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Finding MYCure

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ABSTRACT

Inhibiting the nuclear protein MYC involved in the majority of human cancers has long been considered an impossible mission and several technical challenges have discouraged the development of MYC inhibitory strategies. Nevertheless, in our recent publication in Science Translational Medicine “Intrinsic cell-penetrating activity propels Omomyc from proof of concept to viable anti-MYC therapy”, we demonstrate for the first time the feasibility of pharmacological MYC inhibition *in vitro* and *in vivo* using an Omomyc-based mini-protein.

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Text

Let's be honest: working in cancer research is both a blessing and a curse. On one hand, one feels that we are fighting the good fight, looking for the ideal cancer drug that will potentially spare the lives of millions of people; on the other, the fight seems unfair, against an impossible enemy that displays the capacity to develop resistance to whichever therapy we come up with. Can we do better than that?



The answer to this question might be found by redefining our concept of the ideal cancer drug. We can all agree, for example, that such a drug should target a non-redundant function in cancer cells, ideally essential only for tumor cells but not for normal tissues. However, the majority of our targets so far are instead in the most redundant compartments of cells and pathways that can quickly rewire to compensate for our attacks. Current approaches should not be dismissed and it is apparent that, in many instances, they have led to a significant degree of success, especially in personalized medicine, which is clearly effective at least in a certain percentage of patients. Nevertheless, these approaches can be complemented by alternatives. Novel opportunities, for instance, might lie in the identification of central, less evolutionarily degenerate nodes in cancer, which might be non-redundant and offer unprecedented therapeutic strategies not yet explored. Some of these functions might be identified, for example, in the nuclei of cells (a compartment less accessible to standard drugs) and fall into the category of transcription factors, master regulators of the oncogenic programs that can contribute to the cancer phenotype. Among those, an even more challenging group is represented by intrinsically disordered proteins, which lack a defined three-dimensional structure amenable to attack by canonical small molecule inhibitors.

But are these challenges sufficient to dismiss these targets as “undruggable”? Our answer is definitely not. In our last publication in Science Translational Medicine,¹ we pre-

clinically established the feasibility of pharmacologically targeting MYC – not only a well-characterized central node in cancer but also a nuclear transcription factor and intrinsically disordered protein² – by making use of a cell-penetrating polypeptide called Omomyc.

MYC is known to be deregulated in the majority of cancers, either following gene amplification or mutation of many upstream signalling pathways – the Kirsten Rat Sarcoma GTPase (commonly known as KRAS), Phosphatidylinositol-3 Kinase (PI3K), Wingless-related integration protein (better known as WNT), etc. – which can lead to steady, non-stop MYC function.² Many studies have now clearly established the therapeutic utility of targeting MYC for cancer treatment.³ However, as MYC is essential during embryonic development and for normal function of proliferative tissues, dramatic side effects were expected from its complete inhibition. Previous strategies to drug MYC have attempted to inhibit it at many levels, from transcription to translation, or even protein stability.³ In the few cases in which some of these attempts have reached the clinic, they have been discontinued due to evidence of toxicity. Interestingly, though, this clinical toxicity did not seem to arise directly from the MYC blockade, but because of the use of ineffective inhibitory strategies and lack of specificity for the target. In this respect, our proposed therapeutic mini-protein approach is different.

The MYC transcription factor is composed of a DNA binding and dimerization domain (DBD) and a transactivation domain (TA). In order to function, MYC must form heterodimers with the MYC associated factor X (better known as MAX), its obligate partner, which enables binding to Enhancer box (E-box) DNA sequences. We previously designed Omomyc, a MYC-dominant negative consisting of the DBD of MYC containing four amino acidic mutations. Thanks to these mutations and its altered dimerization properties compared to the wild type DBD of MYC, Omomyc is able to both inhibit MYC/MAX interaction and their binding to DNA. In fact, not only can Omomyc sequester

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MYC in dimers unable to recognize the E-box, it can also compete for MYC/MAX DNA binding in the form of Omomyc/Omomyc homodimers or Omomyc/MAX heterodimers.⁴ Omomyc was initially used *in vivo* in its transgenic form to establish for the first time the therapeutic potential of MYC inhibition to stop tumor progression, and even led to tumor eradication, while also providing validation of its safety in multiple mouse models of cancer, independently of their tissue of origin or driving oncogenic lesions.^{5–8} Despite this undisputable therapeutic opportunity, though, Omomyc was deemed too bulky and unfit to ever become a drug.⁹

And this is where our last publication is really proving this assumption wrong. Cell-penetrating peptides (CPPs), also known as protein transduction domains, have the ability to allow intracellular delivery of multiple cargos,¹⁰ and have recently received considerable attention because of their high transduction efficiency and low cytotoxicity. In Beaulieu et al., 2019,¹ making use of a purified, recombinantly produced Omomyc polypeptide, we demonstrated for the first time that Omomyc's basic region is a CPP itself. Treating several cancer cell lines with increasing concentrations of fluorescently labeled Omomyc, we were able to observe internalization of the protein and partial localization in the nuclei at concentrations as low as 0.3 μM , causing growth arrest with an IC₅₀ in the low micromolar range. We also confirmed that the mini-protein acted as its transgenic counterpart, being able to form Omomyc/MYC

heterodimers, incapable of DNA binding, as well as Omomyc/Omomyc homodimers and Omomyc/MAX heterodimers, displaying instead DNA binding ability. All these dimers putatively contribute to MYC displacement from ~98% of its genomic locations. The displacement of MYC from its target promoters results in a marked transcriptional reprogramming of cancer cells, especially evident as reversion of the expression of MYC-related gene signatures.

Our results *in vitro* prompted us to assess the Omomyc mini-protein's therapeutic utility in a mouse model of KRas-driven Non-Small-Cell lung cancer (NSCLC). Our first attempt was through intranasal administration of the polypeptide, three times per week, at a dose of 2.37 mg/kg. A 4-week treatment prevented tumor progression and caused regression to a lower tumor grade, as a consequence of both reduced proliferation and increased cell death (Figure 1). Following Omomyc treatment, we also observed recruitment of intratumoral T cells, in line with the observed transcriptional reprogramming of cytokines and chemokines gene sets.

Similar results were also obtained with intravenously administered Omomyc mini-protein to mice carrying xenografts of human NSCLC H1975 cells, which are EGFR (epidermal growth factor receptor), PI3K and P53 (tumor protein TP53) mutant, in addition to being resistant to erlotinib. Also in this case, Omomyc treatment significantly reduced tumor

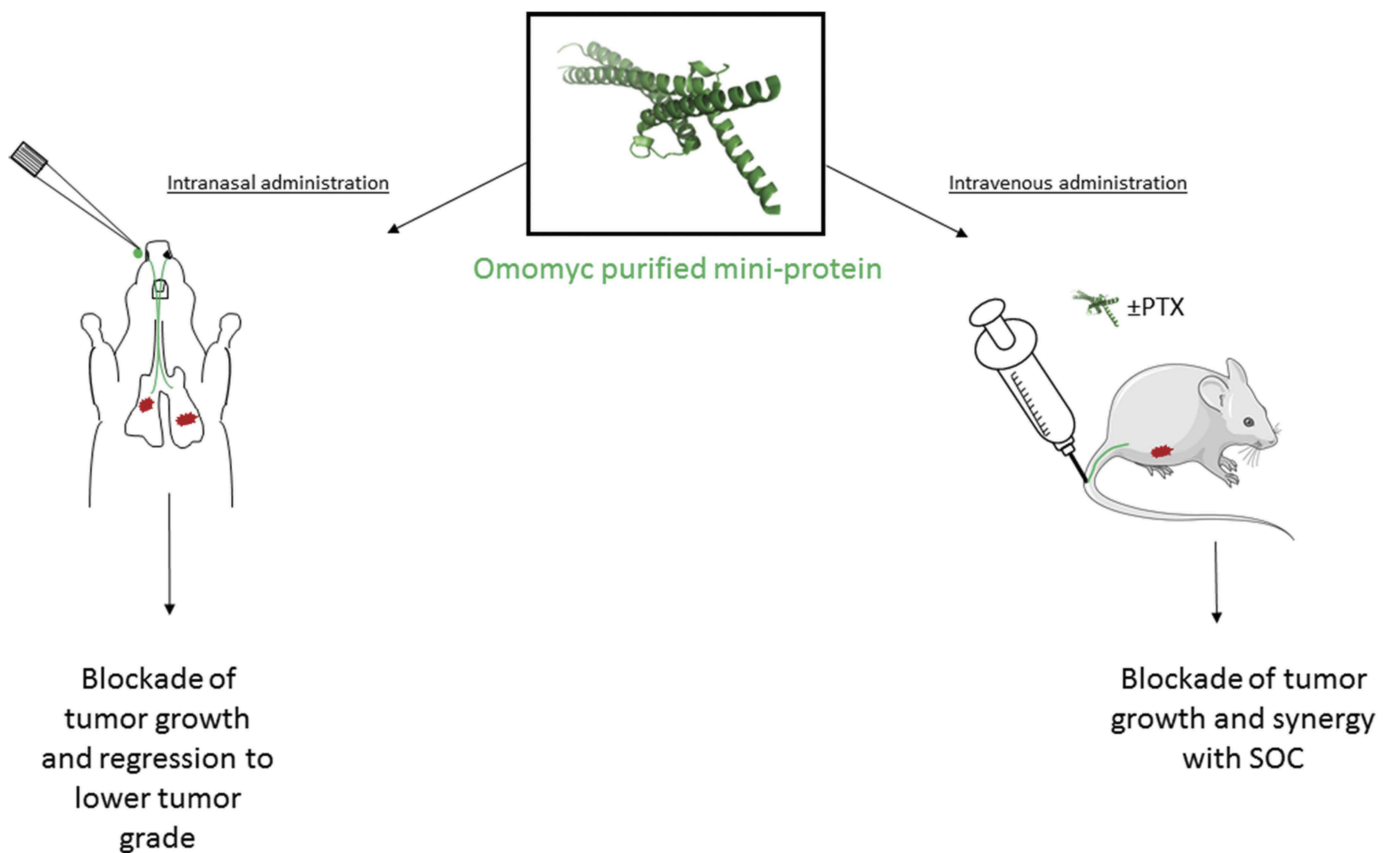


Figure 1. Proof of concept of the pharmacological application of the Omomyc mini-protein as a therapeutic for the treatment of Non-Small-Cell Lung Cancer (NSCLC). The Omomyc mini-protein was administered intranasally (on the left) in a mouse model of KRAS-driven NSCLC and intravenously (on the right) in a xenograft model of human NSCLC H1975 cells, where it was either used alone or in combination with paclitaxel (PTX), considered in this case as standard of care (SOC).

progression. Moreover, when given in combination with paclitaxel (PTX), Omomyc had a higher therapeutic impact, significantly extending the survival of the animals. (Figure 1)

Overall, our results provide the first evidence and preclinical validation of the Omomyc mini-protein as a specific pharmacological MYC inhibitor and excellent candidate for clinical development. The molecule is predicted to reach clinical trials in 2020.

Importantly, our paper¹ also provides the proof of concept for the use of therapeutic polypeptides to inhibit a well-known difficult-to-target protein such as MYC, suggesting that a similar approach might be extended to other challenging targets within cancer cells.

Conflict of interest

MEB and LS are both founders and shareholders of Peptomyc S.L.

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