

## OPINION OPEN ACCESS

# Prof. Manuel Espinosa Padrón (1942–2024): A Superb Plasmid Biologist and a Gentle Colossus

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Prof. Espinosa, affectionately known to his colleagues, family and friends as Manolo, and to one of us (DC) as Bro for the past four decades, spent his professional life to understand mainly functions of plasmids. These are parasitic DNA common in bacteria and are maintained outside of the bacterial chromosome. Plasmids became an exciting field of research in molecular biology and biotechnology when they proved indispensable as cloning vectors in the early '80s. With advent of the sequencing era, it also became apparent that plasmids have contributed heavily to evolution of the bacterial genome. Decades earlier, plasmids were known to carry drug-resistance genes and could transfer them to other bacteria willy nilly. This also brought infamy to plasmids, nonetheless, made them a serious object and an autonomous discipline of study. A niche journal *Plasmid* was started (1976), a Gordon conference mainly on plasmids (named 'extrachromosomal DNA' which included chloroplast and mitochondrial DNA) started being organised on a regular basis and another biennial series of meeting more inclusive of plasmid biologists became the main forum for reporting progress in the field. This meeting became a society meeting upon creation of the International Society of Plasmid Biology (ISPB, formed in 2004). As long as we have bacteria within and without us, plasmids will remain part of our lives.

## 1 | Why Call a Colossus?

Manolo has been a successful scientist by all conventional criteria and the volume of his contributions is unquestionably colossus. He was active in science till his last breath. His last four papers (203rd–206th) appeared in 2023 and a fascinating



The two Bros at the ISPB meeting in Bariloche, Argentina, 2010.

series of chapters together with his wife and scientific partner Dr. Alicia Bravo (*The One Earth Series*, CIB Margarita Salas, CSIC, Madrid) appeared in April–May 2024, where they espoused the importance of 'entente cordiale' between humans and bacteria—'we must share, we must co-exist'. Drawing attention to the concept of *One Earth* exposes what a passionate humanist he was. Besides papers, Manolo contributed nearly 40 book chapters, supervised 13 PhD students, served as reviewers for about 50 journals and in editorial capacity several journals, most noteworthy being the journal *Plasmid*. He was one of the longest serving Editorial Board members of *Plasmid* (1998–2022), and co-edited special issues on two occasions. He

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was also passionate about supporting the *Frontiers* journals and coedited with one of us (TV) special topics on several occasions (2017–2022). He must have been a very well-organised person in his thoughts and actions to be such a doer.

## 2 | Why Call Gentle?

Despite the colossal accomplishments, Manolo was always relaxed, overtly social and well-liked irrespective of the nature of your relationship with him. You don't have to be even close to him to feel his warmth—it was apparent even if the link was through the cyberspace (he addressed DC as 'Bro' much before we met). At the end of day, we all aspire to be remembered as a nice person. Like any far-sighted person, what is important in life was clear to him from the outset. His final thoughts on the *One Earth* Series is a testament to his concern for our common good.

## 3 | Education and Affiliations

Manolo was from Canary Islands and became a citizen of Madrid, where he received his PhD (1969) under Prof. Antonio Portolés' supervision, a well-known Spanish microbiologist. He had stints abroad in Prof. Gerard Venema's laboratory at the Institute of Genetics, Groningen University, The Netherlands (1974), in Dr. Mirosława Piechowska's laboratory at the Institute of Biochemistry and Biophysics, Warsaw, Poland (1978) and in Dr. Sanford Lacks's laboratory, at the Brookhaven National Laboratory, Upton, USA (1980–1981). Manolo's initial work was on antibiotic resistance and subsequently in competence development and gene transfer in *Bacillus subtilis*. His work became more plasmidic in mid-'80s when he started as a group leader in 1984 in an institute with the current name Centro de Investigaciones Biológicas Margarita Salas (CIB). He was associated with CIB in various capacities including becoming its director (1992–1993) and head of the laboratory on gene expression and gene transfer (1995–2012). He remained at CIB till the very end.

## 4 | Contributions to Plasmid Biology and Biotechnology

Manolo was a plasmid biologist with distinction. Even before plasmids proved to be tractable objects for mechanistic studies on their maintenance functions and an indispensable tool of biotechnology, it was clear that plasmids can be of different kind. This warranted studying them individually. At least 20 or so labs spread around the world started studying different plasmids, initially to understand mechanisms of their autonomous replication. Everybody's favourite plasmid was distinct enough that we could work peacefully without stepping into each other's toes. By and large the plasmid community was a happy bunch, and this was possible because of comrades like Manolo. The plasmids being studied mostly belonged to *E. coli* and the world of Gram-negative bacteria. Manolo's was one of a few labs that studied plasmids from Gram-positive bacteria, mainly *Streptococcus pneumoniae* and *B. subtilis*. Manolo's lab worked on two modes of plasmid replication, one by which plasmids are

maintained by vertical transmission in dividing cells like chromosomes, and the other by which plasmids are transferred horizontally (the process termed horizontal gene transfer or HGT) from one to another bacteria by conjugation. The HGT mode is believed to have accelerated evolution of bacterial chromosomes more than anticipated. The horizontal transfer of plasmid also means transfer of drug-resistance genes they carry and HGT is believed to have accelerated emergence of drug-resistant bacteria faster than new antibiotics could be developed, which is proving to be an existential threat to us. Thus, although vertical transmission is the usual mode of plasmid maintenance, HGT's impact on bacterial and human life has been quite profound.

Manolo was catholic in his approach to science and did whatever science demanded to do a good job; these included studies in vivo, in vitro, in silico, in structural biology, in synthetic biology and what have you. Although plasmid biology was the face of his research, at the core, his research interest was understanding of mechanisms of gene expression. One of his classy oeuvres was on DNA topology, showing the role of DNA bending in transcription initiation (Perez-Martin J. and Espinosa M. *Science* 260:805–807,1993). The DNA topology also proved crucial for initiation of plasmid replication (del Solar G. and Espinosa M. *Molecular Micro* 37:492–500, 2000). Having studied both the vertical and HGT modes of replication, it is not surprising that Manolo's lab was the first to demonstrate cross-talk between the two modes (Lorenzo-Díaz, F. et al. *Nucleic Acids Research* 45:7774–7785, 2017).

Manolo was an avid inventor in several patents with remarkable impact in Biotechnology. For example, his patent 'plasmids containing the gene for DNA polymerase I from *S. pneumoniae*' (issued Patent No. [US 5,002,875A](#)) describes generating 50-fold greater amounts of the DNA Pol I enzyme. The plasmids from the patent have been deposited to American Type Culture Collection (Rockville, Maryland, USA) under ATCC Nos. 67496-8. The patent 'Method for producing and purifying the carboxy-terminal fragment of DNA polymerase I from *S. pneumoniae*' (issued Patent No. [EP 0470230 B1](#)) describes obtaining the enzyme without exo-nuclease activity with high yield and low production cost. Both patents permit industrial production of DNA PolI enzyme for basic science and biotechnological purposes. The patent 'procedure for obtaining and detection of fluorescent Gram-positive bacteria' and the two improved procedures (issued Patents No. [ES 2166671B1](#), [ES 2182628B1](#) and [ES 2184568B1](#)) describe a new method of detecting strains of *S. pneumoniae* and *Lactobacillus lactis* in culture utilising the overproduction of the green fluorescent protein. These patents allow (1) detection of the colonising capacity of the pathogenic microorganism *S. pneumoniae* in cultures of human tissue and in animal models used by the pharmaceutical industries, and (2) the colonising capacity of the microorganism that integrates the *L. lactis* starter cultures during cheese ripening, which is of interest to dairy industries.

## 5 | Outreach Activities

Manolo's outreach activities were as colossal as his scientific communications. He organised the 1992 *Plasmid Biology* conference in Magalia Castle near Madrid and the 1998 Juan March

Workshop on *Initiation of DNA Replication in Prokaryotic Extrachromosomal Elements* in Madrid. He was a coordinator of the *Spanish Network of Extrachromosomal Elements* (REDEEX), and a co-lead in the *European Science Foundation Network* (Plasnet) that helped bring together the Molecular and Environmental Microbiologists interested in plasmids. He was an important member of the EU programme MECBAD (*Mobile elements contributions to bacterial adaptability and diversity*) and served EU in several other programmes (*Human Capital and Mobility for the CIB*, *Commissions to evaluate EMBO Long Term Fellowships*, and *EMBO Young Investigator Programme and Installation Grants*). Deservedly, he was recognised as an EMBO Fellow (1996) and as ISPB President 2012–2024.

In closing, Manolo will be remembered not only as a great bacteriologist with incisive contributions in the fields of gene expression, gene transfer, DNA replication and resistance to antibiotics but also as a great mentor and for his interest in the science of others that he exhibited by organising meetings, writing reviews and engaging with collaborators, far and near. He exemplified that you could accomplish a lot in a fair and square way and still be well-liked. It is upon us to continue his legacy horizontally and hopefully vertically to coming generations. Goodbye, Manolo—thank you for your humility, optimism and warm friendship. We will miss you.

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#### Author Contributions

**Tatiana Venkova:** writing – original draft. **Dhruba Chattoraj:** writing – original draft.

#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

This is an opinion article with no data.