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William G. Kaelin Honored with Gairdner International Award

HHMI investigator William G. Kaelin is one of five scientists who have been honored with the prestigious 2010 Canada Gairdner International Award in recognition of their contributions to medical science.

Presented to medical scientists worldwide whose work is expected to significantly improve the quality of life, the Gairdner Award is one of the most esteemed awards in medical research. In addition to Kaelin, 23 current HHMI investigators are recipients of the Gairdner Award. According to the Gairdner Foundation, 76 of the 298 scientists who have received the Gairdner in the past 51 years have gone on to win the Nobel Prize.

The Gairdner Foundation honored Kaelin, together with Peter J. Ratcliffe of the University of Oxford and Gregg L. Semenza of the Johns Hopkins University School of Medicine, for their discoveries of how cells in the body monitor and respond to oxygen levels. Oxygen sensing is crucial for cell survival and plays a role in a variety of diseases, including cancer and heart disease.

Each Gairdner awardee will be presented with their award, which comes with a \$100,000 cash prize, at a ceremony in October. The awardees are chosen through a rigorous two-stage peer-review process, by two medical advisory committees made up of leading medical scientists from Canada and around the world.

Kaelin, an HHMI investigator since 1998 whose lab is at the Dana-Farber Cancer Institute, discovered key aspects of how cells sense and adapt to changing oxygen levels through his studies of a protein that is impaired in the hereditary cancer von Hippel-Lindau (VHL) disease. Kaelin discovered that the VHL protein normally helps regulate the levels of an oxygen-sensing protein called HIF. A hydroxyl group – composed of oxygen and hydrogen – attached to the HIF molecule signals to VHL to bind and mark HIF for destruction. When there isn't enough oxygen to provide the hydroxyl group, HIF remains unadorned and VHL leaves it alone, allowing it to persist in the cell. The lingering HIF then triggers the growth of new blood vessels and other processes that restore a healthy oxygen supply.

Kaelin's long-term goal is to lay a foundation for the development of new anticancer therapies, and his work is already being translated into clinical medicine. His group determined that kidney cancer often involves nonhereditary VHL mutations that lead to overproduction of the HIF-controlled protein VEGF (vascular endothelial growth factor). This in turn promotes the growth of blood vessels that supply a tumor with the oxygen it needs to survive. Those findings provided a rationale for clinical trials testing VEGF inhibitors for kidney cancer, and four such drugs have now been approved by the FDA for treatment of the disease.

Kaelin's lab now hopes to identify genes that cooperate with VHL mutations to promote kidney cancer. They are also identifying molecules that become important for cellular survival only when *VHL* is missing, which could guide the development of drugs that preferentially kill cancer cells by targeting those proteins.