Preclinical validation of Myc inhibition by a new generation of Omomyc-based inhibitors

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Deregulated Myc is associated with most human cancers suggesting that its inhibition would be a useful therapeutic strategy. Indeed, we have shown that Myc inhibition displays extraordinary therapeutic benefit in various transgenic mouse models of cancer (i.e. skin, lung, pancreatic cancer and glioma) and causes only mild, well-tolerated and reversible side effects in normal tissues. Furthermore, we demonstrated that Myc has a non-degenerate function in cancer that cannot be replaced by other pathways, even in the most aggressive p53-null tumors. Therefore, Myc could be targeted safely and successfully without eliciting resistance to therapy.

For these studies we employed a dominant negative inhibitor of Myc, called Omomyc, which is an effective inhibitor of Myc transactivation function both *in vitro* and *in vivo*. Omomyc has so far been utilized exclusively as a transgene and served as a successful proof of principle. Here we discuss our current research with Omomyc and our efforts to develop a clinically viable approach to Myc inhibition. One is based on the direct use of Omomyc itself as a peptide since we have discovered that it natively possesses cell-penetrating activity and it rapidly biodistributes to the lung and brain after intranasal administration. We are finding that the Omomyc peptide - like its transgenic counterpart before – has a therapeutic impact and we are continuing with the preclinical validation of this innovative therapeutic approach to pharmacological Myc inhibition. The second approach takes advantage of state-of-the-art nanocarrier technology to deliver Omomyc systemically, that can be combined with tumour-targeting ligands. These two novel Myc inhibition strategies have the potential to be translated rapidly to the clinic.