Profile

Giovanna Mallucci: redefining neurodegeneration

When it comes to research, Giovanna Mallucci, an Associate Director of Cambridge University's UK Dementia Research Institute (DRI) and van Geest Professor of Clinical Neuroscience, has a guiding maxim: let the data speak to you. "You might start with one idea", she says. "But when the data don't agree with it, that's the truth and that's what you have to follow." If this means a change of direction, with new thinking, so be it. A lot of what Mallucci herself has come up with, she admits, started out as an attempt to answer a different question. Asked if she can account for her success as a researcher, she attributes it to "a passion for understanding biology". A sometime colleague, Professor Martin Bushell of the Beatson Institute in Glasgow, has no hesitation when rating the importance of Mallucci's contribution to understanding and, potentially, managing Alzheimer's disease and other such conditions. "She's redefined how we look at neurodegeneration", he says.

Although suspecting that her Italian cell biologist father had a subliminal influence on her career choice, Mallucci dates it to her pre-teens. "It sounds a bit nerdy", she laughs, "but I was reading a book about Marie Curie and knew that was what I wanted to do. Discovery and research." This interest led to studying medicine at Oxford University, where the teaching so vividly illustrated the appeal of an academic career that she had to be dissuaded from abandoning medicine in favour of full-time science. The advice was well founded because she subsequently discovered the satisfactions of working with patients—and, even now, manages a day per month in the clinic. Research climbed back up the agenda when she began to specialise in neurology, drawn to it by her fascination with neuroscience and the realisation of how little could be done about neurodegenerative disease. From the National Hospital for Neurology and Neurosurgery, she moved via a fellowship at Imperial College London's Prion Disease Group to the MRC's Prion Unit at the Institute of Neurology in London, UK. As she explains, "I picked prion diseases because I thought they were mechanistically simpler—and they are, because there's this folded protein that's the obvious cause." Science is easier if you can isolate a key variable. Even so, she admits her ambitions ran ahead of her experience: "Only someone unbelievably naive could have taken on such a big project." While most research on prion disease had been directed at the abnormal form of the prion protein, Mallucci decided to see what would happen in a mouse model if you stopped the production of the normal form from which it came. To her delight, and surprise, the disease was halted. "This was a remarkable finding because it showed that the early steps of neurodegeneration are reversible", says Roger Morris, Professor of Molecular Neurobiology at King's College London.

Having opened up a new line of research, Mallucci wanted to be part of it. "I was offered an irresistible job at the MRC Toxicology Unit in Leicester, where I was given a budget and told to get on with it for 5 years." She began studying the unfolded protein response [UPR], the pattern of events that plays out in any cell in which these aberrant molecules have accumulated. "This response includes shutting down all protein synthesis, except for those that would be involved…in getting the protein to fold correctly", explains Morris. Sustained activation of the UPR has been implicated in several neurodegenerative diseases. "The cell's response becomes dysregulated, like a broken thermostat", Mallucci explains. She set out to inhibit it—and succeeded. "What was so exciting was showing that you could tackle [the UPR] chemically", says Professor Anne Willis, Director of the MRC Toxicology Unit. "Once you can manipulate the pathways chemically you've got an opportunity…for new drug development." The next task was to find the right agent. "Our first experimental drug cured the brain but poisoned the [animal] patient", as Mallucci rather pithily puts it. One of the drugs she's since tried is already licensed and safe. "So we've bypassed years of testing and millions of pounds on drug development. We can go straight into the later stage clinical trials looking for efficacy." Trials are planned to start soon and smaller experimental medicines studies are already underway. She doesn't commit herself but talks with optimism: "If you halt Alzheimer's disease and related dementias or just slow it down, the impact on quality of life for individuals and carers is potentially transformative, as well as on the economy and health service."

The UPR isn't Mallucci's only focus of interest. Inspired by the regeneration of synapses in animals that have woken up following hibernation, she's also investigating another biological pathway that might be druggable in neurodegenerative disease. Mallucci is amusing and a pleasure to talk to. "If you were at a dinner, she'd be the person you'd want to sit next to", says Willis. "She's a really social person who loves to interact, to collaborate", adds Bushell. "I think that's one of her defining features… She inspires people." Indeed, it's not hard to guess that it wasn't only her discoveries that led to her leadership of the UK DRI's Cambridge hub. Mallucci and her fellow directors of the other five DRI centres meet regularly to discuss policy and coordinate what they are doing to become "more joined up", as Mallucci puts it. Their combined efforts are expelling the air of hopelessness that has for so long hung over the diagnosis of a neurodegenerative disease.

Geoff Watts