Mechanism of Action
Overview
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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.
- 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).
- ~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).
- 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.
- 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*)
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).

Breaking the Metabolic Circuit of Cancer

1) Induce Uptake of Tyme’s Dysfunctional Tyrosine

2) Protein Synthesis Fails

3) Protective Mucin Layer Compromised

4) Cell Death From Oxidative Stress

Free Radicals (ROS)

Immune Response
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 ([*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 ↑ reactive lipids from liver → Tumor microenvironment accumulates lipids → ↑ Reactive lipid in cancer cells

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](https://www.fda.gov/)). 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](https://www.nature.com/articles/njsci2014195)).

Melanin production is known to produce free radicals ([Biochimica et Biophysica Acta 2009, J Inv Dermatology 2014](https://www.ncbi.nlm.nih.gov/pubmed/20639414)), and can produce systemic hydrogen (H$_2$) that may alter the overall oxidative state of a person ([Pharmacological Research 2016](https://www.sciencedirect.com/science/article/pii/S0149700615305957)).

Methoxsalen has also shown to have immunomodulation effects ([Phenolic Compounds - Biological Activity 2017](https://www.ncbi.nlm.nih.gov/pubmed/28824793)) and PUVA therapy has shown to have effects in graft vs. host disease ([Bone Marrow Transplantation 1999](https://www.ncbi.nlm.nih.gov/pubmed/10584690)).
## SM-88 Profile: Efficacy Summary

### First Human Study (Monotherapy SM-88)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>30</td>
</tr>
<tr>
<td>ORR (RECIST 1.1)</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Stable Disease (RECIST 1.1)</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>Median OS (all patients)</td>
<td>29.8 months</td>
</tr>
<tr>
<td>Median OS (Stable Disease)</td>
<td>29 months</td>
</tr>
</tbody>
</table>

Tumor responses observed in breast, lung, and thyroid cancers

### 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

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

<table>
<thead>
<tr>
<th>Primary Disease Origin</th>
<th>Complete Response</th>
<th>Partial Response</th>
</tr>
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<tbody>
<tr>
<td>Prostate Cancer</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tonsil Squamous Cell Carcinoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Glioma</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Bile Duct Cancer</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8/57 (14%)</strong></td>
<td><strong>19/57 (33%)</strong></td>
</tr>
</tbody>
</table>

Overall Response Rate* = 47%

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3/4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperpigmentation</td>
<td>29 (97%)</td>
<td>1 (3%)</td>
<td>-</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (43%)</td>
<td>4 (13%)</td>
<td>-</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
<td>-</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (3%)</td>
<td>-</td>
<td>-</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Burning Sensation</td>
<td>1 (3%)</td>
<td>-</td>
<td>-</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>29 (97%)</td>
<td>5 (17%)</td>
<td>-</td>
<td>30 (100%)</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Score</th>
<th>Start</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Average**: 1.6 → 0.6

*Eastern Cooperative Oncology Group Performance Score: 0 (asymptomatic), 1-3 (symptomatic), 4 (bedbound), 5 (death).*
### SM-88 Summary

**Rationale**
- SM-88’s design was based on well-documented biologic principles of cancer biology and physiology.
- Selection of components that could work together to drive ROS-driven apoptosis of the cancer cell.

**Design**
- Efficacy of SM-88 parallels the presence of the Warburg Effect and associated biology across cancers.
- A majority of cancers employ aerobic glycolysis and upregulate mucin, which are the key targets of SM-88.

**Broad Activity**
- Absence of SAEs and improvement in patient function is a break from the norm in cancer therapy.
- The high therapeutic index offers multiple potential avenues for combination approaches going forward.

**Favorable Safety**
- We aim to change the approach to cancer therapy.
- Combining existing areas of knowledge to create cancer therapies with patient-friendly profiles.

**Changing the Paradigm**
- Combining existing areas of knowledge to create cancer therapies with patient-friendly profiles.
Relevant Literature

Warburg Effect and Tumor Metabolism

Molecular Pathways: Trafficking of Metabolic Resources in the Tumor Microenvironment. Clinical Cancer Research (2015) vol 21, is. 4


Cancer Cell Metabolism: Warburg and Beyond – Cell. 2008; 134:5

Cancer as a Metabolic Disease. Nutr Metab. 2010;7:7


Metabolic requirements for cancer cell proliferation. Cancer & Metabolism. 2016; 4:16
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**Mucin-1 Core Protein Is Expressed on Multiple Myeloma Cells and Is Induced by Dexamethasone.** Blood; 93: No 4

**MUC1 activates JNK1 and inhibits apoptosis under genotoxic stress.** Biochemical and Biophysical Research Communications; 440:1

**MUC1 IS A POTENTIAL TARGET FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA STEM CELLS.** Cancer Res. 2013; 73:17

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**Mucins in cancer: function, prognosis and therapy.** Nature Reviews Cancer. 2009; 9

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**Membrane-bound mucins: the mechanistic basis for alterations in the growth and survival of cancer cells.** Oncogene 2010; 29:20
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Tumor microenvironment derived exosomes pleiotropically modulate cancer cell metabolism. eLife 2016;5

Targeting amino acid metabolism for cancer therapy – ScienceDirect


Amino Acid Transporters in Cancer and Their Relevance to "Glutamine Addiction": Novel Targets for the Design of a New Class of Anticancer Drugs. Cancer Research 2015; 75:9

Cellular Processing of D-Amino Acids

The ribosome can discriminate the chirality of amino acids within its peptidyltransferase center. PNAS 2015;112:19

Aminoacyl-tRNA synthetases and tumorigenesis: more than housekeeping. Nature Reviews Cancer 2011; 11


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**mTOR Signaling at a Glance**. Journal of Cell Science 2009; 122:20

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**Phenytoin and Role of Lipids in Cancer Metabolism**

*The sodium channel-blocking antiepileptic drug phenytoin inhibits breast tumour growth and metastasis.* Molecular Cancer. 2015;14:13

*Decreased total antioxidant capacity and elevated lipid hydroperoxide concentrations in sera of epileptic patients receiving phenytoin.* Life Sciences. 1997;61:4

*Metabolic consequences of antiepileptic drugs.* Current Opinion in Neurology 2010;23:2

*Pancreatic cancer cell growth requires lipids released by tumor-induced stroma autophagy.* Cancer Research. 2017; 77:13

*Lipid metabolic reprogramming in cancer cells.* Oncogenesis, 2016; 5


*The Tumor Microenvironment Modulates Choline and Lipid Metabolism.* Front. Oncol.,2016; 6
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**Methoxsalen and Melanocytes and Role of Lipids in Cancer Metabolism**

*Melanocytes as Instigators and Victims of Oxidative Stress* - J Inv Dermatology 2014

*What are melanocytes really doing all day long…? : from the ViewPoint of a keratinocyte: Melanocytes – cells with a secret identity and incomparable abilities.* Scientific Reports. 2016;6:26643

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