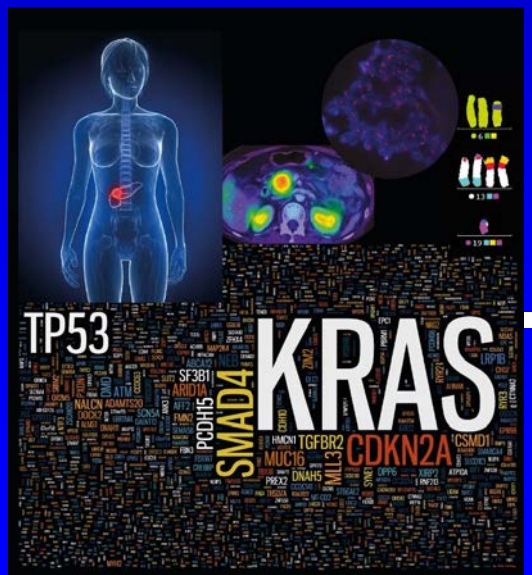
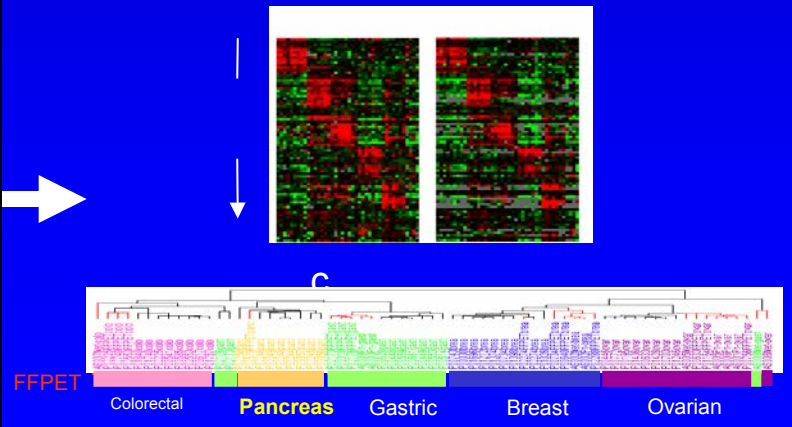
Why is pancreatic cancer so difficult to treat

CECOG 4th Pancreas academy meeting Vienna Nov 2019

Harpreet S. Wasan
Consultant / Reader in Medical oncology
Department of Cancer Medicine
Hammersmith Hospital, Imperial College London
h.wasan@imperial.ac.uk





My Disclosures in respect of this talk

- Consulting or Advisory Role, Honoraria, Speaker:

  Celgene, Servier, Shire, ERYTECH Pharma, Lily, OncoSil
  Merck KGaA, Sirtex Medical, Array BioPharma,
  Roche Pharma AG/Genentech/FMI,
  Incyte, BTG

- Research Funding:

  Sirtex Medical (Inst), Merck KGaA (Inst), Pfizer (Inst), Merck Sharp & Dohme (Inst)

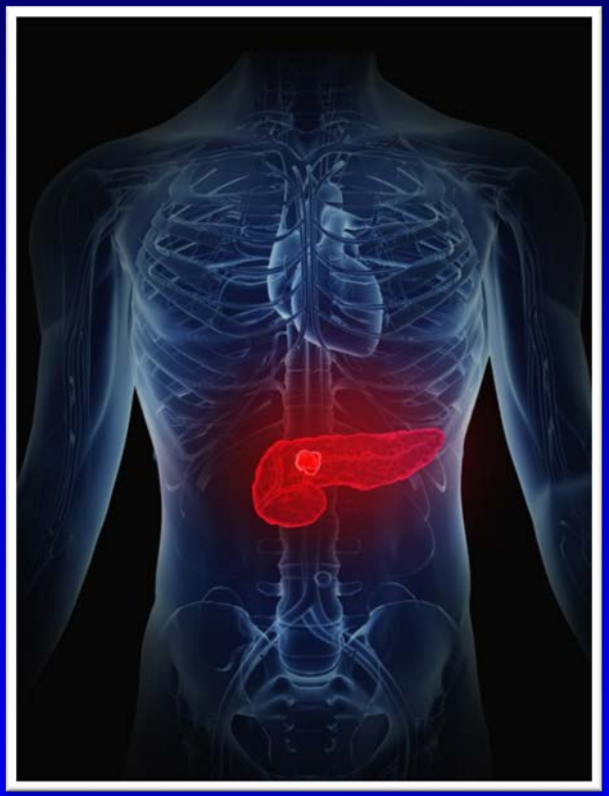
  Charitable / Governmental

  CRUK; NIHR: Plum/Layton Trust; Steele Charitable Trust

1 Key challenges in the understanding of the fundamentals of pancreatic cancer:

to improve treatments and outcomes

- Anatomical Location
- Late diagnosis & micro-metastatic disease[1]
- Low curative surgical resection rates
- Patient function, nutrition & adverse prognostics
- Thrombosis Cachexia
- Complex Biology and characteristics of pancreatic tumour cells[2]
  - Stroma –Desmoplasia / microenvironment
  - Heterogeneity: Molecular & Cellular
  - Primary (impaired drug delivery) and acquired Resistance to conventional treatments[3]



1. SEER Stat Fact Sheet Pancreas. Available at:http://seer.cancer.gov/statfacts/html/pancreas.html
2. Von Hoff et al *J Clin Oncol* 2011;29:4548-4554
3. 3. Hermann et al *Cell Stem Cell* 2007;1:313-323

2. Key challenges in the understanding of the fundamentals of pancreatic cancer:
to improve treatments and outcomes

- Evolutionary Robustness
  - Physiology and function of normal Pancreas
  - Immune-evasion: “cold”
  - Microenvironment
    primed to be highly immunosuppressive

- Research funding for pancreatic cancer is disproportionately low
  - Compared with other cancer types:
  - mortality rate: 4th for cancer-related deaths in developed nations

1. SEER Stat Fact Sheet Pancreas. Available at:http://seer.cancer.gov/statfacts/html/pancreas.html
2. Von Hoff et al *J Clin Oncol* 2011;29:4548-4554
3. 3. Hermann et al *Cell Stem Cell* 2007;1:313-323

Pancreatic Cancer, Incidence ~ Mortality
..... 2018 Pancreas Deaths > Breast cancer

Estimated New Cases*

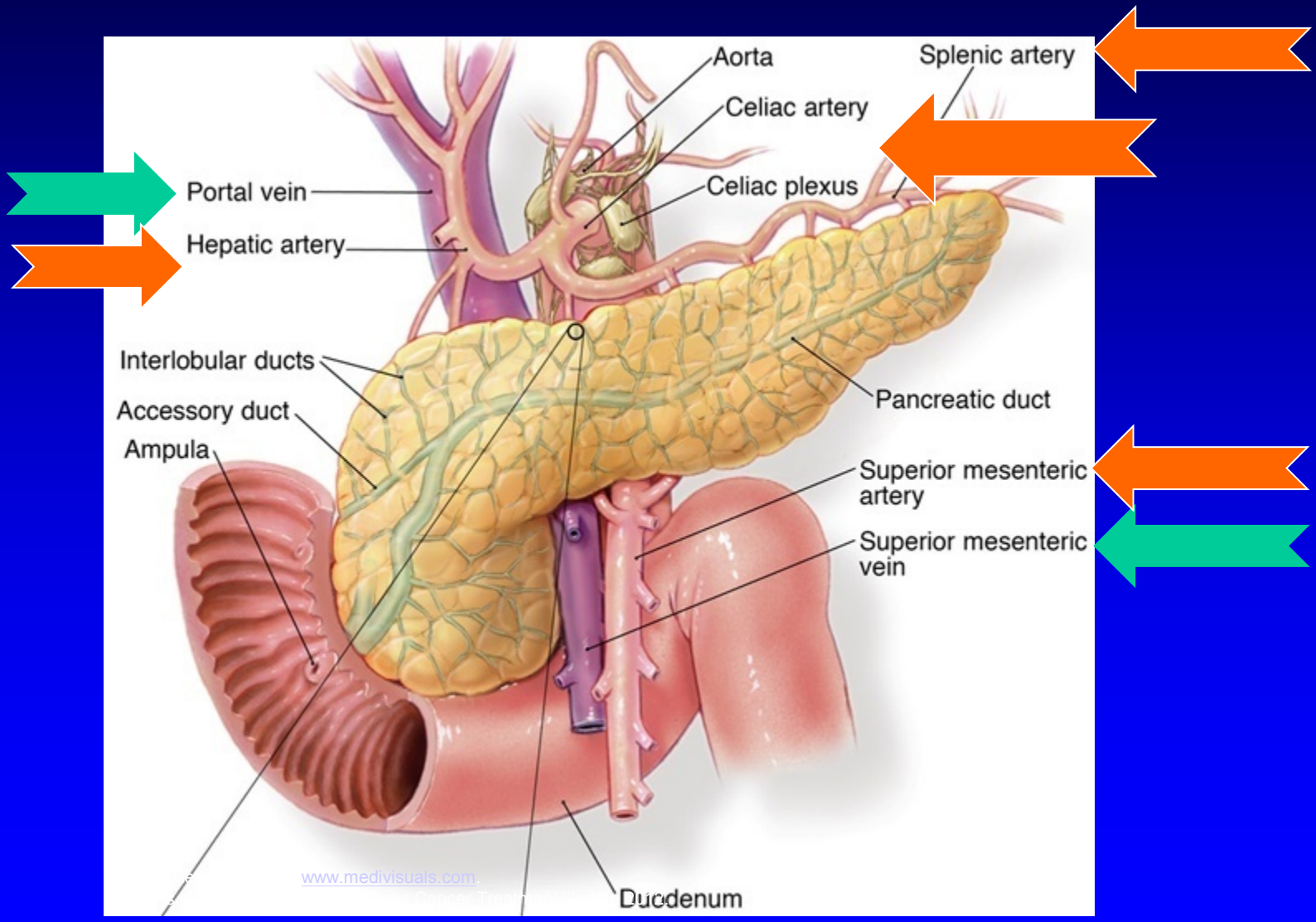
Males			Females		
Prostate	241,740	29%	Breast	226,870	29%
Lung & bronchus	116,470	14%	Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%	Colon & rectum	70,040	9%
Urinary bladder	55,600	7%	Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%	Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%	Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%	Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%	Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%	Ovary	22,280	3%
Pancreas	22,090	3%	Pancreas	21,830	3%
All Sites	**848,170**	**100%**	**All Sites**	**790,740**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	87,750	29%	Lung & bronchus	72,590	26%
Prostate	28,170	9%	Breast	39,510	14%
Colon & rectum	26,470	9%	Colon & rectum	25,220	9%
Pancreas	18,850	6%	Pancreas	18,540	7%
Liver & intrahepatic bile duct	13,980	5%	Ovary	15,500	6%
Leukemia	13,500	4%	Leukemia	10,040	4%
Esophagus	12,040	4%	Non-Hodgkin lymphoma	8,620	3%
Urinary bladder	10,510	3%	Uterine Corpus	8,010	3%
Non-Hodgkin lymphoma	10,320	3%	Liver & intrahepatic bile duct	6,570	2%
Kidney & renal pelvis	8,650	3%	Brain & other nervous system	5,980	2%
All Sites	**301,820**	**100%**	**All Sites**	**275,370**	**100%**

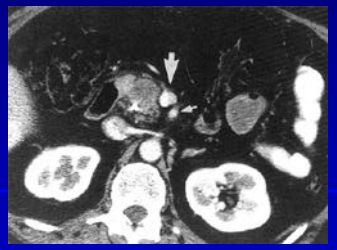
Siegel R, et al. CA Cancer J Clin. 2012;62:10-29.

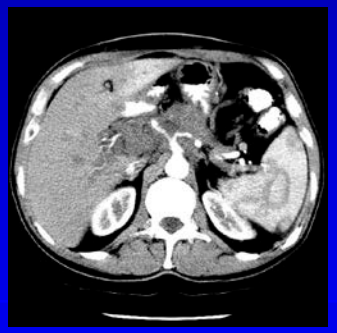
The Pancreas: Anatomy & Biology dictates early involvement of critical vasculature

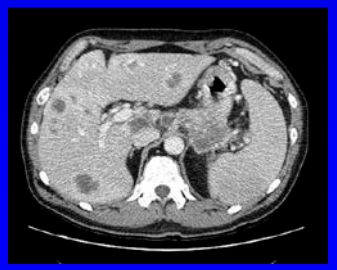


Pancreatic Cancer by Stage
(SEER Database)

Stage Classification	% at Diagnosis	5-Yr Survival, %
Localized - Potentially Resectable	8	22
Locally advanced/ unresectable	27	9
Metastatic	53	2





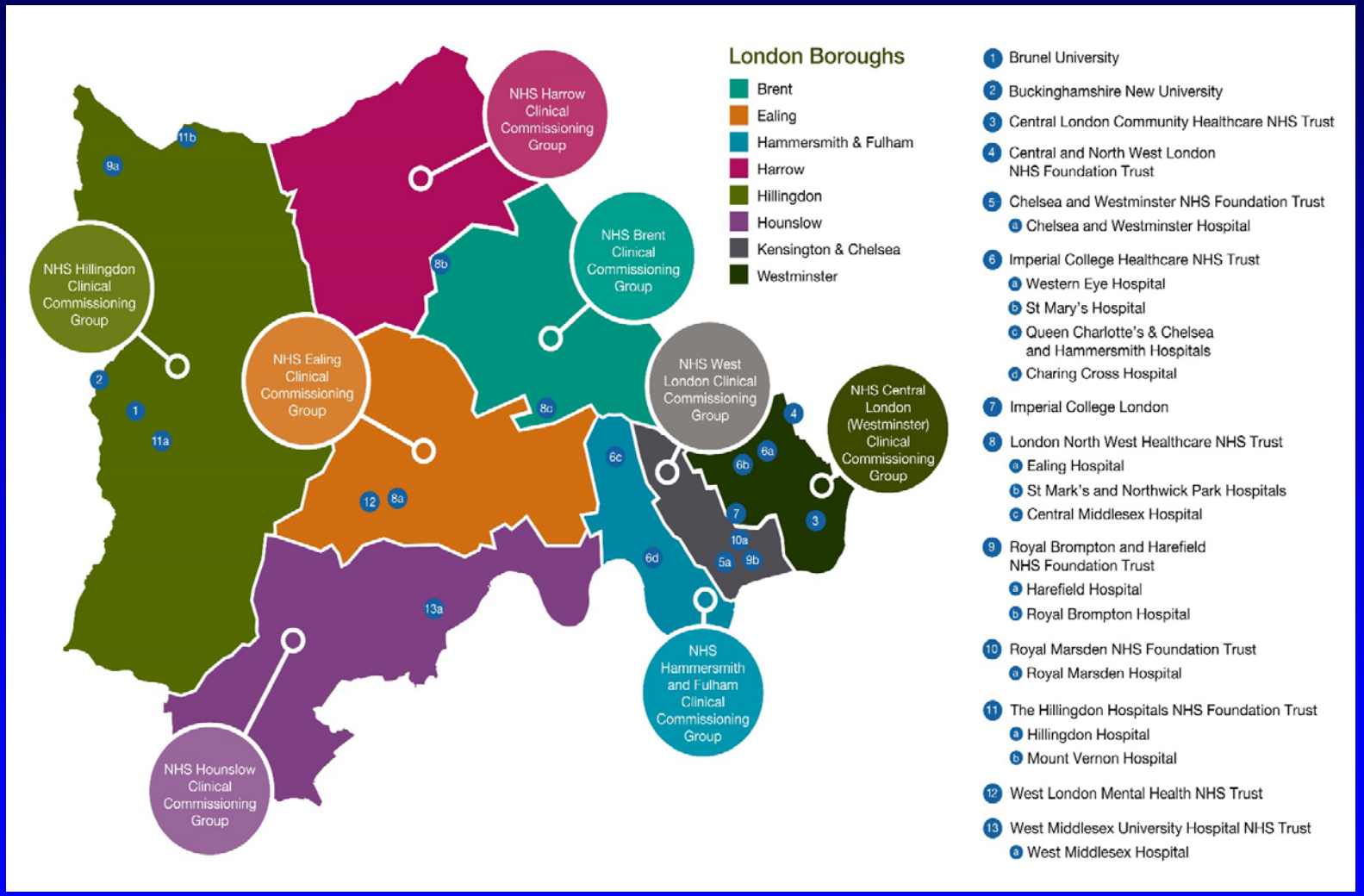


Siegel R, et al. CA Cancer J Clin. 2012;62:10-29.

discover
creating a healthier future through research

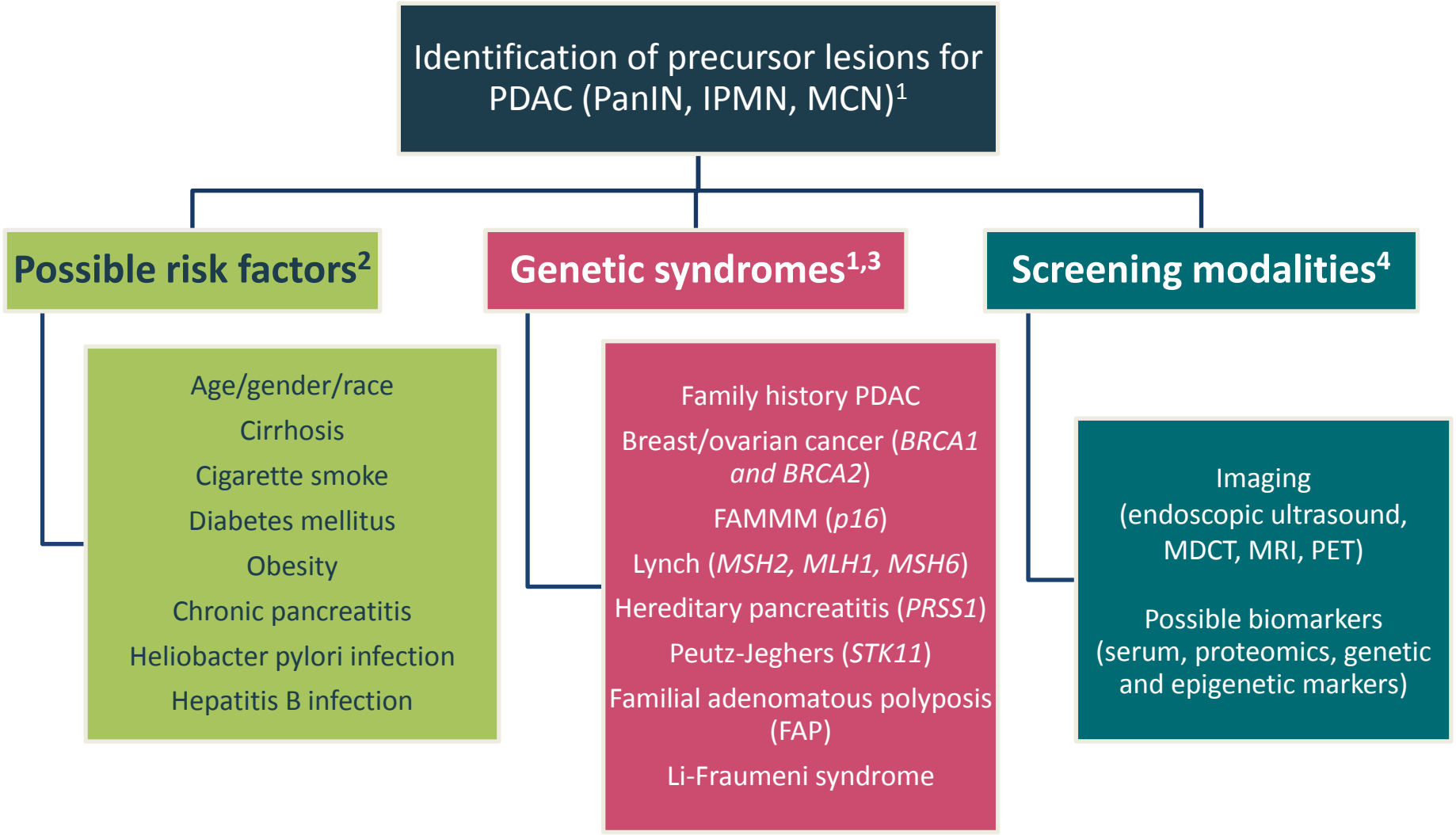
IMPERIAL COLLEGE HEALTH PARTNERS

Imperial CHP – Volumes drive better outcomes partners in North West London



Early detection strategies in pancreatic cancer

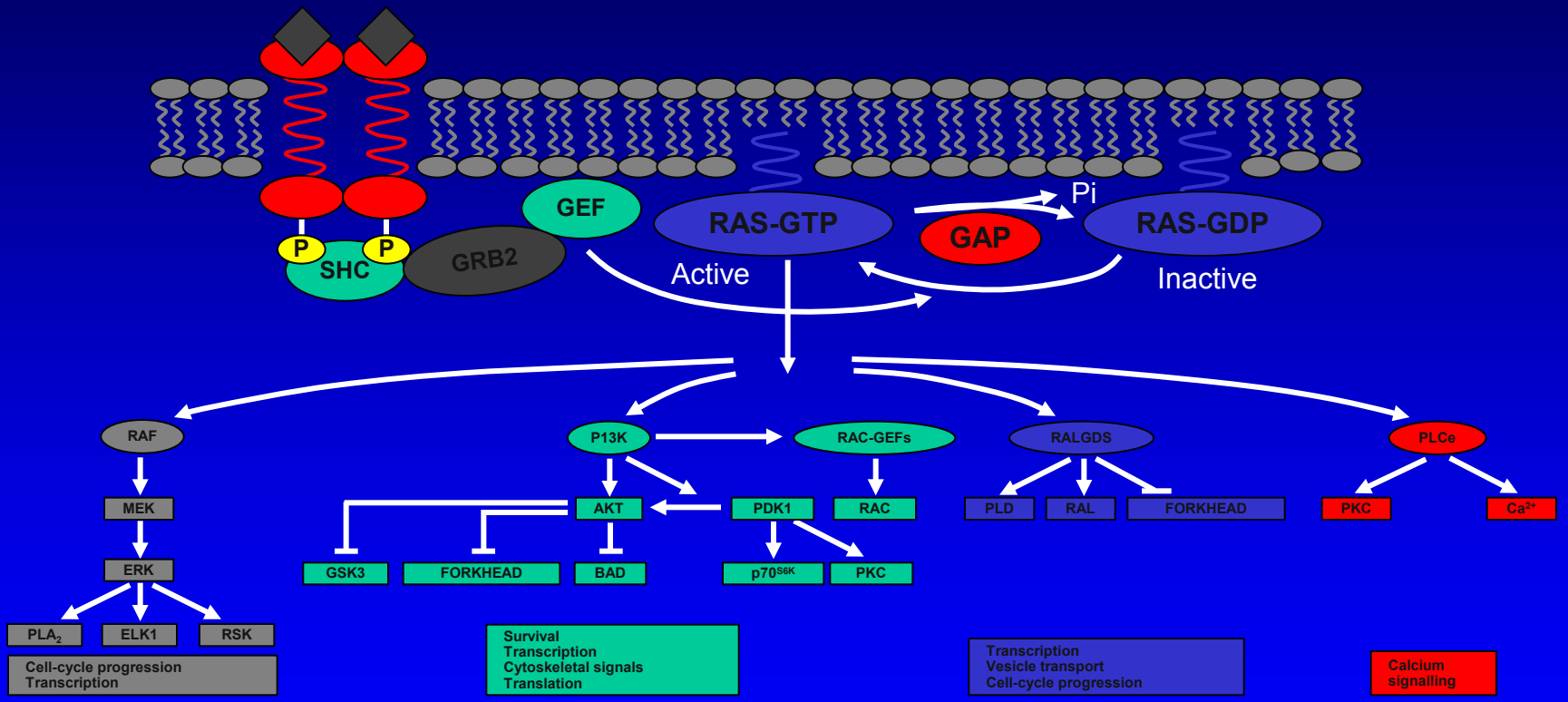
Date of preparation: November 2014
UK-ABR140176m



1. Haugk B. *Histopathology* 2010:57 503–14; 2 Cancer.net. *Pancreatic Cancer: Risk Factors*. http://www.cancer.net/cancer-types/pancreatic-cancer/risk-factors [Last accessed 31 October 2014]; 3. Pancreatic Cancer UK. Familial risk of pancreatic cancer fact sheet. http://www.pancreaticcancer.org.uk/media/49973/familial_risk_of_pancreatic_cancer_fact_sheet.pdf [Last accessed 31 October 2014] 4. Okano K, *et al. World J Gastroenterol* 2014; 20(32): 11230–11240.

Genomic landscape of pancreatic cancer

Mutations in the *KRAS* Oncogene Are Found in Majority of Pancreatic Cancers

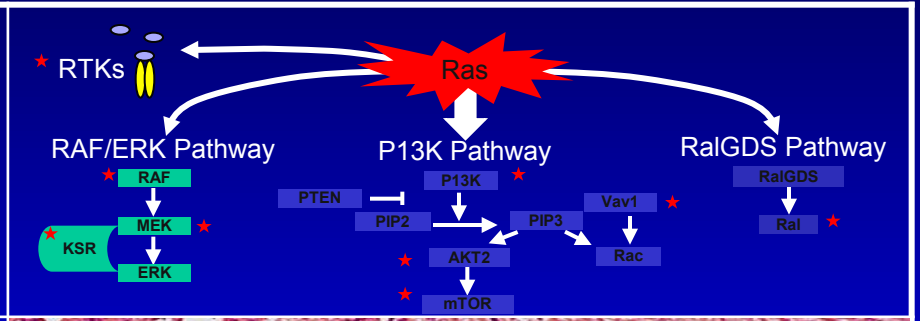


- Multiple therapeutic strategies targeting this gene and its effector pathways are being investigated

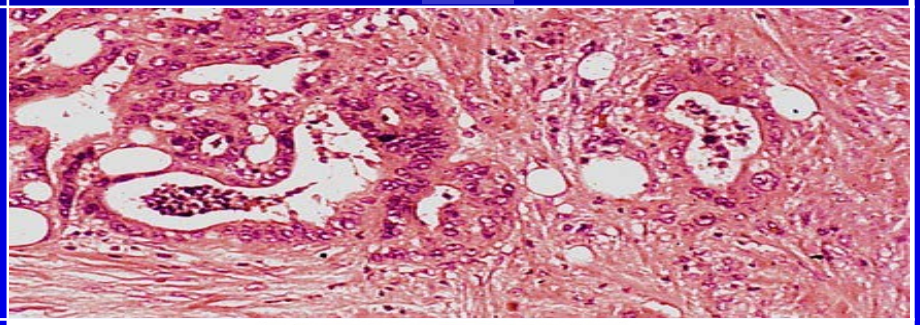
Chappell WH. Oncotarget. 2011;2:135-64.

Possible Reasons for Pancreatic Tumor Resistance to Treatment

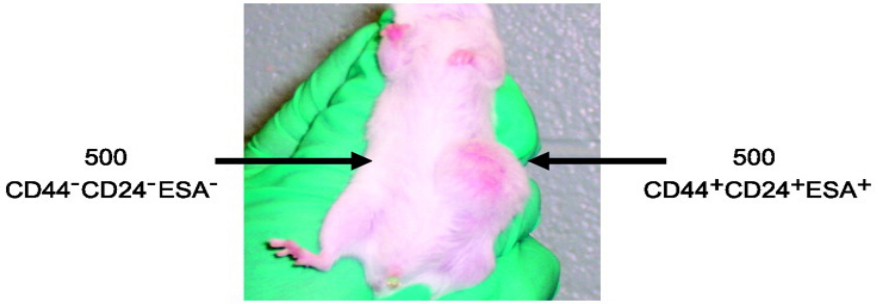
Signaling redundancy:
single targeted agent less likely to be effective



Surrounding desmoplasia:
role of supporting connective tissue elements?



Pancreatic cancer stem cells:
highly tumorigenic, can generate phenotypic diversity within the tumor; may be resistant to standard therapies



Li C, et al. Cancer Res. 2007;67:1030-1037.

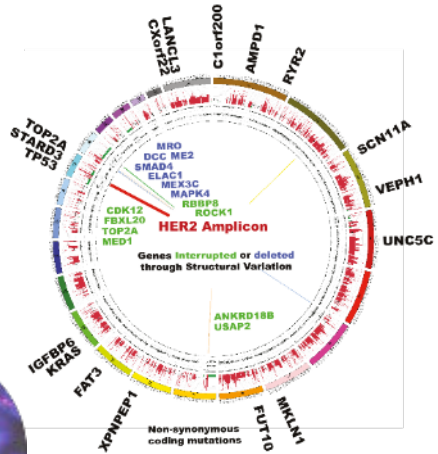
This satellite symposium has been organised and funded by Celgene. The prescribing information for *nab*-paclitaxel can be found at the end of this presentation

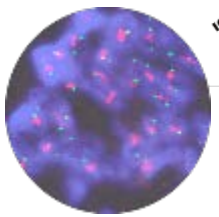
Pancreatic Cancer Molecular Pathology Atlas

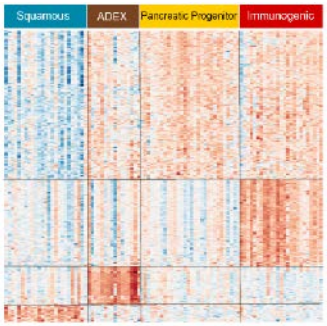
Large dataset of PDAC:

456 patient samples

Next generation models:
>50 patient-derived cell lines
>200 PDX
>30 organoids
… and growing



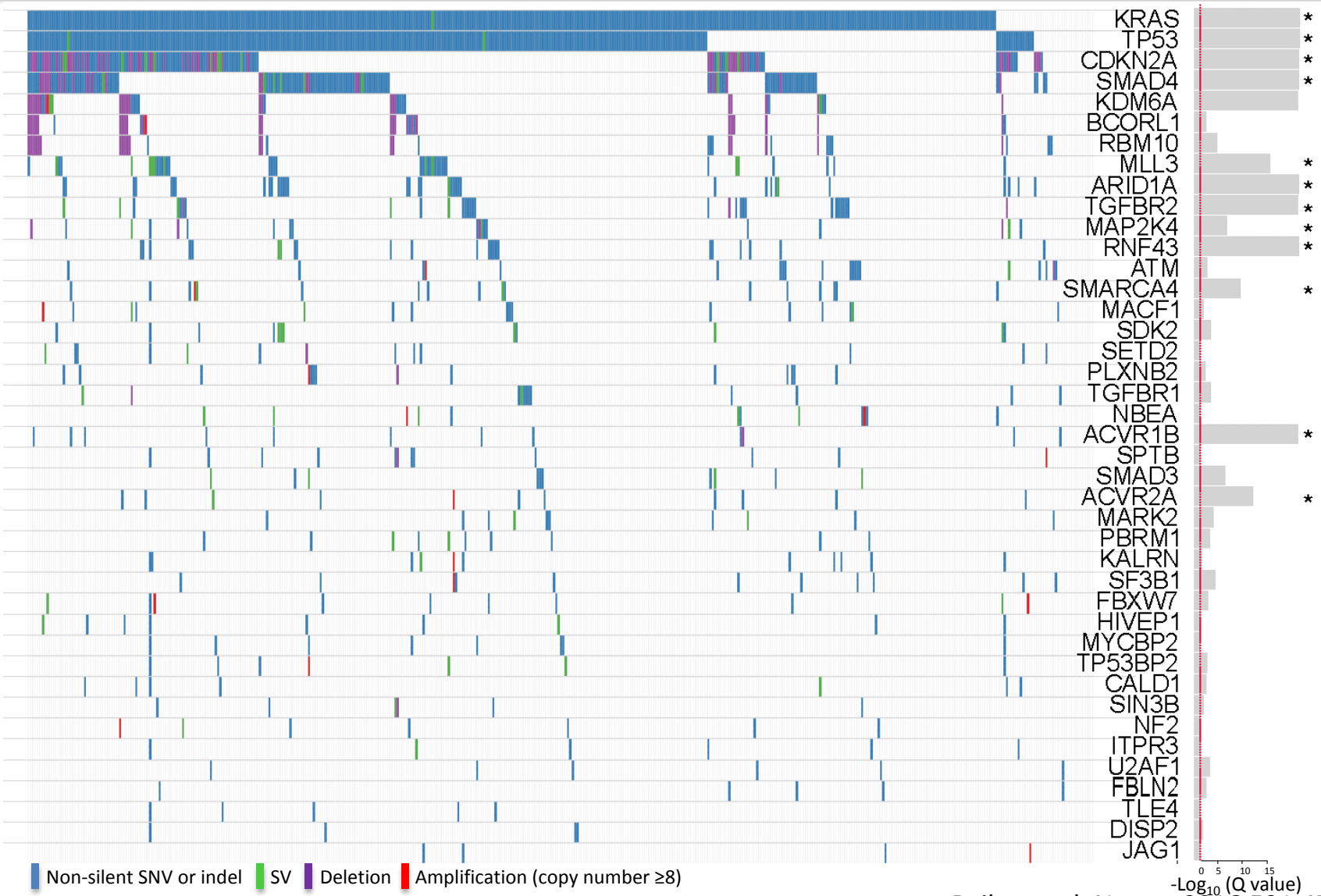




CLINICAL CORRELATES
SPECIES CONSERVATION
ANIMAL MODELS
FUNCTIONAL SCREENS
METABOLOME
KINOME
PROTEOME
CHIPseq
METHYLOME
miRNA
STRUCTURAL VARIATION
RNAseq
EXPRESSION ARRAYS
CNV ARRAYS
EXOMES
GENOMES

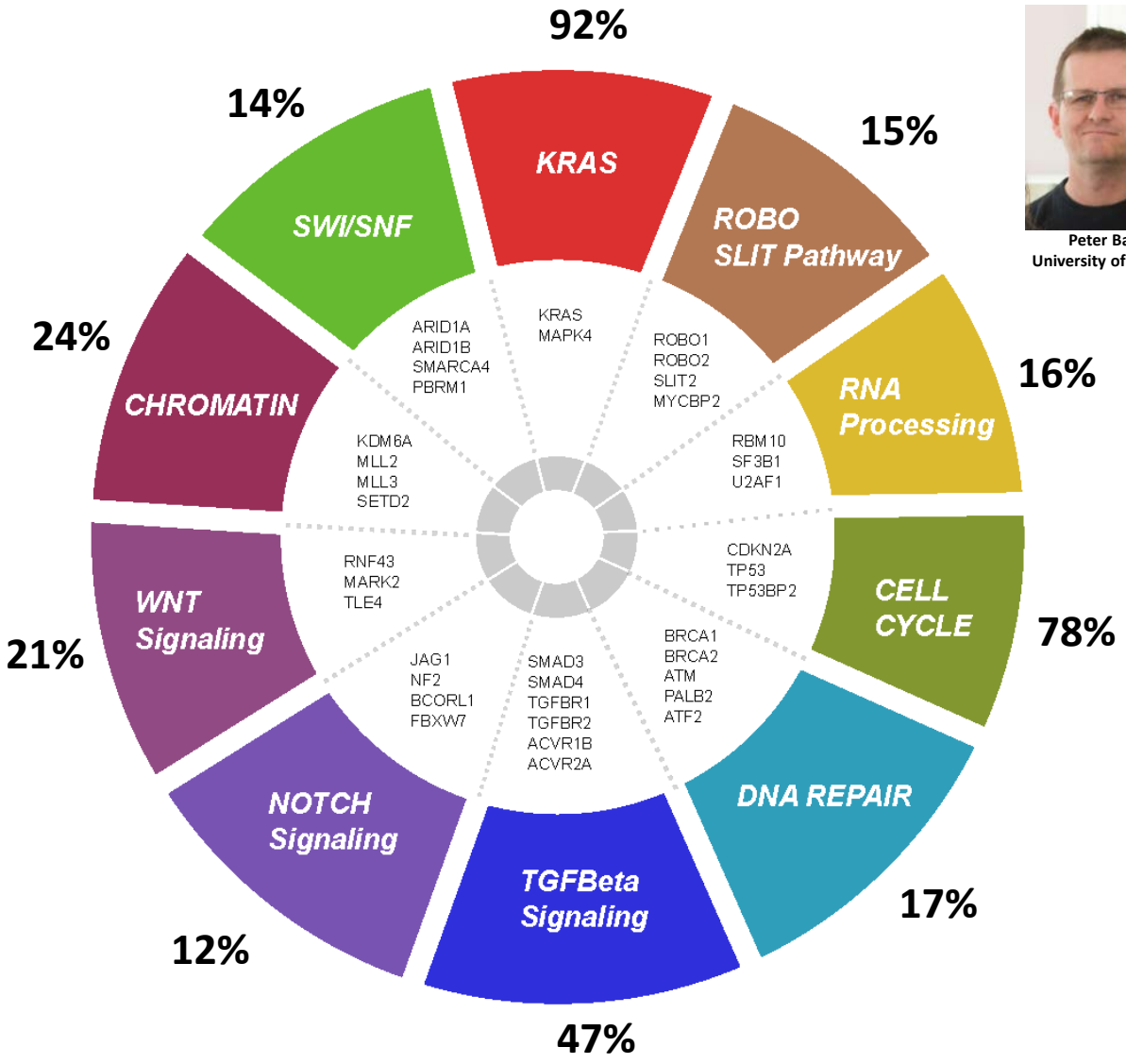
Bailey et al. Nature 2016;531:47-52;
Chou et al. Genome Med 2013;5:78

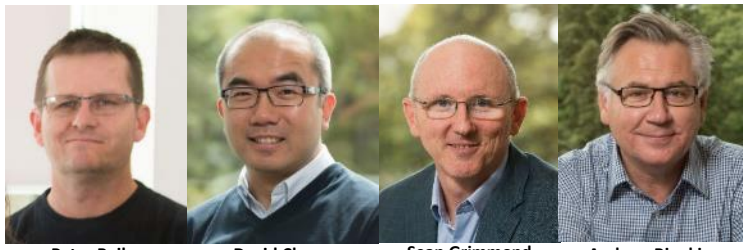
Genomic landscape of pancreatic cancer (n=456)



Bailey et al. Nature 2016;531:47-52

Key molecular mechanisms and potential novel vulnerabilities (n=456 multiplatform -omic analysis)





Peter Bailey
University of Glasgow

David Chang
University of Glasgow

Sean Grimmond
University of Glasgow

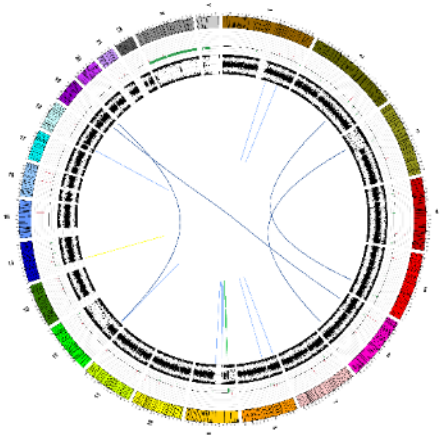
Andrew Biankin
University of Glasgow

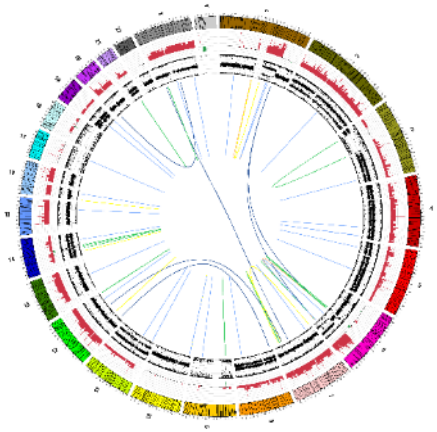
Hudson et al. Nature 2010;464:993-8
Biankin et al. Nature 2012; 491:399-405
Perez-Mancera et al. Nature 2012;486:266-70
Mann et al. PNAS 2012; 109:5934-41
Alexandrov et al. Nature 2013;500:415-21
Weissmueller et al. Cell 2014;157:382-94
Waddell et al. Nature 2015;518:495-501
Biankin et al. Nature 2015;526:361-70
Bailey et al. Nature 2016;531:47-52

Bailey et al. Nature 2016;531:47-52

Patterns of structural variation in PDAC

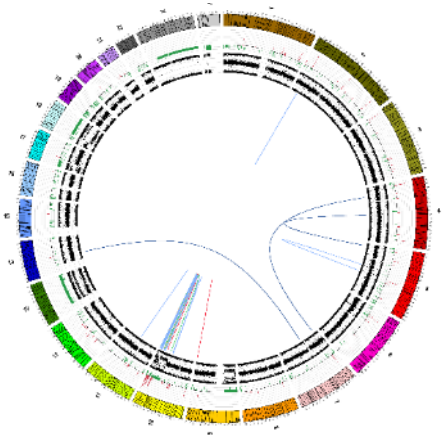
20%
Stable
(<50 events)

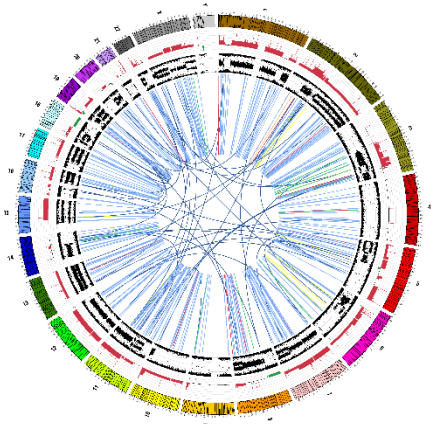




36%
Scattered
(50 – 200 widespread)

30%
Locally rearranged
(50-200, 50% on 1-2 chromosomes

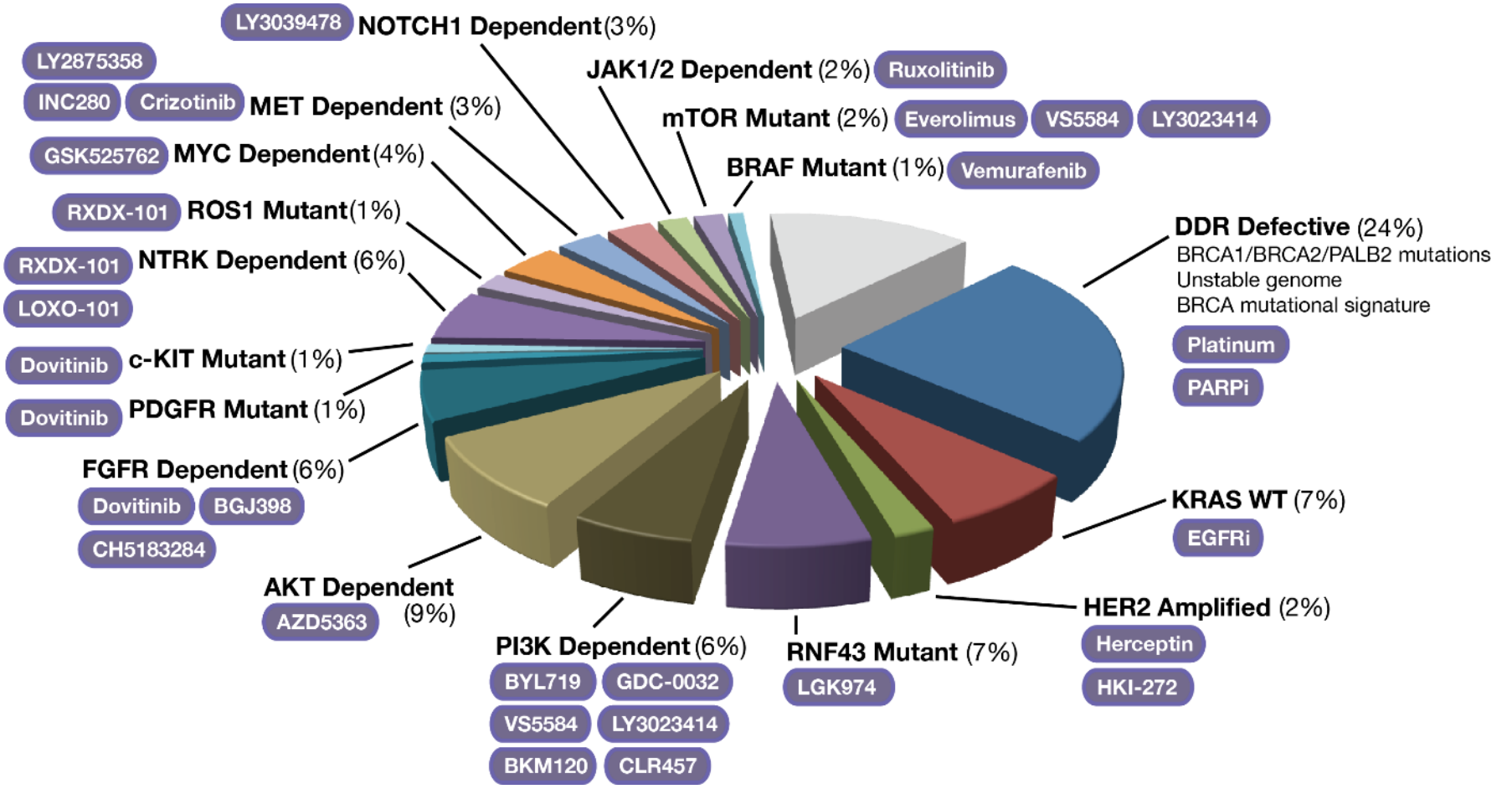




14%
Unstable
(>200 widespread)

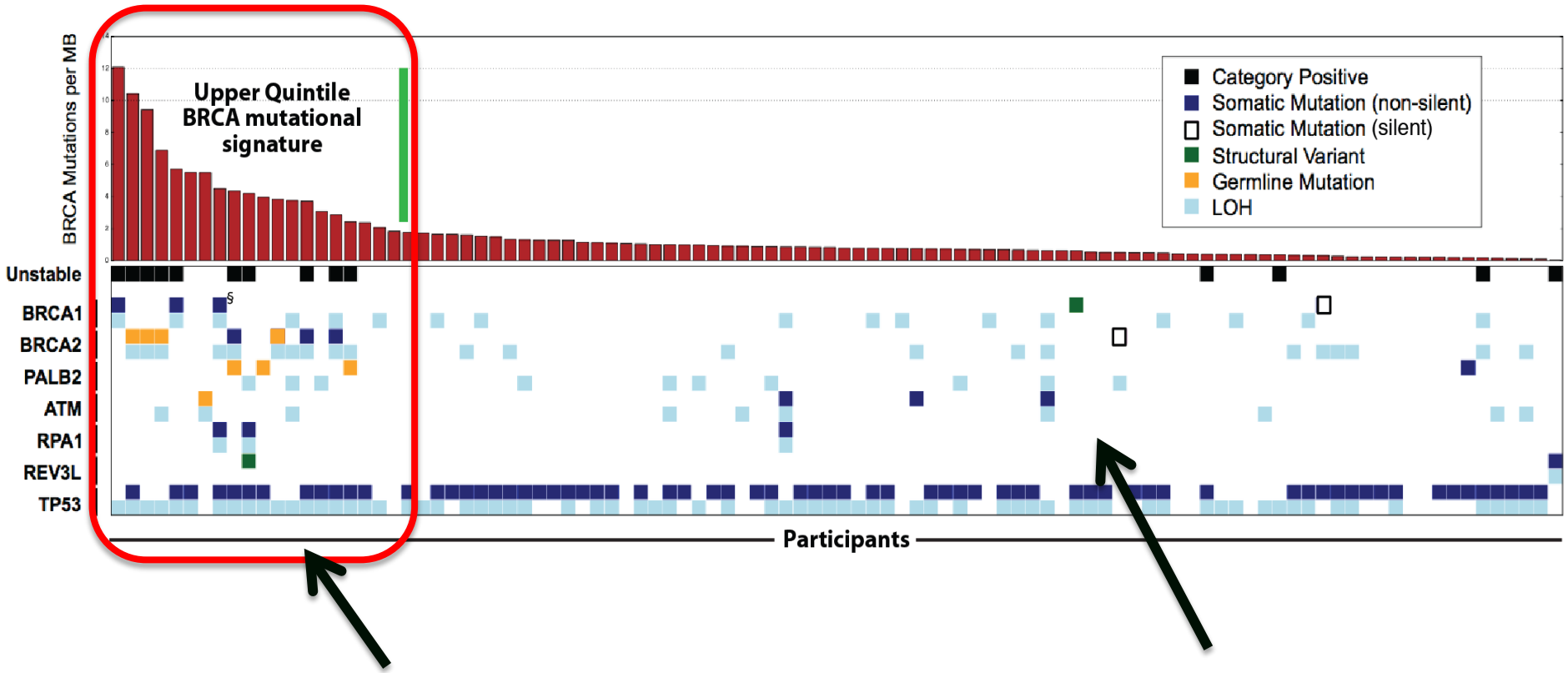
Waddell et al. Nature 2015;518:495-501

Pancreatic cancer “druggable” ?



Platinum Therapy Responsiveness: DDR deficiency in PDAC

BRCA Mutational Signature Vs Unstable Genome Vs Gene Mutation



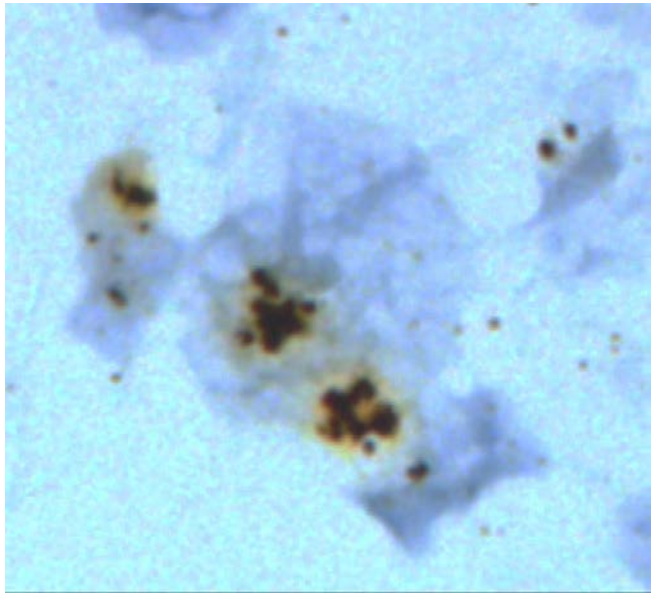
6/7 responses including 2 CRs

8/8 No Response

Unstable tumours associated with a high *BRCA* mutational signature and deleterious mutation in *BRCA* pathway genes

Probable Current Actionable Phenotypes

- **Generic to all cancers**
- **? Tumour agnostic**
  - **BRCA**
  - **MSI;**
  - **NTRK fusions**
  - **HER-2,**
  - **FGFR fusions**
    - **All rare**

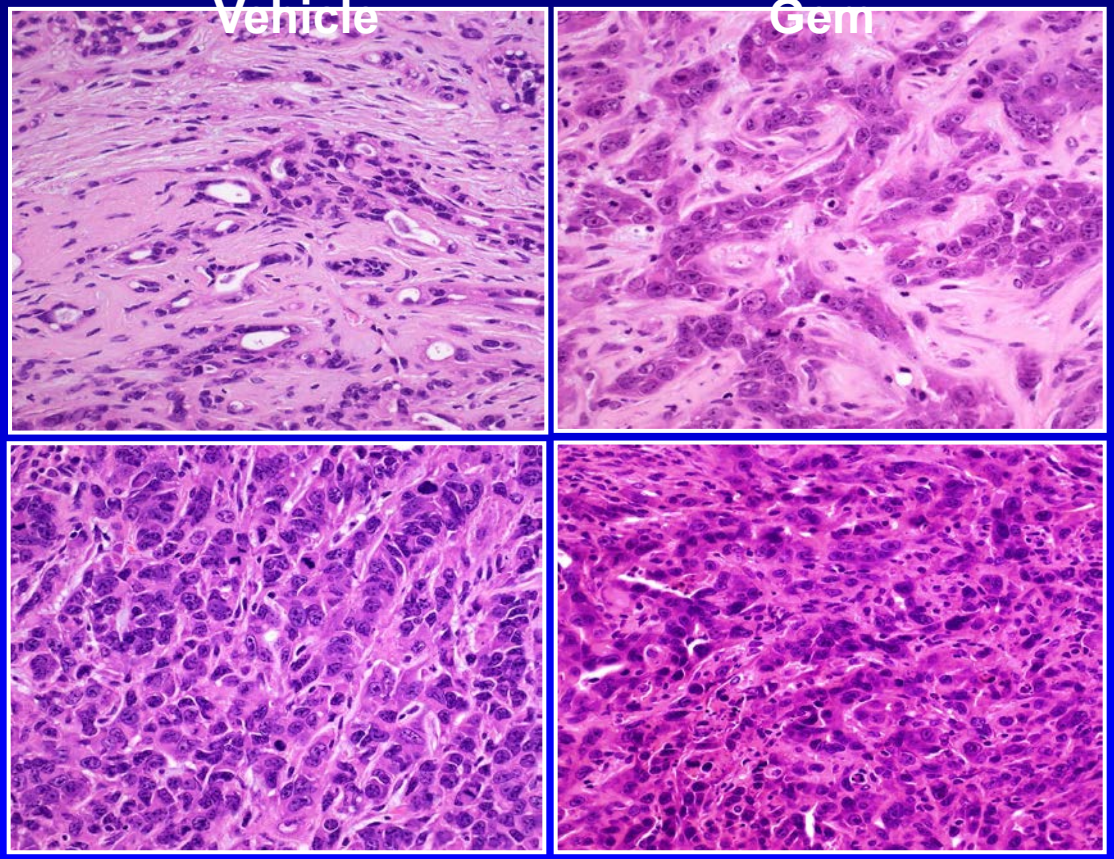


Ontogeny & Development are integral to Oncology: Gaining Clues From Developmental Biology

- **Hedgehog** originally identified as a segment polarity gene in *Drosophila*; vertebrate Hedgehog homologues subsequent discovered, including in mice and humans
- Critical role in normal development of pituitary gland, teeth, limbs, lungs, neural tube, and GI tract

Hedgehog Signaling Critical in Tumor- Stroma Interactions in Pancreatic Cancer

Hh Inhibitor IPI-926 Depletes Stroma in Mouse Pancreatic Cancer Models



Olive KP, et al. Science. 2009;324:1457-1461.

Immuno-oncology strategies

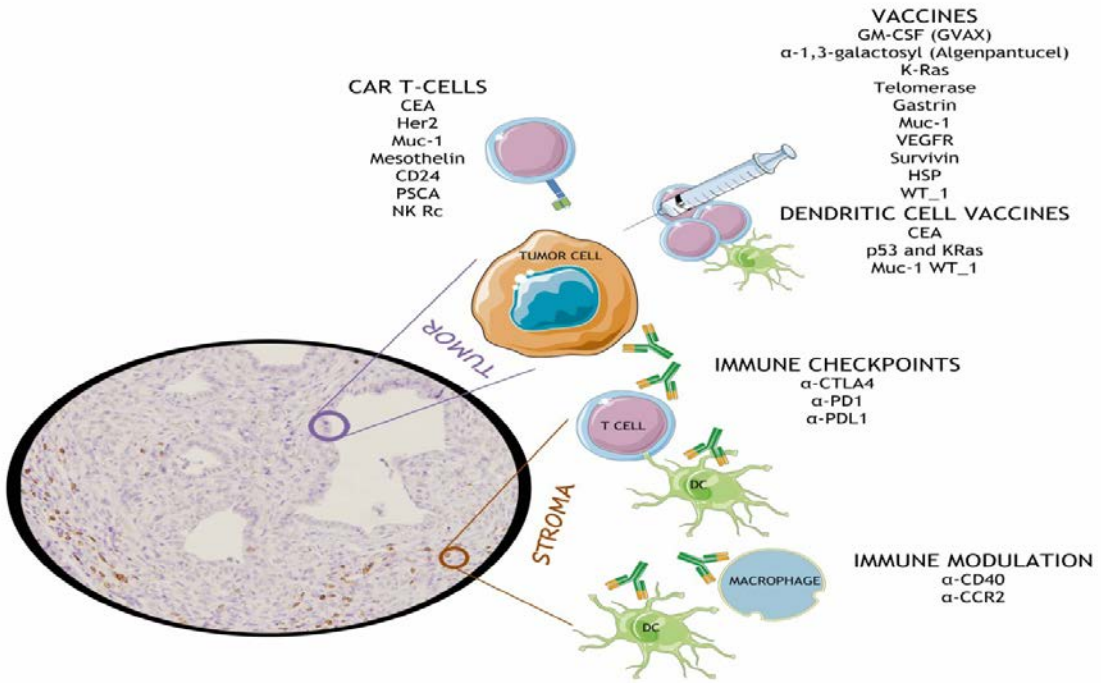


Figure 1. Immunotherapy strategies that have been considered in PDA therapy. Targeting immune checkpoints, the use of vaccines, CAR T-cells or immune modulating molecules have been included in pancreatic cancer clinical trials. CEA: carcinoembryonic antigen; Her2: human epidermal growth factor receptor 2; Muc-1: mucin-1; CD24: Cluster of differentiation 24; PSCA: prostate stem cell antigen; NK Rc: natural killer receptor; GM-CSF: granulocyte-macrophage colony-stimulating factor; VEGFR: vascular endothelial growth factor; HSP: heat shock protein; WT-1: Wilms tumor 1; CTLA4: cytotoxic T lymphocyte-associated protein 4; PD1: programmed cell death protein 1; PDL1: programmed death ligand 1; CD40: cluster of differentiation 40; CCR2: C-C motif chemokine receptor 2.

Therapeutic cancer vaccines using cancer cell antigens mixed with agents that stimulate patient immune responses have shown impressive results in several tumors and are also in the spotlight in

Complex molecular landscape of pancreatic cancer

is leading to 4 possible sub-types that may be useful for prognostics and predictives if reproducible

(1) pancreatic progenitor or classical PDA,
express early pancreatic development genes
i.e., PDX1, FOXA2/3, HES1

(2) squamous / quasimesenchymal tumors, have TP53 mutations, upregulated TP63ΔN
activated TGF-β signaling and MYC pathways
poor prognosis;

(3) aberrantly differentiated endocrine/exocrine tumors,
KRAS over-activation
and exocrine (NR5A, RBPJL) and endocrine (NEUROD1, NKX2-2) markers;

(4) immunogenic PDA. molecular similarities to classical PDA,
also expresses genes associated to immune phenotypes, eg Toll-like receptors, antigen presentation molecules and genes related to infiltrating B and T cells, both T-cytotoxic (CD8+) and Tregs.

Summary Many Medical innovations will be needed to overcome the challenges in the treatment of pancreatic cancer

Challenge

- Late diagnosis / micrometastatic disease[1]
- Location
- Unique characteristics of cells[2]
  - Stroma / microenvironment as a barrier
  - Heterogeneity
  - Primary and acquired Resistance to conventional treatment[3]

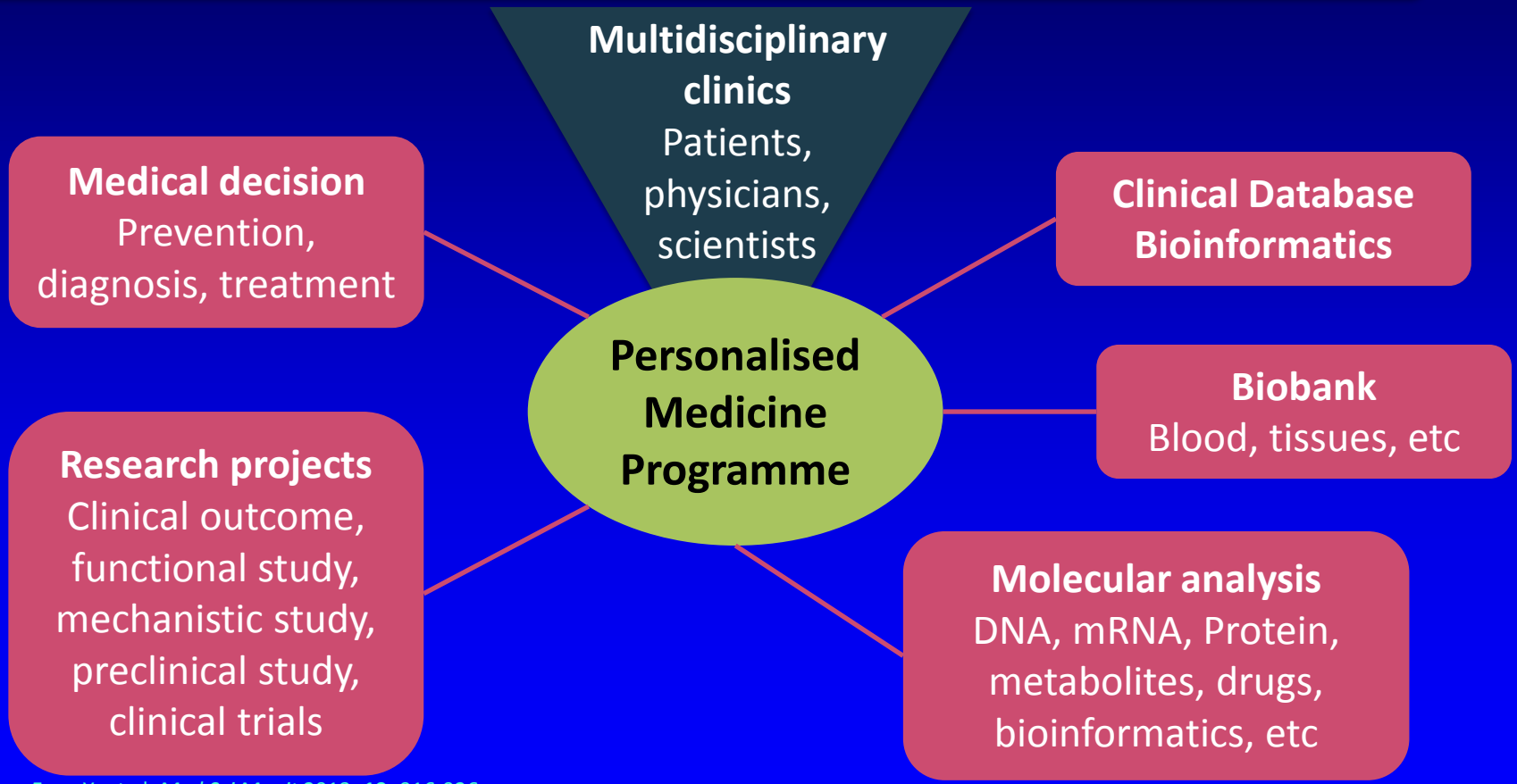
innovation

- Health Education
  - Biomarkers/CTC's
  - Radiological
- **Neoadjuvant**
- **Attenuate Stroma**
- **Local control**
  - Radiotherapy ++
    - Intra-Pancreatic (Oncosil- EUS / intraoperative
    - IRE Nanoknife
- New Technologies
- New Targeted agents
- Clinical studies &Research

1. SEER Stat Fact Sheet Pancreas. Available at: http://seer.cancer.gov/statfacts/html/pancreas.html 2. Von Hoff et al *J Clin Oncol* 2011;29:4548-4554 3. Hermann et al *Cell Stem Cell* 2007;1:313-323

Personalised medicine in PDAC

***It's far more important to know what person the disease has than what disease the person has* – Hippocrates**



Adapted from Fang Y, et al. *Med Sci Monit* 2013; **19**: 916-926.

FDA. October 2013. Paving the Way for Personalized Medicine. http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf [Accessed 22 October 2014]; Fang Y, et al. *Med Sci Monit* 2013; **19**: 916-926.

Thank you !

Especially to all the patients & their families past, present and future who contribute to pancreatic cancer research