GLIAXAL MEDICAL FOOD FOR THE ENHANCED TREATMENT OF GLIOMA

GLIOBLASTOMA
ASTROCYTOMA
OLIGODENDROGLIOMA

Use of a Designated Orphan Drug for the Treatment of Brain Cancer
Oxaloacetate is a new “Orphan Drug” for the treatment of Glioma

After Review, US FDA Designates Oxaloacetate As an “Orphan Drug” for the Treatment of Gliomas. Designation (12-3704)

Terra Biological LLC
5033 Searchase Street
San Diego, California 92130

Attention: Alan Cash
Chief Executive Officer

Re: Designation request # 12-3704

Amendment Dated: June 26, 2012
Amendment Received: June 27, 2012

Dear Mr. Cash:

Reference is made to your request for orphan-drug designation of oxaloacetate for the “treatment of glioblastoma.”

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of oxaloacetate is granted for treatment of gliomas. Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated. Please note that the indication granted is broader than the indication proposed in your designation request.
Oxaloacetate is a new patented compound for Cancer Treatment

European Patent Agency
Approved Cancer Treatment
Claim:

“A pharmaceutically effective amount of a composition of oxaloacetate for use in the treatment of cancer, wherein oxaloacetate refers to oxaloacetic acid, the salt of the acid, or oxaloacetate in a buffered solution, or mixtures thereof.”

Other patents pending worldwide.
Oxaloacetate is a new patented compound for Cancer Treatment

Australian Patent Officer
Approved Cancer Treatment

Claim:

"Use of a pharmaceutically effective amount of a composition selected from the group consisting of oxaloacetate, oxaloacetic acid and an oxaloacetate salt in the manufacture of a medicament for treating cancer"

Other patents pending worldwide.
Oxaloacetate is Available Now as a Medical Food for Glioma Patients

- “Gliaxal” is a medical food composed of oxaloacetate and ascorbic acid. It is available now for patients with glial tumors under legislation within the “Orphan Drug Act”.
  - Medical Foods are to be administered under the supervision of a physician
  - Gliaxal is for the clinical dietary management of the metabolic needs of Glial tumor patients.
- *Using Gliaxal as an adjunct treatment to standard therapy may increase overall efficacy.*
The Current Standard Therapy for Glioblastoma

- Surgery plus radiation therapy for elderly patients
- BCNU-Impregnated polymer (chemotherapeutic Gliadel wafer) implanted during initial surgery
- In younger patients, surgery with Gliadel wafer, radiation therapy, and the chemotherapeutic Temozolomide.
- The combination of surgery, radiation therapy and Temozolomide increases median survival time from patients receiving surgery, wafer and radiation alone from 12.2 months to 14.6 months (20% increase).
- Five year survival ranges from 2 to 5%.
A pressing need

- While increasing median survival from 12.2 to 14.6 months is a step in the correct direction, clearly there is room for improvement.

- An overall five-year survival of 2 – 5% leaves much room for improvement.

- The National Cancer Institute estimates that 22,910 adults (12,630 men and 10,280 women) will be diagnosed with brain and other nervous system tumors in 2012. It also estimates that in 2012, 13,700 of these diagnoses will result in death.
Case studies indicate that Gliaxal, either alone or in combination with other therapies, stopped tumor growth in 88% of the patients (N = 17)
Oxaloacetate Improves Malignant Glial Tumor Treatment

- Data shown includes Gliaxal used alone and in combination with other therapies:
  - Ketogenic Diet
  - Chemotherapy
    - Temodar, Everolimus, Cabozantinib, Carboplatinum, Nilotinib and Avastin
  - Radiation
- In slow growing tumors, Gliaxal can be used alone. In more aggressive tumors, Gliaxal can be used as an adjunct agent to improve the Standard Therapy.
Mechanisms of Action

- Glutamate overproduction is directly tied to the growth of malignant gliomas, their invasiveness, and ability to destroy neighboring brain tissue.
- Glutamate level reduction will allow HIF-1 to decompose, reducing the rate of tissue growth.
- Reducing Glutamate via Oxaloacetate Supplementation is very successful in treating Gliomas in animal studies.

“Blood Glutamate scavengers prolong the survival of rats and mice with brain-implanted gliomas”

Ruban, A. et al, Invest New Drugs 2012
Mechanisms of Action

Glioblastoma Growth 7 days after implantation.

Rubin, Inv. New Drugs 2012
Combining Oxaloacetate with Chemotherapy Improves Treatment

21 day tumor growth in nude mice. Ruban, Investigative New Drugs 2012
Morphology of Glioma Tumors

Reduced Tumor Cell Nuclear Density with OAA and Chemo

Ruban, Invest. New Drugs 2012
Oxaloacetate and Temozolomide Reduce Tumor Cell Invasion

Astrocyte Levels remain high With Oxaloacetate/ Chemo Combination.

Ruban, Investigative New Drugs, 2012
Oxaloacetate with Chemotherapy Greatly Improves Survival (237%)
Gain of Function mutations in Isocitrate dehydrogenase (IDH1 and IDH2) that produce D-2-hydroxyglutarate (D-2HG) are found in the majority of gliomas.

D-2HG abundance greatly increases the risk of glioma.

_D-2HG is “competitively inhibited” by Oxaloacetate_

Oxaloacetate \& IDH1/IDH2

Oxaloacetate competitively Inhibits IDH2

(Kranendijk, 2011)
Oxaloacetate & IDH1/IDH2

- Oxaloacetate is currently in Phase I clinical trial at the University of California, San Diego for the reduction of D-2HG in D-2-hydroxyglutaric Aciduria (Type 2). Reductions of 45% were seen in D-2HG levels with oxaloacetate supplementation.

- IRB approval for up to 6,000 mg/day of oxaloacetate in infants. Very low toxicity profile.
AMPK/FOXO3 Activation inhibits tumor initiating Potential of Cancer Stem-Cells

- FOXO3 Activation via AMPK activation induces differentiation of glioma-initiating cells. *This allows stem cells that were producing cancer cells to differentiate normally instead.*

“Glioma-Initiating Cell Elimination by Metformin Activation of FOXO3 via AMPK”

Sato, A et al., Stem Cells Translational Medicine, November 2012.
AMPK activation increases survival

Sato, 2012
AMPK Activation Decreases Tumor Weight

Sato, 2012
Comparison of Metformin and Oxaloacetate Additions for Survival

Histology Report:
No Cancer Cells Detected in survivors

Oxaloacetate Supplementation
(Rubin 2012)

Metformin Supplementation
(Sato 2012)

Survival (%)

0 20 40 60
Time (days)

Percent survival

0 25 50 75 100
Time (days)

Control

OxAc/hGOT

TMZ

TMZ/OxAc/hGOT
Oxaloacetate also activates FOXO3 via AMPK activation

- One of the reactions of oxaloacetate in the body is to react to malate. During this reaction, NADH is converted to NAD+. This activates AMPK and resulted in a 70% up-regulation of the FOXO3 gene.*

- FOXO3 proteins allow cancer producing stem cells to produce normal cells instead.

*“Oxaloacetate supplementation increases lifespan in Caenorhabditis elegans through an AMPK/FOXO-dependent pathway”
Williams, D.; Cash, A et al, Aging Cell 2009
Oxaloacetate increases NAD+ levels which may reverse the Warburg Effect

Oxaloacetate supplementation increases NAD+ levels.

Low NAD+ levels in the Nucleus have been suggested to cause the Warburg Effect via disturbed OXPHOS signaling.


*Increasing NAD+ levels have been proposed to reverse the Effect.*
Multiple Advantages to Gliaxal Medical Food for Glioma Treatment

- Case studies support the use of Gliaxal to stabilize Glioma.
- Oxaloacetate is proven to work synergistically with the standard therapy (Temozolomide) to greatly improve survival and in 30% of the treated animal group, elimination of all traces of the implanted tumor.
- Can be given to older patients without increases in side effects.
- Oxaloacetate is proven to reduce glutamate levels in the brain associated with growth of malignant gliomas, their invasiveness, and ability to destroy neighboring brain tissue.
- Oxaloacetate is proven to activate AMPK, which has been shown to inhibit tumor proliferation/return.
Primary Support Summary: Oxaloacetate Improves Glioma Treatment

- Oxaloacetate Supplementation has been shown in human case studies to stabilize glial tumors.
- Oxaloacetate retards the growth of human Glioblastoma tissue in animals by 50%.
- Combining Oxaloacetate Supplementation with Standard Chemotherapy may improve treatment Efficacy
- Tests with Human Glioblastoma Tissue in nude mice show a 237% Increase in survival by adding oxaloacetate to standard treatment.
- An AMPK activator, Oxaloacetate may reprogram Cancer Stems cells to differentiate normally, reducing reoccurrence.
- Oxaloacetate competitively inhibits IDH2 production of D-2-hydroxyglutarate.
- Oxaloacetate increases NAD+ levels which may reverse the Warburg Effect.
Oxaloacetate increases the amount of alpha-ketoglutarate (through glutamate reduction and sGOT conversion). This may allow proper histone demethylation which has also been tied to proper stem cell differentiation, reducing/eliminating the cancer source.

“Glioma-Derived Mutations in IDH1 Dominantly Inhibit IDH1 Catalytic Activity and Induce HIF-1alpha”

Oxaloacetate has also been shown to drive human lung cancer cells into senescence, while normal lung tissue was not affected. The lung cancer cells were followed for a period of six weeks after a single application of oxaloacetate.

“Differential modulation of intracellular energetics in A549 and MRC-5 cells”
Secondary Support: Oxaloacetate Improves Glioma Treatment

- Calorie Restriction increases prevention of cancer in general, and specifically has been used to improve the outcome of Glioblastoma.*

- Oxaloacetate is a “Calorie Restriction Mimetic” and a ketone.

Oxaloacetate lowers fasting glucose levels, which may benefit cancer treatments, as cancer has a strong dependence on glucose.

“Studies on the anti-diabetic effect of sodium oxaloacetate”
Secondary Support: Oxaloacetate Improves Glioma Treatment

- Oxaloacetate increases the NAD+/NADH ratio by up to 900%

The addition of 20 μM oxaloacetate to rat liver mitochondria increases the NAD+/NADH ratio by 900% in under 2 minutes. From Haslam & Krebs, 1968.

□, NADH + NADPH. Enzymic assays: ■, NADH; △, NADPH; ○, NAD⁺; ●, NADP⁺.
Increasing the NAD+/NADH ratio inhibits metastasis and prevents disease progression in breast cancer. Other cancers may benefit from this metabolic adjustment.

In a case study, Gliaxal Medical Food has been shown to drop PET SUV values in a metastatic breast cancer patient by 30% in 30 days. The patient combined Gliaxal with a Ketogenic Diet.
Oxaloacetate supplementation in humans as a nutritional supplement has no reported side effects in six years of use, and the oral supplementation can be easily combined with many other standard therapies.

Combining oxaloacetate supplementation with existing treatments for Glioblastoma may provide a synergistic response, increasing survival and quality of life while decreasing reoccurrence.
Oxaloacetate Studies outside of Cancer

- Oxaloacetate reduces fasting glucose levels by 25% (average) in diabetics without side effects in clinical trial.

“Studies on the anti-diabetic effect of sodium oxaloacetate”.

Oxaloacetate Studies outside of Cancer

- Clinical Trial testing oxaloacetate supplementation for the treatment of Parkinson’s Disease. Parkinson’s Disease and Movement Disorder Center, University of Kansas. In progress. See [http://clinicaltrials.gov/ct2/show/NCT01741701](http://clinicaltrials.gov/ct2/show/NCT01741701)

- Clinical Trial testing oxaloacetate supplementation for Alzheimer’s Disease. Phase 1 study. See [http://clinicaltrials.gov/ct2/show/NCT02063308](http://clinicaltrials.gov/ct2/show/NCT02063308)

- Clinical Trial testing oxaloacetate supplementation for Pediatric Brain Cancer. Starting 2014

- Clinical Trial for D-2-hydroxyglutarate aciduria Type 2. University of California, San Diego. In progress.

- Clinical Trial for Type 1 and Type 2 Diabetes, Tohoku University Japan, Completed.
Summary of Oxaloacetate for the treatment of Gliomas

- **Safety**
  - Oxaloacetate is a human metabolite found in the Citric Acid Cycle, and is found in every cell of the body.
  - Oxaloacetate is central to energy metabolism.
  - Oxaloacetate is available as the medical food *Gliaxal*, with few reported side effects (increased burping).
  - The LD50 of oxaloacetate is greater than 5,000 mg/kg (mice), classifying it as “non-toxic”.
Summary of Oxaloacetate for the treatment of Gliomas

- **Efficacy**
  - Case Studies to date show 88% of the patients stabilized their disease (N=17)
  - Animal studies with human glioblastoma tissue shows a 237% increase in survival when oxaloacetate is added to chemotherapy.
  - Oxaloacetate alone reduces tumor size and increases survival. Oxaloacetate combined with chemotherapy eliminated all detectable cancer cells in 30% of the glioblastoma treatment group (animal study).
  - An AMPK activator, Oxaloacetate may reprogram Cancer Stems cells to differentiate normally, reducing reoccurrence.
  - As a Glutamate scavenger, Oxaloacetate may reduce the invasiveness of glioblastoma tumors.
Summary of Oxaloacetate for the treatment of Glioblastoma

- Simplicity
  - The medical food Gliaxal combines oxaloacetate and ascorbic acid for Glioma patients.
  - Gliaxal is water soluble allowing for easy oral supplementation.
  - Oxaloacetate has been shown to have synergistic effects with standard chemotherapy and can be easily integrated with any treatment protocol.
For More Information

To find out more about Gliaxal for Gliomas, contact us:

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