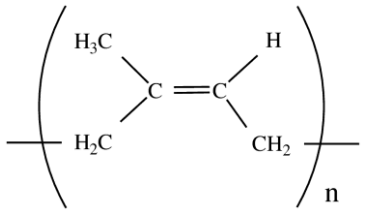
Special Topic II:
Synthesis and Reactions of Biopolymers

16:160:509 – Polymer Chemistry

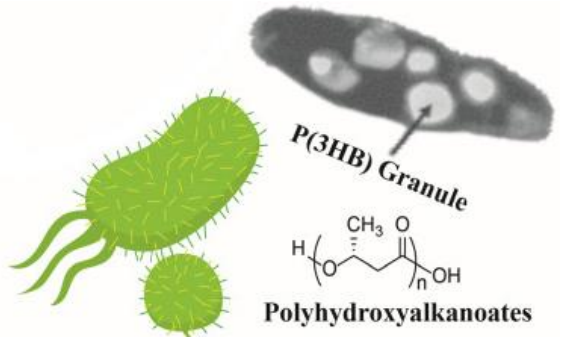
Lecture 21

RUTGERS
School of Arts and Sciences
DEPARTMENT OF CHEMISTRY
AND CHEMICAL BIOLOGY

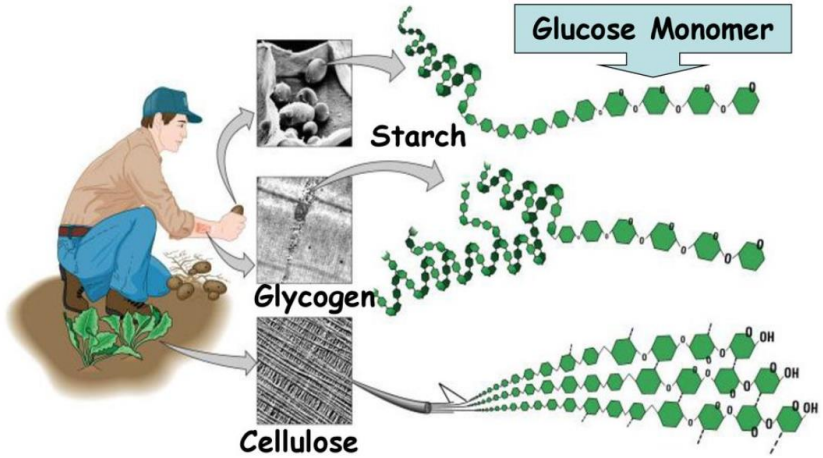
Biopolymers



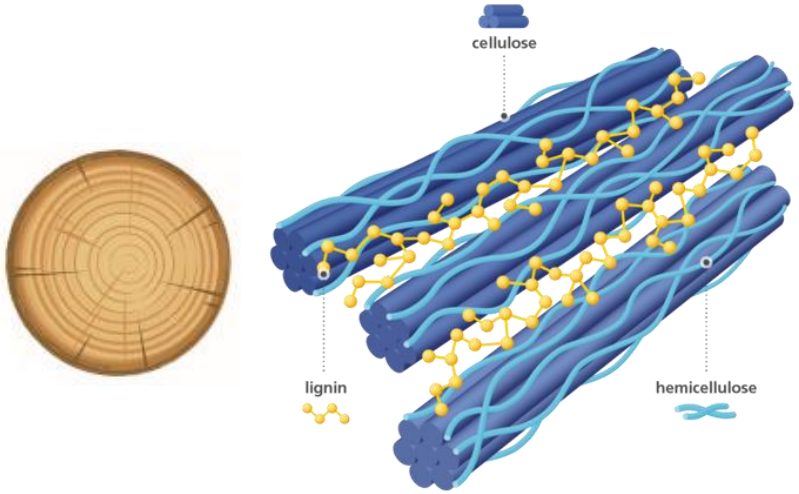
Natural rubber



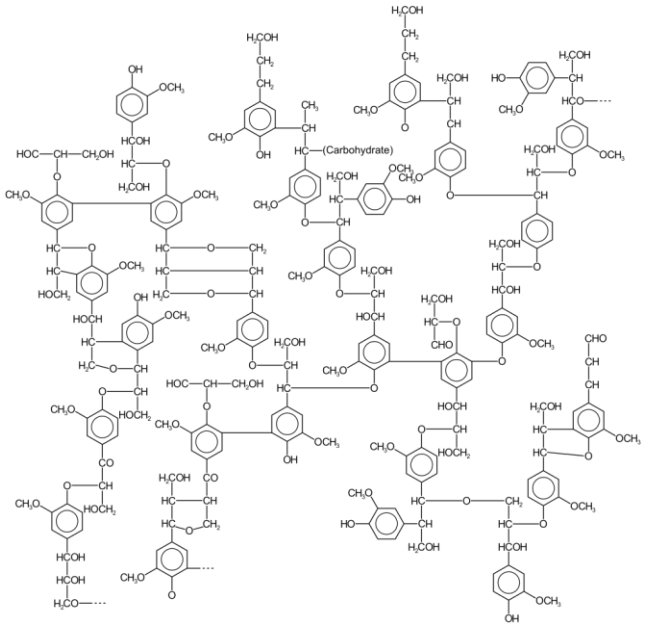
Polyhydroxybutyrate

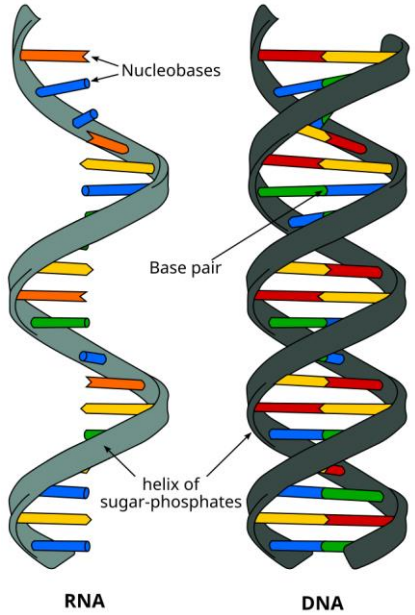


Polysaccharides

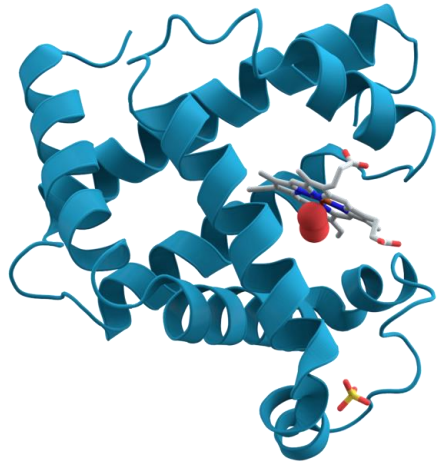


Lignin



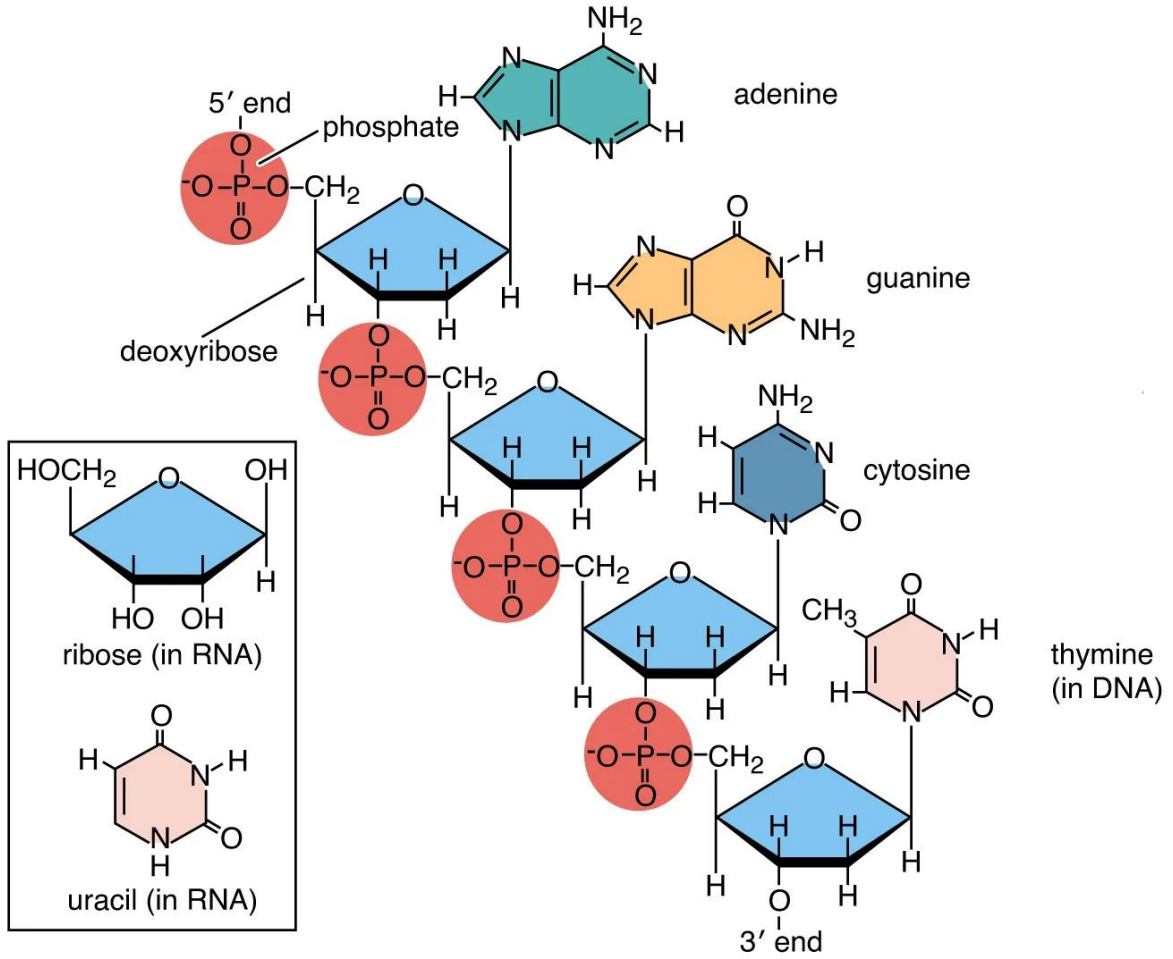


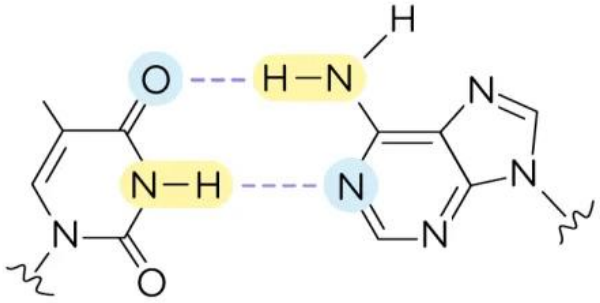
Nucleic acids



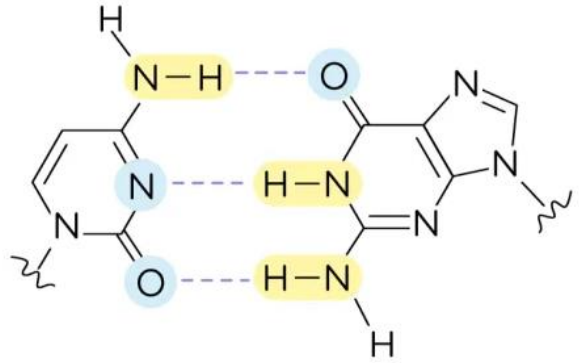
Proteins

Nucleic Acids



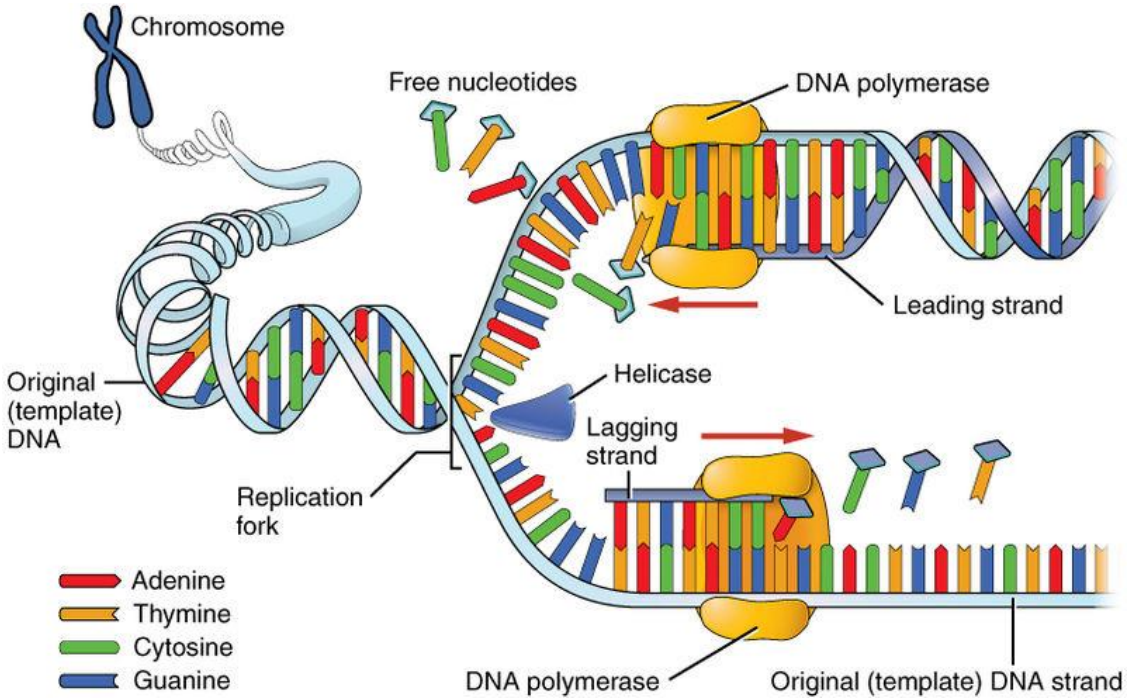


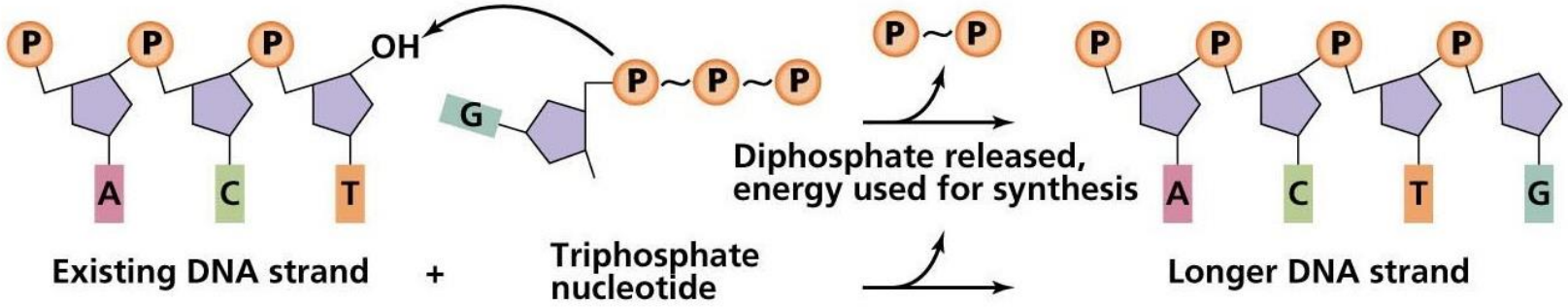
T : A base pair

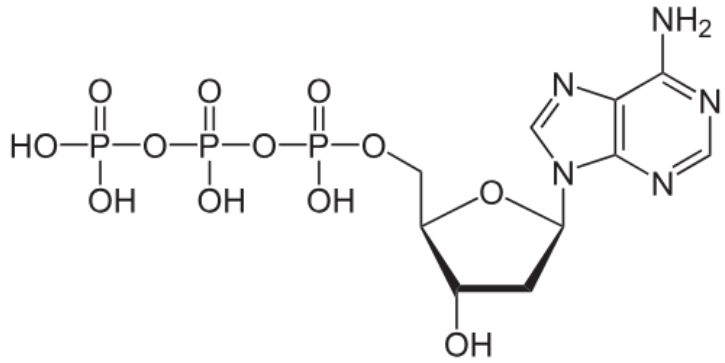


C : G base pair

Biological Synthesis of DNA (DNA Replication)

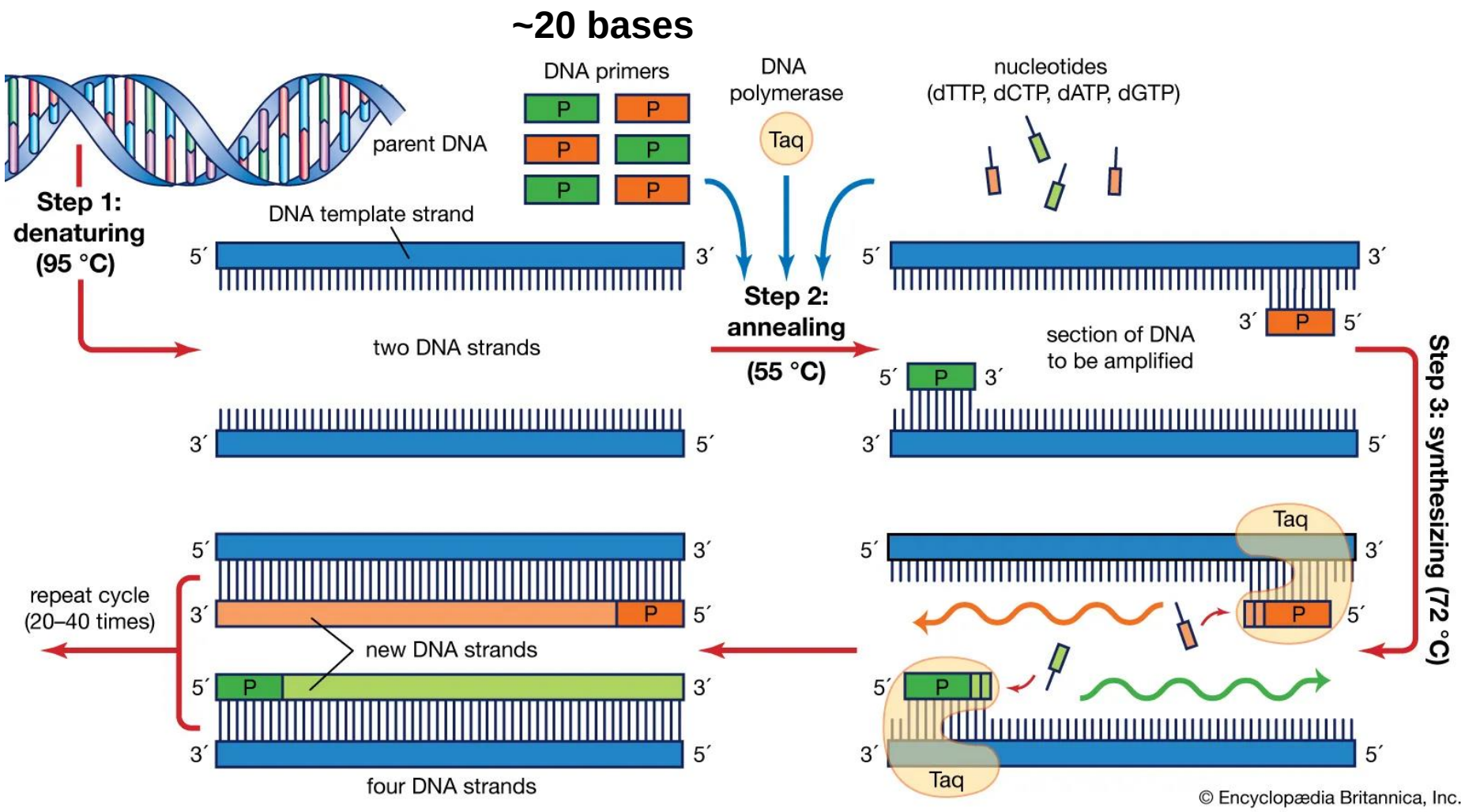


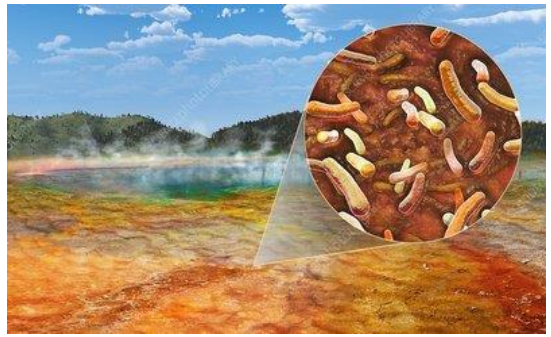




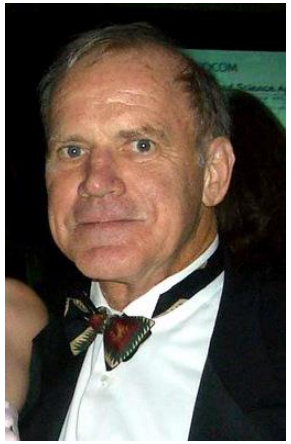
dATP

Polymerase Chain Reaction (PCR)



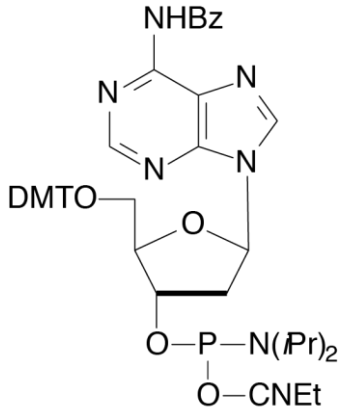


***Taq* polymerase**:
thermostable (75–80 °C)
DNA polymerase

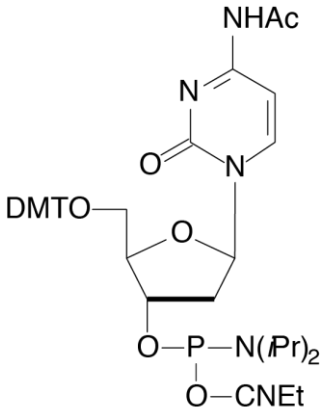


Invented by Kary Mullis in 1983
1993 Nobel Prize in Chemistry

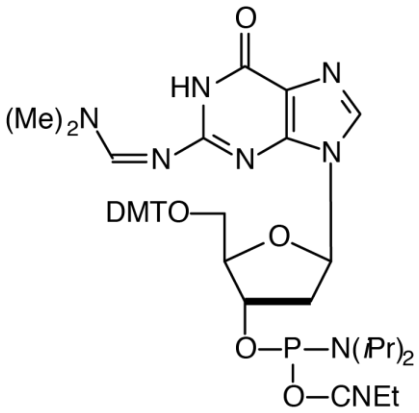
Solid-Phase DNA Synthesis



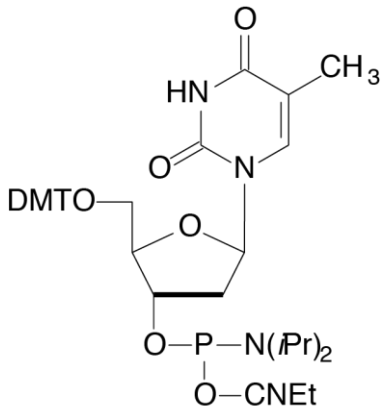
A



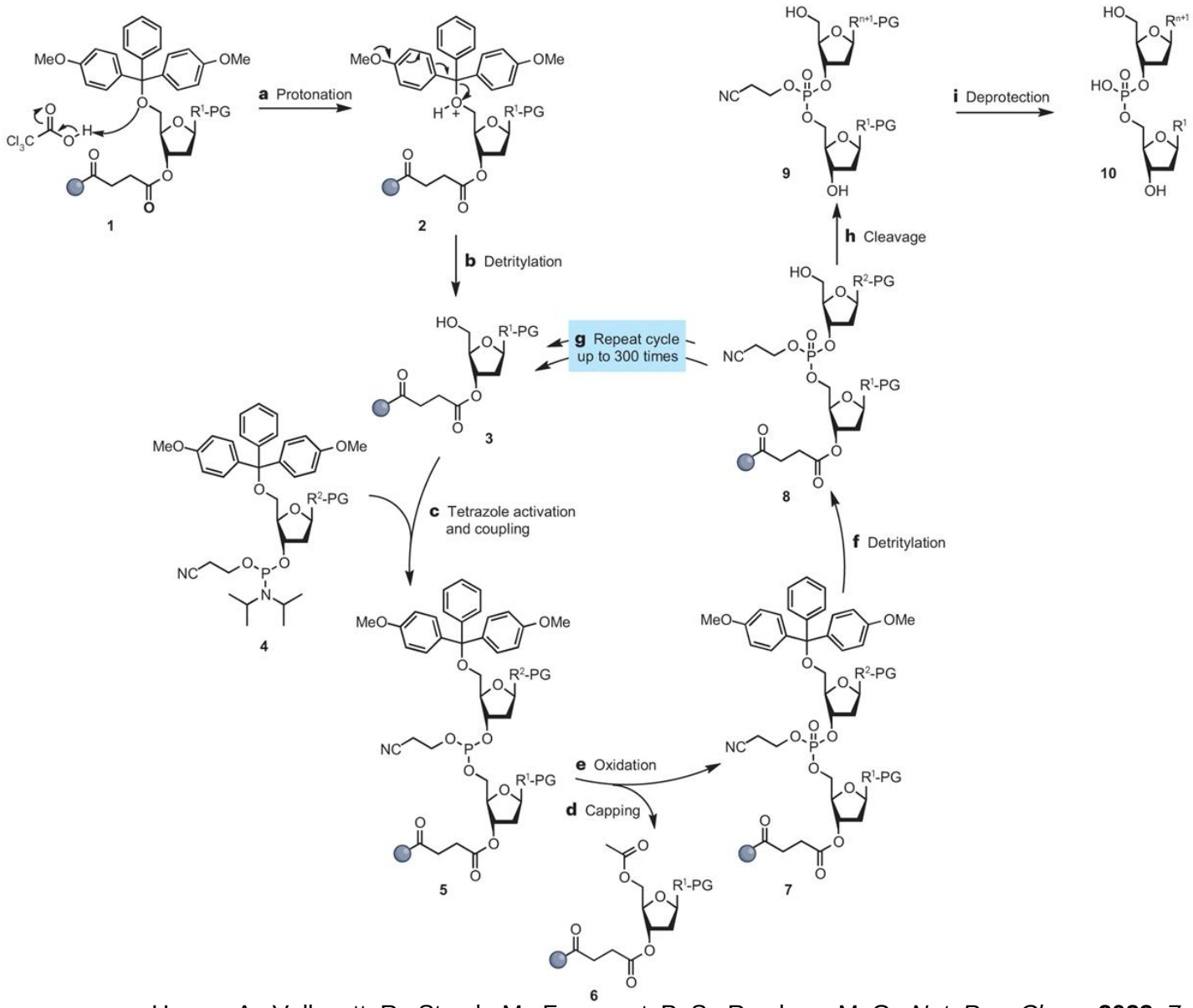
C



G

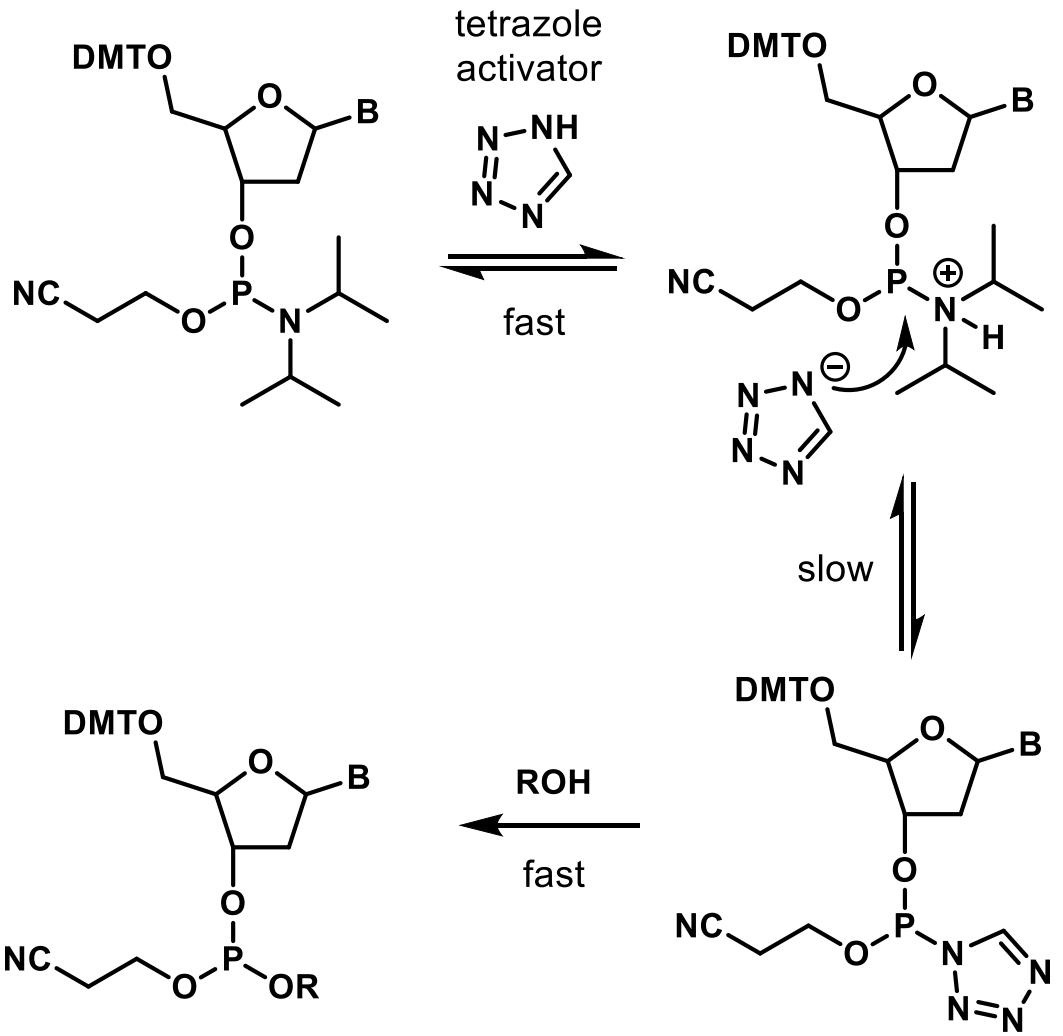


T

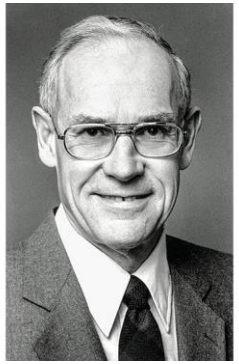


Hoose, A.; Vellacott, R.; Storch, M.; Freemont, P. S.; Ryadnov, M. G., *Nat. Rev. Chem.* **2023,** *7*, 144-161.

Solid-Phase DNA Synthesis



Phosphoramidite: stable precursor activated by tetrazole



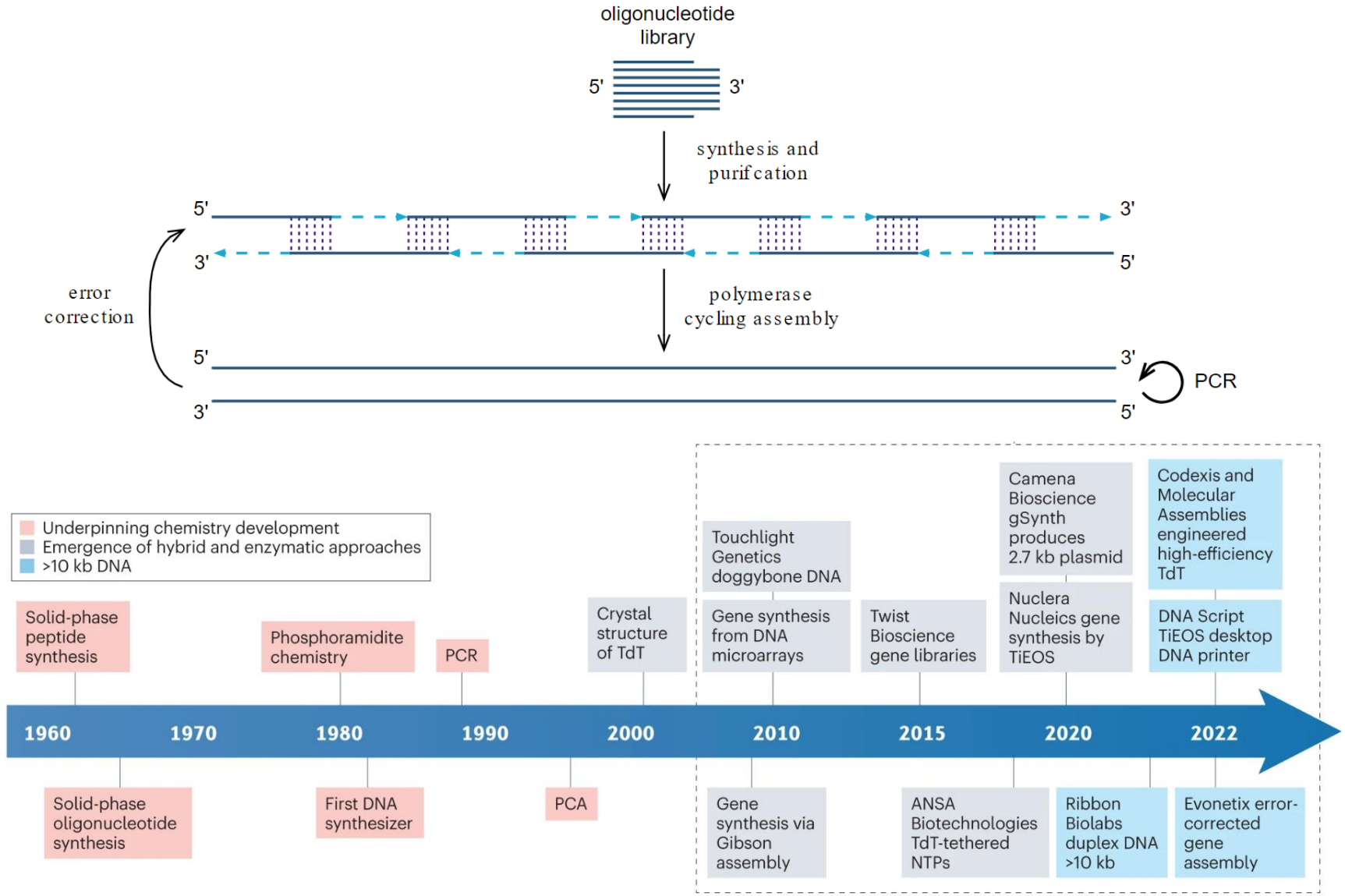
Robert Letsinger

Marvin Caruthers

Commercial DNA synthesizer

Beaucage, S. L.; Caruthers, M. H., *Tetrahedron Lett.* **1981,** *22*, 1859-1862.

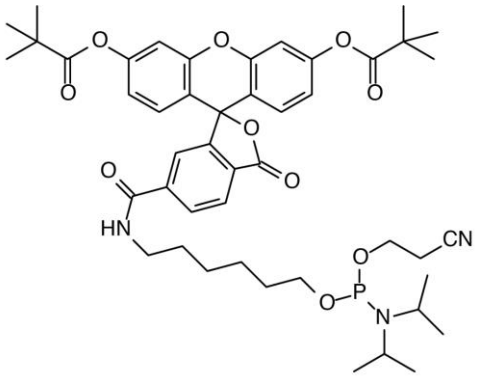
Assembly of Gene Block from Synthetic DNA Fragments



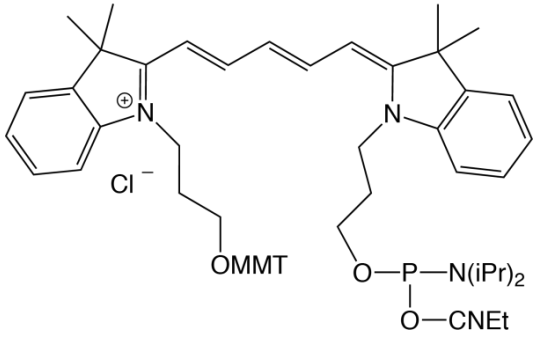
Hoose, A.; Vellacott, R.; Storch, M.; Freemont, P. S.; Ryadnov, M. G., *Nat. Rev. Chem.* **2023,** *7*, 144-161.

Applications of Synthetic Oligonucleotides

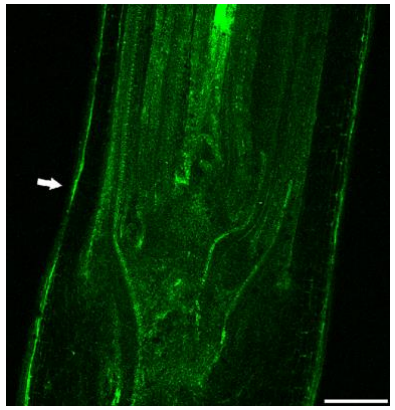
Fluorescent labeling of oligonucleotides

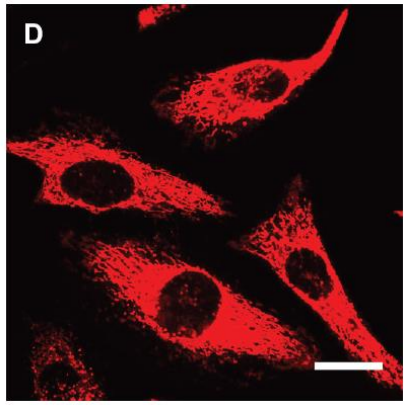


Fluorescein labeling

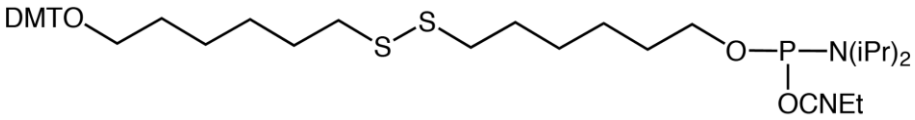


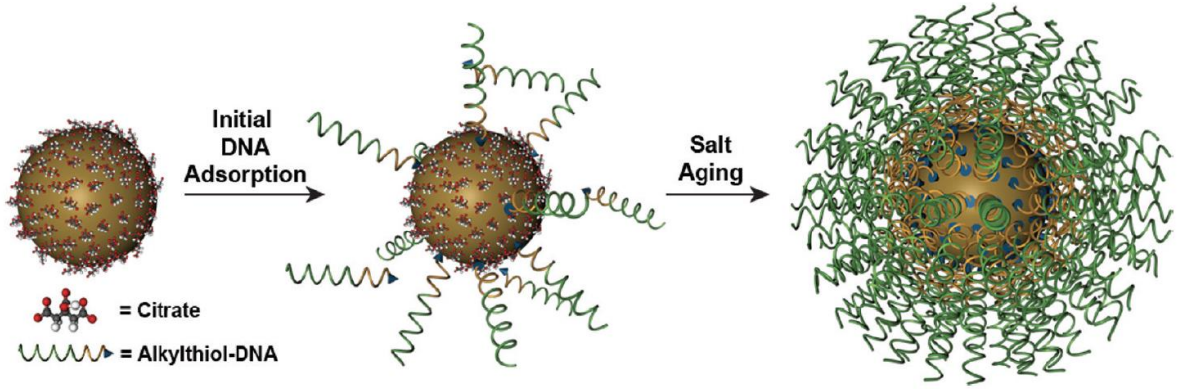
Cy5 labeling

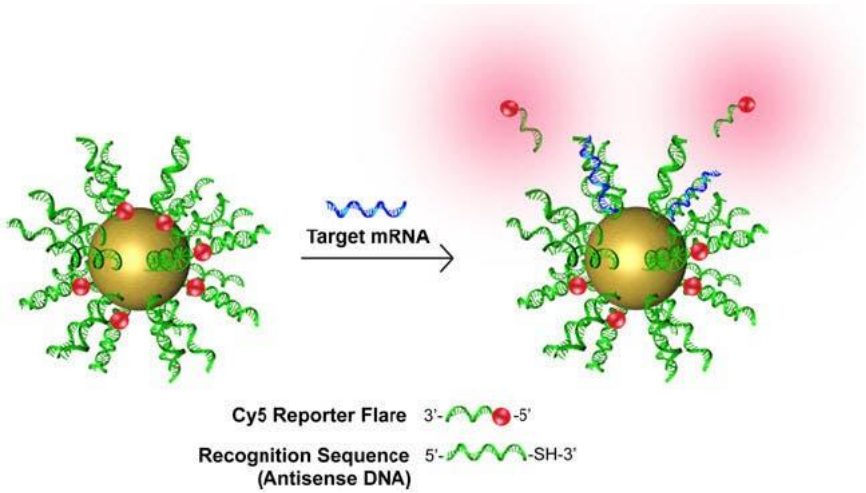




Surface functionalization with DNA

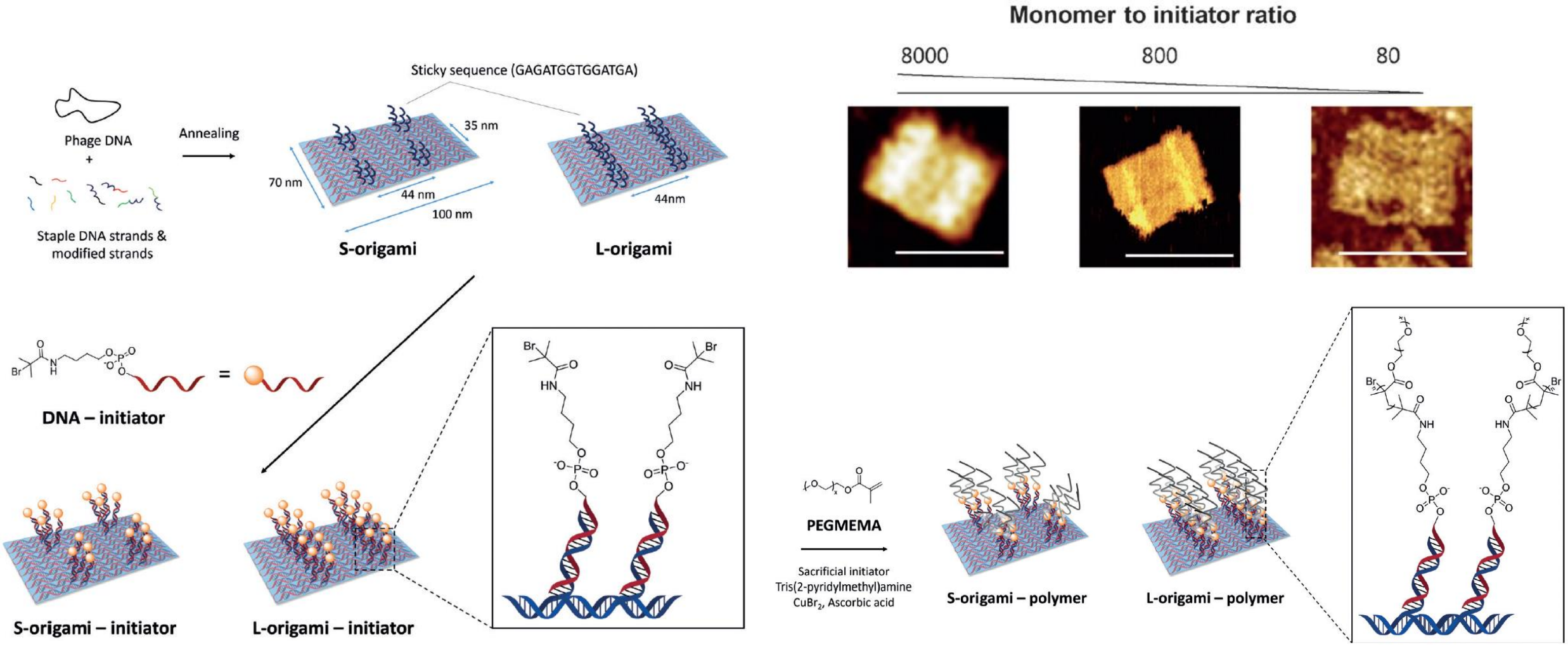






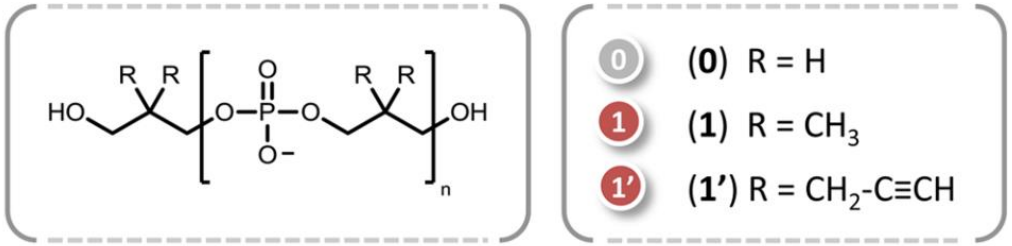
Cutler, J. I.; Auyeung, E.; Mirkin, C. A., *J. Am. Chem. Soc.* **2012,** *134*, 1376-1391.

Grafting Polymers from DNA



Tokura, Y.; Jiang, Y.; Welle, A.; Stenzel, M. H.; Krzemien, K. M.; Michaelis, J.; Berger, R.; Barner-Kowollik, C.; Wu, Y.; Weil, T., *Angew. Chem. Int. Ed.* **2016,** *55*, 5692-5697.

Synthetic Sequence-Encoded Polymers



Sequence-encoded non-natural polyphosphate

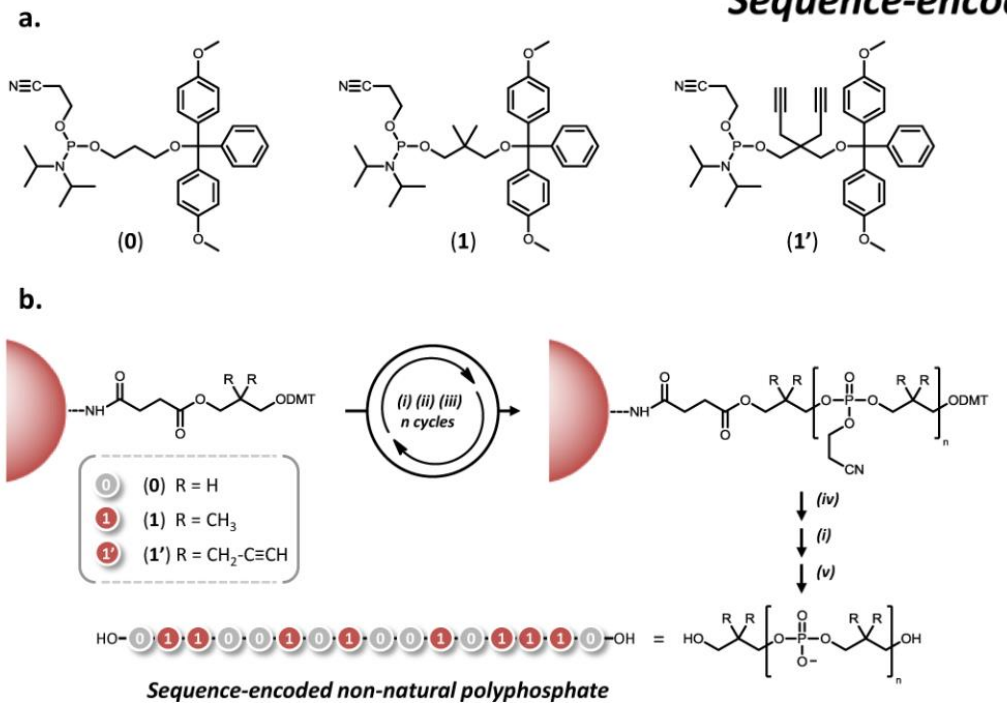
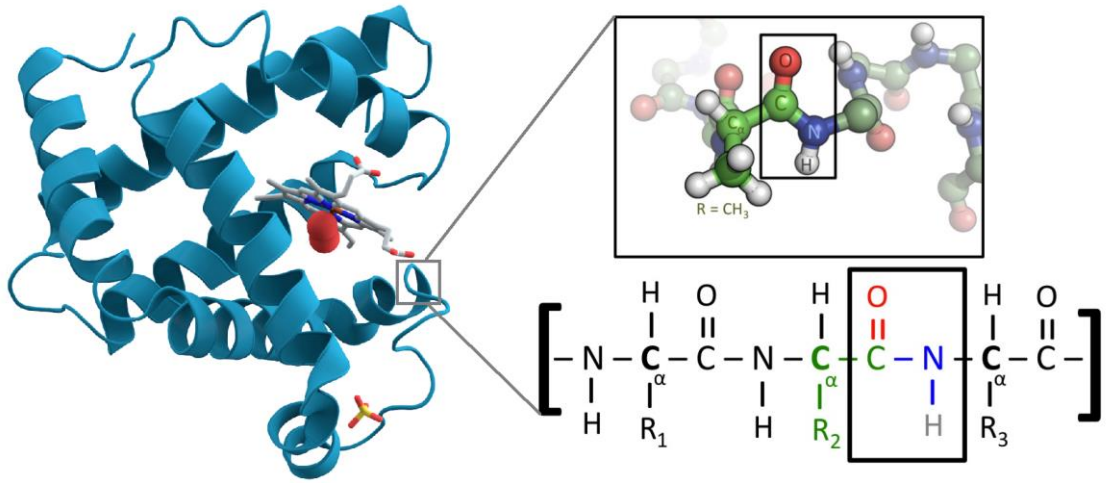


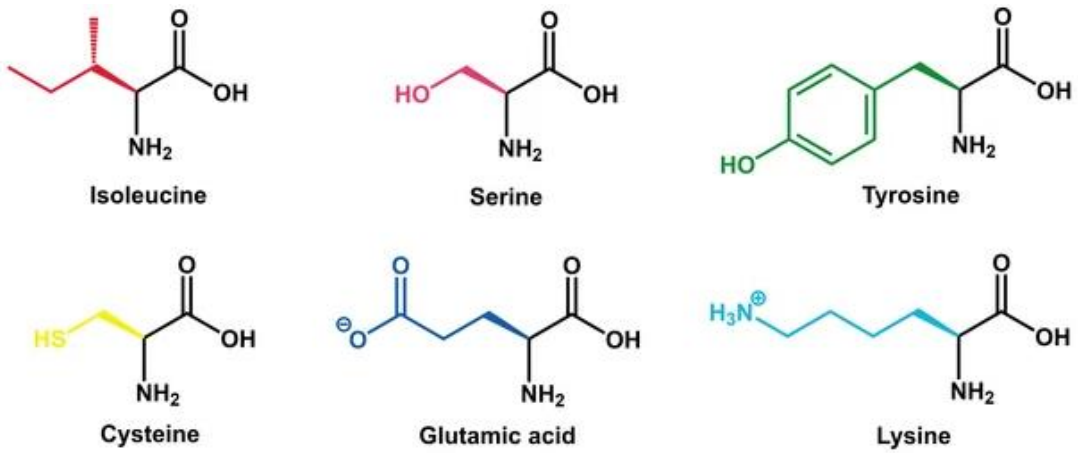
Table 1. Characterization of Polyphosphodiester Homopolymers (H) and Copolymers (C) Synthesized by Solid-Phase Chemistry

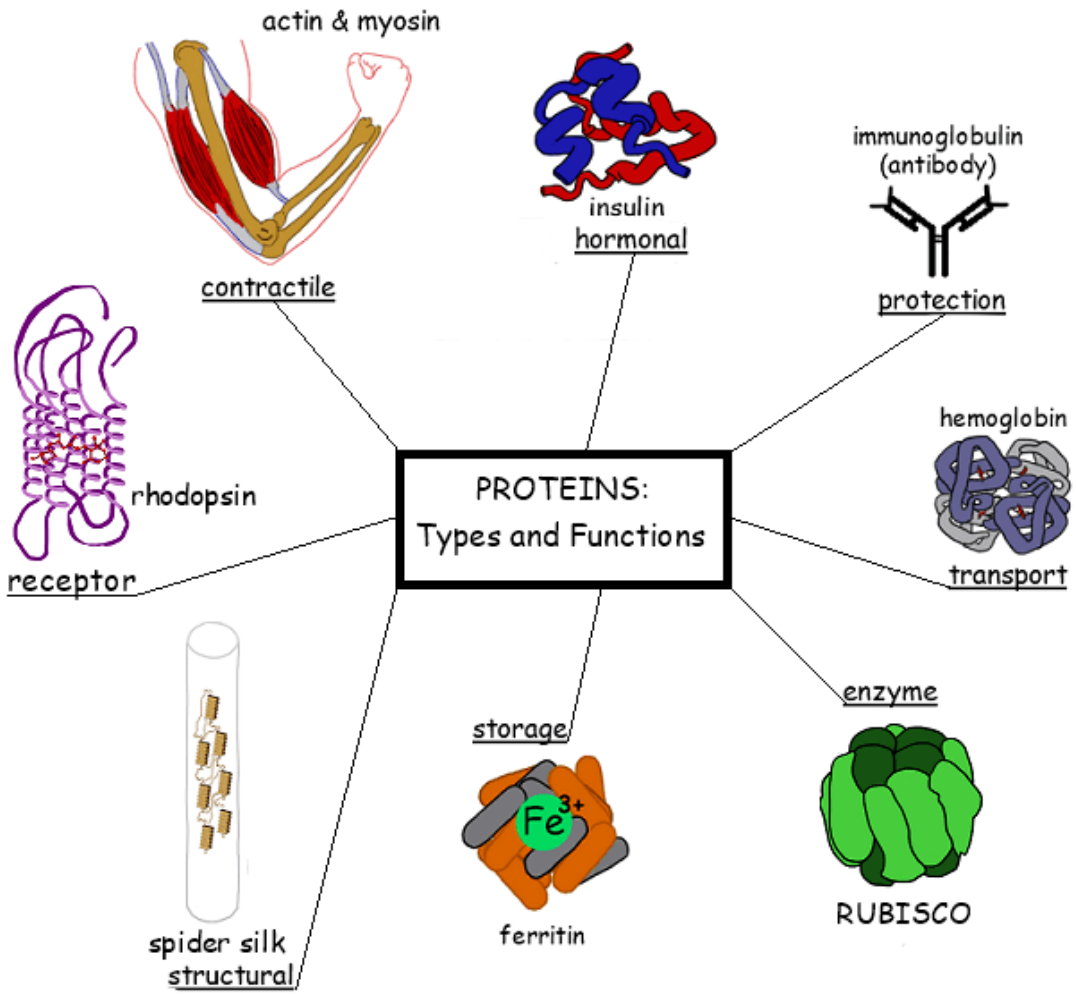
	sequence	yield [%][a]	M_n [g·mol^{-1}][b]	M_w/M_n[b]	m/z_{th}	m/z_{exp}
H1	00000	≥98	650	1.04	629.0925 $[M + H]^+$	629.0916[c] $[M + H]^+$
						629.0923[d] $[M + H]^+$
H2	00000000	≥98	1040	1.03	522.0622 $[M + 2H]^{2+}$	522.0610[c] $[M + 2H]^{2+}$
					1043.1171 $[M + H]^+$	1043.1155[d] $[M + H]^+$
H3	0000000000000000	≥95	1850	1.01	2147.1827 $[M + H]^+$	2147.1779[d] $[M + H]^+$
C1	01010	≥98	730	1.05	685.1551 $[M + H]^+$	685.1564[c] $[M + H]^+$
						685.1544[d] $[M + H]^+$
C2	0100101001010010	≥95	2000	1.07	2315.3705 $[M + H]^+$	–[e]
C3	0100100010000100	≥98	1850	1.07	2259.3079 $[M + H]^+$	2259.3050[d] $[M + H]^+$
C4	00100010000010000001000000	≥87	2950	1.08	3363.3734 $[M + H]^+$	–[e]
H1′	1′1′1′1′1′1′1″1′	≥98	–[f]	–[f]	826.1874 $[M + 2H]^{2+}$	826.1861[c] $[M + 2H]^{2+}$
					1651.3675 $[M + H]^+$	1651.3652[d] $[M + H]^+$
C1′	1′01′001′01′	≥98	–	–	674.1248 $[M + 2H]^{2+}$	674.1248[c] $[M + 2H]^{2+}$
					1347.2428 $[M + H]^+$	1347.2392[d] $[M + H]^+$
C2″	1′11′111′11′	≥98	1799	1.02	730.1874 $[M + 2H]^{2+}$	730.1863[c] $[M + 2H]^{2+}$

Al Ouahabi, A.; Charles, L.; Lutz, J.-F., *J. Am. Chem. Soc.* **2015,** *137*, 5629-5635.

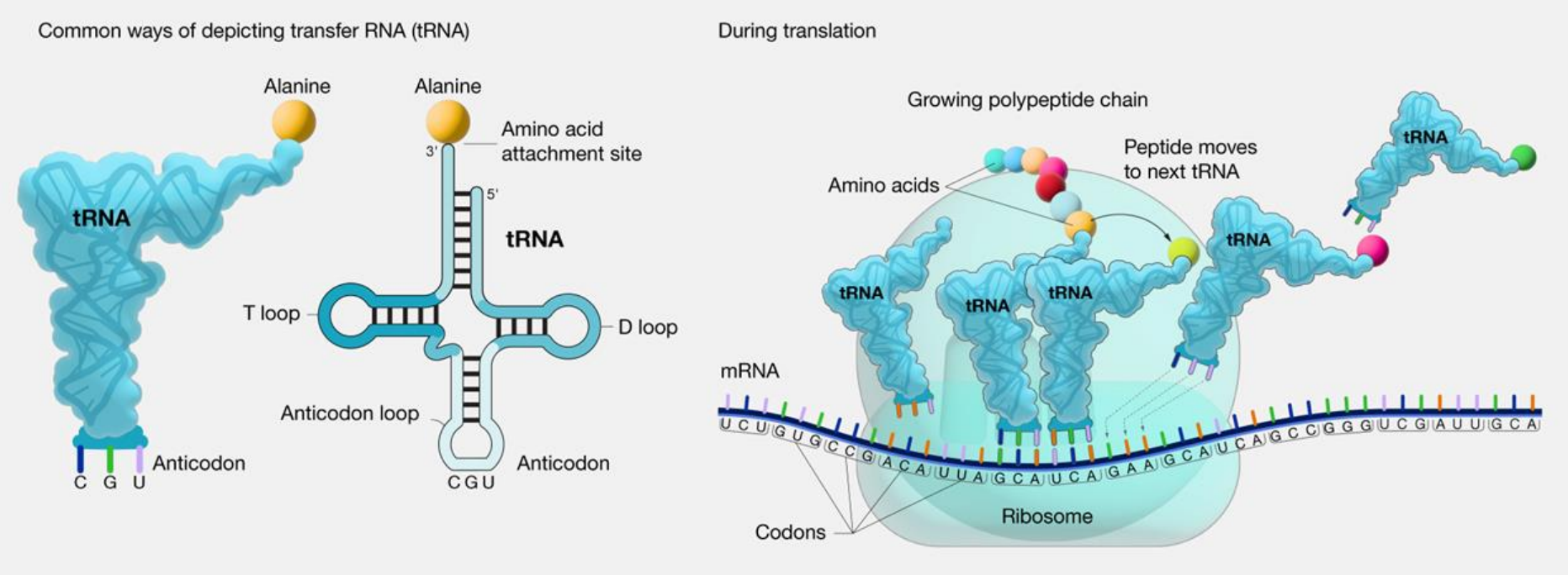
Proteins

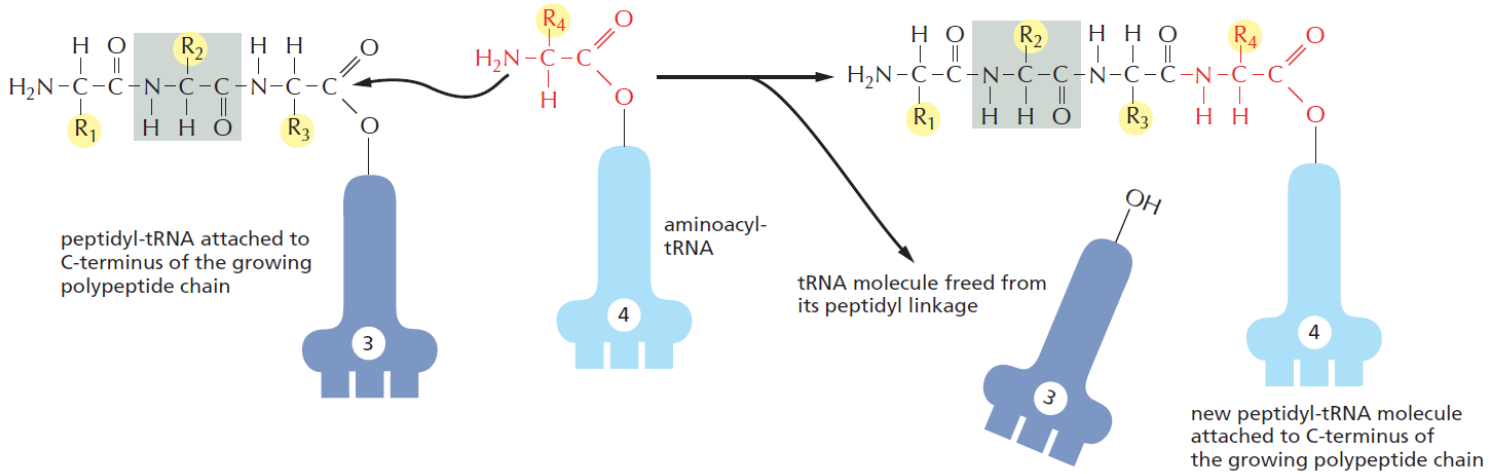

R = CH3


Isoleucine
Serine
Tyrosine
Cysteine
Glutamic acid
Lysine

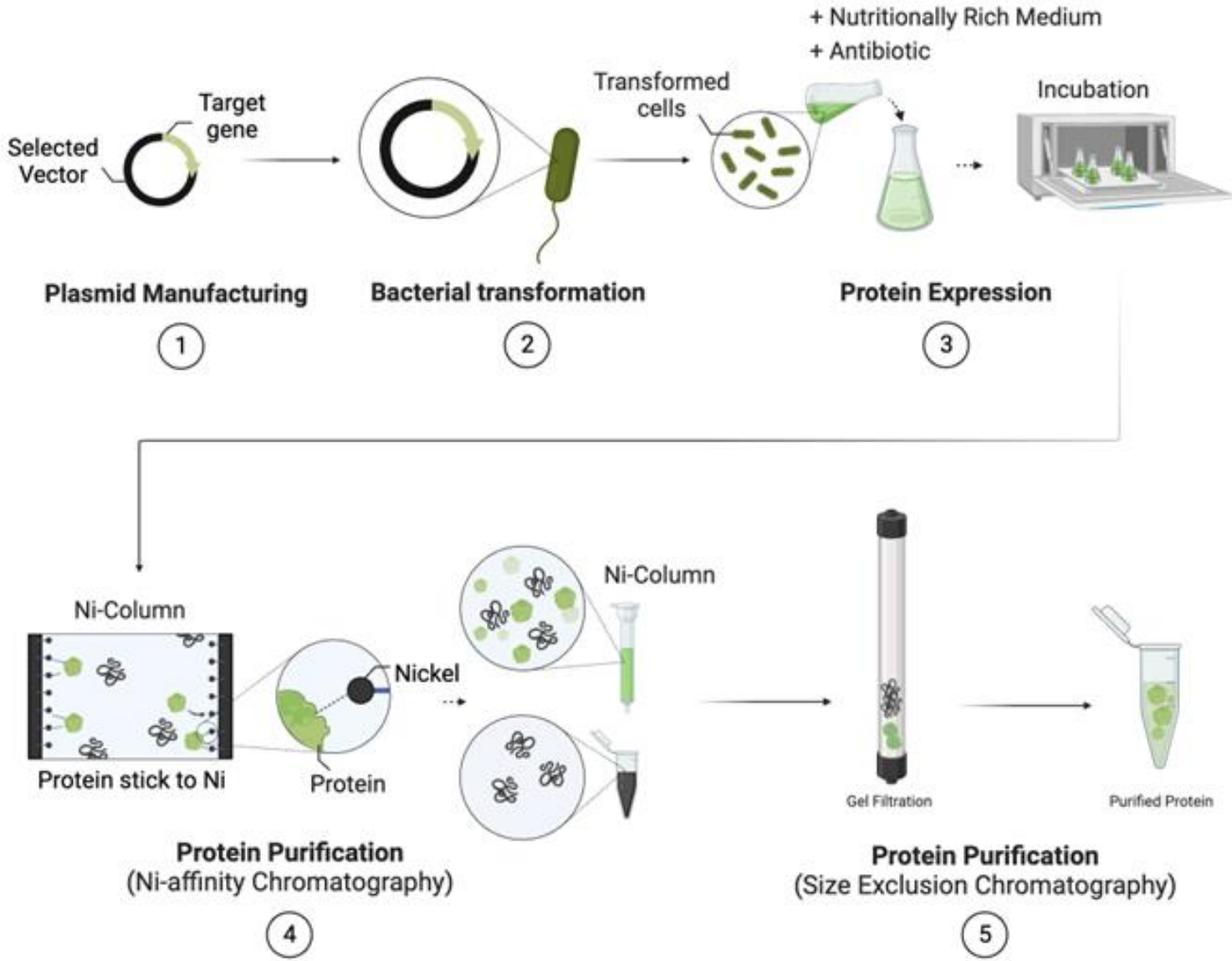

actin & myosin
contractile
insulin
hormonal
immunoglobulin
(antibody)
protection
rhodopsin
receptor
PROTEINS:
Types and Functions
hemoglobin
transport
enzyme
RUBISCO
storage
ferritin
spider silk
structural

Biological Synthesis of Proteins





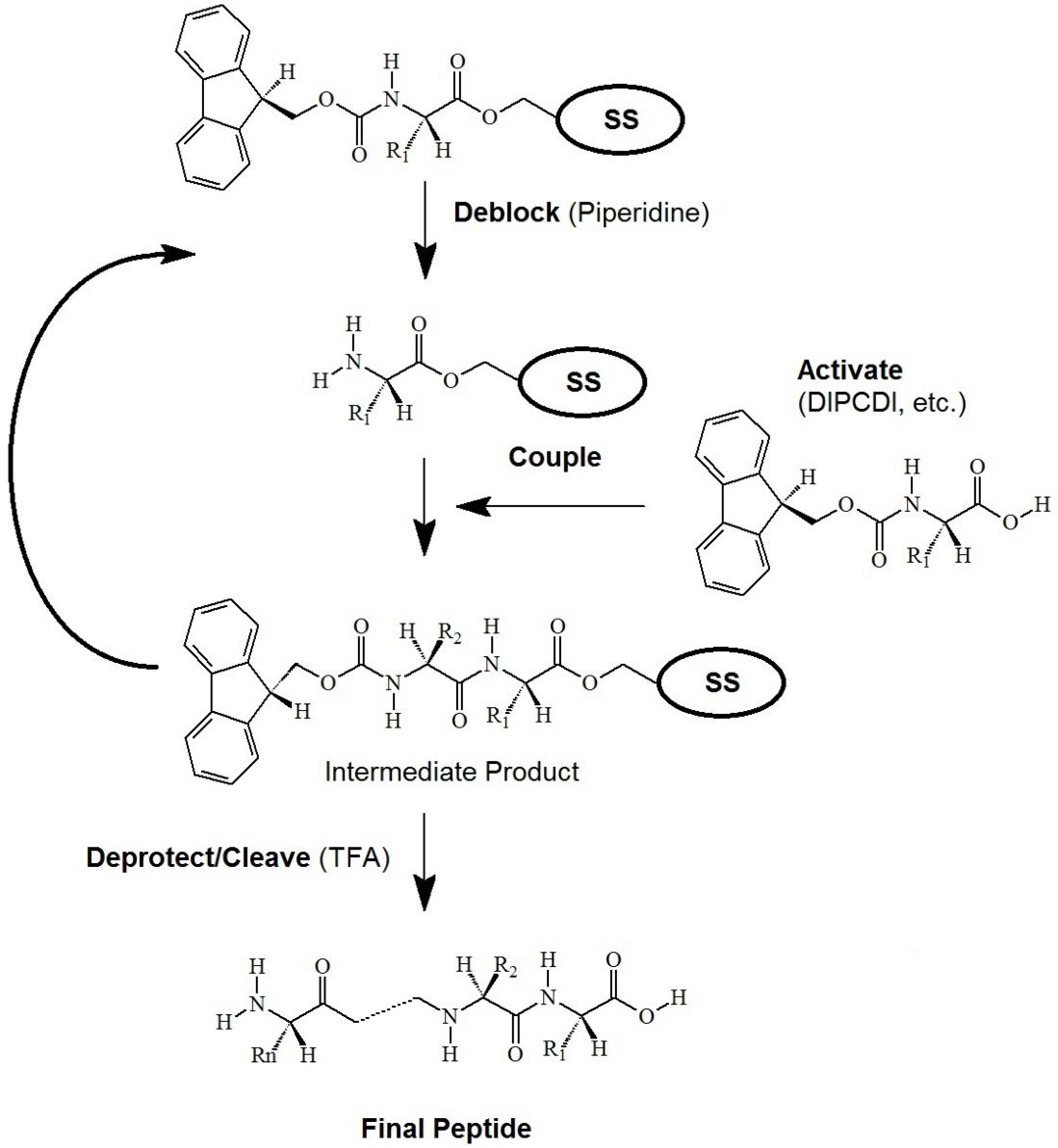
Recombinant Protein Expression

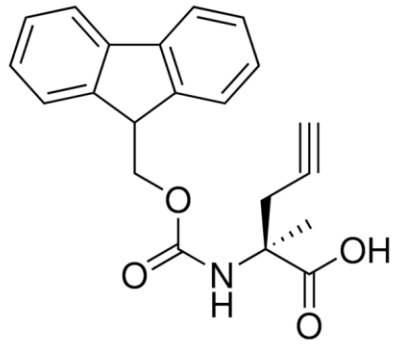


Solid-Phase Peptide Synthesis (SSPS)

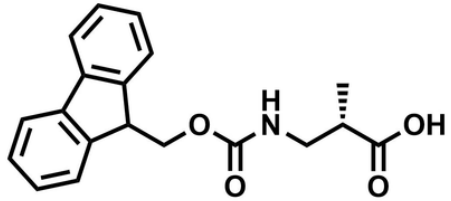
Robert Bruce Merrifield
1984 Nobel Prize in Chemistry

Peptide Synthesizer

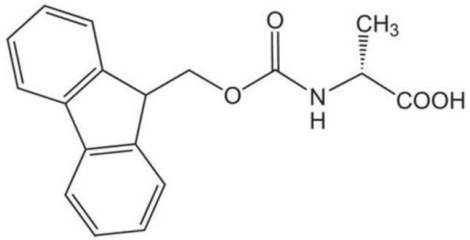




Unnatural amino acid

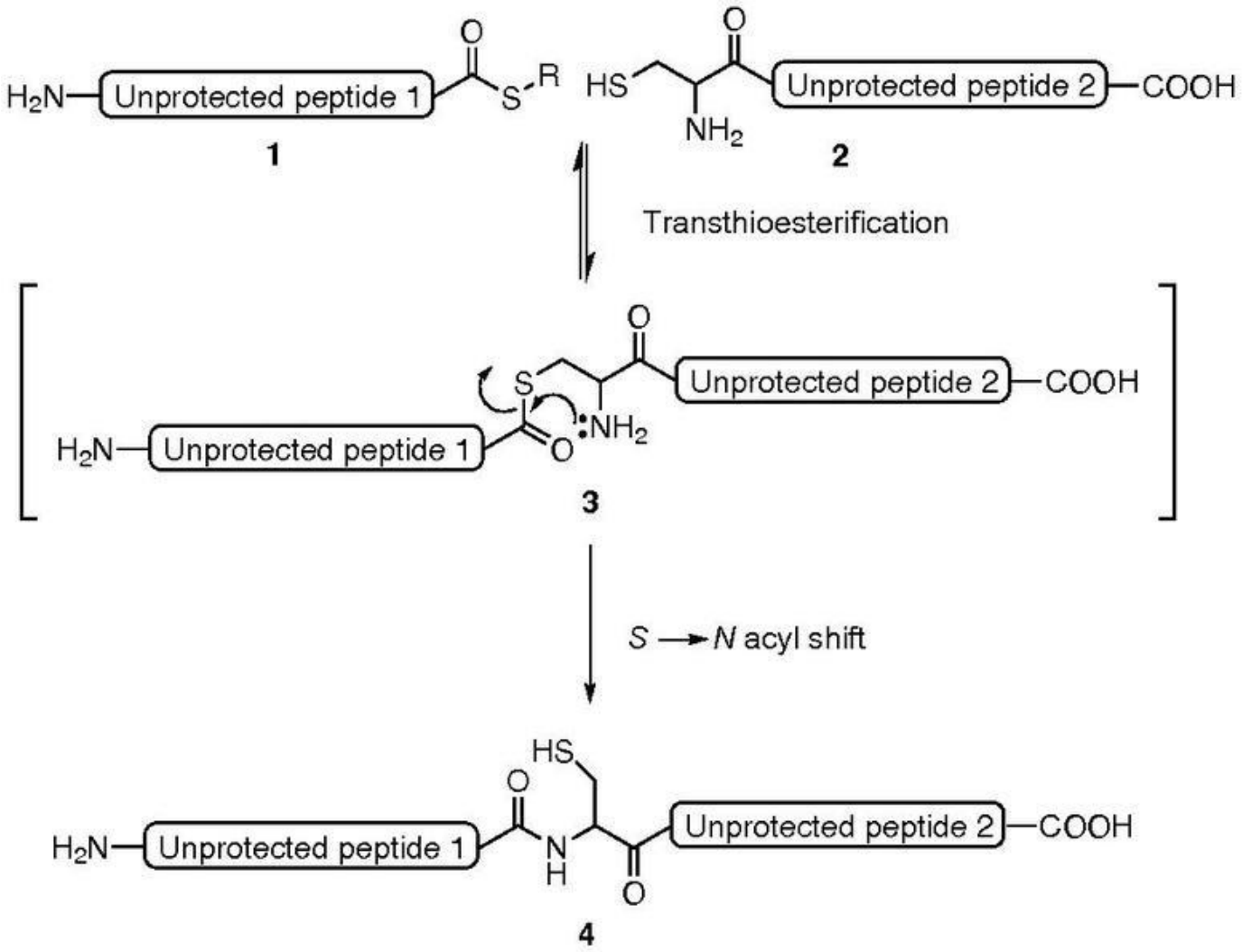


β-amino acid



D-amino acid

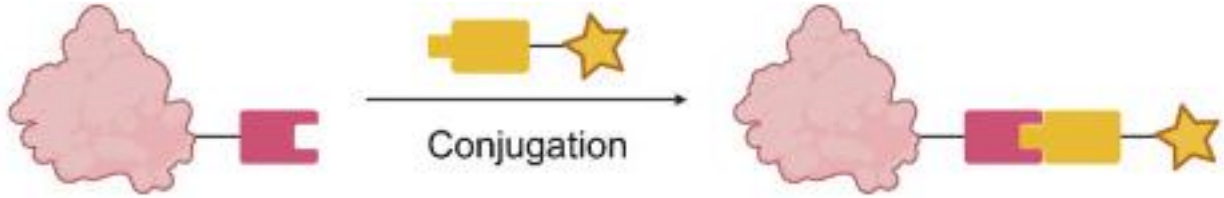
Native Chemical Ligation (NCL)



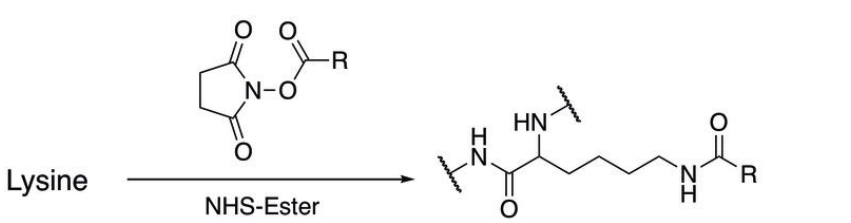
- The coupling efficiency in SSPS is less than 100%, which poses challenges in synthesizing long peptide chains.
- Peptide thioesters can be directly obtained from SPPS and efficiently used to construct larger polypeptides through condensation with another peptide via NCL.
- Protein thioesters can be generated via recombinant protein expression and reacted with a Cys-terminated peptide, a method known as expressed protein ligation. This approach integrates recombinant protein expression with SPPS to generate highly complex polypeptides.

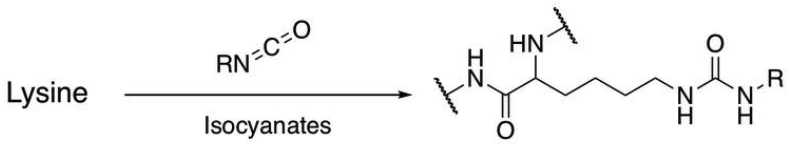
Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. H., *Science* **1994,** *266*, 776-779.
Muir, T. W.; Sondhi, D.; Cole, P. A., *Proc. Natl. Acad. Sci. USA* **1998,** *95*, 6705-6710.

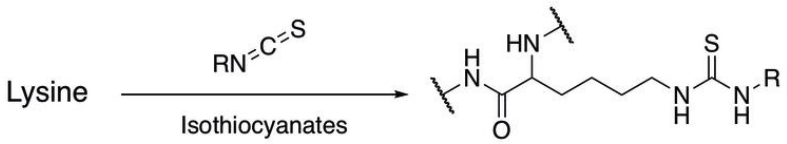
Protein Bioconjugation

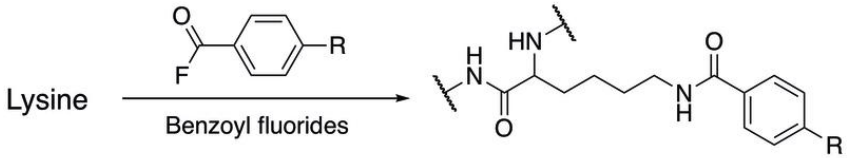


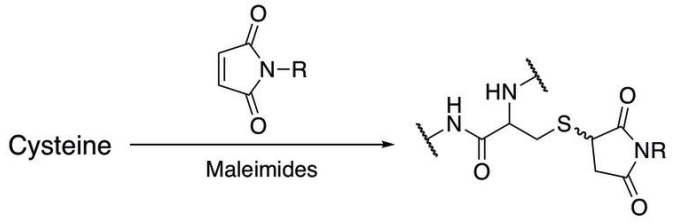
Bioconjugation: a chemical process that creates a stable link between a biomolecule and another molecule.

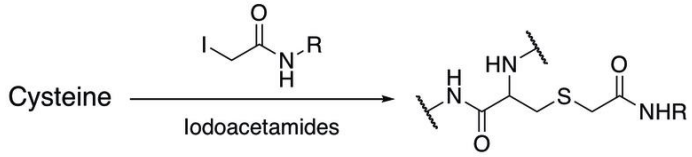


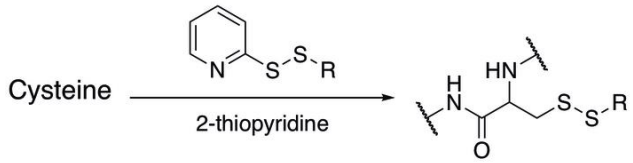


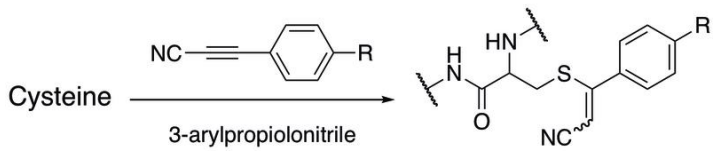










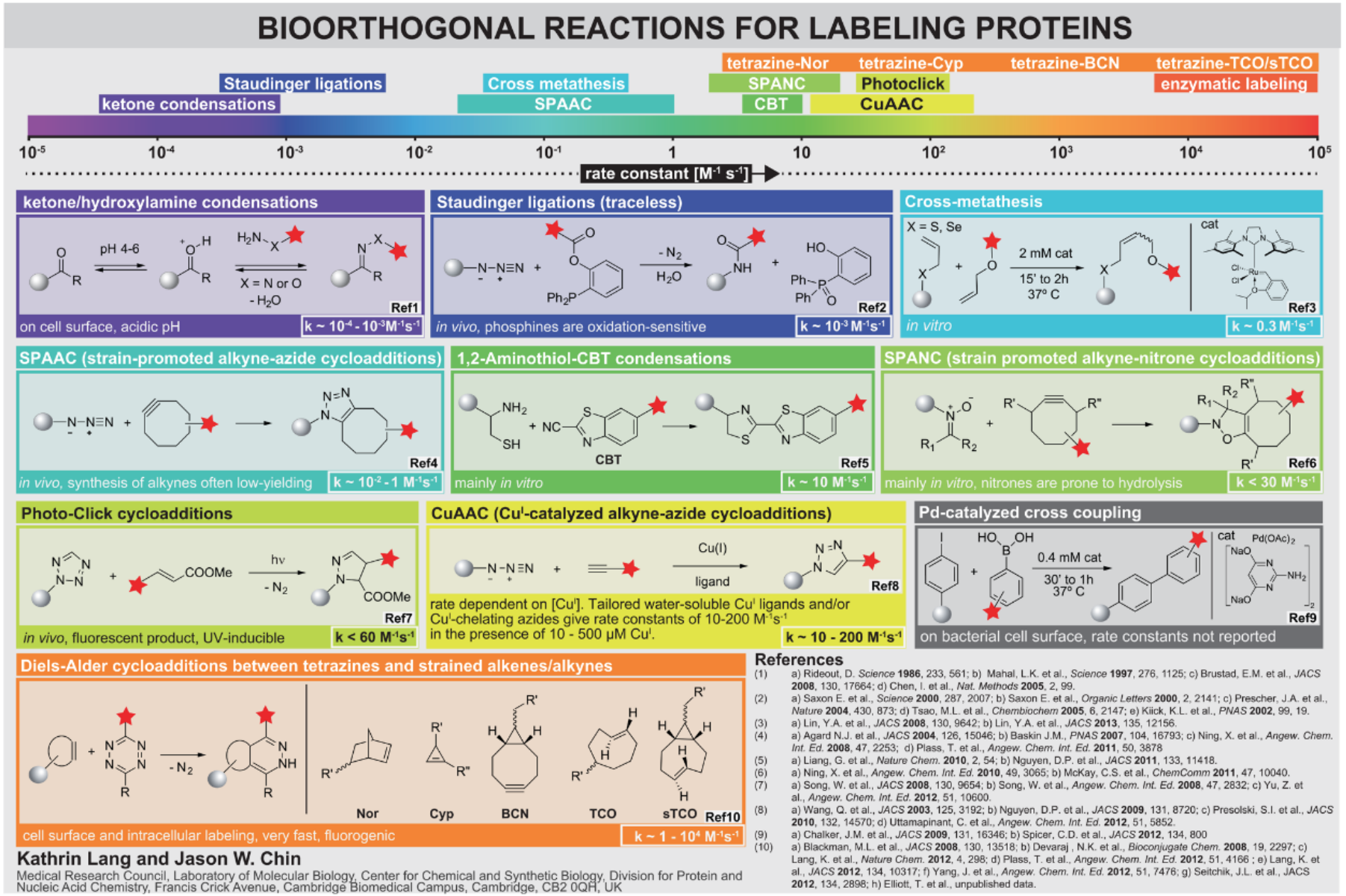


Lysine and cysteine are the two most commonly used amino acids for protein bioconjugation.

Shadish, J. A.; DeForest, C. A., *Matter* **2020,** *2*, 50-77.

Site-Specific Protein Bioconjugation: Bioorthogonal Reactions

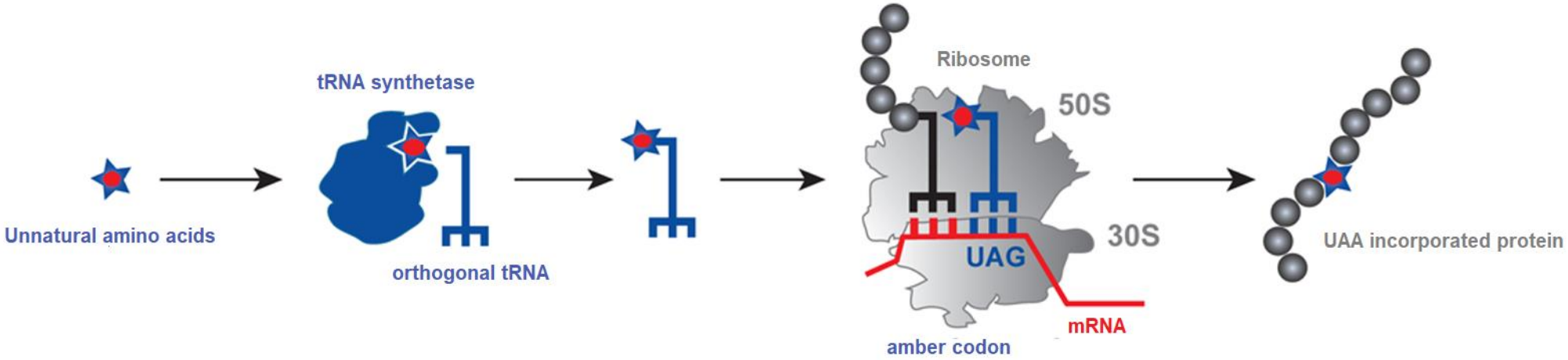
Carolyn Bertozzi
2022 Nobel Prize in Chemistry

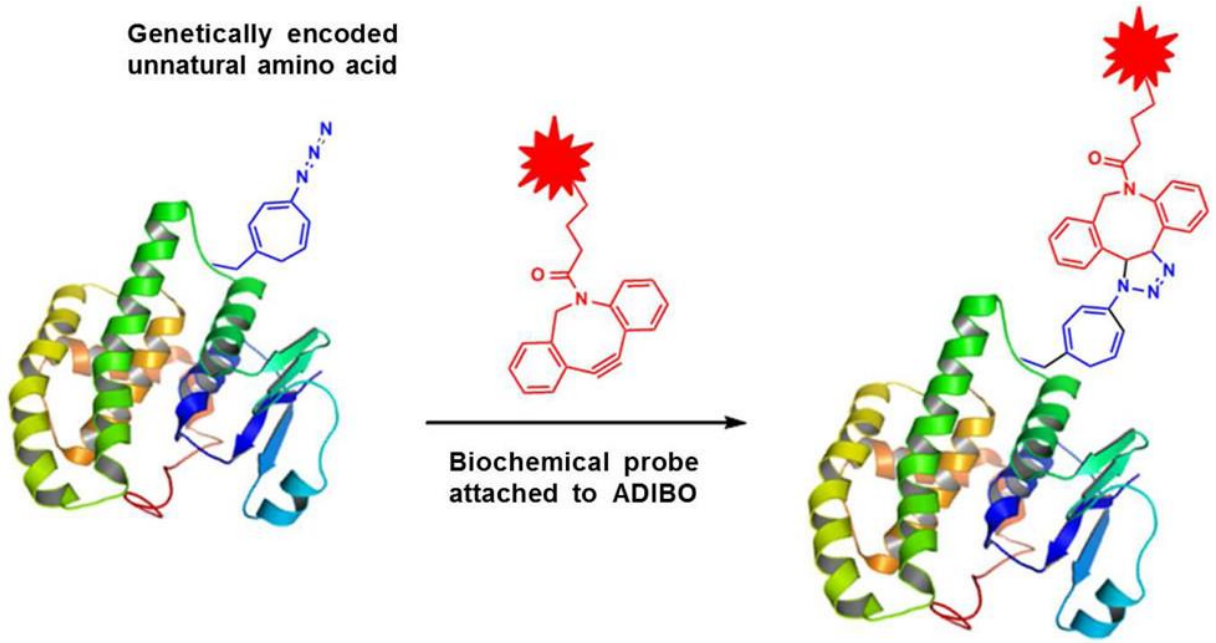


RUTGERS
School of Arts and Sciences

Lang, K.; Chin, J. W., *ACS Chem. Biol.* **2014,** *9*, 16-20.

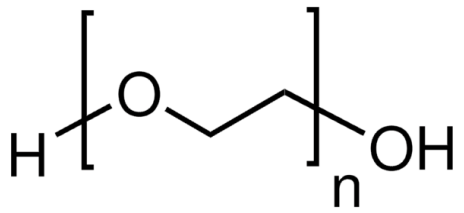
Unnatural Amino Acid Incorporation



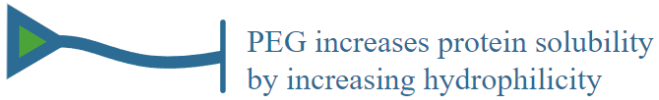


Noren, C. J.; Anthony-Cahill, S. J.; Griffith, M. C.; Schultz, P. G., *Science* **1989,** *244*, 182-188.
Lang, K.; Chin, J. W., *Chem. Rev.* **2014,** *114*, 4764-4806.

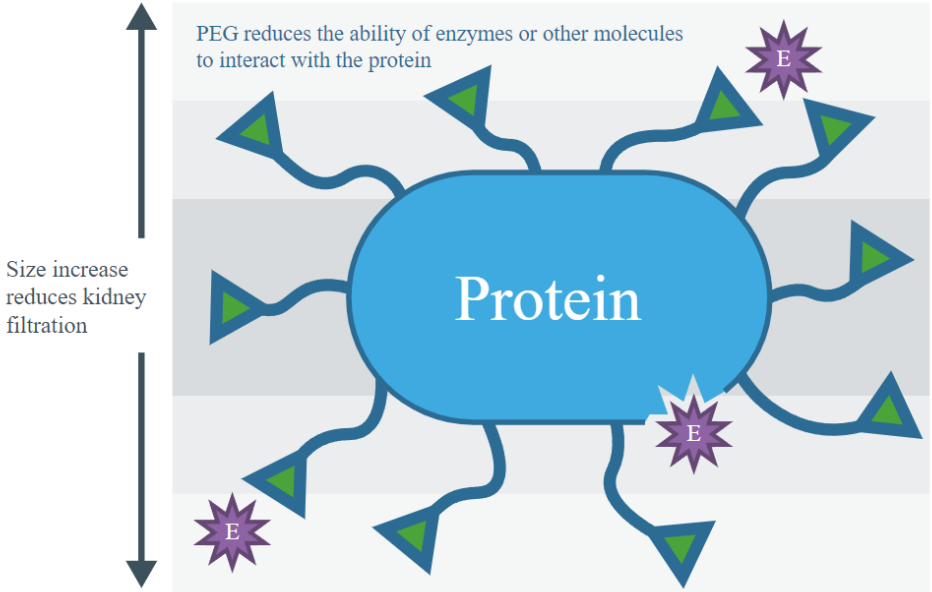
Protein-Polymer Conjugate: PEGylation



Polyethylene glycol (PEG)



PEG increases protein solubility by increasing hydrophilicity



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Vol. 252, No. 11, Issue of June 10, pp. 3578-3581, 1977
Printed in U.S.A.

Alteration of Immunological Properties of Bovine Serum Albumin by Covalent Attachment of Polyethylene Glycol*

(Received for publication, December 6, 1976)

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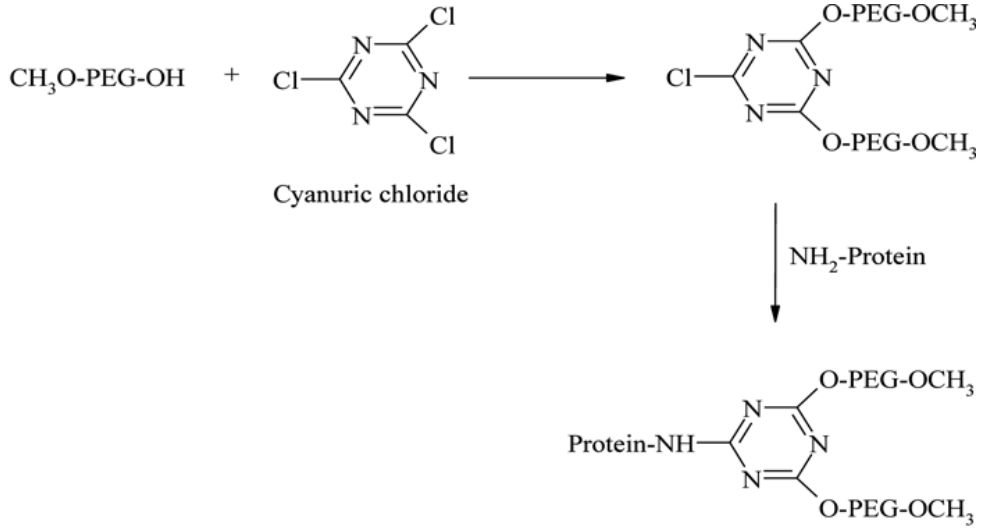
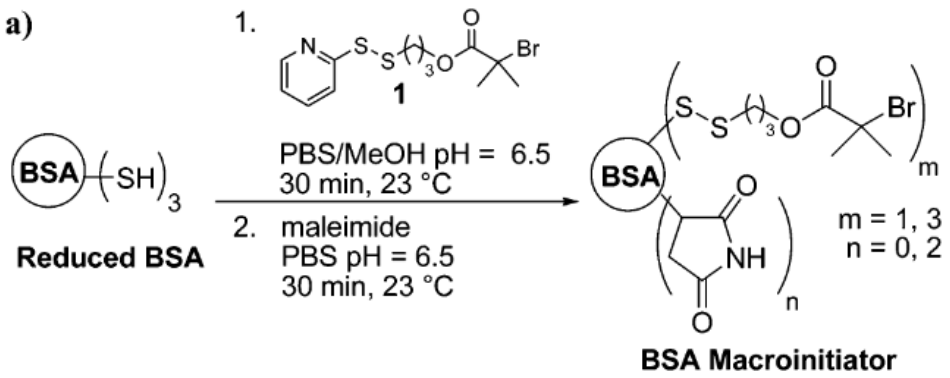
From the Departments of Biochemistry and Zoology, and the Bureau of Biological Research, Rutgers University, New Brunswick, New Jersey 08903

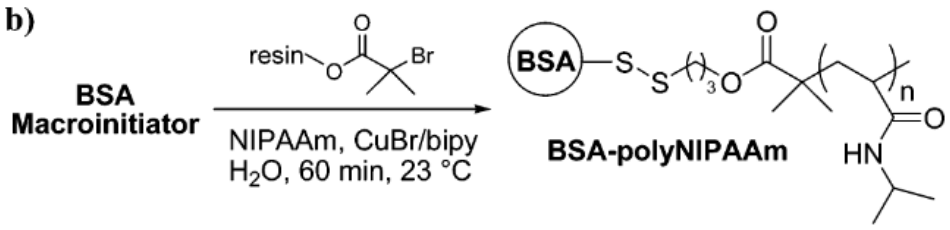


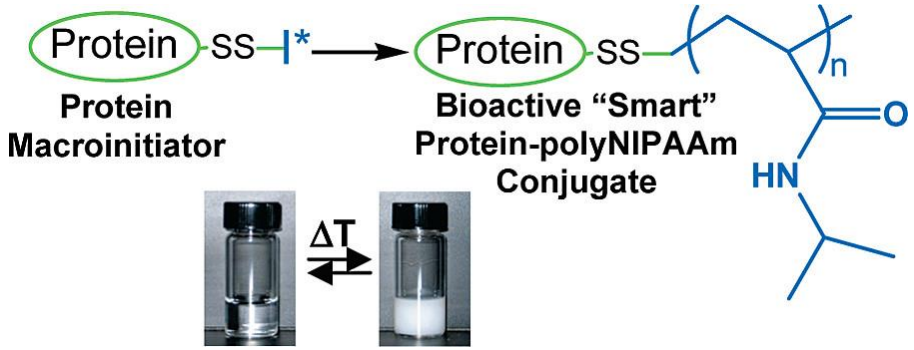
Abuchowski, A.; van Es, T.; Palczuk, N. C.; Davis, F. F., *J. Biol. Chem.* **1977,** *252*, 3578-3581.
Davis, F. F., *Adv. Drug Deliv. Rev.* **2002,** *54*, 457-458.

Protein-Polymer Conjugate: Graft-From

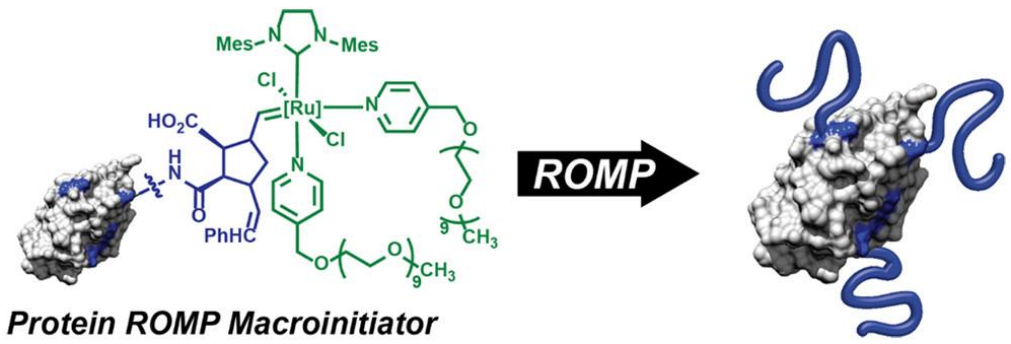
ATRP

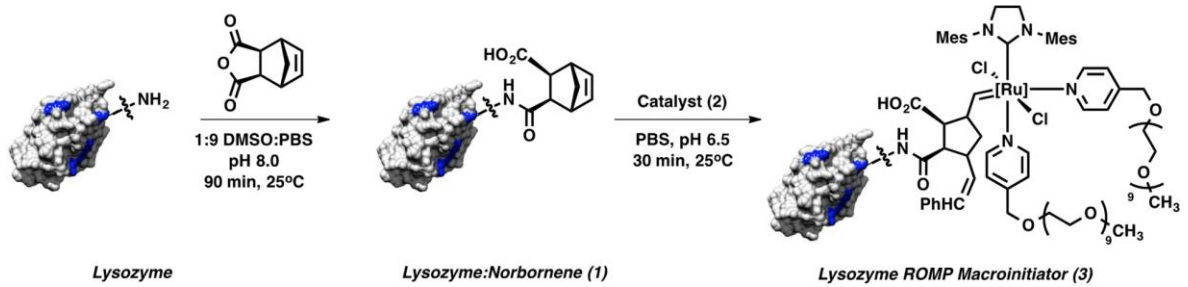


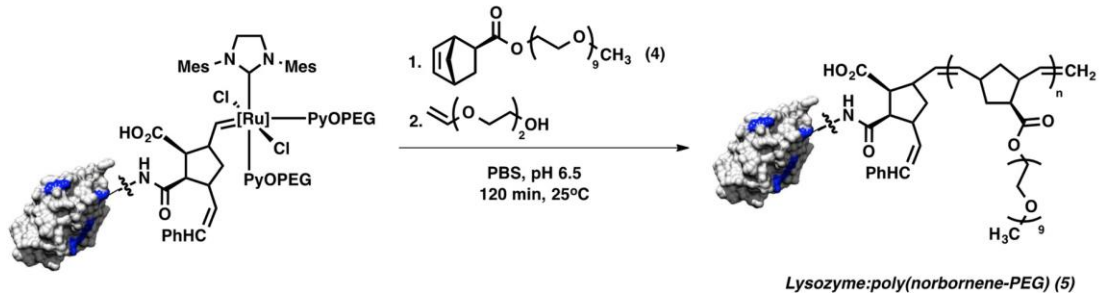




ROMP

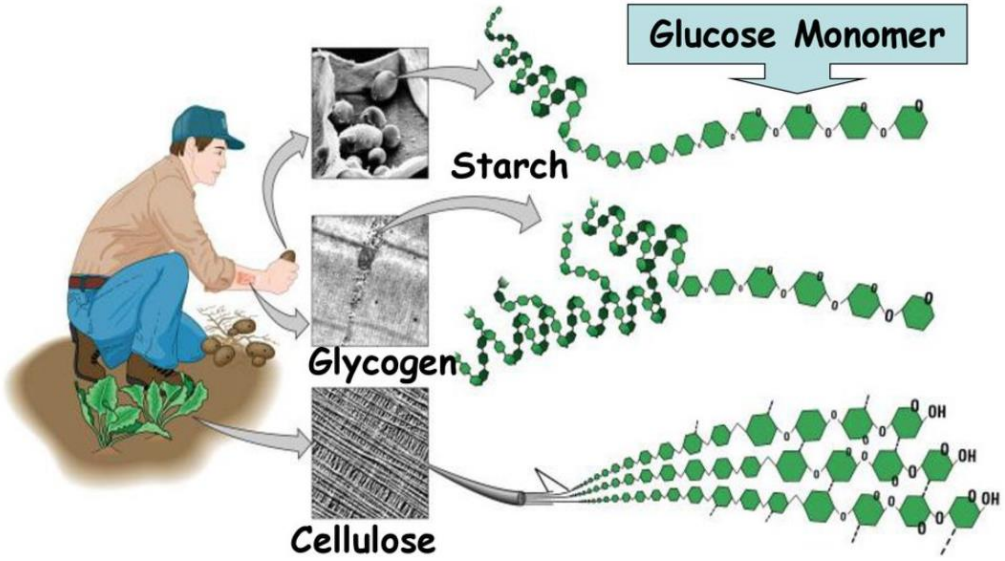


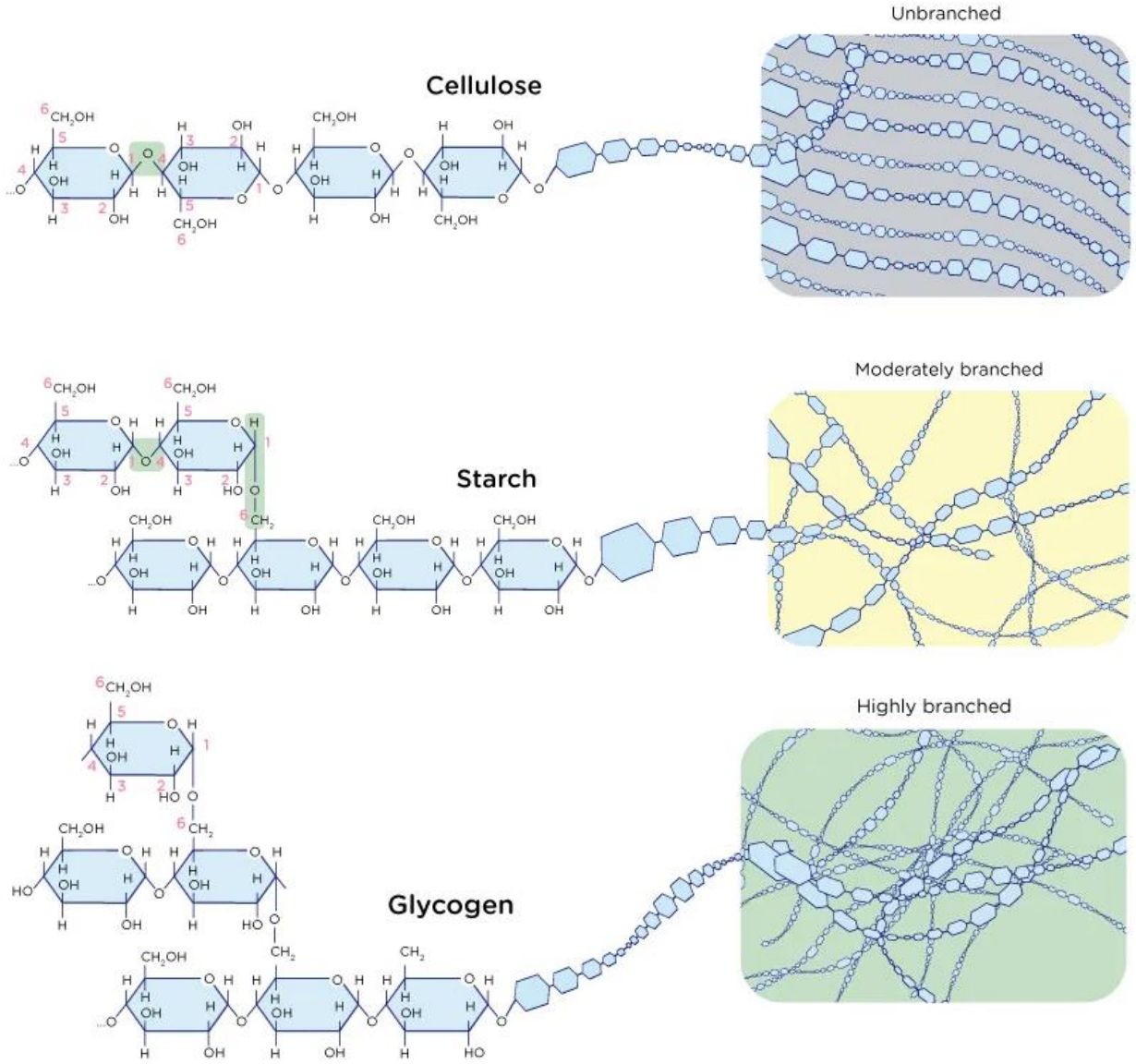




Heredia, K. L.; Bontempo, D.; Ly, T.; Byers, J. T.; Halstenberg, S.; Maynard, H. D., *J. Am. Chem. Soc.* **2005,** *127*, 16955-16960.
Isarov, S. A.; Pokorski, J. K., *ACS Macro Lett.* **2015,** *4*, 969-973.

Polysaccharide





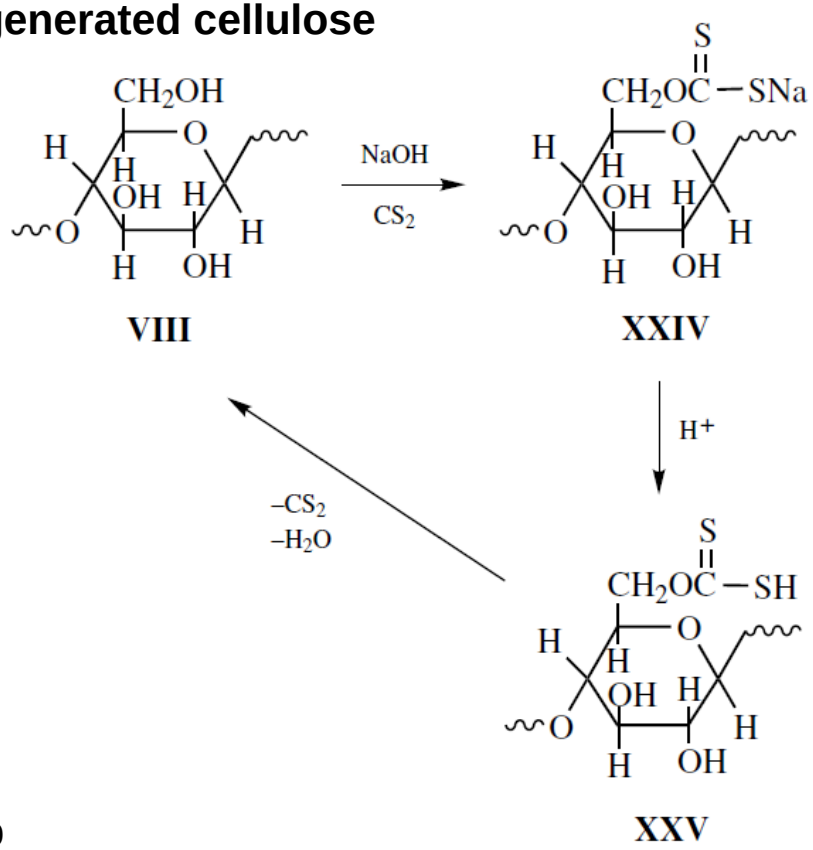
Regenerated Cellulose

How can natural cellulose be spun into fibers?

Challenge: cellulose is nearly impossible to dissolve in common solvents.

Cellulose xanthate:
soluble and spinnable

Regenerated cellulose



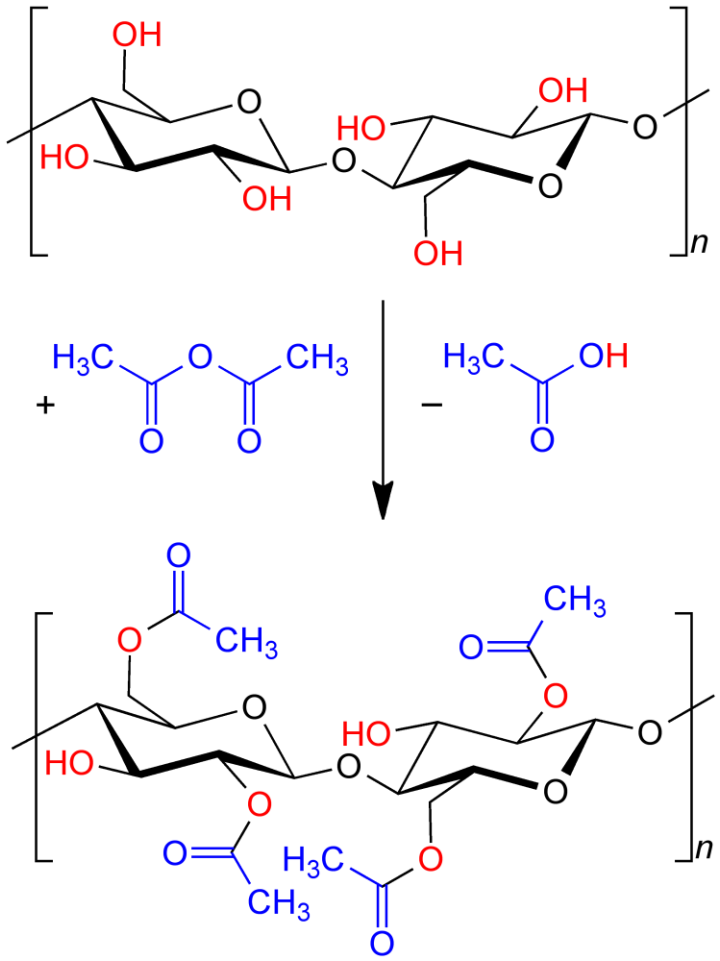
Rayon

Syringe filter

Dialysis tubing

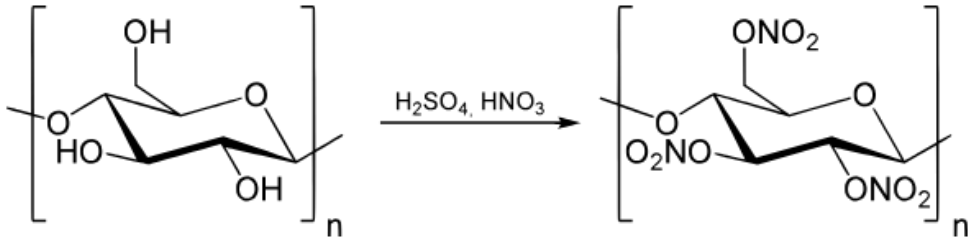
Cellulose Esters

Cellulose



Cellulose acetate

Nitrocellulose

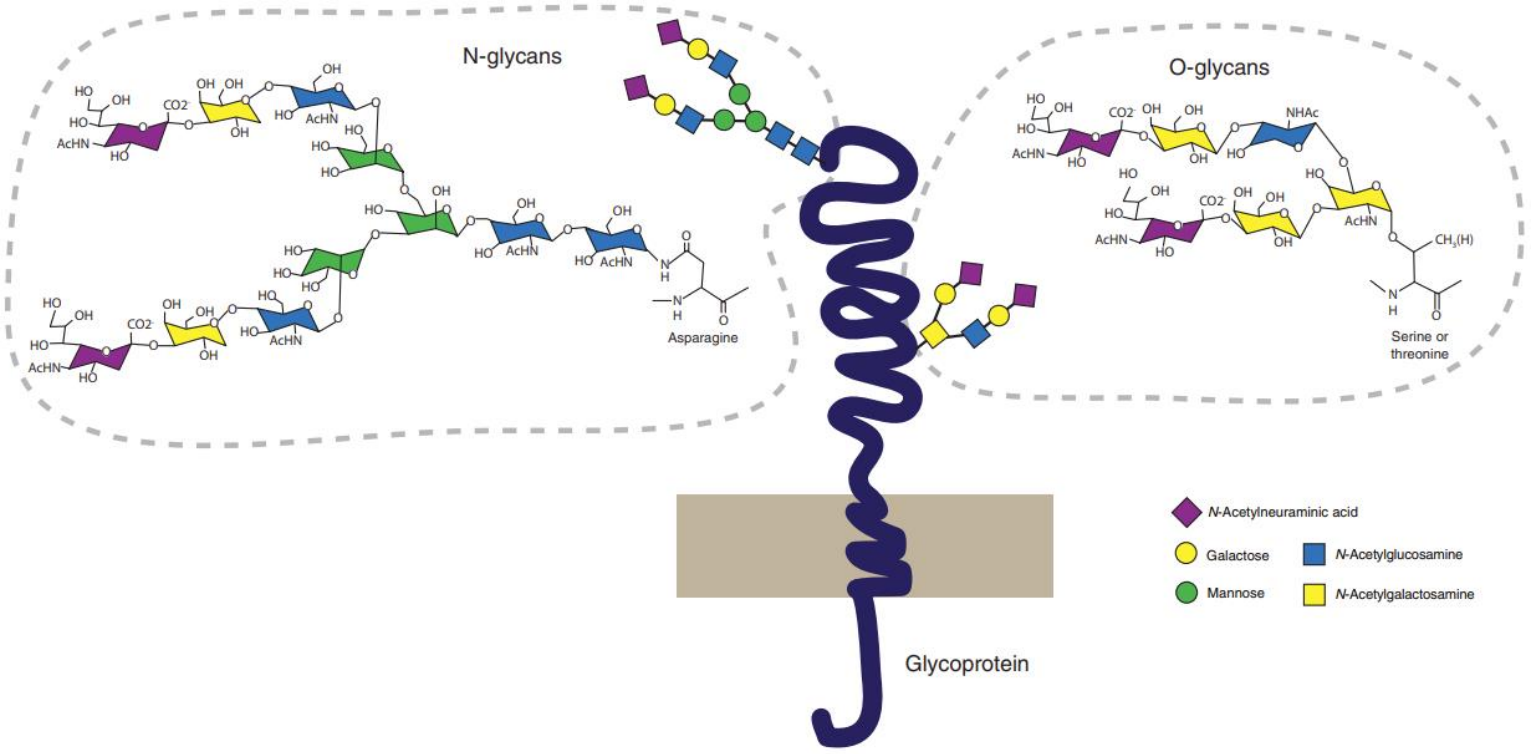


John Wesley Hyatt

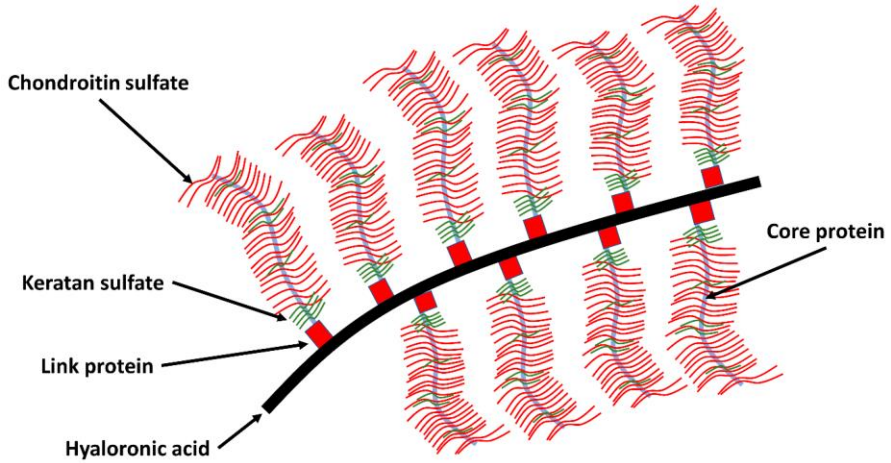
“Celluloid”: patented in 1870

Old celluloid film rolls

Sugars Can Have Very Complex Structures

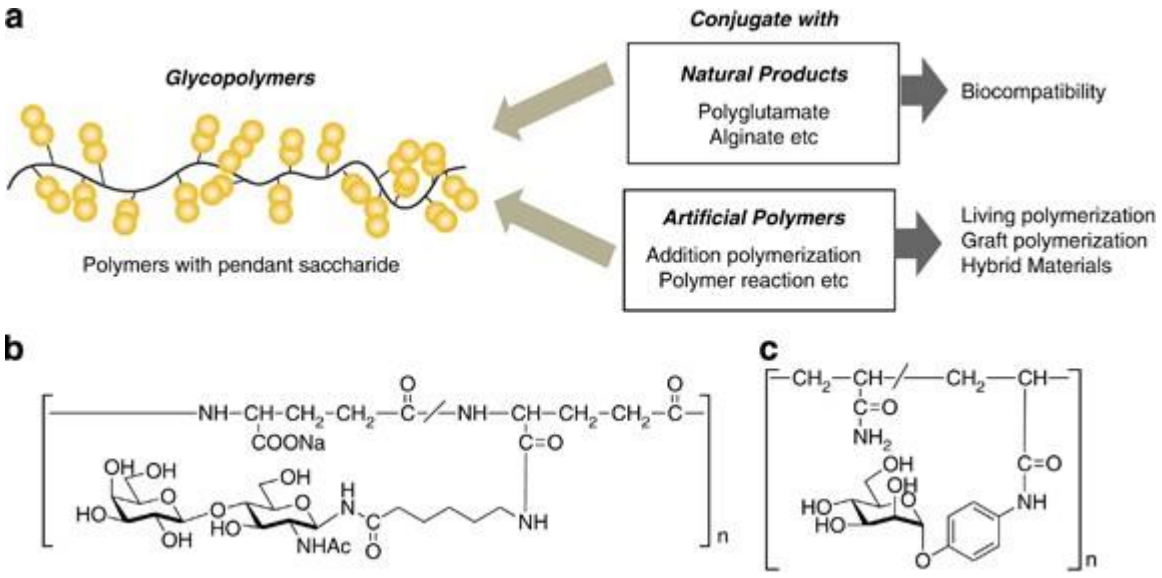


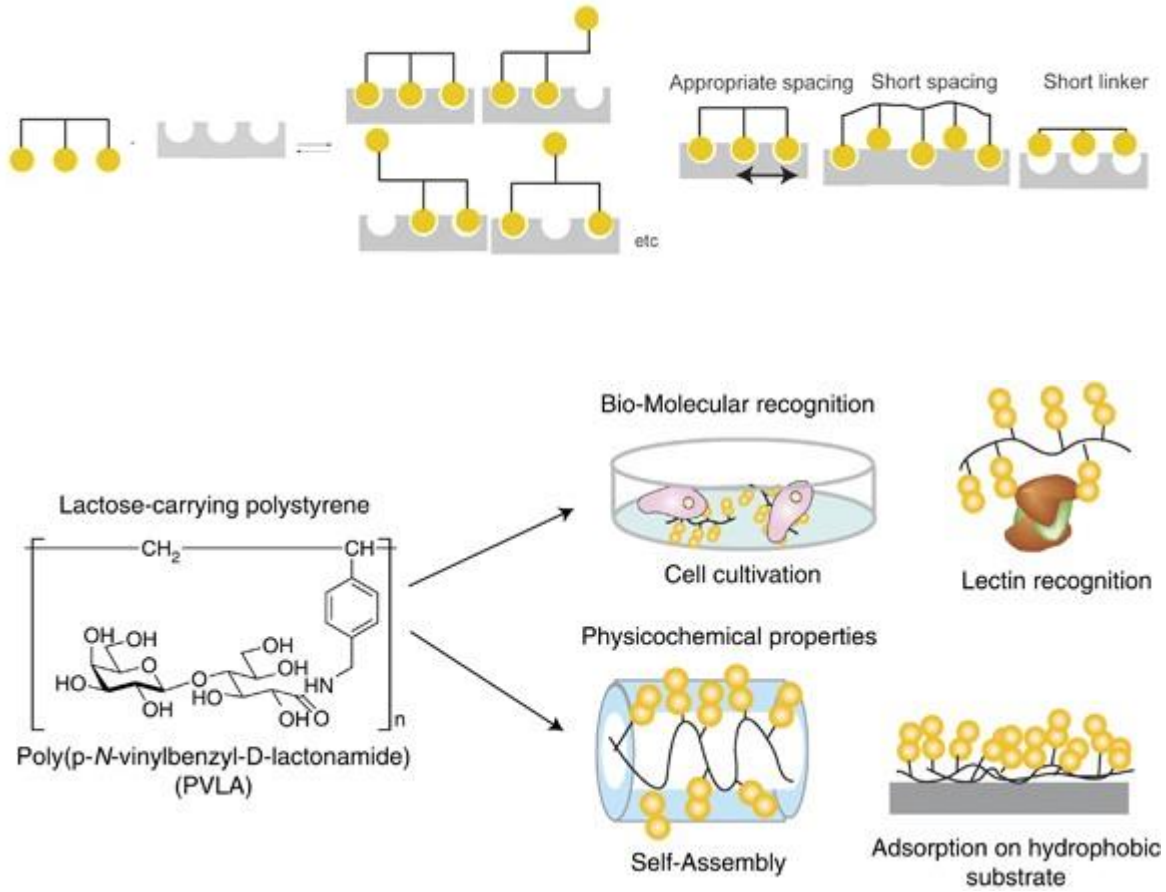
Glycoprotein



Proteoglycan

Glycopolymers





Glycopolymer is synthetic polymer with pendant carbohydrates.

Miura, Y., *Polym. J.* **2012,** *44*, 679-689.