

A Mass Spectrometric Map for Cancer-Associated Proteins

Martin Soste

Institute of Molecular Systems Biology

ETH Zurich

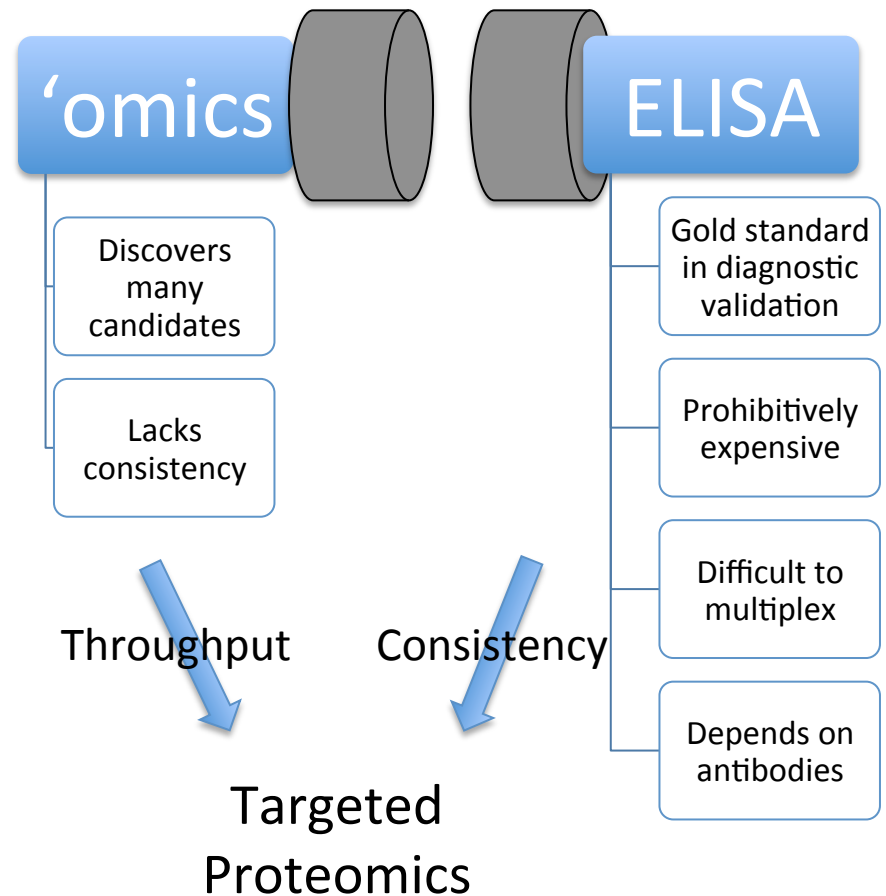
soste@imsb.biol.ethz.ch

BSPR-EBI Meeting – July 13, 2011



Biomarkers so far... “low return on investment”

- Clinical need for cancer diagnostics and drug targets
- Sift many candidates to find those with real clinical value
- Must compare many case vs. control samples
- Need bridging technology to fill the gap in the biomarker pipeline



Quote from Whiteaker *et al.* (2011) A targeted proteomics-based pipeline for verification of biomarkers in plasma. *Nature Biotech* Epub ahead of print

Mapping Proteins with Targeted Proteomics

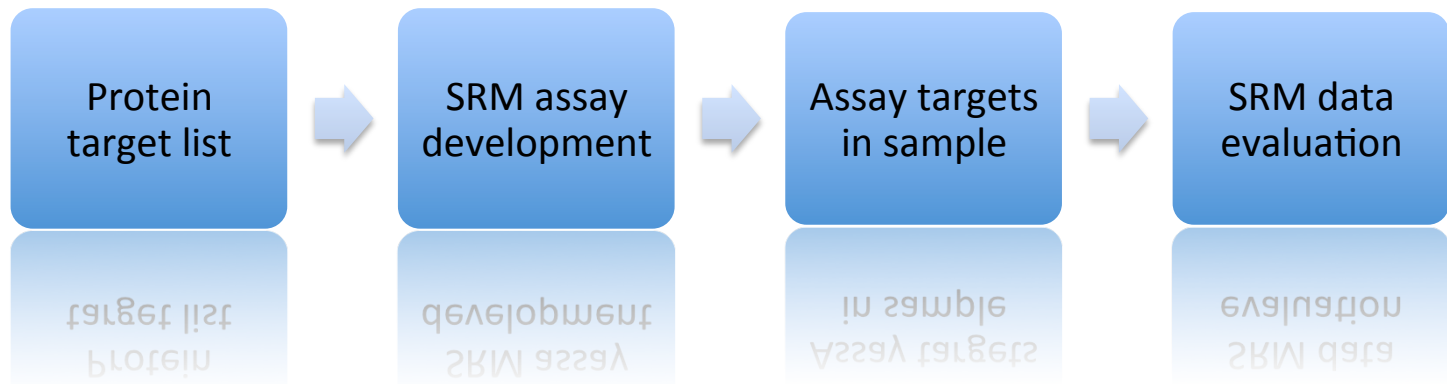
We define a protein map as...

- a **set of specific assays** for predetermined proteins
 - a resource used to consistently identify/quantify targets in various samples
- Navigate through proteomes with selected reaction monitoring (SRM) coordinates

Peptide	Fragment	Q1	Q3	RT	Rel Int
YGFIEGHVVIPR	y8_1	693.88	906.52	22.9	100
YGFIEGHVVIPR	y7_1	693.88	777.47	22.9	91
YGFIEGHVVIPR	b3_1	693.88	368.16	22.9	77
YGFIEGHVVIPR	y4_1	693.88	484.33	22.9	53
YGFIEGHVVIPR	y3_1	693.88	385.26	22.9	42



Targeted Proteomics Workflow



Synthetic peptide libraries
have benefits over ELISA



Where are candidate
biomarkers accessible by
SRM?



Picotti P *et al.* (2010) High-throughput generation of selected reaction-monitoring assays for proteins and proteomes.
Nature Methods 7, 43-46



Targeting Cancer-Associated Proteins

A List of Candidate Cancer Biomarkers
for Targeted Proteomics

Malu Polanski and N. Leigh Anderson

The Clinical Plasma Proteome:
A Survey of Clinical Assays for Proteins in
Plasma and Serum

N. Leigh Anderson¹

Differentially
expressed in cancer



Have an FDA-
approved assay

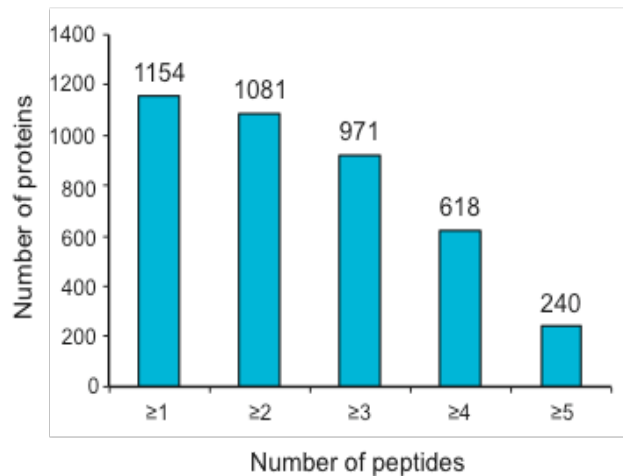
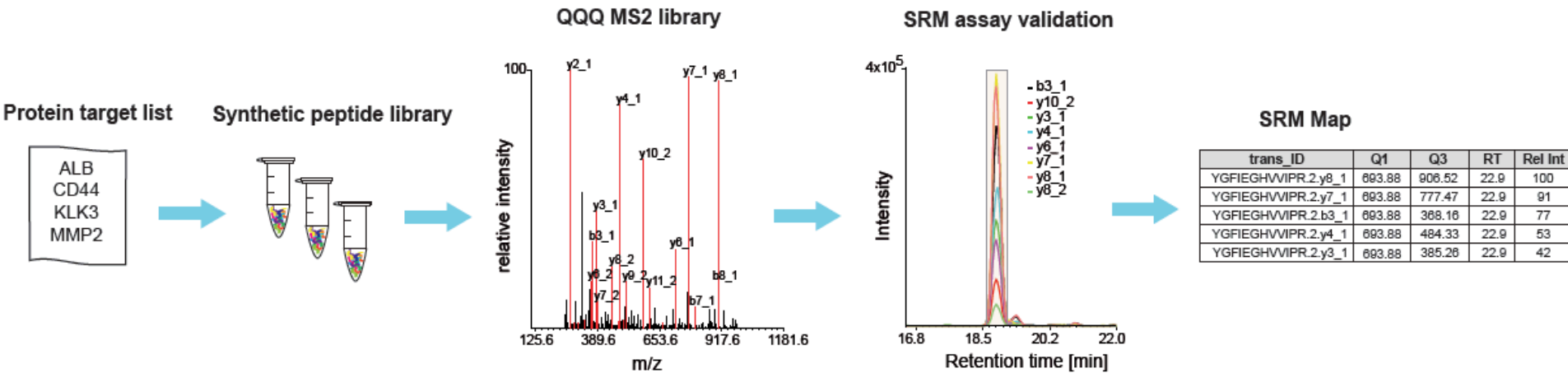


1172 Cancer-Associated Proteins (CAPs)



Polanski M, Anderson NL (2006) A List of Candidate Cancer Biomarkers for Targeted Proteomics. *Biomarker Insights* 2: 1-48
Anderson NL (2010) The clinical plasma proteome: a survey of clinical assays for proteins in plasma and serum. *Clinical Chemistry* 56, 177-185

Building the Map



Validated assays

- 4010 peptides (73%)
- 1154 proteins (98%)

Picotti P *et al.* (2010) High-throughput generation of selected reaction-monitoring assays for proteins and proteomes. *Nature Methods* 7, 43-46

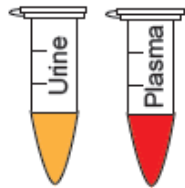
Hüttenhain R *et al.* A mass spectrometric map for cancer associated proteins applied to human plasma and urine. *In preparation*



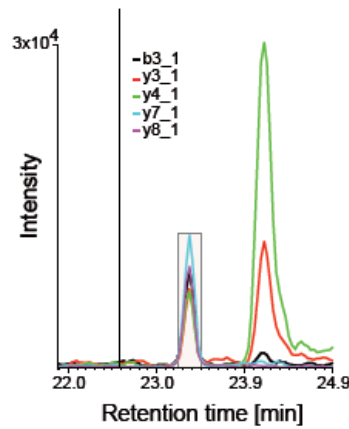
Targeting in Plasma and Urine

SRM map for 1154 CAPs

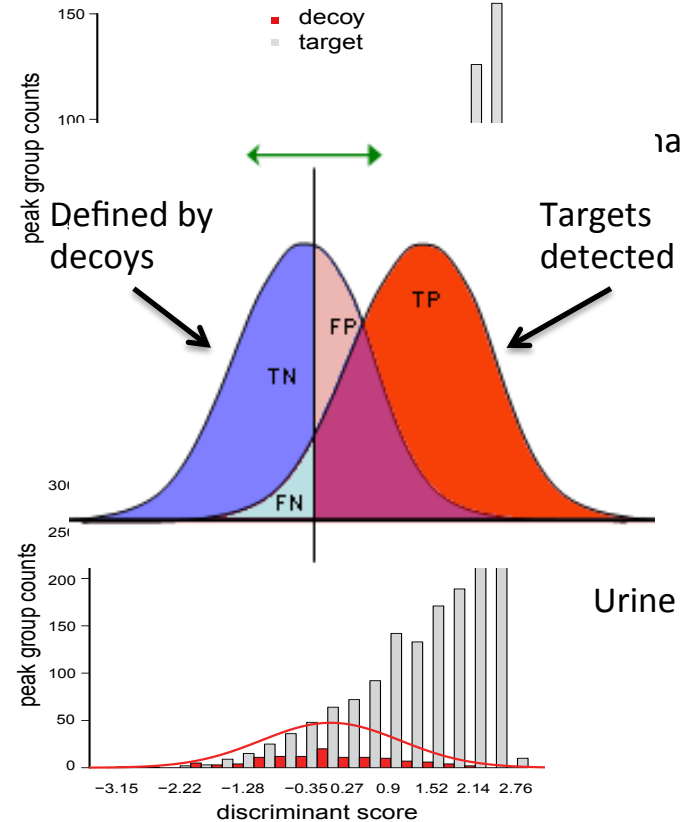
trans_ID	Q1	Q3	RT	Rel Int
YGFIEGHVVIPR.2.y8_1	693.88	906.52	22.9	100
YGFIEGHVVIPR.2.y7_1	693.88	777.47	22.9	91
YGFIEGHVVIPR.2.b3_1	693.88	368.16	22.9	77
YGFIEGHVVIPR.2.y4_1	693.88	484.33	22.9	53
YGFIEGHVVIPR.2.y3_1	693.88	385.26	22.9	42



Endogenous peptide detection



mProphet probabilistic scoring model

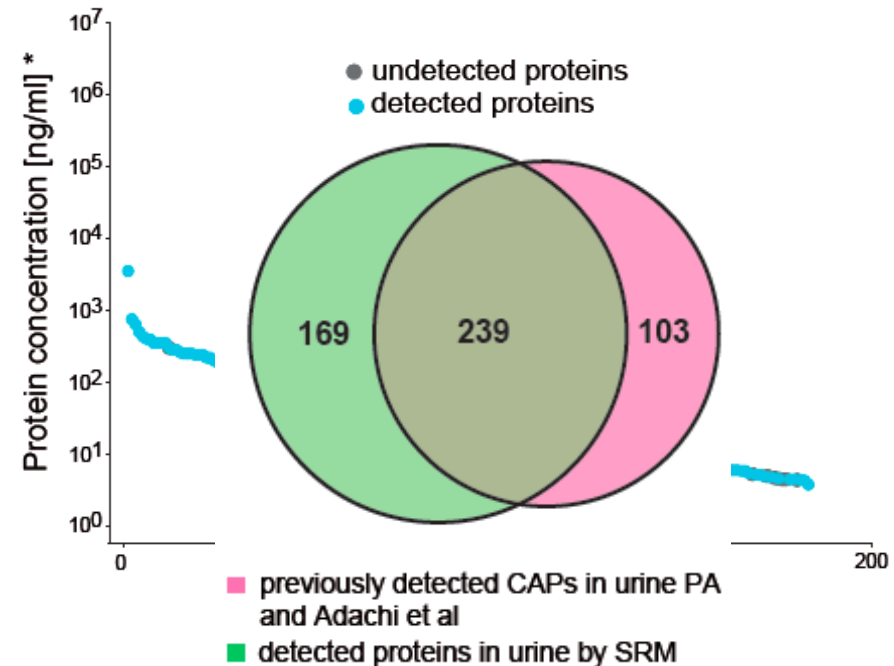
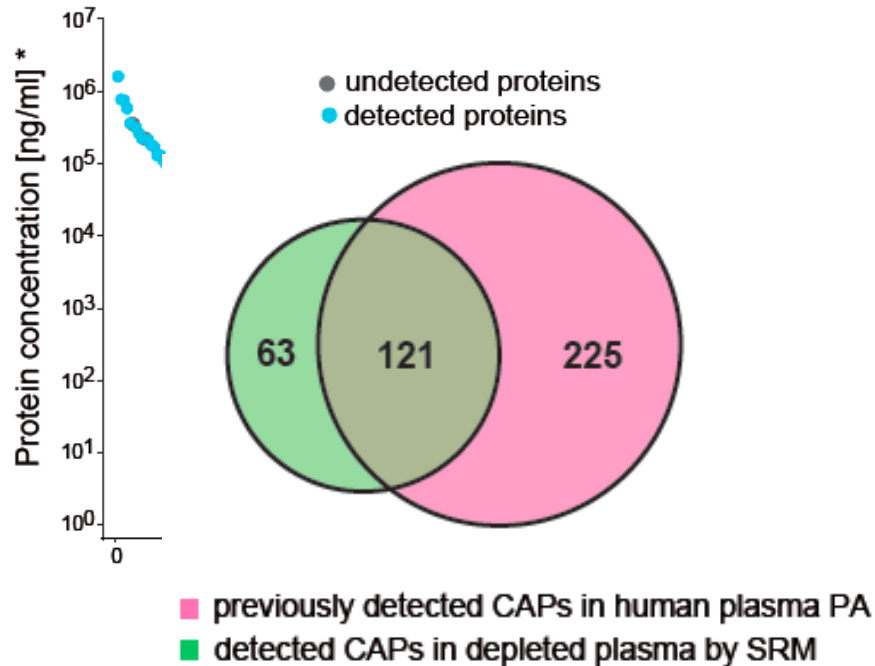


Reiter L *et al.* (2011) mProphet: automated data processing and statistical validation for large-scale SRM experiments. *Nature Methods* 8, 430-435

Detection Results

➡ Plasma: 184 proteins, 302 peptides

➡ Urine: 408 Proteins, 661 Peptides



*estimated concentrations from PeptideAtlas <www.peptideatlas.org>

Hüttenhain R *et al.* A mass spectrometric map for cancer associated proteins applied to human plasma and urine. *In preparation*
 Farrah T *et al.* (2011) A high confidence human plasma proteome reference set with estimated concentrations in PeptideAtlas. *MCP*
 In press

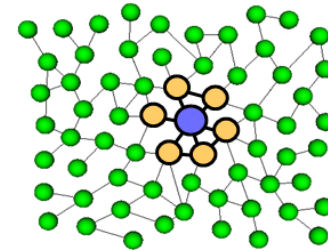


Future Target Lists: Network Coverage and Expansion

Example of a new list from...

- Exome sequencing of 7 cancers → 379 potential driver mutations
- A functional interaction network

Are detectable CAPs in the neighbourhood of mutations driving cancer development?



- 144 detectable CAPs are either drivers *or* functionally related to them



Our map could potentially indicate the status of 38% of the drivers or their networks



Wu, G *et al.* (2010) *Genome Biology*, Jiao Y *et al.* (2011) *Science*, Jones S *et al.* (2010) *Science*, Jones S *et al.* (2008) *Science*, McLendon R *et al.* (2008) *Nature*, Parsons D *et al.* (2008) *Science*, Parson D *et al.* (2011) *Science*

Take-home Messages

- Demonstrated the detection of cancer-associated proteins using the SRM coordinates of a mass spectrometric map
- SRM maps should be expanded and paired to high-throughput hypothesis generation from computational biology

We have created an [SRM resource](#)

- for systems biology and biomarker verification
- publicly-accessible [coordinates for candidate cancer biomarkers](#)
- [detectability information](#) in two clinically relevant samples



Acknowledgements

ETH Zurich

Ruth Hüttenhain
Nathalie Selevsek
Atul Sethi
Hannes Röst
Christine Carapito
Paola Picotti
Bernd Wollscheid
Ruedi Aebersold

BIOGNOSYS AG, Zurich

Oliver Rinner
Lukas Reiter
Claudia Escher

ProteoMediX AG, Zurich

Ralph Schiess

ISB, Seattle

Terry Farrah
Dave Campbell

IMP, Hradec Kralove

Alena Fucikova

PPI, Washington

Leigh Anderson

