IN SILICO PREDICTIVE ANALYTICS: ACCELERATING IDENTIFICATION OF POTENTIAL DISEASE-MODIFYING COMPOUNDS FOR PARKINSON'S DISEASE

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BACKGROUND

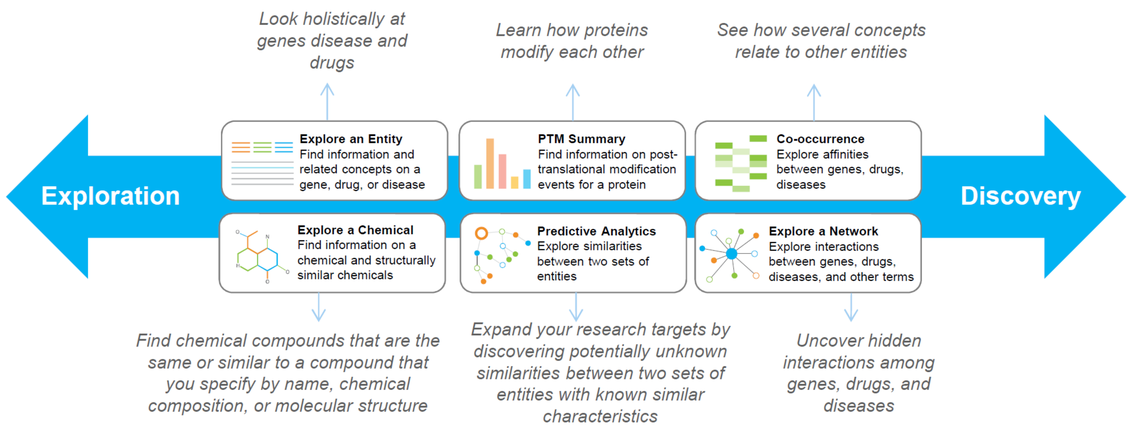
- Emerging evidence supports a key role for α-synuclein oligomers in the neurodegenerative process in Parkinson's disease and thus α-synuclein oligomers are attractive therapeutic targets for disease modification.
- Development of disease-modifying therapies for Parkinson's disease and translation into clinical use is expensive and slow. Repurposing of compounds previously proven to be safe in humans and approved by regulatory agencies could reduce costs and accelerate drug development.
- However, methods to prioritize candidate drugs for repurposing are needed. IBM Watson for Drug Discovery is a cognitive computing platform able to extract domain-specific text features (e.g., drugs, diseases) from the literature and identify connections between entities of interest.
- Here, we use IBM Watson for Drug Discovery to generate a predictive model to rank potential candidates for drug repurposing for Parkinson's disease.

OBJECTIVES

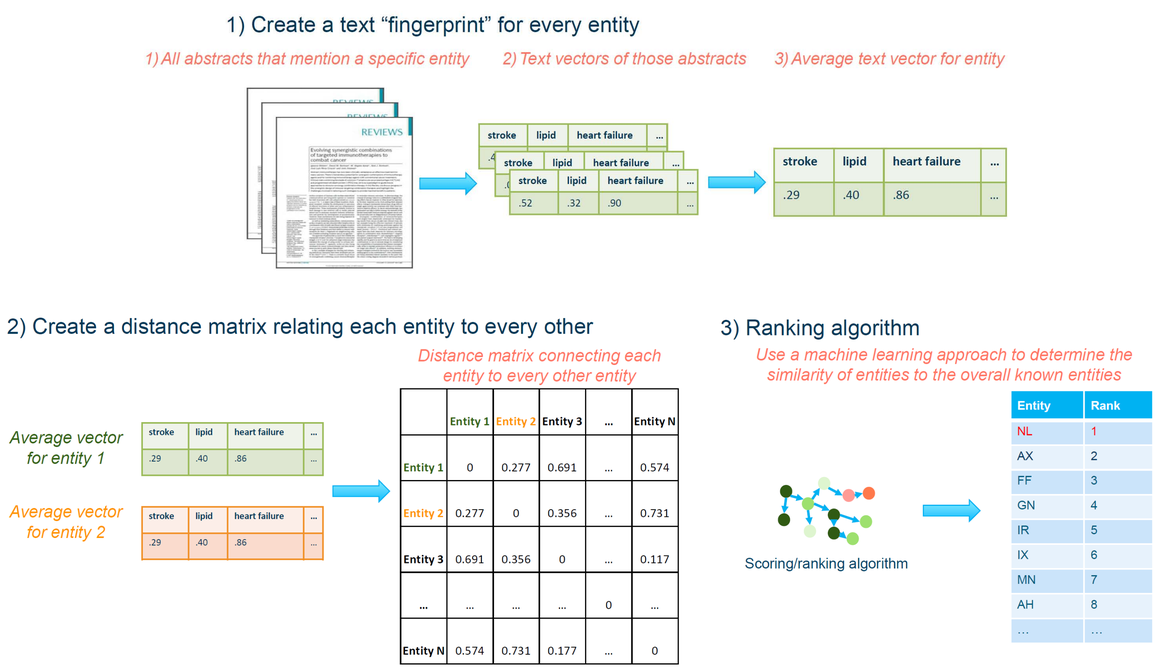
- To use IBM Watson for Drug Discovery to identify compounds that may have potential to reduce α-synuclein oligomers and are amenable to drug repurposing for Parkinson's disease.

IBM WATSON FOR DRUG DISCOVERY (WDD)

1 WDD Core Capabilities



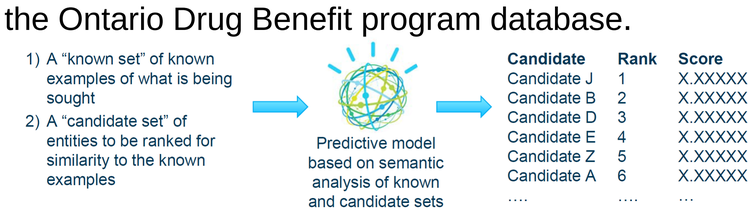
2 WDD Predictive Analytics Methodology



METHODS

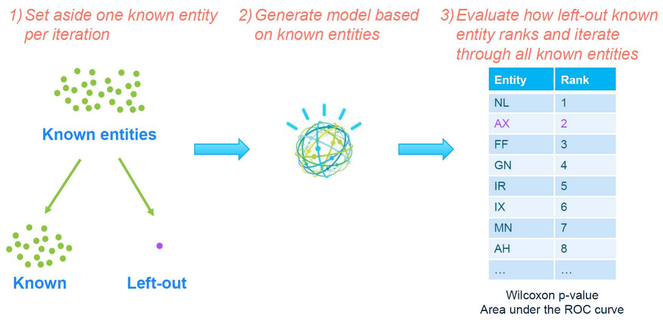
Known set: We developed a known set of 15 chemical compounds previously shown to reduce α-synuclein oligomers *in vitro* or *in vivo* in published studies.

Candidate set: We developed a candidate set composed of 620 individual active compounds in the Ontario Drug Benefit program database.



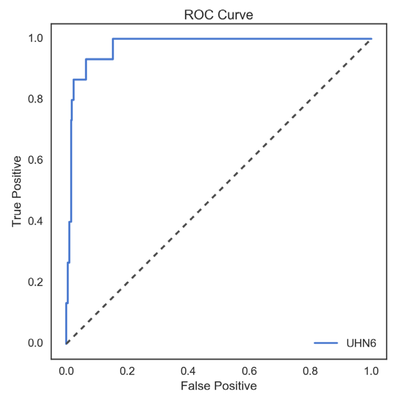
RESULTS

1 Leave-One-Out Cross Validation



KNOWN COMPOUND	SCORE	RANK*
Curcumin	0.026572896	1
Resveratrol	0.024891593	2
PD169316	0.020369345	6
SB239063	0.020314941	7
Baicalein	0.018408176	11
Geldanamycin	0.018190702	12
17-AAG	0.013898701	17
Isorhynchophylline	0.01359914	18
TBBz	0.011656517	19
Myricetin	0.011613904	20
Rosmarinic acid	0.011587948	21
Cyclosporine	0.010528345	23
AICAR	0.009317443	28
Anle138b	0.004580211	54
Tacrolimus	0.002258231	110

*For each known compound, the rank is computed from the score the compound gets when it is left out of the known set



Wilcoxon p-value comparing known and candidate scores = 7.02×10^{-10}

AUC (area under the receiver-operating-characteristics curve) = 0.975

2 Ranked Candidates from WDD Predictive Analytics

620 CANDIDATES

WDD Predictive Analytics

52 TOP RANK CANDIDATES

- 2 Acetylcholinesterase inhibitor
- 3 Anti-hypertensive
- 11 Anti-inflammatory
- 3 Anti-lipemic
- 6 Anti-microbial
- 9 Anti-neoplastic
- 2 Immunosuppressant
- 3 Vitamin/Mineral
- 13 Other

Directed PubMed® searches

Exploration using WDD applications

21 FINAL CANDIDATES*

- 1 Acetylcholinesterase inhibitor
- 3 Anti-hypertensive
- 4 Anti-inflammatory
- 2 Anti-lipemic
- 2 Anti-microbial
- 3 Anti-neoplastic
- 2 Immunosuppressant
- 4 Other

*9 with existing evidence for inhibition of α-synuclein aggregation, 12 compounds not previously associated with α-synuclein but with biologically plausible links to α-synuclein aggregation

FUTURE WORK

- Next steps will include performing validation of prioritized compounds using both *in vitro* and *in vivo* models of α-synuclein toxicity, as well as epidemiologic studies assessing incidence and outcomes in Parkinson's disease.

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