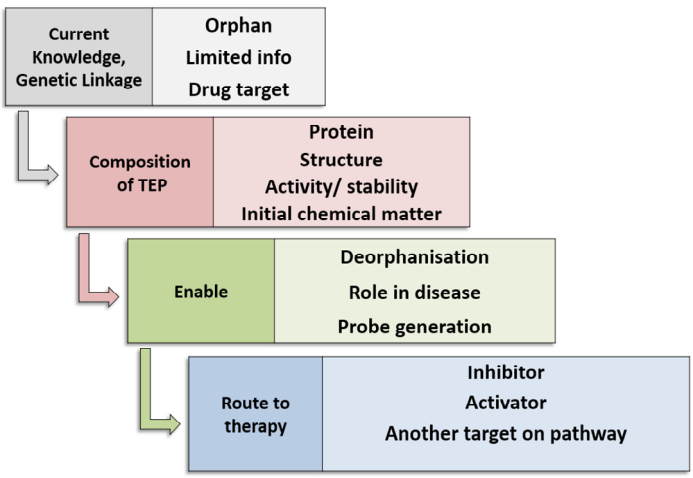
Human T-box Transcription Factor T (TBXT)

A Target Enabling Package (TEP)

Chordoma is a rare cancer occurring along the spinal cord (OMIM: 215400). Chordoma is derived from an embryonic tissue, the notochord, and over-expresses the embryonic transcription factor T-box transcription factor T, the homologue of mouse Brachyury (1-6). Chordomas are "genomically silent" cancers that do not carry an extensive mutation load. Recent studies indicate that expression of TBXT is essential for persistence and growth of chordoma cells (7). As TBXT is not expressed in any post-embryonic tissues, it could be an excellent target for treatment of chordoma. The long-term aim of this project is to test whether TBXT can be targeted with small molecules with sufficient affinity and specificity to be therapeutically useful. In this TEP we have determined crystal structures of the DNA-binding domain (DBD) of TBXT with and without cognate DNA oligonucleotides. The DNA-free protein crystals were used in a high-throughput fragment screen to identify 29 fragments bound in 6 clusters. The crystal structures of the bound fragments provide starting points for development of stronger binders which could be used to disrupt TBXT activity or to induce the degradation of the protein through a Proteolysis-targeting chimeric molecule (PROTAC) approach (8).

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 TBXT TEP.

For more information regarding any aspect of TEPs and the TEP programmes, please contact teps@thesgc.org or visit https://thesgc.org/tep

1. 10.1002/path.1969; 2. 10.1002/path.2816; 3. 10.18632/oncotarget.13616; 4. 10.1038/s41467-017-01026-0; 5. 10.1016/j.bbcan.2014.08.004; 6. 10.1038/ng.454; 7. 10.1038/s41591-018-0312-3; 8. 10.1073/pnas.141230798;