Development of the Anti-Parasitic Drug Mebendazole for High Grade Glioma Therapy

Seminar for Neuro-Oncology Updates Meeting, Nashville, TN

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Parasitic Indications for mebendazole

Hookworms

Pinworm (enterobiasis)

Common Roundworm (ascariasis)

Echinococcus granulosus (cystic) or multilocularis (aveolar)

MBZ structure
Mebendazole is a Benzimidazole that binds Tubulin and used against parasitic worms

<table>
<thead>
<tr>
<th>Antiplatyhelmintic agents (schistosomicides)</th>
<th>Antitrematodals</th>
<th>Anticestodals (taeniacides)</th>
<th>Binds tubulin</th>
<th>Binds tubulin</th>
<th>benzimidazole (Triclabendazole*)</th>
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<td>Al</td>
<td>Other/unknown</td>
<td>phosphonic acid (Metrifonate)</td>
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<td>quinoline (Praziquantel*, Oxamnique*)</td>
<td>phenol (Bithionol)</td>
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<tr>
<td>Antinematal agents (including macrofilaricides)</td>
<td>Chloride channel</td>
<td>Other/unknown</td>
<td>benzimidazole (Albendazole*)</td>
<td>salicylanilide (Niclosamide)*</td>
<td>aminoacridine (Quinacrine)</td>
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<td>butyrophenone (Desaprid)</td>
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<tr>
<td>Binds tubulin</td>
<td>benzimidazole (Mebendazole*, Albendazole*, Thiabendazole, Fenbendazole, Ciclobendazole, Flubendazole)</td>
<td>salicylanilide (Niclosamide)*</td>
<td>aminoacridine (Quinacrine)</td>
<td>butyrophenone (Desaprid)</td>
<td>chlorimidazole</td>
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Categories: Benzimidazoles | Aromatic bases
Anti-Helminthics: a chance discovery of anti-tumor activity

Medulloblastoma xenografts stopped growing in our mouse colony (no tumor engraftment)
This corresponded with pinworm infection and flubendazole treatment of mouse colony.
Fenbendazole, mebendazole, and albendazole tested, with mebendazole showing the best increase in survival in animal models.
Mebendazole is FDA approved.
Mebendazole and other benzimidazoles show anticancer activity


The antihelmintic flubendazole inhibits microtubule function through a mechanism distinct from Vinca alkaloids and displays preclinical activity in leukemia and myeloma. BLOOD, 10 JUNE 2010 VOLUME 115, NUMBER 23.

Figure 1- MBZ works as single agent increasing survival better than ABZ
**Figure 2-** MBZ increases survival also in 060919

<table>
<thead>
<tr>
<th></th>
<th>ABZ</th>
<th>MBZ</th>
<th>TMZ</th>
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<tr>
<td>IC50 µM</td>
<td>0.10</td>
<td>0.11</td>
<td>148</td>
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Invasive growth of 060919 xenograft

Survival of 060919 GBM xenograft

- **control n=6 m=48d**
- **TMZ n=3 m=51d**
- **ABZ n=4 m=43d**
- **MBZ n=6 m=65d**

P=0.0016

Day 0 treatment

Day 20 treatment

Counts in 10^6

Days post tumor implantation
Figure 3- MBZ bins and disrupts Tubulin as mechanism
Overall survival results for MBZ trials in GL261
MEBENDAZOLE MONOTHERAPY AND LONG-TERM DISEASE CONTROL IN METASTATIC ADRENOCORTICAL CARCINOMA

Irina Y. Dobrosotskaya, MD, PhD; Gary D. Hammer, MD; David E. Schteingart, MD; Katherine E. Maturen, MD; Francis P. Worden, MD

ABSTRACT

Objective: To describe successful long-term tumor control in metastatic adrenocortical carcinoma, a rela-

Conclusion: Mebendazole may achieve long-term disease control of metastatic adrenocortical carcinoma. It is well tolerated and the associated adverse effects are minor. (Endocr Pract. 2011;17:e59-e62)

Fig. 1. Regression of hepatic metastatic lesions after treatment with mebendazole. Axial computed tomographic images of the abdomen with contrast performed 1 month before (Panel A), 4 months after (Panel B), and 19 months after (Panel C) the initiation of mebendazole treatment.
Mebendazole Clinical Trial Design and Progress

- Phase I dose escalation trial up to 200mg/kg/day plus Temozolomide for newly diagnosed HGG.
- Expanded cohort at highest tolerated dose
- In-person review by the JHU Cancer Research Committee completed.
- Underwritten with initial funding from ABC² (accelerate brain cancer cure) foundation
Mebendazole next steps Future

• Securing an affordable drug supply and FDA application are the most urgent next steps.
• Deeper investigation into mechanism
• Improved formulation and drug delivery
• Combination with radiation or other therapeutics
• Use on other cancers?
The Brain Tumor Biology and Therapy Laboratory at Johns Hopkins

- Gregory Riggins, MD PhD- Laboratory Director griggin1@jhmi.edu
- Gary Gallia (co lab- PI)-AKT inhibitors and tissue collection
- I-Mei Siu- stem cell based drug screen and animal models
- Renyuan Bai- liposomal, anti-parasitic and bacteriolytic therapy
- Brenda Raymond- Administrative Assistant
- Sasha Borodovsky- IDH1 drug screen
- Genevieve Weber- Glioblastoma Genomics and Invasion
- Verena Staedtke- Glioblastoma Bacteriolytic Therapy and animal models
- Avadhut Joshi- Drug Screens and ion channels
- Meghan Seltzer- IDH1 and metabolism (emeritus)
- Gilson Baia- Meningioma, MPNST, NF1, NF2
- Kelli McDowell- Drug synergy with AKT, Temozolomide
- Callen Riggins- Sample Database, IT support, 3D imaging
- Otavia Caballaro- MELK, CT antigens, Associate Investigator, Ludwig
- Robert Strausberg-Director of Collaborative Research, LICR.
- Andy Simpson- Scientific Director, Ludwig Institute of Cancer Research
- Qi Zhao- Bioinformatics, Ludwig Institute of Cancer Research

Other Collaborators: Johns Hopkins-Animal Testing and Toxicity- Betty Tyler and Henry Brem; Univ Sao Paulo- Suely Marie JHU Oncology and Ludwig Center- Bert Vogelstein & Ken Kinzler, Victor Velculescu, Nick Papadopoulos, Shibin Zhou, Luis Dias LICR San Diego- Andy Shiau and Tim Gahman

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