Gene Expression and Microarrays

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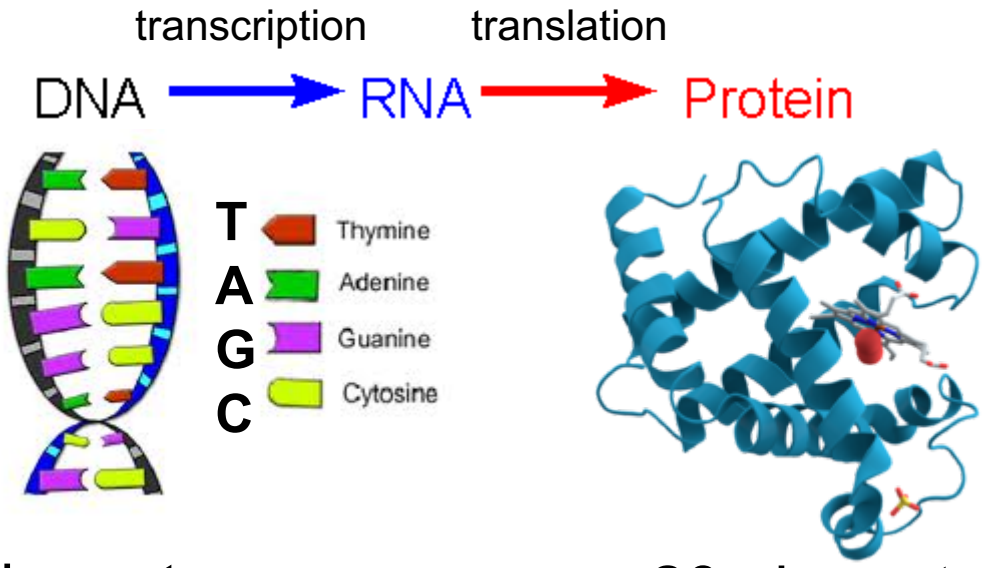
Note: All images from slides 3-6 on are from Campbell Biology, 9th edition,

Overview of gene expression

Central Dogma of Molecular Biology:



4-character alphabet → 20-character alphabet

- A *gene* is a unit of hereditary (DNA) that makes a functional RNA or protein
- The human genome is 3 billion characters long
- The human genome contains ~ 25,000 genes

Overview of gene expression: DNA → RNA → Protein

- Genes are made of DNA, a **nucleic acid** made of monomers called nucleotides
- A gene is a unit of inheritance that codes for the amino acid sequence of a polypeptide

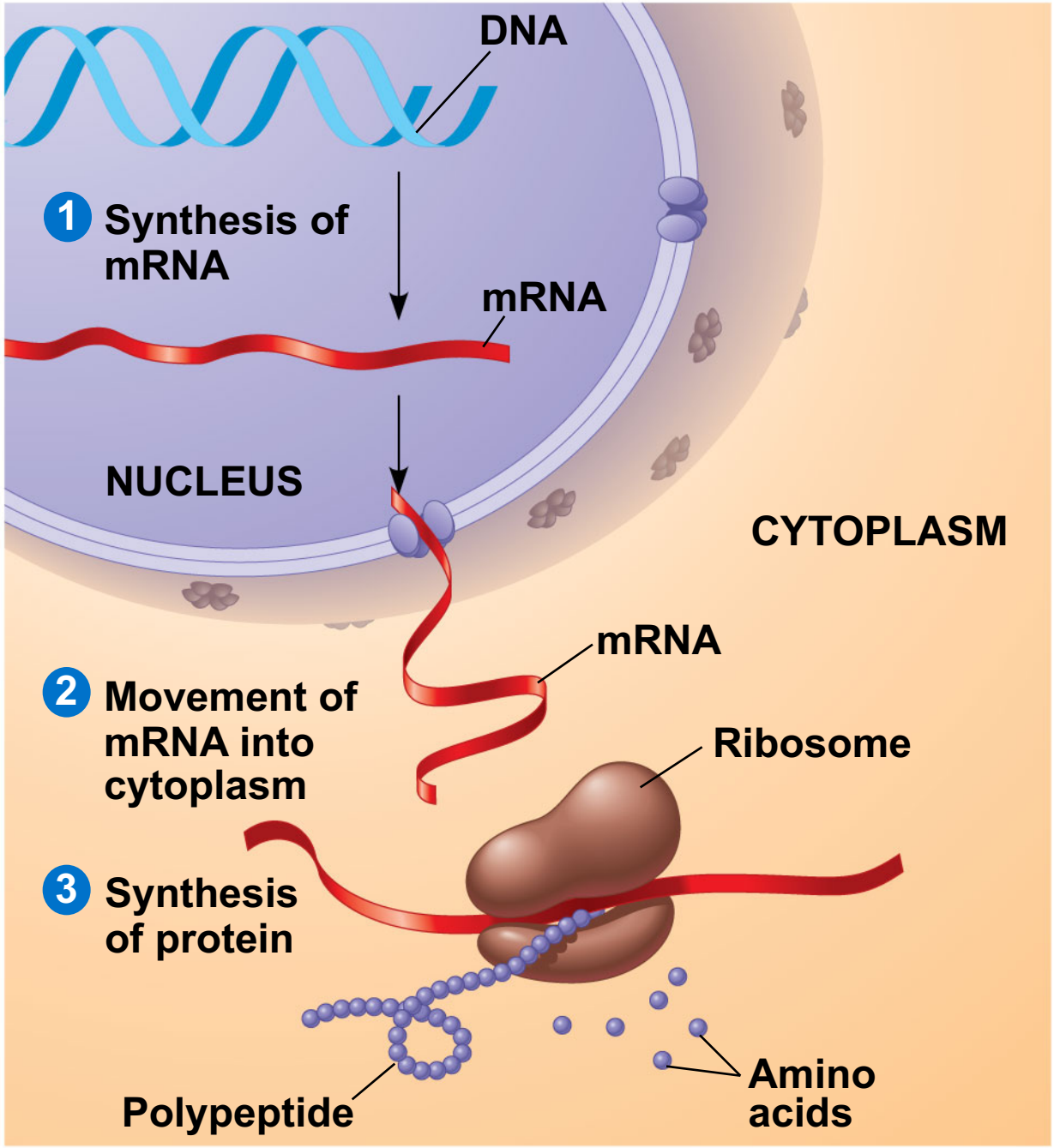
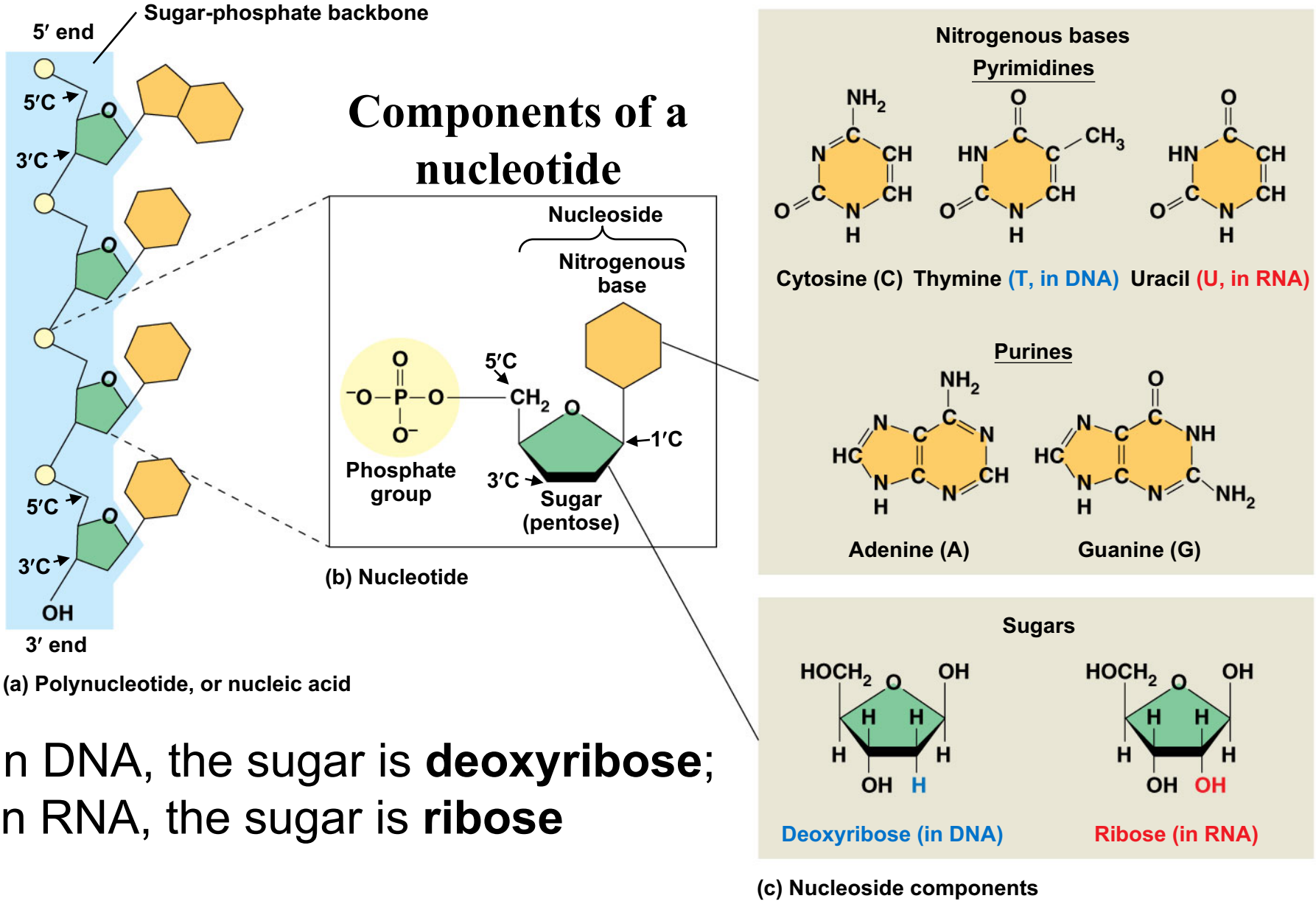


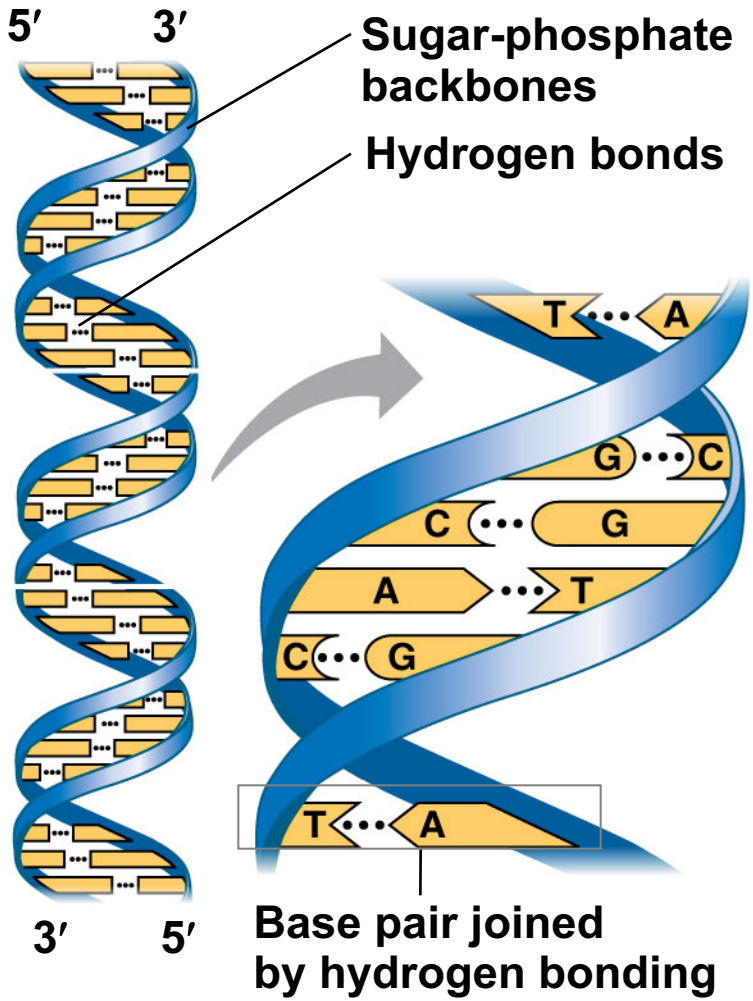
Figure 5.26



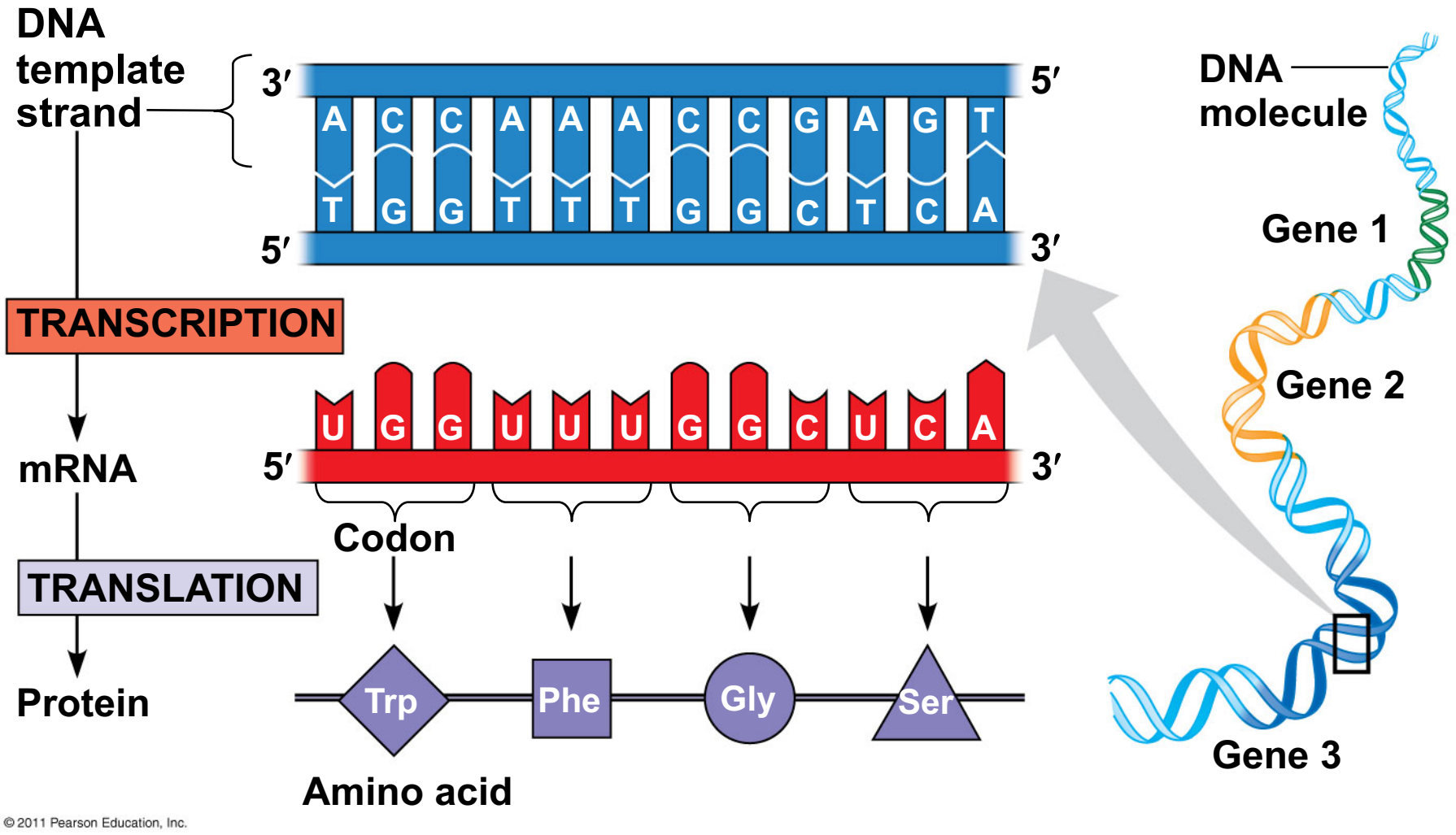
In DNA, the sugar is **deoxyribose**; in RNA, the sugar is **ribose**

Nucleic Acids are made up of nucleotides

Figure 5.27



- Complementary base pairing
  - The nitrogenous bases in DNA pair up and form hydrogen bonds: adenine (A) always with thymine (T), and guanine (G) always with cytosine (C)
  - Complementary pairing can also occur between two RNA molecules or between parts of the same molecule
- In RNA, thymine is replaced by uracil (U) so A and U pair



- The **genetic code** is a triplet code where a 3-nucleotide DNA word codes for a 3-nucleotide mRNA word (a **codon**) which codes for an amino acid

Mutations of one or a few nucleotides can affect protein structure and function

- **Mutations** are changes in the genetic material of a cell or virus
- **Point mutations** are chemical changes in just one base pair of a gene
  - May or may not change the protein
- **Insertions/deletions** may cause **frameshift** mutations that have a disasterous effect on the protein

Sickle-Cell Disease: A Change in Primary Structure

- A slight change in the amino acid (primary structure) can affect a protein's structure and ability to function
  - What causes a change in the primary structure?
- **Sickle-cell disease**, an inherited blood disorder, results from a single amino acid substitution in the protein hemoglobin

Point mutation that causes sickle cell disease

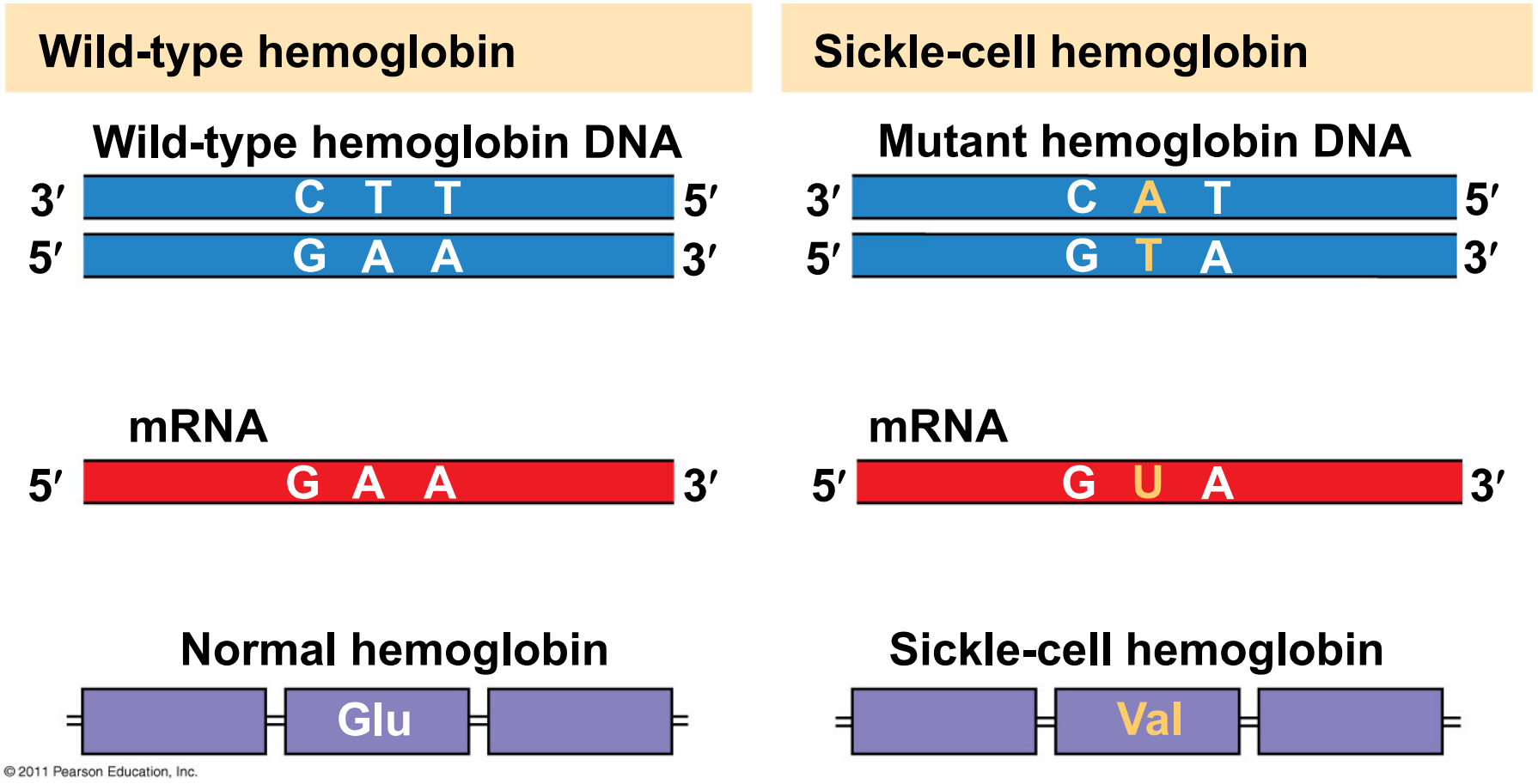
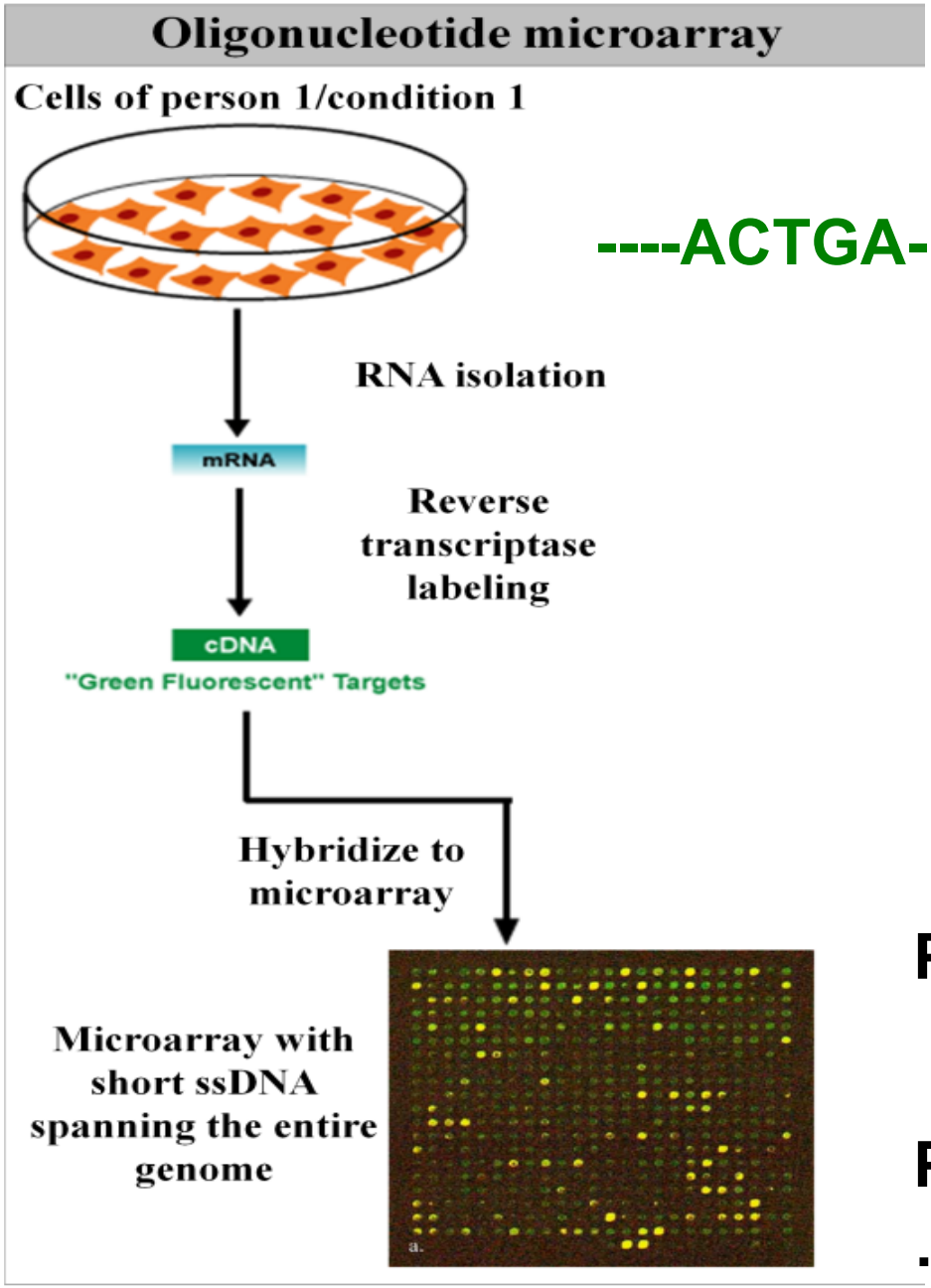


Figure 5.21

	Primary Structure	Secondary and Tertiary Structures	Quaternary Structure	Function	Red Blood Cell Shape
Normal hemoglobin	1 Val 2 His 3 Leu 4 Thr 5 Pro 6 Glu 7 Glu	β subunit	Normal hemoglobin α β α β	Molecules do not associate with one another; each carries oxygen.	10 μm
Sickle-cell hemoglobin	1 Val 2 His 3 Leu 4 Thr 5 Pro 6 Val 7 Glu	Exposed hydrophobic region β subunit	Sickle-cell hemoglobin α β α β	Molecules crystallize into a fiber; capacity to carry oxygen is reduced.	10 μm



----ACTGA----

----ACTGA----

----GAGAT----

Probe 1: TGACT

Probe 2: CTCTA

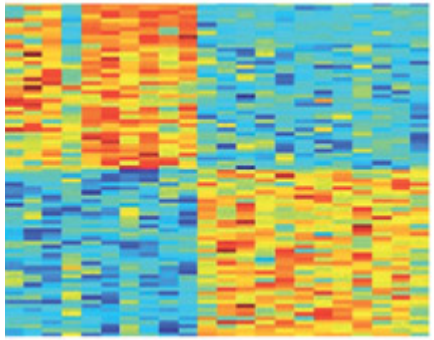
…

Probe 20000: TTTAG

Biomarkers and personalized medicine

Gene expression profiles

Samples

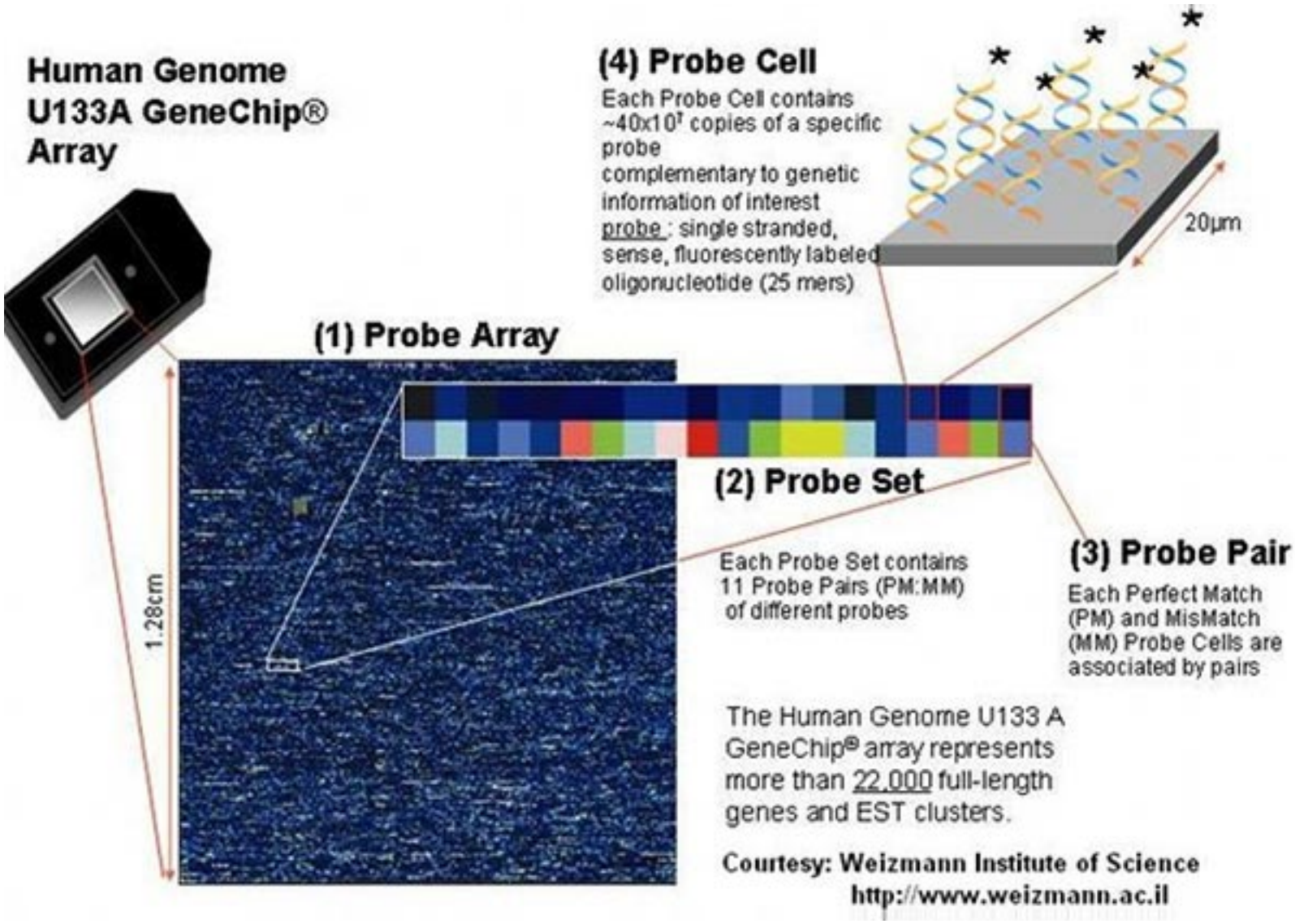


- Bioinformatics challenges
  - Identification of genes or gene signature
  - Choice of classification method or gene model

Possible comparisons

A	B	**Biomarker identification (gene or gene signature)**
Tumor	Normal	*Diagnostic*: predictive of a clinical variable
High risk	Low risk	*Prognostic*: predictive of disease outcome
Responder	Non-responder	*Predictive*: predictive of therapeutic response

Microarrays in more detail



http://www.oceanridgebio.com/images/system_rev_630.jpg

Microarray Analysis

- Analysis will be performed using several Bioconductor packages (http://bioconductor.org)
- Data is available from the Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo/)
  - We will look at how to download raw and processed data from GEO

Gene Expression Omnibus (GEO)

- GEO (http://www.ncbi.nlm.nih.gov/geo/) is a public functional genomics data repository for gene expression (microarray) and sequence-based data.
- There are four kinds of records on GEO (http://www.ncbi.nlm.nih.gov/geo/info/overview.html)

Gene Expression Omnibus (GEO)

- A **GEO sample** (GSM*) describes an individual sample, including the experimental conditions in which it was collected, and the gene expression value for each element on the array.
- A **GEO platform** (GPL*) is a summary of the array used, and links the array probes to genes
- A **GEO series** (GSE*) links together a collection of samples with one or more platforms for a particular experiment or study (such as profiling gene expression from 100 patients with lung cancer)
- A **GEO dataset** is a curated collection of samples that allows for user-friendly analysis. Not all series exist as datasets.