LEONARDO BIOSYSTEMS

A Revolution in the Treatment of Metastatic Cancer

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Leonardo's Platform is Unique

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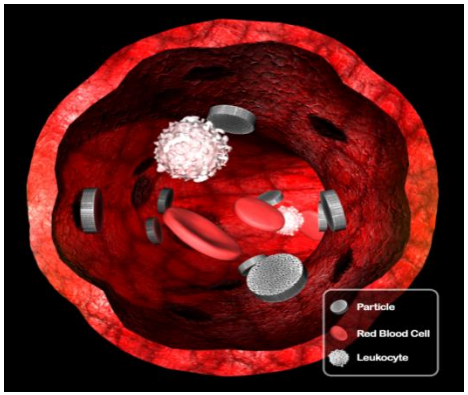
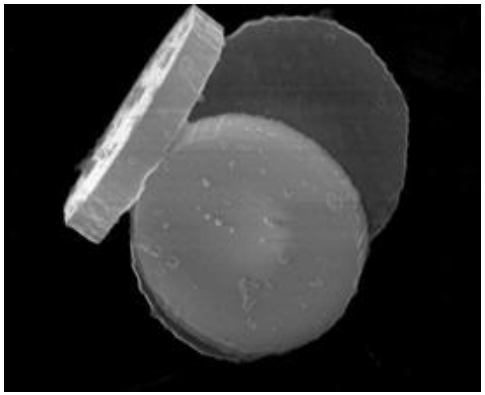
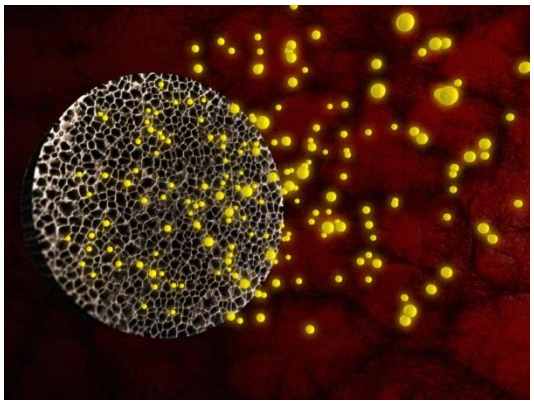
The Multistage Vector (MSV) Drug Delivery System







- First stage silicon particles concentrate in primary and metastatic tumor sites and release large amounts of second stage particles with Active Ingredients
- Release rate of second stage particle is controllable from days to weeks
- Second stage design optimized for local action

Keys to Translational Research

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- Determine Unmet Market Needs
- Identify Critical Product Attributes
- Identify Key Regulatory Requirements
- Map “Complete” Process Flow
- Determine Critical Process Parameters (CPC)
- Identify Key Scale Up risks for “Practical Process”
- Develop Reproducible Pilot Scale Results!!!
- Establish a “Clear Commercial Path”

Dramatic Gains in Metastatic Cancer Therapeutic Index

- **Redefines how we attack metastatic cancer:**
  - Concentrates therapeutic agents at metastatic target sites
  - Significant reduction in systemic toxicity effects
  - Capacity to carry 800 times the payload to target site
  - Flexibility to deliver new RNAi payloads past natural defenses
  - Ability to sustain localized drug release for several weeks
  - Higher localized concentrations proven effective on therapy resistant cancer cells

Improved late stage metastatic cancer outcomes

Extensive Pipeline Opportunities

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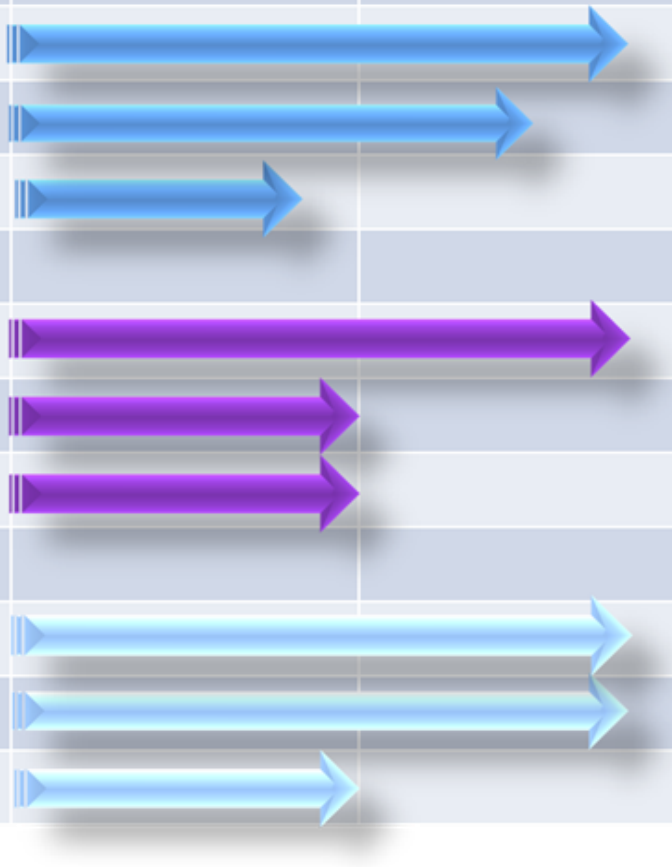
	Discovery	Development	Preclinical	Phase 1
Oncology				
Triple Negative Breast Cancer				
Ovarian Cancer				
Bone Cancer				
Tissue Targeting				
Lung Metastasis				
Pancreatic Cancer				
Bone Metastasis				
Established Payloads				
Small Molecule drugs				
siRNA therapeutics				
Thermo Nano Shells				

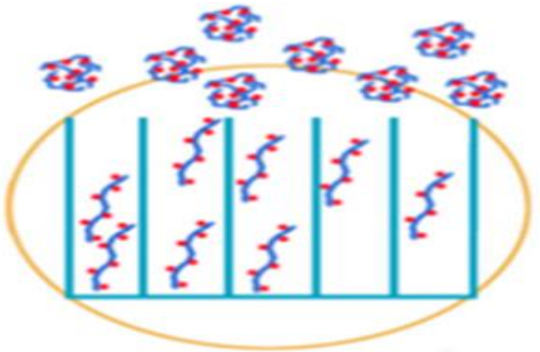


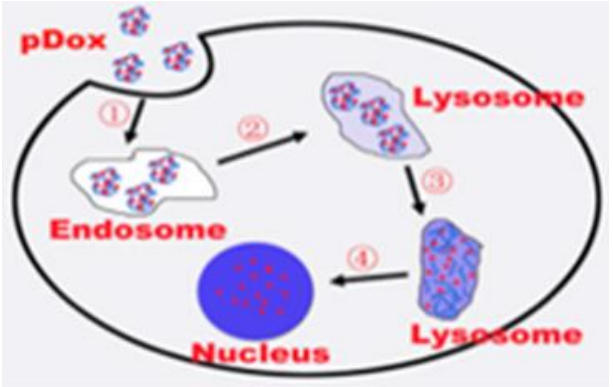
Identify Critical Product Attributes

- Effective Treatment of Metastatic Cancer!!!
- Particle Size/Shape
- Particle Surface Charge
- Drug Assay and Impurity Profile
- Drug Release Rate
- Sterility
- Stability

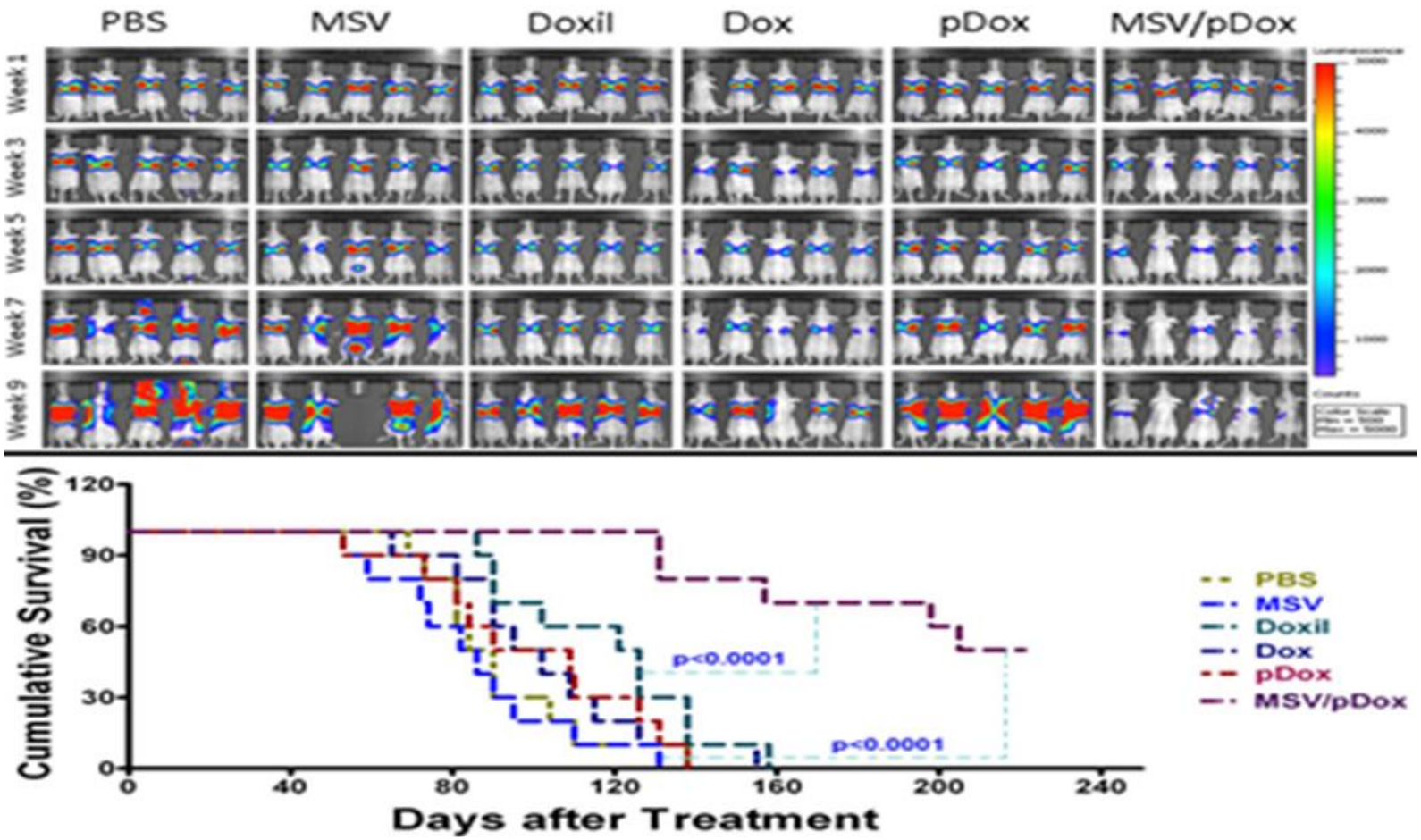
Data on metastatic TNBC Drives Selection for Lead Product: pDox

- Doxorubicin is a broad spectrum anti-cancer molecule currently limited by severe toxicity
- When attached to glutamic acid polymers, circulating doxorubicin is systemically inert and safely cleared
- When loaded into MSVs it is concentrated at tumor sites
- Locally released pDox particles are taken up by tumor and free Dox released to kill the tumor





50% Overall Survival Achieved in metastatic Triple Negative MDA-MB-231Animal Studies



Top: Lung metastasis progression monitored with Xenogen IVIS system
Bottom: Kaplan-Meier plot showing **50% Overall survival of MSV/pDox group**

- Shen, H et al, Manuscript in review

Map "Complete" Process Flow

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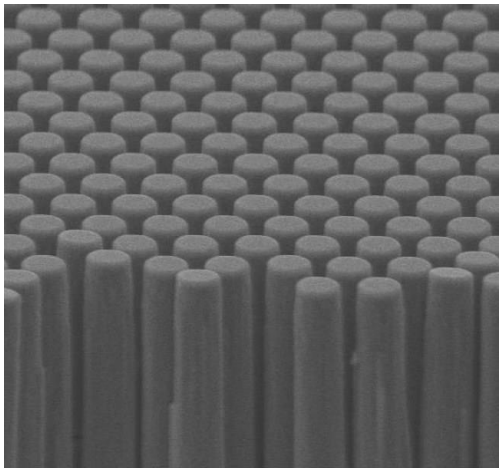
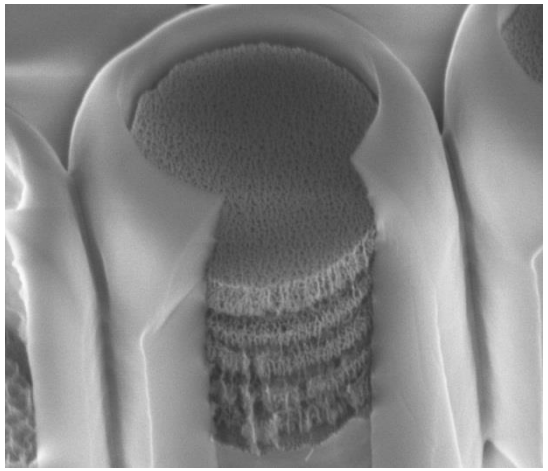
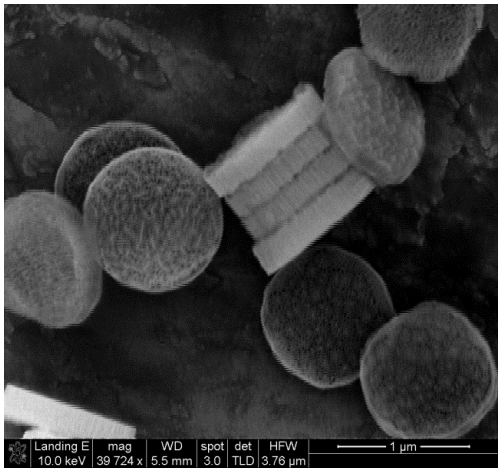
- Mfg MSV First Stage particles
- Surface Modify MSV particles
- Mfg pDox Second Stage particles
- Load pDox particles in to MSV particles
- Fill and Dry Finished Product
- Test and Release Finished Product
- Reconstitute and Inject Finished Product

MSV First Stage Manufacturing: Breakthrough Achieved



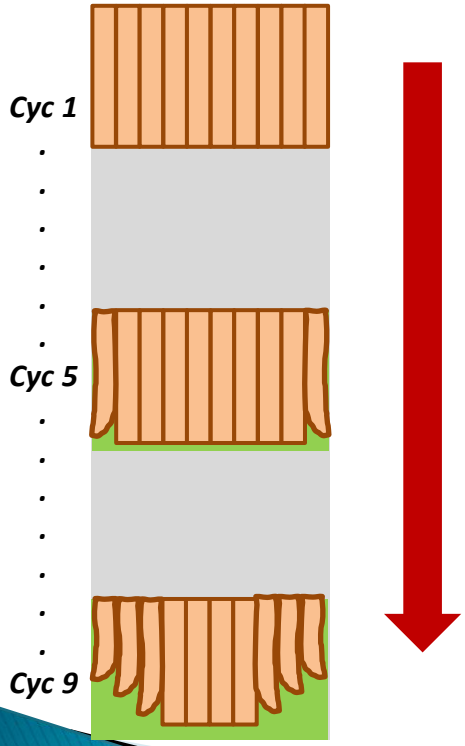




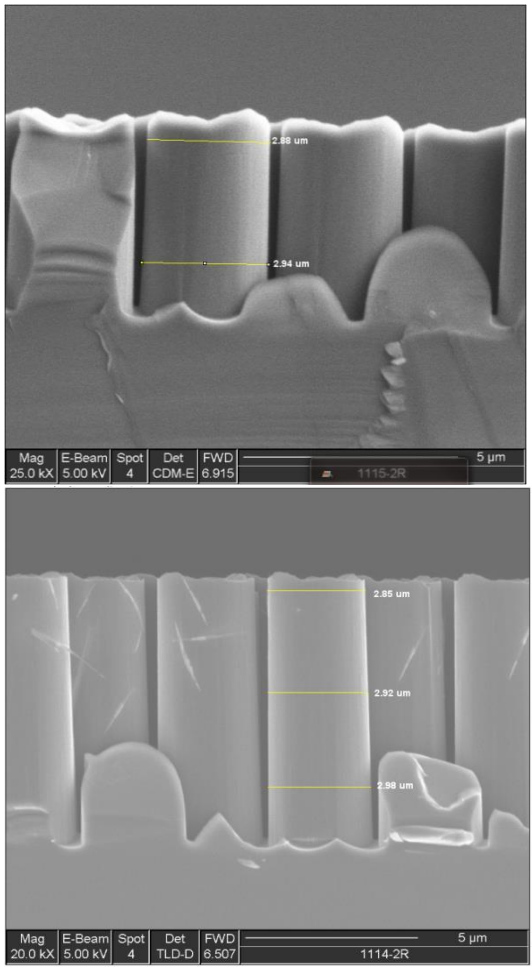
- Starting materials are high purity silicon wafers- forming particles with consistent size, shape, and porosity – Lab scale to Commercial Fab!
- Original single layer process (1 bb/wafer) evolved to a high density, multi-layer system (160 bb/wafer) to achieve capacity and cost targets
- System has been successfully scaled up and conversion to cGMP operations is underway
- Process has one patent issued and others pending

Overcoming Multilayer Scale Up Challenge

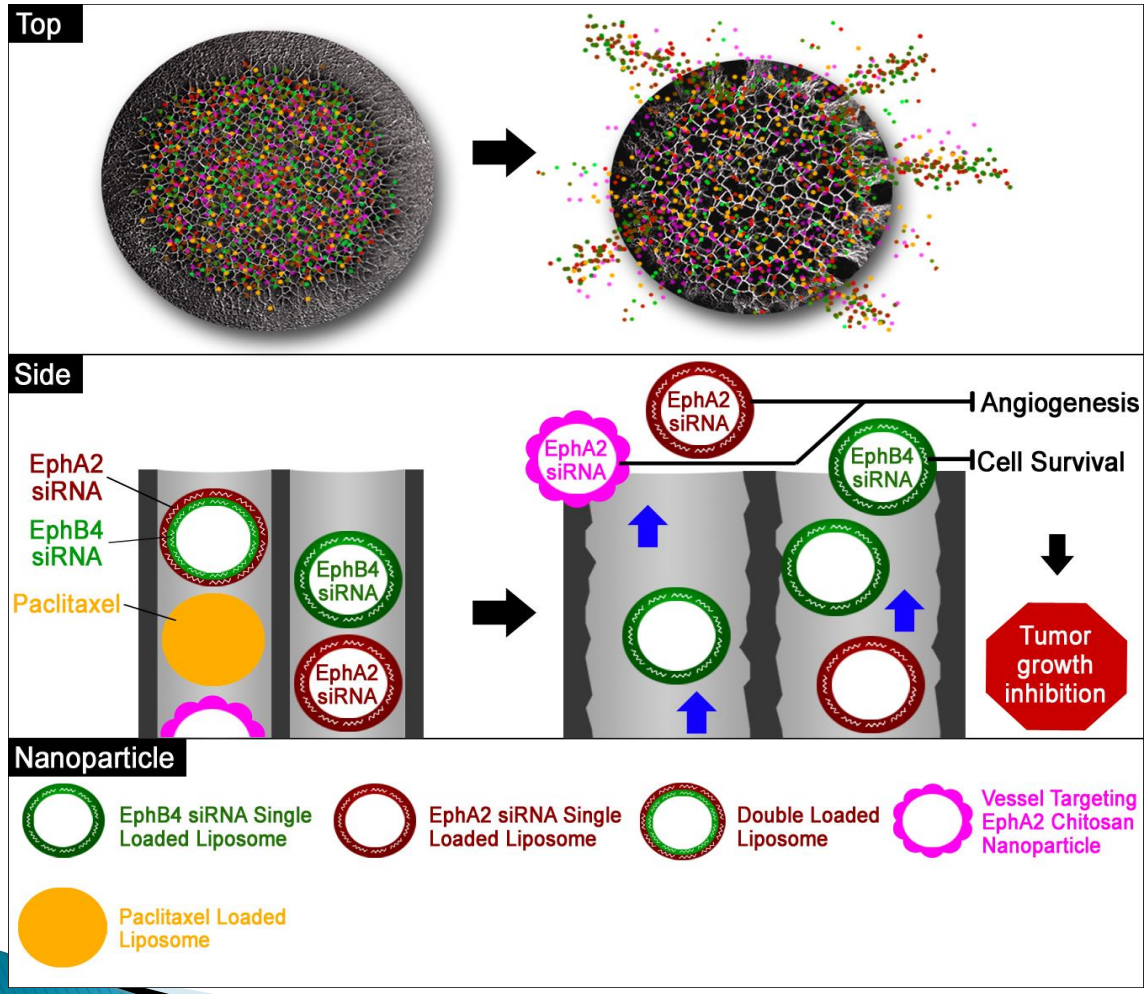
- Etching depth- aspect ratio challenge
- Annodization depth- flux control



Increase in depth *'l'*, leads to difference of potential drop of the electrolyte



MSV First Stage Active Loading: Breakthrough Achieved



Surface charge of First Stage optimized to target inflamed tissues to concentrate particles

Surface charge of Second Stage optimized to be compatible with target site cellular penetration

Loading solvent charge optimized to make both Stages "compatible" and allow efficient loading

Regulatory Considerations

- **ICH Q8- Quality by Design (QbD)**
  - "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management"
  - Defined Target Product Profile
  - Designed product and processes
  - ID critical attributes and Design Space
  - Develop adequate manufacturing process controls

Regulatory Considerations

- **FDA- 505.b(2)**
- Establish QC Functions
- Establish cGMP Facility and Equipment
- Control of Components, Containers, and Labeling
- Lab and Manufacturing Controls/Records
- Sterility
- GLP Toxicity Studies
  - Immunotoxicity
  - Acute Toxicity
  - Repeated treatment Toxicity
  - Cardiovascular and Respiratory Safety
- Stability

Key pDox Scale Up Factors

- Initial lab batches produced ~100 mg
  - Utilized dangerous solvents at high levels
  - Took 4 days to complete once batch
- Pilot Scale – 10 grams– 100x scale up limit
  - Utilized less flammable solvents
  - Reduced solvent use by 5x (1 truckload to 55 gal)
  - Reduced batch time to 2 days
  - Reduced cost/gram by factor of 30
- Production Scale – 1 kg– 100x scale up limit
  - Heat transfer controls required due to surface area
  - Aseptic controls required for cGMP testing

The Final Plan!!!

		Total				Q1			Q2			Q3			Q4			Q5			Q6			Q7			Q8			Q9			Q10		
	Activities	Checks	Start	Finish	Duration																													
		Cost	Weeks			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1) Optimization Phase																																			
	Leonardo Lab Set Up	208	0	12	12 wks	208																													
1,868.0	cGLP Particles from NMS	460	0	8	12 wks	35	25	25	25	25	325																								
	Wafers from SVCT	1000			8 wks	1000																													
204	pDox Process optimization -MRI	40	0	12	12 wks	10	10	10	10																										
	pDox Materials	4				4																													
	MSV Surface Treatment opt -MRI	20	4	12	8 wks			10	10																										
	Clean Room for ST optimization	200			16 wk	200																													
	MRI Sponsored Research	144				12	12	12	12	12	12	12	12	12	12	12	12																		
140	Analytical Methods for pDox	40	8	16	8 wks			20	20																										
	Test Methods for MSV/pDox Product	60	8	16	12 wks			20	20	20																									
	Microbial Methods (Mic load/EU)	40	10	14	8 wks				20	20																									
	Sub Total	**2,216.0**																																	
2) cGMP Sourcing Phase																																			
	Contract with cGMP CMO Sources	10			4 wks			10																											
	MSV Supply with ST	0			12 wks				0	0	0																								
740	pDox cGMP Supply	120			12 wks				40	40	40																								
	pDoxMaterials	180							40			40					100																		
	MSV/pDox loading process	120			12 wks					40	40	40																							
	MSV/pDox fill/dry/finish process	320			20 wks				40	40	40	40	40	40			40	40																	
260	Method Transfer and Validations	80			8 wks							40	40																						
	Tox Finished Product test/release	40			2 wks									20						20															
	Product Stability program	60			16 wks										20	20	20																		
	Long Term Stability program	80			120 wks															30												30			
	Sub Total	**1,010.0**																																	
		Cost			Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
3) Pre-Clinical Phase																																			
	Analytical Methods for Animal Species	60			6 wks								30	30																					
	ID and contract Tox Study CRO	0			4wks																														
	Request Pre-IND Meeting	0			8wks																														
	Assemble Pre-IND package	10			8 wk								5	5																					
	FDA Pre-IND Meeting	12			1 day									12																					
710	Dose Ranging Study - Rat and Dog	50			4 wks										50																				
	Ex vivo Hemocompatability	20			8-12 wks											20																			
	Small Animial Tox- Rat	180			8-12 wks											180																			
	Large Animal Tox- Beagle	400			8-12 wks											400																			
	Prepare IND Submission	70			12 wks												20	20	30																
	Prepare IRB Package	0			2 wks																														
	FDA IND Update Meeting	5			1 wks														5																
	IND Filed and approved by FDA	0			4 wks																														
	Sub Total	**807.0**																																	
		Cost			Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
4) Clinical Phase- Phase 1 Trial																																			
312	Select and Contract CRO's	150			4 wks											150																			
	Obtain IRB Approvals	25			4 wks																25														
1,140.5	Recruit patients (Rolling 3 site study)	640.5			12-56wks																30.5	30.5	30.5	30.5	30.5	30.5	30.5	30.5	30.5	30.5	30.5	30.5	30.5	30.5	30.5
	Dosing phase (Every 3 wks- 8 max)	500			24 wks																	25	25	25	25	25	25	25	25	25	25	25	25	25	25
	Summary Report	40			8 wks																														
	Long Term Stability Report	0			4wks																														
	Sub Total	**1,355.5**																					$317								499.5				

Ready to Move to the Clinic

- **Initiating Pre-Clinical Tox Studies**
- **Capital Requirements- Delivers completed Phase I trial**
  - $10 million Series A round- Funds through year 3
  - cGMP scale up of manufacturing systems
  - Phase I Clinical Study completed
  - Second program Phase I ready
  - Capital sparing infrastructure supports ongoing product development