Translational Therapeutics

Translation of the promise of basic discoveries to realize novel therapeutics, diagnostics and approaches to management that benefit the public health
1. The Shape of the Enterprise

A Trillion Dollar Industry

Global annual pharmaceutical industry revenues, in billions of dollars

2003: 499
2014: 1,043

Source: CMR

Average profit margins by industry, in percent

- Pharma
- Media
- Oil/gas
- Auto

Current as of 2013
Source: Forbes
a Success rates by phase
Percentage likelihood of moving to next phase, 3-year rolling average*

b Cumulative success rate Phase I to launch
Percentage likelihood of moving from Phase I to launch

Nature Reviews | Drug Discovery
A game of chance: up from the trough?
Biotech Bubble?
The Opportunity
Biologics to the fore

a Cumulative success rates over time
Percentage likelihood of moving from Phase I to launch

b Success rate by phase, 2012–2014
Percentage likelihood of moving to next phase

Nature Reviews | Drug Discovery
Exciting Times

- Solavadi for hep C
- CAR-T cells for leukemia
- PD-1 blockade and B-Raf inhibitors in cancer
- PCSK9 inhibitors and refractory dyslipidemia
- Vaccines for herpes, malaria and MERS
- Topical chemo for lymphoma
The Gene Therapy Example

• ~$10Bn invested over the past 20 years
• Promise in several immunodeficiency disorders, hemophilia B, a form of congenital blindness, beta-thalassemia and metachromatic leukodystrophy.
• Despite generating no revenue 5 companies valued at $4Bn
• One time therapy, Orphan disease act and ultrarare disorders

Orkin and Reilly Science 2016
The Challenge
Prospects may be looking up, but...

- Half of the 39 approvals in 2012, had orphan status, diseases or indications affecting fewer than 200,000/yr in the US.
- Median peak sales forecast for newly approved drugs is $400k/yr.
- Estimated need to generate at least $600k/yr to cover development costs.
- Half went through 'fast track', 'accelerated approval' or 'priority review' designations.
Increasing peak sales from New Therapeutic Drugs
VINTAGE INDEX: the ratio of the first 7 years of revenue for all innovative launches in a given year to the corresponding portion of R&D investment over the previous 7 years

43% of consensus forecasts overestimated actual revenues by more than 40%

Source of uptick: 45% decreased spend; 55% higher revenue
Some dramatic breakthroughs but...

- Solavadi for hep C doesn’t require concomitant interferon and cures ~ 90%.
- Costs $80,000 for 12 week course.
- If all patients were treated would cost $227 billion versus $260 billion for all drugs yearly.
- Gilead made $2.4Bn Q1 2014 – largest ever.
- $11Bn to acquire. IP at work.
- Payer consolidation and competitors
Costs per patient of managing selected disorders

These approximate estimates are drawn from references (10–13). CFTR, cystic fibrosis transmembrane conductance regulator.

<table>
<thead>
<tr>
<th>DISEASE ENTITY</th>
<th>MANAGEMENT PLAN</th>
<th>~COST/YEAR ($)</th>
<th>~COST/LIFETIME ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>General support</td>
<td>25,000</td>
<td>750,000</td>
</tr>
<tr>
<td></td>
<td>Drug to enhance CFTR function (Kalydeco)</td>
<td>300,000</td>
<td>5,000,000</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Regular enzyme replacement</td>
<td>200,000</td>
<td>5,000,000</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>Prophylactic or periodic factor administration</td>
<td>300,000</td>
<td>5,000,000–10,000,000</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>General medical support and hydroxyurea as standard of care</td>
<td>25,000</td>
<td>1,000,000</td>
</tr>
</tbody>
</table>
RECENT TRENDS IN PRESCRIPTION DRUG COSTS

After Several Years of Modest Growth, Prescription Drug Spending Rose Sharply in 2014

Prescription drug costs are projected to grow more modestly in coming years, averaging about 5% annual per capita growth through 2024.

Medicare’s Share of National Prescription Drug Spending Rose From 2% in 2004 to 29% in 2014

Nearly 1 in 4 People in the United States Taking Prescription Drugs Report Difficulty Affording Them

Many Specialty Drugs Are Priced Higher in the United States Than in Other Developed Countries

Most People in the United States Favor Action to Keep Drug Prices Down

**PERCENTAGE WHO SAY THEY FAVOR EACH OF THE FOLLOWING:**

- Report how prices are set: 86%
- Allow Medicare to negotiate: 83%
- Limit charges for high-cost drugs: 76%
- Import drugs from Canada: 72%

Authors: Cynthia Cox, MPH; Rabah Kamal, Anne Jankiewicz, and David Rousseau, MPH; for the Kaiser Family Foundation


Please cite as: JAMA. 2016;315(13):1326. 10.1001/jama.2016.2646
Change in cancer drug spending per head
% change, 2010-2014

UK | US | Germany | Canada | S Korea | Japan | Italy | France | Spain
---|----|---------|--------|---------|-------|-------|--------|-------
0  | 20 | 40      | 60     | 80      |

Cancer mortality rates
Deaths per 100,000 population, selected EU countries, 2011

Men | Women
---|-----
Hungary | Croatia | Denmark | Netherlands | Ireland | Poland | UK | Belgium | Italy | Germany | Austria | France | Portugal | Greece | Spain | Sweden | Finland | Bulgaria | Cyprus
500 | 300 | 200 | 100 |

Cancer drug decisions by Nice
Recommendations for cancer technology appraisals, Mar 2000 - Mar 2015

Optimised Only in research
Yes | No 7 | 8 |
90   | 50  |
Infrastructure
A New Era in Clinical Research

• A shift from detection of large average effects to information relevant to individual patient decisions

• Harvest EHR and linked biobank at scale to uncover unexpected disease associations (e.g. AD – IBD) and interrogate mechanism

• Use of iPS cells and deep phenotyping to establish POC: **Human Phenomic Science**

• Mendelian randomization – PCSK9

• More focused and creative trial design

• Seek internal consistency from non – RCT data

FitzGerald GA Sci Transl Med. 2015 Apr 22;7(284):284fs15
Breakthrough Treatments in Cancer

• Assessment of combinations of different therapeutic modalities held pre approval in different companies
• Sequencing these interventions
• Cost
• Variance in drug response at combinatorial scale
PATIENTS

• Informed, participants, advocates
• Compassionate use, social media and ethical triage
• N=1 vs small RCTs in drug development
Parsing Variability in drug Response
Genomic Variance is One Hand Clapping

- Comparison of intra vs inter individual variability of drug response permitted calculation of maximum contribution from fixed sources of variance – such as the genome (if we could measure it comprehensively)
- Maximal estimate ~30% in young male volunteers studied under controlled conditions
- Most variance from unrecognized environmental inputs interacting with our genomes – need for unbiased readouts of metabolome etc
- Imagine the maximal contribution of genomic variance in typical patient target populations….
### Clock-regulated drug targets

<table>
<thead>
<tr>
<th>Rank</th>
<th>Sales</th>
<th>Trade name</th>
<th>Drug</th>
<th>Indications</th>
<th>Circadian-gene targets</th>
<th>Organs in which targets oscillate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>$1.46 b</td>
<td>Nexium</td>
<td>esomeprazole</td>
<td>Gastritis, GERD, Esophagitis</td>
<td>Atp4a</td>
<td>liver</td>
</tr>
<tr>
<td>5</td>
<td>$1.28 b</td>
<td>Advair Diskus</td>
<td>fluticasone + salmeterol</td>
<td>Asthma, Chronic obstructive pulmonary disease</td>
<td>Agrp2</td>
<td>kidney, lung, skeletal muscle</td>
</tr>
<tr>
<td>11</td>
<td>$794 m</td>
<td>Rituxan</td>
<td>rituximab</td>
<td>Rheumatoid arthritis, Non-Hodgkin's lymphoma</td>
<td>Fgr2b, Ms4a1</td>
<td>kidney, skeletal muscle</td>
</tr>
<tr>
<td>20</td>
<td>$538 m</td>
<td>Diovan</td>
<td>valsartan + hydrochlorothiazide</td>
<td>Hypertension, Heart failure</td>
<td>Kenma1</td>
<td>liver</td>
</tr>
<tr>
<td>27</td>
<td>$431 m</td>
<td>Vyvanse</td>
<td>lidexametamine</td>
<td>Attention deficit hyperactivity disorder</td>
<td>Agrp1b</td>
<td>liver</td>
</tr>
<tr>
<td>32</td>
<td>$392 m</td>
<td>Tamiflu</td>
<td>oseltamivir</td>
<td>Influenza</td>
<td>Neu1, Neu2</td>
<td>liver, kidney, lung, cerebellum</td>
</tr>
<tr>
<td>33</td>
<td>$383 m</td>
<td>Ritalin</td>
<td>methylphenidate</td>
<td>Attention deficit hyperactivity disorder</td>
<td>Slc6a4</td>
<td>kidney, adrenal gland</td>
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<tr>
<td>37</td>
<td>$348 m</td>
<td>AndroGel</td>
<td>testosterone</td>
<td>Hypogonadism</td>
<td>Ar</td>
<td>brown fat, aorta, brainstem</td>
</tr>
<tr>
<td>38</td>
<td>$346 m</td>
<td>Lidoderm</td>
<td>lidocaine</td>
<td>Pain</td>
<td>Egfr</td>
<td>heart</td>
</tr>
<tr>
<td>44</td>
<td>$304 m</td>
<td>Seroquel XR</td>
<td>quetiapine</td>
<td>Bipolar disorder, Major depressive disorder</td>
<td>Hir2a, Drd4, Hir2c, ...</td>
<td>liver, kidney, lung, brown fat, heart, a...</td>
</tr>
<tr>
<td>45</td>
<td>$289 m</td>
<td>Viagra</td>
<td>sildenafil</td>
<td>Erectile dysfunction</td>
<td>Pde5a, Pde6g</td>
<td>brown fat, adrenal gland</td>
</tr>
<tr>
<td>47</td>
<td>$281 m</td>
<td>Niaspan</td>
<td>niacin</td>
<td>Hyperlipidemia</td>
<td>Qpr</td>
<td>kidney</td>
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<tr>
<td>48</td>
<td>$279 m</td>
<td>Humalog</td>
<td>insulin lispro</td>
<td>Diabetes mellitus T2</td>
<td>Igrf1r</td>
<td>kidney</td>
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<tr>
<td>49</td>
<td>$274 m</td>
<td>Alimta</td>
<td>pemetrexed</td>
<td>Mesothelioma, Non-small cell lung cancer</td>
<td>Tmys, Gart, Atic</td>
<td>liver, lung, aorta</td>
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<tr>
<td>54</td>
<td>$267 m</td>
<td>Combivent</td>
<td>ipratropium bromide + salbutamol</td>
<td>Asthma, Chronic obstructive pulmonary di...</td>
<td>Chrm2, Agrp2, Agrp1</td>
<td>kidney, lung, heart, skeletal muscle, br...</td>
</tr>
<tr>
<td>56</td>
<td>$262 m</td>
<td>ProAir HFA</td>
<td>salbutamol</td>
<td>Asthma, Chronic obstructive pulmonary di...</td>
<td>Agrp2, Agrp1</td>
<td>kidney, lung, skeletal muscle</td>
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<tr>
<td>62</td>
<td>$240 m</td>
<td>Janumet</td>
<td>metformin + sitagliptin</td>
<td>Diabetes mellitus T2</td>
<td>Prkab1, Dpp4</td>
<td>kidney, heart, brainstem, hypothalamus</td>
</tr>
<tr>
<td>66</td>
<td>$236 m</td>
<td>Toprol XL</td>
<td>metoprolol</td>
<td>Hypertension, Heart failure</td>
<td>Agrp2, Agrp1</td>
<td>kidney, lung, skeletal muscle</td>
</tr>
<tr>
<td>71</td>
<td>$220 m</td>
<td>Vytorin</td>
<td>cetzimibe + simvastatin</td>
<td>Hyperlipidemia</td>
<td>Anpep, Soat1, Hmger</td>
<td>liver, lung, brainstem</td>
</tr>
<tr>
<td>78</td>
<td>$209 m</td>
<td>Aciphex</td>
<td>rabeprazole</td>
<td>Gastritis, GERD, Esophagitis</td>
<td>Atp4a</td>
<td>liver</td>
</tr>
<tr>
<td>90</td>
<td>$189 m</td>
<td>Lunesta</td>
<td>esopilocone</td>
<td>Insomnia</td>
<td>Tspo, Gabra3</td>
<td>kidney, lung, adrenal gland</td>
</tr>
<tr>
<td>98</td>
<td>$173 m</td>
<td>Prilosec</td>
<td>omeprazole</td>
<td>Gastritis, GERD, Esophagitis</td>
<td>Atp4a</td>
<td>liver</td>
</tr>
<tr>
<td>99</td>
<td>$171 m</td>
<td>Focalin XR</td>
<td>dexmethyllphenidate</td>
<td>Attention deficit hyperactivity disorder</td>
<td>Slc6a4</td>
<td>kidney, adrenal gland</td>
</tr>
</tbody>
</table>

**Table 1:** Drugs from the top-100 best-selling drugs list that target circadian genes AND have half-life < 6h. For full table, see Dataset S1. Rank and sales are based on USA 2013 Q1 data from Drugs.com.

Zhang and Lahens et al. PNAS 2014
Time dependent hypotensive effect of low dose aspirin in mice on HSD

Wang et al 2016
A circadian gene expression atlas in mammals: Implications for biology and medicine

Ray Zhang\textsuperscript{a,1}, Nicholas F. Lahens\textsuperscript{a,1}, Heather I. Ballance\textsuperscript{a}, Michael E. Hughes\textsuperscript{b,2}, and John B. Hogenesch\textsuperscript{a,2}

\textsuperscript{a}Department of Pharmacology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104; and \textsuperscript{b}Department of Biology, University of Missouri, St. Louis, MO 63121

Edited by Joseph S. Takahashi, Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX, and approved September 19, 2014 (received for review May 13, 2014)

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UGUCAGAAGUUG--ACCGUCGAA


CCCATCCAGATCTTTGCTTTGTCGCCAGCTGTCTCT

Ptgs1 (COX-1)
O'Donnell's Expanded View of the Human Platelet Lipidome

12-HETE  \[\rightarrow\] AA  \[\rightarrow\] COX-1  \[\rightarrow\] TxA2

12-HETE \[\rightarrow\] cPLA2

thrombin  \[\rightarrow\] PAR 1/4  \[\rightarrow\] aggregation

aspirin  \[\rightarrow\] multiple lipids  \[\rightarrow\] oxPL re-esterification

aspirin  \[\rightarrow\] mitochondrial \[\beta\] oxidation  \[\rightarrow\] Acetyl CoA  \[\rightarrow\] ATP

coagulation  \[\rightarrow\] PI Assymetry  \[\rightarrow\] thrombosis
Bi-directional Interaction between NSAIDs and the Microbiome

A. Clearance (mL/h)
B. Kel (h)
C. AUC total (ng.h/ml)
D. t1/2 (h)
E. Vd (mg/Kg)

N = 6/group

Abx: Neomycin and Vancomycin

Liang et al Elife 2015

T1/2 and V_d have significantly different variance
COX-1 acetylation reflects aspirin exposure
Differential interaction with other NSAIDs

Interaction by mixed, but not COX-2 selective inhibitors to undermine antiplatelet effects of aspirin

- Li X et al. PNAS. 2014;111(47):16830
Human Capital
ITMAT: Creating a Workforce

**Undergraduate**
- Pipeline, Awareness, Exposure
- Symposium

**Certificate**
- TR
- POR

**Masters**
- TR
- CR
- Reg Sci
- BMI

**Predoctoral**
- MD, PhD, DMD, VMD, MSN

**Postdoctoral**
- Residents, Fellows, Postdocs, Faculty

Professionals with defined expertise in Clinical and Translational methodology

TR: Translational Research
POR: Patient Oriented Research
CR: Clinical Research
Reg Sci: Regulatory Science
BMI: Biomedical Informatics
Vertical Disintegration

The Sharing Economy

**a Cumulative success from Phase I to launch**
Percentage likelihood of moving from Phase I to launch, 3-year rolling average*

**b The advantage of partnering**
Difference between the probability of success by phase for in-licensed versus non-partnered compounds

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Nature Reviews | Drug Discovery
Career Development and The Graduate Gap

New models needed that straddle organizational boundaries

Objectives

• Increase trainees with expertise in HPS
• Utilize masters programs to project basic science into the clinic
• Create the opportunity to form partnerships; don’t dictate them
• Enable trainees to function in fragmented modular space
Choosing Winners and Measuring Impact
Figure 1. Correlation between Countries’ Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.
ITMAT Network Dynamics
Measurement of Success

• Satisfaction – surveys (crude, response rates)
• Trainees – funding success, papers, appointments (accomplishments ?)
• Funded projects – conversion into NIH support, papers, disclosures, patents. Collaborations (actual discoveries ?)
  
  YES – after 10 years at least four
Lessons

- It takes a long time
- Before it attracts the private sector and philanthropy, NIH is often not enough
- Shots on goal as picking winners is tricky
- Success is rarely unequivocal
- Success has many mothers whose individual contributions can't be parsed
Fostering Entrepreneurship
Fostering Entrepreneurship

THE DAY BEGINS AT A COPYRIGHT LAW OFFICE
Precompetitive participants. Collaborations and consortia can be open or restricted both in terms of those who directly contribute (for example, scientifically) (Contributors) versus those who will directly access the outputs (Output access), suggesting four potential combinations: restricted/open (blue); restricted/restricted.
IP is focused on the Composition of Matter

Perhaps a 1:40,000 chance of becoming an approved drug
IP for free
Create a Pot of Gold

- Charities – Wellcome, Gates etc
- Companies – Pharma, Oil etc
- Governments – Global treaties for underserved populations
  - Credit Default Swaps
  - Tradable shares in intellectual Property
Modeling Success

DAVID BECKHAM
IP Reform

- Modeling drug targets; biological networks; PK/PD; market share and pricing
- Model the barriers to success and prospectively allocate relative reward
- Use the courts to resolve discrepancies
- Postpone reward until value actually realized

The Dominant (if disputed) IP
Conclusion

• It is risky and expensive but life altering breakthroughs continue to be made
• Create the infrastructure to allow academia to play in modular space; this will accelerate the process, decrease cost and increase efficiency
• Enlarge the creative commons, mandate transparency where necessary, incent early investigation of the full spectrum of drug action and listen to patients