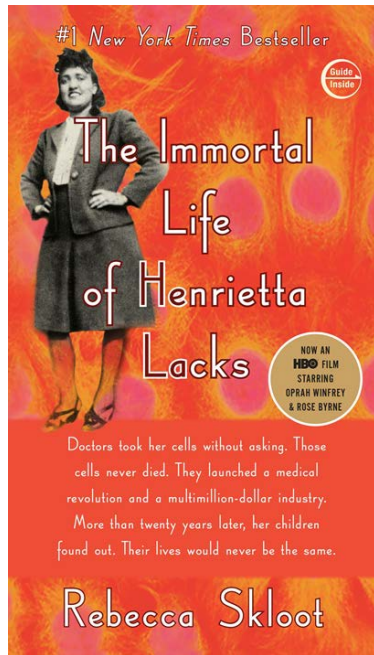


HENRIETTA LACKS: IT'S A WONDERFUL LIFE

What if Henrietta Lacks and HeLa Cells had Never Been?

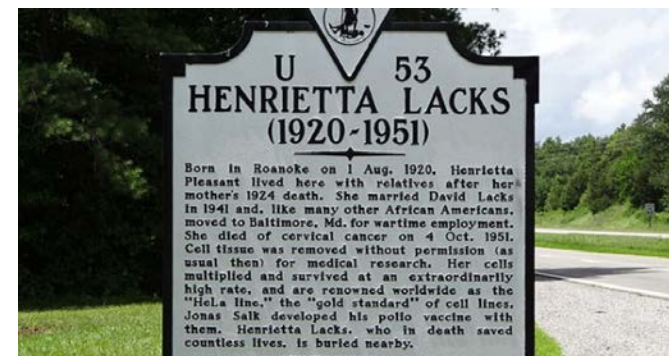


Ken S. Rosenthal, Ph.D.

Professor Biomedical Science and Director of Microbiology and Immunology,

Roseman University College of Medicine

Professor Emeritus, Northeast Ohio Medical University



Jimmy Stewart's character, George Bailey, in "It's A Wonderful Life", declared that he wished that he never existed.

What if Henrietta Lacks never existed?

60TH ANNIVERSARY EDITION

JAMES STEWART

DONNA REED

FRANK CAPRA'S

IT'S A WONDERFUL LIFE



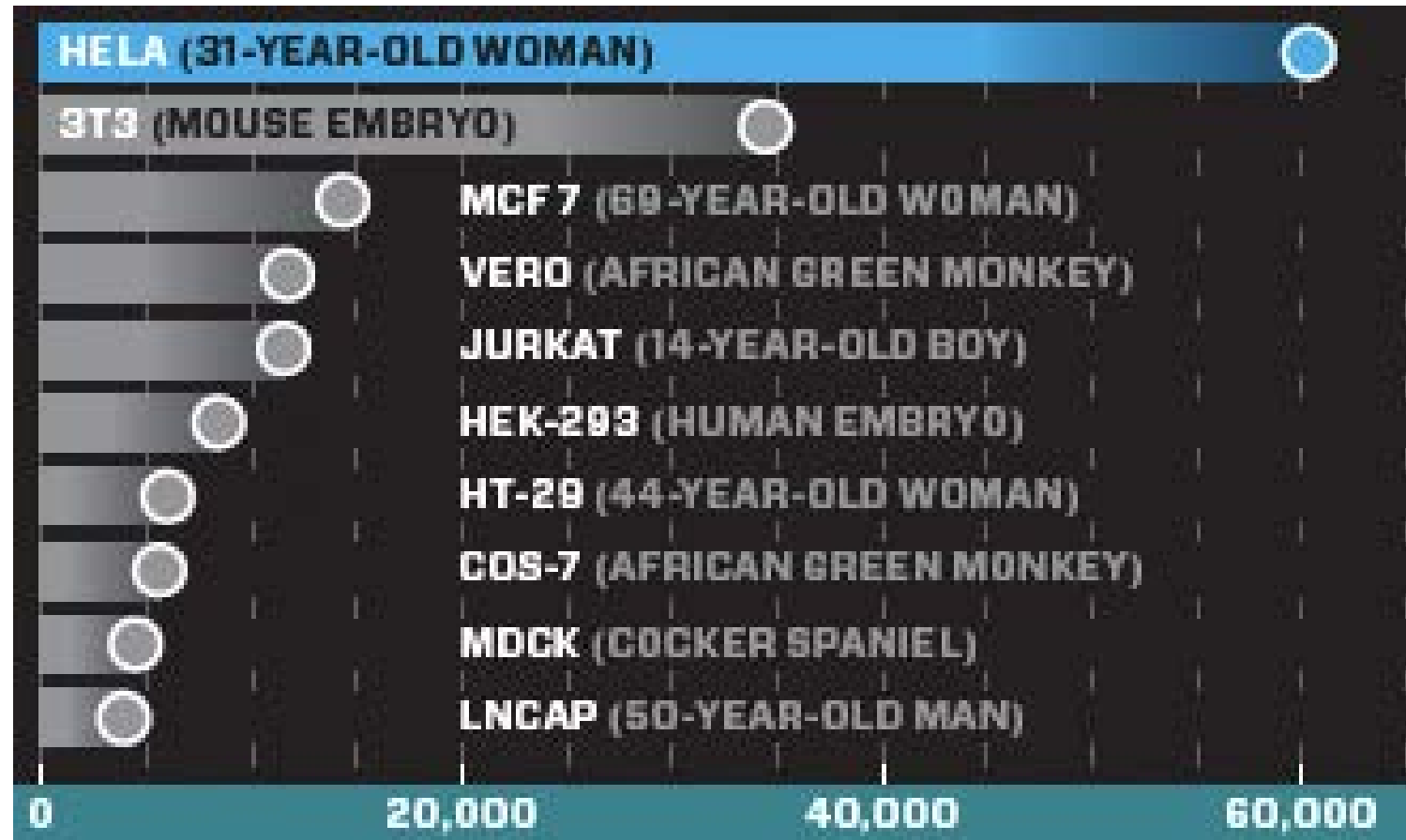
<https://www.youtube.com/watch?v=IYYUn83xzwA>

6:30-7:30 minutes

What if?

- What if Henrietta Lacks never existed?
- What if Henrietta Lacks never got infected with human papilloma virus 18
- What if Henrietta Lacks never got cervical carcinoma?
- What if her physician, Howard W. Jones, at Johns Hopkins never took a biopsy?
- What if Dr. George Otto Gey never put her biopsy cells into cell culture?
- What if Dr. Gey never shared the cells with others?
- What if the ATCC and other companies never made the HeLa cells available for scientific use?

Lots of Scientists Use HeLa Cells in Research



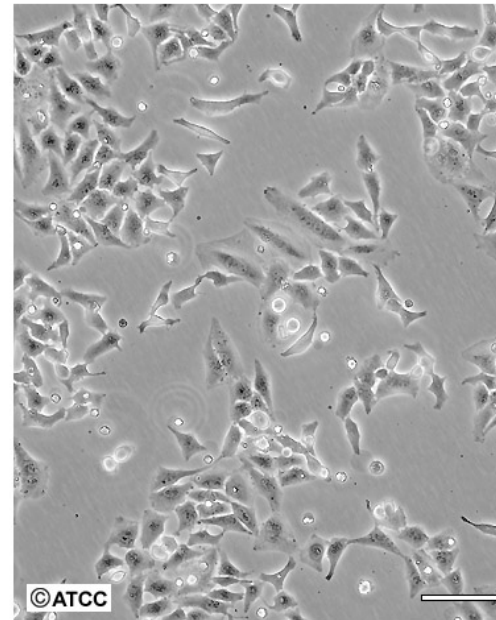
Number of publications using different cell lines as of 2010

https://www.wired.com/2010/01/st_henrietta/

What are HeLa cells?

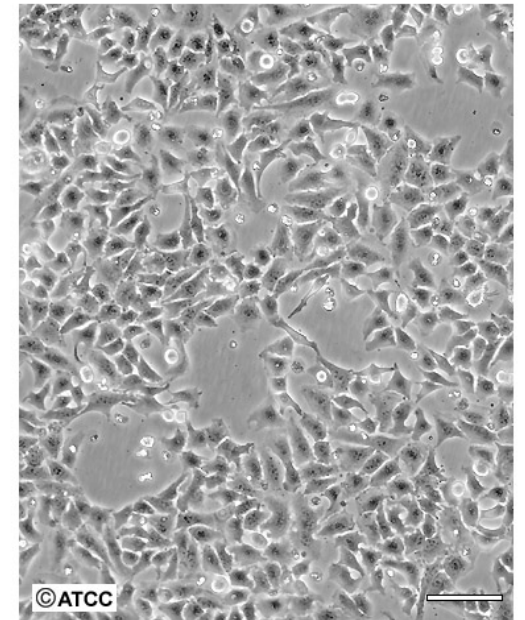
- The first human cell that could be grown in tissue culture without senescence.
- Epithelial cells, representative of a major type of human cell.
- HeLa is a model cell for many normal biochemical functions.
- HeLa is a 'transformed' cell and is a model for cancer cells, with differences from normal cells.
- HeLa is infected with HPV18
- HeLa is a model for how HPV 18 causes cells to lose growth control and have the potential to become a cancer.

ATCC Number: **CCL-2**
Designation: **HeLa**



Low Density

Scale Bar = 100µm



High Density

Scale Bar = 100µm

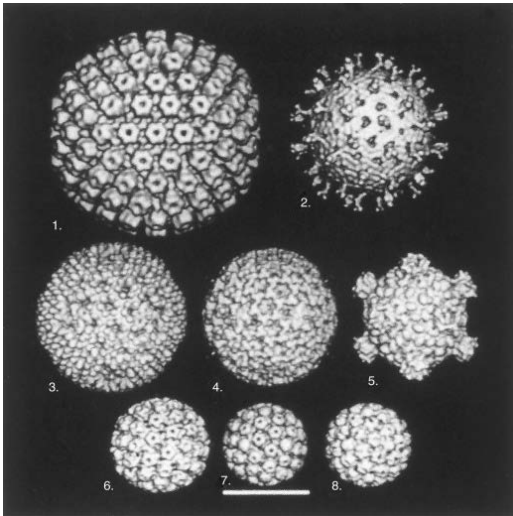
Benefits from HeLa

- Virology
 - Viruses can be easily grown in HeLa.
 - To study how they replicate.
 - To produce large quantities of virus.
 - HeLa is infected with Human papillomavirus 18
 - How and Why?
 - How to treat?
- Cell Biology
 - Structure and function of human cells
 - Structure and function of human cancer cells
 - Effect of drugs and other molecules on human cells
- Vaccines
 - Early polio vaccines
 - Large quantity of virus for vaccine
 - Large quantity of virus to use in challenge studies
 - Ability to test quality of antibody produced by vaccine
- Cancer biology
 - How does HPV promote cancer?
 - Testing cancer treatments on HeLa before animals or humans.

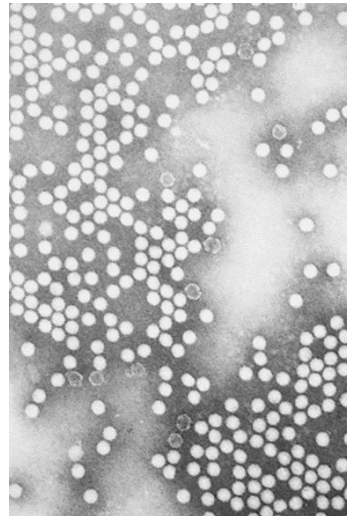
What is a virus?

DNA or RNA genome in a protein or membranous package.

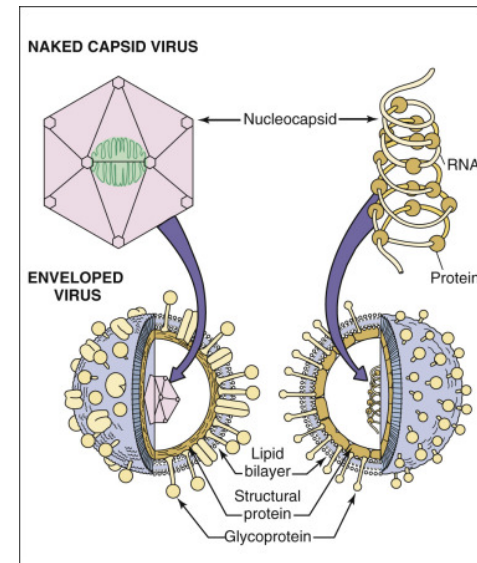
Protein Packaged (Encapsidated)



Figures from Murray, Rosenthal and Pfaller, Medical Microbiology 8E, Elsevier 2016

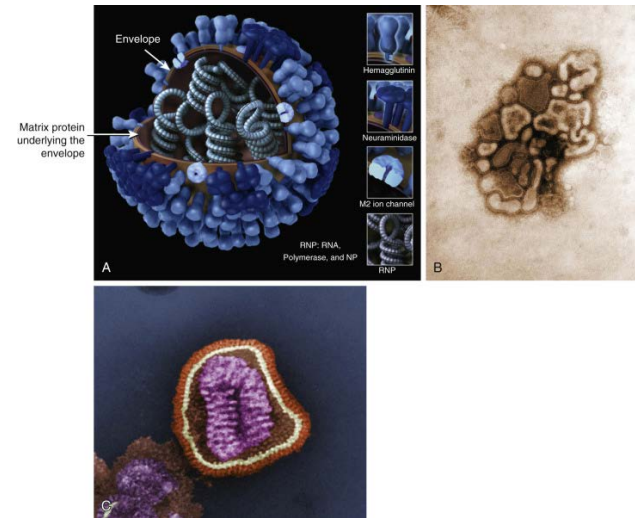


Polio

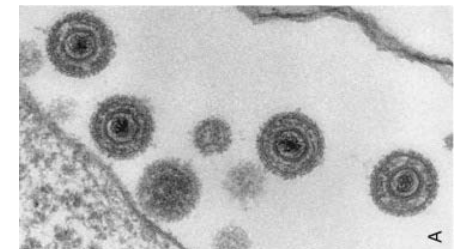
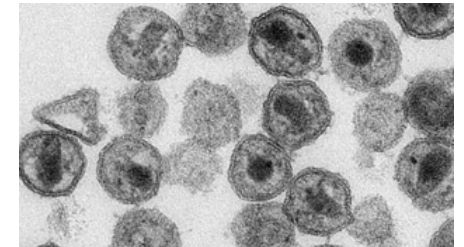


Membrane (Enveloped) viruses

Influenza



HIV



Herpes simplex virus

Viruses: How do they replicate?

- Viruses are incapable of independent multiplication.
- Requires human or animal cells to replicate.
 - Cell provides energy
 - Protein synthesis
 - Other functions

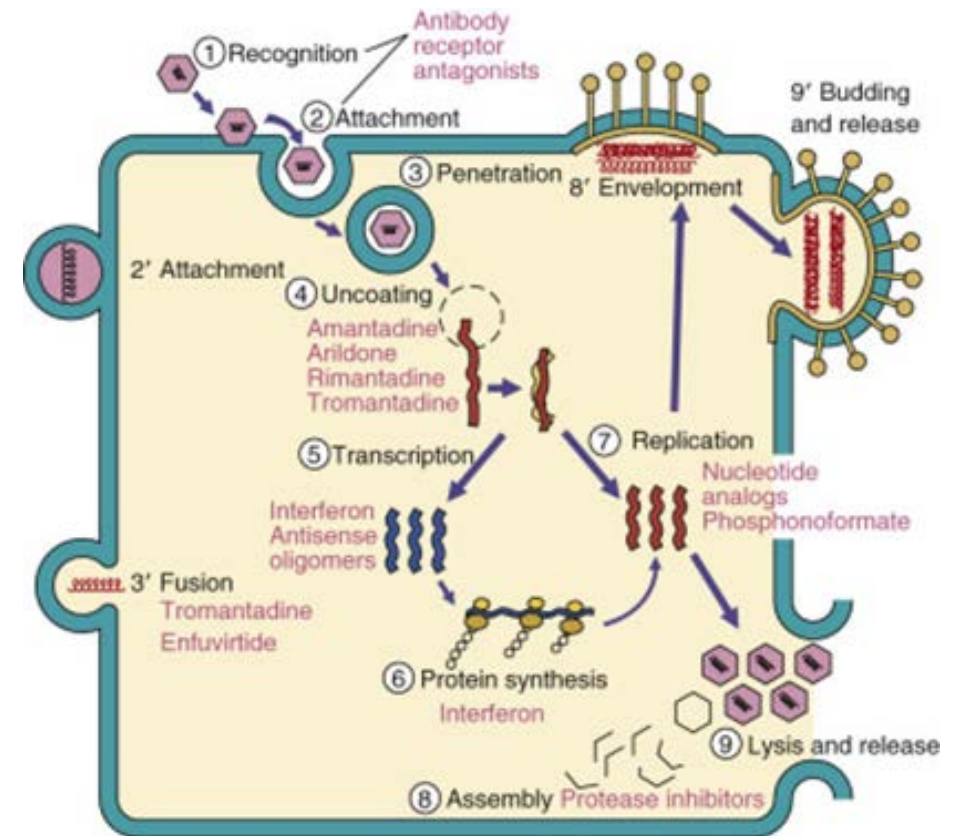


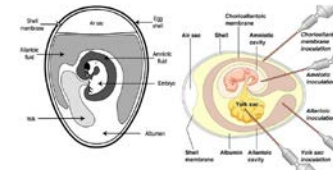
Figure from Murray, Rosenthal and Pfaller, Medical Microbiology 8E, Elsevier 2016

Virology Before HeLa Cells

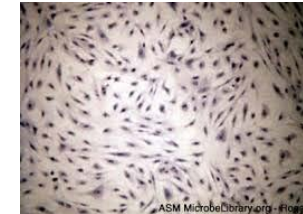
- Ways to grow virus
 - Grow in animals (mice, monkeys)
 - Grow in embryonated eggs
 - Grow in cell dispersion from animal tissue (baby rabbit kidney)
- Steps in growing virus in cells
 - Euthanize animal
 - Remove organ
 - Disperse cells using scalpel and enzyme
 - Grow cells in animal serum
 - Infect cells
- Problems
 - Requires many animals
 - Limited cell yield
 - Must be done over and over
 - TIME
 - MONEY
 - EXPERTISE



Mouse



Embryonated Egg

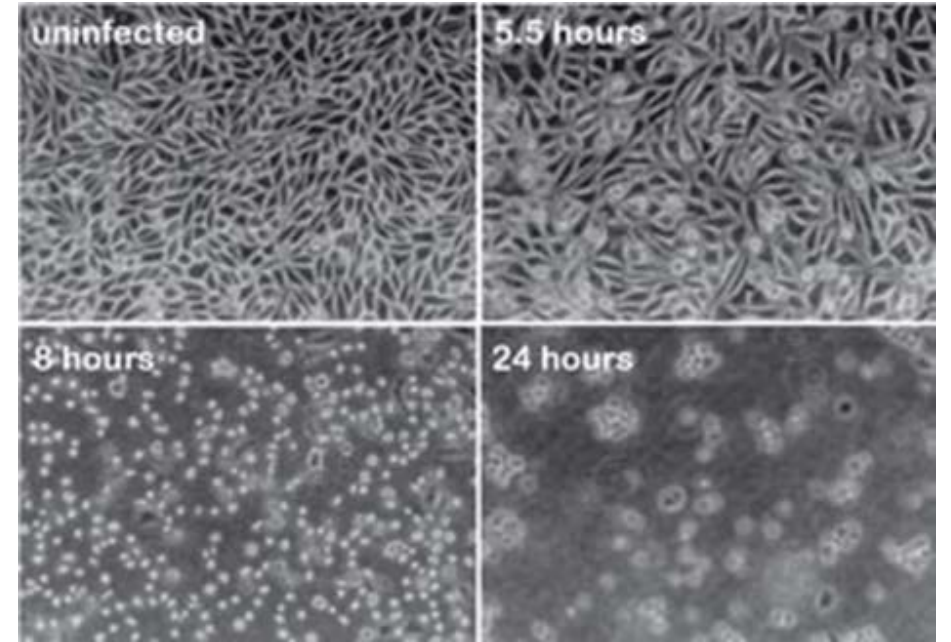
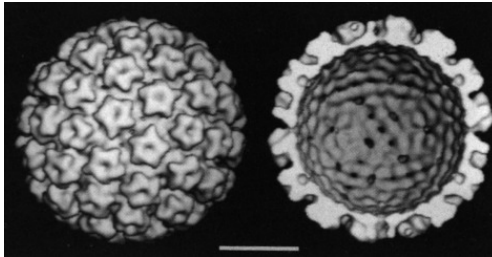


Baby rabbit or monkey kidney cells



HeLa cells for Virologists

- The cells are always available for use.
- Viruses can be easily grown in HeLa.
 - To study how they replicate.
 - To produce large quantities of virus.
- HeLa is infected with Human papillomavirus 18
 - Model to study HPV18



Polio infection of HeLa cells
(CDC)

Virus Vaccines Before HeLa

- Smallpox virus vaccine
 - Cowpox isolated from animal lesions
- Rabies
 - Infected Rabbit spinal cord or brain extract
- Yellow fever
 - Embryonated egg
- Influenza (experimental)
 - Embryonated egg
- Polio (experimental)
 - Monkey kidney cells



What is a vaccine?

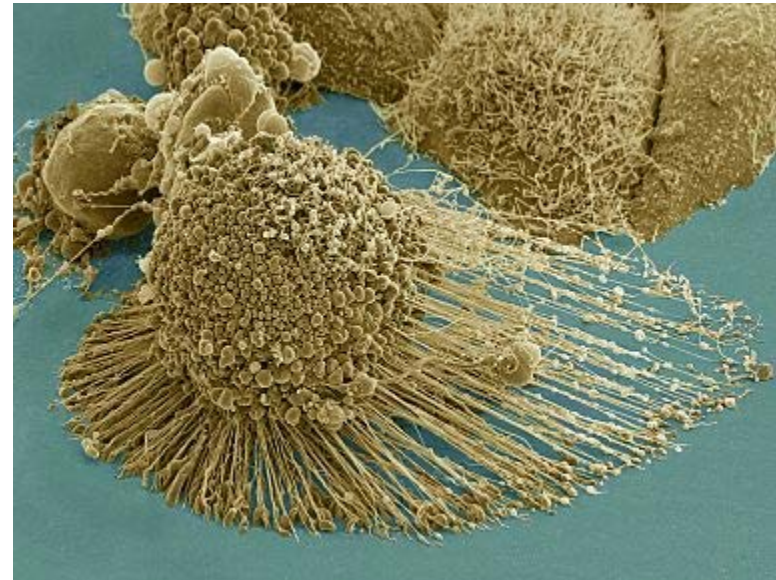
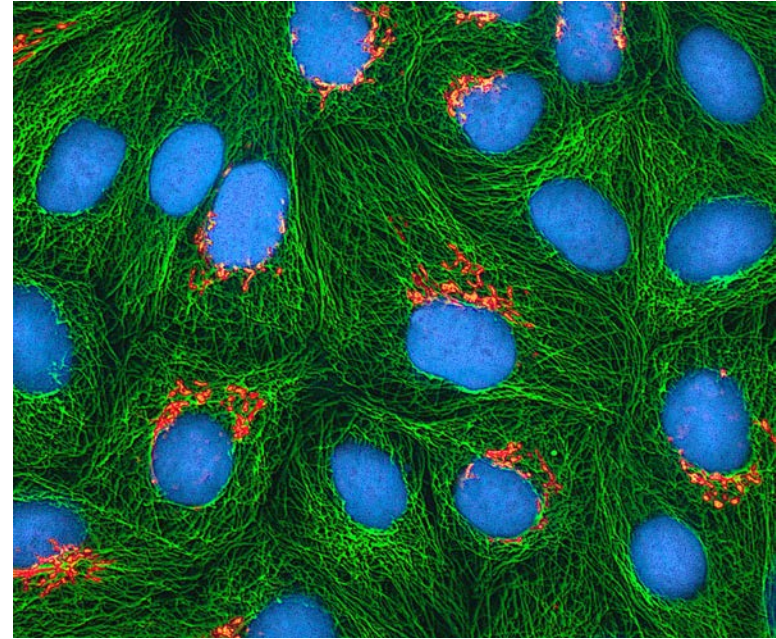
Purposeful treatment to elicit protective memory immune responses:

- Exposure to pieces/parts of microbe
 - Antibody protections
 - Sufficient for toxins and some viruses
 - Examples: DPT, pneumococcus, Salk polio vaccine, HPV
- Infection with attenuated strain of microbe or non-disease causing related microbe.
 - Antibody and attack cell mediated protections
 - More important for viruses and tuberculosis
 - Examples: Measles, Mumps, Rubella, Varicella zoster..
- Newer approaches

Vaccines after HeLa

Grown in Cell Culture

- Polio: Inactivated (Salk)
- Polio: Live Attenuated (Sabin)
- Measles
- Mumps
- Rubella
- Adenovirus
- Etc.



Polio Before (and after) HeLa



<https://www.historyofvaccines.org/content/polio-1-0>



<http://www.gettyimages.com/detail/photo/during-the-1950s-as-polio-swept-across-the-high-res-stock-photography/128574934>

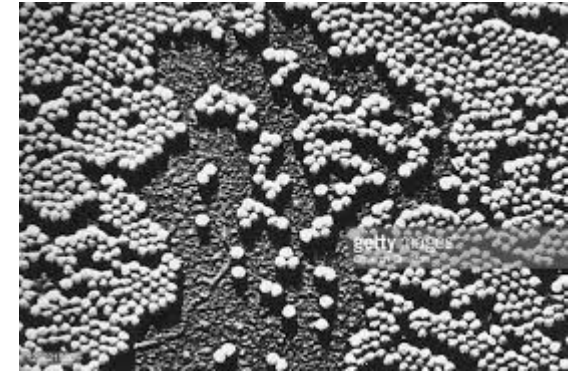


Itzhak Perlman

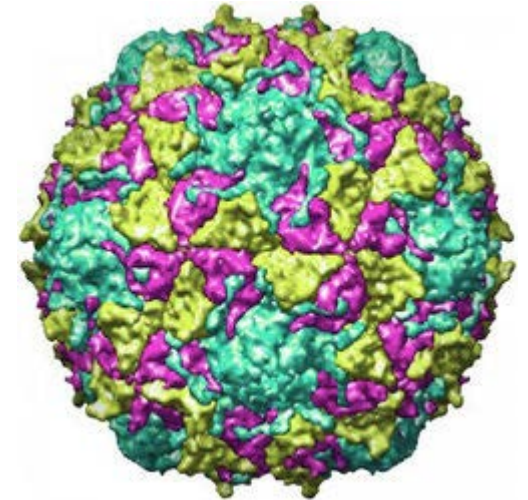


Polio

- Small encapsidated virus with RNA genome.
- 3 different types: Type 1, Type 2, Type 3
- ALWAYS KILLS THE INFECTED CELL
- Transmitted by fecal-oral route in food, water and by dirty hands.
- Can travel in blood to the brain and nerves to cause paralysis of limbs, diaphragm, etc.
- Disease ranges from mild to paralysis.
- Large outbreaks occurred every summer.
- No treatment other than repair or rewiring of neurons to the paralyzed area.
- Post polio syndrome occurs many years later due to overuse and death of the remaining nerves.



<http://www.gettyimages.com/photos/polio-virus?excludenudity=true&sort=mostpopular&mediatype=photography&phrase=polio%20virus>



https://microbewiki.kenyon.edu/index.php/Poliovirus_and_its_three_serotypes

Quantum Leap in Polio Vaccine Development Due to HeLa

- Testing

- Able to make large quantity of quality virus as prototype of vaccine.
- Large quantity of virus to evaluate use in animal challenge studies to test vaccine.
- Allowed quality control testing to ensure inactivation of vaccine
- Large quantity of virus to test whether a person's antibody can stop infection of cells in the lab.
 - Allowed evaluation of serum from 2,000,000 immunized volunteers.



<https://www.historyofvaccines.org/content/empty-title-0>

Current Polio Vaccines: Salk

Inactivated (Salk) vaccine

- First tested on humans 1954 in USSR
- Produced in Vero (African green monkey kidney cell line) cells.
- Contains Type 1, Type 2 and Type 3 polio viruses.
- Cannot cause infection if properly prepared.
- Infectability of vaccine (bad) and antibody produced in response to vaccine tested with HeLa cells
- Relatively large dose of vaccine required.
- Preferred vaccine in the U.S.A.

Eradication of Polio in most of the world

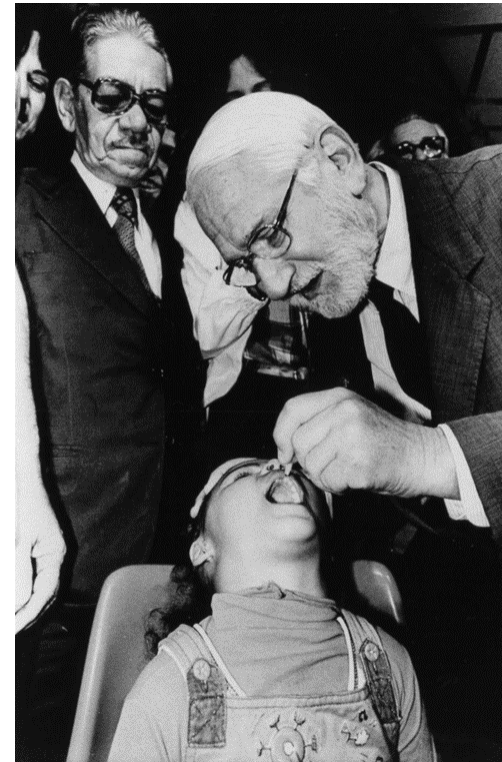


Current Polio Vaccines: Sabin

Oral Live Attenuated vaccine

- First tested on humans 1959
- Contains INFECTIOUS MUTANTS of Type 1, Type 2 and Type 3 polio viruses.
- Viruses can replicate in the gut but not in nerves (no disease)
- Inexpensive and small dose required
- Preferred vaccine outside of U.S.A.
- Rare mutations can revive virulence and cause disease or prevent immunization

Eradication of Polio in most of the world

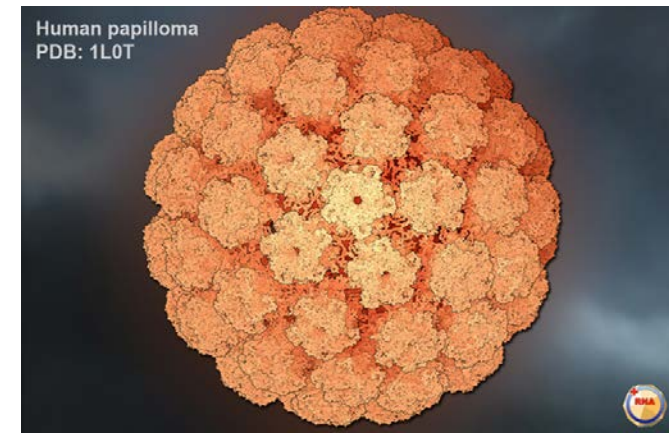


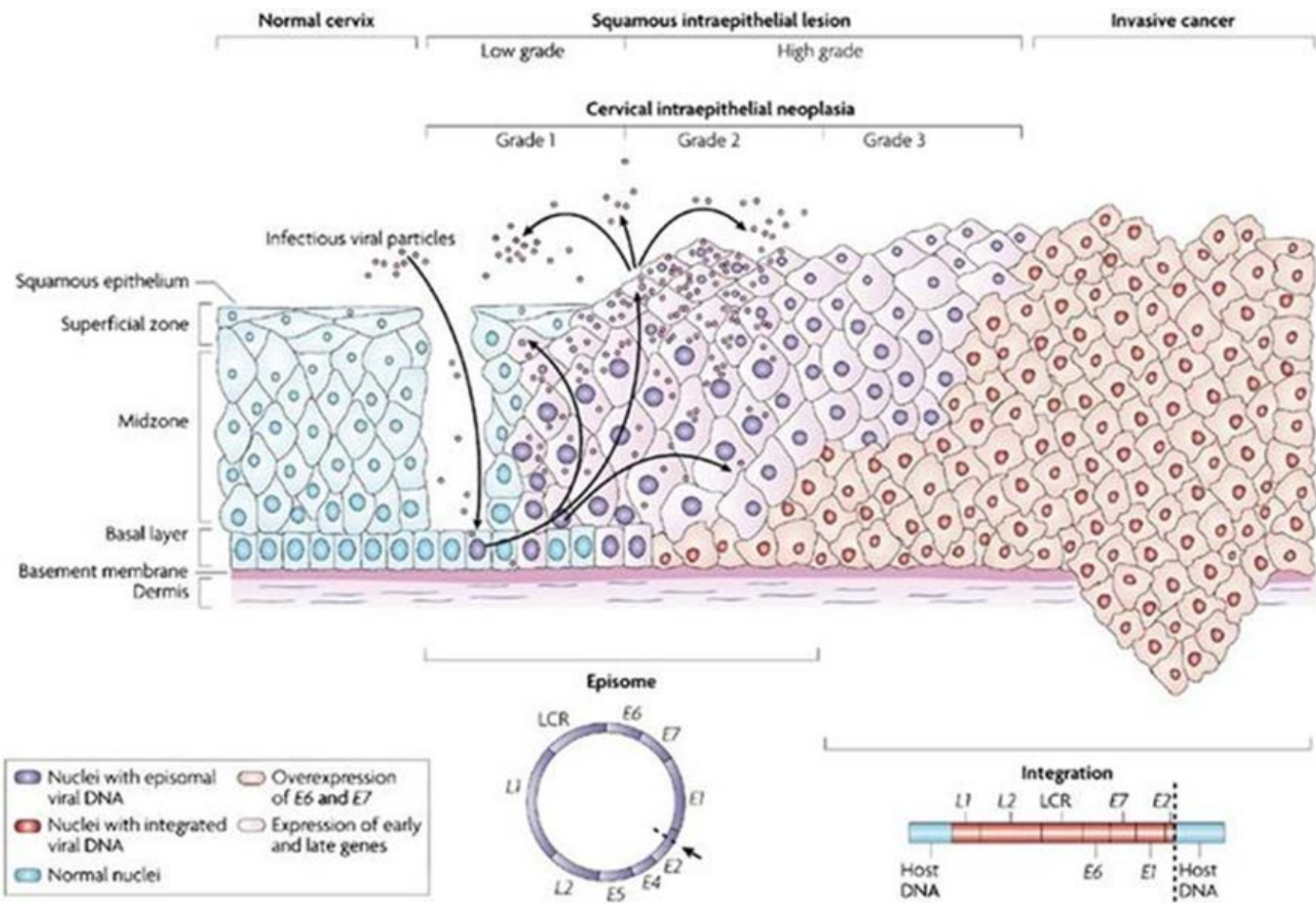
Human Papillomaviruses Before HeLa

- Human papillomaviruses (HPV) cause warts and condylomas.
- Wart and wart-like growths can occur on skin or the mucous membranes in the mouth, throat, anus, vagina, etc.
- Warts are contagious and spread by contact.
- Warts are slow growing.
- Warts cannot be gotten from frogs or toads.

HeLa and HPV 18

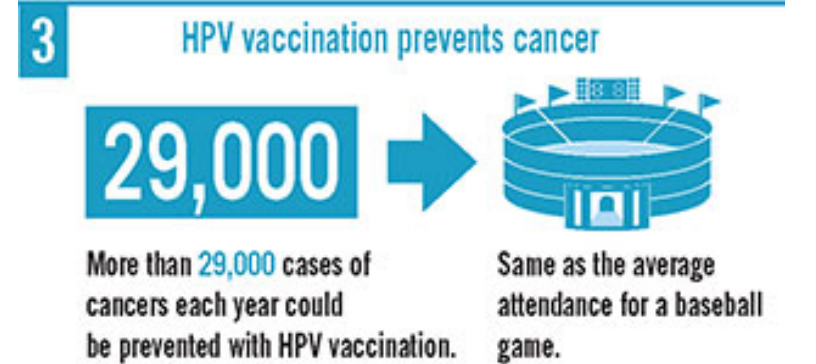
- HPV is a simple DNA virus that **must stimulate the cell to divide** so that the cell provides the machinery for virus production.
- HPV 18 E6 and E7 proteins inactivate the cell's growth suppressor protein (RB p105) and error checking protein (p53).
- HPV 18 E6 and E7 proteins inactivate the cell's growth suppressor protein (RB p105) and error checking protein (p53).
- HPV 18 viral DNA integrates into the human chromosome.
 - This inactivates a gene essential for virus production and cell killing
 - Stimulation of cell growth continues.
- HPV 16, 18 and other HPVs are high risk and cause cervical dysplasia that can progress to cancer.





HPV after HeLa

- ZurHausen proved that HPV16 and 18 are necessary for 99% of all cervical carcinomas.
- Molecular tests for viral DNA developed to detect HPV in Pap smears.
- HPV DNA tests used instead of Pap smear.
- HPV vaccines: girls and boys age 11-25
 - *Gardasil*: HPV 6, 11, 16, 18, 6, 11
 - *Cervarix*: HPV 16, 18
 - *Gardasil 9*: 6, 11, 16, 18, 31, 33, 45, 52, 58
- HPV vaccine and hepatitis B virus vaccines prevent cancer.



If there were a vaccine against cancer, wouldn't you get it for your kids?

Talk to the doctor about vaccinating your 11-12 year old sons and daughters against HPV.

www.cdc.gov/vaccines/teens



HPV vaccine is cancer prevention.



The HPV Vaccine: The Who's And The When's

All kids ages 11 to 12 should begin the 3-dose series.

Women can be vaccinated until age 26.

Men can be vaccinated until age 21.



Source: Centers for Disease Control and Prevention.



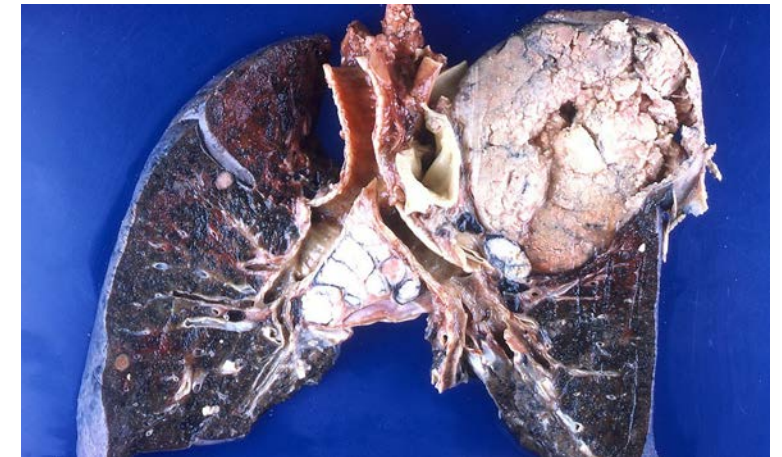
Cancer Biology before HeLa (pre 1953)

- Tumors consist of cells that grow out of control.
- There is a genetic predilection for tumors (animal and humans (retinoblastoma))
- Chemicals and radiation can cause tumors
- Mutations and DNA damage can lead to tumors
- In chickens, a virus can cause tumors (Rous sarcoma virus)
- Tumor cells evade immune control
- George Papanicolaou develops the Pap smear to detect cervical cancer development



Metastatic tumors in the liver.

https://commons.wikimedia.org/wiki/File:Secondary_tumor_deposits_in_the_liver_from_a_primary_cancer_of_the_pancreas.jpg



Lung tumor

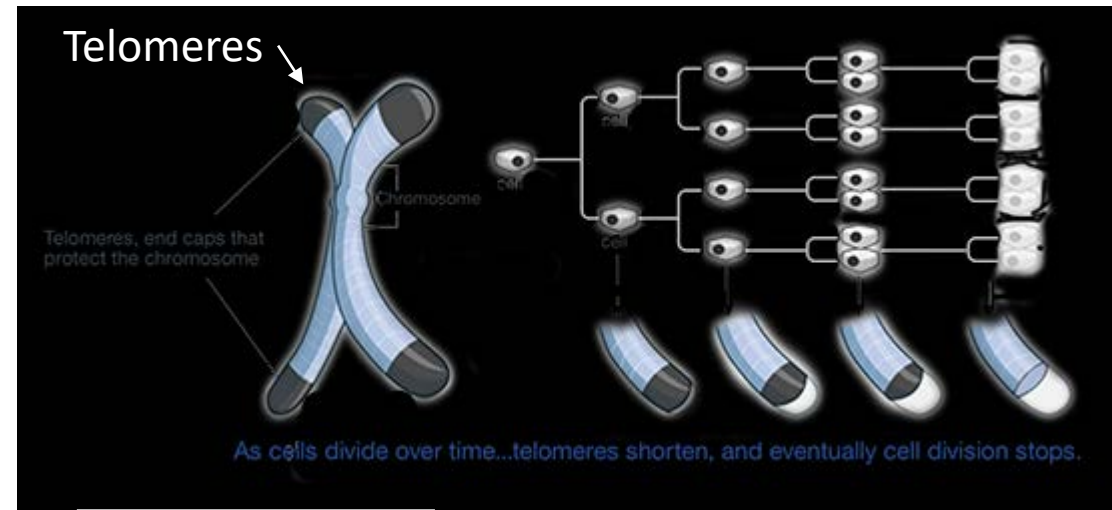
[https://commons.wikimedia.org/wiki/Category:Gross_pathology_of_cancers_of_bronchus_and_lung#/media/File:Carcinoma,_type_unspecified_\(3922612069\).jpg](https://commons.wikimedia.org/wiki/Category:Gross_pathology_of_cancers_of_bronchus_and_lung#/media/File:Carcinoma,_type_unspecified_(3922612069).jpg)

Cancer Biology before HeLa: Questions and Observations

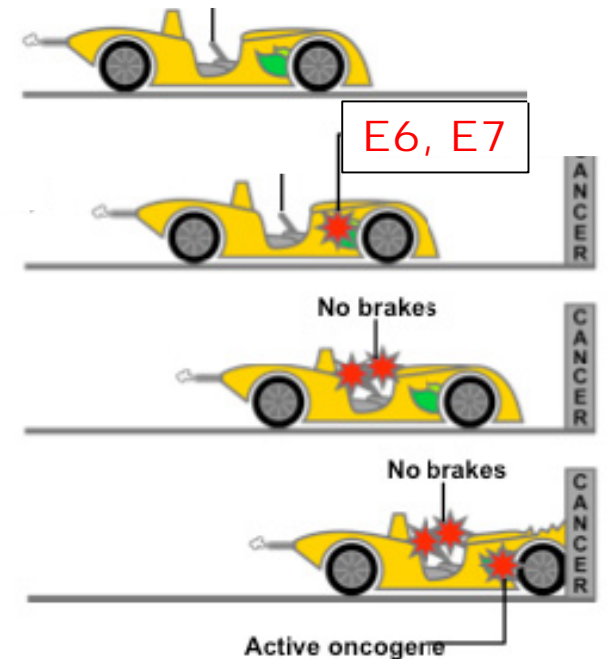
- Why do HeLa cells continue to grow without senescence?
 - Normal cells: Hayflick phenomenon- 120 cell divisions
- What makes Tumor cells grow?
 - Growth can either be accelerated or the brakes removed.
- How are tumor cells different from normal cells?
 - Different metabolic requirements and processes
 - More like active muscle cells
 - Warburg effect: aerobic glycolysis
 - Senseless to signals from other cells to stop growing (contact inhibition)
 - Continue to grow without senescence (but not all tumors are easy to grow in cell culture)
 - Accumulate mutations that become selected for growth and survival in the body or tissue culture.
 - Immune escape
 - Angiogenesis (blood supply)
 - Metastasis

Cancer Biology after HeLa

- Why do HeLa cells continue to grow without senescence?
 - HeLa cells continue to grow.
 - Able to regenerate telomeres
- What makes Tumor cells grow?
 - For HeLa, the brakes are removed and DNA error checking is inactivated.
- How does HPV 18 and other high risk HPVs promote cervical tumorigenesis?
 - HPV 18 is integrated into the HeLa chromosome
 - The circular viral DNA was cut and then spliced into the cell's chromosome.
 - Cutting and splicing also cut a viral E2 gene into parts and inactivated it.
 - Without the E2 protein, the virus does not get made and cannot kill the infected cell.
 - The viral E6 and E7 proteins are made and inactivate the growth suppressing RB105 protein and the DNA and replication error checking p53 protein.
 - Cells grow and make genetic mistakes (mutations)
 - Some mutations cause the infected cells to change and become invasive.



The cell's pit crew (p53) checks the DNA and if ok, then activates growth using accelerator proteins (oncogenes). Rb105 is the brakes that keeps cell under control.



Areas of Discovery

- Viruses
- Materials
- Lab techniques
- Cancer
- Bacteria
- Genetics

1952

VIROLOGY

Researchers infect HeLa cells with everything from mumps and measles to herpes, and the modern field of virology is born.

1952

POLIO

Researchers discover that HeLa is susceptible to polio, paving the way for its use in the largest vaccine field trial to date.

1951

BIOPSY

Tissue taken from Henrietta Lacks without her knowledge or consent is developed into a surprisingly hardy cell line for scientific research.

1952

SCIENTIFIC STANDARDS

HeLa is used to develop processes for growing cells in bulk and to test glass used in slides and beakers.

1952

LIVE CELL TRANSPORT

Scientists working with HeLa come up with a way to send cells through the mail without killing them. Before this, couriers had to carry vials of cells in their pockets on airplanes.

Cryogenics
Frozen embryos

1953

GENETIC MEDICINE

A researcher working with HeLa discovers that a stain called hematoxylin makes cell chromosomes visible.

1954

CLONES

Thanks to the hardiness of the HeLa line, scientists are able to devise a method for isolating a single cell and keeping it alive long enough for it to replicate and create a perfect copy of itself.

Gene therapy
In vitro fertilization
Stem cell isolation

1954

FOR-PROFIT DISTRIBUTION OF CELLS

Microbiological Associates begins mass-producing HeLa in a former Fritos factory.

Biological materials as commodities

1960

SPACE BIOLOGY

Packed in a Soviet satellite, HeLa goes to space before any astronauts. NASA later includes HeLa in the first manned US missions, discovering that the cancer cells grow faster in space.

Animal cloning

1965

GENETIC HYBRIDS

By fusing HeLa and mouse cells, scientists create the first cross-species hybrid. It helps in mapping human genes.

Development of cancer drug Herceptin

Blood type identification

1973

SALMONELLA

Scientists use HeLa to model the invasiveness of salmonella, gauge its infectiousness, and study its behavior inside human cells.

1966

ETHICS

After a scientist injects HeLa cells into unwitting test subjects to study how cancer spreads, an NIH investigation leads to the institution of medical review boards and informed consent by patients.

2005

NANOTECH

Researchers subject HeLa cells to various forms of nanotech—from injecting them with iron nanowires to testing how they absorb silica-coated nanoparticles.

1993

TUBERCULOSIS

Researchers infect HeLa cells with tuberculosis DNA to learn how the bacterium attacks human cells.

1984

HPV

A German virologist uses HeLa to help prove that the human papillomavirus causes cancer, a discovery that would earn him the Nobel Prize.

HPV vaccine

1986

HIV

Scientists figure out how to infect HeLa with HIV, shedding light on the virus' infection mechanism by identifying a key receptor.

1989

TELOMERASE

A Yale researcher publishes the discovery that the cancerous HeLa cells contain an enzyme called telomerase, which prevents cells from dying.

Telomerase inhibitors for cancer treatment
Longevity research



Biological supplies industry

- Discovery of genetic links to diseases like Down syndrome
- Genetic disease diagnosis
- Amniocentesis for genetic disease testing
- Preimplantation genetic screening for IVF

1954

FOR-PROFIT DISTRIBUTION OF CELLS

Microbiological Associates begins mass-producing HeLa in a former Fritos factory.

Biological materials as commodities

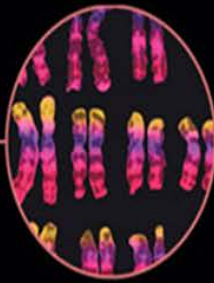
1965

GENETIC HYBRIDS

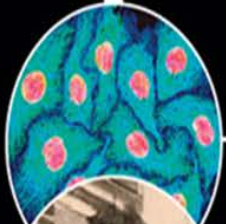
By fusing HeLa and mouse cells, scientists create the first cross-species hybrid. It helps in mapping human genes.

Development of cancer drug Herceptin

Blood type identification



Gene mapping



What is your answer to: What if
Henrietta Lacks and HeLa cells
never existed?

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where noted.