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Spotlight

Bacteria without their phages are just not competitive

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The microbial world is interconnected and only makes sense when one looks at the big picture. Meet José Penadés, a new editor of *microLife* and member of the European Academy of Microbiology (EAM).

Through ups and downs to find passion

As a veterinarian by training, José Penadés never thought he would stick with a scientific career. For his PhD, he already switched gears and worked on the human autoimmune disease Goodpasture syndrome. However, he quickly realised that studying autoantigens gave him quite a hard time and 'immunology was just not [my] his thing'. Afterwards he decided to stay in Valencia, Spain, and get some teaching experience at a private school. Yet, here, he recognised that indeed he was missing research.

So, José chose to go back to a previous lab where he could apply his newly acquired molecular biology toolbox to their project on bacterial biofilms. He focused on the Gram-positive *Staphylococcus aureus* and studied how this pathogen forms biofilms to persist in the host. He and his team found a new cell-wall associated protein that they called Bap for biofilm-associated protein showing that proteins are integral parts of bacterial biofilms (Cucarella et al. 2001). They discovered that *S. aureus* produces Bap and attaches it to its outer membrane as a sensor. Upon contact with a surface or another cell, for example during infection, Bap is cleaved off the bacterial membrane and released to the surrounding. During an inflammatory response in the human body, the pH of the local environment drops. This triggers the N-terminal amyloid-like regions of Bap to form aggregates that further become functional scaffolds of the biofilm matrix (Taglialegna et al. 2016).

With this dip into the microbiology world, José was more determined and started to enjoy the scientific process. In comparison with immunological studies, he found microbiological experiments more rewarding, since 'it is easier to see a phenotype. You can complement and move genes between bacteria as you like and you are pretty confident about the results that you see.'

Infected with curiosity

Fuelled by his curiosity to understand the origin of life, José visited and worked in several labs in Spain and the United States and was appointed Professor of Microbiology at the University of Glasgow in the UK. During this time, he switched his focus and started to look at how *S. aureus* is evolving and interacting with other partners of the microbial world. He found one previously underappreciated partner to be bacteriophages and became fascinated by their impacts on bacteria.

His new project led to the discovery of a new mechanism of DNA transfer that is mediated by temperate phages. These can either establish a prophage state integrated but repressed within the bacterial chromosome or they undergo the lytic life cycle. Upon activation of the lytic cycle, the DNA segments containing the prophages are being replicated to create several integrated prophages in parallel. Some of these then excise from the genome and enter the productive lytic cycle. At the same time, other prophages together with core bacterial genes are packaged into the phage heads and prepared for export (Chen et al. 2018). By having several prophage lineages present in the bacterial cell at the same time, the transfer of large DNA sequences is highly efficient and even succeeds that of other transferring mechanisms like conjugation or generalized transduction. As expected, these findings threw off the microbiology community since mobile genetic elements and the so-called 'mobilome' had to be newly defined. While before this term encompassed plasmids, phages and phage-like elements as well as transposable elements, José suggested that the bacterial chromosome needed to be included as well (Humphrey et al. 2021).

Big discoveries like these helped José get awarded with prestigious ERC grants as well as Spanish and European Fellowships. In 2020, he was appointed as Director of the MRC Centre for Molecular Bacteriology and Infection and Chair of Microbiology at Imperial College London in the UK and in 2022, he became a fellow of the EAM.

Little is needed to be competitive

This success did not stop him from unravelling the interconnected microbial world. Driven by results that he cannot fully understand, he keeps infecting his lab members with his passion and competitive drive. And this has pushed several of them to develop their own creative approaches to science so that their persistence led to many interesting experimental results. Like most research group leaders, he enjoys the moments when all the puzzle pieces fall into place and 'everything just makes sense, which is then the best day'.

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The persistent approach also reflects on the stories that his papers are telling—always with the aim to shed light on how 'phages impact the mobilome, the biology of bacteria and ultimately the big microbial picture'. One type of mobile elements that José and his team keep exploring in detail is the Phage-Inducible Chromosomal Island (PICI) . PICIs were initially identified in *S. aureus* (Penadés and Christie 2015) as pathogenicity islands carrying the genes for virulence factors like the toxic shock syndrome toxin and other superantigens. They then characterized PICIs as molecular parasites and discovered the elegant mechanisms by which PICIs use other phages for their own spread (Tormo-Más et al. 2010). For that, PICIs encode mechanisms to interfere with the reproduction of the hijacked phage or other plasmids and can thus even protect their hosts.

In the following years, José and his team discovered and characterised PICIs also in many other bacteria like *Escherichia coli*, where PICIs are involved in classical molecular piracy mechanisms. It is now assumed that these elements are present in more than 200 different bacterial species. They showed that the *E. coli* PICIs hijack phage machineries for their own packaging while blocking the packaging of the hijacked phage (Fillol-Salom et al. 2019). For José, findings like these challenge the classical view of phages within the microbial network: 'People always say viruses as the least evolved entity because they are so simple while [I] he always thought it was the opposite. They are so simple and yet they do such evolved things'. So, you actually don't need too many things to become highly competitive. Based on this view, he came up with the theory that 'phages might not even exist as an entity but only as part of the bacterial community'. This would be similar to eukaryotic cells containing functional organelles or bacteria producing outer membrane vesicles that upon release become their own functional units. Such a theory will likely spark a lot of controversial discussions within the microbiology community and hopefully will be followed by more interesting and enlightening publications.

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