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# 1974-1994







The cover of 20 Years On symbolises EMBL's contributions to the European scientific community. Our service function is represented in the upper right photo of the site of the newest EMBL Outstation, the EBI, and the inset CD ROM upon which sequence databases are stored and distributed throughout the world. The impact of EMBL's instrumentation development is shown by views of a corrector system that extends the resolution of transmission electron microscopes. Below it, representing EMBL research and instrumentation collaboration, is a confocal micrograph displaying localisation of a motor protein on the chromosomes and spindle of a mitotic cell. The photo of predoctoral students in the Heidelberg teaching laboratory symbolises EMBL's multi-faceted training function. The complexity of biological organisation and EMBL research themes are portrayed by the comparison of pattern formation in the fly and chicken wings, a subnuclear structure depicting cell biological approaches to RNA processing, the structure of a membrane containing virus – Semliki Forest virus, and the sequence of the HPRT gene.

# EMBL Twenty Years On 1974-1994



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This 20th anniversary report of the European Molecular Biology Laboratory is intended to present to the public a well rounded view of the goals and accomplishments of the institution. It describes the history of the Laboratory, its four major functions within the European scientific community (research, service, instrumentation development, and training of young scientists), as well as other relevant facts and information. It also serves as the main component of EMBL's 1994 Annual Report. It is supplemented with a separate brochure giving statistics on:

Finances Staff of each unit and visitors Official visitors and Laboratory tours Council, advisory groups and committees Publications Seminars Courses Collaborations

# **EMBO and EMBL:** Proud Achievements of European Scientists

### **By François Jacob**

he birth of a new kind of biology evolved from the decisions made by a small number of scientists between the end of the 1930s and the beginning of the 1950s. The research workers involved came from very different disciplines: biology, physics, medicine, microbiology, chemistry, crystallography, etc. Realising that the questions raised by genetics were essential to the study of the living world, they invented molecular biology. They were not told to do this. They received little encouragement from individuals or institutions. It was, on the contrary, the curiosity of these few men and women, their new way of looking at old questions, that led them to solve the problem of heredity. This history of molecular biology is a good illustration of how original research evolves independently of possible applications.

A similar situation occurred when the question arose of coordinating European forces in biology. Again, no organisation, no minister suggested that European molecular biologists should intensify their cooperation. The scientists themselves felt the necessity of such a European organisation.

It all started thirty-two years ago, when some of them met in Geneva with the Director General of the "Centre Européen de Recherche Nucléaire" (CERN). Leo Szilard, the nuclear physicist, who became a biologist after Hiroshima, was there. He suggested that molecular biologists should attempt to follow their physicist colleagues in persuading their governments to create a European laboratory for molecular biology according to the CERN model. The scientists responded enthusiastically to this idea. A private association was set up, the European Molecular Biology Organisation (EMBO) with a

board chaired by Max Perutz, and with John Kendrew as the General Secretary. EMBO received small grants from private sources and began to organise courses and give fellowships to scientists working temporarily in laboratories of other European countries.

The road to a European laboratory, however, turned out to be more difficult than anticipated. For the situation in biology was quite different from that in particles physics: there was no need for accelerators in biology, for machines big enough to convince governments to join forces in building a European laboratory. Yet, biologists persisted in the belief that it was important to have a central laboratory and a place to hold symposia, give courses and train students from various countries together. To achieve this goal, it was necessary to operate in two steps.

The first step consisted of getting governmental support for EMBO. This was rather easy to attain. Within a few years a Conference was convened to organise governmental funding of a programme proposed and administered by EMBO. This was quite an unusual situation in which government funds from West European countries were transferred to a private international association. Since that time, there has been an agreement between the European Molecular Biology Conference (EMBC), an intergovernmental body that provides the budget, and EMBO, a private organisation of individual scientists, which spends the money.

The second step, getting governments to agree to support a laboratory, was more difficult. At first, governments did not see the convincing advantages of such a laboratory over national ones. EMBO scientists had to persuade their governments of the importance of the project. Finally, after years of lobbying, the governments agreed to create a European Laboratory for Molecular Biology. The Conference met in 1974 and affirmed that a laboratory should be built in Heidelberg. John Kend-

rew, who had been at the centre of all the diplomatic network, became the first Director General.

Despite occasional difficulties, EMBO and EMBL have both fulfilled their respective missions: to promote European cooperation in fundamental research and to provide facilities not readily available at the national level. Molecular biolo-

gists can be proud of what they have accomplished in three decades. The three successive Directors General, John Kendrew, Lennart Philipson, and Fotis Kafatos, as well as the scientists who have worked there, have established the EMBL as a world centre for molecular and cell biology. This laboratory has spawned a remarkable school of young biologists who are now leaders all over the world.

At a time when political Europe is not in very good shape, EMBO and EMBL, like CERN, provide very good examples of what Europe can achieve when European countries agree to pool their resources and work toward a common goal.

> François Jacob is a Nobel Laureate and Professor of Molecular Biology at the Institut Pasteur in Paris.



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# Scientific Vision and European Unity The History of EMBL: 1962-1994

Two nuclear physicists conceived the idea of the European Molecular Biology Laboratory in Geneva in 1962. It took twelve years of careful planning and patient political work by a prestigious group of scientists before EMBL was created in 1974. Sir John Kendrew, the acknowledged leader of the effort and the Laboratory's first Director General, was both midwife and adoptive parent. His emphasis on international cooperation, scientific collaboration, and independent positions for young scientists are still hallmarks of EMBL. From 1982 to 1993, his successor, Lennart Philipson, expanded the laboratory and implemented a new structure of scientific programmes, while preserving the lab's original ideals. During its twenty year existence, EMBL scientists have built the laboratory's reputation for outstanding achievement in fundamental research and instrument development. As the original planners envisioned, EMBL has become an international training centre for molecular biology. It prepares group leaders, post and predoctoral fellows for careers in Europe's national institutions. It also hosts many conferences and internationally recognised advanced courses. Throughout its history, scientific excellence and service to the European community have been the institution's principal goals. The new Director General, Fotis Kafatos, who took over in 1994, is committed to this tradition.

# The Conception of a European Laboratory for Molecular Biology 1962-1974

The year was 1962, with U.S.-Soviet political tension building to a crescendo. Leo Szilard, a Hungarian nuclear physicist who had turned his attention to biology in the late 1940s, boarded a

flight bound for Switzerland. He was leaving his adopted home in New York because of the threat of nuclear war brought on by the Cuban Missile Crisis. There was a great irony in this, for Szilard had not only worked with Oppenheimer and Fermi developing the atomic bomb, but had also devoted great effort trying to prevent its use after the Second World War.

When Szilard climbed off the flight in Geneva, Vicktor Weisskopf, another collaborator and friend from the days of the Manhattan Project, picked him up. An Austrian by birth, Weisskopf had also emigrated to the United States before World War II, but

had returned for five years to Europe in 1961 to direct the Centre Européen de Recherche Nucléaire (CERN).

Szilard stayed in Geneva for several months, and one afternoon in Weisskopf's office, they discussed the danger of the decline of European science. The centre of the scientific world appeared to be shifting westward across the Atlantic, where large public investment and the breadth of the research pool gave the United States a significant competitive advantage. Moreover, the new facilities in the U.S.

were draining away much of the best European talent.

Szilard volunteered that Weisskopf's institute, CERN, was a unique European collaboration that kept Europe competitive in nuclear physics. He lamented the fact that other sciences had not shown the same foresight and suggested that Europeans harness CERN's international format to the emerging discipline of molecular biology. Weisskopf, who had ambitions of expanding CERN into an international science university, was intrigued by the idea.

Weisskopf and Szilard called two colleagues, Jim Watson at Cold Spring Harbor and John Kendrew

at Cambridge, and arranged a meeting. Both had just won Nobel Prizes: Watson along with Francis Crick and Maurice Wilkins for their discovery of the double-helix structure of DNA, and Kendrew with Max Perutz for unravelling the first atomic structure of two protein molecules, myoglobin and haemoglobin.



Leo Szilard

1898-1964

In December of 1962, following their Nobel presentations in Stockholm, Watson and Kendrew met with Szilard and Weisskopf in Geneva. There they began to nurse the concept that would develop 12 years later into the European Molecular Biology Laboratory.

### Ravello and the Founding of EMBO

The following August, Szilard, Kendrew, and Watson attended a meeting with a group of prominent biologists in Ravello, Italy. There they won enthusiastic support for the establishment of a European laboratory for molecular biology and, at the suggestion of geneticist Conrad Waddington, they added to the plans a programme of advanced practical courses and fellowships for use at European national institutions. Finally, they decided to form a new association to promote these projects: the European Molecular Biology Organisation (EMBO).

Initial funds for EMBO were obtained from the Volkswagen Foundation (and later Interpharma and the government of Israel), enough to put the fellowship and course programmes into place. This

provided an immediate boost to molecular biology in the national laboratories. The laboratory programme, of course, was much more ambitious and costly. And in spite of the enthusiasm of its supporters, it proved to be more controversial.

Leo Szilard died in 1964 and the reins of the project passed into the hands of John Kendrew. From this point onward, the laboratory project would bear his personal mark. Kendrew had extensive help from a prestigious committee of colleagues, including Adriano Buzzati-Traverso, Arne Engström, François Jacob, Alfonso Liquori, Ole Maaløe, Max Perutz, Sydney Brenner and Jeffries Wyman.

### Interdisciplinarity and Independent Positions: Early Laboratory Proposals

In 1965, this EMBO committee presented a proposal at a meeting in Paris for a "Centre Européen de Recherche Biologique" (CERB). Excellent fundamental science was the foundation of the proposal, with a mixture of international cooperation, scientific interdisciplinarity and collaboration to serve as the mortar binding it together. Research was to cover biological, chemical, and biophysical specialities, with a laboratory organisation designed to break down rigid departmental boundaries and hierarchies. The proposal encouraged independent ap-

proaches by young scientists, with an unusually large number of positions for postdoctoral fellows, as well as facilities for short-term visiting scientists.

Turnover among scientists was key to this and subsequent proposals. The majority of staff were to have temporary contracts that returned them to the national systems - a novel idea at the time. There were four essential reasons for this mobility: 1) to provide a constant influx of fresh ideas to the laboratory; 2) to allow for flexibility in adapting quickly to new scientific trends; 3) to provide a significant number of independent positions in Europe, to help reverse the trans-Atlantic "brain-drain;" and, most importantly, 4) to create a highly trained pool of molecular biologists for Europe.

The laboratory would also be a central location for expensive state-of-the-art equipment for scientists from the national labs. An important fea-

> ture was to bring together engineers and physicists with biologists and chemists to develop new instruments. Furthermore, the laboratory would serve as a centre for advanced courses to train scientists in the newest molecular techniques.

> The laboratory would be expensive - more than any single nation could afford. But this was a primary rationale for the facility: if Europe were to remain competitive in this emerging field, the price would have to be paid.

> During the mid 1960s, EMBO made steady progress promoting the laboratory at professional conferences, in scientific journals, and via personal contacts of its mem-

bers. Support was not universal: some scientists believed the laboratory was an extravagance, fearing that every scientific sub-discipline would soon demand an international institute of its own. A few claimed that molecular biology was not a discipline at all, but rather a temporary flash in the biological pan. Kendrew and the other supporters stubbornly persisted, gaining active assistance from a growing number of influential colleagues throughout Europe, including Hans Tuppy, Jaap Cohen, Manfred

"EMBL has been a stimulus to molecular biology throughout Europe, while also providing an exciting place to visit in Heidelberg. Its international flavour is something we try to emulate at NIH, because it demonstrates the importance molecular biology is likely to have in efforts to solve some of the world's most pressing problems."



Sir John Kendrew in the 1960s

Eigen, Alberto Monroy, Hubert Chantrenne, Hans Zachau, Alfred Tissières and especially Jeffries Wyman.

### Credibility and Funding: Establishment of the EMB Conference

E MBO reached the end of its financial resources in 1968 and was looking for long-term funding. With Switzerland's help, a European Molecular Biology Conference (EMBC) was founded, formally associating the governments of 14 nations with EMBO. The governments provided the Conference with stable funds for the fellowship and training programmes and gave renewed credibility to the proposed laboratory, which was henceforth called the European Molecular Biology Laboratory (EMBL).

Negotiations over the laboratory were still tedious. Nevertheless, with each meeting, the project appeared more plausible. Italy, Switzerland, Spain, France, Germany, Austria, and Denmark strongly supported the lab. Seven other countries committed themselves in principle. Among them, Sweden, Belgium, the Netherlands, and the United Kingdom voiced serious concerns about the size and cost of the laboratory, along with fears that it might drain needed funds and personnel from national labs and that the laboratory had no unique technological basis. Despite delays, the laboratory committee pursued the political process diligently. They reinforced support among national delegates and made adaptations and additions to address the critics.

### Big Machines and Phased-in Growth: The 1969 Lake Constance Proposal

n extensively changed proposal was submitted A in 1969 at a meeting at Lake Constance, cutting the overall size of the facility and phasing in growth to soften the financial burden. It also changed the role of technology at the laboratory. Previously, machinery on the scale used at institutions like CERN had been down-played. The 1969 proposal included large cell culture facilities, electron microscopes, nuclear magnetic resonance machines, instruments for automated protein sequencing, and the use of synchrotron radiation for X-ray structural analysis. The new emphasis on large machinery was made for two reasons: to strengthen the service function of the laboratory and because technology-driven science appeared to be the direction in which molecular biology was moving.

In 1969, Ken Holmes, who knew Kendrew from his days at Cambridge, was developing new methods using synchrotron radiation beams as a source for X-ray diffraction from muscle fibres. At that time, the facility he used at the Deutsches Elektronensynchrotron (DESY) in Hamburg was the first of its kind in the world. Holmes suggested to Kendrew that EMBL coordinate international use of DESY's beams for biological structure research. Successful results, he added, would provide the laboratory committee with the concrete scientific accomplishment it needed to demonstrate the value of the EMBL idea. EMBO gave Holmes modest funds to pursue experiments at DESY, and an outstation at Hamburg was added to the EMBL proposal, along with another outstation in Grenoble, where EMBL would coordinate the biological uses of the neutron beams produced by the Institut Laue-Langevin (ILL).



Kendrew with then University of Heidelberg Rektor Rolf Rentdorff and Ken Holmes

Holmes stretched his authority as far as he could at Hamburg, negotiating with DESY, the Deutsche Forschungsgemeinschaft (DFG) and EMBL. He not only began experiments, but authorised construction of an EMBL laboratory attached to the DESY ring. It was a serious gamble, as the EMB Conference had yet to approve any of the laboratory proposal. Moreover, outstations added to the cost of the laboratory at a time of heavy pressure to cut items. Fortunately for Holmes, his professional insight and political intuition were borne out. The early synchrotron experiments provided both ground-breaking results and a practical example of the quality of basic research and services an international laboratory would offer the European community. This provided decisive help in obtaining approval for the laboratory project.

### A Home is Found in Heidelberg for the Main Laboratory

As early as 1968, the laboratory proposal was taken seriously enough to elicit site offers from Greece, Belgium and France. Influential French scientists like Jacques Monod and François Jacob promoted a site at Nice, which came very close to fruition, while Weisskopf lobbied to build the lab next to CERN on the Swiss/French border. The latter was preferred by most of the EMBL committee members because of the collaborations and shop facilities that CERN promised.

Germany entered the competition in 1970, offering several potential sites, plus twelve million DM for capital expenditures. During this time, two scientists from Heidelberg, Hermann Bujard and Peter von Sengbusch, were working to establish their city as a home for EMBL. Heidelberg had an excellent university, a recognised cancer research centre (the DKFZ), as well as Max Planck Institutes for Medicine and Physics in the vicinity. The latter was adjacent to the proposed site and willing to share its workshop facilities. Heidelberg was also ideally located: 5-6 hours by train to Amsterdam, Paris, Milan, Vienna and Berlin, shorter trips to the pharmaceutical centres of Basel and Mannheim, and an hour's drive from the Frankfurt airport. In 1971, the Conference and German Government agreed in principle on Heidelberg as a site for the laboratory.

After site selection and two more years of lobbying, Kendrew grew more confident of obtaining approval for the lab. In June of 1973, he established a project office in Heidelberg, where he began to elaborate EMBL's research programme. It was a delicate process: recent advances in molecular concepts and methods were revolutionising studies of genetics, proteins and immunology. If similar advances in other areas were around the corner, he wanted to be flexible enough to adapt to them. Kendrew tried to keep the scientific programme as broad and loose as the political pressure at the conference would allow. He penned in three preliminary divisions: Instrumentation, Cell Genetics and Biological Structures - the latter two because they would fit well with the plans for simultaneous development of technology by biologists and Instrumentation engineers. With the new scientific programme and recent successes in Hamburg, Kendrew prepared a final effort to secure Conference approval and governmental ratification.

## EMBL Becomes a Reality - The Kendrew Era 1974 - 1982

On July 4, 1974, the EMBC met in Heidelberg. It was a sunny afternoon with a palpable sense of anticipation in the air. Finally, Ernst Andres of the Swiss delegation announced that France had ratified

the EMBL agreement, pushing the number of signatory countries over the legal minimum required to put it into force (Austria and Italy signed soon afterwards). Delegates from Austria, Denmark, France, Germany, Israel, Italy, the Netherlands, Sweden, Switzerland and the United Kingdom joined Kendrew in celebration. After 12 years of intensive work, the European Molecular Biology Laboratory had become a legal entity.

Kendrew now had authority and funds, but no laboratory buildings, no equipment, and no scientists to begin research. A massive amount of practical work remained. Kendrew found temporary office and laboratory space at several locations in Heidelberg: at the DKFZ, the University, and the two Max Planck Institutes. Architectural plans were solicited and contracts signed to begin construction in a wooded area above the city in the middle of the next year. More importantly, the new Director General

addressed the task of recruitment.

Kendrew had hoped to bring in a small constellation of senior research scientists around which he would build the EMBL staff. Unfortunately, enthusiasm expressed during the 12 years of planning did not translate



into personal commitments. To leave established positions, no matter how attractive the EMBL concept or promised facilities, was simply a risk that few senior scientists were willing to take. Furthermore, Kendrew was intent on maintaining an egalitarian structure among the staff and refused to offer fiefdoms to scientists to attract them.

Kendrew was forced to adapt his strategy and he worked closely with EMBL's newly formed Scientific Advisory Committee (SAC) to resolve the

"For the past two decades, EMBL has shown Europe how to run a flexible and internationally successful biological research laboratory in which young scientists can pursue their own ideas. It has been instrumental in helping to change many obsolete scientific structures throughout Europe, in part because so many of its former staff members are now scientific leaders in their respective home countries. Now, as Europe tries to unify her research efforts, EMBL as well as EMBO can again serve as models on how to do this well."

Europäische aboratorium für

Molekularbiologie

unt Baulatung

- Gottfried Schatz, Biozentrum der Universität Basel-

*Sir John Kendrew* was EMBL's first Director General and a Nobel Prize winning structural biologist. He is now retired and lives near Cambridge, England.

**EMBL:** Can you tell us a bit about the early support for the EMBL?

**Sir John:** The first big meeting was a rather happy accident. Alfonso Liquori had invited a lot of people to Ravello, Italy for a summer course. And they happened to be interested in the lab. At first, all the talk was about the lab, but then Conrad Waddington, the British geneticist, injected the idea of also having courses, meetings, and research grants. Politically, that turned out to be much easier than the lab. The meeting resulted, of course, in the founding of EMBO, which was successful right from the start and helped morale. In fact, at the beginning we thought EMBO and the lab would be the same.

**EMBL:** There was strong British opposition to the lab in the early days. Was that particularly frustrating for you?

Sir John: There was resistance at the Royal Society, but persuading governments was the biggest problem. A lot of people felt that it was hopeless. In the end, the British political support came from two women, Shirley Williams and Margaret Thatcher, who were both ministers in the Department of Education and Science in successive British governments. Long

before she became Prime Minister, Margaret Thatcher had read chemistry at Oxford. The first time I ever met her, she remarked "I too am a protein crystallographer." Well, it wasn't strictly true (he laughs), but she did do a research project with the crystallographer Dorothy Hodgkin. Margaret, of course, really wanted a political career, and moved over to law. Well, as the new Conservative Secretary of State for Education and Science, she apparently took the EMBL file home one weekend - it was about a foot thick - and came back on Monday morning and said, "We join!"

**EMBL:** CERN, the international physics lab, and the UK's Laboratory of Molecular Biology seem to have had a large influence on the design of the EMBL.

**Sir John:** The internationalism of CERN was, of course, a major influence. We felt creating the right atmosphere and building a critical mass of biologists in a wide range of fields could best be done at a European level. CERN, of course, had a big machine. You couldn't do that nationally. That was a big political advantage. The trouble with biology was that there was no big machine. It was only in the late 60s that large machines came into play with



molecular biology - the synchrotron facility, for example. By then we argued for at least 50% instrumentation. But we always wanted to incorporate some instrumentation at the EMBL. Of course, the UK Laboratory of Molecular Biology was a major influence - after all, I had worked there for many years and one of the advantages we had at Cambridge, for example, was that at first we were in the physics department with lots of big shops. In the early days of protein crystallography, almost all of the equipment was made in the laboratory.

**EMBL:** What were the scientific strengths of the early EMBL?

Sir John: We were very strong in instrumentation, so things like EM at Heidelberg and crystallography at Grenoble and Hamburg were going to do well. Incidentally, the Hamburg outstation was really a bit of personal generosity on the part of Ken Holmes and Gerd Rosenbaum. This was also the time when molecular cell biology was getting off the ground, a rather obvious area. One very important article was by Ari Helenius and Kai Simons on how viruses get into cells. The paper was turned down at first - the editor said it wasn't "interesting" (he laughs), but it turned out to be one of the most inter-

esting papers in the field.

**EMBL:** When EMBL started, you had no facilities. How did you convince scientists to come?

**Sir John:** A lot of senior people played with the idea, but for one reason or another didn't come. It was easier to get young people because they didn't have such entrenched positions. We looked for excellence and promise. We took a strong position with our Council that we were not going to have national quotas. We had our Council in all the countries, and good friends in America, like Paul Doty and Jim Watson.

**EMBL:** Any personal reflections on the time you worked on the EMBL?

**Sir John:** Well, it was the most interesting twenty years of my life. You see, starting something from zero presents a rather unusual opportunity. You have so much freedom to be creative. Personally, I believe that international activity is very important in building world peace. And science has always been the most developed international activity that there is. It is as simple as that.

problem. (The original SAC included, among others, Brenner, Eigen, Weisskopf, Maaløe, Luzzati, Fasella, and Tuppy). Using personal contacts in the United States and Europe and exploiting the growing list of EMBO members, Kendrew and the SAC solicited recommendations of promising young scientists, whom Kendrew then personally courted.

Kai Simons, today a Programme Coordinator in Cell Biology, was 35 years old when he came to EMBL in 1975 from Finland. He had been encouraged to apply by his advisor, Vittorio Luzzati. Simons'

group had encountered funding problems in Finland and the future there seemed unsure. He brought two of his colleagues, Henrik Garoff and Ari Helenius, expecting to spend three years at EMBL before returning home to better conditions. Simons never went back to



Garoff with Simons

Finland. Instead, he and several new EMBL colleagues began to convince other young molecular biologists that they should apply to the innovative laboratory.

Upon completion in 1978 of the Heidelberg laboratory construction, "veteran"

EMBL scientists happily left temporary downtown labs or on-site huts and, along with a wave of fresh recruits, moved into the new buildings in the woods. Kevin Leonard, 33 at the time, was one of And them. if Leonard still had to order his own pencils, the generous laboratory space he

had been assigned



Leo de Maeyer, Paulo Fasella, Jeffries Wyman, and Bernard Bach inspecting EMBL construction

was filled with the latest equipment to tackle his EM and STEM studies on macromolecular assemblies.

The excellent resources, promise of independence and spirit of adventure attracted an international group of young researchers. Many of them, like Leonard, Richard Herzog, Daniel Louvard, Riccardo Cortese and Bernhard Dobberstein, had returned to Europe after postdoctoral fellowships in the U.S. Others, like Christiane Nüsslein-Volhard, Eric Wieschaus, Jacques Dubochet, Wilhelm Ansorge, and Graham Warren, came from within Europe. By 1980, the laboratory had a critical mass of highquality scientists and was beginning to build momentum.

> Research and Instrumentation in the Kendrew Era

The study of cell biology was undergoing an historical transition from a morphological to a truly molecular approach. EMBL was at the centre of these changes, with its newly installed

cell biologists working on virus-producing cells and membrane model systems. Beginning with a biochemical study of viruses, their work turned to infection pathways inside the cell. Gradually, as EMBL expanded and collaborations between the Cell Biology and Structural Divisions unfolded. EMBL scientists, including Simons,

François Jacob with Manfred Eigen at early EMBL festivity

Griffiths, Warren, Dobberstein, and Louvard, built up a wide range of fruitful studies on the cellular mechanisms of membrane traffic.

This was also the period when Christiane Nüsslein-Volhard and Eric Wieschaus carried out their genetic screens of *Drosophila* embryos at EMBL. Their innovative approach to finding developmental mutants would soon make an international

impact and revitalise the field. By 1979, under the leadership of Heinrich

"Since its inception, EMBL has been a pole of attraction for young scientists throughout Europe. The reasons for this are obvious: the laboratory provides a stimulating scientific atmosphere, a favourable environment for young scientists to complete their training and an outstanding place for more advanced researchers to expand the technical and conceptual repertoire of European science. Many of those who have benefited by exposure to the ambience of EMBL have subsequently established themselves as effective group leaders in their own countries. The EMBO organization, in conjunction with EMBL, has also had a major impact on scientific interactions in Europe by the meetings that they organize regularly at Heidelberg and by the many exchanges they sponsor by the EMBO fellowships. I sincerely hope that EMBL will continue to function in good conditions."

Stuhrmann, the Hamburg Outstation at DESY had created a boom in synchrotron radiation experiments, both by EMBL and guest scientists. New equipment and beam lines were added at the facility during the late 1970s and early 1980s, providing increasing access to the radiation for small-angle

scattering, high resolution X-ray spectroscopy, and, of course, protein crystallography experiments.

The Grenoble Outstation began as a collaboration between EMBL and the Institut Laue Langevin (ILL) to facilitate the biological uses of the neutron beams. Under the direction of Andrew Miller, the Outstation opened its

doors in the fall of 1976. Visiting scientists began using the lines almost immediately. Grenoble also had a small in-house research group, which worked closely with its own and Heidelberg instru-

mentation scientists developing biological applications for neutron and X-ray beams. The development of multi-wire proportional counters for detecting X-rays by André Gabriel at Grenoble was a major technical achievement. They are now used throughout the world at laboratory and synchrotron X-ray sources.

Crystallography at Heidelberg was carried out during this time by Reuben Leberman and Dietrich

Suck, performing their experiments in downtown Heidelberg in collaboration with Ken Holmes' group at the Max Planck Institute for Medicine. These collaborative experiments provided a nucleus for later expansion of protein crystallography at the Heidelberg laboratory from 1981 onward and led eventually to solving of the structures of DNase I and actin.

Electron microscopy was an early research strength in the Structures Division during Ken-

drew's era, with rapid advances in specimen preparation by Jacques Dubochet. These successes also fertilised electron microscope technical developments in the Instrumentation Division, the Head of which was the Australian Arthur Jones; the CryoTEM and Cryo-STEM projects were the kind of joint projects that Kendrew had so hoped to cultivate.

Computer specialists had joined with biologists and other physicists very early on to improve technology and analysis. They worked closely with the microscopists to improve the EM analyses, as well as

> to help develop early confocal optical scanning microscopy. They collaborated with groups at Heidelberg, Hamburg and Grenoble to construct data acquisition systems and analysis packages for structural problems - most notably for fast

EMBL buildings shortly after construction

time-resolved synchrotron radiation experiments. They also came up with early interactive computer graphics for X-ray crystallography and molecular modelling, a mini-revolution that replaced balsa wood and mechanical models.

In 1978, new DNA sequencing techniques developed in England and the U.S. ushered in a wave of research in molecular genetics. In 1979, Kendrew hired group leaders working on molecular mechanisms of gene expression, who also spearheaded development of instrumentation for DNA analysis. He also began to add theoretical biocomputing to the EMBL equation.

The rush of technical developments created a revolution in the field of DNA research. International interest in sharing DNA sequences was grow-

> ing, but no one had yet undertaken the task of coordinating the data collection. In 1980, EMBL became the first organization worldwide to fund a central depository of nucleotide sequences. It was called the "Data Library" and during the next decade would mushroom into a major facility for molecular biologists worldwide.

> In 1982, an era at EMBL came to a close when John Kendrew stepped down from the Directorship of EMBL. He had spent

twenty years of labour placing his stamp on the institution. His personal commitment, vision and leadership were the undeniable driving force in both the planning and early phase of the laboratory. Without him, there would have been no EMBL.



DNase I - DNA complex



# Growth and Evolution - The Philipson Era 1982-1993

L ennart Philipson, a Swedish physician turned Virologist, was chosen in 1982 as EMBL's second Director General. During his administration, the laboratory progressed from a pioneering experiment to an institute of international renown. Philipson was as committed to internationalism, interdisciplinarity and collaboration as his predecessor, and he doggedly pursued projects that Kendrew had not had time to complete. But Philipson left his own imprint on EMBL by reorganising and expanding the institution and adding new research and training features. If Kendrew cleared the forest and planted the seeds, Philipson cultivated and fertilised the field in which quality science flourished.

#### Scientific and Administrative Adaptation

Philipson began by reorganising the three Heidelberg divisions into thematic groupings, bolster-

ing small-scale molecular technology, and strengthening ties between instrumentation and basic research at the Outstations and main laboratory. He also changed the personnel structure and gradually expanded the size of the laboratory and its scientific activities.

Philipson knew before coming to EMBL that a number of research groups had already coalesced into thematic constellations, notably around gene expression and cell membrane studies. Philipson split and added to the three Heidelberg divisions, creating seven programmes: Cell Biology, Biological Structures, Biocomputing, Differentiation, Biological Instrumentation,

Physical Instrumentation, and Biochemical Instrumentation. He also added more basic research at Grenoble and Hamburg to supplement their service functions.

When Philipson arrived, EMBL had nearly 300

scientists and support staff. His long-term plans to expand and reorganise would, he knew, also require administrative reforms. EMBL had been blessed with a generous budget during its first years, but the economic realities of the 1980s were quite different from the previous decade. Philipson tightened financial control of the laboratory, including spending limits and yearly budgets for the new programmes. He also divided EMBL's scientific staff into four categories: programme coordinators, group leaders, staff scientists and technicians. Group leaders were responsible for small teams of technicians, postdoctoral fellows, staff scientists and visitors. Programme coordinators were also group leaders. As senior scientists, however, they were also responsible for guiding recruitment and facilitating programme and laboratory policy discussions.

These changes were at first controversial, as two "traditional" EMBL principles were the absence of confining departmental boundaries and a minimum

> of hierarchy. Philipson moved quickly to undercut these concerns, emphasising that research themes were recruitment guidelines, intended to fertilise collaboration, not to mandate research. Investigators' independence remained sacrosanct.

> Maintaining a sharp scientific competitive edge was a constant concern. Philipson instituted new external peer review policies, using prestigious international panels to evaluate the programmes. He also codified EMBL's rolling tenure system. Most EMBL staff worked on limited term contracts, but with no clear rules about extensions, there was a great deal of internal ambiva-

lence: some people felt that the limits hindered recruitment of senior scientists and prevented the laboratory from keeping its best young researchers, the first generation of whom were beginning to leave EMBL. But Philipson reasserted that permanent con-

"During the six years I served on the Scientific Advisory Committee of EMBL, I anticipated with pleasure my April pilgrimages to Heidelberg for the annual meeting. I could confidently anticipate a veritable banquet of exciting science to feast upon. EMBL has few parallels on either the European or international scene, for its mission is to nurture young scientists. Only rarely can newly independent researchers pursue their own ideas in a vigorous and interactive scientific environment that includes the whole range of molecular investigations - from biocomputing and diffraction to sophisticated cell biological approaches. EMBL has a spectacular record, in terms of both its contributions to molecular biology and the positions which EMBL scientists subsequently assume. But its impact is also catalytic, for those who have initiated their careers in Heidelberg return to their home countries to build the same traditions of excellence and interaction that characterise science at EMBL."

- Joan Steitz, Howard Hughes Medical Institute, Yale University, New Haven, USA -



Lennart Philipson while EMBL Director General

tracts, however tempting, undermined the laboratory's training function. He implemented strict shortterm contracts for nearly all staff, renewable upon review to a maximum of nine years.

Instead of viewing the limited contracts as a handicap, EMBL used them to strengthen itself. It concentrated on harnessing young scientists' creativity and willingness to try new approaches. And, as predicted, the constant turnover injected a steady stream of ideas into the laboratory and helped maintain flexibility in adapting to the rapid changes in molecular biology.

When Philipson arrived at EMBL, the majority of its budget was devoted to large-scale instrumentation. Reorganisation shifted EMBL back toward the original plans for smaller-scale technology. Coupling instrumentation with strong in-house research gave EMBL credibility and helped publicise the technology that EMBL offered to the European community.

Change often brings controversy; and some of the EMBL staff were at first put off by Philipson's aggressive approach. This did not stop him from pressing ahead with his vision. He quickly became known for saying exactly what he thought, and expected an equally straightforward response from the scientists. In addition, Philipson put to use a committee of senior scientists to advise him. Gradually, the staff grew accustomed to the changes of style and substance, and the scientific reputation of the institution continued to grow.

### Fundamental Research Under Philipson

Philipson picked Kai Simons to coordinate the Cell Biology Programme, in which increasing attention was focused on dissecting the molecular

machinery responsible for cell organisation. During the next ten years its scientists developed several major experimental themes to obtain a comprehensive view of cell organisation. These included membrane trafficking, cytoskeletal networks, the cell nucleus and changes in cellular organisation before and after cell division. This focus led to a rich harvest of information, which has been well documented in molecular cell biology textbooks.

Structures was initially coor-

dinated under Philipson by Jürg Rosenbusch and Demetrius Tsernoglou. Although the Programme contracted for a number of years, it was during this time that crystallography was seriously introduced at the Heidelberg site. After Dietrich Suck and Stephen Fuller took positions as new joint coordinators, Structures began to grow, recruiting scientists with backgrounds in electron microscopy, nuclear magnetic resonance, crystallography or biochemis-



Thomas Graf

try. In 1990, the Biocomputing Programme, then coordinated by Chris Sander, merged with Structures. The consolidation resulted in EMBL's largest programme, with a broad range of approaches to structural problems - a rarity among European labs. A number of collaborations among structural, biocomputing and other molecular biologists emerged during this period, resulting in several joint studies, including the solution of the first Rab protein structure, the structural mapping of the centriole and a seven group collaboration on SH3 domains.

Historically, EMBL's Data Library was part of the Biocomputing programme. During the 1980s, rapidly improving molecular technologies led to a huge increase in the amount of new DNA sequence data produced in laboratories around the world. The Library staff was acutely aware of the long-term need for robust systems to manage and analyse this information and was assisted by Biocomputing theoreticians and other computer specialists, who created hardware, software, network, as well as theoretical applications for the library. In 1988, these collaborative efforts established the European Molecular Biology Network (EMBnet), which provided scientists throughout Europe with direct access to sequences and software packages. The Library was growing so rapidly in size and scope that a pressing need had arisen for a full-fledged outstation which efficiently integrated basic research and data management of sequence, genome, cellular, and organismic information. A new outstation, the European Bioinformatics Institute (the EBI) near Cambridge, England was created in 1993.

Philipson also added several new programmes at Heidelberg, including the Differentiation Programme. Oncogenes, retroviruses and molecules that control cell growth had emerged as important fields of study. In 1983, Philipson brought in a programme

> coordinator from outside EMBL, Thomas Graf, to recruit groups working in these areas. Most of Differentiation's initial research groups focused on oncogenes and how they convert normal cells to cancerous ones. This emphasis was soon broadened to include normal processes, as it became clear that decision-making during differentiation and development frequently uses the same (proto-)oncogenes and signal transduction pathways. This broadening led to the recruitment

of several developmentally oriented groups.

Another new Programme, Biological Instrumentation, was created to develop recombinant DNA techniques and small scale instrumentation. The impact of the new methods on our understanding of eukaryotic genes meant, however, that the focus quickly shifted to fundamental research and the programme was renamed Gene Structure and Regulation. Until then, research had revolved around transcriptional control; as the Programme grew, it adopted a broader approach, reflecting more accurately the multiplicity of steps along the pathway of gene expression in eukaryotic cells. The Programme was again renamed: Gene Expression. Riccardo Cortese and then Iain Mattaj led the Programme through these changes. Major efforts included the study of tissue and cell type-specific transcription, the regulation of translational initiation and the cell

biology and mechanics of pre-mRNA and prerRNA processing.

Philipson assigned the task of coordinating the Biochemical Instrumentation Programme to Wilhelm Ansorge. Computer hardware, software, robotics, and biochemical approaches were all combined in the Programme's early successful efforts to build innovative automated DNA sequencer and synthe-



Riccardo Cortese

siser machines, coupled with ultra-thin gel and novel labelling technology. The engineers and scientists also developed important automated cell microinjection systems and then expanded efforts later in the decade, developing mass spectrometry techniques to analyse proteins and peptides, as well as an automated multiple peptide synthesiser. EMBL researchers exploited the Programme's sequencing and other services extensively throughout the Philipson era. The practical improvements in speed, quality and cost of

research, which were demonstrated by EMBL researchers, helped promote the technology's use outside of EMBL. Many of these developments, especially sequencing and microinjection technology, were quickly adopted by labs throughout Europe and the world, particularly in cell biology and genome research.

Physical Instrumentation was first led by Arthur Jones, and later by the triad of Christian Boulin, Max Haider, and Ernst Stelzer. It specialised in innovative types of microscopy, detectors and specimen preparation techniques. During this time, it added to EMBL's international reputation by developing five additional generations of confocal microscopy. Its engineers also worked with Heidelberg and Outstation structural scientists and engineers to develop X-ray detectors, associated analogue electronics, digital signal processing, and image processing applications. Unique technical achievements were also underway, which would lead to development of aberration correctors for the low voltage scanning electron microscopes, further development of scanning tunnelling microscope and atomic force microscope technology. Instrumentation advances contributed directly, for example, to EMBL research that involved localisation of proteins and structures in epithelial cells - experiments which required the 3-D resolution provided by confocal microscopy for their successful completion. They helped non-EMBL scientists as well; computer applications to X-ray studies, for example, improved the speed of time-resolved experiments at the Hamburg Outstation by 20 to 30 fold, allowing the study of rapid dynamics and enabling more scientists to use the beam lines. These and other EMBL advances were soon adopted by other synchrotron facilities throughout the world.

The technical developments in Physical and Biochemical Instrumentation induced EMBL to pursue patents and update its policy toward collaborative interactions with European industry in order to streamline the technology transfers.

By the time Philipson arrived, synchrotron radiation was firmly established as a most important source of high intensity X-rays for crystallographic studies of macromolecular structures. The Ham-

burg Outstation, which designed and built the beam lines for molecular biology experiments at DESY, was a leading facility in the world for such research. The demand for access to this radiation by visiting scientists had intensified considerably and the EMBL Outstation, under Michel Koch, Juan Bordas and later Keith Wilson, directed considerable efforts to increasing the number of beam lines (there are now 6) and improving the associated technology. This required development of two-dimensional detectors, and the Outstation produced the first on-line imaging plate scanner for protein crystallography, which is now commercialised and very widely used. Recently the instrumentation group has built a so-

"EMBL is an important and prestigious institution in the varied and complex sphere of European cooperation in research. It is considered as such because of its pioneering work twenty years ago in opening the way for cooperation in the field of molecular biology, because for many years it represented the only point of reference, and because of the quality of its scientific work. The wealth of experience it has accumulated is a vital asset in the wider framework created, among other things, by the increase of European Union research programmes in the last ten years. These are the features on which can be founded the objective of strengthening and developing cooperation for the benefit of scientists working in this sector."

Iain Mattaj

- Antonio Ruberti, Member of the European Commission, Brussels -

*Lennart Philipson* was Director General of EMBL from 1982-93. He is now Director of the Skirball Institute and Professor of Cell Biology at the New York University Medical Center.

**EMBL:** Why did you reorganise the scientific programme when you came to EMBL?

**Philipson:** When I arrived, the divisions were already emphasising interdisciplinarity, but I felt we should guide that by dividing them up into biological problem-oriented programmes. I wanted every new group leader to represent a different outlook on a main problem of the programme. So that in building up the Cell Biology Programme, you bring together the electron microscopists, lipid chemists, confocal microscopy representatives, and biologists to analyse membrane traffic problems. I think this helped build up Cell Biology, for example, to first class level.

**EMBL:** How did instrumentation fit into the plans?

Philipson: I wanted to integrate instrumentation closely within the biological programmes. We had Biochemical, as well as Physical Instrumentation. Ansorge really broke the ice with DNA technology at an early stage, and the confocal microscope developed at EMBL was comparable, if not better than others around the

world. The fusion of instrument development with significant contributions from biological fields--I think that was the scientific accomplishment that satisfied me the most while I was at EMBL, because it showed instrument development needs biological feedback or the technology doesn't work.

**EMBL:** You and John Tooze initiated EMBL's predoctoral programme. Why?

**Philipson:** John should be given much of the credit for showing that you can create a European graduate program of this type. I had good students at Columbia and MIT and felt EMBL must be exposed to students--a logical part of our training mission, the international graduate school idea.

When we first proposed the pre-doctoral programme,

called "wiggler" beam line to give substantially enhanced intensities. Encouraged by Philipson, Wilson continued to strengthen Hamburg's in-house research, based on the knowledge that EMBL scientists with a vested interest in the technology were the most likely to fuel technical improvements and provide effective support to visitors. A major interest of the crystallography group has been the study of proteins at atomic resolution. In collaboration with



some of the national universities were worried we would drain away quality students. So we made it clear to the Council that we couldn't take more than 20-25 per annum. We wanted to award the Ph.D. ourselves, but it didn't happen. So we got accreditation from the national universities. In retrospect, this worked better because it raised the level of consciousness about the quality of work at EMBL back in the member countries, where the theses had to be read.

It's important to bring teaching and training together in any research institute. You can't be in an ivory tower and not expose yourself to the outside.

That's also why we expanded the advanced practical courses and meetings.

EMBL: You also expanded the meeting and guest facilities.

**Philipson:** Well, building the conference centre and seminar rooms was absolutely critical, but I think you also have to facilitate the social aspects of an international institution. You don't want staff or guest scientists to have to worry about these things; they have to

get on with their work. So we started guest house and hotel activities to make it easier for new-comers and visitors. Konrad Müller and the plant maintenance crew were the driving force behind all the building projects and they also, together with the scientists, really spearheaded the day care centre for people with young families.

EMBL: What has been major reason for the growth in EMBL's reputation?

**Philipson:** You have to see it as a collaborative effort. There is never one person responsible. Kendrew and many others played important roles; and in my era, all the co-ordinators, scientists and administrators worked toward a single goal: that was to make EMBL *the* centre for molecular biology in Europe. Others can judge whether we have succeeded.

groups in Lisbon and Göttingen this has recently led to the first ever de novo phasing of a protein, cytochrome C6. A report in Current Biology in 1992 showed Hamburg in a favourable position in terms of numbers of structures published from data collected at a synchrotron site - at the top.

The Grenoble Outstation went through a major transition during the Philipson era. Bernard Jacrot had moved two years earlier from his position as Assistant Director of the ILL to become EMBL's new Head of Outstation. Jacrot, a physicist who had turned to biological questions, knew that EMBL must help improve the neutron technology for biological applications. He and Philipson also agreed that EMBL should establish a critical mass of inhouse research scientists at the Outstation. In 1984-85, EMBL and the ILL collaborated to build a unique neutron diffractometer for the study of biological crystals of complexes of macromolecules. Jacrot brought in new research topics, such as the structure of viruses, and the Outstation strengthened its tools



and methodology, including the biochemical deuteration laboratory used for neutron experiments. It also added electron microscopy, X-ray analysis, and DNA cloning so that a more complete approach to structural biology could be undertaken on-site - both by visitors and EMBL's own scientists.

Bernard Jacrot

In late 1989, Stephen Cusack took over as Head of Outstation and was almost immediately dealt a heavy blow - the shutdown of the ILL's reactor. Cusack and his colleagues adapted quickly and turned attention to development of their structural research on viruses and protein synthesis, using the X-rays and other tools still available to them at Grenoble. Moreover, the Outstation was given a major boost during this time by the decision to build the new European Synchrotron Radiation Facility at Grenoble. It was to be the world's most powerful synchrotron and Cusack and Philipson negotiated an agreement with the ESRF for EMBL to provide the biological support to scientists using the new facility. Not only did the ESRF begin practical operations in 1994, but ILL's reactor also came back on line. Coupled with the Outstation's growing research reputation in neutron and X-ray structural studies, EMBL was placed in a perfect position to become biological liaison to the two most powerful sources of research radiation of their kind in the world.

### EMBL as an International University

One of Philipson's major goals as Director General was to reinforce the lab's role as a European training centre. Providing more positions for group leaders, postdoctoral fellows, and visiting scientists at EMBL was an important goal of the research expansion. Reinforcing the turnover system also played a role by ensuring that scientists returned to their home countries with scientific and laboratory management skills. Over 180 EMBL group leaders, staff scientists, and postdoctoral fellows have gone on to positions such as professors, lecturers, and group leaders in national institutions and industry.

Philipson, however, was also intent on turning the laboratory into an "international university" by strengthening the advanced courses and injecting predoctoral training. He acquired an important ally in this effort - John Tooze, the Executive Secretary of EMBO. Ties between EMBL and EMBO had always been strong; Kendrew, for example had invited Tooze in the mid-1970s to move EMBO headquarters from Brussels to free office space at EMBL. However, on Philipson's arrival, an intense decade-long collaboration between the new Director General and Tooze began and within a year Tooze was also serving as EMBL's Scientific Coordinator.



John Tooze, Philipson, and Günther Kreil presenting to the EMBL Council

Tooze and Philipson both believed EMBL training had one major gap - the lack of a predoctoral programme. Some national institutions initially resisted the notion of EMBL entering this domain, but Tooze and Philipson persuaded sceptics that exposing students to EMBL's remarkable blend of re-

"All of the key principles necessary for the durable success of a biological research laboratory have been successfully respected in Heidelberg: recruitment and evaluation of young group leaders based on the sole criterion of excellence, a very limited number of permanent senior scientists in order to ensure a constant rejuvenation of the lab, and the encouragement of interdisciplinary projects to achieve the critical mass in fields which move very fast both conceptually and technically. Thus, EMBL is an example of what can be done when the "viscous" principles and structures which are prevalent in most European Universities and National Research Agencies are replaced by a dynamic, flexible organisation. In addition the EMBL meetings and courses give an opportunity to young European scientists to exchange ideas and learn the latest techniques.

- Pierre Chambon, Institut de Chimie Biologique, INSERM, CNRS, Strasbourg -

search, instrumentation, and internationalism was a unique contribution of EMBL to European training. Other roadblocks were overcome by negotiating accreditation for the programme through the national university systems. In 1984, the first seven graduate students were chosen. In 1993, the year of Philipson's and Tooze's departures, the number of new predoctoral students entering EMBL had reached 25 per year.

EMBO and EMBL had long projected EMBL as a centre for advanced training courses. Heidelberg

was a very logical site and some courses had already been instituted during Kendrew's era. But a shortage of adequate facilities at Heidelberg had severely restricted potential in this area. In 1986, new funds became available to the laboratory after Finland, Greece, Spain and Norway joined EMBL as member countries (Belgium would enter two years later). Tooze and Philipson convinced the EMBL Council to improve facilities at Heidelberg for conferences and mini-courses, as well as for EMBL's on-going seminar series. Construction followed in 1988 on the expanded seminar rooms, teaching

laboratories, and the large Operon Conference Centre (named in honour of Jacques Monod and François Jacob's "operon" model, which suggested how genes are regulated in *E*.coli - a not-so-subtle play on words describing EMBL's new "scientific theatre"). Soon, scientists from throughout Europe began coming to EMBL - Heidelberg for meetings and hands-on experience with the latest developments in molecular biology.

### New Labs, Guest Houses, and Support Facilities

During Philipson's eleven years at EMBL, the number of scientists at the laboratory more than tripled; the numbers of visitors rose 20-fold, and the number of participants in advanced courses

> and workshops at EMBL (sponsored by both EMBO and EMBL) increased 350%. EMBL and visiting scientists rapidly filled in empty working space and the limited guest accommodations of the original Heidelberg buildings. In addition to the conference rooms and training labs, new research labs were constructed over the Operon Centre, a larger animal care centre was built to support the scientific programmes, and a new NMR facility was started in 1991. In 1984, the first of several EMBL guest houses was constructed and leased by EMBL to provide temporary housing for EMBL employees and visiting sci-

entists who worked at the laboratory or attended symposia and workshops. Canteen facilities were also expanded and improved at the lab. And in 1988, as administrators became more sensitive to the needs of scientists with young families, especially with the influx of women scientists, full-time childcare facilities were organised at the lab.

# Continuity and Change The On-going Evolution of EMBL

Philipson left EMBL in 1993. He enacted important adaptations and extensions to the original

programme and achieved tremendous growth in the laboratory in size and most importantly in the reputation of its research, service, and training programmes. What is perhaps more intriguing, however, is the overall continuity of vision - from Szilard and Weisskopf's first conversations about the lab, into the early years under Kendrew and through the era of Philipson. In 1963, in Ravello, Italy, a synthesis of training opportunity and com-

petitive scientific accomplishment were starting points for a proposal for an international laboratory.

EMBL has certainly evolved, but a close look reveals that the original ingredients of scientific independ-

> ence, opportunity for young creative thinkers, multidisciplinarity, internationalism and collaboration remain the central logic of EMBL philosophy. After a brief interim Directorship, ably performed by John Tooze, Fotis C. Kafatos came in February 1994 to guide EMBL. His Directorship is, of course, too young to treat in an historical sense. Nevertheless it is no accident that when he speaks of his vision for EMBL, the new

Director General invariably emphasises these same basic principles.

- David States -





# A Look to the Future

Under the new Director General, a Scientific Programme for the next five years of EMBL was developed after an extensive internal and external consultation process. It combines continuity with change, taking account of the major achievements of the past and the unique features of EMBL, while addressing changing needs and opportunities. The plans for Heidelberg are based on recycling resources under steady state, to add a Developmental Biology Programme and expand access to visitors and the focus on interdisciplinarity, while streamlining the existing successful Programmes. Growth will take place at the Outstations to support our commitment to service and research in the fields of structural biology and bioinformatics, partly in collaboration with the European Union. A research programme on mouse genetics is being set up at Monterotondo, Italy, complementing an EU-supported European Mouse Mutant Archive.

## **The Starting Point**

In the short span of the two decades, EMBL has become one of the best centres for modern biology in the world. Building on the goals, principles and policies established by its visionary founding generation, its scientists, its successive leaders and its advisors (drawn from the top ranks of European and American science), the Laboratory has achieved a well recognised institutional character, with a unique blend of activities that are complementary and mutually reinforcing. It has succeeded

admirably in its four-fold mission: to promote the development of European molecular biology through cooperative front-line research; to provide advanced training at multiple levels, notably including the formation of young independent investigators who prove themselves at EMBL and then move on to enrich the national research systems; to operate state-of-the-art specialised facilities accessible to the scientific community of all member states; and to develop new techniques and instrumentation. Our paramount goal for EMBL in the next decade is to continue and reinforce this multifaceted success.

pendence to organise and lead their own groups, during term appointments that cannot exceed nine years in total. Early independence engages their full creativity, and turnover provides a continuous ferment of ideas in a youthful setting. The group leaders' appointments are sufficiently long to permit their taking on novel directions rather than settling for safe science, but short enough for them to move to national institutions at a highly productive age, even to do their best work there. Only a small



The EMBL system is successful only because it is embedded in a remarkably open, cooperative culture. A tradition of spontaneous collabora-

EMBL Director General Fotis C. Kafatos

To do so, we must safeguard not only the scientific excellence of the Laboratory, but also three underlying key features: flexible organisation, open and cooperative culture, and critical mass. Flexibility is based on the turnover system which combines stability and change in a mix well suited to an international institution. Most of our stringently selected research faculty are recruited right after the post-doctoral stage and are given scientific indetions was established by design from the very start of EMBL and is enhanced by the minimal hierarchy, the relatively small size of the groups, the youthfulness of the faculty and their rapid turnover. Each small and transient group cannot hope to become completely self-sufficient, but naturally turns to colleagues for complementary expertise and advice, both in-house and outside. This collaborative climate makes it possible to combine specialties in



novel ways, greatly helps recruitment, and results in greater scientific return on investment. Moreover, it provides the natural setting for an active visitors programme and for the successful operation of unique service facilities - both of which are distinguishing features of the Laboratory.

Finally, critical mass - in personnel and resources - is a prerequisite for the success of EMBL, especially in an era when molecular biology is tackling questions that are immensely more complex and diverse than in years past. Already in 1966 the EMBO report that proposed a blueprint for a central Laboratory emphasised that critical mass is especially important because of the desirability of thematic breadth and multidisciplinarity within the same institution. Indeed, even though EMBL does not and should not attempt to do everything, breadth and multidisciplinarity under one roof are amongst the most unusual features and a strong rationale for the Headquarters Laboratory in Heidelberg.

Only with adequate human and material resources can EMBL continue to chart new paths in research and training across present fields of specialisation, and maintain its tradition of serving as hot-house for developing scientific leaders. Highly promising (and sought-after) young scientists will accept clearly impermanent positions only if they are attracted by unusually favourable scientific climate and working conditions;



Three of our newest Group Leaders at Heidelberg: Michael Way, Ramon Eritja, and Tommy Nilsson

if they know that they can "hit the ground running" in establishing their research programme and that they can maintain their momentum subsequently. Among the important factors for this calculation are the quality of the facilities and the diversity of the institution, i.e. the prospect for collaborations with a wide spectrum of peers – structural and functional biologists, chemists, physicists, engineers, mathematicians.

### Charting a Plan for the Future

I assumed the leadership of EMBL at a significant juncture: the beginning of the third decade of its existence and the time to propose a new Scientific Programme for the next five years. It has been an important opportunity to reflect on the past while formulating a blueprint for the future.

First, I had to get to know the Laboratory. Although its fundamental features - some of them summarised in the previous section - could not be missed, I needed a detailed and in-depth knowledge. I brought forward the schedule of external reviews of the Programmes and Outstations so that by now I have attended the peer reviews of most activities of the Laboratory. I visited each of the Outstations. And in Heidelberg I met individually with the research groups, for several hours each, to hear their ongoing work and future plans.

Second, it was important to recognise changes in the environment within which the Laboratory operates. Much has changed in the last twenty years world-wide. Molecular strategies and new tools have transformed virtually every subdiscipline of biology. The road is open for applying them to biological systems of increasing complexity, especially in determining the integrated functions of cells and organisms, including humans.

On the strength of this "molecular revolution", biology has become the focus of greatest excitement and promise among the fundamental sciences. A whole new commercial sector - biotechnology - has been spawned by basic molecular biological research,

and makes rapidly growing contributions to pharmaceutical and agricultural industries. The input of molecular and, most recently, cellular biology is having a profound effect on medical practice, including prediction, diagnosis and treatment. The growth of "molecular medicine" is accelerating, especially in the fields of genetics and viral diseases.

Paralleling the rapid advances in molecular biology and

biotechnology, the EMBL itself has grown, especially in its training programme. Strong, productive national research capacities have been developed in many of our member countries. A major science and technology programme has been developed by the European Union, largely directed to increasing industrial and agricultural competitiveness.

Yet an outside observer would have to say that this continent is making a terrible mistake in not supporting adequately the life sciences - the research frontier of the 21st century. To quote from Bruce Alberts' 1995 report to the US National Academy of Sciences "according to Laura Tyson, chair of the President's Council of Economic Advisers, different analyses find that the fundamental scientific research carried out in the United States produces a rate of return on the financial investment of between 20 and 50 percent per year – an enormous yield compared to other organised endeavours." Yet with a few recent exceptions, the economic crisis has resulted in stagnation and across the board cuts in European research budgets.

Despite the strength of European molecular biol-

ogy, the US remains at the forefront in many areas, reflecting the advantages of an open and flexible system, unimpeded mobility, a strong tradition of peer review and substantial investments in both the public and private sectors. It is not accidental that even in an era of budget cutting fever in the US Congress, the threatened cuts to the NIH were reversed (with the support of a mobilised scientific community), and that in a recent editorial in Science magazine the chairman of the Labor, Health and Human Services and Educa-

tion Subcommittee of the House posed the question "How high a priority is biomedical research at NIH?", only to answer "There is hardly a more vital endeavour." We need to speak up clearly about the necessity of greater support for all of European molecular biology (EMBL included), even as we tailor our plans to realistic goals.

The third step in charting the future was an unprecedented consultation exercise, which began in September 1994 and lasted till this summer. This has been conducted in the spirit of

cooperation, which I promised at my inaugural address at EMBL. A substantial Draft Scientific Programme was prepared at the outset, to present the Laboratory's vision for the future. It sketched EMBL's history and evolution, analysed its functions, made detailed pro-

posals and posed general and specific questions. The draft was widely circulated among Council members, Scientific Advi-Committee sory (SAC) members, EMBLalumni, EMBO members and other interested scientists, and received a generally favourable response.

In parallel, I visited all of the mem-

ber countries to discuss with policy makers (and often leading scientists) the Programme and associated financial costs, and to gain first-hand appreciation of the members' needs and views. The consultation process included an informal detailed discussion with Council

in March 1995, and consideration of the Programme's central proposals by SAC in April 1995. It culminated with a formal Council discussion in June 1995, to be followed by a Council decision on our final proposal in December.

External consultation was paralleled by intensive in-house discussions, largely involving the EMBL leadership (Director-General, Administrative Director, Scientific Coordinator), the Outstation heads and the Heidelberg Informal Committee (the collegial body of



Coordinators that advises the leadership on an ongoing basis). Presentations were also made to the Senior Scientists and then to the entire faculty. This process has engendered a broad internal consensus for our final plan - all the more important because the plan en-

A meeting of the EMBL Council

tails cuts in successful ongoing programmes at Heidelberg, to release resources for new activities there.

The scientific plan is a compromise between what we consider ideal, and what the member countries may be able to fund. It is coupled with a financial request

that envisages 3%, 3%, 2%, 1% and 1% increases in ordinary national contributions (before inflation adjustment) in the next five years. In putting forth this request, the Laboratory gratefully acknowledges that the member states have supported it with generosity over the past twenty years, through both ordinary and voluntary contributions. However, at the present stage of planning it has to be recognised that there is currently no Reserve Fund; there is chronic underinvestment in capital equipment and building maintenance; there are Council-approved commitments to expand activities in Grenoble

and Hinxton and to establish 4 research groups at Monterotondo; and the Heidelberg Laboratory - although the average size of its groups is not large by world standards for leading institutions - is crowded and requires some additional laboratory space if the

"EMBL stands at the cross-roads of European molecular biology, productively mixing together scientists from scientifically richer and poorer European traditions. The courses, workshops and symposia held there act as a superb focus for European molecular and cellular biology. Its role as a melting pot is invaluable. The early opportunity that EMBL provides for future research leaders by giving them substantial resources rapidly to build up their own area of work is unrivalled elsewhere in Europe. An increasing number of universities and research institutes round the world are now hosts to world-class research groups which were initially spawned at EMBL. The style of the lab is very much that of a hot-house with the fervent and youthful vigour that arises from its policy of very rarely giving tenure and then only to a tiny proportion of its staff. Finally, it provides a scientifically idealistic philosophy that is free of nationalistic rivalry and tries to encourage cooperation."

Edward Hough at the University of Tromsø, Norway.

- Max Perutz, Nobel Laureate, MRC Laboratory of Molecular Biology, Cambridge -

EMBL's Director General Kafatos visited each of the Member Countries in 1994-95. Here he is seen with Prof. programmatic goals (including an enhanced visitors' programme) are to be met. It is now urgent that commitments and resources are brought into better alignment, and this is the reason that the financial request to the member states is "front loaded".



In recent years, an additional important partner of the EMBL has emerged, the European Union. This relationship is both welcome and natural. As is true for national institutions, the EMBL receives support from the EU on the principle of

subsidiarity for competitively selected activities beyond those funded by the national governments. In our case, these activities include fellowships for increased postdoctoral mobility; multi-locus research networks permitting close collaborations with teams elsewhere in Europe; and, most importantly, joint funding of major infrastructure facilities for the European academic and industrial research communities.

A prime example of the latter type has been the

EMBL Data Library - now the EBI - which is the European constituent of a world-wide collaboration also involving the NCBI in the United States and the DDBJ in Japan. Although still inadequately funded (as compared, for example, to the NCBI), the Data Library/EBI is irreplaceable and would have had to be established de novo and funded in full by the EU, if not already organised and partly funded by the EMBL, as an efficient, widely recognised central facility.

Similarly, a novel collaboration between the EU and EMBL is the development of a mouse research facility at Monterotondo, near Rome: in that case EMBL is organising and funding a Programme of research groups, complementing and mutually supporting an EU-funded European Mouse Mutant Archive (EMMA).

Increased collaboration with EMBL and other international institutions is envisaged in the recently launched EU Fourth Framework Programme for research and technology. To facilitate this collaboration, an Administrative Arrangement has been signed between the EU and EMBL, and the EU has been granted observer status in the EMBL Council.

## The Scientific Programme 1996-2000

## Strategic Planning for Scientific Excellence

**E** MBL's Scientific Programme leading to the year 2000 entails a significant shift in the structure of EMBL, in that all the planned growth is directed at sites other than the central Laboratory in Heidelberg. For example, non-Heidelberg sites now account for 19% of the group leaders, but will reach 30% by the year 2000. However, the critical mass of the Heidelberg Laboratory will not be undercut - it will be maintained at steady state with some of its resources redirected to meet evolving needs.

In particular, the Laboratory will use its inherent flexibility to accomplish new tasks in Heidelberg by recycling existing resources. The introduction of a new Developmental Biology Programme, the initiative towards even greater interdisciplinarity and the enhancement of the visitors' programme including access to advanced facilities, will be largely funded by measured shrinking through attrition or refocussing of groups in four successful existing Programmes: Structural Biology (including Biocomputing), Differentiation, Gene Expression and Cell Biology.

I am convinced that any further cuts would not only be unwarranted but would endanger what has already been achieved – the seamless robe of mutually supportive EMBL activities, enriched by diversity and an unusual degree of cooperation and interaction at all levels: research, training and development of new technologies in the central Laboratory that is, after all, the bedrock of the EMBL system.

### Major goals

In our final proposal eight major goals have been selected for the next quinquennium.

- Maintenance of the Heidelberg main Laboratory at steady state, by recycling resources to meet new programmatic needs.
- Maintenance of Hamburg at steady state, in a manner that permits its long-term operation.
- Strengthening the service and research operations at the EBI, to meet rapidly increasing demands and to stay abreast of developments in bioinformatics.
- Strengthening the service and research operations in Grenoble, to make full use of the unique opportunities that our collaboration with ESRF creates for European structural biology.
- Enhancing exploitation of the unusual potential of EMBL for inter-disciplinary studies, by reserving some appointments to be made across Programme boundaries in Heidelberg.
- Reinforcement of the links with the scientific communities of the member states, through an enhanced visitors programme in Heidelberg, including increased access to specialised facilities.
- Establishment of a Developmental Biology Programme in Heidelberg, to capitalise on the existing strengths of EMBL in addressing some of the most exciting problems in molecular biology at the multicellular level.
- Contribution to the establishment of a European centre for mouse genetics, through setting up a cluster of research groups at Monterotondo.

### Plans for Sites Outside Heidelberg

### The EBI - Hinxton



The Data Library has been a major achievement for EMBL and has succeeded in attracting substantial external funding. The credibility of its successor, the EBI, and its ability to play a significant role in this rapidly moving field criti-

cally depend on our ability to develop the research environment within which the service programme can prosper; we must begin making soon some research group appointments, complementing the expected increase in EU support for the service programme. We project 4 new group leader additions during the early part of the planning period, heading groups that will be small, as recommended by our ad hoc Advisory Committee for the EBI (January 1994). The searches will be aimed to candidates complementary to the currently existing strength in 3D protein structure and protein sequence analysis. We will seek specialists in genome analysis; mapping and linkage analysis; and molecular evolution.

#### Grenoble

It is widely recognised that the Grenoble Com-

mon Site, of which the EMBL Outstation is part, currently represents a unique concentration of facilities for structural biology world-wide. These include the unparalleled high brilliance beams of the ESRF, which are now coming on line, and the powerful neutron source of ILL, which is again becoming operational.

EMBL has made major contributions in collaboration with both in-

EMBL Outstation building at Grenoble

stitutions, and notably has participated in the construction of the high brilliance beams for crystallography; it provides the biological laboratory support for both sister institutions, and it hosts their visiting biology users. Applications of biologists for use of the ESRF beams are increasing rapidly, lending some urgency to the expansion of the Outstation, which is now possible with the completion of the building extension. Significant applications for EU support are planned. From EMBL funds, we project addition of service staff coupled with recruitment of one additional group leader in crystallography in 1997.

It must be noted that the framework agreement with ESRF should be renewed this year, and specific agreements for individual beam-lines also need to be added. This is an opportunity for our role to be clarified and our contributions to be recognised, in the context of a well-functioning collaboration. In addition, the Outstation is discussing with French institutions in the area possible modes of strengthening interaction, so as to increase synergy for the benefit of structural biology and all institutions concerned.

### Hamburg

The oldest Outstation of EMBL continues to be oversubscribed by users (applications three-fold higher than available slots), and this is expected to continue throughout the decade, as synchrotron ra-

> diation becomes a routine tool for crystallographers. Following the 1994 review, I am convinced that the continuing high level of demand by outside users mandates maintenance of the Hamburg Outstation. This is a very cost-effective operation which cannot be replaced simply by shifting users to Grenoble. The forthcoming commissioning of a new beam line will increase capacity, but per-

"Like most births, the founding of EMBL took time and labour: governments and even some of the scientists had to be persuaded of the need for a European transnational laboratory. Twenty years later, the outstanding success and non-replaceable role of EMBL is recognised by all. Thanks to EMBL, cohorts of top level young molecular biologists reached early responsible independence and developed their research in a dynamic intellectual environment, stimulated by the diversity of Europe. Many, upon leaving EMBL, have established themselves as leaders in universities and research institutions throughout Europe, or in the U.S. Member States provided EMBL with significant yet limited means. EMBL, therefore, could not cover all fields. Plant molecular biology and neurobiology were not among the preferred ones. Inspired by the success of EMBL and EMBO and spurred by the need to overcome structural fragmentation, Europe developed additional systems of collaboration. The European Union promotes networks linking several high level laboratories in common research projects, such as AMICA for plant biology and the Yeast Genome network for the study of chromosomes. EMBL and the EU pursue the same goals by complementary means: their collaboration is natural. The establishment of BIO Data banks is a typical case. In the future, collaboration should increase. An obvious field is the development and support of infrastructures through a close involvement of the scientists who create and use them."

- Paolo Maria Fasella; Director General; Science, Research and Develeopment; Joint Research Center; the European Commission, Brussels -

sonnel is limiting. Within a steady-state budget we expect to restore staffing to the 1994 level, which is the minimum needed for a smooth service operation. This plan makes provision for the appointment of another crystallographer group leader by beginning 1997, in a manner coordinated with planned developments in Heidelberg (see below).

### Monterotondo

The 1990's and beyond will be a period of increased emphasis on mammalian biology. Mapping and then sequencing the human genome will soon reveal the structure of most human genes, but for their functional analysis the use of the mouse as a model system has unparalleled advantages. It is now feasible specifically to mutate any mouse gene and examine the consequences during development of the whole organism. It has become clear

that transgenic and knock-out mouse strains are of enormous value both for the understanding of basic biological processes and for the creation of models of human disease.

For these reasons, the EU has agreed to launch a European Mouse Mutant Archive (EMMA) with a central facility at Monterotondo for collection, storage and distribution of mutant strains, and a second site at Orléans. The plan is for EMMA to be closely associated with a wide network of national facilities, which is still to be formed.

In a related decision, the EMBL Council has agreed to contribute to the success of EMMA

by providing research expertise at the same site; EMBL research groups working on mouse biology are to be established at Monterotondo and selection of group leaders is currently underway. We expect that this EMBL Programme will collaborate closely both with EMMA and with existing and new Italian national institutions to be located on the Monterotondo campus. Beyond its specific scientific value, this should prove an interesting experiment in EMBL complementing and mutually supporting EU and national activities towards a common goal that would be difficult to attain otherwise.

### Plans for the Heidelberg Laboratory

### Structural Biology & Biocomputing

The increasing importance of these fields is well recognised, as are the potential advantages of the EMBL Programme in Heidelberg, because of its breadth (electron microscopy and electron diffraction, NMR, X-ray crystallography, biochemistry and theoretical studies), and the opportunity for close interaction with other in-house Programmes. Given the limited resources, the commitments to two Structural Biology Outstations, and the other needs of the Laboratory it will be necessary to shrink this Programme by attrition over the quinquennium (loss of 3 of the current 16 group leader positions), simultaneously ensuring the further strengthening of its quality.

For this purpose, we intend to recruit as Coordi-

HUB AND SPOKES

Heidelberg

Hinxton

Monterotondo

Grenoble

Hamburg

nator a structural biologist of stature and strong leadership qualities, as recommended by the 1994 review panel. The intention is for this Coordinator to be a senior crystallographer who also serves as Head of the Hamburg Outstation. The group leader to be recruited in Hamburg could then serve as Deputy Head in charge of the day-to-day operation of the Outstation.

This arrangement will be advantageous in multiple respects. It will be coupled with reserving some of the newly added beam time at Hamburg for Heidelberg crystallographers, thus helping interaction between Hamburg and Heidelberg, as well as increasing the attractiveness of the Coordinator

position for a senior crystallographer. At the same time the arrangement will help secure the future of the Outstation while facilitating recruitment of its leadership. Finally, the arrangement will be an opportunity to establish an in-house EMBL Steering Committee for Structural Biology, including the new Coordinator, the Head of the Grenoble Outstation, and the Deputy Head of the Hamburg Outstation. This will help coordination and rational consolidation of our dispersed activities in Structural Biology, optimising the use of resources and facilitating interaction between all three sites.

### Gene Expression and Cell Biology

These successful Programmes have made and continue to make central contributions to the reputation of EMBL. Because of the availability of excellent candidates in the last year, they have been allowed to grow by anticipating future vacancies. They will shrink to or just below the 1993 level, together releasing 4 out of 20 group leader positions.

### Cell Biophysics and Biochemical Instrumentation

These two Programmes are small but serve unique and important functions. The only change anticipated is termination of large scale

electron microscopy development, and use of these resources in Cell Biophysics to recruit someone working at the border between physics and biology. An example would be someone working on the dynamics of complex biological systems such as the cytoskeleton, or on the dynamics of transcription factor and signal transduction complexes. We believe that this type of interdisciplinary input from physics is very timely, and would be especially fruitful in the collaborative atmosphere of EMBL. It would provide a powerful and urgently needed

tool for understanding the behaviour of complex biological systems, where the reductionist approach based on the analysis of individual components is reaching its limit. Close interaction with biologists would ensure the relevance of the quantitative and modelling approaches introduced from physics.

### Differentiation/Cell Regulation and Developmental Biology

Differentiation has been a successful Programme which evolved considerably since its inception in 1982, adapting to changing opportunities in the field. In recent years the Programme has acquired increased emphasis on Development, but by the same token it has not had the resources to cover other centrally important areas. The plan is to add resources saved from other Heidelberg activities (4 groups in total) and split the Programme into two: Developmental Biology (6 groups) and Cell Regulation (6 groups). The two halves will be housed in adjacent space and retain close interactions. Developmental Biology will begin with three existing Differentiation groups and will acquire a Coordinator, before other appointments are made. The other half will be renamed Cell Regulation, in recognition of its broadened focus on the regulation of cell signalling, signal transduction, the cell cycle and growth control, as well as cell differentiation.

Because Developmental Biology will be a new Programme, it is worth examining in some detail its rationale, which has three components: the inherent importance of the field, its appropriateness for EMBL considering existing strengths, and its desirability for enhancing EMBL's involvement with molecular biology at the multicellular level.

> The importance of Developmental Biology is widely recognised. It is one of the frontier fields of modern biology, where major insights have been obtained in the last two decades (including the well-known pioneering studies at EMBL by C. Nüsslein-Volhard and E. Wieschaus 15 years ago), and where major questions still remain, with a high probability for resolution in the coming decades. We now have a broad picture of how the complex pattern of the body plan arises during embryonic development, and how the major classes of regulatory genes oper-

ate in higher organisms. Nevertheless, important challenges remain for the future. How are the detailed decisions coordinated as the body plan becomes more complex during development? What are the system properties of regulatory genes, which seem to operate combinatorially and with high redundancy, and yet yield discrete, alternative decisions? How do functional tissues and organs, rather than simply a collection of differentiated cells, arise? How do multicellular assemblies assume their form (morphogenesis)? How is morphogenesis "canalised", so that it can respond to external signals and yet be largely heritable? Can we understand how the interrelated form and function of a complex organ such as the brain arise? These questions are central to a fundamental understanding of life, and at the same time will be especially important in the next era of genomics and molecular medicine, when the challenge will be not to isolate a gene that underlies a phenotypic trait, but to understand how it determines the phenotype.

The above sketch of Developmental Biology also

"EMBL is a model of a scientific institution in the biosciences. One reason for the tremendously positive impact EMBL has had on the development of molecular biology in Europe has been its flexible organisation with independent research groups clustered together in programmes. This had led to the training of independent researchers in upcoming research areas such as molecular cell biology. This impact has been felt strongly in Germany and in all of western Europe. My hope is that some similar institution could be established in eastern Europe to promote the development of molecular biology in these countries."

- Bert Sakmann, Nobel Laureate, Max-Planck-Institut für Medizinische Forschung, Heidelberg -



Frank Gannon, EMBL's Scientific Coordinator and present Coordinator of Structural Biology

argues for its appropriateness for an institute with the specific features of EMBL. The study of development is multidisciplinary, intersecting with and profiting from studies of multimolecular interactions, cell biology, and cell regulation and differentiation. It draws upon genetics (classical and reverse), standard molecular biology, protein biochemistry and diverse methods of morphological analysis. Developmental biology can be studied effectively in a research centre such as EMBL, where strong programmes in several of these disciplines coexist under the same roof, and where a strong collaborative spirit facilitates multidisciplinary investigations.

Finally, the establishment of a Developmental Biology Programme is an important step toward strengthening our studies of organisational principles of multicellular systems. Here EMBL lags significantly, in contrast to our strength at the molecular and subcellular levels. This gap will become more serious as molecular biology increasingly moves into the study of tissues, organs and organisms. The trend in this direction is already evident and is propelled by a number of causes: successes at under-

standing lower levels of organisation, recent breakthroughs in understanding developmental principles, the coming emphasis on vertebrate and human biology, the emergence of molecular medicine. It is telling, for example, that in its recent report the "foresight" panel advising the UK government on future research priorities in the life and health sciences recently gave top



Senior Scientists Committee Meeting at Heidelberg

priority to "integrative biology," defined as "research integrating molecular biology and genetics with cell and tissue biology and whole organism studies."

Consistent with the above ideas, our Developmental Biology Programme should focus on the elaboration and coordination of developmental patterns, with special emphasis on multicellular morphogenesis and organogenesis. Development of the nervous system could be one specific focus. Topics of interest might include establishment of developmentally relevant cell asymmetries; developmental cell signalling and interactions; cell motility, adhesion and path-finding in organogenesis; redundancy and dominance in developmental regulatory circuits. As already mentioned, the methodological approaches should be broad, including genetics (classical and reverse), standard molecular biology, protein biochemistry and diverse methods of morphological analysis. The choice of organisms is secondary to the conceptual and methodological framework, but should take into account the importance of genetic analysis and of the evolutionary perspective. It is important to include both invertebrate and vertebrate systems, for example Drosophila, mouse and probably zebrafish. Despite the small size of the Programme, there will be room for the future Coordinator to develop his/her own ideas within this general framework – which is viewed as a guide flexible enough to accommodate the most exciting candidates we can find.

### Interdisciplinary Appointments

We intend to reserve three group leader positions, saved from other Heidelberg activities, to complement spontaneous collaborations that are so prevalent at EMBL with interdisciplinary appointments. These will cross Programme boundaries and may facilitate the development of concerted inter-Programme projects. The intention is that two or more Programmes will be able jointly to bid for an appointment of common interest. Several interdisciplinary areas of interest will be selected after discussion in the Senior Scientist Committee, and the final choice

for appointment will be dictated by the quality of the candidates. Once appointed, the new Group leader would have his/her choice of which Programme to be allied with administratively, with joint scientific appointment in a second Programme. The position would not be "captured" by any Programme, but would join the common pool when vacated. We consider

such appointments of great importance for further exploiting the unusual interdisciplinary potential of EMBL and for catalysing research in novel directions. They would also add to the flexibility of the institution, balancing the planned devolution of resources to individual Programmes.

#### The Visitor/Training/Advanced Facility Programme

The consultation exercise, notably my visits to the member states, revealed a marked enthusiasm for an expanded visitors programme in Heidelberg, linked to the training mission and to the use of advanced facilities. This gratifying enthusiasm which is fully consistent with our vision and our increased focus on inclusiveness - is strongest among the smaller states (which see the EMBL as a unique centre that cannot possibly be duplicated at the national level), but is also noticeable in larger member countries. The sentiment we encountered led to the decision to expand and formalise our activities for visitors to the central Laboratory in the next



quinquennium.

In addition to the service functions of the Outstations, the Heidelberg Laboratory has always provided important access to short-term visitors who come for formal training (courses, workshops, conferences), for participation in research activities, or for use of specialised facilities. Such visits are very effective for transfer of technology and ideas to distant laboratories, and for creating collaborative projects. They will be expanded as permitted by available resources, including space.

Outside researchers typically make arrangements for visiting EMBL directly with the pertinent group leader, and this is an appropriate, non-bureaucratic way of operation. However, we have now appointed a small committee to ensure that the visitor/training/advanced facility Programme operates properly as it expands in size. The tasks of the committee will be to coordinate and stimulate course offerings; to disseminate information and help make contacts for potential visitors who do not have contacts in the Laboratory already; and to be the nucleus of priorities committees for selecting applicants for use of advanced facilities, when these are structured so as to provide service without necessarily involving formal collaborations. As we plan the details of the enhanced visitors programme, we will welcome further input from the member states.

We do not have space problems at EBI, thanks to the generosity of the Wellcome Trust and the MRC. Similarly, the recently completed building extension at Grenoble, funded by the national and regional French governments, and with part of the voluntary 1993-1994 contributions of Austria, Israel, Norway, Switzerland and the UK, meets our needs. At Monterotondo, ENI and CNR are making available fully functional space. In Heidelberg, we intend to build a floor extension adjacent to the current Differentiation space. Without this extension, both the Visitors and the Developmental Biology Programmes would be problematic. Fortunately, generous voluntary contributions from Germany and from Land Baden-Württemberg have been announced which, together with a limited contribution from the general EMBL budget, will permit this space extension to take place in 1996.

Currently some office space (formerly belonging to the Data Library) is available in Heidelberg, and progressively additional laboratory space will be released by the planned shrinkage of existing Programmes. While it is too scattered to be of use for the Developmental Biology Programme, this existing space would be ideal for interdisciplinary groups and visitors. It will be placed under control of the central administration, which will make part of it available as needed for visitors of Programmes and facilities. Space and some funds for capital equipment will also be made available for high-demand facilities, such as a center for advanced microscopies and advanced macromolecular (DNA and protein) sequencing facilities.

### Concluding Remarks

The next decade will mark a transition for EMBL, from a period of rapid overall growth to a period of consolidation coupled with targeted growth for selected, clearly justified activities, such as the Outstations, Developmental Biology, and increased outreach to the member states. Part of the agenda that we initially sketched in the Draft Scientific Programme - such as increased interface with medicine and industry – remain to be discussed further. The final plans that we have formulated after the consultation exercise are modest, and represent the minimum that the Laboratory needs to maintain its vitality and impact. In seeking support of our funding partners, we clearly restate our commitment to continuous critical assessment and quality control of the scientific activities with the help of the Scientific Advisory Committee, and persistent pursuit of administrative efficiency, leading to even greater value for money. Most of all, we restate the guiding principles that I stressed in my inaugural address: excellence, cooperation, inclusiveness.

# The Development of Synchrotron Radiation

The successful determination of protein structure is dramatically influenced by the intensity and other properties of X-ray beams directed at a protein crystal under study. In the late 1960s, the best X-ray sources available to crystallographers were of the rotating anode design. Ken Holmes had been attempting to carry out time-resolved X-ray diffraction experiments on muscle fibres, with a view to understanding the molecular basis of contraction. He was frustrated by the lack of progress, due in part to the low intensity of the X-ray beams available to him. He soon became interested in the spectral properties of synchrotron radiation for his experiments. At the time, the Deutsches Elektronensynchrotron in Hamburg was the most powerful synchrotron source in Europe. Holmes joined forces with Jean Witz, an expert on X-ray optics, and Gerd Rosenbaum, a doctoral student, to design, build and install an X-ray window and optical bench on the synchrotron beam line. In 1970, they obtained the first X-ray diffraction pattern with synchrotron radiation. Realising the potential of this method for structural biology, Holmes had already persuaded Sir John Kendrew of the wisdom of including an Outstation at Hamburg in proposals for EMBL. The aim was to take advantage of the synchrotron source to design and build X-ray beam lines and detectors for the community of structural biologists. The laser-like properties of the synchrotron beam enabled high resolution data to be collected from even small crystals. The continuous technical developments made by the EMBL staff, and their dedication to the provision of service to external users, has made the Hamburg Outstation the most productive synchrotron facility for structural biology in the world.

The first applications of X-ray diffraction techniques in the study of biological macromolecular structures were performed in Cambridge and London more than fifty years ago. This method achieved early and spectacular success with the elucidation of the double helical structure of DNA by Crick and Watson. Studies in protein crystallography and muscle proceeded more slowly because of two factors. Firstly, new methods had to be developed for solving the "phase problem" (see inset on page 24). These were pioneered by Max Perutz and first successfully used in the determination of the three-dimensional structures of haemoglobin and myoglobin by Perutz and John Kendrew - EMBL's first Director General. Secondly, the diffraction from such large molecular structures is weak compared to small molecules. It was therefore extremely tedious and time consuming to acquire the X-ray data with a conventional sealed-tube X-ray generator. Collection of the first low resolution data on haemoglobin and myoglobin with precision photography required many months!

The problem with a sealed-tube X-ray generator was that its output is limited by the heat load on a stationary metal anode. Although the anode is watercooled, the power load and intensity of X-ray photons are restricted to about 10<sup>7</sup> photons per mm<sup>2</sup> per second.

The next development in the X-ray generator field fused the techniques of several groups. In 1962, the macromolecular structure group from the Cavendish laboratory moved to the newly established Laboratory of Molecular Biology in Cambridge, where it was joined by a group led by Aaron Klug from Birkbeck College, London. The latter included a young staff member, Ken Holmes.

A rotating anode generator had already been developed in Cambridge, which allowed an overall increase in intensity over a sealed tube, the advantage being the dissipation of the heat created over an increased surface area as the anode rotates. This, however, was a broad focus machine spreading the radiation over a relatively large area. The Birkbeck group had taken over a French design (Beaudouin) of a fine focus X-ray generator from the time which Rosalind Franklin had spent in Paris. These two concepts were fused by Holmes and Bill Longley from Birkbeck, along with the technical skill of Tony Wollard, to produce a fine-focus rotating anode. As might be expected from such a French-English device, the initial machines were somewhat temperamental. Nevertheless, this fusion of ideas led to the manufacture of the first high intensity rotating anodes by Elliot Brothers.

The rotating anodes allowed considerable progress in data collection; Hugh Huxley and his colleagues were able to record the low angle diffraction pattern of striated muscle much more accurately than before. Huxley had started his Ph.D. studies in Cambridge under John Kendrew. After a lengthy and tedious calculation of a haemoglobin Patterson synthesis, he left the solution of the structure to his supervisor and moved on to investigate muscle. Over ten years later, he returned to Cambridge and exploited the Holmes-Longley development. He introduced a focusing system composed of a monochronomator and mirror, which allowed optimum use of the rotating anode. This optical arrangement proved also to be crucial for the first synchrotron radiation experiments.

The system was sufficiently good for Huxley's group to carry out gound-breaking experiments showing differences in the X-ray patterns from frog muscle in the resting and activated states. These experiments required absolute dedication and experimental ability: the detector was X-ray film and many cycles of stimulation, recording and relaxation were required to obtain significant patterns. However, it was still not possible to record sequences of significant X-ray patterns on the millisecond time scale required to follow the process of muscle contraction. The technology was pushed a little further by the production of an anode of large diameter to increase the linear velocity, the socalled big wheel, which increased the intensity of the X-ray beams by a factor of 3-4. However, this kind of physics was at an end. The typically avail-

able intensities were about 10<sup>8</sup> photons per mm<sup>2</sup> per second.

The Introduction of Synchrotron Radiation in Structural Biology

research uscle continued to play a fundamental role in the development of X-ray structural research, providing the motivation for the first use of synchrotron X-ray radiation as a source. In 1968, Ken Holmes took direction of the Department of Biophysics at the Max Planck Institute for Medical Research in Heidelberg. Working on insect flight muscle, Holmes almost immediately became interested in the

possibility of using synchrotron radiation for diffraction studies in the X-ray region based on the theoretical work of Julius Schwinger.

The major advance expected from these early studies was a gain in the intensity of the beam. The parameters of the Deutsche Elektronensynchrotron ring (DESY) in Hamburg suggested that at least a factor of 10 could be gained over a rotating anode. Moreover, the optical properties of the synchrotron beam were very good.

Holmes approached the "F41" group at DESY, led by Ruprecht Hänsel, almost as soon as he moved to Heidelberg. The F41 group was already starting to set up a facility for hard vacuum ultra violet radiation. In 1969, Gerd Rosenbaum, a student from F41, moved to Holmes' group in Heidelberg. They were soon joined by Jean Witz, an expert in X-ray optics. Together, they undertook the first experiments in synchrotron radiation X-ray studies.

# Synchrotron Radiation and the First, EMBL Outstation

The initial studies by Holmes, Rosenbaum and Witz were carried out under extremely restrictive conditions! The work had to be carried out in pairs of shifts (16 hours) on the DESY ring. Within this time, it was necessary to remove part of the vacuum beam line and install the optical elements for the X-ray studies. The sample holder and detector (the wonderful Ilford Industrial G X-ray film, before it became extinct) also had

> to be mounted. Before the end of the 16 hours, the bench had to be returned to its pristine state for the next experiment.

results of The the synchrotron radiation experiments, obtained in 1969 and 1970, were most timely with regard to EMBL. Since 1964, John Kendrew had been the moving force in establishing an EMBL. By the late 1960s, the committee trying to raise support for the laboratory had reached a consensus that a major portion of the activities of the new laboratory should centre on instrumentation, as such large scale developments as EM, NMR, and automated sequencing were difficult to support in typical national laboratories. At a planning meeting in October, 1969, chaired by Huxley, Ken

Holmes presented his first exciting results on muscle diffraction using synchrotron radiation. Synchrotron radiation at DESY and, indeed, neutron studies at the ILL were almost immediately added to the planned programmes for EMBL through Outstations at Hamburg and Grenoble.

Holmes, Rosenbaum and Witz continued experimenting with synchrotron radiation. In spite of almost insurmountable problems, spectacularly successful results were achieved and published in *Nature* in 1971. The paper, entitled "Synchrotron Radiation as a Source for X-ray Diffraction," describes in detail the experimental set-up for these early studies, summarises the theory behind synchrotron radiation A-ray work: a diffraction pattern from insect flight muscle. The muscle pictures were recorded an estimated 10 times faster than was possible on a rotating anode. The experiments at DESY not only made an immediate

"EMBL plays a vital role by bringing together scientists in Europe to reach the critical mass necessary to carry out world class science today. Increasingly important are their meetings and courses that bring the latest techniques and ideas to younger European scientists, as crucial for the enlightened foundation of an integrated Europe."

Synchrotron Radiation as a Source for X-ray Diffraction ROSENBAUM & K. C. HOLMES - 11 00 Ground-breaking 1971 Nature Paper; inset photo of Ken Holmes last year on his 60th birthday

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# What is Synchrotron Radiation?

The use of visible light microscopy for observing objects is limited in resolution (i.e. the secolution objects is limited in resolution (i.e. the smallest features which can be "seen") in two senses. First, the experimental limitation requires that the lens system should be perfect and its aperture large enough to capture and focus all the light scattered by an object. Even if this is achieved, a more serious theoretical limit takes over: it is impossible to resolve features smaller than the wavelength of visible light, roughly 500 nm. The typical size of atoms is of the order of 0.1 nm and in order to resolve these, we require radiation or particles with such a wavelength. Three types of radiation have been successfully applied in achieving this: electrons, X-rays and neutrons. Electron microscopy has been widely used. Neutrons are only used for special cases as they require a nuclear reactor to produce them and are expensive. As with electrons, X-rays have been extensively used as they can also be generated in a conventional laboratory. Amongst many other applications, X-ray crystallography and related diffraction studies have been used to study the atomic structure of matter for approximately sixty years.

A conventional X-ray generator uses a stream of electrons generated by high voltage to bombard a metal, producing an X-ray beam with a wavelength characteristic of the metal target. Copper or molybdenum are the most common targets as they provide radiation of wavelengths 0.07 and 0.15 respectively, roughly equivalent to typical interatomic distances, and therefore ideal for resolving atomic features. There is no lens system available for X-rays (this is the so-called phase problem). The role of the lens is taken over by the crystallographer and a computer.

What is synchrotron radiation? Within High energy physics rings, particle beams, such as electrons and positrons, are circulated in opposite directions in ultra-high vacuum. The path of the particles in the normally circular ring is controlled by a series of electromagnets. The particles are accelerated at close to relativistic speeds. The orbits of the opposing sets of particles are fixed so that they collide at a small number of points around the ring. This allows the observation and study of the sub particles that are produced. Synchrotron radiation was originally observed as an irritating side effect in the operation of such particle rings. As the particles are accelerated around the ring at relativistic speeds, they emit energy in the form of polarised radiation, in the forward direction. The radiation can cover a broad spectral band (wavelength) from microwaves to highly penetrating X-rays. The so-called critical energy or wavelength (above which half of the radiated energy is emitted) depends on the energy and the curvature of the ring. By the late 1960s several rings, such as NINA (at Daresbury in the U.K.) and DESY (Deutsches Elektronensynchrotron) in Hamburg, had critical energies which gave substantial radiation in the 0.1 nm region suitable for diffraction studies.

impact on studies in structural biology, but provided a practical example of how an international molecular biology facility could foster novelty.

Holmes' results paved the way for synchrotron radiation X-ray work at DESY, which then had the most intense source in Europe. Ray Appleyard, the EMBO Secretary General, gave Holmes modest funds left over from EMBO's original Volkswagen Foundation grant to continue work at DESY. The experiments also inspired Huxley to establish synchrotron radiation muscle studies at NINA in Daresbury. Holmes was able to gain the support of the DESY directorate for establishing a second bunker on the DESY ring to be used for X-ray work. This was initially financed by DESY and the DFG (Deutsche Forschungsgemeinschaft). In Hamburg, Rosenbaum was joined by Barrington Leigh, then Rolf Chors and Arnold Harmsen. The beam line optics that were installed were based directly on the experience already gained in Cambridge. All mechanical movements for alignments of the beam onto optics and samples had to be operated by remote control from outside the experimental area because of the danger of particle showers. This was achieved by the use of roughly 100 small electric motors. The focus achieved was 200 by 500 microns, not to be surpassed for a number of years. This created an intensity gain of a factor of 350 as compared to a rotating anode.

The build up of the proposed EMBL Outstation at Hamburg was carried out in two phases. First, the Xray bunker II on the DESY synchrotron itself was built in 1972 to be taken over by EMBL at the earliest opportunity (the EMBL agreement had not yet been ratified). It contained an experimental area itself, plus a support laboratory for sample preparation and workshop facilities for beam line development. However, Holmes already knew that the use of the DESY synchrotron as a source was limited for a number of technical reasons. Work on this ring was viewed as a way to gain vital experience by the time a new storage ring, called "DORIS", was completed in 1975/76. The DORIS ring was designed to carry a much more stable and useful current for synchrotron radiation, and dedicated one-third of its time to the uses of synchrotron radiation (the rest was given to high energy physics experiments, when synchrotron radiation could only be used in parasitic mode). A second building, Bunker IV, on the DORIS ring also went into the EMBL blueprint. This was to be the final EMBL facility and again would contain an experimental synchrotron radiation hall, laboratories, office space and workshops. The building was to accommodate up to fifteen staff in the first instance, a limit imposed by some member states, who were worried about the growing size of the planned laboratory.

After the go-ahead from the DESY directorate for Bunker II and the incorporation of the Hamburg Outstation into the EMBL plans, Holmes continued to run the operation in Hamburg and made courageous decisions about committing what were then virtual funds! The experience gained by Holmes, Rosenbaum and their colleagues during this time was fundamental to the progress made at the Outstation later.

In a spirit of scientific generosity, Holmes essentially handed synchrotron radiation research in Hamburg to EMBL on a plate. On April 21, 1975, the agreement setting up the Hamburg Outstation was signed by DESY Director General Herwig Schopper, EMBL Director General Sir John Kendrew and DESY Director of Administration Heinz Bergaus. The Bunker IV building was completed in 1976 and staff recruitment began. Victor Renkwitz was appointed to organise the mechanical workshop and continues to provide excel-

lent support to this day. Heinrich Stuhrmann was appointed first Head of Outstation. Holmes would remain a major supporter of the Outstation from his position at the Max Planck Institute in Heidelberg and continued to row on the Neckar River!

Setting up a truly functional facility supporting in-house and visitors' research demanded dedication and hard work. DORIS I started up in 1976 and EMBL has since designed and built other beam lines for small angle scattering, EXAFS Mossbäuer spectroscopy and later protein crystallography. There are currently six beam lines operational at the Outstation. All are dedicated to molecular biology applications.

The development of synchrotron radiation as a methodological tool for structural studies by Ken Holmes and his colleagues vastly

improved the ability of biophysicists to analyse molecular biological structures. Synchrotron radiation is still the most efficient and productive source of radiation for these kinds of studies. The combination of the creativity in adapting this radiation to biological research and the courage to organise the Outstation for European scientists remains one of the most important scientific accomplishments associated with the European Molecular Biology Laboratory.

#### A Look to the Future

A swe look into the future, one sees an ever increasing role for synchrotron radiation in biological research, reflecting an ever increasing interest in the atomic structure of macromolecules and complexes. Indeed, biology is about to experience a paradigm switch engendered by the genome sequencing projects. The reductionist programme foresees a progression of understanding, spanning molecules to organisms. Within a few years genome sequencing projects will provide us with a complete menu of all DNA, RNA, and protein molecules in a number of organisms and will thereby define the canonical inventory of life. To make full use of all these data is a major challenge to cell biology. In particular, we will need to understand the macromolecular interactions which control cell signalling and gene activation in their exquisite precision. The prerequisite to a predictive understanding of such interactions will be a detailed and accurate description of the structure of the relevant macromolecules. At present, only X-ray protein crystallography

> yields a molecular anatomy of adequate resolution for this task. Thus, there would seem to be a need for thousands of X-ray crystallography groups working on proteins if full use is to be made of the flood of genetic information arising from the sequencing projects. However, the methodology of X-ray diffraction is already stretched: conventional Xray structure determination is inadequate to deal with large protein complexes and organelles. Moreover, crystallization is difficult and often yields exclusively small crystals which diffract weakly.

Synchrotron radiation has been of inestimable importance for extending the scope of X-ray diffraction methodology. The laser-like optics and tremendous brilliance allow Xray diffraction data to be collected from ever smaller crystals of ever larger complexes and organelles. "In-

sertion devices" (wigglers, undulators) placed in the circulating electron beam of electron storage rings greatly enhance performance. The brilliance and unlimited bandwidth of synchrotron radiation make it possible to obtain data using the *Laue* method, which enables a full set of diffraction data to be obtained in fractions of a second. Thus, in favourable cases, enzy-matic processes can be investigated structurally with high time resolution. The first of such investigations was carried out at the Hamburg Outstation.

The success of the initial experiments at DESY quickly led to "second generation" laboratories - from DORIS to those in the U.S., England, France, and Japan. The joint success of these laboratories has led to the spawning of "third generation facilities," dedicated storage rings highly optimised for producing radiation. Grenoble (ESRF) and Argonne (APS) will extend the methodology by orders of magnitude. These developments bode well for the future of structural biology.

- Keith Wilson -

"The EMBL has made a dramatic contribution to the establishment of molecular biology in Europe. One of its successes is the development of supranational infrastructure core facilities dedicated to specific research areas. The network of these facilities is a model that should be extended and located in various sites in Europe."



Ken Holmes at the Hamburg Outstation

# A Twenty Year Journey Through the Cell Membrane Traffic Research at EMBL

The study of membrane trafficking at EMBL has a twenty year history. In this time, EMBL researchers have spearheaded the molecular approach to cell biology. When Kai Simons and his collaborators Henrik Garoff and Ari Helenius joined EMBL in 1975, they brought with them a simple enveloped virus, Semliki Forest virus. They used the viral membrane to find out how plasma membranes are made and to follow the biogenesis of viral glycoproteins. This led to the mapping of the pathway followed by membrane proteins from the endoplasmic reticulum through the Golgi complex to the cell surface. They also investigated how the virus infects the host cell, discovering the endocytic route for virus entry. These findings proved generally applicable to other viruses, such as influenza virus. Successive research groups of the Cell Biology Programme have pursued spin-offs from these studies, for example, the use of viral glycoproteins to elucidate the organisation of the Golgi complex and the details of the endocytic pathway. EMBL scientists also applied the viral approach to the polarised MDCK epithelial cell line introduced to EMBL by Daniel Louvard. This enabled exploration of the biogenesis of the epithelial cell surface via the polarised delivery of membrane components. The strategy has recently been extended to neurons. The polarised endocytic and transcytotic pathways have been mapped in both epithelial cells and neurons and the molecular mechanism responsible for the polarisation of these pathways is being investigated.

uring the early 1970s, with the European Molecular Biology Council closing in on the agreement to establish EMBL, the EMBC laboratory committee was outlining the first scientific programme for the new lab. It included a Division of Cell Biology. At the time, there were few biologists using a molecular approach to elucidate cell organisation. In fact, cell biology was essentially still a morpho-

tific career. He ran into another Finn in New York,

Leevi Kääriäinen, who told him about an insect virus

he might use - the Semliki Forest virus. There is a

simple elegance to the Semliki Forest virus - it is

logical study of the parts of the cell, with microscopic description serving as the main methodology. The EMBL plan therefore looked more toward the future, hoping to capitalise on new techniques and methodologies.

During this time, biochemists were working out the general structure of biological membranes, but almost nothing was yet known about how these membranes assembled. Kai Simons, a young Finnish biochemist, was completing a postdoctoral project on serum proteins at the Rockefeller Institute in New York. Simons was casting about for a new problem that might provide a productive niche for his scienessentially a nucleocapsid, consisting of RNA and one single protein, surrounded by a membrane made up of a lipid bilayer and another single protein. Simons saw the Semliki virus as a prototype he could use to find out how plasma membranes are built. He took the virus model back to Finland to set up his laboratory and fill the niche he sought.

Simons and Kääriäinen collected several gradu-



Kai Simons in 1994

ate students, including Henrik Garoff and Ari Helenius, to work on the Semliki system. In the meantime, the EMBL agreement had been ratified and Kendrew, the new Director General, had begun recruiting scientists for the lab. He offered Simons a position with plenty of independence and support. Faced with funding problems at home, Simons accepted the offer, bringing Garoff, Helenius and the Semliki system with him. They did not know it at the time, but enveloped viruses were to become the single most important thread running through EMBL's cell biology research. Simons, Helenius and

Garoff were convinced that the

enveloped virus held the key to unlocking the question of how membranes are assembled. The premise was straightforward: a virus turns infected cells into a factory for making more viruses and, instead of hundreds of different types of cellular proteins being made, infected cell makes only a few types of viral proteins in very large numbers. Given the techniques available at the time, the protein signal could then be easily followed.

Simons' group initially continued their work on the structure of the virus itself, which they believed would give insights into how the virus functions. One goal was to take the virus apart and put it back together again. These studies led to experiments with detergents to disassemble the virus (their methodology using detergents on membranes has since become a citation classic). As is often the case in fundamental research, Simons and his colleagues came upon unexpected results: they discovered that clusters (or micelles) of viral membrane proteins elicited an immune response several orders of magnitude higher than that obtained using conventional preparations of viral proteins. This offered medical benefits in the form of improved vaccination technology.

Their next challenge was to understand how enveloped viruses infect cells. At the time, it was believed that viruses entered cells through their plasma membranes, then moved through what is called the endocytic pathway-

a route normally involved in the uptake of nutrients. The accepted view at the time was that the endocytic pathway led directly from the cell membrane to the lysosome; the problem with this model was that the lysosome is full of enzymes that normally degrade viruses. It was difficult to understand how a pathway leading into this hostile environment could result in productive infection. Ari Helenius and others at EMBL and elsewhere solved this apparent contradiction by showing that the virus evades the lysosomal defence mechanism; instead of going directly into the lysosome, it enters the cell cytoplasm through an earlier compartment called the endosome. They learned that the low pH in the endosome catalyses the fusion of the viral and endosomal membranes, thus expelling the nucleocapsid into the cytoplasm and infecting the cell. This mechanism enables the virus to release its cargo of nucleic acid without being exposed to the digestive enzymes in the lysosome. This was a major discovery, which proved generally applicable to other viruses that use the same "Trojan horse" trick to infect cells, such as influenza virus.

The simplicity of the viral system had given EMBL scientists the necessary tools to take the first steps in a new direction. Before 1977, the Semliki virus had been the centre of study, but once experiments had turned to the way the virus binds to the cell surface and moves through the endocytic pathway, the focus of study shifted to the cell itself. At EMBL, the endocytic pathway experiments were a symbolic turning point for the move into modern molecular cell biology.

These years were a transition period for all of cell biology, with the first molecular methodology being developed in a few isolated institutions throughout the world. Many of the changes were being pioneered by younger scientists. And, clearly, Simons, Garoff and Helenius were not alone in engineering EMBL's transformation. Simons, who had been paying close attention to this trend, had quietly sent a series of letters to like-minded young scientists, encouraging them to apply for the lab's many new independent positions. Most of the scientists who answered the call were trained as biochemists, but each of them was already moving intuitively towards a molecular study

of cell organisation. EMBL quickly found itself in the vanguard of this scientific movement.

In order to proceed further, the new recruits brought or developed new tools such as immunofluorescence microscopy, new viral and experi-

mental cell systems, antibodies, fractionation and recombinant DNA techniques, and assays to measure the complicated processes occurring in organelles. These tools allowed EMBL scientists to undertake a formidable range of membrane traffic studies. The problem of how proteins are transported into and out of the cell (the endocytic and exocytic pathways) were the first projects that the new cell biologists attempted to address. The membrane focus then led to studies of the transport through and the function of such organelles as the endoplasmic reticulum and Golgi apparatus. Research on immune responses and how transport differs in polarised epithelial cells were also added to the early agenda.

### Outlining the Basic Traffic Patterns for Membrane Proteins

O ne of the first new recruits to arrive was Bernhard Dobberstein. Like Simons, he was returning to Europe from New York, where he and Gunther Blobel had begun to develop pioneering assays to study protein translocation across the membrane vesicles derived from the endoplasmic reticulum.

"The establishment of EMBL has been one of the most exciting developments of molecular and cell biology that has occurred in Europe. It has provided an outstanding environment for high quality research and training, particularly for younger scientists, and acts as an excellent role model for an integrated and collaborative approach to science in Europe."



EMBL Cell Membrane Group - 1981

Dobberstein and Henrik Garoff used these assays to demonstrate that the membrane proteins of the Semliki Forest virus are inserted into the membrane of the endoplasmic reticulum during their biosynthesis and then transported via the Golgi complex to the plasma membrane. Although there were doubts expressed at that time about the validity of using virus proteins as model systems, these were laid to rest when Dobberstein showed that a mouse histocompatability antigen followed exactly the same rules of assembly in the endoplasmic reticulum. This also led directly to the first complementary (c) DNA sequence of a mouse histocompatability antigen by Kvist, Dobberstein, and collaborators.

Graham Warren, who came to EMBL shortly after Dobberstein, and Gareth Griffiths, a new electron microscopist, combined forces early on to detail the mechanisms of cell organisation and membrane proGolgi apparatus. The existence of this new compartment was confirmed by Warren and John Tooze using coronavirus, another enveloped virus which has the unusual feature of budding not at the cell surface, but into this "intermediate compartment." Subsequent work by others has shown that this compartment performs an important quality control function for the exocytic pathway by regulating precisely which proteins are allowed to leave the endoplasmic reticulum. Without the viral transport studies, however, the existence of the intermediate compartment might have been entirely overlooked.

Simons and his group found that, at a slightly higher temperature (20°C), the viral proteins accumulate in another new compartment on the exit side of the Golgi stack. This is now called the trans Golgi network. Following this discovery, work by Griffiths, Simons and others showed that this compartment is crucially



Tony Hyman Andy Ziemiecki Kai Simons Thomas Kreis Steve Fuller Carol Featherstone Brigitte Jockusch Mark Mars Gareth Griffiths Graham Warren Ari Helenius Matti Sarvas Daniel Louvard Hubert Reggio Karl Matlin

tein transport. Again, Warren and Griffiths took advantage of the viral system, tracking the progress of membrane proteins through the exocytic pathway. Like most enveloped animal viruses, Semliki Forest virus populates the plasma membrane of the infected cell with its own membrane proteins, the spike proteins, and then leaves the cell by wrapping itself in the cell's plasma membrane, a process called budding. Warren and Griffiths applied the newly-developed method of immuno-electron microscopy, using thawed frozen sections in conjunction with biochemical approaches, to show the path that the viral spike proteins take through the cell. This new technique offered a much more dynamic view of the cell than conventional electron microscopy, because for the first time specific proteins could be localised to particular organelles. Warren and Griffiths used low temperatures and drugs that inhibit protein transport to show that the viral proteins move from the endoplasmic reticulum, through each compartment (cisterna) of the Golgi stack, to the plasma membrane. This was the same pathway already shown for cellular secretory proteins, but mapped in finer detail than had ever been possible.

This kind of approach led to the identification of new compartments of the exocytic pathway, which were not obvious based on structure alone. At low temperature (15°C), the spike proteins were shown by other scientists to accumulate in a tubulo-reticular structure between the endoplasmic reticulum and the involved in sorting proteins to their correct destination and that proteins destined for lysosomes and secretory granules are separated from plasma membrane proteins and packaged into distinct vesicles at this site.

### Another Level of Complexity: The Polarised Epithelial Cell

nother new recruit was Daniel Louvard. While working at the University of California at San Diego (UCSD) with Jonathan Singer, Louvard had become interested in how certain types of cells, such as kidney or gut epithelial cells, are "polarised," maintaining a difference between two types of surfaces. In such cells, the apical surface and the basolateral surface have dramatically different morphologies and perform distinct functions. Singer encouraged Louvard to use the kidney "MDCK" cell line to study the different membrane domains. On his way to his new post at EMBL, Louvard visited David Sabatini and Enrique Rodriquez-Boulan in New York, who by chance were about to publish data showing that different enveloped animal viruses budded from different membranes in MDCK cells. When Louvard arrived at EMBL in 1978, he brought both new immunofluorescence techniques and the MDCK cells, which would prove to be the model system for the next major step in EMBL's membrane transport studies.

At EMBL, Louvard began investigating the development and maintenance of polarity, as well as
intracellular transport and secretion in the MDCK cells. Within a year, he presented the first evidence that, like the virus proteins, the MDCK cells' own endogenous proteins have a polarised distribution. The experiments also proved that membrane proteins at the cell surface recycle, going rapidly into the cell and back out again. This process would later be shown to be critical for antigen presentation in immune responses. This work clearly established the MDCK line's value as a model system.

The new immuno-EM techniques that were introduced by Griffiths provided the means of localising proteins to particular organelles on the secretory pathway. The organelles, however, could only be identified by their morphology. Louvard realised that in order to dissect these organelles in better detail, new tools were required. He began to raise antibodies to isolated organelles, such as the endoplasmic reticuBy the end of the 80s, the knowledge gained from studying viral protein transport in epithelial cells was applied to a very different type of polarised cells neurons. Carlos Dotti and Simons showed that cultured neurons use mechanisms that are remarkably similar to those employed by epithelia, as a method of delivering proteins to axons and dendrites. This implies that the basic mechanisms of generating cell polarity follow universal rules. It also suggests that what is learned from studying kidney cells today may one day be applied to treating neurological disorders.

## From Pathways to Molecules

As the basic pathways of protein transport took shape, EMBL investigators began to ask questions at a more molecular level. They wanted to know, for example, what is different about the vesicles des-



: Marsh Stella Hurtley Carl-Henrik von Bonsdorff Kristian Prydz Oddmund Bakke Sanjay Pimplikar Isabelle Vernos Bernard Hoflack John Armstrong Rafaele Matteoni Patrizia Rosa Marino Zerial Christian Vannier Fotini Gounari Ed Hurt

lum, the Golgi apparatus, and lysosomes. These antibodies provided valuable markers to study the passage of the transported proteins. Such painstaking developments have since become a hallmark of the EMBL approach to cell biology, an approach which would not have been possible in traditional university environments, where immediate results are required for continued grant funding. More than ten years later, many EMBL-developed antibodies are still widely used to study intracellular traffic.

In the early 1980s, Simons and his group also began exploiting the MDCK system and the newly developed antibodies to great effect. This time Simons applied the Vesicular Stomatitis virus to the cell line. Using the two viruses that bud at opposite surfaces of MDCK cells, Simons asked where in the transport pathway, the two diverge. He and his group were able to show that the decision to send the viral spike proteins to one of the two membrane domains is taken at the trans Golgi network, where different spike proteins are packaged into different vesicles. The mechanism for this sorting is still a subject of intense investigation around the world. tined for the different surfaces of a polarised cell. But again, new tools were needed. Using conventional techniques, it was impossible to separate different membranes of similar density, such as the vesicles formed at the trans Golgi network. Taking advantage of another EMBL-style investment in technology, Kathryn Howell's group developed immuno-affinity methods to pull out the different membranes using specific antibodies bound to magnetic beads. Viral spike proteins again provided the basis for the technique, which has today made it possible to study the biochemistry of organelles with otherwise similar physical properties.

Cell-free systems that reconstitute cellular processes also became an important new tool. Studying the molecular mechanism of endocytosis, Graham Warren's group was the first to show that the early stages of endocytosis could be reconstructed in a cell-free system. This work was continued at EMBL by Jean Grünberg, using the immuno-affinity methods he developed in Howell's laboratory. As a new group leader, Grünberg, in collaboration with Griffiths, was able to identify the vesicle which transports proteins

"EMBL serves as a model for a very vigorous international collaboration in molecular biology. In addition to the many important discoveries that have been made there, this lab has educated a large cohort of outstanding young people, who promulgate its uniquely interactive style as they move to occupy important research positions throughout Europe." from early to late endosomes and to show that this process is dependent on the cell's microtubule cytoskeleton.

Marino Zerial showed that endocytosis is regulated by a large family of small GTPases, the Rab proteins. These proteins use cellular energy in the form of GTP to ensure unidirectional flow of protein transport. In addition, they appear to give specificity to protein transport, regulating the docking of transport vesicles with the correct membrane. Since there are scores of specific vesicle docking steps, there are scores of different Rab proteins localised to different membranes. Most of these have been cloned, sequenced and localised at EMBL, largely by Zerial's group along with Rob Parton. The role of GTPases as regulatory switches is fast becoming a new paradigm in cell biology and once again EMBL is at the vanguard of this field.

Earlier research in protein transport had fo-

present in sequences in its cytoplasmic tail. They have recently shown that even this address tag can be regulated - phosphorylation turns it off.

Other address tags were found to be more subtle. Wieland Huttner set up the first cell-free system to study the formation of secretory granules. He found that the overall properties of their proteins, rather than a specific tag, lead them to aggregate with each other in the presence of calcium ions and low pH. This "condenses" granules in the milieu of the trans Golgi network. Gerrit Van Meer and Simons also proposed that some proteins are sorted on the basis of their association with lipids. They found that some proteins destined for the apical membrane in epithelial cells associate in clusters, or "rafts," with glycolipids, which are themselves polarised in these cells. They have put forward a novel idea suggesting that these glycolipid rafts deliver proteins to the apical membrane.



 Bernard Hoflack
 Ann Mutvei
 Petra Schrotz
 Ute Hamann
 Lukas Huber
 Rob Parton
 Carlos Dotti
 Eric Karsenti

 Briggite Brake
 Jean Marc Berrez
 Angus King
 Vesa Olkkonen
 Johan Peränen
 Liane Meyn
 Bernhard Dobberstein

cused on finding chemical address tags, which are carried by proteins to ensure that the proteins reach their destination within the cell. These tags are important from the very beginning of membrane transport. When the mRNA sequence is read into a membrane protein by ribosomes, a signal sequence is revealed, which addresses the new protein for insertion into the endoplasmic reticulum. The protein complex that recognises this sequence is the signal recognition particle (SRP). David Meyer and Dobberstein showed that once SRP has bound to the signal sequence, the whole complex binds to a "docking protein" on the membrane of the ER. This work explains how the cell distinguishes between membrane and cytoplasmic proteins and inserts only secretory and membrane proteins into the endoplasmic reticulum.

Other address tags are important for delivery of the transported proteins to their final destinations. The first address tag to be identified is still the best understood. Outside scientists showed that lysosomal enzymes are modified with an unusual sugar, mannose-6-phosphate. This sugar is recognised by a membrane receptor, which brings the proteins to the lysosome. Working on the question as a postdoc with Stuart Kornfeld in St. Louis, Bernard Hoflack recognised that the question had merely been set back one protein - what "addresses" the receptor to the lysosome? Hoflack then came to EMBL, where he showed that the receptor targeting information is

Protein transport studies at the molecular level continue to be a major thrust of Cell Biology research at EMBL. The goal now is to understand how all the different components of the transport machinery interact in the context of the intact cell. One major question is how vesicles include cargo and exclude resident proteins. Here, vesicle coat proteins play an important role. Thomas Kreis discovered one of the coat components and many more have since been identified. New questions beg to be answered. How does the vesicle fusion machinery confer directional membrane flow? How do the receptor proteins which recognise the address tags actually lead to movement of the vesicles containing the cargo protein to the appropriate cellular compartment? Answering these types of questions requires a more holistic approach to protein transport. This is the next challenge for the programme.

The impact of Cell Biology at EMBL on membrane transport studies owes much to the vision of Kai Simons and the interactive environment he fostered. Most of the scientists, especially in the early days, began their careers at EMBL under Kai's watchful eye and are now back in their home countries pursuing work that they started at EMBL. This method of fertilising a new field has succeeded beyond all expectation. As an example of European cooperation it is a model to all.

- Janis Burkhardt, David States and Graham Warren -

# A Turning Point in the History of Developmental Genetics

The publication of a single paper in Nature in 1980, entitled "Mutations Affecting Segment Number and Polarity in Drosophila," revolutionised the field of developmental genetics. The two authors, Christiane Nüsslein-Volhard and Eric Wieschaus, working together in a small laboratory at EMBL, had systematically searched for mutant genes that affect the formation of segments in the eggs of a small fruit fly. Their goal was to identify all of the genes of this type and, through them, understand the processes that govern development in the Drosophila embryo. It was a novel and courageous approach. Few scientists had bothered to look at embryos by genetics, and fewer still believed that such a task was manageable. Nüsslein-Volhard's and Wieschaus' techniques, as often is the case in good science, were deceptively simple. Their patience and care in conducting massive screenings of embryos and the intuition that led to their conclusions were superb. The two scientists identified an initial set of 15 lethal mutants in this seminal paper. More importantly, they categorised the mutants as representing three different types of genes, which they believed controlled an increasingly complex organisation of the organism. The paper was a turning point in the history of developmental biology and set off a chain reaction of impressive research on development, first in Drosophila and then in other organisms, including vertebrates. The work also helped build a bridge between the fields of developmental genetics and cell biology. Note added in proof: Nüsslein-Volhard and Wieschaus have been awarded the Nobel Prize in Physiology or Medicine for the work described below.

How is the progressive development of a living organism controlled? What are the rules that govern the early organisation of an embryo and the subsequent creation of ever more

complex structures in the mature organism? Are they interrelated? Geneticists have studied the small fruit fly *Drosophila* since the beginning of the 20th century, exploring questions about inheritance using what we now call classical genetics. But serious progress in establishing the connections between genetics and the progressive development of an organism is relatively recent.

By the mid 1970s, a number of biologists had turned serious attention to *Drosophila* development. Certain mutations in the adult fly, like the "Bithorax complex" (mutations leading to development of two sets of wings) and the "Antennapedia complex" (substitution of legs for antennae), had caught attention as a way to

explore how insects develop. The concept of cell lineage "compartments" in developing structures had gained support. Almost all of this research concentrated on the determination and development of the structures of the adult fly. Although a number of known mutations affected embryonic development, most research involving embryos tended to focus on tracing back a single mutation from the adult backward. No one had yet taken a comprehensive approach to investigate mutations affecting the em-

> bryos themselves. After all, most of these mutations killed the embryos; few scientists considered them as a key to understanding how normal development might work.

# Nüsslein-Volhard and Wieschaus Meet in Basel

C hristiane Nüsslein-Volhard and Eric Wieschaus were among the very few who did. These two scientists met each other in 1975 in Walter Gehring's laboratory in Basel, Switzerland. Nüsslein-Volhard had been trained as a biochemist and had gone to Basel to understand the genetics of fly development. Wi-

eschaus was finishing his own Ph.D. work with Gehring and ready to leave for postdoctoral work in Zurich. The two immediately established personal and professional rapport, and began discussing their common interests in studying *Drosophila* embryos. They would remain in close contact with each other,



even after Wieschaus had left Basel for Zurich and after Nüsslein-Volhard had left for a second postdoc in Freiburg.

Normal *Drosophila* embryos are elongated ovals, but they soon divide along one axis into distinct segments. One end of the embryo eventually develops into a head region (anterior), the other the tail end (posterior) of the fly, with the segments in between forming the thoracic and abdominal regions of the fly. In the mid 1970s, one of the few known embryonic mutations was *bicaudal*, a "maternal effect" mutation that created a mirror-image duplication of the posterior at both ends of embryos laid by mutant females.

The *bicaudal* mutation piqued the interest of Nüsslein-Volhard and Wieschaus. They began to ask themselves how the embryonic pattern, the number and special properties of the segments, are determined? How do they become different over time? They asked themselves if maternal effect genes are unique as developmental determinants, or whether genes expressed in the embryo (zygotic genes) also contribute essential information. Did one gene explain formation of the segmental pattern, or was there a family of genes? More importantly, was it possible to determine what each "pattern formation" gene was doing by studying its mutations?

As is often the case with major scientific breakthroughs, innovative ideas often flow against the intellectual tide. Today, the connections between

early segmentation of the Drosophila embryo and development of the body structure in the adult fly might seem quite obvious. But this was not the case in the mid-1970s. At the time Nüsslein-Volhard and Wieschaus began to travel down this road, there were few other scientists who believed their course would be fruitful. Despite this scepticism, Nüsslein-Volhard and Wieschaus chose to focus their research on the identification of the genes that affect gross

morphology of the embryo. Their basic faith that they could understand *Drosophila* development by studying mutant embryos was unusual, but it led quickly to a major scientific breakthrough.

# Intellectual Courage and Research Independence

This choice of research programme was particularly courageous for two scientists who were at an early stage of their career, when gambles can be very costly. However, if the courage of their own convictions was critical, EMBL played an important enabling role. In 1978, the laboratory was still recruiting its first wave of group leaders. On the basis of strong recommendations by their previous research supervisors and others, both Nüsslein-Volhard and Wieschaus were invited to take independent Scientist positions in the new EMBL's Division of Cell Biology, where they would be free to follow their line of research.

Already at this time, EMBL's basic philosophy was to recruit bright young researchers and give them the freedom to pursue their ideas. Early independence was considered a fundamental correlate to creative research. The two scientists were given a small laboratory space in EMBL's main building the small size of which has taken on almost mythical proportions in the folklore of Drosophila researchers. If their laboratory was small, however, they had no teaching responsibilities, no grants to write, and no major professor's dictates to follow. Nüsslein-Volhard and Wieschaus were already good friends and EMBL was an environment that encouraged collaboration. Despite two strong personalities and professional equality, which could have easily prompted them to pursue separate research directions, they decided to collaborate. This decision was fateful for the discipline of developmental biology.

Nüsslein-Volhard and Wieschaus were initially interested in very broad morphological questions about the embryo. Prompted by *bicaudal*, they wanted to explore how the pattern of development is already determined during oogenesis by mater-

> nal-effect genes. They thought that segmentation probably also required the expression of zygotically active genes. They did not, however, have any idea how many maternal or zygotic genes might be required for segmentation, what the relative importance of these different types of genes was, or if they had any role in later development of the fly. When they began working with mutations of maternal effect genes, they quickly realised that this

represented a massive undertaking because it meant sorting (screening) thousands of flies in three successive generations. And, frankly, the original screens they devised for maternal genes simply did not work.

# A Search for All Zygotically Active Mutants: The "Saturation" Screens

N üsslein-Volhard and Wieschaus decided to change tactics and screen first for zygotically active mutants, which would be detectable more easily in two generations. The logic of their screen was simple: mutants in genes that are essential for



embryonic pattern formation should lead to embryonic lethality. Still, the specifics of the screens were not straightforward, especially as they had made the critical decision to search for all of the genes responsible for spatial organisation of the embryo, rather than being satisfied with studying one or two mutants. Without this decision, their work would never have had its current impact. As we now know, the genes which they found through tireless "saturation" screens proved to work together in a step-wise process to form the embryo and, indeed, to support the overall development of the fly. Their decision

tuated with stimulating discussions made possible by the use of the dual microscope. Nüsslein-Volhard and Wieschaus often found themselves debating whether a particular embryo constituted a new mutant or discussing how a gene might be functionally relevant. These discussions were often continued during dinner at the nearby farm restaurant, Bierhelderhof, before returning to the lab for the "night shift." More screenings, more discussion, and more thinking about what it all meant. After screening through half of the fly's genome, 15 genes affecting segmentation had been discovered, plus another

meant that they would have to do screens on a very large scale, involving the study of progenies of thousands of individual flies for two generations (required to bring the mutations to homozygosity). Then they would have to search through very many eggs for dead embryos with segmentation defects. Furthermore, in order to make these screens practical, they had to develop new methods to make the embryos transparent so that their pattern would



The "Bierhelderhof" Restaurant, where discussions between "shifts" of saturation screens took place

be easily visible. Again, the methods they devised were relatively simple, but essential for detecting mutants on a mass scale and for describing accurately the overall pattern defects.

For a year, Wieschaus and Nüsslein-Volhard (later joined by Gerd Jürgens as a postdoc) sat opposite each other, day after day, at a table in their small laboratory, carefully examining a microscope stage filled with new stocks of Drosophila embryos. They used a special dual microscope, simultaneously observing the same embryos. Because their goal was to identify every gene involved in forming a proper embryonic pattern, the search had to be massive: no one knew how many genes to expect and there was fear that the numbers might be unmanageable. And it was important to describe carefully the phenotypes of the abnormal embryos to give clues as to what could be wrong in each case. As Nüsslein-Volhard now recalls, "It was a very difficult, but very exciting task. It also was great fun, as so many interesting discoveries were made."

These tedious "saturation screens" were punc-

distinct categories. They called them gap, pair-rule, and segment-polarity, depending on what was missing from the embryo: a large domain of the body,

smaller domains spaced every other segment, or

50 or so affecting other

A New Paradigm for

**Embryonic Development** 

R emarkably, the phe-notypes could be

easily classified into three

notypes could be

aspects of the pattern.

even smaller domains within each segment. As they continued to accumulate more mutants, it became clear that they all fell into one of these three distinct categories, even if details (e.g. the exact borders of the missing domains) differed.

Wieschaus and Nüsslein-Volhard believed that their exhaustive screens disproved the traditional view that the details of the body plan are already laid down by maternal effect genes. They proposed, instead, that embryos develop from much simpler beginnings, using a few maternal-effect genes and a larger number of zygotic genes. Most importantly, coupling careful observation and a good dose of brilliant intuition, they concluded that the tripartite classification of the zygotic genes reflects stepwise refinement of the body plan of the fly in early embryogenesis. The genes disrupted in gap mutants, they decided, affect broad regions of the embryo; pair-rule genes then operate on smaller regions that are spaced two segments apart; and finally, the segment-polarity genes affect part of each individual segment. They suggested that these three

"EMBL is a place where the major discoveries are being made, a breeding ground where talent can mature, a meeting place that vibrates with excitement, a prolific source of high-level training courses, a major source of new technology and bioinformatics, and all these are important functions of EMBL. The most important, however, in my perception, is its model function. This is how top science should be done, this is how a centre of excellence should be run. EMBL sets a unique example of quality, flexibility and efficiency in a European landscape where scientific mobility is low, where tenure comes early but scientific independence late, and where narrow national quota and bureaucratic procedures impede scientific excellence. By setting an example EMBL has been a source of inspiration for European molecular biologists."

- Piet Borst, The Netherlands Cancer Insitute, Amsterdam -

types of genes were responsible for a progressive subdivision of the embryo, starting with a rough sketch of the embryo body pattern and then filling in finer and finer details as two new waves of genes become active.

The paper was immediately accepted by Na-

ture. It greatly impressed many developmental biologists, although, as is often the case with innovative new work, it was not universally appreciated. As carefully as their observations had been made, Nüsslein-Volhard's and Wieschaus' theories were still derived from descriptive analysis of phenotypes. The molecular studies that would prove them unequivocally correct came later, both from

their own labs and those of a rapidly expanding group of scientists who would henceforth combine molecular and genetic approaches.

## An Historical Turning Point in the Study of Embryology

Wieschaus' and Nüsslein-Volhard's work was momentous in itself and it tore down a perceived barrier to research in this field. Before 1980, studying embryology had seemed a hopeless task. Suddenly, with a few key steps understood, it looked simple. A wave of new researchers were stimulated to search for other *Drosophila* (and, later, nematode and mouse) mutant genes affecting development both zygotic and maternal-effect.

Soon afterwards, molecular biology cloning techniques allowed many developmental mutants to be characterised at the molecular level. Many were shown to code for transcription factors, thus explaining how they can directly control subsequent chapters in the embryo's developmental programme. Others were shown to be involved in signal emission, reception or interpretation by the interacting cells of the embryo - thus explaining how the complexity of the embryo as a whole increases over time. Approximately 150 developmental regulating genes that affect gross morphology in *Drosophila* have now been characterised.

To everyone's surprise, virtually all the genes involved in early development of *Drosophila* turn out to be represented also in vertebrates, proving an amazing conservation of regulatory mechanisms

> across over 600 million years of evolution. Now our understanding of how genes control development has progressed far beyond what Nüsslein-Volhard and Wieschaus discovered at EMBL fifteen years ago. But, as Matthew Scott, another leading figure in the field, says, "Their views of how these genes probably work have influenced everyone in the field and it is

really viewed as the revolution in developmental genetics."

### **Developmental Research Returns to EMBL**

 $R_{ ext{EMBL}}$  soon after Nüsslein-Volhard and Wieschaus chose to move on to new positions in 1981. In the last few years, however, this field has been reintroduced within the EMBL Differentiation Programme, and currently is represented by several group leaders, including three who work on Drosophila. Under EMBL's next Scientific Programme, the Laboratory plans to continue strengthening this area. A new Developmental Biology Programme is foreseen, which will focus on the next step, not only how specialised cells arise out of the rapid divisions of the early embryo, but also how these cells are integrated into a coherent whole, to give the nascent organism its overall form (morphogenesis) and its complement of functional organs. In developing this area, EMBL will draw upon the strength of existing Programmes to nurture a multidisciplinary study of development. And it will draw on the tradition represented by Eric Wieschaus and Christiane Nüsslein-Volhard's work at EMBL: early independence, collaboration and originality.

- David States and Fotis C. Kafatos -

"Since its creation, EMBL has been a leading institution for biological research in Europe. From the beginning, it has played a very active role at an international level in the development and evolution of the life sciences: from the molecular and physico-chemical biology of informational structures to mechanisms of genetic regulation, developmental biology and, more recently, reverse genetics, the genome programme and bioinformatics. Many European leaders in biology have been formed at EMBL, and the laboratory continues to have a major role to play in training for young European scientists. Beyond its essential catalytic function for many fields of research, EMBL contributes to the development of advanced technologies and key infrastructures for sequencing, bioinformatics, and three-dimensional structure determination. Today, under the leadership of Fotis Kafatos, EMBL has opened up even further to the European scientific community. It is no doubt essential that the links between EMBL and the European Union be reinforced, for the benefit of the life sciences and their applications throughout Europe. It is also important for EMBL to function as a mobiliser for all the member states, by pursuing its efforts towards inclusiveness."

François Gros, Département de Biologie Moléculaire, Institut Pasteur, Paris -



# The Hamburg and Grenoble Outstations

Structural Biology Research, Service and Technology

The EMBL Outstations at Hamburg and Grenoble have played major roles in the history of EMBL and in the advancement of structural biology. Both Outstations were included in the original EMBL scientific programme and have evolved to become an invaluable resource for European academic and industrial researchers in molecular biology and biotechnology. The older Outstation - Hamburg has been a veritable workhorse of synchrotron radiation, while EMBL plans to enlarge the Grenoble Outstation during the next decade to take full advantage of its unique juxtaposition between the world's leading neutron radiation source and its most powerful synchrotron ring. Each Outstation unites technological development, research and service in an internationally co-operative environment. Visiting scientists' research is a priority at the Outstation and the EMBL staff devotes a substantial portion of its time assisting visitors. Each Outstation also has a relatively small in-house research programme, which establishes the high quality intellectual environment at the Outstations. Finally, continuous technological development is critical to improving their effectiveness and international competitiveness.

# EMBL's Service to Europe Began at Hamburg

ore than twenty years ago, the EMBL project introduced the use of synchrotron radiation for the analysis of biological structures to the world. The first biological synchrotron radiation experiments by Ken Holmes, Gerd Rosenbaum and Jean Witz gave spectacular results, launching international biological interest in the use of these powerful X-rays. The source required for

such radiation - in this case the Deutsches Elektronen-synchrotron (DESY) - was clearly unaffordable to normal laboratories and the planners of the EMBL project funded the early experiments to demonstrate the rational benefits of European scientific cooperation. In 1975, EMBL formally agreed to coordinate the international use of DESY's radiation for molecular biology studies.

Hamburg is still one of the most widely-used synchrotron facilities in Europe. While Grenoble now has the world's most powerful synchrotron

source, the brightness and stability of the Hamburg beams are still more than adequate for the large majority of research projects. Moreover, since synchrotron radiation has become a routine tool for structural biology and the field is rapidly expanding, the number and quality of lines at Hamburg remain an essential resource for European biology.

# Hamburg Provides High Intensity X-rays to Visiting Scientists

E MBL is especially proud of its service accomplishments at Hamburg. The Outstation

specialises in serving scientists where research requires high resolution data on a wide range of proteins. In practical terms, this means working with a large number of visitors - more than 200 in a typical year - who often stay for relatively short periods of time. Essentially all EMBL staff scientists work with the visitors and internal research at Hamburg has over the years emphasised close collaboration with users.

Research is the reason the Outstation exists - regardless of whether the results are the work of visitors, EMBL scientists, or combinations of the two. The

Outstation was, of course, conceived with visiting researchers in mind, but quality research is not simply a matter of plugging into new and better machines. Interactive researchers created the original techniques that made Hamburg a magnet for structural studies. In continuing to pursue their research,

EMBL scientists keep technical developments up to date and bring the potential applications of the Outstation to the attention of other scientists.

Fair and competitive allocation of the synchrotron radiation "beam time" to scientists is ex-

tremely important. Beam time at Hamburg is assigned by an international priorities committee which is appointed by the EMBL Director General and meets once a year to review applications. The Committee has ten members who represent the diversity of the European community and the sub-disciplines associated with the Outstation. Some members are cho-



EMBL's Hamburg Outstation

sen because of their familiarity with the Outstation, while others are specifically selected because they have no vested interest in allocation of the beam time.

The proof of the EMBL service philosophy lies in the quality and amount of research that comes out of Hamburg. In fact, a recent independent report showed that for an eighteen month period, out of all protein structures published in the world involving use of synchrotron radiation, the majority were based on data recorded at EMBL Hamburg.

# Research at the Hamburg Outstation: EMBL Scientists Work Closely with Visitors

In-house research covers protein crystallography, non-crystalline systems and EXAFS. The Outstation also has a small biochemistry and molecular biology group that works closely with the crystallographers. Simply put, the Outstation has been the most productive synchrotron facility worldwide for the recording of high-quality atomic resolution data for proteins. Of the numerous crystal structures determined at the Outstation, many were

solved by collaborating teams of EMBL and visiting scientists.

Hamburg has carried out pioneering work in another field of research - X-ray time-resolved measurements. This technology has been applied both to biological systems and to synthetic polymers. It is especially important for studying non-crystalline systems, such as biological mem-

branes and muscle, which unlike stable crystals require analysis through time. Creative experimental techniques for studies of muscle have been a speciality. In fact, until 1985, time-resolved muscle experiments were almost exclusively performed at Hamburg. Visiting scientists have extensively exploited the Outstation to broaden our understanding of the mechanism of muscle contraction and used the technology to describe the structural dynamics of microtubules.

A third technique used extensively at Hamburg is X-ray spectroscopy (EXAFS). This is used to determine the detailed structure surrounding metals in proteins or other biological materials. For example, scientists have deduced the principal structural features of Cd complexes with the important plant peptide phytochelatin. Another application has been the study of metal deposition in bones of neonatal rats. Future collaborations will play an



# Jan Drenth is Professor of Structural Chemistry at the BIOSON Research Institute, University of Groningen, The Netherlands.

"My laboratory used Hamburg throughout Heinrich Stuhrmann, Michel Koch, Juan Bordas and Keith Wilson's time as Heads of Outstation. I first visited the Outstation with some students while the beam was still under construction. Later, we used it to study protein crystals. At the beginning, we had a great opportunity to simply gather a lot more data; it was much faster, the intensity of the synchrotron beam much higher and better focused than the home instruments. Later, with all the technical advancements, especially the new area detectors, we could collect data on extremely small crystals.

"During the early period, we went to Hamburg with maybe six or seven people, working in two or three shifts, twenty-four hours day for a several days to collect the data. One crystal that we worked out there was hemocyanine, a large protein with a molecular weight of 450 thousand. The smaller crystals came later. Of course, work continued to go faster because of improved X-ray beams and because of the new detectors, the most popular one being the MAR image plate, which is much more sensitive than photographic plates. And we always had a lot of help from the EMBL staff for using the beams and for finding accommodation.

"The ESRF in Grenoble is obviously the next generation synchrotron and will be very important for Xray protein crystallography, but the Hamburg Outstation is still excellently suited for fulfilling nearly all the needs of protein crystallographers. And, coming from Groningen, it is much easier to reach than Grenoble." important role here, as the work of the Hamburg EXAFS group increasingly overlaps with that of crystallographers in the development of multiple wavelength anomalous scattering. This development allows direct experimental solution of the major problem in X-ray crystallography, the socalled "phase problem."

# Technology Development is Critical to Competitiveness

C learly, the single most important accomplishment at Hamburg has been the development of the technology, infrastructure and facilities that allowed synchrotron radiation to be used for the study of biological structures. Without this development, none of the subsequent protein crystallography, EXAFS or time-resolved measurements by EMBL and hundreds of visiting scientists could have taken place.

Technical advances are typically the result of collaborations. DESY's assistance, of course, has been essential in establishing and improving the Outstation. DESY has generously provided radiation into the experimental halls at zero cost - a significant financial contribution on the part of our German hosts. EMBL scientists from Heidelberg, Hamburg, and Grenoble frequently join forces to develop equipment such as fast gas-filled detectors and the associated electronics - the first such detectors for biological uses of X-rays and now used worldwide. Interactions with the users are particularly important for constant adaptations of equipment. Other major advances in instrumentation at the Outstation include the creation of on-line image plate scanners, and advances in lasers, temperature jump technology and detectors that have allowed time resolved studies for small angle scattering experiments.

EMBL continues to upgrade its beam lines. A second protein crystallography wiggler beam line will soon be commissioned at Hamburg. An undulator line is expected on the "PETRA" ring in the next two years, which will provide monochromatic radiation several orders of magnitude more intense than currently. The Outstation plans to exploit this high-intensity radiation on a part-time basis. DESY has proposed construction of a linear collider, as the next generation of particle accelerators, which would create unprecedented possibilities for biologists.

# The Grenoble Outstation Neutrons Join Forces with a Powerful New Synchrotron

N eutron beams, like X-ray beams, can be used to investigate biological structures. Soon after the

biological systems, the dynamics of proteins, and protein-nucleic acid or protein-lipid complexes.

1975 Hamburg accord, EMBL signed a parallel agreement with the Institut Laue Langevin (ILL) in Grenoble to establish a second Outstation on the site of the world's leading research nuclear reactor. In 1976, under the direction of Andrew Miller, EMBL began its fruitful collaboration with the ILL in developing neutron scattering techniques and instrumentation. Since that time, it has been EMBL's responsibility to provide



EMBL Outstation, ESRF, and ILL at Grenoble

biological support to visiting scientists doing measurements using these beams, which are especially suited to structural studies of the role of water in crystals of complexes such as the nucleosome, the ribosome, viruses and membrane proteins. Jacrot, his successor, Stephen Cusack (1989-present) and

"EMBL is the flagship of European molecular cell biology. Its rational organisation, interactive environment, commitment to innovative instrumentation, and impressive record of scientific achievement serve to make it a model institution, which propagates by leaving its imprint on group leaders that seed universities and research institutes throughout Western Europe. EMBL, like CERN, has set the standard for how European collaboration can and should work."

The Grenoble Outstation made significant leaps forward during the late 1980s and early nineties. Under a new Head of Outstation, Bernard Jacrot, EMBL reinforced the Outstation's technology development and service functions, while building a tradition of strong in-house research. In 1984-85, the ILL and EMBL jointly designed and built a unique diffractometer, which has been used to study the structure of their colleagues also added to the lab's collection of biochemical and molecular biological tools, including important facilities for production of deuterated biological material, electron microscopy, and X-ray crystallography. The shutdown of the ILL reactor in 1990 dealt a temporary blow to European structural studies using neutrons. However, diversification of the in-house research during the previous decade and development of biological tools gave the Outstation the flexibility to withstand what might have been a crippling blow. Moreover, after a complete refurbishment, the reactor was restarted and reopened its doors in 1994 to biologists who need this unique form of radiation.

The importance of the Grenoble Outstation was reinforced by the decision to build the European Synchrotron Radiation Facility (ESRF) adjacent to the ILL. In 1992, EMBL and ESRF signed an agreement to facilitate European biologists' use of

the synchrotron's radiation. On September 1, 1994, the ESRF opened its doors for visitors to use the world's most 'brilliant' X-ray beams (a technical term indicating a combination of very high intensity and very narrow diameter). These are especially suited to crystallographic studies of weakly diffracting samples, such as small crystals or crystals with large unit cells, e.g. viruses or the ribosome. They also have new advantages for time-resolved crystallography; indeed for the first time images can be taken from crystals with exposure times of

billionths of a second (picoseconds)

The combination and quality of ESRF Xrays, ILL neutron radiation and the strong EMBL research programme and biological facilities at Grenoble promise to make the Outstation a new world centre for structural biology.

# Technological Development: Maintaining a Cutting-Edge

The design, construction and running of the special instrumentation that takes advantage of the intense neutron and X-ray beams are, of course, a major focus of the Outstation's attention. EMBL and ESRF, for example, are currently collaborating on the design and maintenance of three new biological beam lines for the synchrotron.

EMBL research biologists and instrumentation specialists and ILL and ESRF physicists are continuing to work together to solve numerous associated technical problems. Among the most important have been the development of multiwire proportional counters for detecting X-rays (EMBL scientists from Hamburg and Heidelberg joined forces with Grenoble here). Grenoble continues to concentrate on the development and testing of X-ray detectors (improved image-plate scanners, CCD detectors and the multi-wire detectors), and other technology such as cryo- cooling of protein crystals, extremely fast and high accuracy data collection methods. Construction of new neutron detectors, is also underway for a new high resolution neutron diffractometer to be built at the ILL.

## New Resources Promise Expanding Role for Visiting Scientists at Grenoble

The Grenoble and Hamburg Outstations are designed to complement one another as service institutes. Grenoble, where the brilliance of the new synchrotron beams is unparalleled, will emphasise novel and challenging experiments (using, for example, very small crystals and large

> and complex structures with big unit cells). And as the number of beam lines increase, larger numbers of visiting scientists will be accommodated at Grenoble. Grenoble, of course, also offers access to neutron radiation and, because of its historical development, is well setup to cater to users who require longer stays and greater access to biochemistry and molecular biology facilities.

> With both ESRF and ILL facilities now on line, the Grenoble Outstation's service role will grow dramatically. EMBL is

nearly doubling the size of the laboratory building and intends to expand the staff of the Outstation to take full advantage of the available ILL and ESRF resources. At the same time, EMBL plans to enlarge Grenoble's internal scientific programme to reach a critical mass of scientists; experience has clearly shown that service and research goals are complementary. Finding new staff who are equally committed to both functions will, of course, be one of the major new challenges, but a carefully expanded Outstation will provide European structural biology with an environment strong in biology and physical techniques to support the work of an increasing number of sabbatical visitors and young scientists.

Access to both radiation facilities at Grenoble is organised differently than at Hamburg. At Grenoble, EMBL is represented on ILL and ESRFappointed review panels that determine the relative merit of research proposals. Once access is awarded, visiting scientists make formal requests to EMBL for use of the Outstation's biological laboratories and technical assistance. This may range from biochemical preparations of samples to assistance at the beam lines.



Stephen Cusack - Head of Outstation

### Strong In-house Research and Collaborations

**S** mall angle neutron scattering and low resolution crystallography particularly on viruses, were the early strengths of Grenoble. This was greatly stimulated by external collaborations with groups such as that from the University of Leiden, Holland. EMBL and visiting biologists used the neutron diffractometer technology to study biological crystals of complexes of macromolecules. The methodology EMBL and ILL scientists developed at Grenoble made it possible to study crystals of nucleosomes, plant viruses, ribosomes and the photosynthetic reaction centre. Among their major accomplishments, the biologists and physicists made a unique application of neutrons to characterise the dynamic behaviour of myoglobin and other proteins. These experi-

myoglobin and other proteins. ments were designed to explore the nature of atomic motions in proteins and have contributed to the current understanding that proteins are by no means rigid systems, but in fact have mobility and flexibility, properties essential for their function.

EMBL research at Grenoble also unravelled the 3-dimensional structure of the E. coli servltRNA synthetase, an essential enzyme involved in protein biosynthesis. This was fundamental research at its best. It provided the first structural evidence for a second class of aminoacyl-tRNA synthetases (a totally unexpected discovery), and thereby showed that there were two distinct

pathways in the evolution of this fundamental group of enzymes. This led in turn to the recent determination of the crystal structure of seryl-tRNA synthetase complexed with tRNAser - one of the very few atomic resolution structures giving details of how proteins specifically recognise RNA.

In-house research in structural biology at Grenoble will continue to be mostly oriented to structural studies involving protein-RNA complexes. The work involves collaborations between the in-house groups combining molecular biology, biochemistry, X-ray crystallography and electron microscopy. Strong collaborations have developed with a number of external groups (notably in Geneva, Basel, Madrid and Paris, as well as in the USA). The Outstation will also increase collaborations with the Heidelberg Laboratory, where the molecular study of RNA/ protein complexes involved in RNA processing and transport is well advanced, and where the trend of structural studies is towards increasingly large multimolecular complexes.

One major focus of study is on structures involved in protein synthesis and another on the proteins of RNA viruses. The project on aminoacyl-

tRNA synthetases (mentioned above) is largely concerned with

bacterial systems, but is moving in the direction of the more challenging eukaryotic synthetases (e.g. on the asparaginyl-tRNA synthetase from the parasite, Brugia malayi, which is a major antigen found in the blood of humans suffering from lymphatic filariasis). The Outstation has worked on influenza virus for many years (as a result of its early connection with the University of Leiden). Work is underway to characterise the RNA binding properties and function of the nucleo-protein, NS1, and the three viral polymerase subunits, with a view to eventual crystallisation trials.

Some of this work is in collaboration with the Wellcome Foundation, which may ultimately be important for the development of antiviral agents.

- David States -

"Over the past forty years, the Life Sciences have grown exponentially, both in terms of acquired knowledge as well as in power and complexity of the available tools. Almost any problem in basic or applied science (medicine, agriculture) is now within our reach. But this requires concerted intellectual efforts, as well as a wide range of sophisticated expertise and physical equipment. Nowhere in Europe is the added value of building up the necessary critical mass better illustrated than at EMBL. EMBL is the flagship of Europe in the Biological Sciences and fulfils a unique role as a training centre in the multi-faceted discipline, which is Molecular Biology. There are numerous examples, including in Belgium, of EMBL staff members who had acquired an international reputation and came back to set up a successful research laboratory in their country of origin."

- Walter Fiers, Laboratorium voor Moleculaire Biologie, Gent -



# **Genomes, Proteins, Sequences & Theories The European Bioinformatics Institute**

The European Bioinformatics Institute, or EBI, is the newest Outstation of EMBL. It continues and expands the work of the EMBL Data Library, the first central repository for nucleotide sequence data in the world. The EBI is dedicated to providing computerised information for use in molecular biology research, and to exploring new theoretical territory in computational molecular biology.

n the late 1970s, a revolution in recombinant DNA cloning and sequencing techniques created a new demand for computerised support to cope with a flood of raw sequencing data. In 1980, EMBL founded its "Data Library," becoming the first organisation in the world to fund a database of nucleotide sequences. The European Bioinformatics Institute, EMBL's newest Outstation, is the direct descendant of the Data Library and the Biocomputing Programme. Based at

possible by the Wellcome Trust and the government of Great Britain through the UK Medical Research Council. Thirty-nine staff members from ten different EMBL member states are now working in temporary offices at Hinxton Hall and a custom designed building is under construction. The Hinxton complex, shared with the MRC's Resource Centre for the Human Genome Mapping Programme and the Sanger Centre, which specialises in genome-scale sequencing, is a

> very attractive site for the EBI Outstation.

# **Research and Development:** The Need for Continual Innovation

n just over a decade, the EMBL Data Library has grown to in-

> clude a total of 217 million nucleotides of DNA sequence information. The pace continues to accelerate; major genomic sequencing projects are beginning to add to this avalanche of data. Technical innovation has paralleled this rapid growth. Today's sequence information management

Hinxton, England, near Cambridge, the EBI is already recognised as the central molecular biological data bank in Europe. Among its many services, it provides access to genetic sequences and computerised biological information to scientists throughout the world. It also includes research and development components to assure



that its resources develop healthily and are exploited as efficiently as possible.

At the time the Data Library was founded, the potential of computing in molecular biology was just beginning to be

tapped. During the years that followed, innovations in technology for determining, storing, and analysing nucleotide sequences spurred each other on in an accelerating cycle. In 1986 a significant research effort in computational biology was initiated under the name of Biocomputing. By the end of the 1980s advances in molecular biology and informatics coupled with increasingly sophisticated user demands called for drastic improvements in the original approaches.

To cope with these developments and provide the scientific community with world-class information services, EMBL established the EBI in 1993. The new outstation also addresses the needs of the European Union, a significant supporter of the Data Library. The relocation to the Hinxton site was made

EBI, MRC Resource Centre and Sanger Centre complex under construction

is a far cry from the early days when EMBL annotators abstracted all the information from scientific journals. Nowadays, data are transmitted directly over computer networks and specialist software tools are used to incorporate them into the databases.

Additionally, the EBI provides central access to diverse specialist databases, some developed in-house and others by remote collaborators. It also acts as an efficient dissemination point for free molecular biology software developed by scientists throughout the world.

Applied bioinformatics research plays a critical role at the Outstation, constantly helping to update and improve databases and software. The EMBL Nucleotide Sequence Database, for example, has gone through several cycles of redesign. The nucleotide database will be complemented by protein sequence and structure databases, collaboratively developed. Because of the proliferation of specialist databases and benefits of using electronic networks, the EBI is currently designing interfaces between systems and developing unified userfriendly access protocols.

Basic bioinformatics research, in which EBI scientists explore uncharted theoretical territory and develop prototype software tools, is scheduled to play an important role at the Institute. This research must be strong enough to provide a critical mass for innovation. Who knows what theoretical tools will be needed by molecular



Chris Sander has a research group in genome analysis and protein design at the EBI. He brings to the new Outstation extensive experience in biocomputing from EMBL's Heidelberg laboratory.

"Within the next five to ten years, as a result of genome projects worldwide, the

EBI will be able to offer a database of all important genes of key organisms: the letters and words in the 'book of life'. We face the exciting challenge of unravelling the meaning of the sentences, paragraphs and chapters in this book; of bridging the gap between the fragmented bits of genomic data and unified biological knowledge; and of describing and understanding the ways in which genomic information determines the elementary processes of living cells. To meet this challenge, bioinformatics research draws on computer science and mathematics, on biology and chemistry, on statistics and physics in a truly multidisciplinary approach. The results are embodied in new theories, mathematical models, and computer software and provide the basis for improved information services made available to the scientific community over tomorrow's information highways."

Program, at EMBL Heidelberg, Hamburg and Grenoble, as well as with numerous national academicand industrial laboratories in Europe.

A crucial EBI collaboration is with EMBnet - the European Molecular Biology Network, which electronically links molecular biologists throughout Europe. Initiated in 1988 by EMBL, it was created to facilitate immediate access to sequence information maintained at the Data Library. An independent foundation since 1994, EMBnet consists of a network of centres that are closely tied to the EBI and receive daily updates of its databases. EMBnet provides informatics services through national nodes in 17 European countries, as well as additional locations at the European Patent Office in Brussels and at

> of services. A particularly fruitful collaboration with

> the University of Geneva

now results in the joint production of the SWISS-PROT

protein sequence database,

initiated by Amos Bairoch.

Other collaborations make

available specialist collec-

tions such as the Drosophila

database - FLYbase, or in-

corporate data from major

projects. The EBI is also ac-

tive in worldwide collabora-

sequencing

biologists a decade from now?

# Worldwide Collaborations From EMBnet to Genome Projects

Service and service-oriented research do not long survive outside of the context of molecular biology

research. Basic science researchers are "customers" providing constant pressure for improvement of services; contact with those who produce and use scientific data widens the EBI's horizon regarding new research requirements and helps the development of data acquisition methods. The EBI is eager to take advantage of the multifaceted benefits of decentralised European science. Its researchers mainlaborates with informatics leaders from these national centres who provide training and support in their own countries.

biotechnology industry locations. The EBI also col-

Collaborations with national and international organisations help continuously expand the EBI's range



tain extensive links with molecular biologists at the nearby Sanger Centre and Human Genome Mapping tion. It coordinates technological developments and shares sequence information with partners in the

European

"EMBL provides a unique opportunity for young investigators to do independent, original research in an international, competitive environment. The facilities are excellent, and in most areas of modern molecular biology the EMBL has reached the critical mass to carry out research at the forefront of science. As a chairman of the Scientific Advisory Committee, I was impressed by the increasingly high standards of research. A large number of group leaders have become faculty members at universities all over Europe, which has a long-lasting effect on the quality of research and teaching in Europe. EMBL also serves the community of European molecular biologists by teaching practical courses, organising workshops and meetings, establishing data bases and teaching graduate students. EMBL has become an internationally recognised focal point of molecular biology in Europe."

- Walter Gehring, Biozentrum der Universität, Basel -



Paolo Zanella is the new Head of the EBI. He comes to EMBL from CERN, where he spent thirty years combining computing, data handling and particle physics.

"European laboratories can have a significant impact worldwide in the dissemination of innovative approaches, methods, and systems, and in raising the information technology

awareness of the research community. I tend to see the EBI as the "informatics services and applications" arm of EMBL. In Europe it has to interface properly with the user community, collaborate with the EMBnet, and expand its role as the European reference point in bioinformatics. And it must continue to be both a partner and a competitive player at the same level as the best equipped bioinformatics laboratories in the U.S. and in Japan.

"There are so many opportunities for cross-fertilisation at the interface between molecular biology and computer science. New applications of informatics to molecular biology should have a visible impact on the way research is done. High-performance computers and networks will certainly contribute dramatically to the advancement of molecular biology.

"This entails finding the correct blend of services and R&D to fuel them. The services are the essential product, but the R&D is critical to their success. The EBI has to gain the acceptance and the respect of its users. Which means in practice carrying on the essential services well while introducing new ones and taking initiatives to exploit the relevant information technologies."



Graham Cameron is Head of the Services Division of the EBI. He has been with the EMBL Data Library-EBI since its beginning.

"Rapid advances in biology and informatics ensure that our task always remains challenging and interesting.

"The mission for the EBI is to further biological research by providing excel-

lent information services. Enthusiasm for the subject matter of basic biological research is a central motivation in the services, and the EBI balances nicely the different motivations and skills of the research scientist and service worker. Scientists work on what I call a "proof of concept" approach — the novelty of a discovery or process is a key motivator. Sustainability excites service workers — proving it's possible to efficiently replicate quality work on a larger scale and provide a robust service 365 days a year. Driving EBI services forward is bit like being a ship's engineer — crucial to this exciting scientific voyage, but not useful without well-thought-out destinations. In that sense, the research wing helps pilot the ship.

"We have to embrace the service mission and maintain close ties with our constituents — the scientists who depend on our work. We must provide excellent support for them and respond continuously to their needs. This way we can build a partnership, which ensures that European science optimally exploits the information technology that will be crucial to the advances of the coming years." USA and Japan. Recently, it has begun to be involved in the rapidly growing area of threedimensional macromolecular structure information, expecting to collaborate with the similar U.S.-based effort (Protein Data Bank) for joint development of an expanded global structural database. Continued energetic involvement of the EBI in such collaborations is crucial to ensure global availability of biological data in the public domain — a principle pioneered by the Data Library and central to the mission of the EBI.

# Service: the EBI Ensures that Advanced Technology Remains User-friendly

A dvanced technology and information which researchers are not able to use easily are of little value. For this reason, user support — training, documentation and consultancy — are crucial activities within the EBI.

As the Institution develops, its scientific and technical staff will give scientists advice over the telephone and electronic mail and provide in-depth assistance to those who come to the institute to use its resources or develop similar ones of their own. The Outstation intends to have a fullscale guest scientist programme, inviting scientists from academia and industry to typically spend several months using EBI facilities and expertise for their own projects, such as characterising a particular set of sequence patterns or working on a new algorithm. The guest scientists will contribute, in turn, to EBI research projects. Finally, continuing the tradition of successful practical courses at EMBL laboratories, the EBI will organise advanced bioinformatics training courses using a facility custom designed for that purpose. These courses cover topics ranging from the use of specific EBI products to theoretical overviews of bioinformatics.

In the final analysis, whether it is negotiating agreements at the international level, promoting innovative bioinformatics research at EMBL, providing user-support, or simply performing the difficult task of keeping the EBI information networks running twenty-four hours a day, three hundred sixty-five days of the year, all of the EBI staff are unified behind the same principle - making the wealth of biological information available in ways which facilitate leading edge research in molecular biology in Europe and the rest of the world. - David States -

# Instrumentation Development An Integrated Approach

The field of molecular biology has been led and fed by technological advances. Maintaining an environment in which research biologists interact with instrumentation specialists is one of the major strengths of EMBL. Instrumentation programmes benefit European research on three levels: they increase the efficiency and quality of work done by experimental scientists at EMBL, including visitor scientists; they help European industry remain competitive; and, through associated practical courses and commercial licensing, bring proven state-of-the-art technology to scientists in the national laboratories.

**Here and Contract States A Second States A** 

sional dialogue between engineers, physicists, and practising biologists. This ensures that complicated theoretical ideas are developed into practical, userfriendly technology.

# Cell Biophysics

**E** MBL's Physical Instrumentation Programme has recently changed its name to Cell Biophysics. Historically, the Programme has developed sophisticated light microscopy, electron microscopy, and microcomputing instruments. Over the years, it has collaborated particularly closely with biologists

from the Outstations, Biological Structures, and Cell Biology.

The change of name to the Cell Biophysics Programme underscores the continuing evolution and interdependence between instrumentation specialists and biologists. Over the last twenty years, the study of cells and organisms has evolved from simple structural description to a dynamic view of the molecular mechanisms within cells and organisms. This was a gradual process; the questions scientists were asking pushed the technology developed by EMBL's engineers and physicists; the results generday, biologists are trying to decipher the nature of the interactions between molecules of proteins, lipids, and nucleic acids, as well as to analyse the complex behaviour of the supramolecular structures over time and in three dimensions. They must perform biochemical tests and manipulations at the cellular level, precisely identifying molecules and their functional integration

ated by advances in instrumentation raised new

questions and new technological requirements. To-

**Ernst Stelzer** is a group leader in the Cell Biophysics Programme

"Creativity in developing instrumentation is based on working within limited borders. The biologist defines a problem

to be addressed; the physicist brings a theoretical perspective and technological expertise that pushes the biologist in new directions to address the problem. It's only within such a prescribed boundary that a problem is clearly conceived. And only with clear problems is it possible to find solutions." their functional integration in the cell or organism. Increasingly complex technology and closer communication between the biologists and instrumentation specialists are now more important than ever.

The history of the development of confocal microscopy mirrors this process. This technology is now taken for granted by cell biologists around the world, but fifteen years ago, EMBL was one of only two institutions worldwide exploring its uses. At the time, EMBL cell biologists asked their physicist counterparts to help find ways to examine thick cells

three-dimensionally. Their "classical confocal" was the first of seven generations of this microscope. Since then, constant use, critique, and improvement of the microscope has led to development of a compact confocal (widely used in the video scanning of live samples) and most recently to a high-speed beam-scanning confocal microscope. This development has been complemented by advancements in optical tweezers - twin lasers that can be used to actively manipulate cellular parts within the examining field. These instruments are especially useful for studies in cell biology, differentiation, and developmental biology.

The Cell Biophysics Programme, with theoretician Harald Rose at the University of Darmstadt, has recently made a unique technical achievement - the construction of an aberration corrector for low voltage scanning electron microscopes (LVSEM). Scientists have been searching for a solution to this problem since 1947. The new multipole-corrector represents the first real improvement in LVSEM resolution since that time. In practical terms, this means that structural biologists will now be able to get an extremely detailed look at cell surfaces, components, and structures such as the nuclear pore complex.

The microcomputing and data acquisition group has contributed major components at the Hamburg and Grenoble Outstations such as fast real-time digital encoders for X-ray detection systems. One of the future goals of the group is to provide X-ray detectors with improved spatial resolution and higher counting rates. These systems will be very useful to scientists visiting the Outstations, because they will allow them to explore the kinetics of molecular reactions with improved time resolution. The group also has a long history of contributions to electron and light microscopy systems. They have developed a novel silicon quadrant electron detector, hardware and software for a fast front-end parallel processor system used on the Cryo-STEM. This allows scientists to fully exploit the analytical capabilities of this instrument. The computer engineers have applied parallel processing to sequence homologies computations, using Digital Signal Processors. The design

of the basic building blocks can be configured in parallel and pipelined architecture. They have also developed image processing tools to help assess the 3D distribution of gene expression domains for development biology.

## **Biochemical Instrumentation**

**B**iochemical Instrumentation scientists have been very energetic at EMBL, creating a broad range of automated tools, many of which are now commercially produced and widely used in the fields of molecular biology and biotechnology.

Perhaps the most important contribution has been an array of DNA technology, including automated DNA sequencers, synthesisers, analysers, robotics, and ultrathin gel technology. Automated microinjection techniques and equipment have also been developed at Heidelberg.

These advances have been used throughout the world, greatly increasing the speed and efficiency with which research can be done. The three main uses for this technology are analysis of molecular biology projects in research labs, diagnostics of genetic mutations in clinics (90% of the market for this technology is clinical), and an important and prestigious new application: the human, yeast and *Drosophila* sequencing projects. In fact, early decisions about the feasibility of the Human Genome Project were based partly upon the accuracy and speed of EMBL-developed DNA sequencing machinery.

EMBL biologists extensively exploit the Bio-

#### Christian Boulin is a Programme Coordinator in Cell Biophysics.

"Today, the use of microcomputers, hardware and software in the design of instrumentation demands a very intuitive approach. This is probably the force behind successful development of a large variety of instruments for EMBL's Outstations in the last 15 years.

"At the end of the 1970s, we realised that it was very important to provide high speed data acquisition systems in order to improve the use of synchrotron radiation. At the time, the photographic film was still the most common detector for experiments with X-rays. Optical scanners quantified the results. My first job when I arrived at EMBL was to develop the first standard computer interface for such machines.

"The initial work - with the help of CERN, I might add - allowed

us to make a big step forward and ultimately enable a lot more visiting biologists to carry out timeresolved experiments at the Hamburg Outstation. The previous equipment could record 15,000 events per second and our work allowed the biologists to collect 20 to 30 times more. "We've had many developments for synchrotron instrumentation and we've always paid attention to standardisation, modularity and reliability. Because of this, most are now being used at the other synchrotron facilities in Europe: in LURE,

> in Daresbury, at HasyLab. Some of it was also transferred to labs such as KFA Jülich or the Department of Chemistry of Hamburg University for non-biological applications such as material science or polymer physics.

> "Now we are looking for even more advanced systems based, for example, on the use of technologies such as silicon strips and pixel detectors or scintillating optical fibres. This means collaborating again with the CERN technology groups, with whom we maintain excellent rela-

tions, and with the semiconductor industry. These new technologies are absolutely essential, considering the European effort put into the construction of the ESRF at Grenoble and EMBL's service commitment to the European biological user community."



chemical Instrumentation innovations. Not surprisingly, this often gives EMBL scientists a competitive edge when it comes to their research. EMBL's new peptide sequence service is a good example. Determining amino acid sequences is a critical first step in many molecular biology projects. Thanks to the new mass spectrometry techniques, EMBL scientists can obtain sequence information from much smaller amounts of protein than was previously possible. Furthermore, the properties of proteins are often influenced by post-translational modifications such as phosphorylation and or glycosolation. The development of new mass spectrometry techniques at EMBL has allowed scientists from Gene Expression to quickly identify both the type and position of modified amino acids in a polypeptide chain, a prerequisite to study of the functional outcome of many modifications. Other important results were developed by the nucleic acid chemistry group of Brian Sproat (see next page).

The heavy in-house use of the technology also



ing ground for the new instruments and techniques. Andit stimulates creative solutions to new questions that come up in the process of related investigations.

serves as a

practical test-

Matthias Mann's group develops methods and provides service in the areas of mass spectrometry, micro sequencing, and peptide synthesis.

# Spreading EMBL's Technology: Workshops to Industrial Collaborations

Because EMBL is a centre for technical innovation, it is not surprising that the EMBO and EMBL both exploit the labs instrumentation staff and its most active collaborators to spread word of the technology and how to use the equipment through the many practical courses that are given here.

EMBL also actively promotes the distribution and use of its technological developments to the national systems through alliances with industry. Although EMBL's main obligation is to further fundamental research, the interests of pharmaceutical and biotechnology industries and research institutions are frequently compatible.

Industry clearly has better facilities to com-

Wilhelm Ansorge is Programme Coordinator for Biochemical Instrumentation.

"EMBL's Biochemical Instrumentation has concentrated mostly on the DNA and protein technology and service. Over the years, we have made great strides in speed and quality, from thin-gel technology to fluo-

rescent labelling, robotics to laser detection systems. Between 1978 and 1992, the amount of information we could obtain had increased in real terms 100-fold. And we can still look for improvements

"Our job is to improve quality and speed of the technology, as well as service to EMBL scientists. We do the sequencing for practically every EMBL group and they expect a very high standard from us. But our role is also to shine on a worldwide scale. One sign that something is good is when it penetrates other labs. You see that with our DNA sequencing and synthesis equipment and the automated microinjection systems, which are in thousands of labs and clinics. We transfer the technology through licensing agreements with commercial partners. This helps keep European industry competitive with the U.S. and Japanese and, of course, we receive a modest amount of money, which frees up a little funding for research in an era of tight budgets.

"Matthias Mann's group is starting to make the same kind of progress developing peptide sequencing and services. After only a couple years, they have made real advances in protein analysis sensitivity, so that scientists need 1/10 to 1/100 of the material necessary to do the analysis.

"I think EMBL has hired very good people in its instrumentation programmes. Comparable places usually have two to three times as many people for the same work. This has forced us to look more closely at the designs and be more efficient. But this is generally true at EMBL. Maybe this pressure is what makes EMBL so special. People are challenged and they must be disciplined; sometimes they cover many subject areas. My group is half engineers and half biologists, all with computing experience. We have hardware, software, robotics and automation experts. Everybody has to have one foot on the ground; now and then they prepare the samples - just as our scientific "customers" - and everybody does a bit of service so that they know why the work is being done. This has really been a successful strategy. It ensures that we get direct feedback from users and spot the practical bottlenecks much more quickly."

"EMBL has pioneered the development of groundbreaking new technologies for biotechnology. From automated DNA sequencing to one of the world's most successful databases for DNA sequences, no other institution in Europe has a better record for technological contributions to modern biology and medicine. Technology development coupled with superb biology makes EMBL truly a unique scientific institution."

mercially develop and distribute EMBL's functional prototypes. The practical improvements, for example, of the EMBL advanced DNA sequencing prototypes have led to joint projects with the company, Pharmacia, as have advances in microscopy together with Zeiss. As a result, national labs obtain this technology more cheaply and quickly than if EMBL had to provide this on its own.

Prudent collaborations between research institutions and industry are mutually beneficial. EMBL registers patents and carefully negotiates agreements with industry so that it protects its intellectual property rights and earns income, which it reinvests into basic research. This both lightens the fiscal burden on governments for support of EMBL and gives European industry an opportunity to harness EMBL's multidisciplinary research and instrumentation expertise to strengthen its competitiveness in the international marketplace.

EMBL's own fundamental research takes priority, but in the current environment, it is naive to assume that molecular biologists can continue to ignore the role of industry in the economic welfare of Europe. Japan and the United States certainly do not.

- David States -

**Angus Lamond** and **Brian Sproat** have been group leaders in Gene Expression and Biochemical Instrumentation respectively. A casual conversation led them gradually into a broad collaboration. Sproat has recently left EMBL to direct a small biotechnology company in Germany.

Lamond: "I've had quite a number of successful collaborations with instrumentation groups at the EMBL. I published with Wilhelm Ansorge and had lots of help from Ernst Stelzer and the confocal group. My collaboration with Brian started typically: Brian was in charge of the oligonucleotide service here; I saw him in the canteen and asked if we could fix a technical problem. I wanted some RNA oligonucleotides for a specific experiment -DNA oligos weren't doing well - and I asked him if he could help make oligoribonucleotides.

Sproat: "Making RNA chemically was not trivial and I was explaining the differences between RNA and DNA structure.

Lamond: I casually said, "We should test to see, if you block it, whether it will survive the synthesis, because I don't really care if it is genuine or synthetic or modified RNA, as long as it works for this experiment."

**Sproat**: I'd just seen a report in a science journal describing some new RNA analogues that were stable to base and were nu-

clease resistant. As it turned out, I couldn't use the methods described, but decided to make the RNA analogues using some new synthetic procedures.

Lamond: So Brian had a go at making a 2'-Omethyl RNA homopolymer. It looked promising initially, but it was only after a few months of playing with it that we gradually realised it might be much more widely useful than we had imagined. **Sproat**: The 2'-O-methyloligoribonucleotides bound very tightly to RNA. They were as easy to synthesise as the more commonly used DNA, but offered a number of important advantages. We realised they could have many applications, including uses in affinity chromatography and diagnostics. Further chemical developments of this generic type of RNA analogue also led to improvements that enhanced their performance in biological experiments.

Lamond: Once we had the idea, we had the resources and funding that allowed us to do something useful, even though we had no absolute

> proof. We could never have got that funding elsewhere or by writing a grant. The idea was too exploratory. But at EMBL, we could try something innovative. This is where the flexible EMBL system has real advantages. The opportunity to easily combine someone doing chemistry and molecular biology right next door to each other is quite unusual. Even in the biggest labs in the USA, this kind of interaction can be difficult

Brian Sproat and Angus Lamond

to establish. Bigger labs are often more self contained and you always have to ask in advance who's grant pays for what.

**Sproat**: I was pleased that this collaboration enabled me to focus my expertise in organic chemistry upon solving problems with direct biological relevance. The experience has certainly encouraged me to maintain close contact with biologists in the future.

# THE RAIN FORE



# **Training Scientists for Europe's Future**

EMBL is one of Europe's most important molecular biology training centres. One of EMBL's primary functions is to return its scientists to posts in national universities and research laboratories with scientific and leadership skills. The Laboratory provides a training environment rich in the latest technology, with a wide range of methodological approaches to molecular biology. It offers independent positions to group leaders and staff scientists at an unusually early stage in their careers. It provides valuable opportunities to postdoctoral fellows and has an outstanding predoctoral programme. Visiting scientists are also encouraged to participate at EMBL. They learn new techniques in research laboratories and take advantage of the many advanced practical courses and international symposia hosted by EMBL.

# Training Programmes and Scientific Mobility Create a Dynamic EMBL

From the time of the earliest EMBL proposals, one of the laboratory's basic objectives has been to train young scientists in new molecular techniques and to instil a multidisciplinary ap-

proach to their craft. EMBL firmly believes that strong training and research programmes reinforce one another. It offers a rare educational experience to pre and postdoctoral fellows, but it also helps more advanced scientists to further develop whether they are EMBL's own group leaders and staff scientists or visiting biologists.

EMBL is deeply

Group Leader Werner Kühlbrandt

committed to the principle of scientific mobility; with very rare exceptions, even its best scientists are encouraged to leave the laboratory's protective embrace. EMBL gives its scientific offspring the skills and maturity for professional independence, then pushes them out into the world to make creative contributions in the outside community, where they continue to demand a high standard of achievement from themselves and their new institutions.

A strict turnover system is in place staff may stay at EMBL a maximum of nine years. This creates a constant influx of new

junior scientists, who acquire skills at the laboratory and bring in fresh ideas that flourish in EMBL's intellectually intense, yet supportive environment.

# Grooming Group Leaders and Staff Scientists for Key Roles in the National Systems

One of EMBL's most important training goals is to provide its faculty (group leaders and staff scientists) with advanced technical, methodological, and organisational skills so that they can lead suc-

cessful research groups within the national systems. Most group leaders and staff scientists come to EMBL immediately after finishing postdoctoral training. The average age of the current group leaders, for example, was 32.7 years when they first arrived. This represents a critical stage in a scientist's career when he or she is most productive, yet still open to new scientific approaches. These future leaders learn through creative interaction with their peers, as well as through mentorship of senior scientists.

Once at EMBL, group leaders are given complete scientific independence and extraordinary

> access to advanced instrumentation, technology, and material support rarely available at such an early point in one's career. The result is an outstanding record of creative solutions to modern biological problems. This environment cultivates the young scientists' ability to manage a laboratory and to conduct independent research with new tools and in new directions.

> During its first twenty years, EMBL has developed a reputation that attracts an outstand-

ing calibre of applicants to these positions. An individual candidate's research record is the major determinant in selection, but EMBL also prefers scien-



Predoctoral Fellow Andrea Musacchio's research on cover of Nature Structural Biology



tists who are collaborative and interactive.

Even the few faculty members who hold Senior Scientist positions only receive rolling tenure. The great majority of faculty hold fixed-term appointments and stay for a relatively short period of time (an average of 6-7 years for group leaders). In essence, EMBL intentionally "loses" its best scientists in order to advance molecular biology throughout Europe. For example, the first generation of group leaders in the Differentiation Programme, whose research focused on oncogenes, has left and established outstanding research groups all over the continent, carrying the message of new technology, methods, and scientific internationalism with them. Senior EMBL "alumni," such as cell biologist Daniel Louvard, are making a major impact on scientific policy. As the Research Director at the Curie Institute in Paris, Louvard consciously synthesises the scientific and structural strengths of both EMBL and the French national system.

Finally, the professional contacts made while at EMBL are long lasting. Over the last 15 years, EMBL's turnover has created a formative European network of molecular biologists. Such international scientific communication is a critical element in the future competitiveness of European molecular biology.

# Postdoctoral Fellows: A Rare Breadth of Molecular Biology Approaches

There are only a few institutes in Europe that can claim the combination of chemical, biochemical, physical, structural, biological, and cellular approaches in molecular biology found at EMBL. Most of the laboratory's postdoctoral fellows come explicitly to learn and exploit this broad range of techniques while building their Curricula Vitae for future positions. They train for at least 2 years and many stay 3-4 years, allowing them to pursue relatively long-term, innovative research projects. By the time they leave, they have usually become infected with the contagious interdisciplinary and collaborative culture that permeates the laboratory.

This year, the number of postdoctoral fellows at EMBL is more than triple (136 fellows) the 1984 count. Twenty percent of them receive fellowships from EMBL itself. The remainder are supported by a wide range of national and international agencies, including significant support from the European Union and the Human Frontiers Science Programme. The quality of these postdoctoral fellows is best demonstrated by the fact that more EMBO long-term fellows choose to conduct their research at EMBL than at any other university or research centre in Europe.

# Visiting Scientists Build Skills and Professional Networks at EMBL

 $\mathrm{E}^{\mathrm{MBL}}$  also has many short-term visiting fellows and the laboratory goes to great lengths to make



**Björn Vennström** came to the EMBL in 1983 to study the molecular biology of (proto-) oncogenes and their roles in cell differentiation. Today he is a professor of developmental biology at the Department of Cell and Molecular Biology of the Karolinska Institute in Stockholm.

"I wanted to come to EMBL

because I realised that it was impossible in Sweden for young scientists to receive research grants sufficient for establishing an internationally competitive research group without the direct financial support of senior benefactors. I had worked for two years as a postdoc in San Francisco, and returned after that to Sweden. After three years in my previous department, the situation became untenable: I spent twice as much money as my own grants allowed me. The job offer from EMBL would allow me to completely independently run my own group, and furthermore work in close collaboration with groups at EMBL I already collaborated with.

"Working at EMBL was much better than I had anticipated. Everybody was focused on scientific achievements. Collaborations and the international environment stimulated me to start projects in new research areas such as molecular endocrinology.

"I used my experiences from EMBL for establishing my new group at the Karolinska Institute. More than half of the people in my present group are from outside Sweden, which favours discussions and intellectual stringency. Moreover, the milieu at EMBL prompted me to continue and expand collaborations with laboratories elsewhere in Europe, such as Spain, Britain, Germany, Austria, Holland and Estonia. Finally, I try my best to make graduating Ph.D. students at the Karolinska Institute realise that much good research is being done in Europe, and that a network of European scientific contacts is easier to maintain and cooperate with than transatlantic ones."

their experience scientifically worthwhile and comfortable. Whether they stay for one week or six months, at the main Laboratory or the Outstations, the Laboratory provides materials and technology, interested collaborators, and an open environment. EMBL also helps arrange accessible and affordable housing at its Guest Houses or similar facilities.

The number of visiting fellows between 1990 and 1994, was more than triple (236) the number who came in the previous five year period. Typically, twenty-five percent receive EMBO short-term fellowships, while many others receive funding from outside agencies. Most of these visitors come to learn specific new skills or to use technology not available in their own laboratories. More often than not, they also leave with long-term research networks firmly in place.

# **Training Scientists for Europe's Future**



**Carol Featherstone** has been the editor of the journal Trends in Cell Biology since its inception in 1991. She came to the EMBL for her first postdoctoral fellowship, staying from 1983-86.

"I was a graduate student in England. I was quite young

and naive. I had strayed by accident into membrane biochemistry. Graham Warren came through and gave a talk about the Golgi complex which impressed me. When it came time for a postdoc, most people were going to the United States. I was a bit nervous about this; I thought it would be too aggressive, but I did want to go abroad and thought Germany would be a good place. I remembered Graham's lecture. His cell biological approach to membranes appealed to me after struggling with biochemistry for my PhD, so I applied to him.

"I got a Royal Society postdoctoral fellowship to work in Graham's lab. When I arrived I didn't know one end of the secretory pathway from the other. Ironically, I found the environment much more intellectually aggressive and demanding than I'd expected. Certainly at least as rigorous as my subsequent experiences in the USA at Johns Hopkins or Scripps. It was a tough learning experience for me. If you could defend yourself in an EMBL Cell Biology seminar, you could do so anywhere! EMBL gave me a lot of confidence

"Although the science was a challenge, EMBL had a really good supportive atmosphere. Lots of parties and young people around. It had a kind of island feel where people didn't dash off home in the evening. The bar was a great meeting place and lots of scientific collaborations were set up there. The friendliness and sense of community was really what permitted people to be intellectually demanding of each other."



Matthias Hentze's group in the Gene Expression Programme



Ana Tramontano was a Staff Scientist at EMBL for over two years. Today, she is head of the Biocomputing Department at the IRBM, a basic research laboratory for industry near Rome.

"I received my Laurea in physics and worked in Naples, as well as the U.S., collaborating in developing a molecular

graphics programme called *Insight*. I was asked by Arthur Lesk to come to EMBL as visiting scientist and was more than happy to come. Arthur is one of the best scientists I have ever met and EMBL was an ideal place in Europe to learn biocomputing. Biocomputing is in the middle of many fields and it is very difficult to find a place like EMBL, where all the expertise is collected together. There was an especially strong relationship with Structures. Later, a staff scientist position opened and I applied for it.

"I arrived with experience in molecular graphics and protein structure. I worked on immunoglobulin structures and protein loops and was in charge of part of the molecular graphics system. Apart from my research experience, it was useful seeing how a laboratory should be organised. EMBL is much larger than the IRBM, of course, and my projects have changed, because our focus is ultimately on business. But in many ways, the IRBM is a small replica of EMBL. In my new position, I have more responsibilities than I had at EMBL; we have to maintain the databases, software and the molecular graphics for the IRBM and collaborate with several groups in the institute. But I have tried to copy the methodological tools of EMBL - both databases and software packages to analyse structures. I organise the biocomputing group using ideas that grew from my experience at EMBL.

"The IRBM is connected to EMBnet through the node at Bari and we have EMBL sequences and others updated every week. In fact, I still call EMBL for technology and have on-going contact with people who have been there. A lot of the scientists I work with came from EMBL and ... (the phone rings and Tramontano answers, then returns to the interview). That's an example. That was a former colleague from EMBL. He is coming to Rome on Tuesday and wants to discuss a structure. These are people, although Italians, who I would never have met without my experience at EMBL. EMBL is not the only good lab, but when someone asks me for a good place to work, I keep advising that they can gain a network of relationships at EMBL, which they will never lose."

"EMBL is a successful experiment in integrating research in the fundamental field of structural and cell biology. Outstanding young scientists find there the opportunity of developing their research initiatives in an atmosphere of collaboration and multidisciplinarity, attitudes they then transfer to new generations of students upon return to their home countries. EMBL has become a model for European research institutions and its premises the headquarters for planning future avenues in European biology."

- Antonio Garcia-Bellido, Centro de Biologia Molecular, Madrid -



Angus Lamond came to EMBL in 1987 as a group leader in Gene Expression. He has accepted a position as Research Professor at the University of Dundee, Scotland.

"I had just finished a postdoc at MIT in the US. I was interested in RNA processing and splicing and wanted to follow up certain ideas. There were only two choices - the UK, where I had done my

Ph.D., and EMBL. EMBL was ideal for me as a young scientist. I was first attracted by the offer to run my own lab, but the structure, the interactions between groups, the central funding, and potential contacts with other Europeans scientists swayed my decision.

"The support package offered by EMBL was ideal. There was limited teaching and I could focus on research without having to worry about grants. No one likes writing grants, but at the time, I didn't feel I had the independent research record to compete. Now my lab has strong projects, papers published, and I can write grants in ways I couldn't when I arrived. That's what EMBL is about, giving people a start.

"EMBL is a jewel in the crown of European molecular biology. We need to protect this success story. In my experience, its research record compares extremely well to the top institutes, like the MRC and MIT. There are limitations. Because small groups are emphasised here, ultimately there is a limited amount of space and postdocs you can have. But that's part of the system. I enjoyed it, but now I'm ready to move on. That is where the national system comes in. When I leave, I'll develop the project I started here. I think that is absolutely the way it should work. EMBL and the national systems are complementary."

*Fulvia Verde* came to the EMBL from Pisa, Italy as a predoctoral fellow in 1987. She completed a dissertation in 1991. She is currently a post doctoral fellow in Paul Nurse's laboratory at the Imperial Cancer Research Fund in London.

"EMBL was a great opportunity for me as a graduate student. My project on the cell cycle was very challenging and Eric Karsenti was a wonderful super-

visor. He was relaxed and enthusiastic and gave me an immense amount of freedom. The facilities and general support structures were extremely good and there were many fruitful interactions between different laboratories. I enjoyed the atmosphere at EMBL very much, and was exposed to a very dynamic way of thinking and doing research. Now I am continuing my studies on the cell cycle in Paul Nurse's lab. I miss EMBL, but I am enjoying my time in London, my project, the people, and city.



"EMBL was a widening cultural experience. I was able to meet people from many different countries. Most of my friends were French, German, and English.

> From these experiences I changed and acquired a new way of thinking about my own country. If and when I return to Italy, I will bring these ideas back with me; a new way of seeing Europe, not only scientifically, but economically, historically, etc. Of course, I miss Italy and I'd love to go back, but it is not so easy at the moment. Hopefully, Italy will continue to develop its programmes in cell biology and, perhaps someday, we can also have an institute like the EMBL, attracting

scientists from all corners of the world."

Herbert Jäckle came to EMBL as a Group Leader in 1980. He worked on genes which are active in the salivary glands of flies. Today he is Director of the Department of Molecular Developmental Biology at the Max-Planck-Institut für Biophysikalische Chemie, in Göttingen, Germany.

"I came to the EMBL when I was 30. I already had more than two years of postdoctoral experience in classical zoology. I felt EMBL was the place for me to work with phage and recombinant DNA techniques in Europe. I wanted this technique to use with a system in Drosophila to answer questions I had for a long time.

"I came for the molecular biology, but I was also exposed to the beauty of genetics and this really brainwashed me. Just having people in the next lab working on something different widened my perspective. My experience at EMBL allowed me to synthesise the molecular biology and genetics approaches on a fundamental biological problem that was clear from my zoological background. Without having been there, I might have either done simple protein gels with Drosophila or something else very stupid.

"In this environment, it became very clear where I wanted to go with my career. I first took my project to Tübingen, where I had a junior position. It has absolutely affected the running of my lab today. I try to create an international environment and take peo-

ple on who have different scientific backgrounds. I came from a completely different background into something new and grew from it. I want to create this opportunity for other young people. Keep people from falling into this narrow - "This is MY problem" way of thinking."





**Daniel Louvard** came to EMBL as a Group Leader in 1978. Today, he is the Research Director of the Curie Institute in Paris.

"I had done a postdoc in America and I knew at the time I would have difficulty developing independence in France. I was only 30; it was unthink-

able for such a young person to run a lab. I took a risk of being forgotten at EMBL - it did not have a reputation yet - but I wanted to develop my own ideas.

"Every group at EMBL was small, but very ambitious. You could not carry on projects without the help of others. It wasn't planned, but we were intimate. We had a constellation of people with different training, and ideas were fed by others' thinking.

"We got to know the important scientists in the field of membrane trafficking during this time. This was when the annual EMBL courses got started. We had famous cell biologists working with young people. It gave us contacts. My work went well; EMBL became better known; Jacob came to talk to us. So I wasn't forgotten by French biologists.

"Clearly, EMBL had a great influence on me. I supported, for example, the Director of CNRS, Claude Paoletti, to fund competitive start-up grants for equipment and research for young investigators. If you are provided a chance to write grants proposals, but not need to justify every step, you can be very innovative.

"Recently, I had the luck to be asked to direct the research at the Curie Institute. We synthesise the best of the EMBL and the national systems. CNRS provides stability; people know they have a secure position; it allows them to pursue long-term projects. But offering independence and responsibility to the young investigator makes the system much better. When recruiting junior group leaders, we use an international review committee. We divide scientists into smaller problemoriented groups. Young investigators are chaperoned by a few senior scientists to show them how to run a lab, but the research is left to Staff Scientists who lead the small groups. And we now have a special five-year agreement at Curie for starting groups. The scientists, of course, have a permanent job at CNRS, but after five years at Curie they must compete again for a larger group and space. Some might stay, while others go elsewhere and disseminate ideas about independent science. This could give us a scientific flux and mobility that France needs."

Predoctoral Fellows: Enthusiasm and Ideas Exchanged for Experience and Distinguished Qualifications

The EMBL predoctoral programme became an integral part of the its training system in 1983. Today, EMBL has 91 predoctoral students, each spending three to four years completing his or her thesis.

Competition for predoctoral positions at EMBL is vigorous. The laboratory advertises its predoctoral programme in major European scientific journals and solicits applications from over 1000 institutions throughout Europe. Top applicants are invited to an intense week-long visit to the laboratory, with every student interviewed by the group leaders from two prospective scientific programmes. Scientists examine students' technical knowledge, desires and motivations, but they also have to take into account very different early training and cultural backgrounds. In 1994, EMBL accepted twenty-five very strong candidates to begin their research careers at the laboratory.

During their first year at the laboratory, the students participate in required coursework and are exposed to a rich series of seminars by EMBL scientists and outside molecular biologists with international reputations. But the students critical edge is honed by developing their own research projects, conducted under the supervision of group leaders. Many of the students are surprised how seriously their own intellectual contributions are taken by the more senior staff. In response to this treatment, they inject a wealth of enthusiasm and energy into the laboratory's intellectual life and contribute significant investigative results.

Since 1983, over 80 EMBL predoctoral students have received doctorates for theses written at EMBL. Theses are read and approved by national universities in the member states. The EMBL Ph.D.s go on to compete very successfully for EMBO and other postdoctoral long-term fellowships. In open competition for EMBO fellowships, for example, EMBL Ph.D.s have a 60% success ratio as compared to 28% for all EMBO applicants combined. Virtually all of EMBL Ph.D.s find postdoctoral positions in excellent European and American laboratories.

"In this unique Centre, renowned for scientific research and achievements of the highest quality, advanced technology, and a flexible, exemplary structure of the working groups, the spirit of a unified Europe is alive in the most practical and profitable terms. This refers to both the international collaboration within EMBL and EMBL's continuous interaction with the outside scientific community through working visits, the EMBL Database, training courses, postdoctoral training and the recruitment of EMBL scientists to academic institutions and industry across and beyond Europe. The European Community should be proud of EMBL and give it all possible support!"

- Klaus Rajewsky, Insitut für Genetik der Universität zu Köln -

Ramón Serrano Salom was a Group Leader in Biological Structures from 1986-92. He is now Professor at the Universidad Politécnica de Valencia.

"I'll never forget the call from Demetrius Tsernoglou offering me a position at EMBL. I had been frustrated by a lack of facilities and adequate funding and I was thinking seriously of leaving research. Suddenly, for the first time in my life, I was not limited by the means for doing research; at EMBL, everything seemed possible, from crystallising a protein and resolving its structure with X-rays to having access to the most recent data banks and sophisticated bioinformatics programs. We had equipment

and services for automatic sequencing techniques, protein synthesis, microinjection, and so many other things. All this topped with an excellent library (with the best librarian I have known in my life - Mary Holmes). I remember telling Hans Flösser, the director of the workshops, that I felt like a little boy on the day the Three Wise Men had come and brought everything he had ever dreamed of.

"The social atmosphere was excellent and I will never forget my scientific conversations with scientists like

Simons, Philipson, Dobberstein, Kühlbrandt, Sander, Graf, Tooze, Cortese, Jones, Pattus, Saraste, di Lauro, Tollervey, Dotti, and Hurt, just to name a few. Over 25 people from all over the world worked in my lab in those five years. One could find new crystallographic structures, new oncogenes, new molecular developmental mechanisms, protein components of nuclear envelopes and transcription factors - and you could talk at any moment with the scientists that were behind these discoveries. Every week there were more than a dozen seminars given by scientists of international calibre, many times with Nobel prizes. During the entire first year, I felt I should work every possible minute because I might never get an opportunity like this again.

"Centres like the EMBL have a great utility early in a career, when you are immersed in your "war of scientific independence." This phase is the key to any investigator's career, when one is developing their own original line of investigation. Rarely can one do this while under the protection of an established group. A place like EMBL opens a range of possibilities for young Spanish scientists. The

technical basis of molecular biology may be possible in smaller laboratories, but molecular biology is more than technology. The conceptual complexity and experimental overlap make it necessary to work in an interdisciplinary environment, where one can combine aspects of cell biology, classical genetics, microbiology, biochemistry, biophysics, biocomputing and genetic engineering. This is difficult to attain in small dispersed research centres. This is why you find the great advances in molecular biology made in a

few labs, like the LMB, Cold Spring Harbor, and EMBL.

"EMBL isn't perfect; I have criticisms. I would like to see more group leaders from countries like Spain. But we should also look closely to see how the political structure of science in Spain contributes to the shortage of applications for positions. I'm encouraged by Kafatos' attempts to deal with these issues. And my criticism doesn't change my view that EMBL is a model organisation that we should imitate here in Spain. At the moment, our challenge is integration into Europe and centres like EMBL are a compass that will constantly show the way."



Jolanda Blom is predoctoral student at the University of Amsterdam, She participated in a two-week long EMBL Practical Course on Membrane Proteins, organised by EMBL's Matti Saraste and former EMBL Group Leader Franc Pattus (now in Strasbourg).

"In Amsterdam, we had isolated three genes encoding mitochondrial membrane proteins in yeast, but we didn't have much experience in membrane proteins. I saw an announcement for the workshop, so I

thought it was an excellent opportunity to get some more insight. It was a competitive application. I paid for travel and EMBO paid the rest.

"I think these workshops are really worthwhile. I'm learning a great deal about how to work with membrane proteins. We have been observing how much detergent can bind to one purified membrane protein on a column in order to learn the size of the

protein. Part of the workshop is theoretical - a couple of lectures each day, but then the rest is just practical, and that's what I like. I've been to conferences and lectures on membrane proteins, but I've never done anything like this. This is much better. Not every part is useful for my work in Amsterdam, but I want to broaden my career after my PhD.

"I would love to do this again. You learn practical things and meet a lot of people in the field. I'm giving a talk on my own work - everyone does. That is also nice, because you have people from all over the world and different disciplines and everyone has to present their work. This gives insight about what is being done internationally, not just what you are doing yourself, but other membrane work with other organisms. It's great."



**Oddmund Bakke** was at EMBL as a postdoc/visiting scientist from 1988-90. He is currently Professor in the Department of Biology, University of Oslo.

"I came to EMBL to learn membrane biology techniques which were needed in my project in Norway. I had a background in biophysics - I am probably one of the few people who has also been a fellow at the

European institute for high energy physics, CERN. Comparing these, EMBL works really well for international integration. The laboratory is relatively small and the various groups consist of people from many countries. The groups have extensive contact with each other.

"The small size of the individual groups was important. Group leaders couldn't afford to have non-producing people. This created a very exciting atmosphere. At EMBL, we were given a chance to be in the vanguard of science. The attitude was - If you are going to do something, do it well. The aim was to

## A Centre for Advanced Courses and Symposia

EMBL has evolved into the largest European centre for advanced courses and meetings in molecular biology. It organises large symposia, such as those on oncogenes and mouse development, held in alternating years. It also sponsors small workshops (about 50

people each) from time to time. Most importantly, it conducts an extensive programme of advanced practical courses, held at the Heidelberg teaching laboratory. These provide instruction in new research methods for groups of approximately 20 selected students. The majority of the participants are at the postdoctoral level and come from all over the

world. Course topics have included X-ray and electron microscopic determination of macromolecular structure, DNA sequencing, computer protein design, 2D and 3D light microscopy, DNA-protein interaction, recombinant DNA and genetic engineering techniques, and methods in cell biology.

A number of the practical courses teach methods developed at EMBL, such as automated DNA sequencing, automated microinjection of cells and cryoelectron microscopy. One of the functions of EMBL's



Poster session at a recent EMBL conference

get valuable information, not just a thesis or publication.

"I was very practical. There were techniques I wanted to learn. I got many new tools and wound up with a project that I was able to take back to Norway - the biology behind antigen presentation, which is now very much in fashion. This gave me a basis for my present work in Oslo and really gave me an advantage.

"Personally, I was glad to come as a visiting scientist and not as a group leader. I had a chance to see all different kinds of group leaders without being swamped with the responsibilities myself. I looked at the way things were organised and how the problems were attacked. People passing by, exchanging information, finding out what has already been done within a field. People were open and it was always possible to get advice and learn from others. It was altogether very useful for setting up my lab and follow up an extensive international collaboration."

new European Bioinformatics Institute, complementing its service and research objectives, will be to serve as a European advanced biocomputing instructional centre for sequence database management and analysis. The Grenoble Outstation will be taking an increasingly important role in providing courses in structural biology, taking advantage of its unique access to pow-

erful neutron and synchrotron radiation sources.

The advanced training programmes are an example of the synergism between EMBL and EMBO. Many of the courses, for example, are organised and funded jointly by EMBO. EMBL scientists participate in many EMBO workshops and courses held at other sites in Europe. EMBL

and its parent organisation, EMBO, are leaders in promoting professional networks. At their practical courses and meetings, participants learn state-of-theart techniques, which are then applied in their own national laboratories. This is one of the most costeffective ways of transferring technology and skills across Europe. And for EMBL, it forges important links between national laboratories and EMBL's research groups.

- David States -

"EMBL is a unique model for the world as the only unified action of sovereign countries for the purpose of biological research and training. It has served European molecular biology well, providing a venue for the development of many of the present-day tenured faculty of the member countries. It has also done some of the most important research work emanating from Europe, its courses have trained innumerable people in modern technology, and it has provided a focus for interaction with the rest of the world. It should be an example to Asian and other countries of the joint use of scarce resources to bring progress in biomedical science and to develop a base for participating in the industrial revolution of biotechnology."

- David Baltimore, Nobel Laureate, Massachusetts Institute of Technology, Cambridge, USA -

# Social Life in an International Environment

Over the years, the scientists and staff of EMBL have developed a strong sense of community and shared mission. The universal language of science, the experience of living in an international setting and the compact environment of the Laboratory have played a part in creating these bonds. As a uniting Europe approaches the 21st Century, EMBL offers one of the very best examples of the benefits of internationalism, both in professional and cultural terms.

International institutions, especially those with a mobile staff and constant stream of visitors, have special needs. EMBL puts great effort into solving difficul-

ties that staff and visitors initially face, from language to finding housing in a new country. There are clear benefits to be gained by making the staff and visitors' lives more comforthelping able: with bureaucratic requirements of legal residency in the host nation, for



Guy Fawkes Day - British festival every 5th of November

example, frees scientists to concentrate on their work and promoting good internal social relations rein-

forces professional bonds that last long after the scientists' return to their home countries.

As one might expect, language plays a very important role at any international institution. There are, of course, three official languages at EMBL and the realities of functioning within the host countries demand that special attention be paid to language instruction. EMBL therefore organises instruction in German, English and French. In addition, stimulated by daily contacts with colleagues from many different cultures, a

number of EMBL scientists learn additional languages. English is the common scientific language and more often than not, the common social language as well, especially at the main lab in Heidelberg. Still, the multilingual environment is one of

the attractive features of EMBL.

# Pleasure and Science Mix

While EMBL personnel in the Outstations are part of a larger community at their individual locations, the relatively isolated site of the Heidelberg Laboratory and its self-sufficient community create unique challenges and opportunities. Providing good food at EMBL is essential for morale and, frankly, it keeps the scientists on site. Moreover, there is little doubt that the canteens and cafés are the stage upon which a great deal of EMBL's pro-

fessional interactions are played out. It is a truism that more quality scientific discussions take place

> over a cup of coffee than at the lab bench.

The tightknit EMBL community has evolved from the early days of the laboratory, when intimate weekly seminars and dinners "held the laboratory together." Christmas parties and the annual Fasching (Carnival) costume parties were events

that included everyone from the Director General to the dishwashers. Social events like these still play an

Mountain climbing in the Alps



important role at EMBL. Scientists and support staff from one country regularly organise national theme parties to celebrate their pride in country with colleagues. EMBL's biting sense of humour about itself comes out most clearly at these times; Italian scientists, for example, were teased mercilessly by the other scientists at a large get-together to watch the 1994 World Cup football final. These activities introduce new scientists and bring together colleagues from different programmes; humour stands next to serious intellectual discussion; and many a scientific collaboration has begun with scientists not dressed in lab coats, but draped in costumes.

Sport is also a popular way for scientists to get together. Programme Coordinators, technicians, and support staff - both men and women - take part regularly in football, basketball and other team sports. There is a sauna and a weight room in one of

the Guesthouses. Their have been frequent memorable group trips, especially to the Alps for skiing. And in the summer, EMBL at Heidelberg reserves time at a nearby lake for water-skiing, where one can typically find 20-30 scientists making fun of each others' desperate attempts to make it around the lake.



Technician Alexa Charlesworth

children (34 children) and a "Kindergarten" for children three to six years of age (32 children). EMBL

also provides a tutor who works with older children after regular hours in Heidelberg at a nearby international school. Both the Kinderkrippe and Kindergarten are open from 8:30 to 18:00.

The children join in traditional activities, such as artwork, games, story telling and outside play, but they also participate in an international laboratory of their own. Here children from all over the world learn respect, tolerance, and how to enjoy new friends from many cultural backgrounds from an early age. German, not surprisingly, is the common language, but at any given time, many languages can be heard as pairs of children run off to play in one corner or as the parents pick up their little ones. Most of the teachers are bilingual

and they make a special effort to help new children through the confusing transition of coming to a

> foreign country. The children respond to this environment with amazing grace and flexibility. One likes to think that these experiences will influence them for a lifetime.

# Families and Childcare

t is not surprising that many scientists at EMBL are raising families, given the role of the laboratory in training young scientists. In fact, many scientists leave with strong affection for EMBL not only because of fond scientific memories, but because their children were born during their stay here. Establishing a scientific career, however, is particularly challenging when combined with the responsibilities that come with rearing young children. This is especially true for families with two active scientists, or for single

parents. These responsibilities are often felt most strongly by women scientists, who are not only trying to make headway in a discipline traditionally dominated by men but who, despite modern trends, still often bear the greater burden for care of children.

Conscious of these needs, EMBL has its own facilities in Heidelberg for the children of EMBL scientists and employees. Initiated in 1988 by Personnel Director Konrad Müller and assisted by scientists like Patricia Kahn and Thomas Graf, EMBL first opened a small childcare centre in the



E MB ratory ar Heidelb

Children at the EMBL Kindergarten

**Relations with Other Communities** 

**E**<sup>MBL's host communities have graciously accommodated the Laboratory and its Outstations. Furthermore, Heidelberg, Grenoble, Hamburg, and Cambridge have built their own reputations as interesting cities, with many exciting activities in the areas surrounding the main Laboratory and the Outstations. Neighbourliness, of course, goes both ways, and EMBL recognises its responsibilities toward the communities within which it rests. In the past,</sup>

EMBL has organised tours and other special events



Heidelberg on the Neckar River

for the public. The Laboratory would like to strengthen these efforts further, improving networks with related European scientific institutions, organising liaison programs with schools, and sponsoring special events so that host communities and

EMBL get to know each other better.

- David States -

# **EMBL** Facts and Figures

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A short list of the most important dates and events during the history of EMBL.

Requests for additional information about EMBL should be directed to:

David States Public Relations Telephone (49) 6221 387 252 EMAIL: States@embl-heidelberg.de

		Current EMBL	1994 Ordinary No	ational Contribution	
Country	Date of Entry	Council Delegates	Percent	DM 1994	
Austria	1974	E. Wintersberger	2.20	1,487,161	
Belgium	1990	A. Bollen M. van Montagu	2.91	1,967,108	
Denmark	1974	M. Bennum J.E. Celis	1.82	1,230,290	
Finland	1984	J. Aalto M. Kivirikko	1.84	1,243,808	-
France	1974	G. Fouan M. Colomb	16.96	11,464,658	
Germany	1974	A. Freytag P. Gruss	22.04	14,898,645	
Greece	1984	A. Evangelopoulos	0.99	669,224	÷
Israel	1974	Y. Degani M. Edelman	0.73	493,468	\$
Italy	1974	E. Campo G. Tocchini-Valentini	16.20	10,725,686	
Netherlands	1974	M. Vintges P. van der Vliet	4.25	2,872,925	
Norway	1985	J.R. Lillehaug K. Sletholt	1.47	993,694	
Spain	1986	C. Martinez-A. E. Montoya	7.10	4,799,474	
Sweden	1974	J.E. Gustavsson BM. Sjöberg	3.24	2,190,183	
Switzerland	1974	M. Bertschi B. Hirt	3.81	2,575,493	٠
United Kingdom	1974	M. Davies N. Winterton	14.44	9,761,183	
			100%	67,373,000	

# **EMBL Member Countries**

# Current Members of the EMBL Scientific Advisory Committee (SAC)

Francesco Blasi, Milan (*Italy*) 1990-1995 Maurizio Brunori, Rome (*Italy*) 1991-1996 Margaret Buckingham, Paris (*France*) 1995-1997 Marc Chabre, Nice (*France*) 1991-1996 Walter Fiers, Gent (*Belgium*) 1991-1996 Frank Grosveld, London (*Netherlands*) 1993-1995 David Hogness, Stanford (*USA*) 1994-1996 Leroy Hood, Seattle (*USA*) 1995-1997 Louise Johnson, Oxford (UK) 1994-1996 Alwyn Jones, Uppsala (Sweden) 1992-1997 Mary Osborn, Göttingen (Germany) 1992-1997 Hugh Pelham, Cambridge (UK) 1994-1996 Klaus Rajewsky, Köln (Germany) 1995-1997 Joel Sussman, Rehovot and Brookhaven (Israel and USA) 1995-1997 Kurt Wüthrich, Zürich (Switzerland) 1990-1995

# **EMBL Council Delegates (1974-Present)**

(Listed by Country and Chronological Order of Service)

#### Austria

W. Grimburg G. Zamostny H. Schacher H. Tuppy G. Kreil M Schweiger O. Meixner E. Wintersberger

#### Belgium

N. Henry A. Bollen M. v. Montagu

#### Denmark

N.O. Kjeldgaard N.O. Gram N. Groth H. Østergaard-Anderson B. Clark B. Sode-Mogensen C. Sørensen B. Rosengreen O. Norén M. Bennum J. Celis

#### Finland

M. Niemi S. Loikkanen M.-L. Tolonen K. Kivirikko J. Aalto

#### France

A. Alline R. Monier J.P. Ebel M. Rey F. Normand P. Chambon P. Laget I. Weil J.F. Stuyck-Taillandier M. Stakic P. Jeanteur I. Rover I. Hanoune H. Rouillé d'Orfeuil J. Damagnez M. Colomb G. Fouan

# Germany

C. Zelle H. Zachau H.-M. Spilker C. Patermann W. Franke W. Mönig W. Dörfler A.-M. Hansen P. Gruss A. Freytag

#### Greece

F. Kafatos C. Krimbas C.E. Sekeris M. Papamichail M. Maniatis A. Evangelopoulos

#### Israel

Y. Saphir M. Sela M. Avron A. Keynan F. Soffer Y. Degani M. Edelman

## Italy

P. Fasella B. Purificato G. Cortelessa G. Armento C. Saccone M.C. Moschetti L. Alberghina M. Lener W. Alles M. Melli S. Tokdemir G. Carante M. Brunori E. Campo G. Tocchini-Valentini

#### Netherlands

W. Hutter A. Rörsch E.C. Slater J.A.M. Goemans R.F. Heyn C.A. Ladage J. Drenth M.J. Rietveld J.v.d. Donk M. Vintges P.v.d. Vliet

#### Norway

H. Prydz A. Andersen B. Mørland J.R. Lillehaug K. Sletholt

## Spain

V. Larraga A.M. Municio J. Ortín Monton E. Montoya C. Martinez-A.

#### Sweden

P. Reichard A. Engström M.A. Ottosson L. Philipson I. Argrell K. Brådy K. Stråby M. von Glehn B. Daneholt C.-I. Brändén C. G. Kurland J.E. Gustavsson B.-M. Sjöberg

#### Switzerland

E. Andres N. Roulet J.O. Quinche A. Kamer B. de Riedmatten O. Uhl W. Schmidt J. Streuli L. Erard J. Leutert B. Hirt M. Bertschi

#### United Kingdom

J. G. Duncan K. Levy S.G. Owen F. Rushton D. Noble B. Loder J. Alwen N. Morris B. Dodd M. Davies N. Winterton

# Scientific Advisory Committee Members (1971-Present)

(Listed alphabetically with years of service)

Baltimore, D. (USA) 1982-1987 Birnstiel, M. (Austria & Switzerland) 1975-1976 Blasi, F. (Italy) 1990-1995 Blow, D. (UK) 1982-1985 Brändén, C. (Sweden) 1984-1989 Brenner, S. (UK) 1971-1975 Bricogne, G. (France) 1985-1990 Borst, P. (Netherlands) 1985-1990 Brunori, M. (Italy) 1977-1982; 1991-1996 Buc, H. (France) 1979-1984 Buckingham, M. (France) 1995-1997 Cantor, C. (USA) 1989-1994 Caspar, D. (USA) 1976-1981 Chabre, M. (France) 1991-1996 Chambon, P. (France) 1976-1981; 1983-1988 Changeux, J-P. (France) 1977-1978 Drenth, J. (Netherlands) 1979-1984 Eigen, M. (Germany) 1971-1976 Fasella, P. (Italy) 1971-1977; 1983-1988 Fiers, W. (Belgium) 1991-1996 Gallwitz, D. (Germany) 1986-1991 Gehring, W. (Switzerland) 1989-1994 Gierer, A. (Germany) 1978-1983 Grosveld, F. (Netherlands) 1993-1995 Grunberg-Manago, M. (France) 1971-1976 Harris, H. (UK) 1971-1976 Helmreich, E. (Germany) 1980-1985 Hogness, D. (USA) 1994-1996 Hood, H. (USA) 1995-1997 Huxley, H. (UK) 1976-1981 Jerne, N. (Switzerland) 1971-1975 Johnson, L. (UK) 1994-1996 Jones, A. (Sweden) 1992-1997 Kafatos, F. (Greece and USA) 1984-1989 Kellenberger, E. (Switzerland) 1977-1982 Klug, A. (UK) 1971-1975 Le Douarin, N. (France) 1990-1992 Levitt, M. (Israel) 1983-1988 Lodish, H. (USA) 1988-1993 Luzzati, V. (France) 1971-1975 Maaløe, O. (Denmark) 1971-1976; 1978-1983 Magnusson, S. (Denmark) 1985-1990 Melchers, F. (Switzerland) 1982-1987 Monroy, A. (Italy) 1978-1983 Nurse, P. (UK) 1989-1994 Osborn, M. (Germany) 1992-1997 Oesterhelt, D. (Germany) 1989-1994 Pelham, H. (UK) 1994-1996 Rajewsky, K. (Germany) 1977-1979; 1995-1997 Reichard, P. (Sweden) 1971-1977 Rigler, R. (Sweden) 1977-1982 Rörsch, A. (Netherlands) 1971-1976 Schatz, G. (Switzerland) 1982-1987 Schweiger, M. (Austria) 1978-1983 Sela, M. (Israel) 1976-1981 Steitz, J. (USA) 1988-1993 Sussman, J. (Israel and USA) 1995-1997 Thomas, R. (Belgium) 1971-1975 Tocchini-Valentini, G. (Italy) 1984-1989 Tuppy, H. (Austria) 1975-1977 Unwin, N. (UK) 1988-1993 van Deenen (Netherlands) 1976-1981 Walker, P. (UK) 1977-1982 Waterfield, M. (UK) 1986-1991 Weber, K. (Germany) 1984-1985 Weiss, R. (UK) 1983-1988 Weisskopf, V. (USA) 1971-1974 Weissmann, C. (Switzerland) 1971-1974 Wüthrich, K. (Switzerland) 1990-1995

Country	Financial Contribution	All Main Personnel	All Scientists	Faculty **	Fellows ( Post & Predoc)	Technical & Administrative
Austria	2.35%	2.63%	2.50%	2.54%	2.73%	2.79%
Belgium	2.47%	1.05%	1.27%	1.86%	0.93%	0.68%
Denmark	2.09%	1.59%	0.95%	0.62%	1.06%	2.34%
Finland	1.76%	1.80%	2.23%	2.03%	2.22%	1.13%
France	19.47%	13.37%	12.28%	11.48%	12.92%	14.64%
Germany	25.42%	33.79%	27.87%	28.97%	26.95%	40.71%
Greece	1.04%	2.58%	4.04%	3.59%	4.50%	0.30%
Israel	.76%	1.06%	0.54%	0.85%	0.22%	1.67%
Italy	14.55%	7.86%	13.38%	7.55%	17.98%	1.39%
Netherlands	5.20%	5.19%	4.71%	5.32%	4.01%	5.75%
Norway	1.65%	0.70%	1.13%	0.00%	1.68%	0.00%
Spain	4.92%	3.25%	4.62%	1.45%	6.11%	1.05%
Sweden	3.76%	2.38%	2.65%	2.62%	2.28%	2.06%
Switzerland	3.99%	2.36%	3.49%	5.62%	2.45%	1.05%
United Kingdom	15.33%	23.76%	21.85%	29.35%	16.54%	26.00%
Non Members***	-	12.30%	18.71%	18.57%	17.73%	3.40%

# Personnel and Finances, 1975-94\*

\* Percentages for Member Countries are calculated considering Member Countries only. They are based on the years of each country's actual membership, which vary and therefore cannot be expected to add up precisely to 100%. Supernumeraries, diploma students, or trainees below the predoctoral level are not included.

\*\* Faculty Scientists = EMBL Group Leaders and Staff Scientists.

\*\*\* Non-members' percentage is calculated considering Member and Non-Member Countries combined.



# Percentage of All EMBL Scientists

	EMBL Publicatio	ns in Selected Jo	ournals, 1983-92	
Year	Publications in refereed journals	Publications in 8 selected journals	Member states' ordinary contributions constant prices (Million DM)	Member States' ordinary contributions current prices (Million DM)
1983	124	53 (42,8%)	33,2	33,2
1984	143	72 (50,4%)	34,9	36,0
1985	189	66 (34,9%)	36,6	38,2
1986	201	76 (37,8%)	40,3	41,7
1987	223	100 (44,8%)	42,7	44,6
1988	207	69 (33,3%)	42,7	46,1
1989	206	75 (36,4%)	43,1	48,5
1990	251	93 (37,0%)	44,6	52,6
1991	266	105 (39,5%)	45,9	56,2
1992	328	116 (35,4%)	46,9	60,8

Table1 : The eight selected journals are in alphabetical order:

- Cell - EMBO J. - J. Biol. Chem.

- Nature - Proc. Nat. Acad. Sci. USA

- J. Cell Biol.

- Science

- J. Mol. Biol.

# **EMBL** Alumni in Europe

# Former EMBL group leaders, staff scientists, postdoctoral and predoctoral fellows holding independent positions

Allan, Viki - Group Leader		Bernués, Jordi - Group Leader		Camilloni, Giorgio - Assoc. Professor	
MRC Structural Studies Division	GB	Centro de Investigación y Desarrollo, CSIC	E	University of Rome	1
Armstrong, John - Group Leader		Beug, Hartmut - Senior Scientist		Carmo-Fonseca, Maria - Group Leader	
University of Sussex	GB	University of Vienna	Α	Universidade de Lisboa	Р
Arnold, Berndt - Assoc. Professor		Bianchi, Marco - Assoc. Professor		Cesareni, Giovanni - Professor of Gene	tics
DKFZ Immunology Department	D	University di Milano	Ι	University of Torvergata	I
Bakke, Oddmund - Professor		Böhm, Michael - Professor		Chanat, Eric - Group Leader	
University of Oslo	Ν	Fachhochschule, Hamburg	D	Lab. Biol. Cellul. Molecul., Jouy-en-Jo	sas F
Banner, David - Group Leader		Bomsel, Morgane - Group Leader		Charnay, Patrick - Director	
Hoffman la Roche	CH	Institut Pasteur, Paris	F	INSERM Unit 368, Paris	F
Banting, George - Lecturer		Bordas, Juan - Head, Synchotron Radiation		Chavrier, Philippe - Research Director	
University of Bristol	GB	SERC, Daresbury Laboratory	GB	Centre de Immunologie de Marseille-Lumin	ny F
Barlow, Denise - Group Leader		Bossi, Nello - Research Director		Ciliberto, Gennaro - Programme Coord	inator
University of Vienna	А	CNRS, Gif-sur-Yvette	F	IRBM, Pomezia	Ι
Bartunik, Hans Dieter - Group Leader		Bowles, Dianna - Professor		Clague, Michael - Group Leader & Lectur	
MP-AG Struc. Molec. Biol. Hamburg	D	University of York	GB	University of Liverpool	GB
Baudet, Sylvie - Group Leader		Brandli, Andre W - Group Leader		Clarke, Paul - Group Leader	
Université-Sud, Paris	F	ETH, Zürich	CH	University of Manchester	GB
Bäuerle, Patrick A - Professor		Bryan, Richard - Director of Computing	5	Colanturi, Vittorio - Assoc. Professor	
University of Freiburg	D	Oxford University	GB	Universita Federico II, Napoli	I
Berkenstam, A - Assoc. Professor		Burgert, Hans-Gerhardt - Assoc. Profess	sor	Constanzo, Francesco - Professor	
Karolinska Institute	S	MPI Für Biologie, Freiburg	D	University Frederico II, Napoli	1

# (EMBL Alumni in Europe continued)

Cortese, Ricardo - Director IRBM, Pomezia	I	Fiorella, Altruda - Assoc. Professor Univesity de Torino	Ι	Jockusch, Brigitte - Professor University of Braunschweig	D	
Cosson, Pierre - Group Leader Basel Institute of Immunology	СН	Frain, Monique INSERM Unit 368, Paris	F	Jurgens, Gerd - Professor University of Munich	D	
Cutler, Daniel - Group Leader MRC, University College London	GB	Frank, Rainer - Group Leader ZMBH, University of Heidelberg	D	Kneale, Geoff - Lecturer University of Portsmouth	GB	
Dabauvalle, Marie - Assist. Professor University of Würzburg	D	Freeman, Bob - Head of Scientic Purcha ESRF, Grenoble	se F	Koch-Brandt, Claudia - Professor Gutenberg Universität, Mainz	D	
Damm, Klaus - Forschungsleiter Thomal, Biberach	D	Fries, Eric - Assoc. Professor University of Uppsala	S	Kokkinidis, Michael - Group Leader Inst. of Molecular Biology, Heraklion	GR	
Davey, John - Group Leader University of Birmingham	GB	Frischauf, Anne-Marie - Professor ICRF, London	GB	Koller, Barbara - Group Leader University of Lund	S	
Davoust, Jean - Research Director INSERM, Marseille	F	Fuhrmann, Ulrike - Group Leader Schering, Berlin	D	Koshy, Rajen - Senior Lecturer Hammersmith Hospital, London	GB	
de Curtis, Ivan - Group Leader Milano	I	Garoff, Henrik - Professor Karolinska Institute	s	Kreis, Thomas - Professor Sciences III, Geneva	СН	
De Francesco, Raffaele - Group Leader IRBM, Pomezia	I	Gausepohl, Heinrich - Technical Directo ABIMED Analyse Technik	or D	Kurzchalia, Teymuras - Group Leader Max-Delbrück Zentrum Molekul. Med., Berlin	D	
Delius, Hajo - Group Leader DKFZ, Heidelberg	D	Giesen, Ursula - Group Leader Boehringer, Tutzing	D	Lehrach, Hans - Director Max Planck Institut, Berlin	D	
De Martin, Rainer - Group Leader Sandoz, Vienna	А	Gilberg, Eric - Professor University of Münich	D	Kvist, Sune - Professor & LICR Membe Ludwig Inst. for Cancer Research, Stockholm	r S	
De Mey, Jan - Professor Institut Jacques Monod, Paris	F	Gorvel, Jean-Pierre - Group Leader INSERM-CNRS, Marseille	F	Laggner, Peter - Director Österr. Akademie der Wissenschaften	A	
De Meyer, Leo - Professor Max Planck Institut, Göttingen	D	Greulich, Otto - Professor University of Jena	D	Lakey, Jeremy - Lecturer University of Newcastle	GB	
De Simone, Vincenzo - Assoc. Professo University Federico II, Napoli	or I	Gruenberg, Jean - Professor University of Geneva	СН	Lemaire, Patrick - Group Leader II CNRS and Wellcome/CRC Institute, Cambridg	e GB	
De Vendittis, Emmanuele - Assoc. Prof University of Napoli	fessor I	Hamm, Jörg - Staff Scientist IRBM, Pomezia	I	Lepault, Jean - Research Director CNRS Centre Génétique Molécul., Gif sur Yve	tte F	
Di Lauro, Roberto - Professor of Geneti University of Udine	ics I	Hendrix, Jules - Founder & Owner X-ray Research, Hamburg	D	Lesk, Arthur M - Reader University of Cambridge	GB	
Di Nocera, Paolo - Assoc. Professor Universita Federico II, Napoli	I	Herrmann, Bernhard Max Planck Institut, Tübingen	D	Leutz, Achim - Assoc. Professor MDC Berlin Buch	D	
Dobberstein, Bernhard - Professor ZMBH, University of Heidelberg	D	Herzog, Richard - Group Leader Thomson-CSF/LCR, Corbeville	F	Lipp, Joachim - Group Leader VIRCC, Vienna	А	
Dubochet, Jacques - Professor University of Lausanne	СН	Hille-Rehfeld, Annette - Group Leader University of Göttingen	D	Lorenzetti, Rolando - Group Leader Centro Ricerche DOW LEPETIT Gerenzano		
Duboule, Denis - Professor University of Geneva	СН	Hurtley, Stella - European Editor Science. Cambridge	GB	Louvard, Daniel - Director of Biology Divisi Institut Curie, Paris	ion F	
Ducommun, Bernard - Professor University of Toulouse	F	Huttner, Wieland B - Professor	D	Lübben, Matthias - Group Leader Ruhr-Universität, Bochum	D	
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Edström, Jan-Erik - Professor, MD	s	Iribarren, Adolfo - Group Leader IRBM, Pomezia	I	Makarow, Marja - Group Leader	FIN	
Etzerodt, Michael - Group Leader	DV	Jäckle, Herbert - Professor/Director	D	Marsh, Mark - Group Leader	CD	
Featherstone, Carol - Editor,	DK	Jarmolowski, Artur - Group Leader	U	McCrae, Malcolm - Professor	GB	
Trends in Cell Biology, Cambridge	GB	A-Mickiewicz University	PL	University of Warwick	GB	

# **EMBL** Facts and Figures

(EMBL Alumni	in Eur	ope continued)		Speck, Peter - Founder & Owner Imagin, Karlsruhe	D
Meijers, Carel - Group Leader Erasmus University, Rotterdam	NL	Petratos, Kyriacos - Assoc. Professor Inst. of Molecular Biol. & Biotechn., Heraklion	GR	Spena, Angelo - Staff Scientist MPI für Züchtungsforschung, Köln	D
Melli, Marialuisa - Professor Centro Ricerche Sclavo SpA, Siena	I	Pettifer, Robert - Professor University of Warwick	GB	Stabel, Sylvia - Group Leader Max Planck Institut, Köln	D
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Morein, Bror - Professor The Royal Veterinary College, Uppsala	s	Quinn, Paul - Group Leader University College London	GB	Van Meer, Gerrit - Group Leader University of Utrecht	NL
Morrone, Gianni - Assoc. Professor Dip. Medicina Sperimentale, Catanzaro	I	Raugei, Giovanni - Assoc. Professor University degli Studi di Firenze	I	Vannier, Christian - Group Leader INSERM U298, CHRU D'Angers	F
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Nicosia, Alfredo - Group Leader IRBM Pomezia	I	Rüden, T. von - Group Leader Sandoz, Vienna	A	Wagner, Erwin - Senior Scientist IMP, Vienna	A
Niehrs, Christoph - Group Leader DKFZ, Heidelberg	D	Rüther, Ulrich - Professor Hannover Medical School Molecular Biology D		Warren, Graham - Professor ICRF, London	GB
Nüsslein-Volhard, Christiane - Professor Max Planck Institut, Tübingen	D	Santoro, Claudio - Assoc. Professor University di Torino, ICGEB, Trieste	I	Weiß, Hans - Professor Heinrich-Heine-Universität Düsseldorf	D
Oliviero, Salvatore - Assoc. Professor Istituto Ricerche Immunobiologiche, Siena	Ι	Sarvas, Matti - Group Leader KTL, Helsinki	FIN	Wijnandts van Resandt, Roel - Director Heidelberg Instruments, Heidelberg	D
Olkkonen, Vesa - Group Leader National Public Health Institute	FIN	Schaller, Chica - Professor ZMNH II, University of Hamburg	D	Winkler, Fritz - Head of X-ray & Crystallogra Hoffmann-La Roche, Basel	aphy CH
Page, Malcolm - Group Leader Hoffmann-La Roche, Basel	СН	Scherly, Daniel - Group Leader University of Geneva	СН	Zabeau, Marc - Director Plant-Genetic-Systems Laboratories, Gent	В
Palmgren, Michael G - Assist. Professor Royal Veterinary University, Copenhagen	DK	Schneider, Claudio - Professor CIB Laboratories, Trieste	I	Zenke, Martin - Group Leader University of Vienna	A
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Pattus, Franc - Director of Research CNRS, IBML, Strasbourg	F	Sorrentino, Vincenzo - Group Leader DIBIT, Milan	I	Zulauf, Martin - Group Leader Hoffman-La Roche, Basel	СН

# **Means of Contact**

# Heidelberg Main Laboratory

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Administrative Director: Barton Dodd (49) 6221 382 201

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#### Heidelberg Scientific Programmes

Biochemical Instrumentation Programme Programme Coordinator: Wilhelm Ansorge

Structural Biology Programme (including Biocomputing) Programme Coordinator: Frank Gannon

Cell Biology Programme Programme Coordinator: Kai Simons

Cell Biophysics Programme Programme Coordinators: Christian Boulin and Eric Karsenti

Differentiation Programme Programme Coordinator: Thomas Graf

Gene Expression Programme Programme Coordinator: Iain Mattaj

**Postdoctoral Candidates:** contact pertinent group leaders directly at main Laboratory or Outstations.

**Predoctoral candidates:** the Predoctoral Programme is centrally administered for all units. Contact Ingrid Clay at (49) 6221 387 331.

National Delegates: in order to contact EMBL delegates, write Frieda Glöckner, Meetings Secretariat, EMBL main Laboratory. Or call (49) 6221 387 250.

# **Grenoble Outstation**

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## European Molecular Biology Organisation

EMBO, an independent organisation, maintains its offices on the site of EMBL's Heidelberg Laboratory.

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Executive Secretary: Frank Gannon
## EMBL on the World Wide Web

For more detailed information on the European Molecular Biology Laboratory, see EMBL's presentations on the World Wide Web. The Internett address is:

## http://www.embl-heidelberg.de/





- 1962 Leo Szilard, Victor F. Weisskopf, James D. Watson, & John Kendrew meet in Geneva to discuss possibility of establishing an international laboratory for molecular biology.
- 1963 Scientists at a professional meeting in Ravello, Italy decide to pursue the idea of the laboratory. They form the European Molecular Biology Organisation (EMBO) in order to realise this goal. International fellowships and advanced courses are added to the EMBO agenda.
- **1968** The European Molecular Biology Conference is founded, associating 14 governments with EMBO, providing stable funding combined with scientific independence.
- **1969** The first proposals to include outstations and stronger emphasis on technological development and service functions for the European Molecular Biology Laboratory (EMBL) are made at a meeting at Lake Constance.
- **1971** Heidelberg is chosen as the site for the main laboratory.
- **1973** Delegates of the participating countries agree to and sign a draft accord in Geneva to establish a European Molecular Biology Laboratory.
- **1974** On July 4th, it is announced that the French government has formally ratified the draft agreement, so pushing the number of ratifying governments over the 70% required threshold. The EMBL thus becomes a legal entity, and the EMBC appoints Sir John Kendrew its first Director General.
- 1975 Construction of Heidelberg Facility begins.

Official agreement is signed with German officials to establish the Hamburg Outstation at the DESY synchrotron ring.

## Important Dates in EMBL History

- **1976** An agreement is signed establishing the Grenoble Outstation at the site of the ILL.
- **1978** Scientists move from temporary facilities into newly completed laboratory at Heidelberg.
- **1980** EMBL Data Library is founded the first central depository of nucleotide sequence data in the world (precursor to the EBI Outstation).
- **1982** Lennart Philipson becomes Director General. EMBL is reorganised into new research and instrumentation programmes.
- 1984 Predoctoral training programme is established.

Construction of EMBL guest houses for visiting scientists and newcomers are built.

- **1983** Differentiation is added to EMBL research programmes.
- **1985** A unique neutron diffractometer is built at Grenoble in collaboration with the ILL.
- **1988** EMBL and others establish EMBnet, the international sequence database network.

The Operon Conference Centre and seminar facilities are built.

The first EMBL childcare facilities are opened.

- 1991 Construction of EMBL's NMR facility begins.
- 1993 Fotis C. Kafatos is chosen as Director General.

The EMBL Data Library moves to the EBI Outstation at Cambridge, England.

**1994** The ESRF synchrotron facility at Grenoble, in collaboration with EMBL, opens doors to biological experiments.



