

W0659

**Crystal Structure of the Hypoxia-Inducible Factor Prolyl Hydroxylase 2 (PHD2): Structural Insights to Cellular O<sub>2</sub> Sensing.** †McDonough, M.A., §Li, V., †Flashman, E., †Chowdhury, R., §Mohr, C., †Liénard, B.M.R., §Zondlo, J., †Oldham, N.J., †Clifton, I.J., §Lewis, J., ‡McNeill, L.A., §Kurzeja, R., †Hewitson, K. S., §Yang, E., §Jordan, S., and §Syed, R.S. / †Schofield, C.J. †Dept. of Chem., Univ. of Oxford, Oxford, OX1 3TA, UK; §Amgen Inc., Thousand Oaks, CA 91320-1789 USA.

The cellular response to low  $pO_2$  is mediated by the hypoxia-inducible factor (HIF), which initiates the transcription of an array of genes including EPO and VEGF. HIF is active as an  $\alpha/\beta$  heterodimer whose subunits are both constitutively expressed. However, during normoxia the  $\alpha$ -subunit (HIF- $\alpha$ ) can be hydroxylated by three HIF prolyl hydroxylase isozymes (PHD 1, 2, and 3), which are Fe(II) and 2-oxoglutarate dependent dioxygenase family members. Hydroxylation of 2 prolines in HIF- $\alpha$  promotes its interaction with pVHL, thus targeting it for proteasomal degradation. Inhibition of the PHD enzymes in cells mimics hypoxia and results in increased HIF- $\alpha$  levels and the upregulation of HIF target genes. The crystal structure of the catalytic domain of PHD2 has been solved in space group  $P6_3$  using anomalous differences from an Fe(II), iodine and several protein sulfur atoms with an in-house rotating anode. The structure of PHD2 is aiding the development of selective inhibitors with therapeutic potential.

