



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



College of Pharmacy



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NOBCChE

New Orleans, LA

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

Estimated New Cases*		Estimated Deaths	
Male	Female	Male	Female
Prostate 238,590 (28%)	Breast 232,340 (29%)	Lung & bronchus 87,260 (28%)	Lung & bronchus 72,220 (26%)
Lung & bronchus 118,080 (14%)	Lung & bronchus 110,110 (14%)	Prostate 29,720 (10%)	Breast 39,620 (14%)
Colon & rectum 73,680 (9%)	Colon & rectum 69,140 (9%)	Colon & rectum 26,300 (9%)	Colon & rectum 24,530 (9%)
Urinary bladder 54,610 (6%)	Uterine corpus 49,560 (6%)	Pancreas 19,480 (6%)	Pancreas 18,980 (7%)
Melanoma of the skin 45,060 (5%)	Thyroid 45,310 (6%)	Liver & intrahepatic bile duct 14,890 (5%)	Ovary 14,030 (5%)
Kidney & renal pelvis 40,430 (5%)	Non-Hodgkin lymphoma 32,140 (4%)	Leukemia 13,660 (4%)	Leukemia 10,060 (4%)
Non-Hodgkin lymphoma 37,600 (4%)	Melanoma of the skin 31,630 (4%)	Esophagus 12,220 (4%)	Non-Hodgkin lymphoma 8,430 (3%)
Oral cavity & pharynx 29,620 (3%)	Kidney & renal pelvis 24,720 (3%)	Urinary bladder 10,820 (4%)	Uterine corpus 8,190 (3%)
Leukemia 27,880 (3%)	Pancreas 22,480 (3%)	Non-Hodgkin lymphoma 10,590 (3%)	Liver & intrahepatic bile duct 6,780 (2%)
Pancreas 22,740 (3%)	Ovary 22,240 (3%)	Kidney & renal pelvis 8,780 (3%)	Brain & other nervous system 6,150 (2%)
All sites 854,790 (100%)	All sites 805,500 (100%)	All sites 306,920 (100%)	All sites 273,430 (100%)

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

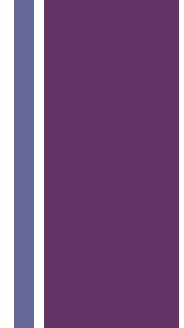
©2013, American Cancer Society, Inc., Surveillance Research

■ 2<sup>nd</sup> leading cause of death

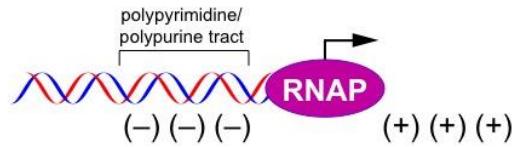
■ 1 in 4 people will develop cancer in their lifetime



# Targeting Cancers Achilles Heel

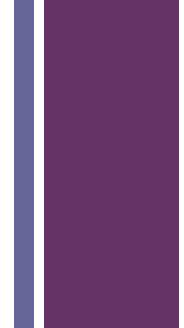


- G-quadruplex
- i-Motif

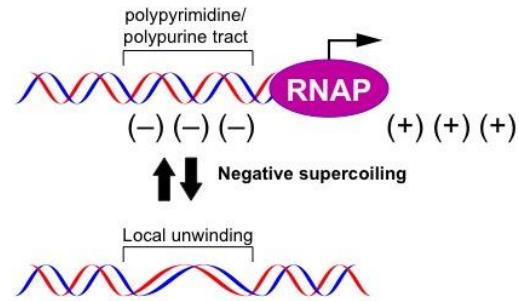




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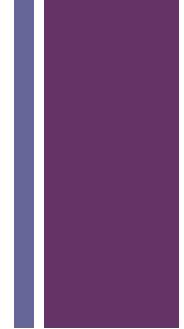


- G-quadruplex
- i-Motif

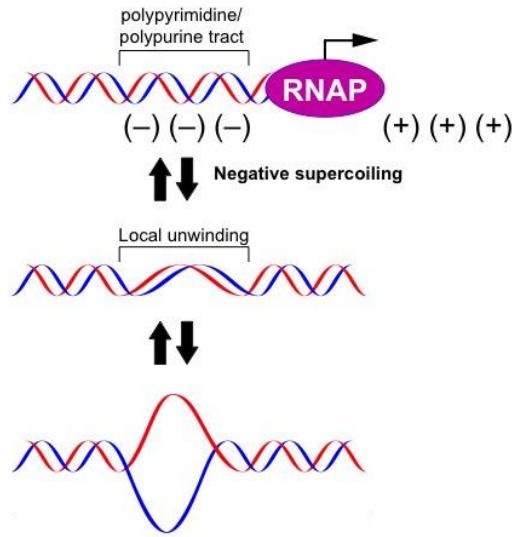




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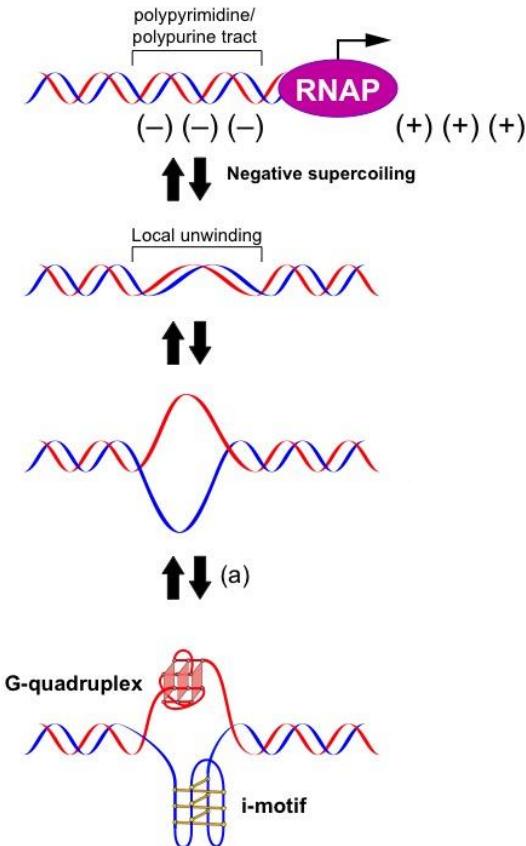
- G-quadruplex
- i-Motif





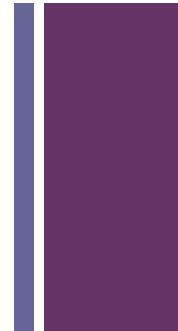
# Targeting Cancers Achilles Heel

- G-quadruplex
- i-Motif

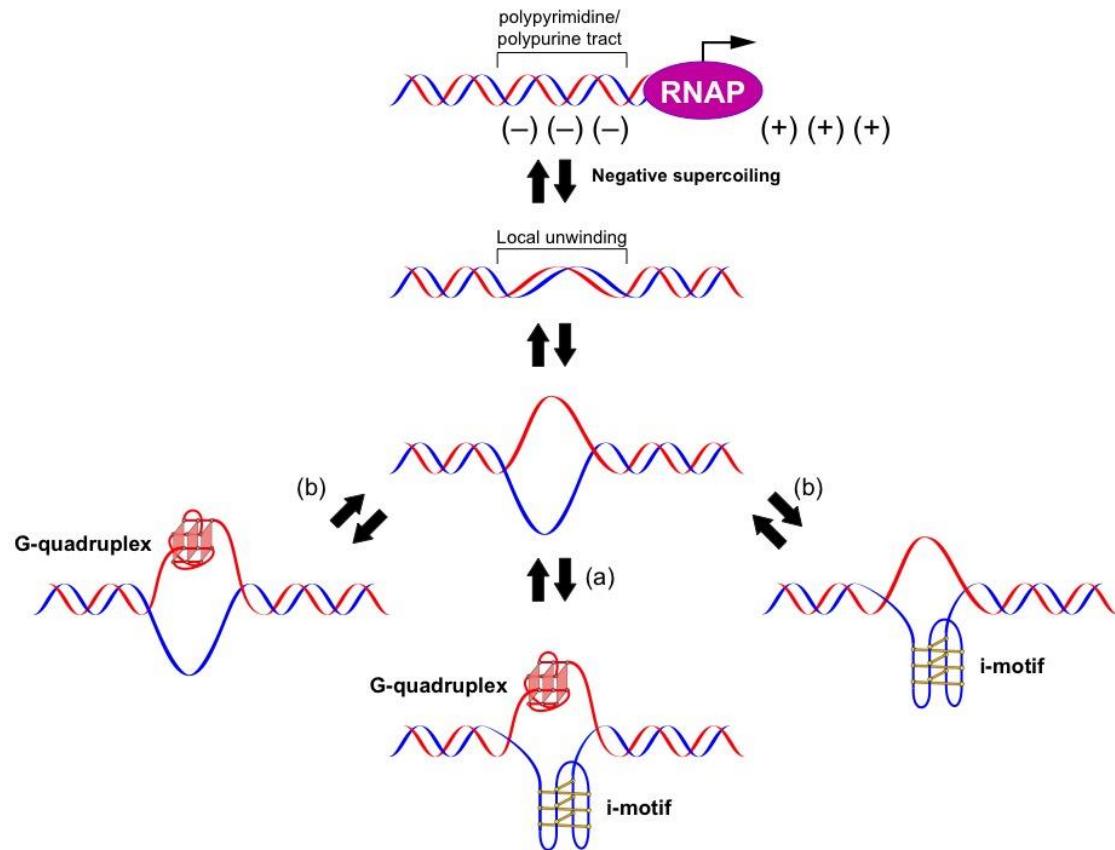




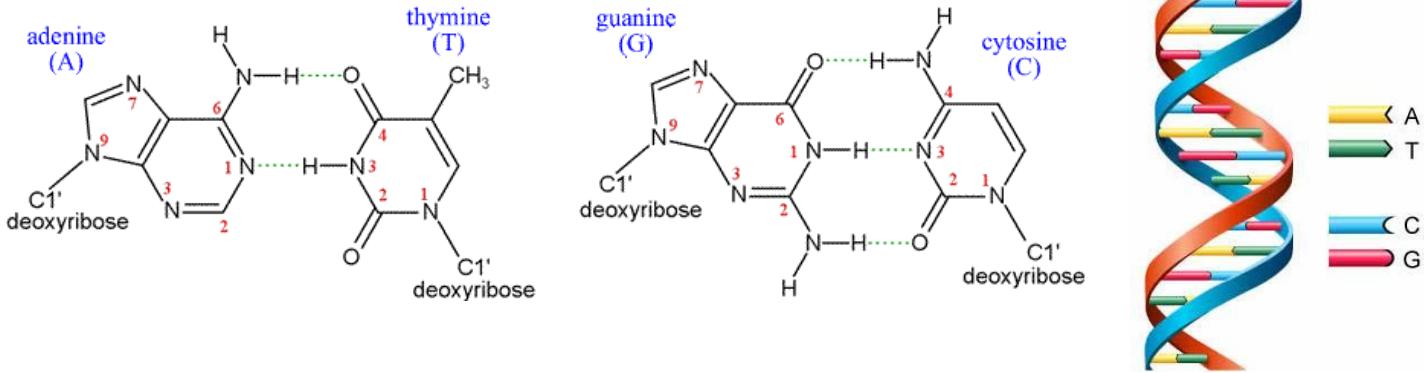
# Targeting Cancers Achilles Heel



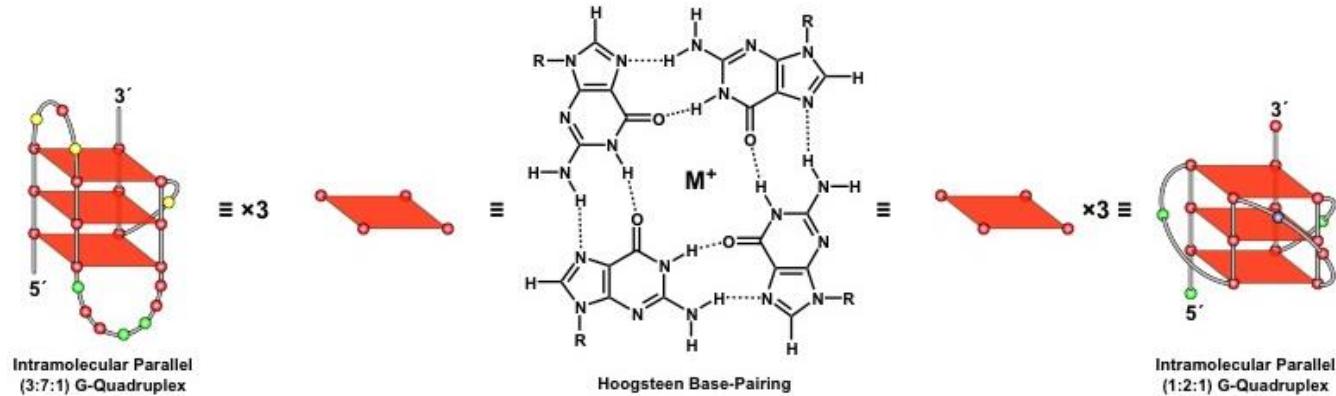
- G-quadruplex
- i-Motif



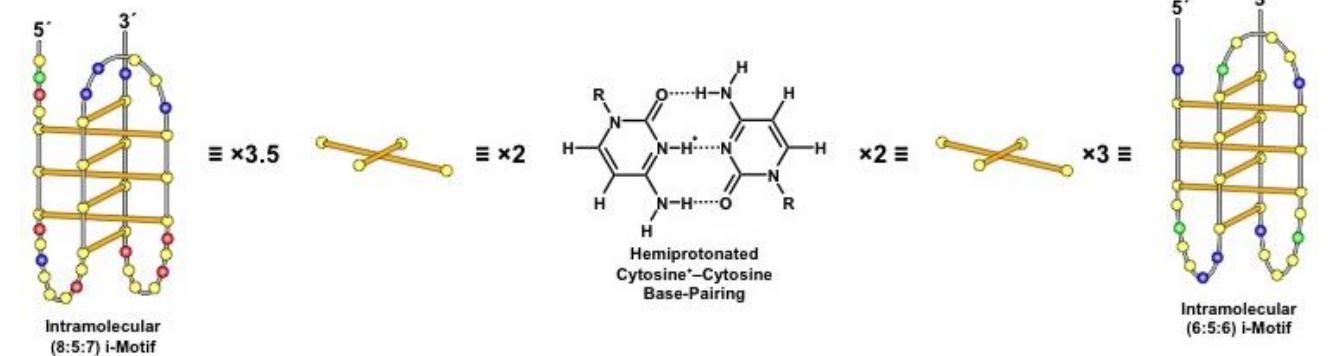
# Watson & Crick Base Pairing



## G-quadruplex

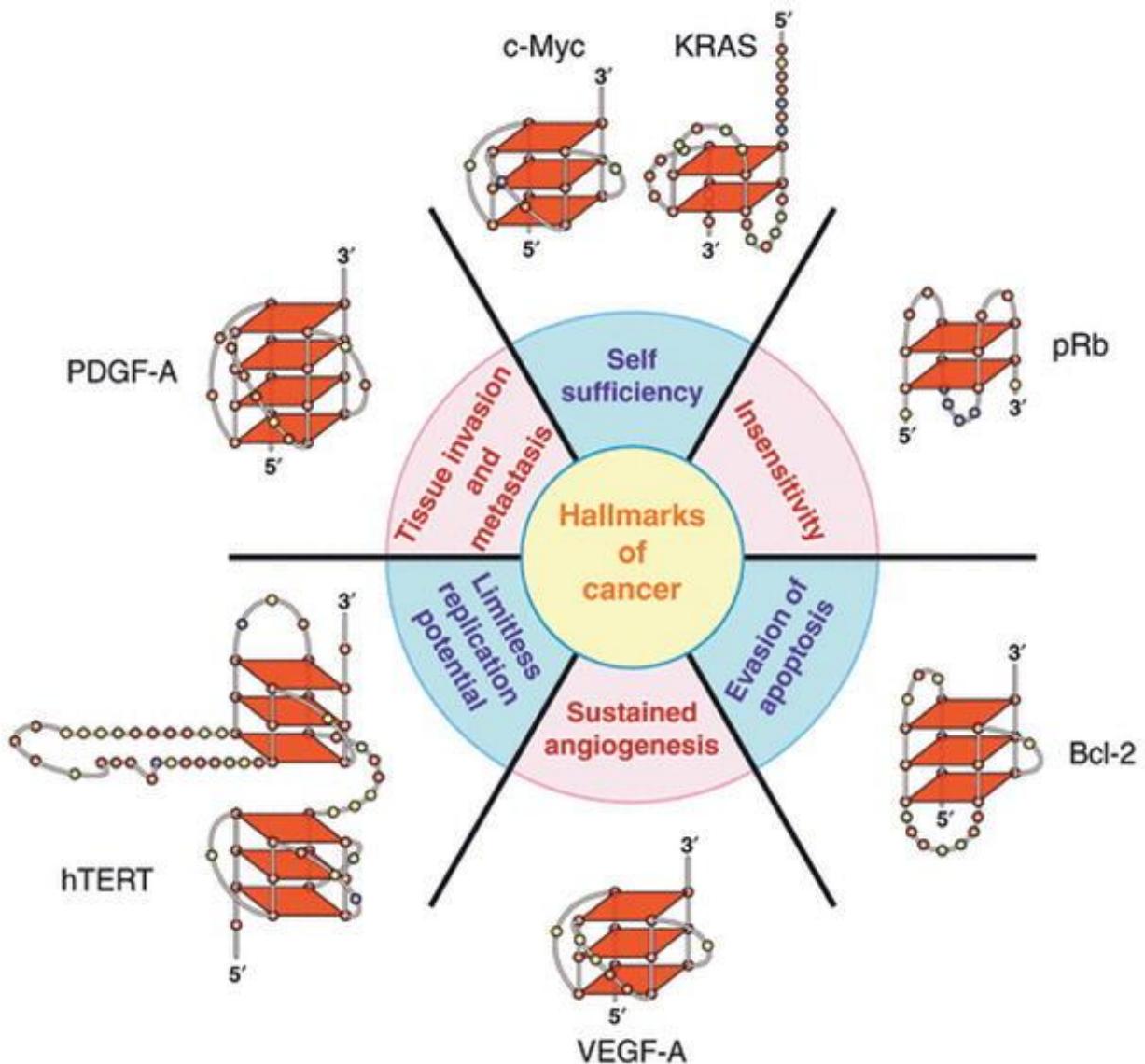


## i-Motif



# +

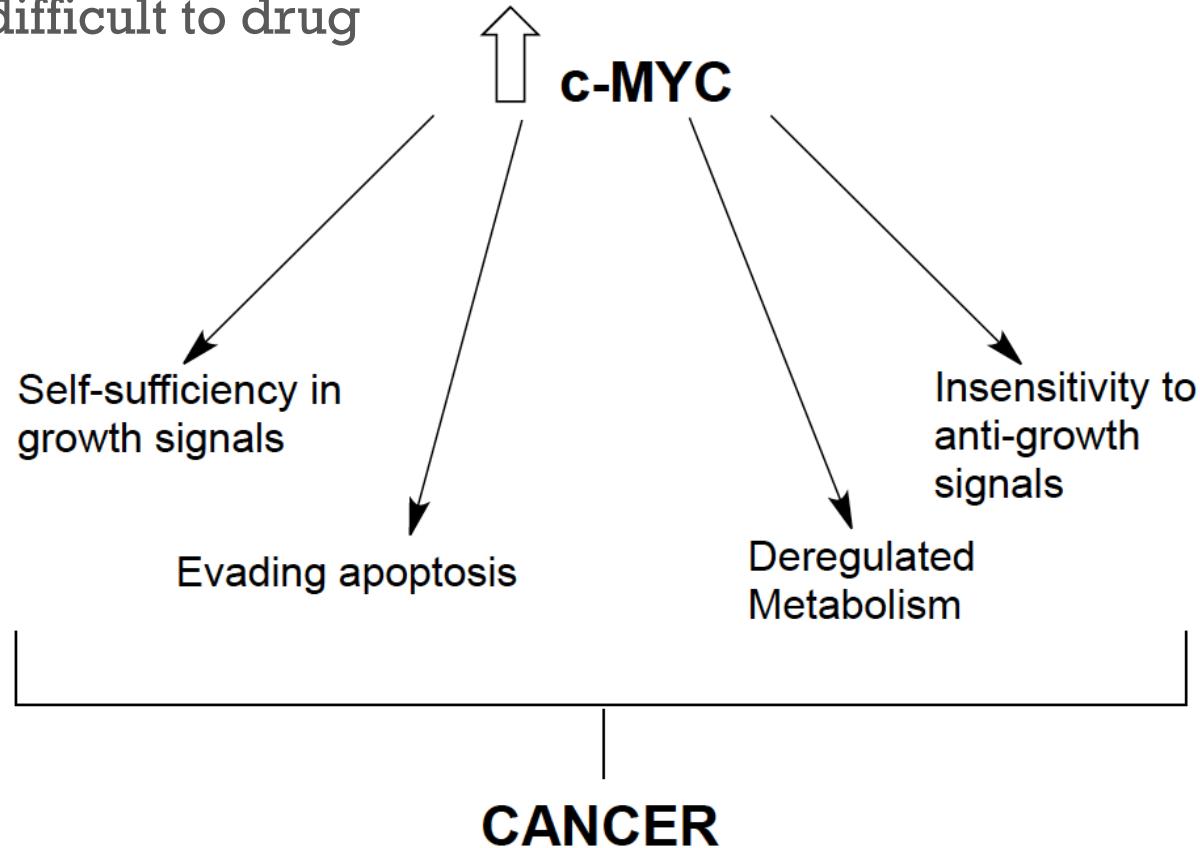
# Hallmarks of Cancer





# 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

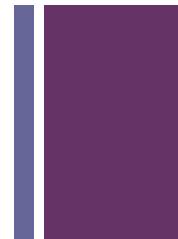
## Dehydrating Agents

- Glucose
- Glycerol
- Acetonitrile

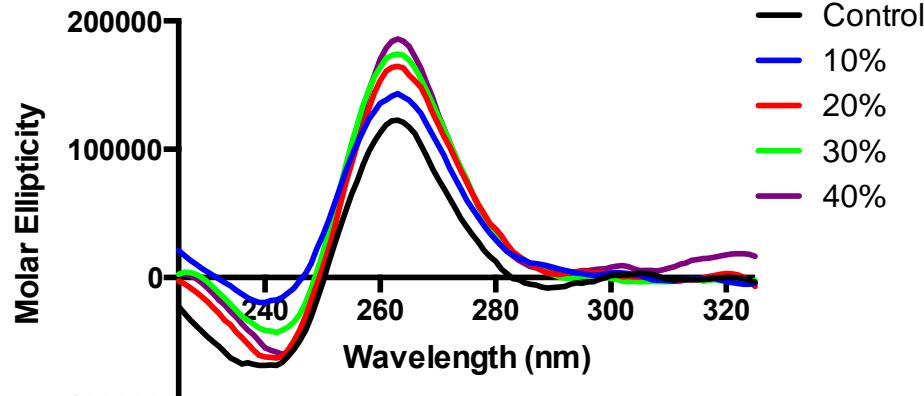
# + Results



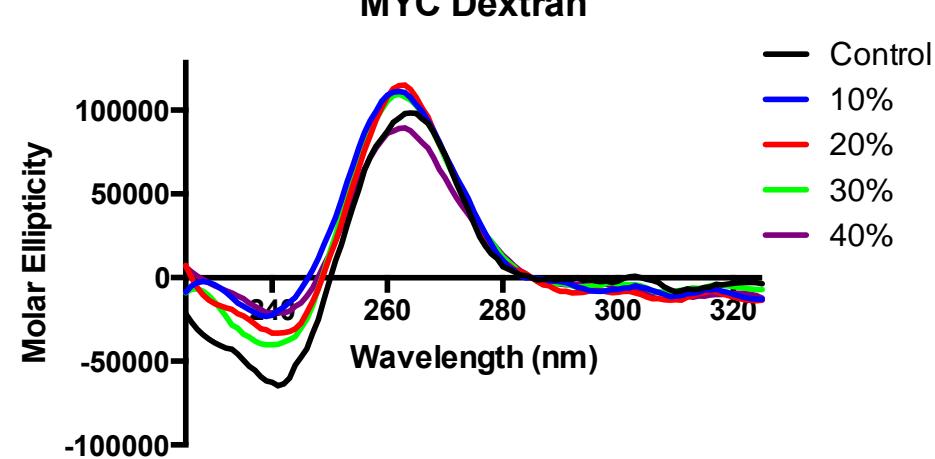
# c-MYC: Crowding Agents



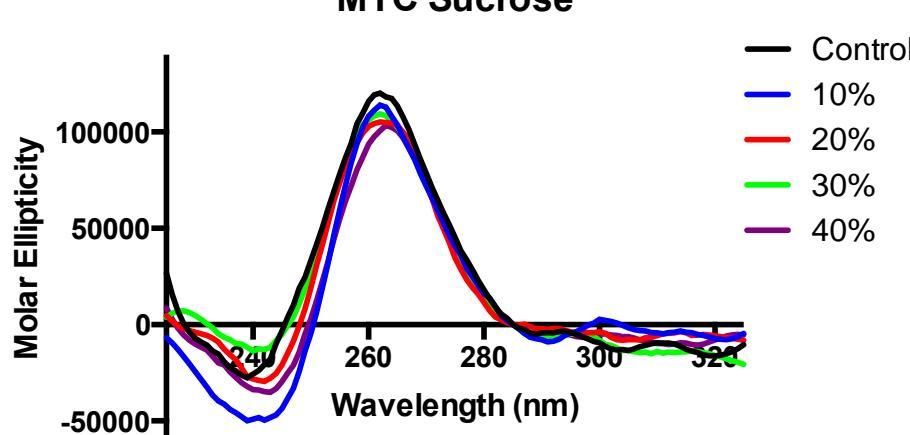
MYC PEG 300



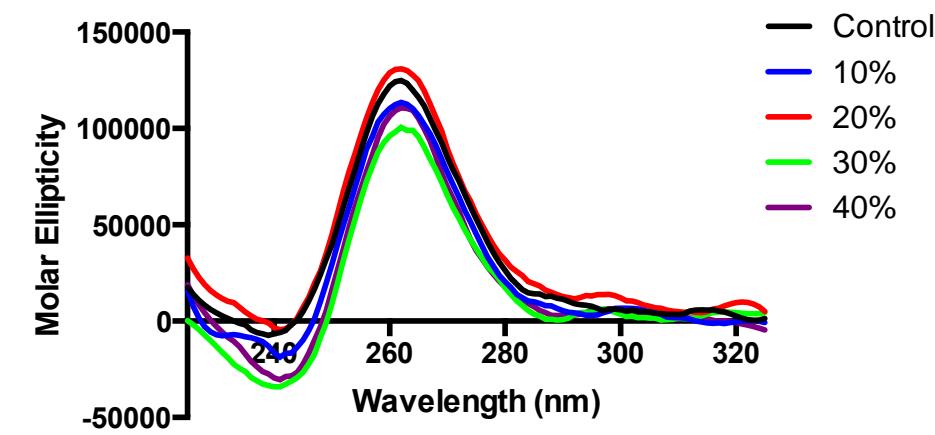
MYC Dextran



MYC Sucrose



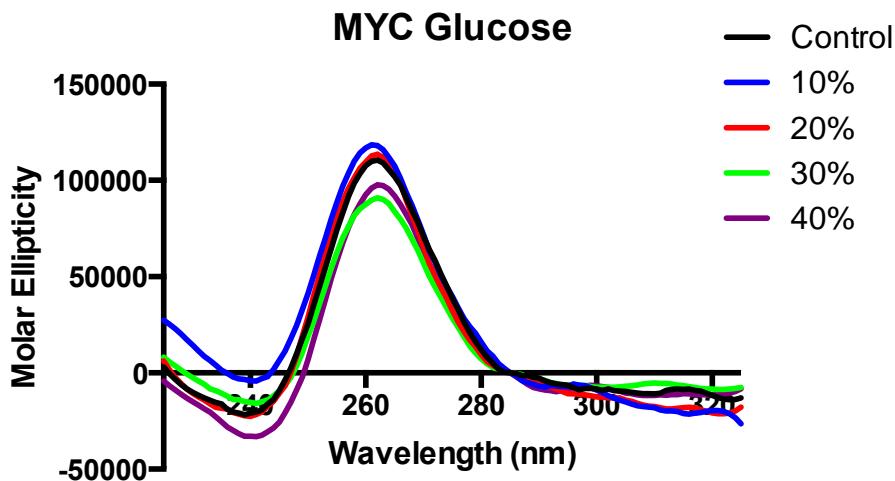
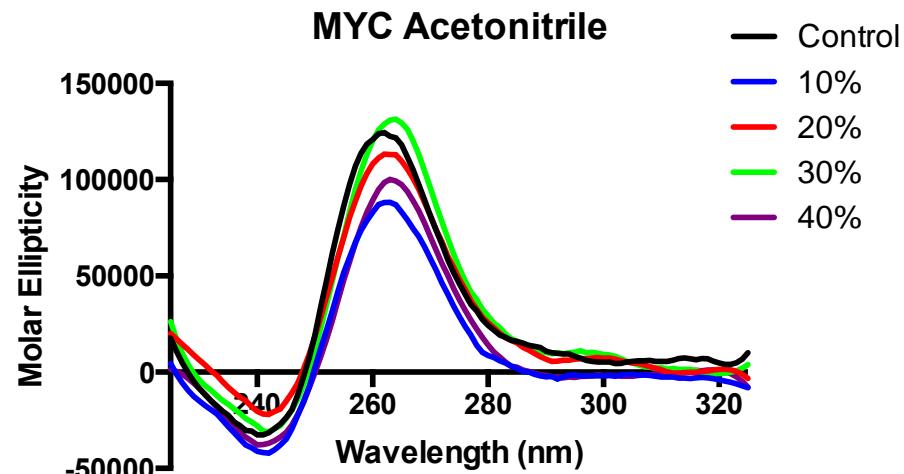
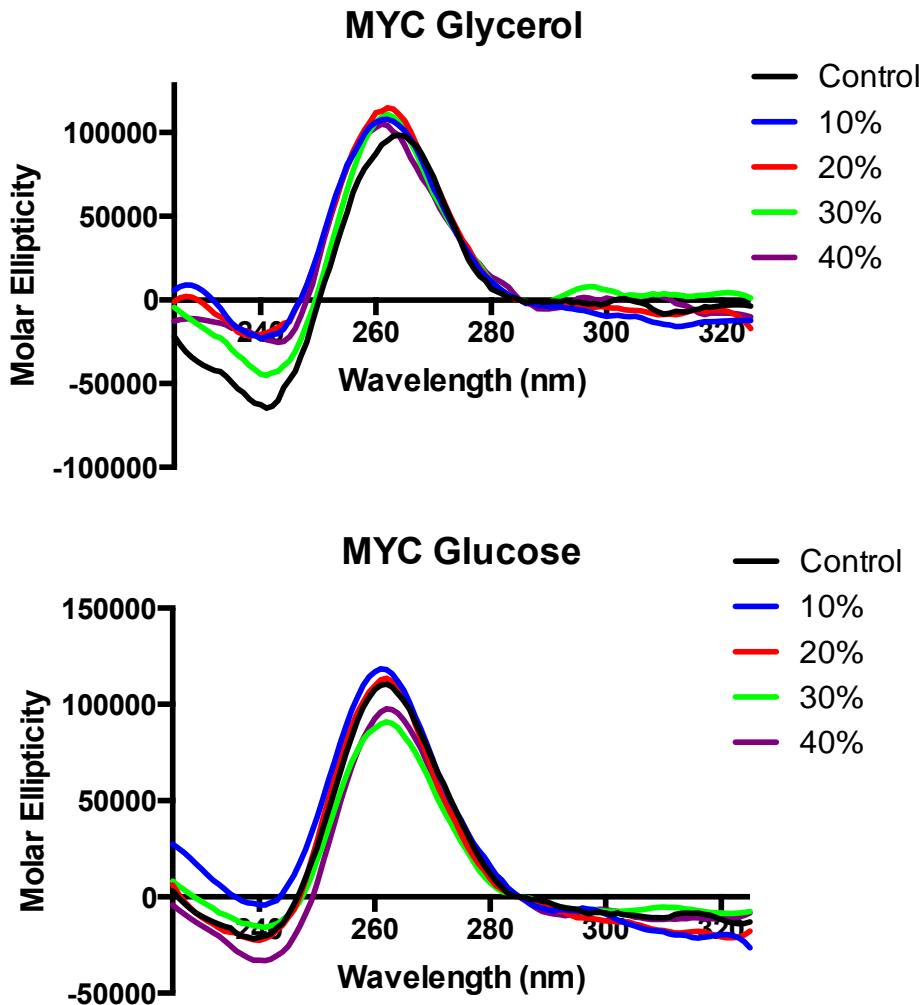
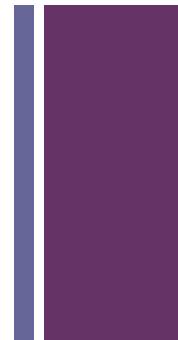
MYC Ficoll70



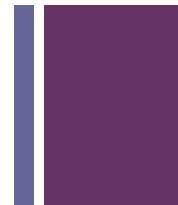
50mM Tris-HCl 10mM KCl



# c-MYC: Dehydrating Agents

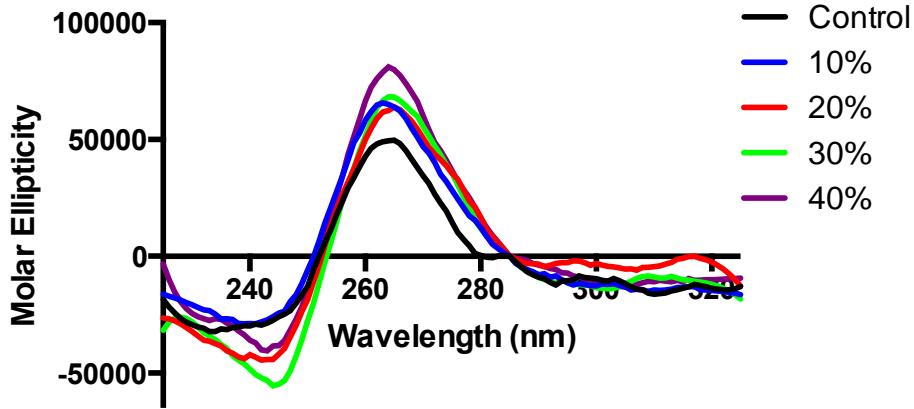


50mM Tris-HCl 10mM KCl

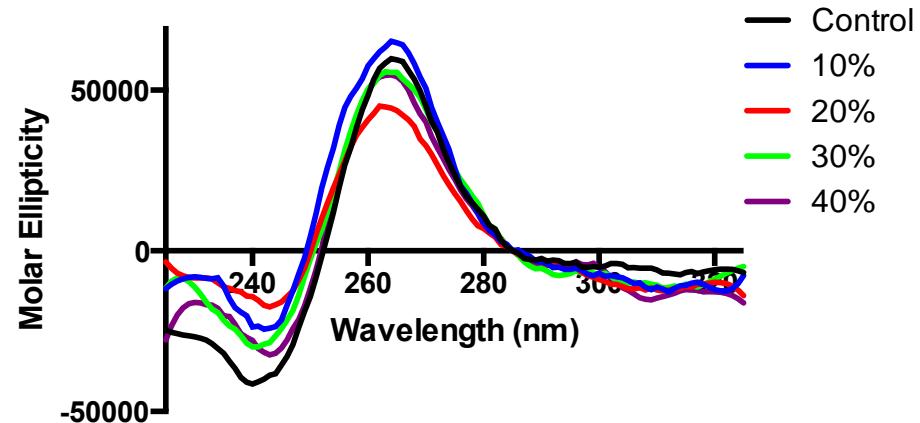


# VEGF: Crowding Agents

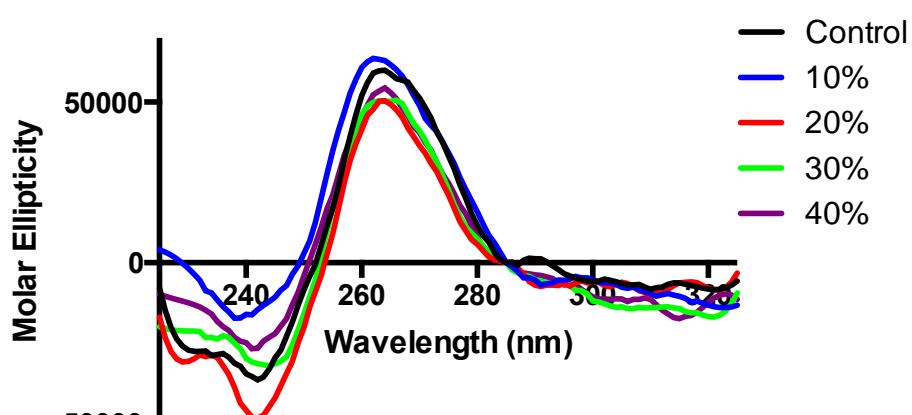
VEGF PEG 300



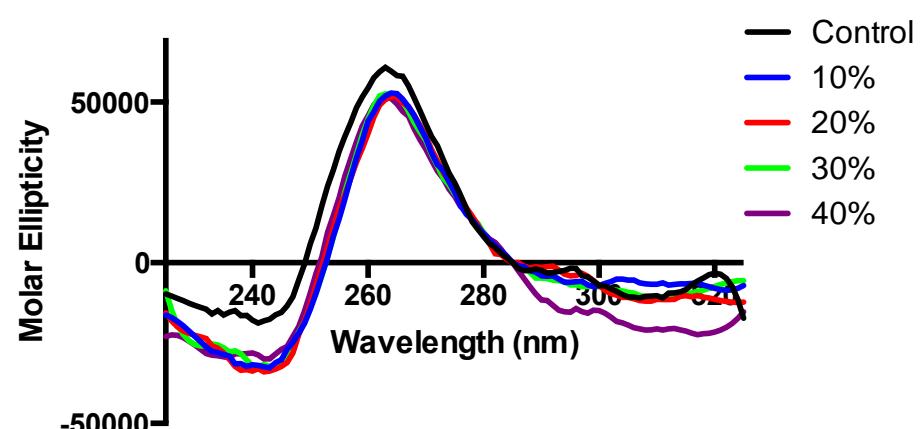
VEGF Dextran



VEGF Sucrose



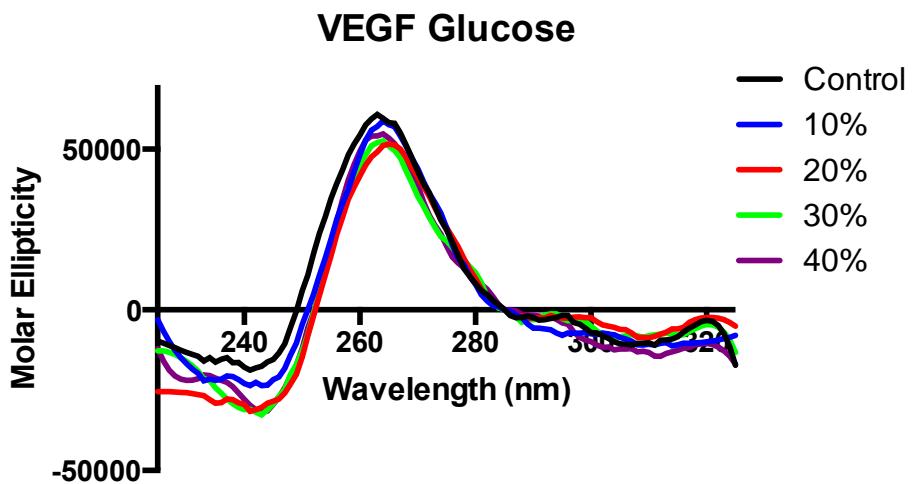
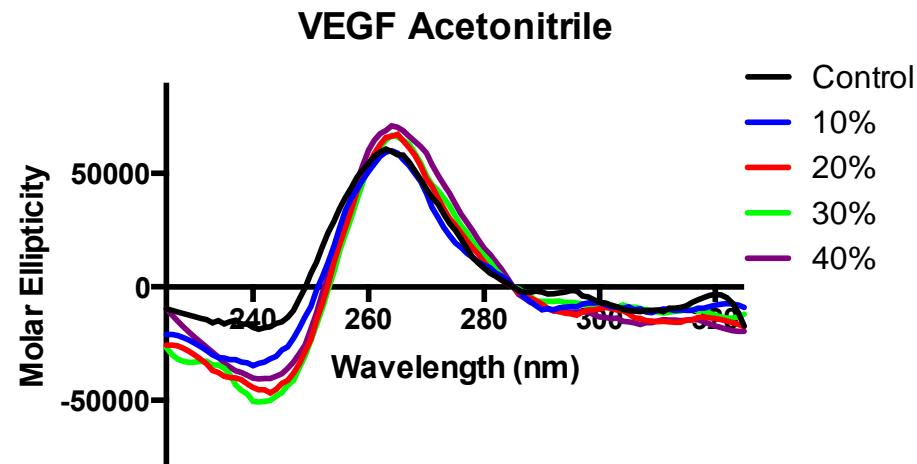
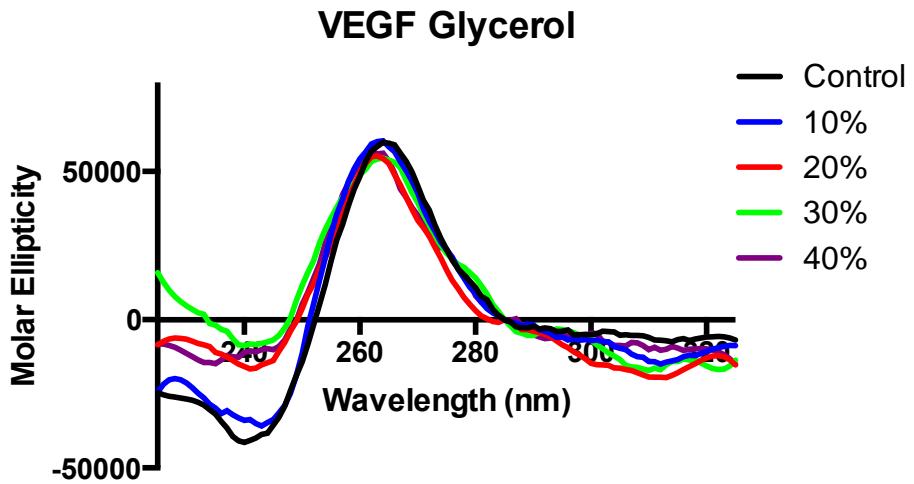
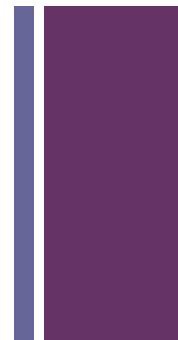
VEGF Ficoll70



50mM Tris-HCl 10mM KCl



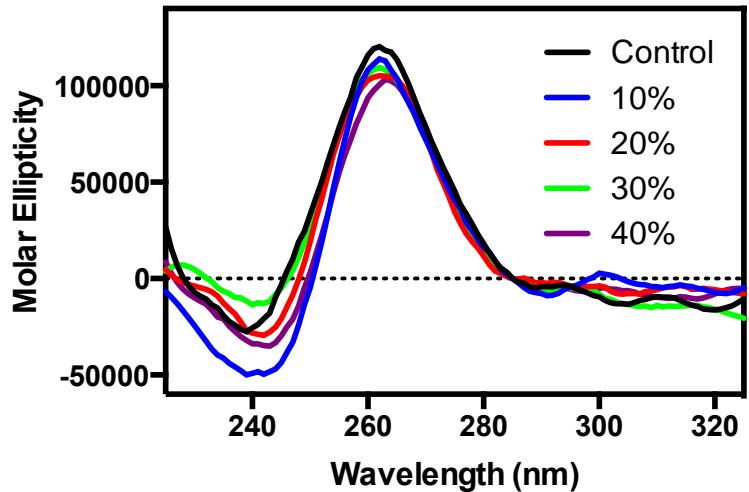
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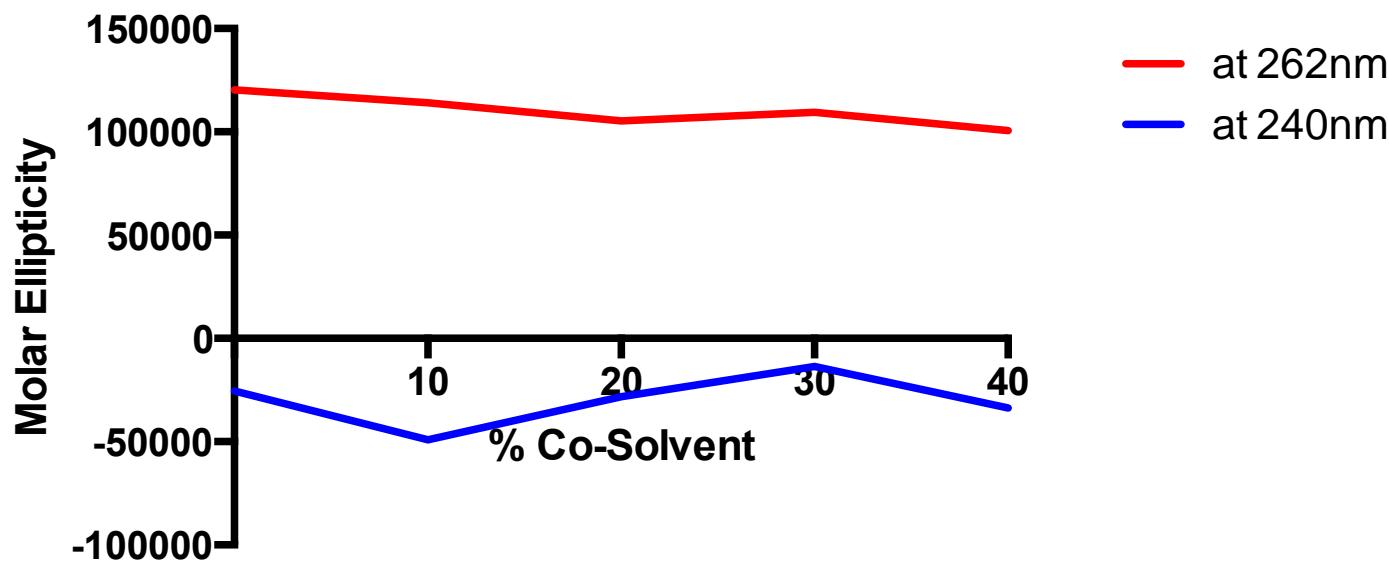
50mM Tris-HCl 10mM KCl



# 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 varies 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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