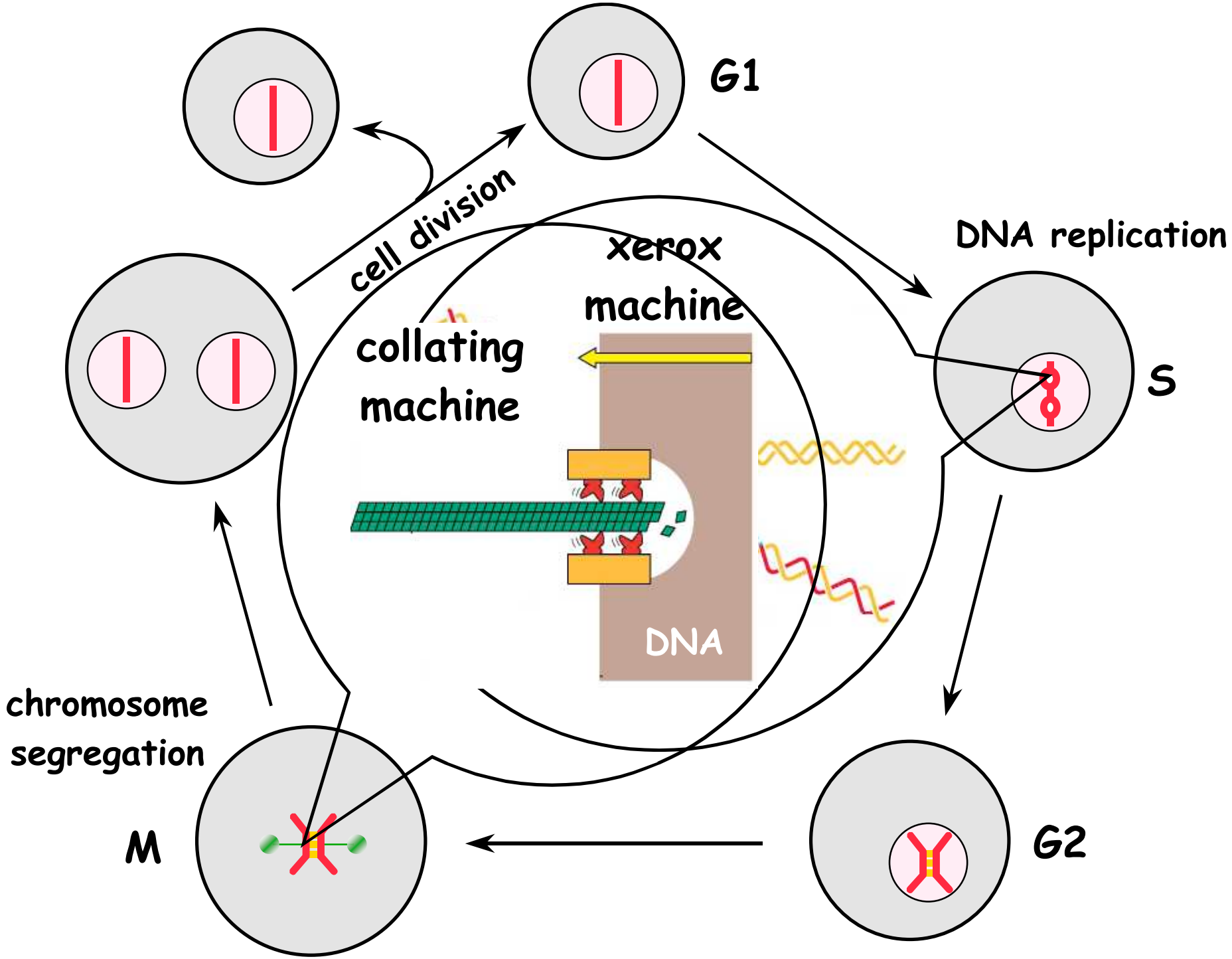
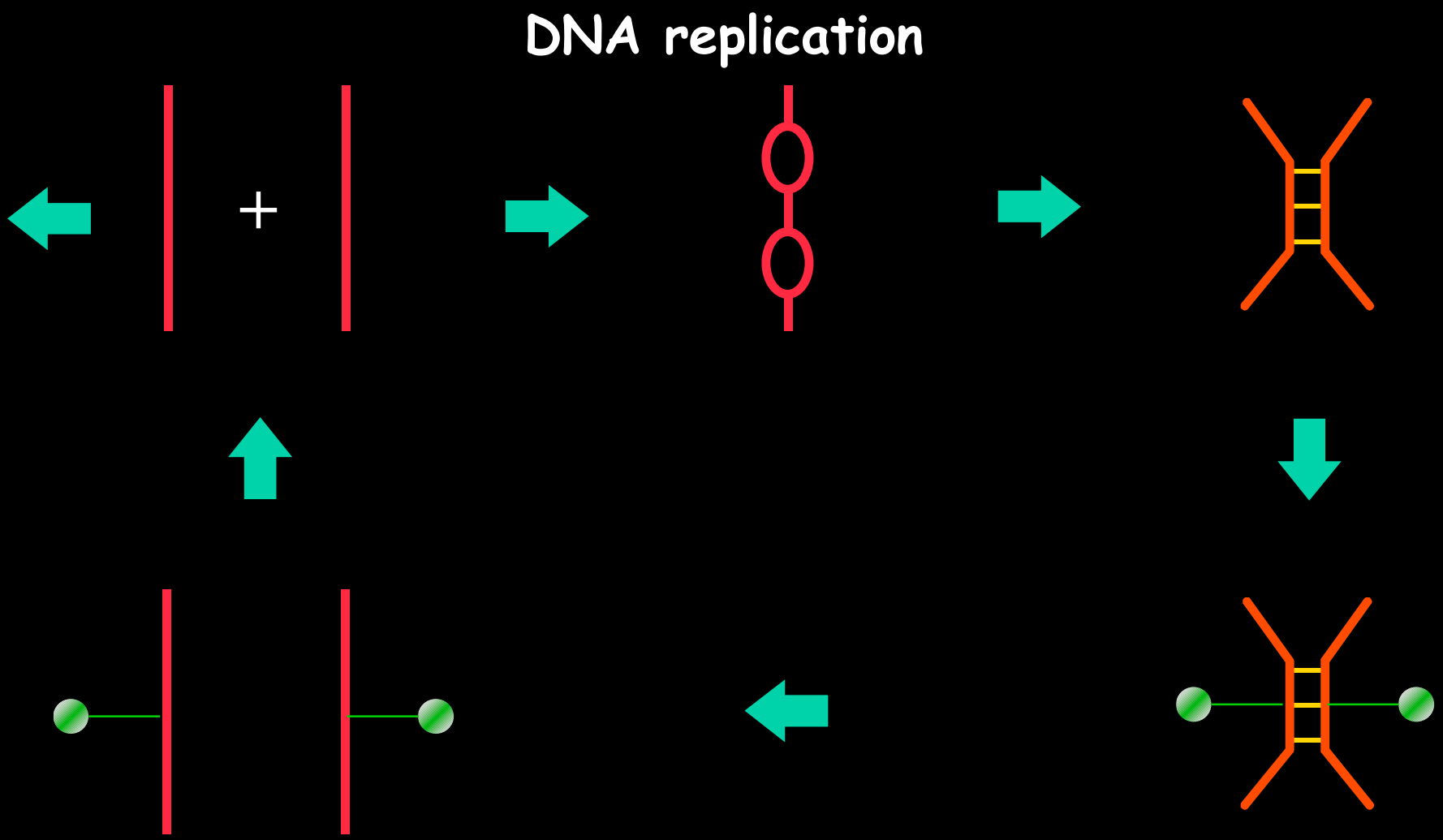
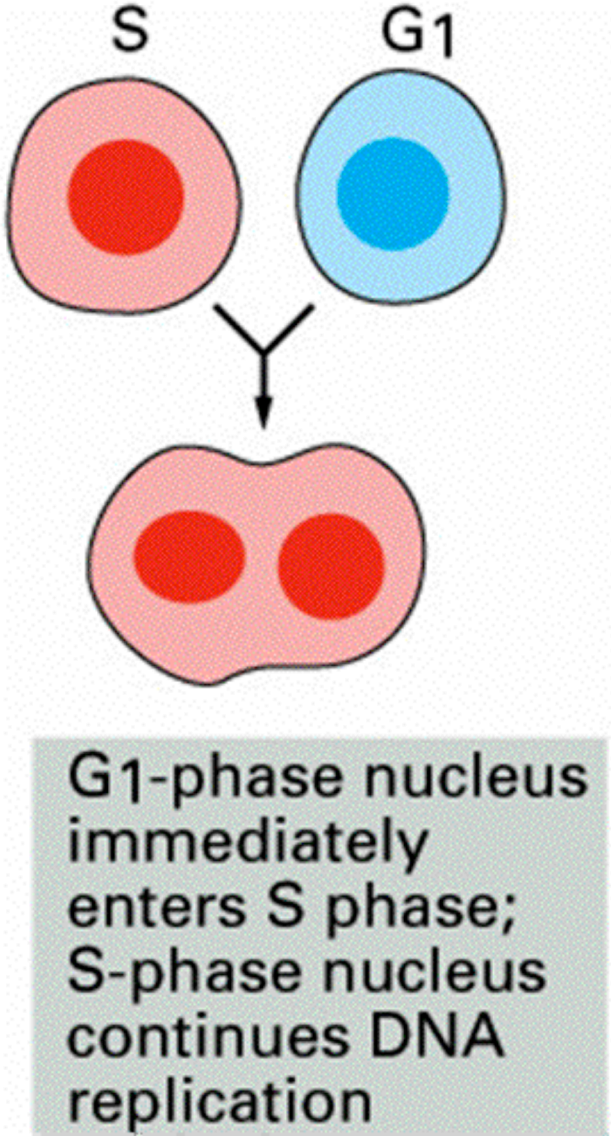

G1
DNA replication
S
G2
chromosome
segregation
M
cell division
xerox
machine
collating
machine
DNA

# Alternation of DNA replication and chromosome segragation



# The logic of the cell cycle:

## cell fusion experiments (Rao & Johnson)

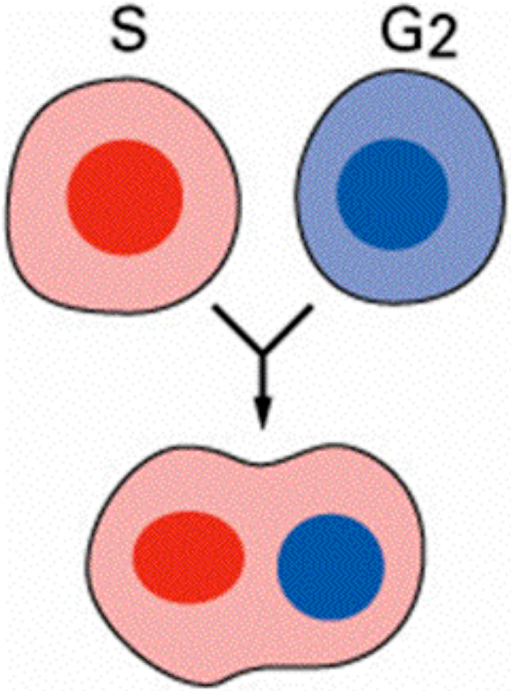



S phase cells contain
a factor that can trigger
DNA replication in G1 cells:
**S phase Promoting Factor**

# The logic of the cell cycle:

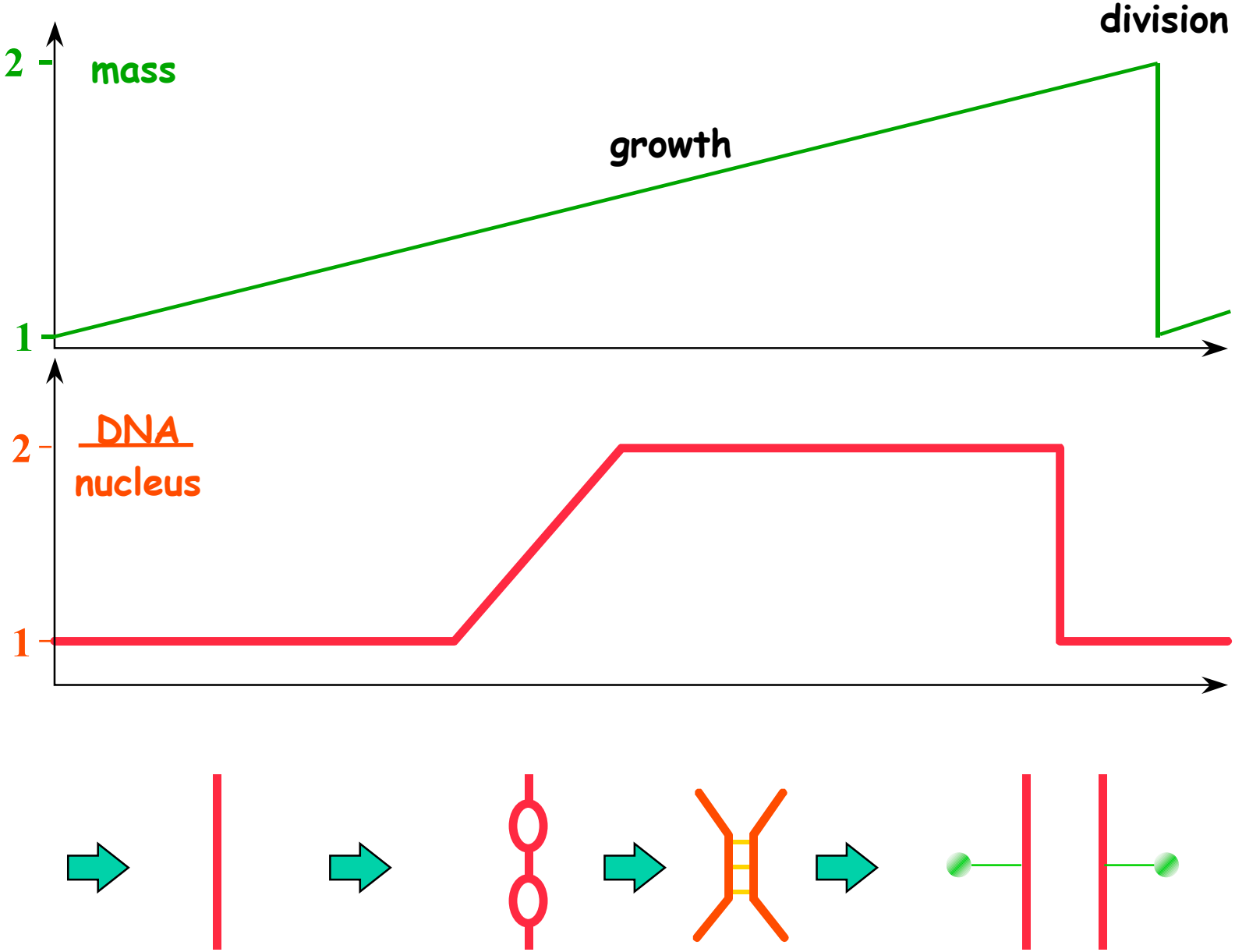
## cell fusion experiments (Rao & Johnson)

**block of re-replication**

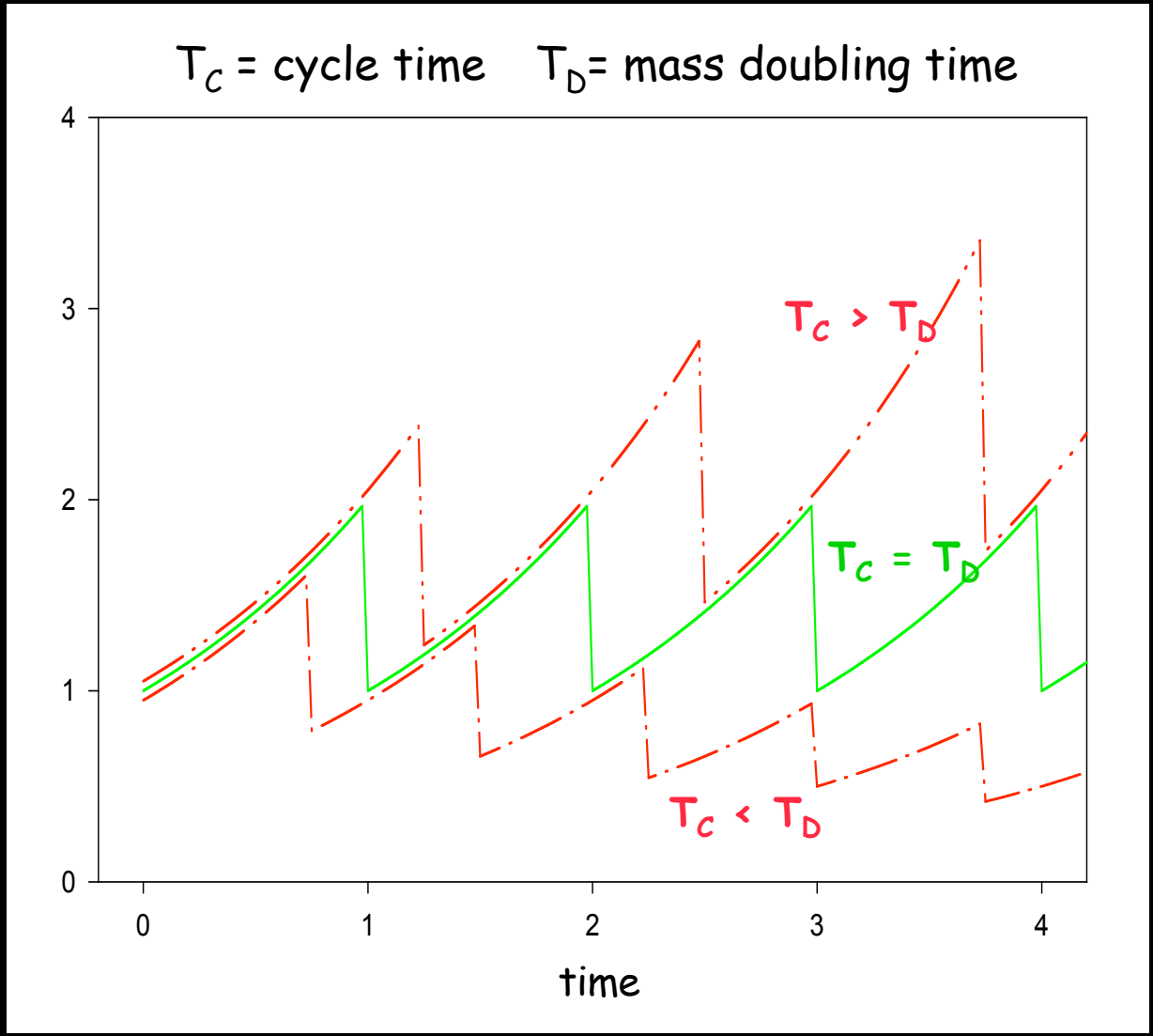


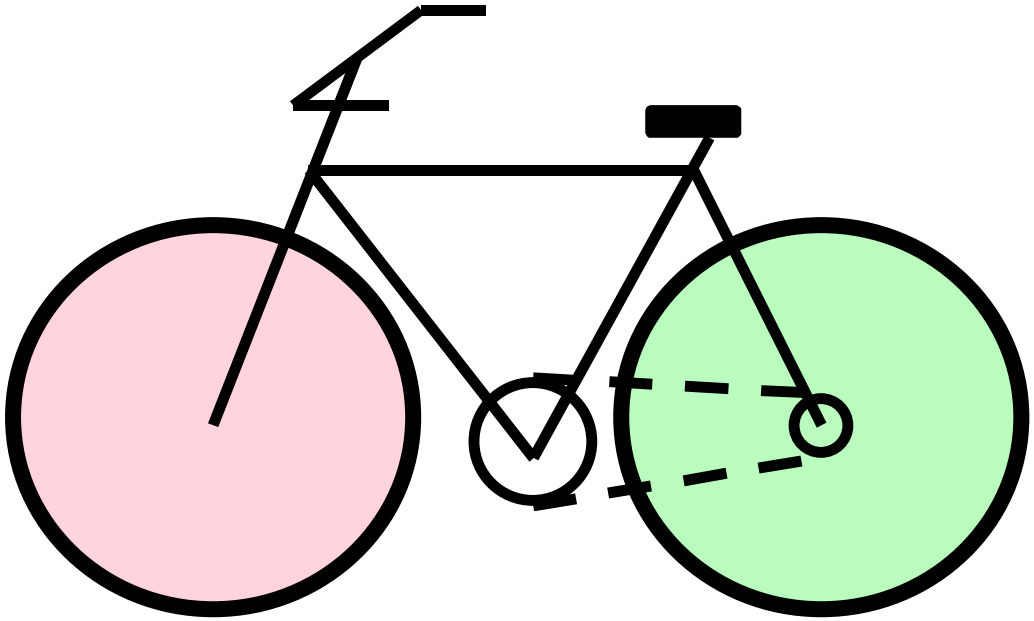

G2-phase nucleus stays in G2;
S-phase nucleus continues DNA replication

# The Cell Division Cycle



# Balanced growth and division





**Chromosome cycle**

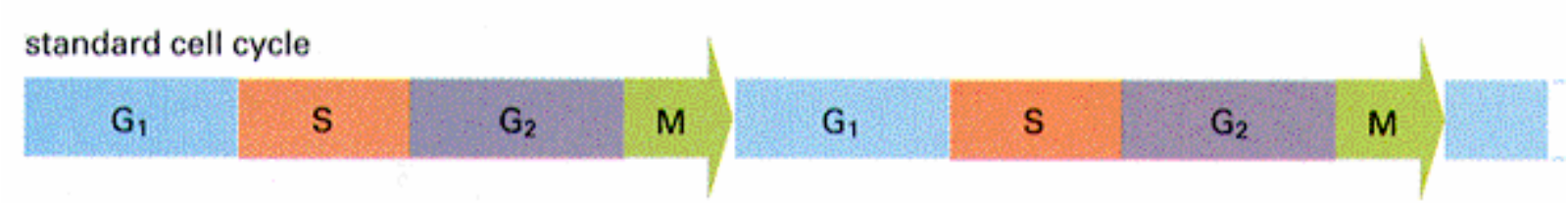
- DNA replication
- mitosis

(precise replication and segregation)

**Growth cycle**

- cytoplasmic growth
- cell division

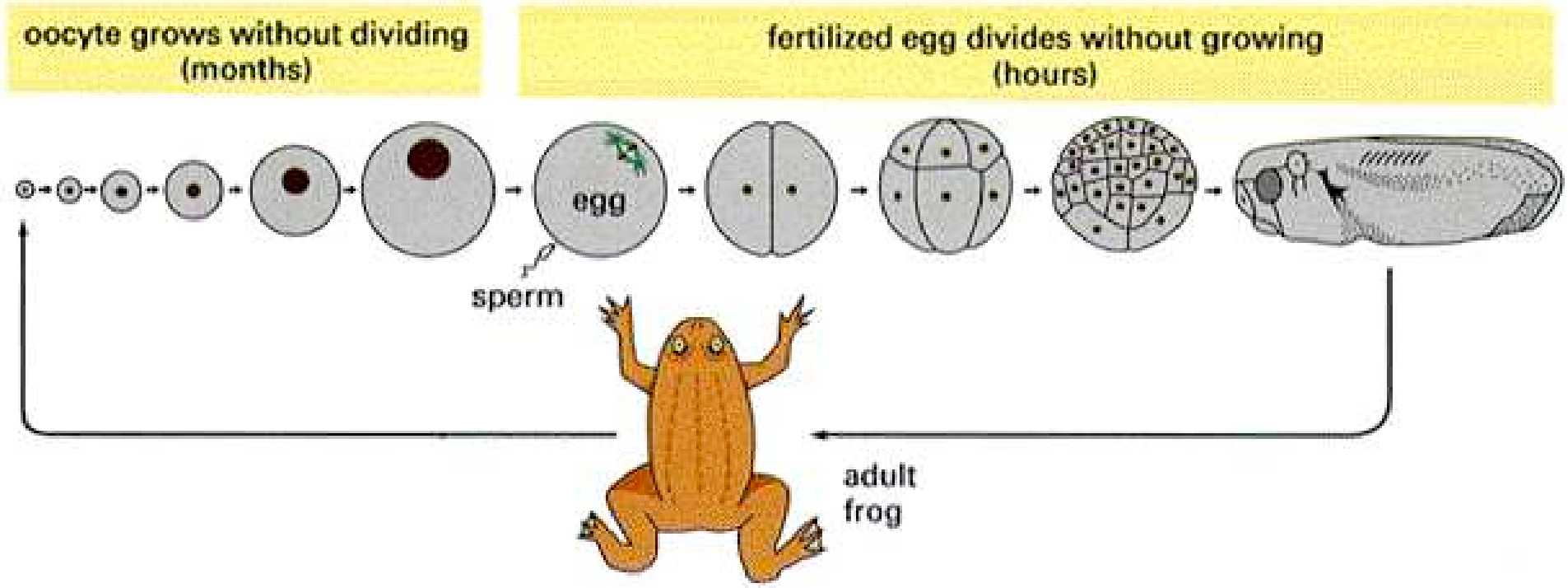
(approx. doubling and halving)

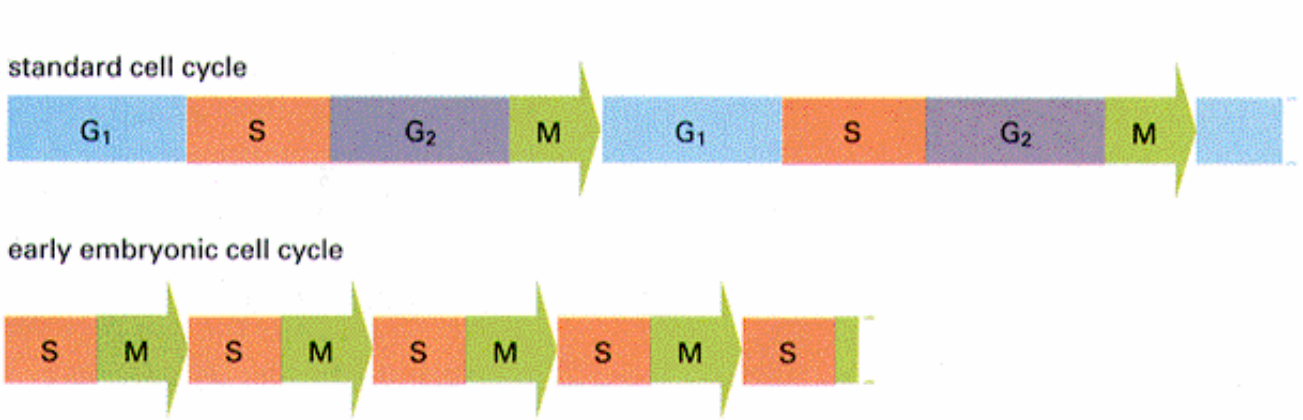


# Dissociation of growth and chromosome cycle

## Oogenesis

## Embryogenesis



# The Nobel Prize in Physiology or Medicine 2001

"for their discoveries of key regulators of the cell cycle"


## Leland H. Hartwell

USA

Fred Hutchinson Cancer Research Center
Seattle, WA, USA

1939 -


## R. Timothy (Tim) Hunt

Great Britain

Imperial Cancer Research Fund
London, Great Britain

1943 -

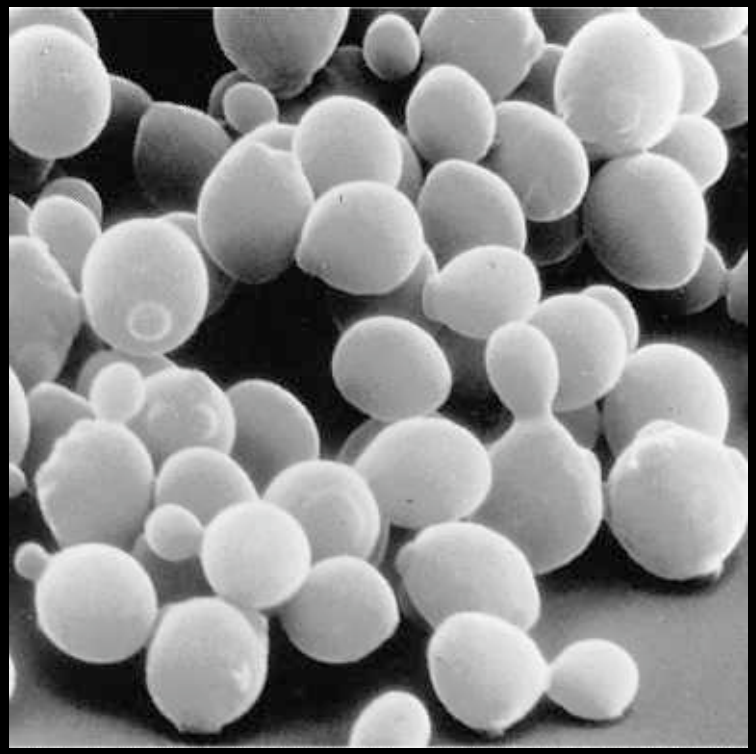

## Paul M. Nurse

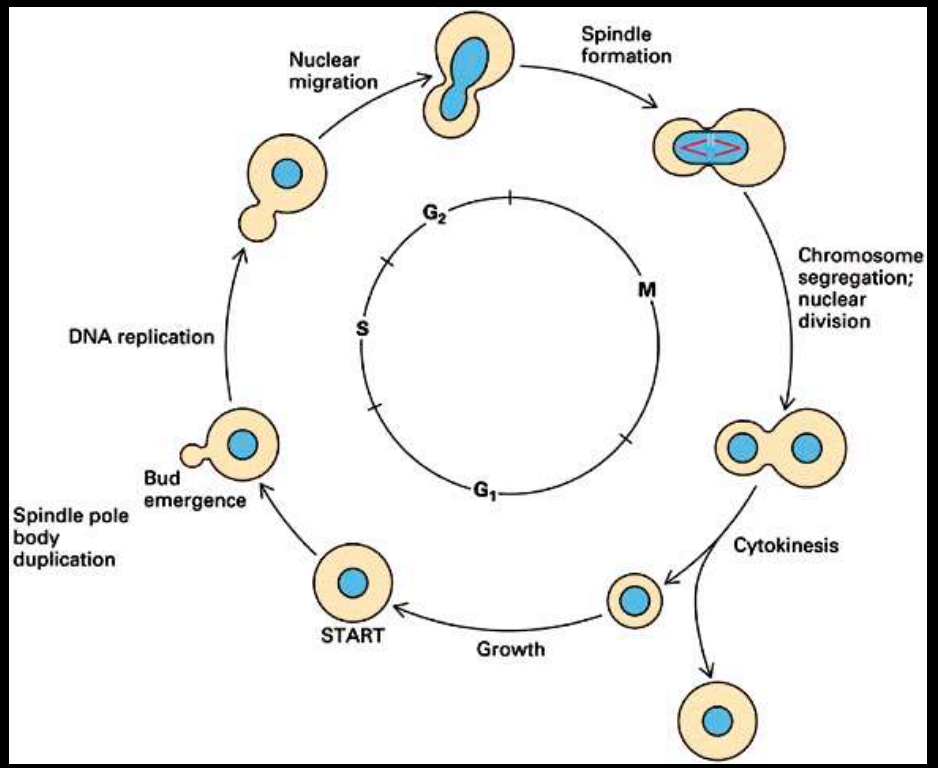
Great Britain

Imperial Cancer Research Fund
London, Great Britain

1949 -

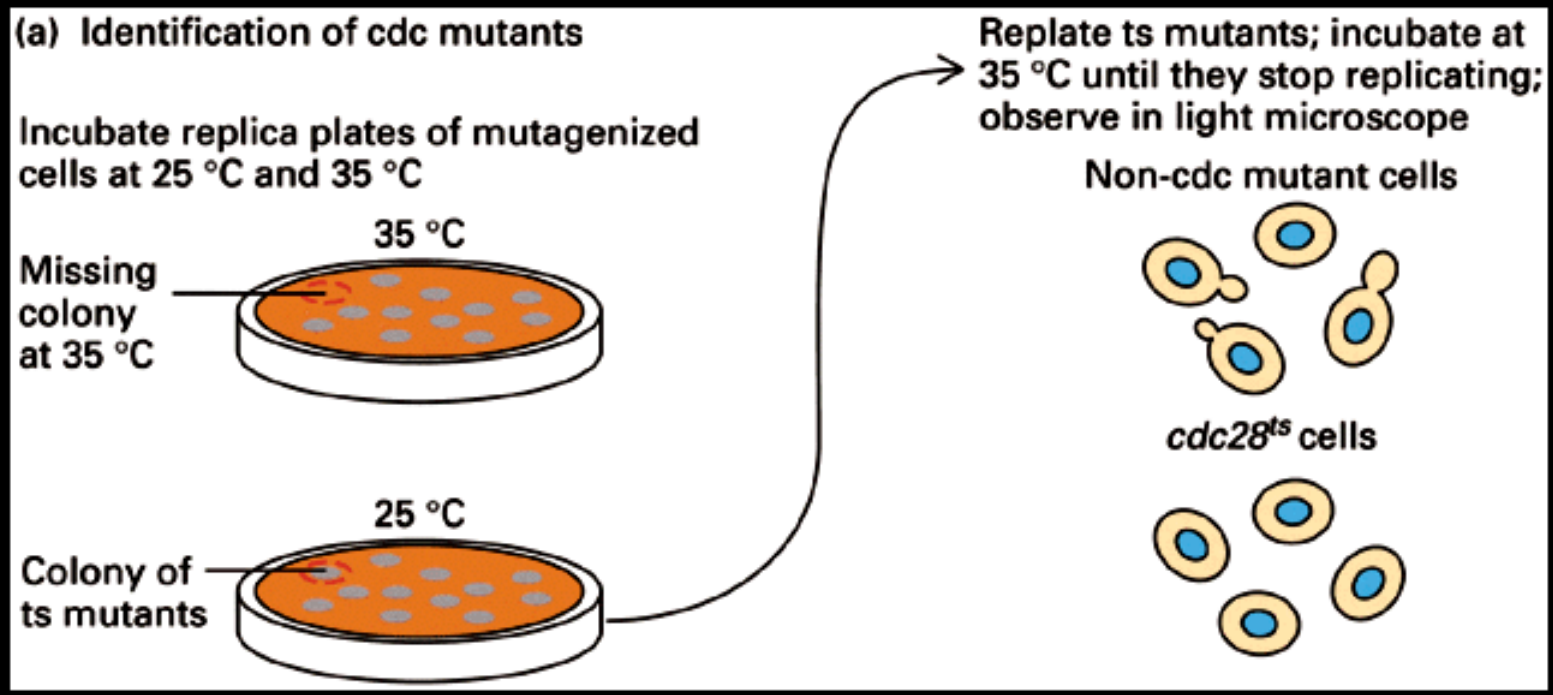
# *Saccharomyces cerevisiae*

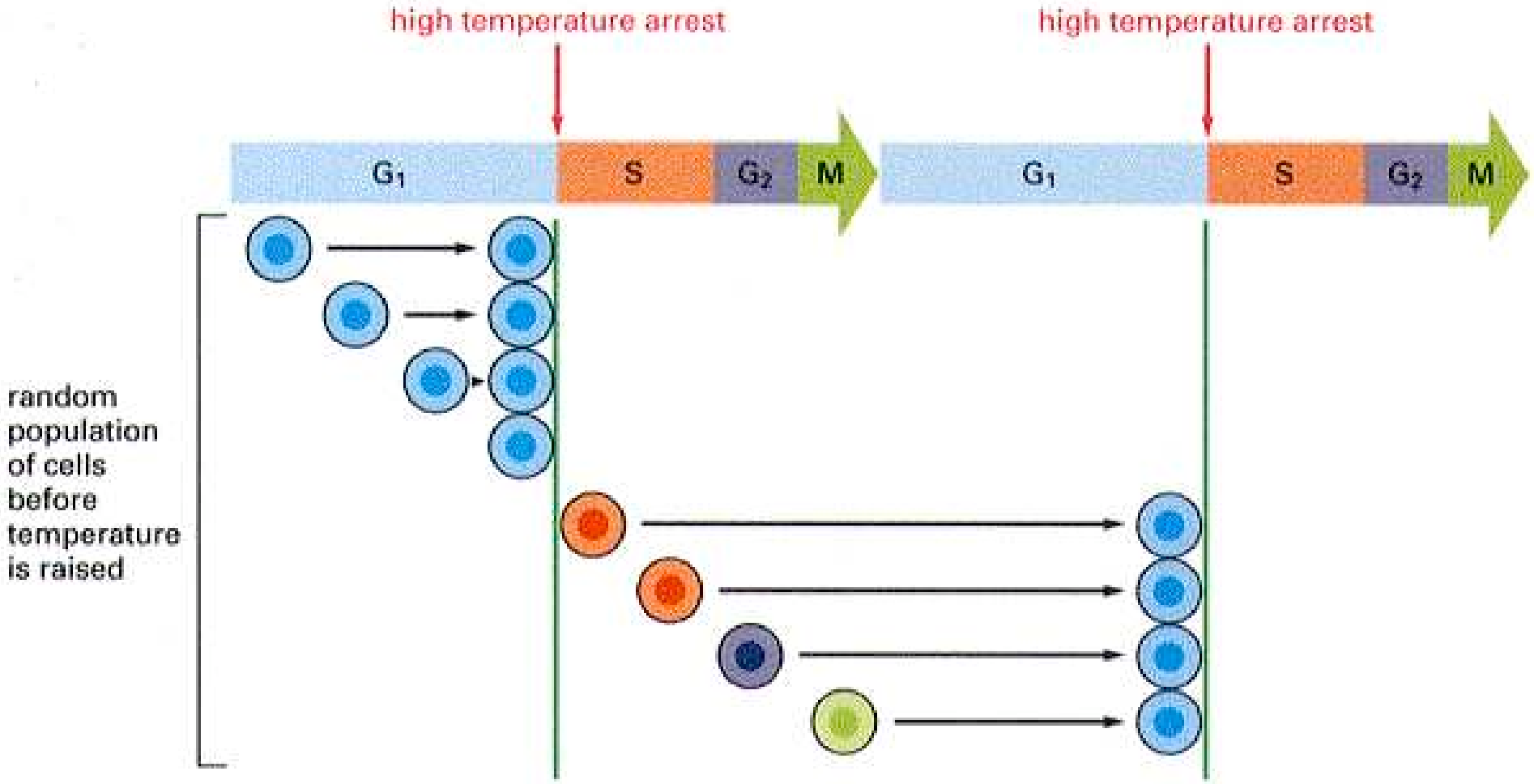




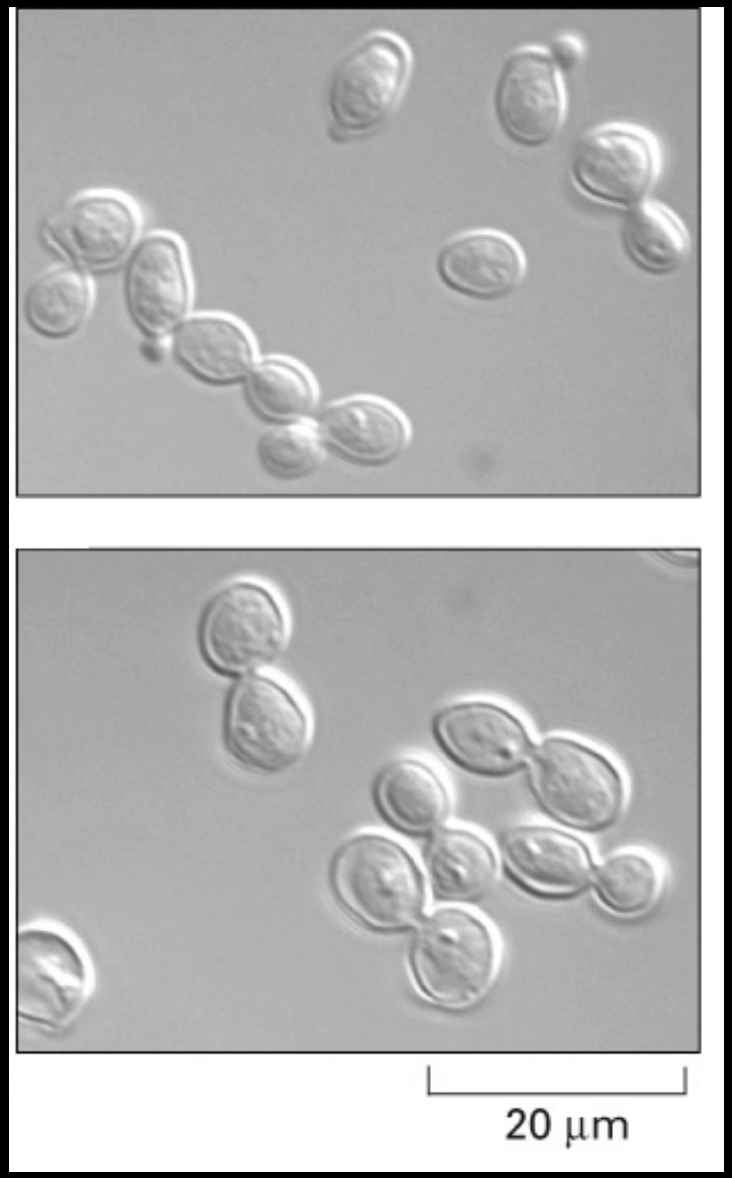

Lee Hartwell

# Isolation of temperature sensitive *cdc*$^{ts}$ mutants




high temperature arrest
high temperature arrest
G1
S
G2
M
G1
S
G2
M
random population of cells before temperature is raised

# Phenotype of *cdc* mutants




asynchronous culture

cdc mutant with problem of mitotic exit

# Cdc28 is responsible for the first genetically controlled event

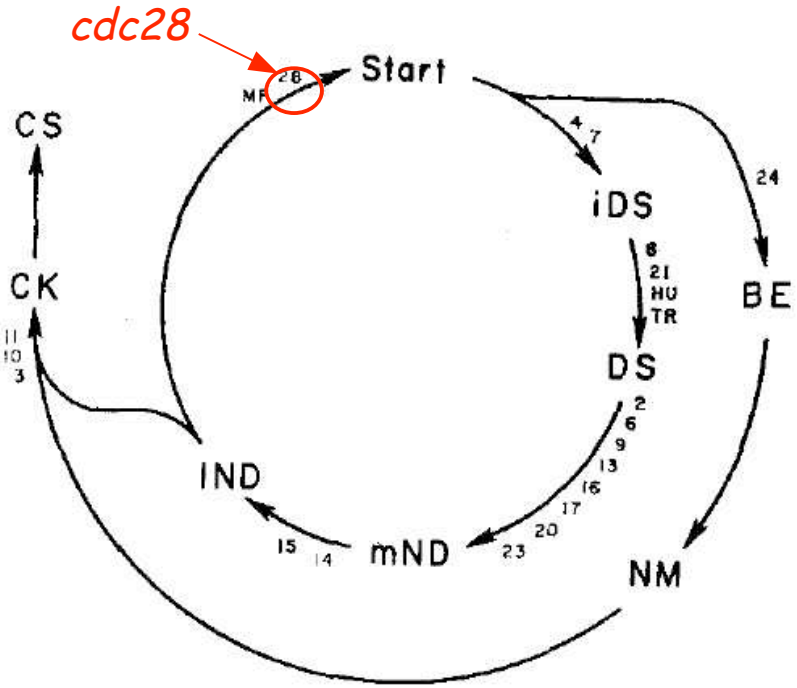
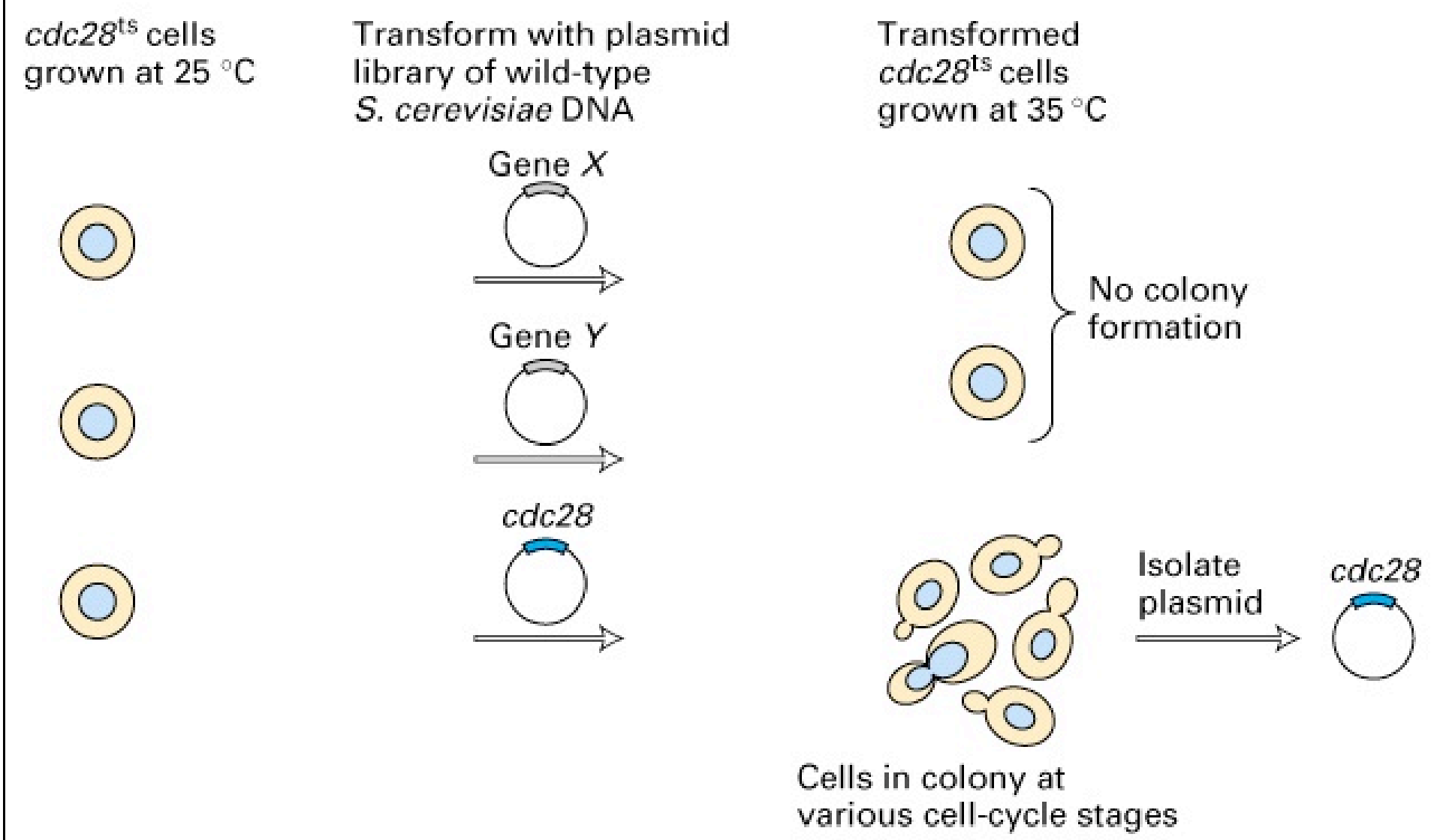


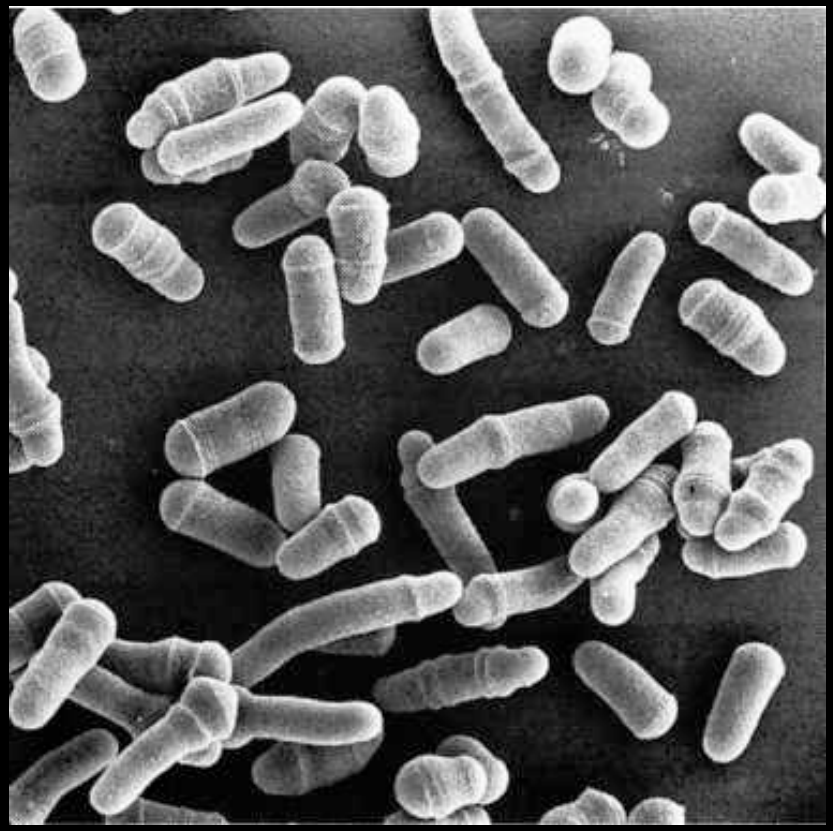

Fig. 3. The circuitry of the yeast cell cycle. Events connected by an arrow are proposed to be related such that the distal event is dependent for its occurrence upon the prior completion of the proximal event. The abbreviations are the same as in Fig. 1. Numbers refer to *cdc* genes that are required for progress from one event to the next; *HU* and *TR* refer to the DNA synthesis inhibitors hydroxyurea and trenimon, respectively; *MF* refers to the mating factor, $\alpha$ factor.

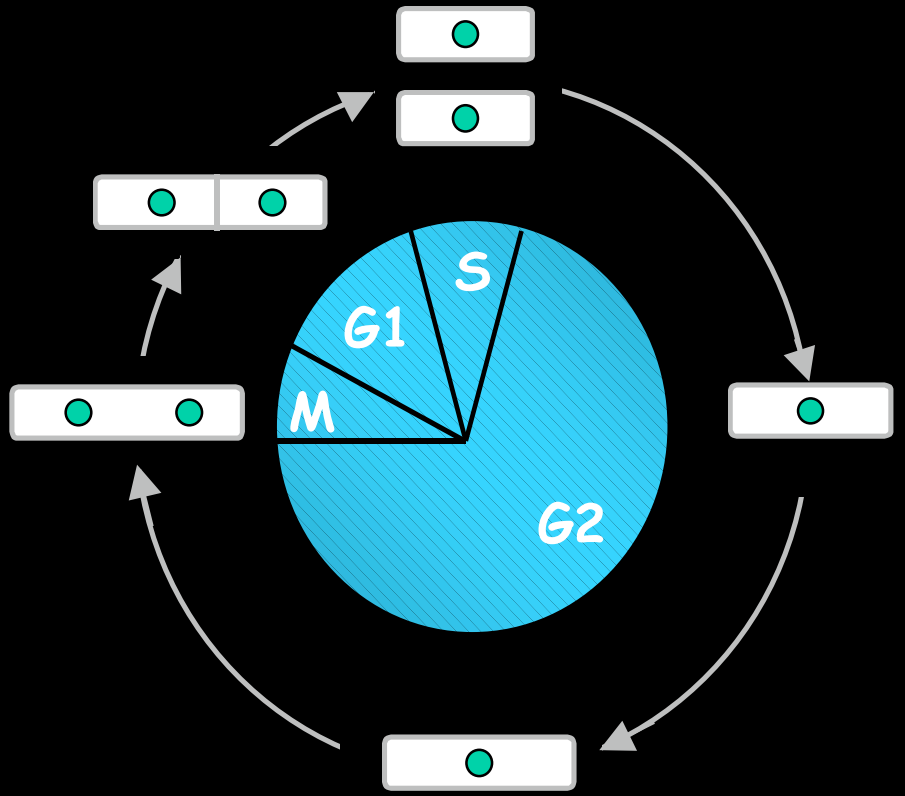
# Cloning of *cdc*$^{ts}$ genes




**Cdc28 is a protein-kinase**

# *Schizosaccharomyces pombe*

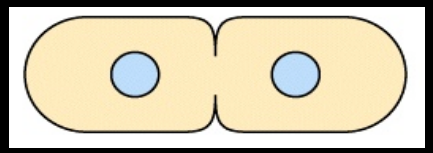




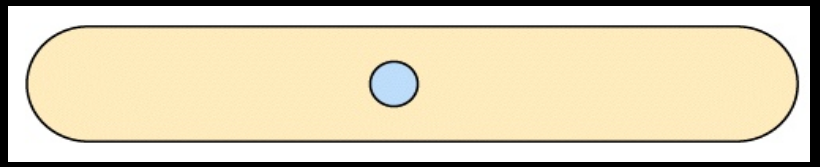

Sir Paul Nurse

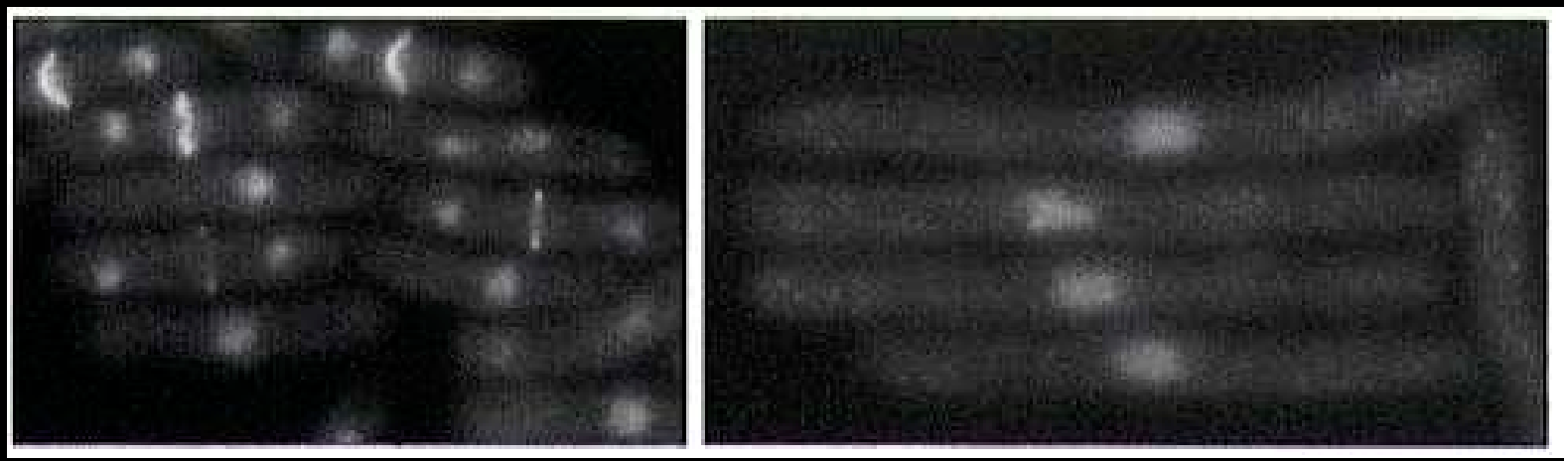
Murdoch Mitchison

wildtype



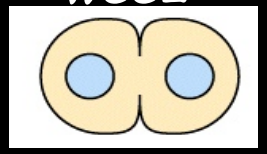
*cdc2ts*
*cdc25ts*
*cdc13ts*



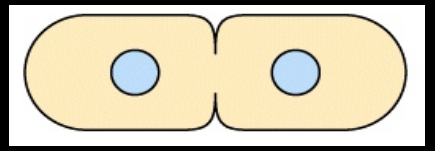


*wee1*$^{ts}$

*wee2*$^{ts}$ = *cdc2*$^{D}$



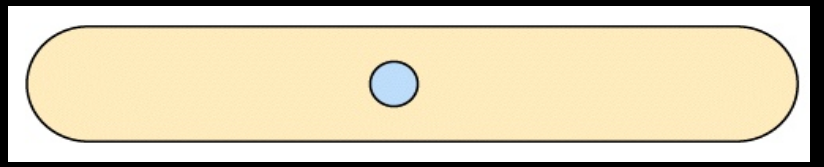
wildtype

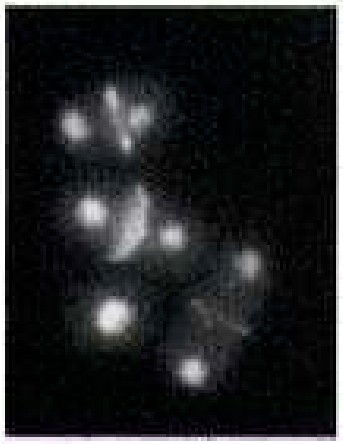


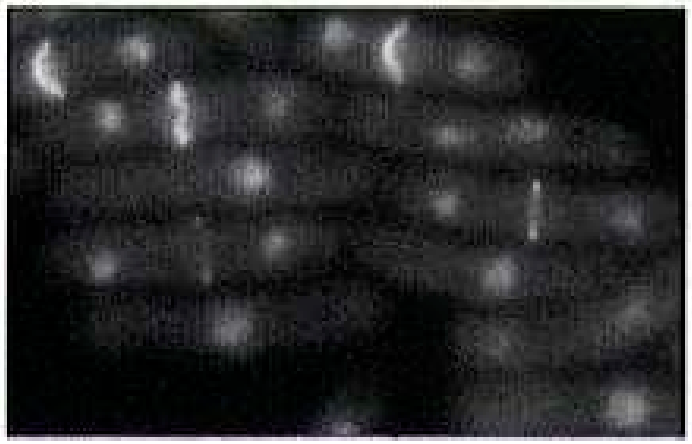
*cdc2*$^{ts}$

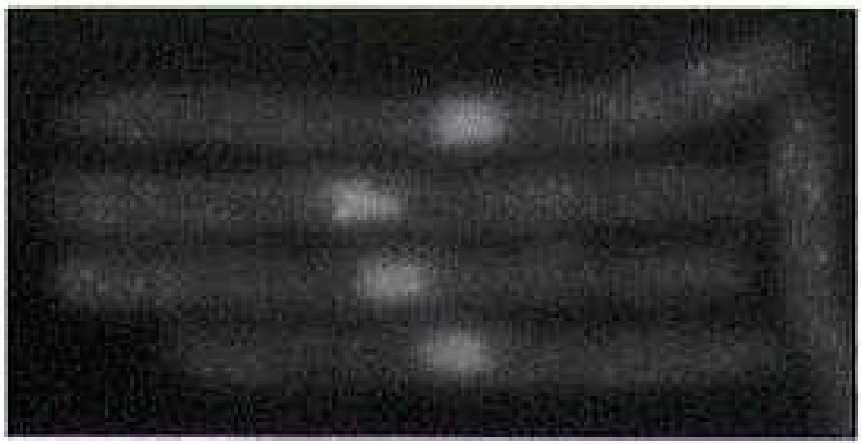
*cdc25*$^{ts}$

*cdc13*$^{ts}$

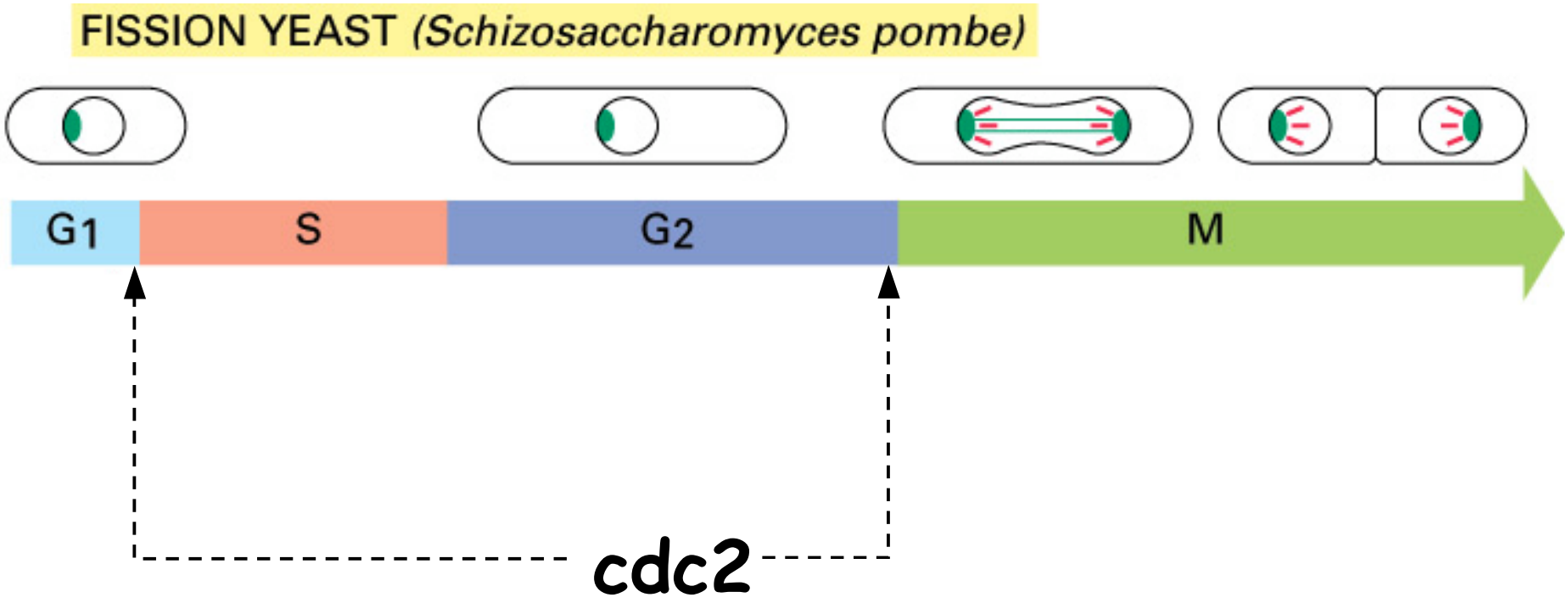






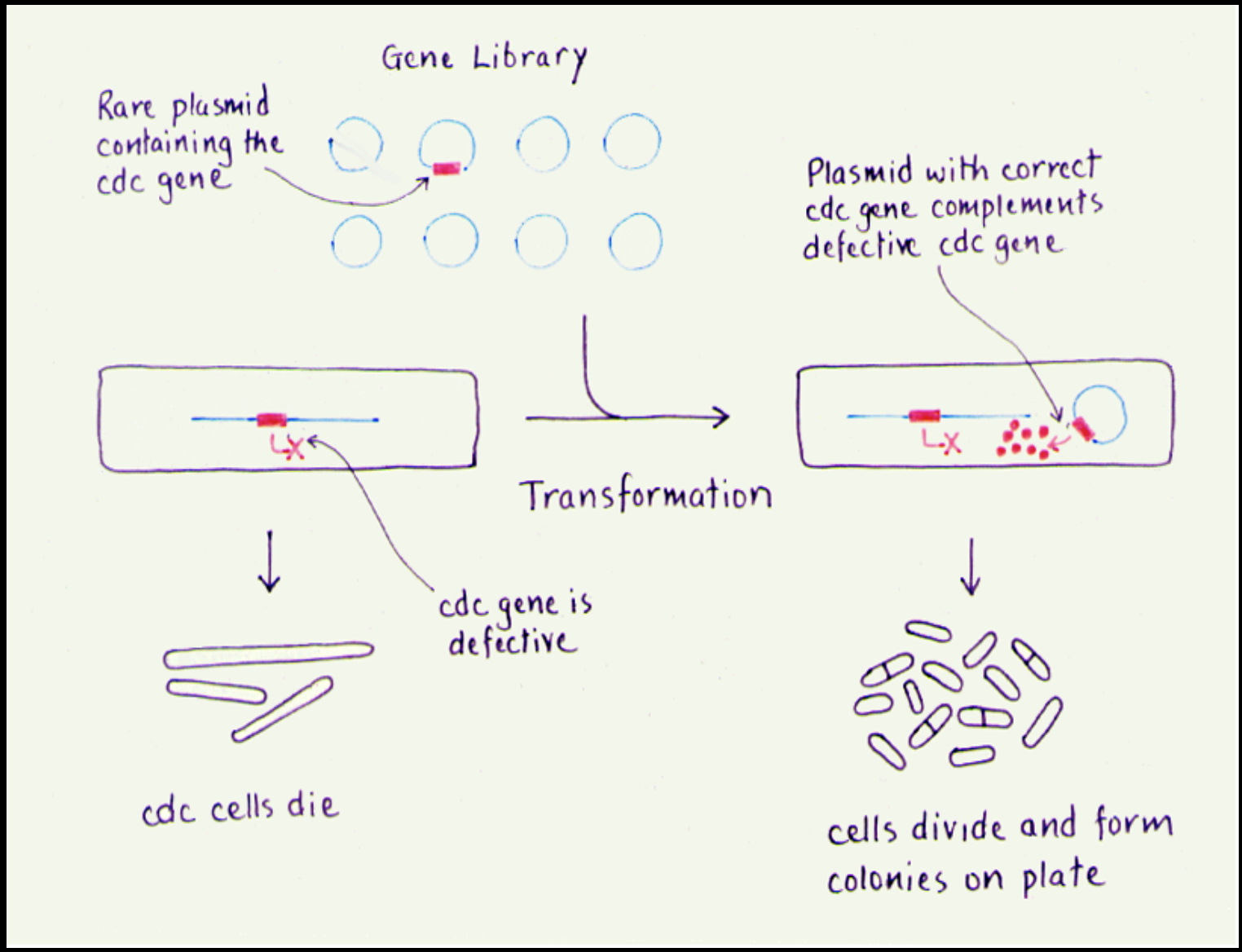


# cdc2 is required at two points during the cell cycle




$cdc28^{S.c.}$ and $cdc2^{S.p.}$ are functional homologs

# Do human cells have the same gene?



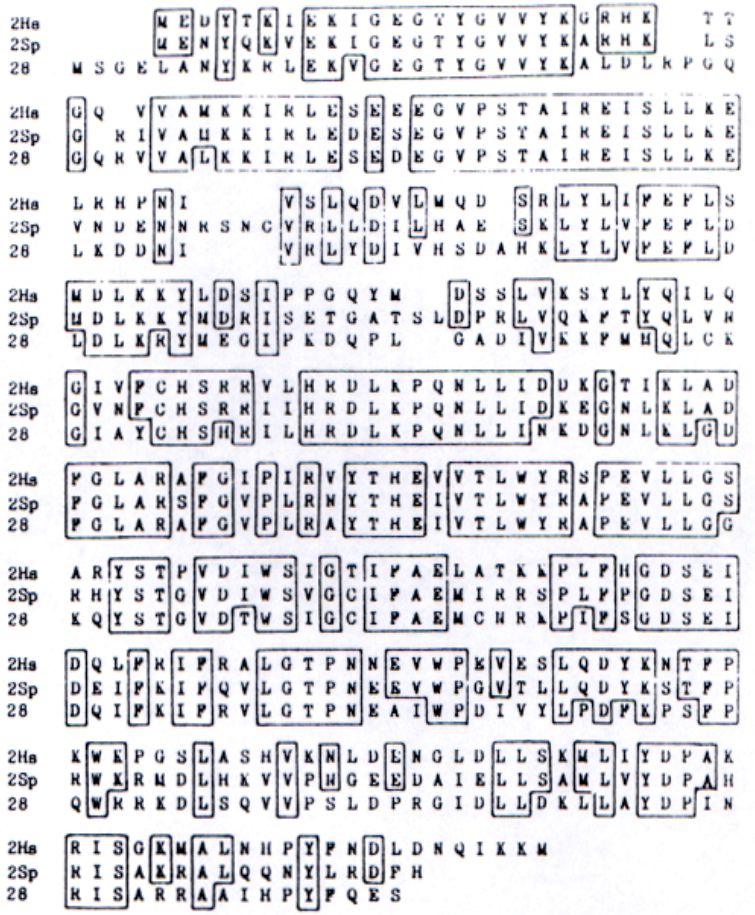
*Nature, Vol, 327, No. 6117, pp. 31-35, May 7, 1987*

# Complementation used to clone a human homologue of the fission yeast cell cycle control gene *cdc2*

**Melanie G. Lee & Paul Nurse**

Cell Cycle Control Laboratory, Imperial Cancer Research Fund, Lincoln's Inn Fields, London, WC2A 3PX, UK

Melanie Lee



*Cell, Vol. 45: 145-153, April 11, 1986*

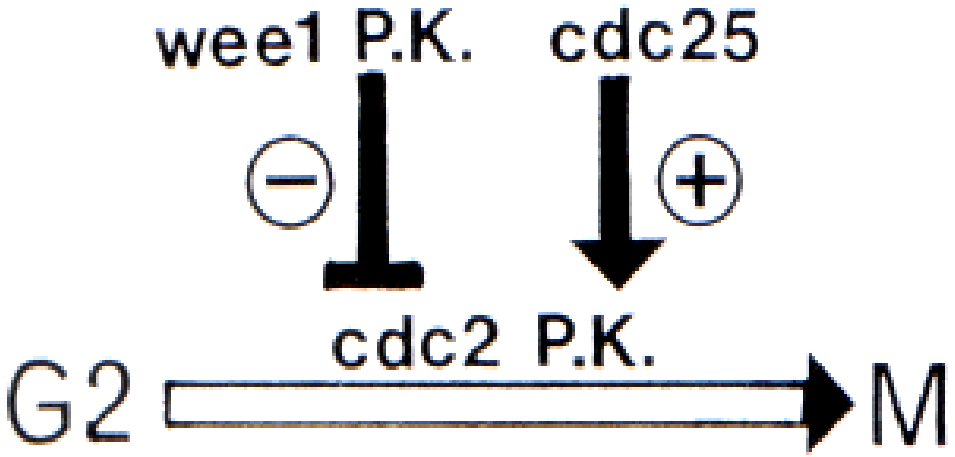
# *cdc25*$^{+}$ Functions as an Inducer in the Mitotic Control of Fission Yeast

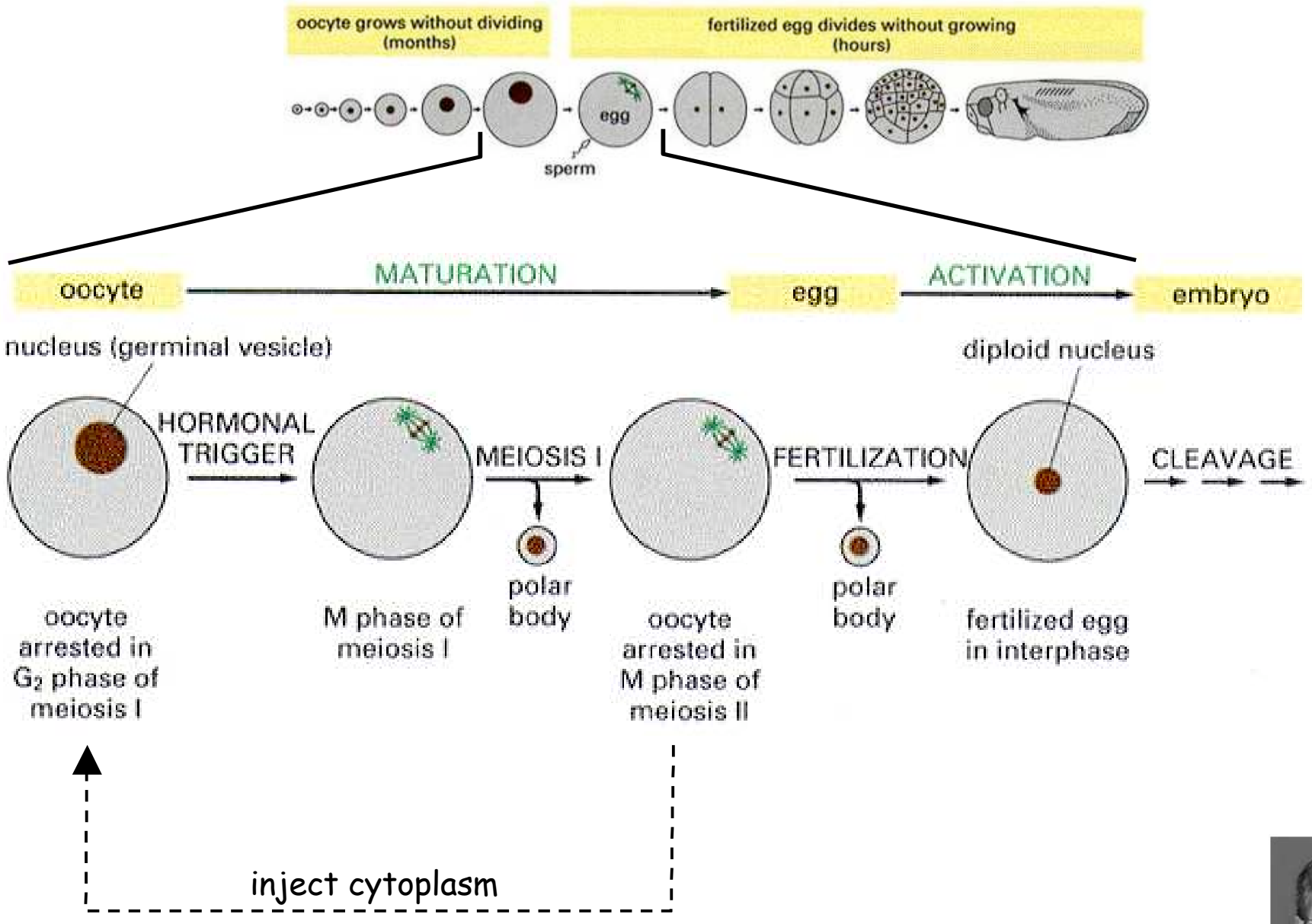
**Paul Russell and Paul Nurse**
Cell Cycle Control Laboratory
Imperial Cancer Research Fund
Lincoln's Inn Fields
London, WC2A 3PX, England

*Cell, Vol. 49: 559-567, May 22, 1987*

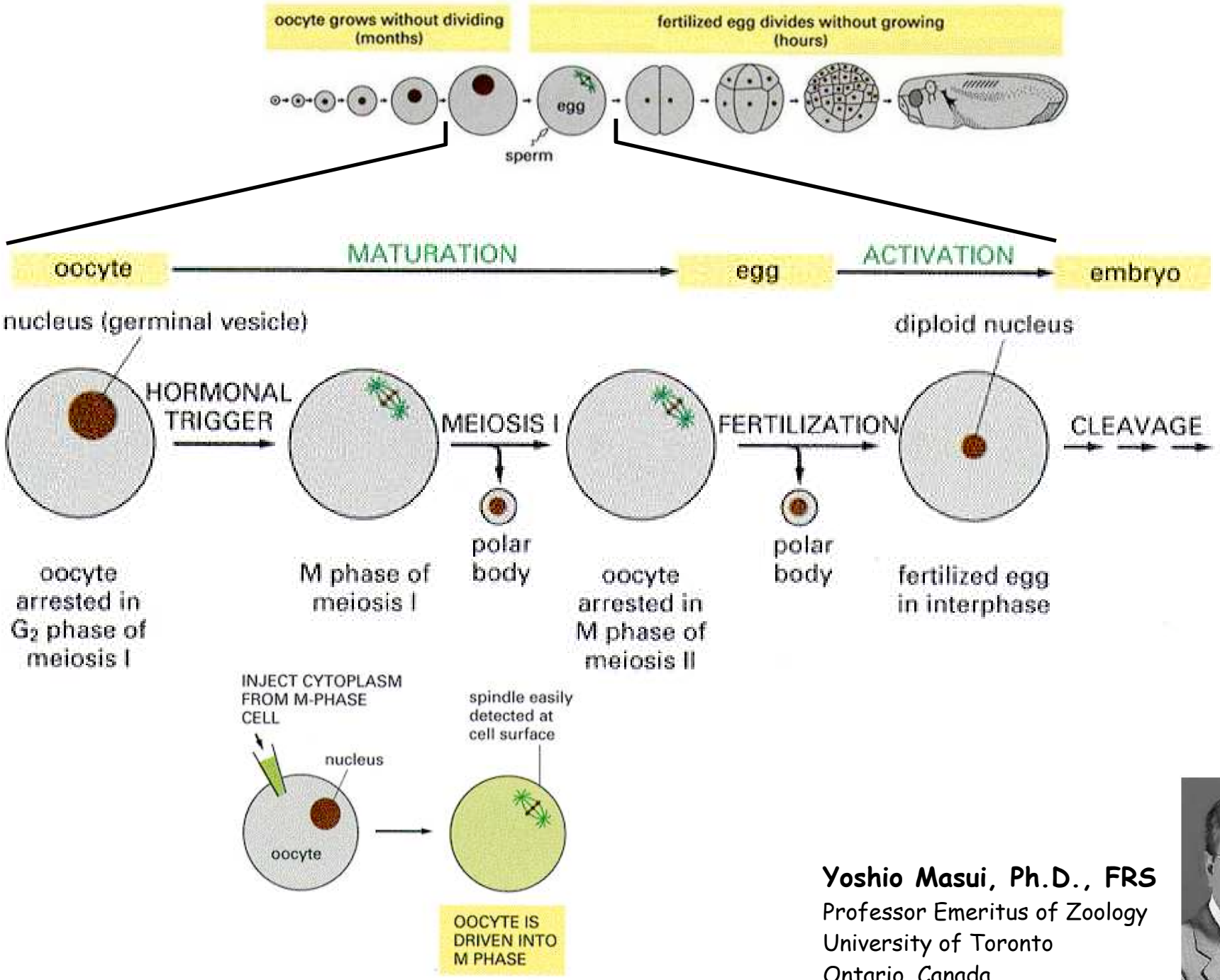
# Negative Regulation of Mitosis by *wee1*$^{+}$, a Gene Encoding a Protein Kinase Homolog

**Paul Russell and Paul Nurse**
Cell Cycle Control Laboratory
Imperial Cancer Research Fund
Lincoln's Inn Fields
London WC2A 3PX, England

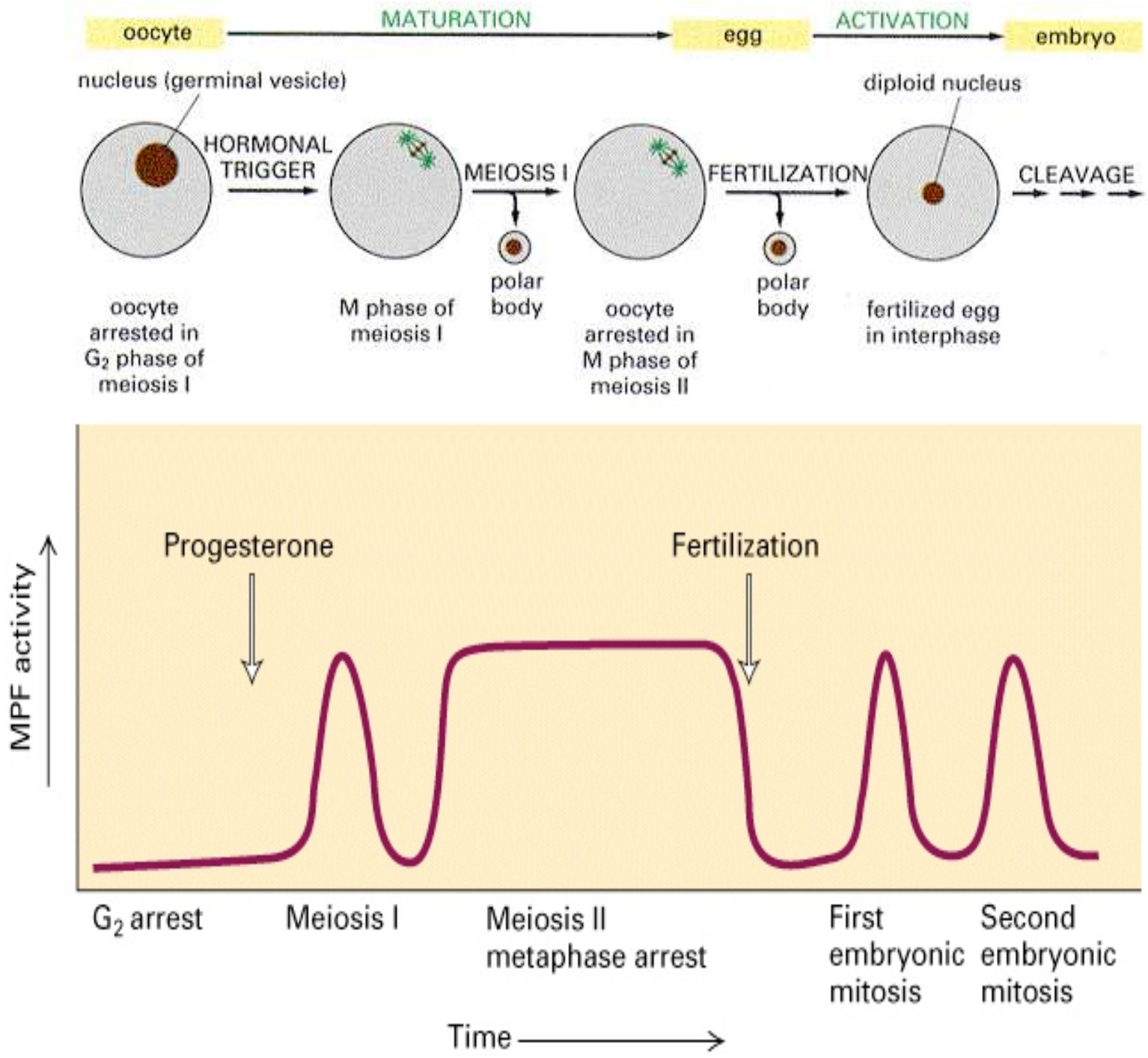


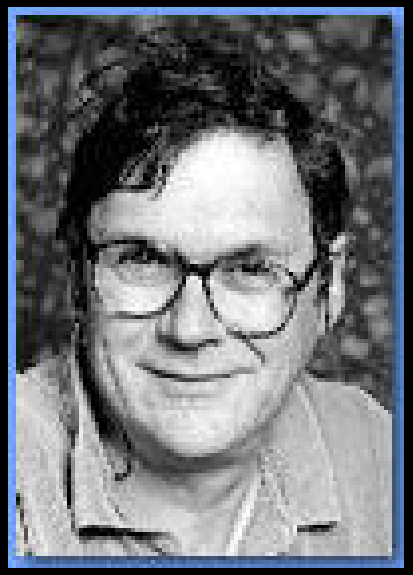



**Yoshio Masui, Ph.D., FRS**
Professor Emeritus of Zoology
University of Toronto
Ontario, Canada



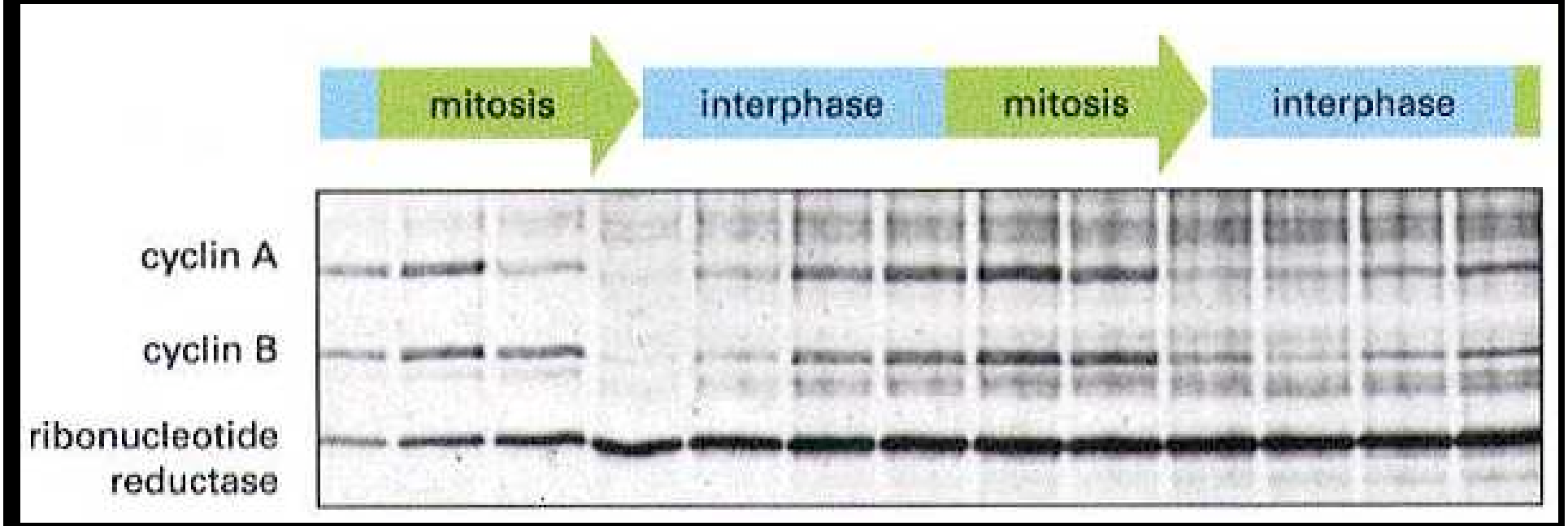

**Yoshio Masui, Ph.D., FRS**
Professor Emeritus of Zoology
University of Toronto
Ontario, Canada


oocyte
MATURATION
egg
ACTIVATION
embryo
nucleus (germinal vesicle)
HORMONAL TRIGGER
MEIOSIS I
FERTILIZATION
diploid nucleus
CLEAVAGE
polar body
polar body
oocyte arrested in G2 phase of meiosis I
M phase of meiosis I
oocyte arrested in M phase of meiosis II
fertilized egg in interphase
MPF activity
Progesterone
Fertilization
G2 arrest
Meiosis I
Meiosis II metaphase arrest
First embryonic mitosis
Second embryonic mitosis
Time



Tim Hunt

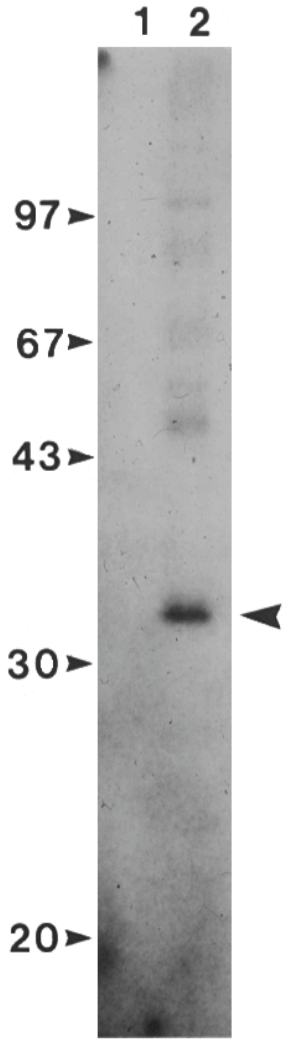
# Periodic proteins (cyclins) during early embryonic development



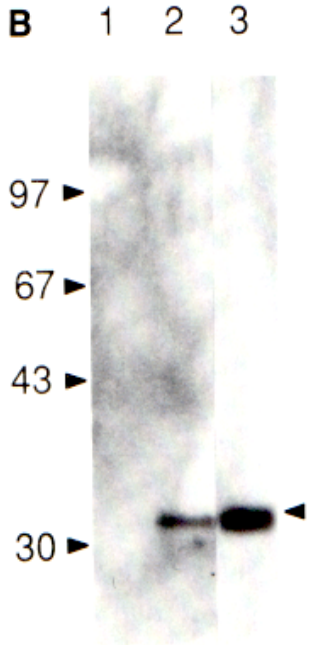
# Purified Maturation-Promoting Factor Contains the Product of a Xenopus Homolog of the Fission Yeast Cell Cycle Control Gene *cdc2*+

**Jean Gautier,* Chris Norbury,† Manfred Lohka,*‡ Paul Nurse,† and James Maller***
*Department of Pharmacology
University of Colorado School of Medicine
Denver, Colorado 80262
†ICRF Cell Cycle Control Laboratory
Microbiology Unit
Department of Biochemistry
University of Oxford
Oxford OX13QU, England

Jim Maller



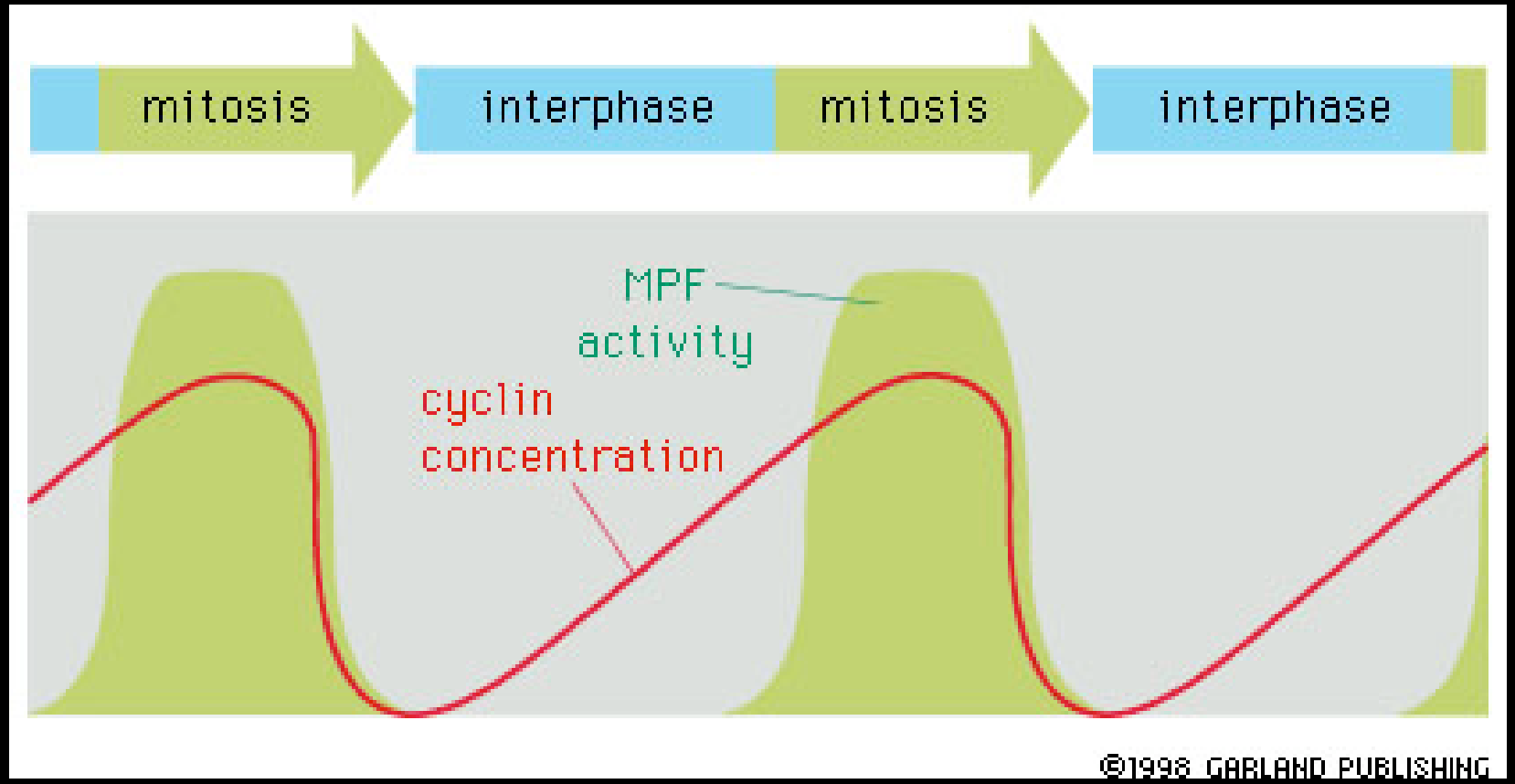

IP




Western

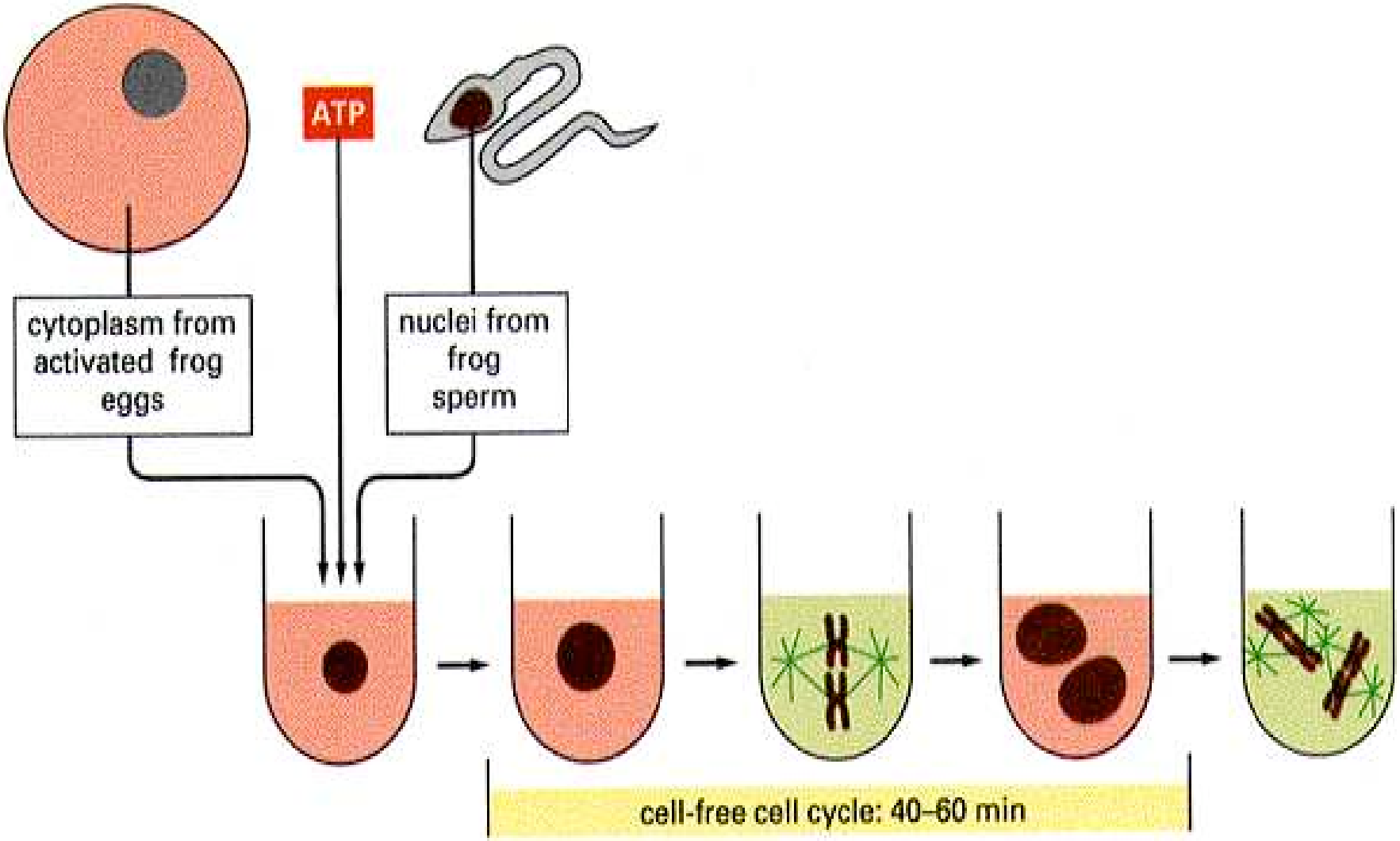
# MPF is a cyclin-dependent protein-kinase

# Cyclin and MPF levels during early mitotic cycles

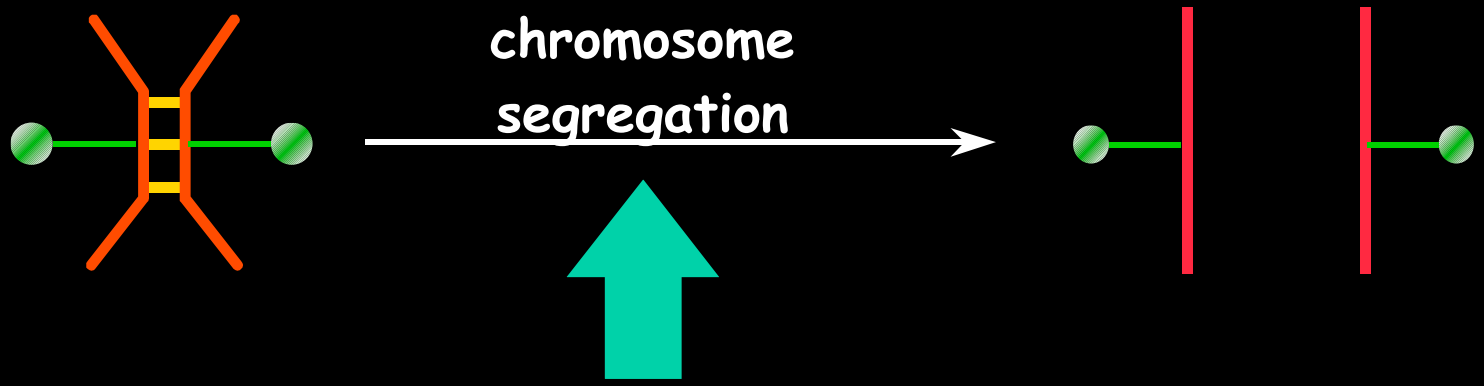


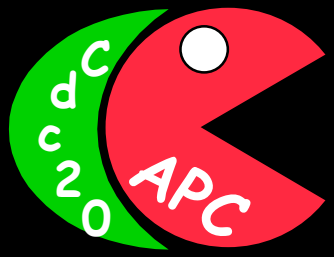

Questions: What causes the fast disappearance of cyclins?
What is the reason of the delay between cyclin and MPF?

# Cycling cell free extract



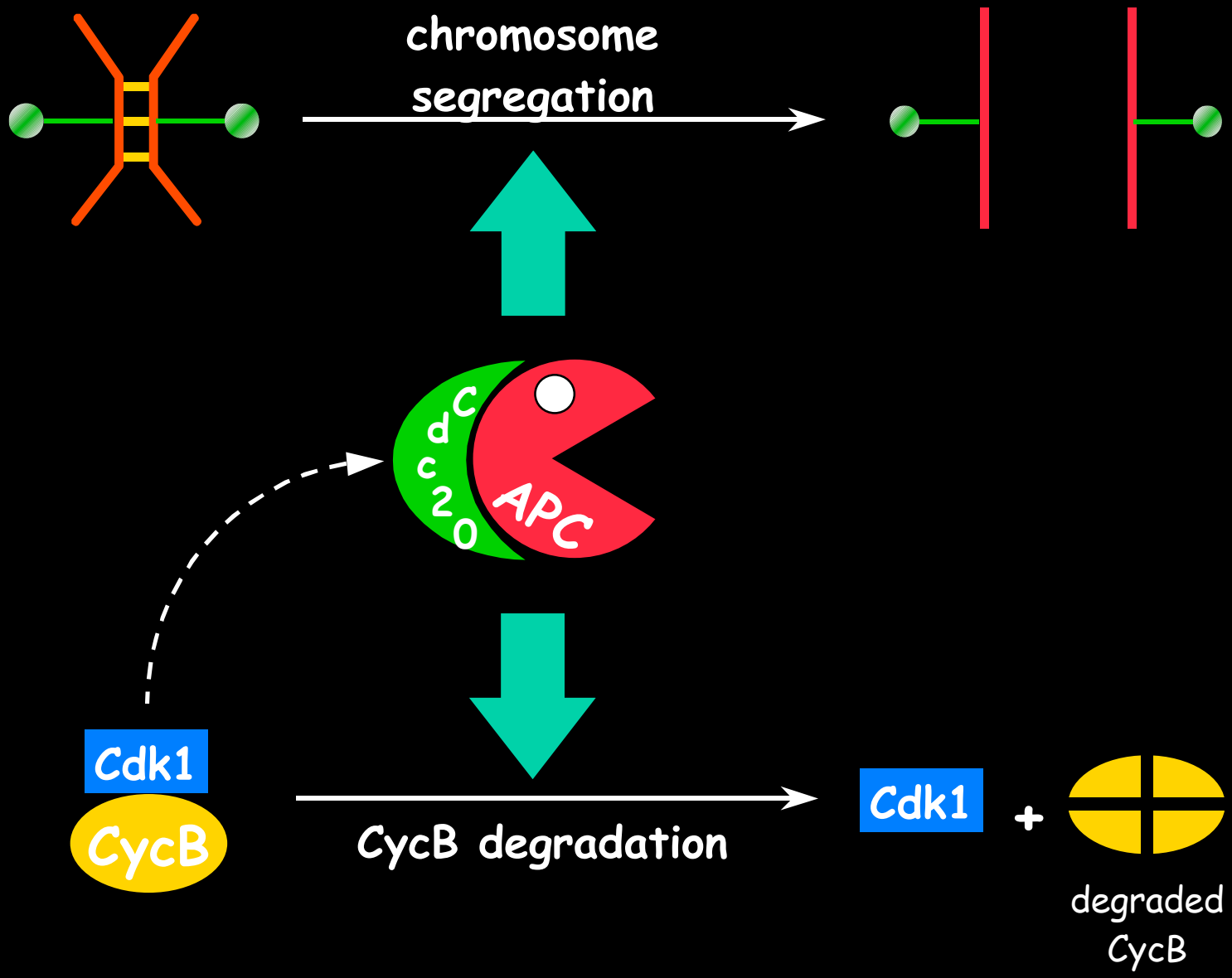
# Anaphase Promoting Complex or Cyclosome



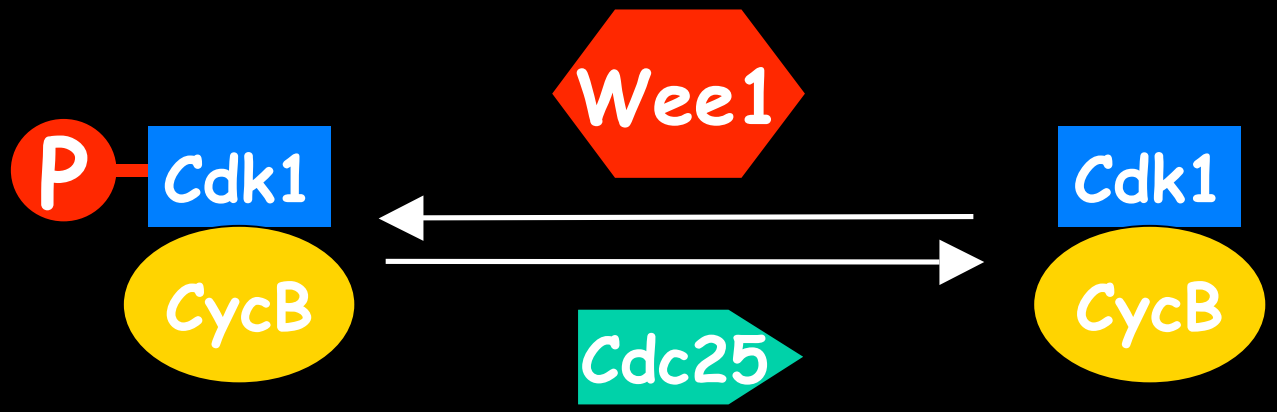




Kim Nasmyth

# Anaphase Promoting Complex or Cyclosome



# The G2/M transition is regulated by post-translational modification



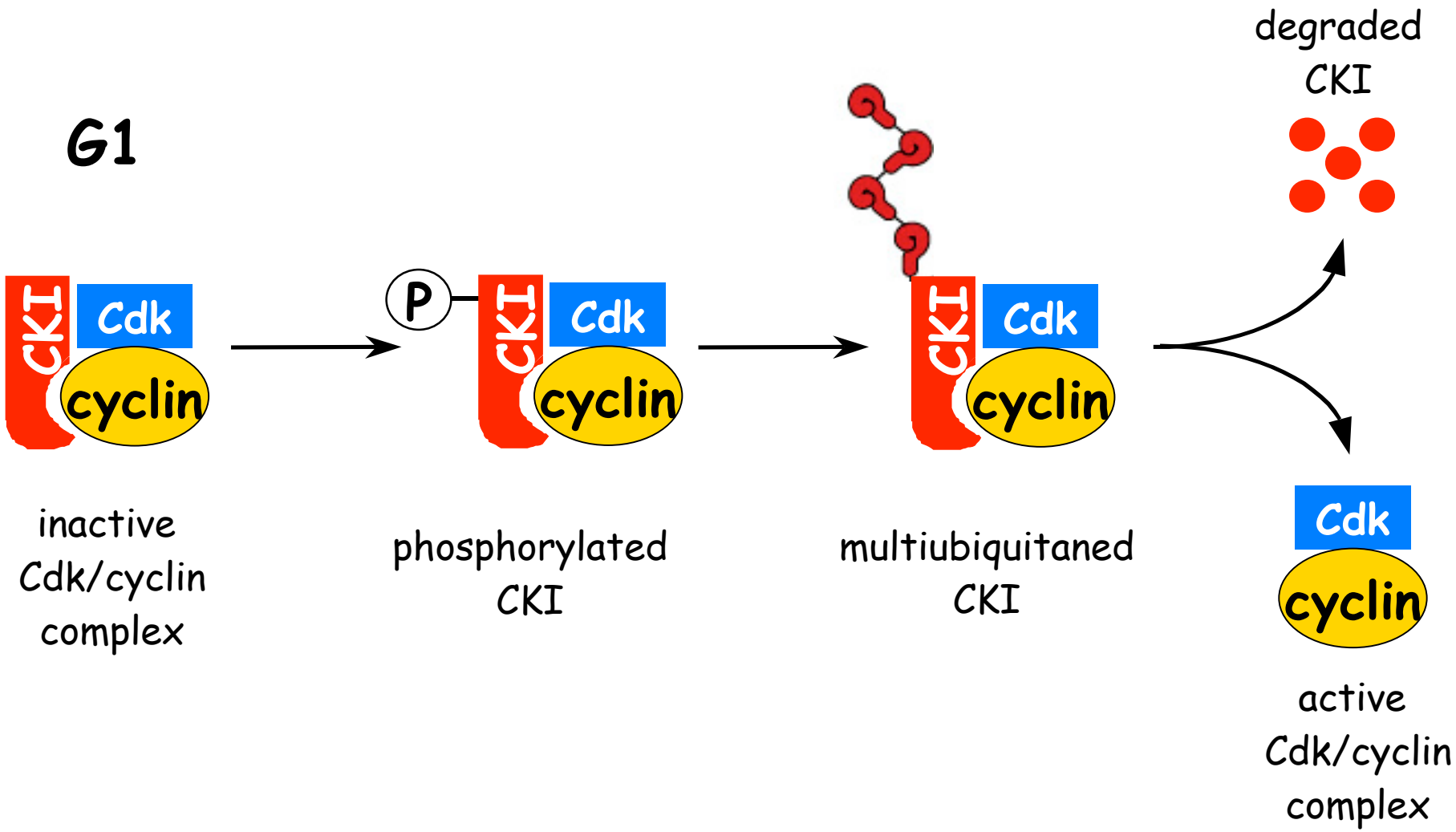

inactive (preMPF)

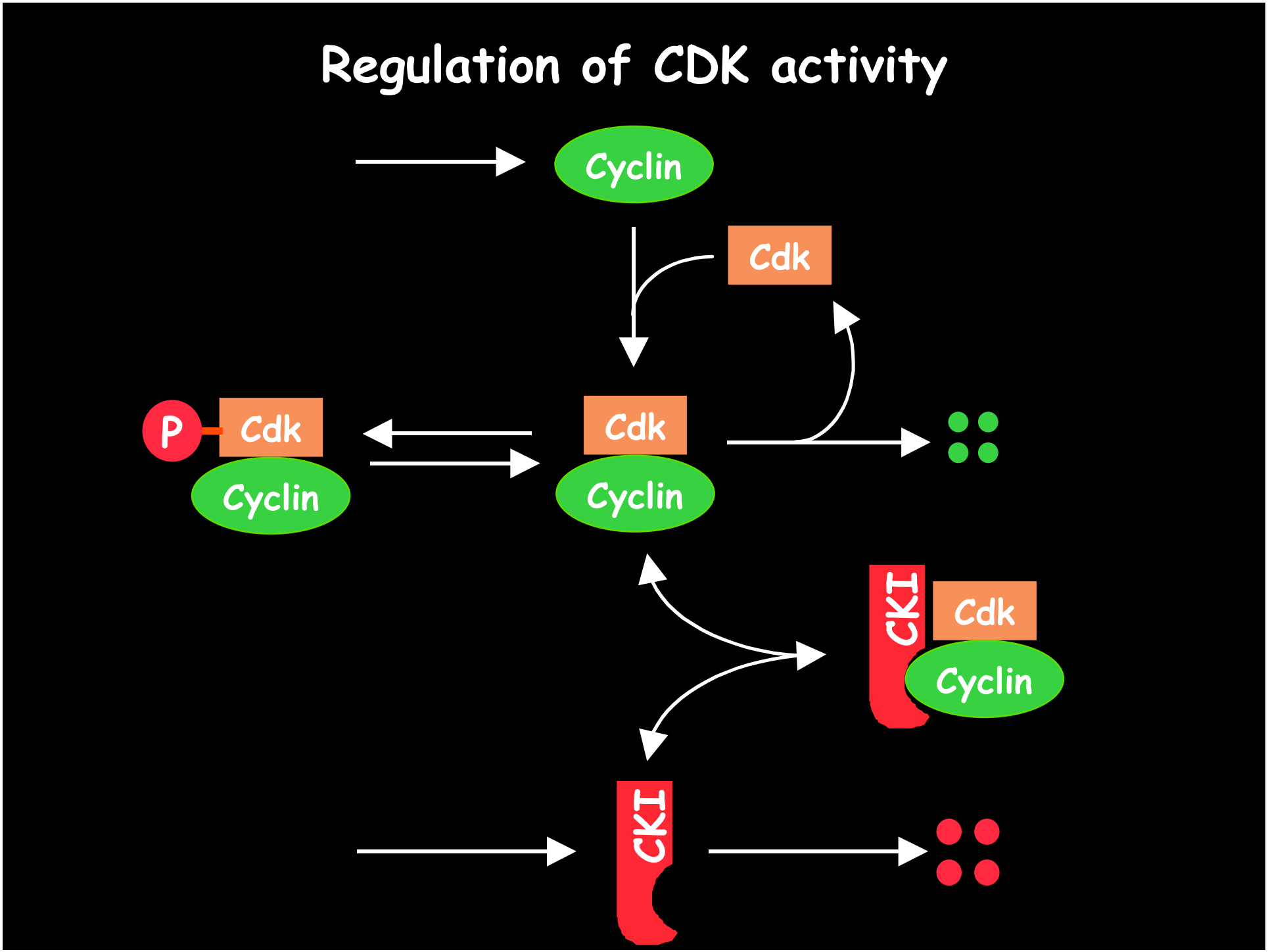
active (MPF)

Wee1 is a tyrosine-kinase

Cdc25 is a tyrosine-phopshatase

# Start of DNA replication is also controlled by proteolysis




Regulation of CDK activity
Cyclin
Cdk
P
Cdk
Cyclin
Cdk
Cyclin
CKI
Cdk
Cyclin
CKI