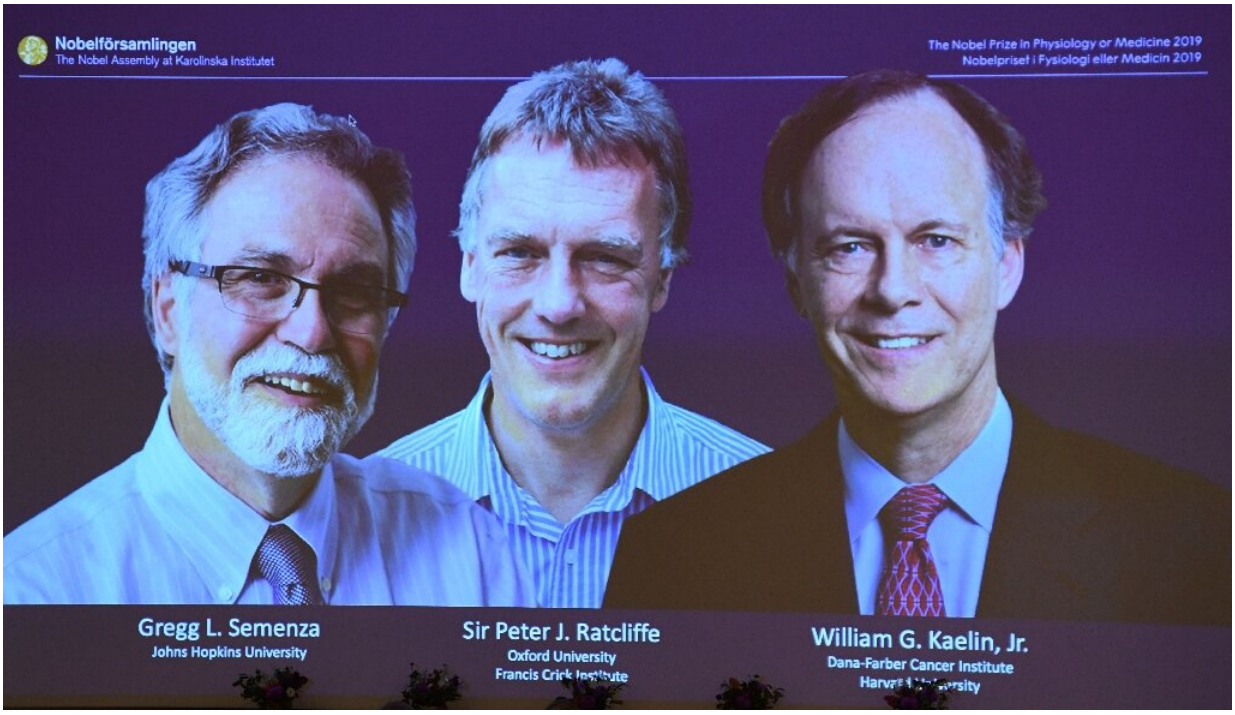
# Trio win medicine Nobel for work on how cells adapt to oxygen

October 7 2019




William Kaelin and Gregg Semenza of the US and Peter Ratcliffe of Britain were announced as the winners of 2019 Nobel Medicine Prize for discoveries on how cells sense and adapt to oxygen availability, which is paving the way for new cancer treatments

Three researchers from the United States and Britain on Monday shared the Nobel Medicine Prize for research into how human cells sense and adapt to changing oxygen levels, opening up new strategies to fight such

diseases as cancer and anaemia.

Americans William Kaelin and Gregg Semenza, and Britain's Peter Ratcliffe, split the nine million Swedish kronor ($914,000, 833,000 euros) award.

While the fact that humans need oxygen to survive has been understood for centuries, how the body registers and responds to oxygen was little known prior to the trio's pioneering work.

Semenza studied a gene known as EPO which causes the body to create more red blood cells and isolated the specific DNA segments that help it to adapt to low oxygen levels.

Ratcliffe and Semenza then applied this knowledge to show that the oxygen sensing mechanism was present in virtually all human tissues.

Kaelin identified another gene, present in patients with a genetic disorder that puts them at far greater risk of certain cancers. The gene rewires the body's ability to prevent the onset of cancer, and it plays a key role in how cancer cells respond to low oxygen levels.

Their work has shed new light on the specific, cell-level processes the body undergoes when low on oxygen—from helping our muscles function during exercise to adapting to life at high altitude.

Cells' oxygen-sensing ability is also essential during foetal development and in creating new blood vessels.

Gregg Semenza, 63, is director of the Vascular Research Program at the Johns Hopkins Institute for Cell Engineering

## Drugs being developed

A large number of diseases are linked to EPO, including renal failure and severe anaemia.

Cancerous tumours use the body's oxygen-regulating tools to hijack blood vessel formation and allow the cancer cells to spread. The Nobel committee said Monday that several trials were underway developing drugs to interrupt this process, potentially short-circuiting tumour growth.

For treatment of anaemia—where the body lacks sufficient red blood cells to carry enough oxygen to tissues—medicines seek to stimulate EPO creation. One such drug has already been approved in China.

This essentially tricks the body into thinking it is at higher altitude, prompting the creation of new red blood cells.

Kaelin, 61, works at the Dana-Farber Cancer Institute in Boston and is a professor at Harvard Medical School in the United States.

William Kaelin of the US identified a gene present in patients with a genetic disorder that puts them at far greater risk of certain cancers

Semenza, 63, is director of the Vascular Research Program at the Johns Hopkins Institute for Cell Engineering.

Ratcliffe, 65, is director of clinical research at the Francis Crick Institute in London, and director of the Target Discovery Institute in Oxford.

Kaelin told reporters it was a moment he had dreamt of for a long time. "I think any scientist who says he's never or she's never considered this moment is probably lying," he said.

When the phone rang at around 5:00 am, he wasn't sure if he was dreaming.

He then noticed the caller ID was from Europe, "And at that point my heart started racing," the 61-year-old told AFP.

"I sort of had this out-of-body feeling of just great appreciation," he said, adding he was accepting the prize partly on behalf of his late wife Carolyn, a cancer surgeon.

British scientist Peter Ratcliffe said he was writing a grant proposal when he learned of the award

Semenza on the other hand missed the first call he got, and waited several anxious minutes by the phone, answering it second time around.

"I was in a daze," he said, adding he had not been expecting the honor but had since celebrated with champagne.

## Discovery science

Kaelin said the win highlighted the value of basic research, rather than setting out to cure a specific disease.

"Here I am as a cancer biologist helping to contribute to a new drug for haematological condition, namely anaemia," he told AFP.


Nobel 2019
MEDICINE
2019 How cells sense and adapt to oxygen levels
William G. Kaelin Jr. (US)
Sir Peter J. Ratcliffe (Britain)
Gregg L. Semenza (US)
2018 Immunotherapy for treatment of cancers
J. P. Allison (US)
T. Honjo (Japan)
2017 The biological clock
J. C. Hall (US)
M. Rosbash (US)
M. W. Young (US)
2016 Cell autophagy
Y. Ohsumi (Japan)
2015 Treatments for infections caused by roundworm parasites and malaria
W. C. Campbell (Ireland)
S. Omura (Japan)
Y. Tu (China)
2014 The brain's "GPS system"
J. O'Keefe (Britain -US)
M.-B. Moser (Norway)
E. I. Moser (Norway)
2013 Intracellular transport
J. E. Rothman (US)
R. W. Schekman (US)
T. C. Suedhof (Germany)
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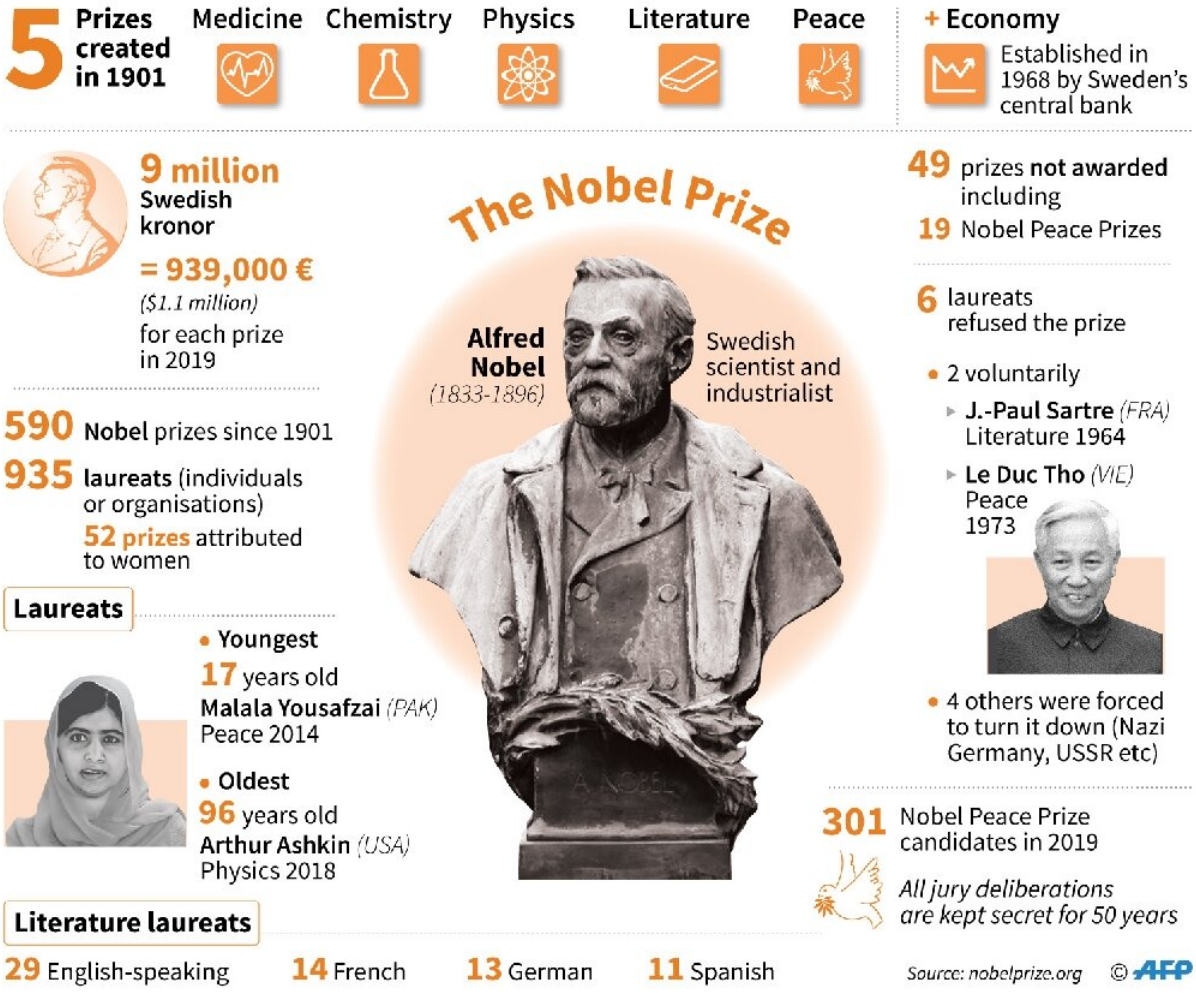
Semenza, whose first breakthrough came in 1995, told AFP that the Nobel prize created the false impression that great science was done by older people, when the opposite was in fact true.

"We made the discoveries when we were young, but we get recognised when we're old," he said, adding it was younger scientists at his lab driving cutting-edge work.

The Peace Prize will be awarded in Oslo on Friday, with speculation rife that Swedish teenage activist Greta Thunberg could win for her campaign to raise awareness about climate change.




Factfile on the Nobel Prize, including winners since 1901, youngest and oldest laureates, and prizes not awarded.

Before that, the Physics Prize will be announced on Tuesday and the Chemistry Prize on Wednesday.

On Thursday, the Swedish Academy will announce one literature laureate for 2018 and one for 2019, after postponing last year's award due to a sexual harassment scandal that exposed deep rifts among its 18

members.

The announcement of the Economics Prize will wrap things up on Monday, October 14.

## Press release: The Nobel Prize in Physiology or Medicine 2019

The Nobel Assembly at Karolinska Institutet

has today decided to award

the 2019 Nobel Prize in Physiology or Medicine

jointly to

William G. Kaelin Jr., Sir Peter J. Ratcliffe and Gregg L. Semenza

for their discoveries of how cells sense and adapt to oxygen availability

## SUMMARY

Animals need oxygen for the conversion of food into useful energy. The fundamental importance of oxygen has been understood for centuries, but how cells adapt to changes in levels of oxygen has long been unknown.

William G. Kaelin Jr., Sir Peter J. Ratcliffe and Gregg L. Semenza discovered how cells can sense and adapt to changing oxygen availability. They identified molecular machinery that regulates the activity of genes in response to varying levels of oxygen.

The seminal discoveries by this year's Nobel Laureates revealed the mechanism for one of life's most essential adaptive processes. They established the basis for our understanding of how oxygen levels affect cellular metabolism and physiological function. Their discoveries have also paved the way for promising new strategies to fight anemia, cancer and many other diseases.

## Oxygen at center stage

Oxygen, with the formula O2, makes up about one fifth of Earth's atmosphere. Oxygen is essential for animal life: it is used by the mitochondria present in virtually all animal cells in order to convert food into useful energy. Otto Warburg, the recipient of the 1931 Nobel Prize in Physiology or Medicine, revealed that this conversion is an enzymatic process.

During evolution, mechanisms developed to ensure a sufficient supply of oxygen to tissues and cells. The carotid body, adjacent to large blood vessels on both sides of the neck, contains specialized cells that sense the blood's oxygen levels. The 1938 Nobel Prize in Physiology or Medicine to Corneille Heymans awarded discoveries showing how blood oxygen sensing via the carotid body controls our respiratory rate by communicating directly with the brain.

## HIF enters the scene

In addition to the carotid body-controlled rapid adaptation to low oxygen levels (hypoxia), there are other fundamental physiological adaptations. A key physiological response to hypoxia is the rise in levels of the hormone erythropoietin (EPO), which leads to increased production of red blood cells (erythropoiesis). The importance of hormonal control of erythropoiesis was already known at the beginning of the 20th century,

but how this process was itself controlled by O2 remained a mystery.

Gregg Semenza studied the EPO gene and how it is regulated by varying oxygen levels. By using gene-modified mice, specific DNA segments located next to the EPO gene were shown to mediate the response to hypoxia. Sir Peter Ratcliffe also studied O2-dependent regulation of the EPO gene, and both research groups found that the oxygen sensing mechanism was present in virtually all tissues, not only in the kidney cells where EPO is normally produced. These were important findings showing that the mechanism was general and functional in many different cell types.

Semenza wished to identify the cellular components mediating this response. In cultured liver cells he discovered a protein complex that binds to the identified DNA segment in an oxygen-dependent manner. He called this complex the hypoxia-inducible factor (HIF) . Extensive efforts to purify the HIF complex began, and in 1995, Semenza was able to publish some of his key findings, including identification of the genes encoding HIF. HIF was found to consist of two different DNA-binding proteins, so called transcription factors, now named HIF-1α and ARNT. Now the researchers could begin solving the puzzle, allowing them to understand which additional components were involved and how the machinery works.

## VHL: an unexpected partner

When oxygen levels are high, cells contain very little HIF-1α. However, when oxygen levels are low, the amount of HIF-1α increases so that it can bind to and thus regulate the EPO gene as well as other genes with HIF-binding DNA segments (Figure 1). Several research groups showed that HIF-1α, which is normally rapidly degraded, is protected from degradation in hypoxia. At normal oxygen levels, a cellular machine called the proteasome, recognized by the 2004 Nobel Prize in Chemistry

to Aaron Ciechanover, Avram Hershko and Irwin Rose, degrades HIF-1α. Under such conditions a small peptide, ubiquitin, is added to the HIF-1α protein. Ubiquitin functions as a tag for proteins destined for degradation in the proteasome. How ubiquitin binds to HIF-1α in an oxygen-dependent manner remained a central question.

The answer came from an unexpected direction. At about the same time as Semenza and Ratcliffe were exploring the regulation of the EPO gene, cancer researcher William Kaelin, Jr. was researching an inherited syndrome, von Hippel-Lindau's disease (VHL disease). This genetic disease leads to dramatically increased risk of certain cancers in families with inherited VHL mutations. Kaelin showed that the VHL gene encodes a protein that prevents the onset of cancer. Kaelin also showed that cancer cells lacking a functional VHL gene express abnormally high levels of hypoxia-regulated genes; but that when the VHL gene was reintroduced into cancer cells, normal levels were restored. This was an important clue showing that VHL was somehow involved in controlling responses to hypoxia. Additional clues came from several research groups showing that VHL is part of a complex that labels proteins with ubiquitin, marking them for degradation in the proteasome. Ratcliffe and his research group then made a key discovery: demonstrating that VHL can physically interact with HIF-1α and is required for its degradation at normal oxygen levels. This conclusively linked VHL to HIF-1α.

## Oxygen sHIFts the balance

Many pieces had fallen into place, but what was still lacking was an understanding of how O2 levels regulate the interaction between VHL and HIF-1α. The search focused on a specific portion of the HIF-1α protein known to be important for VHL-dependent degradation, and both Kaelin and Ratcliffe suspected that the key to O2-sensing resided somewhere in this protein domain. In 2001, in two simultaneously

published articles they showed that under normal oxygen levels, hydroxyl groups are added at two specific positions in HIF-1α (Figure 1). This protein modification, called prolyl hydroxylation, allows VHL to recognize and bind to HIF-1α and thus explained how normal oxygen levels control rapid HIF-1α degradation with the help of oxygen-sensitive enzymes (so-called prolyl hydroxylases). Further research by Ratcliffe and others identified the responsible prolyl hydroxylases. It was also shown that the gene activating function of HIF-1α was regulated by oxygen-dependent hydroxylation. The Nobel Laureates had now elucidated the oxygen sensing mechanism and had shown how it works.

## Oxygen shapes physiology and pathology

Thanks to the groundbreaking work of these Nobel Laureates, we know much more about how different oxygen levels regulate fundamental physiological processes. Oxygen sensing allows cells to adapt their metabolism to low oxygen levels: for example, in our muscles during intense exercise. Other examples of adaptive processes controlled by oxygen sensing include the generation of new blood vessels and the production of red blood cells. Our immune system and many other physiological functions are also fine-tuned by the O2-sensing machinery. Oxygen sensing has even been shown to be essential during fetal development for controlling normal blood vessel formation and placenta development.

Oxygen sensing is central to a large number of diseases (Figure 2). For example, patients with chronic renal failure often suffer from severe anemia due to decreased EPO expression. EPO is produced by cells in the kidney and is essential for controlling the formation of red blood cells, as explained above. Moreover, the oxygen-regulated machinery has an important role in cancer. In tumors, the oxygen-regulated machinery is utilized to stimulate blood vessel formation and reshape metabolism for effective proliferation of cancer cells. Intense ongoing efforts in

academic laboratories and pharmaceutical companies are now focused on developing drugs that can interfere with different disease states by either activating, or blocking, the oxygen-sensing machinery.

## Key publications

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William G. Kaelin, Jr. was born in 1957 in New York. He obtained an

M.D. from Duke University, Durham. He did his specialist training in internal medicine and oncology at Johns Hopkins University, Baltimore, and at the Dana-Farber Cancer Institute, Boston. He established his own research lab at the Dana-Farber Cancer Institute and became a full professor at Harvard Medical School in 2002. He is an Investigator of the Howard Hughes Medical Institute since 1998.

Sir Peter J. Ratcliffe was born in 1954 in Lancashire, United Kingdom. He studied medicine at Gonville and Caius College at Cambridge University and did his specialist training in nephrology at Oxford. He established an independent research group at Oxford University and became a full professor in 1996. He is the Director of Clinical Research at Francis Crick Institute, London, Director for Target Discovery Institute in Oxford and Member of the Ludwig Institute for Cancer Research.

Gregg L. Semenza was born in 1956 in New York. He obtained his B.A. in Biology from Harvard University, Boston. He received an MD/PhD degree from the University of Pennsylvania, School of Medicine, Philadelphia in 1984 and trained as a specialist in pediatrics at Duke University, Durham. He did postdoctoral training at Johns Hopkins University, Baltimore where he also established an independent research group. He became a full professor at the Johns Hopkins University in 1999 and since 2003 is the Director of the Vascular Research Program at the Johns Hopkins Institute for Cell Engineering.

**More information:**
www.nobelprize.org/prizes/medicine/2019/summary/