

Partner in drug design

De Novo Pharmaceuticals is a drug discovery solutions provider to Pharmaceutical and Biotechnology companies. De Novo has developed SkelGen, a new generation computational drug design platform and employs a team of experienced drug designers, who, apart from SkelGen, have access to a wide array of commercial computational drug design applications.

De Novo's structure generating technology, SkelGen® enables rapid and cost effective design of novel drug candidates against a wide variety of drug targets. An estimated 90% of generated drug candidates are both novel and chemically tractable. The technology can even propose preferred synthesis routes for in-silico generated structures. Typically, the hit-to-lead development time for hits generated by SkelGen is substantially shorter than for hits found through screening compound libraries.

Structure Based Design

If reliable target protein structure data are available (X-ray crystallography, NMR, or good homology data), SkelGen can be used directly to generate novel candidate structures within the protein active site.

Ligand Based Design

If the protein structure is not available, as is still the case for most targets, sets of active ligands known to interact with the target can be used by De Novo's technology to generate *extended pharmacophores*, feature rich active site models that can be used by SkelGen as starting points for drug design or focused library design.

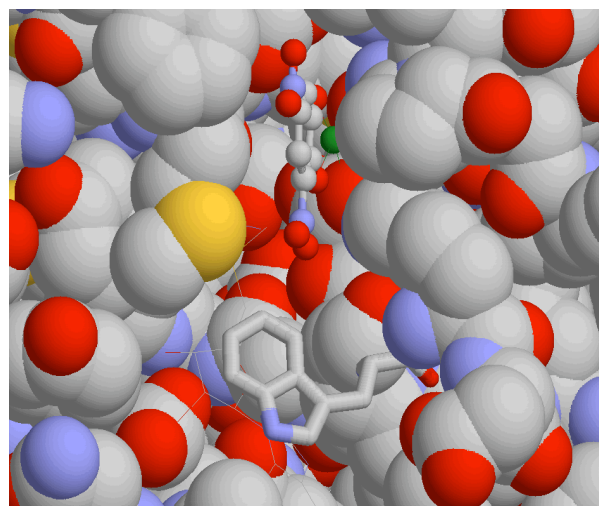
A paradigm shift in drug discovery

Whereas identification of new targets has been revolutionised and a vast number of new targets are coming our way, drug discovery has not fundamentally changed for 20 years. Essentially, most companies are looking for random hits by screening vast numbers of compounds. If a hit is found, medicinal chemists are engaged to find a lead molecule with suitable properties. This process is often costly and time-consuming.

Through SkelGen, the performance of computational drug design is now such that we can expect a significant number of hits after a relatively small number of in-silico generated structures have been synthesized and tested. This new rational approach strongly reduces the hit-to-lead development time and cost and can replace or be used alongside compound library screening.

Advantages of computational drug design

Traditional HTS libraries cover a number of chemical compounds of the order of 10^6 . Our technology gives access to a vast chemical space of over 10^{12} drug like molecules. As a result, 80% of the chemical structures generated by SkelGen are patentable. An important part of SkelGen is a set of 1700 fragments with chemical rules for attachment, which is the reason that most of the structures generated by SkelGen are readily synthesizable.



Hit-to-lead development time is often considerably shorter for SkelGen generated structures than for hits found through screening. Some of the reasons are the exclusion of known toxicophores in the structure generation process, the inherent understanding of the Structure Activity Relationship around those structures and the fact that the majority of generated structures are patentable.

Various ways to use SkelGen include:

- **Scaffold hopping**

Structural modification of an active compound, whilst retaining its biological activity. The purpose could be to improve patentability, ADMET properties, manufacturing issues etc.

- **Intelligent multi-fragment linking**
SkelGen can be used to grow "intelligent" links between fragments, which contribute to the overall activity of the created molecules.
- **Low affinity fragment-based design**
If low affinity fragments are known, SkelGen can grow drug like molecules from those fragments.
- **Virtual HTS**
After target site model creation we can screen any virtual library to find hits.
- **Focussed library design**
A focussed library of analogs can be generated around a hit, as part of lead optimisation.

Validation

Recently De Novo completed a validation project to show that De Novo's technology can generate novel hits competitively. SkelGen was used to generate ligands for the estrogen receptor. After the top ranking structures were synthesized and tested, 30% of these were identified as nanomolar or low micromolar hits. 83% of these hits were found to be novel. The entire project was completed within 6 months. (A detailed report is available on request).

SkelGen was developed in collaboration with Roche, who are now using the technology successfully as an integrated part of their drug discovery process.

Partnering

De Novo offers access to its technology through Drug Discovery Partnerships and through technology licenses.

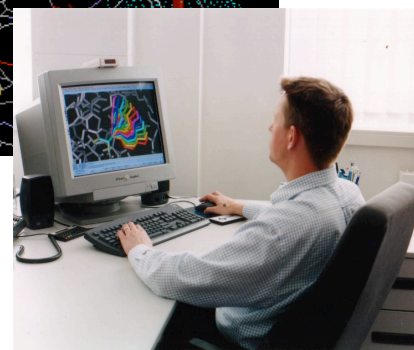
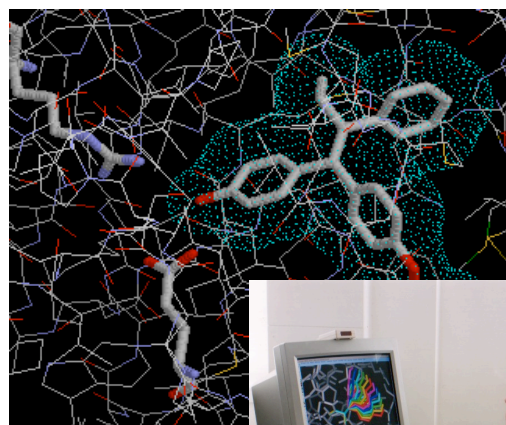
Drug Discovery Partnerships

De Novo has a strong drug design team and a wealth of know-how and experience across a wide range of target families. We offer companies access to the benefits of our technology through Drug Discovery Partnerships. De Novo will work on targets with our partners (under target exclusivity if required). In this way De Novo becomes an extension of our partner's internal project team, providing timely input into their discovery process.

The commercial structure for these collaborations typically contain a technology access or license fee, FTE payments and success related milestones. We do not require royalty payments.

Technology Licensing

The core of our technology can be made available for licensing to organisations that have the computational facilities and skills necessary for advanced computational chemistry at scale. These organisations may deploy De Novo's technology in-house on their own targets.



For more information on De Novo and our range of drug discovery solutions please visit our website:
www.denovopharma.com

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