Dr. Guns has been commissioned by KOP Therapeutics to provide a review and expert opinion on the scientific merit and potential of antisense oligonucleotides under development by Dr.'s Thakur and Wickstrom for the treatment of cancer. Dr. Guns is expertly experienced in the first hand use of most laboratory tools for pharmacological research involving in vitro cell culture, animal models for cancer, human samples for proof of principle validation as well the assessment of clinical trial design. The review is intended for a lay readership. Dr. Guns has been chosen in light of her strong science-communication record and career-long experience in the drug discovery domain as a scientist, reviewer and ethics board member at UBC. The links below describe Dr. Guns accredited experience: LinkedIn profile, Dr. Guns: https://www.linkedin.com/in/emma-guns-8683994b/ (Tomlinson) Guns Scientific Publication record: https://scholar.google.ca/citations?user=UOCF5nEAAAAJ&hl=en Dr. Guns Faculty website at University of British Columbia (UBC): https://www.prostatecentre.com/about-us/people/dr-emma-s-tomlinson-guns KOP Scientific Advisory Board Member: https://kopindustries.ca/science-research-team

**Introduction to KOP Drugs**

Each of us has a unique DNA code. Cancer is caused by mutations in our DNA. KOP are in the process of designing drugs to block those mutations from acting in our bodies.

Research leading to the creation of KOP drugs began in 1869, when Swiss scientist Friedrich Miescher identified DNA as a component of cells. Almost a century later, in 1953, British scientists Rosalind Franklin and Francis Crick, and American scientist James Watson deduced the three-dimensional structure of DNA, now familiar as the double helix. This two-stranded curling ladder is the instruction set for every part of our bodies. It not only dictates our original physical and chemical structures, but also ensures that these parts can be replaced and repaired throughout our lives.

DNA stays in the nucleus of every cell in our bodies. When people need a gene to turn on to maintain our blood and organs, an enzyme called DNA polymerase copies short pieces of our DNA genetic code into an RNA message. Inside the cell, the genetic code in each RNA messenger is decoded into the proteins that build our bodies.
Sometimes a person’s DNA mutates, causing them to develop cancer. People can be born with these mutations or develop them during their lifetimes. As scientists, we can slow or stop the cancer if we can stop the mutant RNA message that codes for it from being translated.

In order to stop the decoding of the cancer-driving messages, we have to discover the exact code that drives the cancer. Then we design an imitation RNA that binds to the cancer-driving message to block its decoding. This is like putting gum between gears so they can’t turn.

**History of Imitation RNA Drugs**

Researchers around the world have been designing and testing imitation RNA drugs to treat diseases for the past 40 years.

Each design is tested first in cells in petri dishes, then in mice and larger animals. If an imitation RNA looks successful in these early tests, then it is ready to be tested in people during carefully monitored clinical trials that meet FDA guidelines. Only drugs that pass their clinical trials can be put on the market to treat patients.

The five imitation RNAs described below passed all the tests required of them to be approved by the FDA, made into drugs, and put on the market.

The first imitation RNA that qualified for testing was **Vitravene™** (fomivirsen), designed to treat cytomegalovirus infections of eyeballs. **Vitravene™** took 10 years of laboratory and clinical research before it was approved for patients in the US by the FDA in 1998, and in 1999 for use in Europe by the EMEA. Since then other imitation RNA drugs have been approved to treat other human diseases.

In 2013, **Kynamro™** (aka mipomersen) was made available to treat high cholesterol. However, **Kynamro™** causes liver toxicity in some people, so patients must be watched carefully. Scientists are working on new imitation RNA drugs that will be safer for everyone.

In September 2016, **Exondys 51™** (aka eteplirsen) was approved by FDA for the treatment of Duchenne muscular dystrophy. Because it targets a specific mutation, **Exondys 51™** is only useful in 1% of cases.

In contrast to **Kynamro™**, **Exondys 51™** does not make people feel sick. Understanding why side effects happen with some drugs and not others helps us make safer drugs in the future.

Later in 2016, **Defibrotide™** (now known as **Defitelio™**) was approved by FDA after testing to treat liver disease, with minimal side-effects.

The most exciting imitation RNA so far is **Spinraza™** (aka nusinersen), approved by FDA in December 2016. **Spinraza™** saves the lives of children who are born with spinal muscular atrophy, a rare neuromuscular disorder.
In each case, imitation RNA drugs saw success as the technology and skill-set used to make them improved over time. Work on imitation RNA drugs over the past four decades has improved the following characteristics:

- remain longer in the body tissues where they are targeted
- deliver effective levels with fewer doses.
- block messages from the genes in our body that cause us to have disease
- fewer side-effects.

The KOP Drug

The KOP drug design specifically targets cancer cells and avoids harming normal cells. Cells become locked into a cancerous state when they produce large numbers of “lock” proteins that force them to grow rapidly. The KOP drug includes a “key” that enters cancer cells through their “lock” proteins. That key is a scientific breakthrough by Professors Eric Wickstrom and Matthew Thakur, who developed this new approach at Thomas Jefferson University in Philadelphia PA. They have been working on their imitation RNA designs since 1984.

Inclusion of the specific targeting “key” enables the KOP drugs to open the corresponding “locks” on cancer cells. Once inside the cancer cells, the KOP drugs block the cancer gene messages. The KOP drug design leaves normal parts of the body untouched, thereby avoiding the toxicity of other chemotherapies that make cancer patients feel sick or nauseous.

What Has Been Done So Far?

In their most recent experiments on prostate cancer cells, Professors Wickstrom and Thakur identified a previously unrecognized cancer gene. When they blocked that cancer gene message with an imitation RNA, prostate cancer cells stopped growing, and began to die.

What is being licensed by KOP?

Professors Wickstrom and Thakur have designed several imitation RNAs to test against prostate cancer cells. The professors will discover which of the imitation RNAs work best to block the cancer growth messages in a series of experiments. Wickstrom and Thakur are doing the necessary laboratory work to prepare KOP drugs for testing in animal cancer models, then in
human cancer patients, following national and local approvals. It is possible that multiple types of cancer could be treated using a single KOP drug design.

The Scientists and Their Work

Professors Thakur and Wickstrom have been working together at Thomas Jefferson University in Philadelphia for over two decades. Their areas of expertise in cancer imaging and cancer gene blocking are highly complementary, allowing for a synergistic team approach to solve many scientific problems related to cancer and genetics over the long term. They are both members of the Sidney Kimmel Cancer Center, which has state-of-the-art facilities. Between their two laboratories, Professors Wickstrom and Thakur have published over 700 papers, patents, reviews, and chapters, and written 6 books on molecular design, nucleic acid structure, gene function, mRNA translation, protein structure, and cell biology.

Professor Mathew L. Thakur, PhD, specializes in Radiology, Radiation Oncology & Urology. He earned a Bachelor’s degree in Chemistry from Bombay University, India. His doctoral research in Radiochemistry earned him a PhD from the University of London, England. Prof. Thakur has pioneered a series of diagnostic and therapeutic radiopharmaceutical innovations over the last 4 decades.

Professor Eric Wickstrom, PhD specializes in Biochemistry and Molecular Biology. He earned his bachelor’s degree in Biology with Honors from the California Institute of Technology in Pasadena, California. His doctoral research in Chemistry earned him a PhD from the University of California, Berkeley, California. Dr. Wickstrom pioneered imitation RNA cancer therapeutics over 3 decades ago at the University of South Florida before recruitment to Jefferson.

Together, over the course of their long and combined careers, Professors Thakur and Wickstrom have been pioneers in the development of this new, exciting field. The facilities in which they carry out their work are world-renowned and equipped with everything required to overcome challenges and complete the tests required for drug approval.

The Sidney Kimmel Medical College and Cancer Center at Thomas Jefferson University

The Sidney Kimmel Medical College has awarded more than 31,000 medical degrees and has more living graduates than any other private medical school in the nation. The Sidney Kimmel Cancer Center at Thomas Jefferson University Hospital has been one of 70 National Cancer Institute (NCI) - designated cancer centers in the U.S. since 1993. The Cancer Center pursues the latest developments in cancer research, technology, and treatment for patients in the city of Philadelphia and synergizes the efforts of cancer scientists working in laboratories with physicians from all parts of the campus to move new discoveries rapidly into clinical trials. The physicians and scientists of the Sidney Kimmel Cancer Center have helped pioneer new
approaches to cancer treatment by transforming scientific discoveries into improved patient care. Cancer patients are invited to take part in over 120 clinical trials at Thomas Jefferson University Hospital for new cancer treatments being conducted at Jefferson at any given time.

Summary

Over the course of my career I have evaluated many cancer research projects and I am confident that this project is one of the best. The importance of this project lies in the fact that it promises to kill cancer selectively and with minimal or no toxicity. The therapy should also be able to treat many different forms of cancer.

This therapy has been conceived and will be executed by well-established and internationally renowned investigators Drs. Thakur and Wickstrom who have worked together for more than two decades at the National Institute of Health designated Kimmel Cancer Center of Thomas Jefferson University located in Philadelphia PA. The infrastructure needed to complete the proposed work in a timely and cost-effective manner exists and is accessible to the investigators.

To help my evaluation numerically, I have developed a weighted scale which scores specific aspects of the research which are relevant to the project’s success. The scale is made up as follows:

A. Impact and Novelty (maximum score of 5).
B. Expertise of Scientists (maximum score of 3).
C. Evidence of demonstrated Scientific Publication (maximum score of 5).
D. Facilities and Resources available (maximum score of 5).
E. Budget and timeframe (maximum score of 2).

The total score available is 20.

In light of the above, I believe the project merits a maximum score in each category making for a total score 20/20. While 20/20 is unusual, given the pedigree of the Scientists and the capabilities and commitment of the University, I believe it is well deserved.

In summary, I conclude that KOP’s therapy is novel, highly promising and has a high likelihood of success as a cancer therapy.

August 22nd 2019

Dr. Emma Guns

Date
Glossary of Terms and Acronyms

Clinical Trial - testing in people as an experiment to determine benefit

Defibrotide™ - imitation RNA drug tested and FDA approved

DNA - Deoxyribonucleic Acid, the hereditary material in humans and almost all other organisms

EMEA - European Medicines Evaluation Agency

Etelirsen™ - imitation RNA drug tested and FDA approved  FDA - Federal Drug Administration

Formavirsen™ - imitation RNA drug tested and FDA approved

Kynamro™ - imitation RNA drug tested and FDA approved

Mipomersen™ - imitation RNA drug tested and FDA approved

Molecular - describing a chemical building block

Nusinersen™ - imitation RNA drug tested and FDA approved

RNA - Ribonucleic Acid, molecule derived from DNA, essential in various biological roles in messaging

Radiopharmaceutical - a substance that is labeled using a radioactive tag and used in medicine to image part of the body

Spinraza™ - imitation RNA drug tested and FDA approved

Therapeutic - used in medicine to help treat disease