National Cancer Institute

Technological Innovation, Public Health, and the Private Sector

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The views expressed are my own and do not necessarily reflect those of NCI/NIH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Disclosures

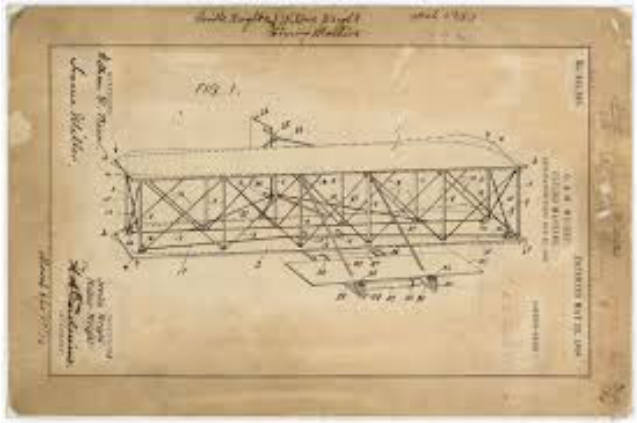
- National Institutes of Health (NIH) has patents on papillomavirus L1 virus-like particle (VLP) vaccine technology. I am an inventor.
- NIH has licensed the L1 VLP technology to Merck and GlaxoSmithKline, the two companies with commercial versions of the vaccine.
- Licensees of other NIH technologies of which I am an inventor: GlaxoSmithKline, Sanofi, Shanta Biotech, Cytos Biotech, Aura Biosciences, Etna Biotech, Acambis, PanVax

The motivation to invent

- The usual goal of an invention in biomedicine is to overcome a deficiency or inefficiency in conducting research and/or managing patients
- Most **inventions** involve an idea that leads to development of a **product**
  - Most inventors don't make the commercial product; therefore, **most inventors need attract investment from at least one company that could make the commercial product**; this requires developing the idea

Key steps for inventions

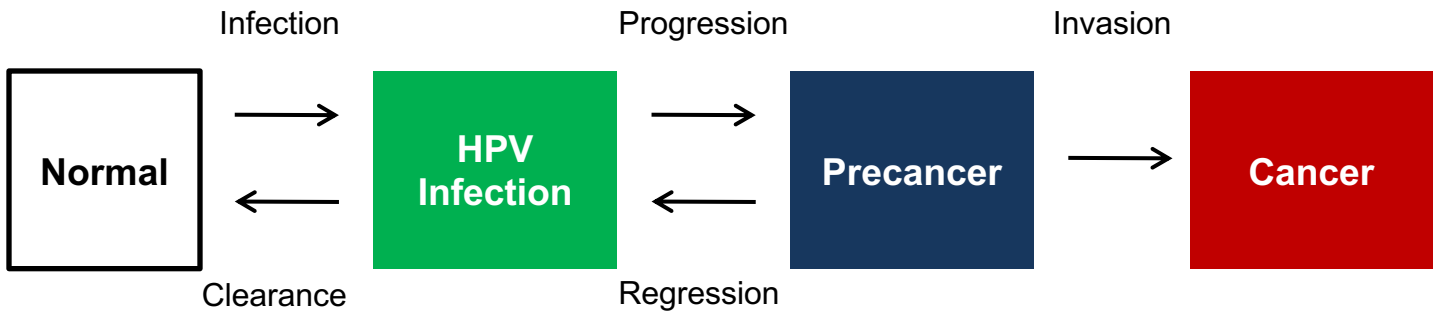
- Have **a potentially useful idea** that presumably isn't already be done by others
- Make sure you believe in it and are willing to work for its development
- Develop **intellectual property**; often depends on **technological innovation**; show the invention can work; **"reduce the idea to practice"**
- Determine what more needs to be done to interest investment by a commercial entity



The HPV vaccine: an invention that has led to a commercial product

Medical need for an HPV vaccine

- Several HPV types cause virtually all cases of cervical cancer and a high proportion of anal, vulvar, vaginal, penile, and oropharyngeal cancer
  - >30,000 cases per year in the US; >250,000 deaths per year worldwide; ~8% of female cancer deaths worldwide
  - HPV16 predominates (causes >50% of cervical cancers, >80% of the other HPV-associated cancers)
  - HPV also causes genital and non-genital warts



Technology Transfer at NIH

- NIH has clear priorities for technology transfer
- The primary goal: **improving public health**
- Secondary goals:
  - Encouraging technology development and public-private partnerships
  - generation of income for NIH and inventors
- If public health and income come into conflict, public health predominates

The HPV vaccine: Could we develop the idea?

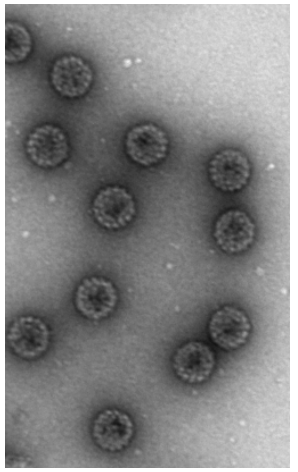
- Our experience in basic papillomavirus biology? **Yes**
- Scientific freedom and collaborative spirit of NCI intramural program? **Yes**
- Our experience in vaccines? **No**
- Our experience in immunology? **No**
- Our experience in translational research? **No**
- Our experience in papillomavirus structural proteins? **No**

Our first invention (1992)

- **A single structural papillomavirus protein**, when expressed in eukaryotic cells, **efficiently self-asssembled into virus-like particles (VLPs)** (Reinhard Kirnbauer, now Derm Dept, Vienna)
- **The VLPs induced high titers of neutralizing antibodies** when injected in animals
  - This class of antibodies interferes with viral infection and is the cornerstone of most preventive vaccines
- We initially used bovine papillomavirus (BPV), rather than HPV
  - We had a source of infectious BPV, and Israel Dvoretsky (now Derm Dept Yale) had developed a quantitative assay to measure neutralizing antibodies against BPV
  - At the time, there was no comparable assay for the oncogenic HPVs

Reinhard Kirnbauer

VLPs



Our second invention (1993)

JRNAL OF VIROLOGY, Dec. 1993, p. 6929–6936 Vol. 67, No.
2-538X/93/126929-08$02.00/0

Efficient Self-Assembly of Human Papillomavirus Type 16 L1 and L1-L2 into Virus-Like Particles

REINHARD KIRNBAUER,[1] JANET TAUB,[1] HEATHER GREENSTONE,[1] RICHARD RODEN,[1] MATTHIAS DÜRST,[2] LUTZ GISSMANN,[2] DOUG R. LOWY,[1] AND JOHN T. SCHILLER[1]*

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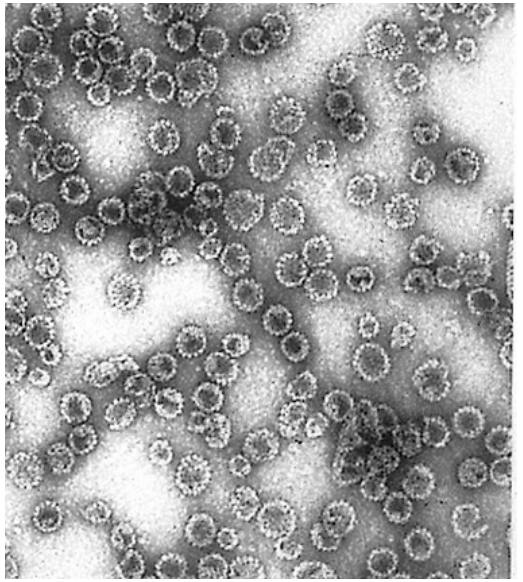
Received 14 June 1993/Accepted 18 August 1993

VLPs



- HPV16 L1 from the HPV16 reference strain was a mutant. The critical mutation was Histidine at amino acid 202, while wild type HPV16 and other HPVs encode Aspartate at this residue.
- Wild type HPV16 L1, isolated from benign lesions, formed VLPs efficiently, in contrast to the HPV16 reference strain.

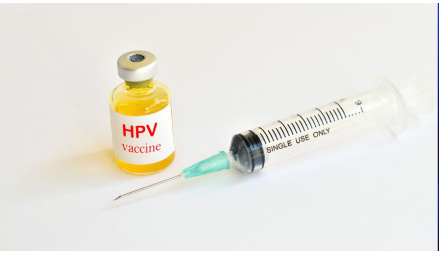
Early Phase Human Trials

- 1996: We initiated our own phase I trial because of uncertainty of pharmaceutical company commitment
  - Requested by the NCI Director; I assembled a trans-NIH group with expertise in vaccine development; we worked collaboratively with the Johns Hopkins Center for Immunization research because they had expertise in early phase vaccine trials
- I took a course in good clinical practices, became involved in GMP vaccine produced by a contract laboratory, wrote and held the IND
- In a phase I double-blind placebo-controlled trial, we showed the HPV16 L1 VLP vaccine was well tolerated and highly immunogenic in young men and women (2001)

Interest from Pharma: licensing, but not collaboration

- 1992-1996: We tried to find a pharmaceutical company that would collaborate with us to develop the vaccine
  - We were not successful (despite several good starts)
  - A key skepticism of the companies: prior attempts to develop a vaccine against a local STD (HSV) had failed
- 1996-2000: Two companies (Merck & Medimmune/GlaxoSmithKline) licensed our intellectual property
  - Both companies developed their HPV commercial vaccines without collaborating with us

Phase III HPV vaccine trials & FDA licensure



- **2002-present: In uninfected patients, HPV vaccination can confer >95% protection against new infection and disease attributable to the HPV types targeted by the vaccine**
  - **The vaccine is not therapeutic**
- 2006: FDA licenses the quadrivalent vaccine (Gardasil, Merck). (Licensed for boys in 2009.)
- 2009: FDA licenses the bivalent vaccine (Cervarix, GlaxoSmithKline) (Licensed only for girls)
- 2014: FDA licenses the 9-valent vaccine (Gardasil 9, Merck) (Licensed for boys and girls)

The HPV vaccine: From its underutilization to a recent vaccine shortage

- Following FDA approval, initial worldwide vaccine demand was limited
- In countries with high vaccine uptake, the impact of the vaccine on disease – drastic reductions genital warts and cervical dysplasia – has led to recent increases in vaccine demand
  - Progressively more countries are: 1) incorporating HPV vaccination in their national vaccine programs, 2) expanding vaccination to boys, 3) increasing their vaccine uptake
- Worldwide HPV vaccine shortage announced in 2018; will last at least 5 more years

How public health considerations at NIH have predominated over profit from the vaccine (1)

- Regional manufacturers can produce and sell the HPV vaccine in low- and middle-income countries
  - Such an agreement was made possible because NIH had intellectual property, and chose to leverage its position to promote public health over profits
  - One candidate HPV vaccine produced by a regional company is very close to licensure; others are in the pipeline

The challenge to global HPV vaccination

- >107 million girls 10-14 years old have received at least one dose of the HPV vaccine since it was approved in 2006
- However, <5% of eligible girls have been vaccinated in Low- and Middle-Income Countries, where ~90% of cervical cancer deaths occur
- To control of cervical cancer worldwide, should vaccinate 40-50 million girls in each birth cohort
  - Worldwide >60 million girls are now born annually

Prioritizing public health over profit (2)

- Our proposed solution is to hypothesize that a single HPV vaccine dose can confer long-term protection
  - One dose would decrease cost and simplify logistics
  - Hypothesis is based on strong post-hoc data
- We are conducting a large clinical trial in Costa Rica (>20,000 young women) to test this hypothesis
  - Partial support from the Bill & Melinda Gates Foundation

The Costa Rican clinical trial team for the HPV vaccine

You as an inventor

- "Qualify" your invention or idea
  - Identify the medical (or laboratory) need
  - Make sure it is an **invention** (patent search)
  - Verify that developing your idea or prototype into a product can be **feasible, practical, and scalable**
- If you're not already an expert in the area of the invention, **become an expert**

You and Pharma/Biotech

- Involve pharmaceutical or biotech companies as soon as possible
- However, do not expect Pharma or Biotech to immediately recognize the brilliance, utility, and high market value of your invention
- Try to find out what additional evidence and further development may be needed before Phama/biotech might be interested; test the waters periodically
  - Consider applying for a grant:
    - NCI IMAT program (**I**nnovative **M**olecular **A**nalysis **T**echnogy)
    - SBIR: NIH grants to biotech (**S**mall **B**usiness **I**nnovation **R**esearch)
    - STTR: collaborations between academia and biotech (**S**mall Business **T**echnology **T**ransfer **R**esearch

Developing a product is a big undertaking

- Assemble the best team you can
- Recognize the limits of your expertise; collaborate with others if it will speed development
- IP development towards commercialization requires commitment, persistence, and dedication
  - But ask yourself periodically: “Is this still the correct path?”

Three take home messages

- Make sure your invention will be useful if its development is successful
- Be clear about your primary goal(s)
  - Achieving it (them) may require a willingness to compromise on some other issues
- “The dictionary is the only place where ‘success’ comes before ‘work’” – Vince Lombardi

Thank you!