HARVARD UNIVERSITY
Office of Technology Development

Platform Technology for Small Molecule Modulators of Autophagy

Principal Investigator

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Technology

Autophagy is an essential lysosomal degradation pathway for the breakdown of intracellular proteins and organelles. It is an evolutionarily conserved, fundamental process operating as a homeostatic mechanism in all eukaryotic cells. During this process, an autophagosome encloses the cellular component to be degraded and fuses with a lysosome which degrades the component.

Discoveries from the Yuan lab provide insights into the global regulation of autophagy and pinpoint potential new targets for manipulation of autophagy in human disease. This platform includes:

- A suite of high throughput screening assays used to identify genes involved in the regulation of autophagy as well as the downstream molecular pathways
- A small molecule screen developed and used to identify modulators of autophagy
- A series of new targets within the autophagy pathway
- Tool compounds for both stimulation and inhibition of autophagy
- A proprietary small molecule autophagy inhibitor demonstrating activity in disease models, with additional small molecules currently designed by a med chem contractor

High throughput screening assays: The Yuan lab developed an image-based primary assay to screen a genome-wide human RNAi library. Close to a dozen secondary screens were then used to elucidate the molecular pathways involved in the regulation of autophagy by these candidate genes. Results from these screens were integrated to identify new autophagy targets. The lab compared the candidate genes to known genes. Known modulators are available for a signficant number of these genes and the Yuan lab is initiating an effort to use those as tool compounds to further study the role of these targets and the effects of their modulation in various disease models. Ultimately, the lab's plan is to focus on the best validated targets and develop small molecule inhibitors for them.

Small molecule screening assay: The lab also developed a small molecule screening assay to identify specific autophagy modulators. This assay detects long-lived protein degradation, enabling the lab to distinguish those compounds that induce autophagic degradation from those that nonspecifically increase levels of the measured protein. Using this screen, the lab identified several previously known compounds further shown to induce autophagy, and a novel small molecule inhibitor of autophagy.

Proprietary small molecule: The small molecule screen identified a proprietary small molecule, C43, shown to be an effective inhibitor of autophagy in a cell based assay. Medicinal chemistry studies are underway to synthesize additional C43 derivatives to identify an optimized inhibitor of autophagy. The derivatives will be tested for their efficacy in inhibiting autophagy and their *in vivo* metabolic stability. Preliminary *in vivo* evidence in an animal model of pancreatitis demonstrates that C43 significantly reduces the levels of autophagy induced by cerulein injection. The lab plans to collaborate with a CRO to further test C43 derivatives as stand-alone agents and with an anti-angiogenesis drug in animal models of cancer and acute pancreatitis. Also under way is a collaboration targeted at demonstrating the effect of C43 in treating viral infection. The small molecule screen also identified a series of autophagy inducers with identified targets. Medicinal chemistry has improved one series with the best derivatives having IC50 at ~0.2 μM.

Market and Applications

Dysfunction of autophagy has been directly associated with neurodegeneration, cancer, pancreatitis, and inflammation. Modulation of this pathway, therefore, is a novel therapeutic approach to a wide variety of diseases:

- **Autophagy activators for the treatment of neurodegenerative diseases**: Down-regulation of autophagy contributes to neurodegeneration by increasing the accumulation of misfolded proteins, a hallmark of many neurodegenerative diseases. Compounds that stimulate autophagy in neurons and other cells may be used to treat a host of neurodegenerative diseases, such as ALS, Huntington's, Alzheimer's and Parkinson's disease.

- **Autophagy modulators for the treatment of cancers**: Activation of autophagy has been shown to promote tumor cell survival under metabolic stress. The Yuan lab further demonstrated that inhibition of autophagy selectively kills a subset of cancer cells. Many cancer therapeutics as well as radiation therapy have been shown to induce autophagy, which is thought to promote stress protection and resistance to these DNA-damaging therapies. Inhibition of therapy-induced autophagy, therefore, may provide a novel strategy for the treatment of cancers.

- **Autophagy inhibitors for the treatment of pancreatitis**: Autophagy has been shown to play an important role in mediating cellular damage induced by acute pancreatitis. Since autophagy exerts a detrimental effect on pancreatic cells, inhibitors of autophagy may provide important new, first-in-class therapeutics for acute pancreatitis.

- **Autophagy inhibitors for the treatment of viral infection**: Autophagy machinery is hijacked by a subset of important pathological viruses which use autophagosomes in a part of their reproductive cycle. Thus, autophagy inhibitors have the potential as general anti-viral agents. The effect of C43 in viral models is currently under study by the Yuan lab and a collaborator.

Product Advantages

Modulation of the autophagy pathway is a novel therapeutic approach to a wide variety of diseases. For example, it may provide a novel strategy for the treatment of cancers and neurodegenerative diseases, as well as new, first-in-class therapeutics for acute pancreatitis.

Licensing Opportunity:

An IP portfolio supporting the discoveries made by the Yuan lab is available for licensing. The platform technology is proposed as the basis for a collaborative sponsored research program with the Yuan lab.

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