HUMAN HEALTH CARE

ライフサイエンスの未来へ
　ー１０年先のデータベースを考える

バイオマーカー・薬剤作用機序研究における データベースの必要性と課題

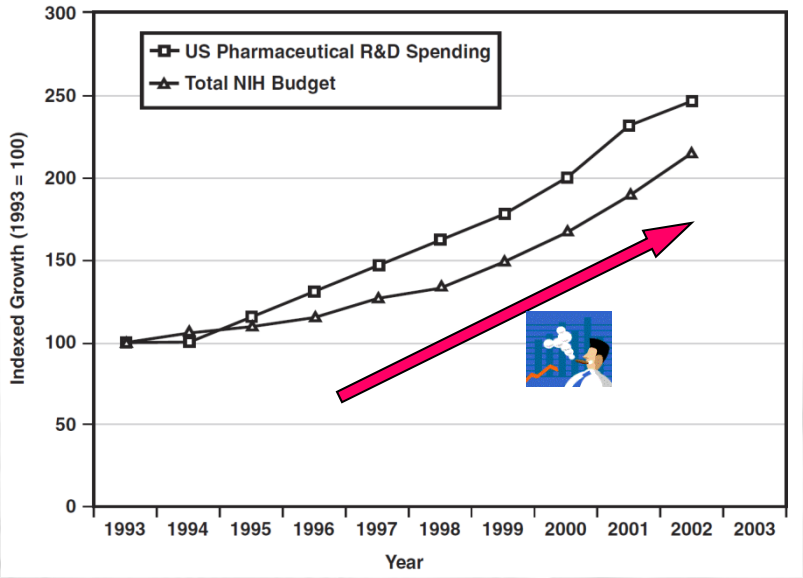
青島　健

エーザイ・プロダクトクリエーション・システムズ
バイオマーカー＆パーソナライズド・メディスン
機能ユニット

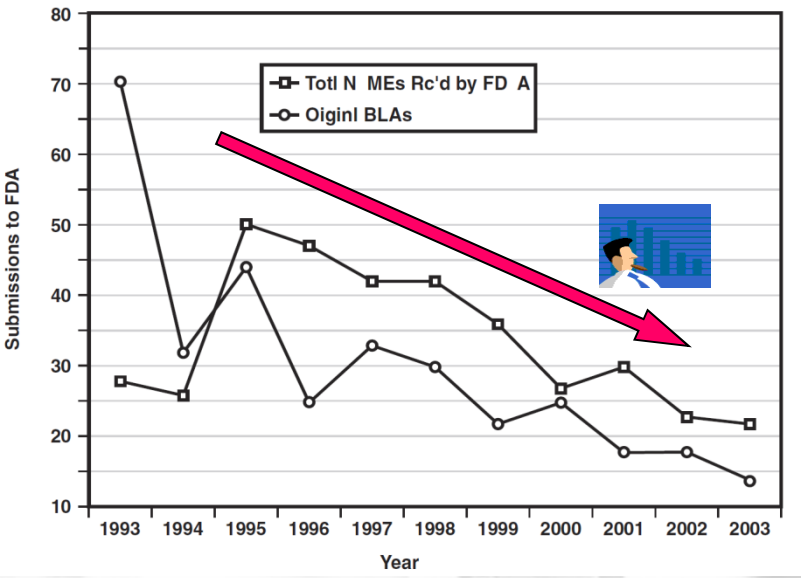
Oct 5, 2010

10-Year Trends

in Biomedical Research Spending



in Major Drug and Biological Product Submissions to FDA



FDA report 2004

従来型創薬研究の限界

- 毎月のように病気の原因分子を特定したという報道があるが、ほとんどが治療に至らず基礎研究に留まっている。
- 製薬企業は標的として約500種類の分子を検討し、大手各社では200万種類以上の化合物ライブラリーを使ってスクリーニング
- 既存品や先行品との医薬品の差別化が主目的であり、それも患者さんの感覚という主観的な根拠も利用
- ベータブロッカー薬は15－30%の人には効かず、抗うつ薬は20－50%、インターフェロンは30－70%の患者さんには効かない
- 今までは標的分子のバリデーションが欠如しているため薬剤がヒトに作用せず、臨床試験での失敗につながっている

Critical Path Opportunities List

March 2006

Critical Path Opportunities List, Mar 2006

Topic 1: Better Evaluation Tools

Developing New Biomarkers and Disease Models to Improve Clinical Trials and Medical Therapy

U.S. Department of Health and Human Services
Food and Drug Administration
March 2006

and Standards

development and facilitate integration of personalized medicine into clinical practice.

2. Standards for Microarray and Proteomics-Based Identification of Biomarkers. Microarray and proteomic technologies hold vast potential to identify biomarkers. However, a gap exists between technologies in use today and the technological level required for their application during product development and regulatory decision making. This gap results from the limited availability of accepted standards for demonstrating comparability of results, for data normalization and analysis, for validation of

Biomarker

- Diagnostic biomarker
- PK/PD biomarker
- Efficacy/MOA biomarker
- Safety biomarker
- Patient stratification biomarker

Critical Path Opportunities List, Mar 2006

TOPIC 3: HARNESSING BIOINFORMATICS

Data Pooling and Simulation Models

U.S. Department of Health and Human Services
Food and Drug Administration
March 2006

Bioinformatics

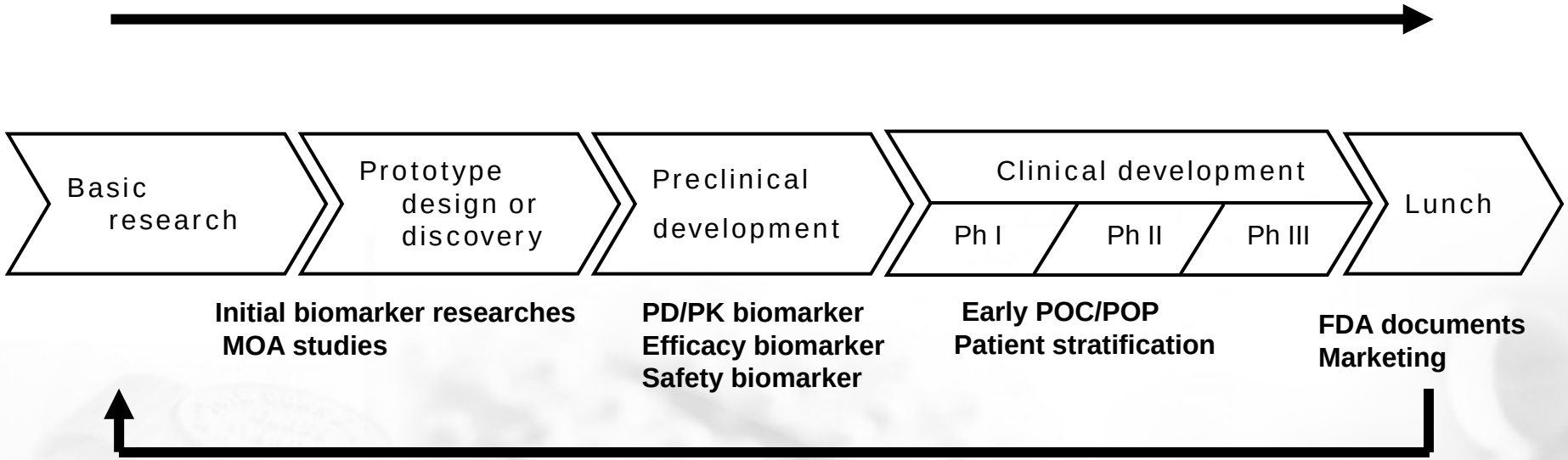
46. Identification and Qualification of Safety Biomarkers. Collaborative efforts to pool and mine existing safety an
sources for identi
biomarkers. For e
preclinical and cl
risk could help u
of QT interval pr
clinical studies, a
individuals who
Similarly, eviden
metabolism that
toxicity, and new
would enable

comorbidities and could elucidate drug interactions. This knowledge could the

- Indentification and Quanlification of Safety Biomarkers
- Virtual Control Groups in Clinical Trials
- Adverse Event Data Mining
- Multiple Complex Therapies
- Modeling Device performance
- Clinical Trial Simulation
- Failure Analysis
- Natural History Databases for Rare Disease

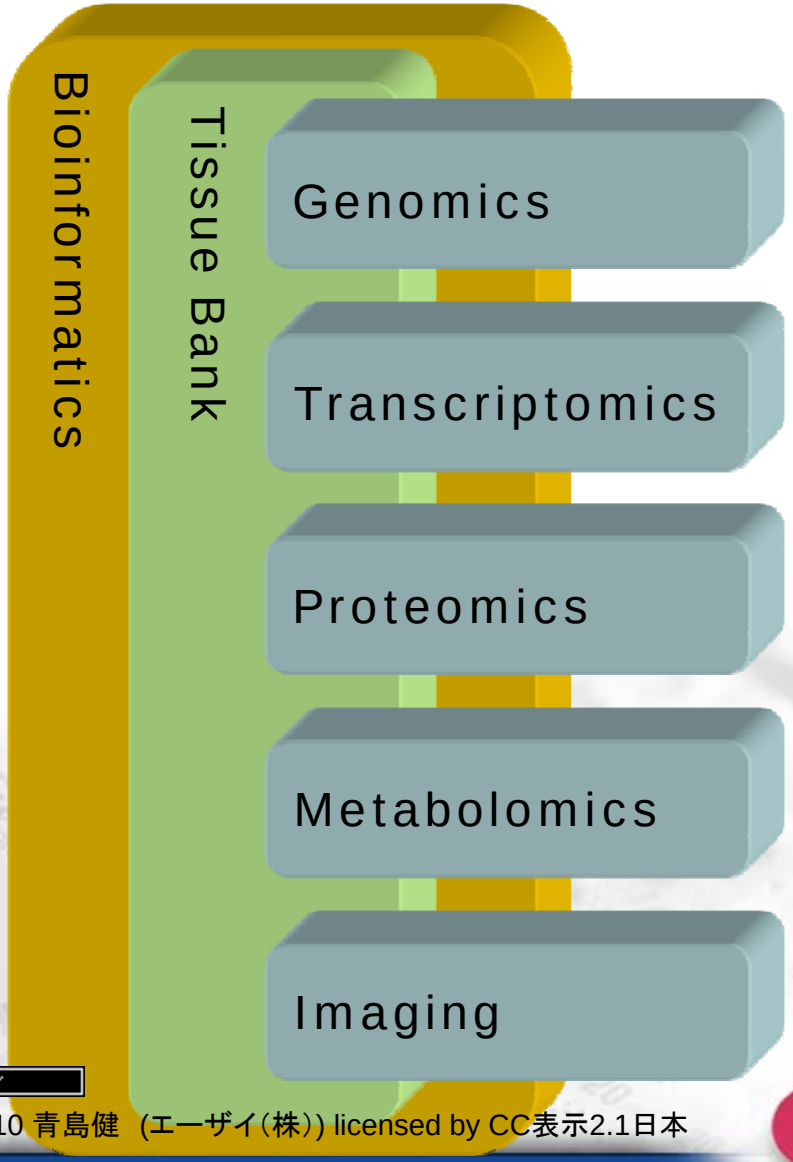
Contribution of biomarker research in different stages

Translation Researches to shorten timelines



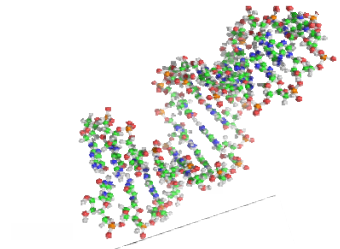
Reverse translation researches to assist new ideation

Cross-omics for translational researches

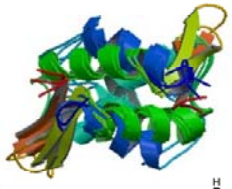


DNA

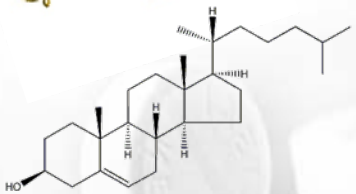
RNA



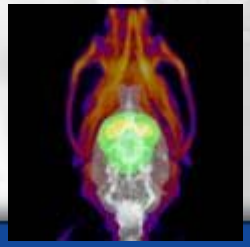
Proteins

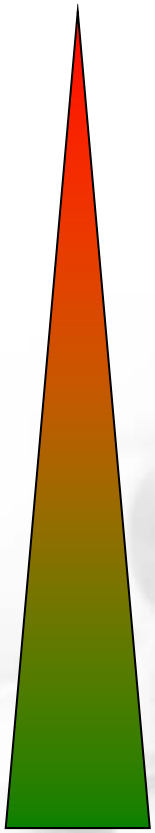


Metabolites



Phenotypes

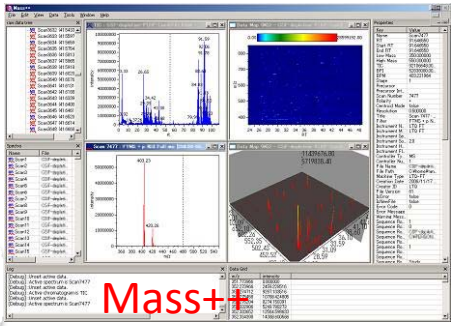




Natural Level Complexity

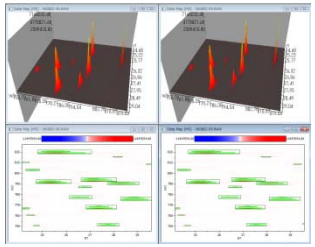
Eisai

In-house built software for proteomics



RAW DATA

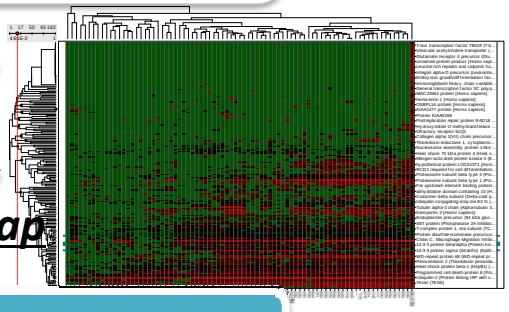
Original Format



AB3D

Advanced Peak Picking Algorithms
&
Quantitation Algorithms

Biostatistical analysis
Candidate Peaks/Markers



In-house built clickable heat map

Identification

Pathway Analysis

IPA, Metacore

BIOLOGICAL VALIDATION

New Drug Targets/MOA

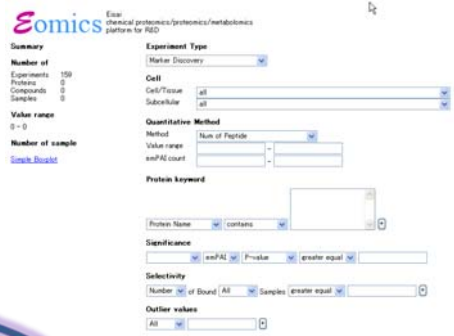
Name	ID Seq	Full_Seq	emPAI	Symbol	Function	Component	Process	Annotation(Human)
mitogen	APEVILGM	MSDSKSD	2.6308	Mapk9	nucleotide	nucleus.	protein ar	Mitogen activated protein kinase
calcium/	AGAYDFPS	MASTTTC	1.5929	Camk2d	nucleotide	nucleus.cyto	G1/S tra	Calcium calmodulin dependent pr
mitogen	ALDLLDK	MAAAAAA	1.2275	Mapk1	nucleotide	nucleus.cyto	MAPKKK	Mitogen-activated protein kinase
mitogen	IPEQILGK	MPKKKPT	0.5849	Map2k1	nucleotide	binding prote	protein ar	Mitogen-activated protein kinase
mitogen	HTDDEMT	MSQERPT	0.5505	Mapk14	nucleotide	spindle pole	DNA dam	Mitogen activated protein kinase 1
cyclin-d	GGAAR LL	MGRRFLV	0.5199	Cdkn2a	DNA bindi	granular com	regulation	Cyclin dependent kinase inhibitor

In-house built annotation system

In house DB

Public DBs
(NCBI, SwissProt etc)

Accumulated and annotated in house multi-OMICS database system



Eomics

MOA/Target Hunting/Biomarker Discovery

Genomics

Clinical information

Chemical proteomics

Phospho Proteomics

Transcriptomics

Metabolomics

Public DBs

Samples: **397**
Compounds: **166**

Samples: **6,075**
Phosphorylation : **13,255** sites

Samples: **2,383**
Compounds: **160**

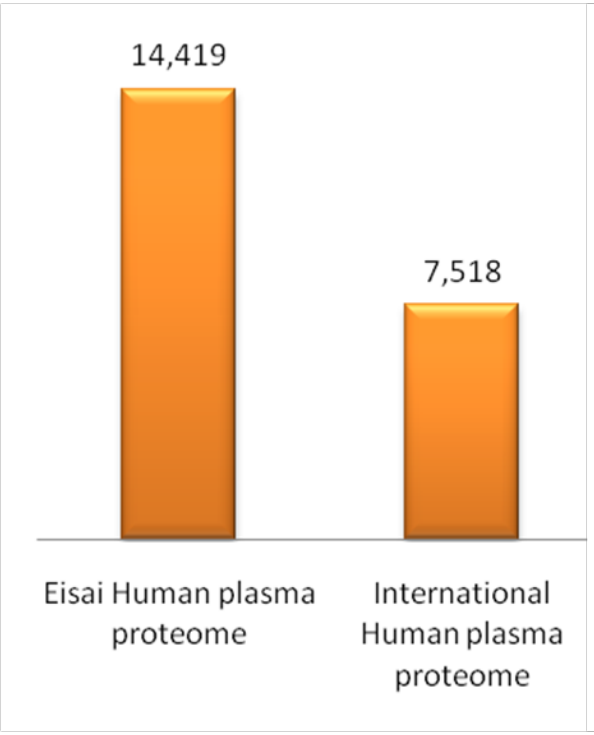
Samples: 2114
Compounds: 62

Eisai Tissue Bank

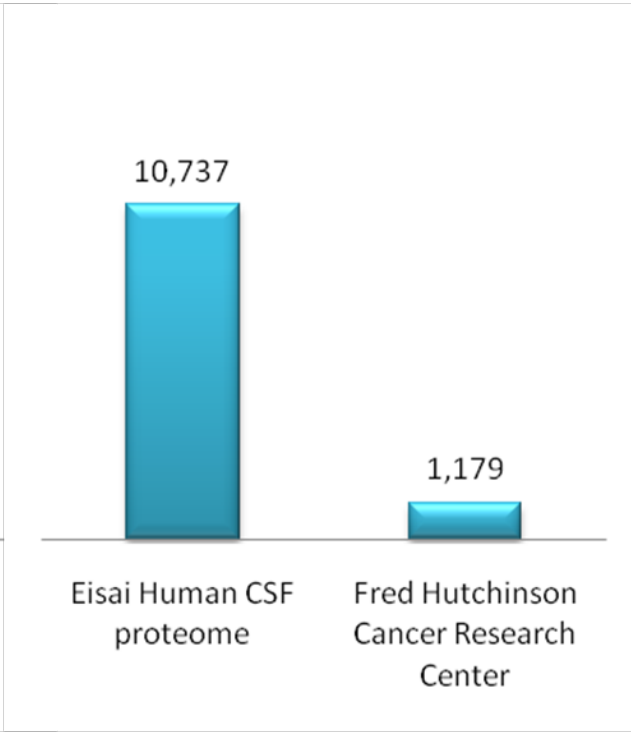
Up to Jan 2010

世界におけるエーザイのプロテオミクス研究のレベル

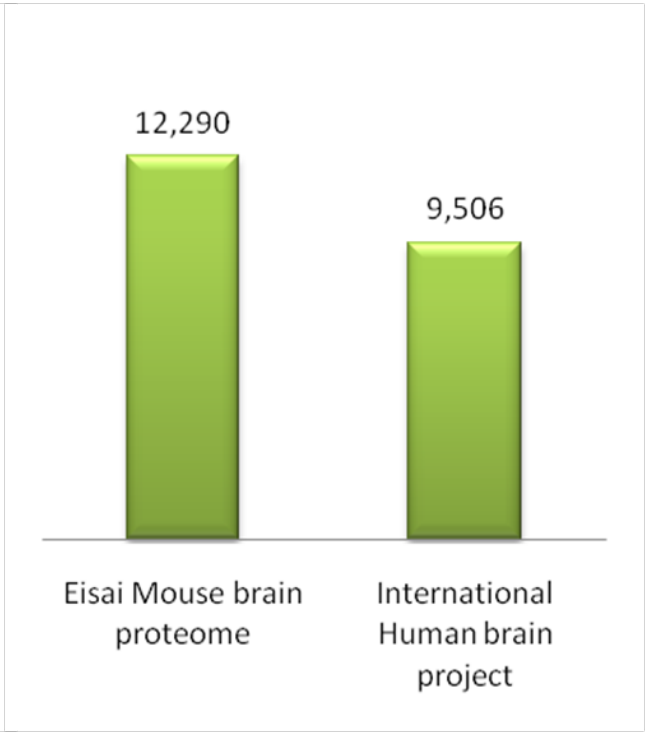
- 高速化・高感度化により数多くのタンパク質を同定



ヒト血漿サンプル



ヒト脳脊髄液サンプル



マウス／ヒト脳サンプル

アルツハイマー病の発病メカニズム（仮説）と診断ツール

老人斑ができる過程

APP → アミロイドβタンパク質（Aβ） → アミロイド線維

β･γセクレターゼ　　重合（凝縮）

神経原線維変化(PHF)がおこる過程

タウ → 異常リン酸化タウ → PHF

リン酸化　　重合

神経細胞が脱落していく過程

神経細胞障害 → 神経細胞死

認知症（AD）

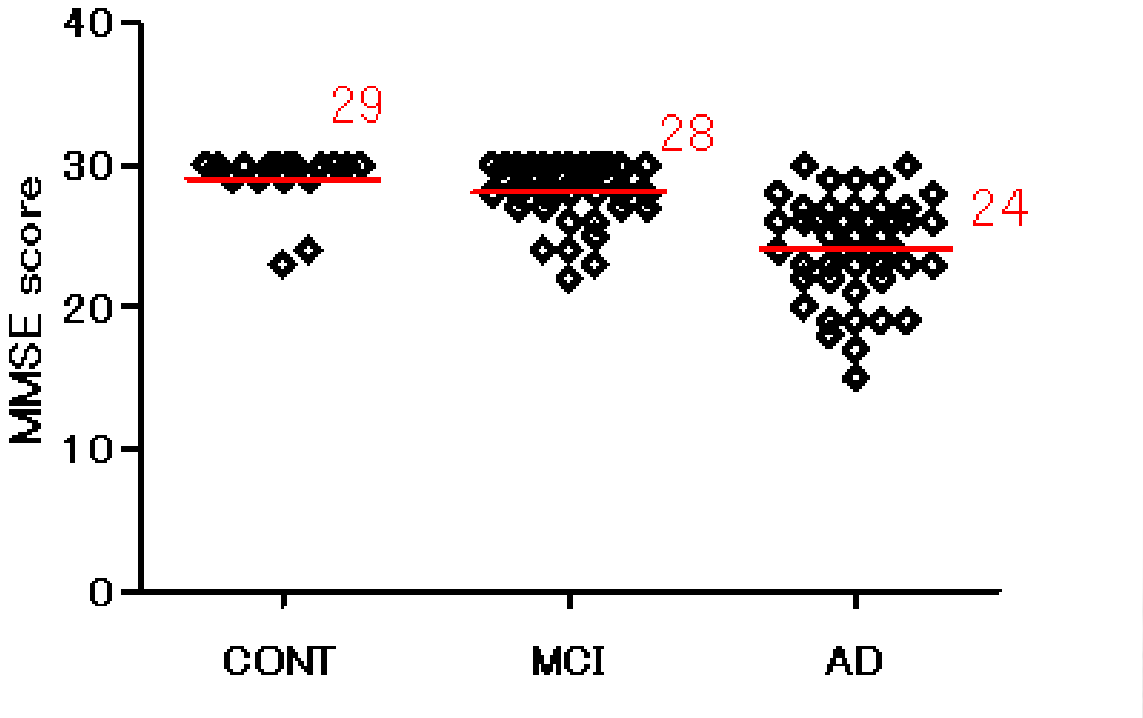
脊髄液のAβ42、リン酸化タウ測定

より侵襲性を低く
血液マーカーの開発

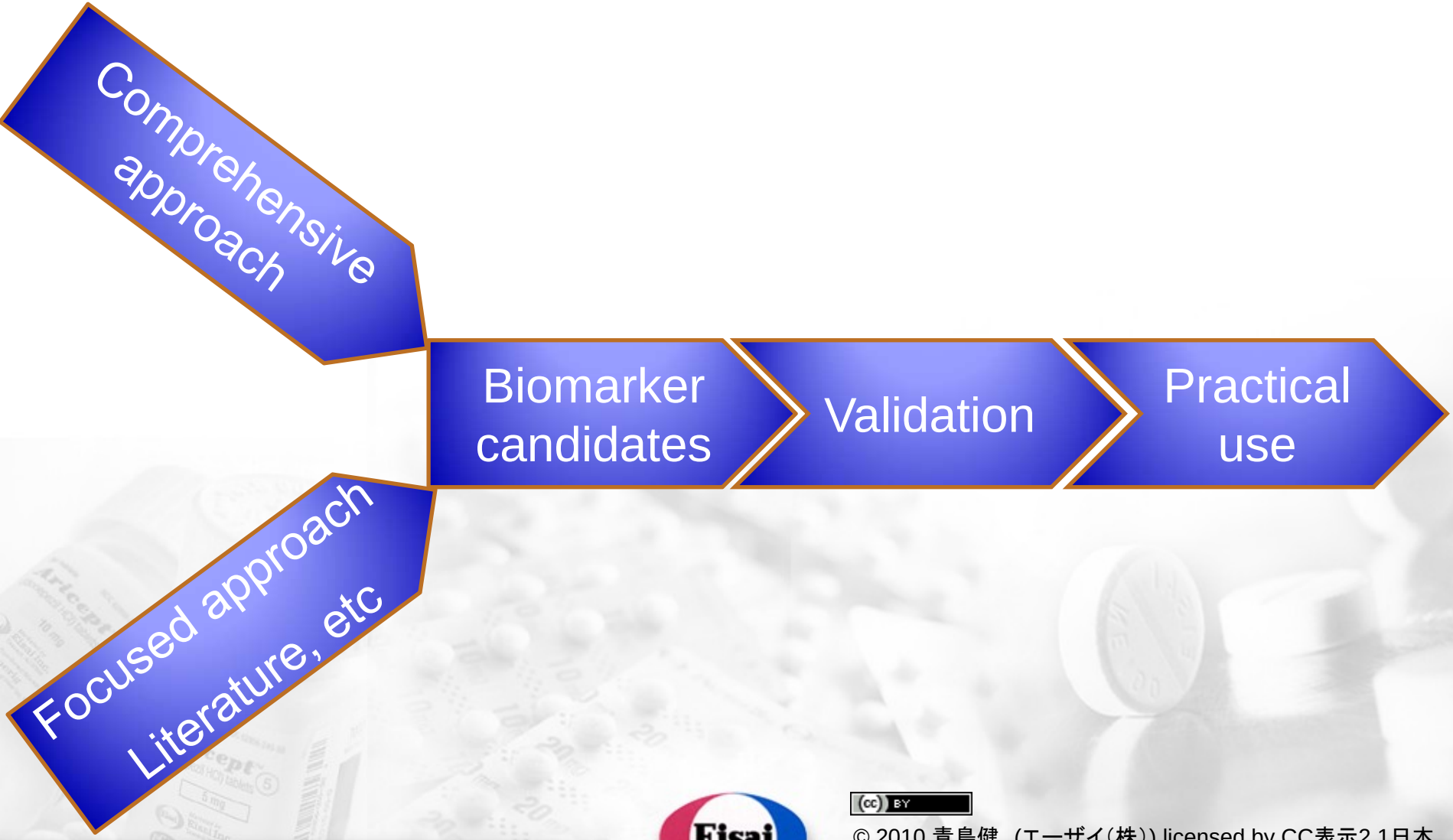
脳形態画像、
脳機能画像（血流、代謝）
問診(神経心理学的検査)

アルツハイマー病発病への時間的経過

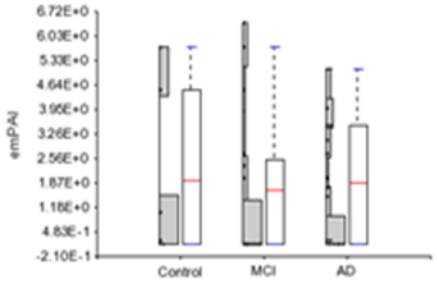
MMSE(Mini-Mental State Examination)



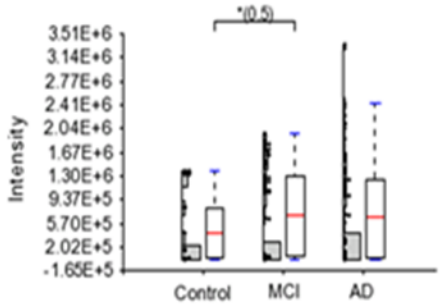
Strategy for biomarker discovery



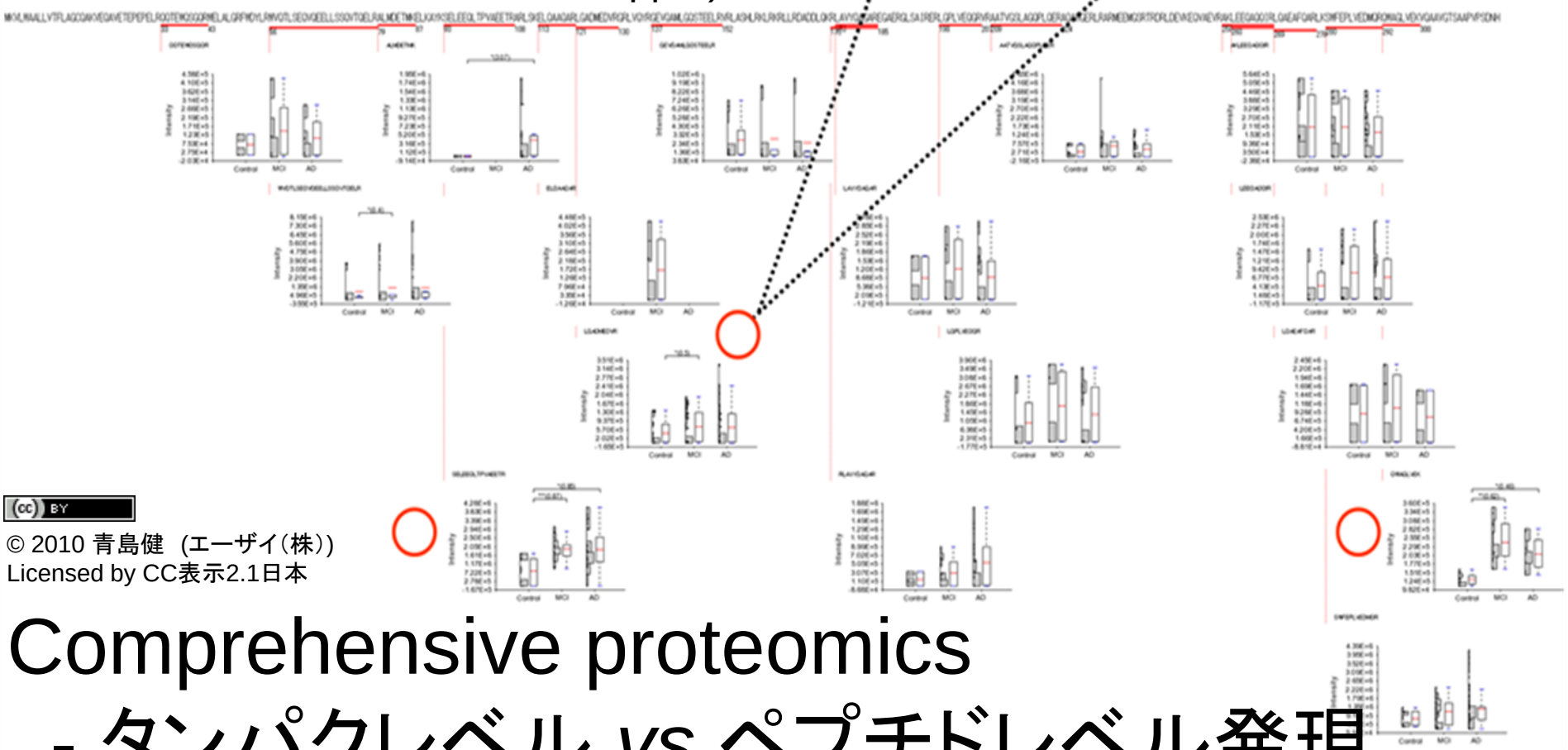
タンパク質レベルの発現(ApoE)



ApoE4: LGADMEDVR



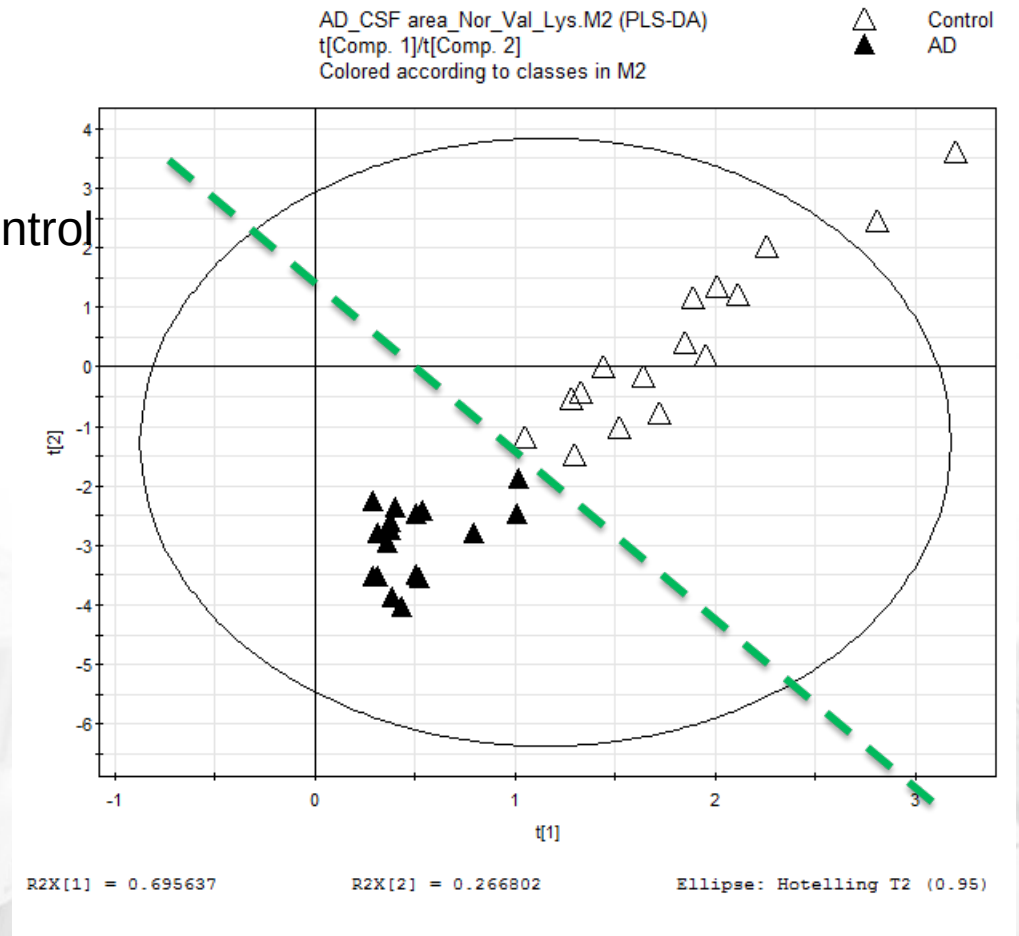
ペプチドレベル発現ビューワ（Pepper)



Comprehensive proteomics
- タンパクレベル *vs* ペプチドレベル発現

Focused metabolomics

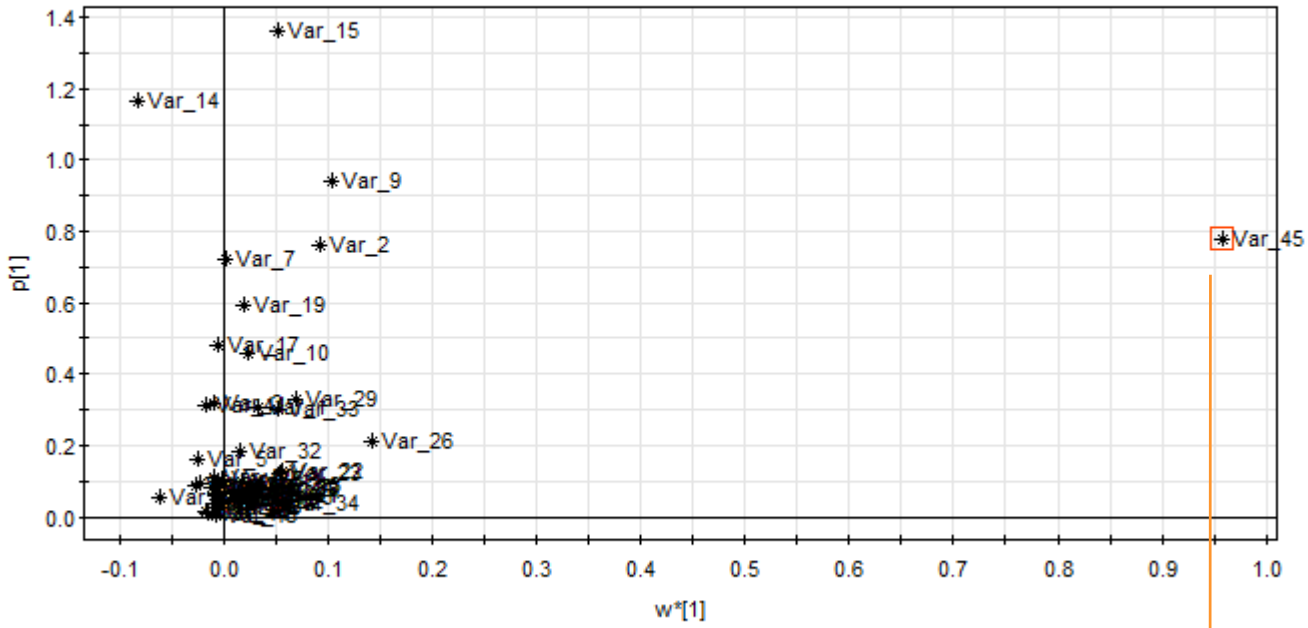
17 AD *vs* 17 control



AD_CSF area_Nor_Val_Lys.M2 (PLS-DA)
w*[Comp. 1]/p[Comp. 1]

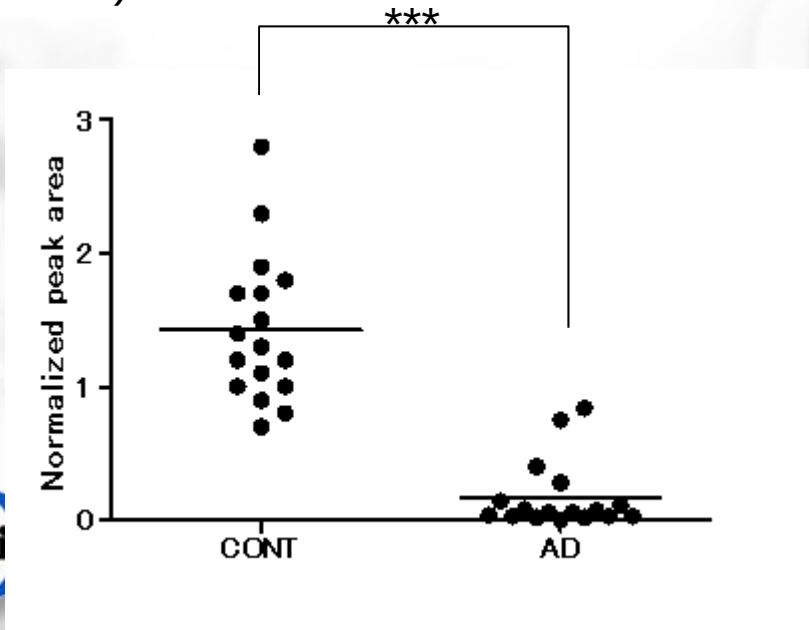
S-plot

PC1(variable reliability)



Weight(variable magnitude)

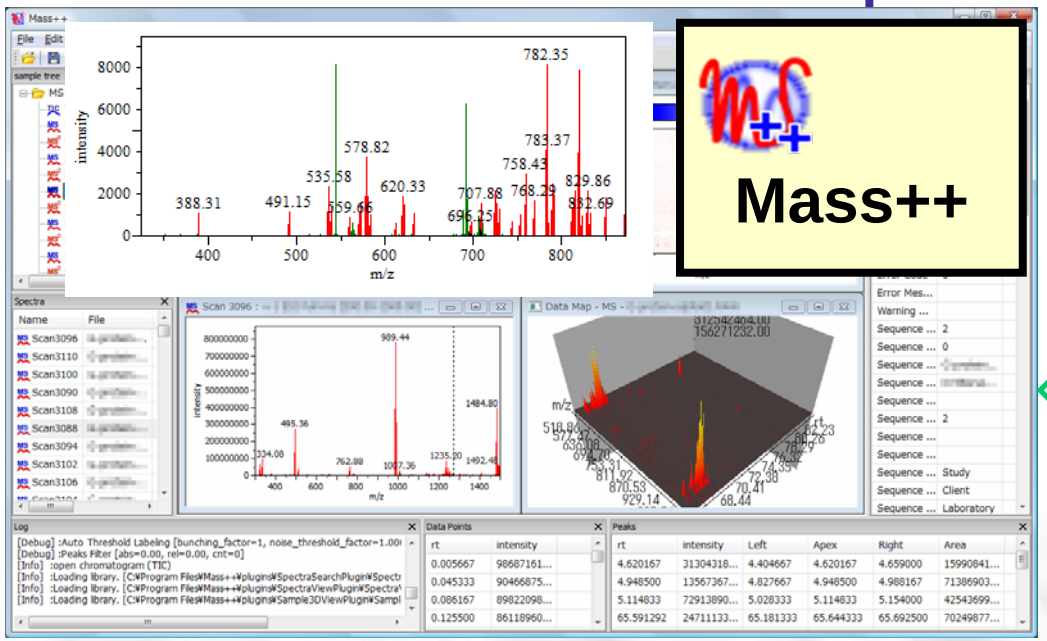
fold: 8.2
P=1.5E-9

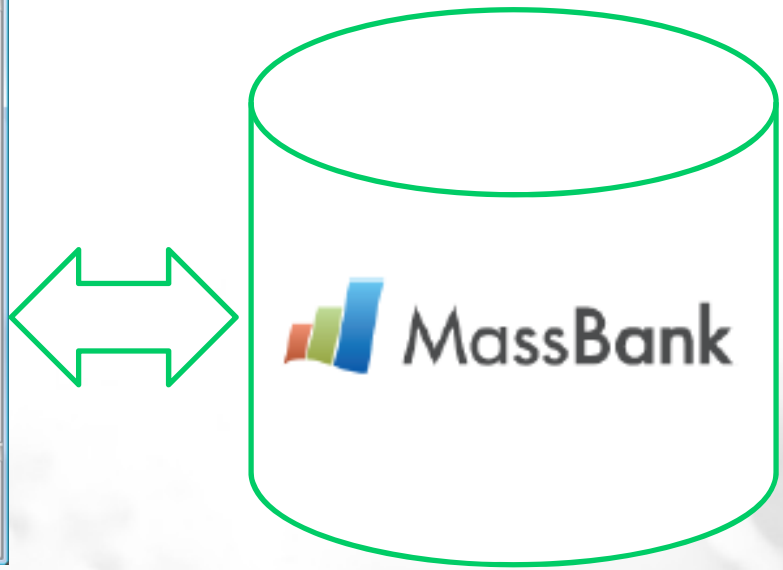


創薬分野におけるデータベースの課題

- Development of metabolome database
- Development of public biomarker database
- Development of safety and toxicology database
- Development of a public database of information from trials of unsuccessful products
- Natural history databases for rare diseases
- Multiple complex therapies database

Development of metabolome database for Mass spectral ID





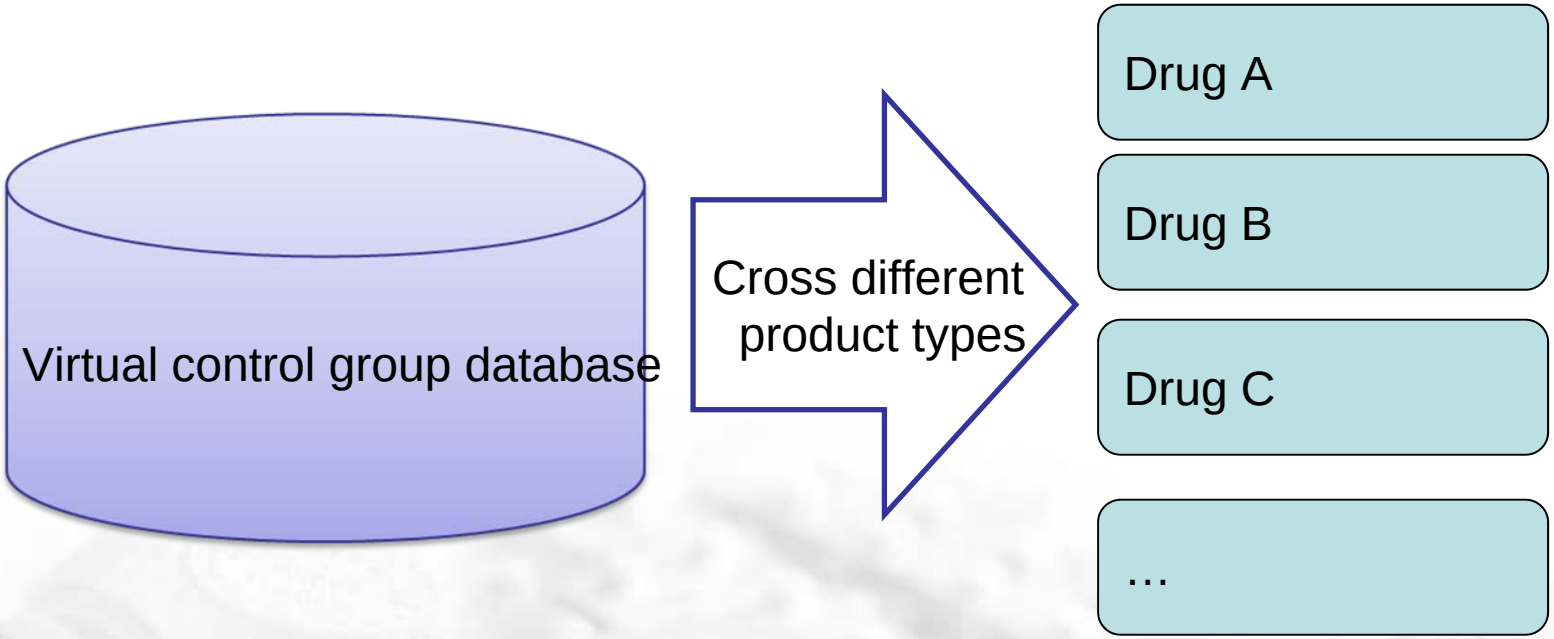
- ✓ MassBank レコード作成
- ✓ 類似 スペクトル検索
- ✓ Peak Search, Peak Difference Search
- ✓ 検索結果表示

2010年09月24日現在　｜　総スペクトル数：※1 29,796
http://www.massbank.jp/

"MassBank: A public repository for sharing mass spectral data for life sciences", H. Horai, et al *J. Mass Spectrom.*, **45**, 703-714 (2010).

Eisai

Development of virtual control database



Reduce the neccisary size of control groups

Development of trials of unsuccessful products database

Pharmaceutical A

Pharmaceutical B

Pharmaceutical C

…

Summary

- Success to discover AD diagnostics biomarkers using multi-OMICS technologies
- Those biomarkers could be expected as a tool to shorten time line of product creation
- To accelerate preclinical and clinical speed by fully utilizing bioinformatics
- To development public domain databases for pharmaceutical needs

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