

## Targeting eIF4F in Cancer

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The diversity of the mutations and their large number in tumors suggests that drug development strategies targeting specific oncogenic lesions are too narrow to develop broadly acting chemotherapeutics. Rather, targeting key signalling nodes found downstream of oncogene-activated pathways may offer broader acting therapeutic opportunities. Translational control is one such regulatory node - making this process an attractive molecular target for cancer therapy. Indeed, dysregulated protein synthesis is considered a hallmark of cancer and is linked to aberrant proliferation, survival, angiogenesis, alterations in immune response and cancer energetics. A key step of this process is under control of the PI3K/mTOR signaling pathway and controls assembly of eukaryotic initiation factor (eIF)4F. Whereas there is much pharmaceutical interest in targeting the PI3K/mTOR pathway in cancer, resistance mechanisms to these approaches can arise due to increased activity of eIF4F. Hence, "drugging" eIF4F is considered as an emerging anti-neoplastic approach.

Using focussed synthetic lethal shRNA screens, novel murine models that inducibly suppress eIF4F at the organismal level, and genetic manipulation of the translation apparatus in the powerful Eu-Myc lymphoma model, we have shown that deregulated translation in tumor cells is an important component of initiation, maintenance, metastasis and chemoresistance. Following the prosecution of >400,000 compounds in 2 HTS assays targeting translation initiation, we isolated and characterized 3 natural products (silvestrol, hippuristanol, and pateamine A) that selectively target the eIF4A subunit of eIF4F. I will discuss the biological properties of these compounds and their anti-neoplastic activity in pre-clinical cancer models. We hope to obtain mechanistic insight into the eIF4F regulatory node and its relationship with cancer progression and drug response.