Cancer phenotypic lethality, exemplified by the non-essential MTH1 enzyme being required for cancer survival

Modern targeted anti-cancer treatments often come in the form of small molecules or antibodies (biologics) that bind to a specific protein and inhibit its function. We just describe a small molecule inhibitor which inhibits a novel target MTH1, and selectively eradicates cancer but not normal cells [1, 2]. The concept of inhibiting MTH1 differs from targeting oncogenes, which represent a majority of the targeted therapies. Instead, inhibition of MTH1 falls into the category of ‘non-oncogene addiction’ targets [3], and most likely requires a different approach to be successful in the clinic. Also, several novel non-oncogene addiction targets do not fall under the personalized medicine paradigm and biomarkers have not been successfully implemented for patient selection. Here, I put MTH1 and other novel non-oncogene addiction targets in perspective.

targeting oncogene addictions

Oncogene addiction is a genetic defect in the cancer that drives the disease and can potentially be tailored for treatment. The development scheduling is logical and was beautifully exemplified by imatinib, which is a molecularly targeted treatment of the BCR-Abl tyrosine kinase present on the Philadelphia chromosome in chronic myeloid leukaemia, converting a fatal cancer into a manageable chronic condition [4]. There is a strong rationale for targeting oncogenes and novel targetable gene mutations are now identified at an unprecedented pace by the next generation sequencing of cancers. Pharmaceutical industry has successfully employed this strategy in the rapid introduction of novel anti-cancer treatments. Typically, it used to take 10–15 years developing a treatment until it reached the market. The first targeted therapy that changed this paradigm was the B-RAF inhibitor vemurafenib. The original B-RAF mutation was identified at the Sanger Centre in Cambridge in 2002 [5] and intensive follow-up work demonstrated that it was an oncogene in 2004 [6], this subsequently led to initiation of several drug discovery programmes, and approval of vemurafenib in B-RAF mutant melanoma in 2011, which essentially halved the expected drug development time to market. Several other novel oncogene-targeting drugs have reached the market within record time, such as the ALK inhibitor crizotinib and the expectation is that many more novel targeted drugs will appear in the near future, accompanied by a distinct, often target-related, biomarker.

targeting non-oncogene addictions

Many clinicians have now integrated novel targeted treatments into practice and, for some indications, such targeted agents are replacing traditional first-line cytotoxic treatments. The widespread use of genetically identifying and tailoring treatments is a paradigm shift in oncology. However, there is yet another group of targeted therapies not based on targeting oncogenes. Broadly, these treatments are classified as ‘non-oncogene addiction’ targets for anti-cancer treatments [3]. These share the common feature of targeting processes that are used for cancer cell survival, typically to a higher degree than in normal cells. There are numerous examples how we are able to exploit cancer-specific dependencies, such the proteasome inhibitor bortezomib, which targets the increased requirement for proteasome activity in cancers [7], or Chk1 and ATR kinase inhibitors that are required to mediate survival in cancer owing to their high load of DNA damage at replication forks [8]. Since healthy cells inherently generate much lower levels of DNA damage, they are much less dependent on these targets for survival and, hence, the therapeutic index is variable between different cancers, in combination with various treatments and in different contexts. Consequently, it is not straightforward to identify biomarkers to determine responding patient cohorts.

synthetic lethal concept for treatment of cancer

Gene mutations in cancer results in activation of oncogenes which drive the cancer and inactivation of tumour suppressors. Tumours suppressors are not easily targeted therapeutically as cancers have lost the gene function. They can however be targeted indirectly by inhibiting other pathways, the mutated cancer cells become dependent on, through the concept of synthetic lethality. The concept of synthetic lethality is an approach to target a normally non-essential pathway that becomes essential for cancer survival only in the context of a pre-existing gene mutation. Hence, the therapeutic index achievable with this approach is much wider than when targeting pathways that are also required for the survival of healthy cells. The classic example of synthetic lethality is our earlier discovery that PARP inhibitors selectively kill BRCA1- or BRCA2-mutated tumours [9, 10]. PARP1 knockout mice are viable and grow old, so inhibition of PARP is unlikely to be associated with acute toxic effects. However, some dose-limiting side-effects are observed in patients after administration of PARP inhibitors in monotherapy which may potentially be related to the PARP1 protein being trapped on to DNA following inhibition which may in turn also be toxic. The obvious experiment is to use PARP1−/− mice to test if the side-effects with PARP inhibitors are target
related, but such experiments have not been carried out to my knowledge. In any case, many PARP inhibitors are overall well tolerated and can be used as maintenance treatment in platinum-sensitive relapsed ovarian cancer, with favourable results [11].

cancer phenotypic lethality in anti-cancer treatment

The idea of targeting a normally non-essential enzyme, which only becomes essential in cancer cells is very attractive as it would avoid the dose-limiting side-effects associated with many current treatments. Unfortunately, the synthetic lethal concept suffers from similar resistance problems as many other treatments targeting the genotype and resistance does emerge, likely through additional genetic changes [12, 13]. For instance some BRCA-mutated cancers fail to respond to PARP inhibitor treatment and the responses obtained are rarely complete [14]. Ideally, one would want to use the synthetic lethal concept more generally, to identify a non-essential enzyme, generally essential in cancer. In two recent papers using different approaches, we come to the same conclusion that the normally non-essential enzyme MTH1 becomes crucial for survival in cancers [1, 2]. This provides an example of a more general approach for the treatment of cancer. Here, I use the term ‘cancer phenotypic lethality’ to describe a treatment that targets a non-essential enzyme in normal cells generally required for the survival of the cancer phenotype (Figure 1). Such treatment may be advantageous to targeting the genotype, as it can potentially be used more broadly, irrespectively of the genotype in cancer. This is a great advantage, as many targetable mutations, e.g. ALK mutations in non-small-cell lung cancer, are infrequent and some cancers appear to have few targetable mutations at all, e.g. small-cell lung cancer. Also, a general treatment targeting the cancer phenotype can be useful in many rare cancers that are today neglected. The most obvious benefit would of course be that a non-essential enzyme is being targeted, therefore minimizing acute side-effects, and allowing it to be given as a maintenance therapy in many indications. Of course, this all depends on the ability to identify a drug that is free from off-target effects at other essential enzymes. Emerging resistance is a general problem when targeting the cancer genotype, as many different genotype combinations are allowed to manifest the disease. In contrast, many cancers share altered metabolic pathways, such as the glycolysis activation (Warburg effect), and there are hopefully fewer phenotypic alterations allowed for cancer survival.

There are many challenges ahead in translating non-oncogene addiction, as patients cohorts are likely not easily identifiable. Clearly, the effective use of these inhibitors creates a demand for increased scientific input into clinical trials design and the ability to think outside the box. A very exciting time lies ahead.

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![Image](https://example.com/image.png)

**Figure 1.** Different strategies for targeted anti-cancer therapies. Targeting ‘oncogene addiction’ (A) is the most straightforward, and so far the most widespread targeted anti-cancer treatment. Many oncogenes also have essential roles in normal cells and targeted therapies are often associated with target-related side-effects. There are several strategies for targeted non-oncogene addiction, such as ‘cancer dependencies’ (B), where up-regulated activities are targeted to obtain cancer-specific cell toxicity. An advantage is that this type of treatment is not limited to cancer genotype and may be more widely applicable. However, these therapies target essential pathways which can result in dose-limiting toxicity. In the ‘synthetic lethal’ (C) treatment of cancer, a normally non-essential enzyme is targeted that becomes essential in the mutated cancer. In this approach, a favourable therapeutic window is most likely obtained owing to the non-essential nature of the target. However, further genetic changes are associated with emerging resistance. By ‘cancer phenotypic lethality’ (D), a normally non-essential enzyme is targeted that becomes essential in the cancer phenotype. This approach is clinically unexplored, but should give few side-effects while being useful in many indications since the treatment is not limited to a specific cancer genotype. Green designates wild-type protein, pink designates mutated protein, filled designates essential protein and unfilled designates non-essential protein.
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references


The results of conservative (fertility-sparing) treatment in borderline ovarian tumors vary depending on age and histological type

Epithelial ovarian tumors are heterogeneous neoplasms and are primarily classified according to cell type into: serous, mucinous, endometrioid, clear-cell, transitional, and squamous cell tumors [1–3]. Paradoxically, none of these cell types are found in the normal ovary and their development has long been attributed to Müllerian ‘neometaplasia’ of the ovarian surface epithelium (mesothelium) or, alternatively, to a germ-cell origin in cases of mucinous tumors [1]. Most endometrioid and clear-cell tumors are thought to arise from endometriosis [4]. Over the last decade, there has been increasing evidence that many early-stage high-grade serous carcinomas from BRCA+ patients arise from precursor epithelial lesions in the limbrated end of the fallopian tube [5]. Recently, however, it has been hypothesized that embryonic/stem cells would be capable of Müllerian differentiation in inclusion cysts resulting from ovarian surface epithelium invaginations [6]. Epithelial ovarian tumors differ not only morphologically, but also from the viewpoint of epidemiology, molecular genetic events during oncogenesis, and biologic behavior. In other words, these tumors are inherently different diseases.

Epithelial ovarian tumors are further subdivided into benign, borderline, and malignant (carcinoma), and this subdivision is the most important since it correlates with behavior [1–3]. Borderline ovarian tumors show epithelial proliferation greater than that seen in their benign counterparts and variable nuclear atypia; however, in contrast to carcinomas, there is no destructive stromal invasion, and their prognosis is much better than that of carcinomas. In spite of the lack of stromal invasion, serous borderline tumors, particularly those with exophytic growth, can implant on peritoneal surfaces and, rarely (about 10%) of peritoneal implants), progress to low-grade serous carcinoma (LGSC) and invade the underlying tissues [7, 8].

Although favorable in the vast majority of cases, the biologic behavior of the borderline tumors differs from that of the obviously benign tumors of the same cell type(s) and, rarely (<1%–3%), progression to invasive carcinoma occurs justifying the term ‘borderline tumor’. Alternative terms such as ‘proliferating’, ‘atypical’, and ‘atypical proliferative’ [9] are not recommended since they are nonspecific; i.e. all non-benign epithelial tumors (borderline and carcinomas) are proliferative neoplasms which exhibit nuclear atypia; also, these terms are misleading as they do not take into account the malignant potential of a small but significant number of these tumors and discourage follow-up [7, 8]. Similarly, the subdivision of the serous borderline group into benign and malignant, based on the presence of a micropapillary architecture [10], is artificial since serous borderline tumors (SBT) with or without micropapillary pattern may rarely be associated with invasive peritoneal implants and poor outcome [7, 8]. A recent study of gene expression profiling of 13 SBTs and 3 low-grade serous carcinomas showed that SBTs with (one case) and without micropapillary pattern were equally