Translational Research in the Context of the Changing Dynamics of Biopharmaceutical Innovation

Prepared for: Todai

Tokyo, February 1st, 2017
Agenda

• By Way of Introduction
Working primarily for Biopharma, Catenion has a proven track record of creating value for clients and patients.

- Largest team exclusively focused on Biopharma R&D
- Objectivity and independent thought
- Assessed >1,000 projects, often in collaboration with R&D project teams
- Helped develop more than 10 marketed drugs
- Value creation through portfolio strategy and optimization
- Trusted partners of top executives in Europe, the US and Japan

Source: Catenion
It is sometimes useful to remind ourselves of the context within which biopharma operates: Science, technology, healthcare, as well as rules and regulations: The “Biomedical Innovation System”

Source: Catenion

25 years, $bn and high risk
The funding mechanisms for innovation in this “Biomedical Innovation System” are often taken for granted.

Source: Catenion
The main hypothesis of this presentation: Current trends are putting Translational Research at centre stage and will change business models of all players.

Source: Catenion
Agenda

• What is Biopharma Innovation and What Are We Measuring?
  • Biopharma Innovation Cycles
  • Changing Roles of Different Players in Translational Research and Innovation
  • Brief Summary
Innovation is not the same thing as invention – for an invention to become an innovation, it needs to be adopted into practice.
Not all creative ideas have proven to be practical
Biopharmaceutical innovation requires R&D at the front end (invention) and translation into clinical practice at the back end (adoption) – multiple players have to co-operate for this to happen.

Invention:
- New technologies lead to better products and services
- Industry (biopharma, diagnostics, medical products) and regulators

Adoption:
- Use/application/compliance lead to improved processes and outcomes
- Clinicians, patients and payors

Source: Catenion
Invention saves lives – Strimvelis, lentivirus-based ex vivo stem cell/gene therapy for ADA-SCID (adenosine deaminase deficiency severe combined immuno-deficiency)

- 58 patients treated, first treated patient still alive and well after 13 years
- Approved by EMA in 2016

Source: Catenion
Adoption saves lives, too but it can take time - the story of Ignaz Semmelweiss - Hand-washing by doctors and nurses dramatically reduces death rates in obstetric yards

Source: Catenion
How can we measure the impact of innovation on medicine over time?

Life Expectancy would be a first choice parameter.
“For 160 years, best-performance life expectancy has steadily increased by a quarter of a year per year, an extraordinary constancy of human achievement“


Start of

• „Modern Medicine“ around 1900
• „Modern Rx Industry“ around mid-1930‘s

Why is there no visible effect on survival?
If Life Expectancy were a direct function of biomedical innovation, then innovation would have to be represented by a straight, upwards sloping line.

Major surrogate parameters do not look like straight lines at all and seem implausible as representations of biomedical innovation over time.
The original drivers of bio-medical innovation are to be found in the fields of Science & Technology, so the classic S-curve might be a good starting point.

Source: Catenion
Also, we would expect a number of S-curves to follow and supersede each other in time..

Source: Catenion
New curves have very long lead times before they mature and incremental innovation continues to take place on the „old“ S-curve in parallel to breakthroughs on the new one.

Source: Catenion
But what measure can we use for the y-axis? Clearly, life expectancy does not do the job – and no other single parameter will either, so we need a composite qualitative index.

Science & Technology View
S-Curve

Effectiveness
= Impact on medical practice
= f(effect size, quality of life and # of patients)

Decades

Source: Catenion
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To make a new drug, four basic dimensions must be addressed:

1. **Drug format**
2. **Molecular Target**
3. **Drug Substance**
4. **Target Population**

Source: Catenion
In this framework, bio-pharmaceutical innovation as represented by the first S-curve from the 1930s onwards was essentially driven by what might be called „Pure Phenotypic Discovery“…

Source: Catenion
Bio-pharmaceutical innovation on the first S-curve: Phenotypic discovery by trial and error and straightforward clinical development

- Contribution of many different disciplines, but limited exploratory clinical research
- Sometimes translational insights in the clinic

Source: Catenion
The first pharma S-curve – starting to take off in the 1930s with sulfa drugs and rapidly accelerating in the 1940s, then peaking in the 1950s and 60s

- Many new drug classes, among them: sulfa drugs, anti-infectives, hormones, vitamins, immunosuppressants, psychotropics, hypoglycemics, first cytotoxics and many more
- Prescription drugs as a % of all medicines in US
  - 1929: 32%
  - 1969: 83%

The first 50 golden years – massive innovation, small sales per product, mid-sized companies – no VCs/ no biotechs/no Big Pharma...

- Top-selling product in US
  - 1965: Librium: $59mn
  - 1970: Valium $125mn
  - 1975: Valium $273mn
  - 1980: Tagamet $233mn

- Mid-sized companies (by today's standards), often subsidiaries of chemical conglomerates
  - Worldwide Rx Sales of top company Hoechst
    - 1975: $1.3bn
    - 1980: $2.6bn

Stagnation from the mid-80s onwards – the slowing of innovation and the emergence of Big Pharma and blockbusters

- Stagnation of NCE launches in the face of escalating R&D budgets
- New drug classes with marginal benefits: ACE-inhibitors, SSRIs, atypicals, statins
- Start of modern global branding & marketing of drugs and “diseases”

Source: Catenion
Steep sales growth for pharmaceuticals in the US since the late 1980s - at a time when innovation was slowing down

Source: IMS
Industry consolidation as a sign of innovation decline: Of the PhRMA members active in 1988, by 2011 only one quarter remained active – all others had disappeared through M&A

<table>
<thead>
<tr>
<th>PhRMA members active in 1988</th>
<th>PhRMA members remaining in 2011</th>
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<tr>
<td>Abbott Laboratories</td>
<td>Eli Lilly</td>
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<td>American Cyanamid</td>
<td>Merck</td>
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<td>A.H. Robins</td>
<td>Novartis</td>
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<td>Astra</td>
<td>Pfizer</td>
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<td>BASF</td>
<td>Sanofi-Aventis</td>
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<td>Boehringer Ingelheim</td>
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<td>Ciba Geigy</td>
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<td>Connaught Laboratories</td>
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<td>DuPont Pharmaceuticals</td>
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<td>Eli Lilly</td>
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<td>Marion Laboratories</td>
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<td>Procter &amp; Gamble</td>
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<td>R.P. Scherer</td>
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<td>Sterling Drug</td>
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<td>Upjohn Company</td>
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<td>Warner-Lambert</td>
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<td>Wellcome</td>
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<td>Zeneca</td>
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Big Pharma emerged driven by flattening innovation curve, economies of scale and rapidly rising Rx budgets

Increasing economies of scale in R&D, manufacturing and sales

Mid-sized Pharma (up until 1980‘s)

Big Pharma (1980 to 20xx)

Governments
- Massive funding of basic science and technology (NIH)
- Professionalisation of approval and global IP rights
- Hunger for novelty, limited price sensitivity, exploding Rx budgets

Source: Catenion
At the same time, a new biopharma S-curve slowly started to emerge in the late 1970’s (mainly in the US) and is currently accelerating.

Effectiveness = Impact on medical practice = f(effect size, quality of life and # of patients)

- First successes with antibodies and mono-genetic diseases
- Bayh-Dole Act 1980
- Deregulation of financial system 1979 onwards
- e.g.: Work on antisera for immunisation since around 1900

Source: Catenion
In the proposed framework, the current - and anticipated future - acceleration of bio-pharmaceutical innovation is based on a number of factors working in conjunction…

- Huge investments in target discovery and validation
- Initially fuelled by the rise of genomics
- Increasingly multi-target treatment approaches

- Drug format
  - Increasing choice of different formats

- Drug Substance
  - Increasingly optimised

- Molecular Target
  - Increasingly starting point

- Target Population
  - Increasingly defined by target
    - (biologics) and/or relying on phenotypic stratification

- Structure-based approaches
- Better screening techniques
- Better pre-clinical models
- Tox, PK, PD simulations
- etc

- Different anti-body formats
- siRNA, gene therapy, cell-based therapies, therapeutic vaccination, oligonucleotids, etc

Source: Catenion
…taken together, these enabling technological changes considerably widen the scope for breakthrough innovation over and above that represented by the first S-curve…

Source: Catenion
Redefining disease states constitutes a novel dimension of biomedical innovation – table after Prof Sir John Bell

<table>
<thead>
<tr>
<th>Disease Taxonomy</th>
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<tbody>
<tr>
<td>Symptom-based</td>
<td>Irritable Bowel Syndrome, Fibromyalgia</td>
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<tr>
<td>Histology</td>
<td>Angioimmunoblastic Lymphadenopathy</td>
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<td>Physiology</td>
<td>Hypertension, Diabetes</td>
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<tr>
<td>Eponymous</td>
<td>Alzheimer's Disease, Bell's Palsy</td>
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<tr>
<td>Organ-based</td>
<td>Breast Cancer, Ovarian Cancer</td>
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<tr>
<td>End-of-the-Road</td>
<td>Heart Failure, Liver Failure</td>
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</table>

e.g.: Neo-glucogenesis by the liver vs dysregulated fatty acid metabolism, etc

Source: Prof Sir John Bell https://www.youtube.com/watch?v=GBiYP6Pxxv0
In this environment, exploratory clinical development takes center stage, implying a massive need for collaborative TRANSLATIONAL RESEARCH of basic and clinical scientists.

Source: Catenion
For many drug development projects, the likelihood of success will increase the more stratified the population is for which it is tested.

Source: Catenion
Emerging players on the second biopharma S-curve from 1980 onwards – universities, Biotechs and VCs, driven by deregulation, science focus, risk and increasing upsides; of course now joined by Pharma big and small..

Source: Catenion
So now we have three innovation cycles running in parallel with unprecedented innovation potential combining invention with adoption, but in an unsustainable funding model.
Especially on the second and now the third S-curve, price levels have continued to move up leading to pushback from payors, limitations of access and ultimately raising the question of sustainability of the current model.

Source: Hartung et al., 2015 Neurology

US list prices of MS drugs up more than six-fold since early 2000’s
Agenda

- What is Biopharma Innovation and What Are We Measuring?
- Biopharma Innovation Cycles
- **Changing Roles of Different Players in Translational Research and Innovation**
- Brief Summary
Translational Research is not everything but it will be increasingly crucial to biomedical innovation

**Disease biology**

plus

**Exploratory clinical research**

**New targets, modalities and drugs**

plus

**New definitions of disease states**

Translational Research = Collaborative efforts between academia, university hospitals and industry

Source: Catenion
Advances in science and technology as well as economic pressures are changing the role of biopharma in biopharmaceutical innovation

R&D productivity crisis in Pharma

- Scaling back of in-house discovery in favour of „open innovation“ approaches
- Long-term industry/academia research alliances for specific fields
- Investment by pharma earlier in the value chain
- Increasing pressure by payors for highly clinically-differentiated drugs in the place of „just novelty“ as the basis for premium pricing

Emerging drug formats which Pharma does not know how to deal with

- Most new drug formats beyond small molecules originate in universities and require CMC know-how for development
- This know-how is typically generated by a new breed of CROs, not by pharma
- Autologous gene cum cell therapies do not fit the traditional pharma business model

Source: Catenion
Mid-sized companies with strong therapeutic focus show the highest R&D productivity

Source: Catenion Analysis, 1) % of Assets in Largest Two Therapeutic Areas
In the last decade, many universities have started translational initiatives to take advantage of the changing innovation dynamics.

Mostly triggered and supported by national or regional government initiatives..
- E.g.: approx 30 CTSA grants from NIH (Harvard, NYU, Kansas, Iowa…) – total of $500mn
- Sweden, Flanders, Bioregions in Germany, Alberta, Wales...

..and/or embedded in strong biomedical innovation ecosystems
- E.g.: Boston, South san Francisco, Golden Triangle, Flanders, Bio-regions in Germany...

What will drive success in the Translational Research required to leverage scientific potential into medical interventions?

Source: Catenion
First of all, the deep cultural divide between academia and industry needs to be tackled; this is rooted in values, lack of mutual understanding and (often) arrogance.

**Culture**

<table>
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<tr>
<th>Academia</th>
<th>Industry</th>
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<tr>
<td>Scientific excellence</td>
<td>Commercial Success</td>
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<tr>
<td>Curiosity &amp; Creativity</td>
<td>Focus on IP</td>
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<tr>
<td>Academic freedom</td>
<td>R&amp;D Productivity</td>
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<tr>
<td>Focus on publications</td>
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<td>Poor replicability</td>
<td>Little room for serendipity</td>
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<td>Poor project management</td>
<td>Constantly changing strategies and priorities</td>
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<td>Lack of discipline</td>
<td>Intransparent decision-making</td>
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*Source: Catenion*
Translation by definition cuts across domains, so it is not surprising that some of the key cultural divides are to be found INSIDE each of the players.

Culture

Source: Catenion
Universities should combine academic values with professional project management - the world will be poorer if universities become profit-driven enterprises – example SPARK Stanford

Culture

- Collaborative, bottom-up initiative initiated and driven by a protein chemist and a clinician
- Focus on education and mentoring of PIs for selected high-impact projects
- Virtual organisation domiciled within the Stanford School of Medicine

Strong Set of Values

- Academic freedom, scientific excellence and potential clinical impact
- Commercial potential is just one criterion
- Culture of open discussion and challenging regardless of hierarchy („check your ego at the door“)
- Voluntary contribution of time and advice by scores of pharma advisors
- No agreements with pharma in search of financial return

Source: SPARK, Catenion, more detailed information is available from Catenion
Due to the historical development of TTOs and Translational Research, there are additional fault lines inside universities.
“Translational Research” in traditional university speak aims at bridging the “Valley of Death” in order to generate IP that can be licensed or spun off into a start-up company („from target to candidate“)

**Scope of Translational Research**

- **Target ID to Lead ID**
- **Lead Optimisation to Pre-clinical**
- **IND to PoC**
- **Full Development to Approval**

- **Classic University Domain**
- **„Valley of Death“**
- **Classic Biotech Domain**
- **Classic BigPharma Domain**

„Translational Research“ in „University Speak“ from Target to Compound

Source: Catenion
So where can universities play in the emerging environment? A priori, the scope is large if the work is carried out according to the professional standards of industry required to get drugs to market...

Scope of Translational Research

- **Drug repurposing**, often no or weak IP and/or not-for-profit

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>Target ID to Lead ID</td>
<td>Breakthrough scientific discoveries</td>
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<tr>
<td>Lead Optimisation to Pre-clinical</td>
<td>Biopharma and CROs</td>
</tr>
<tr>
<td>IND to PoC</td>
<td>Translational research in collaboration with Biopharma</td>
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<tr>
<td>Full Development to Approval</td>
<td>Biopharma</td>
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**Novel drug formats and tech platform supported by specialised CROs with drug delivery in hospitals**

Source: Catenion
In any event, in order to build a competitive position in Translational Research, the focus of universities needs to expand forward into the early clinic („from bench to bedside“)

Source: Catenion

Scope of Translational Research

Target ID to Lead ID

Lead Optimisation to Pre-clinical

IND to PoC

Full Development to Approval

Classic University Domain

„Valley of Death“

Classic Biotech Domain

Classic Big Pharma Domain

Source: Catenion
…but as the cost escalates once projects move into the clinic, this strategy requires either collaborative approaches with pharma or a different funding model (e.g.: CTSA grants).

Source: Catenion; CTSA = Clinical and Translational Science Awards, granted by NCATS, the NIH National Center for Advancing Translational Sciences
Universities and other biomedical players are often engaged in heated local competition....

Getting on the Map
...forming a biomedical innovation cluster will attract third parties and make all participants stronger in global competition (which is the one that really counts)
As biopharma and VCs are chasing good ideas in academia, collaboration models are evolving rapidly into more strategic/long-term set-ups, increasingly reaching into the clinic.

**Historic model: small annual grants to basic researchers**

- Takeda/Flagship/New York Tri
- Versant/Inception/Rx/academia

**Timeline**

- **Target ID to Lead ID**
- **Lead Optimisation to Pre-clinical**
- **Exploratory Clinical Research**
- **Full Development to Approval**

- **German Centre for Neurodegenerative diseases/Orion**

Source: Catenion
Historic funding models have used a high proportion of private “money at risk” to finance biomedical innovation – this needs to be compensated by high returns and puts sustainability at risk.

Source: Catenion
If we want lower prices, we need to rely less on private risk money – is Telethon Italia (originators of the SCID therapy) a model for things to come?

**Funding Models**

**Fondazione Telethon Italia**

- **Scientific Excellence**
  - Telethon scientific publications 1991-2014: 10,222 articles in peer-reviewed journals
  - Impact second only to MRC

- **Charity Funding**
  - €45mn in grant volume pa
  - 2/3 intra-mural research, 1/3 to single researchers in Italy

- **Professional Management**
  - First research lab to receive GLP certification for gene and cell therapy toxicity and bio-distribution studies

- **Industrial Partnerships**
  - Collaborating with GSK, Biogen, Shire, Biomarin

Source: Telethon Italia
Another potential model of things to come: DNDi – Drugs for Neglected Disease initiative – why only for neglected diseases?

**Funding Models**

- Not for profit virtual model
- Numerous co-operations with biopharma and CROs
- Funding from private donors and public agencies
- Attrition-adjusted cost of NCE $110-170mn (estimate)

Source: DNDi – Drugs for Neglected Disease initiative
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In the future, policy-makers will hold the keys to unlocking innovation potential based on translational research at affordable prices.

- Support the creation of clusters to attract scientists and companies from everywhere to drive excellence
- Increase the amounts of grant funding for translational projects including in the early clinic
- Gradually reduce price levels as more grant-funded drugs come on stream

- Move from R&D funding by rewarding past success to funding based on the merits of current projects

Source: Catenion
If R&D funding gradually shifts from high reimbursement levels to direct R&D grants, universities, mid-sized biopharma and not-for-profit players stand to play a larger role, especially if integrated into regional innovation clusters.

Source: Catenion
To finish, three burning questions for you to think about

- Why is Tokyo not one of the leading global hubs for biomedical innovation?
- What does it take to get there?
- Are more Japanese Big Pharmas, VCs and start-ups really the answer?
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