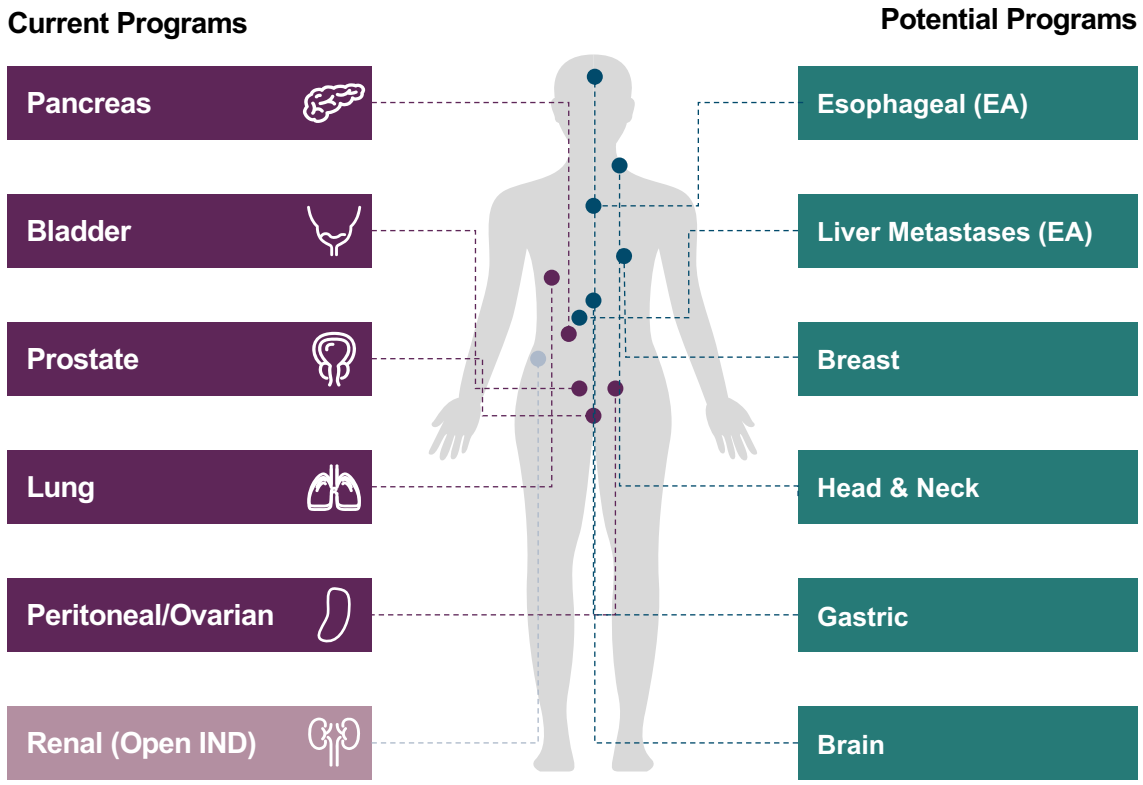
January 2023

Clinical Stage Oncology Company

Drug platform engineered for optimal solid tumor-directed therapy

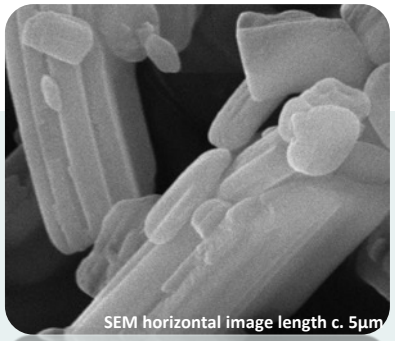
- Patented large surface area microparticle (LSAM) oncology drug platform engineered for solid tumors
- LSAM-PTX (paclitaxel) and LSAM-DTX (docetaxel) in clinical development
- 7 clinical trials / 5 solid tumors / > 170 subjects
- Promising tumor response data
- Clinical evidence of immunomodulation (pancreas, lung, bladder)
- Excellent tolerability profile
- Tumor-directed therapy with multiple routes of local administration



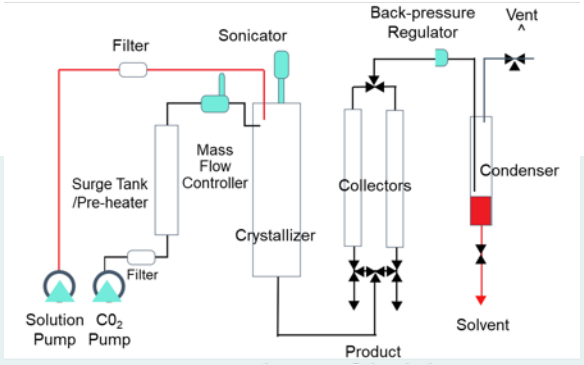
Large Surface Area Microparticles (LSAMs)

Enabled by a proprietary supercritical precipitation (SCP) production technology platform

API Crystals

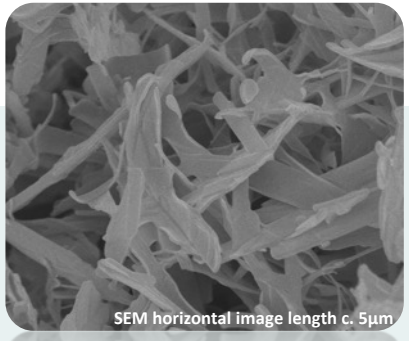


- ✓ Large and bulky crystals
- ✓ Large distribution around mean particle size
- ✓ Poor uniformity of suspensions
- ✓ Poor drug release due to small surface area
- ✓ Limited to dissolution in solvent as a solution for IV delivery



- ✓ API crystals dissolved in organic solvent and injected into precipitation chamber
- ✓ Sonicated into small uniform droplets via sonic probe
- ✓ Solvent stripped away from droplets via supercritical fluid carbon dioxide
- ✓ Stable microparticles of pure drug precipitated and collected on harvesting filters
- ✓ GMP commercial scale
- ✓ **SCP platform technology established for multiple drugs (taxanes, TKIs, PARPIs, cisplatin)**

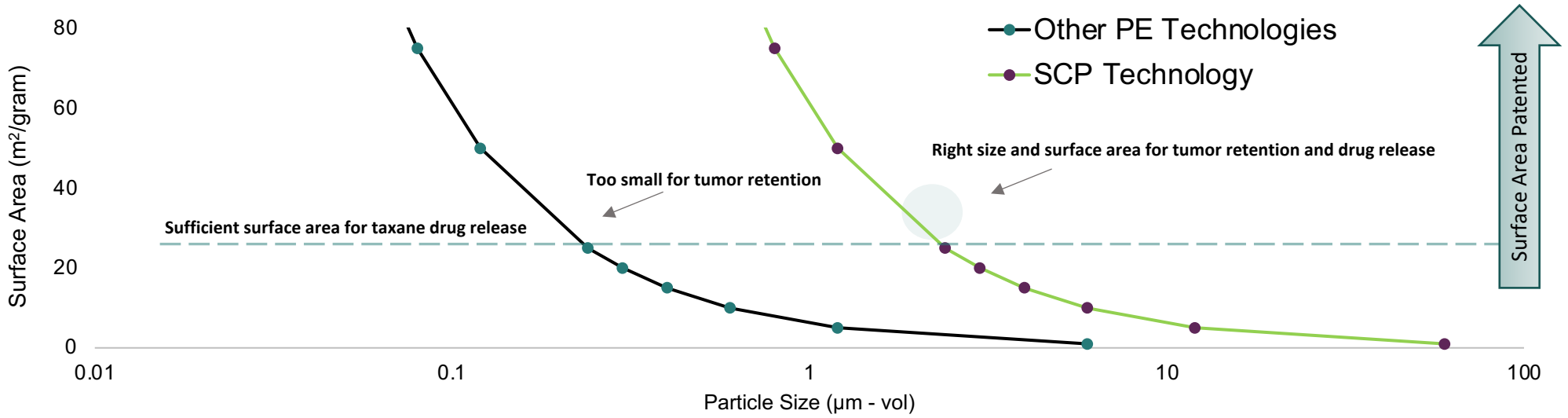
LSAMs



- ✓ Narrow mean particle size distribution
- ✓ Excellent suspension uniformity
- ✓ Microparticles each containing > 1 billion drug molecules suspended in saline-based fluid for local delivery
- ✓ Disproportionately large surface area to particle size ratio allows for:
  - ✓ Particle entrapment
  - ✓ Prolonged therapeutic drug release

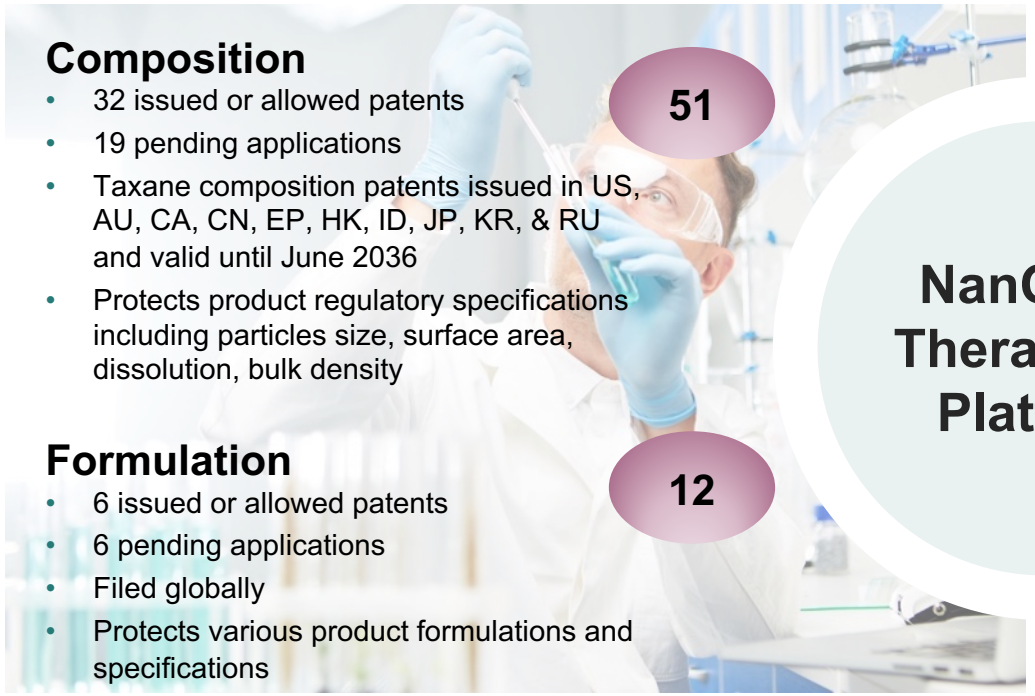
The Uniqueness of the PE Technology That Forms LSAMs

- The SCP technology is different from all other particle engineering (PE) technologies (spray drying, milling, CESS, RESS)
- The SCP technology has a unique ability to engineer **large particles with surface area of a much smaller particle**
- This uniquely **disproportionate surface area to particle size ratio** is optimal for tumor-directed delivery
- The larger size allows for **retention** in the tumor and large surface area for molecular drug **release**
- Taxane **particles with surface area ≥ 18 m^2/g** are protected by a **composition of matter patent** valid until June 2036



Growing Global IP Portfolio

IP protection like a new chemical entity



Composition

51

- 32 issued or allowed patents
- 19 pending applications
- Taxane composition patents issued in US, AU, CA, CN, EP, HK, ID, JP, KR, & RU and valid until June 2036
- Protects product regulatory specifications including particles size, surface area, dissolution, bulk density

Formulation

12

- 6 issued or allowed patents
- 6 pending applications
- Filed globally
- Protects various product formulations and specifications

NanOlogy Therapeutic Platform

Uses/Indications

128

- 49 issued or allowed patents
- 79 pending applications
- Filed globally
- Protects broad uses: key cancer indications, solid tumors, neoplasia
- Protects routes of administration: IT, IP, inhalation, instillation, topical
- Combination with immune checkpoint inhibitors

Process

76

- 65 issued or allowed patents
- 11 pending applications
- Filed globally
- Protects equipment, assembly, nozzle, methods, precipitation, collection

As of Oct 2022

Includes

- Combinations with IO
- TKIs, PARPs, Cisplatin
- Orphan designation (ovarian)
- Reducing & Inhibiting Metastasis
- Cancer vaccines/ adoptive cell therapy

Robust Clinical Development Pipeline

Product	Therapeutic Area	Delivery	IND	Phase 1	Phase 2	Phase 3
LSAM-PTX for Sterile Suspension	Locally Advanced Pancreatic Adenocarcinoma	Intratumoral				
	Mucinous Cystic Pancreatic Neoplasms	Intracystic				
	Peritoneal Malignancies / Ovarian Cancer	Intraperitoneal				
	Prostate Cancer	Intratumoral				
	Lung Cancer	Intratumoral				
LSAM-DTX for Sterile Suspension	High-Risk Non-Muscle Invasive Bladder Cancer	Resection Bed Injection & Intravesical Instillations				
	Muscle Invasive Bladder Cancer	Resection Bed Injection & Intravesical Instillations				
	Renal Cell Carcinoma	Intratumoral				
	Prostate Cancer	Intratumoral				
LSAM-PTX for Inhalation	Lung Cancer	Nebulized Inhalation				
Topical Submicron Particle Paclitaxel (SOR007)	Cutaneous Metastases of Breast Cancer (CMOBC)	Topical				

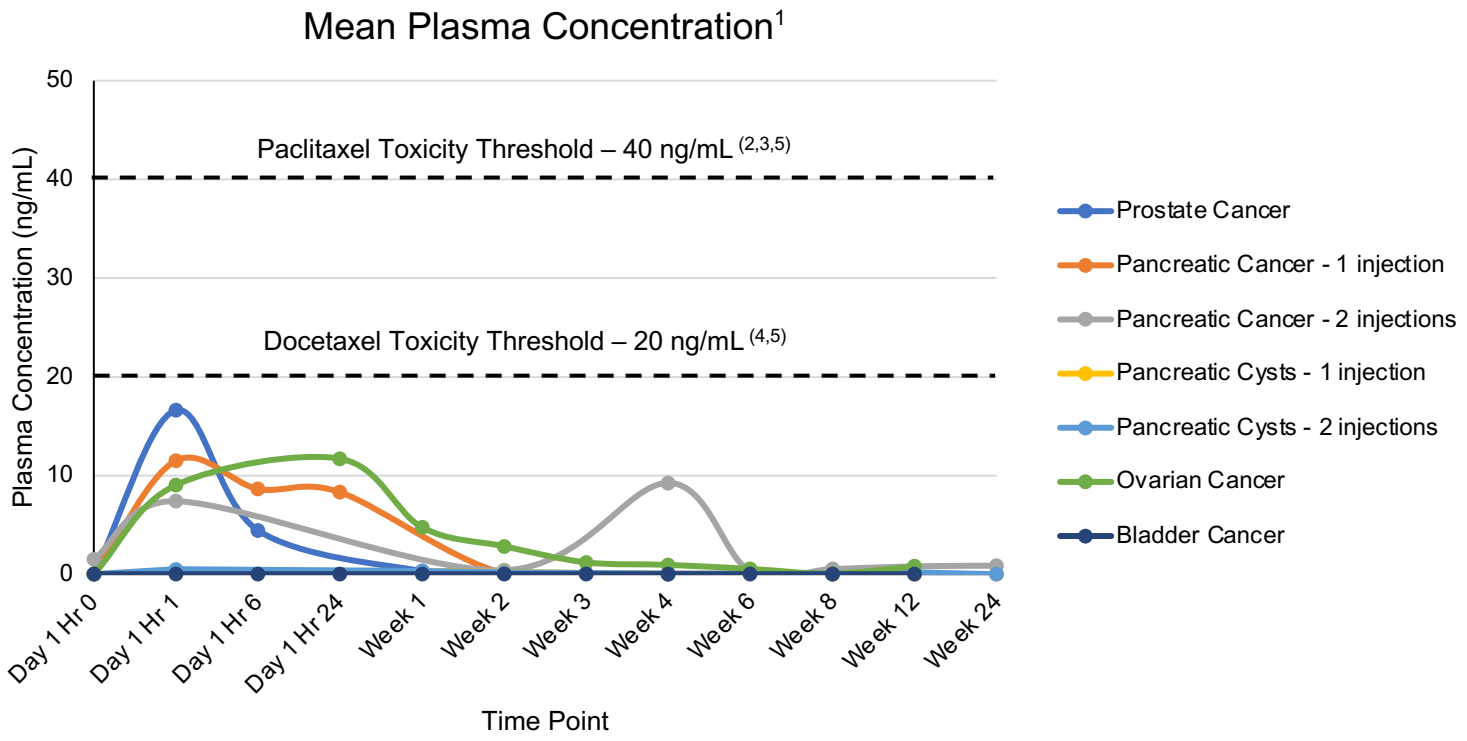
Excellent Tolerability Profile

	Clinical Trial	Subjects	Events		Systemic SAEs			Local SAEs		
			TEAE	SAE	Possibly Related	Probably Related	Definitely Related	Possibly Related	Probably Related	Definitely Related
LSAM-PTX	Pancreatic Cancer	54	419	50	0	0	0	6	0	0
LSAM-PTX	Pancreatic Cysts	19	99	5	0	0	0	0	1	0
LSAM-PTX	Peritoneal Malignancies	21	332	24	1	0	0	1	0	0
LSAM-PTX	Ovarian Cancer	10	208	13	0	0	0	7	0	0
LSAM-PTX	Prostate Cancer	17	76	0	0	0	0	0	0	0
LSAM-PTX	Lung Cancer	18	196	17	0	0	0	0	0	0
LSAM-DTX	Bladder Cancer (NMIBC)	19	144	1	0	0	0	0	0	0
LSAM-DTX	Bladder Cancer (MIBC)	17	74	3	0	0	0	0	0	0

As of December 2022

Plasma Levels from NanOlogy Clinical Trials

Subtoxic plasma drug concentrations at all timepoints demonstrated by clinical PK analysis



Avoids the systemic toxicities associated with systemic cancer treatments:

- Neutropenia
- Thrombocytopenia
- Peripheral neuropathy
- Alopecia
- Nausea & vomiting
- Colitis & severe diarrhea
- Rash & pruritis
- Hepatotoxicity
- Dose reduction or discontinuation

1. LSAM-DTX in bladder cancer only; all others LSAM-PTX
2. Clin Cancer Res 1999;5:767-774
3. S07-GM-01-2017
4. British Journal of Cancer (2007) 97, 290 – 296
5. LLOQ paclitaxel = 25 pg/mL; LLOQ docetaxel = 10 ng/mL

Selected Recent Publications

American Urological Association

THE JOURNAL of UROLOGY®

Official Journal of the American Urological Association | auajournals.org/jurology

Open Access | Journal of Urology | Adult Urology | 16 May 2022

Phase 1/2 Trial Results of a Large Surface Area Microparticle Docetaxel for the Treatment of High-Risk Nonmuscle-Invasive Bladder Cancer

Max Kates, Ahmed M. Mansour, Donald L. Lamm, Neal Shore, Holly Maulhardt, Alison Wendt, James Verco, Alyson Marin, Karan Dewnani, Shelagh Verco, and Gere S. diZerega

View All Author Information

https://doi.org/10.1097/JU.0000000000002778

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Abstract

Purpose:

We investigated the safety, preliminary efficacy, and immune effects of large surface area microparticle docetaxel (LSAM-DTX) administered by direct injection after transurethral

Clinical trial | Open Access | Published: 26 April 2022

Phase 1/2 study of topical submicron particle paclitaxel for cutaneous metastases of breast cancer

Mario E. Lacouture, Shari B. Goldfarb, Alina Markova, Sant P. Chawla, Karan Dewnani, Marc Iacobucci & Julie E. Lang

Breast Cancer Research and Treatment **194**, 57–64 (2022) | Cite this article

3706 Accesses | **51** Altmetric | Metrics

Link

Abstract

Purpose

This Phase 1/2 study evaluated safety and efficacy of a topical submicron particle paclitaxel (SPP) in an anhydrous ointment base (SOR007), primarily in breast cancer patients with cutaneous metastases (CM).

Medical Oncology (2021) 38:106
https://doi.org/10.1007/s12032-021-01555-1

ORIGINAL PAPER

Submicron particle docetaxel intratumoral injection in combination with anti-mCTLA-4 into 4T1-Luc orthotopic implants reduces primary tumor and metastatic pulmonary lesions

Holly Maulhardt[1] · Alyson Marin[1] · Holly Hesseltine[1] · Gere diZerega[1,2]

Received: 1 March 2021 / Accepted: 24 July 2021 / Published online: 31 July 2021
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Link

Abstract

We describe here characterization of the response of local and metastatic disease and immunomodulation following intratumoral (IT) injection of submicron particle docetaxel (SPD) administered alone or in combination with systemic antibody anti-mCTLA-4 (anti-mCTLA-4) in the metastatic 4T1-Luc2-1A4 (4T1) murine breast cancer model. In-life assessments of treatment tolerance, tumor volume (TV), and metastasis were performed ($n = 10$ animals/group). At study end, immune cell populations in tumor-site tissues and peripheral blood were analyzed using flow cytometry. Signs of distress typical of this aggressive tumor model occurred across all animals except for the combination treated which were asymptomatic and gained weight. TV at study end was significantly reduced in the combination group versus untreated [43% reduced ($p < 0.05$)] and vehicle controls [54% reduced ($p < 0.0001$)]. No evidence of thoracic metastasis was found in 40% of combination group animals and thoracic bioluminescence imaging (BLI) was reduced vs. untreated controls ($p < 0.01$). Significant elevations ($p < 0.05$) in CD4 + T, CD4 + helper T, Treg, and NKT cells were found in tumor and blood in SPD or combination treatment compared to controls or anti-mCTLA-4. Combination treatment increased tumor-associated CD8 + T cells ($p < 0.01$), peripheral B cells ($p < 0.01$), and tumor associated and circulating dendritic cells (DC) ($p < 0.05$). Tumor-associated NK cells were significantly increased in SPD ± anti-mCTLA-4 treatments ($p < 0.01$). Myeloid-derived suppressor cells (MDSC) were reduced in bloods in SPD ± anti-mCTLA-4 groups ($p < 0.05$). These data demonstrate that both SPD and anti-mCTLA-4

nistered in

Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-022-01226-2

REVIEW ARTICLE

Local administration of large surface area microparticle docetaxel to solid carcinomas induces direct cytotoxicity and immune-mediated tumoricidal effects: preclinical and clinical studies

Holly Maulhardt[1] · Shelagh Verco[1] · Michael Baltezor[2] · Alyson Marin[1] · Gere diZerega[1,3]

Link

Accepted: 8 August 2022
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Abstract

This report describes local administration of large surface area microparticle docetaxel (LSAM-DTX: ~ 3.5- to 7.5-µm-sized particles with high relative surface area) in preclinical oncology models and in a clinical trial in urothelial carcinoma. Reductions in tumor volumes were found following intratumoral (IT) injection of LSAM-DTX into human urologic carcinoma cell lines and syngeneic murine renal and breast cancer cell lines. Compared to IT injections of docetaxel solution typically administered intravenously, IT LSAM-DTX results in 40-fold more docetaxel retained within the tumor. The long residence time of LSAM-DTX within the tumor acts as a drug depot, allowing for continuous release of docetaxel, exposing tumor cells to high, therapeutic levels of chemotherapeutic for several weeks. Local LSAM-DTX results in tumoricidal effects at the site of deposition as well as in distant tumors, and IT LSAM-DTX in combination with immune checkpoint inhibitor therapy reduces or eliminates metastatic spread. Tumoricidal effects of local LSAM-DTX are accompanied by immunomodulation including increases in innate and adaptive immune cells in the tumor microenvironment and peripheral blood. Encouraging clinical results indicate that local administration of LSAM-DTX may provide therapeutic benefits for non-muscle invasive bladder cancer and muscle invasive bladder cancer patients; treatments were well-tolerated with few local and systemic adverse events and negligible systemic docetaxel exposure. Results of preclinical and clinical investigations summarized here indicate that local administration of LSAM-DTX may augment tumor response to systemically administered chemotherapy, targeted therapy, or immunotherapy without contributing to systemic toxicity.

Response of Locally Advanced Pancreatic Cancer to Intratumoral Injection of LSAM-PTX: Initial Report of Safety and Clinical Outcome
--Manuscript Draft--

Manuscript Number:	
Article Type:	Original Article: Human Clinical Trial
Keywords:	locally advanced pancreatic cancer; LAPC; intratumoral injection; LSAM-PTX; EUS-FNI
Corresponding Author:	Gere diZerega, MD US Biotest, Inc. San Luis Obispo, CA UNITED STATES
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Manuscript Region of Origin:	UNITED STATES
Abstract:	Background and Aims Large surface area microparticle paclitaxel (LSAM-PTX) was developed to provide an intratumoral (IT) depot for local tumor kill. Safety, tolerability, and tumor response to IT LSAM-PTX in unresectable locally advanced pancreatic cancer (LAPC) tumors (1.5-6cm) using endoscopic ultrasound-fine needle injection (EUS-FNI) was assessed

Submitted for publication
Pancreas

Intracystic Injection of Large Surface Area Microparticle Paclitaxel for the Treatment of Mucinous Pancreatic Cysts

Mohamed Othman*, Kalpesh Patel*, Somashekar G. Krishna‡, Antonio Mendoza-Ladd§, Shelagh Verco‖, Wasif Abidi*, James Verco‖, Alison Wendt‖, and Gere diZerega‖,¶

Gastroenterology and Hepatology Section, Baylor College of Medicine Medical Center, Houston, Texas; ‡Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, Columbus, Ohio; §Internal Medicine, Texas Tech University Health Sciences Center at El Paso, El Paso, Texas; ‖US Biotest, Inc., San Luis Obispo, California; and ¶NanOlogy, LLC., Fort Worth, Texas

Link

Clinical Data Highlights

	Indication	Subjects	Trial Phase	Dose	Dose Range	Clinical Data Summary

LSAM-PTX	Locally Advanced Pancreatic Cancer NCT03077685	54	Phase 2a	**EUS-FNI**
				• 1st cohort: dose rising single intratumoral (IT) injection
				• 2nd cohort: 2 x monthly IT injections
				• 3rd cohort: 4 x monthly IT injections
					20% tumor volume (up to 5 mL)
					6, 10, and 15mg/mL
						• Safe/well tolerated; mild/mod transient abdominal pain; no reports of pancreatitis
						• 1st cohort complete (n=10):
						• 2nd cohort complete (n=22):
						  • Neoadjuvant subset (n=14/22):
						  • 8/14 restaged (57%); 6 resected ; 5/6 R0 (83%); 1 x pCR; 3 x >80% pCR
						  • mOS: 35.2M/18.9M (resected/nonresected subjects)
						• 3rd cohort enrollment complete (n=19): final readout 3Q23
						• **Evidence of tissue/systemic immunomodulation**

	Pancreatic Cysts (MCN/IPMN) NCT03188991	19	Phase 2a	**EUS-FNI** • 1 intracystic injection • 2 intracystic injections (12 weeks apart)	Equal to volume aspirated from cyst 6, 10, and 15mg/mL	• Cyst volume reduction in 14/19 (74%) subjects at 6M • Evidence in selected subjects of epithelial lining necrosis (-DNA or endomicroscopy) • PK analysis of cyst fluid at 3M > 250ng/mL (ULOQ) paclitaxel
	Lung Cancer NCT04314895	18	Phase 2a	**EBUS-TBNI** • Up to 3 x monthly IT injections • (28 days before prostatectomy)	20% tumor/node volume 15mg/mL	• Safety established in initial subjects • Preliminary data on initial 11 subjects: > 40% tumor volume decrease (6/11); > 18 wk durability (5/10); final readout 4Q23 • **Evidence of systemic immunomodulation**
	Peritoneal Malignancies NCT00666991	21	Phase 1	**Intraperitoneal** • 1 to 6 intraperitoneal infusions	50 – 275mg/m^2	• 6/21 (29%) subjects (salvage patients) survived > 1 year • Peritoneal fluid concentrations 450-2900 times greater than peak plasma drug concentrations/plasma concentration subtoxic at all timepoints
	Ovarian Cancer NCT03029585	10	Phase 2	**Intraperitoneal** • 1 intraperitoneal instillation at end of debulking surgery	100 – 200mg/m^2	• PFS 60% ≥ 6M • ORR 50% (CR 20%; PR 30%) • OS 70% > 1 year
	Prostate Cancer NCT03077659	16	Phase 1	**TPUS-guided-FNI** • 1 intralobular injection • 28 days before prostatectomy	20% lobe volume (up to 5 mL) 6, 10, and 15mg/mL	• Safe/well tolerated; no reports of prostatitis • Mean tumor volume reduction 46% • Mean PSA-density decrease 35%
LSAM-DTX	hrNMIBC NCT03636256	19	Phase 1/2	**Cystoscope-guided-IMI & IVT** • Intramural (IMI) post TURBT • Intravesical Therapy (IVT) x 10	3-15mg 50-75mg	• CR 4M 15/19 (79%) (all doses) • CR >7M 7/9 (78%) (high dose cohort) • **Evidence of tissue immunomodulation**
	MIBC NCT03636256	17	Phase 1/2	• IMI/IVT post TURBT x 1	3-15mg 50-75mg	• CR 45 days 9/17 (53%) • Series of 5 subjects with long-term CR following TURBT + IMI/IVT NanoDoce

As of December 2022. Preliminary data for trials in process.

NanOlogy

Clinical Immunomodulation in Pancreas, Bladder, Lung

- MultiOmyx™ multiplex immunofluorescence analysis of tumor tissue in pancreas/bladder trials pre/post LSAM injection
  - Increases in cytotoxic T cells
  - Increases in NK cells
  - Decreases in MDSCs
  - Increased density of PD-L1
- Flow cytometry analysis of blood in pancreas/lung trials pre/post LSAM injection
  - Increases in cytotoxic T cells
  - Increases in NK cells
  - Decreases in MDSCs
- Preclinical synergy shown with LSAM + ICI in metastatic breast cancer and melanoma models

US patent allowed: *Local Delivery of Antineoplastic Particles in Combination with Systemic Delivery of Immunotherapeutic Agents for the Treatment of Cancer*

- **Valid through 2038 and corresponding filings globally**
- **Product life cycle extension possibility for immune checkpoint inhibitors facing patent expiration**

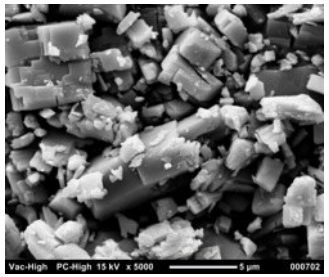
As of Oct 2022. Preliminary data.

LSAM Technology Platform Expansion

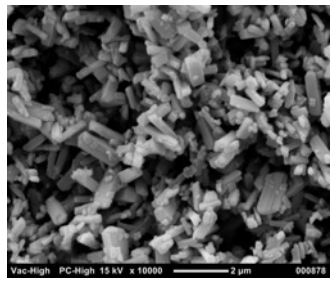
Feasibility established in a wide range of molecules

Preprocessed Cisplatin

D_{V50} (µm)	11
SSA (mg^2/g)	2.4
Density (g/cm^3)	1.0



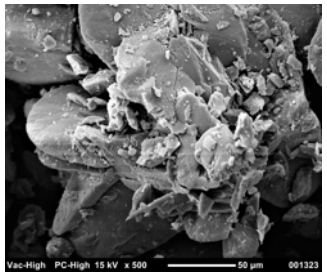
LSAM-Cisplatin(1)



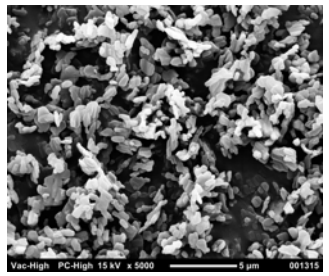
D_{V50} (µm)	2
SSA (mg^2/g)	4.4
Density (g/cm^3)	0.4

Preprocessed TKI

D_{V50} (µm)	98
SSA (mg^2/g)	0.9
Density (g/cm^3)	0.7



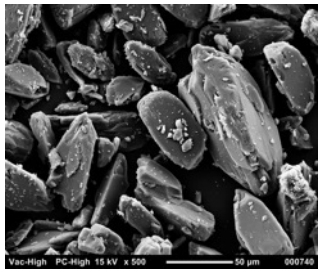
LSAM-TKI(2)



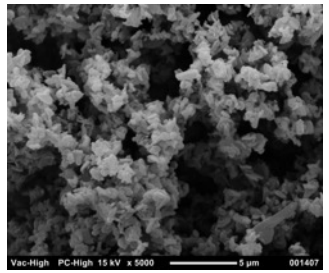
D_{V50} (µm)	2
SSA (mg^2/g)	10.0
Density (g/cm^3)	0.1

Preprocessed PARPI

D_{V50} (µm)	103
SSA (mg^2/g)	0.7
Density (g/cm^3)	0.6



LSAM-PARPI(3)



D_{V50} (µm)	5
SSA (mg^2/g)	12.0
Density (g/cm^3)	0.1

- ✓ **Particle size optimized for tumor-directed delivery**
- ✓ **Significant increase in specific surface area (SSA) for therapeutic drug release**
- ✓ **Significant decrease in bulk density for suspendability in formulation**

NanOlogy

1. CT-2021-01-C; SC2104
2. CT-2020-03-A; CT-2021-06-B (example shown sorafenib)
3. CT-2021-03-A; CT-2021-06-B (example shown niraparib)

Development Priorities

- Initiate RCT of neoadjuvant IT LSAM-PTX + SOC (ICI + CT) vs SOC in lung cancer (2023)
- RCT of neoadjuvant IT LSAM-DTX + SOC vs SOC in high-risk early breast cancer via planned clinical collaboration with leading breast cancer institution (2024)
- Further preclinical/clinical studies on immunomodulatory effect of tumor-directed LSAMs (Ongoing)
- Continue technology platform expansion with IND (lung) for LSAM-cisplatin (2024)
- Continue business development discussions on clinical collaboration or broader deal (Ongoing)