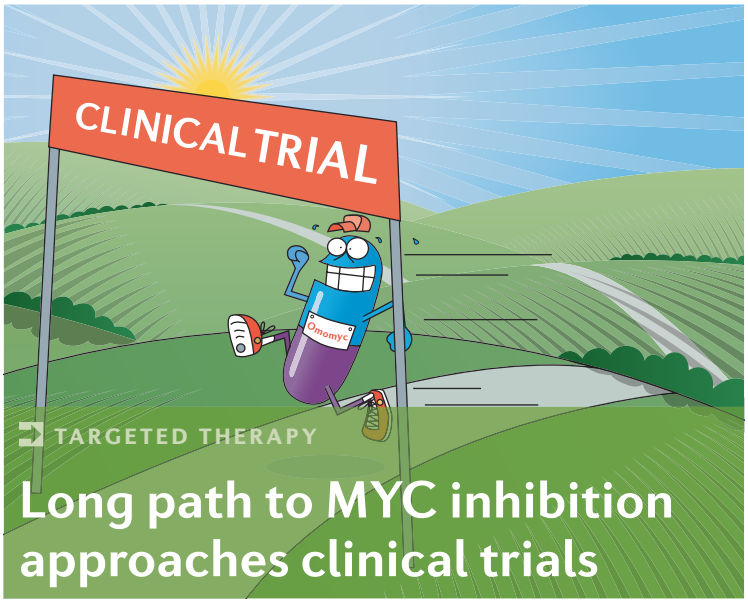

Credit: S. Harris/Springer Nature Limited

TARGETED THERAPY

Long path to MYC inhibition approaches clinical trials

> Treatment with Omomyc slowed tumour progression and, when given in combination with paclitaxel, almost completely abrogated tumour growth, extending mouse survival

The transcription factor MYC is frequently deregulated and hyperactive in cancer, and many tumours depend on MYC to grow. However, despite being an obvious target, inhibiting MYC therapeutically has proved to be challenging. Now, a team led by Laura Soucek has shown that Omomyc, a MYC dominant-negative gene product that is used to inhibit MYC for research purposes, can penetrate cancer cells in vitro and in vivo, bringing it closer to evaluation in the clinic.

The relevance of targeting MYC in cancer has long been clear, and Soucek has been working on this for more than 20 years. "Back then, MYC inhibition was considered to be an impossible mission, owing to both the technical challenges (attacking an intrinsically disordered protein hidden inside nuclei), and the fear of the catastrophic side effects that inactivating a protein implicated in normal cell proliferation could cause," she explains. Her research in the late 1990s led to the design and validation of the first transgenic tool to inhibit MYC in vitro, known as Omomyc. The gene consists of the MYC dimerization domain (a basic-helix–loop–helix leucine zipper (b-HLH-LZ) domain) with four mutations in the leucine zipper. Omomyc forms dimers with MYC and MYC-associated factor X (MAX), competing with all the MYC members for their target promoters. In vivo, transgenic expression of Omomyc in different mouse models of cancer showed that MYC inhibition was a safe and potent approach to treat cancer in different tissues, and in the presence of various oncogenic mutations.

Despite these promising results expressing Omomyc as a transgene, a route to take this knowledge forward to the clinic was not clear. Intracellular delivery to the nucleus of Omomyc in its peptide form was a challenge. "We had no pharmacological tool to inhibit MYC nor did we have another means to reproduce the efficacy of the Omomyc transgene," explains Soucek. "Omomyc was consequently considered merely a proof of concept, without any potential application as a drug, particularly due to its size (91 amino acids) and peptidic nature."

However, other b-HLH-LZ-containing proteins were reported to efficiently cross the cell membrane, translocate to the nucleus and inhibit c-MYC transcriptional activities. In the current article, Soucek and colleagues decided to test whether the purified Omomyc peptide itself could also have cell-penetrating activity.

First, the authors confirmed that the purified Omomyc peptide acted as a MYC–Omomyc heterodimer — interfering with MYC binding to DNA — as well as a MAX–Omomyc heterodimer, which competitively displaced MYC from its target genes.

Then, the authors treated several cancer cell lines with increasing concentrations of fluorescently marked Omomyc and observed internalization and partial localization in the nuclei at concentrations as low as 0.3 μM. An analysis of the MYC-driven transcriptional programme and MYC occupancy revealed that treatment with Omomyc reverted the expression of MYC-related gene signatures and displaced MYC throughout the genome, with complete displacement observed in ~80% of genes. Importantly, Omomyc did not suppress gene sets for other transcription factors involved in lung cancer, confirming Omomyc specificity.

Finally, the authors assessed the potential therapeutic utility of the Omomyc mini-protein in a mouse model of lung adenocarcinoma by intranasal administration of the polypeptide. Treatment with Omomyc administered three times per week stalled tumour progression and increased recruitment of T cells to the tumour site. The authors also tested the treatment in mice carrying xenografts from human lung cancer H1975 cells, which are resistant to tyrosine kinase inhibitors. Treatment with Omomyc slowed tumour progression and, when given in combination with paclitaxel, almost completely abrogated tumour growth, extending mouse survival.

These results suggest that Omomyc could become the first specific MYC inhibitor to reach clinical trials. Soucek and co-author Beaulieu have created a spin-off company, Peptomyc, to develop Omomyc-derived peptide therapeutics. "We are currently pursuing the industrial production process and hope to be able to initiate clinical trials in 2020 to assess its safety and efficacy," concludes Soucek.

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ORIGINAL ARTICLE Beaulieu, M.-E. et al. Intrinsic cell-penetrating activity propels Omomyc from proof of concept to viable anti-MYC therapy. *Sci. Transl Med.* **11**, eaar5012 (2019)
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