# Case study: Pharmaceutical

## Finding new indications of existing compounds

*Disclosed under written authorization from the customer

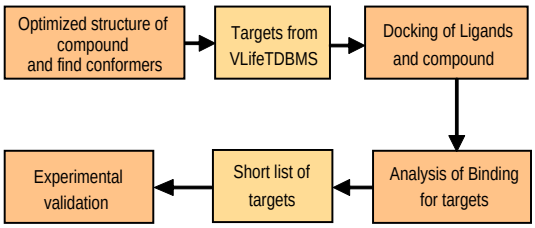
### Customer type

**A research division of leading pharmaceutical company**

### Software modules & Technology

**BioPredicta, GRIP**
**VLifeEngine, VLifeTDBMS**
**VLifeRVHTS**

### General scheme of work:




### Application

**Life cycle management, revival of failed compound, identifying potential of pipeline compound, Compound assessment for in-licensing**

## Background:

A leading pharmaceutical company requested VLife to provide research service aimed at life cycle extension and management of their product line by identifying potential new indications with VLife's computational expertise, proprietary technologies and the knowledge in discovery research. Considering the existing limitations in experimental screening of such nature, company has seen value in VLife's proposition to take up such comprehensive study.

VLife utilized VLifeTDBMS which is an in-house database of protein structures and models of therapeutically relevant targets, VLifeRVHTS technology for virtual high throughput screening and utilized proprietary software GRIP, BioPredicta and VLifeEngine for analysis.

## Study objective:

Finding new potential indications for the existing compounds of the customer, disclosed to VLife under CDA

## Design challenge:

The conventional computational approaches can identify ligands binding to the target (finding right key for the lock) to varied levels of accuracy. The challenge was to find out putative targets for the ligand of interest (finding the lock(s) which are likely to get opened by the known key). This research required;

A) The vast nature of screening which included 692 therapeutically relevant targets for which either X-ray structure were available or models could be built

**VLife Sciences Technologies Pvt. Ltd.**
Pride Purple Coronet, 1st Floor,
Baner Road, Pune - 411 045, India

Phone: +91 20 2729 1590
Web: www.vlifesciences.com
E-mail: products@vlifesciences.com

# Case study: Pharmaceutical

Techniques

**Protein structure analysis**

**Protein - ligand docking**

**Interaction analysis**

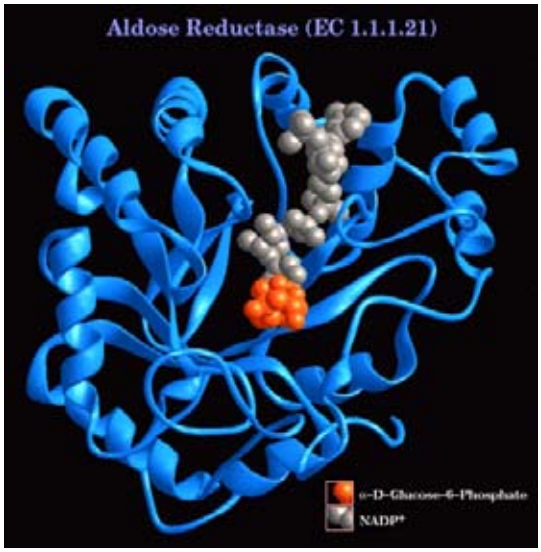



Fig. A: Structure of ALR

B) Generation of structural database of therapeutically relevant targets including useful models where X-ray structures were not available

C) Virtual high throughput screening of these targets for the given ligand

D) The scientific knowledge and understanding to interpret thecompu tational results to identify useful outcomes for the study objective

## VLife approach:

VLife employed a wide range of technologies and knowledge bases developed over the years and the scientific resources for conducting such research. In addition, VLife utilized in-house ability to customize the workflows to meet the specific requirements of the customer mandate given uniqueness of the compounds provided.

A) Proprietary technologies used: VLifeTDBMS, VLifeRVHTS

B) Proprietary know-how employed: Protein structure analysis, protein - ligand docking, multi-parameter based docking analysis

C) Proprietary software used: BioPredicta, GRIP, VLifeEngine

D) Infrastructure used: Cluster of 32 dual core computers (64 procesors)

## Methodology:

VLifeTDBMS is an in-house database of therapeutically relevant targets. This database of targets has been prepared by obtaining X-ray structures from protein databank and updated from time to time. In addition, this database also includes models of structures for targets whose X-ray structures are not available in the protein databank.

**VLife Sciences Technologies Pvt. Ltd.**
Pride Purple Coronet, 1st Floor,
Baner Road, Pune - 411 045, India

Phone: +91 20 2729 1590
Web: www.vlifesciences.com
E-mail: products@vlifesciences.com

# Case study: Pharmaceutical

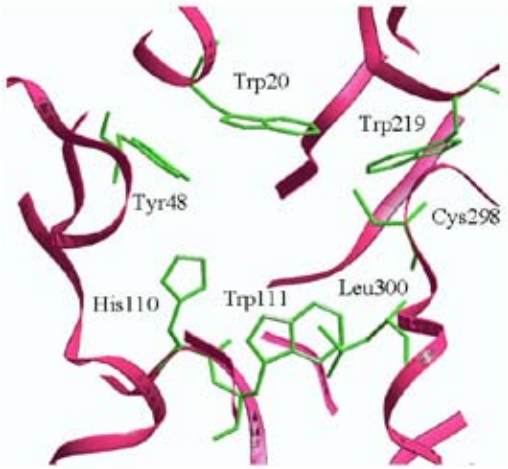



Fig. B: Active site residues of ALR

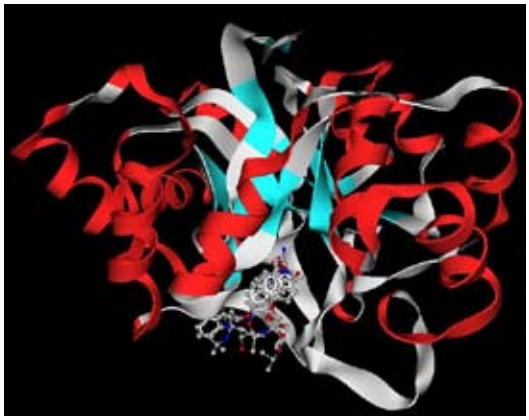


Fig. C: Docked compound along with superposed co-crystallized ligands in the active site of ALR

All these models are prepared using X-ray structures of homologue proteins having > 50% similarity. The resulting models were optimized with relevant force fields and form an integral part of the VLifeTDBMS database. VLifeTDBMS also collates information about the active sites of targets as well as other biologically relevant information about targets from multiple credible data sources and reading of scientific publications.

The ligands provided by the Customer were optimized and their conformers were generated and unique low energy conformers were identified. VLifeRVHTS technology was used to enable virtual high throughput screening by systematically docking each unique conformer of a ligand of interest in each target available in VLifeTDBMS. The resulting docked poses were optimized using relevant force field to find binding energy of ligand with the corresponding receptor. VLifeRVHTS technology is a scalable technology that works on computer clusters with distributed computing facility.

The results for the customers' compounds were analyzed taking reference of the binding of the known ligands for each target (where available) generated also from conventional docking approach. In addition, available scientific information was used to corroborate the usefulness of the results for the Study objective.

## Results and interpretation:

After virtual screening, the best pose of known ligands for the target and of the customers' compounds were selected based on binding energy. The targets for which customers' compounds exhibits comparable or better binding than their known ligands were short listed. For each target, the selected best pose of customers' compound was analyzed for its binding affinity, binding mode and interactions with the active site.

**VLife Sciences Technologies Pvt. Ltd.**
Pride Purple Coronet, 1st Floor,
Baner Road, Pune - 411 045, India

Phone: +91 20 2729 1590
Web: www.vlifesciences.com
E-mail: products@vlifesciences.com

# Case study: Pharmaceutical

A detailed report describing above information for promising targets was provided to the customer for decision making. The priority list of targets was proposed to the customer for experimental validation. The experimental validation with one of the targets showed promising results confirming computational predictions and utility of this approach in identifying new indications of compounds. This compound has been taken further by the customer for development and has filed IND in new therapeutic area with USFDA.

**VLife Sciences Technologies Pvt. Ltd.**
Pride Purple Coronet, 1st Floor,
Baner Road, Pune - 411 045, India

Phone: +91 20 2729 1590
Web: www.vlifesciences.com
E-mail: products@vlifesciences.com