“We investigate the mechanisms connecting cell metabolism to growth control by studying an ancient signaling pathway that goes awry in both cancer and type 2 diabetes. By understanding the connection between these diseases, we pave the way to better therapies for both.”

While investigating one of the most commonly mutated genes in lung cancer, LKB1, Shaw’s lab discovered that the gene directly activates a metabolic master switch known as AMPK. This direct connection of LKB1 to AMPK provided a stronger molecular link between cancer and diabetes than was ever known previously. The lab went on to molecularly decode a number of new components of this biochemical pathway that connects nutrition to both cancer and diabetes. In the past two years, their studies have led to the discovery of new therapies for both cancer and type 2 diabetes.

Recently, Shaw’s group found that AMPK initiates a cellular recycling process known as autophagy, which allows cells to dispose of toxins, by activating an enzyme known as ULK1. To test the effects on autophagy of deregulating these enzymes, the group focused on large intracellular structures called mitochondria, whose role is to generate energy. Mitochondria are easily damaged in detoxifying tissues like liver, and defective mitochondria are turned over through a special form of autophagy called mitophagy. The researchers found that the ability to recycle their defective mitochondria allowed cells to survive starvation better. This work suggests that drugs regulating ULK1 itself may be useful for treating certain forms of cancer or metabolic disease.

The Shaw lab also discovered another new set of AMPK targets, but in this case focused on targets that may be key for diabetes, knowing that AMPK is one of the critical enzymes controlled by the widely used diabetes drug metformin. They discovered that proteins known as histone deacetylases (HDACs) are regulated by AMPK and play a vital role in directing glucose production in the liver. Normally, in response to fasting, hormonal cues tell the liver to produce its own glucose from scratch to keep the body alive, and these HDACs are required in liver cells for the hormone to transmit that signal. This new finding—that HDACs play a critical role in diabetes—further connects metabolic disease with cancer. Prior to this, a number of HDAC inhibitor drugs were being evaluated in clinical trials as potential treatments for cancer, some of which now may find utility in the treatment of diabetes.

For more information, please visit www.salk.edu/faculty/shaw

From left to right: Reuben Shaw, Daniel Garcia, Bibiana Ferreira, Dan Egan, Debbie Vasquez, Matthew Chun, Portia Lombardo, Rob Svensson, Nate Young, Rebecca Kohnz, Erin Toyama, Maria Mihaylova, Benjamin Stein