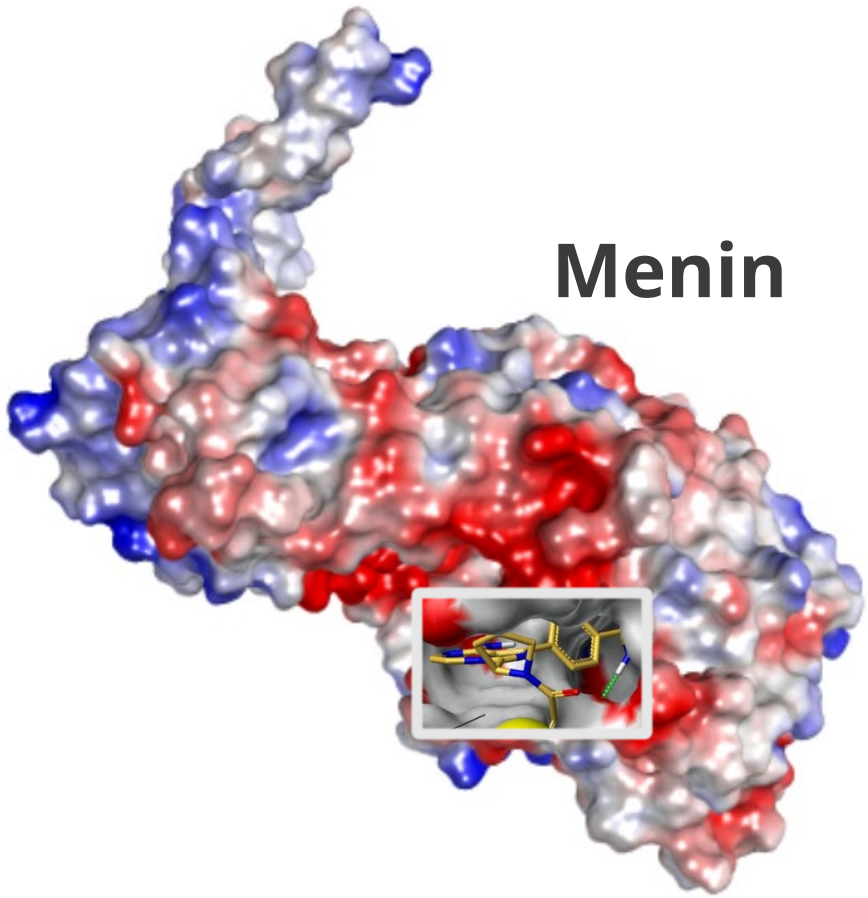
Backgrounder

BMF-219's Mechanism of Action In Diabetes and Oncology

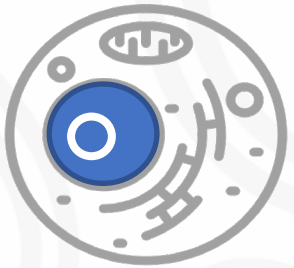
biomea FUSION™

BMF-219’s Mechanism of Action

BMF-219 Exerts Transient Decrease in Menin Protein



Menin Half Life Varies By Compartment



Half Life in Cytoplasm: <1hr

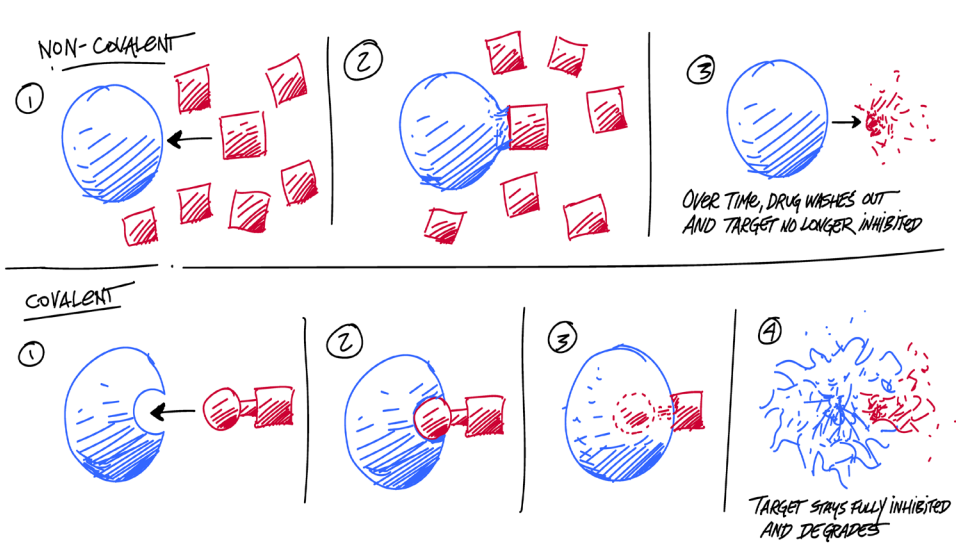
Half Life in Nucleus: 6-8 hrs

Menin's half-life in nucleus is most relevant for pharmacological intervention

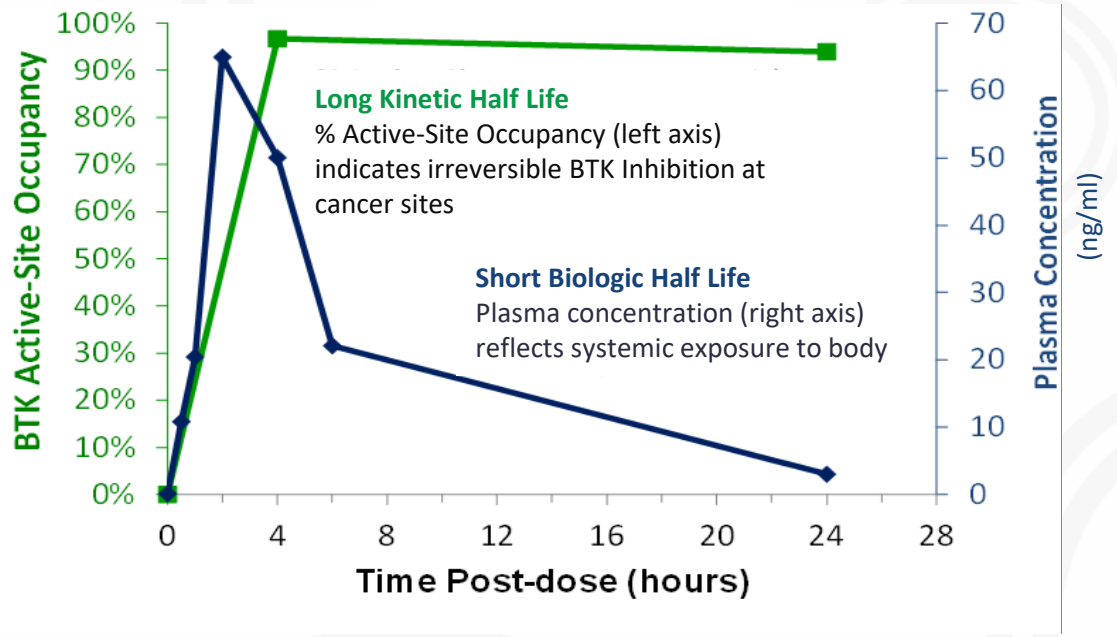
- BMF-219 produces **robust decrease in expression of target protein** (Menin)
- **Effect continues beyond established nuclear half-life** of menin, indicating robust effect that is not impacted by protein turnover

BMF-219 is a Covalent Binding Agent – High Affinity and Long Residence Time

Non-Covalent vs Covalent Inhibition



Covalent Inhibition Profile

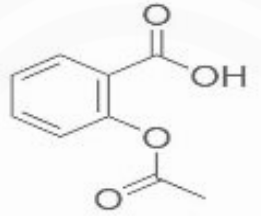


Target inhibition persists after the drug has been cleared from the system leading to lower drug doses and less frequent dosing regimens versus non-covalent approaches

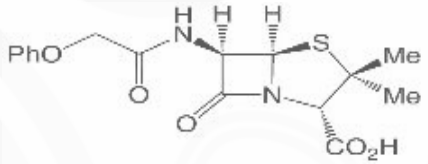
Covalent Inhibitors - A History of Medical & Commercial Success

Notable Covalent Inhibitors

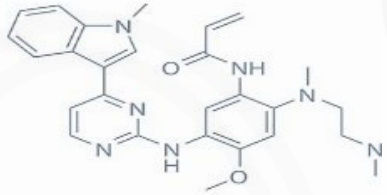
Aspirin

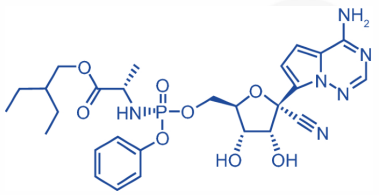


Penicillin

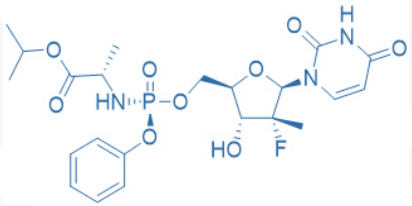


Osimertinib (TAGRISSO)

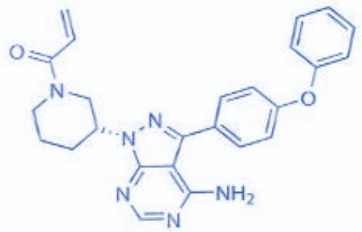




Remdesivir (VEKLURY)



Sofosbuvir (SOVALDI)



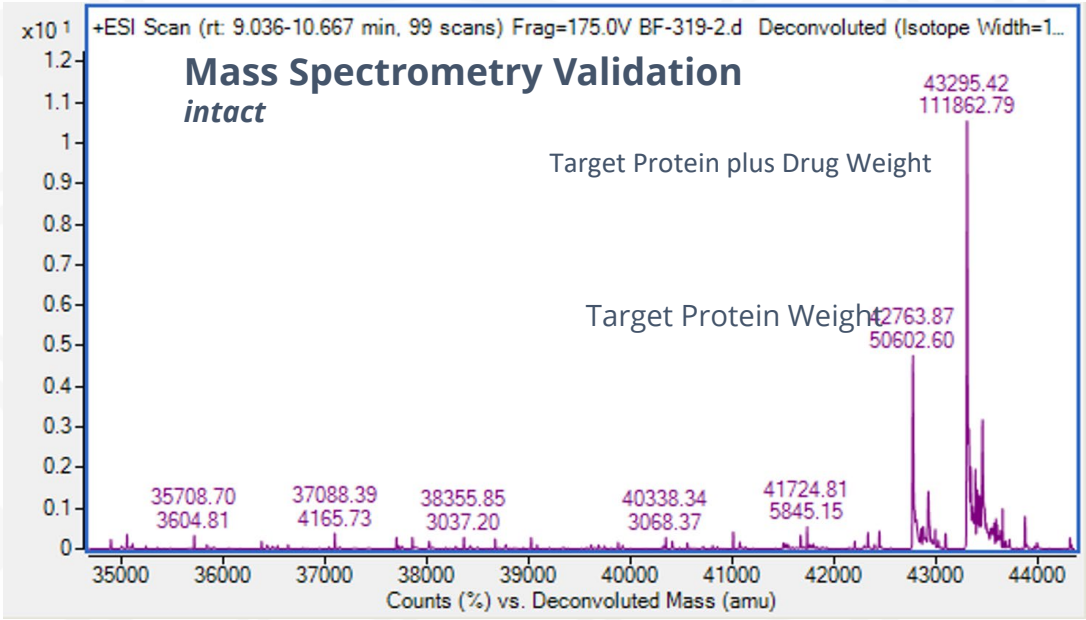
Ibrutinib (IMBRUVICA)

- **Aspirin** was the first commercialized covalent drug
- Notable precision oncology and infectious disease programs leverage covalent mechanisms
  - Precision Oncology**:**
    Osimertinib and **Ibrutinib** both target kinases and are used in subpopulations with specific genetic biomarkers
  - Antivirals**:**
    Remdesivir and **Tenofovir** both target reverse transcriptases and are leveraged to treat HCV and other viruses including HIV and COVID-19

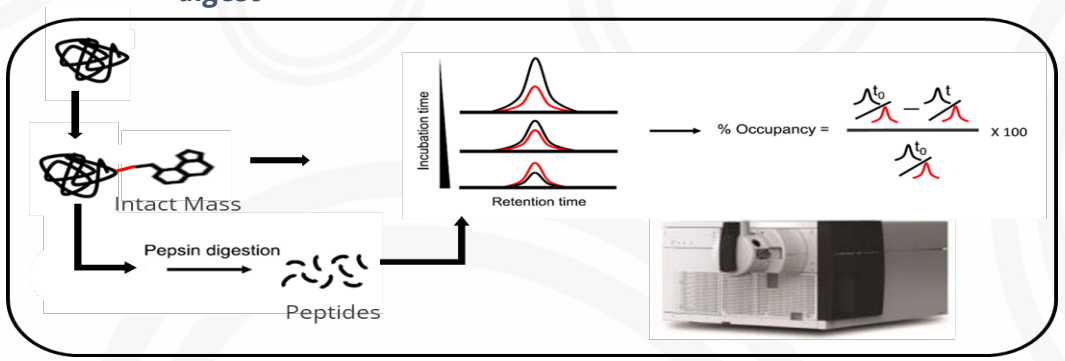
Compounds in Blue Were Co-Invented or Co-Developed by Biomea Fusion Senior Leadership

Biomea Fusion End-to-End Research Capabilities

- In-house chemistry and research labs with approximately 40 experienced R&D staff
- Established CRO relationships in US, Europe, China and India
- Biochemical, biophysical, and cellular assays run in house and at CROs
- Fast synthesis/assay testing cycle times
- In-house confirmation of covalent adducts by Mass Spectrometry (intact and digest)



Mass Spectrometry Validation
digest



Target identification to IND candidate in 18 months

Target to Hit

Covalent target/ligand validation
Visual integration of crystal structures of target and reactive cysteines

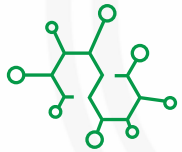
Utility:
Differentiated insights from X-ray crystal structures, identifying target cysteines

Custom Lead

Custom engagers
Proprietary AI platform with VR validation matches novel custom engagers to cysteines. No physical library screening.

Utility:
Covalent starting leads provided for AI/VR scoring

Lead Optimization



Custom scaffold creation
Custom built synthesis to create candidates with desired properties

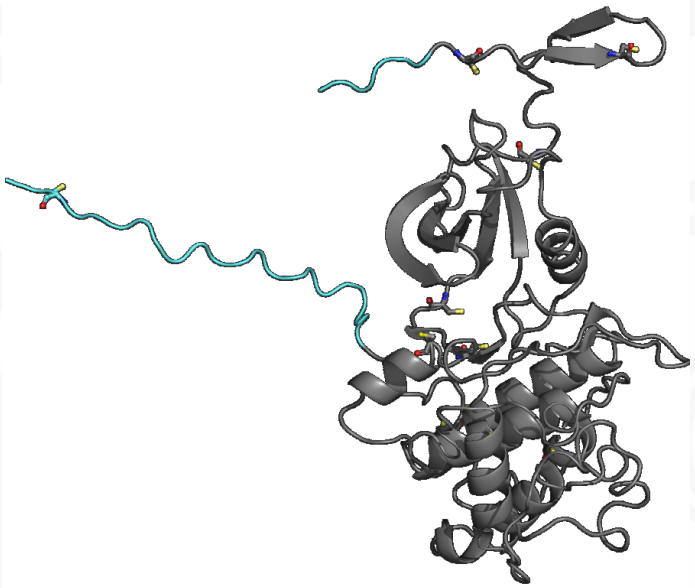
Utility:
AI/VR program platform yields 20-30 scaffolds, which are synthesized for in vitro testing

IND

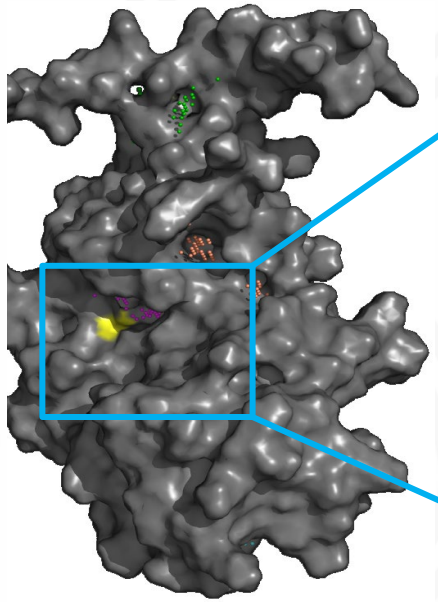
Refinement
Building in drug-like properties, optimizing PK/PD profile, and maintaining specificity

Utility:
Scaffolds are further refined with Mass spec, animal, and cell-based assays

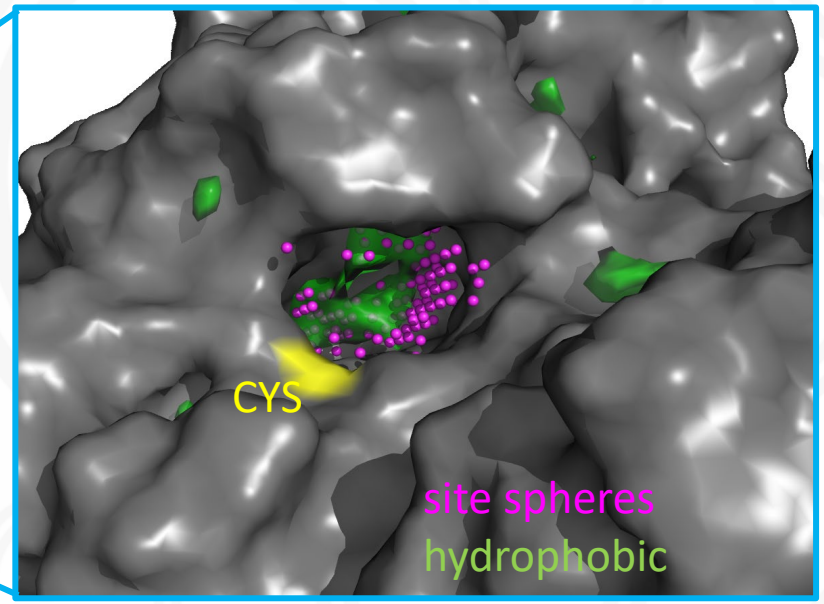
Biomea Fusion System – Discovery and Development of Novel Covalent Inhibitors against High-Value, Validated Disease Targets



- Predicted structures for ~23,400 human genes; 14,200 novel vs PDB.
- Analyze individual domains if needed – potential artificial inter-domain pockets
- Manual curation for high interest targets



- AlphaFold2.0 are apo (without ligand) structures
- Pocket identification using established methods "bindability" ranking



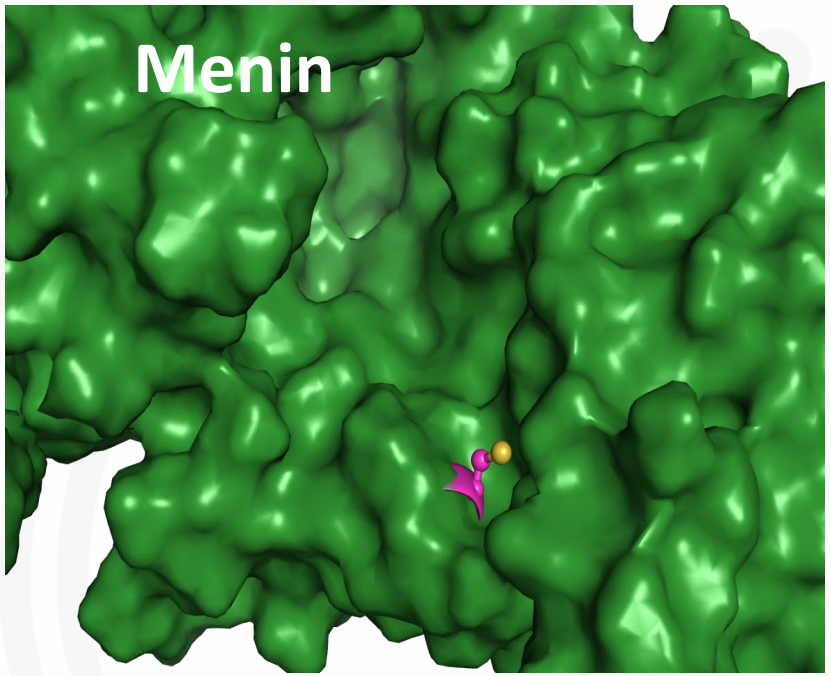
- Top ranking pocket with sufficient hydrophobic character

→ Virtual screening for ligands

→ Biomea Linker/Warhead Determination Protocol

→ Lead Molecule(s)

BMF-219: Evidence of Binding to Specific Cysteine in Menin



Targetable Cysteine	Binding Selectivity
CYS1	100.0%
CYS2	0.0%
CYS3	0.0%
CYS4	0.0%
CYS5	0.0%
CYS6	0.0%

Peptide Mapping Results Summary

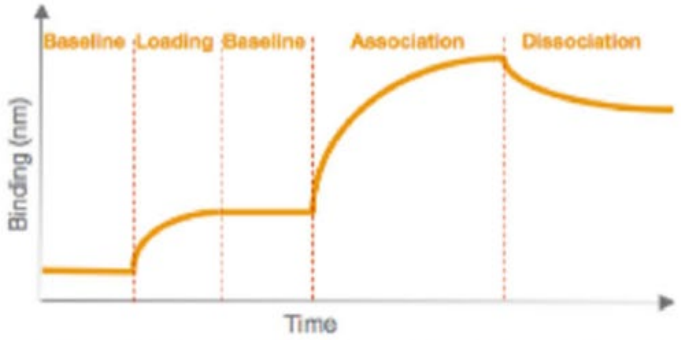
- Analyzed all reactions through Freestyle
- Only observed BMF-219 attached to Cys1 (Biomea numbering)
- Did not observe BMF-219 attached to any other cysteine

Peptide Mapping Data: BMF-219 binds only to single, desired target cysteine

BMF-219: Evidence of Target Engagement (Kd) with Menin

Compound	Kd (nM)
BMF-203	250
BMF-219 (Compound D)	<0.001
BMF-222	1,250
BMF-224	1,804
BMF-5	3,191

*Compound D displays a K_{dis} rate that supports covalent engagement

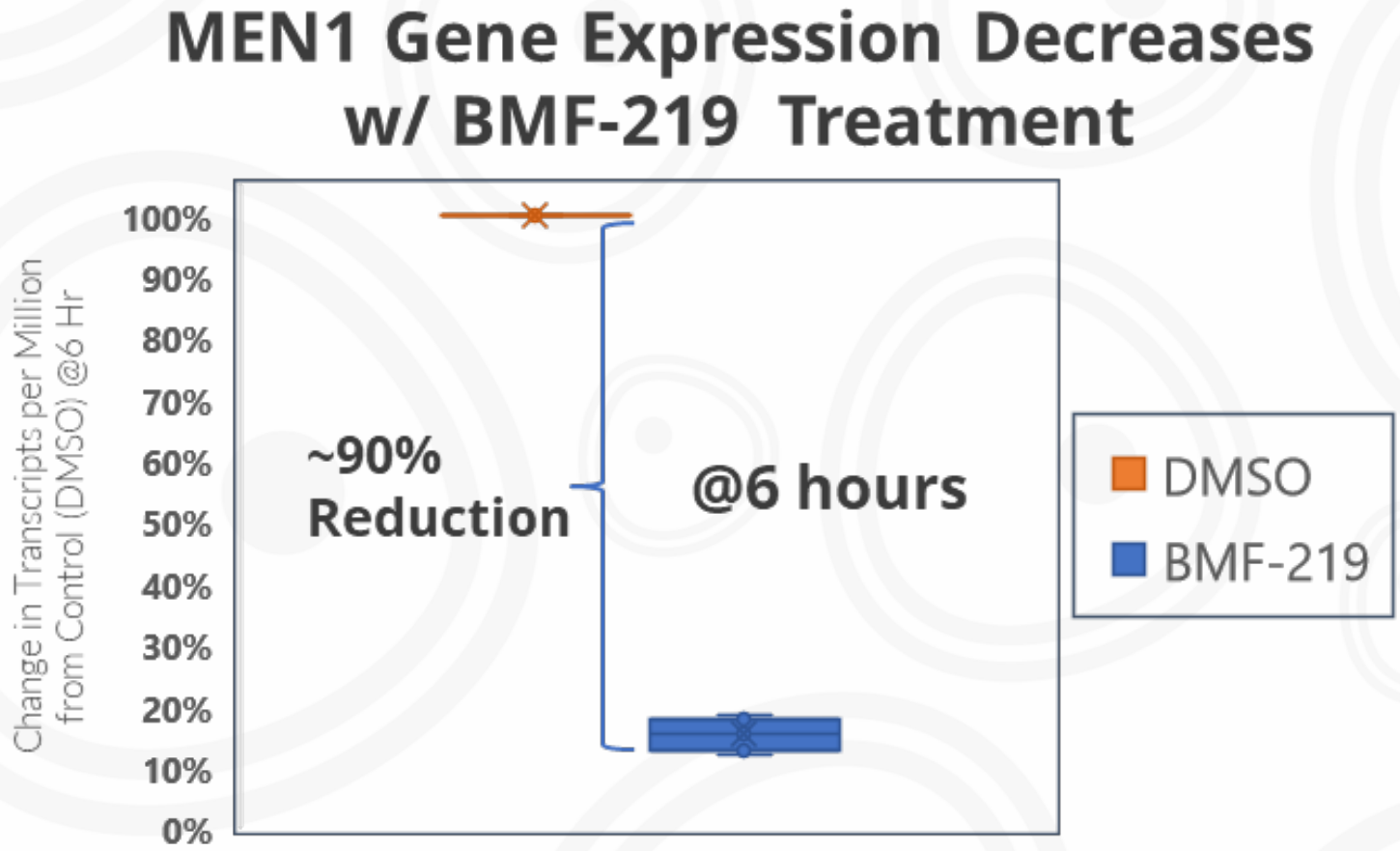


Measuring the shift over time enables the determination of binding

Comments:
Samples A-F were tested by Octet BMIA for affinity to Menin-Biotin.
SA sensors were loaded with Menin-Biotin
Binding constants were calculated for association and dissociation of 7 dilutions of each compound.
1:1 Curve Fits were applied and Global Fits were calculated as:

Analyte ID	K_D	k_{on}	k_{dis}	R^2
Compound A	1.478E-06	8.101E+02	1.197E-03	0.718
Compound B	9.965E-05	7.179E+02	7.154E-02	0.977
Compound C	2.274E-07	1.698E+03	3.861E-04	0.568
Compound D	<1.0E-12	4.009E+02	<1.0E-07	0.713
Compound E	7.049E-06	3.367E+03	2.373E-02	0.636
Compound F	9.461E-05	4.085E+02	3.865E-02	0.987

BMF-219 effectively Downregulates Menin Expression



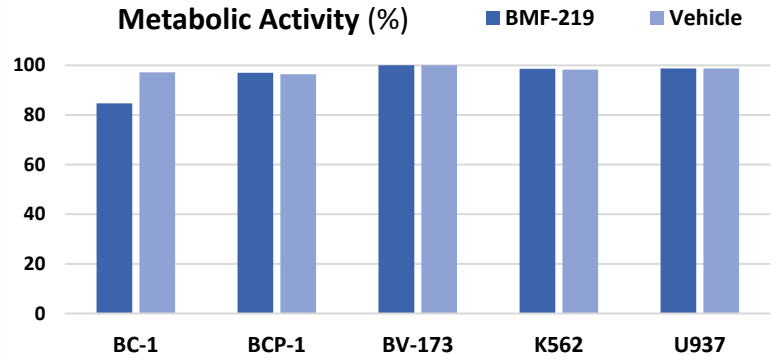
Clean Safety Profile Observed for BMF-219 in Nonclinical Toxicology Studies

✓ Kinase Screening

169 kinases screened; only **two** showed >50% inhibition with BMF-219

✓ Oncopanel Cell Line Screen

Minimal impact of BMF-219 on cell metabolism in leukemia and lymphoma cell lines that have **wild type MLL1**



✓ Safety Screen

SafetyScreen44 panel (CEREP/Eurofins Discovery)* showed **no meaningful impact** (>50% activation or inhibition)

*SafetyScreen44 *in-vitro* panel of 44 common selected targets to identify significant off-target interactions

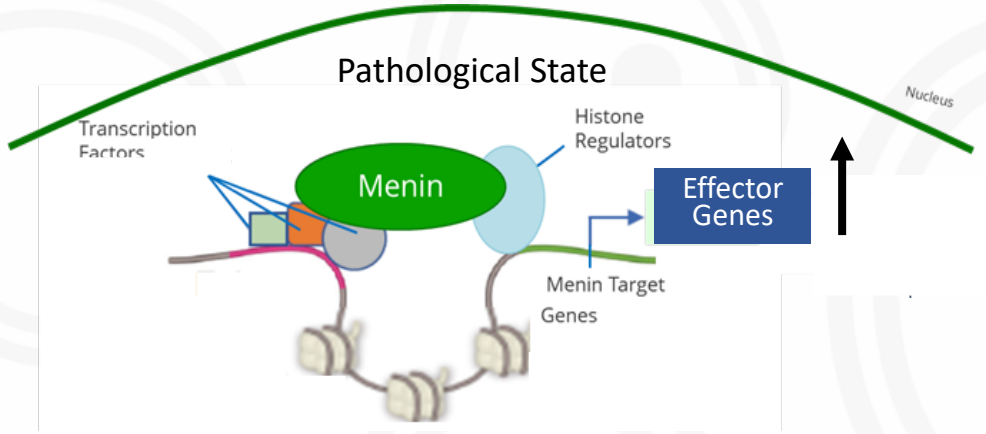
✓ Glutathione Reactivity

BMF-219 had **less reactivity than the approved covalent drugs omeprazole and neratinib**

Drug	Mean half-life (min)
Omeprazole	123.3
Neratinib	197.7
Ibrutinib	>360
BMF-213	322.3
BMF-214	>360
BMF-219	>360

BMF-219 Mechanism of Action - impact in Diabetes

Restoring Balance in Menin Dependents Diseases is Context Specific

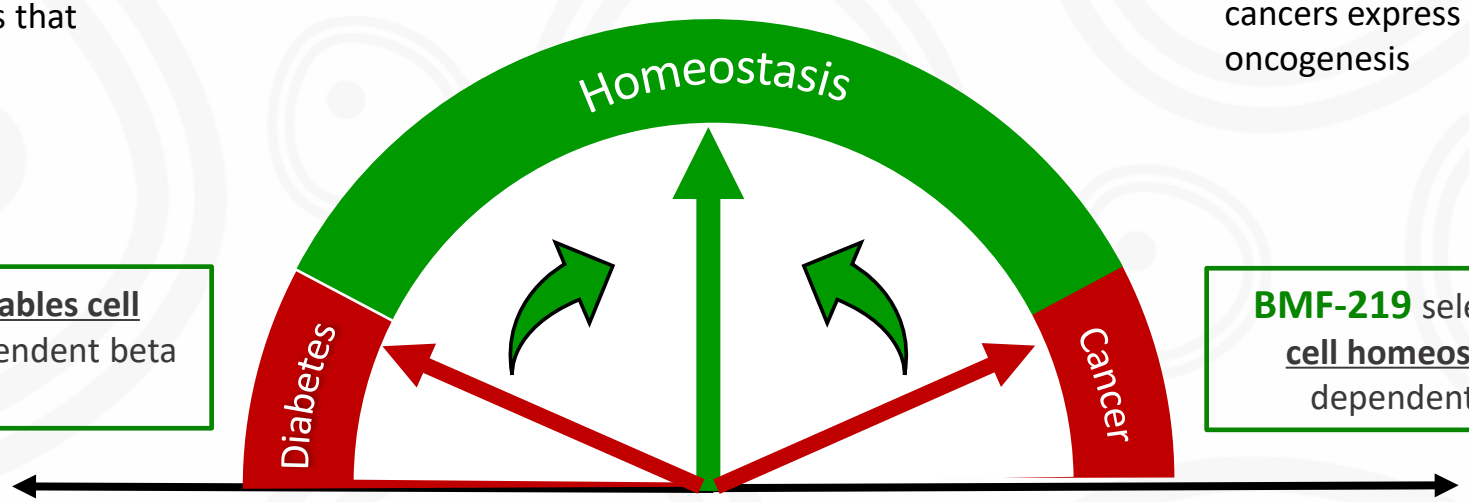


Treating Diabetes

Menin dependent effector genes in beta-cells express proteins that repress beta-cell growth

Treating Cancer

Menin dependent effector genes in certain cancers express or regulate proteins that drive oncogenesis



BMF-219 selectively **enables cell homeostasis** of menin dependent beta cells

BMF-219 selectively **enables cell homeostasis** of menin dependent cancer cells

Menin **suppressing** cell homeostasis

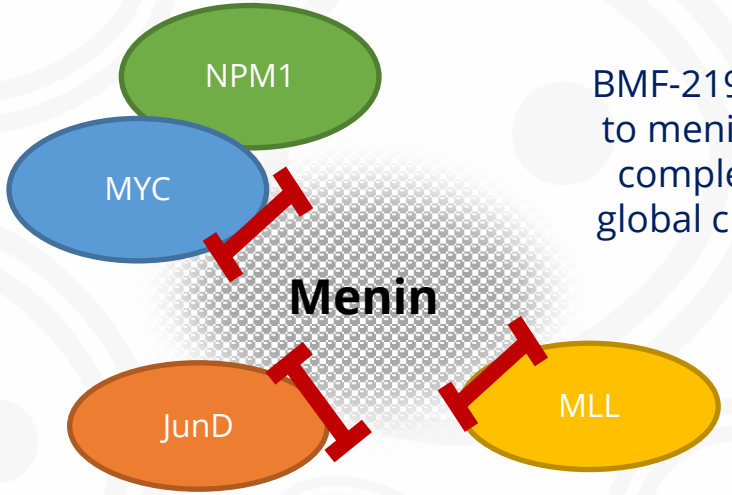
Menin **disrupting** cell homeostasis

Inhibition of Menin Allows for Beta-cell Regeneration

Potential Mechanism of Menin in Diabetes

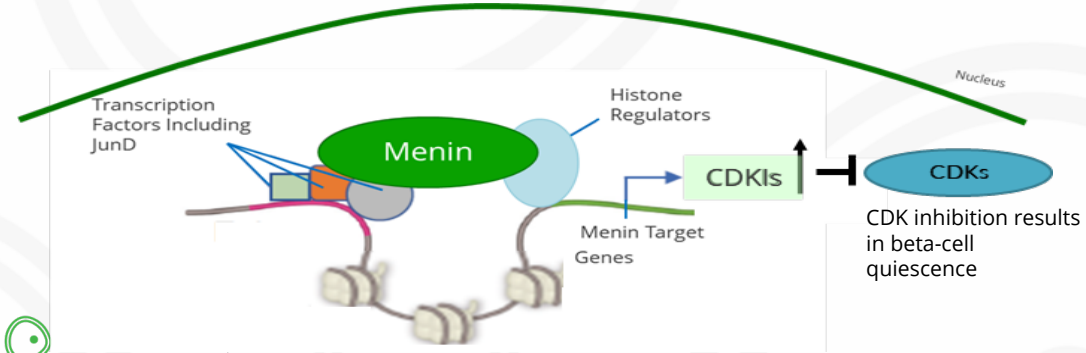
- Menin is an epigenetic protein that plays a key role in regulating beta-cell proliferation and function.
- Menin inhibition has previously been shown to improve glycemic control in high fat-induced diabetic mice (Ma et al., 2021)
- Inhibition of menin/JunD complex reduces the expression of Cyclin Dependent Kinase Inhibitors (CDKIs), allowing CDKs to drive beta-cell proliferation.

BMF-219: A selective covalent menin inhibitor



BMF-219 covalent binding to menin disrupts menin complexes, resulting in global change of function

Menin regulates beta-cell quiescence (cell cycle arrest)



Menin inhibition by BMF-219 allows for beta-cell regeneration (cell cycle entry) and glucose homeostasis

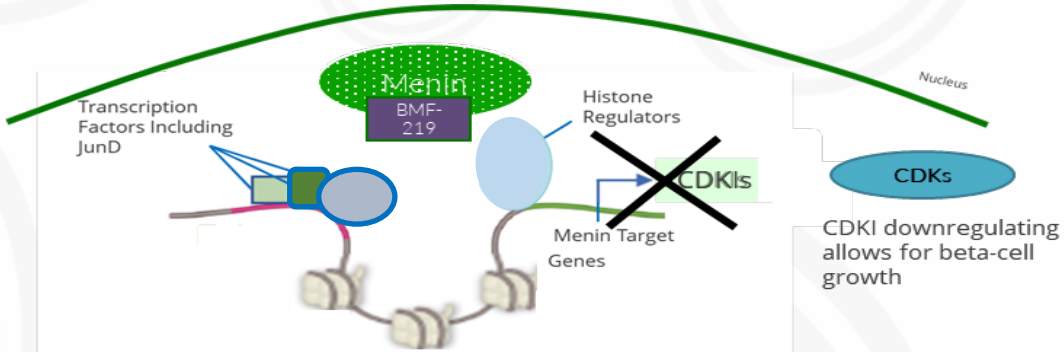
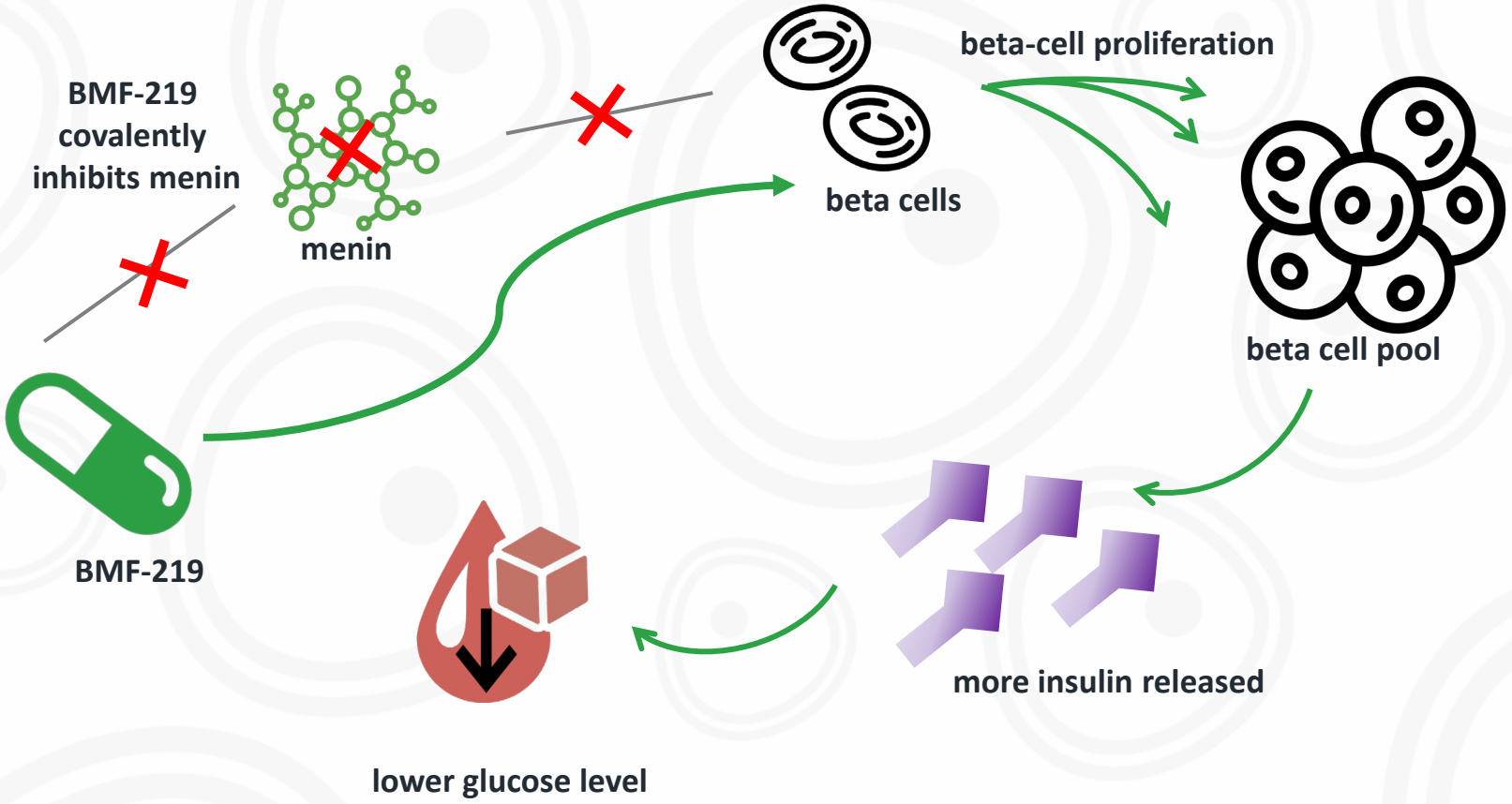


Figure adapted from Issa et al. *Leukemia* **35**, 2482–2495 (2021).

BMF-219 Controls Beta-Cell Proliferation and Mass by Inhibiting Menin

- Menin is a transcriptional scaffold protein that controls the expression of proteins that regulate beta-cell proliferation.
- Menin is thought to act as a brake on beta cell turnover / beta cell growth. Inhibition of menin could be a disease-modifying approach to treat diabetes.



Dr. Kim, S.K. et al., Science. 2007 Nov 2. doi: 10.1126/science.1146812.; Linnmann et al. American Society for Nutrition. Adv. Nutr. 5: 278–288, 2014; F. A. Van Assche et al. British Jornal of Obstetrics and Gynaecology, 1978 November; Hughs et al. Endocrinology, March 2011, 152(3):847–855

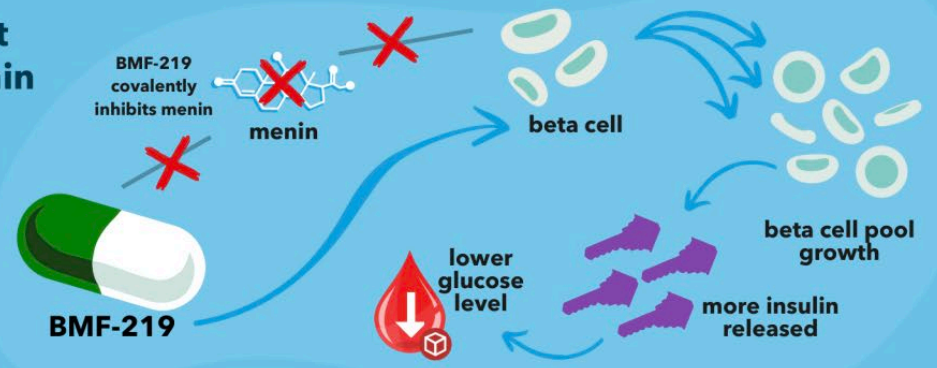
Inhibition of Menin Has been Observed to Occur Naturally During Pregnancy

HOW DOES BMF-219 INTEND TO IMPACT BETA CELLS?

BMF-219 inhibits an important protein that potentially controls beta cell growth - menin

BMF-219 is a first-in-class investigational oral molecule in clinical development directly targeting menin.

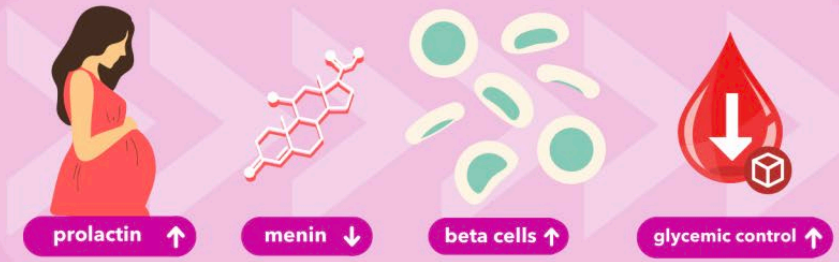
BMF-219 explores the potential to cure diabetes by naturally regenerating insulin-producing beta cells through the potent and durable inhibition of menin.



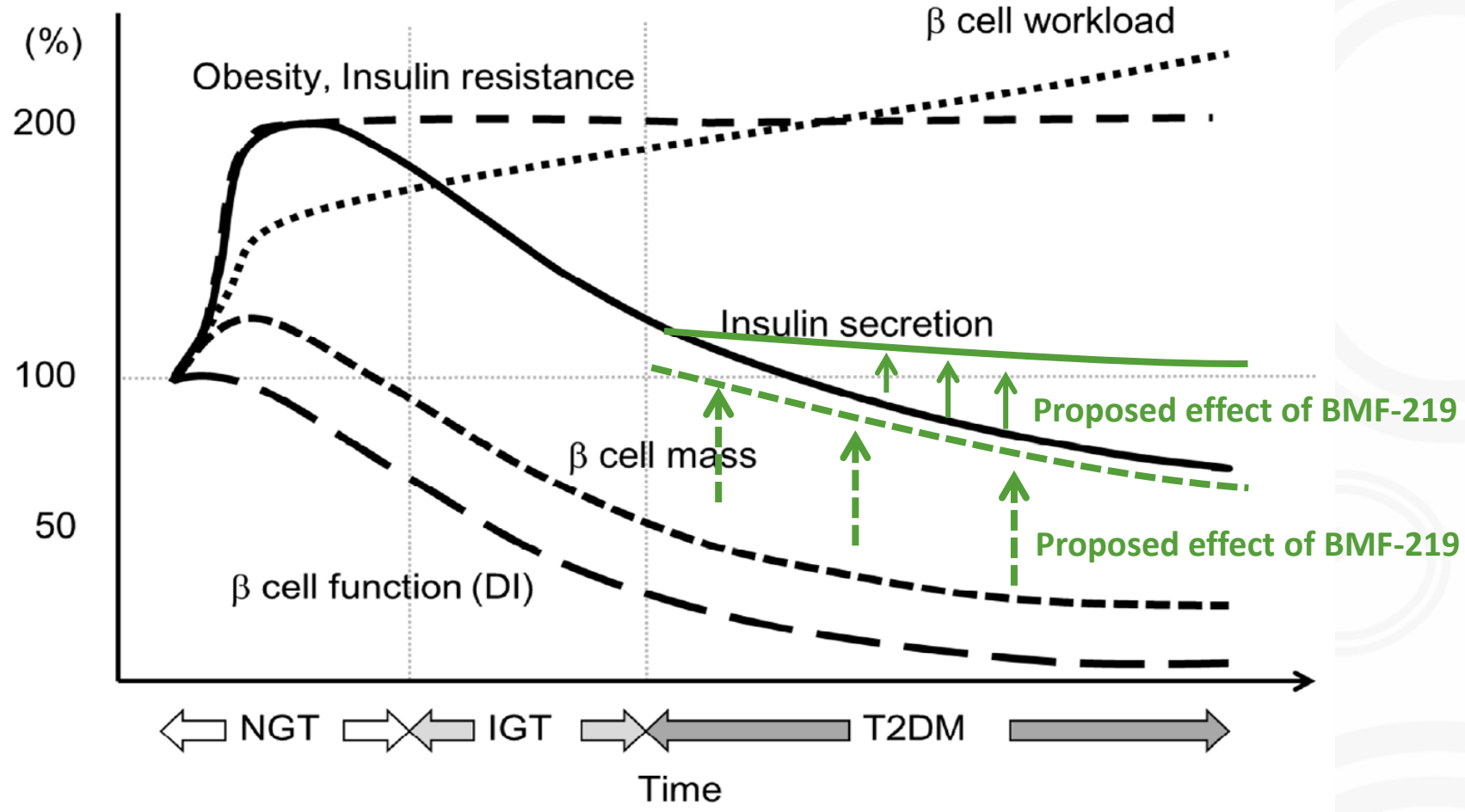
IS THERE A NATURALLY OCCURING PROOF-OF-CONCEPT?

Stanford researchers* have demonstrated preclinically that during pregnancy, the hormone prolactin down-regulates menin, which results in the proliferation of maternal pancreatic beta cells, increased insulin production, and the maintenance of normal glucose levels to prevent gestational diabetes.

*Menin Controls Growth of Pancreatic b-Cells in Pregnant Mice and Promotes Gestational Diabetes. Science, (2007), 801-806, 318



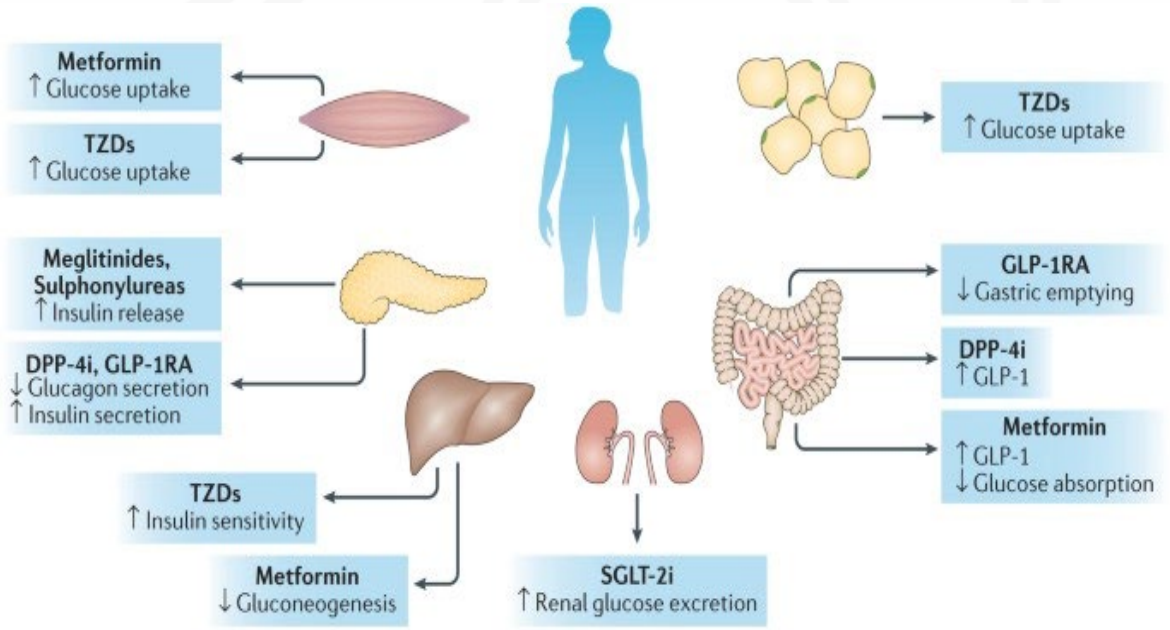
The Goal for BMF-219 is to Improve Glycemic Control without Continuous Medication



BMF-219 is aimed to increase beta cell mass and function, thereby increase insulin production in order to achieve glycemic control - without the need of continuous medication.

*Int. J. Mol. Sci. 2016, 17, 744; doi:10.3390/ijms17050744

BMF-219 is a Potential First in Class Diabetic Agent – Addressing the Root Cause of Disease



Nat Rev Endocrinol 12, 337–346 (2016). https://doi.org/10.1038/nrendo.2016.51

Currently Approved Therapies Are Chronic Treatment		
Drug MoA	HbA1c Change (%, Wk 52)	Avg Duration of Glycemic Control
DPP4	−0.63 (−0.68, −0.58)	23 months
SGLT2	−0.80 (−0.87, −0.72)	-
GLP1	−0.99 (−1.20, −0.78)	29 months
MET	−0.96 (−1.16, −0.76)	45 months

NIH.gov; Nathan et al., NEJM 2022

Currently approved therapies are primarily targeting the **Symptoms of Type 2 Diabetes: *Hyperglycemia***

Investigational BMF-219 Has a Unique Value Proposition

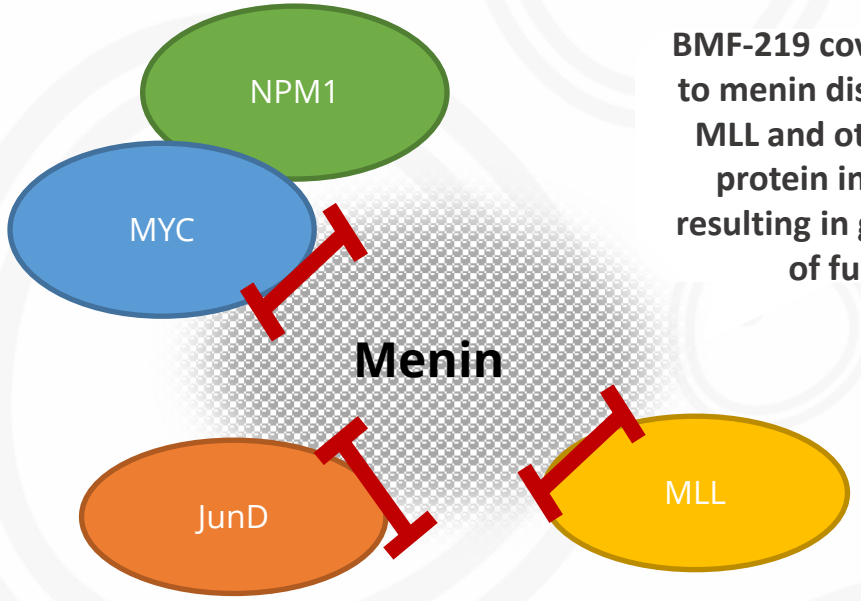
How is BMF-219 Differentiated from Currently Available Diabetes Therapies?

- Oral Small Molecule
- Complementary Agent to Available Diabetes Therapies
- Non-Chronic Dosing
- Well-Tolerated Safety Profile after First Read Out
- Disease Modifying Potential Addressing the Root Cause of Diabetes
- Continued Glycemic Control even after Cessation of Dosing
- Addressable Population may Include All People with Diabetes

BMF-219 Mechanism of Action – In Oncology

BMF-219 Has the Potential to Impact Important Binding Partners in Multiple Tumors

Proposed Mechanism of Action



BMF-219 covalent binding to menin disrupts menin-MLL and other protein-protein interactions, resulting in global change of function

Resulting change of function of menin impacts important binding partners involved in oncogenesis

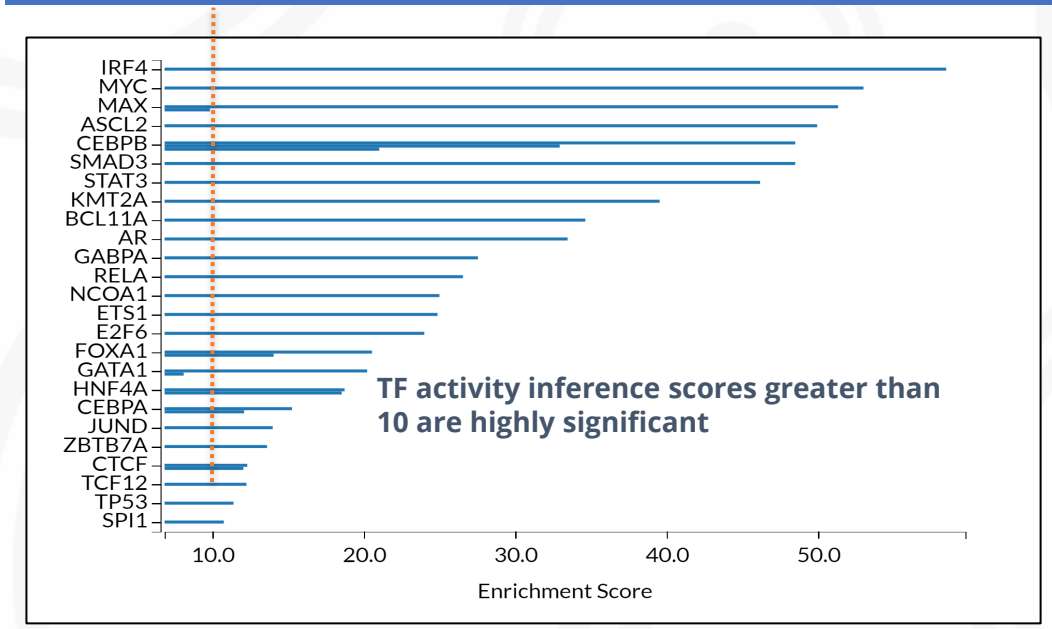
Target Patient Population

- Acute Leukemia: MLL-r
- Acute Leukemia: NPM1 mutant
- Acute Leukemia: Ras mutant
- DLBCL: DHT / DEL
- Multiple Myeloma: MYC addicted
- KRAS mutant Solid Tumors:
  Colorectal
  Lung
  Pancreatic
- CLL: r/r population
- Liquid and Solid Tumors

BMF-219 reduces menin levels and function, and has the potential to address additional patient populations with tumors that are dependent on menin or some of its binding partners

BMF-219 Disrupts Multiple Binding Partners of Menin, including MYC, MLL, and JUND

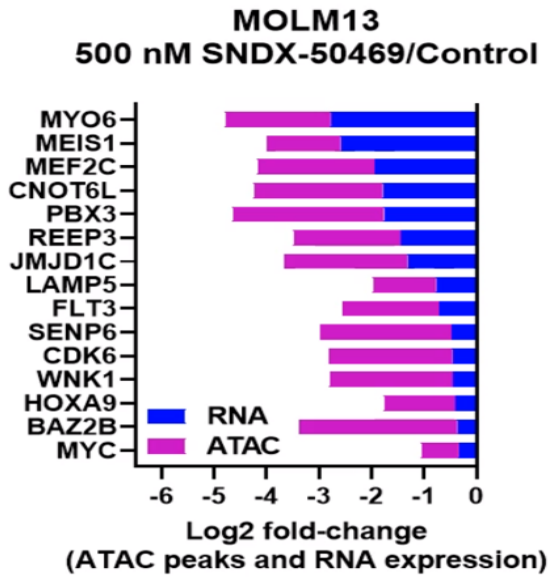
Covalent Menin Inhibitor – BMF-219



TF activity inference using ChIP-seq of differentially expressed genes in MOLM-13 cells incubated with 500 nM BMF-219 at 24 hours. Each bar represents a study in the GEO repository using the specified TF antibody.

- **In MOLM-13 cells treated with BMF-219, the top transcription factors regulating gene expression are MYC and MAX**
- IRF4, MYC, and MAX are known drivers for some forms of DLBCL, (addicted) multiple myeloma, and multiple additional tumors

Non-Covalent Menin Inhibitor – SNDX-50469



***Blood* (2021) 138 (Supplement 1): 3340.**

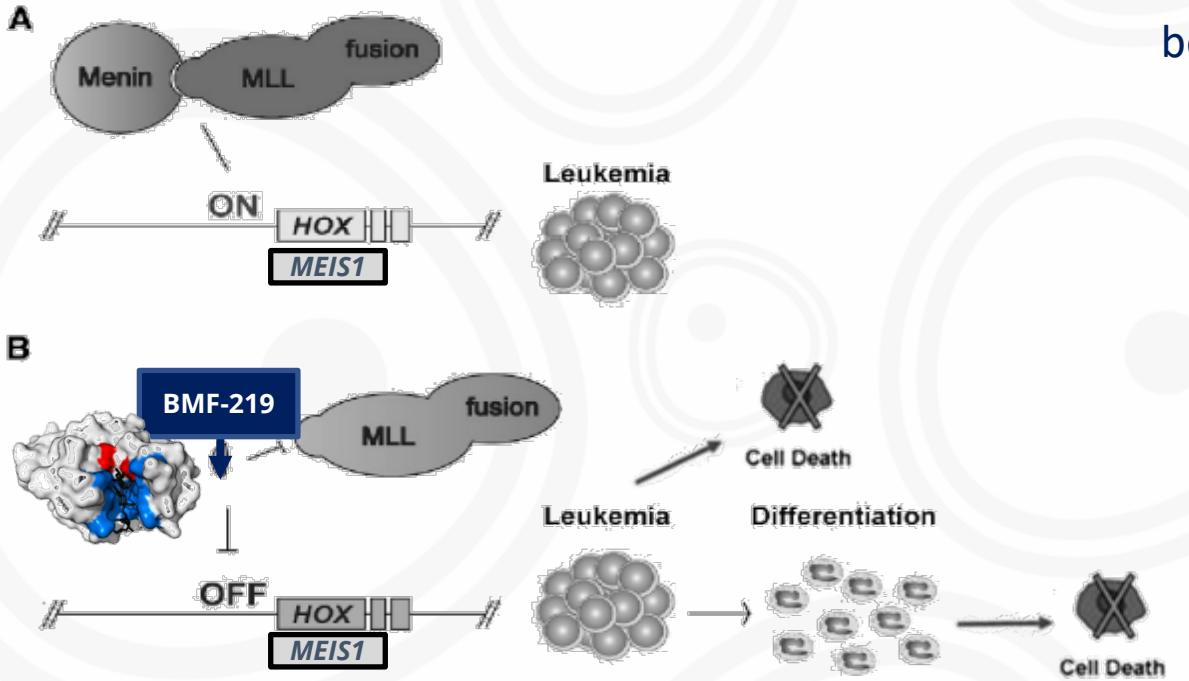
- **Significantly less impact on *MYC* expression** (2x fold) and genomic function by clinical non-covalent menin inhibitor
- In contrast, **BMF-219 treatment led to a ~100-200x reduction in *MYC*** expression at 24 hours

biomea FUSION™ We Aim to Cure™

BMF-219 in AML / ALL Liquid Tumors

Inhibits a Complex Interaction Independent of the MLL Fusion Partner

Role of Menin-MLL Complex



Modified after Uckelmann (Scott Armstrong Lab) , ASH 2018, Abstract # 546

Menin-MLL Fusions

Different fusions result in different binding affinities between MLL fusion proteins and Menin

MLL Fusions (AML/ALL)	Prevalence (%)
AF4	**36%**
AF9	**19%**
ENL	**13%**
AF10	**8%**
ELL	**4%**
PTD	**4%**
…80+ additional fusions	**16%**

Source: Meyer, C. et al. (2017). The MLL recombinome of acute leukemias in 2017. Leukemia, 32(2), 273–284.

BMF-219 : a covalent inhibitor at the Menin-MLL interface

BMF-219 - MYC Dysregulation is Believed to Play an Important Role in Multiple Tumors:

Diffuse Large B-cell Lymphoma (DLBCL), Multiple Myeloma (MM) and Chronic Lymphocytic Leukemia (CLL)

Development Stage: Phase I Clinical Trial (COVALENT-101) enrolling patients with relapsed/refractory DLBCL, MM and CLL

Key Facts

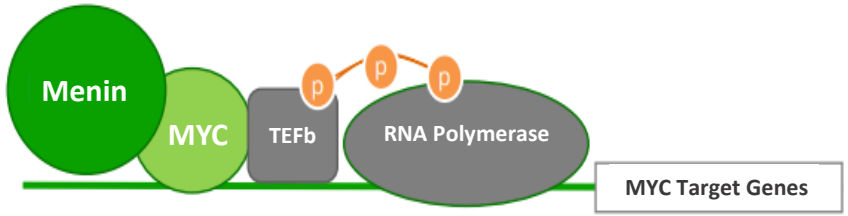
Estimated Addressable Population

Disease (r/r with MYC Implication)	Estimated US Patient Population (Annual Incidence)
DLBCL	~6,500
MM	~9,500
CLL	~8,000

- MYC addiction tends to increase with stage and line of therapy
- ~20-50% MYC dysregulation or translocations in newly diagnosed MM patients
- ~50-70% of advanced r/r MM patients have MYC dysregulation
- ~10,000 (40%) of DLBCL patients are Double and Triple Hit and Double expressors (BCL2 and MYC overexpression)
- >50% of relapsed/refractory DLBCL are double expressors

Proposed MOA

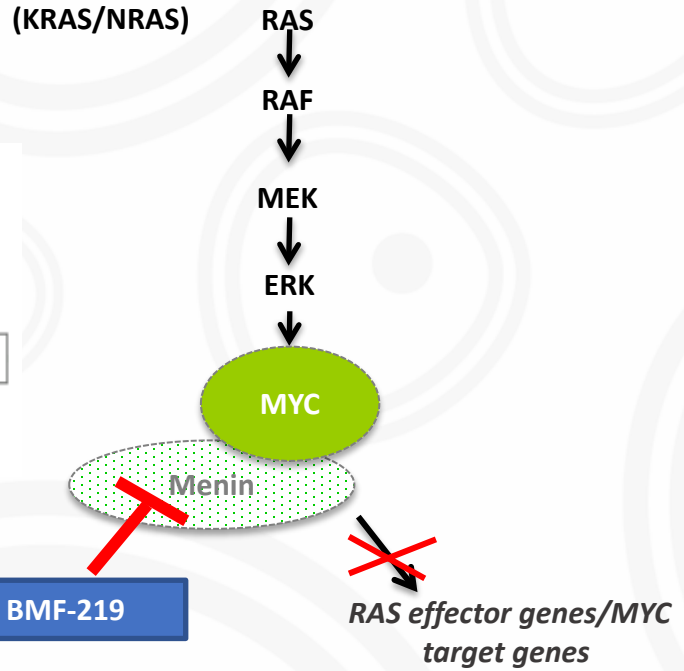
Menin complexes with MYC in the expression of MYC target genes. BMF-219 robustly decreases MYC gene expression and genomic function.
(Blood (2021) 138 (Supplement 1): 4318.)



Source: *Madden et al., Molecular Cancer volume 20, Article number: 3 (2021); Martínez-Martín et al. Cancer Drug Resist 2021;4:842-65; Xia Y. et al., Acta Haematol 2020;143:520–528; Zhu L., et al. (2017).. Nat. Commun. 8, 15278.; Musti et al., Oncogene . 2002 Sep 19;21(42):6434-45.*

Relevant Pathway

Tumor leverages MAPK pathway



Xia et al.. 2020;143(6):520-528. doi: 10.1159/000505892. Epub 2020 Feb 19
Crump et al. Blood (2017) 130 (16): 1800–1808. doi.org/10.1182/blood-2017-03-769620

Menin-MYC Interaction is Observed to Play an Important Role in KRAS Mutant Solid Tumors (Lung, Colon, Pancreatic)

Key Facts

Estimated Addressable Population

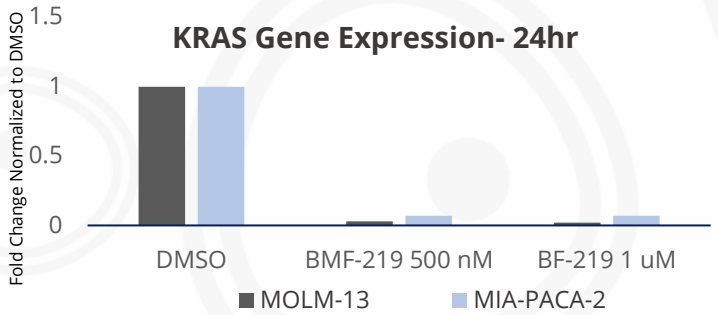
Tumor Type (KRAS Mutant)	Estimated US Patient Population (Annual Incidence)
Lung (NSCLC)	~58,000
Colon (CRC)	~60,000
Pancreatic (PDAC)	~53,000

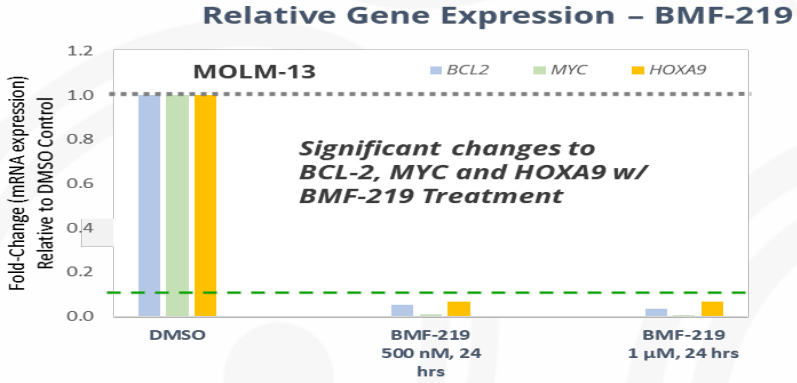
- MYC is a major downstream effector of the MAPK pathway in KRAS-activated tumors
- BMF-219 robustly decreased MYC gene expression and genomic function and drove cell killing in numerous MYC driven ex-vivo tumor samples.

Proposed MOA

BMF-219 inhibits the menin/ MYC interaction and downregulates expression of MYC and MYC target genes, including KRAS

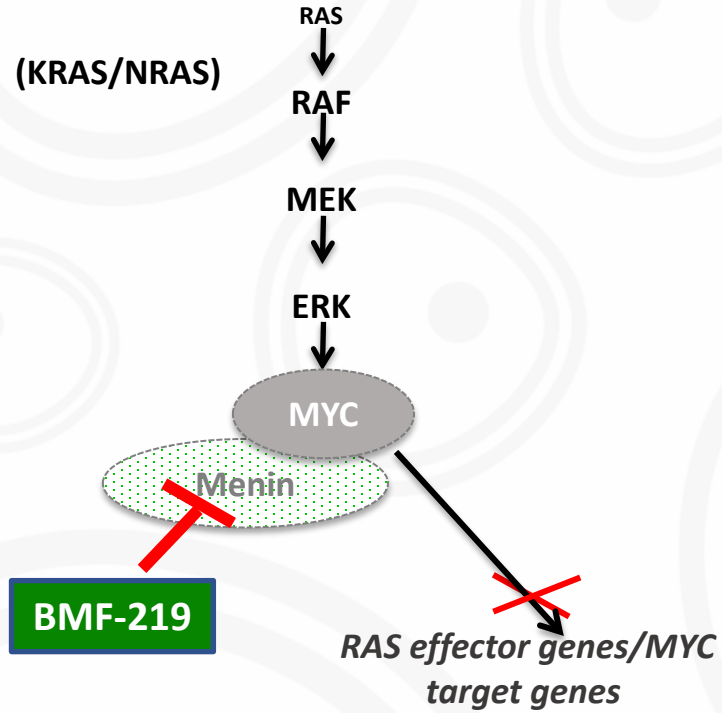
(Blood (2021) 138 (Supple. 1): 4318.)





Relevant Pathway

Tumor leverages MAPK pathway



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THANK YOU

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