18th World Congress of Basic and Clinical Pharmacology

The Role of Public Sector Research in the Discovery of Drugs and Vaccines

An Update

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Acknowledgements

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Untold numbers of colleagues in technology transfer offices who graciously answered intrusive questions!

Agenda

- Background
- Methodology
- Drugs discovered in U.S. Public Sector Research Institutions
- Drugs discovered in non-U.S. Public Sector Research Institutions
  - Preliminary data
- Case Studies
  - Complex pathways — Checkpoint inhibitors
  - Private investment needed — Androgen receptor antagonists

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Drug R&D

Basic Research	Applied Research	Development
Disease mechanisms Targets for intervention	Lead molecules Preclinical development	Safety Efficacy
Public Sector 75-80% Private Sector 20-25%	Private Sector 100%	Private Sector 100%

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Then the Roles Started to Change

1975 - 1980

- Basic tools of biotechnology developed
  - Monoclonal antibodies
  - Recombinant DNA
- Legal framework changed
  - Bayh-Dole Act
  - Stevenson-Wydler Act

1980 - present

- Public sector is performing some of the applied research

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Drug R&D

Basic Research	Applied Research	Development
Disease mechanisms Targets for intervention	Lead molecules Preclinical development	Safety Efficacy
Public Sector 75-80% Private Sector 20-25%	Public Sector x% Private Sector (100-x)%	Private Sector 100%

The Research Question: What is “X”?

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Criteria for Inclusion

- Products which have received FDA approval by either:
  - Center for Drug Evaluation and Research (CDER) or
  - Center for Biologics Evaluation and Research (CBER)
- A license to intellectual property was signed (or enforced by the Courts)
- US Public Sector Research Institutions only
  - National Laboratories
  - Universities
  - Hospitals
  - Non-profit Research Institutes
- Parallel study of non-U.S. institutions

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Criteria for Inclusion

- Includes:
  - Vaccines
  - Small molecule drugs, inc. OTC
  - Biologics
  - *In vivo* diagnostics
- Excludes:
  - Very old drugs
    - Insulin, yellow fever vaccine, flu vaccine, measles vaccine, penicillin, semi-synthetic penicillins, streptomycin, neomycin contraceptive pill, etc.
  - Platform technologies that contribute to the development of whole classes of drugs
    - Cohen-Boyer, Riggs-Itakura, Cabilly, Axel, Herzenberg-Morrison
  - Nutritionals
  - Donated patents
    - Juxtapid, Krystexxa, Latisse

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SPECIAL ARTICLE

The Role of Public-Sector Research in the Discovery of Drugs and Vaccines

Ashley J. Stevens, D.Phil., Jonathan J. Jensen, M.B.A., Katrine Wyller, M.B.E., Sabarni Chatterjee, M.B.A., Ph.D., and Mark L. Rohrbaugh, Ph.D., J.D.

ABSTRACT

BACKGROUND

Historically, public-sector researchers have performed the upstream, basic research that elucidated the underlying mechanisms of disease and identified promising points of intervention, whereas corporate researchers have performed the downstream, applied research resulting in the discovery of drugs for the treatment of diseases and have carried out development activities to bring them to market. However, the boundaries between the roles of the public and private sectors have shifted substantially since the dawn of the biotechnology era, and the public sector now has a much more direct role in the applied-research phase of drug discovery.

METHODS

We identified new drugs and vaccines approved by the Food and Drug Administration (FDA) that were discovered by public-sector research institutions (PSRIs) and classified them according to their therapeutic category and potential therapeutic effect.

RESULTS

We found that during the past 30 years, 153 new FDA-approved drugs, vaccines, or new indications for existing drugs were discovered through research carried out in PSRIs. These drugs included 93 small-molecule drugs, 36 biologic agents, 15 vaccines, 8 in vivo diagnostic materials, and 1 over-the-counter drug. More than half of these drugs have been used in the treatment or prevention of cancer or infectious diseases. PSRI-discovered drugs are expected to have a disproportionately large therapeutic effect.

CONCLUSIONS

Public-sector research has had a more immediate effect on improving public health than was previously realized.

From the Institute for Technology Entrepreneurship and Commercialization (A.J.S.) and Office of Technology Development (A.J.S., J.J.J.), Boston University School of Management, Boston; the Norwegian Radium Hospital Research Foundation, Oslo (K.W.); and the Office of Technology Transfer, National Institutes of Health, Bethesda, MD (S.C., M.L.R.). Address reprint requests to Dr. Stevens at Boston University School of Management, 53 Bay State Rd., Boston, MA 02215, or at astevens@bu.edu.

N Engl J Med 2011;364:535-41.

Sources for Study

Primary:

- FDA – Orange Book, CDER and CBER databases
- SEC – EDGAR database
- Cortellis (formerly ReCap)
- USPTO
- CRISP
- iEdison
- Sunshine Act

Secondary:

- AUTM Surveys (e.g. Better World Report)
- University of Virginia Patent Foundation research
- Press articles
- Lawsuits
- Personal communications, etc.

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Methodology

1. Assemble leads of all drugs that appear to have a PSRI connection
2. Check FDA approval status
3. Obtain positive confirmation of PSRI IP and IP transaction
4. Toughest are:
   - Public companies
     - Transactions generally non-material and hence not reportable
   - Inventor spin-put companies that quickly get acquired
   - Private non-U.S. companies
     - U.S. disclosure rules are the toughest in the world

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Update Study

- Original study included FDA approvals through August 31, 2009
- Update includes FDA approvals through December 31, 2016
  - Plus additional pre 2009 drugs whose PSRI connections have only just been discovered

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Types of Products

	Number		
	Old	**New**	**Combined**
New Chemical Entity	93	58	151
Biologic	36	20	56
Vaccine	15	5	20
Over the counter	1	0	1
In-vivo diagnostic	8	9	17
Total	153	92	245

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Therapeutic Categories

	Old	Update	Total
Oncology	40	20	60
Infectious Disease	36	15	51
Metabolic	12	19	31
CNS	12	15	27
Cardiology	12	5	17
Renal	7	3	10
Gastroenterology	4	5	9
Ophthalmology	6	2	8
Dermatology	7	1	8
Immunology	6	0	6
Women's Health	3	2	5
Pulmonary	2	1	3
Urology	2	1	3
Allergy	2	0	2
Anaesthesiology	1	1	2
Dental	1	0	1
Emergency Medicine	0	1	1
Otolaryngology	0	1	1
Total	153	92	245

Discovering Institutions

Discovering Institution	Number
National Institutes of Health	27
U. of California	20
Emory University	15
Tufts Medical Center	10
Memorial Sloan Kettering	9
Tufts University	9
Columbia University	8
Baylor College of Medicine	7
Yale University	7
Children's Hospital, Boston	6
MIT	6
Rockefeller University	6
U. of Michigan	6
Dana-Farber Cancer Institute	5
Massachusetts General Hospital	5
New York University	5
Salk Institute	5
Scripps Research Institute	5
U. of Colorado	5
U. of Minnesota	5
U. of Texas	5
U. of Wisconsin	5

Initial Developers

Type of Entity	Number	%
Large Entity	85	34.7%
Small Entity	105	42.9%
Start-Up	55	22.4%
Total	245	

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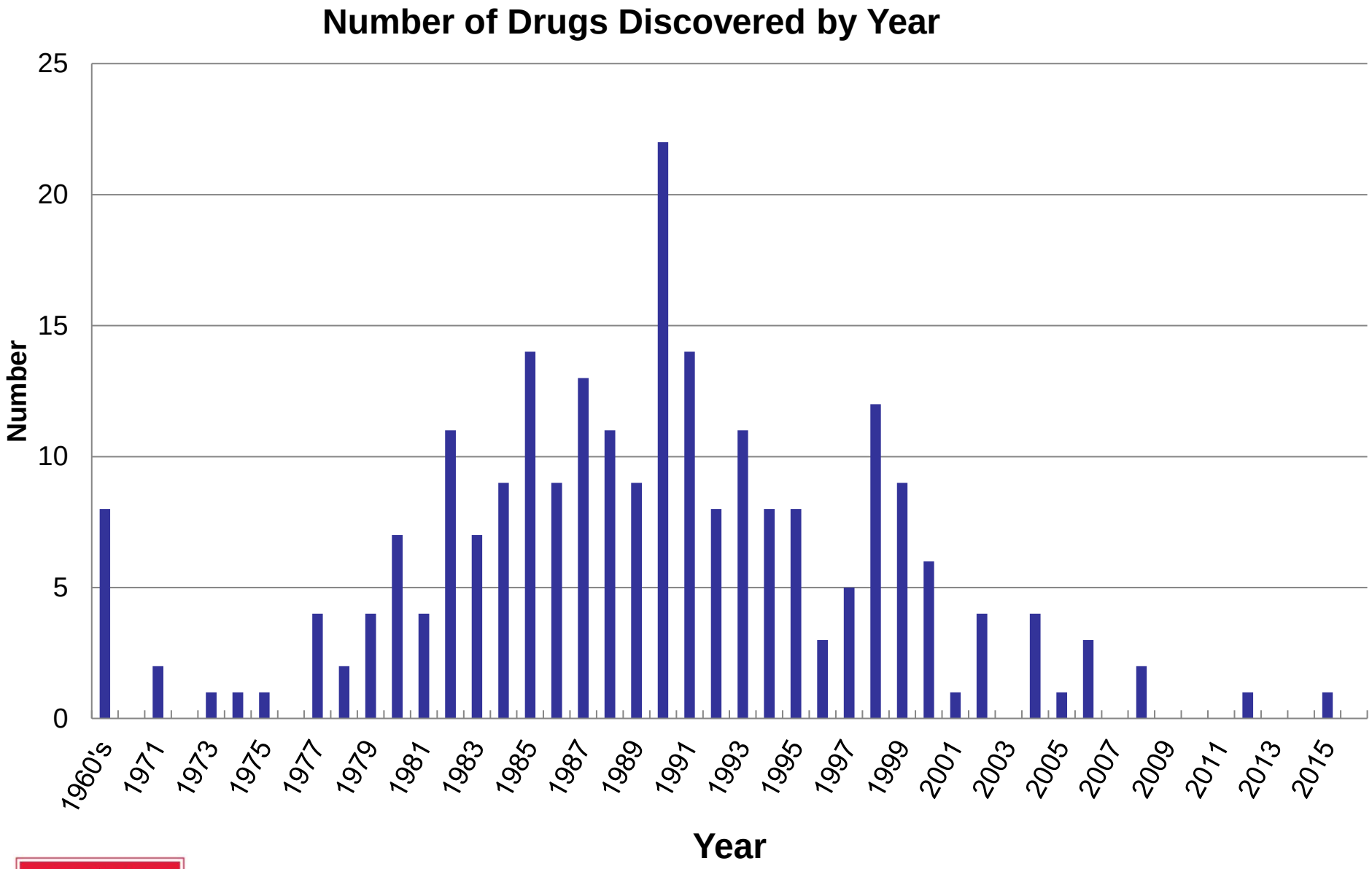
Current Marketers

Current Marketer	Number
Merck	18
Pfizer	14
GlaxoSmithKline	13
J&J	12
Bristol Myers-Squibb	9
Eli Lilly	8
Gilead	8
Novartis	8
Baxter Healthcare	7
Shire	7
Amgen	6
AstraZeneca	6
Allergan	5
Baxalta	5
Biogen	5
Braintree Labs	5
Eisai	5
Roche	5
Takeda	4



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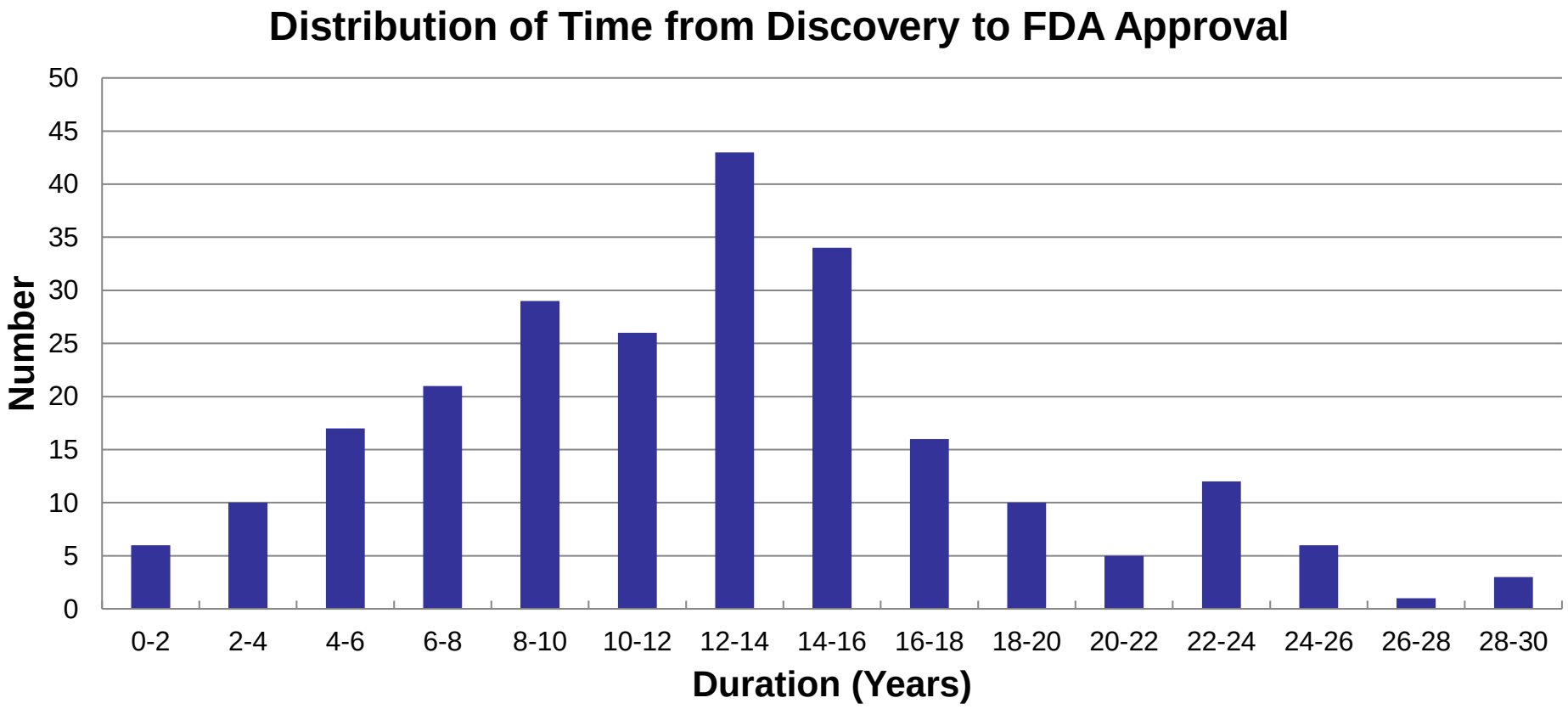

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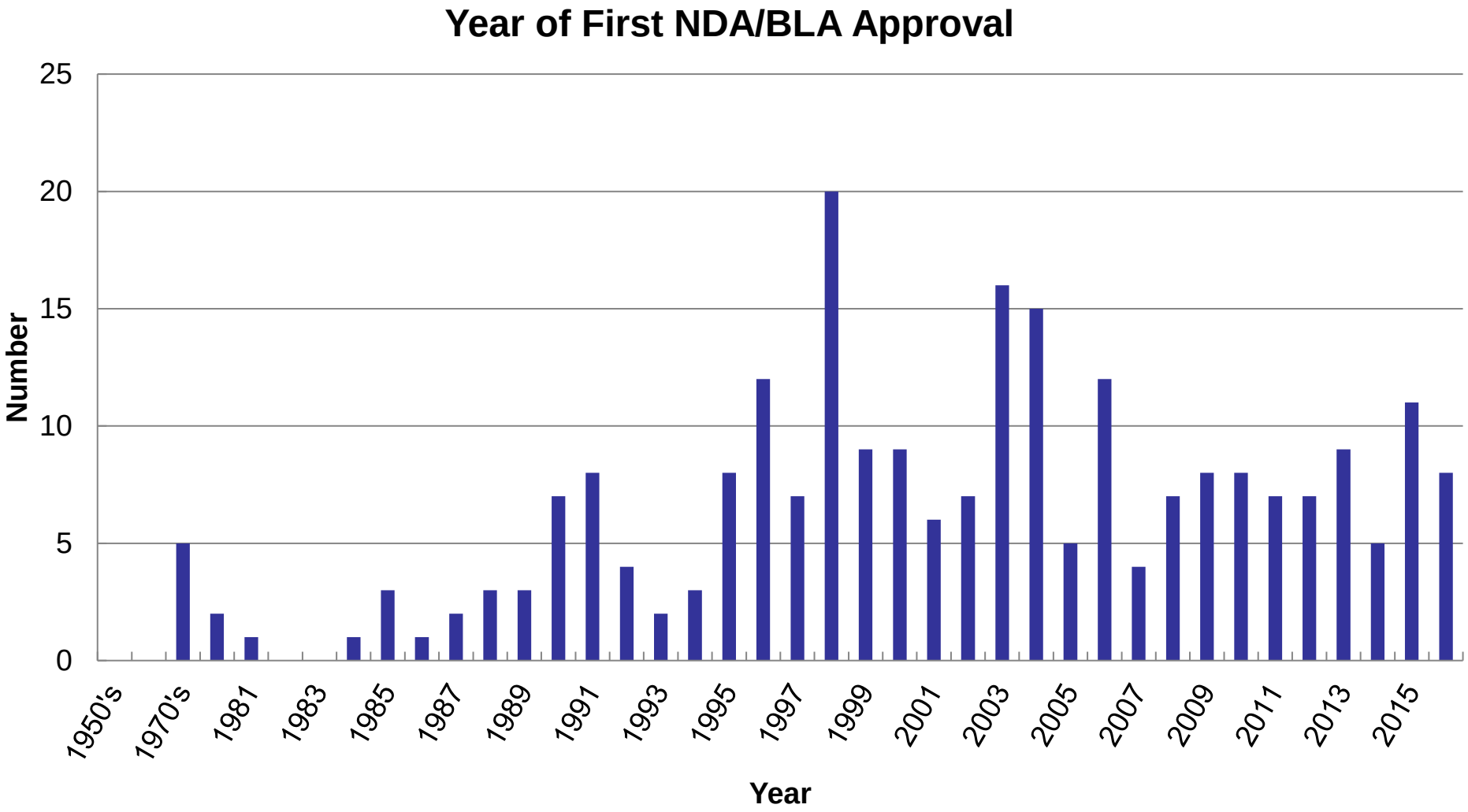

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So, How Many Drugs Originate in PSRI's?

- 1990-2007 Approvals
  - Data for update still being developed
- All NDA approvals: 9.3% from PSRI's
- NCE with Priority Review 21.1% from PSRI's

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Commercialization Pathways

- Found that the classical models for commercialization of public sector research:

PSRI ➔ Large Pharma ➔ Market

and

PSRI ➔ Biotech ➔ Large Pharma ➔ Market

are considerable over-simplifications

- There are frequently one or more additional transactions both pre- and post-FDA approval.

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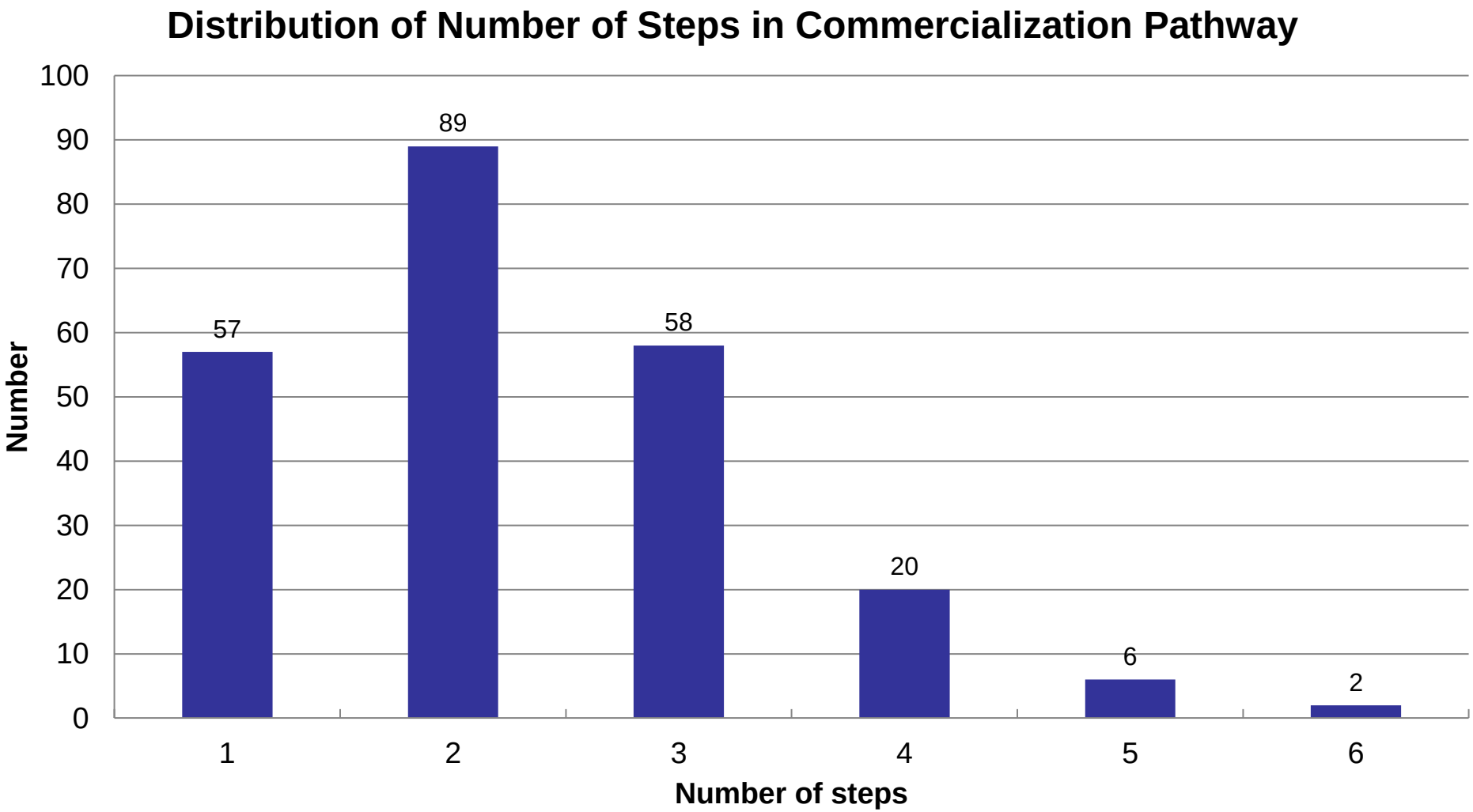

Commercialization Pathway vs. Initial Developer

	Number of Steps in Development Pathway						
	1	2	3	4	5	6	Total
Large Entity	44	20	11	3	1	0	79
Small Entity	10	51	24	11	2	2	100
Start-Up	3	18	23	5	3	1	53
Total	57	89	58	19	6	3	232

Economic Impact

- Inventor
- Developer

Impact on Inventing Institutions

- Royalty sales
- 43 transactions 1990 – 2018
- $5.712 billion in proceeds

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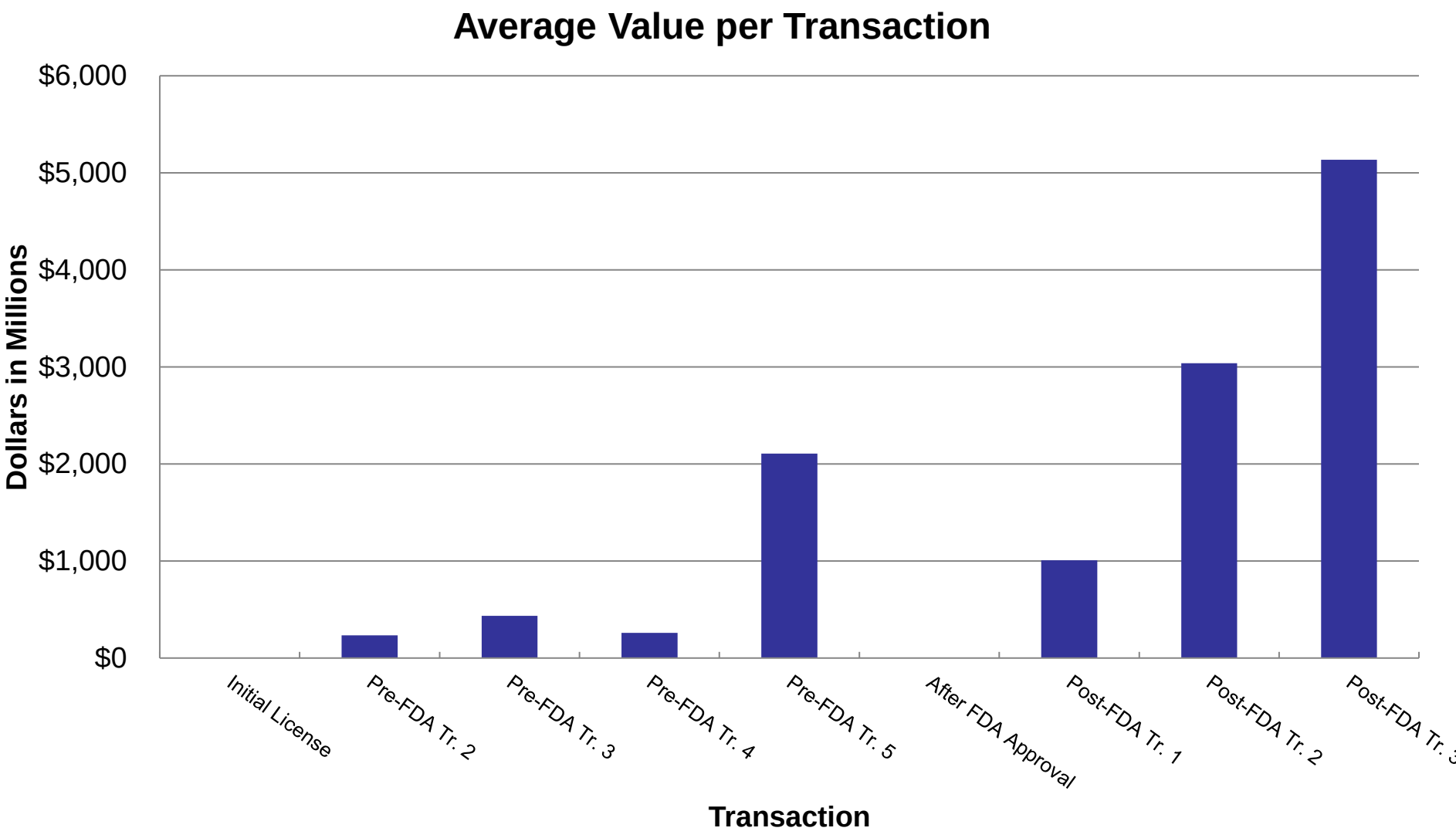

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Impact on Developing Companies

Transaction	Number	Value*	Avg. Value / Transaction*
Pre-FDA Approval			
Initial License	40	$159.3	$4
Pre-FDA Tr. 2	84	$19,637.7	$234
Pre-FDA Tr. 3	26	$11,341.6	$436
Pre-FDA Tr. 4	8	$2,070.6	$259
Pre-FDA Tr. 5	3	$6,324.0	$2,108
After FDA Approval			
Post-FDA Tr. 1	77	$77,548.5	$1,007
Post-FDA Tr. 2	24	$72,928.8	$3,039
Post-FDA Tr. 3	4	$20,543.0	$5,136
Total	266	$210,553.5	

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Drugs Discovered by PSRI's Outside the U.S.

Preliminary Data

- Drugs divided into two groups
  - Those co-discovered with one or more U.S. institutions
  - Those discovered by only non-U.S. institution

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	Co-Discovered With U.S. Inst.	Discovered by Non-U.S. Alone	Total
2011 Study	16	19	35
Update	28	47	75
Total	44	66	110

- Therefore 311 FDA approved drugs discovered or co-discovered by PSRI's worldwide

Discovering Countries

Country	Number of Drugs
Germany	23
Canada	22
UK	21
Japan	17
Australia	11
Israel	10
France	8
Czech Republic	6
Belgium	5
China	4
Sweden	3
Holland	1
Norway	1

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Case Study: Complex Pathways from Bench to Bedside

Checkpoint Inhibitors

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Yervoy's 16 year Journey

Granrts CA 40041,
CA 09179

Filed July 25, 1995
5,811,097

October 1998
Excl. option
3% royalty

March 1999
Acquired for %550 mm
3% royalty

2012
Royalty buy-out
$87.5 million +
$40 million milestones

March 1999
Exclusive sublicense

December 1999
Ipilumab+Denitrophage
for prostate cancer
$4.5 mm

July 2004
Medarex bought
out royalty obligations
for $8.5 mm

May 2003
Ipilumab+GVAX
for prostate cancer

September 2004
Cross-license
Trelemimubam

January 2010
Co-development

November 2004
Collab and Co-Promotion
$$665 mm 45% profit share

July 2009
Acquisition, $2.4 billion

October 2011
Rights for monotherapyt

March 2011
FDA Approval
2017 Sales $1.2 billion

Summary

- 16 years from Berkeley's initial patent application till FDA approval
  - Only 4 years left on patent
    - Monetized for only $87.5 mm + $40 mm milestones (not achieved)
- First 3 formulations as an adjunct to other primary API's
- Passed through the hands of 9 companies
- Gilead accepted just $8.5 million to monetize its royalty rights in 2004

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Opdivo and Keytruda's More Straightforward Pathway

GENETICS INSTITUTE

DANA-FARBER CANCER INSTITUTE

KYOTO UNIVERSITY FOUNDED 1897

Filed July 3, 2003
7,595,048

December 22, 2004
Assigned

ono

May 2005
Medarex gets US;
Ono gets RoW
4% royalty

MEDAREX

August 2016
Monetized royalty interest in
Tercentriq and 2 others
$168 million

Genentech
A Member of the Roche Group

September 2011
BMS acquired rights to
RoW except for Japan,
Taiwan and S. Korea
15% royalty

July 2009
Acquisition
$2.4 billion

July 2014
Collaboration in Japan,
Taiwan, S. Korea
50:50 Profit Share

Bristol-Myers Squibb

March 2015
FDA Approval
2017 Sales $4.9 billion

Observations

- Path 5 years faster than for Yervoy
- Both Yervoy and Opdiva went through Medarex
  - Importance of ability to create fully human mAb's cheaply
  - Medarex obviously beginning to believe in checkpoint inhibitors
- BMS's acquisition of Medarex one of the great deals of all time:
  - Paid $2.4 billion in 2009
  - Brought Yervoy and Opdivo
    - 2017 revenues $6.1 billion
      - Capitalizes to ~$31 billion
  - Royalty bearing deals on a number of mAb's Medarex had created for other companies
  - Equity stake in Genmab

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Keytruda's Journey from Europe to Merck via Kyoto

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Filed June 18, 2008
8,354,509

Organon

March 2007
mAb humanization deal

MRC T

March 2007
Acquired, $14.4 billion

July 2016
Royalty monetization
$150 million

Schering-Plough

March 2009
Acquired, $41 billion

January 2017
Settled: $650 million upfront
6.5% royalty through 2023
2.5% royalty through 2026

September 2014
Infringement
lawsuit filed

Bristol-Myers Squibb

MERCK

September 2014
FDA Approval
2017 Sales: $3.8 billion

Filed July 3, 2003
7,595,048

Observations

- Development pathway even faster than Yervoy and Opdivo
- The incredible value of the Honjo patents
- The two acquisitions in quick succession delayed development by ~ 1-2 years
- Need for humanization technology

Case Study – Private Investment Required

Androgen Receptor Antagonists

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2005
$2.8 mm; 4% royalty

2009
$765 mm; 50:50 profit share U.S.
Low teens - low twenties ex-U.S.

Grant 5 P50 CA092131
$1,160,000

7,709,517, 8,183,274,
9,126,941

2016
$14 billion

2012
FDA approval
2017 sales $2.2 billion
sales

2013
$1 billion

8,445,507, 8,802,689

2018
FDA approval

Grant W81XWH-04-1-0129
$170,192

2014
$1.7 billion

8,648,105, 9,126,941

2016
UCLA monetizes its royalty stream
$1.14 billion +$300 million

UCLA's Economics

- SPORE grant 5 P50 CA092131:
  - $2.3 million / year
  - $290,000 / year to Sawyers
    - $1,160,000 2003-2006
- Army grant W81XWH-04-1-0129:
  - $170,192
- Total grant funding
  - $1,330,192
- 3 drugs resulted
  - Average investment
    - $443,397 / drug

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Medivation's R&D Spend, by Program

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Dimebon	$3,077	$5,186	$10,721	$27,910	$40,594	$35,327	$12,116	$2,164				$137,095
Xtandi	$261	$3,021	$2,619	$8,845	$12,054	$23,454	$42,335	$67,086	$73,076	$102,669	$74,616	$410,036
MDV380											$12,454	$12,454
MDV390										$5,949	$59,099	$65,048
Early Stage									$36,140	$61,063	$59,071	$156,274
Other		$198	$748	$3,481	$6,050	$9,258	$14,088	$19,190				$53,013
Indirect	$1,934	$3,420	$9,311	$14,659	$29,030	$4,189	$4,893	$7,188	$9,736	$19,889	$26,860	$131,109
Total	$5,272	$11,825	$23,399	$54,895	$87,728	$72,228	$73,432	$95,628	$118,952	$189,570	$232,100	$965,029

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Medivation and Astellas' Economics

Medivation	
Direct R&D spend on Xtandi	$410,036
Pro rata share of Indirect	$64,466
Astellas	
Equal to Medivation, 10/09-12/2015	$387,214
Total R&D Spend, U.S.	$861,716
Estimated R&D Spend, ex-U.S.	$861,716
Grand Total	$1,723,431

Return to UCLA, Medivation and Astellas

	Investment		Return		Multiplier
UCLA	$ 0.44	0.30%	$1,440	9.6%	380x
Medivation/Astellas	$ 1,723,431	99.70%	$13,485	90.4%	15x
Total	$ 1,723,431		$14,925		

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Thank you for listening.

Questions?

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