IDL-2965: A SELECTIVE, HIGHLY POTENT, CLINICAL-STAGE INTEGRIN ANTAGONIST FOR THE TREATMENT OF NASH

Karl Kossen[1], Caralee Schaefer[1], Sharlene Lim[1], Marshall Michener[1], David Griggs[2], Peter Ruminski[3], Ramachandran Radhakrishnan[1], Bill Bradford[1], and Scott Seiwert[1]

[1]Indalo Therapeutics, Cambridge, MA USA; [2]Saint Louis University, St. Louis, MO USA; [3]Washington University, St. Louis, MO USA

Abstract

BACKGROUND AND AIMS: Clinical outcome in NASH is associated with the stage of liver fibrosis. RGD-binding integrins are attractive therapeutic targets for the treatment of fibrosis. IDL-2965 is a potent, small molecule integrin antagonist of that is currently being characterized in a Phase 1/1b clinical program including healthy subjects, NASH patients and IPF patients.

METHOD: A robust drug discovery campaign identified integrin antagonists with strong antifibrotic activity and favourable PK. IDL-2965 emerged from these screens and was characterized for potency, selectivity, and antifibrotic efficacy, as well as for safety in a formal toxicology program.

RESULTS: In cell-based ligand displacement assays, IDL-2965 displayed IC_{50} values of 1.6, 1.4 and 0.3 nM against αvβ1, αvβ3 and αvβ6, respectively. In a cell co-culture system of TGF-β activation, IDL-2965 displayed an EC_{50} of 110 nM. IDL-2965 was metabolically stable in hepatocytes and microsome fractions across species, including humans ($t_{1/2}$ > 240 min). Following oral dosing in rat and primate, IDL-2965 displayed an apparent $T_{1/2}$ of 7.4 hr and 8.5 hr, respectively. In rat, ^{14}C-IDL-2965 was eliminated by both hepatic and renal routes. In a rat CCl_4 model, prophylactic once daily oral treatment with IDL-2965 significantly reduced liver fibrosis (via histopathology) at 1 mg/kg. In a mouse CDAHFD model, once daily oral therapeutic treatment with IDL-2965 significantly reduced fibrosis scores, liver hydroxyproline, and plasma CK-18 at 3 mg/kg. In a DIO-NASH model in ob/ob mice, therapeutic treatment with IDL-2965 reduced collagen and αSMA relative to baseline, and reduced plasma CK-18 and hyaluronic acid relative to vehicle treated animals at 3 mg/kg. An improvement in NAFLD score was driven by a reduction in hepatocyte ballooning, with no impact on steatosis or inflammation. Pharmacodynamic studies in the DIO-NASH model further demonstrated that IDL-2965 reduced plasma CK-18 and TIMP-1 within one week, and reduced circulating hyaluronic acid by week 4. IDL-2965 displayed a favourable safety profile in formal toxicology studies up to the limit dose of 1000 mg/kg in both in rat and primate.

CONCLUSION: IDL-2965 potently suppresses fibrosis and related biomarkers in preclinical models of liver fibrosis and its characterization in an ongoing phase 1 program including NASH patients is warranted.

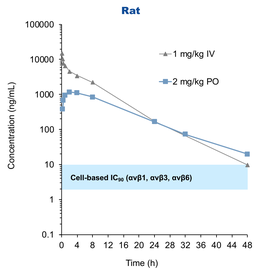
IDL-2965 Potency & DMPK

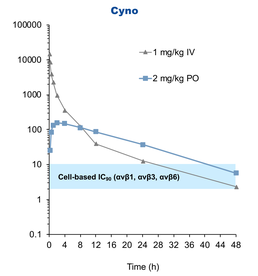
Cell-based IC50 (nM)		
αvβ1	αvβ3	αvβ6
1.6	1.4	0.3

Hepatocyte Intrinsic Clearance		
Species	CLint (μL/min/10^6 cells)	$T_{1/2}$ (min)
Mouse, Rat, Cyno, Human	< 2.9	> 480

		CYP450 Inhibition IC_{50} (μM)							
		1A2	2B6	2C8	2C9	2C19	2D6	3A4*	3A4**
Hepat.		>10	>10	>10	>10	>10	>10	>10	>10
HLM	Direct	>50	40.3	>50	>50	>50	>50	>50	>50
	Time dep.	>50	>50	>50	>50	>50	>50	>50	>50

CYP450 Induction IC_{50} (1, 3 & 10 μM)			
	1A2	2B6	3A4
Enzyme activity	Negative	Negative	Negative



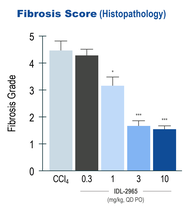


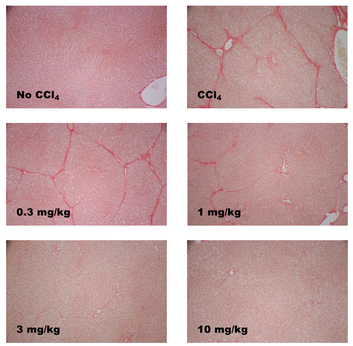
	Rat	Cyno
T_{max} (h)	3.3	1.7
C_{max} (ng/mL)	1,307	167
$AUC_{0\text{-}inf}$ (ng.h/mL)	16,290	2,624
$T_{1/2}$ (h)	5.0	8.7
IV Vd_{ss} (L/kg)	0.13	0.23
IV Cl (mL/min/kg)	0.38	1.68

	Percent of the Administered Dose Recovered (%)				
Gender (Number)	Urine	Feces	Cage Rinse/Wash	Bile	Total Dose Recovered (%)
Female (n=4)	15.48±2.09	61.4±4.25	1.45±0.56	15.78±7.78	94.11±2.29
Male (n=4)	12.79±5.75	66.09±8.42	1.39±0.44	13.59±6.6	93.85±1.87
Male and Female (n=8)	14.13±4.26	63.74±6.66	1.42±0.47	14.68±6.78	93.98±1.94

IDL-2965 Inhibits CCl_4-induced Liver Fibrosis

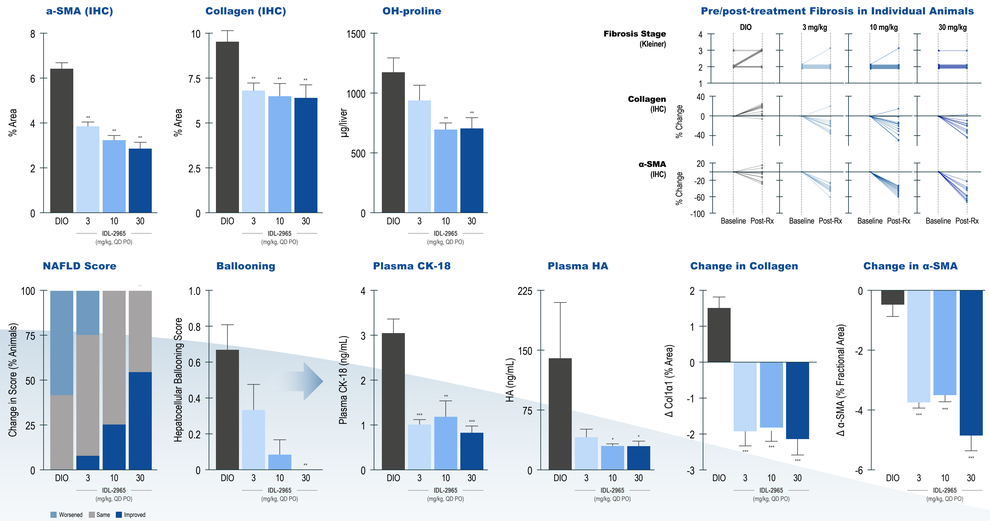
- IDL-2965 was evaluated in an 8 week CCl_4-induced liver fibrosis model in rat
- Prophylactic treatment with IDL-2965 strongly reduced fibrosis
  - Minimum effective dose: 1 mg/kg





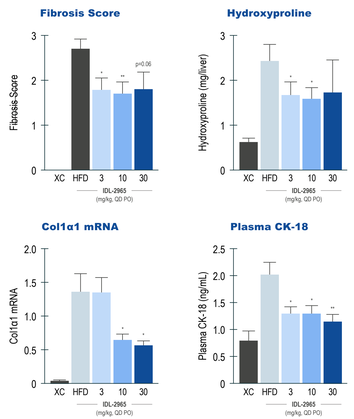
IDL-2965 Reverses Liver Fibrosis in a DIO-NASH Model

- IDL-2965 was evaluated in a DIO-NASH model in ob/ob mice
- Therapeutic IDL-2965 treatment strongly improved multiple measures of fibrosis
  - Minimum effective dose: 3 mg/kg (lowest tested)
- IDL-2965 improved NAFLD score
  - Driven by a reduction in ballooning
  - No effect on steatosis or inflammation
- Consistent with a reduction in ballooning, IDL-2965 significantly reduced plasma CK-18
- A comparison of collagen in biopsies taken pre- and post-treatment demonstrates that IDL-2965 reduced pre-existing fibrosis



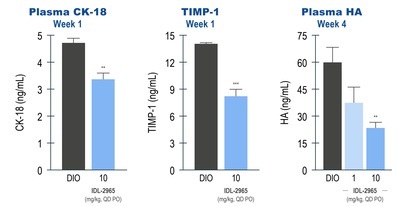
IDL-2965 Reduces CDAHFD-induced Fibrosis

- IDL-2965 was evaluated in a mouse CDAHFD model
- Therapeutic IDL-2965 treatment strongly improved multiple measures of fibrosis
  - Minimum effective dose: 3 mg/kg (lowest tested)
- IDL-2965 significantly reduced plasma CK-18



IDL-2965 Rapidly Reduces Plasma Biomarkers

- The kinetics of an IDL-2965 mediated biomarker response were evaluated in the DIO-NASH model
- IDL-2965 significantly reduced plasma CK-18 and TIMP-1 in < 1 week
- IDL-2965 reduced plasma HA in a dose and time dependent manner—significant at week 4



Conclusion

- IDL-2965 has strong antifibrotic effects in multiple models of liver fibrosis at low, once-daily, oral doses
- IDL-2965-mediated reductions in liver fibrosis are accompanied by rapid changes in relevant plasma biomarkers
- Clinical studies of IDL-2965 are ongoing with plans for evaluation in NASH patients

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