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FROM DISCOVERY THROUGH CLINICAL SUPPORT

# Drug Metabolism Related Safety Considerations in Drug Development

**Larry Wienkers, Ph.D.**

# Drug Metabolism Related Safety Considerations in Drug Development

Abstract: Approximately 30 years ago, sub-optimal DMPK properties were recognized as the primary contributor to the failure (~40%) of potential new therapies in early clinical trials. This observation precipitated a renaissance period across the discipline which served to align DMPK efforts within discovery to assist in selecting optimal drug candidates to advance to clinical testing. As a consequence, the failure rate for NCEs due to poor DMPK attributes is currently below 5%. While the success of DMPK groups to resolve issues is impressive, there is still a critical need to understand the activity and safety implications of key drug metabolites as part of the overall evaluation of the NCE. This overview will touch upon strategies for building phase appropriate packages for metabolites to account for pharmacological activity, **potential drug interaction** and associated metabolism-dependent drug safety concerns.

Larry C. Wienkers
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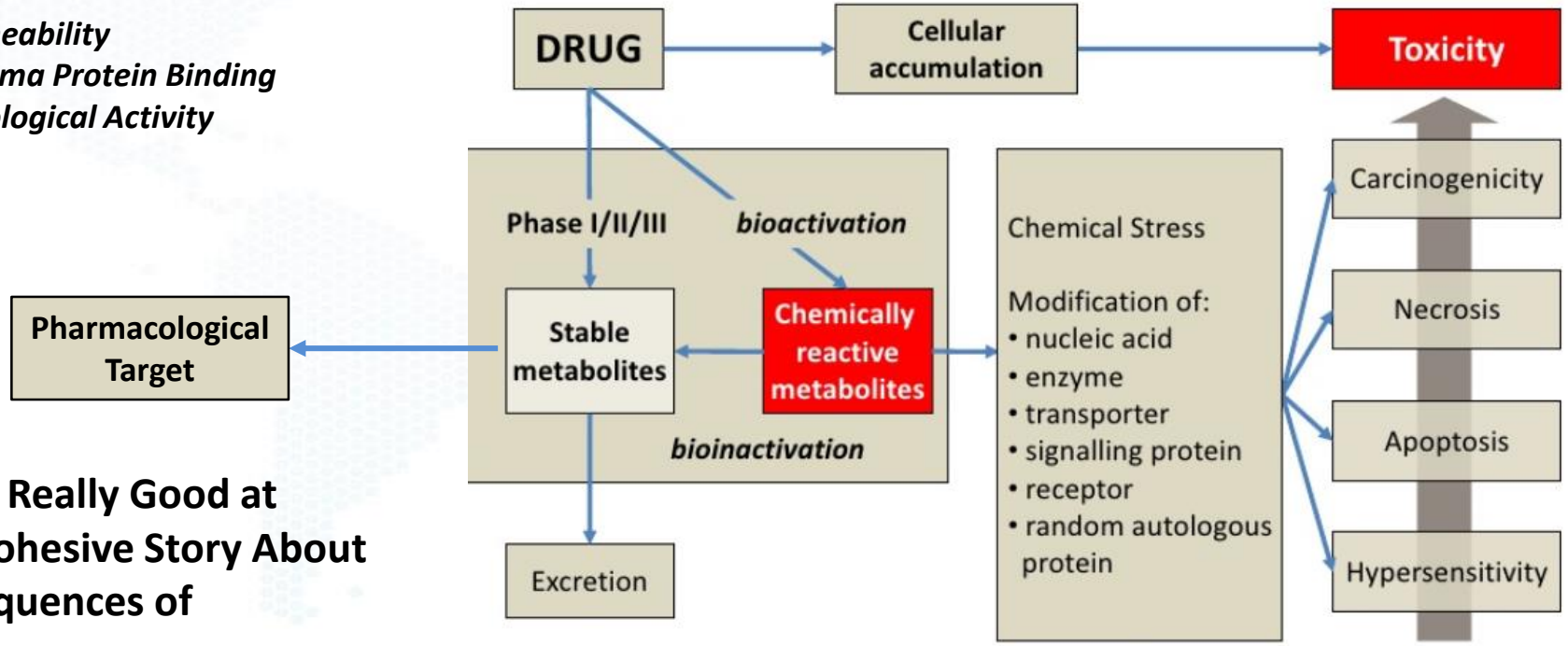
# Outline for Today: Compound Developability & Safety Considerations in Drug Development:

***Developability is defined by how well a compound reflects ADME-related characteristics that are relevant to drug development***

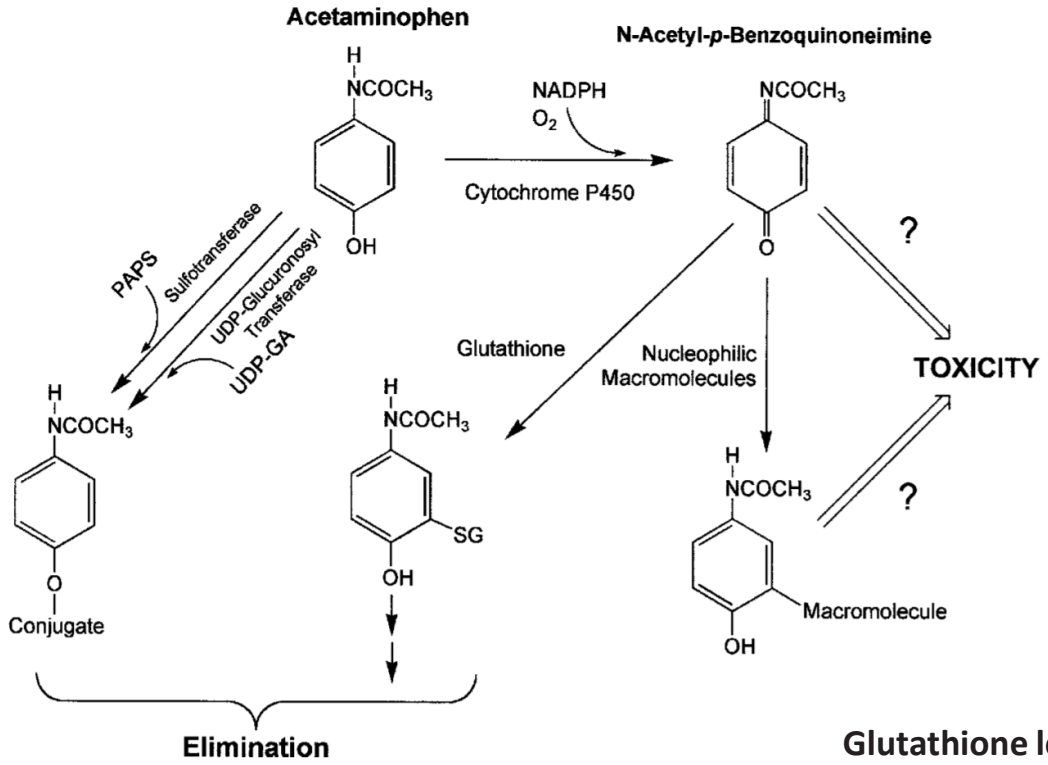
***High developability compounds are defined as having:***

- ✓ *Low Toxicity nominal Metabolic Activation*
- ✓ *High Solubility*
- ✓ *High Membrane Permeability*
- ✓ *Low to Moderate Plasma Protein Binding*
- ✓ *Predictable Pharmacological Activity*



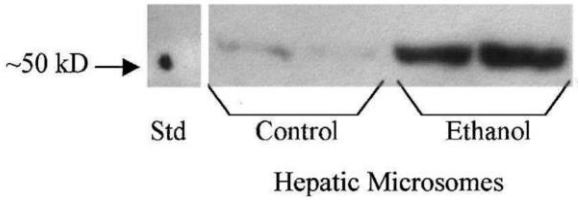

**DMPK Scientists are Really Good at Pulling Together a Cohesive Story About the Drug and Consequences of Metabolism**

# Drugs Whose Metabolites are Toxic

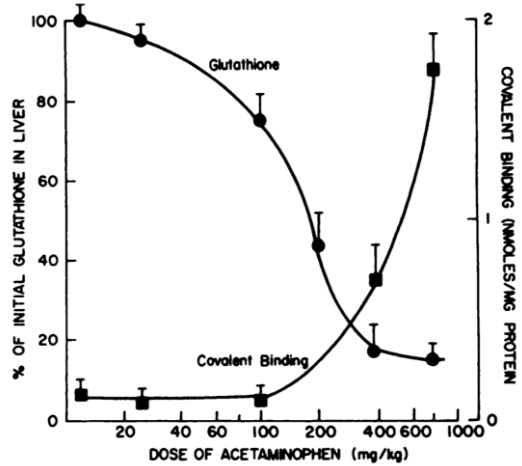



90% of APAP elimination is catalyzed by UDP-glucuronosyltransferases (UGT1A1 and 1A6) and sulfotransferases (SULT1A1, 1A3/4, and 1E1), respectively. As a consequence, Gilbert's Syndrome and other reductions in UGT activity putatively reduce the amount of APAP being cleared via this pathway. Moreover, SULT1A3 and SULT1A4 genotypes possess significant differences in binding affinity and catalytic activity towards analgesic compounds (including acetaminophen).

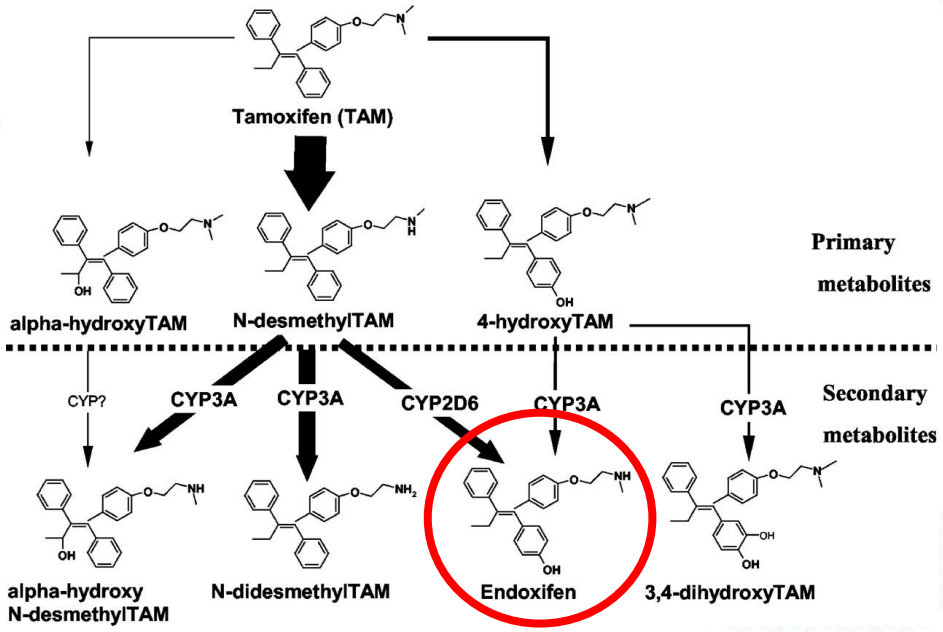
Activation of acetaminophen is primarily carried out by CYP2E1, an ethanol-inducible cytochrome P450. CYP2E1 is developmentally regulated, under liver-specific control, and undergoes substrate-induced protein stabilization. It is also regulated by starvation and diabetes through insulin-dependent mRNA stabilization.




Glutathione levels in the body may be reduced by a number of factors, including poor nutrition, environmental toxins, and stress. Its levels also decline with age.

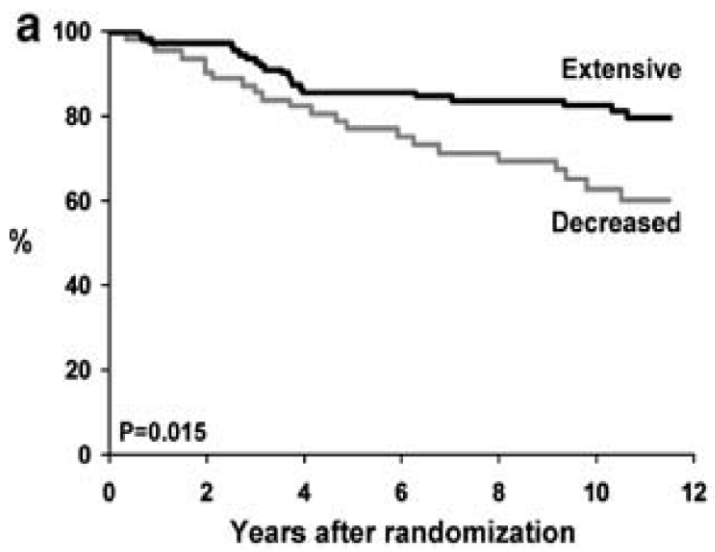


# Drugs whose Metabolites are Pharmacologically Active

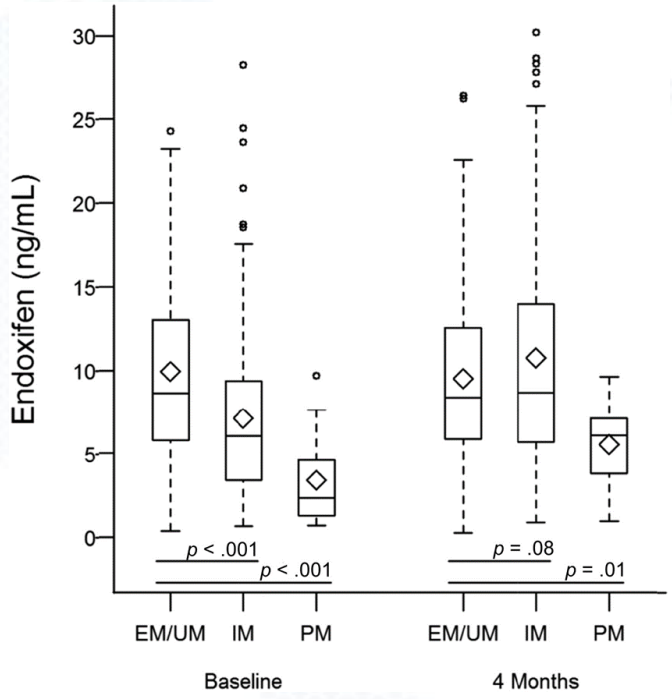



Desta Z, et al., J Pharmacol Exp Ther. 310(3):1062-75 (2004)

*Kaplan–Meier estimates of time to breast cancer recurrence based on CYP2D6 metabolism (extensive vs. decreased)*




Goetz MP et al., Breast Cancer Res Treat. 101(1):113-21 (2007)




Daniel L. Hertz et al. The Oncologist 2016;21:795-803

**Tamoxifen is widely used to reduce the risk of breast cancer (BC) recurrence and extend disease-free survival among women with estrogen-sensitive breast cancers. Tamoxifen efficacy is thought to be attributable to its active metabolite, endoxifen and 4-hydroxytamoxifen (4-HT), have been shown to be up to 100 times more potent estrogen receptor (ER) antagonists than the parent compound and are therefore likely to contribute to target inhibition and, thereby, the outcome of therapy.**

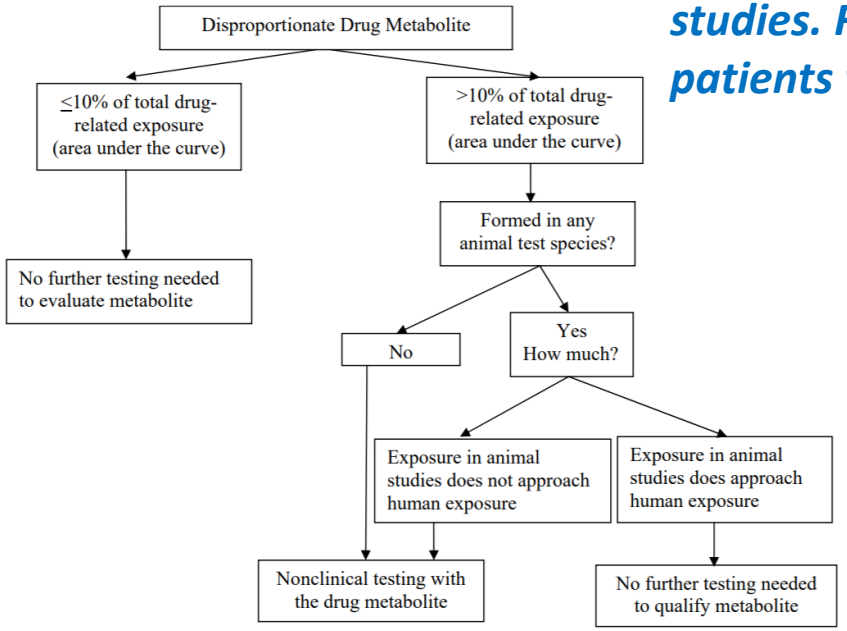
# Problem Statement: Regulatory Guidance from the FDA and ICH on Metabolites

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2016
Pharmacology/Toxicology

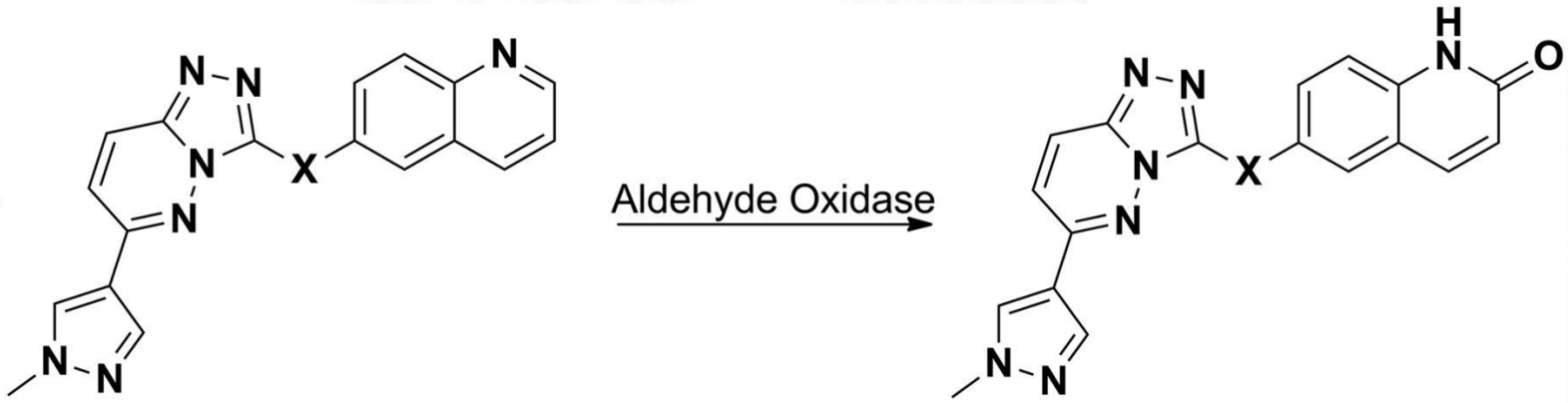
Revision 1

APPENDIX A:
DECISION TREE FLOW DIAGRAM




***The 'scope' section of ICHM3(R2) states that 'Pharmaceuticals under development for indications in life threatening or serious diseases (e.g., advanced cancer, resistant HIV infection, and congenital enzyme deficiency diseases)without current effective therapy also warrant a case-by-case approach to both the toxicological evaluation and clinical development in order to optimize and expedite drug development. In some cases, metabolites that have been identified in humans have not been qualified in nonclinical studies. For these metabolites, a separate evaluation is generally not warranted for patients with advanced cancer.***

# Characterization of Major Metabolites: Routes of Elimination and Physical Attributes (cMet Inhibitors)




X = $CF_2$; JNJ38877605
X = S; SGX-523

Insoluble Quinolone Metabolite

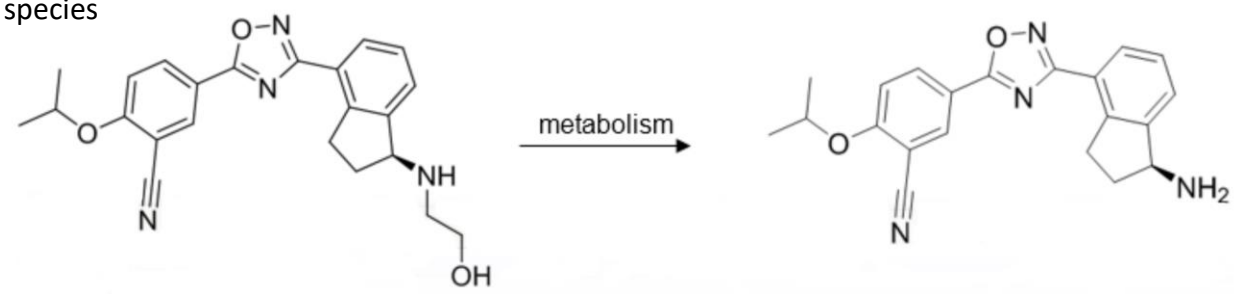
**The transfer of protons (H+) or hydride ions (H) clearly plays a key role in metabolite solubility. In Medicinal Chemistry, introducing an amide may enhance hydrogen bonding relative to hydrocarbons, that said amides typically are regarded as compounds with low water solubility.**

***The significance of pH dependent excretion is highly dependent upon the molecule's physicochemical properties such as pKa and lipid solubility. This is particularly important in the kidney where concentration of filtrate/urine is in play. Under these conditions its possible for the relative concentration of an insoluble molecule can increase by as much as 180-fold. For these cMet metabolites, having low solubility they were prone to crystallize in the kidney, which was linked to the observed nephrotoxicity and ultimately clinical failure of both drug candidates.***

Diamond et al., Species-Specific Metabolism of SGX523 by Aldehyde Oxidase and the Toxicological Implications. Drug Metabolism and Disposition 38 (8): 1277-1285, 2010

# Characterization of Major Metabolites: Pharmacological Activity (Ozanimod)

- In 2015, Celgene acquired Receptos for $7.2 billion as a means to expand the immunology franchise. The primary driver for the acquisition was for the rights to the drug, Ozanimod, then, described as a potential best-in-class, oral, once-daily, selective sphingosine 1-phosphate 1 and 5 receptor modulator and was expected to bring in 4-6 billion in peak sales.
- Ozanimod is metabolized in humans to form one major (active) metabolite CC-112273:
  - Structurally similar to Ozanimod and possessed similar potency and selectivity to S1P1 and S1P5 as Ozanimod
  - The metabolite possesses a Tmax of 6-10 hours with a Half-life of 10-13 days, as a consequence, it accounts for the majority of the pharmacological activity observed in humans
  - While Receptos conducted safety studies of ozanimod in rodents for six months and in primates for nine months, it was observed that CC-112273 was a minor metabolite in preclinical safety species



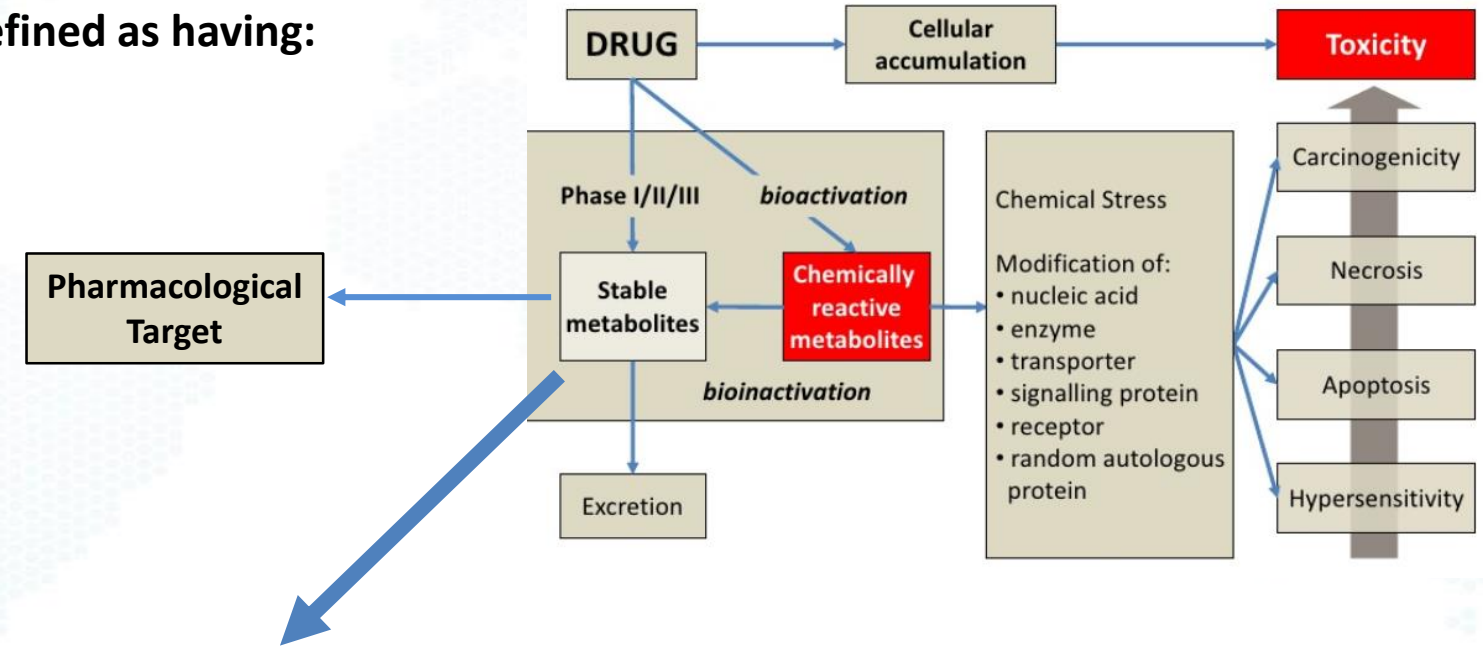

***In February 2018, a Refusal to File (RTF) letter was sent to Celgene. The Refuse-to-file communications was based around deficiencies identified in a drug application (note: the notification gives a company the chance to address the deficiencies before a "complete response letter," which amounts to an FDA rejection). In brief, the FDA found that the non-clinical and clinical pharmacology sections of its application were "insufficient to permit a complete review. The RTF notice was based on Celgene's omission of preclinical and clinical pharmacology information on the oral pill, which meant a complete review of ozanimod could not take place. Basically the NDA lacked any meaningful information regarding the characterization of disposition and tox coverage for CC112273.***

# Outline for Today

***Obviously, the regulatory guidelines on the Safety Testing of Drug Metabolites reflects the importance of qualifying metabolite exposure as part of the safety evaluation of new drugs. Based upon what has been published, there is no single strategy for qualifying the safety of drug metabolites in humans. That said, all ADME activities should be focused towards two overarching thoughts: 1) exposure to metabolites in humans needs to be reflected in preclinical safety species; and 2) that the characterization of major metabolites should be agnostic to the interpretation of guidelines based upon the drugs indication.***

**High developability compounds are defined as having:**

- ✓ **Low Toxicity**
- ✓ **High Solubility**
- ✓ **High Permeability**
- ✓ **Low to Moderate Protein Binding**
- ✓ **Pharmacological Activity**
- ✓ **Low CYP3A Inhibition Liability**

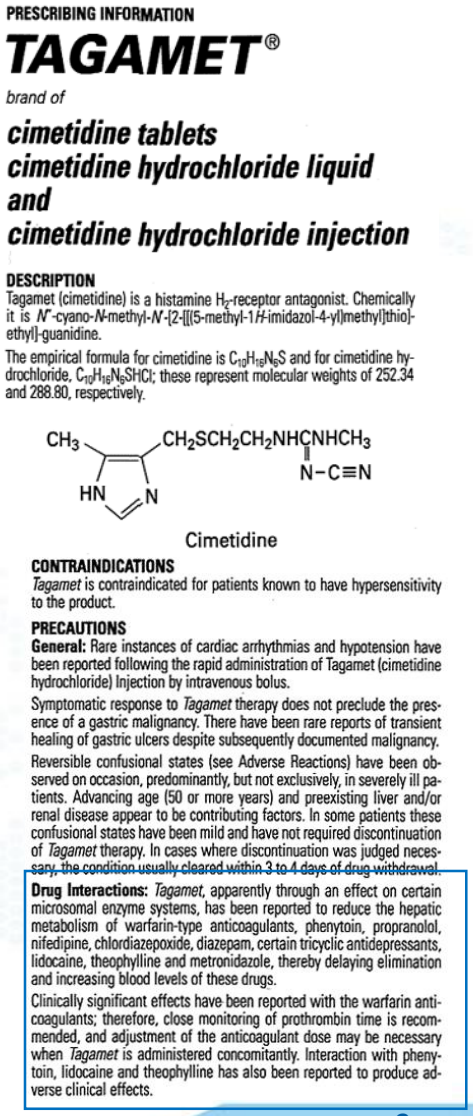



**Drug Metabolites as Potent CYP3A4 Inhibitors**

# Why studying DDIs is still an Important Activity

- Adverse drug reactions (ADRs) are still responsible for around 100K deaths per year in the US.
  - Drug drug interactions (DDIs) represent a major source of ADRs (~25%)
- Most DDIs are associated with cytochrome P450 inhibition
  - Nearly 75% of all drug prescribed undergo P450 metabolism (50% are through CYP3A4)
- In light of the risk for ADRs, early assessment of P450 inhibition liabilities are conducted to "pick the winner" as well as generate risk migration strategies to be deployed during the drug development process.

**In addition to underwriting the safety of new medicines, early understanding of DDIs associated with molecules can also serve as a critical differentiator in a competitive market place**



PRESCRIBING INFORMATION

**TAGAMET®**

*brand of*

***cimetidine tablets***
***cimetidine hydrochloride liquid***
***and***
***cimetidine hydrochloride injection***

**DESCRIPTION**

Tagamet (cimetidine) is a histamine $H_2$-receptor antagonist. Chemically it is *N*″-cyano-*N*-methyl-*N*′-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]-ethyl]-guanidine.

The empirical formula for cimetidine is $C_{10}H_{16}N_6S$ and for cimetidine hydrochloride, $C_{10}H_{16}N_6SHCl$; these represent molecular weights of 252.34 and 288.80, respectively.



Cimetidine

**CONTRAINDICATIONS**

*Tagamet* is contraindicated for patients known to have hypersensitivity to the product.

**PRECAUTIONS**

**General:** Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagamet (cimetidine hydrochloride) Injection by intravenous bolus.

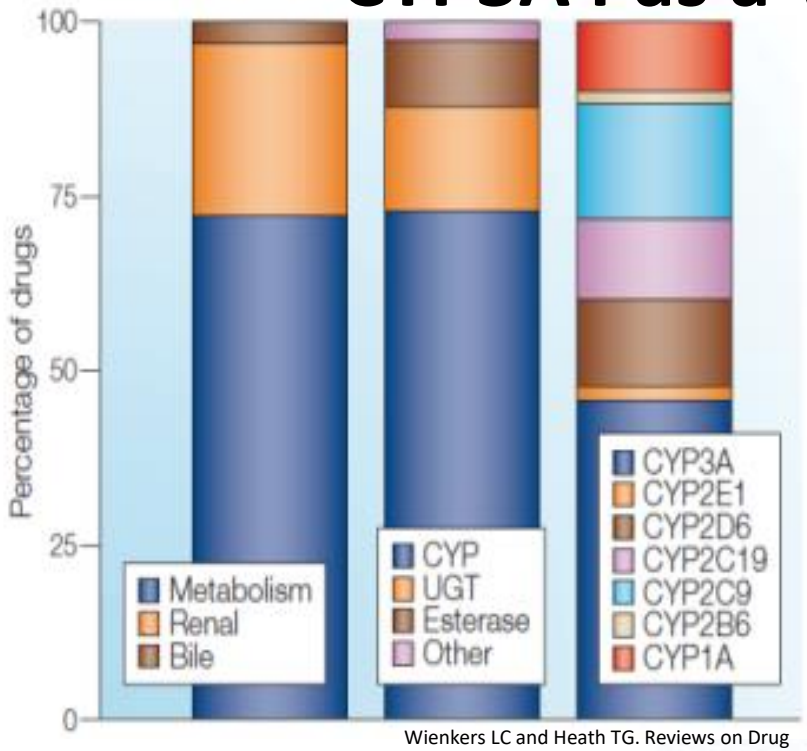
Symptomatic response to *Tagamet* therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (see Adverse Reactions) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and preexisting liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of *Tagamet* therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3 to 4 days of drug withdrawal.

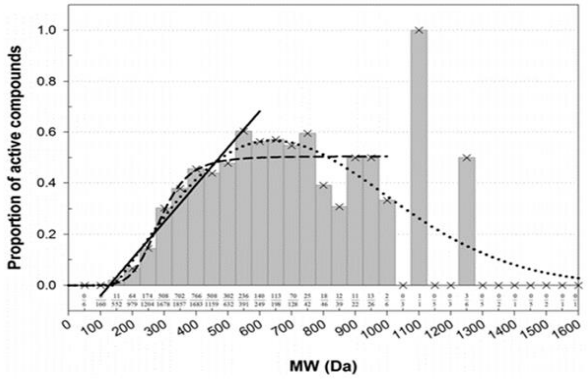
**Drug Interactions:** *Tagamet*, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when *Tagamet* is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

# CYP3A4 as a Victim in Clinically Meaningful Drug Interactions

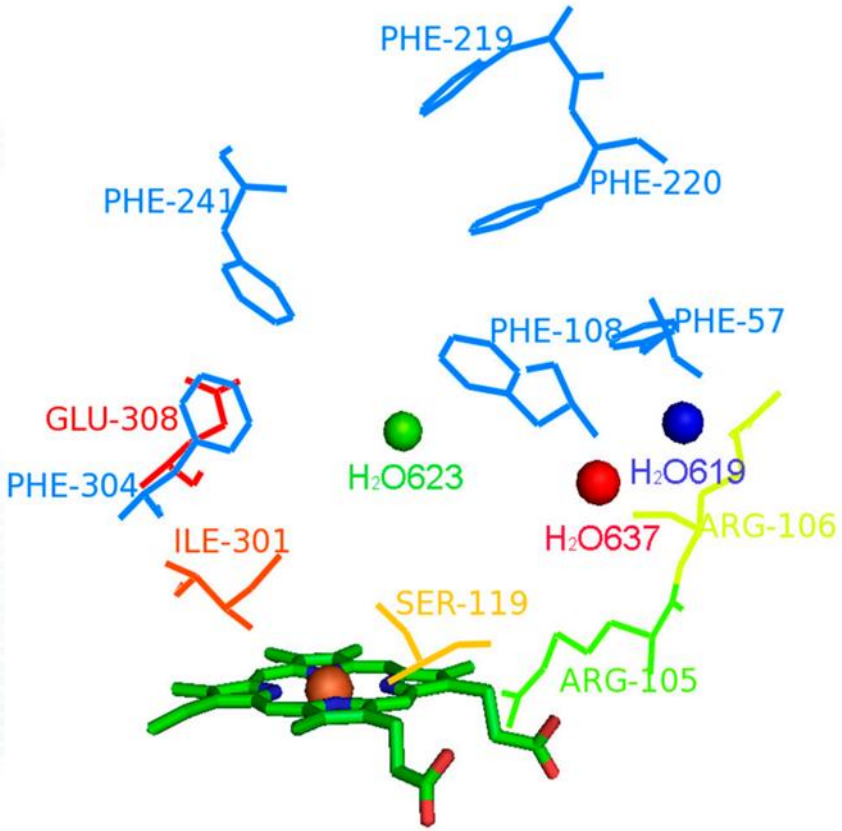



Wienkers LC and Heath TG. Reviews on Drug Discovery. 4(10):825-833. (2005).

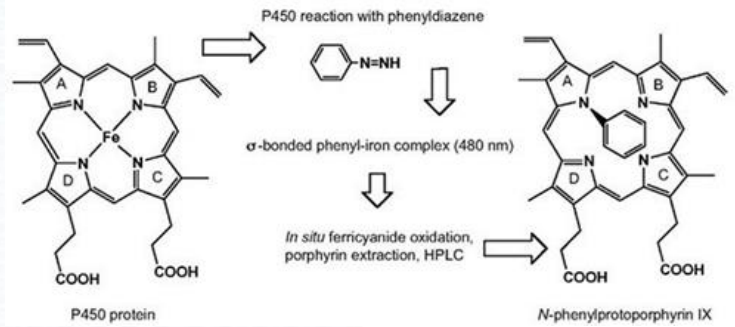


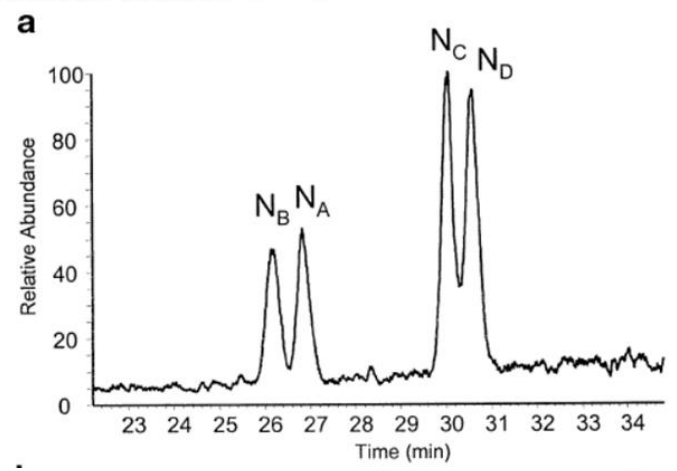

Tie et al., Modeling Chemical Interaction Profiles: II. Molecular Docking, Spectral Data-Activity Relationship, and Structure-Activity Relationship Models for Potent and Weak Inhibitors of Cytochrome P450 CYP3A4 Isozyme. Molecules 17:3407-3460, 2012

***The P1 and P2 sites are hydrophobic pockets that are adjacent to the phenylalanine cluster consisting of Phe-108, Phe-213, Phe-215, Phe-219, Phe-220 , Phe-241 and Phe-304, located above the active site and forming a hydrophobic core through pi-pi stacking.***




DAI et al., A Mechanism-Based Model for the Prediction of the Metabolic Sites of Steroids Mediated by Cytochrome P450 3A4 . Int. J. Mol. Sci. 16: 14677-14694, 2015




Schrag, Wienkers. Drug Metab Dispos. 28(10):1198-201 (2000).

XENOTECH
A BioIVT Company

# DDIs and the Evolving Strategy in Cancer Therapy

***The dynamic nature of cancer has been a pivotal challenge for developing efficient and safe therapies. Cancer treatments using a single therapeutic agent often result in limited clinical outcomes due to tumor heterogeneity and drug resistance. Combination therapies using multiple therapeutic modalities can synergistically elevate anti-cancer activity while lowering doses of each agent, hence, reducing side effects.***

**Chemotherapy**

- Not tumor specific
- Targeted all rapidly dividing cell
- Highly toxic

**Targeted therapy**

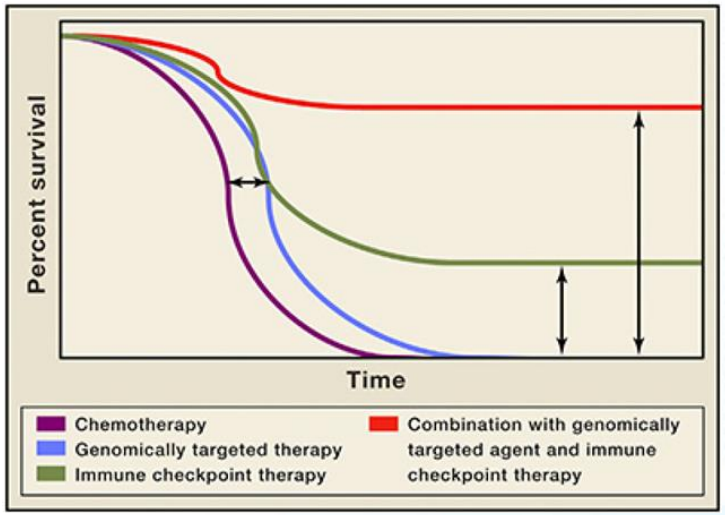
- Targets specific genes/proteins found in tumors
- Rapid response
- Better tolerated

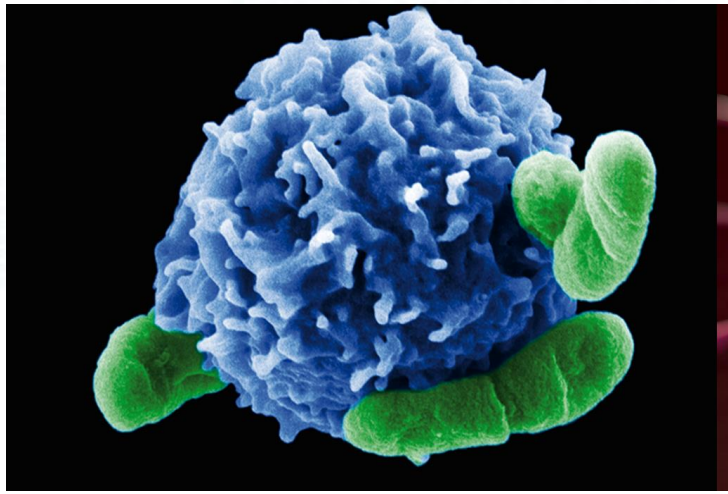
**Immuno-oncology**

- Stimulates immune system to activate against tumor
- Long-lasting response in subset of patients w/ a variety of tumors

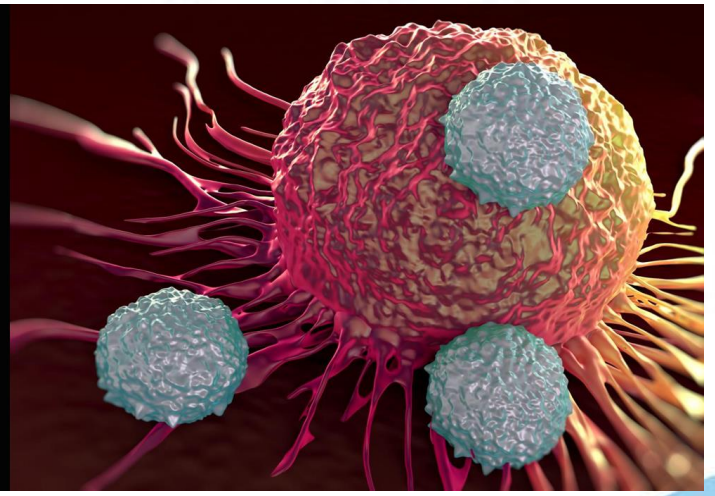
**Immuno-oncology Combinations**

- Combination of I/O w/ targeted therapy or I/O & I/O
- Perhaps higher response rates



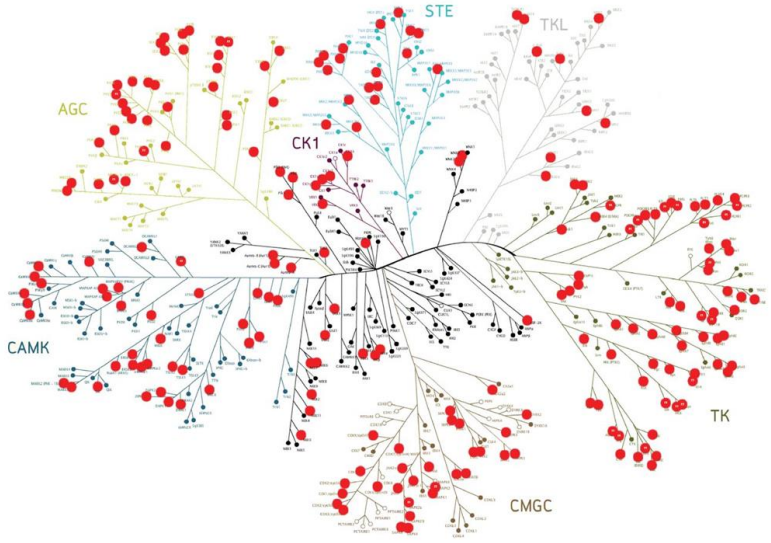



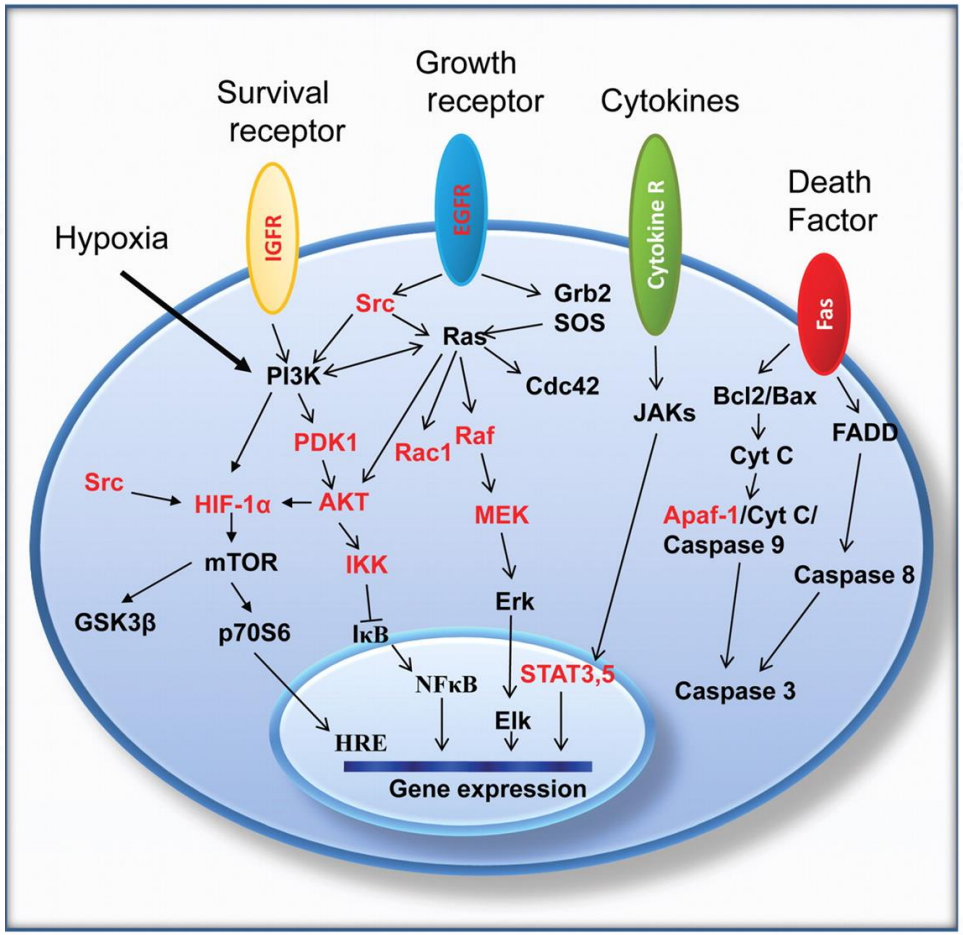
Antibiotic & Immune Response



Debulking Agent(s) & Immune Stimulation

# Issue: Kinases and the Biological Rationale to Target Cancer




**Key Initial Events**

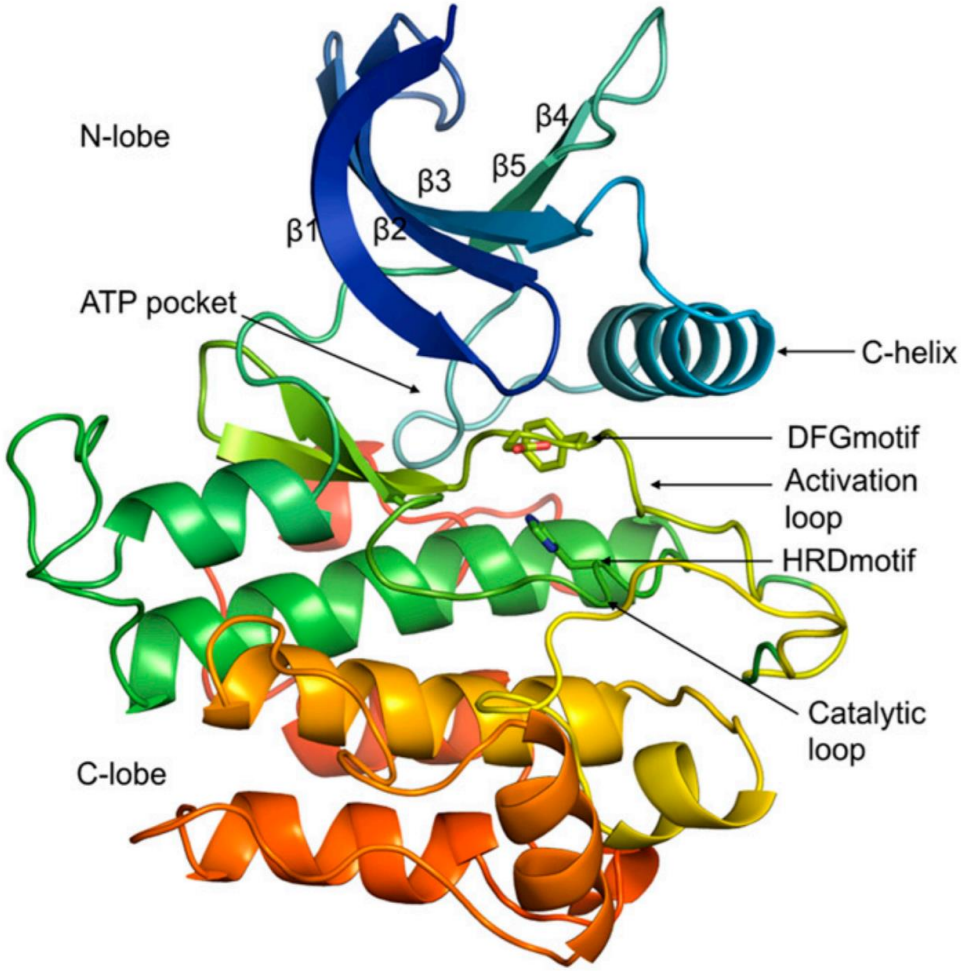
| 1978 | 1981 | 1984 | 1991 |
|---|---|---|---|
| First oncogene was identified as a kinase inhibitor | Tumor-promoting phorbol esters were potent activators of protein kinase C | Staurosporine identified as a nanomolar inhibitor of PKC | First three-dimensional structure of a protein kinase was identified |

**FDA Approval of Kinase Inhibitors**

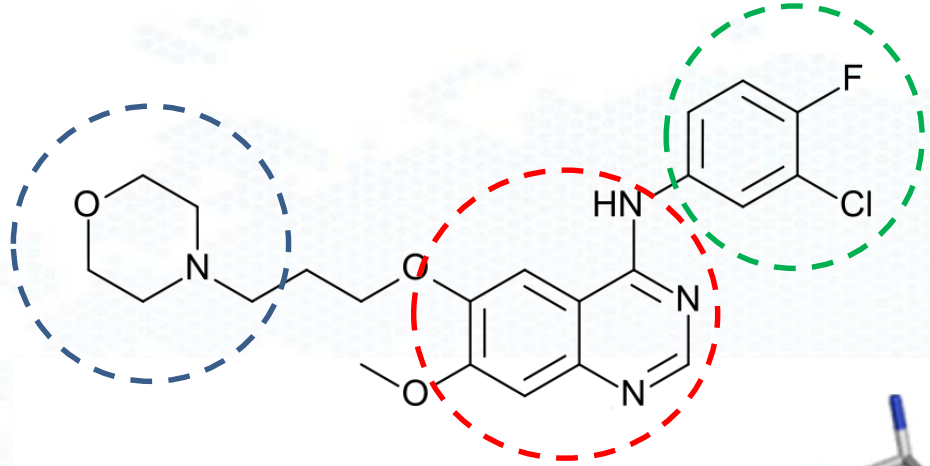
| 2003 | 2004 | 2005 | 2006 | 2007 | 2009 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|---|
| Imatinib | Erlotinib | Sorafenib | Sunitinib | Lapatinib | Temsirolimus | Vemurafenib | Axitinib | Afatinib | Ceritinib |
| Gefitinib | | | | Dasatinib | Everolimus | Vandetanib | Regorafenib | Dabrafenib | Idelalisib |
| | | | | | Nilotinib | Ruxolitinib | Pazopanib | Trametinib | Nintedanib |
| | | | | | | Crizotinib | Tofacitinib | Ibrutinib | Alectinib |
| | | | | | | | Cabozantinib | | |
| | | | | | | | Bosutinib | | |
| | | | | | | | Ponatinib | | |

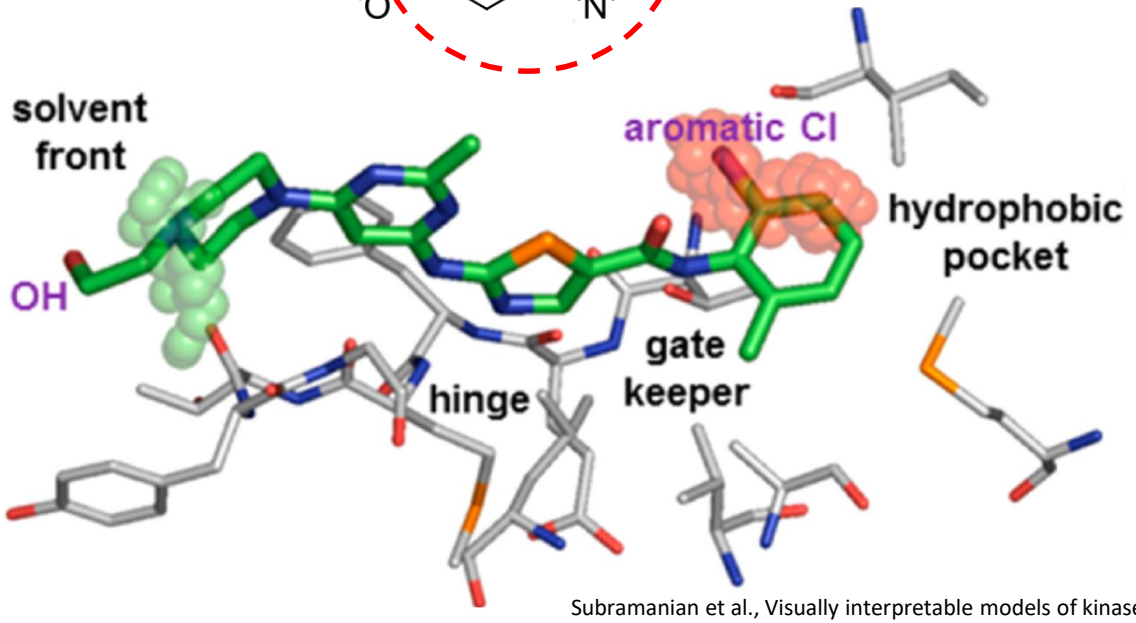
| 2015 | 2016 | 2017 |
|---|---|---|
| Lenvatinib | | Brigatinib |
| Osimertinib | | Alectinib |
| Palbociclib | | Ribociclib |
| | | Midostaurin |
| | | Osimertinib |

# Basic Structural Components of Kinase Inhibitors




Modi and Dunbrack. Defining a new nomenclature for the structures of active and inactive kinases. Proc Natl Acad Sci. 2019



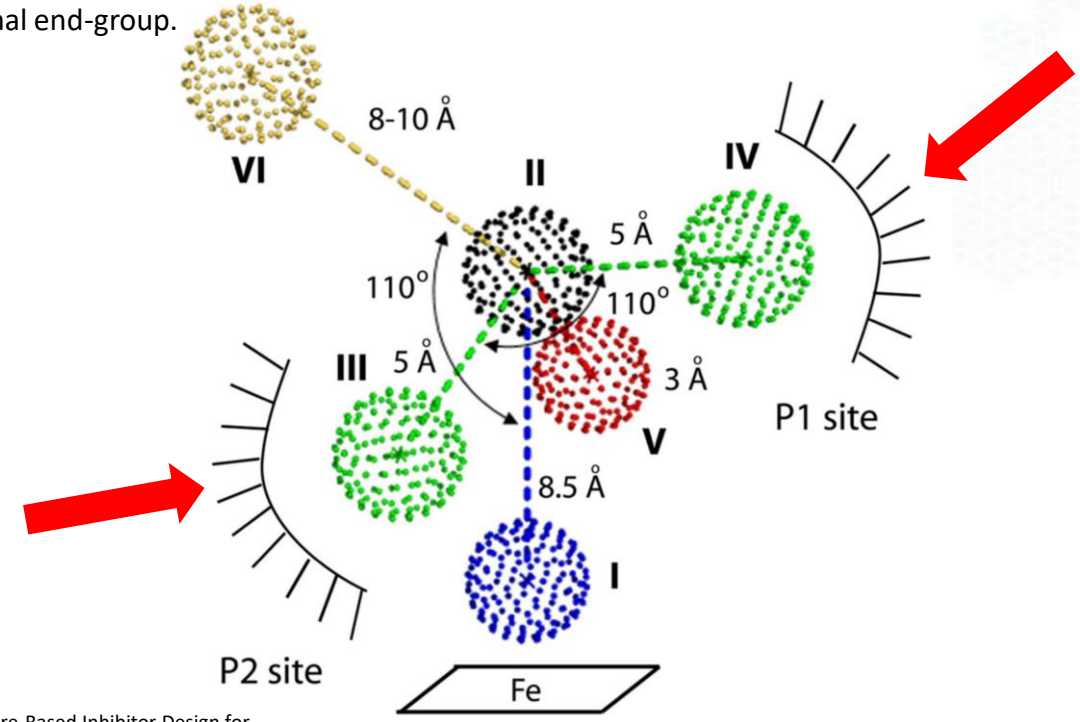




Subramanian et al., Visually interpretable models of kinase selectivity related features derived from field-based proteochemometrics. J Chem Inf Model. 25;53(11):3021-30, 2013.

# Overlap of Kinase Pharmacophore with CYP3A4

The active site of CYP3A4 is very flexible and is able to interact with a wide variety of ligands, because the ligand accessible regions can change their structure dramatically. It does appear that there is an amphipathic nature of CYP3A4 inhibitors. In this fashion, the molecular shape specifically hydrophobicity (higher log P), electronegativity, and polarizability are the most important quantities relevant to the potency of CYP3A4 inhibition.

Pharmacophore model for a CYP3A4-specific inhibitors. Key pharmacophoric determinants (for type II inhibitor)are the following: I, strong heme-ligating nitrogen donor; II, flexible backbone; III and IV, aromatic and hydrophobic moieties, respectively; V,hydrogen donor/acceptor; IV, polyfunctional end-group.




Kaur et al., Structure-Based Inhibitor Design for Evaluation of a CYP3A4 Pharmacophore Model. J. Med. Chem. 59: 4210−4220, 2016

TABLE 6. Characteristics of human P450 substrates

| CYP | General properties displayed by most substrates |
|---|---|
| 1A2 | Planar molecules, moderately basic, medium volume and low ΔE values. |
| 2A6 | Non-planar molecules, medium volume with two hydrogen bond acceptors at about 2.5 Å apart and 5–7 Å from the site of metabolism. |
| 2B6 | Non-planar molecules, neutral or weakly basic, fairly lipophilic with one or two hydrogen bond acceptors. |
| 2C9 | Weakly acid, fairly lipophilic with one or two hydrogen bond donor/acceptors at 5–8 Å from the site of metabolism. |
| 2C19 | Neutral or weakly basic, moderately lipophilic with two or three hydrogen bond donor/acceptors at about 4.5 Å apart and 5–8 Å from the site of metabolism. |
| 2D6 | Basic, relatively hydrophilic, usually contain an aromatic ring and a hydrogen bond donor/acceptor, basic nitrogen at 5–7 Å from the site of metabolism. |
| 2E1 | Low volume, neutral, hydrophilic, relatively planar, structurally diverse with one or two hydrogen bond donor/acceptors at 4–6 Å from the site of metabolism. |
| 3A4 | High volume, relatively lipophilic, structurally diverse with one or two hydrogen bond donor/acceptors at 5.5–7.5 Å and 8–10 Å from the site of metabolism. |

Lewis. On the Recognition of Mammalian Microsomal Cytochrome P450 Substrates and Their Characteristics. Biochemical Pharmacology, 60: 293–306, 2000

**Box 1. Summary of substrate/selectivity rules for P450 isoenzymes**

**CYP1A2** Neutral or basic, lipophilic, planar molecules with at least one putative hydrogen bond donating site. Principal substrate is theophylline.

**CYP2D6** Aryl-alkyl amines (basic), with site of oxidation a discrete distance from a protonated nitrogen. Substrates are lipophilic, particularly when measured or calculated for the neutral form. Principal substrates are β-adrenoceptor blockers, class I antiarrhythmics and tricyclic antidepressants. Often hydroxylation occurs in an aromatic ring or an accompanying short alkyl side-chain.

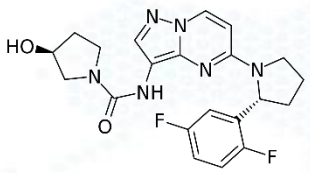
**CYP2C9** Neutral or acidic molecules with site of oxidation a discrete distance from hydrogen bond donor or possibly anionic heteroatom. Molecules tend to be amphipathic, with a region of lipophilicity at the site of hydroxylation and an area of hydrophobicity around the hydrogen bond forming region. Principal substrates are nonsteroidal anti-inflammatory agents. Oxidation often occurs in an aromatic ring or an accompanying short alkyl side-chain.

**CYP3A4** Lipophilic, neutral, or basic molecules with site of oxidation often nitrogen (*N*-dealkylation) or allylic positions. Wide range of substrates covering all fields of pharmaceuticals.

**CYP2E1** Small (molecular weight of 200 or less), normally lipophilic, linear and cyclic molecules. Principal pharmaceutical compounds are volatile anaesthetics.

Smith et al., Properties of cytochrome P450 isoenzymes and their substrates part 2: properties of cytochrome P450 substrates. Drug Discovery Today. 2(11): 479-486, 1997

# Problem 1: Kinase Inhibitors and DDI potential



**7 DRUG INTERACTIONS**

**7.1 Effects of Other Drugs on VITRAKVI**

Strong CYP3A4 Inhibitors

Coadministration of VITRAKVI with a strong CYP3A4 inhibitor may increase larotrectinib plasma concentrations, which may result in a higher incidence of adverse reactions *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If coadministration of strong CYP3A4 inhibitors cannot be avoided, modify VITRAKVI dose as recommended *[see Dosage and Administration (2.4)]*.

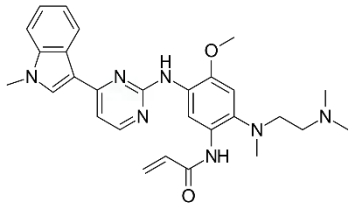
Strong CYP3A4 Inducers

Coadministration of VITRAKVI with a strong CYP3A4 inducer may decrease larotrectinib plasma concentrations, which may decrease the efficacy of VITRAKVI *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of VITRAKVI with strong CYP3A4 inducers, including St. John's wort. If coadministration of strong CYP3A4 inducers cannot be avoided, modify VITRAKVI dose as recommended *[see Dosage and Administration (2.5)]*.

**7.2 Effects of VITRAKVI on Other Drugs**

Sensitive CYP3A4 Substrates

Coadministration of VITRAKVI with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of VITRAKVI with sensitive CYP3A4 substrates. If coadministration of these sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.



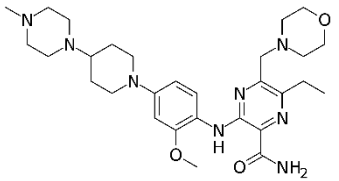
**7 DRUG INTERACTIONS**

**7.1 Effect of Other Drugs on Osimertinib**

Strong CYP3A Inducers

Coadministering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone *[see Clinical Pharmacology (12.3)]*. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid coadministering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when coadministering with a strong CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4)]*. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.



**7 DRUG INTERACTIONS**

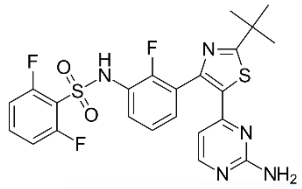
**7.1 Effect of Other Drugs on XOSPATA**

*Combined P-gp and Strong CYP3A Inducers*

Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases gilteritinib exposure which may decrease XOSPATA efficacy *[see Clinical Pharmacology (12.3)]*. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

*Strong CYP3A Inhibitors*

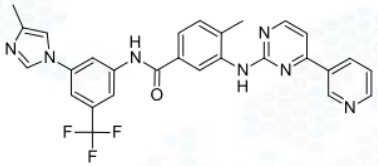
Concomitant use of XOSPATA with a strong CYP3A inhibitor increases gilteritinib exposure *[see Clinical Pharmacology (12.3)]*. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity *[see Dosage and Administration (2.3)]*.

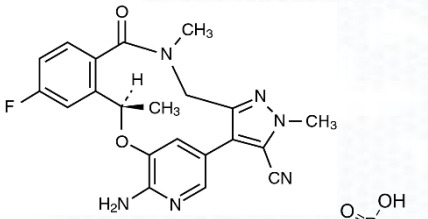


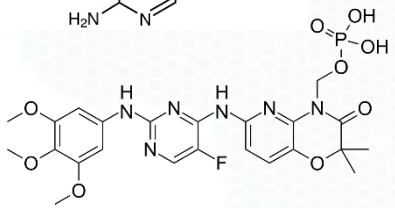
**7 DRUG INTERACTIONS**

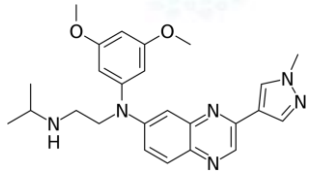
**7.1 Effects of Other Drugs on Dabrafenib**

Strong inhibitors of CYP3A4 or CYP2C8 may increase the concentration of dabrafenib *[see Clinical Pharmacology (12.3)]*. Substitution of strong inhibitors of CYP3A4 or CYP2C8 is recommended during treatment with TAFINLAR. If concomitant use of strong inhibitors of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors.









**7 DRUG INTERACTIONS**

**7.1 Effects of Nilotinib on Drug Metabolizing Enzymes and Drug Transport Systems**

Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 in vitro, potentially increasing the concentrations of drugs eliminated by these enzymes. In vitro studies also suggest that nilotinib may induce CYP2B6, CYP2C8 and CYP2C9, and decrease the concentrations of drugs which are eliminated by these enzymes.

In patients with CML, multiple doses of Tasigna increased the systemic exposure of oral midazolam (a substrate of CYP3A4) 2.6-fold. Tasigna is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of drugs metabolized by CYP3A4 (e.g., certain HMG-CoA reductase inhibitors) may be increased when coadministered with Tasigna. Dose adjustment may be necessary for drugs that are CYP3A4 substrates, especially those that have narrow therapeutic indices (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when coadministered with Tasigna.

Single-dose administration of Tasigna to healthy subjects did not change the pharmacokinetics and pharmacodynamics of warfarin (a CYP2C9 substrate). The ability of multiple doses of Tasigna to induce metabolism of drugs other than midazolam has not been determined in vivo. Monitor patients closely when coadministering Tasigna with drugs that have a narrow therapeutic index and are substrates for CYP2B6, CYP2C8, or CYP2C9 enzymes.

**7.2 Effect of LORBRENA on Other Drugs**

CYP3A Substrates

Concomitant use of LORBRENA decreases the concentration of CYP3A substrates *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of these substrates. Avoid concomitant use of LORBRENA with CYP3A substrates, where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with approved product labeling.

**7.2 Effect of TAVALISSE on Other Drugs**

CYP3A4 Substrates

Concomitant use of TAVALISSE may increase concentrations of some CYP3A4 substrate drugs. Monitor for toxicities of CYP3A4 substrate drug that may require dosage reduction when given concurrently with TAVALISSE *[see Clinical Pharmacology (12.3)]*.

**7.2 Effect of BALVERSA on Other Drugs**

Table 6 summarizes the effect of BALVERSA on other drugs and their clinical management.

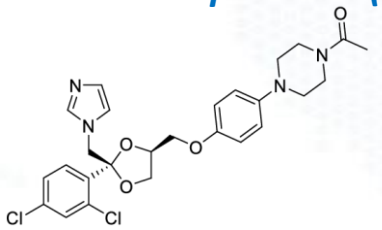
**Table 6: BALVERSA Drug Interactions that Affect Other Drugs**

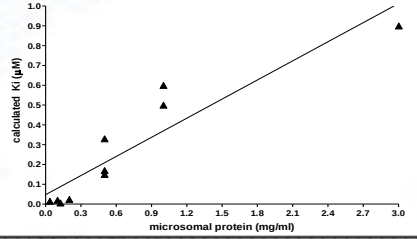
| | |
|---|---|
| **CYP3A4 Substrates** | |
| Clinical Impact | • Co-administration of BALVERSA with CYP3A4 substrates may alter the plasma concentrations of CYP3A4 substrates *[see Clinical Pharmacology (12.3)]*.<br>• Altered plasma concentrations of CYP3A4 substrates may lead to loss of activity or increased toxicity of the CYP3A4 substrates. |
| Clinical Management | • Avoid co-administration of BALVERSA with sensitive substrates of CYP3A4 with narrow therapeutic indices. |
| **OCT2 Substrates** | |
| Clinical Impact | • Co-administration of BALVERSA with OCT2 substrates may increase the plasma concentrations of OCT2 substrates *[see Clinical Pharmacology (12.3)]*.<br>• Increased plasma concentrations of OCT2 substrates may lead to increased toxicity of the OCT2 substrates. |
| Clinical Management | • Consider alternative therapies that are not OCT2 substrates or consider reducing the dose of OCT2 substrates (e.g., metformin) based on tolerability. |
| **P-glycoprotein (P-gp) Substrates** | |
| Clinical Impact | • Co-administration of BALVERSA with P-gp substrates may increase the plasma concentrations of P-gp substrates *[see Clinical Pharmacology (12.3)]*.<br>• Increased plasma concentrations of P-gp substrates may lead to increased |

# Kinase Inhibitors and Undetected DDI Liability

***There have been numerous reports of these molecules being potent CYP3A4 inhibitors in the clinic although based upon in vitro enzyme and inhibition kinetics many of these kinase inhibitors were not predicted to be inhibitors. One reason why investigators have missed the DDI potential of these molecules is due to nonspecific binding within the incubation mixture. Typically, kinase inhibitors are lipophilic (log P values 2.5) weak organic bases, which are frequently nonionized at physiologic pH. Therefore, it is not surprising that many kinase inhibitors exhibit significant nonspecific binding. The consequences of substantial microsomal binding is that the apparent Km and Ki values will be significantly overestimated which in turn negatively impacts the accuracy of the predicted in vivo drug-drug interaction potential based upon traditional in vitro–in vivo extrapolation (PBPK) approaches.***

Burns et al., The Nonspecific Binding of Tyrosine Kinase Inhibitors to Human Liver Microsomes. Drug Metab Dispos 43:1934–1937, 2015

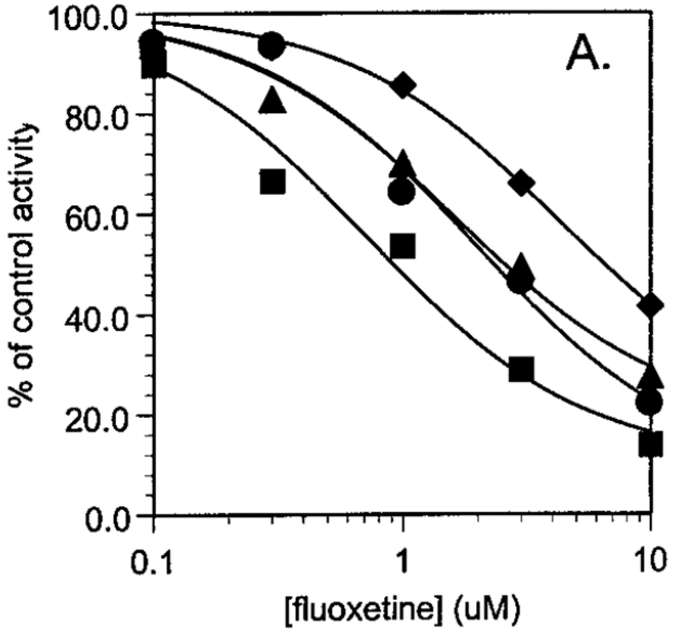


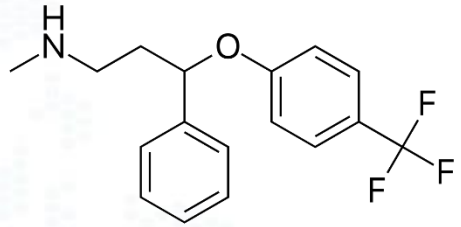



| 3A4 substrate | Protein conc. (mg/ml) | In vitro $K_i$ (μM) | Reference |
|---|---|---|---|
| Midazolam | 0.035 | 0.015 | Gibbs et al., 1999 |
| Sildenafil | 0.1 | 0.02 | Hyland et al., 2001 |
| Triazolam | 0.125 | 0.006 | von Moltke et al., 1996a |
| Terfenadine | 2 | 0.024 | von Moltke et al., 1996b |
| Dihydroqinqhaosu | 0.2 | 0.28 | Grace et al., 1999 |
| Quinidine | 0.5 | 0.15 | Nielsen et al., 1999 |
| Vinblastine | 0.5 | 0.17 | Zhou-Pan et al., 1993 |
| β-Arteether | 0.5 | 0.33 | Grace et al., 1998 |
| Brotizolam | 1.0 | 0.5 | Senda et al., 1997 |
| Buprenorphine | 1.0 | 0.6 | Iribarne et al., 1997 |
| Cortisol | 3.0 | 0.9 | Abel and Black, 1993 |

Wienkers LC. Factors confounding the successful extrapolation of in vitro CYP3A inhibition information to the in vivo condition. Eur J Pharm Sci. 15(3):239-42, 2002

**Inhibition of CYP2D6 catalyzed bufuralol 1`-hydroxylase activity**



Margolis JM & Obach RS. Impact of nonspecific binding to microsomes and phospholipid on the inhibition of cytochrome P4502D6: implications for relating in vitro inhibition data to in vivo drug interactions. Drug Metab Dispos. 31(5):606-11, 2003

Symbols are defined as follows: control, ■; 0.2 mg/ml, ●; 0.5 mg/ml, ▲; 2.0 mg/ml, ♦.

# P450 MBI: Survey & Diagnostic Experiments

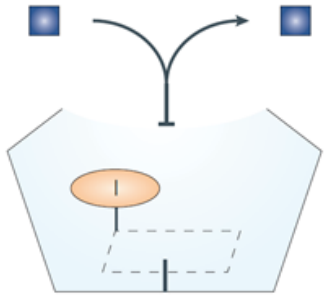
$$E + I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EI \xrightarrow{k_2} EI^* \xrightarrow{k_4} EI^{\dagger}$$
$$EI^* \xrightarrow{k_3} E + P$$

*Drugs and other compounds known to cause time-dependent inhibition of drug-metabolizing human cytochrome P450 enzymes*

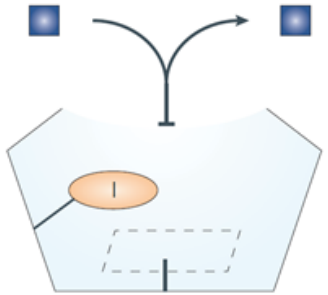
| | |
|---|---|
| 1-Aminobenzotriazole (several) | Methoxsalen (CYP2A6) |
| Amiodarone (CYP3A) | 3,4-Methylenedioxymethamphetamine (CYP2D6) |
| Amprenavir (CYP3A) | 3-Methylindole (CYP2F) |
| Azamulin (CYP3A) | Mibefradil (CYP3A) |
| Azithromycin (CYP3A) | Midazolam (CYP3A) |
| Bergamottin (CYP3A) | Mifepristone (CYP3A) |
| Cannabidiol (CYP3A) | Nefazodone (CYP3A) |
| Carbamazepine (CYP1A2) | Nelfinavir (CYP3A) |
| Chlorgyline (CYP1A2) | Nicardipine (CYP3A) |
| Cimetidine (CYP2D6) | Paroxetine (CYP2D6) |
| Clarithromycin (CYP3A) | Phencyclidine (CYP2B6) |
| Clopidogrel (CYP2B6) | Phenelzine (several) |
| Delavirdine (CYP3A) | Pioglitazone (CYP3A) |
| Diclofenac (CYP3A) | *n*-Propylxanthate (CYP2B6) |
| Dihydralazine (CYP1A2) | Raloxifene (CYP3A) |
| 6,7-Dihydroxybergamottin (CYP3A) | Resveratrol (CYP3A) |
| Diltiazem (CYP3A) | Rhapontigenin (CYP1A1) |
| Disulfiram (CYP2E1) | Ritonavir (CYP3A) |
| Efavirenz (CYP2B6) | Rofecoxib (CYP1A2) |
| EMTPP (CYP2D6) | Rosiglitazone (CYP3A) |
| Enoxacin (CYP1A2) | Roxithromycin (CYP3A) |
| Erythromycin (CYP3A) | Rutaecarpine (CYP1A1, 1B1) |
| Ethinyl estradiol (CYP3A) | Saquinavir (CYP3A) |
| 2-Ethynylnaphthalene (CYP1A) | Silybin (CYP3A) |
| Fluoxetine (CYP3A) | Suprofen (CYP2C9) |
| Furafylline (CYP1A2) | Tabimorelin (CYP3A) |
| Gemfibrozil glucuronide (CYP2C8) | Tamoxifen (CYP3A) |
| Gestodene (CYP3A) | ThioTEPA (CYP2B6) |
| Glabridin (CYP2B6) | Ticlopidine (CYP2B6, 2C19) |
| Hydrastine (several) | Tienilic acid (CYP2C9) |
| 4-Ipomeanol (CYP3A) | Troglitazone (CYP3A, 2C8, 2C9) |
| Irinotecan (CYP3A) | Troleandomycin (CYP3A) |
| Isoniazid (several) | Verapamil (CYP3A) |
| Lopinavir (CYP3A) | Zafirlukast (CYP3A) |
| Menthofuran (CYP2A6) | Zileuton (CYP1A2) |

Grimm SW, Einolf HJ, Hall SD, He K, Lim HK, Ling KH, Lu C, Nomeir AA, Seibert E, Skordos KW, Tonn GR, Van Horn R, Wang RW, Wong YN, Yang TJ, Obach RS. Drug Metab Dispos. 2009 Jul;37(7):1355-70.

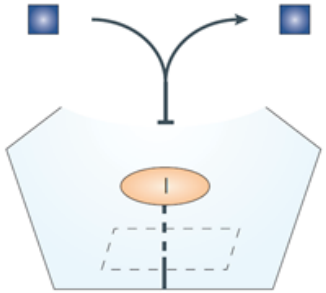
## Heme Destruction



## Apoprotein Adduction

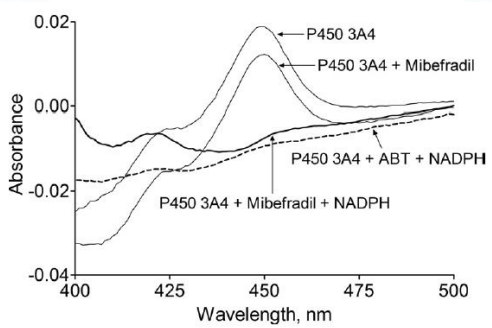


## Complex w/ Heme Iron

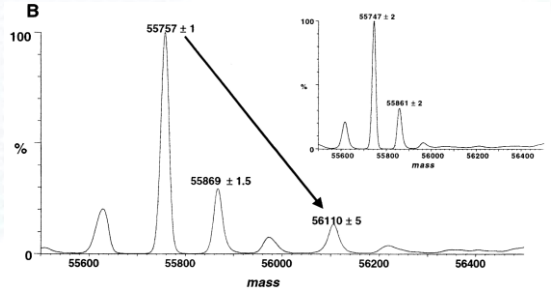


Wienkers LC and Heath TG Nature Reviews on Drug Discovery. 4(10):825-833, (2005).

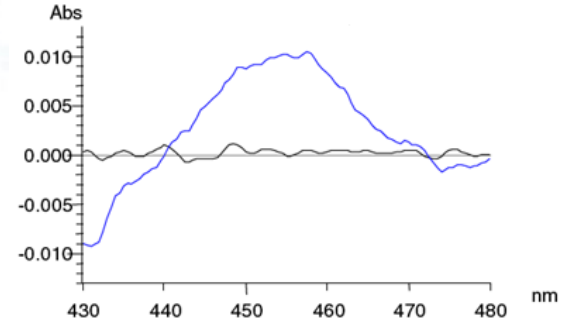
***Each of these mechanisms sets up a unique biochemical signature that can be experimentally differentiated:***




Foti RS, Rock DA, Pearson JT, Wahlstrom JL, Wienkers LC. Drug Metab Dispos. 39(7):1188-95 (2011).




Hutzler JM, Steenwyk RC, Smith EB, Walker GS, Wienkers LC. Chem Res Toxicol. 17(2):174-84, 2004

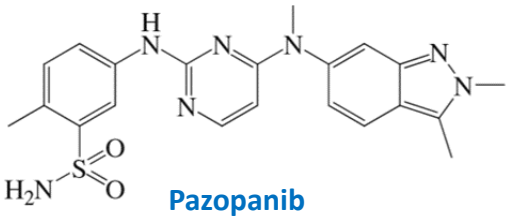


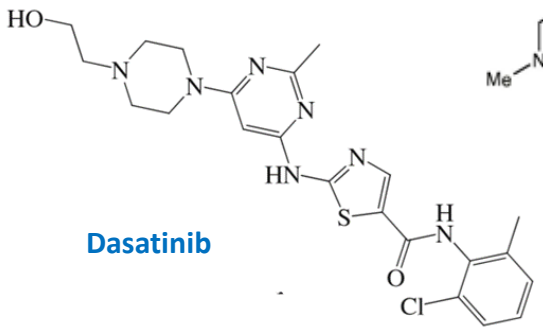

Hutzler JM, Melton RJ, Rumsey JM, Bolden CM, Locuson CW, and Wienkers LC. Chemical Research and Toxicology 19(12):1650-1659, (2006).

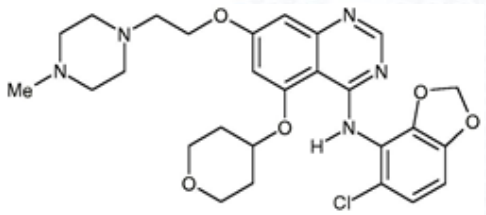
XENOTECH
A BioIVT Company

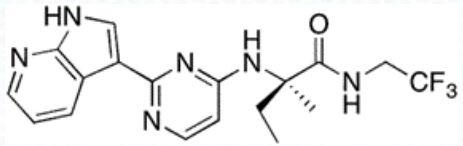
# Problem 2: Kinase Inhibitors as Potent CYP3A4 MBIs

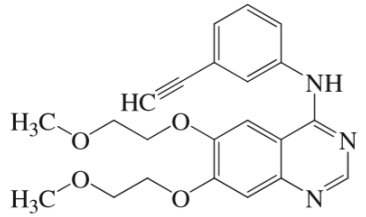
**The active site of CYP3A4 is very flexible and is able to interact with a wide variety of ligands, because the ligand accessible regions can change their structure dramatically. It does appear that there is an amphipathic nature of CYP3A4 substrates. In this fashion, the molecular shape specifically hydrophobicity (higher log P), electronegativity, and polarizability are the most important quantities relevant to the characteristics of CYP3A4.**

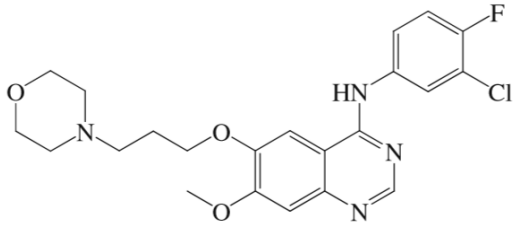

Pazopanib


Dasatinib


Saracatinib


Decernotinib


Erlotinib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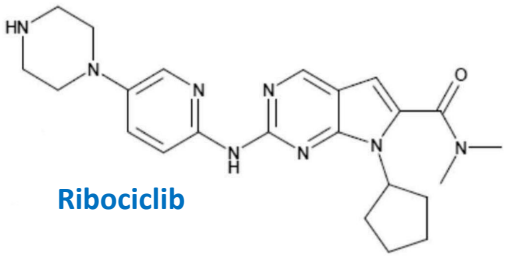
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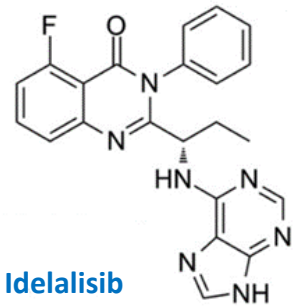
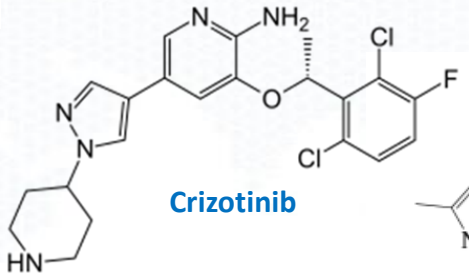

Idelalisib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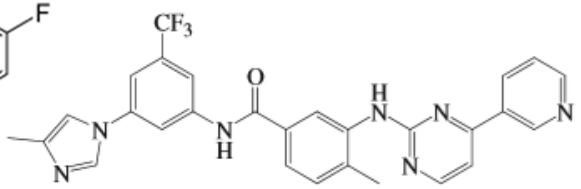
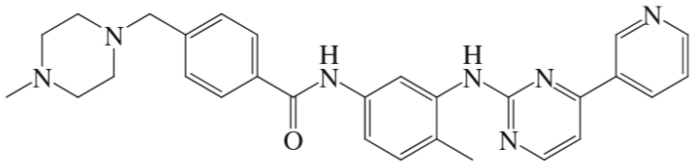
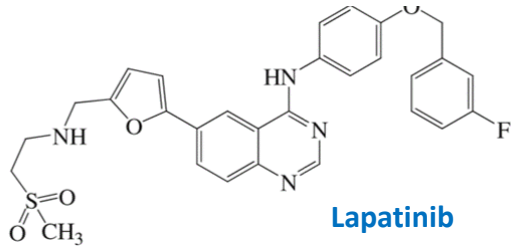
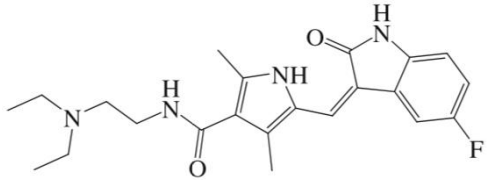
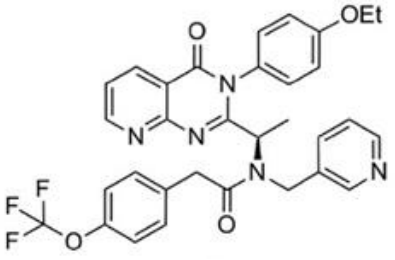

Nilotinib


Imatinib


Lapatinib


Sunitinib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J Kenny, S Mukadam, C Zhang, S Tay, C Collins, A Galetin, SC Khojasteh Pharm Res. 29:1960–1976, 2012

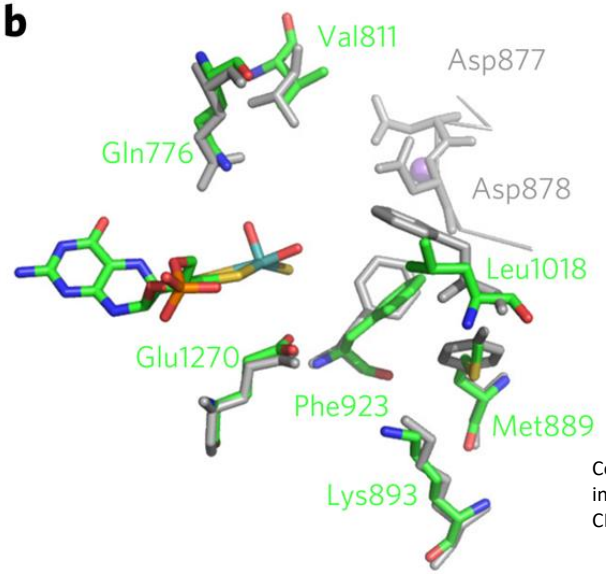
J Towles, R Clark, M Wahlin, V Uttamsingh, A Rettie & K Jackson Drug Metab & Dispos. 44(10):1584-1597, 2016

Zetterberg, et al. Drug Metab Dispos 44:1286–1295, 2016

Amaya et al.,. Chem. Res. Toxicol. 31: 570−584, 2018

K Henne, T Tran, B VandenBrink, D Rock, D Aidasani, R Subramanian, A Mason, D Stresser, Y Teffera, S Wong, M Johnson, X Chen, G Tonn and B Wong. Drug Metabolism and Disposition 40(7): 1429-1440, 2012

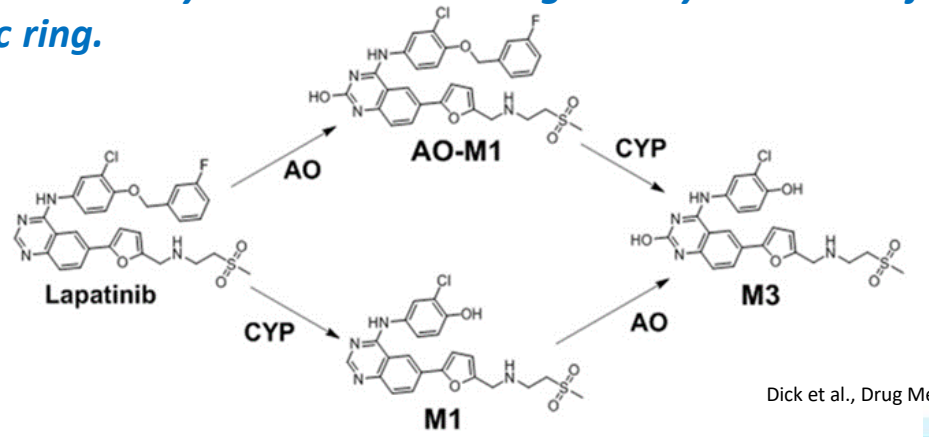
# SAR for AO Resembles CYP3A4



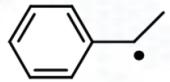
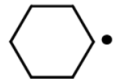

Coelho et al., Structural insights into xenobiotic and inhibitor binding to human aldehyde oxidase. NATURE CHEMICAL BIOLOGY 11: 779-783, 2015

***Just like CYP3A4, the AO active site also has a hydrophobic region (Phe885, Phe655, Leu1018 and Ala1023) which facilitates a hydrophobic interaction. Besides a hydrophobic pocket in the active site of enzyme, there is also additional a π-π interaction possible between the benzene ring typically fused to the heterocyclic ring of substrate and Phe923 of active site.***

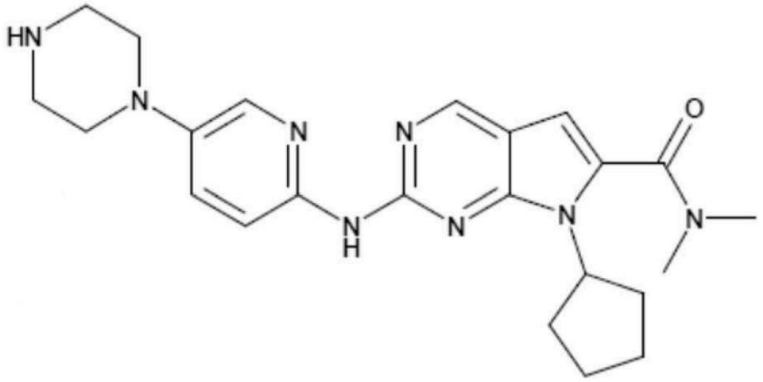
***Electronegative nitrogen in an aza-aromatic ring can reduce electron density of carbons of the aromatic ring. The oxy-iron species of the CYP enzyme is electrophilic in nature; hence, the decrease in electron density in the aromatic ring is likely the reason for the metabolic stability of the aza-aromatic ring.***




Dick et al., Drug Metabolism and Disposition 46(6): 846-859, 2018

| Radical | $\delta\Delta H_f$ Kcal/mole | Reaction Type |
|---|---|---|
| $H_2N-\dot{C}H_2$ | 17.3 | N-dealkylation |
|  | 19.6 | benzylic hydroxylation |
| $H_3C-O-\dot{C}H-CH_3$ | 26.6 | O-dealkylation |
| $H_3C-\dot{C}H-CH_3$ | 27.7 | aliphatic hydroxylation |
|  | 28.6 | aliphatic hydroxylation |
| $H_3C-CH_2-\dot{C}H_2$ | 33.0 | ω-hydroxylation |

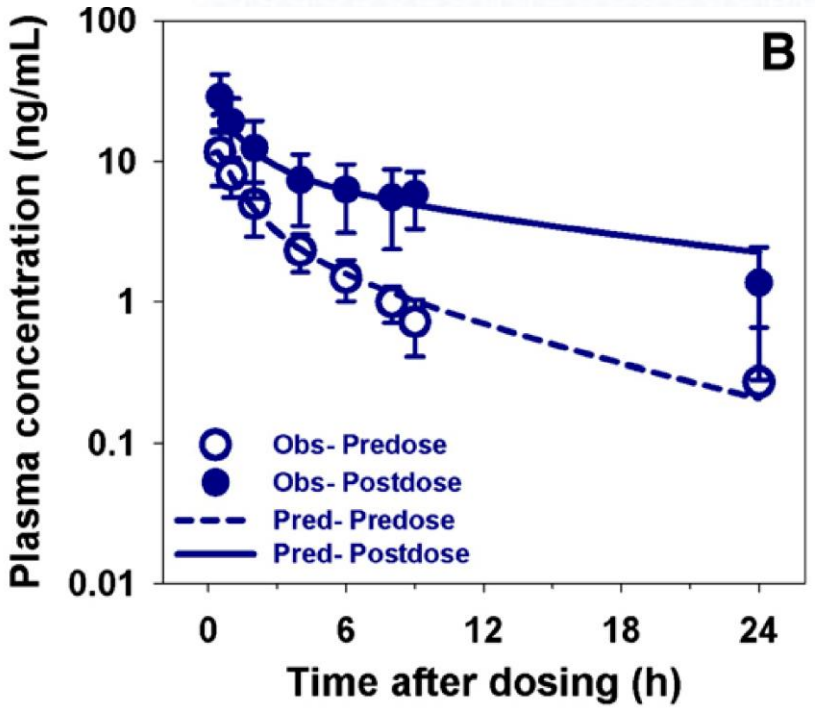
# Kinase Inhibitors with CYP3A4 TDI Activity

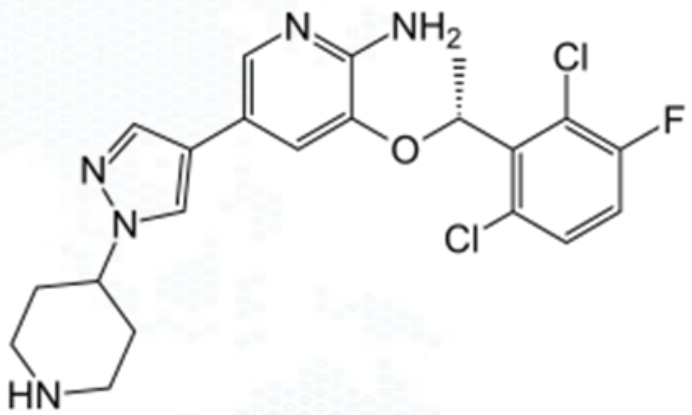


In vitro, ribociclib showed reversible (Ki,u = 30.0 μM) and mechanism-based inhibition (KI,u = 4.44 μM, kinact =0.02/min) of CYP3A. Based on the basic model (FDA, 2012), ribociclib was predicted to inhibit CYP3A at clinically relevant concentrations (Cmax = 4 mM at 600 mg once daily in cancer patients). Indeed, according to PBPK models, ribociclib was predicted to increase midazolam AUC 5.17-fold at clinical doses of 600 mg once daily for 8 days, suggesting that it is a strong inhibitor of CYP3A. In agreement with that prediction, when ribociclib was administered to healthy subjects at a lower dose of 400 mg once daily for 8 days, a 3.89-fold increase in midazolam AUC was observed.

Curigliano et al., Pharmacokinetic drug evaluation of ribociclib for the treatment of metastatic, hormone-positive breast cancer. Expert Opin Drug Metab Toxicol. 13(5):575-581, 2017

In vitro studies determined that Crizotinib inactivation constant (KI) and maximum inactivation rate constant (kinact) for TDI were estimated as, respectively, 0.37 mM and 6.9 h21 in HLM and 0.89 mM and 0.78 h21 in HSP. Thus, crizotinib inactivation efficiency (kinact/KI) was ~20-fold lower in HSP relative to HLM.

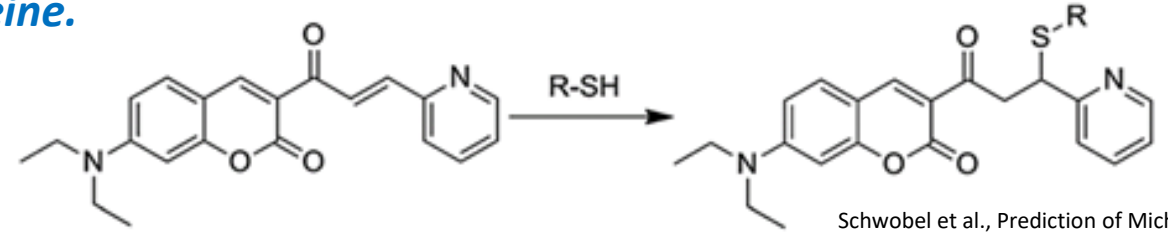


Mao et al., Prediction of Crizotinib-Midazolam Interaction using the Simcyp Population-based Simulator: Comparison of CYP3A Time-Dependent Inhibition between Human Liver Microsomes versus Hepatocytes. Drug Metab Dispos 41:343–352, 2013

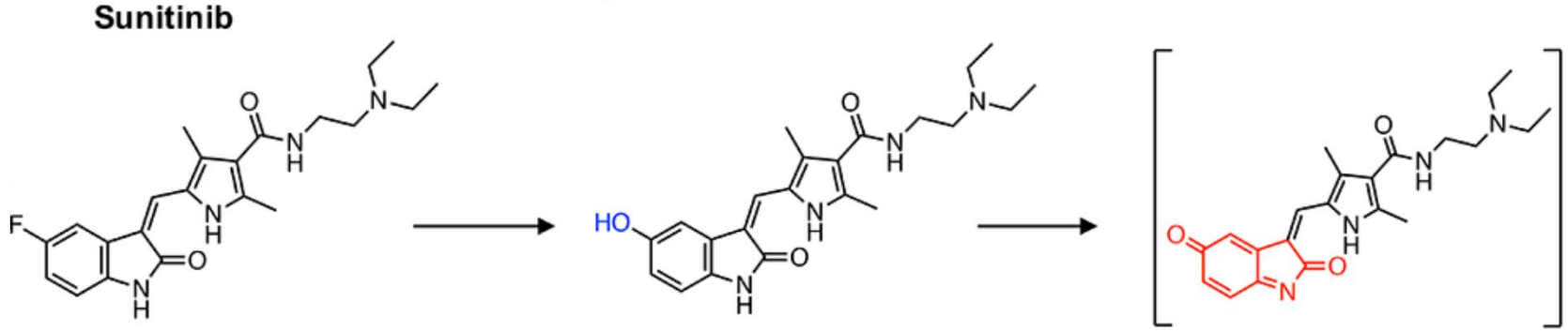
# Linking Kinase Inhibitors and CYP3A4 TDI

***For these molecules we can easily hypothesis on the reactive species leading to CYP3A4 TDI as being a Michael acceptor. This chemical species is regarded as a soft electrophile where the most common type of reactive metabolites are typically are various quinone species, such as quinone-imines, quinone-methides, or imine-methides. In this context, these species are capable of forming irreversible bonds with biological macromolecules, such as proteins and are characterized as having carbon-carbon double adjacent to electron-withdrawing substituents. In this instance, there is a polarizable electron density at the π-bond, where the -carbon atom is positively polarized and becomes the preferred site of an attack for soft nucleophiles, for example, glutathione (GSH) or an active site cysteine.***




Schwobel et al., Prediction of Michael-Type Acceptor Reactivity toward Glutathione Chem. Res. Toxicol. 2010, 23, 1576–1585

***For the sake of our example, the formation of the Michael acceptor can be via metabolic oxidation by aldehyde oxidase or CYP3A4 occurring through one or two metabolic steps, where the final step is the oxidation the substrate into a quinone species.***




Amaya et al., Cytochromes P450 1A2 and 3A4 Catalyze the Metabolic Activation of Sunitinib. Chem. Res. Toxicol. 31: 570−584, 2018

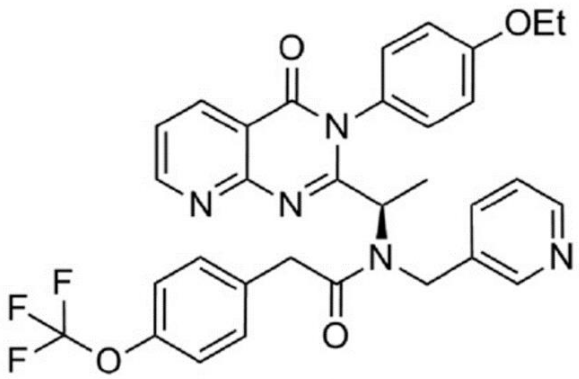




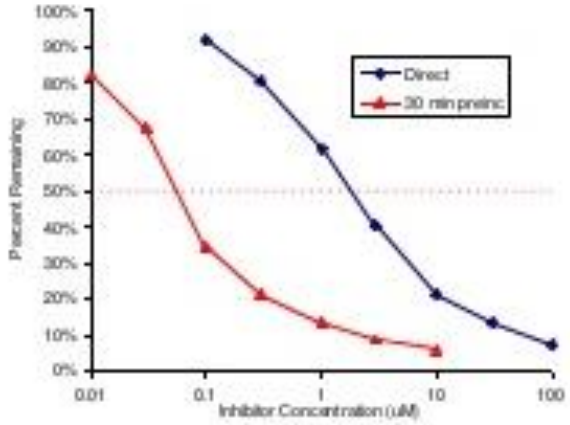
21

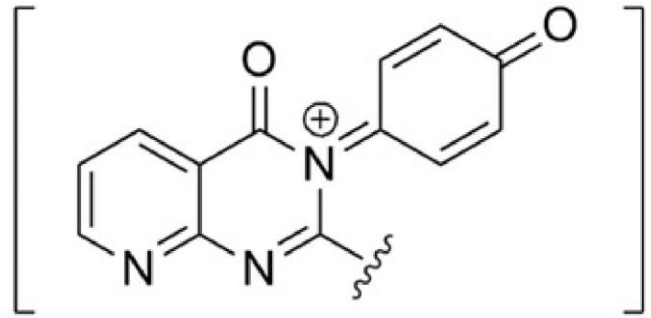
# Linking Kinase Inhibitors and CYP3A4 MBI

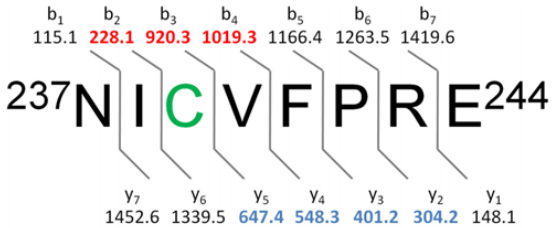
## Example AMG 487 CYP3A4 MBI

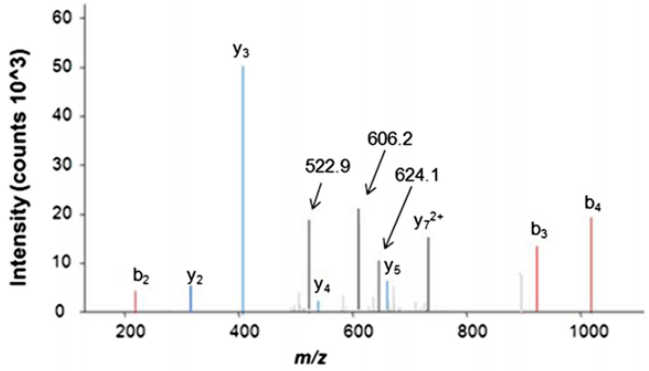



M2

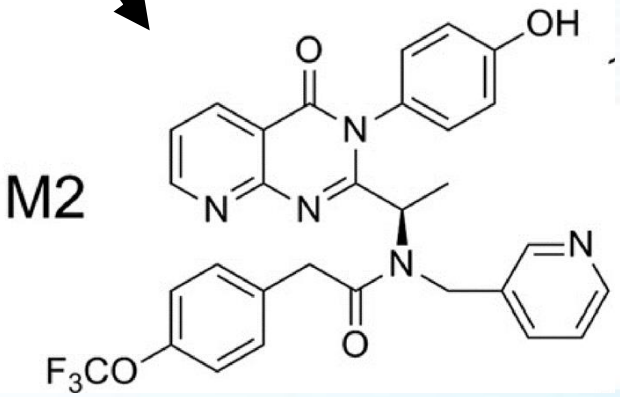


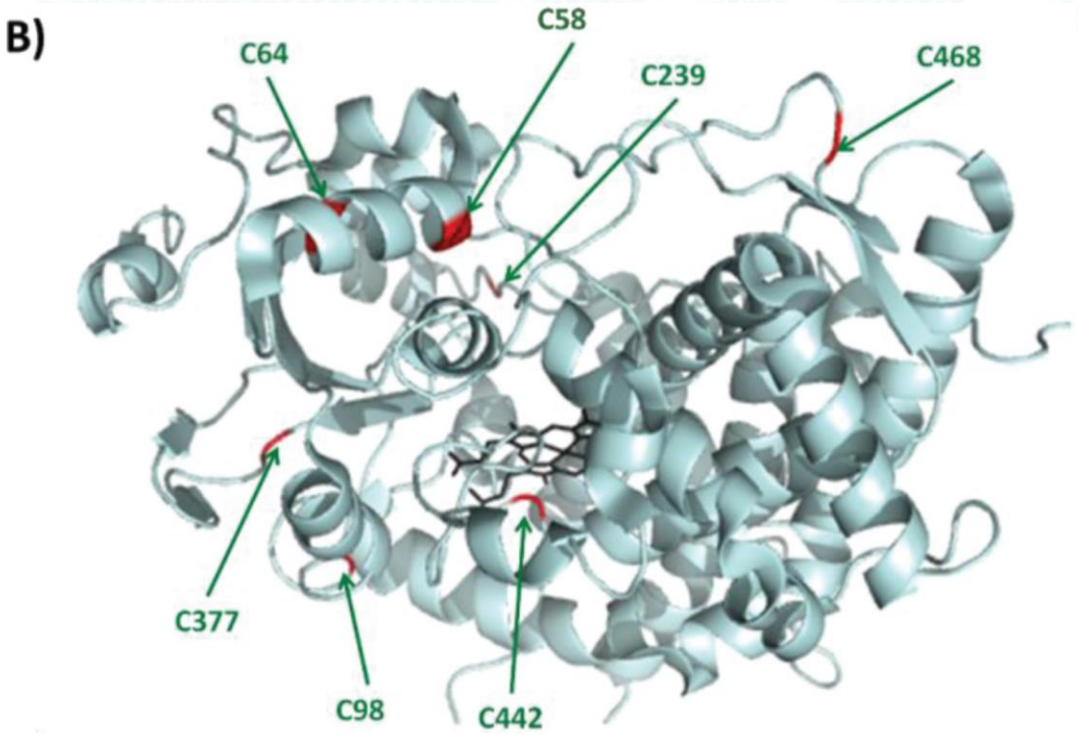

M2



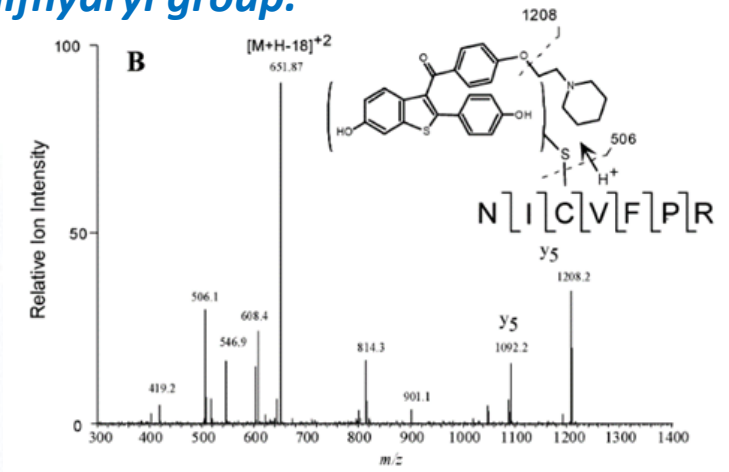

K Henne, T Tran, B VandenBrink, D Rock, D Aidasani, R Subramanian, A Mason, D Stresser, Y Teffera, S Wong, M Johnson, X Chen, G Tonn and B Wong. Drug Metabolism and Disposition 40(7): 1429-1440, 2012

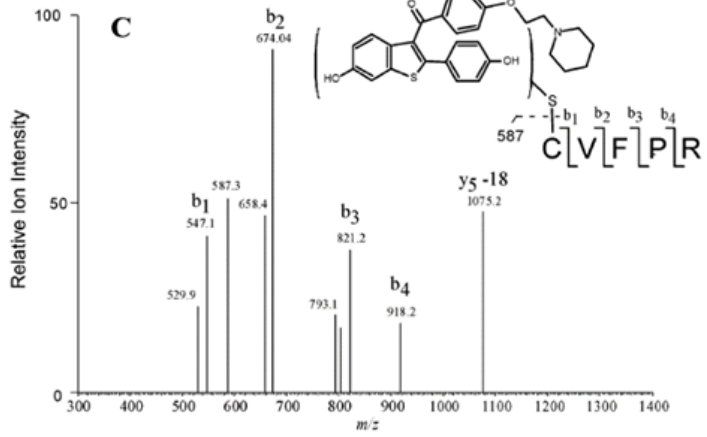
# Understanding CYP3A4 Protein Adduction and MBI

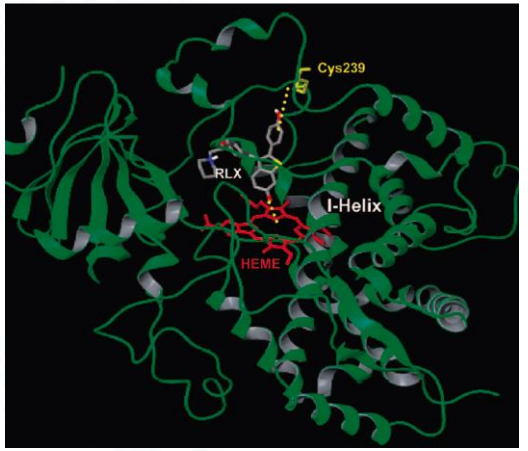
***Basically, the reactivity of the different functional groups in a protein relies on the nature of the nucleophile and the accessibility of the amino acid side chain to the activated. For soft electrophiles, cysteine is perhaps the most common target for adduction owing to the strongly nucleophilic side chain sulfhydryl group.***




Menard et al, Site-Specific Fluorescent Labeling and Oriented Immobilization of a Triple Mutant of CYP3A4 via C64. | Bioconjugate Chem. 23: 826−836, 2012



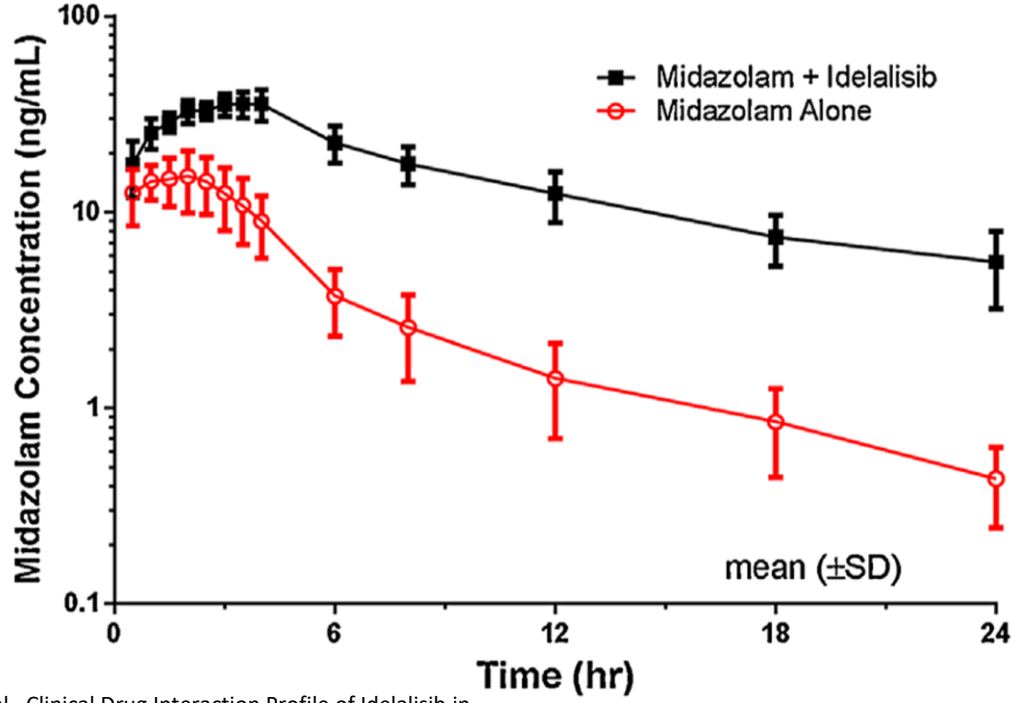




Baer B, Wienkers LC and Rock DA. Chemical Research and Toxicology 20(6):954-964, (2007).

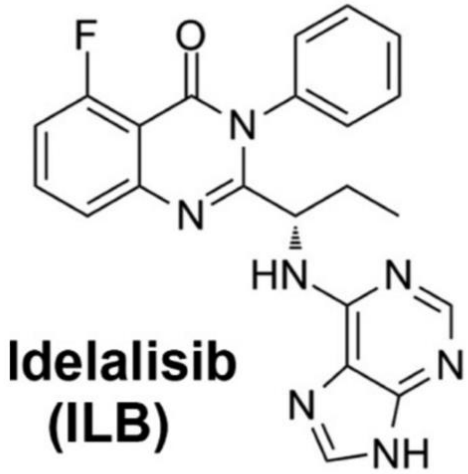
**Chemical modification of CYP3A4 cysteine residues at positions: 239, 468 and 98 have all triggered marked conformational changes and subsequent loss of enzyme activity.**

# Metabolites Contributing to Clinical DDI: Idelalisib

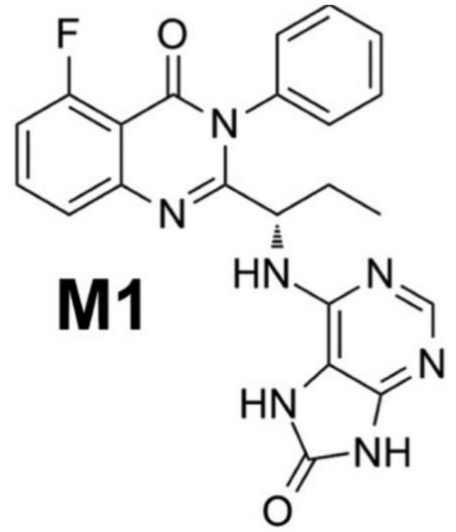
The elimination of idelalisib is predominantly mediated by hepatic oxidative metabolism is mainly mediated by AO and in part by CYP3A to form M1 (GS-563117), a metabolite that has no Pharmacological activity. Based upon PBPK models, Idelalisib itself is not a clinically relevant inhibitor of CYP3A (IC50, ~44μM), however it was determined that M1 is a time-dependent inhibitor of CYP3A ( Ki = 0.2μM; and rate of enzyme inactivation [kinact], 0.033 $min^{-1}$) and is responsible for the observed clinical DDI. In addition, circulating concentrations of this metabolite are approximately 60% greater than the parent drug in humans.




Feng et al., Clinical Drug Interaction Profile of Idelalisib in Healthy Subjects The Journal of Clinical Pharmacology. 55(8): 909–919, 2015




Idelalisib (ILB)

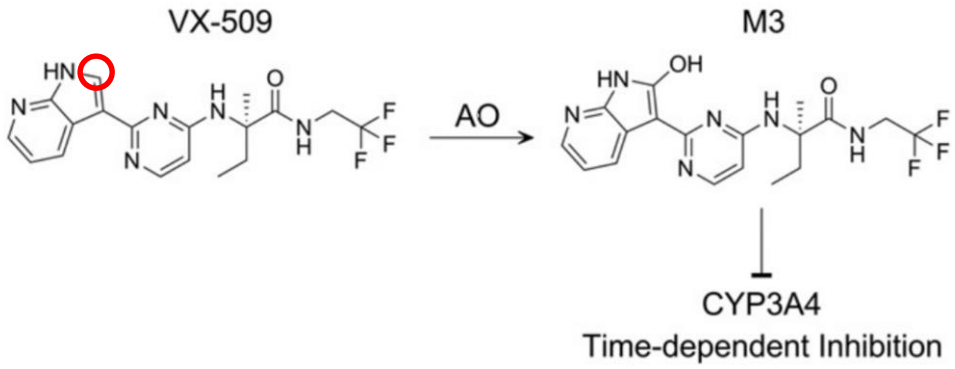


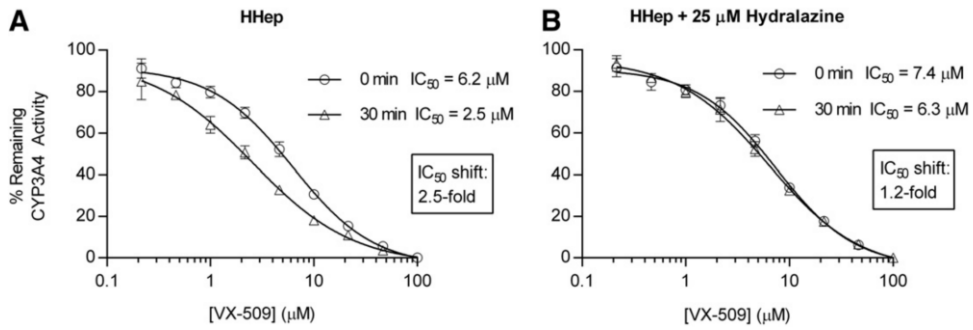

M1

Robert S. Foti and Deepak K. Dalvie. Cytochrome P450 and Non–Cytochrome P450 Oxidative Metabolism: Contributions to the Pharmacokinetics, Safety, and Efficacy of Xenobiotics. Drug Metabolism and Disposition. 44 (8) 1229-1245, 2016

# Dissecting the Role of AO in CYP3A4 MBI: Decernotinib

***Although in vitro studies assessing competitive inhibition and TDI using HLM suggested a low risk for CYP3A4-mediated DDI in the clinic, VX-509 increased the area under the curve of midazolam by almost 7 fold. Thru in vitro mechanistic studies & isotope experiments, the rate limiting step for MBI was determined to be via AO oxidation.***




Zetterberg, et al., VX-509 (Decernotinib)-Mediated CYP3A Time-Dependent Inhibition: An Aldehyde Oxidase Metabolite as a Perpetrator of Drug-Drug Interactions. Drug Metab Dispos 44:1286–1295, 2016

**Table 1. Statistical Comparisons of Exposures to Midazolam Co-administered with and without VX-509 or [2H]-VX-509**

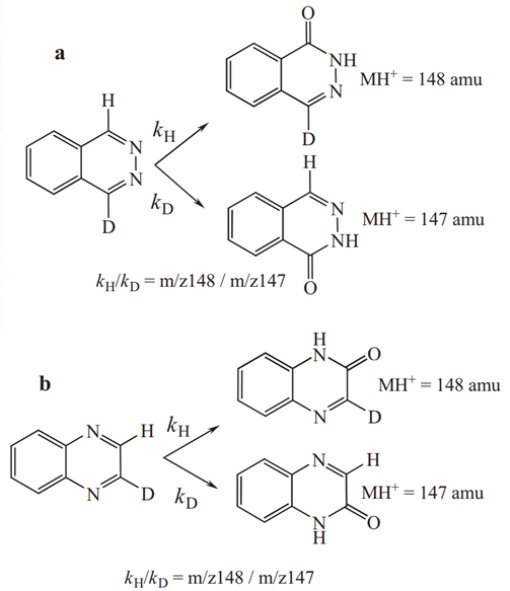
| VX-509 Dose | MDZ PK Parameters | GLSM Ratio | 90% CI of GLSM Ratio |
|---|---|---|---|
| VX-509 (100 mg qd) | $C_{max}$ (ng/mL) | 2.54 | (2.31-2.80) |
| | $AUC_{0-\infty}$ (hr*ng/mL) | 6.93 | (5.98-8.04) |
| [2H]-VX-509 (100 mg qd) | $C_{max}$ (ng/mL) | 2.02 | (1.80-2.26) |
| | $AUC_{0-\infty}$ (hr*ng/mL) | 4.23 | (3.48-5.14) |
| [2H]-VX-509 (200 mg qd) | $C_{max}$ (ng/mL) | 2.69 | (2.32-3.13) |
| | $AUC_{0-\infty}$ (hr*ng/mL) | 8.40 | (6.68-10.56) |

Note: GLSM: Geometric least square mean; CI: confidence interval.

**Table 2. Pharmacokinetic parameters of VX-509 and M3 (Mean, CV%)**

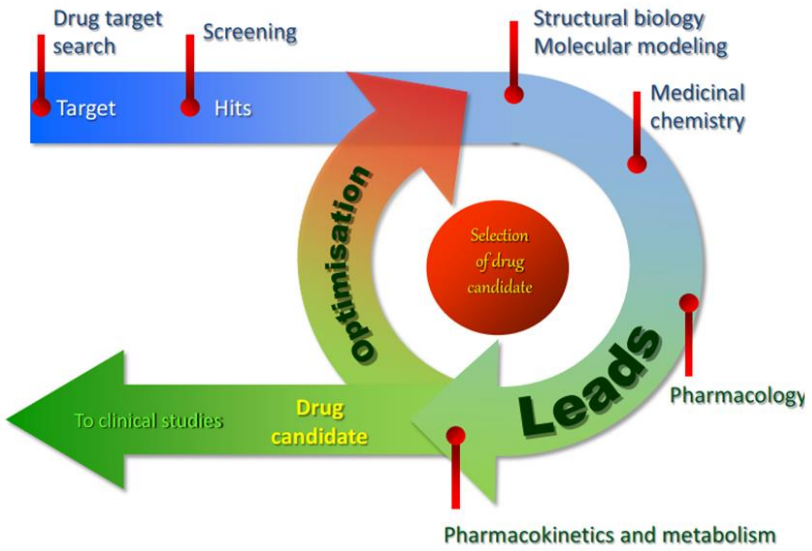
| VX-509 Dose | VX-509 or [2H]-VX-509 | | M3 | |
|---|---|---|---|---|
| | $C_{max,ss}$ (ng/mL) | $AUC_{tau,ss}$ (hr*ng/mL) | $C_{max,ss}$ (ng/mL) | $AUC_{tau,ss}$ (hr*ng/mL) |
| VX-509 100mg qd | 1060 (33.3%) | 7530 (28.7%) | 164 (32.9%) | 1910 (32.1%) |
| [2H]-VX-509 100mg qd | 877 (34.1%) | 6730 (44.1%) | 53.8 (44.0%) | 663 (52.5%) |
| [2H]-VX-509 200mg qd | 2300 (24.0%) | 20900 (28.6%) | 149 (31.0%) | 2090 (32.0%) |

Intramolecular deuterium isotope effect for oxidation of 2-[2H]quinoxaline and 1-[2H]phthalazine by aldehyde oxidase was ~5.



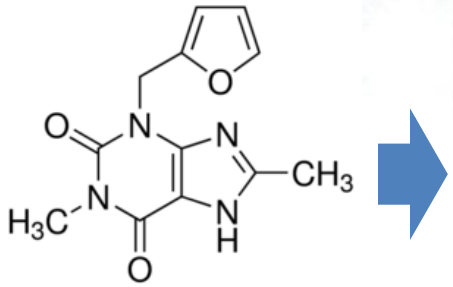

Sharma et al., Deuterium isotope effects on drug pharmacokinetics. I. System-dependent effects of specific deuteration with aldehyde oxidase cleared drugs. Drug Metab Dispos. 40(3):625-34, 2012

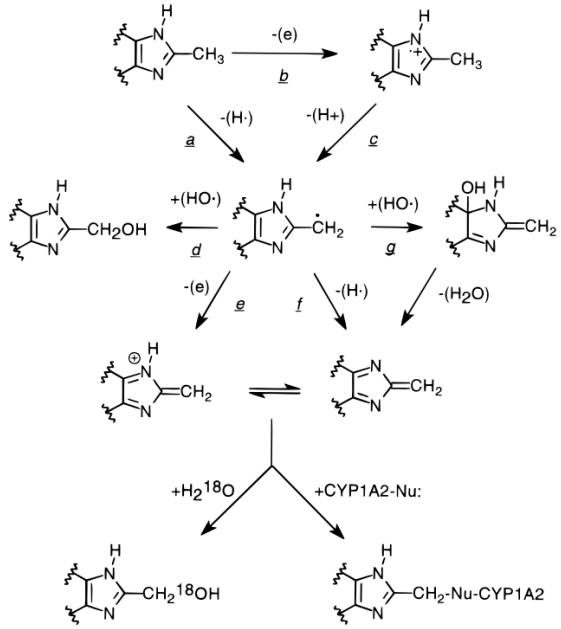
# Final Thoughts: Identifying the Basis for P450 MBI has Value




***We have access to the in vitro tools, models and knowledge which can enable the Discovery Chemist to place the CYP DDI liability of a drug candidate into perspective but more importantly we also have the wherewithal to provide structural information to aid in the optimization of chemical drug design to this risk completely.***

- ***Simple inspection of the structure may not always be sufficient to identify the moiety responsible for inhibition. Moreover, sometimes these groups cannot always be avoided in drug design.***
- ***For example, when furafylline was found to be a MBI of human CYP1A2, it was commonly thought that epoxidation of the furan ring was responsible the observed inactivation, however detailed mechanistic studies demonstrated that it was actually the oxidation at the 8-methyl position which was responsible.***

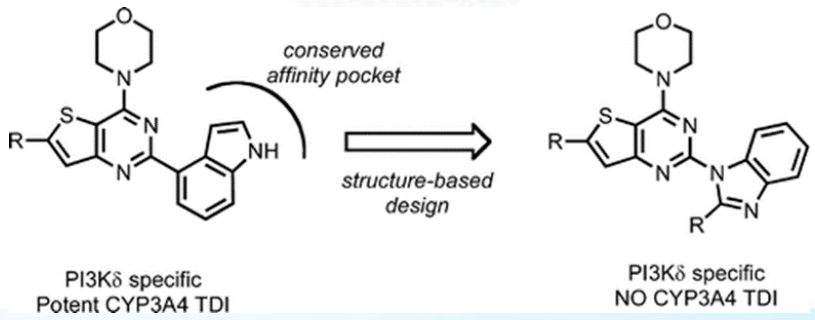





J Racha, A Rettie, and K Kunze.
Biochemistry 37: 7407-7419, 1998

# Concluding Remarks

- **In addition to adequate potency against the target protein and an acceptable safety profile, a balance of optimized PK parameters and minimized drug-drug interaction (DDI) potential maximizes the chance of a candidate drug becoming a successful therapy.**
  - Based upon the physical chemical nature of the molecule factors such as microsomal free fraction need to be accounted for to accurately determine apparent Ki values, before applying this information into PBPK models.
  - A wide range of functional groups are known to undergo P450 mediated bioactivation, which require some level of investigation around possible activation. Moreover, simple inspection of the structure may not always be sufficient to identify the moiety responsible for inhibition.
- **Therefore its imperative that ADME/DMPK scientists design relevant studies to address various ADME issues at different stages for as a means to de-risk candidate molecules as much as possible to avoid clinical surprises early in development.**
  - Given that AO is a cytosolic enzyme that is capable of robust metabolic rates, it is important to get an early read in the drug discovery process whether to rely on liver microsome or hepatocyte stability data for determination of structure-activity relationships and DDI potential.
  - So while TDI is typically evaluated using HLM, I hope these examples illustrate the limitations of this experiment when the perpetrating metabolite is formed via a nonP450–mediated pathway (AO).
  - If the physical chemical characteristics of the molecule reflect the susceptibility to be metabolized by multiple enzymes, such as microsomal and cytosolic enzymes, hepatocytes may be a prudent decision when exploring TDI potential accounting for the totality of in vivo metabolic pathways for the drug.
- **Therefore, scholarship around metabolites is a means to ensure patient safety, allow combination therapies to provide maximal benefit and may be the most cost-effective means of differentiating your molecule from competitor molecules in the same class.**




*Electron-donating groups and steric hindrance have been found to affect AO metabolism. Early ID and working with the synthesis group, DMPK scientists can help guide the direction of chemistry and avoid developing molecules with structural liabilities.*

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- S9 Fractions
- Cytosol
- Homogenate
- Lysosomes & Tritosomes
- Mitochondria
- Extrahepatic Fractions

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### Substrates & Metabolites

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