Ratcliffe and his team later found that the protein expressed by *VHL* interacts with a component of HIF, turning off responses to low-oxygen conditions by marking the HIF component for destruction once oxygen levels rise.

And in 2001, teams led by Kaelin and Ratcliffe elucidated more details about this process. They discovered that, when oxygen is present, a chemical modification to the VHL protein called prolyl hydroxylation allows VHL to bind HIF, which leads to the latter's breakdown. But this modification is blocked when cells are oxygen-starved, kick-starting the activity of HIF.

As a result, cells can react to low oxygen levels by simply blocking the breakdown of HIF, notes Mark Dewhirst, a cancer biologist at Duke University in Durham, North Carolina. "The cell can respond in minutes."

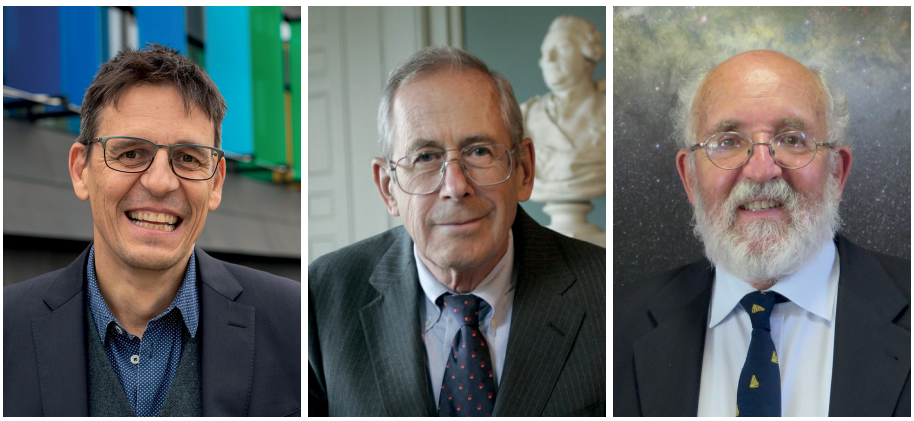
DRUG DEVELOPMENT

The work has led researchers to develop drugs that target oxygen-sensing processes, including those in cancer. Drugs, called prolyl hydroxylase inhibitors, that prevent VHL from binding to HIF and causing its degradation are also being investigated as treatments for anaemia and renal failure. Chinese regulators approved the first of these drugs in 2018.

"You could argue that some aspect of this is going to be germane to all diseases you can think of," says Simon.

Colleagues hailed the trio as role models for other scientists. "They are extremely humble people," says Dewhirst. "All three of them hold scientific rigour and reproducibility to the absolute highest standard," adds Simon.

Kaelin, in particular, has taken his field to task for pursuing possible cancer treatments that aren't backed up by strong evidence. "The most dangerous result in science is the one you were hoping for, because you declare victory and get lazy," he told scientists at a 2018 talk at the US National Institutes of Health in Bethesda, Maryland. ■



Didier Queloz (left), James Peebles (centre) and Michel Mayor.

LEFT TO RIGHT: UNIV. CAMBRIDGE; TORBJÖRN ZADIG; INAMORI FOUNDATION

PHYSICS PRIZE

Planet pioneers win physics Nobel

Exoplanet astronomers share award with cosmologist whose theories describe Universe's evolution.

BY ELIZABETH GIBNEY & DAVIDE CASTELVECCHI

Cosmologist James Peebles and astronomers Michel Mayor and Didier Queloz have won the 2019 Nobel Prize in Physics for discoveries about the evolution of the Universe and Earth's place in it.

In 1995, Mayor, at the University of Geneva, Switzerland, and his then-student Queloz made the first discovery of a planet orbiting a Sun-like star (M. Mayor and D. Queloz *Nature* **378**, 355–359; 1995). Their work launched a field that has become one of astronomy's hottest. They detected the exoplanet through its tiny gravitational pull on its star, 51 Pegasi, a technique that is now used to study some of the more than 4,000 exoplanets now known to exist.

Peebles, who is at Princeton University in New Jersey, developed a theoretical framework that underpins modern understanding of the Universe's history (P. J. E. Peebles and J. T. Yu *Astrophys. J.* **162**, 815; 1970). In particular, he helped to lay the theoretical foundations for the cosmic microwave background (CMB), the 'afterglow' of the Big Bang, and to establish the current 'standard model' of the Universe's evolution. In this model, the mysterious substance known as dark matter plays a central part in assembling large-scale structures of the cosmos, such as galaxies and clusters of galaxies.

Mayor and Queloz share one half of the prize, worth 9 million Swedish kronor (US$910,000), and Peebles will receive the other half.

Mayor and Queloz's discovery "started modern exoplanet science", says Guillem Anglada-Escudé, an astronomer at the Institute for Space Sciences-CSIC in Barcelona, Spain.

Researchers had discovered exoplanets orbiting spinning cores of dead stars known as pulsars, but not around stars similar to our own, which could host habitable planets. The pair's discovery came as a surprise. The planet they detected, called 51 Pegasi b, is a gas giant, a type that astronomers had expected would orbit the outer reaches of a solar system. But it was orbiting much closer to its star than Mercury is to the Sun — an early sign that other planetary systems might not be like our own.

The finding was remarkable for being almost completely unambiguous and quickly confirmed, says Anglada-Escudé.

PROBING FIRST LIGHT

Meanwhile, Peebles' theories have allowed cosmologists to understand much more about the CMB and the Universe's beginnings.

"Were it not for the theoretical discoveries of James Peebles, the wonderful high-precision measurements of this radiation over the last 20 years would have told us almost nothing," said Mats Larsson, a molecular physicist at Stockholm University and chair of the 2019 Nobel physics committee, when he revealed the prize.

Peebles developed a model of the Universe's evolution known as the 'cold dark matter' theory, which describes how cosmological structures formed as the Universe expanded and cooled from its hot, dense beginnings. Together with the later addition of ideas about dark energy, this has become the standard framework of modern cosmology.

Although the precise nature of dark matter has yet to be understood, several high-precision surveys of the Universe have lent support to this theory; these include studies of the CMB and the mapping of galaxies across large swathes of the sky. "This is such a long-deserved recognition," says François Bouchet, an astronomer at the Institute of Astrophysics in Paris.

It is unusual for exoplanets and cosmology to be paired up in the same prize, but both lines of work "give a fresh perspective of the place humans have in the cosmos", says Bouchet. ■