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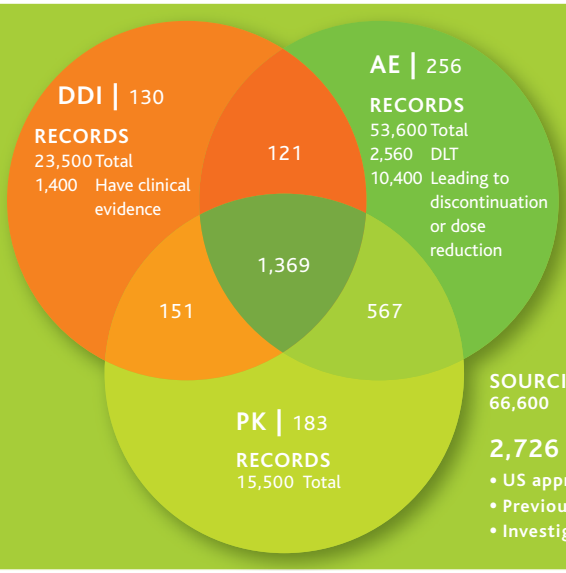
Using Inxight Database to Establish PK-Toxicity Relationships

Rancho was deeply involved in the creation of NCATS Inxight Drugs **https://drugs.ncats.io**, a web portal that incorporates a wealth of data on ingredients in medical products, provides marketing and regulatory status, rigorous drug ingredient definitions, biological activity, clinical use, and more. Rancho supported extending the dataset to aid with repositioning of existing and approved drugs, by adding manually curated information about pharmacokinetics (PK), adverse events (AE), drug-drug interactions (DDI) and sourcing.

NIH National Center for Advancing Translational Sciences

Inxight Drugs | FRDB

Approval status · Targets · Indications · Properties



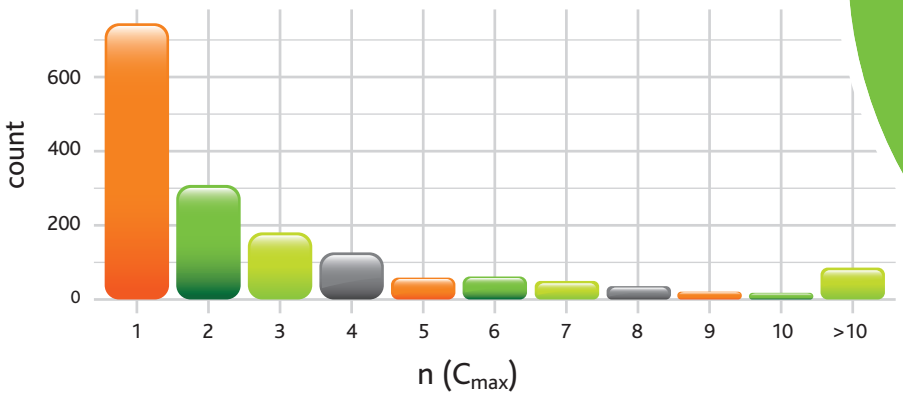
SOURCING RECORDS
66,600

2,726 Total Drugs

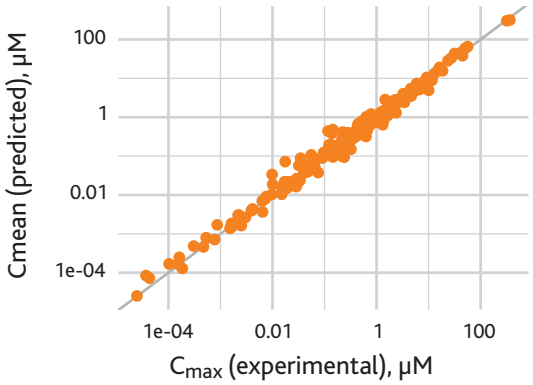
- US approved
- Previously approved
- Investigated

66% of drugs contained in FRDB have more than one PK data point. Standardization of Cmax and AUC units enables building of dose-concentration relationships and extrapolation of drug plasma concentration to toxic doses.

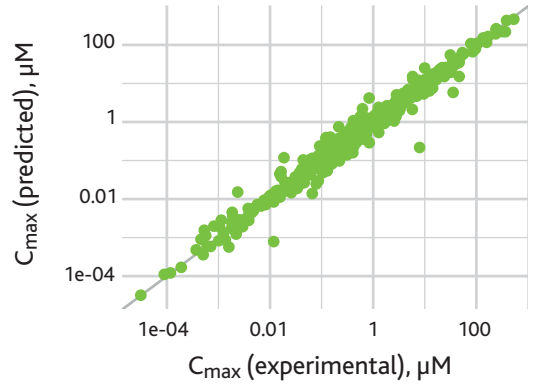
Counts of drugs with different C_{max} values



Cmean interpolation



C_{max} interpolation



TOP 5 ANTI-TARGETS

Cmean	Cmax
hERG.	VEGR2
5-HT2C.	VEGFR1
5-HT2B	VEGFR3

Inxight FRDB contains toxicology information about the highest dose tested in clinical trials for each administration route and regimen, adverse events leading to drug discontinuation, dose reduction or interruption, dose-limiting toxicities (DLTs) and maximum tolerated doses (MTDs). FRDB also contains data on overdosage reports with corresponding AEs and AEs resulting in FDA black box warnings, and a selected AEs for recommended doses.

Toxicology data and PK predictive modeling can be used to discover relationships between drug dose, adverse events and target engagement, as well as to find anti-targets – targets, which are effectively inhibited only at toxic doses and not inhibited at safe doses based on drug Cmax or Cmean.