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Proteomic Strategies to overcome Tumor Resistance to Oncology Targeted Medicines

Extending development and treatment options through precise molecular profiling



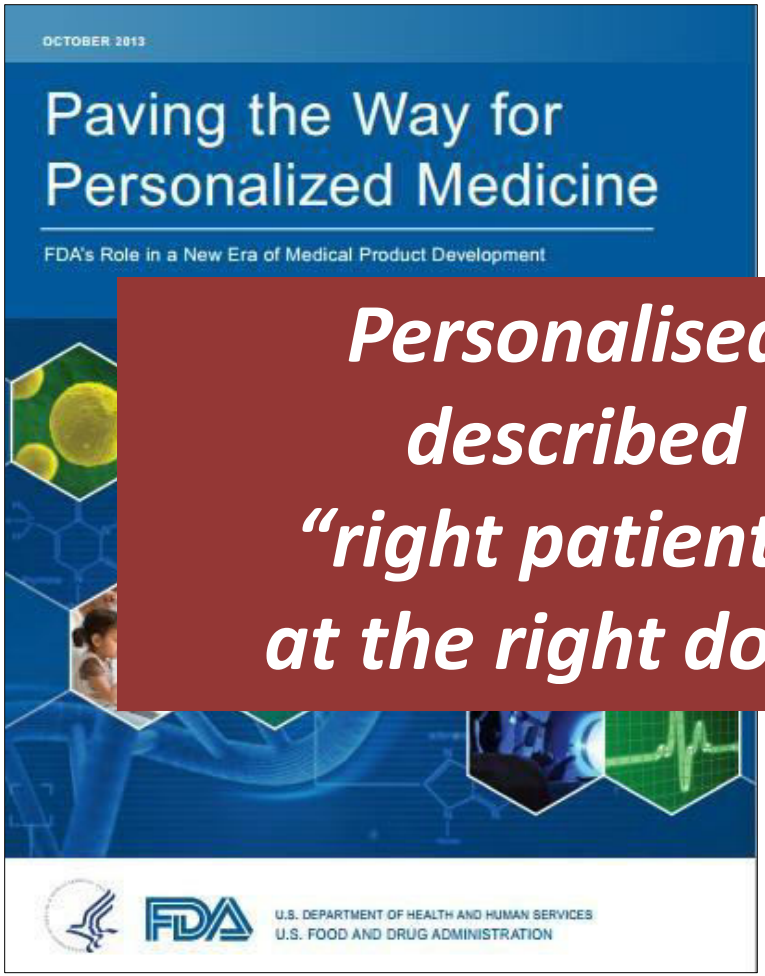


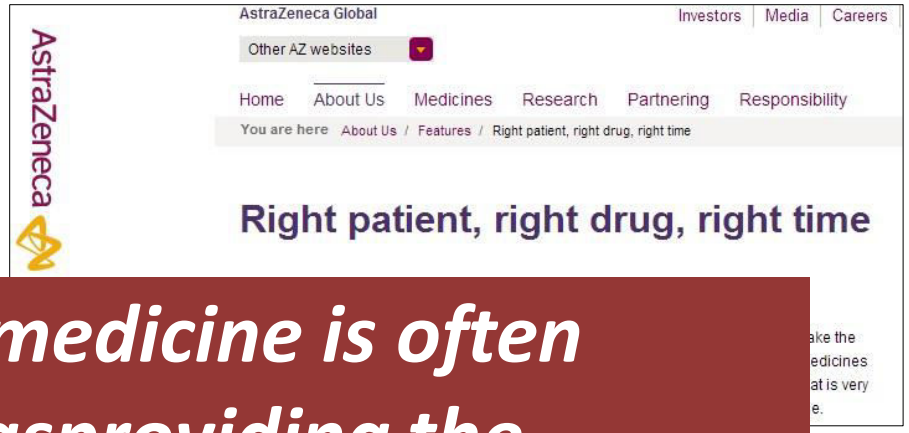

6th International Conference on Biomarkers and Clinical Research,
Toronto,
Canada.

1st September 2015

Chee Gee See, PhD, MICR,
Director of Personalised Medicine,
Proteome Sciences plc,
Coveham House,
Cobham, Surrey
UK.

Personalised Medicine





Personalised medicine is often described asproviding the "right patient with the right drug at the right dose at the right time".



http://www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf
http://www.astrazeneca.com/About-Us/Features/Article/20100311--Right-patient-right-drug-right-time

Personalised Medicine

Drug Maker	Personalised Medicine	Indication	Diagnostic Biomarker	Biomarker Frequency in Population	Overall Response Rate	Median Time To Progression
Roche	Herceptin	mBC & EBC	HER2 overexpression	20%	15%	9.1 mths [1]
Roche	Herceptin	mGC & mGEJC	HER2 overexpression	20%	47.3%	7.6 mths [2]
GSK	Tykerb	mBC	HER2 overexp / EGFR	20%	22%	8.4 mths [3]
AstraZeneca	Iressa	NSCLC	EGFR mutation	10 % (30-50%)	71.2%	8.35 mths [4]
Roche	Tarceva	NSCLC	EGFR mutation	10 % (30-50%)	65%	10.4 mths [5]
Pfizer	Xalkori	NSCLC	ALK-EML4 FISH	3-6%	50-61%	5.5 – 8 mths [6]
Amgen	Vectibix	mCRC	kRAS ^{wt}	50%	55%	9.6 mths [7]
BMS	Erbitux	mCRC	kRAS ^{wt}	50%	57%	9.5 mths [8]
Roche	Zelboraf	Melanoma	BRAF ^{V600E} mutation	50-90%	52%	6.5 mths [9]

1). Cobleigh et al 1999. J Clin Oncol. 17:2639-2648. 2). NICE appraisal guidance document 208 3). Tevaarwek & Kolesar 2009. Clin Ther 31, 2332 – 2348. 4). Mok et al 2009. N Engl J Med ;361:947–57. 5). EURTAC study 6). PROFILE 1005 (PhII) & 1001 (PhI) studies 7).PRIME trial, FDA approval.. 8). CRYSTAL trial, FDA approval 9). FDA approval note for Vemurafenib.

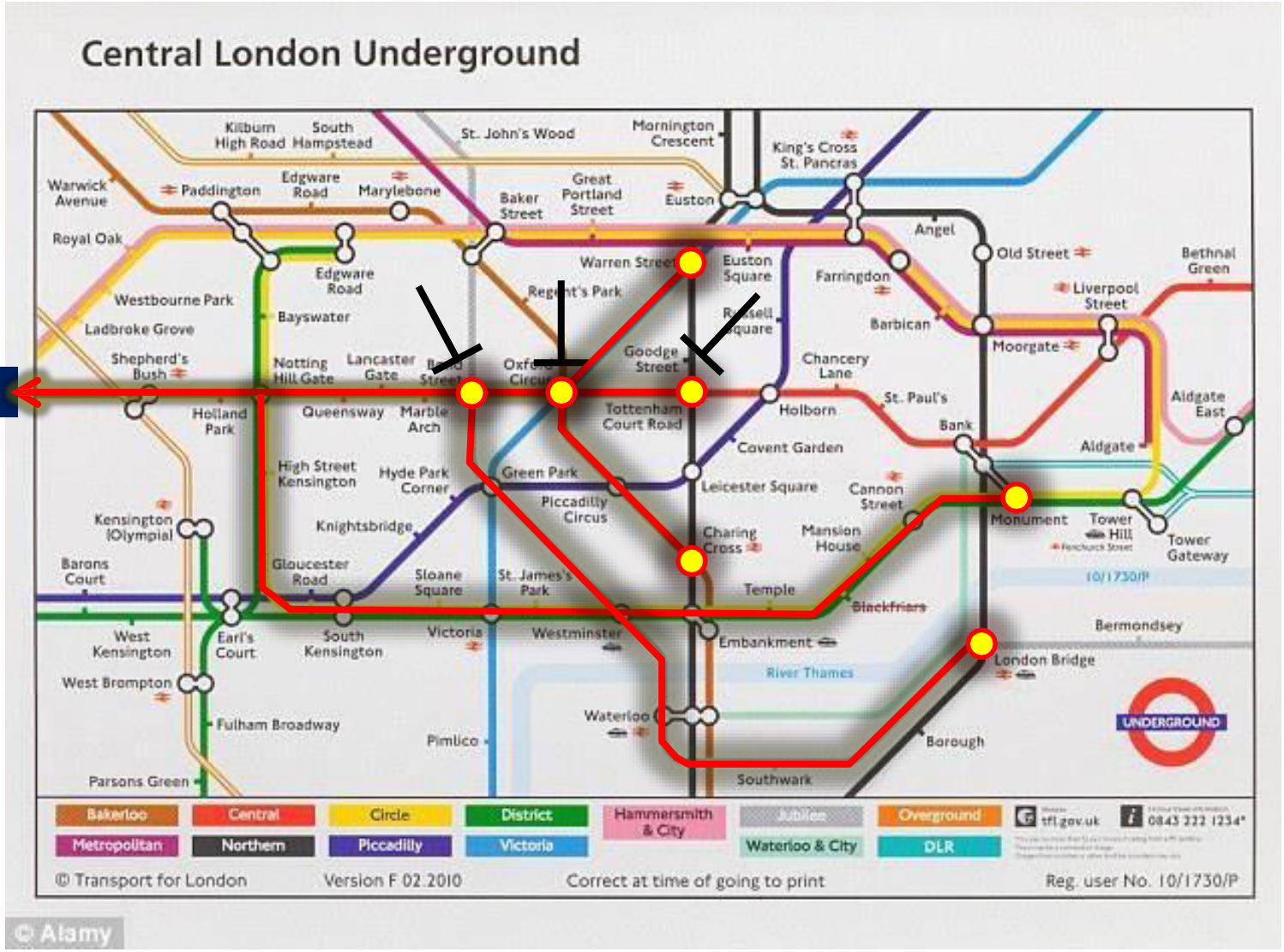
Personalised Medicine



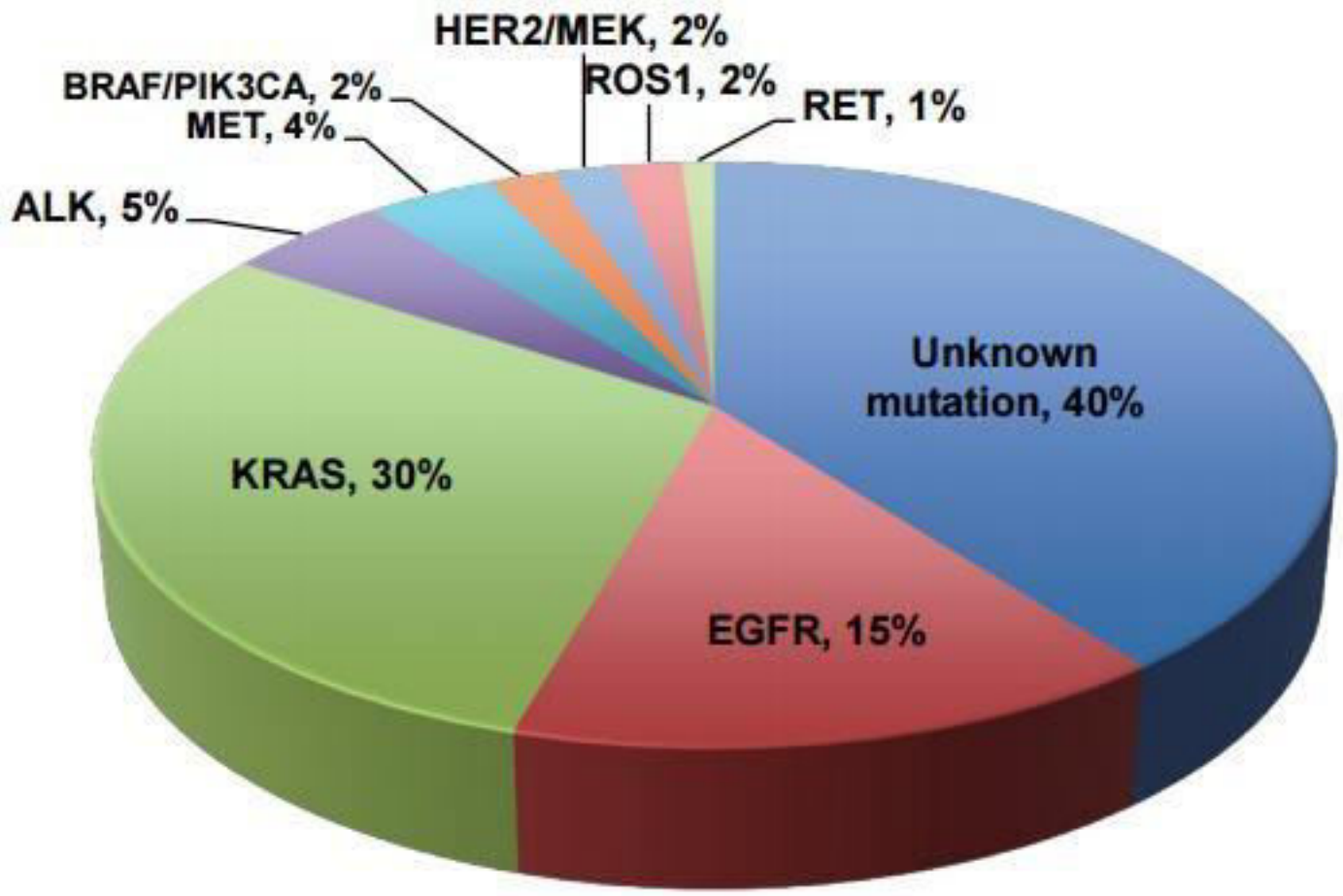
The lack of sustained durability of our most precious personalised medicines is costly to the drug manufacturer, the health service, the physician and the patient

Wagle et al. 2011. J Clin Oncology 29, 3085-3096

Has the closure of one or two stations on the Tube ever stopped you from getting around?



NSCLC oncogenic driver mutation landscape

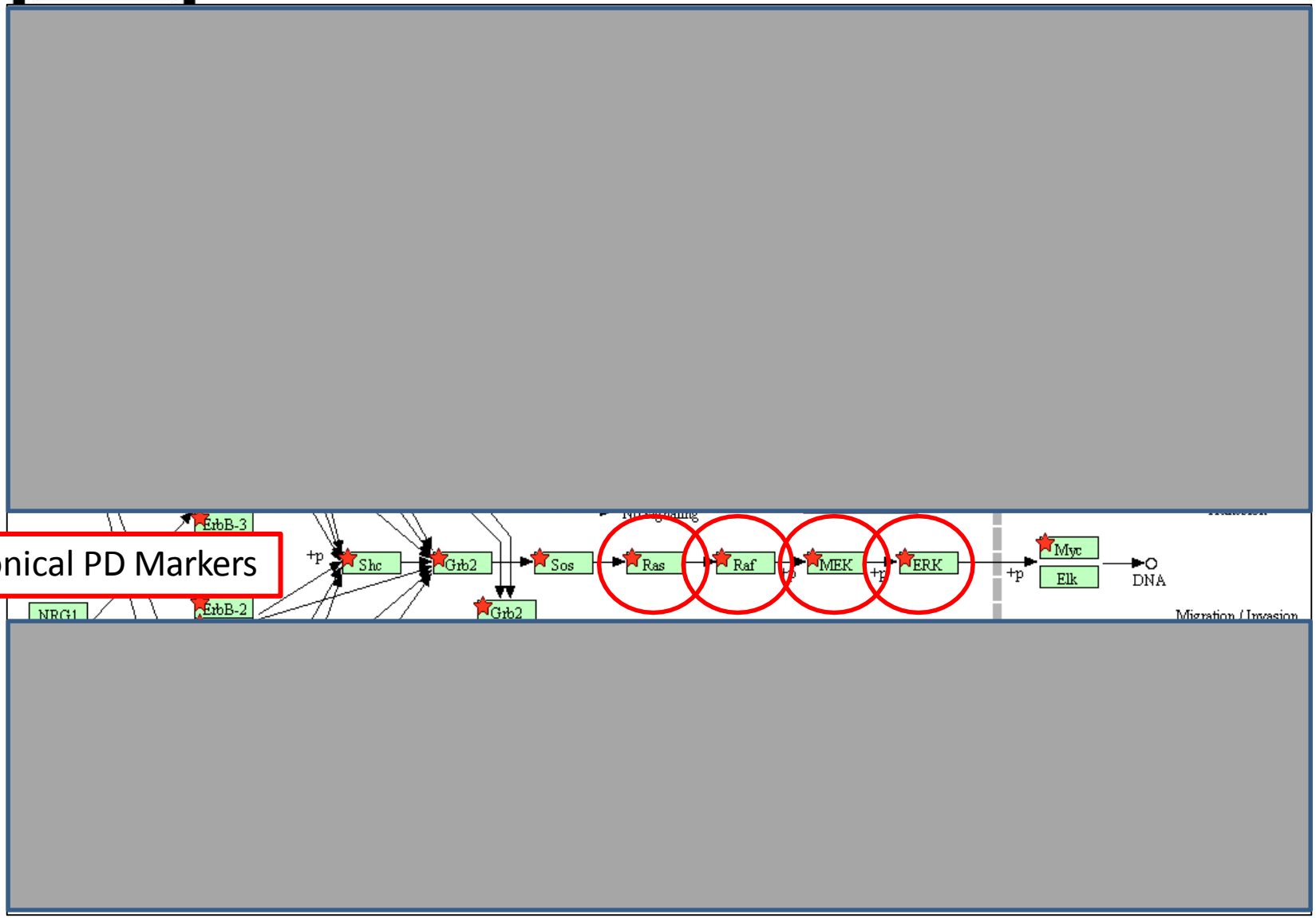


2015

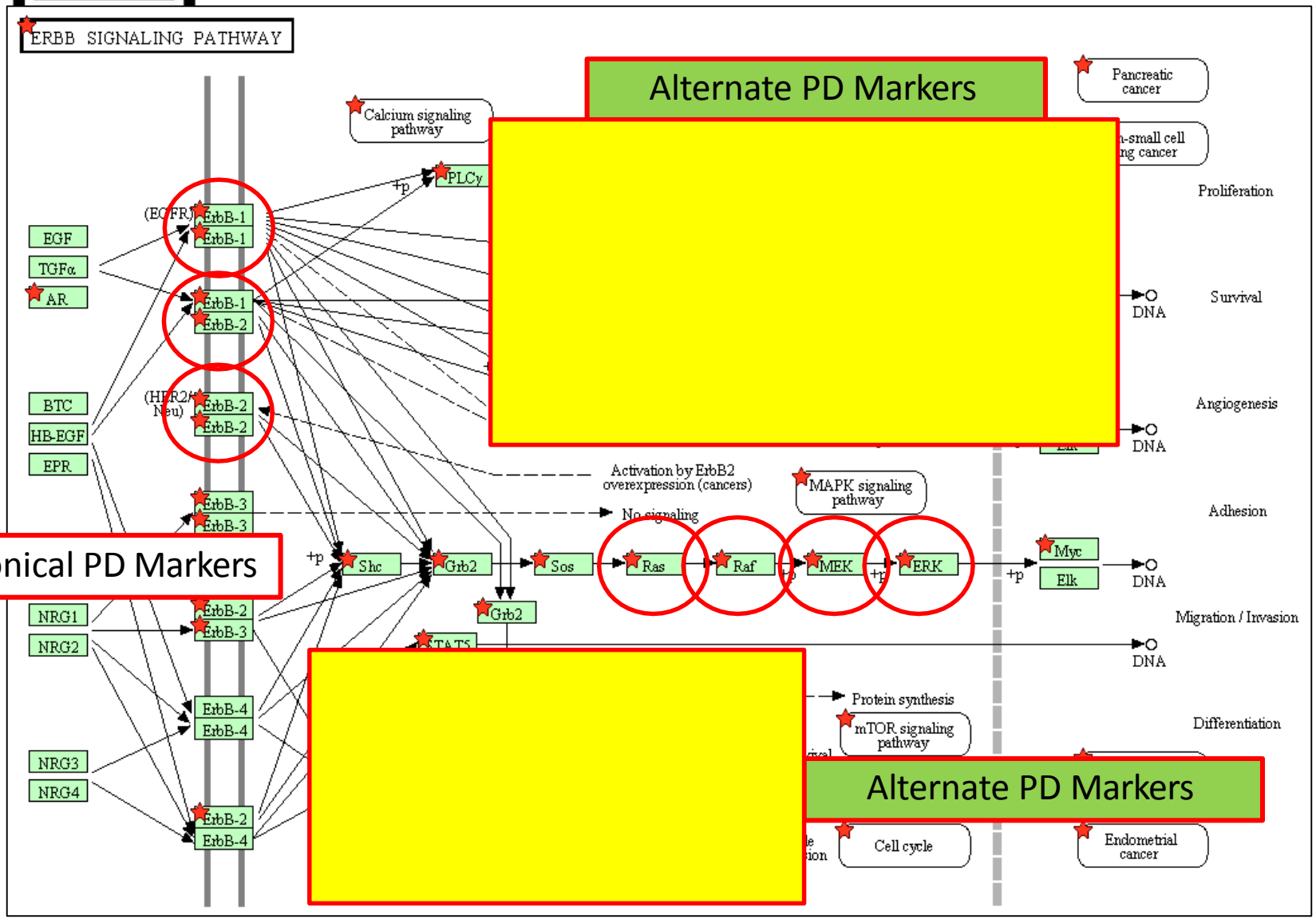
Chan & Hughes Feb 2015. Transl Lung Cancer Res 2015;4(1):36-54

Canonical disease pathway analysis

Canonical PD Markers



Comprehensive disease pathway analysis



After 20 years in Personalised Medicine: What next?

- We need to treat the patient, not the disease label
- Unpacking individual disease complexity is key
- Ability to counter disease resistance and increase durability will add value to personalised medicines

After 20 years in Personalised Medicine: What next?

Today, proteomics has the ability to

- Comprehensively unpack cancer disease biology with a single-shot approach
- Point to intelligent actionable therapeutic options through such functional analysis.
- Anticipate likely disease resistance routes
- Offer the cancer patient a realistic hope of managing their illness

SysQuant®
A Unique Phosphoproteomic Workflow

- We developed SysQuant® to provide comprehensive personal maps of regulatory pathways for any disease – starting with phosphorylation
- Individual samples of tumour and non-tumour treated to preserve phosphorylation status during sample preparation
- SysQuant® combines standard proteomics with phosphopeptide enrichment on latest mass spectrometry platforms
- Data Visualisations based on KEGG & GO Term enrichment
- Results in 4 weeks @ $6-10,000 per patient

© Proteome Sciences plc

SysQuant® in Pancreatic Cancer

- 338,000 new cases of PC were diagnosed worldwide in 2012 (~8,000 in UK per annum)
- In the UK, PC is 5th most common cause of cancer death in both sexes, despite being only 10th most common cancer overall
- Overall, only 3% of PDAC patients will have a 5 year PFS, which has not improved much since the 1970s
- High death rates mainly due to late diagnosis
- No targeted therapies available – mix of DNA damaging agents and microtubule stabilisers
- **Identification of common and personal tumour drivers may support drug repurposing**

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Pancreatic Cancer Clinical Study: Study Details

We applied SysQuant® to two cohorts of pancreatic cancer patients

- 12 surgically resected cases run on Velos with SysQuant v1.0
- 20 surgically resected cases run on Fusion with SysQuant v2.0

	TMT8plex1	TMT8plex2	TMT8plex3	TMT10plex1	TMT10plex2	TMT10plex3	TMT10plex4	TMT10plex5
#PSMs	55,449	59,700	63,817	411,817	312,663	331,097	307,264	276,072
#Unique Peptides	**18,906**	**21,016**	**22,820**	**136,615**	**119,059**	**125,542**	**117,414**	**105,958**
#Unique Phos-peptides	**5,637**	**7,616**	**6,829**	**39,963**	**38,366**	**39,656**	**37,029**	**28,765**
#Unique Non-Phos peptides	13,269	13,400	15,991	96,652	80,693	85,886	80,385	77,193
Unique PhosPeptide Sequences >=75% pRS	4,423	6,054	6,286	25,411	24,844	25,636	23,686	18,630
#Protein Groups	**3,487**	**3,891**	**3,923**	**8,727**	**8,368**	**8,738**	**8,401**	**8,267**
#Protein Groups identified by phos-pep	1,115	1,464	1,279	1296	1509	1,400	1,419	1,280
#Protein Groups identified by non-phos-pep	1,846	1,845	2,009	4457	4034	4,325	4,148	4,415
#Protein Groups identified by phos&non-phos pep	526	582	635	2974	2825	3,013	2,834	2,572
Total# Unique Sites >=75% pRS (Prot grouped)	**3,152**	**4,420**	**4,028**	**13,040**	**12,875**	**14,043**	**13,520**	**11,520**

Peptide Result Filter: 1% FDR
Protein Result Filter: ≥ 1 Rank 1 Peptide per protein

Fusion delivers 2.2 x Protein Groups and 3.4 x Phosphorylation Sites vs. Velos in 1/3 of MS run time

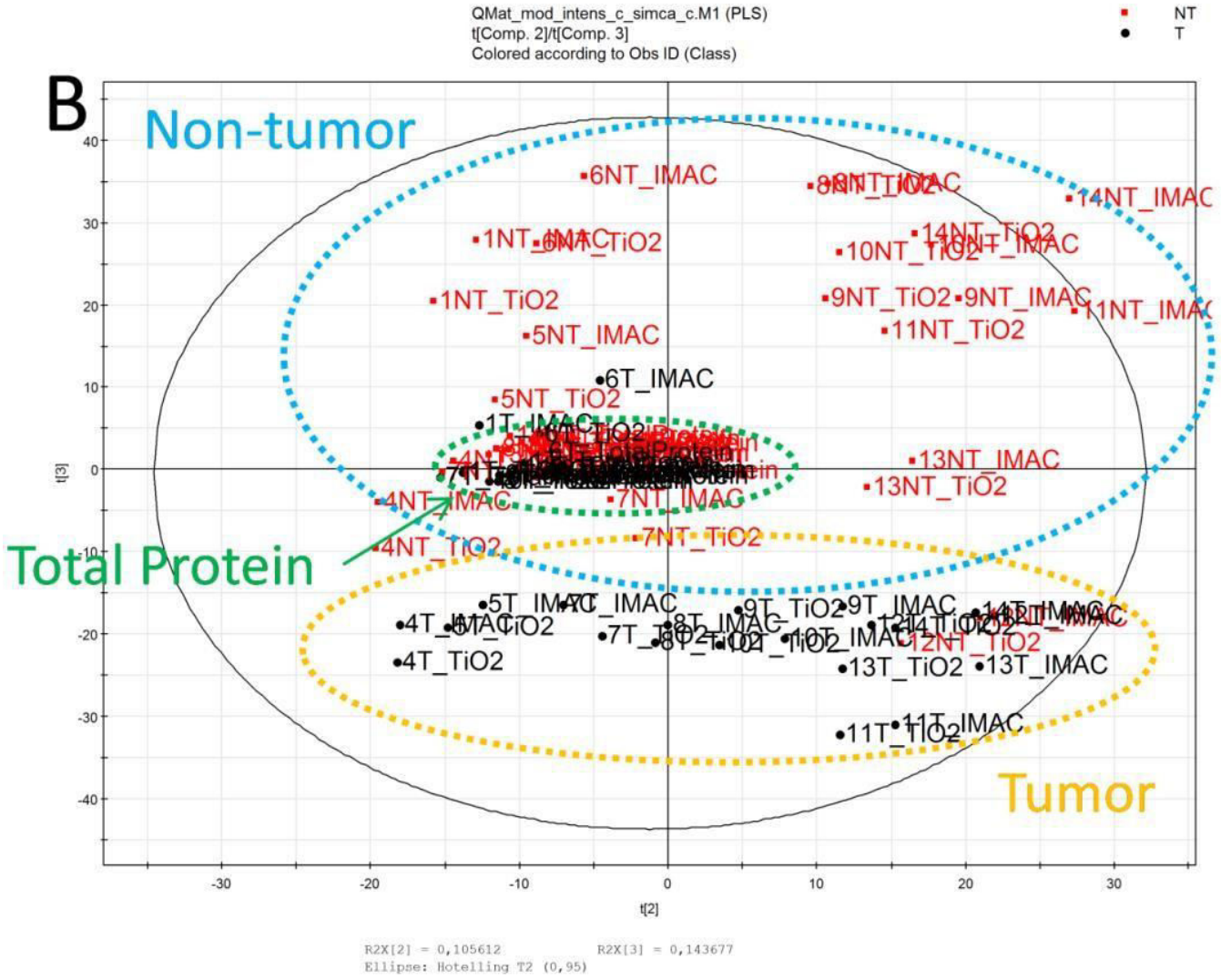
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Dynamic profiling of individual disease

- SysQuant® analysis of human pancreatic tumours
- 32 cases with tumour and healthy adjacent tissue
- Total of ~8,000 protein groups & ~ 13,000 unique phosphorylation sites
- Most comprehensive map of human pancreatic cancer
- Identified key pathways related to cancer and activity of multiple drug targets

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The Phosphoproteome is a More Potent Disease Classifier



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KEGG Enrichment Reveals Common Pathogenic Processes

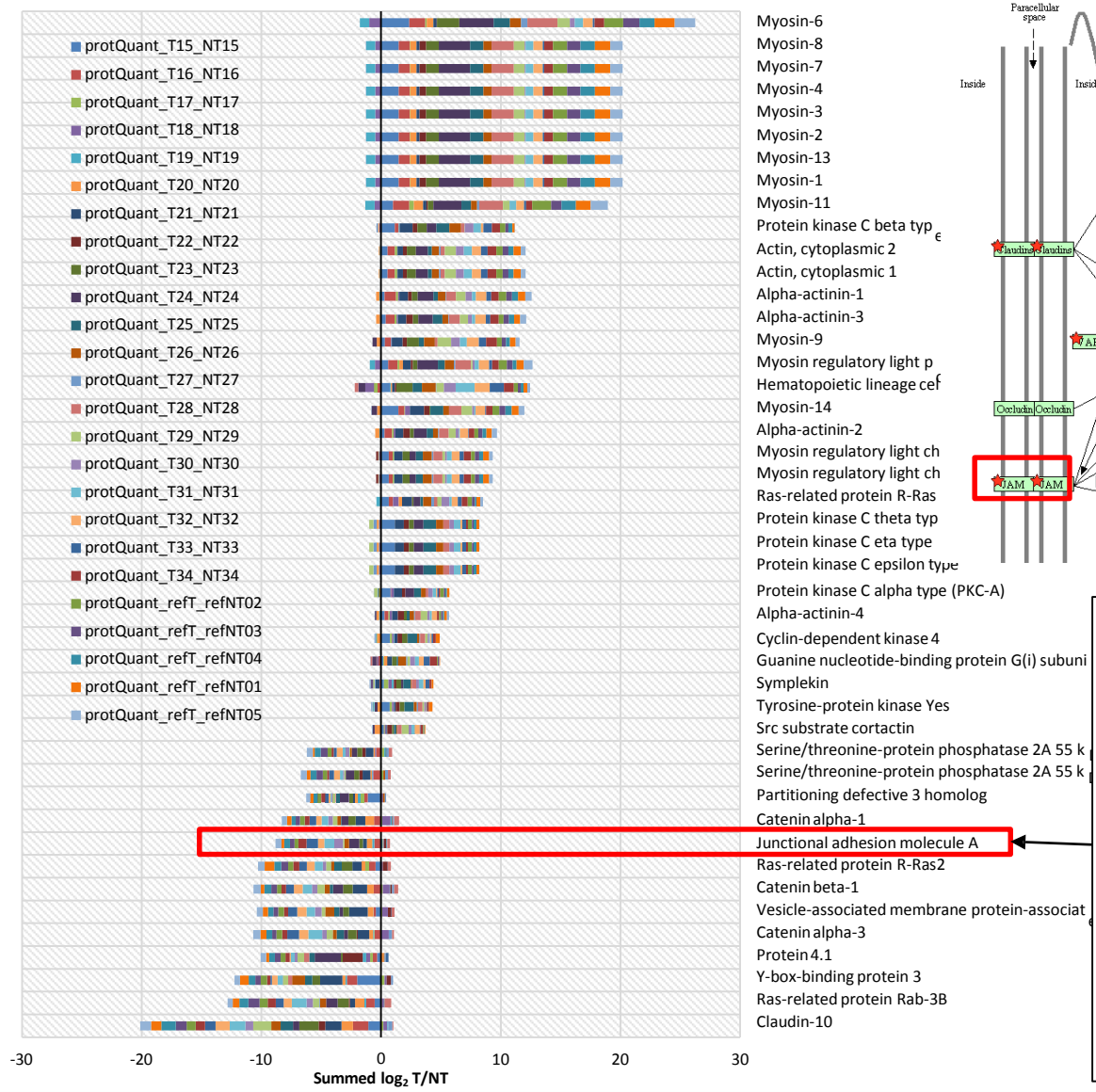
Experiment 1 – 12 PC cases on Velos

DAVID Bioinformatics Tool output from all proteins with $\log_2$ T/NT ratios of ≥ 1, or ≤ -1

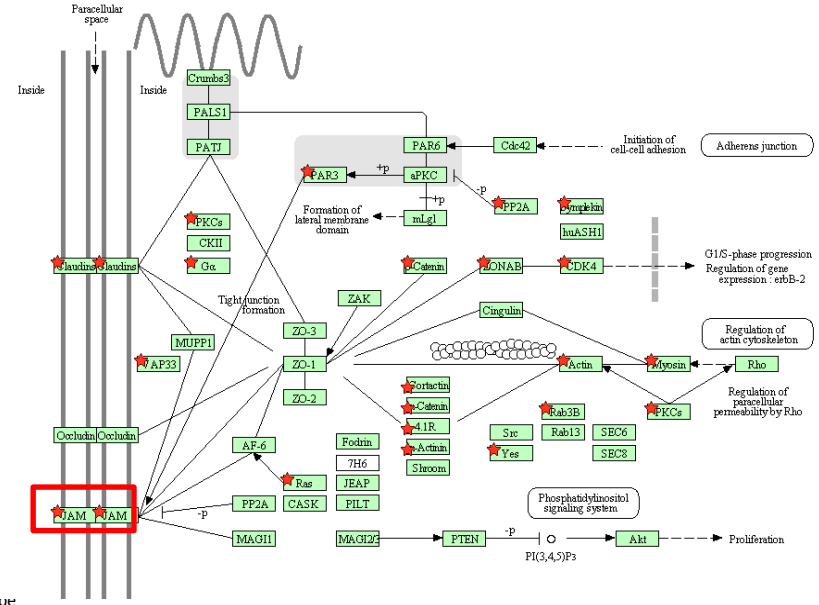
Case	Term	Count	PValue	Benjamini
T1/NT1	hsa04530:Tight junction	16	**1.67E-07**	1.92E-05
T1/NT1	hsa04520:Adherens junction	11	**5.71E-06**	3.28E-04
T4/NT4	hsa04530:Tight junction	13	**1.18E-06**	1.15E-04
T4/NT4	hsa04660:T cell receptor signaling pathway	8	**1.65E-03**	7.76E-02
T5/NT5	hsa04270:Vascular smooth muscle contraction	11	**8.26E-05**	8.88E-03
T5/NT5	hsa04530:Tight junction	10	**1.55E-03**	8.01E-02
T6/NT6	hsa04530:Tight junction	11	**1.97E-05**	1.77E-03
T6/NT6	hsa04910:Insulin signaling pathway	8	**3.25E-03**	1.36E-01
T7/NT7	hsa04520:Adherens junction	9	**9.44E-06**	8.77E-04
T7/NT7	hsa04510:Focal adhesion	10	**1.75E-03**	7.81E-02
T8/NT8	hsa04530:Tight junction	20	**2.15E-06**	2.84E-04
T8/NT8	hsa03040:Spliceosome	18	**1.49E-05**	9.84E-04
T9/NT9	hsa04530:Tight junction	13	**1.24E-03**	1.40E-01
T9/NT9	hsa04510:Focal adhesion	16	**2.04E-03**	1.17E-01
T10/NT10	hsa04530:Tight junction	18	**5.76E-05**	7.29E-03
T10/NT10	hsa04012:ErbB signaling pathway	13	**3.32E-04**	2.09E-02
T11/NT11	hsa04530:Tight junction	23	**6.44E-08**	8.56E-06
T11/NT11	hsa04270:Vascular smooth muscle contraction	16	**1.04E-04**	6.90E-03
T12/NT12	hsa04530:Tight junction	4	**1.68E-02**	5.09E-01
T12/NT12	hsa05412:Arrhythmogenic right ventricular cardiomyopathy (ARVC)	3	**3.85E-02**	5.62E-01
T13/NT13	hsa04530:Tight junction	20	**6.65E-09**	6.91E-07
T13/NT13	hsa03040:Spliceosome	16	**2.86E-06**	1.49E-04
T14/NT14	hsa04530:Tight junction	20	**3.65E-07**	4.79E-05
T14/NT14	hsa03040:Spliceosome	16	**5.58E-05**	3.65E-03

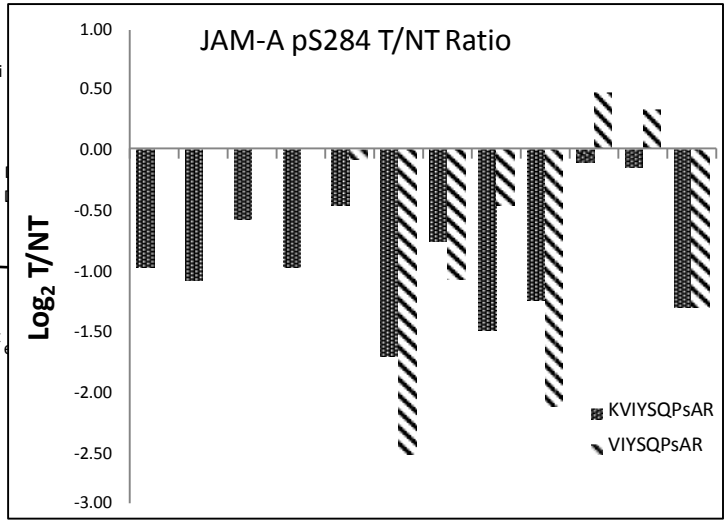
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SysQuant® reveals common loss of pS284 on JAM-A



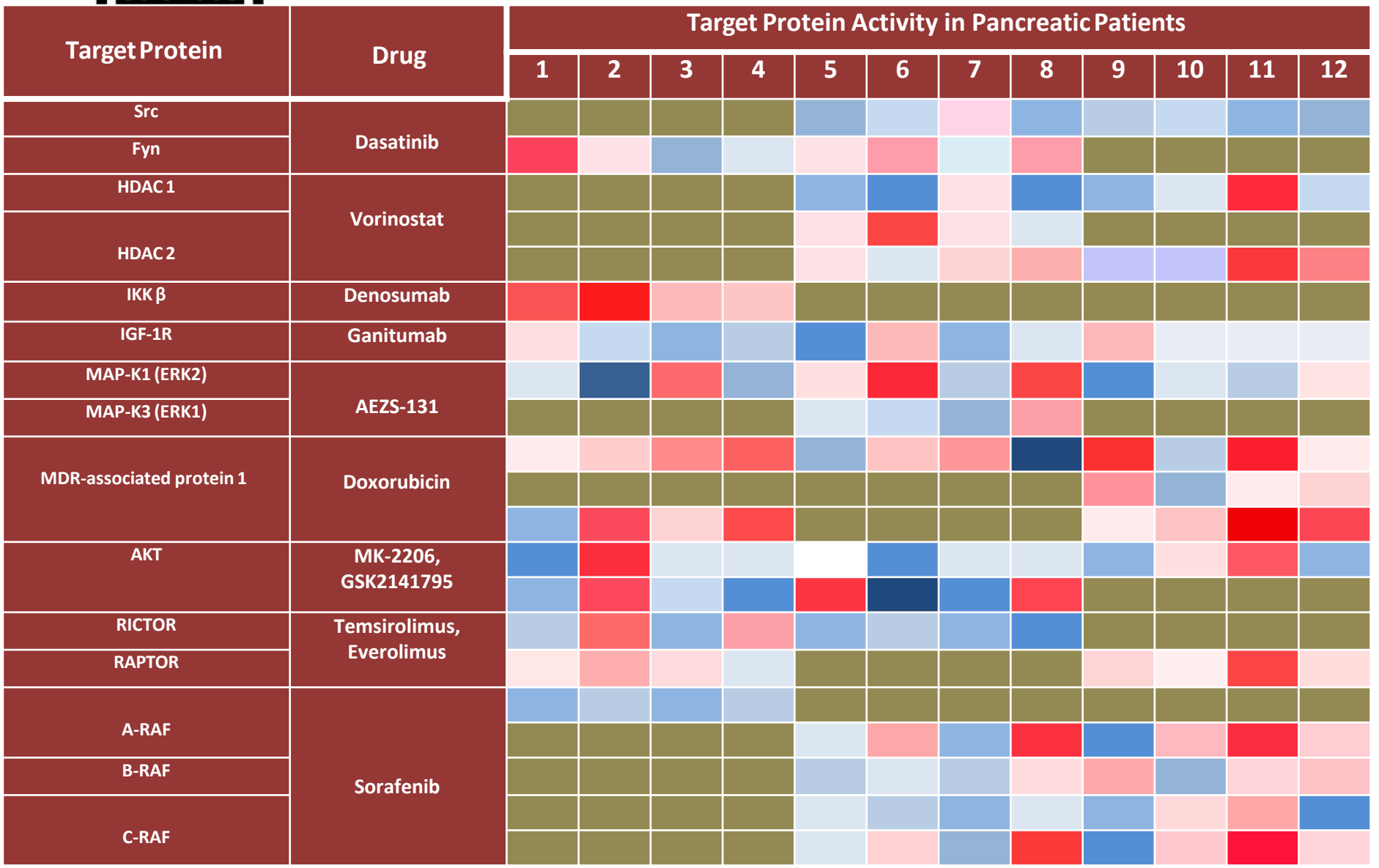
Myosin-6
Myosin-8
Myosin-7
Myosin-4
Myosin-3
Myosin-2
Myosin-13
Myosin-1
Myosin-11
Protein kinase C beta typ
Actin, cytoplasmic 2
Actin, cytoplasmic 1
Alpha-actinin-1
Alpha-actinin-3
Myosin-9
Myosin regulatory light p
Hematopoietic lineage cel
Myosin-14
Alpha-actinin-2
Myosin regulatory light ch
Myosin regulatory light ch
Ras-related protein R-Ras
Protein kinase C theta typ
Protein kinase C eta type
Protein kinase C epsilon type
Protein kinase C alpha type (PKC-A)
Alpha-actinin-4
Cyclin-dependent kinase 4
Guanine nucleotide-binding protein G(i) subuni
Symplekin
Tyrosine-protein kinase Yes
Src substrate cortactin
Serine/threonine-protein phosphatase 2A 55 k
Serine/threonine-protein phosphatase 2A 55 k
Partitioning defective 3 homolog
Catenin alpha-1
Junctional adhesion molecule A
Ras-related protein R-Ras2
Catenin beta-1
Vesicle-associated membrane protein-associat
Catenin alpha-3
Protein 4.1
Y-box-binding protein 3
Ras-related protein Rab-3B
Claudin-10





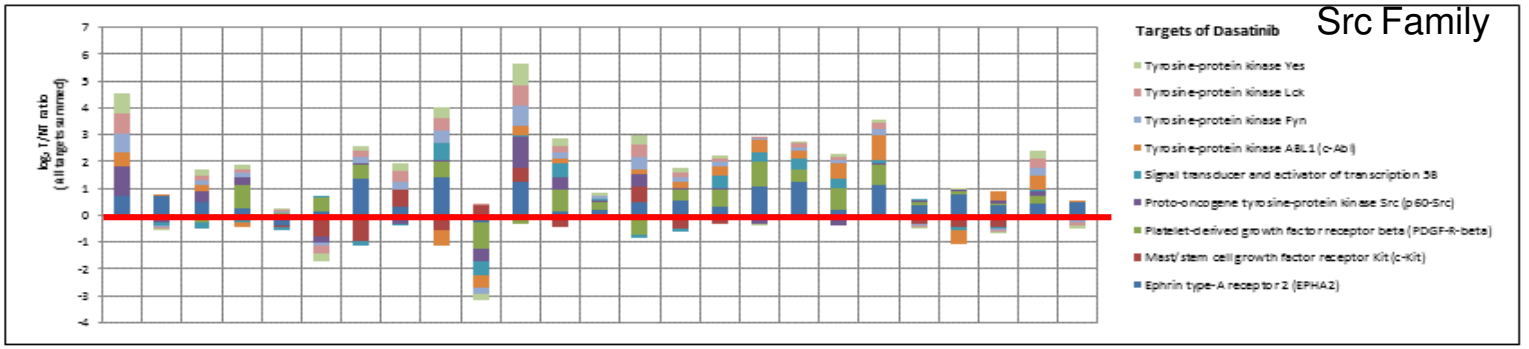
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SysQuant® Delivers Personal Disease Profiles

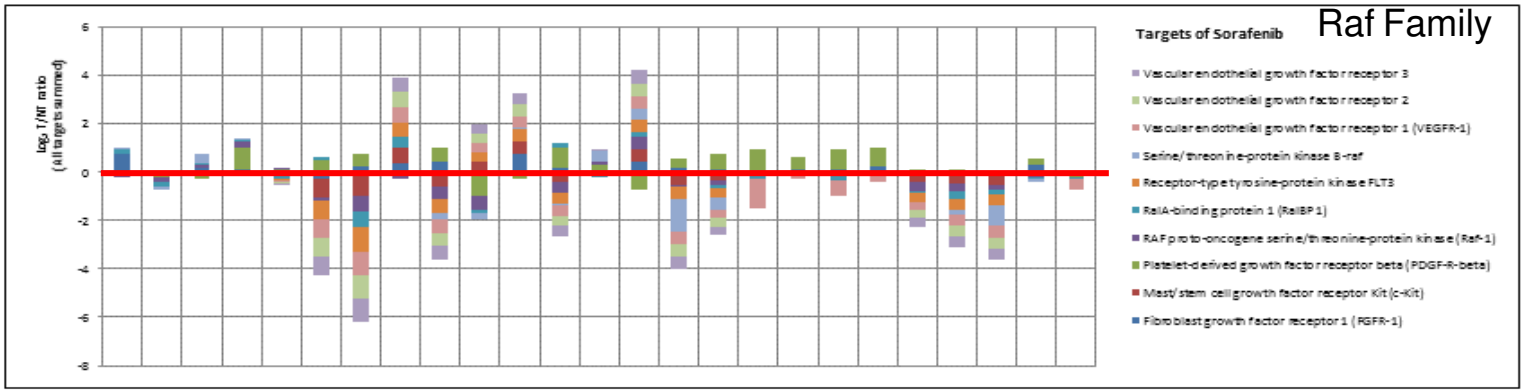


Dynamic profiling of individual disease

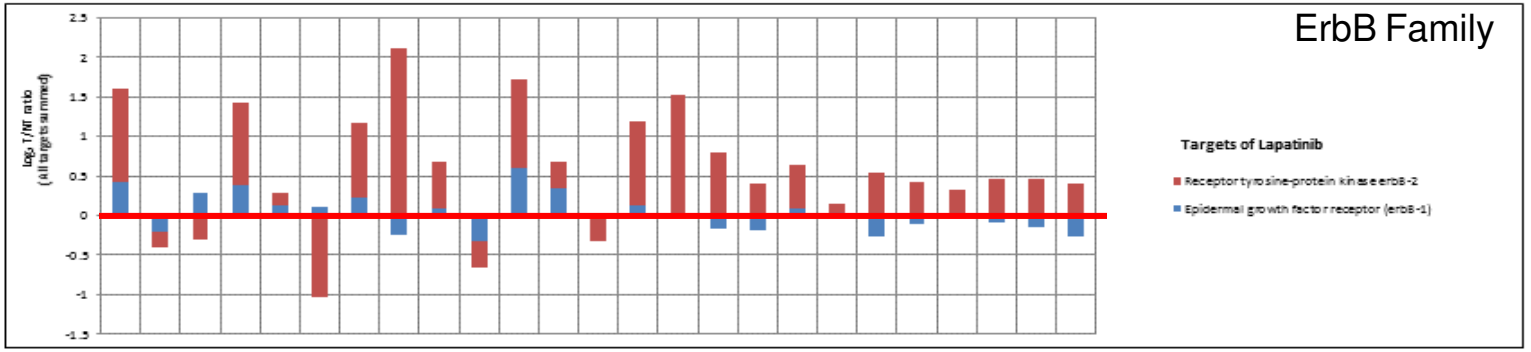
A



B



C



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SysQuant® molecular profiling offers incisive and actionable clinical treatment options

- SysQuant® is a cost and time appropriate method for detailed biological characterisation of individual tumours
- Changes in regulatory phosphorylation linked with total protein expression data can produce actionable treatment options
- Drug selection is now based on total biology, including potential resistance mechanisms, not organ location or single driver mutations
- Ability to re-analyse recurrent/resistant tumours and alter therapy on a logical rather than empirical basis

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Thank you & contact details

Q&A






Chee Gee See, PhD, MICR,
Director of Personalised Medicine,
Proteome Sciences plc,
Tel: +44-1932-865065
Cell: +44-7837576861
Email: cheegee.see@proteomics.com

Team Biomarkers welcomes you all to the next chapter – 7th International Conference on Biomarkers & Clinical Research scheduled for Nov 28-30, 2016 in Baltimore, USA

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