

## Drug Repositioning in Cancer

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The development of new therapeutic agents, in any kind of disease, requires either long time or high costs; indeed 10 - 15 years of research are required to market a drug, resulting in an overall cost of about 1.8 billion dollars [1]. In addition, drug development in oncology is very challenging due to cancer biological complexity, actually comprising several subtypes of diseases carrying different molecular features. Despite over the last decades a high number of drugs (cytotoxic, targeted agents and emergent immunotherapeutic approaches) have been developed [2], on average just one in fifteen drugs with an oncology indication entering phase I clinical trials is finally approved by the FDA [3]. In order to overcome these issues, the strategy of “drug repositioning” aims to apply “old” and well known drugs for the treatment of certain diseases (other than cancer) to new indications, thus allowing a good knowledge on their safety, pharmacology and toxicology. New effective cancer therapies may be ready in a cost-effective and fast way. The best-known example of successful drug repositioning in cancer is thalidomide. This drug was employed in 1950s to treat morning sickness and in 1961 discontinued to cause serious birth defects. Its anti-cancer properties were found later, from the observation made by Folkman and colleagues in 1994 that thalidomide inhibited the angiogenesis induced by fibroblast growth factor 2 (FGF2) *in vivo* [4]. In May 2006, the US FDA's approved the use of thalidomide in combination with dexamethasone for the treatment of newly diagnosed multiple myeloma [5].

Since then, many fascinating hypothesis on the anticancer activity exerted by very well-known drugs have been explored. Some of the most exciting findings concern very common molecules such as Aspirin, acetylsalicylic acid, used historically as an anti-inflammatory agent and more recently as an antiplatelet drug; Metformin, the first-line medication for the treatment of type 2 diabetes; Statins, a class of lipid-lowering drugs and Valproate (VPA), primarily used to treat epilepsy and bipolar disorder. To date, Aspirin revealed WNT-targeting activities in various cancer types, both *in vitro* and *in vivo* [6]; about Metformin, numerous epidemiological and pre-clinical data have shown its favorable effect against tumors, leading to launch 55 clinical trials (still ongoing), aimed to meet different endpoints on a large diversity of cancers [7]. Statins have shown promising anti-tumor effects *in vitro*, however, the results of clinical studies are controversial [8]. Finally, Valproate has been recently proposed in combination with cetuximab and cisplatin, in a phase II clinical trial, as a less toxic and more effective first-line chemotherapy regimen in patients with recurrent/metastatic squamous cell carcinoma of the head and neck [9].

As an overall evaluation from the existing literature, it is evident that drugs to be repositioned should be employed in combination with other anticancer agents, in order to target multiple pathways.

However, nowadays we need to carefully evaluate strategies to optimize the concept of drug repositioning, mostly because we have diverse powerful tools available to explore the potential of drugs to be “repositioned”. On one hand, *in silico* techniques represent a great tool to “build assumptions”, because of their wide potential in understanding and predicting how drugs are able to affect biological systems, for example through gene expression analysis or drug–target interactions. But, the great amount of data potentially generated need then to be validated through methodologies that need to be improved still [10]. From the other hand, among the strategies convenient and widely used to “validate assumptions”, it is worth to mention the Meta-analysis, a statistical approach to combine results from different studies in order to increase the power over individual studies. However, it's essential to consider the greatest number of possible

information (such as patients age, sex, body mass index and cancer type, cancer stage) which constitute variables affecting either the Meta-analysis itself or drug's effectiveness in each individual study [8].

### Bibliography

1. Paul SM., *et al.* "How to improve R&D productivity: the pharmaceutical industry's grand challenge". *Nature Reviews Drug Discovery* 9.3 (2010): 203-214.
2. Martin-Liberal J., *et al.* "Immuno-Oncology: The Third Paradigm in Early Drug Development". *Targeted Oncology* 12.2 (2016): 125-138.
3. Hay M., *et al.* "Clinical development success rates for investigational drugs". *Nature Biotechnology* 32.1 (2014): 40-51.
4. D'Amato RJ., *et al.* "Thalidomide is an inhibitor of angiogenesis". *Proceedings of the National Academy of Sciences of the United States of America* 91.9 (1994): 4082-4085.
5. Zhou S., *et al.* "Thalidomide-a notorious sedative to a wonder anticancer drug". *Current Medicinal Chemistry* 20.33 (2013): 4102-4108.
6. Ahmed K., *et al.* "A Second WNT for Old Drugs: Drug Repositioning against WNT-Dependent Cancers". *Cancers (Basel)* 8.7 (2016): 66.
7. Chae YK., *et al.* "Repurposing metformin for cancer treatment: current clinical studies". *Oncotarget* 7.26 (2016): 40767-40780.
8. Ishida J., *et al.* "Repurposing of approved cardiovascular drugs". *Journal of Translational Medicine* 14 (2016): 269.
9. Caponigro F., *et al.* "Phase II clinical study of valproic acid plus cisplatin and cetuximab in recurrent and/or metastatic squamous cell carcinoma of Head and Neck-V-CHANCE trial". *BMC Cancer* 16.1 (2016): 918.
10. Brown AS and CJ Patel. "A review of validation strategies for computational drug repositioning". *Brief Bioinform* (2016).

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