…still cycling

It gave the greatest of pleasure to learn that two of our Editorial Board members, Paul Nurse and Tim Hunt, are to share this year's Nobel Prize for Physiology or Medicine together with Lee Hartwell. On behalf of the *Journal of Cell Science* and the Company of Biologists, for which Tim is also a Director representing the interests of the journal, I would like to congratulate each of them on this well-deserved award.

Such news gives just cause for reflection about the impact of the work of these three men that has been recognised by this accolade. Their research has defined the tenet of cell cycle regulation and is not just about their discovery of the major cell cycle kinases and their regulatory cyclin subunits, but the importance of cycles of phosphorylation and degradation of regulatory proteins. The discovery of these central players in cell cycle progression stems from Lee Hartwell's seminal work published in the early 70s. I first became aware of Lee's work at coffee table discussions when I was a graduate student at the Imperial Cancer Research Fund. I was surrounded by people influenced by Renato Dulbecco's studies on the small DNA tumour viruses SV40 and Polyoma. Lee had worked in Dulbecco's lab and naturally enough conversations turned to how Lee was trying to solve the yeast cell cycle by systematically assembling a collection of temperature-sensitive cell division cycle mutants. His series of papers on this topic began with the description of how he proposed to achieve his goal (Hartwell et al., 1970) and went on to describe mutants affecting every stage of cell cycle progression. In characterising the phenotypes of these mutants he defined not only the major cell cycle transitions in budding yeast but also the principal checkpoints, including START, the point at which nutritional, hormonal and cell size controls are imposed to regulate cell cycle progression. Above all, Lee's insight was to recognise the one key player, the *CDC28* gene, that we now know to encode the major cell cycle kinase that is activated at START.

Paul Nurse's work was undoubtedly influenced by Hartwell. Paul began characterising cell division cycle mutants in fission yeast in the mid 70s, his first description being of *wee* mutants, so called because they enter mitosis before they have grown big enough (Nurse, 1975). The appreciation of the cellular physiology of the division cycle apparent in Paul's papers from this time, and indeed throughout his career, shows the guiding influence of Murdoch Mitchison, in whose lab he carried out this early work. My first contacts with Paul were in 1983, when he was kind enough to let us have the cloned *cdc2* gene in order that we could look by nucleic acid hybridisation for its *Drosophila* counterpart. At that time, we were newcomers to the cell cycle field and Paul was particularly encouraging of our efforts. Paul had himself recognised at that time the importance of *cdc2* in regulating mitotic entry in fission yeast. Together with David Beach he had also shown *cdc2* to be the functional counterpart of the all-important budding yeast gene *cdc28* (Beach et al., 1982). Our own experiments to isolate the fly *cdc2* failed miserably – there is simply insufficient homology between the fly and yeast genes at the nucleic acid level. Paul, by contrast, was much more courageous. He encouraged Melanie Lee to try and rescue a *cdc2* mutant with human cDNA, and the outcome was a spectacular success (Lee and Nurse, 1987). The central mitotic kinase was conserved in function from yeast to man! Later Paul's lab was to teach us some fission yeast tricks, and together we successfully isolated the fly *cdc2* gene and genes for two fly isoforms of *cdc25*. The latter had been shown by Paul Russell, with Nurse, to activate Cdc2 function in fission yeast (Russell and Nurse, 1986) and indeed, it seemed, in all metazoans.

Tim Hunt (left) and Paul Nurse (right), photographed at Imperial Cancer Research Fund Central Laboratories, London. Photograph courtesy of the ICRF

Meanwhile, in what then seemed to be another biological universe, Tim Hunt had been studying patterns of protein synthesis in marine invertebrates – at the time not an unusually eccentric endeavour for Tim (Rosenthal et al., 1980; Evans et al., 1983). What Tim and his colleagues found was an immediate cause for speculation: proteins that were synthesised throughout the early embryonic division cycles and underwent periodic degradation late each mitosis, which they consequently termed cyclins. Could the cyclins be instrumental in mediating the mitotic oscillations seen in anucleate egg cytoplasm (Hara et al., 1980)? Could they even be a component of maturation promoting factor (MPF), an activity described much earlier (Masui and Makert, 1971) that was present in M-phase frog eggs and that could mediate M-phase entry assayed by meiotic maturation? It wasn't until 1988 that MPF was eventually purified by Jim Maller's lab (Lohka et al., 1988) and shown to comprise two major polypeptides: one was indeed the frog homologue of Cdc2, and the other was later identified as cyclin B. Tim's lab was then soon able to use antisense oligos to show that cyclin B is necessary for mitotic entry in an in vitro system (Minshull et al., 1989). Complementary experiments by Murray and Kirschner indicated that that translation of cyclin B mRNA is alone sufficient to drive similar extracts into mitosis (Murray and Kirschner, 1989).

The excitement of these times was electric. The realisation that the same molecular engine is required to drive cells into mitosis in yeasts, frogs, flies and man was intoxicating. I remember particularly the euphoria of a Roscoff cell cycle meeting at about this time when the participants would give each other rather silly Churchillian-style ‘Cdc2-finger’ salutes.

The Nobel Prize is a fitting recognition of how the understanding of a phenomenon of major medical significance has been made by three scientists each working with small research groups and using ‘low-tech’ approaches on model systems to examine a fundamental problem in cell biology. This is a success that stems from modest beginnings. In the UK, Paul’s career was forged during a time when he did not have a secure position but was moving from one ‘soft’ post to another at Edinburgh and Sussex Universities before taking a position at ICRF. Tim’s insights also came through simple and elegant experiments, much of the work being carried out in dilapidated laboratories on the Downing Street site in Cambridge, UK (although he was frequently ‘let out’ to visit Wood’s Hole), before he too escaped to ICRF. He has been as equally encouraging to his wider field of colleagues as Paul and would be constantly popping in and out of one or another lab to find out how we were all getting along. In Britain and further afield, Tim and Paul have had an influence that goes beyond their own science. They have been ambassadors for cell biology, and their enthusiasm has encouraged the first steps of many a young scientist. Indeed, features common to each of the three laureates are not only their ability to recognise within biological complexity the key steps of fundamental importance but also their scientific generosity and the help they have given to others. Lee, Tim and Paul: congratulations!

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