Repurposing non-cancer drugs for breast cancer? An emerging opportunity.

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Background

- **Drug repurposing can speed up access to new therapeutic options** (Bertolini 2015). Much effort is expended to find new cancer indications for existing anticancer drugs. However, **little attention is given to finding anticancer uses of non-cancer drugs, while non-cancer drugs represent a way to adapt to new knowledge about cancer**
- **> 2000 drugs** are approved and available worldwide, there are **6 relevant targets per drug** on average (Mestres, 2008). Even monoclonal antibodies are being repurposed (Fornoni 2011).
- We call off-patent non-cancer drugs that are candidates for cancer repurposing "financial orphan drugs" (Sukhatme 2014) as they offer no return on investment and less scientific reward, (e.g. high-impact publications), compared with new molecules.
- As of 2 March 2018, the ReDO project (Pantziarka 2014) have found 246 non-cancer drugs supported by evidence for use in cancer (Table 1).

Table 1: Selected characteristics of the 246 non-cancer drugs of the ReDO list	N	%
Human data *(at least 1 case report, 1 obs. study or 1 clinical trial)*	**177**	**72%**
At least 1 clinical trial performed	**163**	**66%**
Drug Off-Patent	**208**	**85%**

List is pre-published (open) https://www.biorxiv.org/content/early/2017/10/06/197434

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Objectives & Methods

- **Objective: Estimate the number of breast cancer repurposing opportunities** of non-cancer drugs & select drug candidates suitable for trials in specific breast cancer subtypes.
- **Methods:**
  - We started from our ReDO list of 246 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 "breast cancer" and screened titles in search of articles reporting activity of the drug against breast cancer. If at least one paper reported *in vitro*, *in vivo* or human data, it was considered positive. For a given drug, if all articles were about the management of disease-related or treatment-induced symptoms, it was not considered positive (e.g. antidepressant, anti-emetics).
  - Based on clinical and pharmacology aspects, we selected 7 candidate drugs focusing on recent hypotheses applicable to specific breast cancer subtypes.

Results

- Of the 246 ReDO drugs, **173 (72%) had at least one article reporting *in vitro*, *in vivo* or in human activity against breast cancer.**
- We selected **7 drugs that we consider particularly interesting to be investigated in trials** in the current breast cancer context (Table 2)

Table 2: Selection of drugs particularly interesting for repurposing in specific breast cancer subtypes

Drug *Primary indication*	BC Subtype	Setting	Potential biomarkers	Evidence *Main article(s)*	Trials registered?	Comments and some possible/suggested developments
Propranolol *Hypertension*	HER2+ ER-	Neoadj	Beta Adrenergic Receptors	Human & in vivo *Liu Oncogene 2016*	4 incl. 1 with results	Several ongoing trials in all BC. No specific trial in HER2+ despite rationale for combining with anti-HER2.
Statins *Hypercholes-terolemia*	TNBC IBC ER+	- Neoadj - Residual disease after neoadj - Presurgical - Advanced - Early stage	- Mevalonate pathway / Yap-Taz Hippo pathway - Proliferative biomarkers - Resistant Protein	Human & in vivo *Brewer BJC 2013 / Lacerda Stem Cells Transl Med 2014*	11 trials incl. 3 with results	Several ongoing trials in all BC (both hydrophilic and lipophilic statins). Some in neoadjuvant TNBC (Atorvastatin); in Basal Subtype (Simvastatin); no specific trials in IBC despite rationale for combining with Chemo and Radiotherapy (Simvastatin).
Leflunomide *Rheumatoid arthritis*	TNBC	- Neoadjuvant - Metastatic	Blocking the pyrimidine synthesis pathway/DNA repair	In vivo *Brown Cancer Discov 2017*	No	Some trials in solid and hematologic tumors, but no trials in BC. Good rationale in association with doxorubicin in TNBC (vulnerability).
Losartan *Hypertension*	HER2 negative AGTR1 over-expression	Neoadj	AGTR1 receptors MALT1 Tumor fibrosis	In vivo *Rhodes PNAS 2009*	No	Some trials in other tumors (pancreatic/NSCLC/Glioma) other trials for pulmory fibrosis, hypertension. Selective treatment for aberrant high expression of AGTR1 (15-20% of BC, high in HER2 negative); interesting relationship with pCR & survival.
Maraviroc *HIV infection*	Basal like / TNBC expressing CCR5 receptor	Adjuvant Oligometastatic disease	CCR5 /CCL5 axis	In vivo *Ban Cancer Res 2017*	No	Potent blocker of CCR5 with limited side effects. Some trials in solid tumor in particular liver metastases of colon cancer (expressing CCR5). Increased expression of CCL5 and its receptor CCR5, but not CCR3, in the basal and HER-2 genetic subtypes.
Nelfinavir *HIV infection*	HER2 positive	Metastatic Neoadjuvant	HSP90 Pi3K/AKT	In vivo *Shim JNCI 2012*	No	Proposed as HER2 selective anti-breast cancer drug. Several trials in solid tumors (HN, Cervical, NSCLC, Pancreatic, Melanoma, Hematologic, Glioblastoma, Kaposi, Oligometastases).
Tigecycline *Antibiotic*	TNBC RB1-p53 deficient	Metastatic neoadjuvant	Mitochondrial protein transition	In vivo *Jones JCI 2016*	No	Two studies in leukemia and 1 in septic shock. Potent inhibitor of RB1-p53 deficient tumor cell proliferation (esp. TNBC). Very selective mechanism of action - targeted treatment.

AGTR1: Angiotensin II receptor type 1; BC: Breast cancer; CCL5: Chemokine (C-C motif) ligand 5; CCR3: C-C Chemokine receptor type 3; CCR5: C-C Chemokine receptor type 5; ER: Estrogen receptors; HER2: Human epidermal growth factor receptor 2; HIV: Human immunodeficiency virus; HN: Head & neck cancers; HSP90: Heat shock protein 90; IBC: Inflammatory breast cancer; MALT1: Mucosa-associated lymphoid tissue lymphoma translocation protein 1; NSCLC: Non-small cell lung cancer; pCR: pathological complete response; Pi3K/AKT: Phosphatidylinositol-4,5-bisphosphate 3-kinase/Protein kinase B; RB1: Retinoblastoma protein gene; TNBC: Triple-negative breast cancer.

Conclusion

- **The number of opportunities to repurpose non-cancer drugs in breast cancer is large**. Almost three quarter of the ReDO drugs have shown activity against breast cancer.
- **Making an objective selection is difficult because of the amount of data and of the heterogeneous quality** of the articles. Several drugs are already being studied in breast cancer trials (aspirin, metformin, propranolol, statins …).
- Besides these well-known examples, **we have presented several other drugs that have a strong rationale to be trialed in specifc breast cancer subtypes**. The development of more targeted studies and the results of different clinical trials that are in progress will help to better clarify the role of different drugs that can be repurposed in breast cancer.