University of Glasgow

BASL

~~Non-coding~~ RNAs and the biology underpinning potential new precision medicines in cholangiocarcinoma

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Glasgow, UK

CCA-UK

Neil Blenkinsop memorial lecture

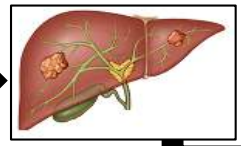
Nottingham, 14h November 2019

Our research journey

SURGERY

POST-OPERATIVE CHEMOTHERAPY

RECURRENCE



SYSTEMIC TREATMENT

CIS-GEM

SECOND LINE

Folfox

FGFR-i / IDHi

Can we better select patients for adjuvant treatment?

Can we improve the effect of available treatments?

Can we introduce novel therapeutics?

Immune-related transcripts as prognostic and predictive factors

MIR1249 as mediator of chemo-resistance

A.L.A.N. score

UC.158 as biomarker for Wnt-i

MIR21 as biomarker for HSP90-i

Patient derived organoids

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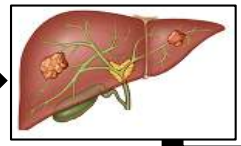

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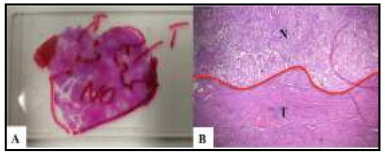
Is the immune-related transcriptome altered in resected tumours?

Exploratory set of FFPE resected tumours

(N=22)



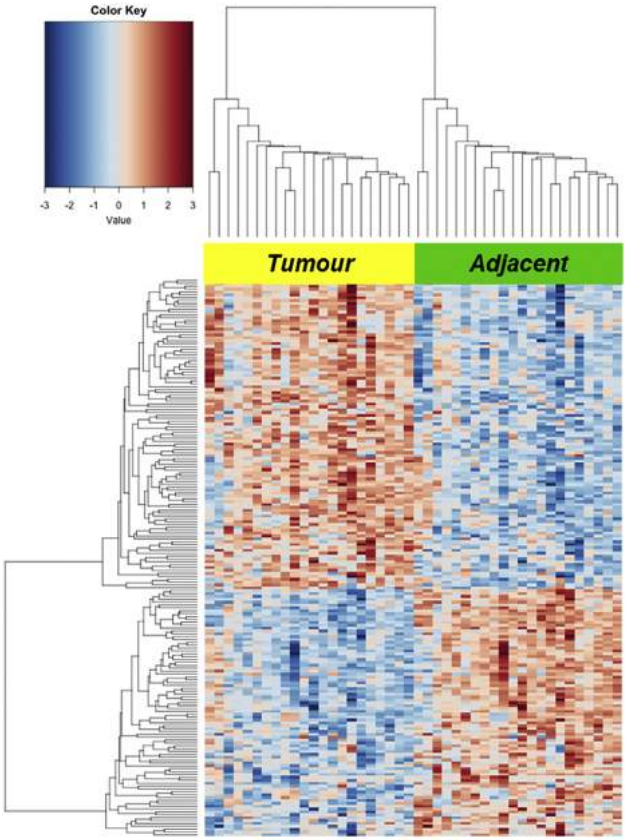
Microscopic dissection

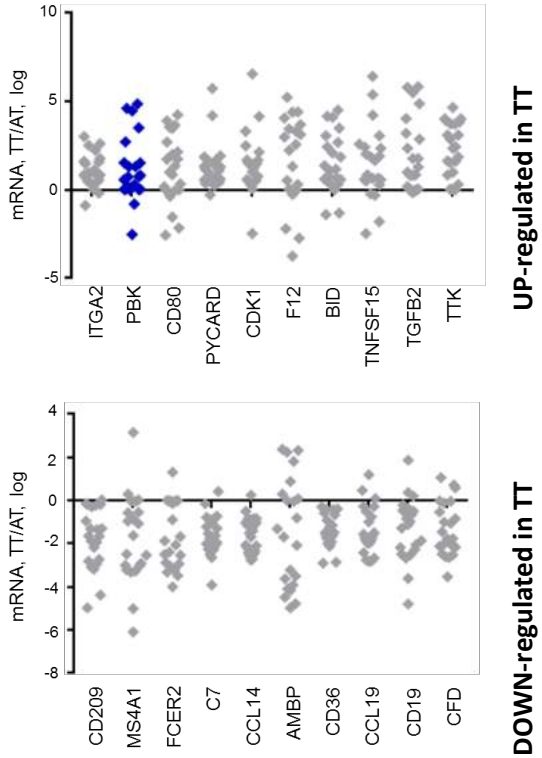
TT and AT

Immune profiling in TT and AT

(770 immune-related genes)

Deregulation of the immune transcripts in resected BTC





Ghidini, EJC 2017

Risk of relapse is associated with a greater number of genes deregulated in the peritumoural area

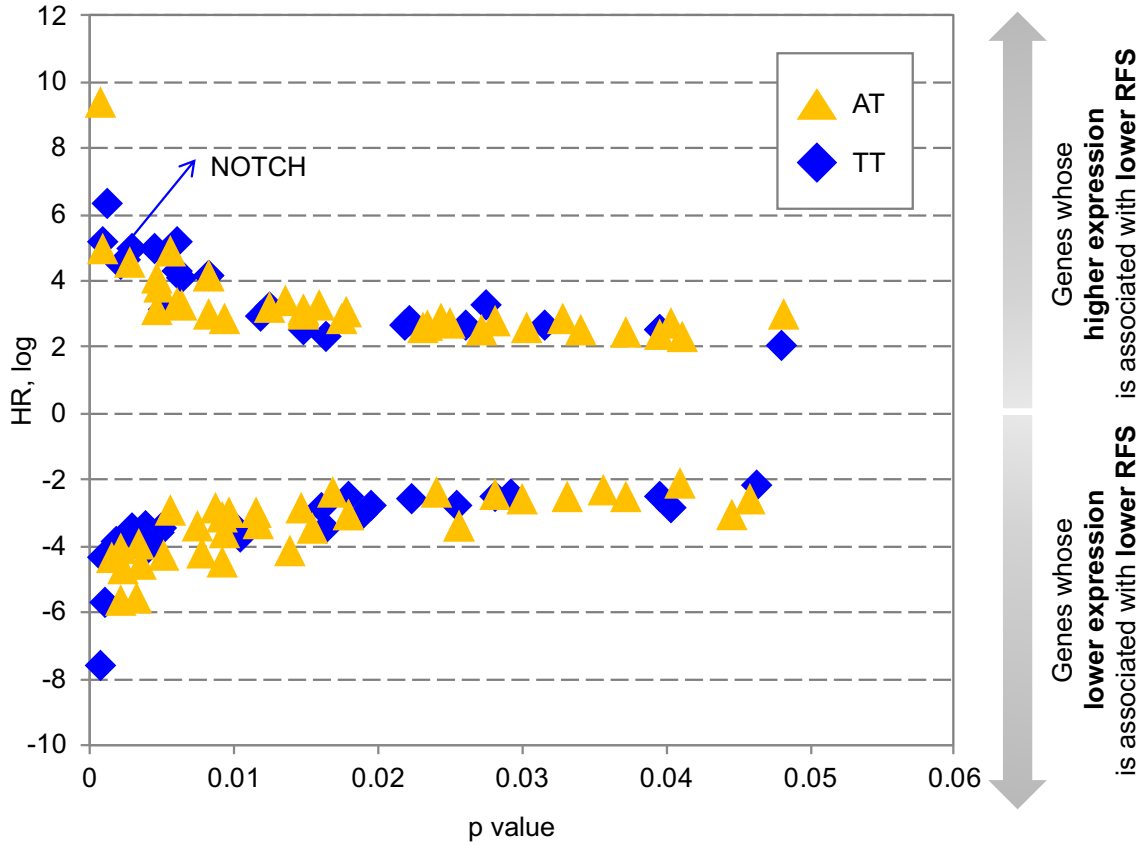
Seed and soil theory

SEED = TUMOUR (TT)

Genes in the tumoural area that were associated with risk of recurrence

SOIL = PERITUMOUR (AT)

Genes in the peritumoural area that were associated with risk of recurrence



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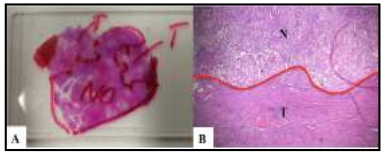
CTLA4 expression in AT is associated with risk of relapse in an expanded cohort of patients

Validation set of FFPE resected tumours

(N=53)



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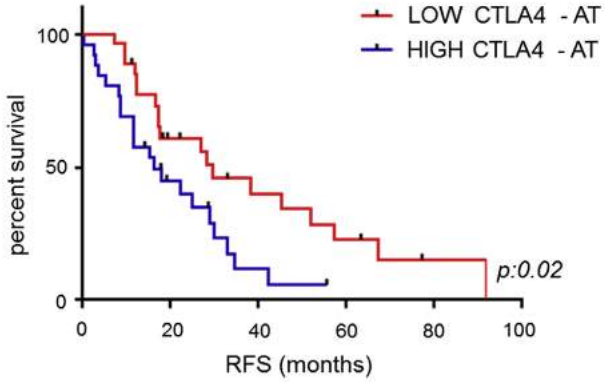
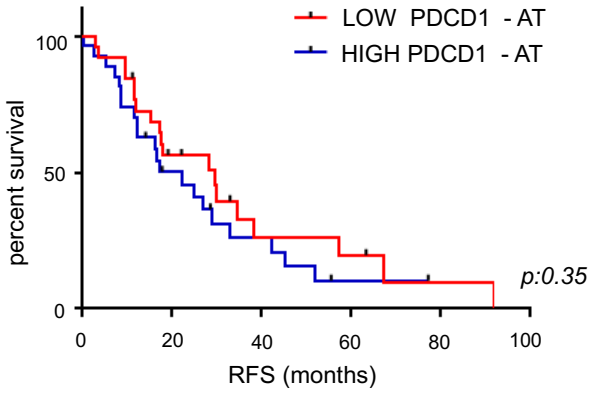
Adjacent Tissue

Transcript	p-value	HR	95% CI Low	95% CI High	
CCL22	0.0002	6.84	2.50	18.69	transcripts whose HIGH EXPRESSION is associated with LOWER RFS
ENG	0.0001	6.30	2.45	16.25	
LGALS3	0.0135	5.50	1.42	21.27	
F13A1	0.0039	5.05	1.68	15.16	
COLEC12	0.0056	4.80	1.58	14.53	
DOCK9	0.0046	4.17	1.55	11.20	
SLAMF1	0.0099	4.09	1.40	11.92	
IL1R1	0.0042	4.01	1.55	10.41	
LCN2	0.0166	3.95	1.28	12.17	
CD209	0.0080	3.72	1.41	9.82	
HLA-DQB1	0.0022	3.64	1.59	8.31	
SLC11A1	0.0182	3.36	1.23	9.17	
CD276	0.0077	3.25	1.37	7.75	
IL2RA	0.0052	3.23	1.42	7.36	
LTF	0.0086	3.13	1.34	7.34	
CD200	0.0184	3.12	1.21	8.06	
TLR6	0.0177	2.99	1.21	7.38	
BCL2	0.0037	2.94	1.42	6.08	
CKLF	0.0062	2.90	1.35	6.23	
TNFRSF1B	0.0095	2.87	1.29	6.37	
HLA-DMB	0.0269	2.85	1.13	7.22	
RUNX1	0.0315	2.84	1.10	7.33	
CARD11	0.0275	2.75	1.12	6.77	
LAIR2	0.0194	2.75	1.18	6.42	
CD9	0.0494	2.70	1.00	7.26	
JAM3	0.0188	2.69	1.18	6.14	
CTLA4	0.0191	2.65	1.17	6.00	
POU2AF1	0.0146	2.59	1.21	5.57	
MEF2C	0.0482	2.50	1.01	6.21	
JAK3	0.0292	2.49	1.10	5.65	
FCGR1A	0.0359	2.28	1.06	4.93	
IL21R	0.0282	2.23	1.09	4.56	
GPATCH3	0.0263	0.40	0.18	0.90	transcripts whose LOW EXPRESSION is associated with LOWER RFS
EIF2B4	0.0342	0.36	0.14	0.93	
IRF1	0.0020	0.27	0.12	0.62	
DEFB1	0.0003	0.21	0.09	0.49	
PSMB7	0.0014	0.19	0.07	0.53	
C1QBP	0.0009	0.19	0.07	0.51	
CCL16	0.0169	0.18	0.04	0.73	
ABCB1	0.0047	0.14	0.04	0.55	
LAMP2	0.0009	0.11	0.03	0.41	
IL1RAP	0.0000	0.07	0.02	0.24	

High CTLA4 mRNA – worse prognosis



PDCD1 mRNA – no difference



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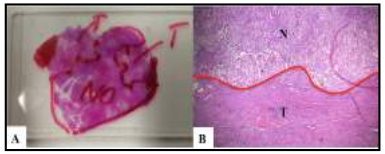

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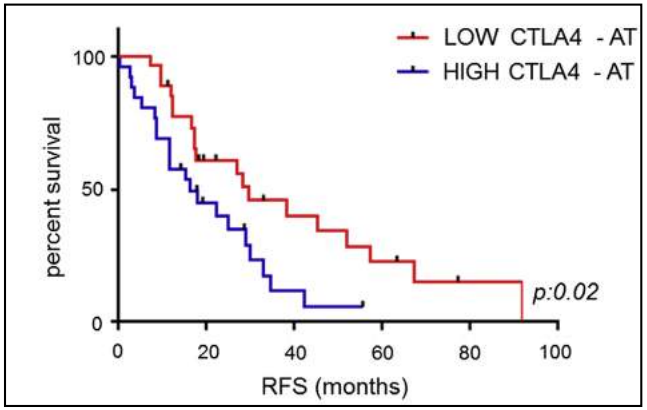
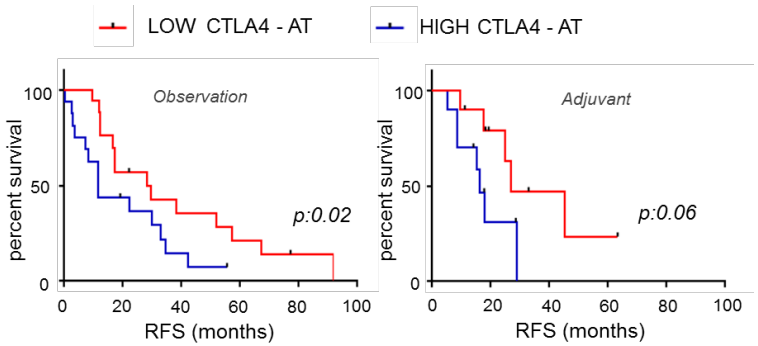
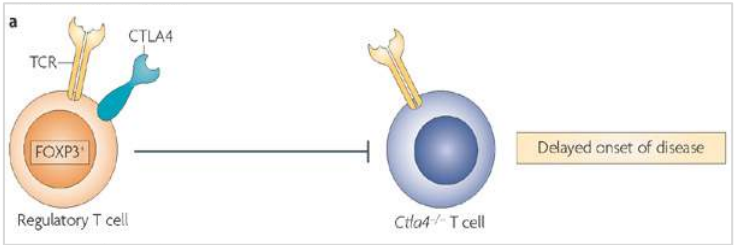


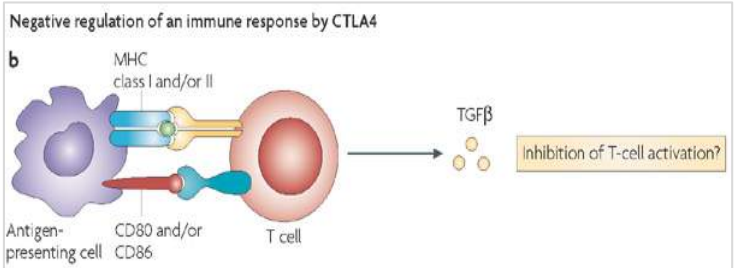


Ghidini, EJC 2017

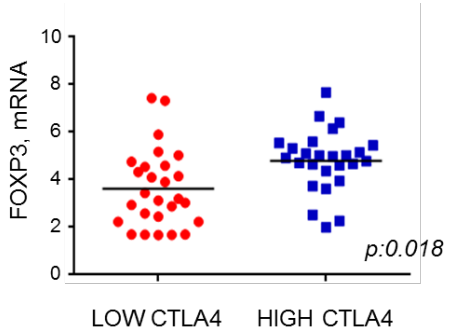
CD80 (but not CD86) expression in AT is associated with risk of relapse

CTLA4 as a marker of Treg

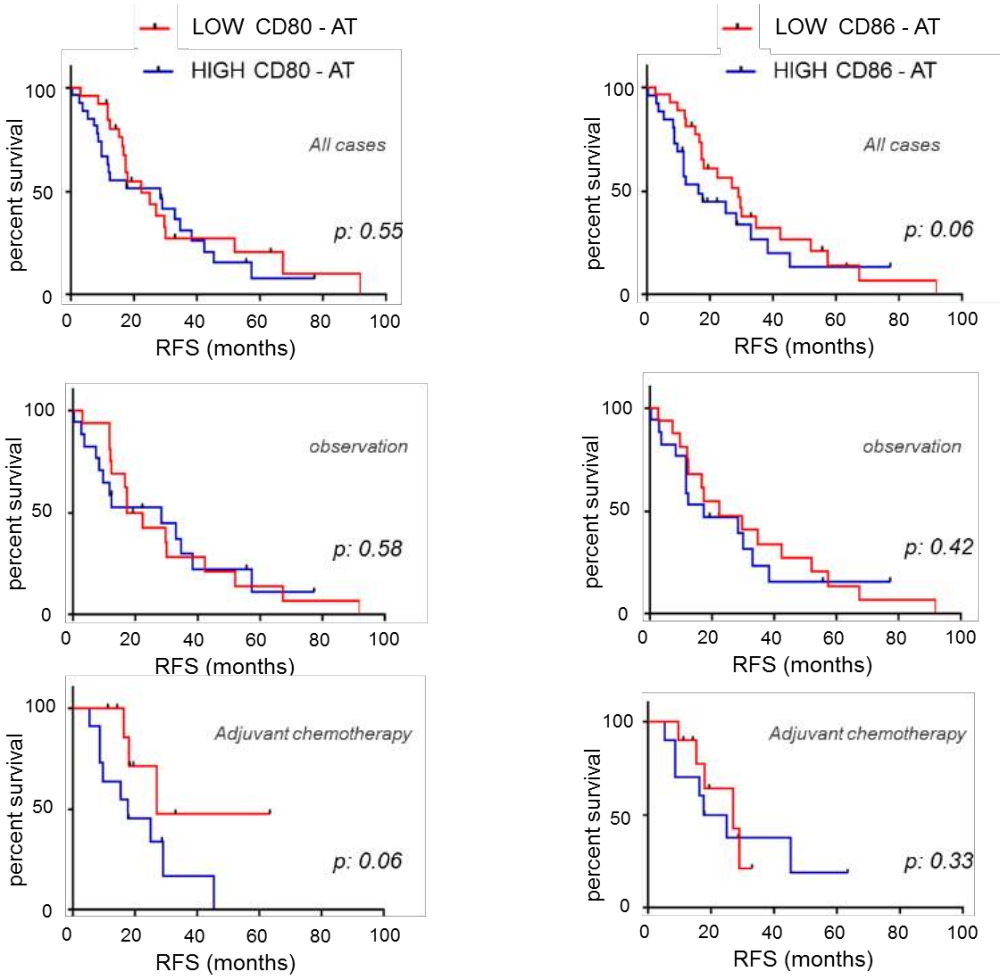




Rudd E, Nat Rev Immun 2008



CD80 mRNA is prognostic in patients receiving adjuvant chemotherapy

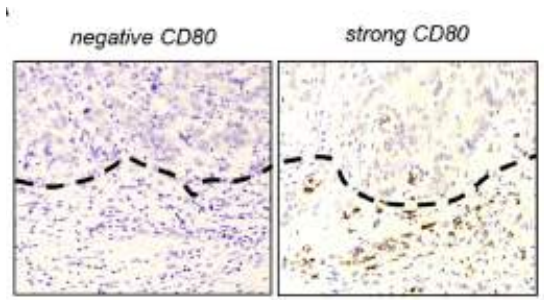


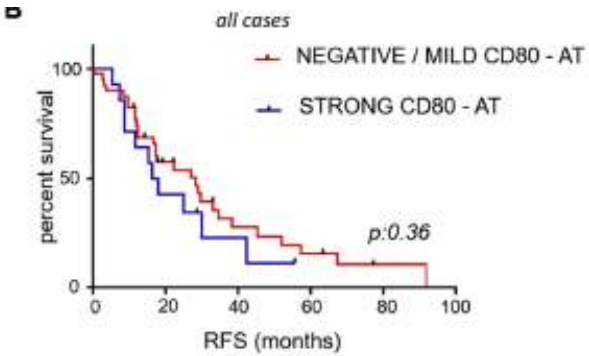
Ghidini, EJC 2017

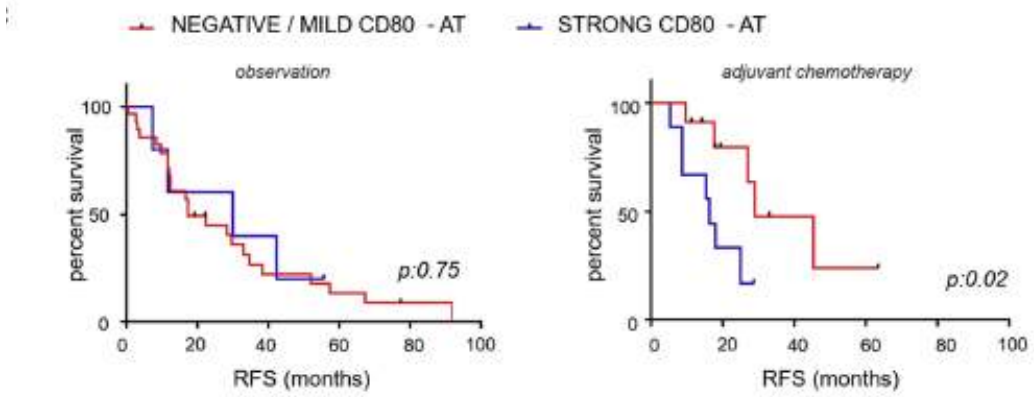
CD80 may represent a predictive biomarker of response to adjuvant treatment

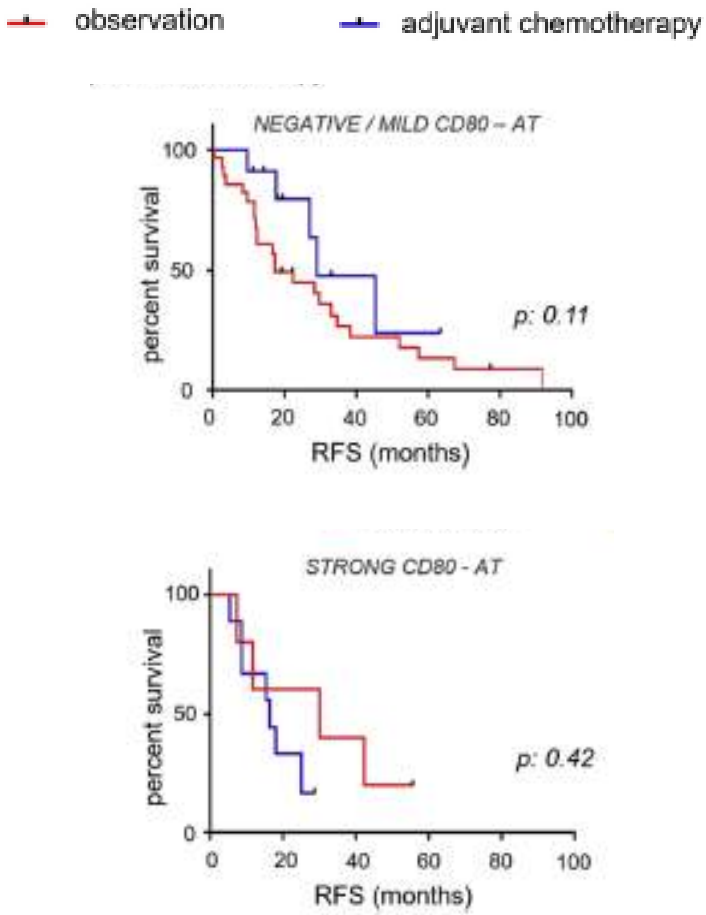
CD80 protein expression is associated to better prognosis in patients receiving adjuvant treatment

Benefit from adjuvant treatment seems to be absent in case of strong CD80 expression









Ghidini, EJC 2017

Immuno-related parameters affect prognosis / chemosensitivity

Exploratory set of ABC

(N=123)

Multivariate analysis in the exploratory cohort.

Covariate	HR	95% CI	p value
LMR			
<2.1	1.60	1.02–3.08	0.045
Albumin gldl			
<3.5	1.62	1.04–2.50	0.031
NLR			
>3	1.74	1.03–2.97	0.042
ANC			
>8000	2.12	1.27–3.54	0.004
Performance status			
ECOG ≥2 versus 0-1	2.16	1.28–3.64	0.004
Disease status			
Metastatic versus LA	2.22	1.30–3.78	0.003
CEA nglml			
>9.5	2.59	1.55–4.32	<0.001

ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; ANC, absolute neutrophil count, CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazards ratio; LA, locally advanced

Variables that resulted statistically significant in the multivariate analysis are reported. Shrinkage (overfitting) 0.099. c-Harrell Train 0.702 Test 0.692.

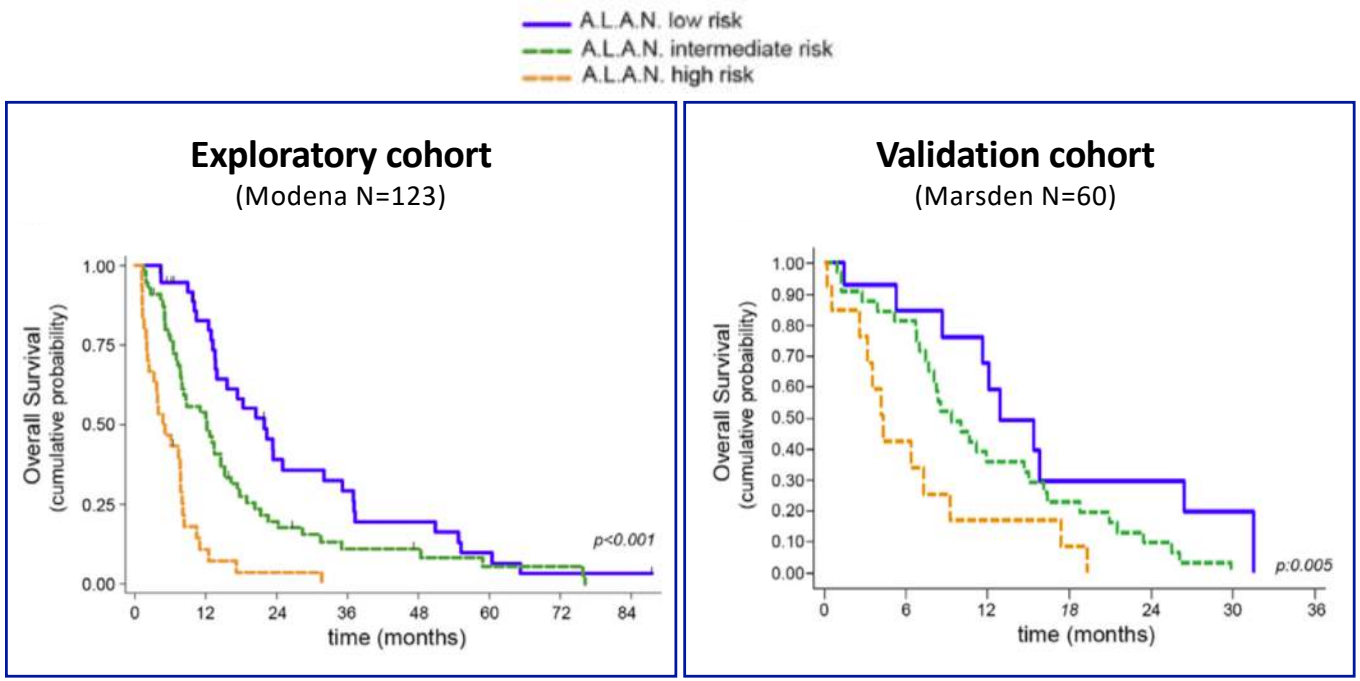
Clinical parameters associated to survival in ABC undergoing first line chemotherapy

A ANC – Absolute Neutrophil Count

L LMR – Lymphocyte Monocytes Ratio

A Albumin

N NLR – Neutrophil Lymphocytes Ratio



Salati, EJC 2019

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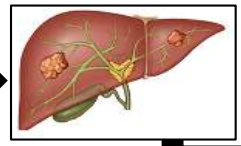

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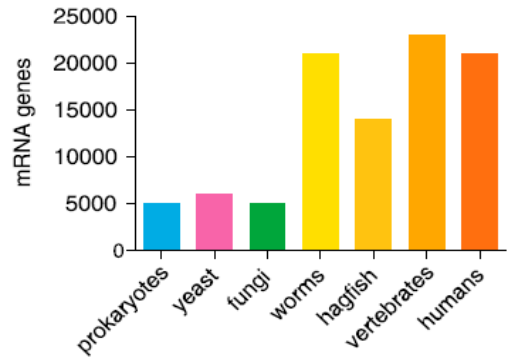
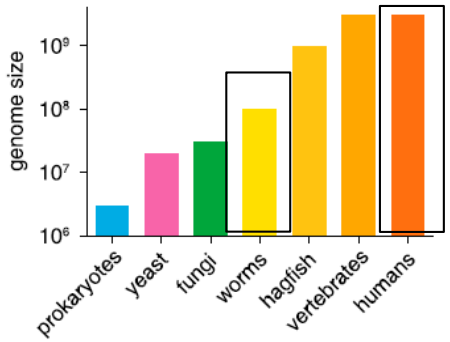
Is non coding RNA important?

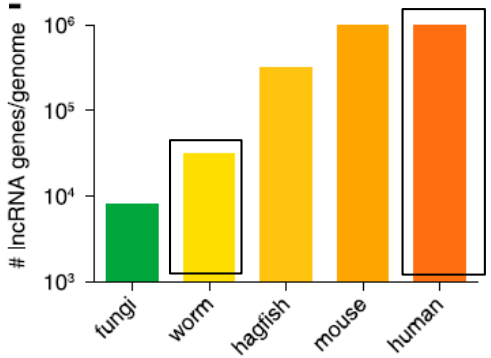


Worms and humans share the same number of protein coding mRNAs (20,000)

The human genome is 30 times larger than the worm genome



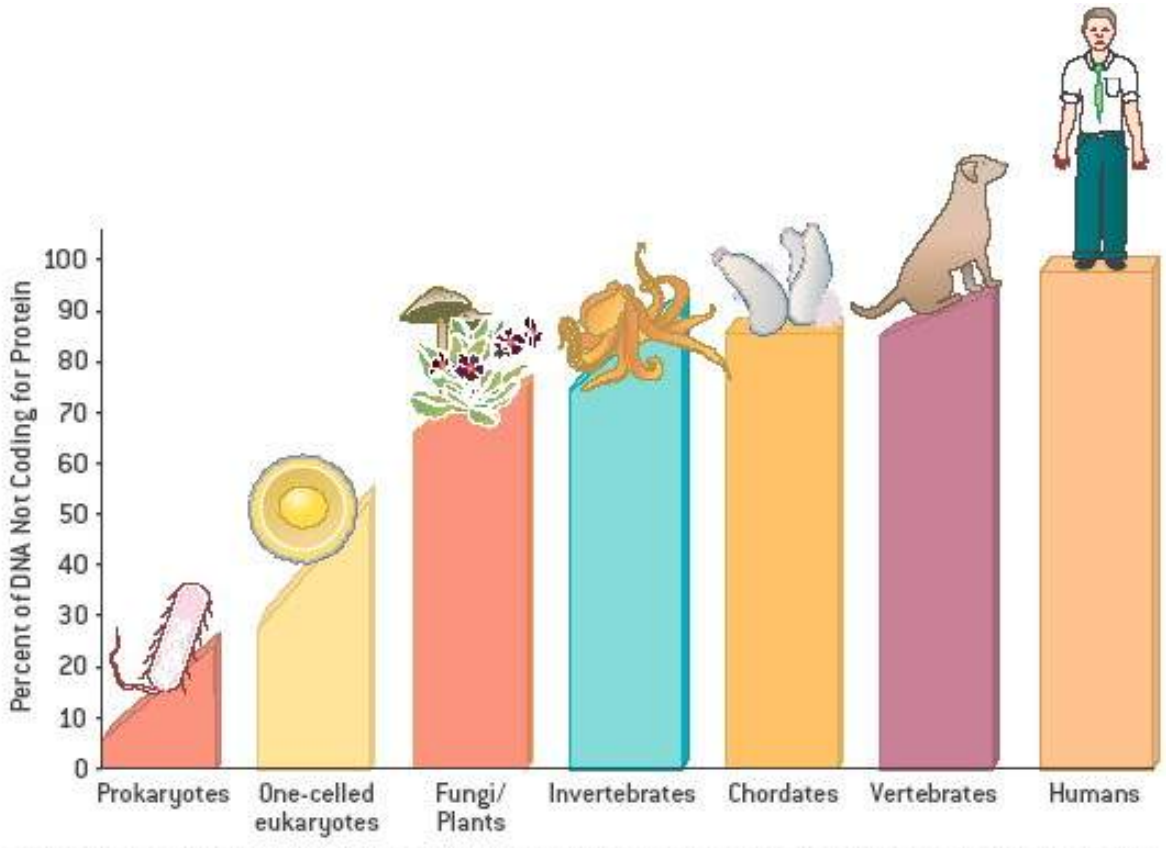
Humans and other vertebrates produce ~1 million unique ncRNA genes
Worms produce ~ 300,000 ncRNAs



Aune, Journal of Leukocyte Biol 2016

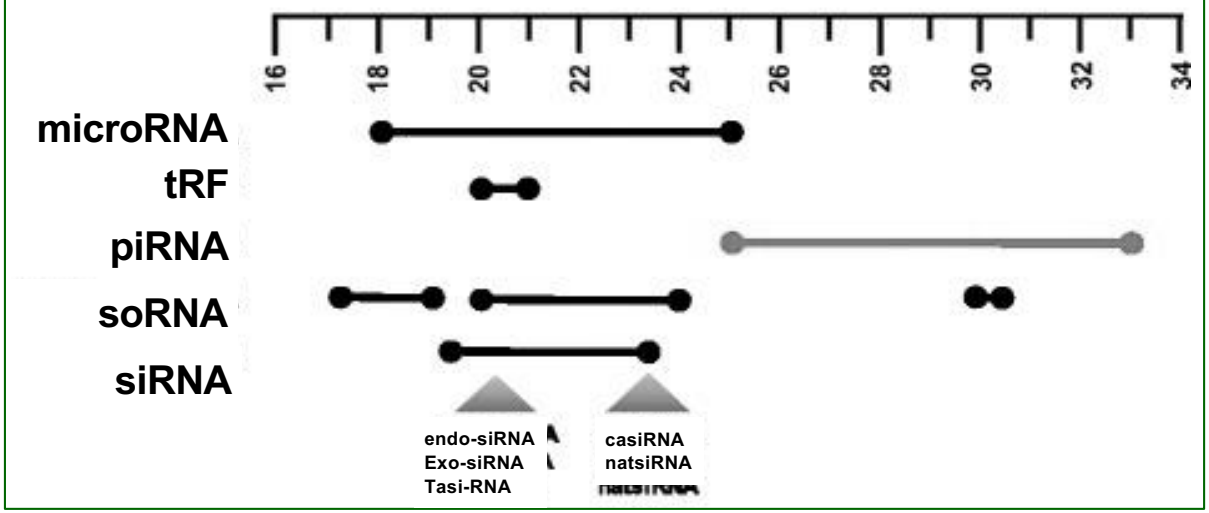
ncRNA: the master- regulator of species complexity

ncRNA has been considered "junk", but perhaps it actually helps to explain organisms' complexity

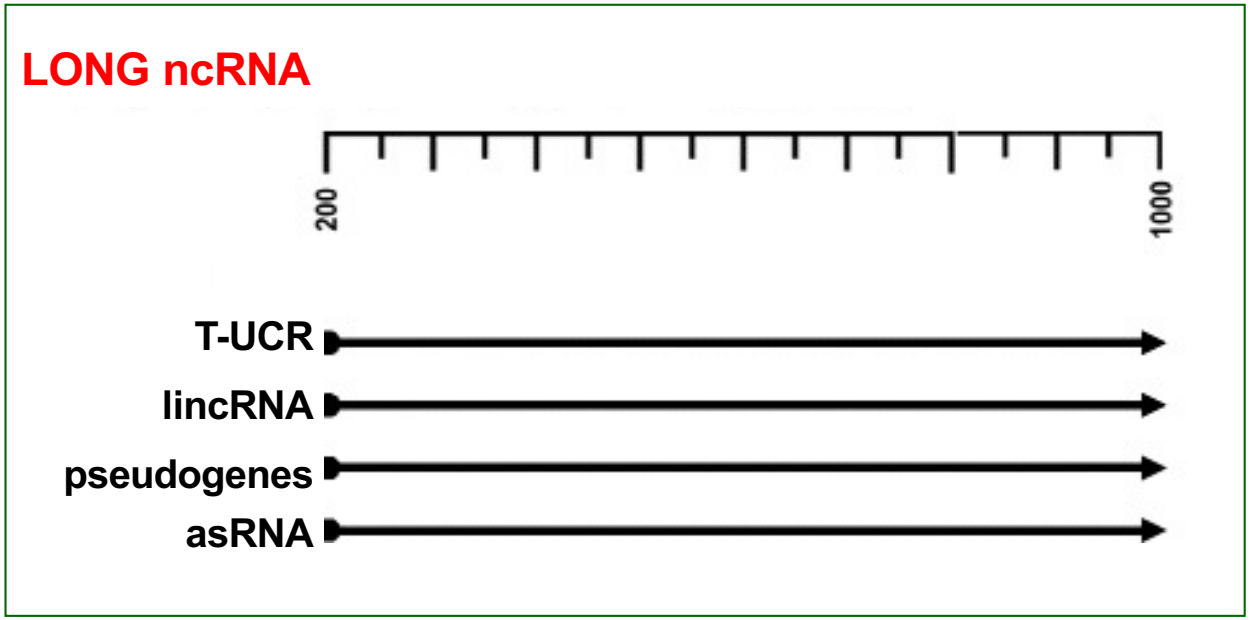


How many types of ncRNAs?

SMALL ncRNA

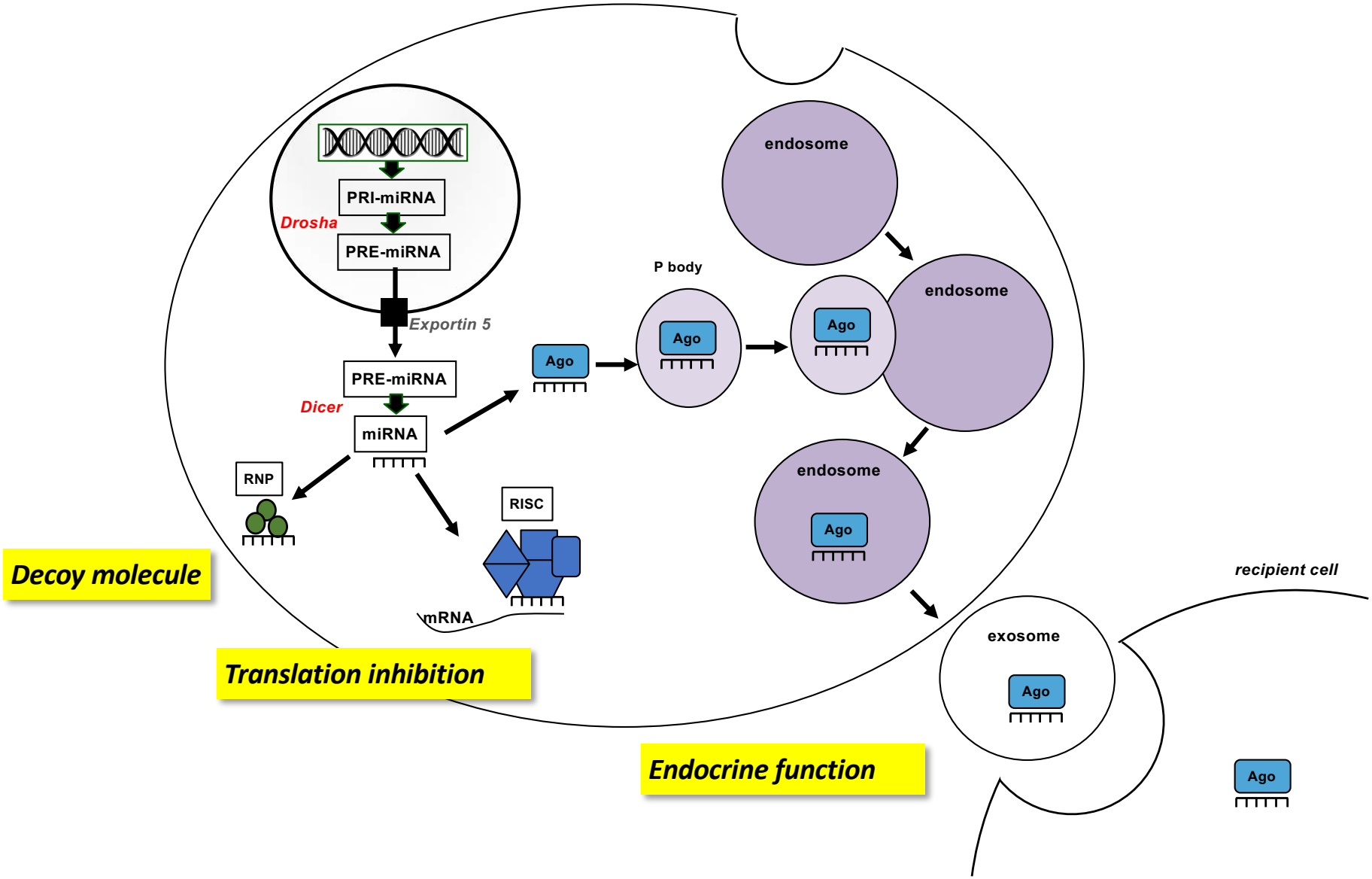


LONG ncRNA



Ng Molec Cancer 2016

How do microRNA work?



microRNA deregulation in CCA

Table 1 Selected oncogenic miRNAs involved in cholangiocarcinoma initiation and progression

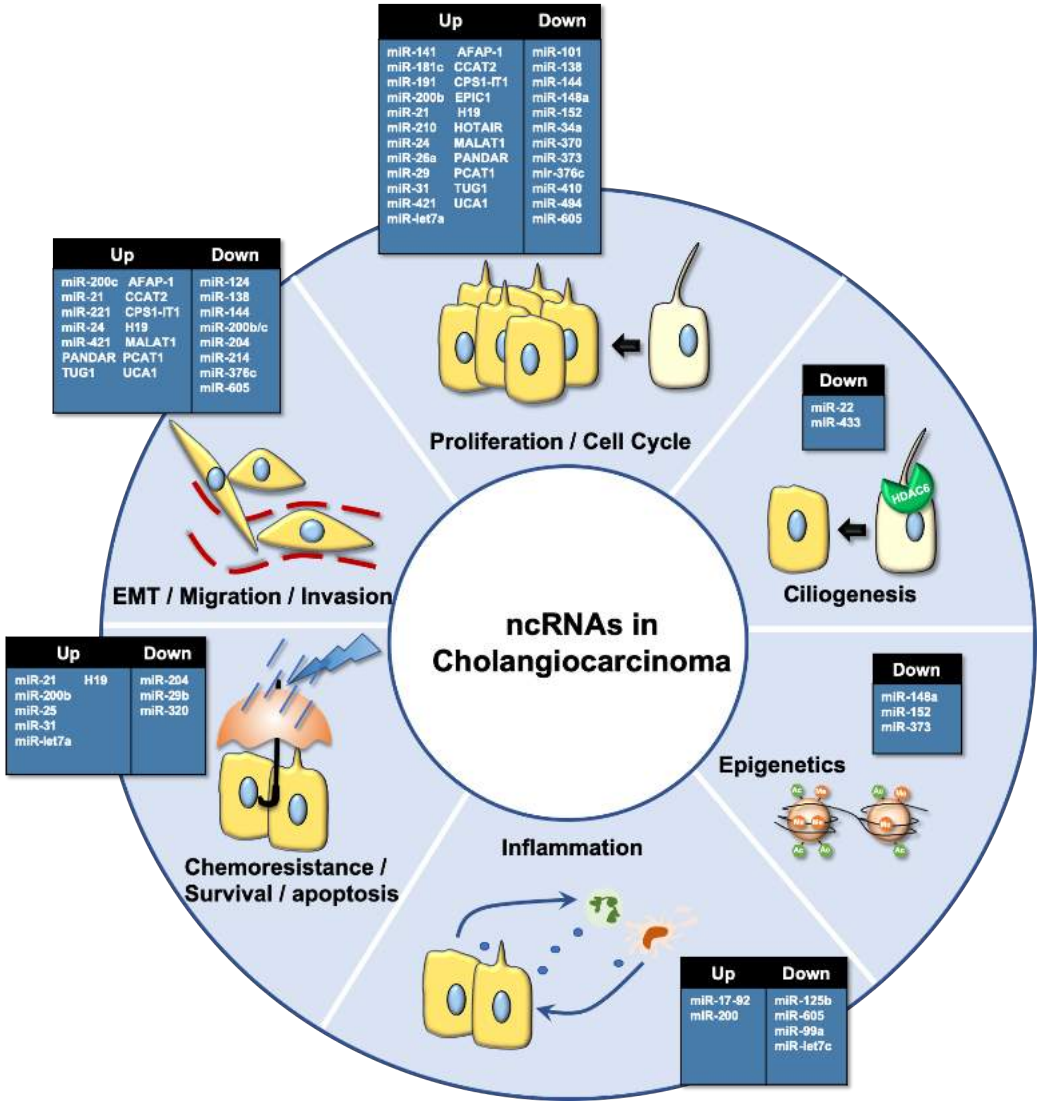
miRNA	Expression[a]	Tumor type	Target genes	Function	Source	Ref.
miR-21	Up	CCA, iCCA, Op-CCA	*PI3K, PDCD4, TIMP3, RECK, TPM1, 15PGDH, PTPN14, PTEN, KLF4, AKT, ERK*	Tumor growth, invasion, migration EMT,	Human cell lines, human tissue, mouse tissue	24,25,29,34,35,46
miR-25	Up	CCA	*DR4*	Antiapoptotic	Human cell lines, human tissue,	32
miR-26a	Up	CCA	*GSK-3β*	Tumor growth	Human cell lines, human tissue, mouse tissue	26
miR-31	Up	iCCA	*RASA1*	Proliferation, antiapoptotic	Human cell lines, human tissue,	27
miR-141	Up	CCA	*CLOCK*	Proliferation	Human cell lines, human tissue, mouse tissue	24
miR-210	Up	CCA	*MNT*	Proliferation	Mouse tissue	105
miR-221	Up	eCCA	*PTEN*	Invasion, migration, EMT	Human cell lines, human tissue,	37
miR-421	Up	CCA	*FXR*	Proliferation, migration	Human cell lines, human tissue	106
Let-7a	Up	CCA	*NF2*	Survival	Human cell lines, mouse tissue	42
miR-24	Up	iCCA, eCCA	*MEN1*	Proliferation, migration, angiogenesis	Human cell lines, human tissue, mouse tissue	107

Table 2 Selected oncosuppressor miRNAs in cholangiocarcinoma initiation and progression

miRNA	Expression[a]	Tumor type	Target genes	Function	Source	Ref.
miR-34a	Down	eCCA, CCA	*Per-1, SMAD4*	Proliferation, invasion, migration, EMT	Human cell lines, human tissue	103,108
miR-29b	Down	CCA	*Mcl1*	Antiapoptotic	Human cell lines	31
miR-26a	Down	CCA	*KRT19*	Suppression of tumor growth	Human cell lines, human tissue, mouse tissue	83
miR-101	Down	CCA	*VEGF, COX-2*	Angiogenesis	Human cell lines, human tissue	109
miR-124	Down	HCV-iCCA	*SMYD3*	Invasion, migration	Human cell lines,	110
miR-138	Down	CCA	*RhoC*	Proliferation, invasion, migration	Human cell lines	38
miR-144	Down	CCA	*LIS1*	Proliferation, invasion, migration	Human cell lines, human tissue, mouse tissue	111
miR-148a miR-152	Down	CCA	*DNMT-1*	Proliferation	Human cell lines, mouse tissue	44
miR-200b/c	Down	CCA, iCCA	*SUZ12, ROCK2, NCAM1*	Invasion, migration, EMT, drug resistance	Human cell lines, human tissue, mouse tissue	112
miR-204	Down	iCCA	*Slug, Bcl-2*	Invasion, migration, EMT, antiapoptotic	Human cell lines, human tissue	91
miR-214	Down	iCCA	*Twist*	EMT	Human cell lines, human tissue	36
miR-320	Down	CCA	*Mcl-1*	Antiapoptotic	Human cell lines, human tissue	91
miR-370	Down	CCA	*MAP3K8, WNT10B*	Proliferation	Human cell lines, human tissue, mouse tissue	43,113
miR-373	Down	pCCA	*MBD2*	Proliferation	Human cell lines, human tissue	114
miR-376c	Down	iCCA	*GRB2*	Proliferation, migration	Human cell lines	115
miR-410	Down	CCA	*XIAP*	Proliferation	Human cell lines, human tissue, mouse tissue	43
miR494	Down	CCA	*CDK6, PLK1, PTTG1, CCNB1, CDC2, CDC20 TOP2A,*	Proliferation	Human cell lines, mouse tissue	30,116
let-7c/ miR-99a/ miR-125b	Down	CCA	*IL-6, IL-6R, IGF1R*	Inflammation, invasion, migration	Human cell lines, human tissue, mouse tissue	41

Salati, Semin Liver Dis 2018

Multi-tasking players in cancer promotion and progression



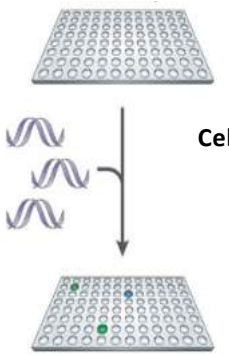
Braconi – Gradilone
In: Banales, Nat Rev Gastr & Hepat 2019

miRNAs as modulators of chemoresistance in CCA

Highthroughput screening to identify miRNA-i that reverse chemotherapy resistance in human CCA cellS

Functional approach that modulates expression of miRNAs involved in cell dynamics

LNA microRNA inhibitors library
(Exiqon, miRCURY LNA, v3)

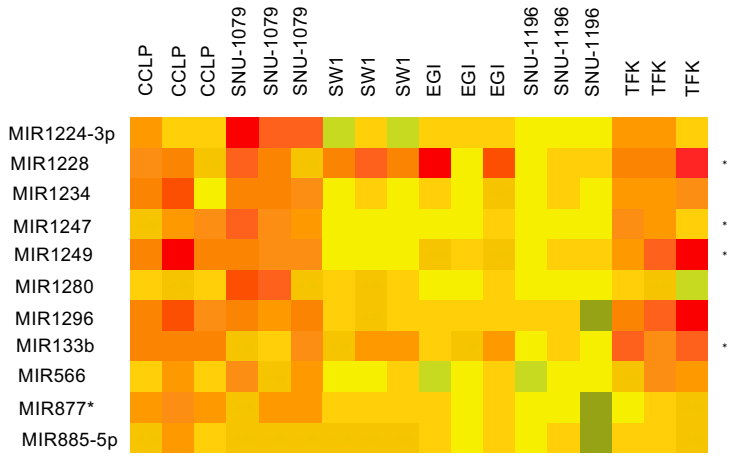


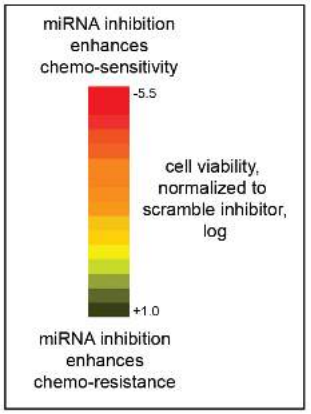
24 hrs

Cells treated with CG

48 hrs

effect on cell viability
(CellTiterBlue Assay)



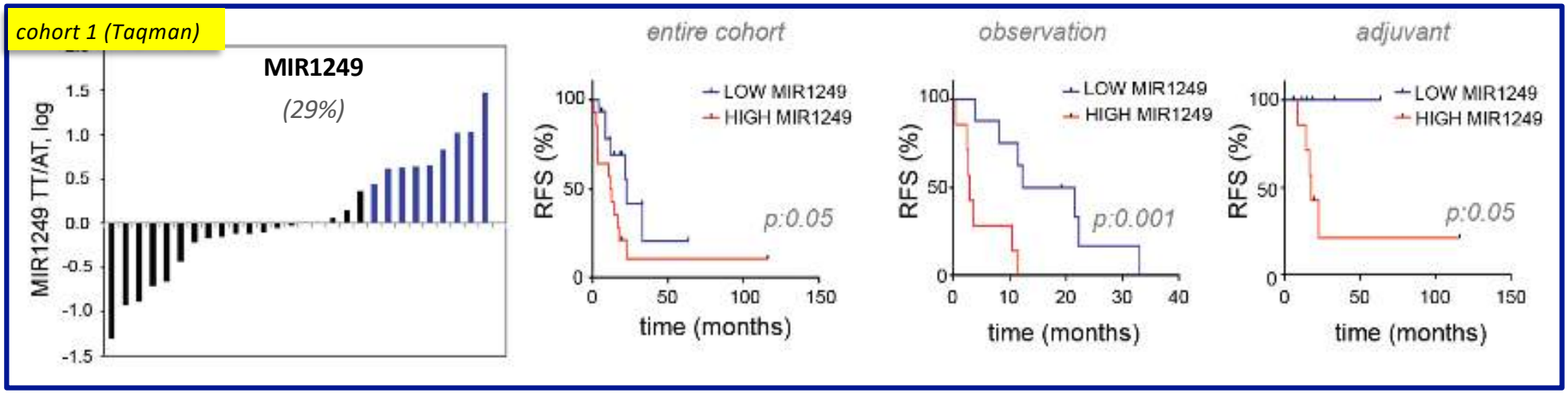


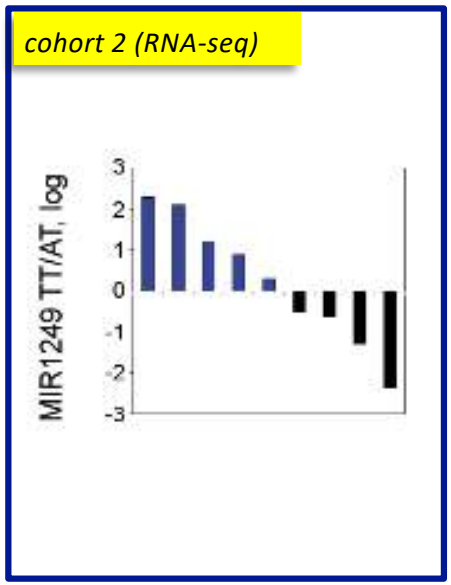
Analysis of the HTS: For each replicate: cell viability assessed for each hit normalized to averaged NEG CTRLs across the plates. For each cell line: t-test of normalized values for 3 replicates (p value < 0.05).

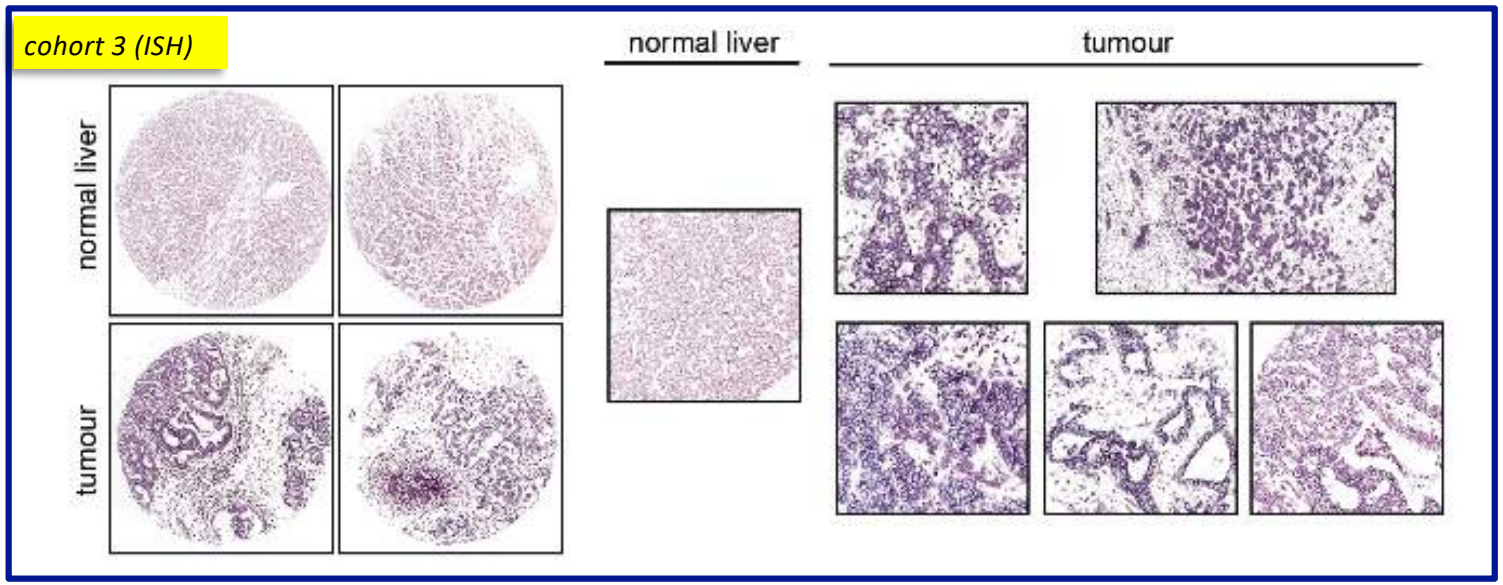
Carotenuto, under revision

MIR1249 is clinically relevant

MIR1249 is over-expressed in 30-50% of human CCA tissues



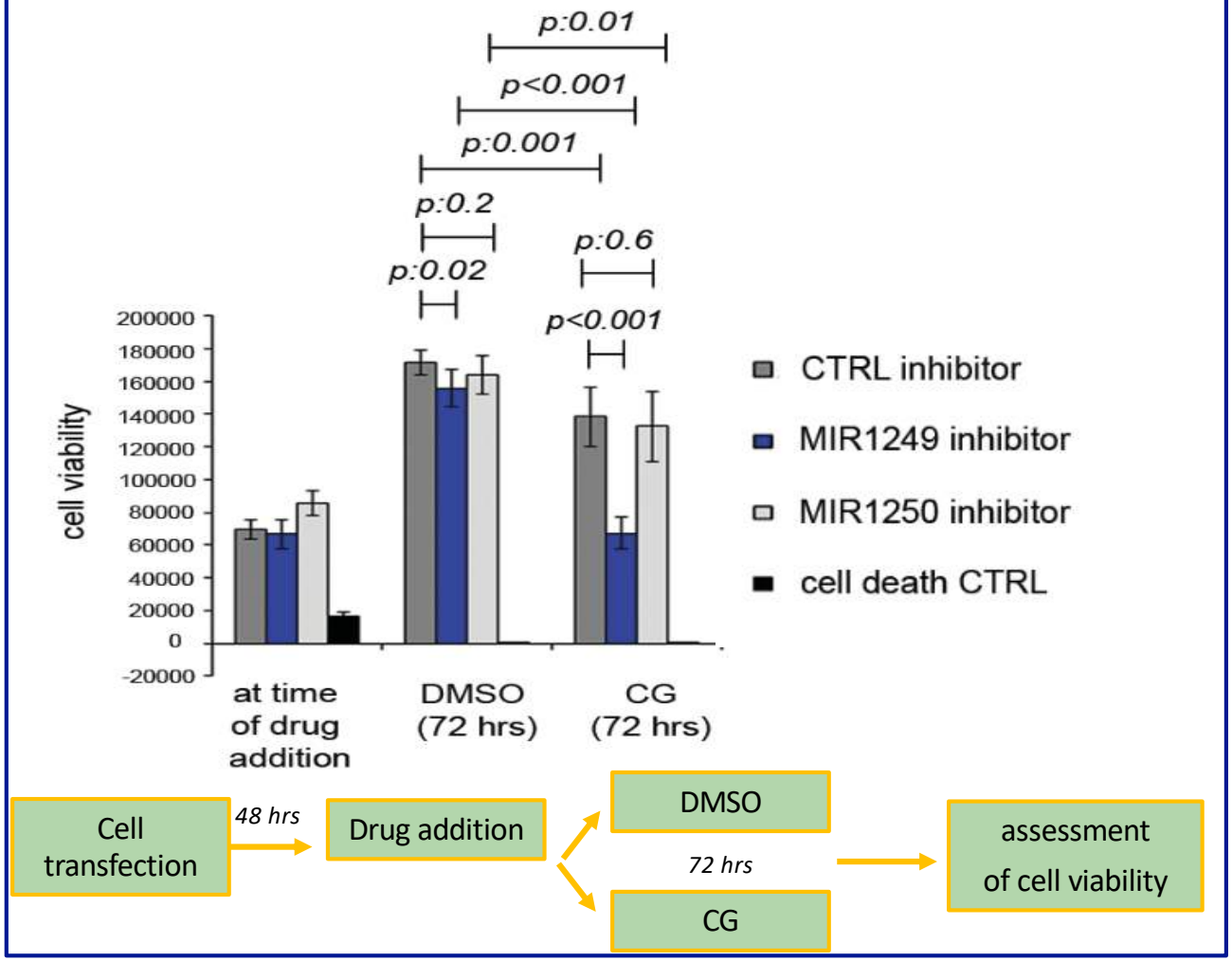




Carotenuto, under revision

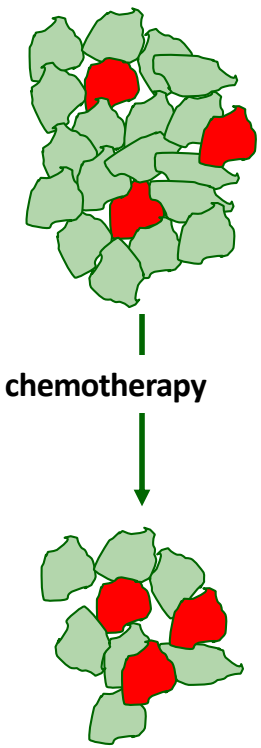
MIR1249i activity is specific for chemotherapy treatment

MIR1249i decreases cell viability only in CG-treated cells



Hypothesis:

MIR1249 drives survival and growth of chemo-resistant cells

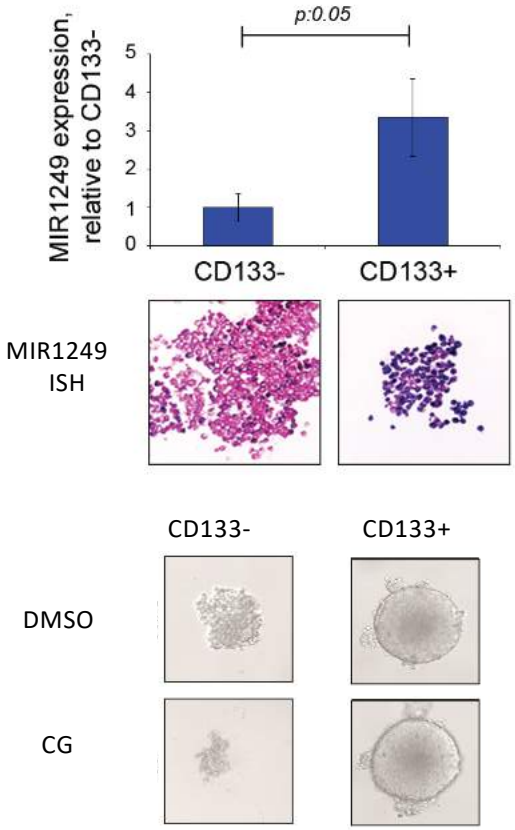


Carotenuto, under revision

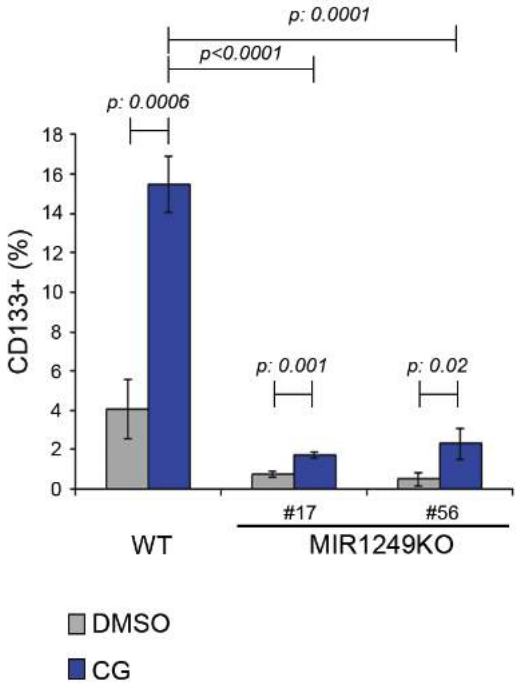
MIR1249 drives expansion of CD133+ cells

MIR1249 inhibition sensitizes CCA cells to CG chemotherapy by reducing expansion of CD133+ cells

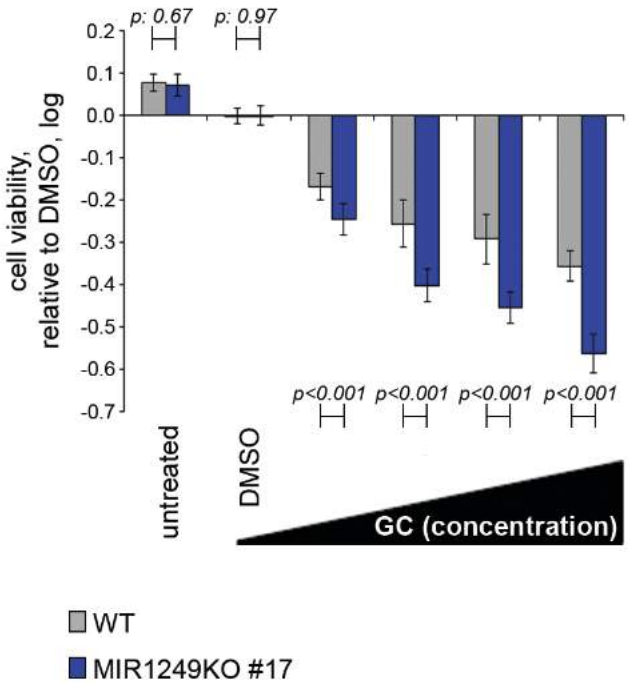
MIR1249 expression is increased in chemo-resistant CD133+ CCA cells



MIR1249KO cells have impaired expansion of CD133+ cells



MIR1249KO cells are more sensitive to CG in a dose-dependent manner



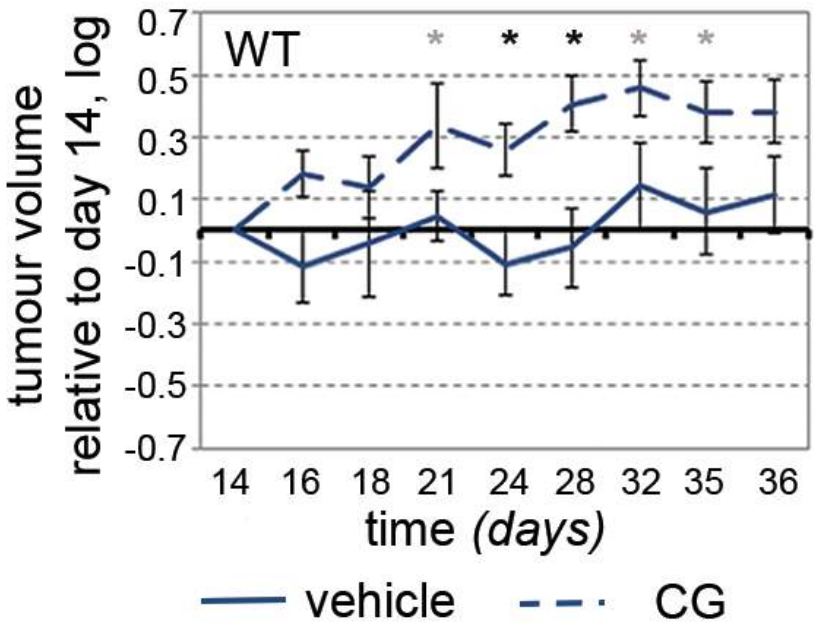
Carotenuto, under revision

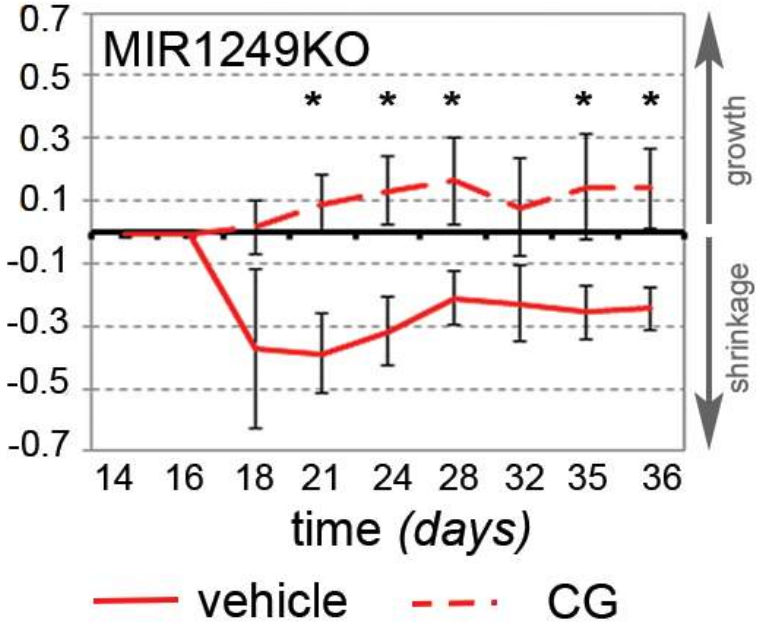
MIR1249i induces tumour response *in vivo*

CG chemotherapy sensitivity is enahnced in MIR1249KO mice xenografts

CG induces stabilization of disease in WT

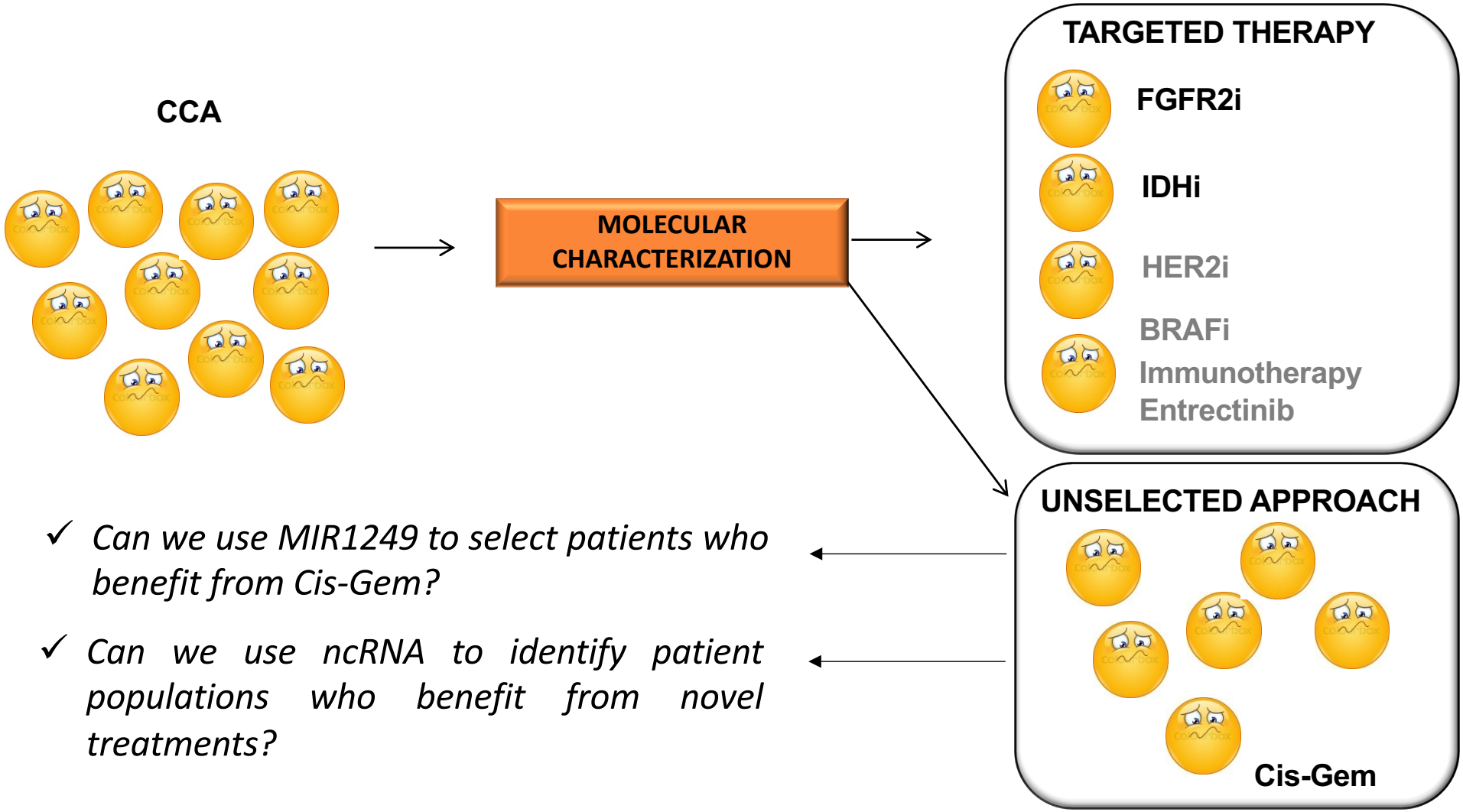
CG induces tumour shrinkage in animal models with lack of MIR1249





Carotenuto, under revision

Expanding precision oncology beyond mutational status



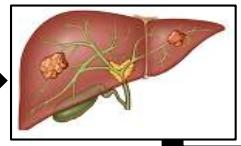
- ✓ *Can we use MIR1249 to select patients who benefit from Cis-Gem?*
- ✓ *Can we use ncRNA to identify patient populations who benefit from novel treatments?*

Our research journey

SURGERY

POST-OPERATIVE CHEMOTHERAPY

RECURRENCE



SYSTEMIC TREATMENT

CIS-GEM

SECOND LINE

Folfox

FGFR-I / IDHi

Can we better select patients for adjuvant treatment?

Can we improve the effect of available treatments?

Can we introduce novel therapeutics?

Immune-related transcripts as prognostic and predictive factors

MIR1249 as mediator of chemo-resistance

A.L.A.N. score

UC.158 as biomarker for Wnt-i

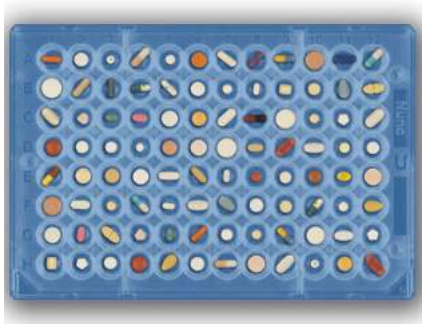
MIR21 as biomarker for HSP90-i

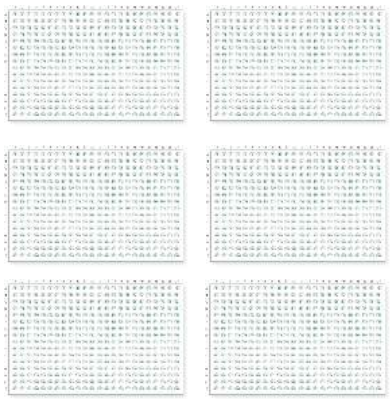
Patient derived organoids

Our experience of integration of non coding RNAs and organoid models in drug discovery projects in CCA

Preclinical testing of small molecule drugs in CCA disease model (cell lines)

Highthroughput screening of small molecule compounds (n=500)





80nM

200nM

800nM

Cells plating in 384 plates

48 hrs

Drug/DMSO addition through the Labcyte Echo system

72 hrs

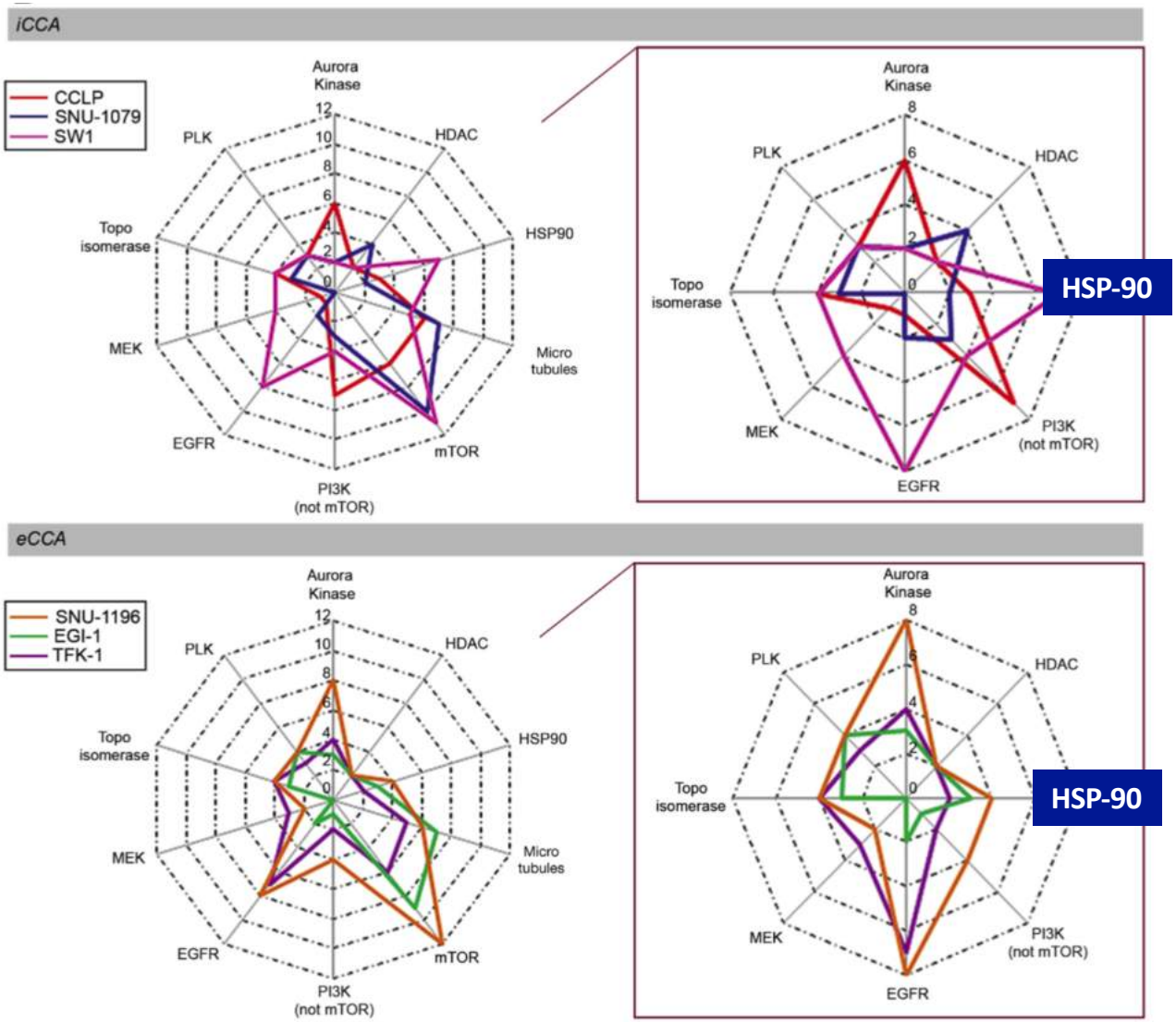
Cell viability (cell titer blue)

CCA cell lines

Cell line	Tumour type	Origin	Mutations
EGI-1	ECC	Extrahepatic bile ducts	**TP53**
TFK-1	ECC	Middle common bile duct	**BAP1** **PBRM1**
Snu-1196	ECC	Hepatic duct bifurcation	**SMAD4** **TP53**
Snu-245	ECC	Distal common bile duct	**KRAS** **TP53**
Snu-869	ECC	Ampulla of Vater	**TP53**
Snu-478	ECC	Ampulla of Vater	**MLH1** **TP53**
Witt (MzCh-A)	GBC	Adenocarcinoma of Gallbladder	**SMAD4** **TP53**
Snu-308	GBC	Adenocarcinoma of Gallbladder	**TP53**
SW1	ICC	Intrahepatic cholangiocarcinoma	**-**
CC-LP	ICC	Intrahepatic cholangiocarcinoma	**BAP1**
Snu-1079	ICC	Intrahepatic cholangiocarcinoma	**IDH1** **PBRM1**

Lampis, Gastroenterology 2018

Enrichment pathway analysis identifies therapeutic opportunities for CCA



Enrichment for microtubule associated drugs and mTOR inhibitors in all cell lines.

Clinical trials are ongoing for these compounds.

Enrichment of HDAC inhibitors for Snu-1079 that harbours mutations in IDH1 and PBRM1 chromatin remodeling genes.

in line with previous observations
(Chao, Nature. 2012)

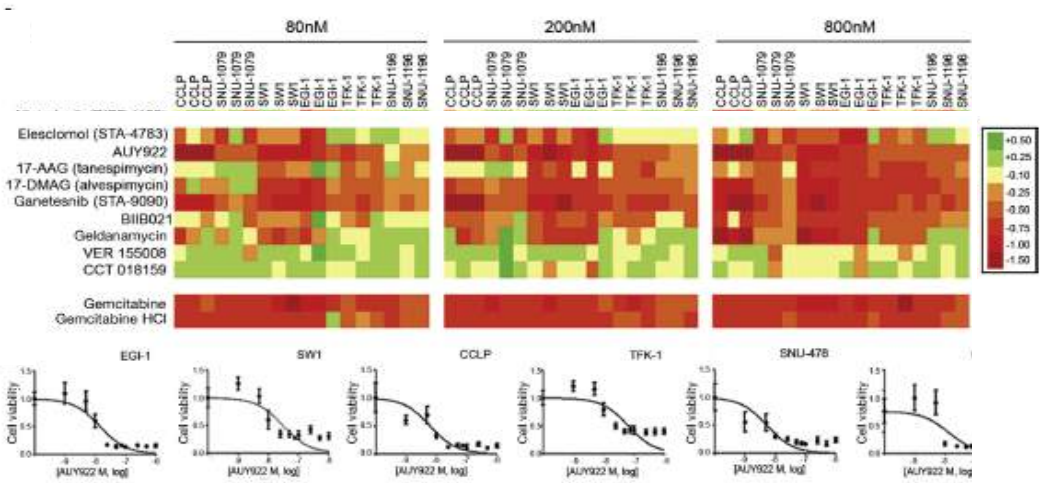
Heat Shock Protein (HSP) 90 inhibitors were effective in all cell lines

HSP-90 inhibition has recently proved effective in CCA preclinical models
(Shirota, Mol Cancer Ther. 2015)

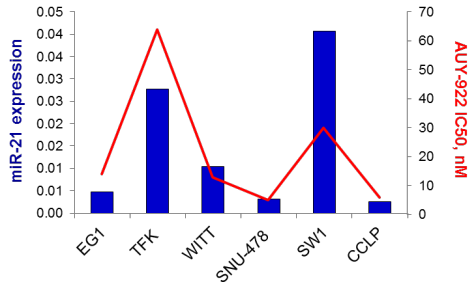
Lampis, Gastroenterology 2018

HSP90i is effective and its activity is increased by lack of MIR21 expression in human CCA cells

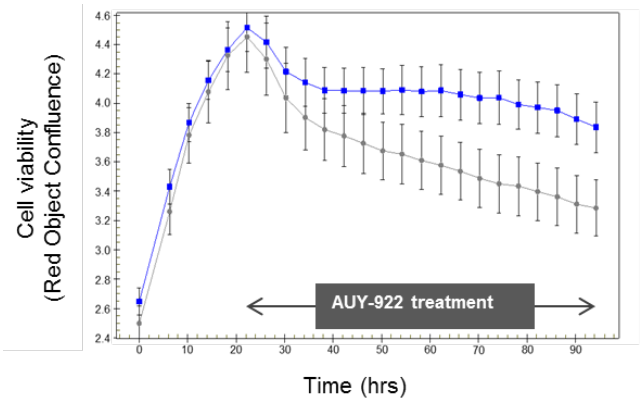
Highthroughput screening of small molecule compounds (n=500) identifies HSP90-i as effective drugs in human CCA cell lines



Response to HSP90-i is inversely related to MIR21 expression



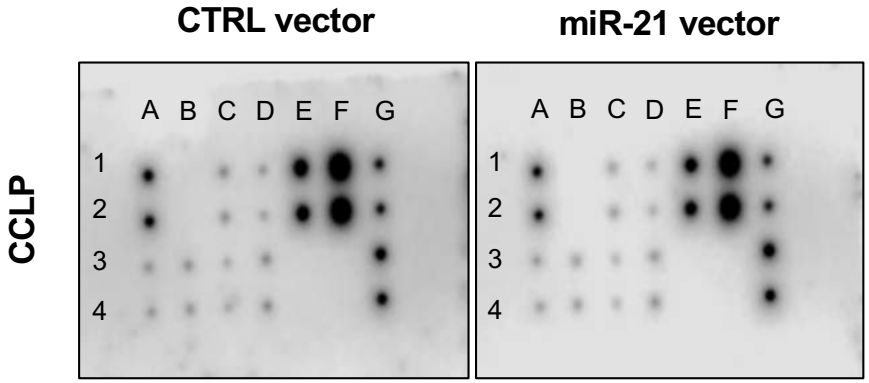
MIR21 inhibition increases sensitivity to HSP90-i



Lampis, Gastroenterology 2018

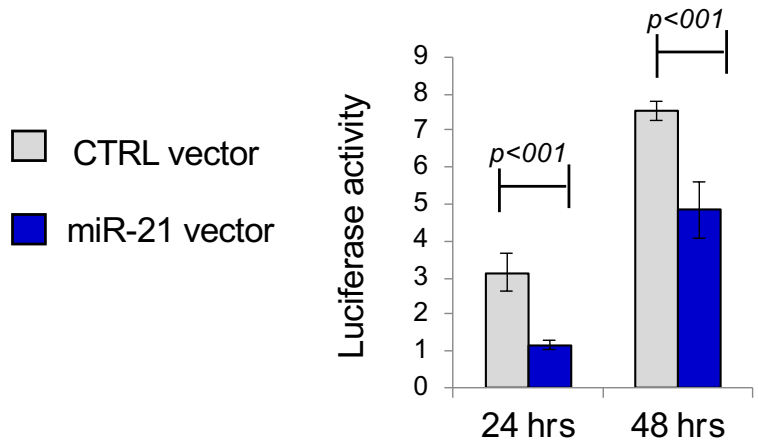
miR-21 can target DNAJ5B mRNA

HSP protein array in CCLP cells over-expressing miR-21

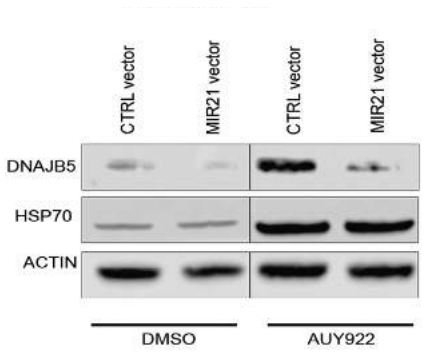


Each antibody is spotted in duplicate	A	B	C	D	E	F	G
1, 2	POS	NEG	HSP27	HSP32	HSP40	HSP60	HSP70
3, 4	HSP90	GRP75	Ubiquitin+1	HSP10	NEG	NEG	POS

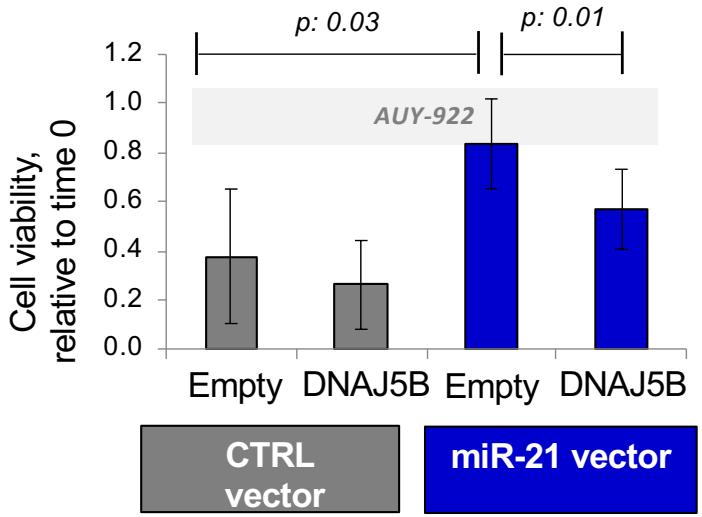
Luciferase assay confirms direct binding between miR-21 and DNAJ5B 3'UTR



DNAJ5B protein expression reduces after miR-21 expression

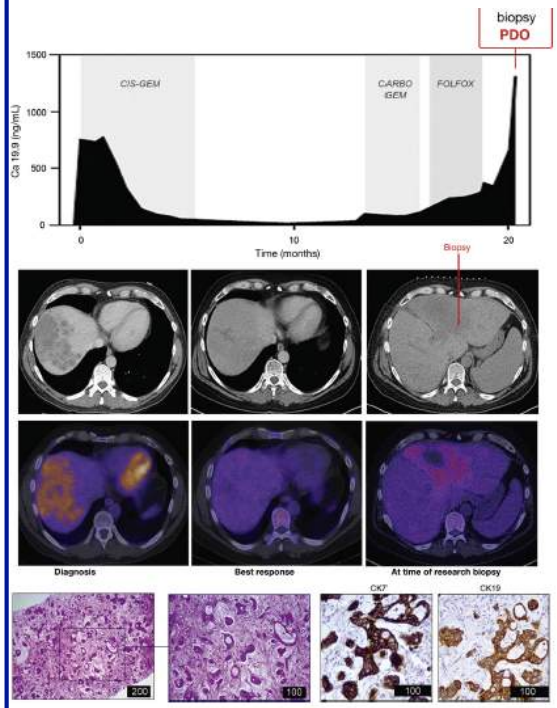


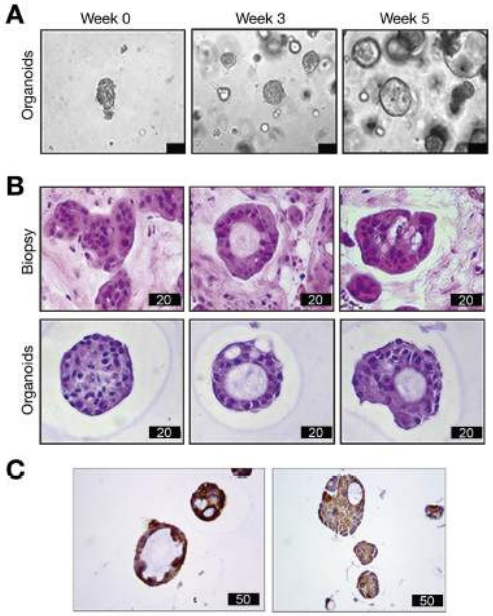
Co-transfection of miR-21 and DNAJ5B rescues biological effect



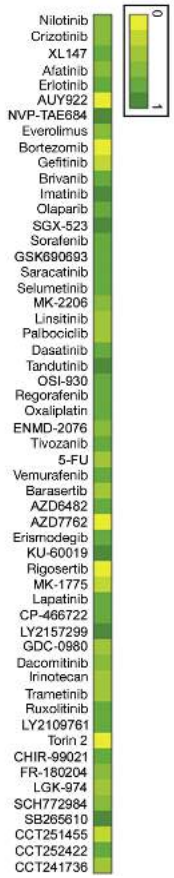
MIR21-dependent HSP90i activity has been confirmed in patient's derived preclinical models

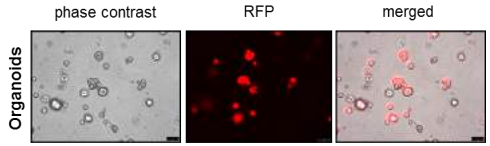
Patients derived organoids were established from chemo-refractory CCA patients

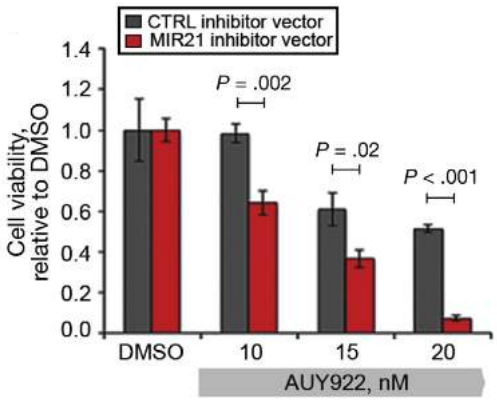




HSP90-i remains effective in CCA organoids, but its activity was significantly increased by MIR21 silencing





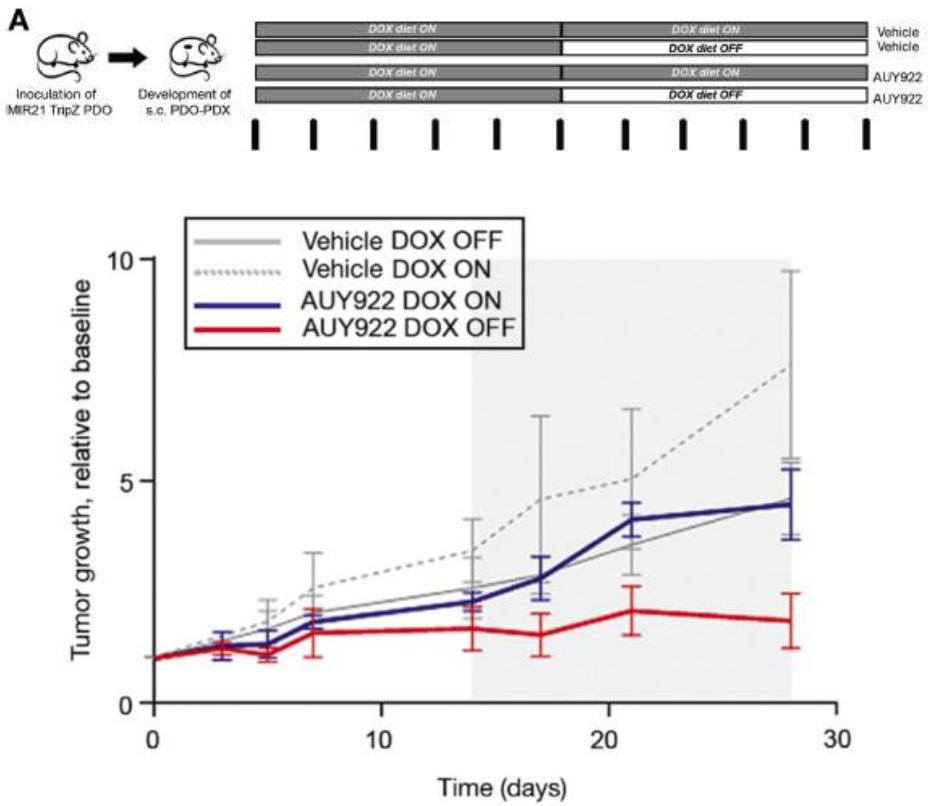


Lampis, Gastroenterology 2018

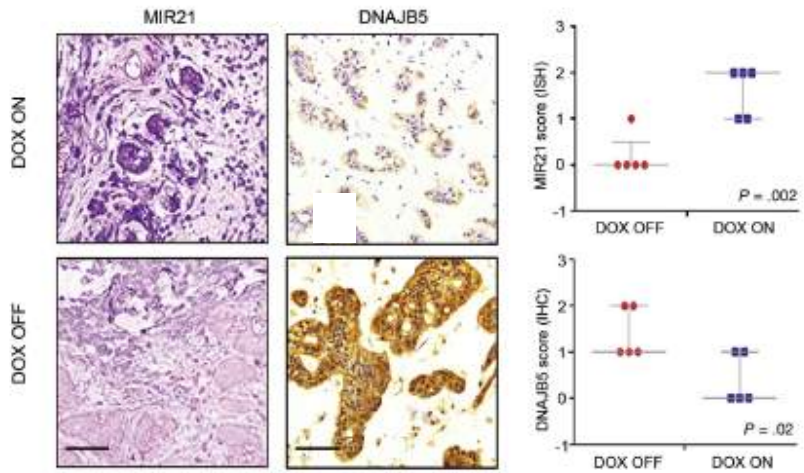
Modulation of MIR21 in vivo controls HSP90i efficacy

PDO-derived PDX confirmed dependence of HSP0-i efficacy on MIR21

MIR21 expression was modulated in a PDO-xenograft with a doxycycline-inducible diet

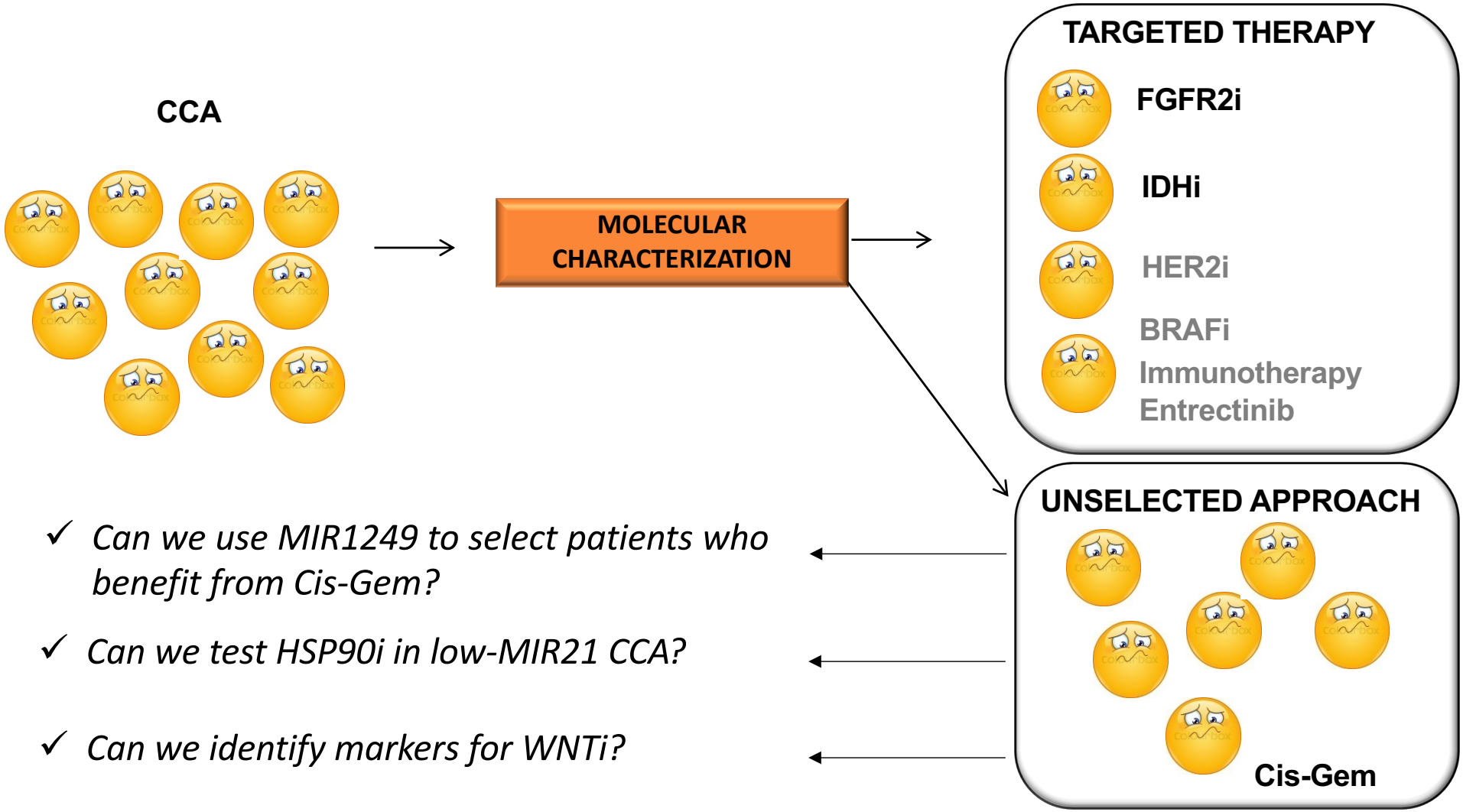


Specificity of MIR21 to the HSP90 pathway was due to the targeting of DNAJB5



Lampis, Gastroenterology 2018

Expanding precision oncology beyond mutational status



- ✓ *Can we use MIR1249 to select patients who benefit from Cis-Gem?*
- ✓ *Can we test HSP90i in low-MIR21 CCA?*
- ✓ *Can we identify markers for WNTi?*

Can ncRNAs be downstream of WNT pathway in liver cancer?

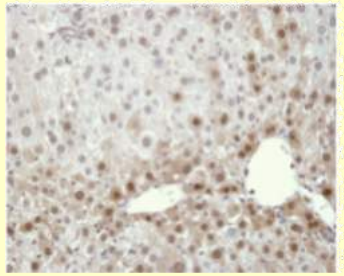
HCC
Apc fl/fl mice

NORMAL LIVER
Apc +/+ mice

$Apc^{fl/fl}$ /Cre

b-catenin in the nuclei

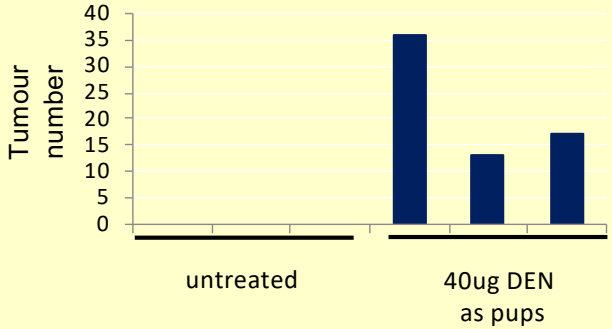
Wnt pathway ↑



Buchert M, PLoS Genetics 10

HCC
DEN treated mice

NORMAL LIVER
untreated mice



Global gene expression profiling

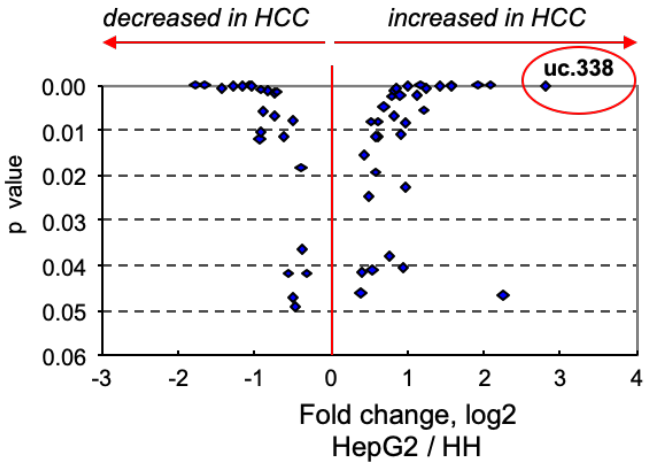
lncRNA

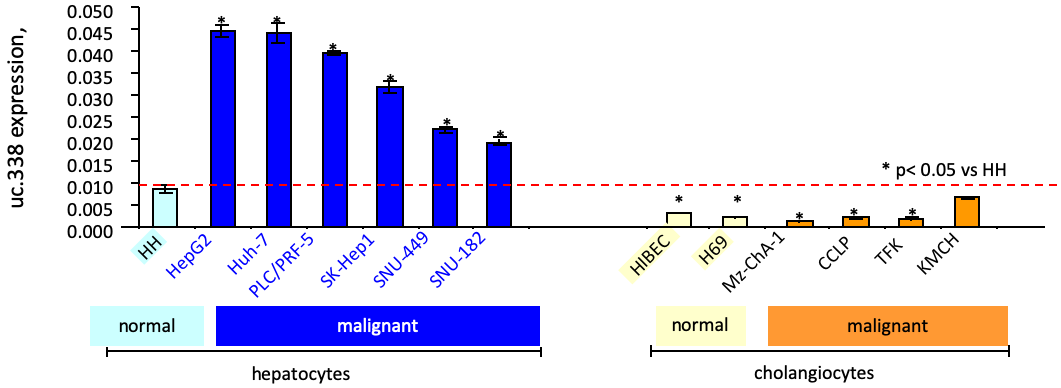
mRNA

miRNA

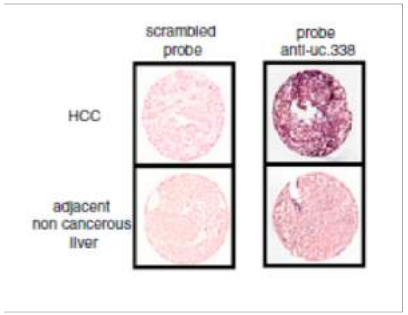
Transcribed-Ultraconserved Regions (T-UCR):
long non-coding RNAs conserved across species

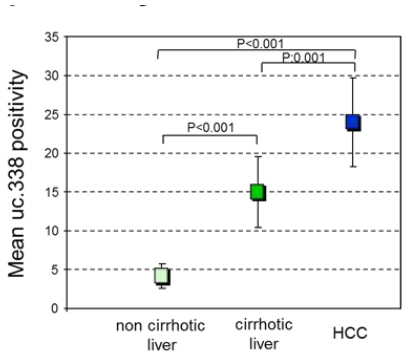
T-UCR are aberrantly deregulated in liver cancer cells



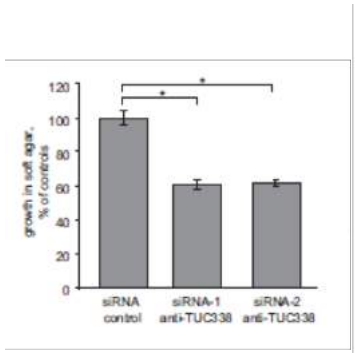


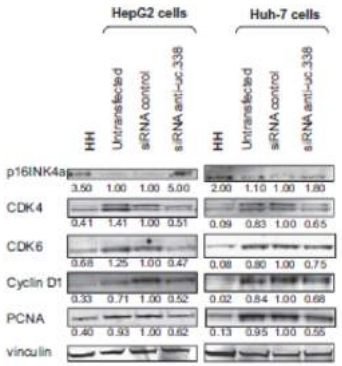
T-UCR deregulation increases with malignant transformation





T-UCR deregulation affects cell growth





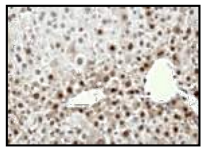
Braconi, & Patel, PNAS 2011

Can T-UCRs be downstream of Wnt pathway?

WNT-dependent liver tumours

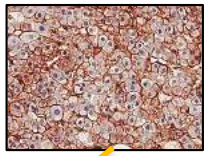
NORMAL LIVER
Apc +/+ mice

HCC
Apc fl/fl mice

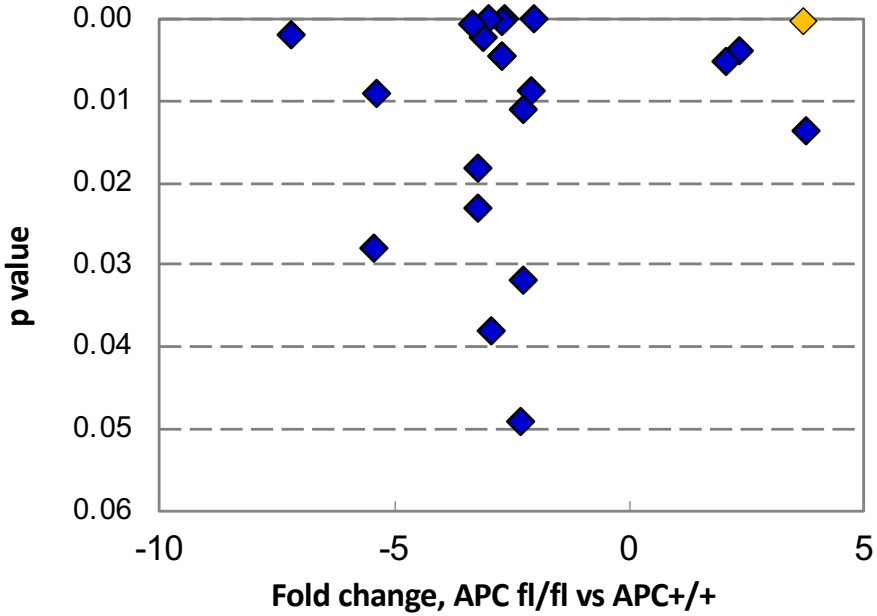


Buchert, PLOS Genet 10

DEN-induced HCC



Profiling T-UCR expression (Arraystar platform)

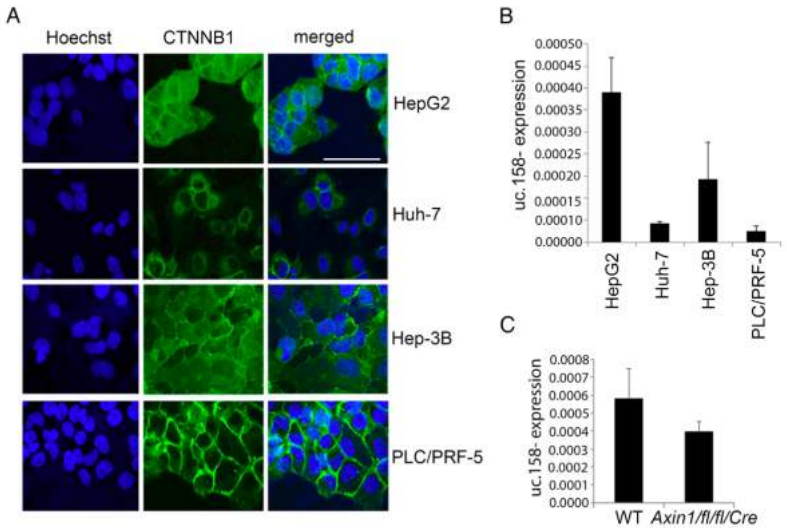


T-UCR	APC fl/fl vs APC +/+	APC fl/fl vs DEN	Genomic location
uc.158 -	3.73	2.21	Intergenic
uc.196+	-2.27	-6.4	Intergenic
uc.82 -	-2.68	-2.62	Intergenic
uc.455 +	-5.43	-3.65	overlap RBM39

Carotenuto, Gut 2016

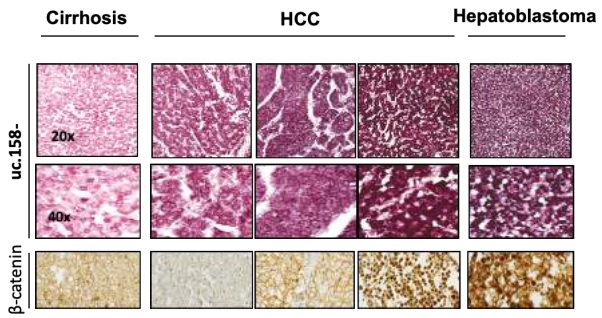
uc.158- expression is specific for β-catenin dependent tumours and modulate cellular growth and invasion

In vitro



In vivo

Swiss cohort

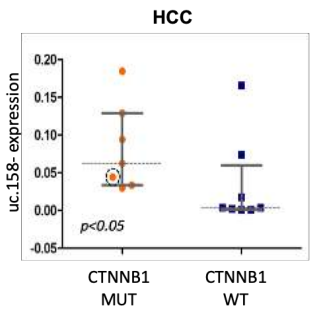


Samples: FFPE tissues

uc.158- detection: RNA In Situ Hybridization

β-catenin detection: Immunohistochemistry

Italian cohort

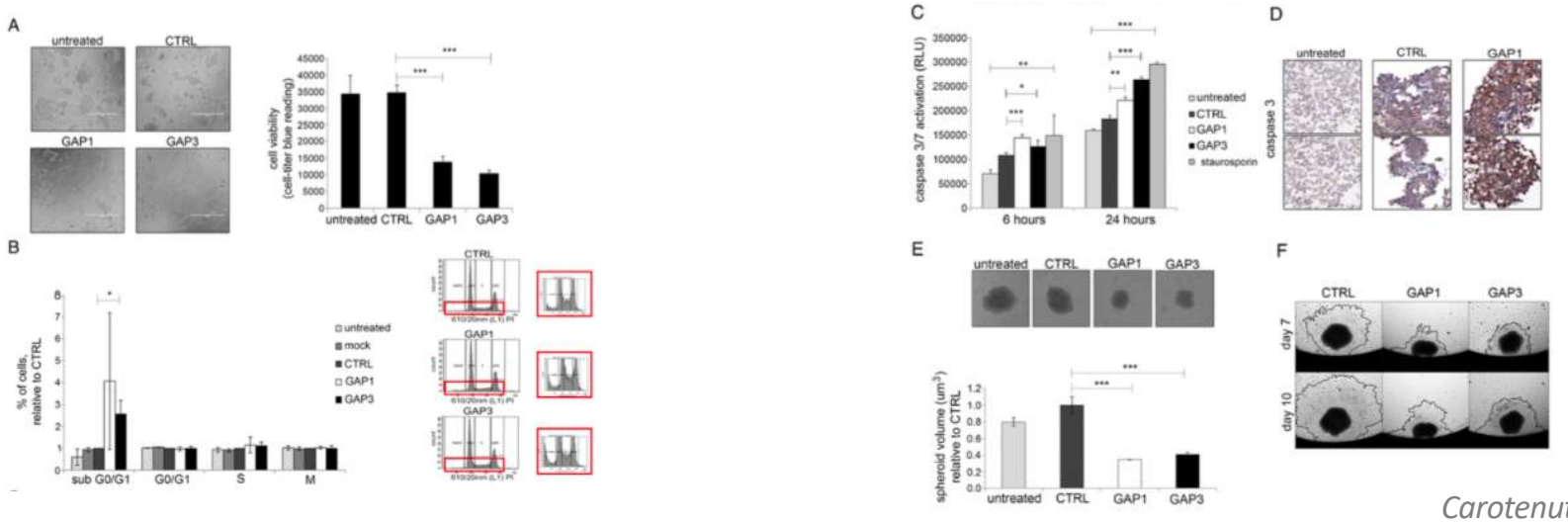


Samples: fresh frozen tissues

uc.158- detection: real time PCR

β-catenin : ex.3 sequencing

Biological Effects

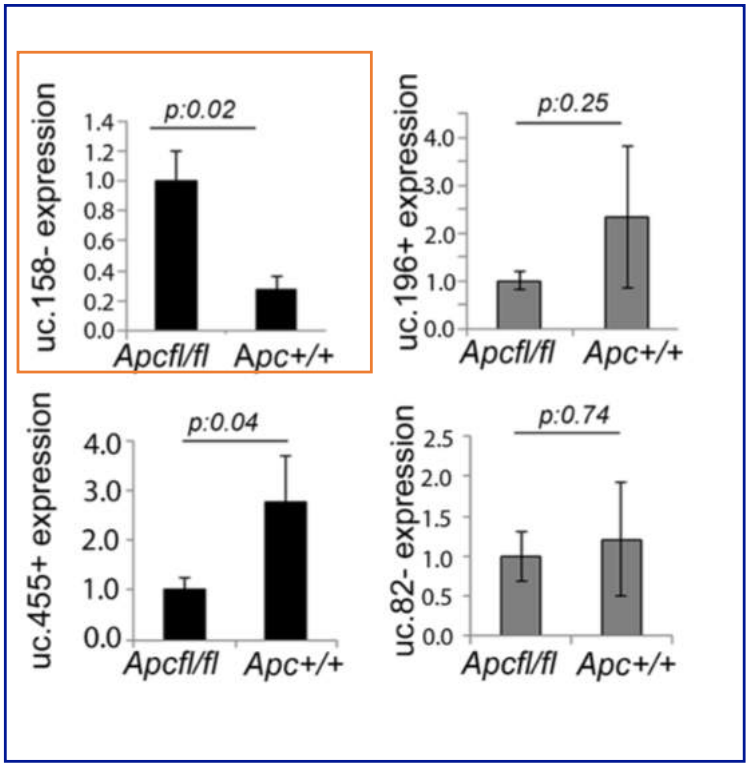


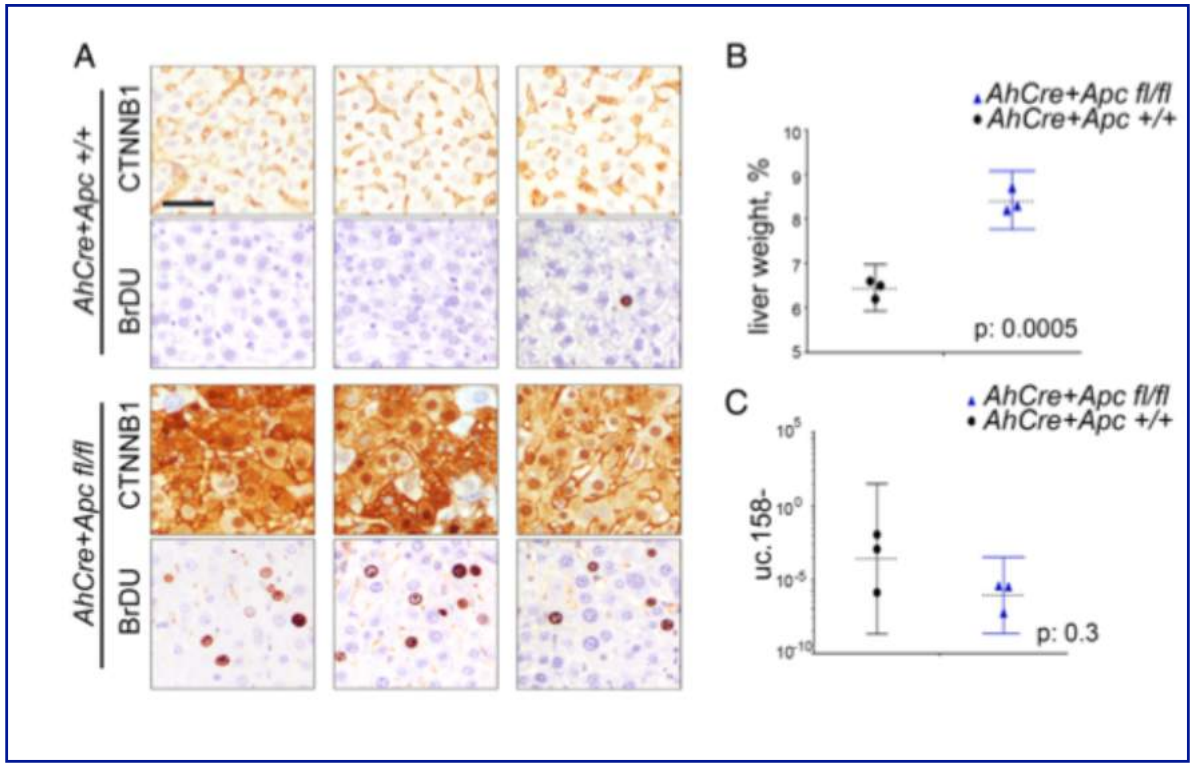
Carotenuto, Gut 2016

uc.158- was induced only in WNT-dependent malignant transformation

uc.158- was increased in WNT-dependent liver cancer

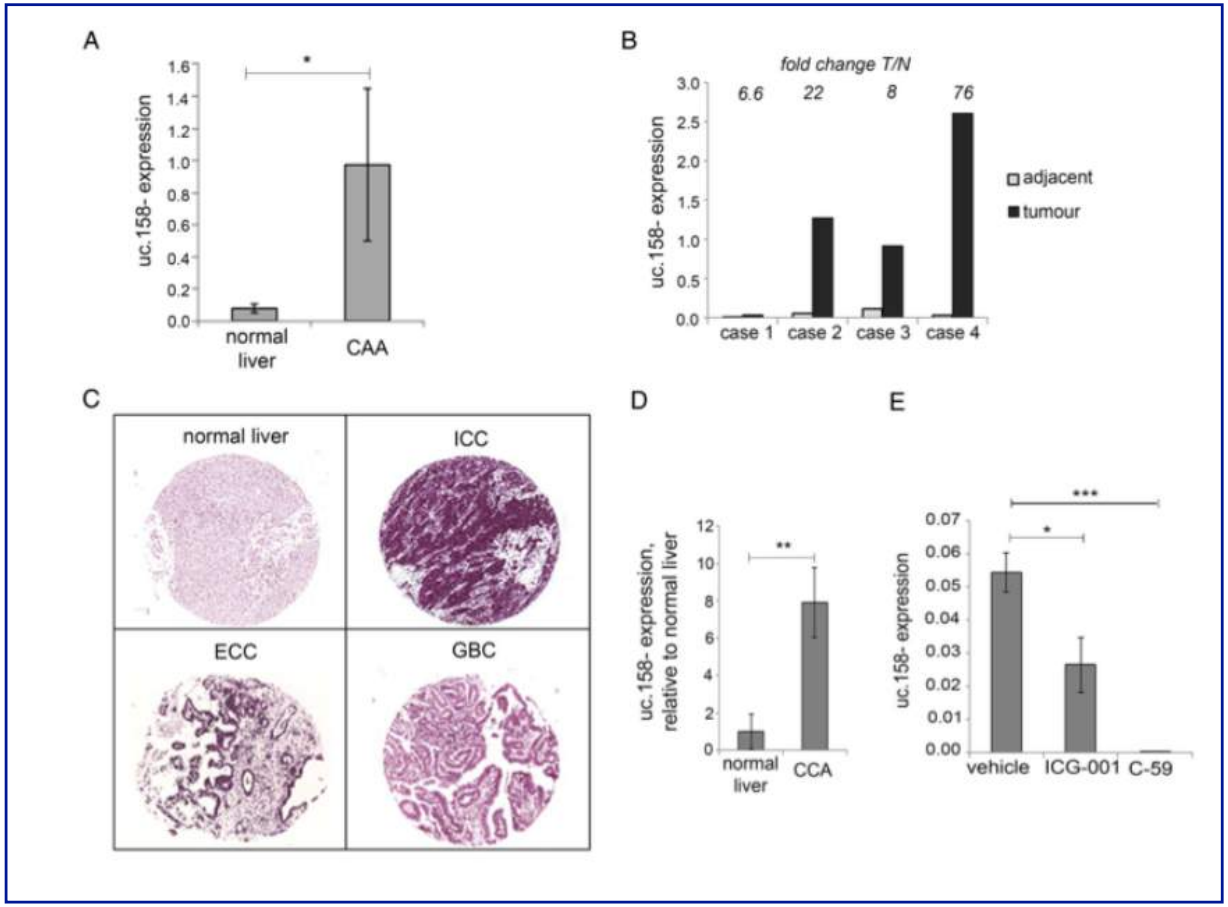
uc.158- does not change in WNT-dependent liver cell proliferation





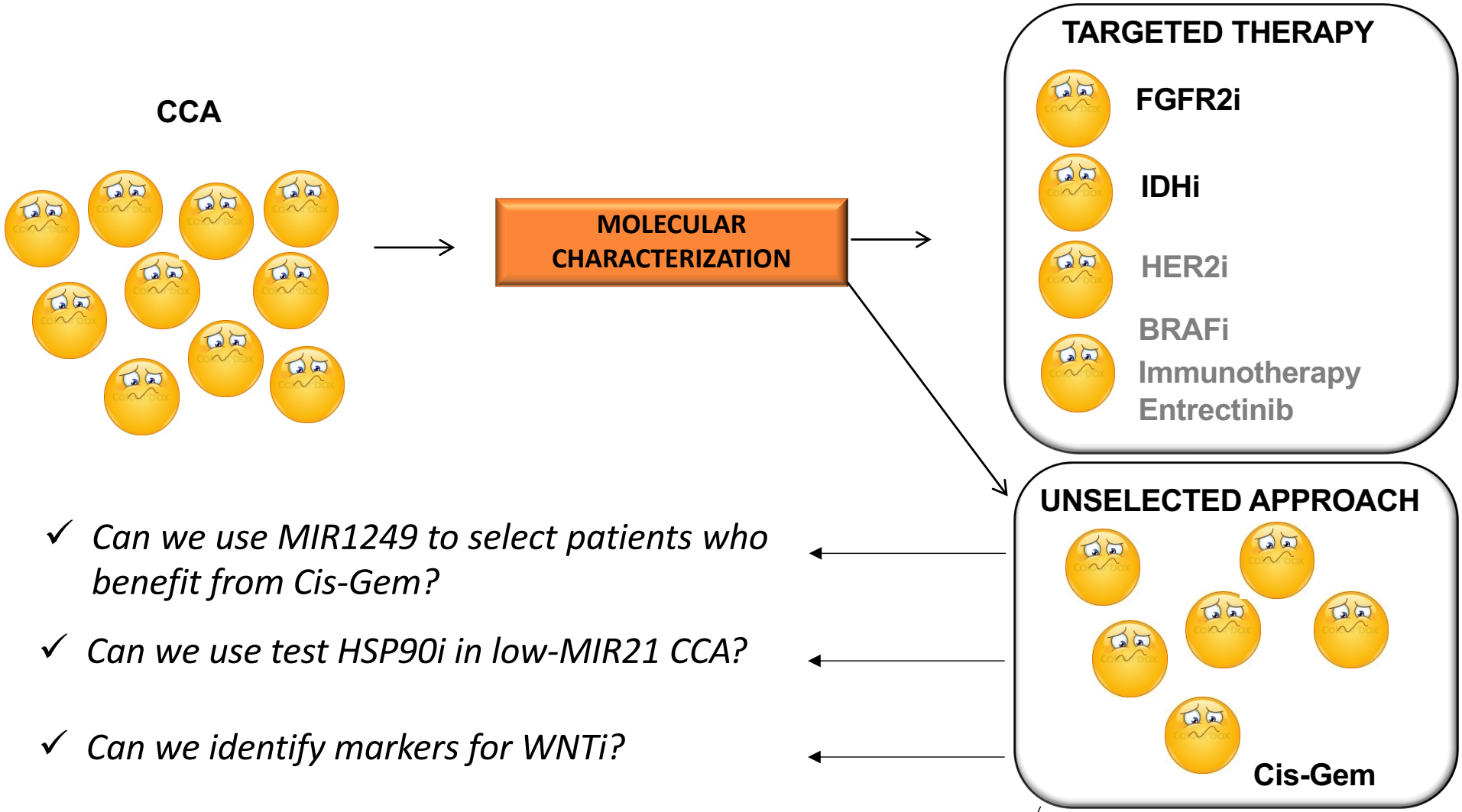
Carotenuto, Gut 2016

uc.158- is upregulated in iCCA



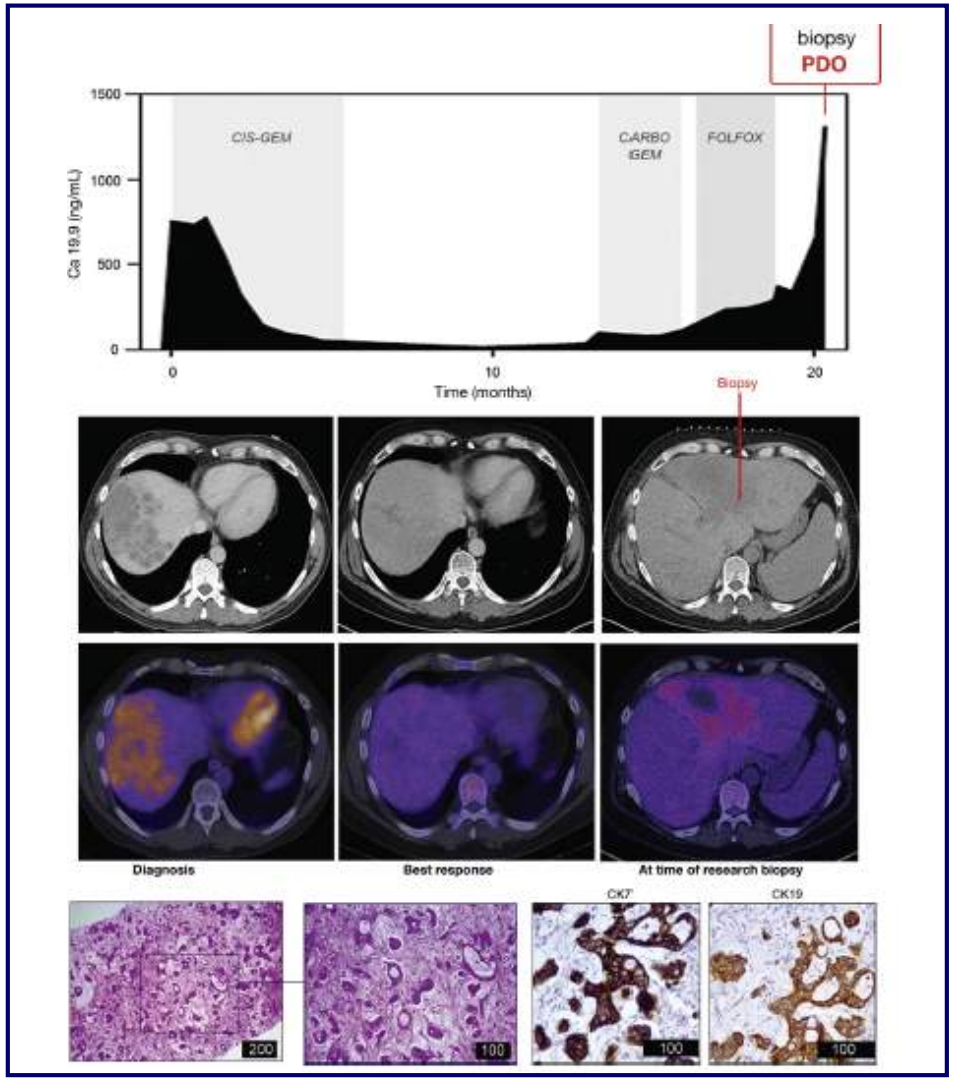
Carotenuto, Gut 2016

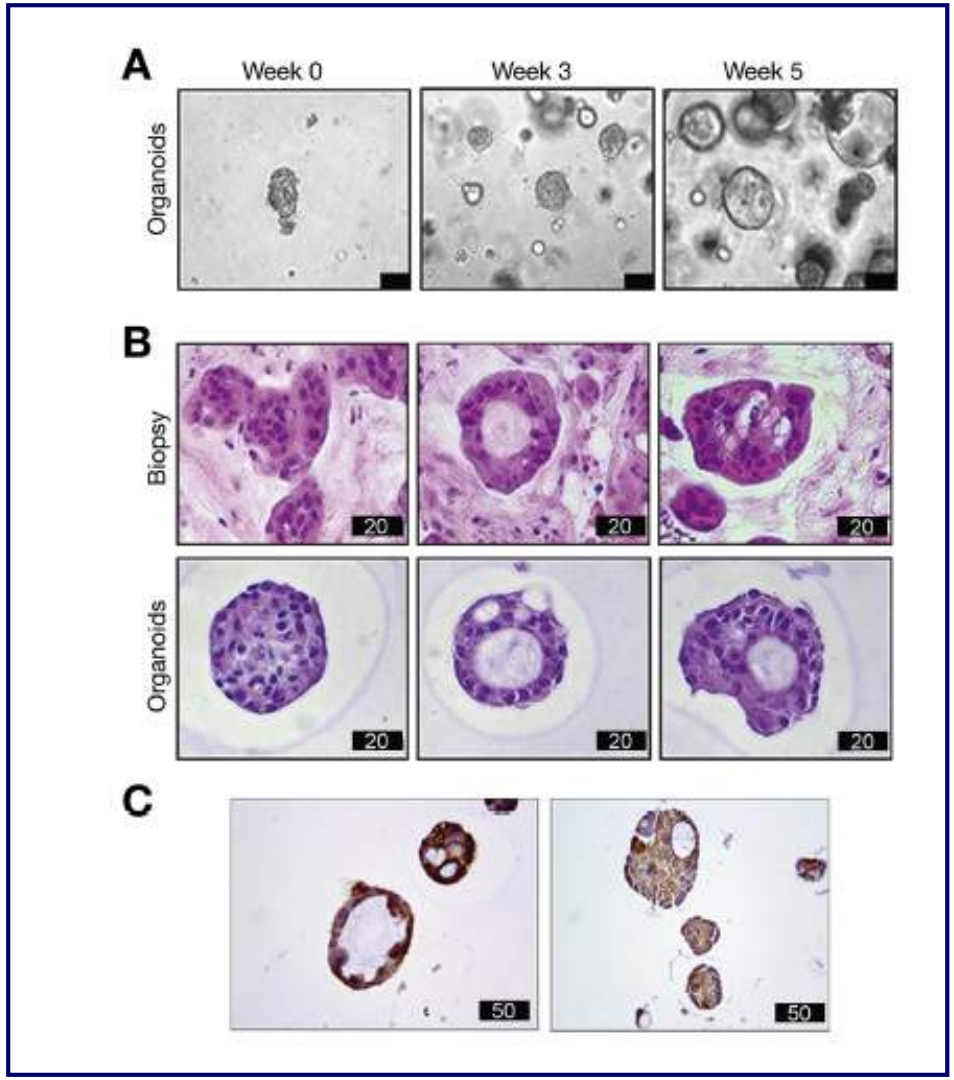
Expanding precision oncology beyond mutational status



- ✓ *Can we use MIR1249 to select patients who benefit from Cis-Gem?*
- ✓ *Can we use test HSP90i in low-MIR21 CCA?*
- ✓ *Can we identify markers for WNTi?*
- ✓ *Can we individualize treatment with a patient-specific model?*

Advanced CCA PDOs recapitulate pathological phenotype of source tissue



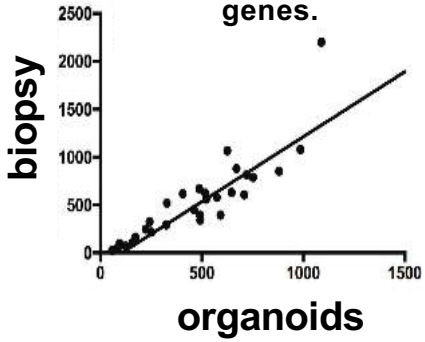


Lampis, Gastroenterology 2018

Advanced CCA PDOs recapitulate genomic landscape of source tissue

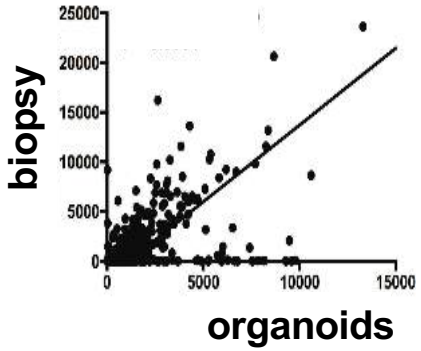
TRANSCRIPTOMIC (nanostring analysis)

Only house-keeping genes.



r: 0.91 [0.82-0.96]
p<0.0001

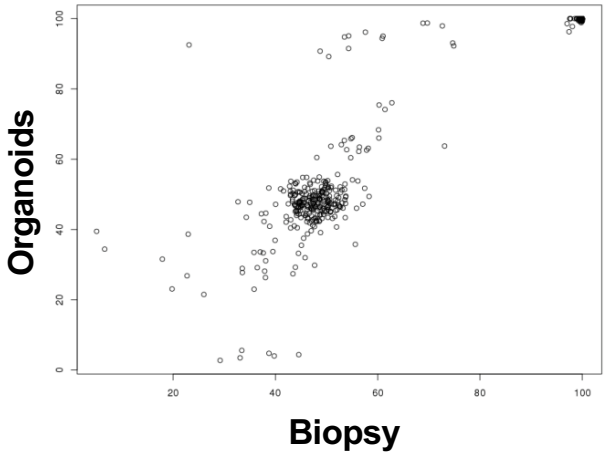
All genes



r: 0.61 [0.56-0.65]
p<0.0001

GENETIC (NGS)

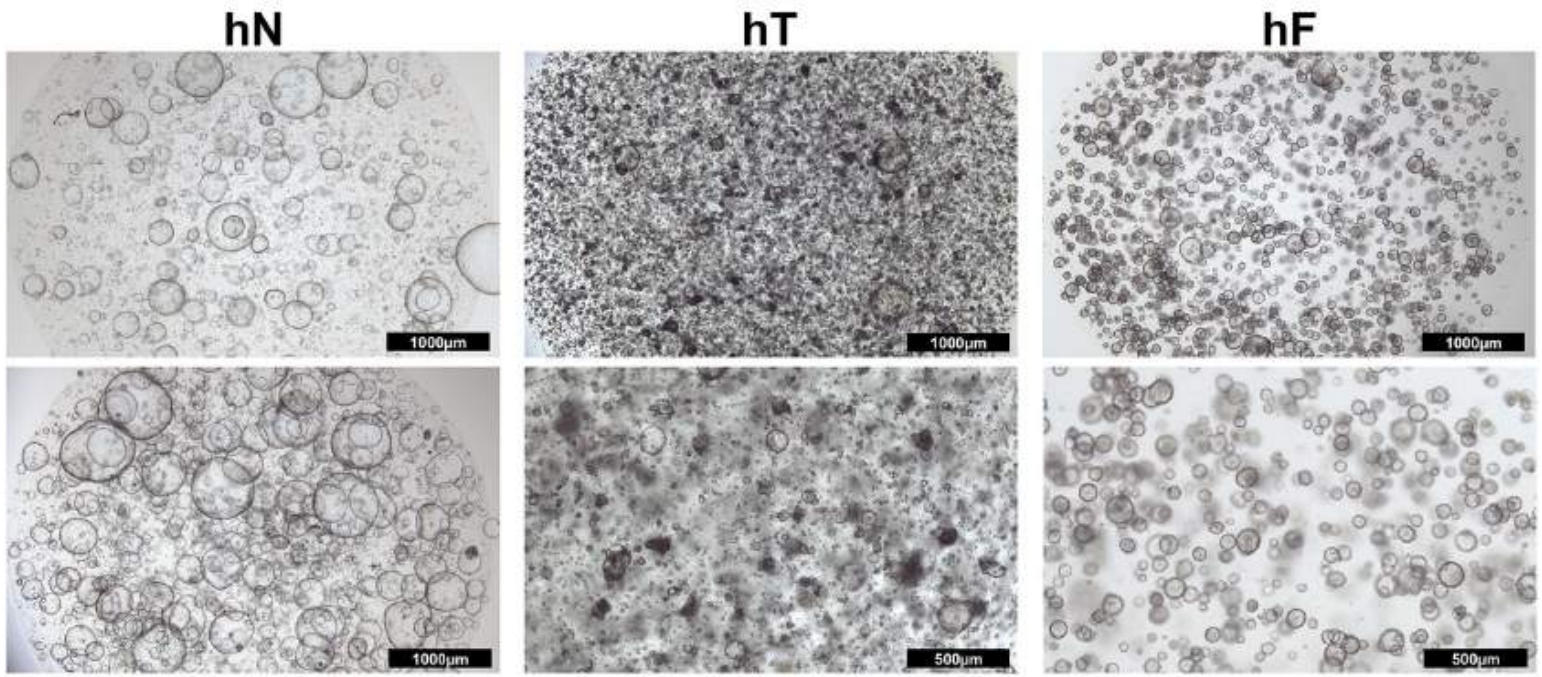
Variant Read Frequency



r: 0.94
p < 0.00001)

Lampis, Gastroenterology 2018

PDO can be derived from pancreatic cancer (resection and EUS-FNB)

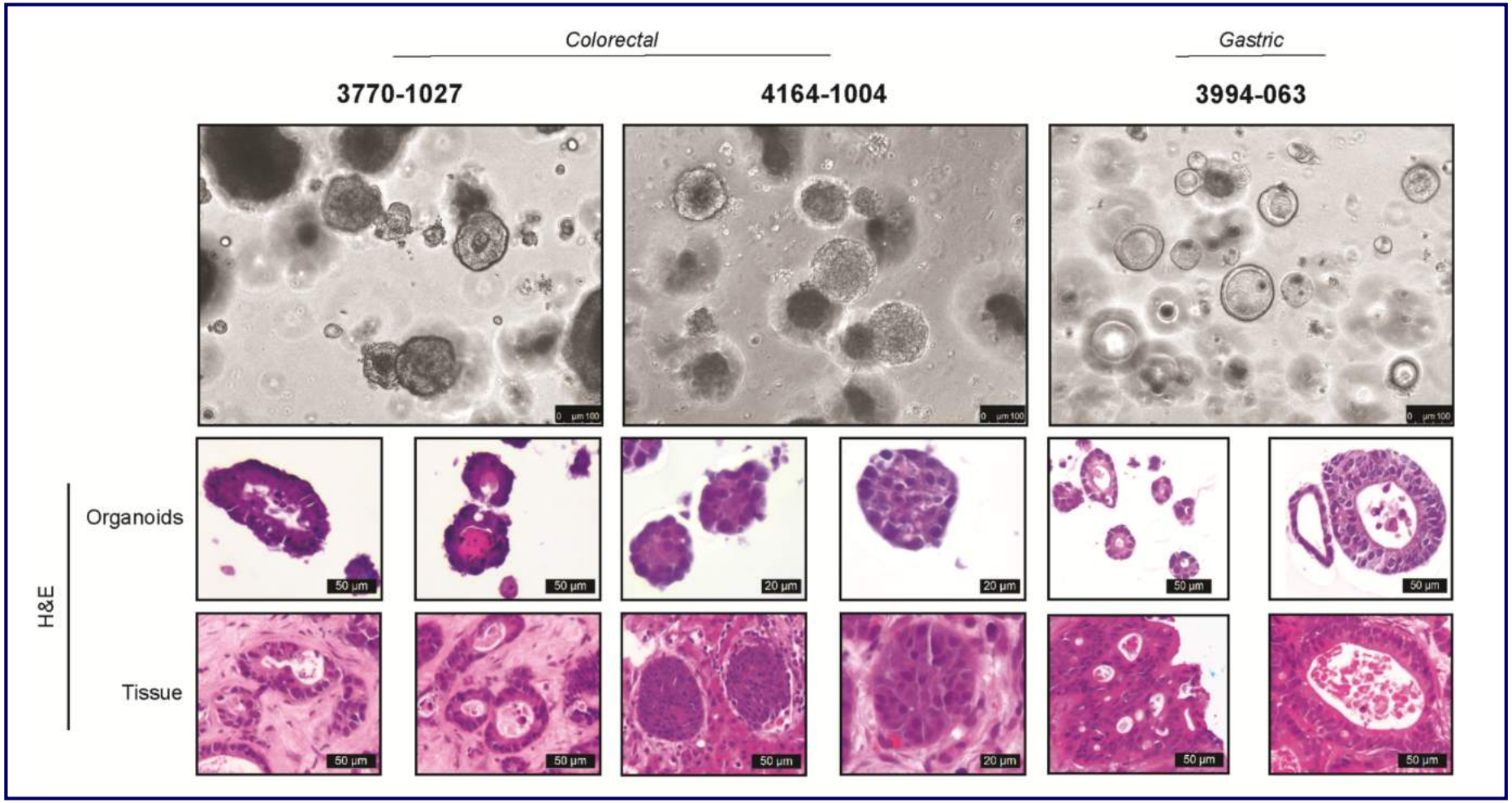


Surgical specimen:	**78%**
FNB:	**72%**

Tiriac, Cancer Discovery 2018

PDOs establishment can be escalated into the generation of a biobank

Efficiency rate of PDO establishment: 70% in the clinical setting

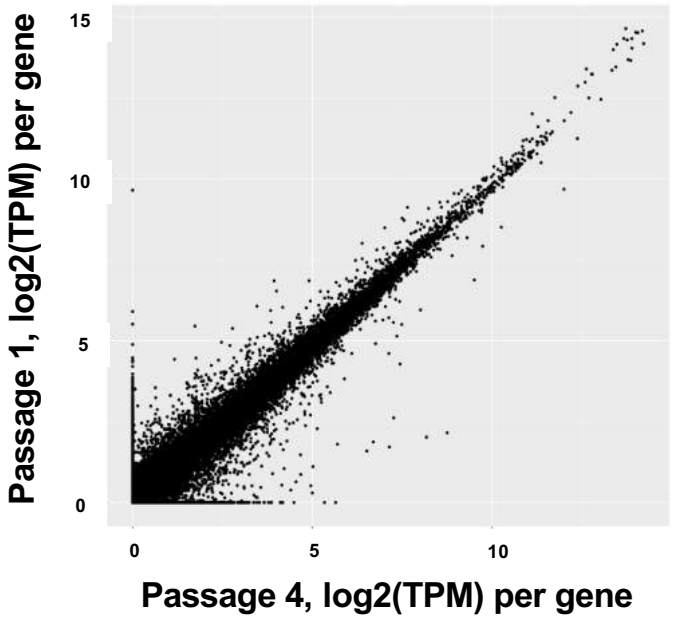


Vlachogiannis, Science 2018

PDOs maintain the phenotype over time

RNA-seq

Advanced CCA PDO

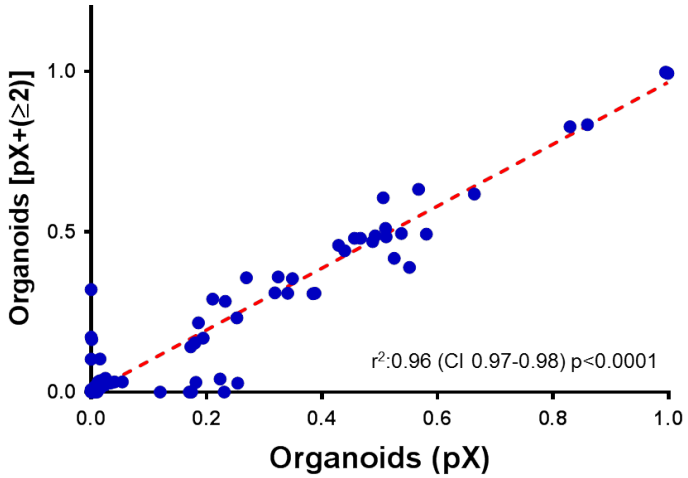


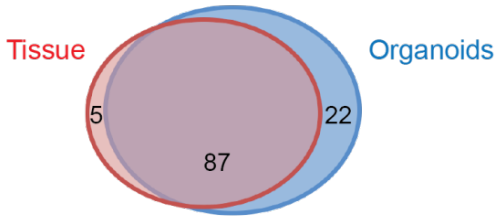
Pearson correlation is 0.9
p-value < 2.2e-16).

In collaboration with J. Andersen

Mutational profile

Bio-bank of advanced GI cancers

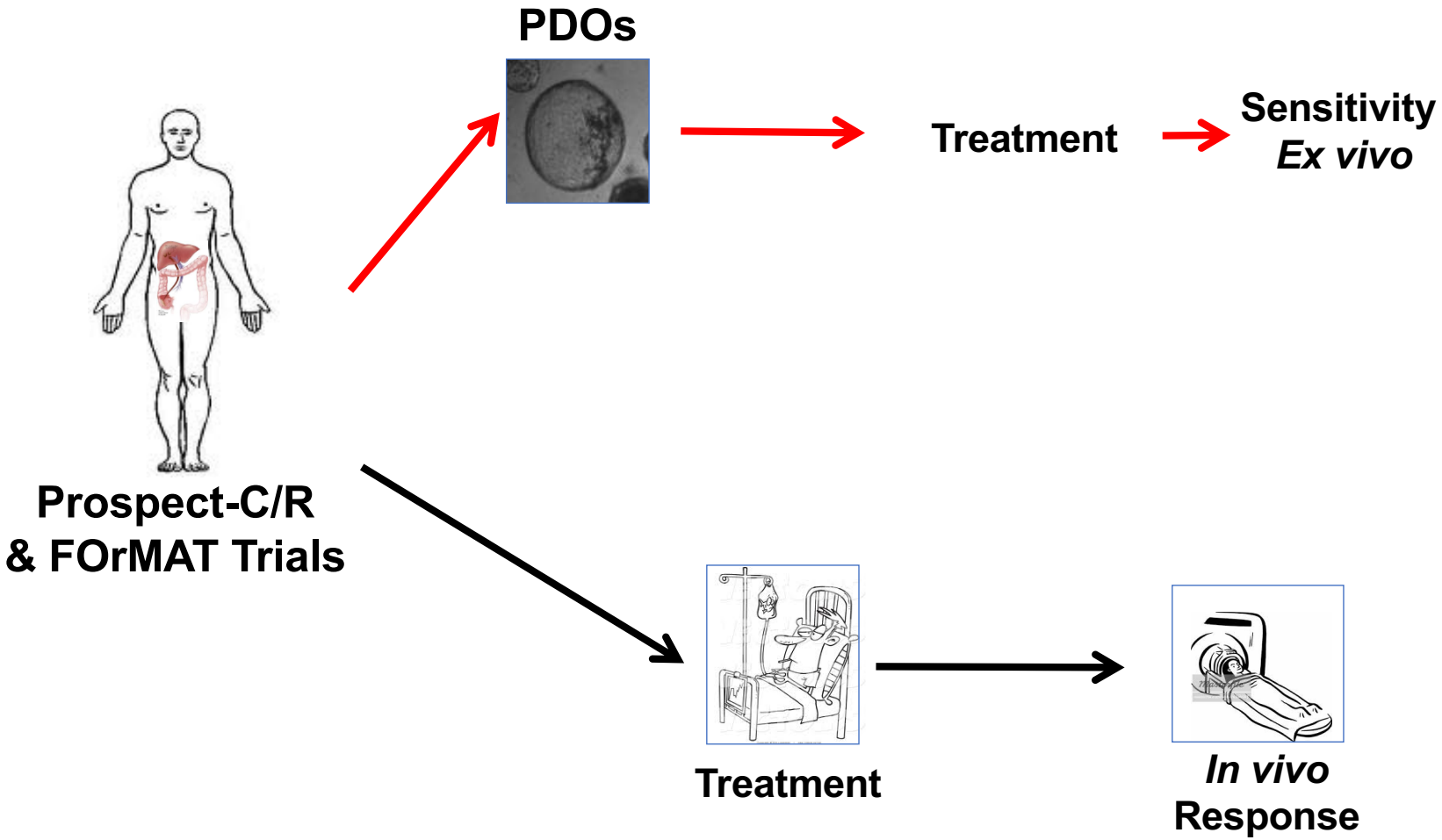




Vlachogiannis, Science 2018

PDOs can be used for "live" drug screening

Our co-clinical trial experience

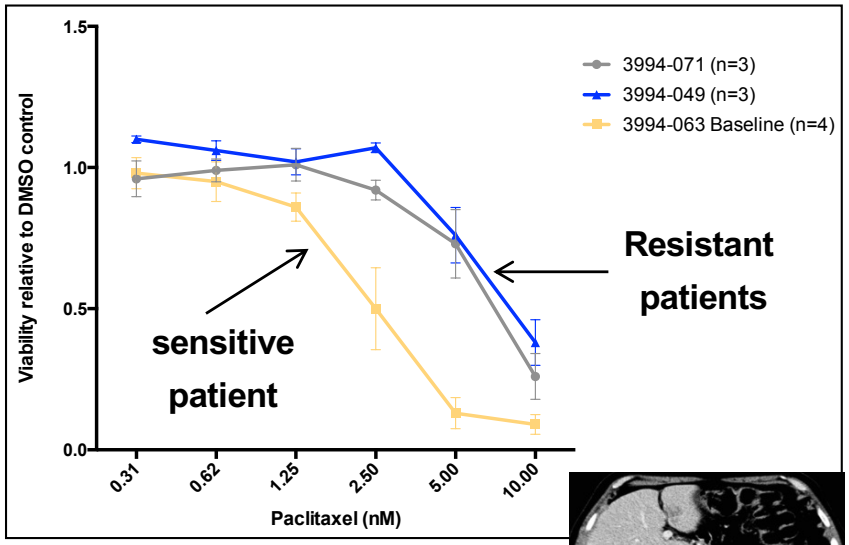


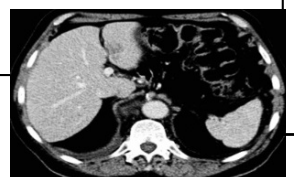
PDOs can be used for "live" drug screening

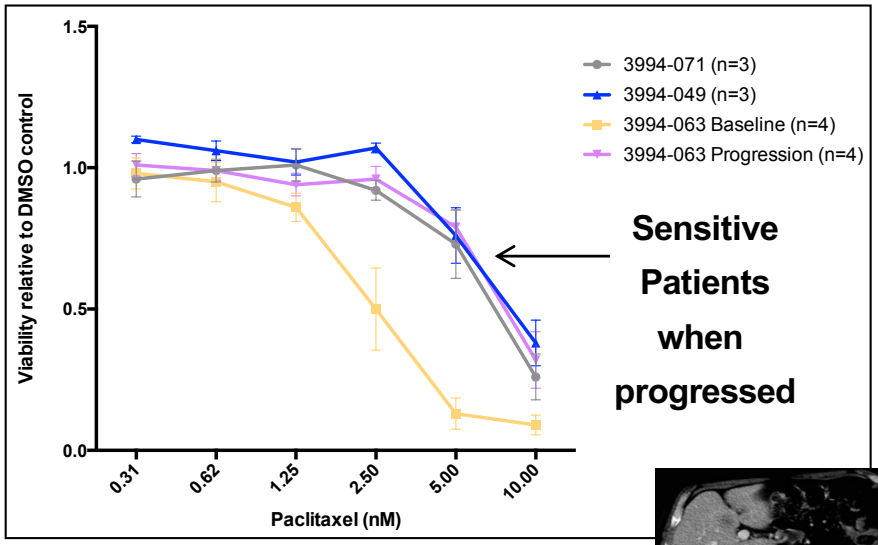
PDOs mimic response in the clinic

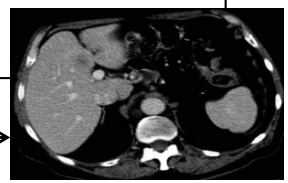
CHEMOTHERAPY

- Three metastatic gastric cancer FOrMAT patients:
  - 3994-049 (Paclitaxel Resistant)
  - 3994-071 (Paclitaxel Resistant)
  - 3994-063 (Paclitaxel Sensitive)



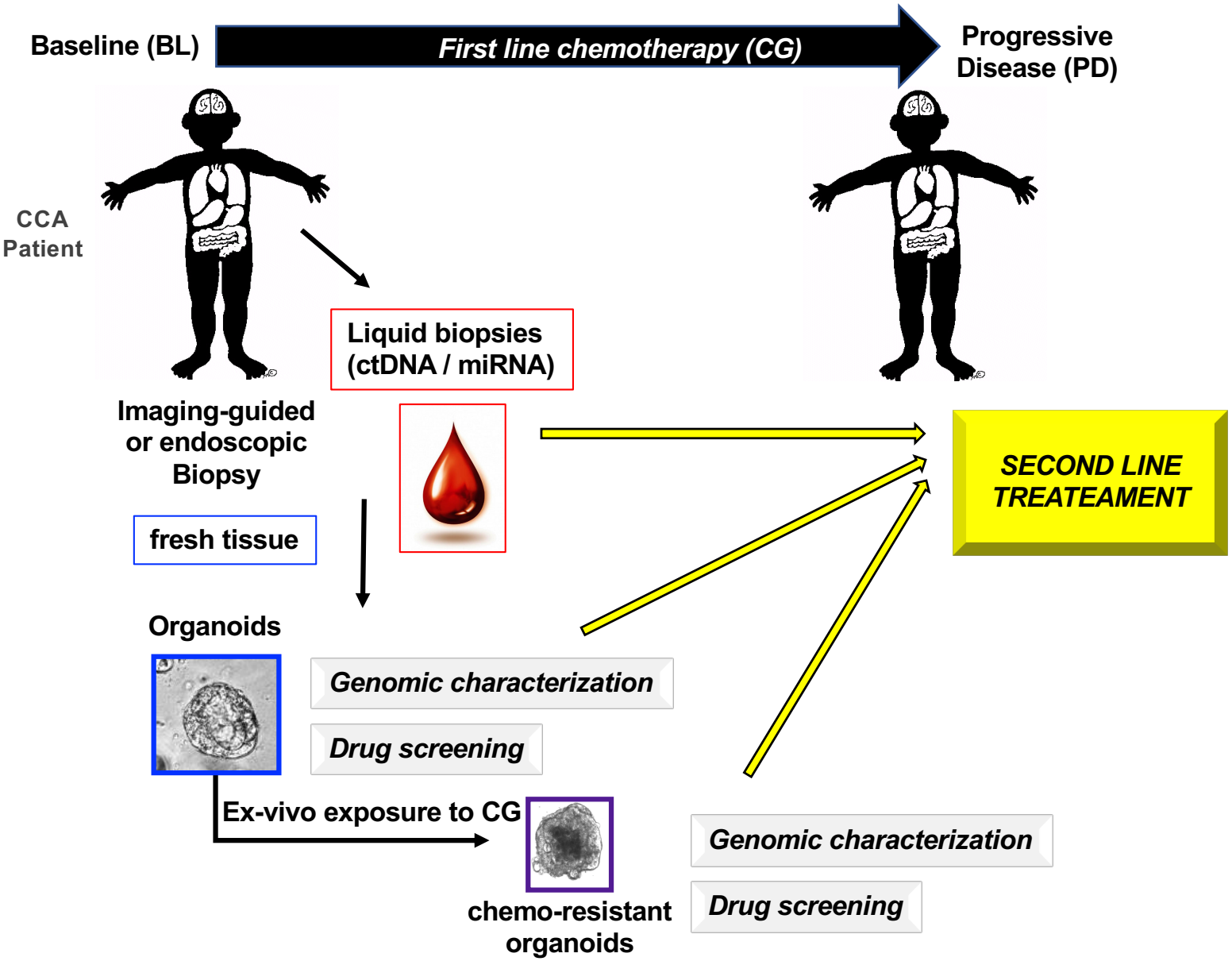






Vlachogiannis, Science 2018

A true pathway to have science at patients' service



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University of Glasgow

LKAS
stands for
Lord Kelvin Adam Smith
Abbreviations.com

European Commission

NHS
National Institute for Health Research

PANCREATIC CANCER UK

pancreatic cancer action

Post-doc position available in the team

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