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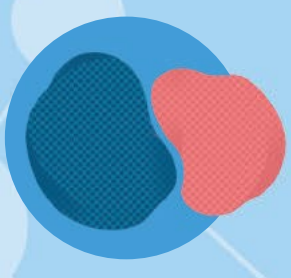
WuXi AppTec 药明康德

DRUGGING THE UNDRUGGABLE: LEVERAGING THE RIGHT SCREENING METHODS FOR CHALLENGING TARGETS

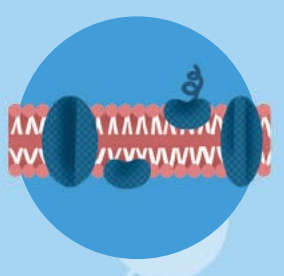
"In the past, thousands of proteins were considered undruggable. This meant that previous efforts to develop a drug against them failed. Today, the combination of novel chemical modalities and advanced technical approaches has resulted in new clinical candidates for previously undruggable targets."

Nuska Tschammer, Head of DEL Lab Operations Europe at WuXi AppTec HitS/CRELUX

EXAMPLES OF CHALLENGING TARGETS



Protein-Protein Interactions



Membrane Proteins

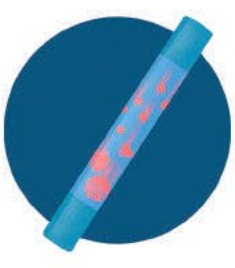
RNA/DNA Interacting Proteins

KEY CHARACTERISTICS OF CHALLENGING TARGETS

- Lack of catalytic active sites
- Presence of metal ions
- Lipophilicity of residues
- Featureless binding sites
- Need for adaptive conformational changes

ADDRESSING FORMERLY UNDRUGGABLE TARGETS WITH THESE SCREENING METHODS...

Affinity Selection Mass Spectrometry (AS-MS) Screen

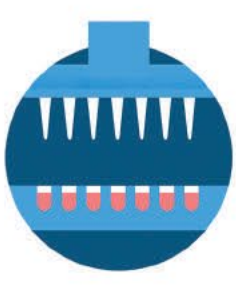


DEFINITION	# SCREENED MOLECULES	ADVANTAGES	LIMITATIONS
A method to assess the binding of the compound to soluble protein target	~300K	• Ultra-high throughput • Also applicable for solubilized membrane proteins • Depending on their solubility, low-affinity compounds (~100 µM) can still be detected	• Low-affinity binders hard to detect due to high off-rates • Protein-ligand complexes may be fully or partially distorted in the process

DNA Encoded Libraries (DEL)

DEFINITION	# SCREENED MOLECULES	ADVANTAGES	LIMITATIONS
In DEL, compounds are individually coupled to DNA tags, which are used as amplifiable identification barcodes	80B+	• Several screenings for different targets can run in parallel • Billions of compounds can be screened in a small format inside an Eppendorf tube • Low protein requirements	• Resynthesis of hits without the DNA linker required • Limited synthesis possibilities due to aqueous chemistry • Requires deep sequencing to detect lower frequency hits

High Throughput Screen (HTS)

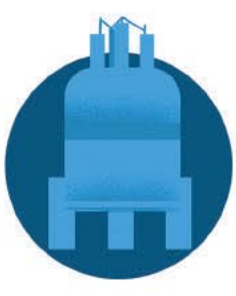


DEFINITION	# SCREENED MOLECULES	ADVANTAGES	LIMITATIONS
A method for the identification of active compounds or biologics that modulate a particular biomolecular pathway	~300K	• Information about the activity of the compound • Biochemical, automated microtiter plate assay • Compounds can be screened in intact cells for phenotypic/functional responses	• Only compounds with a strong affinity (< 10 µM) are identified • Problems screening more difficult targets, such as protein-protein interactions • Usually requires known binding site or activity

Microscale Thermophoresis (MST) Fragment Screen

DEFINITION	# SCREENED MOLECULES	ADVANTAGES	LIMITATIONS
A technology for detecting the movement of fluorescent molecules in temperature gradients	3,5K+	• Low protein consumption • Applicable to solubilized membrane proteins • High sensitivity	• Requires fluorophore labeling • Requires strong intrinsic fluorescence of the target

Nuclear Magnetic Resonance (NMR) Fragment Screen



DEFINITION	# SCREENED MOLECULES	ADVANTAGES	LIMITATIONS
Ligand-observed NMR confirms ligand binding to unlabeled protein Protein-observed NMR monitors changes in the protein signal upon ligand binding	~1,5K	• Suited for studying protein-fragment interactions • Unlabeled ligand & protein in every experiment • Can derive structural information	• Requires large amounts of isotopically labeled protein • Large library screening is challenging • Highly sensitive to false-positives

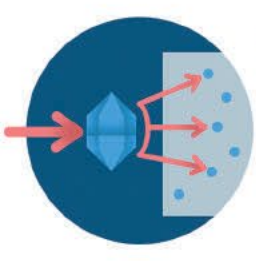
Surface Plasmon Resonance (SPR) Fragment Screen

DEFINITION	# SCREENED MOLECULES	ADVANTAGES	LIMITATIONS
An optical biosensor that measures the interactions between immobilized molecules and molecules in solution	3,5K+	• Low protein consumption • High sensitivity • Accurate affinity & kinetics measurements	• Immobilization can cause inactivation of low-stability proteins • Signal may be affected by the solvent effect

Virtual High Throughput Screening (vHTS)

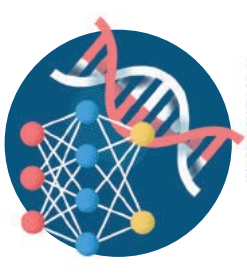
DEFINITION	# SCREENED MOLECULES	ADVANTAGES	LIMITATIONS
A computational method to screen *in silico* collections of compound libraries to identify the binders for a given target	~200M	• Screening can be performed without physically existing compounds • Saves time compared to HTS • Make-on-demand libraries facilitate access to compounds	• Requires structural information on the target or its homologs • Access to compounds is not always possible • False positives & false negatives possible

X-ray Crystallography Fragment Screen



DEFINITION	# SCREENED MOLECULES	ADVANTAGES	LIMITATIONS
A method that uses the fragments' crystal structure to determine its binding mode	~1K	• Structural information at atomic resolution • Fine mapping of fragment binding site • Can even identify weakly-binding fragments	• Requires large quantities of homogeneous protein • No affinity information • Relatively low throughput

DEL Enhanced Virtual Screening



DEFINITION	# SCREENED MOLECULES	ADVANTAGES	LIMITATIONS
A virtual screening method based on DEL data and deep learning to maximize the opportunities of hit discovery	2B+	• Increased success of hit discovery • Experimental data-driven, structure-independent modeling • Cost-effective compound acquisition • Lead-like chemical space	• Accuracy depends on DEL selection data quality • New method yet to be fully evaluated

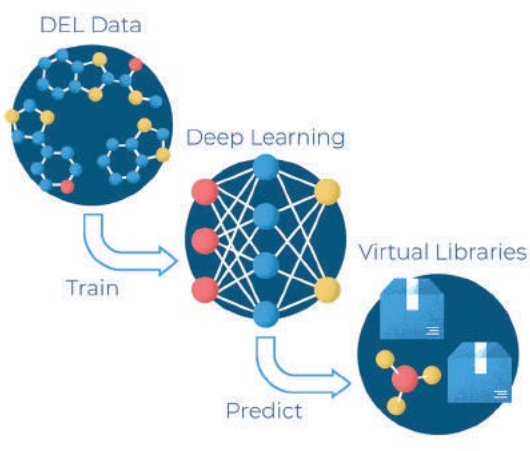
How WuXi AppTec Leveraged Its Expertise of DELs and Virtual Screening to Increase the Success of Hit Discovery for Aurora A Kinase

CASE STUDY

Aurora A is a serine/threonine kinase that plays an important role in healthy cell proliferation during mitosis and meiosis. However, this enzyme has also been found to be highly expressed in a number of tumor types, indicating an interesting target for cancer therapy.

A number of small molecule Aurora A inhibitors have been developed and tested in preclinical and clinical trials as a monotherapy or in combination. With the help of the right screening methods, even more target molecules can be found.

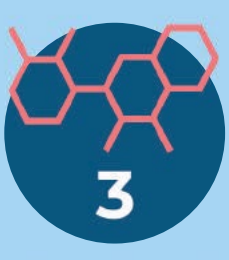
SCREENING METHODS USED...



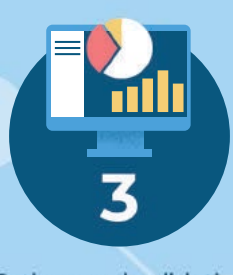
Based on the advantages of experimental data-driven, structure-independent modeling, combined with cost-effective compound acquisition, and a lead-like chemical space, the DEL virtual screening platform at WuXi AppTec brings together experimental big data from DEL and the learning capability of machine learning to increase the success of hit discovery.

RESULTS

Micro-molar hits validated



Novel chemical structures found



Orthogonal validation assays used: SPR, MST, ADP-glo

Downstream optimization

CONCLUSION

In this proof-of-concept study, the team at WuXi AppTec demonstrated the use of the DEL and deep learning screening method for the identification of novel hit molecules for Aurora A kinase target protein.

Using in-house biophysics, biochemical, and cellular assays, WuXi AppTec was able to validate multiple micro-molar hits. These compounds contain novel chemical structures and the team is in the process of examining their patentability.

In conclusion, the team at WuXi AppTec developed a scalable deep learning pipeline for DEL-ML virtual screening and demonstrated an end-to-end solution from DEL selection data to compound acquisition and validation.

Are you working with a challenging target and struggling to find the right lead finding option? Learn more at www.wuxiapptec.com/ or get in touch with our expert:

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SOURCES

WuXi AppTec, Journal of Chemistry & Biology, FEBS Letters, Progress in Biophysics and Molecular Biology, Journal of Biomolecular Screening, The International Journal of Student Research, Journal of The American Society for Mass Spectrometry, Bioinformation, ACS Medicinal Chemistry Letters, Cell Chemical Biology, Small Molecule Targets In Immuno-Oncology, Journal of Molecular Cancer

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