobbies to keep my life enjoyable. To mark the tenth anniversary, a different approach to the previous Symposia was suggested to our distinguished speakers for 1998. For the first time there was a fixed general topic, "Life, Evolution and Future", for all presentations. It is not difficult to guess that I have a penchant for the subject, but I honestly believed that it might also fulfil the expectations of many other scientists. Evolution has been a recurring topic in the CIBE Symposia, so important that "evolution" was, in fact, the reason for the 1994 and 1995 Symposia.

In this Tenth Symposium we had two Spanish lecturers, designated as "primus inter pares" among the Spanish participants from previous Symposia. Also, the selection of lecturers was based on the fact that their research was close to the chosen subject. There were of course suggestions about the possible topics to tackle, but these remained as simple suggestions; it was clear that versatility had been a constant for CIBE Symposia and that we should remain faithful to tradition. So, the following topics were discussed with a few variations: "The origin and evolution of life" (Ricardo Guerrero), "Evolution of RNA viruses" (Andrés Moya), "Bacteriophage ϕ29" (Margarita Salas), "Antibiotics as tools in evolution studies" (Ricardo Amils), "Bacteria response to environmental changes" (Víctor de Lorenzo), "Evolution of resistance to β-lactamics" (Juan F. Martín), "Evolution of microbial resistance over time" (Rafael Gómez-Lus), and "Evolution in prokaryotes and eukaryotes" (Fernando Baquero).

Finally, the last part of our proposal was that the presentations should be published. I must thank the lecturers once more for their generosity in providing the manuscripts of their contributions. Had it not been for them, we would not have been able to prepare this issue of INTERNATIONAL MICROBIOLOGY, the renewed and excellent journal of the Spanish Society for Microbiology. Nor would it have been possible without the kind support of Prof. R. Guerrero, who has allowed CIBE to take advantage of his editing experience and his friendly help. Our intention has been to offer quite a complete vision of the "events in the evolutionary history of life" as we see them now, in the light of our present knowledge: an overview, beginning in the origins; followed by the different and encountered perspectives from the microbe and antibiotic side and, above all, the key word: evolution.

As you will see in this issue, Julian Davies, Arnold Demain, Richard Lenski and Lynn Margulis, four of the most distinguished international chairpersons these Symposia have had, have kindly agreed to participate with their articles. These, as always, captivate our interest and make us reflect. It is my pleasure to state publicly how grateful CIBE is to them for giving us the credit and, even more, for having dedicated us their precious time and attention.

Summarizing ten years of CIBE Symposia

Coming back to the story of these meetings, let us recall the different topics dealt with over the previous nine years. Obviously, the main interest, shared by both the participants in these Symposia and CIBE, has been microbiology in general and antibiotics in particular. Just as an example, some of the issues addressed throughout these years are listed below. I would be very happy if the readers find them to be appealing topics.

Biopoiesis and ecopoiesis, life and cell origin, evolution of RNA viruses, evolution in bacterial symbiosis, prokaryotic promoters, ecological reasons for the production of secondary metabolites by microorganisms, initiation of secondary metabolism in bacteria, application of recombinant DNA for the production of antibiotics, control of antibiotic biosynthesis and characterization of the genes involved, genomics, the present and the future of antibacterial agents, and others. Along with the other side of the coin: microbial resistance to

antibiotics, and their mechanisms and evolution.

I am sure that the reader will agree with me that these Symposia have accomplished their ultimate goal: to open the minds of researchers working, like myself, on very specific subjects, to questions not very well known, about which not much work has been done or which have just begun to be dealt with; questions that have already been demonstrated and solved; questions for which the scientific community thought to have found the right answers, but which were modified soon after viewing them in the light of new discoveries or perspectives, which at a later stage might have turned out to be also wrong themselves. And, above all, we had the opportunity to reflecting many issues upon which we are far from understanding completely. For example, some of the issues would be those we face day in and day out in our work, along with their ups and downs. But in the end we always seem to be advancing and discovering a new way to go further. For me, this is the real "grandeur" of science.

I cannot end without expressing our deepest gratitude to all the friends that have made this note possible; for their collaboration, for the interest they have shown, for the support received from them, and for all that CIBE and myself have learned from them. I am specially thankful to the president of the Spanish Society for Microbiology, Prof. Francisco Ruiz-Berraquero. Before presenting the detailed list of the participants and the Symposia to which they contributed during the last nine years, let me devote my special remembrance to Prof. Francisco Martín Luengo, whom many of us will never forget.

Titles and lecturers in the ten CIBE Symposia (1989–1998):

- 1989. Biological functions of secondary metabolism. Julian Davies, Ricardo Amils, Fernando Baquero, Luis Carrasco, Antonio Jiménez.
- 1990. Modern aspects of antibiotic research. Arnold Demain, Alfredo Brañas, Paloma Liras, Francisco Malpartida, Juan Francisco Martín.
- 1991. The impact of the β-lactamic antibiotics in the clinical research. Alexander Thomas and Josefina Linares, Rubens López, Miguel Ángel de Pedro, Juan A. Sáez Nieto.
- 1992. Evolution of antimicrobial resistance. David Schlaes, Javier Garau, Juan García Lobo, Juan García Riestra, Rafael Gómez-Lus, Josefina Linares, Francisco Martín Luengo, Jesús Martínez Beltrán, María del Carmen Mendoza.
- 1993. Perspectives in research on inhibitors of cell function. To commemorate the fifth anniversary, the participants were again Julian Davies, Ricardo Amils, Fernando Baquero, Luis Carrasco, Antonio Jiménez.
- 1994. Microbes and evolution. Lynn Margulis, Ricardo Amils, Isabel Esteve, Ricardo Guerrero, Juli Peretó.
- 1995. Microbial evolution in theory and practice. Richard Lenski, Fernando Baquero, Víctor de Lorenzo, Andrés Moya.
- 1996. Special features of prokaryotic genomes. David A. Hopwood, Francisco Malpartida, Margarita Salas, Juan Evaristo Suárez, Miguel de Vicente.
- 1997. Genomics and drug discovery. Julian Davies, Fernando Baquero, Stewart Cole, Francisco Malpartida, Juan F. Martín, Stephen Oliver, Francisco del Portillo.
- 1998. Life: evolution and future. Ricardo Guerrero, Andrés Moya, Margarita Salas, Ricardo Amils, Fernando Baquero, Víctor de Lorenzo, Juan Francisco Martín, Rafael Gómez-Lus.

Last but not least, CIBE would also like to thank the assistance it has received for years from the responsible managers of the Autonomous University of Madrid, Center for Molecular Biology and National Center for Biotechnology. They have supported us and have provided, kindly, not only the meeting rooms but, most importantly, the academic environment we needed for the Symposia. In fact, the possibility for young scientists and students to attend and participate in the Symposia has always been one of the main reasons for holding them.

There are forty-seven Merck employees working on the CIBE program. Twenty-five of them are scientists, most of them with microbiological and biochemical backgrounds. Along with the U.S. Merck employees, their job is to provide us with "unknown" compounds with a therapeutical potential in any of our research lines. Without their continuous effort and interest, without their support and high spirits, neither my work nor those ten magnificent Symposia would have been possible. I would like to send my love and acknowledgement to all of

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Director of the CIBE since 1989. Her scientific career has been linked to Merck, Sharp & Dohme for more than forty-five years, starting shortly after completing her studies in Biology and her training in specialized fields of biochemistry, clinical microbiology and molecular biology. She has been actively involved in the screening of natural products. Through a life devoted to microbiological research she has achieved an in-depth technical and scientific knowledge of the structure, physiology and metabolism of microorganisms. She was a pioneer in the setting up of antibiotic research in Spain. For a more detailed explanation about the role of the CIBE and Sagrario Mochales in the scientific research on antibiotics in Spain, see her article in the December 1994 issue of *Microbiología SEM*, the journal which preceeded INTERNATIONAL MICROBIOLOGY. (Cfr. Mochales, S. 1994. Forty years of screening programmes for antibiotics. *Microbiología SEM* 10, 331–342)

the members of the CIBE team.