AXL-RTK Inhibition and Photodynamic Therapy as Combinatorial Treatment for Glioblastoma Multiforme

Nada Fadul[1,2,3], Louise Carroll[1,2,3,4], Farah Farrag[1,2,3], Dilan Gangar[1,2,5], Anna Shaw[1,2,3], Jennifer Yeon[1,2,3], Huang-Chiao Huang[1,2,5]

[1]University of Maryland, College Park, College Park, MD 20742, USA.
[2]Gemstone Honors College, University of Maryland, College Park, MD 20742, USA.
[3]College of Computer, Mathematical, and Natural Sciences . [4]College of Behavioral and Social Sciences . [5]Fischell Department of Bioengineering

Introduction

Glioblastoma Multiforme: The Story of a Deadly Brain Disease

Glioblastoma multiforme (GBM)

- 5-year survival rate of only 6.9%[5]
- Average life expectancy of just 8 months after diagnosis[5]

Clinical Challenges

- 90% recurrence post-treatment[8]
- Highly invasive[1]
- Immunosuppression & hypoxia[1]
- Blood brain barrier[1]

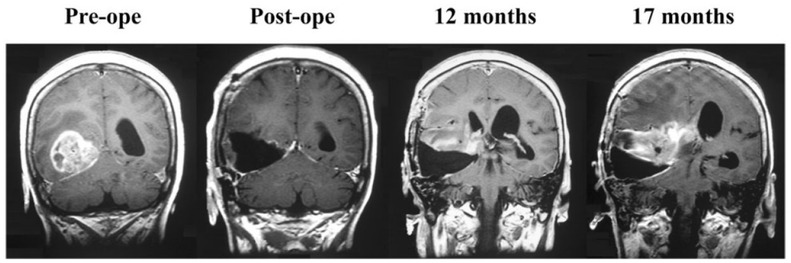


Figure 1. MRI scans of a glioblastoma patient who underwent surgical resection and chemotherapy treatment of GBM tumor in the right occipital lobe. 12 months after treatment, tumor recurrence was found in an MRI scan.[4]

Photodynamic Therapy & AXL-RTK Inhibition

Photodynamic Therapy (PDT): Minimally Invasive Cancer Treatment

1. Administer photosensitizer (NanoVP)[6]
2. Light activation of NanoVP → cell death[6]

NanoVP: Nanoformulation of Verteporfin improves PDT efficacy compared to liposomal Verteporfin.[6]

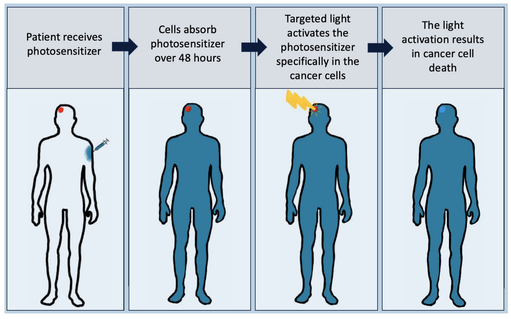


Figure 2. Representation of the application of PDT in the treatment of GBM

AXL-RTK Inhibition

1. GBM: High AXL-RTK expression significantly decreases tumor progression time from 8.9 to 3.9 months.[2]
2. Bemcentinib (Bem): In clinical trials, Bem is an AXL-RTK inhibitor with proven anti-cancer effects.[3]

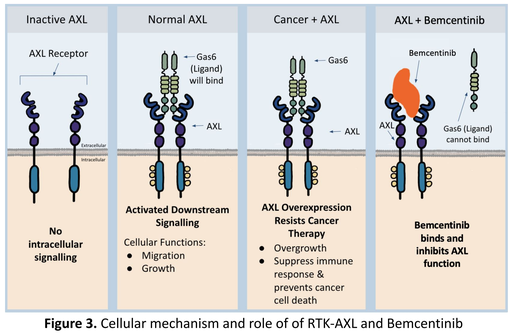
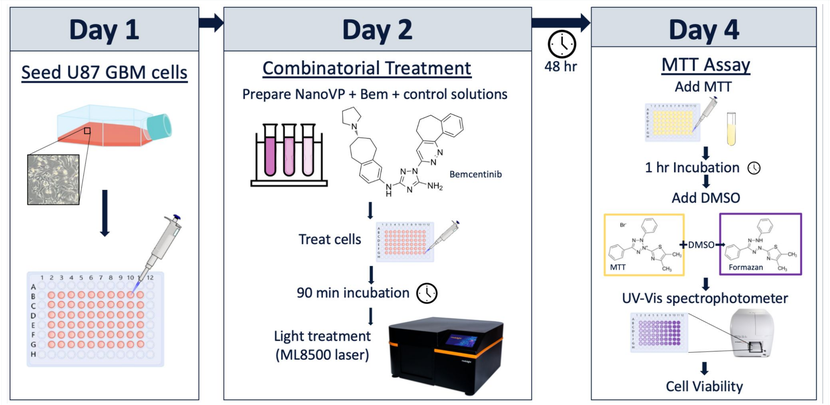


Figure 3. Cellular mechanism and role of of RTK-AXL and Bemcentinib

Objectives

Investigate synergistic combination therapeutics that incorporate photodynamic therapy, AXL-RTK inhibition, and nanoliposomal drug delivery to effectively target and treat primary and recurrent glioblastoma cancer cells.

Methods



PDT Treatment in Glioblastoma

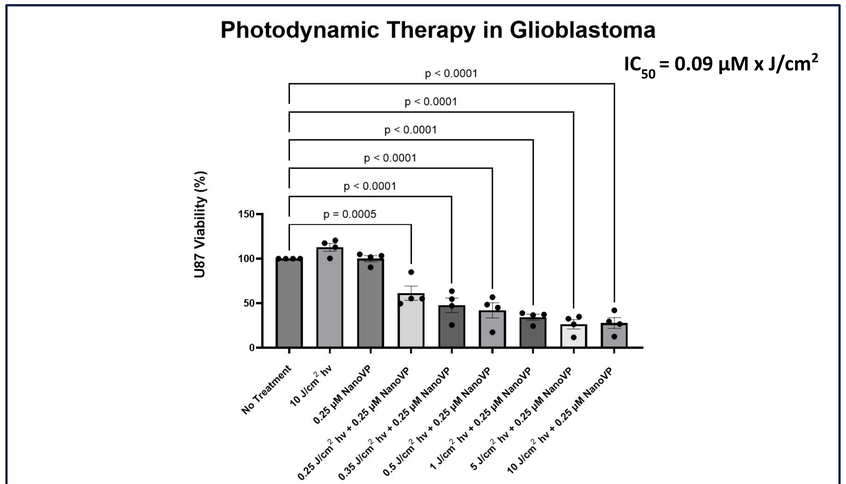


Figure 4. Cytotoxicity of PDT was tested on U87 glioblastoma cancer cells with 0.25 µM NanoVP across a range of light doses up to 10 J/cm^2. Cell viability was measured via MTT assay and normalized to no treatment control.

AXL-RTK Inhibition in Glioblastoma

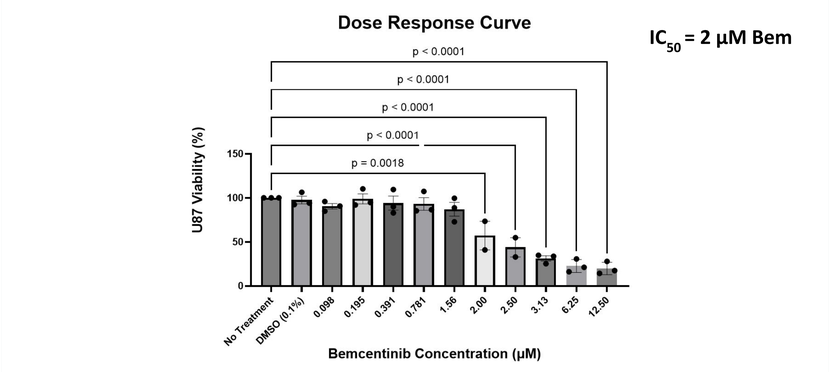


Figure 5. Cytotoxicity of AXL-RTK inhibition was tested on U87 glioblastoma cancer cells using Bemcentinib. A drug dose response curve was developed across a range of concentrations up to 12.5 µM. Cell viability was measured via MTT assay and normalized to no treatment control.

Combinatorial Treatment

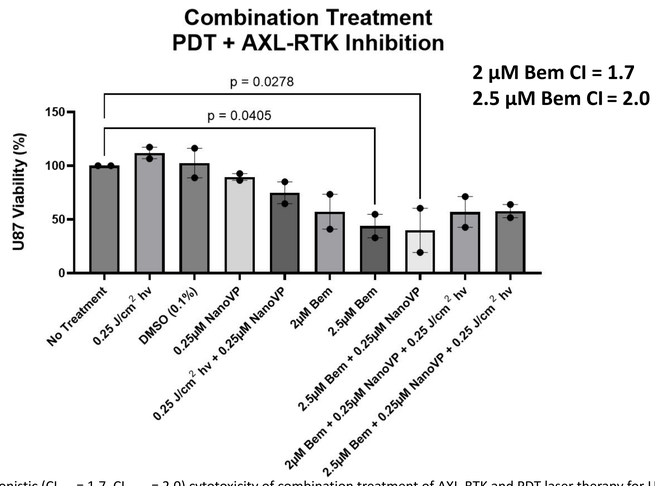


Figure 6. Antagonistic ($CI_{2\mu M}$= 1.7, $CI_{2.5\mu M}$= 2.0) cytotoxicity of combination treatment of AXL-RTK and PDT laser therapy for U87 glioblastoma cancer cells as measured by MTT assay and analyzed with cell viability normalized to no treatment control (*p=0.0104*). Preliminary experiments were developed with a priming light dose of 0.25 J/cm^2, 0.25 µM NanoVP, and an IC50 concentration of the AXL-RTK inhibitor Bemcentinib.

Conclusions

1. In initial experiments, we explored the effects of PDT on a GBM cancer cell line and observed an **anti-GBM PDT effect in a light-dose dependent manner** (Fig. 4).
2. An **anti-GBM effect of Bem. was also observed in a drug dose-dependent manner** (Fig. 5).
3. Preliminary experiments of our combination treatment with NanoVP-PDT and Bemcentinib demonstrated an **antagonistic effect**, with a significant anti-GBM effect of AXL-RTK inhibition on U87 cancer cell viability (Fig.6).
4. Future experiments will reveal whether varying combinations of PDT and RTK-AXL inhibition have a **synergistic effect** on treatment of glioblastoma cells.

Research Timeline & Future Directions

Spring 2023
- Literature review
- Thesis proposal
- Proposal defense
- LanchUMD fundraiser
- Budget plan

Fall 2023
- *In vitro* laboratory training w/ U87 GBM cell line
- LaunchUMD fundraiser
- VP-PDT *in vitro* exp. w/ ML6610 laser

Spring 2024
- NanoVP PDT *in vitro* exp. w/ ML8500
- AXL inhibition exp. w/ Bemcentinib
- Preliminary *in vitro* combination therapy
- Undergraduate Research Day
- Neuroscience Research Fair

Fall 2024
- Continue *in vitro* combination therapy exp., exploring the synergistic effects of varying parameters of phototherapy & AXL-RTK inhibition
- Thesis development

Spring 2025
- Complete data analysis
- Revision of thesis
- Thesis presentation
- International PDT conferences
- Development of manuscript/ publication

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References