

From Gene Discovery to Belzutifan, an FDA-Approved Drug

How the discovery of a gene at UT Southwestern became a journey to develop a medicine for kidney cancer.



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Director, Kidney Cancer Program

Illustrations by ChatGPT

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FDA approval of belzutifan culminates 25-year journey at UTSW from gene discovery to a first-in-class drug

August 21, 2021

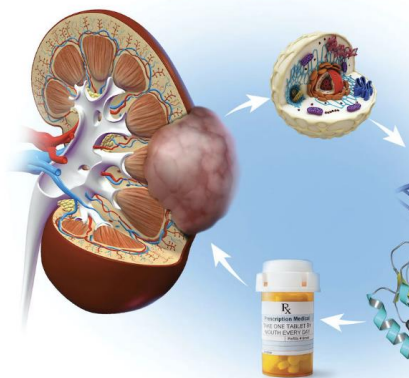


DALLAS – Aug. 21, 2021 – A first-in-kind kidney cancer drug developed from laboratory and translational studies conducted at UT Southwestern Medical Center received [approval from the Food and Drug Administration](#), providing a new treatment for patients with familial kidney cancer.

Merck's belzutifan grew out of the discovery at UT Southwestern of a protein, hypoxia-inducible factor 2-alpha (HIF-2α), that is key to fuel the growth of kidney and other cancers. HIF-2α was discovered by Steven McKnight, Ph.D., Professor of Biochemistry.

"This is an exciting milestone for patients with inherited forms of kidney cancer who are in need of more effective therapies," said David Russell, Ph.D., Vice Provost and Dean of Research, and Professor of Molecular Genetics, who collaborated in the early stages of the research.

The drug, once called PT2977, was developed based on a backbone discovered by UTSW researchers, with further drug development efforts conducted by a spinoff company named Peloton Therapeutics, which was launched on the UTSW campus and eventually acquired by Merck.



FDA approval of belzutifan culminates a 25-year journey at UTSW from discovery to a first-in-class drug.

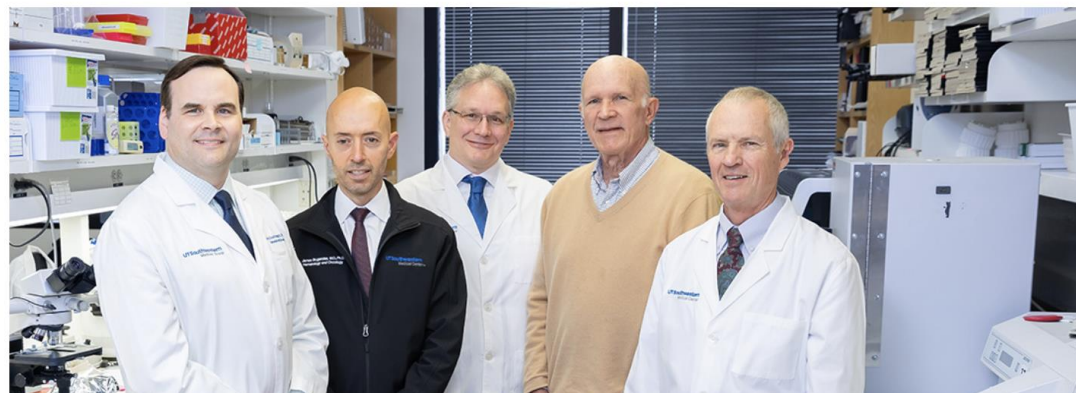
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Drug developed by UTSW spinoff approved for metastatic kidney cancer

December 15, 2023

FDA's expanded use for belzutifan culminates nearly 30-year journey from gene discovery to first-in-class drug



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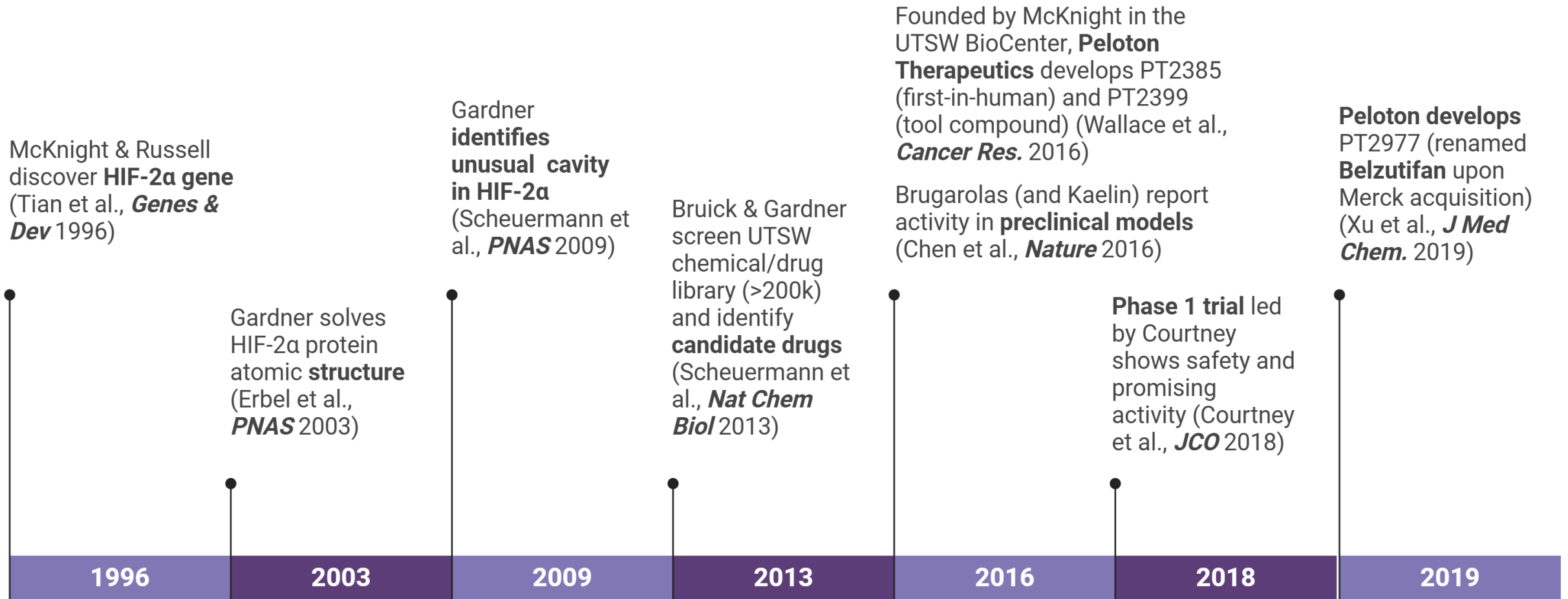
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Fundamental Discoveries that Changed Kidney Cancer Treatment

From HIF-2 α Discovery to First-in-Class FDA Approved Drug



HIF-2 (HIF-2 α + HIF-1 β) turns kidney cells into cancer



1 Two proteins join

2 They land on DNA

3 They turn genes ON

4 Cells grow out of control

HIF-2 α identified

**Steven McKnight and M. L. Russell
identify the HIF-2 α gene.**

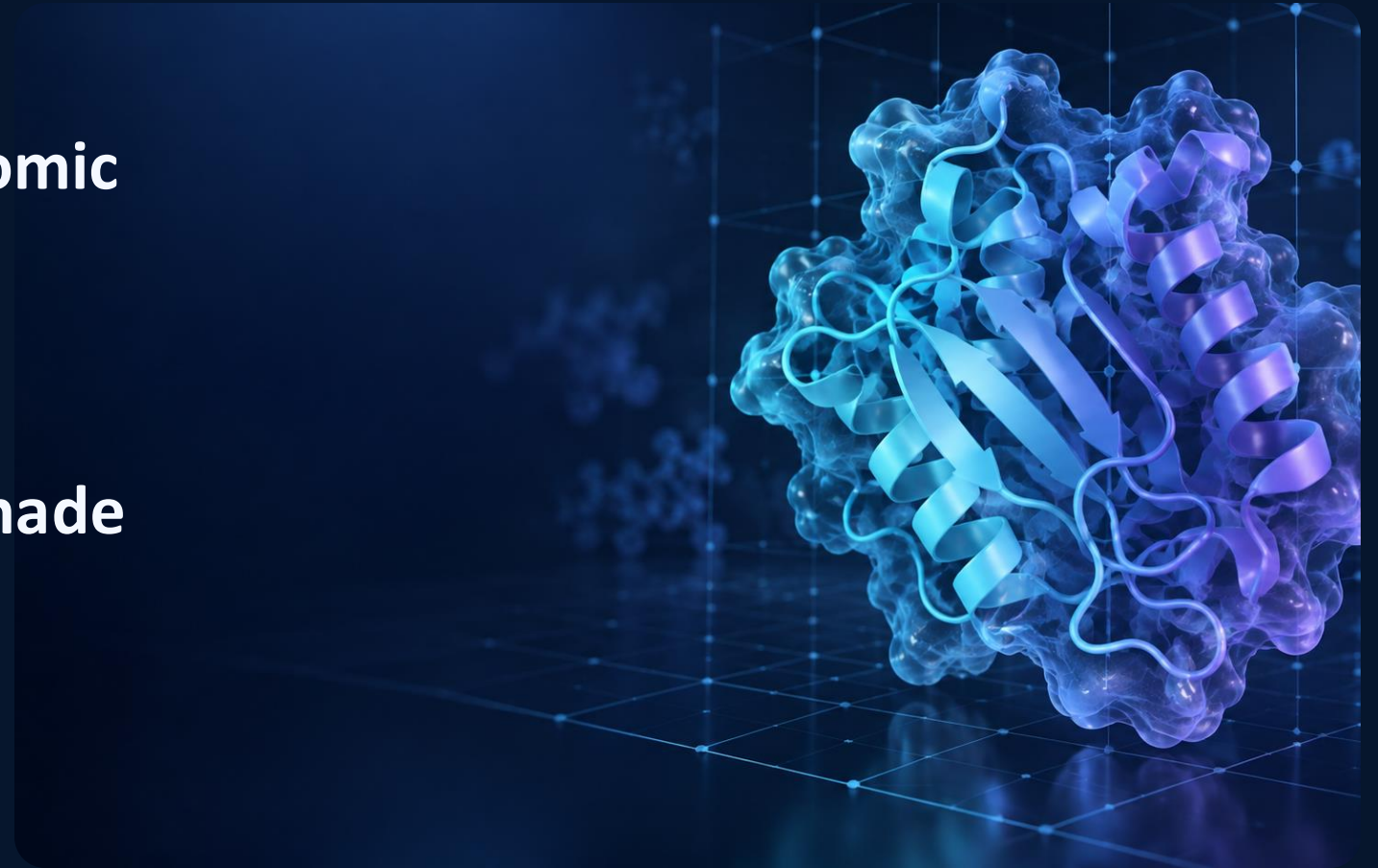
Tian et al. Genes & Development, 1996



HIF-2 α atomic structure

Kevin Gardner solves the atomic structure of HIF-2 α .

Seeing the protein's shape made future drug discovery conceivable.



A druggable cavity in HIF-2 α

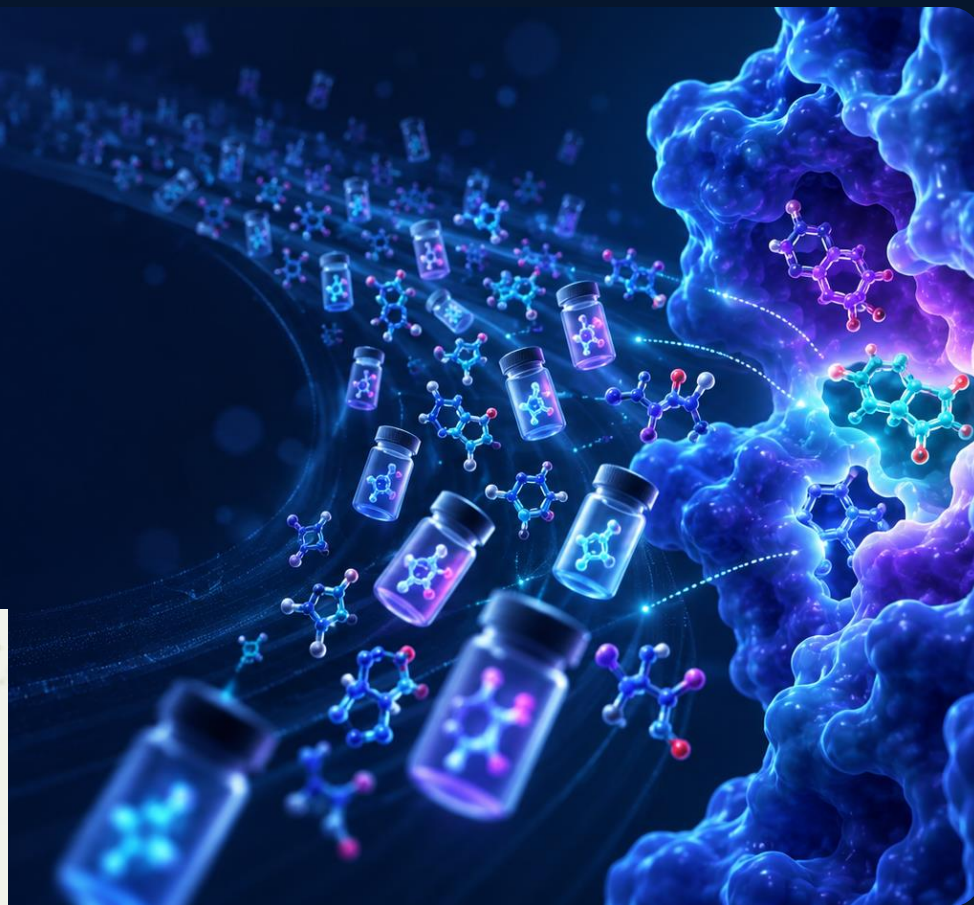
Kevin Gardner identifies a cavity
in HIF-2 α .

The finding revealed a physical
place where a drug could bind.



The UT Southwestern chemical-library screen

Bruick and Gardner screen 200,000 chemicals of the UT Southwestern library and identify a chemical that binds to and blocks HIF-2 α from partnering HIF-1 β .



McKnight founds Peloton Therapeutics

The Dallas Morning News

BUSINESS

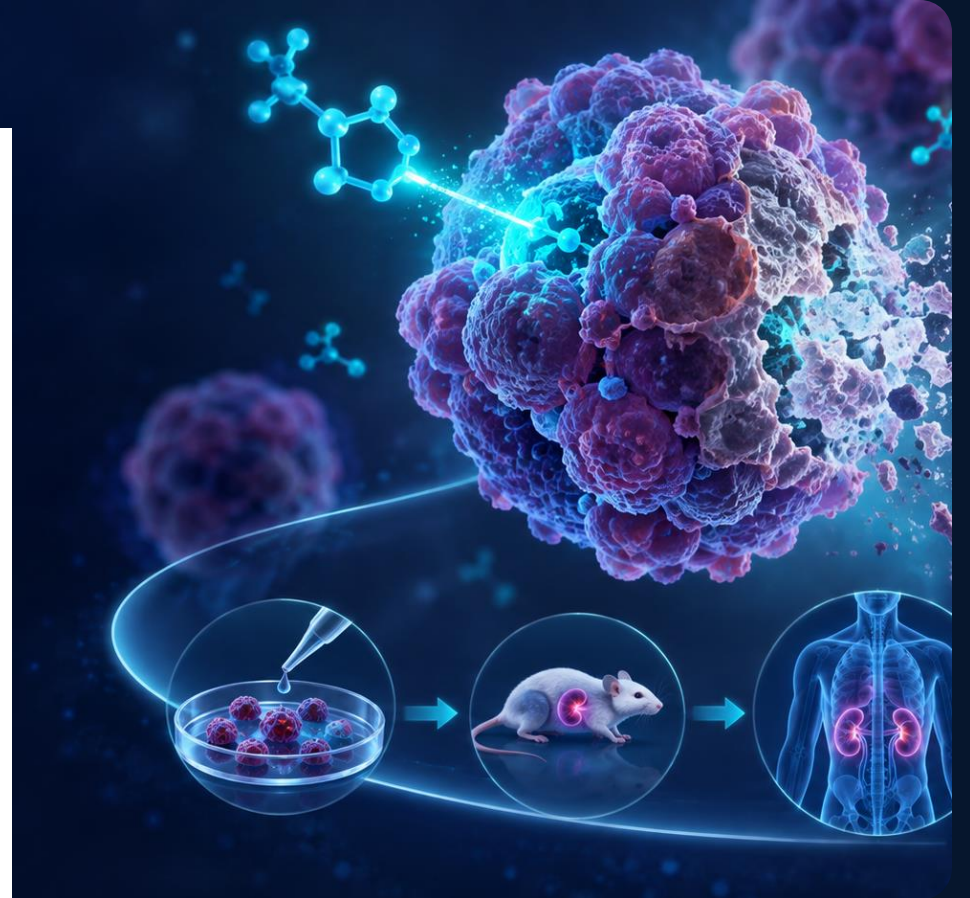
Founder hopes Peloton Therapeutics is a catalyst for UTSW's BioCenter



BioCenter at Southwestern Medical District photographed October 26, 2011. The building is designed to be the hub for commercial life-science in the Dallas area. (Evans Caglage/The Dallas Morning News)

By dallasnews Administrator
3:36 PM on Oct 29, 2011

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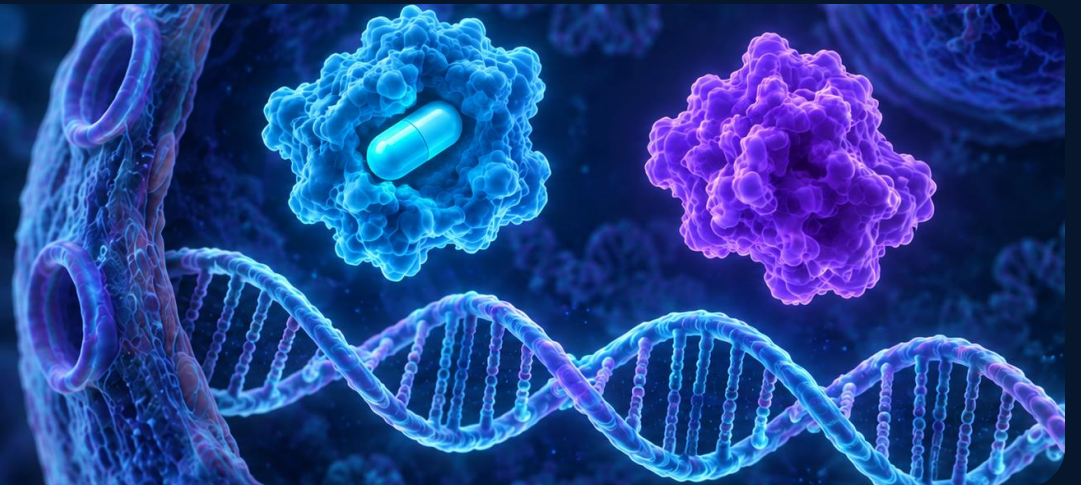


Peloton refines UT Southwestern drug-like chemicals

Peloton develops several chemicals (PT2385, PT2399 & PT2977) that bind HIF-2 α blocking its pairing with HIF-1 β .



Split from HIF-1 β , HIF-2 α cannot bind DNA, turn on target genes and cause cancer.



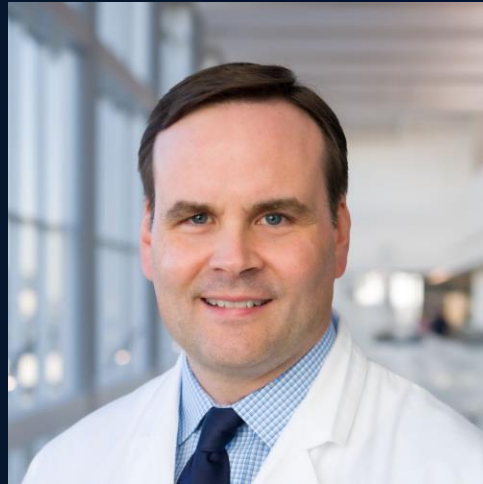
Peloton drugs are tested against kidney cancers from patients transplanted into mice in the Brugarolas Lab

Peloton drugs block the growth of human kidney tumors in mice.



The first clinical trial

Courtney leads phase 1 clinical trial showing safety and promising anti-tumor activity.



Recipient of the Patricia and William L. Watson Jr., M.D.
Award for Excellence in Clinical Care (2026)

UTSouthwestern
Medical Center
Kidney Cancer Program



Courtney et al. Journal of Clinical
Oncology, 2018

Peloton makes further improvements leading to PT2977/Belzutifan

A scientific concept becomes a first-in-class medicine.



Peloton Therapeutics is bought by Merck in 2019

**Merck renames
Peloton's PT2977,
belzutifan.**

Merck Buys Peloton Therapeutics in \$2.2 Billion Deal

Published: May 21, 2019 | By Mark Terry





U.S. FOOD & DRUG
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FDA approves belzutifan for cancers associated with von Hippel-Lindau disease

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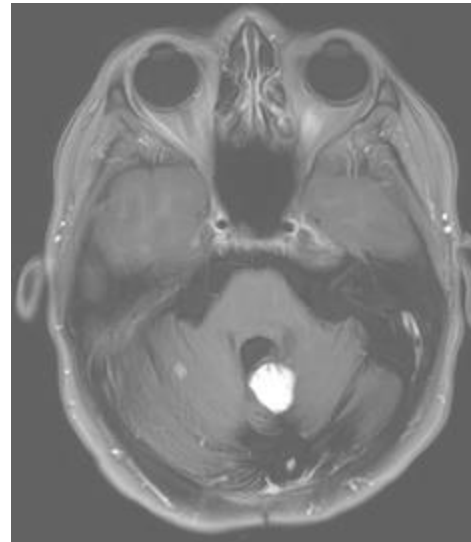
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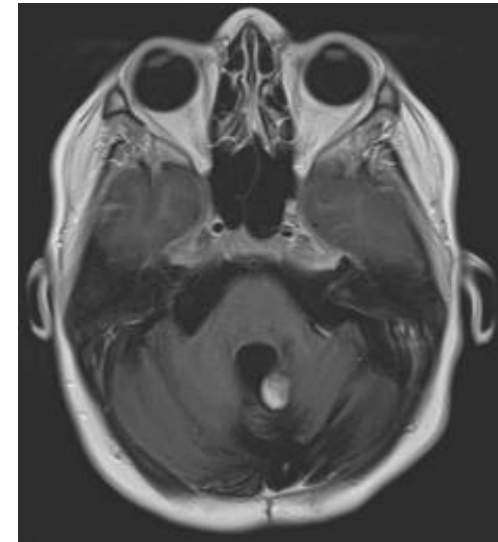
[Oncology \(Cancer\) /](#)
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On August 13, 2021, the Food and Drug Administration approved belzutifan (Welireg, Merck), a hypoxia-inducible factor inhibitor for adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET),

September 2021



April 2022



A 36-year-old woman with VHL syndrome and cerebellar hemangioblastomas (previous surgeries) presents with a progressing 1.9 cm (1 in) tumor and headaches, which resolve after she starts belzutifan (PT2977).



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FDA approves belzutifan for advanced renal cell carcinoma

On December 14, 2023, the Food and Drug Administration approved belzutifan (Welireg, Merck & Co., Inc.) for patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

Full prescribing information for Welireg will be posted [here](#).

Efficacy was evaluated in LITESPARK-005 (NCT04195750), an open-label, randomized, head-to-head trial of 746 patients with unresectable locally advanced or metastatic clear cell RCC that had progressed following both a PD-1 or PD-L1 checkpoint inhibitor and a VEGF-TKI. Patients were randomized 1:1 to receive 120 mg belzutifan or 10 mg everolimus once daily. Randomization was stratified by International Metastatic RCC Database Consortium risk category and number of prior VEGF-TKIs.

The major efficacy outcome measures were progression-free survival (PFS) assessed by blinded independent central review and overall survival (OS).

A statistically significant improvement in PFS was demonstrated for belzutifan compared with everolimus, with a hazard ratio of 0.75 [(95% CI: 0.63, 0.90); 1-sided p-value=0.0008]. Kaplan-Meier curves reflected non-proportional hazards with similar median PFS estimates of 5.6 months (95% CI: 3.9, 7.0) in the belzutifan arm and 5.6 months (95% CI: 4.8, 5.8) for those receiving everolimus. While OS results were immature



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Cancer Accelerated
Approvals

Withdrawn | Cancer
Accelerated Approvals

Other | Cancer
Accelerated Approvals

FDA approves belzutifan with pembrolizumab for adjuvant treatment of renal cell carcinoma

On June 12, 2026, the Food and Drug Administration approved belzutifan (Welireg, Merck & Co., Inc.) in combination with pembrolizumab (Keytruda, Merck & Co., Inc.) or pembrolizumab and berahyaluronidase alfa-pmph (Keytruda Qlex, Merck & Co., Inc.) for the adjuvant treatment of adults with renal cell carcinoma with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Full prescribing information for Welireg, Keytruda, and Keytruda Qlex will be posted on [Drugs@FDA](#).

Efficacy and Safety

Efficacy was evaluated in LITESPARK-022 (NCT05239728), a multicenter, double-blind, randomized trial in 1,841 patients with prior nephrectomy for ccRCC who were at intermediate-high or high risk of recurrence, or who had resected metastases with no evidence of disease. Patients were randomized (1:1) to receive belzutifan in combination with pembrolizumab as adjuvant therapy or placebo in combination with pembrolizumab until disease recurrence or unacceptable toxicity or for up to 54 weeks of belzutifan or 12 months of pembrolizumab.

The major efficacy outcome measure was investigator-assessed disease-free survival (DFS), defined as time to recurrence, metastasis, or death. A statistically significant improvement in DFS was demonstrated at a prespecified interim analysis with 186 events in the belzutifan with pembrolizumab arm and 246 events in the placebo with

From discovery to patients

A 25-year path from a gene to an approved medicine

Gene discovery

Protein structure

Drug design

Mouse models

Clinical trials

FDA approval

x4

