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
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-assembled 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
 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 in 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 (Innovative Molecular Analysis Technology)
    • SBIR: NIH grants to biotech (Small Business Innovation Research)
    • STTR: collaborations between academia and biotech (Small Business Technology Transfer Research)
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!