1. History of Bioprocessing

10,000 - 7,000 BC	Wine making develops in Eastern Mediterranean. Dionysus credited with invention.
7,000 - 5,000 BC	Beer develops in Egypt and Babylon.
5,000 BC	Cheese making - some medicinal properties believed
4,000 BC	Yeast used for leavening bread.
500 BC - 0	Vinegar referenced in old testament.
0 - 500 AD	Algae cultivated for food by Aztecs.
?	Yogurt, sauces and fermented meats in orient

1600 Fermentation used (latin for “yeast” = fermentum), meaning a chemical change accompanied by effervescence.

1680 Antonie Van Leeuwenhoek observed yeast cells in fermented beer.

1721 First inoculation of smallpox in England and the colonies. Lady Mary Wortley Montagu and Zabdiel Bolyston.

1781 Pressed Baker’s Yeast produced by Dutch Process. Improvement in handling of yeast through mid-1800s.

1798 Edward Jenner demonstrated ability to confer resistance to smallpox by vaccination.

1837 Cagniard-Latour, Schwann and Kutzing independently hypothesized that yeast was a “living thing.” Cell Theory. Notion ridiculed by leading chemists.

1847 Blondeau (Physics professor) studied fermentations of lactic acid, butyric acid, acetic acid and urea. Hypothesized that different fermentations carried out by different fungi.

1856 Pasteur demonstrated that living yeast cells ferment sugar into ethanol and CO_2. Also noted cylindrical organisms produce butyric acid only in absence of oxygen.

1859	Darwin publishes The Origin of Species.
1877	Pasteur noted relationship between microorganisms and infectious disease.
1881	Koch developed techniques for the handling and maintenance of pure cultures of organisms. Heralded modern industrial fermentation technology. Commercial production of lactic acid by an anaerobic fermentation.
1894	Takamine patented process to isolate diastatic enzymes from molds (enzymes which break down starch in malt).

1916 - 1918	Germany produces Baker's Yeast grown on molasses as a protein supplement, and produces glycerol by fermentation. Great Britain produces acetone-butanol. (Last ABE fermentation in RSA in mid-1980s.)
1921	Banting, Best, Macleod, Collip extracted and purified insulin from dog pancreas and eventually fetal calves. Administered to children to demonstrate that it reversed effects of diabetes. Banting and Macleod receive Nobel Prize in Medicine (1923).
1923	Commercial production of citric acid by surface cultures. (By late 1980's 100% of world production is by submerged fermentation.)

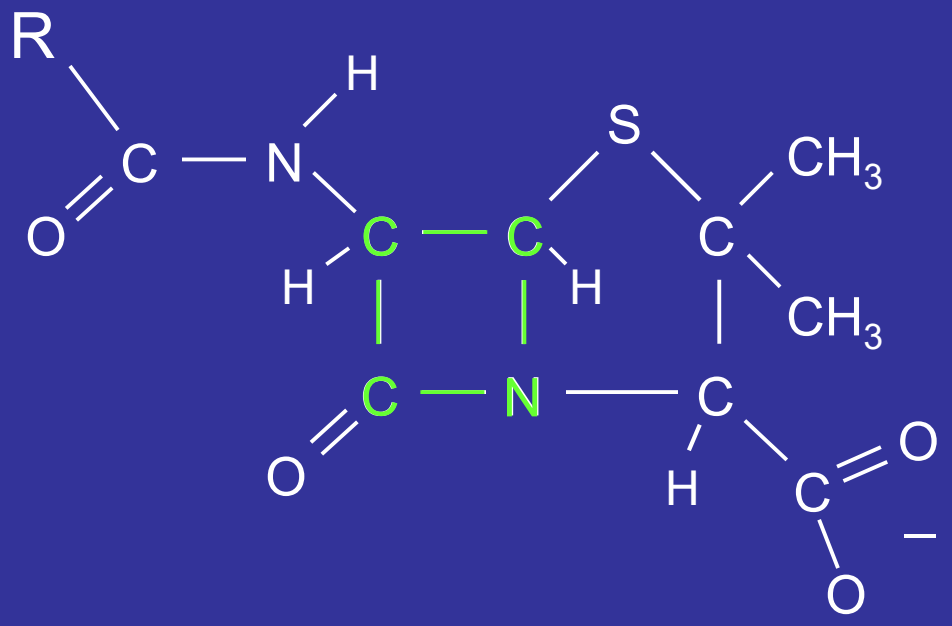
1929 Fleming demonstrated that mold contaminant on a petri dish caused bacterial death.

1934 Gautheret successfully cultured plant cells.

1940 Howard Florey and Ernst Chain isolated penicillin, theorized its structure and demonstrated its bactericidal properties. Developed process to produce penicillin. Nobel Prize 1945 with Fleming.

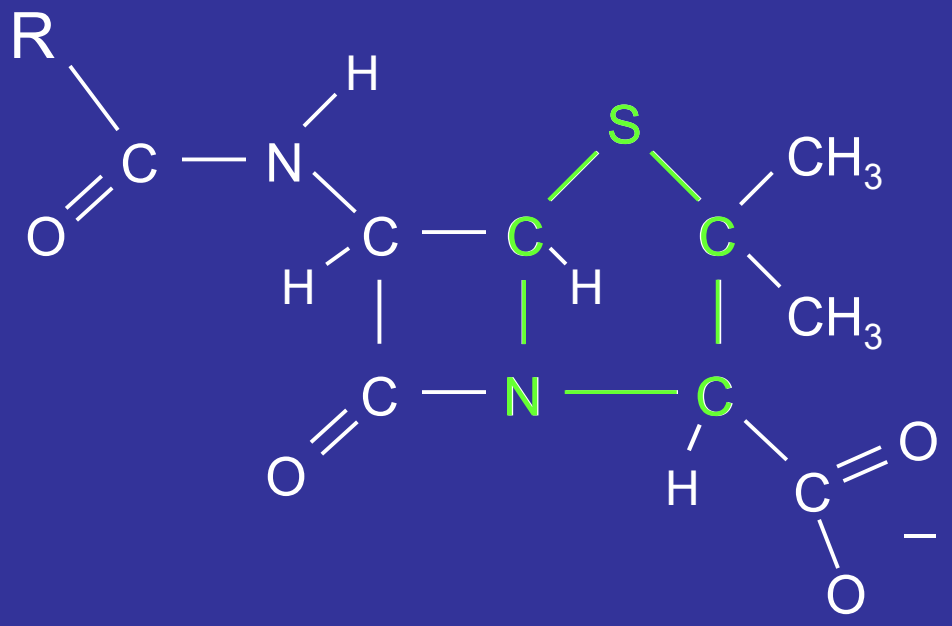
1945 Dorothy Crowfoot Hodgkin pioneered X-ray crystallography for determination of molecular structure. Solved structure of penicillin (1945), vitamin B_{12} (cobalamin, 1955) and insulin (1969). Nobel Prize 1964

Penicillin



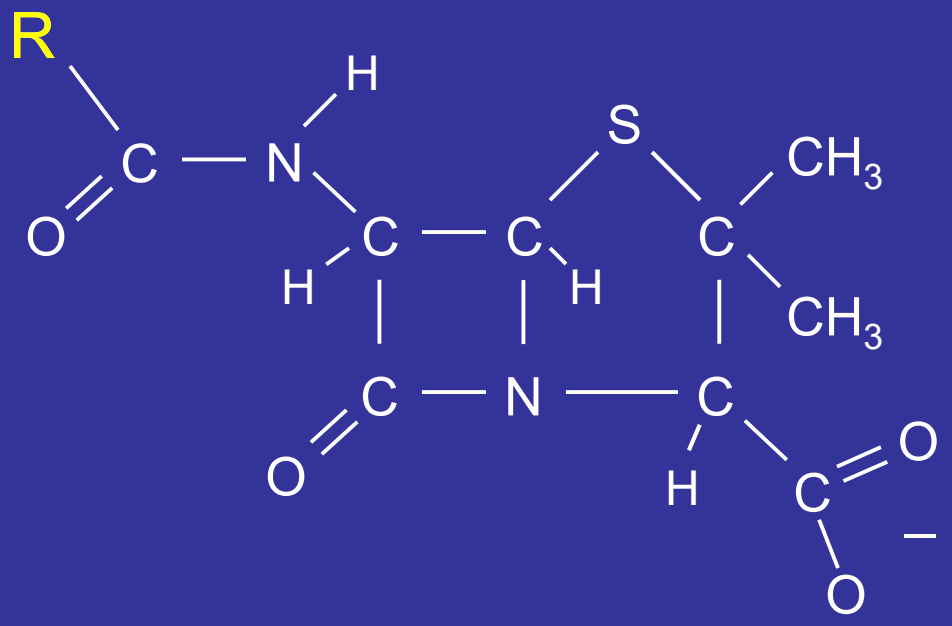
β-Lactam Ring

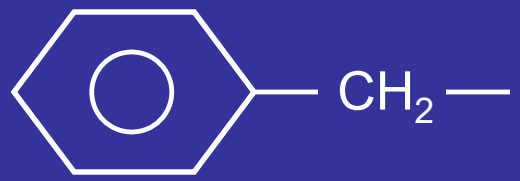
Penicillin



Thiazolidine Ring

Penicillin



R = 

Penicillin G

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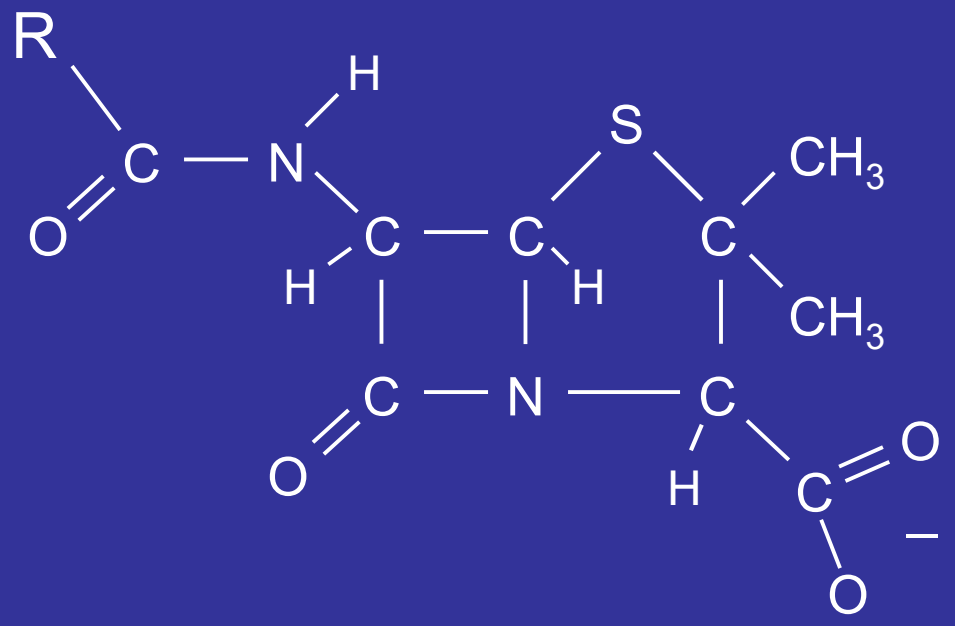

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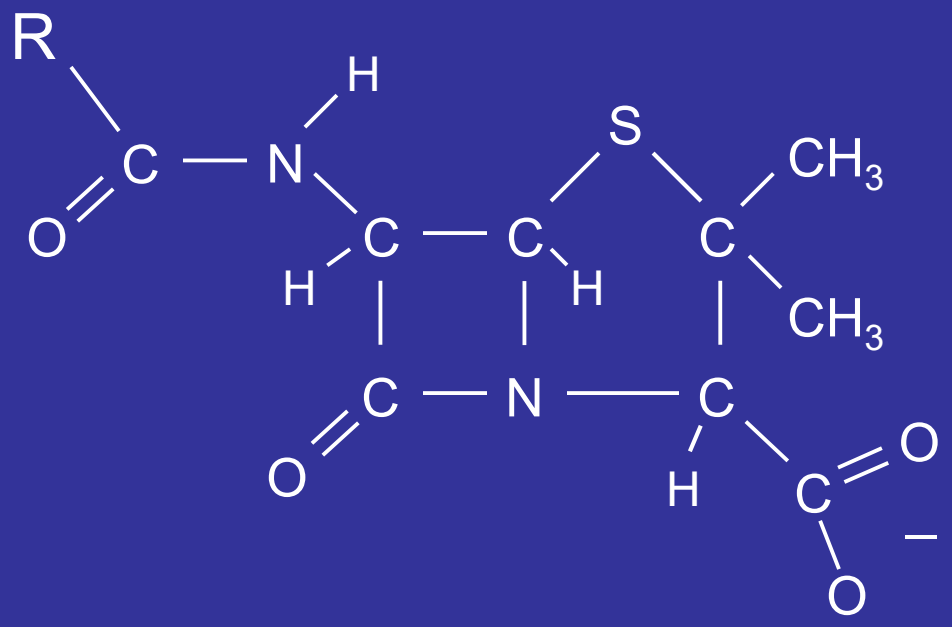

- Original strain (Fleming) produced penicillin at 1.2 mg/L. Current strains produce penicillin at 50 g/L.
- Inhibitor of bacterial cell wall synthesis
- Inhibits transpeptidase and alanine carboxypeptidase
- Very low mammalian toxicity
- Extremely unstable

Penicillin

Original motivation was just to produce enough penicillin for the war effort. Used bran surface cultures - slow, impractical, with low productivity.

http://www.youtube.com/watch?v=UJ6KTKVxkcM
https://www.youtube.com/watch?v=896YNlWxZI0

Engineering challenges for submerged cultures:

1) Need sterilizable tanks, seals, piping, valves, etc.
2) Need high flowrate of sterile, clean air (1.0 vvm max)
3) Need large agitators to dissolve oxygen from air
4) Need to remove heat from metabolism and agitation
5) ~~Need recovery operation (i.e., purify 1.2 mg/L penicillin)~~

Beyond the scope of this course

1940s Streptomycins
Vitamin B12 (still exclusively produced by fermentation)

1950s Cortisone ($200/g ⟶ $16/g)
Polio and pertussis vaccines

1960s Xanthan gum
Alkaline proteases (detergents)
http://www.youtube.com/watch?v=x4q1qXX4yhI
http://www.youtube.com/watch?v=2xPG1KXfUwU

1970s Glucose isomerase for production of HFCS
Kohler and Milstein develop monoclonal antibodies.

1980s Poly(hydroxybutyrate)

1990s	Lysine, Threonine, Isoleucine
	Antibodies
	Lactic acid (rebirth)
2000s	1,2 - Propanediol
	Xylitol
	Hydroxypropanoic acid
2010s	1,4 – Butanediol (Genomatica)
	Succinic acid (Myriant, BASF)