Aposense Ltd.

ATT-11T - From Depot to Target Enhancing Drug Effects

APOSENSE®
Targeting New Healthcare Horizons

Aug, 2015

FORWARD LOOKING STATEMENTS

The following slides contain forward-looking statements that include, but are not limited to, projections about our business and our future revenues, expenses and profitability. Forward-looking statements involve known and unknown risks, uncertainties and other factors which may cause the actual events, results, performance, circumstances or achievements of the Company to be materially different from those expressed or implied by such forward-looking statements due to factors that include, but are not limited to: (1) our ability to develop and bring to market new products, (2) our ability to successfully complete any necessary or required clinical studies with our products, (3) our ability to receive regulatory clearance or approval to market our products or changes in regulatory environment, (4) our success in implementing our sales, marketing and manufacturing plans, (5) the level of adoption of our products by medical practitioners, (6) the emergence of other products that may make our products obsolete, (7) protection and validity of patents and other intellectual property rights, (8) the effect of competition by other companies and technologies, and (9) our ability to obtain reimbursement for our products from government and commercial payers. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of these slides. The Company undertakes no obligation to update any forward-looking statements, to report events or to report the occurrence of unanticipated events that may lead to the actual events, results, performance, circumstances or achievements of the Company being different than as envisaged by such forward looking statements.

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About Aposense

- Aposense is an Israeli publicly traded biopharmaceutical company (TASE: APOS) with a unique platform based on the conjugation of approved drugs with selected small chemical proprietary moieties

- Conjugation with these moieties enables harnessing of drug membrane interactions, thus providing the new, conjugated compound with improved drug properties such as **extended pharmacokinetic profile**, **reduced toxicity** and **selective activation at target site**

- Each conjugate is designed, in terms of both the selected Aposense moiety and the selected chemical linker, so as to address the limitations of the known therapies

- Aposense products under development include:

    - **ATT-11T**, which is based on a conjugate of Aposense moiety with SN-38, the active metabolite of irinotecan, which is a highly potent topoisomerase I inhibitor

    - **ATT-LD**, a new generation pro-drug of Levodopa, being developed for the treatment of Parkinson's disease

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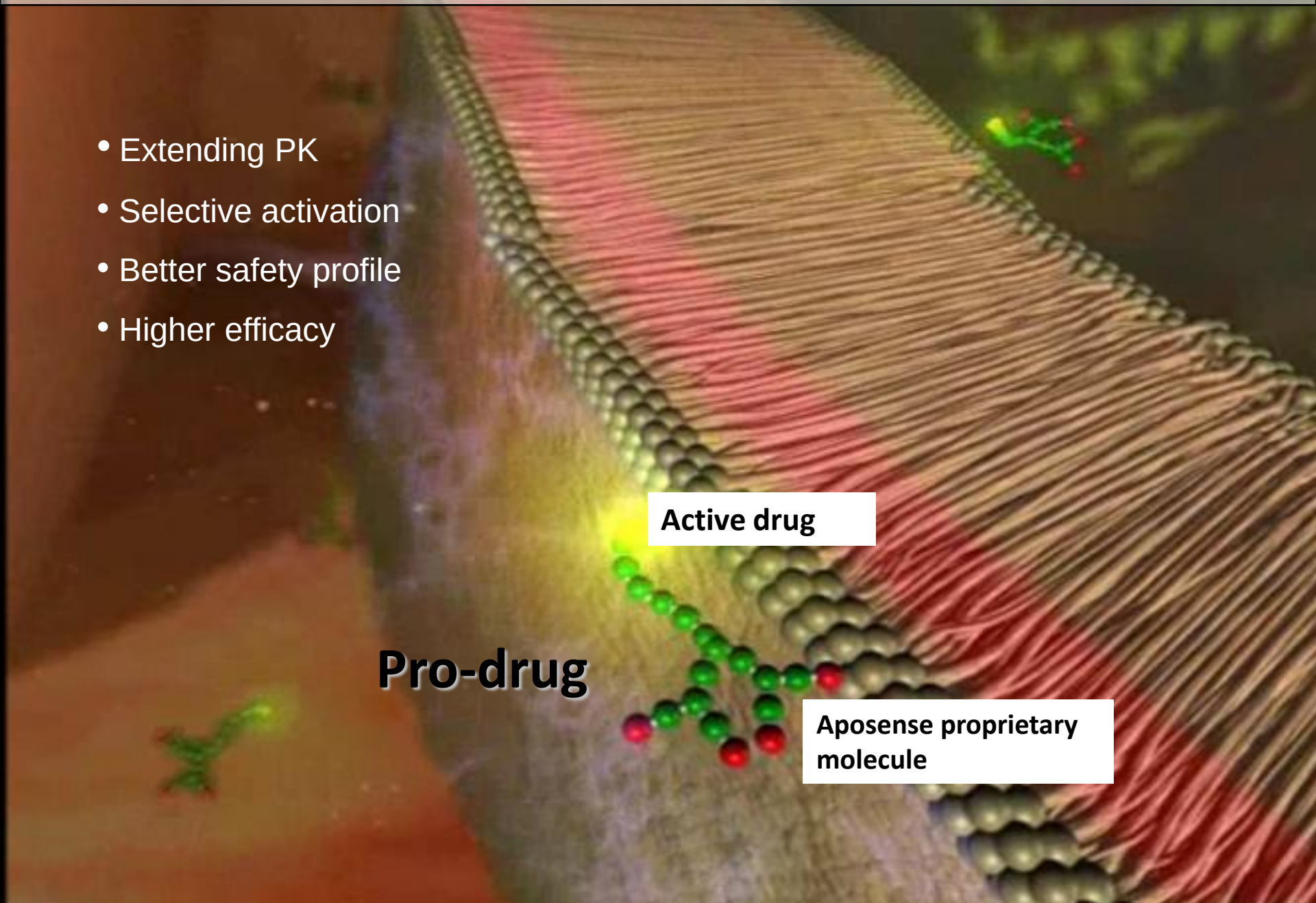
Technology: Leveraging Drug-Membrane Interactions

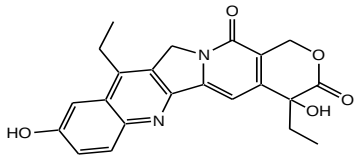
- Extending PK
- Selective activation
- Better safety profile
- Higher efficacy



ATT-11T

- **ATT-11T** is an improved molecule version of **irinotecan**, developed by Pfizer and marketed under the commercial name **Camptosar®** with peak annual sales of nearly $1Bn before patent expiry in 2008*.
- **Irinotecan** (active metabolite - SN-38) is a potent but highly toxic chemotherapy, thus its use is limited.
- **ATT-11T** showed increased efficacy and reduced toxicity in various pre-clinical cancer models.

ATT-11T



Active drug SN-38

* See Pfizer 2007 10-K

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Technological Innovation

- A novel NCE pro-drug based on SN-38 and an Aposense proprietary moiety
- Unique mechanism of action harnessing drug membrane interaction to provide:
  - An inactive pro-drug depot that releases slowly to maximize solid tumor suppression
  - Selective activation of the active drug, predominantly within the tumor-target tissue
  - Gradual and continuous conversion to SN-38
  - Improved safety profile
- Novel i.v. micro-emulsion formulation for high lipophilic compound
- Improved pharmacokinetic profile with extended plasma half-life, increased AUC and larger volume of distribution
- Improved therapeutic window

Development of a novel NCE that synchronizes the pharmacokinetic profile of SN-38 and its selective, sustained and constant formation within the tumor-target tissue

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ATT-11T: Target Product Profile (TPP)

ATT-11T is a pro-drug of SN-38 for the treatment of metastatic solid malignancies	
Mechanism of Action	Extension of SN-38 half-life ($t_{1/2}$) derived from ATT-11T depot and selective activation at the tumor-target tissue
Administration	i.v. micro-emulsion
Indications	Primary: 1st and 2nd line therapy in patients with mCRC Other potential indications: esophagogastric carcinoma, refractory ovarian carcinoma,1st line therapy in advanced stage small-cell lung carcinoma
Attributes	Extended $t_{1/2}$, tumor selectivity, superior efficacy and better safety profile compared to irinotecan
Efficacy Endpoints	Primary: Superiority in overall survival, over irinotecan Secondary: Superior progression free survival (PFS) over irinotecan
Safety	Improved safety and tolerability profile over irinotecan

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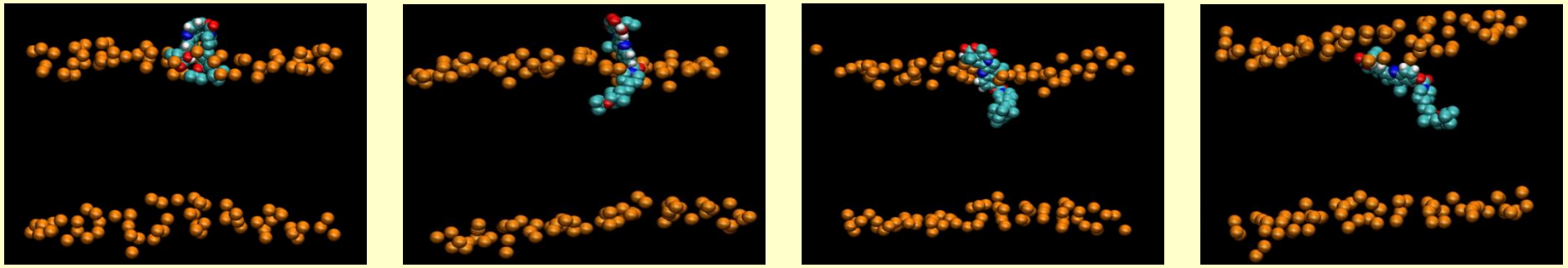
ADME

ADME Studies

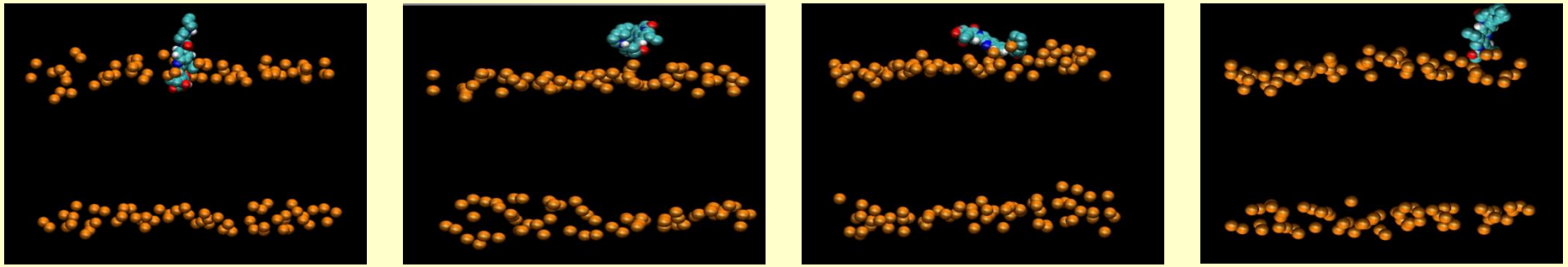
- Several in-vitro and in-vivo studies were performed in order to evaluate the ADME characteristics of ATT-11T :
- In -vitro
  - Interspecies plasma stability
  - Blood partitioning
  - Metabolic profiling (phase 1 metabolism and metabolic turnover by glucuronidation) in mouse, rat, dog, mini-pig and human liver microsomes
  - Metabolites identification of ATT-11T in primary rat and human hepatocytes.
- In -vivo
  - PK studies, single dose, following intravenous routes in
    - Mice
    - Rats
    - Dogs
    - Mini-pigs
  - Metabolic conversion in vivo to SN-38 and SN-38G
  - PK modeling, repeated dose, for animal dosing based on the above results
  - Bio-distribution in tumor bearing mice
- Along with the quantified metabolites SN-38 and SN-38G further metabolism related products were evaluated and characterized in-vitro for ATT-11T

ATT-11T Penetration into Membrane Leads to In-active Depot Formation

ATT-11T start point | 2 nsec | 10 nsec | 40 nsec



Irinotecan start point | 2 nsec | 10 nsec | 40 nsec



Legend:
- Carbon
- Oxygen
- Nitrogen
- DPPC's phosphorous

Computerized simulations were performed in a DPPC lipid bilayer model, by the GROMACS 4.0.7 software (Bioinformatics unit, Tel-Aviv University).

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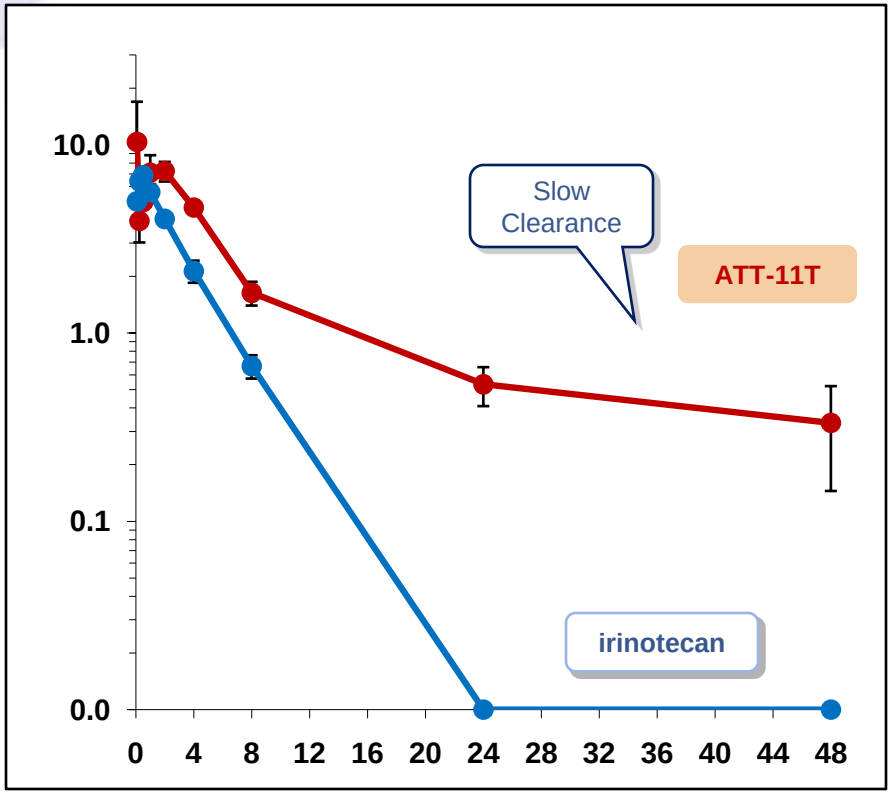
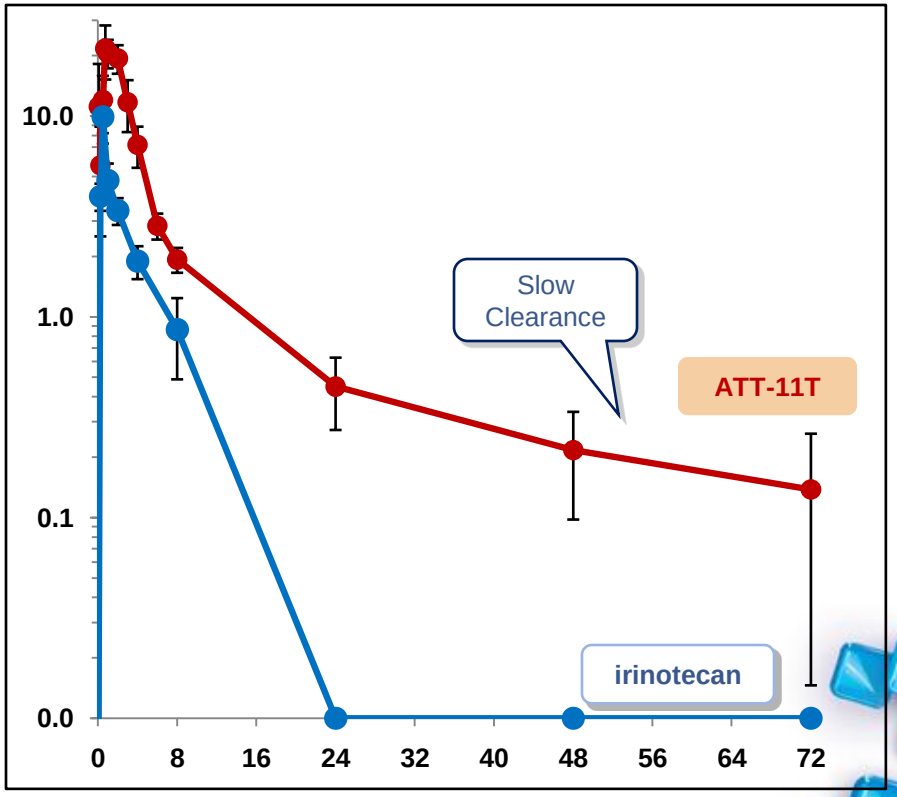
Pharmacokinetic Profile of SN-38 (active moiety) Derived From ATT-11T vs. Irinotecan: Non-rodent Species

Beagle dogs



Mini-pigs



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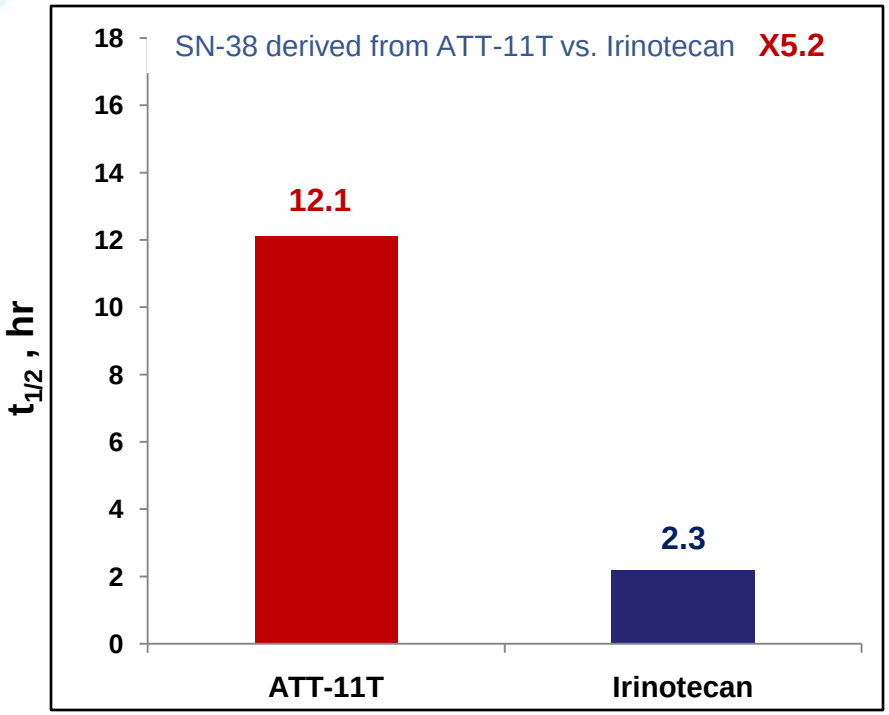
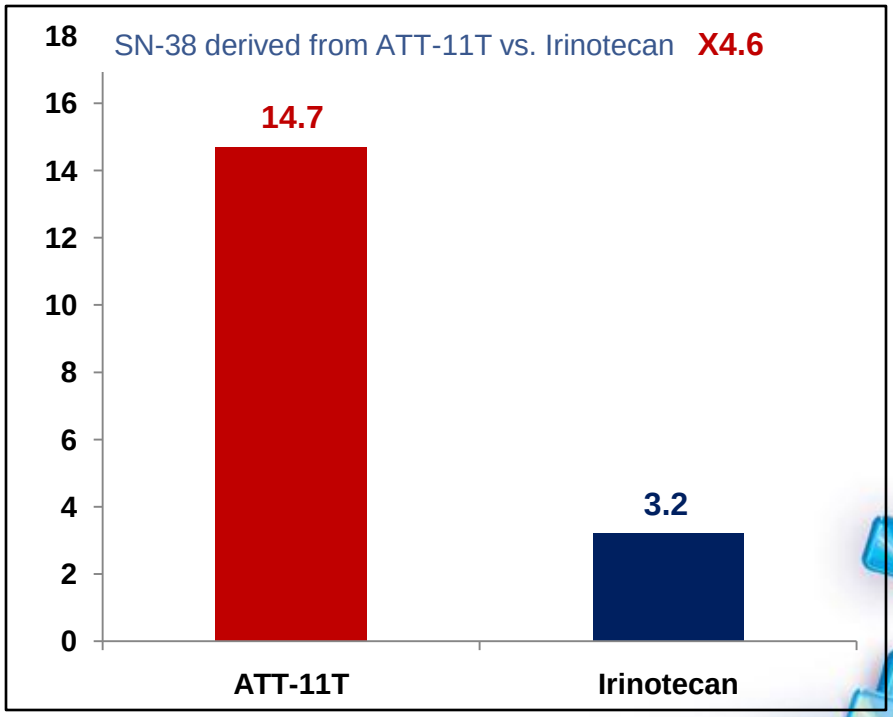
Five-Fold Extension of SN-38 Plasma Half-life ($t_{1/2}$)

Beagle dogs



Mini-pigs



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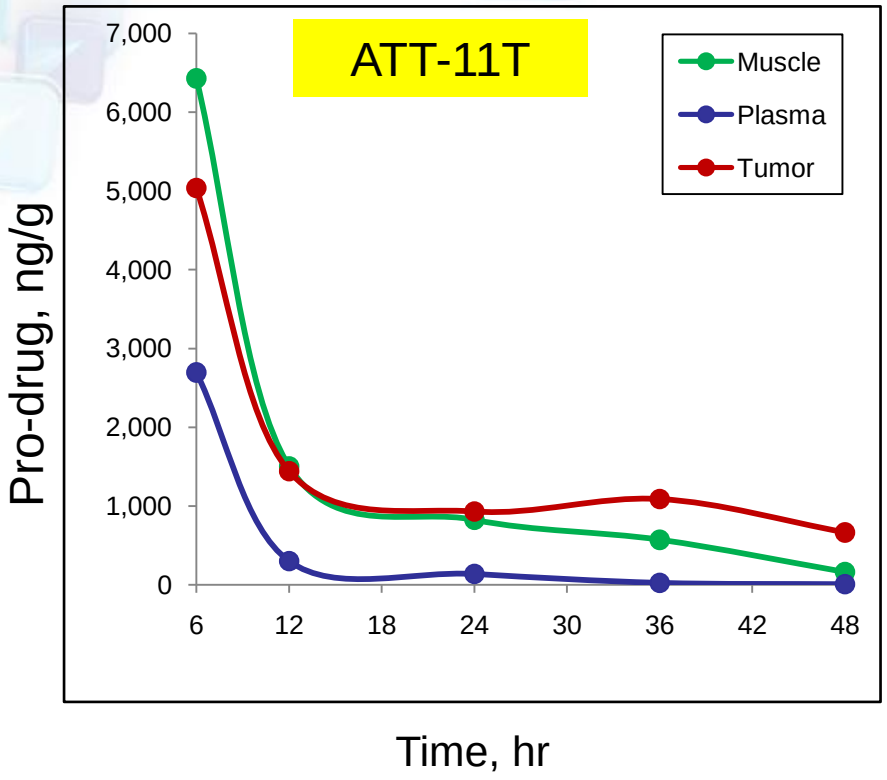
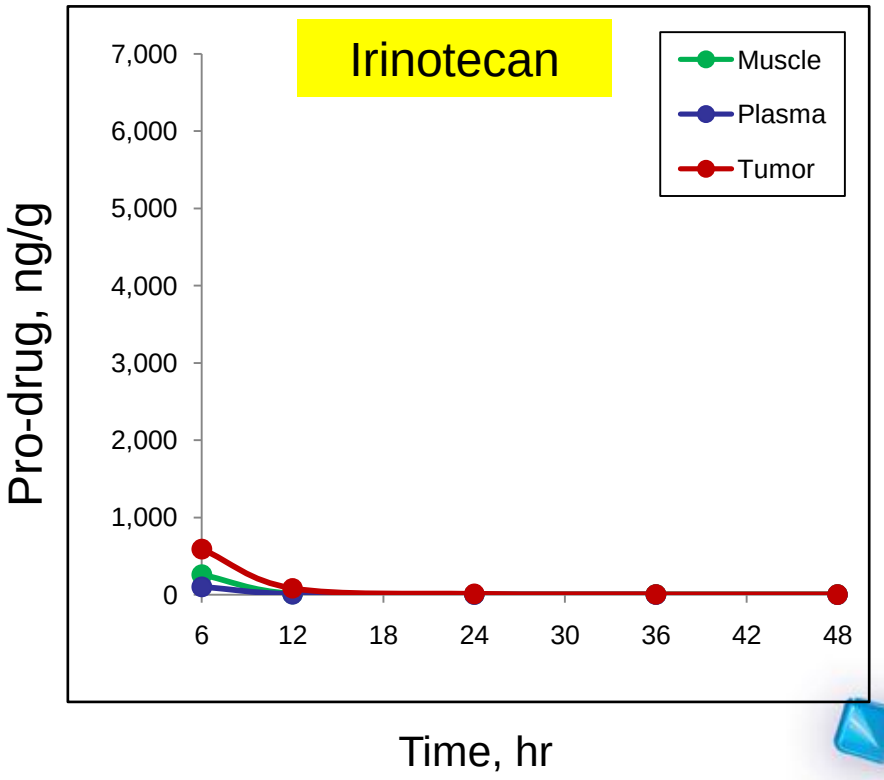
Ten-Fold increase in Tumor Pro-drug Levels

Bio-distribution study in tumor-bearing mice





Study design: Melanoma (A375)-tumor bearing mice, single dose of 30mg/kg, sacrificed at 6,12,24,36 & 48hr post dose

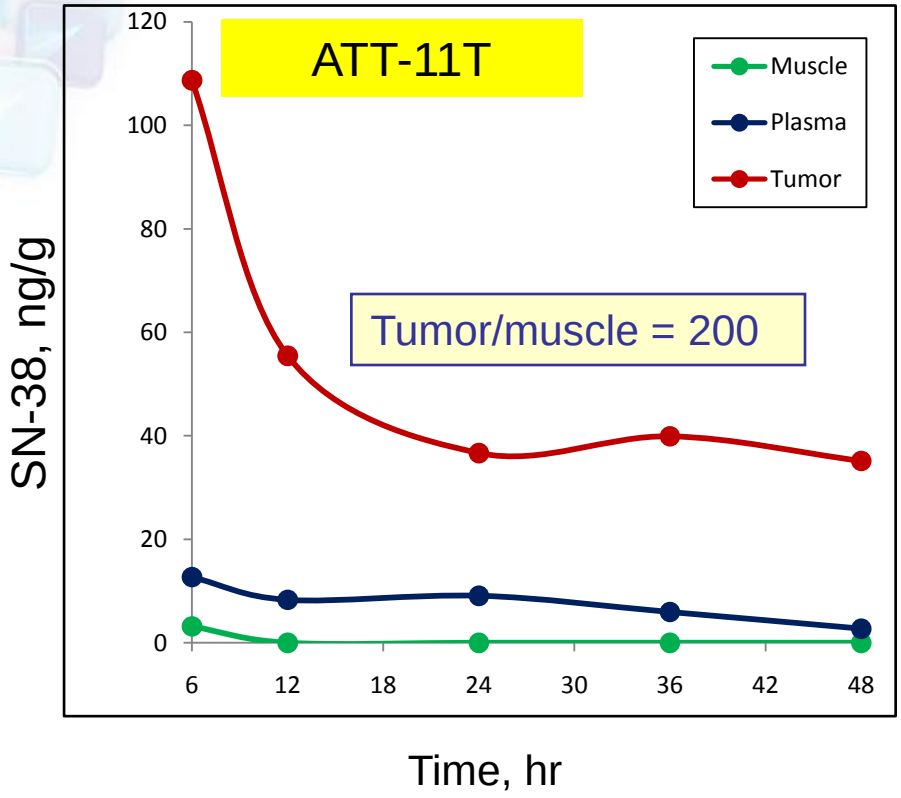
Tissue	AUC, ng/g*hr
Tumor	161,216
Plasma	93,441
Muscle	155,195

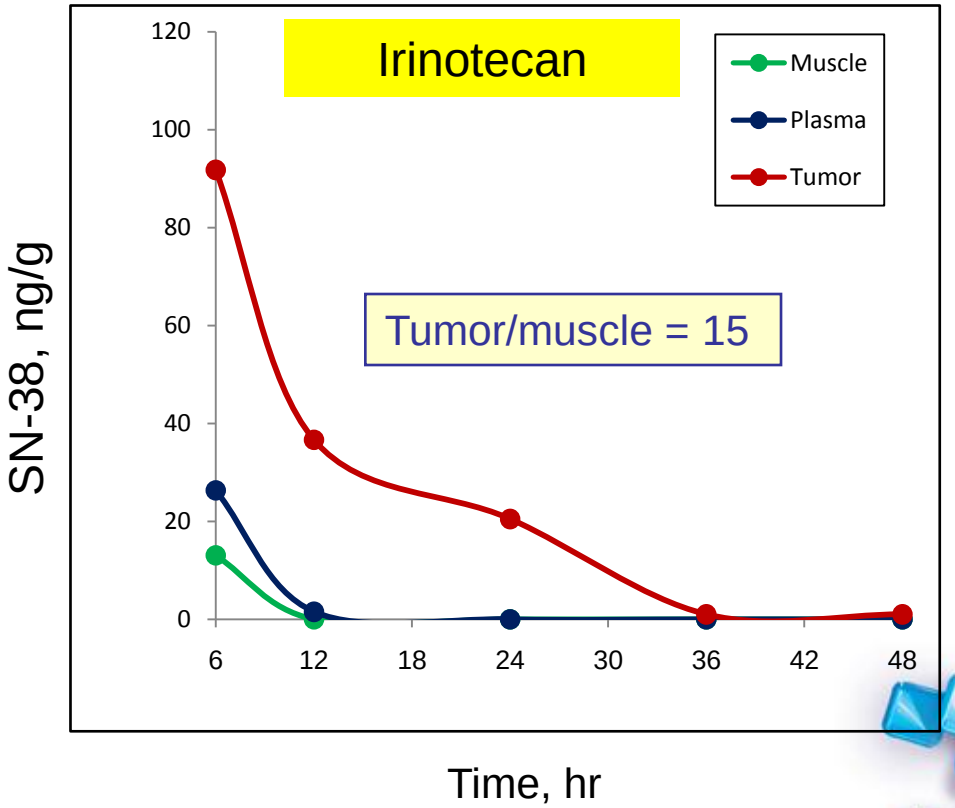
X9.4

Tissue	AUC, ng/g*hr
Tumor	17,119
Plasma	7,815
Muscle	23,518

ATT-11T Yields Higher and Selective Tumor Exposure to SN-38

Bio-distribution study in tumor-bearing mice





Tissue	AUC, ng/g*hr
Tumor	3,855
Plasma	403
Muscle	19.2

x3.34

x0.25

Tissue	AUC, ng/g*hr
Tumor	1,153
Plasma	172
Muscle	78

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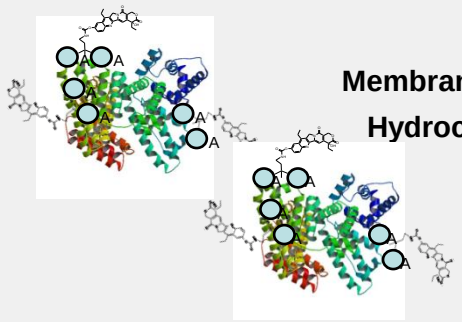
From Depot to Target

Drug released slowly from the depot and preferably activated at the tumor target tissue

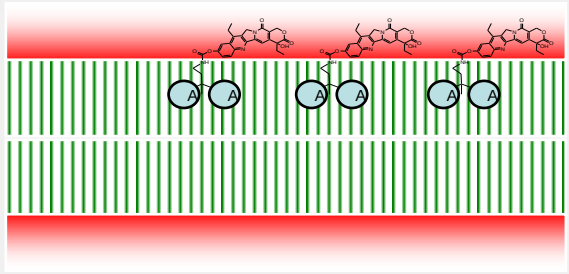
Depot



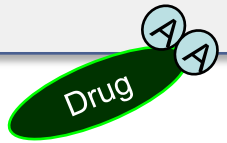
Membrane interface

Hydrocarbon core

Cytoplasm

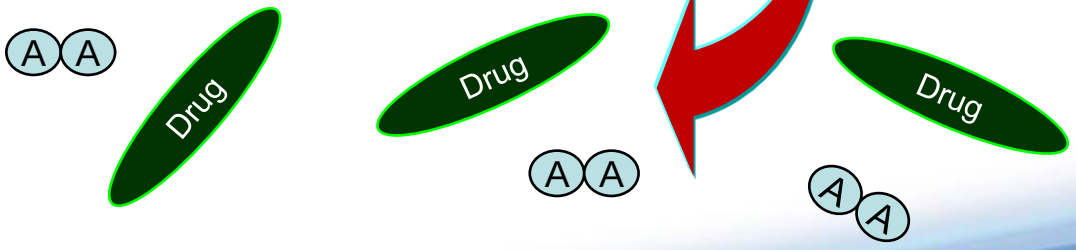


Fast, wide distribution of the pro-drug to organs / tissues upon administration, including binding to plasma proteins and anchoring to cell membranes.



At the tumor target tissue, ATT-11T is selectively cleaved enzymatically, and exposes the active cytotoxic moiety, thus enhancing the anti-cancer drug effect.

Target Tissue



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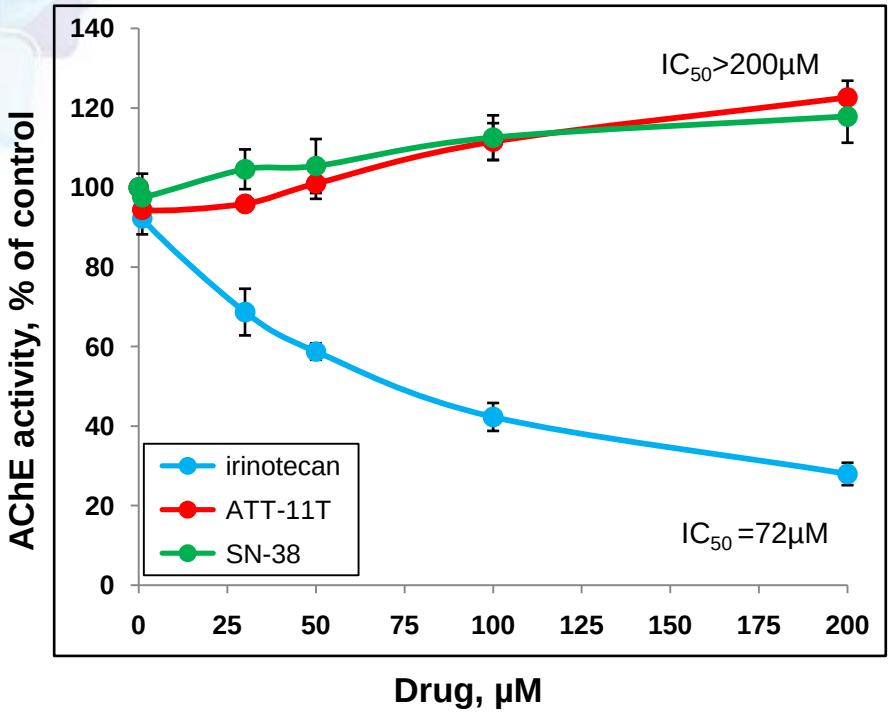
Safety

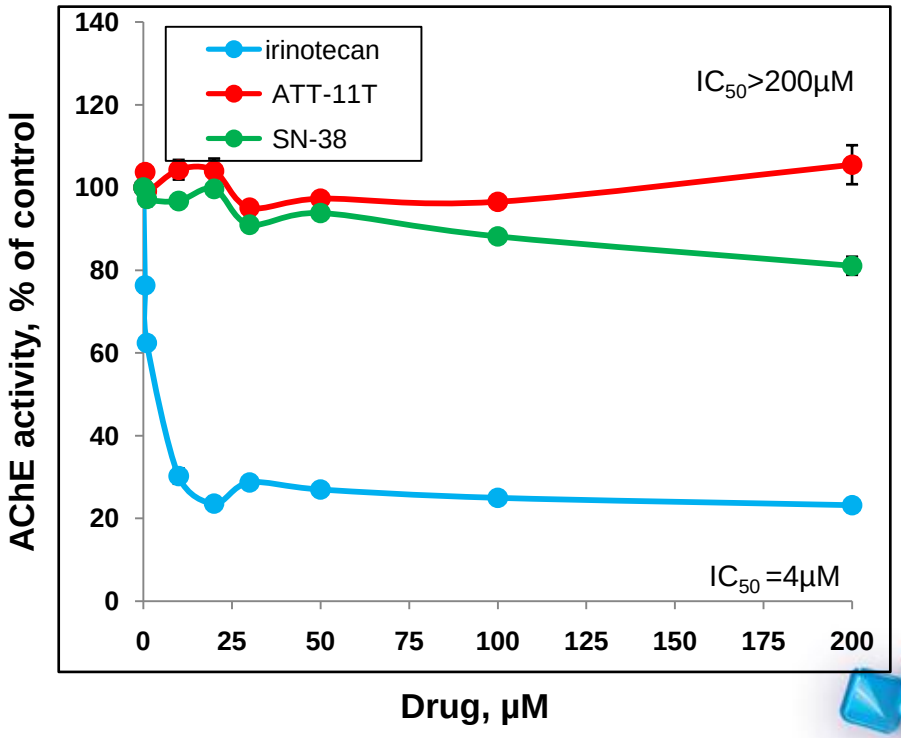
ATT-11T Does not Affect AChE Activity

in-vitro Study

Human Plasma



Rat Plasma



The cholinergic side effects often observed in patients treated with irinotecan are related to the inhibition of AChE

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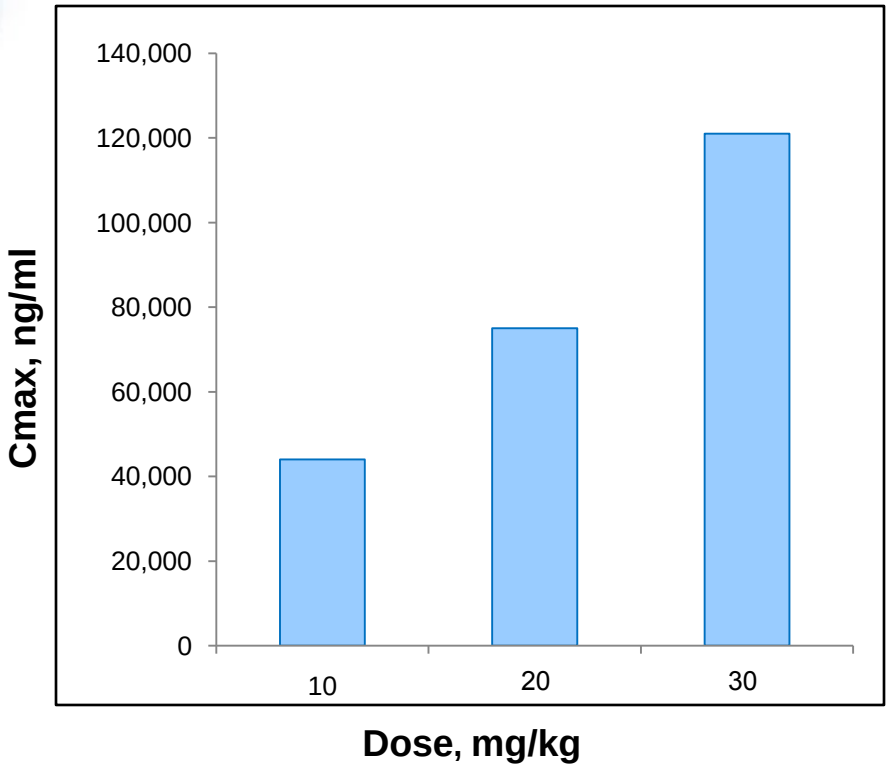
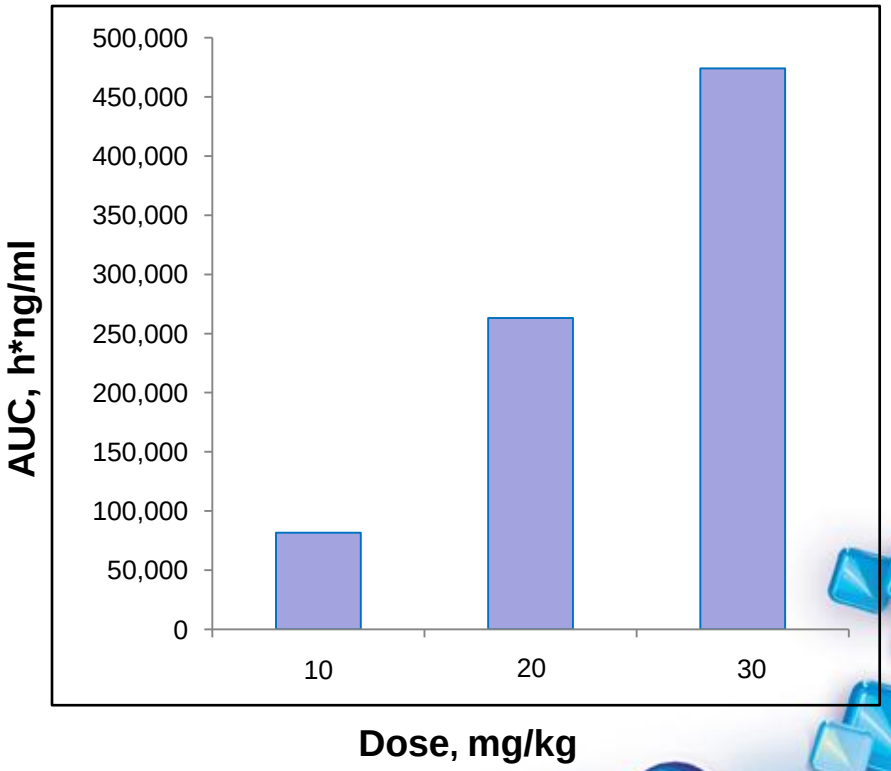
High Exposure to ATT-11T Without Adverse Events

Escalating Dose Following a Single i.v. Dose in Mini-pigs

Cmax



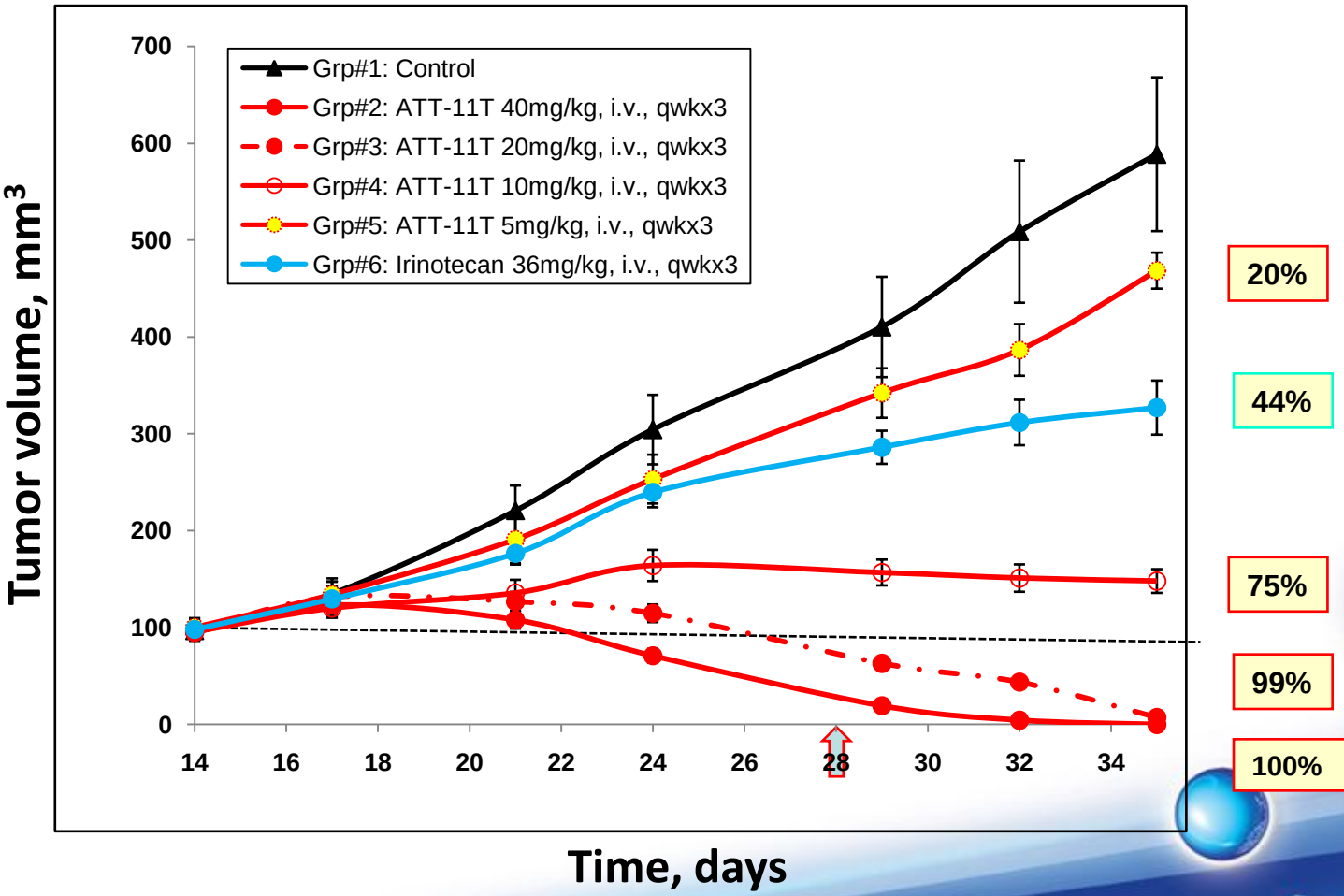
AUC



"In -life" response and cardiovascular toxicology was evaluated throughout the dosing. No overt effects were observed.

Efficacy

Colon Carcinoma Model (SW620):
Dose response of ATT-11T Administrated Once a Week

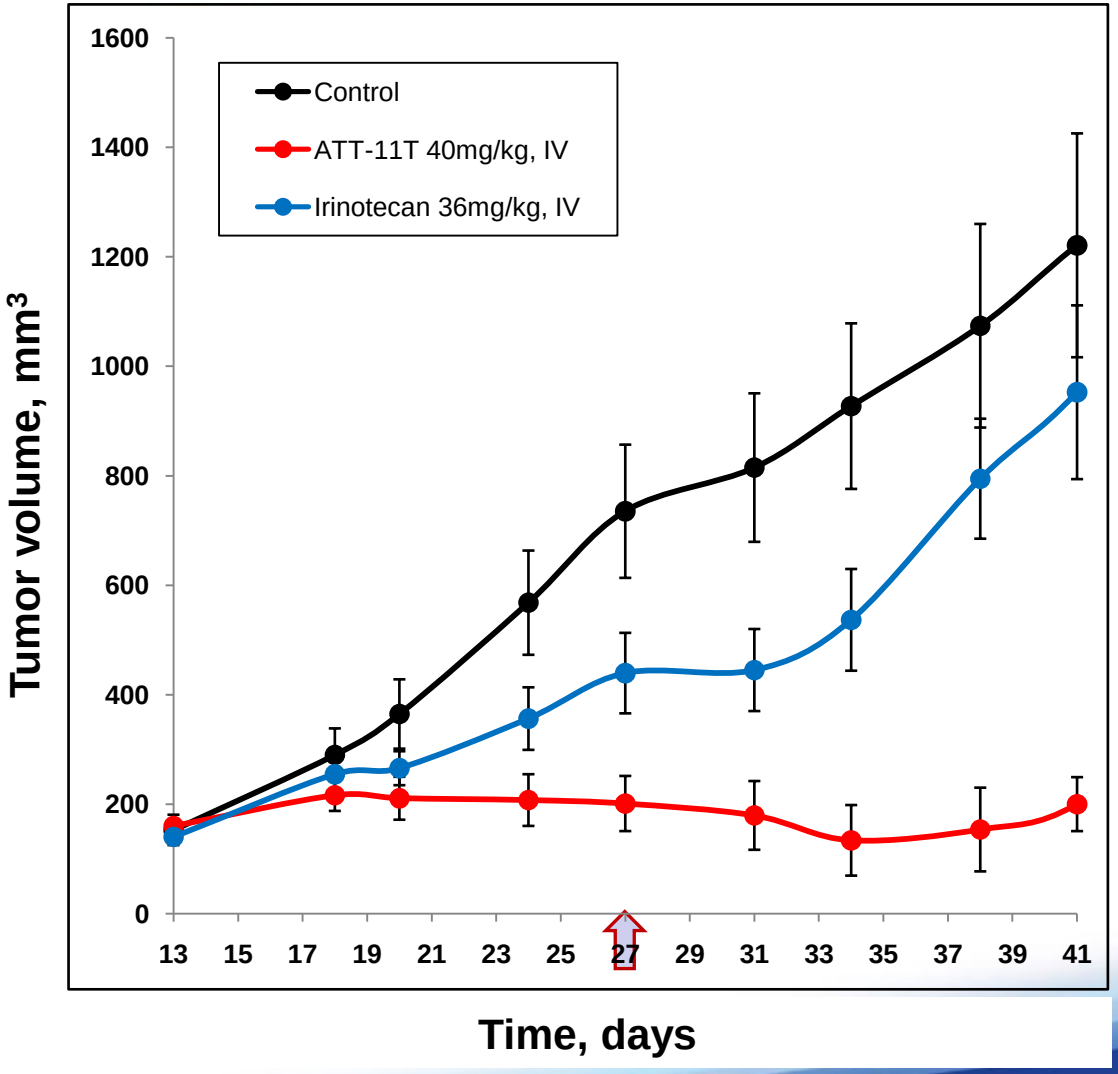


n=9-10 mice/group

⇧ End of Tx

No weight loss or other adverse effects observed

Superior Efficacy of ATT-11T Over Irinotecan in Tumor Growth Inhibition: Pancreatic Carcinoma MiaPaCa Model



n=8 mice/group

⇧ End of Tx

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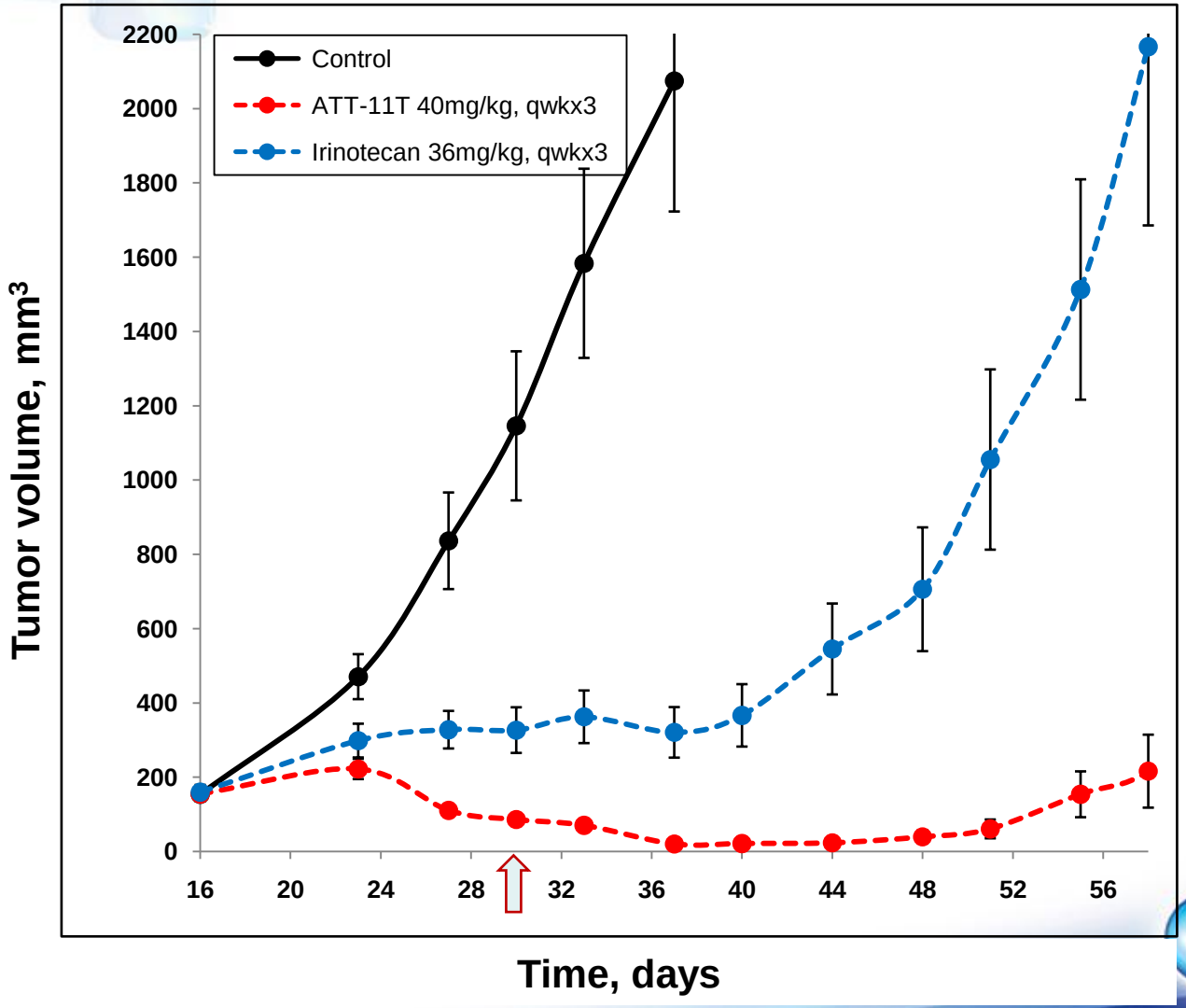
ATT-11T Demonstrates Superior Efficacy at Equimolar Doses Over Irinotecan in Small-Cell Lung Carcinoma Model



n=8-9 mice/group

⇧ End of Tx

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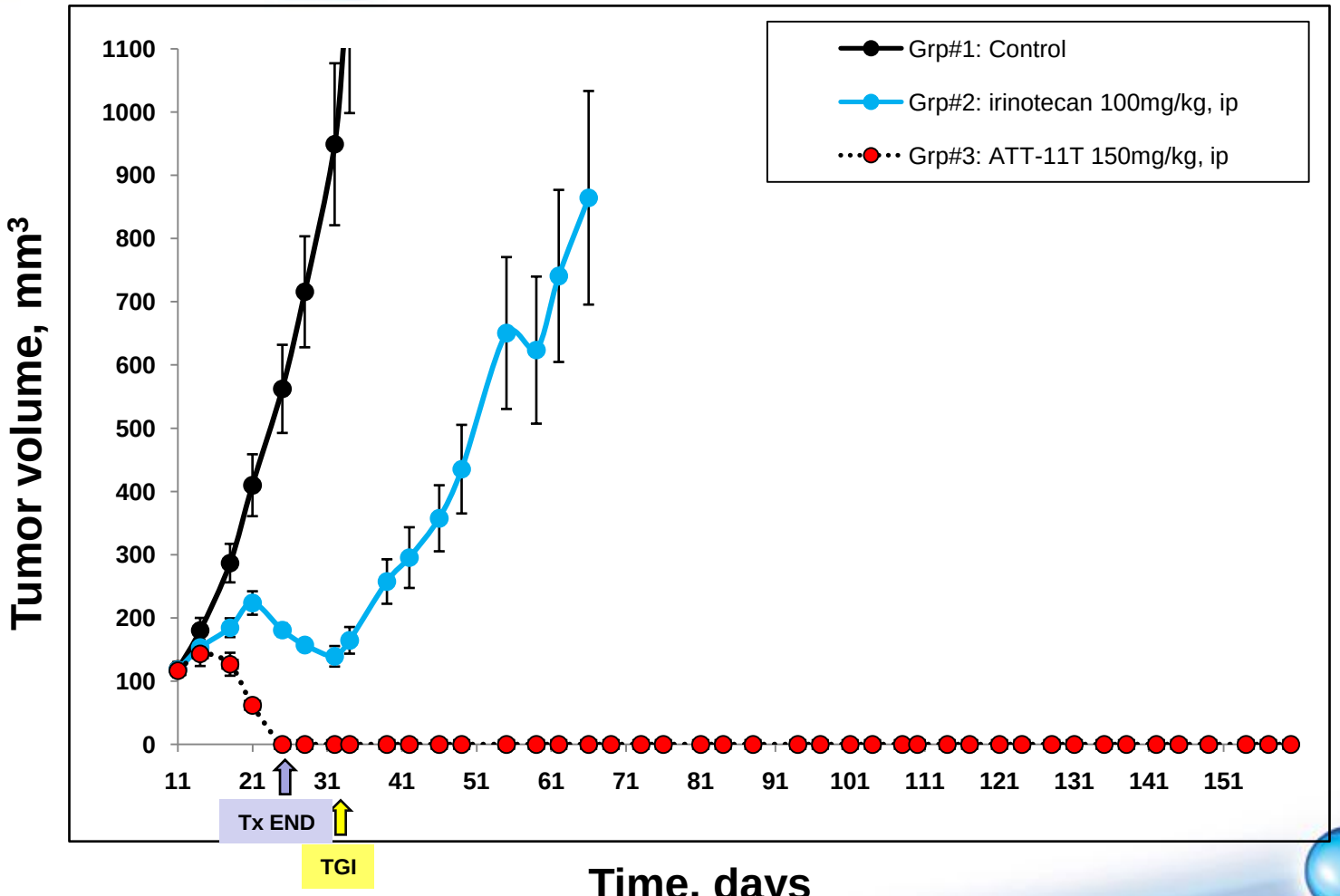
Anti-tumor Efficacy at Equimolar Doses of ATT-11T and Irinotecan in Various Human Xenograft Cancer Models

Tumor	Compound	Treatment	N° tumors	Anti-tumor effect (%Tumor/Control)	Anti-tumor effect
H-69: Small Cell Lung Carcinoma	ATT-11T	80mg/kg, q2wx2	9	93	Stasis
	Irinotecan	72mg/kg, q2wx2	9	67	
SW620: Colorectal Carcinoma	ATT-11T	40mg/kg, qwx3	10	100	Regression
	Irinotecan	36mg/kg, qwx3	10	44	
MiaPaCa: Pancreatic Carcinoma	ATT-11T	40mg/kg, qwx3	8	86	Regression
	Irinotecan	36mg/kg, qwx3	8	42	
H-82: Small Cell Lung Carcinoma	ATT-11T	20mg/kg, qwx3	9	80	Stasis
	Irinotecan	18mg/kg, qwx3	8	57	
OVCAR-3: Ovarian Carcinoma	ATT-11T	20mg/kg, qwx3	10	98	Regression
	Irinotecan	18mg/kg, qwx3	10	77	
HCT-116: Colorectal Carcinoma	ATT-11T	10mg/kg, qwx3	8	79	Stasis
	Irinotecan	9mg/kg, qwx3	8	66	
A375: Melanoma	ATT-11T	5mg/kg, q3dx9	10	100	Regression
	Irinotecan	75mg/kg, qwx3	9	91	

ATT-11T Demonstrates Superior Efficacy at MTD over Irinotecan in SW620 Xenograft Model



n=8-9 mice/group

⇧ End of Tx

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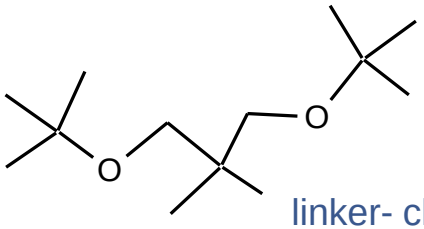
Intellectual Property

- Patent coverage:
  - Application covers compounds:



linker- cleavage site-drug

- Applications and status:

US patent No. 8,530,444 filed June 1, 2010 and granted on Sep. 10, 2013. A divisional patent No. 8,916,537 on the method of treating cancer was granted on December 23, 2014. An additional divisional application on the method of treating was allowed and will be granted soon.

PCT (international) patent application (filed: 1-June-2011; Priority 1-June-2010)

Israel, Japan, Europe, Canada, China (granted), India (filed: 1-December-2012)

- Additional patent applications underway for process and formulation

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ATT-11T: Value Proposition

Value proposition	ATT-11T	Irinotecan	Irinotecan new formulations	SN-38 conjugations
Therapeutic window	Wider than irinotecan due to selective activation in target tissue	Pro-drug but severe adverse effects	Improved efficacy mainly due to EPR effect. Toxicity similar to irinotecan.	Very potent. Narrow therapeutic window. Toxicity related to SN-38
Molecule size	Small molecule pro-drug. Entry into tumor core and micrometastases	Small molecule pro-drug	Macromolecules	Macromolecules
Mechanism of action	Inactive depot and selective activation in tumor target tissue	Soluble pro-drug of SN-38	EPR effect. Local tumor concentration	Pro-drug of to increase solubilization
Adverse effects	Improved safety profile in comparison with irinotecan. Substantial reduction of diarrhea	Severe diarrhea. Myelosuppression	Same as irinotecan	Narrow therapeutic window
AChE inhibition /Cholinergic effect	Lack of cholinergic effect due to rational drug design	AChE inhibition, cholinergic side effect	Same as irinotecan	No expected AChE inhibition

ATT-11T: Value Proposition

- ATT-11T small molecule with accessibility to tumor core and micrometastases while competitors mainly macromolecules
- Inactive depot formation and sustained, selective activation at target tissue, while leading competitors based on long circulation in the blood
- Structural modifications of ATT-11T carrier molecule avoids toxic limitation of irinotecan
- Less complex CMC compared to the macromolecule

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ATT-11T: Summary

Innovation

Unique mechanism of action

- Inactive pro-drug depot
- Selective activation at the tumor target tissue
- Extended PK
- Improved therapeutic window

- NCE & new IP (valid till 2030)

Feasibility

Lead compound in advanced preclinical assessment

- Superior anti-tumor activity
- Extended $t_{1/2}$ demonstrated in rodent and non-rodent species
- Bio-distribution studies support inactive depot formation and selective activation at the tumor target tissue
- Preliminary toxicology study indicates favorable safety profile
- CMC support formal toxicology and phase I studies

Market

- **Large market opportunity ($1-1.7Bn)**

- **High unmet need**
  Irinotecan is a very potent cytotoxic drug - but critically limited:
  - Short half-life
  - High toxicity

  ⇒suboptimal efficacy; severe side effects

Potential for effect in several solid tumors such as CRC, Ovarian & Lung carcinomas

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