

NCATS Inxight FRDB: Fast Response DataBase for Drug Repositioning

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Background and Goal

During healthcare emergencies, it is **critical to discover treatments very quickly**. The only solution to this is the repositioning and repurposing of existing approved and investigational drugs.

To test a drug candidate in the clinic, one should have answers to these questions:

- Is the compound active against its presumed target?
- Is it possible to achieve the required concentration in patients?
- How toxic is the compound? Can it be used in combination with other drugs?
- How to source the compound?

Here, we describe Fast Response DataBase (FRDB), a web resource designed to answer those questions. FRDB leverages an existing **NCATS¹ Inxight Drugs** web portal² and adds manually curated data about drug **pharmacokinetics, adverse events, drug-drug interactions, and sourcing** to aid drug repositioning and PK/PD modeling.

¹ This research was supported in part by the Intramural/Extramural research program of the NCATS, NIH.

² Sriramshetty VB, Grishagin I, Nguyen DT, et al. NCATS Inxight Drugs: a comprehensive and curated portal for translational research. *Nucleic Acids Res.* 2022;50(D1):D1307-D1316. doi:10.1093/nar/gkab918

FRDB Core Data

Pharmacokinetics (PK)

- **Key metrics:** C_{max} , AUC, $t_{1/2}$, $F_{unbound}$ for parent drug and active metabolite
- **Administration:** route, dose, and frequency
- **Population metadata:** health status, food status, sex
- **Reference:** FDA labels, review documents, articles, reviews, ClinicalTrials.gov, etc.

Adverse Events (AEs) / Toxicity (Tox)

- **Highest dose** tested in clinical trials for each administration route and regimen
- AEs leading to drug **discontinuation, dose reduction or interruption**
- Dose-limiting toxicities (**DLTs**) and maximum tolerated doses (**MTDs**)
- **Overdosage reports** with corresponding AEs and AEs resulting in FDA black box warnings
- **AEs for recommended dose** (for limited subset of drugs)
- **Administration:** route, dose, and frequency

Drug-Drug Interactions (DDIs)

- **Relationships** between **drugs** and their **metabolites, DDI and Tox** targets
- *In vitro* **IC₅₀**, **inhibition %** at specific concentrations, **Ki**
- **Clinical relevance:** strength of interactions, type of experiment, exposure change

Inxight Drugs

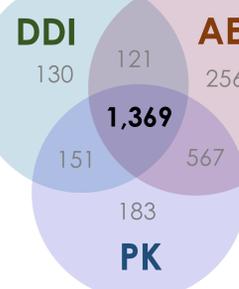


- Approval status
- Targets
- Indications
- Properties

FRDB Stats

Records
23,500 Total
1,400 Have clinical evidence

Records
15,500 Total



Records
53,600 Total
2,560 DLT
10,400 Leading to discontinuation or dose reduction

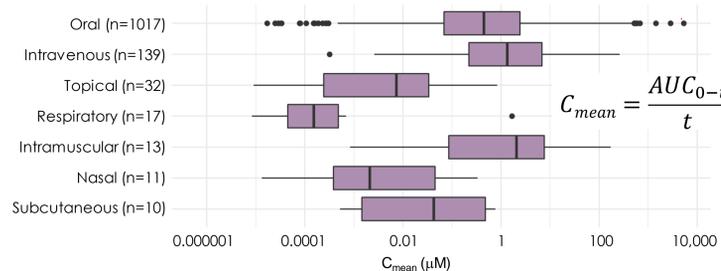
Sourcing Records
66,600

2,726 Total Drugs

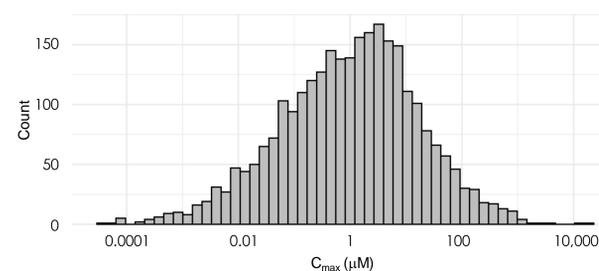
- US approved
- Previously approved
- Investigational

FRDB use case: PK prediction

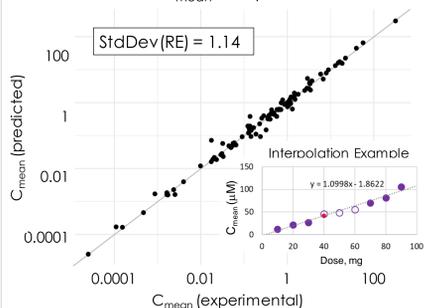
Distribution of C_{mean} for Different Routes of Administration



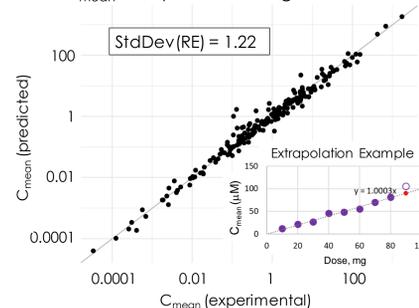
Distribution of C_{max} after Oral Administration



C_{mean} Interpolation



C_{mean} Extrapolation to High Doses

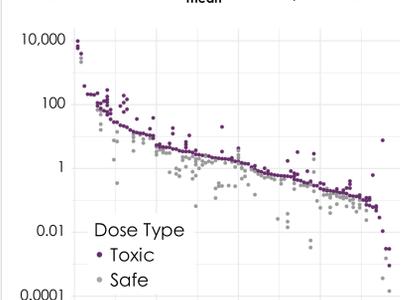


Pharmacokinetic data from FRDB can be used to build dose-concentration relationship and interpolate/extrapolate AUC and C_{max} to doses for which there is no PK data available. Mean relative error in AUC extrapolation is 22%.

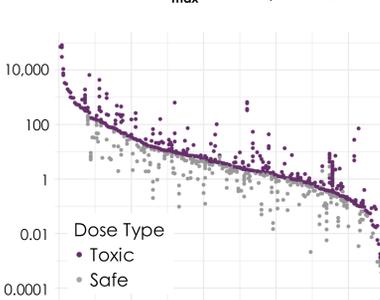
$$RE = \frac{C_{mean}(predicted)}{C_{mean}(experiment)}$$

FRDB use case: anti-targets

Distribution of C_{mean} for Safe/Toxic Doses



Distribution of C_{max} for Safe/Toxic Doses



Tox data and PK predictive modeling can be used to discover relationships between drug dose, adverse events and target engagement.

C_{max} and C_{mean} from NCATS FRDB and ChEMBL can be used to assess anti-targets – targets which are selectively inhibited in toxic doses but not in safe doses.

Top 5 Anti-Targets

C_{max}	hERG	5-HT2C	5-HT2B	erbB1	SERT
C_{mean}	VEGFR2	VEGFR1	VEGFR3	erbB1	FLT3



FRDB data are publicly available at <https://drugs.ncats.io>. Complete dataset is available for direct download as well at <https://drugs.ncats.io/downloads-public>

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