National Cancer Institute

Moving Translational Discoveries into the Clinic via Public and Private Sectors: An NIH Lab Perspective

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AAD Forum: Development of Molecularly Targeted Therapies for Skin Diseases
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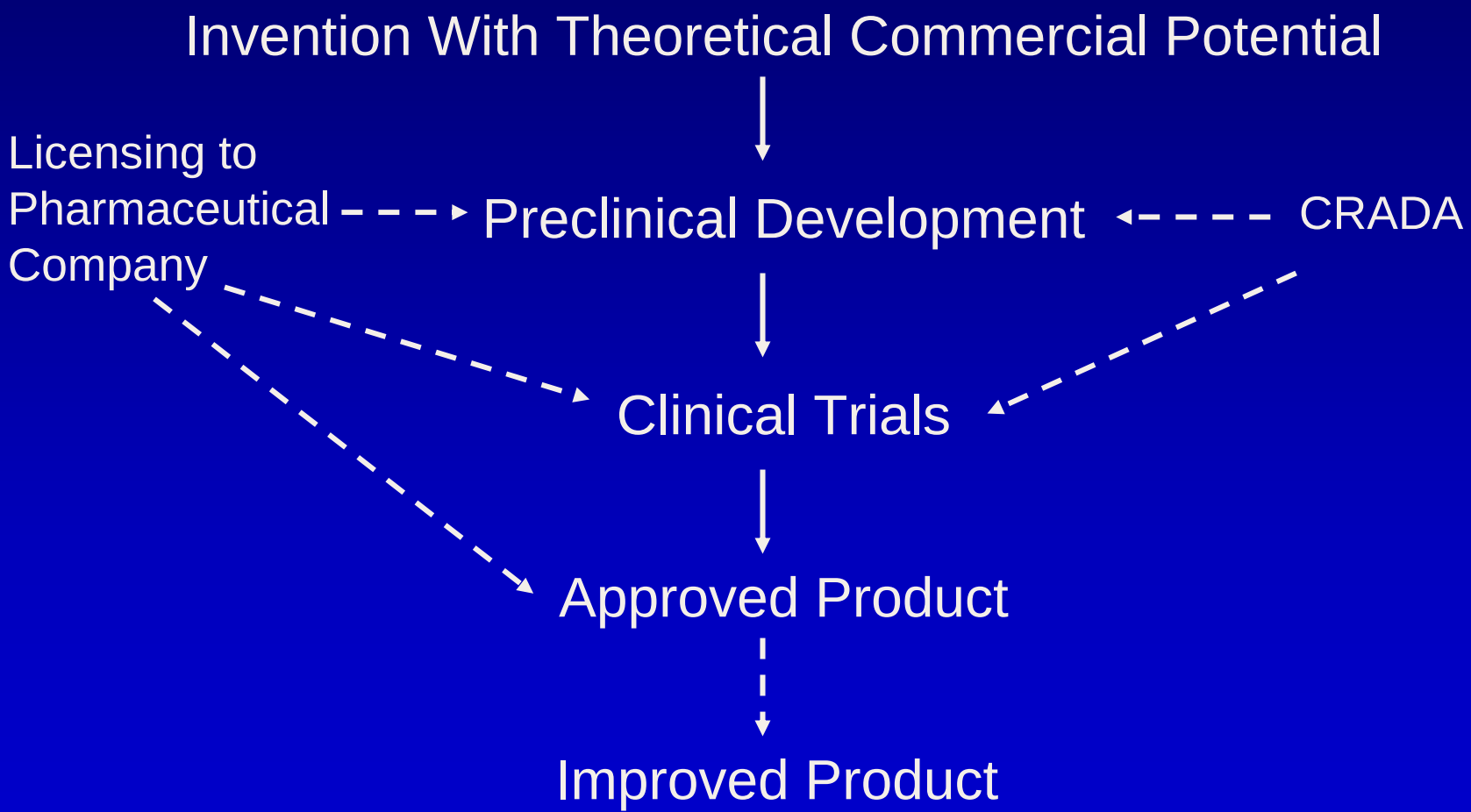
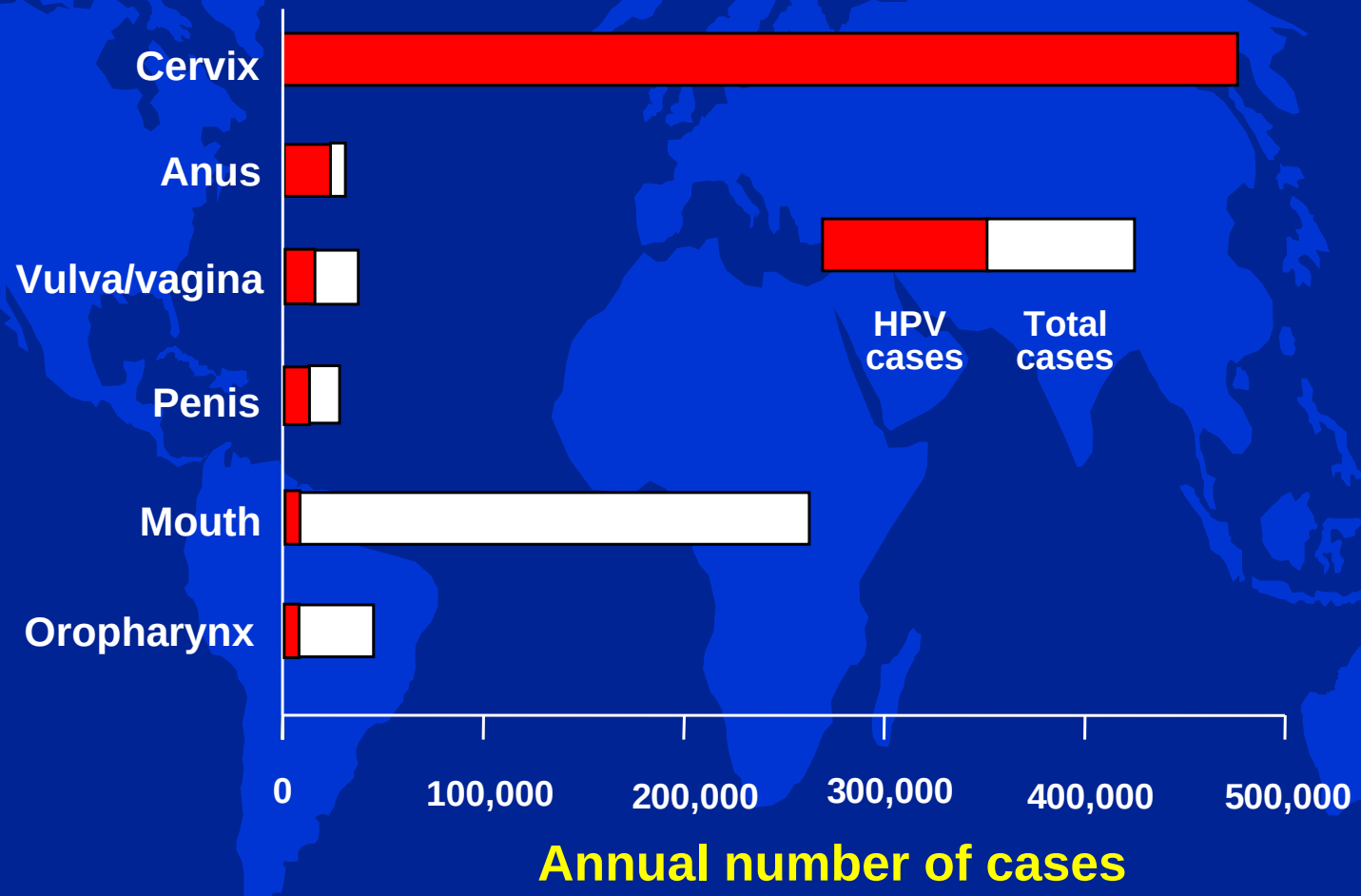
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Technology Transfer & Product Development



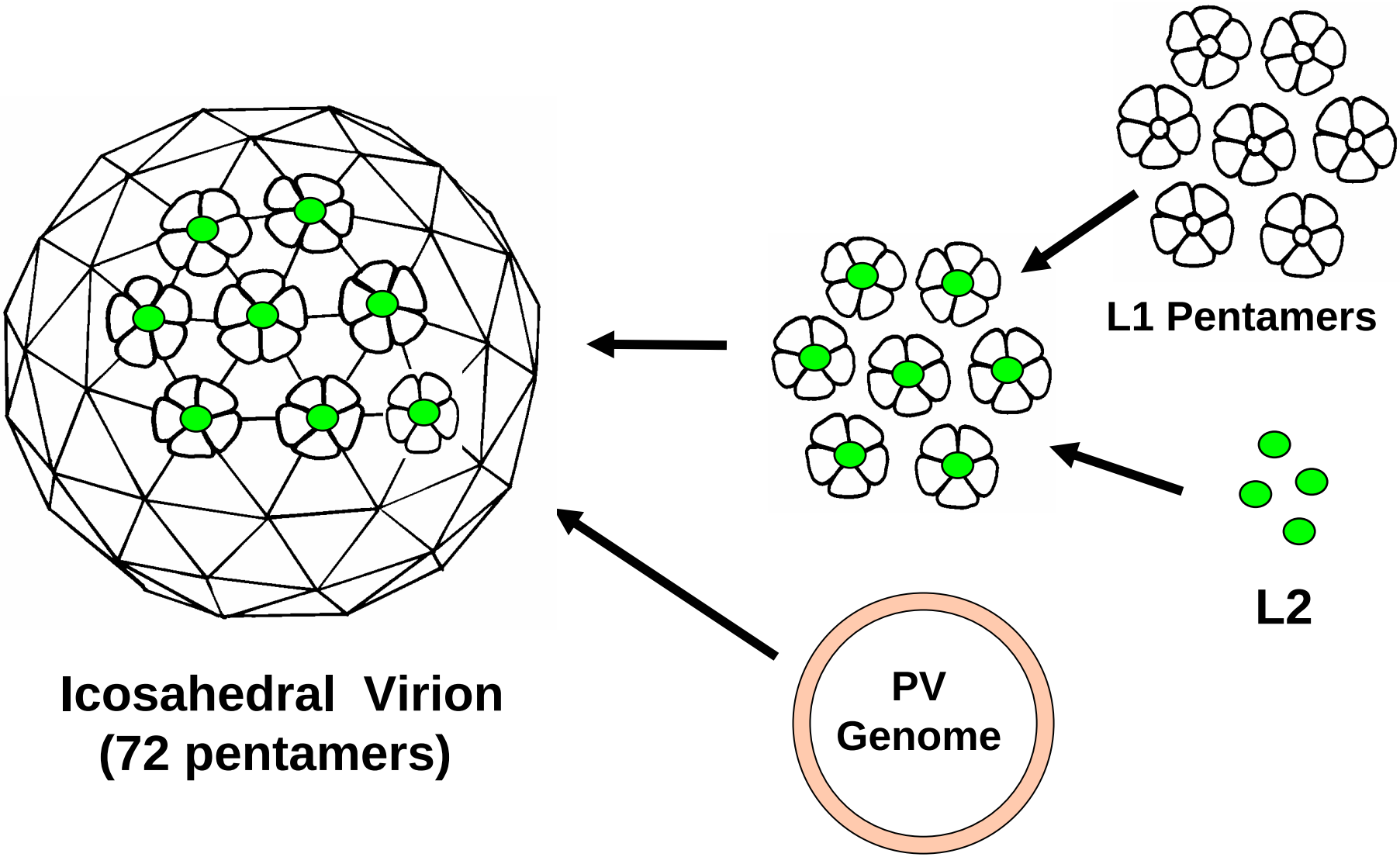
Worldwide Incidence and Distribution of Cancers Attributable to HPV



Cervical cancer represents ~10% of all female cancers worldwide

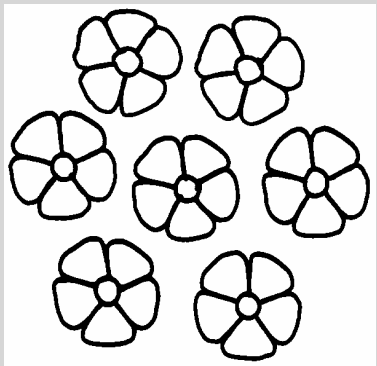
Adapted from Parkin, Int J Cancer 118:3030, 2006

Formation of Papillomavirus Virions



L1 & L2 each contain neutralization epitopes

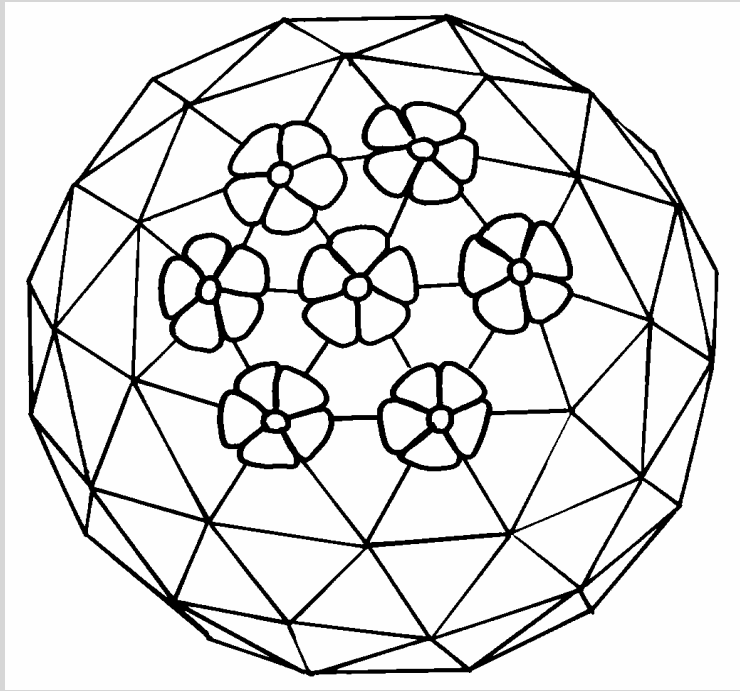
L1 Self-assembles to form Virus-like Particles (VLPs)



L1 Pentamers

Self-assembly

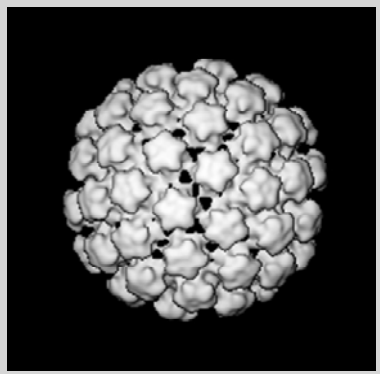
Into VLPs



Virus-like Particle (VLP)

L2 is not needed

HPV16 L1 VLP: 3D reconstruction cryo-electron Micrograph; from Benes Trus & Chris Buck, NIH



Our Inventions for an HPV Vaccine (1)

- The L1 major structural viral protein when expressed in cells self-assembled into virus-like particles (VLPs) that morphologically resembled authentic papillomaviruses.

- Systemic immunization of rabbits with VLPs induced high levels of serum neutralizing antibodies. Native particles were required, as immunization with denatured particles did not induce neutralizing antibodies.

- We used bovine papillomavirus as our model, because there was a quantitative neutralization assay, in contrast to the HPVs associated with cervical cancer.

- Kirnbauer et al., PNAS, 1992.

Our Inventions for an HPV Vaccine (2)

- We noticed that the HPV16 L1 protein from the reference strain did not efficiently self-assemble into VLPs.

- We postulated that HPV16 L1, which had been isolated from a cervical cancer, was a mutant.

- We obtained HPV16 L1 from benign lesions, found they self-assembled, and identified a functionally critical point mutation in HPV16 L1 from the reference strain.

- Kirnbauer et al, J. Virology, 1993

These Inventions did <u>not</u> lead directly to a pharmaceutical partner or a licensee

- Non-scientific issues:
  - Competing IP
  - Reluctance to work with Govt
- Scientific issues:
  - Poor track record of experimental vaccines against STI's (HSV)
  - Skepticism that systemic immunization would protect against a mucosal infection
  - Skepticism that (serum) neutralizing antibodies could prevent a local infection that does not have a viremic phase

JOURNAL OF VIROLOGY, June 1995, p. 3959–3963
0022-538X/95/$04.00+0

Vol. 69, No. 6

Immunization with Viruslike Particles from Cottontail Rabbit Papillomavirus (CRPV) Can Protect against Experimental CRPV Infection

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- Systemic CRPV L1 VLP vaccination induced protection (>95%) against experimental high dose CRPV skin challenge.
- Passive transfer of immune IgG to naïve animals protected them against CRPV challenge, implying that protection is primarily attributable to neutralizing antibodies.
- In oral mucosal infection by BPV4 (Kirnbauer et al, 1996), BPV4 VLP vaccination prevented new infection but did not affect established infection.

Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 11553–11557, December 1995
Immunology

Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas

JoAnn A. Suzich*†, Shin-je Ghim†‡, Frances J. Palmer-Hill*, Wendy I. White*, James K. Tamura*§, Judith A. Bell¶, Joseph A. Newsome‡, A. Bennett Jenson‡, and Richard Schlegel‡

*MedImmune, Inc., Gaithersburg, MD 20878; ‡Georgetown University Medical Center, Washington, DC 20007; and ¶Marshall Farms, Rose, NY 14516

Communicated by Lloyd J. Old, Ludwig Institute for Cancer Research, New York, NY, July 24, 1995

BUTTERWORTH HEINEMANN

0264-410X(95)00103-4

Vaccine, Vol. 13, No. 16, pp. 1509–1514, 1995

0264-410X/95 $10+0.00

Vaccination with yeast-expressed cottontail rabbit papillomavirus (CRPV) virus-like particles protects rabbits from CRPV-induced papilloma formation

Kathrin U. Jansen*, Mark Rosolowsky, Loren D. Schultz, Henry Z. Markus, James C. Cook, John J. Donnelly, Douglas Martinez, Ronald W. Ellis and Alan R. Shaw

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Disclosure

The NIH has patents on papillomavirus vaccine technology, and I am an inventor of this technology. The NIH has licensed this technology to Merck and GlaxoSmithKline, the two pharmaceutical companies developing commercial versions of the vaccine.

Two Distinct HPV VLP Vaccines Are Under Commercial Development

GlaxoSmithKline: **Cervarix**

HPV16
HPV18
} **70% of Cervical Ca**

ASO4 Adjuvant (Aluminum + MPL)

Made in insect cells

Merck: **Gardasil**

HPV16
HPV18
} **70% of Cervical Ca**

HPV6
HPV11
} **90% of Genital Warts**

Aluminum Adjuvant

Made in yeast

IM Injections at 0, 1 or 2, and 6 months

Gardasil: Phase III Prophylactic Efficacy Results

	Vaccine		Placebo			
	n	Cases	n	Cases	Efficacy	C.I.
*HPV16 or 18 CIN 2/3 or AIS	8487	0	8460	53	100%	93–100
**HPV16 or 18 VIN2/3 or VaIN2/3	8641	0	8667	24	100%	83-100
*HPV6, 11, 16, 18 Genital warts	7897	1	7899	91	99%	94–100

Results in HPV DNA and seronegatives at baseline after three doses (*) or after at least one dose (**), as reported in Gardasil package insert.
Average Duration of Follow-up: 1.5 Years After the Last Vaccination

Lessons from this Experience

- Achieving success in translational research may require considerable additional research and development beyond the initial invention.
- We have tried to promote inventions that are practical and scalable.
- In vitro and in vivo preclinical models are key. The ones we used were predictive of effects in humans (issue of therapeutic HPV vaccine).
- Non-scientific issues (e.g., IP issues) may make it difficult to find a corporate partner.
- Pharmaceutical companies prefer to minimize risk.

Aspects of NCI Funding

- **Intramural: We have the flexibility to choose our research projects, which we then defend every 4 years.**
- **Extramural: NCI has programs for supporting the movement of compounds from the laboratory through phase I clinical trials (production of GMP materials, IND filing, trial support).**
  - **Therapy: RAID program (Rapid Access to Intervention Development; DCTD)**
  - **Prevention: RAPID program (Rapid Access to Preventive Intervention Development; DCP)**

Second Generation Vaccine Development: Public and non-profit Private Funding

- **Production of L1 pentamers in E. coli: may be less expensive (Bob Garcea, U. Colorado; supported by Gates Foundation).**
- **Production of L2 peptide vaccine: may be a pan-HPV vaccine, less expensive (Richard Roden [our collaborator], Johns Hopkins U; supported by NCI RAPID program).**
- **Regional production of VLP vaccine; 30% of cervical cancer in the world occurs in India.**
- **All of the above is being carried out by Shantha Biologicals in India (a major provider of Hepatitis B virus vaccine to WHO for less than 50 cents/dose).**

Key Collaborators

John Schiller

Current LCO papillomavirus lab members: Chris Buck, Patricia Day, Rhonda Kines, Michelle Mergler, Susana Pang, Jeffrey Roberts, Cynthia Thompson

Former LCO lab members: Reinhard Kirnbauer, Richard Roden, Diana Pastrana, Heather Greenstone, Bernadete Nonnenmacher

Collaborators in CCR, NCI: Peter Choyke, Marcelino Bernardo

Collaborators in DCEG, NCI: Mark Schiffman, Allan Hildesheim, Phil Castle, Ligia Pinto

Other intramural collaborators: Brian Murphy, *NIAID*; Benes Trus & Naiqian Cheng, *CIT*; Alasdair Steven, *NIAMS*

Extramural collaborators: Clayton Harro, *Johns Hopkins*; Denise Nardelli-Haefliger*, University of Lausanne, Switzerland*