Project:
NanoInnovation Initiative
NANOTECHNOLOGY plan

Company: EBEWE-pharma

Presenter: Tamar Chachibaia, Tbilisi, Georgia

Strategic Initiative

Nanotechnology - Implication in Oncology

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Nanotechnology is Here

- Nanoscale drug delivery devices are being developed to deliver anticancer therapeutics specifically to tumors. Liposomes are one such "first generation" nanoscale device. Liposomal doxorubicin is used to treat specific forms of cancer, while liposomal amphotericin B treats fungal infections often associated with aggressive anticancer treatment. Commercialization of these liposome encapsulated drugs produced by **Nexstar** with sales over $20 million in 1999.
- Recently, a nanoparticulate formulation of the well-known anticancer compound taxol was submitted as a new treatment for advanced stage breast cancer.

Nanotechnology Could Be The Solution To Chemotherapy Solutions

- As terrible as cancer can be, chemotherapy treatments can make one think that the disease might be the lesser of two evils. The basic premise behind chemotherapy is to poison the patient's system with a cocktail of drugs. Not only does the cancer get attacked but so too does the entire body.
- If the drugs aren't water soluble the need to be dissolved in another solvent so they can be injected. Often this solvent is highly toxic and causes strong side effects. American Pharmaceutical Partners have announced that its cancer fighting drug Abraxane (consisting of 130 nanometer spheres of protein and paclitaxel) has demonstrated greater tumour reduction and fewer side effects when compared to a solvent dissolved equivalent.

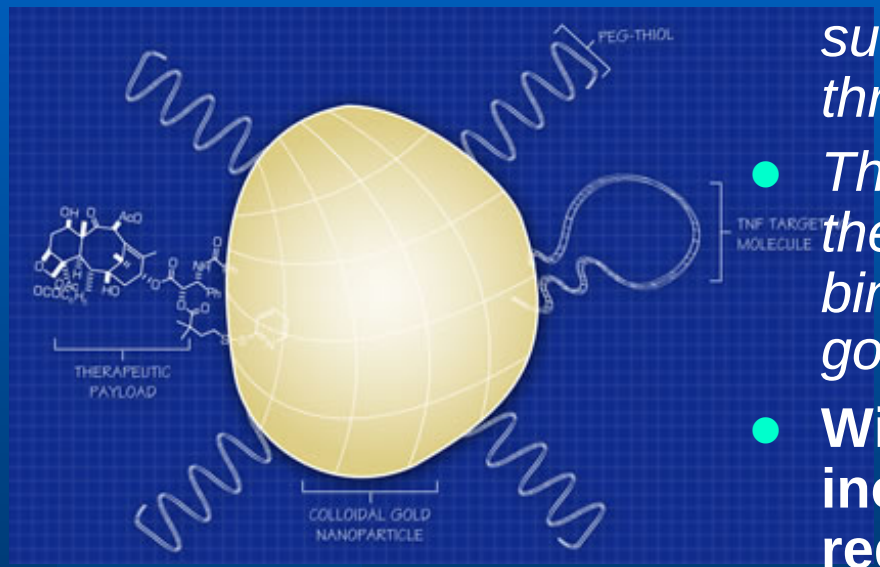
ABRAXANE™ (Paclitaxel) was approved in February 2005 by the FDA.

- **ABRAXANE™ - for Injectable Suspension is the first and only approved taxane for the treatment of metastatic breast cancer in a new class of albumin-bound nanotechnology that is free of solvents.**
- **As a solvent-free chemotherapy agent, ABRAXANE increases the convenience of administration.**
- **For the first time, the anticancer drug paclitaxel can now be delivered using the protein albumin rather than a chemical solvent.**

Abraxane™ is trademark of BioScience, Inc.(USA)

- American Pharmaceutical Partners have announced that its cancer-fighting drug Abraxane (consisting of 130-nanometer spheres of protein and paclitaxel) has demonstrated greater tumour reduction and fewer side effects when compared to a solvent-dissolved equivalent.
- ABRAXANE ™ for Injectable Suspension launched by Abraxis Oncology, the proprietary drug division of (APP) American Pharmaceutical Partners, Inc.

CytImmune - PEGilated gold nanoparticals - A Novel Vector for Tumor Directed Drug Delivery



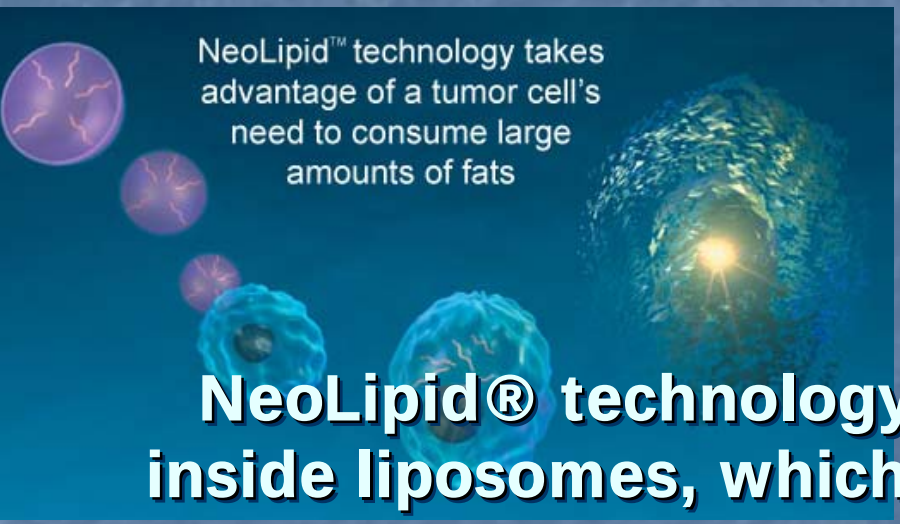
- *In 2000, CytImmune discovered that pegylated colloidal gold nanoparticles bind anti-cancer therapeutics on their surface and carry these drugs safely through the blood stream.*
- *Thiolated forms of small molecule therapeutics, such as paclitaxel, TNF, bind directly to the surface of colloidal gold nanoparticles.*
- **With tumor targeting resulting in increased drug levels in the tumor and reduced drug uptake by healthy organs, the technology improves efficacy and reduces toxicity.**

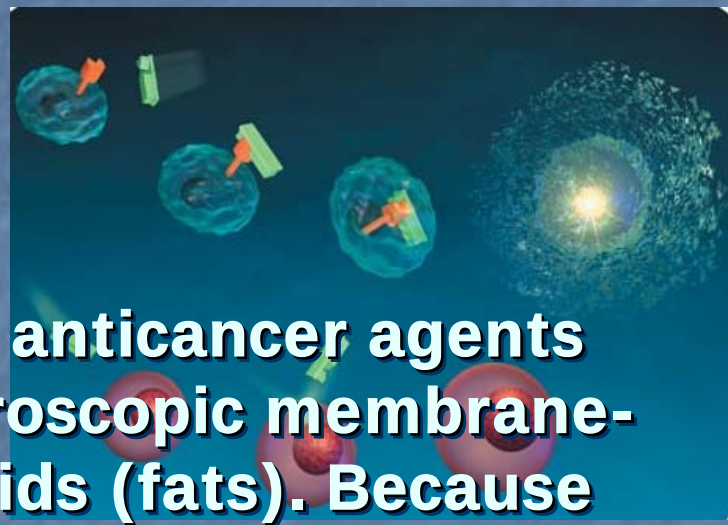
An example of industry-government partnerships in this area is the project "Using nanosized particles for more effective cancer therapy" (National Institute of S&T, National Institutes of Health, National Cancer Institute, CytImmune Sciences Inc., and EntreMed, Inc.).

How works Colloidal Gold?

- Polyethylene glycol (PEG) masks particles from immune recognition preventing uptake by liver and spleen
- Nanoparticles exit circulatory system only at the tumor neovasculature due to leakiness of blood vessels
- Particles too large to exit circulation elsewhere
- TNF targeting molecule on particle's surface binds to receptors causing rapid absorption of drug in and around tumor.

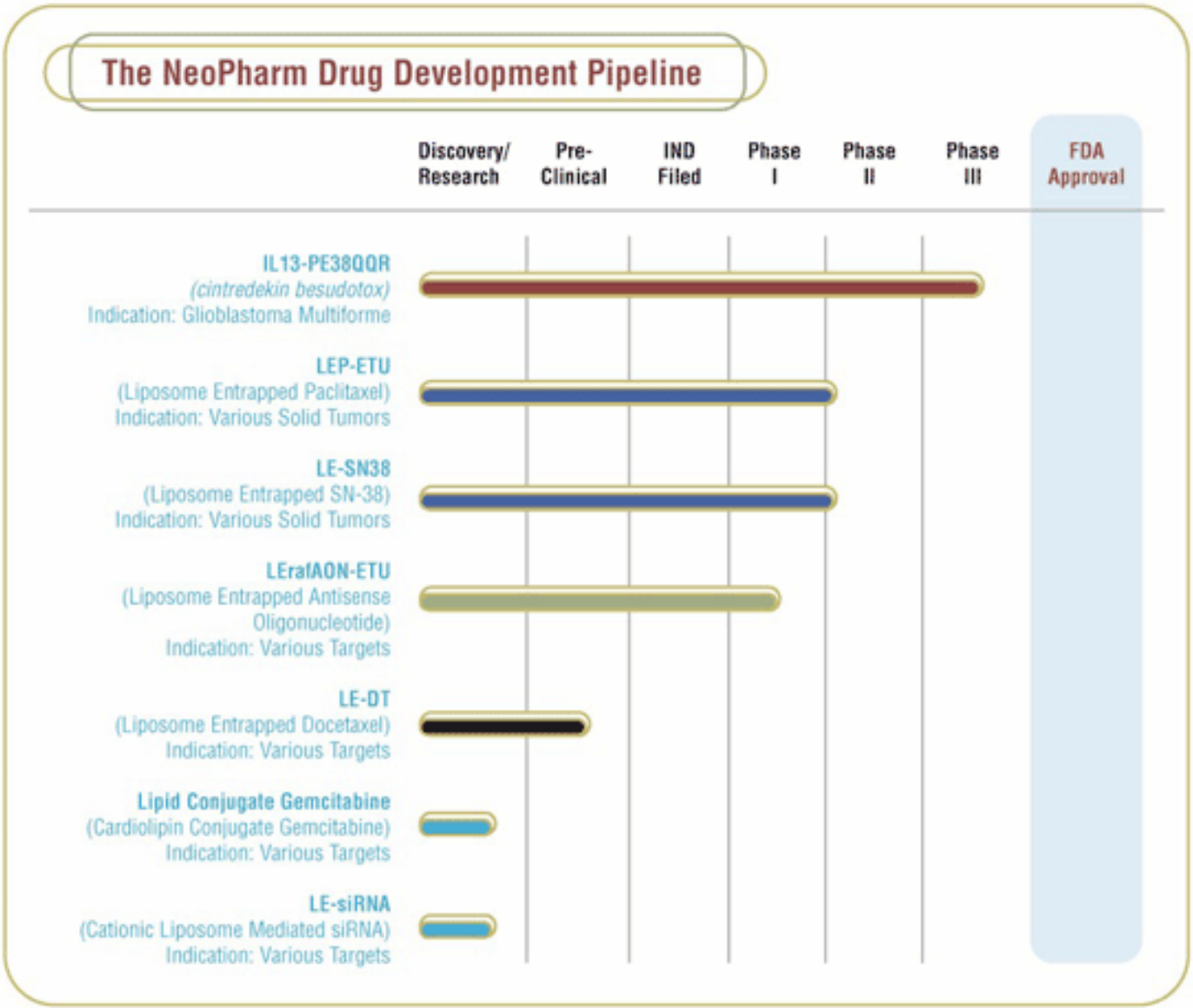
NeoPharm is a biopharmaceutical company dedicated to the research, discovery, and commercialization of new and innovative cancer drugs for therapeutic applications. NeoPharm has built its drug portfolio based on its two novel proprietary technology platforms: a tumor-targeting platform and the NeoLipid® drug delivery system.





NeoLipid® technology entraps anticancer agents inside liposomes, which are microscopic membrane-like structures created from lipids (fats). Because tumor cells need to consume large amounts of fats to sustain their rapid growth, they eat the liposome, while at the same time absorbing the anticancer agents.

NeoLipid® DRUG DELIVERY PLATFORM



ACUSPHERE Inc. is a specialty pharmaceutical company that develops new drugs and improved formulations of existing drugs using its proprietary porous microparticle technology.

AI-850, our initial product candidate utilizing our HDDS technology, is a readily dissolving formulation of the hydrophobic drug, paclitaxel, the active ingredient in the cancer drug, Taxol. To dissolve paclitaxel, Taxol contains Cremophor, which is believed to cause severe hypersensitivity reactions, such as an extreme allergic reaction called anaphylaxis. Therefore, Taxol is typically administered using pre-medications and by long infusions to patients with cancer. By putting nanoparticles of paclitaxel into sponge-like microparticles, is created a paclitaxel formulation that is free of Cremophor and consists of paclitaxel nanoparticles in a porous, hydrophilic matrix, composed primarily of a sugar that has been proven to be innocuous in other injectable drugs.

BioDelivery Sciences International, Inc.

Drug	Indication	Status
Emezine	Nausea/Vomiting	Partnered
BEMA Fentanyl	Breakthrough pain	Proprietary
Bioral Amphotericin B	Fungal infections	Proprietary
Bioral NSAID	Pain	Licensed
Bioral paclitaxel	Oncology	Avail. for Licensing
Bionasal Amphotericin B	Chronic rhinosinusitis	Partnered
Biorazyme	Gauchers Disease	Avail. for Licensing
Bioral siRNA	Infectious disease/cancer	Avail. For Licensing

Aphios Corporation is developing enhanced therapeutics for health maintenance and the treatment of human diseases with a focus on infectious diseases, cancer and quality-of-life medicines

- Aphios has utilized its patented *SuperFluids™CFN* technology to form nanosomes (small, uniform liposomes) of paclitaxel. Liposomes are microscopic vesicles of phospholipid bilayers comprised of single or multiple lipid bilayers. Most liposomes are non-toxic, non-antigenic and biodegradable in character since they have the molecular characteristics of mammalian cell membranes. Hydrophobic compounds are trapped inside the lipid bilayers, masking the toxic nature paclitaxel and permitting a biocompatible formulation to be administered.

TaxosomesTM

- Aphios has developed and patented a nanosomal formulation of Paclitaxel, *Taxosomes.*™ The formulation is Cremophor-free and produced by Aphios' patented phospholipid nanosomes technology [U.S. and European Patents, 1995, 1997, 1998 and 2002]. Harvard Medical School researchers have demonstrated that *Taxosomes*™ is much less toxic *in vitro* than Taxol,® while being twice as effective in the in vivo treatment of nude mice with breast cancer xenografts.

NanoMed Pharmaceuticals, Inc.

- **NanoMed has developed a scaleable nanoparticle manufacturing technology (Nanotemplate Engineering) to deliver small molecules, peptides, proteins, plasmid DNA, and diagnostic agents.**
- **The company is utilizing this novel platform technology to develop new and improved formulations for two approved chemotherapeutic drugs -- paclitaxel (Paclitaxel NP™) and doxorubicin (Doxorubicin NP™) -- and a new indication for a third approved therapeutic agent for use as a novel anti-cancer drug (NAC NP). The therapeutic focus is breast, lung, and colorectal cancer.**

SONUS pharmaceuticals

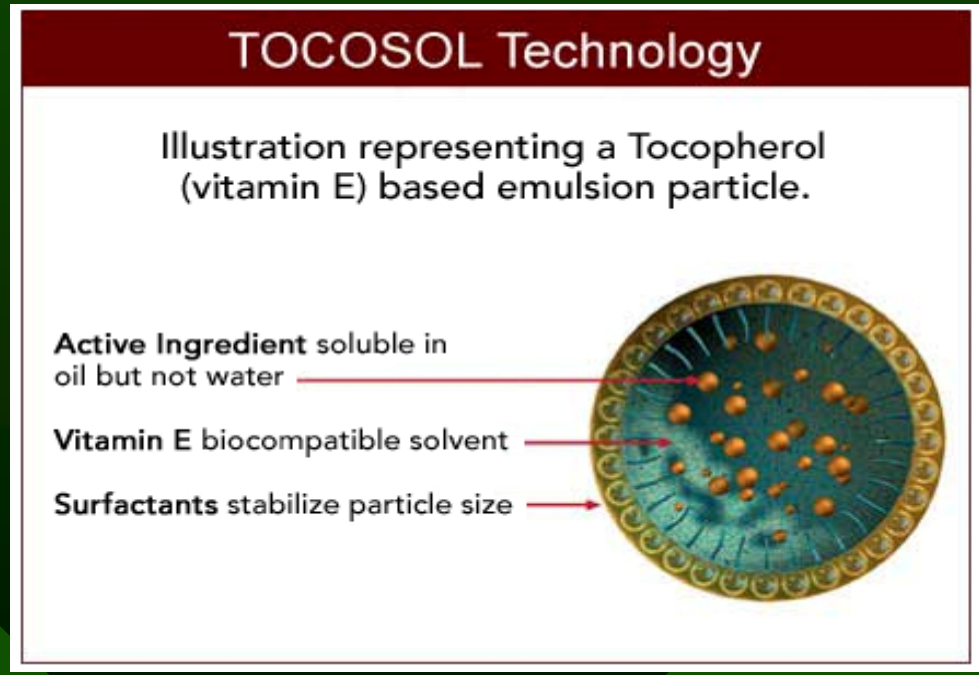
- **The Company's lead product candidate is TOCOSOL® Paclitaxel, an injectable, ready-to-use formulation of the widely prescribed anti-cancer drug paclitaxel.**
- **The product is administered to patients in a short 15-minute infusion compared to the prolonged three-hour infusion required with Taxol. TOCOSOL Paclitaxel has been designed to overcome the limitations associated with Taxol® and generic paclitaxel-based chemotherapy, including time consuming and expensive preparation of the products prior to administration, long infusion times and undesirable or treatment-limiting side effects.**
- **Sonus has completed patient enrollment in Phase 2a studies of TOCOSOL Paclitaxel in non-small cell lung, bladder and ovarian cancers, and Phase 2b studies are ongoing in bladder and breast cancers. In addition, the U.S. Food and Drug Administration has completed a Special Protocol Assessment (SPA) for the pivotal Phase 3 trial of TOCOSOL Paclitaxel, which Sonus expects to initiate in 2005.**

SONUS pharmaceuticals

- The TOCOSOL® technology uses vitamin E and vitamin E derivatives to solubilize, stabilize and formulate drugs with the goal of enhancing their delivery, safety and efficacy. The Company's development strategy is:

- Develop proprietary formulations of therapeutic drugs utilizing the TOCOSOL technology platform; and

- Identify and acquire additional therapies and technologies in oncology and related fields in order to expand product pipeline and corporate capabilities.

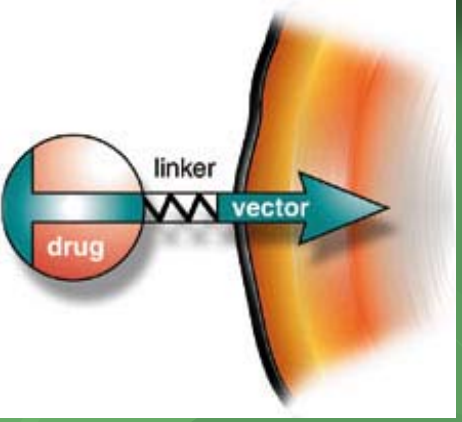


Synt:em announces its acquisition by Sonus Pharmaceuticals

About Synt:em

Synt:em S.A. is an emerging drug discovery company developing novel drugs using its proprietary drug design technologies to discover and develop drug transport conjugates. Company employs its technology platform to design short peptide vectors, known as Pep:trans vectors.

Pep:trans™ peptide-derived vectors transport drugs across biological membranes and bring them directly to their site of pharmacological action.
Drugs linked to Pep:trans™ typically have shown up to 100-fold enhancement in brain uptake resulting in an associated improvement of pharmacological activity in animal models.



Synt:em has developed short peptide vectors, termed SynB vectors, that are able to cross cellular membranes. In an effort to address the problem of MDR in cancer chemotherapy, scientists at Synt:em coupled the anticancer agent doxorubicin with various SynB vectors and tested their *in vitro* cytotoxicity in human erythroleukemic (K562/ADR) resistant cells. The conjugate showed potent dose-dependent inhibition of cell growth against K562/ADR cells as compared to treatment with doxorubicin alone. Doxorubicin exhibited IC50 concentrations that were 20 times higher than vectorized doxorubicin.

Synt:em announces its acquisition by Sonus Pharmaceuticals

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ALZA Corporation's STEALTH® liposomal technology

- ALZA Corporation's STEALTH® liposomal technology, developed for state-of-the-art intravenous drug delivery, is the basis for the anticancer agent Doxil® (doxorubicin HCl liposome injection).
- ALZA is now applying this technology to the delivery of other cancer therapeutics and gene therapy vectors.
- The proprietary STEALTH® liposomes evade recognition by the immune system because of their unique polyethylene glycol (PEG) coating.

Advectus Life Sciences, Inc.

Advectus Life Sciences Inc. holds the exclusive worldwide rights including patents to this nanoparticle-based technology for the delivery of approved cancer fighting drugs across the blood-brain barrier for the treatment of brain tumors. Preliminary tests have shown that this technology may have the potential to overcome major obstacles in treating brain cancer.

P80DOX-NP is a novel delivery method for Doxorubicin that crosses the blood-brain barrier. This series of pre-clinical studies will test the responsiveness of tumors in the brain to this compound. Successful demonstration of an antitumor effect could serve as a basis for a clinical trial using P80DOX-NP to treat the large group of patients with brain metastases. The study is designed to lead into Phase I Clinical Trials.

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Spherics, Inc

Schedule and Dose Adjustments for Improved Bioavailability of an Oral Repeat-dose Paclitaxel Nanoparticle Formulation

(Feasibility study - 2004)

Paclitaxel exists in several states, e.g., semicrystalline, dehydrate and amorphous and is generally supplied in the semi-crystalline state. A micronization method that could reduce particle size and reduce crystallinity of paclitaxel would increase absorption of both particulate and soluble drug.

The paclitaxel nanoparticle formulations in the present study were prepared using a proprietary phase-inversion precipitation technique, to produce discrete particles of amorphous paclitaxel in the size range of 300 nm. The oral pharmacokinetics of the PNF were evaluated after single and repeat dosing in fasted mice. Paclitaxel nanoparticles were fabricated via a phase inversion technique.

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•Presented at the 2005 Annual Meeting (Cincinnati, OH)

1.Fabrication of micro and nanoparticles of paclitaxel-loaded Poly L Lactide for controlled release using supercritical antisolvent method: Effects of Thermodynamics and Hydrodynamics

2. Paclitaxel-loaded Biodegradable Nanoparticles Developed by Dialysis and ElectroHydrodynamic Atomization Methods

3.Micro- and Nano-Particles Developed by Electrohydrodynamic Atomization for the Sustained Delivery of Paclitaxel to Treat C6 Glioma

4. In vitro study of anticancer drug doxorubicin in PLGA-based microparticles

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Implantable 5-FU-Microspheres

Implantierbare 5-FU-Bio-Mikrosphären

Philippe Menei, M.D., Ph.D., Neurochirurg an der Universitätsklinik Angers in Frankreich, versucht, Gliome Lokal zu bekämpfen, indem er in eine Trägersubstanz ein radiosensibilisierendes Chemotherapeutikum einbettet, das dann am Tumor über einen längeren Zeitraum freigesetzt wird.

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