Cervical Cancer

HPV Vaccines to Prevent Cervical Cancer and other HPV-associated Diseases

John Schiller, Center for Cancer Research, NCI

- HPV and Cancer
- Vaccine Efficacy/Effectiveness
- Key Implementation Issues
- Why they work so well
Cancers attributable to HPV

**Worldwide Incidence and Distribution of Cancers Attributable to HPV**

HPVs cause 5% of all cancers

- Cervix
- Anus
- Vulva/vagina
- Penis
- Oropharynx

Annual number of cancer cases worldwide

HPV16/18:
- ~70%

HPVs cause 5% of all cancers

HPV cancers

United States: Annual Incidence and Distribution of Cancers Attributable to HPV in 2004-2008

- Cervix: ~70%
- Anus: >90%
- Vulva/vagina
- Penis
- Oropharynx

Annual number of cases

- Pap screening has reduced the incidence of cervical cancer by ~80%
- Incidence of HPV-positive oropharynx cancer 1988-2004 increased 225%

MMWR Weekly 61:253-80, 2012
HIV genome

HPV16 Double Stranded Circular DNA Genome

URR
Promoter and enhancer elements
Viral ORI

Early genes
E1–Replication
E2–Replication and transcription
E4–Viral release
E5–Immune evasion
E6–Binds p53
E7–Binds pRB

Expressed In Cancer

Late genes
L1–Major capsid protein
L2–Minor capsid protein

8 Kilobase
**Virion**

**Papillomavirus Virion**

- Non-enveloped icosahedral shell formed by 72 pentamers of L1
- 60 nanometer diameter
- A second capsid protein L2 is present at up to 72 copies
- 8kb circular dsDNA genome (chromatinized)
HPV life cycle

HPV Life Cycle in a Stratified Squamous Epithelium: Designed for Immune Evasion

Moody and Laimins Nat Rev Micro 2010
HPV infection

HPVs have evolved to exploit the limited immuno-surveillance of the upper layers of skin and mucosal membranes.
Cervical cancer

Female Reproductive Tract Anatomy & Histology

Initiation Site of Cervical Cancers

HPV carcinogenesis

Molecular Mechanisms Involved in HPV Carcinogenesis

Why have Oncogenes?
Virus needs to induce DNA replication in terminally differentiated keratinocytes to replicate its genome

Moody and Laimins Nat Rev Micro 2010
Cellular proteins

Cellular Proteins and Pathways Affected by HPV E7

Moody and Laimins Nat Rev Micro 2010
HPV pathways

Cellular Proteins and Pathways Affected by HPV E6
HPV infection time line

Time Line of Cervical HPV Infections And Progession to Cervical Cancer

- Lifetime incidence of genital HPV infection >80% in U.S.
- Most infections clear spontaneously, eliminating cancer risk for that infection.
- Persistent infection with a high-risk HPV, especially HPV16 or 18, is the single most important risk factor for progression to precancer and cancer.

Adapted from Schiffman & Castle, New Eng J Med 353:2101-4, 2005
HPV infection

Rapid Acquisition of Genital HPV Infection in Young Women With Their First Sexual Partner

Cumulative Risk of HPV (%)

- US (18-22 years old; N=130)
- UK (15-19 years old; N=242)

- 20% in 4 months
- 45% in 26 months

Time Since First Intercourse (Months)

Pap screening

Current Pap Screening Is “Secondary” Prevention of Cervical Cancer

Infection HPV → Immunologic Resolution

Abnormal Cytology (Pap Smear) → Pre-Cancerous Disease → Treatment

Colposcopy/ Biopsy

Invasive Cancer → Treatment

Low grade → Retest for Resolution/ Progression
Primary prevention

The Future Is Primary Prevention

Prophylactic Vaccination

Infection HPV → Immunologic Resolution

Abnormal Cytology (Pap Smear) → Colposcopy/Biopsy → Resolution of Infection

Pre-Cancerous Disease

Treatment

Invasion

Treatment
Virus like particles

Prophylactic HPV Vaccines Are L1 Virus Like Particles (VLPs)

L1 Insertion into a Baculovirus Expression Vector

Production in Insect Cells

Spontaneous assembly of L1 into VLPs

Induce high titers of virion neutralizing antibodies

Non-infectious, Non-oncogenic

Reinhard Kirnbauer et al. PNAS 1992
Three vaccines

### Three Distinct HPV L1 VLP Vaccines Have Been Commercialized

<table>
<thead>
<tr>
<th>Name</th>
<th>Producer</th>
<th>VLP Types</th>
<th>Adjuvant</th>
<th>Production</th>
<th>Licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervarix</td>
<td>GSK</td>
<td>16,18</td>
<td>AS04*</td>
<td>Insect Cells</td>
<td>2007</td>
</tr>
<tr>
<td>Gardasil</td>
<td>Merck</td>
<td>16,18, 6,11</td>
<td>Alum</td>
<td>Yeast</td>
<td>2006</td>
</tr>
<tr>
<td>Gardasil-9</td>
<td>Merck</td>
<td>16,18,31, 33,45,52,58,6,11</td>
<td>Alum</td>
<td>Yeast</td>
<td>2014</td>
</tr>
</tbody>
</table>

IM Injections at 0, 1 or 2, and 6 months 1, 6 months for <15 yrs in EU, and now in U.S.

* MPL First TLR Agonist Adjuvant to be FDA Approved
Timeline of HPV Association

**Timeline of HPV Association with Cancer vs Vaccine Development**

- HPV16 Discovered
- Molecular Pathogenesis Studies
- Case/Control Cx Ca Studies
- Prospective HPV neoplasia studies
- HPV is a necessary cause of Cx Ca

1982: 1st VLPs Produced
1990: Animal Studies
1992: VLP Clinical trials start
1999: Vaccine Licensure: Females
2001: Vaccine Licensure: Males
2006:
2009:
Precursor Lesions of Cervical Cancer

1° Endpoint – Phase III Trials

Cytology

LSIL

Histology

CIN 1

Moderate dysplasia

HSIL

Severe dysplasia

CIN 2

In situ carcinoma

CIN 3

Invasive carcinoma

Normal

Very mild/mild dysplasia

Virus production, HPV infection

No virus production

High E6 and E7

Viral DNA integration

Microinvasive carcinoma

Lowy & Schiller, J Clin Invest., 2006
Efficacy of HPV Vaccine

### Efficacy of HPV VLP Vaccines Against Incident Disease

*By Vaccine-Targeted Types in Randomized Trials*

No genital HPV infection detected in at entry

<table>
<thead>
<tr>
<th>End Point</th>
<th>Sex</th>
<th>Age</th>
<th>Vaccine</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN III</td>
<td>Female</td>
<td>15-25</td>
<td>Cervarix</td>
<td>100% (90.5-100)</td>
</tr>
<tr>
<td>CIN III</td>
<td>Female</td>
<td>15-26</td>
<td>Gardasil</td>
<td>100% (85.5-100)</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>Female</td>
<td>15-26</td>
<td>Gardasil</td>
<td>96.4% (91.4-98.4)</td>
</tr>
<tr>
<td>AIN</td>
<td>Male</td>
<td>16-26</td>
<td>Gardasil</td>
<td>77.5% (39.6-93.3)</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>Male</td>
<td>16-26</td>
<td>Gardasil</td>
<td>89.4% (65.5-97.9)</td>
</tr>
</tbody>
</table>

Data from Lehtinen Lancet Oncol 2011; Munoz JNCI 2010; Palefsky NEJM 2011; Giuliano NEJM 2011

**CIN III**: Cervical Intraepithelial Neoplasia Grade 3

**AIN**: Anal Intraepithelial Neoplasia of any grade
Gardasil-9

Merck’s Gardasil-9 was FDA approved Dec. 2014

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Frequency</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>15.8</td>
<td>54.6</td>
</tr>
<tr>
<td>HPV-18</td>
<td>70.4</td>
<td></td>
</tr>
<tr>
<td>HPV-33</td>
<td>74.8</td>
<td></td>
</tr>
<tr>
<td>HPV-45</td>
<td>78.5</td>
<td></td>
</tr>
<tr>
<td>HPV-31</td>
<td>82.0</td>
<td></td>
</tr>
<tr>
<td>HPV-58</td>
<td>85.4</td>
<td></td>
</tr>
<tr>
<td>HPV-52</td>
<td>87.9</td>
<td></td>
</tr>
<tr>
<td>HPV-35</td>
<td>89.7</td>
<td></td>
</tr>
<tr>
<td>HPV-59</td>
<td>90.8</td>
<td></td>
</tr>
<tr>
<td>HPV-56</td>
<td>92.2</td>
<td></td>
</tr>
<tr>
<td>HPV-51</td>
<td>92.9</td>
<td></td>
</tr>
<tr>
<td>HPV-39</td>
<td>93.6</td>
<td></td>
</tr>
<tr>
<td>HPV-73</td>
<td>94.1</td>
<td></td>
</tr>
<tr>
<td>HPV-68</td>
<td>94.6</td>
<td></td>
</tr>
<tr>
<td>HPV-82</td>
<td>94.8</td>
<td></td>
</tr>
</tbody>
</table>

- **96% Efficacy** against CIN2/3 by 5 additional types, compared to Gardasil-4.
- Ab responses to HPV6,11,16,18 are non-inferior.

Additions to Merck’s Nonavalent Vaccine

Now available in the U.S.
Clinical Trial Evidence

Clinical Trial Evidence for Vaccine Efficacy Against Infection/Intra-epithelial Neoplasia at Site

<table>
<thead>
<tr>
<th>Location</th>
<th>Annual Number of Cases</th>
<th>Inf/IN*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td></td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Anus</td>
<td></td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Vulva/vagina</td>
<td></td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Penis</td>
<td></td>
<td>Yes/No</td>
</tr>
<tr>
<td>Oropharynx</td>
<td></td>
<td>Yes?/No</td>
</tr>
</tbody>
</table>

* Against Vaccine Targeted Types

MMWR Weekly 61:253-80, 2012
Protection from Initial Infection

Protection From Initial Infection

- Most Vaccinees never tested positive for HPV infection as measured by sensitive PCR Assays.
- “Breakthrough” infection tended to appear early in the trials suggesting that most were emergence of prevalent infection.
- Results imply that sterilizing immunity normally generated.
HPC vaccine

What the HPV Vaccines Don’t Do

- They don’t prevent infection or disease caused by most of the other HPV types that cause cervical cancer.

- They don’t induce regression of established HPV infections or prevent progression of HPV-induced lesions.
Safety record

HPV VLP Vaccines Have an Excellent Safety Record

- Low grade and transient injection site reactions, particularly pain, are common.
- Systemic reactions, when they occur, are mild and self-limiting.
- Syncope (fainting) is sometimes observed (needle related).

### Serious Adverse Events Following HPV Vaccination

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine</th>
<th>% Vaccine</th>
<th>% Control</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Future I</td>
<td>Gardasil</td>
<td>1.8%</td>
<td>1.7%</td>
<td>1.07 (0.71-1.60)</td>
</tr>
<tr>
<td>Future II</td>
<td>Gardasil</td>
<td>0.7%</td>
<td>0.9%</td>
<td>0.83 (0.56-1.24)</td>
</tr>
<tr>
<td>PATRICIA</td>
<td>Cervarix</td>
<td>7.5%</td>
<td>7.5%</td>
<td>1.00 (0.91-1.11)</td>
</tr>
</tbody>
</table>

No patterns of serious adverse events following immunization in trials or post-licensure surveillance that would suggest a causal relation to the vaccine.

Vaccine Effectiveness: Evidence From National Immunization Programs

<table>
<thead>
<tr>
<th>Country</th>
<th>Type-Specific Infection</th>
<th>Genital Warts</th>
<th>Cervical Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Australia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Britain</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>USA</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Canada</td>
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<td></td>
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<tr>
<td>Denmark</td>
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<tr>
<td>Sweden</td>
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<tr>
<td>France</td>
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<tr>
<td>Spain</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Italy</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Israel</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Vaccination

Prevaccination and Postvaccination Prevalence of HPV Types By Age: Cervarix in England

In young women attending Chlamydia screening

David Nesher et al. BMJ Open 2016;6:e009915
Reduction of CIN2+ cervical dysplasia

Effectiveness: Reduction in CIN2+ Cervical Dysplasia by Gardasil in Australia

Prevention of cervical cancer

Prevention of Cervical Cancer?

Annual Incident Rates of Cervical Cancer in U.S. Women 15-24 Years

A 29% decrease 2011-2014 vs 2003-2006

Guo et al Am J Prev Med 2018
HPV vaccines

HPV Vaccines Are Now Established Products

- Commercially available for more than 10 years.
- Licensed in 82 countries.
- Over 270 million doses given globally.
- Increasing evidence of effectiveness in national immunization programs.
Non-vaccine scenario

Non-Vaccine Scenario: 19 Million Cases and 10 Million Deaths From Cervical Cancer

*Worldwide projection for the next 65 years*

[Bar chart showing the number of cases in millions across different income groups and age groups.]
Worldwide HPV vaccine uptake

Worldwide HPV Vaccine Uptake In Females

Only 3% of girls in lower and lower-middle income countries have been vaccinated.

US girls vaccination rate

Vaccination of U.S. Girls Aged 13-17
By Vaccine and Dose: 2006-2015

Reagan-Steiner et al. MMWR 2016
Increasing Uptake, Particularly in Low Resource Settings

- Both companies are committed to sale to GAVI at less than $5 per dose.

- Vaccine manufacture in emerging countries.

- Address vaccination hesitancy by education programs aimed families and health care providers.

- Deliver fewer than three doses.
Post hoc analysis

<table>
<thead>
<tr>
<th>End Point</th>
<th>% Infected (95% CI)</th>
<th>End Point</th>
<th>% Infected (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 doses (N = 2043)</td>
<td></td>
<td>1 dose (N = 134)</td>
</tr>
<tr>
<td>HPV16/18</td>
<td>4.3 (3.5-5.3)</td>
<td>HPV16/18</td>
<td>1.5 (0.3-4.9)</td>
</tr>
<tr>
<td>HPV31/33/45</td>
<td>8.0 (6.9-9.3)</td>
<td>HPV31/33/45</td>
<td>8.2 (4.4-13.8)</td>
</tr>
<tr>
<td>Other Oncogenic*</td>
<td>43.6 (41.5-45.8)</td>
<td>Other Oncogenic*</td>
<td>39.6 (31.5-48.0)</td>
</tr>
<tr>
<td>Nononcogenic</td>
<td>46.2 (44.0-48.3)</td>
<td>Nononcogenic</td>
<td>44.0 (35.8-52.5)</td>
</tr>
</tbody>
</table>

* HPV types 35/39/52/52/56/58/59

M Safaeian et al, J Natl Cancer Inst, 110 (2), 2018
One dose clinical trial results

**Other One Dose Clinical Trial Results**

Cervarix:
4 year post hoc results PATRICIA trial showed similar efficacy for 1, 2 and 3 dose recipients.

Gardasil:
In an interrupted Indian cluster randomized trial, after 7 years, there was similar protection in young women receiving 1, 2, or 3 doses.
*Sankaranarayanan et al. Vaccine, 2018, Epub Mar 15*
Single dose HPV vaccination

Is It Time to Adopt Single Dose HPV Vaccination Programs?

These post-hoc findings provide insufficient evidence to generally promote implementation of single dose HPV vaccination programs.

Early adoption in low resource settings with a contingency plan to boost if needed might be justified.
One or two doses of the HPV vaccine

RCT of One or Two Doses of the HPV Vaccines in Costa Rica

- 4 Arms: 1 vs 2 dose Cervarix
  1 vs 2 dose Gardasil-9
- 5000 12-16 yr old females per arm.
- Primary endpoint: persistent HPV16/18 infection.
- Survey of HPV prevalence in age matched women in region.
- 4 year primary trial; long term follow up.
- NCI and Gates financed.

Clinicaltrials.gov identifier: NCT03180034
Why do HPV VLP vaccines work so well?

- The vaccines are exceptionally good at inducing neutralizing antibodies.
- Infection mechanism make HPVs exceptionally susceptible to neutralizing antibodies.
- HPVs have DNA genomes so can’t evolve rapidly to evade nAb responses.

Provides plausibility for HPV VLPs as the first subunit vaccine to induce long term protection after a single dose.
Antibody responses to VLPs

Consistency of Antibody Response to VLPs

Percent of Women Seroconverting to Individual HPV VLPs in Merck VLP Vaccine Gardasil*

- HPV6 99.8%
- HPV11 99.8%
- HPV16 99.8%
- HPV18 99.5%

*4666 women vaccinated 3 times by intramuscular injection
Persistence of antibodies to Cervarix in females vaccinated at 15–55 years of age

Received Three Doses

10-year kinetics of anti-HPV-16 antibodies

10-year kinetics of anti-HPV-18 antibodies

Cancer Medicine
5 OCT 2017 DOI: 10.1002/cam4.1155
Durability of VLP Ab response

Durability of VLP Ab Responds To 7 Years
Costa Rica Vaccine Trial

100% of 1 dose recipients remain seropositive at 7 years.

HPV VLP-based ELISA assay

Antibody GMTs (EU/mL)

Year

2 3 4 5 6 7

Natural Infection

VLP Ab response

Durability of VLP Ab Responds To 7 Years
Costa Rica Vaccine Trial

100% of 1 dose recipients remain seropositive at 7 years.

Antibody GMTs (EU/mL)

Year
2 3 4 5 6 7

4x lower for 1 dose
9x higher than natural infection

B cells recognize dense repetitive protein arrays

B Cells Recognize Dense Repetitive Protein Arrays as Dangerous Microbial Structures

- Monomeric BCR/Protein Complexes
  - Weak Activation Signals
  - Low Level Antibodies
  - Short duration

- Oligomerization of BCR/Protein Signaling Complexes
  - Strong Survival/Proliferation Signals
  - High Level Antibodies
  - Long Duration

Repetitive Ag structure guides the decision to invest in long term Ab production.
Repetitive antigen display

VLPs Have Highly Repetitive Antigen Display

B cells specifically recognize particulate antigens with epitope spacing of 50-100Å as foreign.

This epitope spacing is commonly found on microbial surfaces, e.g. virus major capsid protein or bacterial pili.

Protein complexes with this spacing rarely occur in vertebrate animals.

So BCRs have evolved as antigen specific pattern recognition receptors.

Bachmann et al. Science 1993; 262: 1448
Vaginal HPV infection

*In vivo Murine Model of Vaginal HPV Infection*

The remarkably slow process of infection makes HPVs exceptionally susceptible to inhibition by antibodies

Occurs over several hours!

Exposure of cell receptor binding site on L1

=Basement Membrane

=HSPG

=Furin

HSPG = Heparan Sulfate Proteoglycan

Rhonda Kines et al. PNAS 2009; 106:20458-63
Cervix Ab response

How Could IM Injection of a VLP Vaccine Induce a Protective Ab Response at the Cervix?

- VLP-specific IgG in women’s cervical mucus after IM vaccination: but 10-100X less than in serum - Nardelli et al. JNCI, 2003
- Cervicovaginal HPV infection in a mouse model requires epithelial trauma: Roberts et al., Nat Med, 2007
Antibody titers and protection

Antibody Titers and Protection

Are the plateau titers after vaccination near the minimum needed for protection?

Will the 4-fold difference between Ab titers after three vs one dose influence long-term protection?
Passive transfer

Passive Transfer of Rabbit Polyclonal Anti-16L1 VLP Sera

Transfer sera 24 hours prior to infection

Avg Radiance (cp/s/cm²/sr)

100x dilution (High Volume)

10,000x dilution (Low Volume)

* Challenged with HPV16. See no protection from infection when challenged with HPV45
Gardasil sera protection

In vitro vs In Vivo Protection of Gardasil Sera Against HPV16 Pseudovirus Infection

Protection detected with 500-fold less sera in vivo than in vitro!
The in vitro assay is missing some potent mechanism of infection inhibition.
Longet et al, J Virol 2011
Mechanisms of in vivo infection

Mechanisms of In Vivo Infection Inhibition by VLP Abs
Day et al, Cell Host Microbe 2010; 8:260-70

High Ab Levels

Low Ab Levels
Conclusions

- The HPV VLP vaccines are very effective at preventing incident infection and disease by the vaccine types.

- Because the VLPs are exceptionally potent induces of neutralizing antibodies and the virus is exceptionally susceptible to inhibition by antibodies.

- The vaccines have great potential for reducing the burden of HPV-induced cancer worldwide.

- The primary challenge now is to see that the vaccines reach the individuals most in need of them.

- Demonstrating sustained efficacy of a single dose in a RCT could transform implementation programs.
Exploiting HPV’s unexpected infection mechanism

Exploiting HPV’s Unexpected Infection Mechanism For Cancer Therapy

- HPV capsids don’t bind or infect normal intact tissues: they lack the necessary HSPG modifications.

- Surprisingly, they do bind and infect most cancer cells: they evolve HSPG modifications that mimic those normally found only the basement membrane.

- So HPV VLPs can be used as “guided missiles” to deliver cytotoxic agents to tumors.
Binding to divergent tissue types
VLPs bind to most tumor cell lines
Can HPV infect tumors in vivo?
HPV capsids for cancer

Applications for HPV Capsids for Cancer
A collaboration with Aura BioScience

Imaging
- Dye (e.g. ICG, FITC, IR)
- Radio label

Drug/Cytotoxin Delivery
- Attached/encapsidated drug (e.g. Doxorubicin, topotecan)
- Nucleic acid delivery expressing toxins/suicide gene (e.g. TK)

Direct killing
- Radio label
- NIR dye
HPV VLP-IR700 conjugates

HPV VLP-IR700 Conjugates:
Dual Specificity for Cancer Therapy

Cytotoxic only if:
- Bound to the cell surface
- Illuminated with infrared light
Occular/uveal melanoma

Ocular/Uveal Melanoma as a 1st Target for HPV VLP-IR700

- Often deadly due to liver metastases.
- Treatment is brachytherapy, often leads to long-term retinal damage and vision loss. Alternative is enucleation.
- Permits noninvasive access by laser.
- A rabbit model have been developed with intrachoroid implantation of human OM cell lines.

A collaboration with Aura BioScience
Xenograft model of uveal melanoma
Xenograft model of uveal melanoma

**Rabbit Orthotopic Xenograft Model of Uveal Melanoma**

Cyclosporine Tx Rabbits

Choroid injection of Human 92.1MEL cells

13 days

Intravitreous VLP/1R700 Injection

2x wkly

6-8 hr

IR Light - 80 sec.

8-9 days

Enucleation, Histology

50 ug

20 ug

5 ug
Clinical trial of uveal melanoma

A Phase Ib/2 Clinical Trial of Uveal Melanoma

Dosing parameters

- Drug Dose (20µg, 40µg, 80µg)
- Frequency of treatments (1, 2 or 3 weekly intravitreal injections)
- Laser administrations (1 or 2 applications separated by 30 min.)

Sponsored by Aura BioScience
Preliminary clinical trial results

Preliminary Clinical Trial Results

- 24 patients treated to date
- No related severe adverse events, or dose limiting toxicities
- Pre-treatment vision preserved in all patients followed at 6 months or longer
- Drug Related Adverse events mild to moderate:
  - Mild/Moderate Anterior Chamber Inflammation (N = 16/24)
  - Mild/Moderate Posterior Chamber Inflammation (N = 15/24)
  - Mild/Moderate Transient Increases in IOP (N = 9/24)
  - Appearing after 2-4 weeks, suggesting adaptive immunity
  - Managed with standard treatment and resolved without clinical sequelae
Most optimistic projection for the technology

A broadly applicable, “off the shelf” cancer therapy. What cancer should be tried next?
Key Collaborators

Present Members of the Lab:

Doug Lowy         Cindy Thompson         Tara Berman
Patricia Day      Susana Pang           Lukas Bialkowski
Nicolas Cuburru   Carla Cequeira        Alex Bell

Past Members of the Lab:

Richard Roden     Diana Pastrana
Chris Buck         Reinhard Kirnbauer
Jeff Roberts       Rhonda Kines
Bryce Chackerian  Rina Kim

DCEG: Allan Hildesheim, Aimee Kreimer, Mahboobeh Safaeian, Mark Schiffman, Sholom Wacholder, Josh Sampson
IARC: Rolando Herrero
Universitaire Vaudois, Lausanne: Denise Nardelli
Aura Biosciences: Eli de los Pinos, Rhonda Kines, Steve Monk