• **Name:** William G. Kaelin, Jr., MD

• **Current Position:** Professor of Medicine

• **Country:** United States

• **Educational Background:**

Duke University, Durham, NC	B.A.	05/1979	Mathematics
Duke University, Durham, NC	A.B.	05/1979	Chemistry
Duke University Medical School, Durham, NC	M.D.	12/1982	Medicine

• **Professional Experience:**

1983	Clinical Assistant, Duke Comprehensive Cancer Center, Durham, NC
1983-1986	Intern and Resident in Internal Medicine, Johns Hopkins Hospital, Baltimore, MD
1986-1987	Assistant Chief of Service, Department of Medicine, Johns Hopkins Hospital, Baltimore, MD
1987-1991	Fellow in Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
1991-1992	Instructor in Medicine, Harvard Medical School, Boston, MA
1992-1997	Assistant Professor of Medicine, Harvard Medical School, Boston, MA
1997-2002	Associate Professor of Medicine, Harvard Medical School, Boston, MA
1998-2002	Assistant Investigator, Howard Hughes Medical Institute
2002-2018	Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA
2002-	Investigator, Howard Hughes Medical Institute
2008-2016	Associate Director, Basic Science, Dana-Farber/Harvard Cancer Center
2009-	Affiliate Member, Broad Institute
2012-2014	Chair, Executive Committee for Research, Dana-Farber Cancer Institute
2018-	Sidney Farber Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

• **Professional Organizations:**

1989-	Member, American College of Physicians
1989-	Member, American Association for the Advancement of Science
1997-	Member, American Society for Clinical Investigation
2000-2005	Member, Board of Scientific Advisors, National Cancer Institute
2002-	Member, American Association for Cancer Research
2002	Member, National Cancer Advisory Board Ad Hoc Working Group on P30 / P50 Cancer Centers
2003-2008	Program Leader, Cancer Cell Biology, Dana-Farber/Harvard Cancer Center
2003-2005	Member, General Motors Charles S. Mott Prize Selection Committee
2003-2006	Elected Member, Board of Directors, American Association for Cancer Research
2004-2014	Member, External Scientific Advisory Committee, Duke Comprehensive Cancer Center
2004-2012	Member, Promotion Advisory Committee, Harvard Medical School Department of Medicine
2006-2016	Member, Clinical Investigator Award Committee, Damon-Runyon
2007-2011	Chair, External Scientific Advisory Board, Cambridge Research Institute
2007-	Member, External Advisory Board, Memorial Sloan-Kettering Cancer Center Human Oncology and Pathogenesis Program (HOPP)
2007-2011	Member, Doris Duke Clinical Scientist Development Award Committee
2008-2014	Member, External Scientific Advisory Board, St. Jude Children's Research Hospital
2015-	Chair, Physician-Scientist Training Award Committee, Damon Runyon

• **Main Scientific Publications:**

1. As a postdoctoral fellow, I showed that the Retinoblastoma Protein (pRB) Binds to the E2F Transcription Factor and was the First to Clone an E2F Family Member (E2F1). Most cancers have mutations that

directly or indirectly compromise the function of pRB. We were one of several groups to show that pRB binds to, and represses, E2F activity. I used a fragment of pRB to expression clone a cDNA encoding E2F1. This enabled many investigators to pursue the mechanisms by which E2F1 regulates cell-cycle progression, apoptosis, and tumorigenesis.

a. Chittenden T, et al. The T/E1A binding domain of the retinoblastoma product can interact selectively with a sequence-specific DNA binding protein. Cell 1991; 65:1073-82.
b. Kaelin WG Jr, et al. Expression cloning of a cDNA encoding a retinoblastoma-binding protein with E2F-like properties. Cell 1992; 70:351-64.
c. Qin X, et al. Deregulated transcription factor E2F-1 expression leads to S-phase entry and p53-mediated apoptosis. Proc Natl Acad Sci 1994; 91:10918-22. PMCID: PMC45137.
d. Sellers W, et al. A potent transrepression domain in the retinoblastoma protein induces a cell cycle arrest when bound to E2F sites. Proc Natl Acad Sci 1995; 92:11544-8. PMCID: PMC40438.

2. Inactivation of the VHL tumor suppressor gene is linked to several cancers including sporadic and hereditary kidney cancer. As an independent investigator we showed that VHL suppresses the growth of VHL-/- kidney cancer cells and linked this to the ability of the VHL protein to form an ubiquitin ligase that downregulates HIF and hypoxia-inducible mRNAs such as VEGF. This provided a conceptual foundation for the successful treatment of kidney cancer with VEGF inhibitors.
   a. Iliopoulos O, et al. Tumor suppression by the human von Hippel-Lindau gene product. Nature Med 1995; 1:822-6.
   b. Iliopoulos O, et al. Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein. Proc Natl Acad Sci 1996; 93:10595-9. PMCID: PMC38198.
   c. Kibel A, et al. Binding of the von Hippel-Lindau protein to Elongin B and C. Science 1995; 269:1444-6.
   d. Ohh, M, et al. Ubiquitination of hypoxia-inducible factor requires direct binding to the b-domain of the von Hippel-Lindau protein. Nature Cell Biol. 2000; 2:423-7.
3. Many diseases of the developed world are linked to inadequate oxygen delivery and hypoxia. We discovered how oxygen is “sensed” by cells and transduced into changes in HIF stability and hypoxia-inducible gene expression. Specifically, we discovered that the HIF alpha subunit is prolyl hydroxylated by members of the EglN (also called PHD) prolyl hydroxylase family in an oxygen-dependent manner, which creates a binding site for pVHL. EglN inhibitors are now in clinical development for anemia and ischemia.
   a. Ivan M, et al. HIFα targeted for VHL-mediated destruction by proline hydroxylation: implications for O_2 sensing. Science 2001; 292:464-8.
   b. Ivan M, et al. Biochemical purification and pharmacological inhibition of a mammalian prolyl hydroxylase acting on hypoxia-inducible factor. Proc Natl Acad Sci USA 2002; 99:13459-64. PMCID: PMC129695.
   c. Min J.-H, et al. Structure of a HIF-1α-pVHL complex: hydroxyproline recognition in signaling. Science 2002; 296:1886-9.
   d. Minimishima YA and Kaelin WG. Reactivation of Hepatic EPO Synthesis in Mice After PHD Loss. Science 2010 Jul 23;329(5990):407. PMCID: PMC3668543.
4. We showed that downregulation of HIF, and specifically HIF2, is both necessary and sufficient for kidney cancer suppression by pVHL, implicating HIF2 as a kidney cancer oncoprotein. In contrast, we showed that HIF1 appears to constrain pVHL-defective kidney cancer growth. This helped to motivate the development of HIF2 inhibitors that are now entering in clinical trials.
   a. Kondo K, et al. Inhibition of HIF is necessary for tumor suppression by the von Hippel-Lindau protein. Cancer Cell 2002; 1:237-46.
   b. Kondo K, et al. Inhibition of HIF2α is sufficient to suppress pVHL-defective tumor growth. PloS Biology 2003; 1:439-44. PMCID: PMC300692.
   c. Shen C, et al**.** Genetic and Functional Studies Implicate HIF1α as a 14q Kidney Cancer Suppressor Gene. Cancer Discov. 2011 Aug; 1(3):222-35. PMCID: PMC3202343.
   d. Cho H, et al. On-Target Efficacy of a HIF2α Antagonist in Preclinical Kidney Cancer Models. Nature. 2016 Nov 3;539(7627):107-111. PMCID: PMC5499381.
5. Recent work has identified mutations affecting IDH1 or IDH2 in a variety of cancers including leukemias and brain tumors. The resulting mutants produce millimolar quantities of the R enantiomer of 2-hydroxyglutarate (R-2HG). We showed that stimulation of EglN activity by R-HG contributes to

transformation of astrocytes and that inhibition of TET2 activity by R-2HG contributes to leukemic transformation. Importantly, we showed that the effects of R-2HG in leukemic transformation are reversible, which helped to motivate the successful clinical development of mutant IDH inhibitors for leukemias driven by IDH mutations.

a. Koivunen P, et al. Transformation by the R Enantiomer of 2-Hydroxyglutarate Linked to EgIN Activation. Nature 2012 Feb 15;483(7390):484-8. PMCID: PMC3656605.
b. Losman JA, et al. (R)-2-Hydroxyglutarate is Sufficient to Promote Leukemogenesis and its Effects are Reversible. Science 2013 Mar 29;339(6127):1621-5. PMCID: PMC3836459.