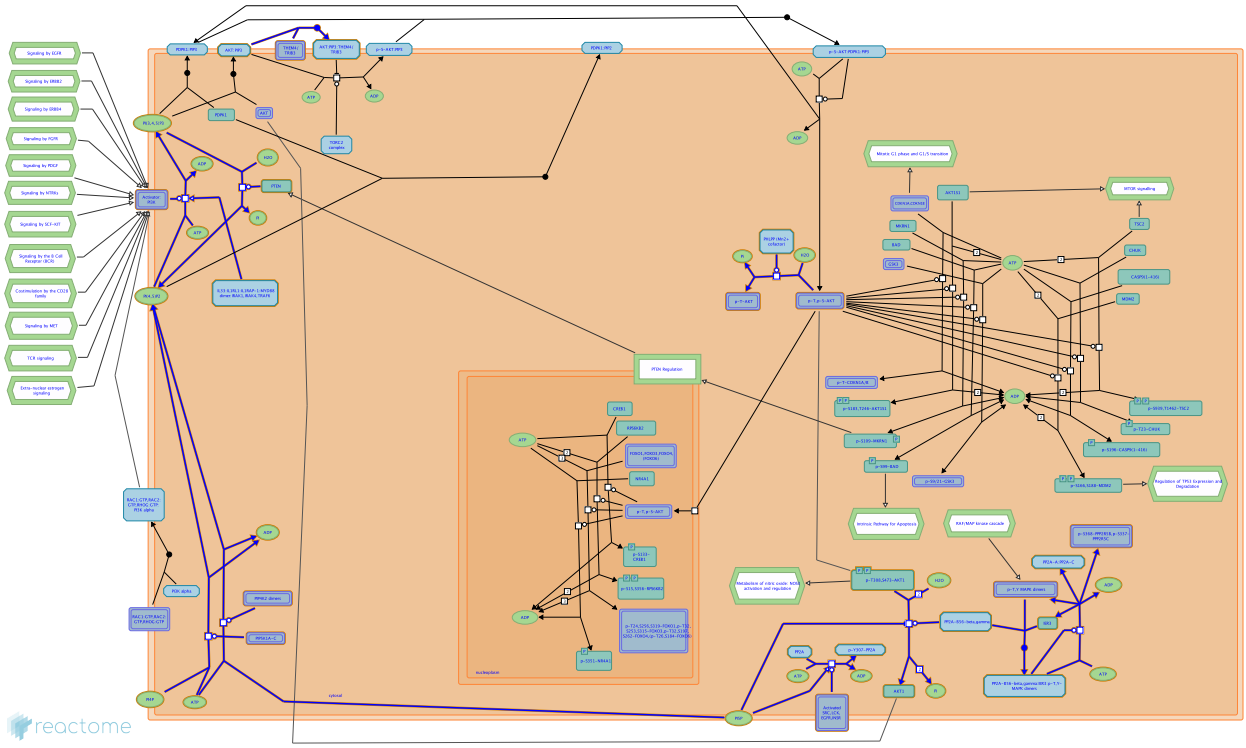
Negative regulation of the PI3K/AKT network



Annibali, D., Greene, LA., Kriplani, N., Leslie, N., Matthews, L., Nasi, S., Orlic-Milacic, M., Porteu, F., Thorpe, L., Wakelam, M., Yuzugullu, H., Zhao, JJ.

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10/09/2021

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

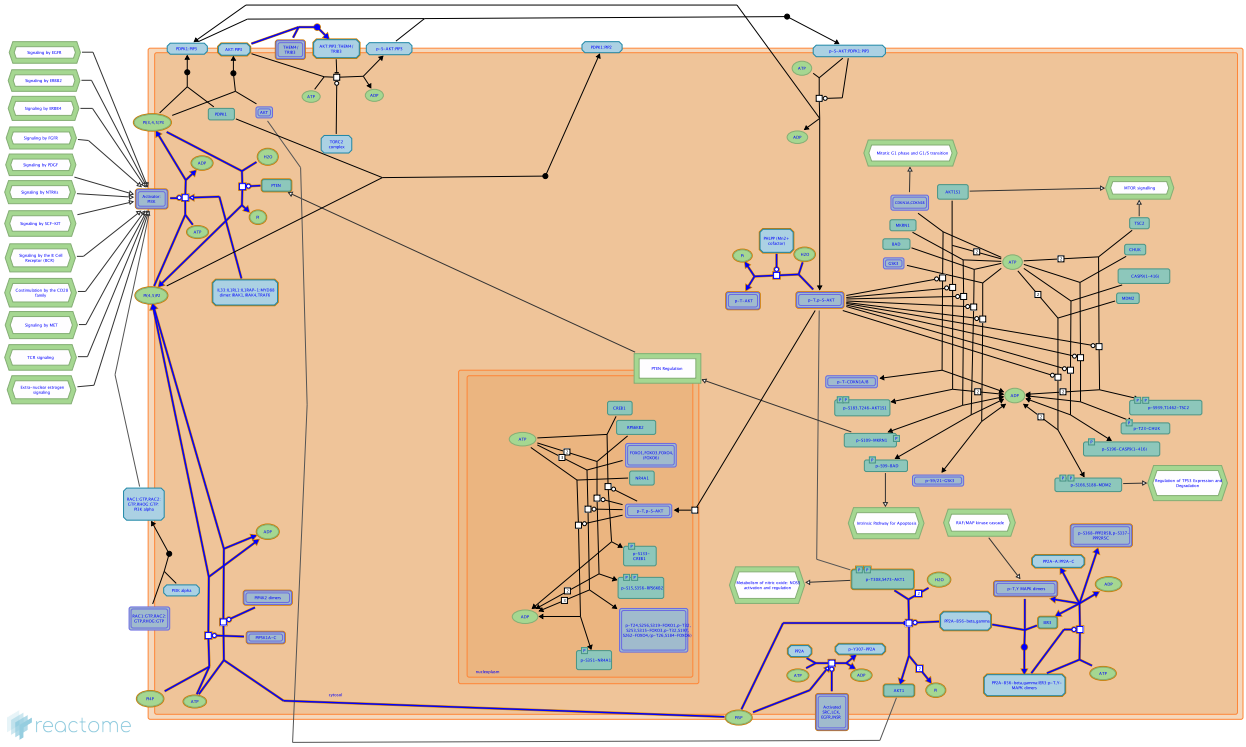
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Negative regulation of the PI3K/AKT network ↗

Stable identifier: R-HSA-199418



The PI3K/AKT network is negatively regulated by phosphatases that dephosphorylate PIP3, thus hampering AKT activation.

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
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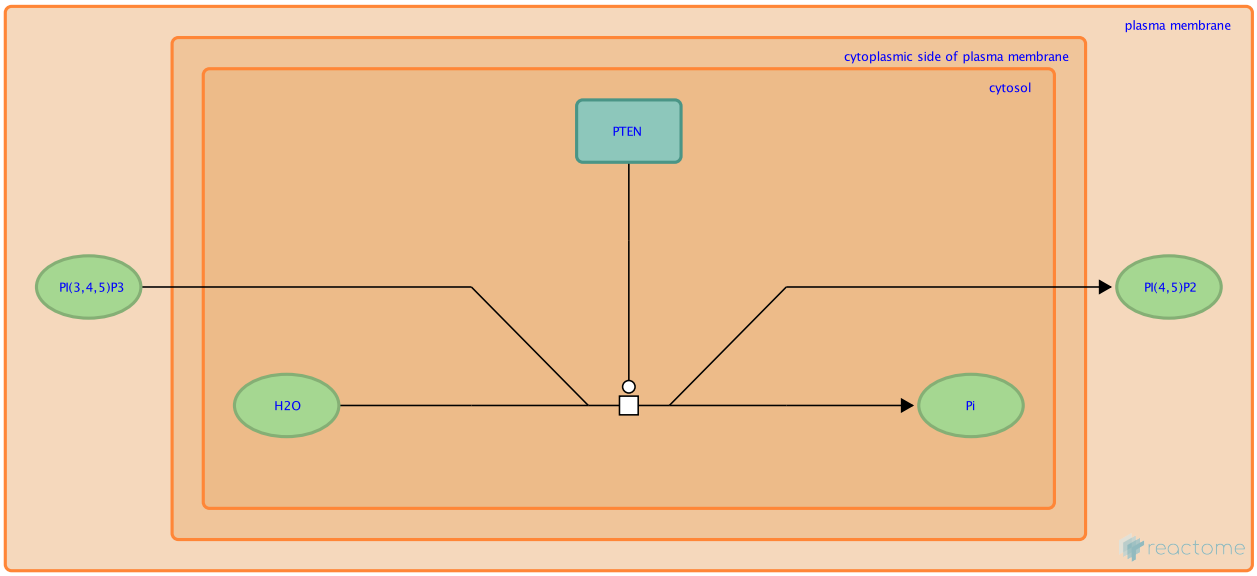
PTEN dephosphorylates PIP3 ↗

Location: Negative regulation of the PI3K/AKT network

Stable identifier: R-HSA-199456

Type: transition

Compartments: cytosol, plasma membrane



At the plasma membrane, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase aka phosphatase and tensin homolog (PTEN) dephosphorylates phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) to phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) (Maehama & Dixon 1998, Myers et al. 1998, Das et al. 2003). The PI3K network is negatively regulated by phospholipid phosphatases that dephosphorylate PIP3, thus hampering AKT activation (Myers et al. 1998). The tumour suppressor PTEN is the primary phospholipid phosphatase.

Early studies indicated that magnesium ion, Mg2+, was needed for the catalytic activity of PTEN isolated from bovine thymus (Kabuyama et al. 1996). Subsequent studies have shown that PTEN was catalytically active in buffers free of magnesium and magnesium was not detected as part of the PTEN crystal (Lee et al. 1999).

Literature references

Das, S., Dixon, JE., Cho, W. (2003). Membrane-binding and activation mechanism of PTEN. *Proc Natl Acad Sci U S A, 100*, 7491-6. ↗

Maehama, T., Dixon, JE. (1998). The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. *J Biol Chem, 273*, 13375-8. ↗

Myers, MP., Pass, I., Batty, IH., van der Kaay, J., Stolarov, JP., Hemmings, BA. et al. (1998). The lipid phosphatase activity of PTEN is critical for its tumor supressor function. *Proc Natl Acad Sci U S A, 95*, 13513-8. ↗

Lee, JO., Yang, H., Georgescu, MM., Di Cristofano, A., Maehama, T., Shi, Y. et al. (1999). Crystal structure of the PTEN tumor suppressor: implications for its phosphoinositide phosphatase activity and membrane association. *Cell, 99*, 323-34. ↗

Kabuyama, Y., Nakatsu, N., Homma, Y., Fukui, Y. (1996). Purification and characterization of the phosphatidylinositol-3,4,5-trisphosphate phosphatase in bovine thymus. *Eur. J. Biochem., 238*, 350-6. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
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2012-07-18	Revised	Orlic-Milacic, M.
2012-08-13	Reviewed	Zhao, JJ., Yuzugullu, H., Thorpe, L.
2016-09-30	Reviewed	Leslie, N., Kriplani, N.

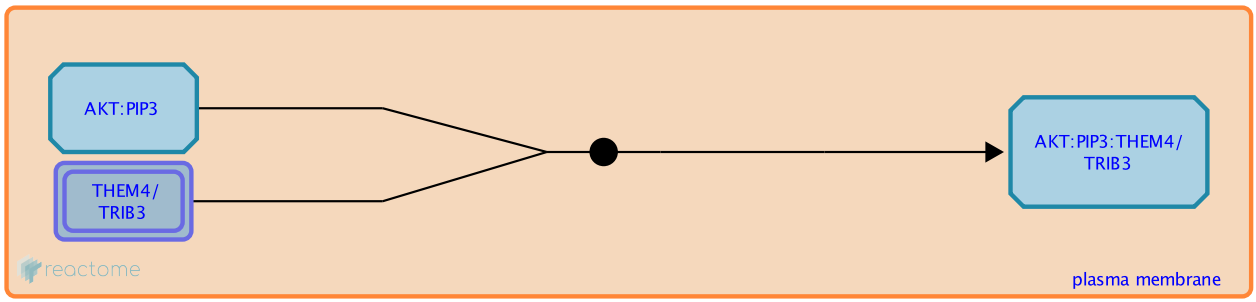
THEM4 (CTMP) and/or TRIB3 inhibit AKT phosphorylation ↗

Location: Negative regulation of the PI3K/AKT network

Stable identifier: R-HSA-199443

Type: binding

Compartments: plasma membrane



The phosphorylation of membrane-recruited AKT at threonine and serine can be inhibited by direct binding of two different proteins, C-terminal modulator protein (THEM4 i.e. CTMP), which binds to the carboxy-terminal tail of AKT (Maira et al. 2001), or Tribbles homolog 3 (TRIB3), which binds to the catalytic domain of AKT (Du et al. 2003).

Literature references

Maira, SM., Galetic, I., Brazil, DP., Kaech, S., Ingley, E., Thelen, M. et al. (2001). Carboxyl-terminal modulator protein (CTMP), a negative regulator of PKB/Akt and v-Akt at the plasma membrane. *Science, 294*, 374-80. ↗

Du, K., Herzig, S., Kulkarni, RN., Montminy, M. (2003). TRB3: a tribbles homolog that inhibits Akt/PKB activation by insulin in liver. *Science, 300*, 1574-7. ↗

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2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.
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2012-08-03	Edited	Matthews, L.
2012-08-13	Reviewed	Zhao, JJ., Yuzugullu, H., Thorpe, L.

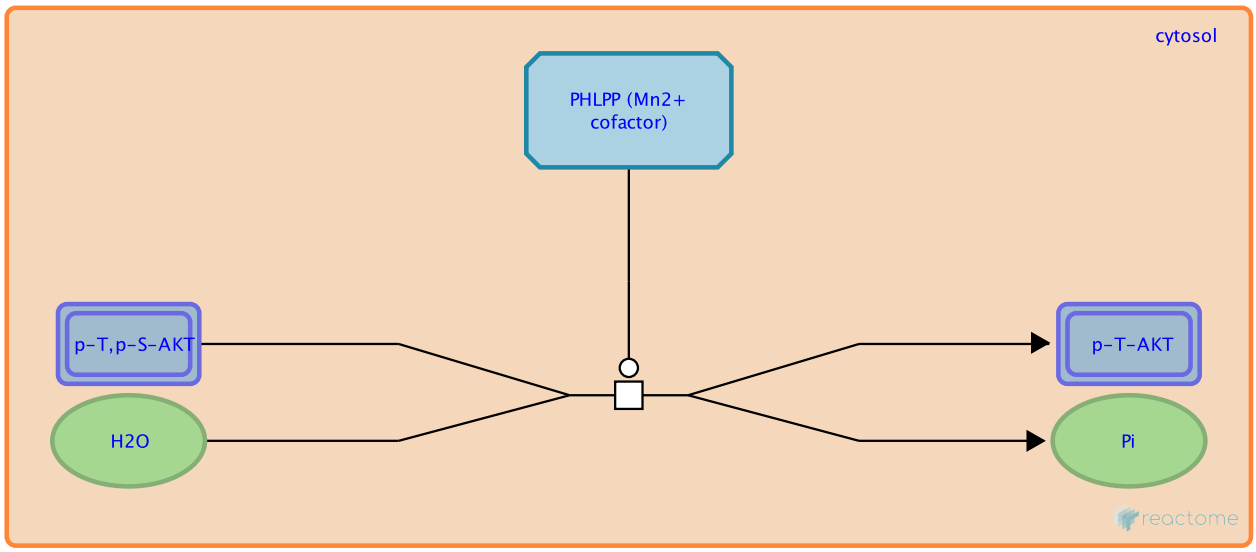
PHLPP dephosphorylates S473 in AKT ↗

Location: Negative regulation of the PI3K/AKT network

Stable identifier: R-HSA-199425

Type: transition

Compartments: cytosol



The PH domain leucine-rich repeat-containing protein phosphatases, PHLPP1 (Gao et al. 2005) and PHLPP2 (Brognard et al. 2007) can specifically dephosphorylate the serine residue and inactivate AKT.

Literature references

Gao, T., Furnari, F., Newton, AC. (2005). PHLPP: a phosphatase that directly dephosphorylates Akt, promotes apoptosis, and suppresses tumor growth. *Mol Cell, 18*, 13-24. ↗

Brognard, J., Sierecki, E., Gao, T., Newton, AC. (2007). PHLPP and a second isoform, PHLPP2, differentially attenuate the amplitude of Akt signaling by regulating distinct Akt isoforms. *Mol. Cell, 25*, 917-31. ↗

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2006-10-10	Authored	Annibali, D., Nasi, S.
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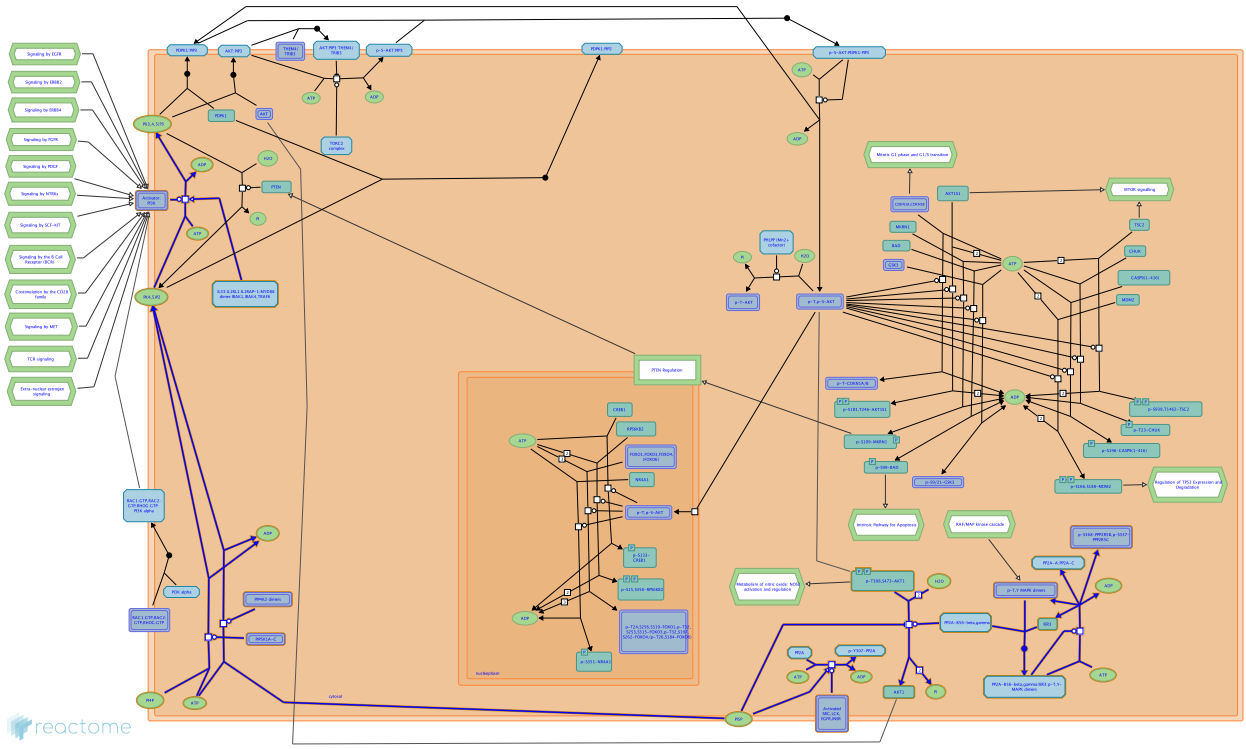
PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling ↗

Location: Negative regulation of the PI3K/AKT network

Stable identifier: R-HSA-6811558



Phosphatidylinositol-5-phosphate (PI5P) may modulate PI3K/AKT signaling in several ways. PI5P is used as a substrate for production of phosphatidylinositol-4,5-bisphosphate, PI(4,5)P2 (Rameh et al. 1997, Clarke et al. 2008, Clarke et al. 2010, Clarke and Irvine 2013, Clarke et al. 2015), which serves as a substrate for activated PI3K, resulting in the production of PIP3 (Mandelker et al. 2009, Burke et al. 2011). The majority of PI(4,5)P2 in the cell, however, is produced from the phosphatidylinositol-4-phosphate (PI4P) substrate (Zhang et al. 1997, Di Paolo et al. 2002, Oude Weernink et al. 2004, Halstead et al. 2006, Oude Weernink et al. 2007). PIP3 is necessary for the activating phosphorylation of AKT. AKT1 can be deactivated by the protein phosphatase 2A (PP2A) complex that contains a regulatory subunit B56-beta (PPP2R5B) or B56-gamma (PPP2R5C). PI5P inhibits AKT1 dephosphorylation by PP2A through an unknown mechanism (Ramel et al. 2009). Increased PI5P levels correlate with inhibitory phosphorylation(s) of the PP2A complex. MAPK1 (ERK2) and MAPK3 (ERK1) are involved in inhibitory phosphorylation of PP2A, in a process that involves IER3 (IEX-1) (Letourneux et al. 2006, Rocher et al. 2007). It is uncertain, however, whether PI5P is in any way involved in ERK-mediated phosphorylation of PP2A or if it regulates another PP2A kinase.

Literature references

Rameh, LE., Tolias, KF., Duckworth, BC., Cantley, LC. (1997). A new pathway for synthesis of phosphatidylinositol-4,5-bisphosphate. *Nature, 390*, 192-6. ↗

Clarke, JH., Emson, PC., Irvine, RF. (2008). Localization of phosphatidylinositol phosphate kinase IIgamma in kidney to a membrane trafficking compartment within specialized cells of the nephron. *Am J Physiol Renal Physiol, 295*, F1422-30. ↗

Clarke, JH., Wang, M., Irvine, RF. (2010). Localization, regulation and function of type II phosphatidylinositol 5-phosphate 4-kinases. *Adv Enzyme Regul, 50*, 12-8. ↗

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Clarke, JH., Giudici, ML., Burke, JE., Williams, RL., Maloney, DJ., Marugan, J. et al. (2015). The function of phosphatidylinositol 5-phosphate 4-kinase Î³ (PI5P4KÎ³) explored using a specific inhibitor that targets the PI5P-binding site. *Biochem. J., 466*, 359-67. ↗

Editions

2015-12-22	Authored, Edited	Orlic-Milacic, M.
2016-02-08	Reviewed	Porteu, F.

Table of Contents