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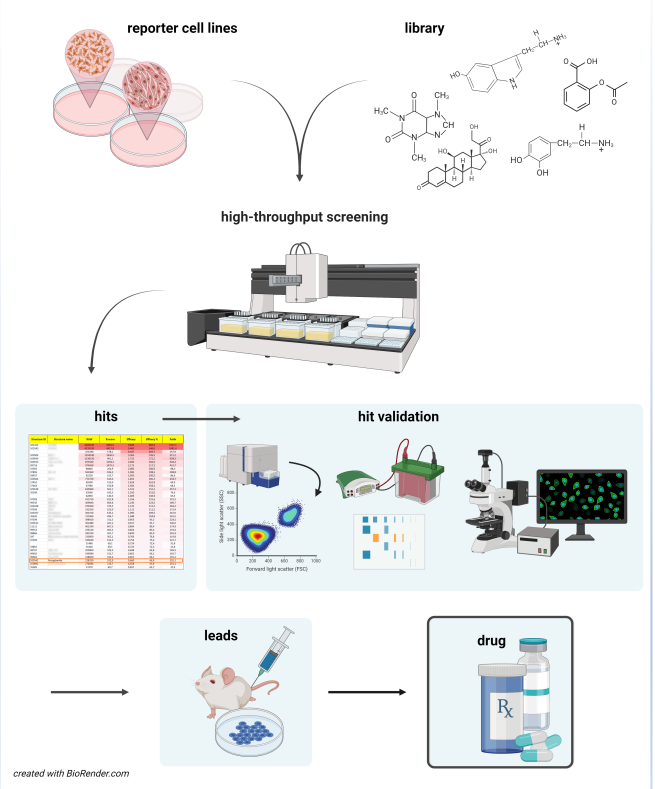
FACULTY OF MEDICINE, MASARYK UNIVERSITY

4TARGET: Novel eIF4F inhibitors for the treatment of drug-resistant melanoma

The eIF4F translation initiation complex is a promising therapeutic target in cancer [1, 2]. In advanced melanoma, the eIF4F protein complex has been identified as a nexus of resistance to clinically used drugs [3]. New eIF4F inhibitors suitable for clinical use could significantly improve the therapy outcomes for melanoma patients bearing tumors resistant to clinically used targeted therapeutics.

Despite eIF4F's attractivity as a therapy target, the portfolio of eIF4F inhibitors is limited, and only one drug candidate targeting the helicase subunit eIF4A made it into clinical testing so far. We developed a robust high-throughput screening (HTS)-compatible chemical libraries screening system and identified as hits novel small-molecule compounds potentially targeting eIF4F. After the planned extensive validation in orthogonal assays, selected best-performing lead compounds will be developed into drug candidates.



Application

- Treatment of melanoma patients who developed resistance to standard targeted therapy with BRAF/MEK inhibitors.
- Preventing melanoma resistance to clinically used drugs.

Market Assessment

Worldwide, an estimated 57,000 melanoma patients died in 2020. These numbers are predicted to rise by 2040 to 96,000 melanoma patient deaths per year [4]. Most advanced melanoma patients die because cancer cells become resistant to clinical BRAF/MEK inhibitors. Many of these patients could be saved if resistance to targeted therapy could be prevented by eIF4F inhibition.

Competitive Advantage

- We developed a unique, cell-based screening system to identify new eIF4F inhibitors.
- In high-throughput screens of chemical libraries (> 80,000 unique structures), we identified over 100 biologically active compounds as potential novel eIF4F inhibitors.
- We developed orthogonal assays to analyze the hits, confirm eIF4F target specificity, and filter out compounds with potential off-target activities.

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IP Protection

Our new, unique HTS-compatible screening method is unpublished. We will assess the patentability of selected drug candidates on an individual basis.

Needs

- Expertise in preclinical drug development.
- Financial support for the preclinical phase of drug discovery and development.

References

[1] doi: 10.1016/j.ccr.2004.05.024
[2] doi: 10.1158/0008-5472.CAN-14-2789
[3] doi: 10.1038/nature13572
[4] doi: 10.1001/jamadermatol.2022.0160

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