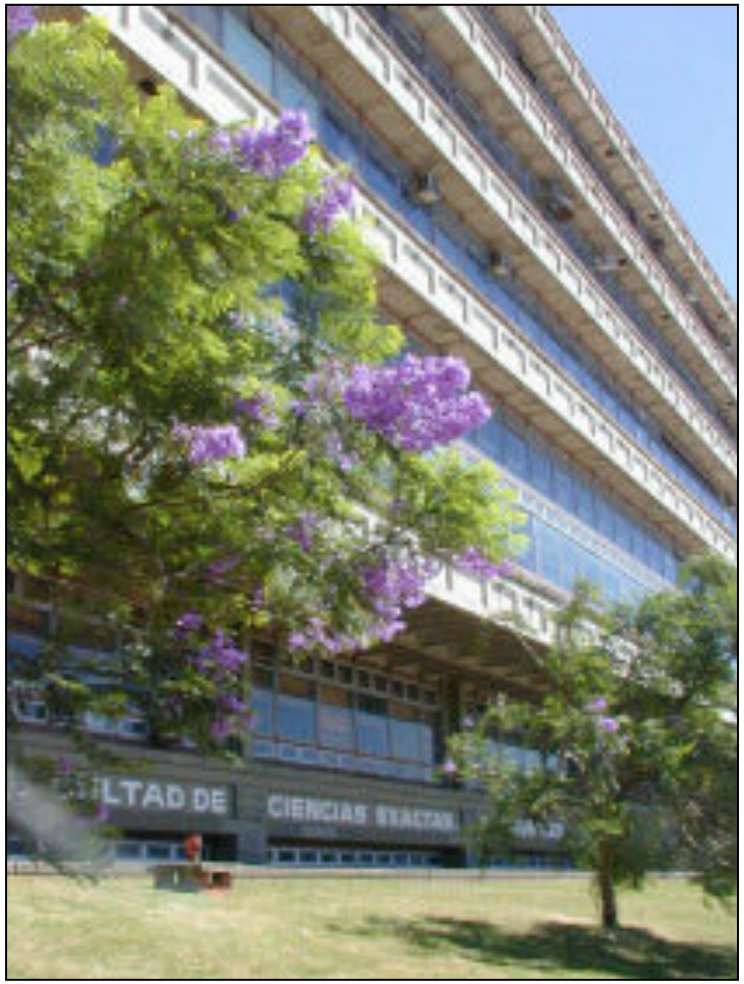
ANCEFN, 30 de mayo de 2014




# *Los caminos del gen a la proteína*

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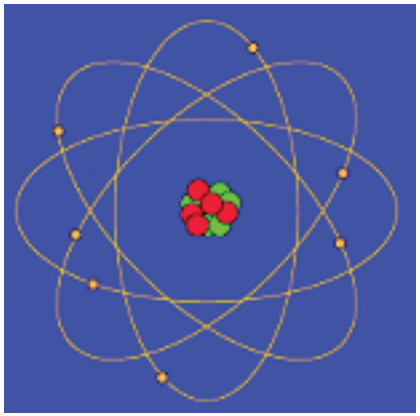
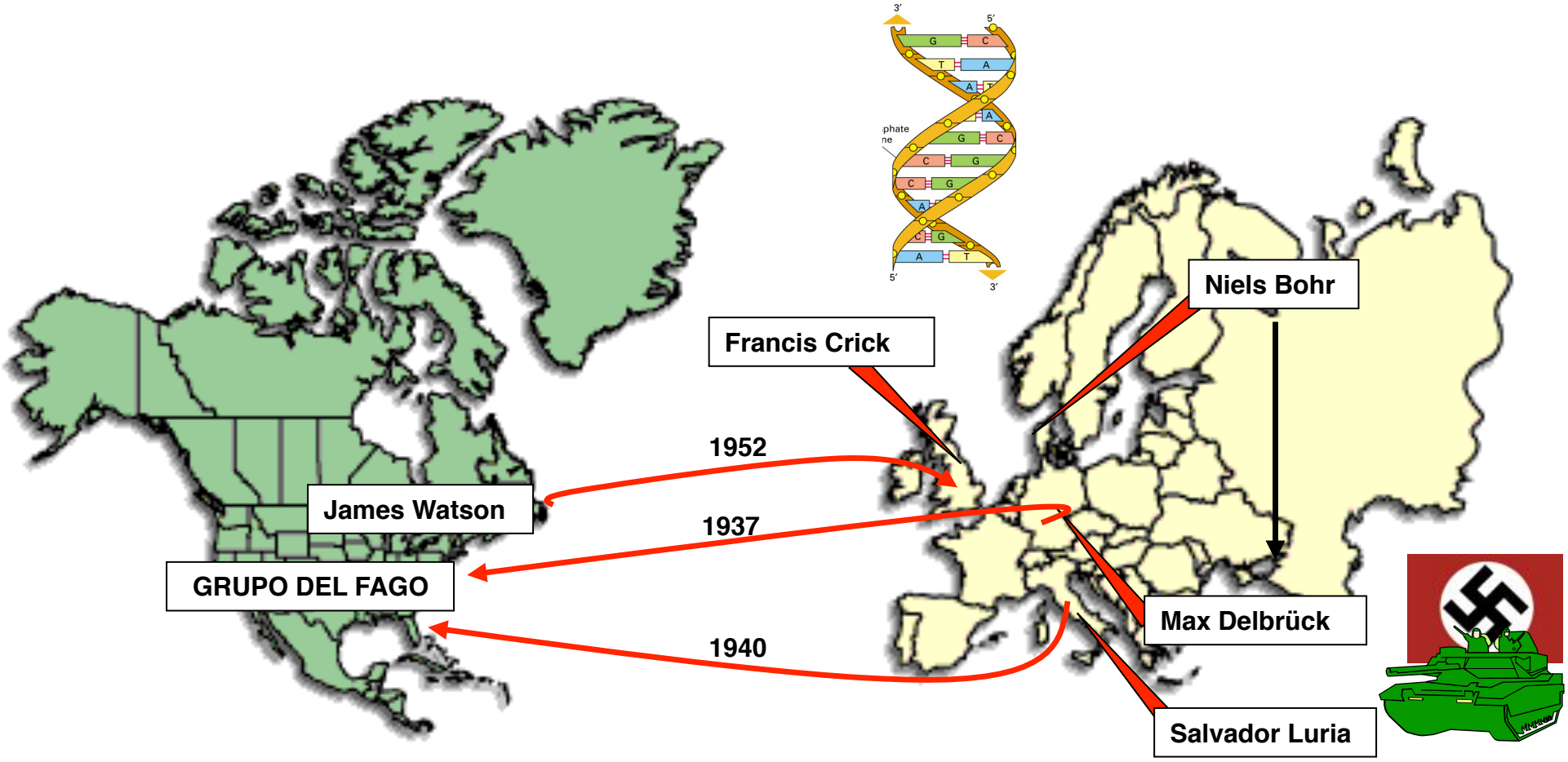
Depto. Fisiol. Biol. Mol. Cel.
Facultad de Ciencias Exactas y Naturales
Universidad de Buenos Aires - Argentina

# La biología molecular moderna nace por el interés de los físicos



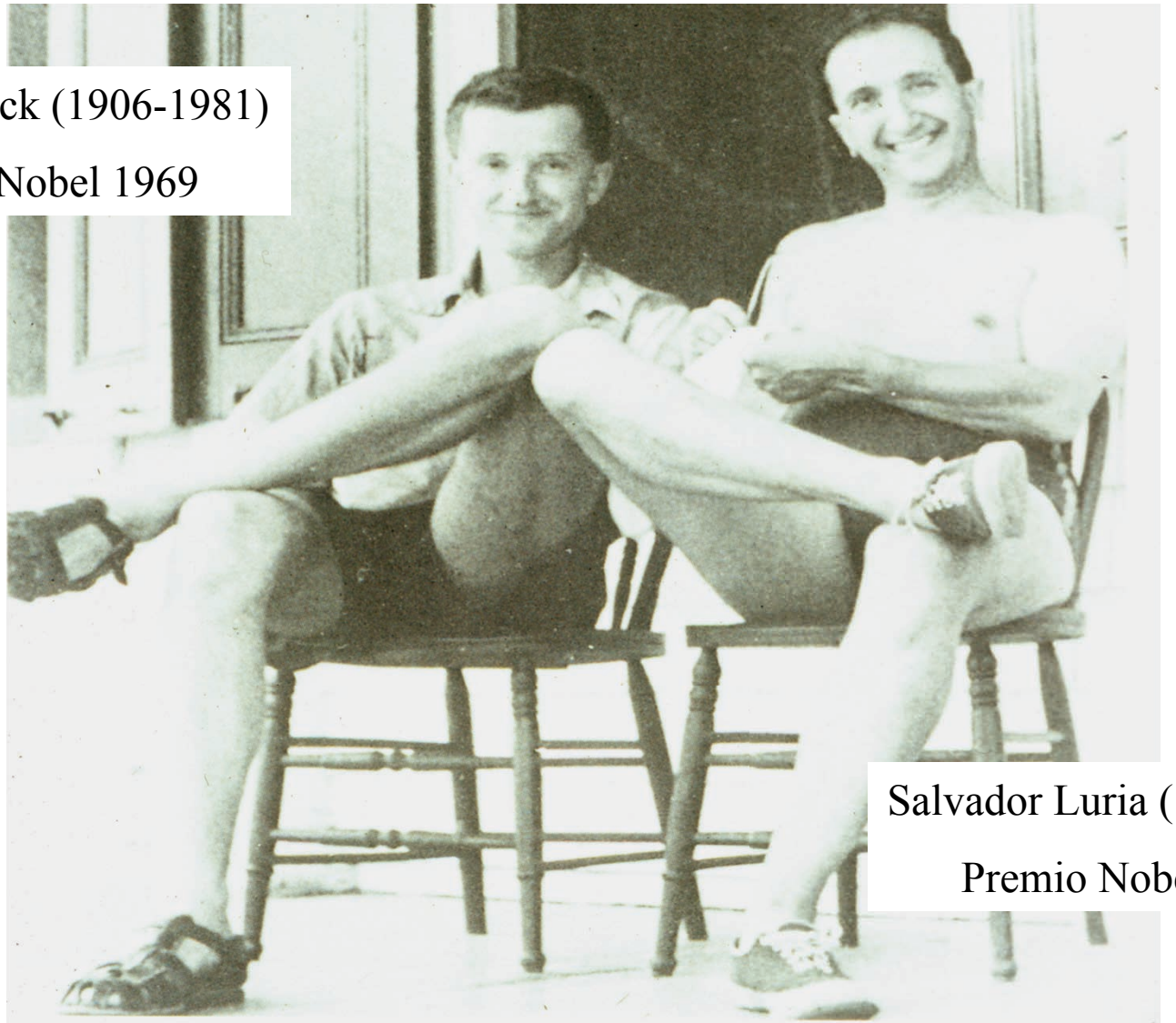
Niels Bohr (1887-1962)

Premio Nobel 1922


Niels Bohr
Francis Crick
1952
James Watson
1937
GRUPO DEL FAGO
Max Delbrück
1940
Salvador Luria

Max Delbruck (1906-1981)

Premio Nobel 1969



Salvador Luria (1912-1991)

Premio Nobel 1969

"Delbrück created at Cold Spring Harbor that spirit of ceaseless questioning, dialogue, and open-armed embrace of a life in science that he had learned from Niels Bohr—but with a down-to-earth American character and a good measure of his own high-minded intolerance of shoddy thinking." Max Delbrück and Salvador Luria at Cold Spring Harbor. PHOTOGRAPH COURTESY COLD SPRING HARBOR LABORATORY LIBRARY ARCHIVES

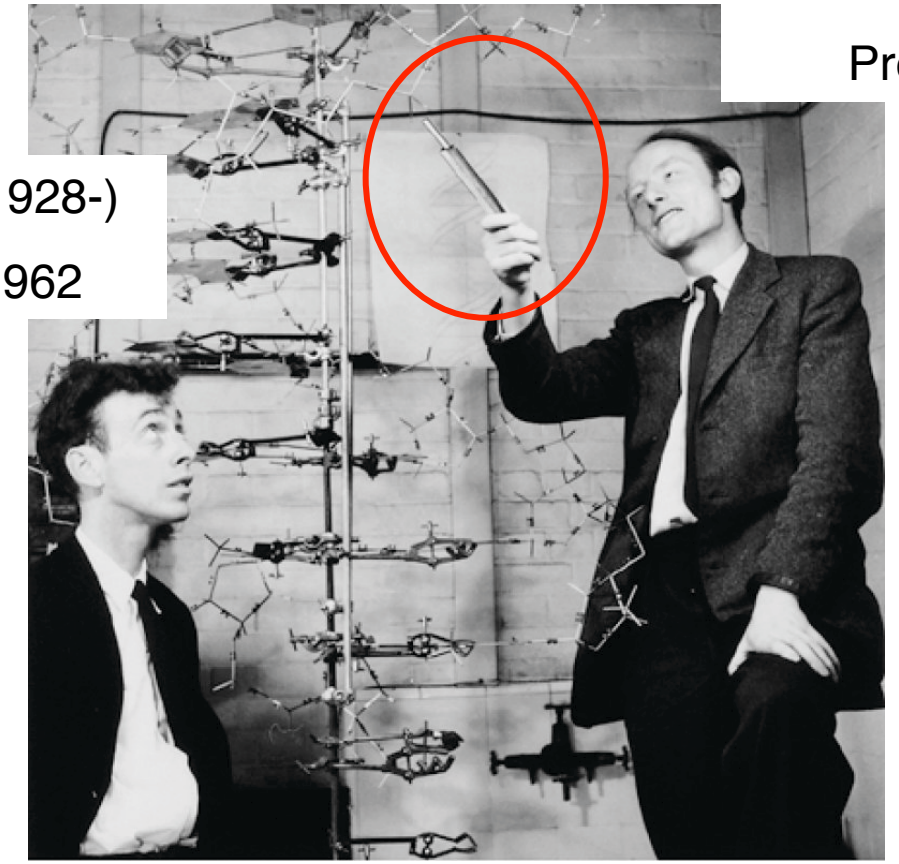
Delbruck y Luria demostraron las bases genéticas de la selección natural de Darwin: la mutación pre-existe a la selección

Francis Crick (1916-2004)

Premio Nobel 1962

James Watson (1928-)

Premio Nobel 1962



1953

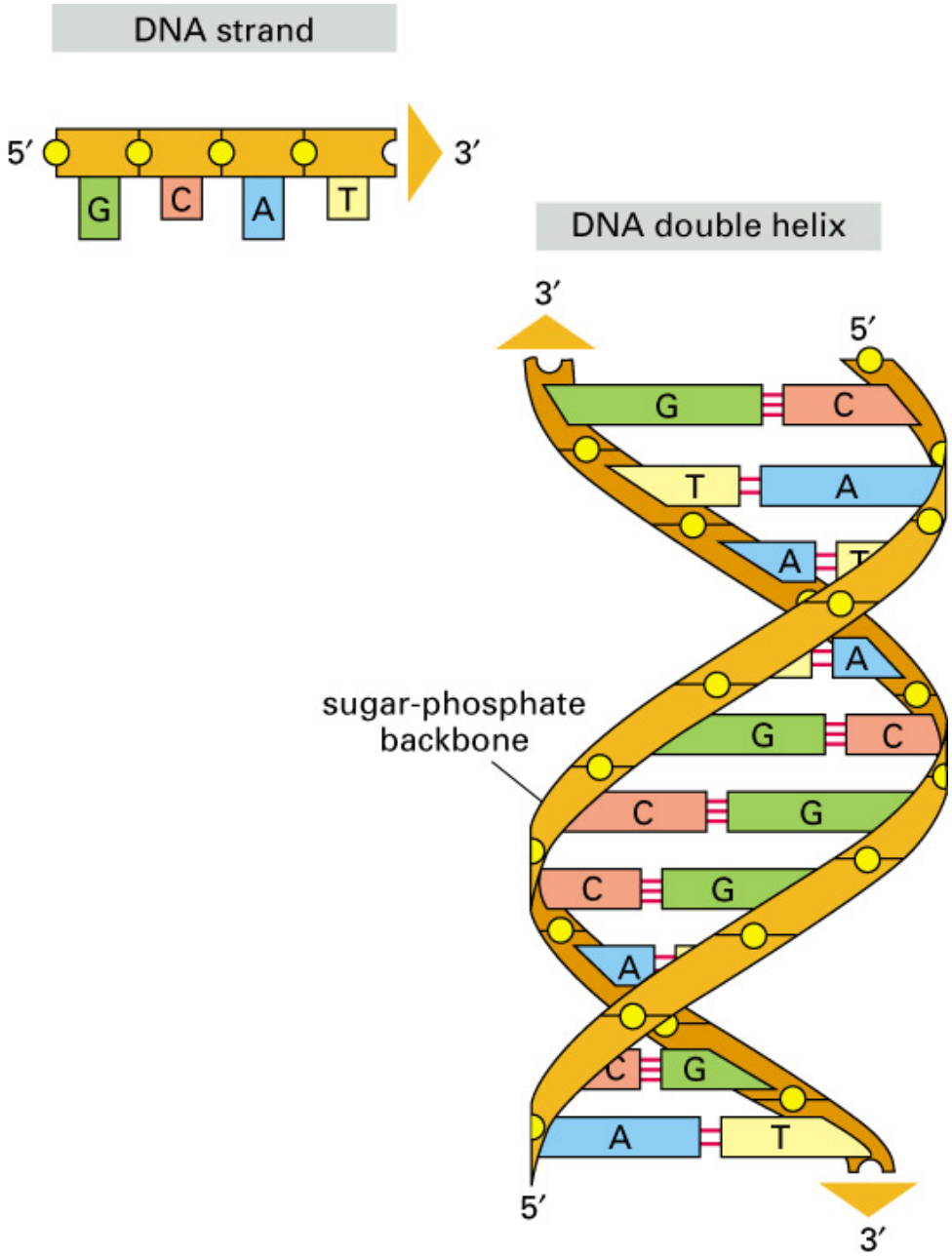



Figure 4–3 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

# MOLECULAR STRUCTURE OF NUCLEIC ACIDS

## A Structure for Deoxyribose Nucleic Acid

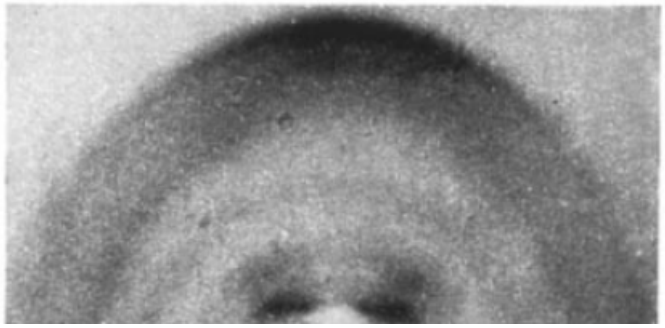


King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

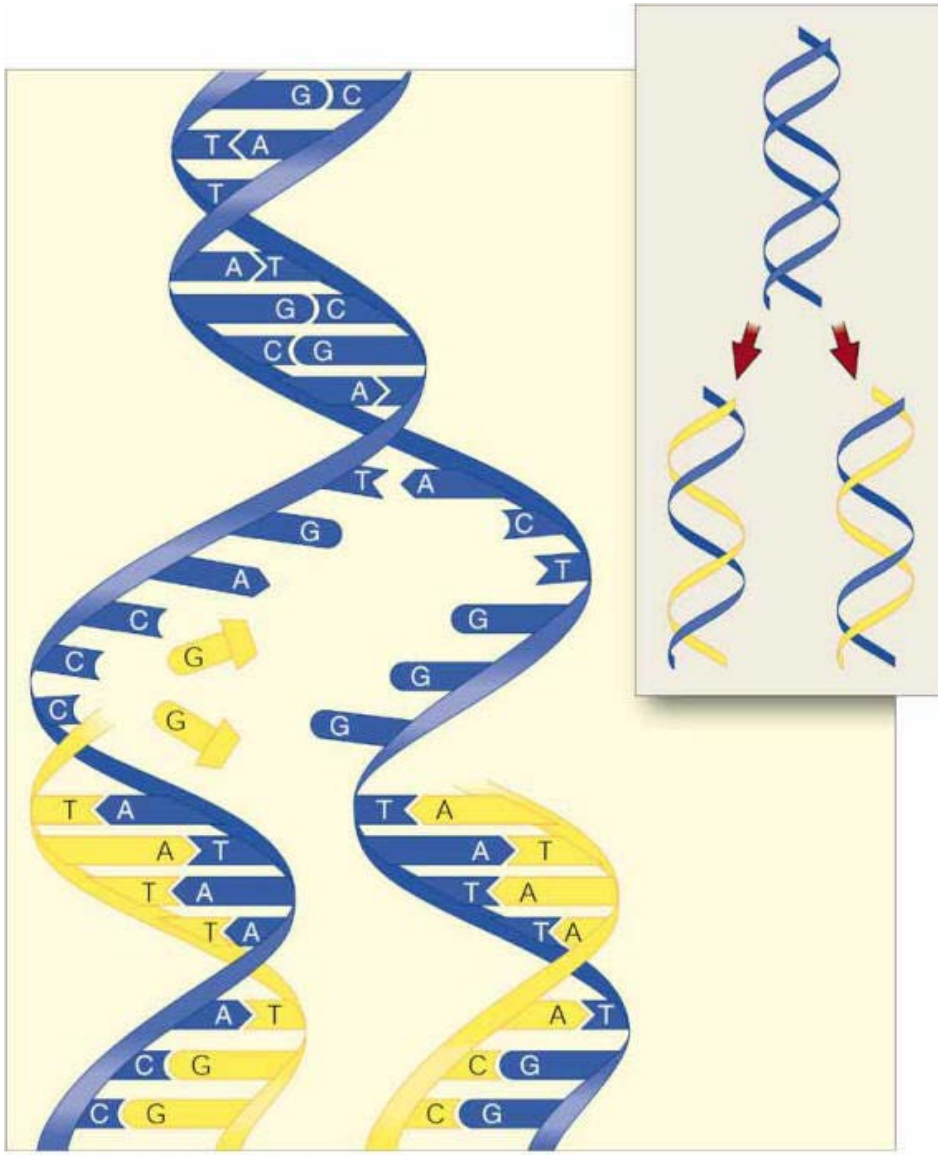
J. D. Watson
F. H. C. Crick

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems,
Cavendish Laboratory, Cambridge.

April 2.



It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.



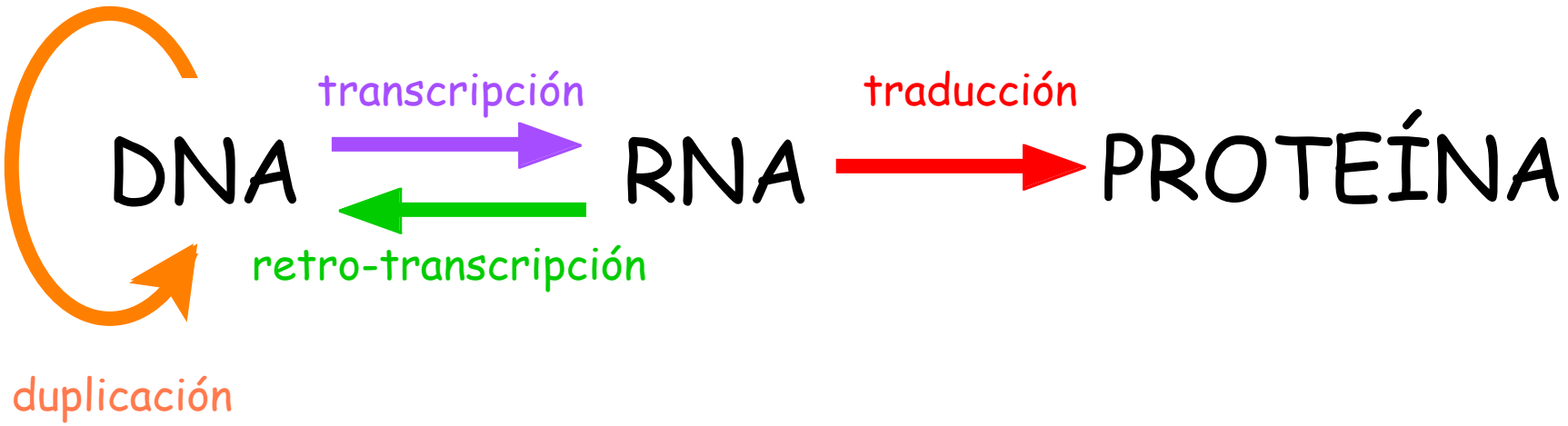
# Los principales productos de los genes son proteínas

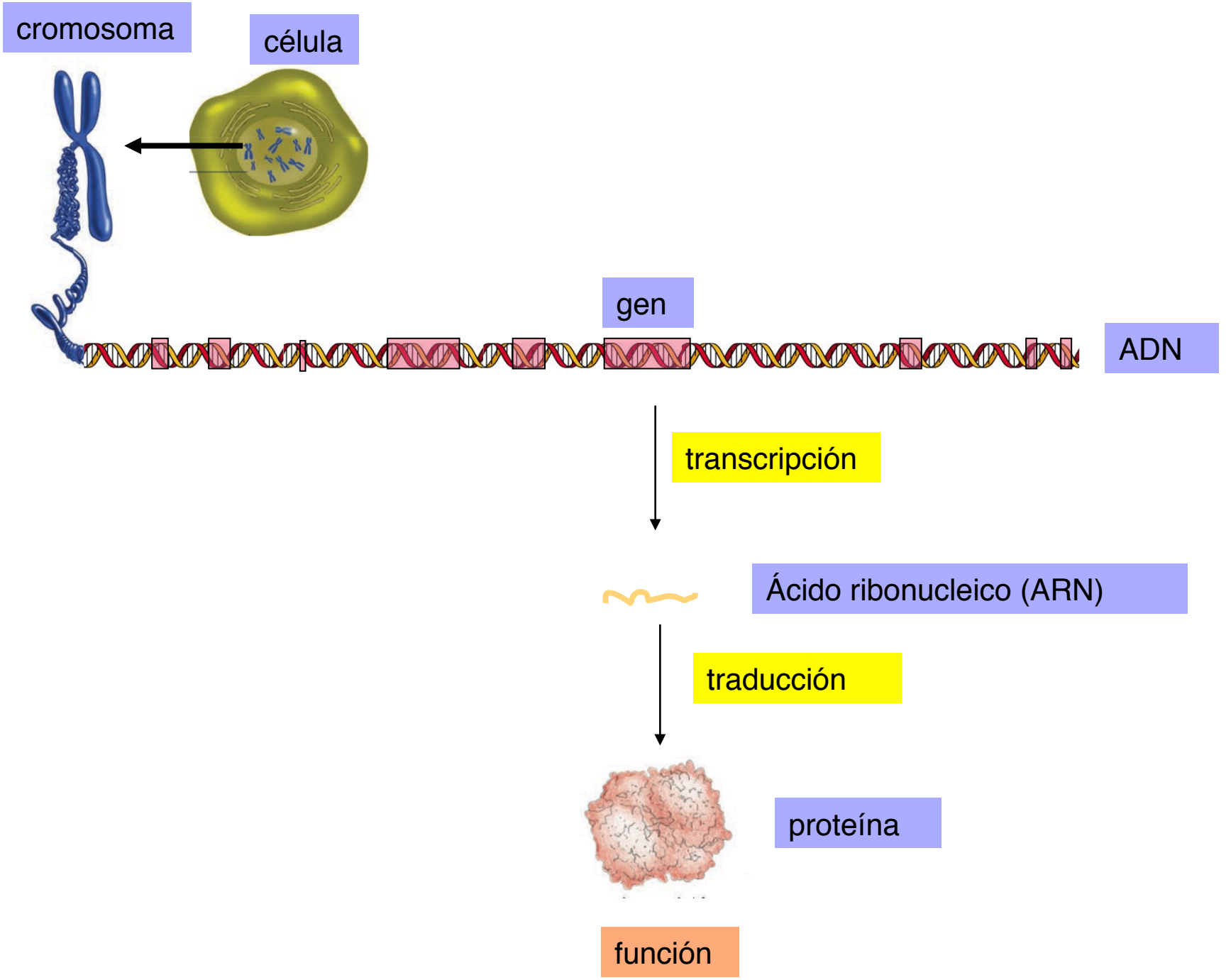
¿Cómo se fabrican?

Dogma (?!) central de la biología molecular

o

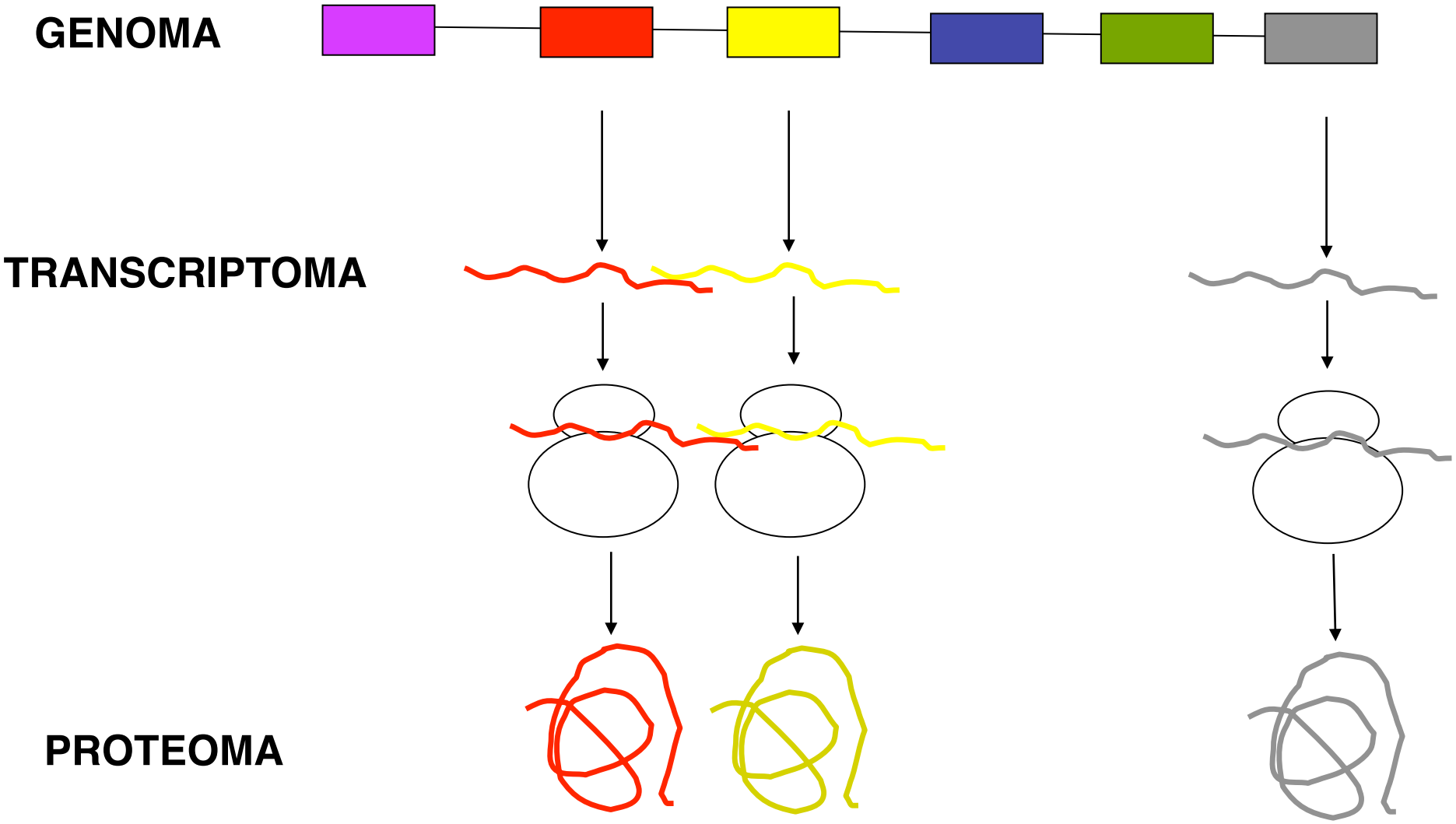
Flujo de información genética


transcripción
traducción
DNA
RNA
PROTEÍNA
retro-transcripción
duplicación


cromosoma
célula
gen
ADN
transcripción
Ácido ribonucleico (ARN)
traducción
proteína
función

¿Cómo es posible que si todas las células de un individuo tienen los mismos genes, se produzca la diferenciación celular?

**EN UN DETERMINADO TIPO CELULAR Y/O EN UN DETERMINADO MOMENTO DEL DESARROLLO SÓLO SE EXPRESA UN SUBCONJUNTO DE LOS GENES**



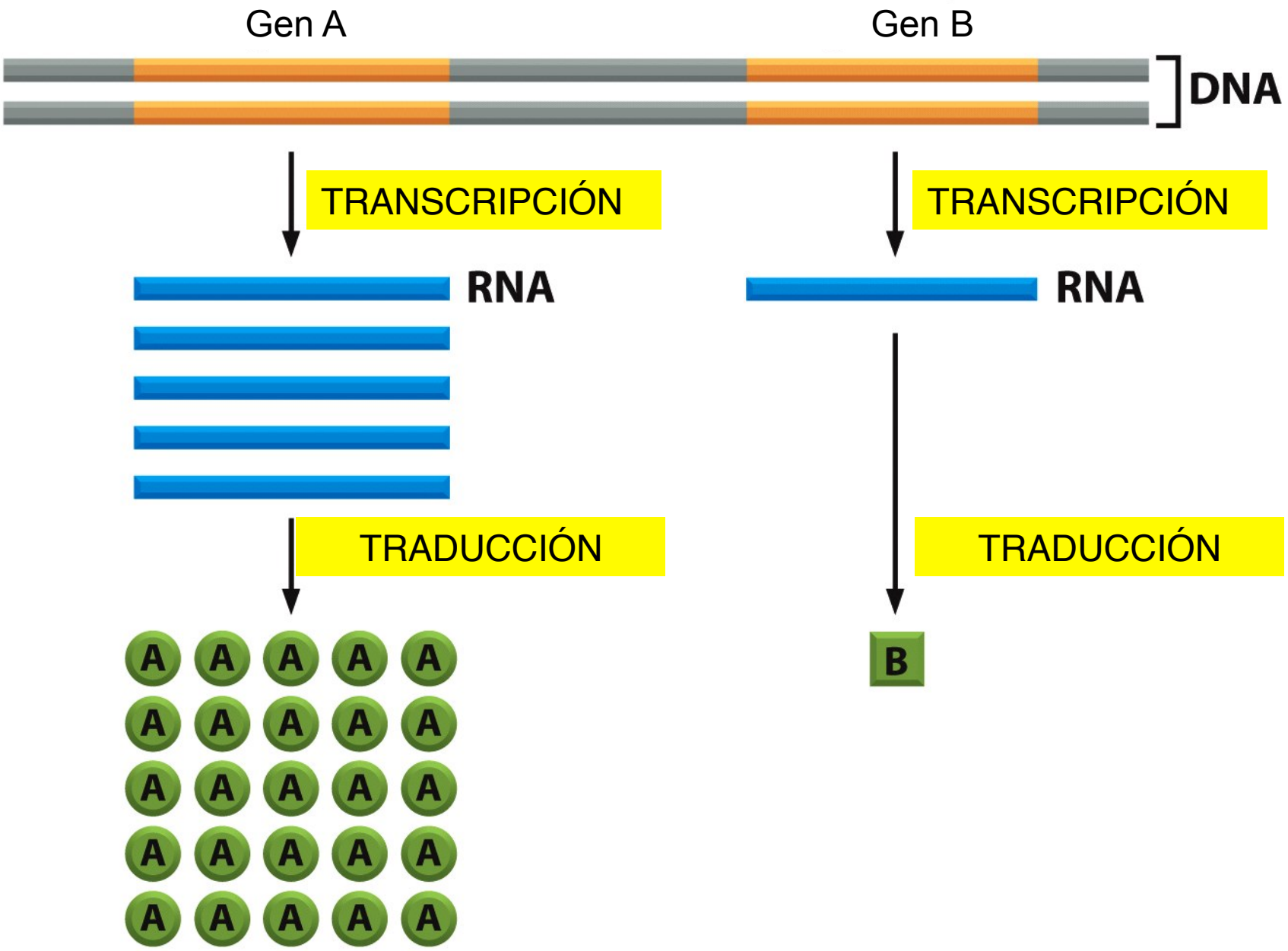
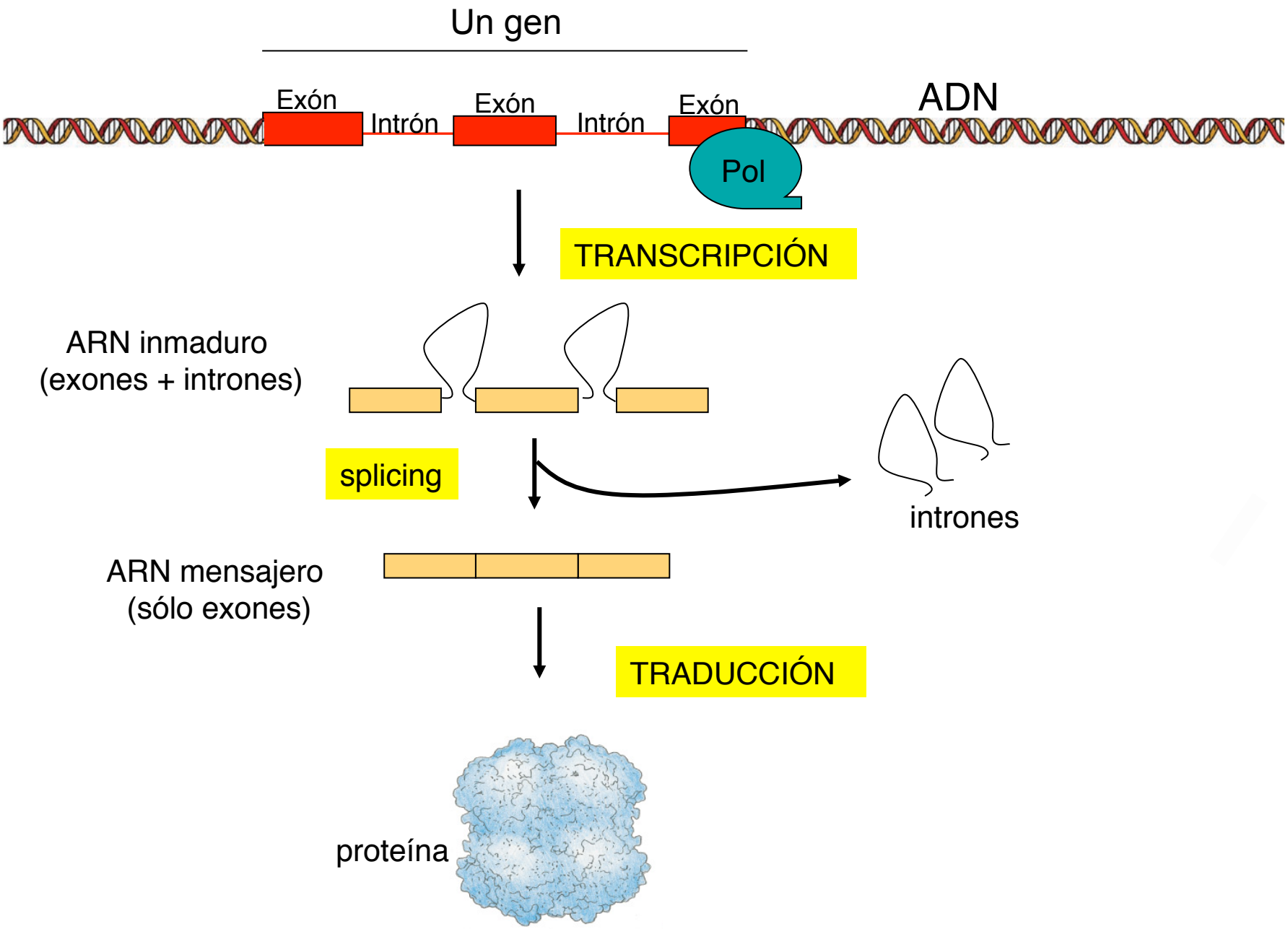
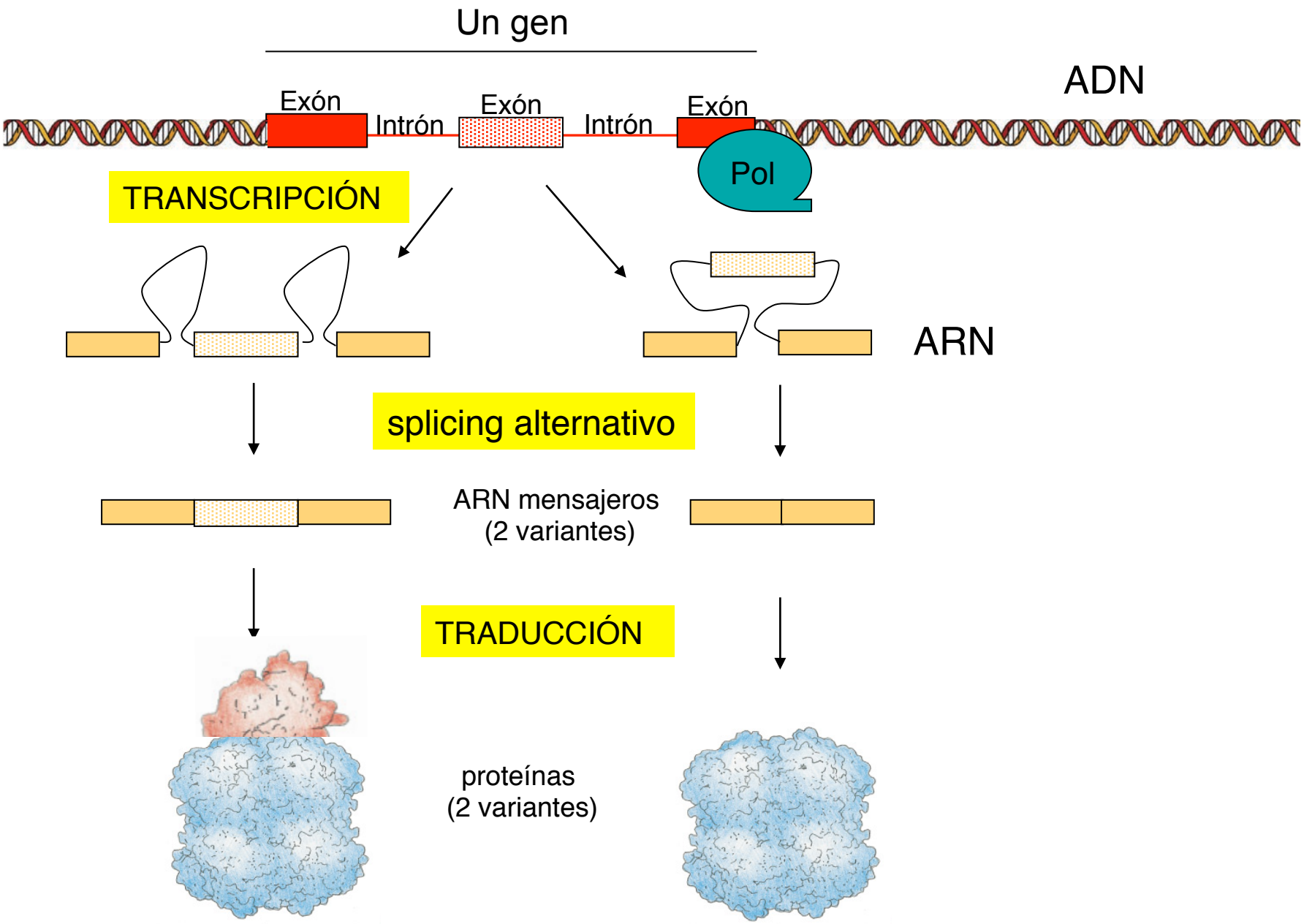


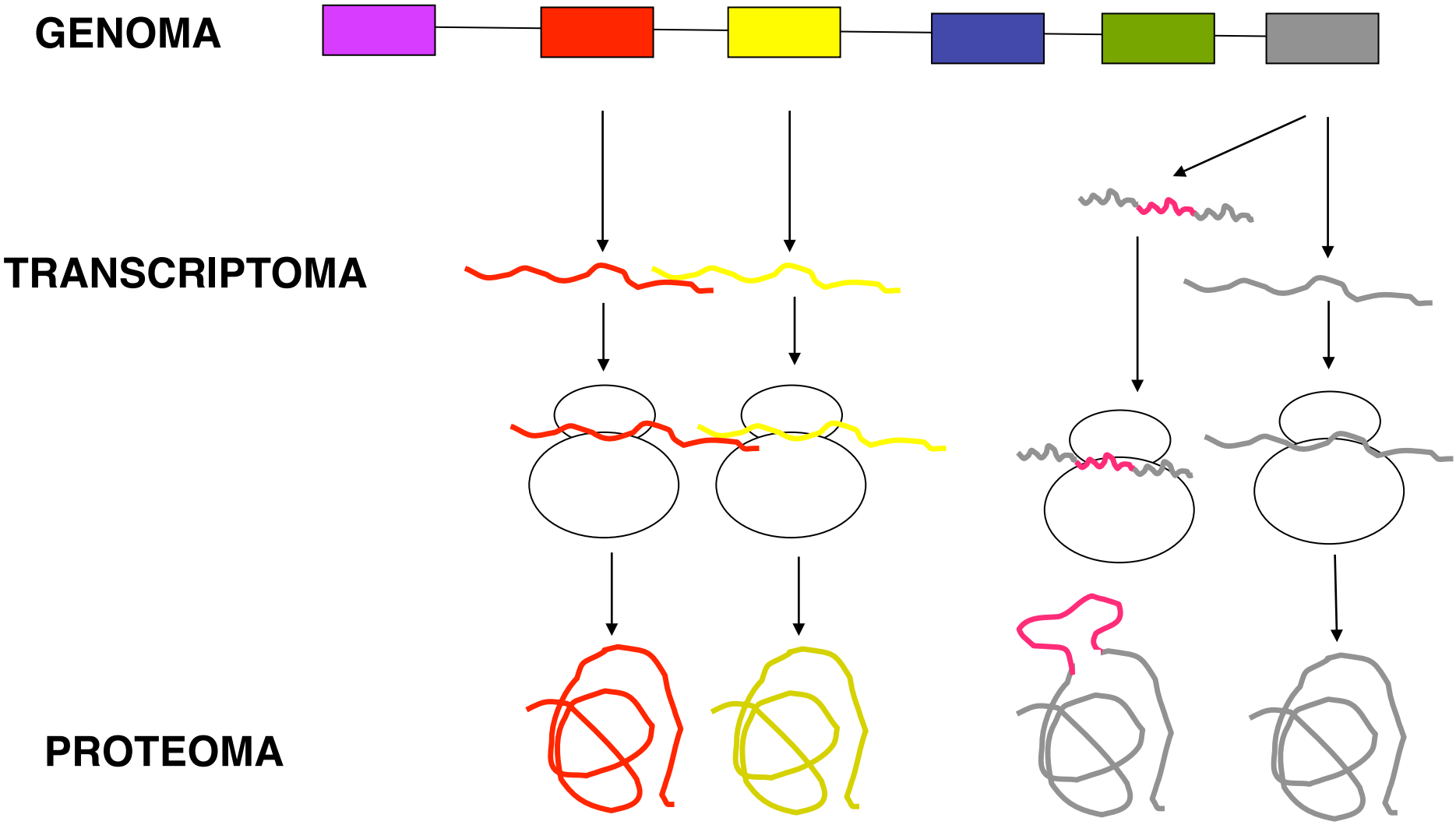

Figure 6-3 *Molecular Biology of the Cell* (© Garland Science 2008)

# ¿Y qué investigamos en nuestro laboratorio?


Un gen
Exón
Intrón
Exón
Intrón
Exón
ADN
Pol
TRANSCRIPCIÓN
ARN inmaduro
(exones + intrones)
splicing
intrones
ARN mensajero
(sólo exones)
TRADUCCIÓN
proteína

# Splicing alternativo

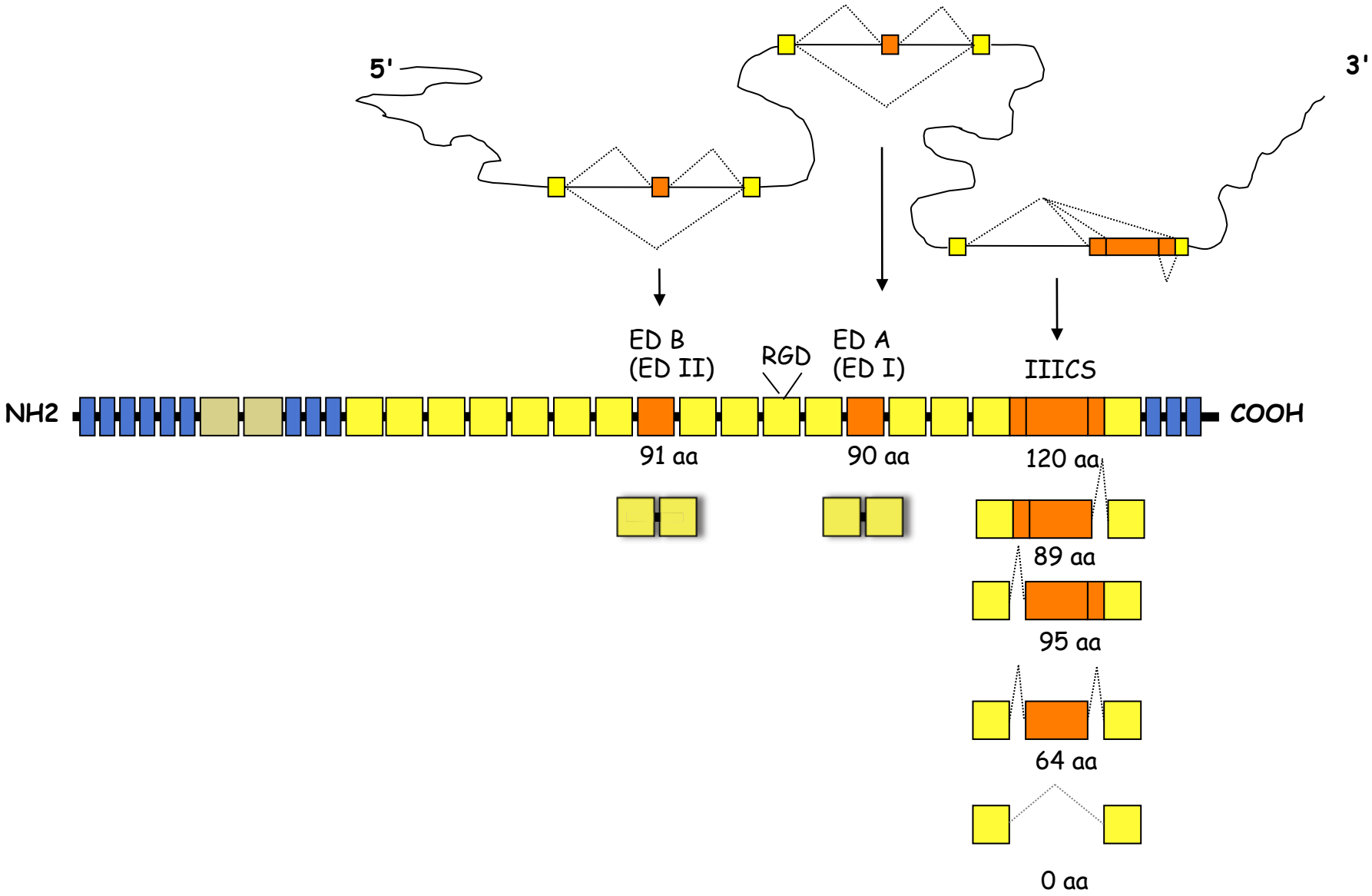

Un gen
ADN
Exón
Intrón
Exón
Intrón
Exón
Pol
TRANSCRIPCIÓN
ARN
splicing alternativo
ARN mensajeros
(2 variantes)
TRADUCCIÓN
proteínas
(2 variantes)


GENOMA
TRANSCRIPTOMA
PROTEOMA

un gen → una proteína

un gen → muchas proteínas

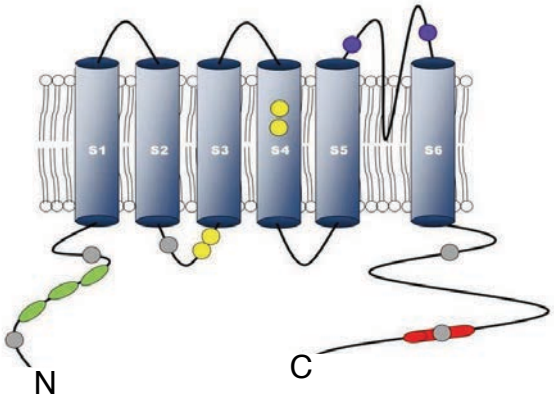
# *Fibronectina humana*

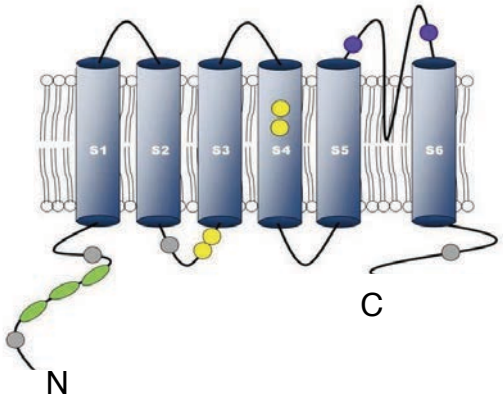



Kornblihtt et al., *FASEB J.* 1996

*Desmodus rotundus*
(murciélago vampiro)

TRPV1 (CANAL IÓNICO)




Ganglios espinales dorsales

>43 ºC

Calor nocivo

DOLOR

Ganglios del trigémino

>30 ºC

Sensado de radiación infrarroja

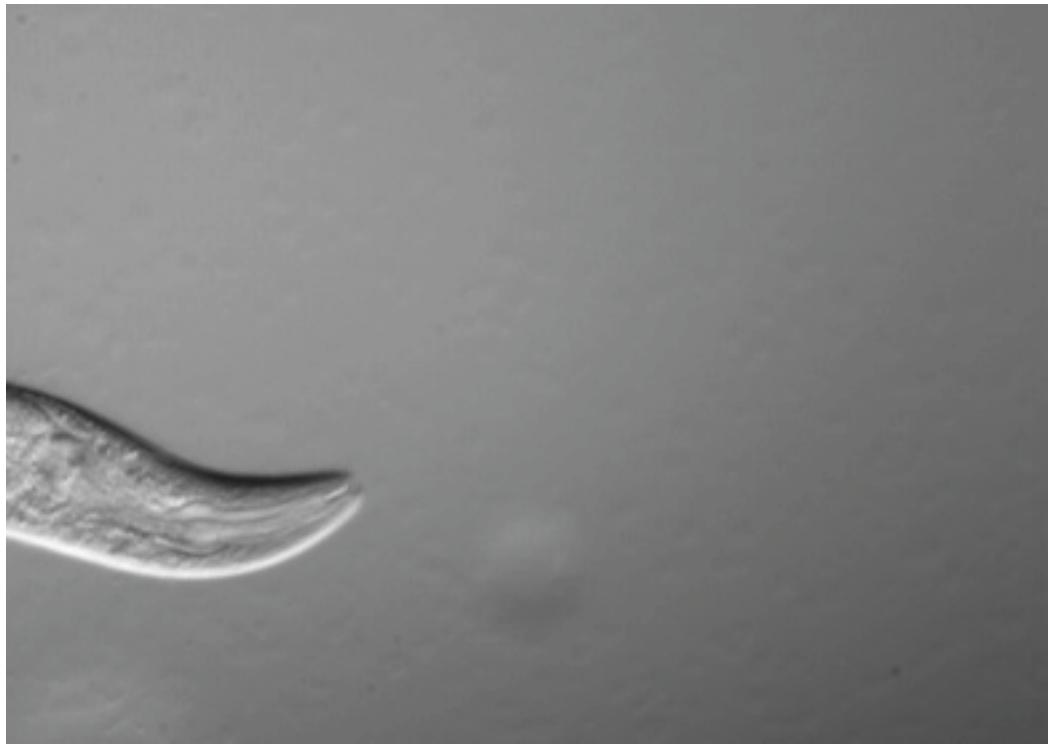
ALIMENTACIÓN

Julius group: Gracheva et al. *Nature* 2011

El splicing alternativo parece ser la causa de la gran complejidad de los vertebrados (nosotros)

# Gusano *Caenorhabditis elegans*

Invertebrado microscópico de 1 mm de largo formado por 1000 células



## 19.000 genes en cada célula

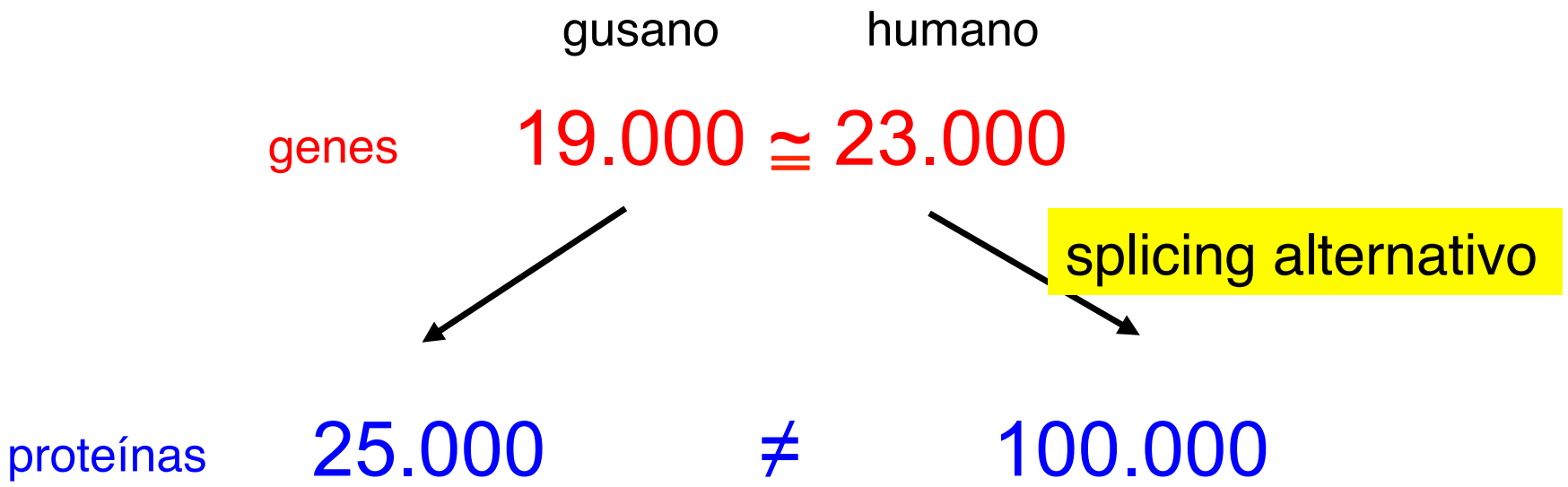
Fuente: http://www.bio.unc.edu/faculty/goldstein/lab/movies.html

*Homo sapiens sapiens*

Vertebrado macroscópico de casi 2 m de largo formado por $10^{13}$ células

23.000 genes en cada célula

No somos más complejos porque tengamos más genes



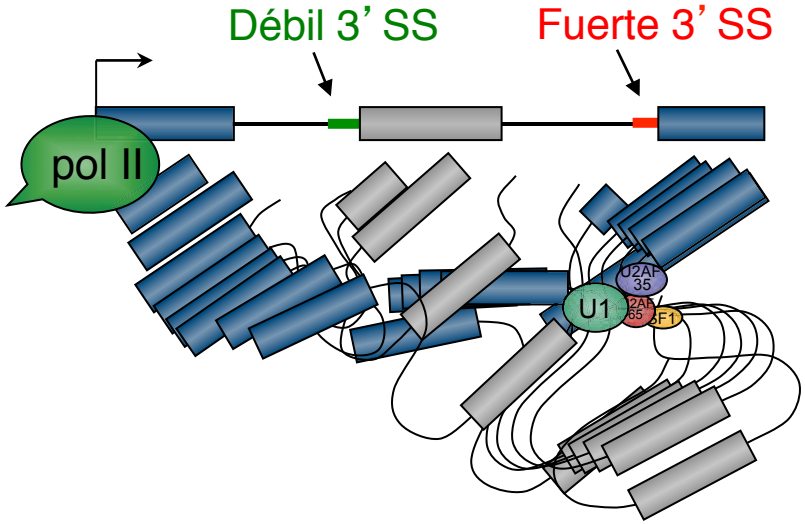

Lo que ocurre es que nuestros genes pueden generar muchas más proteínas que los del gusano

*La velocidad de la transcripción regula el splicing alternativo*


© HHMI

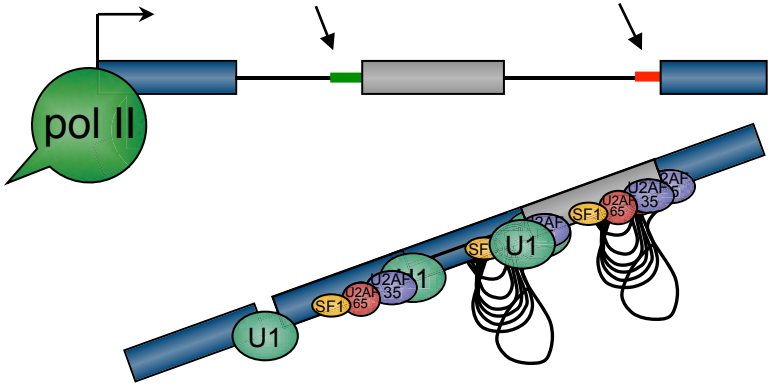
# *Quien llega primero, se sirve primero (versión 2)*

*Transcripción rápida/sin pausas*




Exclusión

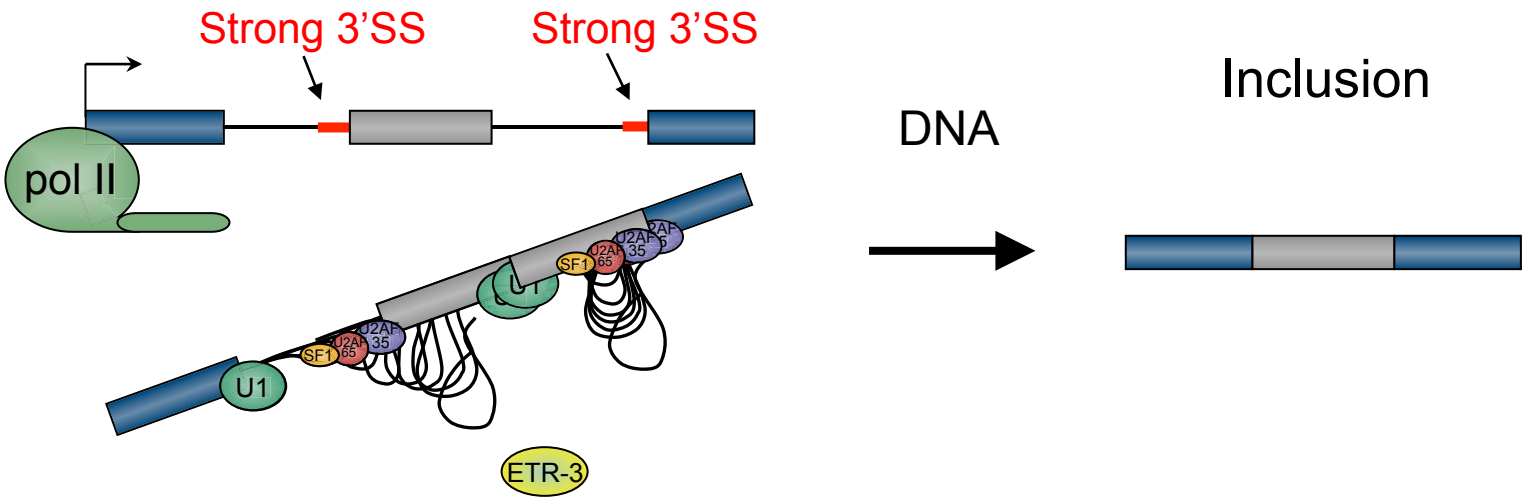
*Transcripción lenta/con pausas*



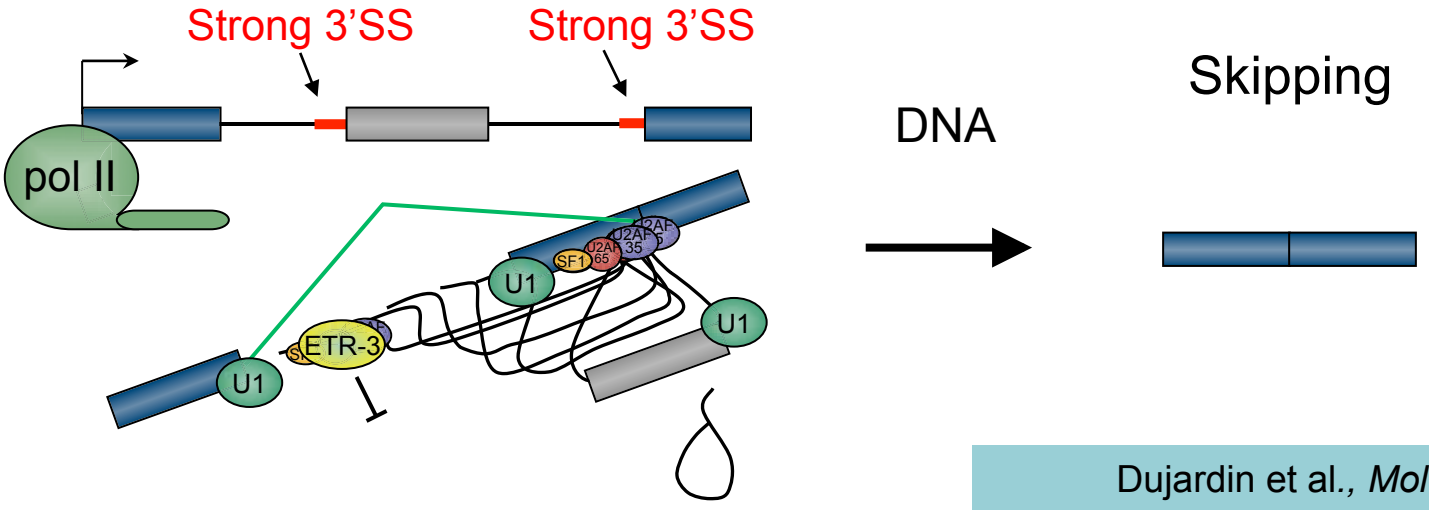

Inclusión

Kadener et al., *EMBO J.* 2001
Nogués et al., *JBC* 2001
de la Mata et al., *Mol. Cell* 2003
Fededa et al., *Mol. Cell* 2005
Alló et al., *NSMB* 2009
Muñoz et al., *Cell* 2009
de la Mata *et al., RNA* 2010

***Fast elongation***

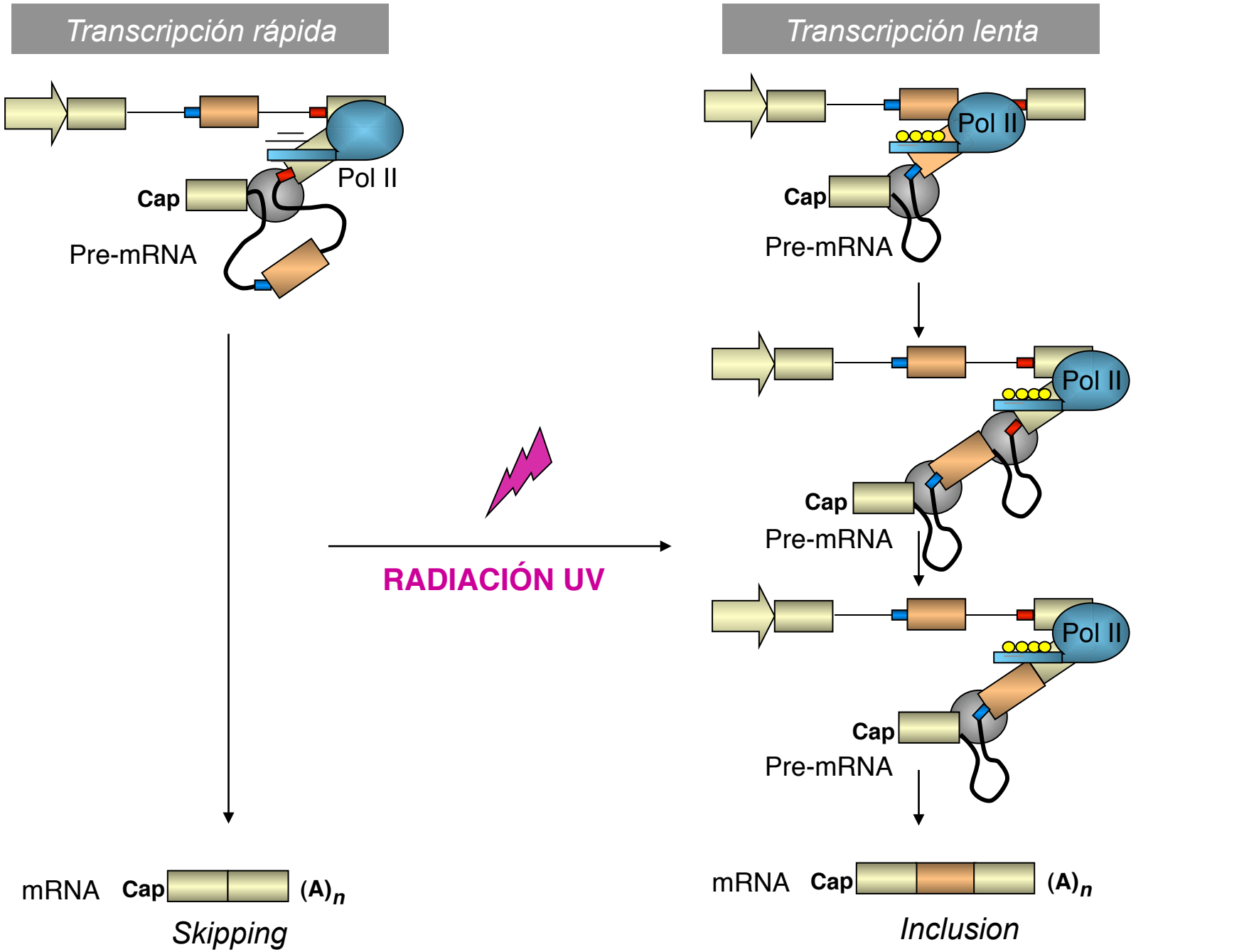



***Slow elongation/pauses***



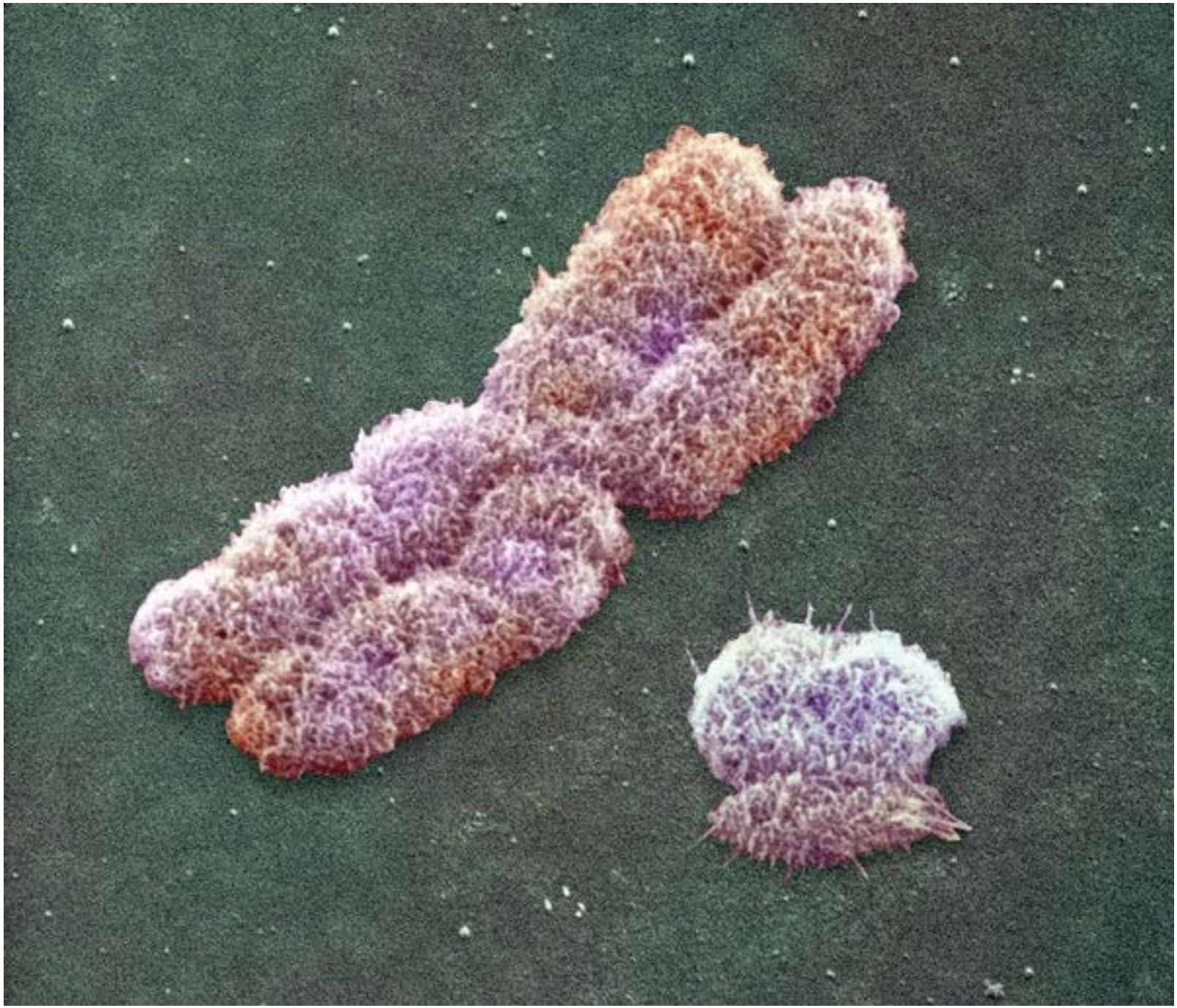

Dujardin et al., *Molecular Cell 2014*

*Radiación UV y splicing alternativo*




Muñoz et al., *Cell* 2009; Muñoz et al. *TiBS* 2010

*Cromatina y splicing alternativo*



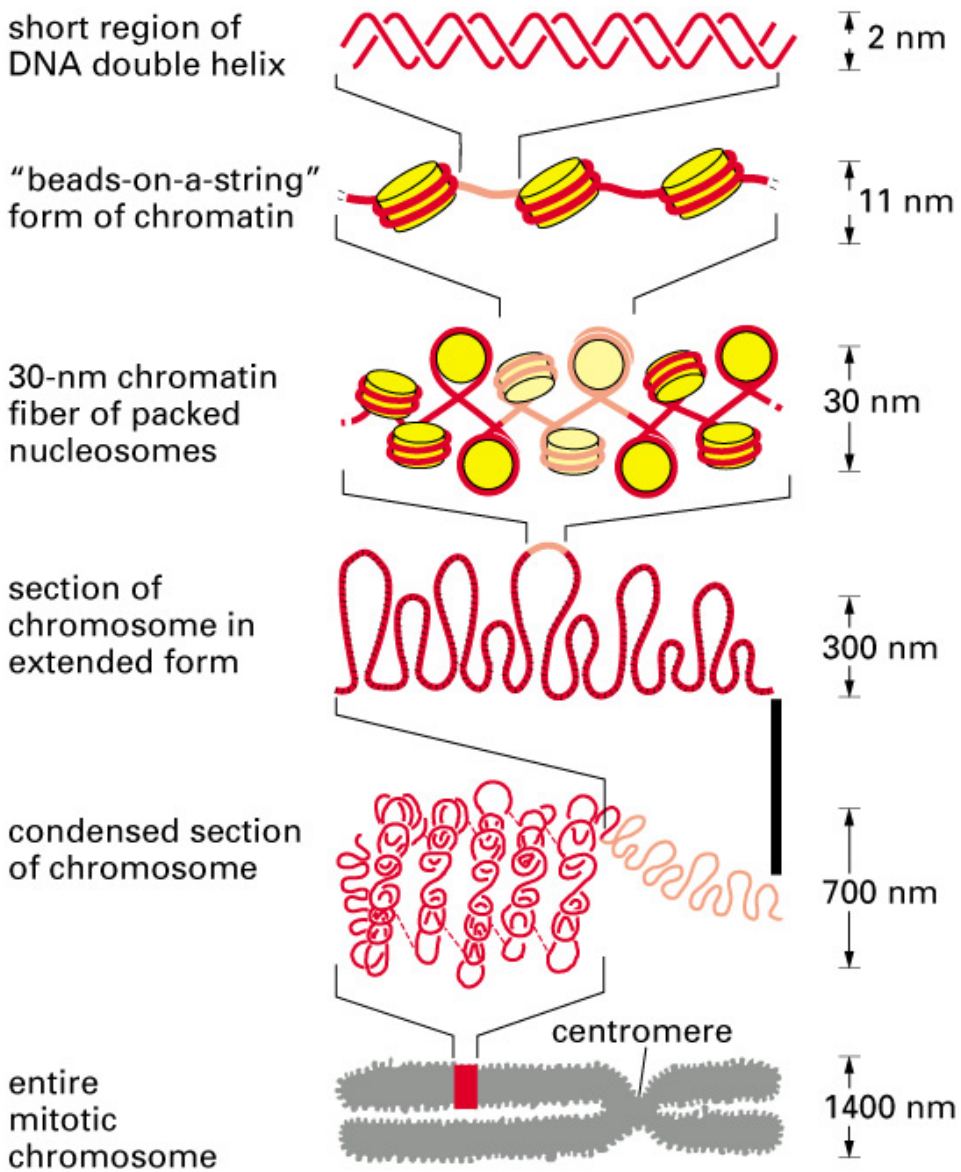



Figure 4–55. Molecular Biology of the Cell, 4th Edition.

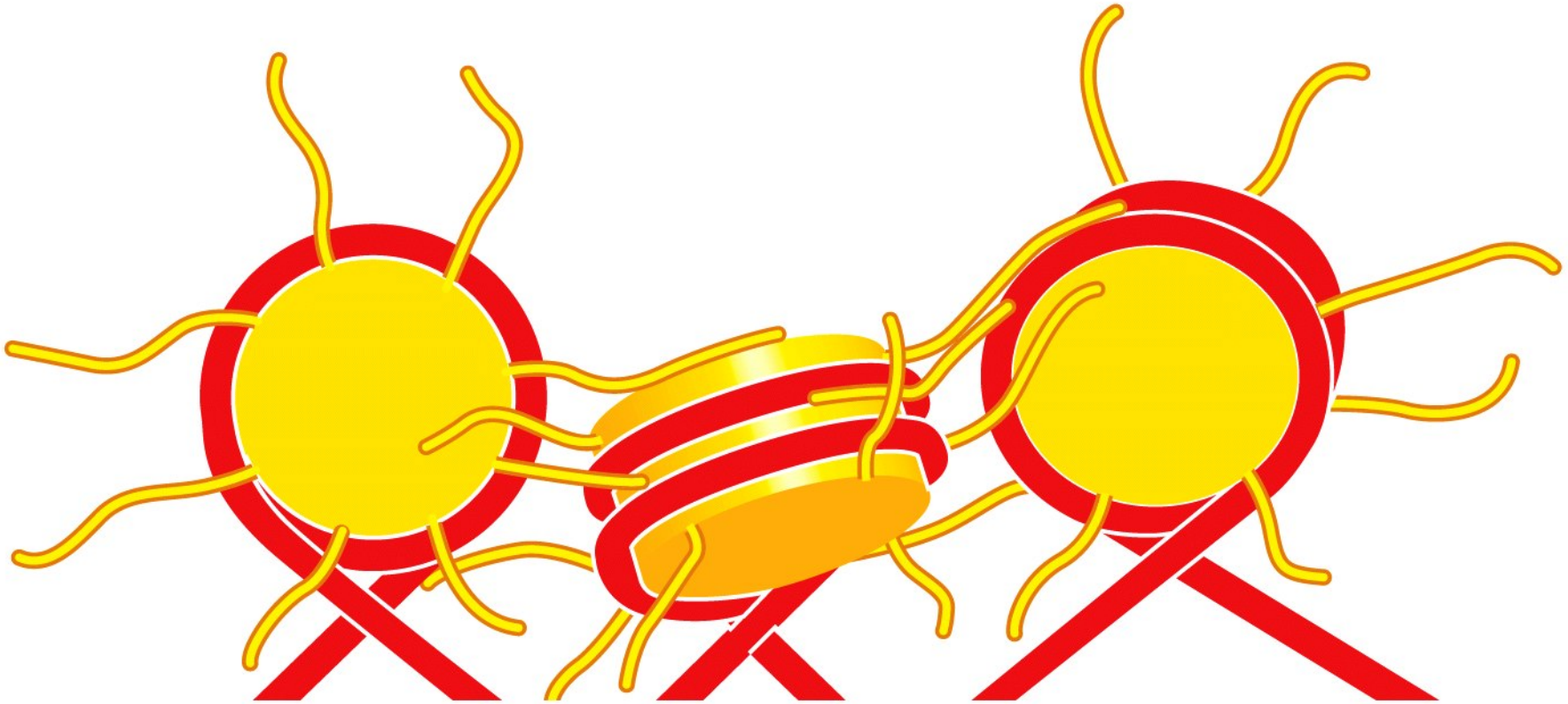
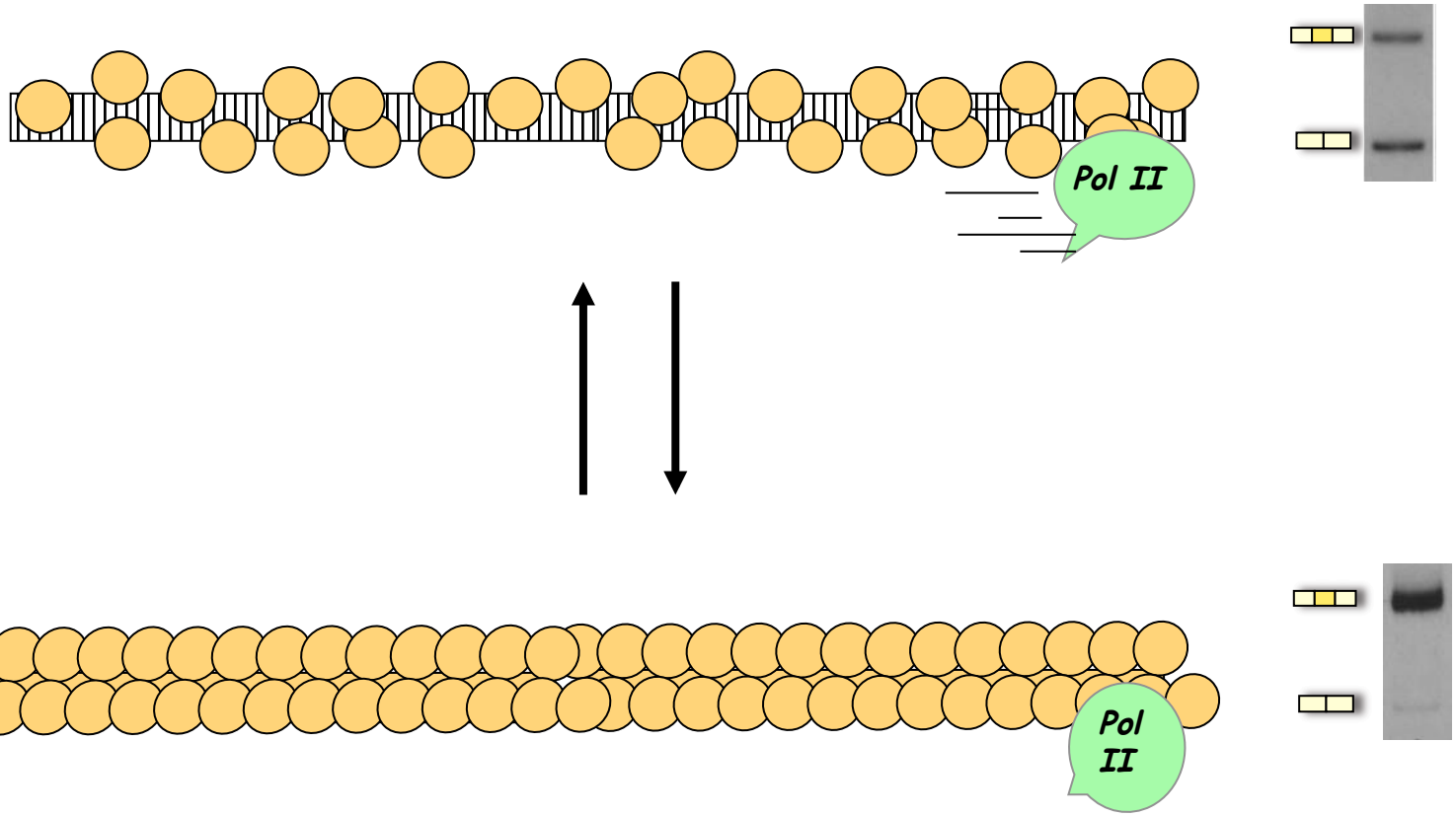
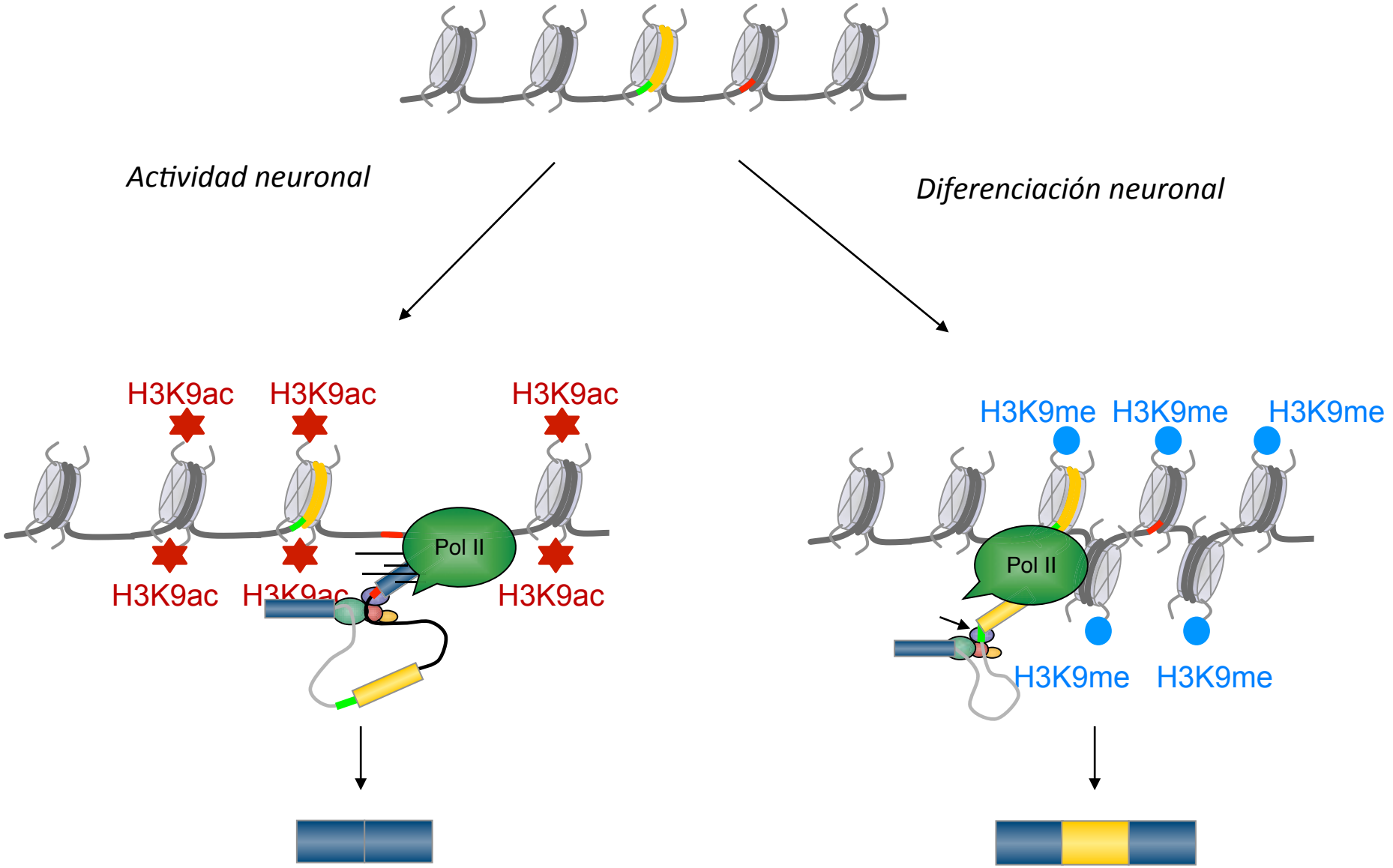


Figure 4-33b *Molecular Biology of the Cell* (© Garland Science 2008)



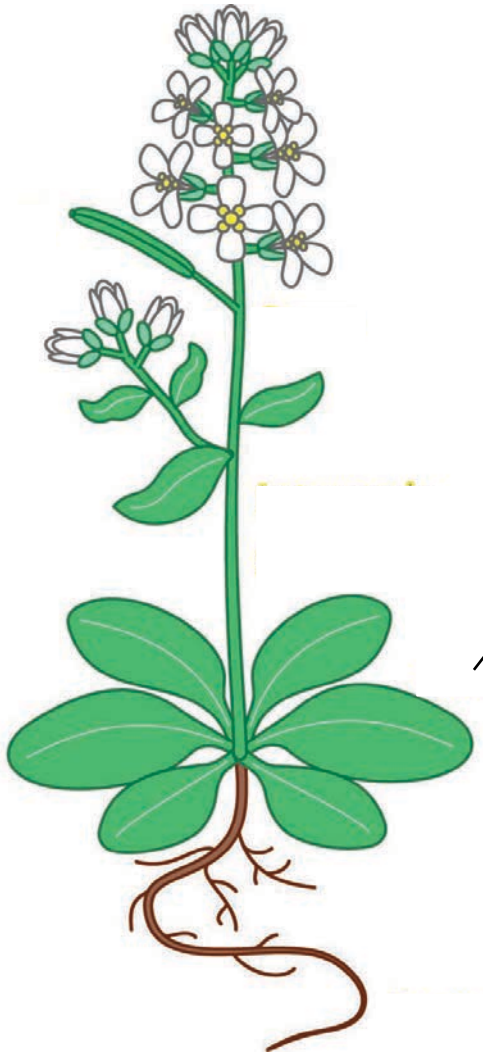

Kadener et al., *EMBO J.* 2001
Nogués et al., *J. Biol. Chem*. 2002

# *Cromatina alternativa, splicing alternativo*

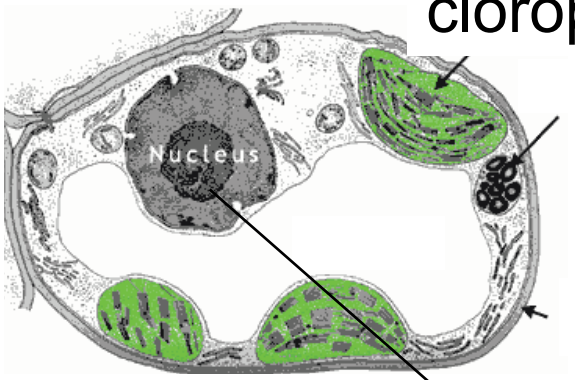



Schor et al., *PNAS 2009 y EMBO J. 2013*.

# *Splicing alternativo en plantas*



*Arabidospis thaliana*
(hierba de la familia de la mostaza)

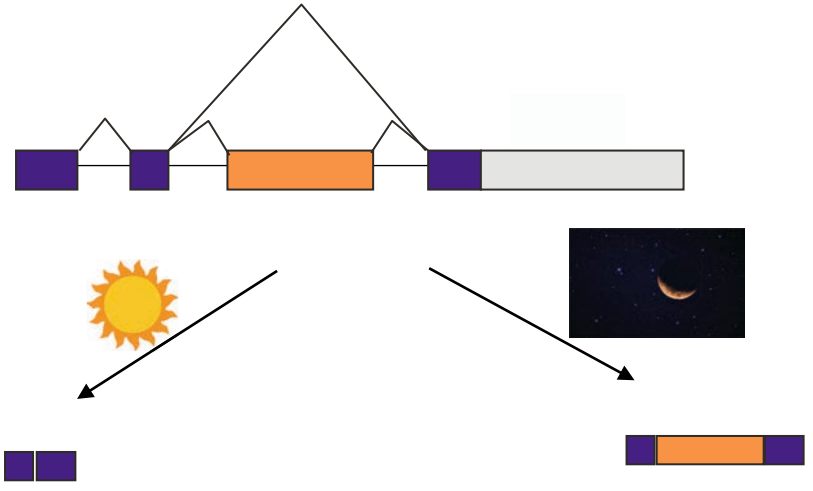


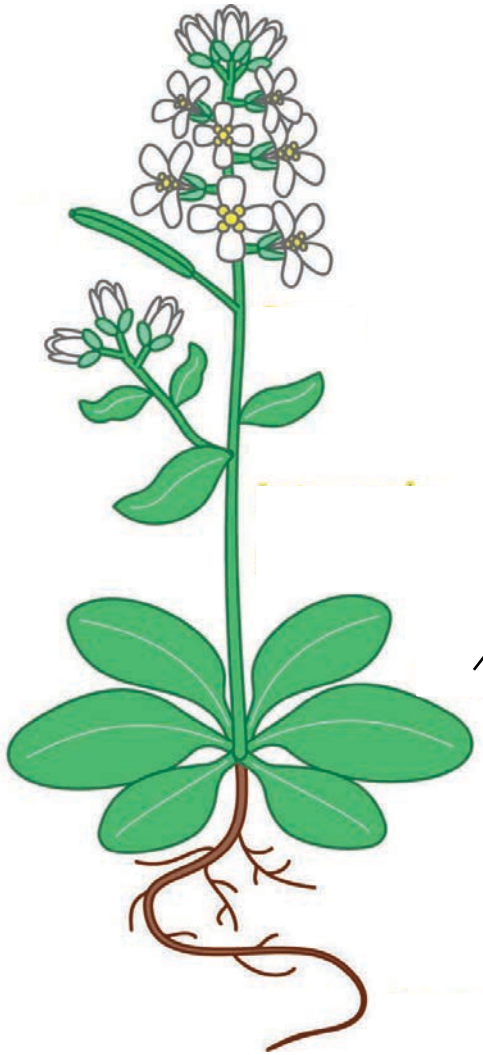

cloroplasto

célula vegetal

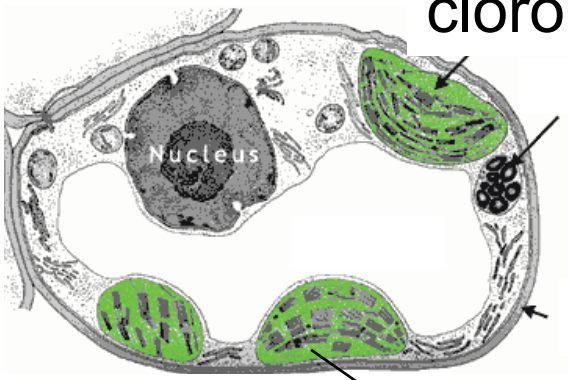
Núcleo
27.000 genes

"splicing" alternativo



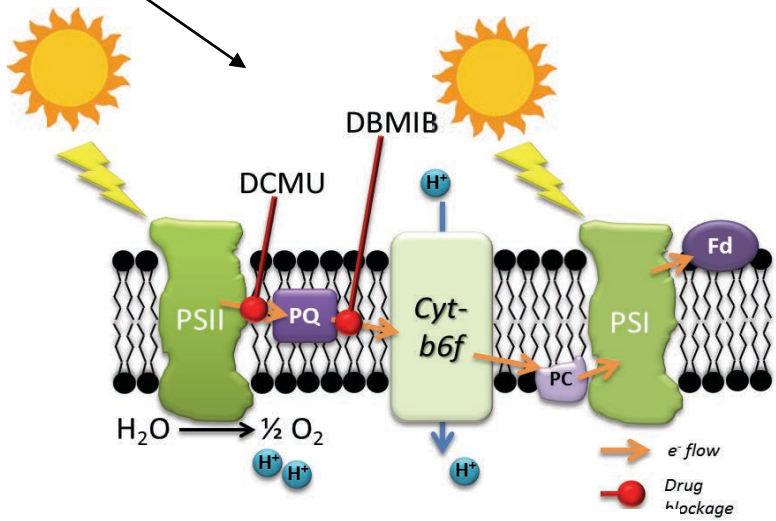


*Arabidospis thaliana*
(hierba de la familia de la mostaza)



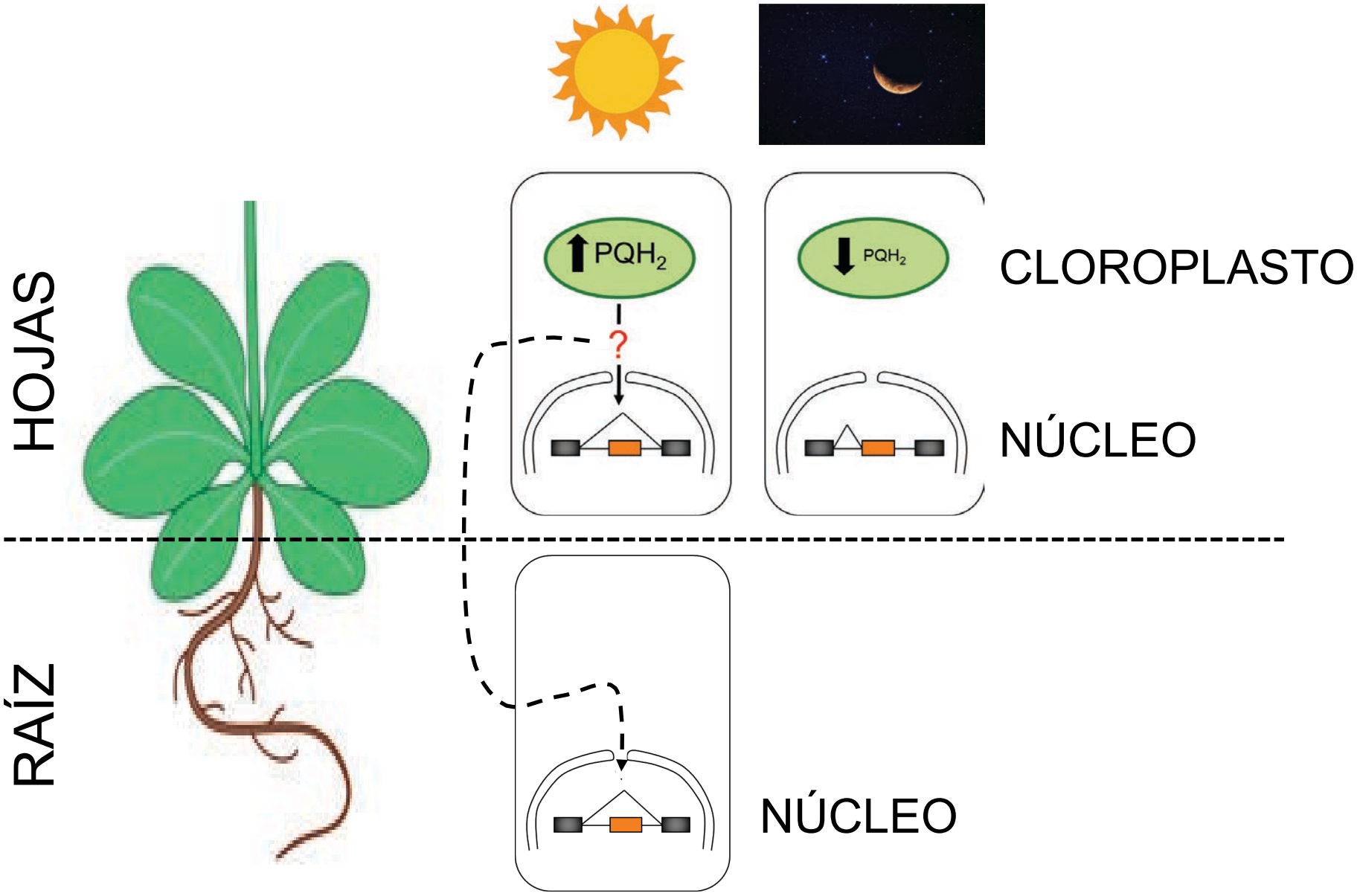

cloroplasto

célula vegetal




Fotosíntesis

CO2 + H2O ⟶ AZÚCARES (ALIMENTO)




Petrillo et al., *Science 2014*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Luciana Gómez Acuña
Micaela Godoy Herz
Nicolás Nieto Moreno
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Mariano Alló*
Gwendal Dujardin*
Ezequiel Petrillo*
Ignacio Schor*
Manuel de la Mata
Paula Cramer
Guadalupe Nogués
Sebastián Kadener
Demián Cazalla
Juan Pablo Fededa
Nicolás Rascovan
Soledad Pérez Santangelo
Anabella Srebrow

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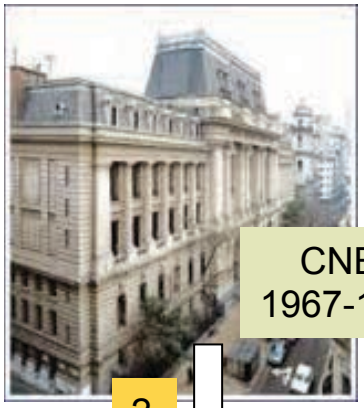
HHMI (USA)
EURASNET (EU)
ANPCyT (Argentina)
Universidad de Buenos Aires
CONICET (Argentina)

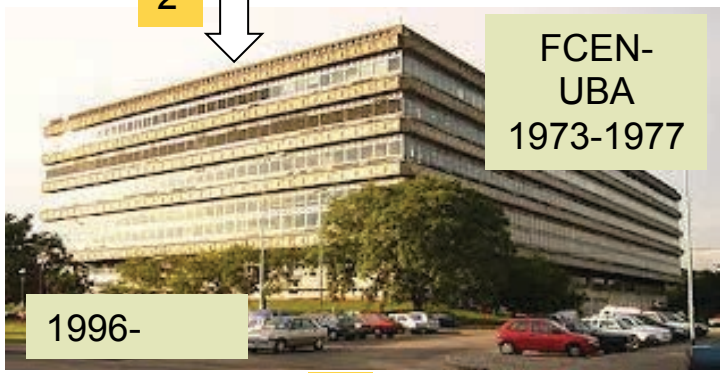
Escuela Manuel Solá 1960-1966

1



CNBA 1967-1972

2



FCEN-UBA 1973-1977

1996-

3

Campomar 1977-1981

INGEBI 1984-1996

8

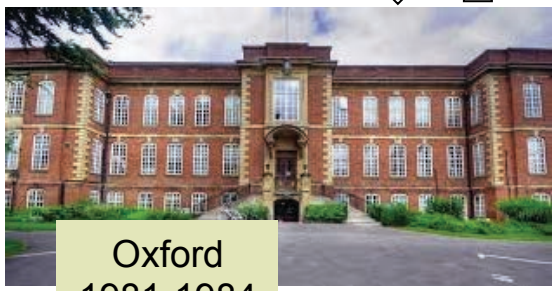
9

4

5

6

7



Oxford 1981-1984


París 1987-1988

Nuevo edificio IFIBYNE ?-

*Rosa Guaglianone*

*Secundario (1967-1972)*

*Héctor Torres*

*Doctorado (1977-1980)*

*Tito Baralle*

*Post-doc (1981-1984)*

*Etel*

Gracias!