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   (2) Companion Diagnostics
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2. Strategy for Establishing Personalized Medicine

Mitsuru Watanabe,
Member of Managing Board and Executive Officer,
Head of R&D

(1) Outline of Technology Strategy
(2) Companion Diagnostics
(3) Founded Course at Kobe University Graduate School
   (Assessment of Clinical Testing)
Overall Medical Market

Medical Treatment

In vivo Diagnosis

Personalized Medicine

Primary Care

In vitro Diagnosis (IVD)

Emerging Markets

Disease Prevention based on testing data

Strengthen the performance/ function of measurement platform

ICT utilization

Establishing personalized medicine through CDx

Organic growth in existing IVD fields
Disease Management and Personalized Medicine

Disease Management

<table>
<thead>
<tr>
<th>Primary Prevention</th>
<th>Medical Examination</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Recurrence Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent disease onset</td>
<td>Diagnose without error</td>
<td>Avoid unnecessary treatment</td>
<td>Prevent recurrence</td>
<td></td>
</tr>
</tbody>
</table>

Focus on processes

Personalized Medicine

Focus on patients

Prevent disease onset, Diagnose without error, Avoid unnecessary treatment, Prevent recurrence.
Strengthening the Technology Platform

Personalized Medicine
Theranostics
Companion Diagnostics

Primary Care
Emerging Markets
Advanced Markets

Cancer, hematology, central nervous system, cardiovascular disease

Cells
Genes
Proteins
Biochemicals

DNA chip
OSNA
FCM
Thrombosis, hemostasis
Chemiluminescence
Bio-simulator
Non- or minimally invasive

FCM: Flow Cytometry

Technology Platforms

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Primary Care with ICT

Hospital A
- Medical practice details
- Tests
- Drugs

Cloud
- Provision as applications
- New Information and Knowledge Simulation

Hospital B

Medical office

Health check Institution

Home
2. Strategy for Establishing Personalized Medicine

(1) Outline of Technology Strategy
(2) Companion Diagnostics
(3) Founded Course at Kobe University Graduate School
   (Assessment of Clinical Testing)
What is Companion Diagnostics?

Companion diagnostics (CDx) is an effective approach for realizing personalized medicine that involves development of therapeutic and diagnostic reagents in parallel.

Benefits and drawbacks of CDx

- Reduced development risk and development time
- Limited Target patients

Patient benefit:
Early realization of personalized medicine
Biomarkers in FDA-Approved Drugs and Companion Diagnostics

(FDA-approved drugs)

- Drugs with description of biomarkers in the package insert
  (Efficacy prediction and patient stratification for conventional drugs)

<table>
<thead>
<tr>
<th>Year</th>
<th>Count</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>69</td>
<td>+64%</td>
</tr>
<tr>
<td>2012</td>
<td>113</td>
<td></td>
</tr>
</tbody>
</table>

Examples
- Herceptin
- Glivec
- Erbitax
- Tarceva

Tegretol
- Warfarin

- Diagnostic testing required prior to administration (companion diagnostics)

<table>
<thead>
<tr>
<th>Year</th>
<th>Count</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>2012</td>
<td>16</td>
<td>+400%</td>
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</table>

Examples
- Xalkori
- Zelboraf
- Vectibix
- Sprycel

- Erbitax
- Herceptin
- Glivec

Ref. Bayer HealthCare; Molecular Med TriCon, Feb. 14th, 2013
Situation in Japan

<table>
<thead>
<tr>
<th>Target disease</th>
<th>Product name (generic name)</th>
<th>Diagnostic testing to predict efficacy (NHI points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Herceptin (Trastuzumab)</td>
<td>Overexpression/proliferation of HER-2 proteins/genes in cancer cells</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Iressa (Gefitinib)</td>
<td>Mutation of EGFR genes in cancer cells (2,000 -&gt; 2,100)</td>
</tr>
<tr>
<td></td>
<td>Tarceva (Erlotinib)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Xalkori (Crizotinib)</td>
<td>Existence of ALK chimera genes in cancer cells (6,520)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Erbitax (Cetuximab)</td>
<td>No mutation of KRAS genes in cancer cells (2,000 -&gt; 2,100)</td>
</tr>
<tr>
<td></td>
<td>Vectibix (Panitumumab)</td>
<td></td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>Glivec (Imatinib)</td>
<td>Existence of BCR-ABL Chimera genes in cancer cells (1,200/2,000)</td>
</tr>
<tr>
<td></td>
<td>Tasigna (Nilotinib)</td>
<td></td>
</tr>
<tr>
<td>Adult t-cell leukemia</td>
<td>Poteligeo (Mogamulizumab)</td>
<td>Existence of CCR4 protein in lymphatic tissue or blood (10,000)</td>
</tr>
</tbody>
</table>
Companion Diagnostics: Issues

Drug Development Process

- Preclinical
- Phase I
- Phase II
- Phase III
- Application for Approval
- Launch

1) Determine the starting point

IVD Development Process

- Marker discovery
  Assay system evaluation
- Diagnostic kit development
- Clinical trial
- Application for Approval
- Launch

2) Establish seamless process

Strength
Timing of Start

1) Early-Stage Collaboration (Investigational New drugs)

Drugs
- Preclinical
- Phase I
- Phase II
- Phase III
- Application for Approval
- Launch

Marker discovery
Assay system evaluation
Diagnostic kit development
Clinical trial
Application for Approval
Launch

2) Late-Stage Collaboration (approval/developed drugs)

Drugs
- Phase I
- Phase II
- Phase III
- Application for Approval
- Phase II
- Phase III
- Approval

Marker discovery
Assay system evaluation
Diagnostic kit
Clinical trial
Application for Approval
Sysmex’s Approach

1) Assay Lab (BMA Lab)

2) Use of Bioinformatics
# Technology Platform Necessary to CDx

<table>
<thead>
<tr>
<th>Current</th>
<th>Near Future</th>
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<tbody>
<tr>
<td>(Biopsy)</td>
<td>(Liquid Biopsy)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Genes</th>
<th>PCR</th>
<th>(High-Sensitivity) PCR Clinical Sequencer</th>
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</thead>
<tbody>
<tr>
<td>Proteins</td>
<td>IHC / ISH</td>
<td>Chemiluminescence (HISCL) Thrombosis/Hemostasis (CS)</td>
</tr>
<tr>
<td>Cells</td>
<td>–</td>
<td>FCM (Cell function analysis)</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- IHC: Immunohistochemistry
- ISH: In Situ Hybridization
2. Strategy for Establishing Personalized Medicine

(1) Outline of Technology Strategy  
(2) Companion Diagnostics  
(3) Founded Course at Kobe University Graduate School  
   (Assessment of Clinical Testing)
What is Assessment of Clinical Testing Medicine?
- The gathering of clinical epidemiological evidence concerning basic evaluations and comparisons of clinical test, as well as the utility in diagnosis and disease state monitoring
- The provision to clinical practices of verification of the availability of testing methods as well as efficient use of clinical test based upon that evidence
Diagnosis for Rheumatoid Arthritis through Serum Cytokine Measurement

Current research: Diagnosis for Early-stage rheumatoid arthritis

Multiparameter Cytokine Measurement

Inflammatory

Anti-inflammatory

Sensitivity: The probability that patients known to have the disease will test positive for it.
Specificity: The probability that patients known not to have the disease will test negative for it.
Summary

- Focusing chronic inflammation, which is caused by a number of diseases, including lifestyle diseases
- Providing of importance of new testing/value
- Establishing evidence-based diagnostics

Chronic inflammation

- Diabetes
- Metabolic Syndrome
- Hyperlipidemia
- Chronic nephropathy
- NASH
- Etc.

Cardiovascular Disease
- Stroke
- Ischemic heart disease
- Etc.

Cancer

Central Nervous System Disease
- Alzheimer’s disease
- Parkinson’s disease
- Etc.

Autoimmune Disease
- Rheumatism
- Psoriasis
- Etc.

NASH: Non-Alcoholic Steatohepatitis
3. Progress on Development Themes

Kaoru Asano,
Executive Officer,
Executive Vice President of the R&D Strategic Planning Div.

(1) New Product Launch (New Products)
(2) Progress Status of Development Theme at Practical Stage
New Models for Immunological Test (Fully Automated Immunoassay Analyzer HISCL®-5000)

New model focusing on midrange and high-end models, which advance functionality and speed.

- **Rapid measurement**
  - Reaction to all parameters in 17 minutes
  - Simultaneous measurement of 24 parameters (max)

- **Highly sensitive measurement**
  - Uses CDP-Star® to achieve a highly sensitive measuring system

- **Minimized samples**
  - Sample amount used for all parameters: 10-30μL

- **High usability**
  - Continuous measurement
  - Flexible connectivity to transport systems
  - Reagent controllability through RF-ID

Continuous measurement: Measurement is conducted continuously, without interruptions to reagent supply
HISCL® Reagents

Infectious disease
- HBs antigen
- HBc antibody
- HBe antigen
- HBe antibody
- HIV antibody
- HIV Antigen antibody
- HCV antibody
- HCV Gr.
- TP antibody

Tumor markers
- AFP
- CEA
- PSA
- CA 19-9
- CA 125
- Pro-GRP
- CK19F

Coagulation molecular markers
- TAT
- PIC
- TM
- t PAI · C

Cardiovascular disease
- Nt-pro BNP

Thyroid disease
- FT3
- FT4
- TSH

Other
- FRN
- Insulin
- HCG
- LH
- FSH

Hepatitis
- M2BPGi

Infectious disease
- HTLV-I antibody

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Liver Fibrosis Markers

Antigen/Antibody Reaction (Conventional technology)

- Detected protein (antigen)
- Magnetic particle
- Antibody

Lectin–Carbohydrate Chain Reaction (New technology)

- Glycosylation
- Magnetic particle
- Lectin

ALP: Alkaline Phosphatase

A serum “sweet-doughnut” protein facilitates fibrosis evaluation and therapy assessment in patients with viral hepatitis

Although liver fibrosis reflects disease severity in chronic hepatitis patients, there has been no simple and accurate system to evaluate the therapeutic effect based on fibrosis. We developed a glycan-based immunoassay, FastLec-Hepa, to fill this unmet need. FastLec-Hepa automatically detects unique fibrosis-related glyco-alteration in serum hyperglycosylated Mac-2 binding protein within 20 min. The serum FastLec-Hepa counts increased with advancing fibrosis and illustrated significant differences in medians between all fibrosis stages. FastLec-Hepa is sufficiently sensitive and quantitative to evaluate the effects of PEG-interferon-α/ribavirin therapy in a short post-therapeutic interval.

http://www.natureasia.com/ja-jp/srep/abstracts/42129

Note: Degrees of fibrosis

Cirrhosis

Stages of liver fibrosis

Featuring high reliability established in the skills of the previous model, these hematology analyzers accommodate expanding demand in emerging markets.

- Touch panel for better operability
- Increased specimen memory
- Space-saving
- Compatible with in-hospital networks and SNCS®
- Silent design

SNCS : Sysmex Network Communication Systems
Expanding Application of OSNA® to Stomach Cancer

Clinical trial results for stomach cancer

<table>
<thead>
<tr>
<th>N=394 lymph nodes</th>
<th>2mm space histopathological examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>OSNA® method</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>45</td>
</tr>
<tr>
<td>Negative</td>
<td>9</td>
</tr>
</tbody>
</table>

Sensitivity: 0.833
Specificity: 0.959
Concordance rate: 0.942

Approved by the Ministry of Health, Labor and Welfare as of July 12, 2012

RD-100i gene amplification detector

LYNOAMP® BC
(Same reagent for breast and colon cancer)
3. Progress on Development Themes

(1) New Product Launch (New Products)
(2) Progress Status of Development Theme at Practical Stage
1) Cervical Cancer Screening
Cervical Cancer Screening: Diagnostic Flow

Cytological Issues

- Low sensitivity (44%~78%)
- Screening results can vary according to the cytologist.
- Shortage of cytologists (especially in emerging markets)

Strong need for automation
3-(2)-1

Relationships between HPV Infection and Cervical Cancer

- **No. of Women**: 10,000
  - Target group: Young women

- **Invasion stage**: CIN1 ≤3,000
  - (Approx. 30% among the young women)

- **Pre-cancerous stage**: CIN2/CIN3
  - 30
    - (1 ~ 6% among the infected)

- **Cancerous stage**: Invasive carcinoma
  - 0.3
    - (0.01% among the infected)

- **Spontaneous Recovery**:
  - 90% (Several weeks ~2 years)
  - 5% (Several years ~ ten-odd years)
  - Few Percent (Several years)

- **Complementary**
  - **Cytology**: ~60 million specimens/year (USA)
  - **HPV Test**: 10 ~ 20 million specimens/year (USA)

CIN: cervical intraepithelial neoplasia
3.-2-1) Cervical Cancer Screening System

Newly-Developed Technologies

1) Pretreatment technology for LBC specimens
   Technology for dissociating cells while maintaining their morphology

2) DNA staining and FCM technology
   Technology for measuring cell diameter, nuclear diameter, and nuclear DNA content

3) Analyzing technology
   Technology for detecting abnormal cells based on original parameters

Development for these technologies

LBC: liquid-based cytology
1) Pretreatment Technology for LBC specimens

- **Cell dispersion (mucolytic agent, mechanical stirring, etc.)**
  Dissociating cell clusters while maintaining cell morphology

- **Concentration of cell density (Using a metal micropore filter)**
  Concentration of epithelial cell density (approximately 10X)
  Reduce the amount of coexisting material, such as blood components and cell debris.

  ![Image of cell dispersion and concentration process](image)
Those cells are exposed to a narrow, long laser beam to measure the nuclear DNA content, cell diameter, and nuclear diameter of individual cells. All of the data acquired is then processed, and the characteristics of sample are analyzed by statistical methods.

DNA staining

Flow cytometry

Signal reception

3 parameters

Pre-treatment with RNase

Epithelial cells stained with intercalator

Sensor part
(expanded View)

(Wavelength $\lambda = 488$nm)

Laser

Signal data acquired from a single cell

Data on cell & nucleus length

Signal intensity

Fluorescent signal area || Nuclear DNA content

Forward-scattered light

Fluorescent signal

→ Cell length (flow direction)

→ Nuclear diameter and nuclear DNA content
3) Analyzing Technology
(Signal Waveform Processing and Judgment Algorithms)

1. Analysis of cell morphology

\[ \text{NCI}_{x} = \frac{\text{Nuclear diameter (N)}}{\text{Cell length (C)}} \]

2. Analysis of DNA content

\[ \text{CPI}_{x} = \frac{\text{Cell numbers in Region B}}{\text{Cell numbers in Region A}} \]

[CPI: Cell Proliferation Index]
## Evaluation of This System

High sensitivity and specificity in detection of moderate or higher-level pathological changes

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>n</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100.0%</td>
<td>15 / 15</td>
</tr>
<tr>
<td>Specificity</td>
<td>85.1%</td>
<td>841 / 988</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Existing testing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>15</td>
</tr>
<tr>
<td>Negative</td>
<td>147</td>
</tr>
<tr>
<td>This system</td>
<td>162</td>
</tr>
<tr>
<td>Positive</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>841</td>
</tr>
<tr>
<td>Total</td>
<td>841</td>
</tr>
</tbody>
</table>

Positive : CIN2 or above  
Negative : CIN1 or below (including normal)
Future Plans

- Japan
  1. Organization for working groups
  2. Implementation of clinical evaluation
  3. Pharmaceutical application

- Outside Japan
  Implementation of clinical evaluation in fiscal 2013 (under preparation)
2) Glucose AUC
(Minimally Invasive Interstitial Fluid Extraction Technology)

AUC : Area Under the blood Concentration time curve
Glucose Monitoring System without blood sampling

Measures glucose area under the curve (AUC) after meal or glucose load

Special features
This system makes it possible to measure glycemic excursion simply and painlessly without blood sampling (Simply by affixing the gel patch after microneedle pretreatment.)
Evaluation of Clinical Utility

1. Screening for early stage diabetes
   Can it easily find early stage diabetes (impaired glucose tolerance) during health checkups?

2. Determining the efficacy of diabetes treatments
   Can the efficacy of diabetes treatments be monitored?

3. Application to the individualized dietary therapy
   Can it be used to determine the optimal diets for individuals?
1) Screening for Early Stage Diabetes

Evaluation Protocol in routine health checkups

- **Blood/Urine sampling**
- **SMBG (1 h) as a reference method**
- **Urine sampling**

**Meal (15 min)**
- **Normal activity at workplace**

- **Stamp**
- **Attach hydrogel patch**
- **glucose AUC measurement (ISF extraction)**
- **Hydrogel patch removal (2 h) / Measurement**

(57g carbohydrate, developed by Japan Diabetes Society test meal working group)

SMBG: Self-Monitoring of Blood Glucose
Screening Performance Using Glucose AUC

Glucose AUC

<table>
<thead>
<tr>
<th>AUC by MIE T (mg·h/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
</tr>
<tr>
<td>400</td>
</tr>
<tr>
<td>300</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

NGT: Normal Glucose Tolerance
IFG: Impaired Fasting Glycaemia
IGT: Impaired Glucose Tolerance

NGT: Normal
IFG: Impaired Fasting Glycaemia (early stage diabetes)
IGT: Impaired Glucose Tolerance

NGT: Normal Glucose Tolerance
IFG: Impaired Fasting Glycaemia
IGT: Impaired Glucose Tolerance

Copyright by Sysmex Corporation
2) Determining the Efficacy of Diabetes Treatments

Subjects: 8 Type-2 diabetes patients being administered an antidiabetic drug (Sitagliptin)

Evaluation protocol envisaging clinical use

75g oral glucose tolerance test (OGTT) → Sitagliptin administration (50mg/day) → Measurement of glucose AUC using MIET during OGTT

Sitagliptin: DPP-4 inhibitor
Controls blood glucose level by inhibiting the enzyme DDP-4, which degrades the gastrointestinal hormone incretin that is secreted after glucose intake.

OGTT: Oral Glucose Tolerance Test
Drug Efficacy Monitoring

OGTT results

Results of glucose AUC monitoring system

PG: Plasma Glucose

3.-2-(2-2)
Glucose AUC monitoring system will be useful for individualized dietary therapy, which enables to understand the relationship between food and glycemic excursion after intake of the food easily.
### Future Plans

#### Planned clinical study and approval application

<table>
<thead>
<tr>
<th>Clinical study details</th>
<th>The screening performance for impaired glucose tolerance using the minimally invasive glucose AUC monitoring system is verified as not inferior to either the combined fasting blood glucose/HbA1c screening or the 2-hour glucose level during OGTT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of target cases</td>
<td>Approximately 180</td>
</tr>
<tr>
<td>Facilities</td>
<td>Five facilities participating in the AUC Study Group</td>
</tr>
<tr>
<td>Period</td>
<td>2Q-4Q fiscal 2013</td>
</tr>
</tbody>
</table>
3) Diabetes Simulation
   (Disease State Simulation Technology)
Quantification of disease states by simulation

Clinical test data

Diabetes Simulator based on mathematical models

Diabetes Simulator

Glucose intake
Glucose production
Insulin intake
Insulin secretion

Liver model
Pancreas model
Peripheral tissue model

Insulin kinetic model

Estimation of model parameters that can reproduce the blood glucose/insulin dynamics of individual patients.

Quantified Disease States
"Disease State Profile"

Insulin dependent/Non-dependent glucose intake

Glucose intake
Insulin intake
Insulin secretion
Pancreas model
Liver model
Peripheral tissue model

Copyright by Sysmex Corporation
Drug selection is based on doctors’ knowledge and experience.
Prediction of Drug Responders Using Diabetes Simulators

Quantification of disease states

Blood sugar

Insulin

Test data → Parameters

Therapy in silico

Prediction of drug effectiveness

Insulin sensitizer

Simulation of glucose change

$\Delta G_{EST\_IS}$

$\Delta G_{EST\_IR}$

Resistivity parameters

Insulin secretion enhancer

Simulation of glucose change

$\Delta G_{EST\_IS}$

$\Delta G_{EST\_IR}$

Secretion parameters

$\Delta G_{EST\_IS}$: Simulated glucose change when insulin secretion is normalized.

$\Delta G_{EST\_IR}$: Simulated glucose change when insulin resistance is normalized.
Verification of Clinical Utility

Prediction of Drug Responders Using Diabetes Simulators

- Planned number of cases: 200
- Drugs: Metformin, Glinides, Pioglitazone, DPP-4 inhibitors
- Participating facilities: Total of five facilities: Shanghai Jiao Tong University School of Medicine, other level 3 hospitals, etc.

**Diagram:**
- Before treatment
- Oral medication (mono-therapy)
- Drug selection by a doctor
- 6 months
- Prediction of responders by the simulator
- HbA1c

Over 10% improvement in glucose level after treatment?
Performance in Drug Responder Prediction (1)

Glinide drugs

<table>
<thead>
<tr>
<th>$\Delta G_{EST.IS}$</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 34</td>
<td>66% ⇒ 79%</td>
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<tr>
<td>Predicted as</td>
<td></td>
</tr>
<tr>
<td>Responsive</td>
<td></td>
</tr>
<tr>
<td>Non-responsive</td>
<td></td>
</tr>
</tbody>
</table>

Thiazolidine drugs

<table>
<thead>
<tr>
<th>$\Delta G_{EST.IS}$</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 42</td>
<td>38% ⇒ 52%</td>
</tr>
<tr>
<td>Predicted as</td>
<td></td>
</tr>
<tr>
<td>Responsive</td>
<td></td>
</tr>
<tr>
<td>Non-responsive</td>
<td></td>
</tr>
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</table>

Medical Specialists Simulator
Performance in Drug Responder Prediction (2)

Metformin drugs

\[ \Delta G_{EST.IS} \]

-40000 -20000 0 10000

N = 49

Predicted as Responsive

Predicted as Non-responsive

\[ \Delta G_{EST.IS} \]

Response rate 39% ⇒ 53%

Medical Specialists Simulator
Future Plans

Medical Software

Current

Medical devices used together

Future

Medical devices using software independently

Diabetes Simulation

Plans to form study groups, implement clinical performance studies, apply for approvals
4) Development of Raw Materials for Diagnostic Reagents Using Silkworms
Protein Expression Using Recombinant Silkworms

1. Introduce gene into larval virus
2. Infect with recombinant virus
3. Recombinant virus produces protein in silkworm
4. Larva
5. Chrysalis
6. Purification
7. Preparation of chrysalides and larvae
8. Protein raw material
### Production Characteristics of Various Recombinant Proteins

<table>
<thead>
<tr>
<th></th>
<th>Productivity</th>
<th>Cost</th>
<th>Production Period</th>
<th>Similarity to Human Type</th>
<th>Sugar Chain Structure (N Type)</th>
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</thead>
<tbody>
<tr>
<td><strong>E. Coli</strong></td>
<td>○</td>
<td>◎</td>
<td>○</td>
<td>×</td>
<td>(None)</td>
</tr>
<tr>
<td><strong>Yeast</strong></td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>△</td>
<td></td>
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<tr>
<td><strong>Silkworm</strong></td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td><strong>Animal</strong></td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>○</td>
<td></td>
</tr>
</tbody>
</table>

- **Acetylgalactosamine**
- **Mannose**
- **Galactose**
- **Sialic acid**
Reagent Development Using Silkworms

Silkworm gene engineering

- Improve accuracy and stability
- Improve product reliability
- Acquire sugar-chain marker antibodies
- Provide standards

Progress in change to human-type sugar chain

- Technology acquired fiscal year ended March 31, 2012
- Technology acquired fiscal year ended March 31, 2013

Comparison of activity with human-type enzymes

Activity acceleration through modification of human-type sugar chain

ASN: Asparagine

Aiming for improved expression efficiency and productivity
5) Malaria Detection Technology
Number of Malaria Deaths

Number of malaria reported deaths, 2010

http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Malaria_ReportedDeaths_2010.png
3.-(2)-5

Malaria Detection Technology

Technology Characteristics

Hematology Analyzer
Flagging infected cells with malaria
Hypothetical data about malaria sample

Mainly tropical African malaria = ring-form
Vivax malaria, mainly in Asia = gametocyte, schizont
1. Reporting Subjects
   - Technical features of Sysmex technologies and products
   - Technical themes on which Sysmex conducts R&D and their clinical utilities
   - Outline of Sysmex technology strategy

2. Policy Regarding Reporting of Technological Themes
   Explain R&D themes at the three stages below:
   <Research stage> Start of research and preliminary evaluation
   - Magnitude of clinical value in practical use
   - Explanation of future R&D plans
   <Practical stage> Elemental research, practical and product commercialization stage
   - Technological impact on characteristics of products
   <Launch stage> Accomplishment of development and introduction to market
   - Details of technological features and superiority
(Reference) Definition of R&D Stage

**Research stage**
Start of research or preliminary evaluation
Objective means of establishment of measurement principles and verification of clinical value

**Practical stage**
Start of full-scale R&D activity towards commercialization

**Launch stage**
Completion of product commercialization and determination of launch

- 10 ~ 50%
- 50 ~ 80%
We Believe the Possibilities.

Sysmex Corporation

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