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REVIEW

Targeting "undruggable" c-Myc protein by synthetic lethality

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Abstract **Synthetic lethal screening, which exploits the combination of mutations that result in cell death, is a promising method for identifying novel drug targets. This method provides a new avenue for targeting "undruggable" proteins, such as c-Myc. Here, we revisit current methods used to target c-Myc and discuss the important functional nodes related to c-Myc in non-oncogene addicted network, whose inhibition may cause a catastrophe for tumor cell destiny but not for normal cells. We further discuss strategies to identify these functional nodes in the context of synthetic lethality. We review the progress and shortcomings of this research field and look forward to opportunities offered by synthetic lethal screening to treat tumors potently.**

Keywords synthetic lethality; undruggable; transcription factor; c-Myc

Introduction

More than 70% of human tumors overexpress either c-Myc or one of its two close paralogs, N-Myc and L-Myc [1,2]. *MYC* family members are broadly implicated in human cancers yet are presently considered "undruggable" due to its nuclear localization and lack of binding pocket and essential physiological functions to the maintenance of normal tissues [3]. Given the considerable relevance of c-Myc to human cancers and current "undruggablity," researchers paid enormous attention to target it by inhibiting the transcription and translation of *MYC* and destroying the stability of c-Myc. However, these methods could cause severe side effects, especially on normal proliferative tissues [4–6]. Trumpp *et al*. reported that the *Myc* gene loss is more severe for proliferation cells, such as stem cells, than other cells. The differentiation of c-Myc-deficiency hematopoietic stem cells (HSCs) of a mouse model is impaired compared with that of normal HSCs [5]. Targeting c-Myc in mouse model and cell lines can incur unfavorable effects. Cleveland and colleagues [7] showed that $Myc^{-/-}$ mice died as an embryo due to defects in growth and cardiac and neural development. Dominguez-Sola *et al*. clarified that transient Myc depletion by RNAi stalls DNA replication and hinders cell cycle [4].

Synthetic lethality could be used to identify pathways and functional nodes essential in the oncogenic c-Myc pathway [8,9]. This concept originates from studies in *Drosophila* model systems, in which a combinational mutation of two or more separate genes incurs death while either gene mutation alone could be buffered [10]. High-throughput screen technology propels the development of research on synthetic lethality. Based on high-throughput technology, synthetic lethal screening has identified over a hundred candidate genes that are potentially lethal to *MYC* [11]. Identifying critical functional nodes in synthetic lethal pathways related to undruggable oncoproteins holds great promise in cancer research area.

c-Myc and undruggability

c-Myc, encoded by *MYC*, is a master regulator of normal and cancer-associated processes [11]. As a key transcriptional factor, c-Myc regulates the expression of many genes with diverse biological functions, such as cell proliferation and apoptosis [12,13]. c-Myc also regulates the expression of mismatch repair genes by binding to the promoters of double-strand break repair genes during DNA damage repair [14,15]. Moreover, recent research depicts the critical roles of c-Myc in regulating metabolism,

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specifically glycolysis and glutaminolysis [16]. The *MYC* oncogene is a central driver in numerous cancers, such as breast cancer [17], liver tumor [6], colorectal carcinoma [18], and prostatic neoplasia [19]. This oncogene is dysregulated in > 70% of human cancers, and the dysregulation is associated with poor prognosis and survival rates [20,21]. Excess c-Myc expression can be caused by chromosomal translocation [22] or amplification. Additionally, malfunctions in either the degradation process of c-Myc or the upstream pathways of c-Myc can increase c-Myc stability and oncogenic activity. The high frequency of *MYC* family dysregulation in human cancers suggests that a strategy to target Myc may benefit a broad population of patients; however, its simple protein structure (Fig. 1) and predominant nuclear location have impeded efforts to exploit it in drug discovery and development.

Potential molecular targets usually fall into two major categories, namely, druggable and undruggable. “Druggability” implies that the target molecule must have structures that should make it vulnerable to attack and inhibition by low-molecular-weight compounds. Moreover, a protein is considered druggable if it contains a cavity, usually a well-defined catalytic cleft. However, most transcription factors, including c-Myc, are widely thought to be undruggable due to the lack of catalytic clefts and the much-sought drug binding pockets. To date, targeting c-Myc in cancers with small molecular agents remains challenging. New strategies are urgently needed to regulate the stability or activity of c-Myc in cancer.

Current methods to target c-Myc

Clinical outcomes for cancer patients with high c-Myc activity remain dismal [23–25]. *MYC*-amplification is a relevant factor with poor outcomes in medulloblastoma [26], multiple myeloma [27], and diffuse large B cell lymphoma [24,25]. One contributing factor is the absence of effective therapeutics against c-Myc. As mentioned above, directly targeting c-Myc with small-molecule inhibitors is difficult [27–29]. Therefore, new agents that could indirectly regulate c-Myc stability or activity may shift the paradigm for treating c-Myc-dependent cancers (Fig. 2).

One method to indirectly target c-Myc is blocking the transcription of *MYC* and the corresponding target genes of the c-Myc protein. Bromodomain-containing 4 (BRD4) is involved in transcription elongation [30–32]. Based on multiple myeloma human cell line assays, a selective small-molecule bromodomain inhibitor, namely, JQ1, competes with BRD4 for binding to acetylated lysines and replaces BRD4 from super-enhancers within the *MYC* oncogene [33]; this phenomenon downregulates c-Myc transcription and leads to genome-wide downregulation of c-Myc target genes [33]. *In vivo* xenograft studies also showed the great potency of JQ1 [33]. JQ1 manifests powerful anti-tumor effects in multiple hematopoietic cancers and pancreatic ductal adenocarcinoma (PDAC) with c-Myc overexpression *in vitro* and *in vivo* [34–37]. Blocking c-Myc protein synthesis is an alternative method. Mammalian target of rapamycin complexe 1 (mTORC1) regulates protein synthesis [38]. The major regulators of protein synthesis downstream of mTORC1 are p70S6K1/2 and eukaryotic translation initiation factor 4E (eIF4E) binding protein 1 (4EBP1), which negatively regulates eIF4E, a key rate-limiting initiation factor for cap-dependent translation [38]. Pharmacological inhibition of the PI3K/AKT/mTOR pathway can suppress c-Myc protein level and may even manifest remarkable potential therapeutic efficacy in *MYC*-driven cancers [39,40]. MLN0128, a powerful mTOR active site inhibitor, inhibits 4EBP1 phosphorylation and achieves great efficacy in *MYC*-driven hematological cancer cell lines and mouse models [40]. Undermining the stability of c-Myc could be another method. The stability of c-Myc is under tight control by ubiquitin-proteasome system in normal tissues [41]. The stability of the c-Myc protein is regulated by

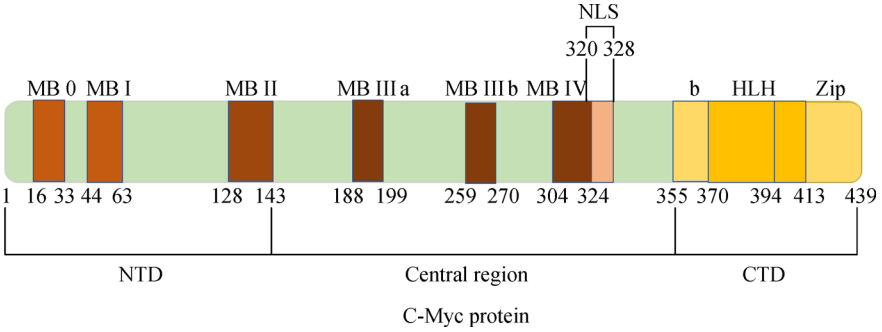

Fig. 1 Structure of human c-Myc protein with MYC Box (MB) 0 to IV, nuclear localization sequence (NLS), basic helix–loop–helix leucine zipper (b-HLH-Zip) regions, and relevant amino positions indicated.

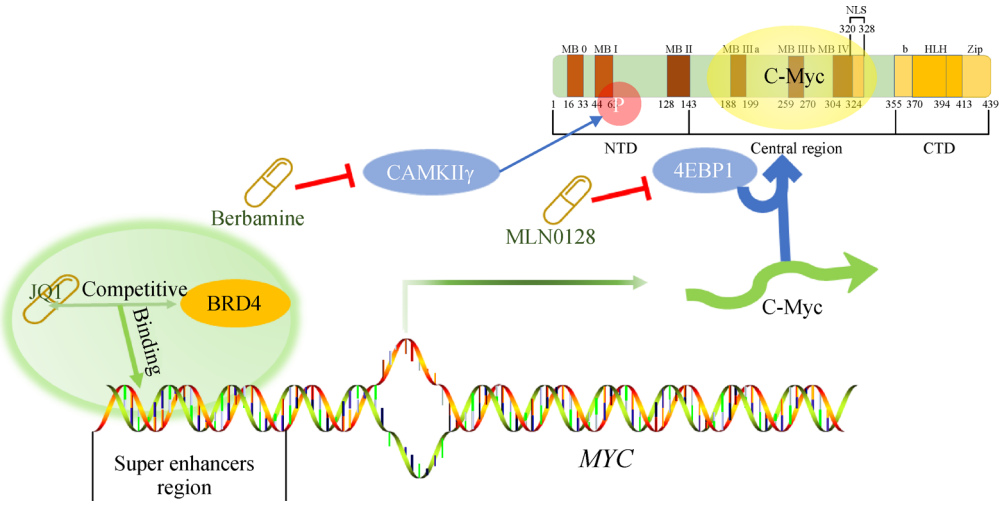

Fig. 2 Example of current ways to inhibit c-Myc in multiple levels including transcription, translation, and protein stability. Left part depicts that JQ1 competes with BRD4 for binding to super-enhancers within the *MYC* gene. After c-Myc mRNA transcription, the inhibition of 4EBP1 by MLN0128 blocks c-Myc translation. Berbamine undermines the stability of c-Myc by targeting CAMKIIγ as indicated in the right part.

phosphorylation at two sites: serine 62 phosphorylation (pS62) stabilizes c-Myc, while threonine 58 phosphorylation (pT58) promotes c-Myc degradation [42]. CAMKIIγ, whose protein level correlates with c-Myc protein level in patients with T cell lymphomas (TCL), stabilizes c-Myc by phosphating it at Ser62 [43]. Pharmacologic inhibition of CAMKIIγ with the specific inhibitor berbamine (BBM) could undermine the stability of c-Myc, suppress TCL development, and reduce the tumor burden [43,44].

During the course of existing cancer treatments, information may surface about the toxic side effects of drug on whole organisms. More importantly, the therapeutic index of an agent directs our attentions, that is, the efficiency with which it affects cancerous tissues compared with its toxic effects on normal tissues. Thus, an ideal agent should have high therapeutic index and wreak havoc on cancer cells while leaving normal tissues relatively untouched. All the methods mentioned above aim to reduce c-Myc expression. c-Myc, which is expressed in cancer cells, is also expressed by their normal counterparts, which is the fundamental obstacle to achieving high therapeutic index in cancer treatments.

Synthetic lethality in cancer

The aim of anti-cancer drug development is to direct drugs to specific molecular targets within cancer cells; if the aberrant biological state of cancer cells is derived from and depends on malfunctioning signaling nodes, then inhibiting or eliminating such nodes should result in a cytostatic response in these cells. Given that these signaling nodes function differently in normal and neoplastic cells, targeting them should yield substantial therapeutic indices, that is, selective killing of cancer cells and potentially reduce side-effect toxicity for cancer patients undergoing treatment.

Practicing synthetic lethality by destroying crucial malfunctioning signaling nodes within c-Myc oncogenic network will be a catastrophe for c-Myc-dependent tumor cells. Numerous redundancies developed in cellular signaling pathways to overcome the impediment of unexpected mutations [45] and maintain cell homeostasis. Intracellular redundant components also endow cancer cells with resistance to different treatments and unfavorable environment. Normal and neoplastic cells share similar protein components but have different ways of transmitting signals. Malfunctioning circuit nodes are critical for cancer cells, but similar pathway nodes may be dispensable or redundant in normal ones. Synthetic lethality can help screen malfunctioning circuit nodes to selectively kill cancer cells. Synthetic lethality originated from classical genetics and elaborated that synchronous mutation of two genes will lead to cell death, yet mutation of either gene alone is viable [46]. This exquisite principle provides a new insight into cancer treatment. After Ashworth and colleagues pointed out the potential of targeting DNA repair defect in *BRCA* mutant cells as a therapeutic strategy and successfully propelled poly (ADP-ribose) polymerase (PARP) inhibitors into clinics, more cancer researchers are embracing the concept of synthetic lethality [47–49]. Thus far, synthetic lethality has been expanded to heterotypic interactions across diverse cell types. LOX inhibition leads to synthetic lethality to *PTEN null* in glioblastoma multiforme (GBM) by markedly suppressing macrophage infiltration and tumor progression

[50,51]. About 20 years ago, Hartwell and colleagues proposed that synthetic lethality could be used to identify new anticancer drug targets [52], especially those that are synthetically lethal to known cancer-causing mutations. When an oncogene mutation exists in certain tumor cells, we can exploit its synthetic lethal genes to induce cell death. Genes, which are synthetically lethal to other genes, do not need to be mutated if their functions are affected by environmental factors. As Robert G. Bristow and Ester M. Hammond reported [53], after severe acute hypoxia followed by reoxygenation or moderate chronic hypoxia treatments, replicating cells gain a homologous recombination defected phenotype, which is synthetically lethal with PARP1 inhibition.

Treatment methods based on synthetic lethality may outperform conventional medical options in the case of functional loss of a tumor suppressor gene (TSG) in a certain cancer regardless of deletion, inactivating mutation, or epigenetic silencing [54,55]. Restoring the TSG protein activity to fulfill its biochemical functions is difficult [56]. Chemotherapy causes indiscriminate harm to normal and cancerous cells, leading to a high risk of adverse events to patients [54]. Attractive prospects exist in targeting “undruggable” driver-mutations, such as *MYC* and *KRAS*, based on synthetic lethality [57,58].

Synthetic lethality may inspire and enrich drug-combinations as therapeutic methods to deal with drug resistance, a severe threat to overall patient survival [9] during cancer treatment. Conventional cancer treatments depend on standard protocols, where a given drug is designated as first-line therapy [9]. Drugs designated as second- and third-line therapies will be recommended in case drug resistance occurs. However, most of later-line therapies appear to be less effective than first-line therapy and do not overcome the resistance well. Drug resistance is a hindrance for conventional treatments but a weakness that can be exploited by synthetic lethality. Further investigation is needed on the drug resistance of cancer after first-line therapy and on how to use it to treat cancer instead. Following the principle of synthetic lethality, drug resistance might be exploited to target drug-resistant cancer cells potently.

Synthetic lethality has potential significance but also present issues that need to be answered. The urgent problem proposed here is how to identify critical functional nodes that are essential in *MYC*-driven tumor cells. These valuable nodes could be potential candidates of synthetic lethal partners with oncogenic c-Myc. Interfering with these critical functional nodes could tilt the relatively balanced cellular circumstance and trigger cell death [56,59,60].

Synthetic lethal screening

In general, synthetic lethal screening methods can be categorized into genetic screening and chemical screening based on platforms used.

Genetic screening

In isogenic human cell lines, large libraries of synthetic short interfering RNAs (siRNAs), libraries of short hairpin RNAs (shRNAs), and large collections of guide RNAs (gRNAs) for CRISPR/Cas9 genome editing, CRISPR interference (CRISPRi), and CRISPR activation (CRISPRa) are applied to identify critical genes and their synthetic lethal partners [61–64]. Fig. 3 depicts a simplified cell-based synthetic lethal screening. The chimaera of the *MYC* gene fused with the hormone binding domain of the human estrogen receptor gene could be valuable for synthetic lethal screening. The activities of its protein product, c-Myc-ER, depend on hormone or its analog 4OH-tamoxifen and could be manipulated reversibly by removing the hormone. Cells with this chimera gene could be categorized into two groups: c-Myc-On and c-Myc-Off. Together with high-throughput screening mentioned, potential synthetic lethal interactions with c-Myc would surface out.

Cancer cell line panels with different *MYC* mutation status could be an alternative model for investigating its intracellular synthetic lethal partners [65,66]. In theory,

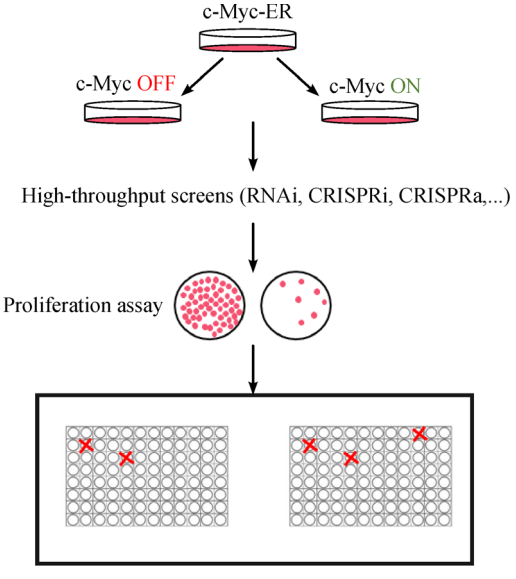

Fig. 3 Synthetic lethal screening in *MYC*-driven cancer cells.

only *MYC* mutation cells, rather than wild-type ones, would die when its synthetic lethal partners are genetically inhibited. The congenital weakness of this model is the enormous genetic complexity of most human cancer cell lines. This genetic background may obscure the results of synthetic lethal combination and even lead to false positive results.

Compared with CRISPR/Cas9 genome editing, shRNA-based gene knockdown incompletely inactivates genes. Moreover, shRNA-based gene knockdown efficiency varies. However, shRNA-based gene knockdown still has its position in synthetic lethal screening. The two aspects to consider are as follows. First, shRNA-mediated technology could mimic the effect of drugs closely. From this perspective alone, it outperforms the CRISPR/Cas9 genome editing technology. Second, a partial silencing of an essential gene may display the dosage-dependent synthetic lethal phenotype [9]. This process would be lethal itself in the case of complete inactivation. In a word, it can be a sharp sword depending on what we need.

CRISPR/Cas9 genome editing is not perfect all the time. Studies have shown that CRISPR targeting can be toxic in amplified genomic regions, especially in those highly aneuploidic ones [67,68]. CRISPRi or CRISPRa, which use a catalytically dead mutant of Cas9 fused to a transcriptional repressor or activator domain, could be an alternative choice. In contrast to genome-editing screening, CRISPRi and CRISPRa screenings are reversible and inducible, indicating the accuracy of the examination of the spatiotemporal dynamics of gene function [69,70].

In large-scale screening of model organisms, potent platforms have been introduced. For example, high-throughput mating methodologies in yeast, such as synthetic genetic array (SGA) analysis [71] and diploid synthetic lethality analysis with microarrays (dSLAM) [72], enable the large-scale construction of double mutants and the quantification of genetic interactions.

Chemical screening

This idea was born in screening for drug-like chemicals, which specifically kill yeast deletion mutations with defects in cell cycle checkpoints or DNA repair, as reported by Hartwell and Friend. The method is gradually extended to human cell lines. Kinzler and coworkers [73] cocultured *KRAS*-mutated colon cancer cells (engineered to produce blue fluorescent protein) with a subclone of which the mutant *KRAS* allele was removed by homologous recombination (and modified with yellow fluorescent protein), and the ratio of blue/yellow fluorescence was used to characterize and monitor differential cell viability. Wang and colleagues [74] discovered the increased sensitivity to the death receptor DR5 agonist tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL) *in vitro* and *in vivo* in human cells, which overexpress Myc and link it to p53-independent induction of DR5 by Myc. Drug–drug interactions also come to the stage in recent years. Borisy and colleagues observed synergistic effects of drug–drug combination through their high-throughput cell-based assays [75]. Although, the underlying mechanism behind this should be further investigated.

Current challenges

Despite that numerous potential synthetic lethal interactions have been discovered, the lack of overlap in results from different screenings is an obstacle for further study and application to clinic trials [65]. First, wide-spreading high-throughput tools, including RNAi and CRISPR-based tools, could not exclude off-target effects completely [76,77]. Off-target effects may lead to false-positive results and contribute to the lack of overlap mentioned above. However, on-target efficiency could be improved by modifying the library of RNAi or guide RNA. Moreover, CAS9-induced DNA damage may lead to false-negative results and thus cover up the truth [78]. Second, screening based on cells with different genetic contexts or from different tissues might account for the lack of overlap [79]. The way that we culture cell lines cannot faithfully mimic the microenvironment around tumor cells in patients. Three-dimensional culture systems may also be helpful [65]. Considering that microenvironmental changes, such as hypoxia and high reactive oxygen species, may also influence synthetic lethality interactions, scholars have encountered difficulty in further *in vivo* studies of potential synthetic lethal interactions [53,79].

Applauding progresses

Selectively killing tumor cells rather than normal ones is important in cancer treatments and is a research direction that is worth pursuing. Synthetic lethality is a potent tool to fulfill this goal and help researchers achieve applauding progress. Genotype-selective synthetic lethality capitalizes on the notion that a mutation gained by cancer cells is also associated with new vulnerability that could be exploited therapeutically. Such vulnerability could be ascribed to stresses inside mutated cells. Thus, normal cells would not display increased sensitivity to synthetic lethality drug target, but cancer cells with specific mutation would. Cells lacking certain mutation can also phenocopy the similar clinical behavior as cells that do have that certain mutation [80,81]. *BRCA* mutation confers homologous recombination (HR) deficiency to cells. Mutations of alternative genes, whose protein products participate in HR process, may also result in HR defect [82]. A research reported hypoxia status as a microenvironmental change could lead

to the phenotype of HR deficiency [53]. Thus, cancer cells with or without certain mutation but sharing similar clinical behavior can be selectively targeted. Developing effective drugs that are synthetic lethal to these genotypes is critical.

At present, PARP inhibitors are the only clinically proven drugs that can selectively target tumors in patients who carry germline mutations in *BRCA1* or *BRCA2* [49]. This finding is a milestone in synthetic lethal research and would constantly inspire future works. Based on this successful synthetic lethal interaction, clinic trials have been extended to "BRCAness" cancers [82,83], which share similar clinical behavior to the *BRCA* mutant one. A clinical trial (NCT01676753) related to synthetic lethality of Myc is ongoing at phase Ib stage. As reported [84], in Myc-overexpressing triple-negative breast cancer xenografts, CDK1 inhibition with dinaciclib results in synthetic lethality and attenuates distant metastasis. In syngeneic models, the combination of dinaciclib with anti-PD1 therapy has synergistic effects and increases immune cell tumor infiltration and activation. This clinical trial is still under further evaluation. Synthetic lethal drug combinations may show greater potency in clinical trials than genotype-selective monotherapy [9]. Moreover, synthetic lethal drug combinations have more realistic significance, when we take into consideration that FDA-approved drugs may exert far more potent efficiency on specific cancers after rationally-designed drug combining based on synthetic lethality. As reported by Liu and colleagues [85], the addition of cediranib to olaparib in a phase 2 study improved the median progression-free survival than olaparib alone in women with platinum-sensitive high-grade serous or endometrioid ovarian cancers. A joint research team reported [86] that the drug combination of olaparib (a PARP inhibitor of diagnosed advanced ovarian cancer with a *BRCA* mutation) and bevacizumab (a vascular endothelial growth factor receptor inhibitor, which may indirectly sensitize olaparib by acquisition of homologous-recombination defect [87]), significantly improved the progression-free survival in patients with advanced ovarian cancer. This finding was substantial in patients with homologous-recombination deficiency-positive tumors, including those without *BRCA* mutation. However, overwhelming work is needed in clinical application of synthetic lethal drug combinations. Undoubtedly, all these progresses have inspired us.

Despite limited clinic trials on synthetic lethality, many meaningful preclinical investigations are ongoing. Zhao *et al*. revealed the synthetic lethal interaction in patient-derived human breast cancer xenograft models with high Myc protein level between X-box binding protein 1 (XBP1) inhibition and c-Myc hyperactivation, which play important roles with inositol-requiring enzyme 1 (IRE1) in unfolded protein response (UPR) that is activated in multiple human cancers and involved in tumor initiation, progression, and therapy resistance [88]. More importantly, they also discovered a pharmacological inhibitor to mammalian IRE1, namely, fourth-generation salicylaldehyde class inhibitor (8866). 8866 could selectively restrain Myc-overexpressing tumor growth *in vivo* in a cohort of preclinical patient-derived xenograft models and genetically engineered mouse models with efficacy comparable with that of the standard-of-care chemotherapy docetaxel. Hsu and collaborators identified *BUD31* as a Myc-synthetic lethal gene in human mammary epithelial cells, and BUD31 is a component of the core spliceosome required for its assembly and catalytic activity [89].

Toyoshima and coworkers identified 102 potential synthetic lethal interactions with c-Myc overexpression in a collection of ~3300 druggable genes by applying high-throughput siRNA screening to an isogenic pair of primary cells (human foreskin fibroblasts); *CAMK2G* was determined to be one of the 102 potential genes involved in synthetic lethal interaction with c-Myc overexpression [57]. Further, we provided evidence that targeting Ca^{2+}/calmodulin-dependent protein kinase II γ (CAMKIIγ), encoded by *CAMK2G*, can effectively inhibit T cell lymphoma (TCL) by destabilizing the c-Myc protein [43]. Moreover, pharmacologic inhibition of CAMKIIγ with specific inhibitor berbamine suppressed TCL development and reduced the tumor burden [44]. Such findings highlight a potential therapeutic strategy whereby c-Myc-associated malignancies could be targeted by synthetic lethality.

Synthetic lethality will be an excellent alternative to drug "undruggable" oncogene. Pathways and functional nodes essential in the context of oncogene but not to normal cells will be identified through a functional genomics approach to reveal an undiscovered therapeutic space linked to a previously "undruggable" oncogene.

Compliance with ethics guidelines

Chen Wang, Hui Fang, Jiawei Zhang, and Ying Gu declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. Pan J, Deng Q, Jiang C, Wang X, Niu T, Li H, Chen T, Jin J, Pan W, Cai X, Yang X, Lu M, Xiao J, Wang P. USP37 directly deubiquitinates and stabilizes c-Myc in lung cancer. Oncogene 2015; 34(30): 3957–3967
2. Sun XX, He X, Yin L, Komada M, Sears RC, Dai MS. The nucleolar ubiquitin-specific protease USP36 deubiquitinates and stabilizes c-Myc. Proc Natl Acad Sci USA 2015; 112(12): 3734–3739
3. Whitfield JR, Beaulieu ME, Soucek L. Strategies to inhibit Myc and their clinical applicability. Front Cell Dev Biol 2017; 5: 10

4. Dominguez-Sola D, Ying CY, Grandori C, Ruggiero L, Chen B, Li M, Galloway DA, Gu W, Gautier J, Dalla-Favera R. Non-transcriptional control of DNA replication by c-Myc. Nature 2007; 448(7152): 445–451
5. Wilson A, Murphy MJ, Oskarsson T, Kaloulis K, Bettess MD, Oser GM, Pasche AC, Knabenhans C, Macdonald HR, Trumpp A. c-Myc controls the balance between hematopoietic stem cell self-renewal and differentiation. Genes Dev 2004; 18(22): 2747–2763
6. Shachaf CM, Kopelman AM, Arvanitis C, Karlsson A, Beer S, Mandl S, Bachmann MH, Borowsky AD, Ruebner B, Cardiff RD, Yang Q, Bishop JM, Contag CH, Felsher DW. MYC inactivation uncovers pluripotent differentiation and tumour dormancy in hepatocellular cancer. Nature 2004; 431(7012): 1112–1117
7. Baudino TA, McKay C, Pendeville-Samain H, Nilsson JA, Maclean KH, White EL, Davis AC, Ihle JN, Cleveland JL. c-Myc is essential for vasculogenesis and angiogenesis during development and tumor progression. Genes Dev 2002; 16(19): 2530–2543
8. Lucchesi JC. Synthetic lethality and semi-lethality among functionally related mutants of *Drosophila melanfgaster*. Genetics 1968; 59 (1): 37–44
9. Beijersbergen RL, Wessels LF, Bernards R. Synthetic lethality in cancer therapeutics. Annu Rev Cancer Biol 2017; 1(1): 141–161
10. Wright S, Dobzhansky T. Genetics of natural populations; experimental reproduction of some of the changes caused by natural selection in certain populations of *Drosophila pseudoobscura*. Genetics 1946; 31: 125–156
11. Toyoshima M, Howie HL, Imakura M, Walsh RM, Annis JE, Chang AN, Frazier J, Chau BN, Loboda A, Linsley PS, Cleary MA, Park JR, Grandori C. Functional genomics identifies therapeutic targets for MYC-driven cancer. Proc Natl Acad Sci USA 2012; 109(24): 9545–9550
12. Carroll PA, Freie BW, Mathsyaraja H, Eisenman RN. The MYC transcription factor network: balancing metabolism, proliferation and oncogenesis. Front Med 2018; 12(4): 412–425
13. Evan GI, Wyllie AH, Gilbert CS, Littlewood TD, Land H, Brooks M, Waters CM, Penn LZ, Hancock DC. Induction of apoptosis in fibroblasts by c-myc protein. Cell 1992; 69(1): 119–128
14. Bucci B, D'Agnano I, Amendola D, Citti A, Raza GH, Miceli R, De Paula U, Marchese R, Albini S, Felsani A, Brunetti E, Vecchione A. Myc down-regulation sensitizes melanoma cells to radiotherapy by inhibiting MLH1 and MSH2 mismatch repair proteins. Clin Cancer Res 2005; 11(7): 2756–2767
15. Bindra RS, Glazer PM. Co-repression of mismatch repair gene expression by hypoxia in cancer cells: role of the Myc/Max network. Cancer Lett 2007; 252(1): 93–103
16. Dang CV. Glutaminolysis: supplying carbon or nitrogen or both for cancer cells? Cell Cycle 2010; 9(19): 3884–3886
17. Korangath P, Teo WW, Sadik H, Han L, Mori N, Huijts CM, Wildes F, Bharti S, Zhang Z, Santa-Maria CA, Tsai H, Dang CV, Stearns V, Bhujwalla ZM, Sukumar S. Targeting glutamine metabolism in breast cancer with aminooxyacetate. Clin Cancer Res 2015; 21(14): 3263–3273
18. Ben-David E, Bester AC, Shifman S, Kerem B. Transcriptional dynamics in colorectal carcinogenesis: new insights into the role of c-Myc and miR17 in benign to cancer transformation. Cancer Res 2014; 74(19): 5532–5540
19. Koh CM, Gurel B, Sutcliffe S, Aryee MJ, Schultz D, Iwata T, Uemura M, Zeller KI, Anele U, Zheng Q, Hicks JL, Nelson WG, Dang CV, Yegnasubramanian S, De Marzo AM. Alterations in nucleolar structure and gene expression programs in prostatic neoplasia are driven by the MYC oncogene. Am J Pathol 2011; 178 (4): 1824–1834
20. Pelengaris S, Khan M, Evan G. c-MYC: more than just a matter of life and death. Nat Rev Cancer 2002; 2(10): 764–776
21. Mossafa H, Damotte D, Jenabian A, Delarue R, Vincenneau A, Amouroux I, Jeandel R, Khoury E, Martelli JM, Samson T, Tapia S, Flandrin G, Troussard X. Non-Hodgkin's lymphomas with Burkitt-like cells are associated with c-Myc amplification and poor prognosis. Leuk Lymphoma 2006; 47(9): 1885–1893
22. Dalla-Favera R, Bregni M, Erikson J, Patterson D, Gallo RC, Croce CM. Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. Proc Natl Acad Sci USA 1982; 79(24): 7824–7827
23. Barrans S, Crouch S, Smith A, Turner K, Owen R, Patmore R, Roman E, Jack A. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol 2010; 28(20): 3360–3365
24. Niitsu N, Okamoto M, Miura I, Hirano M. Clinical features and prognosis of *de novo* diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC translocations. Leukemia 2009; 23(4): 777–783
25. Valera A, López-Guillermo A, Cardesa-Salzmann T, Climent F, González-Barca E, Mercadal S, Espinosa I, Novelli S, Briones J, Mate JL, Salamero O, Sancho JM, Arenillas L, Serrano S, Erill N, Martínez D, Castillo P, Rovira J, Martínez A, Campo E, Colomo L; Grup per l'Estudi dels Limfomes de Catalunya i Balears (GELCAB). MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Haematologica 2013; 98(10): 1554–1562
26. Eberhart CG, Kratz J, Wang Y, Summers K, Stearns D, Cohen K, Dang CV, Burger PC. Histopathological and molecular prognostic markers in medulloblastoma: c-myc, N-myc, TrkC, and anaplasia. J Neuropathol Exp Neurol 2004; 63(5): 441–449
27. Jovanović KK, Roche-Lestienne C, Ghobrial IM, Facon T, Quesnel B, Manier S. Targeting MYC in multiple myeloma. Leukemia 2018; 32(6): 1295–1306
28. Rebello RJ, Pearson RB, Hannan RD, Furic L. Therapeutic approaches targeting MYC-driven prostate cancer. Genes (Basel) 2017; 8(2): 71
29. Horiuchi D, Anderton B, Goga A. Taking on challenging targets: making MYC druggable. American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting 2014: e497–e502
30. Yang Z, Yik JH, Chen R, He N, Jang MK, Ozato K, Zhou Q. Recruitment of P-TEFb for stimulation of transcriptional elongation by the bromodomain protein Brd4. Mol Cell 2005; 19(4): 535–545
31. Price DH. P-TEFb, a cyclin-dependent kinase controlling elongation by RNA polymerase II. Mol Cell Biol 2000; 20(8): 2629–2634
32. Peterlin BM, Price DH. Controlling the elongation phase of transcription with P-TEFb. Mol Cell 2006; 23(3): 297–305
33. Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, Kastritis E, Gilpatrick T, Paranal RM, Qi J, Chesi M, Schinzel AC, McKeown MR, Heffernan TP, Vakoc CR, Bergsagel PL, Ghobrial

IM, Richardson PG, Young RA, Hahn WC, Anderson KC, Kung AL, Bradner JE, Mitsiades CS. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 2011; 146(6): 904–917

34. Dawson MA, Prinjha RK, Dittmann A, Giotopoulos G, Bantscheff M, Chan WI, Robson SC, Chung CW, Hopf C, Savitski MM, Huthmacher C, Gudgin E, Lugo D, Beinke S, Chapman TD, Roberts EJ, Soden PE, Auger KR, Mirguet O, Doehner K, Delwel R, Burnett AK, Jeffrey P, Drewes G, Lee K, Huntly BJ, Kouzarides T. Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. Nature 2011; 478(7370): 529–533
35. Zuber J, Shi J, Wang E, Rappaport AR, Herrmann H, Sison EA, Magoon D, Qi J, Blatt K, Wunderlich M, Taylor MJ, Johns C, Chicas A, Mulloy JC, Kogan SC, Brown P, Valent P, Bradner JE, Lowe SW, Vakoc CR. RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia. Nature 2011; 478(7370): 524–528
36. Mertz JA, Conery AR, Bryant BM, Sandy P, Balasubramanian S, Mele DA, Bergeron L, Sims RJ 3rd. Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Natl Acad Sci USA 2011; 108(40): 16669–16674
37. Mazur PK, Herner A, Mello SS, Wirth M, Hausmann S, Sánchez-Rivera FJ, Lofgren SM, Kuschma T, Hahn SA, Vangala D, Trajkovic-Arsic M, Gupta A, Heid I, Noël PB, Braren R, Erkan M, Kleeff J, Sipos B, Sayles LC, Heikenwalder M, Heßmann E, Ellenrieder V, Esposito I, Jacks T, Bradner JE, Khatri P, Sweet-Cordero EA, Attardi LD, Schmid RM, Schneider G, Sage J, Siveke JT. Combined inhibition of BET family proteins and histone deacetylases as a potential epigenetics-based therapy for pancreatic ductal adenocarcinoma. Nat Med 2015; 21(10): 1163–1171
38. Hsieh AC, Liu Y, Edlind MP, Ingolia NT, Janes MR, Sher A, Shi EY, Stumpf CR, Christensen C, Bonham MJ, Wang S, Ren P, Martin M, Jessen K, Feldman ME, Weissman JS, Shokat KM, Rommel C, Ruggero D. The translational landscape of mTOR signalling steers cancer initiation and metastasis. Nature 2012; 485 (7396): 55–61
39. Liu P, Ge M, Hu J, Li X, Che L, Sun K, Cheng L, Huang Y, Pilo MG, Cigliano A, Pes GM, Pascale RM, Brozzetti S, Vidili G, Porcu A, Cossu A, Palmieri G, Sini MC, Ribback S, Dombrowski F, Tao J, Calvisi DF, Chen L, Chen X. A functional mammalian target of rapamycin complex 1 signaling is indispensable for c-Myc-driven hepatocarcinogenesis. Hepatology 2017; 66(1): 167–181
40. Pourdehnad M, Truitt ML, Siddiqi IN, Ducker GS, Shokat KM, Ruggero D. Myc and mTOR converge on a common node in protein synthesis control that confers synthetic lethality in Myc-driven cancers. Proc Natl Acad Sci USA 2013; 110(29): 11988–11993
41. Paul I, Ahmed SF, Bhowmik A, Deb S, Ghosh MK. The ubiquitin ligase CHIP regulates c-Myc stability and transcriptional activity. Oncogene 2013; 32(10): 1284–1295
42. Pulverer BJ, Fisher C, Vousden K, Littlewood T, Evan G, Woodgett JR. Site-specific modulation of c-Myc cotransformation by residues phosphorylated *in vivo*. Oncogene 1994; 9(1): 59–70
43. Gu Y, Zhang J, Ma X, Kim BW, Wang H, Li J, Pan Y, Xu Y, Ding L, Yang L, Guo C, Wu X, Wu J, Wu K, Gan X, Li G, Li L, Forman SJ, Chan WC, Xu R, Huang W. Stabilization of the c-Myc protein by CAMKIIγ promotes T cell lymphoma. Cancer Cell 2017; 32(1): 115–128.e7
44. Gu Y, Chen T, Meng Z, Gan Y, Xu X, Lou G, Li H, Gan X, Zhou H, Tang J, Xu G, Huang L, Zhang X, Fang Y, Wang K, Zheng S, Huang W, Xu R. CaMKII γ, a critical regulator of CML stem/progenitor cells, is a target of the natural product berbamine. Blood 2012; 120 (24): 4829–4839
45. Prahallad A, Bernards R. Opportunities and challenges provided by crosstalk between signalling pathways in cancer. Oncogene 2016; 35(9): 1073–1079
46. Kaelin WG Jr. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 2005; 5(9): 689–698
47. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O’Connor MJ, Ashworth A, Carmichael J, Kaye SB, Schellens JH, de Bono JS. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009; 361(2): 123–134
48. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434(7035): 917–921
49. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science 2017; 355(6330): 1152–1158
50. Lucchesi JC. Synthetic lethality and semi-lethality among functionally related mutants of *Drosophila melanfgaster*. Genetics 1968; 59 (1): 37–44
51. Chen P, Zhao D, Li J, Liang X, Li J, Chang A, Henry VK, Lan Z, Spring DJ, Rao G, Wang YA, DePinho RA. Symbiotic macrophage-glioma cell interactions reveal synthetic lethality in PTEN-Null glioma. Cancer Cell 2019; 35(6): 868–884.e6
52. Hartwell LH, Szankasi P, Roberts CJ, Murray AW, Friend SH. Integrating genetic approaches into the discovery of anticancer drugs. Science 1997; 278(5340): 1064–1068
53. Chan N, Pires IM, Bencokova Z, Coackley C, Luoto KR, Bhogal N, Lakshman M, Gottipati P, Oliver FJ, Helleday T, Hammond EM, Bristow RG. Contextual synthetic lethality of cancer cell kill based on the tumor microenvironment. Cancer Res 2010; 70(20): 8045–8054
54. Penson RT, Valencia RV, Cibula D, Colombo N, Leath CA, Bidziński M, Kim J-W, Nam J-H, Madry R, Hernández CH, Mora PAR, Ryu SY, Milenkova T, Lowe ES, Barker L, Scambia G. Olaparib monotherapy versus (vs) chemotherapy for germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed ovarian cancer (PSR OC) patients (pts): Phase III SOLO3 trial. J Clin Oncol 2019; 37(15_suppl): 5506–5506
55. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Delaloge S, Li W, Tung N, Armstrong A, Wu W, Goessl C, Runswick S, Conte P. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017; 377 (6): 523–533
56. Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. Cell 2009; 136(5): 823–837
57. Toyoshima M, Howie HL, Imakura M, Walsh RM, Annis JE, Chang AN, Frazier J, Chau BN, Loboda A, Linsley PS, Cleary MA, Park JR, Grandori C. Functional genomics identifies therapeutic targets for MYC-driven cancer. Proc Natl Acad Sci USA 2012; 109(24): 9545–9550
58. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: mission possible? Nat Rev Drug Discov 2014;

13(11): 828–851
59. Weinstein IB, Joe A, Felsher D. Oncogene addiction. Cancer Res 2008; 68(9): 3077–3080
60. Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer 2003; 3(1): 11–22
61. Shalem O, Sanjana NE, Hartenian E, Shi X, Scott DA, Mikkelson T, Heckl D, Ebert BL, Root DE, Doench JG, Zhang F. Genome-scale CRISPR-Cas9 knockout screening in human cells. Science 2014; 343(6166): 84–87
62. Bernards R, Brummelkamp TR, Beijersbergen RL. shRNA libraries and their use in cancer genetics. Nat Methods 2006; 3(9): 701–706
63. Wang T, Wei JJ, Sabatini DM, Lander ES. Genetic screens in human cells using the CRISPR-Cas9 system. Science 2014; 343(6166): 80–84
64. Zhou Y, Zhu S, Cai C, Yuan P, Li C, Huang Y, Wei W. High-throughput screening of a CRISPR/Cas9 library for functional genomics in human cells. Nature 2014; 509(7501): 487–491
65. Downward J. RAS synthetic lethal screens revisited: still seeking the elusive prize? Clin Cancer Res 2015; 21(8): 1802–1809
66. Sharma SV, Haber DA, Settleman J. Cell line-based platforms to evaluate the therapeutic efficacy of candidate anticancer agents. Nat Rev Cancer 2010; 10(4): 241–253
67. Aguirre AJ, Meyers RM, Weir BA, Vazquez F, Zhang CZ, Ben-David U, Cook A, Ha G, Harrington WF, Doshi MB, Kost-Alimova M, Gill S, Xu H, Ali LD, Jiang G, Pantel S, Lee Y, Goodale A, Cherniack AD, Oh C, Kryukov G, Cowley GS, Garraway LA, Stegmaier K, Roberts CW, Golub TR, Meyerson M, Root DE, Tsherniak A, Hahn WC. Genomic copy number dictates a gene-independent cell response to CRISPR/Cas9 targeting. Cancer Discov 2016; 6(8): 914–929
68. Munoz DM, Cassiani PJ, Li L, Billy E, Korn JM, Jones MD, Golji J, Ruddy DA, Yu K, McAllister G, DeWeck A, Abramowski D, Wan J, Shirley MD, Neshat SY, Rakiec D, de Beaumont R, Weber O, Kauffmann A, McDonald ER 3rd, Keen N, Hofmann F, Sellers WR, Schmelzle T, Stegmeier F, Schlabach MR. CRISPR screens provide a comprehensive assessment of cancer vulnerabilities but generate false-positive hits for highly amplified genomic regions. Cancer Discov 2016; 6(8): 900–913
69. Qi LS, Larson MH, Gilbert LA, Doudna JA, Weissman JS, Arkin AP, Lim WA. Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. Cell 2013; 152(5): 1173–1183
70. Gilbert LA, Larson MH, Morsut L, Liu Z, Brar GA, Torres SE, Stern-Ginossar N, Brandman O, Whitehead EH, Doudna JA, Lim WA, Weissman JS, Qi LS. CRISPR-mediated modular RNA-guided regulation of transcription in eukaryotes. Cell 2013; 154(2): 442–451
71. Tong AHY, Evangelista M, Parsons AB, Xu H, Bader GD, Pagé N, Robinson M, Raghibizadeh S, Hogue CW, Bussey H, Andrews B, Tyers M, Boone C. Systematic genetic analysis with ordered arrays of yeast deletion mutants. Science 2001; 294(5550): 2364–2368
72. Pan X, Yuan DS, Xiang D, Wang X, Sookhai-Mahadeo S, Bader JS, Hieter P, Spencer F, Boeke JD. A robust toolkit for functional profiling of the yeast genome. Mol Cell 2004; 16(3): 487–496
73. Torrance CJ, Agrawal V, Vogelstein B, Kinzler KW. Use of isogenic human cancer cells for high-throughput screening and drug discovery. Nat Biotechnol 2001; 19(10): 940–945
74. Wang Y, Engels IH, Knee DA, Nasoff M, Deveraux QL, Quon KC. Synthetic lethal targeting of MYC by activation of the DR5 death receptor pathway. Cancer Cell 2004; 5(5): 501–512
75. Borisy AA, Elliott PJ, Hurst NW, Lee MS, Lehár J, Price ER, Serbedzija G, Zimmermann GR, Foley MA, Stockwell BR, Keith CT. Systematic discovery of multicomponent therapeutics. Proc Natl Acad Sci USA 2003; 100(13): 7977–7982
76. Birmingham A, Anderson EM, Reynolds A, Ilsley-Tyree D, Leake D, Fedorov Y, Baskerville S, Maksimova E, Robinson K, Karpilow J, Marshall WS, Khvorova A. 3′ UTR seed matches, but not overall identity, are associated with RNAi off-targets. Nat Methods 2006; 3 (3): 199–204
77. Fu Y, Foden JA, Khayter C, Maeder ML, Reyon D, Joung JK, Sander JD. High-frequency off-target mutagenesis induced by CRISPR-Cas nucleases in human cells. Nat Biotechnol 2013; 31(9): 822–826
78. Luo J. CRISPR/Cas9: from genome engineering to cancer drug discovery. Trends Cancer 2016; 2(6): 313–324
79. O'Neil NJ, Bailey ML, Hieter P. Synthetic lethality and cancer. Nat Rev Genet 2017; 18(10): 613–623
80. Popovici V, Budinska E, Tejpar S, Weinrich S, Estrella H, Hodgson G, Van Cutsem E, Xie T, Bosman FT, Roth AD, Delorenzi M. Identification of a poor-prognosis BRAF-mutant-like population of patients with colon cancer. J Clin Oncol 2012; 30(12): 1288–1295
81. Tian S, Simon I, Moreno V, Roepman P, Tabernero J, Snel M, van't Veer L, Salazar R, Bernards R, Capella G. A combined oncogenic pathway signature of BRAF, KRAS and PI3KCA mutation improves colorectal cancer classification and cetuximab treatment prediction. Gut 2013; 62(4): 540–549
82. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 2004; 4(10): 814–819
83. Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, Hirte H, Huntsman D, Clemons M, Gilks B, Yerushalmi R, Macpherson E, Carmichael J, Oza A. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011; 12(9): 852–861
84. Chien AJ, Rahmaputri S, Dittrich HF, Majure MC, Rugo HS, Melisko ME, Goga A. A phase Ib trial of the cyclin-dependent kinase inhibitor dinaciclib (dina) in combination with pembrolizumab (P) in patients with advanced triple-negative breast cancer (TNBC). J Clin Oncol 2019; 37(15_suppl): 1072–1072
85. Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, Rimel B, Buss MK, Nattam S, Hurteau J, Luo W, Quy P, Whalen C, Obermayer L, Lee H, Winer EP, Kohn EC, Ivy SP, Matulonis UA. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol 2014; 15(11): 1207–1214
86. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, Fujiwara K, Vergote I, Colombo N, Mäenpää J, Selle F, Sehouli J, Lorusso D, Guerra Alía EM, Reinthaller A, Nagao S, Lefeuvre-Plesse C, Canzler U, Scambia G, Lortholary A, Marmé F, Combe P, de Gregorio N, Rodrigues M, Buderath P, Dubot C, Burges A, You B, Pujade-Lauraine E, Harter P; PAOLA-1 Investigators. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med 2019; 381(25): 2416–2428

87. Dean E, Middleton MR, Pwint T, Swaisland H, Carmichael J, Goodege-Kunwar P, Ranson M. Phase I study to assess the safety and tolerability of olaparib in combination with bevacizumab in patients with advanced solid tumours. Br J Cancer 2012; 106(3): 468–474

88. Zhao N, Cao J, Xu L, Tang Q, Dobrolecki LE, Lv X, Talukdar M, Lu Y, Wang X, Hu DZ, Shi Q, Xiang Y, Wang Y, Liu X, Bu W, Jiang Y, Li M, Gong Y, Sun Z, Ying H, Yuan B, Lin X, Feng XH, Hartig SM, Li F, Shen H, Chen Y, Han L, Zeng Q, Patterson JB, Kaipparettu BA, Putluri N, Sicheri F, Rosen JM, Lewis MT, Chen X. Pharmacological targeting of MYC-regulated IRE1/XBP1 pathway suppresses MYC-driven breast cancer. J Clin Invest 2018; 128 (4): 1283–1299

89. Hsu TYT, Simon LM, Neill NJ, Marcotte R, Sayad A, Bland CS, Echeverria GV, Sun T, Kurley SJ, Tyagi S, Karlin KL, Dominguez-Vidaña R, Hartman JD, Renwick A, Scorsone K, Bernardi RJ, Skinner SO, Jain A, Orellana M, Lagisetti C, Golding I, Jung SY, Neilson JR, Zhang XHF, Cooper TA, Webb TR, Neel BG, Shaw CA, Westbrook TF. The spliceosome is a therapeutic vulnerability in MYC-driven cancer. Nature 2015; 525(7569): 384–388