

151 Proteostasis PI5P4 kinase Inhibitors

► Asset Overview

Product Type	Small molecule
Indication	CNS Diseases
Current Stage	Hit to Lead
Target(MoA)	Inhibit of the PI5P4K enzymes
Brief Description	PI(3)P, the product of VPS34, regulates canonical autophagy; however, mammalian cells can produce autophagosomes through enigmatic noncanonical VPS34-independent pathways. Vicinanza et al. show that PI(5)P can regulate autophagy, even in cells where VPS34 is compromised and acts via PI(3)P effectors. This provides a mechanistic explanation for forms of noncanonical autophagy.
Organization	The Alborada Drug Discovery Institute

► Differentiation

□ Autophagy in clinical neurodegenerative diseases

- Neurodegenerative diseases are a major cause of progressive clinical disability causing impaired quality of life with consequences not only for the patient, but also their carer and the state. The greatest unmet need is the availability of therapeutic interventions that are effective in slowing or preventing progression of the neurodegeneration
- Autophagy is one of the major intracellular machinery to eliminate misfolded proteins and maintain proteostasis. Dysregulated autophagy is increasingly considered to play key roles in most neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis
- The regulation of autophagy is proposed as a potential therapeutic avenue for these diseases

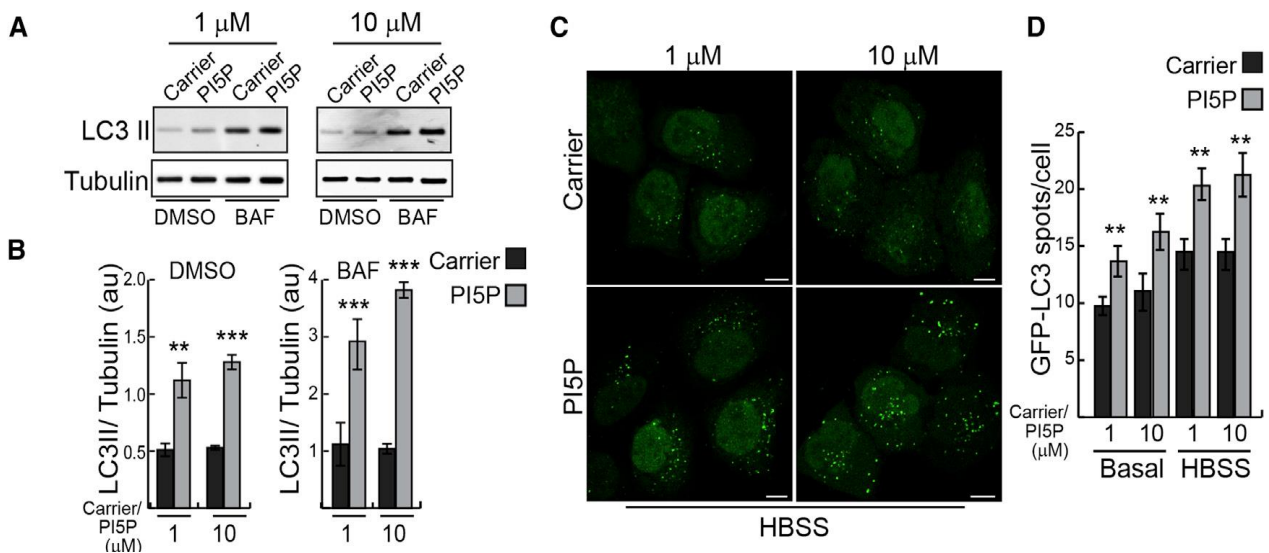
□ PI(5)P Regulates Autophagosome Biogenesis

- PI(5)P positively regulates autophagy
- PIKfyve and PI5P4K2 enzymes are drug-treatable targets and suppression of PI5P4K2's activity increased the clearance of disease-associated autophagic substrates
- Autophagy induction via other signaling effectors has benefits in a wide range of neurodegenerative diseases caused by aggregate-prone intracytoplasmic proteins, like Huntington's and Parkinson's diseases
- Two representative tool compounds show excellent kinase selectivity – hitting only 3-4 other kinases in a panel of 140 protein and 19 lipid kinases

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► Key Data

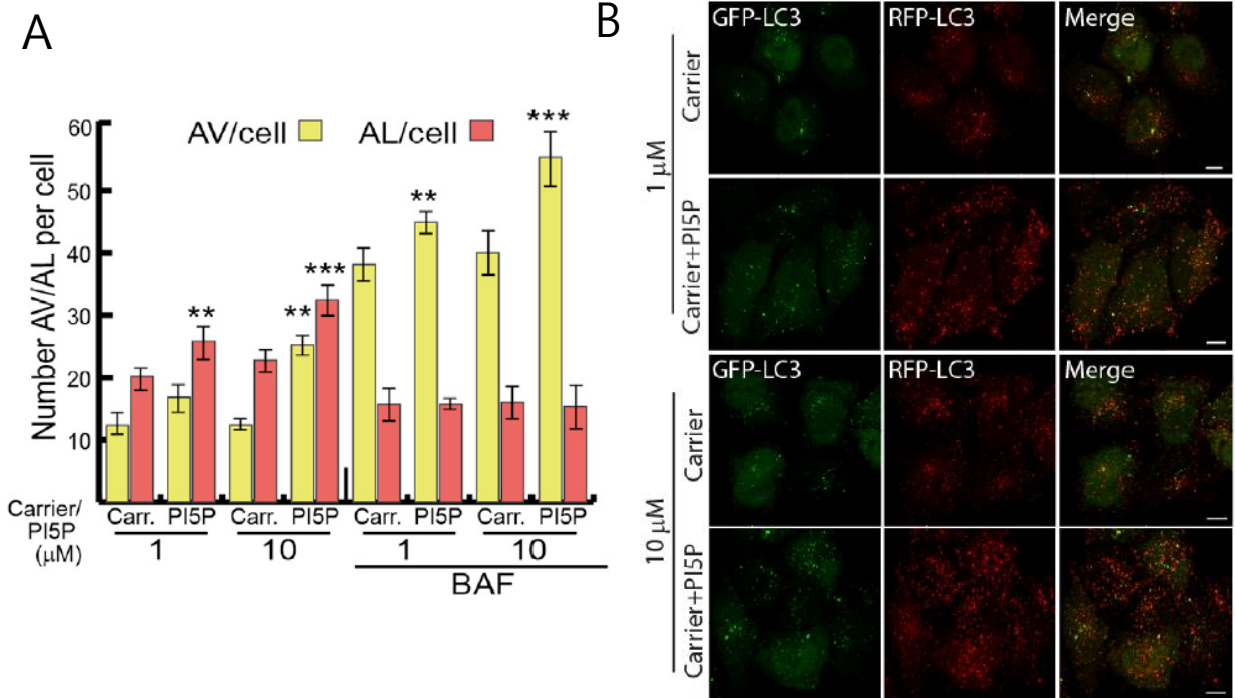
PI(5)P Regulates Autophagosome Biogenesis



Consistent with a role in autophagosome synthesis, PI(5)P increased LC3-II levels, in an apparently dose-dependent manner, when we blocked LC3-II clearance by inhibiting autophagosome-lysosome fusion using Bafilomycin A1 (BAF) (A and B), and resulted in increased numbers of GFP-LC3 puncta (autophagosomes) in both nutrient-replete media and Hank's balanced salt solution (HBSS) (amino-acid/serum starvation and 1 g/l D-glucose, compared to 4.5 g/l in Dulbecco's modified Eagle's medium [DMEM]) (C and D).

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PI(5)P Triggers Autophagy in the Absence of VPS34 Activation



PI(5)P loading in cells stably expressing mRFP-GFP tandem fluorescent-tagged LC3 increased the numbers of autophagosomes and autolysosomes (A and B)

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► Intellectual Property

Patent No.	
Application Date	
Status	
Country	

► Contact Information

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