HELLENIC INDUSTRIAL PROPERTY ORGANISATION

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INTERNATIONAL CONFERENCE
Intellectual Property and Health Innovation – Challenges for the future
April 28, 2014 , Athens, Greece

Research and Innovation in Drug Discovery and Diagnostics

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http://www.eie.gr/nhrf/institutes/ibmcb/index-en_ibmcb.html

NATIONAL HELLENIC RESEARCH FOUNDATION
Athens, Greece

International and European picture
In Drug Discovery and Diagnostics

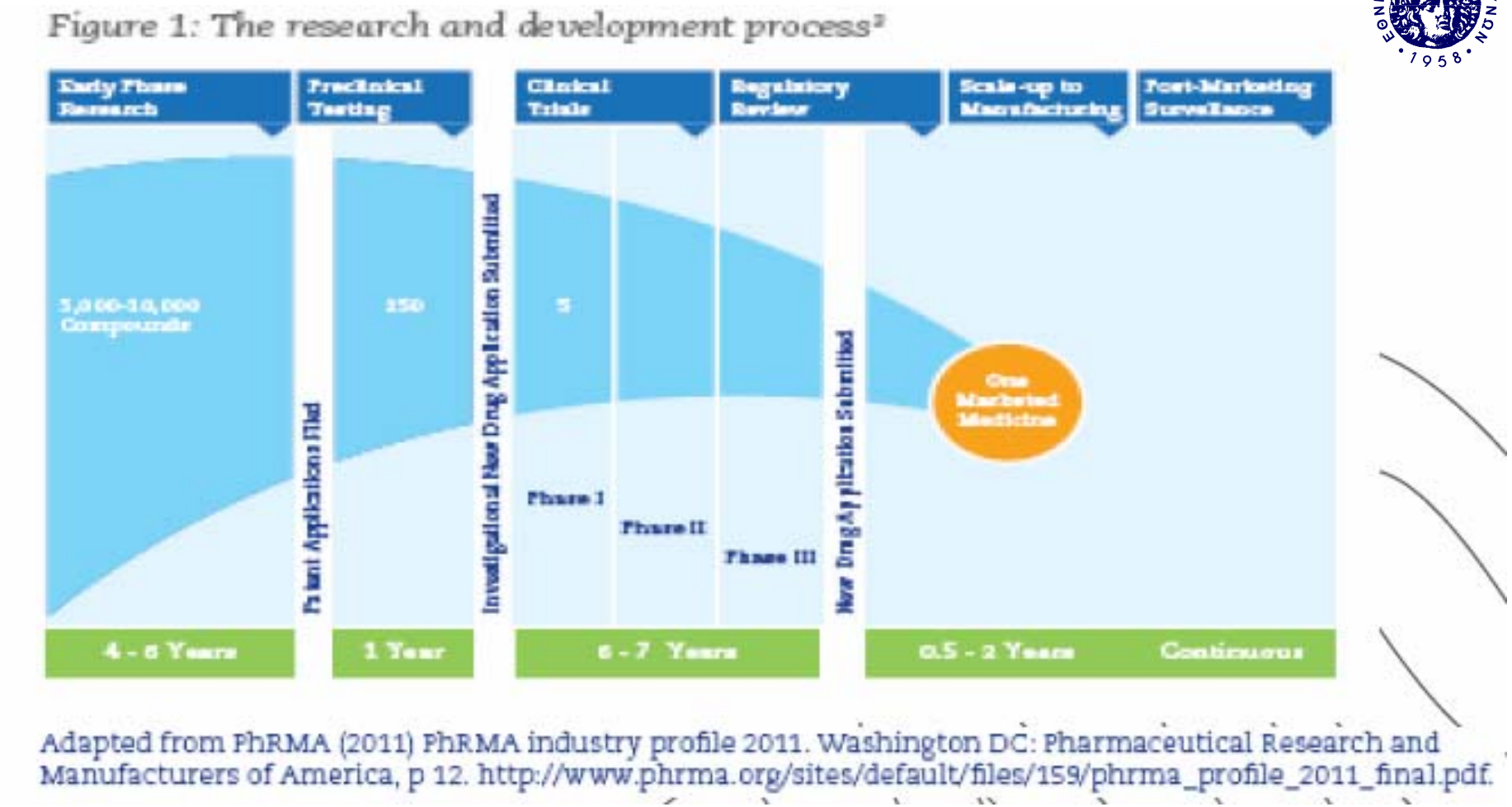


Figure. Research and Development in the Pharmaceutical Industry (source: The Pharmaceutical Industry & Global Health. International Federation of Pharmaceutical Manufacturers & Associations – Facts & Figures 2012)

CDS Images/Alamy

2013 FDA drug approvals

Although the FDA's 27 new approvals are down from the 15-year high of 2012, the newcomers pack powerful commercial potential.

New drug approvals 2013

Table 1 | **CDER's novel approvals in 2013**

Drug (brand)	Company	Properties	Indication	Review
Alogliptin (Nesina)	Takeda	DPP4 inhibitor	Type 2 diabetes	S
Mipomersen (Kynamro)	Genzyme	Oligonucleotide inhibitor of apolipoprotein B100 synthesis	Homozygous familial hypercholesterol-aemia	S, O
Pomalidomide (Pomalyst)	Celgene	Immunomodulatory antineoplastic agent	Multiple myeloma	S, O
Ado-trastuzumab emtansine (Kadcyla)*	Genentech	HER2-targeted antibody and microtubule inhibitor conjugate	HER2-positive metastatic breast cancer	P
Ospemifene (Osphena)	Shionogi	Oestrogen receptor modulator	Moderate to severe dyspareunia due to menopause	S
Technetium TC 99m tilmanocept (Lymphoseek kit)	Navidea	Radioactive diagnostic agent	Lymphatic mapping in patients with breast cancer or melanoma	S
Gadoterate meglumine (Dotarem)	Guerbet	Gadolinium-based contrast agent	Contrast agent to visualize disruption of the blood–brain barrier	P
Dimethyl fumarate (Tecfidera)	Biogen Idec	MOA unknown; activates NRF2 pathway	Relapsing forms of multiple sclerosis	S
Canagliflozin (Invokana)	Janssen	SGLT2 inhibitor	Type 2 diabetes	S
Fluticasone; vilanterol (Breo Ellipta)	GSK	Corticosteroid plus LABA	Chronic obstructive pulmonary disease	S
Radium RA 223 dichloride (Xofigo)	Bayer	Alpha particle-emitting radioactive therapeutic	Castration-resistant prostate cancer	P
Dabrafenib (Tafinlar)	GSK	Kinase inhibitor with activity against $BRAF^{V600E}$, $BRAF^{V600K}$, $BRAF^{V600D}$, wild-type BRAF and other kinases	Unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test	S, O
Trametinib (Mekinist)	GSK	MEK1 and MEK2 kinase inhibitor	Unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test	S, O
Afatinib (Gilotrif)	Boehringer Ingelheim	EGFR (ERBB1), HER2 (ERBB2), and HER4 (ERRB4) kinase inhibitor	First-line treatment of patients with metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test	P, O
Dolutegravir (Tivicay)	ViiV	HIV1 integrase strand transfer inhibitor	HIV1 infection in adults and children, in combination with other antiretroviral agents	P
Vortioxetine (Brintellix)	Takeda	Serotonin reuptake inhibitor	Major depressive disorder	S
Bazedoxifene acetate plus oestrogens (Duavee)	Pfizer	Conjugated oestrogens with an oestrogen receptor modulator	Moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis	S
Riociguat (Adempas)	Bayer	Soluble guanylyl cyclase stimulator	Persistent or recurrent chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension	P, O
Macitentan (Opsumit)	Actelion	Endothelin receptor antagonist	Pulmonary arterial hypertension	S, O
Flutemetamol F-18 (Vizamyl)	GE Healthcare	Radioactive diagnostic agent	PET imaging of the brain to estimate β-amyloid neuritic plaque density in patients who are being evaluated for Alzheimer's disease	S
Obinutuzumab (Gazyva)*	Genentech	Humanized CD20-specific monoclonal antibody	Previously untreated chronic lymphocytic leukaemia	P, O, B
Eslicarbazepine (Aptiom)	Sunovion	MOA unknown, but thought to involve voltage-gated sodium channels	Partial-onset seizures	S
Ibrutinib (Imbruvica)	Pharmacyclics	Bruton's tyrosine kinase inhibitor	Mantle cell lymphoma	P, O, B
Luliconazole (Luzu)	Medicis	Azole antifungal	Interdigital tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum* and *Epidermophyton floccosum*	S
Simeprevir (Olysio)	Janssen	HCV NS3/4A protease inhibitor	Chronic HCV infection, as a component of a combination antiviral treatment regimen	P
Sofosbuvir (Sovaldi)	Gilead	HCV nucleotide analogue NS5B polymerase inhibitor	Chronic HCV infection, as a component of a combination antiviral treatment regimen	P, B
Umeclidinium and vilanterol (Anoro Ellipta)	GSK	Anticholinergic and a LABA	Chronic obstructive pulmonary disease	S

*Biologics license application. B, breakthrough designation status; CDER, Center for Drug Evaluation and Research; DPP4, dipeptidyl peptidase 4; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; GSK, GlaxoSmithKline; HCV, hepatitis C virus; LABA, long-acting β_2-adrenergic receptor agonist; MEK, MAPK/ERK kinase; MOA, mechanism of action; NME, new molecular entity; NRF2, NFE2-related factor 2; NSCLC, non-small-cell lung cancer; O, orphan status; P, priority review; S, standard review. SGLT2, sodium-dependent glucose cotransporter 2.

New approvals with million dollar potential- Approvals by therapeutic area

Table 3 | **New approvals with billion-dollar potential**

Drugs	Company	Forecast (billions of $US)*
Sofosbuvir (Sovaldi)	Gilead	6.8‡
Dimethyl fumarate (Tecfidera)	Biogen Idec	6
Ibrutinib (Imbruvica)	Pharmacyclics	4.5
Ado-trastuzumab emtansine (Kadcyla)	Genentech	4.1
Umeclidinium and vilanterol (Anoro Ellipta)	GlaxoSmithKline	3.1
Fluticasone and vilanterol (Breo Ellipta)	GlaxoSmithKline	2.8
Pomalidomide (Pomalyst)	Celgene	1.8
Canagliflozin (Invokana)	Janssen	1.6
Obinutuzumab (Gazyva)	Genentech	1.5
Dolutegravir (Tivicay)	ViiV	1.4
Afatinib (Gilotrif)	Boehringer Ingelheim	1.3§
Macitentan (Opsumit)	Actelion	1
Alogliptin (Nesina)	Takeda	1‖

*All forecasts are consensus, annual, global sales estimates for 2019, as compiled by Thomson Reuters Cortellis, except where indicated otherwise. ‡The sofosbuvir sales estimates are for 2018. §The afatinib sales forecasts are from BioMedTracker, for 2018. ‖The alogliptin sales forecast is for 2017, after which the drug is forecast to lose blockbuster status.

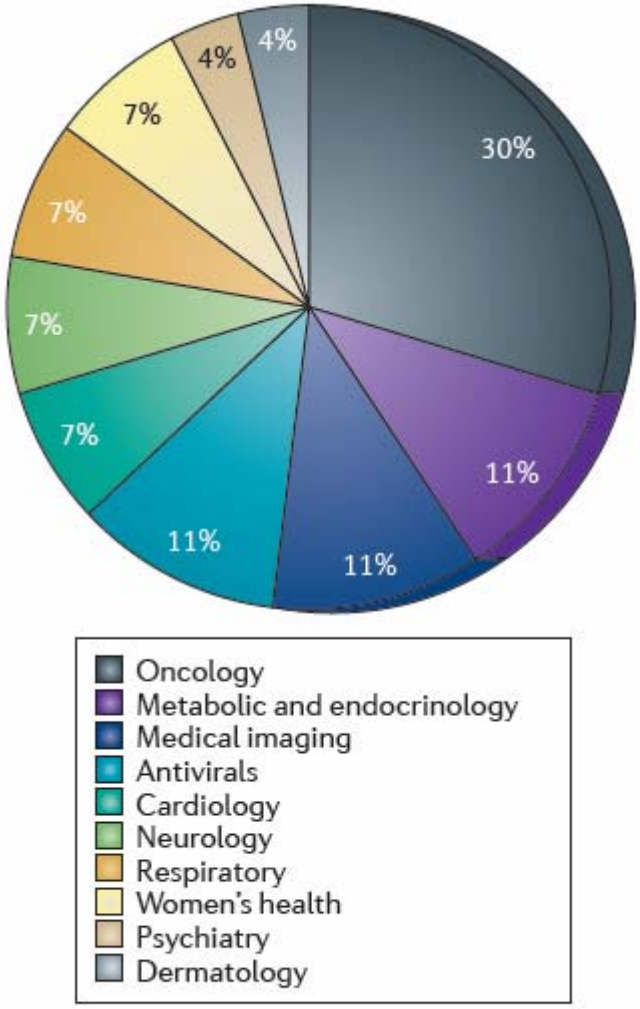


Figure 3 | **Approvals by therapeutic area.**

Where do new medicines originate from in the EU?

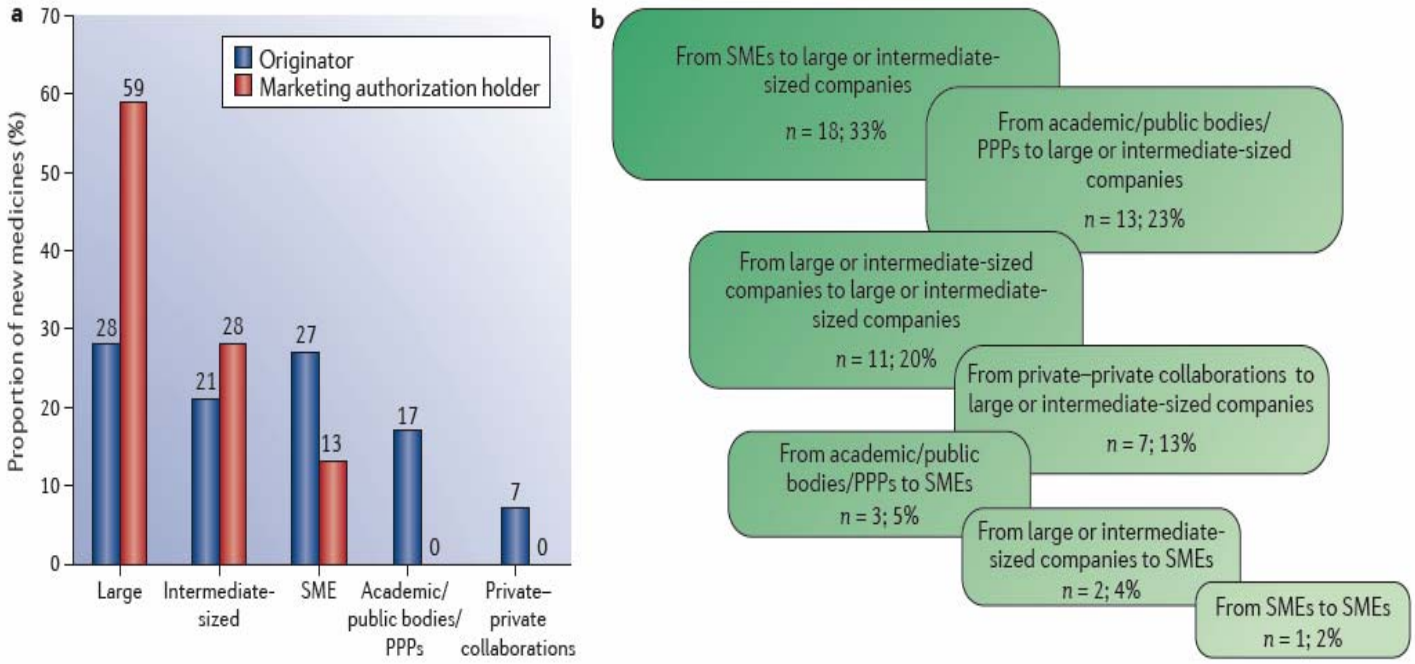


Figure 1 | **Origin of new medicines in the European Union (2010–2012).** **a** | Originator and the marketing authorization holder for all 94 approved products evaluated, divided according to organization type. **b** | Direction of product transfers between organization types during development; the size of the lozenges is representative of the proportion of transfers. PPP, public–private partnership; SME, small or medium-sized enterprise. For details of the data and analysis, see Supplementary information S1 (box).

Although large and intermediate-sized companies still represent the main engine for commercializing new medicines, SMEs, academic institutions, public bodies and PPPs represent an important source of innovation.

Drug discovery research in UK academic groups compared with US academic groups and the pharmaceutical industry

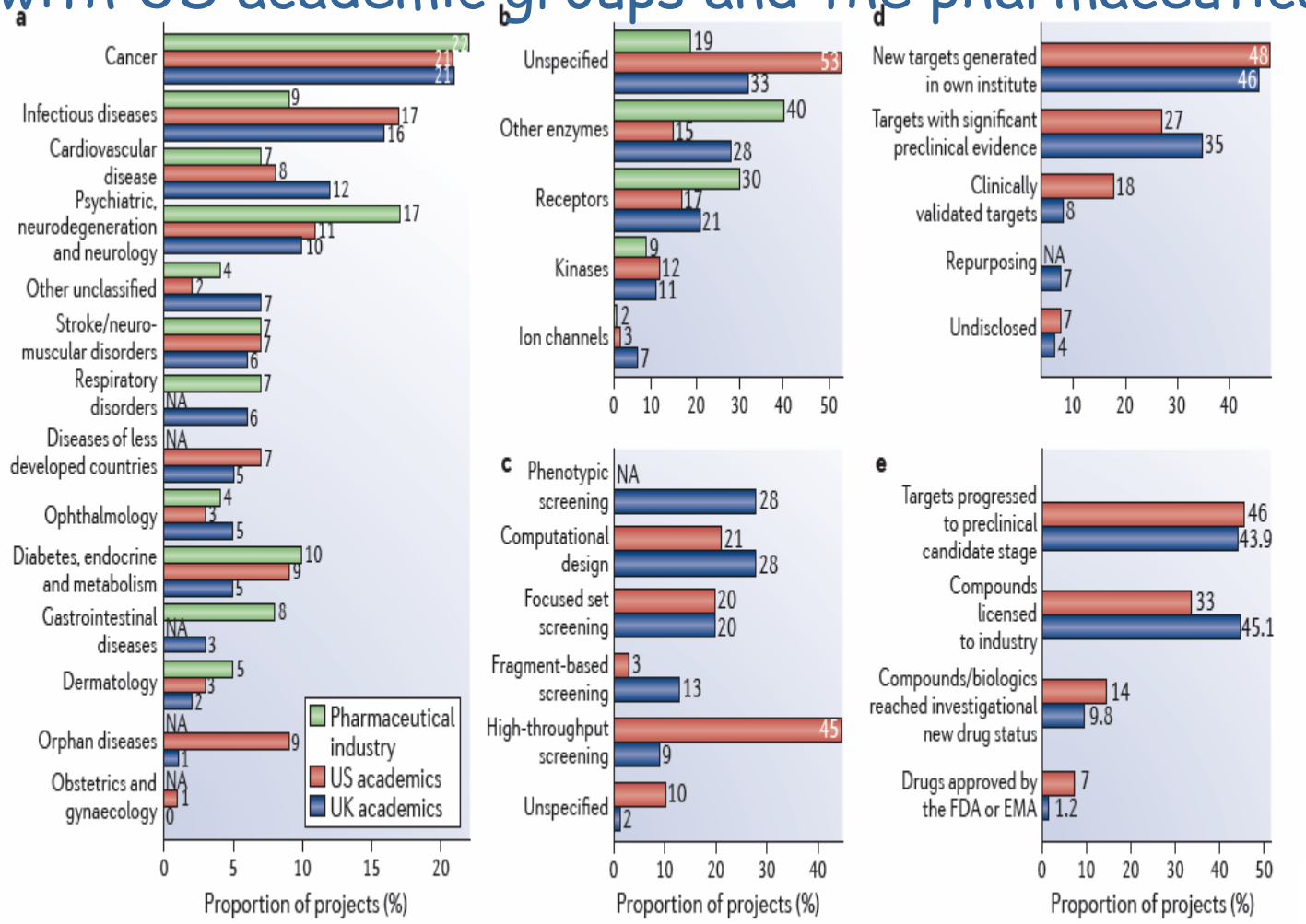


Figure 1 | **Drug discovery research in UK academic groups compared with US academic groups and the pharmaceutical industry.** **a** | Research effort (%) by therapeutic area. **b** | Research effort (%) for individual drug targets. **c** | Hit identification strategies used in academic groups. **d** | Degree of target validation for projects at initiation. **e** | Academic drug pipelines. Sources: survey for the UK (Supplementary information S2 (box)); US data normalized from REF. 1; current data from top-50 pharmaceutical company pipelines from Thomson Reuters Integrity. NA, not available.

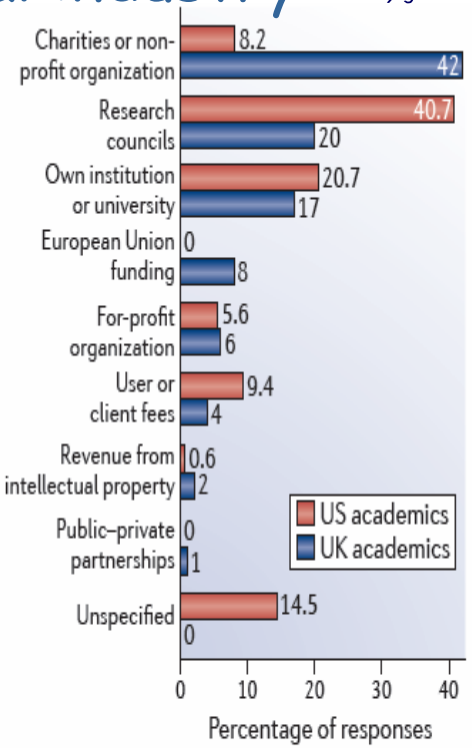
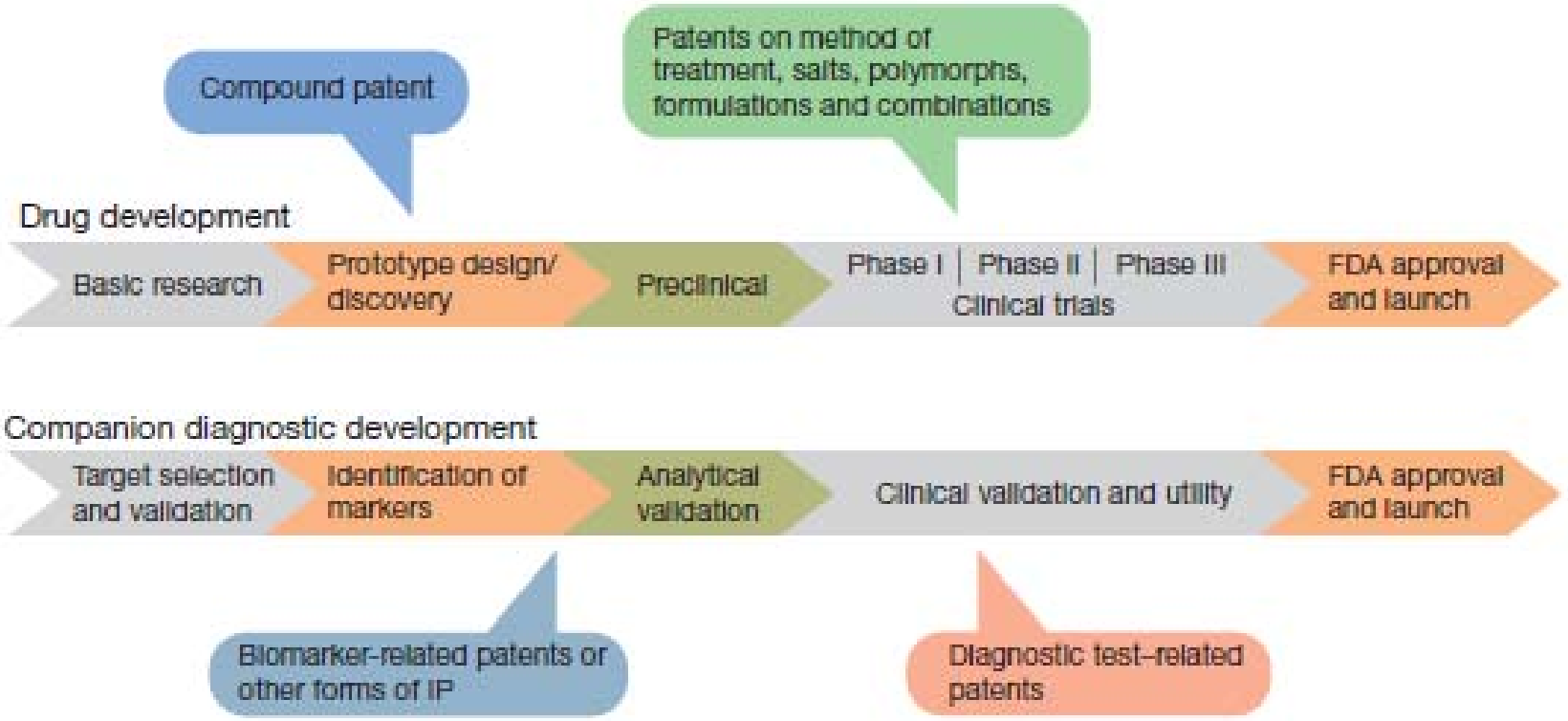


Figure 2 | **Funding sources for academic drug discovery.** See Supplementary information S2 (box) for details.

Biomarker discovery –Companion diagnostics

Biomarker discovery –Companion diagnostics: Drug and diagnostic co-development pathway and patent filings



Coordinated patent filings with joint efforts from both the pharma and the diagnostic companies are critical to a strong and integrated patent portfolio that helps maximize the commercial value of a drug-diagnostic pair.
Highlighted are the key steps along the co-development pathway and various types of patent filings that may be considered at different stages.

FDA-approved stratification biomarkers for targeted therapy in oncology

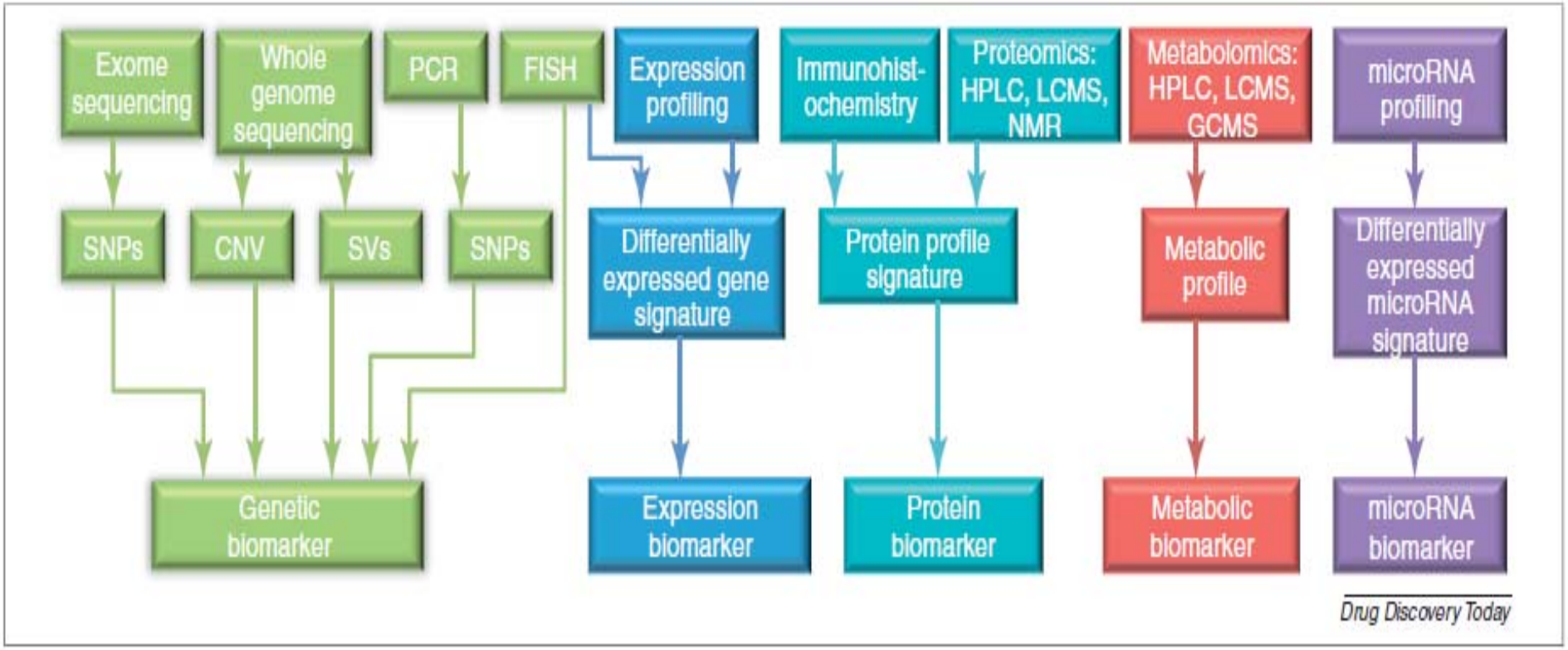
TABLE 1

FDA-approved stratification biomarkers for targeted therapy in oncologyAdopted from: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Functional class	Biomarker	Therapy
Kinase	EGFR	Cetuximab, Erlotinib, Gefitinib, Panitumumab
Kinase	Her2/neu	Lapatinib, Trastuzumab, Pertuzumab
Kinase	PDGFR	Imatinib
Kinase	Estrogen receptor	Fulvestrant, Exemestane
Kinase	ALK	Crizotinib
Kinase	KRAS	Cetuximab, Panitumumab
Kinase	BRAF	Vemurafenib
Immune cell surface receptor	CD20	Tositumumab
Immune cell surface receptor	CD25	Denileukin difitox
Immune cell surface receptor	CD30	Brentuximab vedotin
Immune cell surface receptor	C-Kit	Imatinib
Fusion gene	PML-RARα	Arsenic trioxide
Fusion gene	BCR-ABL	Dasatinib

Avisek Deyati, Drug Discovery Today, Volume 18, 614-624, July 2013

Current technologies and data types used for biomarker discovery in preclinical and clinical research



Abbreviations: CNV, copy number variations; FISH, fluorescence in situ hybridization; GCMS, gas chromatography mass spectrometry; HPLC, high-performance liquid chromatography; LCMS, liquid chromatography–mass spectrometry; NMR, nuclear magnetic resonance; PCR, polymerase chain reaction; SNPs, single nucleotide polymorphisms; SVs, structural variations

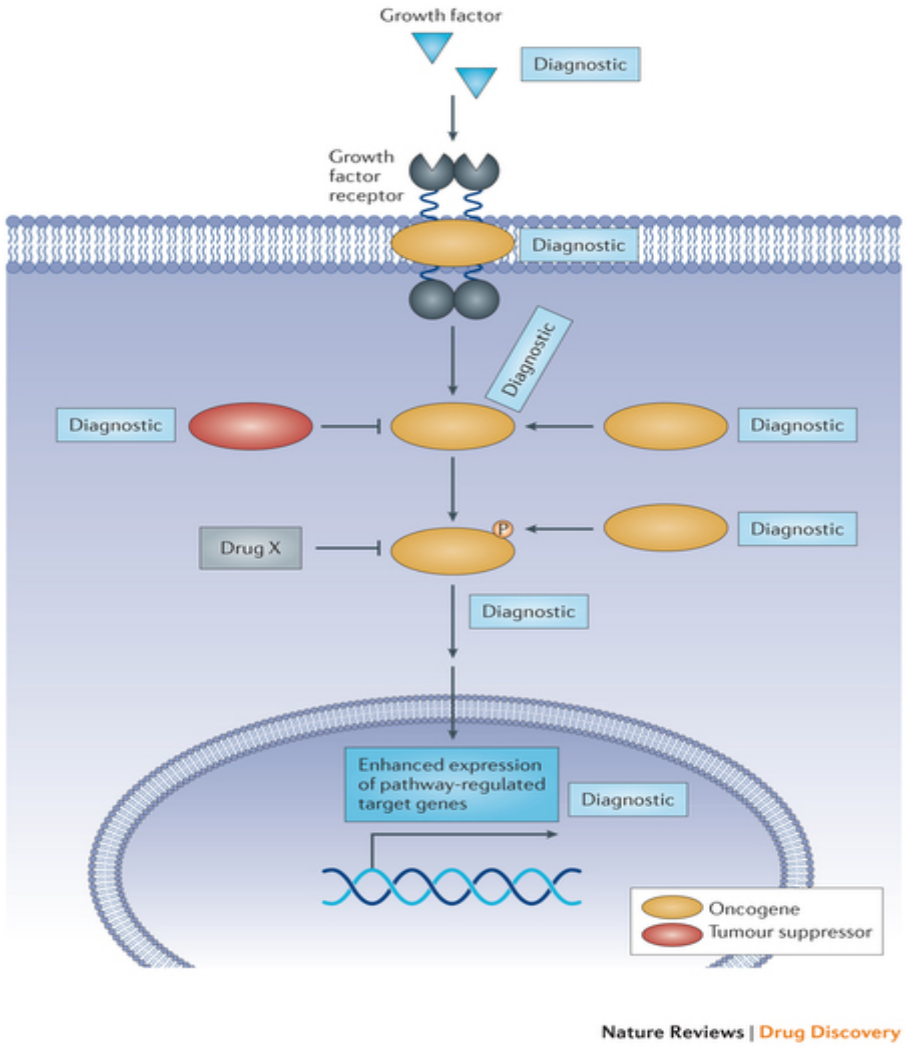
Diagnostic assays used in oncology

Biomarker	Platform or technology	Diagnostic test value type	Drug and diagnostic examples	Challenges
Mutation or mutations	Sequencing	Generally binary	No current examples	Test results depend on the percentage of cells with mutations (that is, there is a lower detection limit); may measure non-specific exons
Mutation or mutations	Quantitative PCR	Generally binary	Cobas 4800 BRAF V600 Mutation Test; TheraScreen K-RAS Mutation Kit	Test results depend on the percentage of mutant sequences, adequate specimen integrity and sufficient DNA to be detected
Protein expression	Immuno-histochemistry staining	• Generally continuous based on the intensity and proportion of cells with the given intensity; ordinal intensity scoring of currently approved tests • Could be treated as binary if the diagnostic readout is a complete loss of signal (for example, a H-score‡ of zero)	Dako HercepTest (detects HER2 protein expression)	Generally semi-quantitative and non-automated evaluation; test results can depend on pre-analytical tissue processing factors
Gene expression	Quantitative real-time PCR	Generally continuous	No current examples	Manual macrodissection may be necessary for samples with low tumour cell content
DNA copy number	FISH or chromogenic *in situ* hybridization	Generally continuous; could be treated as binary if the diagnostic is a complete loss of copy number or high-level amplification	HER2 FISH pharmDx Kit; PathVysion HER-2 DNA Probe Kit; Her2 Dual ISH DNA Probe Kit	Relatively complex assay technology and interpretation
Fusion protein product	FISH	Threshold is set at specific percentage of cells; essentially a bimodal distribution	Vysis ALK Break Apart FISH Probe Kit	Relatively complex assay technology and interpretation
Gene signature	Next-generation sequencing	Could be treated as binary based on gene signature	No current examples	Complex assay technology and interpretation

ALK, anaplastic lymphoma kinase; FISH, fluorescence *in situ* hybridization; HER2, human epidermal growth factor receptor 2 (also known as ERBB2).*This table shows the types of diagnostic assays used in oncology for each type of biomarker and their potential challenges in determining what constitutes a 'biomarker-positive' or 'biomarker-negative' readout. ‡The H-score is a semi-quantitative intensity scale used to describe immunohistochemistry staining, and is calculated by the weighted combination of staining intensities of the cells and the proportion of cells stained at a given intensity.

Jane Fridlyand et al. NATURE REVIEWS | DRUG DISCOVERY VOLUME 12 | OCTOBER 2013 | 743

Identification of a biomarker in tumours with an associated pathway alteration



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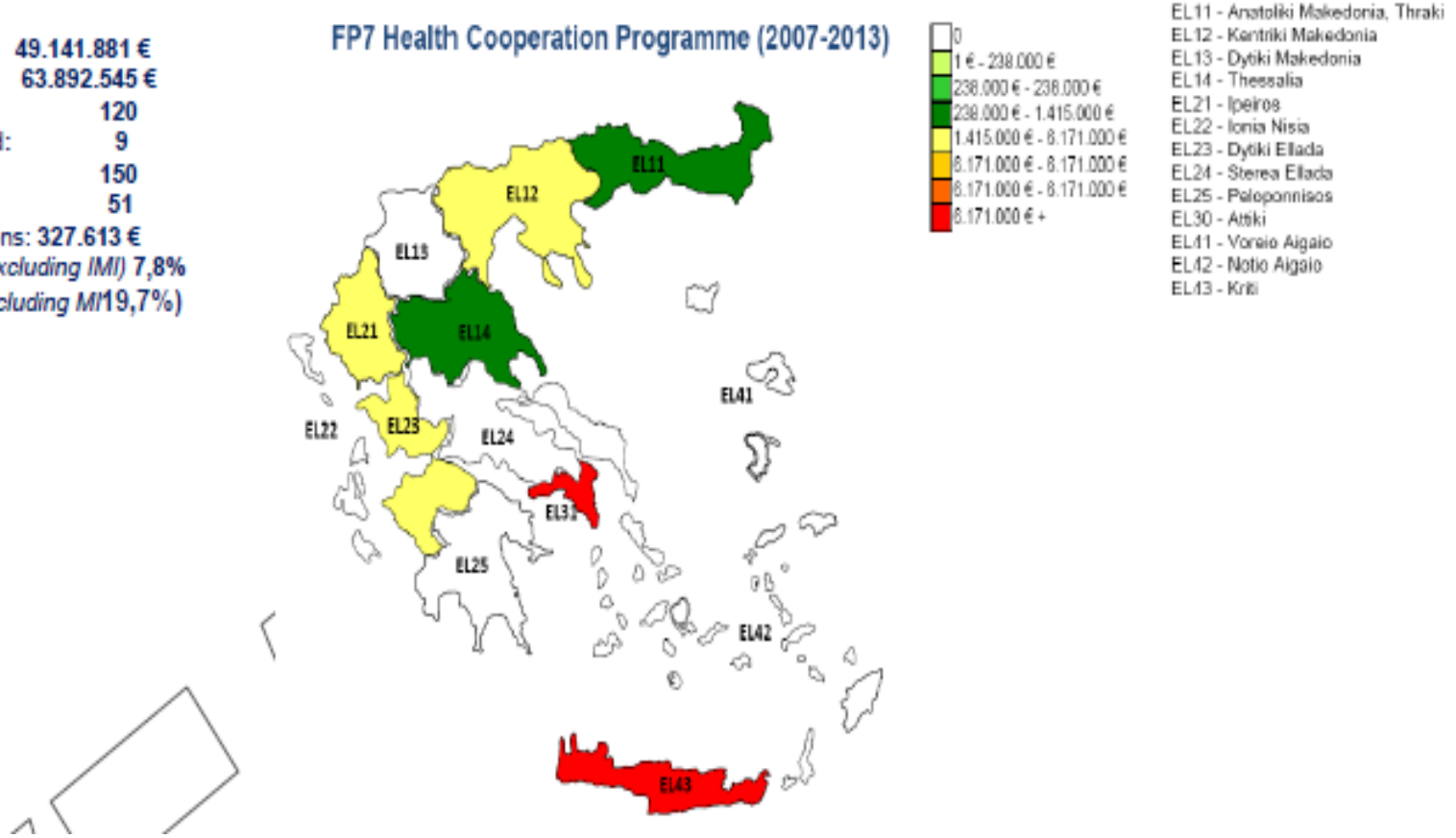
Some data for research and innovation activities in Greece

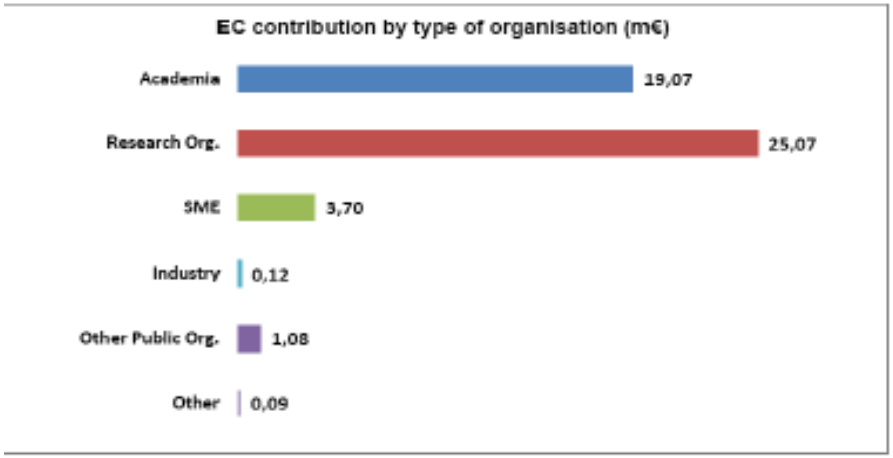
Statistics for the participation of Greece in the 7FP Health

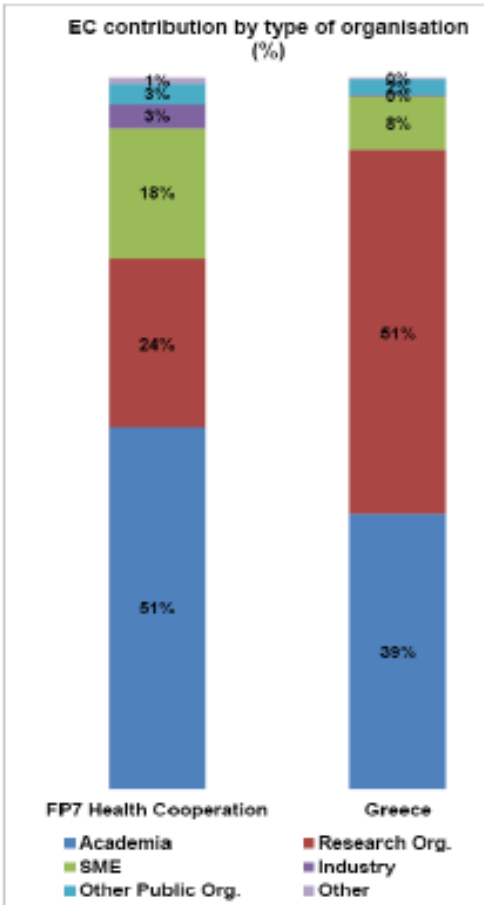
EC contribution:	**49.141.881 €**
Total Costs:	**63.892.545 €**
Number of projects:	**120**
Number of projects coordinated:	**9**
Number of participations:	**150**
Number of organisations:	**51**
Average amount by participations:	**327.613 €**
Coordinator's Success Rate *(excluding IMI)*	**7,8%**
Participant's Success Rate *(excluding MI*)	**19,7%)**



Sources: EU; GSRT

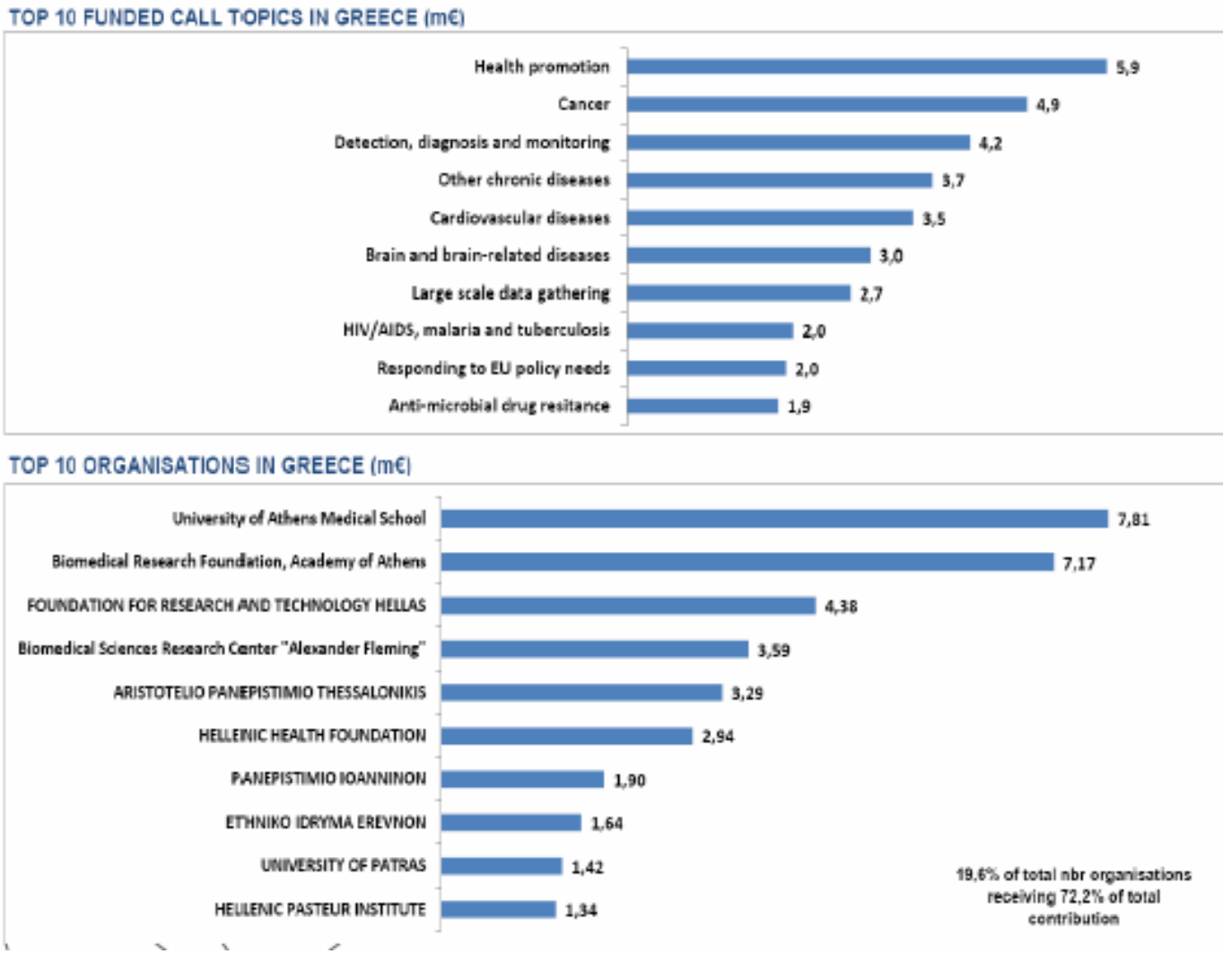
Statistics for the participation of Greece in the 7FP Health





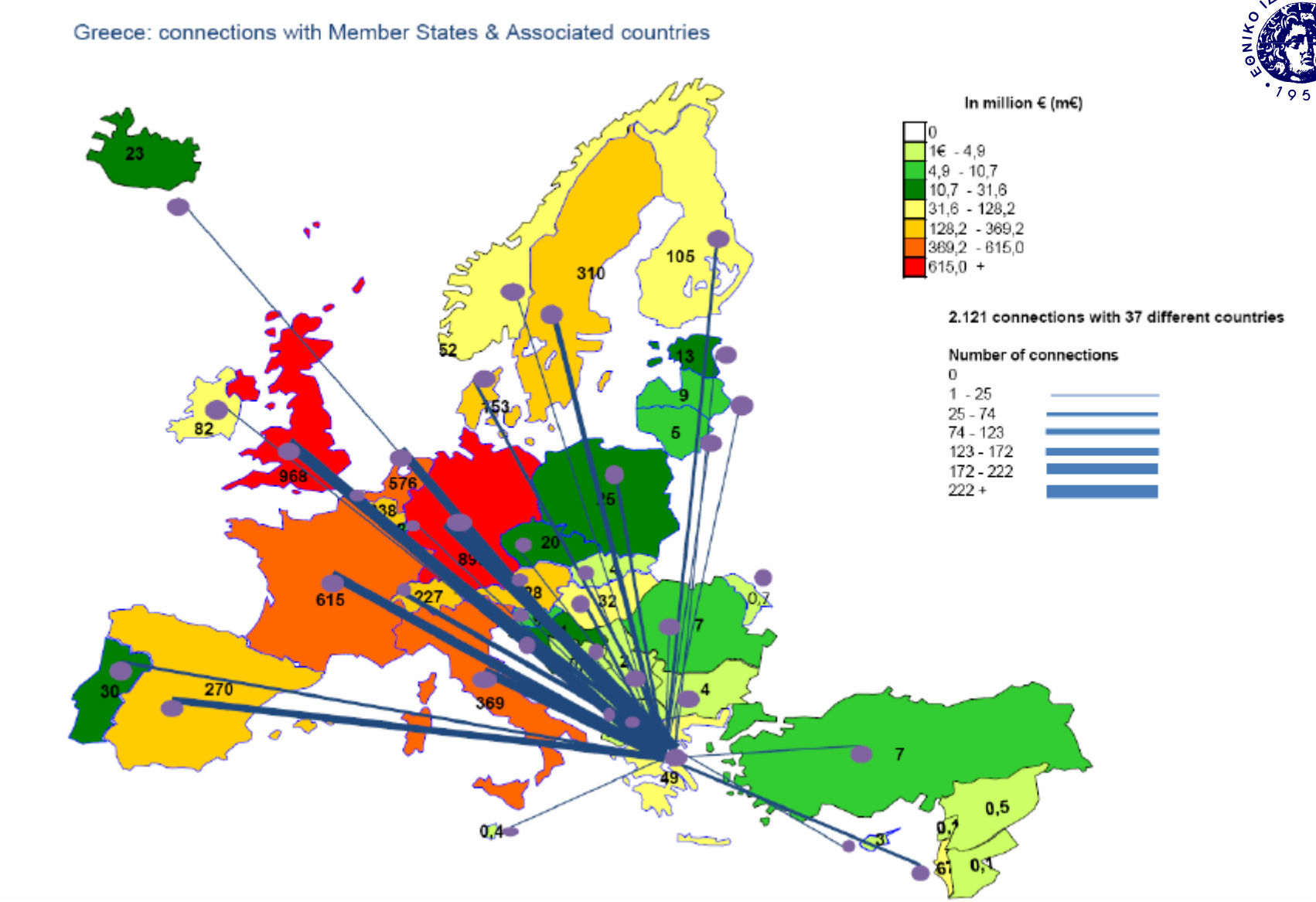
Sources: EU; GSRT

Statistics for the participation of Greece in the 7FP Health



Sources: EU; GSRT

Connections with Member States and Associated countries



Sources: EU; GSRT

Description of the current situation of research and innovation in Greece: SWOT analysis (National Sectoral Scientific Council in Life Sciences)

Strong points

- Capacity to ensure competitive funding from the EU and other external sources
- Existence of islands of excellence and satisfactory research facilities, despite adversity
- Increased competitiveness and efficiency for attracting EU funding

Opportunities

- The presence of researchers with sufficient training and dynamism
- Possibility of increasing cooperation between Research Centers and Universities
- The economic crisis may lead to the restructuring of the productive fabric of the country
- Greece is at breaking point and must decide on its future course.
- Growth in Greece coincides with the aid of Education and Research.

But ... also depends on the transformation of the private sector active in the area of life sciences, from a resale to productive

Threats

- Failure to reform the research system will be a serious problem
- Reduce funds for research because of crisis will not allow economic recovery:

The research funds should not be considered cost, but an investment.

- Inability to install, operate and maintain developmental research infrastructures

•International experience indicates that the private sector is interested and energized to invest in research and innovation when the public sector has established a long-term funding strategy for producing original and internationally competitive new knowledge in specific areas in order to make them attractive for investment.

• It has been estimated that the development of a new drug which is authorized by the FDA in the U.S. costs 1.3 billion dollars. This amount includes the cost of drugs by the same company that eventually failed to get a license, but not the cost of marketing.

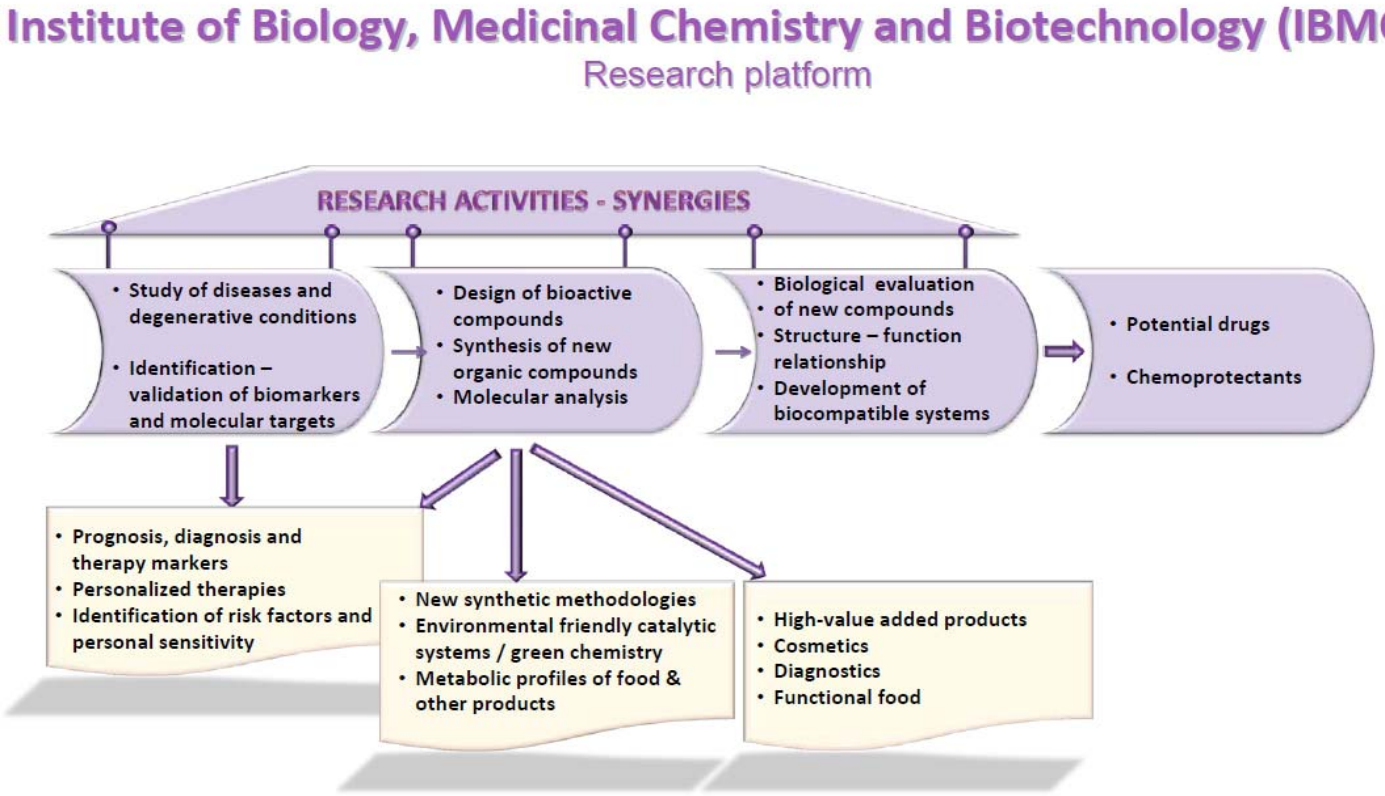
• On average an additional investment of about $50m to commercialize a diagnostic should be factored into the additional cost of targeted therapy if the test is to contribute to enabling the right patient to be treated at the right time.

A few words about the IBMCB/ National Hellenic Research Foundation

INSTITUTE OF BIOLOGY, MEDICINAL CHEMISTRY AND BIOTECHNOLOGY (IBMCB)

The individual Excellence objectives of IBMCB include:

1) Development and improvement of targeted bioactive compounds-drugs
2) Development of drug associated companion diagnostics.
3) Exploitation of modern holistic approaches of chemical and biological analysis.
4) Development of novel nanoformulations and engineered microorganisms



IBMCB activities for exploitation of research

IBMCB Researchers collaborate and provide specialised services for research and technology centers, universities, health agencies, hospitals and industrial sector:

•Synergies and services with a significant number of Public and Private Hospitals in Athens, and University clinics, Univ. Athens Medical School

• Synergies with a significant number of companies Bristol Meyers Squibb SA, Pharmaten, ELPEN AE, GAP AE, UNIPHARMA SA, LAVIPHARM S.A., MEDEXIS SA, PROACTINA SA, BIONATURE SA, MEDOCHEMIE SA, DEMO SA, KORRES AE, Biohellenika, GeneKor, DIAGENODE S.A.,BIOIATRIKI,ELAIS AE, KNORR – Best Foods SA,VIORYL S.A.,ALGAE A.E.

IBMCB activities for exploitation of research

- The IBMCB has 16 patents, of which 7 international

- Commercial products

•ChIP-grade antibodies,

•Anti-aging and anti-wrinkle products,

•A series of enzymatic depilatory products,

•Metal complex as an efficient homogeneous catalyst

- Spin-off company

TAK – EIE Stem Cells Bank
Created in 2007
Stocks partition: NHRF/IBMCB 40%, BIOHELLENICA SA 60%
Agreement: Exploitation of research results of IBMCB in Stem cells
Initial Staff 7
10% of the turnover invested in Research at IBMCB)

- Technology transfer

The Institute has developed significant activity in Technology transfer through participation in three networks funded by the European interregional programs MED and South Eastern Europe.

Main IBMCB facilities

IBMCB

Scientific and Technological Excellence 2005-2012

The fundamental statistics and trends of IBMCB external funding are summarised as follows:

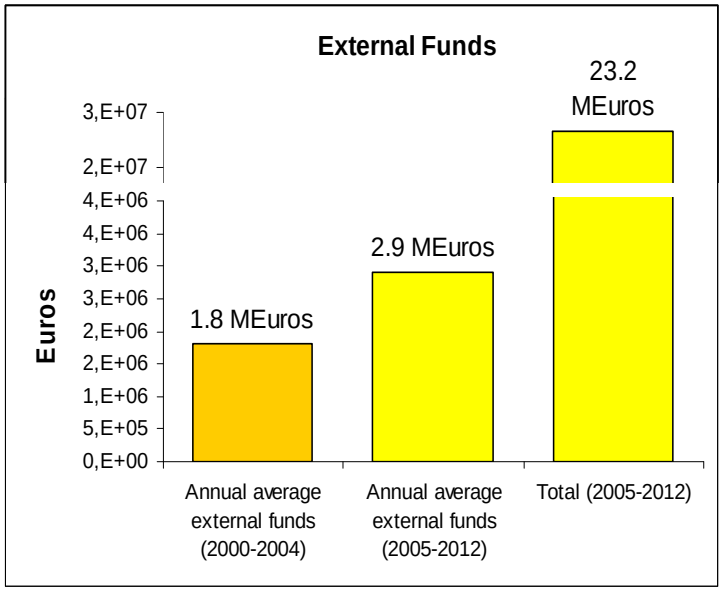
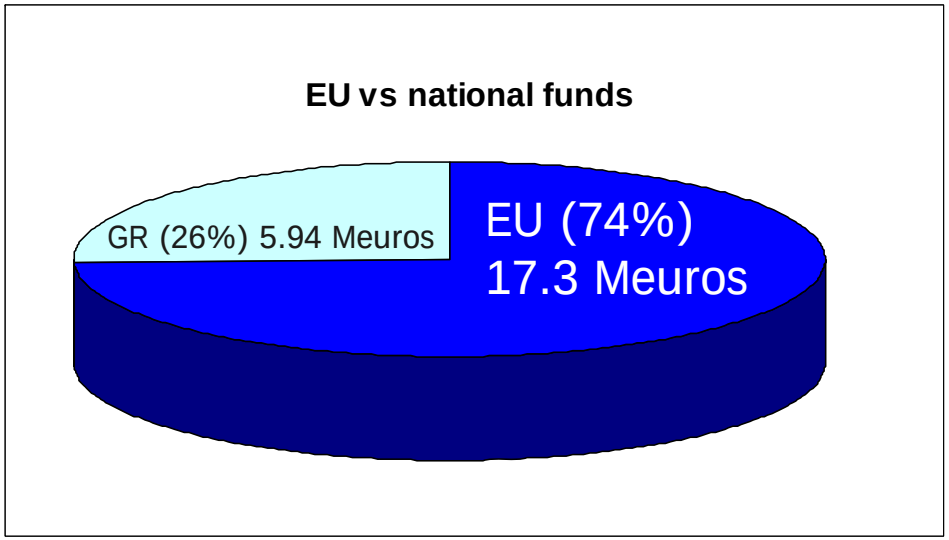


Figure 4. Annual average of IBMCB external funding. Inputs from external Funding sources: 61 % increase (2.9 MEuros/ year)

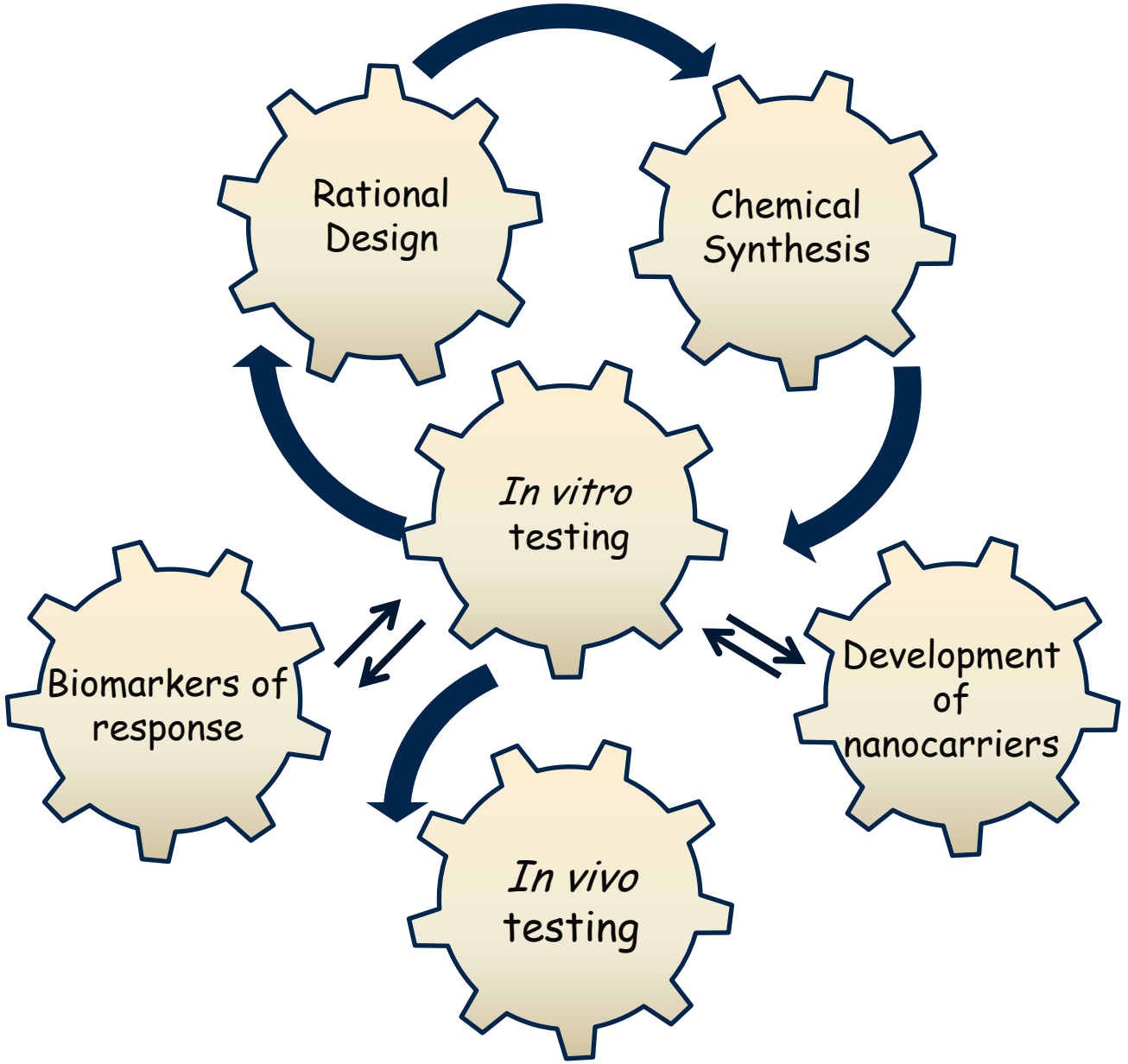


- During 2005-2012 IBMCB Researchers participated in 130 project networks, European (63) and national (67), 20% of which acted as co-ordinators;

- IBMCB also acted, in the context of 10 Marie-Curie Training Programme projects as a pan-European training centre for pre- and post-doctoral researchers.

IBMCB "STHENOS" PROJECT ON DRUG DISCOVERY

Targeted therapeutic approaches against degenerative diseases with emphasis on cancer and aging (STHENOS)



IBMCB developmental objectives (2013-2017)

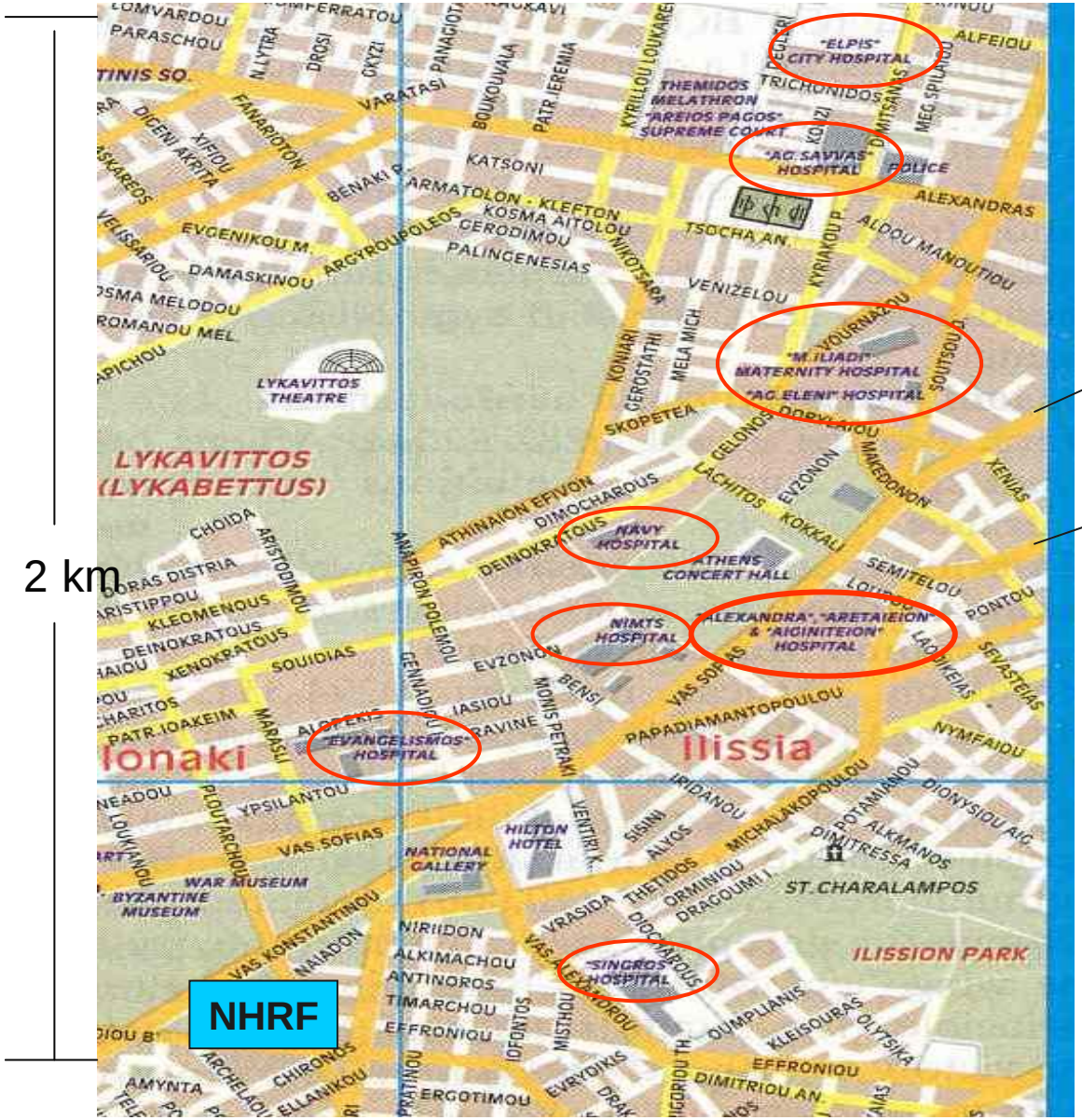
Strengthening partnerships with private and public sector - technology transfer and provision of specialized research services

Every effort will be made to increase the range of potential technology end-users: by approaching potential users in industry and academia; through advertising via the IBMCB website, social networks, mass mail and brochures.
•through Smart Specialisation in the frame of the national Research Programme 2020.

•through hospitals and health providers for the creation of an Athens City Comprehensive Health Center involving Clinical and Basic research.

•Exploitation of research results and innovative applications through patenting and licensing to companies (chemical, pharmaceutical or those producing neutraceuticals, cosmetics, diagnostic biomarkers, catalysts),
•Commercialisation
•through new innovative products and services
•through further development of spin-off companies
•venture capital and business angels.

IBMCB- Objective for a Comprehensive Health Center in Athens City Center



50% of the National Hospital Capacity is based in Athens City Center

HELLENIC PASTEUR INSTITUTE

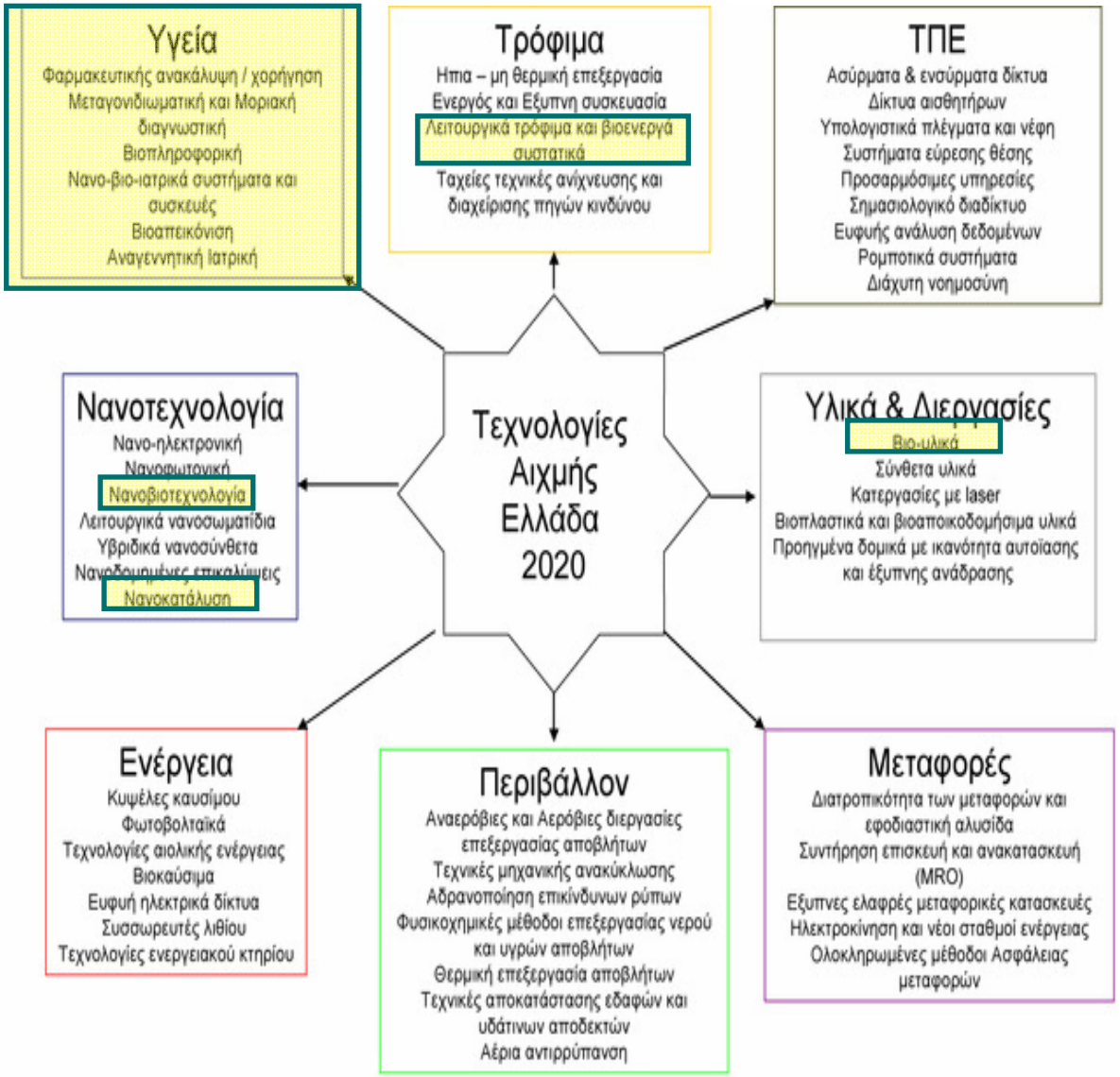
UNIV. ATHENS SCHOOLS OF MEDICINE, PHARMACY LAIKO HOSPITAL

Large number of Biotech, diagnostic companies

Athens City Comprehensive Health Center

Will develop with the aim to improve the health of Athens citizens and will look for funding through Smart Specialisation of the Attika Region.

IBMCB responds to the Cutting-Edge Technologies for Greece 2020



HEALTH
- Drug discovery
- Metagenomics and molecular dignostics
- Bioinformatics
- Nano-biomedical systems and devices
- Bioimaging
- Regenerative Medicine

FOOD
- Functional Food and bioactive ingredients

NANOTECHNOLOGY
- Nanobiotechnology
- Nanocatalysis

- MATERIALS
Biomaterials

Thank you