CLASS 1

Recurring Themes

Unmet healthcare needs from society	Innovations from modern technology	Commercial opportunities

Definition of Biotechnology
Integrated use of biochemistry, microbiology and engineering sciences in order to achieve technological (industrial) application of the capabilities of microorganisms, cultures tissue cells and parts thereof

ABC in Molecular Biotechnology
DNA —transcription→ RNA —translation→ Protein
DNA discovery: Watsons and Crick 1953

CLASS 2 : Recombinant DNA Technology and the Birth of Genentech

What would happen if the error rate of DNA replication were zero?
- No evolution
- No life
- A self-sustaining chemical system capable of Darwinian evolution

In Central Dogma, does biological information always flow from DNA to RNA to Protein?
Reverse transcriptase is an exception.
64 triplet codons
254 quadruplet codons

Genetic Engineering Technology (Genentech)
- It is the foundation of modern biotechnology. Before the biotechnology revolution, drugs were either chemically synthesized/extracted from natural sources/fermentation
- Genetic engineering opens a new ways to make drugs using natures machinery
- Synthetic Biology : each cell is a factory
- Recombinant DNA technology combines the genetic materials of more than one species to produce a new genetic template
- The expression of the recombinant DNA in cell cultures enables the production of protein products

Steps in Gene cloning and Expression
1. Obtain gene of interest
2. Insert the gene into host cells
3. Select cells that contain the desired gene
4. Induce the bacteria to make protein from the “foreign” gene
5. Collect and purify products

Plasmid Vector + DNA fragment to be cloned	
↓	Enzymatically insert DNA into plasmid vector
Recombinant plasmid	
↓	Mix E.Coli with plasmids in presence of CaCl2 Culture on nutrient agar plates containing ampicillin
Transformed E.Coli cell survives Cells that no dot take up the plasmid die on ampicillin plates	
↓	Independent plasmid replication Cell Multiplication
Colony of cells each containing copies of the same recombinant plasmid	

Plasmids: Gene Carriers
1. Plasmid DNA and foreign DNA are both cut with the same restriction enzyme
2. Foreign DNA is inserted into the plasmid, where it inactivates the B-galactosidase gene
3. The recombinant plasmids introduce into the bacterium
4. All treated bacteria are spread on a nutrient agar plate and incubated
5. Colonies that grow on the plate contain a plasmic. Blue contains plasmids without inserts. White colonies contain recombinant plasmids. Cells that do not take up any plasmids do not grow.

Restriction enzymes : Molecular Scissors
1. Restriction enzyme cuts double-stranded DNA at its particular recognition sited
2. These cuts produce a DNA fragment with two sticky ends
3. When two such fragments of DNA cut by the same restriction enzyme come together, they can join by base-pairing
4. The joined fragments will form either a linear molecule or a circular one. Other combinations of fragments can also occur
5. The enzyme DNA ligase is used to unite the backbones production a molecule of recombinant DNA

New Capital
Venture capital feeds the incubation stage providing the initial stage.
The first human protein was successfully made within 9 months

CLASS 7 : Moderm Vaccine Development

Vaccine works since immune system remembers

Defining Business Opportunities for Vaccine Development

1. Science and technology
2. Financing and marketing
3. Management and Regulations

Vaccines against HBV (Hepatitis B Vaccines)

Merck Vaccine Businesses: Merck's interests in the vaccine business originated from it predecessor in early 20th century

Recombivax HB

- The first human vaccine produced using recombinant DNA technology, which gained approval in Europe and US in 1986
- Technology diffusion : given an example of how modern biotechnology revolutionized a division within a large pharmaceutical company
- The Recombivac story illustrates the favourable acts and challenges in developing and innovative product

Need of Vaccine Against Hep B

- Hepatitis B causes liver infection, leading to serious complication (eg. liver cancer)
- Statistics of HBV infection
    - There were about 300 million carriers worldwide
    - Highest frequency in developing countries and ¼ died after contracting the infection
    - In US, 300,000 people infected annually, among them 10,000 required hospitalization and 250 died
    - HBV was the second leading cancer-causing agent
- In 1985, Hep B ranked on top on the priority list for vaccine development by Institution of Medicine in US

Problems and Solutions

- Enemy revealed in 1960s: HBV isolated
- Taking out the enemy was not straightforward
    - Hepatitis B virus cannot be grown in cell culture using conventional methods
- First attempt (1968-81) – Heptavax B
    - Source of HBV antigen: patient blood
    - Heptavax-B was launched in 1982

New Biotechnology Platform for Vaccine Development (1975-1986)

- Recombinant DNA technology has just proven its feasibility around 1980s
- A tempting possibility: produce HBV antigen in microorganism
    - Never been done before
    - Yeast as a host provides the final solution obtain current antigen form (protein folding)
    - New bioprocess plant required for production

Other Sides of the Story

1. Human factors for success
    a. Leadership Collaboration with Chiron and UC
2. Economic Force
    a. Safer product commands higher price (US$149.2 for 3 doses in 1986)
    b. Return to the company croms from private sector
    c. Dilemma faced by Merck in selling vaccines to government and developing countries

Clear and Present Danger of HPV

- Almost all cervical cancer are caused by a few strains of HPV
- The vaccine against cervical cancer is socially acceptable in HK

HIV epidemic

- Since the start of the epidemic, HIV has infected more than 60 million people and AIDS has costed nearly 20 million lives
- HIV continues to spread, causing more than 14,000 new infections every day, 95% of these are in the developing world
- Antiretroviral treatment development in the west is too expensive for developing countries

The Quest For HIV Vaccines

- More than 3 decades have passed since the beginning of AIDS epidemic
- More money has spend of research for a vaccine against than HIV than any other virus in history

Challenges For Find an AIDS Vaccine

- Rapid virus mutation
- HIV hijacks the body's defense system
- HIV is able to thwart attack by antibodies (humoral response): VaxGen's clinical trials using HIV's surface protein (gp120) as antigen failed to show protection
- Merck's T-cell vaccine (triggering cell-mediated response) against HIV failed to offer protection or reduced viral load
- Predictive value of animal model questionable

Concept of DNA vaccines: use engineered DNA to induce an immunologic response in the host against bacteria, parasites, viruses, and potentially cancer

Advantages of DNA Vaccine

- It can recruit T-cells to attack infected cells
- It can elicit response against conserved inter protein
- Manufacturing process for DNA vaccines against different indications is similar

Glimpse of Hope

- Combination of cell mediated and antibody response
- First-ever albeit modest success (~31%) of AIDS vaccine (RV144 trial, a Thailand strain) in 2009
- Some people are born immune to HIV
- Discovery people are born immune to HIV
- Discovery of broadly neutralizing antibodies
- Non-profit organization and charity fund is driving the glocal development of AIDS vaccines

RNA Vaccines

RNA vaccines work by introducing an mRNA sequence (the molecule which tells cells what to build) which is coded for a disease specific antigen, once produced within the body, the antigen is recognised by the immune system, preparing it to fight the real thing

RNA vaccines are faster and cheaper to produce than traditional vaccines, and a RNA based vaccine is also safer for the patient, as they are not produced using infectious elements

Manufacturing of Human Tissues

- Cost-effective and allow for scale-up
- Production quantity of 100–1000 constructs per week
- Bioreactor technology
    - Providing the right chemical and mechanical environment
    - Modeling of constructs in vitro
- Off the shelf availability and shelf life of constructs

Evolution of TE and its commercial development

1. **The best of times (early 1990s—2001)**
    a. Funding mostly from venture investors;
    b. Government support accounts for <10%;
    c. Total private sector investment > USD 3.5 billion
    d. At the end of this era: 70 start-up and business units, 3300 employees, annual expenditure> USD 600 million at an annual growth rate of 16%
    e. Capital value of 16 publicly traded start-ups >USD 2.5 billion
    f. TE products launched: Apligraf®, Carticel®, Dermagraft®
2. **The worst of times (2001-2003)**
    a. Spending declined by 20% following the dot-com crash
    b. 19 out of 73 firms filed for bankruptcy or closed
    c. Genzyme Tissue Engineering downsized
    d. Capital value of publicly traded TE companies fell from USD 2.5 billion to 300 million
    e. All 9 leading TE product candidates failed to obtain FDA approval: unsatisfactory clinical data or abandoned clinical trials
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4. **Rebirth /rebound(2003-present)**
    a. Industry grew by 5 folds in 5 years from 2003-2007. Spent USD 850 million in R&D in 2007.
    b. By mid-2007: ~50 TE firms or business units with over 3000 employees generated annual sales >=USD 1.3 billion
    c. Additional 110 development-stage companies with over 55 products in preclinical/clinical trials, with over 2500 employees
    d. Capital value of publicly traded firms= USD 4.7 billion (2007)
    e. Change of funding structure: less from VCs, more from government (e.g. SBIRS , NIH) and large firms. Worldwide government support ~ USD 1 billion
    f. Product types: from “whole organ” concept to acellular products (“organoid”) or cell-based therapy
    g. Preferred regulatory routes: Device (CDRH) and Institutional Review Board (IRB) over Drugs (CDER) and Biologics (CBER);
    h. Internationalization outside USA: Europe (e.g. Germany, UK, Holland) and Asia (e.g. Singapore, Korea, China)
    i. Dilution of science
    j. Discipline in management