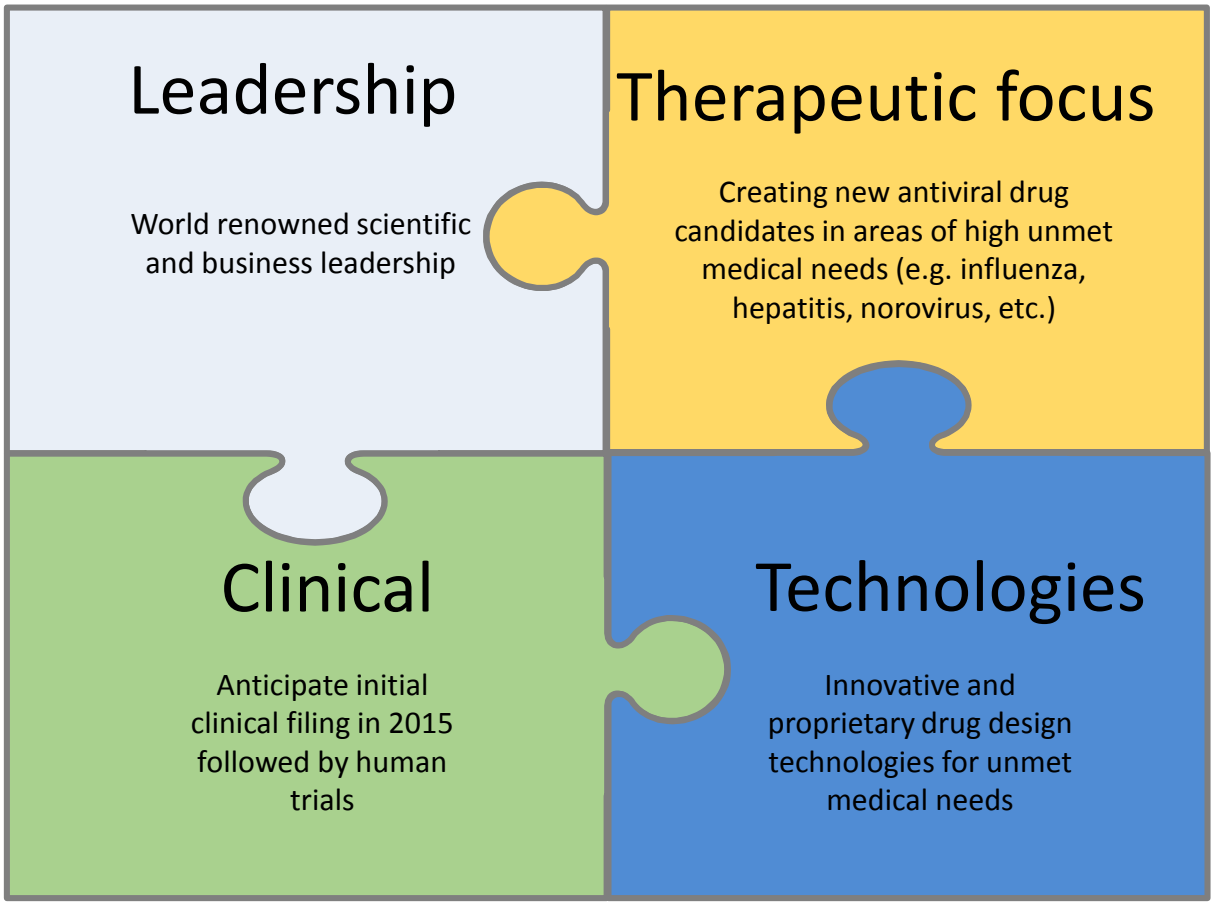

CRYSTAL
PHARMA, INC.
Developing Future
Antiviral Therapies

Forward Looking Statements

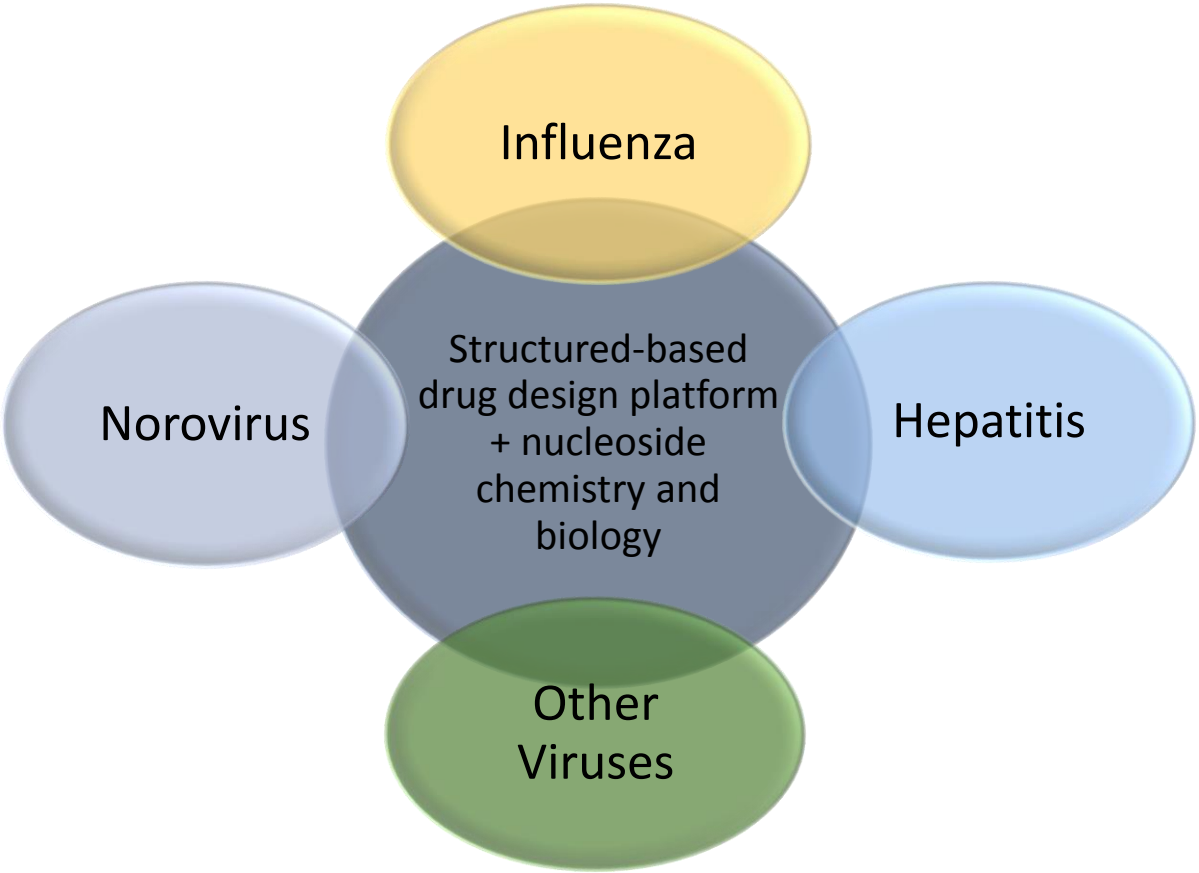
This presentation contains forward-looking statements, including the timing of our drug development programs. Risks include delays in manufacturing created by third parties and the ability of clinical research organizations to recruit patients. Forward-looking statements also are prefaced by words such as "expect," "plan," "intend," "anticipate," and similar words. Forward-looking statements are based on our current expectations and assumptions regarding our business, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict. Our actual results may differ materially from those contemplated by the forward-looking statements for a variety of reasons, including those contained in our Form 10-K, as amended, for the year ended December 31, 2014. We caution you, therefore, against relying on any of these forward-looking statements. They are neither statements of historical fact nor guarantees or assurances of future performance. We do not undertake any duty to update these forward-looking statements.

Company Highlights



Cocrystal Today

Developing the future of antiviral therapies

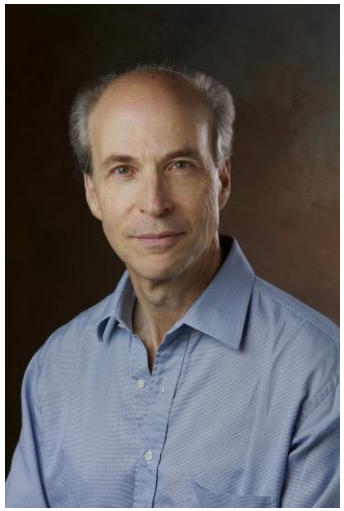


Scientific Leadership

Dr. Roger Kornberg

Cocrystal Co-founder

2006 Nobel prize winner in chemistry

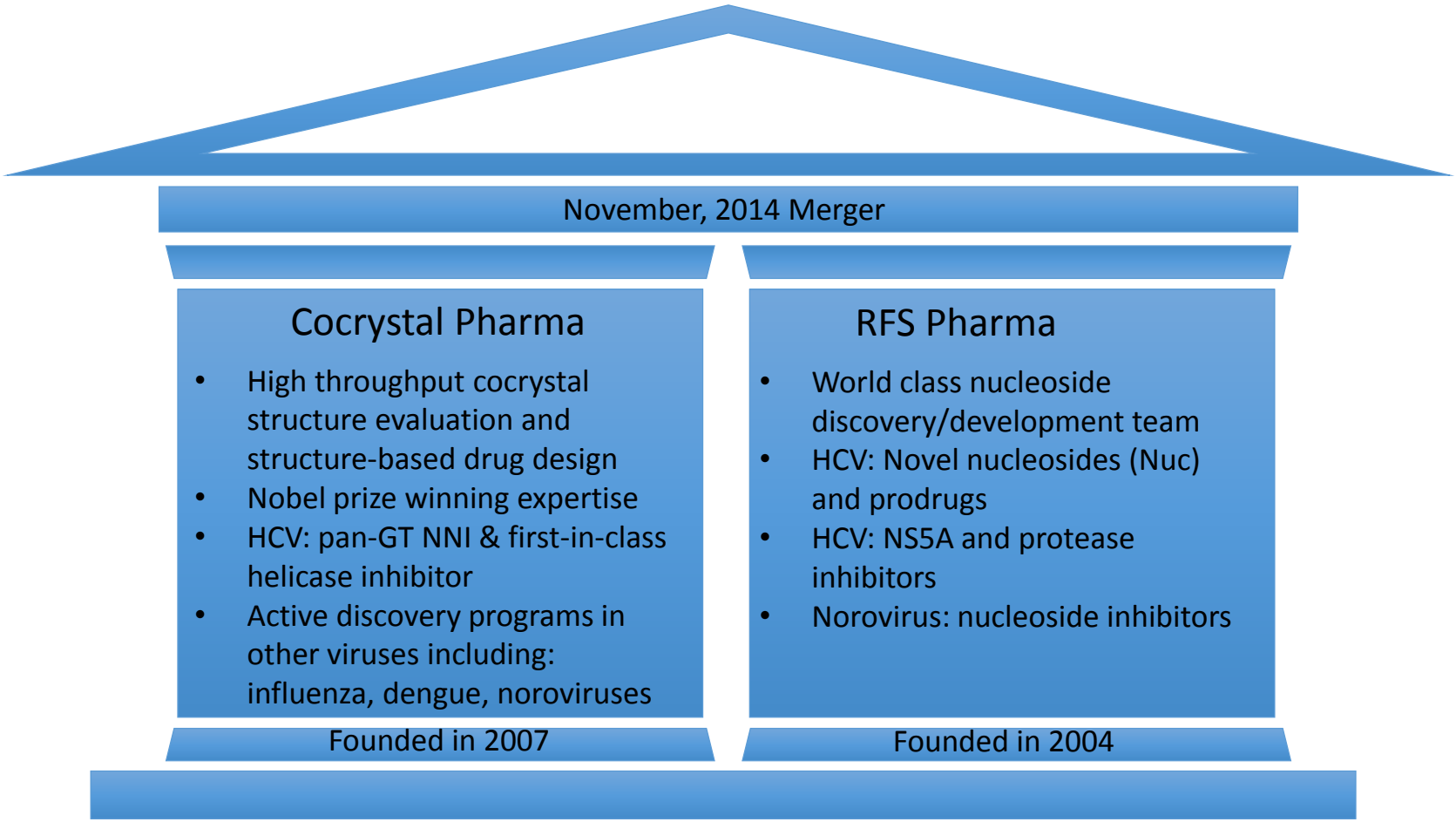


Dr. Raymond Schinazi

Cocrystal Co-founder

Founder of Pharmasset, Idenix, Triangle

Cocrystal Pharma Evolution



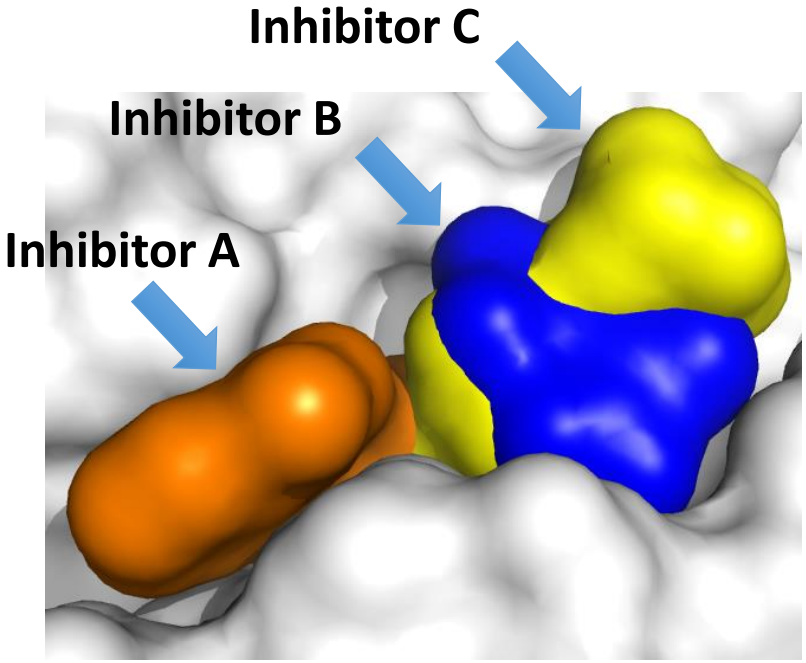
Opportunities

There exists significant unmet medical needs across a large variety of viral infections…

HCV	Noro	Influenza A & B
Leading cause of liver failure and liver cancer	Chronic & Acute gastroenteritis	Seasonal and pandemic
80 - 170 million chronic infections	>250 million acute cases/year	3 - 5 million chronic infections/year
Opportunity for shorter duration and improved accessibility	Economic cost in the US alone is >$5 Billion	Estimated economic impact of seasonal flu in US: $50B to $150B

Structure-based Drug Discovery Technology

Example of HCV fragment hits

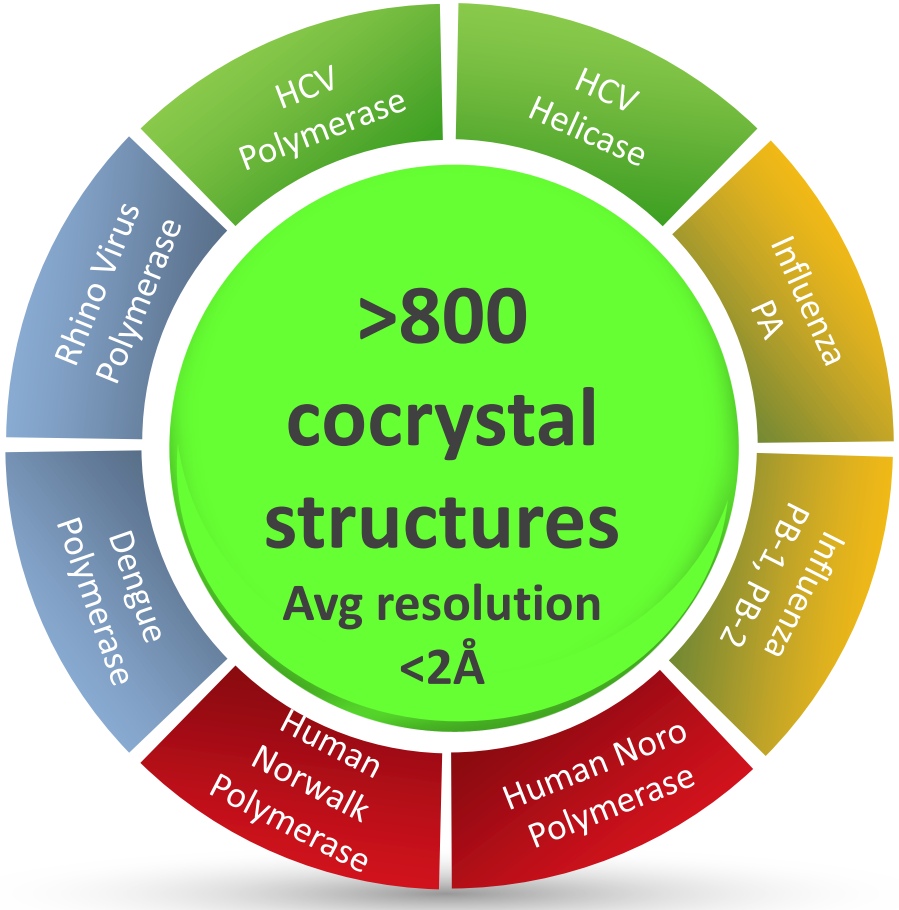


Advantages of the Cocrystal approach

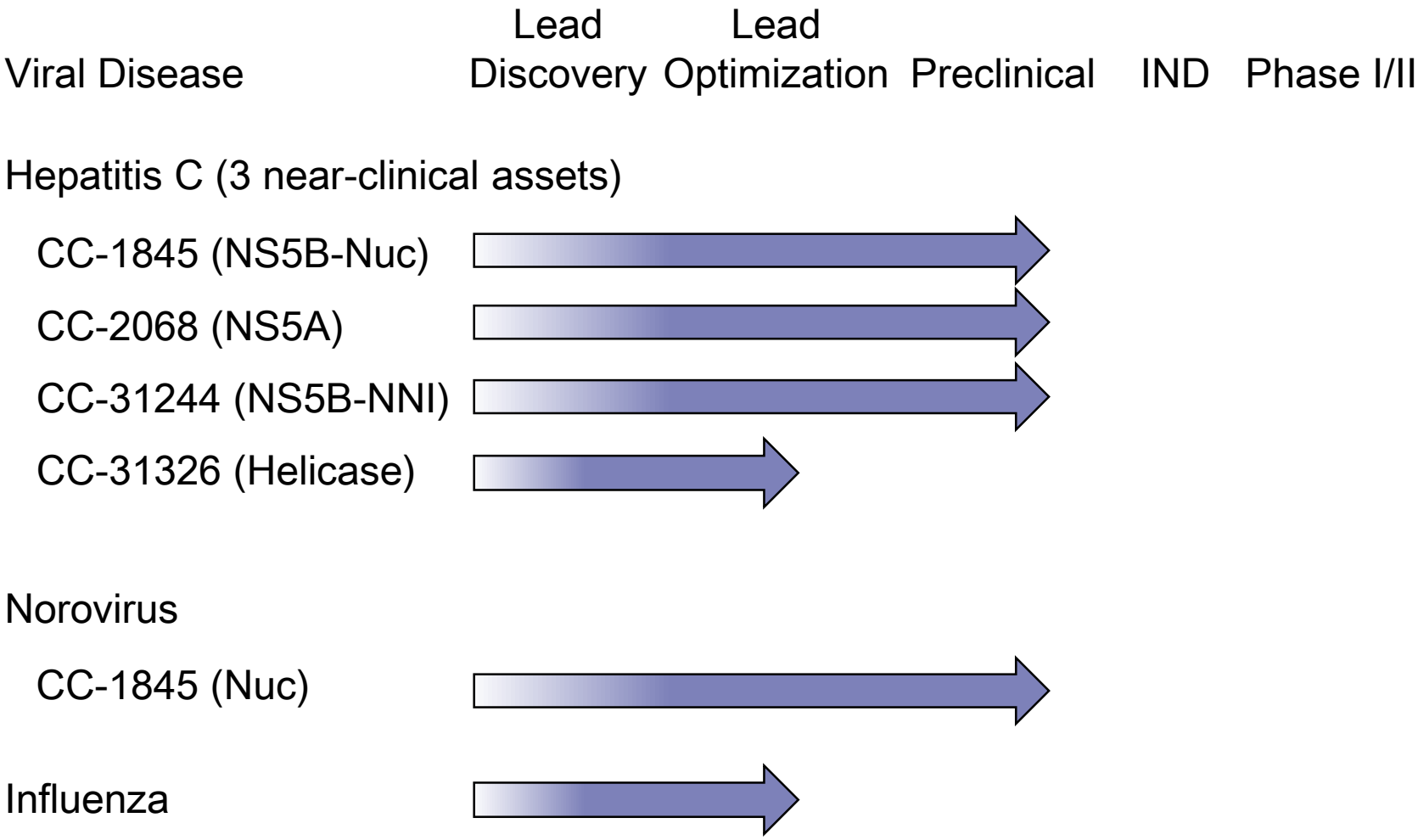
- Provides 3D structure of inhibitor complexes at near-atomic resolution with immediate insight to guide SAR
- Identifies novel binding sites
- Allows rapid turnaround of structural information through highly automated X-ray data processing and refinement

Technology Platform Focuses on Viral Replication Drug Targets Through Cocrystalization

Building a foundation with high resolution X-ray data (<2Å)



2015 Pipeline



HCV Approach: Multiple shots on goal

De-risked near-term approach creating multiple "Shots on Goal"

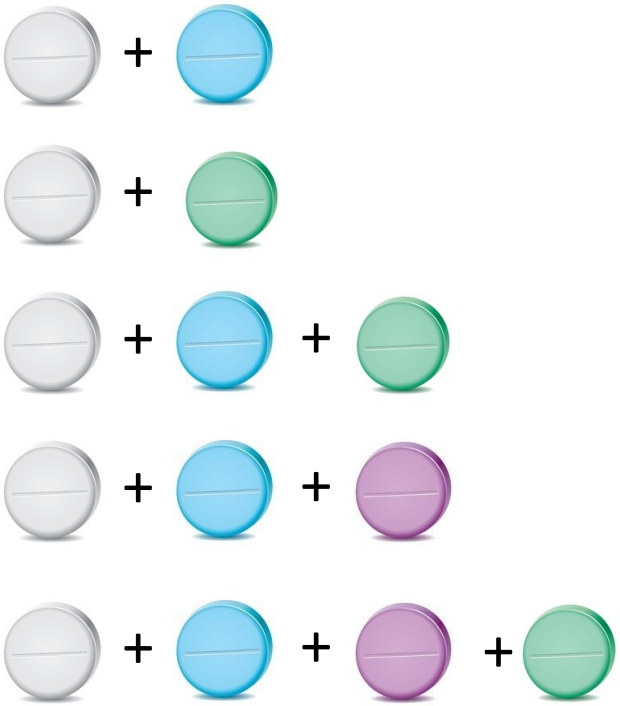
Pan-genotypic NS5B Nuc

Pan-genotypic NS5A Inhibitor

Pan-genotypic NS5B NNI

Pan-genotypic Helicase Inhibitor

Multiple possibilities of an all oral HCV regimen



CC-1845: Compelling HCV Drug Candidate

Nucleoside Prodrug: Potential backbone for next generation combination therapy

- Pan-genotypic
- Delivers multiple active triphosphates
  - Two of the active metabolites show comparable potency to sofosbuvir
- Low cytotoxicity based on preliminary data
- Resistance selection was challenging
  - S282T selected only upon the 5th attempt
- Rapid liver delivery of parent nucleosides and the NTPs (PK studies)
- Synergistic/additive with a proprietary NS5A inhibitor (CC-2068) and NNI (CDI-31244)
- Anticipated QD dosing

CC-1845: Nucleoside Profile

- Potent
- High barrier to resistance
- No drug-drug interactions
- Cascade of rNTP metabolite generation
- Half-lives of rNTP will support once-a-day dosing

Pan-genotypic activity

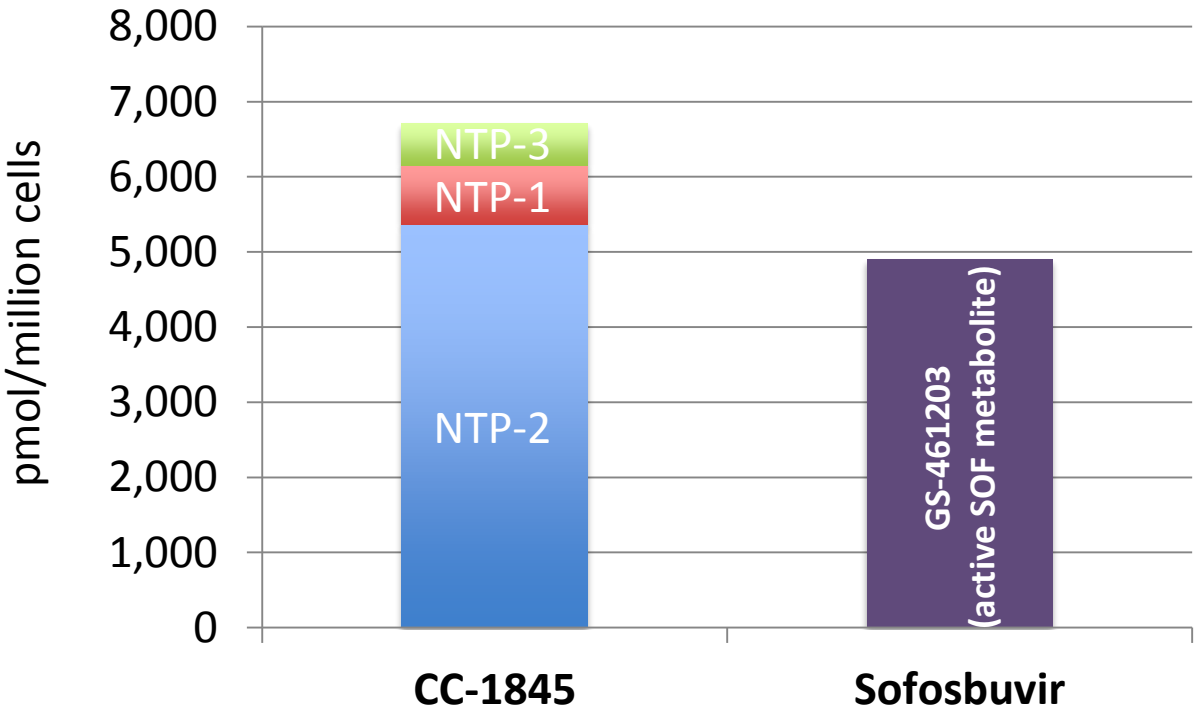
HCV replicon (Huh-7): clinical isolates	EC_{50} (µM)
GT 1a	0.70
GT 1b	0.88
GT 2a	0.19
GT 2b	0.21
GT 3a	0.17
GT 4a	0.38

Preliminary cytotoxicity data

Cells	CC_{50} (µM)
Huh-7	> 100
Human PBM	> 100
Vero	> 100
CEM	> 100
Human bone marrow	> 100
Mitochondrial toxicity	> 50

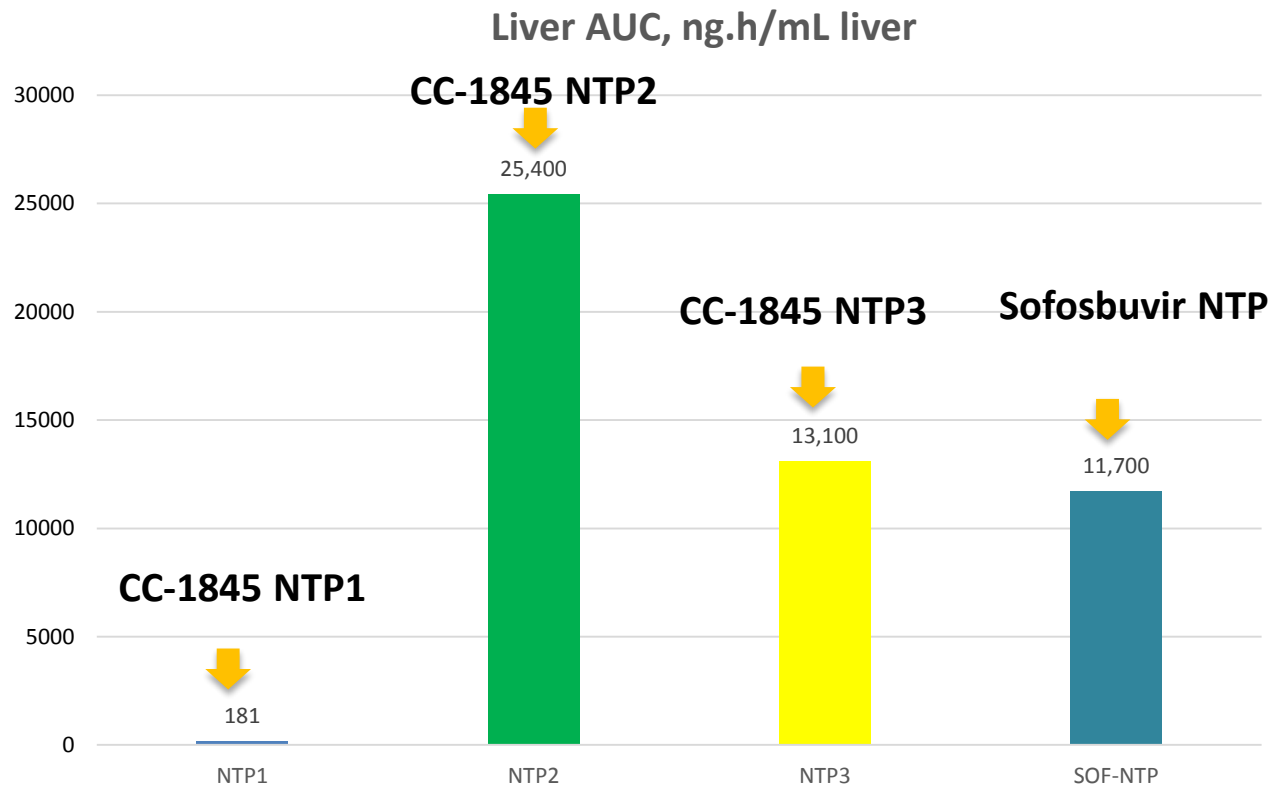
CC-1845: Favorable NTP Formation

CC-1845 and Sofosbuvir incubated with Primary Human Hepatocytes at 50 µM for 4 hours (n=3)



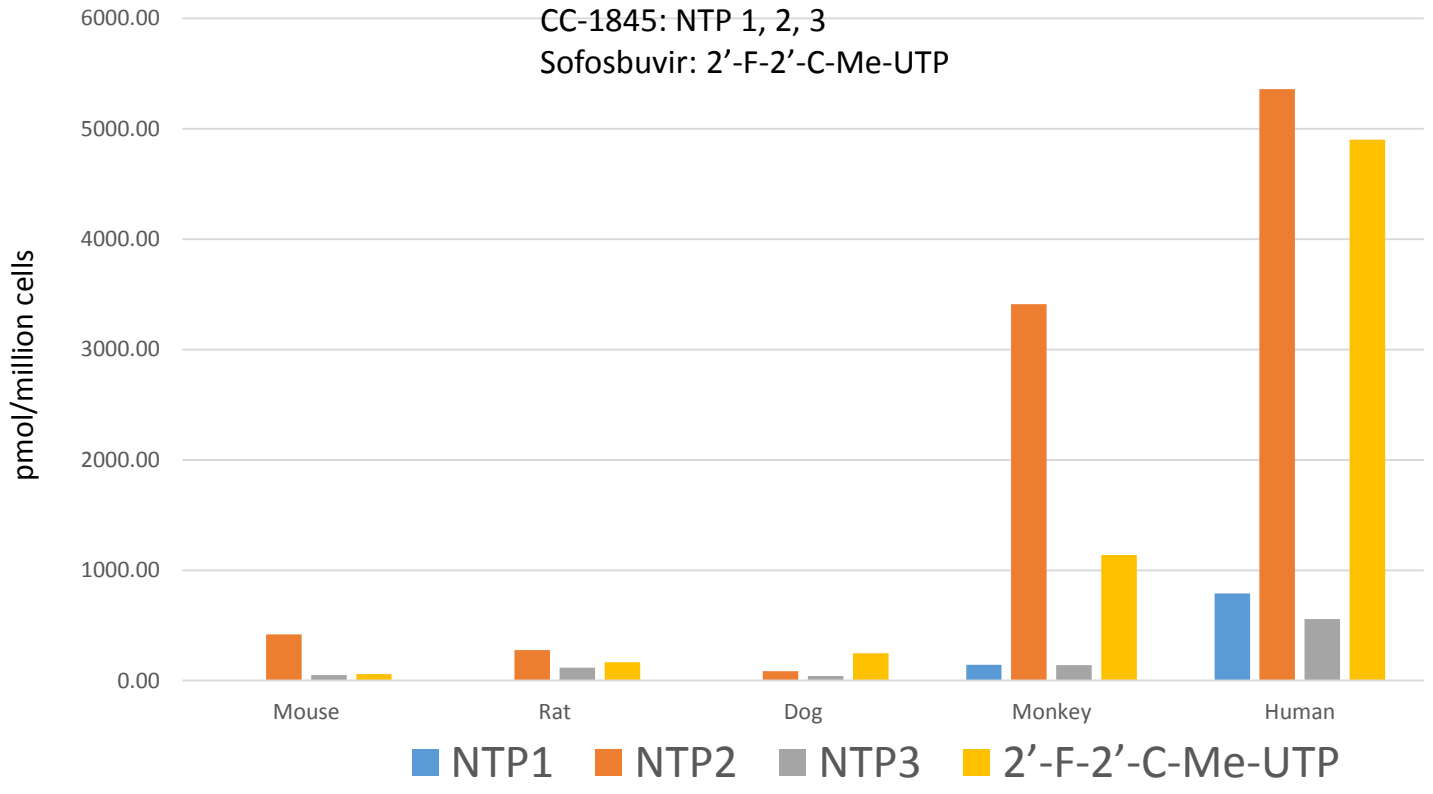
CC-1845: Greater Levels of NTP ***in vivo***

Comparative single IP dosing study in mice with SOF at 10 mg/kg in the liver



CC-1845: Interspecies Hepatocytes

CC-1845 and sofosbuvir comparative study in five species: 50 μM at 4 h



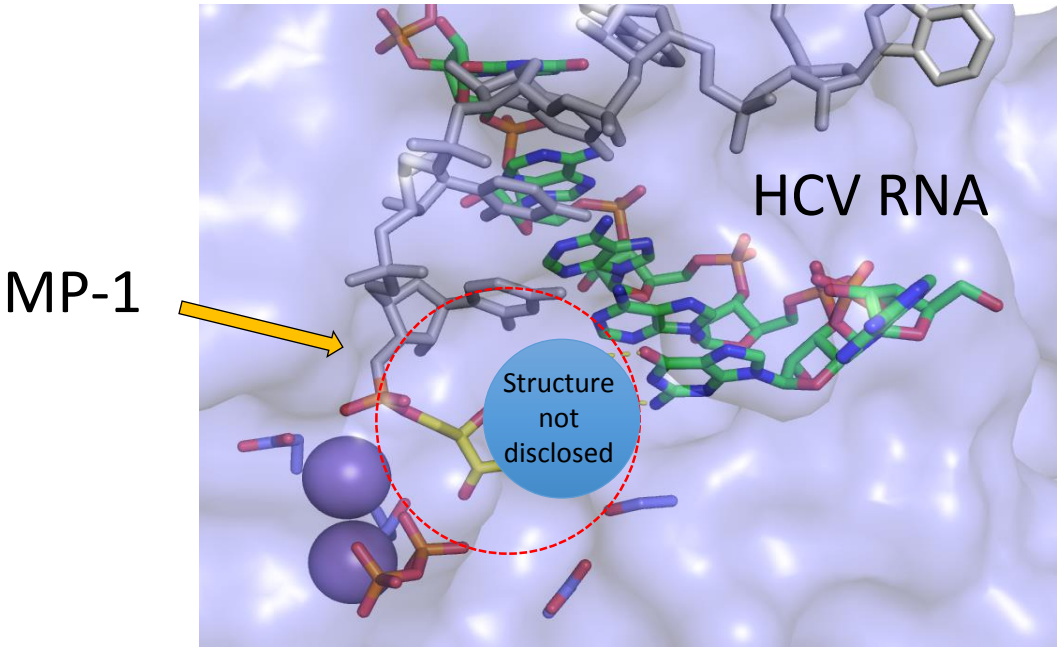
CC-1845: Comparable Potency

2 of the 3 metabolites of CC-1845 showed comparable potency to sofosbuvir against the HCV viral polymerase

NS5B enzyme	IC_{50} (µM)			
	NTP1	NTP2	NTP3	SOF-NTP
GT 1b WT	> 200	4.7 ± 1.4	2.2 ± 0.8	2.9 ± 0.6

CC-1845: HCV Nuc Chain Terminator

CC-1845 terminates HCV RNA replication: X-ray data confirms highly efficient mechanism of action



Cocrystal's high resolution X-ray structure

CC-1845: IND Candidate Properties

Pan-genotypic	**Yes**
GT1b EC_{50}, µM	1.1 ± 0.7 µM
Liver targeting	Yes
Cytotoxicity [includes human cardiomyocytes, Mitotox (galactose vs glucose) & bone marrow toxicity]	Early data shows minimal cytotoxicity at clinically relevant conc. in over 22 human/mammalian cell types (proliferating and non-proliferating); no evidence of *in vitro* mitochondrial toxicity, cardiomyocyte or bone marrow toxicity
1. Selectivity vs. Human DNA pol alpha, beta, gamma 2. Selectivity vs. Human RNA pol II 3. Human mitochondrial RNA pol (POLRMT)	1. > 100 µM for all three NTPs and across all 3 Pols 2. > 100 µM for all three NTPs vs. Human RNA pol II 3. Poor substrate for human POLRMT
1. Human CYP2B6, 2C8, 2C9, 2C19, 3A (direct) 2. Human Transporters: OCT2, ASBT, BCRP, NTCP, OAT1, OAT3, OATP1B1, OATP1B3	1. Low risk of drug-drug interaction thru direct or time-dependent CYP inhibition. 2. No significant inhibition across 8 human transporters
GLP hERG assay	IC_{50} > 30 µM (25% inhibition at 30 µM)
CV/respiratory in dogs (GLP): tested 60, 200, 600 mg/kg single dose	Respiratory parameters were unaffected. Minor fluctuations in blood pressure/heart rate and QT/QTc at 600 mpk, were of minimal clinical significance.
Genotoxicity (AMES, chromosome aberration)	Negative in both assays
Stability in Human liver & human intestinal microsomes	$T_{1/2}$: 39.4 min (liver microsomes) & > 145 min in intestinal microsomes (low clearance in both microsomes)
In vitro combination study	Additive/synergistic with CC-31244 & CC-2068

CC-2068: Pan-genotypic NS5A

- Novel, highly potent, pan-genotypic, NS5A inhibitor (GT1b EC_{50} < 10 pM)
- CC-2068 produces an active metabolite (also a pM HCV inhibitor)
- No cytotoxicity observed
- Favorable PK properties
- Favorable *in vitro* ADMET properties
- Potentially an excellent combination drug candidate with Nuc and/or NNI
- IND-enabling studies in progress

CC-2068: IND Candidate Properties

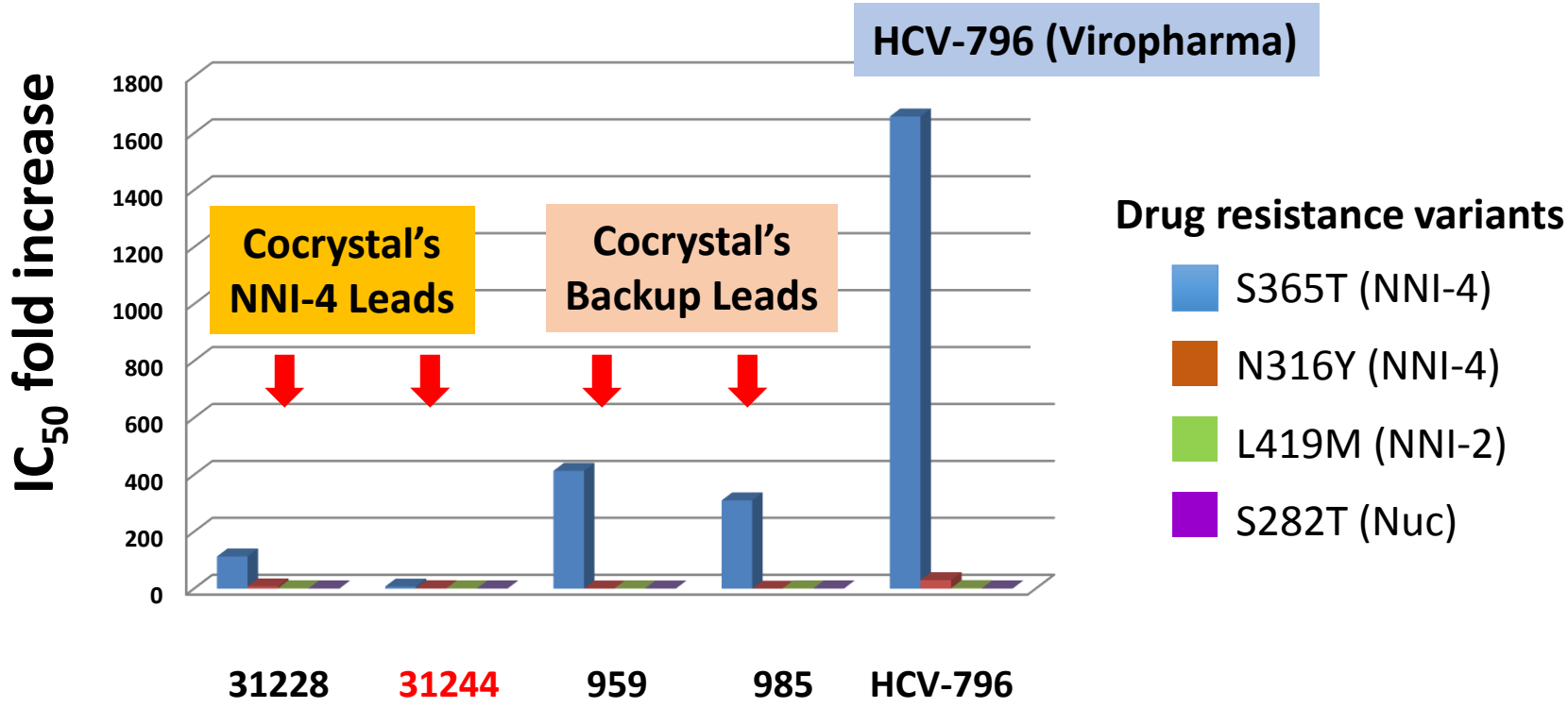
Pan-genotypic	**Yes**
GT1b EC_{50}	2.2 pM; also has a pM active metabolite
Liver targeting	Yes; 2 h dog liver study: 13.4-fold higher liver concentration than plasma & exceeds EC_{50}
Stability in Human liver & human intestinal microsomes	$T_{1/2}$: > 145 min (in both liver & intestinal microsomes) (low clearance in both microsomes)
Cytotoxicity	No
1. Human CYP2B6, 2C8, 2C9, 2C19, 3A (direct) 2. Human Transporters: OCT2, ASBT, BCRP, NTCP, OAT1, OAT3, OATP1B1, OATP1B3	Large margins (> 100-fold) between any inhibitory activity and efficacious concentrations; no risk for clinical drug-drug interaction
hERG	No
Caco2 A-B (at 10 µM), 10^{-6} cm/s Caco2 B-A (at 10 µM), 10^{-6} cm/s	< 0.05 (low forward permeability) < 0.24 (no significant efflux)
Genotoxicity (AMES, chromosome aberration)	Negative in both assays
In vitro combination study	Additive/synergistic with CC-1845 & CC-31244

CC-31244: Pan-genotypic NNI

- Highly potent NS5B polymerase inhibitor (EC_{50} = 7 nM)
- Pan-genotypic activity against all genotypes (1-6)
- No off-target activities and favorable *in vitro* ADMET properties
- No cytotoxicity
- Excellent activity against common drug resistant variants (IC_{50} fold change < 5-fold)
- Favorable PK properties
- Liver targeting
- IND-enabling studies in progress

CC-31244: Pan-genotypic NNI

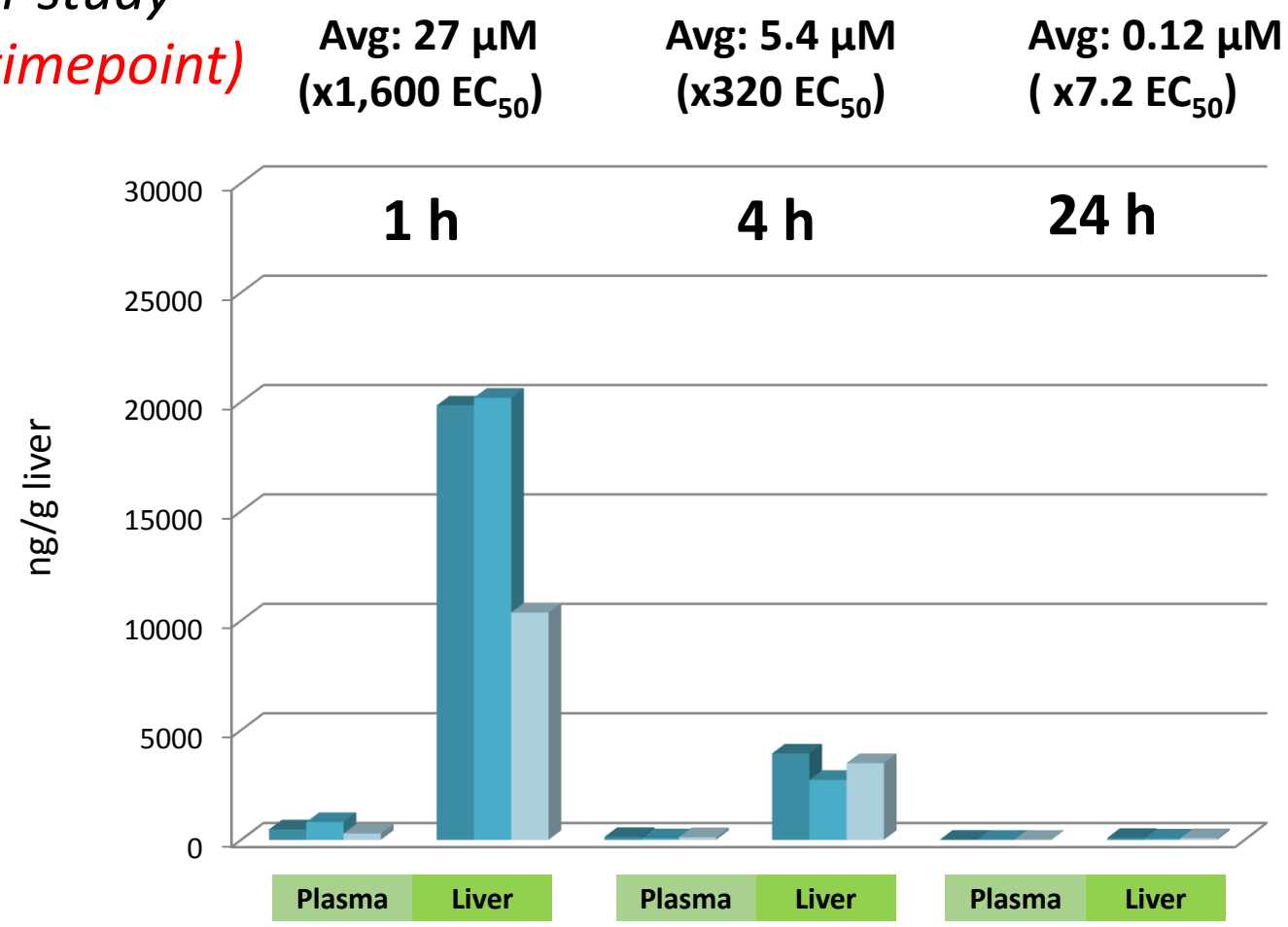
High barrier to drug resistance



CC-31244: Excellent Liver Targeting

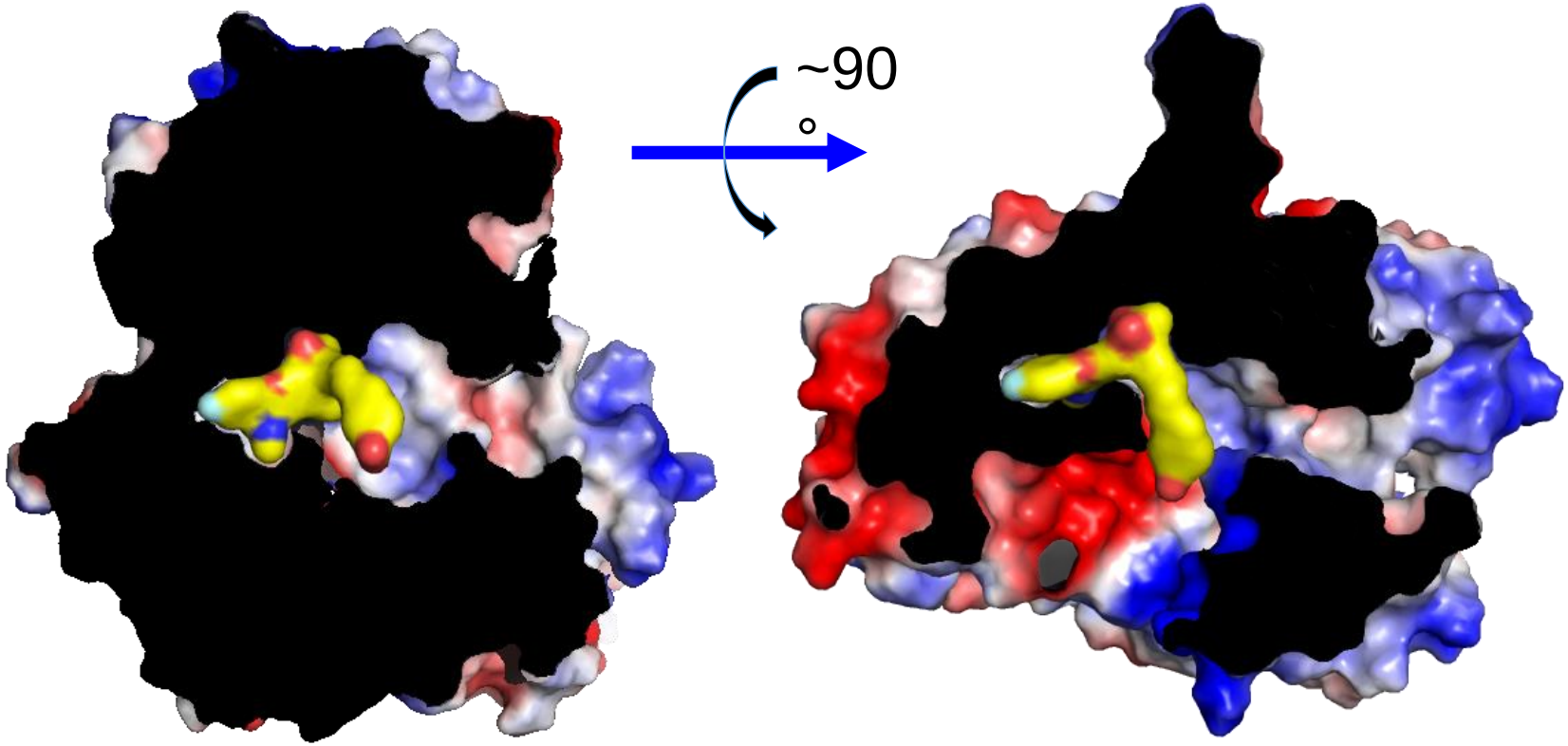
Rat liver study

(n = 3/timepoint)



CC-31244: Structure-guided NNI

CC-31244 extends from NNI-4 to active site



CC-31244: IND Candidate Properties

Pan-genotypic	Yes
GT1b EC_{50}	8.5 ± 1.0 nM
Liver targeting	Yes
Intrinsic clearance (liver microsomes)	Human Cl_{int} = 131 µL/min/mg; Half-life 53 min
Cytotoxicity [includes Mitotox (galactose vs glucose: 3 days)]	No or little cytotoxicity observed in 13 human/mammalian cell types
1. Human CYP 2B6, 2C8, 2C9, 2C19, 3A (direct) 2. Human Transporters: OCT2, ASBT, BCRP, NTCP, OAT1, OAT3, OATP1B1, OATP1B3	Large margins (> 100-fold) between any inhibitory activity and efficacious concentrations; no risk for clinical drug-drug interaction
Genotoxicity (AMES, chromosome aberration)	Negative in both assays
hERG	No inhibition
Caco2 A-B, 10^{-6} cm/s Caco2 B-A, 10^{-6} cm/s	7.1 (high forward permeability) 44.4 (moderate efflux)
Safety (off-target) profile	Excellent
In vitro combination study	Additive/synergistic with CC-1845 & CC-2068

Additional Candidates Identified for HCV

- Nucleoside
  - Four unique nucleoside analogs identified
  - Potency in a genotype 1b replicon assay ranges from 200 to 600 nM
  - No toxicity (> 80 µM) was observed in PBM, CEM and Vero cells
- NS5A
  - Pre-clinical lead selected, CC-2069
  - Excellent *in vitro* profile
- NNI
  - Pre-clinical lead selected, CC-959
  - Excellent *in vitro* profile

HCV Helicase Program

Provides unique opportunities for drug combinations

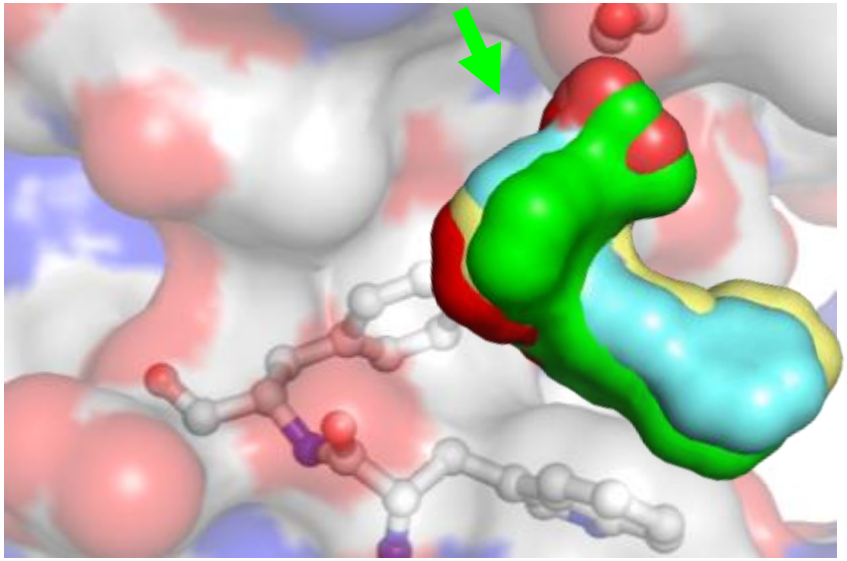
- Creates a new option for HCV combination therapy
- First-in-class pan-genotypic inhibitors (new mechanism of action)
- Highly conserved drug binding mode demonstrated in all genotype crystals developed (1-6)
- Potentially an ideal combination candidate with HCV NS5B Nuc, NNI, NS5A, and/or protease inhibitors
- Inhibits essential viral RNA unwinding process

HCV Pan-genotypic NS3 Helicase Inhibitors

HCV genotype crystals (1-6) developed

GT1b **GT1a** **GT1b FL** **GT2a** **GT3a** **GT4a** **GT5a** **GT6a**

Pan-genotypic binding mode of HCV helicase inhibitor



Genotype 1-6 overlay cocrystal structures

Norovirus Program

Norovirus polymerase leads: nucleoside inhibitor and NNI

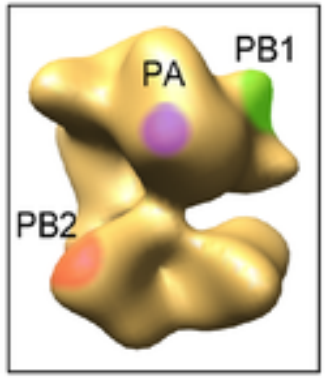
- Novel anti-norovirus Nuc prodrug (CC-1845) developed: confirmed activity based on Norwalk replicon and enzyme assay; also active against HCV
- Favorable PK properties demonstrated
- Drug resistance evaluation for Norovirus (in progress)
- Structure-based NNI lead discovery (in progress)
- Expect to be used as prophylaxis and for acute and chronic norovirus infections; especially in immunocompromised patients

Influenza Program

Influenza leads: PB2, PB1 and PA Inhibitors

- Focus on three different classes of influenza polymerase inhibitors: PB2 (cap-binding), PB1 (polymerase), and PA (endonuclease)
- Expect to complete PB2 lead optimization by Q4
- IND-enabling study of PB2 inhibitor scheduled for 2016

Influenza polymerase complex



2015 Goals

Accelerate transition into a clinical biopharmaceutical company

- Development
  - Progress regulatory filings as soon as possible
  - CC-1845 is first priority, followed closely by CC-31244 and CC-2068
- Research
  - Select lead drug candidate for Influenza
  - Progress norovirus program for both nucleoside and NNI compounds
- Operations
  - Continue transition to a fully-listed, Nasdaq Company
  - Enhance leadership team and technical capabilities

Looking Forward to 2016

Potentially transformational year

- HCV
  - Advance multiple pan-genotypic DAA's into Phase 1
  - Potential unique combination regimen (Nuc+NS5A+NNI)
- Norovirus
  - Initiate clinical program against norovirus
  - Advance additional DAAs
- Influenza
  - Potentially initiate IND-enabling studies for PB-2 inhibitors
  - Develop PB-1, PA leads

Leadership

Board of Directors and Key Management

Raymond Schinazi (Chairman)

Phil Frost

David Block

Jane Hsaio

Steven Rubin

Gary Wilcox

Jeffrey Meckler

Sam Lee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