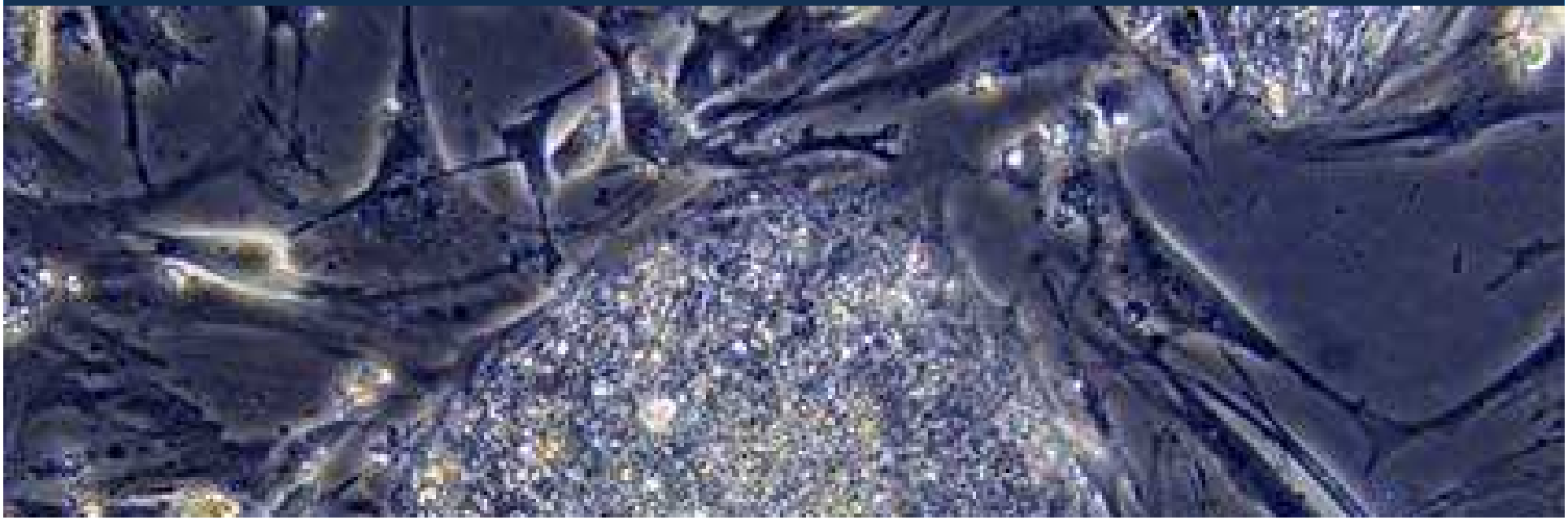
PROTEUS
VENTURE PARTNERS
FUNDING REGENERATIVE MEDICINE

Venture Funding for Regenerative Medicine Companies

Gregory A. Bonfiglio
Proteus Venture Partners

CIRM ICOC Loan Task Force – January 16, 2008



Agenda

- Proteus Venture Partners: Overview
  - Who Are We?
- Funding Environment for RM Companies
  - Where Are We And How Did We Get Here?
  - Current Market Dynamics: Technology Push & Market Pull
- Access To Venture Capital
  - Funding & Value Creation: The Valley of Death
  - Venture Capital Metrics: What Do VCs Want?
  - Typical Venture Terms: What Do VCs Get?

Proteus Fund: Summary

- **Regenerative Medicine Fund**
  - Stage Agnostic
  - Geographically Diverse
  - Top Tier Venture Returns
  - 1st Mover Advantage
- **Technology Focus**
  - Cell Therapies
  - Tissue Engineering
  - Tools & Enabling Devices
  - Aesthetic Medicine
- **Addressing Large Markets**
  - Aging Population
  - Large Unmet Medical Needs
  - Increasing Healthcare Spend

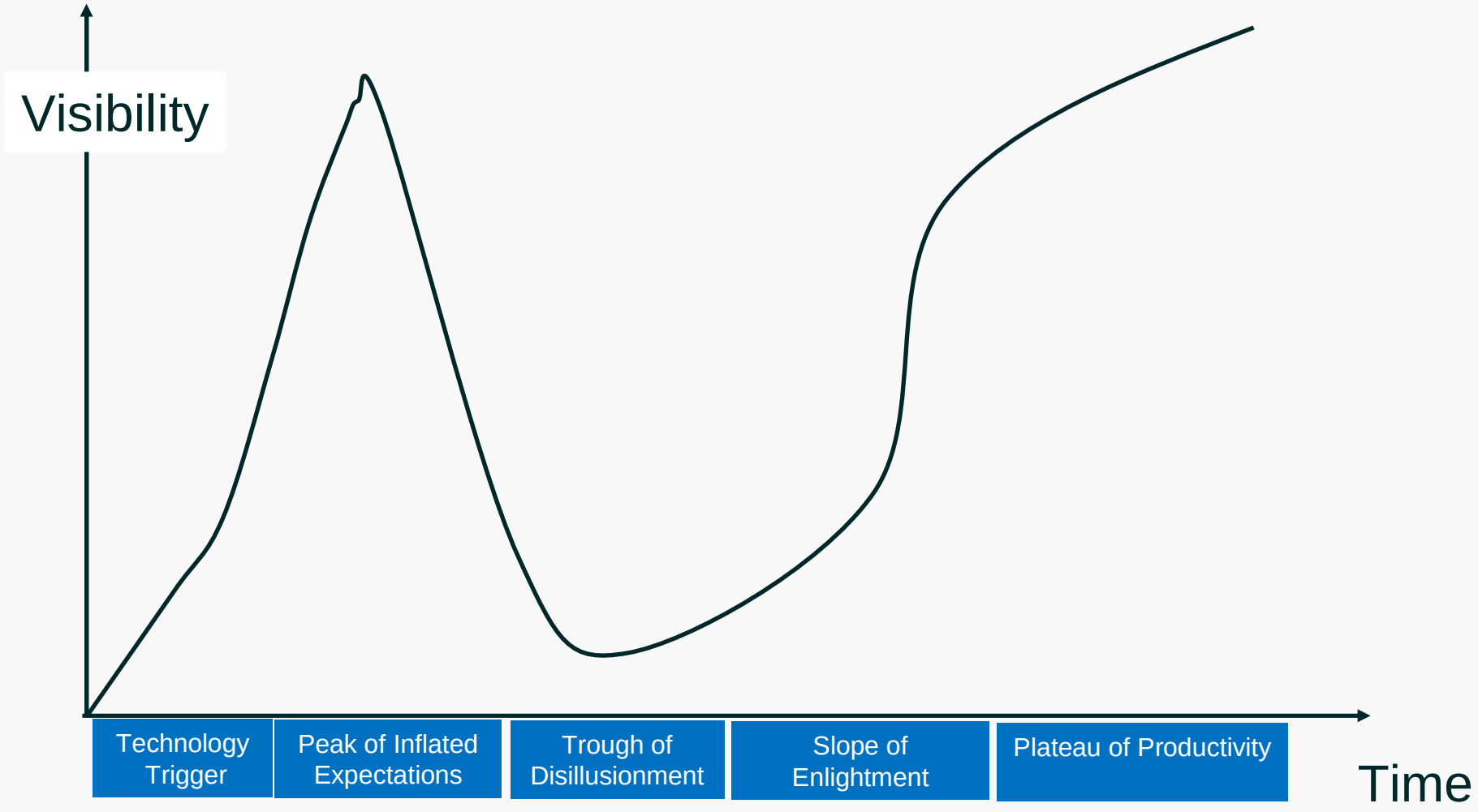
- **World Class Team**
  - Core Team with Complementary Skills
  - Deep Domain Expertise
  - Outstanding SAB & Strategic Partners
  - Industry Visibility & Leadership
- **Disciplined Investment Approach**
  - Proprietary Deal Flow
  - Rigorous Due Diligence
  - Build Value Thru Active Management
  - Timely Exits
- **Target Investments**
  - Outstanding Technology & Team
  - Defensible IP
  - Viable Business Model
  - Near Term Path to Clinic or Revenues

PROTEUS
VENTURE PARTNERS
FUNDING REGENERATIVE MEDICINE

Funding Environment for RM Companies

- Where Are We And How Did We Get Here?
- Current Market Dynamics: Technology Push & Market Pull

Gartner's Hype Cycle of Emerging Technologies



Funding Environment: 1st Cycle 1985-2002

- **Cell Therapies & Tissue Engineering Were Hot In The Early 1990s**
  - VCs Funded The Sector Aggressively
  - Research Projects
  - Grand Business Visions
- **Many New Companies Created**
  - ATS, Curis, Systemix, Bresagen, Organogenesis
- **Products Launched**
  - Carticel; Apligraf; Dermagraf
- **Market Peaked in 2000**
  - 3000 jobs; 73 companies; total market cap of $2.6B
  - Time Magazine: "**TE Number 1 Job in USA**"

PROTEUS
VENTURE PARTNERS

Funding Environment: 1st Cycle 1985-2002

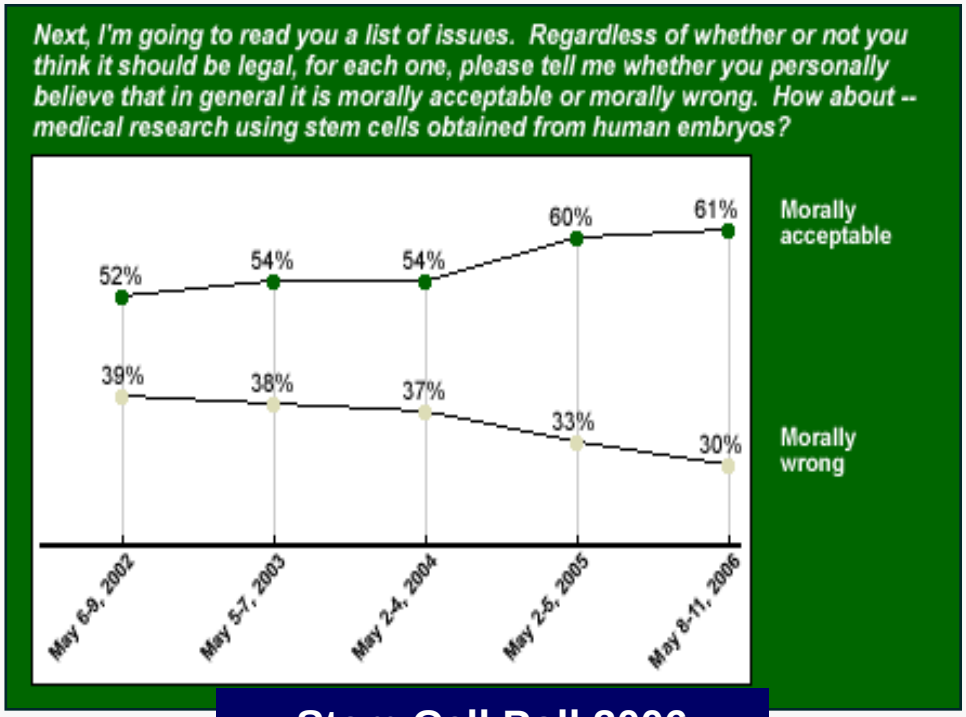
- **Market Collapsed in 2001**
  - ATS, Organogenesis filed Bk in 2002
- **Political Controversy Over hESCs**
- **Many High Profile Failures or Retrenchments**
  - ATS, Curis, PPL, Bresagen, BioTransplant, Organogenesis
- **VCs Withdrew Support For the Sector**
  - Overall Healthcare Funding Remained Strong
  - But RM Companies Got **Under 2%**
  - Many Big VCs had **Nuclear Bombs** in Portfolio

Funding Environment: A New Cycle

- **Gov't Funding Increasing**
  - –**California Prop 71** & Wisc, NJ, NY, MD, etc
  - –UK; Singapore; Australia; Canada

- **Political Risk Declining**

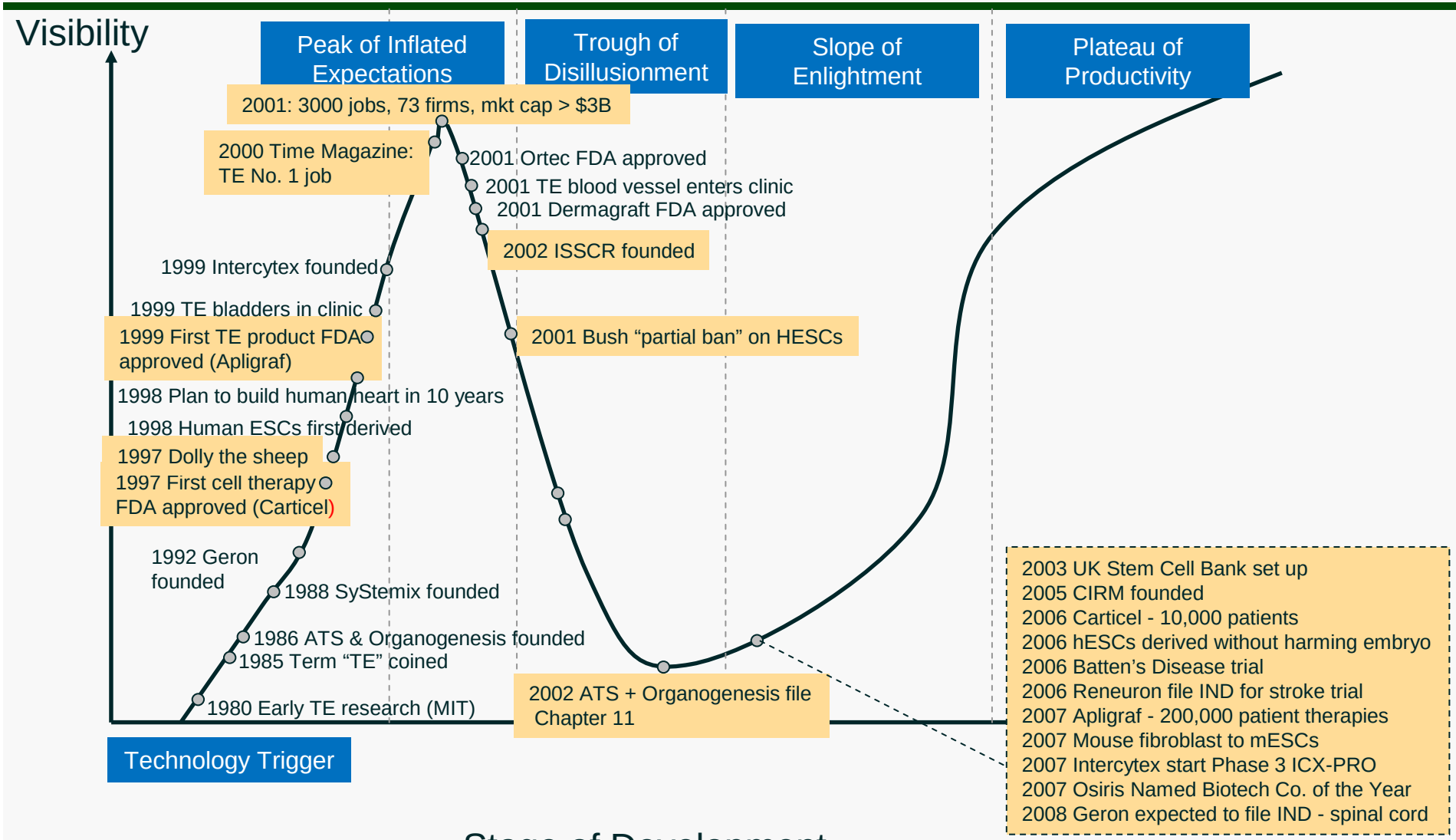
- **RM Market Maturing**
  - –Technology Advancing
  - –Products Entering the Market



Stem Cell Poll 2006

PROTEUS VENTURE PARTNERS

Technology Push: Beginning the 2nd Half of the Gartner Curve



PROTEUS VENTURE PARTNERS

Funding Environment: Market Dynamics

RM is Maturing after 40 Years of Development

- Research programs proliferating: 65+
- Technology maturing
- Clinical activity accelerating (800+ FDA trials)
- Increased Government Funding

300+ Companies

Healthcare Spend is 17% of US GDP Heading Towards 23%

- Demographics: aging populations
- Large unmet medical needs
- Pharma pipeline diminishing
- Public markets receptive

The Market is at a Crucial Inflection Point

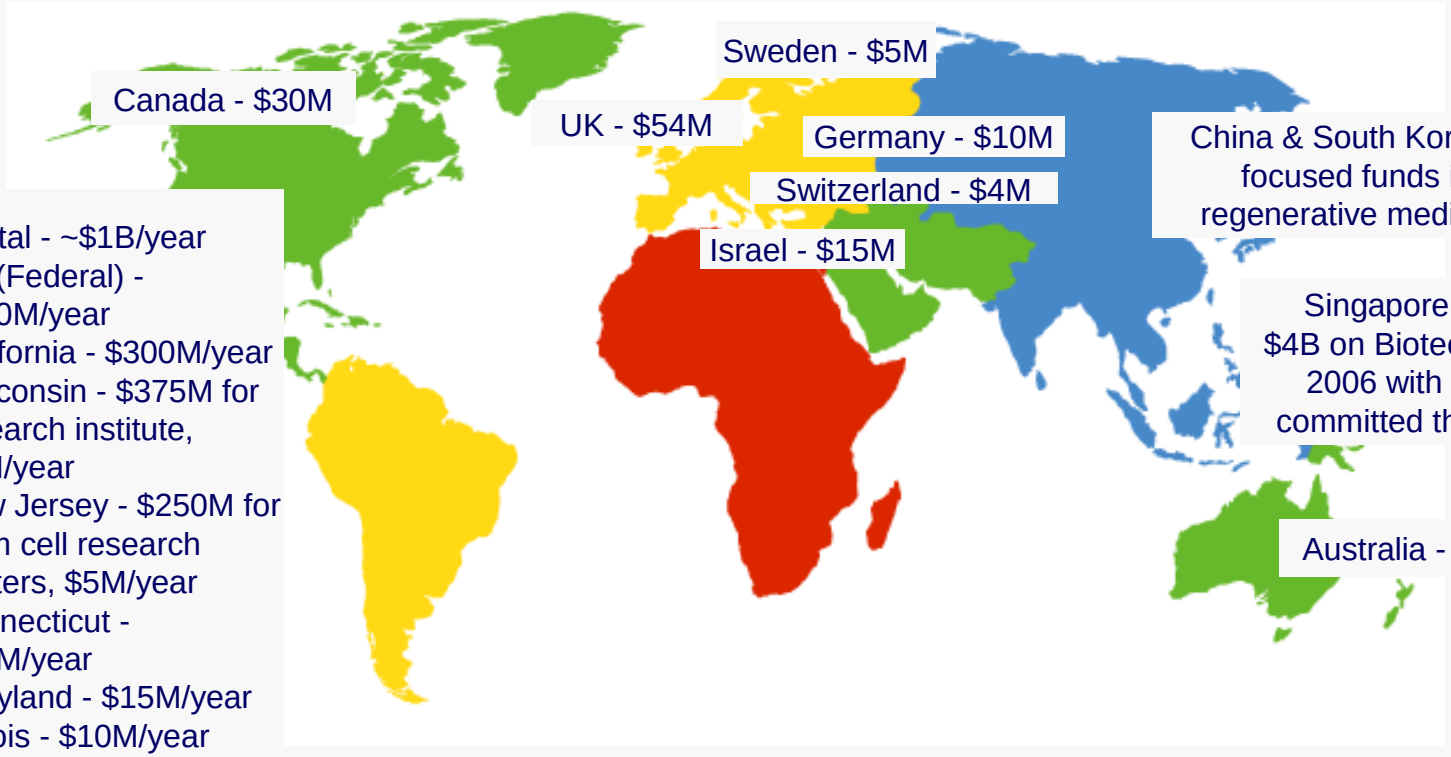
Technology Push: RM Programs Proliferating

Over 65+ Regenerative Medicine Programs Nationwide

Source: TFG Analysis

Technology Push: Increased Gov't Funding

Worldwide Funding for RM Expected to Reach $14B Worldwide in 10 years



US Total - ~$1B/year

- US (Federal) - $600M/year
- California - $300M/year
- Wisconsin - $375M for research institute, $5M/year
- New Jersey - $250M for stem cell research centers, $5M/year
- Connecticut - $20M/year
- Maryland - $15M/year
- Illinois - $10M/year

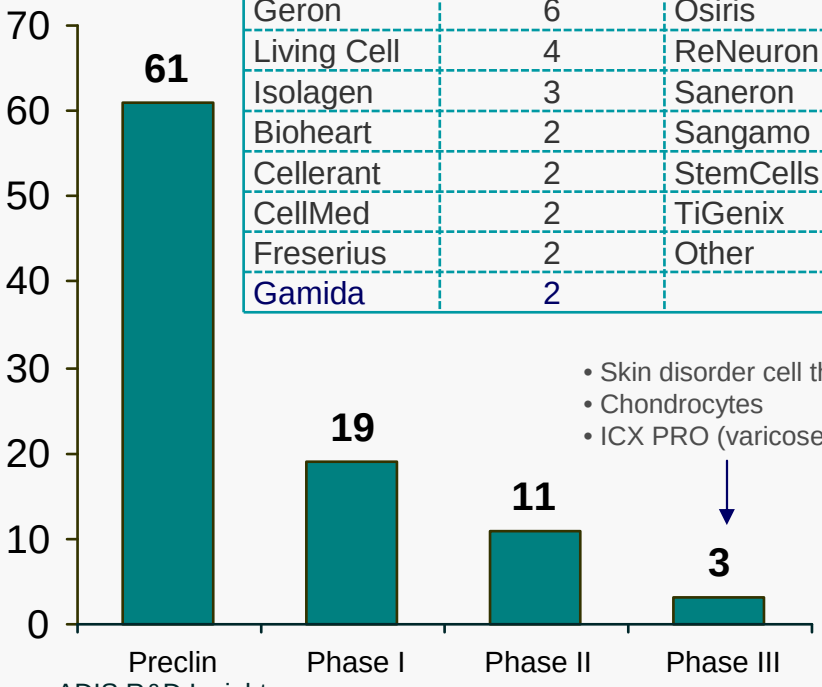
Source: Media Articles, Navigant, TFG Analysis

Technology Push: Products Entering the Market

90+ Programs In Development – 30+ Clinical Trials – 25+ Products Launched

Products in Development By Stage

n = 94

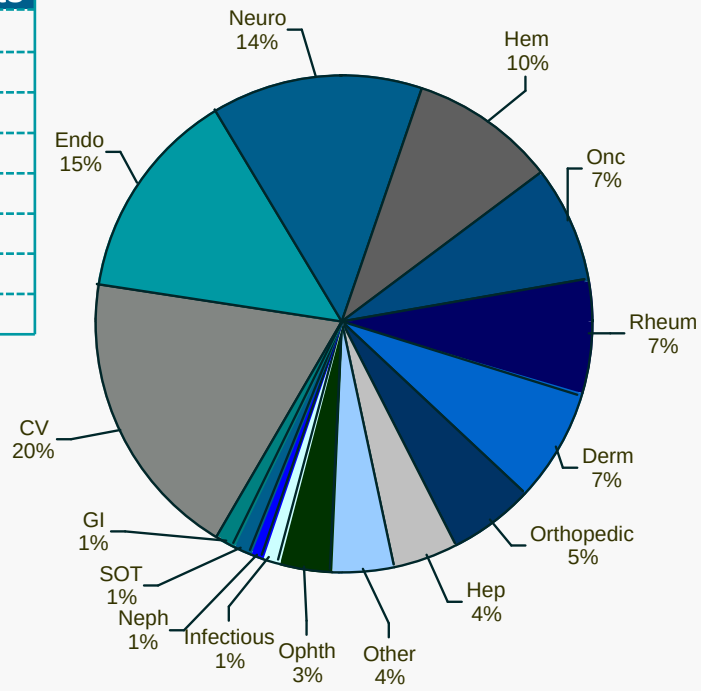


Company	# Products	Company	# Products
Geron	6	Osiris	2
Living Cell	4	ReNeuron	2
Isolagen	3	Saneron	2
Bioheart	2	Sangamo	2
Cellerant	2	StemCells	2
CellMed	2	TiGenix	2
Freserius	2	Other	47
Gamida	2		

- Skin disorder cell therapy
- Chondrocytes
- ICX PRO (varicose ulcer)

Source: ADIS R&D Insight

Products in Devel. by Therapeutic Area



PROTEUS VENTURE PARTNERS

RM Revenues Are Ramping: $130M in 2001 to $1.15B in 2006

Company	Product	Market	2001 ($US M)	2005 ($USM)	2006 ($USM)
Medtronic	INFUSE	BMP (US)	0	500.0*	570
LifeCell	AlloDerm, Cymetra, Repliform, GraftJacket, AllocraftDBM	Skin, Urology, Bone (US)	26.6	88.9	136.8
Genzyme	Carticel	Cartilage (US)	18.4	66	67.5
Tutogen	Tutoplast	Bone	12.8	31.9	37.9
Organogenesis	Apligraf	Skin (US)	20.0*	40.0*	45.0*
Interpore (Biomet)	AGF, Pro Osteon, Bone Plast	Orthobiologics	20.1	21.0*	22.0*
Integra Life Sciences	Neuragen, Integra, Newdeal, Duragen, Collagen Sponge	Skin, Orthopedics (US)	8.7	135	166
Biotissue technologies	BioSeed-S, BioSeed-C, BioSeed Oral Bone	Skin, Cartilage, Bone (GER)	1.3	2.0*	2.0*
Co.don	Chondrotransplant	Cartilage	1.6	0.4	0.6*
Stryker	OP-1	BMP (US)	0.5*	23.0*	25.0*
Orquest (DePuy)	Healos	Bone, Cartilage, Soft Tissue (US)	1.1*	2.0*	2.0*
ReGen	Collagen Meniscus Implant	Cartilage (US Trials)	0.5	0.6	0.6
Isolagen	Autologous Fibroblasts	Skin	0	8.8	6.1
Others	Various	Various	10	40.0*	60*
Total			**~$130M**	**~$900M**	**~$1,150M**

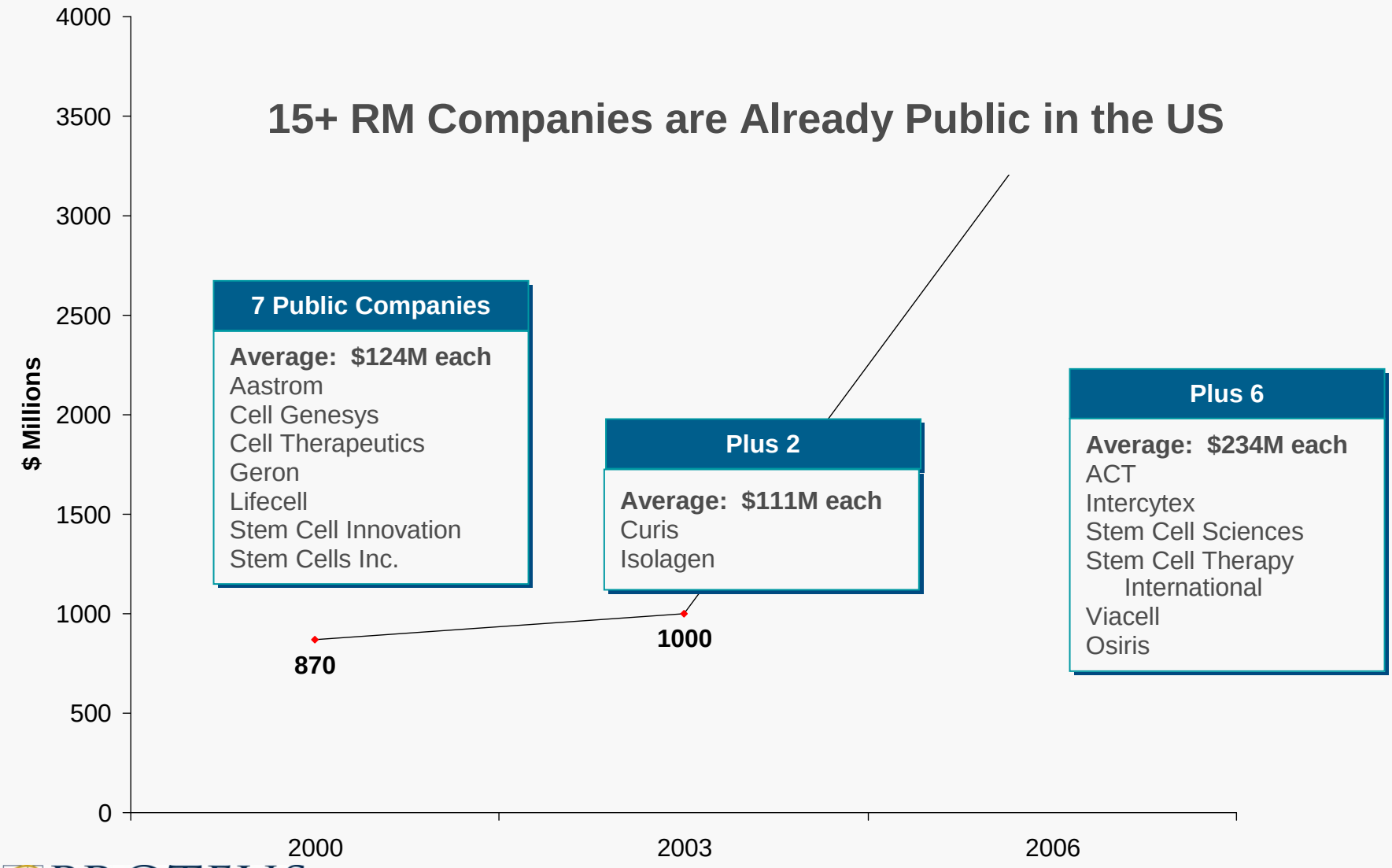
Source: PJB Publications 2003; Equity Research; Company websites; SEC; *=Estimated

New RM Companies Forming

Cell Therapy	Cell Therapy (Cont.)	Genomics/Tools	Tissue Engineering	Aesthetic Medicine
Advanced Cell Technology	CytoMatrix	Aclara Biosciences	Aastrom Biosciences	Allergan
Alexion Pharmaceuticals	Cytori Therapeutics	Affymetrix	Befutur Biotechnologies	Artefill
Allcells, LLC	Dendreon	Agilent Technologies	BioHeart Inc.	Artes Medical, Inc.
Amcell, Inc.	Desmos, Inc.	BioAnalyte	BioMimetic Pharmaceuticals	Candela Corporation
Amcyte, Inc.	Diacrin, Inc.	Caliper Life Sciences	BioTissue Technologies GmbH	Cynosure Inc.
Anergan	Educell d.o.o	Celera Genomics	Cellect Bio	Galderma
Argos Therapeutics	ES Cell International	CuraGen Corporation	Chrysalis BioTechnology	Genaera
Athersys	Gamida Cell	Diversa Corporation	Co.Don	Inamed
BioE	GenOWay	Geneos	CryoLife	Intercytex
Biohybrid Technologies	Geron	GeneLogic	Cytograft Tissue Engineering	Karo Bio
BioMark International	Histostem	HGSI	Dentigenix	Ligand
Cell Transplant International	Interpore International	Illumnia, Inc.	Encelle	MediCor
Cellartis AB	Islet Technology, Inc.	Lab Key	ExacTech	Mentor
Cellerix	Ixion Biotech	Lexicon	Kourion Therapeutics	Milbar Labs
Cellex Biosciences	Medra, Inc.	Luminex Corporation	MG Biotherapeutics	Nastech
Cellpro, Inc.	Nephros Therapeutics	Myriad Genetics	Neuronyx Inc.	Neurogen
CepTor	Orion Biosolutions	Nanogen, Inc.	Orthovita	OrthoNeutrogena
Chromos	Progenitor Cell Therapy	Orchid Biosciences	Osiris Therapeutics	Pherin Pharmaceuticals
Circe Biomedical, Inc.	ReNeuron	Perkin Elmer, Inc.	Osteotech	Predix Pharma
Collagen Corporation	Stem Cell Technologies	Proteome Software	Regeneration Technologies	Phytopharm
Creative Biomolecules	StemCells, Inc.	Sage-N Research	Selective Genetics	Q-med
Cryolife, Inc.	Theravitae Inc.	Sequenom	Thermogenesis	Sapphire Therapeutics

Source: Tissue Engineering 2005, Med Market Diligence, Global Industry Analysts, Global Information, Inc., Company websites, TFG Analysis

Public Markets Increasingly Receptive to RM Companies



Source: Yahoo Finance; Company Websites; SEC

PROTEUS VENTURE PARTNERS

Public Markets Are Rewarding Clinical Progress

Company	Product / Stage	Market	Revenue	Mkt Cap Range / M&A
AnorMED	Mozobil, Phase III	Hematopoietic stem cell transplantation	< $1M	Acquisition by Genzyme: $580M (10/2006)
Aastrom Biosciences	Tissue Repair Cell (TRC) technology: Ph III; Ph IIb Ph I/II	bone regen-osteonecrosis of the femoral head critical limb ischemia non-union fracture	< $1M	$ 140M ($128 - $202M)
Dendreon	Provenge;:FDA review (prostrate cancer) Neuvenge: Ph I (breast, ovarian, colon cancer)	Cellular immunotherapy, monoclonal antibody, and small molecule product candidates to treat various cancers	< $1M	$ 640M ($301M - $ 2.1B)
Geron	Filing IND for spinal cord early 2008	treatment of cancer,spinal cord injury, heart failure, diabetes, and HIV/AIDS	< $4M	$ 551M ($425M - $ 753M)
Intercytex	ICX-PRO, Ph III – in Ph III for VLUs & Ph II for DFUsVAVELTA®, Ph II ICX-TRC, Ph II	Stimulate active repair in chronic wounds Facial rejuvenation Hair regeneration	< $1M	$ 90M (LSE-AIM mkt)
LifeCell	AlloDerm ; GraftJacket; AlloCraft	Tissue-based prods for reconstructive, orthopedic, and urogynecologic surgical procedures	$ 166M	$1.3B $ 650M - $1.3B)
Osiris	Prochymal, Ph III & II Provacel, a phase I	GVHD & Crohn's Disease Acute MI	$10M	$ 377M ($290M - $847M)
ViaCell	UC storage Pre-clinical work in cancer, cardiac & diabetes	Collecting and preserving stem cells from umbilical cord blood	$ 59M	$ 300 (purchased by PerkinElmer 10/02/07 – 52% premium)

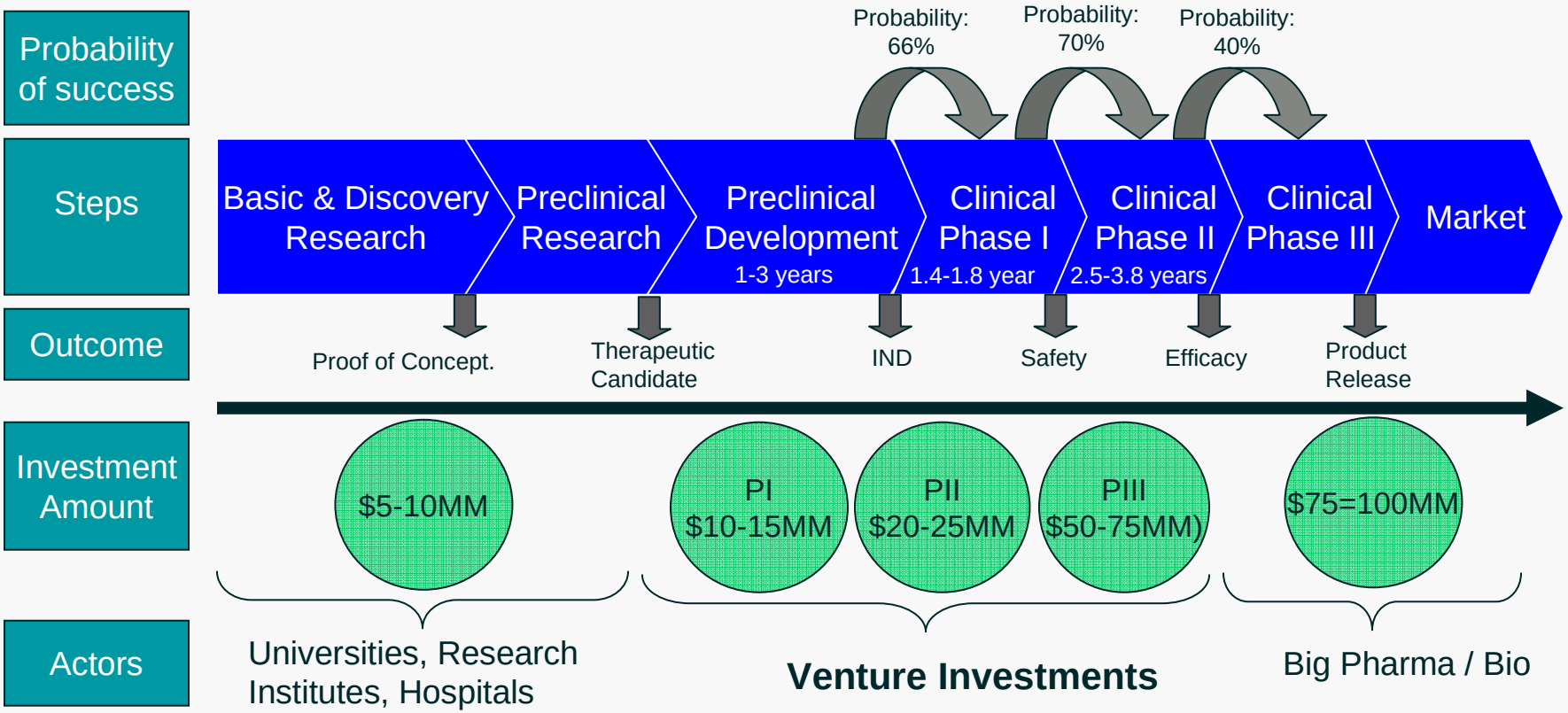
Venture Capitalists Getting Back in the Game

PROTEUS
VENTURE PARTNERS
FUNDING REGENERATIVE MEDICINE

RM Companies - Access To Venture Capital

- Funding & Value Creation: The Valley of Death
- Venture Capital Metrics: What Do VCs Want?
- Typical Venture Terms: What Do VCs Get?

RM Product Development Timeline

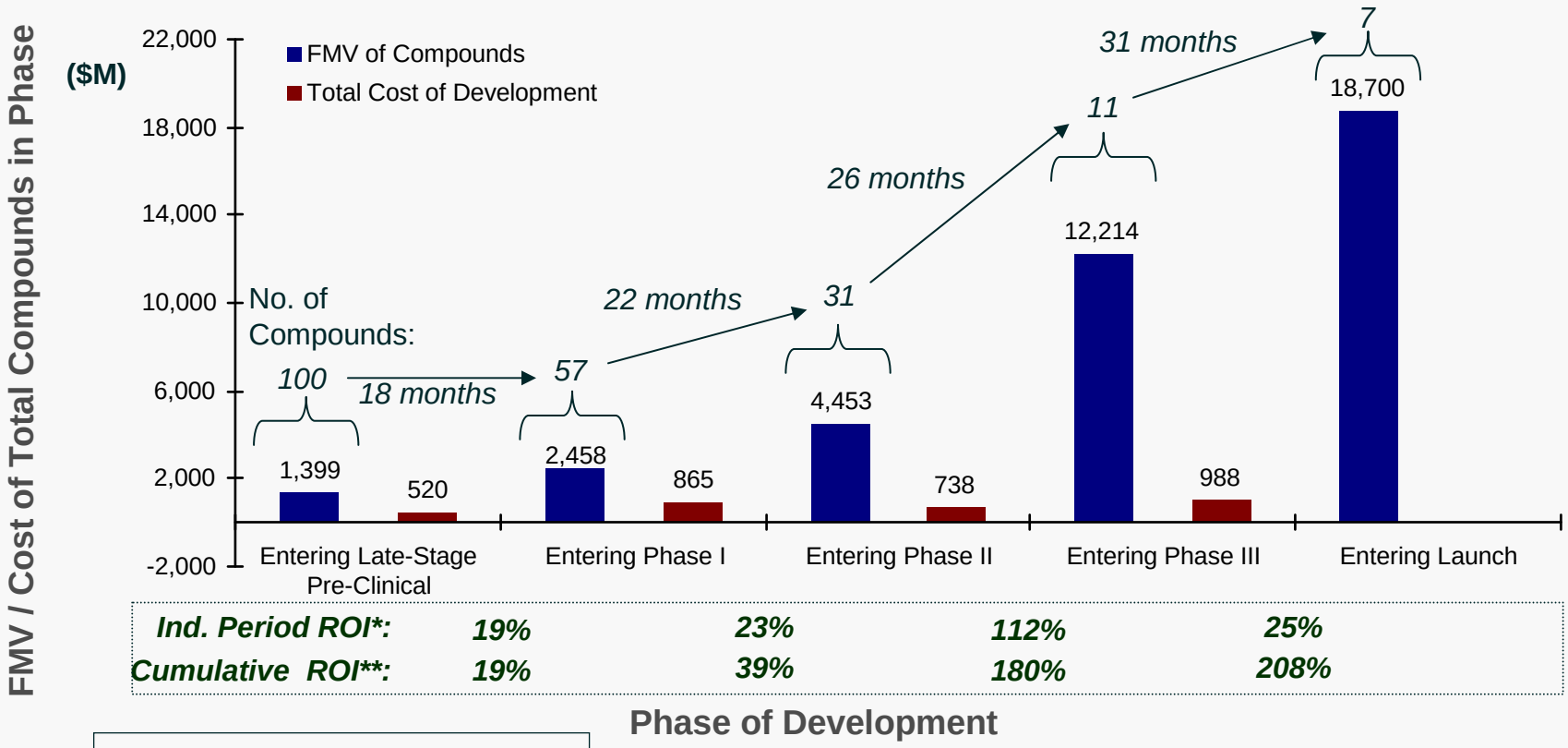


Key Metrics:

- **Average Time to Market: 10-15 Years**
- **Average Costs: $1B**
- **Failure Rate: @90%**
- **Less than 30% of approved drugs recoup development costs**

PROTEUS VENTURE PARTNERS

Valuation Analysis On Risk Adjusted NPV



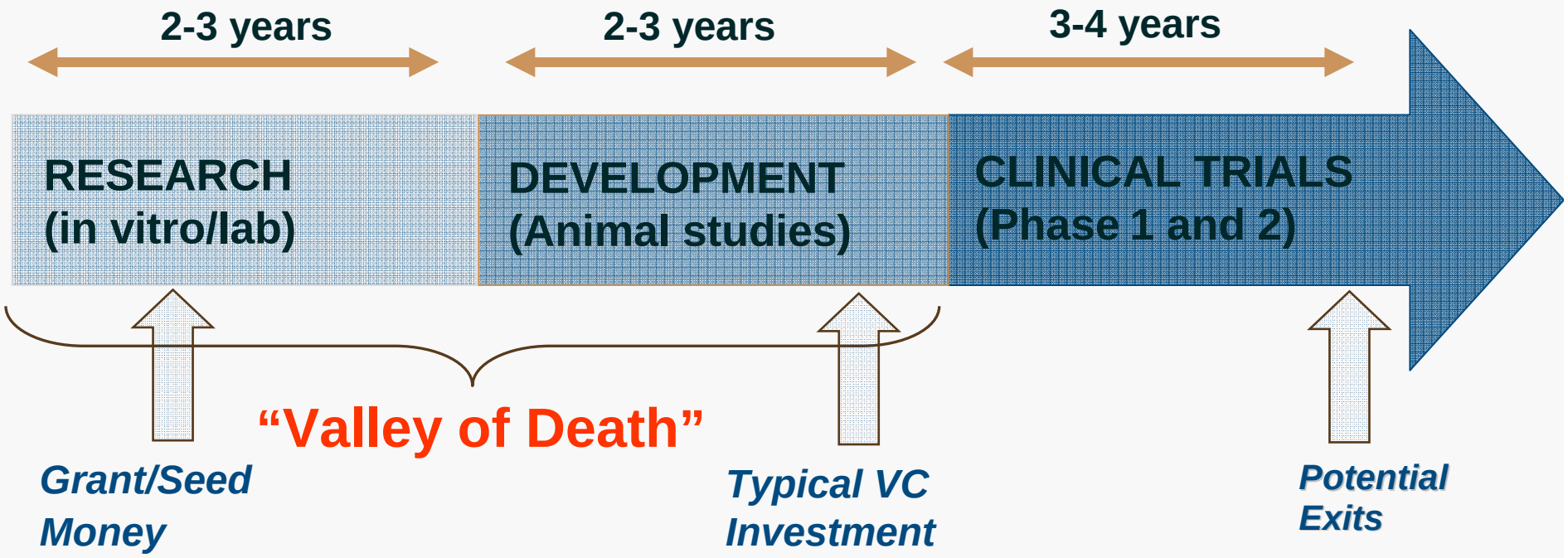
FMV = ~5x peak year revenues of $500M discounted by probability of launching

Source: ADIS, Pharma Projects, Fortis Bank, Paraexel, Jagle, Lehman Brothers, Journal of Health Economics 22:151-185 (2003), TFG Estimates

RM Company Funding Vacuum: *The Valley of Death*

Time to *Start of Phase 3 trials* can be up to *7-10 years*

Time to *1st Venture Interest* can be up to *5-6 Years*



PROTEUS VENTURE PARTNERS

VC Metrics: What Do VCs Want?

Proprietary Commercial Technology
- –Great Science ≠ Great Business
- –Core Research Completed
- –Proof Of Concept Established

- **Strong Management Team**
  - –Board
  - –SAB

- **Solid Intellectual Property Position**
  - –Freedom To Operate
  - –Defensible IP (Patents & Trade Secrets)

- **Large Market Opportunity**
  - –Target markets > $1B/year

- **Defensible Business Model**
  - Allogeneic v. Autologous
  - Product v. Service

- **Differentiation**
  - –How Is Your Approach Different?
  - –Why Is It Better?

- **Exit Strategy**
  - –IPO Vs. M&A (Attractive Products For Acquirer)
  - –Realistic Timeframe

- **Acceptable Risk/Return Profile**
  - –Multiple Chances To Win

PROTEUS
VENTURE PARTNERS

Typical VC Terms: What Do VCs Get?

- **Valuation**
  - –% Ownership; Dilution
- **Dividend Rate:** 8%
- **Preferred Return**: 1X-3X
- **Anti-Dilution Protection**
  - –Full Ratchet; Weighted average
- **Protective Provisions**
- **BOD Seat**
- **Participation Rights**
  - –Right of First Refusal; Follow-on financings

The Final Word

PROTEUS
VENTURE PARTNERS
FUNDING REGENERATIVE MEDICINE

Appendices

PROTEUS
VENTURE PARTNERS
FUNDING REGENERATIVE MEDICINE

RM Commercialization Challenges

- Technology Issues
- Business Models
- IP Issues
- Regulatory Hurdles

Commercialization Challenges: Technology

R&D

- Creation and Characterization of Optimal Cells for Therapy
- Contaminant Free Cell Lines
- Development of Scaffolds & Matrices for Tissue Engineering
- Safe & Reliable Expansion
- Directed Differentiation
- Imaging Technology and Biological Markers to Track Cell Migration & Engraftment

Manufacturing

- Technologies for Scale-Up
  - Commercial Quantities of Product
  - Pathogen Free
  - Consistent Lots
- Reliable Preservation Methods
- Control CoGs
- Standardization in the Field

Commercialization Challenges: Business Models

Autologous Model

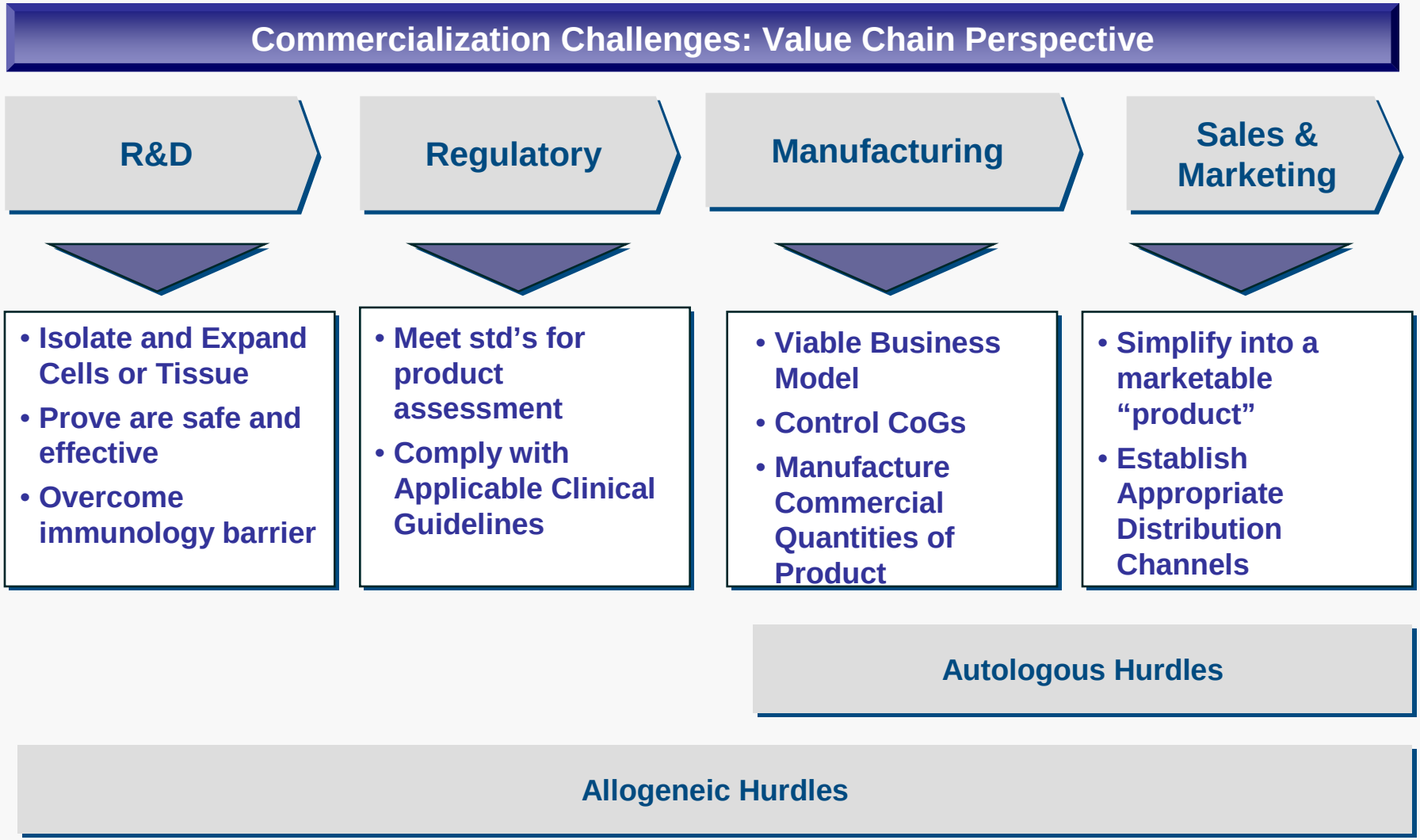
- **Using Pts Own Cells/ Tissue for Therapeutic Effect**
  - –Personalized Medicine
- **Advantages**:
  - –Easier Regulatory Path (GTP)
  - –No Immune Response
- **Challenges**:
  - – Doesn't Scale
  - – COGS

Allogeneic Model

- **Universal Cells in a Bottle**
  - –Big Pharma "Drug Model"
- **Advantages**:
  - –Scalable
  - –Low COGS
- **Challenges:**
  - –More Difficult Regulatory Path
  - –Immune Response

Service vs. Product

RM Business Models: *Major Hurdles*



PROTEUS VENTURE PARTNERS

RM Business Models: *Autologous v. Allogeneic*

Moving From Core Technology to Commercial Product is a Major Challenge

	Autologous	Allogeneic
Broad Product & Large Patient Base	**Flawed Model?** • Therapeutic benefit must be extraordinary • Cost structure is not scalable • Competing with lower cost therapy • High risk of substitution & relatively low barriers to competitive entry	**Large Pharma Model** • Low COGS: Cost structure is scalable • Lower cost therapy targeted to large patient populations • Can compete against biologics & possibly small molecules • Immunogenicity is major issue
Niche Products & Small Patient Base	**Current Model** • Small populations with no current efficacious therapy • "Salvage" therapies • Can be profitable but is not scalable • Creates strong relationships with caregivers and patients	**Specialty Biotech Model** • Efficacious therapy will target populations with high unmet needs • Moderate COGS • Cost structure can possibly be spread across multiple diseases

PROTEUS VENTURE PARTNERS

Autologous Model: *Challenges Are Scale and Competition*

Autologous Promise

	Promise	Reality
Proven safe and efficacious cell source	√	√
Overcome immunology barrier	√	√
Standards for product assessment	√	√
Cooperate with regulatory authorities	√	√
Achieve scaleable cell expansion	√	
Simplify into a 'marketable' product	√	

Multiple Business Models Emerge

- Therapeutic Product
  - Novocell
  - Aastrom
  - ACTC
- Device
  - Cytori
- Service
  - Viacell

Regulatory Risks (FDA Approval) Are Lower, But Costs & Competitive Risks Are High

PROTEUS VENTURE PARTNERS

Allogeneic Model: *Promise of Scale & Marketable Product*

Allogeneic Promise

	Promise	Reality
Proven safe and efficacious cell source	√	?
Overcome immunology barrier	√	?
Standards for product assessment	√	?
Cooperate with regulatory authorities	√	?
Achieve scaleable cell expansion	√	?
Simplify into a 'marketable' product	√	?

Meet Minimum Hurdles

- Immune Response is a unique allogeneic challenge
- Regulatory hurdles are becoming clarified
- Unique ethical / legislative issues arise with hESCs

Drive Broader Market Uptake

- Expansion potential enables scalability
- Simplicity will evolve over time
- Reimbursement ultimately drives broad uptake as well

Regulatory Risks Are Higher,
But So Are Barriers To Entry

PROTEUS
VENTURE PARTNERS

Commercialization Challenges: Other

Regulatory; IP; and Reimbursement

- **Regulatory Environment Needs Clarity**
  - FDA Standards for Safety & Efficacy
  - Standards & Guidelines Are Evolving
  - Cross Border Inconsistencies
- **IP Landscape Is Treacherous**
  - Large Patent Estates Concentrated in Few Entities
  - Inconsistent & Competing Patents: Invites Litigation
  - Need “Freedom To Operate” Opinions
- **Reimbursement Path Unclear**

Commercialization Best Practices

- Business Model
  - –Identify drivers of value and focus on these first
  - –Manange to Valuation Milestones
- IP
  - – File Provisional Patents
  - – Protect Trade Secrets
  - – Identify IP Risks Early
- Reimbursement: Address Early in Process (PI or PII, not PIII)
  - –Begin conversations with *Centers for Medicare and Medicaid Services (CMS)*
- Remain sensitive to the external environment / ecosystem
  - – Alternative approaches in the pipeline
  - – Complementary approaches in the market or in the pipeline
  - – Look for Partners

Total Regenerative Medicine Market

Market Over $11.5B in 2010

CAGR%, 2005-2010

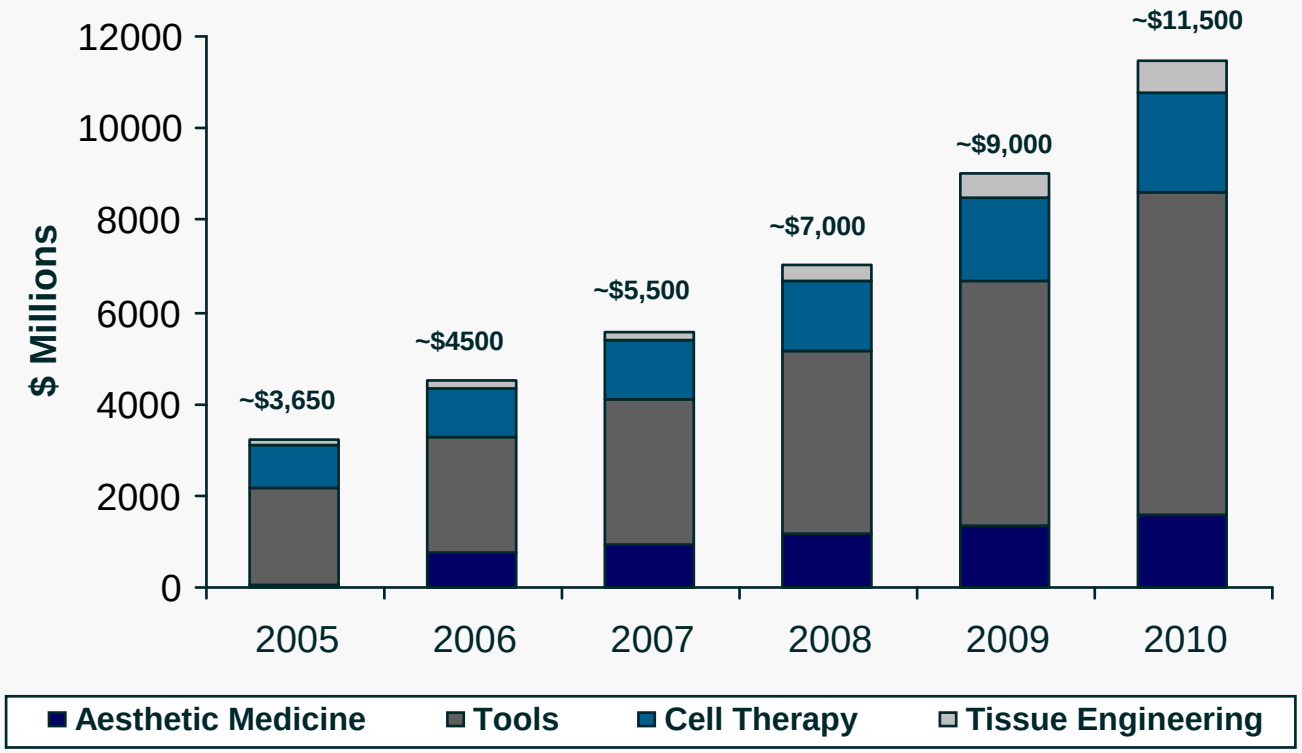
Cell Therapy: 19.3%

Tissue Engineering: 36.9%

Aesthetic Medicine: 21.9%

Regenerative Medicine Tools: 28.3%

Total: 25.7%



Source: MedMarket Diligence, MII News, Global Industry Analysts, TFG Analysis

PROTEUS VENTURE PARTNERS

Recent M&A Transactions in Tissue Regeneration

Date	Buyer	Target	Deal	Notes
Q3 '06	Smith & Nephew	Osteobiologics Inc.	$ 72M	• $3M revenues • Purchase price 20x revenues
Q3 '06	Orthoflix	Blackstone Medical Inc.	$ 333M	• $60M revenues • EBIT $2M • Purchase price 5x revenues
Q1 '06	Smith & Nephew	PLUS Orthopedics	$ 889M	• $300M revenues • EBIT $36M in '06 •Purchase price 3x revenues
Q1 '06	Kyphon	InnoSpine Inc.	$ 2.5M upfront & $27M	• Pre-revenue acquisition • Followed FDA approval
Q2 '04	Biomet	Interpore Cross Int'l	$ 280M	• $68M revenues • Purchase price 4x revenues
Q2 '04	Zimmer	Implex	$ 108M	

Mar 07: S&N announced $1.1.B available for acquisitions

Source: RegenTec, Public Market Data

RM Exit Strategies
Licensing: Key Metrics 2005-2006

Term	*Mean*	*Median*
Upfront Payments	**$19M**	**$32M**
R&D Funding	**$26M**	**$26M**
Milestones	**$187M**	**$244M**
Equity	**$18M**	**$30M**

N = 47 Deals; Source: Recap

PROTEUS
VENTURE PARTNERS

Big Pharma May Fuel M&A Exits / Valuations

Deloitte & Touche Survey of Senior Execs of the Pharmaceutical Industry (Dec. 2006)

- *"More than 50 percent of large pharmaceutical revenues by 2015 will come from products and services they don't offer today."*
- *"Large pharma & biotech need to adopt dramatic changes in their business strategies if they want to maintain their success."*

- Case study: **Pfizer's Pharmaceutical Sales (in M's) WSJ 10/23/07**

Drug	Treatment	3Q '07	3Q '06	Change
Lipitor	Cholesterol	3,170	3,321	-5%
Norvasc	Blood pressure	640	1,208	-47%
Celebrex	Painkiller	577	537	8%
Lyrica	Nerve pain	465	340	37%
Viagra	ED	450	423	6%
Zyrtec	Allergies	428	397	8%
Zoloft	Antidepressant	124	459	-73%