Rhianna K Morgan et al., J Cancer Sci Ther 2015, 7:8
http://dx.doi.org/10.4172/1948-5956.C1.058

OMICS International
conferenceseries.com

5th World Congress on
Cancer Therapy
September 28-30, 2015 Atlanta, USA

G-quadruplex formation in the kRAS mid promoter region and identification of stabilizing small molecules as promising transcriptional silencers

Rhianna K Morgan[1], Khondaker Miraz Rahman[2], and Tracy A Brooks[1]
[1]Department of BioMolecular Sciences, Division of Pharmacology, School of Pharmacy, University of Mississippi, USA
[2]Institute of Pharmaceutical Sciences, King's College, London, England, United Kingdom

Over 60% of pancreatic cancers harbor mutations in the kRAS oncogene, whose promoter has three distinct guanine-rich regions (near, mid, and far) capable of forming higher order G-quadruplexes (G4s). These important structures have transcriptional silencing potential and stabilizing compounds cause selective apoptosis in kRAS-addicted cells. Previous works in our laboratory have identified the mid-G4 region as having the highest silencing capacity, with little apparent roles for the near- or far-G4 regions. The structure of this mid-region G4 is being elucidated by electromobility shift assay, DNA polymerase stop assay, DMS footprinting, and circular dichroism (CD). In addition, small molecules are being screened by the Förster Resonance Energy Transfer (FRET) melt assay and confirmed by CD for their stabilization potential. We have identified multiple, equilibrating, intramolecular G4s forming within the mid-region of the kRAS promoter. Varying buffer conditions (cations, dehydration, and molecular crowding) affect these formations; the predominating isoform is a tetra-stacked mixed parallel and antiparallel structure with an 8:15:7 loop configuration. Over 1,600 compounds have been screened and several are being pursued as leads. Several compounds selectively stabilized the mid-G4 and suppress kRAS transcription. Our work highlights the mid-G4-forming region of the kRAS promoter a therapeutic target with the utmost promise for pancreatic cancer, and further features the stabilizing potential of targeted compounds. Studies are ongoing to vet the potential of other "hit" compounds from the FRET screen, as well as to elucidate the structure of the kRAS mid-G4 in chromosomal DNA.

Biography

Rhianna is a current doctoral student at the University of Mississippi with a focus in pharmacology. She has completed her B.A. at the age of 21 years from Hartwick College in mathematics with a minor in biology. As a second year graduate student, she has published two papers, received first place in the Mississippi INBRE Graduate Scholars Symposium, and has been awarded a Graduate Student Council grant from the University of Mississippi.

rhianna.k.morgan@gmail.com

Notes: