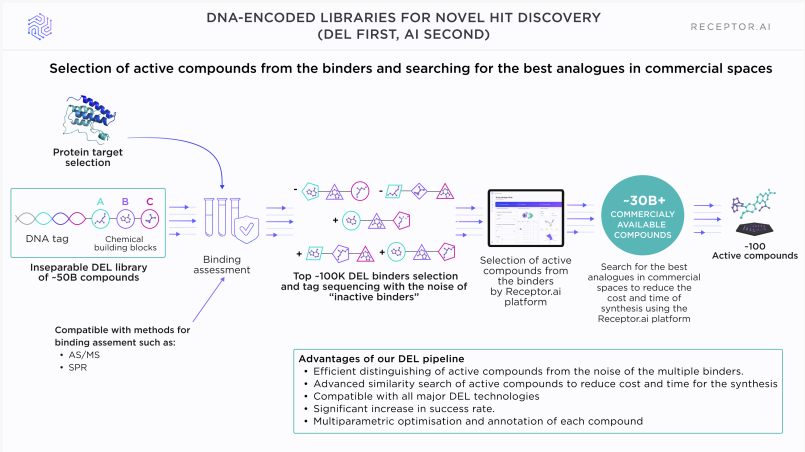
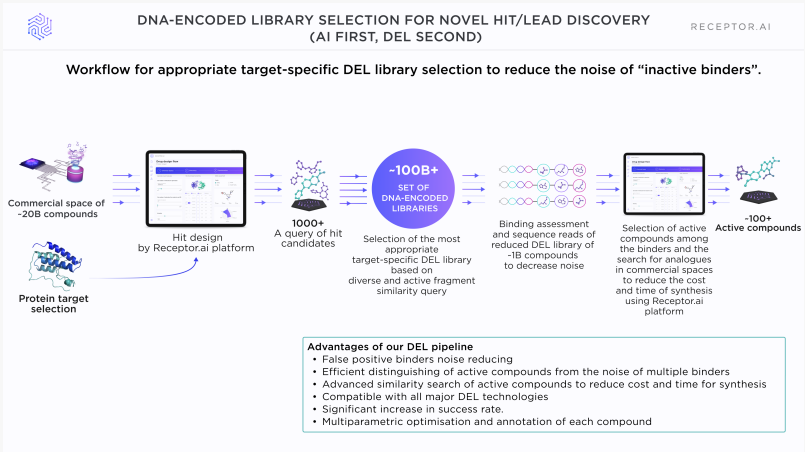
# DEL and AI: a marriage of convenience (article from Receptor.AI)

LONDON, LONDON, UNITED KINGDOM, November 28, 2022 /EINPresswire.com/ -- DELs in a nutshell




DNA-Encoded Libraries for novel Hit discovery (DEL first, AI second)

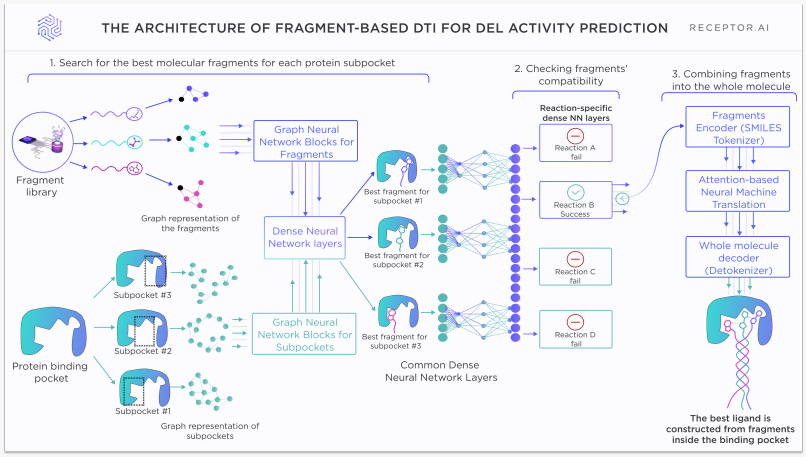



DNA-Encoded Library selection for novel Hit/lead discovery (AI first, DEL second)

DNA-encoded libraries are revolutionizing modern drug discovery by allowing an unprecedented amount of small molecules to be screened automatically. The technology is based on the conjugation of small molecules with unique DNA tags, which could be used to identify those which bind to the protein target of interest. In contrast to traditional HTS, the DEL technology offers the possibility to screen an overwhelming amount (hundred of millions and more) of molecular species in a single experiment.

The traditional screening techniques rely mostly on biochemical assays, which allow some kind of automatic readout. Each compound must be placed on the dedicated cell on the plate, severely limiting the number of molecules that could be evaluated simultaneously. Even the most advanced screening robots are limited by the physical size of the plates and the latency of the corresponding biochemical reactions. Even if physical detection techniques, such as surface plasmon resonance or capacitance sensors, are employed instead of biochemical assays, the “one cell—one compound” restrictions still hamper the scaling of the screening.

## Combining AI with DELs: a pragmatic approach



The Architecture of fragment-based DTI for DEL activity prediction

Although the potential of combining DELs with AI-based virtual screening methods looks obvious, it is surprisingly non-trivial to find the best mode of complementarity between these techniques. For example, it is tempting to propose companies which use DELs to decrease the size of the libraries by using AI-based pre-screening of huge combinatorial chemical spaces. However, this logic appears to be flawed because DELs are nothing like we have seen before in drug discovery. Although it is still counterintuitive for many experts, the DEL-based screenings are so cheap and automated that there is no practical need to decrease the library size or save on their synthesis - these efforts cost more than just brute-forcing the huge DELs.

In the last few months, we performed comprehensive market research and spoke to dozens of companies which employ DELs in their daily activities to formulate the best strategy for AI-DEL interoperability. This allows us to establish two strategies for combining our AI virtual screening techniques and DEL screening in a pragmatic integrated pipeline:

1. Fighting the noise

DEL readouts are very noisy by design. The first type of noise comes from incompletely synthesized compounds or unwanted byproducts, which are inevitable in any large-scale combinatorial synthesis. Although such erroneous molecules may appear to be binders, their DNA tags do not correspond to their chemical structure. AI models could be very helpful for performing quick “sanity checks” of DEL readouts by doing a virtual screening of identified binders against the target protein.

The second type of noise is much more important. This is the “functional” noise from inactive binders: the molecules which have affinity against the target protein but possess no biological activity and are thus useless for further drug development. The number of binders identified by DELs could reach hundreds of thousands, while functional activity assays could be rather complex and expensive to screen all of them efficiently. This is especially true in cases when only cellular or even in vivo assays could be used to confirm biological activity.

AI techniques come to the rescue here because the AI models can predict activity directly. They are able to prioritize active compounds in DEL readouts at a small fraction of the cost of the functional assay and within one day. Moreover, such models learn from experimental feedback and constantly improve themselves by being fed with experimental validation data.

2. Choosing the right DEL

DELs are extremely cheap in terms of per-molecule cost, but each DEL screening still requires a significant amount of labour, costs and resources. Large companies often possess dozens of different DELs, which are based on different sets of molecular building blocks and reactions and often on different combinatorial synthesis technologies. Trying all of them one by one for each new target could be prohibitively laborious and expensive, even for pharmaceutical giants.

As we already mentioned, trying to reduce the size of each particular DEL with AI is counterproductive because once the combinatorial synthesis map is developed, it works automatically, and brute force is more practical than any “smart” filtering technique. However, the rational choice between several DELs could reduce the cost and time of the initial hit discovery by orders of magnitude for big pharma companies and CROs.

AI techniques suit this task ideally. The virtual screening of the combinatorial chemical spaces, which are used for DEL creation, is not only very fast but also predicts the functional activity of the hit candidates directly. After such virtual screening of several DELs, the customer could make a rational choice of the library, which is the most promising in terms of getting a large number of active hit compounds without guesswork or excessive brute forcing.

The Receptor.AI SaaS platform is DEL-ready

The AI-based drug discovery SaaS platform from Receptor.AI is developed with interoperability with DELs in mind. Our platform could be used for both scenarios described above. It provides seamless automated virtual screening of huge chemical spaces and allows for super easy uploading and integration of the custom chemical databases, such as combinatorial databases used for DEL creation.

The platform is also capable of very fast and easy integration of new experimental endpoints as filters for virtual screening. The data of DEL screenings could be uploaded into the system, which will trigger automatic training of the predictive AI model and its integration into the user interface as a custom virtual screening filtering option.

The results of the virtual screening are presented in an informative and easy-to-use web interface, which allows chemists to analyze the molecules for further assessment of screened DEL libraries.

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