

EMANCIPATION

The price of freedom.

BY JOÃO RAMALHO-SANTOS

As she stumbled into the secure underground conference room clutching a stack of overflowing files, Clara mentally tried to organize her presentation. The narrative of what she had uncovered had to be convincing, hopefully even triumphant; one of her guilty pleasures as a scientist.

Clara tackled all her assignments for the Center for Disease Control with the same overzealous principles. Diseases are biological revolts. And, as in all recorded uprisings throughout history, inaugural events often go unnoticed or are explained away as anomalies. To understand anything, one needs to know its reasons, its beginning; search the unheralded edges rather than the full-blown epicentre to which everyone is attracted.

In this particular case, that had involved looking beyond the sudden rise in diverse symptoms. What seemed on the one hand to be an unholy alliance between early-onset cardiac failure and neurodegenerative disorders, and on the other to be simultaneous severe bleeding in the digestive and urinary tracts.

The first question was answered before any of the wild-eyed caffeine-driven scientists in the room had time to ask: Clara's initial meta-analysis had clearly shown that the two sets of symptoms were related; it was just a question of which came first; what caused what. How aggressive haemorrhaging and early-onset ageing were connected worldwide by a phenomenon that did not distinguish east from west, north from south, poor from rich, old from young, male from female. In fact, it was not even partial to any vertebrate species in particular.

"Is it some sort of super-bug?"

The metallic voice came from the conference screen Clara had failed to notice on the far wall. Unidentified stern faces in crisp uniforms stared out at her as the scientists in the room went uncannily quiet, shrinking into their lab coats. Clara had expected to be summoned to a meeting with important people wearing medals and dark sunglasses some time after the presentation. Apparently, they were speeding things up.

"Well, sort of," Clara replied, wishing for a better-thought-out PowerPoint. "In the past few months, microbiology journals have

described an unprecedented amount of putative new bacteria, all found in what were thought to be

well-explored habitats. The genomes of these bacteria are uncannily similar to the mitochondrial DNA of a variety of species, but have acquired what seems to be typically nuclear genes from those very same species."

"And that's the bug that's causing this?"

the screen interrupted, the collected faces clearly twitching with anticipation. A cacophony of questions followed. "Is it man-made?" "Where did it originate?" "Which enemy countries should the drones target?" "Is this evolution gone wrong?" "Can we develop a vaccine?" "How long before priority personnel can be inoculated?"

Clara snapped, shushing the covert guardians of the free world as if they were petulant teenagers. Definitely not a good career move, although she couldn't really say what bothered her most:

the disaster-movie simplicity, or the fact that she wasn't allowed to deliver her story as she'd intended. So she jumped to the end, desperately trying to bring up at least some data on the projector.

"Pathology reports have noted that mitochondria are the only well-preserved organelles in the leaking blood of human patients," she said. "In fact, they seem to have lost their outer membrane — only the inner, bacteria-like one, remains."

Blank looks from the screen.

"Mitochondria used to be bacteria," Clara continued. "And new bacteria that look like weird mitochondria are appearing. This is not a coincidence. Furthermore, dozens of recent biochemistry and cell-biology papers show that all mitochondrial functions are unexpectedly reduced in different cell cultures, animal models and biopsies. Oxidative phosphorylation and ATP production, mitochondria-dependent apoptosis, relationships with the endoplasmic reticulum, oxidative stress, mitochondrial fusion/fission ...

"Analysed individually these are just weird data sets; taken together it seems obvious that the first eukaryote organelle general strike is under way. In other words, it's not a 'bug'. After millennia of successful endosymbiosis within eukaryote cells, mitochondria

are making a bid for independence."

A few of her colleagues shifted uncomfortably in their seats.

"First they took back genes that migrated to the nucleus throughout evolution in order to regain full autonomy. Then they started

to disengage from their cellular functions. Now they are leaving the host cells, initially compromising only the function of organs that need them most, which explains the more visible symptoms.

"The outer membrane, originally inherited from the host, is left behind as a broken shackle. Clearing the easiest possible paths to the exterior, mitochondria are starting life as new bacteria. Apparently, they thought that 'endosymbiosis' was just a fancy word for 'slavery'.

"This is not your average jihad, it is intracellular mutiny. So we need to

stop thinking about bombing the problem, and instead discuss the unique task forces that will have to be assembled."

"Such as?"

"Bioinformatics and systems-biology experts, together with intelligence communication specialists, should work out some sort of code to transmit messages, to try to parley the mitochondria into staying. But maybe negotiating a forgiving exit strategy is more reasonable. In that case, metabolomics gurus, working with supply officers and nutritionists, had better put their heads together to figure out how humans are to survive on glycolysis alone. And if bioengineers could start designing artificial mitochondria with no free will, that might also prove useful."

"Can we really survive this?"

"Take it easy," Clara said with a tired smile, "we might be OK. As long as the centrioles or the Golgi don't start getting any funny ideas." ■



JACEY

João Ramalho-Santos is a collaborative entity employed at the Department of Life Sciences, University of Coimbra, Portugal. He is very interested in the future, as long as it does not distract him too much from the present. This story is dedicated to his mentor Professor Maria da Conceição Pedrosa de Lima, for her role in emancipating students.