giving him time to play with some paper models of planar peptide units. He built them into a helical chain that satisfied the stereo-chemical constraints that he believed were essential for any peptide structure. In 1949 he lectured on, and in 1950 published[5], the fruits of this modeling: α-helix and β-strand structures fully able to account for the battery of diffraction data that Astbury had built up over the previous 30 years.

With hindsight it is clear that all the data necessary to predict the structure of the α-helix are in Astbury's papers, but hindsight is a very good filter for irrelevant information. Sadly, Astbury was unable to see the gold in his pan and even his contemporaries would say of him that "he brought his findings to the market in the green ear, but would not clear the weeds nor suffer the system and technique necessary to bring in the harvest"[6]. Even so it seems iniquitous that he is not better remembered among those who laid the foundations for the X-ray analysis of biomolecular structures.

He died in 1961 and no lesser person than J.D. Bernal wrote his biography for the Royal Society[7].

Christopher Surridge, Web Editor for Nature in London

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An SH2 domain in disguise

The adaptor molecule, Cbl, is involved as a negative regulator in a number of cell signaling pathways. Among its targets are cell surface receptors such as that for epidermal growth factor, and the protein tyrosine kinase ZAP-70. These interactions involve the binding of the N-terminal portion of Cbl to regions containing phosphorylated tyrosine residues. However there has been no indication from Cbl's sequence that it contained an SH2 domain — the archetypal phospho-tyrosine binding motif. Consequently the recent structure of Cbl from Michael Eck's group (Meng, W., Sawasdikosol, S., Burakoff, S.J. & Eck, M.J. *Nature*, **in the press**) has come as something of a surprise.

The structure is of the evolutionarily well conserved N-terminus of Cbl complexed with a phosphopeptide representing its binding site in ZAP-70. What emerge are three very familiar domains: a four-helix bundle (yellow), an EF-hand with bound calcium (green) and an SH2 domain (blue) into which the phosphopeptide slots. The Cbl SH2 domain is lacking part of the β-sheet and a prominent loop found in other SH2 domains, however the EF-hand and four helix bundle press close against these regions so that together they form a coherent binding unit for the phosphopeptide ligand.

Two questions are immediately raised by this structure. First, given the presence of an EF-hand with a bound calcium ion, is the activity of Cbl regulated by calcium? Disruption of calcium binding by mutations in calcium chelating residues of the EF-hand domain abolished the ability of Cbl to bind ZAP-70. But the presence of EGTA had no such effect, suggesting that this N-terminal region of Cbl has a very strong affinity for calcium. However, the same may not be true for the full-length protein. Perhaps regions of the protein missing in this N-terminal fragment reduce the binding of calcium to the EF-hand allowing Cbl's activity to be modulated by this route.

Second, this unexpected appearance of an SH2 domain may force a re-evaluation of the evolution of these signaling units. Prior to the discovery of a STAT-like protein in the slime mould *Dictyostelium discoideum* (Kawata, T. *et al. Cell* **89**, 909–916; 1997) the SH2 domain had been thought to be a metazoan invention. However the *Dictyostelium* SH2 domain was easily recognizable from its amino acid sequence. The sequence of Cbl's SH2 domain is so divergent from those that have been identified before that it may give cause to place the origin of SH2 signaling pathways back before even the emergence of multicellular organisms. *Christopher Surridge*