Liver-Targeting Prodrug (LTP) Technology Offers New Generation Nucleotide Antiviral Agents

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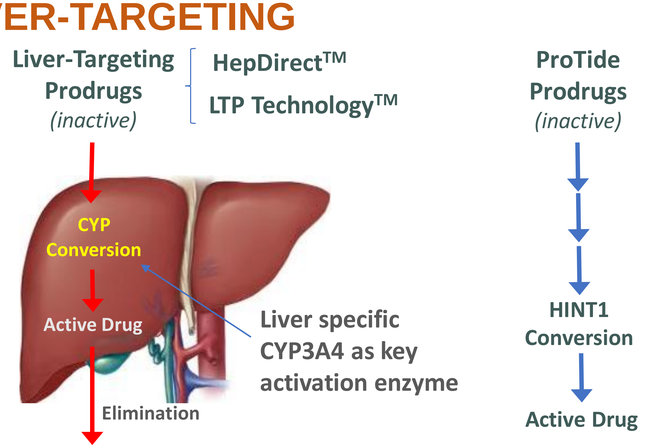
INTRODUCTION

Nucleotide analog reverse-transcriptase inhibitors (NtRTI) have been one of the major antiviral arsenals in combating HBV and HIV. Improving prodrug delivery efficiency over clinically validated nucleotide molecules has proven to be a cost-effective new drug development strategy to offer more effective and safer medicines, e.g. tenofovir alafenamide fumarate (TAF) offers significant clinical advantages over tenofovir disoproxil fumarate (TDF). We report that **LTP Technology** improves prodrug delivery efficiency of tenofovir (TFV), more effectively targeting the liver than HepDirect (HD) technology and ProTide technology.

LIVER-TARGETING



- Liver-targeting prodrugs are inactive.
- LTP Technology™ is second generation liver-targeting technology.
- Conversion of the prodrugs to the active form is initiated by cytochrome P450 enzyme (CYP) metabolism.
- Predominant route of metabolism is via CYP3A, which is expressed primarily in the liver and to a lesser extent in the intestine, with much lower levels of expression in other tissues.
- Tissue-specific expression of CYP3A leads to high levels of active drug in the liver with much lower levels in the systemic circulation.
- In contrast, ProTide prodrugs are cleaved by several enzymes including histidine triad nucleotide-binding protein 1 (HINT1) which have broader tissue distributions.

RESULTS

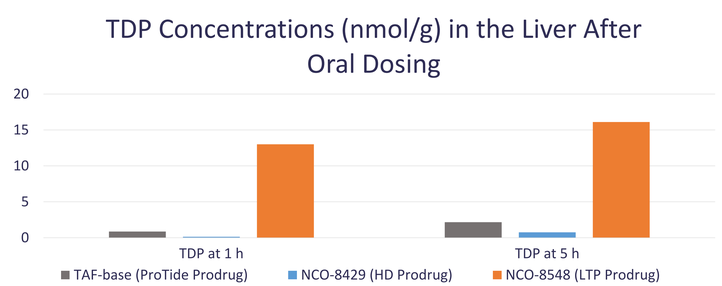
Conversion of the prodrugs to the active tenofovir diphosphate (TDP) is the key step for the antiviral activity. To assess the conversion efficiency *in vivo*, three types of tenofovir prodrugs were orally administered to Sprague-Dawley rats (3/group) at the same doses: ProTide prodrug (tenofovir alafenamide (TAF-base,)), HD prodrug (NCO-8429), and LTP prodrug (NCO-8548). Blood was collected and tissues were harvested and snap-frozen in liquid nitrogen. TDP, TFV, and prodrug concentrations were measured by LC-MS/MS to compare oral delivery and liver-targeting efficiency. The table below summarizes the measured results.

Liver and Blood Concentrations in Male Sprague Dawley Rats at 1 and 5 Hours After Oral Dosing

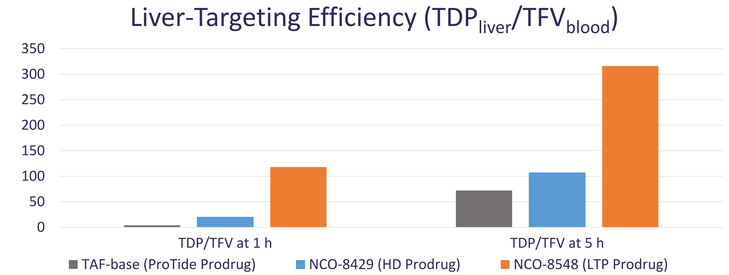
Compound	TAF-base (ProTide prodrug)	NCO-8429* (HD prodrug)	NCO-8548* (LTP prodrug)
TDP_{liver} at 1 hour (nmol/g)	0.86 ± 0.91	0.14 ± 0.06	13.0 ± 9.5
at 5 hour	2.16 ± 1.06	0.75 ± 0.30	16.1 ± 8.2
TFV_{blood} at 1 hour (nmol/mL)	0.22 ± 0.13	<0.007	0.11 ± 0.03
at 5 hour	0.030 ± 0.007	<0.007	0.051 ± 0.007
TDP_{liver}/ TFV_{blood} at 1, 5h	3.9, 72	>20, >107	118, 316
$Prodrug_{liver}$ at 1hour (nmol/g)	<0.02	0.074 ± 0.014	0.32 ± 0.10
at 5 hour	<0.02	0.026 ± ND	<0.01
$Prodrug_{blood}$ at 1 hour (nmol/g)	<0.003	0.015 ± 0.002	0.016 ± 0.006
at 5 hour	<0.003	0.005 ± 0.002	<0.003

* Results are adjusted to the doses that are nucleotide equivalent.

At 5 mg/kg doses, NCO-8548 (LTP-tenofovir) achieved TDP levels in the liver at 1 and 5 hours post dosing more than 92-fold and 21-fold higher than that of NCO-8429 (HD-tenofovir) and more than 15-fold and 7-fold higher than TAF-base (see the figure below). Prodrug concentrations in the liver and blood were low (many close to low level of quantification, LLOQ), which indicates that the three prodrugs were rapidly metabolized after oral route absorption.



In addition to the superior liver TDP concentrations achieved by the LTP prodrug compound, NCO-8548 also demonstrated superior liver-targeting efficiency in the study measured by the ratio of liver TDP concentration over blood TFV concentration. NCO-8548 had ~30-fold and ~4.4-fold higher liver-targeting efficiency at 1 and 5 hours post dosing than that of TAF-base (see the figure below). TFV levels in the blood from NCO-8429 group were below LLOQ of 0.007 nmol/mL, which limit the liver-targeting efficiency calculation to ~20 and ~107 at 1 and 5 hours post dosing. Since NCO-8429 has a conversion mechanism similar to NCO-8548, it is expected the liver-targeting efficiency may be similar to NCO-8548 if the LLOQ was lower.



CONCLUSIONS

LTP-tenofovir compound, NCO-8548, delivered TDP levels in the liver much higher that that of ProTide-tenofovir compound, TAF-base, and HD-tenofovir compound, NCO-8429, which indicates superior draggability of the LTP compound over the other types of prodrugs.

NCO-8548 showed liver-targeting efficiency superior to the HD-tenofovir and ProTide-tenofovir compounds, which demonstrates that the CYP conversion based prodrugs do have superior liver-targeting property.

LTP Technology can be an effective method to increase the therapeutic index of antiviral drugs.

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CONTACT INFORMATION

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