Building a Natural Product-inspired Macrocyclic Toolbox Platform for “Undruggable” Targets

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External

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Prabhat Arya

Executive Summary

SignMod is building a highly unique and proprietary, natural product-inspired macrocyclic chemical toolbox platform for tackling challenging targets, currently defined as “undruggable”. These targets generally involve multiple protein-protein, DNA/RNA-protein-protein interactions and are difficult to handle by conventional, small molecule-based approaches. Our current focus is on cancer targets (and pathways), related to Wnt, c-Myc and K-Ras.

With the continual growth in the complexity of clinically-relevant cancer targets, there is a severe paucity in the small molecule arena having compounds capable of modulating protein-protein, DNA/RNA-protein interactions. Natural products have a proven track record when it comes to modulating protein-protein, DNA/RNA-protein interactions by small molecules. Due to several challenges that are associated with them, we are developing novel methods leading to macrocyclic compounds, classified as “natural product-inspired”. As with most macrocyclic natural products, these compounds have 3D shapes and are rich in sp3 centers. The presence of a large cyclic ring in their architectures also provide the possibility of interacting with the multiple sites. Due to the sufficient complexity of our compounds and an ease of the practical synthesis, they are highly attractive for further developing medicinal chemistry programs.

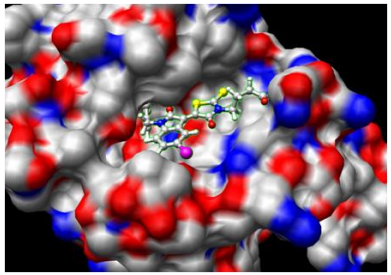
Vision

Build a proprietary, natural product-inspired macrocyclic toolbox for challenging “undruggable” targets that are difficult to handle by traditional small molecules.

Utilize this toolbox in finding novel functional small molecules for protein-protein, DNA/RNA-protein interactions, and in general, for targets related to Transcription and Translation machinery.

Growing Challenges in the Drug Discovery Arena!

Classical Approaches: Simplistic View



Structural information on the target; finding the pocket

Lipinski's rules

Structural guided chem /med chem

Defining the target (could be enzymes or isolated protein(s)

Science (2003)

REVIEW

Assembly of Cell Regulatory Systems Through Protein Interaction Domains

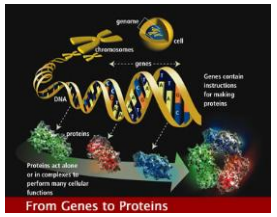
Tony Pawson[1,2*] and Piers Nash[1]

- Multiple protein-protein interactions
- Dynamic and temporal processes!
- Regulation (normal) and de-regulation (disease)

Post-genomic era

genes to pathways:

tough journey



Vol 437|22 September 2005 nature

NEWS & VIEWS FEATURE

PHARMACEUTICALS

A new grammar for drug discovery

Mark C. Fishman and Jeffery A. Porter

To realize the potential of the genome for identifying candidate drugs we must move beyond individual genes and proteins. The signalling pathways in cells provide the right level for such analyses.

DRUG DISCOVERY

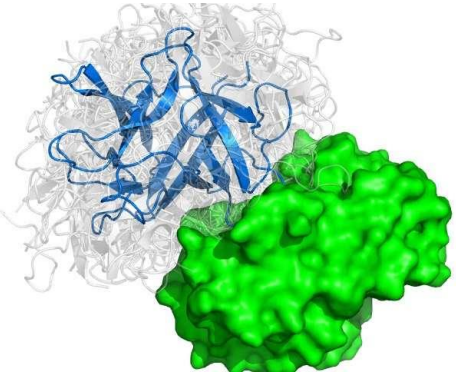
Sci Trans Med (2014)

Turning the Titanic

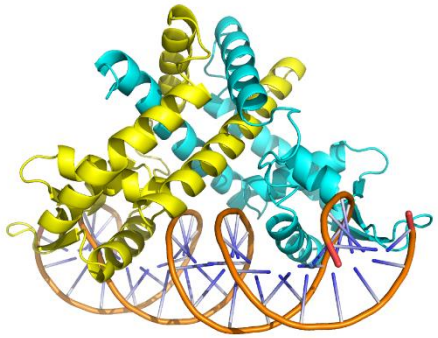
Underestimated the complexity of human biology!

Mismatched Complexity of Biological Targets and Small Molecules

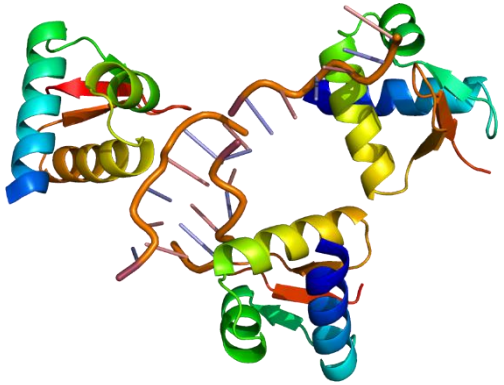
Protein-protein



DNA-protein



RNA-protein

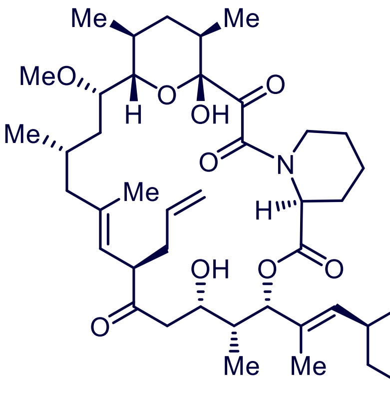


Current Limitations

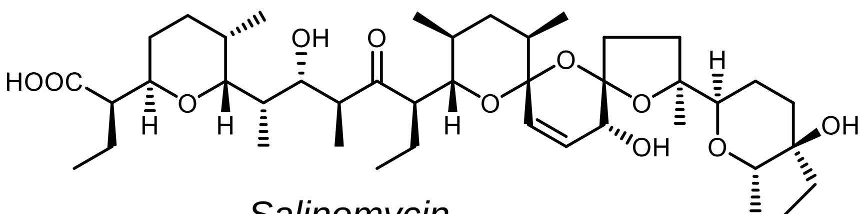
- Limited or no structural biology knowledge as the starting point
- Targets related to transcription and translation machinery
- Mapping large surface area by traditional small molecules is not effective by current approaches

- In general, small molecules are enriched with heterocyclic compounds; not attractive for targets related to multi protein-protein, DNA/RNA-protein interactions
- Lack of our ability to handle these challenging targets classifies them as “undruggable”
- Severely lack of “compounds” within pharma for undertaking “next generation targets”!

Why Looking at Natural Products?

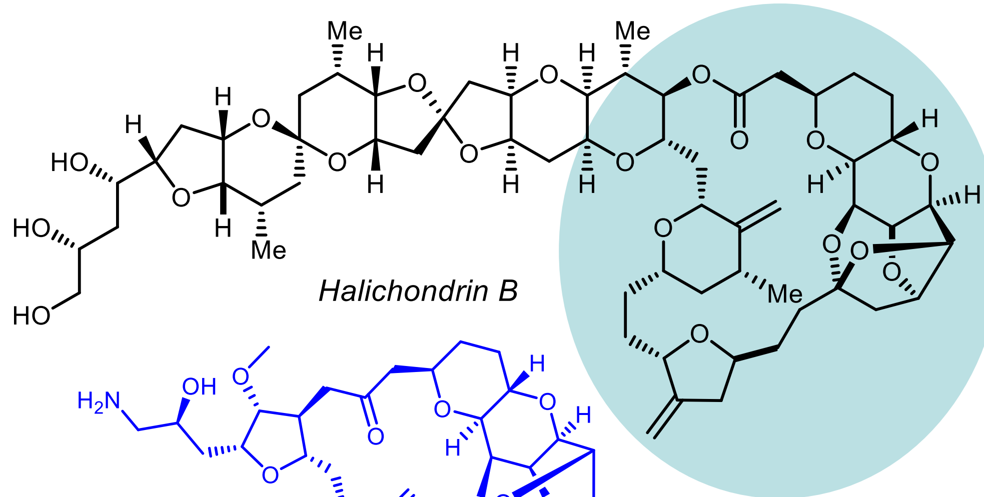


FK506

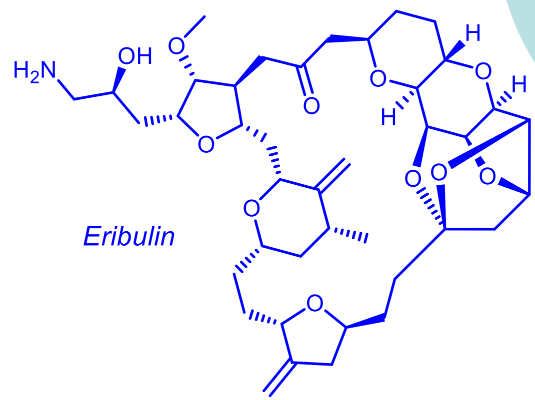


Salinomycin

(for cancer stem cells)



Halichondrin B



Eribulin

The most complex synthetic compound as drug!

- Natural products (biologically validated chemical space) have an excellent track record as modulators of protein-protein interactions.
- Present complex 3D architectures and dense display of stereo-defined groups.
- Due to complex structures, present a challenging task in taking them forward.
- Can serve as a good source of inspiration for developing sufficiently complex, novel scaffolds in the drug discovery arena!

Building A Macrocyclic Natural Product-inspired Chemical Toolbox For “Undruggable” Targets

Bioactive Natural Products

Natural Product Inspired Sub-structures

Natural Product Fragments as Sub-structures

Exploring Macrocyclic Chemical Space!

- Cyclic compounds
- Large surface area
- Pre-organization
- Less freely rotating bonds
- Enhanced cell permeation

Key features in our design:

- 3D architectures; sufficient complexity
- stereochemical and skeletal diversity
- synthesis in a reasonable time-scale
- easy to follow-up medicinal chemistry studies
- ease of scalable synthesis is attractive in our designs

Our Chemical Toolbox Platform

See these research pares from Arya Research Team:

*Chem. & Biol.*163 (2005)
Curr. Opin. Chem. Biol. 247 (2005)
Chem. Rev. 1999 (2009)

Our Track Record in This Arena

Diversity-Based Organic Synthesis in the Era of Genomics and Proteomics**

Prabhat Arya,* Doug T. H. Chou, and Myung-Gi Baek

Angew. Chem. Int. Ed. **2001**

Natural-product-like chiral derivatives by solid-phase synthesis

Prabhat Arya* and Myung-Gi Baek

Curr. Opin. Chem. Biol. **2001**

Chemistry & Biology, Vol. 9, 145–156, February, 2002, ©2002 Elsevier Science Ltd. All rights reserved. PII S1074-5521(02)00105-9

Toward High-Throughput Synthesis of Complex Natural Product-Like Compounds in the Genomics and Proteomics Age

Review

RESCUING COMBICHEM

Diversity-oriented synthesis aims to pick up where traditional combinatorial chemistry left off

STU BORMAN, C&EN WASHINGTON

Natural product-like chemical space: search for chemical dissectors of macromolecular interactions

Ayub Reayi and Prabhat Arya

Curr. Opin. Chem. Biol. **2005**

The natural-product-like compounds produced in DOS have a much better shot at interacting with desired molecular targets and exhibiting interesting biological activity.

Chem. & Eng. News **2004**
(statement from Prabhat Arya)

Chemistry & Biology, Vol. 12, 163–180, February, 2005, ©2005 Elsevier Ltd All rights reserved. DOI 10.1016/j.chembiol.2005.01.011

Exploring New Chemical Space by Stereocontrolled Diversity-Oriented Synthesis

Review

Chem. Rev. **2009**, *109*, 1999–2060

1999

Advances in Solution- and Solid-Phase Synthesis toward the Generation of Natural Product-like Libraries

Jyoti P. Nandy,[†] Michael Prakesch,[†,‡] Shahriar Khadem,[†,§] P. Thirupathi Reddy,[†] Utpal Sharma,[†] and Prabhat Arya*[,†,‡]

Ontario Institute for Cancer Research, MaRS Centre, South Tower, 101 College Street, Toronto, Ontario M5G 1L7, Canada, Steacie Institute for Molecular Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, Ontario K1A 0R6, Canada, and Department of Chemistry, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada

CHEMICAL REVIEWS

Review

pubs.acs.org/CR

2014

Small Molecule Modulators of Protein–Protein Interactions: Selected Case Studies

Madhu Aeluri,[†] Srinivas Chamakuri,[†] Bhanudas Dasari,[†] Shiva Krishna Reddy Guduru,[†] Ravikumar Jimmidi,[†] Srinivas Jogula,[†] and Prabhat Arya*

Dr. Reddy's Institute of Life Sciences (DRILS), University of Hyderabad Campus Gachibowli, Hyderabad 500046, India

Examples of Our Early Work

1

Natural Product-Inspired,
Functionalized 14- and 17-Membered Rings
Macrocyclic Toolbox

2

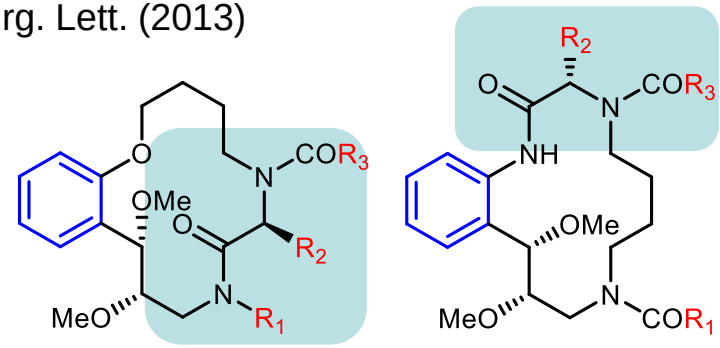
Indoline / Tetrahydroquinoline (Alkaloids)
and Benzofuran (Flavonoids)-Inspired
Macrocyclic Toolbox

3

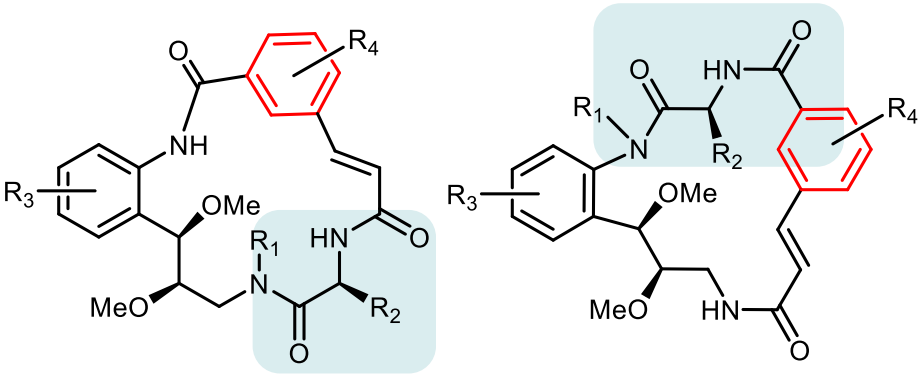
Glyco-based Macrocyclic Toolbox

Examples of Our Early Work (Contd.)

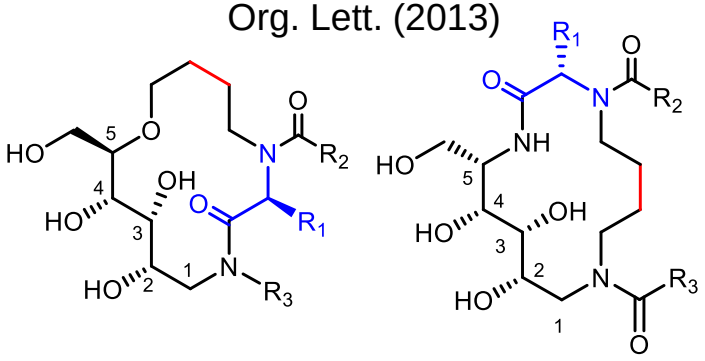
Org. Lett. (2013)



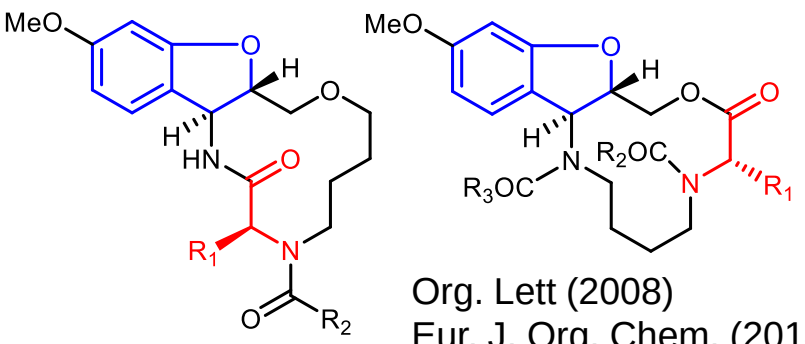
Eur. J. Org. Chem. (2013)



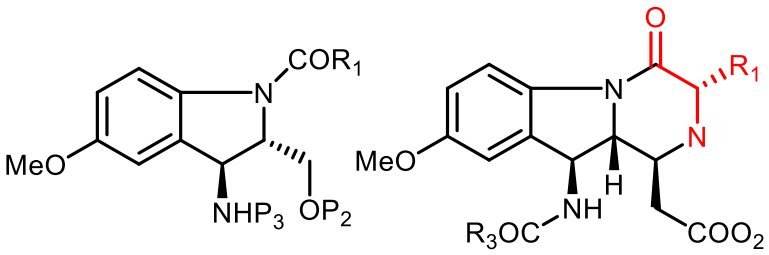
Org. Lett. (2013)



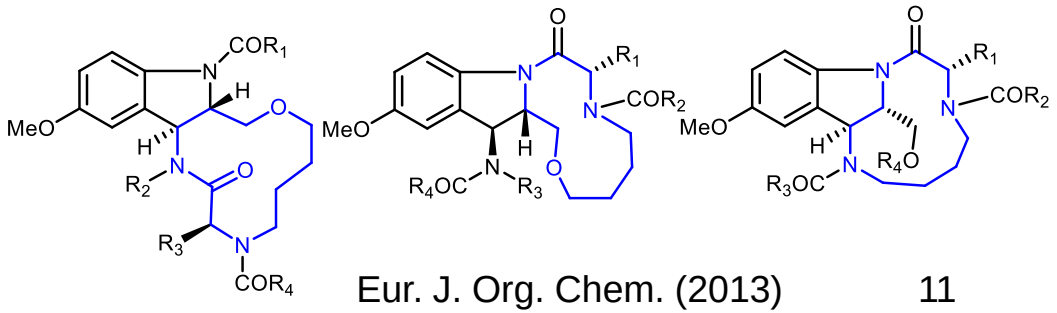
Org. Lett (2008)
Eur. J. Org. Chem. (2014)



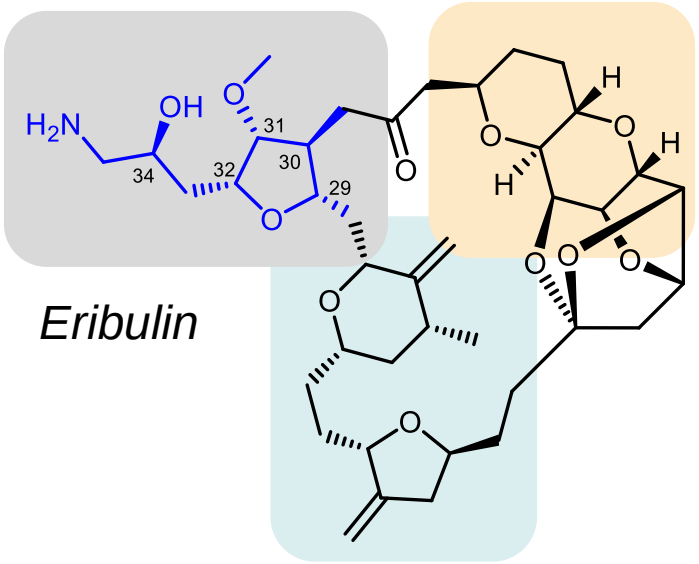
Angew Chem (2005)



Eur. J. Org. Chem. (2013)

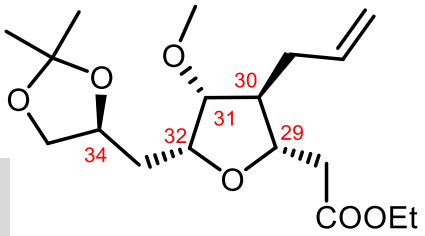


Example: Macrocyclic Toolbox based on Eribulin Sub-structures



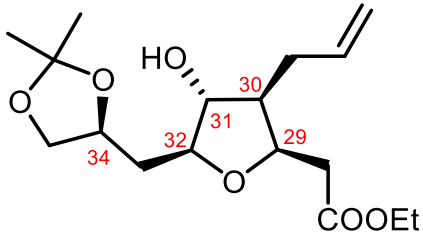
Practical and scalable synthesis

A

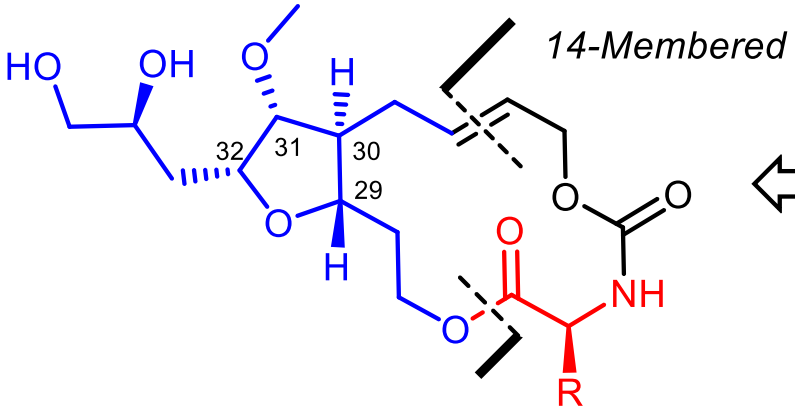


Precise fragment-based

B

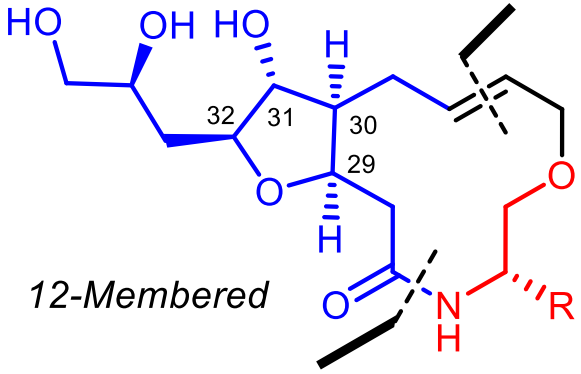


Diastereomeric fragment-based



A

B



Org. Lett. 468-471 (2015)

Applications of Our Chemical Toolbox in Finding Active Small Molecules (as Early Stage Drug Candidates) for Challenging “Undruggable” Targets:

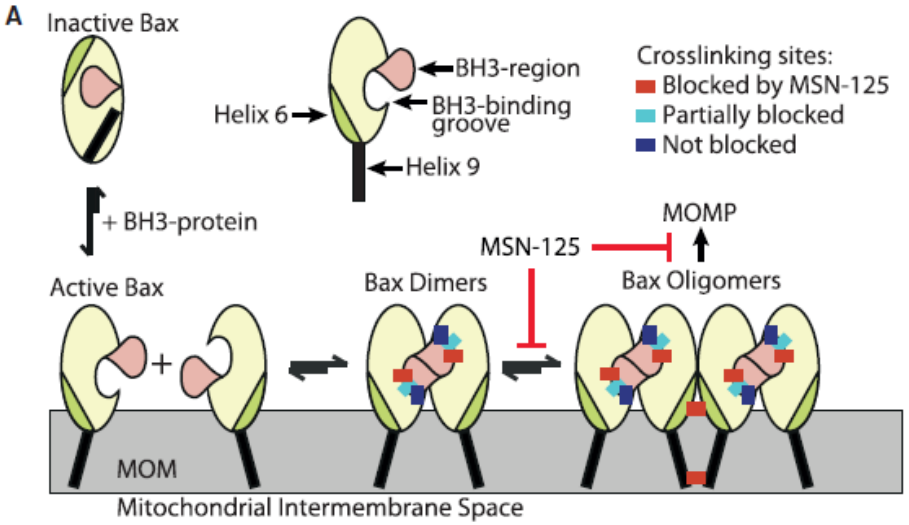
Three Case Studies

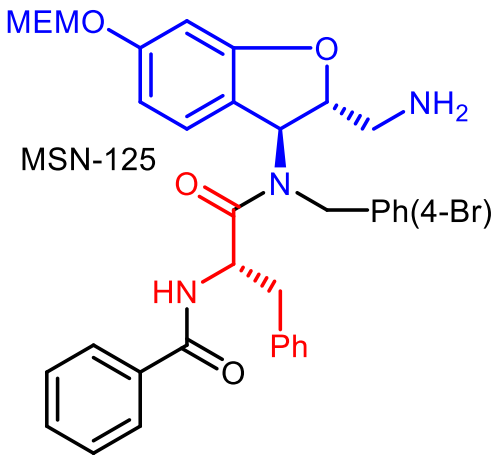
Our Chemical Toolbox-based Screening Application

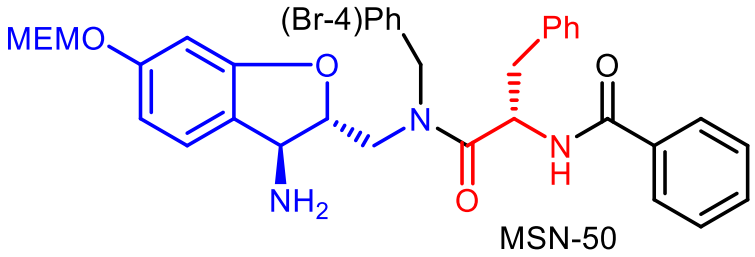
Cell Chemical Biology

A Small-Molecule Inhibitor of Bax and Bak Oligomerization Prevents Genotoxic Cell Death and Promotes Neuroprotection

2017



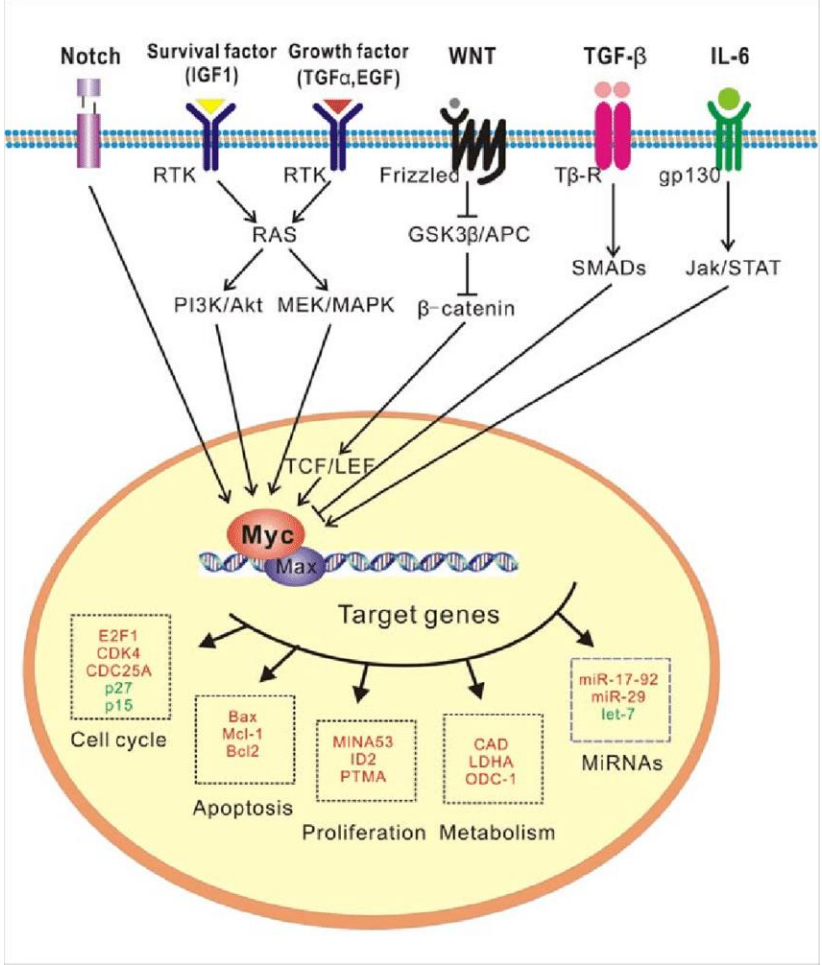




In collaboration with with David Andrews Lab, Univ of Toronto

During the academic tenure (from Arya Group)

Going in for c-Myc: Rationale



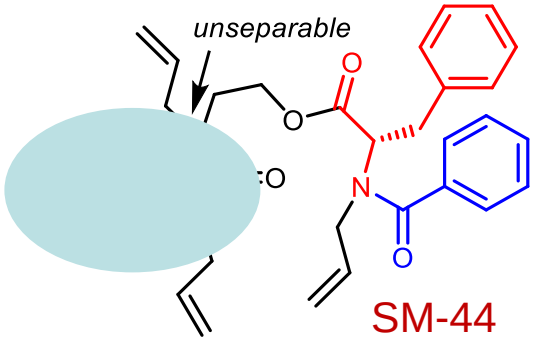
- "*Undruggable*"
- Frequently mutated and overexpressed in many human tumors
- A transcription factor
- Responsible for upregulation of several genes related to cell cycle, apoptosis, and cellular transformation which are directly associated with cancer
- Despite working on this target for more than 3 decades, the current chemistry approaches have not led to producing the effective drug candidates!

Note: Given the track record of working with "undruggable" targets (for ex. BAX), our chemical toolbox platform provide an excellent opportunity to tackle this validated target which is challenging the community for long!

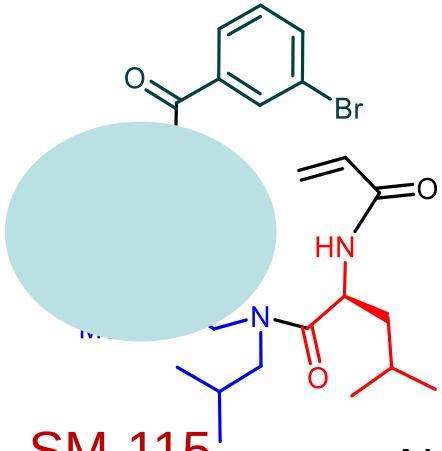
Nat Rev Cancer 2017; Nat Rev Cancer 2008 (Reflecting on 25 Years with Myc)

A Glimpse of Our Data

WST1 Screening Assay

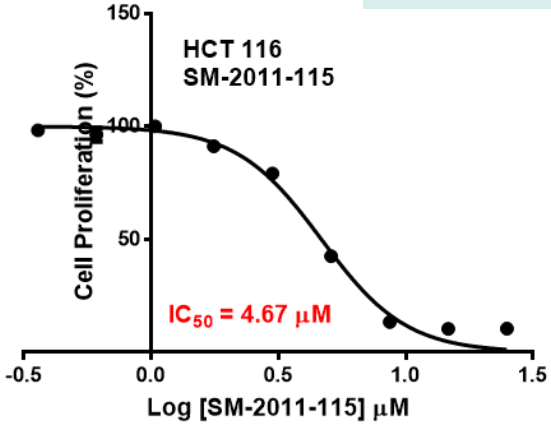


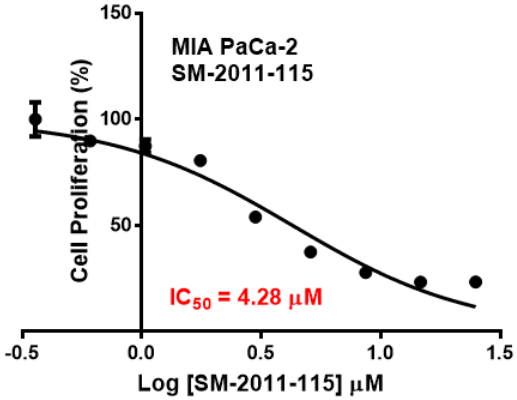
SM-44



SM-115

with SM-115



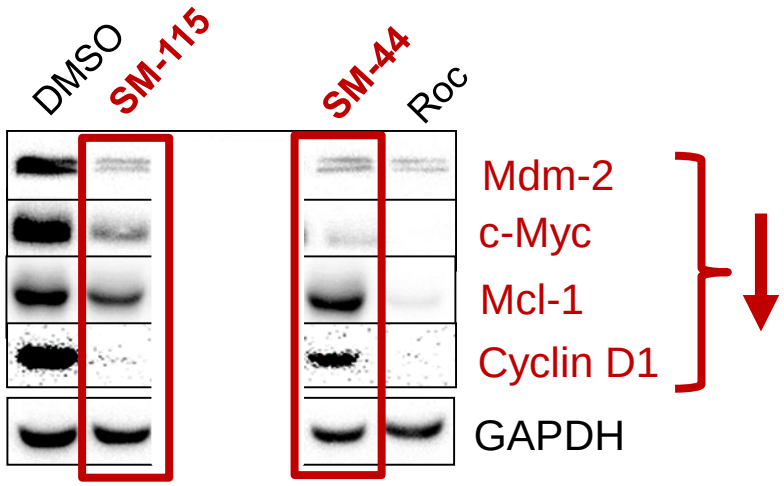


Note: First-in-class small molecule inhibitors of c-Myc translation

A Glimpse of Our Data (contd.)

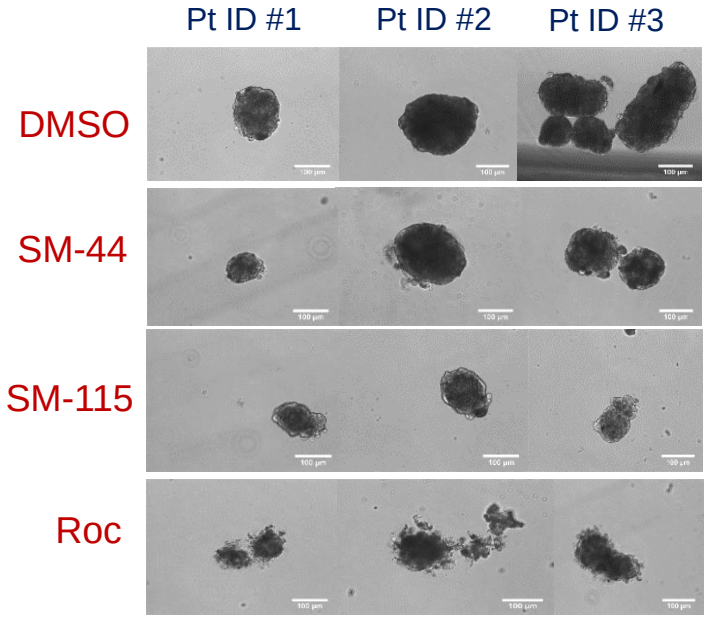
Western Blots

HCT 116 @ 24 h



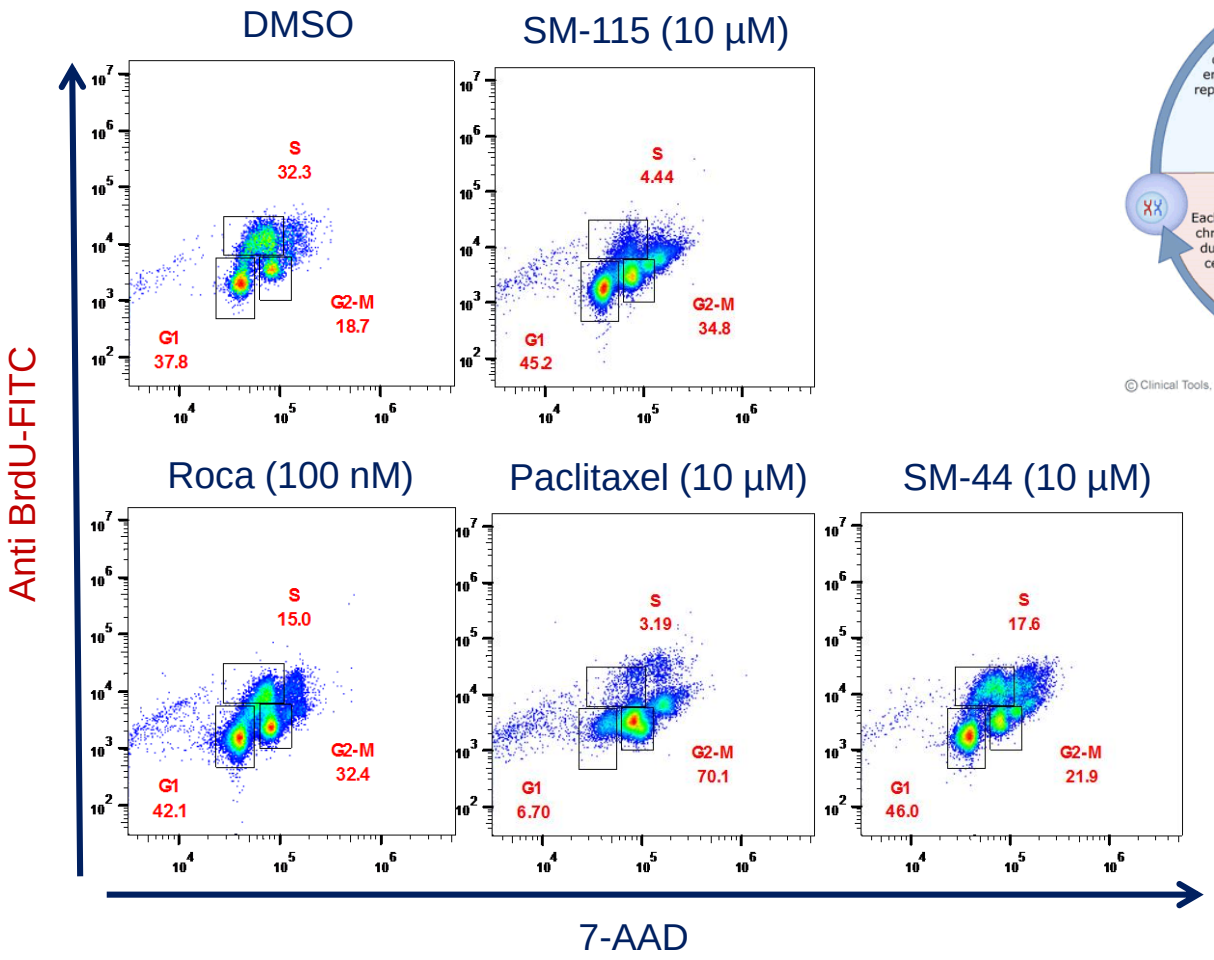
Serious decrease in expression level of c-Myc and target associated molecules like MDM-2, Mcl-1 and Cyclin D1!

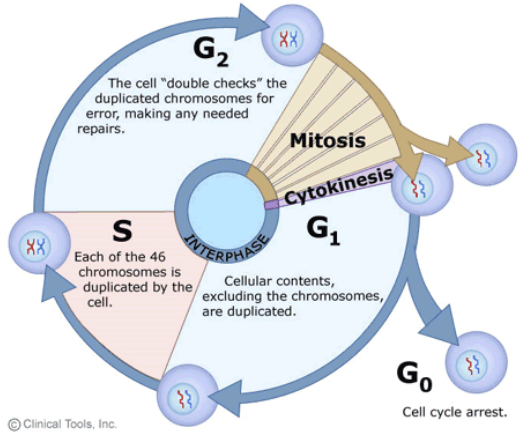
Effect on Patient-derived Tumorspheres at Day 12



Note: First-in-class small molecule inhibitors of c-Myc translation

Flow Cytometry (BrdU Probe for Cell Cycle)





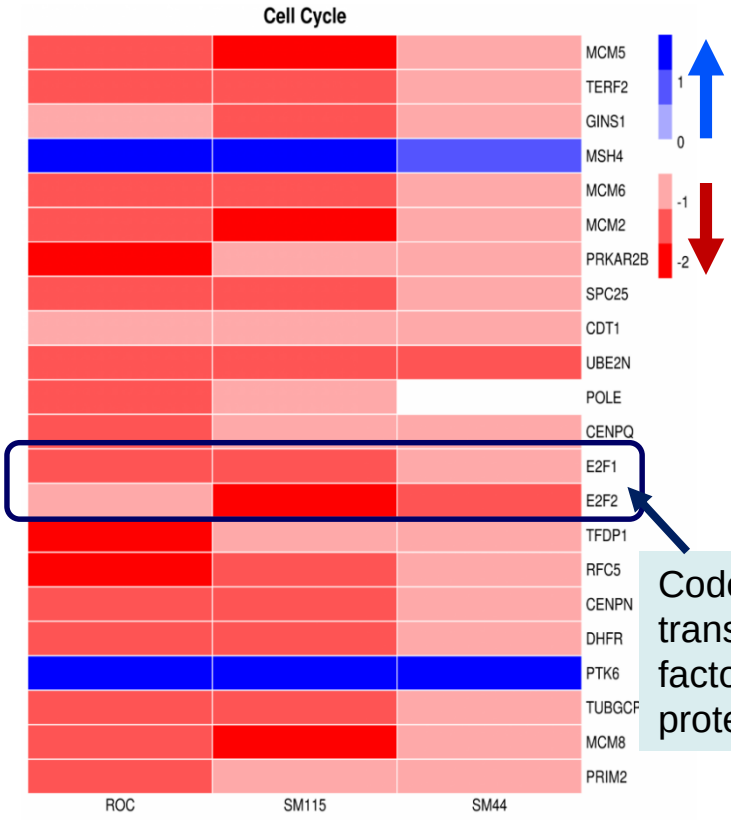
Cyclin D1
CDK4

	G1	S	G2/M
DMSO	36.6	32.3	18.6
SM-115	43	**4.44**	34.5
SM-44	43.2	17.6	21.7
Rocaglamide	36	15	31.1
Paclitaxel	6.19	3.19	69.4

Roca = Rocaglamide

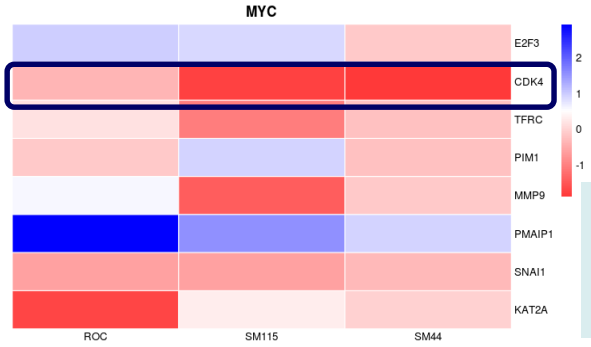
Note: G1 arrest – possible downregulation of Cyclin D1 and CDK4

Our Transcriptomic Study



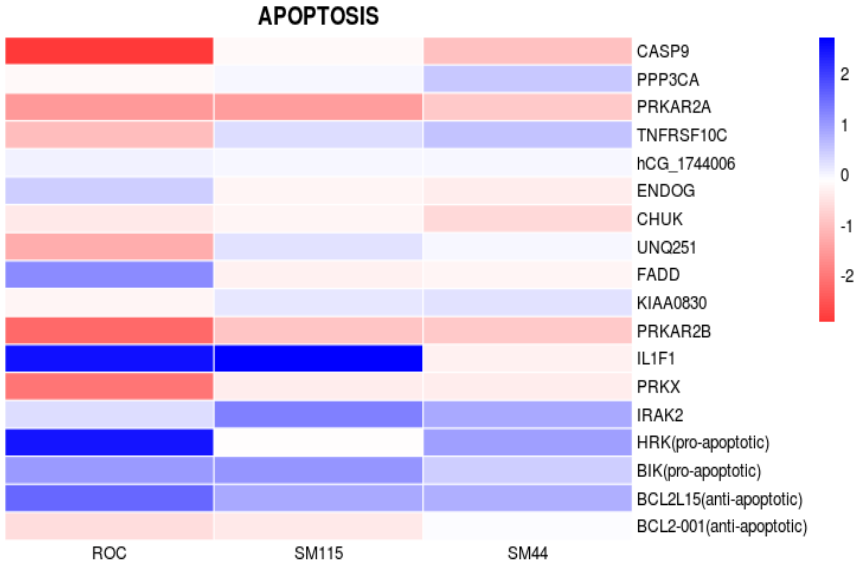
Codes for transcription factor proteins

Note: A similar pattern in cell cycle gene set (see ROC vs SM115 and SM44)



CDK4 gene crucial in cell cycle from G1 to S phase

Note: Downregulation of CDK4 with SM115 and SM44



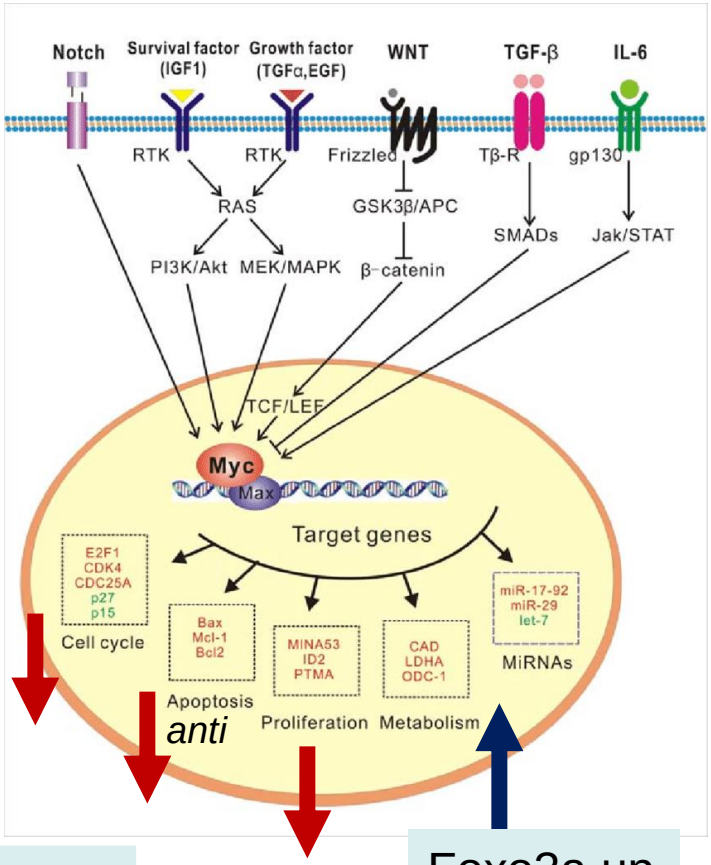
Down regulation of anti-apoptotic gene

Upregulation of pro-apoptotic genes

Note: similar upregulation for BIK (pro-apoptotic gene), BCL2-001 (anti-apoptotic gene)

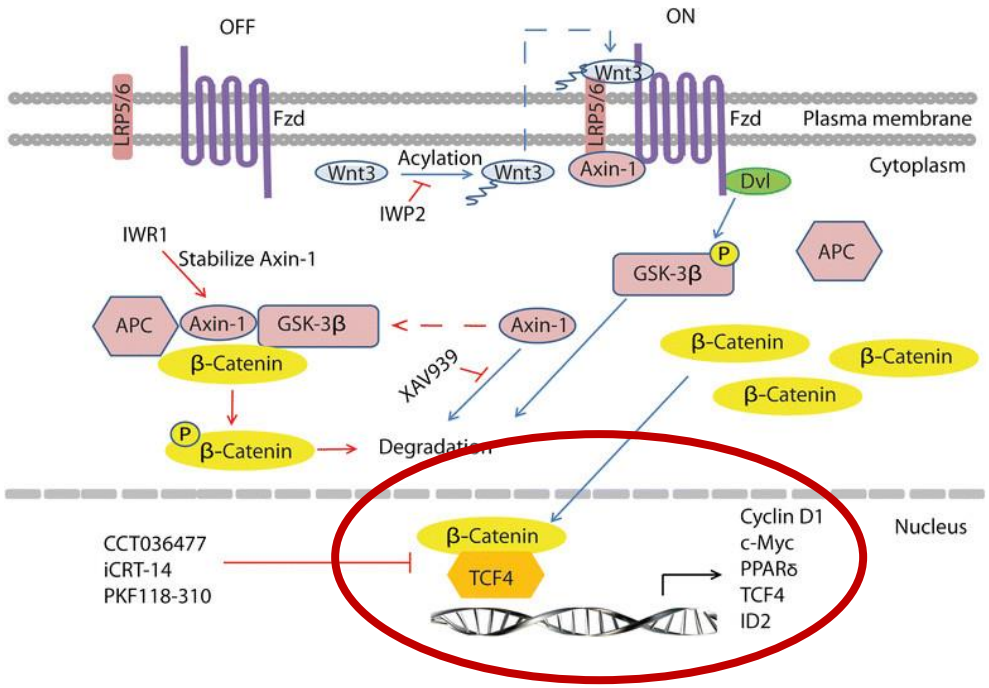
Comparison of data with Rocaglamide (ROC) and our two actives (SM115 and SM44)

Highlights of Our Program



1. Discovered two novel families of small molecules as c-Myc translation inhibitors.
2. Our actives are effective in inhibiting the expression levels of c-Myc, MDM-2, Mcl-1 and Cyclin D1!
3. Our actives are promoters of apoptosis and also exhibit the cell cycle arrest at the G1 phase.
4. Our actives can be considered as the *functional mimics of Rocaglamide*, a natural product, well-known as the c-Myc translation inhibitor.
5. Our cellular studies are supported by the NGS data (for ex, related to seeking info on mode of action)
6. To our knowledge, there are no small molecules known to date; our work opens up a new direction in the field of c-Myc translation-based cancer drug discovery!

Going in for Wnt: Rationale



Small molecule inhibitors of Wnt transcription

Note: no drugs are developed to date

Nat Rev Drug Disc (2014)

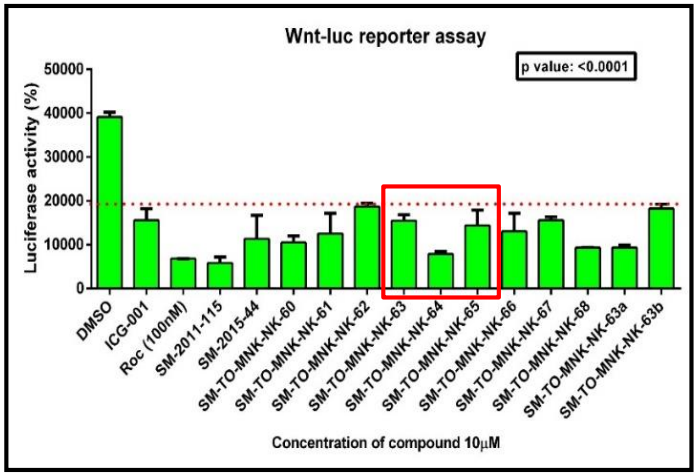
- Undruggable
- Play a key role in stemness, EMT, cancer stem cells and metastasis.
- Aberrant regulation is a common theme seen across many tumor types.
- A highly attractive target due to its role in development and maintenance of cancer stem cells.
- Several small molecules are in clinic but most are not very effective.
- ICG001 is a small molecule going forward in clinic as the Wnt transcription inhibitor.

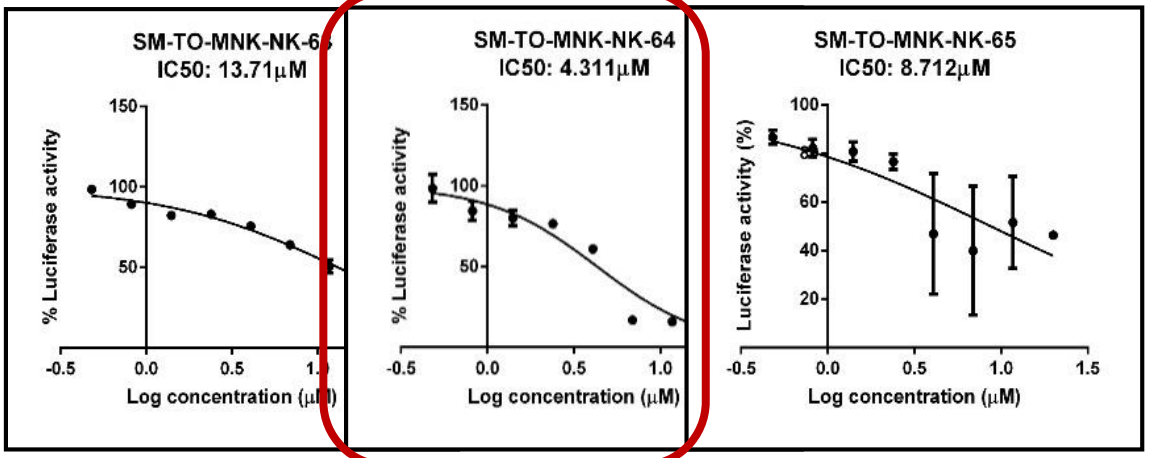
Note: Given the track record of working with "undruggable" targets (for ex. BAX), our chemical toolbox platform provide an excellent opportunity to tackle this target which is challenging the community for long!

Wnt Program: A Glimpse of Our Data

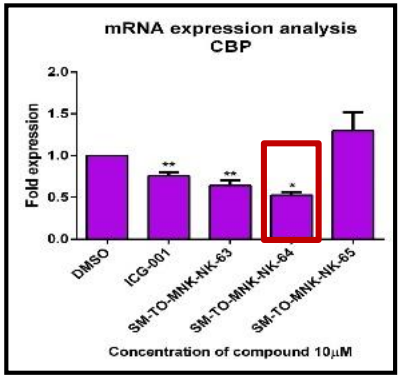
Wnt Luciferase Assay

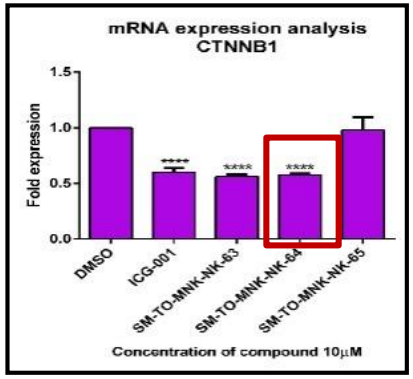
Use of ICG001 as the control

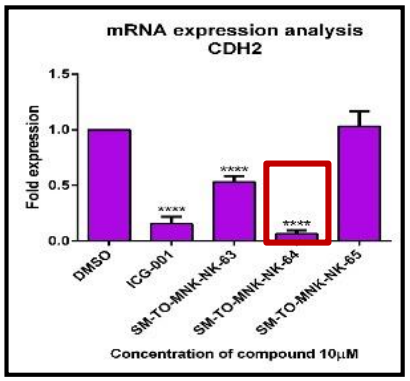


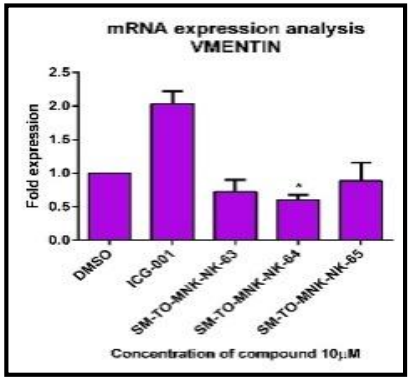


RT-PCR



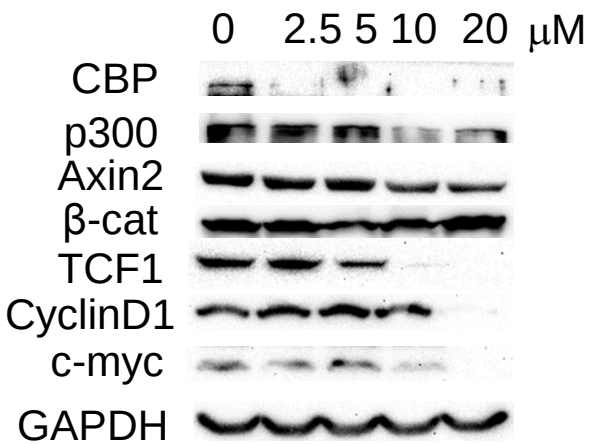




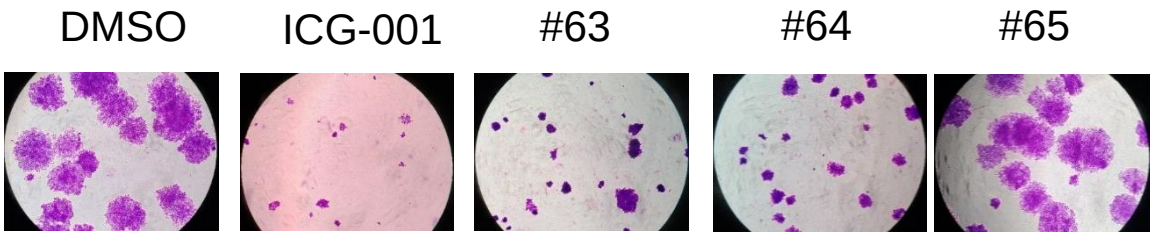


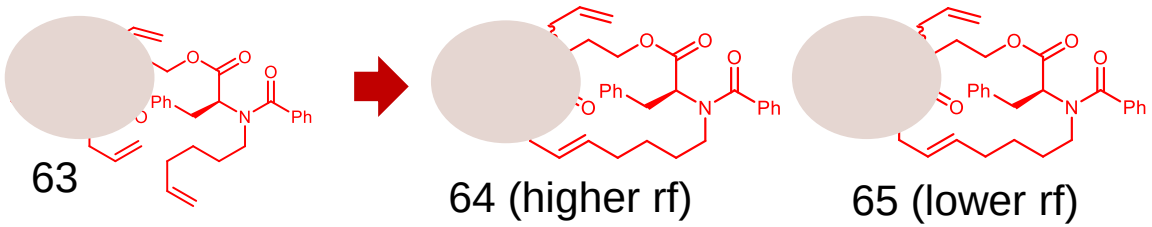
Wnt Program: A Glimpse of Our Data (contd.)

Western Blots



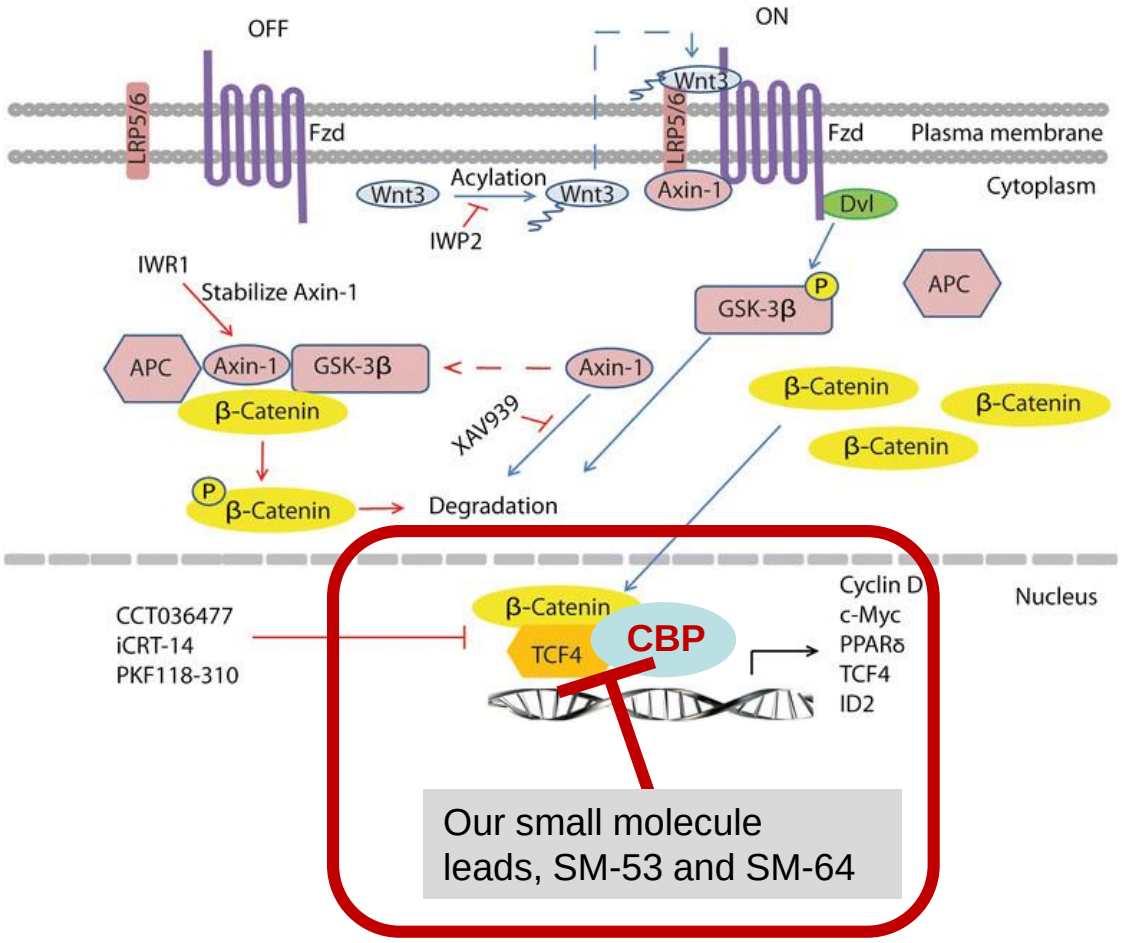
Colony Formation Assay





64 and 65 are diastereomers

Our Working Model



The Next Steps:

- Hit to lead studies (almost finished)
- Thorough evaluation on patient-derived tumorspheres and organoids
- Precise Target ID information
- Detailed studies with tumor metastasis, migration, stem cell maintenance, EMT related to cancer stem cells.
- Finish all pre-clinical studies; reaching the IND stage

Our Patents Portfolio To-date

Wnt Transcription Inhibitors

1. Natural Product-Inspired Macrocyclic Compounds as Wnt Transcription Inhibitors. US Patent Application No. 62862147, Filed June 17, 2019.
2. Natural Product-Inspired Compounds as the Inhibitors of Wnt Transcription Machinery. US Patent Application No. 62863287, Filed June 19, 2019.
3. Substituted furan-based macrocyclic compounds as the Inhibitors Wnt Transcription, Patent in progress, expected filing date: Sept-Oct 2021
4. Isatin-based 16-membered, macrocyclic compounds as the Inhibitors Wnt Transcription, Patent in progress, expected filing date: Sept-Oct 2021

c-Myc Translation Inhibitors

1. Natural Product-inspired Acyclic and Macrocyclic Compounds as c-Myc Translation Inhibitors. US Patent Application No. 62938342, Nov 21, 2019.
2. Inhibition of c-Myc Translation by Natural Product-inspired Macrocyclic Compounds. US Patent Application No. 62947551, Filed Dec 13, 2019.

Our Strong Points and Going Forward

- ✓ Chemical Toolbox: Cutting edge leadership; working in this domain >20 years.
- ✓ 52 PDFs and 12 PhD students contributed to developing novel synthesis methods.
- ✓ Ownership in several novel scaffolds: 50 published; 250 unpublished scaffolds.
- ✓ Our compounds are highly unique (not me too type) and useful to mapping a large surface area for challenging targets.
- ✓ Identified novel small molecules as Wnt transcription and Myc translation inhibitors (filed 4 US prov. patents).
- ✓ Working with BI and one academic group for building a focused macrocyclic toolbox for their needs.

- ❖ Seeking funds to building a macrocyclic toolbox with 20-40K novel small molecules (highly attractive from IP direction) over 3 years period.
- ❖ In addition to utilizing these small molecules in our own drug discovery programs, they can also be shared with others through various business models.
- ❖ Could also build a focused toolbox (through consultation) matching the needs of specific programs of others.

Note: the detailed information on our published and unpublished scaffold data base can be made available as required