The Nobel Prize in Physiology or Medicine

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2010: Robert G. Edwards; The Nobel Prize in Physiology or Medicine 2010 was awarded to Robert G. Edwards "**for the development of in vitro fertilization**"

2009: Elizabeth H. Blackburn, Carol W. Greider, Jack W. Szostak; The Nobel Prize in Physiology or Medicine 2009 was awarded jointly to Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak "**for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase**"

2008: Harald zur Hausen, Françoise Barré-Sinoussi, Luc Montagnier; The Nobel Prize in Physiology or Medicine 2008 was divided, one half awarded to Harald zur Hausen "**for his discovery of human papilloma viruses causing cervical cancer**", the other half jointly to Françoise Barré-Sinoussi and Luc Montagnier "**for their discovery of human immunodeficiency virus**"

2007: Mario R. Capecchi, Sir Martin J. Evans, Oliver Smithies; The Nobel Prize in Physiology or Medicine 2007 was awarded jointly to Mario R. Capecchi, Sir Martin J. Evans and Oliver Smithies "**for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells**"

2006: Andrew Z. Fire, Craig C. Mello; The Nobel Prize in Physiology or Medicine 2006 was awarded jointly to Andrew Z. Fire and Craig C. Mello "**for their discovery of RNA interference - gene silencing by double-stranded RNA**"

2005: Barry J. Marshall, J. Robin Warren; The Nobel Prize in Physiology or Medicine 2005 was awarded jointly to Barry J. Marshall and J. Robin Warren "**for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease**"

2004: Richard Axel, Linda B. Buck; The Nobel Prize in Physiology or Medicine 2004 was awarded jointly to Richard Axel and Linda B. Buck "**for their discoveries of odorant receptors and the organization of the olfactory system**"

2003: Paul C. Lauterbur, Sir Peter Mansfield¸The Nobel Prize in Physiology or Medicine 2003 was awarded jointly to Paul C. Lauterbur and Sir Peter Mansfield "**for their discoveries concerning magnetic resonance imaging**"

2002: Sydney Brenner, H. Robert Horvitz, John E. Sulston; The Nobel Prize in Physiology or Medicine 2002 was awarded jointly to Sydney Brenner, H. Robert Horvitz and John E. Sulston "**for their discoveries concerning 'genetic regulation of organ development and programmed cell death'**"

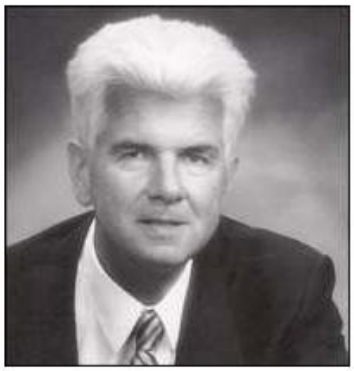
2001: Leland H. Hartwell, Tim Hunt, Sir Paul M. Nurse; The Nobel Prize in Physiology or Medicine 2001 was awarded jointly to Leland H. Hartwell, Tim Hunt and Sir Paul M. Nurse "**for their discoveries of key regulators of the cell cycle**"

2000: Arvid Carlsson, Paul Greengard, Eric R. Kandel¸The Nobel Prize in Physiology or Medicine 2000 was awarded jointly to Arvid Carlsson, Paul Greengard and Eric R. Kandel "**for their discoveries concerning signal transduction in the nervous system**"

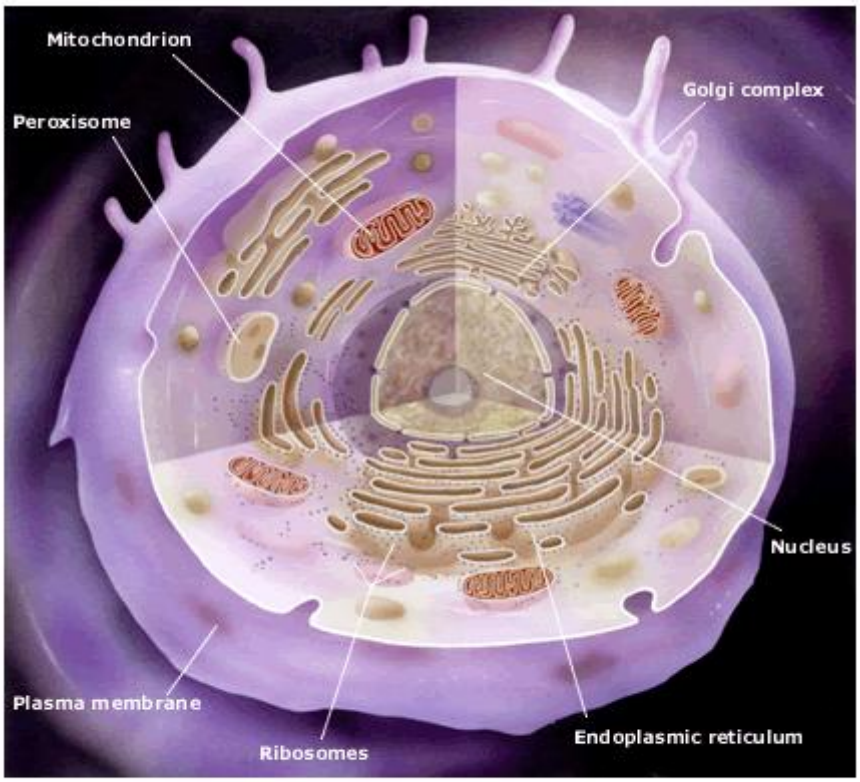
1999: Günter Blobel; The Nobel Prize in Physiology or Medicine 1999 was awarded to Günter Blobel "**for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell**".

The Nobel Prize in Physiology or Medicine 1999

The Nobel Assembly at Karolinska Institutet in Stockholm, Sweden, has awarded the Nobel Prize in Physiology or Medicine for 1999 to **Günter Blobel**, for the discovery that "proteins have intrinsic signals that govern their transport and localization in the cell."



Günter Blobel, born in 1936, works at the Laboratory of Cell Biology, The Rockefeller University, New York



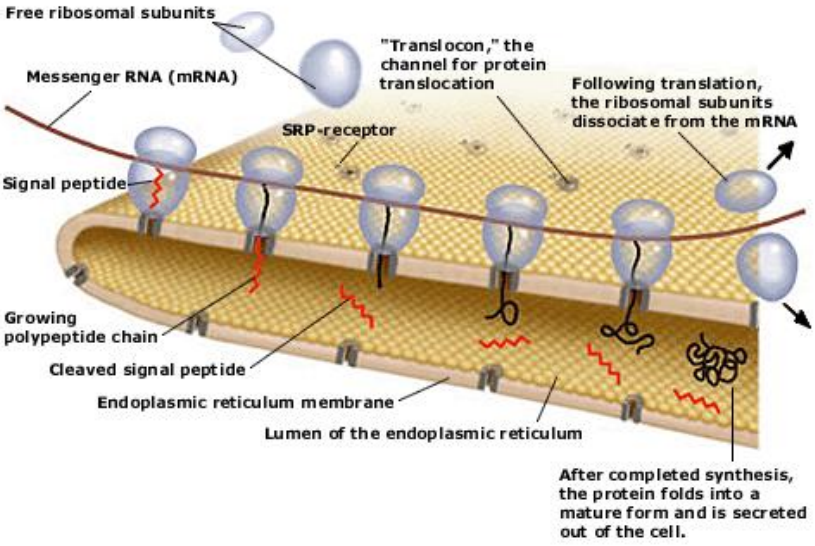
All living organisms are made up of cells. The eukaryotic cell contains a number of different types of organelles each of which is surrounded by a tightly sealed membrane.

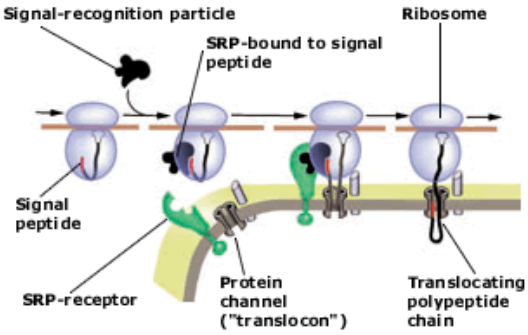
Introduction

The organization of a cell can be compared to that of a big city such as New York. In order to reach its correct destination, a letter has to be provided with an address label and a zip code, similar to the address tags on proteins.

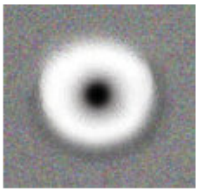
Protein synthesis

How do newly synthesized proteins find their correct destinations within a cell, and how are they able to pass across the tightly sealed intracellular membranes? These were the central questions that Günter Blobel began to address in the late 1960s. He started by analyzing how newly synthesized secretory proteins are first targeted to and then translocated across the membrane of the endoplasmic reticulum (ER). These two steps are prerequisites for secretion of proteins out of the cell.





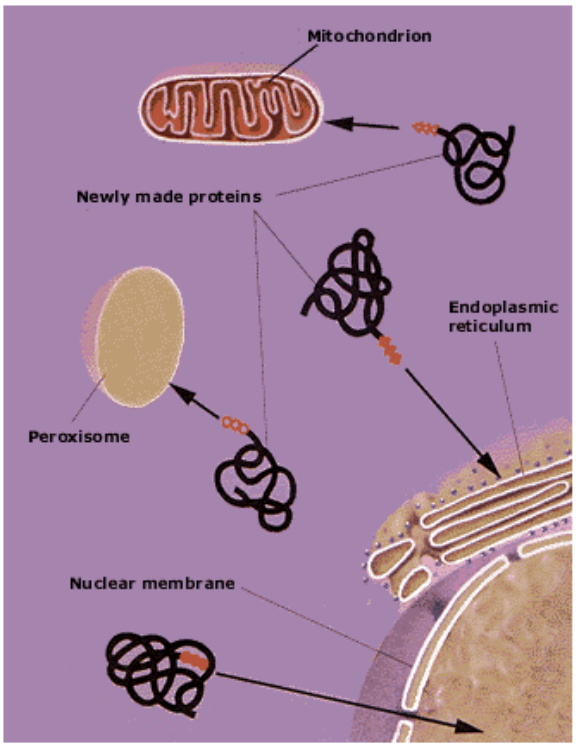
Present view of protein translocation across the ER membrane. The signal peptide, emerging from the ribosome, binds to the signal-recognition particle (SRP). The SRP-ribosome complex then docks to the SRP-receptor and channel ("translocon").
SRP dissociates from the receptor and the nascent polypeptide chain is translocated through the channel into the ER lumen. The signal peptide is finally cleaved and the protein is secreted out of the cell.



Electron micrograph of the protein translocating channel (the "translocon").

Signal sequences

In 1980 Blobel proposed that newly made proteins are targeted to and imported into the various organelles within the cell by built-in signal sequences. The signals are short stretches of amino acids encoded by the gene specifying the protein. They can be located at either end of the protein, or somewhere internally.



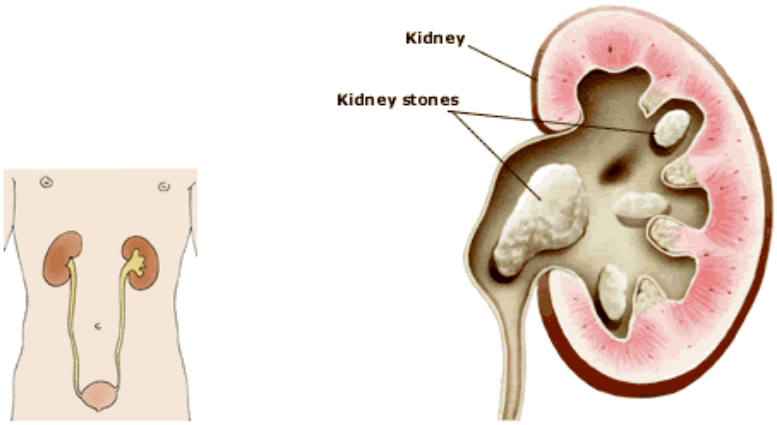
Industrial Synthesis

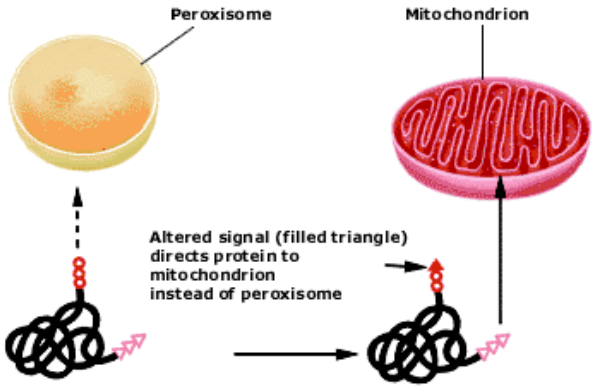
Today many important protein drugs (e.g. growth hormone, erythropoetin, insulin) are produced in living cells. To facilitate easy purification, the proteins are provided with a signal peptide causing them to be secreted out of the cell.

For scale-up production, cells are grown in bioreactors.

Diseases

In many inherited diseases, proteins are mislocalized in the cell due to errors in targeting signals and transport. One example is "primary hyperoxaluria," a rare disease, which results in kidney stones already at an early age. A signal in the enzyme alanine:glyoxylate aminotransferase normally directs it to the peroxisome. In patients, this signal is altered and the protein is mislocalized to the mitochondrion where it is unable to perform its normal function.





BACK

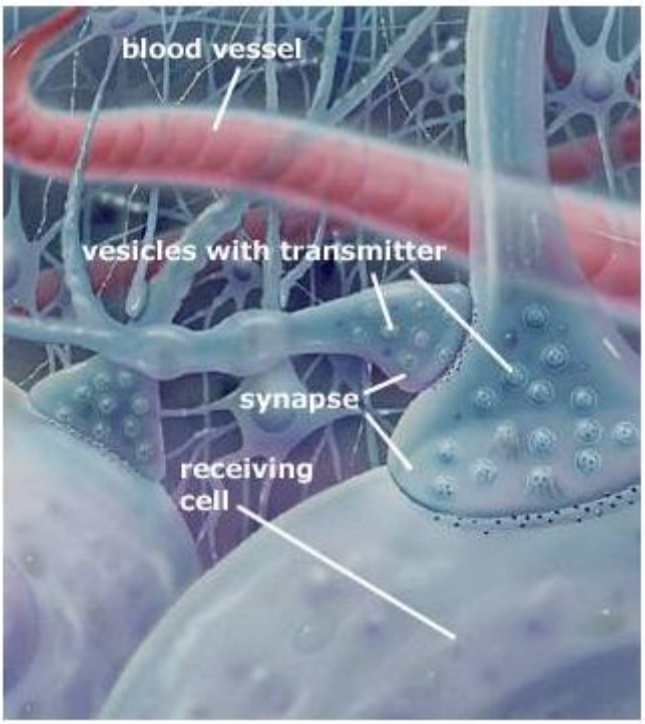
The Nobel Prize in Physiology or Medicine 2000

The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine jointly to **Arvid Carlsson**, **Paul Greengard** and **Eric Kandel** for their discoveries concerning "signal transduction in the nervous system". Carlsson discovered that dopamine is a transmitter, Greengard found that dopamine and other "slow" transmitters act by protein phosphorylation, and Kandel showed that phosphorylation is necessary for the formation of short and long term memory.

Arvid Carlsson,
born in 1923, works at the Department of Pharmacology, Göteborg University, Gothenburg, Sweden.

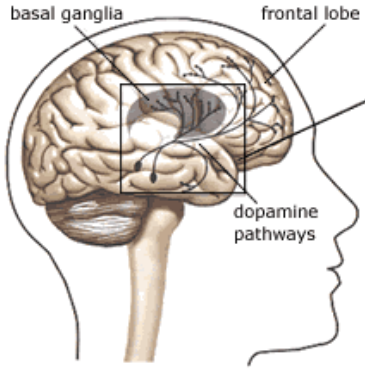
Paul Greengard,
born in 1925, works at the Laboratory of Molecular and Cellular Neuroscience, Rockefeller University, New York.

Eric Kandel,
born in 1929, works at the Center for Neurobiology and Behavior, Columbia University, New York.

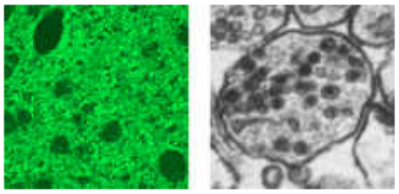


Arvid Carlsson made the seminal discovery in the late 1950's that dopamine is a transmitter in the mammalian brain. Dopamine was found to be located in other regions of the brain than noradrenaline, especially in the basal ganglia, which are involved in the control of movements.

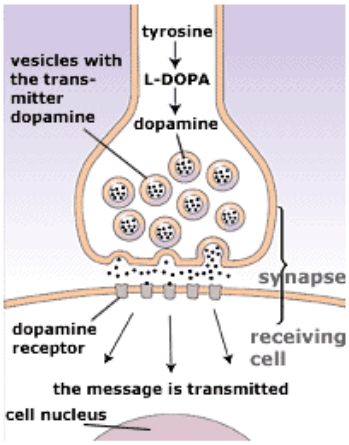
He then made a series of experiments that became the scientific basis for the successful therapy against Parkinson's disease. By giving the drug reserpine to animals he emptied the stores of dopamine in their brains. This produced the symptoms of Parkinson's disease, especially lack of movements (akinesia) and stiffness in the muscles (rigidity).



Parkinson's disease is characterized by degeneration of dopamine nerve pathways in the basal ganglia.



Left picture shows rich presence of dopamine-containing nerve endings (green dots) in the basal ganglia of a rat brain, visualized by fluorescence microscopy. To the right, a close-up of one nerve ending as seen in the electron microscope. The black dots in the vesicles represent stored dopamine.



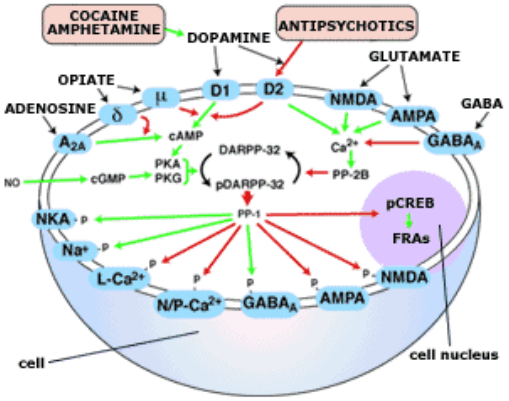
Dopamine, secreted from the nerve terminal, activates membrane receptors in the target cell, leading to formation of messenger molecules in the receiving cell.

Dopamine is synthesized from its precursor L-DOPA. Carlsson, therefore, gave L-DOPA to the reserpine-treated animals. This restored dopamine levels in the brain, and the animals recovered from their akinesia and rigidity. Inspired by Carlsson's research, studies were made in humans. This showed that dopamine neurons degenerated in Parkinson patients and, most importantly, that L-DOPA had the same effect in humans - the patients regained their ability to move. These discoveries enable millions of Parkinson patients to live a normal life for many years.

Paul Greengard

Nerve cells release different transmitters that activate specific receptors located in the cell membrane. Drugs like cocaine and amphetamine enhance the synaptic dopamine levels; other drugs like opiates act directly on receptors. Antipsychotic drugs block dopamine receptors.

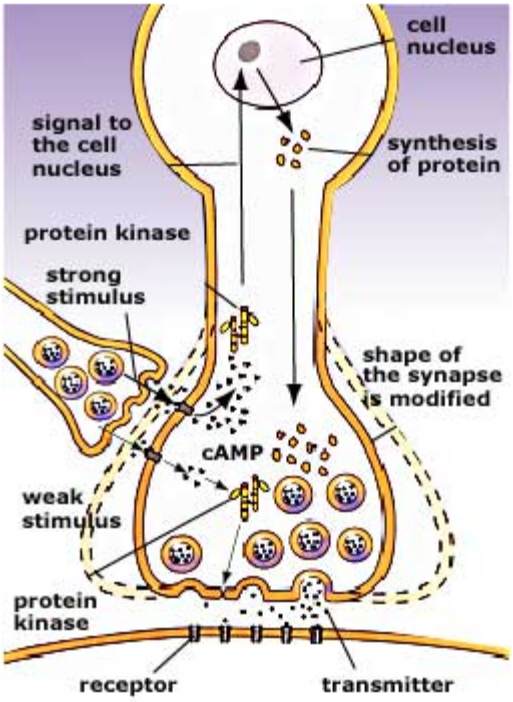
Paul Greengard showed that the activation of receptors changes levels of intracellular messengers like cyclic AMP, which in turn cause a cascade of enzyme reactions. The final result is addition or removal of phosphate groups from target proteins such as ion channels that control the excitability of nerve cells. The phosphate groups change the form and function of the protein.



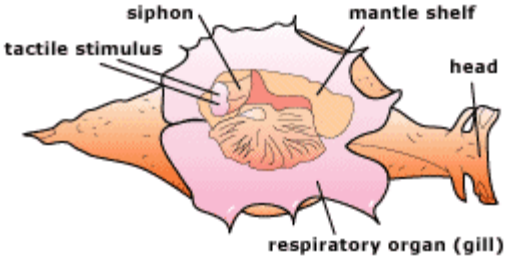
In some nerve cells there is an intermediate stage, with the molecule DARPP-32 serving as a master switch. It orchestrates the degree of phosphorylation in different molecular targets in the cell membrane and cytoplasm.

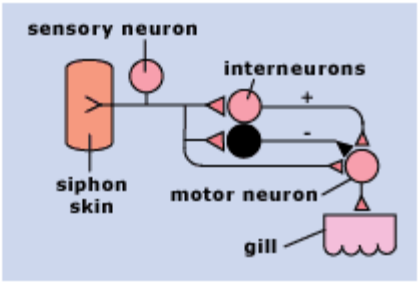
Other targets (e.g. pCREB) regulate protein synthesis by activating genes in the cell nucleus. DARPP-32 is involved in mediating, for instance, the sense of pleasure and is indirectly affected by drugs of abuse.

Eric Kandel



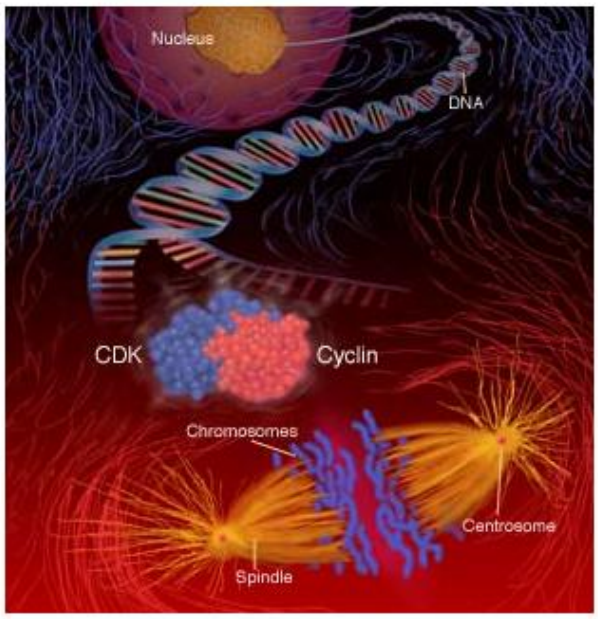
The cellular basis of memory is a long-lasting change in the efficacy of the synapse. This was shown by **Eric Kandel**, using a simple experimental model, the sea slug Aplysia. It has a protective reflex that is modified during learning.





During learning the synapse to the left in the drawing becomes activated. This leads to an increased synthesis of cAMP and protein kinases in the target cell (center). The cell nucleus (above) will be affected by the protein kinase. The final result will be an increased synthesis of new proteins and a growth of the main synapse. In this way the synapse will become more efficient and be able to release more transmitter.

Learning takes place in the synapse between sensory and motor nerve cells. A schematic wiring diagram is shown above. An increased release of transmitter each time the sensory neuron is activated leads to a stronger muscle activation. The learning process is mediated via phosphorylation, initially in the synapse resulting in short-term memory and later via changes in gene activation. This results in growth of the synapse and a long-lasting change of function. Therefore, synapses form the building blocks of memory.

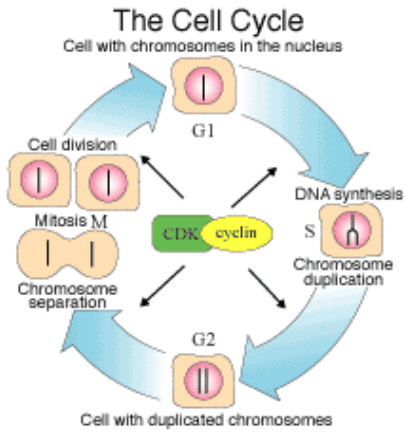


The Nobel Prize in Physiology or Medicine 2001

The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine jointly to **Leland Hartwell**, **Tim Hunt** and **Paul Nurse** for their discoveries of "key regulators of the cell cycle". Using genetic and biochemical methods, they identified the molecules CDK and cyclin that control the cell cycle in eukaryotic organisms. These fundamental discoveries have a profound impact on many aspects of biology and medicine.

CDK and cyclin are key molecules that control and coordinate DNA-synthesis, chromosome separation and cell division. CDK and cyclin together drive the cell from one cell cycle phase to the next.

Nobelprize.org
The Official Web Site of the Nobel Prize



Introduction

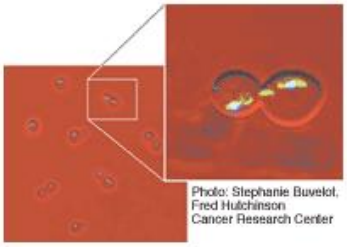
Organisms consist of cells that multiply through cell division. Before a cell can divide it has to grow in size, duplicate its chromosomes and separate the chromosomes for distribution between the two daughter cells. These different processes are coordinated in the cell cycle.

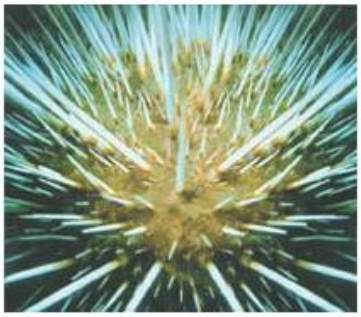
The cell cycle consists of several phases. In the first phase (G1) the cell grows. When it has reached its appropriate size it enters the phase of DNA-synthesis (S), where the chromosomes are duplicated. During the next phase (G2) the cell prepares for division. In mitosis (M) the chromosomes separate, and the cell divides into two daughter cells. Through this mechanism the daughter cells receive identical sets of chromosomes. After division, the cells are back in G1 and the cell cycle is completed. This year's Nobel Laureates have discovered fundamental mechanisms controlling the cell cycle. CDK and cyclin drive the cell from one phase to the next in the cell cycle.

Leland Hartwell

Leland Hartwell, born 1939. Fred Hutchinson Cancer Research Center, Seattle, WA, USA.

Leland Hartwell used baker's yeast, *Saccharomyces cerevisiae,* as a model system for genetic studies of the cell cycle. In an elegant series of experiments 1970-71, he isolated yeast cells, in which genes controlling the cell cycle were altered (mutated). By this approach, he identified genes specifically involved in cell cycle control, so called CDC-genes (cell division cycle genes). One of these genes, designated *CDC28,* controls the first step in the progression through the G1-phase of the cell cycle (the function "start"). Hartwell also identified the fundamental role of "checkpoints" in cell cycle control. These checkpoints monitor that all steps in the previous phase have been correctly executed and ensure a correct order between the cell cycle phases.





Important model organisms for this year's Laureates. Leland Hartwell used baker's yeast, *Saccharomyces cerevisiae* (left). Paul Nurse used another type of yeast, *Schizosaccharomyces pombe* (middle). Tim Hunt used sea urchin, *Arbacia* (right).

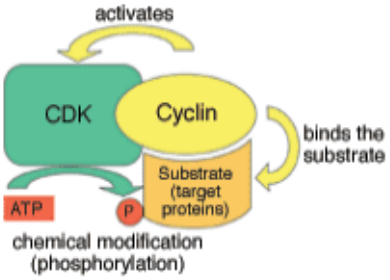
Paul Nurse

Paul Nurse, born 1949. Imperial Cancer Research Fund, Lincoln's Inn Fields, London, UK.

Paul Nurse identified the key regulator of the cell cycle, the gene *cdc2,* during the years 1976-80. He showed that the product of this gene controls cell division (transition from G2 to M). Nurse discovered the gene *cdc2* in the fission yeast *Schizosaccharomyces pombe*. He later showed that *cdc2* had the same function as the gene *CDC28* in the distantly related baker's yeast.

Thus, *cdc2* has more than one function in the cell cycle, controlling both the transition from G1 to S and G2 to M. In 1987 Paul Nurse isolated the corresponding human gene, later called *CDK1*. These findings showed that the CDK function has been conserved through evolution.

The gene *CDK1* encodes a protein that is a member of a family called cyclin dependent kinases (CDK). These molecules function by linking phosphate groups to other proteins (phosphorylation, figure to the left). Today half a dozen different CDK-molecules have been found in humans.



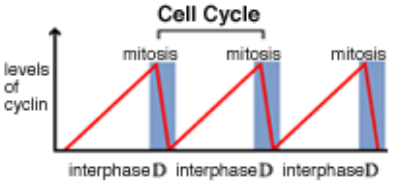
CDK and cyclin together form an enzyme that activates other proteins by chemical modification (phosphorylation). The amount of CDK molecules is constant during the cell cycle, but their activities vary because of the regulatory function of the cyclins. CDK can be compared with an engine and cyclin with a gear box controlling whether the engine will run in the idling state or drive the cell forward in the cell cycle.

Tim Hunt

Tim Hunt,
born 1943.
Imperial Cancer
Research Fund,
Clare Hall
Laboratories,
South Mimms, UK.

Tim Hunt discovered cyclins, proteins that bind to the CDK molecules. Cyclins regulate the CDK activity and select the target proteins to be phosphorylated. The proteins were named cyclins because of their cyclic variation in amount during the cell cycle (figure bottom left). Hunt's discovery that cyclins were degraded during mitosis turned out to be another fundamental control mechanism in the cell cycle.

Tim Hunt discovered the first cyclin molecule in 1982, using eggs from sea urchin, *Arbacia,* as a model system. He also found that cyclins, like CDK, were conserved during evolution. Today around ten different cyclins have been found in humans.



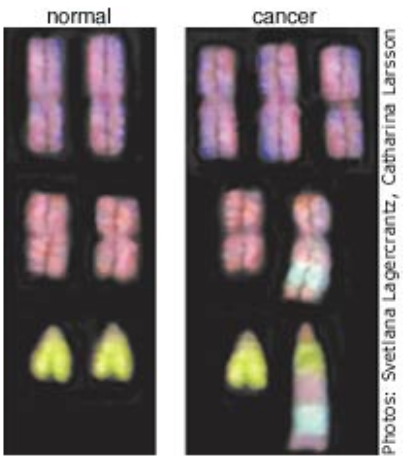
Cyclins are proteins formed and degraded during each cell cycle. Periodic protein degradation is an important control mechanism of the cell cycle. (D = cell division.)

The fundamental molecular mechanisms controlling the cell cycle are highly conserved through evolution and operate in the same manner in yeasts, insects, plants, animals and humans.

Photos: Eva Löfman, Carl Löfman

The Implications of the Discoveries

The basic discoveries made by this year's Laureates will have broad applications within many fields of biology and medicine. The discoveries are important in understanding how chromosomal instability develops in cancer cells, i.e. how parts of chromosomes are rearranged, lost or distributed unequally between daughter cells (figure to the left). The findings in the cell cycle field are about to be applied to tumour diagnostics, and the discoveries may in a long term perspective open new possibilities for cancer therapy.



Photos: Svetlana Lagercrantz, Catharina Larsson

Chromosomal instability in cancer cells may be the result of defective cell cycle control. The figure shows three pairs of chromosomes (1, 3 and 14) in normal cells (left), compared with the same pairs in cancer cells (right). In cancer cells, the chromosome number may be altered (aneuploidy) and parts of chromosomes may be rearranged (visualized by different colours).

The Nobel Prize in Physiology or Medicine 2002

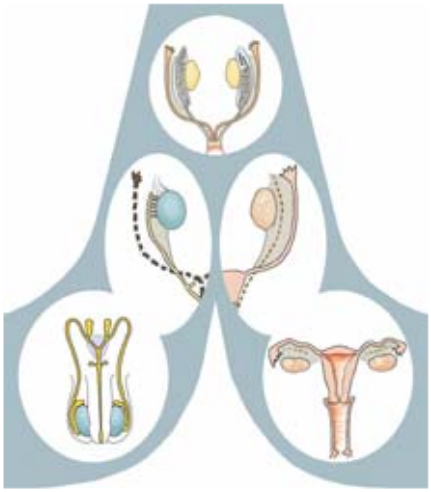
The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine jointly to **Sydney Brenner**, **Robert Horvitz** and **John Sulston** for their discoveries concerning "genetic regulation of organ development and programmed cell death".

By using the nematode *Caenorhabditis elegans* as a model system, the Laureates have identified key genes regulating these processes. They have also shown that corresponding genes exist in higher species, including man.

This year´s Nobel Laureates have identified key genes regulating organ development and programmed cell death in the nematode *C. elegans*. They have also shown that corresponding genes controlling these processes exist in humans.

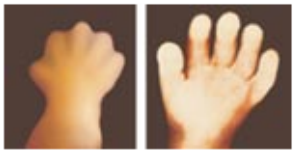
Introduction

The human body consists of hundreds of cell types, all originating from the fertilized egg. During the embryonic and foetal periods, cells increase dramatically in number, mature and become specialized to form tissues and organs. Lots of cells are formed also in the adult body – more than a thousand billion cells each day. To counter cell production and maintain an appropriate number of cells in the tissues, extensive cell death occurs both in the foetus and in the adult. This delicate, controlled elimination of cells is called programmed cell death.

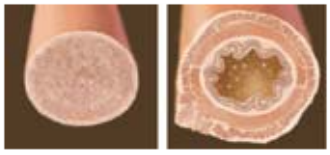


Male Female

Programmed cell death eliminates unwanted structures during the development of the male and female inner reproductive organs.



In the human foetus, the interdigital mesoderm, initially formed between fingers and toes, is removed by programmed cell death.

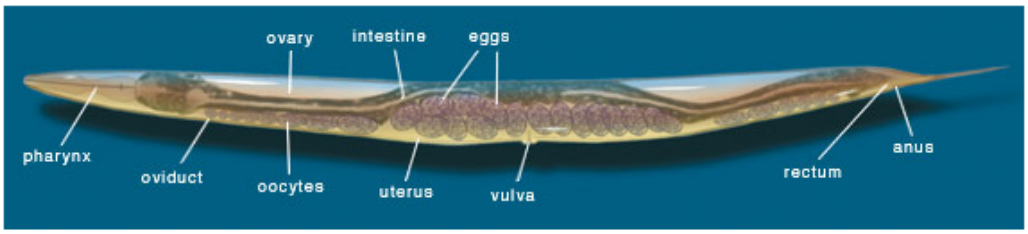


The intestinal lumen and other tissues are sculpted by programmed cell death.

Sydney Brenner,
born 1927,
La Jolla, CA, USA.

Sydney Brenner

Sydney Brenner realized, in the early 1960s, that the nematode *Caenorhabditis elegans* was an ideal model organism to study cell differentiation and organ development. This small worm has a short generation time and is transparent, which made it possible to follow cell division directly under the microscope. In 1974, Brenner demonstrated that specific gene mutations could be induced in the genome of *C. elegans* by the chemical compound EMS (ethyl methane sulphonate). Different mutations were linked to specific genes and to specific effects on organ development. Brenner´s discoveries, carried out in Cambridge, UK, laid the foundation for this year´s Nobel Prize.



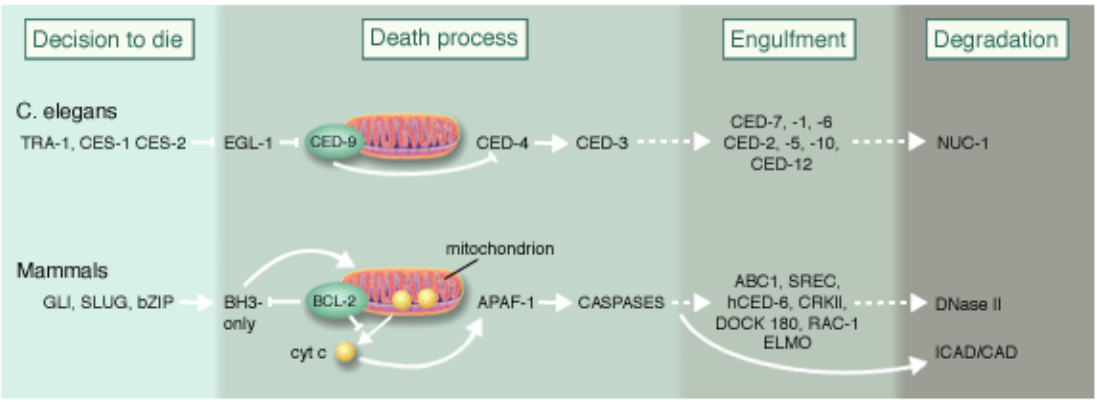
Sydney Brenner established the nematode *Caenorhabditis elegans* as a novel model organism. This transparent worm is approximately one mm long and consists of 959 somatic cells.

Robert Horvitz,
born 1947,
Cambridge, MA,
USA.

Robert Horvitz

Robert Horvitz used *C. elegans* to investigate whether there was a genetic programme controlling cell death. In 1986, he identified the first two "death genes", *ced-3* and *ced-4*. He showed that functional *ced-3* and *ced-4* genes were a prerequisite for cell death to be executed. Later, Horvitz discovered that another gene, *ced-9,* protects against cell death by interacting with *ced-4* and *ced-3*. He also identified genes directing the elimination of the dead cell, and he showed that the human genome contains a *ced-3*-like gene.

We now know that most genes involved in controlling cell death in *C. elegans* have counterparts in humans and are evolutionarily well conserved. In the human signalling pathway *ced-3-*, *ced-4-* and *ced-9*-like molecules participate.



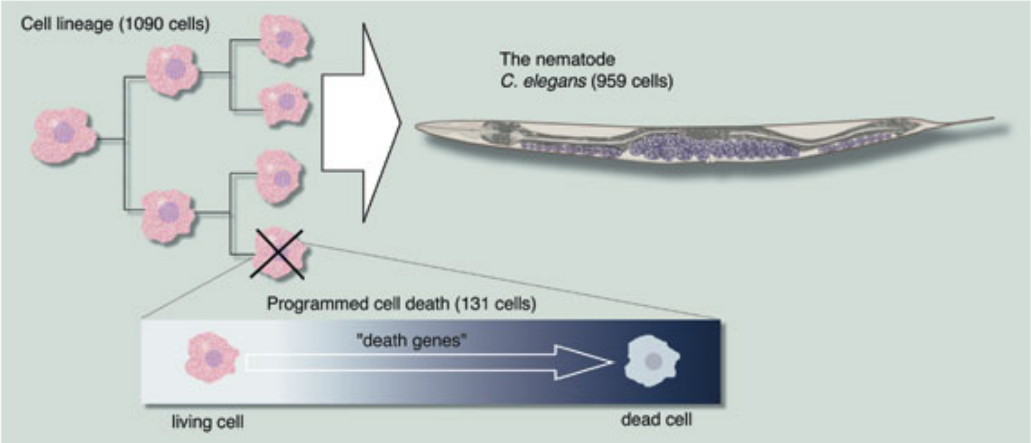
Robert Horvitz identified genes controlling cell death in *C. elegans*. Corresponding genes exist in mammals, including man.

John Sulston, born 1942, Cambridge, England.

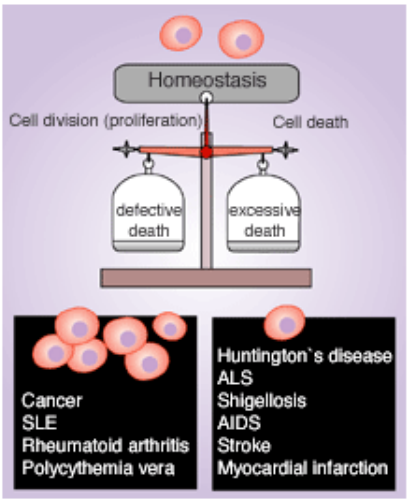
John Sulston

John Sulston developed techniques to study all cell divisions in *C. elegans,* from the fertilized egg to the 959 somatic cells in the adult nematode. In 1976, Sulston described the cell lineage for a part of the developing nervous system. He showed that the cell lineage is invariant, i.e. every nematode undergoes exactly the same programme of cell division and differentiation.

As a result of these findings, Sulston discovered that specific cells in the cell lineage always die by programmed cell death. This could be followed in the living organism. He described the visible steps in the cellular death process and demonstrated the first mutation of a gene participating in programmed cell death, the *nuc-1* gene.



John Sulston mapped a cell lineage in the nematode *C. elegans*. He showed that specific cells undergo programmed cell death during the normal differentiation process.



Some diseases characterized by defective cell death (left) and excessive cell death (right).

The Implications of the Discoveries

The introduction of *C. elegans* as a novel experimental model system, the characterization of its invariant cell lineage, and the possibility to link this to genetic analysis have proven valuable for many research disciplines. For example, this is true for developmental biology and for analysis of the functions of signalling pathways in multicellular organisms.

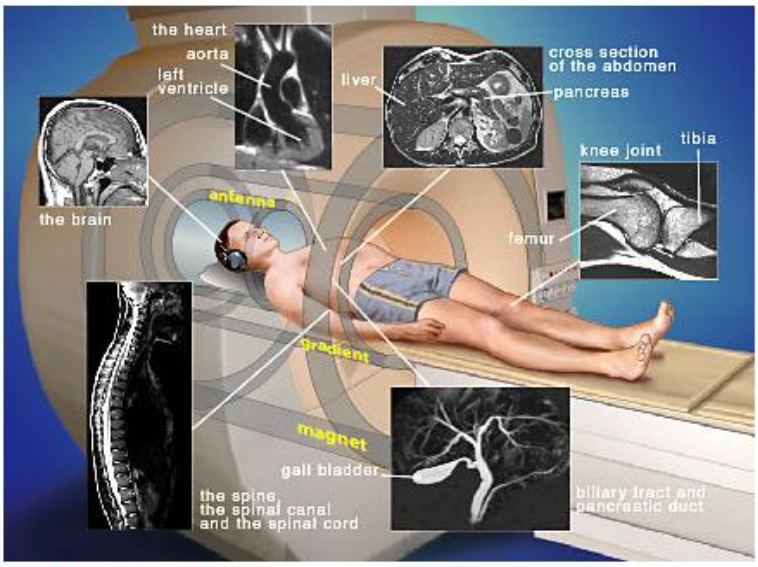
Research on programmed cell death is intense. Knowledge in this field has helped us to understand the mechanisms by which some viruses and bacteria invade and manipulate our cells.

Some diseases, like cancer and certain autoimmune conditions, are characterized by a reduction in cell death, leading to the survival of cells normally destined to die. Many treatment strategies against cancer are based on stimulation of the cellular "suicide programme". This is an interesting and challenging task to further explore in order to reach a refined manner to induce cell death in cancer cells.

We also know that in AIDS, neurodegenerative diseases, stroke and myocardial infarction, cells are lost as a result of excessive cell death. For instance, current research suggests that it is possible to reduce the damage caused by myocardial infarction and stroke by using drugs restraining programmed cell death.

The Nobel Prize in Physiology or Medicine 2003

The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine jointly to **Paul Lauterbur** and **Peter Mansfield** for their discoveries concerning "magnetic resonance imaging". These discoveries made it possible to develop modern magnetic resonance imaging, MRI, which represents a breakthrough in medical diagnostics and research. Worldwide, more than 60 million investigations with MRI are performed each year.

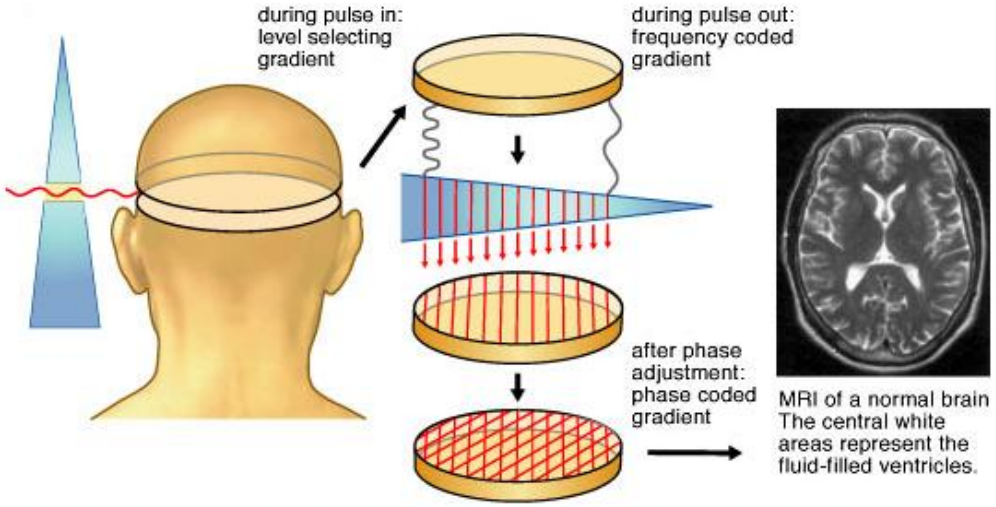


MRI is used for imaging of all organs in the body.

Introduction

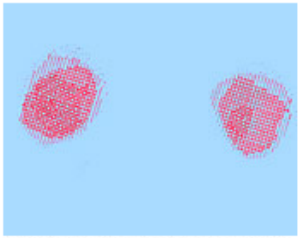
The phenomenon of nuclear magnetic resonance was demonstrated already in 1946 and has previously resulted in Nobel Prizes in both Physics and Chemistry. This year's Nobel Laureates in Physiology or Medicine are rewarded for seminal discoveries making it possible to visualize different structures. These findings provided the basis for the use of magnetic resonance in medical imaging.

A modern MRI unit consists of a very powerful electromagnet. In addition, there are magnetic gradients in three different directions.



MRI of a normal brain
The central white areas represent the fluid-filled ventricles.

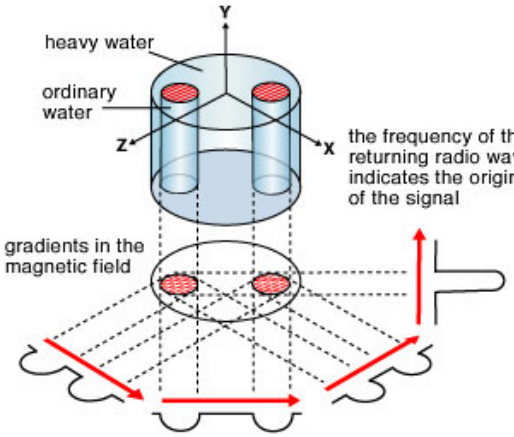
Paul Lauterbur
Born 1929
University of Illinois, Urbana, USA
Photo: Bill Wiegand, University of Illinois



co-ordination of the curves with back-projection calculations results in a transaxial image

Paul Lauterbur

Paul Lauterbur discovered that two-dimensional images could be produced by introduction of gradients in the magnetic field. In 1973, he described how addition of gradient magnets to the main magnet made it possible to visualize a cross section of tubes with ordinary water surrounded by heavy water. No other imaging method can differentiate between ordinary and heavy water.

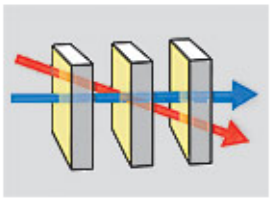


Peter Mansfield
Born 1933
University of Nottingham, England
Photo: Media Centre, University of Nottingham

Peter Mansfield

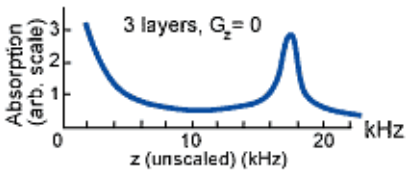
Peter Mansfield discovered that use of gradients in the magnetic field gave signals that rapidly and effectively could be analysed and transformed to an image. This was an essential step in order to obtain MR images. Mansfield also showed how extremely rapid imaging could be achieved by very fast gradient variations (socalled echo-planar scanning). This approach became possible in clinical practice a decade later.

object
(camphor and cardboard)



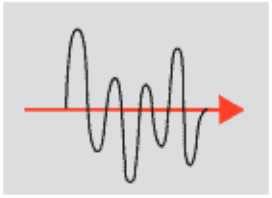
three layers without gradient (blue) and with gradient (red)

spectrum



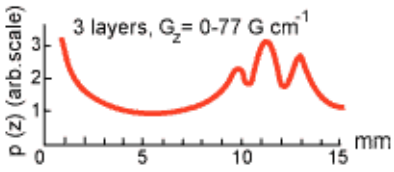
result without gradient – only one peak

signal

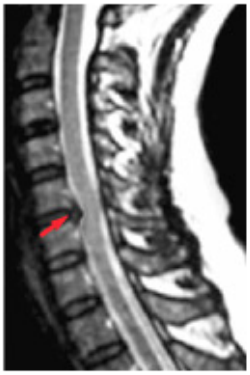


mathematical transformation of the signal

image



result with gradient – three peaks



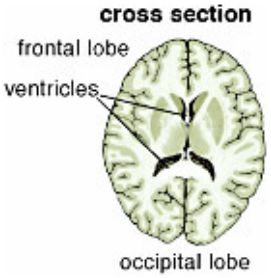
MRI of the neck. The red arrow indicates a disk herniation bulging into the spinal canal.

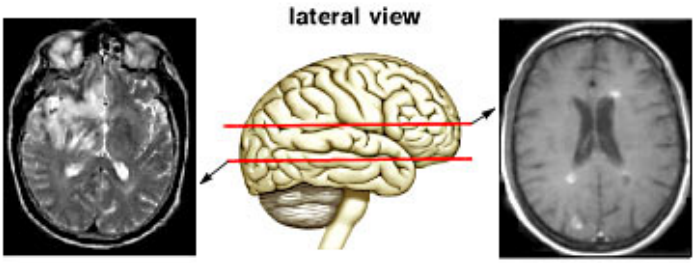
The Uses of MRI

Today, MRI is used to examine all organs of the body. This modality is especially valuable for detailed imaging of the brain and the spinal cord, for example in patients with multiple sclerosis (MS). Examination with MRI is outstanding for diagnosis and follow-up of the disease. MRI is the best modality to demonstrate the pathological MS-plaques. Another example is early demonstration of encephalitis.

MRI examinations are very important in detection, diagnosis, treatment planning and follow-up of many diseases. For instance, the images can reveal the limits of a tumour, contributing to a more precise surgery and radiation therapy. MRI has become a routine method during the last decades, and the method is still in rapid development. This modality is often superior to other imaging techniques. MRI has replaced several invasive modes of examination and thereby reduced the discomfort and the risk of complications for many patients.

In patients with prolonged back pain, it is important to see if the pain is caused by pressure on a nerve or on the spinal cord. MRI examinations have replaced previous methods.





MRI of a patient with herpes encephalitis (white areas).

MRI of a patient with MS (multiple sclerosis). The white round spots represent characteristic MS-plaques.

The Nobel Prize in Physiology or Medicine 2004

BACK

The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine jointly to **Richard Axel** and **Linda Buck** for their discoveries of odorant receptors and the organization of the olfactory system. In a series of pioneering studies the laureates have clarified in molecular detail how our sense of smell works.

Richard Axel
Born 1946
Howard Hughes Medical Institute, Columbia University, New York, USA.

Linda Buck
Born 1947
Howard Hughes Medical Institute, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, USA.

The vivid world of odours

The olfactory system is important for our quality of life. A unique odour can trigger distinct memories from our childhood or from emotional moments – positive or negative – later in life. When something tastes good it is mainly due to activation of the olfactory system.

To lose the sense of smell is a significant handicap; we no longer perceive the different qualities of food and we cannot detect warning signals, for example smoke from a fire.

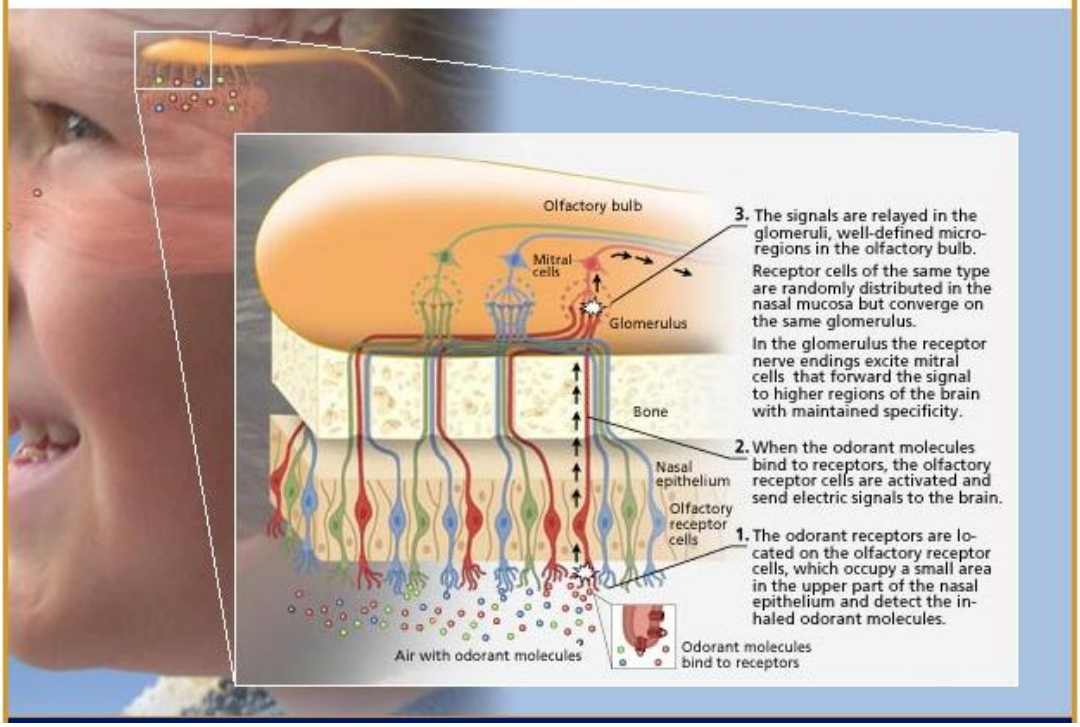
The Nobel Prize in Physiology or Medicine 2004

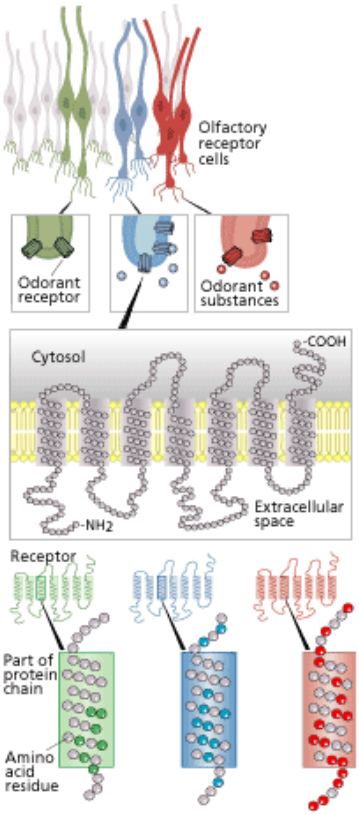
BACK

The olfactory system

The olfactory epithelium contains millions of olfactory neurons, which send messages directly to the olfactory bulb of the brain.

The olfactory receptor cells are the only neurons in the nervous system exposed directly to the external environment.





A large family of odorant receptors

Richard Axel and Linda Buck published their fundamental paper in 1991, in which they described the genes coding for a large family of odorant receptors.

The odorant receptors are located on the olfactory receptor cells in the nasal cavity. Each olfactory receptor cell expresses only one type of odorant receptor, and each receptor can detect a limited number of odorant substances.

The olfactory receptor

Each receptor consists of a protein chain that traverses the cell membrane seven times.

When an odorant substance attaches to an olfactory receptor, the shape of the receptor protein is altered, leading to a G protein activation.

An electric signal is triggered in the olfactory receptor neuron and sent to the brain via nerve processes.

Small variations

All odorant receptors are related proteins and differ only in some amino acid residues (indicated in green, blue and red).

The subtle differences in the protein chains explain why the receptors are triggered by different odorant molecules.

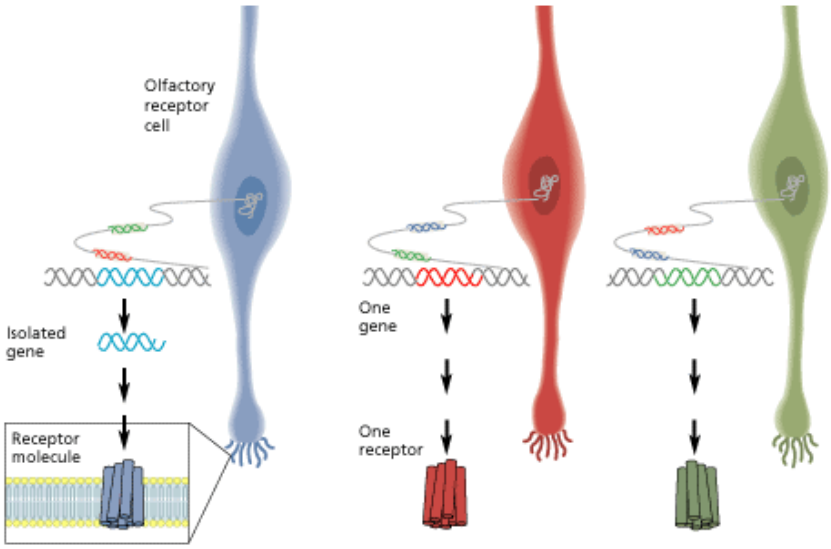
The Nobel Prize in Physiology or Medicine 2004 BACK

A large gene family

Axel and Buck searched for genes coding for proteins expressed exclusively in the olfactory epithelium.

Using molecular biology techniques they discovered a large set of genes coding for olfactory receptors. This large gene family is composed of several hundred different genes encoding receptor molecules.

Today we know that these genes represent around three per cent of the total number of genes in mammals.



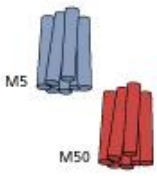
Identification of genes

The genes encoding the receptor molecules were isolated and identified.

An unexpected finding!

Every single olfactory receptor cell expresses one and only one gene of all the genes that code for olfactory receptor molecules.

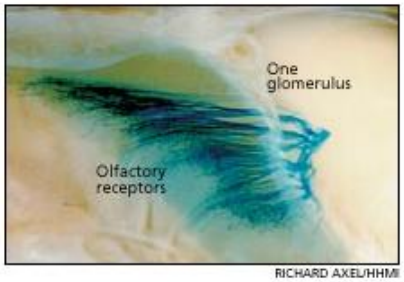
MODIFIED AFTER LINDA BUCK AND COLLEAGUES IN NATURE VOL 414, NOV 8, 2001



The organization of odorant receptor inputs in the olfactory cortex

Signals derived from two different odorant receptors, M5 and M50, are targeted to different, but partially overlapping clusters of cortical neurons.

These clusters have similar locations in the brains of different mice.



RICHARD AXEL/HHMI

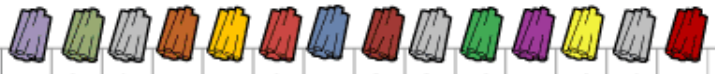
Receptor activation in the bulb

Receptor cells carrying the same type of receptor converge their processes on the same glomerulus.

Combinatorial receptor codes

The odorant receptor family is used in a combinatorial manner to detect odorants and encode their unique identities. Different odorants are detected by different combinations of receptors and thus have different receptor codes. These codes are translated by the brain into diverse odour perceptions.

The immense number of potential receptor combinations is the basis for our ability to distinguish and form memories of more than 10,000 different odorants.



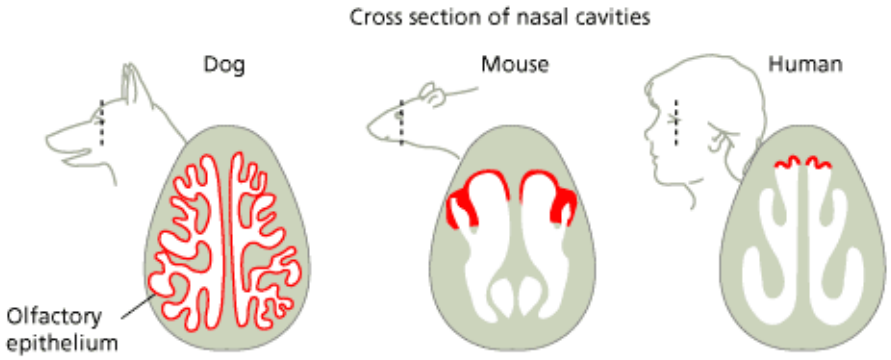
Odorant receptors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Odorants															**Description**
A					●										rancid, sour, goat-like
B		●				●									sweet, herbal, woody
C	●			●	●		●			●	●				rancid, sour, sweaty
D		●			●	●									violet, sweet, woody
E	●			●	●		●	●		●	●	●			rancid, sour, repulsive
F				●	●		●			●					sweet, orange, rose
G	●			●	●		●	●		●		●		●	waxy, cheese, nut-like
H				●	●		●			●		●			fresh, rose, oily floral

MODIFIED AFTER LINDA BUCK AND COLLEAGUES IN CELL VOL 96, MARCH 5, 1999

Species differences

The area of the olfactory epithelium (red) in dogs is some forty times larger than in humans. Mice – the species Axel and Buck studied – have about one thousand different odorant receptor types.

Humans have a smaller number than mice; some of the genes have been lost during evolution. There are several millions of olfactory receptor cells in our olfactory epithelium.



The Nobel Prize in Physiology or Medicine 2005

BACK

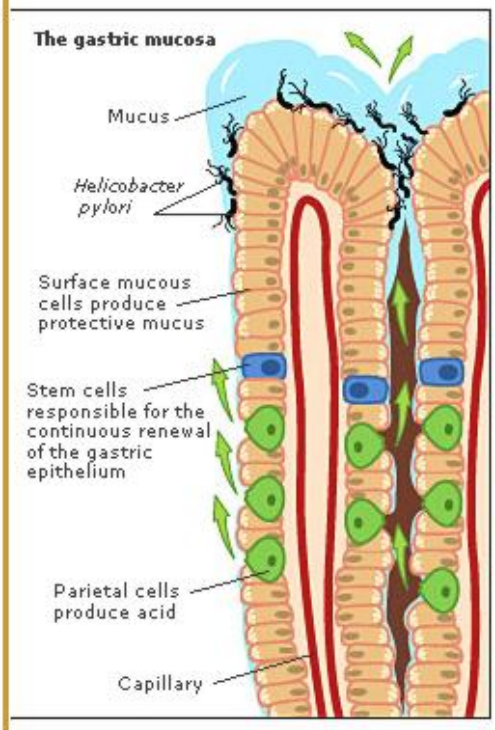
The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine jointly to **Barry Marshall** and **Robin Warren** for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease. Thanks to this pioneering discovery, peptic ulcer disease is no longer a chronic, frequently disabling condition, but a disease that can be permanently cured.

Barry Marshall
Born 1951
Helicobacter pylori Research Laboratory, Queen Elizabeth II Medical Centre, Nedlands, Perth, Australia.

Robin Warren
Born 1937
Department of Pathology, Royal Perth Hospital, Perth, Australia.

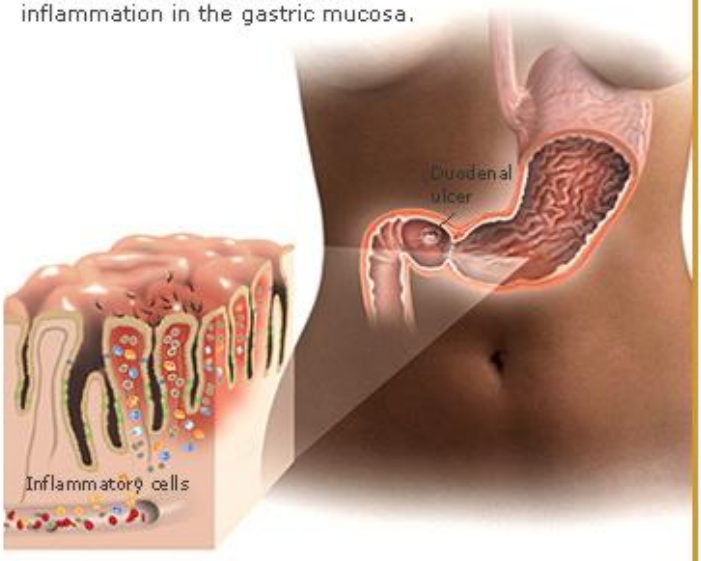
The Nobel Prize in Physiology or Medicine 2005

BACK



Helicobacter pylori is a curved Gram-negative bacterium that has adapted to the environment of the human stomach.

The bacterium infects the lower part of the stomach and causes inflammation in the gastric mucosa.



Nobelprize.org
The Official Web Site of the Nobel Prize

The Nobel Prize in Physiology or Medicine 2005

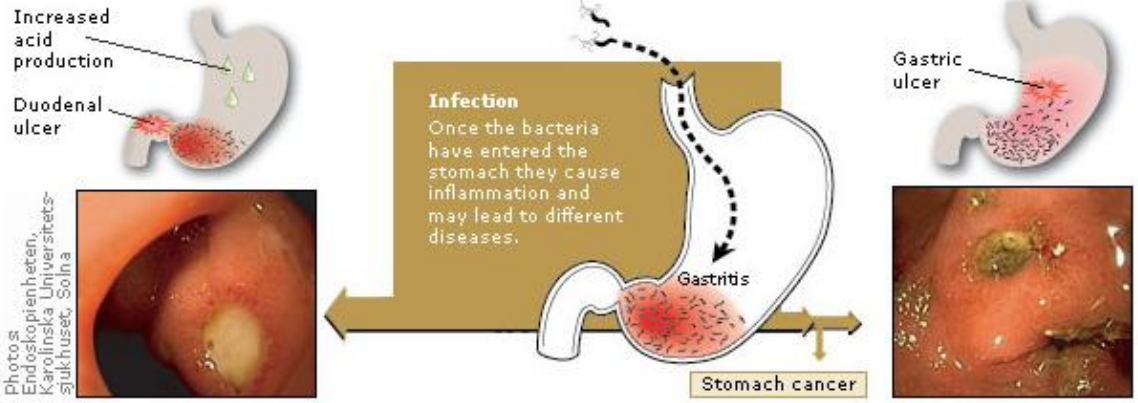
BACK

Chronic infection, inflammation, ulcer and cancer

In most individuals *Helicobacter pylori* infection is asymptomatic. However, 10–15% of infected individuals will at some time experience peptic ulcer disease. Severe complications include bleeding, perforation and obstruction.

Duodenal ulcer
Peptic ulcer disease is more common in the duodenum than in the stomach itself.

Gastric ulcer and cancer
In some individuals *Helicobacter pylori* also infects the corpus region of the stomach. This results in a more widespread inflammation that predisposes not only to ulcer but also to stomach cancer.



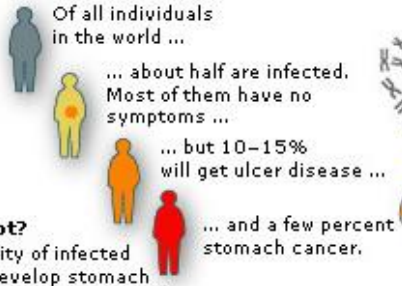
The Nobel Prize in Physiology or Medicine 2005

BACK

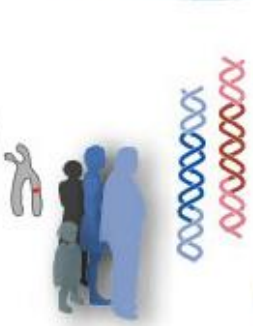
Lifelong infection

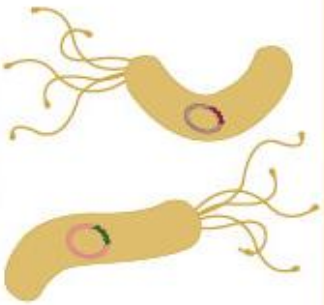
Helicobacter pylori colonizes the stomach in about 50% of all humans with great differences among countries.

Infection is typically contracted in early childhood, frequently by transmission from mother to child. The bacteria may remain in the stomach for the rest of the person's life.



Disease or not?
Only a minority of infected individuals develop stomach disease. The bacterium itself is extremely variable and the variants confer different risks of disease. Genetic variation among humans may also affect the susceptibility to disease caused by *Helicobacter pylori*.

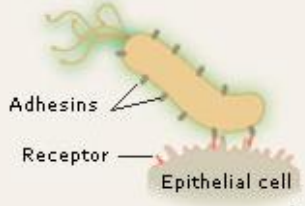

Genetic variation among humans.


Genetic variation among bacteria.

Interplay between the bacterium and the human host.

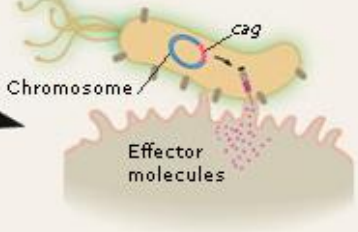
Mechanisms of *Helicobacter pylori* infection

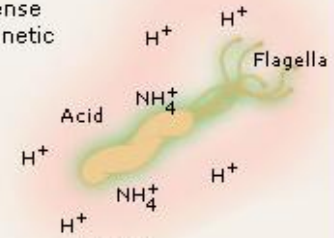
Marshall's and Warren's discovery initiated intense research. Details underlying the exact pathogenetic mechanisms are continuously unravelled.



Adhesion
The bacteria produce adhesive molecules (adhesins) which bind to specific receptors on the gastric epithelial cells.

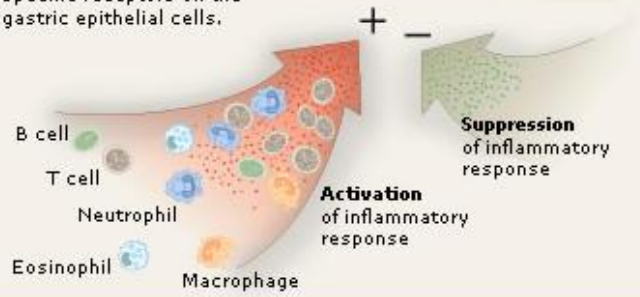
Protection against gastric acid
Helicobacter pylori produces the enzyme urease resulting in neutralization of the acid.





Flagella
Helicobacter pylori drills itself through the mucus layer using flagella as "propellers".

Virulence
Some strains of *Helicobacter pylori* contain in their chromosome a DNA segment *(cag)* which encodes a secretory apparatus that delivers molecules into the gastric cells. These molecules manipulate the host cell to elicit an inflammatory response.



Activation of inflammatory response

Suppression of inflammatory response

Immune evasion and suppression
Even when *Helicobacter pylori* triggers inflammation the bacteria have strategies to avoid and suppress the host's local immune response. For instance they produce a toxin that kills T cells. These strategies permit lifelong infection.

The Nobel Prize in Physiology or Medicine 2005 BACK

Silver staining

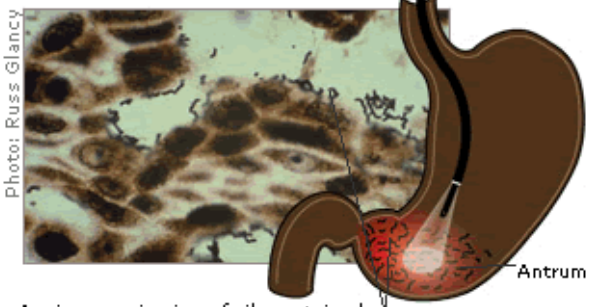


Photo: Russ Glancy

A microscopic view of silver stained *Helicobacter pylori* attached to the gastric epithelium.

Gastroscopy

Culturing techniques

Helicobacter pylori forms colonies visible after 3 to 5 days.

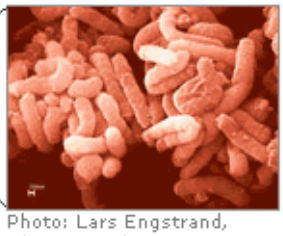


Photo: Lars Engstrand, Christina Nilsson

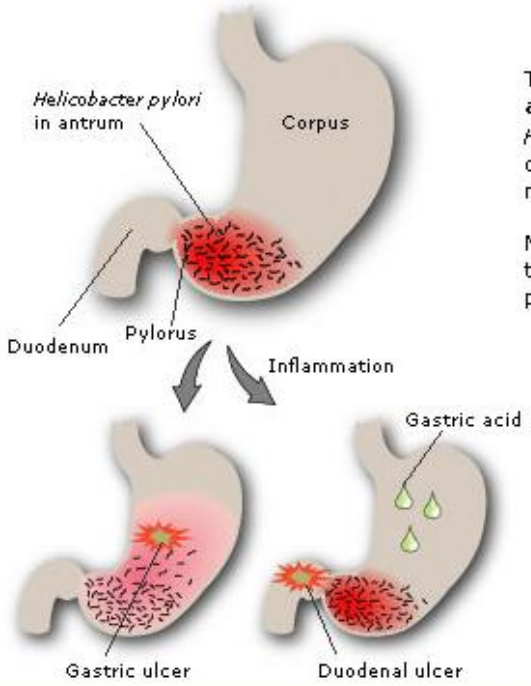
The discovery

Robin Warren observed a relationship between small curved bacteria in the lower part of the stomach (antrum) and gastric inflammation.

Barry Marshall's efforts led to the isolation in 1982 of the curved bacteria later named *Helicobacter pylori* and made them amenable to scientific study.

Marshall and Warren studied a group of patients undergoing gastroscopy and linked inflammation in the gastric mucosa to the presence of *Helicobacter pylori*.

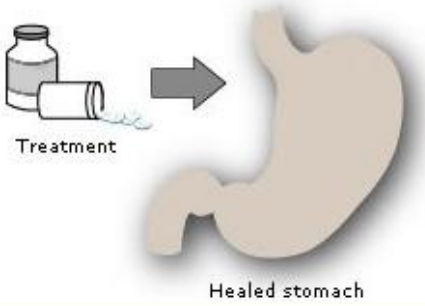
By using technologies generally available (gastroscopy, silver staining of histological sections and culture techniques for microaerophilic bacteria) Marshall and Warren made an irrefutable case that the bacterium *Helicobacter pylori* is causing disease.



The link between bacteria and gastritis

Helicobacter pylori causes inflammation of the gastric mucosa (gastritis). This may lead to duodenal or gastric ulcer.

Marshall, Warren and others found that the elimination of the bacteria results in a permanent cure of peptic ulcer disease.



The Nobel Prize in Physiology or Medicine 2006

BACK

The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine for 2006 jointly to **Andrew Fire** and **Craig Mello** for their discovery of RNA interference – gene silencing by double-stranded RNA.

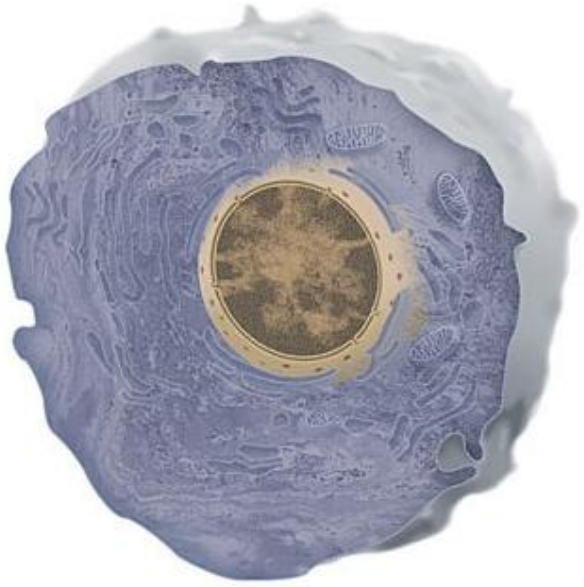
RNA interference is a fundamental mechanism for controlling the flow of genetic information in cells.

L. Cicero/Stanford

R. Carlin/UMMAS

Andrew Fire
Born 1959
Stanford University School of Medicine, Stanford, California, USA.

Craig Mello
Born 1960
University of Massachusetts Medical School, Worchester, Massachusetts, USA.



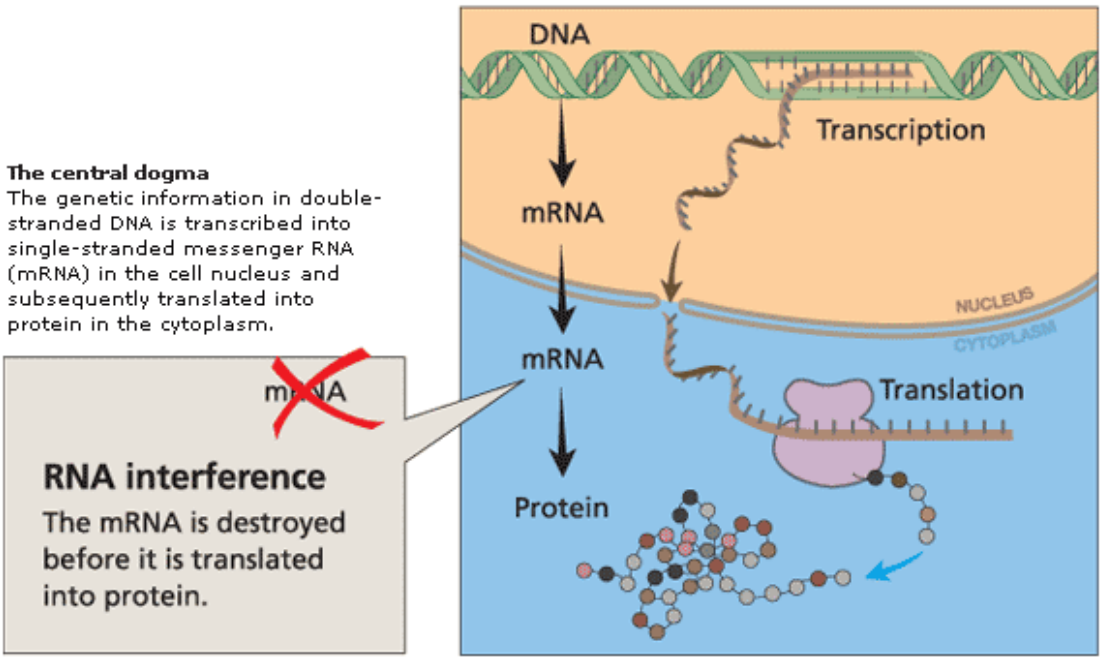
Contents:

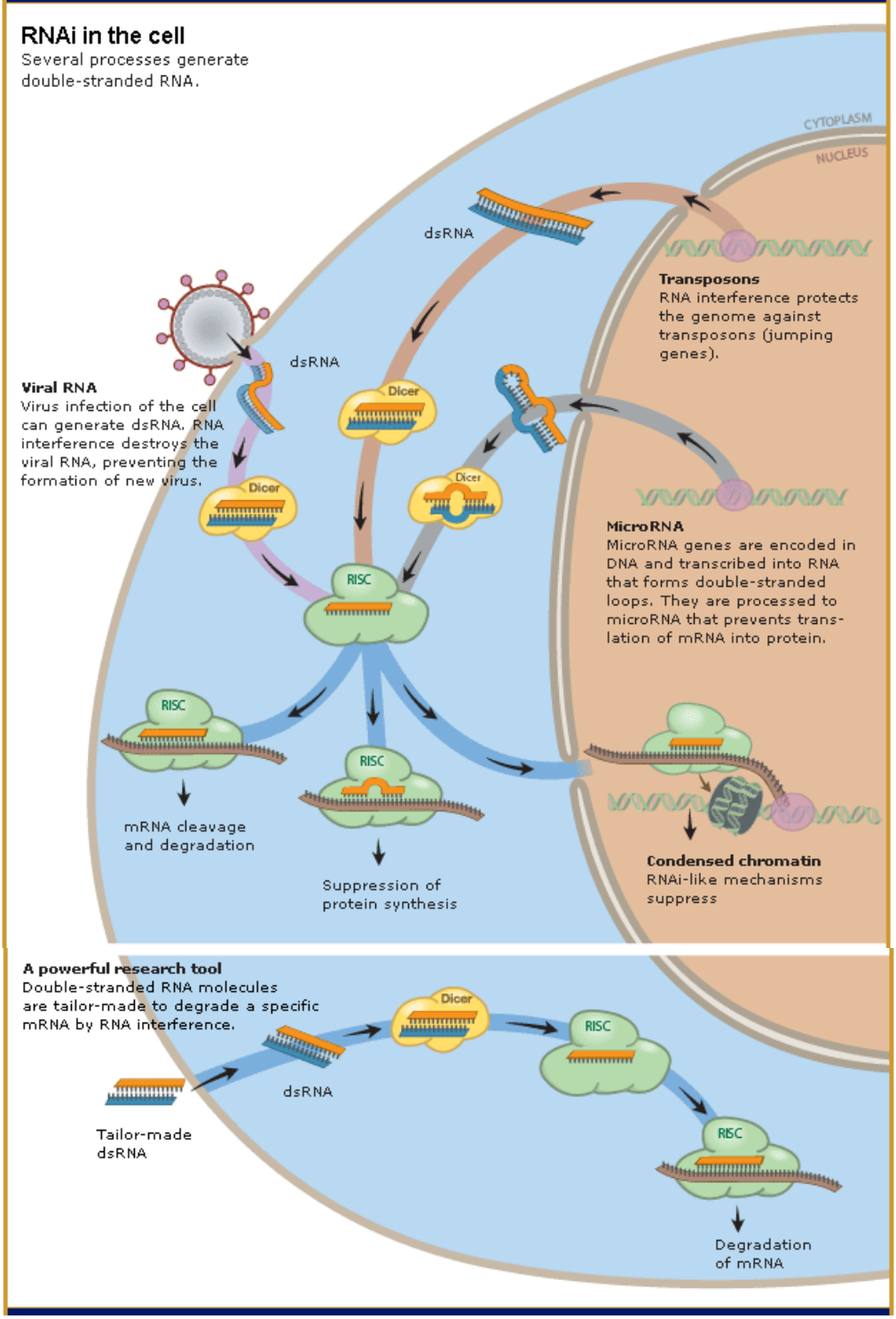
Nobel Poster from the Nobel Committee for Physiology or Medicine, web adapted by Nobel Web

The Nobel Prize in Physiology or Medicine 2006

BACK

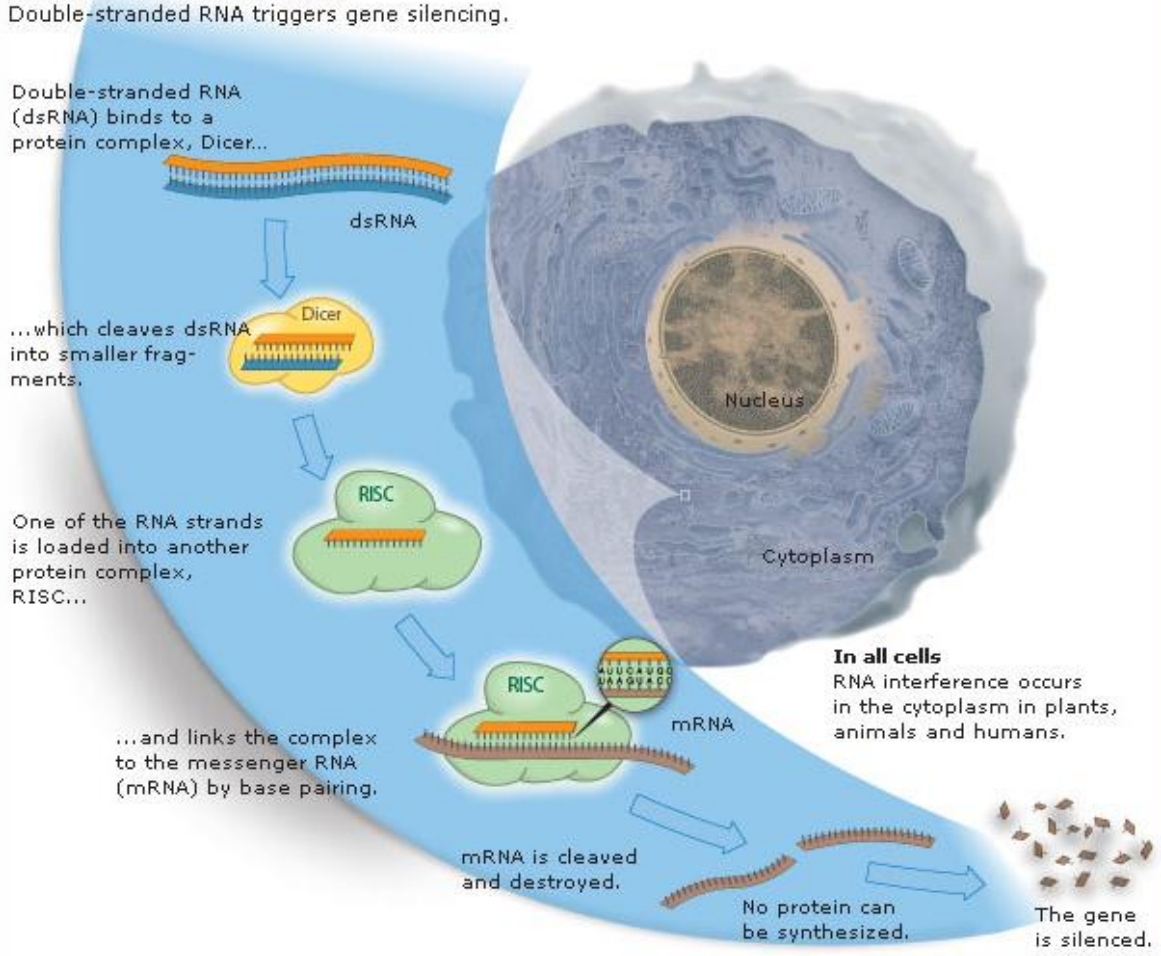
The central dogma
The genetic information in double-stranded DNA is transcribed into single-stranded messenger RNA (mRNA) in the cell nucleus and subsequently translated into protein in the cytoplasm.




RNAi in the cell
Several processes generate double-stranded RNA.
CYTOPLASM
NUCLEUS
dsRNA
Transposons
RNA interference protects the genome against transposons (jumping genes).
dsRNA
Viral RNA
Virus infection of the cell can generate dsRNA. RNA interference destroys the viral RNA, preventing the formation of new virus.
Dicer
Dicer
Dicer
RISC
MicroRNA
MicroRNA genes are encoded in DNA and transcribed into RNA that forms double-stranded loops. They are processed to microRNA that prevents translation of mRNA into protein.
RISC
RISC
mRNA cleavage and degradation
Suppression of protein synthesis
Condensed chromatin
RNAi-like mechanisms suppress
A powerful research tool
Double-stranded RNA molecules are tailor-made to degrade a specific mRNA by RNA interference.
Dicer
RISC
dsRNA
Tailor-made dsRNA
RISC
Degradation of mRNA

RNA interference, RNAi

Double-stranded RNA triggers gene silencing.



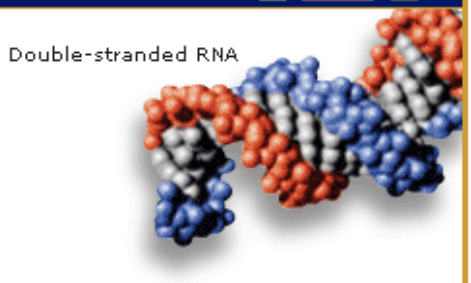
The Nobel Prize in Physiology or Medicine 2006 BACK

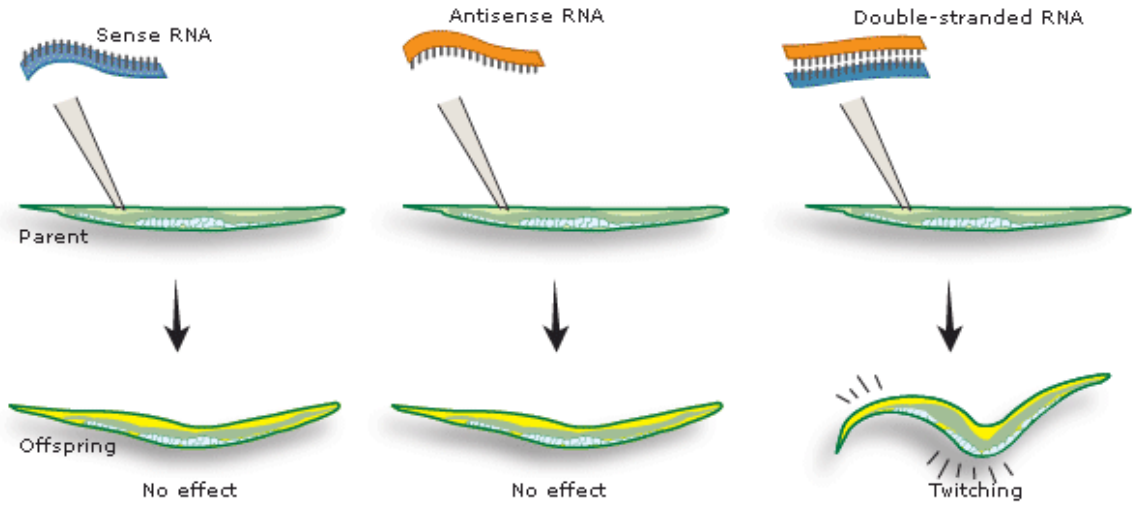
Key experiments

Gene silencing

Fire and Mello injected RNA corresponding to a gene important for muscle function in the worm *C. elegans*.

Single-stranded RNA (sense or antisense) had no effect. But double-stranded RNA caused the worm to twitch in a similar way to worms that lack a functional gene for the muscle protein.





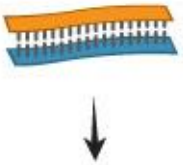
Loss of target mRNA
Fire and Mello injected RNA (*mex-3* RNA) into the gonads of the worm *C. elegans* and studied the effect on the corresponding mRNA.

They found that double-stranded RNA, but not single-stranded RNA, eliminated the target mRNA.

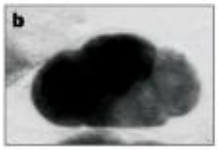
A four-cell embryo from *C. elegans*.

Antisense RNA

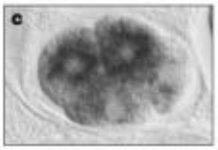
Double-stranded RNA



Uninjected



mex-3 RNA (stained black) is abundant in the early embryo.



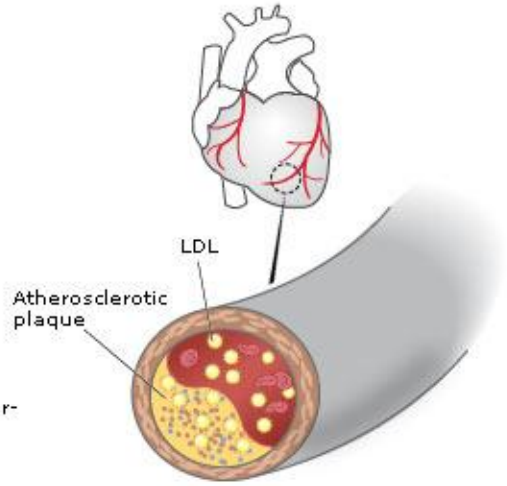
Injection of antisense RNA reduced the content of mRNA to some extent.

The target mRNA was eliminated after injection of double-stranded RNA.

The Nobel Prize in Physiology or Medicine 2006 BACK

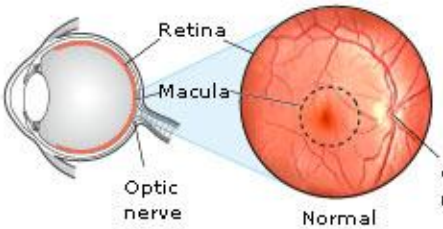
RNAi based therapy – future opportunities
RNAi may become an important principle underlying medical therapy in the future. Clinical trials are already underway for RNAi treatment of RS virus infection and macular degeneration (an eye disease).

Promising results have also been obtained in preclinical studies of influenza, HIV, hypercholesterolemia and several other medical conditions.



Hypercholesterolemia
An excess of cholesterol-containing LDL particles leads to accumulation of cholesterol in blood vessel walls and causes atherosclerosis. RNAi is used to block production of the LDL particles.

Age-related macular degeneration
Small blood vessels grow into the macular area and interfere with vision. RNAi is used to block production of the vascular endothelial growth factor, VEGF, which causes blood vessel growth.



Macular degeneration

The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine for 2007 jointly to **Mario R. Capecchi, Martin J. Evans** and **Oliver Smithies** for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells.


P. Fetters/HHMI


D. Sears

Mario R. Capecchi
Born 1937
University of Utah, Salt Lake City, USA

Sir Martin J. Evans
Born 1941
Cardiff University, UK

Oliver Smithies
Born 1925
University of North Carolina at Chapel Hill, USA

This has led to the creation of an immensely powerful technology referred to as gene targeting in mice. It is now widely used to understand the functions of genes in health and disease

Almost any type of change can be introduced into mouse genes by gene targeting. A common change is to inactivate a gene, thereby creating a knockout "mouse".

Finding the homologous sequence

A targeting vector is like a sentence on a page ...

... which will find a partially identical (homologous) sentence among thousands of pages in a library.

Two ideas come together

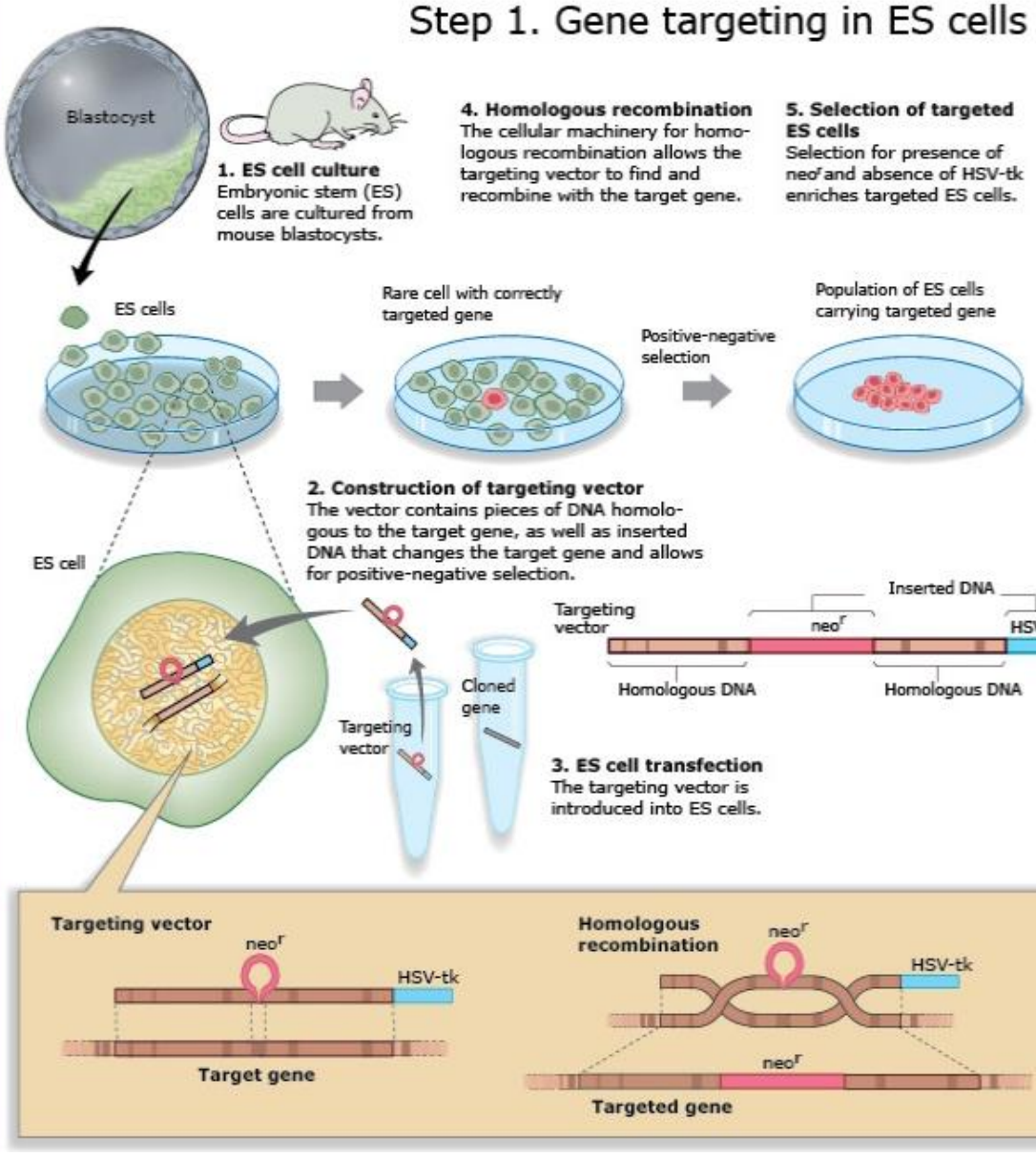
The process of gene targeting involves two steps.

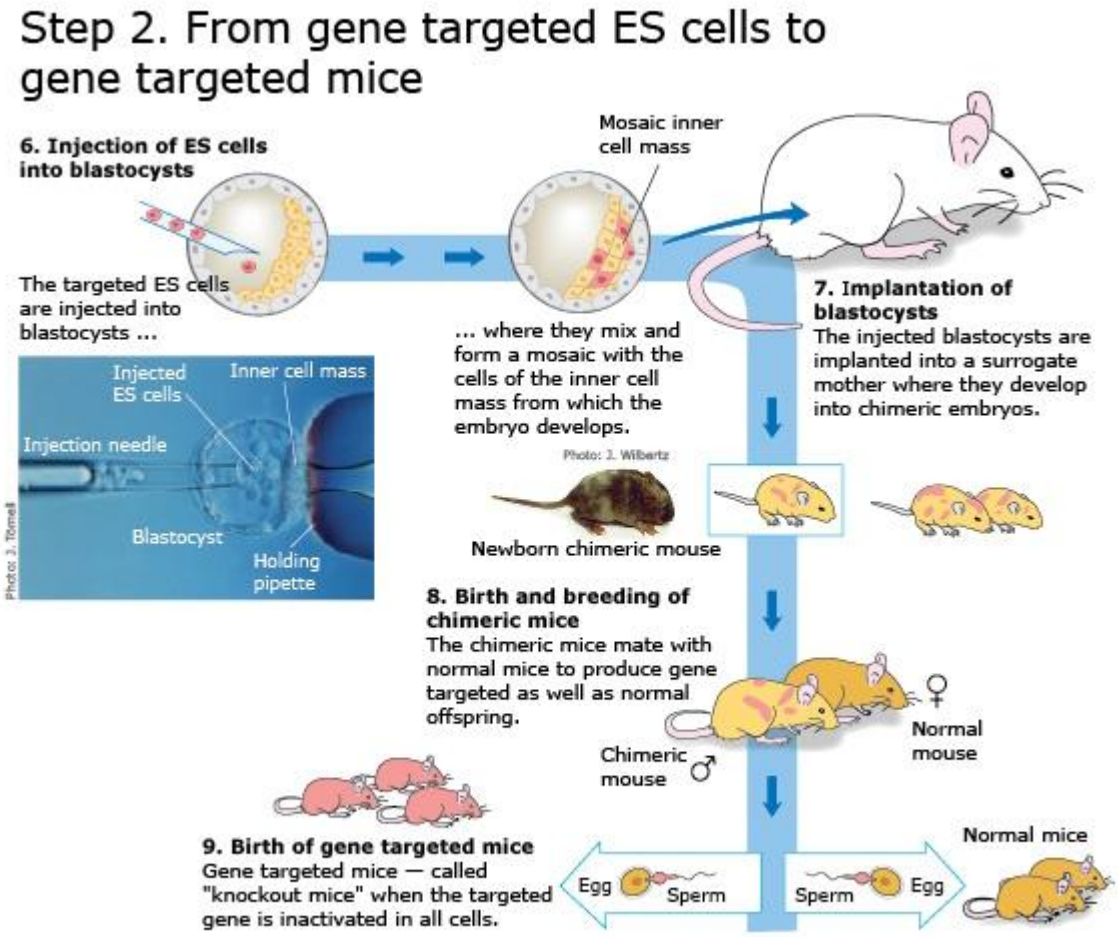
Capecchi and Smithies discovered that homologous recombination could be used to specifically modify genes in mammalian cells.

Evans identified and isolated embryonic stem cells (ES cells) from early mouse embryos (blastocysts). He also showed that ES cells can be used as vehicles to transmit genetic information in mice.

Genes altered in vitro can thus be passed on to future generations.

Step 1. Gene targeting in ES cells





Gene targeting - a versatile technology

The consequences of a gene knockout tell us about the function of that gene. Conditional changes, which can be activated at specific time points or in selected tissues, help in establishing the gene's function at a specific age, or in specific cell types.

It is also possible to introduce precise changes into the protein coding part of a gene. This can be done with the purpose of mimicking a human mutation believed to cause disease. Alternatively, a mouse could be made to produce the human version of a protein. Such studies improve our possibilities for studying human disease mechanisms and for developing and testing new pharmaceuticals.

The genome sequencing projects have taught us that mammals have 22–23,000 genes, more than 90% of which have a function shared between mouse and man.

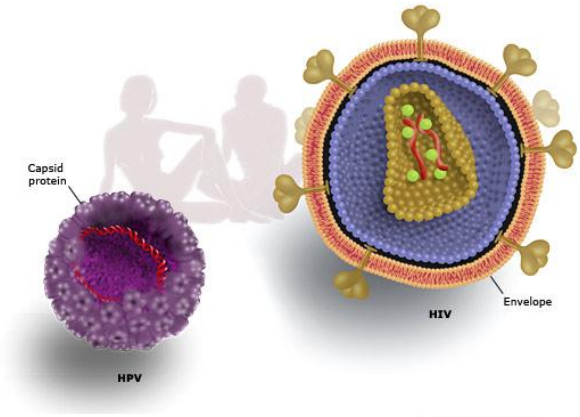
To date more than 10,000 genes have been targeted in mice. More than 500 different models of human diseases have been produced by gene targeting, including models for hypertension, atherosclerosis, cancer, diabetes and cystic fibrosis.

The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine 2008 to **Harald zur Hausen**, **Françoise Barré-Sinoussi** and **Luc Montagnier** for their discoveries of two viruses causing severe human diseases.
One half is awarded to Harald zur Hausen "for his discovery of human papilloma viruses causing cervical cancer" and the other half jointly to Françoise Barré-Sinoussi and Luc Montagnier "for their discovery of human immunodeficiency virus".

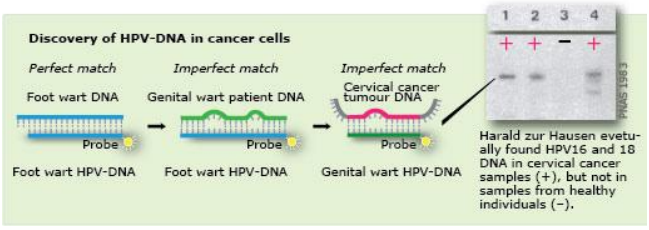
Harald zur Hausen
Born 1936
German Cancer Research Center,
Heidelberg, Germany

Françoise Barré-Sinoussi
Born 1947
Institut Pasteur,
Paris, France

Luc Montagnier
Born 1932
World Foundation for AIDS Research and Prevention,
Paris, France

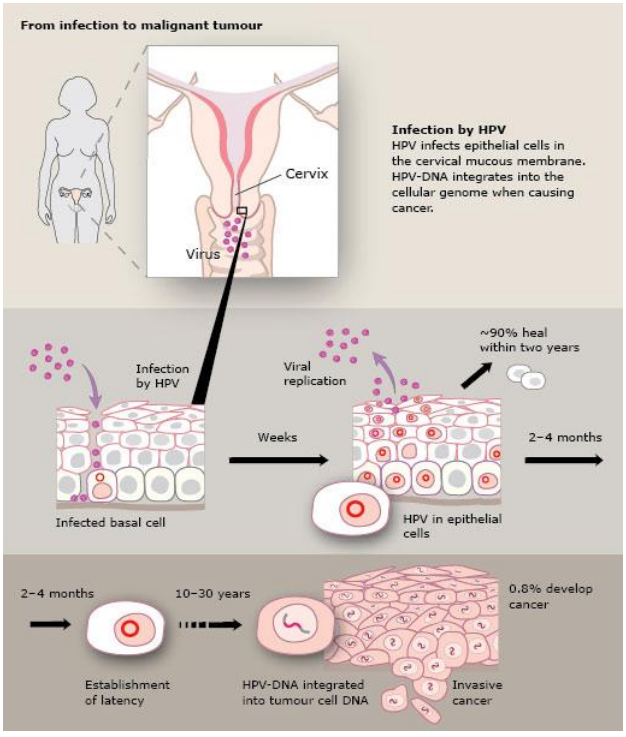


HPV
Human papilloma virus has circular, double-stranded DNA, protected by capsid proteins. Diameter: 55 nm.
HIV
Human immunodeficiency virus is a retrovirus of the lentivirus group. Viral RNA is converted to DNA, which integrates into the cellular genome. Diameter: 90–130 nm.



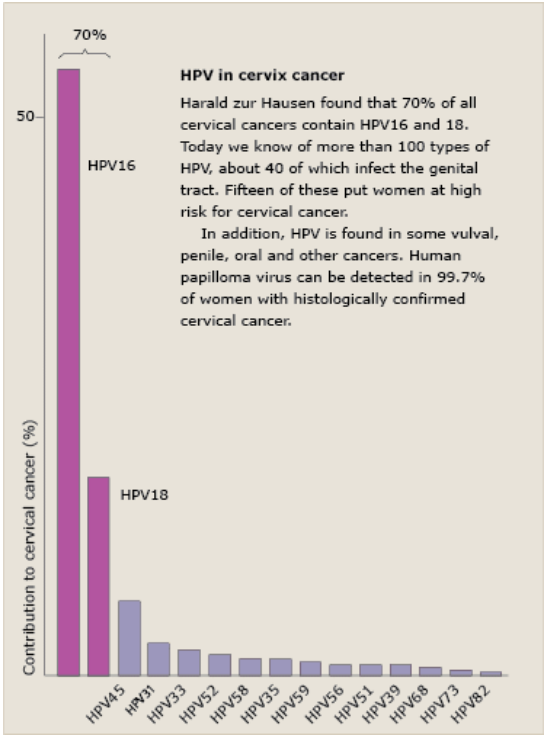
Discovery of HPV, human papilloma virus, in cervical cancer

Against the prevailing view during the 1970s, **Harald zur Hausen** postulated a role for human papilloma virus (HPV) in cervical cancer. He assumed that the tumour cells, if they contained an oncogenic virus, should harbour viral DNA integrated into their genome.



The approach

Harald zur Hausen pursued his idea for over ten years by searching for evidence of HPV forms in tumour cells using probes for known HPV.



Two global health problems

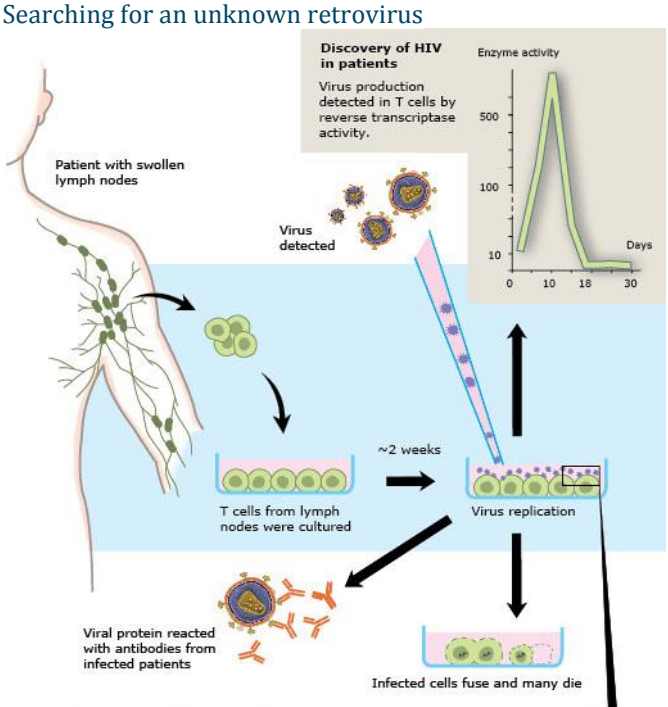
Distribution of cervical cancer

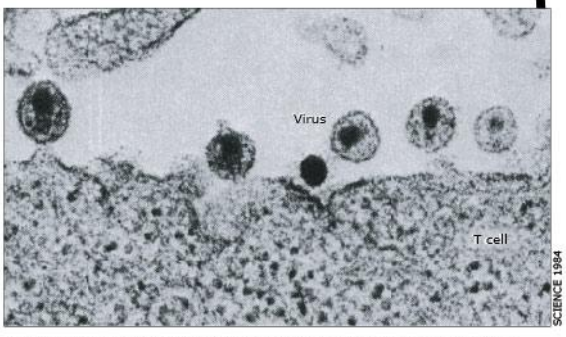
Discovery of HIV, human immunodeficiency virus

Following medical reports of a novel immunodeficiency syndrome in 1981, the search for a causative agent was initiated. **Françoise Barré-Sinoussi** and **Luc Montagnier** isolated and cultured lymph node cells from patients that had swollen lymph nodes characteristic of the early stage of acquired immune deficiency.

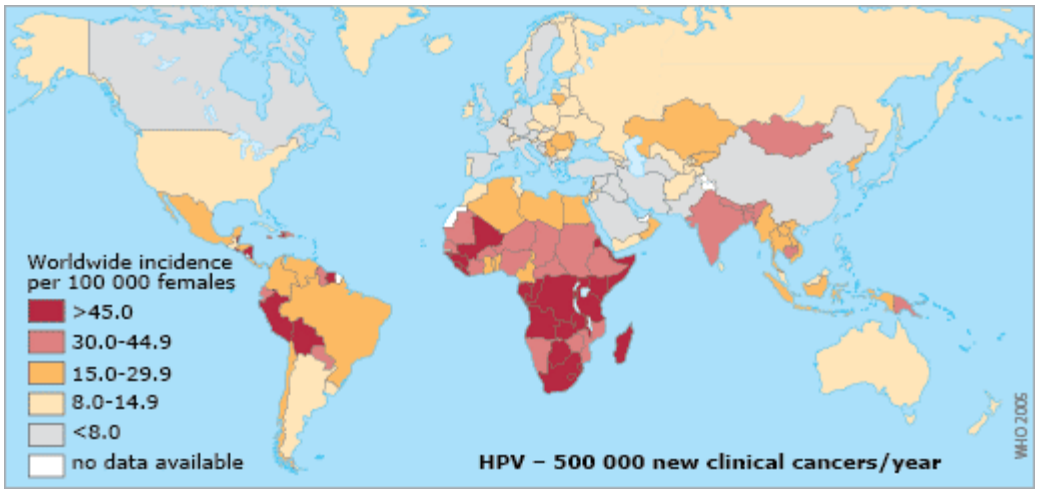
They detected activity of the retroviral enzyme reverse transcriptase, a direct sign of retrovirus replication. They also found retroviral particles budding from the infected cells. Isolated virus infected and killed lymphocytes from both diseased and healthy donors, and reacted with antibodies from infected patients.

Searching for an unknown retrovirus



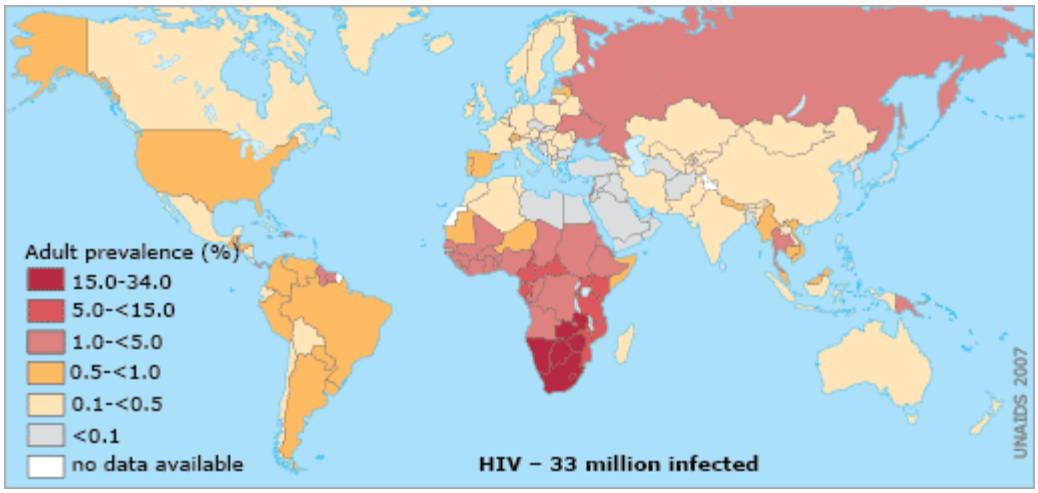


Electron microscopy identified retroviral particles budding from infected T cells



The global public health burden attributable to human papilloma virus is considerable. More than 5% of all cancers worldwide are caused by persistent infection with this virus. Infection by the human papilloma virus is the most common sexually transmitted agent, afflicting 50-80% of the population.

Distribution of HIV-infected individuals



Human immunodeficiency virus has generated a novel pandemic. Successful antiretroviral therapy results in life spans for infected people now reaching levels similar to those of uninfected people. Never before has science and medicine been so quick to discover, identify the origin and provide treatment for a new disease entity.

Credits and references for the 2008 Nobel Poster for Physiology or Medicine

Scientific Advisors, Professors at Karolinska Institutet: Jan Andersson, Infectious Diseases. Bertil Fredholm, Pharmacology, Chair of the Nobel Committee. Hans Jörnvall, Physiological Chemistry, Secretary of the Nobel Assembly. Klas Kärre, Immunology. Björn Vennström, Molecular Biology.

Illustrations and layout: Annika Röhl, Bengt Gullbing

Printed by Alfa Print AB, Stockholm, 2008

Web adapted version: Nobelprize.org

Nobel Poster from the Nobel Committee for Physiology or Medicine, web adapted by Nobel Web
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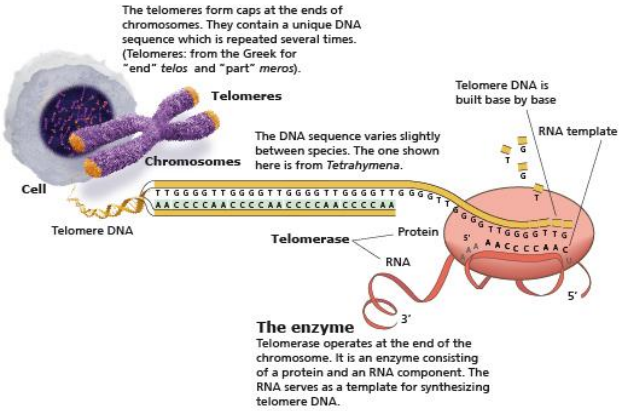
http://www.nobelprize.org/nobel_prizes/medicine/laureates/2008/illpres.html

The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine 2009 jointly to **Elizabeth Blackburn**, **Carol Greider** and **Jack Szostak** for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase.

Elizabeth H. Blackburn
Born 1948
University of California,
San Francisco, USA

Carol W. Greider
Born 1961
Johns Hopkins University
School of Medicine,
Baltimore, USA

Jack W. Szostak
Born 1952
Harvard Medical School,
Boston, USA

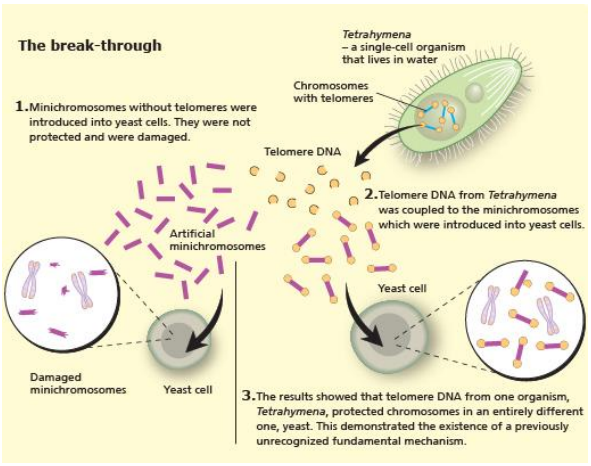


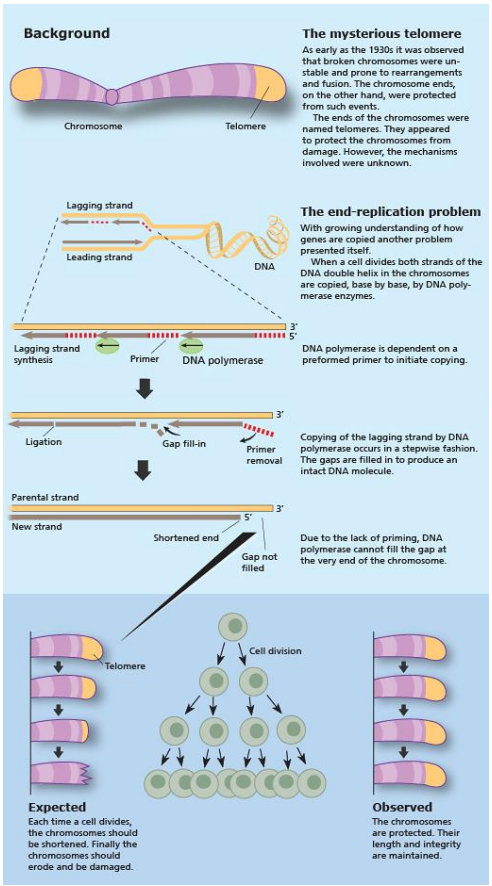
-The award recognizes the discovery of a fundamental mechanism that has added a new dimension to our understanding of the cell, shed light on disease mechanisms, and stimulated the development of potential new therapies.

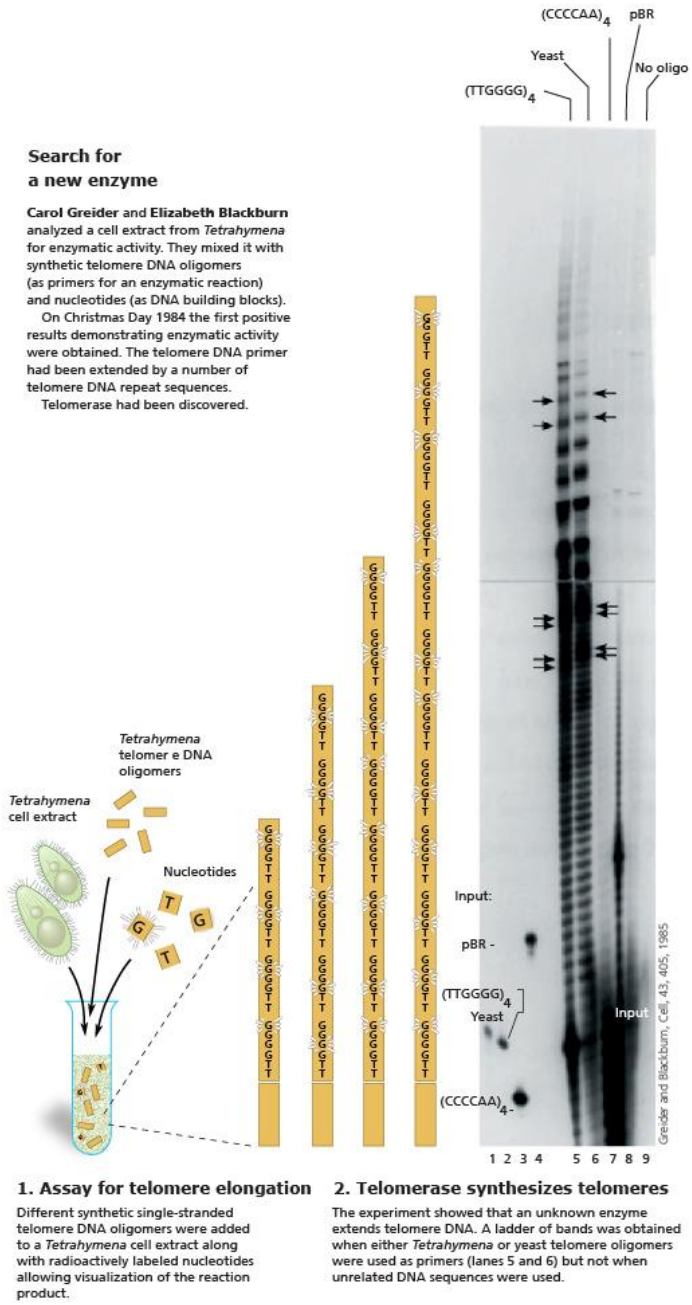
Telomere DNA protects the chromosomes

Elizabeth Blackburn studied the single-cell organism *Tetrahymena thermophila* and had found that the ends of chromosomes contain a short DNA sequence repeated many times.

Jack Szostak studied yeast cells and observed that linear artificial minichromosomes were rapidly degraded. Together they decided to test if telomere DNA from *Tetrahymena* could protect minichromosomes in yeast.





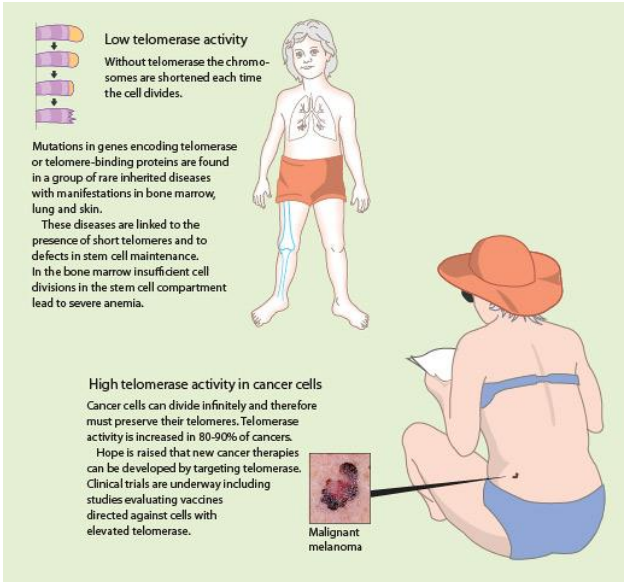


Telomerase builds telomere DNA

How are telomeres formed? **Carol Greider** and **Elizabeth Blackburn** asked if an enzyme might synthesize telomeres.

Telomerase and disease

Th-e discovery of telomere function and telomerase has broad medical implications in many fields including cancer, ageing and certain inherited diseases.



Credits and references for the 2009 Nobel Poster for Physiology or Medicine

Scientific Advisors, Professors at Karolinska Institutet: Göran K. Hansson, Medicine. Secretary of the Nobel Assembly; Klas Kärre, Immunology. Chair of the Nobel Committee; Nils-Göran Larsson, Genetics; Thomas Perlmann, Developmental Biology; Rune Toftgård, Cancer Biology.

Illustrations and layout: Annika Röhl, Bengt Gullbing

Printed by Alfaprint, Stockholm 2009

Web adapted version: Nobelprize.org

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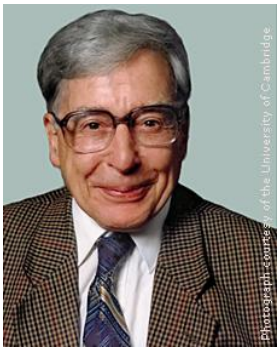
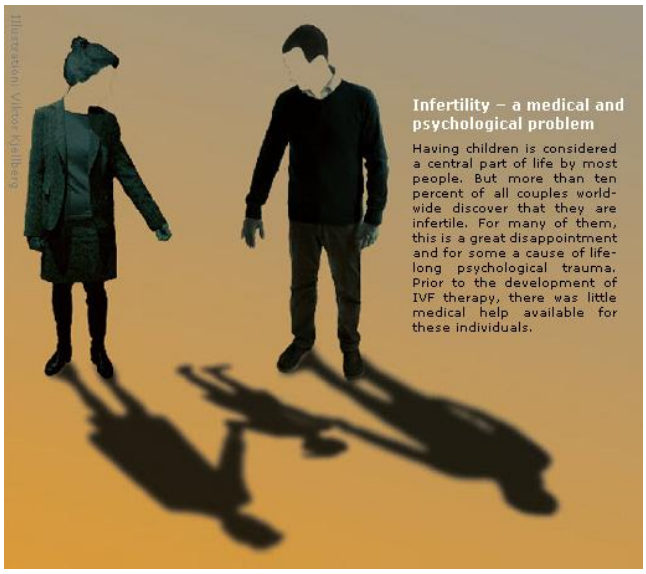
MLA style: "The 2009 Nobel Prize in Physiology or Medicine - Illustrated Presentation". Nobelprize.org. 6 Oct 2011
http://www.nobelprize.org/nobel_prizes/medicine/laureates/2009/illpres.html

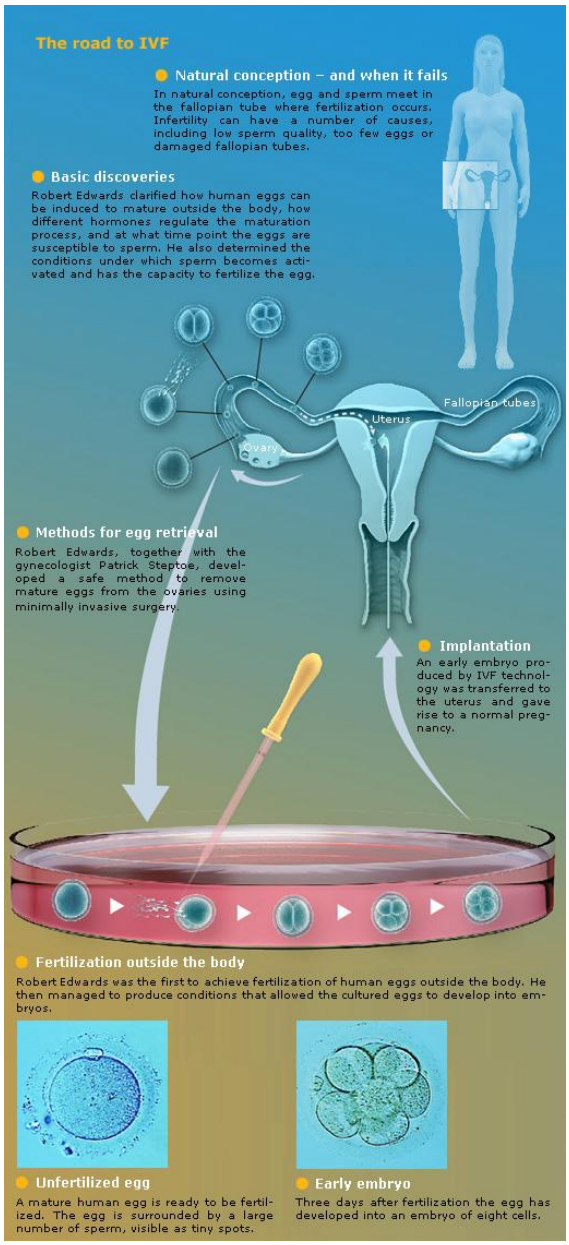
The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine 2010 to Robert G. Edwards for the development of human in vitro fertilization (IVF). His achievements have made it possible to treat infertility, a medical condition afflicting a large proportion of humanity including more than ten percent of all couples worldwide.



Robert G. Edwards

Robert Edwards was born in 1925 in Batley, Yorkshire, UK. During most of his academic career in reproductive physiology, he worked in Cambridge, UK, where he and his coworkers also started the world's first IVF centre, Bourn Hall Clinic. Robert Edwards is currently professor emeritus at the University of Cambridge.





A historic delivery


Daily Mail

And here she is...

THE LOVELY LOUISE

LOUISE BROWN, bright-eyed at 18 hours old! The test tube baby in hospital yesterday

On July 25th 1978 the world's first IVF baby, Louise Brown, was born as a result of Robert Edwards' new treatment. Th-e event attracted worldwide attention and marked the beginning of a new era in medicine.

IVF – a safe and effective treatment

IVF is now an established treatment when sperm and eggs cannot meet by natural means. Twenty to thirty percent of implanted eggs lead to the birth of a child. Complication risks are very small if only one

egg is transferred into the uterus. Long-term follow-up studies have shown that IVF children are as healthy as other children.

Four million children - so far

Approximately four million children have so far been born with the help of IVF technology. Several IVF children have given birth to their own healthy children, and this is perhaps the best evidence for the safety and success of IVF therapy. Robert Edwards' vision is now a reality, and brings joy to families all over the world

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Credits and references for the 2010 Nobel Poster for Physiology or Medicine

Scientific Advisors, Professors at Karolinska Institutet: Göran K Hansson, Medicine, Secretary of the Nobel Assembly; Outi Hovatta, Obstetrics and Gynecology; Christer Höög, Genetics; Klas Kärre, Immunology, Chairman of the Nobel Committee; Hugo Lagercrantz, Pediatrics; Urban Lendahl, Genetics

Medical writer: Ola Danielsson

Illustrations and layout: Mattias Karlén

Web adapted version: Nobelprize.org

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http://www.nobelprize.org/nobel_prizes/medicine/laureates/2010/illpres.html