ESRF	**Experiment title:** Cambridge MRC Block Allocation Group Structural studies of inhibition of phosphoinositide 3-kinase	**Experiment number:** LS1669
Beamline: ID14-1	**Date of experiment:** from: 15/5/00 to: 17/5/00	**Date of report:** 28/8/00
Shifts: 3	**Local contact(s):** M. VanRaaj	*Received at ESRF:*

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Report:

The specific phosphoinositide 3-kinases inhibitors wortmannin and LY294002 have been invaluable tools for elucidating the roles of these enzymes in signal transduction pathways. The X-ray crystallographic structures of PI 3-kinase γ bound to these lipid kinase inhibitors and to the broad-spectrum protein kinase inhibitors quercetin, myricetin and staurosporine reveal how these compounds fit into the ATP-binding pocket. In the previous allocation period we determined the structures of complexes of PI3K with wortmannin and LY294002. In the current period we extended this study to include a 2.7 Å resolution complex with the broad-spectrum kinase inhibitory flavonoid, myricetin. Surprisingly, LY294002 and the lead compound on which it was designed, quercetin, as well as the closely related flavonoid myricetin bind PI 3-kinase in remarkably different orientations that are related to each other by 180° rotations. Staurosporine/PI 3-kinase interactions are reminiscent of low-affinity protein kinase/staurosporine complexes. The results provide a rich basis for development of isoform-specific PI 3-kinase inhibitors with therapeutic potential.

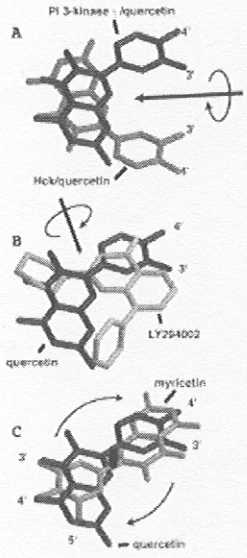

Illustration of the relationships of the orientation of the chromone moieties to each other in the various complexes observed. For each panel, the structures containing the compounds were superimposed on each other using the Cα coordinates of the N- lobe of the catalytic domain. The arrow indicates the location of the approximate dyad axis relating one structure's binding mode to another. (**A**) quercetin binding in the protein kinase Hck as compared with PI 3-kinase γ. (**B**) quercetin binding in PI 3-kinase γ as compared to LY294002 binding to PI 3-kinase γ. (**C**) myricetin binding to PI 3-kinase γ as compared with quercetin binding to PI 3-kinase γ.

Below: A portion of the catalytic domain of PI3K shown with covalently-attached wortmannin superimposed on its electron density.