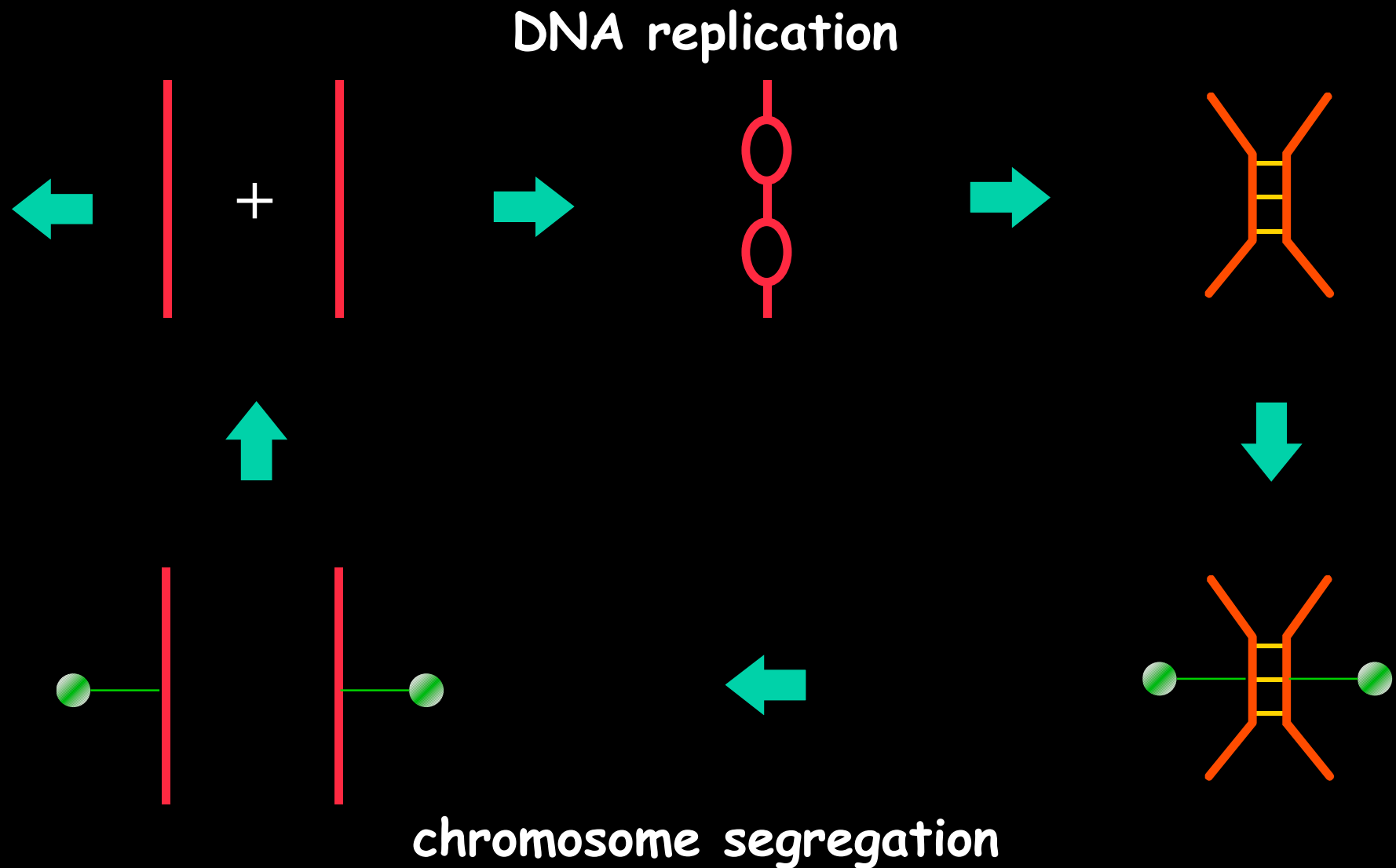
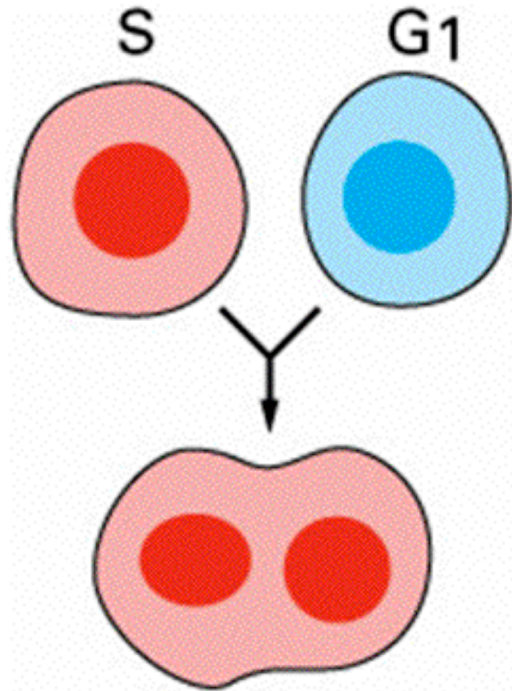


Alternation of DNA replication and chromosome segregation



The logic of the cell cycle:

cell fusion experiments (Rao & Johnson)

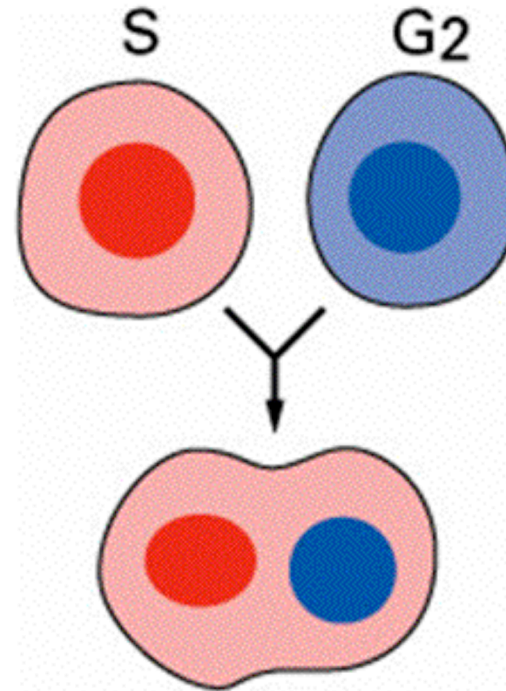


G1-phase nucleus immediately enters S phase; S-phase nucleus continues DNA replication

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

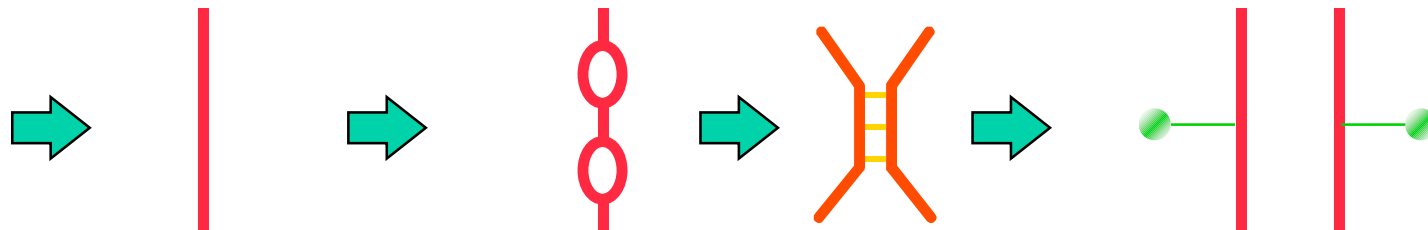
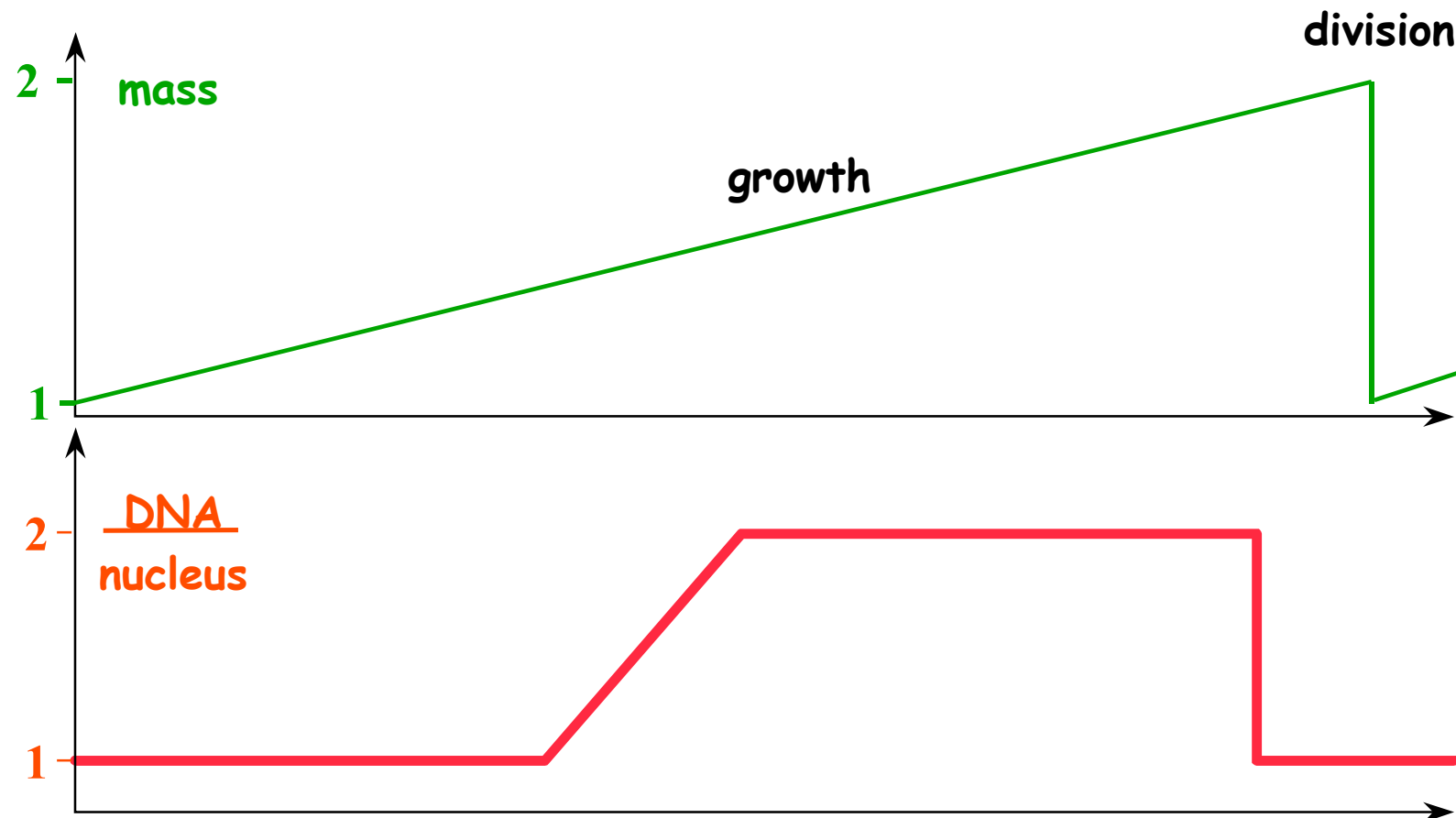
The logic of the cell cycle: cell fusion experiments (Rao & Johnson)

block of re-replication

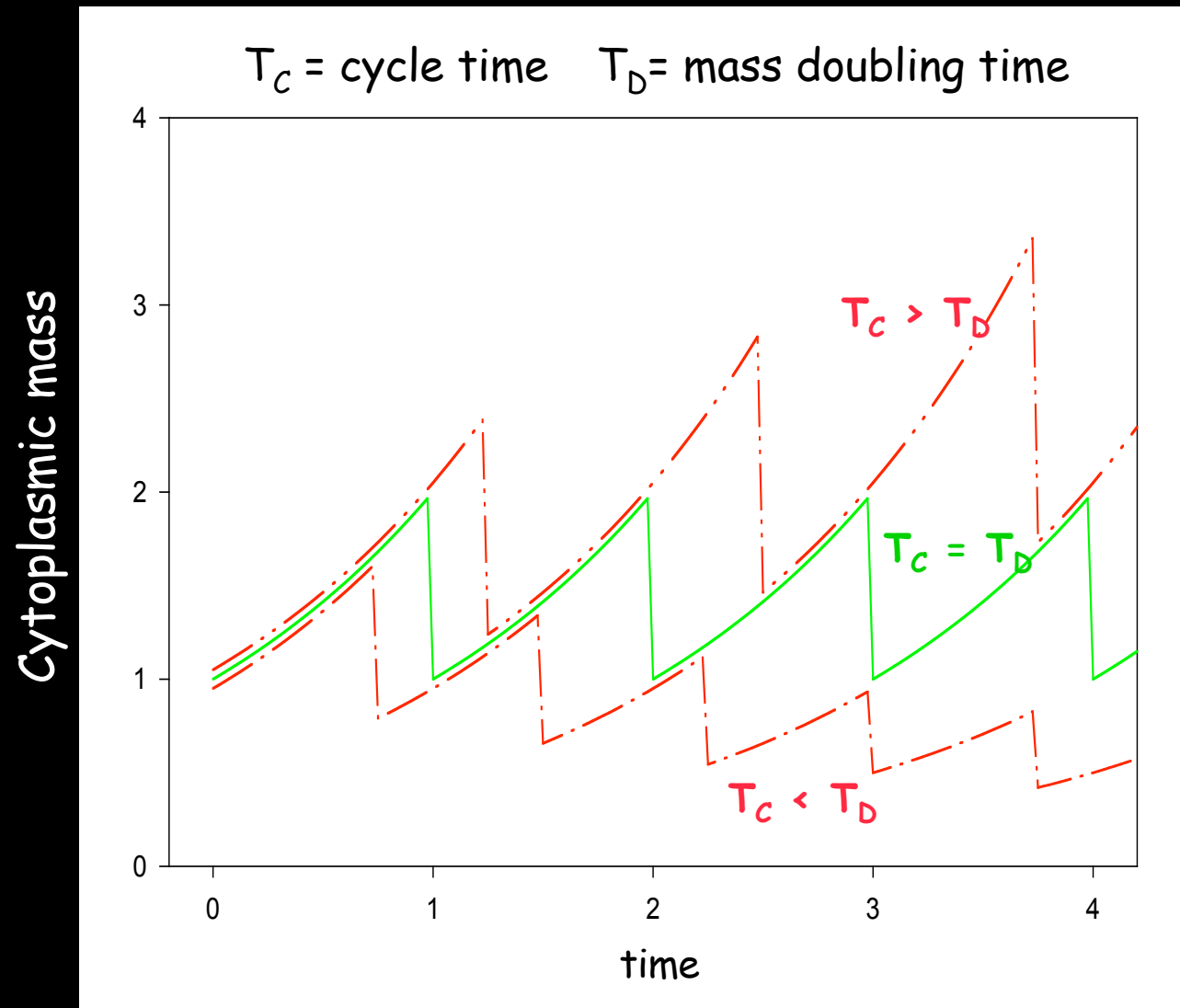


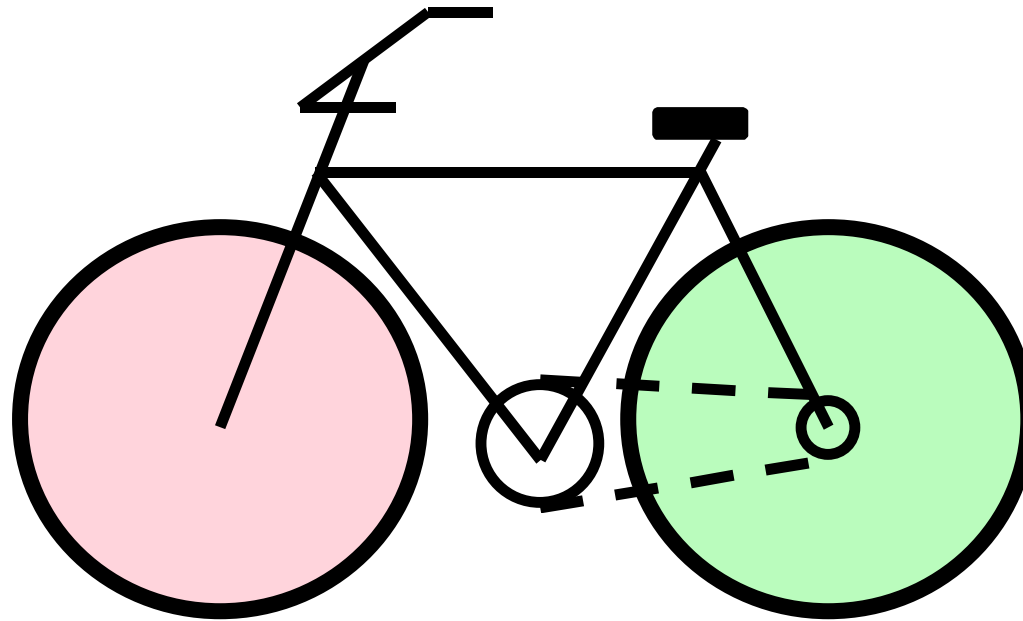
G2-phase nucleus
stays in G2;
S-phase nucleus
continues DNA
replication

The Cell Division Cycle



Balanced growth and division



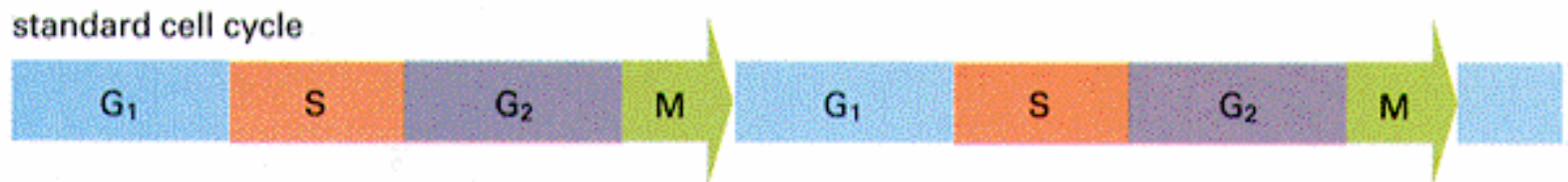


Chromosome cycle

- DNA replication
 - mitosis
- (precise replication
and segregation)

Growth cycle

- cytoplasmic growth
 - cell division
- (approx. doubling
and halving)



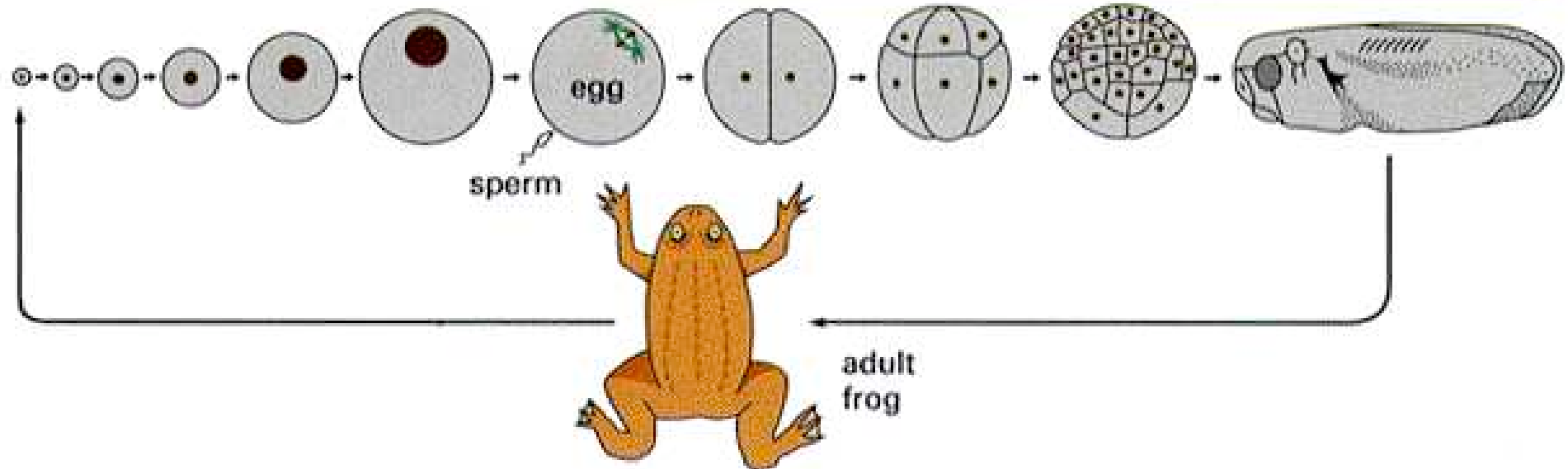
Dissociation of growth and chromosome cycle

Oogenesis

Embryogenesis

oocyte grows without dividing
(months)

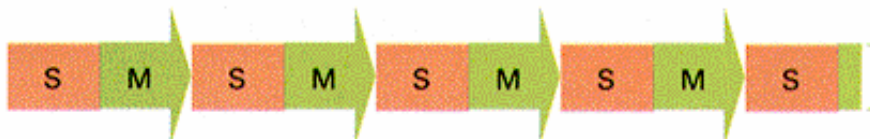
fertilized egg divides without growing
(hours)



standard cell cycle



early embryonic cell cycle





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

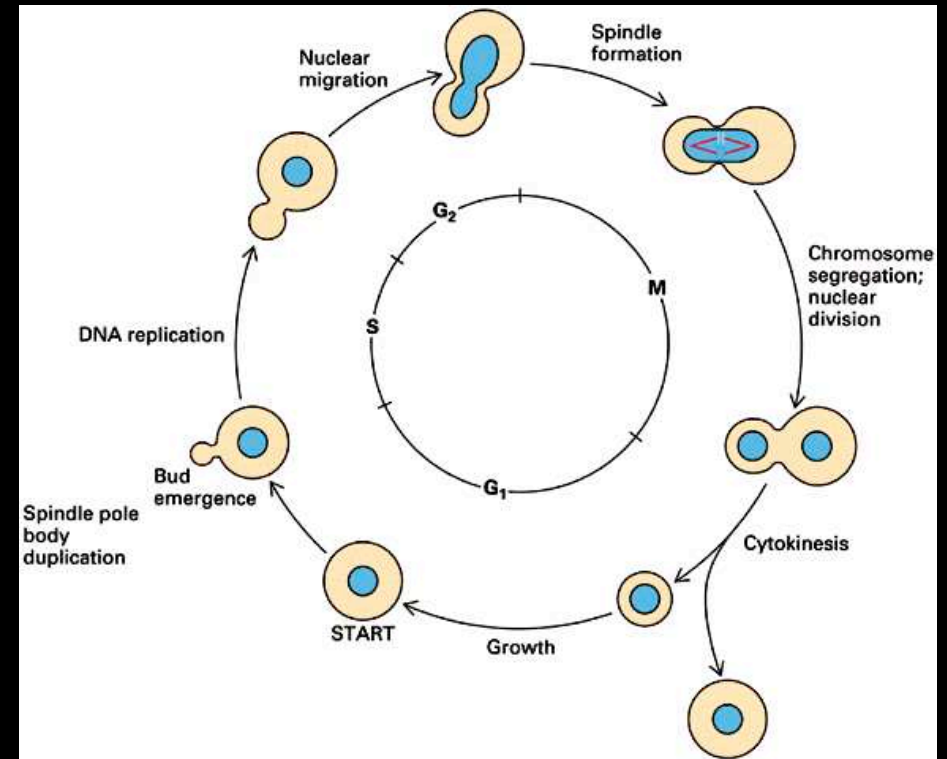
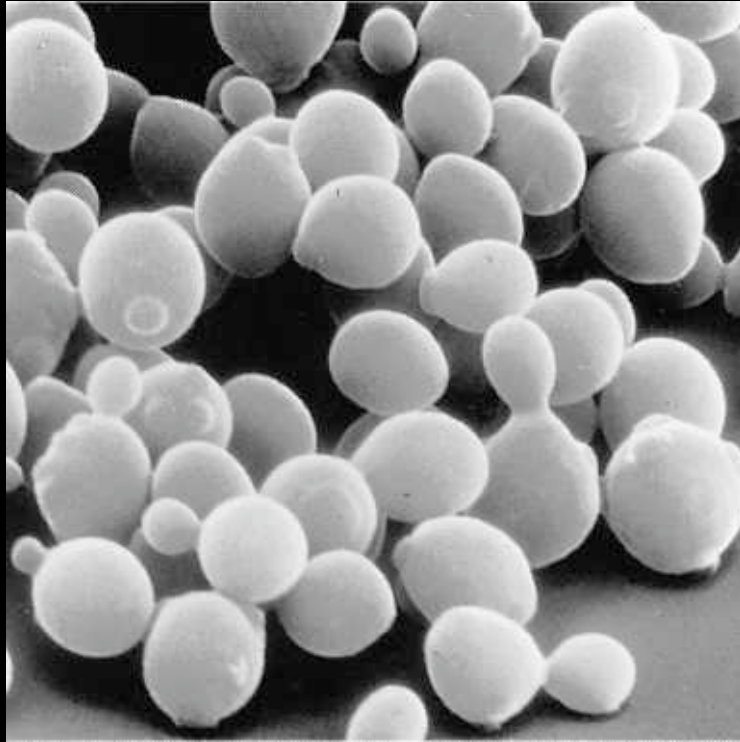


Great Britain

Imperial Cancer
Research Fund
London, Great
Britain

1949 -

Saccharomyces cerevisiae

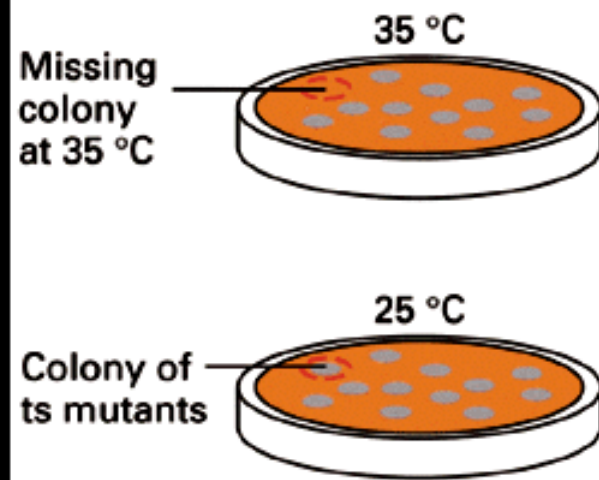


Lee Hartwell

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

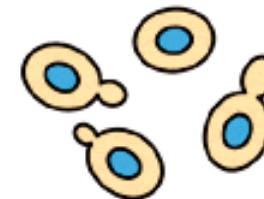
(a) Identification of *cdc* mutants

Incubate replica plates of mutagenized cells at 25 °C and 35 °C

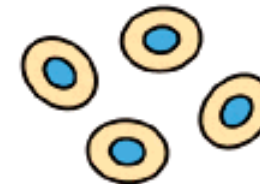


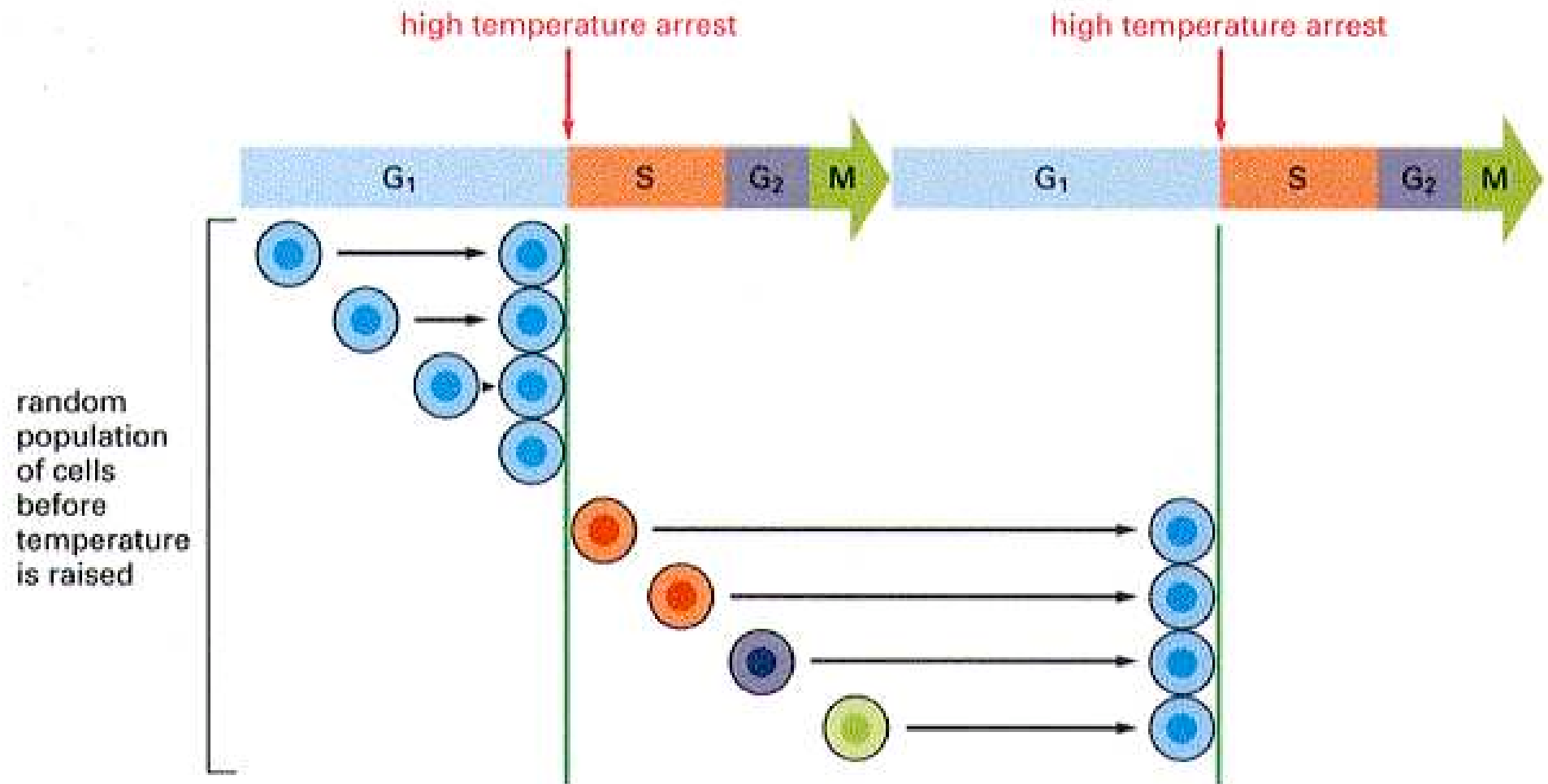
Replate ts mutants; incubate at 35 °C until they stop replicating; observe in light microscope

Non-*cdc* mutant cells

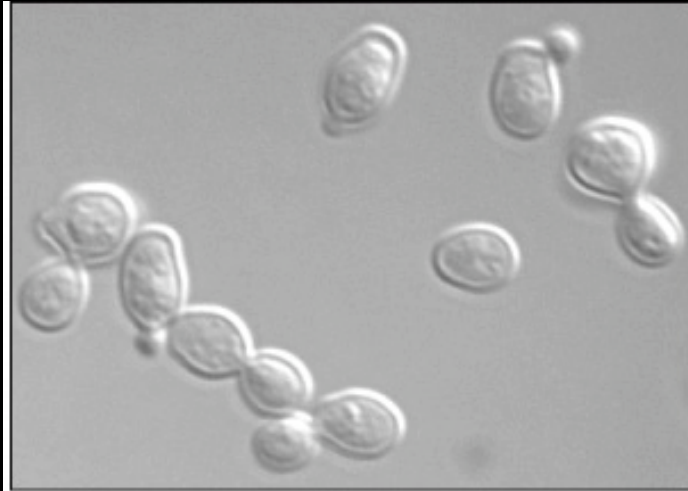


cdc28^{ts} cells

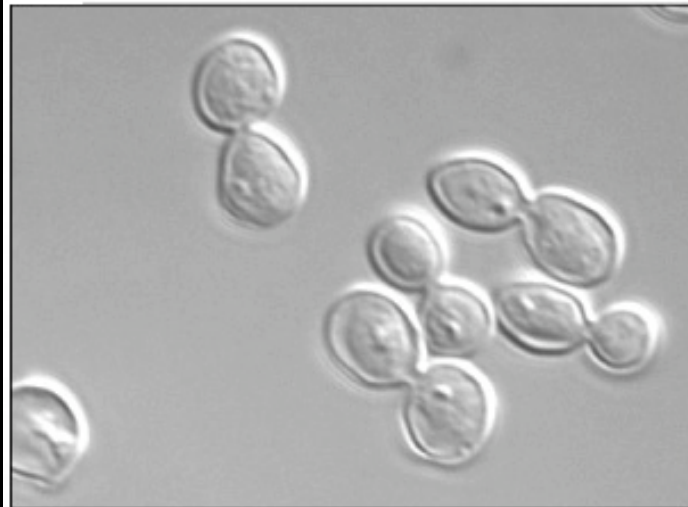




Phenotype of *cdc* mutants



asynchronous
culture



cdc mutant
with problem of
mitotic exit

20 μ m

Cdc28 is responsible for the first genetically controlled event

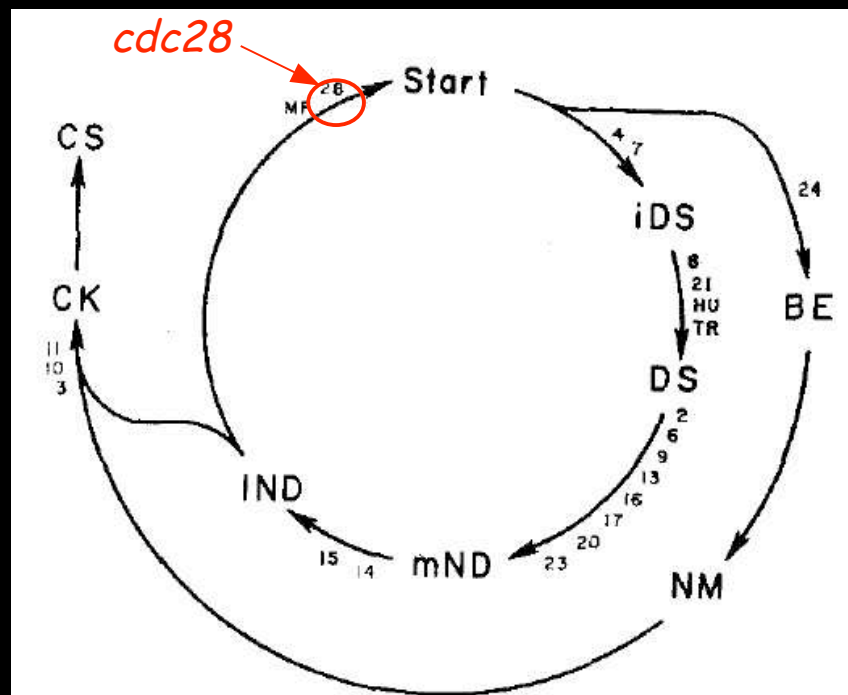
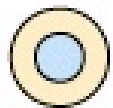
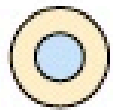
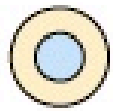


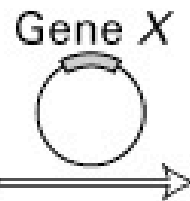
Fig. 3. The circuitry of the yeast cell cycle. Events connected by an arrow are proposed to be related such that the distal event is dependent for its occurrence upon the prior completion of the proximal event. The abbreviations are the same as in Fig. 1. Numbers refer to *cdc* genes that are required 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, α factor.

Cloning of *cdc^{ts}* genes

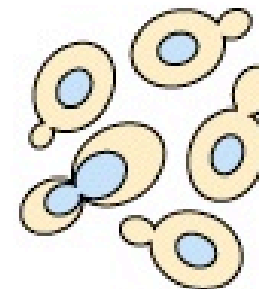
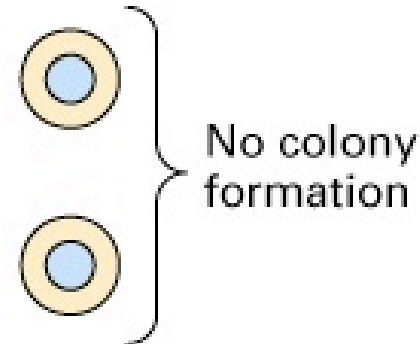
cdc28^{ts} cells
grown at 25 °C



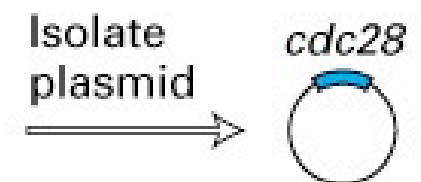
Transform with plasmid
library of wild-type
S. cerevisiae DNA



Transformed
cdc28^{ts} cells
grown at 35 °C

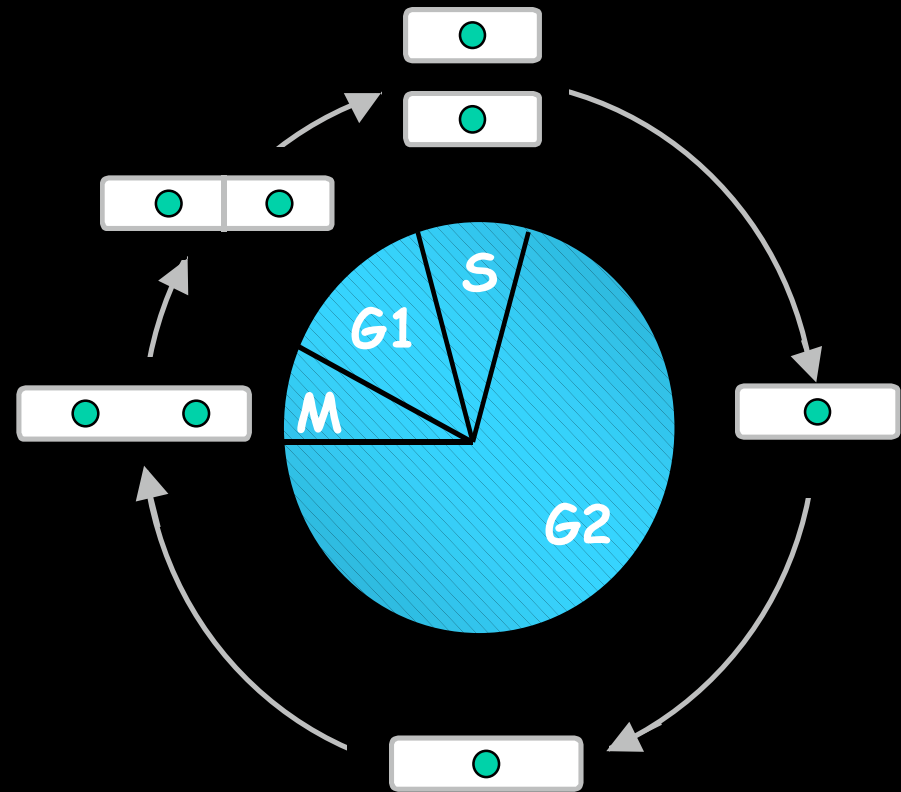
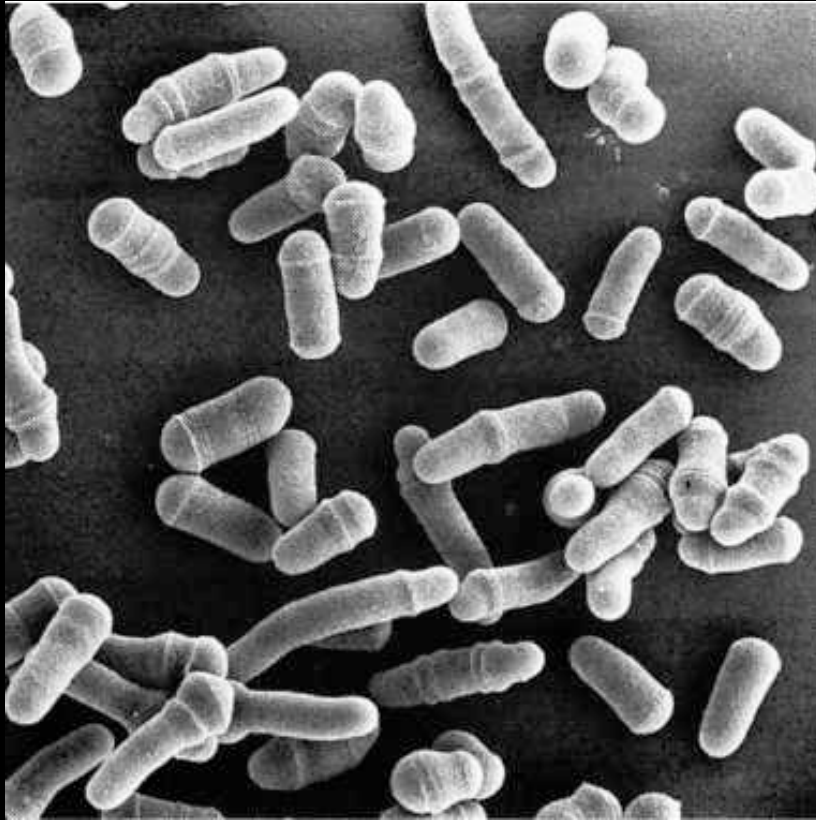


Cells in colony at
various cell-cycle stages



Cdc28 is a protein-kinase

Schizosaccharomyces pombe

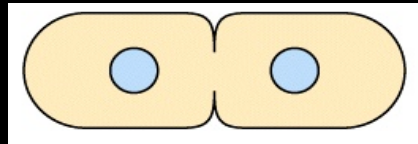


Sir Paul Nurse

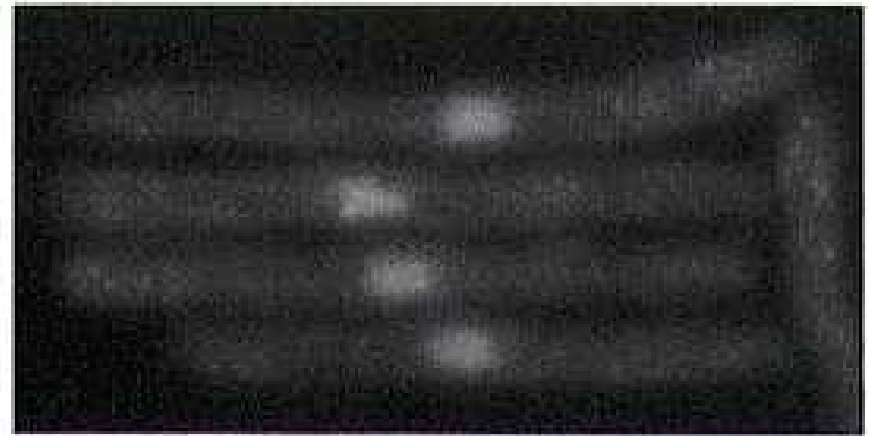
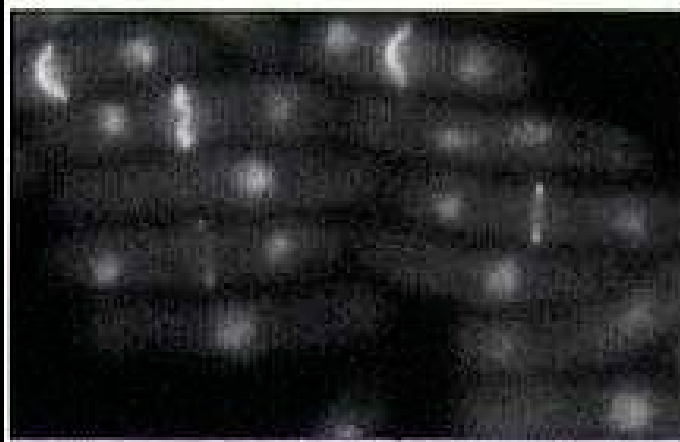
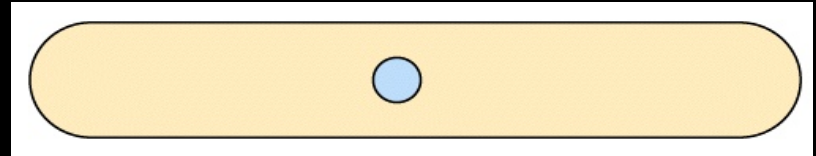


Murdoch Mitchison

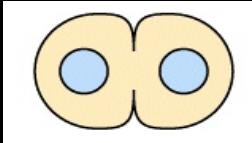
wildtype



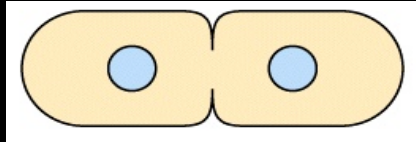
cdc2^{ts}
cdc25^{ts}
cdc13^{ts}



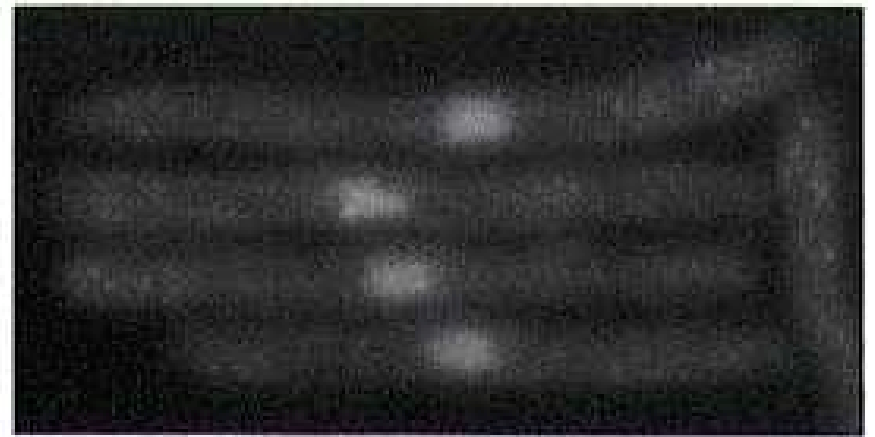
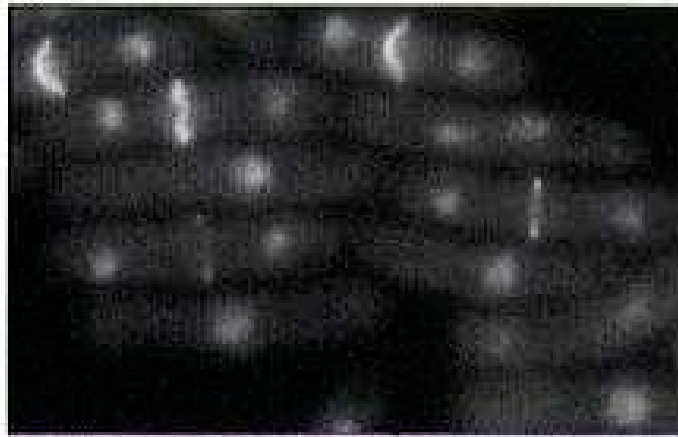
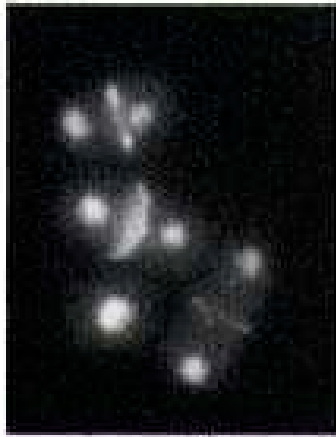
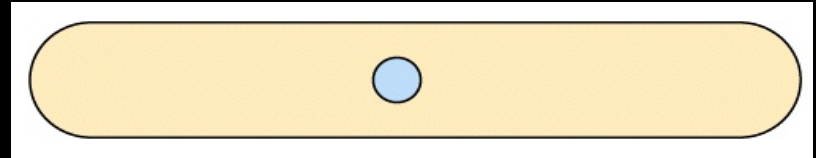
wee1^{ts}
wee2^{ts} = cdc2^D



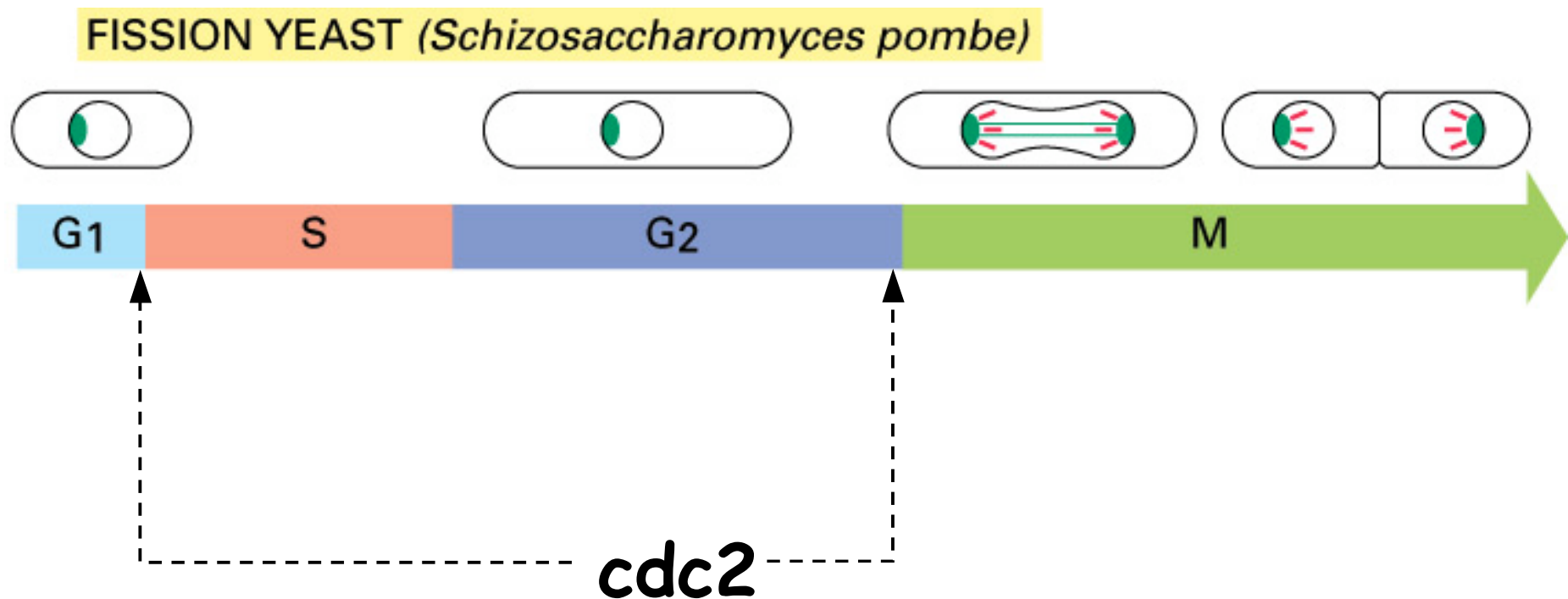
wildtype



cdc2^{ts}
cdc25^{ts}
cdc13^{ts}

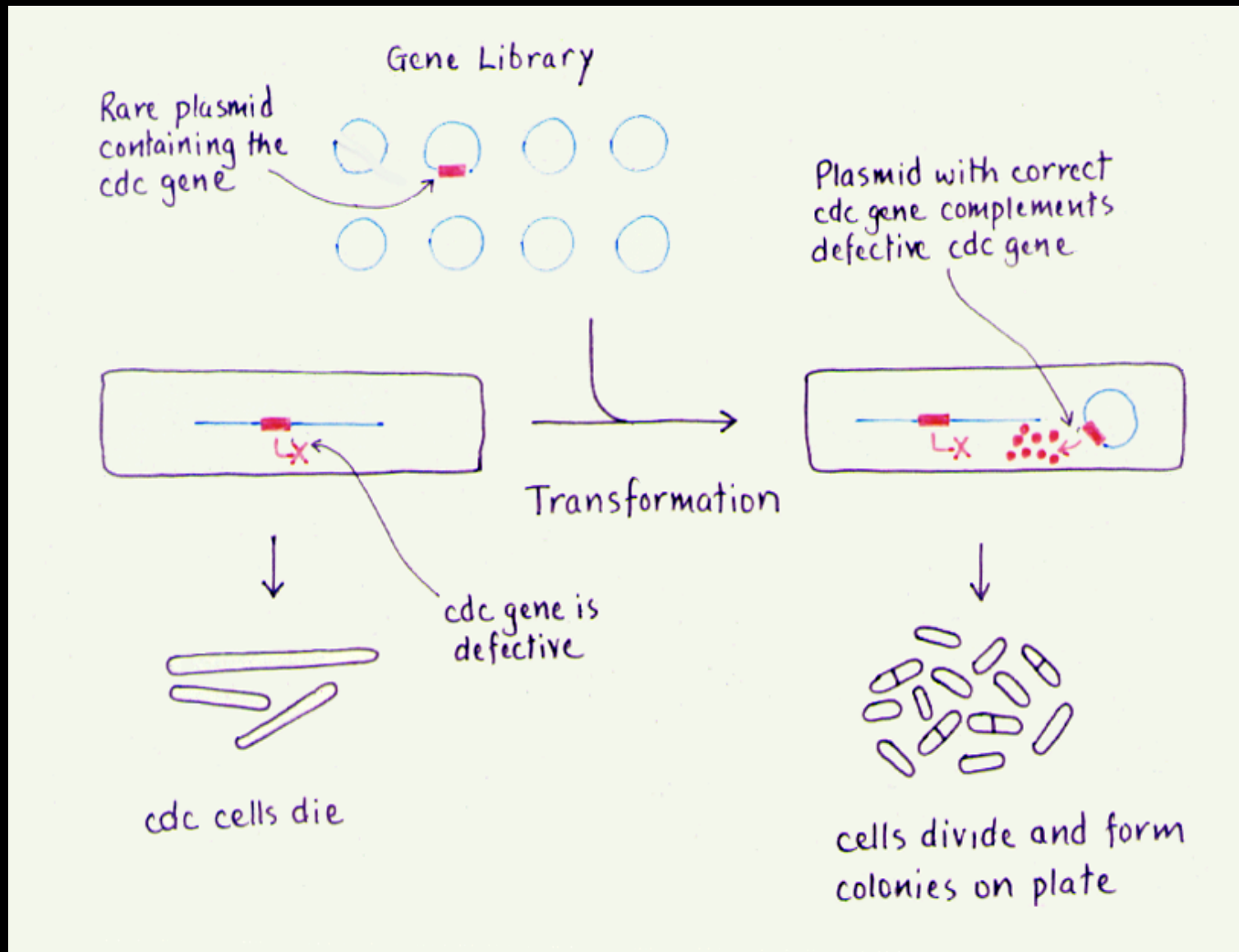


***cdc2* is required at two points
during the cell cycle**



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

```
2Ha  M E D Y T K I E K I G E G T Y G V V Y K G R H K T T
2Sp  M E N Y Q K V E K I G E G T Y G V V Y K A R H K L S
28   M S G E L A N Y K K L E K V G E G T Y G V V Y K A L D L K P G Q

2Ha  G Q V V A M K K I R L E S E E G V P S T A I R E I S L L K E
2Sp  G R I V A H K K I R L E D E S E G V P S T A I R E I S L L K E
28   G Q R V V A L K K I R L E S E D E G V P S T A I R E I S L L K E

2Ha  L R H P N I V S L Q D V L M Q D S R L Y L I F E F L S
2Sp  V N D E N N K S N G V R L L D I L H A E S K L Y L V F E P L D
28   L K D D N I V R L Y D I V H S D A H K L Y L V F E F L D

2Ha  M D L K K Y L D S I P P G Q Y M D S S L V K S Y L Y Q I L Q
2Sp  M D L K K Y M D R I S E T G A T S L D P R L V Q A P T Y Q L V N
28   L D L K R Y M E G I P E D Q P L G A D I V K K P M H Q L C K

2Ha  G I V F C H S R R V L H R D L A P Q N L L I D K G T I K L A D
2Sp  G V N F C H S R R I I H R D L K P Q N L L I D K E G N L K L A D
28   G I A Y C H S H R I L H R D L K P Q N L L I N K D G N L K L G D

2Ha  F G L A R A F G I P I R V Y T H E V V T L W Y R S P E V L L G S
2Sp  F G L A R S F G V P L R N Y T H E I V T L W Y R A P E V L L G S
28   F G L A R A F G V P L R A Y T H E I V T L W Y R A P E V L L G G

2Ha  A R Y S T P V D I W S I G T I P A E L A T K A P L P H G D S E I
2Sp  R H Y S T G V D I W S V G C I P A E M I R R S P L P P G D S E I
28   K Q Y S T G V D T W S I G C I P A E M C N R A P I F S G D S E I

2Ha  D Q L P R I F R A L G T P N N E V W P K V E S L Q D Y K N T P P
2Sp  D E I P K I F Q V L G T P N E E V W P G V T L L Q D Y K S T P P
28   D Q I P K I F R V L G T P N E A I W P D I V Y L P D F K P S P P

2Ha  K W K P G S L A S H V K N L D E N G L D L L S K M L I Y D P A K
2Sp  R W K R M D L H K V V P H G E E D A I E L L S A M L V Y D P A H
28   Q W K R K D L S Q V V P S L D P R G I D L L D K L L A Y D P I N

2Ha  R I S G K M A L N H P Y F N D L D N Q I K K M
2Sp  R I S A K R A L Q Q N Y L R D P H
28   R I S A R R A A I H P Y F Q E S
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Cell, Vol. 45: 145-153, April 11, 1986

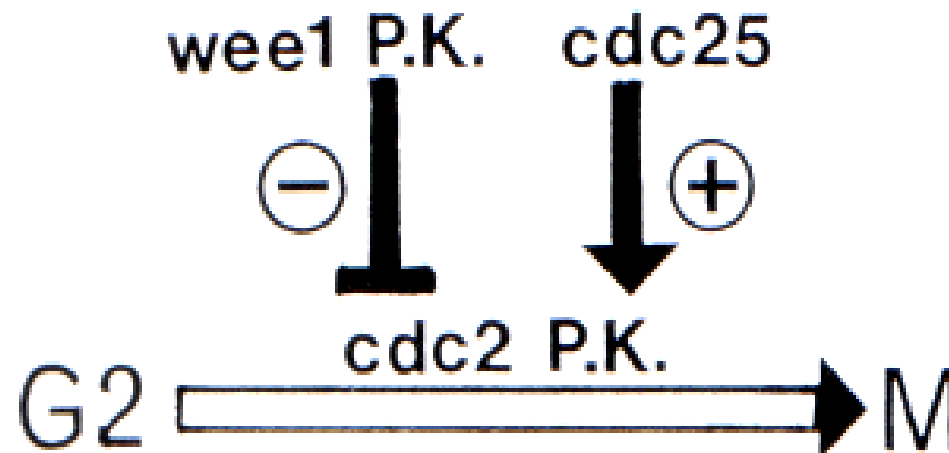
***cdc25*⁺ Functions as an Inducer in the Mitotic Control of Fission Yeast**

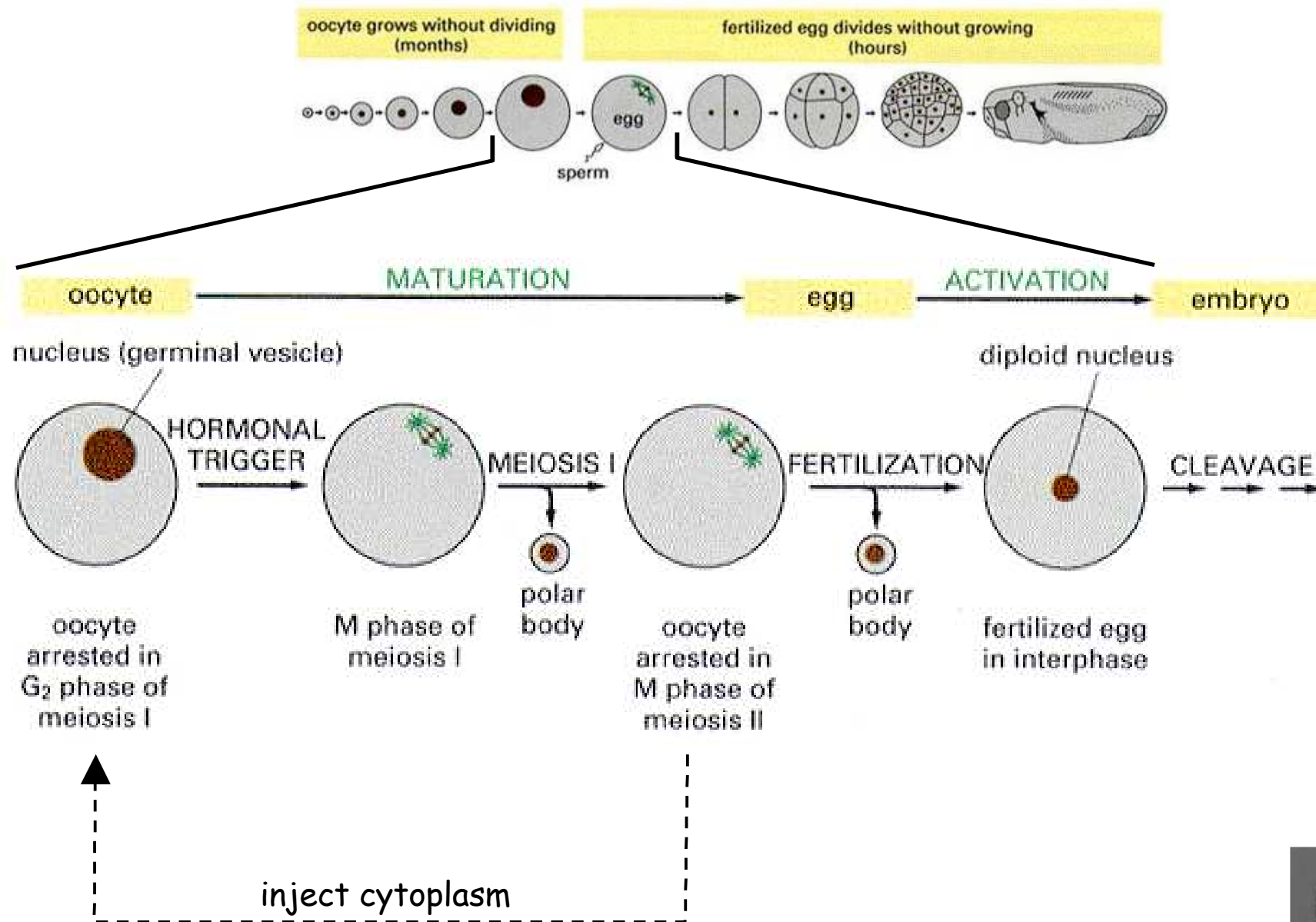
Paul Russell and Paul Nurse
Cell Cycle Control Laboratory
Imperial Cancer Research Fund
Lincoln's Inn Fields
London, WC2A 3PX, England

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

Negative Regulation of Mitosis by *wee1*⁺, a Gene Encoding a Protein Kinase Homolog

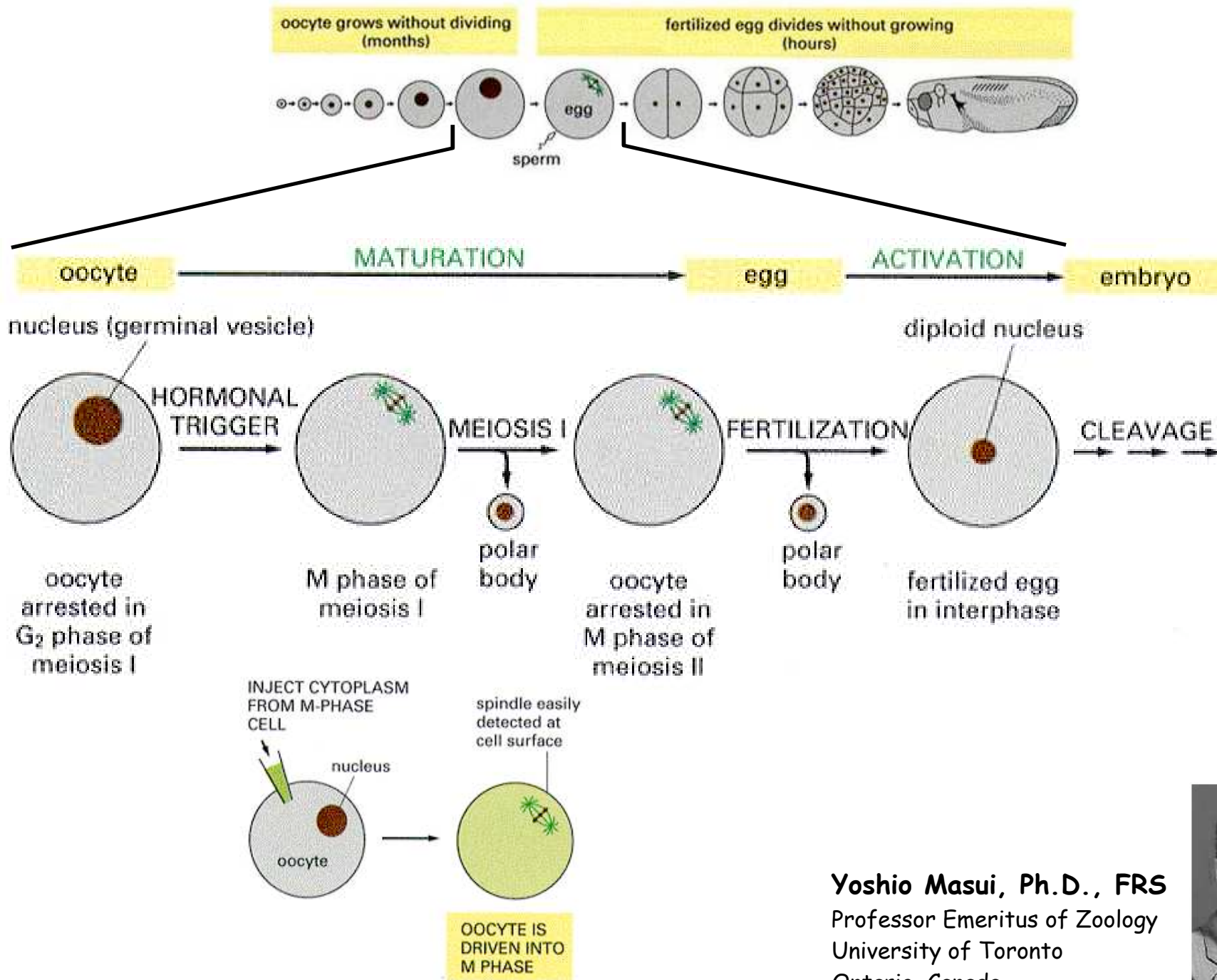
Paul Russell and Paul Nurse
Cell Cycle Control Laboratory
Imperial Cancer Research Fund
Lincoln's Inn Fields
London WC2A 3PX, England





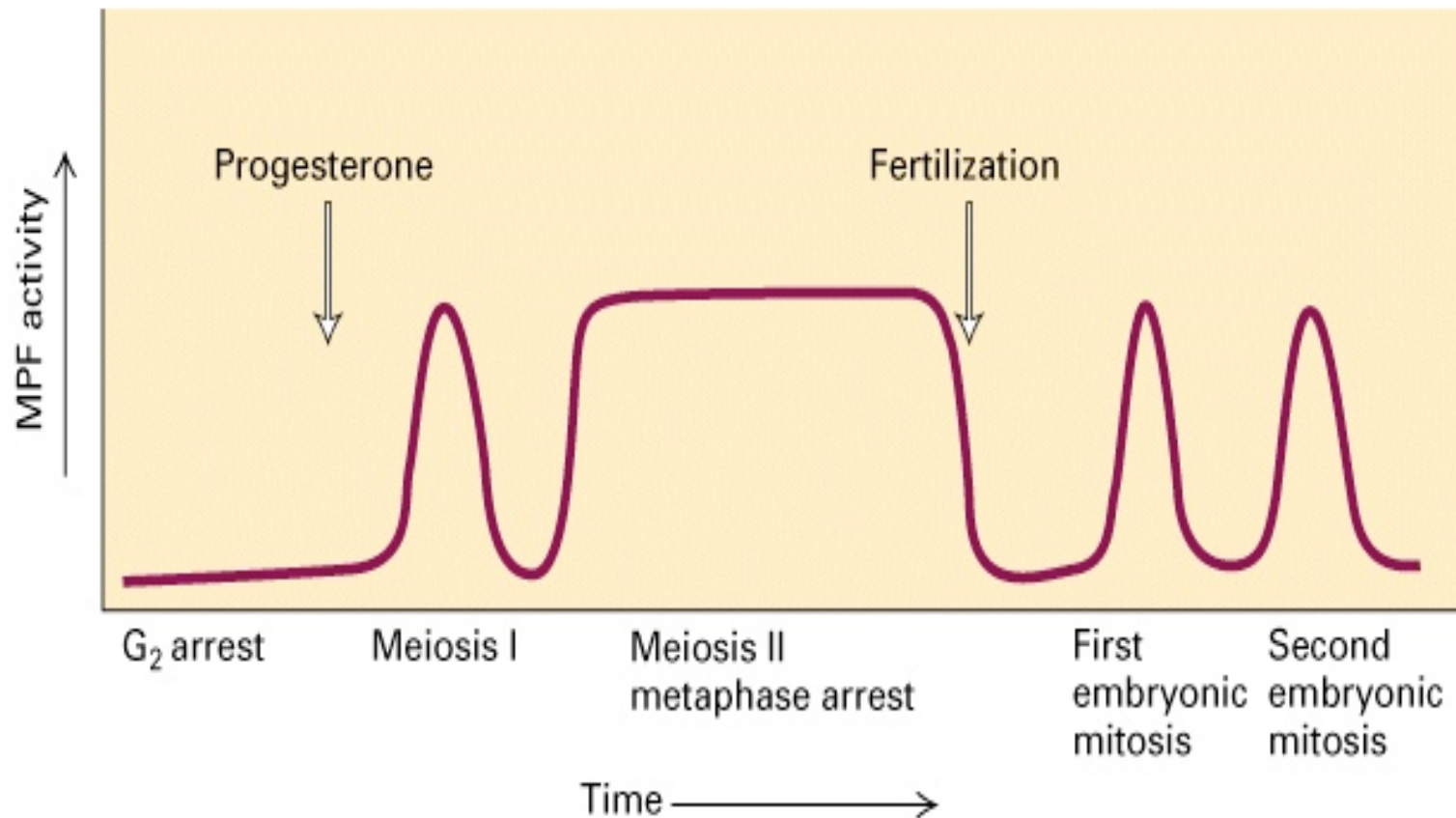
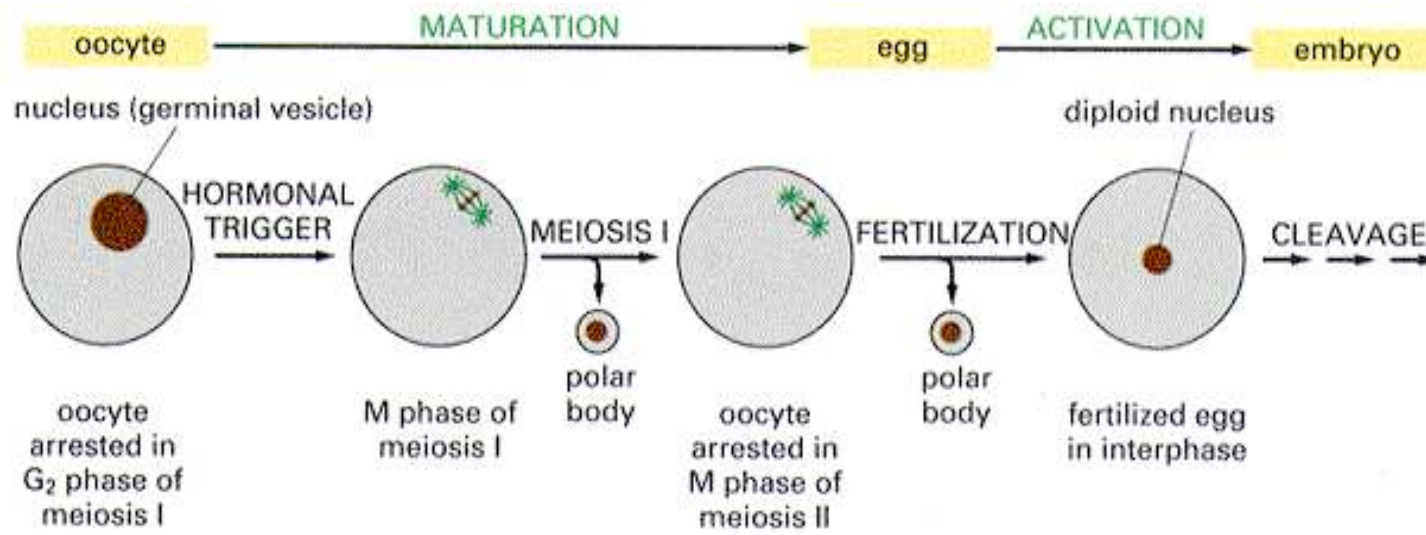
Yoshio Masui, Ph.D., FRS
 Professor Emeritus of Zoology
 University of Toronto
 Ontario, Canada





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





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

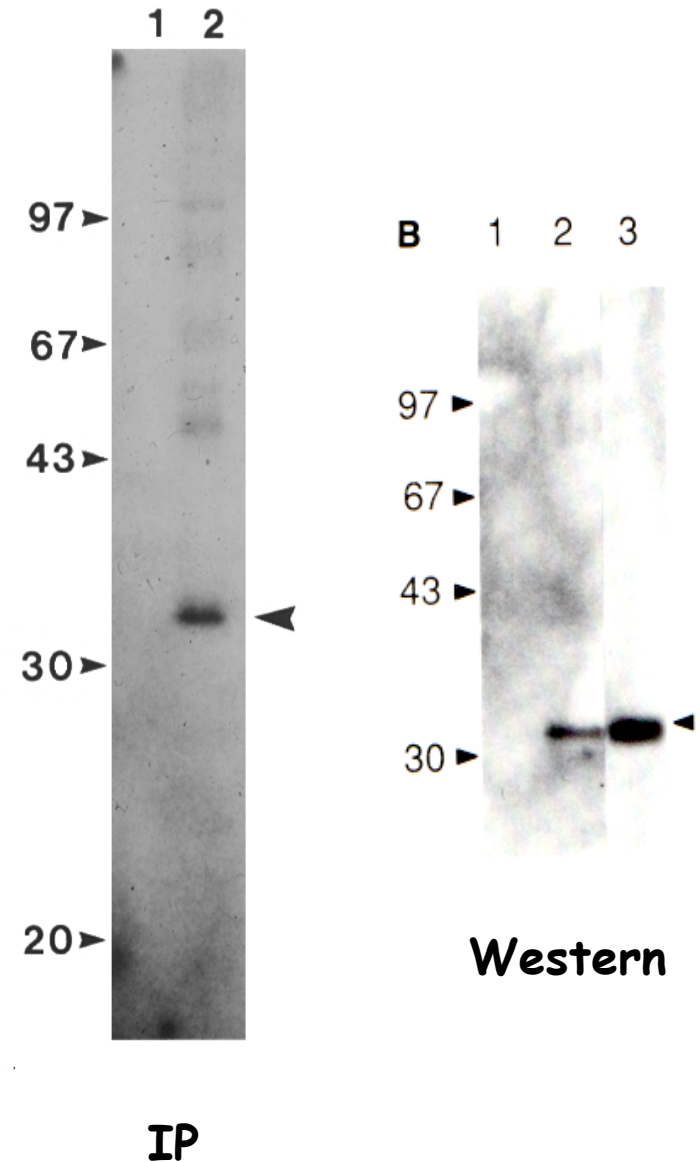
Jean Gautier,* Chris Norbury,[†]
Manfred Lohka,* ‡ Paul Nurse,[†]
and James Maller*

*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



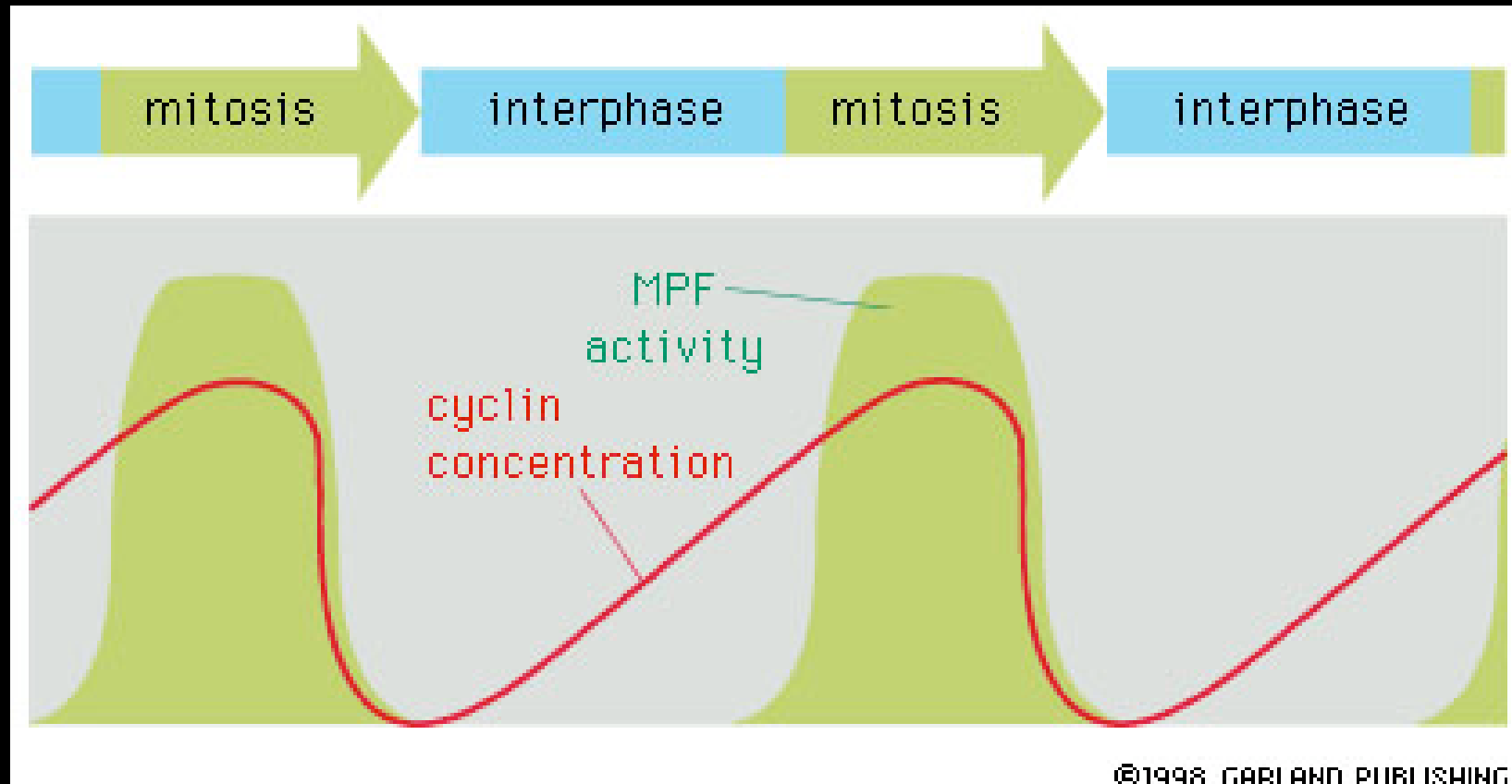
MPF is a cyclin-dependent protein-kinase

Cdk1

CycB

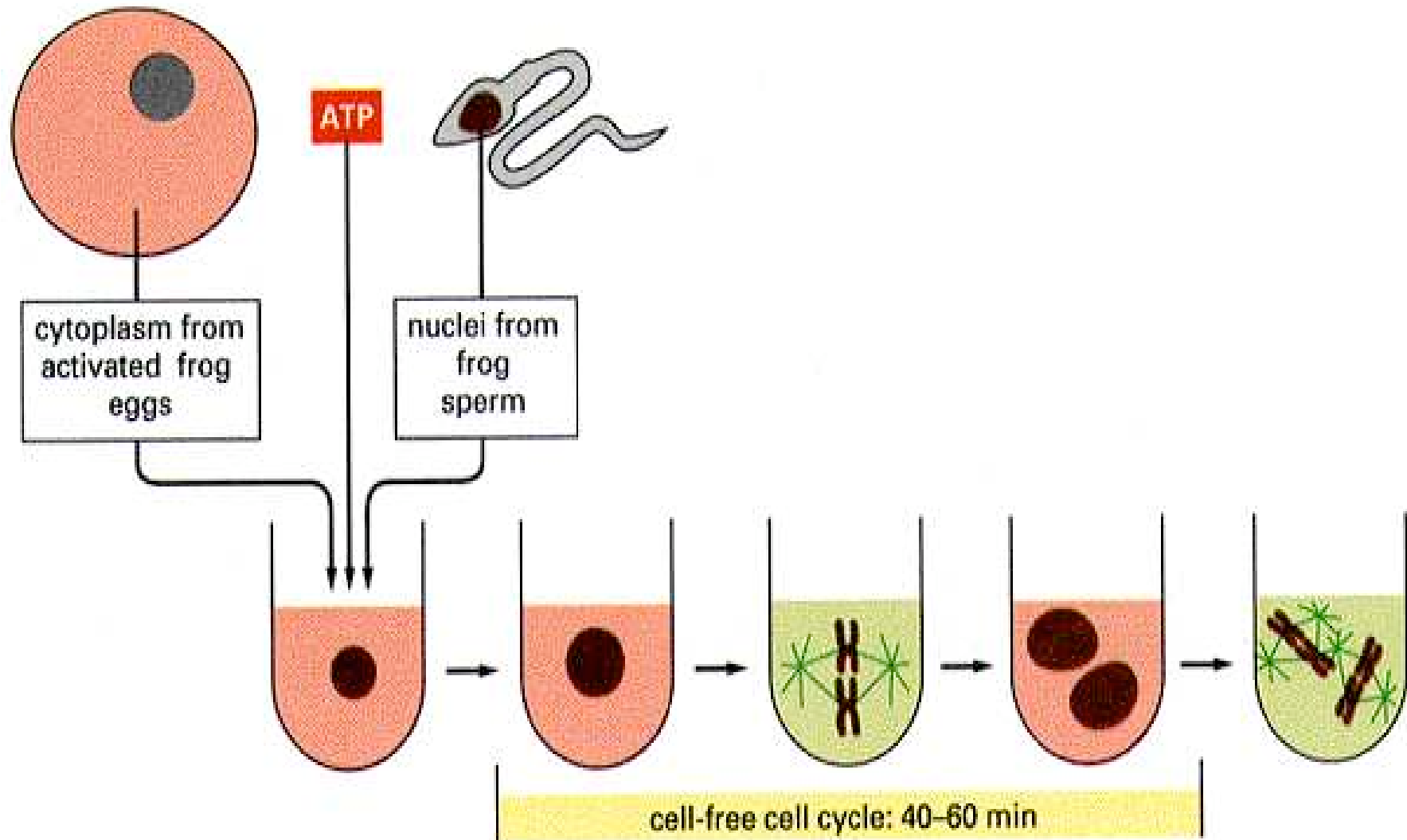
A diagram showing the components of MPF. It consists of a blue rectangle labeled 'Cdk1' positioned above a yellow oval labeled 'CycB'.

Cyclin and MPF levels during early mitotic cycles

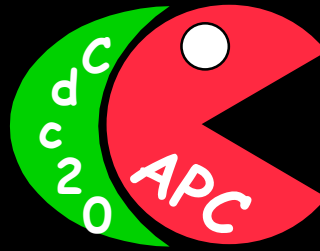
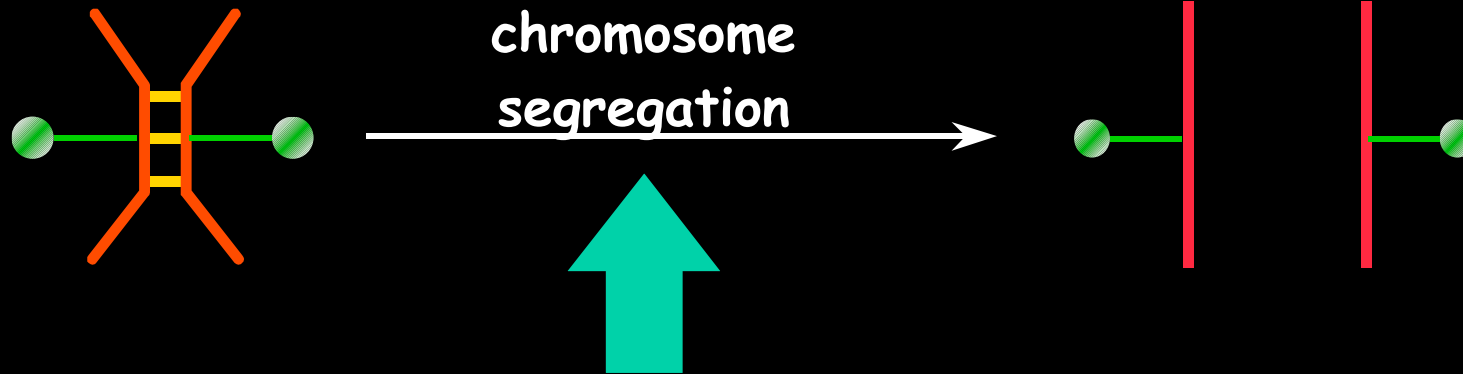


Questions: What causes the fast disappearance of cyclins?
What is the reason of the delay between cyclin and MPF?

Cycling cell free extract

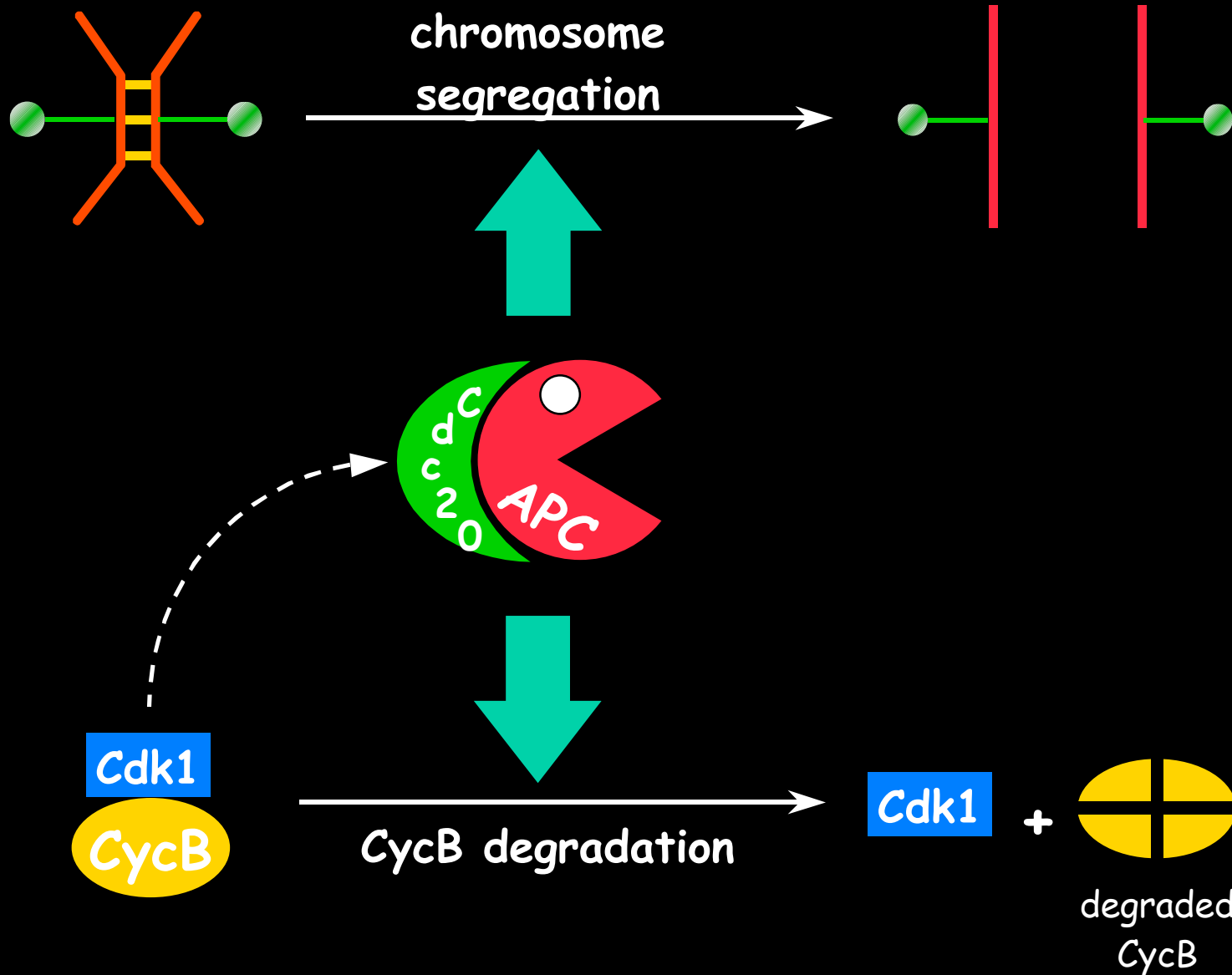


Anaphase Promoting Complex or Cyclosome

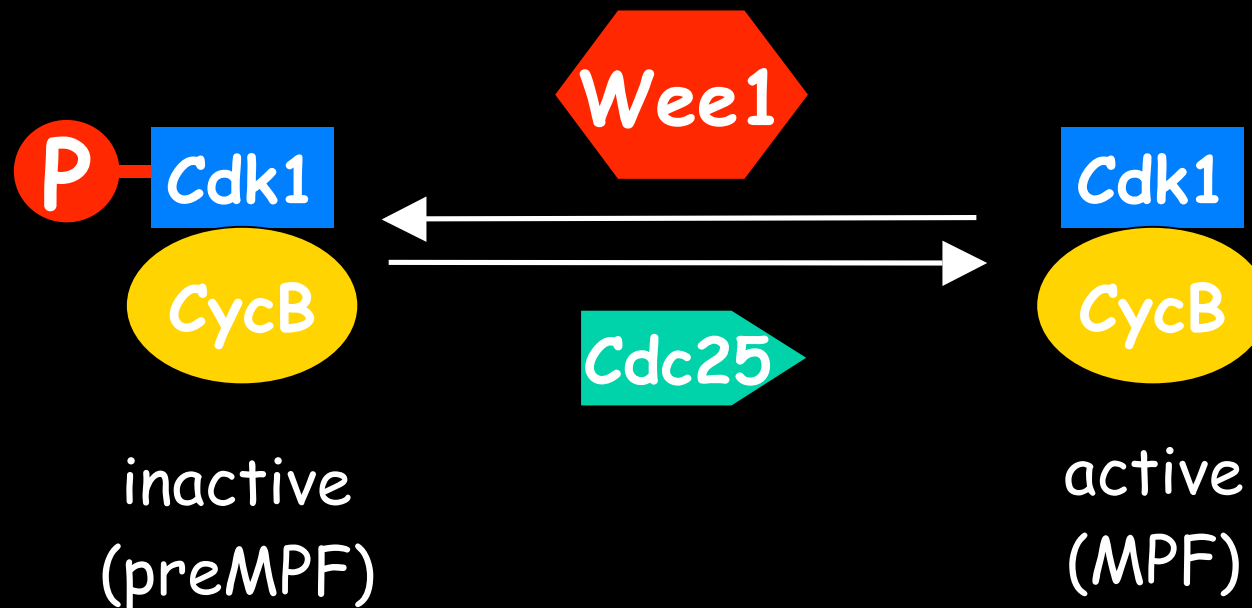


Kim Nasmyth

Anaphase Promoting Complex or Cyclosome

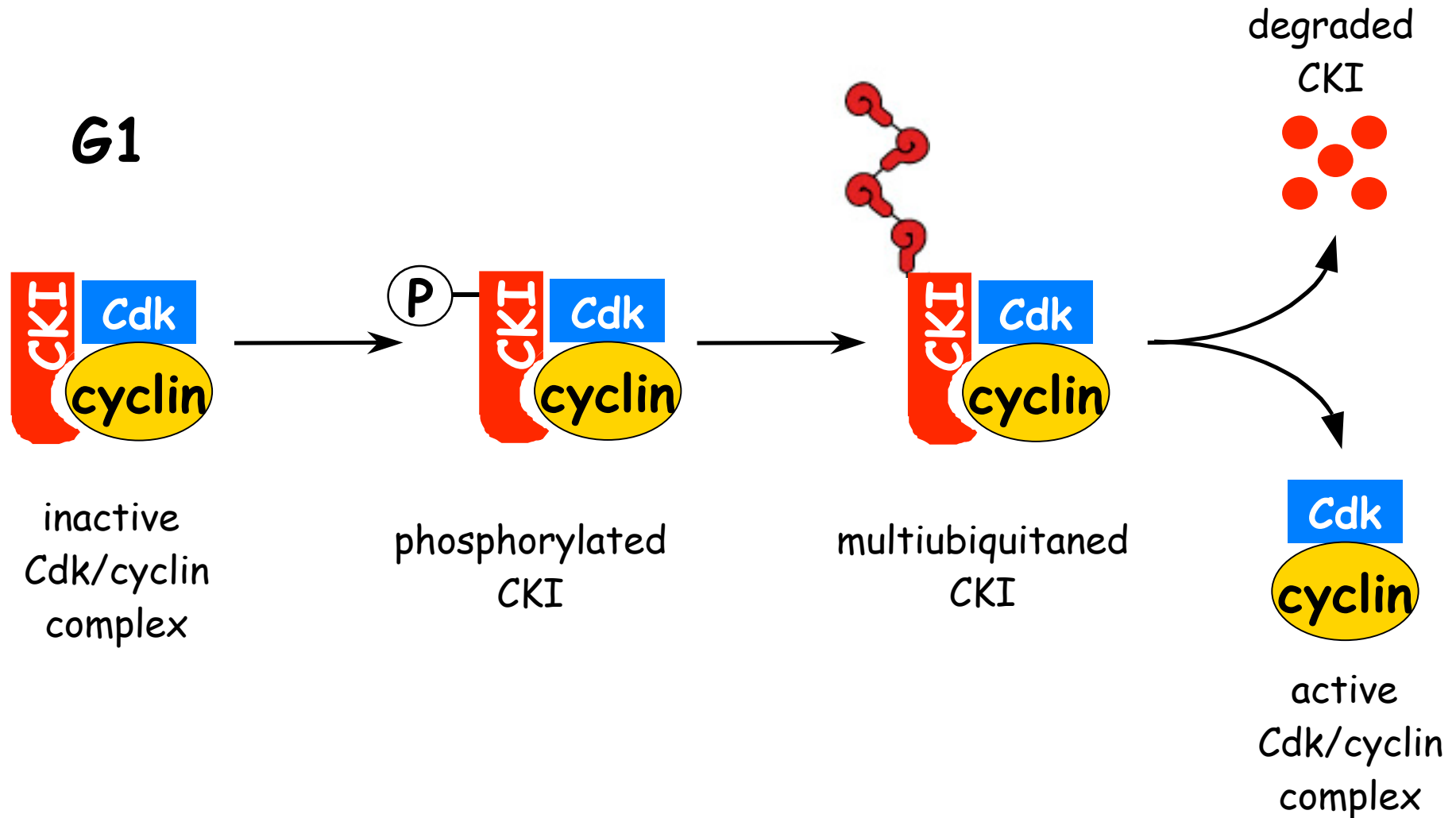


The G2/M transition is regulated by post-translational modification



Wee1 is a tyrosine-kinase
Cdc25 is a tyrosine-phosphatase

Start of DNA replication is also controlled by proteolysis



Regulation of CDK activity

