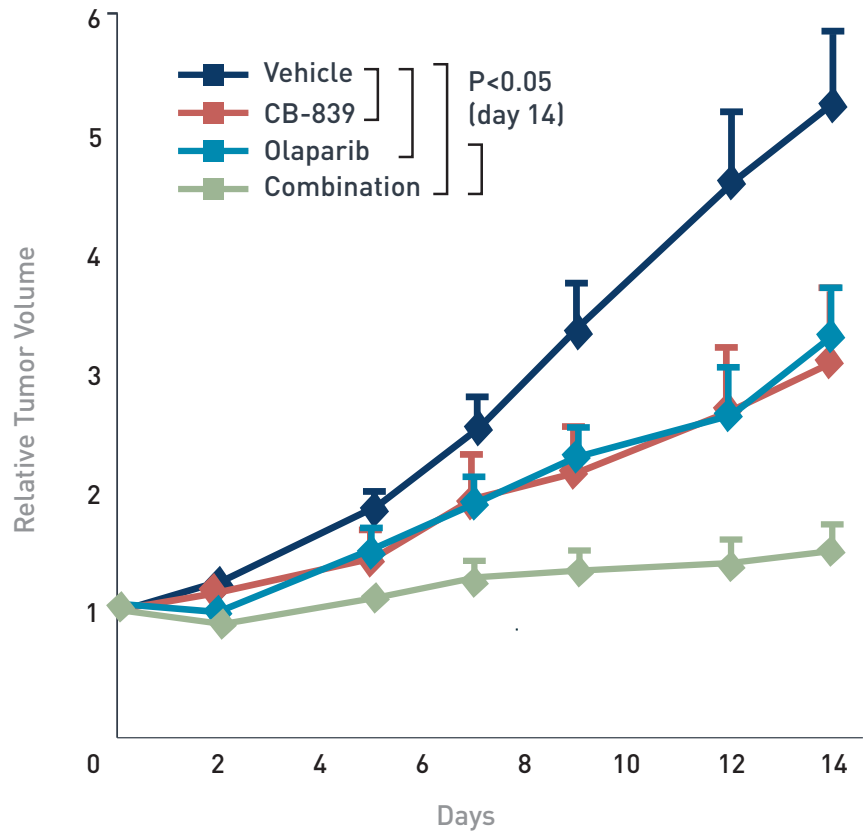


New Combination Therapy for Renal Cell Carcinoma

Can understanding glutamine's role in renal cancer cell metabolism lead to successful treatments for renal and other cancers?

Cancer cell metabolism has only recently become a major subject of study for cancer researchers hunting for cures. Hypoxia, or a shortage of oxygen, is a hallmark of human cancer cells. But because oxygen is critical to cell growth, cancer cells tend to adapt by reprogramming cell metabolism. In particular, researchers have recently learned that these cells rely on amino acid glutamine instead of glucose to metabolize carbon.

Now, for the first time, Othon Iliopoulos, MD, of Massachusetts General Hospital Cancer Center, and a team of researchers have modeled precisely how cancer cells use glutamine to sustain metabolism at the molecular level in human clear cell renal carcinomas. They then used these findings to develop a combination therapy that arrests tumor growth almost completely—not just in renal cancer but potentially in colon, breast and ovarian cancers. Their findings were



Results of treatment with metabolism intervention

Renal cell carcinoma growth almost entirely flattens out after 14 days of treatment with a combination of GLS1 (CB-839) and olaparib.

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“We knew that without glutamine sometimes [cancer cells] die—or sometimes they don’t die, they just don’t grow. But we didn’t know the biochemical consequences that caused these kinds of disturbances in the cell,” said Dr. Iliopoulos, clinical director of the von Hippel-Lindau Disease/Familial Renal

Cell Cancer Program at Mass General Cancer Center. “This is what we set out to understand. What specifically goes wrong if we deprive the cells of glutamine?”

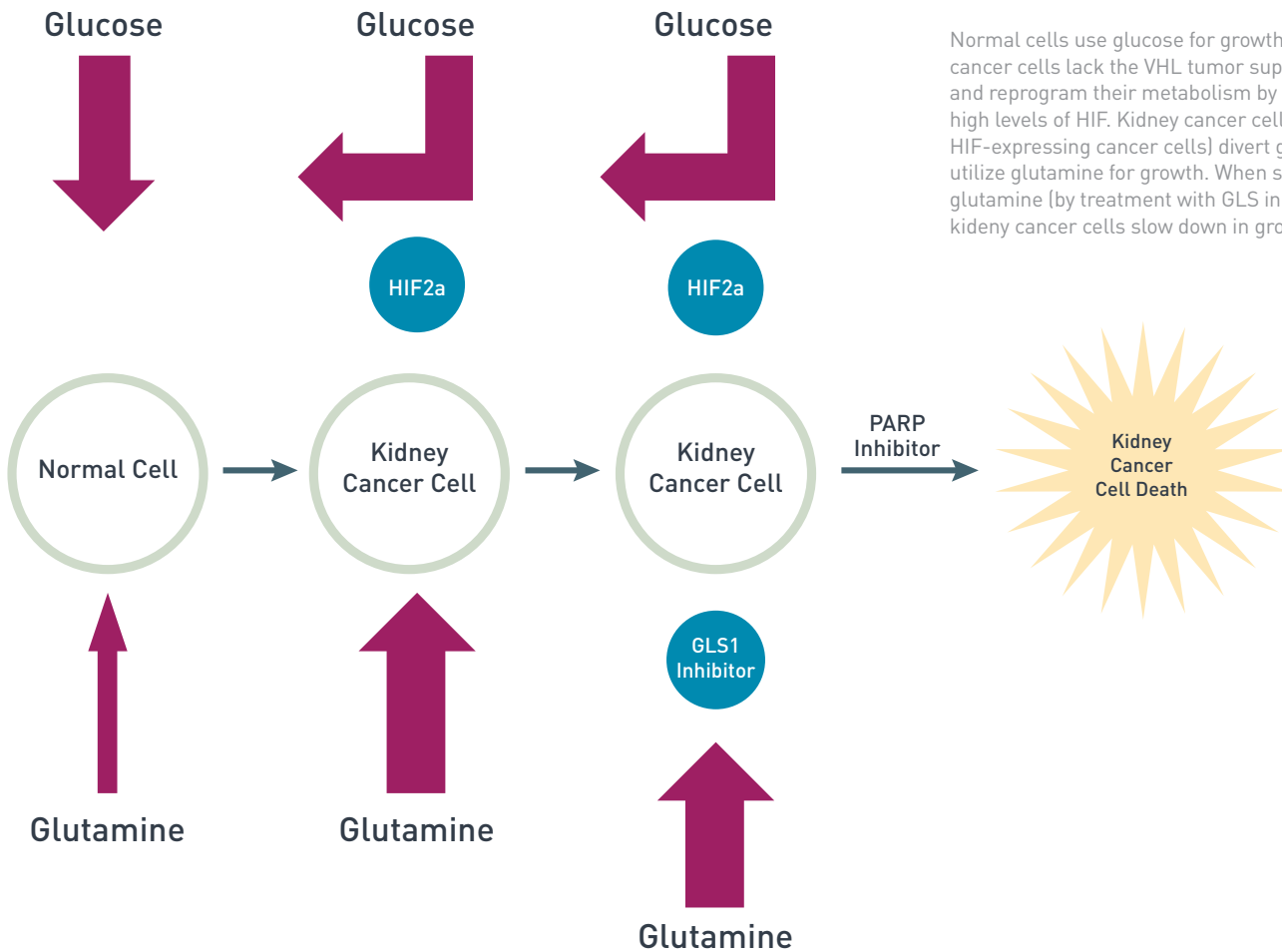
MODELS FOR TREATMENT VIA HIF

Renal cell carcinomas were chosen as a target of study because although they are not typically hypoxic, they act

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Action of glutamine in hypoxic cells

Normal cells use glucose for growth. Kidney cancer cells lack the VHL tumor suppressor gene and reprogram their metabolism by expressing high levels of HIF. Kidney cancer cells (and other HIF-expressing cancer cells) divert glucose and utilize glutamine for growth. When starved from glutamine (by treatment with GLS inhibitors) kidney cancer cells slow down in growth or die.



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like hypoxic cells because they carry a mutation in the von Hippel-Lindau (VHL) tumor suppressor gene. Cell metabolism reprogramming in cancer cells is typically orchestrated by a transcription factor called hypoxia inducible factor (HIF). HIF can also be activated by many cancer-associated mutations, such

as a VHL mutation, which renders the cells VHL deficient. HIF is a major driver of VHL-deficient renal cancer carcinomas and contributes significantly to the growth of many cancers in addition to renal cancer.

Using a series of classic cell assays, Dr. Iliopoulos and his colleagues found that glutaminase

inhibitors, or GLS1, suppress the growth of renal cancer cells that are deficient in VHL, mainly through DNA replication stress. In the absence of glutamine, the cells were unable to produce certain DNA building blocks called pyrimidines, making it impossible for the cells to duplicate their

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DNA. The application of GLS1 also enhanced the production of reactive oxygen species, or ROS, which independently caused DNA replication stress. When Dr. Iliopoulos and his team then filled these GLS1-inhibited cells with the pyrimidine nucleotides, the replication stress was mostly reversed.

Their next step was to see what happened if they prevented the cells from repairing the resulting DNA damage. They tested a combination treatment on the renal cancer cells using GLS1 plus olaparib, an inhibitor of the enzyme poly ADP ribose polymerase (PARP), which plays a role in DNA repair. While either of the two inhibitors in isolation slowed tumor growth, the combination treatment almost completely paralyzed growth of the renal carcinomas. “It very pleasantly surprised us that the cells were that sensitive to these manipulations,” said Dr. Iliopoulos.

Their findings provide a model for treatment of other types of tumors that feature hypoxia or cancer-associated mutations that activate HIF—and possibly also for cancers that show defects in DNA repair pathways. So far Dr. Iliopoulos and his team have had success arresting growth in ovarian, prostate and breast cancers, both in lab cultures and in mouse models. They have

already developed an umbrella clinical protocol for treatment of all four cancer types—renal, ovarian, prostate and breast—and are working on obtaining approval for clinical trials now.



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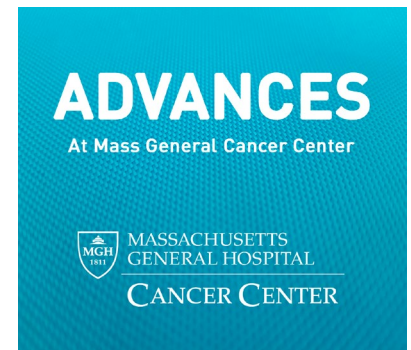
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