DRUG INTERACTION SOLUTIONS

Transforming scientific data into clinical knowledge

SCHOOL OF PHARMACY
UNIVERSITY OF WASHINGTON
Who we are

We are a team of pharmaceutical scientists, pharmacists, and clinicians who together bring over 150 years of cumulative expertise in drug metabolism, transport, pharmacokinetics (PK), drug interactions, and clinical pharmacology. We are research-based at the University of Washington’s School of Pharmacy, Department of Pharmaceutics. We operate as a non-profit endeavor, supported by licensing revenues to cover the costs of scientific and technical maintenance of the database, as well as the development of new content and features.

Dr René Levy founded the Metabolism & Transport Drug Interaction Database program at the University of Washington in the late 1990s, after recognizing the advances made in the field of in vitro to in vivo predictions and the need for more widespread knowledge about the risks of drug interactions.

The University of Washington started licensing access to the database in 2002. It was later expanded with the addition of the pharmacogenetics, food-effect studies, organ impairment data, and additional mechanisms of PK-based drug interactions.

All curation activities and editorial tasks are performed in-house with a team that is dedicated to the overall platform, identified as Drug Interaction Database (DIDB), and user support.

MEET THE TEAM

**UW DRUG INTERACTION SOLUTIONS:**

René Levy, PhD, Founder & Advisor
Isabelle Ragueneau-Majlessi, MD, MS, Co-Founder & Director
Jingjing Yu, MD, PhD, Associate Director
Sophie Argon, PharmD, MS
Marie C. Bodinier, MS, Marketing
Chris Kinsella, IT support
Grace Lee, Admin
Savannah McFeely, PhD
Katie Owens, BPharm, PhD
Ichiko Petrie, PharmD
Tasha Ritchie, PhD
Jessica Tay-Sontheimer, PhD
Yan Wang, MS
Cheryl Wu, PhD
Catherine Yeung, PharmD, PhD, MPH

**UW COMOTION, LICENSING:**

Roï Eisenkot

Our recent publications

**IN VITRO-to-IN VIVO EXTRAPOLATION of TRANSPORTER INHIBITION DATA for DRUGS APPROVED by the U.S. FOOD and DRUG ADMINISTRATION in 2018**

Jingjing Yu and Isabelle Ragueneau-Majlessi
Clinical and Translational Science, Jan 25, 2020

**VARIABILITY in IN VITRO OATP1B1/3 INHIBITION DATA: IMPACT of INCUBATION CONDITIONS on VARIABILITY and SUBSEQUENT DRUG INTERACTION PREDICTIONS**

Savannah J. McFeely, Tasha K. Ritchie, and Isabelle Ragueneau-Majlessi

**PAST, PRESENT, and FUTURE of DRUG–DRUG INTERACTIONS**

René H. Levy and Isabelle Ragueneau-Majlessi
Clinical Pharmacology & Therapeutics, 2019 Jun;105(6):1286-1288

**DRUG-DRUG INTERACTIONS of INFECTIOUS DISEASE TREATMENTS in LOW INCOME COUNTRIES: A NEGLECTED TOPIC?**

Savannah J. McFeely, Jingjing Yu, Ping Zhao, Susan Hershenson, Steven Kern, Isabelle Ragueneau-Majlessi, and Dan Hartman
Clinical Pharmacology & Therapeutics, 2019 Jun;105(6):1378-1385

**IDENTIFICATION and EVALUATION of CLINICAL SUBSTRATES of ORGANIC ANION TRANSPORTING POLYPEPTIDES 1B1 and 1B3**

Savannah J. McFeely, Tasha K. Ritchie, Jingjing Yu, Anna Nordmark, René H. Levy, and Isabelle Ragueneau-Majlessi
What we offer

Drug Interaction Solutions (www.druginteractionssolutions.org) is designed to support research and regulatory scientists in their decision-making when evaluating PK-based drug-drug interactions (DDIs), gene-drug interactions, and drug safety.

- Our main activity is the development of drug interaction content in DIDB
- We also provide customized clinical PK datasets to fit specific solutions.

EXAMPLE OF QUERY

DIDB has the largest manually curated collection of qualitative and quantitative human in vitro and clinical (in vivo) information related to various extrinsic and intrinsic factors. These include interacting co-medications, excipients, food products, herbal products, tobacco, organ impairment, and genetics, that can affect drug exposure in humans. Its easy-to-use web portal allows users to efficiently retrieve the most relevant and up-to-date information from the large body of publications and regulatory documentation.

Information on drug disposition available in DIDB encompasses:

- in vitro drug metabolism, transport, and DDIs (involving metabolizing enzymes, transporters, and their variants)
- Clinical DDIs and case reports
- Other DDI mechanisms including clinical absorption-based interactions (e.g., food-effect, pH-dependence, etc.)
- Clinical hepatic and renal impairment
In practice, we review the latest peer-reviewed publications as well as recent NDA/BLA reviews and drug labels from the FDA and select the content that is most relevant to support drug interaction evaluations at various stages of the drug development process. We create detailed drug monographs that summarize the main mechanistic and quantitative findings including the PK profile, DDI summary, and QT data, as well as information regarding the overall DDI risk level and label recommendations for clinical use.

We maintain an up-to-date Resource Center containing:

- Comprehensive lists of clinical substrates, inhibitors, and inducers of enzymes (CYP) and transporters
- Monthly newsletters highlighting the latest DDI and pharmacogenetic publications added to DIDB
- Regulatory guidances from the FDA, EMA, PMDA, and Health Canada

In addition to data curation:

- We share the results of our own research by teaching courses on drug interactions, contributing to workshops and conferences, and publishing articles and reviews on an ongoing basis.
- We work closely with colleagues from various universities, regulatory agencies, and pharmaceutical companies on the most pressing issues and challenges in the field.
- We assist the end-users of DIDB with highly specific and detailed database searches and outputs, breaking down often complex mechanisms of drug interactions to enable efficient problem solving.
- We continuously expand the database content and improve its functionality based on user feedback.

Our expertise

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DRUG MONOGRAPH AND DDI SUMMARY
(metadata analysis)

1. In vitro, both duvelisib and 5-IPM showed mechanism-based inhibition of CYP3A4, with IC50 values of 3.50 and 0.51 µM and IC50 values of 9.3 and 1.52 nM, respectively. In vivo, co-administration of duvelisib (5 mg/kg) or 5-IPM (10 mg/kg) to rats caused a 6.3-fold increase in the AUC of celecoxib, a CYP3A4 substrate.

2. In vitro, duvelisib and 5-IPM also showed reversible inhibition of CYP3A5, with IC50 values of 9.4 µM and 0.5 µM, respectively. The clinical relevance of these in vitro findings was evaluated using in vivo studies in rats and mice. Co-administration with duvelisib (200 mg/kg) for 6 days was predicted to increase the AUC of a CYP3A5 substrate (25, mg/kg, 0.6 mg/kg) by 4.6-fold in healthy subjects, which was not considered clinically meaningful. A maximal effect (0.5% decrease in the exposure of nifedipine (20 mg/day) was observed in the presence of duvelisib (200 mg/kg), co-administered with duvelisib.

3. In vitro, duvelisib inhibited OCT1, OCT2B1, BCRP, MATE1, MATE2-K, and OCT3, with IC50 values of 1 mg/L, 0.9 mg/L, 0.4 mg/L, and 0.8 mg/L, respectively. Duvelisib did not inhibit P-gp, BCRP, and MRP, but did inhibit OCT1, OCT2, OCT3, or OCT2B1, which are not available in the NDA review. However, in vivo, duvelisib decreased the pharmacokinetics of nifedipine (20 mg/kg), a substrate of P-gp and BCRP, by 5- to 6-fold. Duvelisib also decreased the pharmacokinetics of celecoxib (10 mg/kg), a substrate of OCT2B1.

4. In vitro, duvelisib inhibited OCT1, OCT2B1, MATE1, MATE2-K, and OCT3, with IC50 values of 1 mg/L, 0.9 mg/L, 0.4 mg/L, and 0.8 mg/L, respectively. Duvelisib did not inhibit P-gp, BCRP, and MRP, but did inhibit OCT1, OCT2, OCT3, or OCT2B1, which are not available in the NDA review. However, in vivo, duvelisib decreased the pharmacokinetics of nifedipine (20 mg/kg), a substrate of P-gp and BCRP, by 5- to 6-fold. Duvelisib also decreased the pharmacokinetics of celecoxib (10 mg/kg), a substrate of OCT2B1.

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This process, built over more than 20 years, has been mastered by the team, and is highly-collaborative, allowing the database to be updated with new information daily, and the applications to be enriched with new scientific findings as soon as they become available.

How we work

**SELECTION OF CITATIONS**
We identify the latest, most relevant publications and regulatory documents from NDA/BLA packages for manual curation.

**DATA EXTRACTION**
Prior to integration, the data is carefully and critically evaluated. When appropriate, and sometimes upon discussion with the study authors, comments are attached to the data. The richness of each citation is exploited, generating a highly detailed dataset. The data is formatted for immediate use and to allow meta-analysis of multiple sources.

**DATA ENTRY AND VALIDATION**
Once entered into the database, the data is validated by a second curator, who thoroughly reviews the studies and citations to make sure all the relevant information has been accurately extracted and represented. Only then, is the data released and accessible to end-users.

**DATA RELEASE**
This process, built over more than 20 years, has been mastered by the team, and is highly-collaborative, allowing the database to be updated with new information daily, and the applications to be enriched with new scientific findings as soon as they become available.

Thorough standard internal procedures support the selection, distribution, data entry, and data validation of citations in DIDB.
Who are our users

**PHARMACEUTICAL COMPANIES**
Preclinical and clinical scientists working in drug development and regulatory groups

**REGULATORY AGENCIES**

**ACADEMIC INSTITUTIONS**

**PUBLISHERS of DRUG INFORMATION**

**CONTRACT RESEARCH ORGANIZATIONS**

**NON-PROFIT ORGANIZATIONS**

**PROVIDERS of CLINICAL DECISION SUPPORT SYSTEMS**

The worldwide userbase includes organizations of all sizes

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Benefits of using DIDB

**PROVIDE CONTEXT for the INTERPRETATION of results obtained with candidate compounds**

**OPTIMIZE and VALIDATE PBPK MODELS and static predictions**

**ASSIST with PRIORITIZATION and DESIGN of clinical trials**

**GAIN INSIGHT into DDI RISK and possible clinical outcomes**

**SUPPORT DRUG LABELING RECOMMENDATIONS and the safe use of medications in various patient populations**

**PROVIDE CUSTOMIZED CLINICAL DATASETS and EXPERTISE to support personalized prescription applications**

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**WHY SUBSCRIBE**

The data we select and its presentation are unique reflections of our expertise in drug interactions. As a small and fully independent operation, we are flexible and react rapidly. We are able to continuously incorporate new scientific findings and improve the content and functionality of the database.

**DIDB** is internationally recognized as an authoritative, unbiased, and transparent research tool. Our users have trusted our database for over 20 years.

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**FUTURE DIRECTIONS**

With its mechanistic and quantitative features, and the breadth of its content, DIDB has the potential to become a standard in supporting various healthcare applications and complex clinical decision algorithms. We believe that its integration into clinical tools for healthcare providers and patients is a next step in the development of Drug Interaction Solutions and will constitute a pivotal milestone in the management of adverse drug interactions in the clinic. We foresee that DIDB content will help the emergence of new approaches in personalized medicine that aims at selecting the most appropriate drug and dose for each unique patient.
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