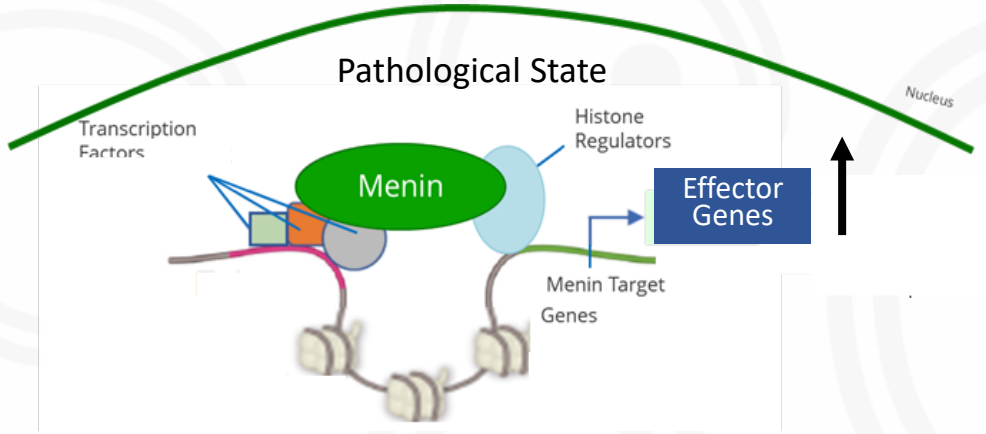
Backgrounder

The Role of Menin in Diabetes and Oncology

biomea FUSION™

The Role of Menin in Diabetes

Restoring Balance in Menin Dependents Diseases is Context Specific



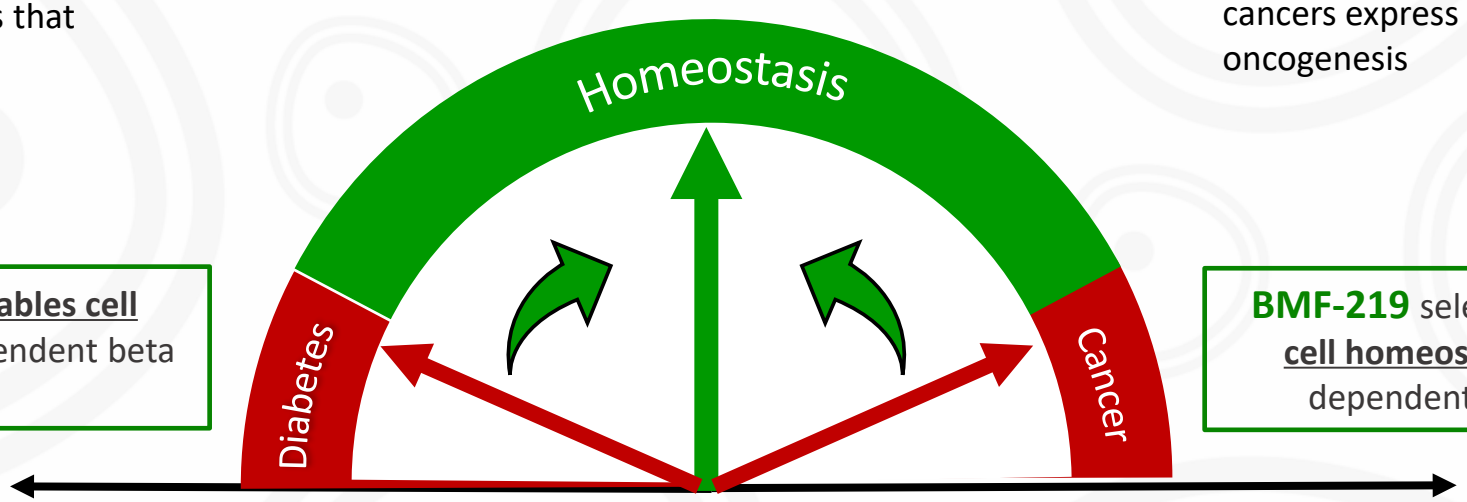
Treating Diabetes

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

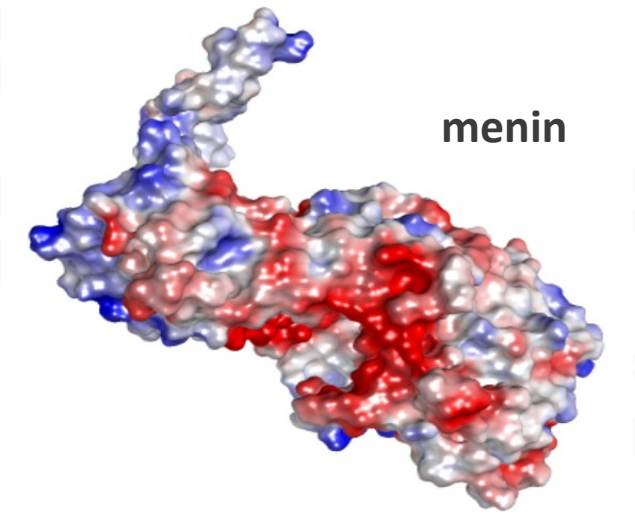


BMF-219 selectively **enables cell homeostasis** of menin dependent cancer cells

Menin **suppressing** cell homeostasis

Menin **disrupting** cell homeostasis

Menin Controls Beta-Cell Proliferation



Menin is a transcriptional scaffold protein that controls the expression of proteins that regulate beta-cell proliferation.

2007 Science AAAS

Menin Controls Growth of Pancreatic β-Cells in Pregnant Mice and Promotes Gestational Diabetes Mellitus

Satyajit K. Karnik,[1] Hainan Chen,[1*] Graeme W. McLean,[1*] Jeremy J. Heit,[1*] Xueying Gu,[1] Andrew Y. Zhang,[1] Magali Fontaine,[2] Michael H. Yen,[1,3] Seung K. Kim[1,3]†

During pregnancy, maternal pancreatic islets grow to match dynamic physiological demands, but the mechanisms regulating adaptive islet growth in this setting are poorly understood. Here we show that menin, a protein previously characterized as an endocrine tumor suppressor and transcriptional regulator, controls islet growth in pregnant mice. Pregnancy stimulated proliferation of maternal pancreatic islet β-cells that was accompanied by reduced islet levels of menin and its targets. Transgenic expression of menin in maternal β-cells prevented islet expansion and led to hyperglycemia and impaired glucose tolerance, hallmark features of gestational diabetes. Prolactin, a hormonal regulator of pregnancy, repressed islet menin levels and stimulated beta-cell proliferation. Dr. Kim, S.K. et al., Science. 2007 Nov 2. doi: 10.1126/science.1146812. mechanisms underlying diabetes pathoge

- **Menin has been found to control islet growth** in pregnant mice.
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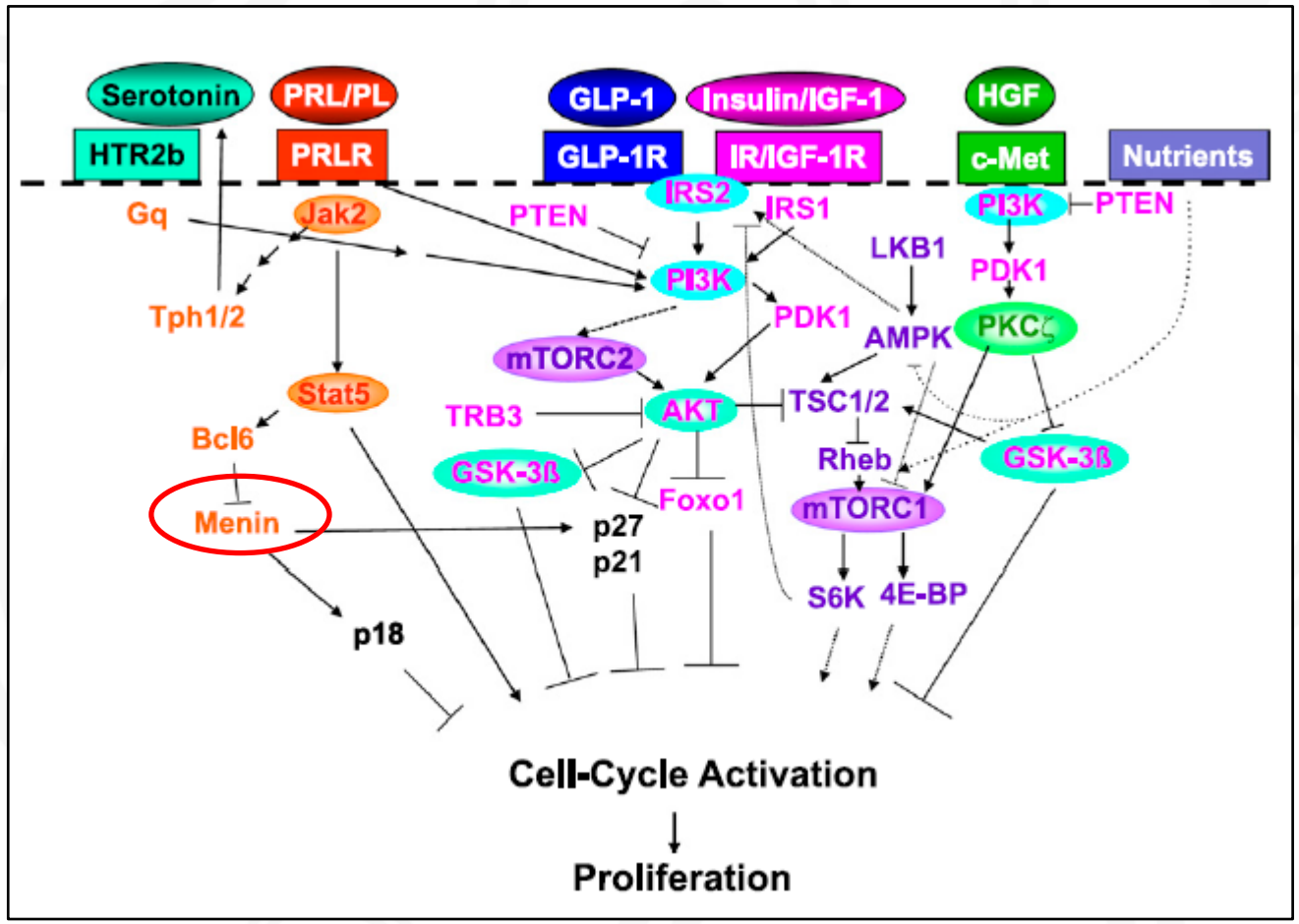
Beta-Cell Proliferation and Signaling



Adapted from Kulkarni et al. Diabetes 61:2205–2213, 2012

- The growth factors (insulin, IGF-I, HGF) and the incretin hormone GLP-1 are linked to the IRS/PI3K pathway, which in turn signals via PDK-1 to modulate Akt and FoxO1.
- During pregnancy, lactogen signaling is activated by the prolactin receptor and acts via Jak2/Stat5 and/or Jak2/Bcl6/menin, where Bcl6 is a suppressor of menin and prevent cell cycle inhibition by menin.
- FoxO1 proteins are normally inhibited by Akt, preventing beta cell proliferation through regulation of cell cycle. Menin and FoxO1 stabilize each other to suppress beta cell proliferation.

Menin Controls Beta-Cell Proliferation and Mass

- Menin is a transcriptional scaffold protein that controls the expression and activity of proteins that regulate beta-cell proliferation.
- Menin is thought to act as a brake on beta cell turnover / beta cell growth, supporting the notion that inhibition of menin could lead to the reactivation, protection, and regeneration of beta cells, which could be a disease-modifying approach to treat diabetes.

- **Menin has been found to control islet growth** in pregnant mice. Pregnancy stimulated proliferation of maternal pancreatic islet beta cells was accompanied by reduced islet levels of menin.
- **Prolactin**, a hormonal regulator of pregnancy, **reduced islet menin levels and stimulated beta cell proliferation**.

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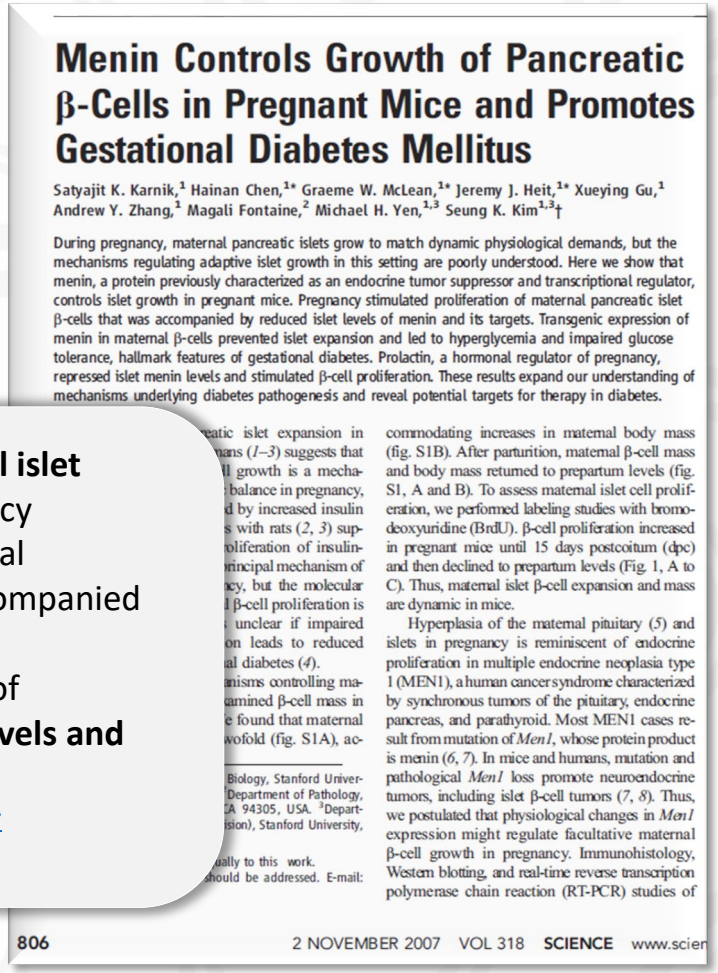

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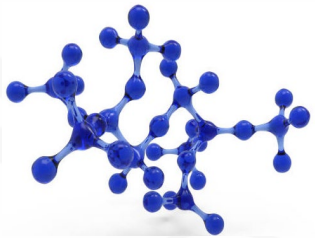
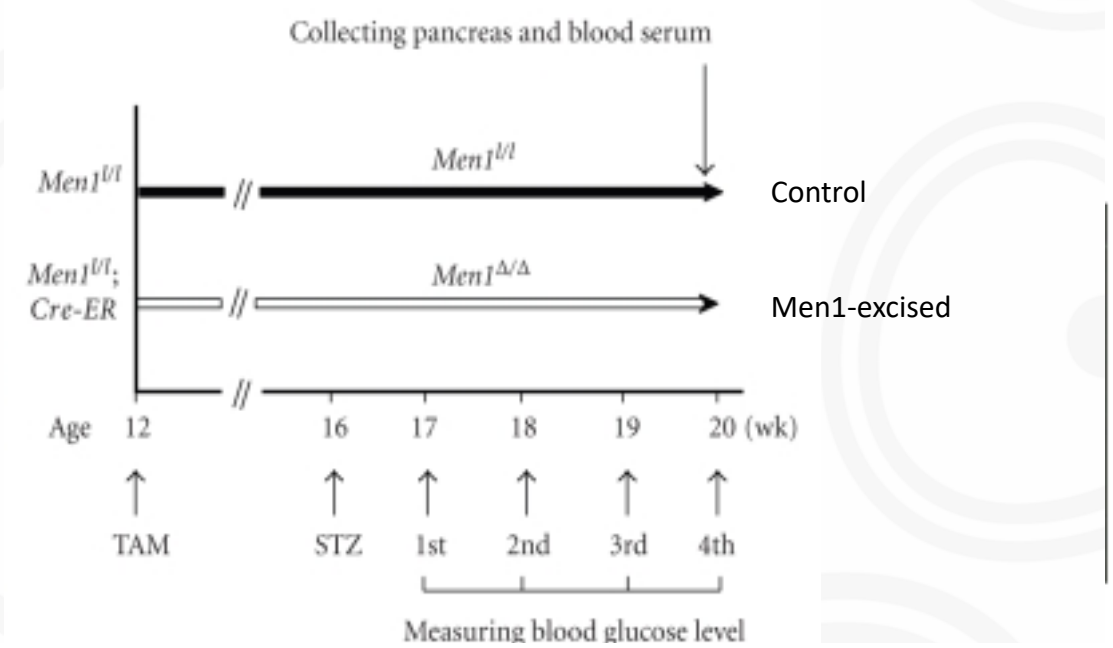
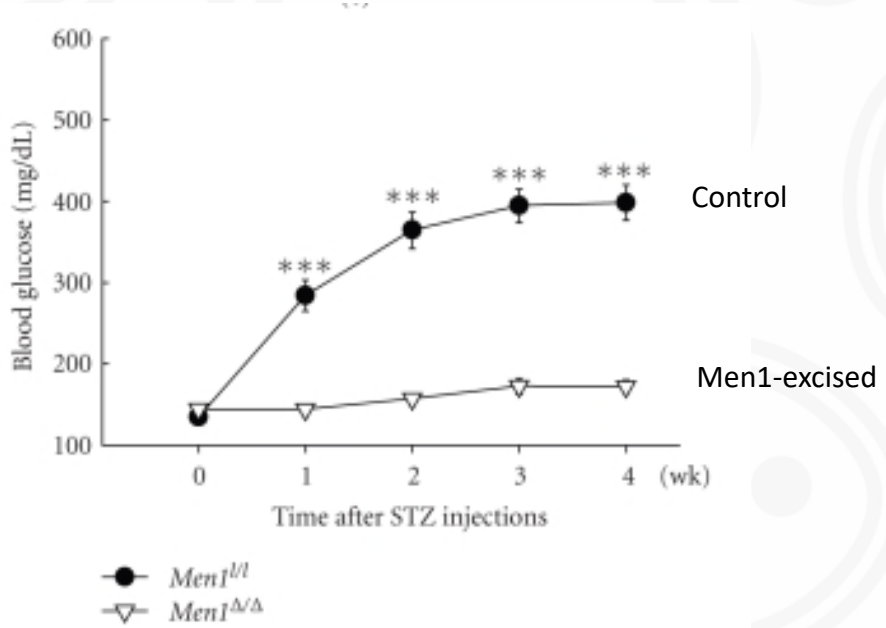


BMF-219 *is a small molecule designed by the Biomea Fusion Team to covalently inhibit menin. Preclinical studies have shown that the inhibition of menin leads to the overall rehabilitation of beta cell health and function, and thereby to increased insulin production and glycemic control. Clinical trials with BMF-219 are under way to investigate oral dosing for a limited time only until the pool of healthy beta cells are restored. The goal is to address diabetes with BMF-219 at the root cause.*

Potential for Menin Inhibition Demonstrated by Beta Cell Ablation Diabetes Model in MEN1-Excised Mice

MEN1 Excision Prevents Development of STZ-induced Hyperglycemia





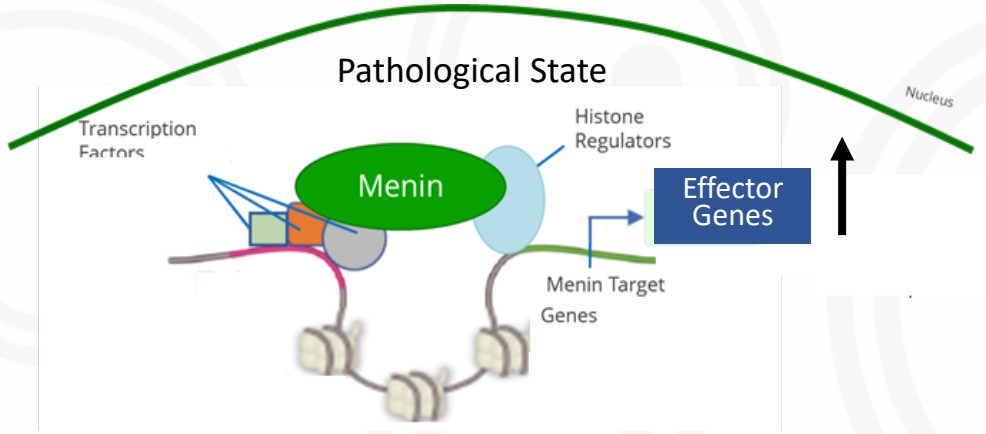
Multiple low-dose streptozotocin (MLD-STZ) administered to the control and *Men1*-excised mice to induce beta cell damage and a diabetes-like environment

***Men1*-excised mice did not develop hyperglycemia in STZ model, which was observed in the control group**

Sources: Yang et al. (2010) Deletion of theMen1Gene Prevents Streptozotocin-Induced Hyperglycemia in Mice. Experimental Diabetes Research, 2010, 1–11. doi:10.1155/2010/876701

The Role of Menin in Oncology

Restoring Balance in Menin Dependents Diseases is Context Specific



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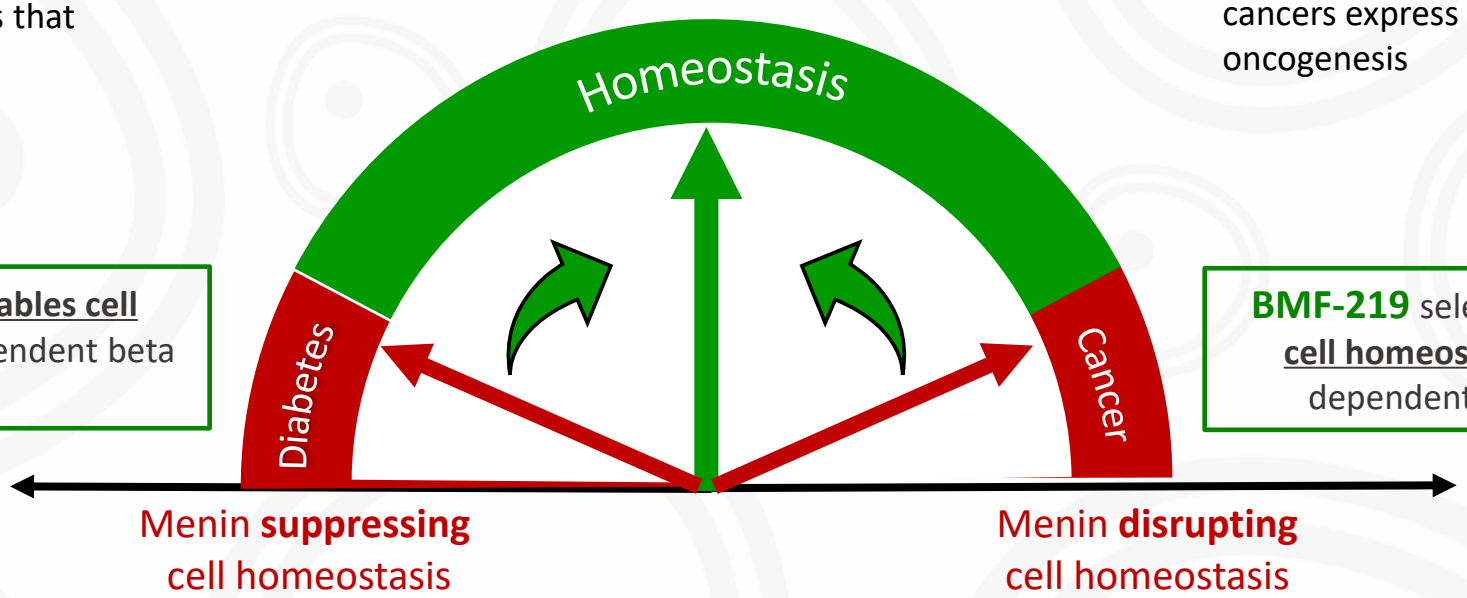
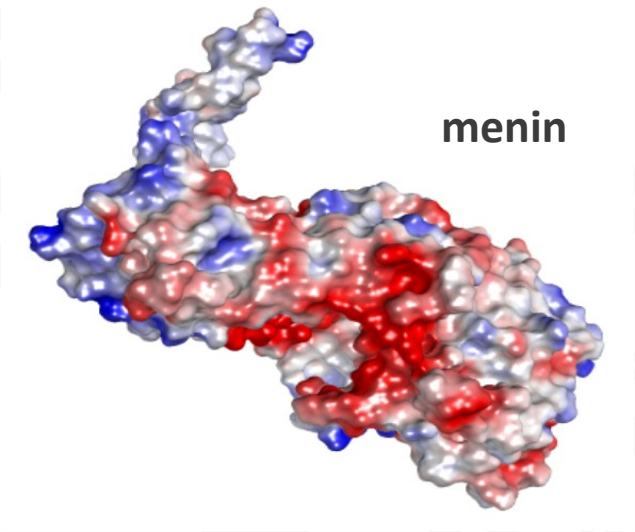


BMF-219 selectively **enables cell homeostasis** of menin dependent cancer cells

Menin Plays an Essential Role in Oncogenic Signaling



Review

Cell PRESS

Menin: a scaffold protein that controls gene expression and cell signaling

Smita Matkar*, Austin Thiel*, and Xianxin Hua

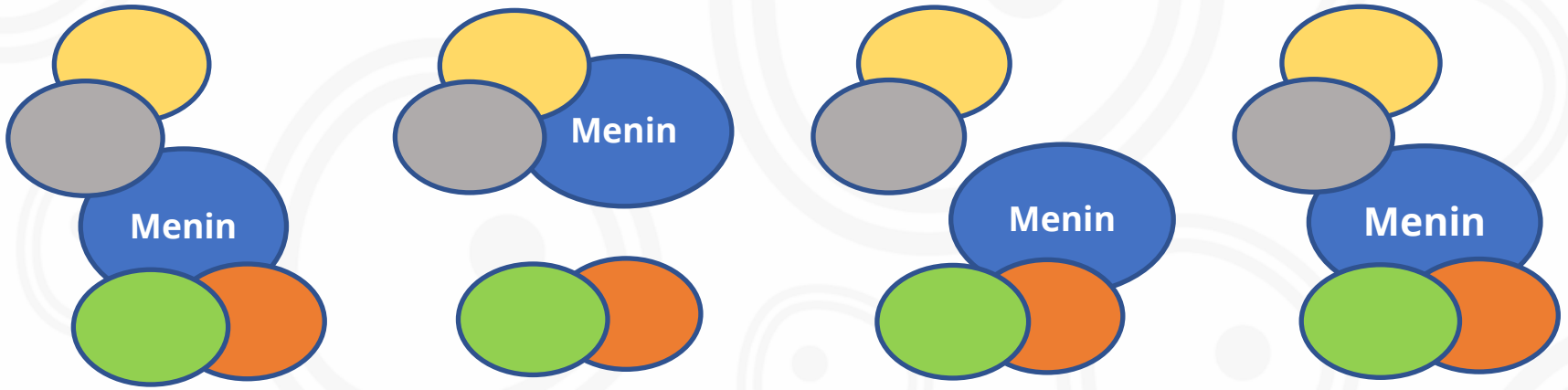
Department of Cancer Biology, Abramson Family Cancer Research Institute, Abramson Cancer Center, the University of Pennsylvania Perelman School of Medicine, 421 Curie Boulevard, Philadelphia, PA 19104, USA

Menin is a transcriptional scaffold protein that plays an essential role in oncogenic signaling in multiple cancer types.

Matkar et al. Cell REVIEW| VOLUME 38, ISSUE 8, P394-402, AUGUST 2013

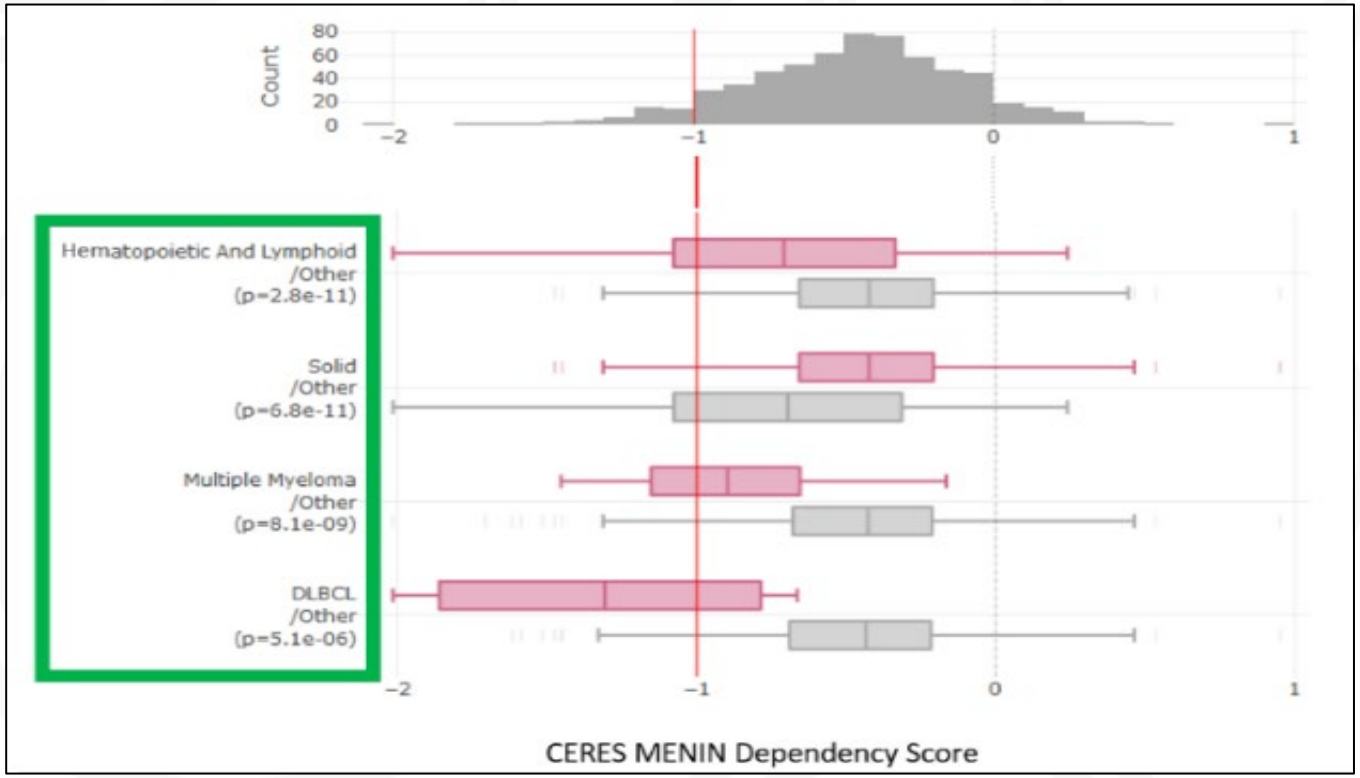
Menin is a Key Protein in Multiple Cancer Driving Complexes

Menin is a scaffold protein that controls gene expression and cell signaling. Menin interacts with various partners to regulate gene transcription and interplay with multiple signaling pathways.



Acute Leukemia, DLBCL, MM & Other Tumor Types Have High Menin Dependency based on Broad Institute DEPMAP Dataset

BROAD Institute Cancer Dependency Map (DEPMAP) for Menin (*MEN1*)

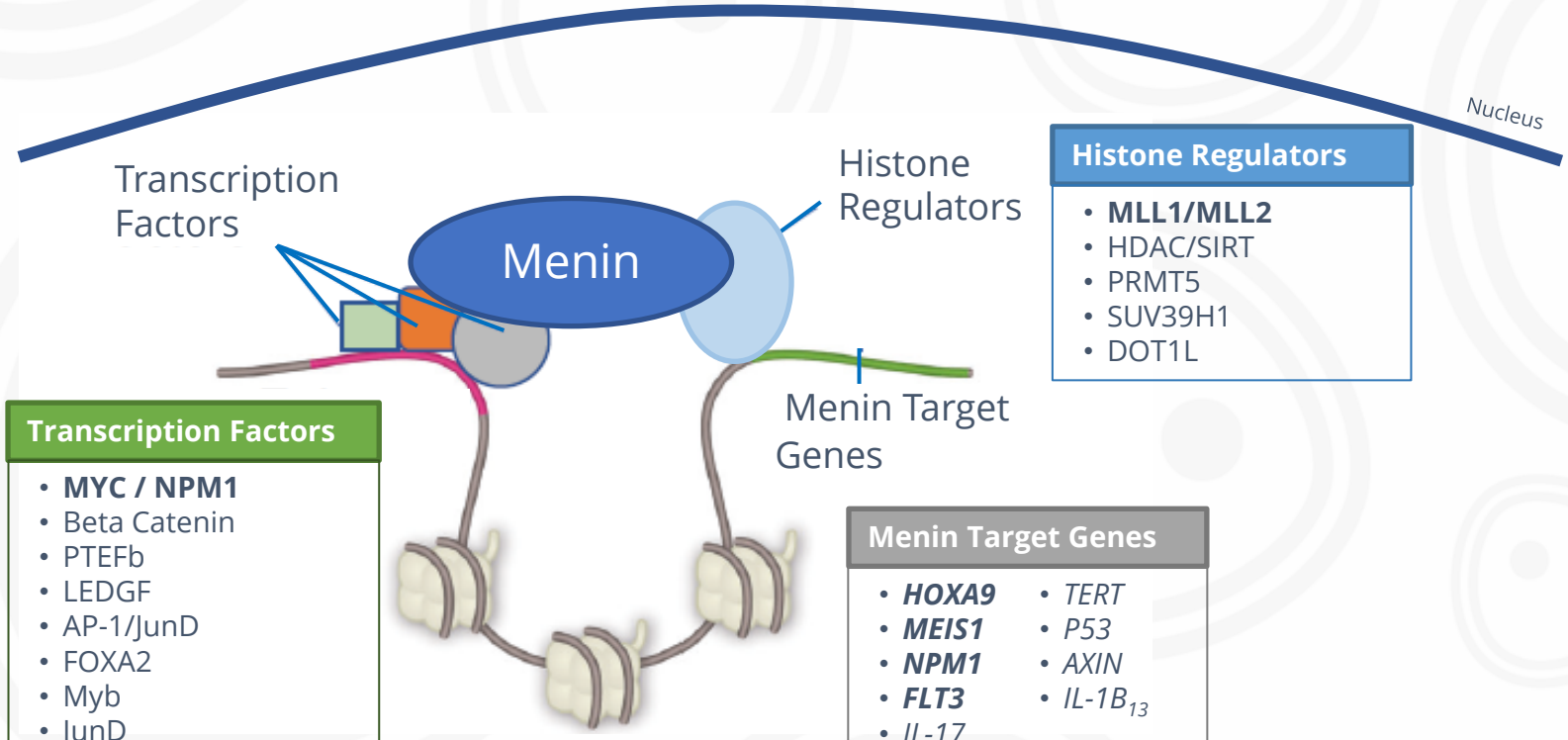


- Cell viability scores have shown that **menin** plays a key role in **survival of multiple tumors**
- **High menin dependency in liquid and solid tumors,** beyond acute leukemias, provides rationale for further analysis in dependent tumor types
- Biomea is exploring the potential for **covalent inhibition of menin in a variety of liquid and solid tumor types**

Note: CERES MENIN Dependency scores less than -1 in the various tumor types tested imply that menin is considered essential for cell survival in those tumor types

*Source: Broad Institute DEPMAP Dataset

Menin Complex Partners Promote Oncogenesis Across Multiple Tumor Types



Histone Regulators

- **MLL1/MLL2**
- HDAC/SIRT
- PRMT5
- SUV39H1
- DOT1L

Transcription Factors

- **MYC / NPM1**
- Beta Catenin
- PTEFb
- LEDGF
- AP-1/JunD
- FOXA2
- Myb
- JunD

Menin Target Genes

- ***HOXA9***
- ***MEIS1***
- ***NPM1***
- ***FLT3***
- *IL-17*
- *TERT*
- *P53*
- *AXIN*
- *IL-1B*$_{13}$

Modified after Issa, G. C., et al. (2021). Therapeutic implications of menin inhibition in acute leukemias. Leukemia, 35(9), 2482–2495.

AML / ALL Implications

- **MLLr**
- **NPM1**
- **FLT3**
- **MYC**
- MYB

DLBCL / MM Implications

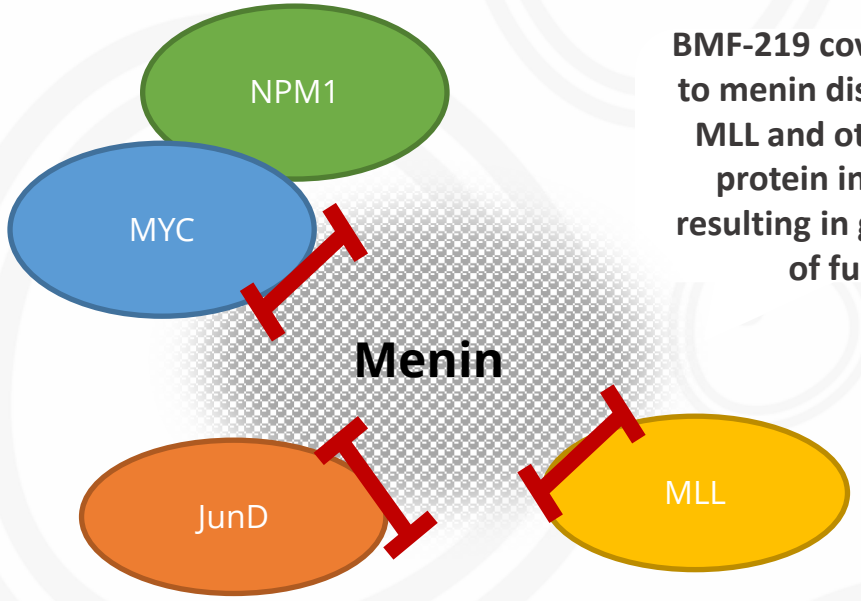
- **MYC**
- BCL2
- **IRF4**
- CREB
- PI3K/MTOR

Solid Tumors Implications

- **MAPK/KRAS**
- **MYC**
- CDK

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

The Role of Menin in Diabetes - Literature References

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The Role of Menin in Oncology - Literature References

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Contact:
Chunyi Zhao PhD
Associate Director of Investor Relations & Corporate Development
czhao@biomeafusion
T: +1 650-460-7759

THANK YOU

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Biomea Fusion
900 Middlefield Road, 4th floor
Redwood City, CA, 94063
biomeafusion.com