Antiviral Activity of the Liver-Targeted Nucleotide HCV Polymerase Inhibitor IDX184 Correlates with Trough Serum Levels of the Nucleoside Metabolite in HCV-infected Chimpanzees

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Disclosure

- Robert Lanford is an employee of Southwest Foundation for Biomedical Research, San Antonio, TX, USA. The Southwest Foundation for Biomedical Research has received compensation from Idenix for conducting preclinical studies of IDX184.

- All other authors are current employees of Idenix Pharmaceuticals, Inc., Cambridge, MA USA

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Future of HCV Treatment: Combination of Direct-Acting Antivirals

Peg-IFNα/RBV fails to provide SVR in 50-60% of HCV-1 patients

Nucleoside/tide Polymerase Inhibitors	Non-Nucleoside Polymerase Inhibitors	Protease Inhibitors
High barrier to resistance Broad genotypic coverage	Low barrier to resistance Restricted genotypic coverage	Intermediate barrier to resistance Moderate genotypic coverage

Nucleoside/tide and protease inhibitors should be preferred double combination due to distinct modes of action, complementary resistance profiles and pan-genotypic activity; Potent non-nucleosides as third component of STAT-C cocktail may replace interferon(s).

Source: Strader DB, et al., Diagnosis, Management & Treatment of Hepatitis C, AASLD Practice Guidelines, Hepatology 2004, p. 1151

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Idenix HCV Cocktail Combination Strategy

Comprehensive HCV Pipeline

Nucleoside/tide Polymerase Inhibitor IDX184

- Potent antiviral activity *in vitro* and *in vivo*
- Liver-targeted with low systemic exposure
- Phase I/II in HCV-1 patients ongoing (QD)

See Poster #966

Non-Nucleoside Polymerase Inhibitor IDX375

- Low nanomolar potency
- Favorable early PK profile (BID,QD)
- IND planned for 2009

See Poster #323

Protease Inhibitor IDX316

- Single nanomolar potency
- Favorable early PK profile (BID,QD)
- IND planned for 2009

See Poster #344

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IDX184: HCV Liver-Targeted Nucleoside/tide Polymerase Inhibitor Program Overview

- IDX184 is a potent and selective inhibitor of HCV *in vitro*
  - Fully active against HCV genotypes 1, 2, 3 and 4
  - Additive to synergistic with PI, NNI, IFN or RBV
- Liver-targeted
  - >95% of absorbed IDX184 is extracted by the liver *in vivo*
  - Preferentially activated in human primary hepatocytes vs. human cell lines
  - Low systemic exposure of parent drug and nucleoside metabolite with high levels of nucleoside-triphosphate (TP) in liver
    - May limit off-target toxicities/increase anti-HCV activity
- Potent antiviral activity in HCV genotype-1 infected chimpanzees (up to 3.8 $\log_{10}$ HCV RNA reduction over 4 days)

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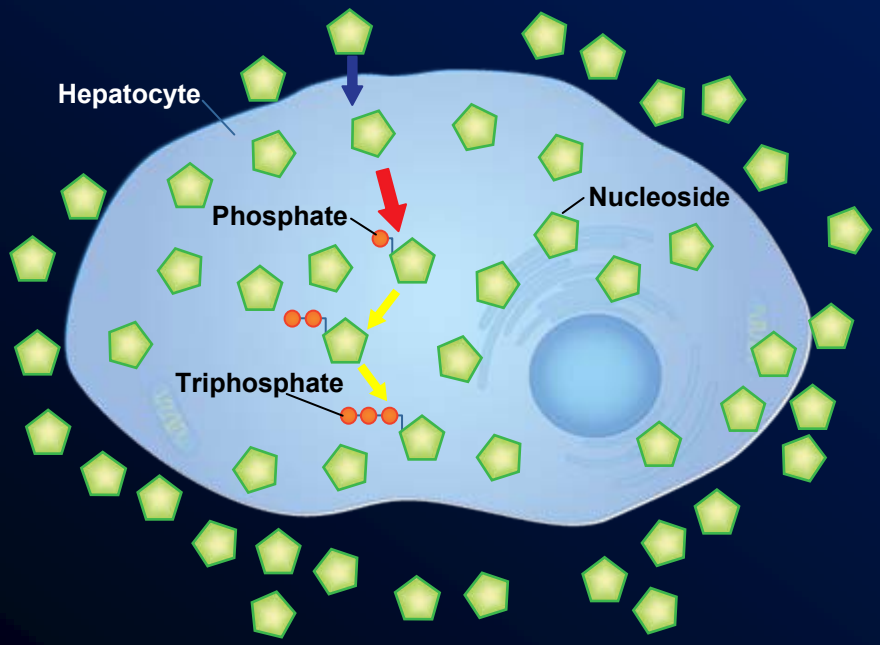
Advantages of Liver-Targeted HCV Nucleotides

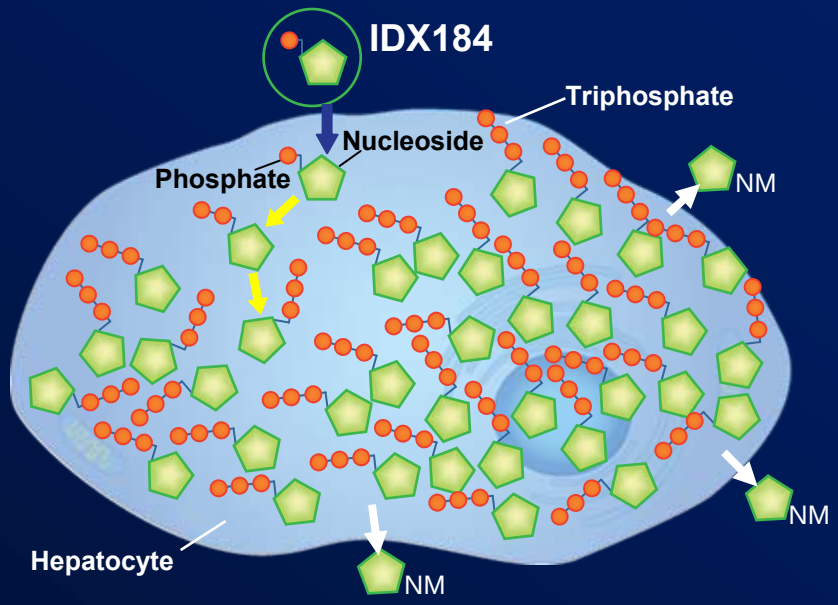
Nucleoside Triphosphate Inhibits Viral Replication

Nucleosides



No PK/PD relationship observed for nucleoside and nucleoside analogues in general.

Liver-Targeted Nucleotide Prodrugs



Nucleoside metabolite (NM) is generated by hydrolysis of nucleotides in hepatocytes.

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IDX184 Study in HCV-Infected Chimpanzees

- Objective
  - To investigate any PK/PD relationship between trough levels of parent drug or the nucleoside metabolite and viral load reductions

- Methods
  - Six HCV genotype-1 infected chimpanzees received IDX184 (10 mg/kg/day) by oral gavage with sedation for 4 days
  - Serum drug/metabolite levels and viral RNA were measured at trough (24 h post dose)
    - 24 samples during a 4-day dosing period
    - 6 samples at day 7
  - IDX184 and NM levels were determined by LC/MS/MS
  - PK/PD relationships were assessed by regression analyses

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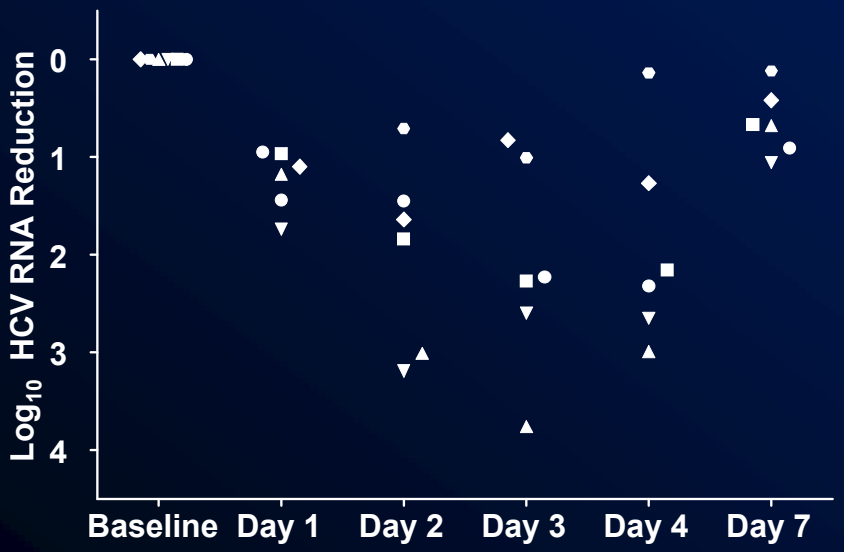
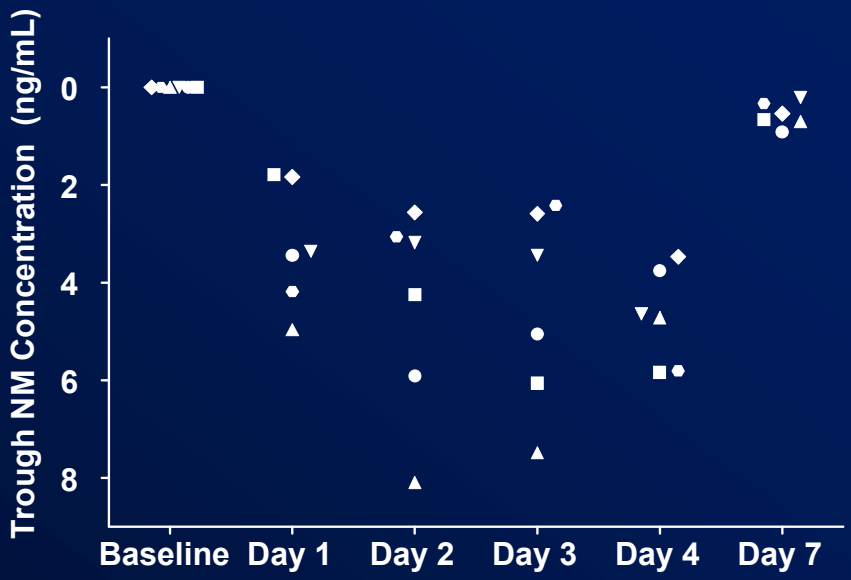
Viral Load Reductions and NM Trough Levels after Oral Administration of 10 mg/kg of IDX184 in HCV-Infected Chimpanzees

Log_{10} viral load reductions by day



Trough NM levels by day



- NM trough levels were 2-8 ng/mL during 4-day dosing period
- These NM levels were low, consistent with a liver-targeted drug

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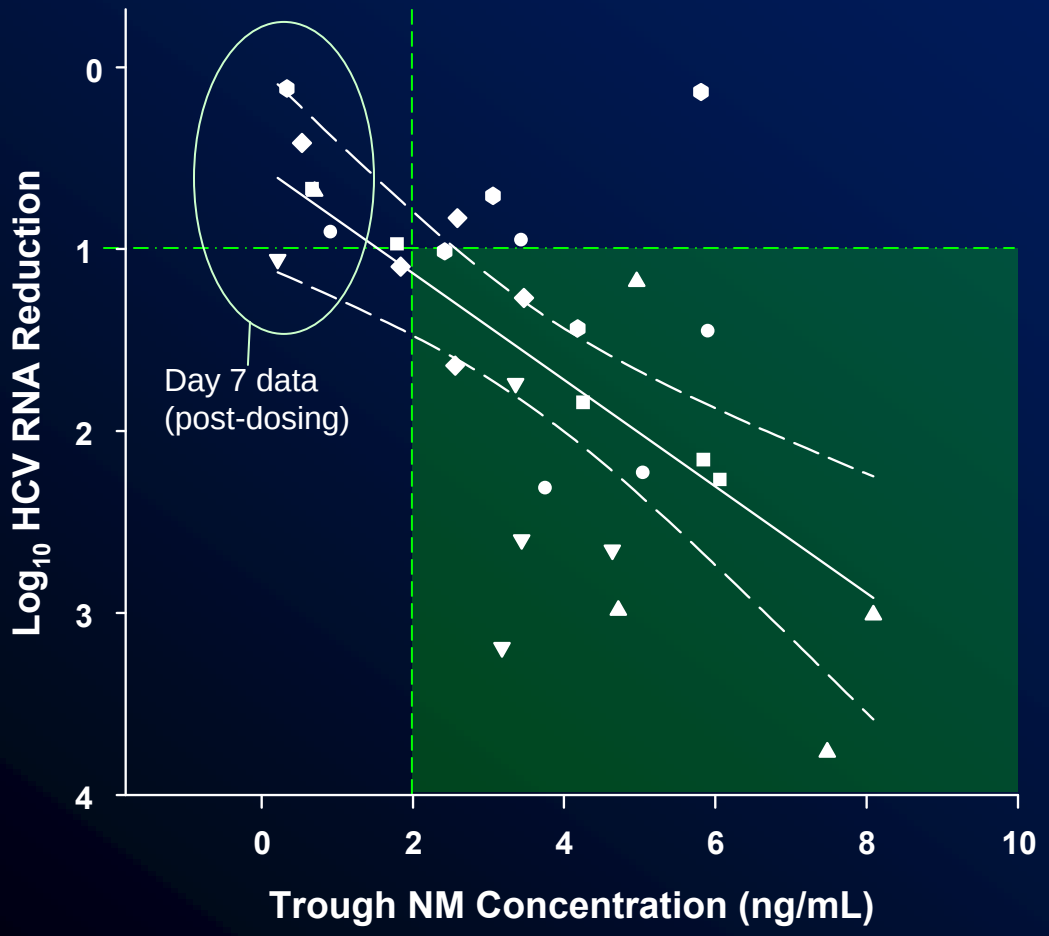
PK/PD Relationship Between Viral Load Reduction and Serum Nucleoside Metabolite Levels in HCV-Infected Chimpanzees

Serum trough NM levels of >2 ng/mL were associated with >1 log_{10} HCV viral load reductions.



Dose: 10 mg/kg of IDX184

$R^2 = 0.42$
$P < 0.001$

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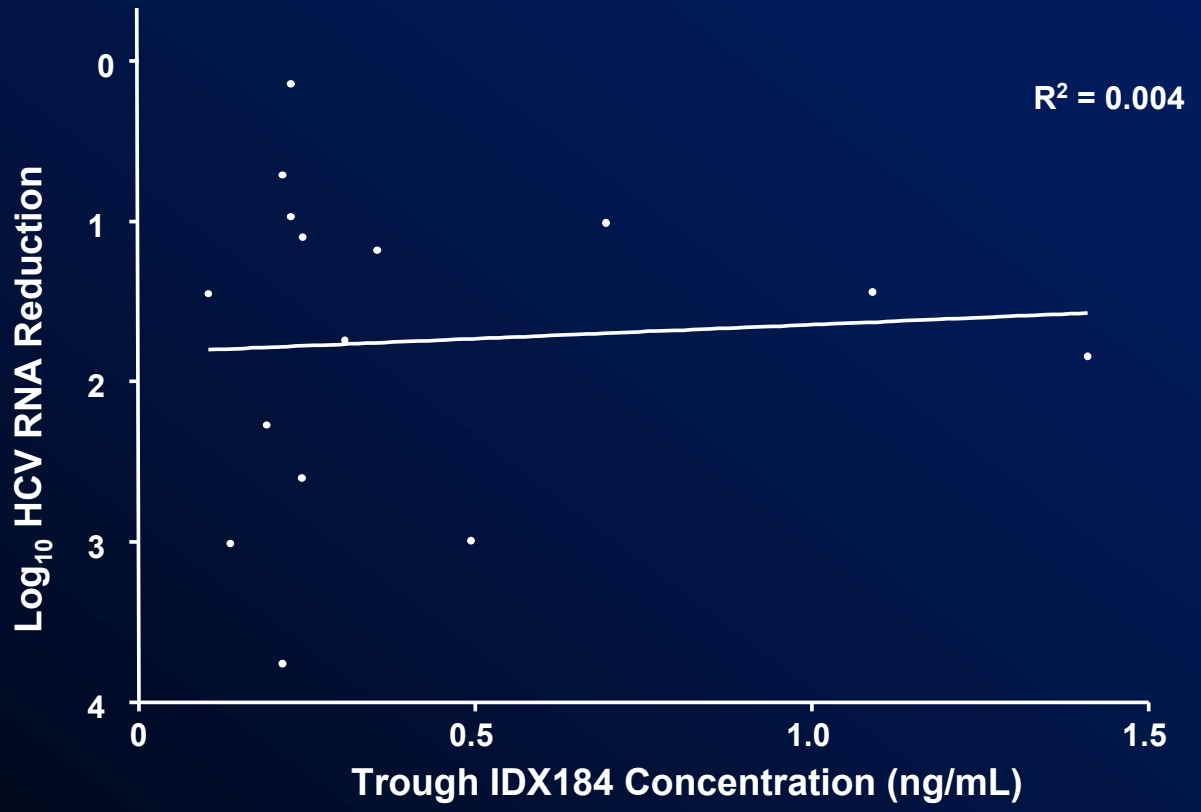
No PK/PD Relationship Between Viral Load Reduction and IDX184 Trough Levels



- IDX184 trough levels were low (<1.4 ng/mL), with many samples undetectable (9/24).

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Resistance Profile of IDX184

- Resistance to IDX184 emerges slowly in the HCV replicon system as compared to NNIs and PIs
- S282T is the only known resistance mutation for IDX184
- S282T mutant HCV replicons replicate at 5% of wild-type capacity
- No evidence for emergence of resistance (S282T) by population or clonal sequencing (20 clones per sample) in chimpanzees showing weak antiviral response or viral rebound

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IDX184 Phase I Dose-Escalation Study

- Design
  - Single rising doses of 5, 10, 25, 50, 75, 100 mg IDX184 with 8 healthy subjects randomized 6:2 (active:placebo) for a total N=48
  - Primary endpoint: safety and tolerability
  - Secondary endpoints: plasma and urine IDX184 and NM intensive PK
- Results
  - IDX184 was safe and well tolerated
  - Pharmacokinetics of IDX184 and NM were consistent with a liver-targeted drug
  - For details, see Poster #966

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Trough Plasma Levels of Nucleoside Metabolite after IDX184 QD Dosing

- NM levels measured at 24 h in the Phase I single-dose study were used to model (non-compartmental superposition) NM trough levels after three daily doses of IDX184 and at steady state (5-7 days).

	Mean NM Trough Levels (ng/mL)		
IDX184 Dose (mg)	1st dose (actual)	3rd dose (predicted)	Steady state (predicted)
25	0.582	1.230	1.776
50	2.880	5.847	8.722
75	2.311	5.640	7.478
100	2.228	7.406	10.266

- These predicted values suggest that administration of 50 to 100 mg/day of IDX184 in HCV-infected patients should lead to NM trough levels associated with >1 $\log_{10}$ HCV RNA reduction in HCV-infected chimpanzees.

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IDX184 Phase I/II Proof-of-Concept Study

- Multi-center, international, randomized, double-blind, placebo-controlled, sequential cohort, dose-escalation study in treatment-naïve HCV genotype-1 patients
- Objectives: safety and tolerability, antiviral activity
- Subjects randomized 8:2 (active:placebo)
- Initiated December 2008; anticipated completion mid-2009

Cohort	N	Dose	Drug Administration
A	10	25 mg	1 x 25 mg capsule (or placebo) QD for 3 days
B	10	50 mg	2 x 25 mg capsules (or placebo) QD for 3 days
C	10	75 mg	3 x 25 mg capsules (or placebo) QD for 3 days
D	10	100 mg	4 x 25 mg capsules (or placebo) QD for 3 days

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IDX184 Conclusions (1)

Animal Model

- Mean serum trough levels of IDX184 and the nucleoside metabolite (NM) were low, consistent with a liver-targeted drug
- A significant PK/PD relationship was demonstrated between NM trough level and HCV RNA reduction
- No such relationship was observed with IDX184
- No evidence for emergence of resistance (S282T)

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IDX184 Conclusions (2)

Clinical

- IDX184 was safe and well tolerated in a Phase I study
- Mean plasma levels of IDX184 and NM were low (<20 ng/ml)
- Predicted NM trough levels after repeated QD administration of 50 to 100 mg of IDX184 in HCV-infected patients are in the range of those associated with antiviral effects (>1 $\log_{10}$ viral load reduction) in HCV-infected chimpanzees
- A 3-day POC study in HCV-1 treatment-naïve patients is ongoing

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