Introduction

- Despite improvements across all stages of drug development, the rate of drug attrition due to clinical trial failures has risen substantially.
- A substantial portion of these failures occur for safety reason.
- A key area of improvement has been the screening for drugs likely to fail clinical trials.
Widely accepted as a useful guide for filtering toxic molecules in the early stages of drug discovery

Lipinski proposed this concept in 1997 with the Rule of 5 (Ro5)

Set of 4 physicochemical features
  (i) < 5 hydrogen-bond donors;
  (ii) molecular mass <500;
  (iii) calculated log P<5 (partition coefficient);
  (iv) < 10 of hydrogen-bond acceptors.

Helps determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans.

Candidate drugs that conform to the Ro5 tend to have lower attrition rates during clinical trials and hence have an increased chance of reaching the market.
Drug-likeness measures

- Ro5 is a conservative measure, and passing the rule does not guarantee drug-likeness.
- Modified rules have been proposed since:
  - Veber’s rule (2002)
  - Ghose’s rule (1999)
- These include additional drug properties, e.g. polar surface area to predict bioavailability.
- These concepts have been shown to reduce attrition rates, however overall clinical trial attrition rates continue to increase.
- Most drugs that failed due to toxicity (FTT) pass these rules. So we are currently lacking in an approach to distinguish between FDA approved drugs and those FTT.
This paper introduced a data-driven approach (PrOCTOR) that directly predicts the likelihood of toxicity in clinical trials.

- Approach uses a combination of drug structure, drug likeness, target expression and other features.
- 48 features: 10 molecular properties, 24 target based features, 4 drug-likeness rule features
Target based features

- Drug targets annotated from DrugBank
- Tissue expression data calculated from Genotype-Tissue Expression (GTEx) project
- Loss of function mutation frequency in target gene extracted from Exome Aggregation Consortium (ExAC) database
- Network connectivity (degree and betweenness) of target was computed using aggregated gene-gene interaction network
- Regulatory network was from ENCODE data, Metabolic enzyme network based on compound reactions in KEGG. Phosphorylation network, signaling network constructed from the SignalLink database. Reactome and NetPath also used.
Modeling

- 784 FDA approved drugs and 100 FTT drugs
- Random Forest models built over 50 bootstrapped decision trees using the 48 features.
- A sub-sampling approach is used to account for the imbalanced ratio of approved drugs to FTT drugs
  - Randomly sampling the FDA-approved class of samples to the size of the FTT drugs.
  - To reduce the odds of poor representatives being sampled, this was repeated 30 times.
  - The labels were assigned by taking the consensus across the set of bootstrapped trees.
- This approach also yields a probability for each test sample.
- This probability is used to calculate an odds score = \( \frac{P(\text{approval})}{P(\text{failure})} \)
Random Forest

- Ensemble approach: A group of weak learners that together form a strong learner

- Begin as a decision tree (weak learner).

- RF combines trees (strong learner).
  - Samples N cases at random with replacement
  - Randomly select m predictor variables
  - Split on the node that provides best performance
  - Repeat
Performance

- ROC curve for PrOCTOR and other scores.
- AUC = 0.8263
- Sens = 0.7544
- Spec = 0.7410
- Statistically significantly better performance than the other metrics.
Feature importance in predicting FTT
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(a) Feature importance based on Mean Decrease Gini index:

- PolarSurfaceArea
- wQED
- maxBtwm
- Molecular.Weight
- Pancreas
- Refractivity
- maxDegree
- XLogP
- Adrenal.Gland
- Kidney
- LogpSolubility
- lossFreq
- Small.Intestine
- Testis
- HydrogenBond.Acceptor.Count
- HydrogenBond.Donor.Count
- Heart
- Rotatable.Bond.Count
- Muscle
- Nerve

(b) Feature importance of PC components:

- PC1
- Polar.Surface.Area
- Q.E.D.
- Target.Degree
- Target.Betweenness
- LOF.Freq
- Molecular.Weight
- PC3
- PC2
- Refractivity
- XLogP
- LogP.Solubility
- HBA.Count
- Rotatable.Bond.Count
- HBD.Count
- Num.Rings
- Formal.Charge
Validation

- Model applied to European and Japanese approved drugs.
Adverse events occur more frequently in predicted failed toxic clinical trial (FTT) drugs compared with predicted approved drugs.

- Validation: Side effects
Summary

- A new approach that includes features beyond the widely accepted molecular properties of a compound was highly effective.
- Data-driven approach (PrOCTOR) that incorporates the target-based information related to a drug, along with the established chemical properties to predict toxic in clinical trial outcomes.
- PrOCTOR was able to significantly separate drugs that were toxic in clinical trials from FDA-approved drugs.
- PrOCTOR identified individual features, as well as combinations of features, that predict toxicity (or absence of toxicity) and thus may help guide the rational drug development process to design less toxic molecules.
- Furthermore PrOCTOR may also help flag drugs for increased post-approval surveillance of adverse effects and toxicity.
Clarivate Implementation

AUC = 0.83

AUC = 0.82