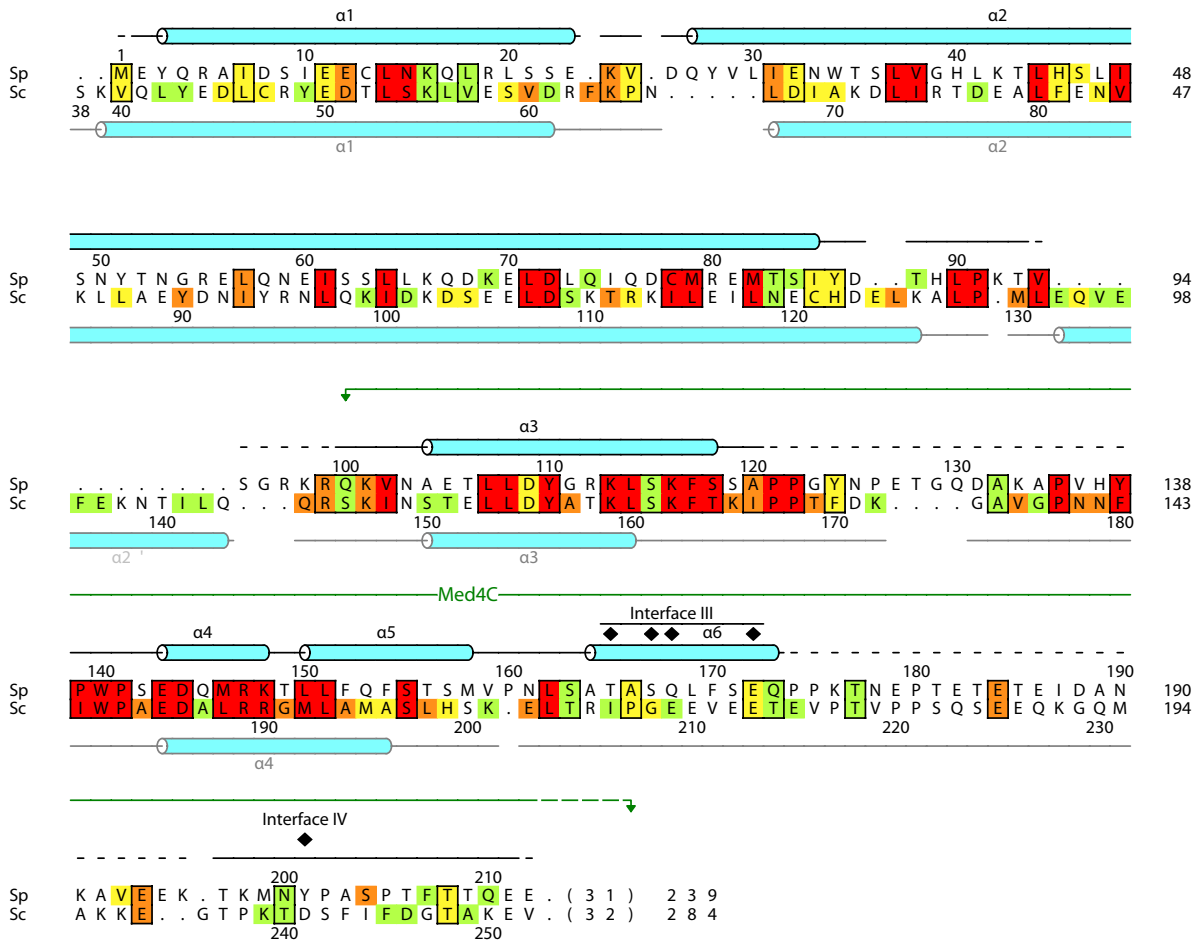


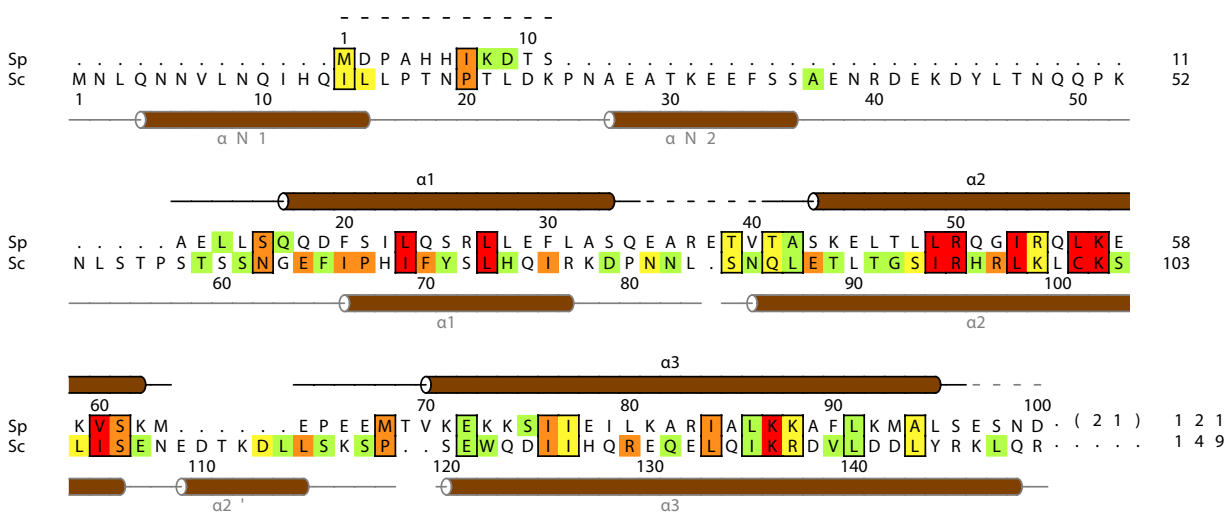
## Supplementary Figure 1 | Sequence alignments for middle module subunits

Amino acid sequence alignments for Mediator middle module subunits from *Schizosaccharomyces pombe* (*Sp*, top), and *Saccharomyces cerevisiae* (*Sc*, bottom). Sequence identity between *Sp* and *Sc* subunits is indicated in brackets next to the protein name. Secondary structure elements are indicated above and below the sequences as observed in the *Sp* cMed structure and the available *Sc* structures (or otherwise as predicted by PSIPRED; dark gray frames), respectively (cylinders,  $\alpha$ -helices; arrows,  $\beta$ -strands; dashed lines, disordered regions). Residue conservation of 50-100% within the yeasts *Sp*, *Sc*, *Candida glabrata*, *Candida albicans*, *Ashbya gossypii*, *Kluyveromyces lactis*, and *Debaryomyces hansenii* is shown in color from green via yellow and orange to red (invariant). Subdomains of each *Sp* subunit, key residues for the head module binding, and known *Sc* mutations are highlighted with a green arrow, a black diamond and a blue triangle, respectively. Similar alignment for head subunits Med6, Med8, Med11, Med22, Med17, Med18, and Med20 were published and used previously to obtain a highly reliable model of the *Sc* head module based on the *Sp* head module crystal structure<sup>13</sup>.

Med4 (22%)

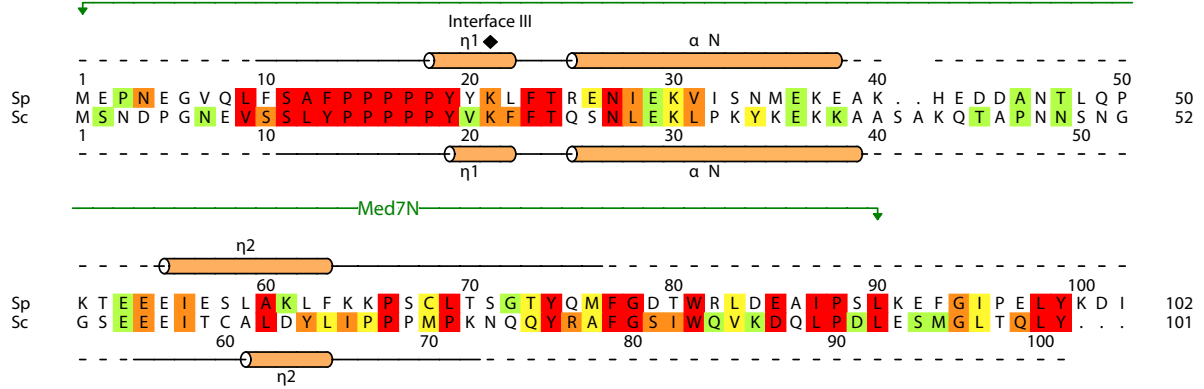


Med9 (14%)

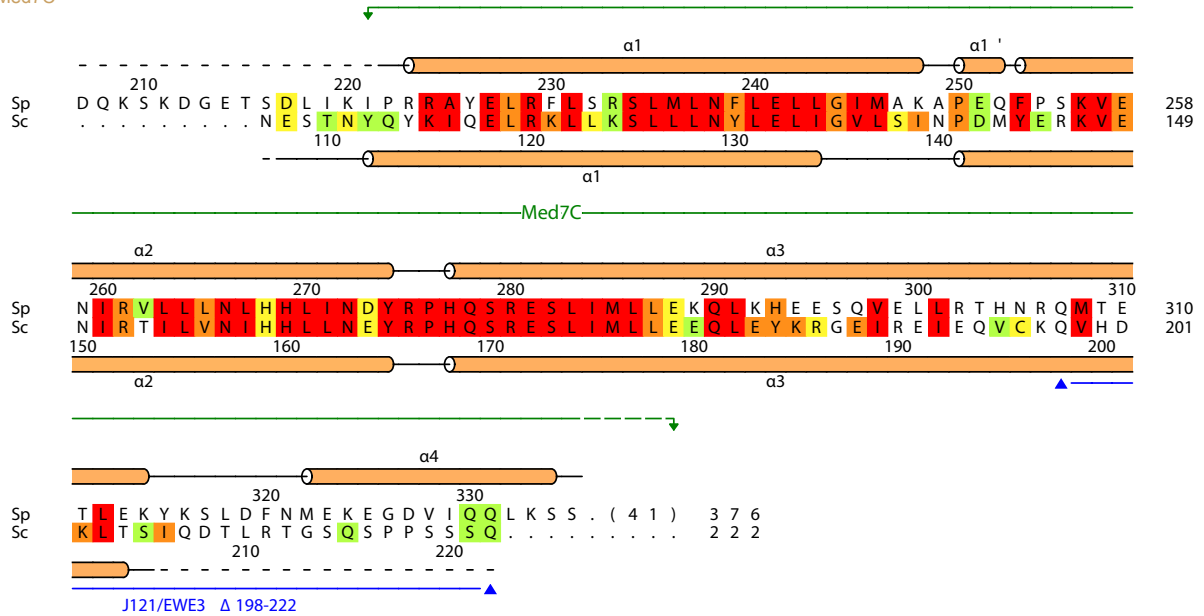


Med7 (40%)

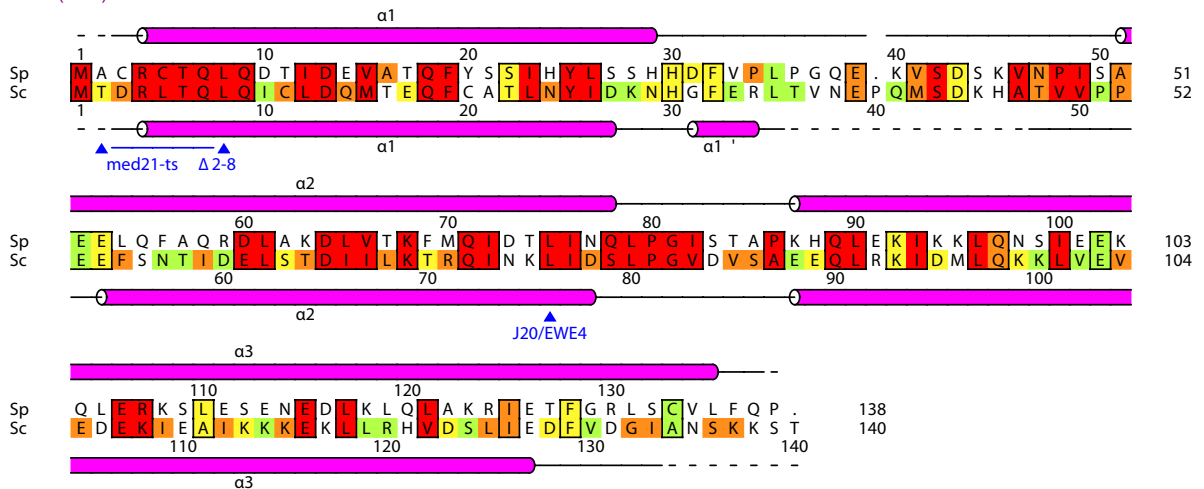
Med7N



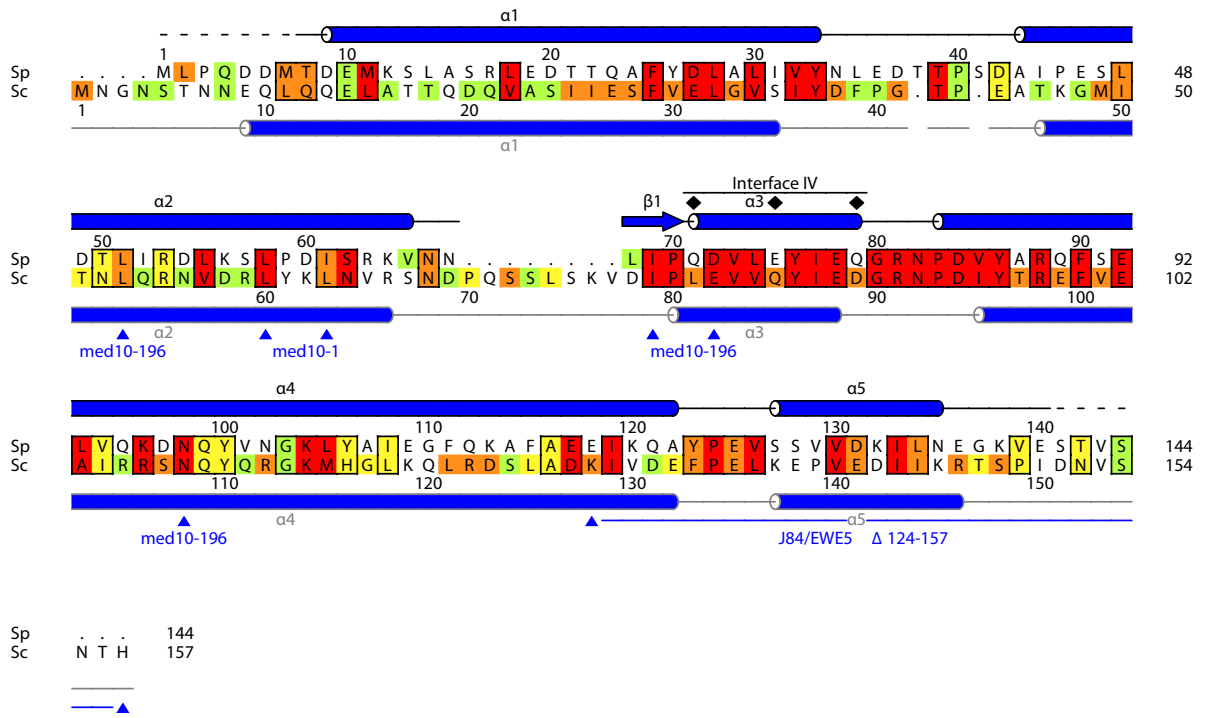
Med7C



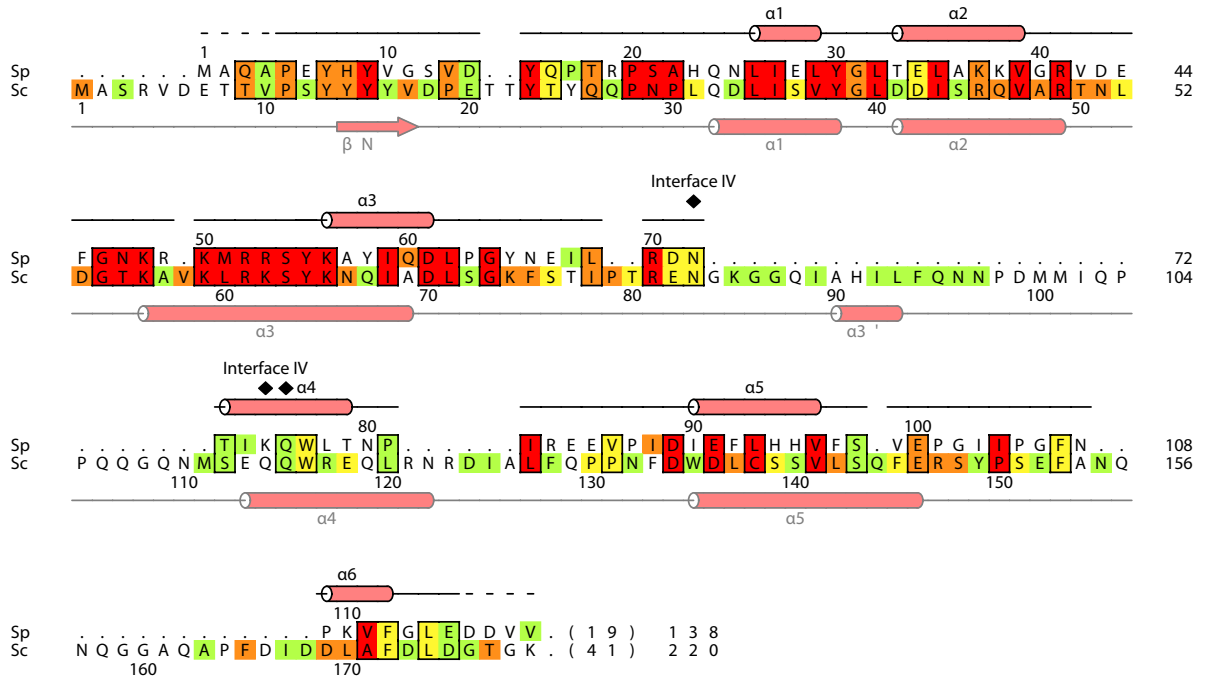
Med21 (30%)



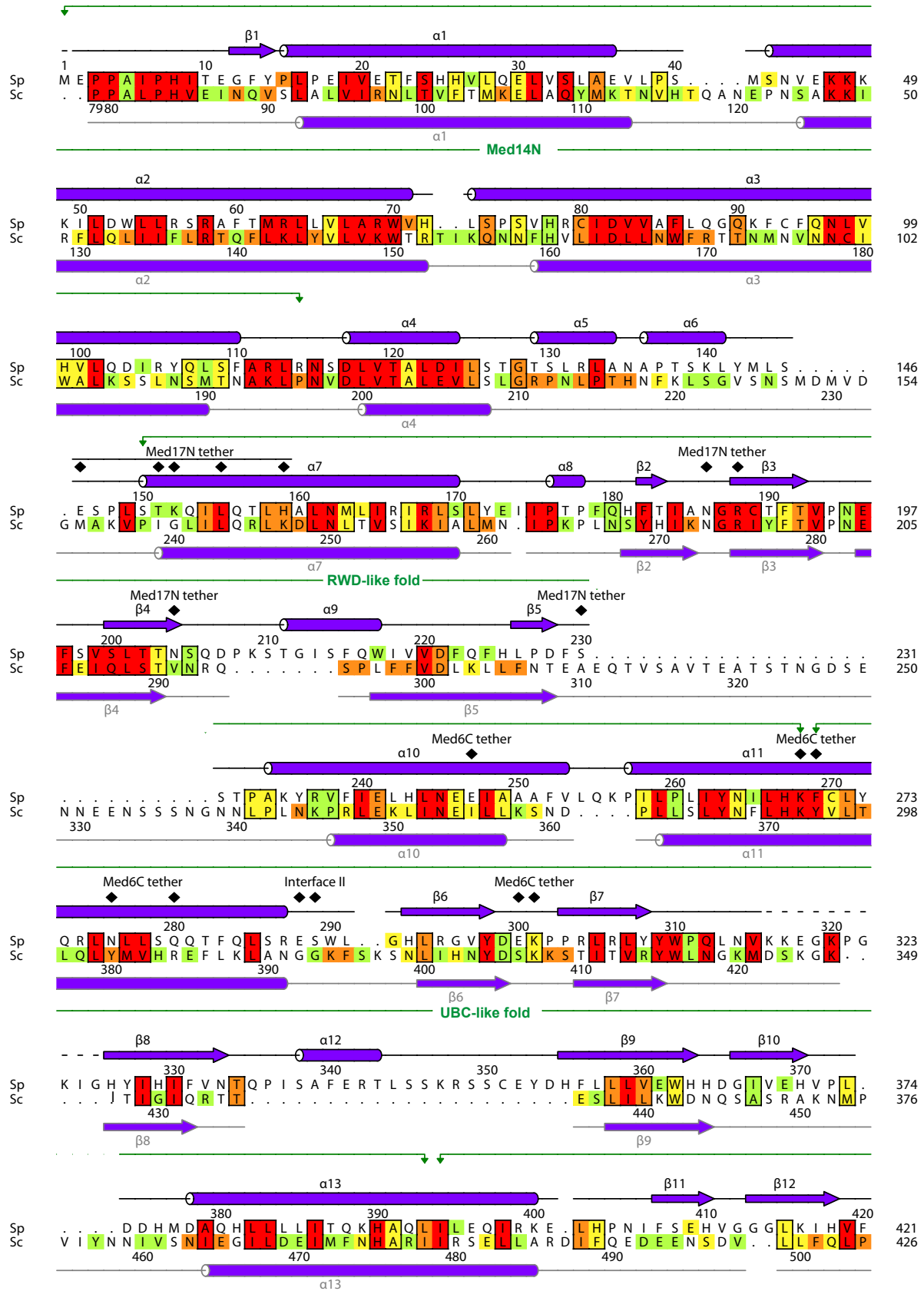
Med10 (22%)



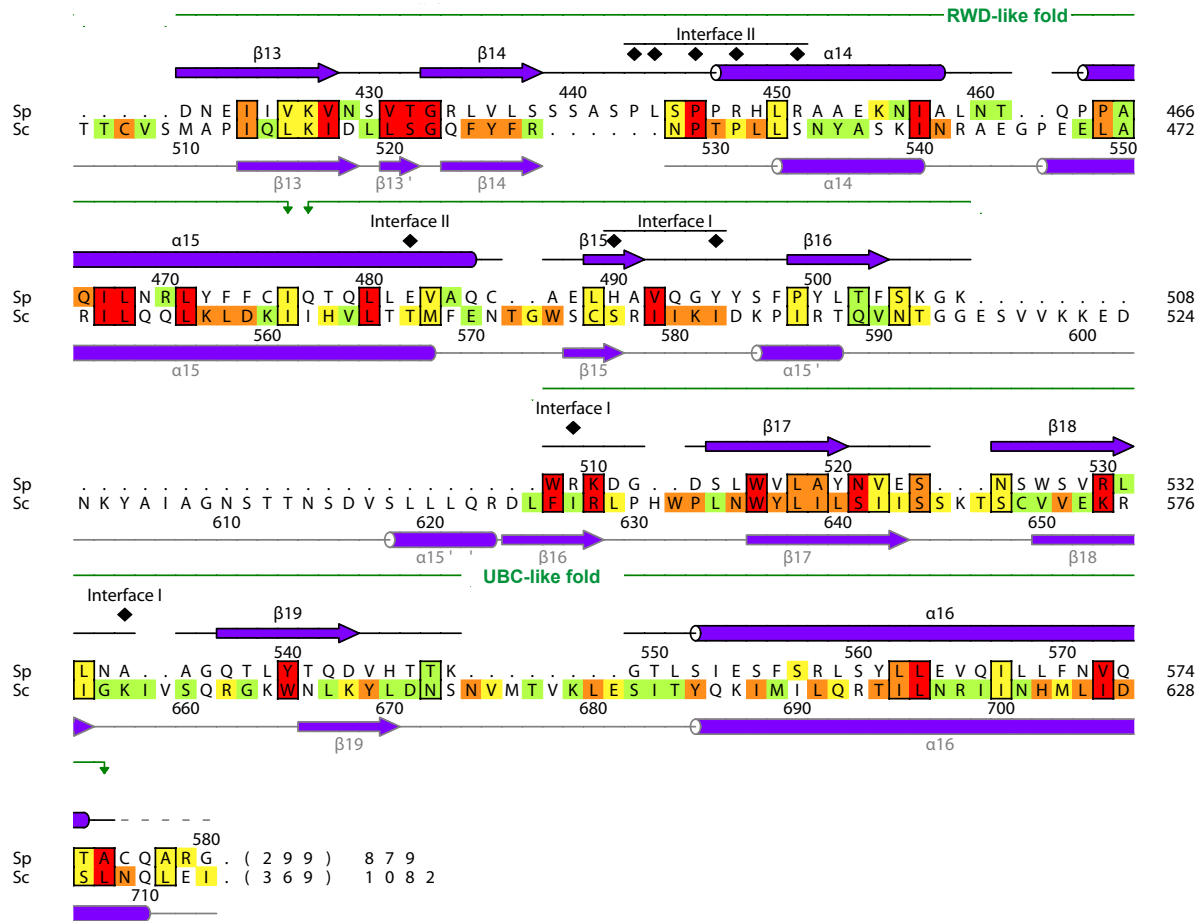
Med19 (19%)



Med14 (16%)



Med14 continuation



Med31 (25%)

