SFB 1078

Protonation Dynamics in Protein Function

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Freie Universität Berlin

Hörsaal B

Colloquium

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Screening the Calibr-Scripps ReFrame library to discover new drugs for treating sickle cell disease

Although sickle cell disease (SCD) can be cured by stem cell transplantation, with curative gene therapies on the horizon, all are expensive and require advanced medical facilities. Consequently, these treatments will not be available to the vast majority of patients suffering from this disease for many years. What is urgently needed now is an inexpensive oral drug to add to hydroxyurea, the only successful anti-sickling drug approved by the FDA. Here we report results of the first phase of our screen of the 12,657 compounds of the Scripps ReFrame drug repurposing library using a recently developed high throughput assay to measure sickling times following deoxygenation to 0% oxygen of red cells from sickle trait individuals. The ReFrame library is a very important compound collection because the vast majority are either FDA-approved drugs or have been tested in clinical trials. From dose-response measurements, 130 of the 12,657 compounds exhibit statistically significant anti-sickling at concentrations ranging from 30 nM to 10 M. Compounds anti-sickling for trait cells are also anti-sickling for SCD cells. As many as 20 of the 130 anti-sickling compounds are potential drugs. This number is based on a comparison of anti-sickling concentrations of the compounds with free concentrations of oral drugs in the Physicians' Desk Reference. Moreover, the expected therapeutic effect for each level of inhibition can be predicted from measurements of sickling times for various sickle syndromes. Our results should motivate others to develop one or more of these 130 compounds into drugs for treating SCD.

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