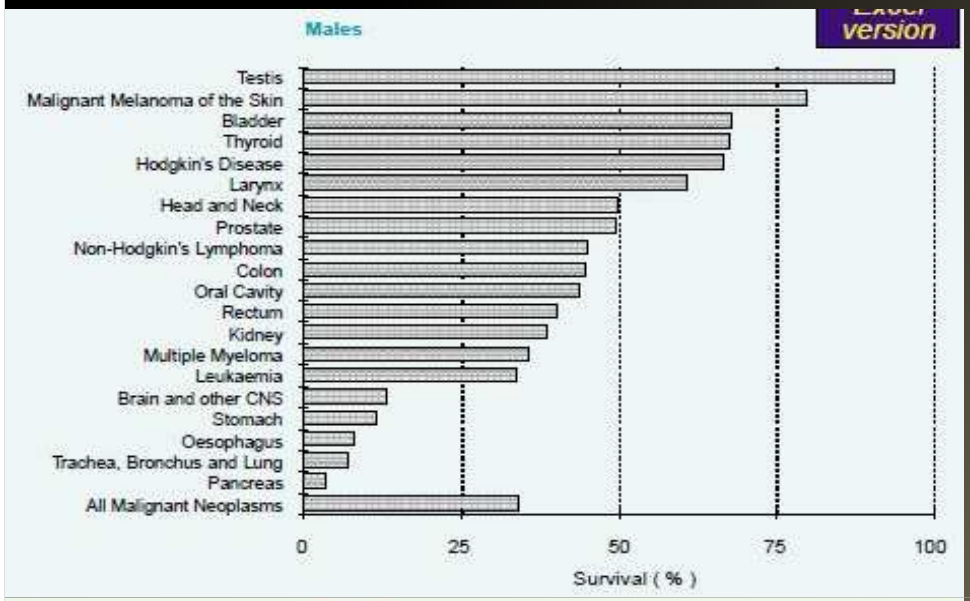
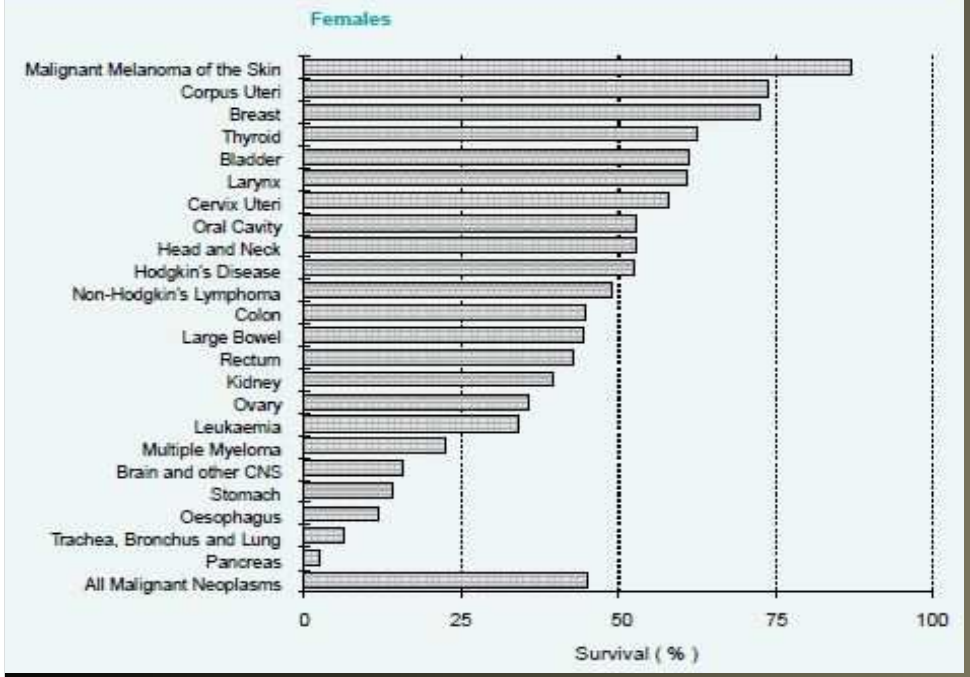
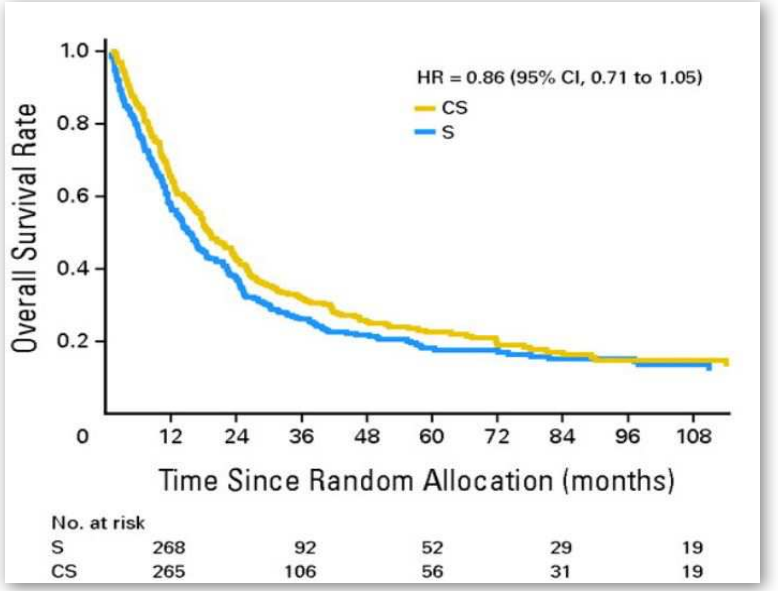
Identification of Therapeutic Targets in Human Cancers





- Cancer patients are living longer
- Surgery can be “curative”
- But in some cancers- of ‘high unmet clinical need” there are no therapeutic benefits of biologic or chemotherapies

OE02 Trial



RCT with n=802. Cisplatin + 5-FU pre-operatively vs. surgery alone.
Adeno data above

Allum W H et al. JCO 2009;27:5062-5067

International Centre For
Cancer Vaccine Science

We are focusing on two therapeutic paths; receptor-target discovery and/or development of neoantigen therapeutics in specific cancers of unmet clinical need

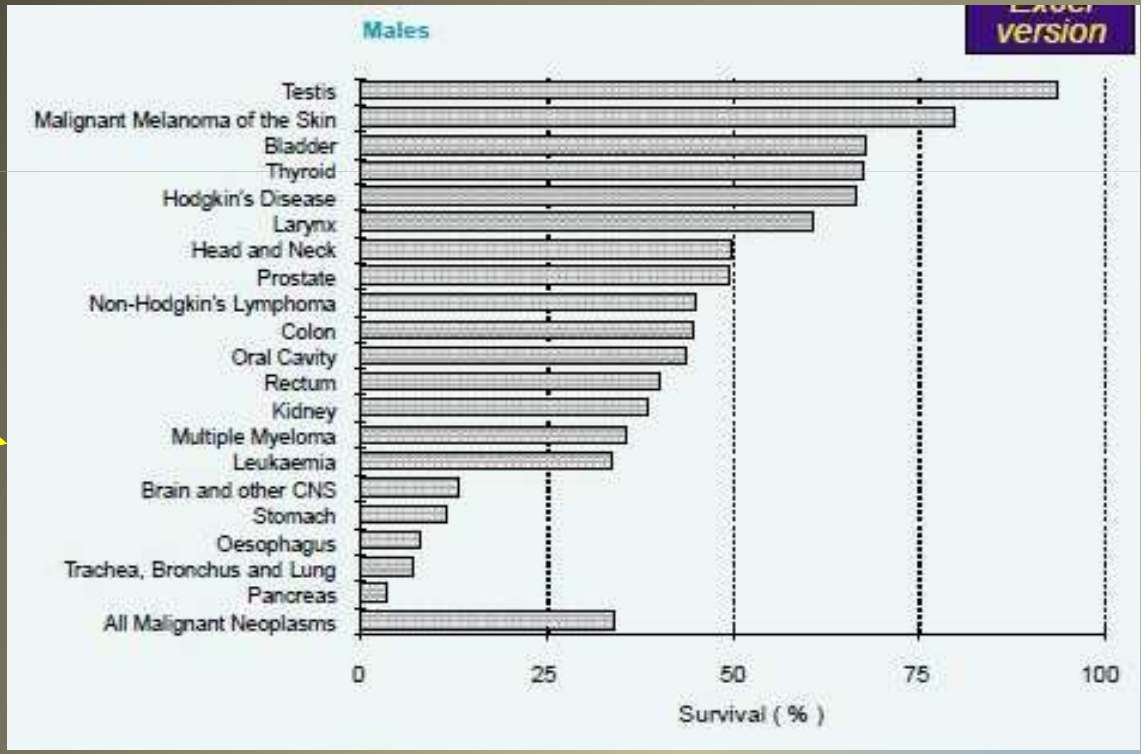
Four common cancers of “high unmet clinical need” include:

Brain

Oesophagus

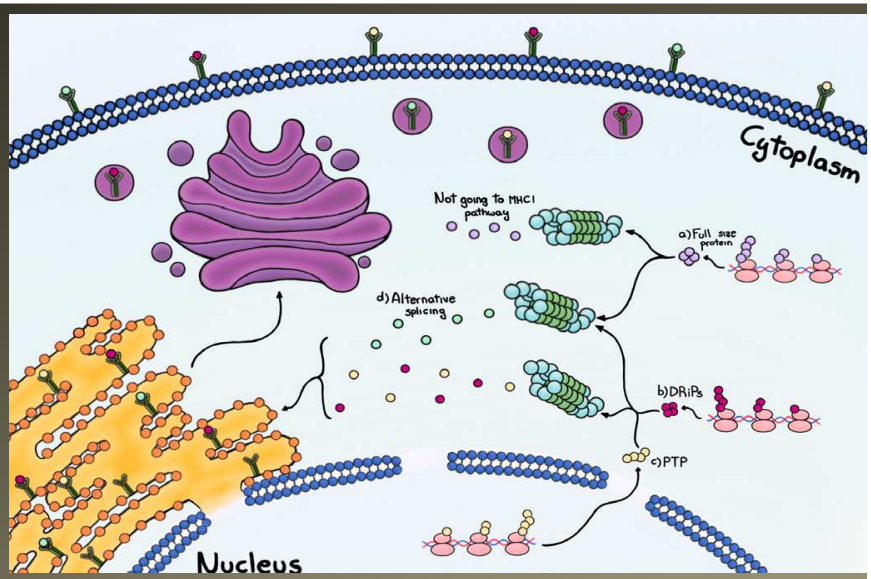
Pancreas

Lung



Scientific questions in the ICCVS

- Where do neoantigens come from in cancer cells?
- What genes regulate the MHC I class landscape in cancers?
- What is the nature of the immune-cancer synapse in cancers of unmet clinical need?
- Can this R&D drive therapeutic developments that exploit the proteogenomic landscape of cancers?



- *Robin Fahraeus: neoantigen science*
- *Natalia Marek-Trzonkowska: cancer immunology*
- *Irena Dapic: Proteogenomics platforms in GBM*
- *Javier Alfaro: Computational Science*
- *Dave Goodlett: Mass Spectrometry and Lipidomics*
- *Ted Hupp: Biologics and Therapeutics*
- *Maciej Parys & David Argyle: veterinary cancer models*
- *Sylwia Rodzewicz-Motowidło: chemical biology*

International Centre For Cancer Vaccine Science

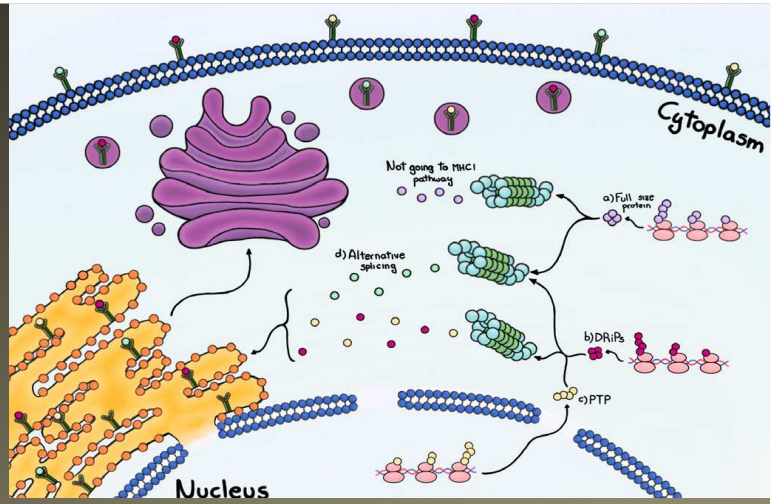
Scientific questions in the ICCVS

- Where do neoantigens come from?

- What oncogenes regulate the MHC
- class landscape?

- What is the nature of the immune-cancer
- synapse in cancers of unmet clinical need?

- Can this R&D drive therapeutic developments
- related to proteogenomic landscape of cancers?

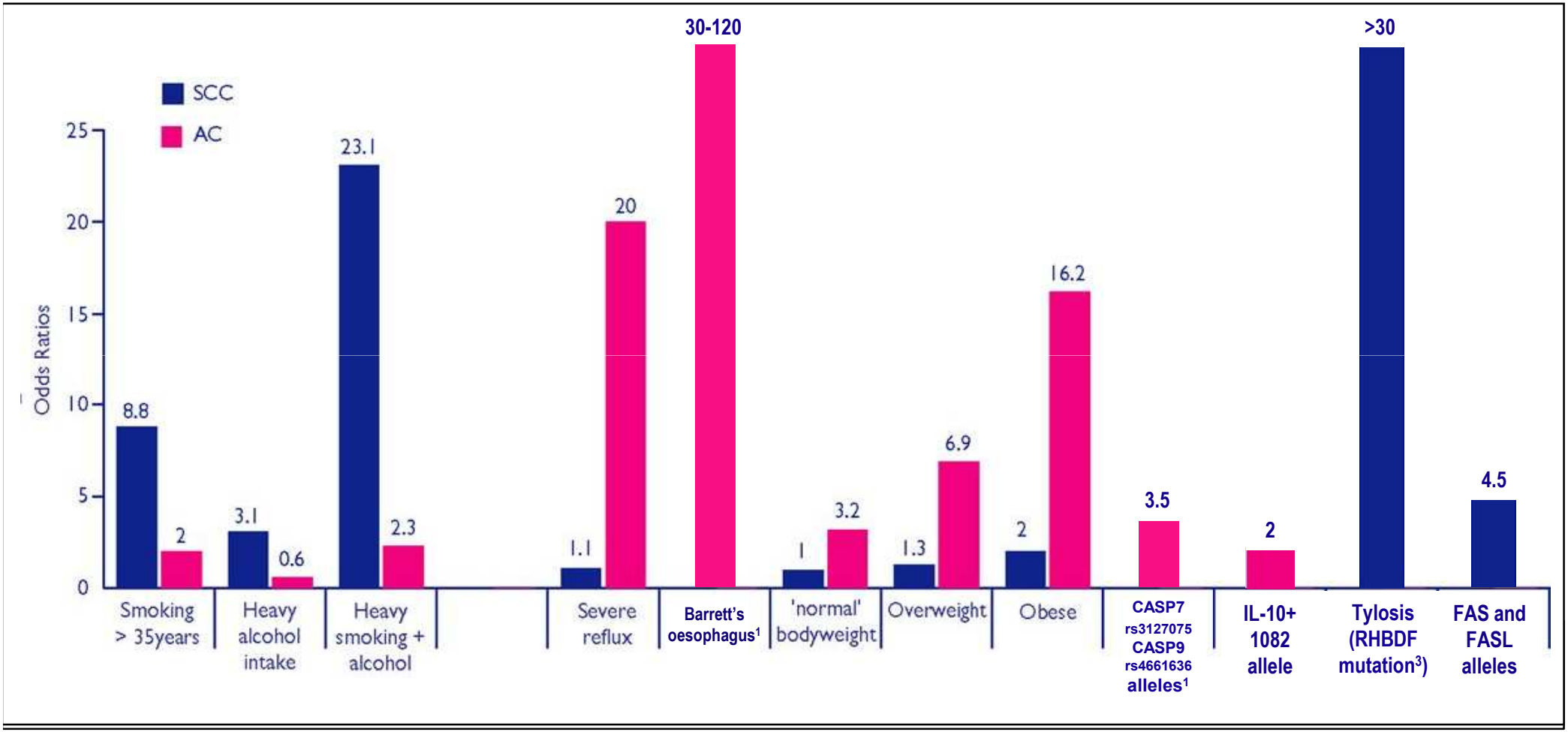


Today's review:

- *The genomic landscape of oesophageal adenocarcinoma*
- *The proteomic landscape of oesophageal adenocarcinoma*
- *Identification of the IFITM1 receptor as a regulator of MHC Class I protein synthesis*

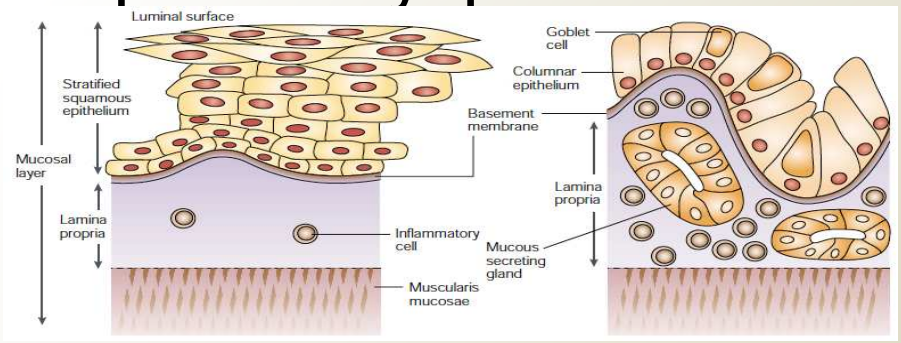
International Centre For Cancer Vaccine Science

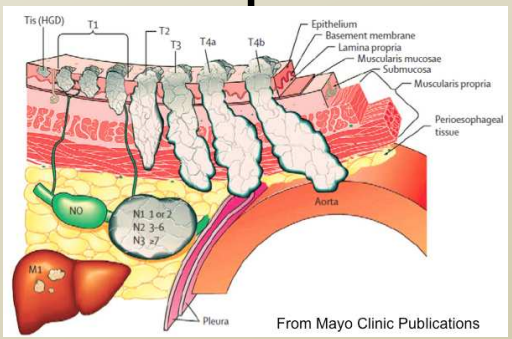
Risk Factors for SCC and ACC of the Oesophagus



Translational Research Priorities in Oesophageal Adenocarcinoma

Metaplasia-Dysplasia-Adenocarcinoma Sequence



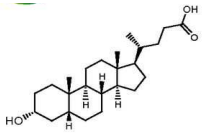


Normal → metaplasia/dysplasia → OAC

676 | SEPTEMBER 2003 | VOLUME 3 www.nature.com/reviews/cancer

Early detection

- Identify patients with Barrett's from the whole population
  - a) Non-endoscopic screening (cytosponge) & Imaging tools for endoscopic surveillance
  - b) Plasma biomarker development
  - c) Steroids impacts as risk factors



Effective Treatment

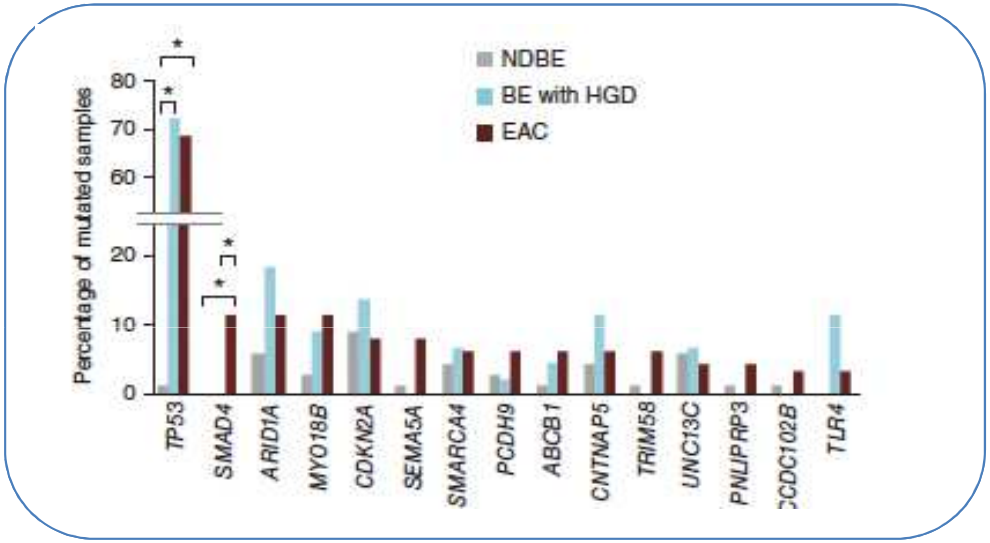
- Identify new therapeutic targets in patients with adenocarcinoma
  - a) Define therapeutic targets based on existing knowledge; for chemotherapies or antibody therapies
  - b) Incorporate whole-genome, transcriptome and proteome data-sets to uncover cancer-specific mutant proteins; neoantigen therapies

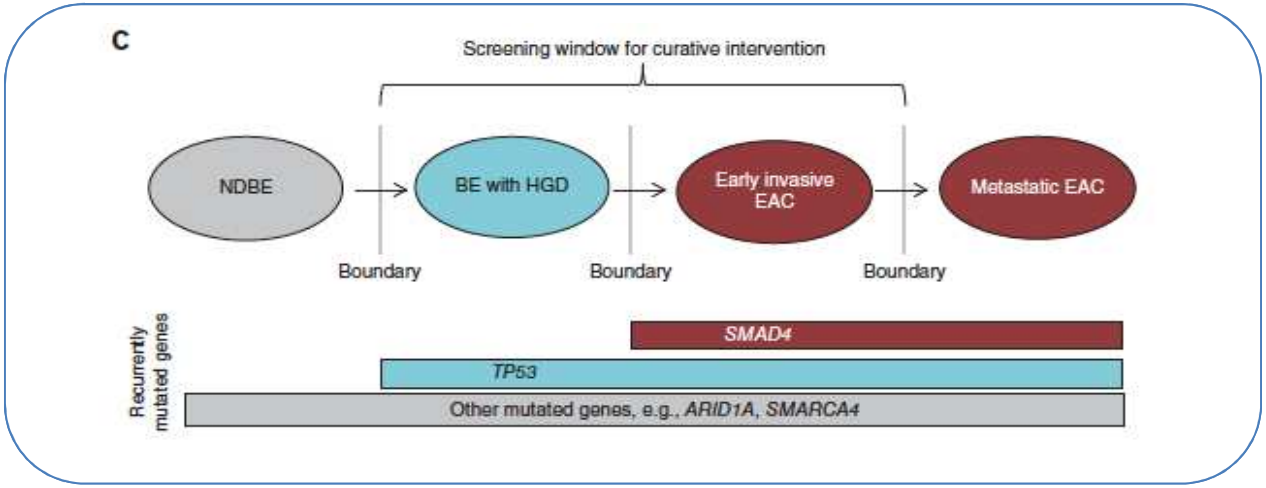
Ordering of mutations in preinvasive disease stages of esophageal carcinogenesis

Jamie M J Weaver[1,11], Caryn S Ross-Innes[1,11], Nicholas Shannon[2,11], Andy G Lynch[2,11], Tim Forshew[2], Mariagnese Barbera[1], Muhammed Murtaza[2], Chin-Ann J Ong[1], Pierre Lao-Sirieix[1], Mark J Dunning[2], Laura Smith[1], Mike L Smith[2], Charlotte L Anderson[2], Benilton Carvalho[2], Maria O'Donovan[3], Timothy J Underwood[4], Andrew P May[5], Nicola Grehan[1], Richard Hardwick[6], Jim Davies[7], Arusha Oloumi[8], Sam Aparicio[8], Carlos Caldas[2], Matthew D Eldridge[2], Paul A W Edwards[9], Nitzan Rosenfeld[2], Simon Tavaré[2], Rebecca C Fitzgerald[1] & the OCCAMS Consortium[10]

nature genetics

2014

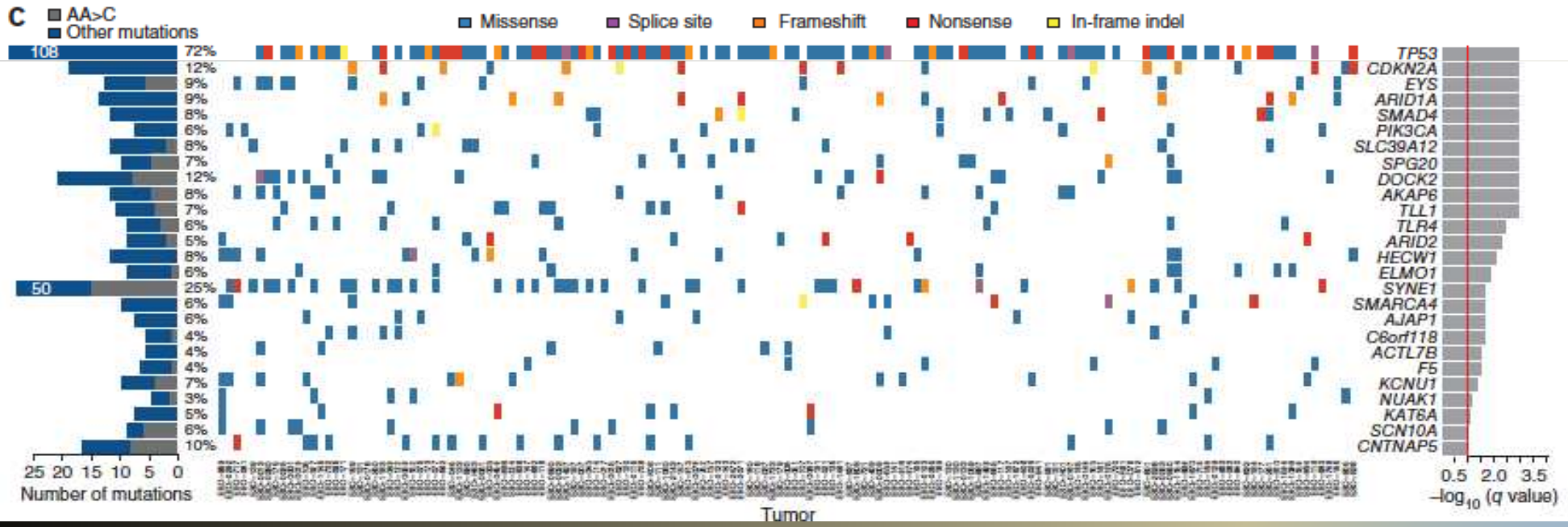


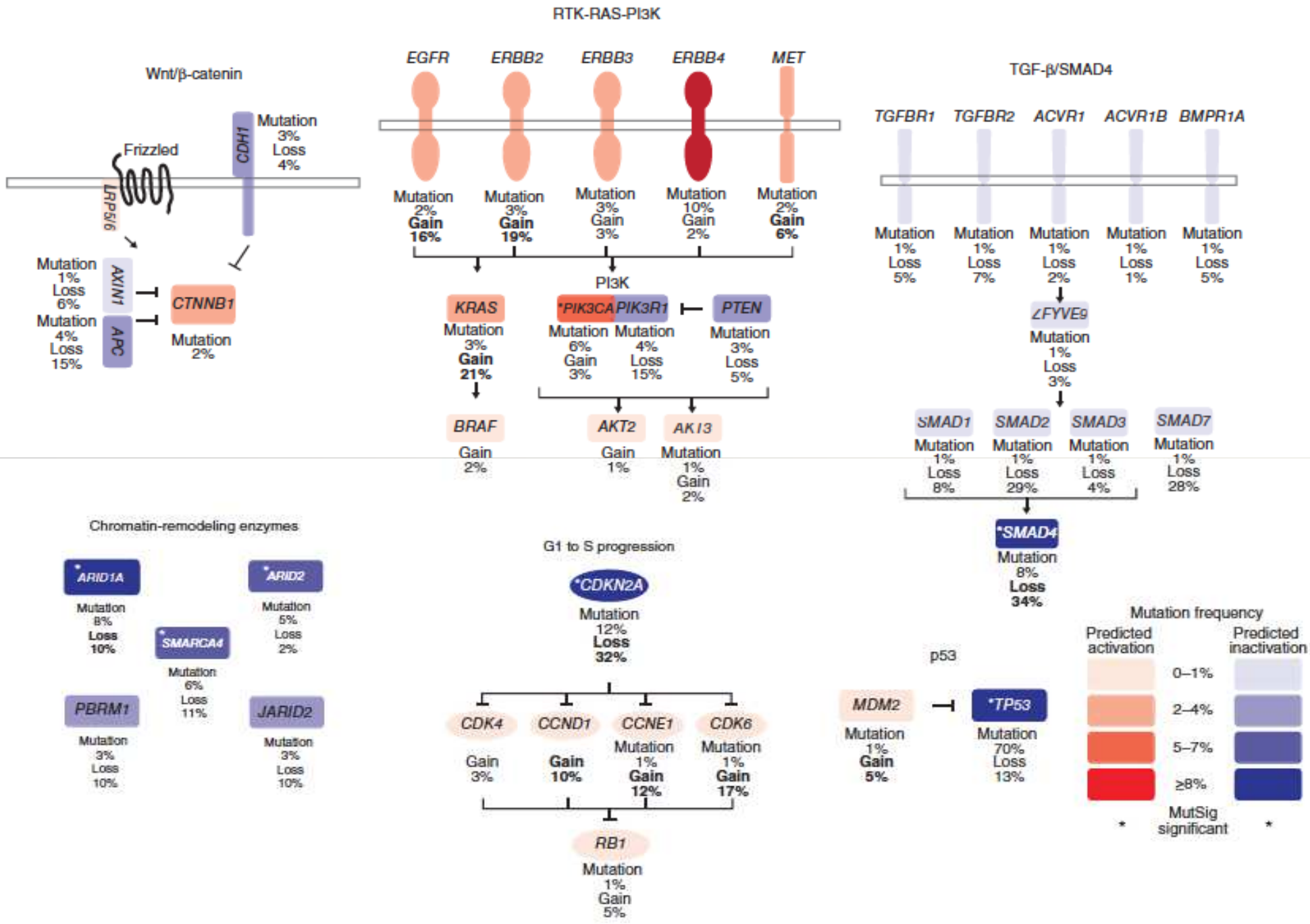


Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity

2015

Austin M Dulak[1,2,13], Petar Stojanov[1–3,13], Shouyong Peng[1,2], Michael S Lawrence[2], Cameron Fox[1], Chip Stewart[2], Santhoshi Bandla[4], Yu Imamura[1], Steven E Schumacher[1,2], Erica Shefler[2], Aaron McKenna[2], Scott L Carter[2], Kristian Cibulskis[2], Andrey Sivachenko[2], Gordon Saksena[2], Douglas Voet[2], Alex H Ramos[2], Daniel Auclair[2], Kristin Thompson[2], Carrie Sougnez[2], Robert C Onofrio[2], Candace Guiducci[2], Rameen Beroukhim[1,2,5,6], Zhongren Zhou[4], Lin Lin[7], Jules Lin[7], Rishindra Reddy[7], Andrew Chang[7], Rodney Landrenau[8], Arjun Pennathur[8], Shuji Ogino[1,6,9,10], James D Luketich[8], Todd R Golub[1,2,6,11], Stacey B Gabriel[2], Eric S Lander[2,3,6], David G Beer[7], Tony E Godfrey[4], Gad Getz[2,12,14] & Adam J Bass[1,2,5,6,14]




Wnt/β-catenin
Frizzled
LRP5/6
CDH1
Mutation 3% Loss 4%
AXIN1
Mutation 1% Loss 6%
APC
Mutation 4% Loss 15%
CTNNB1
Mutation 2%
RTK-RAS-PI3K
EGFR
ERBB2
ERBB3
ERBB4
MET
Mutation 2% Gain 16%
Mutation 3% Gain 19%
Mutation 3% Gain 3%
Mutation 10% Gain 2%
Mutation 2% Gain 6%
PI3K
KRAS
Mutation 3% Gain 21%
BRAF
Gain 2%
*PIK3CA
PIK3R1
Mutation 6% Gain 3%
Mutation 4% Loss 15%
PTEN
Mutation 3% Loss 5%
AKT2
Gain 1%
AKT3
Mutation 1% Gain 2%
TGF-β/SMAD4
TGFBR1
TGFBR2
ACVR1
ACVR1B
BMPR1A
Mutation 1% Loss 5%
Mutation 1% Loss 7%
Mutation 1% Loss 2%
Mutation 1% Loss 1%
Mutation 1% Loss 5%
ZFYVE9
Mutation 1% Loss 3%
SMAD1
Mutation 1% Loss 8%
SMAD2
Mutation 1% Loss 29%
SMAD3
Mutation 1% Loss 4%
SMAD7
Mutation 1% Loss 28%
*SMAD4
Mutation 8% Loss 34%
Chromatin-remodeling enzymes
*ARID1A
Mutation 8% Loss 10%
*ARID2
Mutation 5% Loss 2%
*SMARCA4
Mutation 6% Loss 11%
PBRM1
Mutation 3% Loss 10%
JARID2
Mutation 3% Loss 10%
G1 to S progression
*CDKN2A
Mutation 12% Loss 32%
CDK4
Gain 3%
CCND1
Gain 10%
CCNE1
Mutation 1% Gain 12%
CDK6
Mutation 1% Gain 17%
RB1
Mutation 1% Gain 5%
p53
MDM2
Mutation 1% Gain 5%
*TP53
Mutation 70% Loss 13%
Mutation frequency
Predicted activation
Predicted inactivation
0–1%
2–4%
5–7%
≥8%
MutSig significant
*
*

EGFR inhibition is ineffective in OAC

Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial

Tom Waddell, Ian Chau, David Cunningham, David Gonzalez, Alicia Frances Clare Okines, Andrew Wotherspoon, Claire Saffery, Gary Middleton, Jonathan Wadsley, David Ferry, Wasat Mansoor, Tom Crosby, Fareeda Coxon, David Smith, Justin Waters, Timothy Iveson, Stephen Falk, Sarah Slater, Clare Peckitt, Yolanda Barbachano

Summary

Background EGFR overexpression occurs in 27–55% of oesophagogastric adenocarcinomas, and correlates with poor prognosis. We aimed to assess addition of the anti-EGFR antibody panitumumab to epirubicin, oxaliplatin, and capecitabine (EOC) in patients with advanced oesophagogastric adenocarcinoma.

Methods In this randomised, open-label phase 3 trial (REAL3), we enrolled patients with untreated, metastatic, or locally advanced oesophagogastric adenocarcinoma at 63 centres (tertiary referral centres, teaching hospitals, and district general hospitals) in the UK. Eligible patients were randomly allocated (1:1) to receive up to eight 21-day cycles of open-label EOC (epirubicin 50 mg/m² and oxaliplatin 130 mg/m² on day 1 and capecitabine 1250 mg/m² per day on days 1–21) or modified-dose EOC plus panitumumab (mEOC+P; epirubicin 50 mg/m² and oxaliplatin 100 mg/m² on day 1, capecitabine 1000 mg/m² per day on days 1–21, and panitumumab 9 mg/kg on day 1). Randomisation was blocked and stratified for centre region, extent of disease, and performance status. The primary endpoint was overall survival in the intention-to-treat population. We assessed safety in all patients who received at least one dose of study drug. After a preplanned independent data monitoring committee review in October, 2011, trial recruitment was halted and panitumumab withdrawn. Data for patients on treatment were censored at this timepoint. This study is registered with ClinicalTrials.gov, number NCT00824785.

Findings Between June 2, 2008, and Oct 17, 2011, we enrolled 553 eligible patients. Median overall survival in 275 patients allocated EOC was 11·3 months (95% CI 9·6–13·0) compared with 8·8 months (7·7–9·8) in 278 patients allocated mEOC+P (hazard ratio [HR] 1·37, 95% CI 1·07–1·76; p=0·013). mEOC+P was associated with increased incidence of grade 3–4 diarrhoea (48 [17%] of 276 patients allocated mEOC+P *vs* 29 [11%] of 266 patients allocated EOC), rash (29 [11%] *vs* two [1%]), mucositis (14 [5%] *vs* none), and hypomagnesaemia (13 [5%] *vs* none) but reduced incidence of haematological toxicity (grade ≥3 neutropenia 35 [13%] *vs* 74 [28%]).

Interpretation Addition of panitumumab to EOC chemotherapy does not increase overall survival and cannot be recommended for use in an unselected population with advanced oesophagogastric adenocarcinoma.

Lancet Oncol 2013; 14: 481–89

Published Online
April 15, 2013
http://dx.doi.org/10.1016/S1470-2045(13)70096-2

This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on May 28, 2013

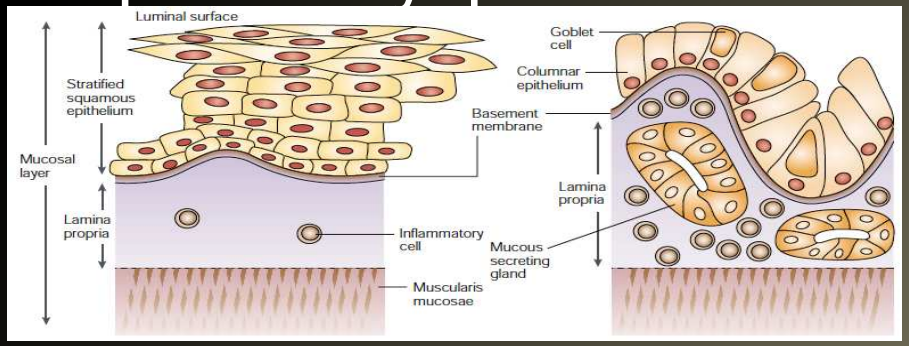
See Comment page 440

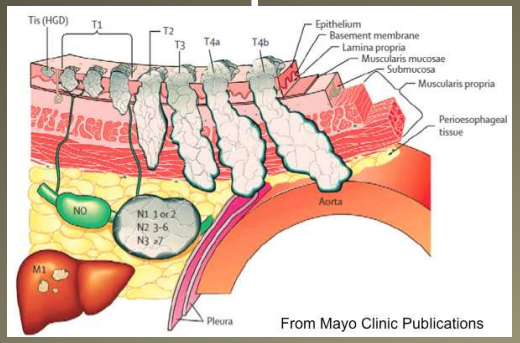
The Royal Marsden NHS Foundation Trust, London and Surrey, UK (T Waddell MBBCh, I Chau MD, Prof D Cunningham MD, D Gonzalez PhD, A F C Okines MBBCh, A Wotherspoon MBBCh, C Saffery, C Peckitt MSc, Y Barbachano PhD); Royal Surrey County Hospital, Guildford, UK (G Middleton MD); Weston Park Hospital, Sheffield, UK (J Wadsley MBBCh); Russells Hall Hospital, Dudley, UK (Prof D Ferry PhD); Christie Hospitals NHS Foundation Trust, Manchester, UK (W Mansoor PhD); Velindre Cancer Centre, Cardiff, UK

NGS tools have not identified a druggable target in OAC

Proteomic approaches to define key features of the Oesophageal Adenocarcinoma Progression Sequence

Metaplasia-Dysplasia-Adenocarcinoma Sequence





Normal ⇄ metaplasia/dysplasia → OAC

676 | SEPTEMBER 2003 | VOLUME 3 www.nature.com/reviews/cancer

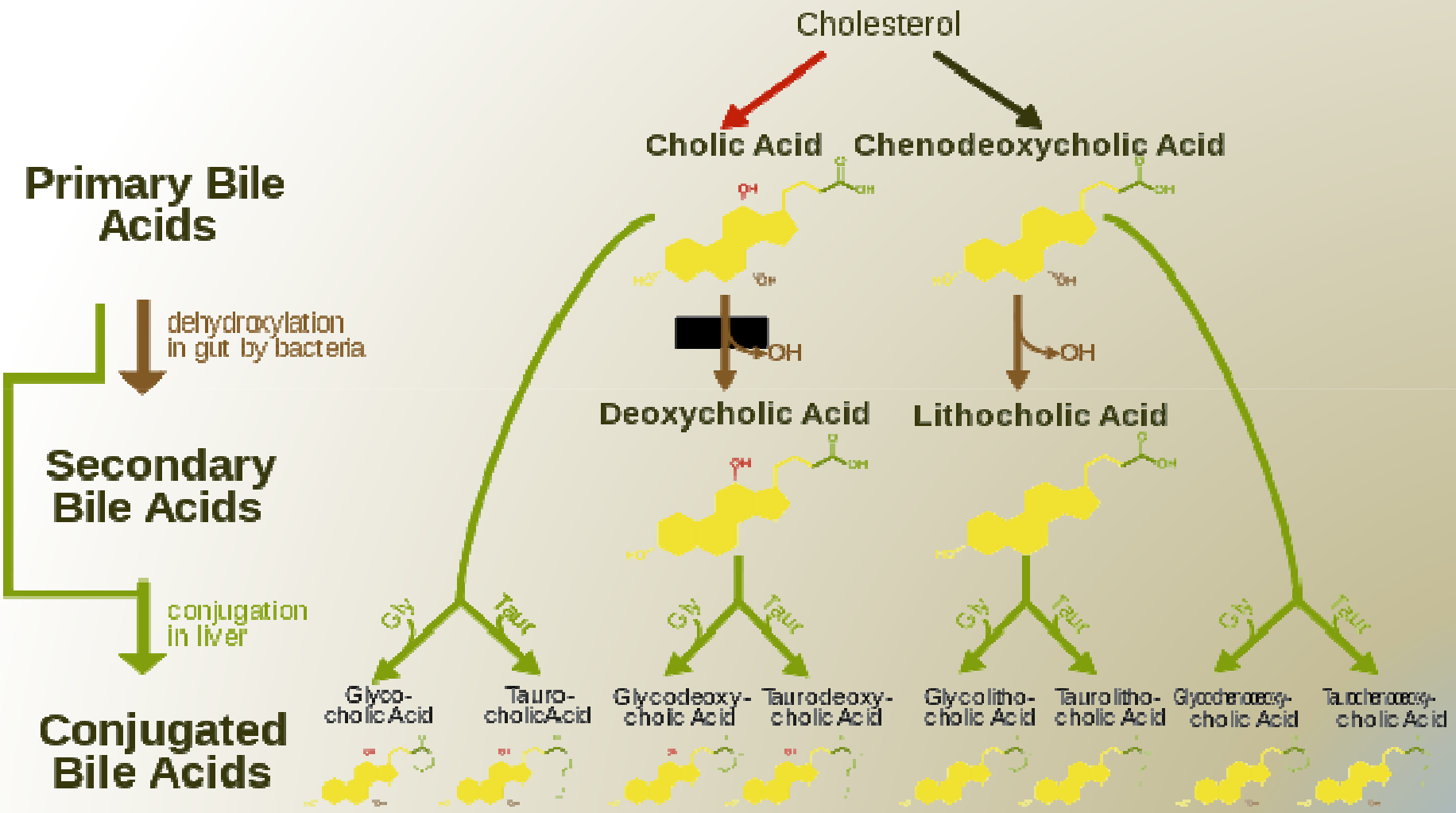
Progression mechanisms

- Identify gene products implicated in bile acid reflux responses in normal tissue and Barretts epithelial cells

Effective Treatments

- Identify & validate oncogenic pathways as potential therapeutic targets OAC

Production of steroids implicated in OAC progression



From Darragh et al.,

Bile signatures in >300 patients

A

Bile Acid	Rt (Min)	RRt	Std ratio
Cholesterol	4.31	0.40	1.69
Lithocholic	5.55	0.52	1.65
Deoxycholic	6.35	0.59	1.11
Chenodeoxycholic	7.19	0.67	1.15
Ursodeoxycholic	7.84	0.73	1.63
Cholic	8.89	0.83	1.16
7-Ketolithocholate	10.74	1.00	1.00

B

Bile Acid	Range uM (cong)	Mean uM (cong)	Range uM (uncong)	Mean uM (uncong)
CA	1-2447	118	1-211	5
CDCA	1-3655	112	1-121	3
DCA	1-1592	63	1-115	3
LCA	1-515	17	1-82	2
UDCA	1-860	13	1-720	5
Total	1-6386	323	1-978	18

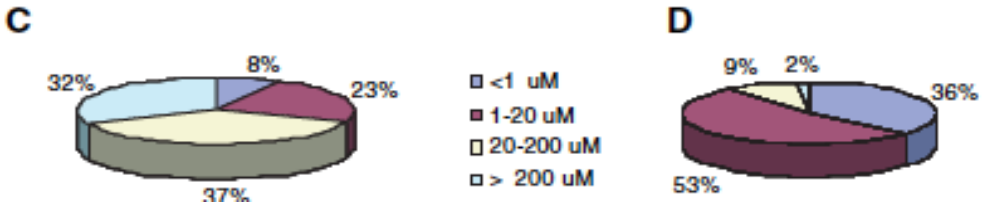
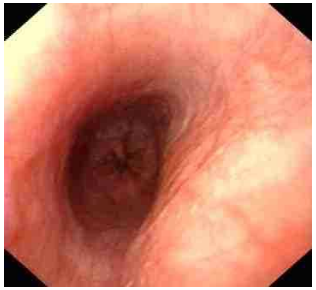


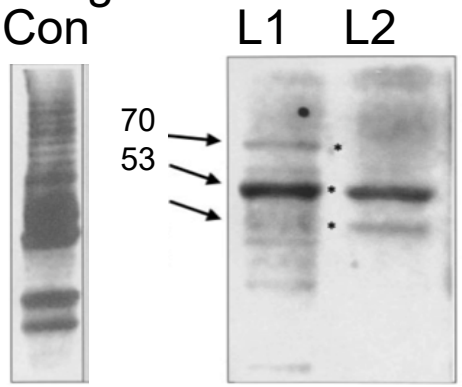
Fig. 2. Concentration of naturally occurring bile acids. (A) Data from a representative chromatogram indicating the retention times of each bile acid. Peaks: 1, cholesterol; 2, LCA; 3, DCA; 4, CDCA; 5, UDCA; 6, CA; 7, 7-ketolithocholic acid (internal standard). The retention (R_t) times and relative retention times (RR_t) of the bile acid standards are shown and were used as a standard to quantify the bile acids from patients. Standard ratios represent the peak area of each 1 mg·mL^{-1} standard compared with the peak area of the internal standard. (B) Summary of the range of the total bile acid concentrations found in gastric fluid samples. (C) Percentage of patients with bile acid concentrations as indicated. (D) Percentage of patients with unconjugated bile acids concentrations as indicated. (E) Ratio of bile

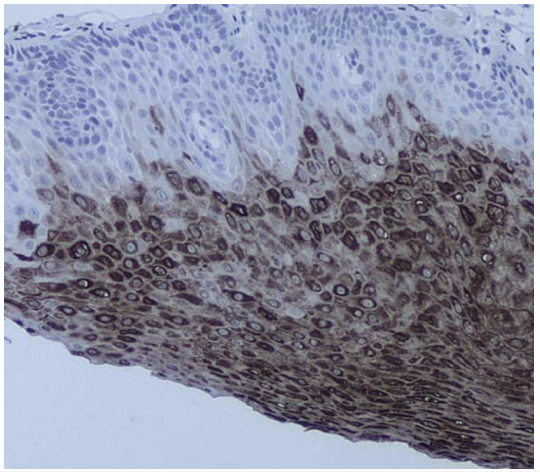
Novel stress genes are expressed in normal oesophageal squamous tissue that protect from bile acid steroid-induced death

ex-vivo exposure in organ culture

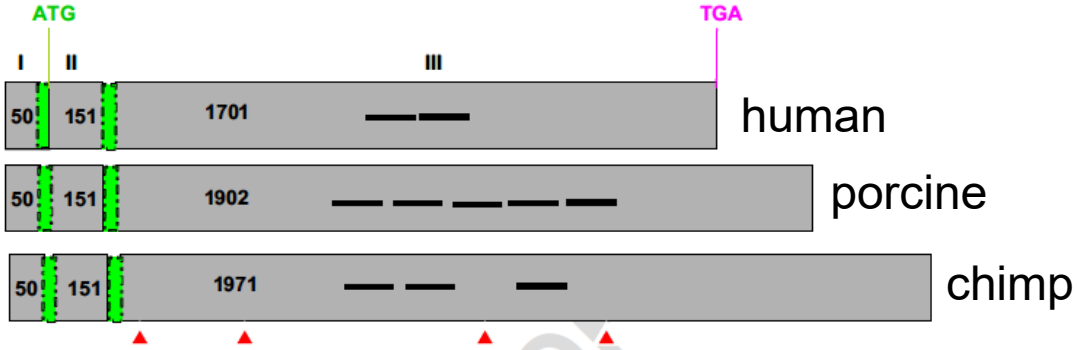


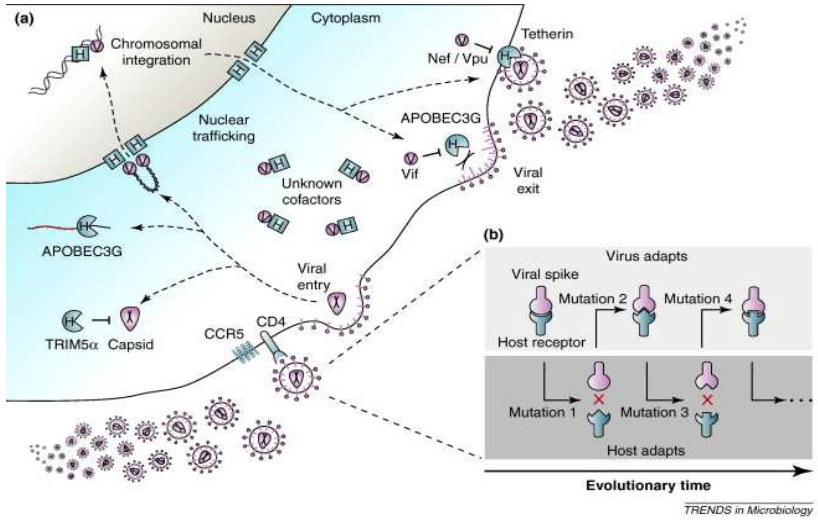
Normal



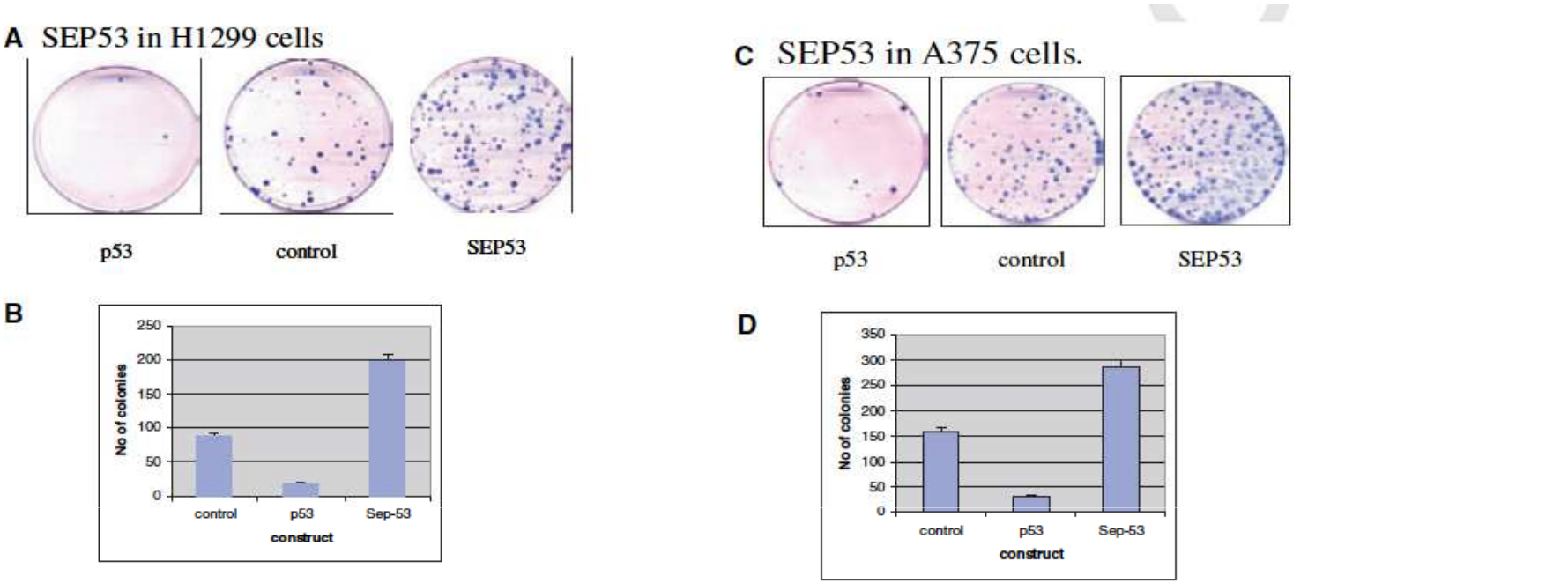


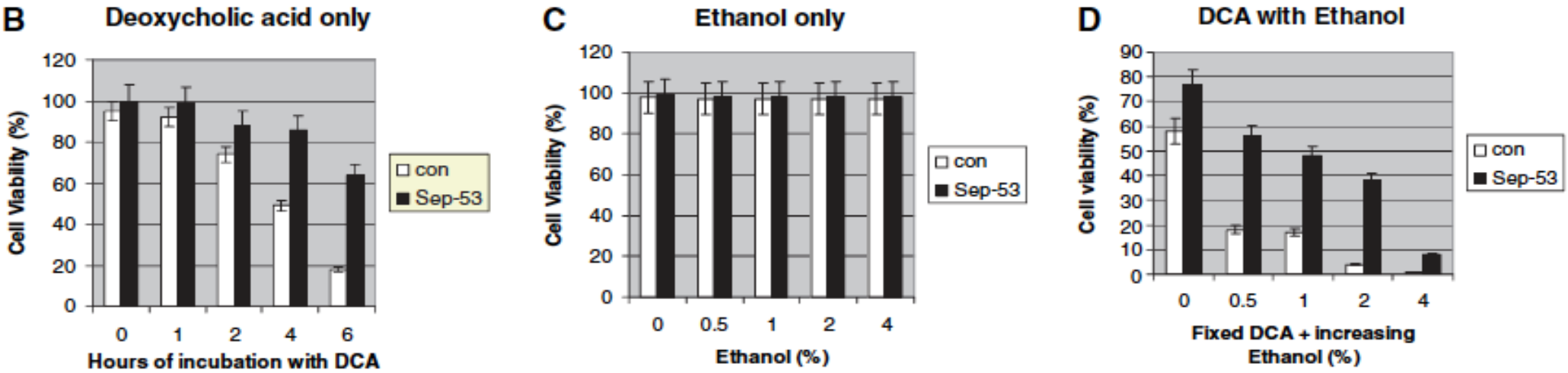
SEP53 is one of the most rapidly evolving genes in mammals with a Ka/Ks ratio of 4.1





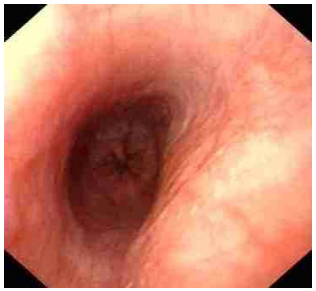
The sep53 gene can reduce bile acid induced cell death

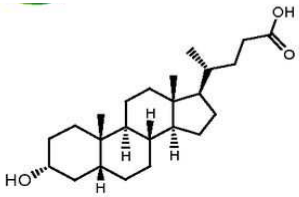


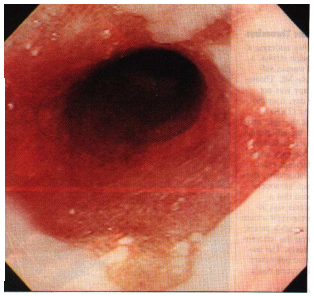


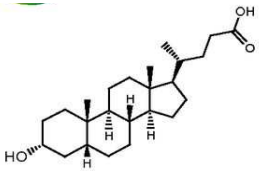
Bile steroids are risk factors for carcinogenesis and the OAC-bile network
Forms a system to understand how stress responses effect cancer development

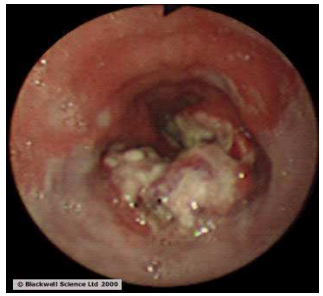
Metaplasia-Dysplasia-Adenocarcinoma Sequence









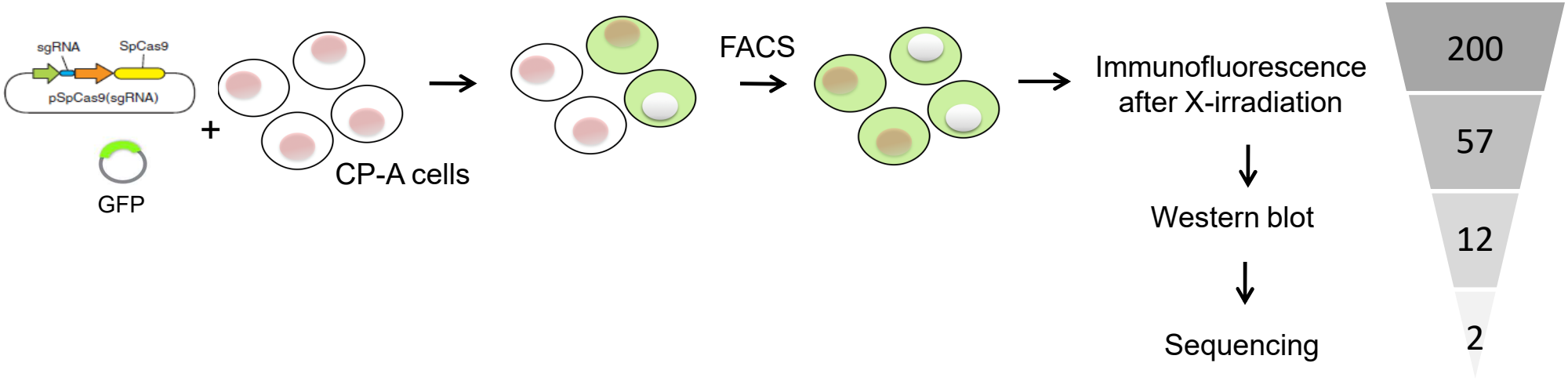


Normal metaplasia/dysplasia Cancer

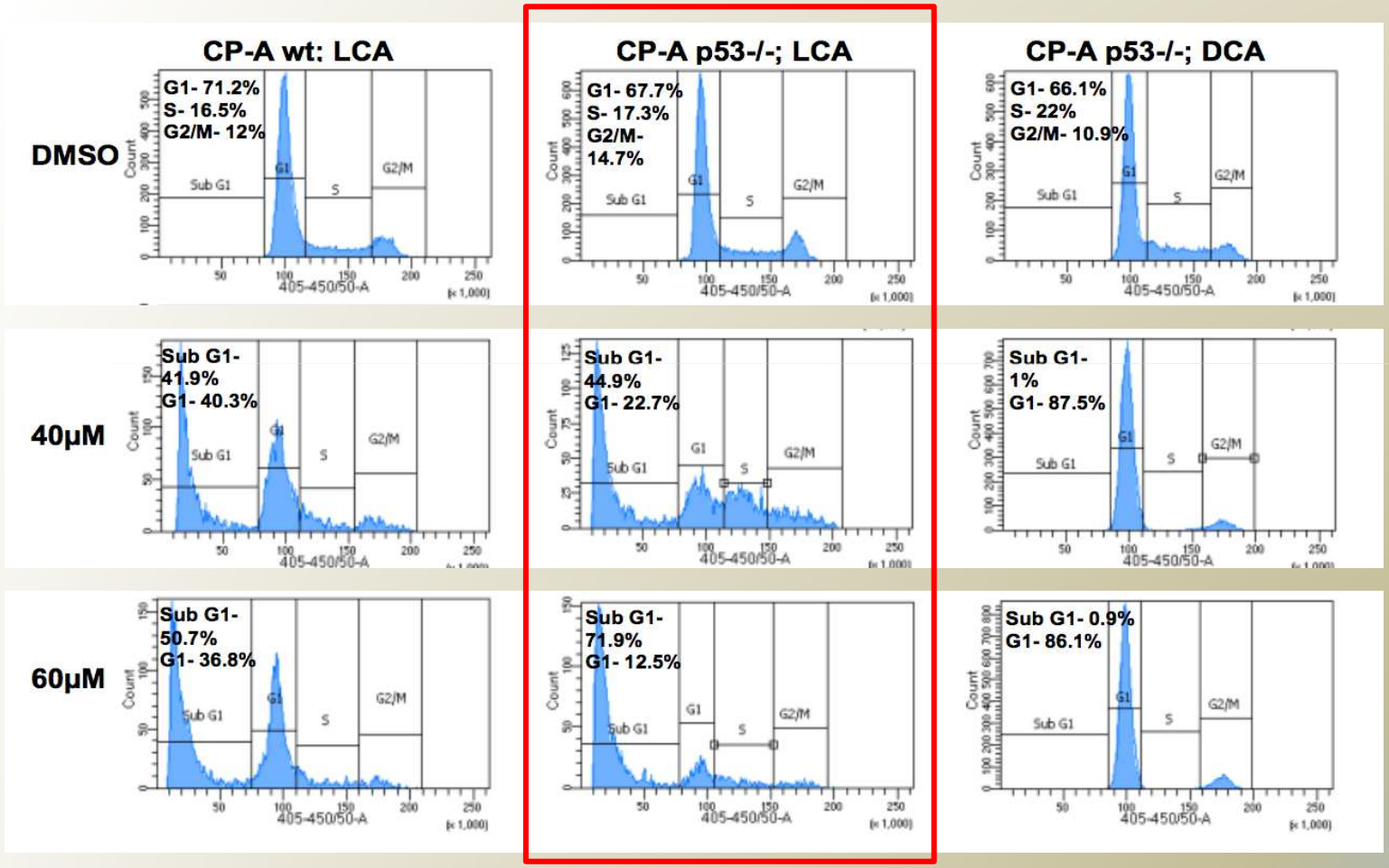
1. An novel “stress” response system exists in squamous cells.

2. What pathways might be bile acid responses in Barrett’s?

Development of isogenic P53 null Barrett's cell lines using CRISPR/Cas gene editing

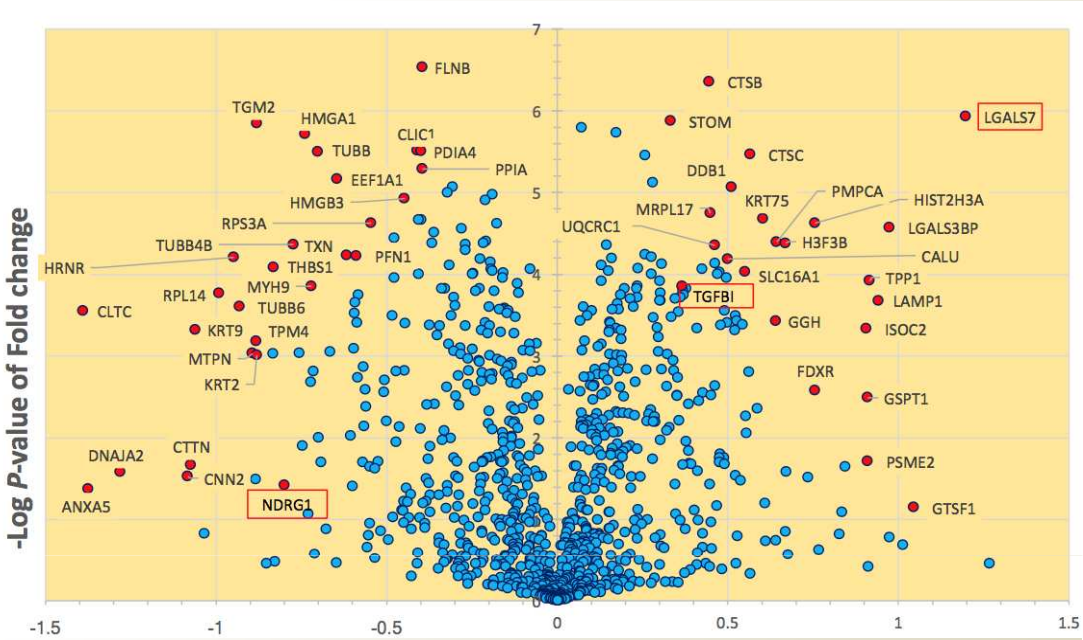


Effect of bile acids on P53 dependent cell cycle checkpoints



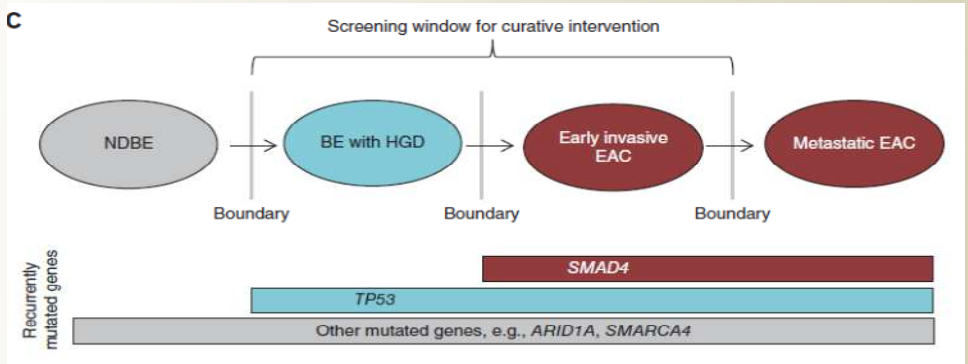
Summary: P53 loss sensitizes to LCA-induced cell death

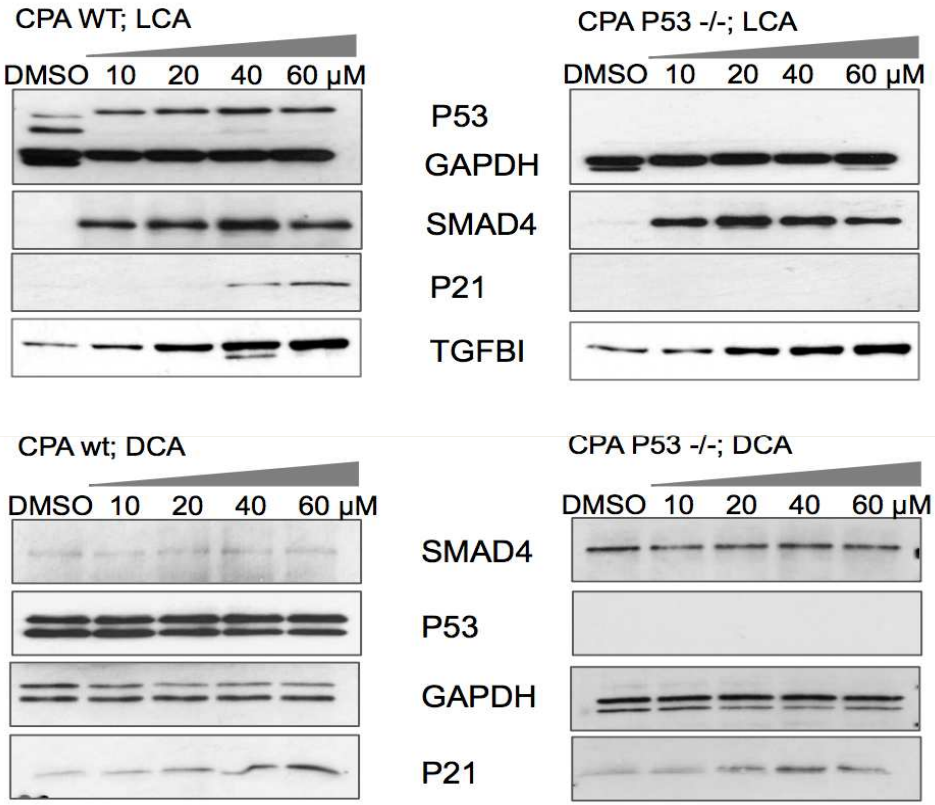
Proteomics screens identify SMAD4 as a target



Ordering of mutations in preinvasive disease stages of esophageal carcinogenesis

NATURE GENETICS VOLUME 46 | NUMBER 8 | AUGUST 2014

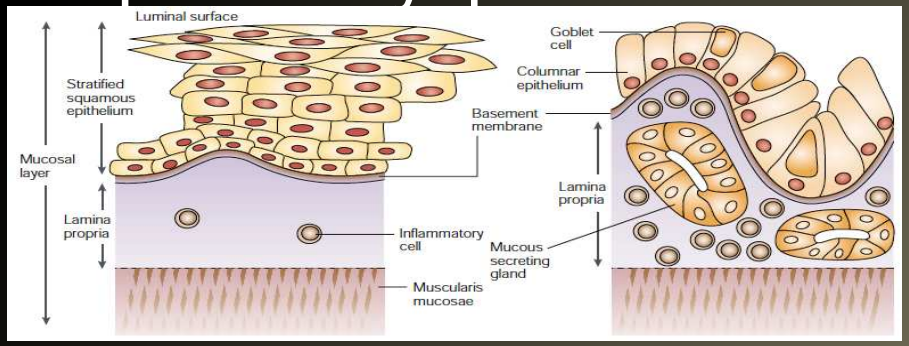


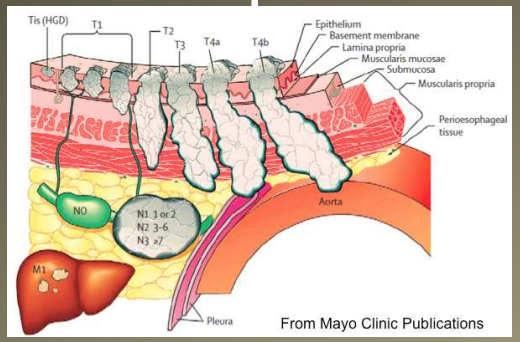


Summary:
LCA induces SAMD4
LCA induces p53

Proteomic approaches to define key features of the Oesophageal Adenocarcinoma Progression Sequence

Metaplasia-Dysplasia-Adenocarcinoma Sequence





Normal ⇄ metaplasia/dysplasia → OAC

676 | SEPTEMBER 2003 | VOLUME 3 www.nature.com/reviews/cancer

Progression mechanisms

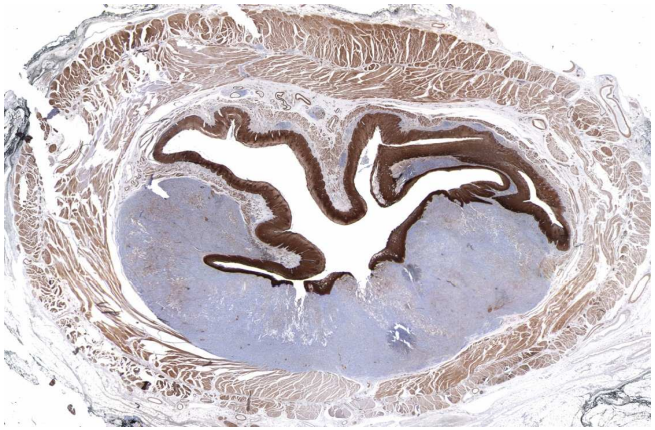
- Identify gene products implicated in bile acid reflux responses in normal tissue and Barretts epithelial cells

Effective Treatments

- Identify & validate oncogenic pathways as potential therapeutic targets OAC

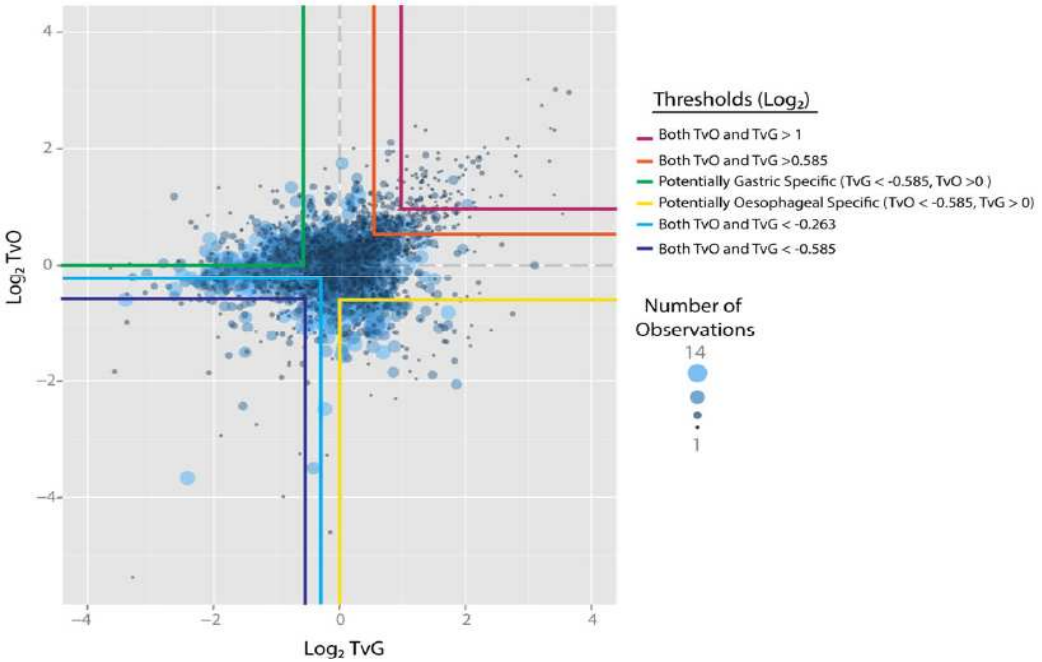
Strategy for Target Discovery in OAC

OAC biopsy section for proteomic analysis



Compared to adjacent normal oesophageal and gastric tissue biopsies

Bioinformatics

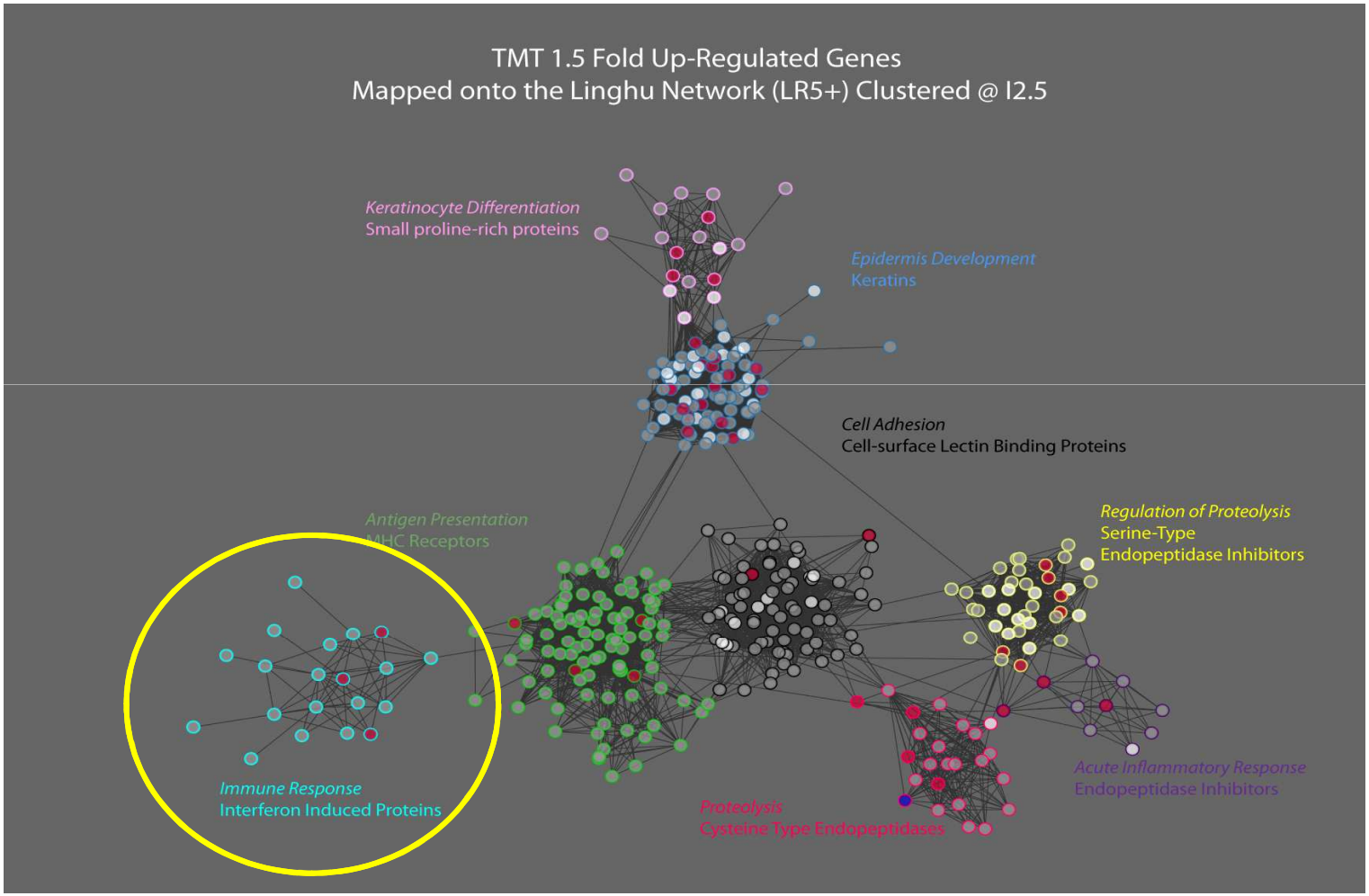


Strategy for Target Discovery in OAC

Pt	Exp	Sex	Age	Loc	NA Rx	Diff	LVI	VnI	NI	R	T	No. +ve Node	Total Nodes	ICGC	Surv (All)	Surv (DSS)
15	Tmt	M	61	I	1xCF	Poor	Y	Y	Y	1	T3	17	29	X	20	20
17	Tmt	M	63	I	2xCF	Poor	Y	Y	Y	1	T3	0	19	x	18	18
23	P	M	57	I	2xCF	Mod	Y	Y	N	0	T2	0	43	12	18.9	18.9
26	P	M	53	I	2xCF	Poor	N	N	Y	1	T3	2	14	14	4.4	4.4
27	P	M	60	OLT	2xCF	Poor	Y	N	N	1	T3	7	20	15	17.9	17.9
32	P	M	57	I	2xCF	Poor	Y	Y	Y	1	T3	7	19	No	19.5	18
45	P	M	78	I	Nil	Poor	Y	Y	Y	1	T3	6	16	7	9	8.9
44	Tmt	M	59	I	2xCF	Mod	Y	N	N	0	T2	2	27	6	12.2	12.2
46	Tmt	M	67	I	2xCF	Poor	Y	N	Y	1	T4a	8	18	8	12.7	12.7
48	*Tmt*	M	*65*	*II*	2xCF	*Poor*	*Y*	*N*	*Y*	*1*	*T3*	*16*	*28*	*8*	*10.2*	*10.2*
50	*Tmt*	M	*59*	*II*	2xCF	*Mod*	*Y*	*Y*	*Y*	*0*	*T3*	*0*	*39*	*11*	*11.5*	*11.5*
51	*Tmt*	M	*41*	*I*	2xCF	*Poor*	*Y*	*Y*	*Y*	*1*	*T3*	*7*	*28*	*16*	*7.3*	*7.3*
53	*Tmt*	*F*	*52*	*I*	2xCF	*Poor*	*N*	*N*	*N*	*0*	*T3*	*1*	*23*	*17*	*5.9*	*5.9*
60	*Tmt*	M	*60*	*OLT*	2xCF	*Poor*	*Y*	*Y*	*Y*	*0*	*T3*	*7*	*21*	*21*	*7.7*	*7.7*
61	*Tmt*	M	*58*	*I*	2xCF	*Poor*	*Y*	*N*	*Y*	*0*	*T3*	*3*	*27*	*No*	*5.5*	*5.5*

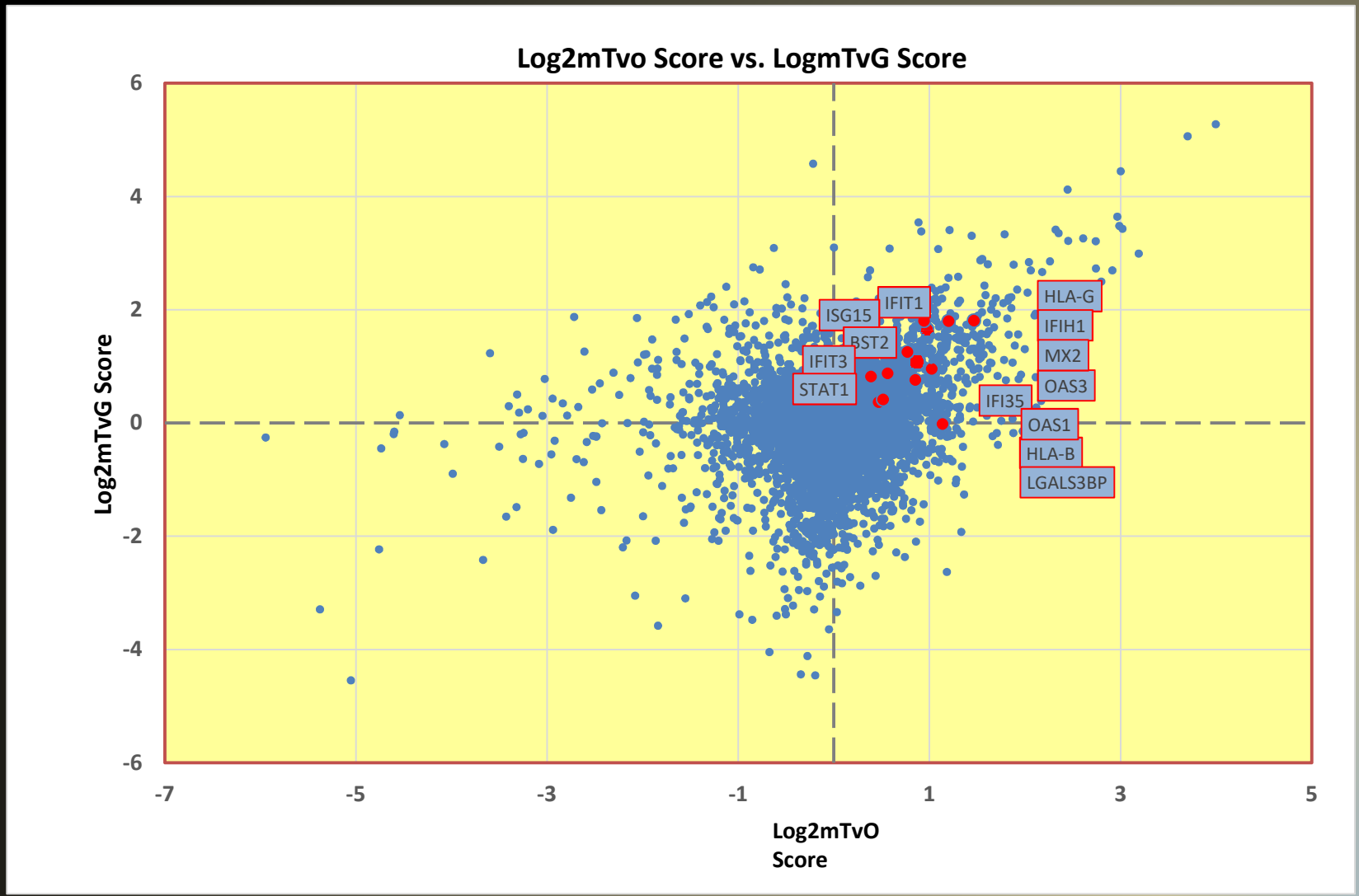
~ 3000 protein identified/patient; ~ 6000 protein total/~60 mutant proteins

Bioinformatics: Network Analysis of the expressed cancer genome

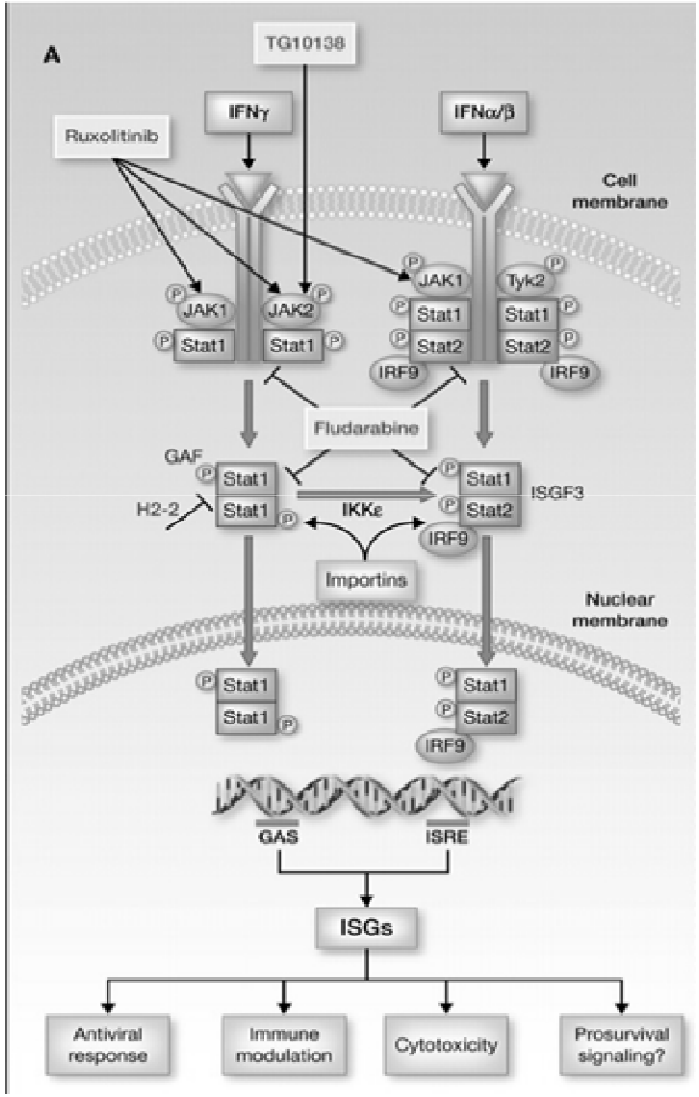


O'Neill et al; Molecular & Cellular Proteomics 2017 Jun;16(6):1138-1150

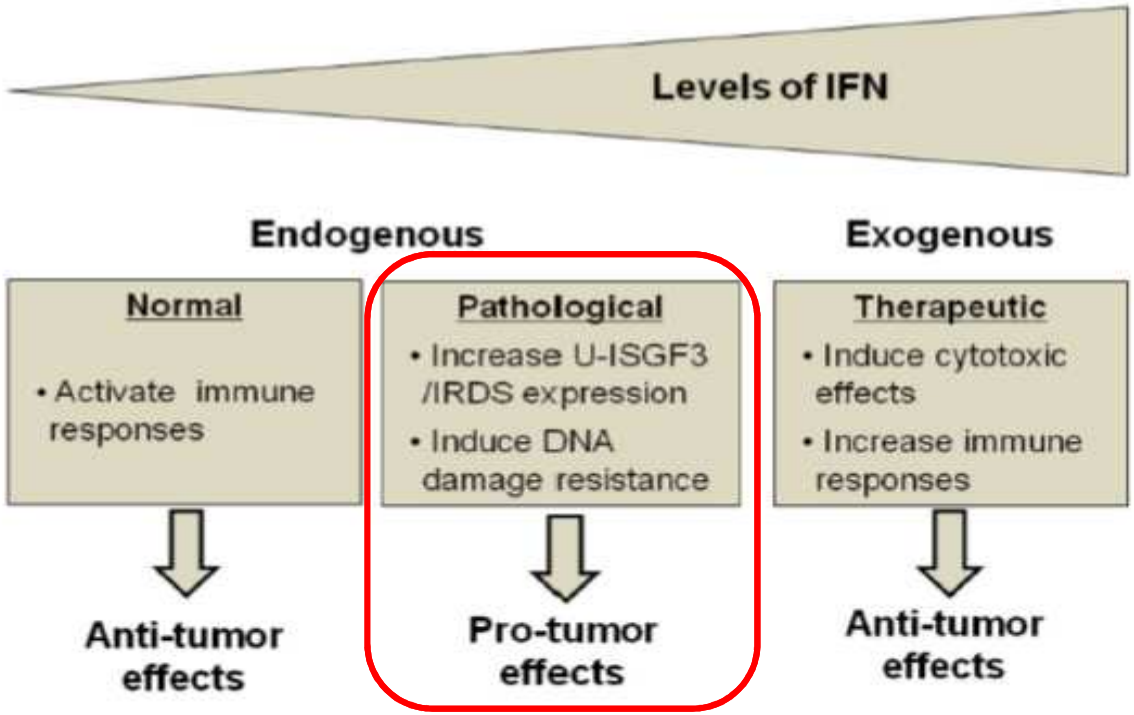
Bioinformatics: Identification of a subset of ISG proteins over-represented in OAC verse normal oesophagus and gastric tissue



Interferon-Stimulated Genes (ISG) Proteins as a therapeutic target)



Cheon H1 et al. EMBO J. 2013 Oct 16. IFNβ-dependent increases in STAT1, STAT2, and IRF9 mediate resistance to viruses and DNA damage.



Cheon et al. Semin Oncol. 2014

ISG protein subset: Interferon Related DNA-damage Resistance Signature (IRDS)

- The IFITM1 protein the only 'oncogenic' receptor in the IRDS pathway

Gene symbol	Alternative symbols	Entrez Gene Name	Association with radio/chemoresistence	Association with oncogenesis
BST2	tetherin	bone marrow stromal cell antigen 2	+	+
CCNA1		cyclin A1	+	+
CXCL1	GRO1; GROA; SCYB1	chemokine (C-X-C motif) ligand 1	+	+
CXCL10	IP10; SCYB10; INP10	chemokine (C-X-C motif) ligand 10	+	+
EIF2AK2	PRKR; PKR; p68 KINASE	eukaryotic translation initiation factor 2-alpha kinase 2 (PKR)	+	+
HERC6	FLJ206371	hect domain and RLD 6		+
HLA-B	SPDA1; MHC Class I HLA heavy chain	major histocompatibility complex, class I, B	+	
HLA-G	TCA; HLA-6.0; HLA60	major histocompatibility complex, class I, G	+	
IFI27	ISG12	interferon, alpha-inducible protein 27	+	+
IFI35	IFP35	interferon-induced protein 35	+	+
IFI44	p44	interferon-induced protein 44	+	+
IFI44L	C1orf29	interferon-induced protein 44-like	+	+
IFI6	G1P3	interferon, alpha-inducible protein 6	+	+
IFIH1	MDA5	interferon induced with helicase C domain 1		+
IFIT1	IFI56; G10P1; ISG56	interferon-induced protein with tetratricopeptide repeats 1	+	+
IFIT3	RIGG; IFI60	interferon-induced protein with tetratricopeptide repeats 3	+	+
IFITM1	IFI17; leu13; fragilis; 9-27	interferon induced transmembrane protein 1	+	+
IRF7	IRF7A	interferon regulatory factor 7	+	+
ISG15	G1P2; IFI15	ISG15 ubiquitin-like modifier	+	+
LAMP3	DCLAMP	lysosomal-associated membrane protein 3		
LGALS3BP	MAC2BP; L3 ANTIGEN	lectin, galactoside-binding, soluble, 3 binding protein		+
LY6E	RIGE; TSA1	lymphocyte antigen 6 complex, locus E		
MCL1	BCL2L3	myeloid cell leukemia sequence 1 (BCL2-related)	+	+
MX1	IFI78; MxA	myxovirus (influenza virus) resistance 1	+	+
MX2	MxB	myxovirus (influenza virus) resistance 2		
OAS1	OIAS	2',5'-oligoadenylate synthetase 1, 40/46kDa	+	+
OAS3	p100	2'-5'-oligoadenylate synthetase 3, 100kDa		
OASL	TRIP14; p59OASL	2'-5'-oligoadenylate synthetase-like		
PLSCR1	MMTRA1B	phospholipid scramblase 1		
STAT1	STAT91	signal transducer and activator of transcription 1, 91kDa	+	+
USP18	UBP43	ubiquitin specific peptidase 18	+	+

Current knowledge of IFITM1 function and regulation

IFITM1 is a tight junction protein that inhibits hepatitis C virus entry

Courtney Wilkins[1], Jessica Woodward[1], Daryl T-Y Lau[2], Amy Barnes[3], Michael Joyce[4], Nicola McFarlane[4], Jane McKeating[3], D. Lorne Tyrrell[4], and Michael Gale Jr.[1]

The C-Terminal Sequence of IFITM1 Regulates Its Anti-HIV-1 Activity

Rui Jia[1,2☯¤], Shilei Ding[2,3☯], Qinghua Pan[2], Shan-Lu Liu[4], Wentao Qiao[1], Chen Liang[2,3]*

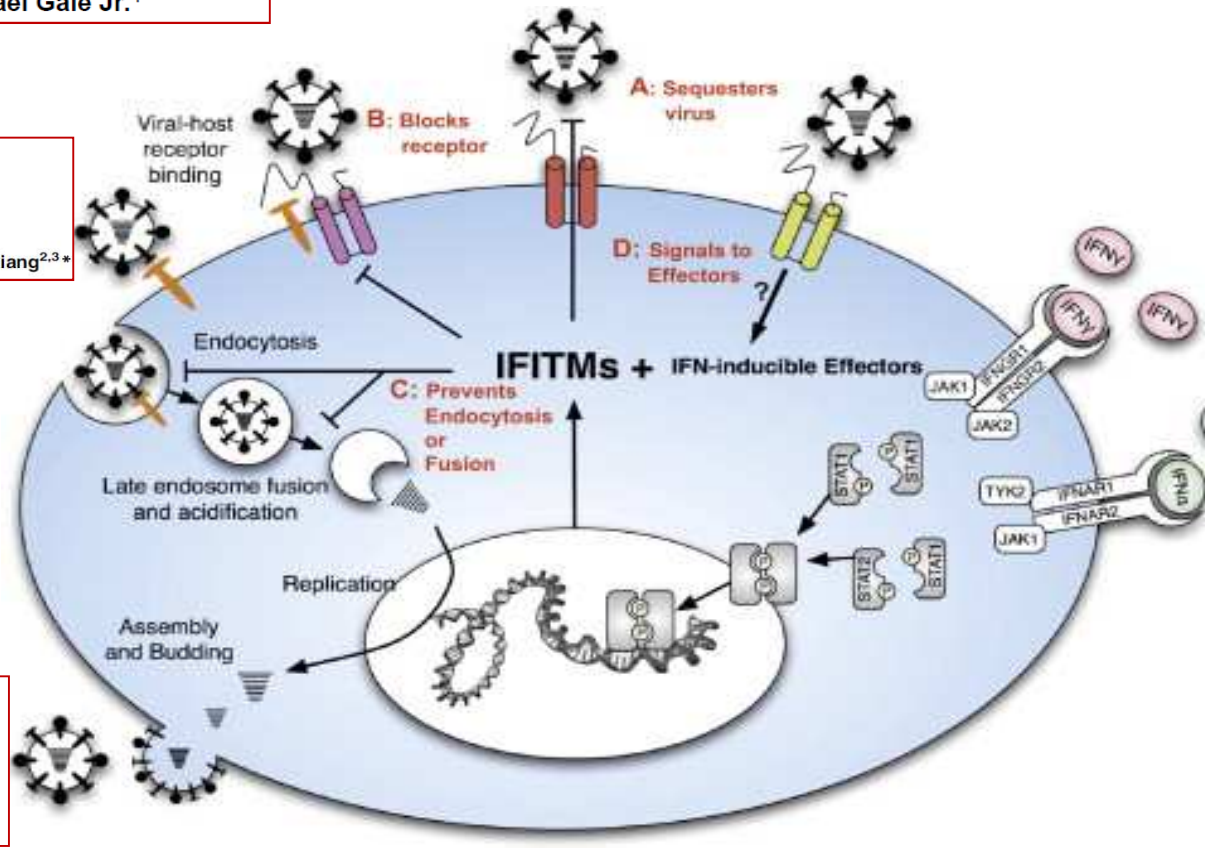
The IFITM Proteins Mediate Cellular Resistance to Influenza A H1N1 Virus, West Nile Virus, and Dengue Virus

Abraham L. Brass,[1,2,4,9,*] I-Chueh Huang,[5,9] Yair Benita,[3,10] Sinu P. John,[1,10] Manoj N. Krishnan,[6] Eric M. Feeley,[1] Bethany J. Ryan,[1] Jessica L. Weyer,[5] Louise van der Weyden,[8] Erol Fikrig,[6,7] David J. Adams,[8] Ramnik J. Xavier,[2,3] Michael Farzan,[5,*] and Stephen J. Elledge[4,*]

Distinct Patterns of IFITM-Mediated Restriction of Filoviruses, SARS Coronavirus, and Influenza A Virus

I-Chueh Huang[1*], Charles C. Bailey[1], Jessica L. Weyer[1], Sheli R. Radoshitzky[2], Michelle M. Becker[3], Jessica J. Chiang[1], Abraham L. Brass[4], Asim A. Ahmed[5], Xiaoli Chi[2], Lian Dong[2], Lindsay E. Longobardi[2], Dutch Boltz[2], Jens H. Kuhn[6,7], Stephen J. Elledge[8], Sina Bavari[2], Mark R. Denison[3], Hyeryun Choe[5], Michael Farzan[1*]

Viral Infection



Abraham L. Brass et al. Cell. 2009 December 24; 139(7): 1243–1254. IFITM Proteins Mediate the Innate Immune Response to Influenza A H1N1 Virus, West Nile Virus and Dengue Virus

Current knowledge of IFITM1 function and regulation

Expression of IFITM1 as a prognostic biomarker in resected gastric and esophageal adenocarcinoma

David Borg*, Charlotta Hedner, Alexander Gaber, Björn Nodin, Richard Fristedt, Karin Jirström, Jakob Eberhard and Anders Johnsson

Cancer

IFITM1 promotes the metastasis of human colorectal cancer via CAV-1

Fang Yu [a], Dan Xie [b], Samuel S. Ng [c], Ching Tung Lum [c], Mu-Yan Cai [d], William K. Cheung [c], Hsiang-Fu Kung [e,f], Guimiao Lin [g], Xiaomei Wang [g], Marie C. Lin [g,*]

Prognostic significance of INF-induced transmembrane protein 1 in colorectal cancer

Jingdong He[1], Jin Li[1], Wanting Feng[1], Longbang Chen[2], Kangqun Yang[3]

J Neurooncol (2011) 103:187–195
DOI 10.1007/s11060-010-0377-4

LABORATORY INVESTIGATION - HUMAN/ANIMAL TISSUE

Knockdown of interferon-induced transmembrane protein 1 (IFITM1) inhibits proliferation, migration, and invasion of glioma cells

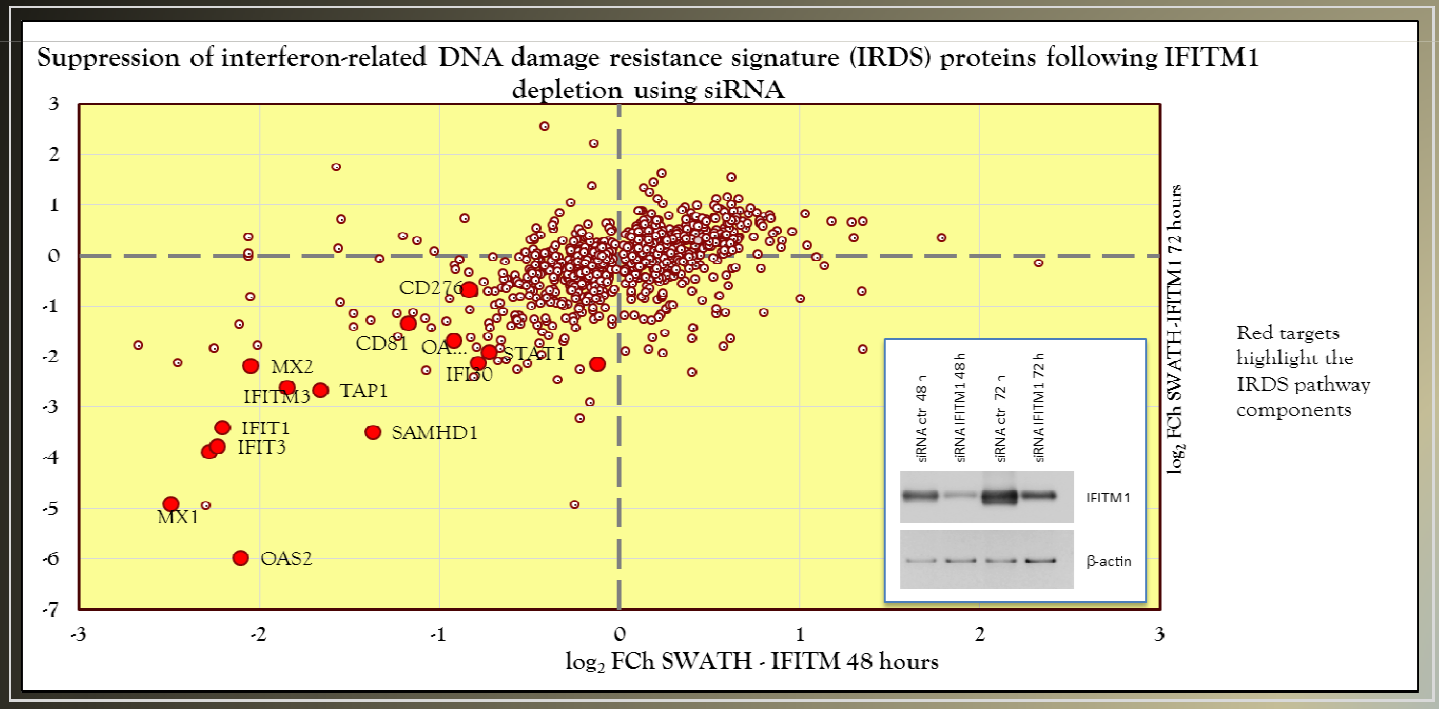
Reduction of IFITM1 reduces components of the IFN and IRDS system

What pathways are being driven by IFITM1?

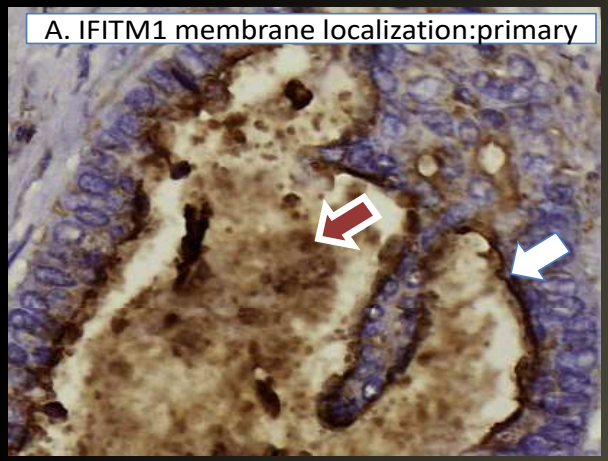
Deplete using siRNA in IFITM1-positive cell lines

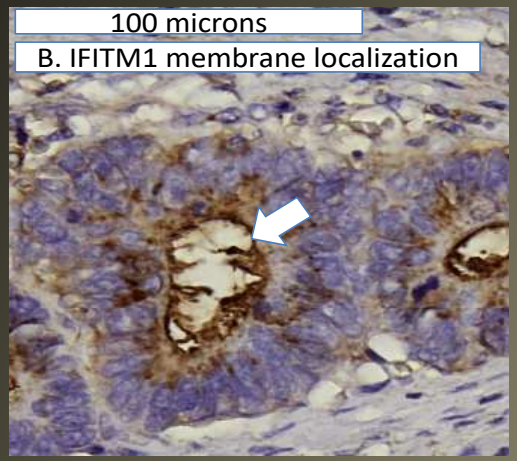
Process cell pellets for differential protein determination using SWATH-MS

Define pathway clusters using bioinformatics

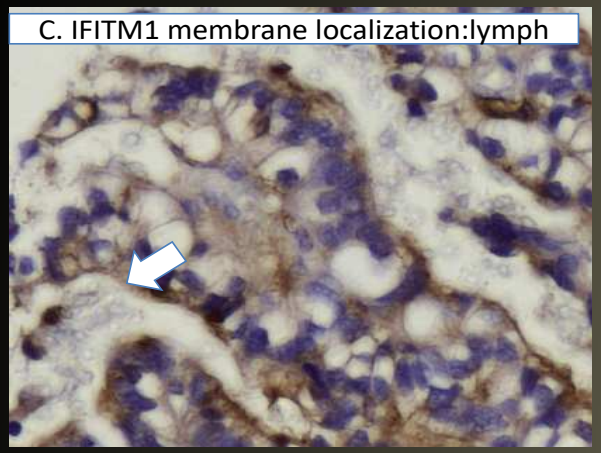


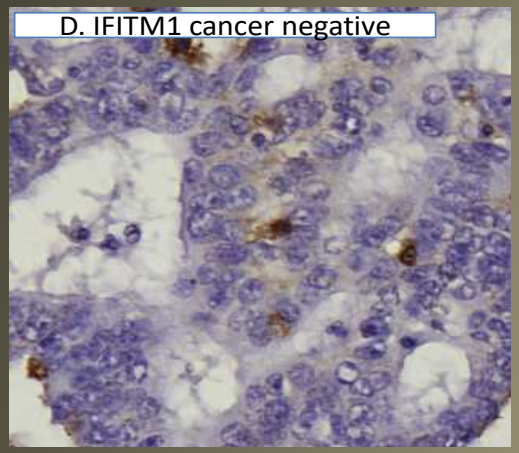
Potential Targets in the IRDS/ ISG pathway
IFITM1 (Interferon Inducible Transmembrane Protein-1) expression in OAC





In a TMA of 115 OAC patient samples, approximately 60% of patients express IFITM1 with 30% showing strong membrane staining





Metastatic lymph node show positivity

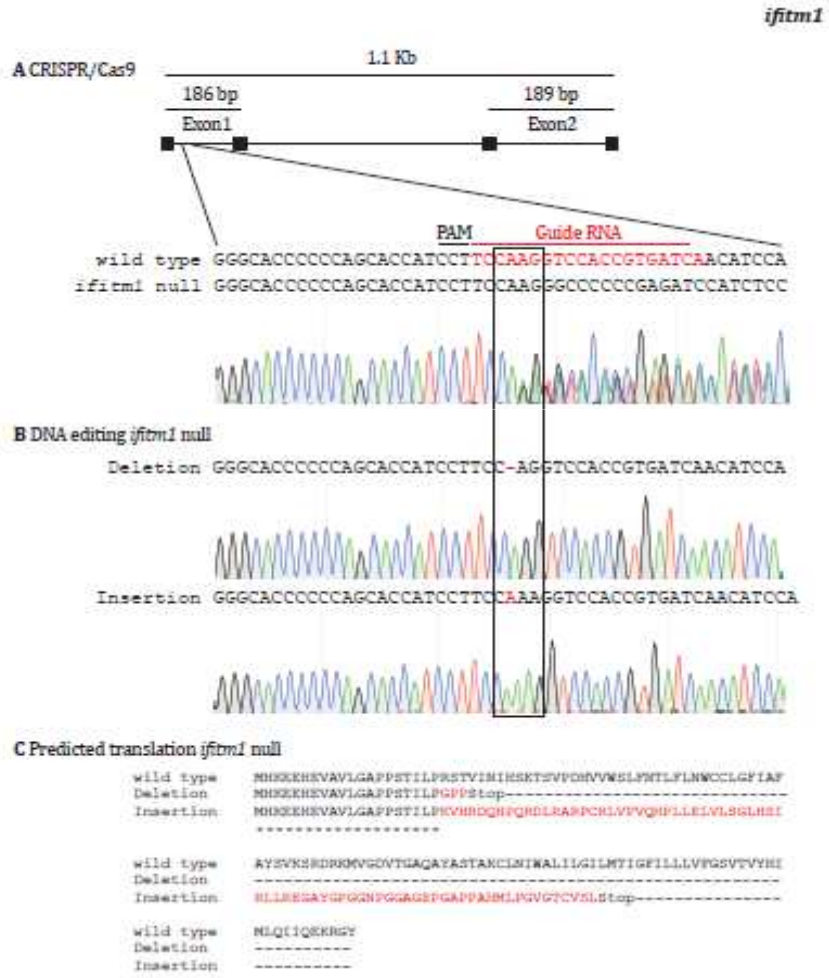
The IRDS in OAC:
Interferon Interferon-induced transmembrane protein 1 (IFITM1)

- What are the IFITM1 driven signalling pathways that might be important for oncogenic functions?

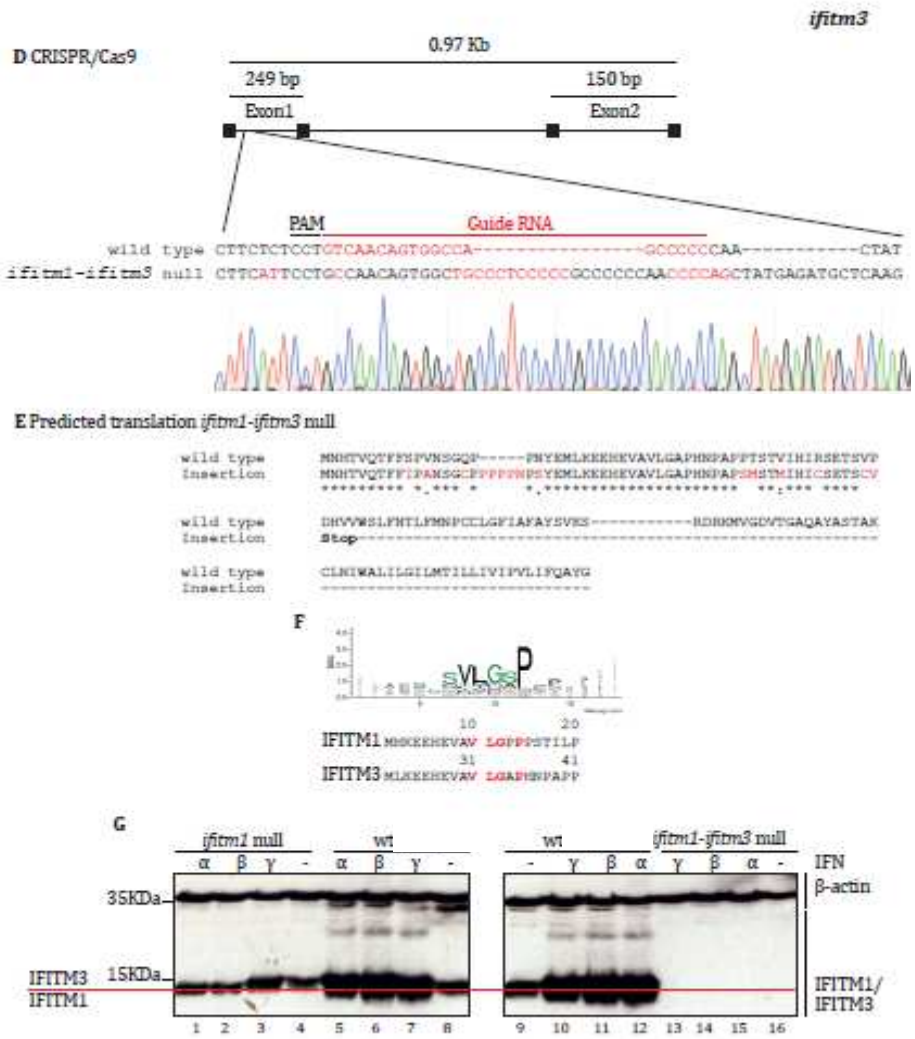
- Is IFITM1 a key upstream signalling receptor in the IRDS pathway in human cancers?

Production of an *ifitm1-ifitm3* double null cell line model

ifitm1 null

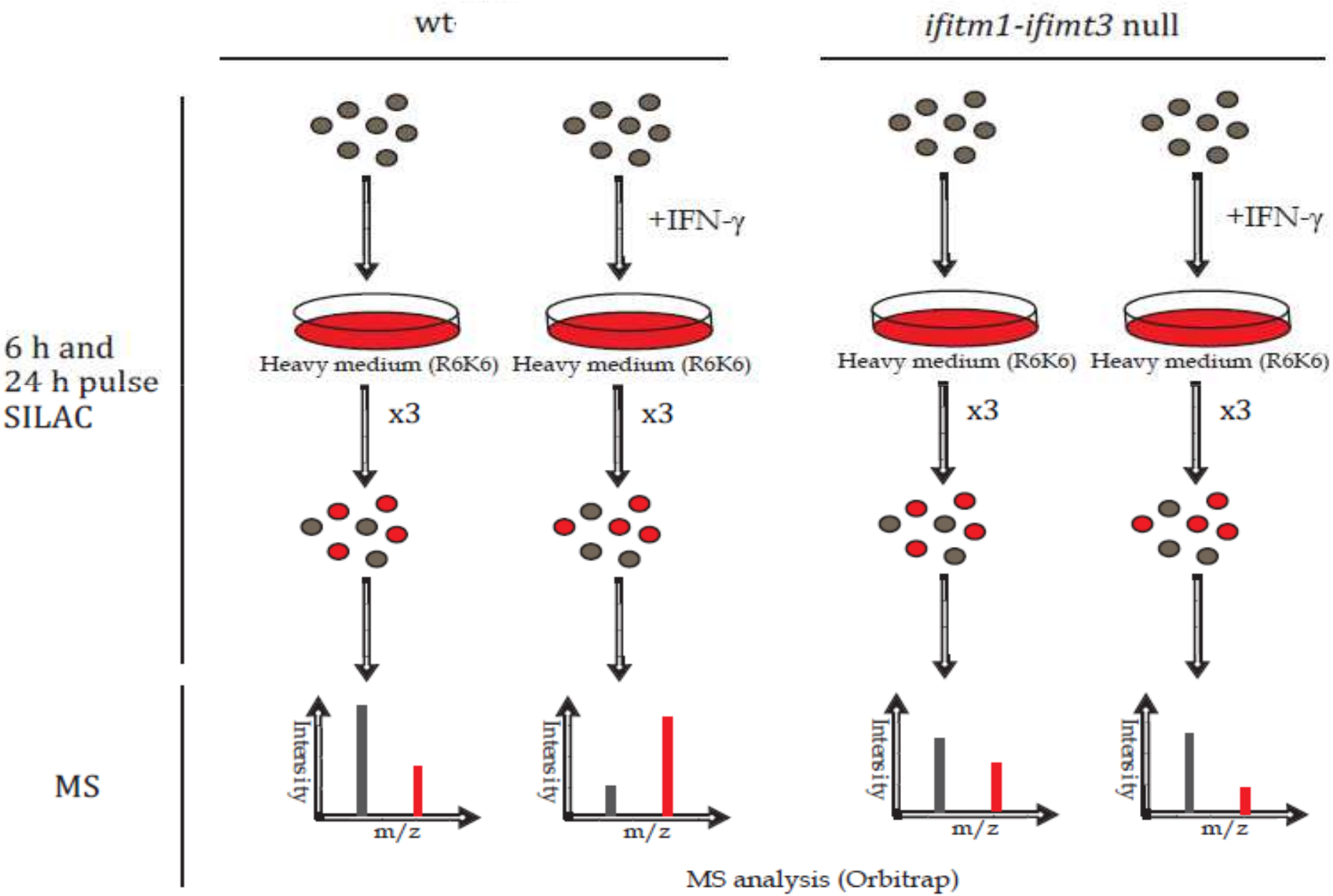


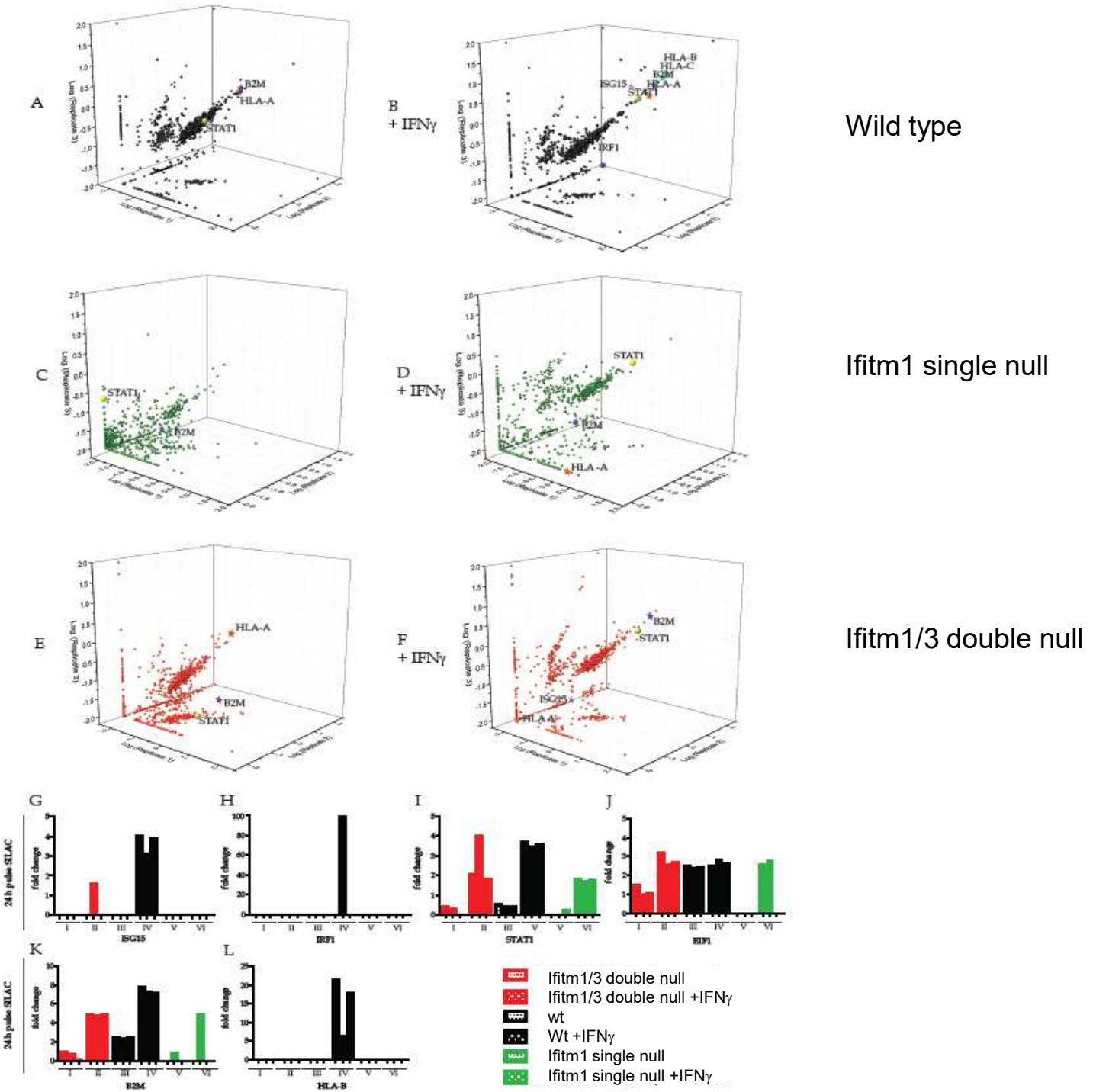
ifitm1-ifitm3 double null



Isogenic cell models for a control to measuring IFITM1-dependencies in cells

Pulse SILAC; can we identify dominant proteins whose synthesis is attenuated after IFN treatment in *ifitm1-ifitm3* double null cells?





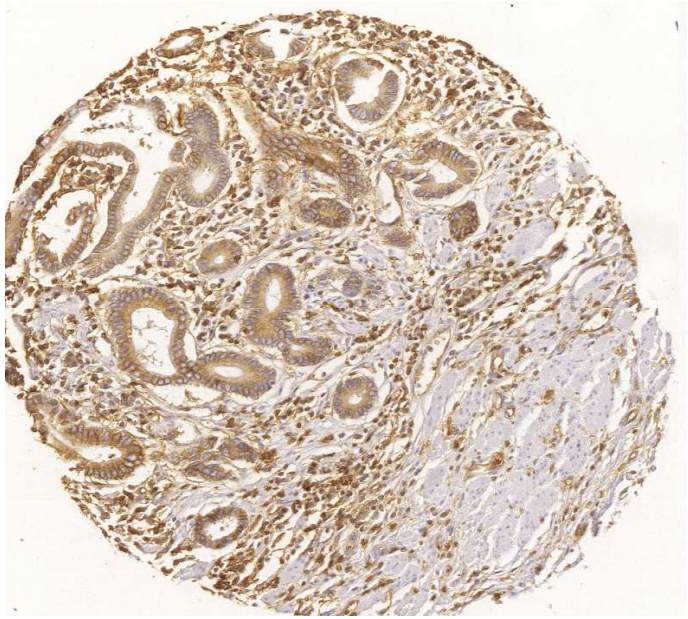
Wild type

Ifitm1 single null

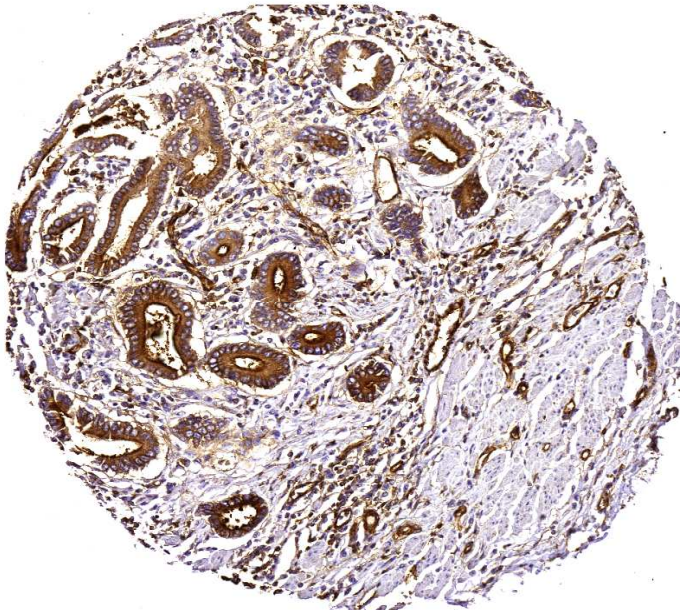
Ifitm1/3 double null

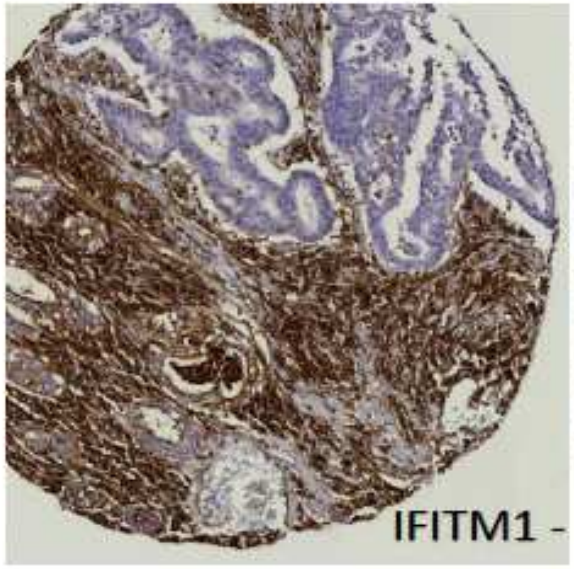
Immunohistochemistry to determine whether IFITM1 & HLA-B co-express in OAC

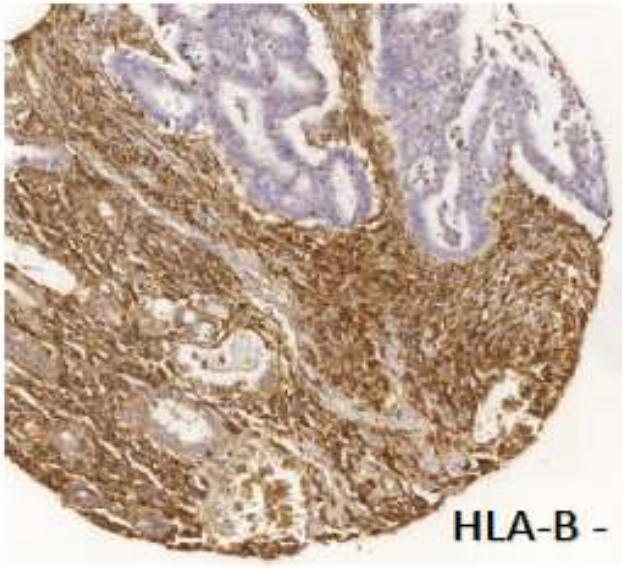
HLAB



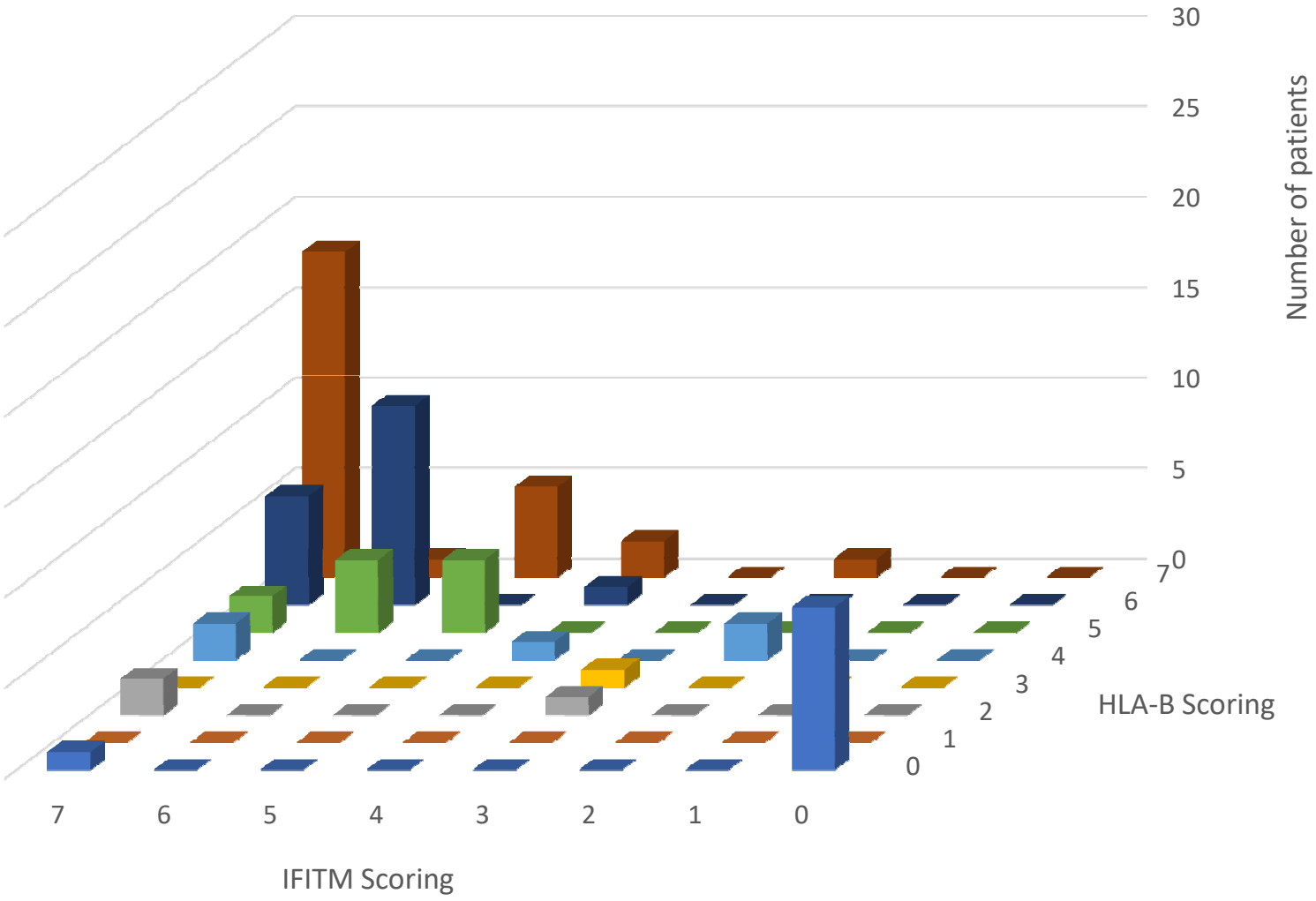
IFITM1







Expression correlation of IFITM1 and HLA-B in OAC



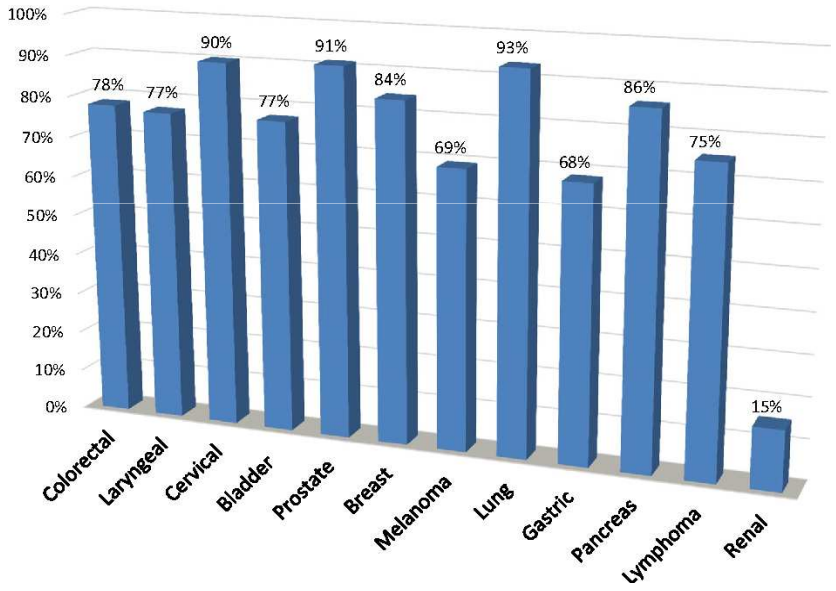
MHC class I HLA-A/-B/-C can impact on immunotherapies

Loss of MHC class I expression is observed abudantly in many types of cancer

MHC class I loss is correlated negatively with cancer survival prognosis

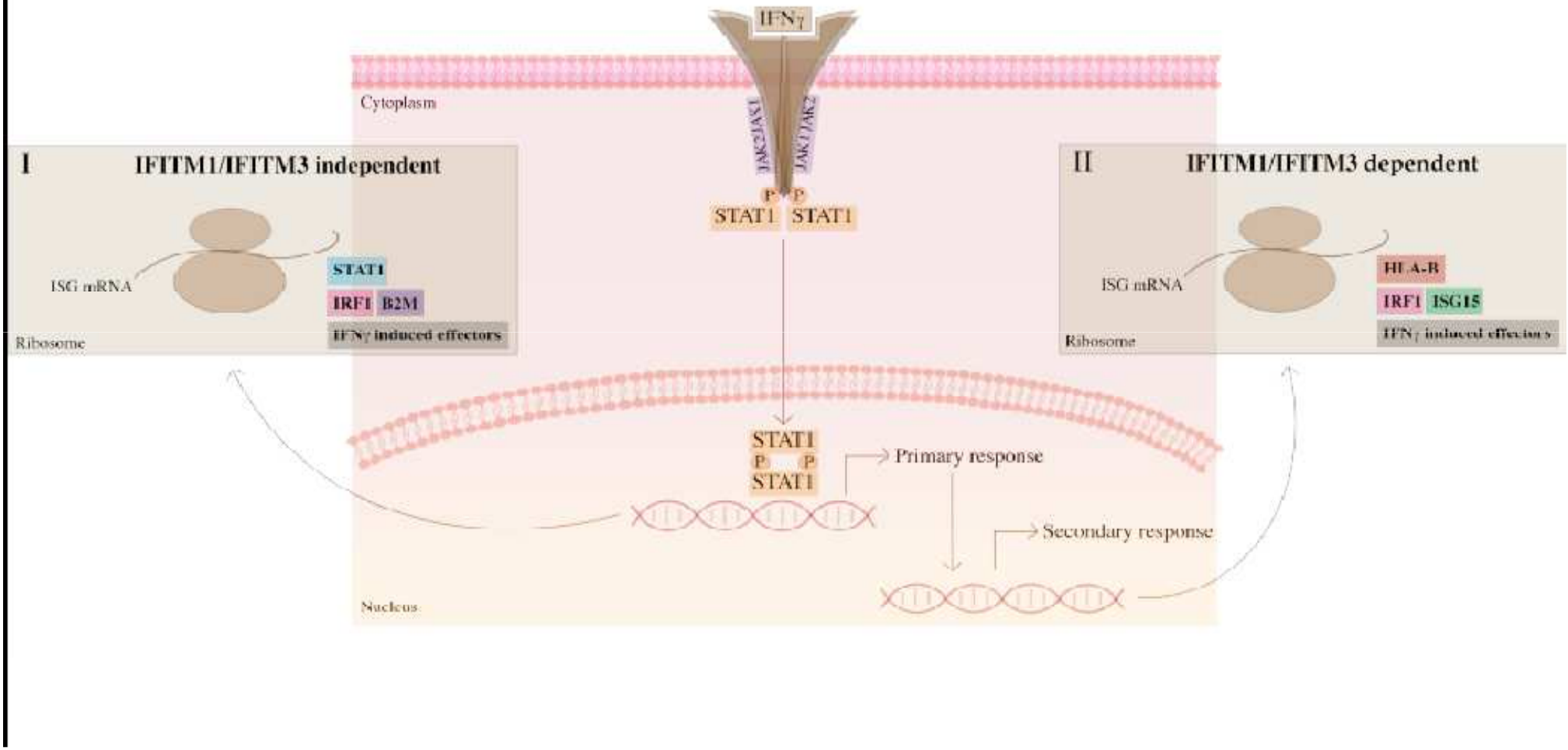
In order to work cancer immunotherpies require a functional antigen processing and presenting machinery

The heterozygosity at HLA-I loci affect response to checkpoint inhibitor immunotherapies (Chowell et al. 2017)

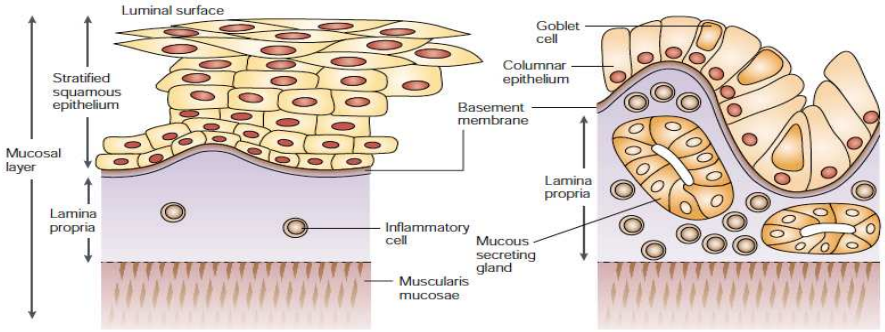


Frequency of HLA-I loss in different types of cancer

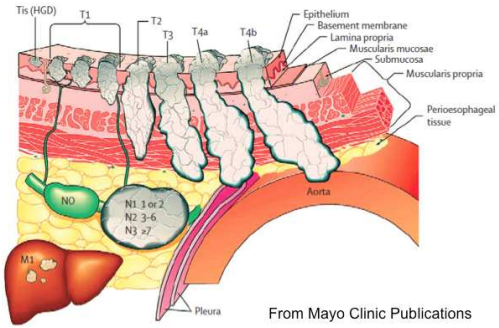
A model that rationalizes IFITM1 as an IFNγ responsive translation factor for HLA-B



Metaplasia-Dysplasia-Adenocarcinoma Sequence

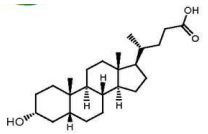


Normal metaplasia/dysplasia



OAC

Cancer progression mechanisms



- What is the role of steroids like LCA as risk factors?
- How might LCA drive selection pressures for loss of p53 and SMAD4?

Therapeutics

- What is the role of IFITM1 in tumour intrinsic INF signalling and/or chemoresistance?
- How might IFITM1 loss impact on MHC class I presentation and immune escape?
- Can we develop vaccine or therapeutic programmes that exploit IFITM1 + or - phenotypes?

University of Edinburgh

Larry Hayward
Donald Salter
Euan Murray
Kathryn Ball

Ian Overton
Erola Pairo-Castineira

Stuart Aitkin
Colin Semple

Anne-Sophie Huart
Jude Nicholson
Rob O'Neill
Ted Hupp

University of Geneva

Alex Scherl
Hui Song Pak

University of Maryland/University of Turku
Dave Goodlett
Young Ah Goo

Masaryk Memorial Cancer Institute, Brno
Borek Vojtesek
Rudolf Nenutil
Adam Krejci

University of Gdansk
Sachin Kote
Javier Alfaro

CLC Bio, Aarhus
(now, Qiagen)
Bodil Oster
Anika Joecker

BBSRC bioscience for the future

FNP Foundation for Polish Science

European Funds Smart Growth

European Union European Regional Development Fund

International Centre For Cancer Vaccine Science