Natural small-molecule sappanone A selectively targets IMPDH2 to inhibit neuroinflammation

With the support by the National Natural Science Foundation of China, a study by the research group led by Prof. Tu Pengfei (屠鹏飞) from the School of Pharmaceutical Sciences, Peking University demonstrates that natural small-molecule sappanone A directly targets IMPDH2 to block its activity, resulting in neuroinflammatory inhibition with less side-effects, which was published in *PANS* (2017, 114(29): E5986－E5994).

Inosine monophosphate dehydrogenase (IMPDH) is an attractive target for immunosuppressive agents. Currently, small-molecule inhibitors do not show good selectivity for different IMPDH isoforms (IMPDH1, IMPDH2), resulting in some adverse effects which limit their use. Tu's group identified Cys140 as an isoform-selective druggable binding site for IMPDH2 inhibition, but not for IMPDH1, which provides a pivotal basis of anti-neuroinflammation therapy via selectively targeting IMPDH2.

Based on high throughput screening, their group identified a natural bioactive small-molecule sappanone A (SA) with significant anti-neuroinflammation effect from traditional Chinese herb *Caesalpiniasappan* L. Then, they chemically converted SA into functional probes via attaching biotin affinity tag or Cy3 fluorescence tag to SA molecular skeleton. Consequently, they successfully identified the direct cellular target of SA as IMPDH2, which plays a key role in immunoregulation and inflammatory response.

Further studies revealed that SA specifically targeted IMPDH2 by interacting with cysteineresidue 140 (Cys140) as a selective druggable site. Upon covalently binding to Cys140, SA exerted an allosteric regulation to block the catalytic pocket of IMPDH2 and further induced IMPDH2 inactivation. Then, SA-mediated IMPDH2 inhibition caused an effective suppression of several down-stream inflammation signaling pathways including IKKβ-NF-κB and p38 MAPK. However, SA did not covalently bind to IMPDH1.

Collectively, their group discovered Cys140 as a novel and druggable site in IMPDH2 using natural small-molecule SA. Cys140 can be selectively targeted to inhibit IMPDH2, which provides great potential for the development of therapy agents in clinical trials for autoimmune and neuroinflammatory diseases with less unfavorable tolerability profile.

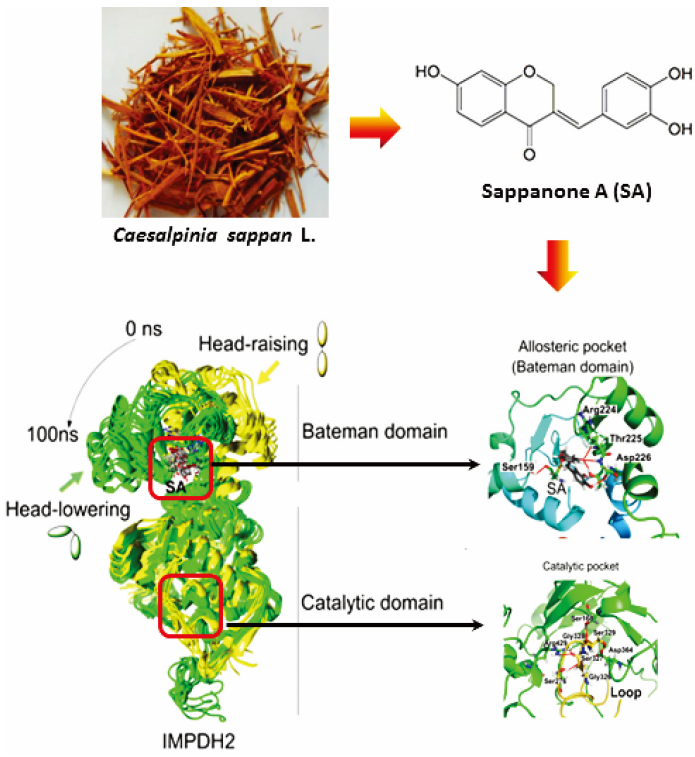

Figure Sappanone A selectively targets IMPDH2.