TYME INC™

*the* **FUTURE** *of* **CANCER TREATMENTS**

# Mechanism of Action Overview

NOVEMBER 2017

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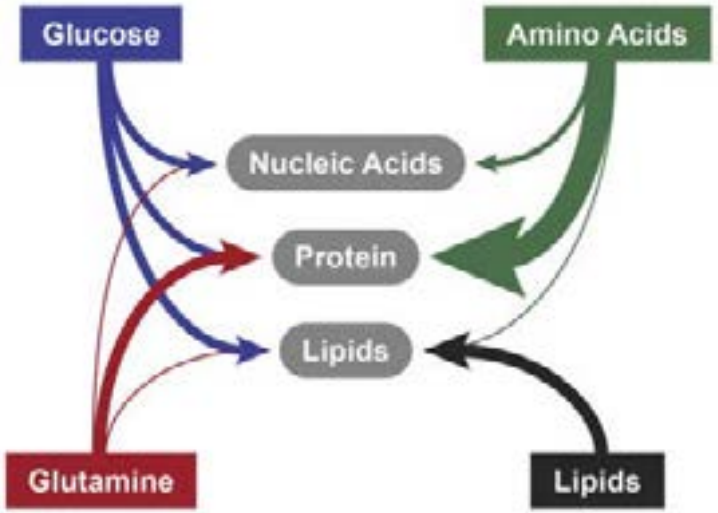
# SM-88 Rationale and Mechanism of Action

| | |
|---|---|
| **TUMOR METABOLISM** | • Tumors require excess nutrients including glucose, amino acids and lipids to support rapid replication<br>• Cancer cells utilize unique metabolic mechanisms to obtain the nutrients they require for growth |
| **TUMOR PHYSIOLOGY** | • Nearly all cancers use aerobic glycolysis (Warburg Effect) resulting in elevated reactive oxygen species (ROS)<br>• ~90% of cancers upregulate mucin, in part to regulate the elevated ROS in cells |
| **SM-88 COMPONENTS** | • Dysfunctional tyrosine derivative acts as a faulty building block for protein synthesis (including mucin)<br>• The other components either 1) drive increased of tyrosine uptake, or 2) increase the reactive potential of the cancer cell |
| **SM-88 PROFILE** | • Safety- Tyrosine's selective uptake by cancer and sub-therapeutic levels of other agents parallels the current profile<br>• Efficacy- The universal nature of the Warburg Effect and ROS imbalance across cancers supports the broad activity of SM-88 |

# Tumor Metabolism- Unique Nutritional Needs

- Cancer requires the accumulation of significant biomass to support rapid proliferation. (Science 2009) Amino acids and lipids make up a substantial portion of the nutrients to support this growth (Dev Cell 2016, Clin Cancer Res 2015)
- Cancer cells upregulate amino acid transporters, a prominent one being LAT1 (L-amino acid transferase-1) (Sem Cancer Biology 2005, Cancer Research 2015, Cancer Research 2015). Tyrosine is transported by LAT1, leading to an elevated tyrosine uptake in cancer cells.
- We also believe tyrosine is an optimal target for cancer therapy since normal cells readily convert phenylalanine to tyrosine versus absorbing it (J Nutr 2007)
- Cancer cells also display elevated levels of lipid intake from the tumor microenvironment (Cancer Research 2017, Clin Cancer Res 2015, PNAS 2013). This is behind our rationale of the inclusion of an agent that creates reactive lipids (phenytoin- Life Sciences 1997)

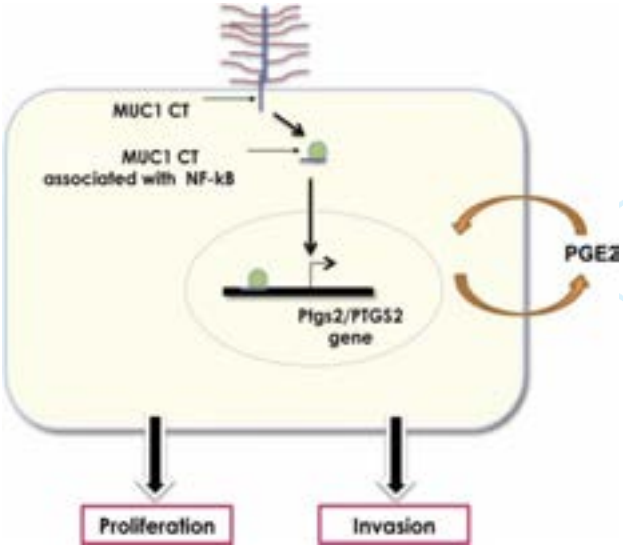


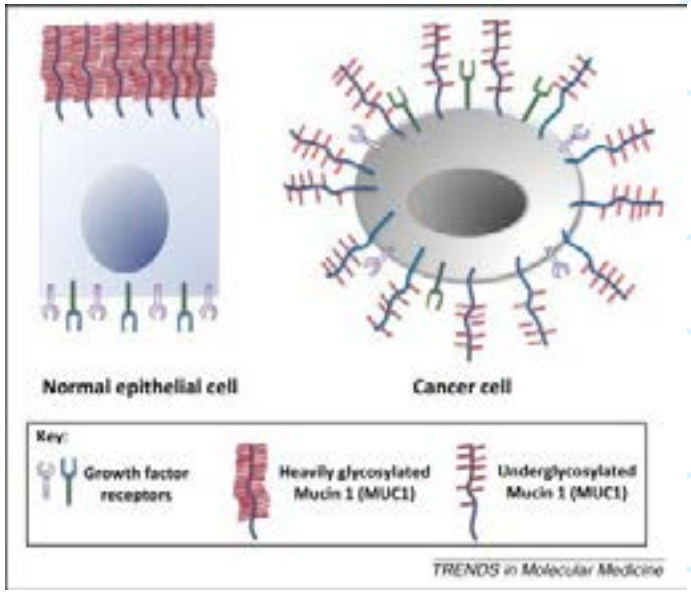
# Tumor Physiology- Managing Hostile Environment

**Cancer's inefficient metabolism (Warburg Effect/ aerobic glycolysis) results in an elevated level of intracellular reactive oxygen species (ROS) (Cell 2008, Trends Biochem Sci. 2016) and microenvironment acidity that requires the cancer cell to protect itself.**

**Transmembrane (TM) mucins (MUC1, MUC4, MUC16) provide important functions for the survival and growth of cancer cells (Oncogene 2010, JBC 2003, Nat Rev Cancer 2009). These include upregulation of ROS scavenging enzymes superoxide dismutase, catalase, and glutathione peroxidase (JCO 2003, Nat Rev Cancer 2009) that protect the cancer cell from apoptosis (Biochem Biophys Res Comm 2013)**

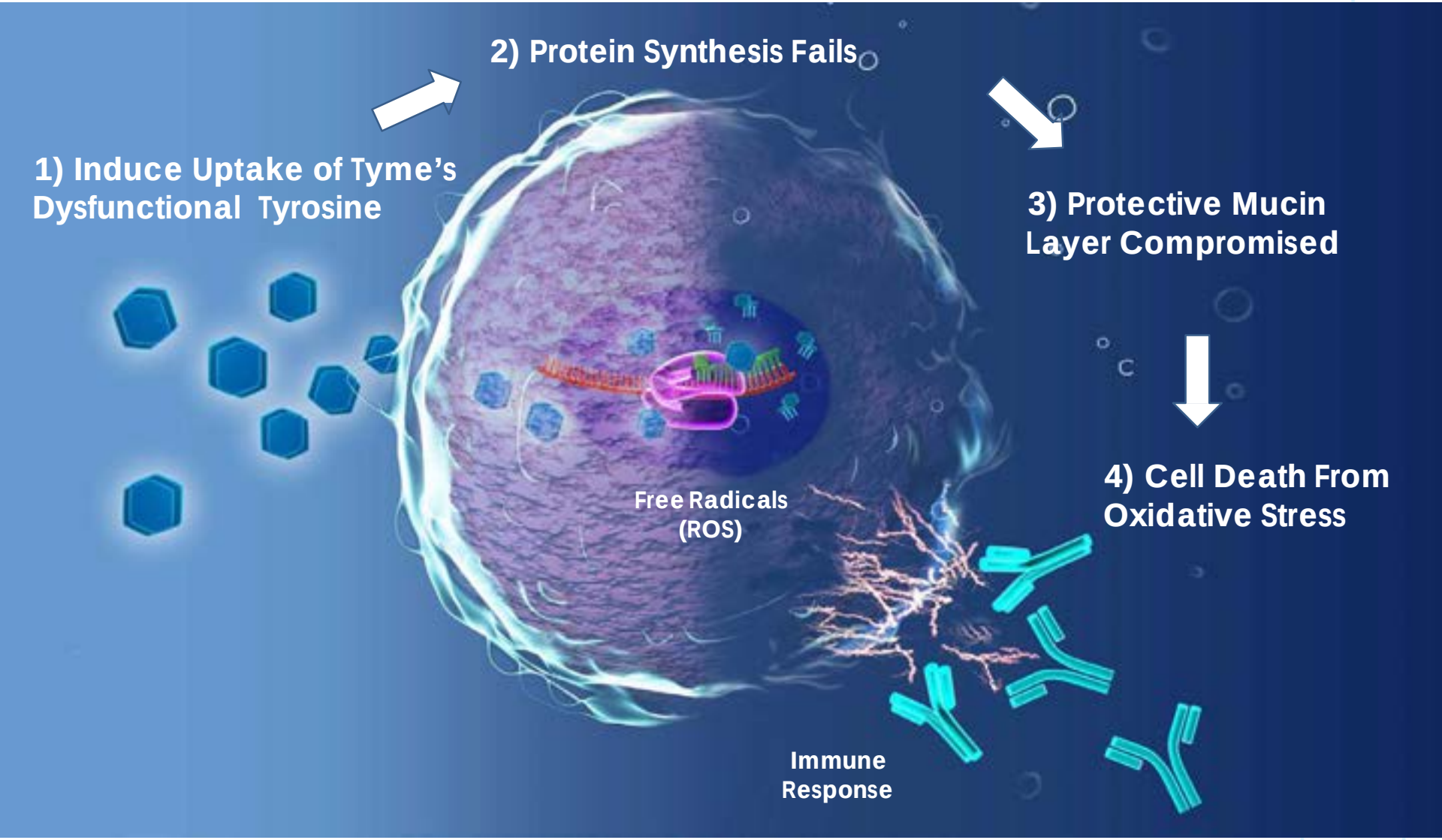
**MUC1 is expressed in a high proportion of epithelial cancers (Trends in Mol Med 2014, Nature Reviews Cancer 2009) as well as hematological cancers (Cancer Res, 2013, Blood 1999). We believe this supports range of activity for SM88 to date.**




1. Nath S, Roy LD, Grover P, Rao S, Mukherjee P Pancreas (2015) and S Nath et.al. tTrends in Molecular Medicine 2014

# Breaking the Metabolic Circuit of Cancer



# SM-88 Components- Rationale

**Tyme approach employs multiple mechanisms intended to optimally target a key cellular process. We believe such an approach is critical in addressing the complex nature of cancer.**

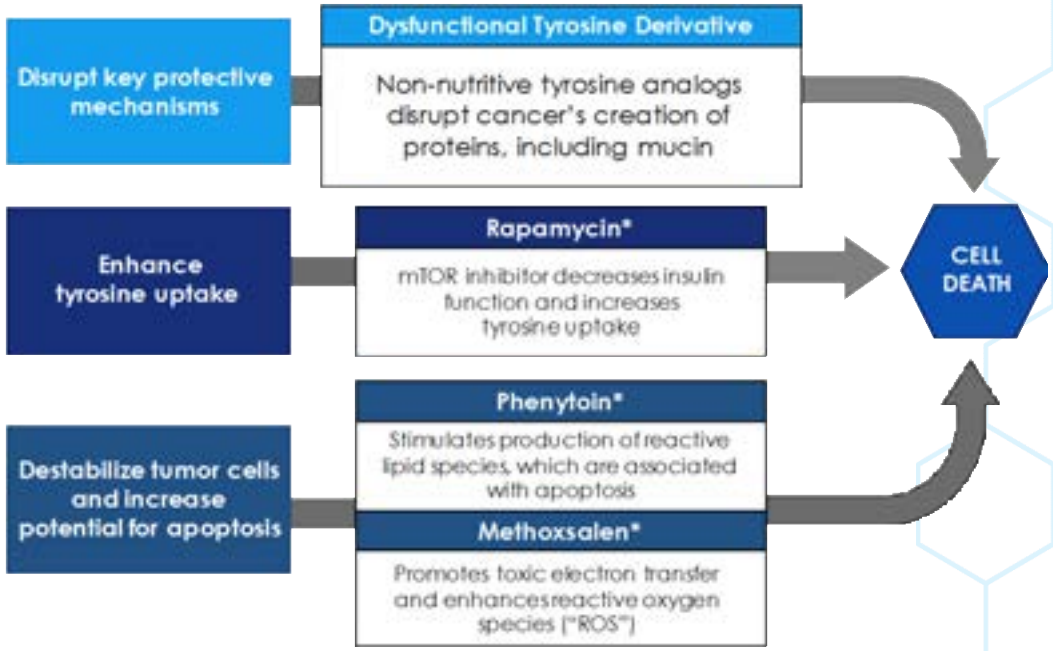
**In combination with a proprietary tyrosine agent, SM-88 leverages well documented properties of repurposed drugs used in low, sub-therapeutic doses, to disrupt key biologic processes specific to cancer cells while sparing normal tissue.**

**SM-88 was designed to increase the level of reactive oxygen species (ROS) in cancer cells to trigger innate apoptotic pathways and cause cancer cell death**

**The core component of SM-88 is a dysfunctional tyrosine derivative that interferes with the production of mucin and other proteins**

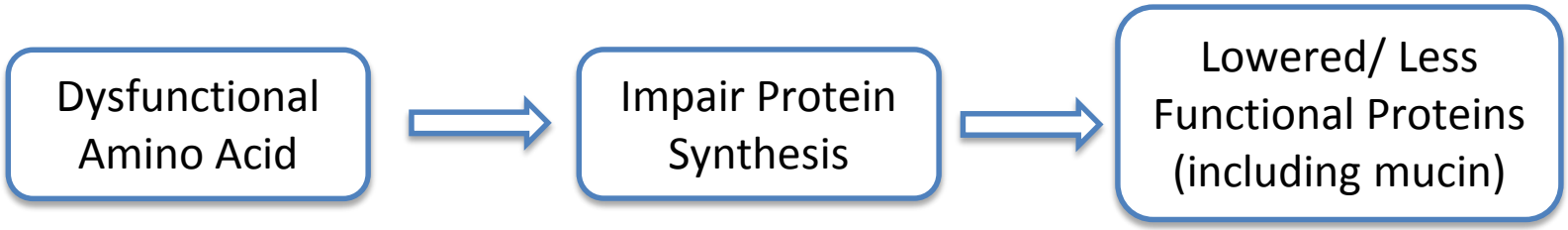
**Mucin is a key defense mechanism for cancer cells against ROS and the immune system**

**The additional components enhance cancer cells' uptake of this dysfunctional tyrosine, or further sensitize the cancer cell to the elevated reactive state**



# SM-88 Components- Tyrosine Derivative

**Bottom Line: Introduce a non-functional protein building block to primarily disrupt the production/fidelity of cancer cell's mucin.**




**The core component of SM-88 is a modified form of the non-essential amino acid tyrosine. This agent is a racemic mix of D-/L-isomers where the L-isomer is aimed to drive the uptake of the D-isomer, and the D-isomer is aimed to interfere with the protein synthesis of the cell (j Controlled Release 2017, World J Gastrointest Oncol 2017)**

**Tyrosine was selected as an amino acid since the literature supported that it is absorbed by cancer cells (Nucl Med Biol. 2011) but that most healthy cells create their required tyrosine by converting phenylalanine to tyrosine (J Nutr 2007).**

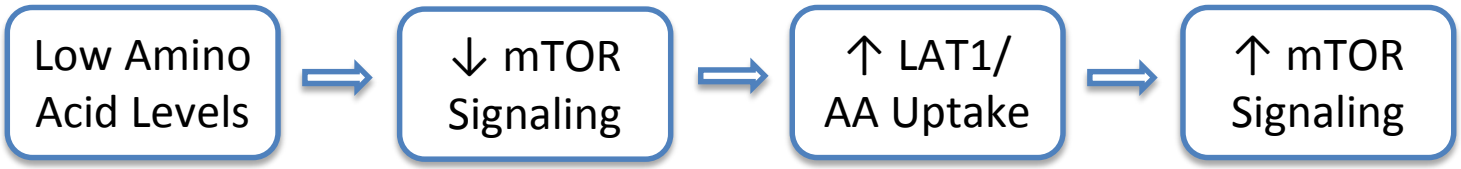
**Additionally the use of radiolabeled tyrosine for PET imaging display high contrast for tumors (Nuclear Science and Techniques 2006) supporting the selective uptake by cancer cells.**

**While the precise disruption mechanism of our product has not fully been elucidated, however, medical literature suggests to us, that the D-tyrosine isomers interference with the tRNA could be central in the process (PNAS 2015, ACS Chem Biol 2015, Nature Rev Cancer 2011, Biochem J 2009).**

**Research has emerged showing D-amino acids can become incorporated into proteins of elderly that impair their functionality (D-Amino Acids 2016, )**

# SM-88 Components- Rapamycin

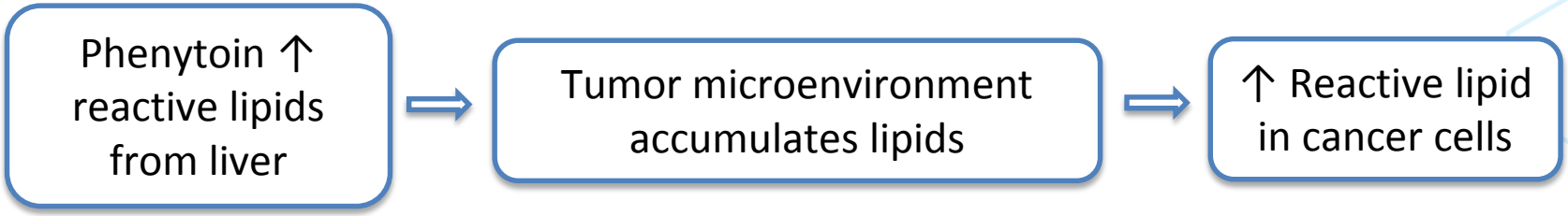
**Bottom Line: Rapamycin is used to enhance uptake of Tyme's tyrosine derivative**




- **Rapamycin (sirolimus) is a mTOR (mammalian target of rapamycin) inhibitor originally approved for the treatment of transplant rejection (Rapamune PI).**
- **Nearly all eukaryotic cells express mTOR which is well documented to have important regulation of cellular metabolism (J Cell Science 2009, Cancer Research 2015) including regulating glucose, lipid and amino acid uptake.**
- **Since cancer cells already have an altered metabolic state (aerobic glycolysis/ Warburg Effect), mTOR inhibition has a different biological effect compared to normal tissues that continue to use aerobic respiration (Br J of Pharmacology 2015).**
- **The mTOR inhibitors can have bi-phasic responses, with sub-therapeutic doses having favorable effects by normalizing mTOR signaling versus full inhibition (Cell 2012 ).**
- **Tyme inclusion of low-dose rapamycin is centered around altering the cancer cells amino acid metabolism (Science 2008, Cancer Research 2015). Specifically, the effect of mTOR inhibition on cancer cells upregulation of L-type amino acid transporter 1 (LAT1/CD98) (Sem Cancer Biology 2005, Biochemical Pharmacology 2010) that is responsible for cancer cells uptake of certain amino acids including tyrosine.**

# SM-88 Components- Phenytoin

**Bottom Line: Increased reactive lipid species in the tumor microenvironment to enhance the redox potential of the cancer cell.**



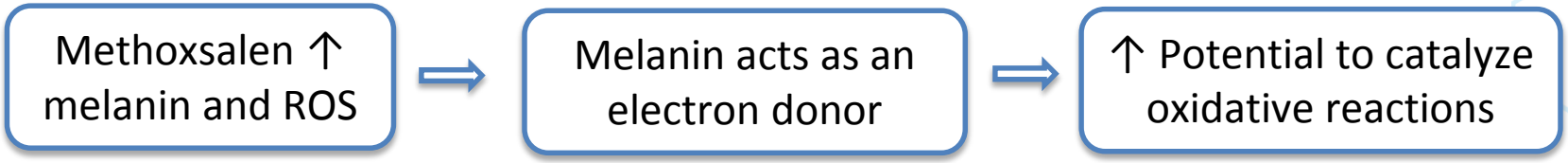

**Phenytoin was originally approved for the treatment of certain forms of epilepsy (FDA label). The drug is recognized as an inducer of certain P450 enzymes (Ann of Neurology 2009) and has been widely reported in increasing plasma lipid levels (Curr Opinion in Neurology 2010). (Note SM-88 uses 50mg of phenytoin vs. the starting dose for seizures is 300mg/day).**

**Tyme's inclusion of phenytoin in SM-88 is for the increase in reactive lipids with a goal of an accumulation of these in the tumor microenvironment (Front. Oncol.,2016, Trends in Cell Biology 2014).**

**Cancer cells consume high levels of lipids (Oncogenesis 2016, Cancer Research 2017) and the uptake of reactive lipids could further drive the cancer cell towards ROS-mediated apoptosis.**

# SM-88 Components- Methoxsalen

**Bottom Line: Increased melanin and reactive oxygen species and serve as a catalyst for oxidative reactions.**




**Methoxsalen (Oxsoralen) was originally approved for the treatment of severe psoriasis in conjunction with UVA treatment (FDA label). The daily dosing for an average weight adult (66-80kg) is 40mg oral for psoriasis, compared to our 10mg dose in SM-88 (without UV therapy).**

**While melanin is frequently associated with protection from UV radiation, it should be noted that melanocytes are located in other tissues including adrenal glands and brain (New Journal of Science 2014)**

**Melanin production is known to produce free radicals (Biochimica et Biophysica Acta 2009, J Inv Dermatology 2014), and can produce systemic hydrogen ($H_2$) that may alter the overall oxidative state of a person (Pharmacological Research 2016)**

**Methoxsalen has also shown to have immunomodulation effects (Phenolic Compounds - Biological Activity 2017) and PUVA therapy has shown to have effects in graft vs. host disease (Bone Marrow Transplantation 1999)**

# SM-88 Profile: Efficacy Summary

| First Human Study (Monotherapy SM-88) | |
|---|---|
| Total Patients | 30 |
| ORR (RECIST 1.1) | 10 (33%) |
| Stable Disease (RECIST 1.1) | 17 (57%) |
| Median OS (all patients) | 29.8 months |
| Median OS (Stable Disease) | 29 months |
| Tumor responses observed in breast, lung, and thyroid cancers | |

**Summary of Antitumor Activity with SM-88 from 57 Compassionate Use Patients**

| Primary Disease Origin | Complete Response | Partial Response |
|---|---|---|
| Prostate Cancer | 2 | 1 |
| Lymphoma | 2 | 0 |
| Breast Cancer | 1 | 4 |
| Pancreatic Cancer | 1 | 2 |
| Sarcoma | 1 | 2 |
| Tonsil Squamous Cell Carcinoma | 1 | 0 |
| Glioma | 0 | 5 |
| Ovarian Cancer | 0 | 3 |
| Bile Duct Cancer | 0 | 1 |
| Colon Cancer | 0 | 1 |
| Total | 8/57 (14%) | 19/57 (33%) |
| Overall Response Rate* | 47% | |

* RESIST 1.1 for solid tumors and relevant respective criteria for hematological malignacies as per investigator assessment

## First Human Study

- Monotherapy efficacy in patients with actively progressive disease
- Survival with SD
- Post SM-88 therapy did not improve survival

## Compassionate use Program

- All patients had progressive disease upon entry
- Tumor responses observed in a range of solid and hematological cancers.
- A minority of patients had additional concurrent therapy

## Overall Efficacy Summary

- Tumor responses observed in 13 different cancer types.
- Reduction of circulating tumor cells in prostate cancer
- High rate of stable disease with extended overall survival

# SM-88 Profile: Safety Summary

- **No drug-related serious adverse events (SAEs) observed with SM-88 in over 100 metastatic patients treated**
- **Only manageable grade 1/2 events observed**
- **Safety profile confirmed in Phase 2 prostate patients**

**Adverse Events Reported in the First Human Study (n=30)[1]**

| Adverse Event | Grade 1 | Grade 2 | Grade 3/4 | Total |
|---|---|---|---|---|
| Hyperpigmentation | 29 (97%) | 1 (3%) | - | 30 (100%) |
| Fatigue[2] | 13 (43%) | 4 (13%) | - | 17 (57%) |
| Pain[2] | 3 (10%) | 1 (3%) | - | 4 (13%) |
| Pruritus | 1 (3%) | - | - | 1 (3%) |
| Burning Sensation | 1 (3%) | - | - | 1 (3%) |
| TOTAL | 29 (97%) | 5 (17%) | - | 30 (100%) |

## Improvement in performance

- **The First Human Study was designed primarily as a safety study and measured EGOG scores at baseline and after one 6-week cycle.**
- **After 6-weeks patients experienced an average 1 point improvement in ECOG performance score**
- **Other improvements including pain scores and reduced analgesic use were reported.**

**ECOG Performance Status* Following 1 Cycle of SM-88 (n = 30)**

| Number of Patients | | |
|---|---|---|
| Score | Start | End |
| 0 | 1 | 14 |
| 1 | 15 | 14 |
| 2 | 10 | 2 |
| 3 | 3 | 0 |
| 4 | 1 | 0 |
| 5 | 0 | 0 |
| Average | 1.6 | 0.6 |

* Eastern Cooperative Oncology Group Performance Score score: 0 (asymptomatic), 1-3 (symptomatic), 4 (bedbound), 5 (death).

# SM-88 Summary

| | |
|---|---|
| **Rationale Design** | • SM-88's design was based on well documented biologic principles of cancer biology and physiology<br>• Selection of components that could work together to drive ROS-driven apoptosis of the cancer cell |
| **Broad Activity** | • Efficacy of SM-88 parallels the presence of the Warburg Effect and associated biology across cancers.<br>• A majority of cancers employ aerobic glycolysis and upregulate mucin, which are the key targets of SM-88 |
| **Favorable Safety** | • Absence of SAEs and improvement in patient function is a break from the norm in cancer therapy<br>• The high therapeutic index offers multiple potential avenues for combination approaches going forward |
| **Changing the Paradigm** | • We aim change the approach the cancer therapy<br>• Combining existing areas of knowledge to create cancer therapies with patient-friendly profiles |

# Relevant Literature

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