

### Introduction

Drug discovery initiatives benefit immensely from structural genomics initiatives, but limited finances and manpower require careful selection of targets to pursue.

**Druggability is an important concept in target selection.**

A protein containing a druggable pocket is more likely to be successfully targeted, compared to other proteins.

*P. aeruginosa* is a major pathogenic agent in opportunistic and nosocomial infections. Crystal structures for 195 proteins from *P. aeruginosa* have been determined in the RCSB Protein Data Bank (PDB).

Here, we present druggability predictions for all protein structures currently available for the *P. aeruginosa* proteome.

### What makes a protein druggable?

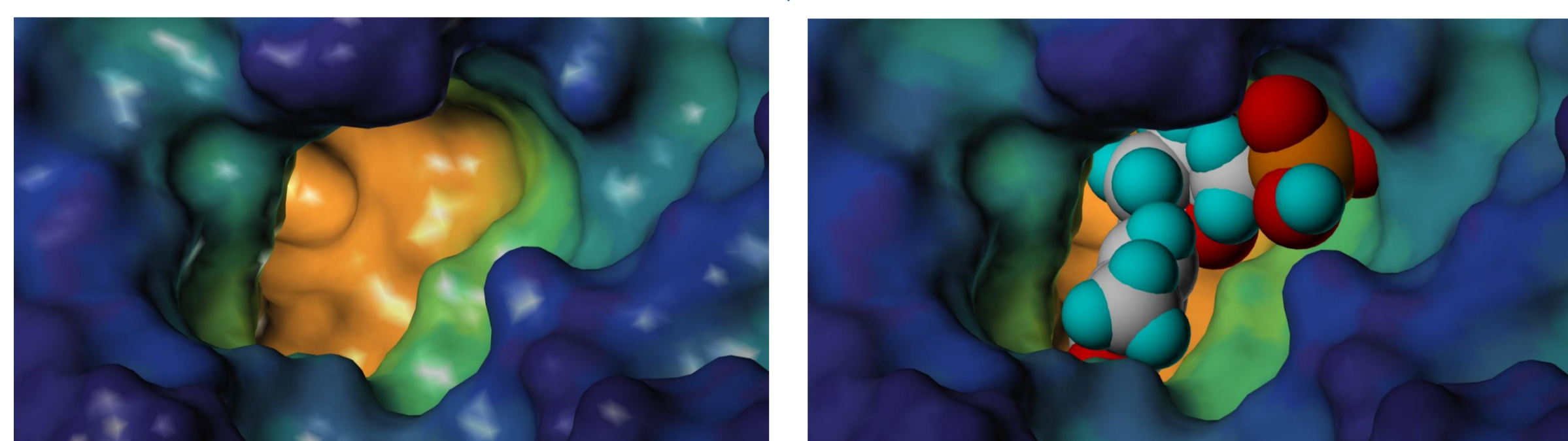
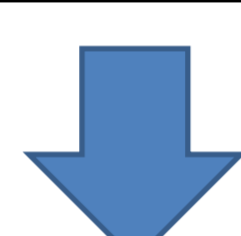
**Druggability is commonly defined as the ability of a protein binding site to bind drug-like, orally bioavailable molecules with high affinity**

#### Binding site properties

Lipophilicity, hydrogen bond forming capacity, compactness, size, maximum achievable desolvation energy



Correct balance of properties maximizes probability of binding drug-like molecules

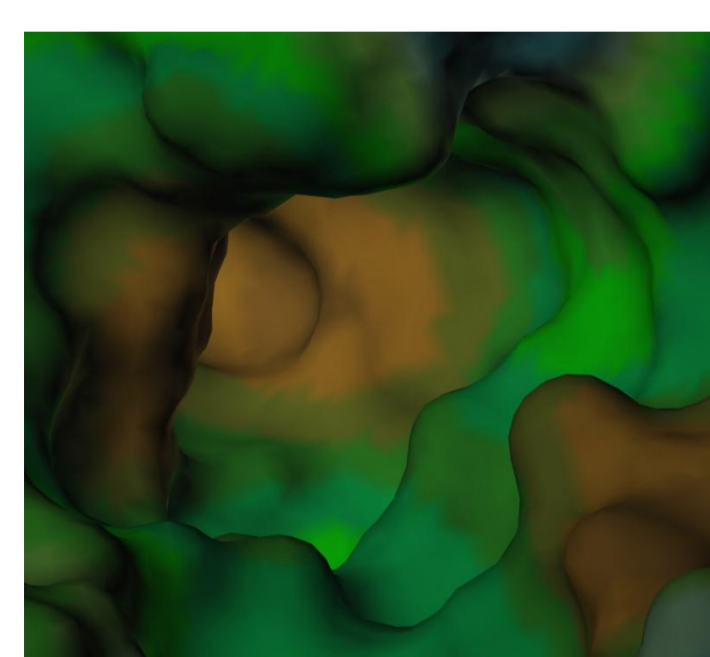


Druggable protein binds drug-like molecules with high affinity

### DrugPred

An *in silico* Protein Druggability Predictor recently established by us, correlating physicochemical properties of binding sites with druggability, capable of discerning druggable binding sites from non-druggable ones with > 90% accuracy.

#### 1. Calculate properties of binding pocket



- Sum of Kyte-Doolittle indices (*h<sub>iaa</sub>*)
- Hydrophobic surface area (*h<sub>sa\_t</sub>*)
- Relative polar surface area (*p<sub>sa\_r</sub>*)
- Relative occurrence of hydrophobic amino acid residues (*h<sub>aa</sub>*)
- Contact surface area (*c<sub>sa</sub>*)

#### 2. Calculate DrugPred Score

Feed descriptors into model derived by Partial least squares projection to Latent Structures - Discriminant Analysis (PLS-DA) to derive score

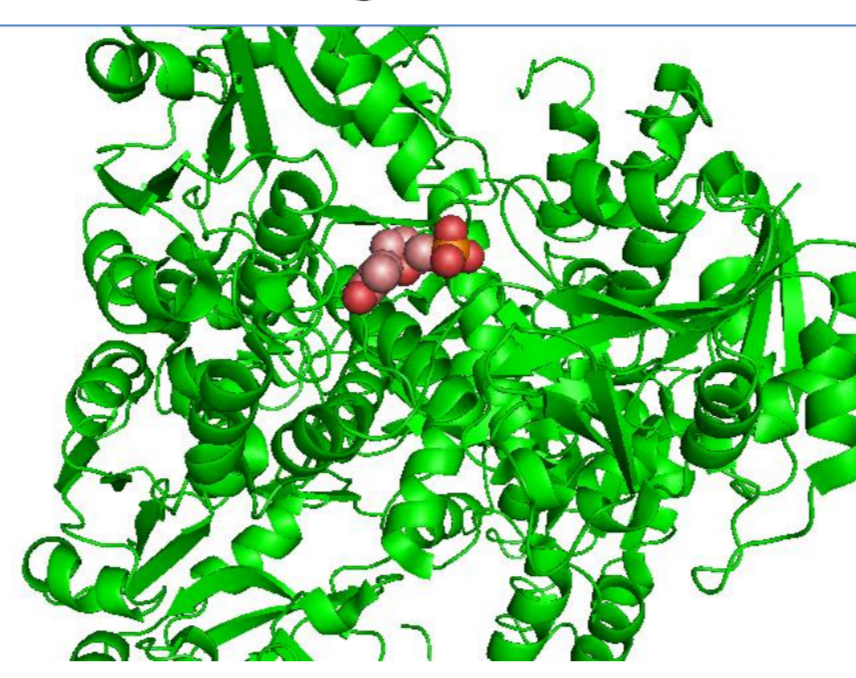
#### 3. Predict Protein Pocket Druggability

Divides proteins into three categories: **Druggable**, **Ambiguous** & **Non-druggable**

### Druggability of *P. aeruginosa* Crystal Structures

#### Identification of binding pocket

Where Ligand Is Present:



Target Protein

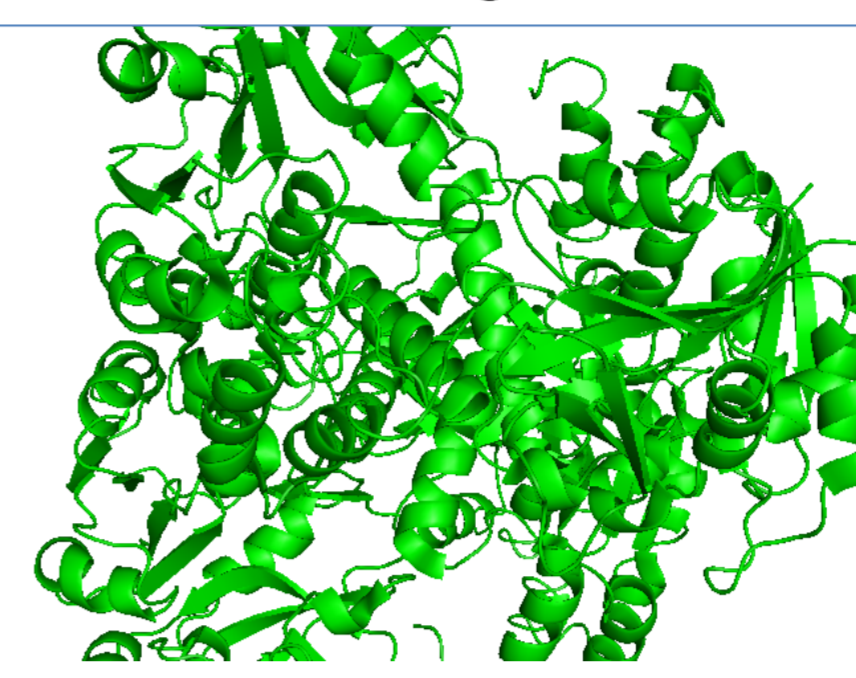


Well Defined Binding Site

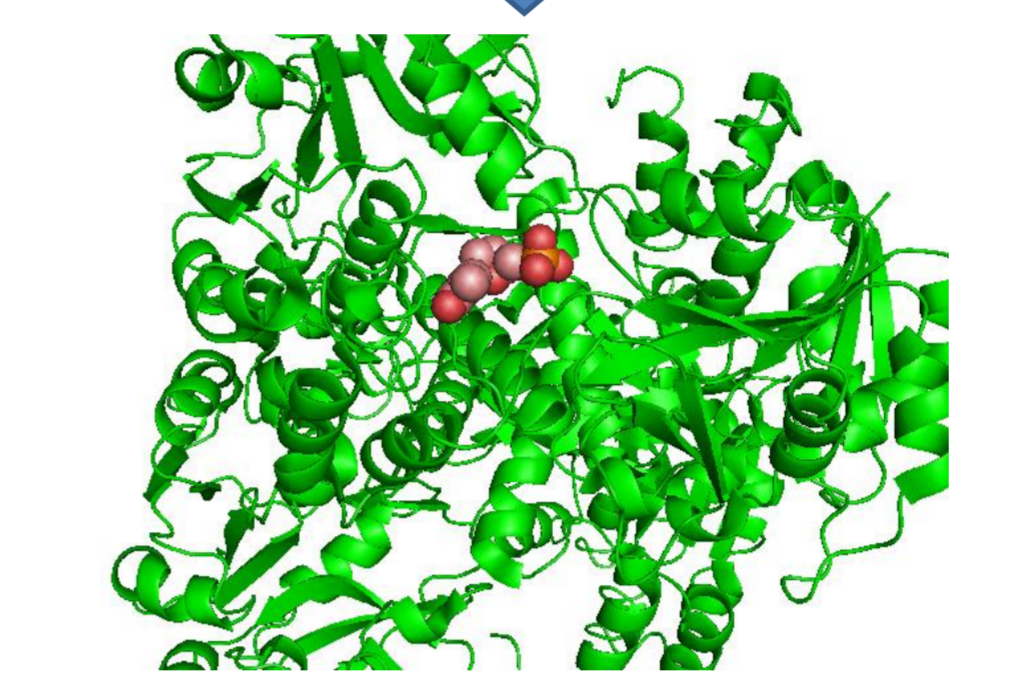


Score

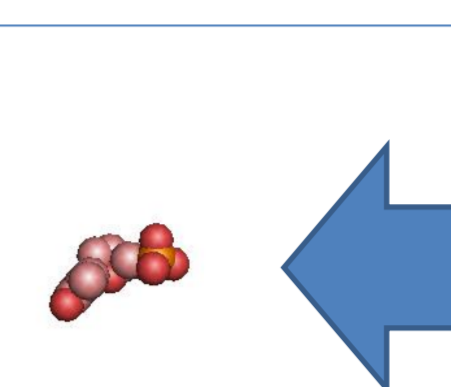
Where Ligand Is Absent:



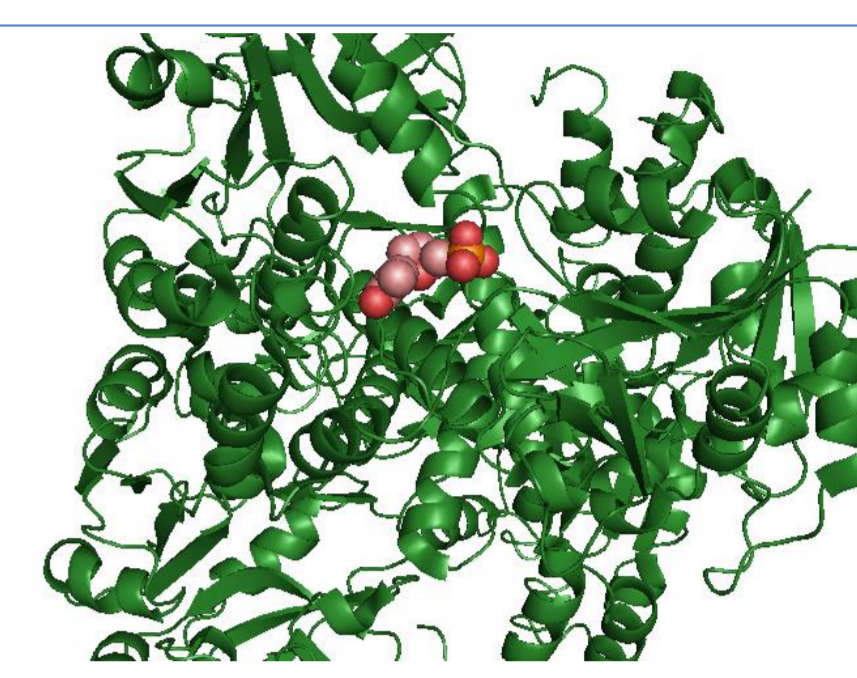
Target Protein



Target Protein In Complex with Borrowed Ligand



Borrow Ligand



Homologous Protein

Binding Site Identified



Score

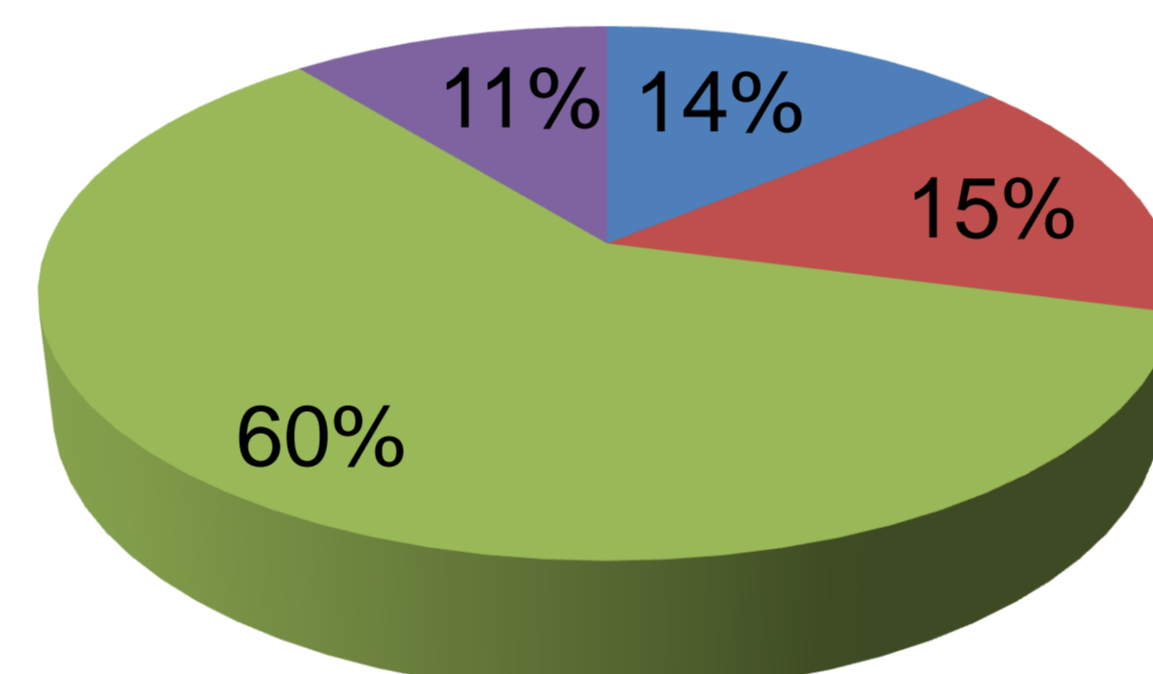
### Results & Conclusions

#### Identification of druggable proteins

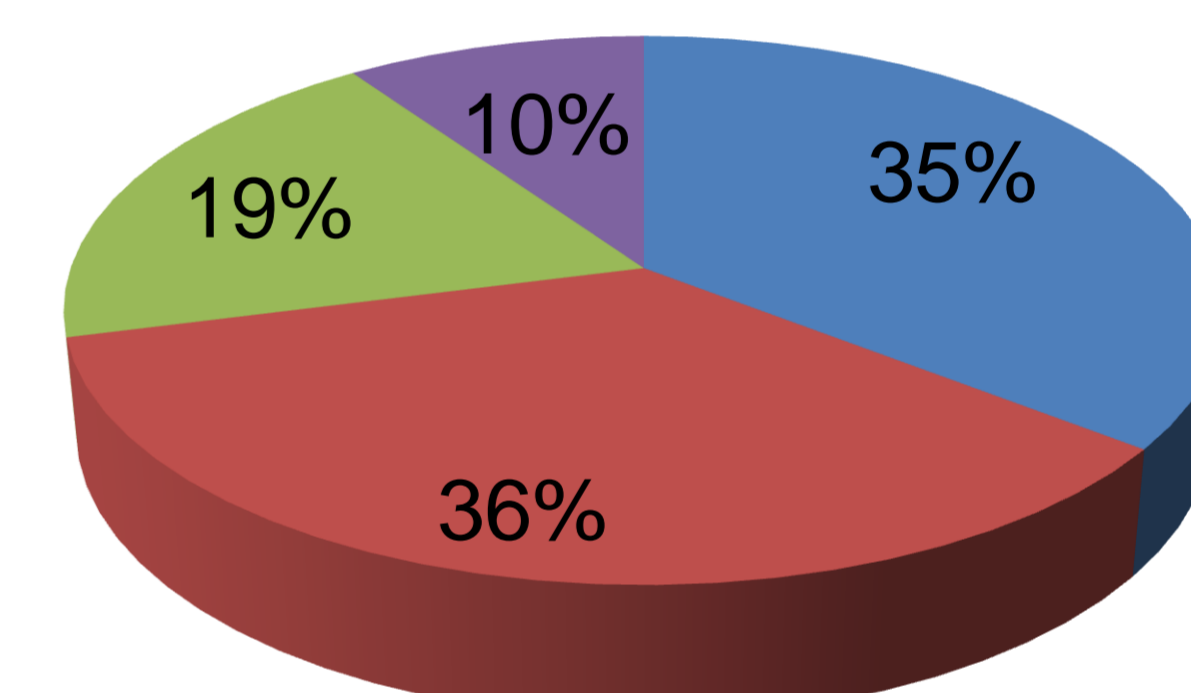
Total number of unique proteins, for which structures present: 195

Total number of structures: 595

#### All structures

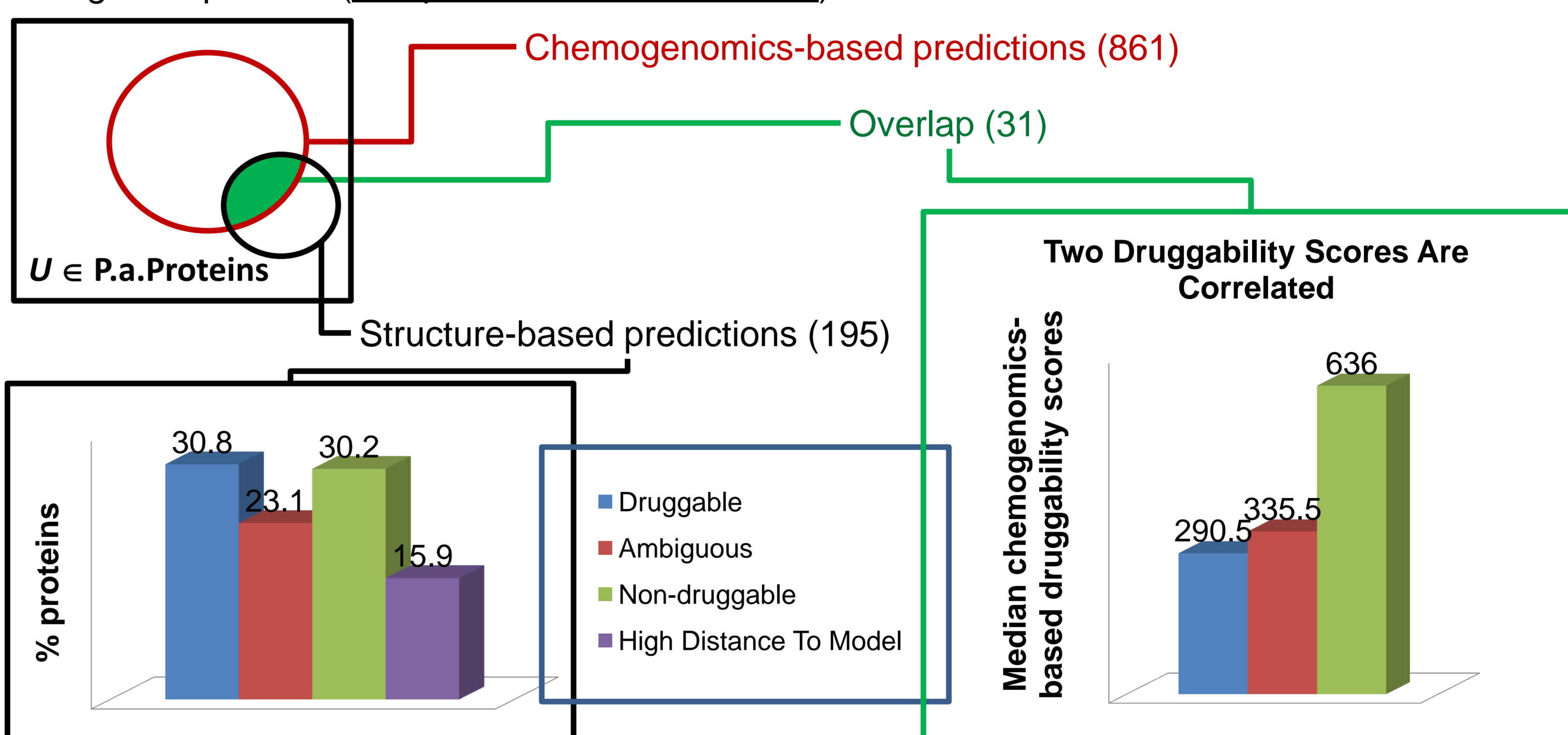


#### Essential structures



#### Comparison with chemogenomics-based druggability predictions

Chemogenomics-based druggability ranking is based on known ligands and is available for 861 *P. aeruginosa* proteins ([aeropath.lifesci.dundee.ac.uk](http://aeropath.lifesci.dundee.ac.uk)).



### Future Directions

- Improvement of scoring function by enlarging dataset of druggable & non-druggable proteins
- Extension to proteins lacking solved structures, so a higher part of the genome can be covered
- Conversion into independent program by resolution of dependencies
- Implementation of web server

### REFERENCES

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2. Hajduk, P.J.; Huth, J.R.; Fesik, S.W. *J. Med. Chem.* **2005**, *48*, 2518-2525.
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4. Krasowski, A.; Muthas, D.; Sarkar, A.; Schmitt, S.; Brenk, R. DrugPred: A structure-based approach to predict protein druggability developed using an extensive non-redundant data set. (**Submitted**)

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