



FULCRUM SP  
PHARMA

***Smart Nano Capsules for Targeted Anti Cancer Drug Delivery***

**Fulcrum SP Pharma's presentation**

# Fulcrum SP Pharma Ltd.

Founded	2007, Subsidiary of Fulcrum SP Ltd.
Technology	Smart nano capsules for an active, targeted, drug delivery
Mission	To develop new anti-cancer drug formulations
Proof of Concept	In-vivo experiments: SP1/PTX (Paclitaxel) complex SP1/Dox (Doxorubicin) complex
Intellectual property	Exclusive, worldwide, unlimited license for all pharmaceutical applications of the SP1 Protein from the HUJI.

# SP1 advantages for drug delivery

- **SP1 encapsulates anti cancer drugs** (Doxorubicin, paclitaxel etc.)
- **Controlled release mechanism in the tumor:**
  - protection of healthy tissues from unwanted effects.
  - Exclusive drug release in prostate cancer metastasis, to be demonstrated:
- **Drug circulation time is prolonged.**
- **Targeting:**
  - Passive retention in tumors or inflamed tissues
  - Active targeting to angiogenic blood vessels, using the RGD peptide
  - Active targeting using tumor specific peptide , to be demonstrated:

# Background

- Conventional anti-cancer therapy
  - Cytotoxics (“Chemotherapy”) – the most common anti-cancer drug class
  - Accounting for 56% of anti-cancer drugs
  - Used in all stages of cancer treatment
- The Problem:
  - Non-Selective – targets both malignant and non malignant cells
  - Poor Solubility - requires the use of toxic solvents
  - Unfavorable Pharmacokinetics
  - Poor Biodistribution
  - Narrow Therapeutic Window – severe side effects
  - Limited treatment possibilities, limited efficacy

**An unmet need for drugs with improved tumor selectivity!**

# New Drug Delivery Mechanism

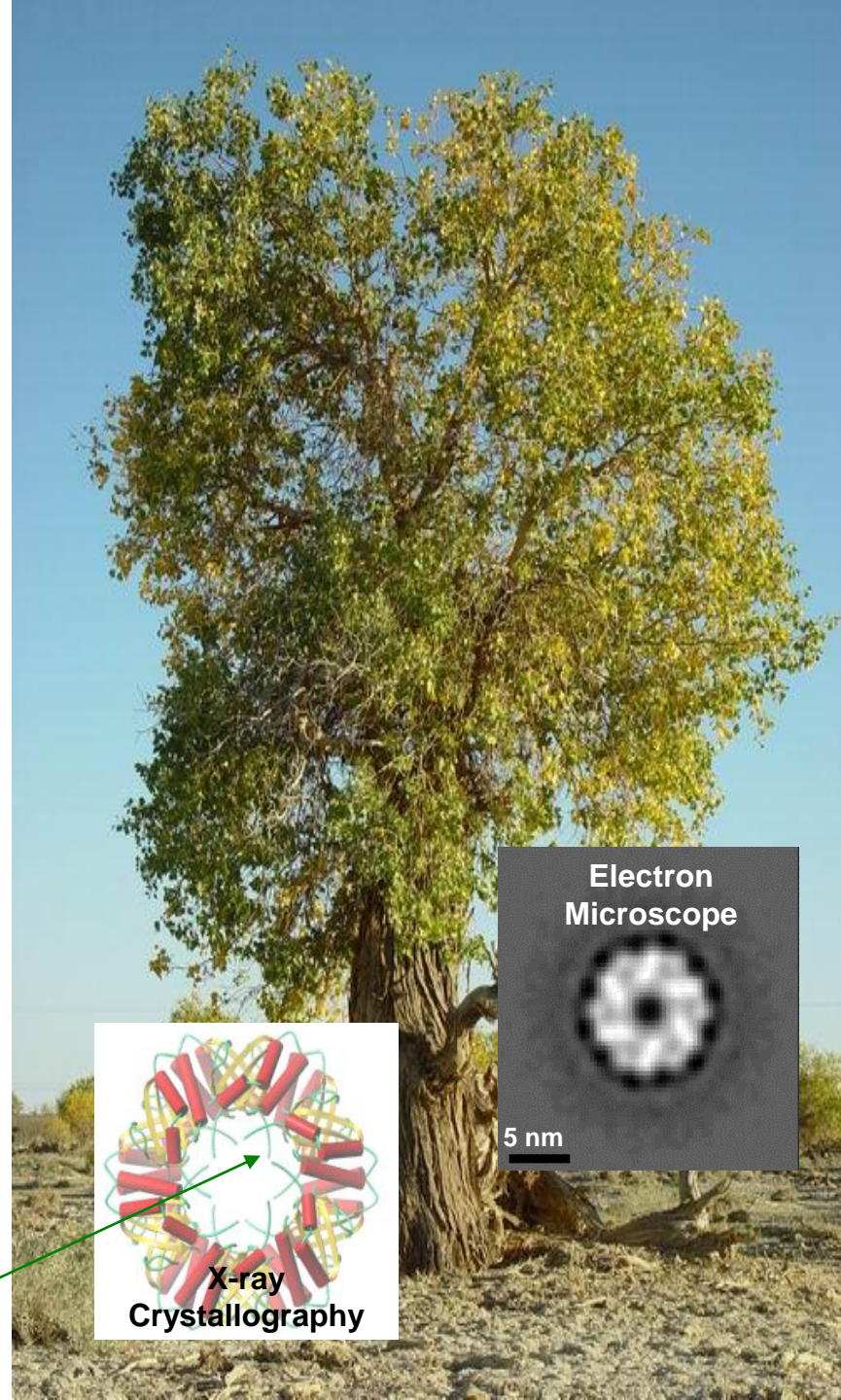
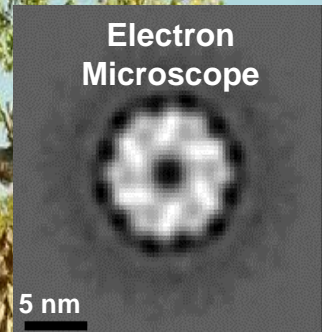
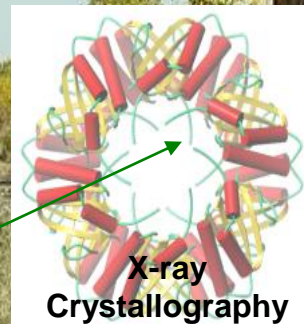
- Increased focus on targeted delivery:
  - Site-specific drug activation / release
  - Drug is inactive in bloodstream and normal tissues
    - minimal exposure of healthy organs to active ingredient
  - Released/ become active in tumor due to tumor-specific conditions
- Ultimate criteria for effective drug delivery:
  - Control & optimize drug accumulation in site of action
  - Localize release in target site
  - Rapidly clear non-targeted fraction
  - Non-toxic, non-immunogenic solvent
- Fusion with bio-active peptides
- Molecular cage for nano particles

# Fulcrum SP's technology

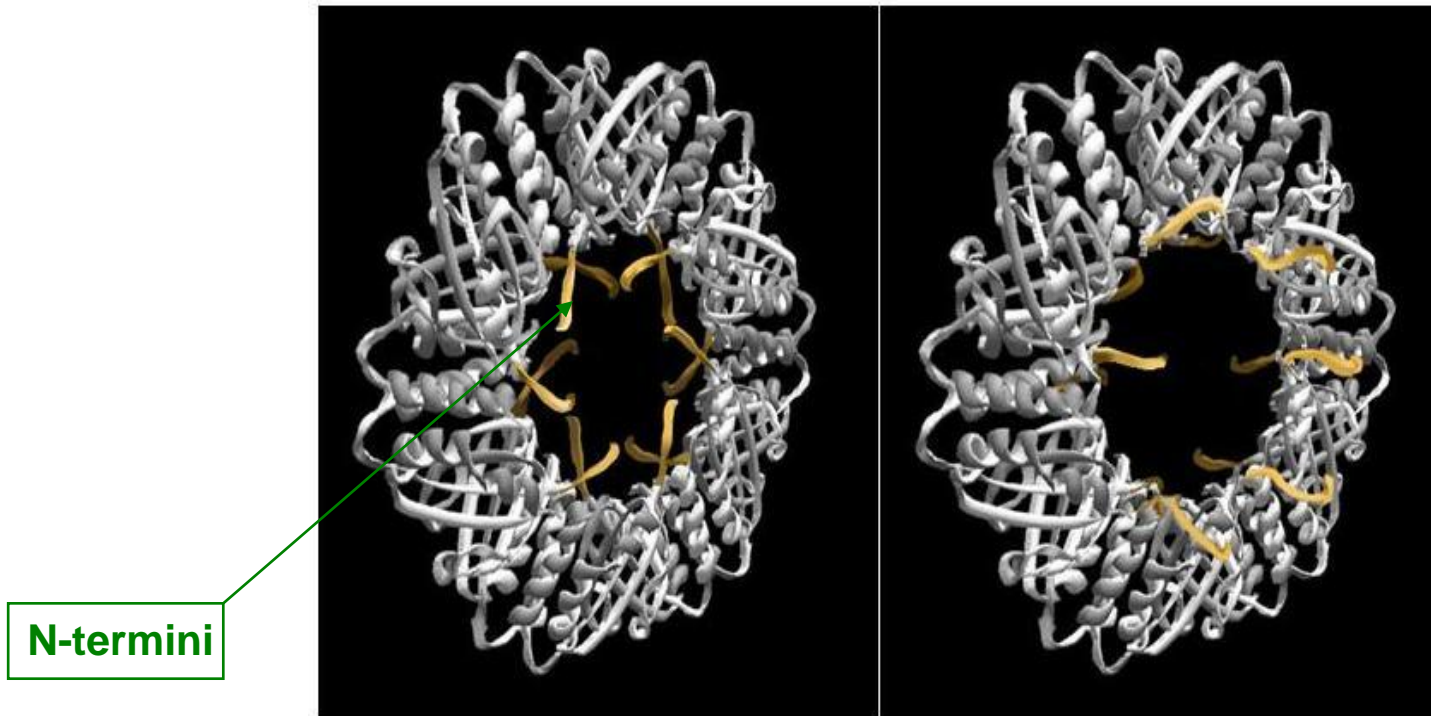
## The SP1 protein complex

- The SP1, was originally produced from aspen trees.
- Exceptionally resistant to extreme conditions, **Inexpensive to produce.**
- The SP1 physical properties can be easily manipulated by genetic engineering.
- The N-termini of the SP1 12 sub-units are exposed to the central cavity.
- Peptides fused to the N-termini enable binding the SP1 to other materials,
- **Vast potential medical applications:**
  - Drug Carriers – anti-cancer targeted drug therapy
  - Treatment of Rheumatoid Arthritis
  - CNS (BBB)
  - Inflammatory Diseases
  - Molecular cage of nanoparticles

**N-termini**



# Presentation of specific peptide, on the N-termini, 6 on each side of the ring



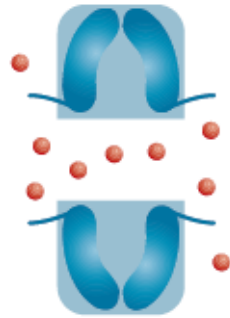
**The SP1 Nano-carrier Platform**

# The SP1 Technology

Drug Encapsulation & Controlled Release:



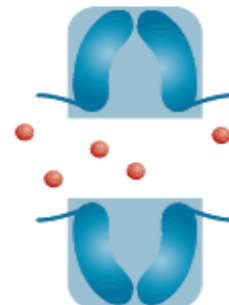
Start point



Drug encapsulation



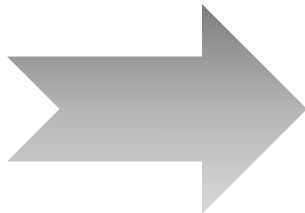
IV injection of encapsulated drug



Controlled release in the target area (under reducing conditions)

# Anti-Cancer Application of the SP-1

- Smart Nano-Capsules for existing anti-cancer drugs:
  - Taxanes
  - Adriamycin
- Allow:
  - Water-based formulations of water-insoluble cytotoxics
  - Passive tumor targeting
  - Tumor specific drug release
  - Slow clearance
  - Safety



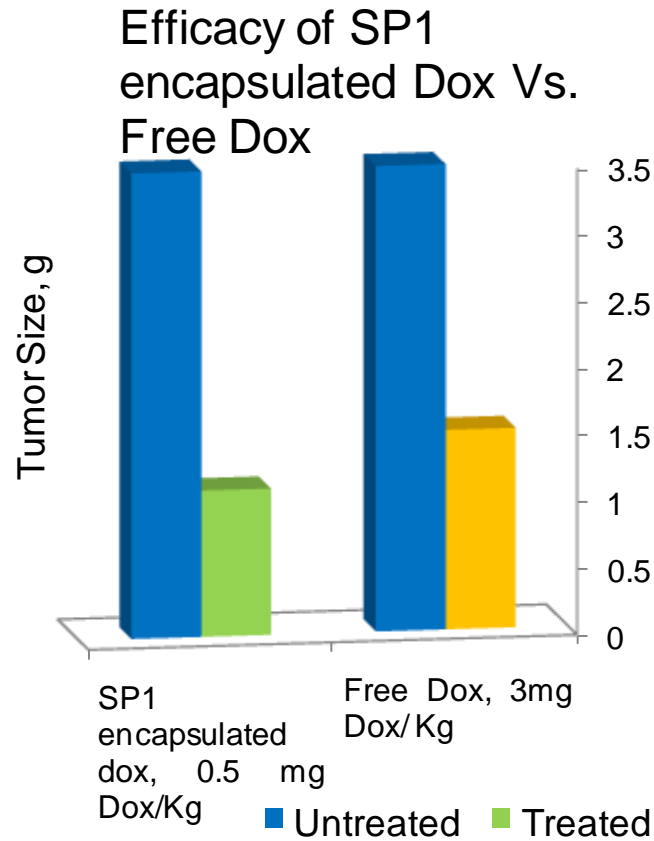
- Increase therapeutic effect of anti-cancer drugs
- Increase maximum tolerated dose
- Extend therapeutic window
- Minimize side effects

# SP-1's Proof of Concept

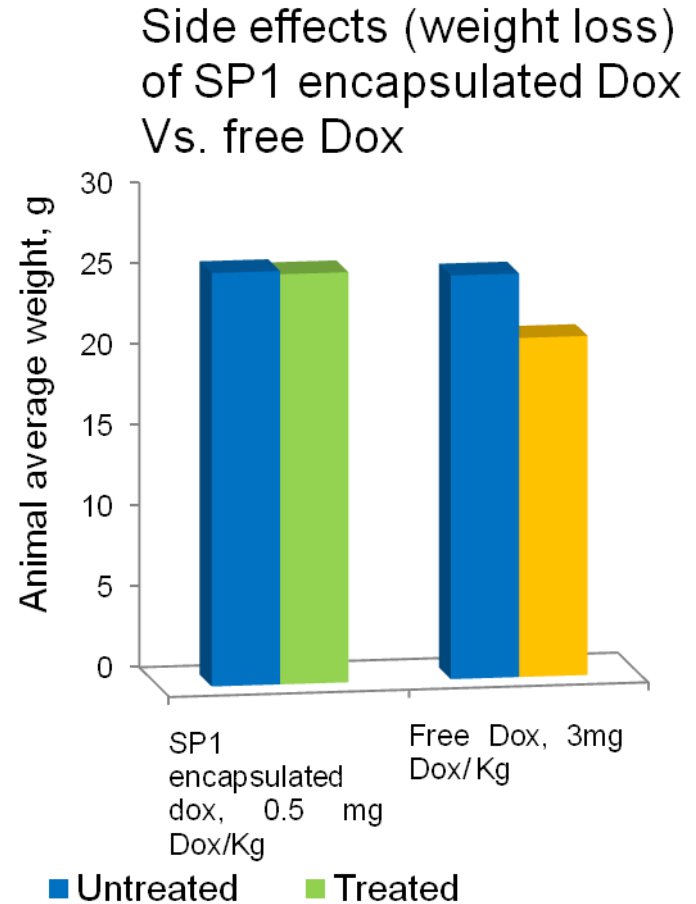
- SP-1 is safe:
  - Normal mice injected with a standalone SP-1 (40mg/Kg) for 2 months:
    - Induced no immunogenic response
    - No liver pathology
  - Suggesting the SP-1, for itself, is inert.
- The effect of SP-1 encapsulated Doxorubicin:
  - Mice were transplanted with a B16F10 Murine Melanoma
  - **Group A** – treated with SP-1 protein encapsulated Doxorubicin (**0.5 mg Dox/Kg**)
  - Group B (Control) – treated with free Doxorubicin (3mg Dox/Kg)

The group treated with SP1 encapsulated Dox exhibited a significantly higher tumor response **despite a six time smaller dose!!!**

# SP-1's Proof of Concept



**Increased Efficacy**



**Negligible Side Effects**

# SP-1's Proof of Concept

Human colon cancer grafted to nude mice



PBS treated mouse, control



SP1/Dox treated mouse

# Nano Carrier Comparison

Parameter		Fulcrum's SP-1 Protein	HSA Nanocarriers (e.g. Abraxane)	Liposome Carriers (e.g. Doxil)
Molecule Dimensions		11nm	150nm	100nm
In- vivo characteristics	Controlled release	Yes	No	No
	Antibody Production	No	?	No
	Clearance from bloodstream	Slow	Slow	Fast
In -vitro characteristics	Stability	High	Poor	Poor
	Size variation	No	High	High
Ability to modify nano-particle	Physical properties alternation	Easy	Hard	Hard
	Display of tumor specific molecules	Yes	No	No
Cost		Low	High	High
Accumulation in tumor		High	High	High
Antineoplastic agent side effects		Not expected	Yes	Yes
Tumor resistance in case of relapse		Low	High	High

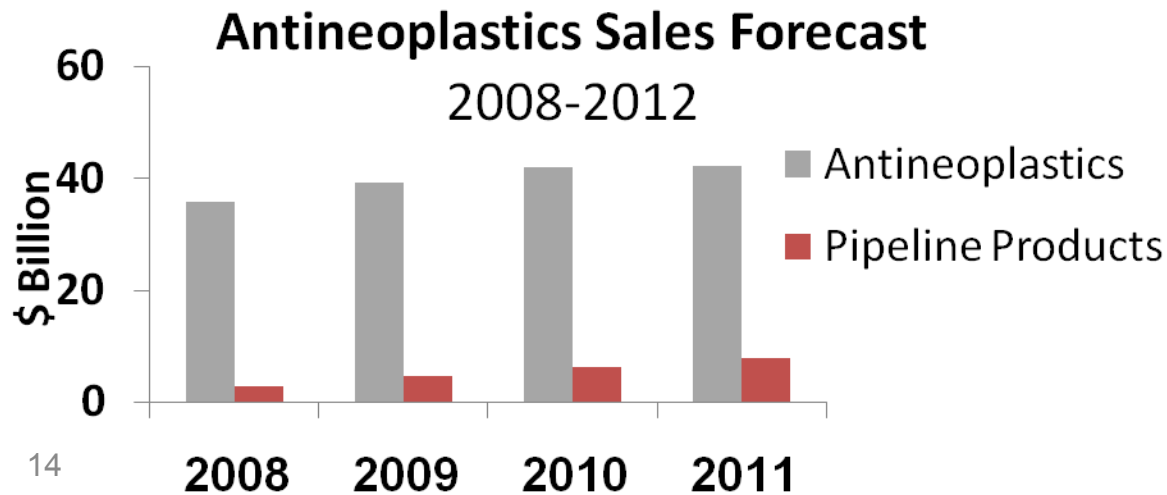
# The Market

- 1.4M new cancer cases diagnosed in the US in 2007
- Approximately 560K (38.7%) die.

## Global cancer market and antineoplastic drug Class, 2003-2006

	Sales (\$M)				1H	Growth	Mkt. Share
	2003	2004	2005	2006	2007	05-06	2006
<b>Antineoplastics</b>	14,127	17,819	21,869	27,218	15,730	24.5%	55.9%
<b>Total</b>	29,068	35,166	41,287	48,663	27,126	17.9%	100.0%

Source: IMS Health; \*1H – Jan to June (6 months)



**Antineoplastics' sales expect a 7.4% CAGR in 2008-2011, Pipeline products expect 46% CAGR!**

# The Market - R&D Pipeline

## Key pipeline oncology drugs using nanotechnology, 2007

Product	Company	Technology	Indication	Stage
Doxil/Caelyx	J&J	Stealth	Breast cancer	Phase III
Doxorubicin	BioAlliance	Transdrug	Liver cancer, HCC	Phase II
Panzem NCD	EntreMed	NanoCrystal	Brain tumors	Phase II
Paclitaxel	BioAlliance	Transdrug	Ovarian, breast and lung cancers	preclinical
Irinotecan	BioAlliance	Transdrug	Colon and rectal cancer	n/a

The SP-1 Protein nanotechnology is aimed at obtaining a substantial market share of the rapidly growing targeted cancer therapy market.

# Strategy

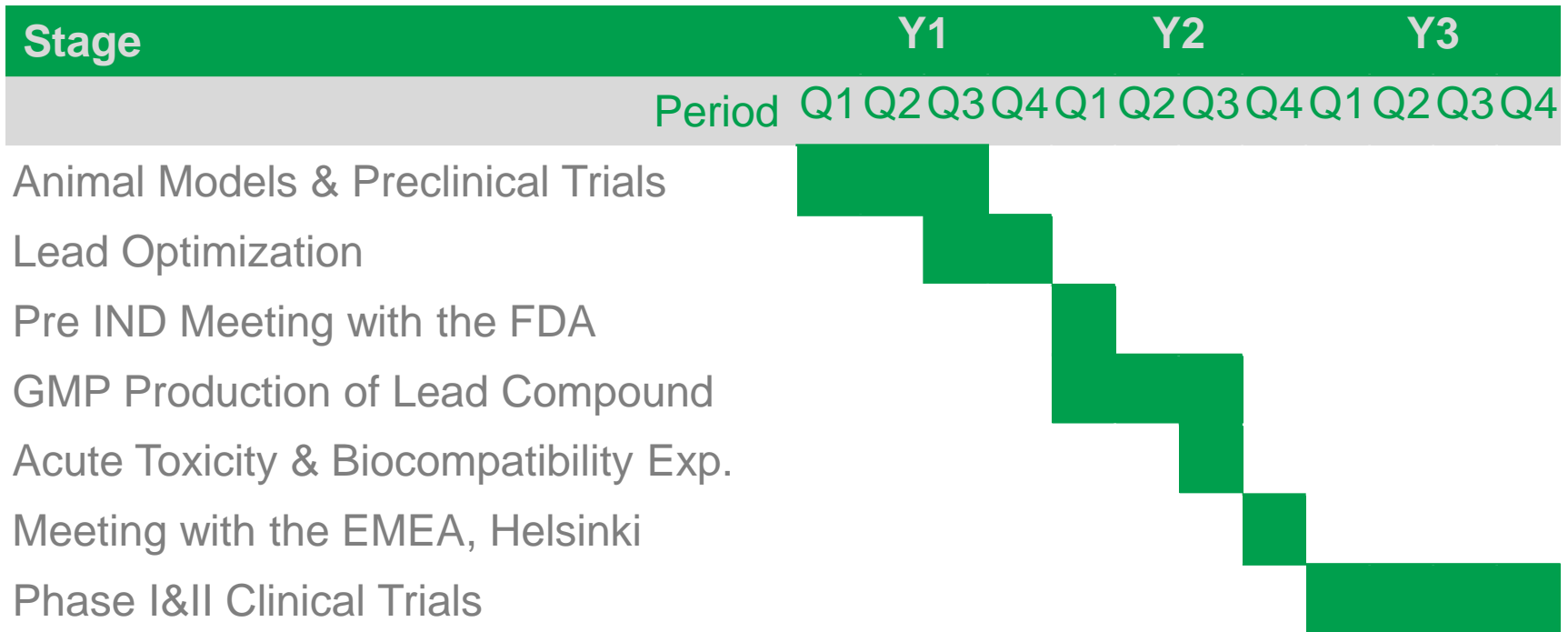
## Targeting a broad and diversified application basis

- Proof of Concept:
  - Initial implementation of the SP1 nanocarrier platform
  - Focusing a single, well established agent (Doxorubicin)
  - Gaining regulatory facilitation –
    - Orphan drug designation
    - Exploratory IND
- Extend original indication
- Expedite growth through aggressive, parallel, out-license deals

## Why Cancer?

- Strongest unmet need
- Shorter TTM
- Best manifestation of SP1 unique qualities

# R&D Roadmap



## Current Status

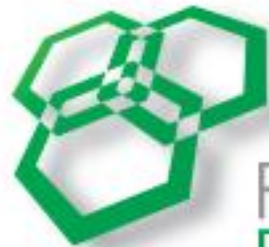
- Preliminary Proof of Concept in animals – Obtained
- Ongoing (independent clinical CRO) :
  - Biodistribution experiment
  - Toxicity & side effects
  - Efficacy experiments – 60 mice

# Intellectual Property

Pub No, Assignee & Priority date	Title
<p>Pub. No.: WO/2002/070647            International Application No. PCT/IL2002/000174            Assignee: Yissum            Publication Date: 12.09.2002            International Filing Date: 05.03.2002</p>	<p><b>DENATURAT STABLE AND/OR PROTEASE RESISTANT, CHAPERONE-LIKE OLIGOMERIC PROTEINS, POLYNUCLEOTIDES ENCODING SAME AND THEIR USES:</b>            Composition of matter of the SP1 protein &amp; its DNA sequence as well as of similar proteins with up to 65% identity with poplar SP1; SP1 protein characterization.</p>
<p>Pub. No.: WO/2004/022697            International Application No.: PCT/IL2003/000723            Assignees: Yissum &amp; Fulcrum SP Ltd            Publication Date: 18.03.2004            International Filing Date: 02.09.2003</p>	<p><b>DENATURAT STABLE AND/OR PROTEASE RESISTANT, CHAPERONE-LIKE OLIGOMERIC PROTEINS,</b>            WO/2002/070647 CIP, Method of SP1 production by heat treatment and protease treatment; further SP1 protein characterization.</p>
<p>Pub. No.: WO/2007/007325            International Application No.: PCT/IL2006/000795            Assignee : Yissum &amp; Fulcrum SP Ltd.            Publication Date: 18.01.2007            International Filing Date:09.07.2006</p>	<p><b>SP1 POLYPEPTIDES, MODIFIED SP1 POLYPEPTIDES AND USES THEREOF</b>            SP1 and modified SP1 variant polypeptides capable of forming reversible molecular associations with substances, compositions-of-matter comprising same, and uses thereof are provided.</p>

# Management & Scientific Advisors

- **Nimrod Litvak**, Chairman and founder. Entrepreneur in the field of bio-tech and nano-tech. Extensive knowledge and experience in composite materials applications for the aviation and the marine markets. Businessman, pilot and skipper. Founder and Director of Bio-Group Technologies Ltd. Economist, graduated of the Hebrew University.
- **Prof. Oded Shoseyov**, Scientific advisor and founder. Professor in the Faculty of Agriculture at the Hebrew University, scientific consultant to several biotechnology companies. Scientific Founder of Nano Bio Pharma Ltd. Scientific Founder of CBD-Technologies Ltd. Prof. Shoseyov holds more than 16 biotechnology-related patents.
- **Prof. Arie Altman**, Scientific advisor and founder. Chair, the Institute of Plant Sciences and Genetics in Agriculture, The Hebrew University of Jerusalem. Chairman, Scientific Founder of Fulcrum SP Ltd.
- **Dr. Amnon Wolf**, CTO and founder. More than 15 years of experience in the biotechnology industry includes management of projects in the areas of drug discovery and high throughput screening of chemical libraries (Peptor, Ltd). graduated of the Weizmann Institute (1990) and Post Doctorate fellow at UC Berkeley.
- **Arie Reichman**, CPA. CFO and Founder. C.P.A (Israel), formerly CFO and consultant of several bio-tech, high growth companies, holds degrees in economics and accounting from the Hebrew University.



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**Thank you!**

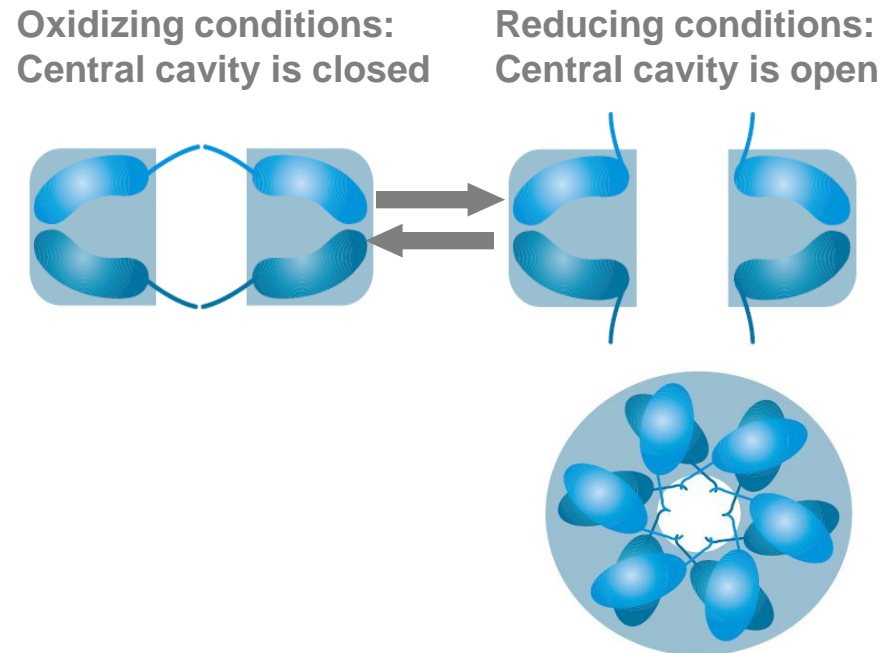


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## **Scientific Index**

# SP1 Variant Designed for Redox-Dependent Drug release

- Oxidizing conditions:
  - Blood stream, heart, and other healthy organs.
- Reducing conditions
  - In a variety of human malignancies.
- A cysteine residue was inserted in the N-terminal region of SP1
  - Forms disulfide bonds between neighboring subunits
  - Creates a molecular lid over the central cavity
  - “Locking” into place the encapsulated drug



# Animal Experiments: Immuno-blot Analysis

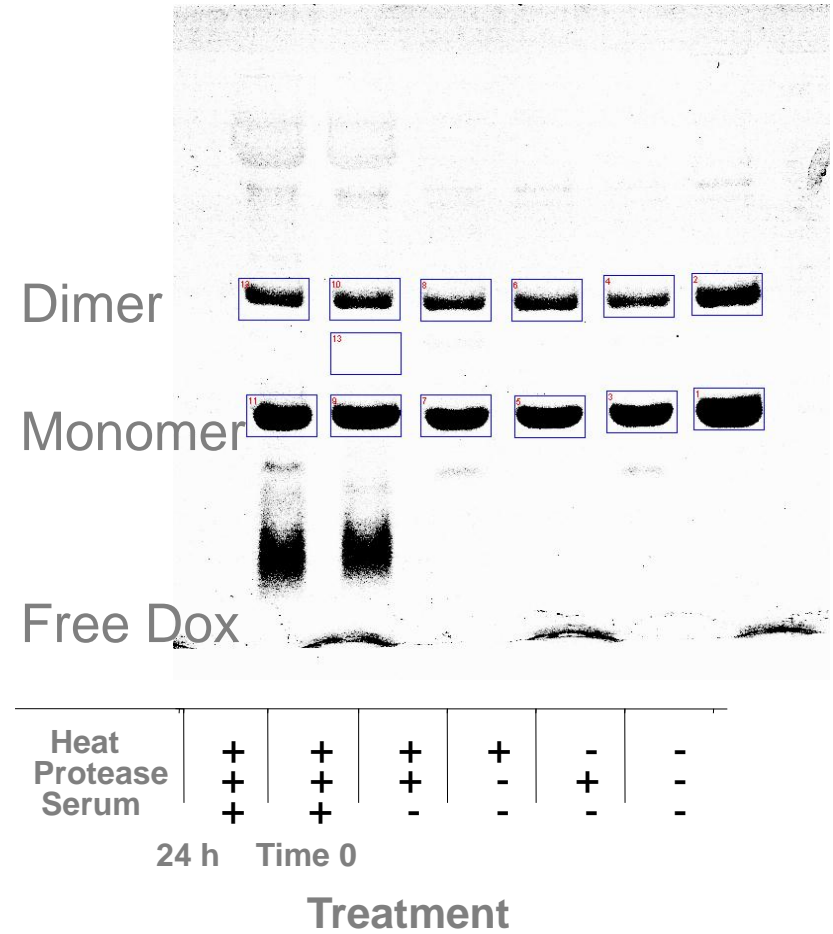
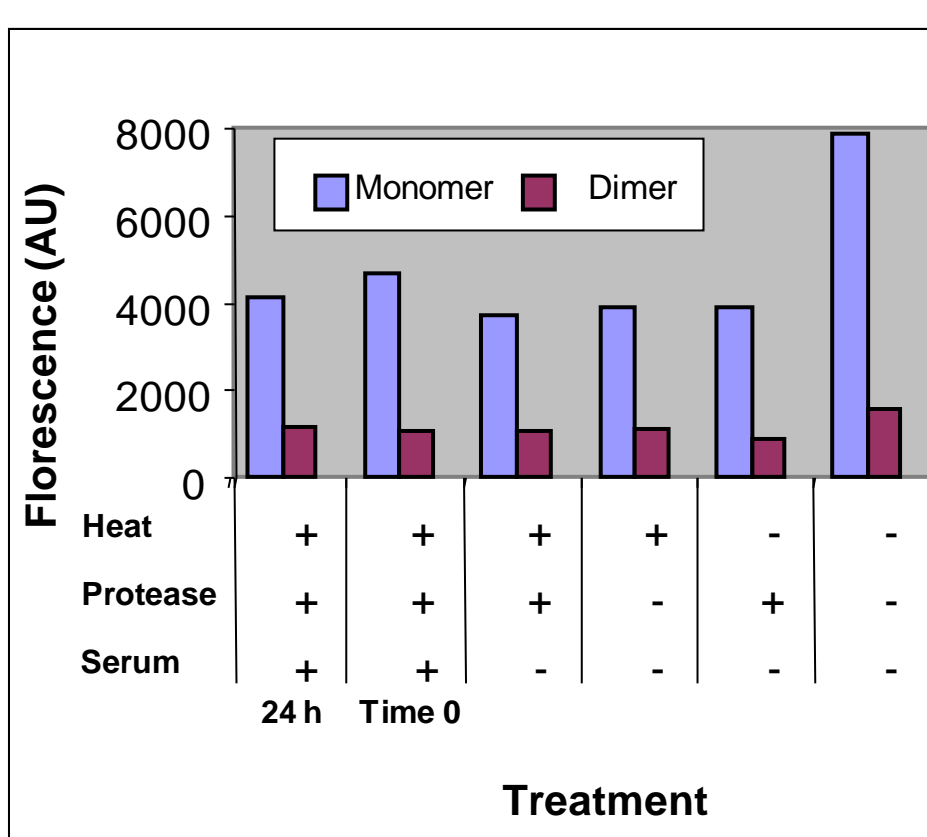
- SP1 slowly clears from the blood stream & accumulated in the tumor
- Tumor:
  - About 2-5% of injected SP1 is contained in the tumor, 24 hrs post injection.



- Serum:
  - About 3-15% of injected SP1 remains in circulation 24 h post injection, In contrast with free Doxorubicin which readily clears from circulation (literature).

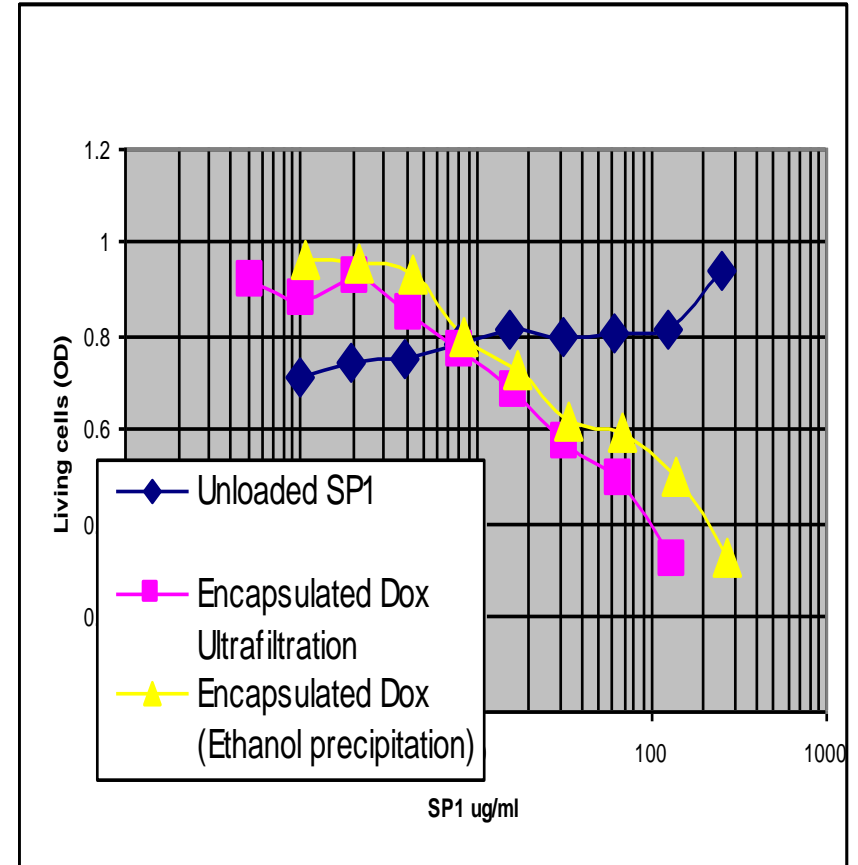
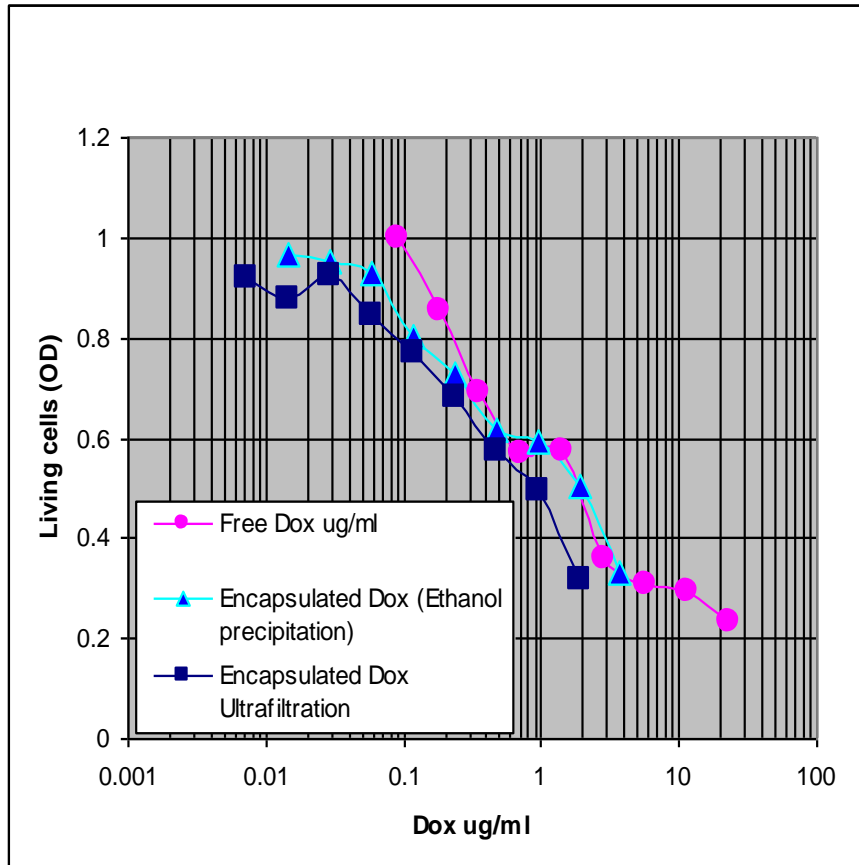


# Resistance to Protease & Heat Treatments



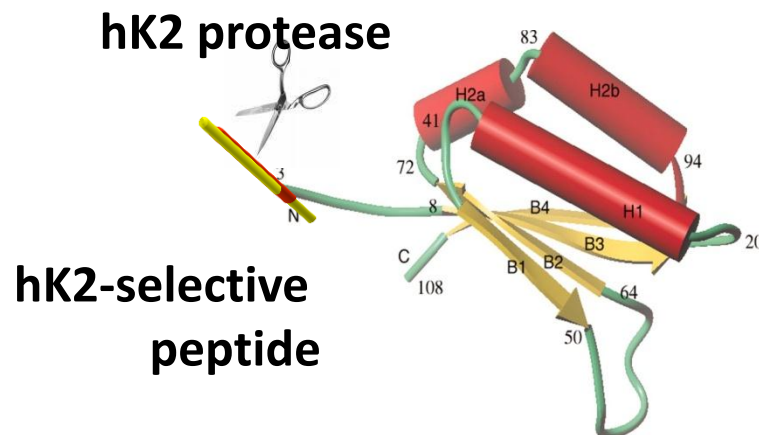
# SP1 Cytotoxicity Assay

SP1-DOX is biologically active as much as free DOX



# Prostate Specific Drug Release

- The prostate-specific proteases hK2 and PSA\* are serine proteases that are produced in most prostate cancer sites. Both enzymes are proteolytically active in the extracellular fluid of prostate cancer, while they are inactive in the bloodstream.
- A highly selective and efficient peptide substrate for each enzymes will be fused with SP1 N-Terminus.
- In prostate tumors the N-termini will be cleaved inducing drug release in the prostate tumor.



# Pipeline: SP1 variant binds gold nano-particles

