

Vaccination

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Scope of vaccination

- Induce active immunity
 - Stimulate an immune response in many that mimics a protective immune response in a few
 - Vaccinia for smallpox prevention
 - Hep B sAg for Hepatitis B prevention
- Prevent/mute immunity
 - Prevent sensitization of Rh⁻ mothers to Rh Ags of fetus/conceptus /newborn
 - Polyclonal anti-RF (RhoGam®) antibodies

Anti-Rh vaccine

- Given at childbirth to Rh⁻ mothers giving birth to Rh⁺ children (anti-Rh antibodies or “RhoGam”)
 - Prevents sensitization to Rh
- Prevents hemolytic disease of newborns
- Developed by Vincent Freda (P&S)
 - With Sir Cyril Clarke, Ronald Finn, John Gorman & William Pollack (shared a 1980 Lasker award)

Successful Vaccinations

- Successful vaccination exploits
 - Elements of protective responses from survivors
 - Directs initial immune response
- Vaccines have only been developed that recapitulate successful responses
 - Smallpox
 - Known to confer protective immunity to survivors
 - Polio
 - Known to elicit protective responses in those who recovered
- Goal of developing vaccines
 - Temporize until other elements of the immune system can resolve (or render latent) the infectious threat

Goals of Vaccination against Infectious Diseases

- Preventative (physician – patient)
 - To prepare the recipient's immune system so that should infection occur, it will result in a tolerable illness
 - Note: Vaccines do not prevent infection of vaccinated individuals
- Therapeutic (physician – patient)
 - Modify the outcome/course of an infection or infectious disease after infection
- Prevent spread of disease (government – citizen)
 - Reduce potential of infected individuals to spread disease
 - Note: Vaccination of populations prevents infection of vaccinated and non-vaccinated individuals
 - Recipients altruistically (or by compulsion) take health risks to protect others, including non-vaccinated, infants, elderly, immuno-compromised, patients with eczema (smallpox)

Protection against Bio-warfare/-terror agents

- Protect military forces against biowarfare agents (government – soldier)
 - Technology from the former USSR to weaponize anthrax and smallpox is believed to be in the hands of potential enemies such as Iran and North Korea
- Protect citizens against bioterror (government – citizens)
 - Domestic “battlefield”
 - Disseminating smallpox is “low tech” and could be employed by enemies like Al-Qaeda
- Constant research is required to protect against new threats
 - Pseudotyped viruses are relatively easy to make and no vaccines exist
 - “I am Legend” Will Smith movie about a virus designed to cure cancer pseudotypes, transforms and becomes epidemic

Accomplishments of Vaccination

- To modify the outcome/course of disease
 - Infectious disease
 - Prevent smallpox disease
 - Prevent polio disease
- Prevent spread of disease
 - Infectious disease
 - Reduce potential of infected individuals to spread disease

Smallpox

- May have been the plague that struck Egypt during the Jewish Passover exodus.
- Struck Athens during the siege laid by Sparta (571 BC) and turned the tide of the Peloponnesian wars (Thucydides).
- Repeatedly struck Roman cities and outposts (100 BC, 100 AD).
- Struck Spain during an early Moorish Conquest (561 AD) and that would presage the later and more sustained Moorish Conquest (1000-1492).
- Struck the Aztecs and helped Cortes conquer Mexico.
- Struck the Incas and led to their defeat (1561).
- Decimated Europe in the 18th Century
- Killed many Native Americans/American Indians

Smallpox and Immunity

- Smallpox was also known for a property somewhat unique among infectious diseases - to leave its survivors protected from contracting smallpox again.
- An early description of protective immunity comes from Thucydides, who describes the 532 BC pestilence in Athens
 - “...happy are those who...” survived
- This protection is now known as “immunity”.

History of Smallpox Inoculation

- Folk medicine in Turkey (“the Levant”) and Africa
- Dr. Emmanuel Timoni (aka, Timmoneus) (1714).
 - Ethnic Greek physician who lived in Istanbul, reported inoculation to Royal Academy.
 - Lady Montague (for whose husband Timoni served as translator) had a child inoculated and then promoted technique upon her return to Turkey
 - Experiment to determine efficacy on prisoners by Dr. Hans Sloane (“commotion in the blood”) and Charles Maitland, a surgeon in 1721 performed on four patients in Margate Prison
- Cotton Mather and Dr. Zebdial Boylston (Brookline, MA & Harvard)
 - Cotton Mather in the US learned about inoculation from his slave Onesimus in 1706 who had been inoculated by the medicine man in his tribe; the Gurumanche in Burkina Faso.
 - Boylston inoculated his only son and two slaves; promulgated technique in US in 1720s
- Technical improvements in inoculation
 - Lower dose, less “preparation” of patients, milder “strains” (Sutton, Dimsdale, Ingelhouz, etc.)

Introduction of Vaccination

- Cowpox vaccine (“vaccinia” – Edward Jenner)
 - Milk maids were protected from serious smallpox
 - Vaccine obtained from sores on cows’ udders, vaccine lesions
- Improvement over Inoculation
 - Vaccine had a lower mortality than Inoculation (tolerable syndrome)
 - Vaccine did not cause epidemics (decreased contagion)
- Science & biotechnology
 - Antigen Mimicry
 - Passage/Attenuation?
 - Jenner described attenuation (Horse hoofs to cow udders pox to milkers’ hands), but may not be related to effect or origin of vaccinia
 - Public health (preventive) – eradicated smallpox in 1980
 - Therapeutic vaccination (infectious cycle is faster than smallpox) could be used on infected patients

Vaccine Controversies

- Vaccine caused a mild illness, but in some cases resulted in severe illness or death
 - Jenner needed data to show that it was safer than inoculation
- Vaccine has some risk of contagion
 - Eczema vaccinatum
 - Jenner needed data to show it had less contagion risk than smallpox
- Did not protect all recipients
 - Vaccination “lymph” and technique was rapidly disseminated and practiced by a variety
 - Jenner needed to instruct on technique and insuring vaccination “took”

Inducing Virology and Immunity

- Virus

- Jenner avoided assertions about whether smallpox or vaccine were “alive”;
 - 1798 introduced the term “virus”
- Pasteur introduced concept of microorganisms, but had little understanding of rabies (viruses)
 - 1885 – Rabies vaccine from dried virus from Rabbits

- Immune system

- Described in the (20th Century)
 - Ellie Metchnikoff – cellular immunity
 - Paul Ehrlich - antibodies

Protective Immunity to Smallpox

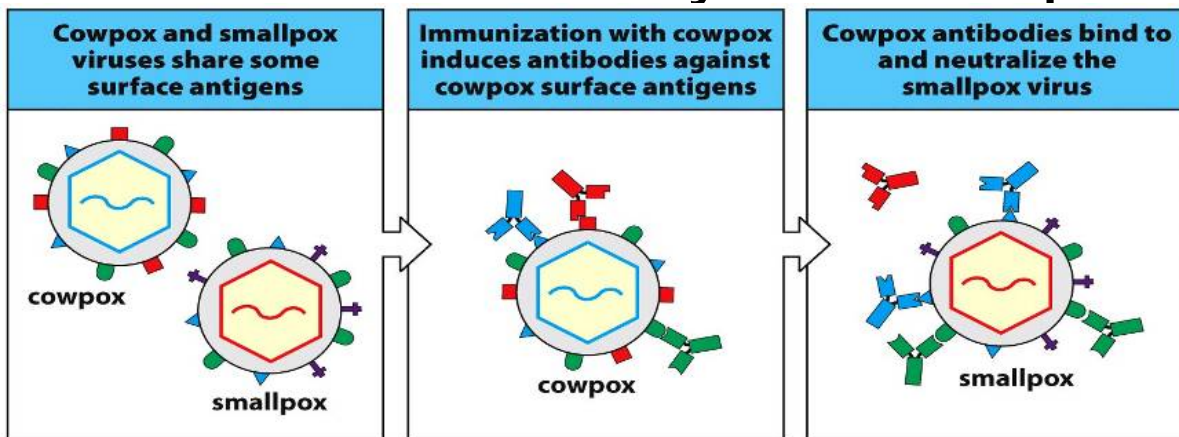


Figure 14.1 The Immune System, 3ed. (© Garland Science 2009)

- Smallpox is caused by the variola virus
- Note that Jenner's cowpox is now called vaccinia and the term "cowpox" is used for another orthopoxvirus

Anti-virals for Smallpox: Potential to reduce vaccinia complications

- Cidofovir (iv) – inhibits viral DNA synthesis
 - Approved as Vistide® (Gilead) for CMV retinitis in AIDS patients (has effects on HSV-1 and -2)
 - hexadecyloxypropyl-cidofovir (HDP-CDV, oral, Chimerix) pro-drug, is 100 times more effective than cidofovir in slowing smallpox replication in human tissue culture
- ST-246 (oral, Siga, Eric Rose is CEO) – binds envelope protein
 - ST-246 is believed to target the product of vaccinia F13L, which encodes a major envelope protein (p37) required for production of extracellular virus
 - In cell culture, ST-246 inhibits plaque formation and virus-induced cytopathic effects
 - Compassionate use is eczema vaccinatum, a potentially fatal vaccinia rash in children or patients with eczema exposed to vaccinia

Vaccinia

- Strain used today to protect against smallpox is the believed to be directly descended from Jenner's
 - Account that “vaccinia” was substituted for “cowpox” is spurious
- Vaccinia is used to express proteins from other viruses
 - Rabies – vaccinia virus (live, expressing Rabies glycoprotein) has been distributed by dropping baited doses from helicopters to immunize wild animals (US and EU)
 - Popular strategy to achieve high level expression of proteins in human cells
 - HIV – vaccinia/gp120 efficiently induces human cells to express HIV *env* in vitro

Vaccine Proliferation

- Polio Vaccines
 - Salk/Sabin – Polio
- Industry
 - Diphtheria, pertussis, tetanus (DPT)
 - Mumps, measles, rubella (MMR)
- Hepatitis B– first vaccine that protects against cancer (hepatocellular cancer)
 - Baruch Blumberg, sAg
- Hemophilus Influenza B (HIB)
 - David H. Smith & Dick Insel (Praxis -> Am. Cyanamid -> Wyeth)
 - Initially polysaccharide alone, later modified to be protein conjugate to assist in Ag presentation
- HPV – second vaccine that protects against cancer (cervical cancer)
 - Harald zur Hausen (Gardasil®, Ceravirx® - Not FDA approved)

Vaccine Design

- Understand disease (how pathogen leads to disease)
- Isolate pathogen
- Induce Immunity that targets pathogenicity
 - Live virus (attenuated)
 - Killed virus
 - Subunit
 - A phase in life cycle (or infectious cycle)
 - Toxin

Elements of Vaccines

Active Ingredients

- “Live” virus
 - attenuated or recombinant
- Killed pathogen
 - Bacteria or virus
- Subunit
 - Purified or recombinant protein(s)
- Polysaccharide
- Toxin
 - Inactivated toxoids

Important Ingredients

- Adjuvant
 - To induce immune response for all but live vaccines
- Preservative
 - Thimerisol is controversial
- Formulation
 - Excipients that control release and stability
- Administration schedule
 - Dose
 - Timing, Boosts

Available vaccines for infectious diseases in humans			
Bacterial diseases	Types of vaccine	Viral diseases	Types of vaccine
Diphtheria	Toxoid	Yellow fever	Attenuated virus
Tetanus	Toxoid	Measles	Attenuated virus
Pertussis (<i>Bordetella pertussis</i>)	Killed bacteria. Subunit vaccine composed of pertussis toxoid and other bacterial antigens	Mumps	Attenuated virus
Paratyphoid fever (<i>Salmonella paratyphi</i>)	Killed bacteria	Rubella	Attenuated virus
Typhus fever (<i>Rickettsia prowazekii</i>)	Killed bacteria	Polio	Attenuated virus (Sabin) or killed virus (Salk)
Cholera (<i>Vibrio cholerae</i>)	Killed bacteria or cell extract	Varicella (chickenpox)	Attenuated virus
Plague (<i>Yersinia pestis</i>)	Killed bacteria or cell extract	Influenza	Inactivated virus
Tuberculosis	Attenuated strain of bovine <i>Mycobacterium tuberculosis</i> (BCG)	Rabies	Inactivated virus (human). Attenuated virus (dogs and other animals). Recombinant live vaccinia-rabies (animals)
Typhoid fever (<i>Salmonella typhi</i>)	Vj polysaccharide subunit vaccines. Live-attenuated oral vaccine	Hepatitis A	Subunit vaccine (recombinant hepatitis antigen)
Meningitis (<i>Neisseria meningitidis</i>)	Purified capsular polysaccharide	Hepatitis B	Subunit vaccine (recombinant hepatitis antigen)
Bacterial pneumonia (<i>Streptococcus pneumoniae</i>)	Purified capsular polysaccharide	Human papillomavirus	Subunit vaccine (virus coat proteins)
Meningitis (<i>Haemophilus influenzae</i>)	<i>H. influenzae</i> polysaccharide conjugated to protein	Rotavirus	Attenuated virus Recombinant live virus

Figure 14.7 The Immune System, 3ed. (© Garland Science 2009)

Current immunization schedule for children (USA)										
Vaccine given	1 month	2 months	4 months	6 months	12 months	15 months	18 months	4-6 years	11-12 years	14-16 years
Diphtheria-tetanus-pertussis (DTP/DTaP)									*	
Inactivated polio vaccine										
Measles/mumps/rubella (MMR)										
Pneumococcal conjugate										
Haemophilus B conjugate (HiBC)										
Hepatitis B										
Varicella (chickenpox virus)										
Rotavirus										
Influenza										
Meningococcus C										
Human papillomavirus										

Figure 14.3 The Immune System, 3ed. (© Garland Science 2009)

Polio (Paralytic Poliomyelitis)

- **Culturing Polio Virus**
 - John Enders, Thomas Weller, Frederick Robbins –1954 Nobel Prize
- **Jonas Salk**
 - Inactivated virus (injection)
 - Refused to patent, National Hero, “Shot heard ‘round the world”
 - The Cutter Incident 1955 – live virus contaminated vaccine stock
- **Albert Sabin**
 - Live attenuated virus (oral)
 - Large field trials (100 million subjects) in the USSR at height of Cold War
 - No longer available, theory about preventing infection of blood
- **Either works**
 - Need to block virus from entering CNS

Influenza A vaccines

- Hemagglutinin (H) and Neuraminidase (N) genes are the epitopes used to type and protect against Influenza A
 - 1918 Influenza A pandemic
 - Spanish flu H1N1 - 50-100 M deaths
 - 2008 Avian flu H5N1
 - Highly pathogenic Avian Influenza (HPAI)
 - 2009 Swine flu H1N1/09
 - Young adults and children are naive

Some diseases for which effective vaccines are not yet available		
Disease	Estimated annual mortality	Estimated annual incidence
Malaria	1.1 million	300–500 million
Schistosomiasis	15,000	No numbers available
Worm infestation	12,000	No numbers available
Tuberculosis	1.6 million	8 million
Diarrheal disease	1.8 million	4–5 billion
Respiratory disease	3.9 million	~360 million
HIV/AIDS	2.7 million	5 million
Measles*	611,000	30–40 million
Hepatitis C	46,000	~170 million †

Figure 14.8 The Immune System, 3ed. (© Garland Science 2009)

Challenges for new Vaccines

Novel

- So far all vaccines are “intensifications of natural phenomena”
 - Imitate successful immune responders
 - To solve remaining infectious diseases, either successful immune responders must be identified and characterized or new approaches are needed
 - Is there protective immunity to HIV, TB, malaria?

Traditional

- Is new vaccine protection worth the risk?
 - HSV vaccine (Lawrence Stanberry, Chrm Peds)
 - EBV vaccine (will be addressed later)

Attenuation (historical)

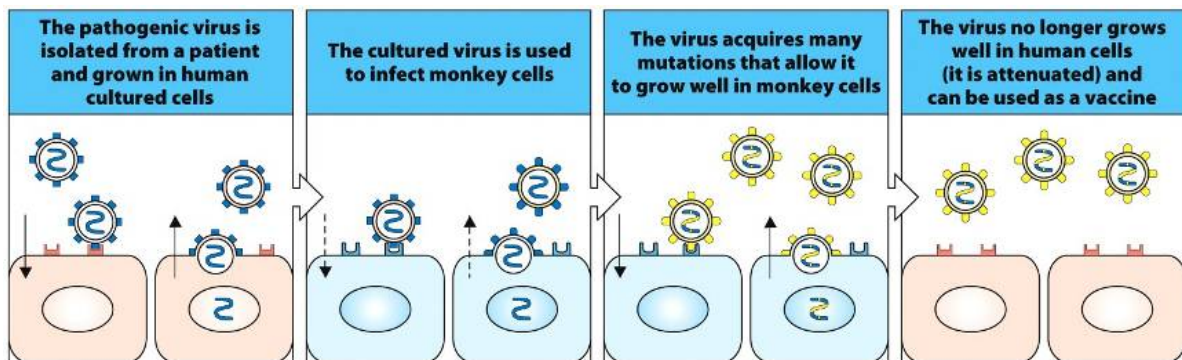


Figure 14.2 The Immune System, 3ed. (© Garland Science 2009)

Molecular Biology Approaches to Attenuation

- Molecular Biology has the potential to take some of the trial-and-error of “passage” attenuation

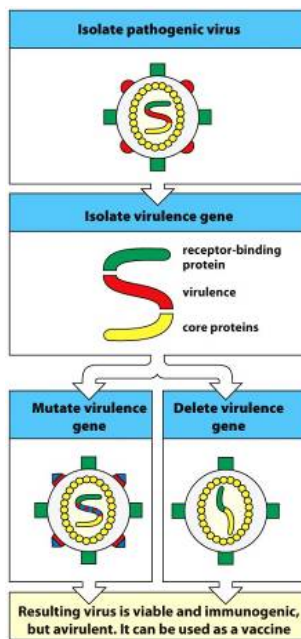


Figure 14.10 The Immune System, 3ed. (© Garland Science 2009)

Recombinant Rotavirus Vaccine

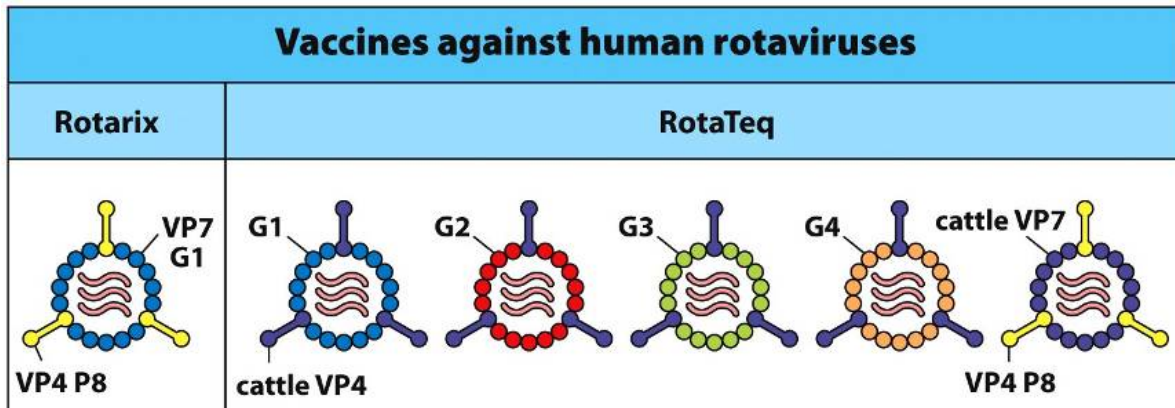


Figure 14.12 The Immune System, 3ed. (© Garland Science 2009)

Subunit Vaccines that load HLA to Stimulate T cells

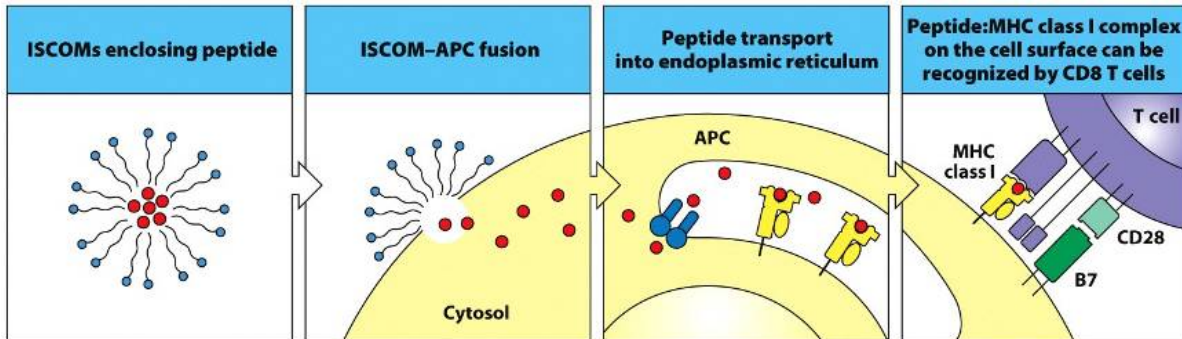


Figure 14.5 The Immune System, 3ed. (© Garland Science 2009)

- In addition to “Immuno stimulating complexes”
 - Naked DNA vaccines
 - Widely used in veterinary medicine
 - Adeno virus vector (and other recombinant viruses)
 - Experimental

Traditional Adjuvants

Adjuvants that enhance immune responses		
Adjuvant name	Composition	Mechanism of action
Freund's incomplete adjuvant	Oil-in-water emulsion	Delayed release of antigen; enhanced uptake by macrophages
Freund's complete adjuvant	Oil-in-water emulsion with dead mycobacteria	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators in macrophages
Freund's adjuvant with MDP	Oil-in-water emulsion with muramyl dipeptide (MDP), a constituent of mycobacteria	Similar to Freund's complete adjuvant
Alum (aluminum hydroxide)	Aluminum hydroxide gel	Delayed release of antigen; enhanced macrophage uptake
Alum plus <i>Bordetella pertussis</i>	Aluminum hydroxide gel with killed <i>B. pertussis</i>	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators
Immune stimulatory complexes (ISCOMs)	Matrix of lipid micelles containing viral proteins	Delivers antigen to cytosol; allows induction of cytotoxic T cells
MF59	Squalene-oil-water emulsion	Delayed release of antigen

Figure 14.4 The Immune System, 3ed. (© Garland Science 2009)

GSK's HPV vaccine Cervarix® (not yet approved by FDA) contains a New adjuvant, AS04 composed of aluminium salt and monophosphoryl lipid A (MPL), an "immunostimulant,"

Future Adjuvants

- CpG oligodeoxynucleotide (ODN) sequences mimic bacterial genomes
 - Activate human Toll-like Receptor 9 (hTLR9)
 - Coley Pharmaceuticals acquired by Pfizer
- IL-12
 - Pre-disposes to a T_H1 immune response
 - IL-12 can be given as peptide or delivered by a plasmid cDNA encoding IL-12

How do viruses cause cancers?

- Transforming Viruses
 - RNA tumor viruses that bear oncogenes have been characterized in other animals
- Chronic inflammation
 - Hepatitis B and Human Papilloma Virus are associated with human cancers and prevented by vaccines
- Infection of partially transformed cells
 - One step in multi-hit model of carcinogenesis
- Immunodeficiency
 - HIV and other immune deficiencies are associated with cancers

Transforming viruses

- RNA Tumor Viruses
 - Peyton Rous 1966 Nobel Prize "for his discovery of tumor-inducing viruses"
 - Oncogene expressing RNA viruses are not currently epidemic threats to humans
 - HTLV-1 is a transforming human retrovirus, associated with an acute T cell leukemia (but also more frequently with tropical spastic paraparesis)
 - Low incidence with blood screening
- EBV (Herpes Virus) transformation
 - EBV transforms B cells in vitro
 - Inhibited by T cells in vitro
 - TRAF-3 co-discovered for role in B cell transformation (Kieff) and CD40 signaling (Baltimore & Lederman)
 - EBV may be "causal" in Burkitt's lymphoma
 - But EBV latency phenotype is different than immunoblastic lymphoma
 - Some Burkitt's tumors are EBV- (don't have EBV genome)

Chronic Inflammation and Cancer

- Hepatitis B (HBV)
 - Baruch Blumberg 1976 Nobel Prize for Surface Antigen led to vaccine
 - Hepatitis vaccines prevent chronic active and chronic persistent hepatitis B
 - Prevent hepatocellular carcinoma
- Human Papilloma Virus (HPV)
 - Harald zur Hausen 2008 Nobel Prize “for his discovery of human papilloma viruses causing cervical cancer”
 - HPV vaccines approved
- Helicobacter pylori
 - Barry Marshall and Robin Warren 2005 Nobel Prize for Helicobacter Pylori
 - Decreased gastritis by antibiotics expected to decrease gastric cancer
- What about chronic inflammation leads to cancer?
 - Tim Wang showed that IL-1beta is sufficient to cause stomach cancer in mice
 - Differentiation of stem cell to differentiated epithelial cell carries risk of transformation
- Vaccines that prevent chronic inflammation can decrease risk of cancer

Infection of partially transformed cells

- One step in Multi-hit model of carcinogenesis
- EBV
 - Burkitt's is associated with immune activation
 - Nasopharyngeal cancer is associated with smoking and other factors

Immunodeficiency

- HIV, Immunosuppression are associated with cancer risk
 - JC Virus (progressive multi-focal leukoencephalopathy)
 - Lymphoma
- Should patients be vaccinated before being immunosuppressed?
 - Art of rheumatology: some patients are given flu shots before immunosuppression (e.g. mAb anti-TNFalpha)
 - HIV: vaccines are largely avoided because of fear that immune stimulation promotes CD4 cell depletion

Vaccines against Pathogens Associated with Cancer

- Transforming viruses
 - RNA Tumor Viruses
 - Be vigilant/be ready
 - EBV vaccine?
 - May be worthwhile
- Chronic inflammatory diseases
 - Hep B approved and widely used (US and China)
 - HPV vaccine approved (Gardasil®)
 - Helicobacter pylori vaccine?

Cancer Vaccines

- “Cancer” is term applied to over 100 distinct diseases related by malignant transformation
 - No “platform” solution, must be approached disease by disease; cancer by cancer
- Immunity and cancer
 - Is it good or bad to induce immunity to cancers?
 - May “break” tolerance and lead to anti-tumor response
 - May increase their blood supply, induce tolerance (Virchow)
 - May increase risk of stem cell transformation (Tim Wang)
 - Some cancers may be immuno-responsive (Renal Cell?)
- Personalized approaches?
 - Idiotypes in B cell cancers

Vaccination - Lederman

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Multiple Myeloma, B cell lymphoma

Future of Vaccines

- New Viruses and Pathogens
 - New pathogens (natural and man-made), new recombinations of old viruses, new toxins
- Beyond Nature
 - So far all vaccines are “intensifications of natural phenomena”
 - Can vaccines induce protective responses where the diversity of natural responses fails to instruct us?
- Cancers
 - Perhaps certain cancers are managed by immune responses in healthy people that can be mimicked by vaccines?
- Substance abuse [Don Landry]
 - Vaccine that mimics the transition state of cocaine hydrolysis (and induces antibodies that hydrolyze cocaine)

Goals of Vaccination

- To modify the outcome/course of disease
 - Infectious disease
 - Prevent Rh sensitization of mothers
 - Prevent Cancer associated with chronic inflammation
- Prevent spread of disease
 - Infectious disease
 - Reduce potential of infected individuals to spread disease

Feedback & Citations

- Questions/comments:

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- Citations

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