frontiers in Cell and Developmental Biology

REVIEW
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DNA Damage Repair Deficiency in Pancreatic Ductal Adenocarcinoma: Preclinical Models and Clinical Perspectives

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Journal club presentation – Session 2

07-04-1401

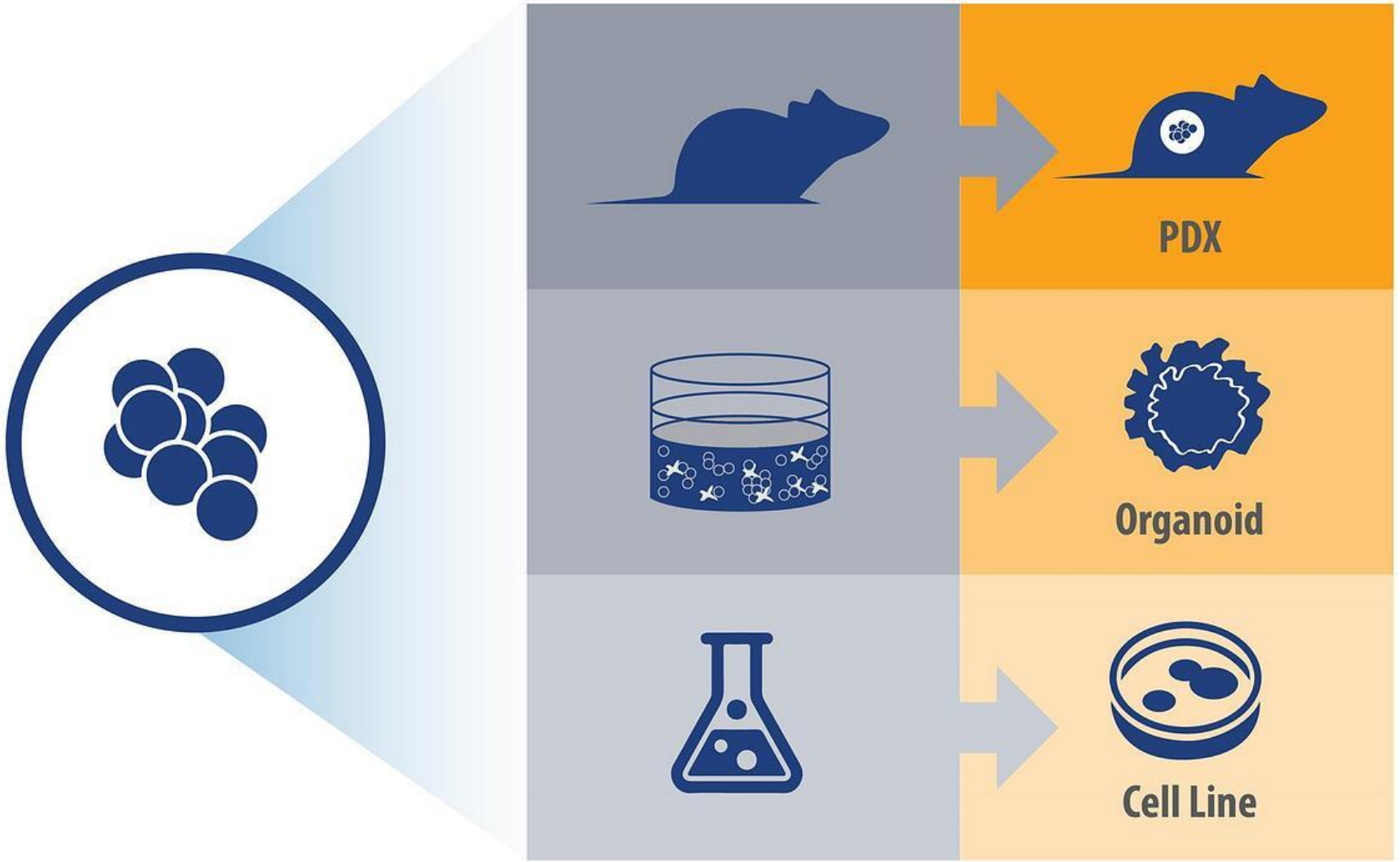
Omidreza Firuzi

From first session

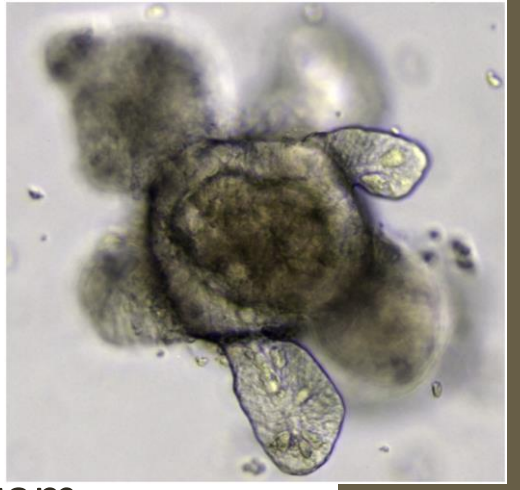
- **DDR genes alterations** are frequently found in PDAC.
- **DDR targeted therapies** are more effective in models **with defects in DNA repair pathways** (principle of **synthetic lethality**).
- The application of DDR targeted therapy in patients with ***BRCA* mutations** has had success in other cancer types (most notably in breast and ovarian cancer)
- The fraction of patients with ***BRCA* mutations is relatively small in PDAC,** but there are **other DDR gene mutations** in PDAC patents (GENIE).

Complementary Preclinical Oncology Models

CrownBio
CONNECTING SCIENCE TO PATIENTS

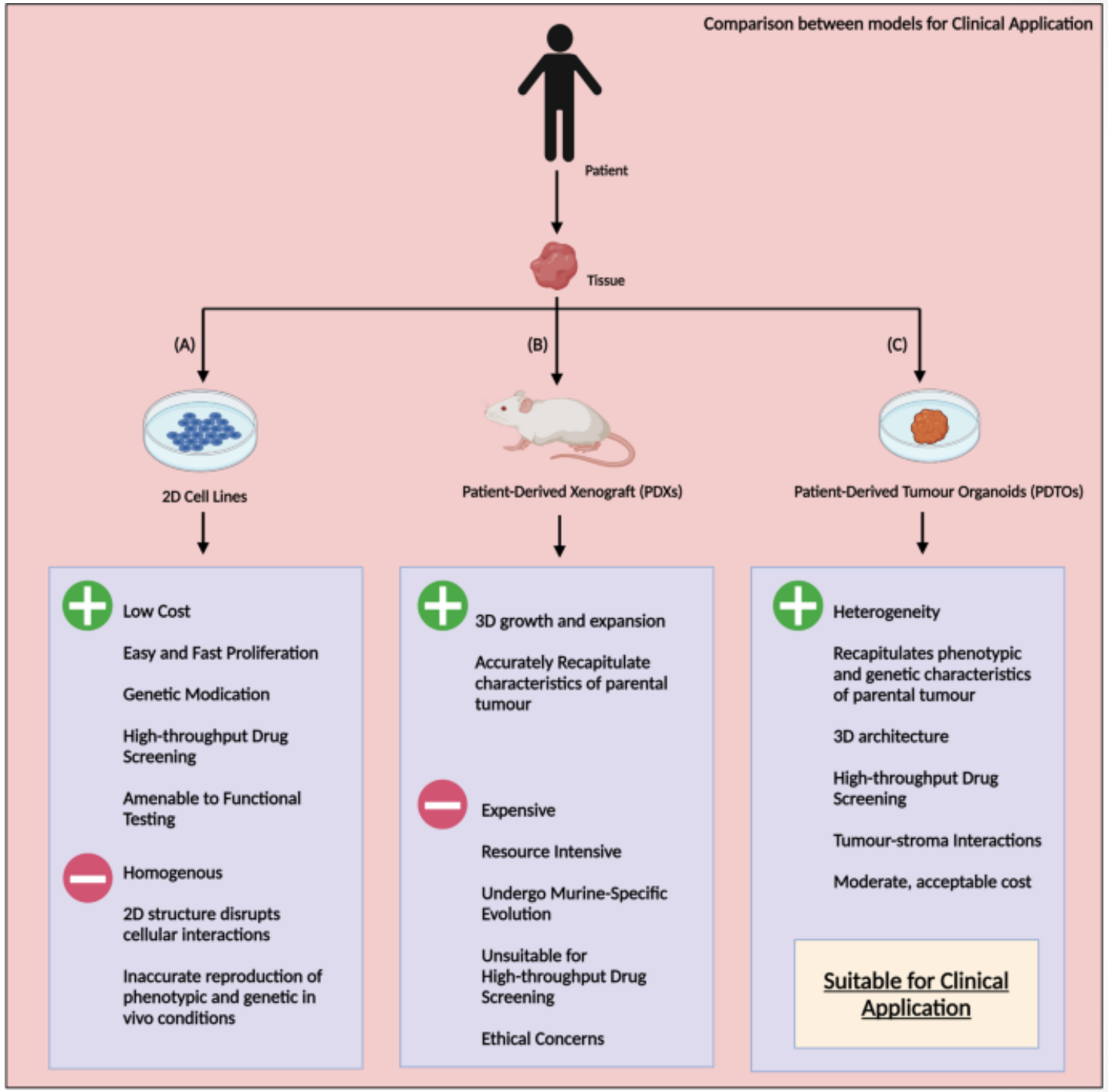


Organoid



- Organoid is an **in vitro 3D structure**, developed from **stem cells (**Embryonic stem cells or induced pluripotent stem cells) and consisting of organ-specific cell types that self-organize in a manner similar to in vivo, to recapitulate tissue or organ functionality and shows **realistic micro-anatomy.**
- They are derived from **one or a few cells from a tissue**
- Cells self-organize in three-dimensional culture owing to their self-renewal and differentiation capacities
- The developmental potential of the starting stem cells will influence how complex the organoid can be.

Patient derived organoid (PDO)



PDAC patient derived organoid (PDO)

- Based on genomic, transcriptomic, and histologic data, organoids are representative models of PDAC
- There is limited information on patient derived organoid (PDO) sensitivity to DDR-targeted drugs.
- However, drug screening and correlation to patient response studies are promising and suggest that organoids are good models to determine drug sensitivity for targeted therapies, and might also be used to identify biomarkers for drug sensitivity.

Driehuis et al. (2019) performed high-throughput drug screening of 76 drugs in 24 PDOs:

- PDOs have a similar response to agents that target the same biological process or molecular pathway.
- Drug response was found to be PDO-specific, thus reflecting patient heterogeneity.
- 1 PDO had a BRCA2 indel and was among the most sensitive PDOs for most of the tested drugs.

- Tiriac et al. (2018): **pharmacotyping** on 66 PDOs for the drugs gemcitabine, paclitaxel, irinotecan, 5-FU, and oxaliplatin.
- PDO response reflected **interpatient variability**.
- For 9 patients, the PDO response could be compared to patient response.
- A trend between olaparib sensitivity and complete loss of PALB2 was observed.
- Single-copy losses of a range of genes involved in **HR do not correspond with olaparib sensitivity**.
- Dreyer et al. (2021): **no correlation between DDR status and the response to ATR or WEE1 inhibition** in the six PDOs

DNA replication stress

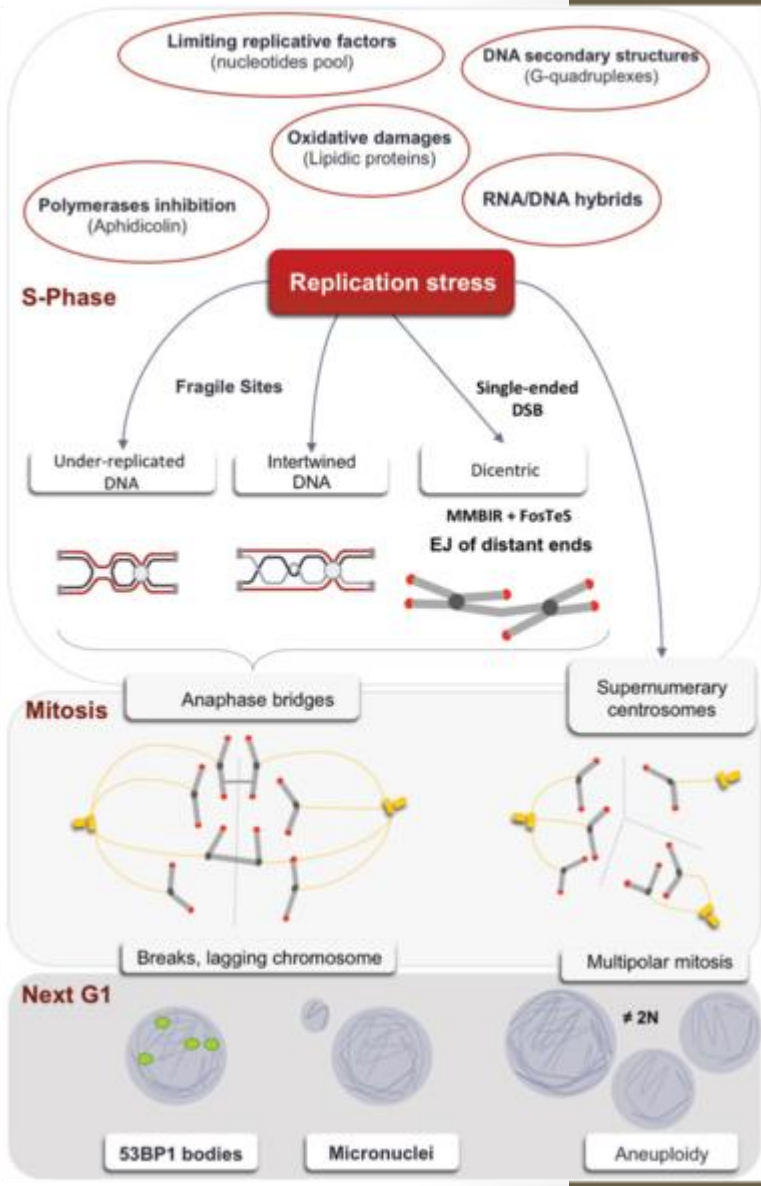
- DNA replication stress refers to the **state of a cell whose genome is exposed to various stresses.**

- Replication stress occurs during DNA replication, and can result in a **stalled replication fork**.

There are many events that contribute to replication stress, including:

- Misincorporation of ribonucleotides
- Unusual DNA structures
- Conflicts between replication and transcription
- Insufficiency of essential replication factors
- Common fragile sites
- Chromatin inaccessibility

ATM and ATR alleviate replication stress.



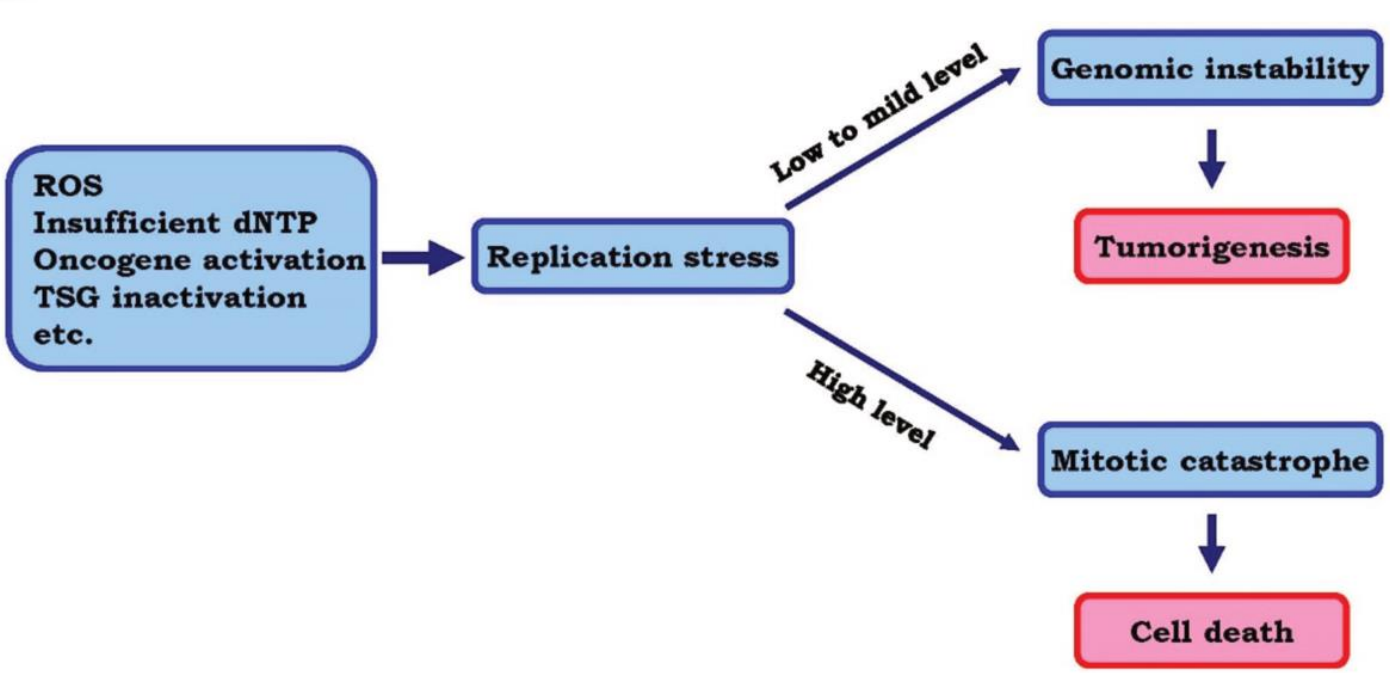
Dreyer et al 2021

Gastroenterology 2021;160:362–377

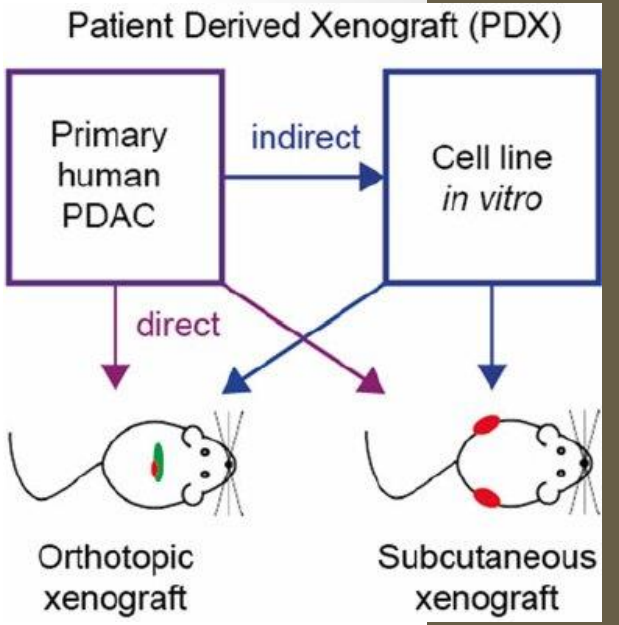
Targeting DNA Damage Response and Replication Stress in Pancreatic Cancer

Stephan B. Dreyer,[1,2] Rosie Upstill-Goddard,[1] Viola Paulus-Hock,[3] Clara Paris,[4] Eirini-Maria Lampraki,[1] Eloise Dray,[5] Bryan Serrels,[1,6] Giuseppina Caligiuri,[1] Selma Rebus,[1] Dennis Plenker,[7,8] Zachary Galluzzo,[7,8] Holly Brunton,[1] Richard Cunningham,[1] Mathias Tesson,[3] Craig Nourse,[3] Ulla-Maja Bailey,[1] Marc Jones,[9] Kim Moran-Jones,[10] Derek W. Wright,[1] Fraser Duthie,[1,11] Karin Oien,[1,11,12] Lisa Evers,[1] Colin J. McKay,[1,2] Grant A. McGregor,[3] Aditi Gulati,[13] Rachel Brough,[13] Ilirjana Bajrami,[13] Stephan Pettitt,[13] Michele L. Dziubinski,[14] Juliana Candido,[15] Frances Balkwill,[15] Simon T. Barry,[16] Robert Grützmann,[17] Lola Rahib,[18] Glasgow Precision Oncology Laboratory,[19], Australian Pancreatic Cancer Genome Initiative[20], Amber Johns,[21] Marina Pajic,[21] Fieke E. M. Froeling,[8,22] Phillip Beer,[23] Elizabeth A. Musgrove,[1] Gloria M. Petersen,[24] Alan Ashworth,[11,25] Margaret C. Frame,[6] Howard C. Crawford,[14] Diane M. Simeone,[26] Chris Lord,[13] Debabrata Mukhopadhyay,[27] Christian Pilarsky,[17] David A. Tuveson,[7,8] Susanna L. Cooke,[1] Nigel B. Jamieson,[1,2] Jennifer P. Morton,[1,3] Owen J. Sansom,[1,5] Peter J. Bailey,[3] Andrew V. Biankin,[1,2,28,§] and David K. Chang[1,2,28,§]

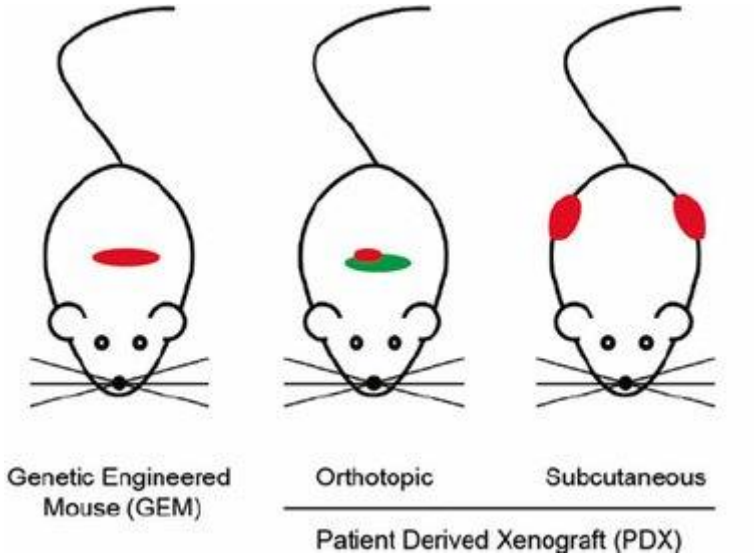
- We interrogated the transcriptome, genome, proteome, and functional define novel therapeutic strategies **targeting DDR and replication stres**
- Validation was done in **patient-derived xenografts and human PC orga**
- **Biomarkers of DDR deficiency**, including a novel signature of homologous recombination deficiency, **correlates with response to platinum (P < .001) and PARP inhibitor therapy** (P < .001) in vitro and in vivo.
- We generated a novel signature of **replication stress that predicts response to ATR and WEE1 inhibitor** treatment in both cell lines and human PC organoids.
- Replication stress was not associated with DDR deficiency.
- WEE1: a nuclear tyrosine kinase that catalyzes the inhibitory tyrosine phosphorylation of CDC2/cyclin B complex, acts as a negative regulator of entry into mitosis (G2 to M transition)
- CONCLUSIONS: **Replication stress and DDR deficiency are independent of each other**, creating opportunities for therapy in DDR-proficient PC and after platinum therapy.

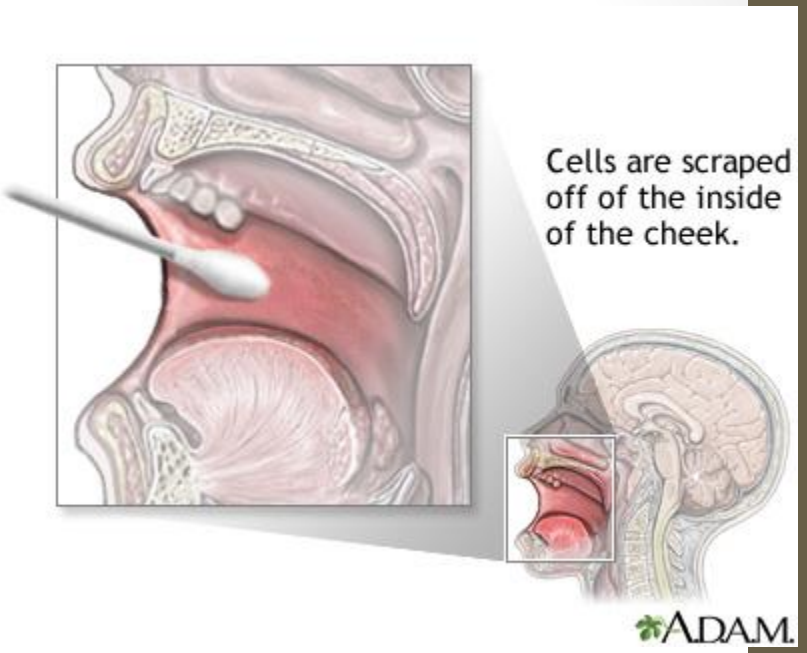

ROS
Insufficient dNTP
Oncogene activation
TSG inactivation
etc.
Replication stress
Low to mild level
High level
Genomic instability
Tumorigenesis
Mitotic catastrophe
Cell death

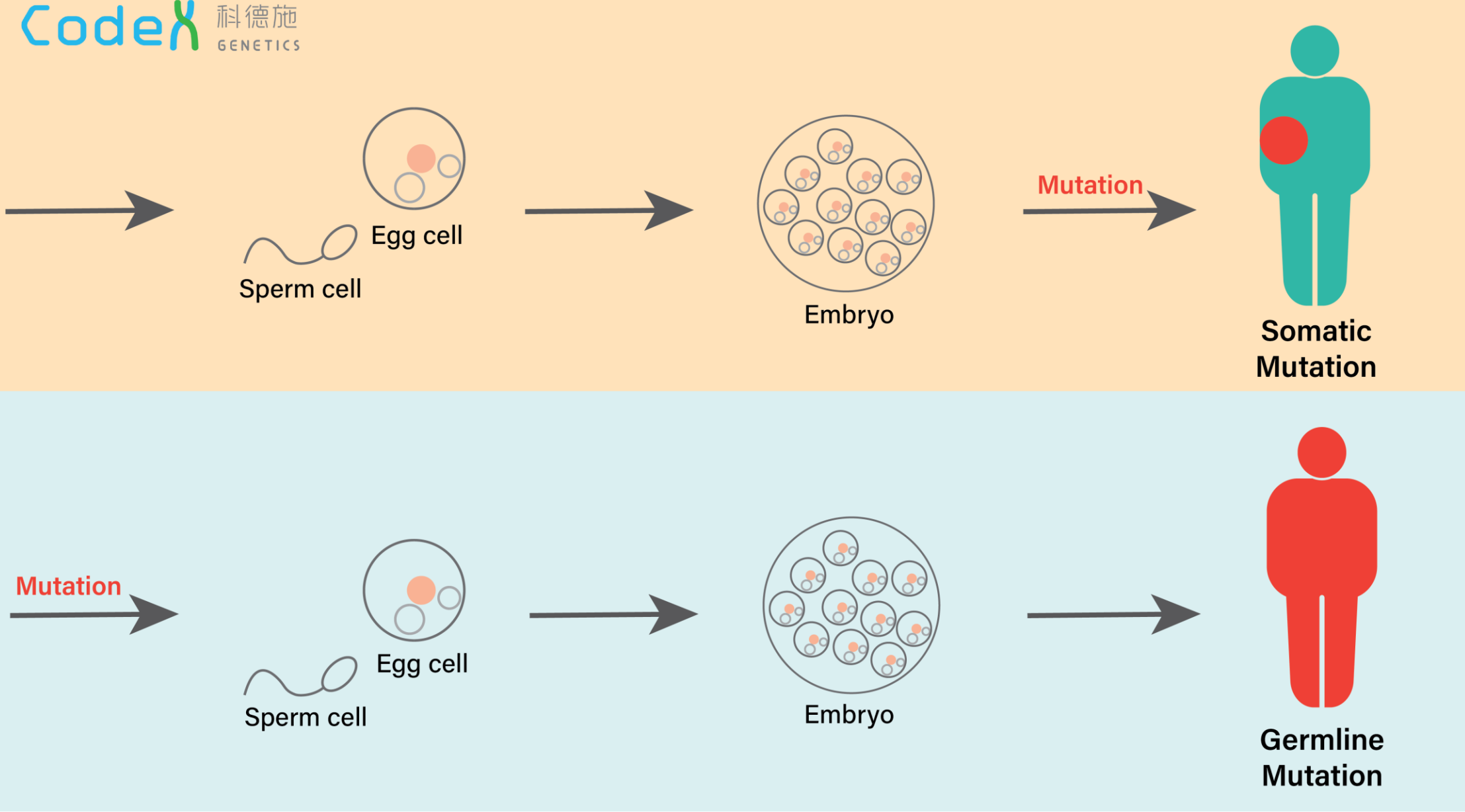
Mouse Models



- Patient-derived and cell line-derived xenograft (PDXs) are well established cancer models and have been reviewed extensively
- PDAC xenografts can be established from **resection, biopsy material, and ascites**.
- Copy number alterations and gene expression profiling are largely maintained between primary samples and PDX and genomic signatures can be fitted to the Collisson, Moffitt, and Bailey subtypes.

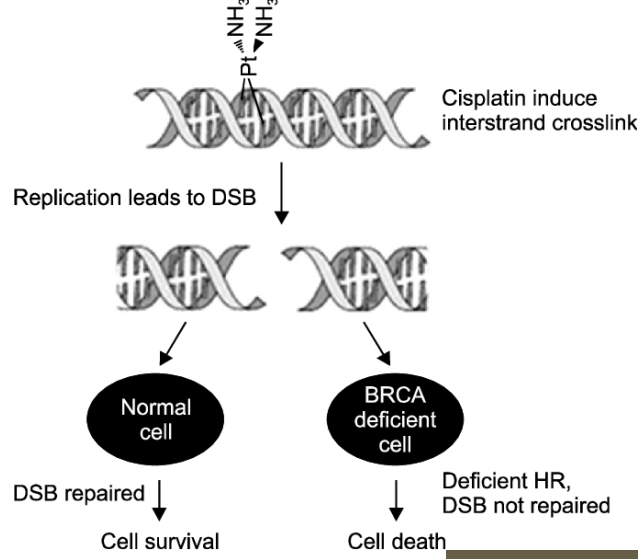

Genetic Engineered Mouse (GEM)
Orthotopic
Subcutaneous
Patient Derived Xenograft (PDX)


Cells are scraped off of the inside of the cheek.
A.D.A.M.


Egg cell
Sperm cell
Embryo
Mutation
Somatic Mutation
Mutation
Egg cell
Sperm cell
Embryo
Germline Mutation

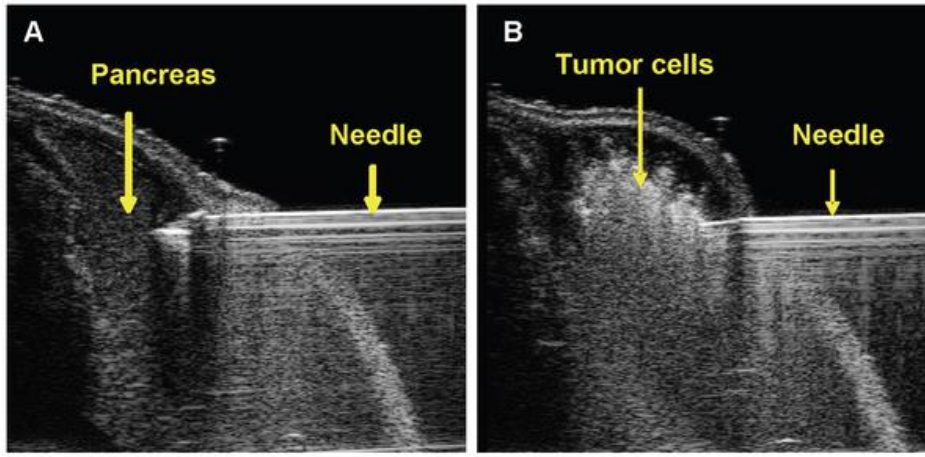
- Golan et al. (2018) developed 6 **PDXs from metastatic lesions** of **germline BRCA-mutated patients**
- 4 models had **bi-allelic inactivation of BRCA1/2** and demonstrated increased somatic mutational load compared to the two models that had retained one wild-type copy.
- Three PDX were treated with olaparib and cisplatin monotherapy,
- **HR deficiency profile** was associated with patient response **to platinum and PARPi**.

Comparing treatment sensitivity of 4 xenografts containing a germline mutation in BRCA1/2 heterozygous or homozygous loss to 3 xenografts with wild-type BRCA1/2.



- Mice were treated for 4 weeks with gemcitabine or cisplatin. The **BRCA mutant xenografts were significantly more sensitive to both gemcitabine and cisplatin** compared to the BRCA wild-type xenografts.
- **No significant difference in sensitivity to radiation treatment or olaparib**.
- Additionally, **olaparib did not sensitize to radiation** but instead **reduced the induction of DNA damage** in the BRCA mutant xenografts which was attributed to **an increased repair of DSBs by the NHEJ pathway** and **activation of DNA-PK** in the BRCA mutant xenograft.

Lohse et al. (2015)



- Comparing cisplatin sensitivity of 3 PDX with an unstable genome and/or high BRCA mutational signature burden to 4 PDX without

- **None of the DDR-proficient xenografts responded to cisplatin**, while **2/3 DDR-deficient xenografts did.**

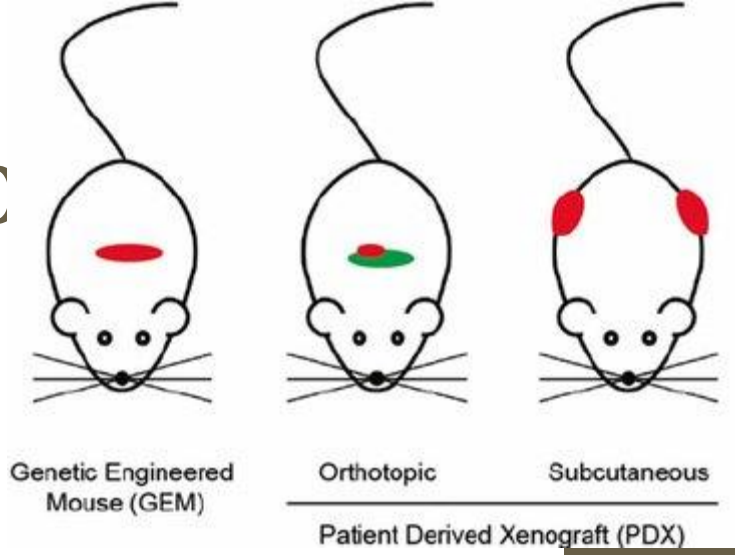
Waddell et al. (2015)

- Comparing the efficacy of multi-DDR interference (combination of olaparib, VE-822 (ATRi), and CC-115 (DNAPKi)) as maintenance therapy to continuous FOLFIRINOX treatment in a **cell line derived xenograft model** (Atm/Kras-deficient PDAC mouse cell lines (AKC) were orthotopically transplanted in mice).

- OS was significantly **longer in the multi-DDR group** compared to the FOLFIRINOX or placebo groups (28.5 vs. 24.5 vs. 18.0 days, $p < 0.02$).

Roger et al. (2020)

Genetically engineered mouse mc



- The advance of genetic manipulation has allowed for the development of genetically engineered mouse models (GEMMs).
- **Germline mutations** induce tumor formation at an early age and at a relatively **high penetrance**.
- In contrast to xenografts, tumors in GEMM **develop progressively** and can therefore also be used to study **precancerous lesions and low grade tumors**.

The most used PDAC models:

- KC mice: germline mutation in Kras (K-ras $^{LSL.G12D/+}$)
- KPC mice: germline mutation in Kras and in Tp53 (p53 $^{LSL.R172H/+}$)

Both models develop PanINs (**Pancreatic intraepithelial neoplasia)** and eventually also PDAC, although the onset and penetrance of PDAC is later and lower in KC mice.

The KC and KPC mouse models have been instrumental in understanding tumor development in **DDR-proficient PDAC,** but have also been used as **a basis for DDR-deficient GEMM models**.

DDR-deficient GEMM models (Brca2-deficient and Atm-deficient) (**Table 3**)

References	Model	Mutations	No. of mice	Phenotype
Hingorani et al. (2003, 2005)	KC	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$	33	100% developed PanIN which progressed to invasive and metastatic PDAC in a small minority.
	KPC	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$; *p53*$^{LSL.R172H/+}$	28	96% developed PDAC which metastasized in over half of the mice. Median survival of 22 weeks.
Feldmann et al. (2011)	CB	*Pdx1-Cre*; *Brca2*$^{flox/flox}$	25	15% developed invasive and metastatic PDAC, more mice developed PanIN. Median survival of 65 weeks.
	CBP	*Pdx1-Cre*; *Brca*$^{flox/flox}$; *LSL-Trp53*^{R172H}	33	100% developed invasive or metastatic PDAC. Median survival of 54 weeks.
Skoulidis et al. (2010)	CB$^{Tr/\Delta 11}$	*Pdx1*-Cre; *Brca2*$^{Tr/\Delta 11}$	24	No development of pancreatic cancer.
	PCB$^{Tr/\Delta 11}$	*Pdx1-Cre*; *Trp53*^{R270H}; *Brca2*$^{Tr/\Delta 11}$	22	No development of pancreatic cancer.
	PCB$^{Tr/WT}$	*Pdx1-Cre*; *Trp53*^{R270H}; *Brca2*$^{Tr/WT}$	25	No development of pancreatic cancer.
	KCB$^{wt/wt}$	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$	40	15% developed PDAC.
	KCB$^{Tr/wt}$	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$; *Brca2*$^{Tr/wt}$	40	30% developed PDAC.
	KCB$^{Tr/\Delta 11}$	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$; *Brca2*$^{Tr/\Delta 11}$	32	19% developed PDAC, though frequent development of pancreatic insufficiency.
	KPCB$^{wt/wt}$	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$; *p53*$^{LSL.R172H/+}$	30	80% developed PDAC. Median PDAC-free survival 24 weeks.
	KPCB$^{Tr/\Delta 11}$	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$; *p53*$^{LSL.R172H/+}$; *Brca2*$^{Tr/\Delta 11}$	30	87% developed PDAC. Median PDAC-free survival 12 weeks.
	KPCB$^{Tr/wt}$	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$; *p53*$^{LSL.R172H/+}$; *Brca2*$^{Tr/wt}$	30	97% developed PDAC. Median PDAC-free survival 20 weeks.
Rowley et al. (2011)	CB2$^{\Delta 11/\Delta 11}$	*Pdx1-Cre*; *Brca2*$^{\Delta 11/\Delta 11}$	12	No development of precursor lesions or PDAC.
	CB2$^{wt/\Delta 11}$	*Pdx1-Cre*; *Brca2*$^{wt/\Delta 11}$	21	No development of precursor lesions or PDAC.
	CPB2$^{\Delta 11/\Delta 11}$	*Pdx1-Cre*; *Trp53*$^{F2-10/F2-10}$; *Brca*$^{\Delta 11/\Delta 11}$	34	High frequency development of pancreatic cancer, >40% of ductal origin
	CPB2$^{wt/\Delta 11}$	*Pdx1-Cre*; *Trp53*$^{F2-10/F2-10}$; *Brca*$^{wt/\Delta 11}$	41	Development of pancreatic cancer, >40 of ductal origin.
	CPB2$^{wt/wt}$	*Pdx1-Cre*; *Trp53*$^{F2-10/F2-10}$	47	Development of pancreatic cancer, predominantly acinar, and undifferentiated.
Russell et al. (2015)	AKC$^{\pm}$	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$, *Atm*$^{flox/+}$	32	Development of PanIN. Median survival 36 weeks.
	AKC$^{-/-}$	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$, *Atm*$^{flox/flox}$	15	Development of PanIN. Median survival 45 weeks.
Drosos et al. (2017)	KC	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$, *Ptf1a*$^{+/cre}$	19	42% developed pancreatic cancer of which >80 of sarcomatoid histology, median survival 61 weeks.
	KCATMΔ+	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$, *Ptf1a*$^{+/cre}$, *Atm*$^{loxP/+}$	21	62% developed pancreatic cancer mainly poor and moderately differentiated, median survival 39 weeks.
	KCATMΔΔ	*Pdx1-Cre*; *K-ras*$^{LSL.G12D/+}$, *Ptf1a*$^{+/cre}$, *Atm*$^{loxP/loxP}$	18	94% developed pancreatic cancer with a mixture of moderate, poor, and undifferentiated tumors, median survival 39 weeks.

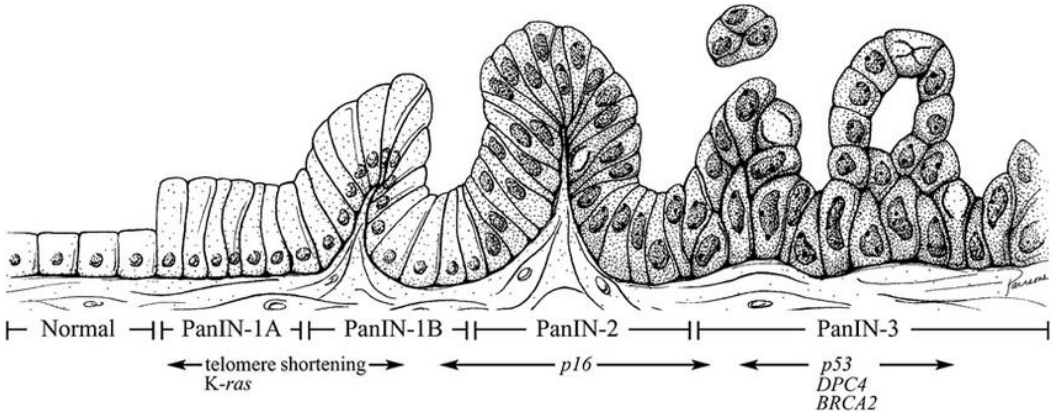
Brca2-deficient genetically engineered mouse model

- Feldmann et al. (2011) established two BRCA2-mutated GEMM:

- CB (Pdx1-Cre; Brca $^{flox/flox}$)
- CBP (Pdx1-Cre; Brca $^{flox/flox}$; LSL^{Trp53R172H})

- Both mice developed PDAC: **Kras mutation is not prerequisite for tumorigenesis in the presence of Brca2** mutation in mice.

- The additional Trp53 mutation in the CBP cohort enhanced the frequency of invasive neoplasia and resulted in earlier mortality (375 vs. 454 days, p = 0.085).



Mouse models with a combination of mutations in Brca2, Trp53, and Kras

- Brca2-deficiency alone **is not sufficient** to induce carcinogenesis, but Brca2-deficienct mice had a longer survival than those with combined Brca2-deficiency and Trp53 loss

- Mice with triple mutation nearly all developed tumors and had the worst survival.

- **Homozygous Brca2 inactivation** did contribute to a significantly more aggressive disease compared to wild-type or heterozygous loss in combination with Kras and Trp53 mutation ($p < 0.002$).

Skoulidis et al. (2010)

Atm-deficient genetically engineered mouse model

- Russell et al. (2015) found that KC mice with floxed Atm (abbreviated as AKC) had developed more acinar-to-ductal metaplasia lesions and PanINs compared with KC mice at 10 weeks old.

Drosos et al. 2015

- The higher tumorigenicity of KC Atm-deficient mice was confirmed (Higher rate of development of Pancreatic cancers (62-94%) compared to 42% in KC mice).

- In addition, the Atm-deficient mice had a significantly reduced median OS.

Clinical Trials Targeting DNA Damage

- Repair Deficiency Pathways
- As of July 2021, there are 51 clinical trials registered on clinicaltrials.gov that investigate **DDR alone or in combination with chemotherapy in PDAC** (either in PDAC alone or as part of a larger cancer patient cohort).
- The majority of these trials (78%, n = 40) focus on PARP inhibitors, although ATM/ATR, CHK1, DNA-PK, and WEE1 inhibitors are also being investigated.
- Except for a single trial, all trials are either phase I or II, with limited numbers of patients and often single-arm treatment protocols which renders efficacy analysis more challenging.

PARP Inhibitors

- The pivotal phase III trial leading to FDA approval for the use of PARPi in metastatic PDAC was conducted by Golan et al. (2019) and evaluated olaparib as maintenance therapy in metastatic **PDAC patients with germline mutation of BRCA**.
- Patients were eligible if their tumor had not progressed on first-line platinum-based chemotherapy (e.g., cisplatin or oxaliplatin).
- Olaparib compared to placebo: significant increase in PFS (7.4 vs. 3.8 months, p = 0.004)
- At interim analysis (data maturity 46%) no significant difference was found in median OS (18.9 vs. 18.1 months, p = 0.68).
- The updated results in 2021: Disappointingly there was again **no difference in median OS** between the groups (OS 19.0 vs. 19.2 months, p = 0.35). Notably, however, **PFS2 (the time from randomization to second disease progression or death) was significantly longer** in the olaparib-treated group (PFS2, 16.9 vs. 9.3 months, p = 0.0061).

- A phase I trial in PDAC patients with locally advanced or metastatic PDAC:

- First line setting, a comparison of **olaparib combined with gemcitabine vs. gemcitabine alone** (n = 22) Patients were eligible for inclusion regardless of genetic/molecular status.

- **No significant benefit** was found regarding objective response rate (ORR), OS, or PFS for the combination treatment.

Bendell et al., 2015

- Phase IB trial of the addition of another PARPi, veliparib, to first line chemotherapy (cisplatin, gemcitabine) demonstrated a striking ORR of 78% in patients with stage III/IV PDAC with BRCA1/2 germline mutations and an equally impressive median OS of 23.3 months.

O'Reilly et al.'s (2018)

- The investigators then proceeded to a phase II trial of this combination in patients with PDAC and germline BRCA or PALB2 mutations (O'Reilly et al., 2020).
- Response rate in the combination arm was 79 vs. 65.2% in the chemotherapy alone arm (p = 0.02).

- **No statistically significant difference in PFS or OS** between the groups (PFS 10.1 vs. 9.7 months, p = 0.73; OS 15.5 vs. 16.4 months, p = 0.6).

- The 2- and 3-year OS of 30.7 and 17.8%, respectively, in this study are the longest ever reported in a clinical trial in this cohort.

O'Reilly et al.'s (2018)

- A phase II study of **veliparib alone in the second line** setting in patients with **BRCA mutant PDAC** reported **no confirmed responses**.

(Lowery et al., 2018).

- Two additional phase II trials:
- The addition of veliparib to FOLFIRI increased toxicity and **did not improve either OS** (5.1 vs. 5.9 months in combination vs. monotherapy arm) or **PFS** (2.1 vs. 2.9 months, HR 1.5, *p* = 0.05).

- Additionally, blood and tumor biopsies were collected at baseline to explore HR or DDR biomarkers.

- 9% of the tumors had **HR deficiency (*BRCA1/2*, *ATM*, *PALB2*, *ATM*, or *CDK12* mutation**), and **20% had mutations in other DDR genes** (*FANC*, *BLM*, *SLX4*, *CHEK2*, *POLD1*, *RIF1*, and *MSH2/6*).

- Correlative analysis of HR or DDR deficiency with treatment response is still ongoing.

- Phase I/II in PDAC patients: **combination treatment of veliparib with modified FOLFOX**.

- For the phase I portion of the study patients were not selected based on genetic history; however, for the phase II part of the trial, patients were **selected based on the presence of HR-DDR deficiency** or family history suggesting breast or ovarian cancer syndrome.

- The ORR was 20% in the phase I unselected cohort (n = 23) and 31% in the phase II cohort (n = 33) selected for HR-DDR deficiency.

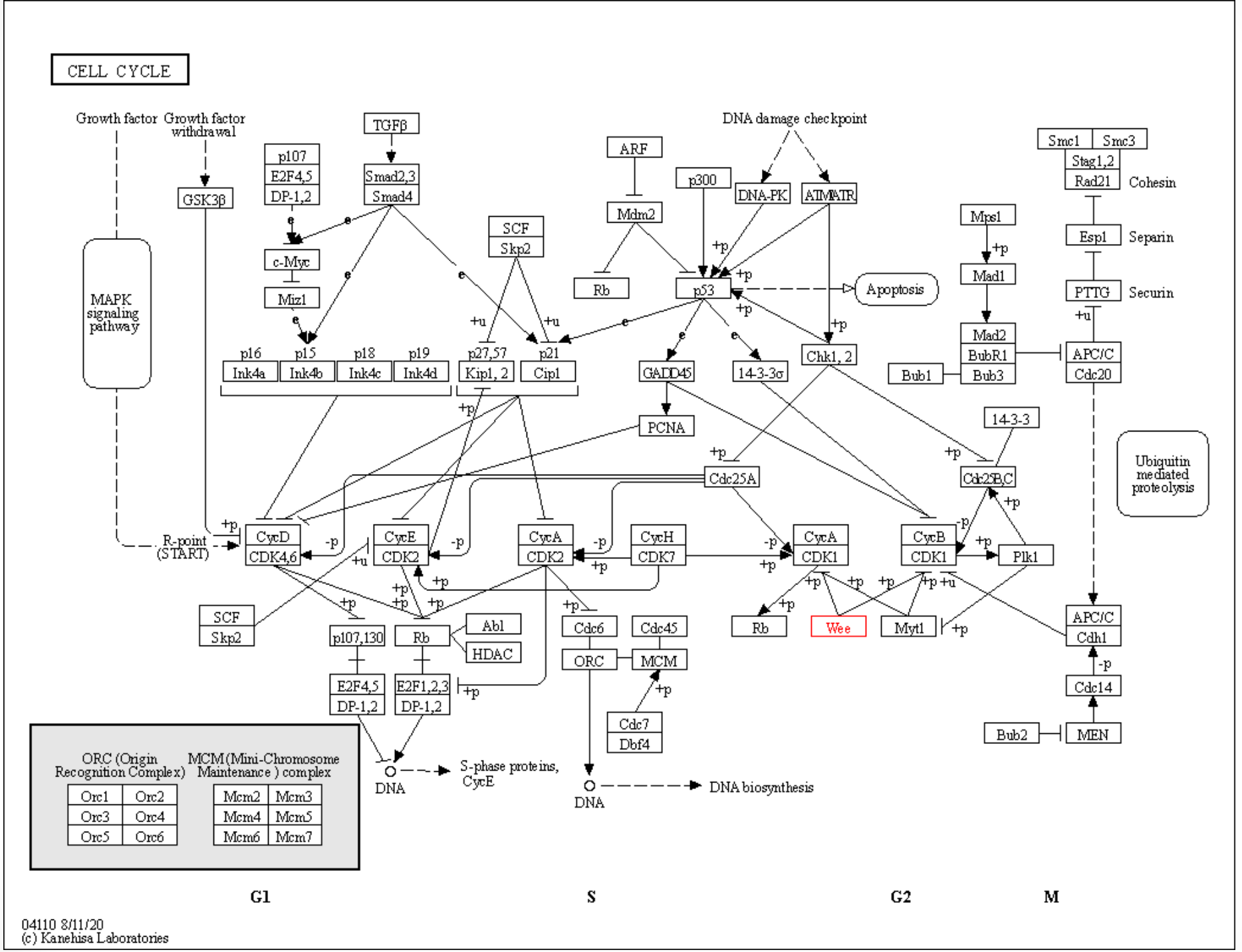
Pishvaian et al. (2020)

CHK1 Inhibitor

- Checkpoint kinases (Chk1 and Chk2) are involved in cell cycle control. Chk1 is a central component of genome surveillance pathways and is a key regulator of the cell cycle.

- Laquente et al. (2017) performed a phase I/II clinical trial for the CHK1 inhibitor rabusertib (LY2603618) combined with gemcitabine vs. gemcitabine alone in patients with locally advanced or metastatic PDAC.

- **No significant differences in OS, PFS, ORR, or duration of response** were found either.


CELL CYCLE
Growth factor
Growth factor withdrawal
GSK3β
MAPK signaling pathway
TGFβ
Smad2,3
Smad4
p107
E2F4,5
DP-1,2
c-Myc
Miz1
SCF
Skp2
ARF
Mdm2
Rb
p300
DNA damage checkpoint
DNA-PK
ATM/ATR
p53
Apoptosis
Chk1, 2
GADD45
14-3-3σ
p16
Ink4a
p15
Ink4b
p18
Ink4c
p19
Ink4d
p27,57
Kip1, 2
p21
Cip1
PCNA
Cdc25A
R-point
(START)
CycD
CDK4,6
CycE
CDK2
CycA
CDK2
CycH
CDK7
CycA
CDK1
CycB
CDK1
Cdc25B,C
14-3-3
Plk1
Mps1
Mad1
Mad2
BubR1
Bub3
Bub1
Smc1
Smc3
Stag1,2
Rad21
Cohesin
Esp1
Separin
PTTG
Securin
APC/C
Cdc20
Ubiquitin mediated proteolysis
APC/C
Cdh1
Cdc14
MEN
Bub2
Abl
HDAC
p107,130
Rb
E2F4,5
DP-1,2
E2F1,2,3
DP-1,2
Cdc6
Cdc45
ORC
MCM
Cdc7
Dbf4
Rb
Wee
Myt1
DNA
S-phase proteins, CycE
DNA
DNA biosynthesis
ORC (Origin Recognition Complex)
Orc1
Orc2
Orc3
Orc4
Orc5
Orc6
MCM (Mini-Chromosome Maintenance) complex
Mcm2
Mcm3
Mcm4
Mcm5
Mcm6
Mcm7
G1
S
G2
M
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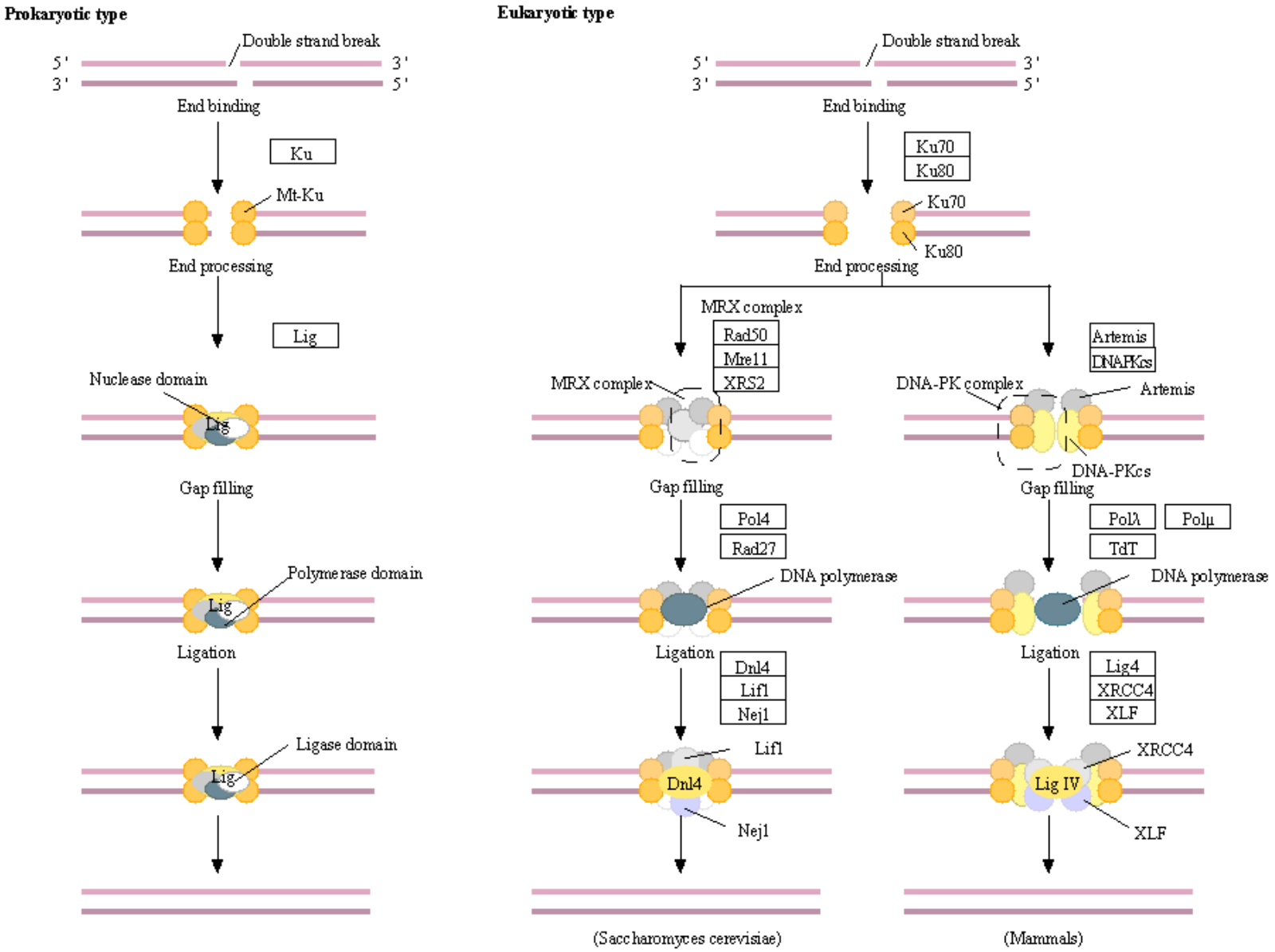
DNA-PK Inhibitor

- A phase II trial on the safety and efficacy of the combination of the *DNA-PK* inhibitor LY3023414 with abemaciclib in previously treated metastatic PDAC patients compared to standard-of-care gemcitabine or capecitabine found that the combination treatment had a **significantly worse PFS** (1.81 vs. 3.25 months, p = 0.012).

NON-HOMOLOGOUS END-JOINING



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Patient Selection

- Preclinical models have shown that several **DDR targeted therapies are more effective in models that defects in DNA repair pathways** and this principle of synthetic lethality has been adapted by clinical trials.

- While the application of targeted therapy in patients with *BRCA* mutations has had success in other cancer types (most notably in breast and ovarian cancer), the fraction of patients with ***BRCA* mutations is relatively small in PDAC** and patients with **other DDR gene mutations may also benefit** from these therapies.

- Alternatively, DDR deficiency might also serve as **biomarker for response to non-targeted therapies.**

Discussion

- So far, clinical trials for DDR targeting drugs have shown limited results beyond the approval of Olaparib in the maintenance setting for patients with germline *BRCA1/2* mutations.
- To improve treatment, **representative models are needed**, especially those that model DDR deficiency, to test drugs and to develop biomarkers that predict patient response.
- Clinical rationale exists to expand the use of DDR targeting agents, however, to date there are **no validated predictors of treatment response** with these agents for patients with DDR deficient tumors beyond *BRCA1/2*.

- Cell lines are by far the most frequently used model for PDAC. However, DDR deficiency studies are mainly limited to the ***BRCA2*-mutant cell line Capan-1.**

- Our query of the PDAC cell lines in the CCLE database for the top 10 most commonly mutated DDR genes (excluding *TP53*) found that **20 cell lines contain one or multiple DDR gene mutations**.