Shining light on orphan receptors

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Group photo of postdoc Álvaro Inglés-Prieto, Ph.D. student Eva Reichhart and Assistant Professor Harald Janovjak (from left to right) standing at IST Austria. Credit: IST Austria, 2015

Light has been used for the first time to activate a receptor for which the

compound binding and controlling it naturally is unknown, as reported in *Nature Chemical Biology* today. A team of scientists including Harald Janovjak, Assistant Professor at the Institute of Science and Technology Austria (IST Austria), Álvaro Inglés-Prieto, first author and postdoc in the Janovjak group, and Eva Reichhart, PhD student in the Janovjak group, using libraries and cells from the Medical University of Vienna and the CeMM, Vienna, employed their novel application of optogenetics to identify a new compound that inhibits the orphan receptor ROS1, which has been linked to several forms of cancer.

The authors demonstrate the power of a new all-optical screening method by carrying out a screen against 'orphan' receptors. These are receptors for which the natural ligand is currently unknown. Therefore, orphan receptors can only be activated in cells using a synthetic approach, such as the artificial light switch introduced in this study. Using the optical screening method, the researchers identify a new active compound that binds to and inhibits ROS1, an orphan receptor which plays a role in a variety of cancers. The inhibitory compound AV-951, also known as Tivozanib, has already been studied in clinical trials and has the potential to treat many forms of cancer.

In their novel, "all-optical", screening method, the researchers use light as both the activator and the read-out of cellular signaling. No assay chemicals are required, which limits the number of steps required in carrying out the screen. By using LEDs, optical activation is both cheap and highly specific.

Light activation has already revolutionized neuroscience research. This study, for the first time, used light to control a protein for which the natural mode of activation is unknown. In addition, this entirely new use for light activation expands optogenetics into the field of drug discovery.

More information: Álvaro Inglés-Prieto et al. Light-assisted small-

molecule screening against protein kinases, *Nature Chemical Biology* (2015). DOI: 10.1038/nchembio.1933