2 Example 1: Phosphatases, Classical Enzyme Targets with Low Druggability

Protein tyrosine phosphatases (PTPs) counterbalance the action of protein kinases and are essential enzymes regulating cell signalling. Similar to protein kinases, many phosphatases are deregulated in disease making a compelling case target these enzymes. There are 107 PTPs encoded in the human genome that can be grouped into four major families: classes I, II and III of cysteine-based PTPs and aspartate-based PTPs. The class I cysteine-based PTP group contains the phosphotyrosine-specific enzymes that are usually referred to as 'classical PTPs' (Alonso et al. 2004). Dual-specificity PTPs and low molecular weight PTPs have very shallow and charged binding sites making inhibitor development a challenging task. Within the classical PTP family, binding cavity properties are more favourable but cellular activity and selectivity remain major challenges (Barr 2010).

Two targets received most of the attention developing PTP inhibitors to date: PTP1B and SHP2 (PTPN11). The phenotype of the PTP1B knockout mice sparked drug development interest as these animals were healthy but displayed enhanced sensitivity to insulin and resistance to a high-fat diet-induced obesity, suggesting that selective PTP1B inhibitors could be beneficial treating both type II diabetes and obesity (Elchebly et al. 1999). In addition, possible applications of PTP1B inhibitors in oncology have been suggested by transgenic mouse studies that showed that PTP1B functions as a positive mediator of the ErbB2 tyrosine kinase signalling leading to breast cancer development and tumour metastasis (Julien et al. 2007). However, PTP1B is highly similar to TC-PTP which share 72% sequence identity and 94% identity considering active site residues. In contrast to PTP1B, TC-PTP knockout mice die shortly after birth as a result of anaemia, hypersensitivity and widespread inflammation strongly suggesting that inhibiting this PTP should be avoided (You-Ten et al. 1997).

There has been also significant drug discovery interest in the development of SHP2 inhibitors for the treatment of cancer. Similar to cytoplasmic tyrosine kinases, SHP2 is kept in an inactive state by its N-terminal SH2 domains (Hof et al. 1998). Binding to phosphorylated tyrosines released the SH2 domain block on SHP2 activity, activating this phosphatase. Mutation in SHP2 (PTPN11) has been associated with Noonan and LEOPARD syndrome and development of several cancer types, and most significantly activating SHP2 mutations are found in 35% of patients with juvenile myeloid leukaemia (JML) (Chan et al. 2008). In addition, high SHP2 expression levels have been associated with increased leukaemia and breast cancer risk (Xu et al. 2005; Zhou et al. 2008). Similar to PTP1B, also SHP2 is closely related to an anti-target: SHP1, a highly similar PTP which is mainly expressed in the haematopoietic system. SHP1 loss of function has been associated with severe autoimmune and immunodeficiency syndrome (Shultz et al. 1997).

The structure of PTP1B with a dually phosphorylated peptide derived from the insulin receptor identified a secondary phosphotyrosine binding pocket (Salmeen et al. 2000) and a potential binding site that can be targeted by small molecules. This secondary pocket is present in a number of PTPs and may have different