Perspective

# The p53 orbit in chronic myeloid leukemia: time to move to patient care

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*Comment on:* Abraham SA, Hopcroft LE, Carrick E, *et al.* Dual targeting of p53 and c-MYC selectively eliminates leukaemic stem cells. Nature 2016;534:341-6.

**Abstract:** Chronic myeloid leukemia (CML) is the paradigm of precision medicine in cancer. CML was the first disease to be effectively treated with selective drug designed to inhibit the causative BCR-ABL oncoprotein activity. BCR-ABL tyrosine kinase inhibitor (TKI), imatinib, was the first FAD approved tyrosine kinase as standard treatment of a specific cancer. However, CML also highlighted TKIs limits: the development of resistance, due to mutations, and the inability to completely eradicate the disease, due to TKI insensitiveness of CML stem cells. Lastly, CML was also shown to be effectively targeted by strategies designed to modulate tumor suppressors. Here, we comment the impressive and recently published combinatorial therapy with p53 and c-Myc modulators in CML stem cells.

**Keywords:** Chronic myeloid leukemia (CML); BCR-ABL; tumor suppressors; p53; c-Myc

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## Introduction

Cancer development and resistance to treatments depend on the balancing between life and death of cancer cells. The tumor suppressor p53 dictates a pivotal role in determining the cells fate, the development of cancer and the sensitivity to treatment (1-3). Almost 30 years of intensive investigations have addressed important aspects of p53 summarized in: (I) TP53 is mutated/deleted in more than half of all cancers (4,5); (II) restoration of p53 expression in TP53-null mice is responsible for cancer regression (6); (III) p53 protein is subject to strict post-translational mechanisms that can functionally inactive it (7). This last aspect offers the most challenging implications from the therapeutic point of view because the functional restoration through targeting its regulatory factors may effectively and selectively promote cancer apoptosis and sensitivity to chemotherapy (8).

Chronic myeloid leukemia (CML) is a myeloproliferative disorder driven by the translocation t(9;22) coding for the chimeric protein BCR-ABL (9-11). This disease encompasses three phases: a chronic phase (CP) followed by the accelerated (AP) and the blast phases (BP), which are characterized by the block of terminal differentiation. While tyrosine kinase inhibitors (TKIs) showed great efficacy in CML treatment, there are mounting evidences that are not able to completely eradicate disease, due to intrinsic resistance of CML stem cells (12-15).

For many years, TP53 was mostly associated with the progression of CML, due to the frequent identification of TP53 mutations in blast crisis patients (16-23) even if the analysis of p53 expression levels suggested a potential role during the early stages of the disease (24). Indeed, mouse models consistently demonstrated that p53 plays a leading role in promoting CML development: p53 restoration was shown to kill primitive leukemia stem cells (25). Furthermore, various works demonstrated that p53 is functionally regulated by BCR-ABL (26). For instance, BCR-ABL modulates p53 through MDM2 (27) and that MDM2 targeting strategies are effective on p53 activation and on CML cells (28). Similarly, BCL6 represses Arf and p53 in CML, with essential implications from the therapeutic standpoint (29),

while BCR-ABL was also shown to modulate p53 cellular compartmentalization through IkB-alpha (30). In line with these considerations, it was proposed that p53 stabilization may be effective strategy in CML cell lines (31).

Recently, following an unbiased approach, Tessa Holyoake's group has elegantly demonstrated that p53 is functionally inactive in CML and that this event may be modulated therapeutically (32). Additionally, this group demonstrated that the c-MYC signature is also aberrantly expressed in CML, offering further therapeutic opportunity. Authors have assessed the protein profile by mass spectrometry in extracts from normal and CML CD34 positive cells, allowing to identify significant changes for p53 and c-MYC signatures. Notably, p53 downstream targets appeared to be down-modulated while c-MYC targets were either up-regulated or down-regulated. These aberrant signatures were also confirmed using previously reported data sets in both the LSC and progenitors' compartments. These observations prompted authors to assess whether simultaneous p53 activation and c-MYC inhibition would represent a powerful strategy to target CML-LSC. They infected CML CD34 positive cells with shMDM2, shc-MYC and both, and demonstrated that the combination of the two short hairpin RNAs have a synergistic effect in targeting CML cells. As we mentioned above, while deleted/mutated p53 is hardly to be considered as targetable, wild-type p53 can be targeted by various approaches. Authors used RITA, which prevents p53 degradation, and CPI-203, a bromodomain and extra terminal protein inhibitor, which promote both p53 and c-MYC down-regulation. The prolonged treatment with the association CPI-203 plus RITA promotes p53 up-regulation in CML $CD34^+$ cells with consequent apoptosis induction. Notably, c-MYC targeting by CPI-203 was also associated with some grade of differentiation. Similarly, Nutlin-3a was shown to be effective as well. Since the major unmet clinical need in CML therapy is the resistance of CML stem cells to TKI, authors have transferred this approach to these cells. They firstly demonstrated that TKI treatment did not change the responses to RITA and/or CPI-203 and that normal CD34 cells are much less sensitive to the drugs. These data suggest that the p53/c-MYC targeting strategy is BCR-ABL dispensable and may therefore be effective especially in those compartments not addicted to BCR-ABL, the CML stem cells. Therefore, they concluded that targeting p53 and c-MYC is indeed highly effective in promoting LSC apoptosis, with sparing normal HSC.

## Conclusions and personal perspective

In our opinion the work by Holyoake's group is a milestone in CML and in cancer research. The reasons are: (I) p53 is functionally and consistently inactive in primary samples of CP CML. While CML was often considered as a particular single hit disease (33), this paper further confirmed the prevailing idea that other factors, such as functional inhibition of tumor suppressor, converge in the CML pathogenesis, also during the CP (30). Moreover, this observation suggests that the functional status of various tumor suppressors should be investigated extensively in other cancers, because it may offer essential implications from the therapeutic standpoint. (II) p53 can be effectively modulated therapeutically. What sounds impressive is that the therapeutic modulation of p53 is BCR-ABL independent and therefore can be used to solve the unmet clinical needs of CML therapy and to target those cells not addicted to BCR-ABL, i.e., the stem cells (14). (III) Parallel to p53 inactivation, the c-MYC signature is aberrantly regulated in CML, as well. While c-MYC is not consistently up- or down-regulated, it could be noted that authors have attributed to this signature an additional targetable pathway that highly synergizes with p53 targeting drugs. Again, this work identified a BCR-ABL independent approach to cure CML.

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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