

A. THE TRIPPLY-LOCKED GATE

COLD TUMOR MICROENVIRONMENT

CD8+ inactive
Treg suppressing
No IFN- β signal
cGAS-STING silent

OUTER MITOCHONDRIAL MEMBRANE (RIGID — HIGH [Chol]/[CL])

HK-II ?
VDAC1 MONOMER
GATE SHUT
Bcl-xL ?
[Chol]/[CL] \uparrow ?

mtDNA CONTAINED

Mitochondrial Matrix

Threshold = $K / [(1-f_{HKII})(1-f_{BclxL})] \times [Chol]/[CL]$

ALL THREE TERMS ELEVATED \rightarrow GATE JAMMED

Untreated MSS CRC:
Triply locked. No mtDNA escape.
No innate alarm. Immune-invisible.

B. LOVASTATIN OPENS THE GATE

PRIMED TUMOR MICROENVIRONMENT

cGAS
STING
IFN- β
CXCL10
CCL5
500-650 bp
mtDNA

LOVASTATIN

OMM — FLUIDIZED ([Chol]/[CL] $\downarrow\downarrow$)

HK-II
VDAC1
~4 nm PORE
Bcl-xL
[Chol]/[CL] \downarrow
mtDNA

Mitochondrial Matrix

Lovastatin \rightarrow HMG-CoA inhibition \rightarrow mevalonate \downarrow
(a) CoQ10 \downarrow \rightarrow mito ROS \uparrow
(b) OMM cholesterol \downarrow \rightarrow [Chol]/[CL] drops
 \rightarrow VDAC1 oligomerization \rightarrow mtDNA leak \rightarrow cGAS-STING

Statin-Treated MSS CRC:
Cholesterol lock broken. Acute mtDNA spark.

C. BOTENSILIMAB CAVALRY

INFLAMED TUMOR MICROENVIRONMENT

BOTENSILIMAB
Fc-enhanced anti-CTLA-4
+ balstilimab (anti-PD-1)

INNATE AMPLIFICATION
Fc γ RIIIa \rightarrow macrophage
+ NK cell activation

TREG ELIMINATION
ADCC \rightarrow Treg depletion
Suppressive brake removed

ACTIVATED CD8+ T CELLS
IFN- γ \uparrow Granzyme B \uparrow Perforin \uparrow

MSS CRC TUMOR CELL
APOPTOSIS + IMMUNOGENIC
CELL DEATH

Botensilimab + balstilimab: 17~20% ORR
Statin + ICI: 20% mortality reduction (n=46,154)
Prediction: statin pre-treatment $\uparrow\uparrow$ ORR