Transforming scientific data into clinical knowledge
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, as well as the development of new content and features.

Dr René Levy founded the Metabolism & Transport Drug Interaction Database (DIDB®) 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. The knowledgebase was later expanded with the addition of the pharmacogenetics (PGx) database (e-PKGene®), 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 knowledgebase 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, MSc
Chris Kinsella, IT support
Grace Lee, Admin
Savannah McFeely, PhD
Katie Owens, BPharm, PhD
Ichiko Petrie, PharmD
Tasha Ritchie, PhD
Jessica Tay-Sontheimer, PhD
Cheryl Wu, PhD
Catherine Yeung, PharmD, PhD, MPH

UW COMOTION, LICENSING:
Roï Eisenkot
Our recent publications

**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
*Clinical and Translational Science, Feb 1, 2019*

**MECHANISMS and CLINICAL SIGNIFICANCE of PHARMACOKINETIC-BASED DRUG-DRUG INTERACTIONS with DRUGS APPROVED by the U.S. FOOD and DRUG ADMINISTRATION in 2017**
Jingjing Yu, Ichiko D. Petrie, René H. Levy, and Isabelle Ragueneau-Majlessi
*Drug Metab Dispos 2019 Feb;47(2):135-144*

**RISK of CLINICALLY RELEVANT PHARMACOKINETIC-BASED DRUG-DRUG INTERACTIONS with DRUGS APPROVED by the U.S. FOOD and DRUG ADMINISTRATION BETWEEN 2013 and 2016**
Jingjing Yu, Zhu Zhou, Jessica Tay-Sontheimer, René H. Levy, and Isabelle Ragueneau-Majlessi
*Drug Metab Dispos 2018 Jun;46(6):835-845*
What we offer

The pillars of Drug Interaction Solutions (www.druginteractioninfo.org) are two best-in-class applications:

- Metabolism and Transport Drug Interaction Database: DIDB®
- Pharmacogenetics Database: e-PKGene®

EXAMPLE OF QUERY

<table>
<thead>
<tr>
<th>DDI Queries</th>
<th>Pharmacogenetics</th>
<th>Latest NDAs entered</th>
</tr>
</thead>
<tbody>
<tr>
<td>16,493 citations with 114,986 entries</td>
<td>2,459 citations with 7,239 entries</td>
<td>Mosalxumab pasudotox 4/10/2019 1 entries</td>
</tr>
<tr>
<td>344 NDAs with 8,883 entries</td>
<td>50 NDAs with 118 entries</td>
<td>Mocamulumbab 4/9/2019 2 entries</td>
</tr>
</tbody>
</table>

DDI queries »

Resource Center
Contains lists of substrates, inhibitors and inducers as well as tutorials, list of all NDAs, and all monthly newsletters.

Resources »

Find a Citation
From NDAs, PubMed and Embase citations

Find by citation number DDI »

Pharmacogenetics queries »

Latest News
Lists of Sensitive Substances, Inhibitors and Inducers updated 4/16/2019
April Newsletter available 4/16/2019
Upcoming release of new features on April 6, 2019!
March Newsletter available 4/1/2019
Read more news »

Latest NDAs entered
- Mosalxumab pasudotox 4/10/2019 1 entries
- Mocamulumbab 4/9/2019 2 entries
- Racemucumab 4/8/2019 4 entries
- Triclabendazole 4/4/2019 50 entries
- Caplacumab 4/2/2019 3 entries
- Ciplxamub 3/25/2019 2 entries
- Diprofloxacin XR 3/25/2019 6 entries
- Asminadine 3/24/2019 9 entries
- Gittertinb 3/15/2019 18 entries

View all NDAs in DIDB »
These two applications support the overall knowledgebase that has been used for over two decades by pharmaceutical and regulatory scientists for the evaluation of PK-based drug-drug interactions (DDIs), gene-drug interactions, and drug safety.

The knowledgebase has the largest manually curated collection of qualitative and quantitative human preclinical (in vitro) and clinical (in vivo) information related to various extrinsic and intrinsic factors. These include interacting co-medications, excipients, food products, herbas, 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 the knowledgebase encompasses:**

- Preclinical drug metabolism, transport, and DDIs (involving metabolizing enzymes, transporters, and their variants)
- Clinical DDIs and case reports
- Clinical pharmacogenetics
- Other DDI mechanisms including clinical absorption-based interactions (e.g., food effect, pH-dependence, etc.)
- Clinical hepatic and renal impairment

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**Drug Queries**
- Search by drug name, using generic names.

**Pharmacokinetic Queries**
- Search for pharmacokinetic measurements of objects and precipitants.

**Hepatic and Renal Impairment queries**
- Search for PK parameters of objects in subjects with HI or RI.

**In Vitro Induction Queries**
- Search by nuclear receptor.

**QT Queries**
- Search for QT interval prolongation data from recent NDAs and DDI studies.

**Other Queries**
- Search by system studied, side effect, or PO effect.

**Citation Queries**
- Search by citation number, journal, author, and year.

**In Vitro Parameter Queries**
- Search for values of $K_{m}$, $V_{max}$, $K_{i}$, $IC_{50}$, $K_{i} & k_{cat}$, and $EC_{50}$ or % fold increase.

**AUC-CL Change Queries**
- Search for AUC and CL Changes observed in DDI studies.

**Drug considered as**
- **object (victim) or precipitant (perpetrator)**
Our expertise

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 PGx publications added to the knowledgebase
• 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 our knowledgebase 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.

Inhibition profile
Enzymes
CYP3A4
In vitro, both duvelisib and IP1-656 showed mechanism-based inhibition of CYP3A4, with Ki values of 3.87 and 0.31 μM and kinact values of 0.9 and 1.02 h, respectively. In vivo, co-administration of midazolam (2 mg SD), a sensitive substrate of CYP3A4, with duvelisib (25 mg BID for 8 days) caused a 4.3- and 2.11-fold increase in the AUC and Cmax of midazolam. According to COPKTRA Product Label, patients should be monitored for signs of toxicities associated with the co-administered sensitive CYP3A substrate.

CYP2C8
In vitro, duvelisib and IP1-656 also showed reversible inhibition of CYP2C8, with Ki values of 0.84 μM and 5.5 μM, respectively. The clinical relevance of these in vitro findings was evaluated using PBPK modeling and simulations. Co-administration with duvelisib (25 mg BID for 8 days) was predicted to increase the AUC of repaglinide (0.25 mg SD), a sensitive substrate of CYP2C8 (also a substrate of CYP3A4), 1.54-fold in healthy subjects, which was not considered clinically meaningful. A minimal effect (<20%) was predicted on the exposure of rosiglitazone (4 mg SD), a moderate sensitive substrate of CYP2C8, upon co-administration with duvelisib.

Transporters
In vitro, duvelisib inhibited OCT1, OATP1B1, OATP1B3, MATE1, MATE2-K, BSEP, BCRP, and P-gp, but not OAT1, OAT3, or OCT2 (details not available in the NDA review). However, the drug label states that “in vitro, duvelisib does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BCRP, or P-gp” (COPKTRA Product Label).

QT summary
Sources
DrugERI - Clinical Reviews
DrugERI - Product Labels
Preclinical data
Duvelisib and its primary metabolite IP1-656 inhibited HER2 kinase current with IC50 values of 48.6 μM and >100 μM, respectively.
Clinical data
No QT prolongation (Brothers QT T2D trial)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Means (EC)</th>
<th>Text</th>
<th>Positive control</th>
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</thead>
<tbody>
<tr>
<td>Dose/Regimen</td>
<td>25 mg BID for 2 cycles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in QRS duration (ms)</td>
<td>25 mg: 11.4 (7.2, 15.6); 75 mg: 5.5 (2.3, 8.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetic profile

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>431.88 g/mol</td>
</tr>
<tr>
<td>Cmax</td>
<td>1.5 (CIV: 0.7-8.4) ng/ml, 3.43 ng/ml</td>
</tr>
<tr>
<td>Dose/Duration</td>
<td>25 mg BID</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>42%</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>&gt;98%</td>
</tr>
<tr>
<td>Clearance</td>
<td>4.2 (CIV: 1.2-10) L/h</td>
</tr>
<tr>
<td>Vd</td>
<td>28.5 (CIV: 5-66) L</td>
</tr>
<tr>
<td>Th</td>
<td>4.7 (CIV: 1-10)</td>
</tr>
</tbody>
</table>

Reference: NDA 211095, Duvelisib Product Label
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 knowledgebase 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 the knowledgebase.
## KNOWLEDGEBASE BY THE NUMBERS
(as of April 2019)

<table>
<thead>
<tr>
<th>Category</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CITATION COVERAGE</strong></td>
<td>1963 to present</td>
</tr>
<tr>
<td><strong>PROGRAM ESTABLISHED</strong></td>
<td>20 years ago</td>
</tr>
<tr>
<td><strong>DRUG-DRUG INTERACTIONS</strong></td>
<td>16,500 citations including 115,000 entries</td>
</tr>
<tr>
<td><strong>DRUG-GENE INTERACTIONS</strong></td>
<td>2,500 citations including 7,300 entries</td>
</tr>
<tr>
<td><strong>OVER 50 queries including</strong></td>
<td>450 possible searches</td>
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<tr>
<td><strong>13,000 total compounds</strong></td>
<td>700 DDI summaries</td>
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<tr>
<td><strong>350 NDAs/BLAs including</strong></td>
<td>50 NDAs/BLAs</td>
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<tr>
<td><strong>700 DDI summaries</strong></td>
<td><strong>120 entries</strong></td>
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## Who are our users

<table>
<thead>
<tr>
<th>PHARMACEUTICAL COMPANIES</th>
<th>REGULATORY AGENCIES</th>
<th>ACADEMIC INSTITUTIONS</th>
<th>PUBLISHERS of DRUG INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical and clinical scientists working in drug development and regulatory groups</td>
<td>Contract Research Organizations</td>
<td>Non-Profit Organizations</td>
<td>Providers of Clinical Decision Support Systems</td>
</tr>
</tbody>
</table>

The worldwide userbase includes organizations of all sizes.

## Benefits of using DIDB® and e-PKGene®

| PROVIDE CONTEXT for the INTERPRETATION of results obtained for candidate compounds | OPTIMIZE and VALIDATE PBPK MODELS and static predictions | ASSIST with PRIORITIZATION and DESIGN of clinical trials |
| GAIN INSIGHT on DDI RISK and possible clinical outcomes | SUPPORT DRUG LABELING RECOMMENDATIONS and the safe use of medications in various patient populations | |

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FUTURE DIRECTIONS

With its mechanistic and quantitative features, and the breadth of its content, Drug Interaction Solutions 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 the drug interaction knowledgebase 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.

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® and e-PKGene® are internationally recognized as authoritative, unbiased, and transparent research tools. Our users have trusted our knowledgebase for over 20 years.