

Status and Trends in *In-Vitro* Diagnostics and Considerations for Reference Materials

SIEMENS

The Future of Reference Materials – Science and Innovation –

**Conference in the frame of the 50th anniversary of the JRC's
Institute for Reference Materials and Measurements**

Geel, Belgium, 23-25 November 2010

Frank Vitzthum, Siemens Healthcare Diagnostics Products GmbH

Overview

Status of laboratory diagnostics in healthcare

Global trends and trends in *in-vitro* diagnostics

Proteomics research

Considerations for reference materials

In-Vitro Diagnostics – Status Quo

In-vitro diagnostics is hardly ,visible‘ any more...



Patient care space



IVD / laboratory space

IVD: the hidden treasure in healthcare

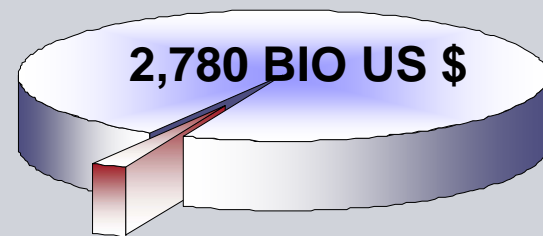
Minimal IVD expenditures save lives and money.

Still, IVD expenditures are deemed too high,
and their value is underestimated.

Impact of IVDs

- contribute up to 94 % of the objective data in clinical records
- influence 60 - 70 % of critical decision making
- reduce mortality and morbidity
- improve quality of life and patient care
- reduce health care costs

**Health Expenditures
World-Wide**



~ 1-2 % IVD

Trends

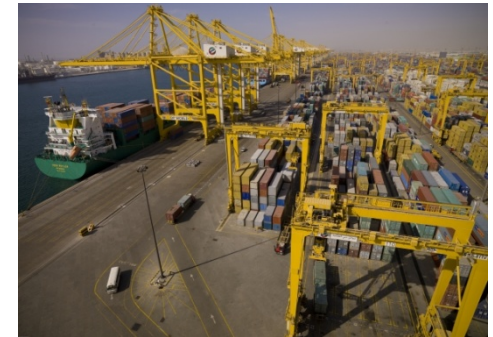
SIEMENS



Megatrends shape our future

Globalization

- From 1950 to 2004, the volume of global trade has increased 27.5-fold.
- The number of global players has grown from 17,000 in 1980 to over 70,000 today.
- Ocean freight has increased over the past four decades from less than 6,000 billion ton-miles to over 27,500 billion ton-miles a year.



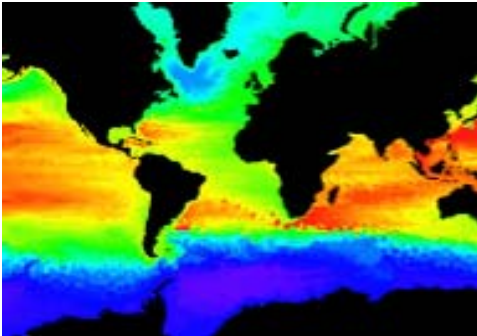
Urbanization



- 2007: for the first time in history, more people live in cities than in rural areas.
- Today 280 million people live in megacities (> 10 million residents)
- 2030: 60 % of the world's population will live in cities
- Urban conglomerations contribute a high share of a nation's economic output: Tokyo provides 40 % of Japan's GDP, Paris generates 30 % of France's GDP.

Megatrends shape our future

Climate Change



- The average global surface temperature has increased by 0.76 °C compared to the 18th century.
- 11 of the 12 years between 1994 and 2005 rank among the 12 warmest since weather observations began.
- Greenhouse gas emissions haven't risen dramatically since industrialization. Today we face the highest CO₂ concentration in the atmosphere for the past 350,000 years.

Demographic Change

- Average life expectancy worldwide will increase to 72 years in 2025 from 46.6 years in 1950.
- World population will grow from more than 6 billion now to 8 billion by 2025.
- 95 % of the global population growth is taking place in developing countries.
- The 65+ generation will nearly double worldwide by 2030 (from 7 % to 12 %),



Key impacts of Megatrends on *In-Vitro* Diagnostics

- Infectious Disease Diagnostics
- Disease of aging or lifestyle, e.g.
 - Neurological diseases
 - Cardiovascular diseases
 - Diabetes
 - Cancer
- Disease prevention
- Globalization of healthcare: ***standardization & harmonization***

Major trends in *In-Vitro* Diagnostics

- Further economization also in healthcare → cost pressure to persist
- Demand for increased efficiency & efficacy
- Consolidation (laboratories, IVD manufacturers, instruments, automation, miniaturization, etc.)
- Process & workflow optimization
- Information management (IT solutions)
- Near patient testing and POC when needed
- Nucleic acid diagnostics
- Improved treatment through IVDs (personalized/stratifying medicine)
- New technologies
- **New biomarkers**
- ***Standardization & Harmonization***

Reference materials: the hidden treasure in IVD

No matter what trends will materialize or not...

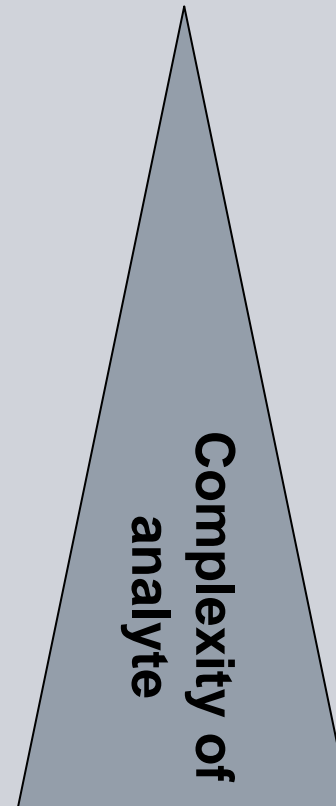
IVD results should be the same

in Geel and in Marburg and all over the world
yesterday, today and tomorrow

Reference materials are essential for reliable reference intervals and decision points to diagnose, monitor and treat patients appropriately.

IVD Biomarkers

Gases
Electrolytes / Trace Elements
Metabolites
Amino acids (derivatives)
Lipids
Nucleic Acids
Carbohydrates
Peptides/Proteins



**Proteins will continue to dominate
the emerging IVD biomarker arena**

SIEMENS

**Protein testing
is usually close
to the phenotype**

Proteomics

New Horizons in Protein Diagnostics?

Despite great expectations and investments for proteomics endeavour, the success in delivering new *in-vitro* diagnostics has been limited so far!

Major challenges

- **Reproducibility & comparability**
- **Preanalytics including the clinical question & study design**
- **Transferability to installed base and/or clinical workflow**
- **Verification challenges by proteomics technologies**
 - **Accuracy versus throughput & multiplexing**
 - **Challenge to discover & measure low abundance protein biomarkers in complex samples such as blood specimens**
- **Verification challenges by immunoassays**
 - **Resources & time for assay development (of multiple tests) (definition of the measurand, antibody development, etc.)**



Can we leverage the strengths of different fields to get clinical relevant and standardized immunoassays faster to the market for the benefit of healthcare and the patients?

How can we leverage different strengths

Communication & collaboration

Leverage methodologies and know-how used in different fields

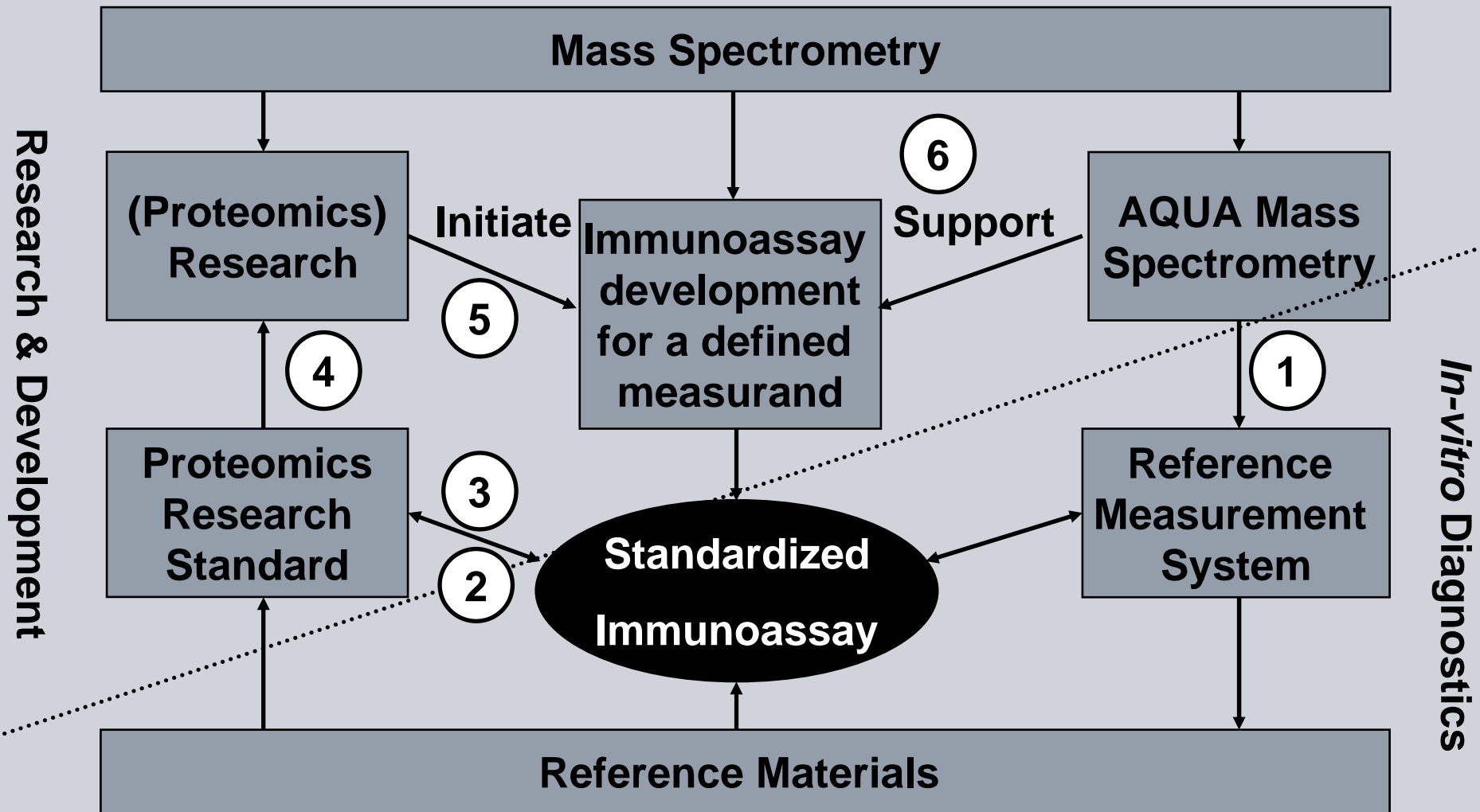
Align & harmonize search for new biomarkers

More rigorous examination of existing biomarkers

Defining the clinically relevant measurand(s)

Leverage existing and develop new reference materials

Reference materials and mass spectrometry for protein & peptide testing in R&D & IVD



ID-LC-MS² under consideration as reference measurement procedure

C-Reactive Protein

Myoglobin

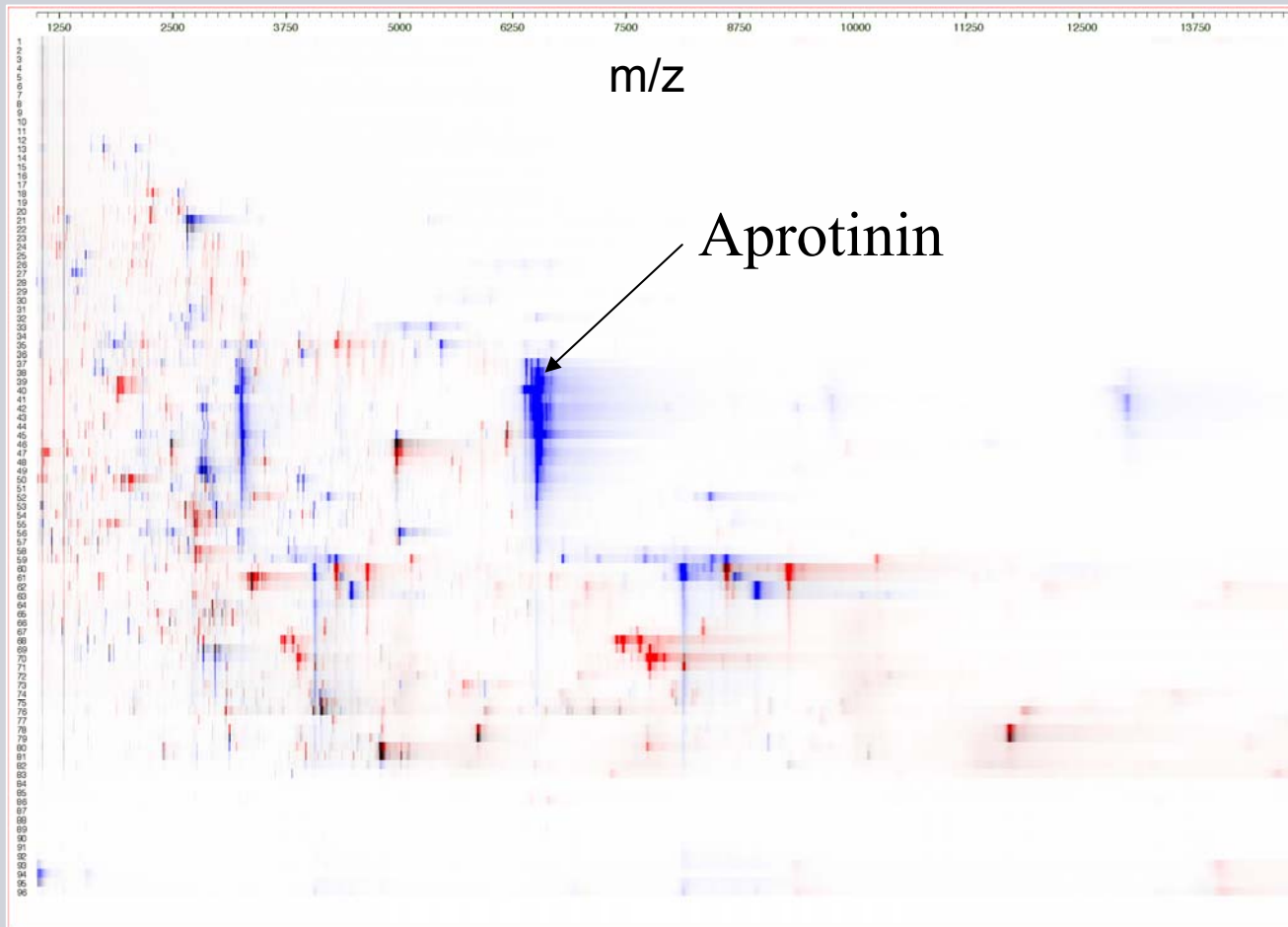
Cystatin C

Insulin

Etc.

Assessment of manufacturer's control for Proteomics research purposes

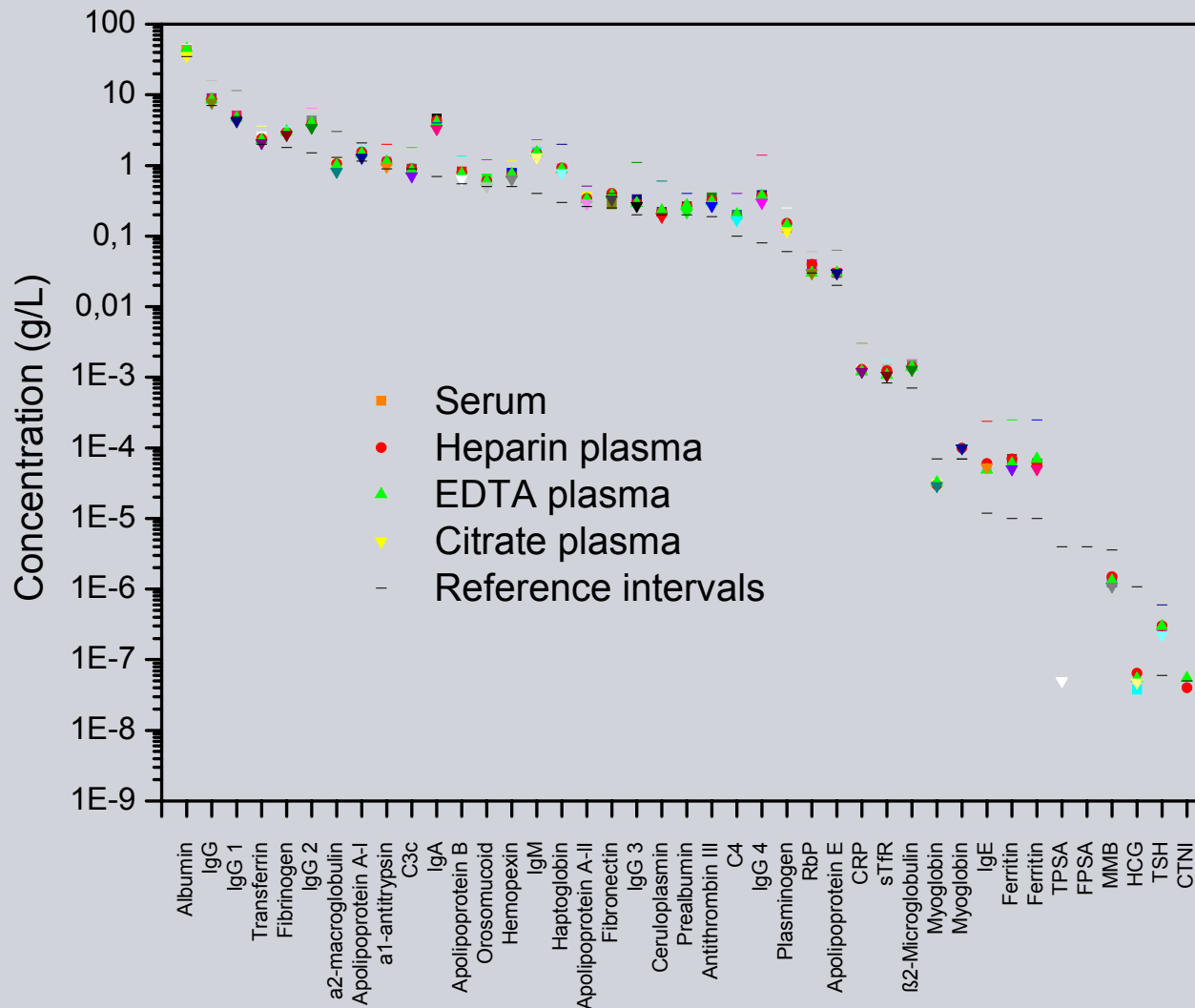
Liquid chromatography fraction #



Overlay of Mean Differential Peptide Display of **Human Plasma (red)** and a Manufacturer's Control (**N/T Protein Control SL Level L (blue)**)

Vitzthum F, Siest G, Bunk DM, Preckel T, Wenz C, Hoerth P, Schulz-Knappe P, Tammen H, Adamkiewicz J, Merlini G, Anderson NL (2007) Proteomics Clin. Appl. 1, 1016-1035.

„Orientation measurements“



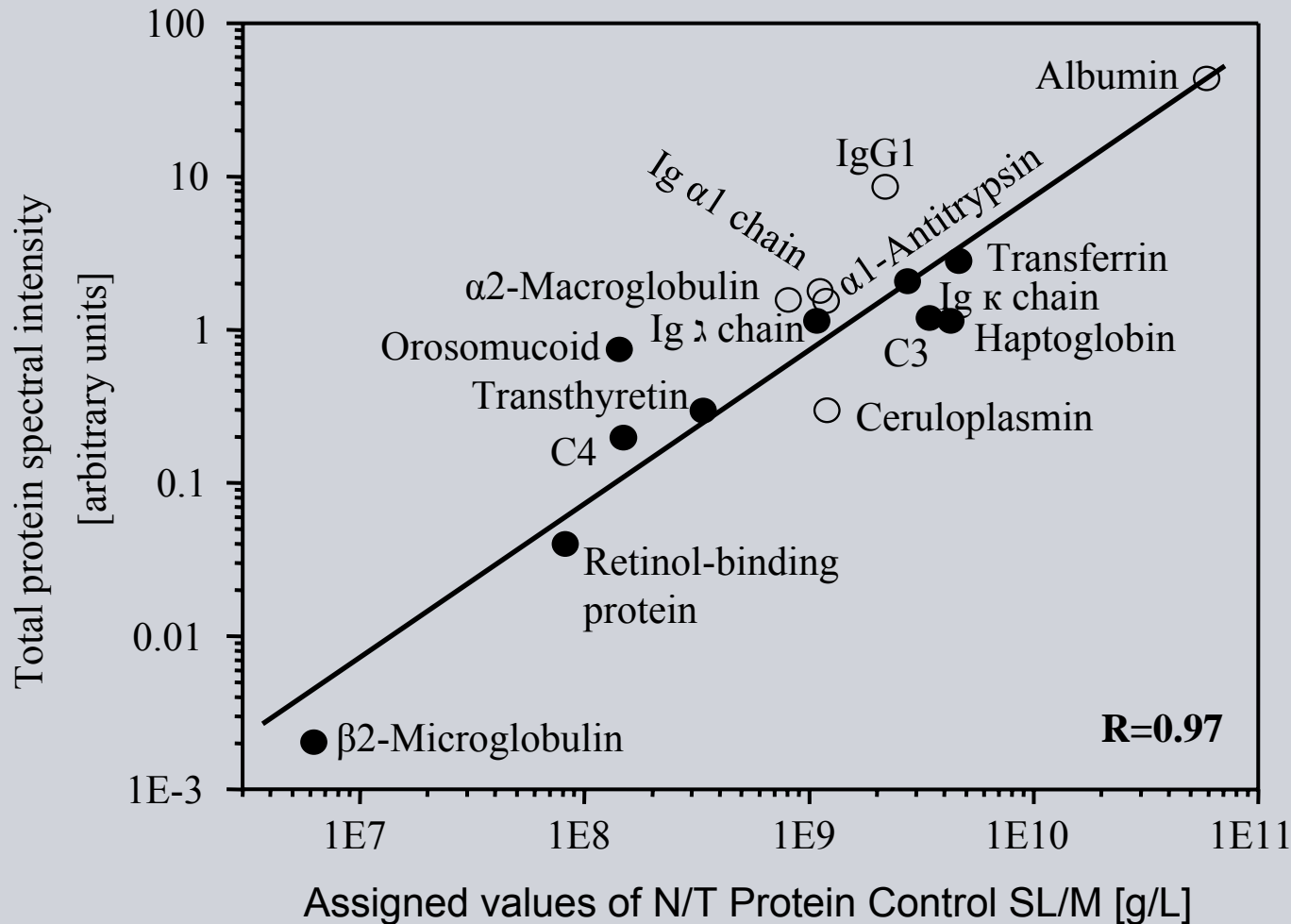
Human Proteome
Organization

Plasma Protein
Project

Pilot Phase

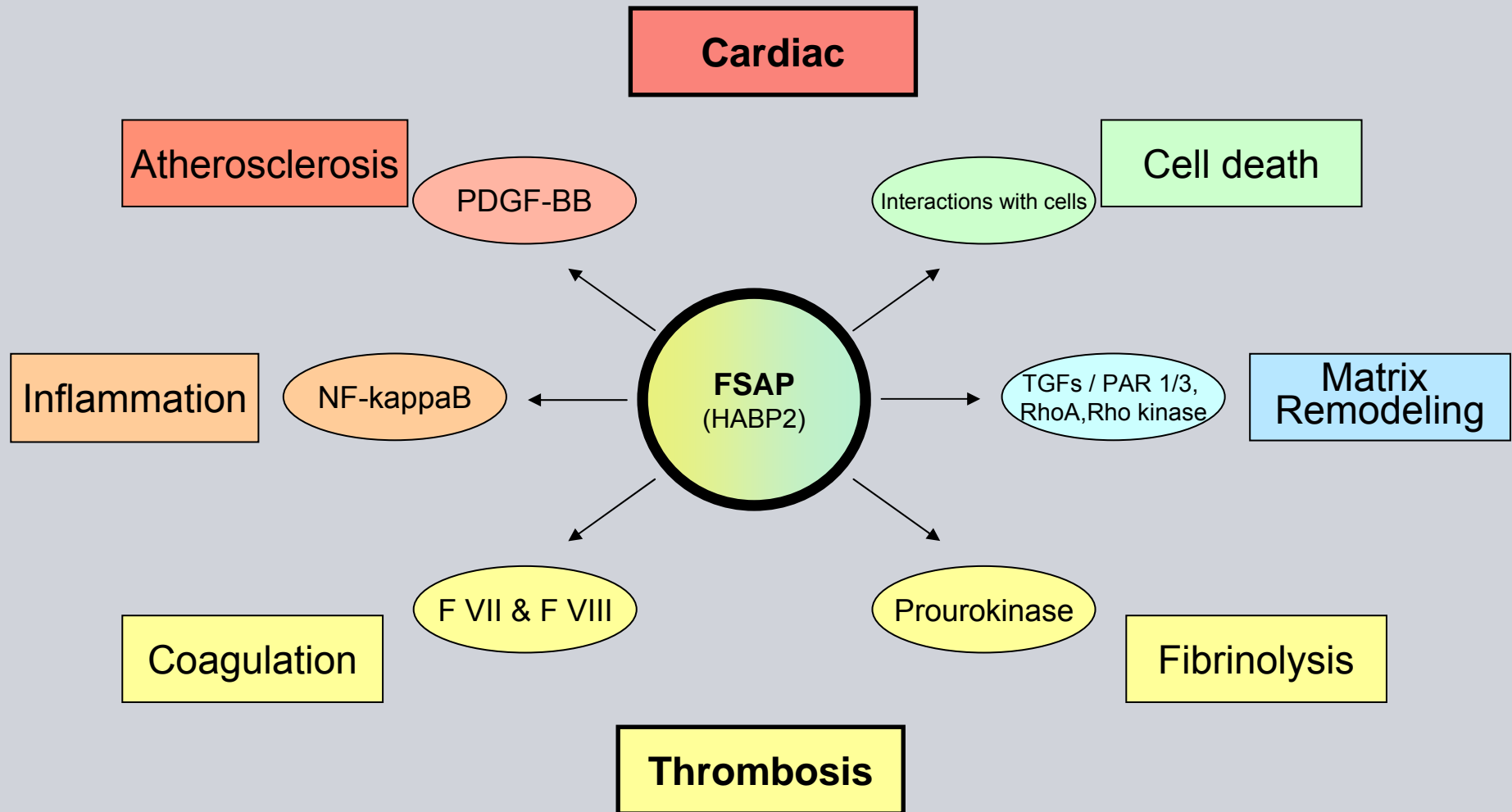
Reference
specimens
evaluation with
traceable tests

Assessment of performance of Proteomics methods



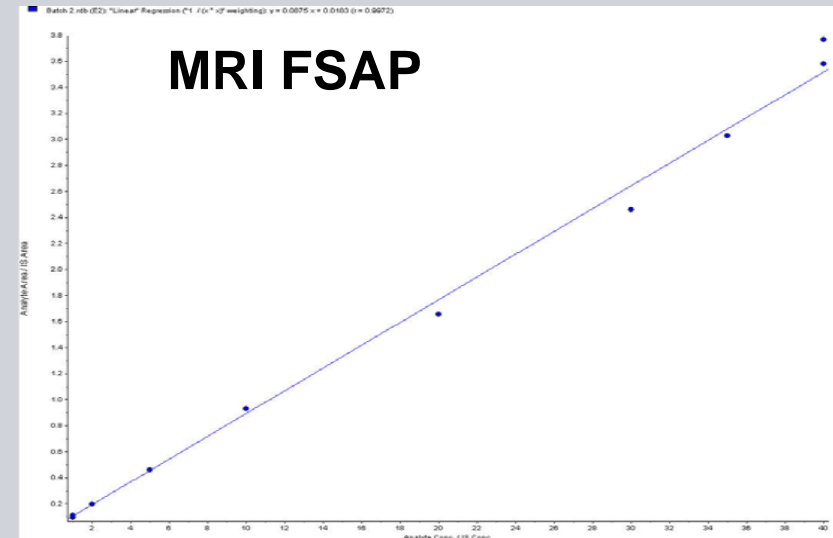
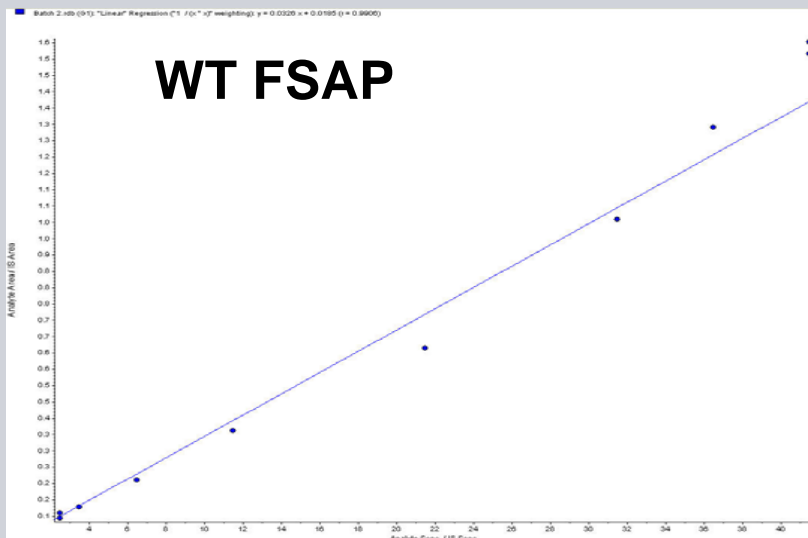
OFFGEL electrophoresis (Agilent Application Note 5989-5814EN) into 24 pl-fractions (pH 4 – 7). Individual fractions were desalted, trypsinated and analysed by C18-RP-MS/MS.

Clinical research on Factor VII-activating Protease (FSAP)



Detection of Marburg I Polymorphism (MRI) of FSAP

LC-MS/MS (Standard Addition Calibration)



Calibration line parameters:

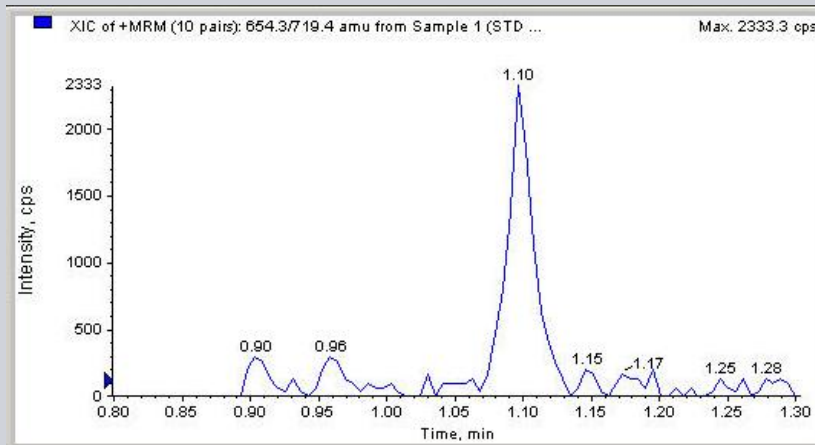
- R2 of 0.9906, 0.9972 (WT and MRI)
- All points within $\pm 20\%$ (± 25 at LLOQ) precision
- All points within $\pm 20\%$ (± 25 at LLOQ) accuracy

QUOTIENT BIORESEARCH

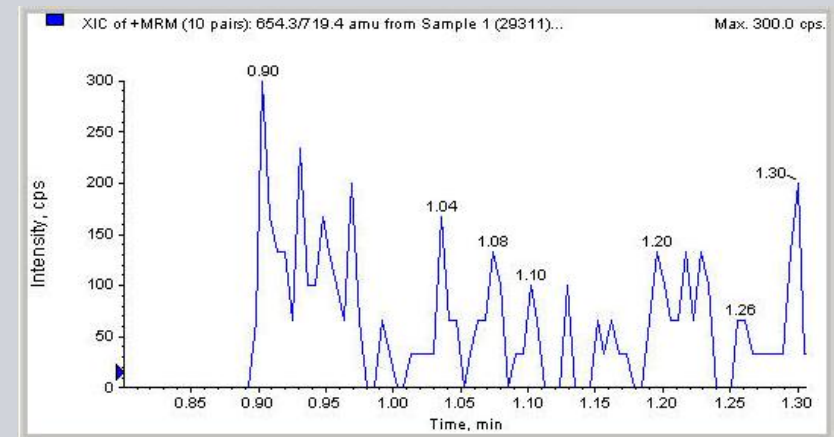


Richard Kay et al.

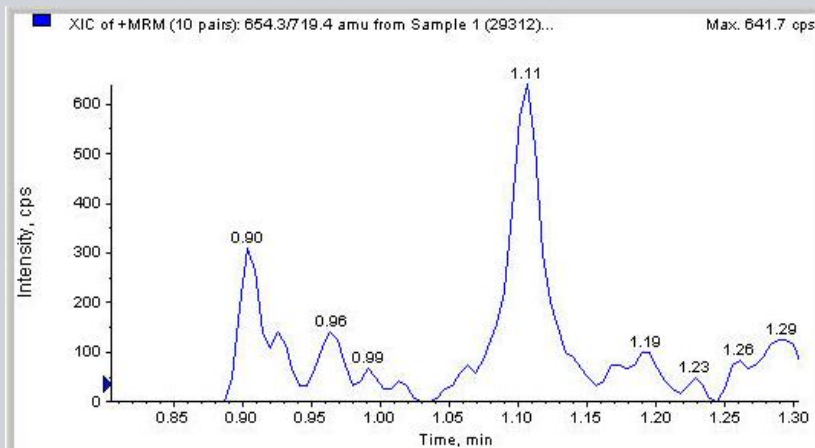
Proteotypic peptide peaks of MR I FSAP



1 µg/mL STD MRI peptide



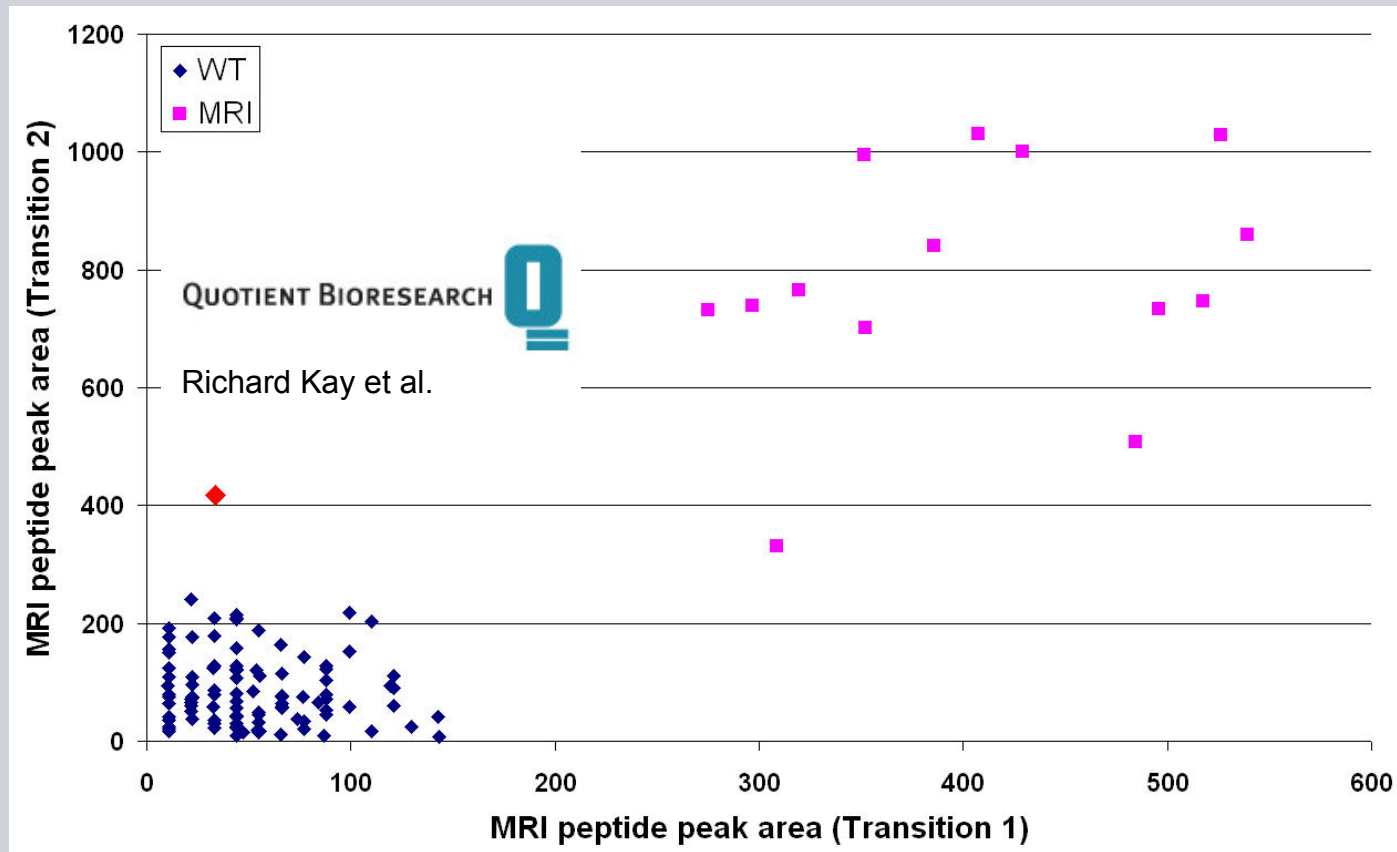
No MRI peptide in plasma



MRI peptide in plasma



Plotted peak areas of both MRI peptide transitions



Conclusions

Reference materials are the hidden treasure in IVD

- **Standardization is important to generate high quality results**
- **Global comparability of test results is key for effective and safe clinical decision making**
- **International standardization and availability of respective reference materials directly impacts healthcare independent of trends**
- **Current trends will support reference material development and application**
- **There may be potential opportunities for standardization & harmonization for biomarker research & development**
- **Is it time to lift the reference material treasure for R&D?**



**Thank you
for your
attention!**