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Selected Publication

Hegarat N, Vesely C, Vinod PK, Ocasio C, Peter N, Gannon J, Novak B, Hochegger H, (2014) PP2A/B55 and Fcp1 regulate Greatwall and Ensa dephosphorylation during mitotic exit. *PLoS Genet* 10: e1004004

Research Aims and Interests

**Developing Greatwall Kinase as A Target for Cancer Therapy - Hochegger lab in Collaboration with Pearl Lab and Peter Schmid (Barts Cancer Centre)**

My lab is investigating the regulatory mechanism that control mitotic entry. We are particularly interested in the regulation and function of Greatwall kinase that plays an important role in inhibiting mitotic phosphatases that counteract Cdk1/cyclinB. Apart from its role in cell cycle control no other functions of Greatwall have so far been reported.

We have found that this kinase is overexpressed in triple negative breast cancer and that its over-expression correlates with poor prognosis. To analyse its function in triple negative breast cancer we are using an inducible shRNA approach in various breast cancer cell models. We found that severe depletion of this kinase to levels of less than 10% does not affect the proliferation of most cells, but has dramatic effects on colony formation capability and growth in xenograft models. This suggests that Greatwall kinase has a novel role in cancer cells that could be exploited for therapeutic purposes. To further investigate this function we are using a combination of genetic and proteomic approaches in tissue culture and xenograft models. In collaboration with the Pearl lab, we have set up tools and assays for inhibitor screening and solved the structure of the Greatwall kinase domain. This allowed us to identify a promising hit molecule that can be further developed to a lead inhibitor. This combination of target validation and small molecule development should allow us to move this project into a clinical setting to investigate the therapeutic benefit of Greatwall kinase inhibition in triple negative breast cancer and possibly other Greatwall dependent cancer types.