Pancreatic Cancer (PDAC) Treatments

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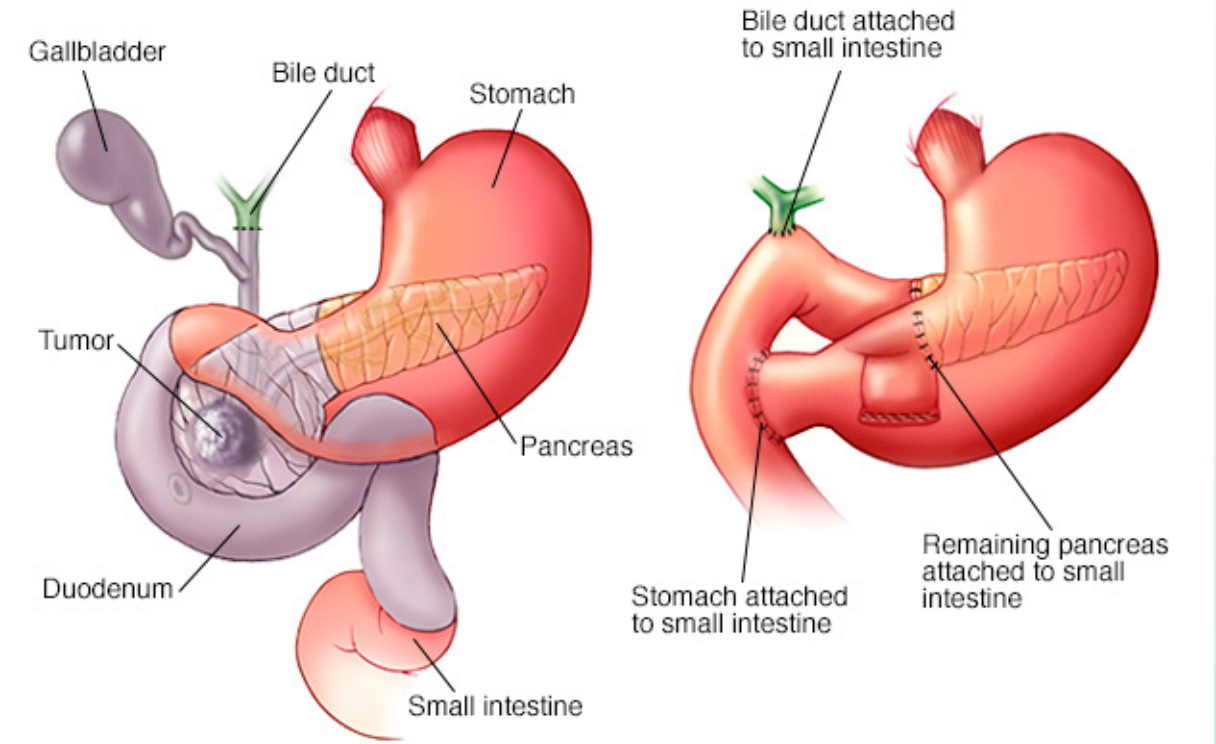
Standard Therapy

Steps	Resectable	BRPC/LAPC	Metastatic
1	Surgery	Neoadjuvant Chemotherapy	Metastatic Chemotherapy (Same as Neoadjuvant Chemotherapy)
2	Adjuvant Chemotherapy	Surgery	
3		Adjuvant Chemotherapy	

Complications: Biliary obstruction, Gastric outlet obstruction
Cachexia and anorexia, Exocrine insufficiency, Depression

Standard Therapies Resectable

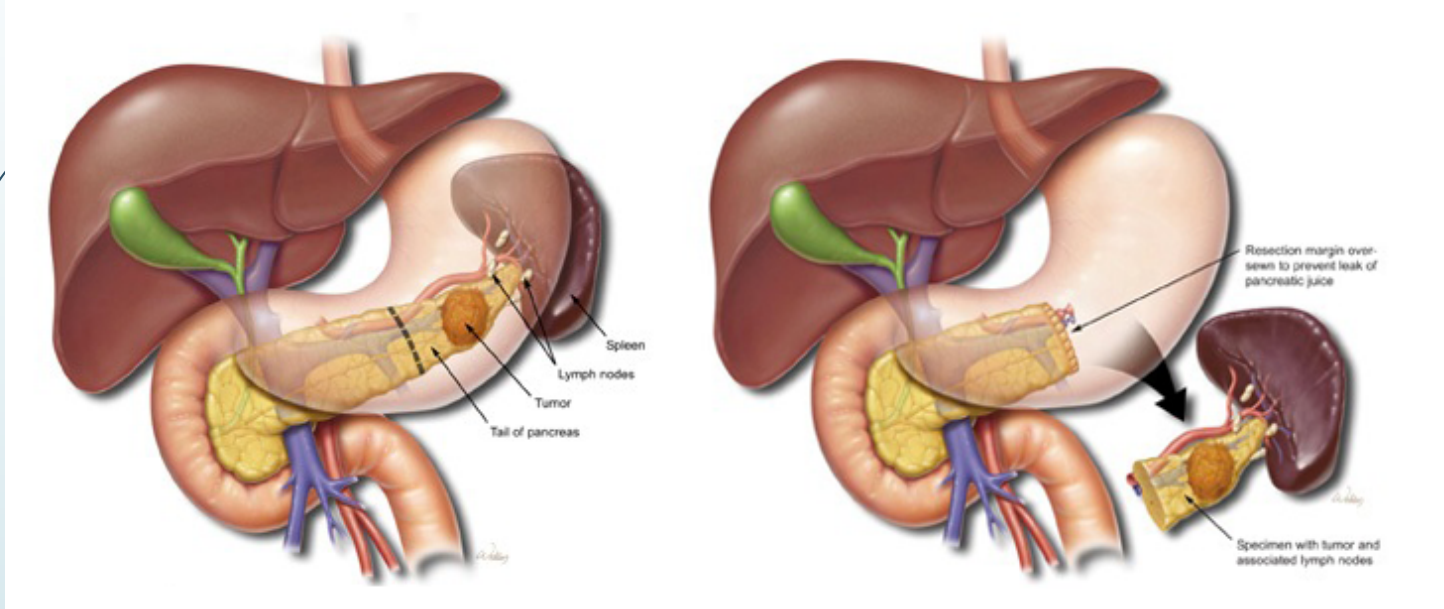
- Partial Pancreaticoduodenectomy (Whipple)



- https://www.mayoclinic.org/tests-procedures/whipple-procedure/home/ovc-20315800

Standard Therapies Resectable

- Distal Pancreatectomy with Splenectomy

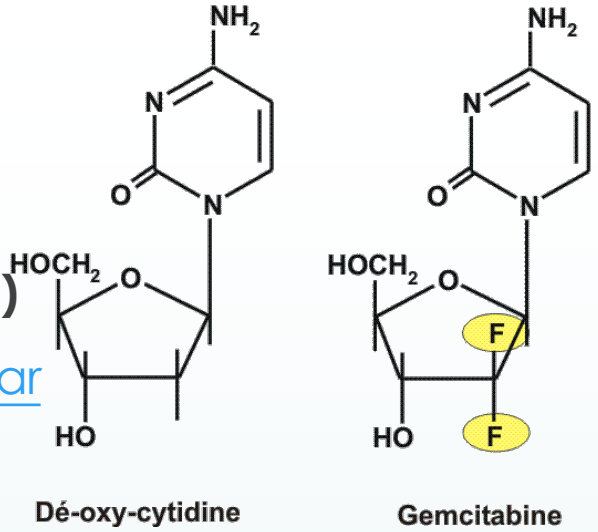


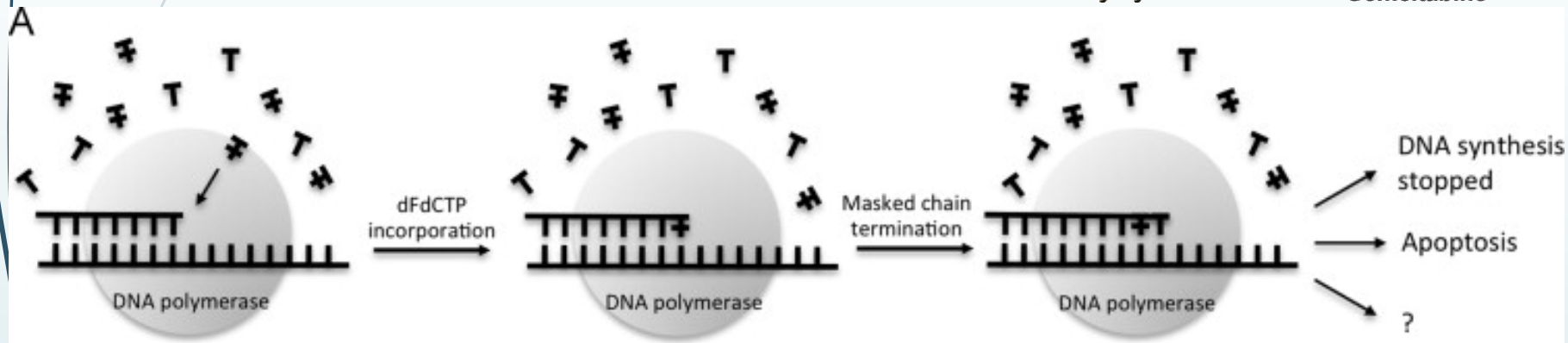
- https://www.bcm.edu/healthcare/care-centers/pancreas-center/procedures/distal-pancreatectomy-splenectomy

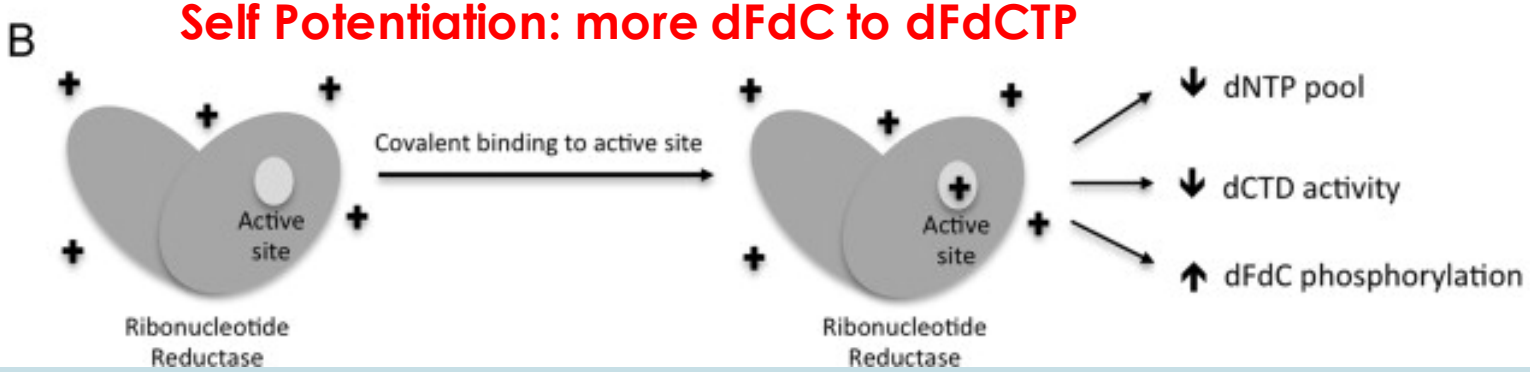
Standard Therapies Resectable - Adjuvant

- **5-Fluorouracil**
  - Thymidylate Synthase (TS) Inhibitor: Inhibit thymidine synthesis
  - ESPAC-1/ESPAC-3(2009) Observationa vs 5-FU: median survival 16.8 vs 23.2 months, p = 0.003
- **Gemcitabine**
  - 2', 2'-difluoro 2'deoxycytidine, dFdC
  - Fake cytidine, eludes base-excision repair, thus creates a irreparable error and leads to cell death
  - CONKO-001(2013) Observation vs Gemitabine: median survival 20.2 vs 22.8 months, p = 0.005

- dFdCTP: 2′,2′-difluoro-2′-deoxycytidine triphosphate (gemcitabine triphosphate)
- Gemcitabine: Metabolism and molecular mechanisms of action, sensitivity and chemoresistance in pancreatic cancer





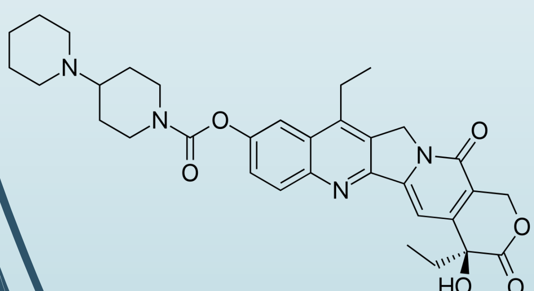


Standard Therapies Borderline / Locally Advanced

- 1/3 initially BRPCs and selected LAPCs become resectable after **neoadjuvant therapy**
- **Gemcitabine + Nab-paclitaxel**
  - Nanoparticle albumin–bound paclitaxel: Prevent normal breakdown of microtubules during cell division
- **FOLFIRINOX**
  - **FOL**inic acid, 5-**F**lurouracil, **IRIN**tecan and **OX**aliplatin
  - **Irintecan**: Topoisomerase inhibitor
  - **Oxaliplatin**: Platinum-based antineoplastic agent, inhibits DNA repair/synthesis

Standard Therapies 2nd Line

- **MM-398**
  - **Nanoliposomal** formulation of irinotecan, prolonged circulation in bloodstream.
  - **NAPOLI-1**: 5-FU/folinic acid (weekly) vs 5-FU/folinic acid + MM-398 (fortnightly): median survival 4.2 vs 6.1 months, p = 0.012



國 家 衛 生 研 究 院 新 聞 稿

發稿日期：104 日 12 月 3 日　　聯絡人：賴璿萱 0921137880

發稿對象：台北醫藥衛生記者

全球第一個證實可延長第一線化學治療失敗之轉移性胰腺癌患者整體存活期 台灣癌症新藥開發史上重要里程碑 刊登頂尖 Lancet

由國家衛生研究院癌症研究所陳立宗特聘研究員兼所長之研究團隊結合台北榮總及成大醫院等 8 個醫學中心共同完成胰腺癌新藥

NAPOLI-1)，是目前全世界

驗中，第一個成功地證明可

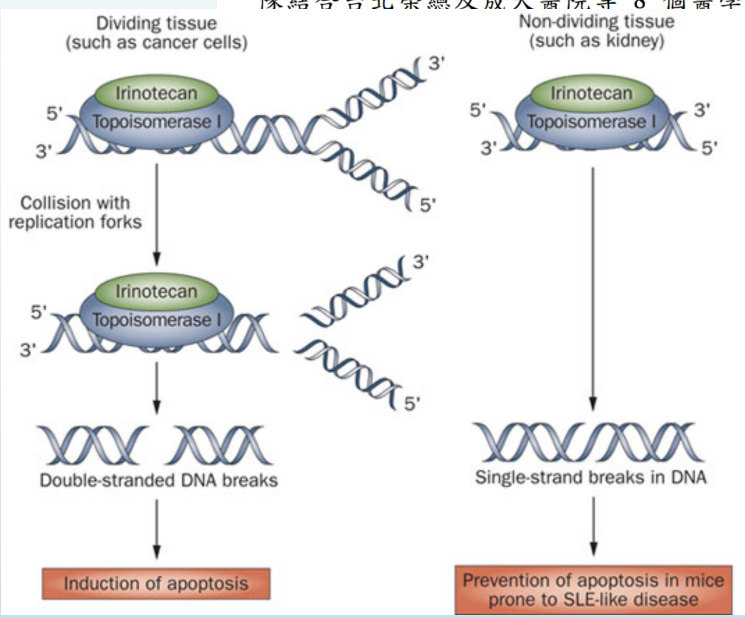
gemcitabine 而無效之轉移

究成果**刊登於本月發表的國**

達 45)，備受國際矚目。而

史上第一個獲得美國 FDA 核

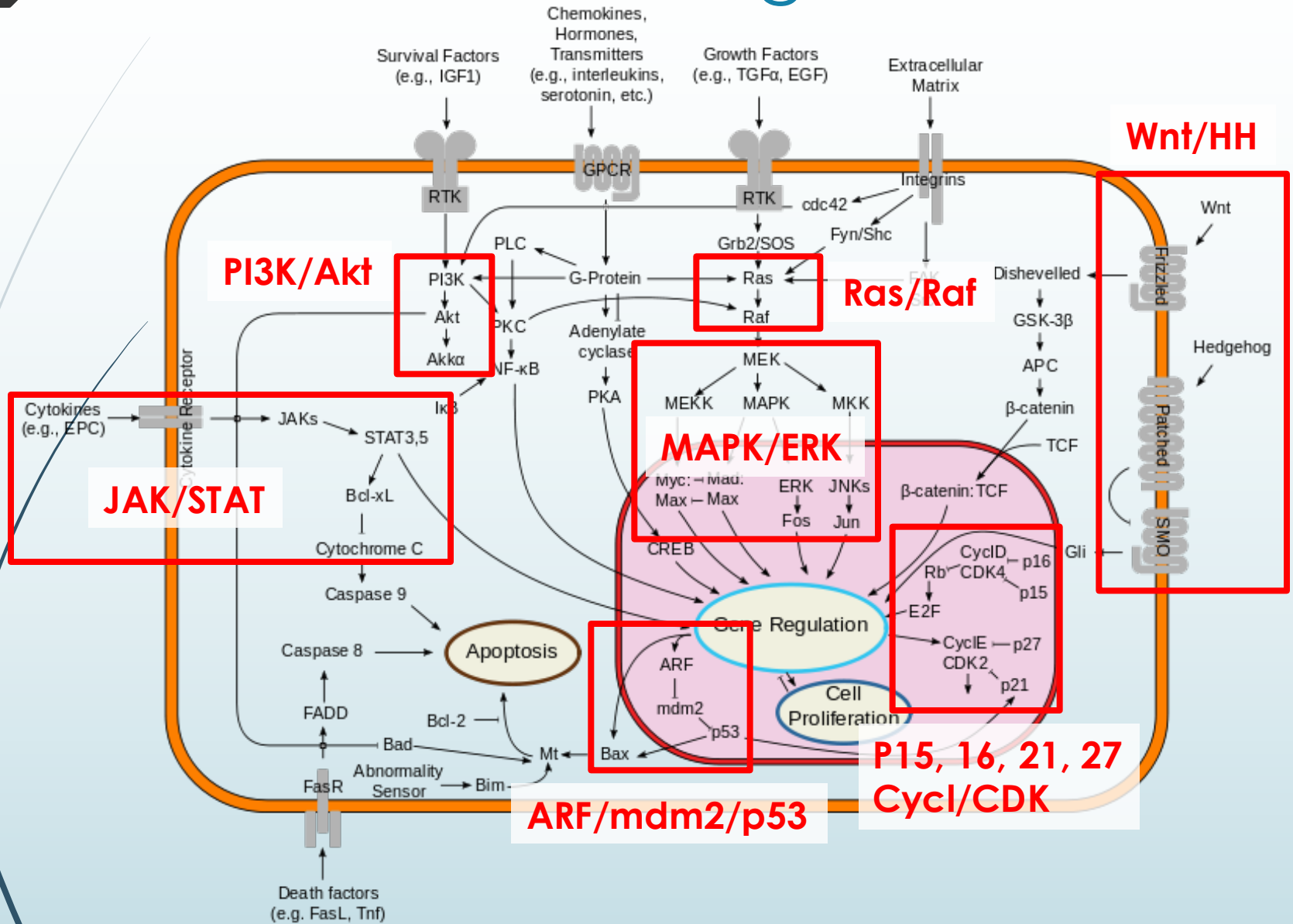
上重要的里程碑。

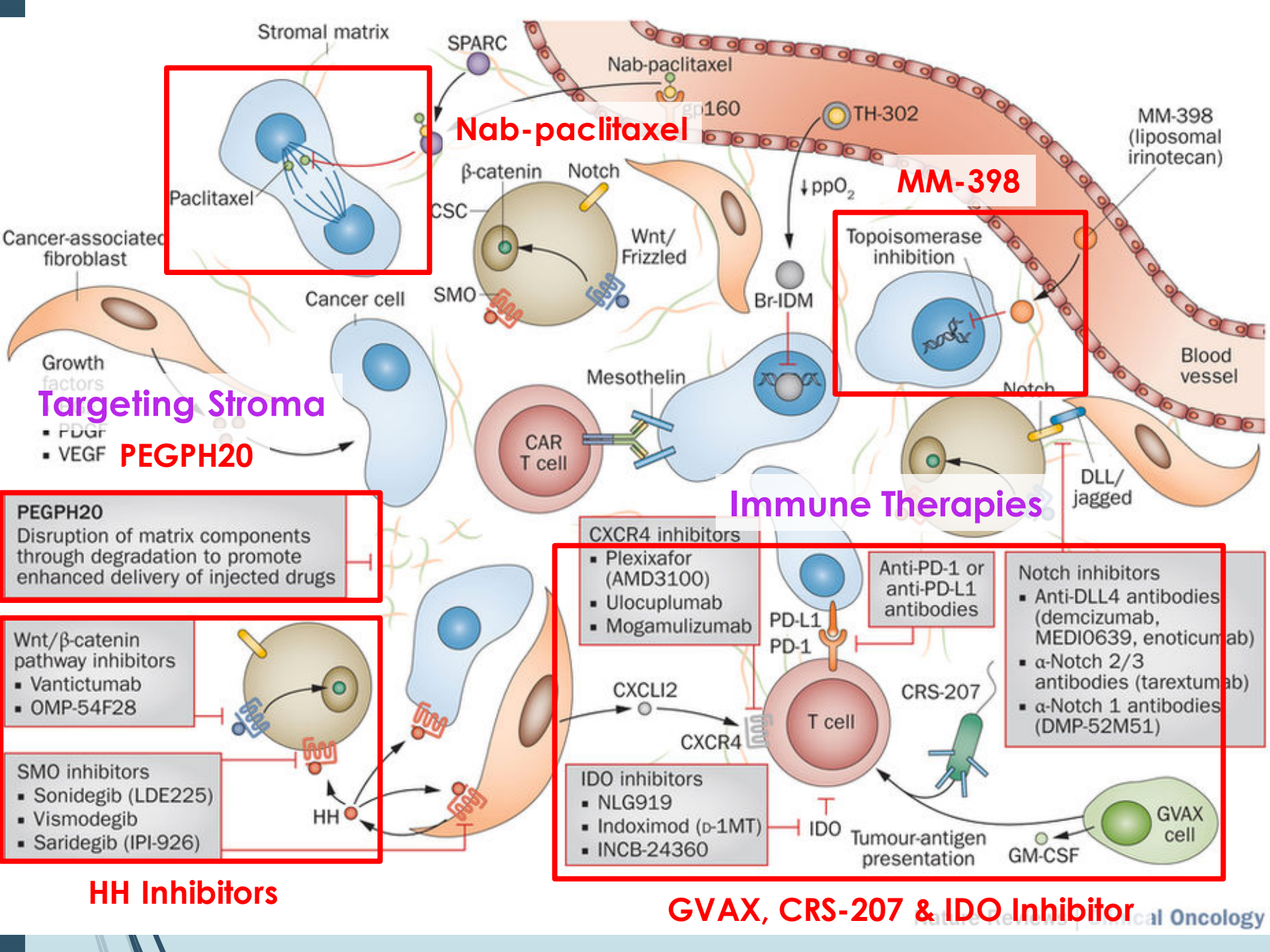


Novel Treatments

Target therapies

Treatment Strategies



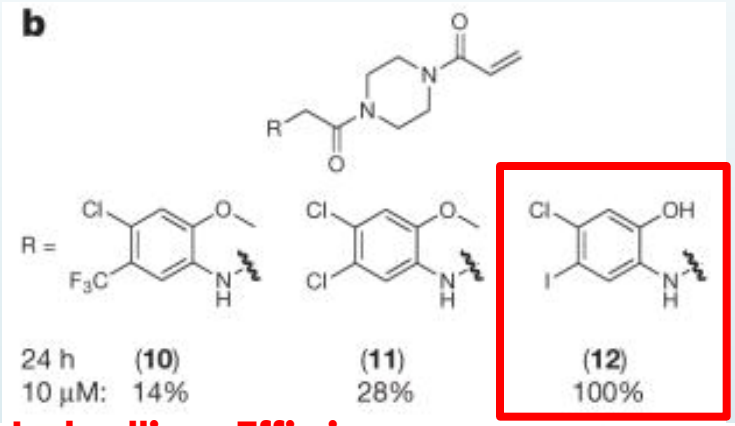

Stromal matrix
SPARC
Nab-paclitaxel
Nab-paclitaxel
gp160
TH-302
MM-398
(liposomal
irinotecan)
MM-398
Paclitaxel
β-catenin
Notch
CSC
Wnt/
Frizzled
SMO
↓ppO2
Br-IDM
Topoisomerase
inhibition
Cancer-associated
fibroblast
Cancer cell
Blood
vessel
Growth
factors
• PDGF
• VEGF
PEGPH20
Targeting Stroma
Mesothelin
CAR
T cell
Notch
DLL/
jagged
Immune Therapies
PEGPH20
Disruption of matrix components
through degradation to promote
enhanced delivery of injected drugs
CXCR4 inhibitors
• Plexixafor
(AMD3100)
• Ulocuplumab
• Mogamulizumab
Anti-PD-1 or
anti-PD-L1
antibodies
PD-L1
PD-1
Notch inhibitors
• Anti-DLL4 antibodies
(demcizumab,
MEDI0639, enoticumab)
• α-Notch 2/3
antibodies (tarextumab)
• α-Notch 1 antibodies
(DMP-52M51)
Wnt/β-catenin
pathway inhibitors
• Vantictumab
• OMP-54F28
CXCLI2
CXCR4
T cell
CRS-207
SMO inhibitors
• Sonidegib (LDE225)
• Vismodegib
• Saridegib (IPI-926)
HH
IDO inhibitors
• NLG919
• Indoximod (D-1MT)
• INCB-24360
IDO
Tumour-antigen
presentation
GM-CSF
GVAX
cell
HH Inhibitors
GVAX, CRS-207 & IDO Inhibitor

Ras Inhibitors
Kras G12D

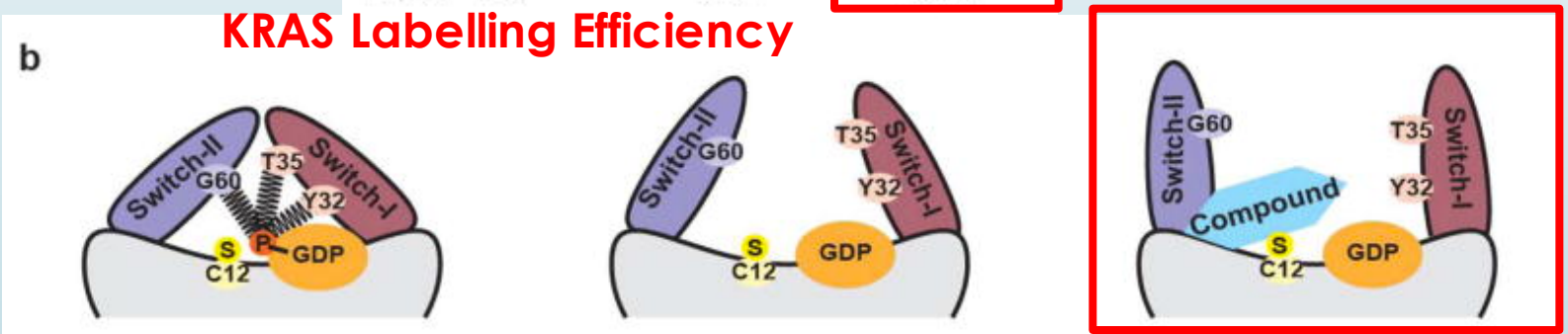
- Ras is traditionally considered undruggable because of great GTP affinity
- point mutation (GGT → GAT) resulting in a single amino-acid change **from glycine to aspartic acid in codon 12 (KrasG12D)**
- Activated KrasG12D is associated with **invasion and metastasis (EMT) of pancreatic cancer cells** through **inhibition of E-cadherin**

RAS Inhibitors
KRAS (G12C) Allosteric Inhibitor

- Mutant Cys 12
- Switch-II pocket (S-IIP)
- Occupy Gly 60 – Disrupt γ-phosphate contact

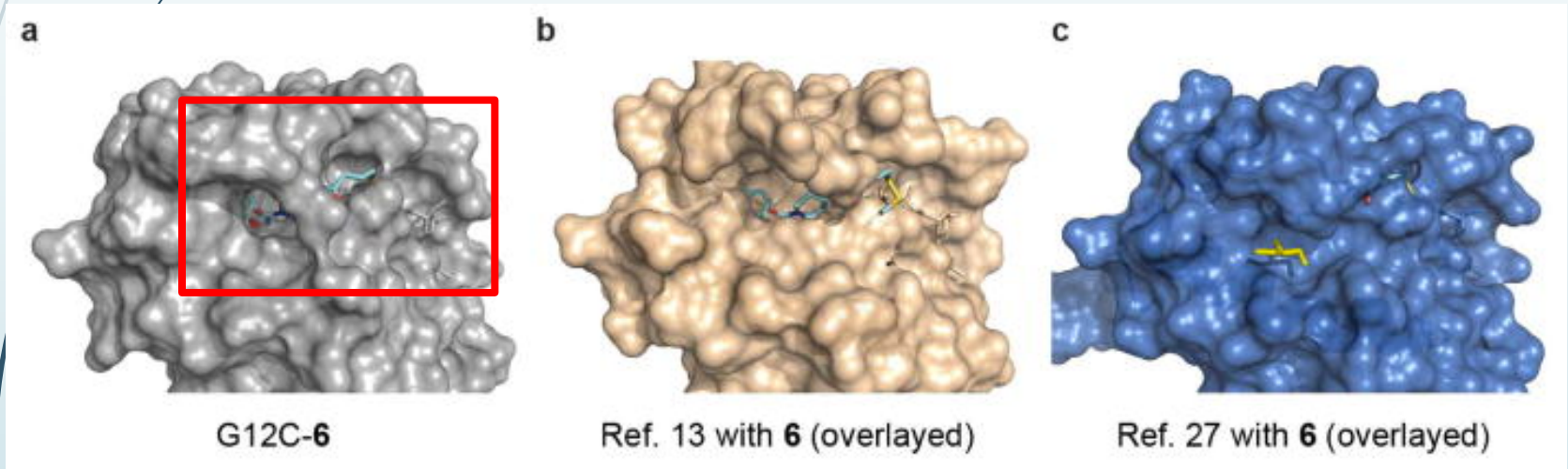


KRAS Labelling Efficiency



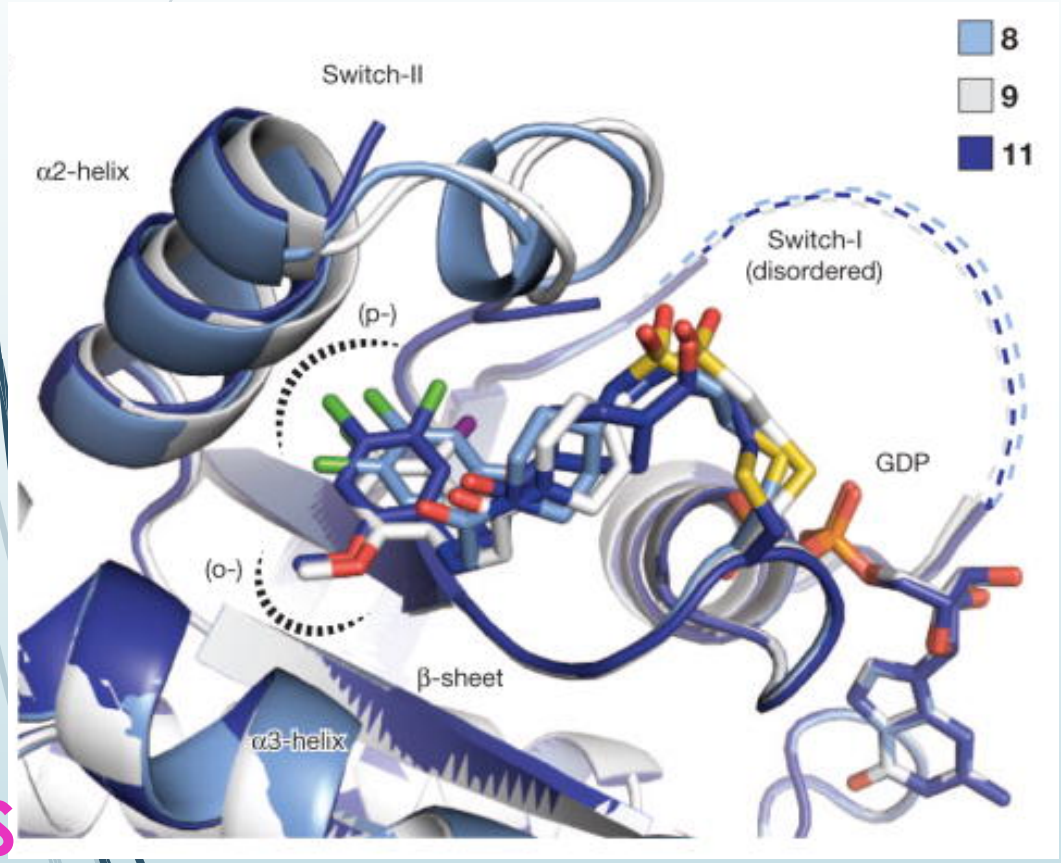
RAS Inhibitors
KRAS (G12C) Allosteric Inhibitor

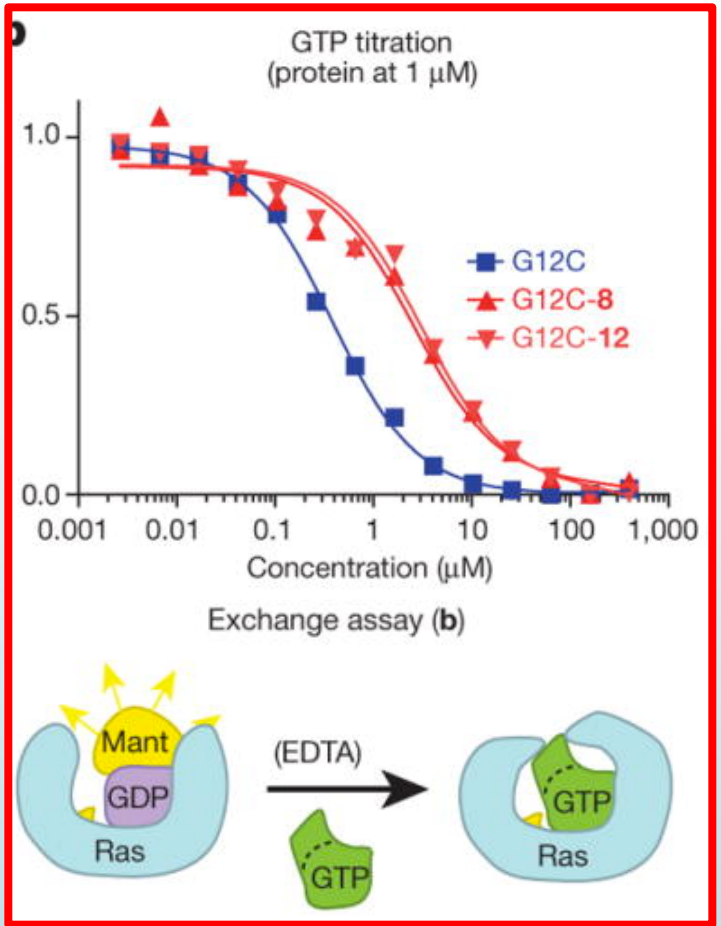
- (a) G12C with compound 6
- (b) wildtype with compound 6
- (c) G12D with compound 6



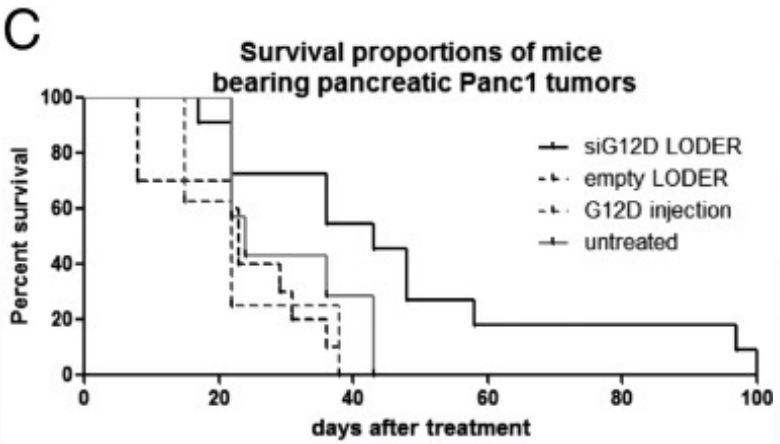
RAS Inhibitors
KRAS (G12C) Allosteric Inhibitor

- GTP affinity is significantly decreased relative to GDP

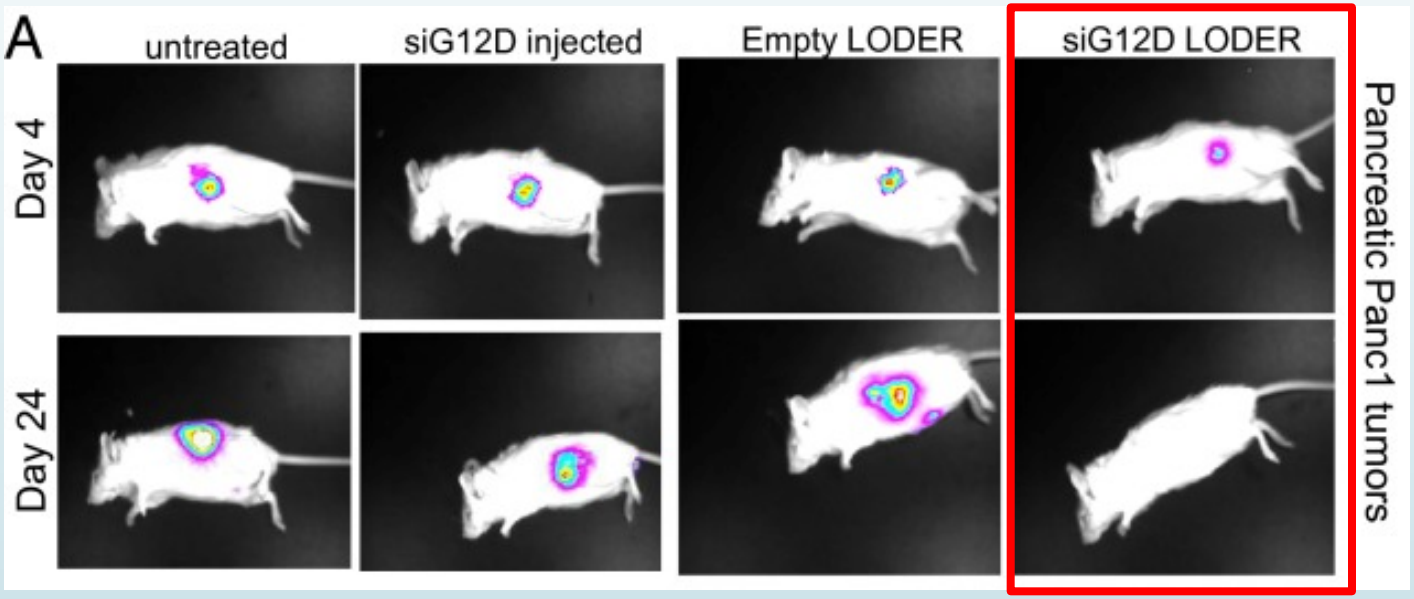




RAS Inhibitors siRNA

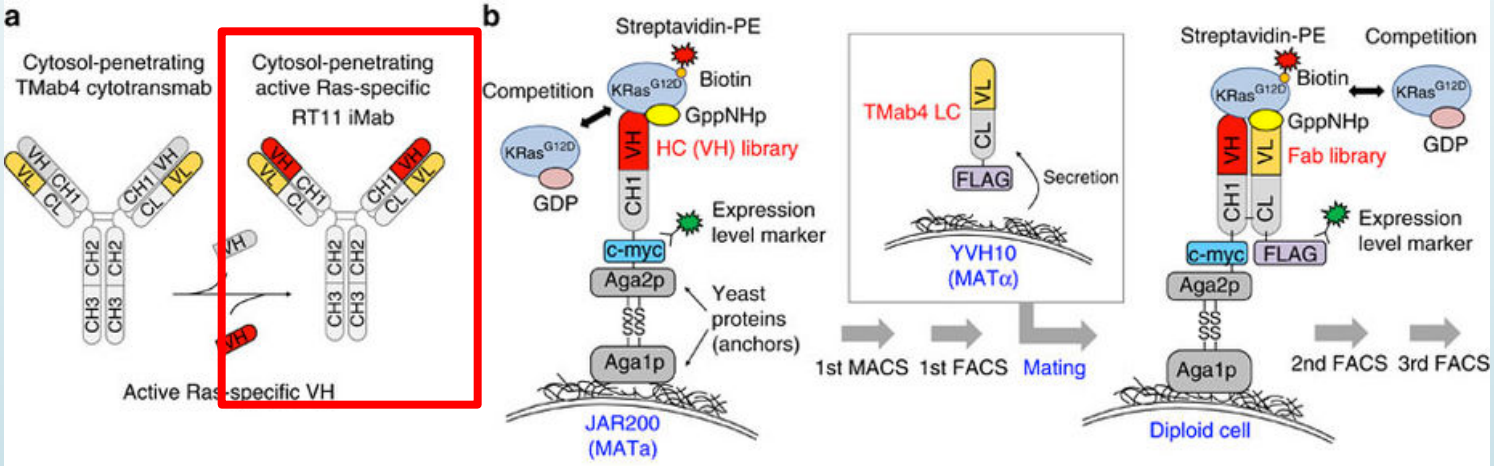


- **anti-KRAS (G12D) siRNA + LODER**
- LODER: Millimetric biodegradable polymeric matrix
  Protection and stable local drug release for 2 months



RAS Inhibitors Antibody

- **Cytosol-penetrating antibody TMab4 (IgG1) VL**
  - clathrin-mediated endocytosis
  - endosomal escape
- **GTP-bound active Ras specific RT11 iMab VH**
  - Anti-proliferative activity weaker than sorafenib (Raf kinase inhibitor) and LY294002 (PI3K-Akt inhibitor)



Other Targeted Therapies

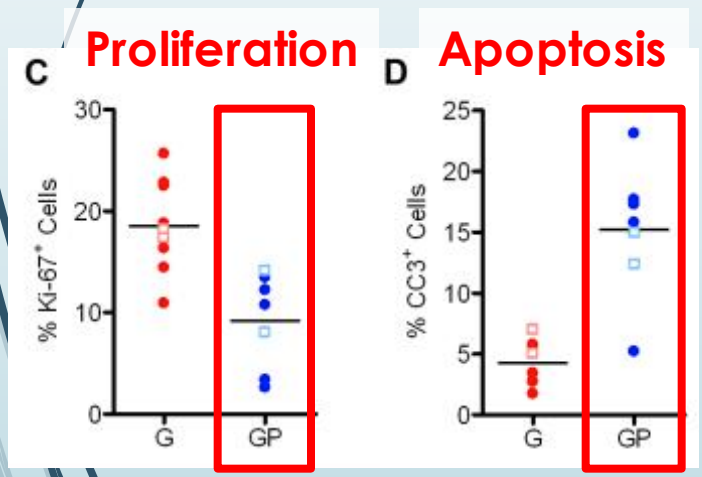
- MEK Inhibitors: Trametinib / Pimasertib
- Farnesyltransferase Inhibitors: block KRAS modification
- PDE delta Inhibitor: Deltarasin, blocks KRAS Transport
- JAK Inhibitor: Ruxolitinib
- Autophagy Inhibitor: Hydroxychloroquine
- PI3K-mTOR Inhibitor: Everolimus
- HH/SMO Inhibitors: Vismodegib, Saridegib

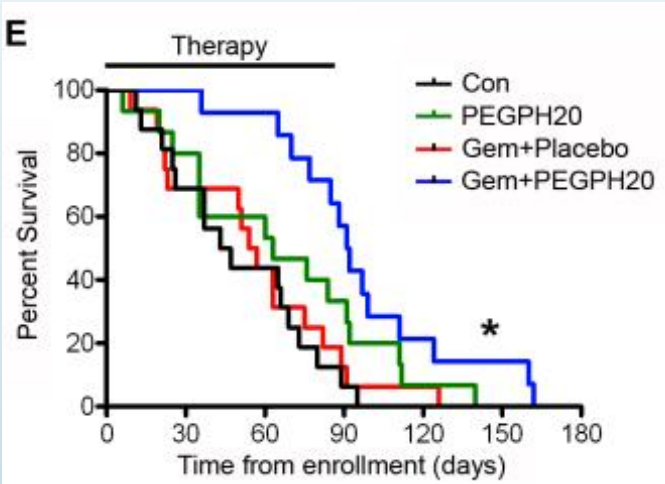
No **P**rogression **F**ree **S**urvival (**PFS**) Benefits !

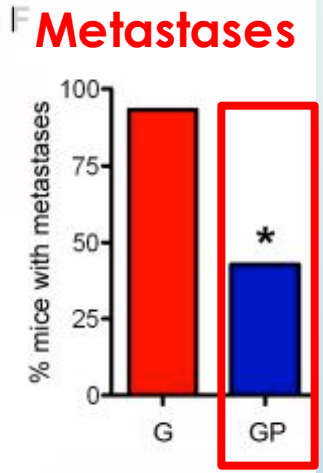
At least for now…

Targeting Stroma Drug Delivery

- **Hyaluronic acid** (glycosaminoglycan) is enriched in the stroma of PDAC(desmoplastic, hypovascular), also increased in expression at metastatic sites.
- **PEGPH20**
  - PEGylated for of **human hyaluronidase(rHuPH20)**, decreased tumor interstitial fluid pressure.
  - Gemcitabine + PEGPH20





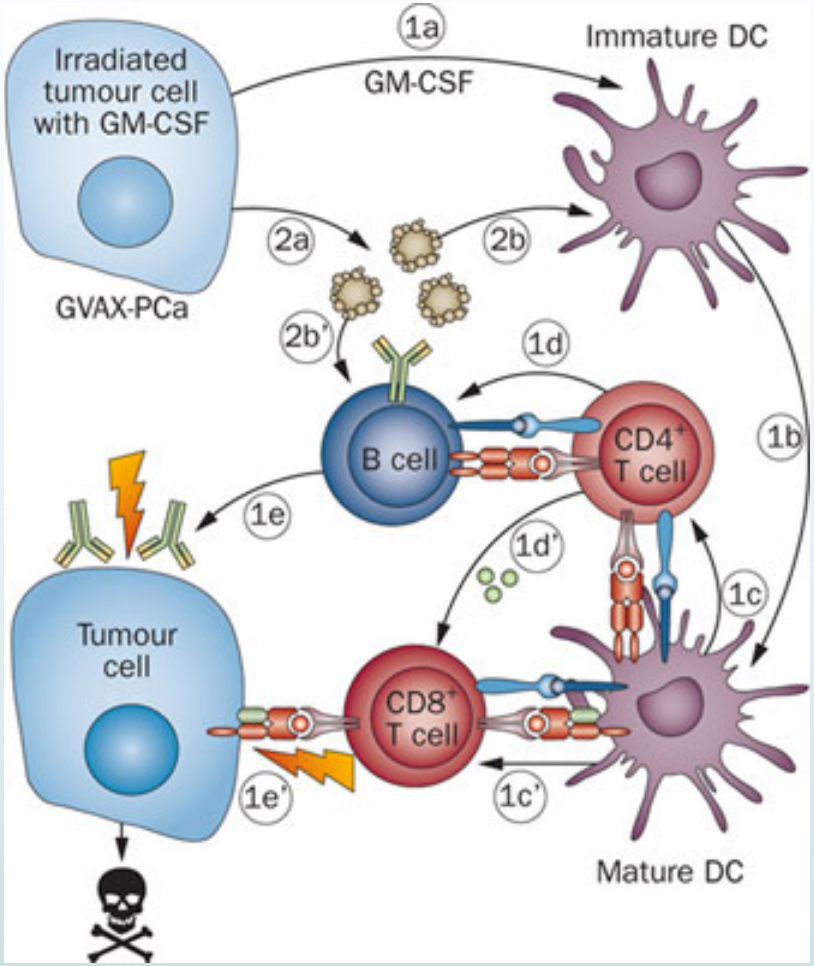


Immunotherapies

Overcoming immunosuppressive environments

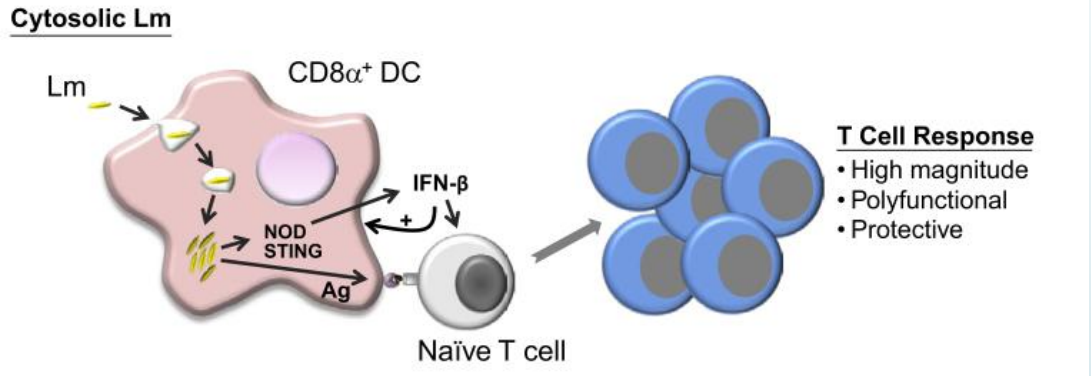
Immunotherapies Cancer Vaccines

- **GVAX**: Irradiated(prevent proliferation) genetically modified whole cancer cell that secrete GM-CSF.
- **Granulocyte-Macrophage Colony-Stimulating Factor** (GM-CSF): Immunostimulatory cytokine, enhance immune response by recruiting and activating DCs at injection site.

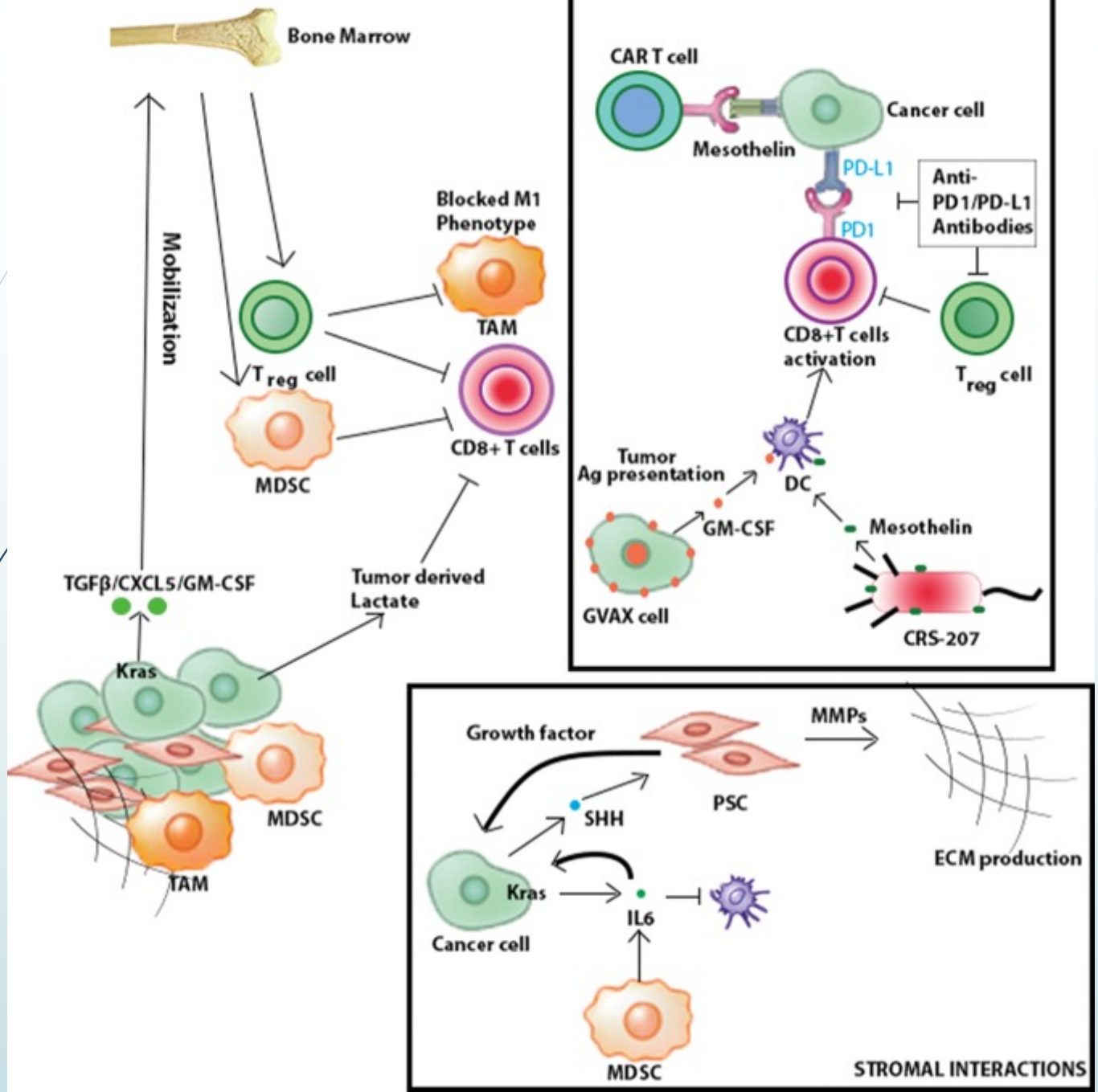


Immunotherapies Cancer Vaccines

- **CRS-207**: **Listeria monocytogenes** invade professional phagocytes within the immune system and **express mesothelin (tumor antigen common in PDAC)**, which may activate a cytotoxic T-lymphocyte (CTL) response against mesothelin-expressing tumor cells.

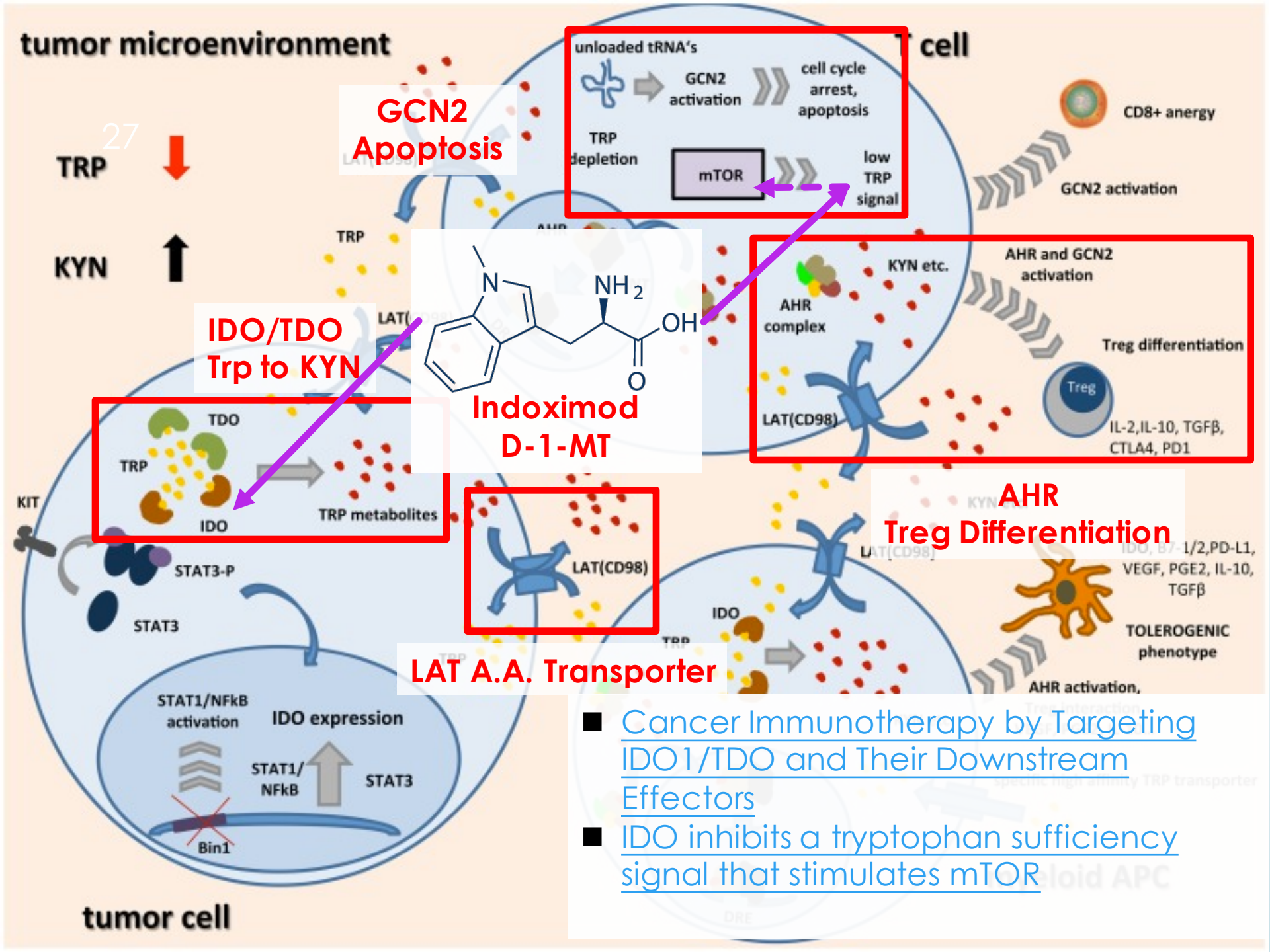


- **PD-1/PD-L1 Inhibitors**: PD-1 (with ligand PD-L1/2) is an immune-checkpoint receptor expressed in stroma and cancer cells that inactivates T-cell response.


Bone Marrow
Mobilization
Blocked M1
Phenotype
TAM
T reg cell
CD8+ T cells
MDSC
TGFβ/CXCL5/GM-CSF
Tumor derived
Lactate
Kras
MDSC
TAM
PROSPECTIVE TARGETS & THERAPIES
CAR T cell
Cancer cell
Mesothelin
PD-L1
PD1
Anti-
PD1/PD-L1
Antibodies
CD8+T cells
activation
T reg cell
Tumor
Ag presentation
DC
GM-CSF
Mesothelin
GVAX cell
CRS-207
Growth factor
MMPs
PSC
SHH
ECM production
Kras
IL6
Cancer cell
MDSC
STROMAL INTERACTIONS

Immunotherapies
IDO Inhibitor

- Tryptophan to Kynurenine by **indoleamine-2,3-dioxygenase** and **TRP-2,3-dioxygenase**
- **T cells**
  - **GCN2 activation (uncharged tRNA) leads to cell cycle arrest and apoptosis, mTOR deactivation (low Trp signal)**
  - **AHR and GCN2 activation leads to Treg differentiation**
  - **Immune Suppression!!!**
- **Indoximod D-1-MT/1-D-MT**: Trp mimetic, inhibits IDO-1, IDO-2 and reverses low Trp signal



- Cancer Immunotherapy by Targeting IDO1/TDO and Their Downstream Effectors
- IDO inhibits a tryptophan sufficiency signal that stimulates mTOR

PFA

I wish I knew

大神不要電我

PDAC treatments
PFA – **P**ray **F**or the **A**nswer

- 略去了很多新的Cytotoxic agent和其他Pathway的Inhibitor(e.g. EGFR, HH, JAK, IDO …)因為目前Clinical Trial表示效果不顯著或在PDAC中不普遍
- 癌症真的很嚴格
  - 通常Preclinical Model (GEMM, Xenograft…)一條龍
  - 到了Clinical Trial就一條蟲
  - 還有很多互相矛盾的理論
- Sequencing與Biomarker有助於治療的Patient Selection(e.g. KRAS G12D)
- PDAC是系統性疾病，只使用單一藥物通常效果不大
- Stroma的Desmoplastic response會對藥物造成阻礙，突破後藥效有機會提升(e.g. MM-398)

PDAC treatments References

- Pancreatic cancer: from state-of-the-art treatments to promising novel therapies
- Survival of pancreatic cancer cells lacking KRAS function
- K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions
- KRAS G12D Mutation Subtype Is A Prognostic Factor for Advanced Pancreatic Adenocarcinoma
- Activated KrasG12D is associated with invasion and metastasis of pancreatic cancer cells through inhibition of E-cadherin
- Mutant KRAS is a druggable target for pancreatic cancer
- Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma.
- Genetics and biology of pancreatic ductal adenocarcinoma
- T-cell programming in pancreatic adenocarcinoma: a review
- Therapeutic vaccination based on side population cells transduced by the granulocyte–macrophage colony-stimulating factor gene elicits potent antitumor immunity
- Clinical Development of Listeria monocytogenes–Based Immunotherapies
- Mesothelin targeted cancer immunotherapy