Pancreatic Cancer (PDAC) Treatments

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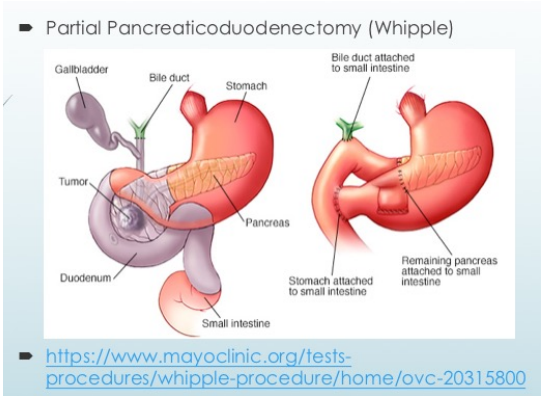
This review will primarily focus on the current standards and future prospects of Pancreatic Ductal Adenocarcinoma (PDAC) treatments.

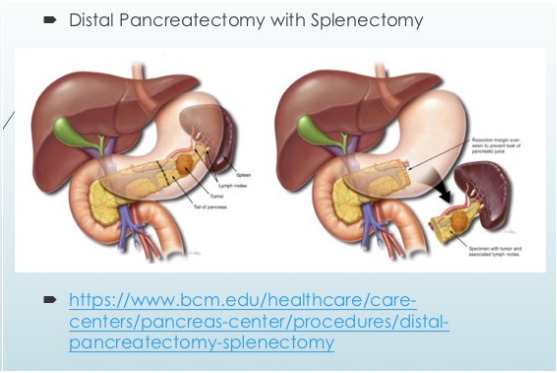
Standard Therapies

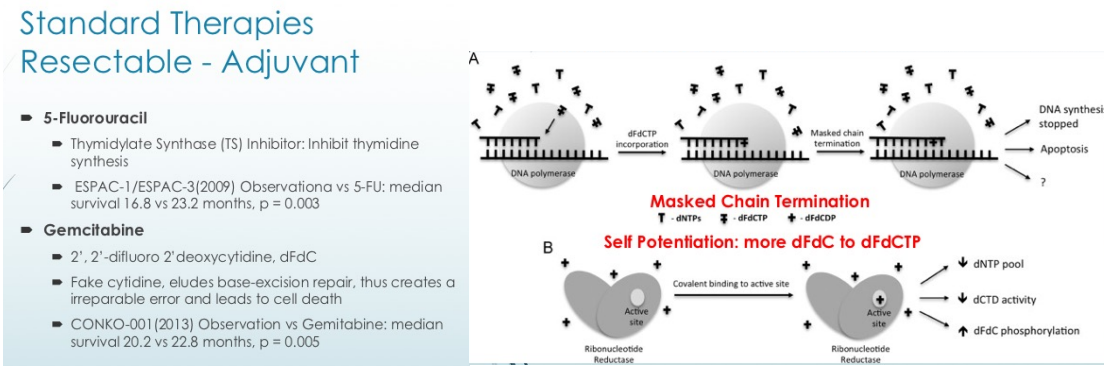
Standard treatment strategies of PDAC can be roughly characterized into 3 different types regarding to the current stage of disease.

<table>
<tr><th>Steps</th><th>Resectable</th><th>BRPC/LAPC</th><th>Metastatic</th></tr>
<tr><td>1</td><td>Surgery</td><td>Neoadjuvant Chemotherapy</td><td rowspan="3">Metastatic Chemotherapy (Same as Neoadjuvant Chemotherapy)</td></tr>
<tr><td>2</td><td rowspan="2">Adjuvant Chemotherapy</td><td>Surgery</td></tr>
<tr><td>3</td><td>Adjuvant Chemotherapy</td></tr>
<tr><td colspan="4">Complications: Biliary obstruction, Gastric outlet obstruction
Cachexia and anorexia, Exocrine insufficiency, Depression</td></tr>
</table>

Firstly, if the PDAC tumor is considered resectable, then surgical removal using Partial Pancreaticoduodenectomy (Whipple Procedure) or Distal Pancreatectomy with Splenectomy is the best solution to eradicating cancer. The surgery is followed by adjuvent chemotherapies, which is either 5-Fluorouracil or Gemcitabine to prevent relapse of cancer. 5-Fluorouracil is a conventional chemotherapy drug that acts as a thymidylate synthase (TS) inhibitor, while Gemcitabine induces masked chain termination of DNA synthesis and is able to self potentiate after entering human body.







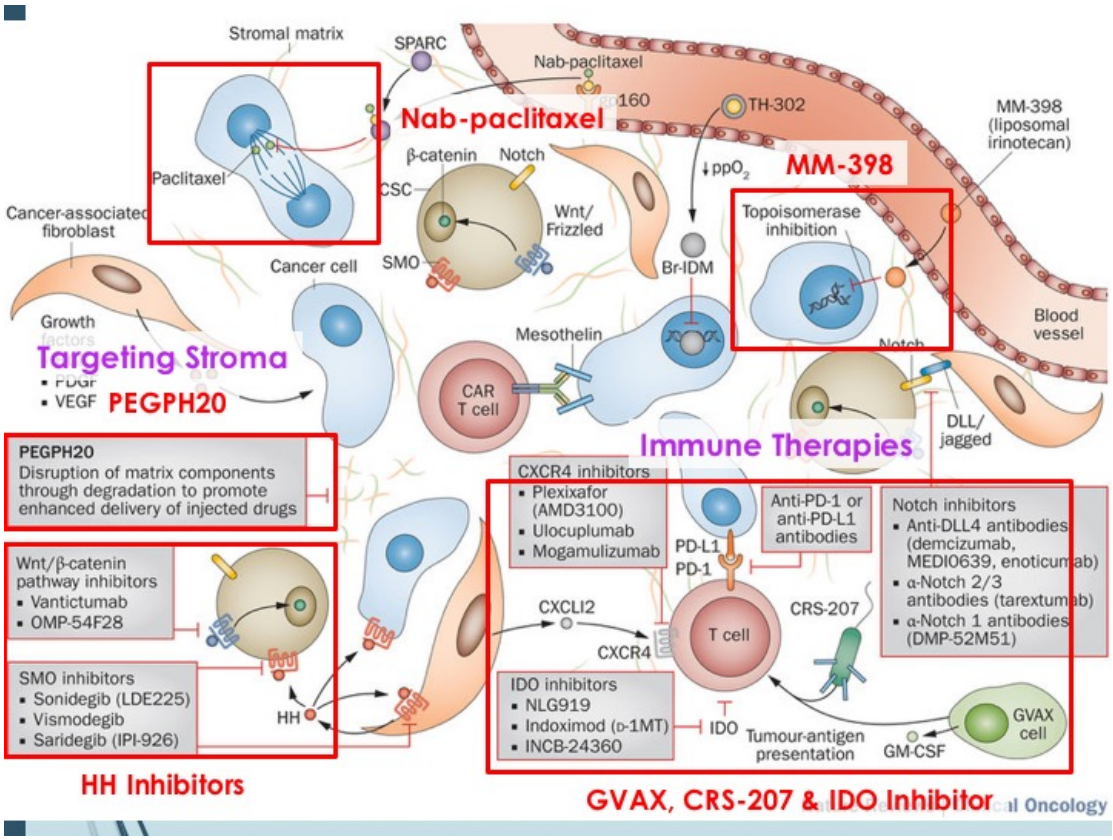
Secondly, if the tumor is borderline resectable (BRPC) or locally advanced (LAPC), employing a neoadjuvant therapy could turn 1/3 patients into surgically resectable pancreatic cancer. Neoadjuvant therapy of PDAC is made up of stronger chemotherapy drugs, such as Gemcitabine plus Nab-paclitaxel (nanoparticle albumin–bound paclitaxel), which prevents normal breakdown of microtubules during cell division or FOLFIRINOX, a hybrid of chemotherapy drugs constituted of FOLinic acid, 5-Flurouracil, IRINtecan and OXaliplatin.

Lastly, if the disease already reached metastic state, using chemotherapy drugs like those used in locally adanced or choosing supportive care are the options left. In addition, PDAC has few second line therapy options once the patient is resistant to first line drugs. One recent second line drug is MM-398, a nanoliposomal formulation of Irinotecan, a topoisomerase inhibitor, allowing its prolonged circulation in bloodstream.

Novel Treatments

Inventing new treatment strategies aiming at PDAC is a constantly innovating field. One of the most popular approach is targeted therapies of signal transduction

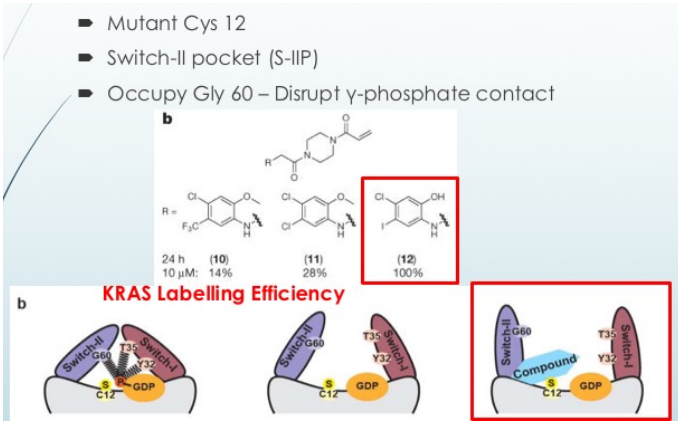
pathways that is activated or deactivated abnormally and eventually caused the pathogenesis of cancer. In addition, new chemotherapy drugs and methods to increase their efficacy, as well as targeting stroma and enhancing immune response in tumor are also promising novel treatments. Here we focused on the advances in targeting one of PDAC's most frequent feature.

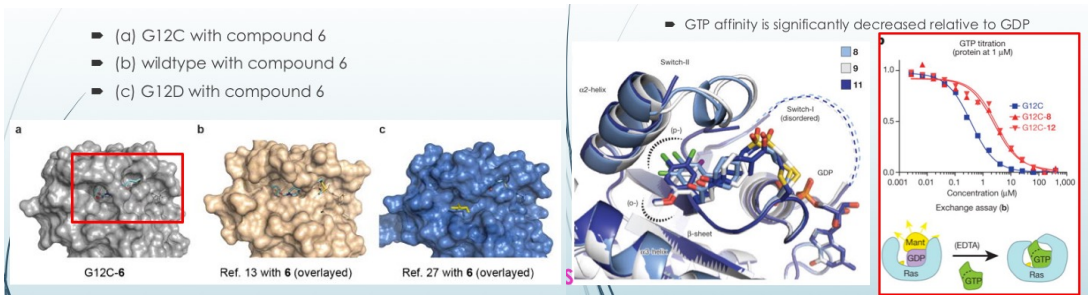


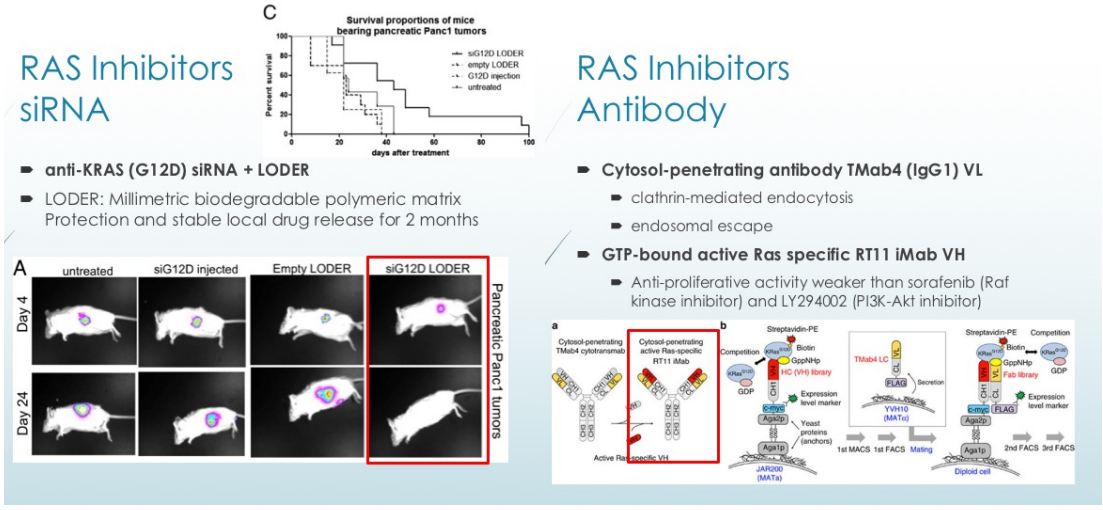
The most common oncogenic mutations in PDAC is KRas G12D, a point mutation (GGT to GAT) resulting in a single amino acid change from glycine to aspartic acid in codon 12. Such mutation is associated with invasion and metastasis (EMT) of pancreatic cancer cells through inhibition of E-cadherin. However, the Ras protein is traditionally considered undruggable because of its great affinity to GTP.

Recently, a small allosteric inhibitor of KRas G12C has been developed. By exploiting its mutant Cys 12, Switch-II pocket and occupying the Gly 60 site, it could efficiently bind to GDP bound state of Ras. This result indicated a potential way to target PDAC tumor cells with KRas G12D mutation, if features of allosteric inhibition can be found in the G12D structure. Other strategies that targets the KRas G12D protein includes using anti-KRas G12D siRNA with a polymeric matrix that stably administered the siRNA and provided siRNA protection from degradation. Also, creating an antibody that can enter a tumor cell and eventually target the KRas G12D protein is also

possible.

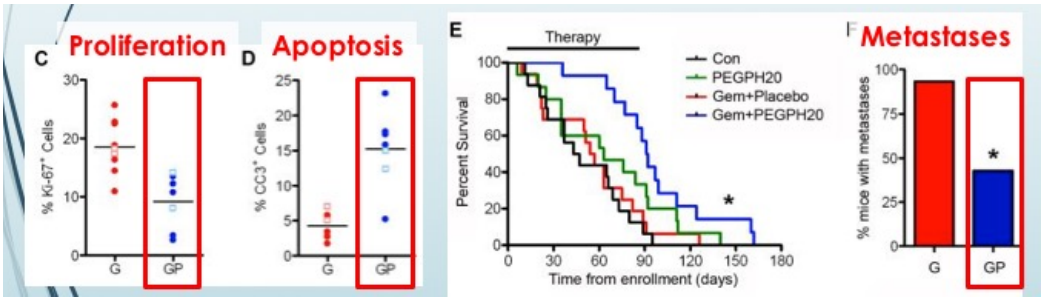






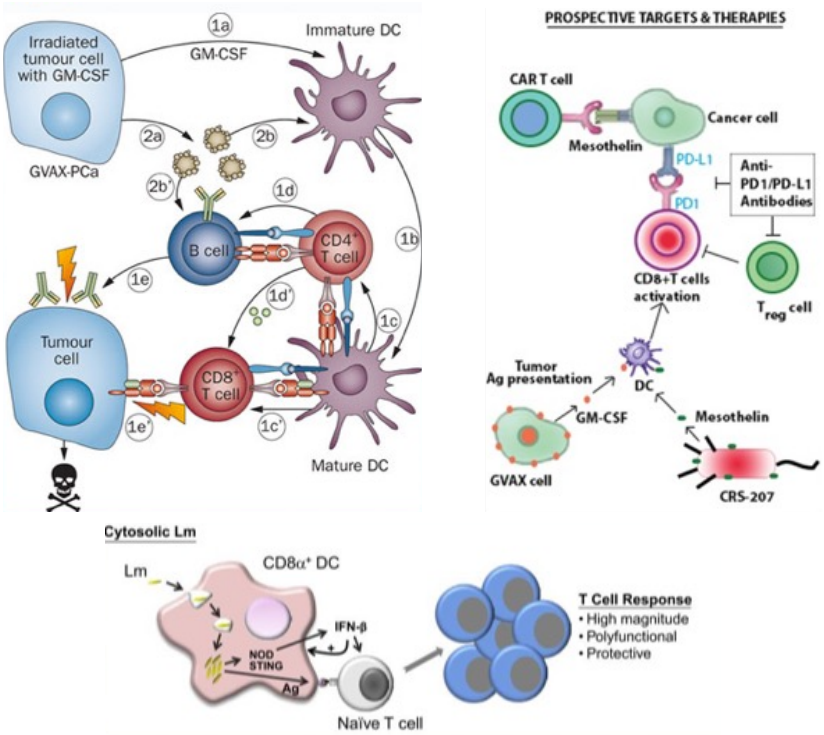
Targeting the Stroma

The PDAC stroma is known to be desmoplastic and hypovascular. Breaking through this barrier can substantially benefit drug responses. One recent drug that addressed this issue is PEGPH20, a PEGylated form of human hyaluronidase. This drug can break through the hyaluronic acid enriched stroma and decrease tumor interstitial pressure. Strong response was shown in preclinical models when PEGPH20 was administered with Gemcitabine.



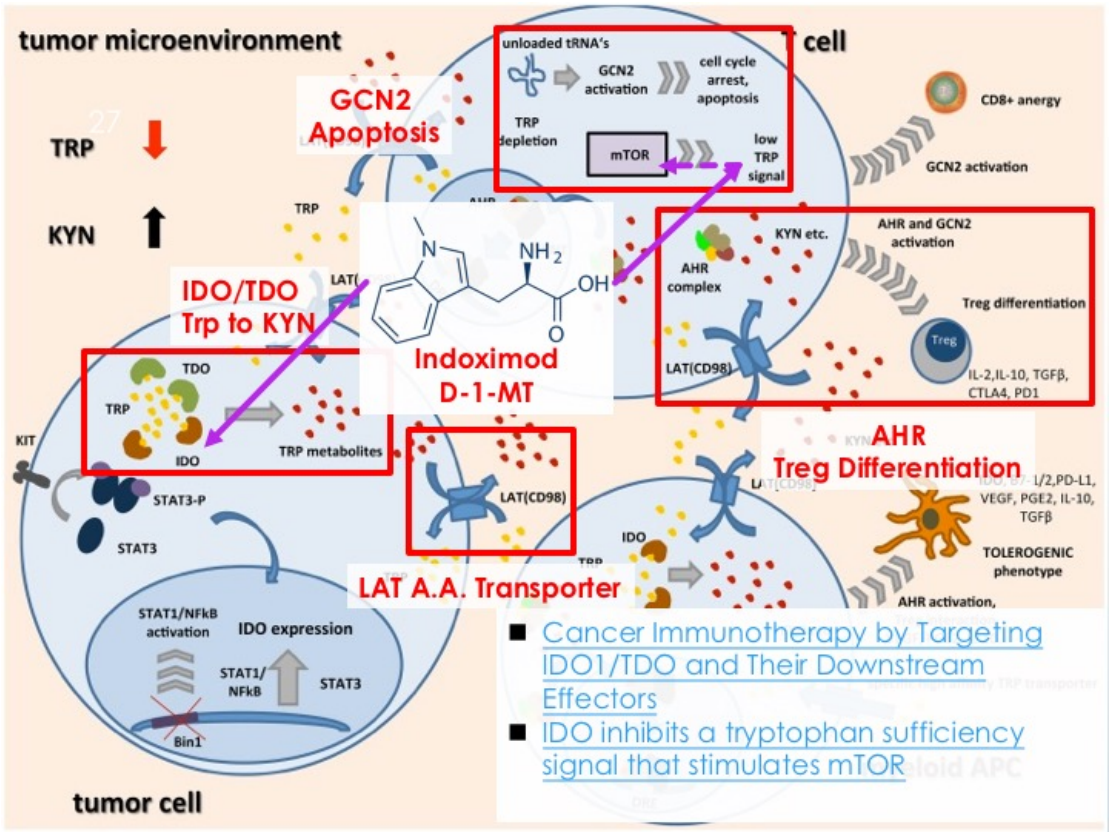
Immunotherapies

Other than targeted therapy, immunotherapies that restore immune response inside the tumor environment is one cutting-edge strategies used in cancer therapy. For PDAC, two cancer vaccines have shown significant results. One is GVAX, irradiated genetically modified cancer cells that secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), which can enhance immune response by recruiting and activating dendritic cells at injection site. Another is CRS-207, a special bacteria Listeria monocytogenes (Lm) that expresses mesothelin, a common tumor antigen for PDAC, and eventually elicit T cell response against tumor cells.



On the other hand, targeting the immune checkpoint pathway PD-1/PD-L1 as well as immune cell metabolism with IDO inhibitors are prominent cancer immunotherapies. In the IDO pathway, tryptophan in tumor cells is metabolized to kynurenine by indoleamine-2,3-dioxygenase (IDO) and TRP-2,3-dioxygenase (TDO). This tryptophan

depletion phenomenon caused GCN2 activation in T cells by uncharged tRNA and mTOR deactivation, leading to cell cycle arrest and apoptosis of T cells. Moreover, GCN2 activation and binding of AHR complex in T cells leads to Treg differentiation. These effects combined largely contributed to immune suppression in the tumor microenvironment. The drug Indoximod, or 1-D-MT, acts as a tryptophan analog that inhibits the IDO-1 and IDO-2 enzyme. Furthermore, Indoximod is also able to reverse the low tryptophan signal in T cell mTOR pathway.



PDAC Treatments: Conclusion

PDAC is undoubtedly a challenging disease to cure. In addition to novel chemotherapy agents and targeted therapy, breaking through the stroma and immunotherapies could be the future decisive factor of PDAC treatment. However, pancreatic tumor cells can develop into lineages with diverse mutations and resistance to current treatments. Therefore, the ability to dynamically adapt is crucial to successful treatments that result in tumor remission and progression free survival.

Using the new biomarkers for drug and patient selection, as well as enhancing the immune system as a flexible and adaptive autonomous drug became a major

direction of future research. Still, new pathways and mechanisms of interactions inside tumor microenvironments, especially with immune cells are yet to be discovered. Limitations of preclinical models can also be observed from previous studies, and new technologies that create models that better represents human will definitely aid PDAC treatment research. More understanding to the pathogenesis of PDAC and more sophisticated harnessing of immunotherapies is expected in the near future.

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