



Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

INDUSTRIALRESEARCH
LIMITED



ROBUST ANTI-CANCER AGENTS

Novel Transition State Analogue Inhibitors of MTAP

Intellectual property portfolio developed by Industrial Research Limited and the
Albert Einstein College of Medicine

Licensing Opportunity

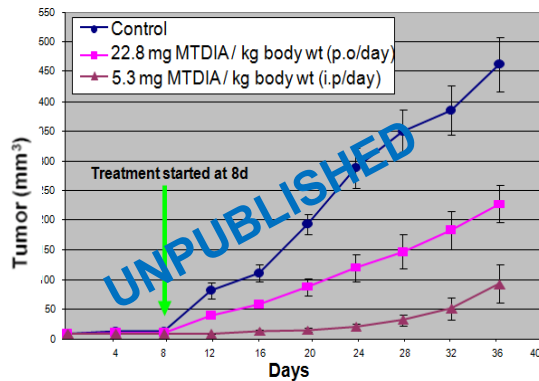
- **Albert Einstein College of Medicine (Einstein)** and **Industrial Research Limited (IRL)** have together developed novel compounds that exhibit anticancer activity.
- The compounds and associated synthetic procedures have robust IP protection.
- The compounds inhibit the enzyme *Methylthioadenosine Phosphorylase* (MTAP) resulting in whole body elevated concentrations of the naturally occurring enzyme substrate *Methylthioadenosine* (MTA) which is the anticancer agent.
- The team has used market relevant models to prove efficacy in 6 cancer indications; prostate, lung, head and neck, colon, breast and cervical cancers.
- Einstein and IRL are looking for partners interested in licensing the IP and know-how to develop therapies for cancer indications.



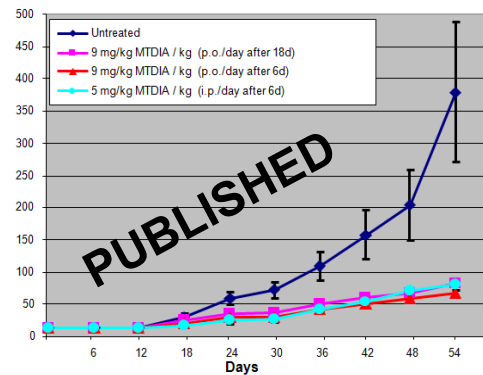
Pharmacology (Efficacy): Key Highlights.

Xenograft Mouse Model Studies

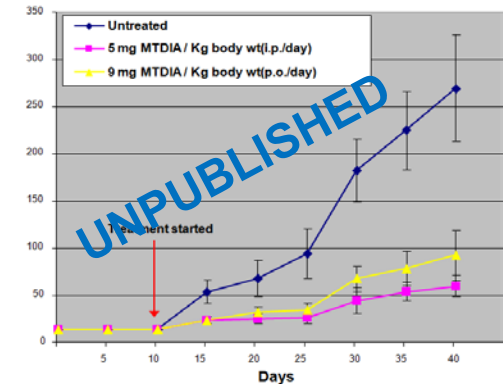
Colon Cancer (COLO205)



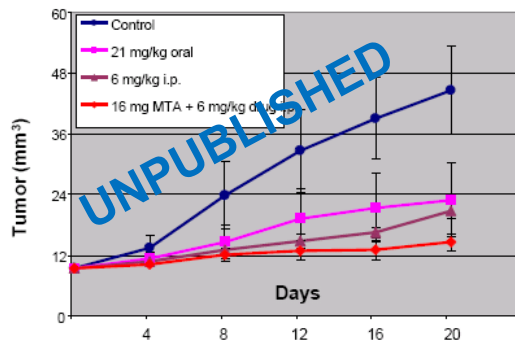
Lung cancer [MTAP(-) A549] *



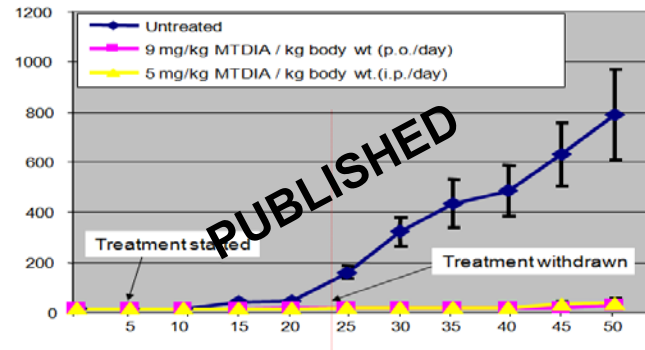
Cervical Cancer [MTAP(+) HeLa]



Breast cancer (ADA-MB-468)



Head & neck cancer (FaDu)



Key points

- Trials show suppression of tumour growth from both oral and i.p. administration of MTDIA
- i.p. administration more effective at a lower dose

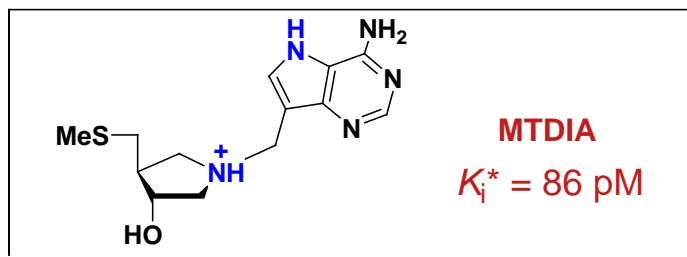
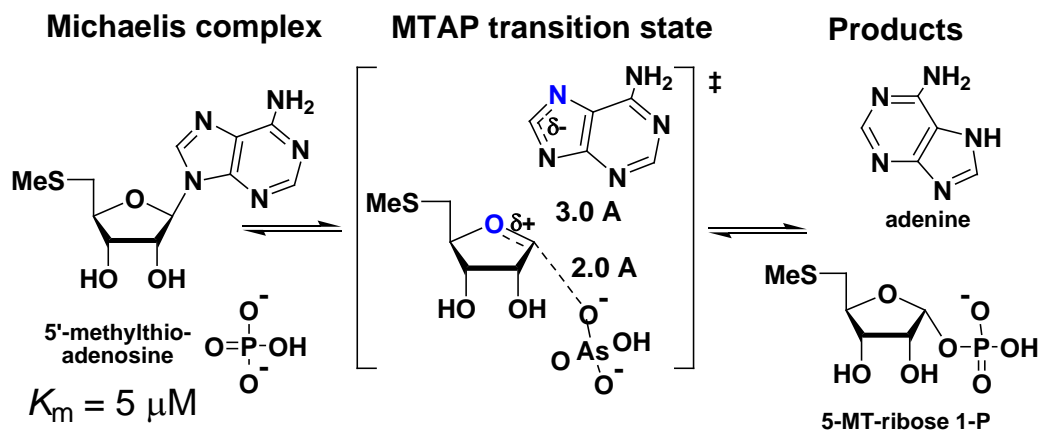
Pharmacology (Efficacy) Summary

- Market relevant cancer models used to determine efficacy
 - prostate (TRAMP) mouse model
 - *in vitro* inhibition of human prostate cancer cell (PC3) growth
 - *in vitro* inhibition of human head & neck cancer cell (FaDu) and lung cancer cell (H358) growth
 - mouse xenograft models for human lung and head and neck (published results)
 - mouse xenograft model for human prostate, colon, cervical and triple negative breast cancers (unpublished results)

- In summary, pre-clinical trials show MTDIA induces
 - Significant reduction in tumour size
 - Significant reduction of metastasis
 - **No toxicity** at all has been observed during > 6 months oral administration in mice.

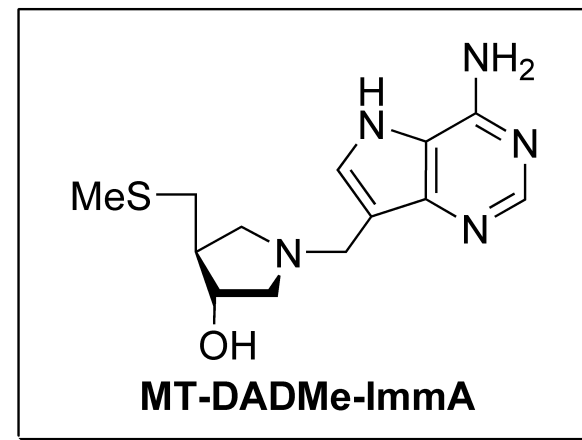
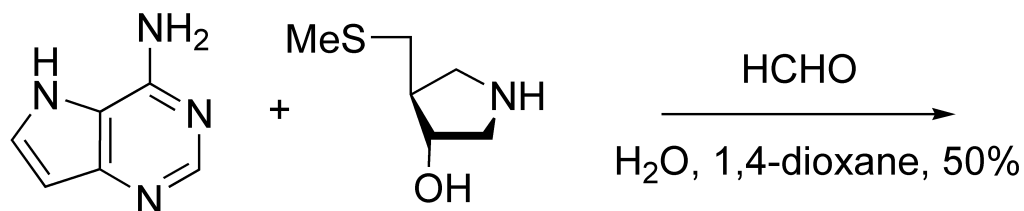
Chemical Properties

- Lead candidate: **MT-DADMe-Immucillin-A (MTDIA)**
 - $K_i = 86 \text{ pM}$ against target enzyme MTAP
 - Stable at room temperature
 - Freely water soluble as salt form



Chemistry, Manufacturing and Control (CMC)

- Product requires a single cGMP step
- Progress to date by GlycoSyn:
 - ▣ Raw materials produced at 100 – 200 gram quantities
 - ▣ Compound currently produced at 10 – 20 gram quantities
 - ▣ Rapid scale up of material for entry in to clinic
 - ▣ Reassurance that CM&C data will get past regulators



Mechanism of Action

- Compound inhibits MTAP *in vivo* by > 96%.
- Enzyme inhibition results in whole body accumulation of MTA.
- MTA accumulation causes:
 - ▣ altered gene expression in rapidly dividing cancer tissue
 - ▣ The major decreases in gene expression are related to
 - ▣ a. methyl metabolism related to SAM
 - ▣ b. polyamine synthesis
 - ▣ c. genes of cell cycle regulation
 - ▣ Altered gene expression causes stasis or cell death in cancer tissues
- Long-term dosing shows no mouse toxicity by histology, blood profile or animal observation

Intellectual Property Portfolio

Comprehensive IP. Includes potent inhibitor compounds, methods of preparing compounds, and use of compounds to treat diseases.

- Nucleoside metabolism inhibitors (8-Substituted Immucillins – 29 Aug 2000) – Granted in US. Pending in JP
- Inhibitors of nucleoside phosphorylases and nucleosidases (Selection patent for 5'-RS-Immucillin-A – 25 Mar 2002) – Granted in AU, CA, CN, JP, NZ, US. Pending in EU.
- **Inhibitors of nucleoside phosphorylases and nucleosidases** (The DADMe-Immucillins – 21 Aug 2002) – Granted in AU, BR, CN, EU, IN, JP, KR, NZ, RU, SG, US. Pending in CA
- **Process for preparing inhibitors of nucleoside phosphorylases and nucleosidases** (Convergent synthesis of DADMe-Immucillins – 4 Feb 2003) – Granted in AU, CN, IN, JP, NZ, SG, US. Pending BR, CA, EU, KR, RU.
- **Improved method for preparing 3-hydroxy-4-hydroxymethylpyrrolidine compounds** (DAD-amine #2 - 4 Jun 2004) – Granted in EU, JP, MX, NZ. Pending – AU, CA, CN, IN, IS, KR, US.
- Methods of treating diseases using inhibitors of nucleoside phosphorylase and nucleosidases (MTA Co-administration with MTAP/MTAN inhibitor – 24 Feb 2006) - Pending in US
- Methods of treating cancer (Treating cancer with MTAP inhibitor – 24 Feb 2006) – Pending in AU, CA, US
- Transition State Structure of Human Methylthioadenosine Phosphorylase (Filed 26 Sep 2006) –Pending in US
- Azetidines Analogues of Nucleosidase and Phosphorylase Inhibitors (22 Dec 2006) – Pending in AU, CA, CN, EU, JP, KR, NZ, US
- Acyclic amine inhibitors of 5'-methylthioadenosine phosphorylase and nucleosidase (Third generation DATMe-Immucillins - 7 Sep 2006) – Pending in AU, CA, EU, US
- **3-Hydroxypyrrolidine Analogues** (New DADMe-Immucillins - 1 Dec 2009), in PCT



Summary of Licensing Opportunity

- The Einstein/IRL MTAP inhibitors provide a **novel class of compound with broad anti-cancer effects in several xenograft models.**
- **Oral and intravenous delivery** allows multiple options for development in a wide range of cancer targets.
- **Low toxicity** also provides long term administration options.
- The **extensive patent portfolio** provides comprehensive IP coverage of a promising new drug candidate.

Contact Information

- To learn more about this portfolio and discuss licensing opportunities, please contact:

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