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 5 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).

Objectives & Methods

- Objective: Estimate the number of breast cancer drug repurposing opportunities of non-cancer drugs & select drug candidate 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-emetic).
  - 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 7 drugs particularly interesting for repurposing in specific breast cancer subtypes

<table>
<thead>
<tr>
<th>Drug discovery indication</th>
<th>BC Subtype</th>
<th>Setting</th>
<th>Potential biomarkers</th>
<th>Evidence Monitor article(s)</th>
<th>Trials registered</th>
<th>Comments and some possible/suggested developments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol Hypertension</td>
<td>HER2+ ER-</td>
<td>Neoadj</td>
<td>Beta Adrenergic Receptors</td>
<td>Human &amp; in vivo Liu Oncogene 2016</td>
<td>4 incl. 1 with results</td>
<td>Several ongoing trials in all BC despite rational for combination with anti-HER2.</td>
</tr>
<tr>
<td>Statins Hypercholes- terolemia</td>
<td>TNBC BRCA1, ER+</td>
<td>Neoadj</td>
<td>Metabolic</td>
<td>Human &amp; in vivo Borner &amp;Cancer Cells Transl Med 2014</td>
<td>11 trials incl. 3 with results</td>
<td>Several ongoing trials in all BC (both hydrophilic and lipophilic statins).</td>
</tr>
<tr>
<td>Leflunomide Rheumatoid arthritis</td>
<td>TNBC</td>
<td>Neoadj</td>
<td>Metabolic</td>
<td>In vivo Brown Cancer Discov 2017</td>
<td>No</td>
<td>Some trials in solid and hematologic tumors, but no trials in BC.</td>
</tr>
<tr>
<td>Losartan Hypertension</td>
<td>HER2 negative ATR1 over-expression</td>
<td>Neoadj</td>
<td>ATR1 receptors MALAT1</td>
<td>In vivo Brown Cancer Res 2017</td>
<td>No</td>
<td>Some trials in other tumors (pancreatic/NSCLC/Glioma) other trials for pulmonary fibrosis, hypertension.</td>
</tr>
<tr>
<td>Maraviroc HIV infection</td>
<td>Basal like / TNBC expressing CCRS receptor</td>
<td>Adjuvant</td>
<td>Oligometastatic disease</td>
<td>CCR5/CCL5 axis</td>
<td>In vivo Ban Cancer Res 2017</td>
<td>No</td>
</tr>
<tr>
<td>Nelirisve HIV infection</td>
<td>HER2 positive</td>
<td>Metastatic</td>
<td>HSP90</td>
<td>In vivo Shlm JNCI 2012</td>
<td>No</td>
<td>Proposed as HER2 selective anti-viral drug.</td>
</tr>
</tbody>
</table>

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 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 specific 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.