VASCULAR DISEASE, VASCULITIS

A PRE-CLINICAL DRUG DISCOVERY CAMPAIGN FOR STURGE-WEBER SYNDROME: A COMPUTATIONAL MOLECULAR MODELING APPROACH FOR DRUG REPURPOSING OF NOVEL GNAQ INHIBITORS

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Background: Sturge-Weber Syndrome is a rare neurocutaneous disorder affecting the skin, eye and brain due to capillary malformations. Current medical interventions are limited. Discovery of GNAQ-activating mutations in capillary endothelial cells illuminates a potentially targetable mechanism. GNAQ is the α-subunit of a heterotrimeric G protein that propagates a signaling cascade upon activation via GDP dissociation/GTP association. p.R183Q mutation is thought to increase rate of GDP dissociation to enhance GTP binding and Gα signalling, creating capillary malformations. Only two GNAQ-selective inhibitors have been reported: YM-254890 and FR900359, both cyclic depsipeptides. However, no non-peptide small molecule GNAQ inhibitors exist. Unlike peptides that are immunogenic and less stable, small molecules have superior pharmacokinetic properties. Thus, computational drug repurposing approaches exploiting the known drug chemical space are desirable.

Objective: To determine critical structural features of GNAQ in the presence of bound YM-254890 inhibitor and identify candidate drugs for repurposing using molecular modelling.

Materials and Methods: YM-254890 inhibitor-bound GNAQ wildtype crystal structure was used for molecular modelling. Molecular dynamics (MD) simulations were conducted for apo-GNAQ (no inhibitor) and YM-GNAQ. Docking and subsequent MD simulations of FDA-approved or withdrawn drugs was performed to identify potential drug repurposing candidates.

Results: 2.5-microsecond timepoint MD simulation showed YM-254890 to stabilize GNAQ such that the interdomain distance (distance between helical and GTPase domains) becomes smaller, thus preventing GDP release and GTP binding. Docking recapitulated the

crystal structure binding pose of YM-254890 as positive control. Docking of an anti-diabetic drug and subsequent 2-microsecond MD simulation revealed it to also stabilize GNAQ interdomain distance.

Conclusions: We present for the first time a computational study of GNAQ bound to the inhibitor YM-254890 with MD simulations extending beyond 1 microsecond. Using YM-GNAQ as our model, we identified an anti-diabetic small molecule drug as a repurposing candidate for GNAQ inhibition through docking and MD simulations.