Drug Repurposing as a Source of Innovative Therapies in Pancreatic Cancer

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Background

- **Pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC) is one of the deadliest tumours with 5-year survival rates still under 10%.**
- **Few drugs have been able to make significant improvements** in patient outcomes and, albeit that there is a pipeline of new agents, many fail in phase 2/3 clinical trials**.**
- **Drug repurposing is an alternative drug development pathway.** Drug repurposing seeks to reuse existing drugs as the source of new treatment options. Repurposing benefits from existing data on safety, dosing and clinical experience (Bertolini 2015).
- As of 11 May 2018, the ReDO project (Pantziarka 2014) has found 254 non-cancer drugs supported by evidence for use in cancer (Table 1).

Table 1: Selected characteristics of the 254 non-cancer drugs of the ReDO list	N	%
Human data *(at least 1 case report, 1 obs. study or 1 clinical trial)*	**181**	**71%**
At least 1 clinical trial performed	**167**	**66%**
Drug Off-Patent	**215**	**85%**
List is partially pre-published (open access) https://www.biorxiv.org/content/early/2017/10/06/197434		

Bertolini F, Sukhatme VP, Bouche G. (2015) Drug repurposing in oncology—patient and health systems opportunities. *Nat Rev Clin Oncol* 12, 732–742
Pantziarka P, Bouche G, Meheus L et al. (2014) The repurposing drugs in oncology (ReDO) project *Ecancermedicalscience* 8:442.

Objectives & Methods

- **Objective:**
  - Provide a non-exhaustive listing of non-cancer drugs for which there is published evidence that they inhibit the pancreatic tumour cells *per se* or target the stromal components.
- **Methods:**
  - We started from the ReDO list of 254 non-cancer drugs with at least one peer-reviewed article showing an anticancer effect *in vitro*, *in vivo* or in humans.
  - We queried PubMed for each drug and the terms “pancreatic cancer” and screened titles in search of articles reporting activity of the drug against PDAC (but not disease-related or treatment-induced symptoms). If a paper reported *in vitro*, *in vivo* or human data, it was included for assessment. Based on this selection of drugs with strong preclinical data, we highlight a number of candidate drugs and stratify them according to the mechanism of action (MOA) on pancreatic tumour cells or their environment.

Results

- Of the 254 ReDO drugs, **130 (51%) had at least one article reporting *in vitro*, *in vivo* or in human activity against PDAC.**
- Based on the restricted search terms, we highlight **10 drugs, acting on the tumour epithelium, the stroma or both, that we consider particularly promising for investigation** (Table 2).

Table 2: Selection of drugs, MOA and type of evidence for repurposing in PDAC

Drug *indication*	MOA		# Refs PubMed	Drug development process*			Reference highlights	Comments
	Tumor	Stroma		1	2	3		
Disulfiram *alcoholism*	Cancer stem cells	Stellate cells	8				Kim SK et al. *PLoS One* 2013 Cong J et al. *Cancer Lett* 2017	only n=1 study in level 2
Losartan *hypertension*		Stellate cells perfusion	11				Chauhan VP et al. *Nat Commun* 2013 Arnold SA et al. *PLoS One* 2012	
(hydroxy)-Chloroquine *malaria*	Autophagy Hedgehog signaling	Stellate cells CXCR4	22				Yang S et al. *Genes Dev* 2011 Endo S et al. *Gastroenterology* 2017 Boone BA et al. *Ann Surg Oncol* 2015	
Plerixafor *mobilisation of hematopoietic stem cells*	PAUF/CXCR4	CAFs Mast cells CXCL12	11				Feig C et al. *Proc Natl Acad Sci U S A* 2013 Ma Y et al. *Cancer Res* 2013	
Fasudil *subarachnoid hemorrhage*	Rho-kinase	CAFs Rho-kinase Perfusion	3				Vennin C et al. *Sci Transl Med* 2017 Whatcott CJ et al. *PLoS One* 2017	approved in some Asian countries incl. Japan & China, not approved by EMA or FDA
Haloperidol *psychosis*	DRD2 antagonist		2				Jandaghi P et al. *Gastroenterology* 2016	
Pirfenidone *pulmonary fibrosis*		Stellate cells	4				Ji T et al. *ACS Appl. Mater. Interfaces* 2016 Suklabaidya S et al. *Oncotarget* 2016 Kozono S et al. *Cancer Res* 2013	
Calcitriol *vitamin D deficiency*	VDR agonist Akt pathway		14				Blanke CD et al. *Invest new drugs* 2009 Yu WD et al. *Cell Cycle* 2010	(synthetic) vit D analogues excluded e.g. Sherman et al. *Cell* 2015 supporting the use of calcipotriol in PDAC with impact on stroma (stellate cells)
Propranolol *hypertension*	Beta-adrenergic receptor antagonist		6				Partecke LI et al. *Pancreatology* 2016 Huang XY et al. *Hepatogastroenterology* 2012	Renz et al. *Cancer Cell* 2018, supporting the use of propranolol in PDAC and adding a new MOA

*Green = supportive of; Red = not supportive of; Grey = not assessed
1 = subcutaneous allo/xenografts; **2** = orthotopic allo/xenografts and/or patient derived xenografts and/or genetically engineered mice; **3** = clinical trial

Conclusion

- **Opportunities to repurpose non-cancer drugs in PDAC exist** with more than half of the ReDO drugs reporting therapeutic potential in PDAC.
- Several drugs are already being studied in pancreatic cancer trials (losartan, disulfiram, hydroxychloroquine …). Many others may also warrant clinical investigation.
- The data on the MOA, in addition to the tumour profiling, can assist in patient stratification.