Harnessing the Power of Viruses for Novel Vaccines and Cancer Therapies

Griff Parks, Ph.D.
Director Burnett School of Biomedical Sciences
Professor of Medicine
University of Central Florida
College of Medicine

April 19, 2016
Outline

1. Why are viruses so hard to stop?
2. How do Viral Vaccines work and what are the types?
   • Three types - using *poliovirus* as an example
   • How safe are vaccines?
   • Why are vaccines not as effective in older population?
3. Viruses can be useful (and essential)
4. Research in the Parks Lab at UCF
   A. Zika Virus
   B. Harnessing Viruses to Treat Cancer
Viruses are Simple...... At Least in What They Are Made of
Viruses are Beautiful......
At Least to Look at in the Microscope

http://fineartamerica.com
www.cnn.com
time.com
en.wikipedia.org
Viruses are Beautiful Structures!

en.wikipedia.org

Viruses have a Simple Growth Cycle......

A Few Particles

Outside

Inside cell

100,000 Particles!

Host Cell

"Assembly Line"
If Viruses are So Simple, Why are They So Hard to Control?

1. They grow very fast
2. They can lay dormant
3. They mutate
4. They grow within cells and require cell machinery

A Few Particles + Host Cell → 100,000 Particles!
How Can We Control Viruses?

Antiviral Drugs - Miracles of Drugs Against HIV and Hepatitis C virus

Used when already infected – sick people
Expensive (need multiple times)
Virus mutates to resistance
How Can We Control Viruses?

**Vaccines**
Used to prevent infection – healthy people
One dose – lifelong immunity
“Natural” substance
Virus don’t easily mutate to resistance (mostly)
The Basics of Vaccines

- **Primary immune response**, slow to build up and not very strong.
- **Secondary response** stronger and more rapid than primary response.
- **Memory cells remain**.

Vaccination → Infection by pathogen
The Idea of Vaccines is >200 Years Old

http://ourworldindata.org/data/health/eradication-of-diseases/
Cowpox and Small Pox - Modern Vaccines are Invented!

Milkmaids have smooth (un-pocked) skin since they are exposed to cow pox - cross protection against the deadly Small Pox

http://america.pink/milkmaid_3017290.html
The Safety of Vaccines is An Old Problem!

James Gilray – ca 1802
The Miracle of Viral Vaccines

**THEN**
Annual US disease cases in the 1900s

- **MEASLES**: 530,217 Cases
- **PERTUSSIS**: 200,752 Cases
- **MUMPS**: 162,344 Cases
- **RUBELLA**: 47,745 Cases
- **DIPHTHERIA**: 21,833 Cases
- **HAEMOPHILUS INFLUENZAE**: 20,000 Cases (est)
- **TETANUS**: 588 Cases
- **POLIO**: 15,316 Cases
- **SMALLPOX**: 20,005 Cases
- **CRS**: 152 Cases

**NOW**
US disease cases in 2010

- **MEASLES**: 61 Cases
- **PERTUSSIS**: 21,291 Cases
- **HAEMOPHILUS INFLUENZAE**: 270 Cases
- **TETANUS**: 0 Cases
- **POLIO**: 0 Cases
- **DIPHTHERIA**: 0 Cases
- **SMALLPOX**: 0 Cases
- **RUBELLA**: 6 Cases
- **CRS**: 0 Cases

What are the various types of viral vaccines?

The Rich History of Poliovirus Vaccines and American Culture

[Image of the book cover: Polio: An American Story by David M. Oshinsky]
Poliovirus Structure

5X Axis of Symmetry

Site of Receptor Binding

Site of Binding for Neutralizing Antibodies

Fecal-Oral Transmit
Asymptomatic 90%
Replication in gut mucosal tissues
Spread to Motor neurons
Death due to respiratory failure

http://www.baike.com
Pre-Vaccine Times and Poliovirus Fears

www.marchofdimes.org
The Miracle of Poliovirus Vaccines
Polio and the March of Dimes

http://www.historyofvaccines.org/content/eddie-cantor
Types of Poliovirus Vaccines #1 - “Killed” or “Inactivated

- Very Safe
- Very cost-effective
- Doesn’t work for all viruses
- Not the most potent vaccines

Dr. Jonas Salk

www.themarkofaleader.com  www.marchofdimes.org
Types of Poliovirus Vaccines #2 - “Live Attenuated”

- Grow virus in laboratory cells over many years
- Virus mutates
- Test virus for causing disease - Poliovirus tested in monkeys
  - Weak virus replicates in GI tract, but can't spread to nervous system
  - Induces very strong immunity without disease

Grow >200 times in non-human cells
Types of Poliovirus Vaccines #2 - “Live Attenuated”

- Very Safe
- Very potent immune responses
- Needs special storage
- Doesn’t work for all viruses

Dr. Albert Sabin

1963 poster

www.wired.com

genelloni.wordpress.com
Poliovirus Eradicated from Western World - 2010
Some Few Areas of Stronghold

1988
350,000 cases
125 countries

2010
1,292 cases
4 endemic countries

Poliovirus Eradication is Now A Political Battle!

http://www.cdc.gov/polio/images/map.jpg
Test Question:
What are the Two Major Types of Flu Vaccines?

Killed

Live Attenuated

www.vaccines.mil

www.flu.gov
Types of Vaccines #3 - “Subunits”

- By far, the safest vaccines are made this way -
  - biologically impossible to have any infectious virus

- Best example is *Hepatitis B Virus* vaccine - produced in yeast
  - Second example is *HPV vaccine* for cervical cancer “Gardasil”

- Cannot be used for all viruses - depends on type of virus
The Miracle of Viral Vaccines
They are Very Safe

THE ODDS A CHILD WILL...

- Be a pilot: 1 in 2,662
- Get struck by lightning: 1 in 10,000
- Make the US Olympic Team: 1 in 380,228
- Get elected to US Congress: 1 in 577,094
- Become a billionaire: 1 in 749,382
- Have severe allergic reactions after the MMR and Hepatitis B vaccines: 1 in 1 million

As you can see, odds are that your child won’t have an adverse reaction after being vaccinated. And in the rare event that it did happen, even a life-threatening allergic reaction could be brought under control at the doctor’s office.

www.vaccines.com
Why Do Older People Not Respond As Well To Vaccines?

- APC becomes weak
- Adjuvants stimulate
- T Cells becomes weak and die
- How can we make them survive?

Antibodies and Killer T cells
Not All Viruses Are Bad!

We all harbor Endogenous RetroViruses (ERVs):

- Viruses inserted into our genome, then mutated!
- We have co-evolved with these invaders over millions of years

- **HERV-W** Essential for development of human placenta –
  - Inserted into human genome ~30 Million years ago
  - Expression usually limited to very few tissues
  - Drives placental development, blood supply, fetal implantation

http://rstb.royalsocietypublishing.org/content/368/1626/20120507
Viruses can be helpful!

- Viruses can be used:
  - To track neuronal connections in the brain
  - To treat inflammatory bowel diseases (at least in mice)
  - For Gene Therapy to correct disease states

- To kill tumor cells but leave normal cells alone
The Parks Lab at UCF

Ariella Saslafsky - Undergrad Student
Candace Newcome - PhD Student
Maria Cruz - PhD Student
Michael Li - Postdoc Scientist
Kritika Kedarinath - MS Student
Namita Varudkar - Lab Technician
Ariella Saslafsky - Undergrad Student
Candace Newcome - PhD Student
Maria Cruz - PhD Student
Michael Li - Postdoc Scientist
Kritika Kedarinath - MS Student
Namita Varudkar - Lab Technician
• Microcephaly

• More widespread damage in population (neurological)

• Mosquito-borne (but also sexual transmission ?)

• Evidence for evolution

• Ask the question of whether Zika Virus was neutralized by normal human serum

• Surprise! Found infectivity enhanced between 5 and 10 fold

• Relevance is at initial site of infection where mosquito deposits virus into blood rich areas

• What is the human factor that enhances Zika Virus infection?
The Parks Lab at UCF

Ariella Saslafsky - Undergrad Student

Candace Newcome - PhD Student

Michael Li - Postdoc Scientist

Kritika Kedarinath - MS Student

Namita Varudkar - Lab Technician

Maria Cruz - PhD Student
Viruses can be helpful!

- First Time FDA approval for use of a virus for human cancer therapy - melanoma
- Based on attenuated Herpes virus engineered to express immune cytokine
Parks Lab at UCF College of Medicine

Engineering Viruses to Selectively Kill Tumor Cells

Oncolytic Viruses – “Tumor Lysing”

Clearance of the Tumor

http://www.viratherapeutics.com
Virus Research in the Parks Lab - Tumor Therapy with Novel Viruses

Human Prostate Tumors Grown in a Mouse Treated with Parainfluenza Virus 5 (PIV5)

Control Group

Virus Infected

Top View

Side View
Parks Lab at UCF College of Medicine

Engineering Viruses to Selectively Kill Tumor Cells

Oncolytic Viruses – “Tumor Lysing”

http://www.viratherapeutics.com
Engineering Viruses to Selectively Kill Tumor Cells - Parks lab at UCF COM

Normal Prostate Cell  →  ?  →  ?  →  ?  →  Virus  Kills Tumor Cell  →  Metastatic Prostate Cancer Cell
Summary

• Viruses are simple, but hard to control because they growth within host cells
• There are three types of viral vaccines – killed, attenuated and subunit
• Vaccines have had a miraculous impact on human health

Parks Lab:
• Examining factors that inhibit and promote Zika Virus infection
• Viruses can be engineered to be selective agents for therapies such as cancer

GET VACCINATED and INVEST IN RESEARCH !!