SickKids
Industry Partnerships & Commercialization

TECHNOLOGY BRIEF

BIOPHARMA

Methods of treating trinucleotide repeat expansion diseases

BACKGROUND

Genetic expansions of CAG/CTG trinucleotide repeat sequences in certain genes have been linked to at least 40 neurodegenerative, neurological, and neuromuscular diseases, including Huntington's disease (HD), fragile X syndrome, myotonic dystrophy, various spinocerebellar ataxias, and amyotrophic lateral sclerosis. These repeat expansions tend to get larger as they are inherited from one generation to the next, resulting in earlier age of onset, increased disease progression and severity. Importantly, the expansions grow in size as the individual ages, are believed to drive the disease onset, progression, and severity. A reduction of a few repeats could delay onset by years, and a method of arresting or reversing somatic CAG/CTG could be used to arrest or even reverse disease onset, progression, and severity (Fig 1).

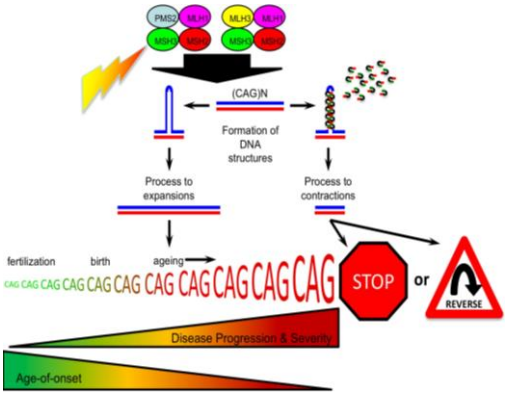

Fig 1. Targeting DNA repair proteins and/or Slipped-DNAs can modulate disease-causing expanded CAG tracts for therapeutic benefit

DESCRIPTION OF THE INVENTION

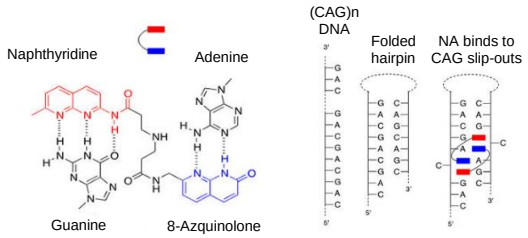

Fig 2: Naphthyridine-Azaquinolone (NA) compound and mechanism of action

The Pearson lab, in collaboration with colleagues at Osaka University, have discovered that a small molecule, Naphthyridine-Azaquinolone (NA), is useful in treating CAG/CTG repeats (Fig 2). NA not only arrests CAG/CTG expansions, but it induces contractions of expanded CAG repeats in HD patient cells and in a HD mouse model. Notably, NA acts specifically upon the mutant expanded repeat with no observed off-target effects (no effect on the non-expanded allele, and without damaging the rest of the genome).

Repeated administrations of NA have additive effects of inducing contractions of the CAG tract *in vivo* (Fig 3), leading to the reduction in the mutant HTT aggregates that are characteristic of HD in the disease mouse model.

KEYWORDS
Trinucleotide repeat, genetic expansions, small molecule, therapy

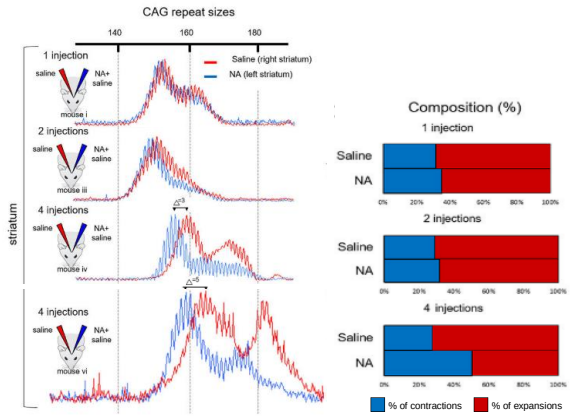

Fig 3: NA induces repeat contractions in vivo

COMMERCIAL APPLICATIONS & ADVANTAGES

This can be a transformative therapy for individuals with a range of neurodevelopment conditions, as there is currently no cure for rare trinucleotide repeat diseases.

DEVELOPMENT STAGE

Preclinical *in vitro* and *in vivo* data in a disease-specific brain region are promising. Next steps include medicinal chemistry, pharmacokinetic, animal efficacy, and toxicology studies.

The Pearson lab has developed a platform to discover chemical matter specific to other trinucleotide repeat diseases. Current work includes fragile X syndrome, amyotrophic lateral sclerosis, Friedreich's ataxia, and myotonic dystrophy.

PATENT STATUS

PCT national phase applications have been filed on the use of the small molecule in trinucleotide repeat diseases.

IP&C is seeking partners to advance this technology.

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