Assessing the binding affinity of a small molecule for the c-Myc oncogene guanine quadruplex for targeted anticancer applications

Petitjean research group. From left to right: Yushi Liang (3rd year undergraduate student), Caitlin Miron (PhD candidate), Dr. Anne Petitjean, and Isaiah Hasham (4th year undergraduate student).

My story

c-Myc Deregulation in Primary Human Cancers

Kalkat et. al (2017) *Genes*

Table 1
Summary of *Myc* deregulation in human tumors

Tumor type	Frequency of <i>Myc</i> aberrations		
Hematological malignancies		Glioblastoma	<i>MYCN</i> amplification (<5%) <i>c-Myc/MYCN/L-Myc</i> overexpression (57–78%)
B-acute lymphocytic leukemia	<i>c-Myc</i> rearrangement/amplification (47–52%)	Hepatocellular carcinoma	<i>c-Myc</i> amplification (33%)
Burkitt's lymphoma	<i>c-Myc</i> translocation (100%) <i>c-Myc</i> overexpression (91%)	Large cell neuroendocrine carcinoma	<i>c-Myc</i> amplification (23%)
Diffuse large cell lymphoma	<i>c-Myc</i> rearrangement/translocation (6–16%) <i>c-Myc</i> overexpression (10%)	Medulloblastoma	<i>c-Myc/MYCN</i> amplification (5–15%) <i>c-Myc</i> overexpression (31%) <i>MYCN</i> overexpression (68%)
Multiple myeloma	<i>c-Myc</i> translocation (15%)	Melanoma, nodular	<i>c-Myc</i> amplification (61%)
Primary plasma cell leukemia	<i>c-Myc</i> rearrangement (13%)	Melanoma, superficial spreading	<i>c-Myc</i> amplification (28%)
Solid tumors		Neuroblastoma	<i>MYCN</i> amplification (25–30%)
Atypical carcinoid lung cancer	<i>c-Myc</i> amplification (17%)	Oesophageal squamous cell carcinoma	<i>c-Myc</i> amplification (10–30%)
Bladder cancer	<i>c-Myc</i> amplification (33%)	Osteosarcoma	<i>c-Myc</i> amplification (7–78%)
Breast cancer	<i>c-Myc</i> amplification (9–48%) <i>c-Myc</i> overexpression (45%) <i>MYCN</i> overexpression (25%) CRD-BP amplification (18%) ^a	Ovarian cancer	<i>c-Myc</i> amplification (40%) <i>c-Myc</i> overexpression (44%) <i>L-Myc</i> amplification (15%) <i>L-Myc</i> overexpression (40%)
Cervix cancer	<i>c-Myc</i> amplification (29%)	Prostate cancer	<i>c-Myc</i> amplification (30–50%) <i>c-Myc</i> overexpression (70%)
Colon cancer	<i>c-Myc</i> amplification (17%) <i>c-Myc</i> overexpression (67%)	Renal clear cell carcinoma	<i>c-Myc</i> amplification (8%)
Gastric cancer	<i>c-Myc</i> amplification (15–30%) <i>c-Myc</i> overexpression (47%)	Retinoblastoma	<i>MYCN</i> amplification (10–20%)
		Rhabdomyosarcoma	<i>MYCN</i> amplification (43–67%)
		Small cell lung carcinoma	<i>c-Myc</i> amplification (20%) <i>L-Myc</i> amplification (13%) <i>MYCN</i> amplification (10%)

Canadian PhD student makes groundbreaking cancer discovery

By Global News

▶ PLAY VIDEO

Queen's University PhD student has identified a chemical compound that could potentially switch off cancer cells.

How tightly does bind to guanine quadruplex in the promoter?

How tightly does bind to guanine quadruplex in the promoter?

Fluorescence Indicator Displacement Assay (FID)

STEP 1: Thiazole orange binds to guanine quadruplex

No fluorescence

fluorescence

STEP 2: Binder displaces Thiazole orange

Experimental Design

FID Titration 1

High binder concentration

Normal Tips

Non-Wet

FID Titration 9

Low binder concentration

Normal Tips

Wet

Overlaid FID Titrations 8 and 9

Low binder concentration

Normal Tips

Wet

FID Titration 14

Low binder concentration

Low Retention Tips

Wet

Overlaid FID Titrations 12, 13 and 14

Low binder concentration

Low Retention Tips

Wet

Species Distribution

Conclusions

- c-Myc is a gene that when deregulated leads to cancer
- A binder discovered in the Petitjean lab can stabilize the guanine quadruplex in c-Myc promoter
- Fluorescence indicator displacement assay (FID) can be used to find the binding affinity, which indicates strength of binding

Future Perspective

- High binding affinity of binder to c-Myc promoter – does it transfer to *in vivo* anti-cancer properties?
- Targeting the c-Myc promoter can prevent spread of many cancer types that c-Myc is a key driver
- Can other oncogenes be targeted?

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