

Death receptors as targets in cancer

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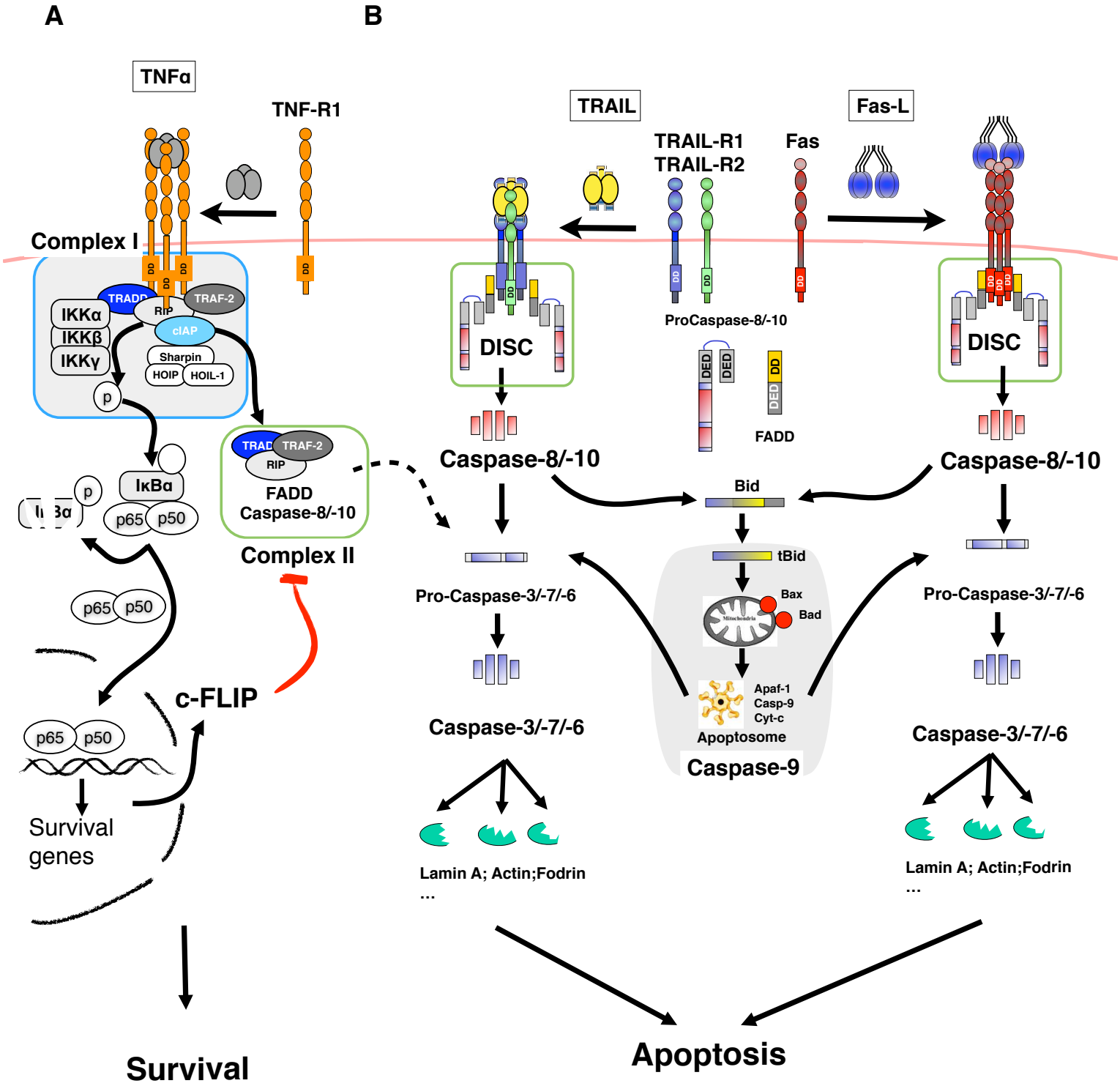

A
B
TNFα
TNF-R1
Complex I
TRADD
TRAF-2
RIP
cIAP
IKKα
IKKβ
IKKγ
Sharpin
HOIP
HOIL-1
p
IκBα
p65
p50
FADD
Caspase-8/-10
Complex II
c-FLIP
Survival genes
Survival
TRAIL
TRAIL-R1
TRAIL-R2
Fas
Fas-L
DISC
ProCaspase-8/-10
DED
DD
FADD
Caspase-8/-10
Bid
tBid
Bax
Bad
Mitochondria
Apaf-1
Casp-9
Cyt-c
Apoptosome
Caspase-9
Pro-Caspase-3/-7/-6
Caspase-3/-7/-6
Lamin A; Actin;Fodrin
...
Apoptosis

Figure 1

A

APO10/Mega Fas Ligand
mACRP30 aa 18-111 fused to Fas ligand aa 139-280

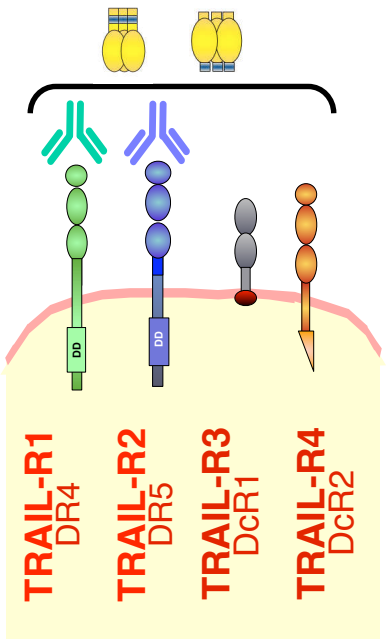
Dulanermin /rhApo2L/TRAIL
TRAIL aa 114-280

CPT/Circularly Permuted TRAIL
TRAIL aa 135-280 fused to TRAIL aa 122-135

Anti-TRAIL-R1 agonistic antibody
Mapatumumab / HGS-ETR1

Anti-TRAIL-R2 agonistic antibodies
Conatumumab / AMG655
Drozitumumab / Apomab / PRO95780
LBY135
Lexatumumab / HGS-ETR2
Tigatuzumab / CS-1008 / TRA-8

B



C

Functional TRAIL-R expression and Sensitivity or Resistance to :

PARA (Ligand or moAb)

	S	S	S	S	S	R
	R	S	S	S	R	S/R
	S	R	S	R	S	S/R

D

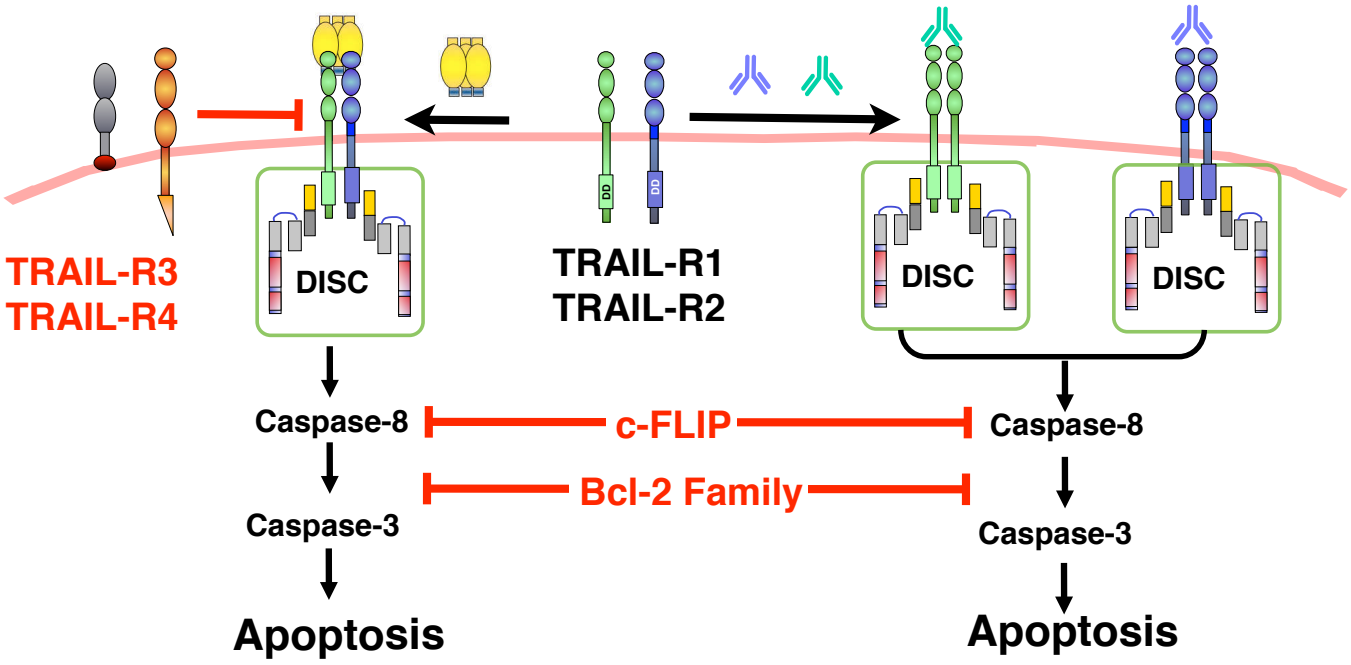


Figure 2

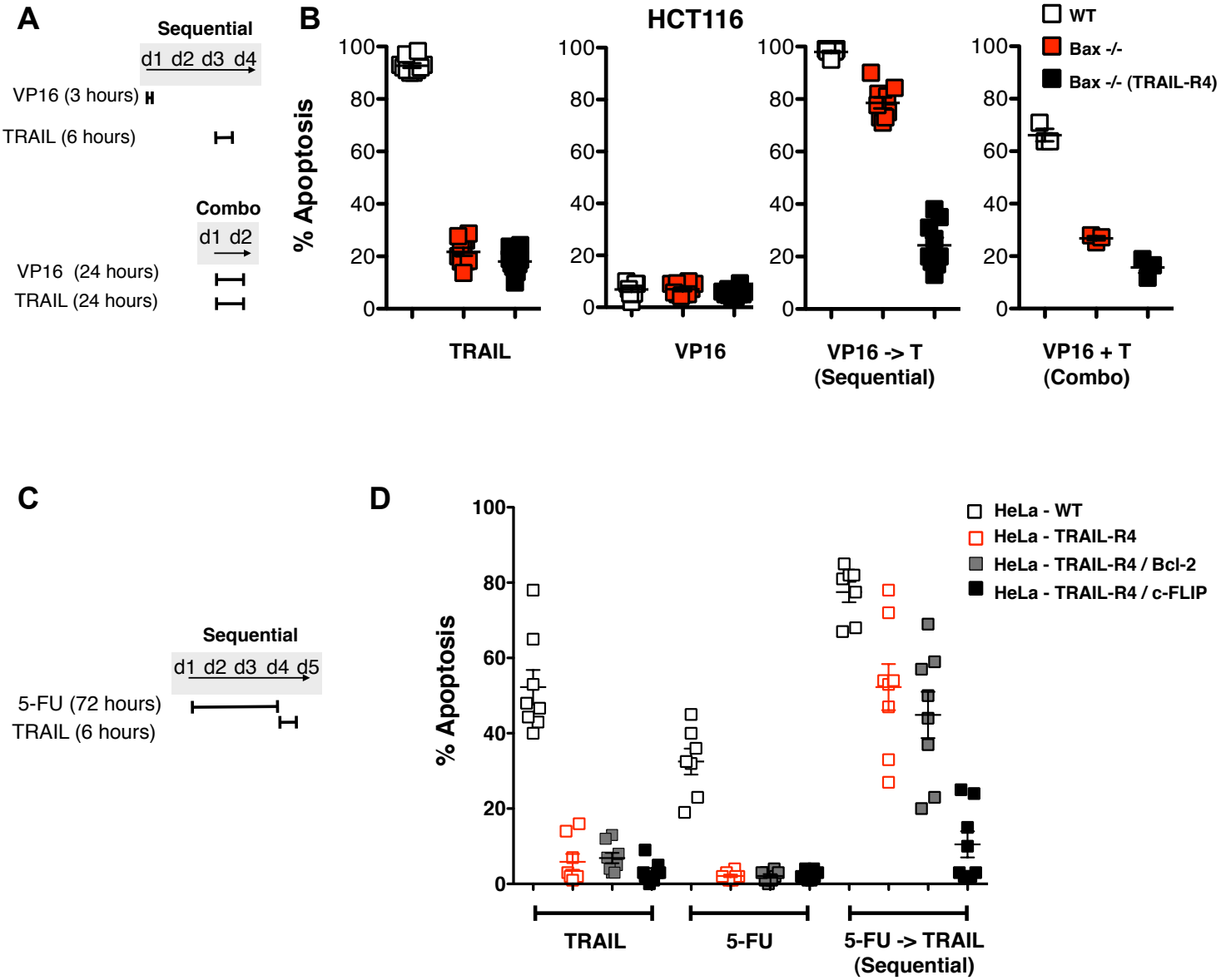

A
Sequential
d1 d2 d3 d4
VP16 (3 hours)
TRAIL (6 hours)
Combo
d1 d2
VP16 (24 hours)
TRAIL (24 hours)
B
HCT116
% Apoptosis
100
80
60
40
20
0
TRAIL
VP16
VP16 -> T
(Sequential)
VP16 + T
(Combo)
WT
Bax -/-
Bax -/- (TRAIL-R4)
C
Sequential
d1 d2 d3 d4 d5
5-FU (72 hours)
TRAIL (6 hours)
D
% Apoptosis
HeLa - WT
HeLa - TRAIL-R4
HeLa - TRAIL-R4 / Bcl-2
HeLa - TRAIL-R4 / c-FLIP
TRAIL
5-FU
5-FU -> TRAIL
(Sequential)

Figure 3