

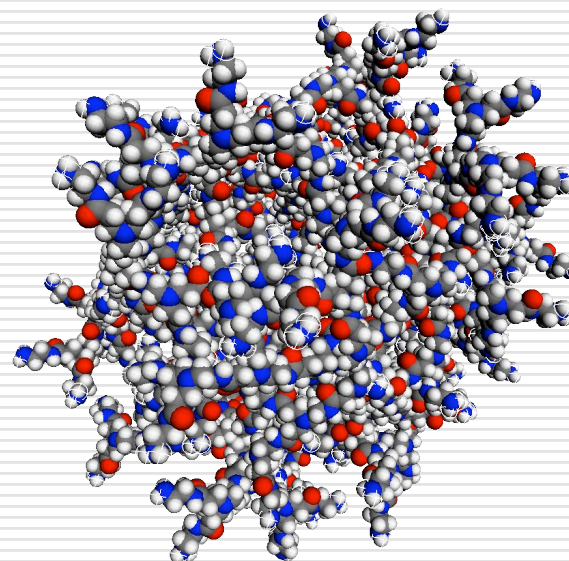


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Dendrimer Technology: A Nanoscale Delivery Platform for the Identification and Treatment of Cancer

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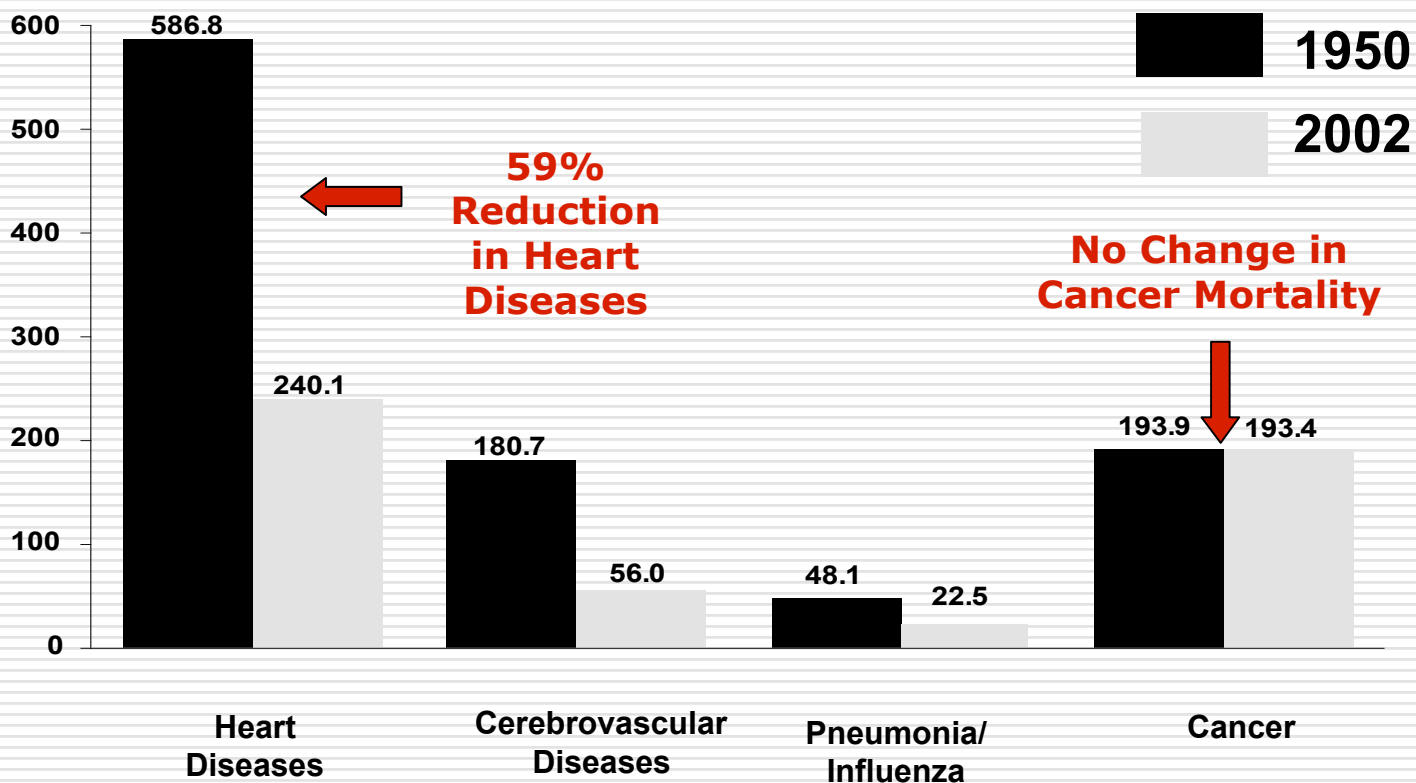


Presentation Agenda

- **Ovarian Cancer – a Medical Priority**
- **DNT Ovarian Cancer Technology Overview**
- **Receptor Targeted Diagnostics for Ovarian Cancer**
- **Targeted Therapeutic Delivery for Ovarian Cancer**
- **Future Research Direction**
- **Questions**

Change in the US Death Rates* by Cause 1950 & 2002

Rate Per 100,000

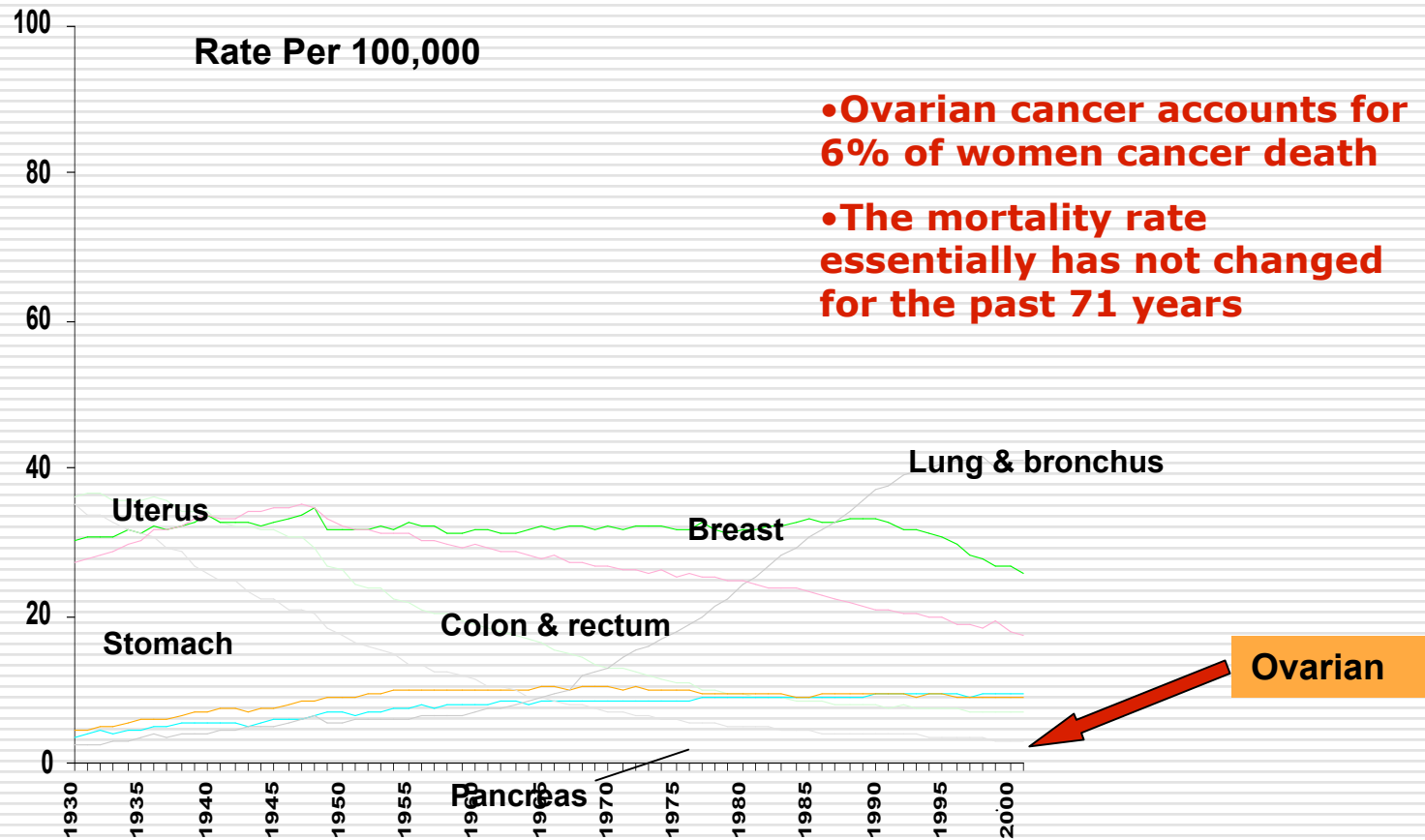


* Age-adjusted to 2000 US standard population.

Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.

2002 Mortality Data: US Mortality Public Use Data Tape, 2002, NCHS, Centers for Disease Control and Prevention, 2004

Cancer Death Rates* for Women in the US 1930-2001



*Age-adjusted to the 2000 US standard population.
 Source: US Mortality Public Use Data Tapes 1960-2001, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2004.



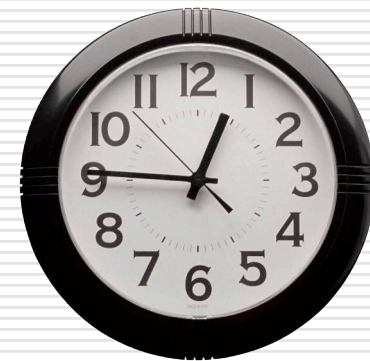
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Medical Priority

The American Cancer Society's statistics for ovarian cancer estimate that there will be 22,220 new cases and 16,500 deaths in 2005.

- **One new case every 23 minutes**
- **One death every 32 minutes**





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
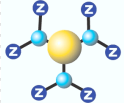
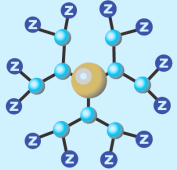
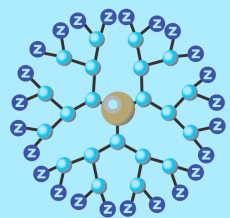
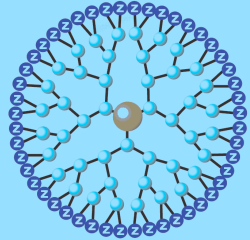
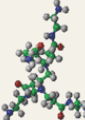
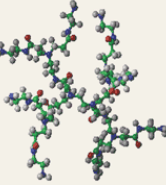
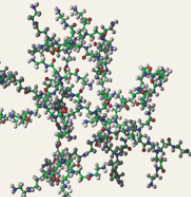
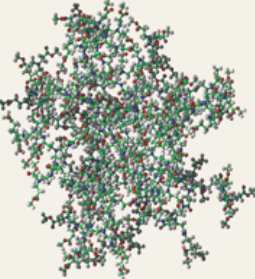
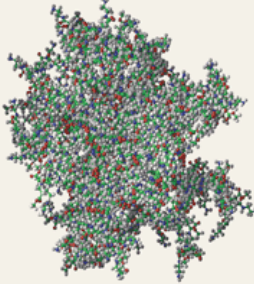
Medical Priority

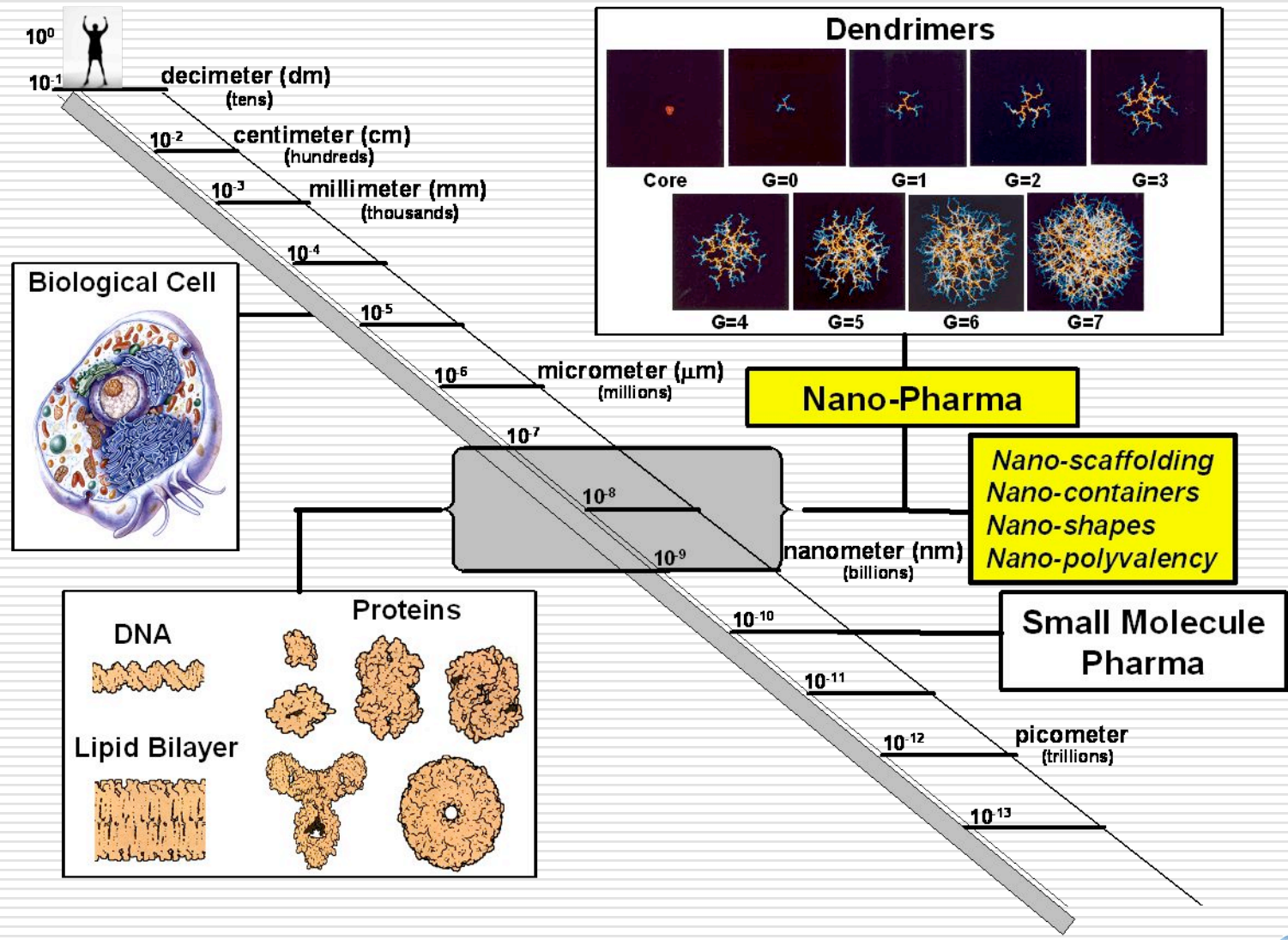
- **70 percent of women with the common epithelial ovarian cancer are not diagnosed until the disease is in an advanced stage III or IV.**
- **The 5-year survival rate of stage III or IV is only 15 to 20 percent, whereas the 5-year survival rate for stage I disease patients approaches 90 percent.**

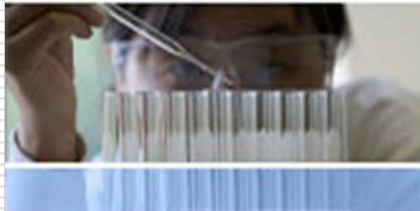
Early diagnosis and treatment is critical!



Ovarian Cancer Imaging and Therapeutic Delivery Dendrimer Structures, Nomenclature, and Attributes

Generation	G0	G1	G2	G3	G4
# of Surface Groups	3	6	12	24	48
Diameter (nm)	1.4	1.9	2.6	3.6	4.4
2D Graphical Representation					
3D Chemical Structure View					



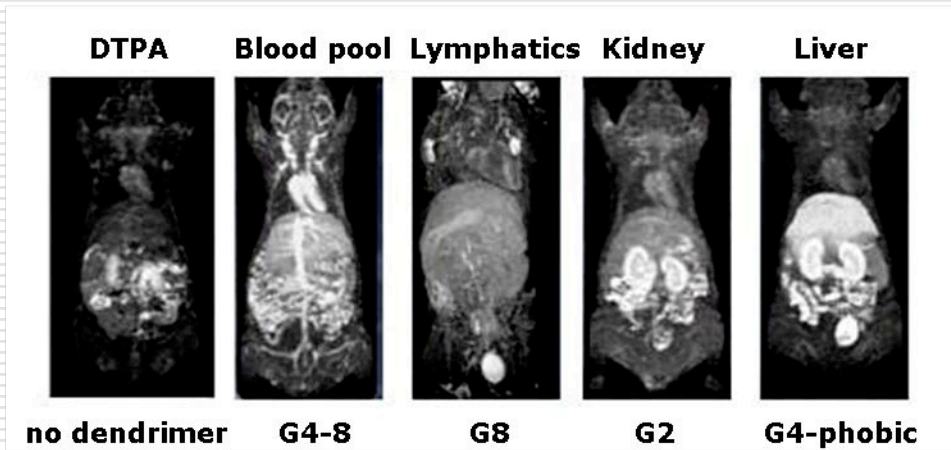


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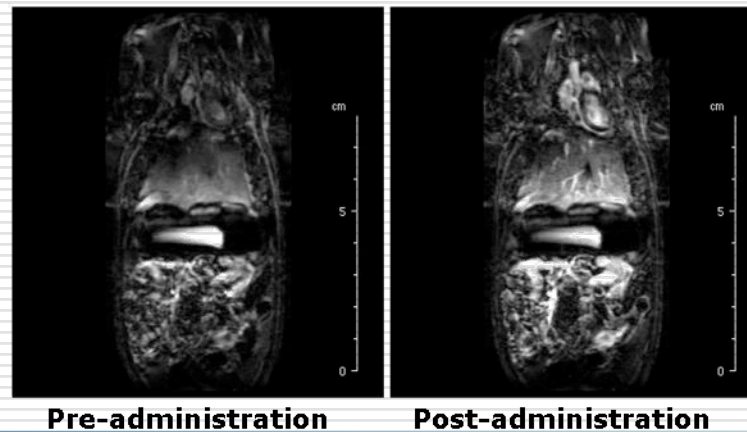
Targeted MRI Diagnostics – Size and Surface Makes a Difference

**Surface Attached
Magnevist®**



**Encapsulated
Magnevist®**

Lead Candidate: DNT 68-BH-07



In cooperation with E.C. Wiener,
University of Pittsburgh Cancer Institute
and
M.W. Brechbiel, National Cancer
Institute

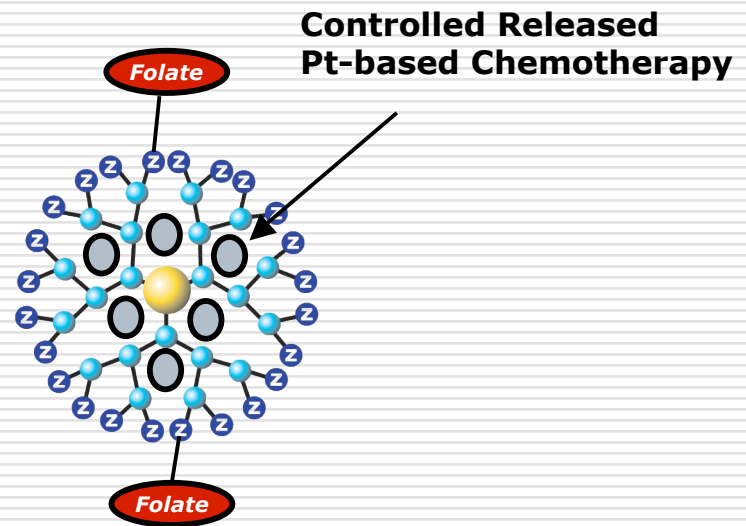
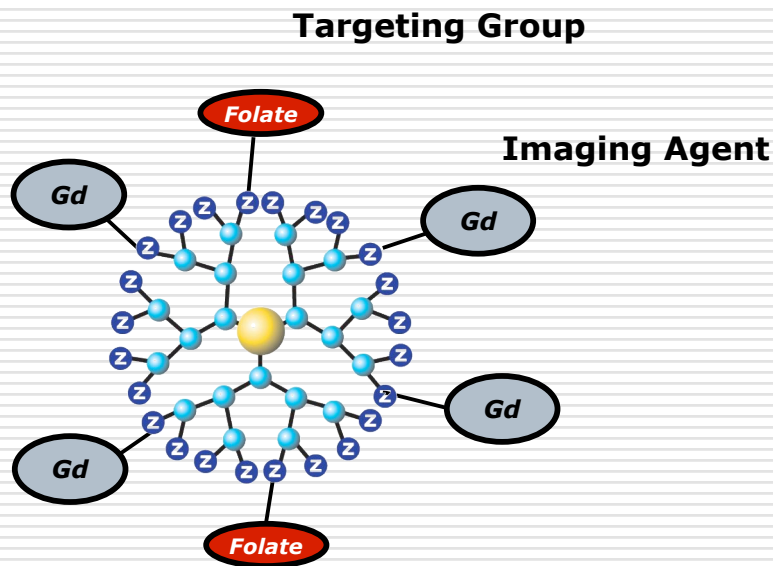


Technology Overview

Ovarian Cancer Imaging and Therapeutic Delivery

Targeted MRI Imaging Agent

Targeted Chemotherapy





Folate Based Targeting of Ovarian Cancer

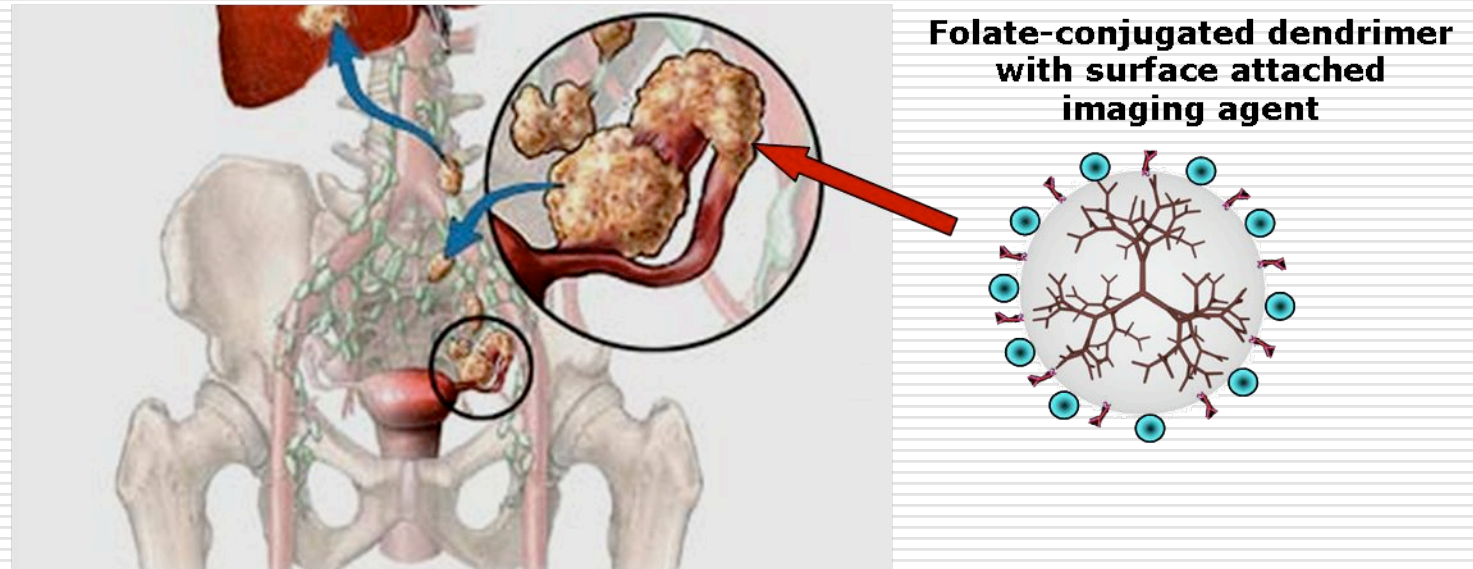
Ovarian cancer cells consistently and uniformly overexpress folate receptors as much as two orders of magnitude higher relative to normal, healthy ovarian epithelial cells.

- *Folate Receptors exhibit limited expression on healthy cells.*

- *Folic Acid is member of the Vitamin B Family and is essential for cell function.*

Cancer	Percentage Cancer Cells that Overexpress Folate Receptors
Ovarian	> 90%
Kidney	> 50%
Breast	~ 50%
Lung	~ 33%
Pancreatic	~ 10%
Colon	< 10%
Prostate	< 10%

Receptor-Targeted Diagnostics for Ovarian Cancer



Medical Priority - Early stage diagnostic for ovarian cancer where detection, classification, and monitoring are crucial.

Solution – Surface conjugated Magnevist® and folate

- good biostability, bioavailability
- superior image enhancement
- targeted organ specificity
- increased retention for imaging

Receptor Targeted Diagnostics for Ovarian Cancer

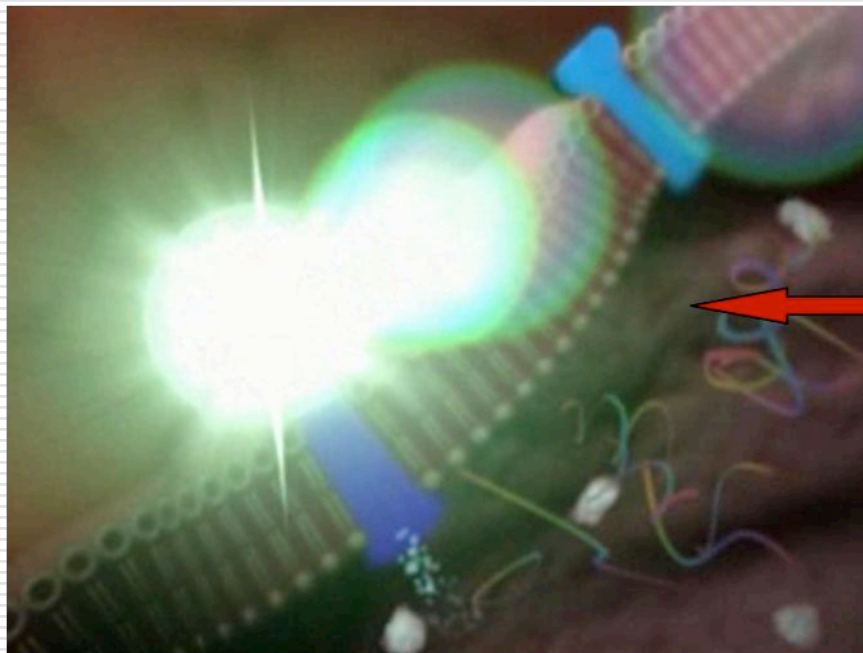
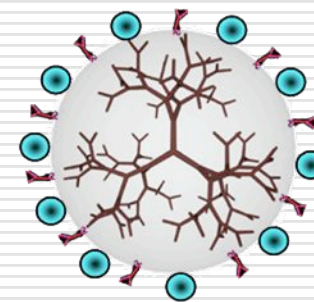


Image courtesy of National Cancer Institute

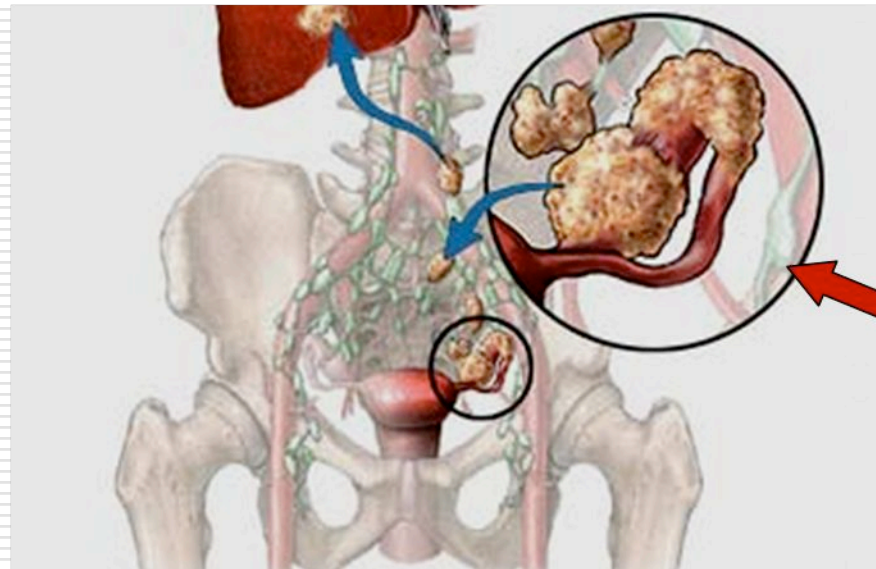
Folate-conjugated dendrimer with surface attached imaging agent



- **Targeted Tumor Images as small as 0.3 mm (currently 0.5 – 1 cm)**
- **Approximately 10x reduction in toxic contrast agent dosage**

Receptor-Targeted Therapeutics for Ovarian Cancer

Folate-conjugated Dendrimer with Chemotherapy



Folate-conjugated dendrimer with surface attached imaging agent and encapsulated therapeutics

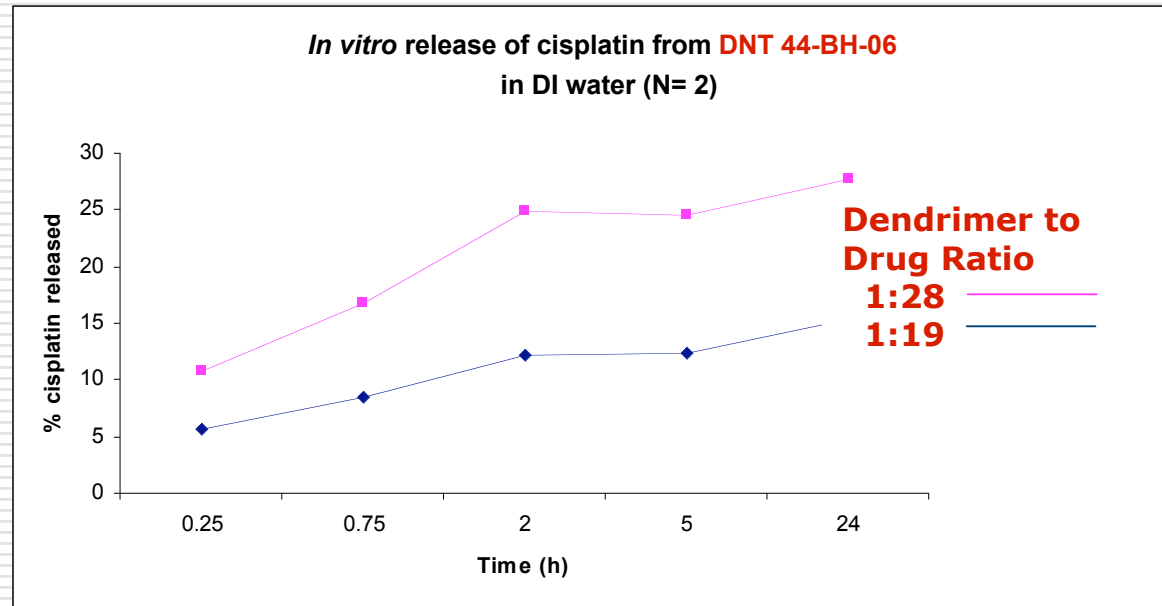
Effective Targeted Delivery of Chemotherapies (Cisplatin, Carboplatin, Paclitaxel) with:

- **Lower Dosage**
- **Improved Solubility**
- **Lower Toxicity**

Targeted Therapeutic Delivery for Ovarian Cancer

Dendrimer Encapsulated Cisplatin

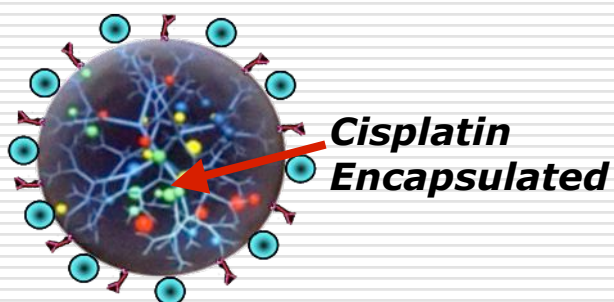
- **Greater Control over Release Profile**



Release studies indicate:

- Initial burst release of cisplatin (5-10 wt%)
- Sustained release over several hours in DI water
- Release rate in PBS ~10% higher than in DI water (data not shown)

Targeted Therapeutic Delivery for Ovarian Cancer Dendrimers Change Therapeutic Properties



- Improved Solubility
- Reduced Toxicity
- Improved Bioavailability

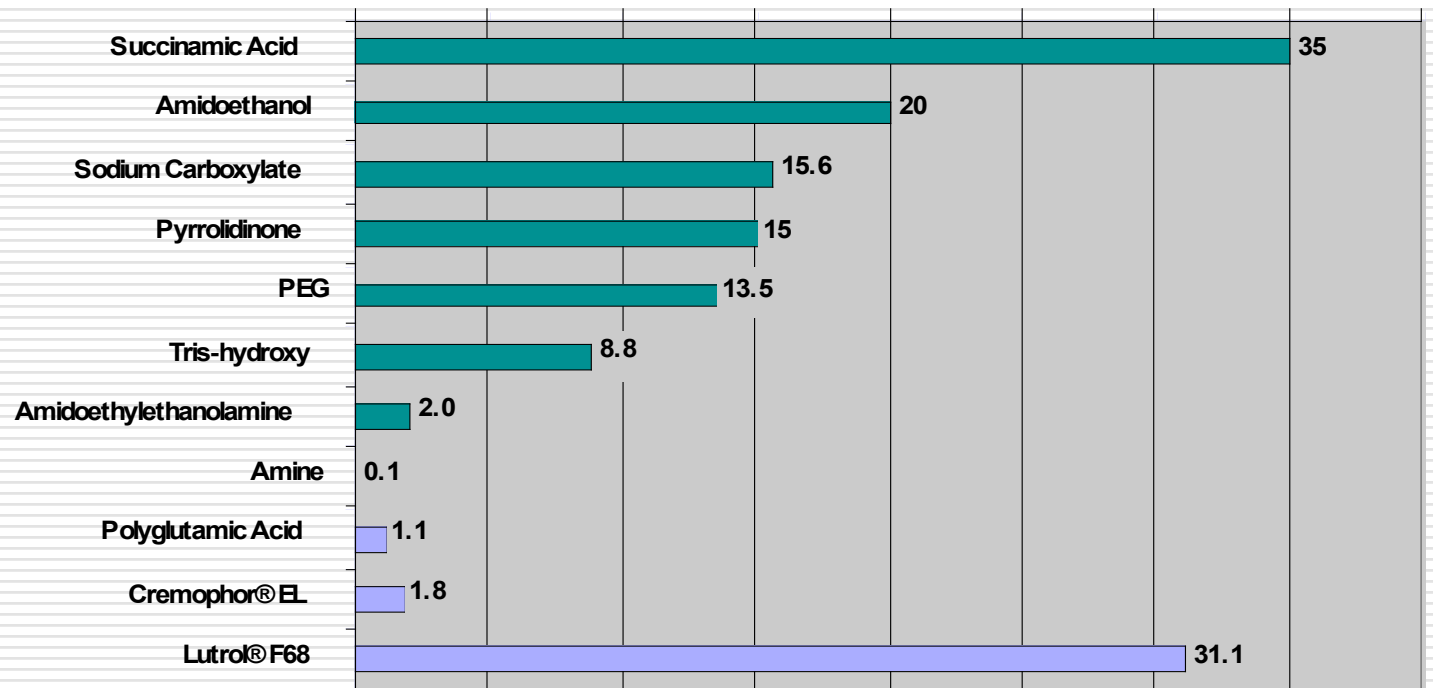
- DNT 44-BH-06 (Lead Candidate) (3.4 nm; MW 13kDa)
- White hygroscopic solid
- Water-soluble
- Demonstrated powder stability (>12 months)

AUC Values ($\mu\text{g Pt/mL}$ blood or $\mu\text{g Pt/organ}$) over 48 Hours; 5 Mice/Data Point:

Organ	cisplatin (1mg/kg)		cisplatin-dendrimer (1 mg/kg)
Tumor	5.3	→	25.4 EPR effect
Blood	9.4		10.7
Liver	51.6		17.0
Kidney	57.6	→	138.1 Size exclusion

5X increase in therapy delivered to tumor with concentration held constant

Targeted Therapeutic Delivery for Ovarian Cancer Surface Affects Dendrimer Cytotoxicity

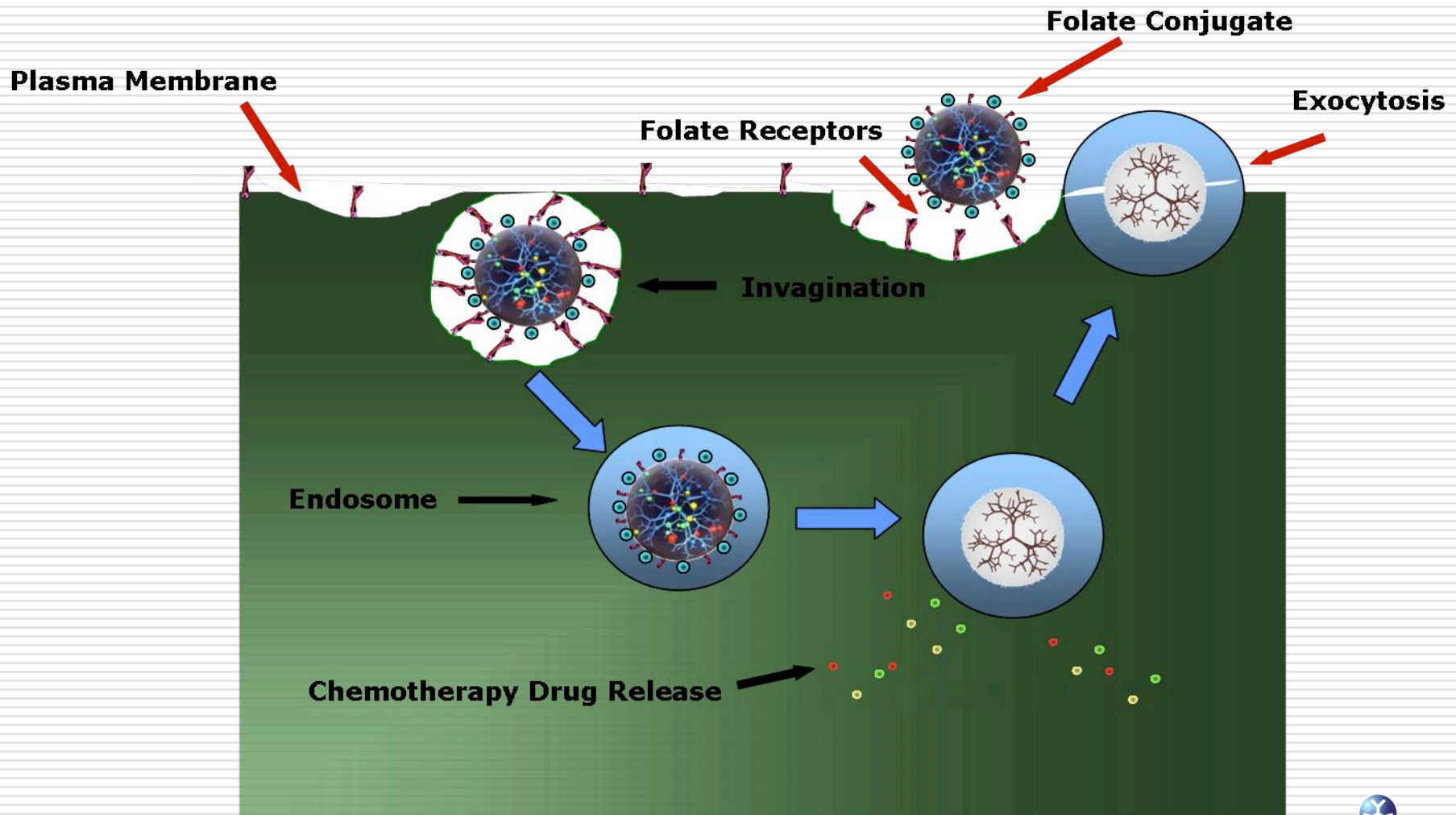


Less Cytotoxic L. Reyna, DNT internal study

IC₅₀ (mg/mL) in
Caco-2 Cells

The cytotoxicity of STARBURST® dendrimers is either similar to or less than commercial excipients

Targeted Therapeutic Delivery for Ovarian Cancer Dendrimer-Based Receptor Mediated Endocytosis Hypothesis



Targeted Therapeutic Delivery for Ovarian Cancer

Dendrimer Transfection Reagent for Nucleic Acids

Future Development Trends



Surface charge ratio and size allows the development of a transfection reagent with enhanced transfection efficiency and decreased cytotoxicity.

Transfection Reagent	Protein down-regulation (%)	
	293	MDCK
Lipid-based Reagent	60%	19%
DNT Proprietary	85%	79%

Dendrimer size, surface charge, and structure are critical transfection parameters.



Current Product Development

Products	Product Status	Timeframe
Intravascular Contrast Agent for MRI Imaging	Lead Candidate Screening NCL Collaboration	IND by Q4 2006
Ovarian Cancer Diagnostic and Therapy	Lead Candidate Screening	IND by Q2 2007
Transfection Reagents for siRNA Delivery	Collaborative Research	Reagent Products in 2006
Priostar™ Dendrimer Technology	Product Development & Scale Up	Q2 2006

Innovate. Collaborate. Succeed.



**DENDRITIC
NANOTECHNOLOGIES, INC.**

*A National Cancer Institute's Nanotechnology
Characterization Laboratory Collaborative Partner.*



The Nanotechnology Characterization Laboratory is performing the preclinical assessment of DNT's STARBURST® dendrimers as macromolecular MRI contrast agents for sensitive, non-invasive intravascular diagnostics to stage a product for clinical trials.

DNT is committed to the discovery, development, and commercialization of dendrimer technologies to create a new generation of innovative products for the identification and treatment of human diseases.

For more information
Visit: www.dnanotech.com

Contact us for more information on partnerships or out-licensing opportunities.

Call: 989.774.6565 or email: info@dnanotech.com.



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Questions