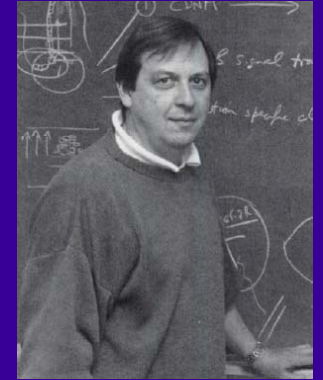




Princess Margaret Hospital and Ontario Cancer Institute



**50th Anniversary Event
16 – 18 October 2008**

**“The Unexpected Consequences of Being a Research Fellow at
PMH/OCI – Psychosocial and Proteomics”**

Peter Selby



Question

Does measuring “patient-centred” variables formally, lead to improved outcomes?

Patient-centred, self-reported information in clinical practice

A personal perspective

- there is a **NEED** for PCSR information in practice
- it can increase **DISCOVERY** of the relevant issues
- it is now **LOGISTICALLY** possible to collect and manage the data
- its use **MAY IMPROVE IMPORTANT OUTCOMES** in some settings
- we are **NOT YET VERY GOOD** at collecting or using the data

Patient-centred, self-reported information in clinical practice

Challenges

- clear conceptual frameworks and choice of topics
- what to collect and when
- how to train clinicians and alter clinical behaviour
- how to adapt healthcare systems
- how to change the culture in healthcare
- how to **ENHANCE** (not replace) the interactions between patients, carers, healthcare professionals and healthcare systems

Patient-centred, self-reported information in clinical practice

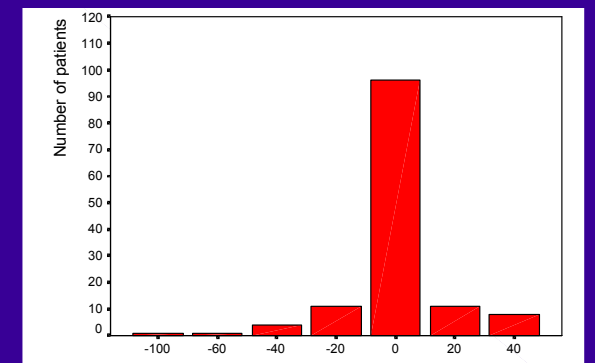
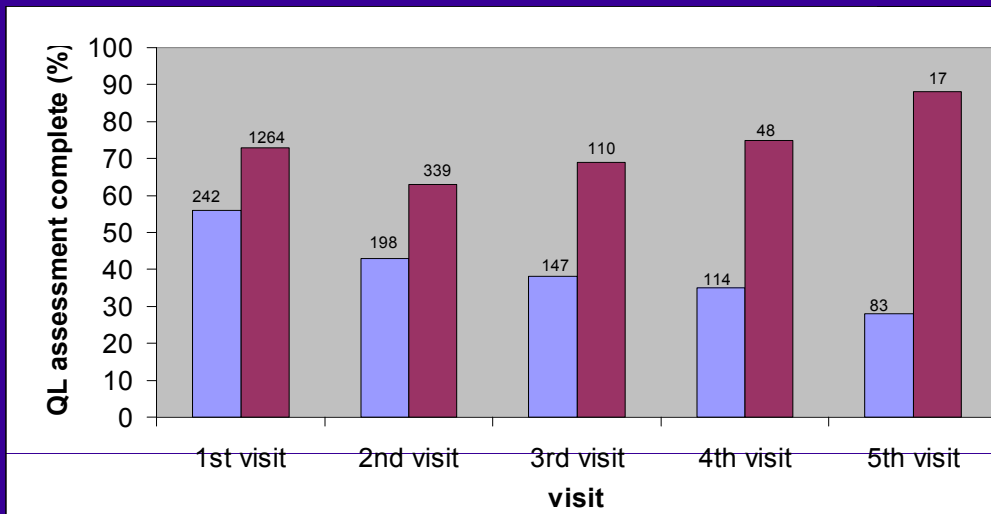
DISCOVERY

	114 Patients reporting on QLQ C30 moderate problems	% in notes
Fatigue	34	29
Pain	24	58
N & V	35	14
Dysnoea	18	56
Sleep	27	7
Appetite	18	39
Constipation	13	8
Diarrhoea	4	25
Finance	14	7

JCO 2002

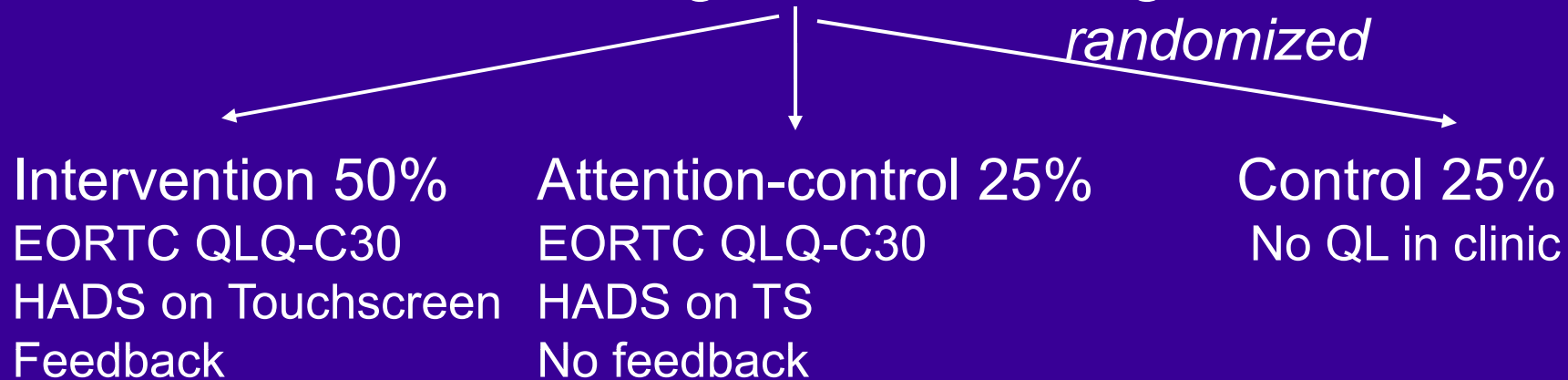
LOGISTICS

- Touch-screen data collection
- Comparison TS vs paper (J Clin Oncol, 1999)
- Patient compliance with regular QOL collection (J Clin Oncol, 2003)



Randomised Trial – Study Design

Patients starting chemo-/biological treatment



Process outcomes: tape-recording of consultations – content analysis

Patient outcomes

FACT-G (QOL Questionnaire)
Continuity & Co-ordination of Care
Satisfaction

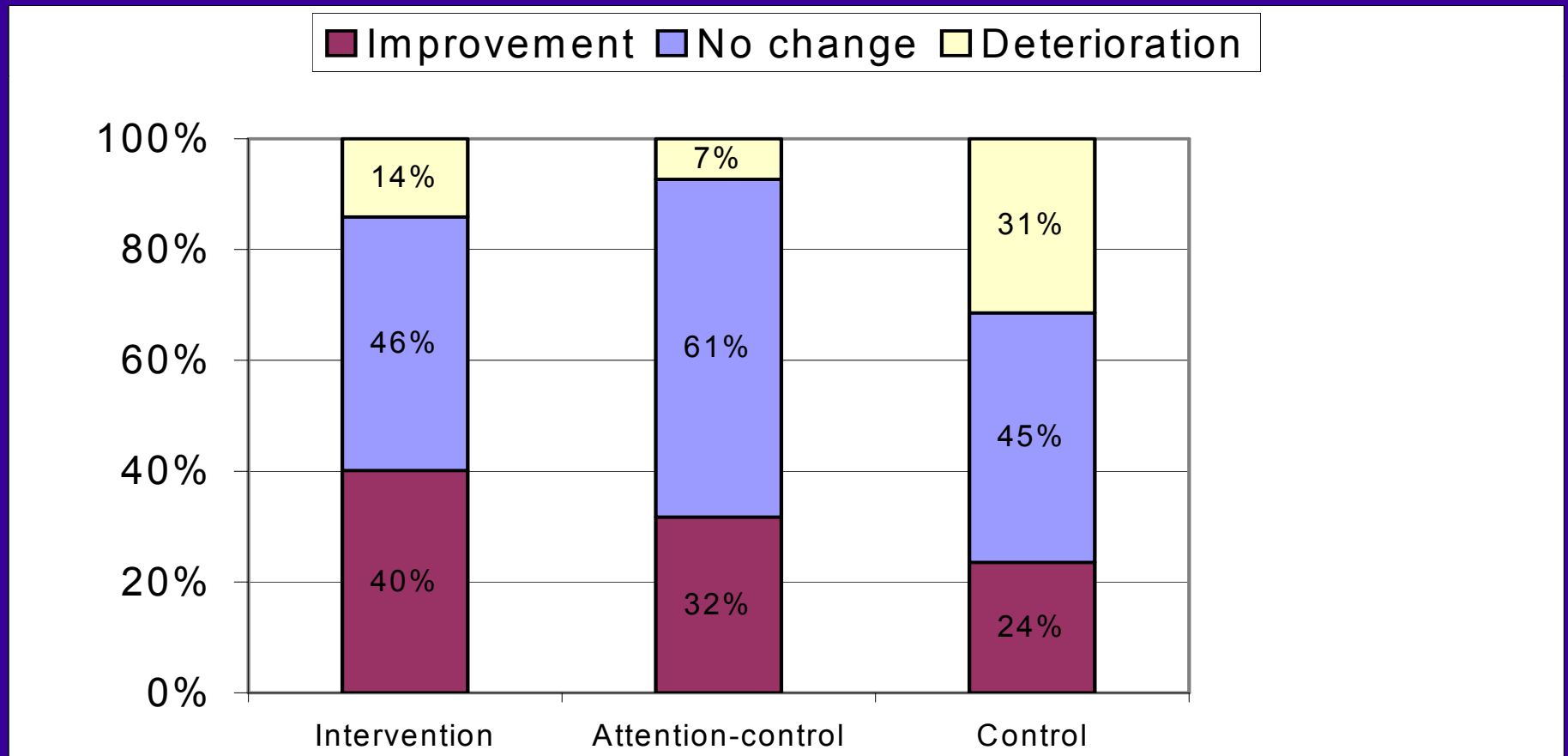


@ baseline
post 3 interventions
@ 4 months
@ 6 months

Results – Patient well-being Proportion of patients with improvement or deterioration in FACT-G scores

NNT = 4.2

Interv vs Attn-contr + Contr p=0.007, Interv + Attn-contr vs Control p=0.003



Further analysis of communication and decision making

Symptoms

- Providing QOL data lead to more consistent discussion of
 - Insomnia (p=0.003)
 - Dyspnoea (p=0.03)
- Symptoms more often raised by doctor
- Discussion of common symptoms depended mainly on whether the problem was raised at baseline
 - Pain, fatigue, nausea, appetite

Functioning

- Providing QOL data lead to more consistent discussion of
 - Physical function (p=0.006)
 - Emotional function (p=0.03)
- Not initiated by doctor
- No effect on social function

Health-Related Quality of Life Assessments and Patient-Physician Communication

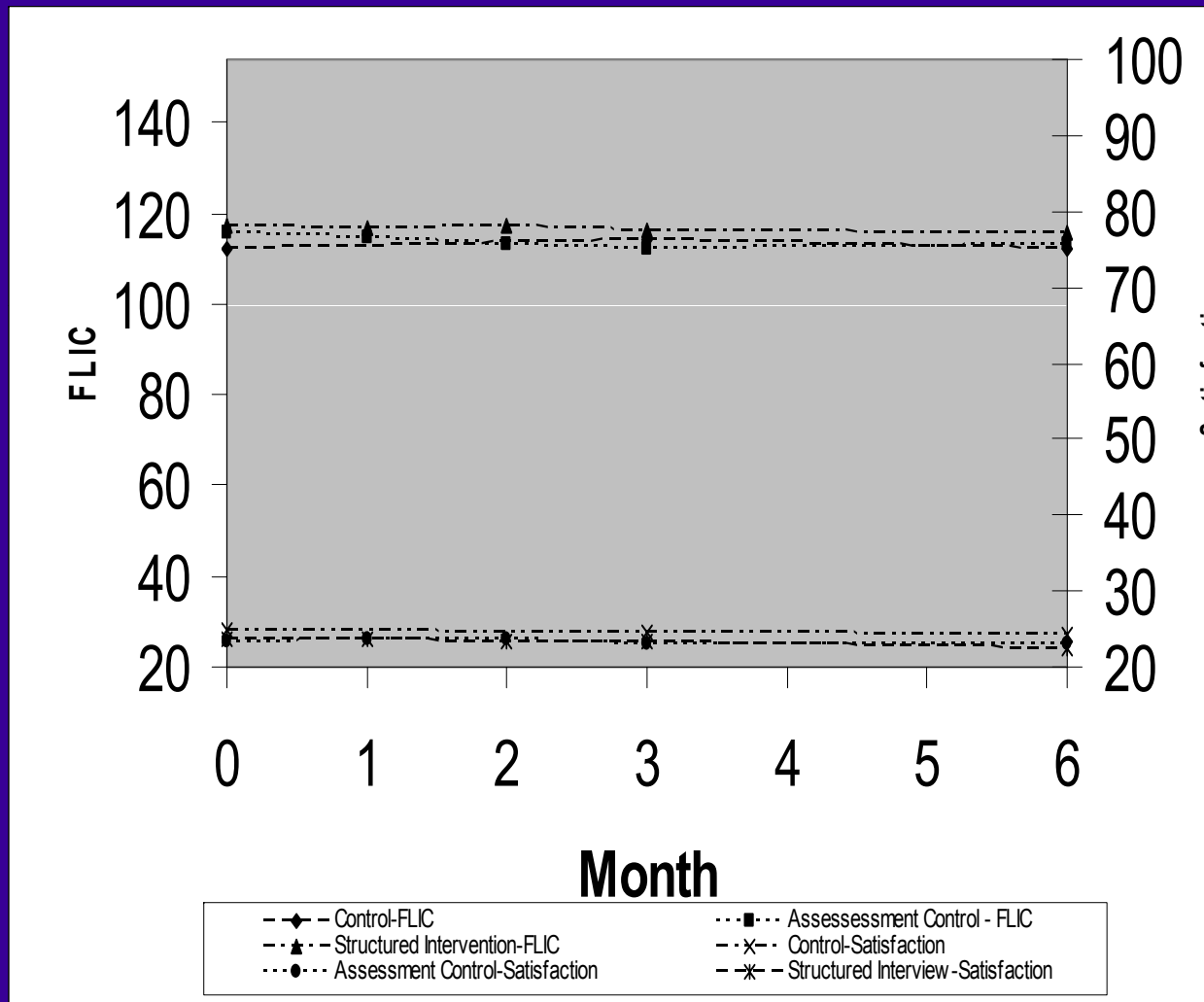
Detmar, Aaronson et al, 2002

Randomised Trial: 214 patients / 10 physicians

Use of QLQ-C30 led to:

- more HRQL issues discussed
- more health problems identified
- support from patients and staff
- **NO CHANGE IN QL** (on SF 36)
- **improvements in EMOTIONAL FUNCTION (.04) and ROLE FUNCTION (.05)**

Health-Related Quality of Life (HRQL) and Satisfaction Scores Over Time



The Social Difficulties Inventory (SDI)

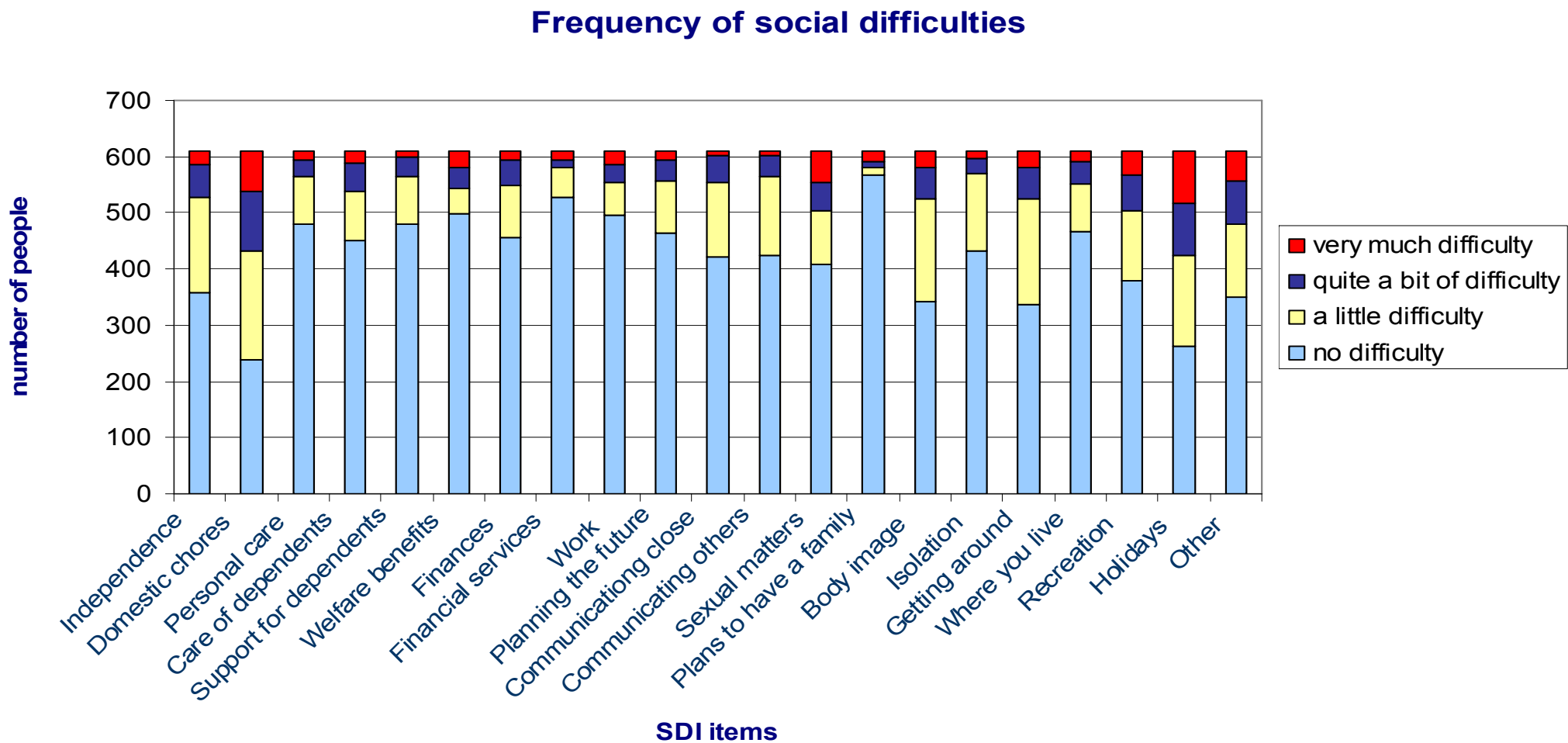
During the past month	No difficulty	A little	Quite a bit	Very much
1. Have you had any difficulty in maintaining your independence?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Have you had any difficulty in carrying out your domestic chores? (e.g. cleaning, gardening, cooking, shopping)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Have you had any difficulty with managing your own personal care? (e.g. bathing, dressing, washing)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Have you had any difficulty with looking after those who depend on you? (e.g. children, dependent adults, pets)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Have any of those close to you (e.g. partner, children, parents) had any difficulty with the support available to them?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Have you had any difficulties with benefits? (e.g. statutory sick pay, attendance allowance, disability living allowance)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Have you had any financial difficulties?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Have you had any difficulty with financial services? (e.g. loans, mortgages, pensions, insurance)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Have you had any difficulty concerning your work? (or education if you are a student)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Have you had any difficulty with planning for your own or your family's future? (e.g. care of dependents, legal issues, business affairs)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Have you had any difficulty with communicating with those closest to you? (e.g. partner, children, parents)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

During the past month	No difficulty	A little	Quite a bit	Very much
12. Have you had any difficulty with communicating with others? (e.g. friends, neighbours, colleagues, dates)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Have you had any difficulty concerning sexual matters?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Have you had any difficulty concerning plans to have a family?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Have you had any difficulty concerning your appearance or body image?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Have you felt isolated?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Have you had any difficulty with getting around? (e.g. transport, car parking, your mobility)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Have you had any difficulty with where you live? (e.g. space, access, damp, heating, neighbours, security)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Have you had any difficulty in carrying out your recreational activities? (e.g. hobbies, pastimes, social pursuits)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Have you had any difficulty with your plans to travel or take a holiday?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Have you had any difficulty with any other area of your everyday life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Thank you for your help

A meaningful SDI scoring system

Individual items



A meaningful SDI scoring system-Rasch analysis

Independence
Domestic chores
Personal care
Care of dependents
Support for those close to you
Welfare benefits
Finances
Financial services
Work
Planning the future
Communication with close
Communication with others
Sexual matters
Plans to have a family
Body image
Isolation
Getting around
Where you live
Recreation
Holidays
Other

Measure of social distress (SD)

16 items

Unidimensional

72% of the variance

Differences in scores are equally spaced

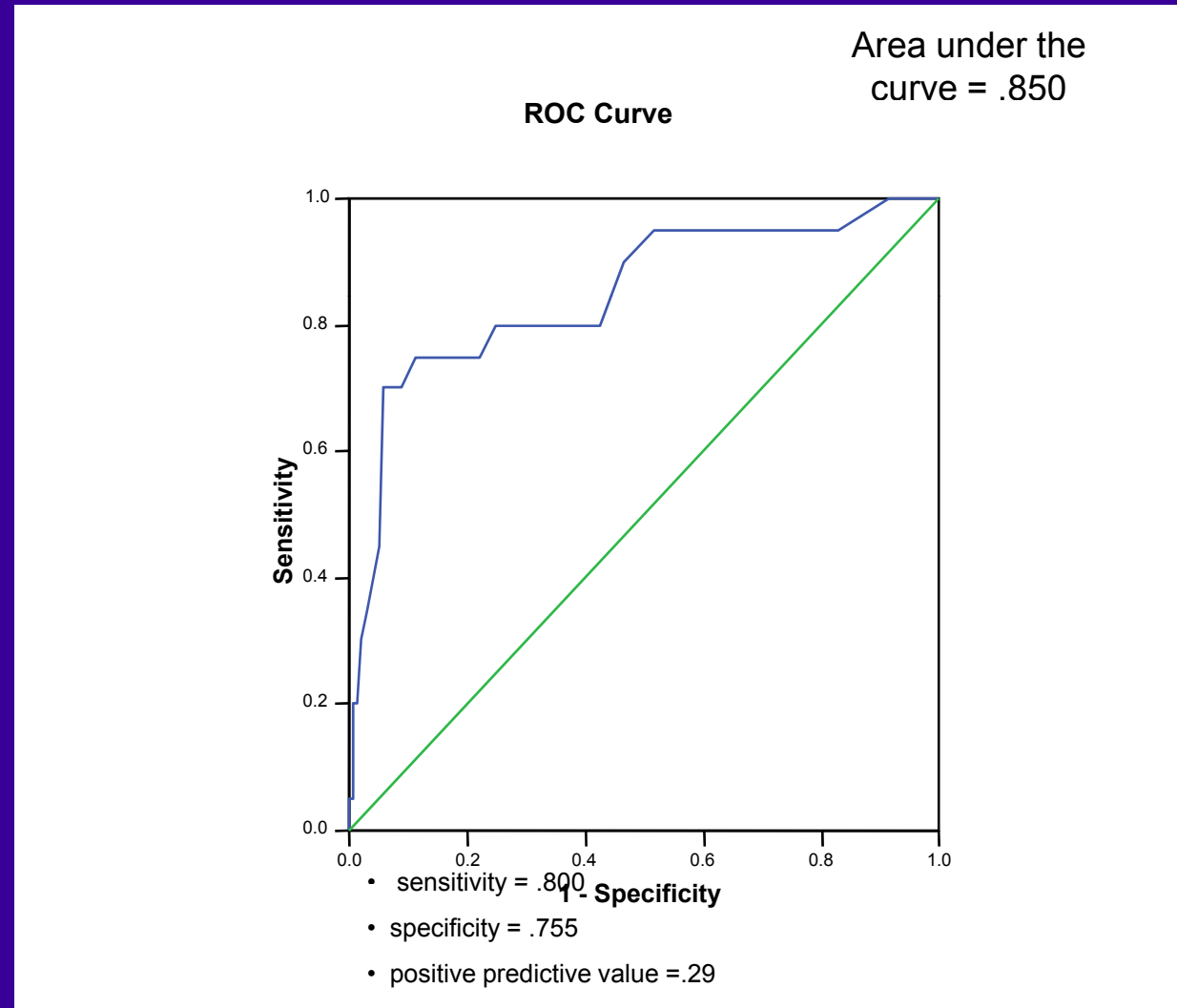
Interval scale

Age, gender, stage & site of disease, deprivation

Results: deriving a cut point

Social Distress (SD) (16 Rasch items)

- Top 10% of researcher SD ≥ 14 (gold standard for SD)
- Using this gold standard the best 'cut-point' was patient SD ≥ 10



Summary

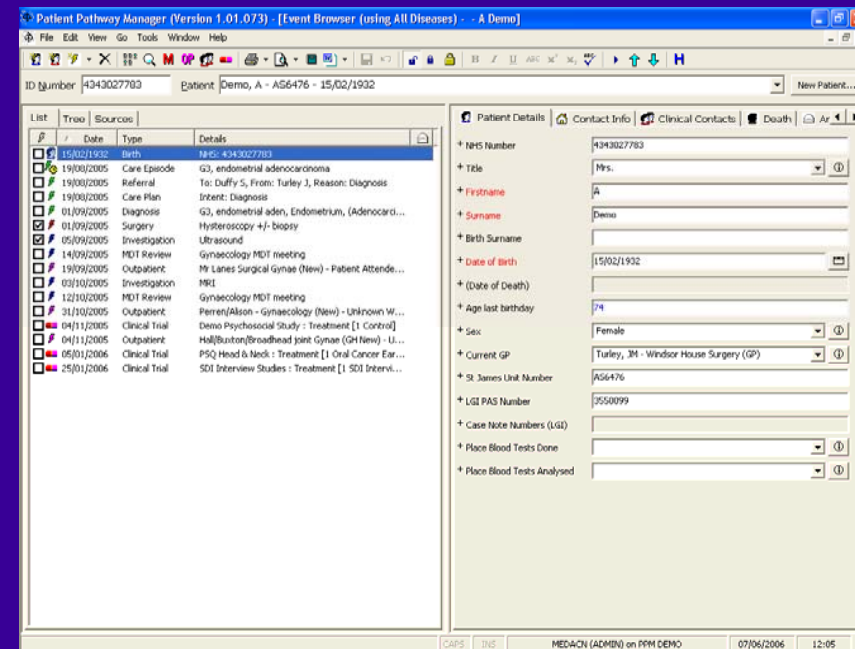
We have the technology

Routine QL assessment does improve QL in some studies

There is potential for making questions asked more specific to individual patients

Future studies

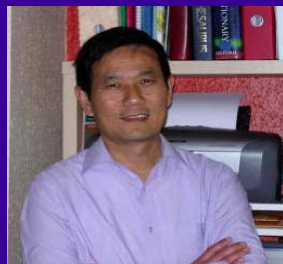
- *Making assessments more individual*
- *The roles undertaken by different members of the multidisciplinary team*
- *How people make decisions*
- *Staff training & patient information needs*
- *Widening access—web based systems*





Galina Velikova

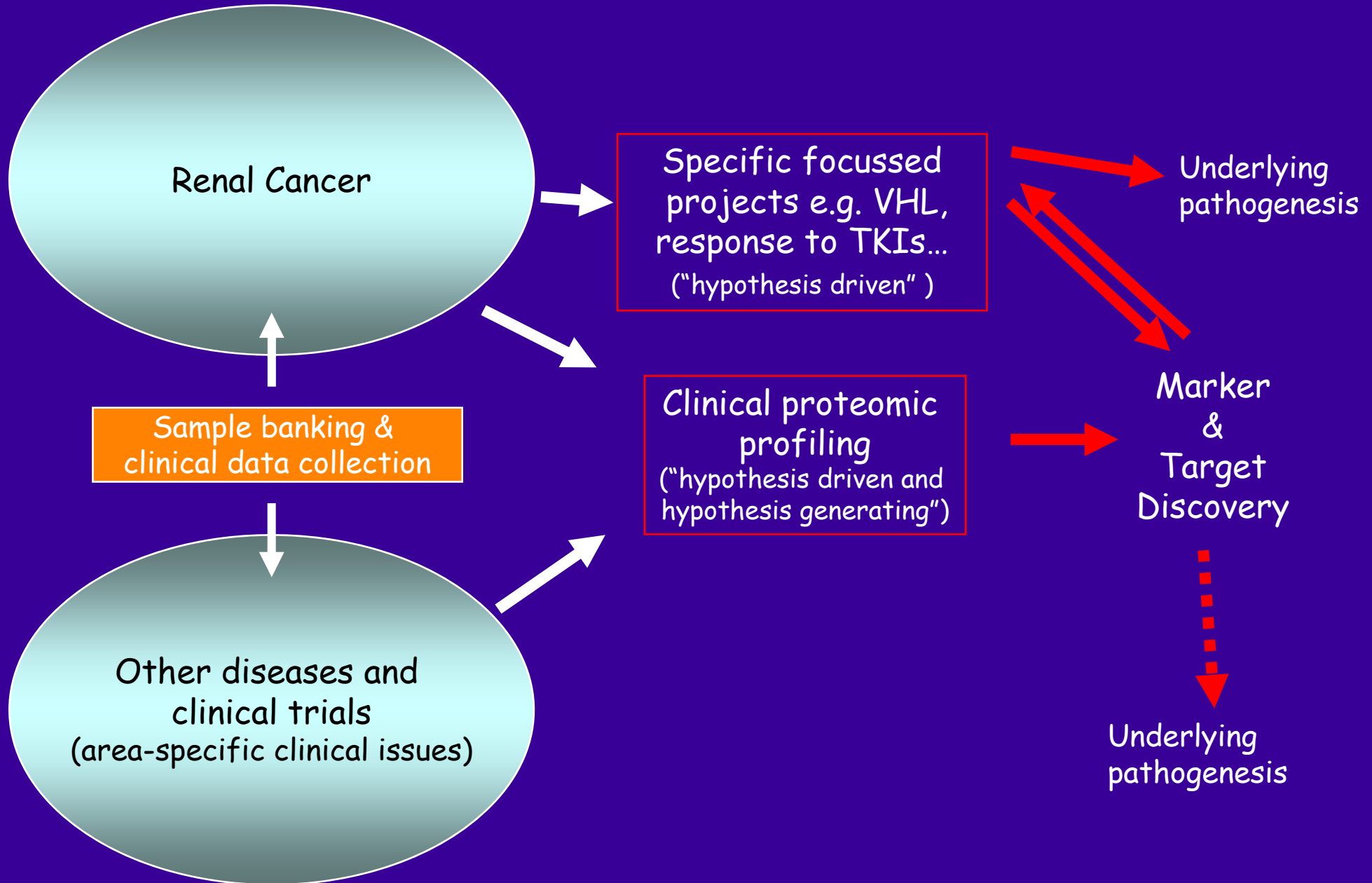
Penny Wright



Question

Can proteomic approaches to biomarker discovery and evaluation improve our management of patients and their outcomes?

Leads Proteomic Activities



Why Proteomics?

Functional entities in biological systems

Post translational modifications

Access in biological fluids

Why not Proteomics alone?

Absences of amplification steps (sensitivity)

Highly multi-professional teams needed and expensive equipment

Clinical Proteomics

- essentially profiling e.g comparison of samples to find differences due to disease, drug treatment etc
- key in marker discovery but also provides biological information

“Cell-Mapping” Proteomics

- addressing the question of protein function from interactions e.g. isolating/characterising protein complexes

Much of proteomics research is **very technology-dependent**:

2D-PAGE

MALDI MS

SELDI MS

LC/LC-MS/MS

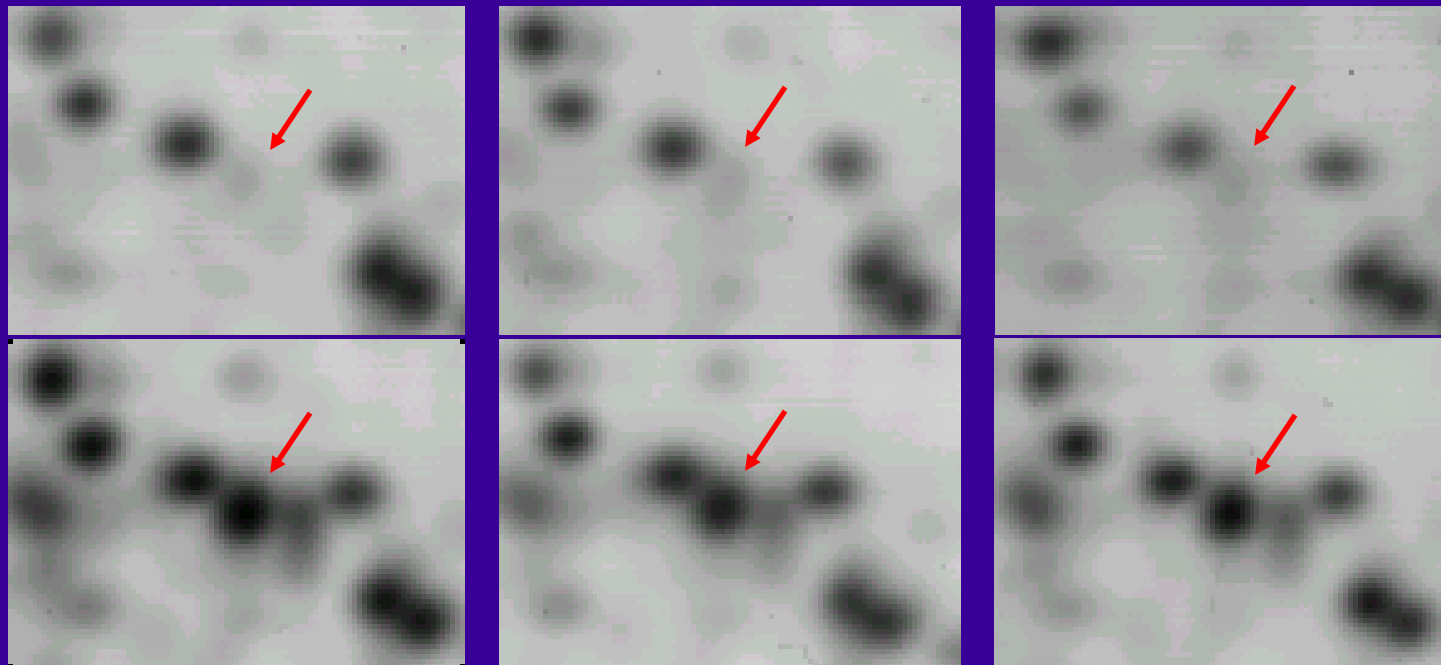
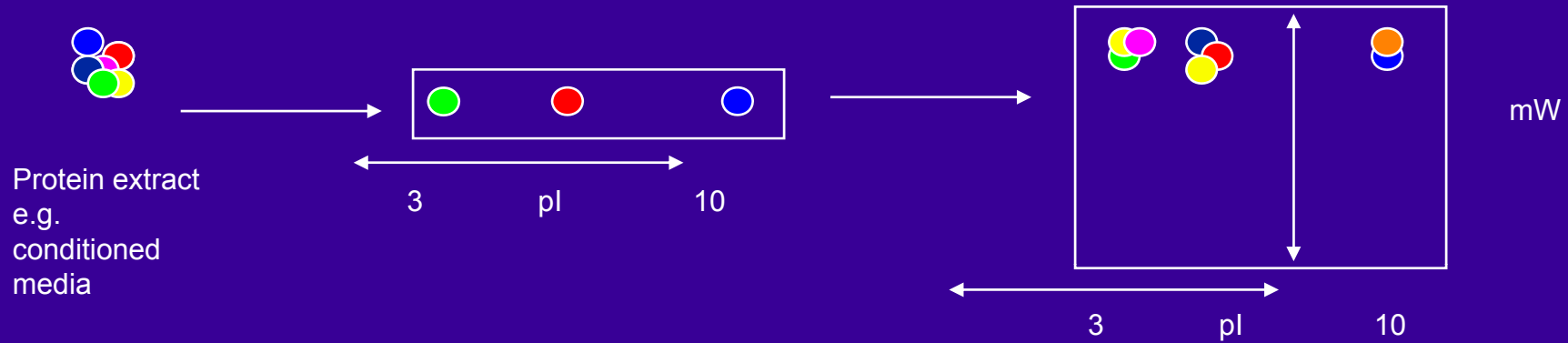
Protein/antibody arrays

ICAT

iTRAQ

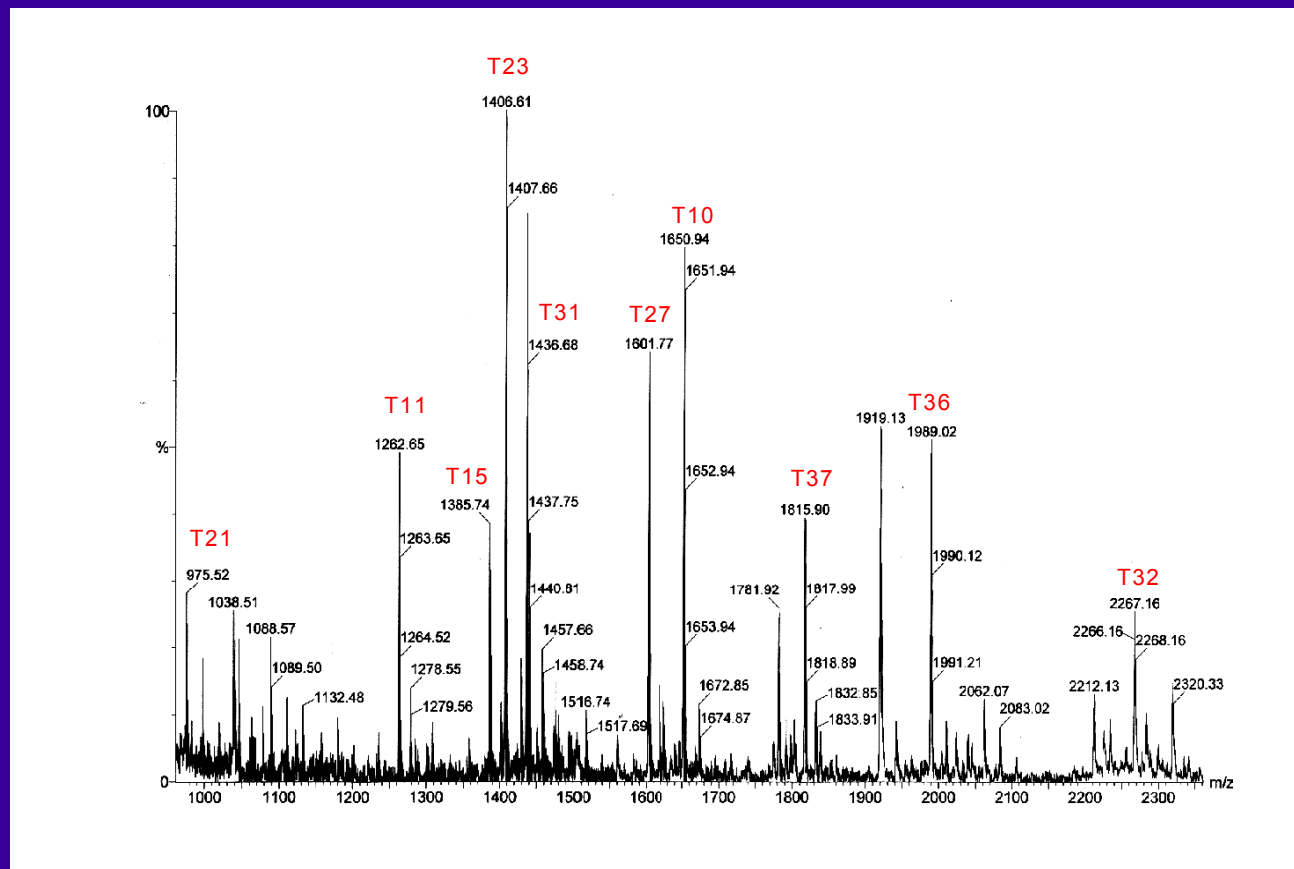
Novel prefractionation

Novel Biomarkers: 2D PAGE



Protein Identification – Mass Spectrometry

Excise protein – digest – MALDI-TOF peptide mass fingerprint (PMF) or MS/MS sequencing – database query – protein ID.



Surface Enhanced Laser Desorption/Ionisation (SELDI™) Mass Spectrometry

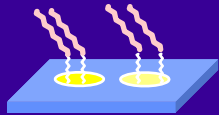
- ProteinChips™ 8/16 spot arrays - different chromatological surfaces – selective protein binding
- Analysed by time-of-flight mass spectrometry
- Optimal <20 kDa



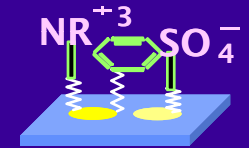
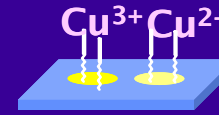
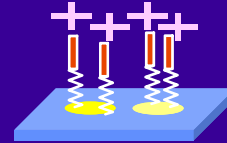
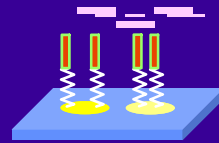
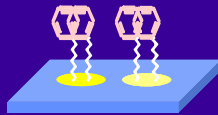
SELDI ProteinChip™ Arrays



By Surface 'Chemistries'



Hydrophobic Sites

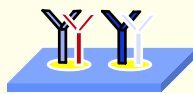


Ionic Sites

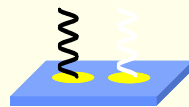
IMAC Sites

Mixed Sites

By Surface 'Biologies'



Antibody Chips



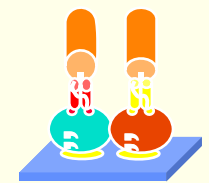
DNA Chips



Enzyme Chips



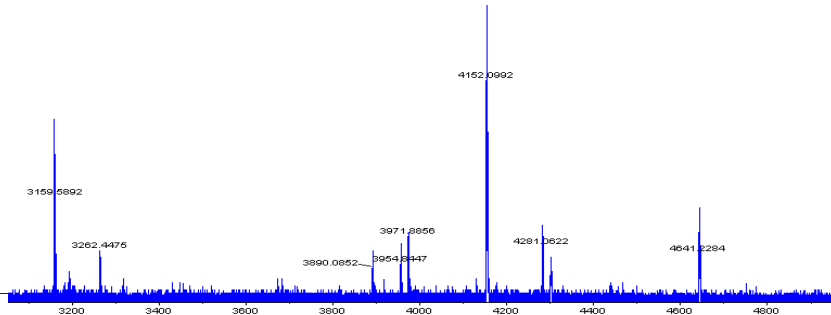
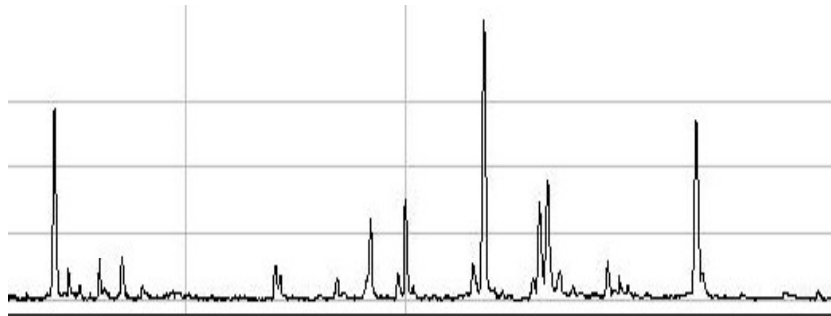
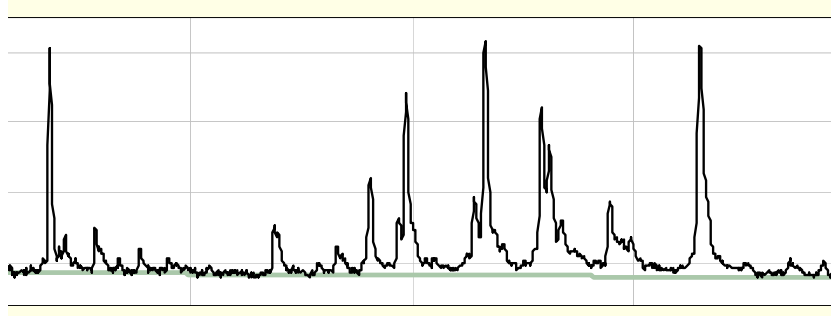
Receptor Chips



scFv Chips

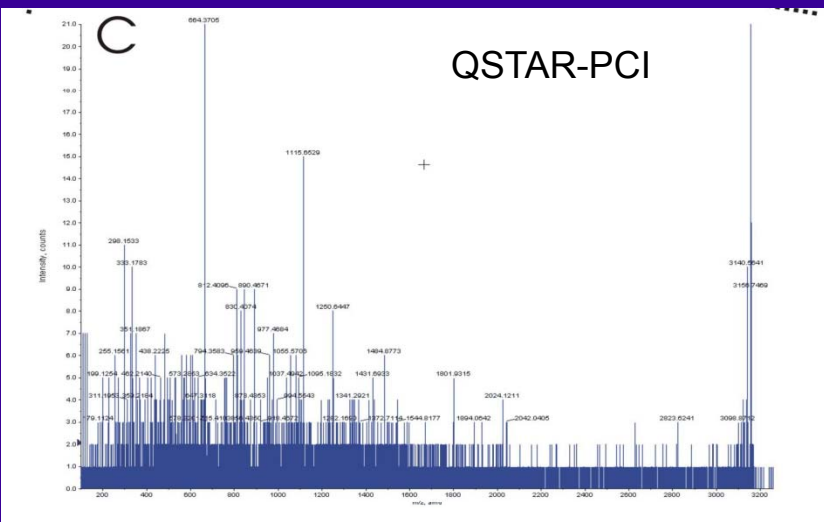
Peak Identification

Serum-CM10



3,000 – 5,000 m/z

Profiling may be useful but ultimately identification of discriminant peaks is key



3156.61
Fragment of PK-120
(inter-alpha trypsin inhibitor H4)

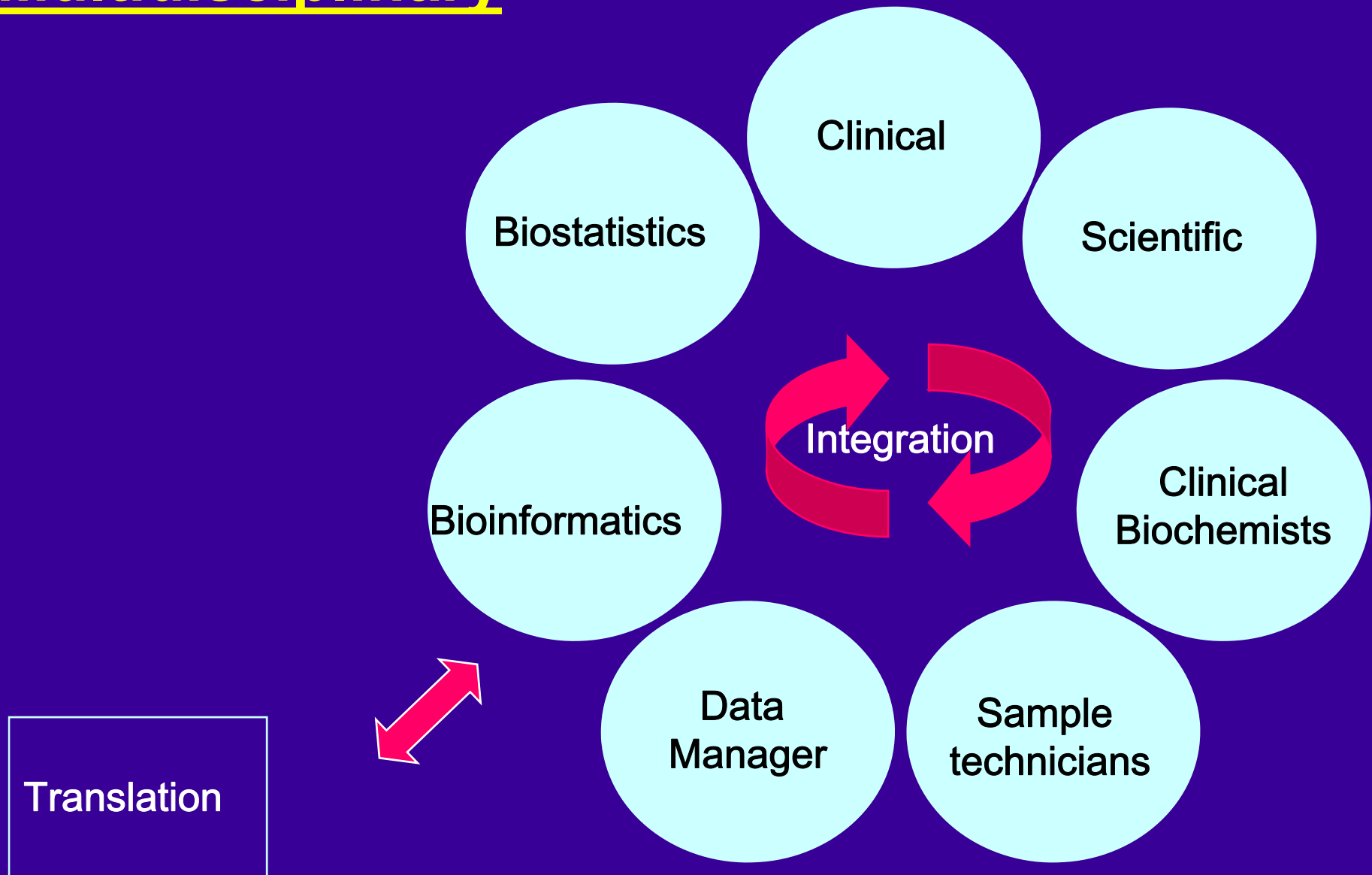
Ideal for examining the “peptidome” or “interactome”.
MW < 6kDa for sequence.
MW < 40kDa for MS profile

PBS-II

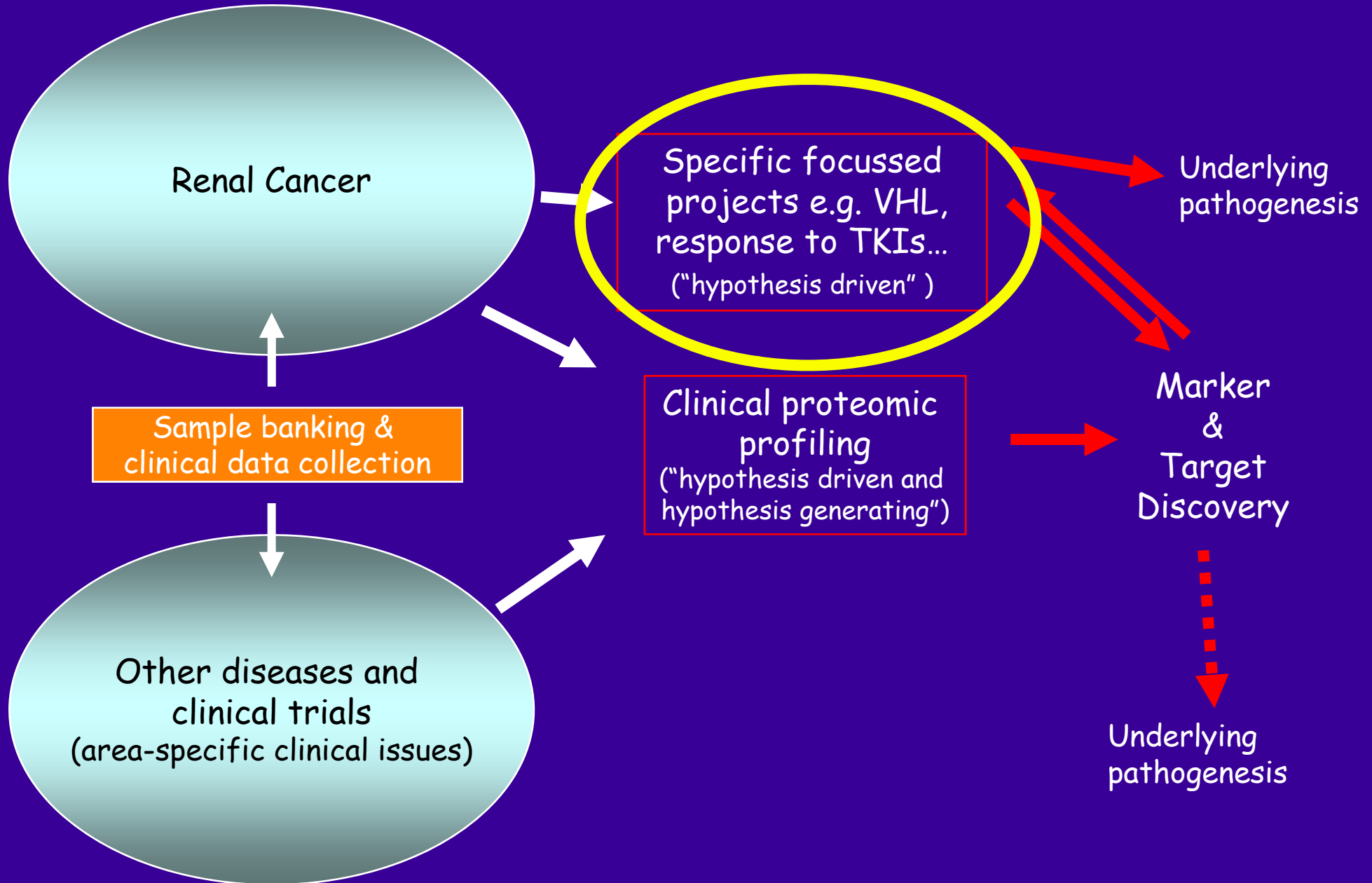
4000

QSTAR
PCI

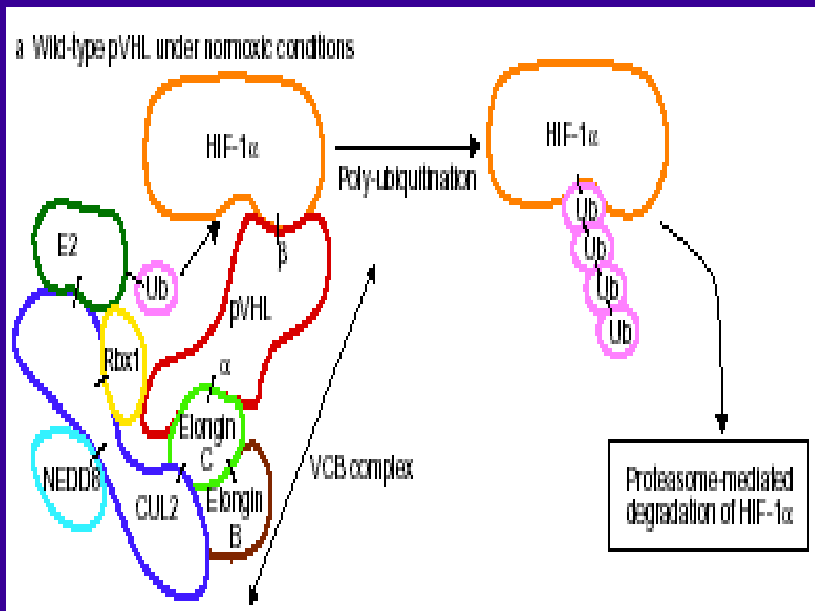
Multidisciplinary



Leads Proteomic Activities

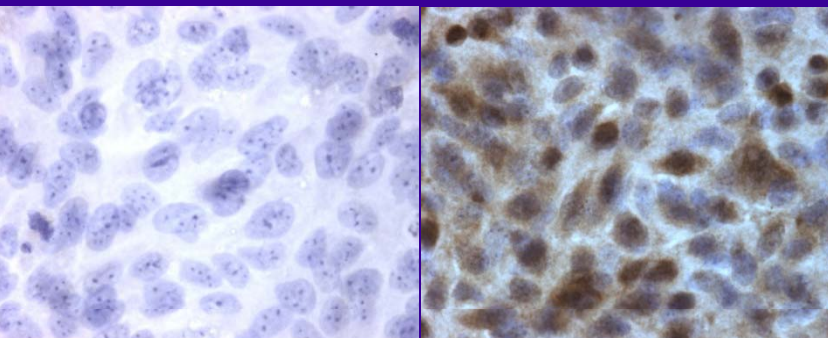
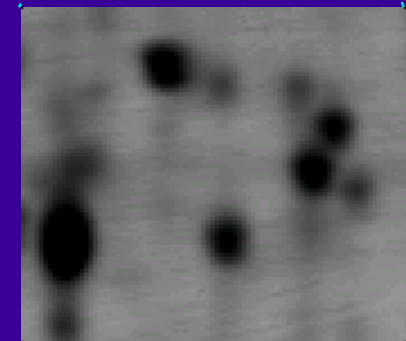
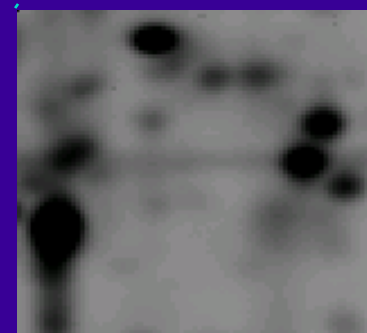
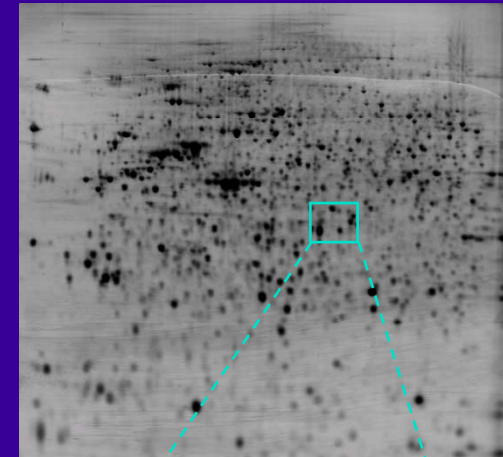
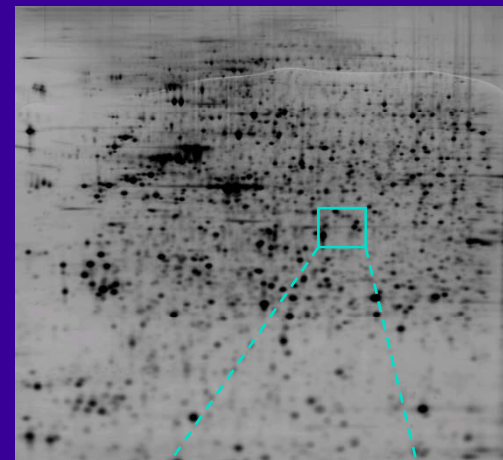


Von Hippel Lindau (VHL)



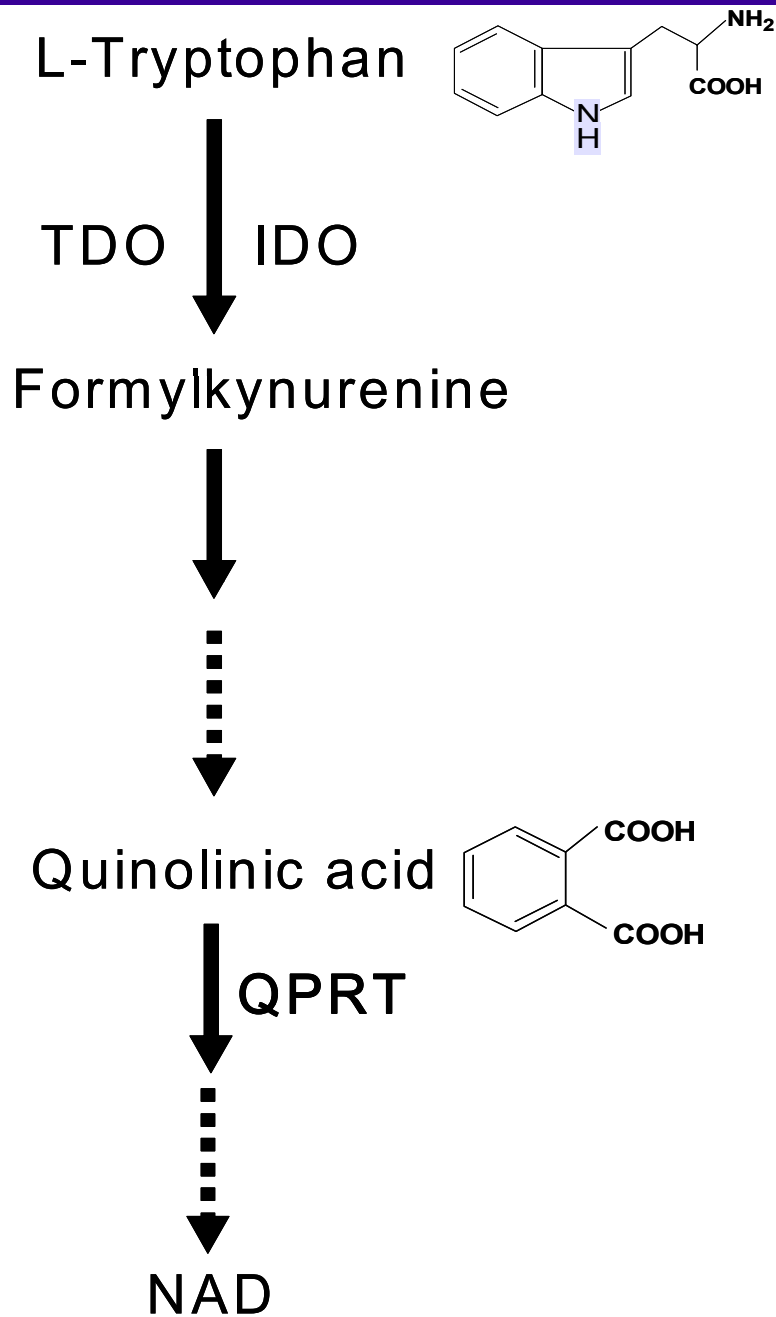
-VHL

+VHL



Antibody validation of QPRT

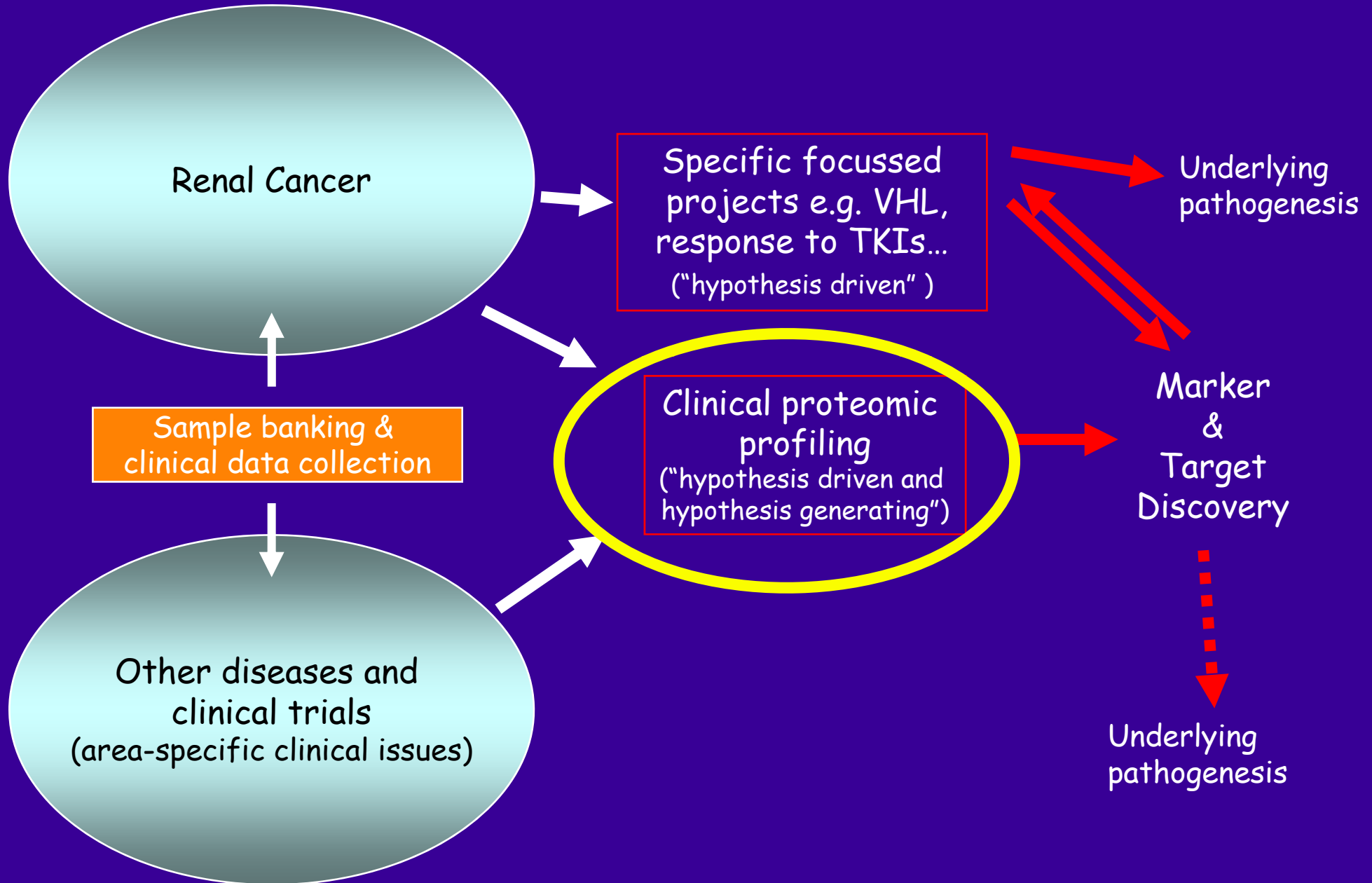
Quinolate phosphoribosyl transferase



QPRT IN Renal Cancer

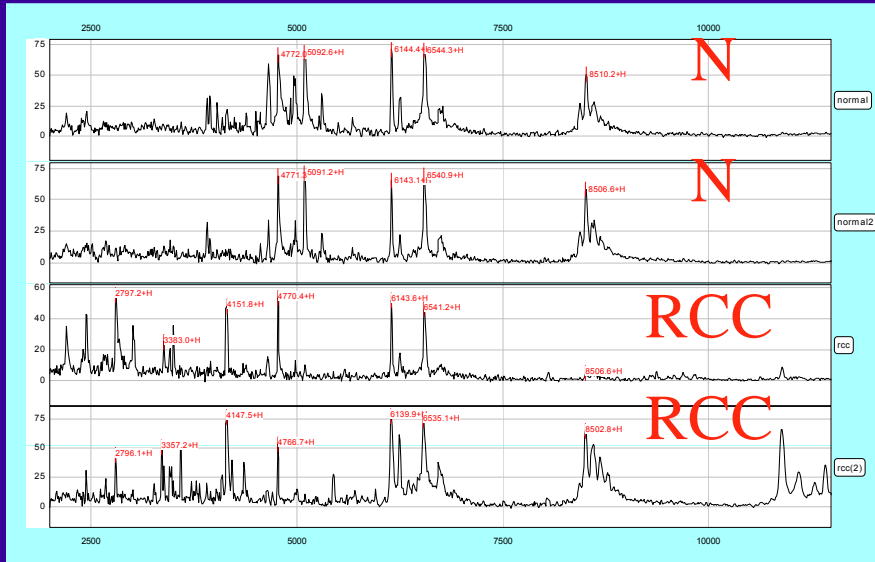
- Loss of QPRT is common in tumours
- Quinolinic acid accumulates
- Q stimulates N-methyl-D-Aspartate receptors
- Targets for cancer therapy

Leads Proteomic Activities

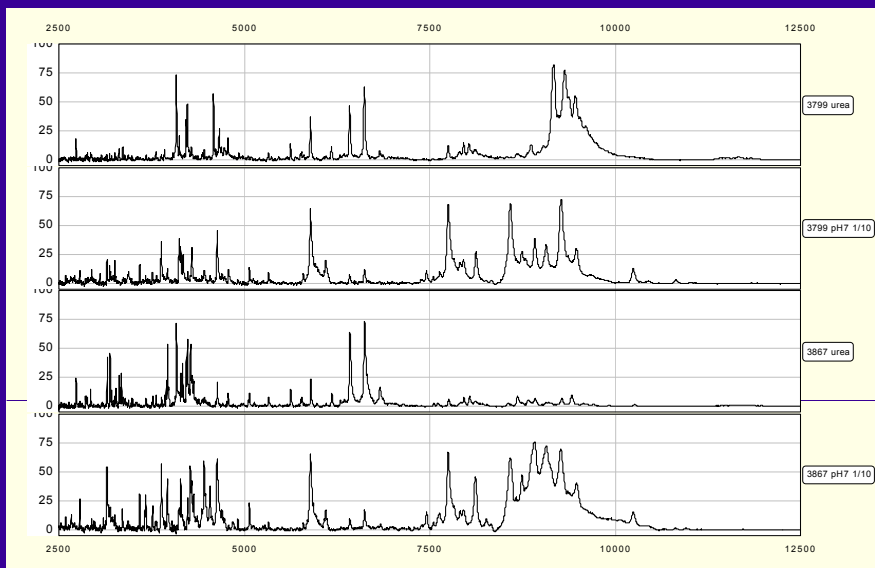


Profiles, peak identification, bioinformatics and statistics

RCC Urine – diagnosis SELDI. WCX2 chip



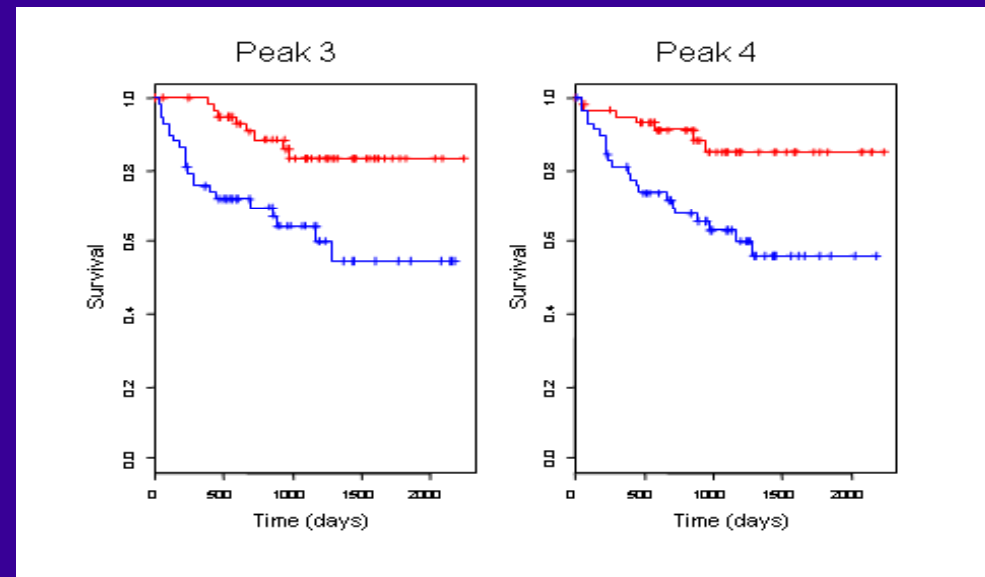
RCC Serum–prognosis SELDI.CM10 chip



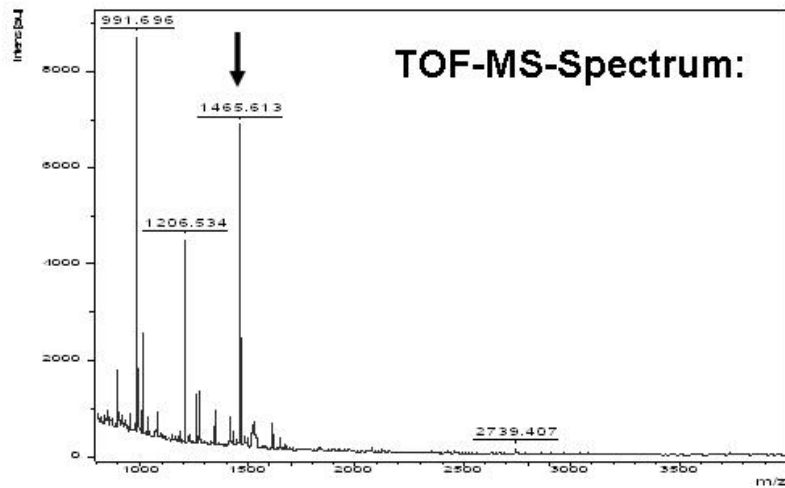
Initial Results (neural network)

	Sensitivity	Specificity
<i>Training</i> RCC (48) vs Controls (38)	100%	100%
<i>Initial Blind</i> RCC (12) vs Controls/benign (20)	83.3%	85.0%

Several discriminatory peaks

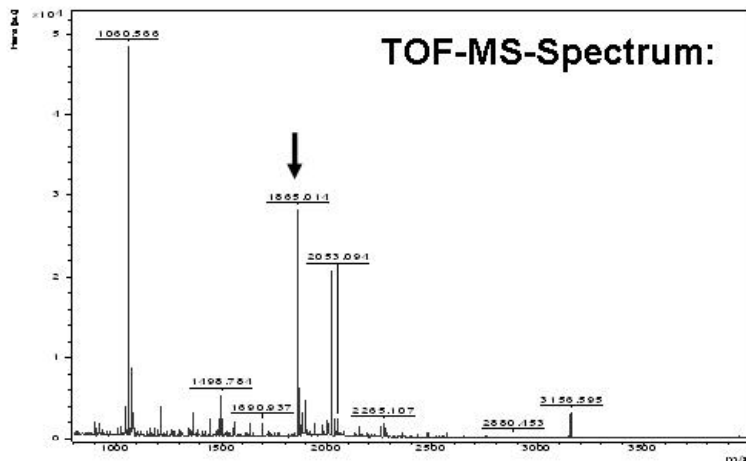


“Fraction 8”



MSMS Spectrum, Mr (observed) = 1464.6131:

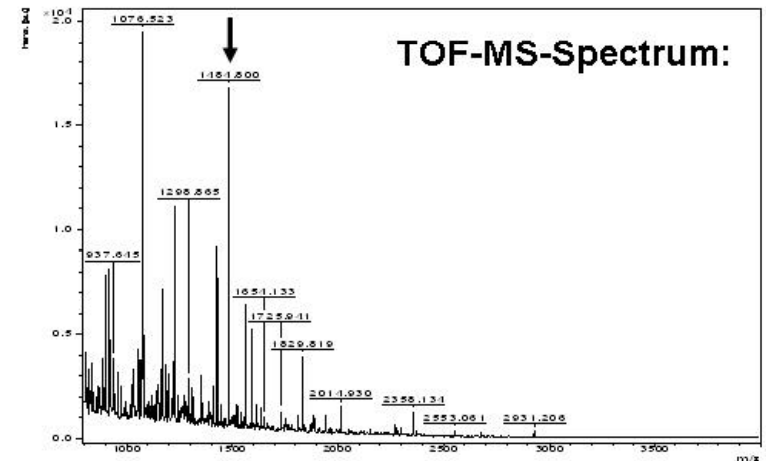
“Fraction 53”



MSMS-Spectrum, Mr (observed) = 1865.0143:

Identification of Prognostic Peaks

“Fraction 62”



MSMS-Spectrum, Mr (observed) = 1484.7998:

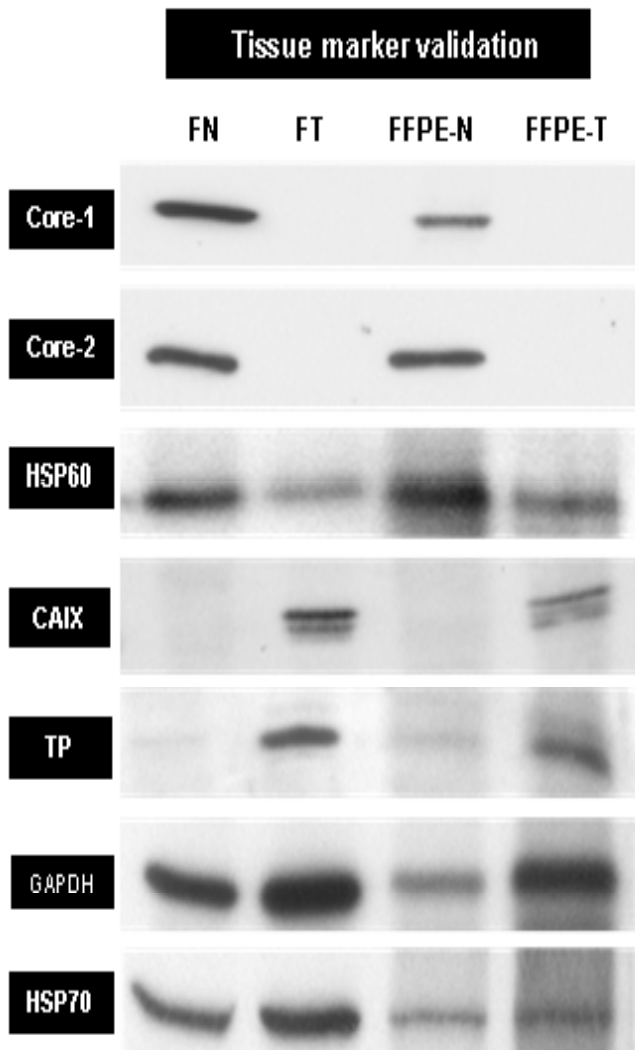


Fig. 5c

Archival FFPE tissue – a major resource But – limited suitability

Excellent correlation in results

Still problems to overcome

- dependence on specific protein
- optimisation of normalisation

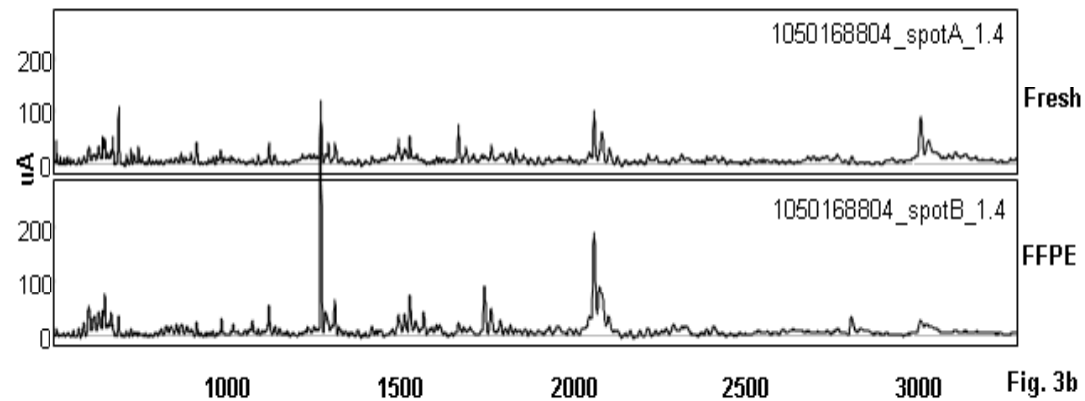


Fig. 3b

NIHR Applied Programme

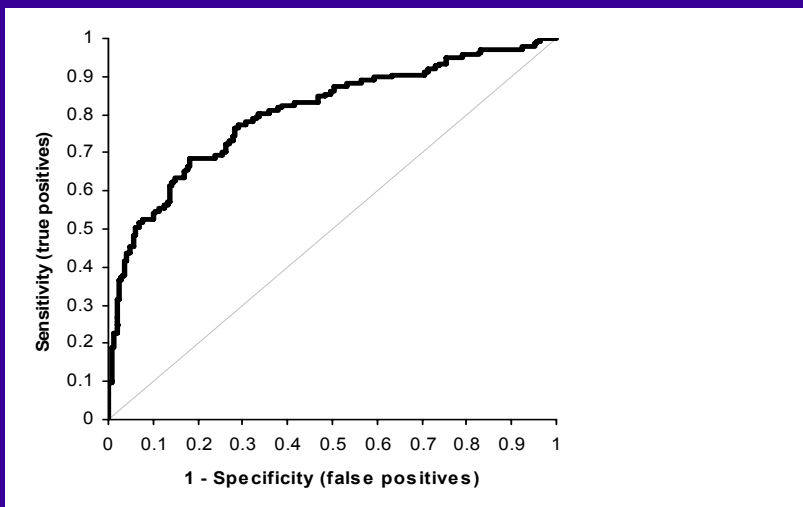
Biomarkers have major potential benefits for patients and the NHS, particularly in contributing to "personalised" and/or "stratified" medicine and improved safety. They may supplement or replace invasive procedures or imaging tests for:

- accurate and early diagnosis
- measurement of the activity and extent of disease
- indication of prognosis
- selection and prediction of optimal treatments
- monitoring for treatment response/toxicity or disease progression

NIHR Applied Programme

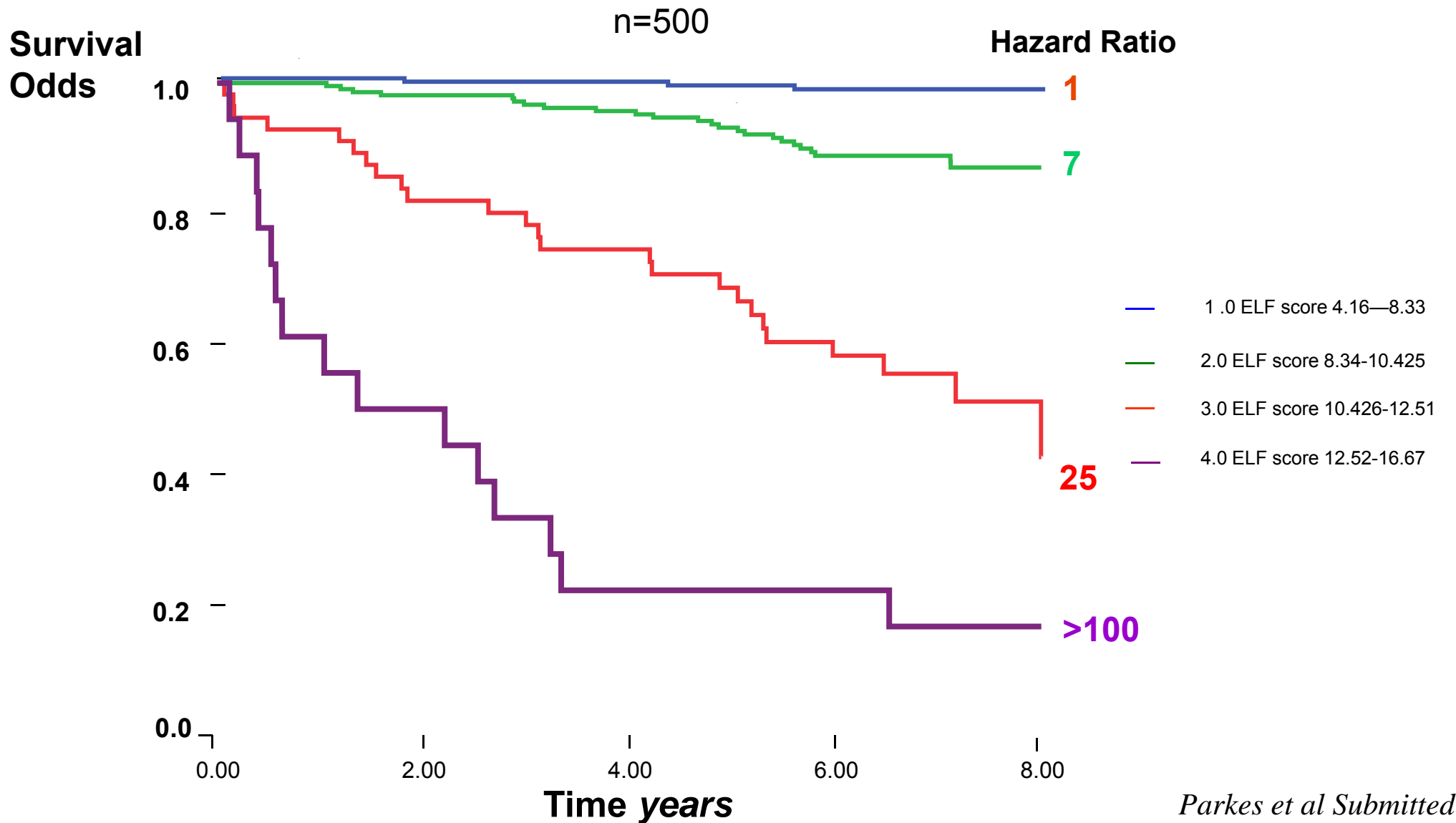
Potential to improve patient care and health service provision is not yet being realised because the pathway linking biomarker research to health services research is still quite poorly defined.

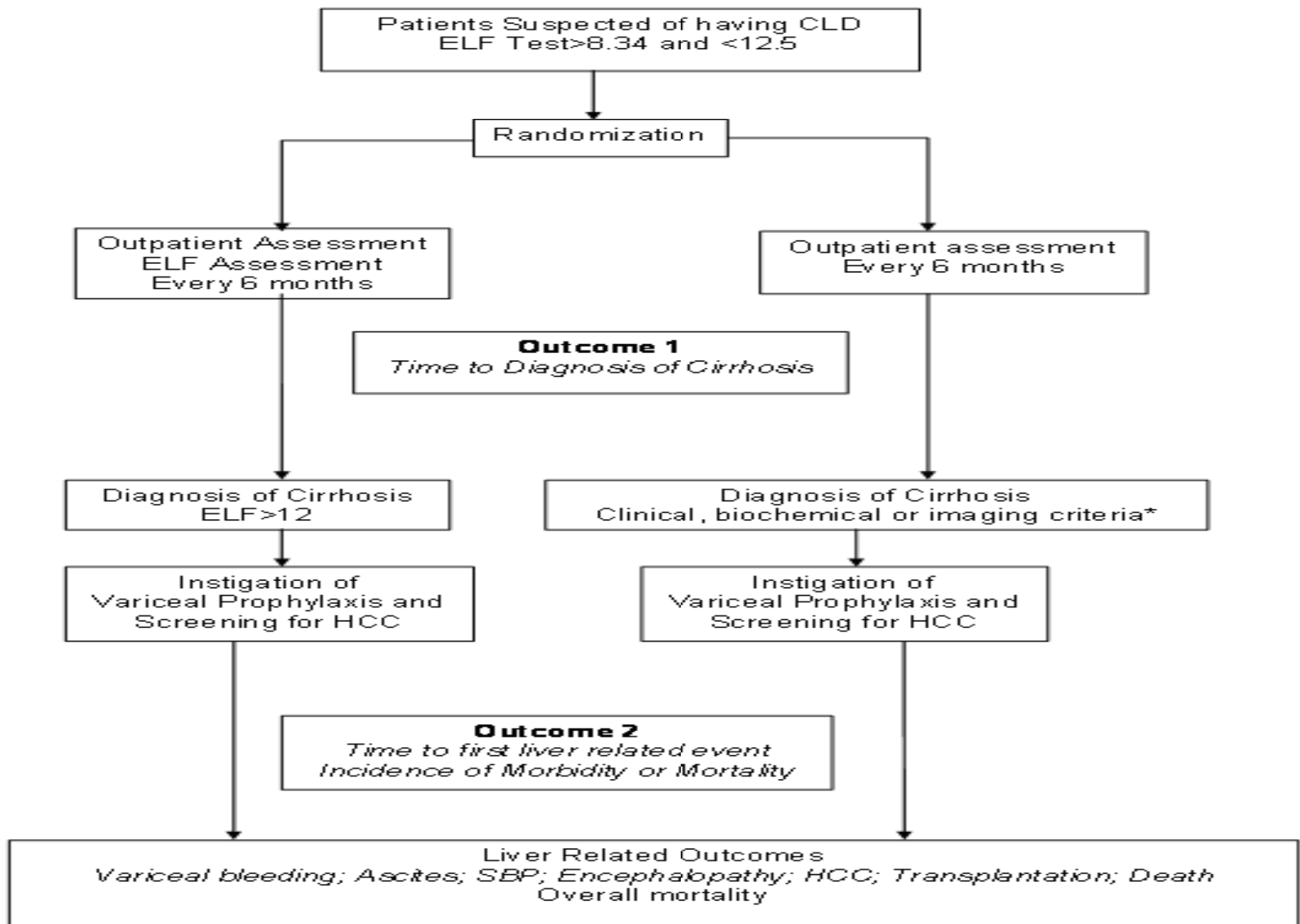
- **Methodological work** to define current best practice and explore innovations
- Clinical biochemistry to rapidly identify protein biomarkers with good clinical characteristics-a **biomarker biobank for renal and liver disease**.
- A RCT of 3 biomarkers for liver fibrosis and cirrhosis-the **ELF test**.



*Compound serum ELISAs
HA, TIMP-1, PIINP*

ELF – liver related events at 7 yrs

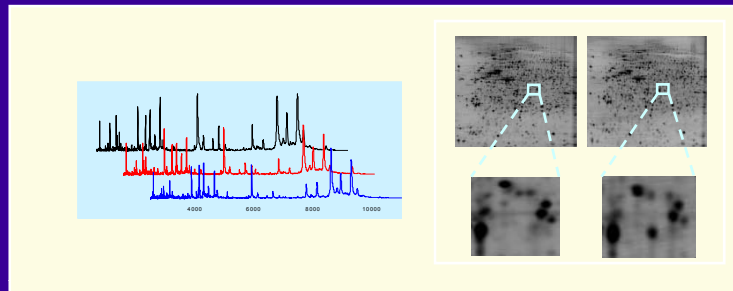




The Clinical Proteomics Experiment

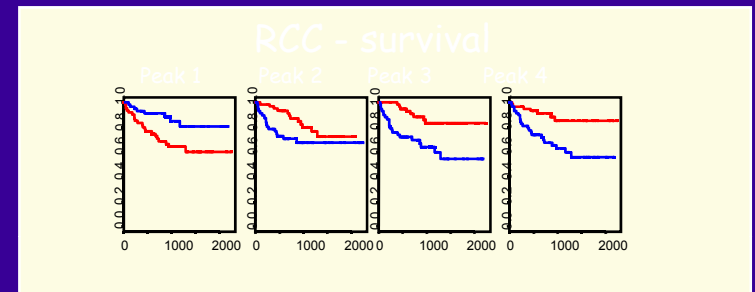
HYPOTHESIS, TECHNOLOGY,
and CLINICAL DATA

Pre-fractionation
and protein profiling



Bioinformatics
& Biostatistics

Association of "peaks" with
clinical "outcome"

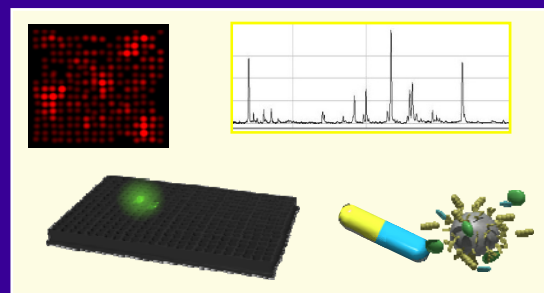


Clinical questions
& samples



Clinical
and NHS
Benefits

Trials and
HSR

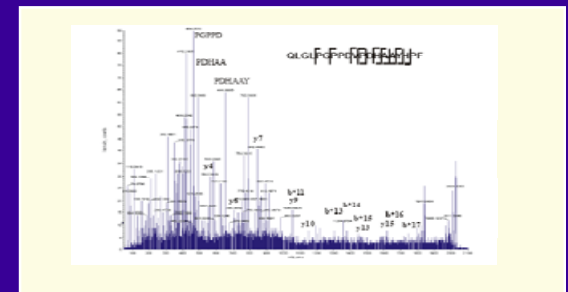


Multiplex assay/drug
development & clinical trials

Initial
validation



Protein
purification



Identification of "peaks"
by mass spectrometry

Cancer Research UK Centre

Vassilis Aggelis
Andrew Bernard
Ann Bogue
Glenn Bonney
Janet Brown
David Cairns
Fiona Collinson
Rachel Craven
Rosie Ferguson
Geoff Hall
Pat Harnden
Sharon Jackson
Satinder Jagdev
Alan Liu
David Perkins
Jianhe Peng
Rumana Rafiq
Liz Sheldon
Sheryl Sim
Annie Stanley
Douglas Thompson
Nav Vasudev
Alison Young



Roz Banks

NIHR Programme

Professor Doug Altman
Professor Roz Banks
Dr Ian Barnes
Professor Jon Deeks
Dr Walter Gregory
Professor Jenny Hewison
Professor Philip Johnson
Professor Chris McCabe
Professor William Rosenberg
Professor Peter Selby
Dr Catharine Sturgeon
Dr Doug Thompson



Medical Oncology and Urology Consultants

Psychosocial Oncology and Proteomics

Lessons from PMH/OCI

- Good scientific methods can be applied to any question
- There are many ways to benefit patients
- Science and medicine are good fun