Metabolism may seem to pose a serious challenge for drug discovery. Metabolism destroys drugs. Metabolism introduces variables such as genetics and inhibition. As it turns out, drug metabolism can also be exploited to the advantage of a drug discovery program. Specifically, metabolism can be used to improve the oral availability of the active form of a drug. The general idea is that the drug is administered in an original, inactive form that is absorbed well. The inactive form is called a prodrug. After absorption, the prodrug is metabolized to reveal the active form of the drug, which can then bind of the target of interest.

Two examples of prodrugs are enalapril and valaciclovir. Enalapril is metabolized through a phase I hydrolysis to enalaprilat. Valaciclovir is metabolized through a phase I hydrolysis to acyclovir. The stories behind the two compounds are somewhat different.

Enalaprilat inhibits angiotensin-converting enzyme (ACE), an key enzyme in the renin pathway that partially regulates blood pressure. Enalaprilat is an effective inhibitor, but it has no oral bioavailability (\(F = 0.00\)). The problem with enalaprilat is that it is extensively charged. At a physiological pH of 7.4, the compound carries three charges, two on the carboxylates and one on the secondary amine. The presence of these three charges greatly hinders the ability of the molecule to cross the intestinal wall and enter the hepatic portal system. Enalapril itself only has one charged functional group, the acid, at pH 7.4. With just one charge, enalapril much more easily crosses membranes for oral absorption. The oral bioavailability of enalapril is a respectable 60% (\(F = 0.60\)).

Acyclovir is an antiviral compound used to treat different herpes infections. The problem with acyclovir is that its oral bioavailability is low at only 10-20%. The problem is not first-pass metabolism. Acyclovir simply is not absorbed well from the digestive tract. To improve the absorption of acyclovir, researchers had the idea to acylate the alcohol with valine, an amino acid. The presence of the valine residue does not improve the ability of the new molecule, valaciclovir, to diffuse across a membrane. Instead, the valine residue causes valaciclovir to
resemble an oligopeptide closely enough to fool a peptide transporter into transporting valaciclovir from the intestines and into the hepatic portal system. The valine residue is then removed by esterases in the liver, and the active form of the drug, acyclovir, is free to act in the patient. The oral bioavailability of valaciclovir is around 55%, a considerable improvement over the 10-20% of acyclovir.
Further studies were established to determine if the high absorption of valacyclovir was due to carrier-mediated transport. The absorption of acyclovir and valacyclovir was studied in cynomolgus monkey intestinal brush border membrane vesicles, where the influx of valacyclovir into the vesicles was six- to 10-fold higher than the influx of acyclovir. Additional studies in Caco-2 cells showed that transport of valacyclovir was seven times higher than acyclovir transport. In rats, L-amino acid ester analogs of acyclovir show better absorption than D or D-L analogs, indicating that the transport was also stereoselective.

Several studies in Caco-2 and transfected cell lines have shown that valacyclovir is transported by rat and human PepT1, even though the prodrug does not have a peptide bond. Recent work has, however, shown that several additional transporters may be involved in valacyclovir transport in humans, and that PepT1 may not be the predominant transporter of this prodrug in humans. Most recently it has been suggested that valacyclovir transport by PHT1 and hPT1 may also be contributing absorption pathways.

The absolute bioavailability of acyclovir when 100 mg of oral valacyclovir prodrug is dosed to healthy human subjects is 54%, compared to only 15 to 20% (200- to 600-mg doses) after acyclovir was dosed orally. Larger variability was observed after dosing of acyclovir than following valacyclovir dosing. The bioavailability of acyclovir from orally dosed valacyclovir is similar in rats and cynomolgus monkeys. Over 99% of valacyclovir that is not absorbed is converted to acyclovir.

When valacyclovir is administered orally, there is a slightly less than dose proportional increase in acyclovir exposure and an increase in $T_{\text{max}}$ with increasing doses. The slightly reduced absorption of valacyclovir, with increasing dose is not likely, due to saturable conversion to acyclovir, because of low urinary recovery of valacyclovir, and because the valacyclovir/acyclovir ratio remains the same with increasing dose. The reduced absorption may be due to saturation of absorption sites along the gastrointestinal tract.

Although valacyclovir is more soluble than acyclovir (174 mg/mL versus 1.3 mg/mL), solubility is unlikely to limit absorption of either compound. This is supported by the fact that many of the other amino acid ester analogs that have been studied also exhibit improved solubility over acyclovir. However, these analogs have very diverse bioavailability, probably due to differences in their carrier-mediated transport.