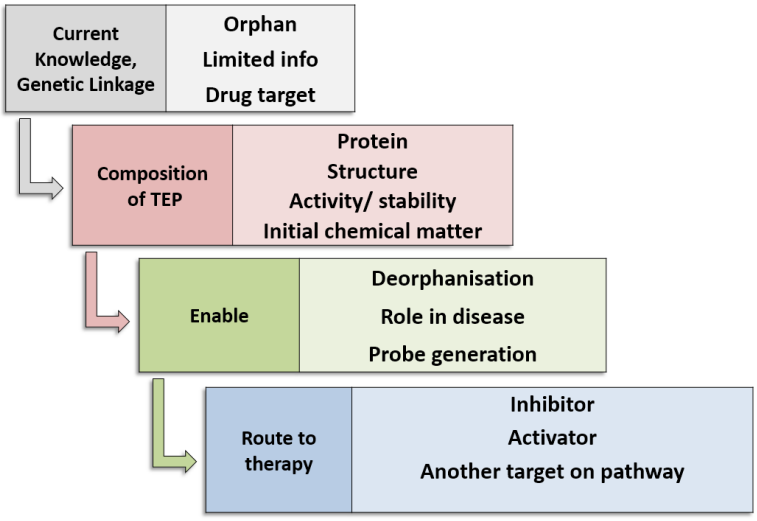
Human Kelch-like ECH-associated Protein 1 (KEAP1)

A Target Enabling Package (TEP)

KEAP1 is a highly redox-sensitive member of the BTB-Kelch family that assembles with the CUL3 protein to form a Cullin-RING E3 ligase complex for the degradation of NRF2. Oxidative stress disables KEAP1 allowing NRF2 protein levels to accumulate for the transactivation of critical stress response genes. Consequently, the KEAP1-NRF2 system is a highly attractive target for the development of protein-protein interaction inhibitors that will stabilise NRF2 for therapeutic effect in conditions of neurodegeneration and inflammation. As part of this TEP we have solved the first crystal structure of a KEAP1-CUL3 complex as well as a structure of the apo-Kelch domain suitable for small molecule soaking. We further established a selectivity assay panel of 17 human Kelch domain-containing proteins and have shown that non-covalent KEAP1 inhibitors from the literature are highly selective for KEAP1. This protein panel offers a resource for future work on KEAP1 as well as 16 other human Kelch proteins.

The Target Enabling Package (TEP) programme's foundation is built upon the recognition that genetic data is proving to be a powerful tool for target validation. As such, TEPs provide a critical mass of reagents and knowledge on a protein target to allow rapid biochemical and chemical exploration and characterisation of proteins with genetic linkage to key disease areas. TEPs provide an answer to the missing link between genomics and chemical biology, provide a starting point for chemical probe generation and therefore catalyse new biology and disease understanding with the ultimate aim of enabling translation collaborations and target/ drug discovery.



Future versions of this document will contain experimental data about the KEAP1 TEP.
For more information regarding any aspect of TEPs and the TEP programmes, please contact teps@thesgc.org or visit https://thesgc.org/tep