A Short History of DNA Technology
1865 - Gregor Mendel
The Father of Genetics

The Augustinian monastery in old Brno, Moravia
1865 - Gregor Mendel

- Law of Segregation
- Law of Independent Assortment
- Law of Dominance
Genetics of *Drosophila*

- Short generation time
- Easy to maintain
- Only 4 pairs of chromosomes
1915 - T.H. Morgan

- Genes located on chromosomes
- Sex-linked inheritance
- Gene linkage
- Recombination
- Genetic mapping (cross-over maps)
1865

1928 - Frederick Griffith

Transformation of *Streptococcus pneumoniae*

“Rough” colonies “Smooth” colonies

Living S cells

Living R cells

Heat killed S cells

Heat killed S cells mixed with living R cells

Living S cells in blood sample from dead mouse

Bacterial Strain

Injection

Results
One Gene - One Enzyme Hypothesis

**Neurospora crassa**

- Ascus
- Fruiting body

- Ascospores placed on complete medium
- Fragments placed on minimal medium

- All grow
- No growth in mutants

- Minimal
- Minimal + vitamins
- Minimal + amino acids
- Minimal plus:
  - Cys
  - Glu
  - Arg
  - Lys
  - His

**X-rays**

Mutant deficient in enzyme that synthesizes arginine

1865

Beadle & Tatum - 1941
1865

**Beadle & Tatum - 1941**

### Wild type

- Minimal Medium
- Ornithine +
- Citruline +
- Arginine +

**Gene A**
- Precursor
- Enz A
- Ornithine
- Enz B
- Citruline
- Enz C
- Arginine

### Class I Mutants

- Minimal Medium
- Ornithine +
- Citruline +
- Arginine +

**Gene B**
- Precursor
- Enz B
- Citruline
- Enz C
- Arginine

### Class II Mutants

- Minimal Medium
- Ornithine +
- Citruline +
- Arginine +

**Gene C**
- Precursor
- Enz A
- Ornithine
- Enz B
- Citruline
- Enz C
- Arginine

### Class III Mutants

- Minimal Medium
- Ornithine +
- Citruline +
- Arginine +

**Metabolic block**
- Precursor
- Enz A
- Ornithine
- Enz B
- Citruline
- Enz C
- Arginine
1944 - Avery, MacLeod & McCarty

Purified DNA as transforming factor

- Work not well-received
- Protein more complex & better able to store information

Oswald Avery

Colin MacLeod

Maclyn McCarty
DNA bases follow certain “rules”

- Base composition is species specific
- A = T, C = G for all species
1952 - Hershey & Chase

Viral DNA (not protein) programs cells

Bacteriophages

Martha Chase & Alfred Hershey
1952 - Hershey & Chase

Radioactive phage infects bacterial cells

T2 Phage

Radioactive protein ($^{35}$S)

Bacterium

Centrifuge and measure radioactivity in pellet and supernatant

Blender separates protein coats from bacterial surface

Radioactivity in supernatant, but not pellet
Therefore, it is the viral DNA, and not protein, that programs cells to make copies of the virus.
1953 - Franklin & Wilkins

Elucidation of the helical nature of DNA

Rosalind Franklin

Photographic film

X-ray source

Crystallized DNA

Maurice Wilkins
1953 - Watson & Crick

Description of the 3-D structure of DNA

Francis Crick & James Watson
What they deduced from:

Franklin’s X-ray data
- Double helix
- Uniform width of 2 nm
- Bases stacked 0.34 nm apart

Chargoff’s “rules”
- Adenine pairs with thymine
- Cytosine pairs with guanine
What they came up with on their own:

- Bases face inward, phosphates and sugars outward
- Hydrogen bonding
- Hinted at semi-conservative model for replication
1957 - Francis Crick

Proposal of the Central Dogma
DNA replication is semi-conservative

1958 - Meselson & Stahl

Conservative Model

Semiconservative Model

Parent cell

First replication

Second replication

Frank Stahl

Matt Meselson
Bacteria grown on heavy nitrogen (\(^{15}\text{N}\)) medium

Bacteria transferred to light nitrogen (\(^{14}\text{N}\)) medium

Centrifuge samples in a density gradient

After 20 minutes (1 replication)

After 40 minutes (2 replications)

Predicted outcome based on the conservative model

Hybrid

Predicted outcome based on the semiconservative model
Discovery of restriction endonuclease

Hamilton Smith
- Discovered *HindII* in *Haemophilus influenzae*

Daniel Nathans
- Used *HindII* to make first restriction map of SV40
1865

1972 - Paul Berg

Produces first recombinant DNA using *EcoRI*

*EcoRI* recognition sites

Plasmid DNA

*EcoRI* cuts DNA into fragments

Sticky end

The two fragments stick together by base pairing

Recombinant DNA

DNA ligase
Transform *E. coli* with recombinant plasmid

- **Kanamycin resistance gene**
- **Tetracycline resistance gene**
- **Plasmid pSC101**

*E. coli* transformed with recombinant plasmid

Transformed cells plated onto medium with kanamycin and tetracycline

Only cells with recombinant plasmid survive to produce colonies

- **Stanley Cohen & Annie Chan**
- **Herbert Boyer**
First human protein (somatostatin) produced from a transgenic bacterium

- Company founded by Herbert Boyer and Robert Swanson in 1976
- Considered the advent of the Age of Biotechnology
1977 - 2000 The Floodgates Open

1977
- Walter Gilbert and Allan Maxam devise a method for sequencing DNA.

1978
- David Botstein discovers RFLP analysis

1980
- U.S. Supreme Court rules that life forms can be patented
- Kary Mullis develops PCR. Sells patent for $300M in 1991

1981
- First transgenic mice produced

1982
- The USFDA approves sale of genetically engineered human insulin
1983
- An automated DNA sequencer is developed
- A screening test for Huntington’s disease is developed using restriction fragment length markers.

1984
- Alec Jeffreys introduces technique for DNA fingerprinting to identify individuals

1985
- Genetically engineered plants resistant to insects, viruses, and bacteria are field tested for the first time
- The NIH approves guidelines for performing experiments in gene therapy on humans
1987
• invention of YACs (yeast artificial chromosomes) as expression vectors for large proteins

1989
• National Center for Human Genome Research created to map and sequence all human DNA by 2005.

1990
• UCSF and Stanford issued their 100th recombinant DNA patent and earning $40 million from the licenses by 1991.
• BRCA-1 discovered
• First gene therapy attempted on girl with immune deficiency
1977 - 2000 The Floodgates Open

1992
- U.S. Army begins "genetic dog tag" program

1994
- The Flavr Savr tomato gains FDA approval
- The first linkage map of the human genome appears

1995
- The first full gene sequence of a living organism is completed for *Hemophilus influenzae*. 
- O.J. Simpson found not guilty despite DNA evidence

1996
- Genome of *Saccharomyces cerevisiae* is sequenced
1977 - 2000 The Floodgates Open

1997
- Dolly cloned from the cell of an adult ewe
- DNA microarray technology developed

1998
- The first animal genome (\textit{C. elegans}) is sequenced

1999
- 1,274 biotechnology companies in the United States
- At least 300 biotechnology drug products and vaccines currently in human clinical trials
- Human Genome Project is on time and under budget, the complete human genome map expected in five years or less

2000?