“Progress in the Drug Discovery and Science Technology”

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Chairman, the FPMAJ
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Chemical Biology
The University of Tokyo

“Merrill Lynch Japan Conference 2008” - Value to Growth
Session: Innovation in Drugs, Medical Technology
Date: 13:00-13:50 September 16 (Tuesday), 2008
Venue: Grand Hyatt Tokyo
Growth Driver of a Pharmaceutical Company: New Products / R&D capability

Yamanouchi (1964 ~ 2005): New product driven value-creation management

- Global Launch of Harnal
- Business Diversification: Nutrition products, food and roses business in Japan and the US
- Perdipine and Gaster launched in Japan and licensed out for overseas

Yamanouchi (1964 ~ 2005): New product driven value-creation management

Net sales
- Operating income
- R&D expenses

Red: in-house, Blue: in-license

Horizon  Tathion  Astomin  Pulsan  Yamatetan  Elen  Smancs  Dorner  Lipitor
Balance  Calomide  Anginal  Lanirapid  Frandol  Atock  Harnal  Hypoca  Micardis
Josamycin  Yamacillin  Perdipine  Gaster  Optiray  Farom  Vesicare
Growth in pharmaceutical industry

Paradigm Shift in Pharmaceutical Business

Innovation in science and technology generates new drugs and changes disease structure and pharmaceutical markets

Market: GP market => Specialty market

Unmet Medical Needs

Golden Age

Hypertension
Hyperlipidemia
Thrombosis
Gastric Ulcer
(Life-Style Diseases)

Cancer
Rheumatoid
Mental Diseases
(Senile Diseases)

Biotechnology
Genome
Protein/Antibody etc

New Science Technology

Original products have programmed death => Patent expiration, Launches of generic drugs
Receptor/Ion Channel/Enzyme - Function analysis - Inhibiting/facilitating biological reaction

Pharmaceutical company-led drug discovery: Antagonist, Inhibitor, Agonist

Drug discovery was not made by disease elucidation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pharmacological Action/Biochemistry/Biological Response</th>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Ion channel: Relaxing vascular smooth muscle</td>
<td>Ca antagonist</td>
<td>Potassium stimulant</td>
</tr>
<tr>
<td></td>
<td>Receptor: Vascular constriction</td>
<td>Angiotensin II antagonist</td>
<td>Endothelin antagonist</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>Receptor: Gastric acid secretion</td>
<td>H2 receptor blocker</td>
<td>Gastrin antagonist</td>
</tr>
<tr>
<td></td>
<td>Proton pump: Gastric acid secretion</td>
<td>Proton Pump Inhibitor (PPI)</td>
<td>-</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Enzyme: Cholesterol synthesis</td>
<td>HMGCoA reductase inhibitor</td>
<td>Squalene synthesis inhibitor</td>
</tr>
</tbody>
</table>
Drug Discovery Based on Pharmacology/Biochemistry
Generated Blockbusters (Sales Ranking in 2006)

- High-quality finished products by Improving original products - Best in class
- Preventive medicine for life-style diseases with a lot of patients - GP (Products for PCP)
- Academic promoting with the mega-study results by a large number of MRs – Power marketing

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipitor</td>
<td>Inhibiting HMG-CoA reductase</td>
<td>Hyperlipidemia</td>
<td>12,886</td>
<td>2011</td>
</tr>
<tr>
<td>Plavix</td>
<td>Antiplatlet</td>
<td>Acute coronary syndrome</td>
<td>6,145</td>
<td>2011</td>
</tr>
<tr>
<td>Norvasc</td>
<td>Antagonizing Ca</td>
<td>Hypertension</td>
<td>5,191</td>
<td>2007</td>
</tr>
<tr>
<td>Nexium</td>
<td>Inhibiting proton pump</td>
<td>Gastric ulcer</td>
<td>5,182</td>
<td>2008</td>
</tr>
<tr>
<td>Diovan</td>
<td>Antagonizing angiotensin</td>
<td>Hypertension</td>
<td>4,223</td>
<td>2012</td>
</tr>
</tbody>
</table>
My Drug Discovery

1960 ~ Veterinary pharmacology at Gifu University
       — Study on Sympathetic nerve receptor in cardiovascular of chickens

1964 ~ Pharmacological study at the Central Research Institutes at Yamanouchi Pharmaceutical
       — Add. tests for licensed-in products incl. circulatory organ drug, Lidofrazine etc.
       — In charge of pharmacological action of in-house discovered β-blocker Pulsan

Age of training: Obtaining Study Method, Techniques etc.

1970 ~ — Invented Perdipine, a Ca antagonist for hypertension
       — Invented Lowgan, an α & β blocker for hypertension
       — Invented Hypoca, a Ca antagonist for hypertension

Grasped know-how of drug discovery, gain the trust internally

1975 ~ — Invented Harnal, an α blocker for benign prostatic hyperplasia

Experienced drug discovery and clinical development business

2000 ~ Appointed President & CEO of Yamanouchi Pharmaceutical

2005 ~ Appointed President & CEO of Astellas Pharma

2006 ~ Appointed Chairman of the Board of Astellas Pharma
Clues to Drug Discovery

Inspiration
- Getting idea of new therapy in terms of mechanism of pathogenesis
  - Information from papers, patients and physicians
  - Underground research

Discovery
- Establishing methods of evaluating efficacy by finding disease-related biological response and vital phenomenon
  - Paper information
  - Experimental observation

Invention
- Creating new drugs by technologies such as organic chemistry, biotechnology, antibodies and RNA
  - Teamwork of variety of scientists (chemists, pharmacologists, molecule biologist, drug metabolism etc.)

Exerting Creativity, Experience
Inspiration: Mechanism of Pathogenesis of Benign Prostatic Hyperplasia

Androgenic hormone makes prostate hyperplastic
Anti-androgenic hormone therapy

- Bladder
- Urethra
- Prostate
- Hyperplasia

Androgenic hormone testosteron

5α-reductase

Active form DHT

Receptor

DNA

Nucleus

Protein synthesis

Chestnuts
What is benign prostatic hyperplasia?
- With aging, prostate becomes hypertroplastic and urethra is closed
- One in five men aged over 55 has benign prostatic hyperplasia
- **Dysuria**: Be very difficult and take a long time to urinate
- **Urinary frequency**: Increasing frequency of urination in mid-night, unable to sleep well
- **Incontinence**: Leaking urine, becoming to dislike going out
- **Anuria**: Unable to urinate completely due to alcohol drinking

Patients’ QOL deteriorates

Urinary dysfunction due to benign prostatic hyperplasia is a controversial point
Not pursing the mechanism of prostatic hyperplasia but rather pursing the mechanism of urinary dysfunction will meet the medical needs of urologists.

Existing therapy: shrinking hyperplastic prostate
- Prostatectomy
- How is degree of satisfaction with anti-androgen hormone agents?
  - Insufficient effectiveness to urinary dysfunction
    - Efficacy is not strong
    - Expression of efficacy is slow (over 6 months)
  - Insufficient side effect
    - Sexual function disturbance

According to epidemiology studies, size of prostate does not correlate with urinary dysfunction
Inspiration: Urinary Dysfunction => Constriction in Prostate and Urethra => Involvement of Sympathetic Nerve α Receptor

Inspiring from reports of other researchers and observation in experiments:

- In 1948 Ahlquist
  The concept of α receptor and β receptor
- During 1960s many researchers
  Smooth muscles in urethra and prostate are constricted by stimulation to α receptor
- Around 1975: observation in experiment high dose administration of Lowgan (an α & β blocker) to hypertensive mouse made their abdomen yellow-colored.
  - colored by incontinence
- In 1976 Caine
  Phenoxybenzamine (Non-selective α1 & α2 blockers) improved urinary dysfunctions in BPH patients.
  Expression of a variety of side effects

Structure of Phenoxybenzamine:

Me

HO

Structure of Phenoxybenzamine
Drug Discovery Target: $\alpha_1$- Receptor

Underground Research: Constriction of Prostate Is Caused by $\alpha_1$- Receptor

Paper: In 1975 Langer; $\alpha$ receptor sub-type,
The concept of $\alpha_1$-receptor and $\alpha_2$-receptor

Sympathetic nerve

Noradrenalin

$\alpha_1$- receptor
(smooth muscle)

$\alpha_2$- receptor
(nerve)

Prostate
Urethra
Constriction

$\alpha_1$- receptor

$\alpha_2$- receptor

$\alpha_1$-receptor blocker
1. Invention of Lead Compound
   Exploring a compound with activity and selectivity for drug discovery target
   - Natural Ligand: Lowgan => Harnal
   - Known Compound
   - Screening for Compound Library (Low molecules, natural products, etc.)
   - Drug Design by computer
2. Weak Points in Lead Compound
   - Pharmacological activity is weak
   - There are toxicity and side effects
   - PK (pharmacokinetics), BA (bioavailability) are low
   - Patentability is weak or nothing
3. Optimization of Lead Compound
   By conquering the above weak points, making chemical modification to invent a compound with a characteristics (proper balance) appropriate for developed compound
**Invention: Drug Design for Tamsulosin**

Dream; If a chemical structure differs, pharmacological activity also changes
Experience; Lowgan (α & β blocker) as a privileged structure

Noradrenalin

\[ \begin{align*}
\text{α & β stimulant}\\
\end{align*} \]

Amosulalol (YM-09538, Lowgan)
Racemic body: \(\alpha_1\) & β blocker (1:1)
S body: \(\alpha_1\) blocking activity > β blocking activity
R body: β blocking activity > \(\alpha_1\) blocking activity

Deoxyamosulalol (YM-11133)
\(\alpha_1\) blocking activity > β blocking activity

Tamsulosin (YM617, Harnal®)
Selective \(\alpha_1\) blocker
Chemist’s Dream: If a chemical structure differs, pharmacological activity also changes

Phenoxybenzamine
α1 & α2 blocker

Tamsulosin (Harnal)
Selective α1 blocker: selectivity for prostate (?)

Prazosin (Minipress)
Selective α1 blocker: selectivity for vessel (?)

Terazosin (Hytrin)
Tamsulosin: Selectivity for Organ (Experiment of affinity to receptors)

Tamsulosin is a new potent α1-AR blocker with higher affinity to the receptor of prostate than to blood vessel.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Affinity (ki: nM)</th>
<th>Selectivity for prostate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prostate</td>
<td>Vessel</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>0.04</td>
<td>&gt; 0.47</td>
</tr>
<tr>
<td>Prazosin</td>
<td>0.26</td>
<td>&lt; 0.18</td>
</tr>
</tbody>
</table>
Clinical Results of Tamsulosin

- “Improvement of functional symptoms of benign prostatic hyperplasia”
  - International clinical trials: Japan, Europe, the USA and China
    Favorable results with repeatability
  - Efficacy: Highly effective to urinary disturbance symptoms, improving QOL, immediate effect (within two weeks)
  - Side effects: Blood pressure unchanged, few orthostatic hypotension (as same in case of placebo)
  - Easy to administer: Sustained release curbing Cmax, single daily dosing, fixed dose from the first dose

■ Launched in 1993: Question from urologists; What is the molecular structure of lower urinary tract selectivity in Tamsulosin?
Classification of $\alpha_1$ Receptor Subtype (After 1980)

1974, Langer et al.

Pharmacological evaluation

1988, Minneman et al. (Binding Assay)

Prostate

Vessels

Gene Cloning (around 1990)
Distribution of α1-receptor Subtype in Human Prostate (Urethra)

- Study by RNase Protection Assay and ISH

Volume of mRNA in α₁ receptor subtypes (pg)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>α₁a</th>
<th>α₁b</th>
<th>α₁d</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hyperplastic Prostate (%)</td>
<td>5.6</td>
<td>0.5</td>
<td>3.1</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>(63)</td>
<td>(6)</td>
<td>(31)</td>
<td></td>
</tr>
<tr>
<td>Hyperplastic Prostate (%)</td>
<td>49.7</td>
<td>0.6</td>
<td>9.2</td>
<td>60.3</td>
</tr>
<tr>
<td></td>
<td>(85)</td>
<td>(1)</td>
<td>(14)</td>
<td></td>
</tr>
</tbody>
</table>


* All α-receptor subtypes are α₁a mRNA in proximal urethra in men
Tamsulosin is selectivity for $\alpha_{1A}$-AR Subtype

<table>
<thead>
<tr>
<th>Drug</th>
<th>Affinity (nM)</th>
<th>$\alpha_{1A}$-AR selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamsulosin</td>
<td>0.03 &gt; 0.87</td>
<td>29</td>
</tr>
<tr>
<td>Terazosin</td>
<td>8.1 &lt; 1.9</td>
<td>0.23</td>
</tr>
</tbody>
</table>
α₁ receptor’s Distribution and Involvement in Diseases: Prostate Selective α₁A Receptor Blocker

- Bladder
- Sympathetic nerve
- Prostate
  - Constriction
  - α₁A receptor
  - α₁B receptor
  - α₁C receptor
  - α₁D receptor

Noradrenalin

Inhibition

A1 Blocker Harnal

Selectively acting on prostate (α₁A), but not acting on vessels (α₁B) (without lowering BP as a side effect)

1988, Minneman

Urinary disturbance

Prostate Hyperplasia

Elevation of blood pressure

High blood pressure
What did I learn from the success of Harnal? (Investing in Genomic Drug Discovery)

**Discovery of Harnal**
- Pharmacological function analysis
- Prostate constriction: $\alpha_1$ receptor

**Compound Selection**
- Optimize a lead compound (Lowgan ($\alpha$ & $\beta$ blocker)) based on chemist’s experience and guess

**What I learned**
- Reverse pharmacology
- Molecule biological receptor
- Cloning analysis
- Prostate receptor; $\alpha_1A$ receptor

**Drug Discovery Target**
- Screen a variety of lead compounds with HTS from a variety of compound library
- Optimizing them by utilizing combinatorial chemistry
- Drug design by using CAD

**Slow**
- Obtaining a variety of candidate compounds at one time (exclusivity)

**Speed**
**Genomic Drug Discovery in 1990s:**
Why super-selective α1A receptor blocker could not be a drug?

<table>
<thead>
<tr>
<th></th>
<th>Selectivity for α1A (compared to α1B)</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rec 15/2739</td>
<td>178</td>
<td><img src="image1.png" alt="structure1" /></td>
</tr>
<tr>
<td>Recordartsi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ro 700-004</td>
<td>60</td>
<td><img src="image2.png" alt="structure2" /></td>
</tr>
<tr>
<td>Roche Bioscience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>30</td>
<td><img src="image3.png" alt="structure3" /></td>
</tr>
<tr>
<td>Yamanouchi</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
News on Genome Analysis in 2000

Jun. 26, 2000
Completion of human genome draft sequence analysis declared

Feb. 15 - 16, 2001
Results of the analysis published in ‘Nature’ and ‘Science’

Approx. 3 billion base pairs
Approx. 22 thousand genes

Discovery of genes relating to diseases
Discovery of new target molecules
Progress in tailor-made medicine
Disease to Gene: Exploring Target Genes from Diseases

Population survey
Clinical data
Genotype
SNPs (single nucleotide polymorphisms)

Model experiment
Model animals
Comparative genome analysis
Knockout mouse

Gene function analysis

Advanced proteomic analysis of gene expression profile

Identifying and exploring drug targets

Exploring targets from phenotype (PTOG) ‘Phenomics’
Changes in Cancer Treatment

■ Cancer has been the No.1 cause of death of Japanese since 1981
  One in three dies of cancer
■ Anti-cancer drugs: anti-metabolites, alkylating agents, platinum-containing drugs, anti-cancer antibiotics, etc.
  They kill not only cancer cells but normal cells => Serious side effects
■ Surgery, radio-therapy were mainstream more than drug therapy
  The market for anti-cancer drugs were small

■ Our approach to our research in 1990:
  Hormone sensitive cancer (few side effects)
  Lyase inhibitor, aromatase inhibitor

■ Research from around 1995:
  ● Progress in the research on cancer genes and cancer suppressor genes
  ● Progress in the molecular biological research such as signaling in cancer and angiogenesis
  ● Development of signaling inhibitors, antiangiogenetic agents and metastasis suppressors
  ● Progress in the research on antibody
  ● Launch of molecular targeted drug: potentiality of blockbuster
## Sales of Molecular Targeted Anti-cancer Drugs
**(In 2006, 100 Million US Dollar)**

<table>
<thead>
<tr>
<th>Brand</th>
<th>Company</th>
<th>Sales (Million US Dollar)</th>
<th>Growth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1 Rituxan (CD20)</td>
<td>Roche (Genentech)</td>
<td>3,871</td>
<td>15</td>
</tr>
<tr>
<td>*2 Herceptin (HER-2/ne u)</td>
<td>Roche (Genentech)</td>
<td>3,142</td>
<td>81</td>
</tr>
<tr>
<td>3 Glivec</td>
<td>Novartis</td>
<td>2,554</td>
<td>18</td>
</tr>
<tr>
<td>*4 Avastin (VEGF)</td>
<td>Roche (Genentech)</td>
<td>2,370</td>
<td>76</td>
</tr>
<tr>
<td>*5 Erbitux (EGF-R)</td>
<td>BMS + Merck (Germany)</td>
<td>1,090</td>
<td>58~55</td>
</tr>
<tr>
<td>6 Tarceva</td>
<td>Roche</td>
<td>650</td>
<td>105</td>
</tr>
<tr>
<td>7 Iressa</td>
<td>AstraZeneca</td>
<td>237</td>
<td>-13</td>
</tr>
<tr>
<td>8 Velcade</td>
<td>Millennium (Excl. sales by J&amp;J)</td>
<td>221</td>
<td>15</td>
</tr>
<tr>
<td>9 Sutent</td>
<td>Pfizer</td>
<td>219</td>
<td></td>
</tr>
<tr>
<td>10 Nexavar</td>
<td>Bayer</td>
<td>165</td>
<td></td>
</tr>
</tbody>
</table>

*Antibody drug

Source:

Market growth:
Drugs for specialty market > Drugs for primary care market

Source: IMS Health MIDAS (05/06/2007)
How to Strive in Response to the Changes in the Market

The Industry until 2005

Mass Market
- Diseases in a large number of patients (ex. hypertension)
- Targeting PCP market
- Seeking the number of details (SOV)
- Power marketing
- Centering on low molecular compounds

Power game
Simple and scale game

The Industry after 2005

New Market
- Diseases in a small number of patients (ex. cancer)
- Targeting experts (specialists)
- Marketing with high expertise
- Responding to tailor-made medicine
- Progress in polymer molecules, biotechnology drugs

Change of a leading player
Complicated and diversified game
<table>
<thead>
<tr>
<th>Date</th>
<th>Acquiring Company</th>
<th>Acquired Company</th>
<th>Price ($million)</th>
<th>Therapy, area, technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/10/07</td>
<td>Eisai</td>
<td>MGI Pharma</td>
<td>3,923</td>
<td>Cancer</td>
</tr>
<tr>
<td>11/26/07</td>
<td>Astellas</td>
<td>Agensys</td>
<td>387(+$150M)</td>
<td>Cancer, antibody</td>
</tr>
<tr>
<td>11/21/07</td>
<td>GSK</td>
<td>Reliant</td>
<td>1,650</td>
<td>CV, DDS</td>
</tr>
<tr>
<td>11/15/07</td>
<td>Pfizer</td>
<td>Coley</td>
<td>164</td>
<td>Cancer, vaccine immunology</td>
</tr>
<tr>
<td>10/5/07</td>
<td>Wyeth</td>
<td>Haptogen</td>
<td>N/A</td>
<td>Protein, antibody</td>
</tr>
<tr>
<td>9/27/07</td>
<td>BMS</td>
<td>Adnexus</td>
<td>430+$75M</td>
<td>Cancer, antibody</td>
</tr>
<tr>
<td>7/25/07</td>
<td>Merck</td>
<td>NovaCardia</td>
<td>350</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>6/6/07</td>
<td>Amgen</td>
<td>Alantos</td>
<td>300</td>
<td>Diabetes</td>
</tr>
<tr>
<td>6/4/07</td>
<td>Amgen</td>
<td>Ilypsa</td>
<td>420</td>
<td>Renal dialysis</td>
</tr>
<tr>
<td>4/17/07</td>
<td>AstraZeneca</td>
<td>MedImmune</td>
<td>15,200</td>
<td>Infectious diseases, antibody, vaccine</td>
</tr>
<tr>
<td>3/22/07</td>
<td>Eisai</td>
<td>Morphotek</td>
<td>325</td>
<td>Antibody</td>
</tr>
<tr>
<td>2/1/07</td>
<td>AstraZeneca</td>
<td>Arrow</td>
<td>150</td>
<td>Infectious diseases</td>
</tr>
<tr>
<td>2/1/07</td>
<td>Pfizer</td>
<td>Biorexis</td>
<td>N/A</td>
<td>Diabetes</td>
</tr>
</tbody>
</table>
**Articles on iPS Cells**

**Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors**

Katsuhiko Hayashi, Katsumi Taniguchi, Katsuhiko Shinya, Takashi Yamanaka, and Jun-ichi Yamanouchi

EXPERIMENTAL

Cell, Vol 131, 861-872, 30 November 2007

**Generation of Pluripotent Stem Cells from Adult Mouse Liver and Stomach Cells**

Tadanori Akiyama, Takeshi Toyokuni, Masahide Ueda, Ichiro Chiba, Shigeki Tanaka, and Ken Sakakibara

EXPERIMENTAL

Cell, Vol 131, 873-882, 30 November 2007

**CORRECTED 1 AUGUST 2008: SEE LAST TWO PAGES**

**REPORTS**

Science 1 August 2008: Vol. 321. no. 5889, pp. 699 - 702

**Corrections**


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**REPORTS**

Science 1 August 2008: Vol. 321. no. 5889, pp. 699 - 702

**CORRECTIONS**

Cell, Vol 132, 1-2, 7 August 2008
Advancement in Pluripotent Stem Cell Research:
Lead to an innovation to medicinal development and medical technology

In August 2006, Shinya Yamanaka (Kyoto Univ.) generated iPS cells from mouse fibroblasts.

In November 2007, Shinya Yamanaka (Kyoto Univ.) and James Thomson (Univ. of Wisconsin) generated iPS cells from human adult fibroblasts.

ES cell (Embryonic stem cell)

- Zygote → Blastocyst → ES cell

SCNT (Somatic cell nuclear transfer)

- Somatic cell → Enucleated oocyte → Blastocyst → ES cell

iPS cell (induced pluripotent stem cell)

- Somatic cell → Transfect four genes into the cell by viral vectors (Oct3/4, Sox2, c-Myc, Klf4) → iPS cell

Immune system rejection occurs
Ethical objection against the destruction of human embryos

Avoid from immune system rejection (genetically identical to the somatic cell donor)
Ethical concerns about requiring a large number of donated eggs

No ethical concerns (not require eggs or embryo-derived cells)
No immunological rejection

Application in the pharmaceutical industry

- In August 2006, Shinya Yamanaka (Kyoto Univ.)
  iPS cells were first generated from mouse fibroblasts
- In November 2007, Shinya Yamanaka (Kyoto Univ.)
  James Thomson (Univ. of Wisconsin)
  iPS cells were generated from human adult fibroblasts
1. Drug manufacturing: undertaken by biotech companies?
   Protein expression in iPS cells: the production of humanized protein therapeutics
   The problem of safety (risk of virus infection), quality control, and profitability ??

2. Regenerative medicine:
   For the production of clinical-grade cell lines, efficient culture system, safety validation, and strict quality control would be needed. Who make it business?

   1) Autologous cell therapy
      ● Neural stem cell (Perkinson’s disease)  
      ● Hematopoietic stem cell (Leukemia)
      ● Pancreatic β cell (Diabetes)
      ● Epidermal cell (sheet, Severe burn injury)  
      ● Corneal cell (sheet, Corneal injury)
      ● Cardiomyocyte (sheet, Myocardial infarction)

   2) Allogeneic cell therapy
      ● Construct an HLA-haplotype bank of iPS cell lines, like the bone-marrow banks. 
      Immunosuppressant is necessary.

3. Drug discovery: pharmaceutical companies

   A cell bank size of only 50 iPS cell lines would be able to find a three-locus match in 90.7% of the Japanese population, if established from HLA-homozygous donors for HLA-A, B and DR haplotypes. (Nature Biotech.26,739,2008)
Application of Human iPS Cells to Drug Discovery (1)
Screening and Lead Optimization

Drug discovery bottleneck: Species difference
The problems of commonly-used human cells:
- **Cell lines** (limited to tumor cell lines or transformed derivatives of native tissues)
- **Primary culture** (limited life span and cellular heterogeneity)

Establishment of various human (normal) cells

1. **Drug screening**
   Screening for drug efficacy using various human cells differentiated from human iPS cells

2. **Toxicity evaluation**
   Toxicity screening using cardiomyocytes (QT prolongation), hepatocytes and kidney cells differentiated from human iPS cells

Overcome the problem of species difference
- Improvement of success probability
Challenge to the solution for unmet medical needs
Application of patient-derived iPS cells

Disease-specific iPS cells:
Analysis of pathogenesis and pathophysiology,
Discovery of novel drug target
Cell-based disease model: drug screening

Lead to the discovery of innovative medicines for the disease whose mechanisms of pathogenesis and progression remain to be clarified.
Japan’s Policy for Fostering the Pharmaceutical Industry

Prime Minister Shinzo Abe’s Policy Speech in September 2006
- Promotion for Innovation
- Pharmaceuticals were given a top priority: The first announcement for expecting for the pharmaceutical industry

Proposals from the Pharmaceutical Industry
- Investment in R&D at life-science area
- Promotion of collaborative R&D among the industry, the government and the academia
- Improvement of the environment for promoting clinical trials
- Improvement of drug approval and review system
- Establishment of a drug pricing system reflecting the value of drugs

Dialogue between the Government and the Private Sector
- Ministries: Cabinet Office, MEXT, MHLW, METI
- Industry: FPMAJ, JPMA, PhRMA, EFPIA
- Education, Research Organizations: National Center, University, etc.
5-Year Strategy for Creating Innovative Drugs and Medical Devices* (1) (The Cabinet Office, MEXT, MHLW, METI)

- Providing the people with the highest level of drugs and medical devices
- Make the pharmaceutical and medical device industry a growth engine for Japan
- The policy aiming at Japan’s drug development ahead of foreign countries and Japan’s participating in simultaneous global development

1. Concentrated infusion of research funds
   - Expansion of giving a priority on budget (MHLW FY2009 budget request; about 33.1 billion yen, an increase of 21.1% compared to the previous year)
   - The Council of Promoting Health Research
   - Specific District for Cutting-edge Medical Development (Super Specific District)

2. Fostering Venture Company, etc.
   - Expansion of research fund
   - Sharing facilities and equipments
   - Utilizing human resources
   - Utilizing “Angel Taxation system”

*Compiled in April 2007, revised in May 2007
3. Improvement of the Environment for Clinical Research and Clinical Trials
   - Bases of global clinical research
   - Medical cluster (Medical collaborative research facility among the government, the industry and the academia)
   - Bases of translational research
   - Bases of regenerative medicine
   - Fostering human resources supporting clinical trials

4. Collaboration with Asia
   - Joint research on important diseases
   - Joint research on utilizing East Asian data

5. Speeding up the Approval Review, Improving Quality
   - Shortening the examination period
   - Doubling the number of reviewers
   - Joint consultation for clinical trials among the reviewing authorities in Japan, the USA and Europe

6. Appropriate Evaluation for Innovation
   - FPMAJ’s Proposal for new drug pricing system

7. Dialogue between the Government and the Private Sector
   - Enhancing collaboration among the related ministries, research institutions and the industry
Establishment of the Council for Promotion of Health Research
Developing Innovative Drugs and Medical Devices, and Promoting
the Translational Research and the Clinical Research by Utilizing the Fruits of Basic Research

The Council for Promotion of Health research
(The Cabinet Office Secretariat)

Minister of Education
Minister of Health, Labor and Welfare
Minister of Economy, Trade and Industry
Intellectuals

- Compiling comprehensive strategy
- Setting up the policy of budget request
- Unifying public offering and evaluation
- Compiling unified policy for investing research funds

Ensuring intensively research funds

Integrated operation of research funds
Ensuring and enforcing the budget for super specific district

Implementing from FY2009

The Council for Science and Technology Policy
Dialogue for Creating New Drugs between the Gov. and the Private Sector

Reflection to opinions from the industry

Budget for Innovative Technology Life science Promotion strategy

Council on Promotion of BT Strategy between the Gov. and the Private Sector

Promotion of comprehensive biotechnology
Cutting-Edge Medical Development Specific District
(Super Specific District)

- **Characteristics:** This is not a specific district in line with the existing administrative district but one focusing on certain theme
  (Complex with a network linking researchers in plural bases)

- **Public Offering Subjects:**
  1. Application of iPS cells
  2. Regenerative medicine
  3. Development of innovative medical devices
  4. Development of innovative biopharmaceuticals
  5. R&D for drugs and medical devices used for important treatment and diagnosis for the people’s health

- **Contents to Implement:**
  - Investing comprehensively and efficiently research funds, matching among the related ministries and agencies
  - Regulatory consultation from the development stage, etc.

- **Research Term:** Around 5 years from FY2009
- **The Number of Research Subjects to Be Adopted:** Around 20 complexes
- **Schedule:**
  - Public offering started on July 25, 2008, deadline on September 12, to determine the subjects in the fourth week of October

- **Evaluation:** Evaluation Committee at the Council of Promoting Health Research
Cooperation between Industry and Academia Network for Drug Discovery

-In industry: Few researchers know diseases
-In academia: Few researchers know drug discovery

-Drug discovery aimed at meeting the unmet medical needs through the utilization of patients’ genomic information
Cooperation between Industry and Academia: AK Project (Project by Astellas and Kyoto University)

Co-research at the innovation center for immunoregulation technologies and drugs of next generation (Funded by Japan Science and Technology Agency)

1. Selection of drug targets suitable for development
   
   Kyoto Univ.: Utilization of research based on the disease and clinical practice
   Astellas: Utilization of established discovery technologies and accumulated database (experience)

2. Long-term relationship
   - Periods: 10 years (3 - 4 - 3 years)
   - Budgets: 0.6-1.0 bil/year
   - Facilities: Aggregated Lab. (Kyoto Univ.), Satellite Lab. (Astellas)

3. Proper intellectual property management

4. Human resources development: Drug discovery researchers, and doctors who have interest in pharmaceutical R&D

Sttd: March 2007
Operation of AK Project

Translational Research Center (Kyoto Univ. Hospital)

Disease

Prof.

Patients

POC

AK Co-research at the innovation center (Kyoto Univ.)

Allergy/Inflammation

Immunosuppressant

Technology support

Cancer/transplant/autoimmunity

Signal/antibody

选Satellite laboratory (Astellas)

Selection of drug target

Technology support

Prof.

Prof.

Prof.
明日は変えられる。