

## Medicinal Chemistry and Research Informatics

Drug discovery is a crucial stage in the R&D process, and a key step that pharmaceutical companies can target to improve their R&D productivity. Selvita's drug discovery services and products, built on proprietary and partners' solutions, allow our pharmaceutical customers to robustly, quickly and cost-effectively conduct all stages of the hit-to-lead drug discovery cycle, therefore increasing productivity of the whole R&D process. We support all stages of modern commercial drug research: target identification, drug hit identification, lead identification and optimization. Our solutions take advantage of Poland's high level of science, political and economical stability, strong IP protection and near-shore logistics coupled with significant price advantages, typical of off-shore locations.

### Proprietary target identification and modeling

Protein modeling *in silico* is a strong competency at Selvita. Selvita's development team has extensive experience in protein modeling, structure prediction and mining of protein structure and sequence data on genomic scale. The full scope and high interoperability of Selvita's protein modeling tools makes Selvita unique among collaboration partners in the field.

Selvita has implemented a wide variety of effective approaches to protein modeling, which allowed it to stand apart from its competitors. Selvita's innovative, comparative modeling strategies enable determination of high quality structures as well as protein fold recognition in more difficult cases, when standard sequence search methods have failed. Selvita's protein modeling technology is based on the CABS model, extensively tested, state-of-the-art approach to protein structure prediction. CABS computational technology has been rigorously tested during CASP6 (Critical Assessment of Techniques for Protein Structure Prediction) world-wide experiment by the Kolinski-Bujnicki group. The group ranked first among over 200 world-leading groups when the consistency of the prediction was used as a criterion (the fraction of the constructed models that were placed among the top 20 of the best predictions).

Selvita's Protein Modeling technology features:

- several modeling strategies including full range of protein structure prediction difficulty
- variety of the most effective approaches, unique or which have recently been published in scientific literature
- if available, utilization of sparse, experimental structure information (e.g. NMR) to enhance protein structure prediction accuracy
- sequence and structure database solutions – efficient managing and mining

Further developments of Selvita's Protein Modeling technology will include:

- fully flexible protein-protein and peptide-protein docking
- fast small molecule docking
- binding site analysis and comparison algorithms

## Virtual screening

In today's drug discovery process the computer-aided identification of active hits and leads plays a major role in accelerating the discovery cycle. With the growth of the computer power, virtual screening of massive diversity compound libraries becomes the integral part of early steps of preclinical drug research. Modern *in silico* methods offer a solution to reduce the number of compounds to be experimentally evaluated via high-throughput screening (HTS) techniques.

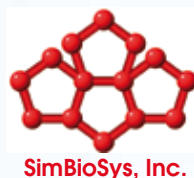
Although the capabilities of the modern HTS seem large, they still constitute just a small fraction of possible drug-like chemical space, which is one of the greatest limitations to drug discovery. Informatics-centered discovery ultimately improves the success of moving discoveries from the laboratory to the patient.

To deliver highest quality virtual screening services Selvita utilizes commercial and academic experience of its team in computer aided drug design. The core of Selvita's virtual screening pipeline is the efficient ligand-protein docking algorithm. Selvita selects potential biologically active compounds based on docking to the binding site of the X-ray structure of biological target. Selvita is able to perform virtual screening by means of molecular docking even if no X-ray or NMR structure of the target is available. In such case Selvita uses its proprietary, high-quality protein models generated with the use of state-of-the-art methods developed in-house.

Selvita uses the docking approach including full flexibility of a target protein. Results are carefully scored using different scoring functions and force fields. Screening can be performed for database of substances available in stock or for customer's corporate library.

Selvita's expertise extends also to ligand-based modeling approaches. In the absence of any target structural information Selvita builds efficient pharmacophore models, both qualitative and quantitative, which are then used to screen compound databases.

For compounds in-stock that were selected as biologically active, Selvita delivers full information needed for easy acquiring of the substances (producer, prices, etc.). Selvita's current virtual screening capabilities are around 50,000 compounds per month and can be easily extended to meet customer's needs. Selvita bases its services on state-of-the-art solutions of its partners, Accelrys and SimBioSys.



## Focused library design and synthesis

Focused compound libraries are collections of compounds with *in silico* predicted high affinity to the target protein. The design of focused libraries is one of the key steps in modern hit-to-lead drug discovery.

Selvita's team members offer their expertise in the design of biologically active compounds and computer aided synthesis design to efficiently propose new active leads. Selvita uses pharmacophore models, X-ray structures of target proteins and its proprietary *in silico* protein models for library prioritization. Alternatively Selvita employs rational de novo design methods, such as LUDI from its partner company, Accelrys.

Using scaffold-hopping technologies Selvita designs bioisosteric replacements for known active structures. Such approach lets obtain novel compounds with the defined biological activity. Selvita optimizes its compounds with regard to the synthesis route and synthetic availability: preferred are compounds that are easy to synthesize with the highest possible yield. Selvita's compounds are also filtered according to the desired physicochemical and ADME/Tox properties. For instance: the library focused on neuroleptics can be

pre-filtered through the hERG channel affinity models, for common side effect for this type of drugs. All the compounds are compliant with the Lipinski's drug-likeness rules.

In the design of targeted libraries Selvita focuses its attention on the most interesting research areas: kinase, G-protein coupled receptors and ion channels.

Selvita has two models of collaboration with its partners:

- focused library, available also to other customers, but very cost-effective
- custom-designed library, developed on demand of particular customer, guaranteed to contain chemically unique compounds

With the access to extensive market data and patent databases Selvita guarantees the highest effort towards generating the unique intellectual property for its customers.

Selvita's synthesis department extensively uses the help of *in silico* retrosynthesis tools from its partner companies, Lhasa and Molecular Networks as well as literature databases to design optimal synthetic pathway. Compounds are synthesized in our state-of-the-art laboratory which benefits from in place analytical service. When necessary samples can be purified by semipreparative HPLC.

Selvita delivers its libraries in a powder form or in DMSO solution.



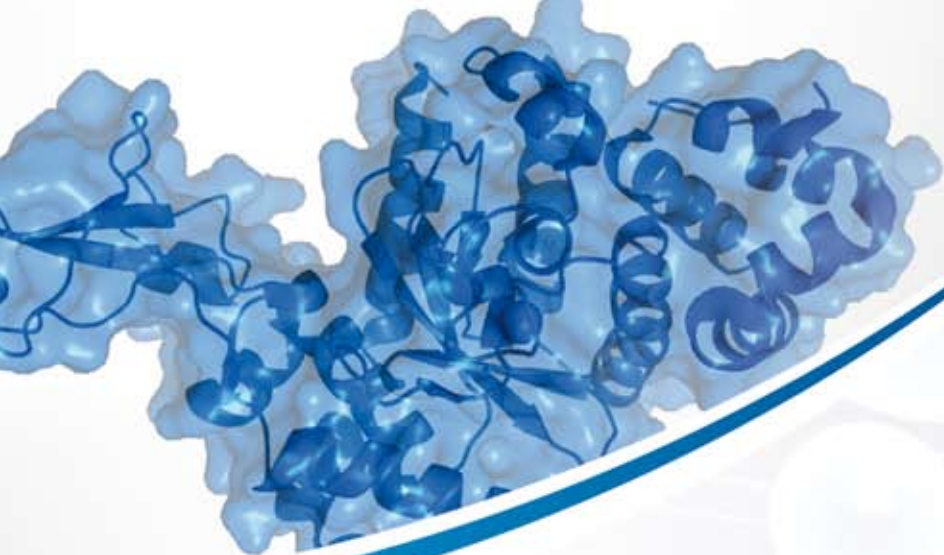
**Molecular Networks**  
Inspiring Chemical Discovery

## Lead optimization

In the lead optimization stage of drug discovery process researchers must select leads with the greatest potential to be developed into safe and effective medicines. During this stage of drug research, one must focus not only on increasing the biological activity, but also on a number of drug-like parameters including permeability, metabolic stability, lipophilicity, solubility, plasma-protein binding, CYP450 interactions, pKa, PK/PD, etc. Preclinical lead optimization technologies must be sufficiently rapid to interface with high-throughput screens without creating any further pipeline bottleneck, be predictive of drug failure, and be highly cost-effective.

Selvita provides a comprehensive set of computational methods to help drive your lead optimization programs. Selvita helps its customers in improving their compound pharmacological profile (affinity, selectivity). Selvita's expertise in pharmacophore modeling and rational ligand design techniques will increase the chances of obtaining valuable preclinical drug candidates. Selvita also has extensive experience in the utilization of more sophisticated and computationally demanding approaches of theoretical chemistry, like FEP (free energy perturbations) or quantum mechanical methods. Those can be used to very efficiently predict the desired modifications in the lead structure if high quality structural information is available (eg. X-ray structure).

Another group of lead optimization methods extensively developed at Selvita is ADME/Tox properties prediction with the use of QSAR technologies, both literature-based and custom. Selvita performs complex, multi-parameters analyses of compound metabolism. For the compound and its metabolites Selvita is able to assess not only possible side effects, like hERG channel activity or inhibition of CYP450 isoforms, but also estimate the compound broad biological profile based on possible interactions with known biochemical pathways, which is a starting point of compound profiling.



## In silico compound profiling, hit and lead prioritization

Selvita, in collaboration with its partner company, GeneGo, offers a compound profiling service, based on world-wide recognized bioinformatics solution MetaDrug. Customer's compounds can be prioritized with respect to biologic potency and possible toxicity. Not only the effects of the studied compound are considered, but also that of predicted metabolites. The assessments of biological activity are made based on well confirmed QSAR models. The construction of custom models, based on any dataset, is possible.

The proposed analysis uncovers relationships between genes, proteins, and the customer's compounds. It is possible to place the action of a NCE in a broader context of cellular biochemical pathways. The methodology allows ranking and prioritization of compounds based on indication, ADME parameters and toxicity. The results of analyses are provided with visualizations of omics data on publication-quality maps and networks. Search for drugs, drug targets, bio-active compounds, substructures (pharmaco/toxicophores) and probe potential bioactivity of new compounds from structural similarity to known drugs. MetaDrug database contains 683 canonical pathway maps representing key biological processes and modes of pharmacological and toxic action, accompanied by 400 predefined networks of drug-perturbed processes linked to toxic effects.



### Our strengths:

- high scientific level of our specialists
- competitive prices
- fully equipped laboratory with modern equipment
- professional project management with remote access to data possible
- strong protection of intellectual property
- near shore logistics
- economical and legal stability of Poland



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