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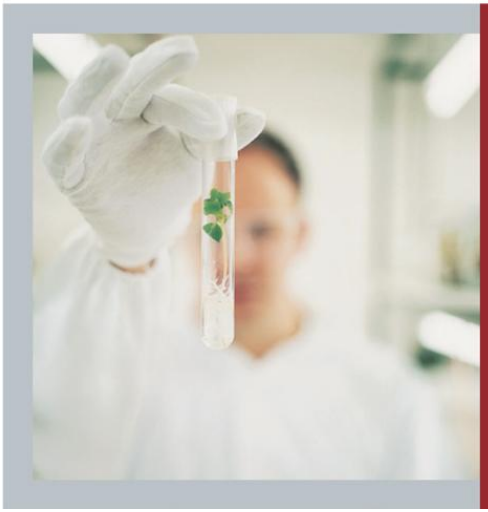

Inovação e transferência de tecnologia – novas tendências

Renée Ben-Israel,
Vice Presidente - Propriedade Intelectual
Yissum, a Universidade Hebraica de Jerusalém

WHERE SCIENCE MEANS BUSINESS

SES - São Paulo – Abril 2013

Yissum Technology Transfer

The Hebrew University of Jerusalem

Agenda

- **Inovação – o contexto**
- **Inovação e universidades**
- **Ex: Indústria Farmacêutica**
- **Novas tendências**
- **Universidade e as novas tendências**

Inovação - o contexto

- O ponto inicial da inovação é a geração de idéias criativas mas a inovação é o processo de levar estas idéias ao mercado e a sua utilização pelo público.

- Inovação tecnológica é um processo complexo e coordenado que requer políticas estruturadas e programas específicos a serem estimulados e mantidos por diversos fatôres

Fatores

- Investimentos de longo prazo em educação superior de alto nível
- Suporte e incentivos governamentais
- P&D nos setores publicos e privados
- Sistemas regulatóricos efetivos
- Infraestrutura moderna de informação
- Programas estratégicos de desenvolvimento

“Outros fatores” ou ecosistemas de inovação

- Suporte das partes participantes
- Capacidade e fundos de pesquisa
- Politicas, processos e boas práticas de trabalho
- Compromisso
- Maturação tecnológica
- Indicadores de atividade e impacto
- Tolerância a insucesso

Objetivos

- Benefício público (saúde, educação, ambiente)
- Desenvolvimento nacional e regional
- Desenvolvimento da economia (mais empregos, insumos, taxas)
- Realizações científicas (prêmios acadêmicos)
- Envolvimento nas tendências globais - científicas, sociais e economicas

- Etc, etc, etc

- Denominador comum => todos são associados a “inovação”

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Inovação e Universidades

- Por que Universidades?
  - Fonte de novo conhecimento e RH capaz
  - Catalista de fundos, equipamento, RH de alto nível
  - Polo de atração a outras partes
  - Estabilidade e compromisso
  - Internacionalmente compatíveis

Inovação e Universidades

- Por que Universidades? (perspectiva universitária)
  - Fonte de novo conhecimento e RH capaz
  - Catalista de fundos, equipamento, RH de alto nível
  - Polo de atração a outras partes
  - Estabilidade e compromisso
  - Internacionalmente compatíveis
  - Requisito da sociedade
  - O fenômeno da inovação aberta
  - Necessidade

Inovação e Universidades

- Inserção das universidades no processo:

  Através da transferência de tecnologia universitária

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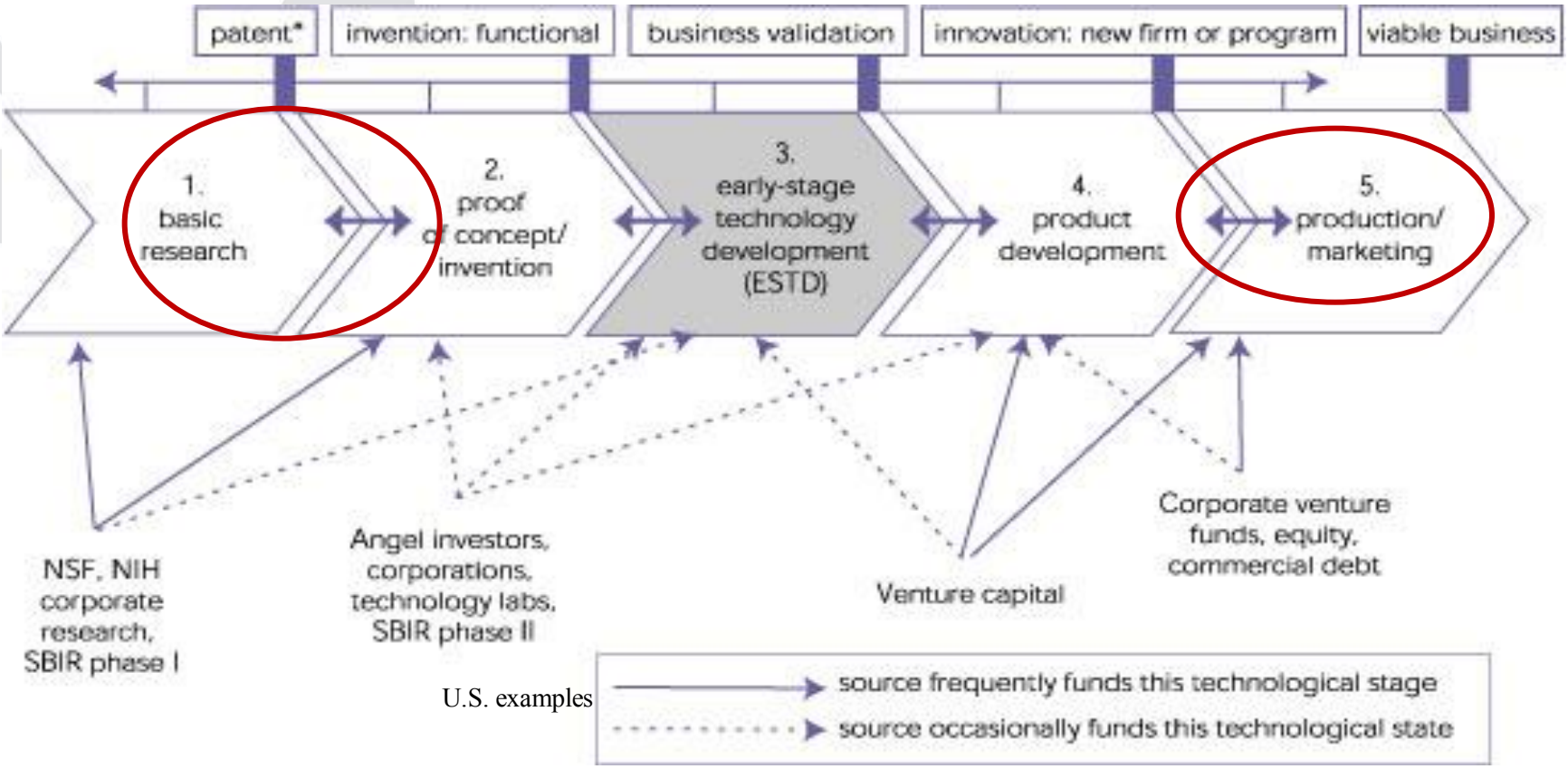
Da invenção ao produto - estágios



Source: US National Institute of Standards and Technology NIST GCR 02–841

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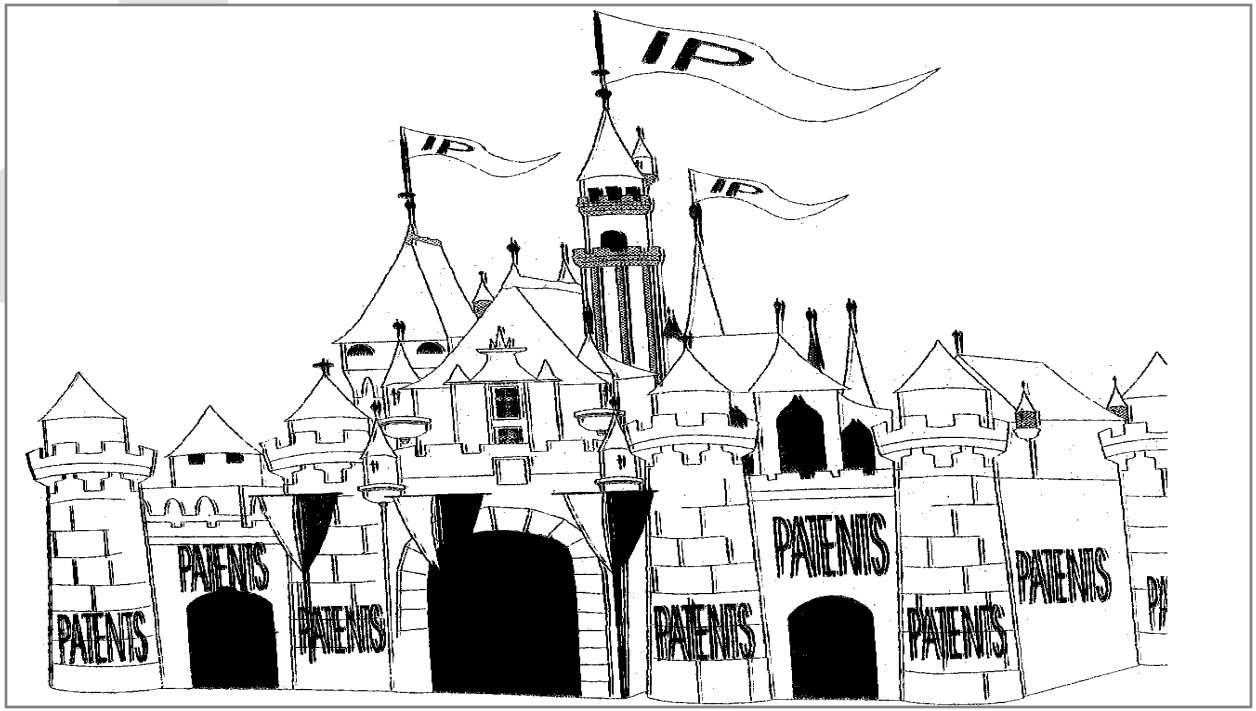
Inovação e propriedade intelectual

- Patentes – fator determinante na possibilidade de proporcionar exclusividade (vantagem competitiva) a quem estiver disposto a assumir o compromisso de desenvolvimento do produto inovador

Inovação e propriedade intelectual – o que é uma patente?



Um monopólio em uma tecnologia definida (em um momento determinado) num territorio específico

Entrada não-autorizada = infração

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Porém

- Um projeto científico é dinâmico
- As necessidades industriais não são estáticas
- O ambiente economico pode mudar
- Politicas governamentais são modificadas
  - A Tranferência tecnológica e um processo contínuo

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Example: Exelon

EXELON (rivastigmine)

NOVARTIS

Exelon®

For Treatment of Symptoms Alzheimer's Disease and Dementia

Prof. Marta Weinstock-Rosin

Department of Pharmacology, Faculty of Medicine

The Hebrew University of Jerusalem

2012 sales over $1 Billion

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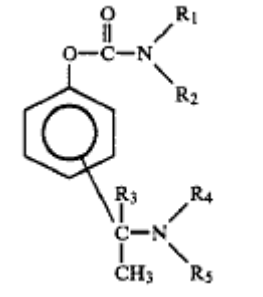
Example: Exelon

- Yissum filed a patent application in Israel (74497 on 05 March 1985) for Phenyl Carbamates Derivatives (with the racemic mixture of the Phenyl Carbamates derivatives)
- Licensed it to Proterra AG (subsidiary of Sandoz, Ltd,) now Novartis AG in Dec 1986
- Sandoz Ltd filed patents protecting the molecule of one of the enantiomers, a novel phenyl carbamate with anticholinesterase activity – ENA 713 (Rivastigmine)
- Rivastigmine is the basis of the Exelon
- Novartis developed two Exelon products: **Exelon (Rivastigmine tartrate) oral** and **Exelon Patch** (in collaboration with LTS Lohmann Therapie-Systeme GmbH)

Example: Exelon



Phenyl Carbamates Derivatives formula

US Patent	Compound Claim	Product Claim	Delivery Oral	Delivery Transdermal (patch)	Proprietary IP
4,948,807	x		x		Yissum/Proterra AG
5,602,176	x	x	x	x	Sandoz Ltd
6,316,023		x		x	Novartis AG/LTS Lohman
6,335,031				x	Novartis AG/LTS Lohman

The project

- Scientific results and on-going work
- Lab capabilities, Know-how
- Intellectual Property
- Information, evaluations
- Partners/Research collaborations
- Investments
- Commercial partner/s

Example: project complexity

The subject:

Optimizing an Extended-Release Drug Product for Epilepsy

MTA with producer of Drug

Grant from US Army

Ex-PhD student at German University

Collaboration with Univ Hospital

Grant from philanthropic organization

Option with Local company

⇒

Clinical study with Indian company

Joint patents with 2 research centres and with Drug producer

Participation in EP consortium

Submission to Univ-Industry programme

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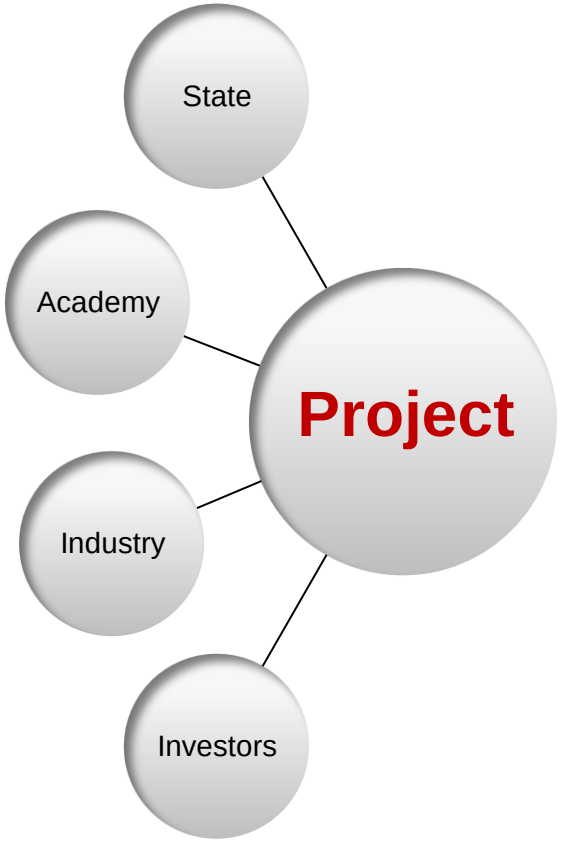
Tech Transfer - the “Combinatory Art”



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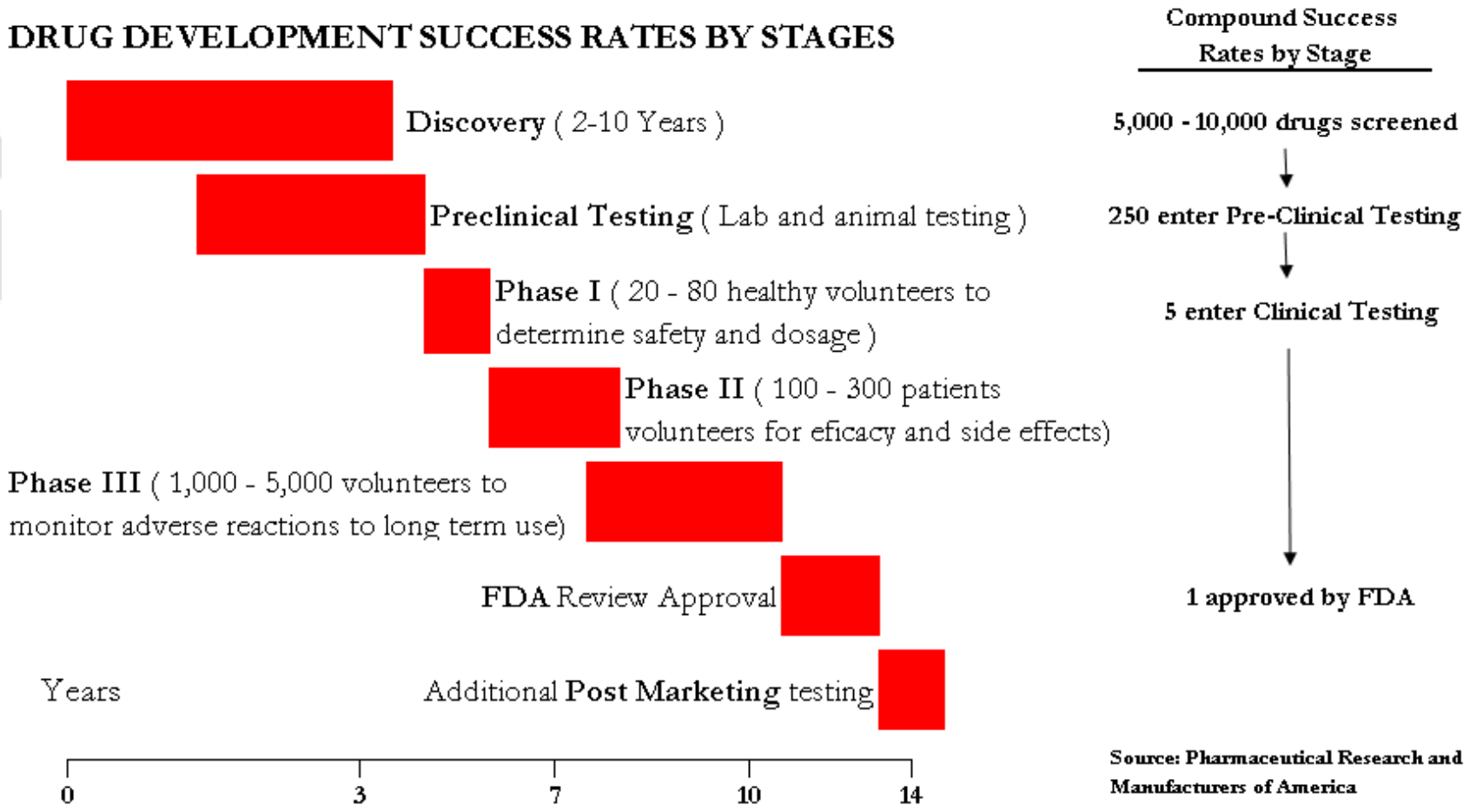
IP protection is particularly critical for development of pharmaceuticals

- Development of a new therapeutic or vaccine product is a particularly high risk activity
  - Time frames are long
  - Financial investment is very high
  - Clinical trials are very difficult
  - Probability of failure is high
- Patent protection is necessary before companies (or biotech investors) will take the risk and make the investment

Pharmaceuticals



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Pharmaceuticals (some history)

From

FIPCOs (Fully Integrated Pharmaceutical Companies)

to

FIPNets (Fully Integrated Pharmaceutical Networks)

Biotechnology and Pharmaceutical Commercialization Alliances*

- The 1940' – 1st antibiotics
  - Vertically integrated business model
    - in-house medicinal chemists isolated natural products from microorganisms, plants, animals, designed analogs and sometimes found new molecules with unexpected activity.
  - Increased manufacturing capabilities and development of sales and marketing organizations
  - Collaboration with universities mainly at personal level

(*) Mark G Edwards, Recombinant Capital, Inc, USA

Antibiotics development

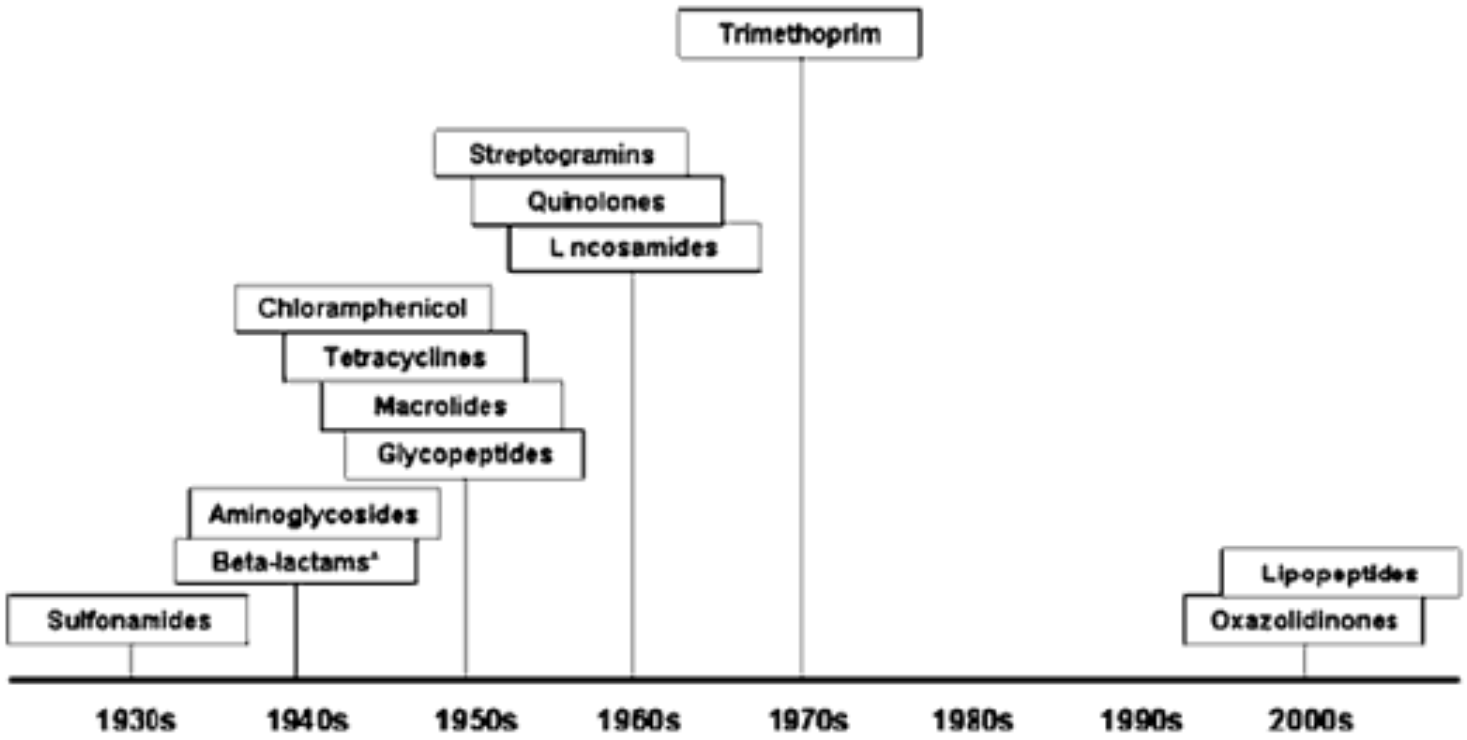


Fig. 6.1 A timeline for the discovery of new classes of antibiotics. Taken from The Bacterial Challenge (2009)

Early 1980’ - The biotechnology new era

- Recombinant DNA and monoclonal antibody (mAb) technologies

  1982 - Humulin, Genentech's human insulin drug produced by genetically engineered bacteria for the treatment of diabetes, first biotech drug approved by the FDA
- Bayh-Dole act, Cohen-Boyer Stanford patent
- Increase in collaboration with universities

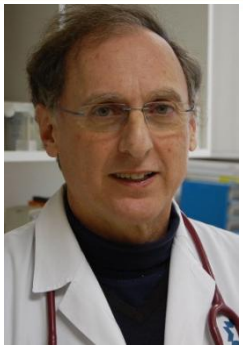
  Strong IP + difficult production methods

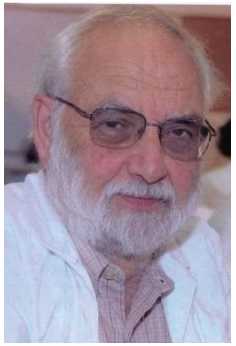
  (to partner with or compete with pharma companies)

Example: Doxil

Johnson & Johnson

Schering-Plough





DOXIL® - Doxorubicin HCl liposome injection

Alza's Lead Product for Oncology

Prof. Yechezkel Barenholz
Department of Biochemistry, Faculty of Medicine
The Hebrew University of Jerusalem

Prof. Alberto Gabizon
Hadassah University Hospital Jerusalem

2012 sales over $500 million

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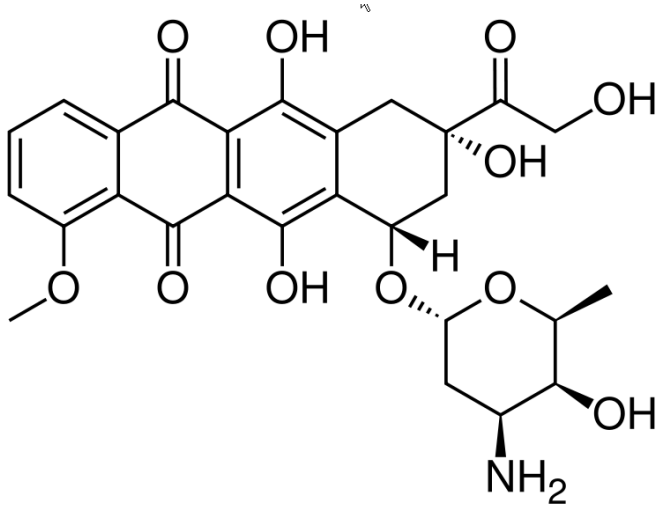
Example: Doxil

Doxil is a pegylated (polyethylene glycol coated) liposome-encapsulated form of doxorubicin formerly made by Ben Venue Laboratories in the United States for Janssen Products, LP, a subsidiary of Johnson & Johnson. It was developed to treat Kaposi's sarcoma, an AIDS-related cancer



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Example: Doxil

1st Licence:
LTI – 1980's

LIPOSOME TECHNOLOGY EXPANDS TRIALS OF ANTICANCER PREPARATION
— Takes Aim at Tumors Resistant to Standard Chemotherapy

MENLO PARK, CAL. 8/3/94 — Liposome Technology, Inc. has begun three additional Phase II trials of its DOX-SL™ product, which consists of the anticancer drug doxorubicin hydrochloride formulated with the company's Stealth® liposome technology to increase the time the drug remains in the body. The new trials will involve patients with either ovarian cancer

2nd Licence: 1995
Sequus Pharmaceuticals
buys LTI

Sequus Pharmaceuticals
filed FDA for Doxil

3rd Licence: 1999 - Alza Corporation
Buys Sequus Pharmaceuticals for US$580M

4th Licence: 2001
J&J Corporation
Buys Alza Corporation for US$10.5 B

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The 1990's – sequencing of the human genome

- The 1990' – new biotech business models
  - **Technology-platform companies** - use of new techniques to discover new drugs and/or improve drug discovery process
  - **Specialty pharma -** target niche and orphan indications historically too small for big pharma
  - Universities sometimes the suppliers of new techniques

Biotechnology and Pharmaceutical Commercialization Alliances

- **Technology-platform companies** => use of proprietary technologies to produce new compounds from oligonucleotides (antisense and gene therapy), lipids, peptides and combinatorial chemistry
- With sequencing of human genome, companies start to discover and validate novel drug targets
- Develop instrumentation and software to handle the new genomic materials, combinatorial libraries and structural information
- Have to rely on partners to pay part of the platform utilization and enhancement

Biotechnology and Pharmaceutical Commercialization Alliances

- **Specialty Pharma**
  - **Disease-focus biotech companies**
    - Avoid products which require considerable primary care detailing and focus on products with easier regulation paths
    - Focus on unmet needs and specialized patient populations (specific types of cancer, dermatology and neurology – preferred areas)
    - Use of innovative products with commercial rights to clinical development and commercialization to selected market niches (repositioning)

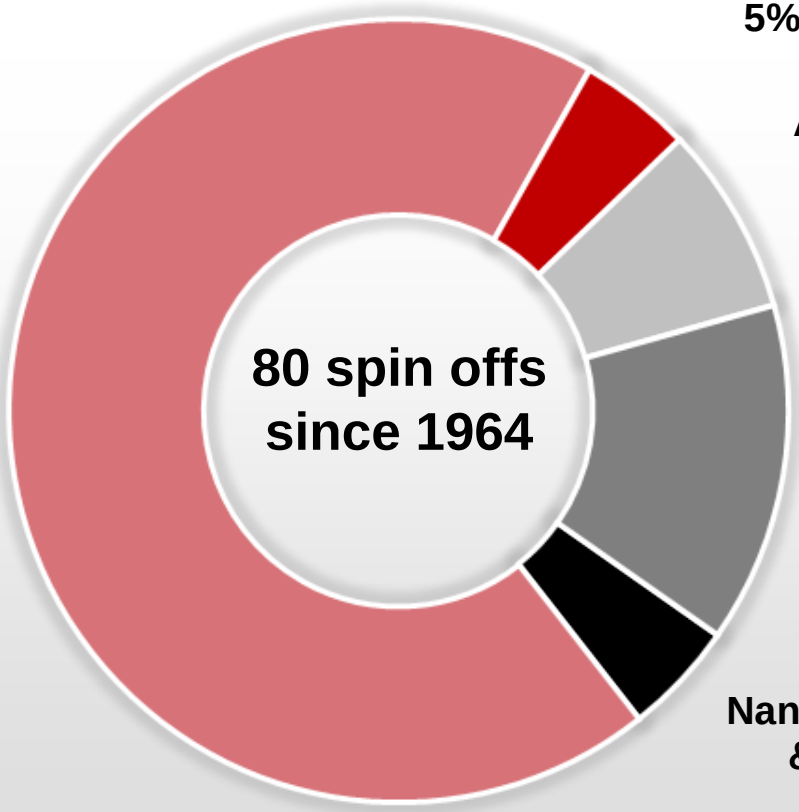
Biotechnology and Pharmaceutical Commercialization Alliances

- **Specialty-pharma business model**
  - Disease-focused biotech companies with cash problems
  - Consolidation of major pharmaceutical companies
  - Big Pharma – “cash rich” but "product poor” => seeking enhanced growth prospects
  - Focus on specialty markets that could be addressed with relatively small sales force (cancer, anti-infective, dermatology)
  - In-licensing of approved and late-stage development compounds from pharmaceutical companies

Biotechnology evolving business models and University Tech Transfer

- Under certain circumstances and with significant IP and/or compounds to offer =>
  - Universities became the upstream licensor of IP and/or compounds to be bundled by a biotech company and sublicensed to a commercialization partner, many times through spun off companies
  - Universities had the possibility to license to a commercialization partner (traditional pharma, emergent biotech or other via specialty firms)

Yissum Spin-Off Companies



Clean Technologies 5%

Agriculture and Nutrition 8%

Computer Science & Engineering 14%

Nanotechnology & Physics 4%

Life science and Biotechnology 69%

The 2000’ s first decade: Big pharma tries many strategies to rejuvenate aging product lineout

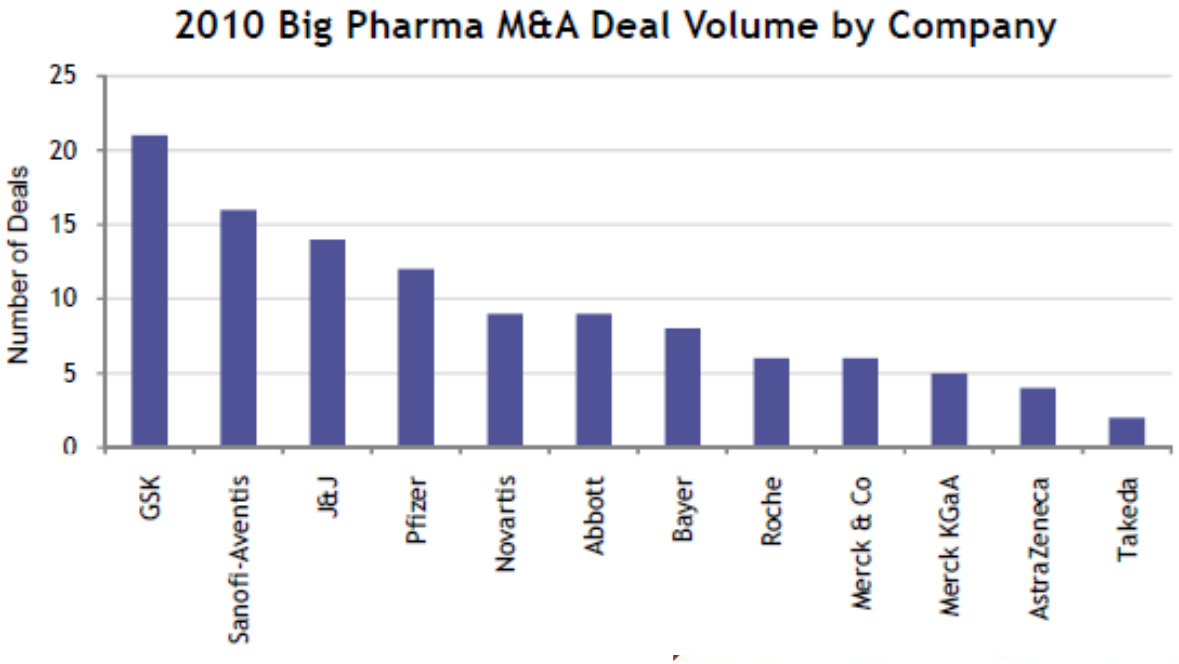
- **Consolidation**
- **R&D reorganizations**
- **Acquisitions of technologies and whole companies**

- But the average number of innovative new medicines that came to market in the U.S. decreased to 22 in the second half of the decade from 28 in the first half, and that despite annually rising R&D expenses.

Big Pharma consolidation of Speciality Pharma Industries

Key acquisitions:

- Alcon (Ophtalmic) in January 2010 by Novartis
- Pfizer's $3.6 billion for King Pharmaceuticals in October 2010 (pain management)
- GSK's $3.6 billion for privately held dermatology company Stiefel Labs, April 2009



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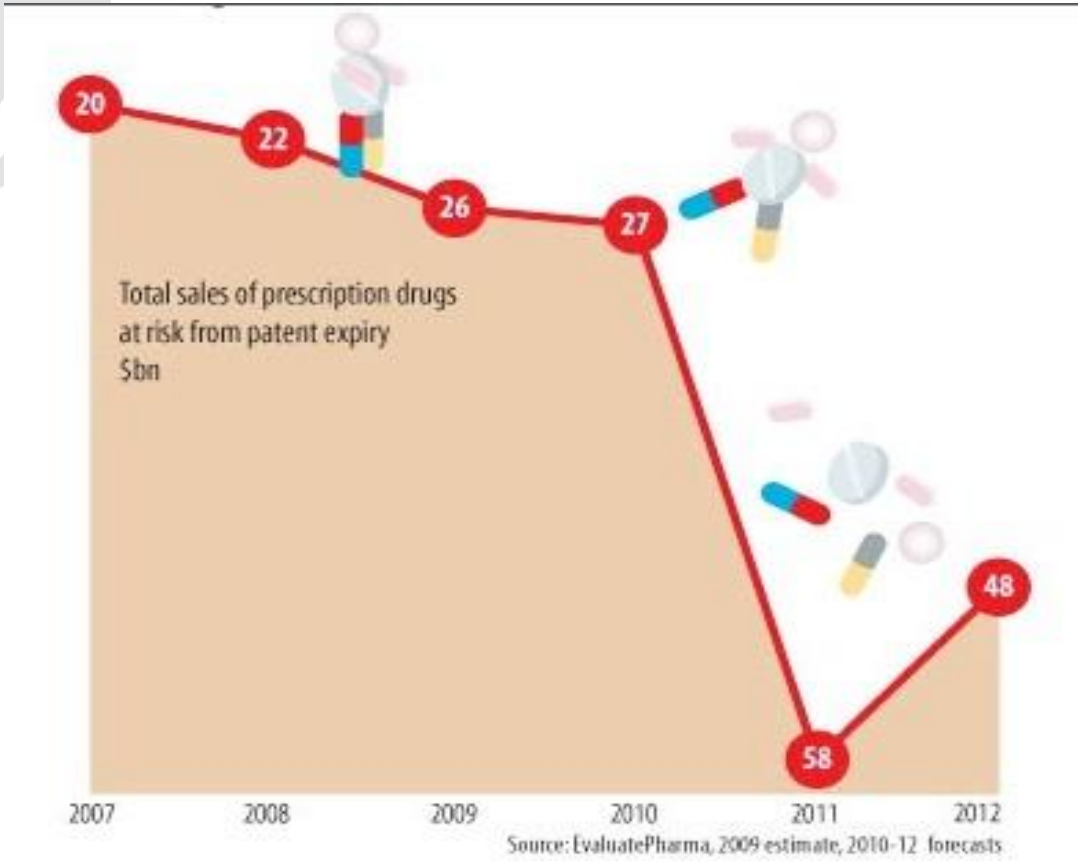
2010 - Pharma revenue constraints

- The patent expiry time bomb -

  ($billions to generic erosion)
- Decrease in R&D productivity – from 2006 twice of R&D investment than 1996, 2/5 of production
- Pricing pressures in healthcare markets - need to justify high costs for patients
- Quest for improved margins and growth - search for cost reductions

As blockbuster drugs lose patent protection, remaining sales drop off a cliff



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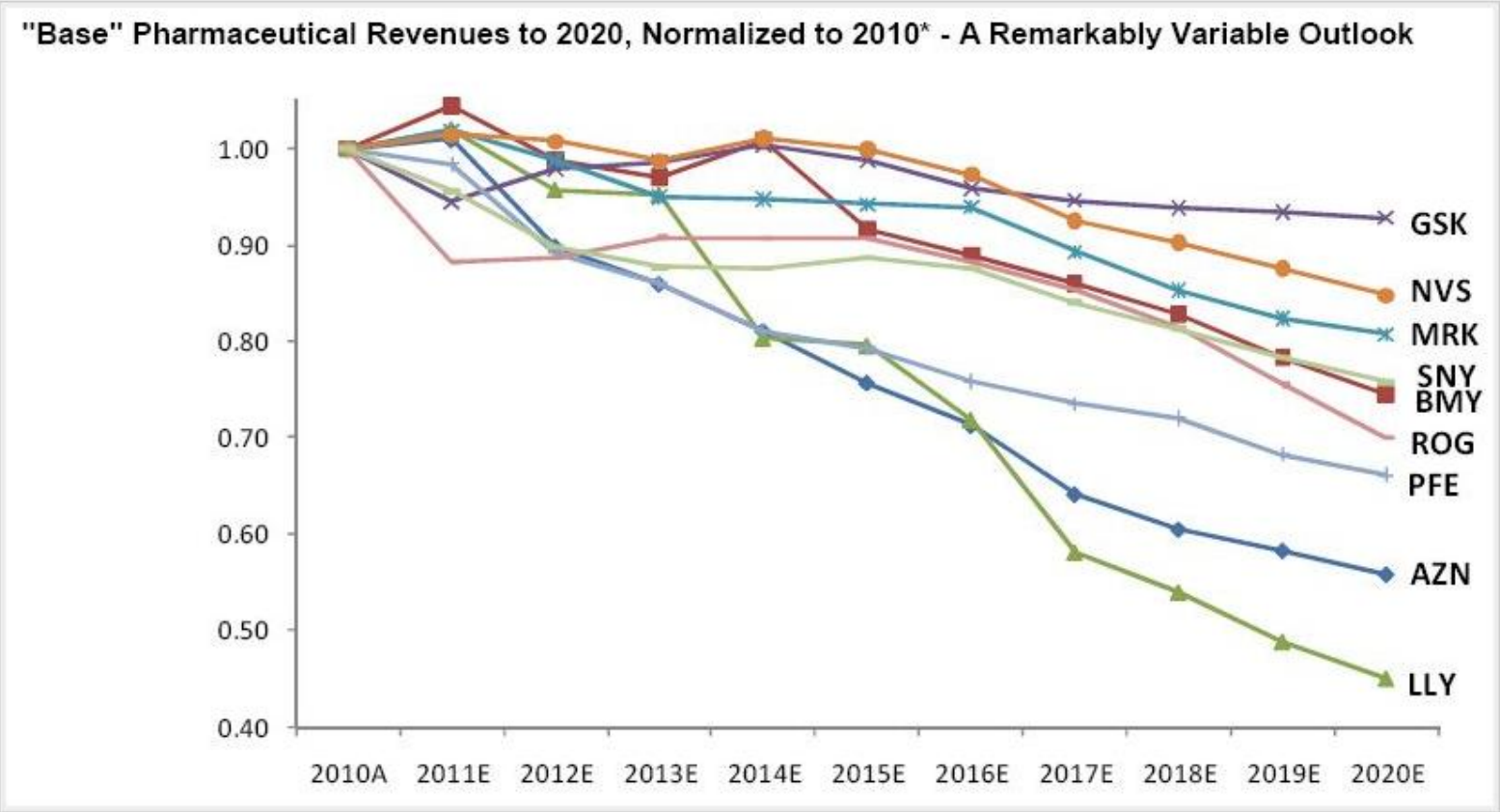
Big Pharma has problems

June 20, 2011 - Not Looking So Good At Eli Lilly (or AstraZeneca)

Expected patent expirations



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The World is Flat*?
Innovation new geography

- **Talent – diffuse**
- **Globalization (new players and new markets)**
- **R&D - expensive**
- **Environment - dissemination of innovation poles**

(*) Thomas Friedman

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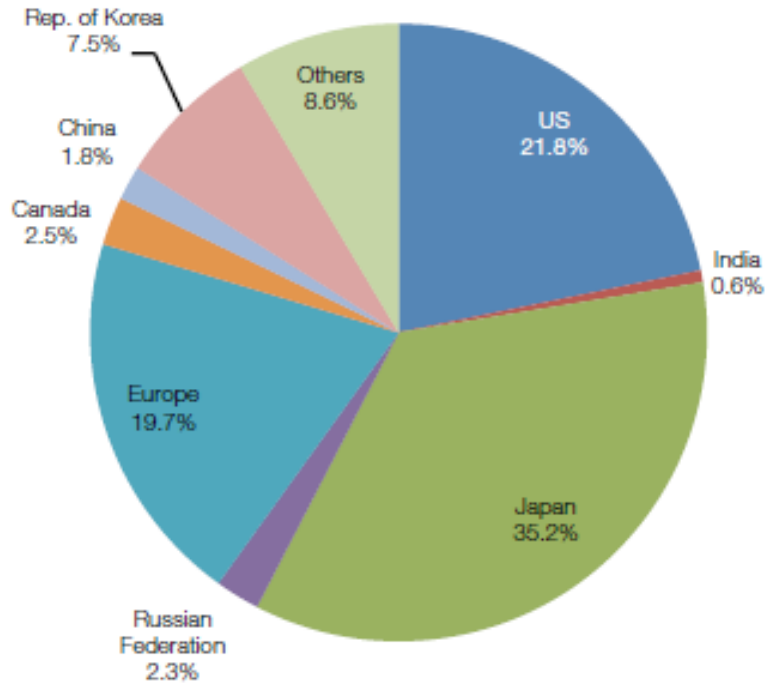
Strategic solutions (or, adapting to the Brave New World*!)

- Presence in Asia (China and also India)
  - growth in end customer market,
  - growth in manufacturing capabilities (CMOs, contract manufacturing organizations with GMP certifications, FDA approval) => 50-80% manufacturing saving
  - Growth in scientific base and capability (doctorates, laboratories)
  - Patient pool – 60% of world's population, clinical trials saving of 60% on costs and 30% patient enrolment time

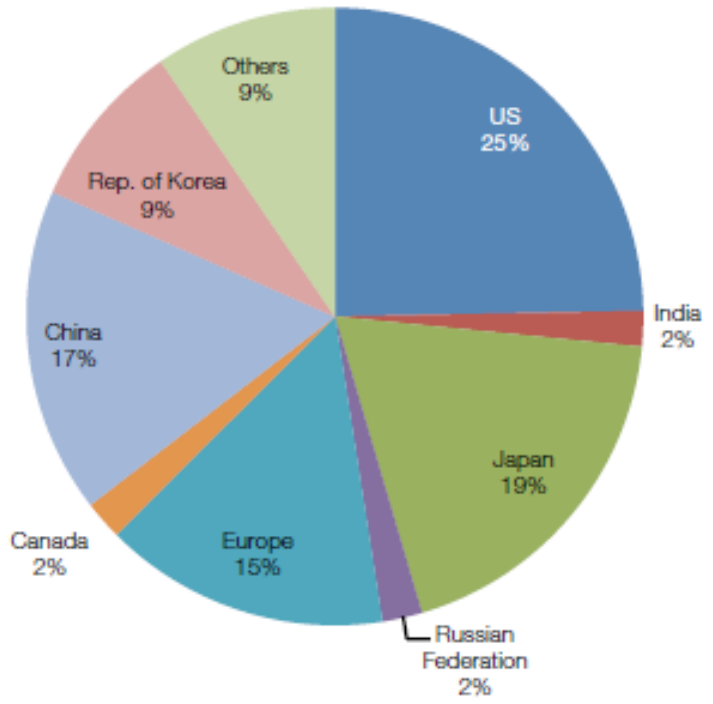
(*)Aldous Huxley

Patent applications shift towards Asian countries

Share of IP offices in world patent applications, in percent, 1995



Share of IP offices in world patent applications, in percent, 2009



Source: WIPO Statistics Database, September 2011.

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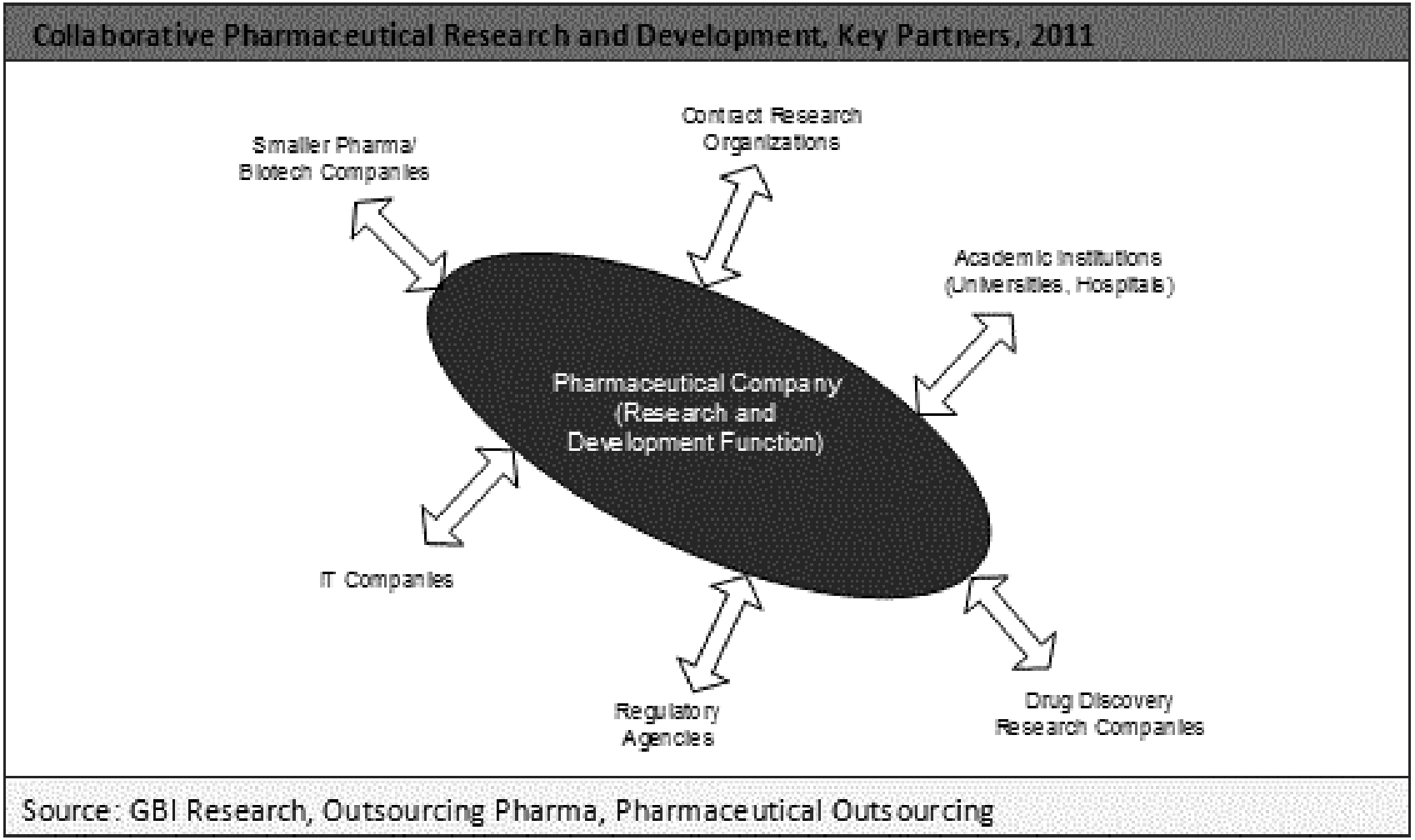
Strategic solutions (or, adapting to the Brave New World!)

- Networked business models => from FIPCO to FIPNet
  - Flexible outsourcing, missing the skills to part of the operations =>need to greater collaboration (strategic partners and not contract manufacturers)
  - Seek cheaper sources of research
  - TP - “Translational Pharma” companies

Outsourcing



Benefits of outsourcing

Figure 3.

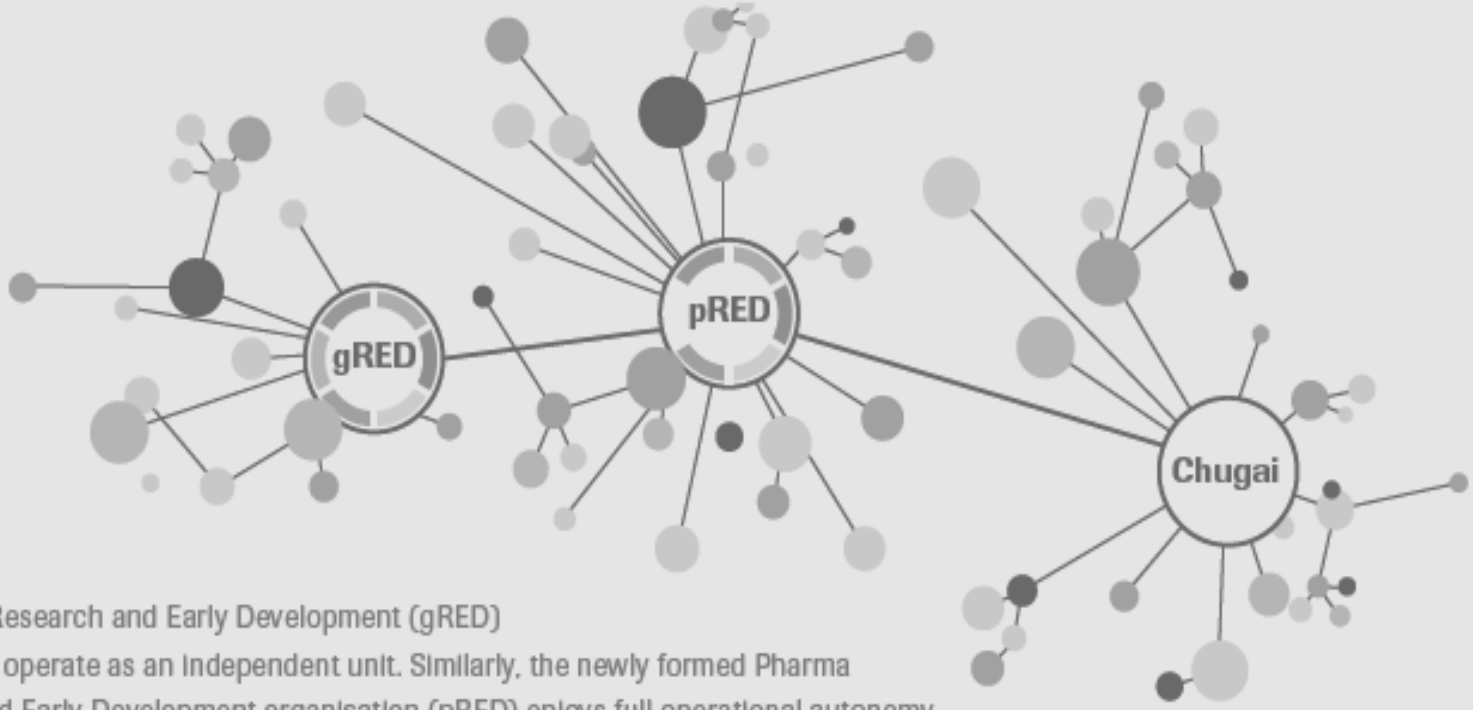
	Conventional	"TP Enabled"
Timeline required pre-regulatory submissions	~6 months	~1 month
Stability program	>3 months	<7 days
Dose strengths	Preselected ahead of FIH dose	Determined in program in response to data
Dose units	Thousands	Hundreds
API consumed	5x	1x
Cost saving	n/a	>$300k
Supply chain management	Up to 4 vendors	Single vendor

click for larger view

FIGURE 3: The benefits the can be achieved by using a translational pharmaceutics platform to deliver a FIH program versus a conventional process.

Source: Mark Egerton, PhDInnovation in the new ecosystem of pharmaceutical R&D

Ex: Roche's network



Genentech Research and Early Development (gRED) continues to operate as an independent unit. Similarly, the newly formed Pharma Research and Early Development organisation (pRED) enjoys full operational autonomy. gRED continues to be inspired by the values and culture that led to Genentech's success, while pRED will expand Roche's capabilities to bring novel medicines to patients.

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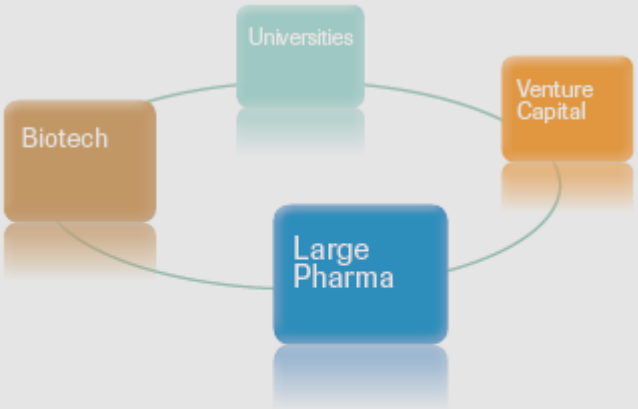
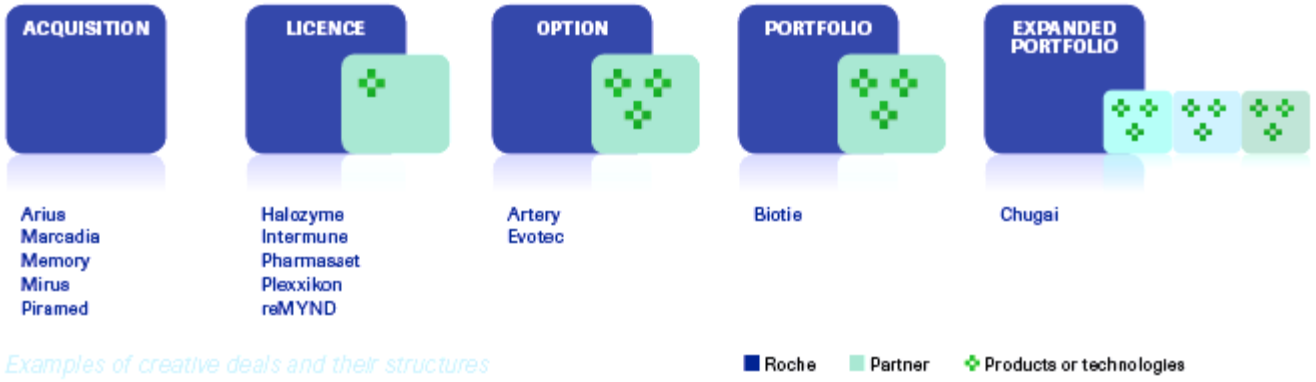
Partnerships



Partnering deals originate from other large pharmaceuticals, biotechnology companies, academia and the venture capital environment.



Examples of creative deals and their structures

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Big pharma goes back to college

Saturday, June 4, 2011, by Sabine Vollmer

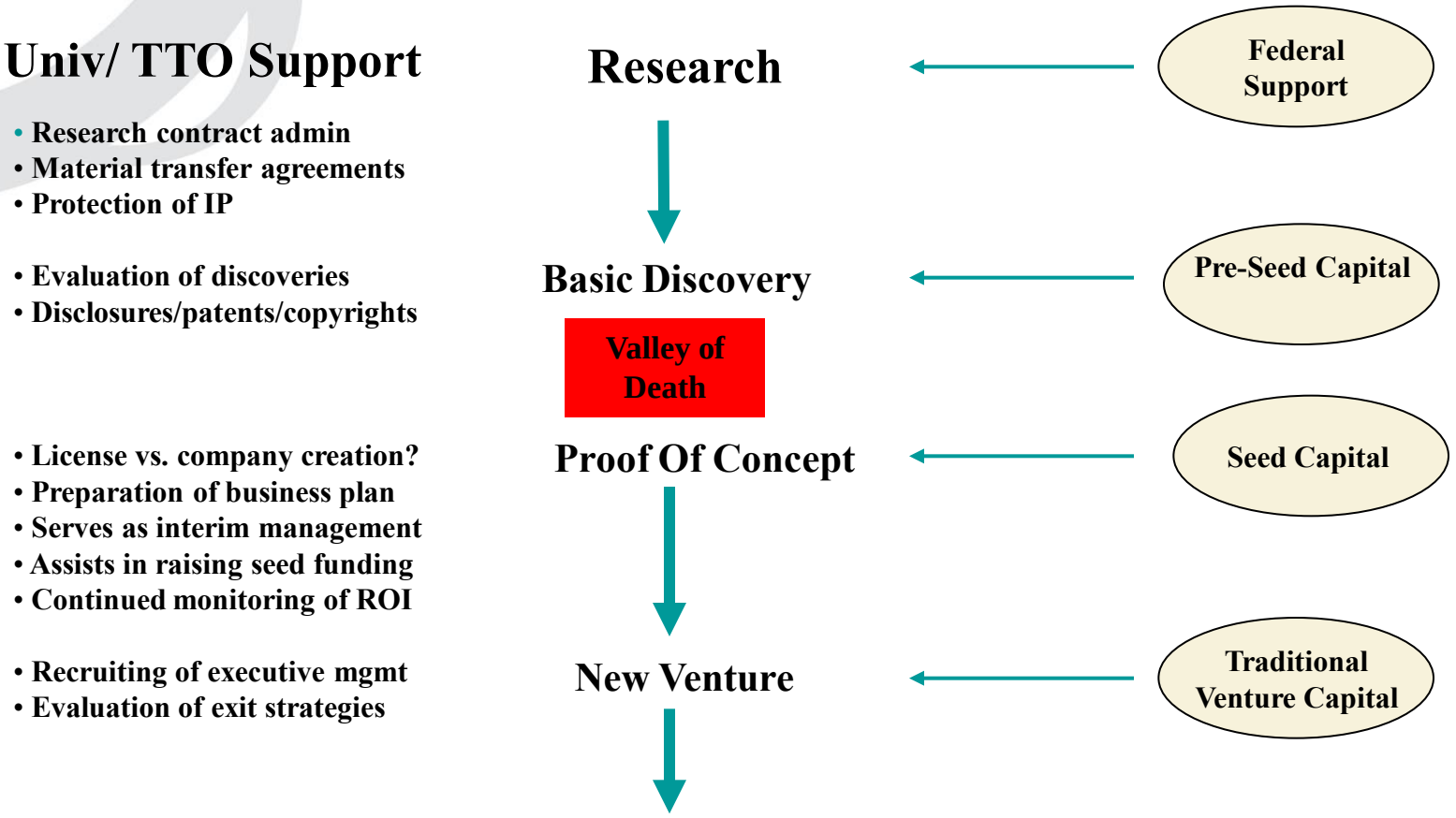
- Pfizer, Sanofi-Aventis, GlaxoSmithKline, AstraZeneca, Novartis, Lilly, Roche, Bayer
  - After trying everything else with insufficient success, large pharma companies bet on universities for inspiration
  - Big pharma companies have begun to troll for marketable innovation at universities – places where science and research are a taxpayer- and tuition-funded way of life – after spending increasing amounts of money on their own and other companies' research and development with meager results.

Win-Win situation?

- For Academia
  - Alternative potential large source of funding as governmental funding becomes more limited
  - Alternative way to cross the “valley of death,” from discovery to clinic where public and private funding is particularly scarce.
- For Pharma
  - New ways to outsource its costs, access more fundamental innovation and impact the relatively high rate of late stage attrition for its drug candidates.
  - *(Cynically)* good press to the effect that is has a new plan

University TT - The Valley of Death

- Commercialization Pathway



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Initiatives – US Gov

- Innovation Strategy Dept of Commerce RFI (Request for Information), Feb 2011
  - Among other recommendations: support and enhancement of Proof of Concept Centres (POCCs), ex: Wallace H Coulter Foundation Translational Partnerships in Biomedical Engineering => 5 grants of >$500K to 10 universities a year to move promising technologies to clinical application + award of ~$100K a year per project

Israel – the Monitor report (2000)

- Recommended the creation of translational companies => to overcome the “Valley of Death”

  See BioLineRx, www.biolinerx.com, pre-clinical drug development company (BLRX IT) Israel TA-25 index. Option for projects at discovery stage to perform POC. EDP (Early Development Programme)

- Teva, J&J, Roche, Sanofi, Merck with early stage development programmes

Ex: Lilly Phenotypic Drug Discovery Initiative, or PD² (PD-squared)

INDIANAPOLIS, June 15, 2009

Eli Lilly and Co Announces New Drug Discovery Initiative

Goal is to foster open collaboration between Lilly and global laboratory researchers.

Eli Lilly and Co will be engaging researchers from around the world for drug discovery in the fields of **Alzheimer's disease, Cancer, Diabetes and Osteoporosis**.

The initiative uses Lilly-developed disease-state assays and a secure web portal to evaluate the therapeutic potential of compounds synthesized in university and biotechnology laboratories. Findings from this initiative could ultimately form the basis for collaboration or licensing agreements between Lilly and external institutions.

Lilly Phenotypic Drug Discovery Initiative, or PD² (PD-squared)

- "Increasingly, innovation depends on a broad network of relationships outside our walls, … PD2 is yet another example of Lilly's evolving transformation from a Fully Integrated Pharmaceutical Company, or FIPCO, to a Fully Integrated Pharmaceutical Network, or FIPNet"

Alan D. Palkowitz, Ph.D., vice president of discovery chemistry research and technologies at Lilly.

Lilly Phenotypic Drug Discovery Initiative, or PD² (PD-squared)

- The programme:
  - Through the automated PD² interface, researchers confidentially submit a structure of their compound for an initial computational evaluation using a set of proprietary Lilly algorithms focused on drug-like properties and structural novelty.
  - If the compound structure meets certain specified criteria, the researcher is then invited to submit a physical sample for biological testing.

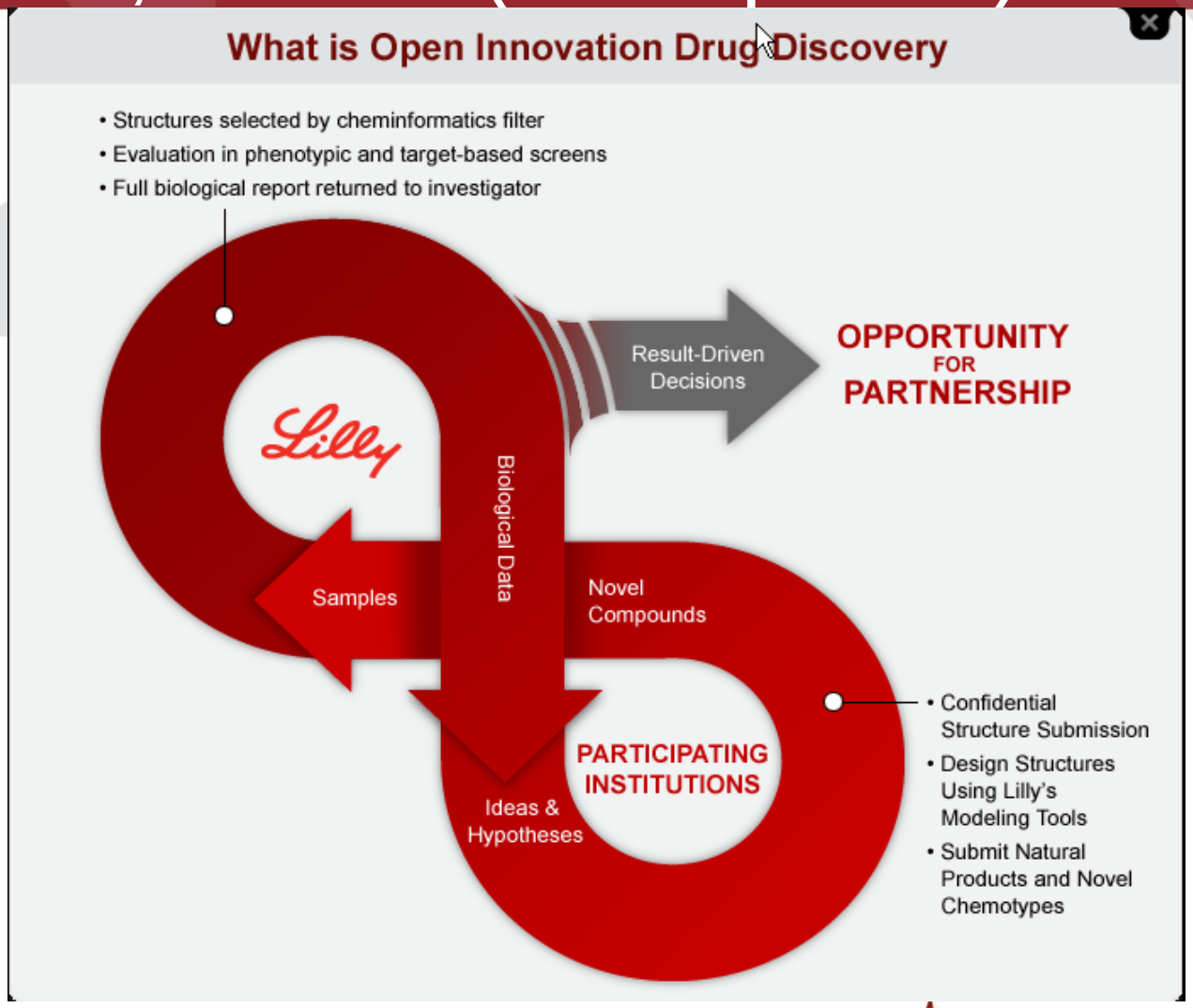
Lilly Phenotypic Drug Discovery Initiative, or PD² (PD-squared)

- The programme (cont):
  - After biological testing is completed, Lilly provides the external researchers a data report with a complete biological profile of the compound across the four assay modules (Alzheimer's disease, cancer, diabetes and osteoporosis) derived from sophisticated and systematic in vitro model systems (usually unavailable at academic or governmental laboratories)
  - In return for these data, Lilly has first rights to exclusively negotiate a collaboration or licensing agreement

Lilly Phenotypic Drug Discovery Initiative, or PD² (PD-squared)

- The programme (cont):
  - If there is no agreement within a defined time period, the researcher is granted no-strings-attached ownership of the data report and can choose to use it in publication or grant proposals, or to further refine structural hypotheses, all of which may advance scientific discovery.

Ex: Lilly Phenotypic Drug Discovery Initiative, or PD² (PD-squared)



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Academic researchers perspective

- *"For researchers… the major potential benefits of PD2 include the ability to test compounds in well-validated assays, the comprehensive nature of the data reports and the opportunity to exchange ideas and hypotheses with Lilly experts on compounds of interest."*

- *"I'm looking for drug discovery experts who can critically evaluate the data on my compounds and engage me in discussing their immediate potential for optimization and perhaps their ultimate impact on specific areas of human health with unmet medical need."*

  Peter Wipf, Ph.D., professor of chemistry and pharmaceutical sciences at the University of Pittsburgh

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Nature News Blog: 15 March 2012 – Posted by Heidi Ledford

Merck forms non-profit research institute for academic collaborations

In the latest union between academia and industry, pharmaceutical giant Merck today announced that it would create a non-profit research entity called the California Institute for Biomedical Research (Calibr). The institute aims to hire about 150 scientists and will be headed by chemist and serial entrepreneur Peter Schultz of The Scripps Research Institute in La Jolla, California.

Calibr will not be associated with any particular institution nor have a specific therapeutic focus, academics from around the world can submit research proposals, which will then be reviewed by a scientific advisory board, The institute will be overseen by a board of directors that includes venture capitalists.

Pharmaceutical companies are eagerly embracing academic collaborations as they seek new drug leads while trimming internal R&D budgets. Merck, based in Whitehouse Station, New Jersey, has cut its R&D budget by over US$600 million since 2009.

Roche R&D partnering

- In response to the increasing risks and costs involved in bringing compounds to market, Roche has developed more creative ways of partnering, based more on risk sharing and adapted to the specific circumstances of any particular opportunity.
- In 2010 Roche Partnering signed a total of 52 new agreements, including one product transaction and 40 research and technology collaborations.

Basel, 7 December 2011- **Roche establishes external Academic Translational Centre in Zurich**

- Collaboration with academia for the development of novel medicines and diagnostics

- Translational medicine is the application of research technologies to patient care. The translational research hub will foster collaborations between Roche and academic researchers from ETH, UZH and USZ in pathology, dermatology, inflammation and potentially other diseases with unmet medical need.

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GSK Trust in Science Programme

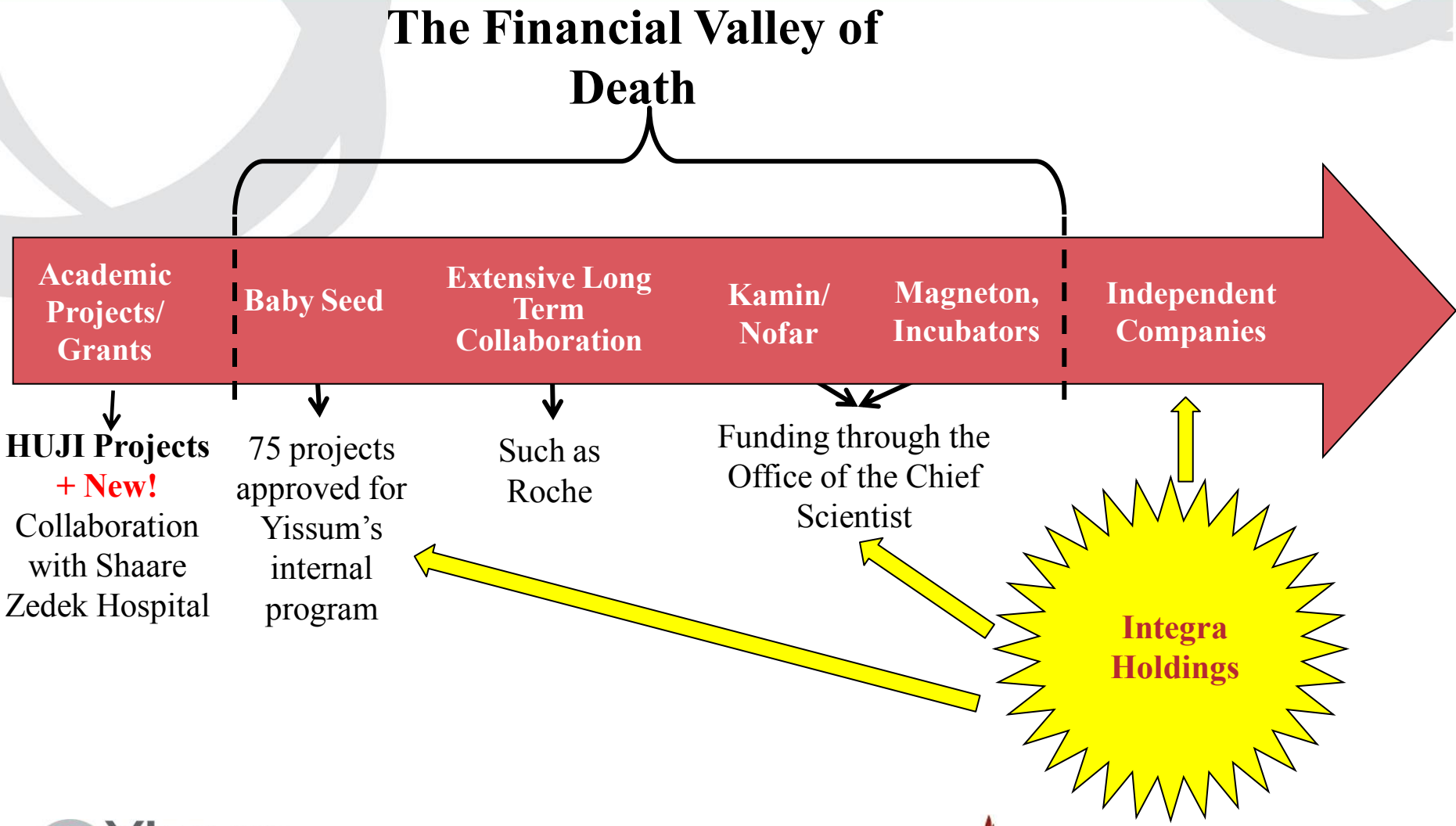
- **Ex: Glaxo Smith Kline Trust in Science programme (Latin America)**
  - *At GSK we recognize that great science happens outside as well as inside our walls. In fact, we see collaborations with other researchers as an important component of our R&D activities, complementing our in-house efforts and advancing scientific understanding in key areas and facilitating the rapid discovery and development of new medicines for patients.*

Nov 16, 2011: FAPESP and GSK in partnership against tropical diseases

Agência FAPESP – On October 21, FAPESP and pharmaceutical laboratory Glaxo SmithKline Brasil (GSK) signed a letter of intent for joint investment to support research on tropical diseases in São Paulo State.

FAPESP President, Celso Lafer, and GSK Director for Latin America and the Caribbean, Rogério Rocha Ribeiro, signed the agreement in São Paulo. Also attending the ceremony were the United Kingdom's Health Minister, Simon Burns, FAPESP's Executive Director, Ricardo Renzo Brentani, and the Consulate General of Great Britain, John Dodrell.

Bridging the Financial Valley of Death



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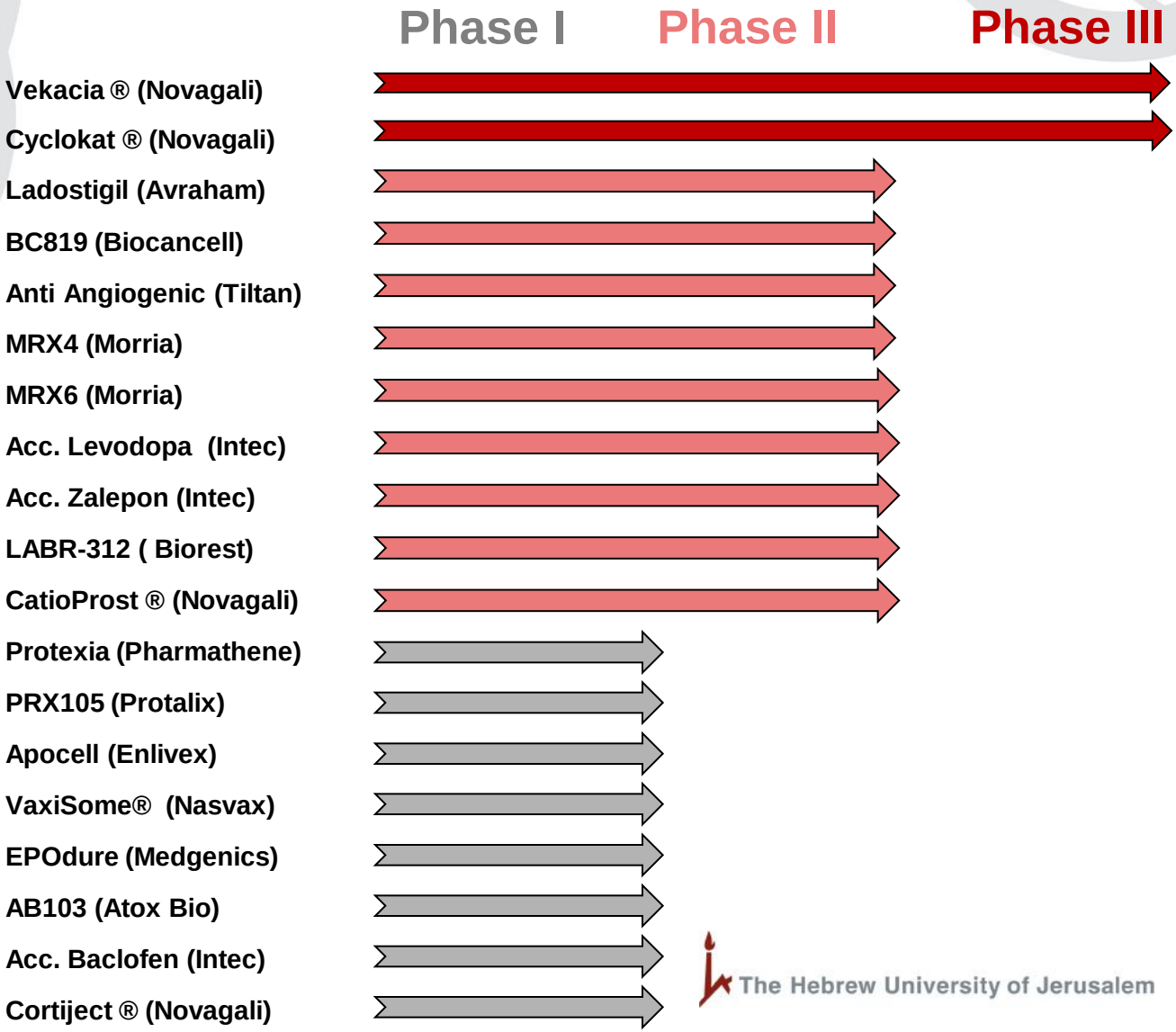
Yissum's Biotech Product Pipeline



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Obrigada pela atenção!

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