



The Role of Chemical Co-Solvents on G- Quadruplex structures in the c-MYC and VEGF proto-oncogene promoters



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September 25, 2014

Overview

Introduction to Cancer

New Targeting Strategy

+ Proto-oncogenes c-MYC
and VEGF

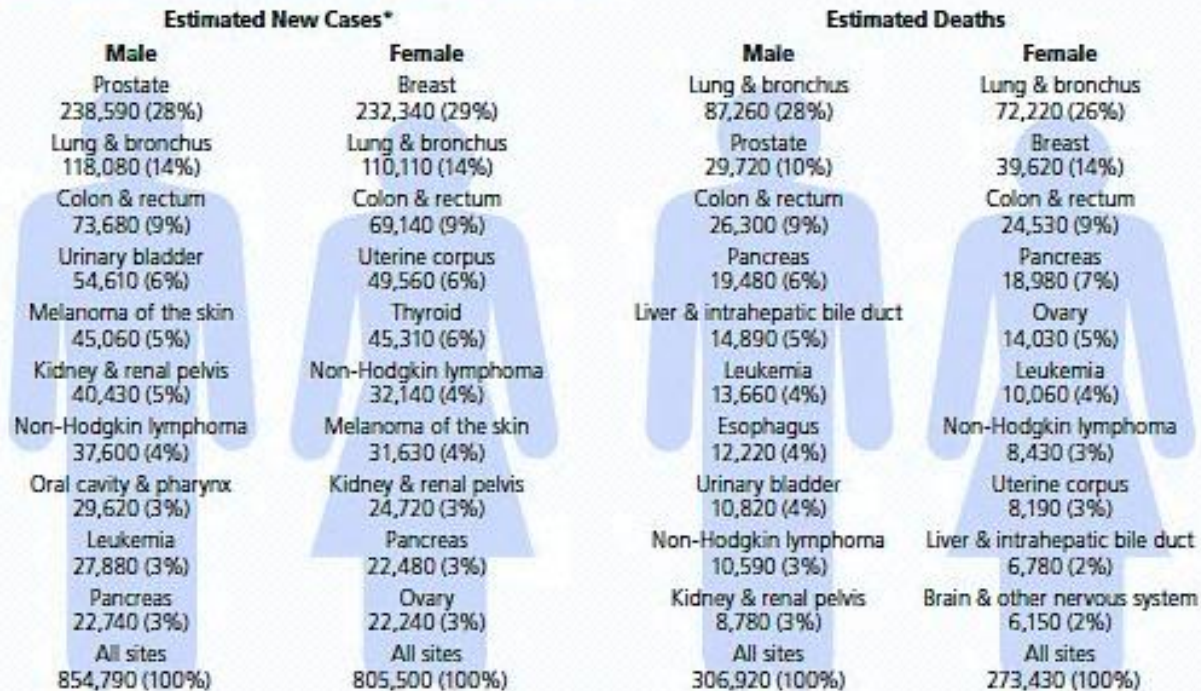
Results

Future Work



Cancer in the United States

Leading New Cancer Cases and Deaths – 2013 Estimates

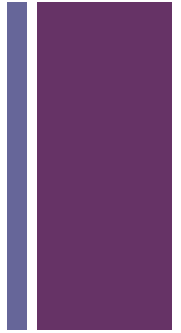


*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

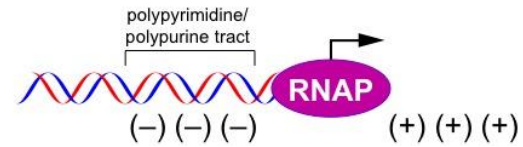
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- 2nd leading cause of death
- 1 in 4 people will develop cancer in their lifetime

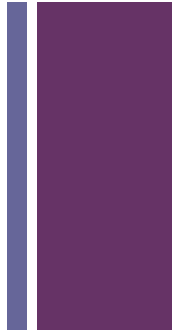
+ Targeting Cancers Achilles Heel



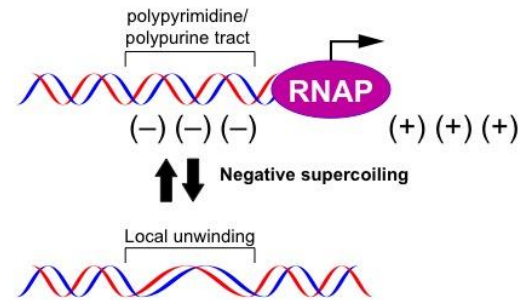
- G-quadruplex
- i-Motif



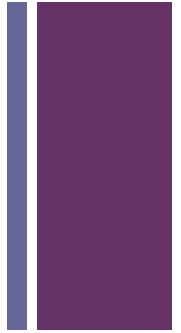
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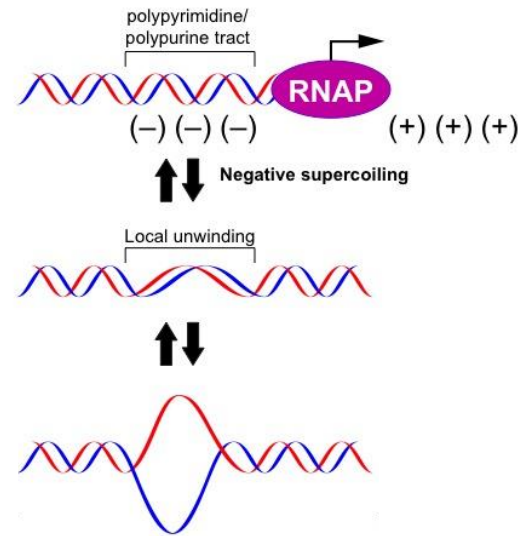
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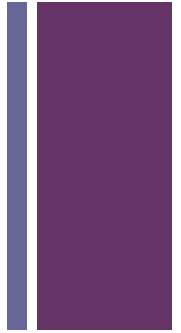
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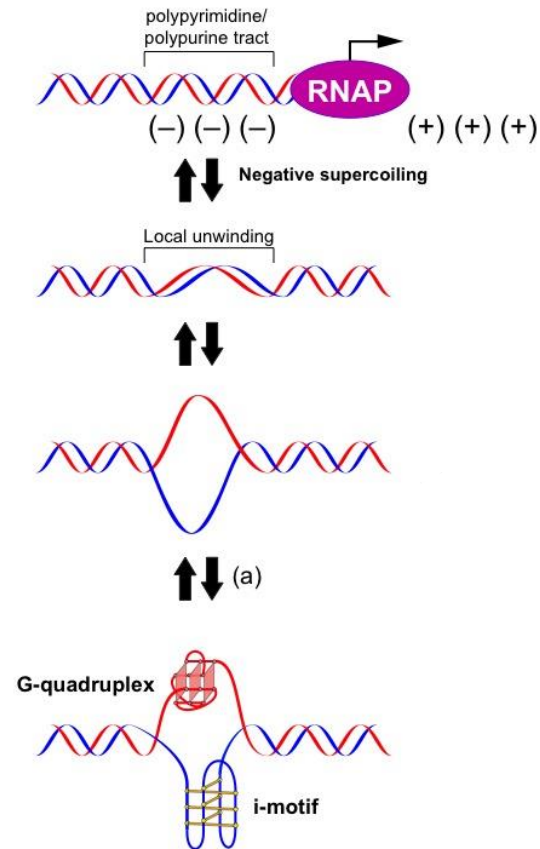
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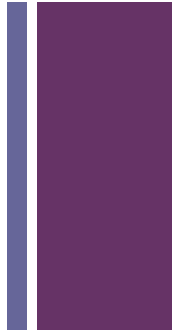
+ Targeting Cancers Achilles Heel



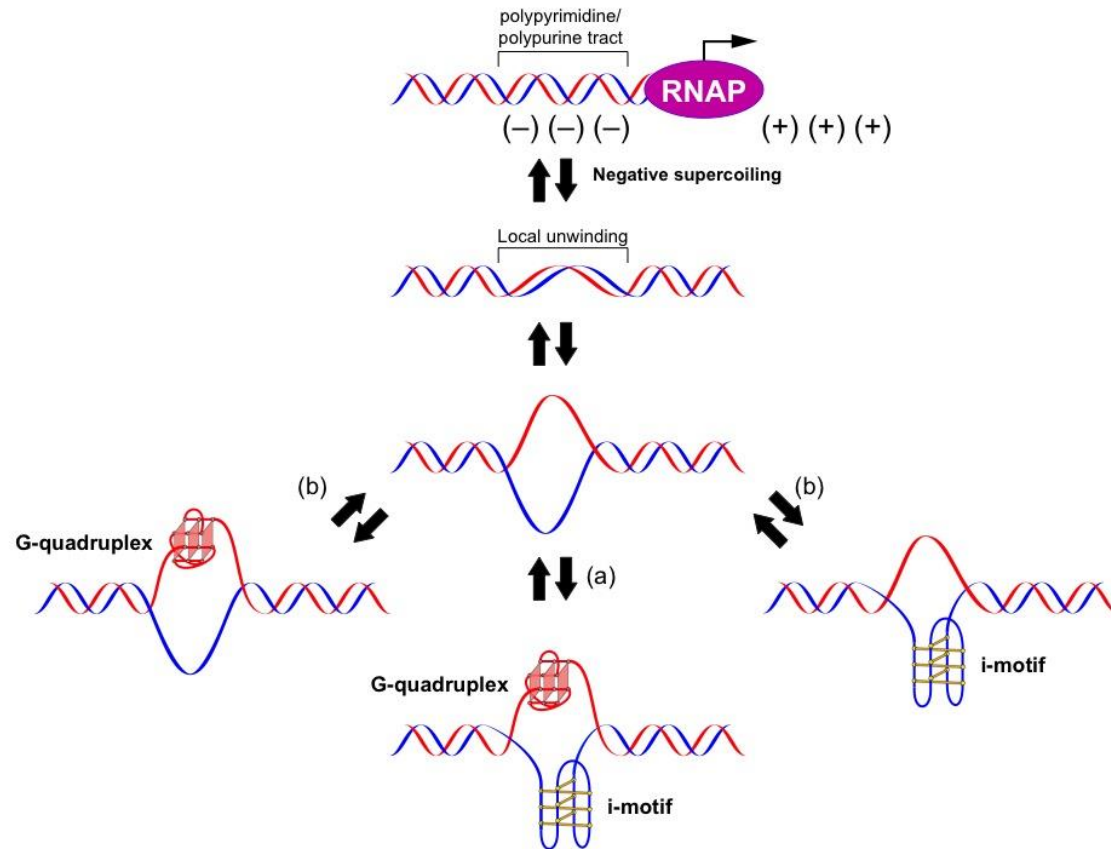
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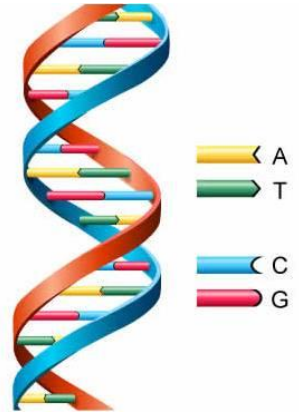
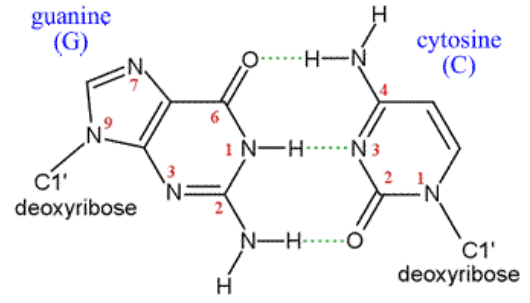
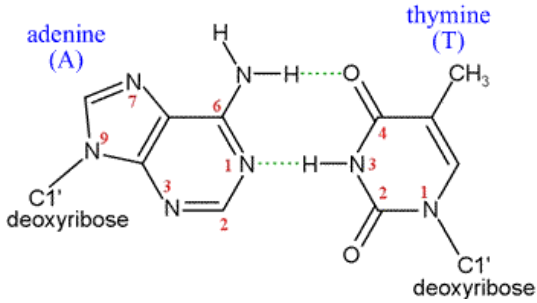
+ Targeting Cancers Achilles Heel



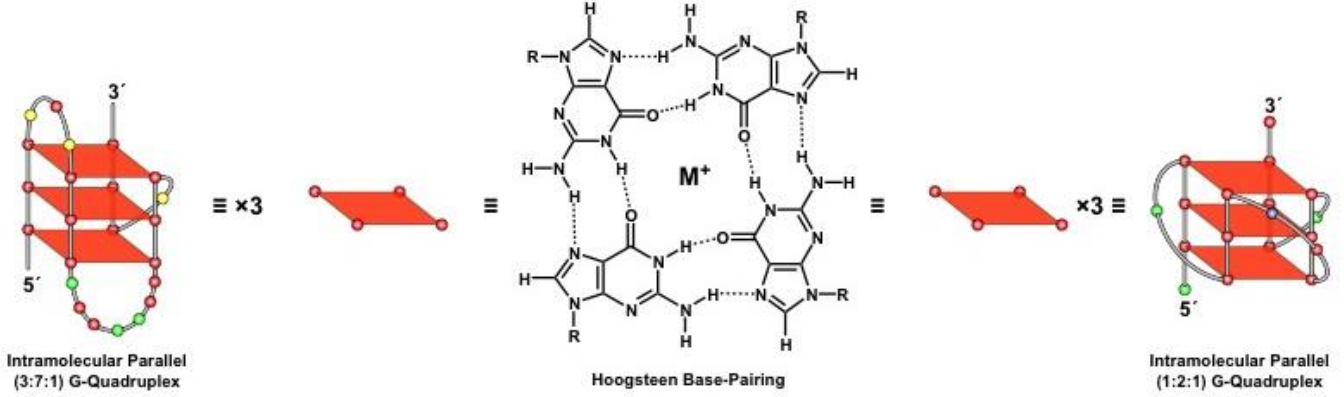
- G-quadruplex
- i-Motif



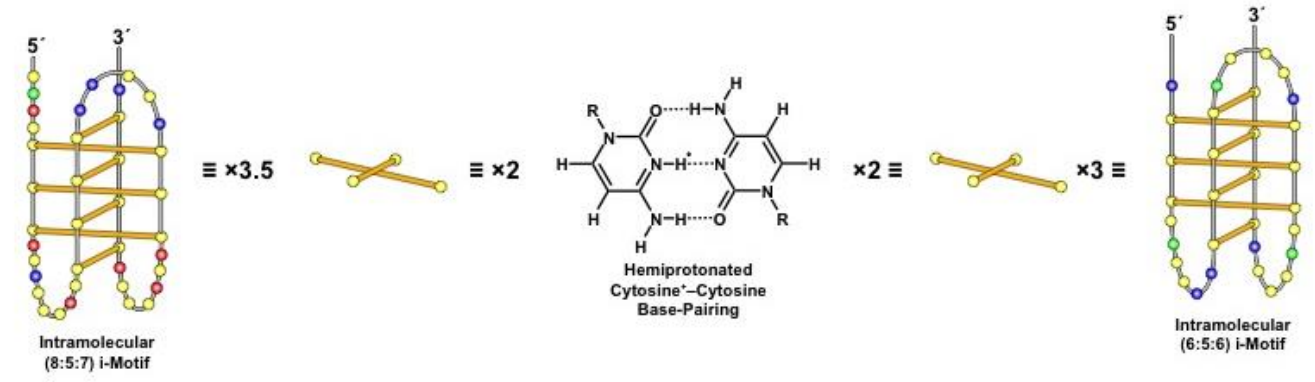
Watson & Crick Base Pairing



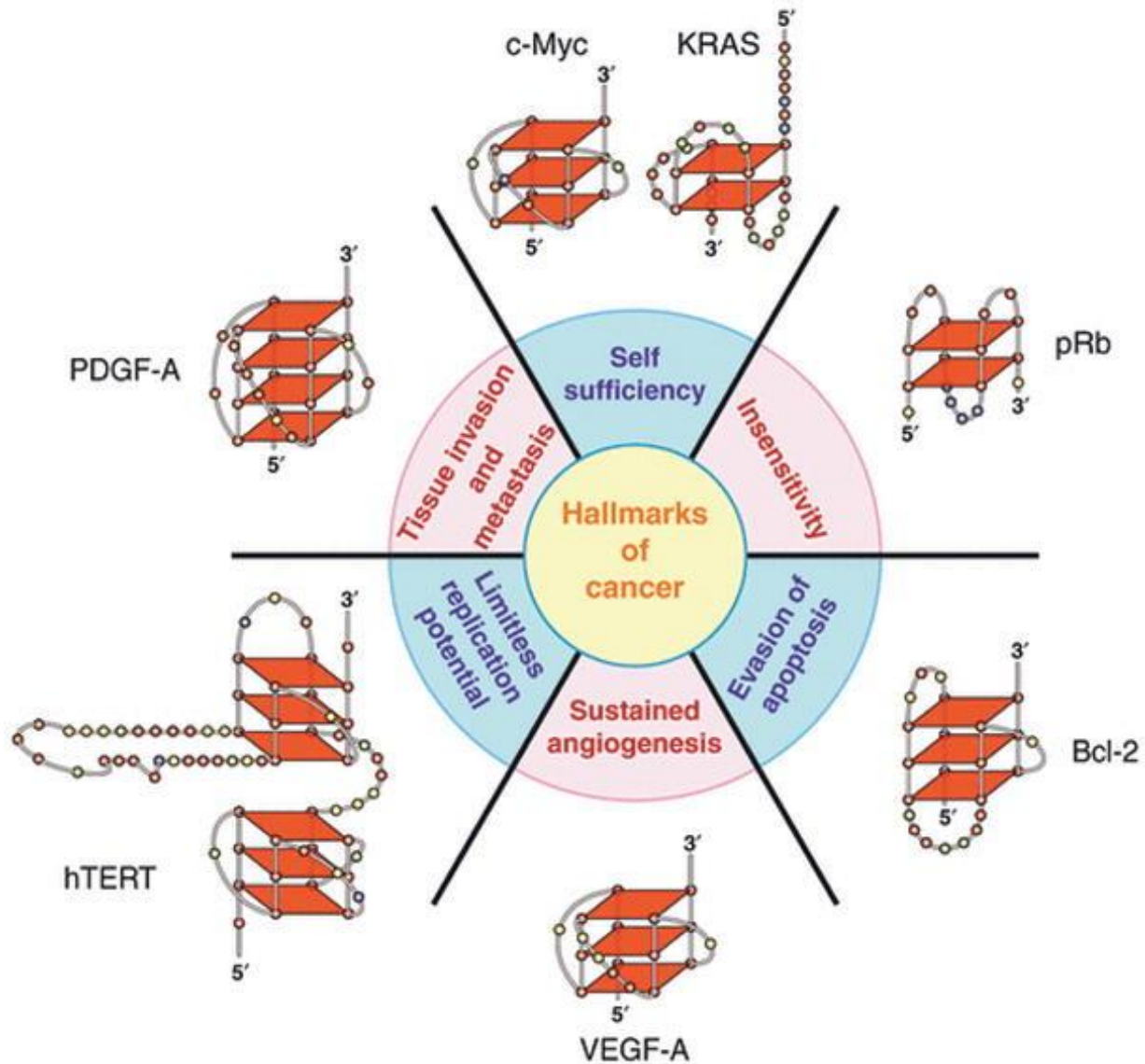
G-quadruplex



i-Motif



+ Hallmarks of Cancer

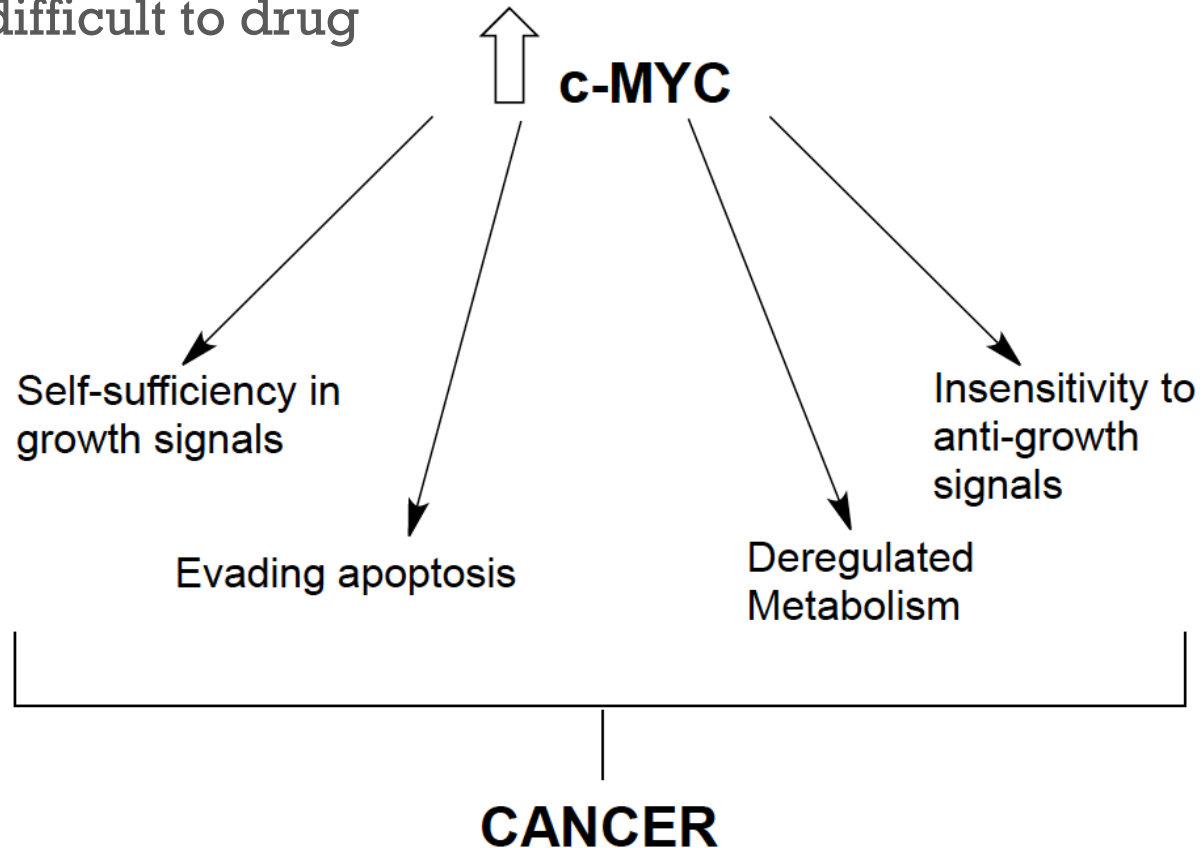




c-MYC in Cancer



- Over expressed in more than 70 % of all cancers
- Extremely difficult to drug



+ VEGF in Cancer



- Vascular Endothelial Growth Factor
- Regular function is formation of new blood vessels
 - Provides oxygen and nutrients to cells
- Tumor cells can “turn on”
 - Angiogenesis
- DNA footprinting data shows formation of G-quadruplex could have potential transcriptional regulation



Intracellular stresses mimicked by Molecular Crowding Agents



Crowding Agents

- Ficoll70
- Dextran Sulfate
- PEG-300
- Sucrose

Dehydrating Agents

- Glucose
- Glycerol
- Acetonitrile



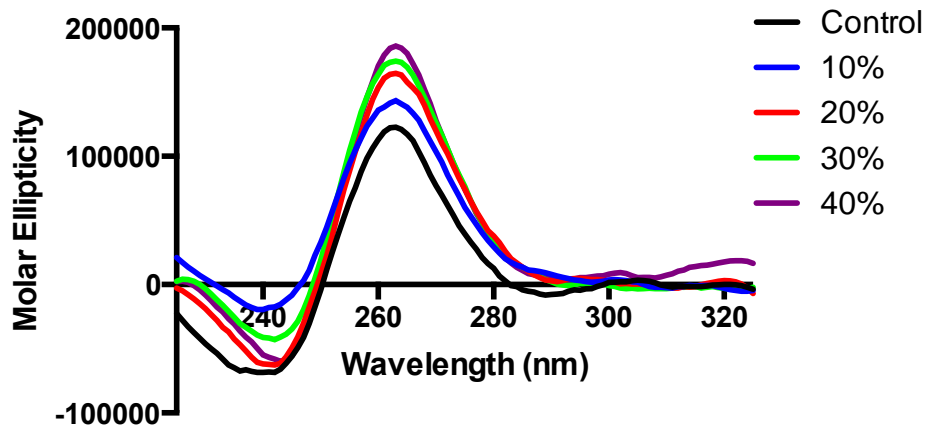
+ Results



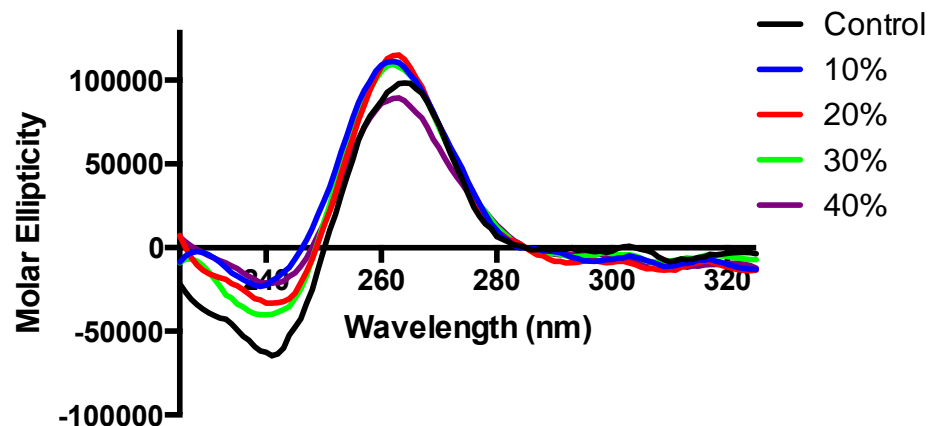
c-MYC: Crowding Agents



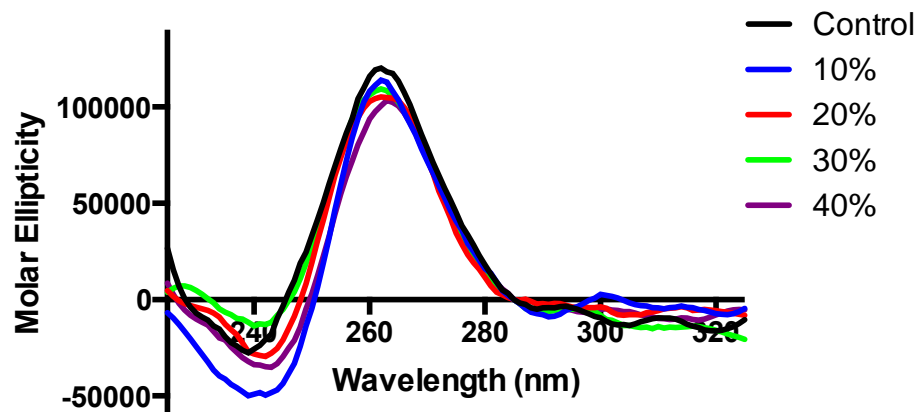
MYC PEG 300



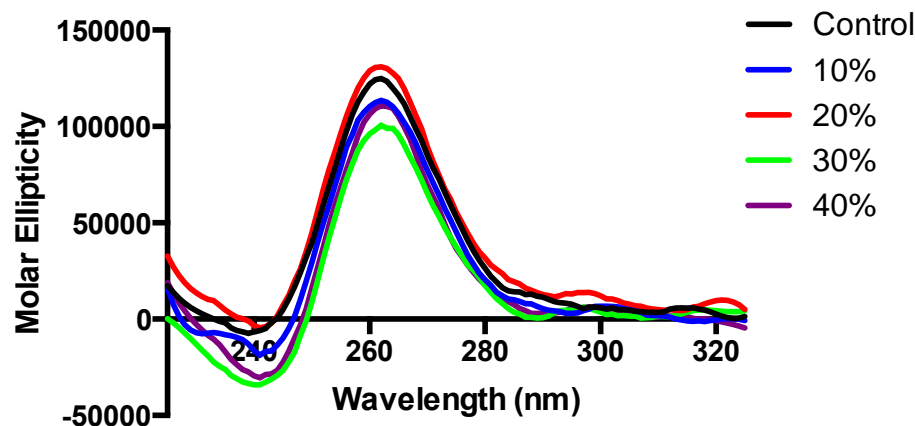
MYC Dextran



MYC Sucrose



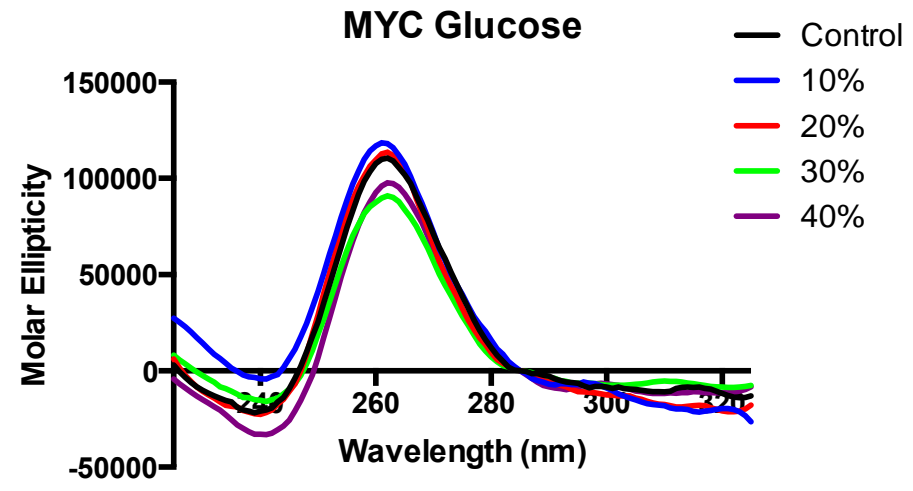
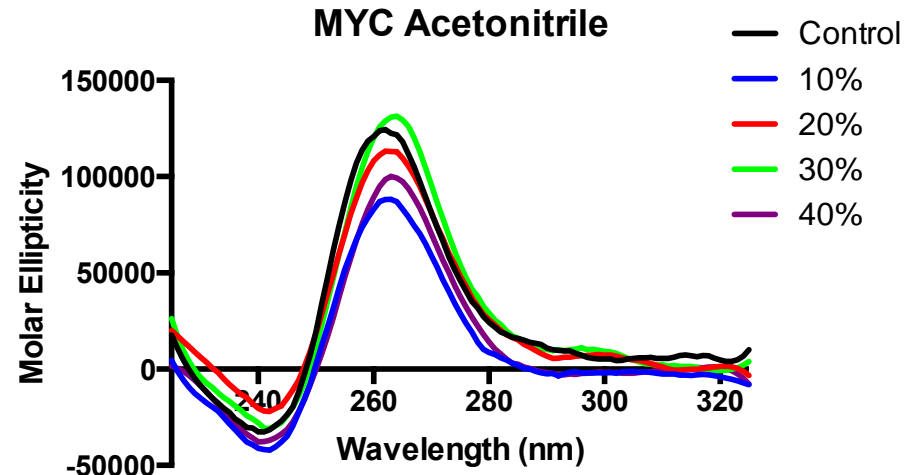
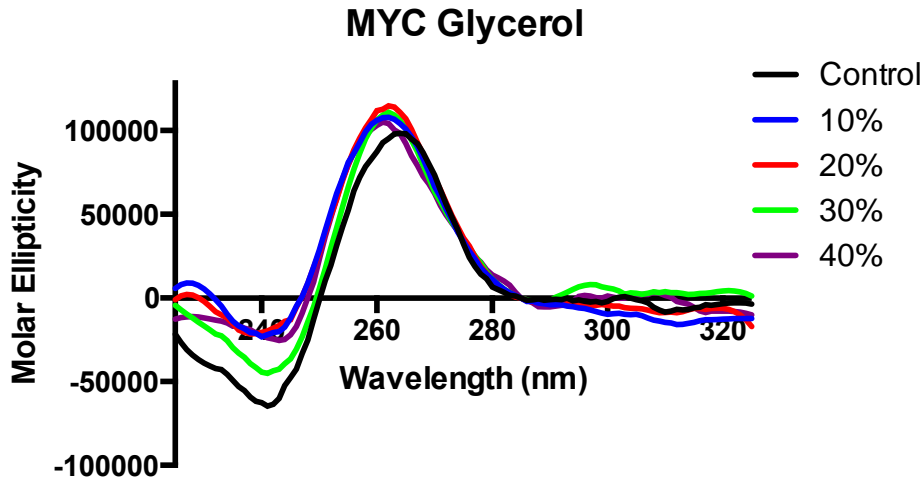
MYC Ficoll70



50mM Tris-HCl 10mM KCl



c-MYC: Dehydrating Agents

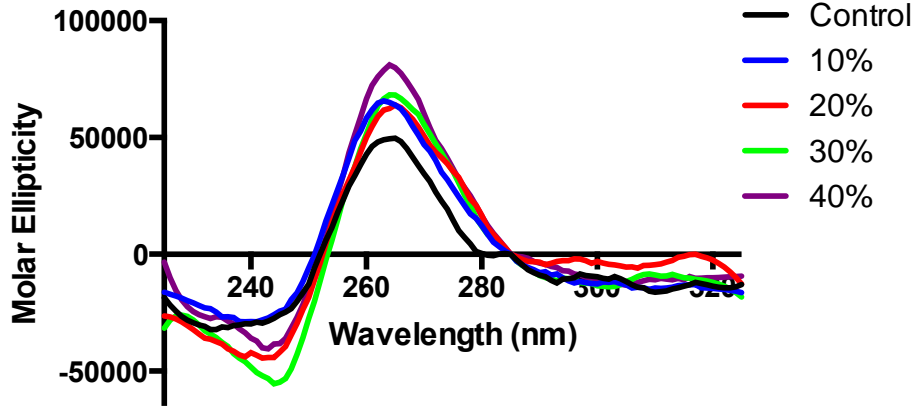


50mM Tris-HCl 10mM KCl

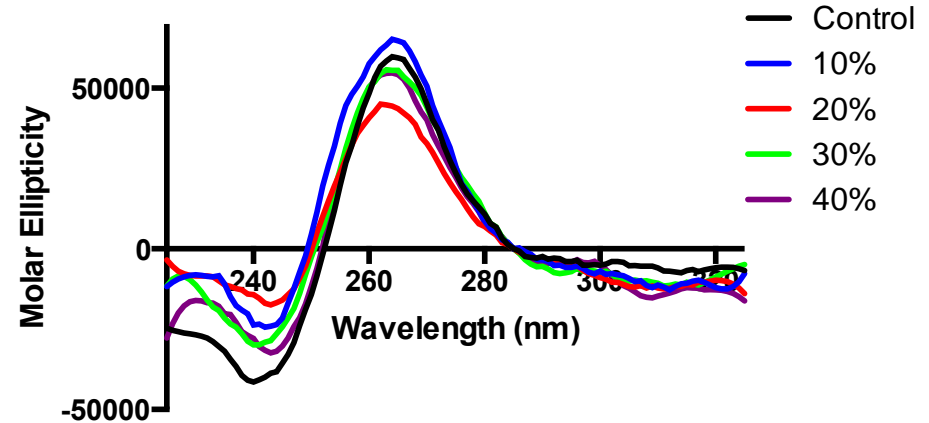
+ VEGF: Crowding Agents



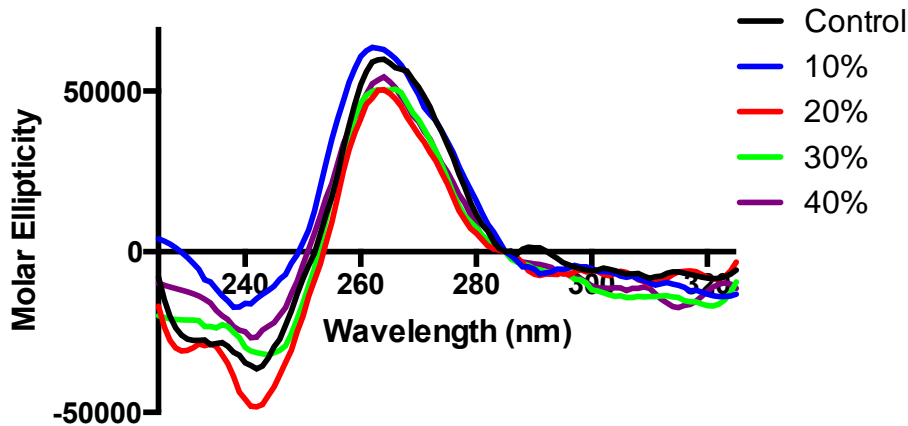
VEGF PEG 300



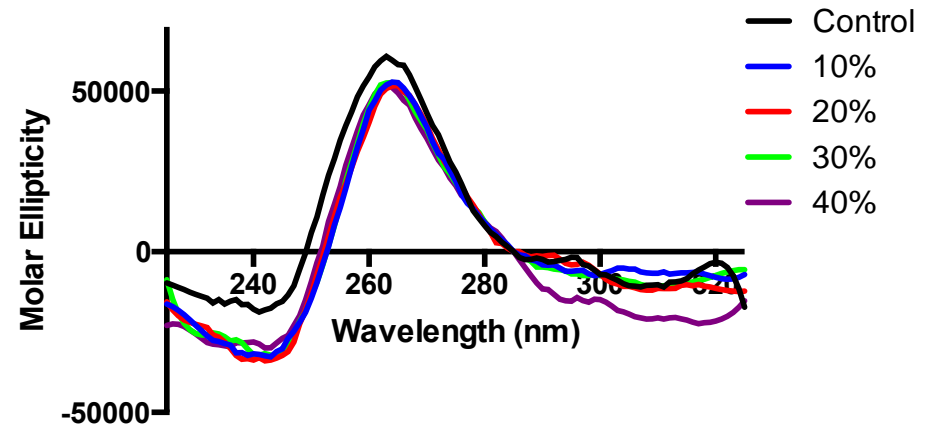
VEGF Dextran



VEGF Sucrose

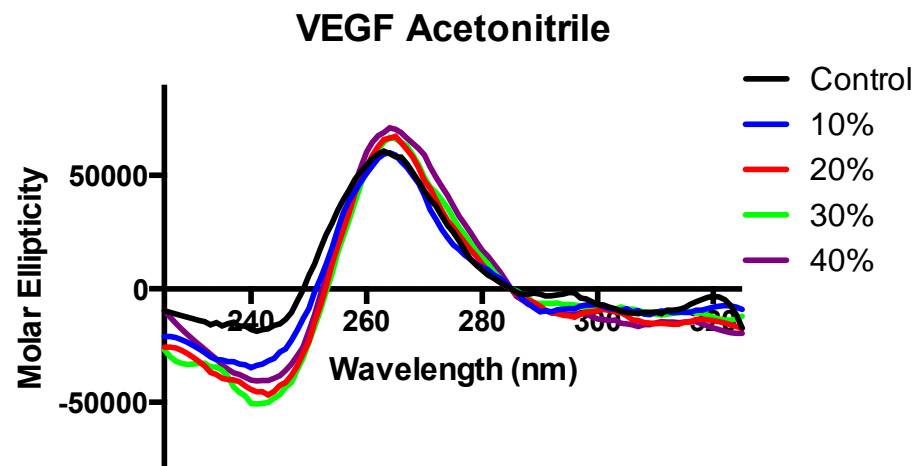
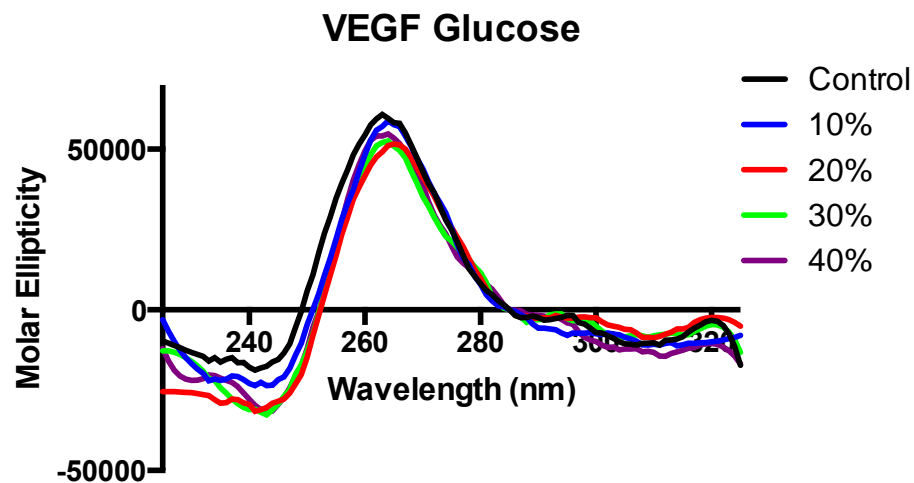
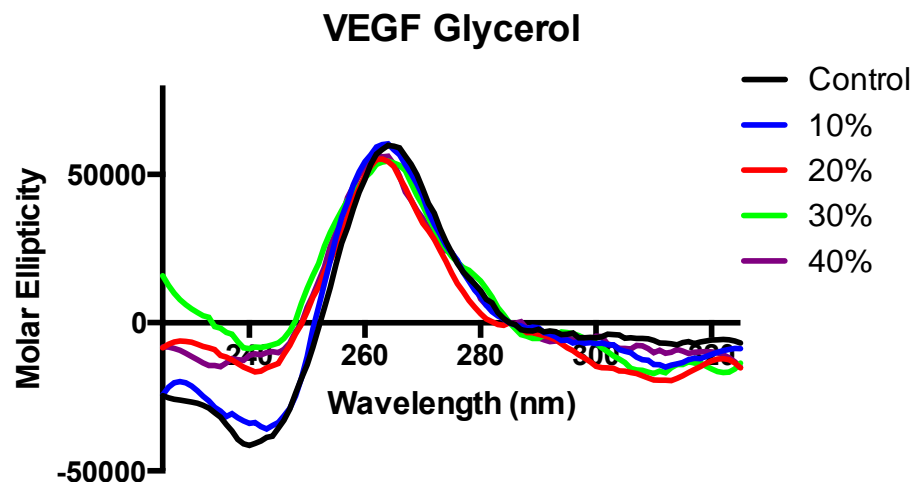


VEGF Ficoll70



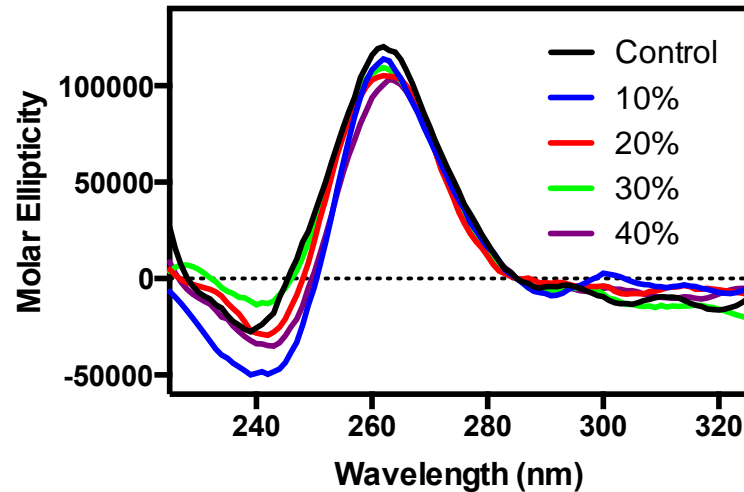
50mM Tris-HCl 10mM KCl

+ VEGF: Dehydrating Agents

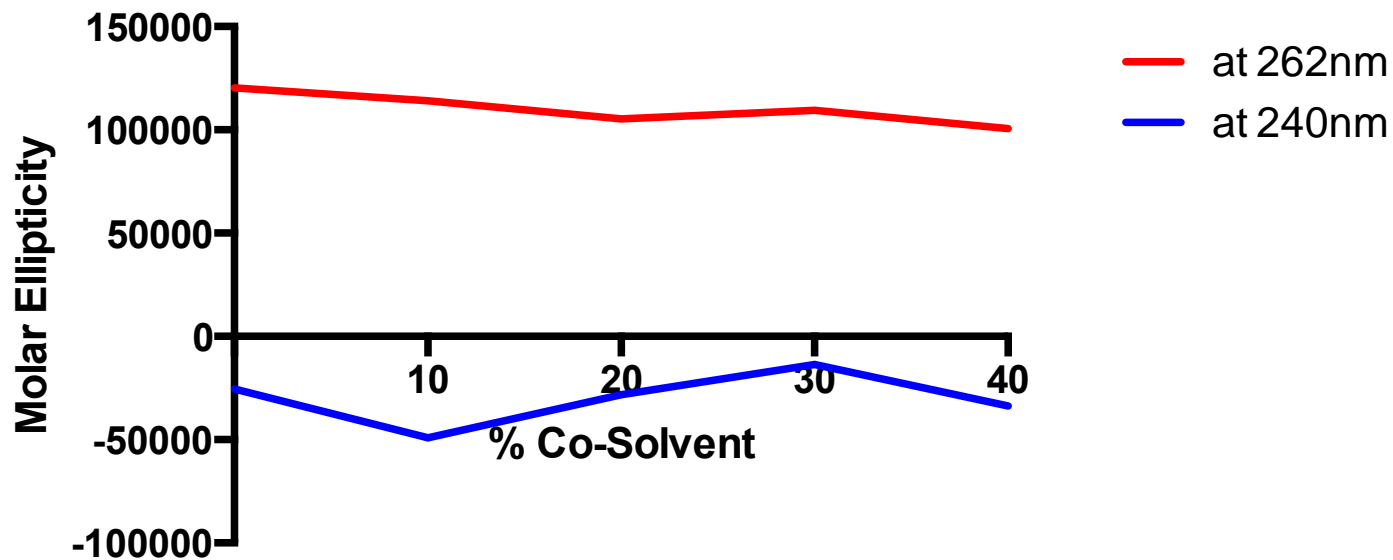


50mM Tris-HCl 10mM KCl

+ Saturation Points



MYC Sucrose Saturation Determination





Future Work: Drug Discovery



- Thermal Melt at saturation points with each co-solvent
- Begin screening c-MYC and VEGF G-quadruplexes with various compounds in nuclear conditions
 - FRET melts
 - Cytotoxicity Assays



Acknowledgments

NOBCChE, The Science Gateway Institute, Dr. Tracy A. Brooks and lab, Dr. Randy M. Wadkins, Dr. Laurence Hurley and lab, Tim O'Neill, The University of Mississippi, The University of Arizona

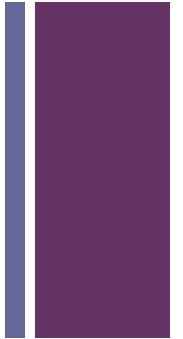




Questions?



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References



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- ③ Hanahan, D. and Weinberg, R. A, (2011) Hallmarks of Cancer: The Next Generation.
- ④ Sun D.; Guo K.; Rusche J. J.; Hurley L. H. Facilitation of a structural transition in the polypurine/polypyrimidine tract within the proximal promoter region of the human VEGF gene by the presence of potassium and G-quadruplex-interactive agents. Nucleic Acids Res.2005, 33186070–6080.