

PERSISTENCE: Mechanisms underlying the central dogma

Announcements:

- Lab write-up due Thurs 5/17; Midterm back next week
- Please fill out house ombuds surveys this week

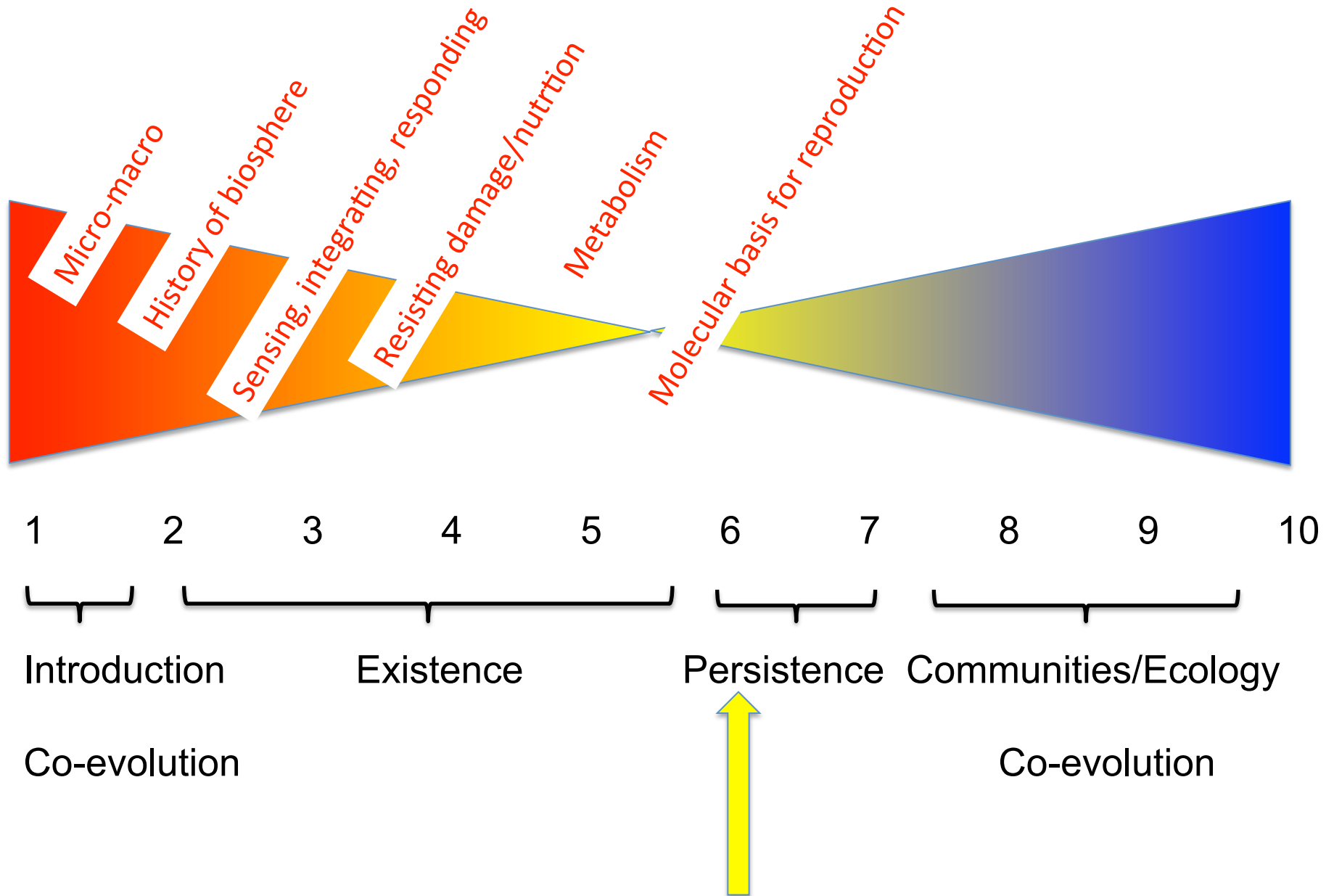
DKN

- Where are we in the course?
- What is the Central Dogma and why does it matter?

MMN

- How does the Central Dogma function in the Eukarya?
- What current research is challenging our views of this process?

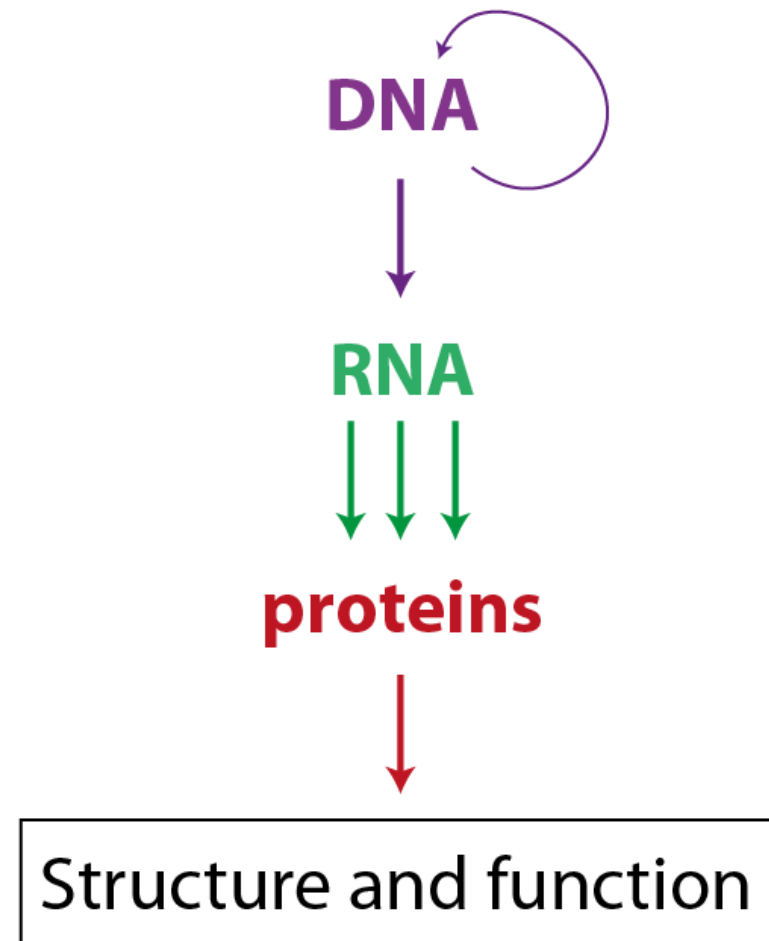
Where have we been, where are we, and where are we going?



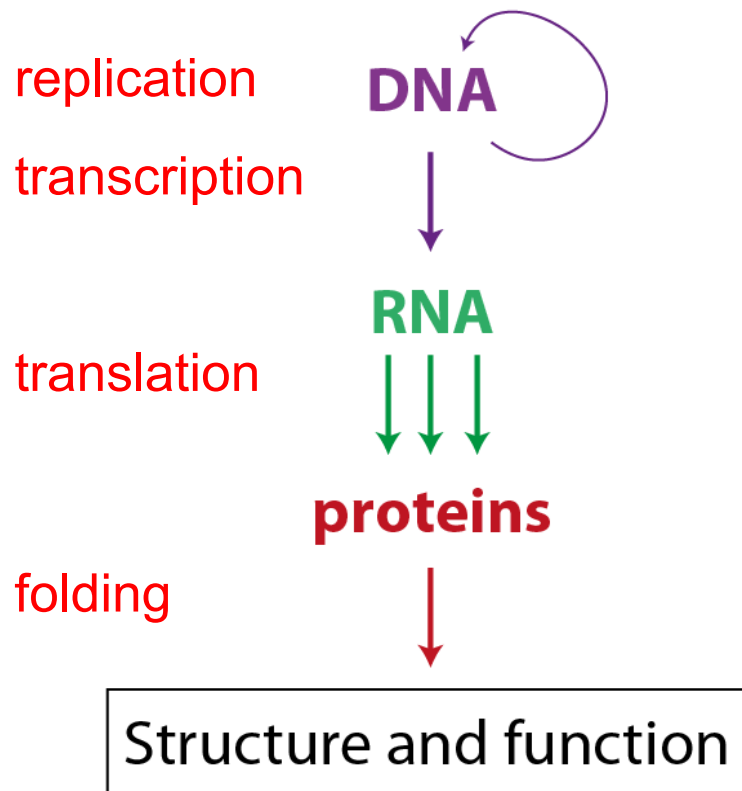
The “Central Dogma”

“This states that once ‘information’ has passed into protein it cannot get out again. In more detail, the transfer of information from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the precise determination of sequence, either of bases in the nucleic acid or of amino-acid residues in the protein.”

Francis Crick, On Protein Synthesis, 1958

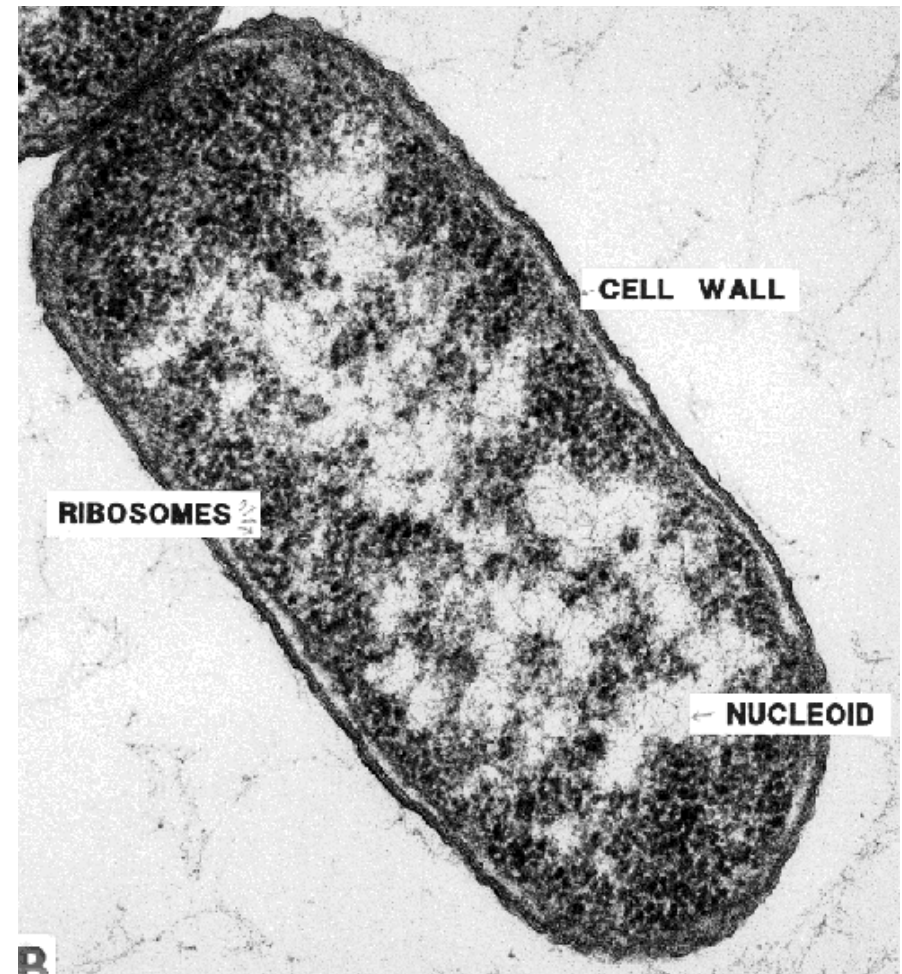


Let's think about how this works in the cellular context:



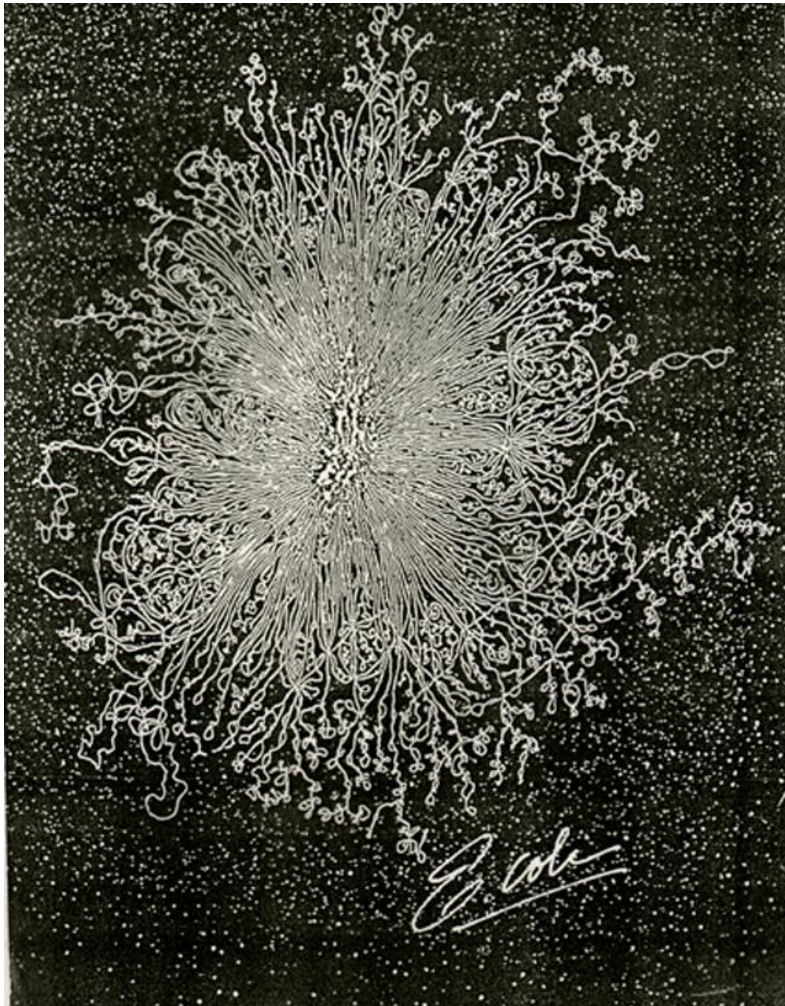
In bacteria:

- Replication, transcription & translation can occur simultaneously
- ½ energy in cell used to make new proteins



How is DNA packed within a bacterial cell? *Ultimate topology problem!*

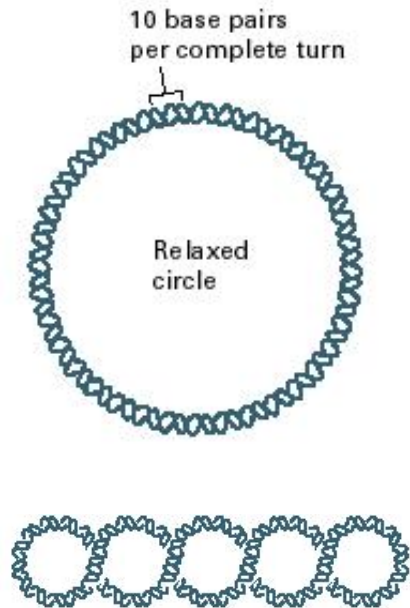
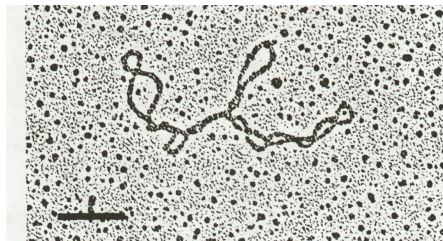
Supercoiled *E. coli* chromosomal DNA



Relaxed plasmid DNA



Supercoiled plasmid DNA



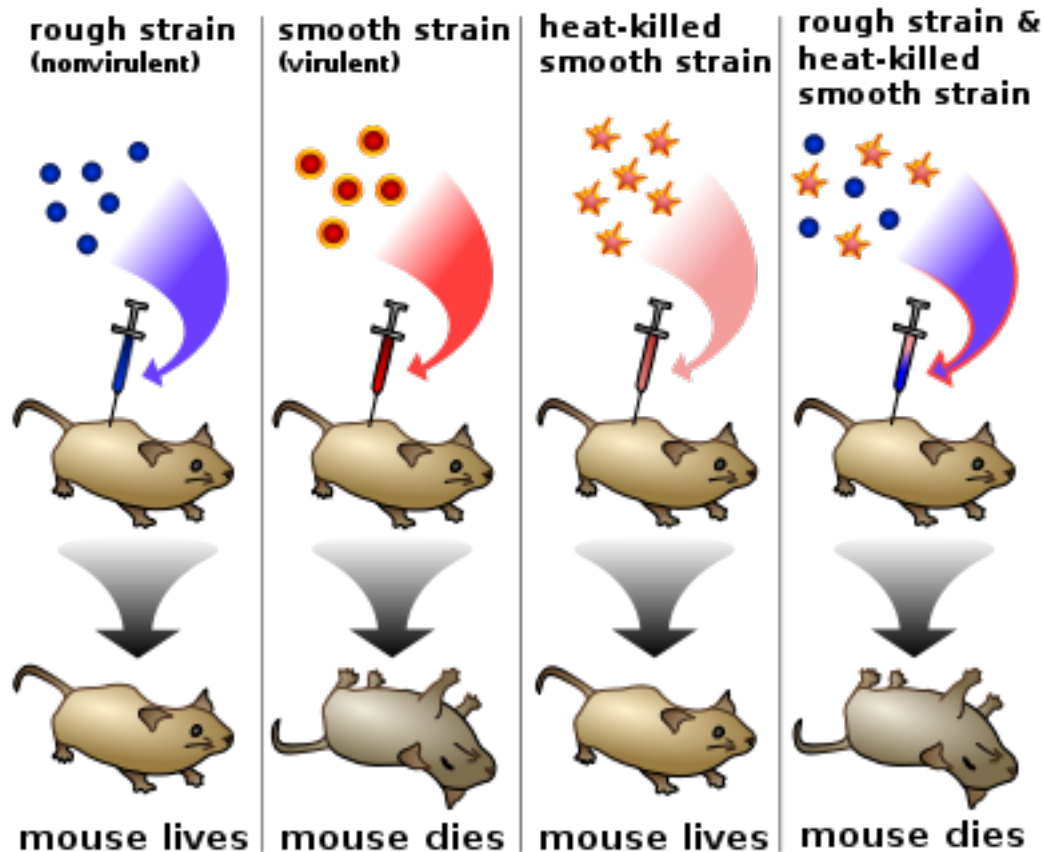
If stretched out the length of ~3 genes in relaxed double-helical conformation, ~long as the entire cell!

Microbial genomes ~ 3,000 genes
→ DNA compacted ~1,000X!

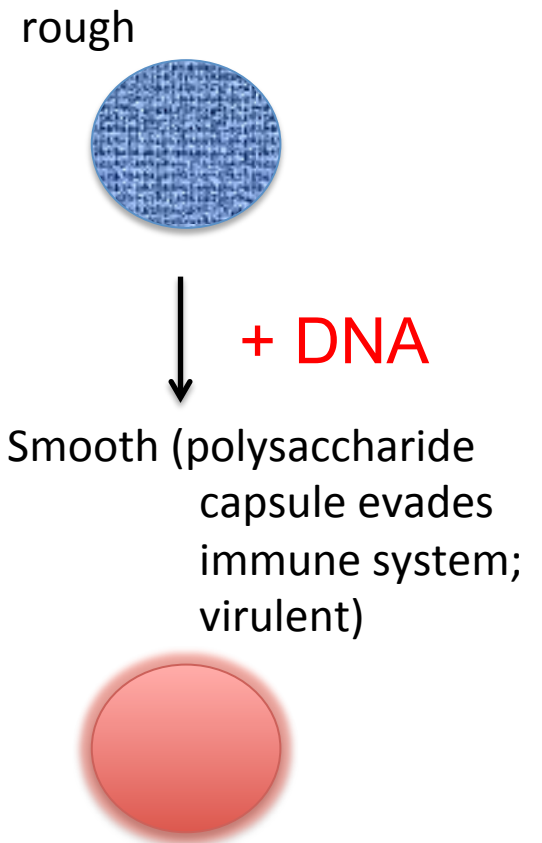
DNA is the ‘Transforming Principle’ (*i.e.* hereditary material of bacteria)
→ like “genes” in higher organisms

Griffith 1924

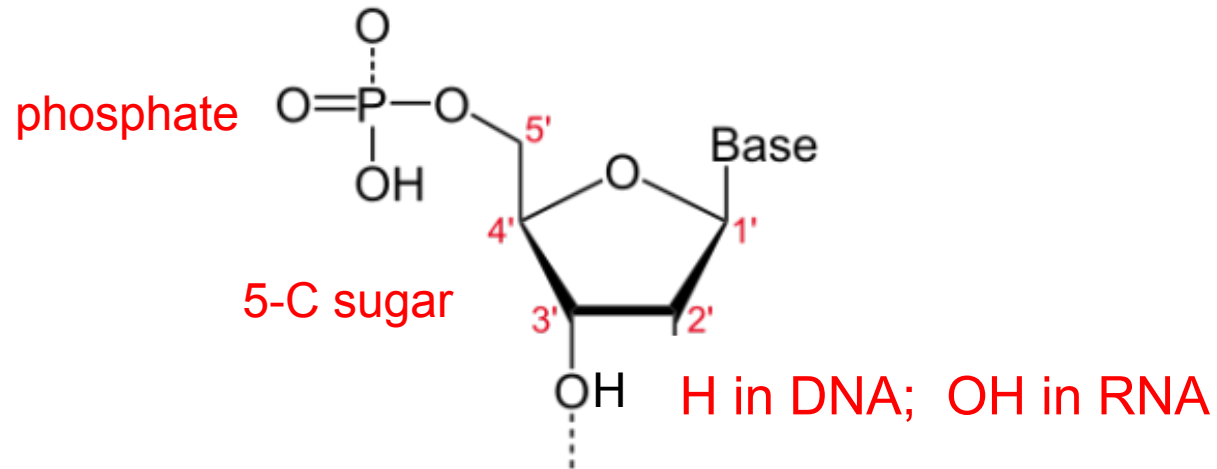
Avery-MacClod-McCarty experiment 1944



Streptococcus pneumoniae

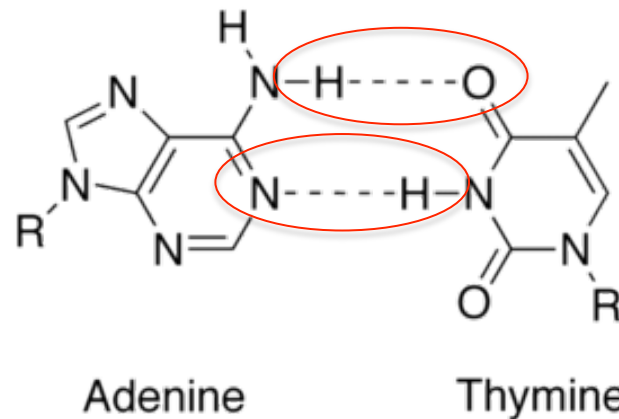
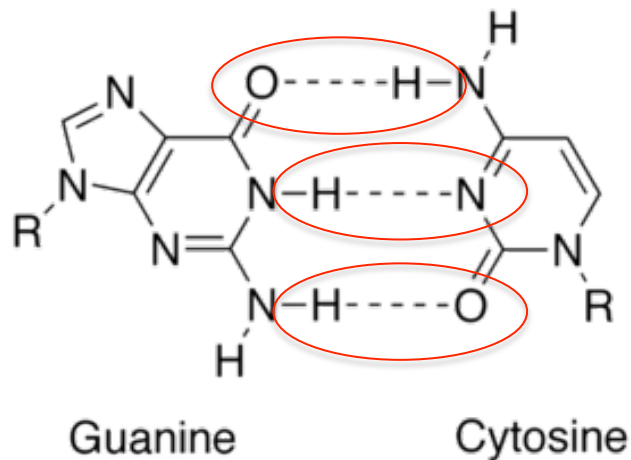


3 components of a nucleotide:



Bases: adenine (A), guanine (G), cytosine (C), thymine (T), uracil (U)
Purine Pyrimidine

Base pairing: G—C and A—T for DNA; G—C and A—U for RNA



H-bonds
↑GC ↑melting T





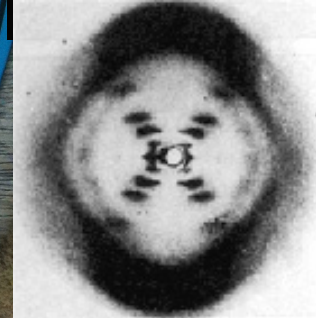
DNA Double Helix 1953

“The secret of life”

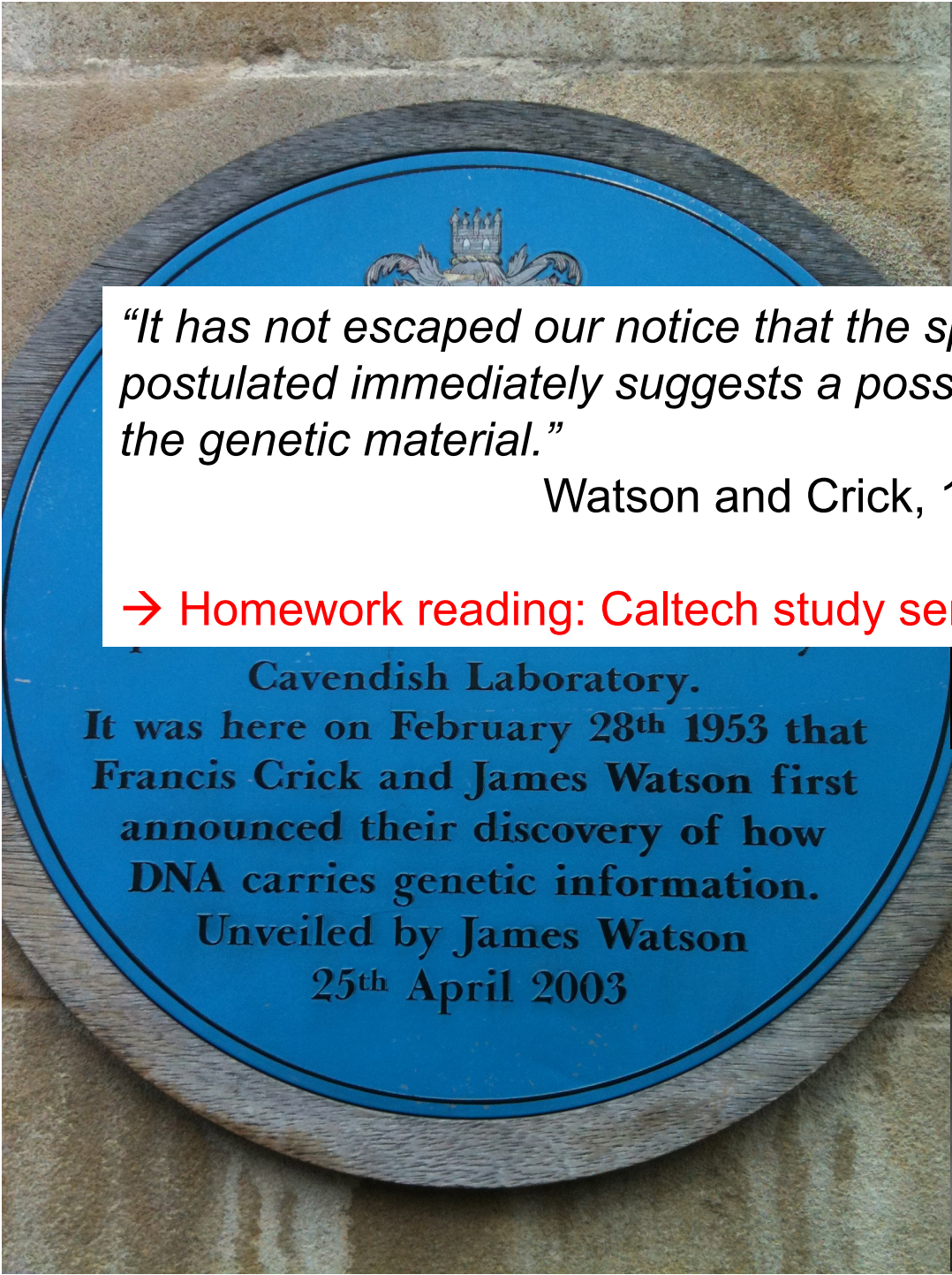
For decades the Eagle was the local
pub for scientists from the nearby
Cavendish Laboratory.

It was here on February 28th 1953 that
Francis Crick and James Watson first
announced their discovery of how
DNA carries genetic information.

Unveiled by James Watson
25th April 2003



Listen to Pauling's Audio

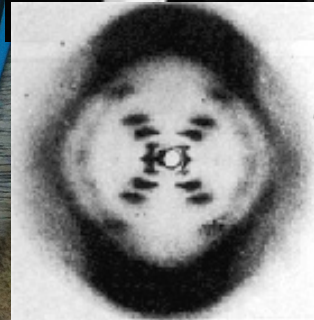


"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

Watson and Crick, 1953, *Nature* **171**: 737-738

→ Homework reading: Caltech study semi-conservative!!

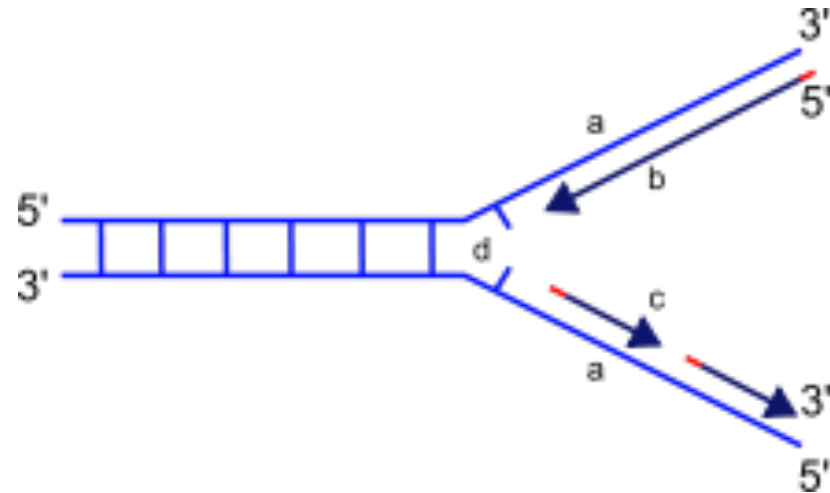
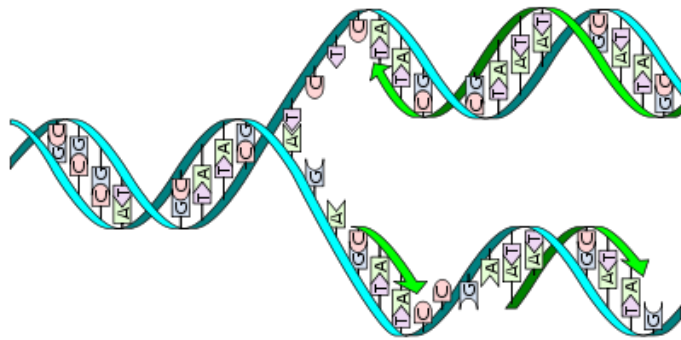
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Copying DNA is called **REPLICATION**



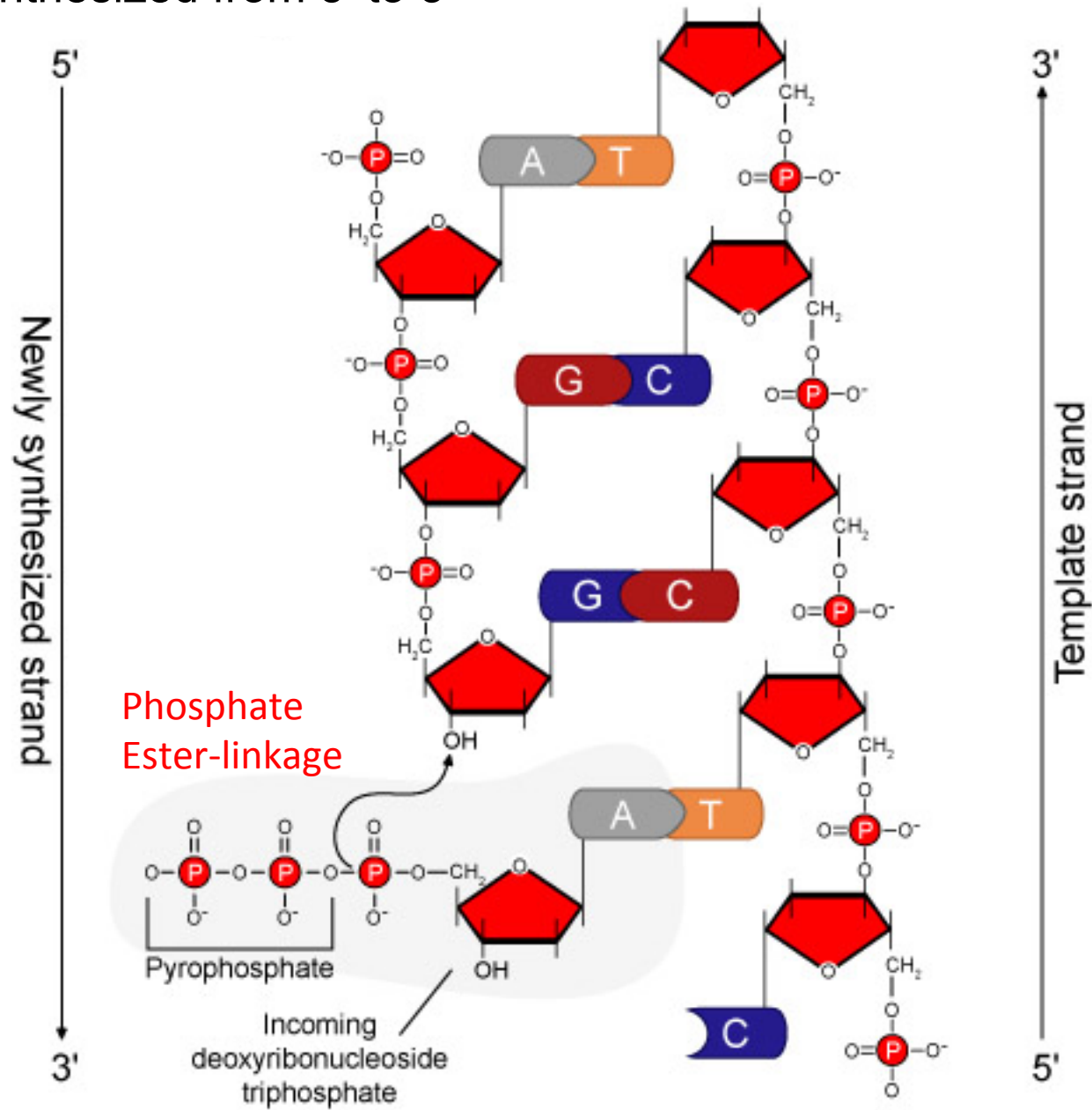
1.) Need to unwind double helix to copy each strand



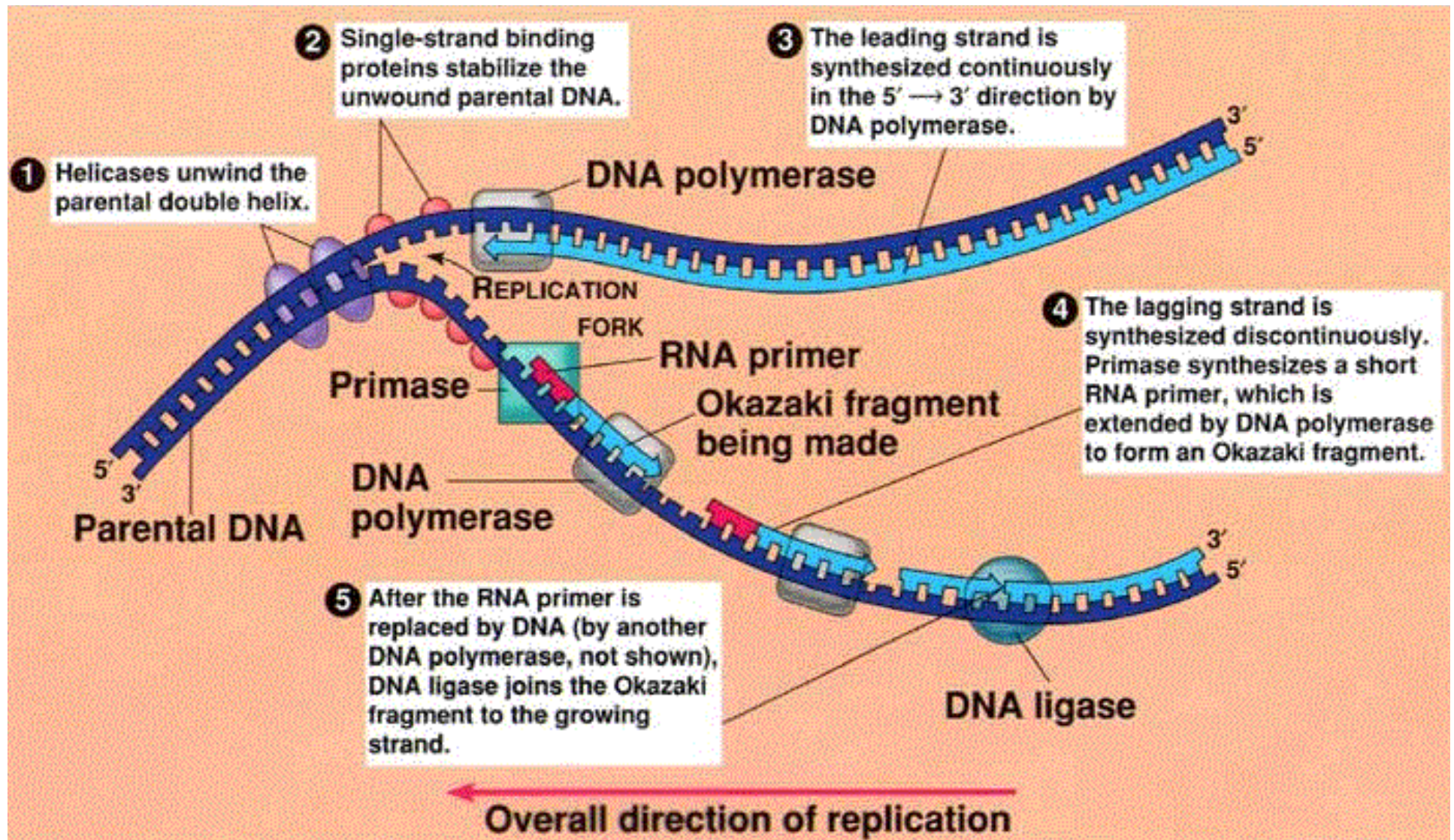
2.) DNA Polymerase is the enzyme that copies DNA

- Elongates from 5' to 3' end
- Proofreads from 3' to 5' end
- Different DNA polymerases have different fidelity!
- Error rate (wrong nucleotide inserted): 10^{-7} to 10^{-8}

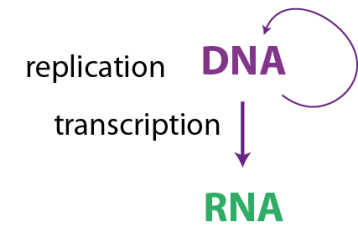
DNA is synthesized from 5' to 3'



Schematic of DNA replication



Converting DNA to RNA is called **TRANSCRIPTION**

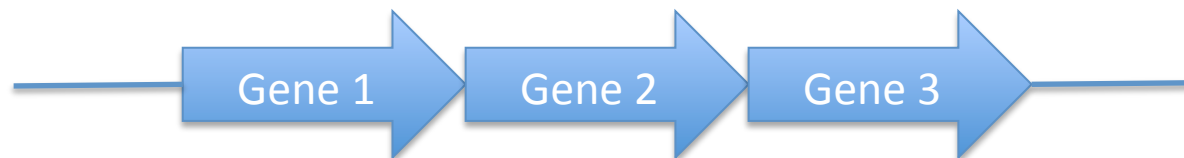


RNA polymerase makes messenger RNA (mRNA)
-message can encode: protein, tRNA, rRNA,
non-coding RNA

DRAW CARTOON: 5 subunits and a single regulatory subunit known as sigma (σ). Different sigma factors help RNA polymerase recognize DNA binding sites (control transcription of a unique set of genes, along with other transcription factors). Only 1 strand (template strand) DNA read from 3' to 5'; creates RNA from 5' to 3' ***Transcription factors: negative regulation: repressors prevent RNAP binding; positive regulation: activators facilitate RNAP binding***

-35.....-10.....Transcriptional start.....stop.start.....stop.start.....stop

Operon structure in bacteria (*average 3 genes, functionally related*)



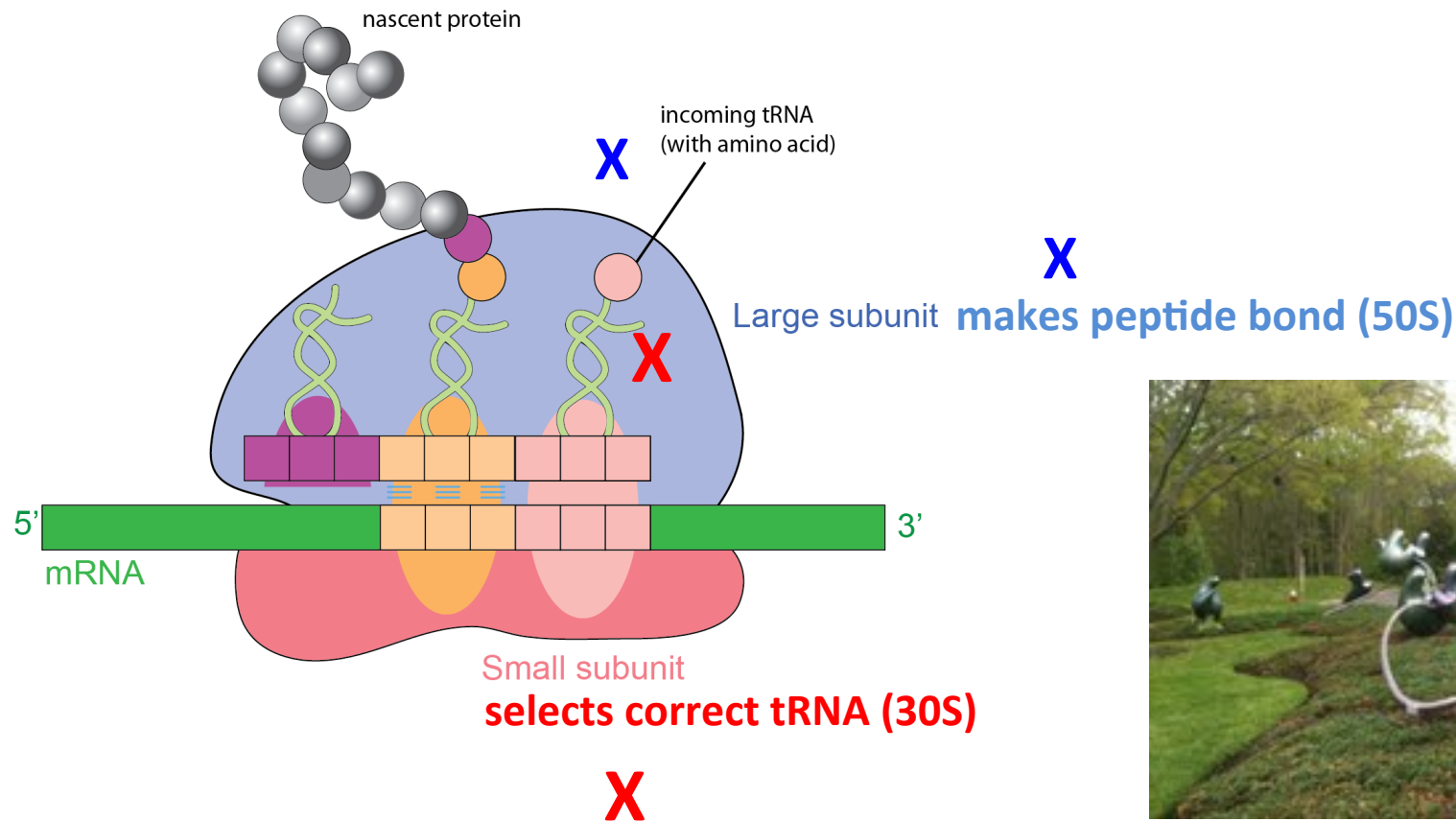
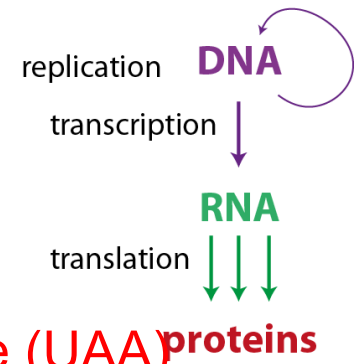
Converting RNA to protein is called **TRANSLATION**

Shine-Dalgarno: recruits ribosome to mRNA

Triplet code: 1 tRNA (3 bases) per amino acid

Start codon (AUG),

Stop codon ('nonsense'): amber (UAG), opal (UGA), ochre (UAA)





Ribosome Structure Nobel Prize Chemistry 2009

Ada Yonath, Tom Steitz, Venki Ramakrishnan

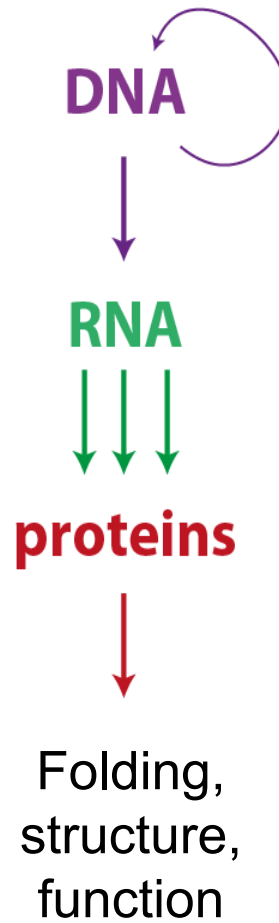
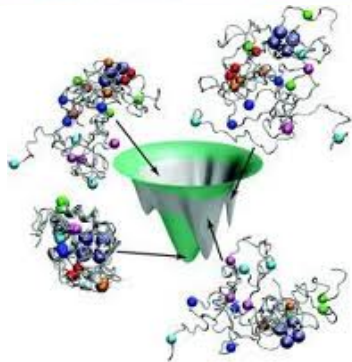
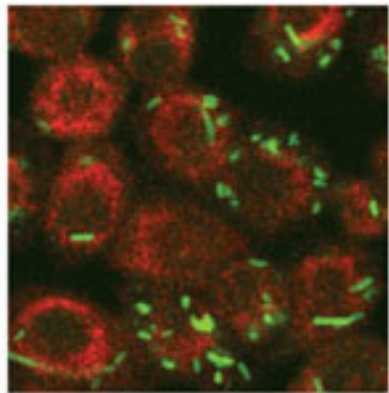
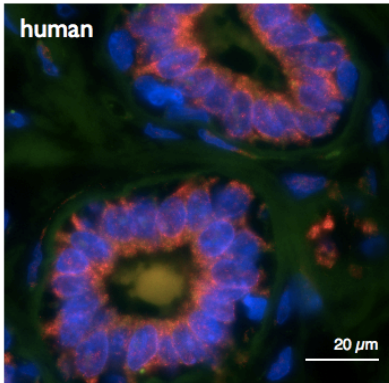


Prof. Clemons
(30S subunit)

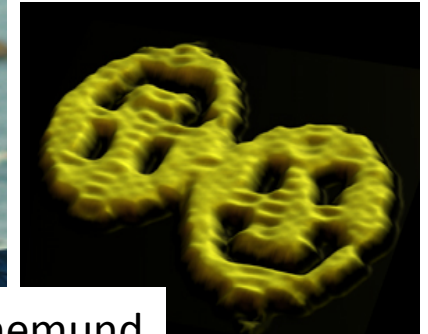


Movie of Decoding
(mRNA-tRNA-peptide bonds)

Caltech research in divisions outside of Biology applying/probing aspects of the Central Dogma



Rothemund



Clemons

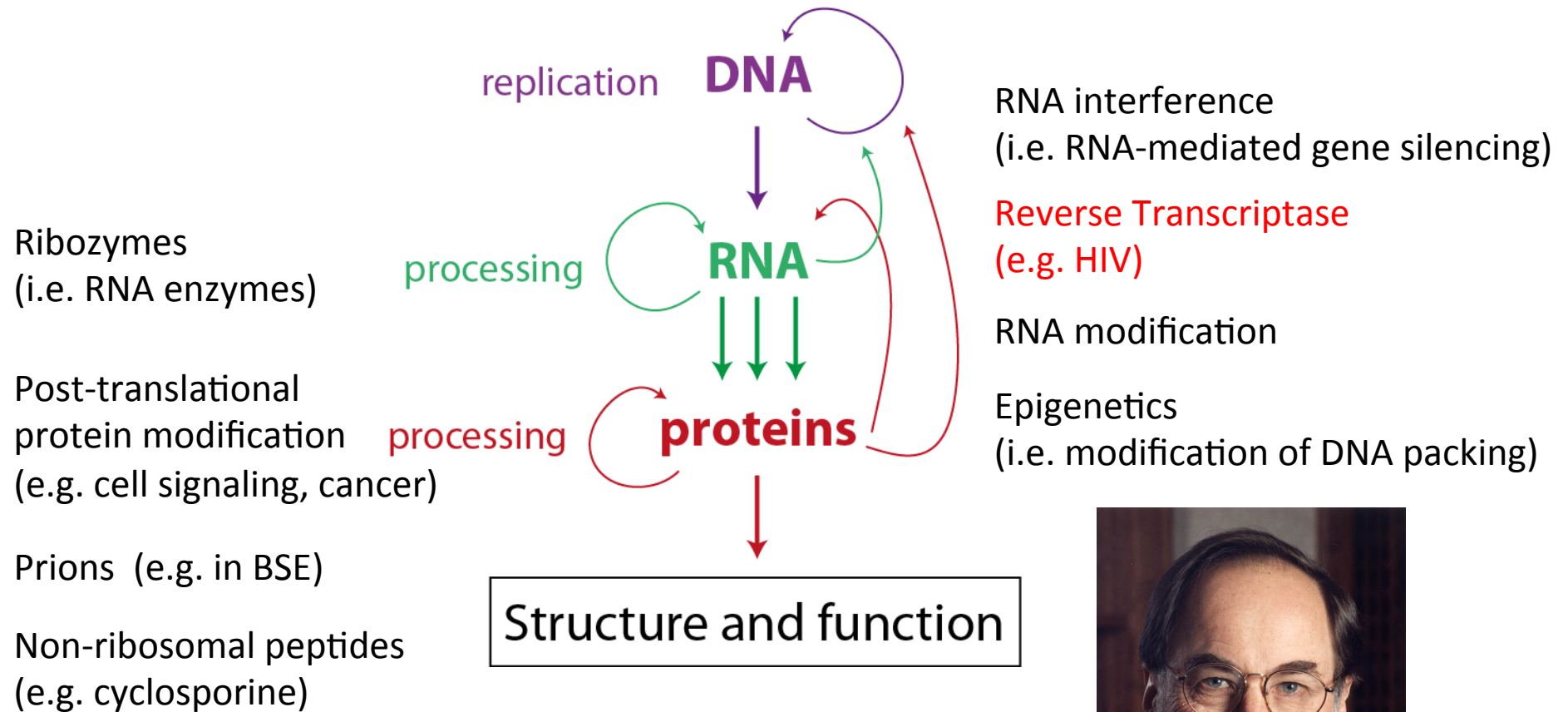


Shan



Mayo

Many interesting processes occur beyond the central dogma



DKN - SUMMARY

- Where are we in the course?

Exploring mechanisms of persistence

- What is the central dogma and why does it matter?
 - molecular rules governing flow of information in cells
 - duplication of genetic code, transcription, translation
 - provides basis for rational drug design
 - synthetic biology (lecture reading assignment)