Laudatio of professor Sydney Brenner as *Doctor Honoris Causa*, by Miguel Beato, Fernando Giráldez, Cristina Pujades and Jaume Bertranpetit

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Sydney Brenner's contribution to molecular biology

It is a real pleasure and a great honor to introduce to you Sydney Brenner in the context of his nomination as *Doctor Honoris Causa* by UPF. Sydney Brenner does not need much of an introduction, as he is one of the most well-known living scientists. But I will try to convey to you my vision of his contribution to biology and most specifically to molecular biology. In fact, as he says in his autobiography, soon after starting to do biological research as a teenager, he already knew that he wanted to study molecular biology. The trouble was that the discipline did not exist at that time. So along with a couple of friends and colleagues he was forced to create it. And this is actually what Sydney Brenner has chosen to do throughout his long scientific life: open up new areas of research.

I have known Sydney since the 1990s, when we were both members of the Scientific Council of the Juan March Foundation for the organization of Workshops in the biomedical field. At that time I was working in Germany, and there were at least two annual meetings of the Council in Madrid. One of the pleasures in attending these meetings was to interact with the two British members of the Council, Cesar Milstein and Sydney Brenner. Both originally came from the very South of our planet, Argentina and South Africa, respectively. They were both very different and nevertheless shared similar destinies. Cesar was a humble person, with a soft low voice, often accompanied by his wife Celia; Sydney was the opposite as a personality, witty, exuberant, incisive and always alone. But they both converged in Cambridge, where their scientific work led to the Nobel Prize, for monoclonal antibodies for Milstein, and for Sydney officially for introducing *C. elegans* as a model organism, but in reality for his groundbreaking contributions to molecular biology. Incidentally, Cambridge is an example of how the creation of excellent research clusters and a creative supportive environment can attract the best minds worldwide and allow then to explore uncharted territories. Sometimes I dare to hope that Barcelona could follow this model.

Sydney Brenner was a precocious mind; he started medicine at the age of 15, did a master's degree in cell physiology and published his first papers at the age of 18, and went to Oxford in 1952 at the age of 25 to work on bacteriophage resistance in bacteria. After a few months there, he learned that two people at Cambridge had solved the structure of DNA. He immediately went to see the model, and rapidly realized that the base complementarity of the double helix was key to understanding many previously intractable biological problems. After a short period in the US, where he reencountered

James Watson, and also met Seymour Benzer, Max Delbrück and Salvador Luria, he went back to Cambridge and to Francis Crick. Although he had to return to South Africa, it was crystal clear to him that he would come back to Cambridge to work on the nature of the genetic code. Crick managed to secure a position for him at the MRC Cavendish Unit, where he arrived in 1956. He spent 20 years there, sharing an office with Francis Crick. In this team, Francis Crick was the most chemical and theoretical mind, while Sydney, despite also being a great thinker, focused more on testing the concepts experimentally. During the initial phase of this period and in long discussions with Crick the basic ideas of molecular biology were born, including the non-overlapping nature of the three letters code, the adaptor tRNA hypothesis, the concept of messenger RNA and many more., Through mutations in E. coli, Brenner, Crick and their colleagues demonstrated that genetic code was made up of triplets of nucleotides, which Brenner named 'codons'. This research was followed by investigations on the relationship of messenger RNA to DNA. Brenner and his colleagues determined that one of the messenger RNA sequences was a 'nonsense' codon that signaled the termination of protein synthesis. It is hard to imagine a period in modern biology when so many brilliant ideas came from the same place; enough to create a new discipline.

While at Cambridge in October 1963 Brenner began to study the genetics, development and nervous system of the tiny roundworm *Caenorhabditis elegans*, which he considered sufficiently simple for a complete description of all its cells and how they are generated during development. It was this work, which has now grown to include a worldwide community of worm researchers, that led to him receiving the Nobel Prize in Physiology or Medicine in 2002, which he shared with Robert Horvitz and John Sulston.

At the end of these extremely fruitful 20 years, Francis Crick left for the Salk Institute in La Jolla, where he pursued a career in neuroscience, while Sydney Brenner was appointed director of the MRC laboratory after Max Perutz's retirement. After 7 years of this administrative load, he started a new small unit at the MRC to work on the pufferfish Fugu, again attracted by the small size of its genome. In 1992, at the age of 65, he moved to California, first to Scripps and finally as a distinguished professor at the Salk Institute, where he rejoined Francis Crick. In California, Sydney promoted the sequencing of the human genome and founded the Molecular Sciences Institute. He has since worked closely with the Singapore Institute of Molecular and Cellular Biology, which he has helped to develop as one of the most attractive research environments in Asia. As he was approaching 80, he said "one should never retire from anything until one has secured one's next job". He continues to move freely between disciplines and between different cultures. Astonishingly, he still travels around the world even today. The secret, he once told me, is to always go in the same direction, but I do not remember whether it was westwards or eastwards.

In retrospect, it is clear that he has been one of the intellectual pillars of molecular biology, and an indefatigable champion of research on every continent. In the meantime, he has been recognized with a multitude of prizes and medals and I doubt that Pompeu Fabra University could have chosen a better life scientist as a *Doctor Honoris Causa*.

Miguel Beato

Laudatio to Sydney Brenner

Entia non sunt multiplicanda praeter necessitatem, attributed to W. Ockham

Among the many contributions that Sydney Brenner has made to Biological and Biomedical Research, we would like to mention two in particular that are related to the field of Developmental Biology. This is the science of how organisms develop. It addresses the fundamental question of how a single cell, the zygote, develops into a fully differentiated organism. This process involves the differentiation of hundreds of cell types in specific locations within the body that are organized into tissues. It involves growth, patterning and morphogenesis, which results in the generation of specific anatomical forms, like eyes, ears, arms or fingers.

How is embryonic development encoded in the genetic material that is passed from one generation to the next? Until the mid-twentieth century, this was a very puzzling question because it was difficult to understand how genes can instruct developmental decisions if all cells carry the same genetic material. In other words, how can genes make different cells if all the cells carry the same genes? This problem was elucidated by the work of Jacob and Monod at the Pasteur Institute, and John Gurdon at Cambridge. Respectively, they demonstrated that the expression of genes is regulated, and that the genetic material of a differentiated adult cell can drive the development of a whole new organism. This placed gene regulation at the core of development, the major challenge being thence to understand how genes are expressed at different times and in different places in the embryo.

In spite of their diverse anatomy and physiology, all animals share developmental mechanisms and use common principles. Crucial information about how genes are regulated during embryonic life was obtained from studies on the fruit fly *Drosophila melanogaster* that helped towards an understanding of many basic principles of development. Conservation of developmental mechanisms is particularly evident among vertebrates, and it is the imprint of evolution. On the other hand, once the first whole genome was sequenced, it became apparent that what makes humans different from other species was not the number of genes. Although the amount of

DNA in our cells is significantly larger compared to other species, the number and types of genes are not that different. What underlies the differences between species must therefore again be how genes are regulated. In short, development requires conserved regulatory networks, and diversity requires specific regulation of those networks.

But how could the regions in DNA that regulate gene expression be found in the vast landscape of thousands of millions of base pairs (Mb) that constitute the vertebrate genome? To tackle this problem, Brenner offered a simple but powerful solution. This was to compare the non-coding regions of the DNA of a given animal species with that of one with a compact genome, or in other words, one containing the entire repertoire of genes but within the smallest possible genome. This is remarkable, because at the time, the notion of regulatory non-coding DNA was rather new, and most considered it "junk DNA". The rationale was that since evolution has put pressure on genetic material, only the regions of the genome that are functionally important would have been preserved along the evolutionary tree. These regions should contain the regulatory elements responsible for building organisms. Brenner and colleagues found a solution in the Fugu fish, the pufferfish, which besides being a Japanese delicacy, also has a genome that contains about the same amount of genes as humans, but compacted into about one tenth of DNA (400Mb as compared to 3200Mb in humans). The comparative analysis of these intergenic DNA regions led to the discovery of conserved domains in the DNA which are responsible for regulating the expression of genes. This means that specific regions dictate when and where genes are expressed during development and in the adult. This discovery has been crucial for the study of gene regulation during embryonic development. It has speeded up the search for regulatory regions in different vertebrates, and the study of the roles played by crucial genes during development.

The second contribution that we would like to mention here led to Sydney Brenner's Nobel Prize award, together with two of his former students John Sulston and Robert Horvitz. This was for their discoveries concerning the genetic regulation of organ development and programmed cell death. Although seemingly paradoxical, death is a cell fate choice during embryonic development. Some cells are programmed to die, and this specific type of cell death is referred to as apoptosis, because it is different from cell death caused by damage or disease. The study of these events led to the discovery of the genetic machinery that controls apoptosis, which is involved in a variety of developmental events, such as sculpting the limbs, kidney and the brain. This contribution was possible thanks to the introduction of *Caenorhabditis elegans (C. elegans)* as a model system. Brenner's idea was to find an organism that would be simple enough for its development to be followed exhaustively, an organism with a development that could be described cell by cell. One in which researchers could follow the fate of the cells throughout their life in the embryo. This was the worm, *Caenorhabditis elegans (C. elegans)*.

C. elegans has many of these ideal properties. The worm is made of a constant number of 959 cells that hold constant positions in the embryo. The completion of the cell lineage of *C. elegans* was accomplished in the 1980s, and its genome was sequenced in 1998, making it the first animal with a completely sequenced genome. *C. elegans* is small, about 1 mm long and transparent, which enables experimental

manipulations and easy observations. *C. elegans* also has a short life cycle and is easy and cheap to cultivate in large numbers, which allows genetic screens and biochemical studies. Besides the discoveries on the developmental functions and the mechanisms of cell death, *C. elegans* has provided a wealth of information on the basic principles of embryonic development and genetics. It has also been used as a model system for studying disease and aging, demonstrating that basic mechanisms are common in "apparently distant" organisms, and it is also a wonderful tool for educators.

Finally, we would not like to end here without a brief mention of the importance of Sydney Brenner to the realms of life science and scientific research in a broad sense. Sydney Brenner has been deeply influential for Science, scientists and institutions. In his own words: "Throughout my scientific life and in all my projects I have been joined by many scientists, young and old, whose work was absolutely essential for the success of our scientific endeavors. Many have gone on to do important scientific work but all remember those wonderful times when we and our science were young and our excitement in meeting new challenges knew no bounds. I believe that a scientist should be judged by the quality of the people he has helped to produce and not by prizes or other honors bestowed on him" (Sydney Brenner, Nobel prize award lecture). His strong thinking has been seminal in different areas of biology, and has inspired several generations of scientists. One example is the recent project at Janelia Farm, one of the Howard Hughes Medical Institutes, in the United States, which acts as an intellectual hub for scientists from diverse disciplines. Its mission is a follow up of Brenner's legacy at the MRC LMB and Bell Laboratories, namely to promote researchers working together in multidisciplinary teams. Collaborative groups are "self-assembling" generating environments that are free from the traditional disciplinary boundaries frequently encountered in academia. This promotes a culture of enhanced freedom, allowing scientists to pursue long-term projects of great significance – in short, a pathway to challenge dogmas.

Fernando Giraldez and *Cristina Pujades*

Sydney Brenner's Gift to Science

To have Sydney Brenner as the first Honoris Causa in Biomedical Sciences at Pompeu Fabra University is extremely meaningful for all of us. He has been one of the very last Biologists, with a capital b and in the most Renaissance sense. He has been a key person in many different fields of Biology and an entire Department of Experimental and Health Sciences like ours may think of him as a good representative and pioneer of its field. Sydney Brenner may be considered the scientific advisor for all of us; he has stirred up most of our fields and has inspired thinking beyond specialized work in most disciplines, be they molecular biology, cell biology and differentiation, genetics and genomics, developmental biology, physiology, neurobiology and behavior or evolutionary biology. And even if he will not agree, I would like to add systems biology; which we will come back to. Beyond biology itself, he has also influenced many fields of thought that biology has inspired.

The biography by Errol C. Friedberg and the book "My Life is Science", translated into Catalan by Juli Peretó contains all the details of his scientific life that can be saved now, but should be required reading for all of us after this ceremony. I would only refer here to some paragraphs written by him and give the contexts and implications of the sentences. These sentences are from different times during his life, but they are lively and illustrate his view of enlightening the future development of biology in general.

First:

How genes might specify the complex structures found in higher organisms is a major unsolved problem in biology (in a paper in Genetics, 1974 and in the Nobel Prize Lecture in 2002).

His appreciation of the problem in 1974 and his insistence since then shows his pioneering view, mainly because the optimistic years of genetics as being able to explain everything using simple rules were still to come. Then and now, the acknowledgment of the huge gap in our comprehension of complex phenotypes remains. Many fields of biology try to extend our knowledge from the genes expanding into gene products, into interactions, into pathways and networks, into

more complex structures, within a given dynamic process. Biology seems to look at the process like the constructors of the tower of Babel, trying to reach heaven. They share a common argument: whether the directions being taken are the correct ones is not known.

Second:

in 1985… I had also come to the conclusion that most of the human genome was junk, a form of rubbish which, unlike garbage, is not thrown away (Nobel Lecture, 2012).

This statement is clearly a vision of the very future understanding of what a big part of the DNA in many species is: junk. Not all languages have an acceptable translation. In Catalan, for example, we do not have a good way to translate the sentence, as junk and rubbish have the same translation. If this distinction had been made well and understood, we would not have had the recent dispute between people in the ENCODE project and evolutionary biologists who protested about the rude definition of function that they produced, with no understanding of the genetic material that may be maintained in genomes without having a function, regardless of replication and transcription.

Third:

Sydney Brenner has argued strongly against system biology, but in my view, not against the discipline itself, but rather against the view of some of its practitioners who in an holistic view hope that system biology is going to be the "functional Rosetta Stone" in which, given the description of the components of a biological system, the full behavior –that is, function- can be predicted. This would be by means of the most detailed description possible of the system at the molecular level, and the appropriate mathematical models that fit and predict the interaction and thus the emergence of all functions.

Brenner says:

There are some who think that all that will be required is the collection of more and more data under many experimental conditions and then the right computer program will be found to tell us what is going on in the cells. This approach is bound to fail because this claim of systems biology is that it can solve the inverse problem of physiology by deriving models on how systems work from observation of their behavior.

This sentence has to be understood within the framework of part of the biology based on "omics" -in some cases a very influential part- that has been defined as: low input,

high throughput, no output. This science exists and it is influential, but this is neither all science nor the best science. I therefore see Brenner's words more as a father's words to children, warning them of perils and asking for wisdom, rather than a real danger in the way biology is developing with the help of the high throughput omics.

The vision that system biology as a whole relies on explaining the behavior of life (say of a cell) with the full description of its components under different experimental conditions and a computer program that integrates them, is biased. There are many cases in system biology in which work is being done at intermediate levels of complexity, where the phenotype-genotype relationship can be achieved in new and complex terms, but no doubt in terms that are required for the advancement of the understanding of real, complex biology. We could in this sense say that most of the work being done to tie the genotype and phenotype are also part of systems biology. This could include interesting breakthroughs, like those of the ENCODE project, the deciphering of the cell differentiation programs and the changes in time in the gene expression program of *C. elegans*, as described by Ben Lehner.

But in this open framework of systems biology, I would even place a program that aims to be its counterpart: the CELLMAP program described by Sydney Brenner. It is a kind of "intermediate path" for studying and comprehending the cell as both the map of the molecules within it and the map of cells within an organism. Maybe this will be the definition of systems biology in the future.

And fourth:

Living organisms may be viewed as the only part of the natural world whose members contain an internal description of themselves. This is why the whole biology must be rooted in the DNA, and our task is still to discover how these DNA sequences arose in evolution and how they are interpreted in to build the diversity of the living world (paper in *Science*, 2012).

This sentence is always present in the introduction of my talks. It is a sentence that goes beyond "Darwin's dangerous idea" as described so well by Dan Dennett. Very far beyond it. Having an internal description of each living being is the most simple and essential definition of life and its form, living organisms.

The way life is rooted and based on DNA is the simplest and most exciting understanding of life and at the same time is the base for planning future understanding. The only thing I regret is that Sydney Brenner did not write and work more on evolution. Maybe you have not had enough time to stir up such a primitive biological science. We will have to wait for another Sydney Brenner.

Jaume Bertranpetit