

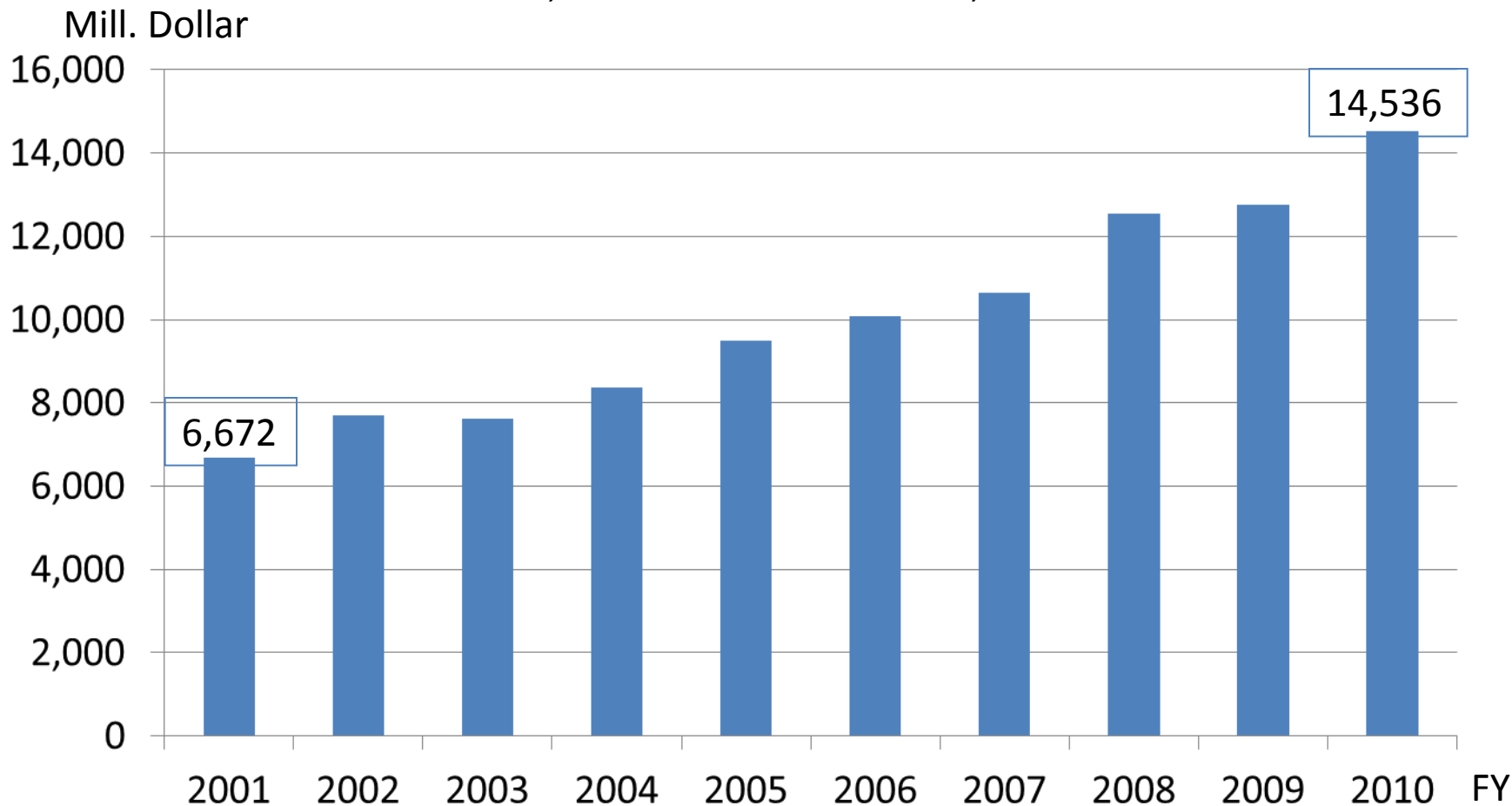
Utilization of microbial resources information :
From perspective of Industry

As a Leverage
for Research in Industry
~ Microbiological Data-base
and Stock Culture ~

Japan Bioindustry Association
Hideharu Anazawa

R&D budget of Japanese Pharmaceutical Industries

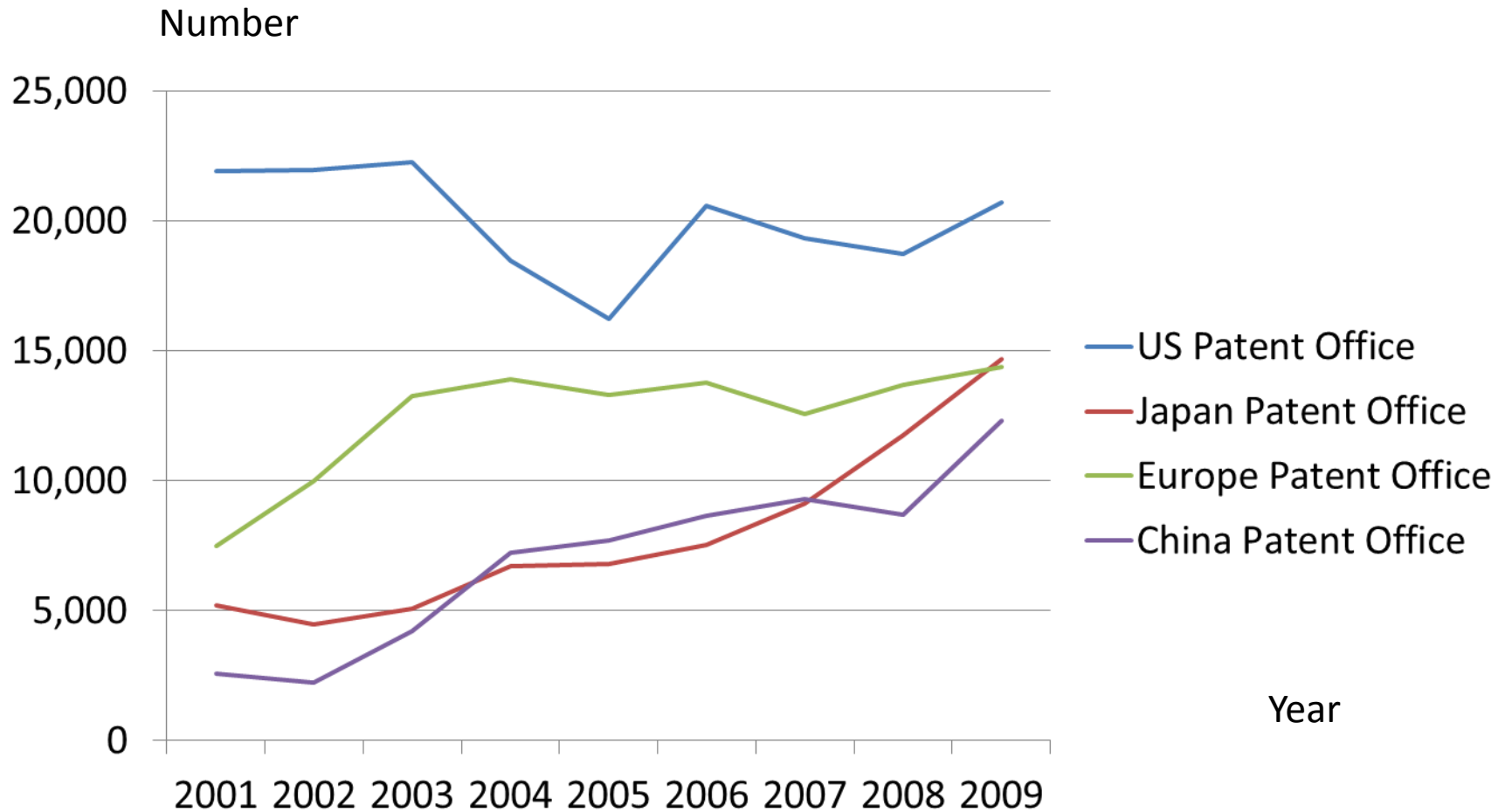
○ R&D budget of Japanese Pharmaceutical Industries is expanding
(2001: USD6,772 mill. → 2010: USD14,536 mill. (X 2.1))



Source : Survey on Research and Development (Ministry of Internal Affairs and Communications)

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Number of Patent grants (Life science)

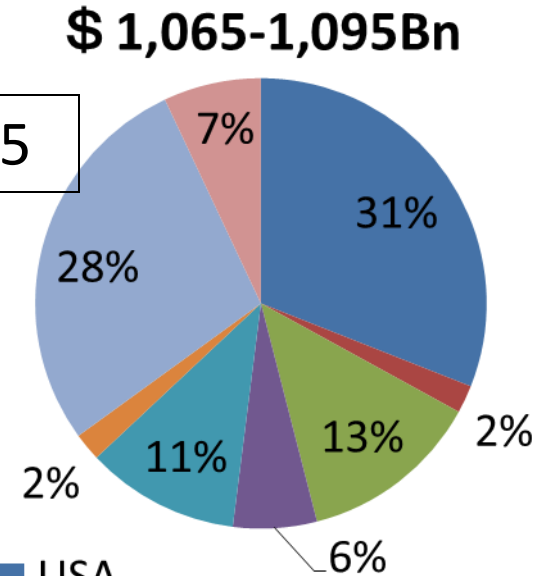
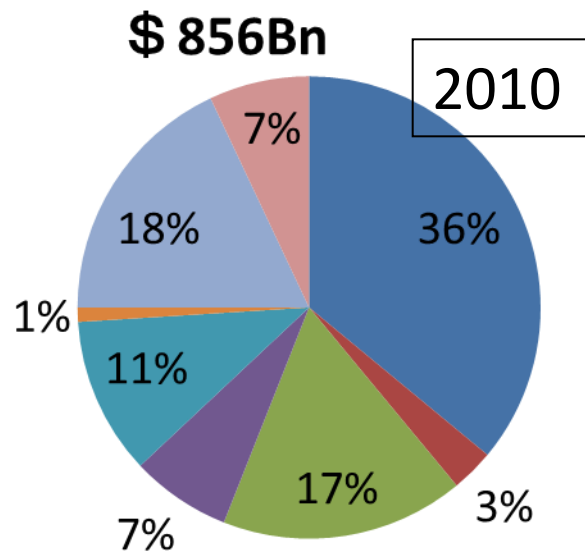
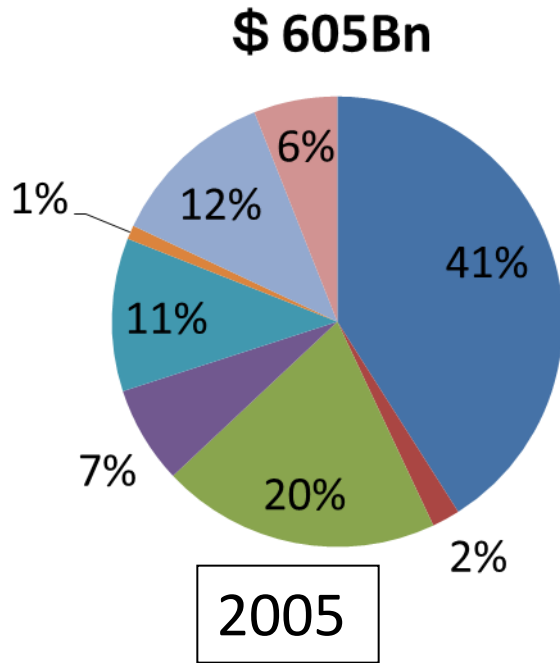


Source: Japan Patent Office

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Global Spending on Medicines

- Japanese market share is 11% in 2010.
- Japanese market will continuously expand under aging society



Source: IMS Market Prognosis,
Apr. 2011

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Main Application of Biotechnology and Microbiology for Industry

- Pharmaceutical/Medicine/Diagnostic reagents
- Food/Fermentation products/Functional food
- Bio-fuel/ Bio-chemicals/Bio-refinery
- Environment Cleaning/Bio-remediation /
Bio-augmentation

Predicted growth of Bio-based Chemical products

Billion US Dollar

	2005		2010		2025	
	Total	Biobased	Total	Biobased	Total	Biobased
Comodity	475	0.9	550	5-11	857	50-86
		(0.2%)		(1-2%)		(6-10%)
Speciality	375	5	435	87-110	679	300-340
		(1.3%)		(20-25%)		(44-50%)
Fine	100	15	125	25-32	195	88-98
		(15%)		(20-26%)		(45-50%)
Polymer	250	0.3	290	15-30	452	45-90
		(0.1%)		(5-10%)		(10-20%)
All	1200	21.2	1400	132-183	2183	483-614
Chemical		(1.8%)		(9-13%)		(22-28%)

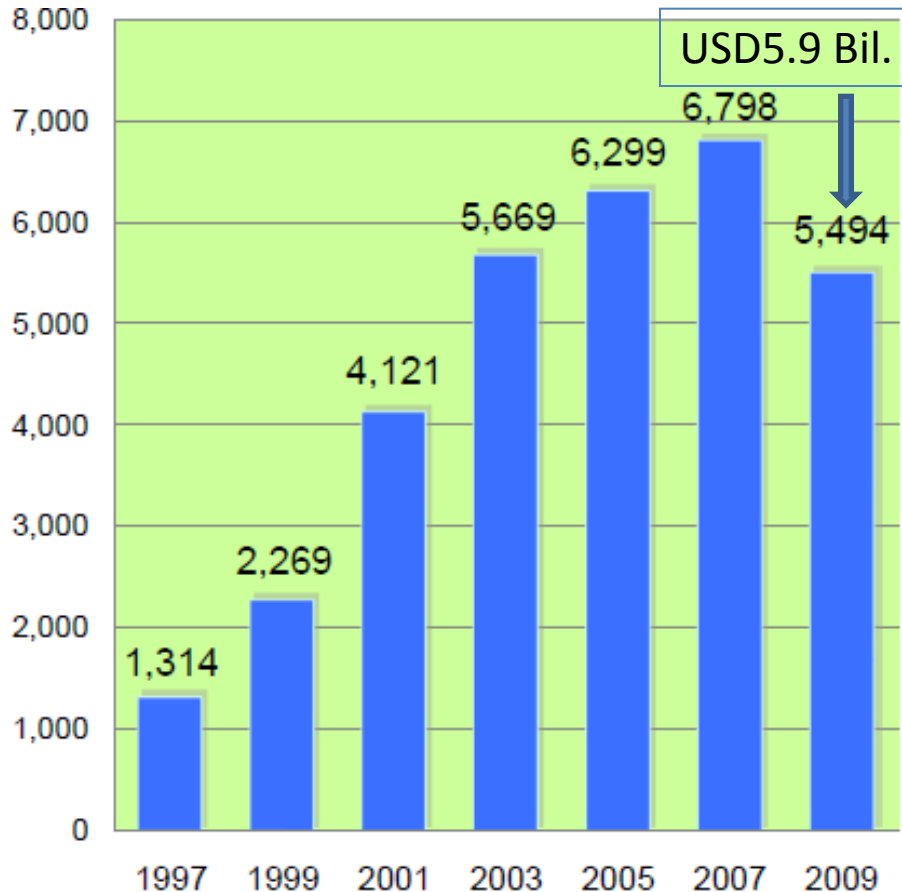
The Bioeconomy to 2030: Designing a Policy Agenda (OECD ,2009)

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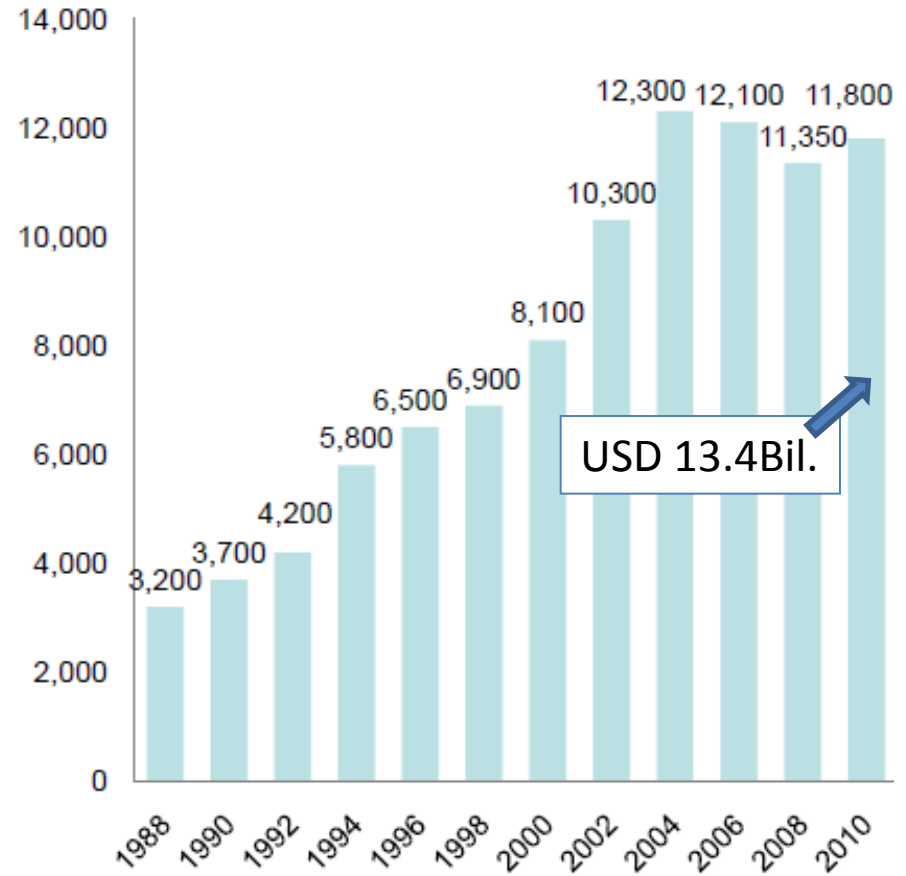
Market of Health Foods

Market of Total health foods USD 19.3 Bil.

¥ hMil. Food for Specified Health Uses(FOSHU)



¥ hMil. Total health foods except FOSHU



Some issues on Screening of active products from microbes

I、 Enzyme Activity (Biological catalyst)

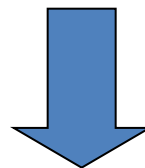
II、 Active chemical compound

- Decrease of discovery of novel compound and few successful drug
 - Database construction by know-how / Early judgment of go or not go
 - Improvement of sensitivity of analytical system
 - Optimization of culture condition / All products should be isolated from a strain
 - Technological Innovation

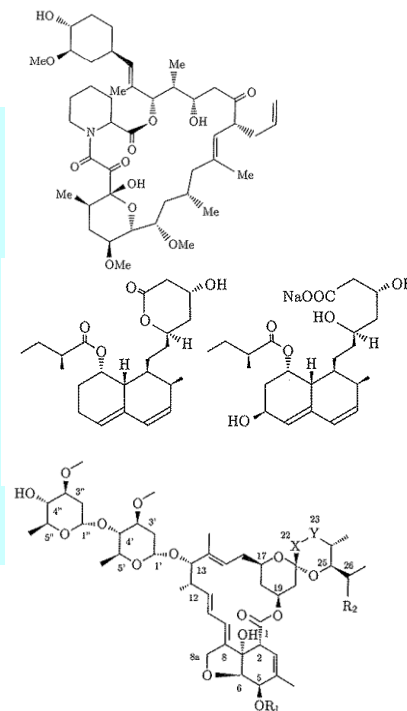
- Diversity of structure
 - Novel protein by genome-shuffling and designing of novel biosynthetic pathway
 - Biological diversity on gene resources

Screening with Natural product

- Natural products was found as Antibiotics, Anticancer, Immuno-suppressive drug
- Cell Based Assay system
- Molecular target assay System is not suitable
- Low reproducibility of Assay result
- High diversity on Structural and Activity



- Increase of Molecular target assay System
- Improvement of High through Put Screening system correlated with High diversity on Structural and activity of extracts
- High sensitivity of analytical system overcomes low reproducibility of production



Important issue for Bioindustry about usage of culture collection

Application of Microbiological information for Bioindustry

1, Primary Screening resource for active compound, enzyme or genes

- Type culture collection
- Information about medium composition of each strain
- Preservation of activity at freshly isolated

2, Secondary screening

- Collection of related or same pieces strains
- Accurate identification of each stock culture

As a database, information of first published scientific paper is important. Origin of strain is one of most important information for industry.

Patentability:
Novelty ,Originality,
Applicability,

Industrial Applicability
Novelty
Inventive Step and non-obviousness

★ **Whole genome information, omics information(m-RNA,Protein, interaction etc)**

Understanding of Biosynthetic pathway、Gene-function

→ Designing of synthetic pathway

→ Breeding of novel fermentation strain

Function of Gene → Understanding of protein function

→ Designing of Advanced Protein (Enzyme、Regulator、Receptor)

→ Creation of Advanced Enzyme comparable to Chemical Catalyst

Methodology with System-Biology

★ **Screening of novel microbe (enzyme) from nature**

Analysis of microbial flora、isolation of unculturable microbe

Extraction of metagenome、Extreme environment habitat、

Genetic resources from the world

→ Improvement of Screening technology and methodology

Utilization of Omics information

Strategy for breeding fermentation strain with omics information

- 1、 Random mutation and selection by productivity
- 2、 Introduction of genes on biosynthetic pathway
- 3、 Selection of effective mutation and amplification

Optimization of genome set Biosynthetic pathway

- Understanding of function of gene product
- Large size genome manipulation technology

Top-selling Pharmaceuticals 2002

PRODUCT	TYPE	SALES(M\$)	PRODUCT	TYPE	SALES(M\$)
Atorvastatin	Hypolipidaemic	7972	Losartan	Angiotensin II antag	2190
Simvastatin	Hypolipidaemic	5580	Resperidone	Antipsychotic	2146
Omeprazole	Proton pump inhibitor	4623	Venlafaxine	Antidepressant	2072
Erythropoietin	Antianaemic	4269	Esomeprazole	Proton pump inhibitor	1978
Amlodipine	Calcium antagonist	3846	Fexofenadine	Antihistamine	1915
Lansoprazole	Proton pump inhibitor	3766	Clopidogrel	Platelet antiaggreg	1638
Olanzapine	Antipsychotic	3689	Insulin	Antidiabetic	1880
Paroxetine	Antidepressant	3067	Oestrone	Hormonal	1880
Celecoxib	Cox-2 inhibitor	3050	Loratadine	Antihistamine	1802
Sertraline	Antidepressant	2742	Amoxicillin	Antibiotic	1778
Interferon-a	Antiviral	2736	Sildenafil	Phosphodiester. inhib	1735
Rofecoxib	Cox-2 inhibitor	2530	Valsartan	Angiotensin II antag	1654
Fluticasone	Antiasthma	2434	Citalopram	Antidepressant	1589
Gabapentin	Anticonvulsant	2269	Leuprolide	Anticancer	1537
Pravastatin	Hypolipidaemic	2266	Oxycodone	Analgesic	1529
Erythropoietin	Antianaemic	2260	Azithromycin	Antibiotic	1516
Alendronate	Bisphosphonate	2250	Montelukast	Leukotriene antag	1505

Natural product derivative / hormone, growth factor

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From Wood Mackenzie

Chemical compounds developed as medicine between 1981 to 2002 in the world

Among 877 chemical compounds 61 % as Natural Product

Natural product	6 %
Natural product derivatives	27%
Natural Core + Chemical conversion	5 %
Natural product Mimic	23%

Antibiotics 78%
Anticancer 74%

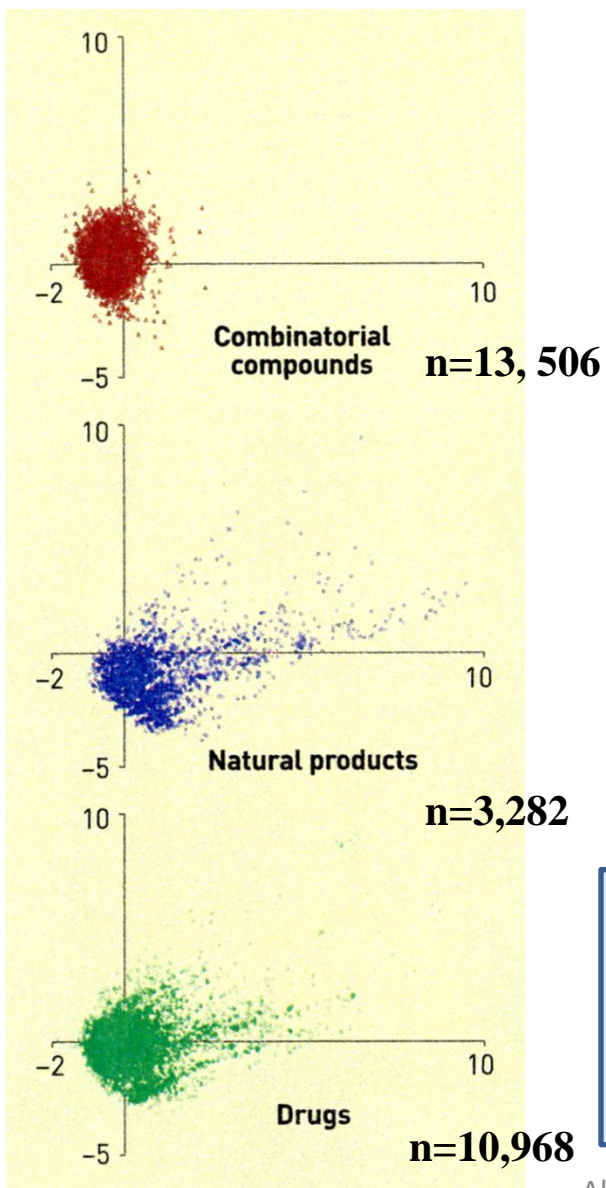
Cholesterol Management
Diabetes
Arthritis
Depression

Natural products have much higher Structural diversity than Combi.Chem. products

Distinctive in chemical diversity space

J. Chem. Inf. Comput. Sci., 43, 218 (2003)

Principal components analysis (PCA)



- molecular weights
- number of chiral centers
- number of N, O, S, halogen atoms
- ring of fusion degree
- number of rotatable bonds

- ◆ **Combi.Chem.products** have limited space
- ◆ **Developed drugs** and **natural products** have broad and similar space

★ Among 1073 medicines approved by FDA between 1981 to 2010 64% chemical compounds come from natural products or derivatives.

Actinomycetes

- Half of 20000 biological active compounds originated from microorganism comes from Actinomyces
- One rare Actinomyces strain produce four novel and five known compounds
- One Actinomyces strain possess over 30 secondary metabolite biosynthetic genes.

Perspectives of Microbial Screening system

Biological Diversity

Discovery of Novel Lead Compound

Only 0.1% of Microbes in Soil is Culturable
Utilization of `Genes` from Unculturable Microbes
Combinatorial Genomics,
Combinatorial Biosynthesis

Full-activation of biosynthetic pathway

Genetic Diversity

Screening of Novel Lead Compound

Combination of Chemical Analysis
and Genomic Data base
→ Efficient Screening for Compound

Development of Novel Lead Compound

Derivatization on Novel Structural Base
by CombiChem
Utilization of Microbial enzymes for Conversion
→ Combinatorial Biocatalysis

Chemical Diversity

Thank you for your attention

**How to improve
a usefulness and serviceability
of microbial data base.**