

LOS MODELOS DE NEGOCIOS Y SU ROL EN LA FINANCIACION DE LA INDUSTRIA BIOTECNOLOGICA: NUEVAS TENDENCIAS Y DESAFIOS

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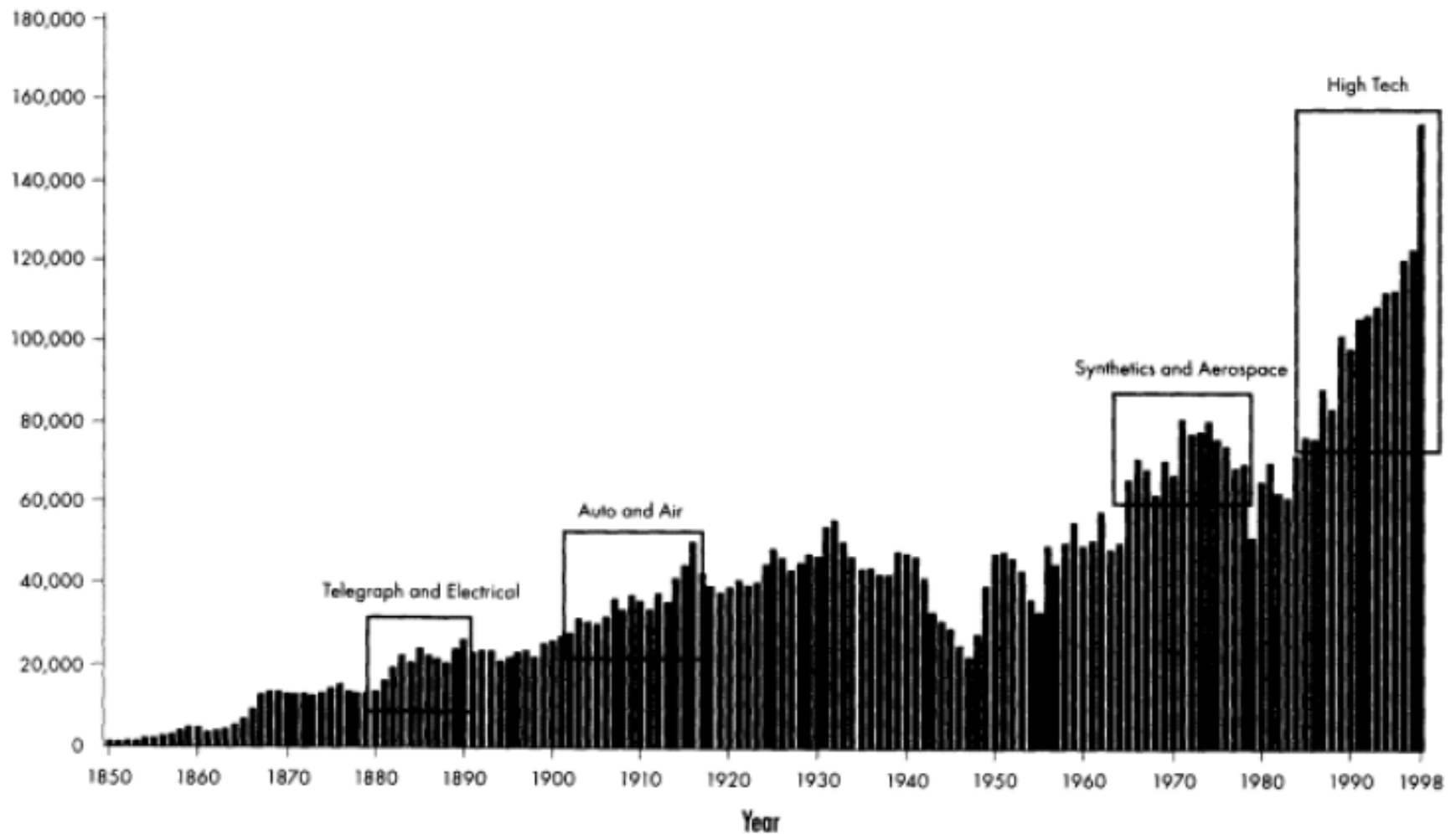
24 de Abril de 2019

INTRODUCCION: LA PI ES LA BASE DEL NEGOCIO

QUE ES UNA PATENTE?

- Una patente es el documento mediante el cual un inventor hace públicos sus inventos a cambio del derecho de excluir a otros de practicarlo.
- Por tanto, una patente es un derecho **NEGATIVO** o de exclusión.
- El titular o licenciatarario de una patente adquiere el derecho a excluir a otros de usar, hacer, vender, ofertar para la venta o importar la invención patentada.
- **UNA PATENTE ES UN ACTIVO!!!!**

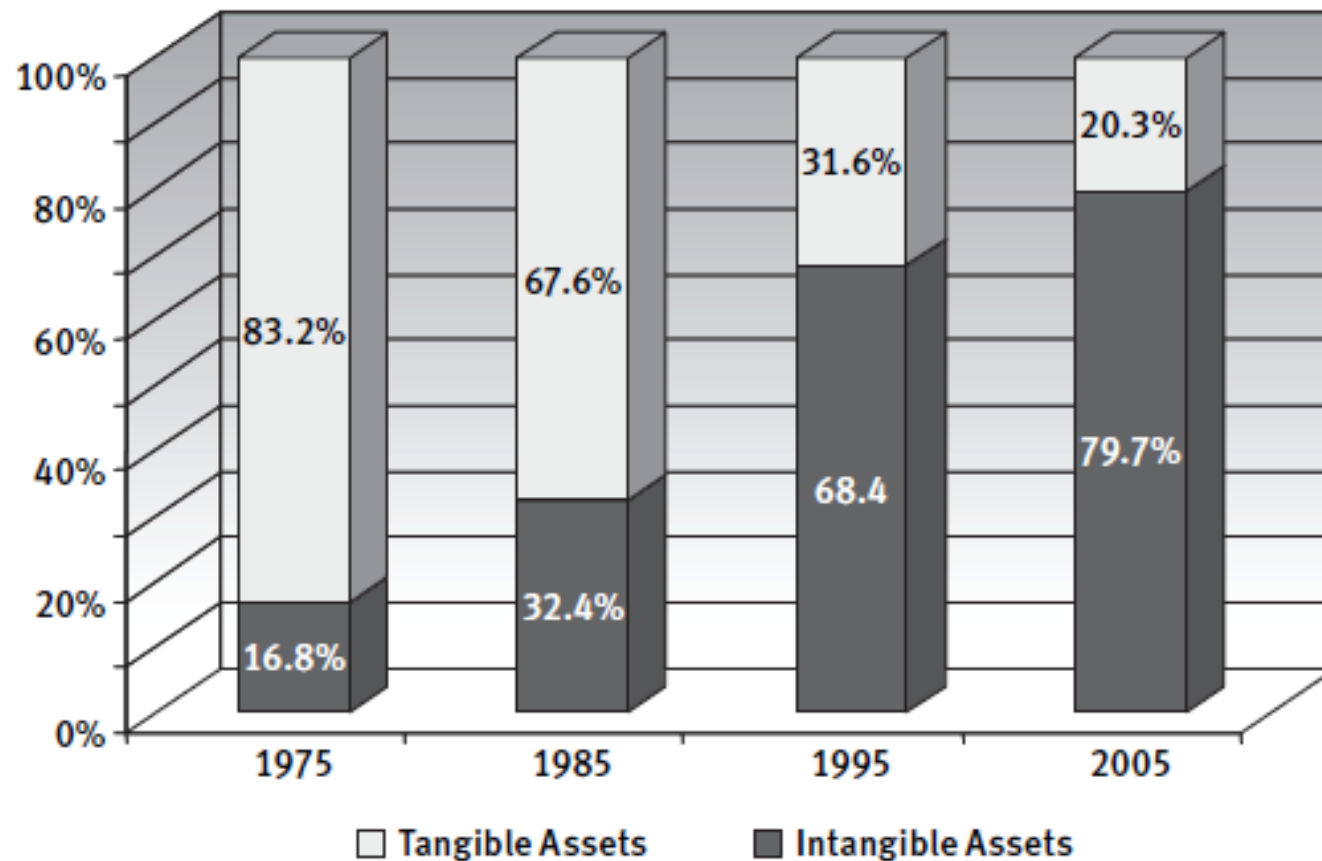
Number of Patents



Rembrandts in the Attic, Harvard Business School Press, 2000

FIGURE 6.1

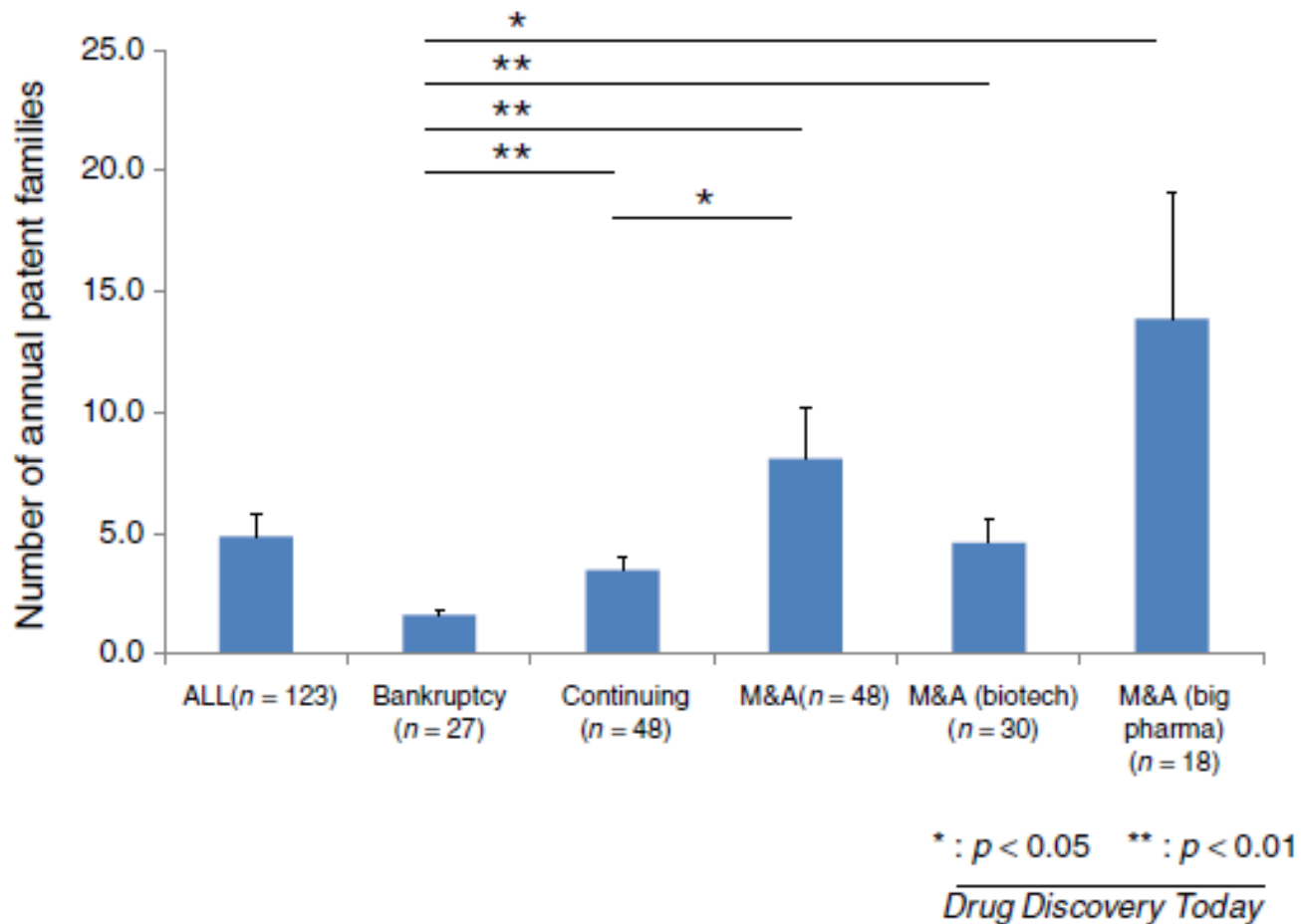
COMPONENTS OF S&P 500 MARKET VALUE



Source: Brookings Institution, Ocean Tomo

IP Value. Even with a correction for the stock market bubble, 80% of the market value of companies in the S&P 500 are comprised of intangible assets, mostly intellectual property.

LA FORTALEZA DE LA CARTERA DE PATENTES CORRELACIONA CON EL ÉXITO DE LA EMPRESA BIOTECNOLÓGICA?



CONTENIDO

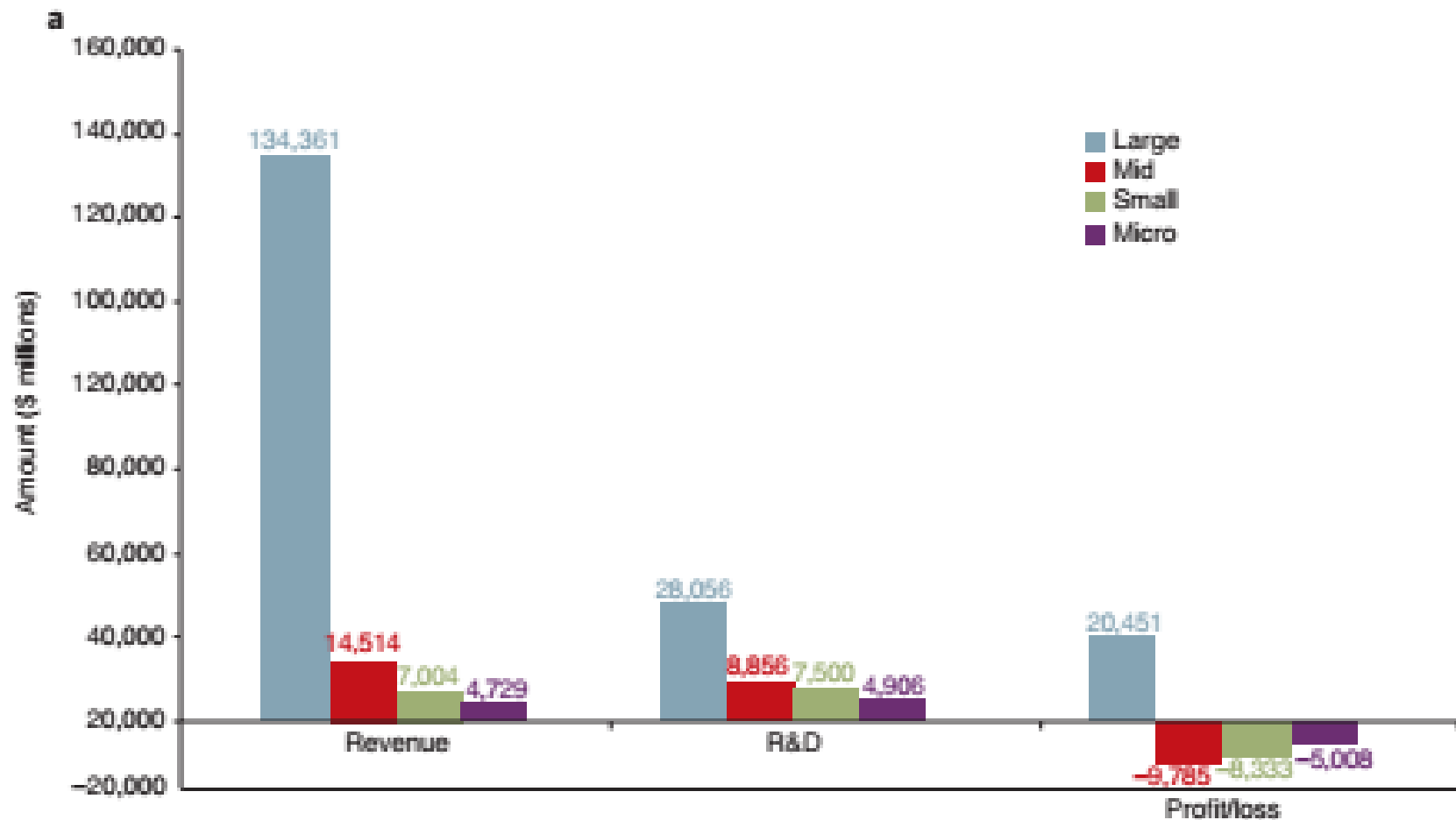
- 1. LA CONCENTRACION DE LA GANANCIA.**
- 2. EL ALTO COSTO DEL DESARROLLO.**
- 3. LA ESCALADA DE PRECIOS.**
- 4. EL BENEFICIO MARGINAL DE LAS TERAPIAS ONCOLOGICAS.**
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1. LA CONCENTRACION DE LA GANANCIA.

Table 3 The 20 top-selling biopharmaceutical products in 2017

Rank	Product	Sales, 2017 (\$ billions) ^a	Cumulative sales, 2014–2017 (\$ billions)	Year first approved	Company	Patent expiry ^b	Biosimilar version(s) approved
1	Humira (adalimumab; anti-TNF)	18.94	62.6	2002	AbbVie, Eisai	2016 (US) 2018 (EU)	Halimataz/Hefiya/Hyrimoz, Amgevita/Amjevita/Solymbic, Cyltezo, Imraldi
2	Enbrel (etanercept; anti-TNF)	8.34	35.4	1998	Amgen, Pfizer, Takeda Pharmaceuticals	2015 (EU) 2028 (US)	Erelzi, Benepali
3	Rituxan/MabThera (rituximab; anti-CD20)	7.78	29.1	1997	Roche, Biogen Idec	2013 (EU) 2016 (US)	Blitzima/Truxima, Ritemvia, Rituzena, Rixathon/Riximyo
4	Remicade (infliximab; anti-TNF)	7.77	35.6	1998	Johnson & Johnson, Merck, Mitsubishi Tanabe Pharma	2015 (EU) 2018 (US)	Zessly, Ixifi, Renflexis/Flixabi, Inflectra/Remsima
5	Herceptin (trastuzumab; anti-HER2)	7.39	27.1	1998	Roche	2014 (EU) 2019 (US)	Herzuma, Kanjinti, Trazimera, Ogivri, Ontruzant
6	Avastin (bevacizumab; anti-VEGF)	7.04	27.0	2004	Roche	2017 (US) 2019 (EU)	Mvasi
7	Lantus (insulin glargine)	6.72	27.4	2000	Sanofi	2014 (EU & US)	Semglee, Lusduna, Abasaglar/Basaglar
8	Eylea (aflibercept; anti-VEGF)	5.93	18.0	2011	Regeneron, Bayer	2020 (EU) 2021 (US)	
9	Opdivo (nivolumab; anti-PD-1 receptor)	5.79	11.4	2014	Bristol-Myers Squibb, Ono Pharmaceutical	2027 (US) 2026 (EU)	
10	Neulasta (pegfilgrastim)	4.53	20.1	2002	Amgen, Kyowa Hakko Kirin	2014 (US) 2015 (EU)	Fulphila
11	Stelara (ustekinumab; anti-IL-12 & IL-23)	4.01	12.2	2009	Janssen Cilag (Johnson & Johnson)	2023 (US) 2024 (EU)	
12	Keytruda (pembrolizumab; anti-PD-1)	3.81	5.7	2014	Merck	2036 (US) 2028 (EU)	
13	Prolia/Xgeva (denosumab; anti-RANKL)	3.54	11.6	2010	Amgen	2025 (US) 2022 (EU)	
14	Lucentis (ranibizumab; anti-VEGF)	3.38	14.3	2006	Roche, Novartis	2016 (EU & US)	
15	Novolog/Novorapid (insulin aspart)	3.31	11.7	1999	Novo Nordisk	2015 (EU & US)	
16	Soliris (eculizumab; anti-C5 complement protein)	3.14	10.7	2007	Alexion Pharmaceuticals	2021 (US) 2020 (EU)	
17	Simponi (golimumab; anti-TNF)	2.94	9.7	2009	Merck, Janssen, Mitsubishi Tanabe	2024 (EU & US)	
18	Humalog mix 50:50 (insulin lispro)	2.86	11.3	1996	Eli Lilly	2014 (US) 2015 (EU)	Insulin lispro Sanofi
19	Xolair (omalizumab; anti-IgE)	2.75	8.7	2003	Roche, Novartis	2017 (EU & US)	
20	Aranesp/Nesp (darbepoetin alfa)	2.62	10	2001	Amgen, Kyowa Hakko Kirin	2016 (EU) 2024 (US)	

^aFinancial data from La Mérie Business Intelligence. ^bPatent data from various sources, including <http://www.gabionline.net/Biosimilars/General/Biologicals-patent-expiries>. HER2, human epidermal growth factor receptor 2; IgE, immunoglobulin E; IL, interleukin; PD-1, programmed cell death receptor 1; RANKL, receptor activator of nuclear factor- κ B ligand; VEGF, vascular endothelial growth factor.



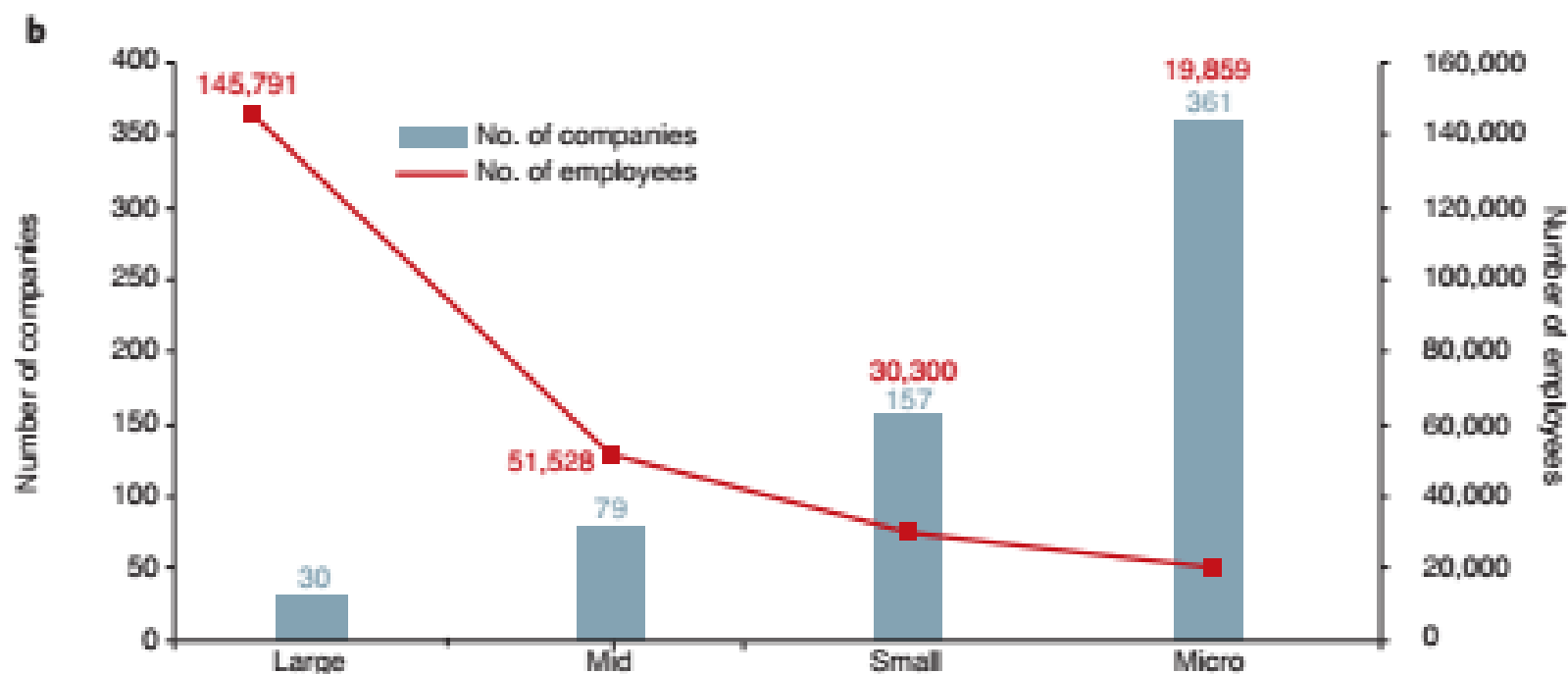


Figure 2 Public biotech barometers. (a) Public biotech company revenue, R&D spending, net profit and loss. (b) Number of companies and employees by market cap. Large cap, \geq \$5 billion; mid-cap, \$1 billion to $<$ \$5 billion; small cap, \$250 million to $<$ \$1 billion; micro-cap, $<$ \$250 million.

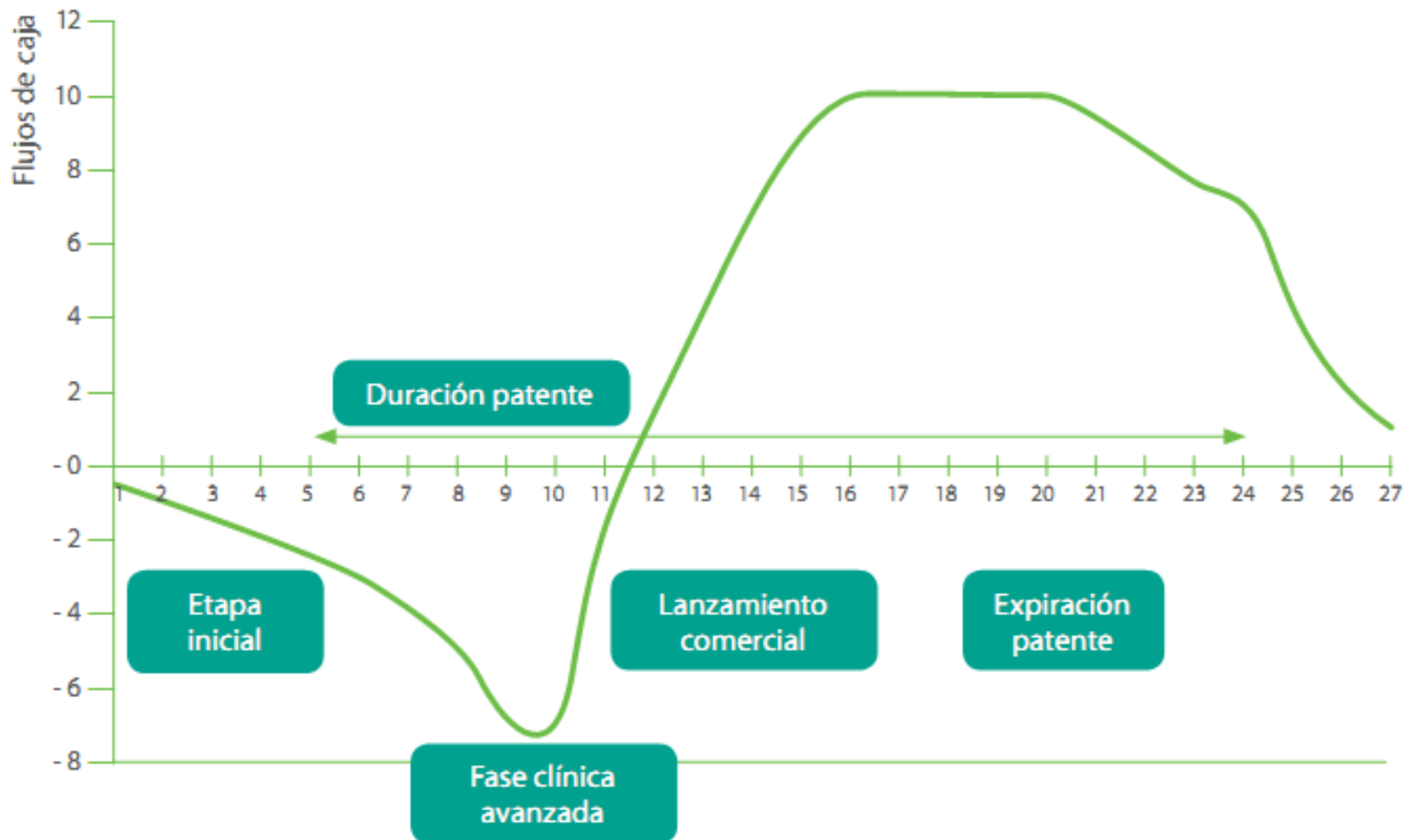
EY survival index, 2015–16

	US		Europe	
	2016	2015	2016	2015
More than 5 years of cash	22%	25%	29%	30%
3-5 years of cash	13%	13%	10%	16%
2-3 years of cash	11%	16%	13%	12%
1-2 years of cash	25%	23%	25%	19%
Less than 1 year of cash	30%	22%	22%	22%

Source: EY, Capital IQ and company financial statement data.

2. EL ALTO COSTO DEL DESARROLLO.

PRODUCT LIFECICLE



UN REPORT 2016: PROMOTING INNOVATION AND ACCESS TO HEALTH TECHNOLOGIES

R&D costs – a wide range of estimates



¹ PWC (2012) From vision to decision: Pharma 2020. Available at: <http://www.pwc.com/gx/en/pharma-life-sciences/pharma2020/assets/pwc-pharma-success-strategies.pdf>

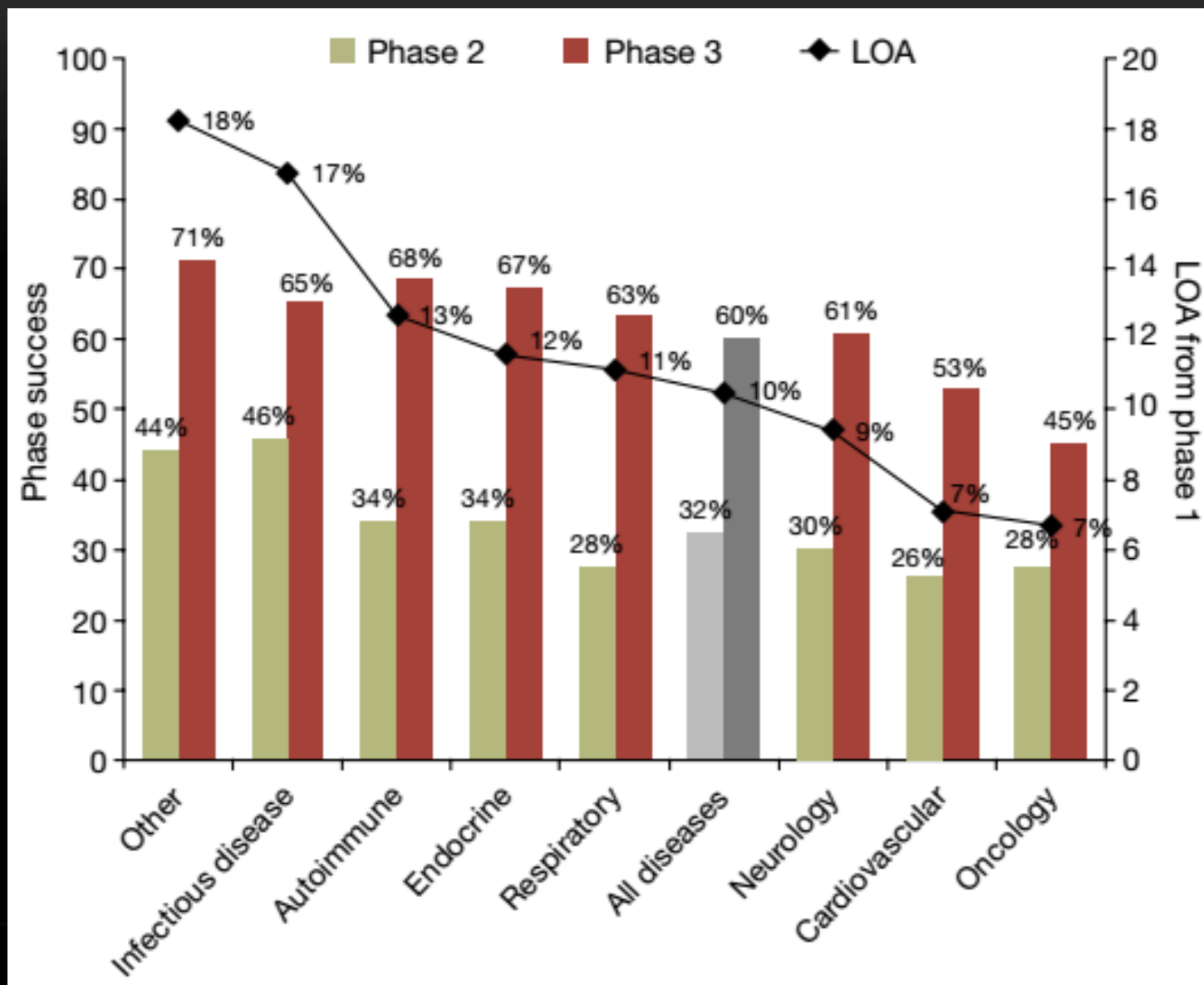
² DiMasi, J.A., et al. 2016 Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics* 22 (2003): 151 – 185. Available at: <http://ids.duke.edu/db?attachment-25-1301-view-168>

³ PhRMA (2015) Profile bio pharmaceutical research industry. Available at: http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf

⁴ Light, W & Warburton, R. (2011) Demythologizing the high costs of pharmaceutical research. *BioSocieties*. Available at: http://www.pharmamyths.net/files/Biosocieties_2011_Myths_of_High_Drug_Research_Costs.pdf

⁵ DNDi (2014) An innovative approach to R&D for neglected patients: Ten years of experience and lessons learnt by DNDi. Available at http://www.dndi.org/images/stories/pdf_aboutDNDi/DNDiModel/DNDi_Modelpaper_2013.pdf

PHASE SUCCESS RATES FOR BIOTECH DRUGS BY INDICATIONS



3. LA ESCALADA DE PRECIOS.

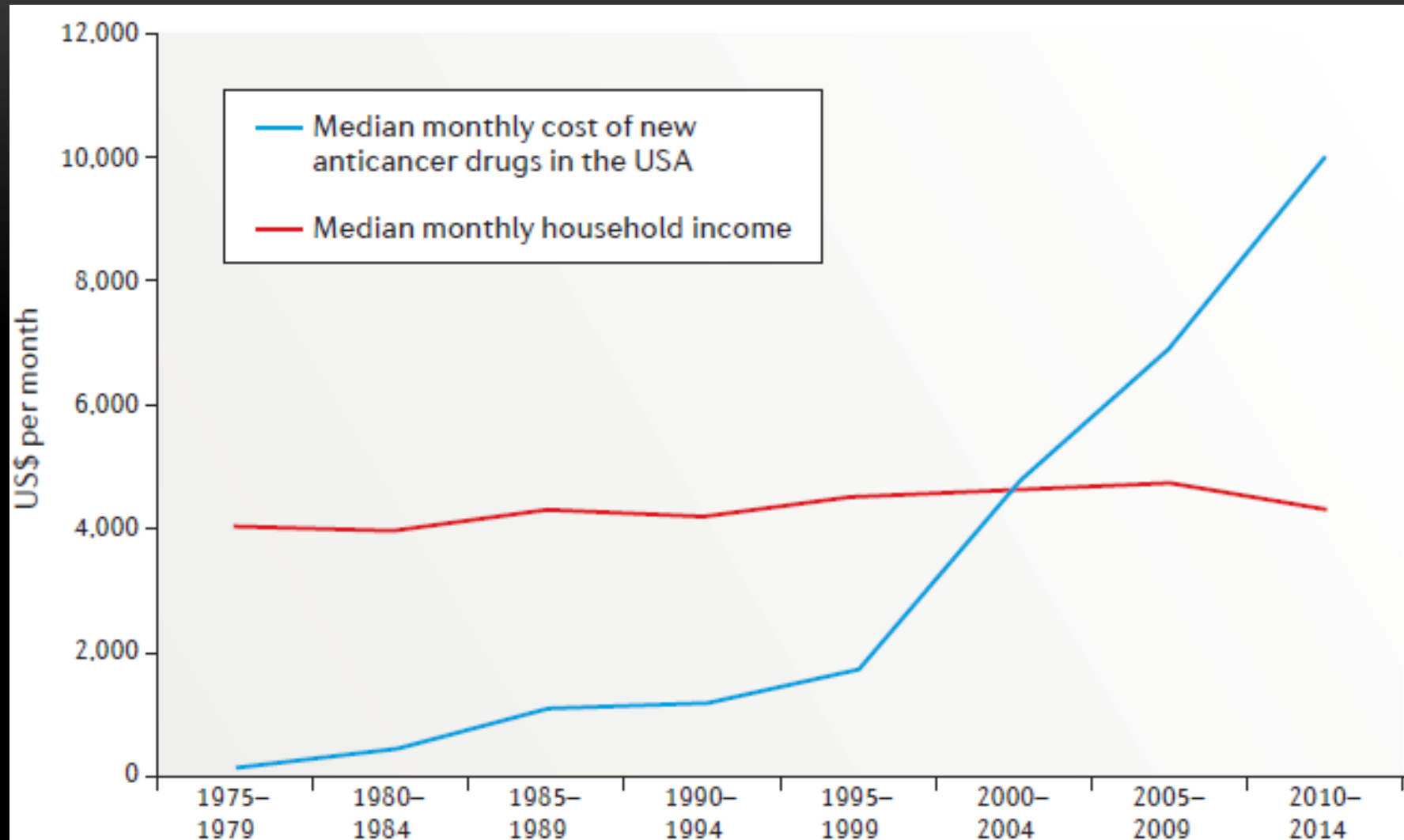


Figure 2 | Median monthly launch price of a new anticancer drug, compared with median monthly household income from 1975–2014 in the USA. Data on household incomes were obtained from the 2015 United States Census¹³⁰, and drug prices were obtained from Bach & Schnorr¹³¹.

HIGH ONCOLOGY DRUG PRICES DO HARM PATIENTS AND SOCIETIES

- In the USA, patients with cancer who require treatment that incurs a high level of medical expense might be forced to declare personal bankruptcy.
- Thus, a diagnosis of cancer is associated with a 2.65 times increased risk of going bankrupt.
- No national health system anywhere in the world can afford to make all new anticancer drugs available to patients.

4. EL BENEFICIO MARGINAL DE LAS TERAPIAS ONCOLOGICAS.

ANTICANCER DRUGS APPROVED DURING LAST 15 YEARS SHOW MARGINAL (LOW-VALUE) BENEFITS ON REAL WORLD POPULATION.

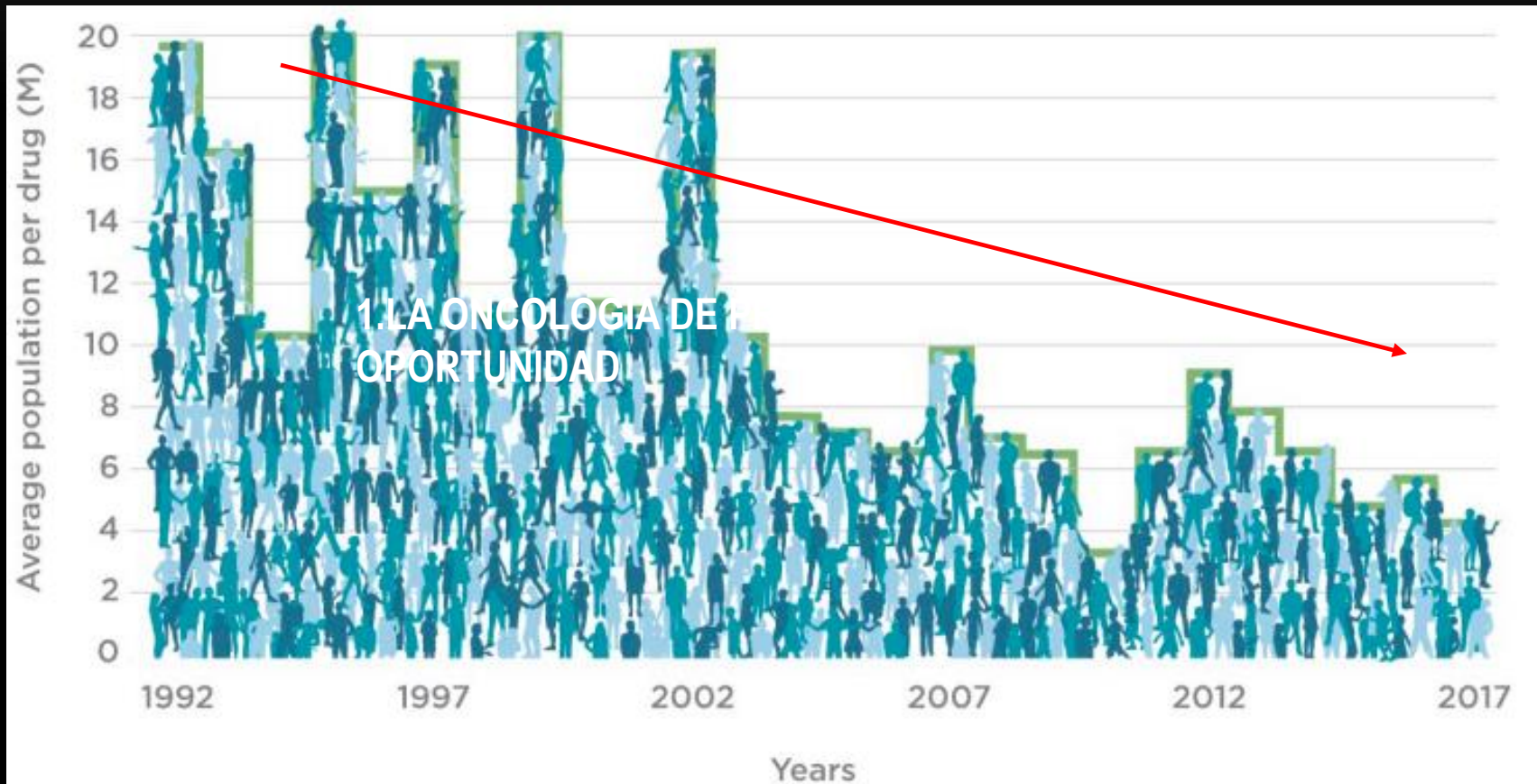
- The median improvements in PFS and OS with 71 consecutive therapies approved by the FDA for metastatic cancer between 2002 and 2014 were 2.5 months and 2.1 months, respectively.
JAMA Otolaryngol. Head Neck Surg. **140**, 1225–1236 (2014).
- In another analysis, of 47 pharmaceuticals approved by the US FDA in 2014–2016, only 9 (19%) met the significant clinical benefit standard with regard to OS established by ASCO.

Ann Oncol. 2017;28(1):157–62

5. LA ONCOLOGIA DE PRECISION: RETO



PO challenge: Deepening the drop in average target population size for new drugs approved by FDA over the last 25 years.

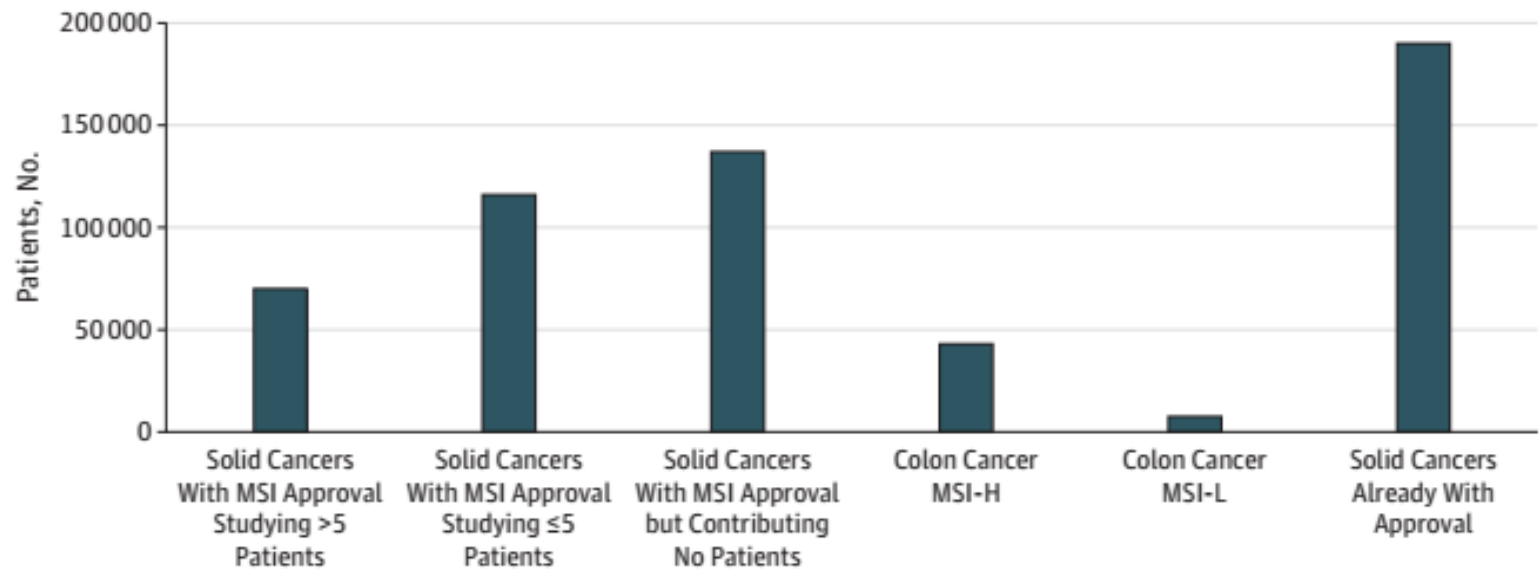


5. LA ONCOLOGIA DE PRECISION: OPORTUNIDAD

PO OPORTUNITY: KEYTRUDA AS A LANDMARK CASE STUDY

- Keytruda (pembrolizumab) received accelerated approval on May 2017 for patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors that have progressed on prior therapy.
- It was the 1st drug authorized for use based on a molecular biomarker rather than a traditional histopathologic diagnosis (**1st tissue-agnostic approval**).
- The approval was based on 59 ptes treated in a series of uncontrolled phase II trials, demonstrating a 46% objective response rate.
- Among these 59 ptes , 14 cancers were represented. Only two of them had more than 10 ptes in the sample.

Figure. The US FDA's Approval of Pembrolizumab in All Solid Tumors With MSI-H or dMMR



6. BIOFARMA 3.0: MODELO DE NEGOCIOS EMERGENTE

BioPharma 1.0

- **Blockbuster model** (drugs selling over a billion USD / year).
- Broad indications for large target populations.
- Market Access through intensive market expenses.

BioPharma 2.0

- Hanging fruit targets were already harvested.
- Patent cliffs created robust generic market.
- Blockbuster replaced by the specialty model (targeting **rare disease with high priced drugs**).
- Market Access through smaller, targeted sale forces.

BioPharma 3.0

- **“Best in class” is about cost-effectiveness.**
- Increasing pressure to end patent extension schemes.
- **Therapeutic solutions + companion diagnostics.**
- Real World Evidence combined with new biological and data tools to add value through the entire life cycle of treatment.
- Data assisted risk management programs for reducing failure rate in clinical trials.

Rx product
ROI

=

$$\frac{(\text{Price per Rx product unit} \times \text{Rx product units sold per year} \times \text{years of sales})}{(\text{Cost of development} + \text{cost of commercialization})}$$

Traditional
OSFA
blockbuster
model

Low

High

Low

High

High

Current
PM
model

High[†]

Low

Low

High[†]

Moderate[†]

'Balanced
value'
PM
model

Moderate[†]

Low

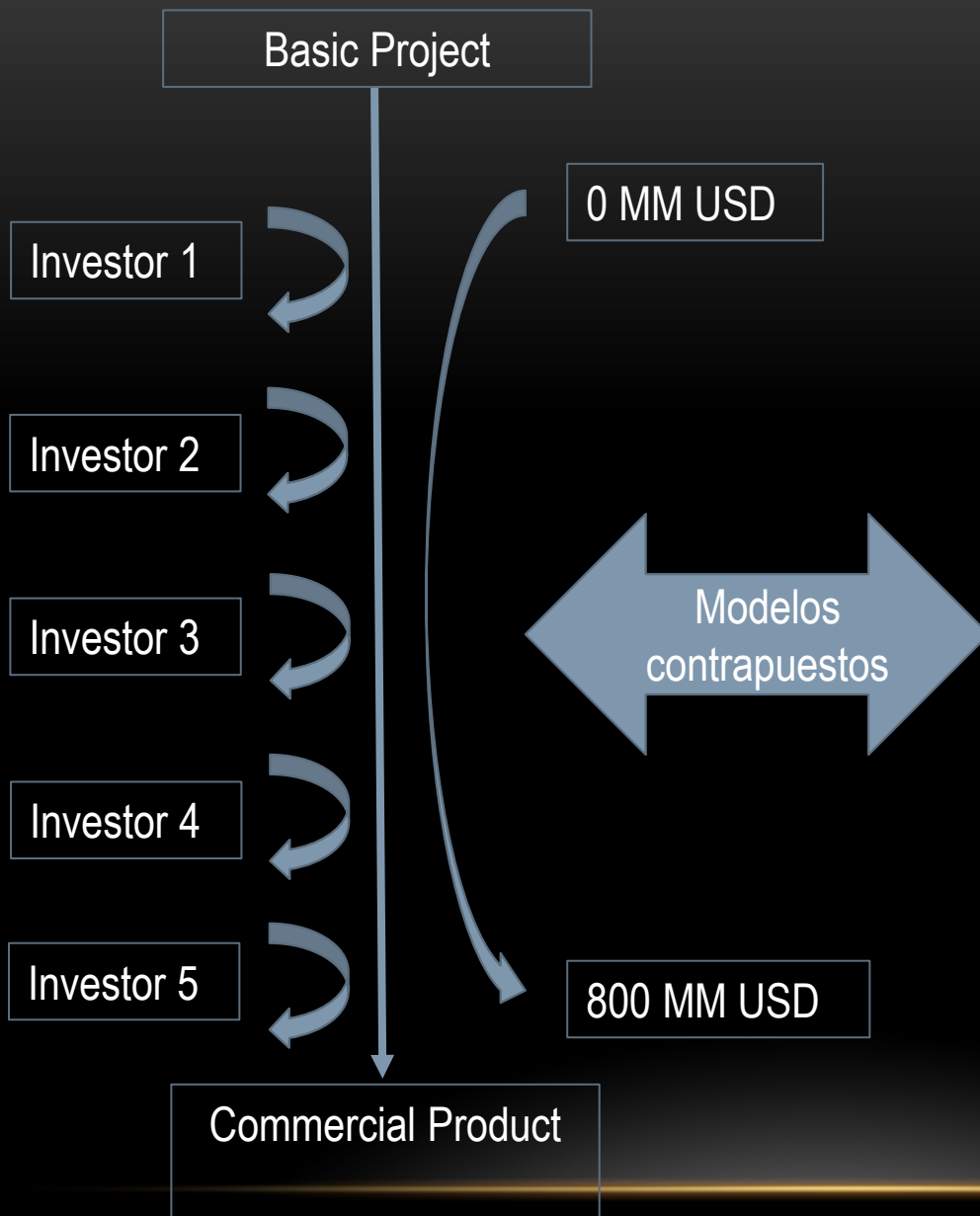
High

Low

Moderate[†]

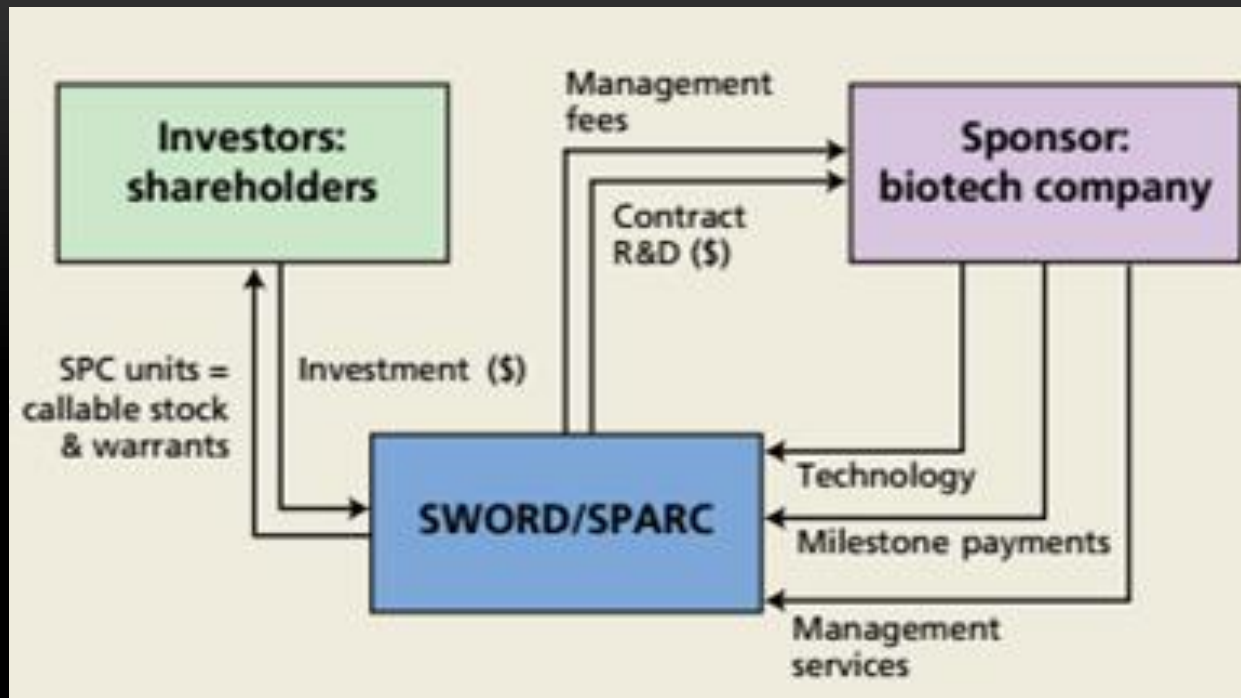
 = critical lever to ensure Rx product profit

6.a COMO VENCER EL VALLE DE LA MUERTE?



Modelo de licencia y codesarrollo:

- Complejo de manejar cuando el licenciante es una empresa grande con un amplio pipeline.
- Falta de foco del equipo de dirección desalienta a los licenciarios.
- Poca transparencia en la asignación de financiamiento por proyectos y en las prioridades de la toma de decisiones.



- La Biotech pone sus activos de PI en una SPV con capacidad legal propia, estados financieros independientes y equipo de dirección dedicado.
- Cede participación a los inversionistas, que aportan financiamiento, pero mantienen control efectivo sobre las operaciones de la SPV.
- La Biotech ofrece garantías al Inversionista en caso de fracaso y ejerce opción de recompra en caso de éxito, en cuyo caso recupera control total sobre los activos. (Ej: Amgen con Filgrastim)

Las fuentes de capital también están concentradas

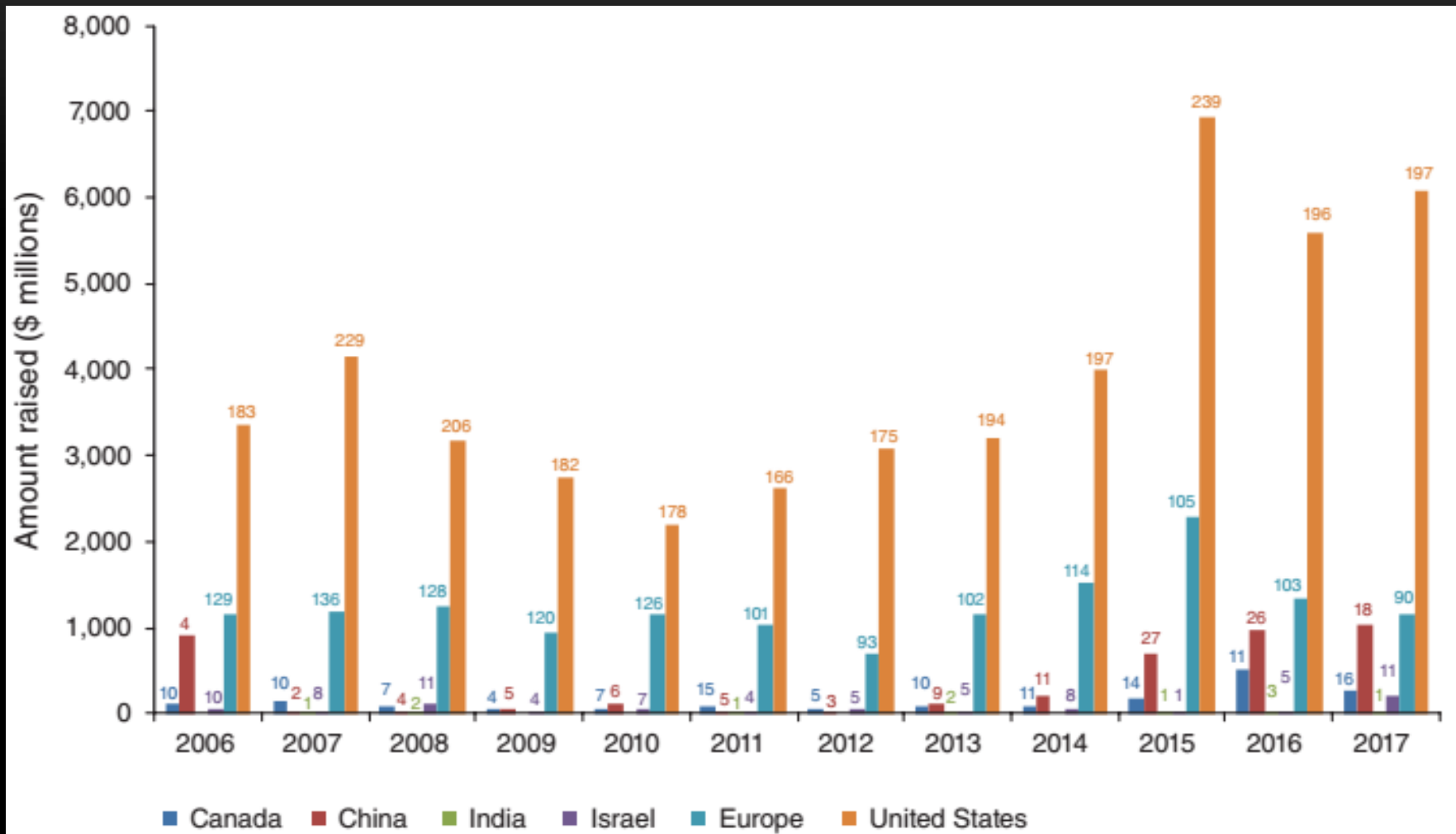


Table 4 Most active investors in leading series A rounds, 2008–2017

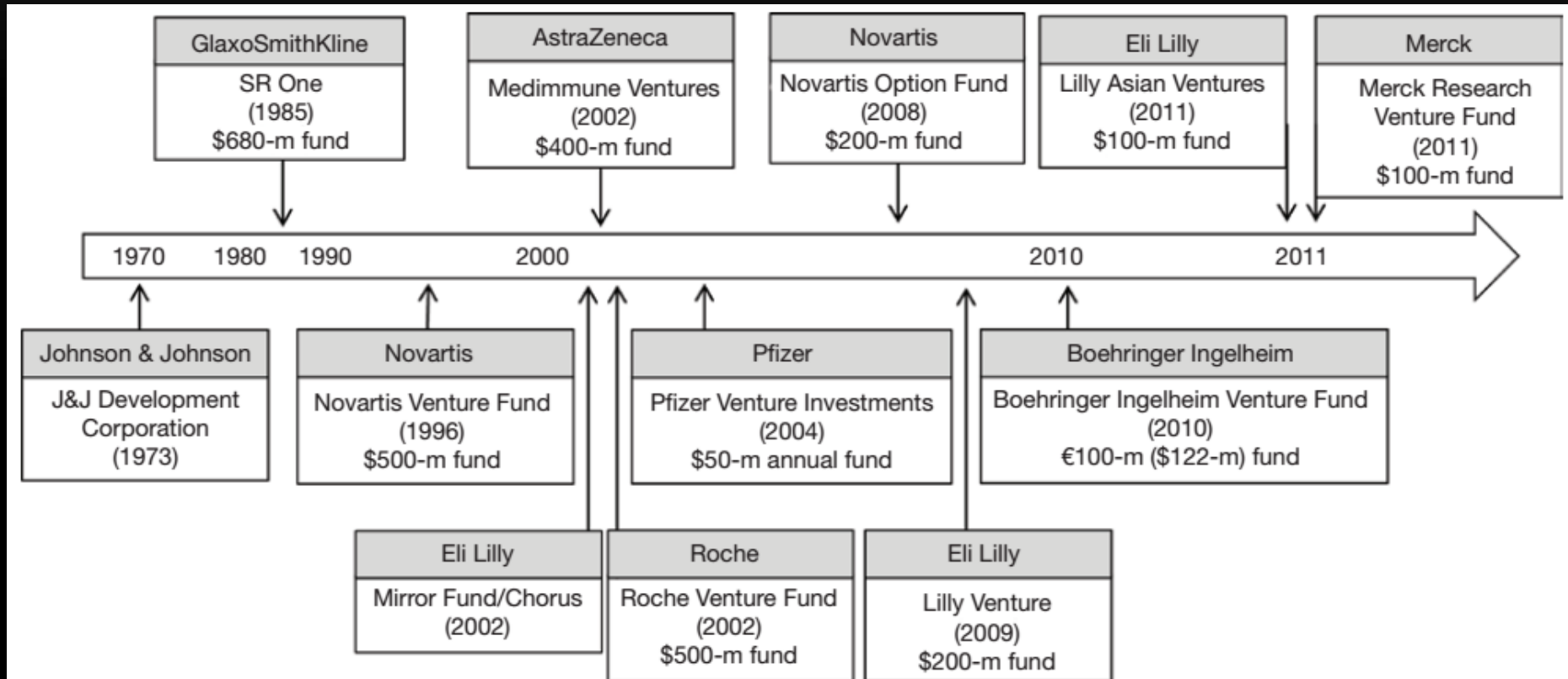
Investor	Number of financings	Total amount raised (\$)
Atlas Venture	26	548,465,450
Third Rock Ventures	24	998,800,000
Arch Venture Partners	19	763,380,455
OrbiMed Advisors	18	508,250,000
MPM Capital	18	477,613,910
Sofinnova Partners	16	325,328,436
Novartis	15	344,742,670
Versant Ventures	15	385,135,850
5AM Ventures	15	399,200,000
New Enterprise Associates	14	400,300,000
Novo Holdings	14	244,499,290
Frazier Healthcare	12	458,800,000
Flagship Pioneering	11	267,600,000
Canaan Partners	10	277,500,000
Avalon Ventures	10	79,400,000

Also with 10: Morningside Group, The Column Group, Boehringer Ingelheim Venture Fund, Touchstone Innovations. Source: BioCentury: BCIQ

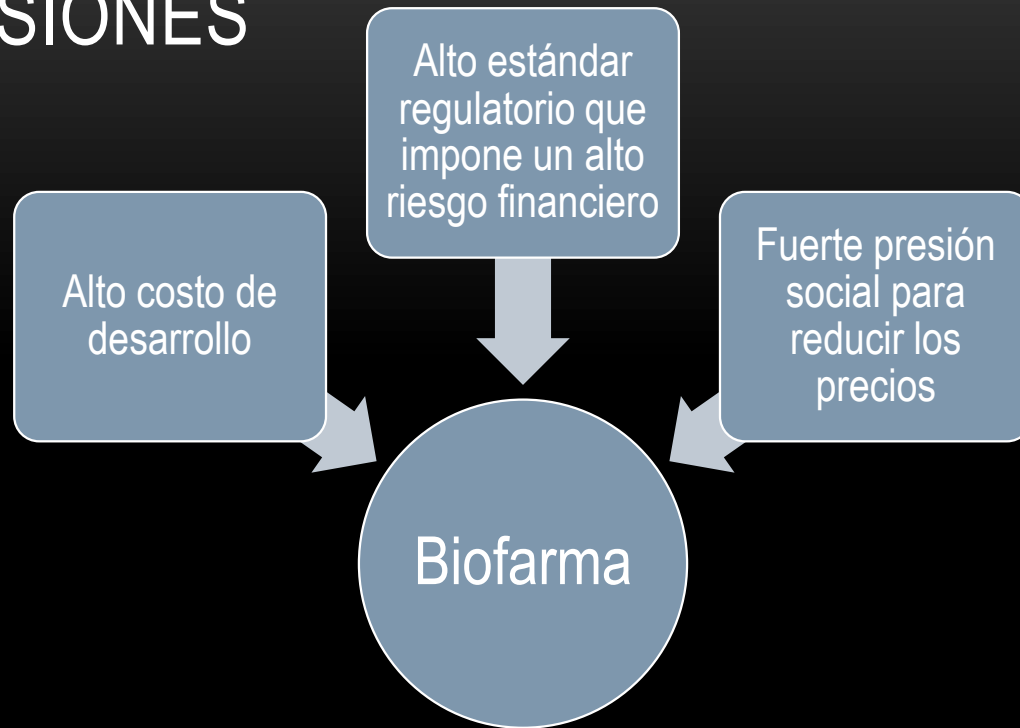
EL PIPELINE DE LOS FONDOS DE INVERSION EN BIOTECH

The screenshot displays the website www.thirdrockventures.com/portfolio. The page features a navigation bar with links to 'Aplicaciones', 'Journals', 'Images', 'Deportes', 'Press', 'UTILITIES', 'Pharmabusiness', 'Radio', 'eBooks', 'Google', 'Configuración', and 'Nacionalidad español'. A 'FILTER BY:' sidebar on the left allows filtering by company status (All Companies, Private, Public, Acquired) and therapeutic areas (Autoimmunity, Cancer, Cardiovascular Disease, Digital/AI/ML, Gastrointestinal, Infectious Diseases, Inflammatory Diseases, Metabolic Disorders, Neurologic/Psychiatric Diseases, Ophthalmology). The main content area, titled 'ALL COMPANIES', displays a grid of nine biotech company logos: ABLEXIS, Afferent PHARMACEUTICALS, agios, ALCRESTA THERAPEUTICS, Allena PHARMACEUTICALS, ALNARA PHARMACEUTICALS, Ambys MEDICINES, bluebirdbio, and blueprint MEDICINES. The Windows taskbar at the bottom shows the search bar, task view, and several open applications, including a file named 'nweResumen-de-....mp4'. The system clock indicates 11:46 a.m. on 08/08/2018.

Las Big Farma han creado sus propios fondos de capital para invertir en activos externos.



CONCLUSIONES



- Nuevo modelo de Negocios:
 - Desarrollo de productos: Medicina personalizada para incrementar eficacia, acortar tiempo de desarrollo y reducir costo. Uso de Biomarcadores, manejo de datos e inteligencia artificial que maximice el beneficio clínico. Enfoque más integral del producto como servicio a largo plazo que justifique los altos precios.
 - Desarrollo de Negocios: Mitigación del riesgo financiero mediante el uso de SPVs. Un producto no es un negocio si no se ofrece en el vehículo empresarial apropiado, con el equipo de dirección adecuado.