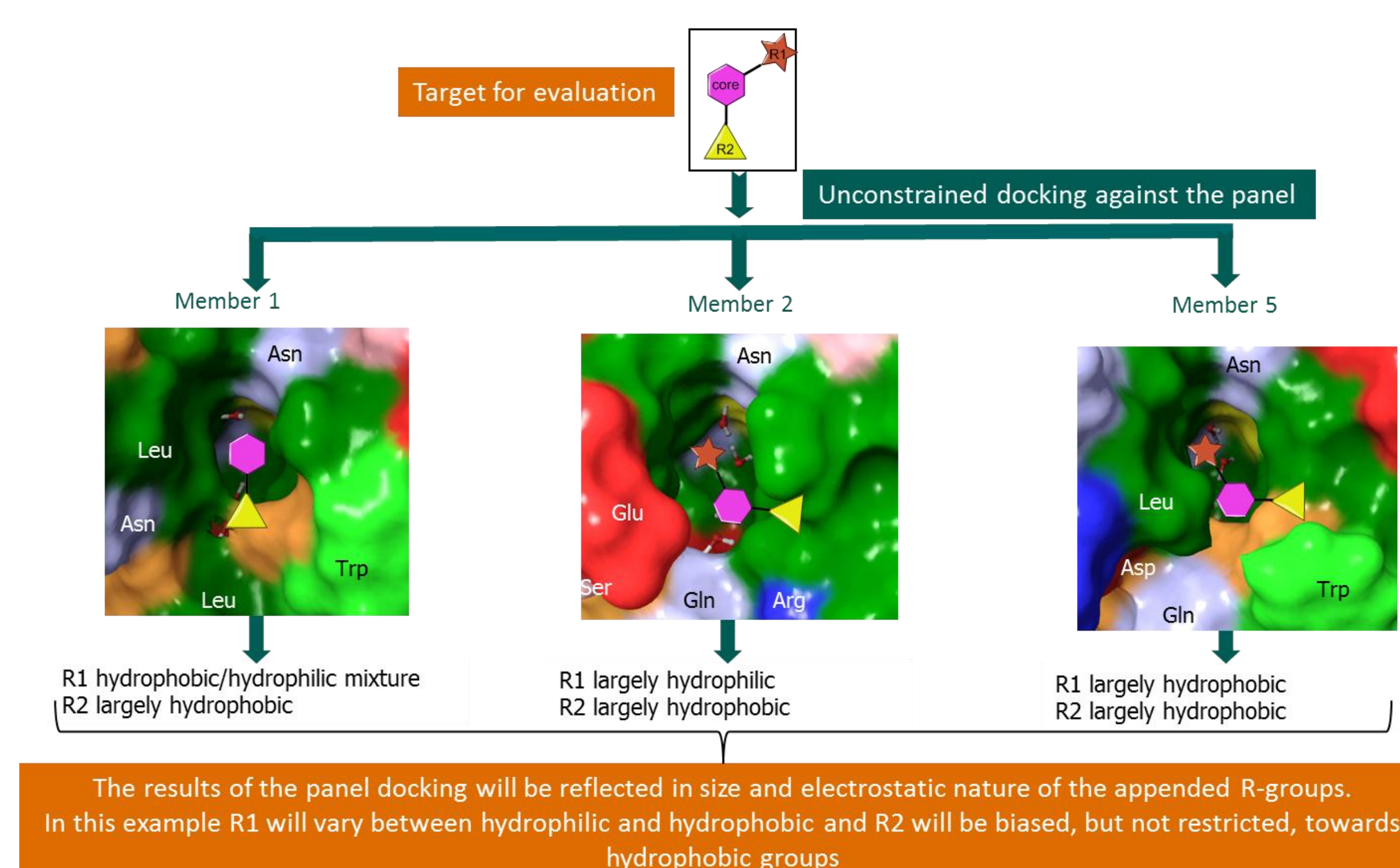


Introduction

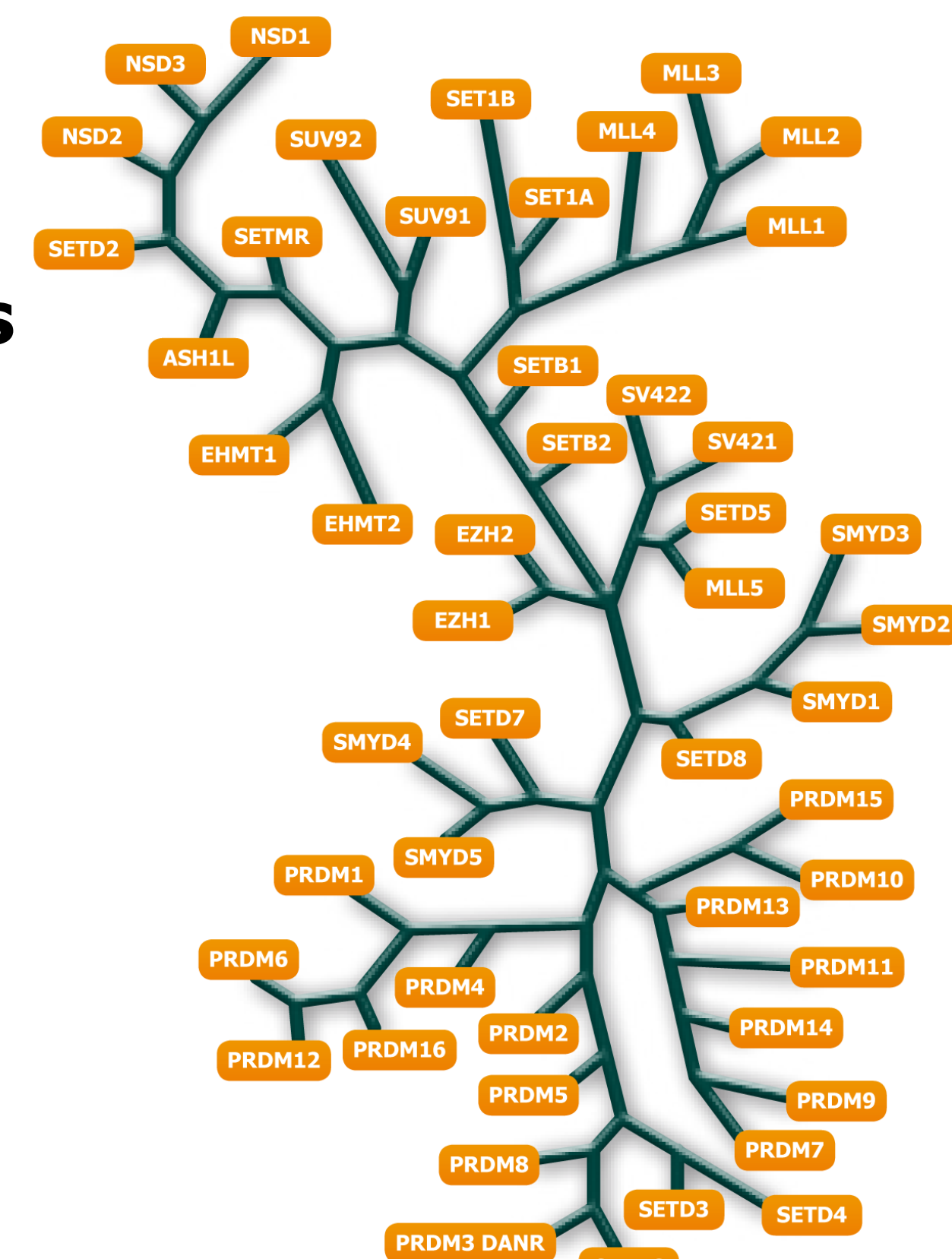
Epigenetics describes the regulation of gene expression that occurs through DNA methylation and post translational modification of histones. The pharmaceutical industry has shown an explosion of interest in this field with new targets emerging. Discovery of novel starting points for hitherto unexplored protein classes remains an issue. We present the application of our extensive expertise and SoftFocus library design strategies towards four epigenetics classes to generate innovative drug-like starting points for drug discovery.

The SoftFocus design strategy - application of 12 years' experience



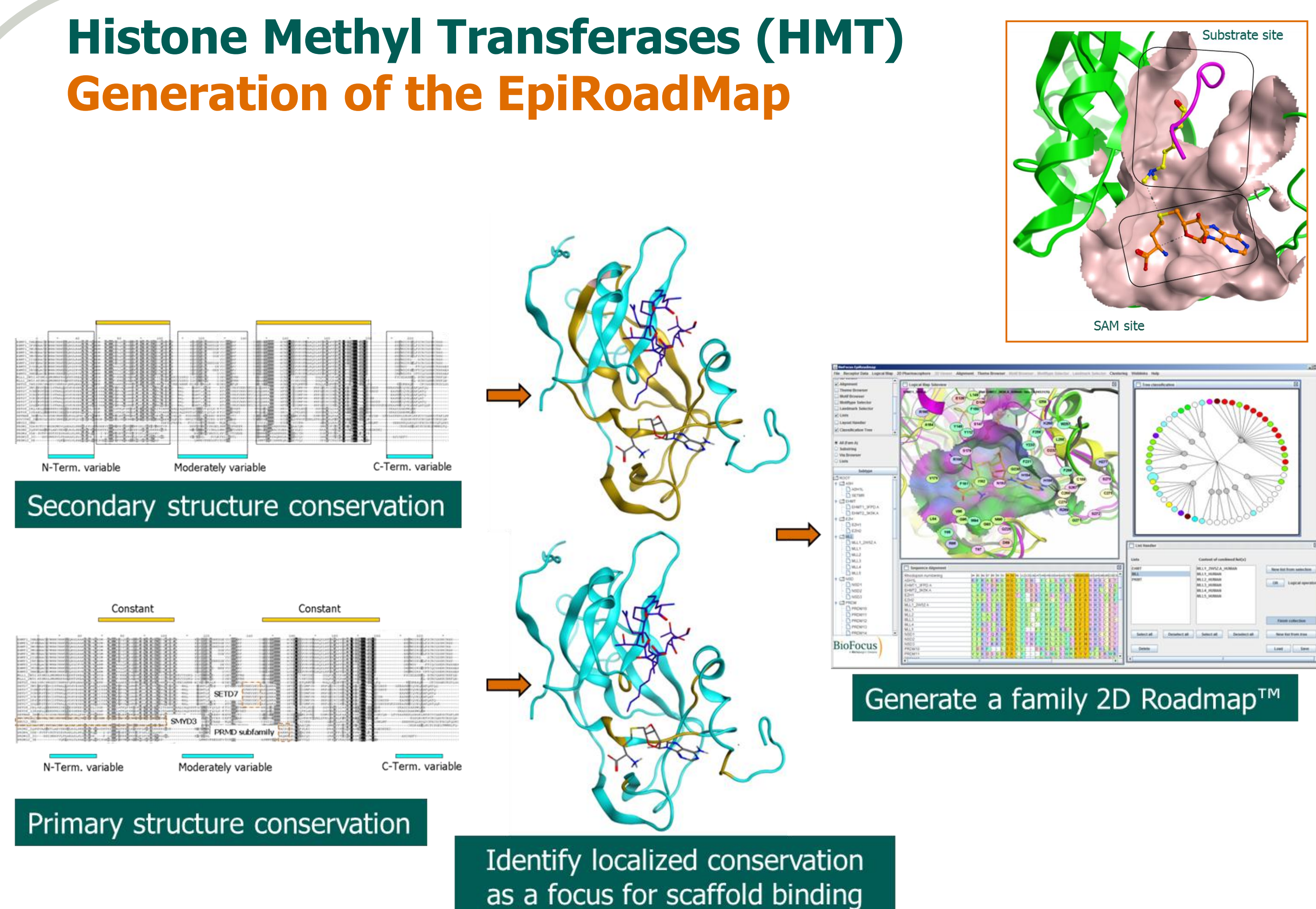
Panel docking example highlighting the influence on R-group selection

- A docking panel is commonly used to assess scaffolds for a SoftFocus library
- Phylogenetic trees represent the sequence similarity relationships between proteins in a family
- A representative subset of the protein family is used to generate a docking panel
- Careful selection of this panel can ensure a broad focus to the library
- Sub-site representation of the phylogenetic tree ensures greater resolution in the design strategy



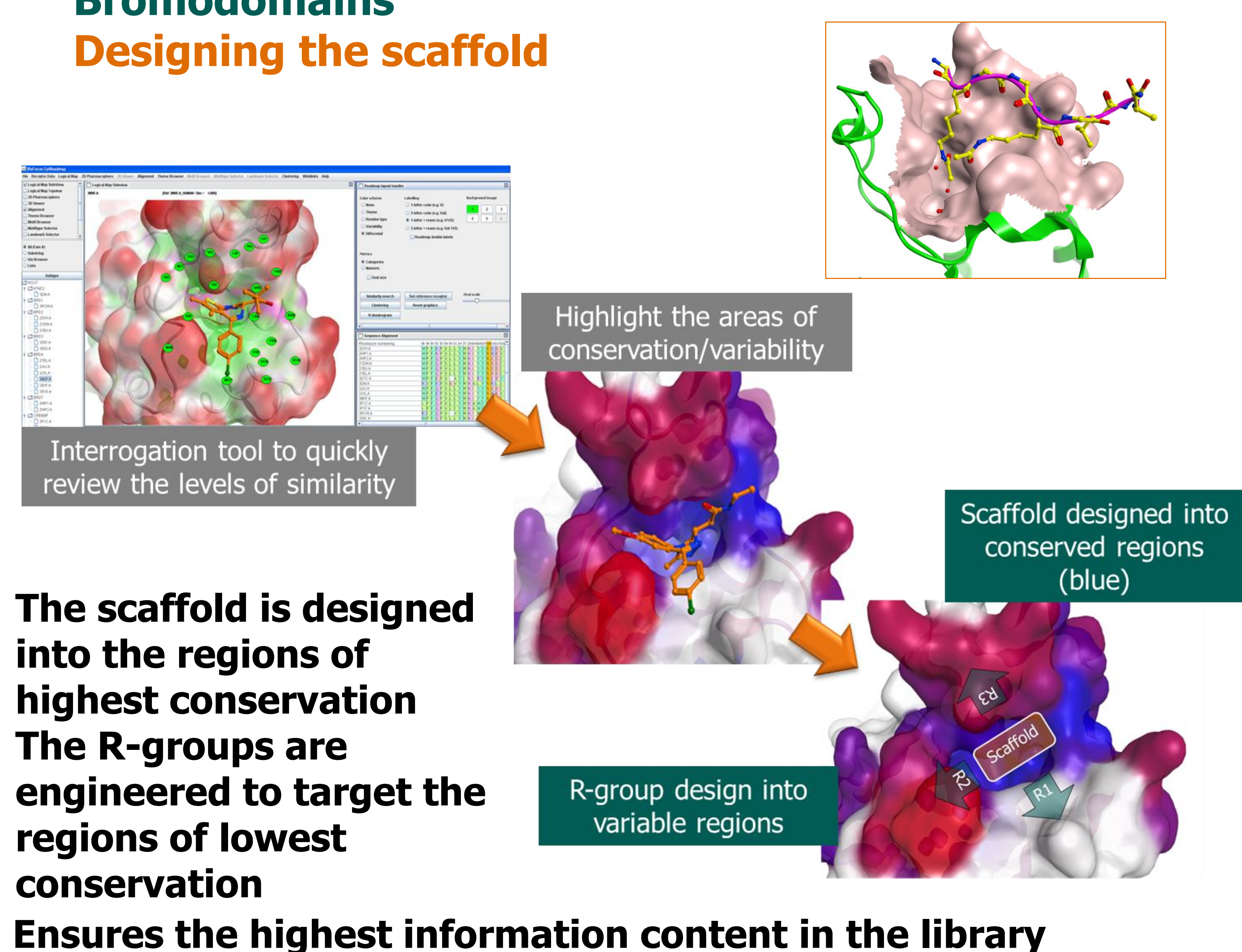
Phylogenetic tree of the PKMT family

Histone Methyl Transferases (HMT) Generation of the EpiRoadMap



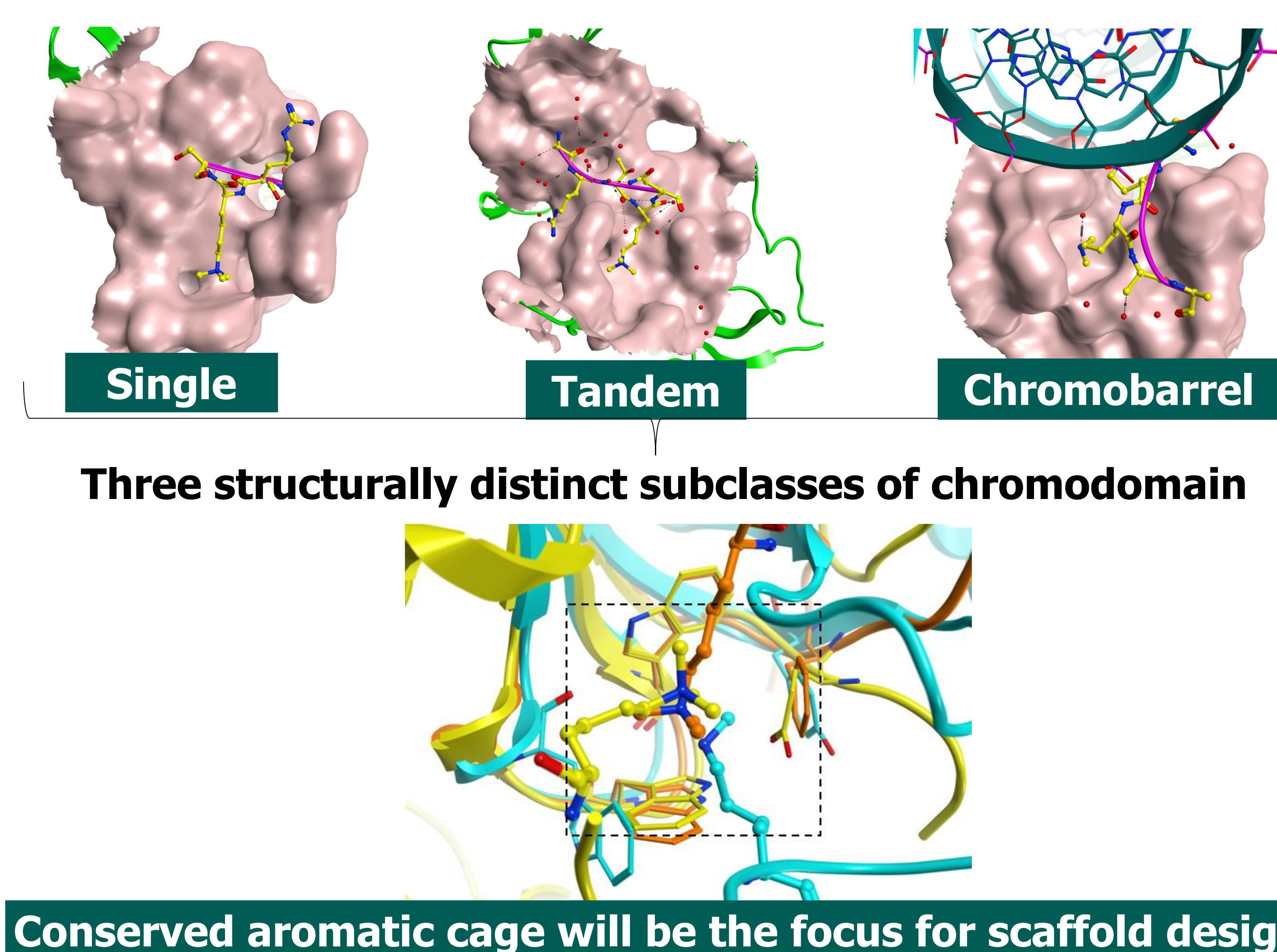
- Structural overlays seed the sequence alignments
- Areas of highest and lowest conservation are identified
- EpiRoadMap - a user friendly sequence interrogation tool

Bromodomains Designing the scaffold

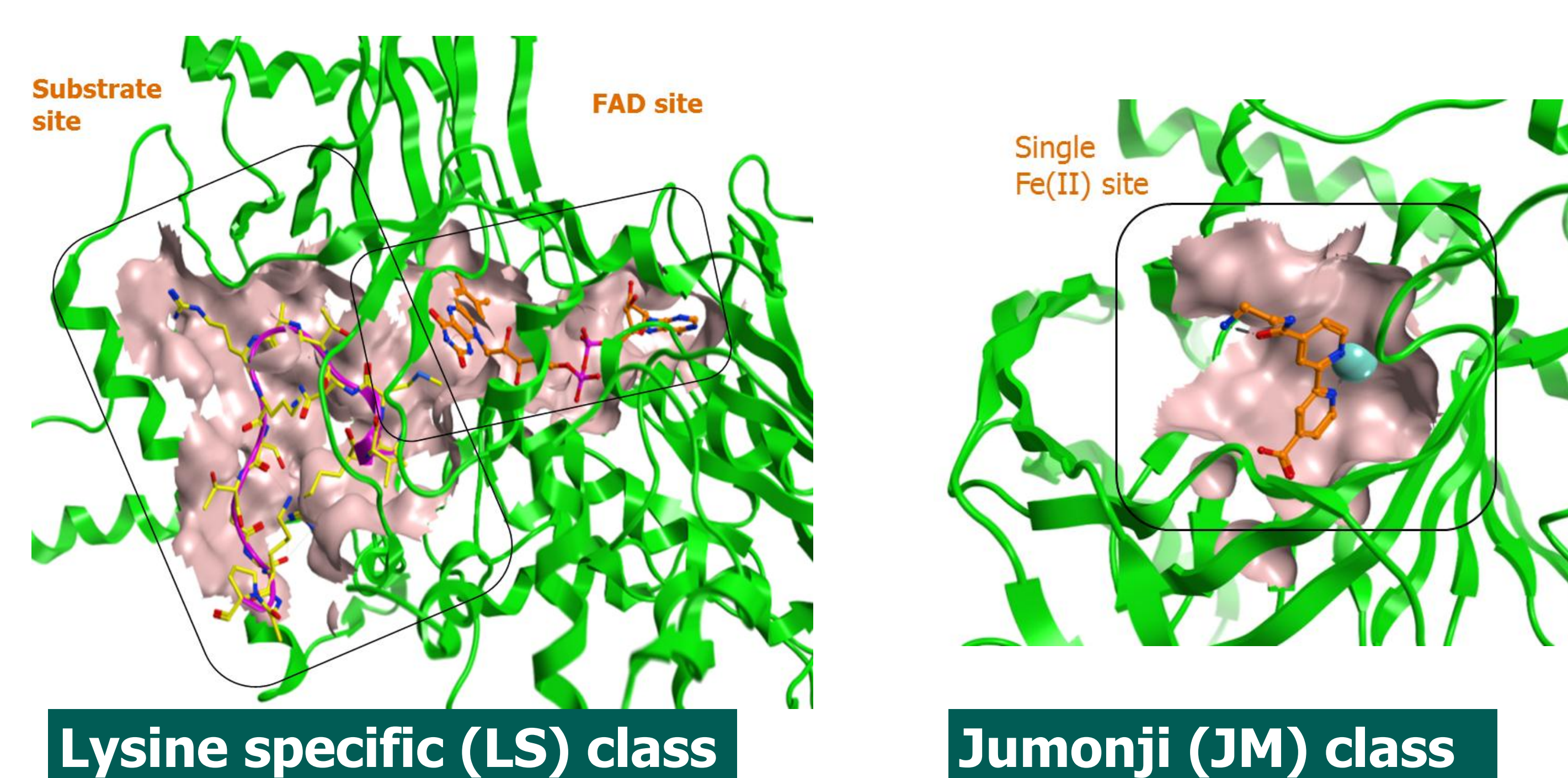


- The scaffold is designed into the regions of highest conservation
- The R-groups are engineered to target the regions of lowest conservation
- Ensures the highest information content in the library

Chromodomains Three distinct subclasses – one strategy



Lysine demethylases Two distinct subclasses – two distinct strategies



- Distinct catalytic mechanisms require specific design strategies
- LS class can focus on either substrate or FAD pockets
- JM class will focus on the single Fe(II) containing site
- Chemotypes expected to differ between classes

Conclusions

- Finding good, drug-like starting points for drug discovery is often difficult to achieve for novel or emerging targets
- BioFocus has over 12 years' experience and an excellent track record in successfully designing and synthesizing compound libraries
- We have applied our SoftFocus chemogenomic design strategy to epigenetics protein classes to generate novel compounds
- EpiRoadMaps help us to guide the scaffold and R-group locations and associated property profiles
- Detailed analysis of the gene families reveals differences in the sub-classes that can require single or multiple design strategies