Title:
Delineating the molecular mechanism of the hyper-modified ribosomal RNA residue 18S.1248.macp[Psi] in cancer translation.

Lay Title:
Onco-ribosomes: targeting the translators of cancer.

Cancers of the lower digestive tract are called Colorectal Cancers (CRC). They are the 2nd most common form of non-skin cancers and will kill 5x more Canadians this year compared to motor vehicle collisions. Alarmingly, today's young adults are 2-4 times more vulnerable to CRC compared to their parents which may be the first indication that CRC may become an even larger public health burden in the coming years.

The human genome was declared complete in 2001, yet several difficult to study areas of our DNA were excluded from this reference genome and remain under explored. One such region encodes for ribosomal RNA (rRNA), the central gene of the ribosome. Ribosomes are responsible for translation, reading messenger RNA and creating proteins. In a pioneering study on rRNA, Dr. Babaian discovered that almost half of CRC patients contain a cancer-specific "onco-ribosome" with a variant rRNA.

Normally, ribosomes create proteins in a tightly controlled and regulated manner. These onco-ribosomes are associated with the most rapidly growing tumors, differing from their normal counterparts by a modification of the rRNA. Normally, this RNA modification is found in the ribosomes of all animals and plants, except for cancer tissues, yet its role in protein synthesis is unknown. The objective of this proposal is to use cancer cells genetically modified to produce only onco-ribosomes to understand how these cancer ribosomes translate proteins differently.

Significantly, onco-ribosomes differ enough from the healthy ribosome that they could be targeted with precision drugs. Fortunately, there already are dozens of common and approved antibiotics which target the ribosome for treating bacterial or parasitic infections. This proposal will also evaluate if it's feasible to re-purpose antibiotic-like compounds for the treatment of colorectal cancers. This would establish an entirely new class of chemotherapies based on a medicine we have used safely used for over 60 years.