



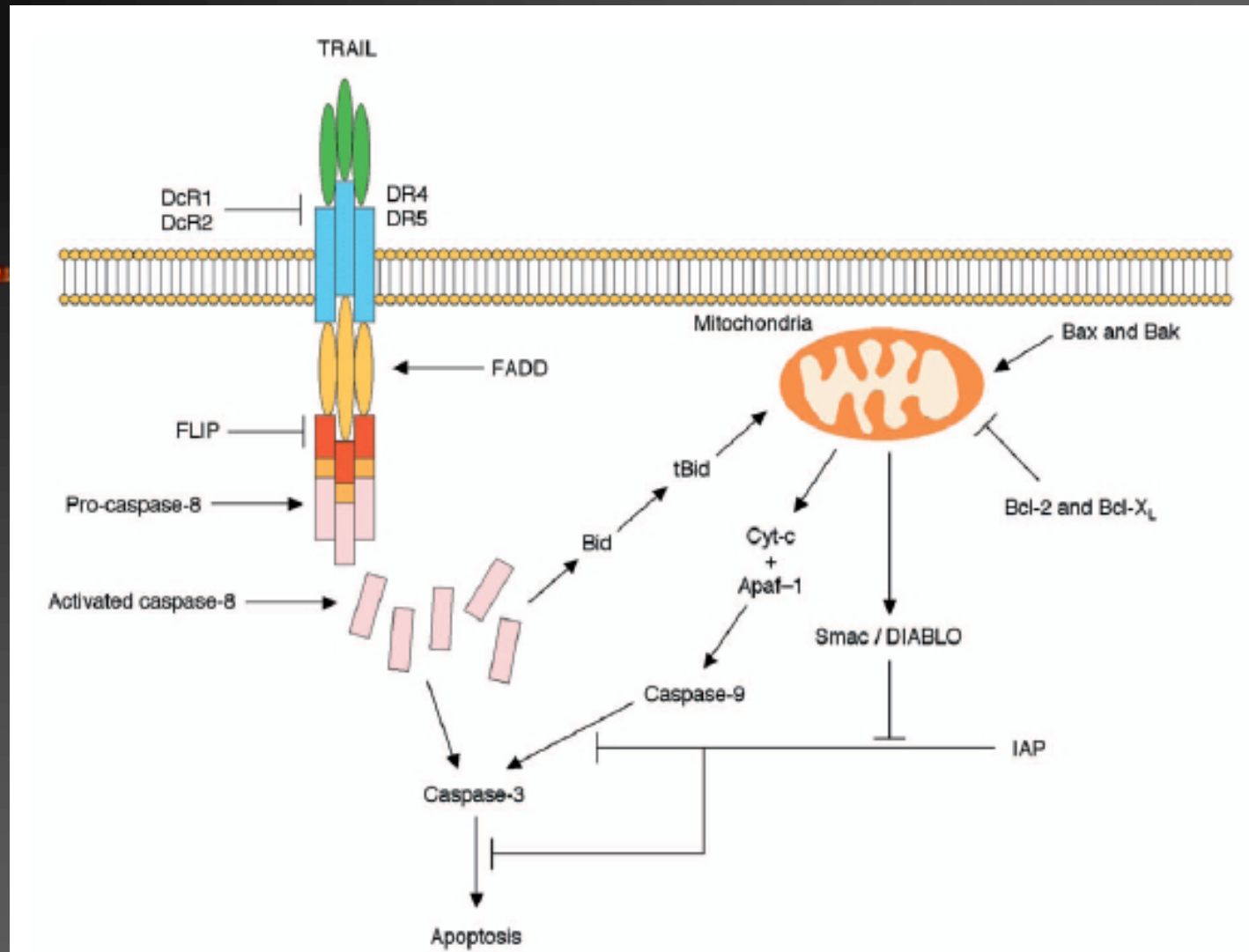
On the TRAIL to Tumor Apoptosis

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The Story

- Tumor necrosis factor (TNF) receptors
 - Involved in apoptosis pathway
 - TRAIL
 - Homotrimer
 - TNF ligand
 - Binds specifically to tumor cells
 - Binding causes trimerization of TNF receptors
 - Signals for cell apoptosis
 - Known targets: DR4, DR5, DcR1, DcR2
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Cell Apoptosis Pathway

Good 'OI Structure

- Resolution: 2.2Å
 - R factor: 22.1%
 - R_{free} : 27.0%
 - Unique reflections: 18,029
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The All-Stars

- Arg 149 containing loop
 - Mutation (SLL)
 - Gln205, Tyr216, Glu236, Tyr237
 - Alanine substitutions
 - Gln205 and Tyr 216
 - Arg 158 and Tyr 237
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The MVP

- Three Cys 230 proximal at trimer interface
 - Mutation to Ala or Ser
 - 70 fold reduction in activity
 - Form disulfide bonds?
 - Yes, but that's not all!
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Overrated or a True Star?

- Zinc? That's a first!
 - Take 'em out!
 - 90-fold decrease in activity
 - Reduction in β -sheet content
 - Tryptophan fluorescence reduction
 - Only two Trp residues conserved: 154, 231
 - Melting temperature 25°C lower
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To Sum It Up

- Trail uses many weaker interactions
 - Different mutation combinations for targeting
 - A promising drug model
 - Zinc site
 - Only TNF ligand with a metal site
 - Contributes to protein stability
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References

- Yagita H. TRAIL and its receptors as targets for cancer therapy. *Cancer Sci* 2004, 95, 777-783.
 - Screaton et al. Structure of the TRAIL-DR5 complex reveals mechanisms conferring specificity in apoptotic initiation. *Nat. Struct. Biol.* 1999, 9, 1048-1053
 - Hymowitz et al. A Unique Zinc-Binding Site Revealed by a High-Resolution X-Ray Structure of Homotrimeric Apo2L/TRAIL. *Biochemistry*, 2000, 39, 633-640.
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That's all Folks!



The Art of Warner Bros. Animation

By Steve Schneider

Foreword by Ray Bradbury