



Stem matters

STEM CELLS AND MATERIALS TECHNOLOGIES THAT REALLY MATTER(S)

**EXPLOITING THE BIOTECHNOLOGY
POTENTIAL OF MARINE RESOURCES**
**CONFERENCE ON EXPLORING AND UTILIZING
THE RESOURCES OF THE SEA**

December 2011

A biotechnology company focused on
the development and marketing of
novel products and services for
cartilage repair and regeneration



Background

Spin-off of 3B's Research Group (U. Minho) focused on application of regenerative medicine to orthopaedic related conditions.

Installed in the same building as the European Institute of Excellence for Tissue Engineering and Regenerative Medicine Research.

Fully independent facilities, comprising:

- 300 m² of clean room (Classes B, C and D);
- 250 m² of R&D and QC laboratories.

Equipped with a GMP compliant facility for the processing of human tissues and cells (2004/23/EC Directive).



Market Driver



- Aging phenomena will drive the demand for regenerative medicine for the coming decades.
- More than 20% of the global population by 2050 is expected to be over 60 years, but physically very active.
- Therapeutic challenge in the orthopaedic field will be to assure compliance between application functional requirements and actual performance of therapies.
- Joint market globally represents USD 13 billion, but faces a decrease in procedural volumes.
- Lack of disruptive technological developments within this sector demands novel combinatorial approaches for joint conditions.



Business Model

Stemmatters operates two business models:



Stemmatters

THERAPEUTICS

Stemmatters Therapeutics targets **the development of therapeutic products for osteoarticular** conditions to be licensed or sold in stages of pre-clinical or clinical development.



Stemmatters

LIFE BANKING

Stemmatters Life Banking **offers innovative isolation and storage services for stem cells** isolated from several tissues, which have been obtained from non dedicated harvesting procedures.

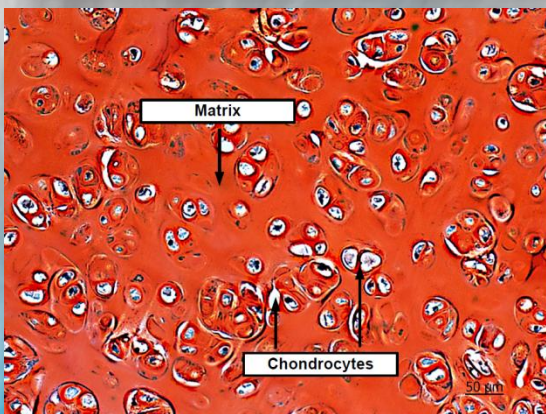
Our Focus

Products under development

New **combined minimally invasive therapeutic strategies for the treatment of focal cartilage lesions**, namely:

- Post-traumatic conditions (Outerbridge grade III);
- Osteochondritis dissecans of articular knee cartilage (Outerbridge grades III and IV);

Focus on a new generation of degradable hydrogels optimized for encapsulation of human mesenchymal stem cells.



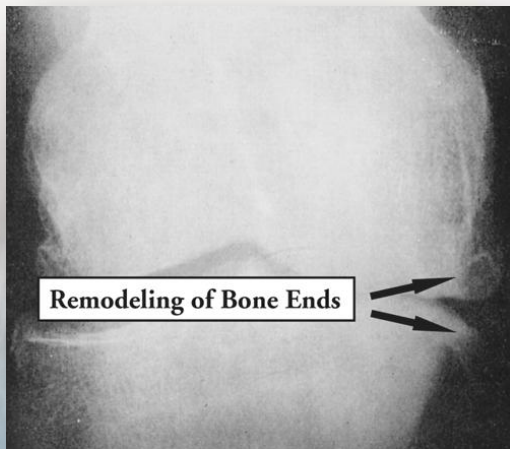
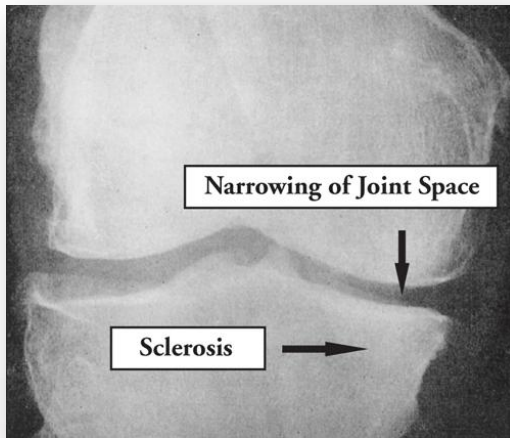
Our Focus

Products under development

Novel **injectable viscosupplement therapies for intra-articular pathologies**, namely:

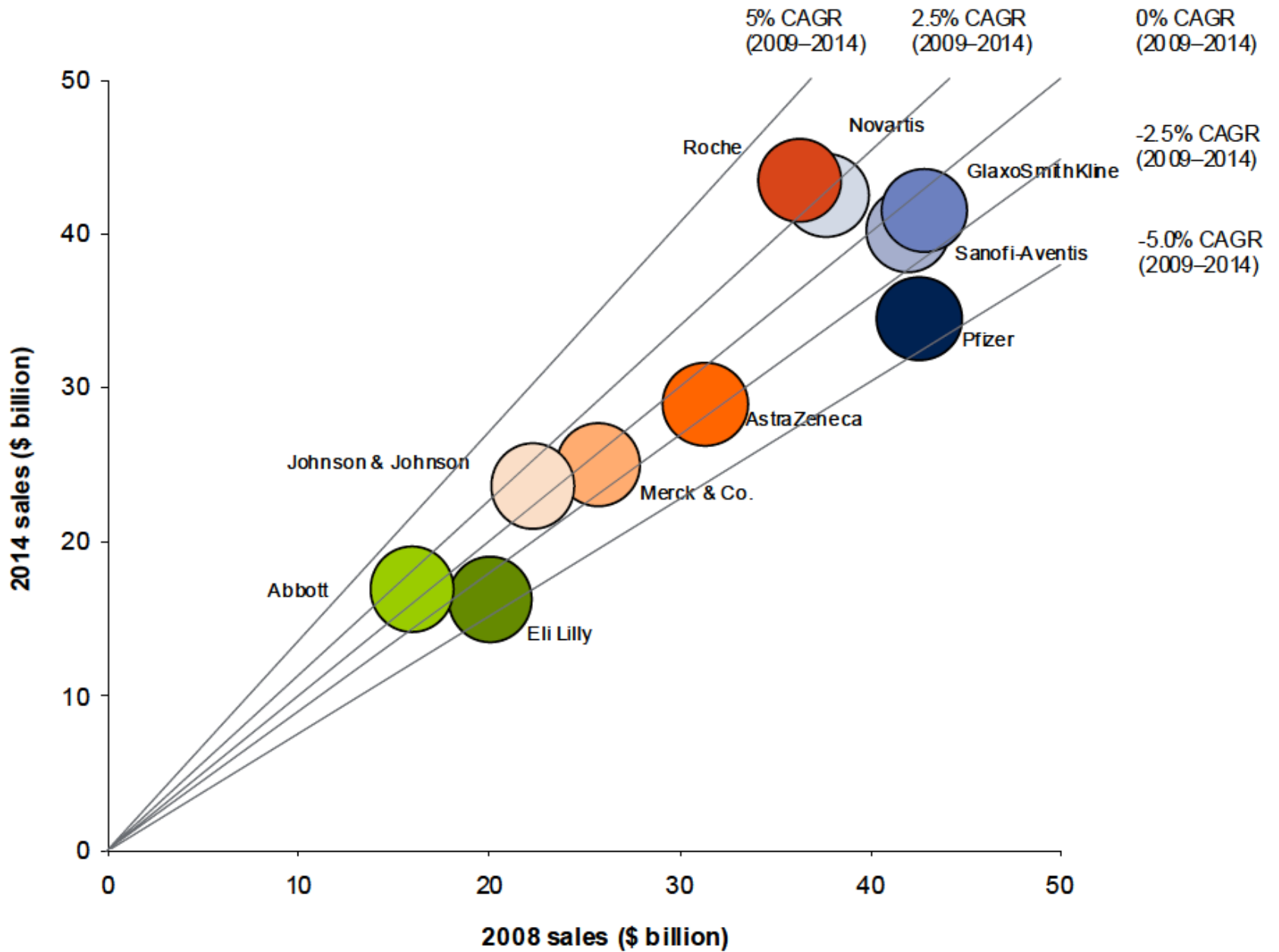
- Osteoarthritic conditions;

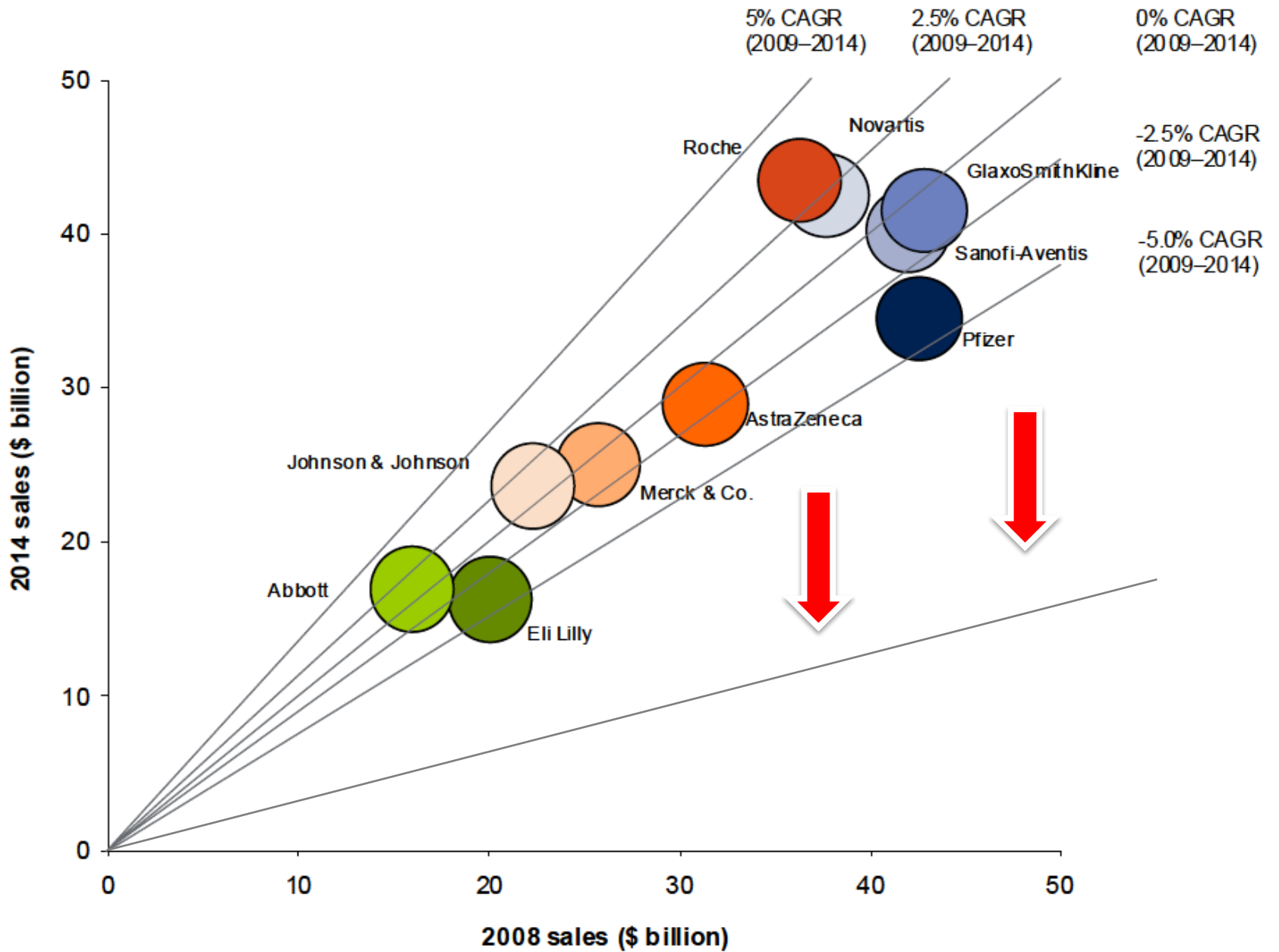
Focus on development of novel medical devices based on heteropolysaccharide hydrogels, exhibiting optimized thixotropic properties and improved physicochemical performance.

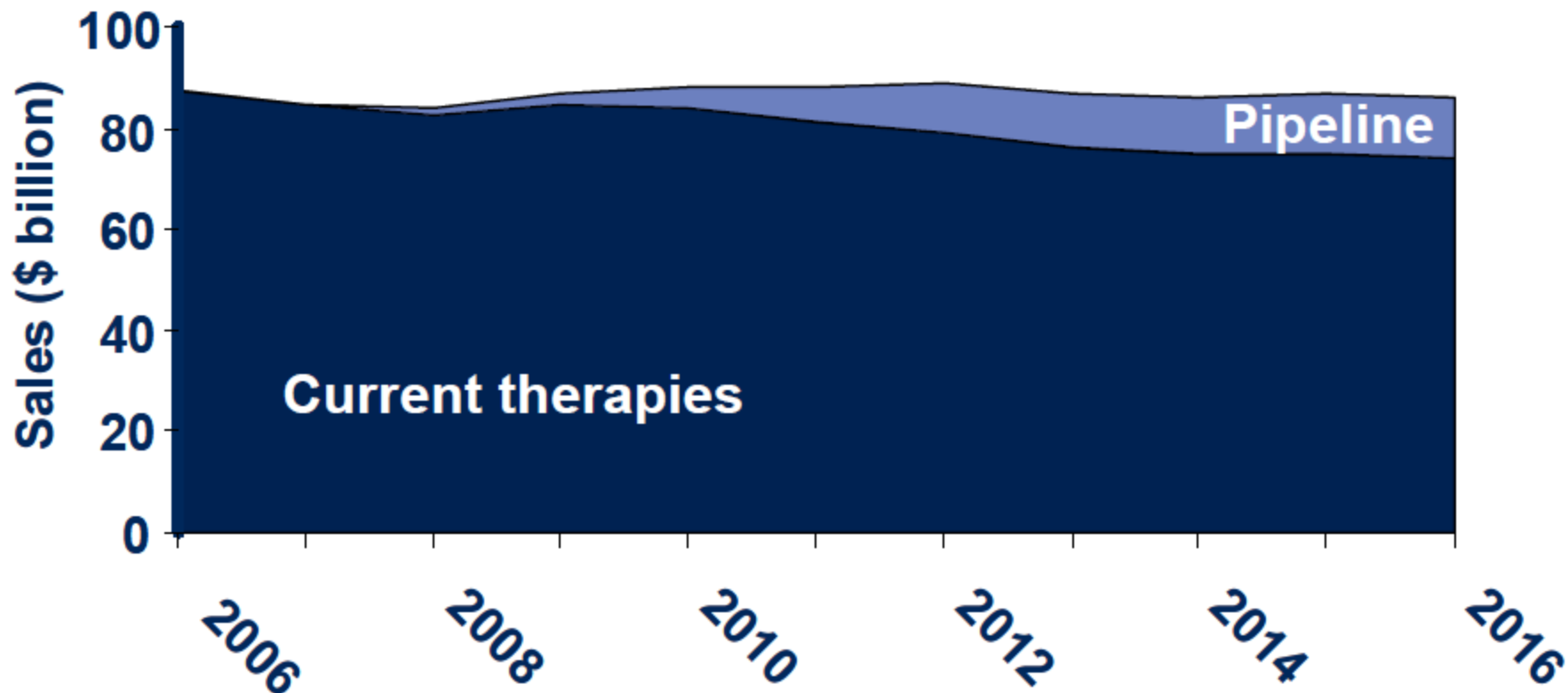


**76% of all therapeutics
reaching end patients
were developed by companies**

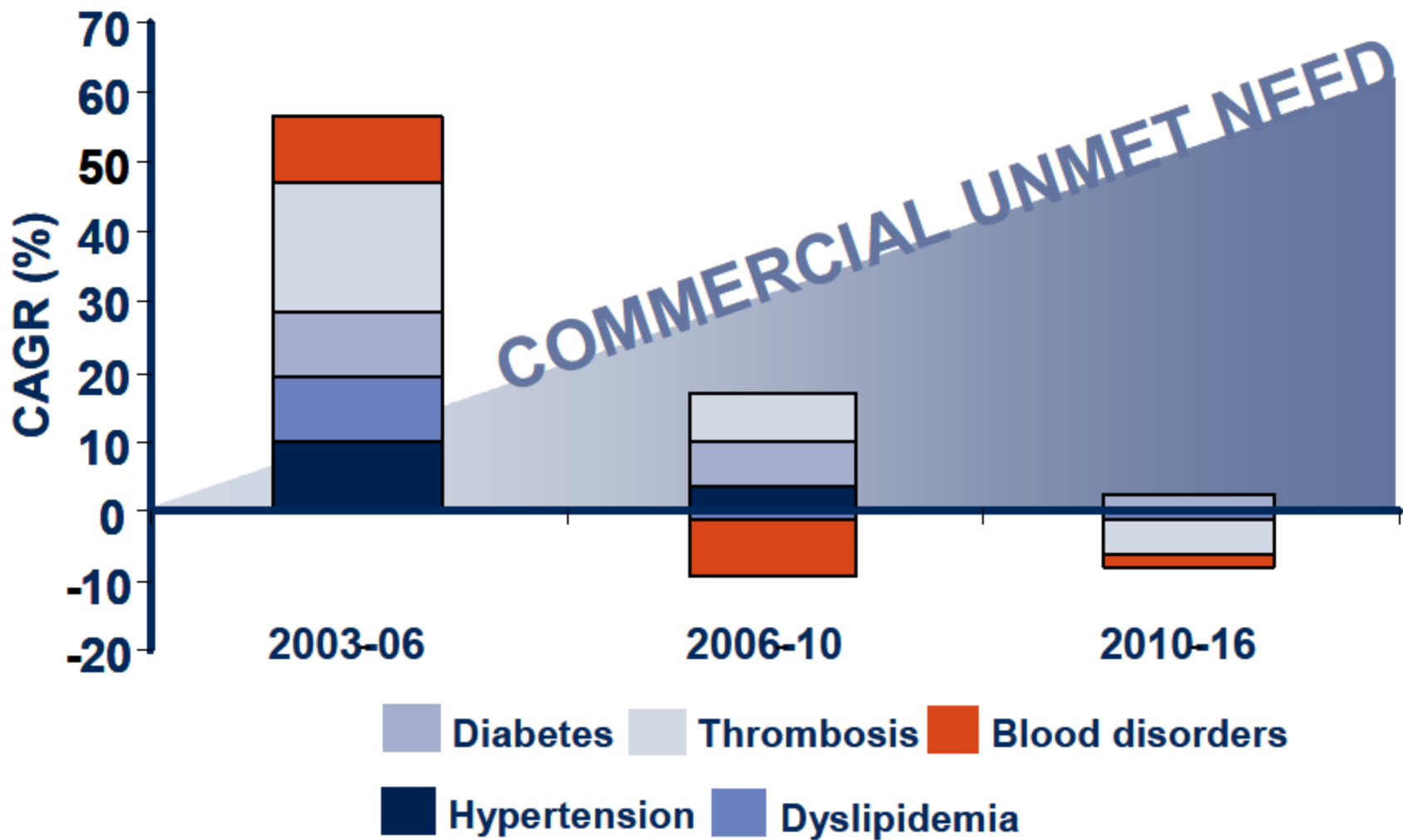
Francis Collins, Director of the US National Institutes of Health (NIH), 2010





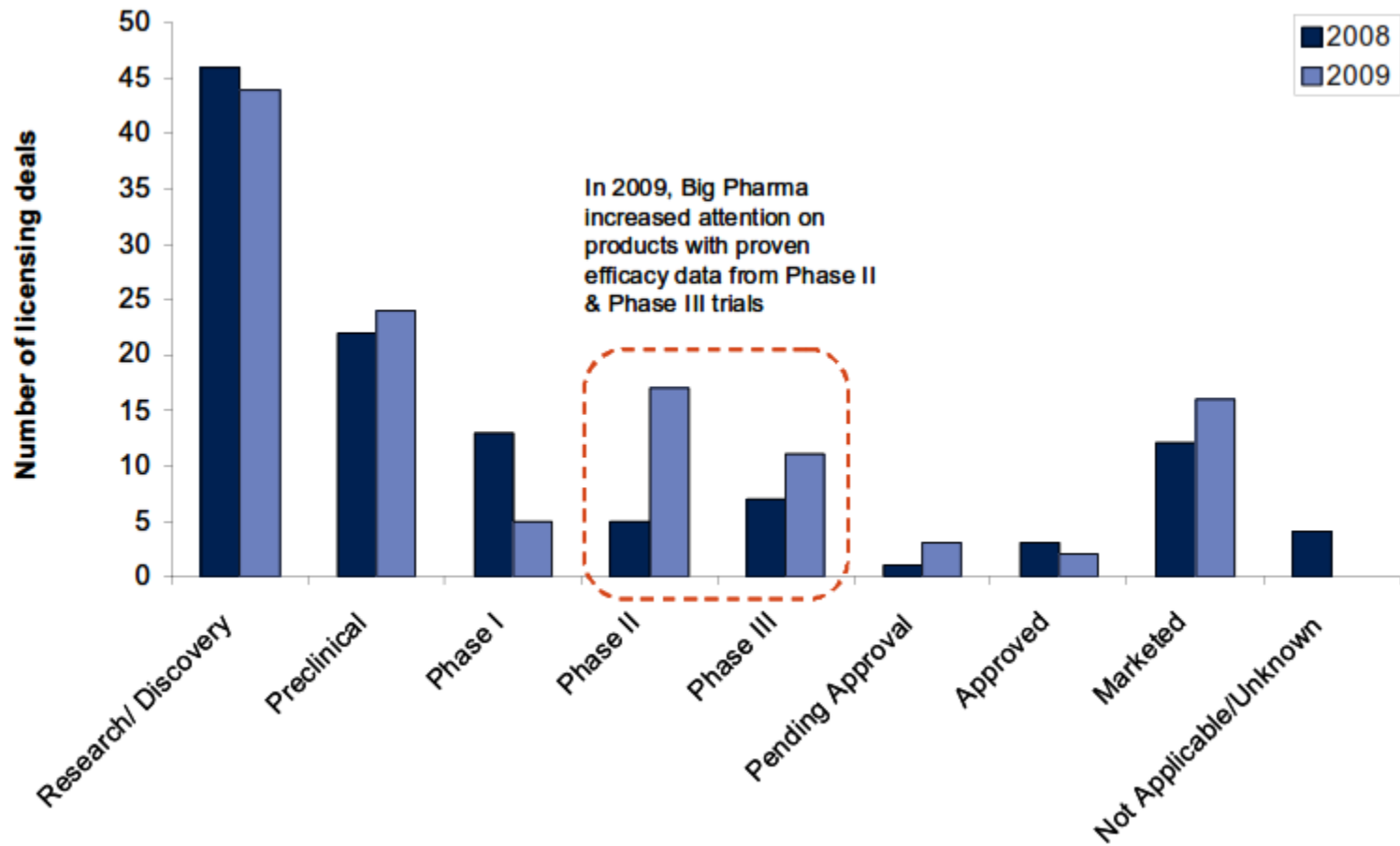


The cardiovascular development pipeline does not have the potential to buoy the overall market value



Facts

- Although the **dynamics and business models of Pharma and Biotech companies differ, they both face common key challenges:**
 - **Development and launch of differentiated novel products;**
 - **Pressure to achieve growth and profitability targets;**
 - **Reacting to context change** (genericization, pricing and reimbursement and regulatory issues, R&D costs);
 - **Balancing short-term challenges against a sustainable future;**
 - **Managing investor expectations;**



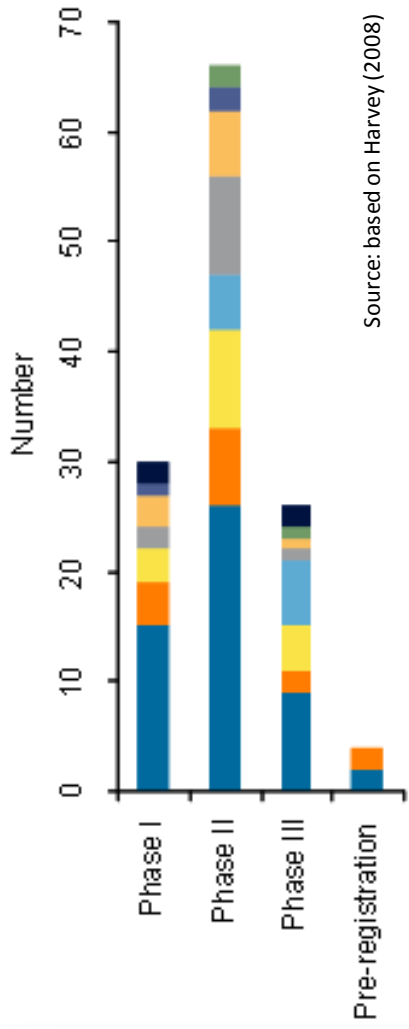
Use of Natural Products in Medicine

Historical perspective

- **Folk medicine in many cultures has promoted the choice of plants and plant extracts to treat various diseases:**
 - More systematized in Chinese and Indian cultures;
- **In Western medicine, crude extracts evolved into increasingly pure single chemical entities, providing therapies:**
 - Such as quinine (for malaria), morphine (for pain), and digoxin (for heart conditions);
- **Synthetic modification of natural products expanded the applications:**
 - e.g. salicylic acid to aspirin; morphine to heroin;
- **Such advances paved the way for the modern exploitation of natural sources in drug discovery:**
 - Such as pharmacological tools, medicinal chemistry leads, and clinical candidates.

Areas of Dominance

Historical perspective



- Natural products span all therapeutic areas but had a significant role in **cancer and anti-infectives**;
- **50% of anticancer drugs from 1940–2006 have natural product origins**;
- **Most antibacterials also based on natural products**, but less influence in antifungals and antivirals;
- Some core products in CNS (e.g. opiates) and inflammatory diseases (e.g. ipratropium bromide) based on natural products;
- **Natural product based statins have created a vast market in cardiovascular**, but otherwise metabolic diseases have been less heavily influenced.



Natural Compounds

Available libraries

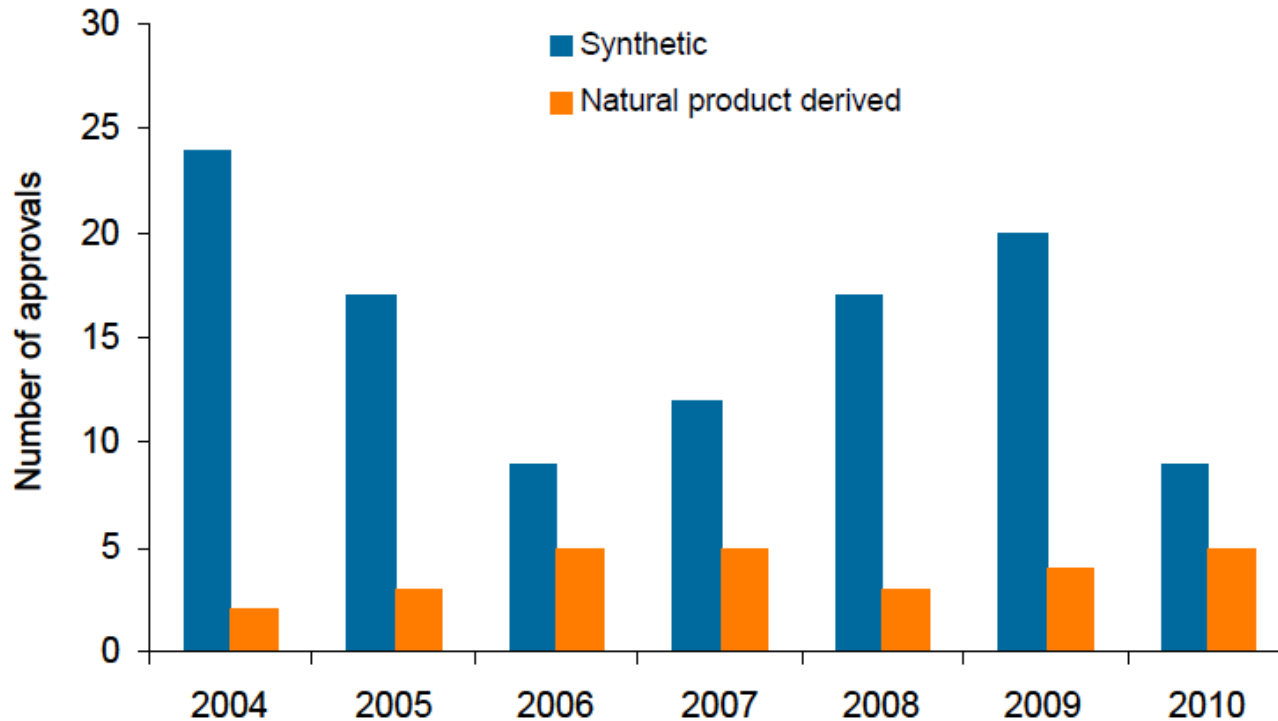
Company	Source	Sample numbers
Hypha Discovery	Higher fungi	10,000
Magellan	Marine microbes	13,000
Magellan	Fungi	60,000
MerLion	Plants	38,750 specimens
MerLion	Fungi	55,817 strains
MerLion	Eubacteria	10,915 strains
MerLion	Actinomycetes	62,623 strains
Phyto Pharmacon	Phytochemicals	40,000
PhytoQuest	Plant carbohydrates	1,100
Cerylid	Diverse biotics	600,000

Source: company websites **BUSINESS INSIGHTS**

The Changing Role of Natural Products in Drug Discovery, Assessment of corporate strategies, case histories, specialist companies, and the future outlook, Business Insights, 2011

Synthetic and Natural New Drug Applications

2004–2010



Source: Norman Consulting

BUSINESS INSIGHTS

The Changing Role of Natural Products in Drug Discovery, Assessment of corporate strategies, case histories, specialist companies, and the future outlook, Business Insights, 2011

FDA approval of Natural Derived Drugs

2008–2011 (May)

Drug	Developer	Indication	Original source	FDA approval
Ciclesonide	Nycomed	Asthma	Hormone	Jan-08
Methylnaltrexone	Progenics, Pfizer	Constipation	Plant	Apr-08
Lacosamide	UCB	Epilepsy	Amino acid	Oct-08
Artemether, lumafentrine	Novartis	Malaria	Plant	Apr-09
Televancin	Theravance	Bacterial infection	Bacterium	Sep-09
Pralatrexate	Allos	Cancer	Plant	Sep-09
Romidepsin	Celgene	Cancer	Bacterium	Nov-09
Everolimus	Novartis	Transplant rejection	Bacterium	May-10
Cabazitaxel	Sanofi	Cancer	Plant	Jun-10
Fingolimod	Novartis	Multiple sclerosis	Fungus	Sep-10
Ceftaroline	Forest, Takeda	Bacterial infection	Bacterium	Oct-10
Eribulin	Eisai	Cancer	Marine	Nov-10

Source: Norman Consulting

BUSINESS INSIGHTS

The Changing Role of Natural Products in Drug Discovery, Assessment of corporate strategies, case histories, specialist companies, and the future outlook, Business Insights, 2011

Challenges of Natural Products

Limitations and disadvantages

- **Availability and access to natural resources**
 - Quantities available
 - Cost of harvesting
 - Cost of purification
 - Sustainability of resource
- **Biological profile of extractable compounds**
 - Adequate selectivity
 - Pharmacokinetic properties
 - Metabolic stability
- **Suitability of alternative synthesis processes**
 - Feasibility
 - Scalability
 - Cost of goods
- **Protection of intellectual property**
 - Limited protection achievable.

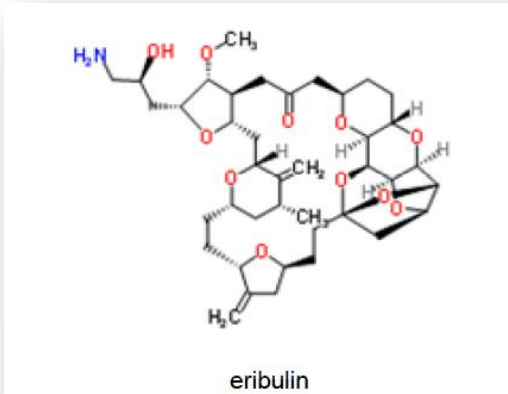
Challenges of Marine Products

Limitations and disadvantages

- **Natural products obtained from marine sources are usually problematic:**
 - Low quantities of compound present;
 - Lack of alternative synthetic synthesis methods.
- **Common impossibility of sourcing large quantities of material for significant clinical studies, or even less probable commercial use.**
- **Trabectedin (Pharmamar):**
 - One gram of compound is isolated from one tonne of sea squirts;
 - Developed an effective semi-synthetic process using an intermediate produced by fermentation of a bacterial strain.

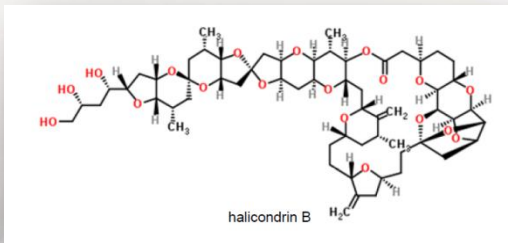
Challenges of Marine Products

Eribulin



- Complex synthetic non-peptidic chemical for treatment of metastatic breast cancer:
 - FDA approval in November 2010;

- **Eribulin is analog of the marine natural product halichondrin B, a polyether macrolide:**



- Isolated from the marine sponge *Halichondria okadae* in 1986;
 - Clinical investigation possible after extraction of 310 mg from a tonne of sponge;
 - Synthetic route reported in 1992, but still unviable.
- **Simplified derivatives offering less demanding process chemists led to identification of eribulin:**
 - Phase I started in 2003;
 - Phase II in breast cancer patients in 2004;
 - Phase III in 2006.

Different Strategies

Business risk

- **Modification of biosynthetic pathways by recombinant technology:**
 - Biotica and EntreChem.
- **Development of formulations of plant-based therapeutics, either as pure chemical entities or as semi-purified mixtures:**
 - GW Pharma, PhyNova, PhytoPharm, PhytoPharmacon, and PhytoQuest.
- **Exploitation and offering of access to libraries of natural products obtained from specific environments:**
 - Hypha Discovery, Magellan Biosciences', MerLion.
- **Exploitation of marine natural products:**
 - Nereus Pharmaceuticals, PharmaMar.
- **Failure of companies focusing on natural products' development :**
 - CalBioMarine and Cerylid ran out of money.
 - Calyx was acquired and changed strategy.
 - Shaman opened bankruptcy.

Take Home Message

Main conclusions

- Marine resources remain a untapped source of valuable active compounds;
- It is clear, from the increasing number of events, publications and patent applications relating to marine natural products that focus on marine natural products, is growing;
- The sourcing and investigation of these raw materials is being approached more systematically and effectively;
- The identification of many new natural products of potential interest to the pharmaceutical industry is expected;
- The success of these molecules will pose challenges to synthetic chemistry but these are not necessarily insurmountable;
- Competition from other libraries of natural compounds exists and will continue to exist, which will raise the competition level.

Take Home Message

Challenges ahead

- Identification of marine resources is a specialized activity which not so many companies afford to integrate;
- Vertical integration of therapeutic development remains an option, but a costly and risky one;
- Partnerships in this area are fundamental to reduce operational leveraging and share risk;
- Cancer will remain the focus of therapeutic development for marine derived substances, but other areas could be of potential value;
- Partnering should be product focused.

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