B28

Increased efficacy and half-life of a novel anti-angiogenesis therapy using αvβ3 integrin targeted dextran coated liposomes

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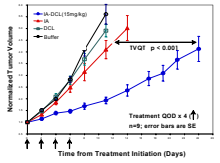
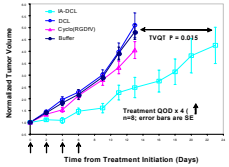
Introduction

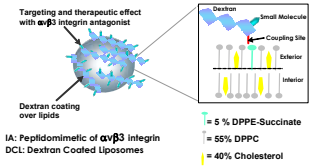
Anti-angiogenesis therapy is a promising anticancer treatment in part because it targets tumor vasculature and is less susceptible to multi-drug resistance, a problem associated with many chemotherapeutics. Integrin αvβ3 is involved in tumor-induced angiogenesis; it is differentially expressed at high levels on a variety of tumor cells and on neovascular endothelial cells. In this study we investigated the efficacy, pharmacokinetics and toxicity of an αvβ3 integrin antagonist (IA) that was covalently attached to the surface of a dextran-coated liposome (DCL).

Improved Efficacy of IA-DCL





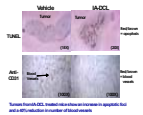
IA-DCL Composition



IA: Peptidomimetic of αvβ3 integrin
DCL: Dextran Coated Liposomes

Anti-Angiogenic Mechanism

	Vehicle	IA-DCL	IA
H & E	Large tumor, viable blood vessels along periphery	Necrotic areas, fewer blood vessels	Intermediate level of necrosis and vessels along periphery
TUNEL	Few foci of apoptotic cells	Large area of apoptotic cells	Intermediate number of apoptotic foci
Anti-CD31	299 blood vessels	179 blood vessels	Comparable to control



Tumors from IA-DCL treated mice show an increase in apoptotic foci and a 40% reduction in number of blood vessels

PK and Safety

PK Parameter	IA-DCL	DCL
Elimination half-life (hr)	23	19
Clearance (gm/hr)	0.09	0.05
Volume distribution at steady state (Vss)	< 1.5 gm	< 1.0 gm

*Mice dosed with 1.1ci/ml of IA-DCL or DCL labeled with ^{14}C-DPPC

Safety

- Mice dosed with 4 doses of 15 mg/kg IA-DCL, IA or DCL to match efficacy dosage
- Necropsy performed 24 hours post last treatment
- No gross pathological or histo-pathological findings in any group

Summary of Key Findings

- Attachment of a small molecule αvβ3 IA to a DCL converted a therapeutically inactive drug to one with significant anti-tumor activity.
- IA-DCL demonstrated a significant therapeutic effect in the M21 melanoma model. Treatment was superior to cyclo(RGDfV), a peptide IA similar to Cilengitide, currently in Phase II trials.
- IA-DCL treatment led to extensive tumor apoptosis and reduced vessel density by ~40% supporting an anti-angiogenic mechanism.
- IA-DCL demonstrated a prolonged plasma half-life (23 hr) implying infrequent dosing in humans.
- IA-DCL demonstrated restricted tissue distribution and vascular compartment confinement. In addition, no gross or histo-pathological toxicity was seen in examined tissues.
- These encouraging data demonstrate the advantages and potential therapeutic application of active drug targeting using the DCL approach.