# PredictSNP Onco: Towards Personalized Medicine in Children's Oncology

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## Introduction

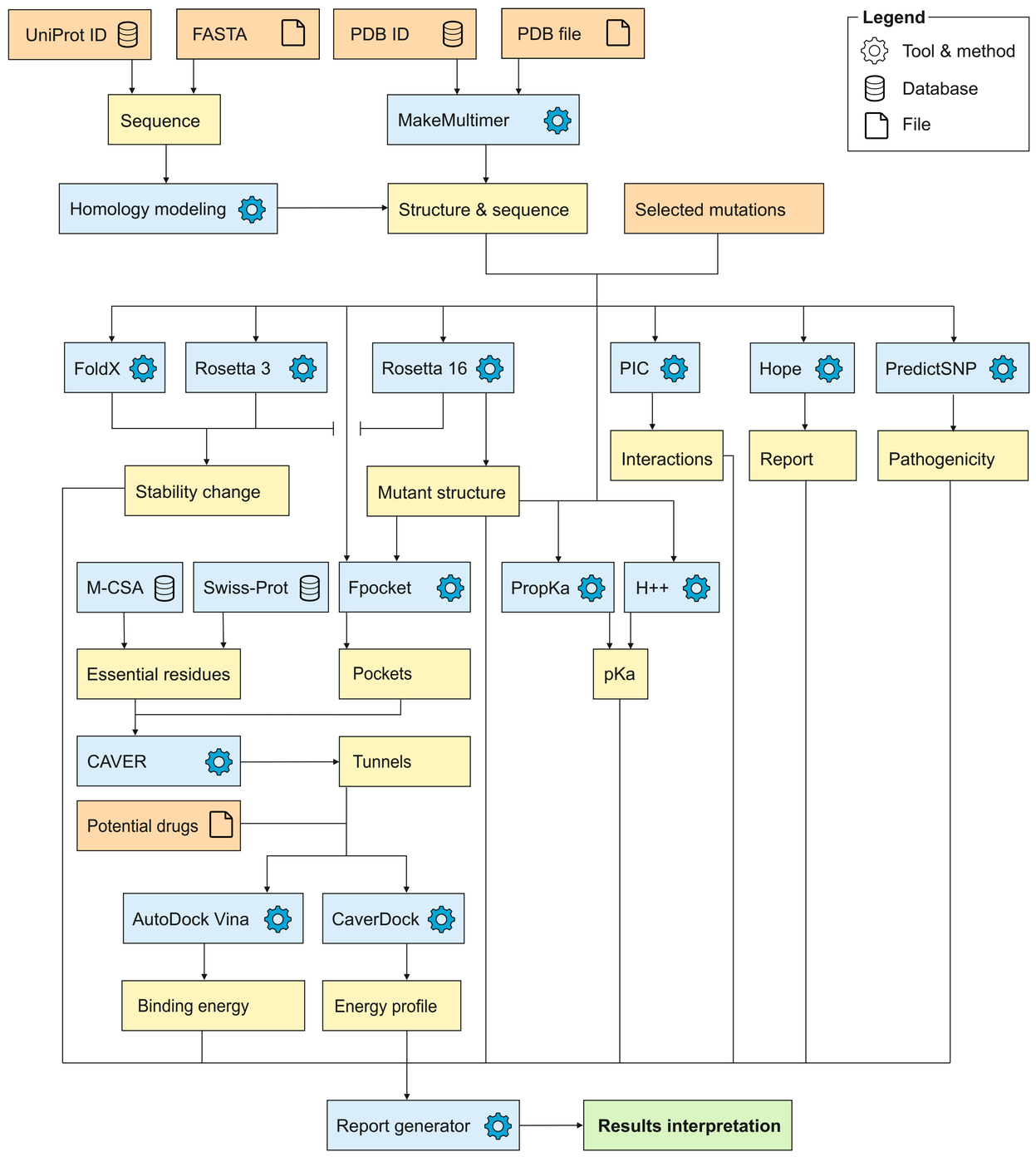
Despite significant recent improvements in pediatric oncology, the success rate for the treatment of certain malignancies remains challenging [1]. Therefore, there is a great demand for novel approaches such as "personalized oncology," which breaks the traditional "one-size-fits-all" paradigm and tries to deliver the right care to the right patient at the right time. It is based on the design of the most suitable therapeutic plan for each patient by the oncology experts in a very limited time frame. The experts have to evaluate a vast amount of data about the patient and the tumor from the detailed molecular characterization and various bioinformatics analyses [2]. Even though this approach requires a lot of effort, it is used in many hospitals around the globe, demonstrating its positive impact [3-5].

This approach is also used in the Department of Children's Oncology of the University Hospital in Brno. Their data acquisition pipeline [6] is based on transcriptome sequencing of the tumor, followed by *in silico* analyses of identified mutations and changes in metabolic pathways. However, structural analysis is missing in the current pipeline. Therefore, structure-based prediction of the effect of mutations and evaluation of binding affinities of possible drugs is of great interest.

## Objectives & Challenges

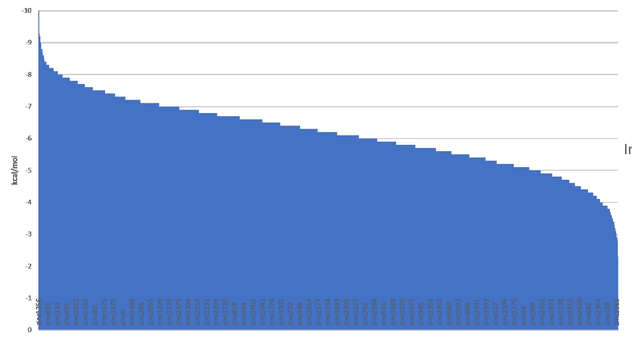
- The service must be **fully automatic** and should not need any user interactions
- The pipeline must provide **all relevant data** about the possible impact of mutation
- The calculations must be **highly parallel** and **executable on supercomputers** to achieve execution time less than 14 days because the Board needs to make the decision quickly
- All the results must be **presented in a comprehensive and straightforward way** using appropriate color coding and visual elements as the medical experts are not protein chemists
- The tool should be **easy to use** and must **not require any knowledge** about the studied proteins
- The tool must provide **interactive and user-friendly web interface** as multiple hospitals around the world can benefit from our analyses

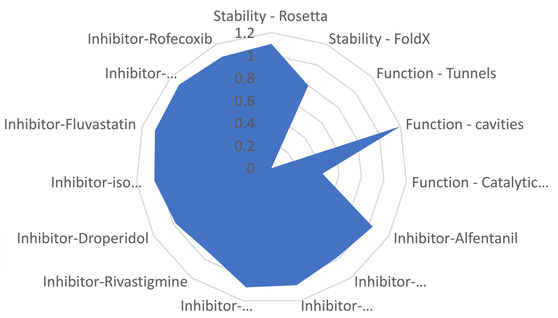
## Workflow




## Report

| Protein PDB ID: **1T0L** | **Wild Type** | | **Mutant R132H** | | **Mutant – Wild Type** | |
|---|---|---|---|---|---|---|
| | ΔΔG (kcal/mol) | | ΔΔG (kcal/mol) | | ΔΔG (kcal/mol) | |
| Predict_SNP | | | | | 87% | |
| | | | | | | |
| **STABILITY - Rosetta** | 0 | | 1.1 | | 1.1 | |
| **STABILITY - FoldX** | 0 | | 0.8 | | 0.8 | |
| | Bottleneck Å | Throughput | Bottleneck Å | Throughput | Bottleneck ΔÅ | Throughput |
| FUNCTION Tunnels | 2.1 | 0.84 | 2.1 | 0.89 | 0 | 0.05 |
| | 1.8 | 0.7 | 1.9 | 0.8 | 0.1 | 0.1 |
| | 1.6 | 0.6 | 1.8 | 0.79 | 0.2 | 0.19 |
| | 1.7 | 0.57 | 1.7 | 0.57 | 0 | 0 |
| | Relevance % | Volume Å$^3$ | Relevance % | Volume Å$^3$ | Average Δ% | Volume ΔÅ$^3$ |
| FUNCTION Cavities | 100 | 3623 | 100 | 4283 | 100 | 660 |
| | 51 | 2131 | 49 | 2152 | 50 | 21 |
| | 32 | 1375 | 31 | 1321 | 31.5 | -54 |
| | Residue name and number | | Residue name and number | | Residue name and number | |
| FUNCTION Catalytic Residues | Arginine 132 | | Histidine 132 | | R132H | |
| | Tyrosine 139 | | Tyrosine 139 | | | |
| | Lysine 212 | | Lysine 212 | | | |
| | Aspartate 275 | | Aspartate 275 | | | |
| | Residue Number pka | | Residue Number pka | | ΔpKa | |
| FUNCTION Catalytic Residues pKa | Arginine 132 - 14.23 | | Histidine 132 - 6.47 | | -7.76 | |
| | Tyrosine 139 - 12.58 | | Tyrosine 139 - 12.58 | | 0 | |
| | Lysine 212 - 11.56 | | Lysine 212 - 10.73 | | -0.83 | |
| | Aspartate 275 - 4.60 | | Aspartate 275 - 3.32 | | -1.28 | |




| **INHIBITORS** CaverDock | Ebound kcal/mol | Emax kcal/mol | RMSD Å | Ebound kcal/mol | Emax kcal/mol | RMSD Å | Ebound ΔE (kcal/mol) | Emax ΔE (kcal/mol) | RMSD ΔÅ |
|---|---|---|---|---|---|---|---|---|---|
| Alfentanil | -8.6 | -4.2 | 0.2 | -8.9 | -4.4 | 0.1 | -0.3 | -0.2 | -0.1 |
| Prostaglandin E2 | -10.9 | -7.9 | 0.9 | -10.7 | -7.4 | 0.4 | 0.2 | 0.5 | -0.5 |
| Propoxyphene | -10 | -5.8 | 1.5 | -10.6 | -5.4 | 1.4 | -0.6 | 0.4 | -0.1 |
| Sulfamethazine | -10.1 | -8.8 | 0.4 | -10.9 | -9.1 | 0.7 | -0.8 | -0.3 | 0.3 |
| Rivastigmine | -10.1 | -7 | 0.6 | -9.4 | -7.4 | 0.9 | 0.7 | -0.4 | 0.3 |
| Droperidol | -9.3 | -6.8 | 1.1 | -9.1 | -6.4 | 0.7 | 0.2 | 0.4 | -0.4 |
| iso Misoprostol | -9.4 | -5.2 | 1.4 | -9.8 | -5.8 | 1.1 | -0.4 | -0.6 | -0.3 |
| Fluvastatin | -9.6 | -5.3 | 0.7 | -10.4 | -5.4 | 1.4 | -0.8 | -0.1 | 0.7 |
| Dehydrocholic acid | -8.8 | -6 | 0.2 | -9.7 | -6.3 | 0.7 | -0.9 | -0.3 | 0.5 |
| Rofecoxib | -10.3 | -6.7 | 0.5 | -11.1 | -6.1 | 0.9 | -0.8 | 0.6 | 0.4 |

## References

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