THE YOUPPIE LECTURE

YOUng Pancreatologist
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Pharmacogenetics to improve new therapeutic approaches in pancreatic cancer

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Incipit


АННА КАРЕНИНА

РОМАНЪ

ГРАФА

Л. Н. ТОЛСТАГО

ВЪ ВОСЬМИ ЧАСТЯХЪ

ТОМЪ ПЕРВЫЙ

МОСКВА.
1878.

“All happy families are alike; each unhappy family is unhappy in it’s own way”

Anna Karenina – L. Tolstoj

Research questions

1. Why PDAC is such an “unhappy family” ?

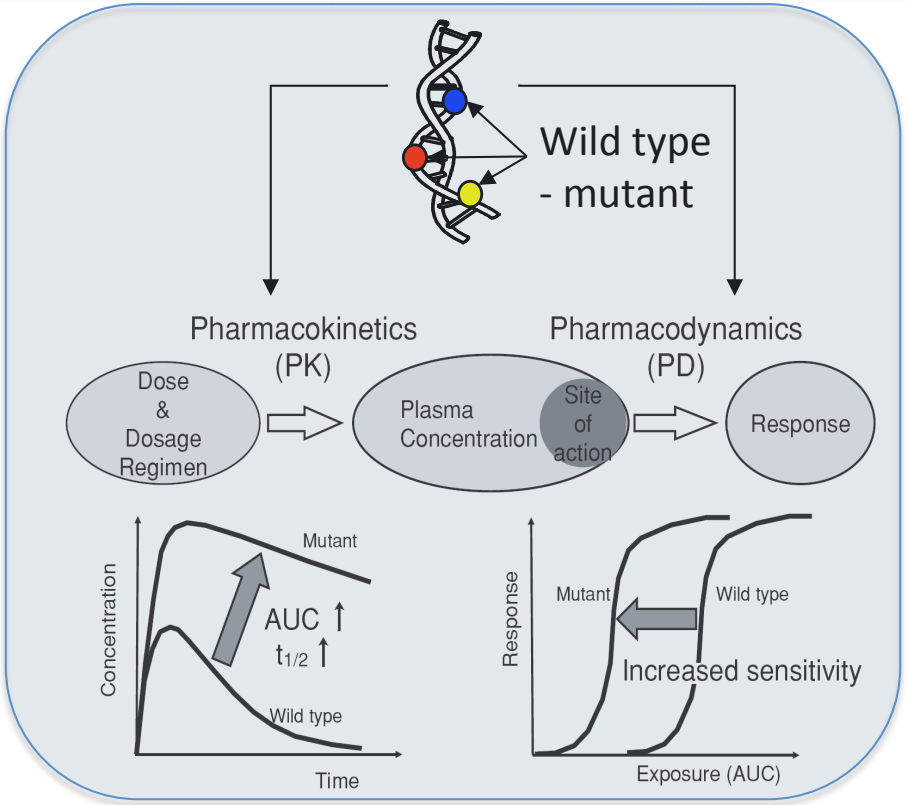
(i.e.: Why it’s so difficult to treat and why haven’t we been more successful ?)

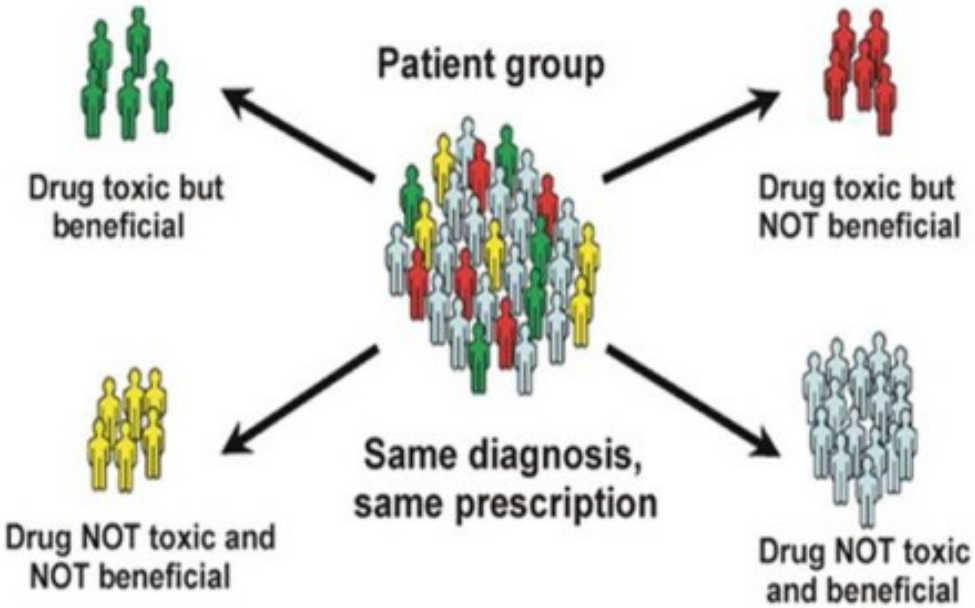
2. How can we discover/use differences among members of this “unhappy family” ?

(i.e.: Is it possible to find biomarkers/novel strategies for maximizing therapeutic efficacy and minimizing useless treatment in PDAC patients ?)

Pharmacogenetics

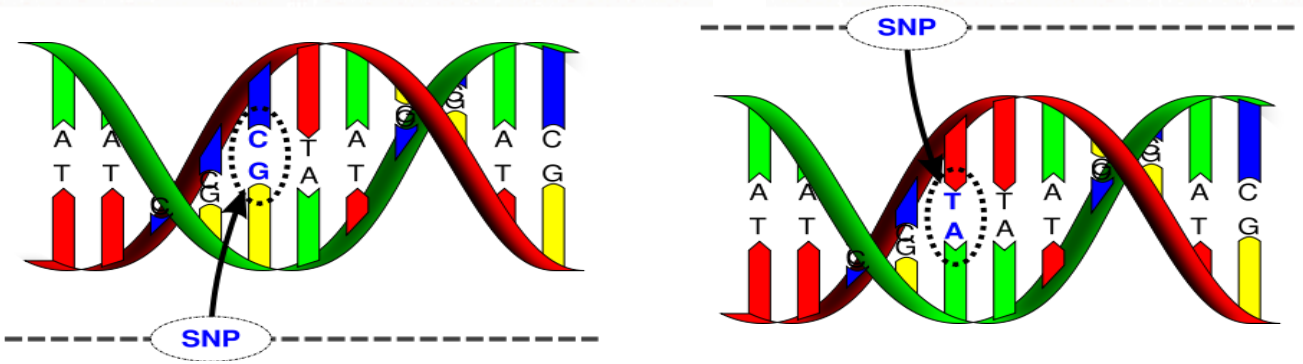
➢**Pharmacogenetics** is the study or clinical testing of **genetic variations** that give rise to **differing drug response**, including disposition, tolerability, and efficacy





➢**Towards personalized medicine**

Pharmacogenetic studies



Single-gene approach

- Analyses the favourite candidate gene
- Requires a large cohort to test the association
- − Carries the risk of not finding an association
- \+ Provides proof of principle if an association is found

Genome-wide approach

- Analyses the whole genome (expression and SNP)
- Requires smaller cohorts to test associations
- − Biological meaning is difficult to assess because this approach carries a risk of false positives
- \+ Might identify new associations

Drug-related phenotype

Candidate-pathway-gene approach

- Analyses several functionally related candidate genes
- Requires a smaller cohort to test the association
- − Carries the risk of missing important genes
- \+ Provides a more biologically meaningful association

Cheok & Evans,
Nat Rev Cancer 2006

Pharmacogenetic studies in pancreatic cancer

Patients	N	Treatment	Polymorphisms	End-point	Significant	References
Potentially resectable	92 / 119	Gemcitabine + radiotherapy (RT)	SNPs in 13 + 6 DNA repair genes,	OS	RecQ1 A159C, RAD54L C157T, XRCC1 R194W, ATM T77C; ATM G60A, CHEK1 G35A	*Li et al, JCO 2006; Okazaki et al, Clin Cancer Res 2008*
All stages	378	Gemcitabine or 5-Fluorouracil (5-FU)+RT	SNPs in 6 + 6 DNA repair genes	OS	RecQ1 A159C, RAD54L C157T, XRCC1 R194W; hOGG1 G2657A, APEX1 D148E, POLB A165G, POLB T2133C	*Li et al, Cancer Res 2006; Li et al, Int J Cancer 2007*
All stages	290	Gemcitabine or 5-FU+RT	SNPs in 3 GST genes	OS	GSTP1*C (in patients treated with 5-fluororacil, N=138)	*Jiao et al, Cancer 2007*
Potentially resectable	88	Gemcitabine or 5-FU+RT	SNPs (12) in 10 cell cycle genes	OS	MDM2 T309G, p16 C580T, p73 5'UTR Ex2 G-to-A & C-to-T	*Chen et al, Ann Surg Oncol 2009*
Potentially resectable	154	Gemcitabine or 5-FU+RT	SNPs in 8 MMR, 7 MDR & 5 glucose metabolism genes	OS	TREX1 EX14-460CT, TP73 Ex2-4GA, EXO1 R354H; MRP5 A-2G, MRP2 G40A; GCK IVS1-C9652T, HK2 N692N	*Dong et al, JCO 2009; Tanaka et al, Dong et al; Cancer 2011*
Potentially resectable	154	Gemcitabine or 5-FU+RT	SNPs (17) in 8 gemcitabine genes	OS	Combined CDA A76C, dCK C-1205T, hENT1 T-549C/C913T	*Okazaki et al, Clin Cancer Res 2010*
Locally advanced	149	Gemcitabine	SNPs (17) in 6 gemcitabine genes	PFS	Combined CDA A76C, RRM1 A33G, C-27A, hENT1 A-210G	*Tanaka et al, Cancer 2010*
Potentially resectable + locally advanced	333 + 373	Gemcitabine or 5-FU+RT	SNPs (41) in 10 IGF-1 genes & SNPs (102) of 13 MMR genes	OS	IGF1R T766T, IGF2R L252V, IFGBP3-202AC, IRS1 4315CG, IRS1 G972R, IRS2 5687TC; , TP73 Ex2-4GA, EXO1 R354H	*Dong et al, Gastroenterology 2010; Dong et al, Oncologist 2011*

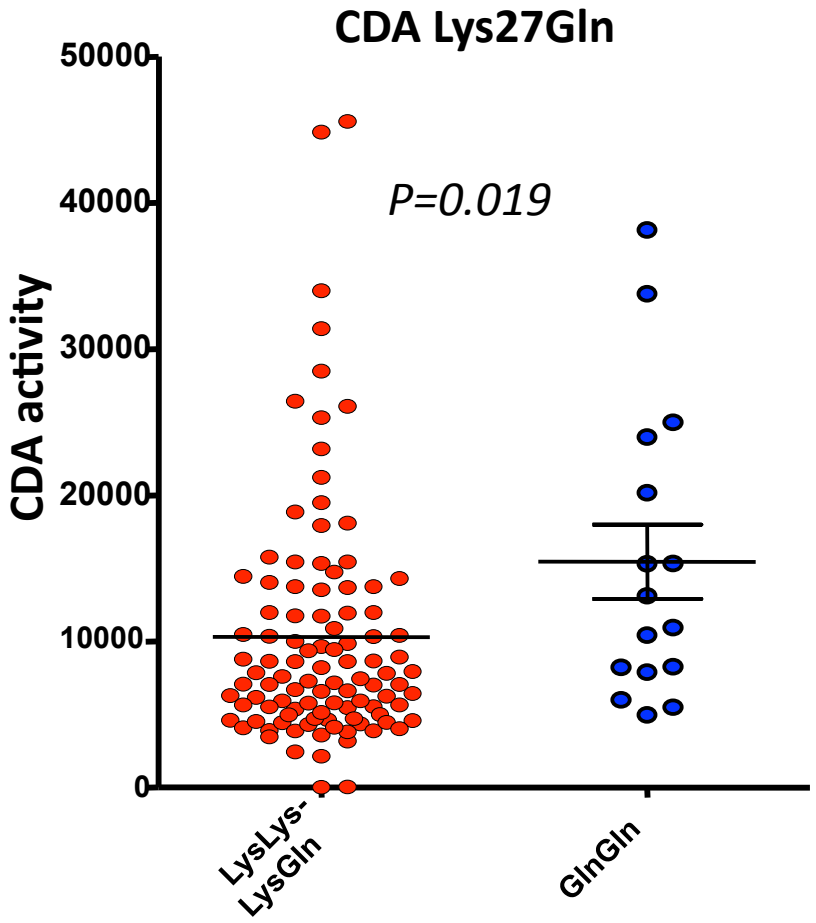
Prospective study

In the RTOG9704 trial, 538 patients were assigned randomly, after surgical resection, to groups that were given either gemcitabine or 5-FU

Genotyping for *CDA Lys27Gln* was performed on 185 cases

	RT+gemcitabine			
	Gln/Gln	*Lys/Gln*	*Lys/Lys*	*Any Lys*
Total number of patients	9	43	35	78
Severe hematological toxicity				
No. of patients	3	26	23	49
Unadjusted OR	RL	0.33	0.26	0.30
Unadjusted *P*-value	—	0.15	0.09	0.10
Adjusted OR*	—	0.17	0.06	0.14
Adjusted *P*-value**	—	0.06	0.01	0.03

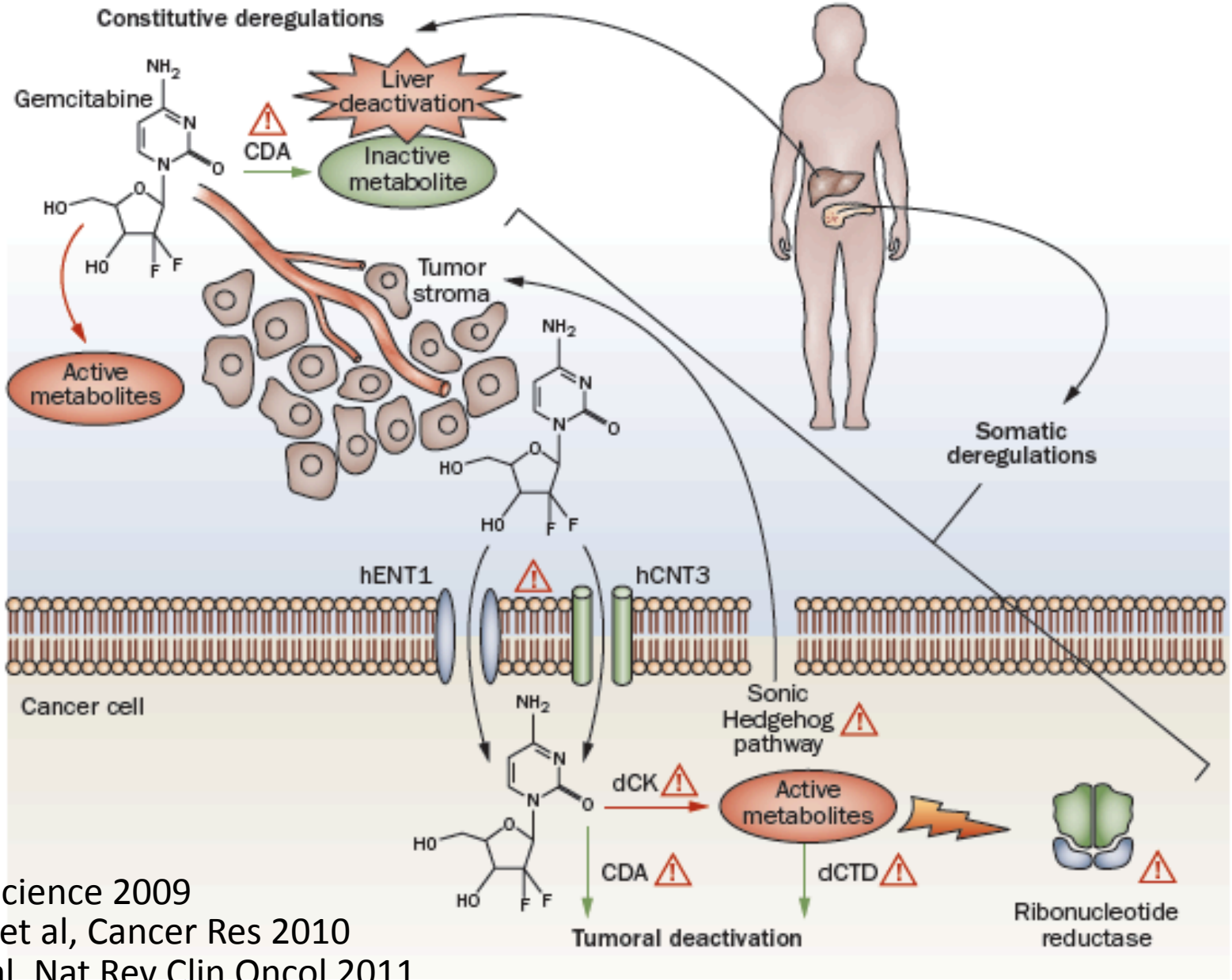
CDA Lys27Lys and *Lys27Gln* were associated with severe hematologic toxicity in the gemcitabine arm (N=87)



Farrell et al, Pharmacogenomics J 2011

Giovannetti et al, Ann Oncol 2011

… more determinants of gemcitabine activity



Olive et al, Science 2009
Giovannetti et al, Cancer Res 2010
Ciccolini et al, Nat Rev Clin Oncol 2011

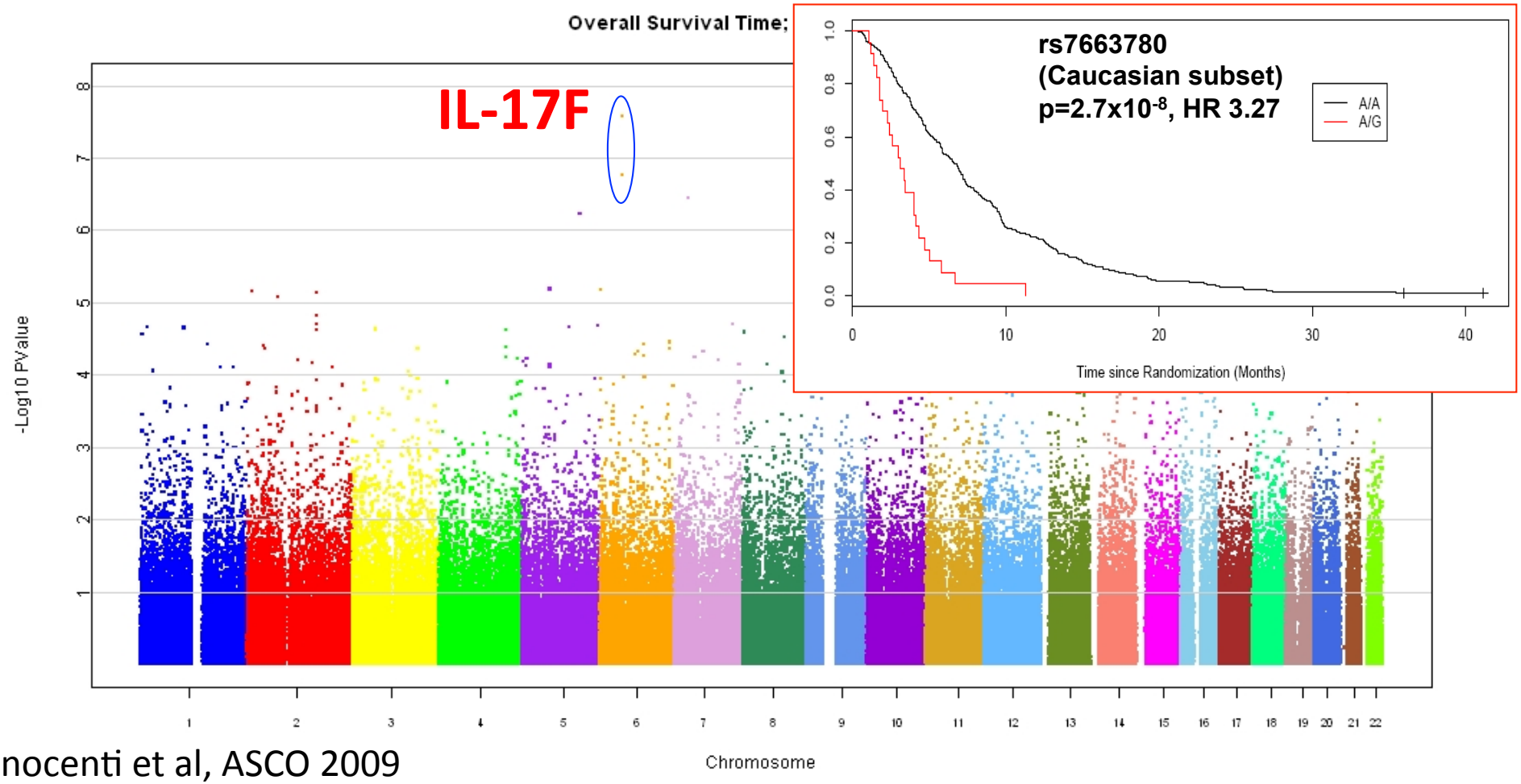
…and other drugs/approaches ?

➢**CALGB-80303 : 294 patients treated with gemcitabine + bevacizumab**

Kindler et al, J Clin Oncol 2010

➢**Genome-wide association study (GWAS)**

for 550,000 germline SNPs (Illumina 550)

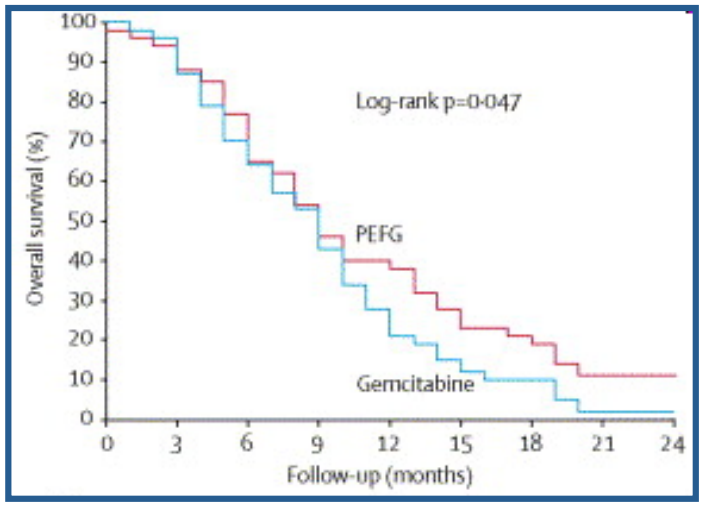


Innocenti et al, ASCO 2009

Pharmacogenetics for polychemotherapy

➢A recent trial showed that the combination of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) is an option for the treatment of metastatic **pancreatic ductal adenocarcinoma (PDAC)** patients with good performance status [Conroy et al, N Engl J Med 2011]

➢Positive results were also obtained in previous studies on **4-drugs combination** (cisplatin, epirubicin (or docetaxel), 5-FU (or capecitabine), gemcitabine) which showed a more favourable outcome in terms of PFS, OS and RR [Reni et al, Lancet Oncol 2005]



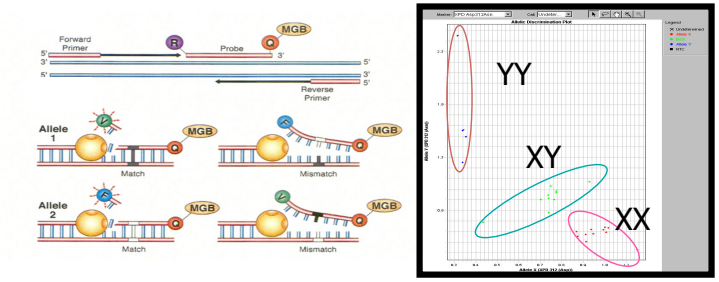
➢**Due to the drug toxicity of polychemotherapy, the identification of predictive factors of drug activity is warranted for maximizing risk-benefit ratio and minimizing ineffective/potentially harmful treatments**

Methods

123 patients affected by histologically confirmed unresectable and measurable PDAC

Genomic DNA extraction from blood samples

Allelic discrimination with TaqMan probes-based assay



SNP analysis

Chemotherapy with four-drugs combination (PEXG, PDXG, EC-GemCap)

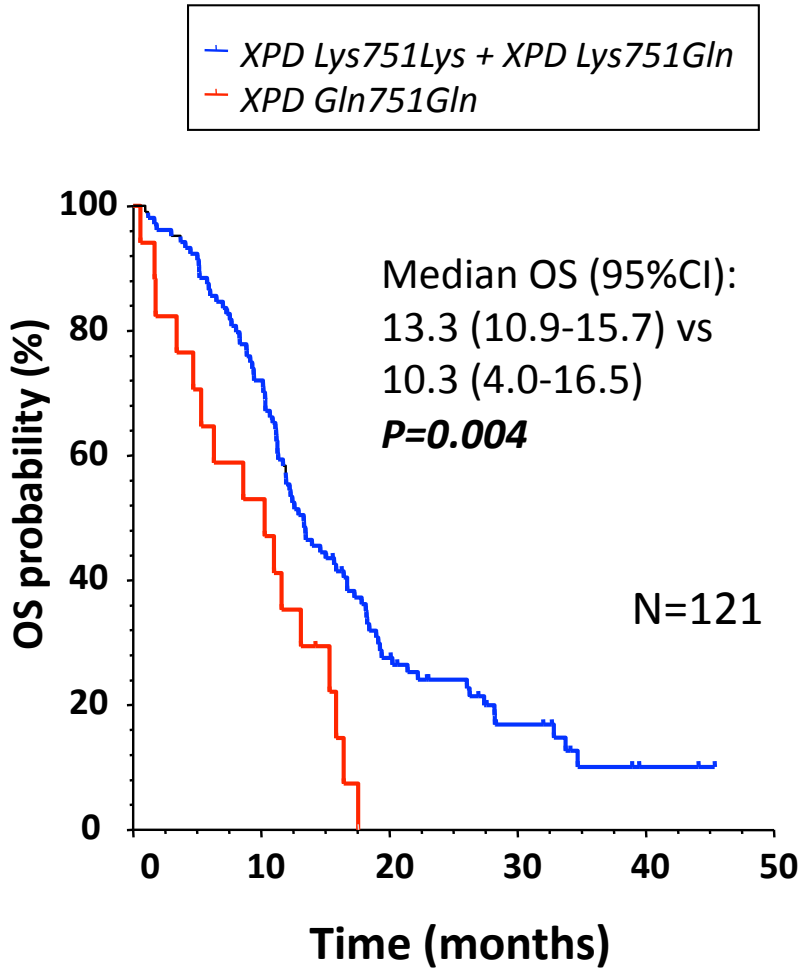
Follow-up

Statistical analysis of correlation between candidate SNPs and OS

Gene	Functional effects on drug activity	Polymorphism	dbSNP
ERCC1	DNA repair of platinum adducts	*ERCC1 C118T*	rs#11615
XPD	DNA repair of platinum adducts	*XPD-Asp312Asn*	rs#1799793
		XPD-Lys751Gln	rs#13181
XRCC1	DNA repair of platinum adducts	*Arg399Gln*	rs#25487
ABCB1	Epirubicin efflux	*C3435T*	rs#13181
CYP1B1	Docetaxel metabolism/target	*Leu432Val*	rs#1056836
	Docetaxel metabolism/target	*Asn453Ser*	rs#1800440
CDA	Gemcitabine catabolism	*A79C*	rs#2072671
RRM1	Gemcitabine target	*A2464G*	rs#1042858
		A2452G	rs#3177016

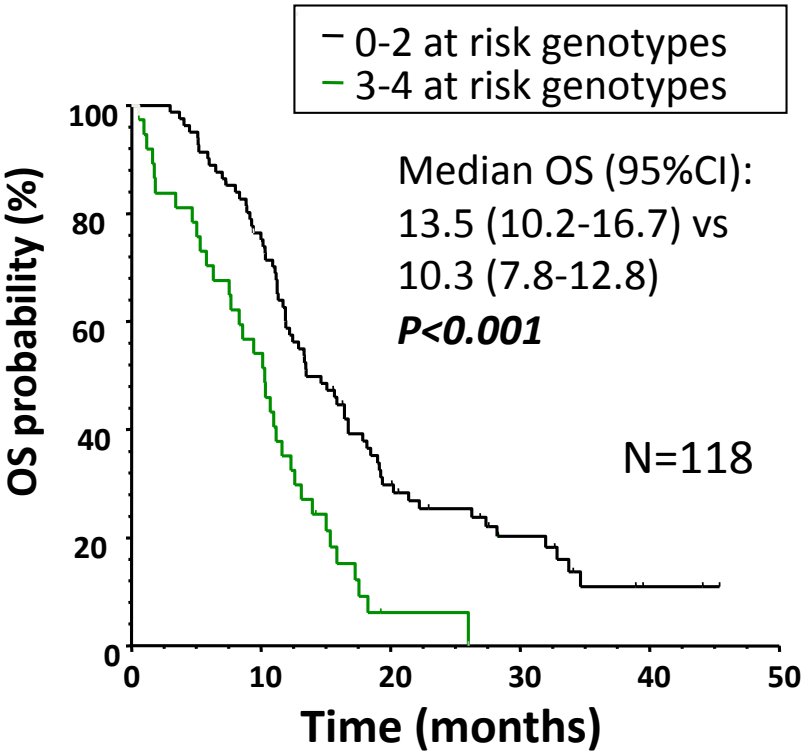
Results

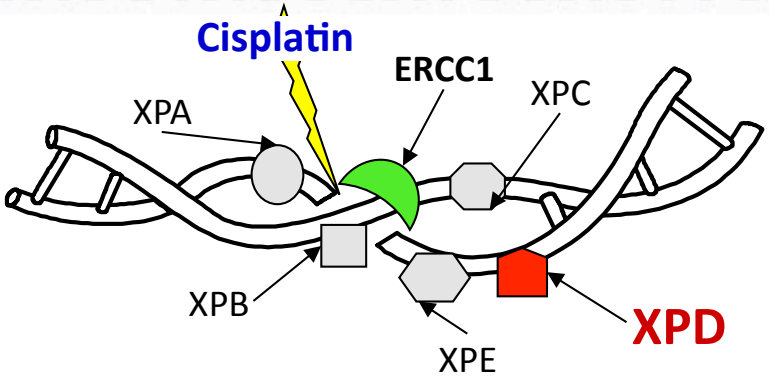
Genotype	Pts. n (%)	HWE-*P*	OS mo. (95% CI)	*P*
ERCC1-118 CC	21 (17.2)	*0.955*	11.9 (9.6-14.2)	*0.111*
CT	54 (44.3)		11.3 (9.4-13.2)	
TT	47 (38.5)		13.3 (9.7-17.0)	
CC+CT	75 (61.5)		11.8 (10.4-13.4)	***0.044***
XPD-312 AspAsp	44 (36.1)	*0.879*	15.1 (10.8-19.4)	*0.010*
AspAsn	61 (50.0)		11.2 (9.5-13.0)	
AsnAsn	17 (13.9)		11.6 (9.3-13.9)	
AsnAsn+AspAsn	78 (63.9)		11.2 (9.9-12.6)	***0.008***
XPD-751 LysLys	54 (44.6)	*0.650*	15.1 (10.6-19.5)	***0.004***
LysGln	50 (41.4)		12.9 (10.2-13.6)	
GlnGln	17 (14.0)		10.3 (4.0-16.5)	
LysLys+LysGln	104 (86.0)		13.3 (10.9-15.7)	***0.003***
XRCC1-399 ArgArg	66 (55.9)	*0.574*	13.3 (9.8-16.8)	*0.078*
ArgGln	39 (33.1)		11.2 (9.2-13.1)	
GlnGln	13 (11.0)		12.2 (8.3-16.1)	
GlnGln+ArgGln	52 (44.1)		11.8 (9.0-13.4)	***0.036***
ABCB1-3435 CC	32 (26.5)	*0.703*	11.2 (7.9-14.4)	*0.079*
CT	65 (53.7)		15.0 (12.0-18.0)	
TT	24 (19.8)		11.0 (9.2-12.7)	
CC+CT	97 (80.2)		13.3 (10.6-16.0)	*0.165*
CYP1B1-432 LeuLeu	16 (13.2)	*0.830*	12.3 (9.1-15.4)	*0.972*
LeuVal	53 (43.4)		13.1 (11.0-14.3)	
ValVal	53 (43.4)		12.2 (10.1-14.3)	
LeuLeu+LeuVal	69 (56.6)		13.1 (11.4-14.8)	*0.884*
CYP1B1-453 AsnAsn	75 (62.0)	*0.970*	13.0 (10.5-15.2)	*0.633*
AsnSer	41 (33.9)		12.2 (8.4-16.0)	
SerSer	5 (4.1)		11.0 (6.5-15.5)	
SerSer+AsnSer	46 (38.0)		11.9 (8.5-15.3)	*0.444*
CDA-79 AA	39 (32.2)	*0.658*	12.6 (9.8-15.3)	*0.658*
AC	64 (52.9)		12.3 (8.4-18.2)	
CC	18 (14.9)		13.3 (8.4-18.2)	
CC+AC	82 (67.8)		12.4 (10.2-14.7)	*0.118*
RRM1-2464 AA	98 (80.4)	*0.994*	12.3 (10.2-14.4)	*0.331**
AG+GG	24 (19.6)		12.4 (10.4-14.4)	
RRM1-2452 AA	29 (23.8)	*0.633*	12.3 (10.3-14.3)	*0.763*
AG	55 (45.1)		13.4 (9.7-17.1)	
GG	38 (31.1)		10.9 (5.3-16.4)	
AA+AG	84 (68.9)		12.4 (11.0-13.9)	*0.994*
TSER 2R2R	25 (20.5)	*0.937*	11.9 (7.4-16.5)	*0.672*
2R3R	40 (32.8)		12.4 (9.8-15.1)	
3R3R	57 (46.7)		12.6 (10.5-14.7)	
3R3R+2R3R	97 (79.5)		12.6 (11.0-14.2)	*0.541*



Giovannetti et al., Pharmacogenomics in press

Results





1) Combinations of the alleles associated with death risk (*ERCC1-C118C+C118T, XPD-Asn312Asn+Asp312Asn, XPD-Gln751Gln and XRCC1-Arg399Gln+Gln399Gln*) resulted in a significantly shorter OS (figure)

2) Conversely, no significant correlations were observed between these SNPs and OS in gemcitabine-alone treated patients (N=65)

3) *XPD-Gln751Gln* resulted as an independent prognostic factor of higher risk of death and progression at multivariate analysis (table)

4) HR of patients (N=37) with >2 vs. patients (N=81) harbouring ≤2 risk-genotypes was 2.7 (95%CI, 1.8-4.2, P<0.001)

OS		Multivariate analysis		
Characteristic/Polymorphism		Hazard ratio (95%CI)	df	*P*
Age	≤65	1.0 (ref)	1	*0.022*
	>65	2.0 (1.3-3.2)		
Sex	Male	1.6 (0.9-2.6)	1	*0.057*
	Female	1.0 (ref)		
PS	≤80	1.8 (1.1-2.8)	1	*0.014*
	>80	1.0 (ref)		
Stage	III	1.0 (ref)	1	*0.001*
	IV	2.0 (1.3-3.2)		
ERCC1-C118T	*CC-TT*	1.2 (0.7-1.8)	1	*0.500*
	TT	1.0 (ref)		
XPD-Asp312Asn	*AspAsp*	1.0 (ref)	1	*0.137*
	AspAsn+AsnAsn	1.4 (0.9-2.4)		
XPD-Lys751Gln	*LysLys+LysGln*	1.0 (ref)	1	*0.003*
	GlnGln	1.9 (1.3-2.9)		
XRCC1-Arg399Gln	*ArgArg*	1.0 (ref)	1	*0.030*
	GlnGln+ArgGln	2.0 (1.1-3.7)		

Conclusions

Pharmacogenetic studies showed association between several polymorphisms and clinical outcome or toxicity

Most studies were retrospective, monocentric, without multiple correction and validation in broader populations

Hopefully, novel pharmacogenetic biomarkers will be validated in prospective studies and used to select pancreatic cancer patients to be treated with differential regimens in the near future