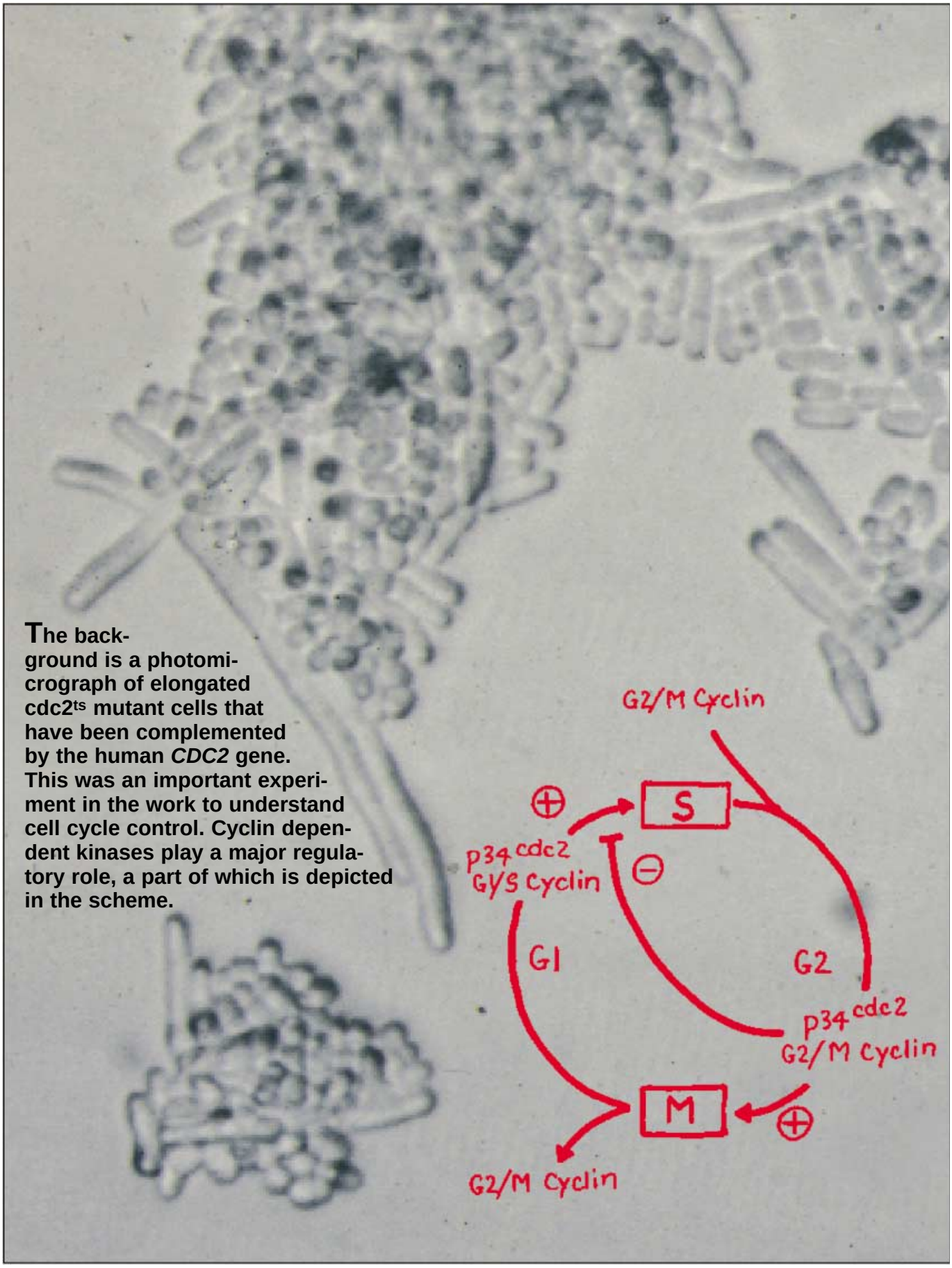

The background is a photomicrograph of elongated cdc2^{ts} mutant cells that have been complemented by the human *CDC2* gene. This was an important experiment in the work to understand cell cycle control. Cyclin dependent kinases play a major regulatory role, a part of which is depicted in the scheme.

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Cyclin Dependent Kinases and Cell Cycle Control (Nobel Lecture)**

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KEYWORDS:
cell cycle control · cyclin dependent kinases · mitosis · Nobel lecture

The cell is the basic structural and functional unit of all living organisms, the smallest entity that exhibits all the characteristics of life. Cells reproduce by means of the cell cycle, the series of events which lead to the division of a cell into two daughters. This process underlies growth and development in all living organisms, and is central to their heredity and evolution. Understanding how the cell cycle operates and is controlled is therefore an important problem in biology. It also has implications for medicine, particularly against cancer where the controls of cell growth and division are defective. In this account I describe the contributions my laboratory has made to understanding cell cycle control, focussing on the major regulators of the eukaryotic cell cycle, the cyclin dependent kinases.

Events and Control of the Cell Cycle

The most important events of the cell cycle are those concerned with replication of the genome and segregation of the replicated genomes into the daughter cells formed at division.[1] In eukaryotic cells these events are separated in time; chromosome replication occurs during S-phase early in the cell cycle, and segregation of the replicated chromosomes occurs during M-phase or mitosis at the end of the cell cycle. The phase before S-phase is called G1 and the phase before mitosis is called G2. The replication of the chromosomes is based on the double helix structure of DNA which unwinds during S-phase to generate two templates used for the synthesis of two new complementary DNA strands. During mitosis a bipolar spindle is formed and the two double helix DNA molecules making up each replicated chromosome become condensed and oriented towards opposite poles of the cell. The DNA molecules attach to microtubules emanating from the spindle poles and move away from each other toward opposite poles to be segregated at cell division. Thus the formation of two genomes during the cell cycle occurs at the molecular level during S-phase and at the cellular level during mitosis.

To ensure that each newly formed daughter cell receives a complete genome the onset and progression of S-phase and mitosis are controlled so that they occur in the correct sequence once during each cell cycle, are corrected for errors in their execution and are coordinated with cellular growth. My laboratory has worked on how these cell cycle controls operate in the single-celled eukaryote fission yeast or *Schizosaccharomyces pombe*, and has also extended these studies to metazoan cells.

Fission Yeast and Cell Cycle Control

The fission yeast was first developed as an experimental model for studying the cell cycle by Murdoch Mitchison in the 1950s.[1] It is a cylindrically shaped cell, 12 – 15 μm length and 3 – 4 μm diameter, typically eukaryotic and yet with a genome of less than 5000 genes.[2] Murdoch used fission yeast to study how cells grow during the cell cycle, devising procedures for physiological analysis and to synchronise cells so they proceeded together through the cycle. Another approach to studying the cell cycle in yeasts was taken by Lee Hartwell in the early 1970s, using the budding yeast *Saccharomyces cerevisiae*.[3] He isolated temperature sensitive cell division cycle (cdc) mutants which were unable to complete the cell cycle when incubated at their restrictive temperature. A similar approach was also possible in principle with the fission yeast, because Urs Leupold working in Bern Switzerland had established the techniques needed for classical genetic analyses of this organism. Thus it was straightforward for me to follow Lee's approach by isolating cdc mutants in fission yeast when I joined Murdoch's Edinburgh laboratory in 1973, having had a brief period of postdoctoral training to learn genetics in Bern with Urs.

The first mutants collected were mainly defective in the events of mitosis and cell division and subsequent screens carried out together with Kim Nasmyth identified more mutants defective in S-phase.[4] These cdc mutants identified genes required for the events of S-phase, mitosis and cell division, but it was not possible to determine which, if any, of these genes were involved in controlling these events. However, the chance observation that mutants could be isolated which divided at a reduced cell size provided an approach to identify such cell cycle controlling

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genes. The reason such wee mutants (wee is the Scottish word for small) were useful is because progression through the fission yeast cell cycle is coordinated with cell growth so that in constant growth conditions division occurs at a fixed cell size. Mutants altered in gene functions which are rate limiting for cell cycle progression result in more rapid progression through the cell cycle, and as a consequence cells undergo division before the normal amount of growth has taken place and divide at a small size. All the initial wee mutants isolated were found to map to a single gene *wee1*.[5] One of these was temperature sensitive, being of almost normal cell size at a low temperature and wee at a high temperature. Shift experiments from low to high temperature demonstrated that the *wee1* gene acted in G2 and controlled the cell cycle timing of mitosis (Figure 1). Experiments with Peter Fantes analysing this and other mutants and wild-type cells in different growth conditions[6, 7] revealed that the onset of both S-phase and mitosis were coordinated with attainment of a critical cell size.

Pierre Thuriaux using classical genetic procedures showed that the *wee1* gene product acted as an inhibitor of mitotic onset.[8] The genetic procedures included suppression of the wee phenotype by nonsense suppressors and the analysis of dominant and recessive mutants, and led to the conclusion that the wee mutant phenotype was associated with loss of the *wee1* gene function. As well as the large numbers of *wee1* mutants there was one dominant mutant that mapped to a second gene called *wee2* which was shown by fine structure mapping to be identical with the gene *cdc2*. The *cdc2* gene function had previously been shown to be required for mitosis,[4] and so these new experiments established that *cdc2* could be mutated in one of two ways: (1) to a loss of function blocking mitosis and (2) to a gain of function, advancing mitosis at a small cell size. We concluded that the *cdc2* gene product functioned as an activator of mitotic onset and proposed that *wee1* and *cdc2* acted together in a regulatory network controlling the onset of mitosis.

Next it was shown that *cdc2* had a role controlling the onset of S-phase. This came about as a consequence of a survey of cdc mutants to look for those which blocked in G1 phase prior to commitment to the cell cycle. The approach followed was that of Lee Hartwell, who had reasoned that budding yeast mutants blocked early in the cell cycle prior to commitment would still be able to conjugate if challenged to do so. $Cdc2^{ts}$ mutants were used as negative controls for the fission yeast experiments because they blocked in G2 and therefore it was assumed that they would be committed to the cell cycle. A low but significant percentage of these $cdc2^{ts}$ mutant cells did conjugate, a result initially thought to be due to some mutant cells leaking past the block point. However, a significant percentage of conjugation continued to be observed with the $cdc2^{ts}$ mutant and so the alternative but unlikely explanation that some cells were blocking in G1 prior to S-phase was tested. Surprisingly these tests established that *cdc2* was unusual in being required twice during the cell cycle, first in G1 for onset of S-phase and then again in G2 for onset of mitosis.[9]

These experiments showed that *cdc2* had a central role controlling the fission yeast cell cycle. In G1 it was required to commit the cell to onset of S-phase, and in G2 it acted as a major rate limiting step determining the onset of mitosis. This was unexpected because the biochemical processes of S-phase and mitosis are very different and yet appeared to be controlled by the same gene function. From this time *cdc2* became my major topic of study.

Paul Nurse became Director General (Science) of Cancer Research UK (CRUK) in February 2002, on the merger of the Imperial Cancer Research Fund with The Cancer Research Campaign. From 1996 until February 2002, he was Director General of the Imperial Cancer Research Fund, prior to that time having served for three years as Director of Research (Laboratories). He also heads the Cell Cycle Laboratory at the CRUK London Research Institute, a research group which studies the genes that prompt cells to divide. This work has greatly enhanced our understanding of the nature of cancer cells and how they grow. He is probably best known for his contribution to the discovery of the mechanism which controls cell division in most living organisms.

Paul Nurse was born in Norfolk, England, in 1949 and was educated at the Universities of Birmingham (BSc, 1970) and East Anglia (PhD in Cell Biology, 1973). He has been a research fellow and professor at several other universities including Bern, Edinburgh, Sussex and Oxford. In 1989 he was elected a Fellow of the Royal Society, in 1995 a Foreign Associate of the US National Academy of Sciences and in 1999 an Honorary Member of the Royal College of Physicians. He has been honoured with awards and medals by numerous institutions in recognition of his contributions to medical research. In 1997 he received the General Motors Cancer Research Foundation Alfred P. Sloan Jr. Prize and Medal, and in 1998 he shared the Albert Lasker Award for Basic Medical Research. Working with fission yeast he discovered a gene which controls the process of cell division, and he was also the first to succeed in demonstrating its human counterpart, so illustrating the universal nature of this mechanism and its profound implications for the field of cancer research.

In 2001, Paul Nurse was awarded the Nobel Prize for Physiology or Medicine together with his colleagues Tim Hunt and Lee Hartwell.

He has served on many national committees and is presently a member of the Council for Science and Technology which advises the Prime Minister and the Cabinet. He is also a member of the International Advisory Boards of the Sloan Kettering Cancer Center in New York and ISREC in Lausanne, and a member of the Scientific Council of the Institut Curie in Paris. He is the author of many scientific papers, and has been on the editorial board of several journals including Cell.

In 1999 Paul Nurse received a Knighthood for services to cancer research and cell biology. He lives with his wife and two daughters in Oxford.

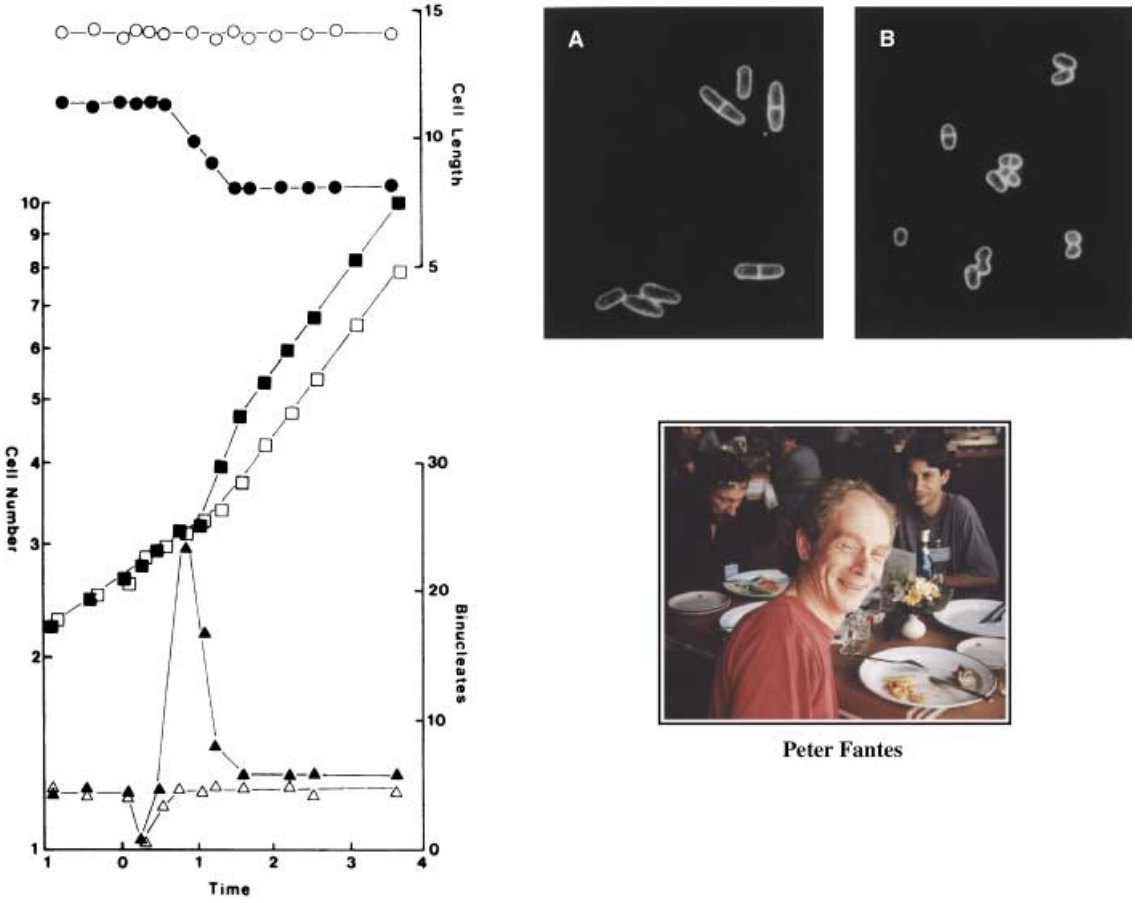


Figure 1. *Wee mutants in fission yeast. The photomicrograph shows fission yeast cells dividing at wild-type size (A) and at a small size as in a wee mutant (B). The graph shows a temperature sensitive wee1 mutant and wild-type cells shifted to high temperature at time 0. The filled triangles follow the percentage of wee1 mutant cells undergoing division and the filled circles their cell size at division. Peter Fantes was an Edinburgh colleague who helped work out the relationship between cell size and cell cycle progression in fission yeast.*

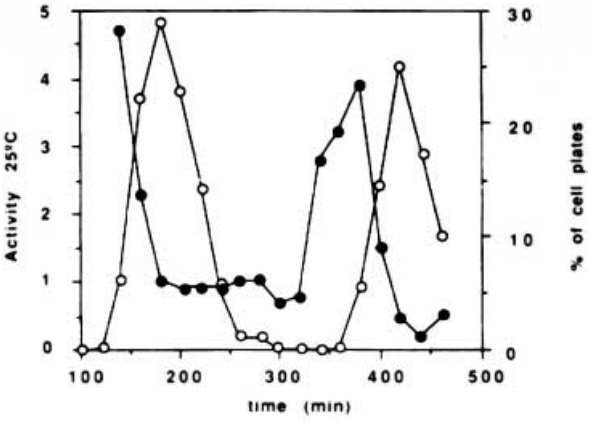
Molecular Characterisation of Cell Cycle Control

The above genetic experiments were abstract in their approach and had revealed nothing about the molecular role of *cdc2* in cell cycle control. This could only be established by cloning the *cdc2* gene but before these experiments could be carried out a DNA transformation procedure needed to be developed for fission yeast. This procedure would enable gene libraries to be introduced into cdc2^{ts} cells, allowing the *cdc2* gene to be cloned by rescue or complementation of the temperature sensitive mutant phenotype. Developing a transformation procedure and other methods for molecular genetics became my first priority on setting up my own laboratory at the University of Sussex near Brighton, where I worked in collaboration with David Beach. The DNA transformation procedure developed was based on methods already available for budding yeast, using both ARS (origins of replication) elements and selectable markers from that organism.[10] Gene replacement procedures were developed, although the efficiency of homologous recombination in fission yeast is less than in budding yeast. The *cdc2* gene was cloned by complementation and the cloned gene was found to fully rescue the cdc2^{ts} mutant defects at both the G1/S and G2/M boundaries.[11]

To check if a gene related to *cdc2* was also present in budding yeast we also transformed a cdc2^{ts} mutant with a budding yeast library and found a segment of DNA that could rescue the cdc2^{ts} mutant. Steve Reed had cloned four cdc genes from budding yeast and provided these to us prior to their publication so we were able to check if the cdc2^{ts} complementing segment of DNA was one of these genes. Hybridisation was found with the budding yeast *CDC28* gene, indicating that the fission yeast *cdc2* gene and the budding yeast *CDC28* gene were functionally equivalent.[11] This was another unexpected result because *CDC28* was thought only to act at the G1/S boundary in budding yeast, although a cdc28^{ts} mutant had been described which became blocked at mitosis.[12] We proposed that *cdc2/CDC28* acted at both the G1/S and G2/M transitions in both yeasts, but in budding yeast it had been difficult to detect the G2/M block point because it occurred very early in the cell cycle just after the G1/S block point, due to the budding mode of cell division.[13] The similarity of the controls between the rather distantly related yeasts also encouraged us to speculate that there might be similar controls in mammalian cells.[11]

The movement of my laboratory from Sussex to the Imperial Cancer Research Fund's Lincoln's Inn Fields laboratories in central London in 1984 provided the environment and resources

for a proper molecular characterisation of the *cdc2* gene function. The gene was shown to encode a protein kinase by two postdoctoral workers, Viesturs Simanis and Sergio Moreno. Viesturs developed antibodies against the Cdc2p protein and showed that immunoprecipitates had protein kinase activity and that this activity was temperature sensitive in vitro in extracts made from cdc2^{ts} mutants.[14] This result confirmed earlier work from Steve Reed's laboratory showing that the budding yeast *CDC28* gene encoded a protein kinase.[15] Sergio optimised the protein kinase assay and demonstrated that activity varied considerably during the cell cycle (Figure 2), peaking just at the onset of mitosis.[16]

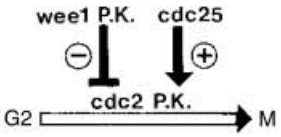


Sergio Moreno

Figure 2. *The Cdc2p CDK activity through the cell cycle. The graph shows CDK activity in a synchronous culture of wild-type cells. The open circles are the percentage of dividing cells and the closed circles the Cdc2p protein kinase activity peaking at mitosis. Sergio Moreno worked in my laboratory for over six years, contributing much to Cdc2p and its regulation.*

The molecular basis of the periodic regulation of the Cdc2p protein kinase was worked on by two further postdoctoral workers, Paul Russell and Kathy Gould. Paul cloned both the *wee1* and *cdc25* genes by complementation, and showed that they acted upstream of *cdc2*. Wee1p had sequence similarity with protein kinases, suggesting that it might phosphorylate Cdc2p directly to inhibit Cdc2p protein kinase activity.[17] The *cdc25* gene was shown to act in a positive manner antagonistically to the Wee1p inhibitor (Figure 3), but the failure to find any sequence similarities with previously identified genes meant that it could only be speculated that Cdc25p was necessary for a protein phosphatase activity that countered the Wee1p protein kinase.[18, 19]

After my laboratory moved to the Biochemistry Department at Oxford University, Kathy Gould carried out a biochemical analysis of Cdc2p phosphorylation. A major phosphorylation site identified was tyrosine 15, the first time tyrosine phosphorylation had been detected in a microbial eukaryote.[20] Phosphorylation of this residue was associated with the G2 phase of the cell cycle when Cdc2p protein kinase activity was at a low level. Tyrosine 15 is located near the adenosine triphosphate (ATP) binding site of the protein kinase, suggesting that phosphorylation of this residue might influence catalytic activity. The physiological relevance of this phosphorylation was confirmed by constructing an 'unphosphorylatable' phenylalanine 15 mutant which advanced cells prematurely into mitosis. Cdc25p was also shown to be required to remove the phosphate from the tyrosine 15 residue in Cdc2p. This work suggested that the Cdc2p protein kinase activity was regulated by tyrosine 15 phosphorylation, and that the level of phosphorylation was regulated by the balance of activities between the Wee1p protein kinase mitotic inhibitor and Cdc25p mitotic activator.



Paul Rusell

Figure 3. *The G2/M regulatory network. Wee1p acts as a negative regulator and Cdc25p as a positive regulator of the Cdc2p protein kinase at the G2/M transition. The* wee1 *and* cdc25 *genes were cloned and their regulatory relationships were determined by Paul Russell when he was a postdoctoral worker with me in Brighton and London.*

One further gene important for *cdc2* regulation is *cdc13*. This was cloned by Booher and Beach.[21] and by my laboratory,[22] and the putative gene product was shown to have significant similarity with cyclins. Tim Hunt and Jon Pines had characterised sea urchin cyclin,[23] and Tim had proposed cyclin as a cell cycle regulator during early embryonic cleavage. Cdc13p cyclin varied in level during the fission yeast cell cycle, and was required for Cdc2p protein kinase activation,[16] establishing that the Cdc13p cyclin is necessary for Cdc2p to bring about the G2/M transition.

Universal Role for Cdc2p in Cell Cycle Control

In parallel with these studies on the molecular characterisation of Cdc2p, my laboratory was also attempting to establish if there was a Cdc2p in metazoan cells. Two major approaches were used, the first being the cloning of the human *cdc2* gene achieved by Melanie Lee.[24] Initially Melanie had tried to clone a human homologue of *cdc2* on the basis of structural similarity. These approaches identified protein kinases, but as there are at least 500 protein kinases in the human genome it was difficult to

know whether the cloned genes were *cdc2* candidates or not. Because of this difficulty Melanie tried a different approach of cloning the gene by complementation of a $cdc2^{ts}$ fission yeast mutant, using a human complementary DNA (cDNA) library from Hirota Okayama. Complementing clones were isolated (Figure 4), and a tense period of a month or so followed whilst alternative, less interesting explanations of this result were

Melanie Lee

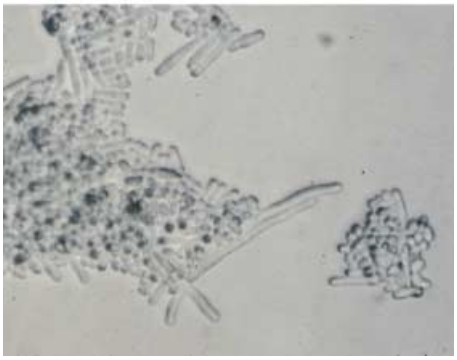


Figure 4. *The cloning of human CDC2. The photomicrograph shows $cdc2^{ts}$ mutant cells being complemented by the human CDC2 gene. The human gene is on a plasmid and when this is lost from cells they are unable to divide and become highly elongated. This bold experiment was carried out by Melanie Lee at the ICRF (now Cancer Research UK) Lincoln's Inn laboratories.*

eliminated. The discovery of a human homologue of *cdc2* had important implications and so we were all worried that our hopes were being raised only to be dashed at the final hurdle! Melanie carefully completed the necessary controls, sequenced the human cDNA, and one exciting morning we were all huddled round the computer when the sequence comparisons between the human and yeast proteins indicated that there was a 63% identity between them. The human *CDC2* gene could fully substitute for the defective fission yeast *cdc2* gene, despite the evolutionary divergences of these organisms of 1000–1500 million years. This result strongly supported the idea that cell cycle control was conserved in yeast and humans, and therefore probably in all other eukaryotes. We speculated that human *CDC2* might act at two points in the cell cycle, at the G1 restriction point known to operate in mammalian cells, and at the G2/M transition where it acted as maturation promoting factor (MPF) known to control M-phase in metazoan eggs and oocytes.

The second approach directly involved MPF itself. Yoshio Masui working in Toronto had identified MPF as a factor which induced frog egg maturation which involved meiotic M-phase.[25] Yoshio also developed cell free assays to monitor MPF[26] which were further developed by Jim Maller and Fred Lokha in Denver who purified MPF from the Xenopus frog.[27] The purified preparation contained two proteins, one of which was 32kD, a molecular mass rather similar to Cdc2p. Western blot and immunoprecipitation experiments using antibodies against a conserved Cdc2p peptide demonstrated that the 32kD component of MPF was indeed a homologue of Cdc2p.[28] Subsequent collaborative work with Marcel Dorée's group in Montpellier established that a periodic mitotic kinase in starfish embryos, also contained a Cdc2p homologue[29] as did starfish MPF.[30] Marcel's work also greatly helped our own biochemical investigations of Cdc2p in fission yeast.

The link with MPF was important because it established that the biochemical mechanisms underlying mitotic onset were the same in yeasts, starfish and frogs. MPF had been shown to 'biochemically' advance starfish and frog eggs into meiotic M-phase whilst Cdc2p had been shown to 'genetically' advance yeast cells into mitotic M-phase. Evidence from this and other work was sufficiently strong to propose that there was a universal control mechanism regulating the onset of M-phase in all eukaryotes.[31] This operates through a G2/M CDK with a catalytic CDK subunit complexed with a cyclin subunit, regulated by a Wee1p protein kinase phosphorylating a tyrosine residue (and sometimes the adjacent threonine) near the catalytic site, and a Cdc25p protein phosphatase which removed the phosphates to activate the CDK. CDKs were also found to regulate the G1 to S-phase transition in multicellular eukaryotes, but a different CDK to the one acting at G2/M is used in these organisms. In contrast, fission yeast CDK can bring about both the G1/S and the G2/M transitions.

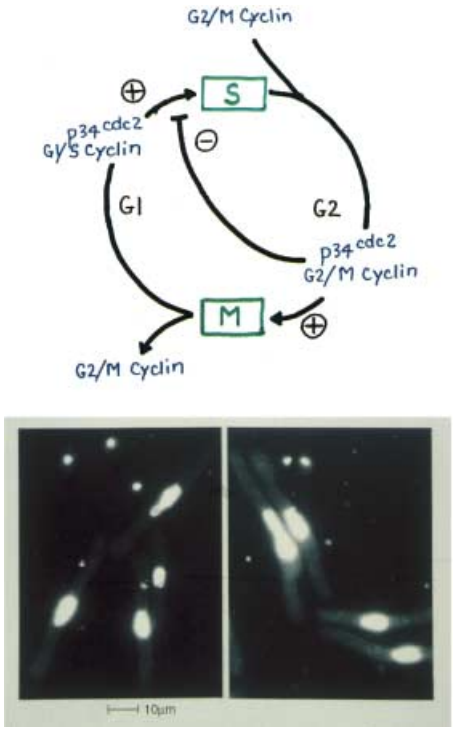
The universality of cell cycle controls in eukaryotes should have been anticipated given the high conservation already noted for biochemical pathways and for many processes of molecular biology. Possibly the rather different appearance of cells and cell division in microbial eukaryotes, plants and Metazoa made universality seem less likely than these other processes. However, Schwann, one of the early proponents of the cell theory had already recognised this possibility in 1839 when he stated "We have seen that…cells are formed and grow in accordance with essentially the same laws; hence, that these processes must everywhere result from the operation of the same forces".[32]

Further Roles for CDKs

In more recent years two further roles for CDKs have emerged. The events of the cell cycle usually occur in a fixed sequence, and if an early event such as S-phase is incomplete then a later event such as mitosis becomes blocked. In principle there are two general types of mechanism that can account for these dependencies. There could be a hard wiring of the two events such that the later event is unable to occur physically or chemically without the earlier event. This is analogous to a metabolic

pathway, with the product from the first enzyme acting as the substrate for the second. Alternatively the two events could be linked by a regulatory loop that inhibits the second until the first is complete. Lee Hartwell developed the second of these two alternatives into the idea of checkpoints whereby the cell monitors or "checks" cell cycle progression at certain "points" in the cell cycle, and if events prior to that point are incomplete then further progression is delayed.[33] The checkpoint idea is also extremely useful for thinking about cell cycle delays in response to DNA damage, and has helped understanding of how genome stability is maintained during cell reproduction.

Tamar Enoch investigated the dependency of mitosis upon completion of S-phase in fission yeast. She showed that this dependency was lost in cells with specific *cdc2* mutations, or in mutants with high levels of the CDK activator Cdc25p.[34] These mutants could undergo mitosis when DNA synthesis was inhibited with hydroxyurea, and so we concluded that the checkpoint control monitoring the completion of S-phase led to inhibition of the G2/M CDK, preventing mitosis until S-phase was complete. This established that CDKs were a part of the checkpoint control ensuring that mitosis only takes place when the genome is fully replicated.



Jacky Hayles

Figure 5. *Repeated S-phase in cells lacking G2/M CDK activity. The photomicrograph shows cells lacking the G2/M cyclin Cdc13p. Their nuclei are stained with DAP1 and are the large nuclei with high DNA content. The nuclei are smaller in wild-type cells. The presence of the G2/M CDK prevents a further round of S-phase during G2. Jacky Hayles has worked in my laboratory for 20 years, and has contributed much to many of the different projects important for understanding how CDKs regulate the cell*

Another role for CDKs is to ensure that there is only one S-phase in each cell cycle. When a cell completes S-phase and enters G2, another S-phase does not take place until the mitosis of that cell cycle is complete. To investigate this control, fission yeast mutants were sought which underwent more than one round of S-phase each cell cycle generating cells of higher ploidy. These were found to be altered in the G2/M CDK Cdc2p/Cdc13p,[35] suggesting that the state of this CDK is important for restraining S-phase during G2. Consistent with this, over-expression of the CDK inhibitor Rumlp was found to inhibit the G2/M CDK, and also to bring about repeated rounds of S-phase.[36] Finally, Jacky Hayles showed that deleting the Cdc13p G2/M cyclin from cells resulted in repeated rounds of S-phase establishing that the presence of the G2/M CDK in G2 cells inhibited S-phase (Figure 5). Only after mitosis when this CDK was destroyed could another S-phase take place,[37] implicating CDKs in the control mechanism maintaining one S-phase per cell cycle.

These two roles further emphasise the importance of CDKs in regulating the orderly progression through S-phase and mitosis during the cell cycle. The onset of S-phase is thought to require two sequential steps: the first of these only takes place if no CDK activity is present whilst the second requires the presence of CDK activity.[38] In early G1 there is no CDK activity allowing progression through step one. Later in the cell cycle at the G1/S boundary CDK activity appears which allows progression through step two and brings about the initiation of S-phase. During G2 the continued presence of CDK activity prevents step one from occurring again and this blocks onset of a further S-phase. At the G2/M boundary there is a further increase in CDK activity which brings about mitosis. Exit from mitosis and the ending of the cell cycle requires destruction of CDK activity, and because the subsequent G1 cells lack CDK activity they are able to carry out step one for S-phase and the whole series of events can be repeated.[39]

What lies in the future for CDKs and cell cycle control?[40] It remains an embarrassment that so few CDK substrates have yet been identified. Until this situation improves understanding of the molecular mechanisms underlying the onset of both S-phase and mitosis will remain incomplete. Solution of this problem will need the development of new procedures to identify in vivo substrates for protein kinases. CDK regulation has been relatively well characterised but needs to be further refined given the importance of tightly regulated kinase activity at different stages of the cell cycle. Theoretical modelling will be required to understand how the temporal changes of CDK activity and spatial location are regulated through the cell cycle. Regulation of CDKs during development and the role this may play in generating tissue and organ form is another interesting problem. The meiotic cell cycle is modified from the mitotic cell cycle so S-phase is suppressed between M-phase I and M-phase II, an altered regulation likely to be due to differences in CDK behaviour between the two types of cell cycles. Such differences may also be relevant for the switch to reductional chromosomal segregation during meiosis.

Working out how CDKs act as major regulators of the cell cycle has been an exciting endeavour and I feel fortunate to have been at the right place and time to have contributed to this

enterprise. As is clear from my account this has been a collaborative venture involving many friends and colleagues, some working in my laboratory and others working in other cell cycle laboratories around the world. Without their efforts the work described here would not have been possible. Finally, it is a real pleasure to acknowledge my two co-awardees Lee Hartwell and Tim Hunt and my long-term colleague Jacky Hayles, and to thank them for their collegiality and inspiration for more than two decades.

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