

Precision Molecularly-Targeted Therapy of Cancer Cannot (in General) Work Optimally by Itself

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This presentation focuses on four aspects of the topic



The Fundamental Problem

The Fundamental Problem: Precise targeting is appropriate only when the target is solitary and not complicated

A sharpshooter can help
you here



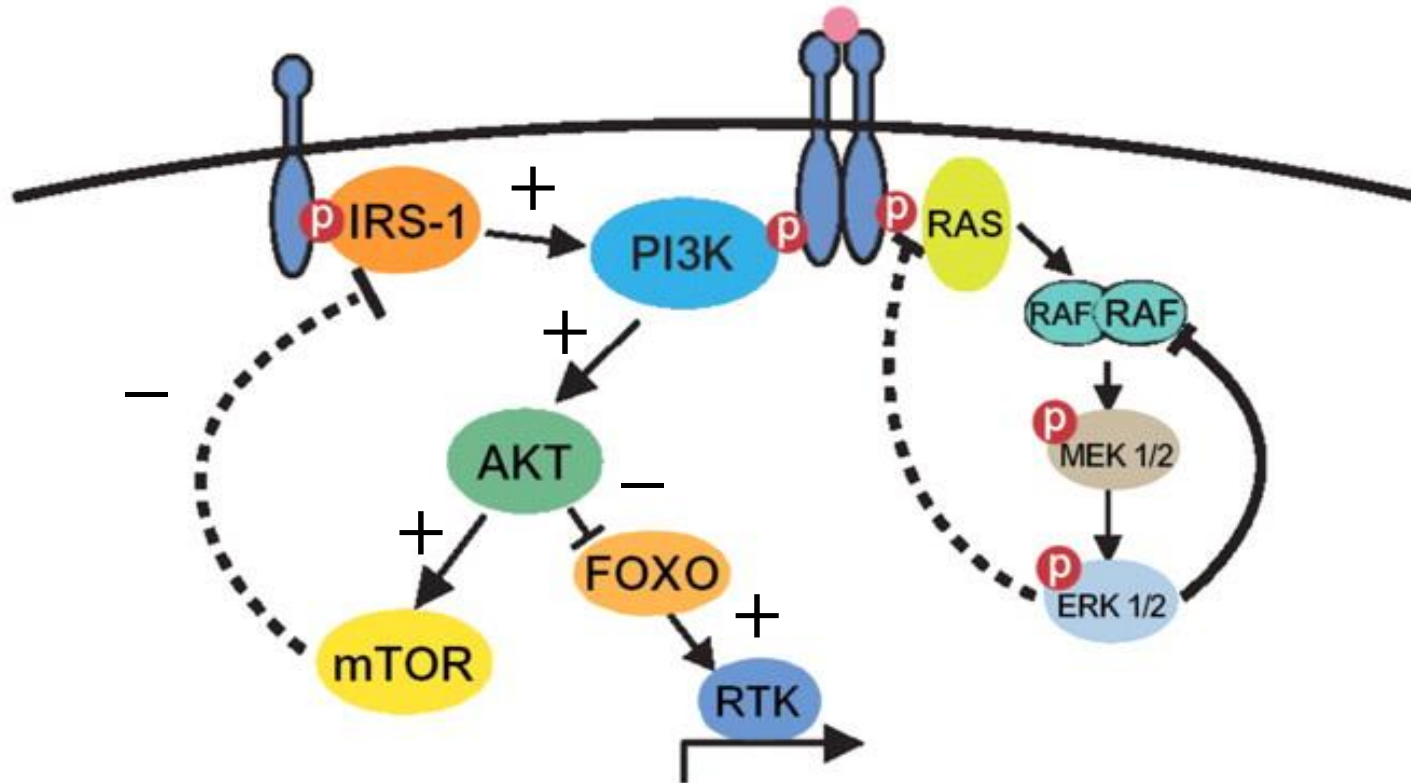
...but not here!



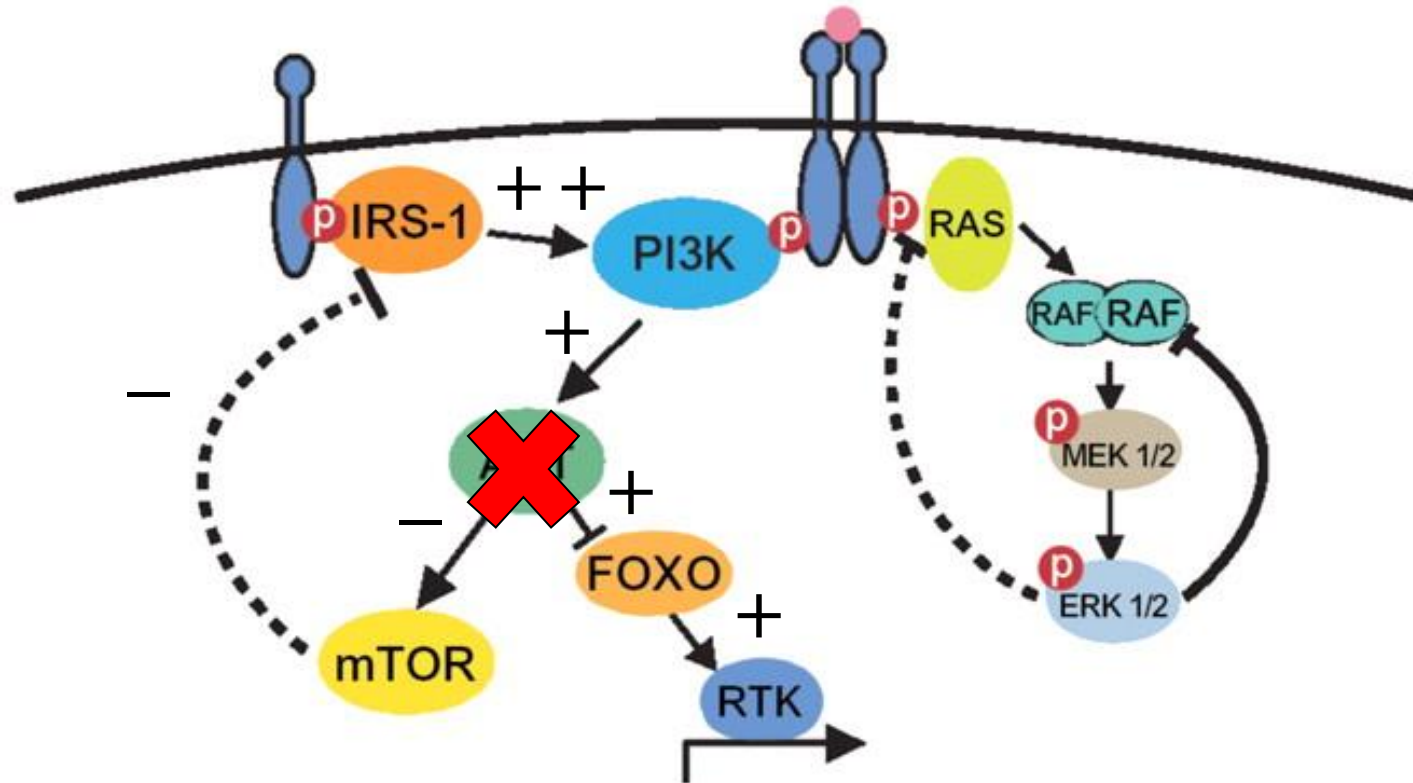


Example # 1: Feedback Loops

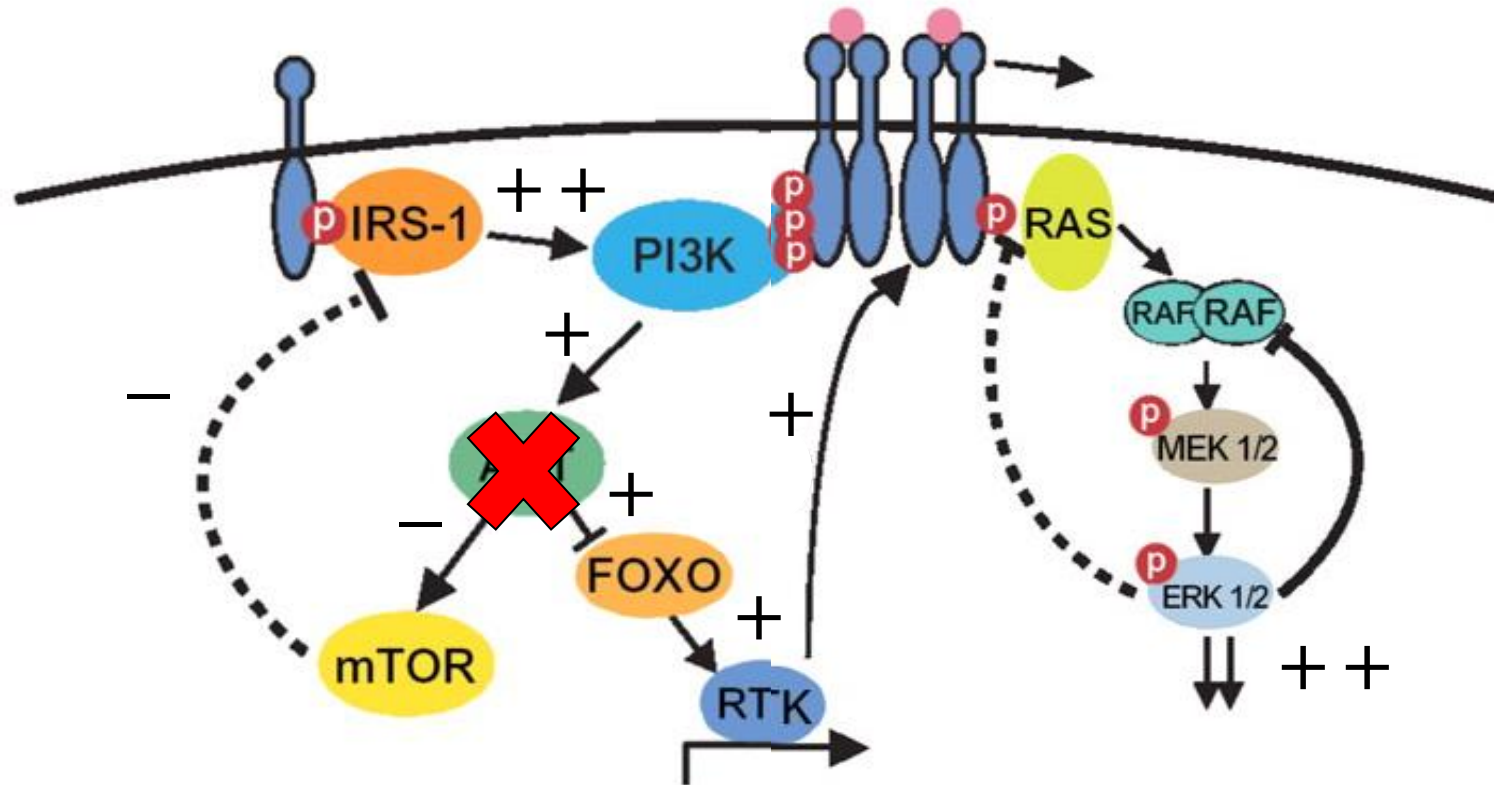
PI3K signaling involves feedback loops



Inhibiting AKT changes the signaling cascade



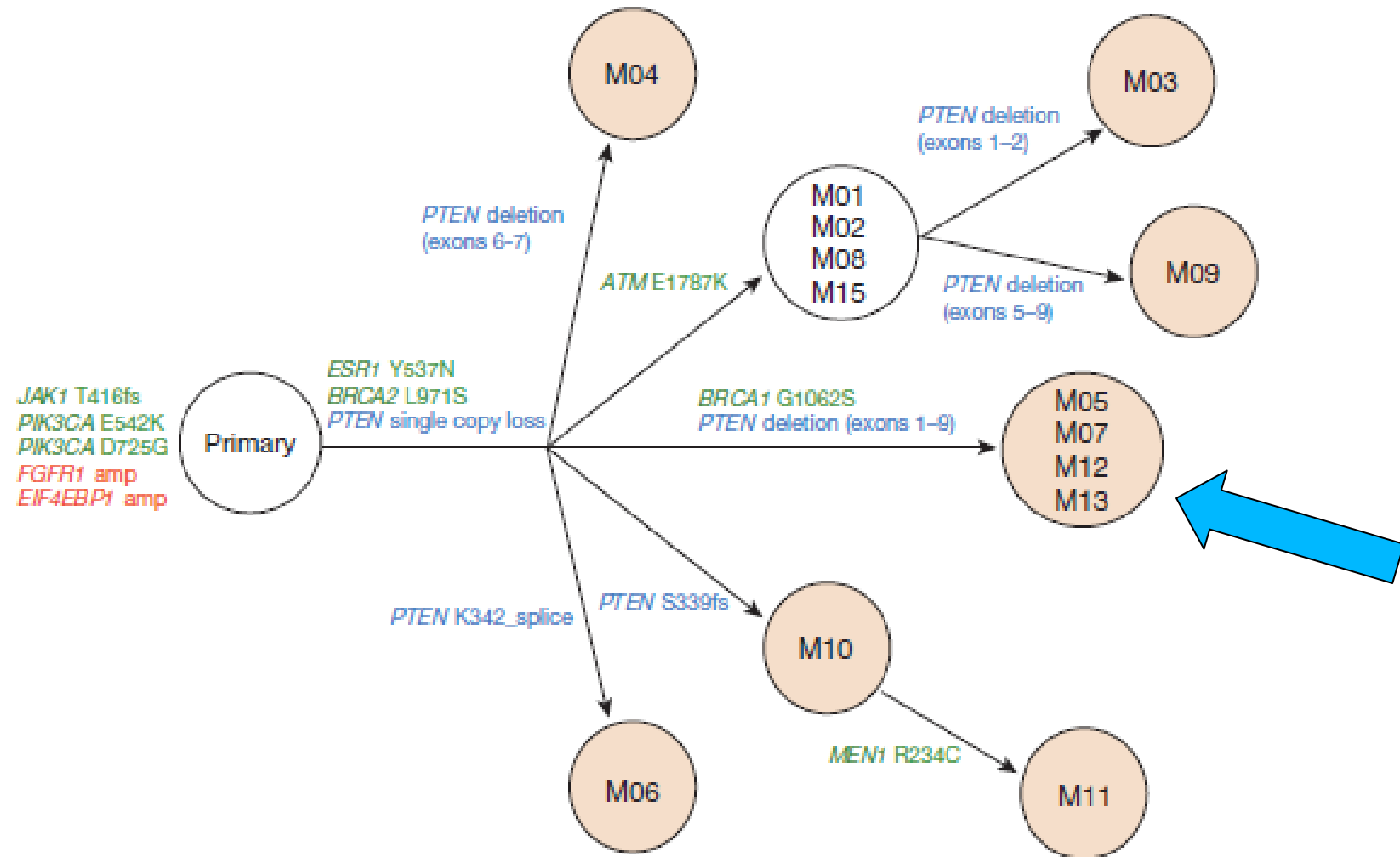
Inhibiting AKT changes the signaling cascade, causing an undesired biological effect





Example # 2: Convergent Evolution

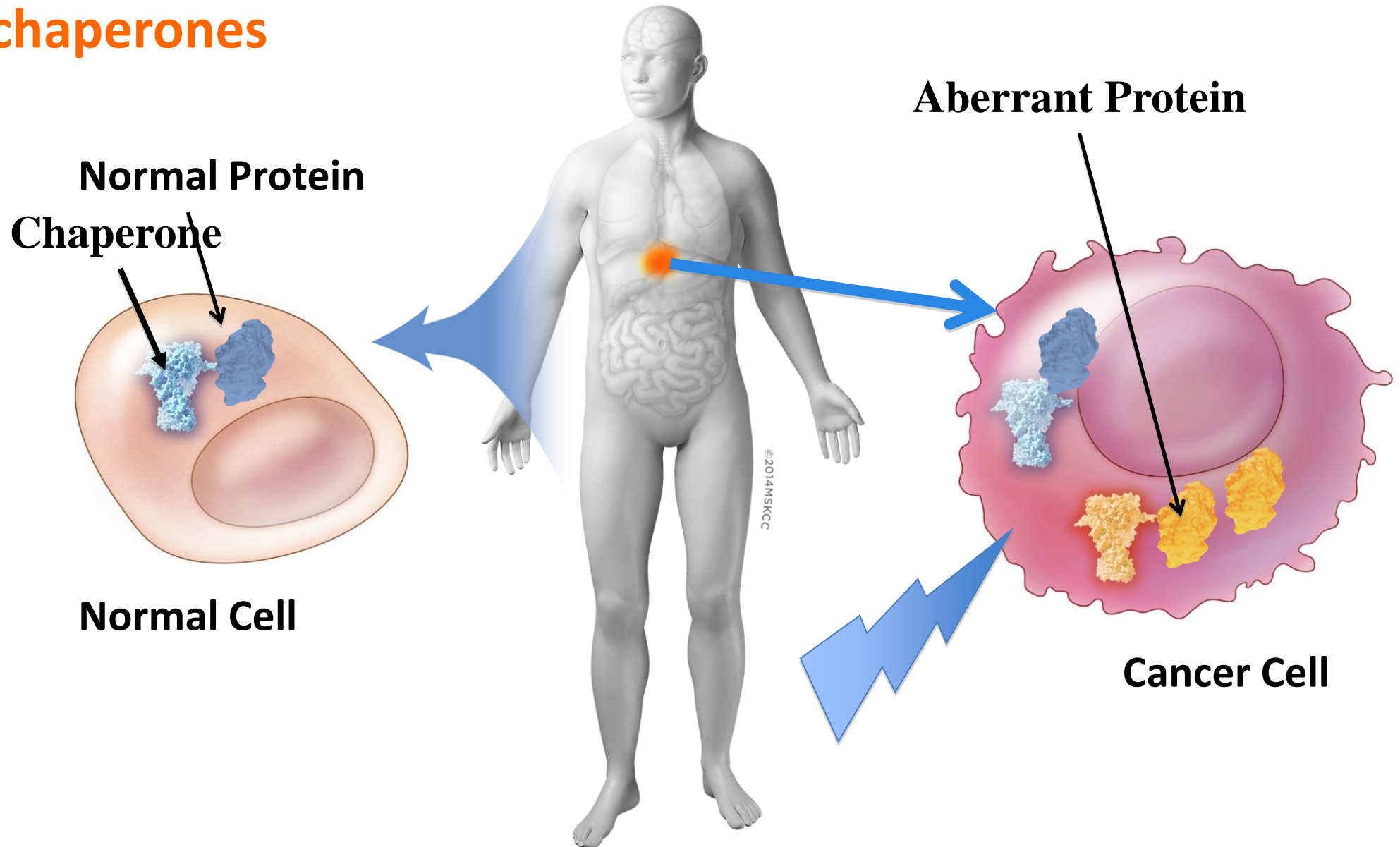
Effective PI3K α inhibition can be thwarted by different mutations that all lead to PTEN loss





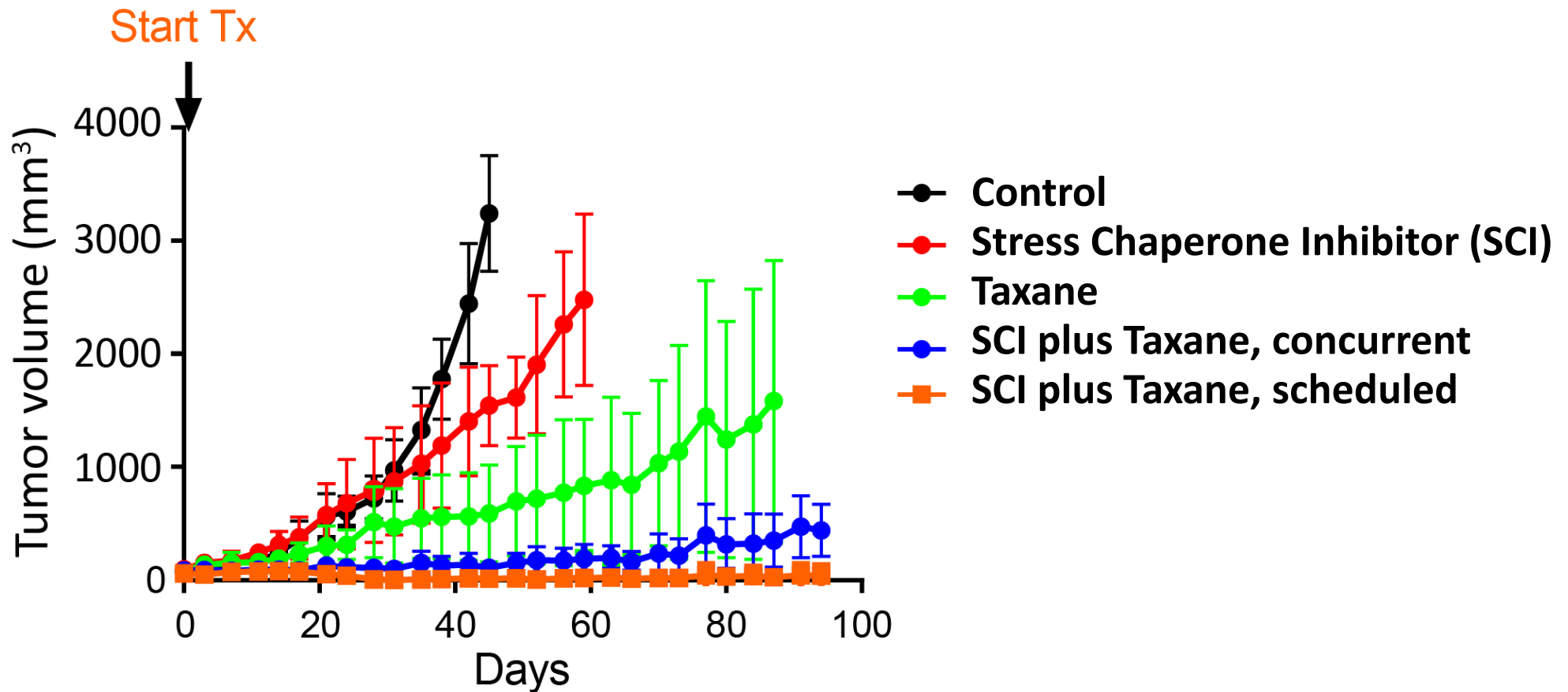
A Solution: Phenotypic Targeting

Aberrant proteins are increased in chemotherapy-treated cancer cells, rendering the cells more dependent on **stress chaperones**

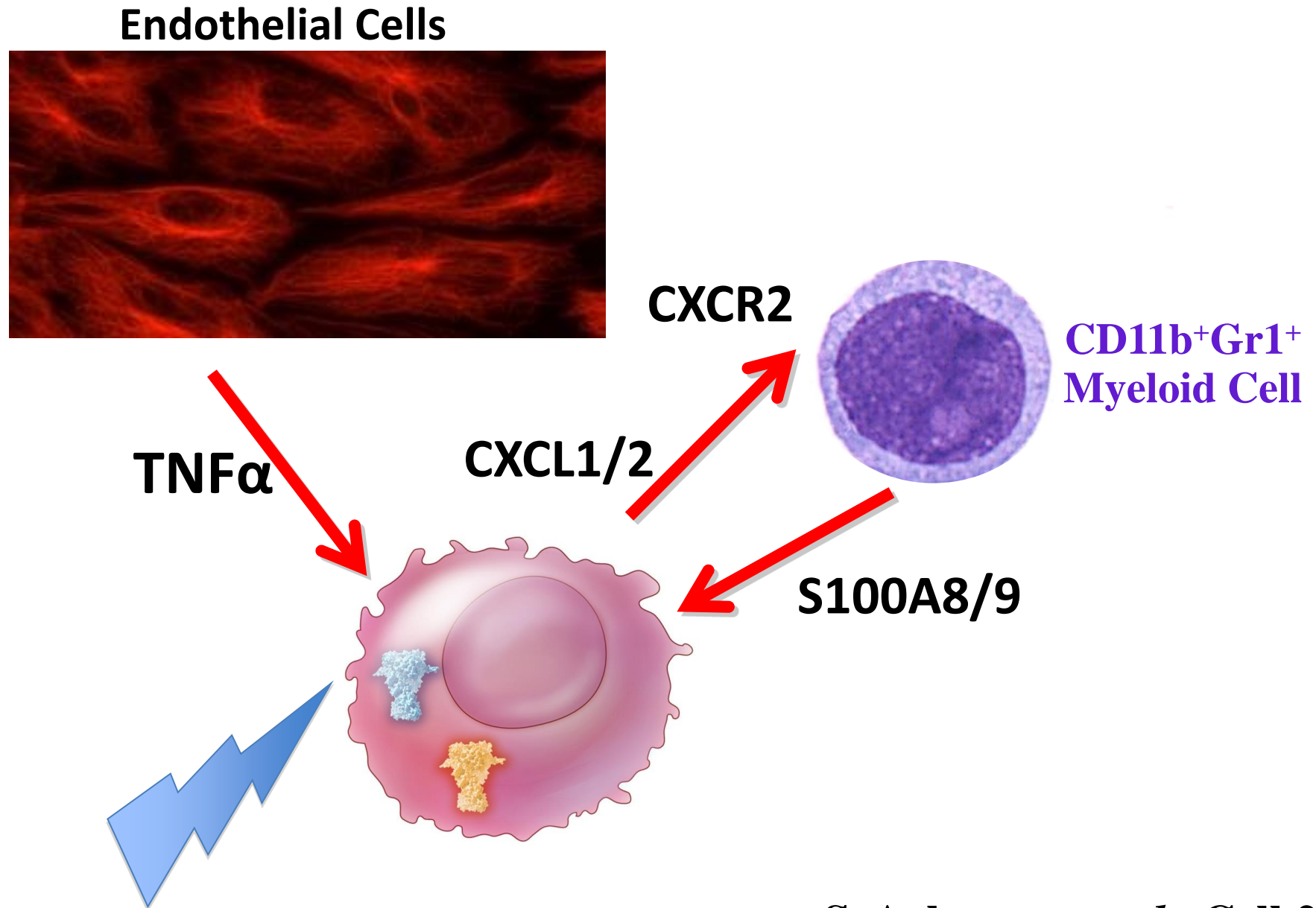


Targeting **stress chaperones** can make sub-curative chemotherapy curative

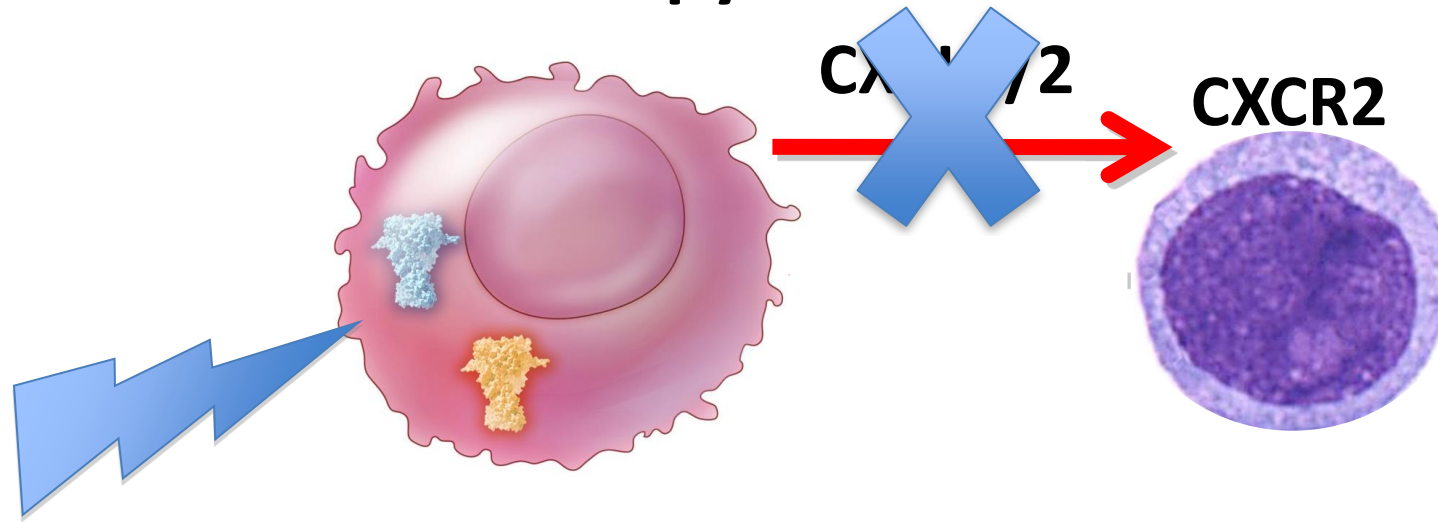
Gemcitabine resistant pancreatic cancer



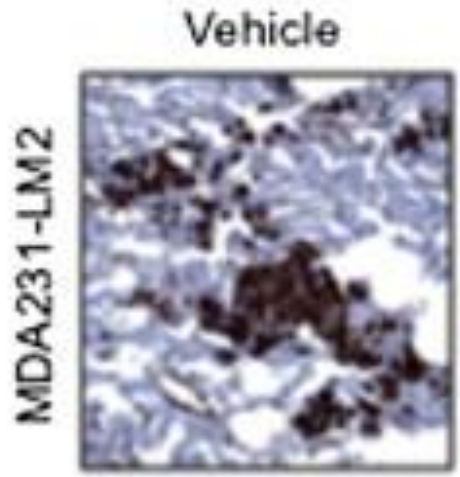
Blood vessels and leukocytes support the survival of the cancer cells exposed to chemotherapy



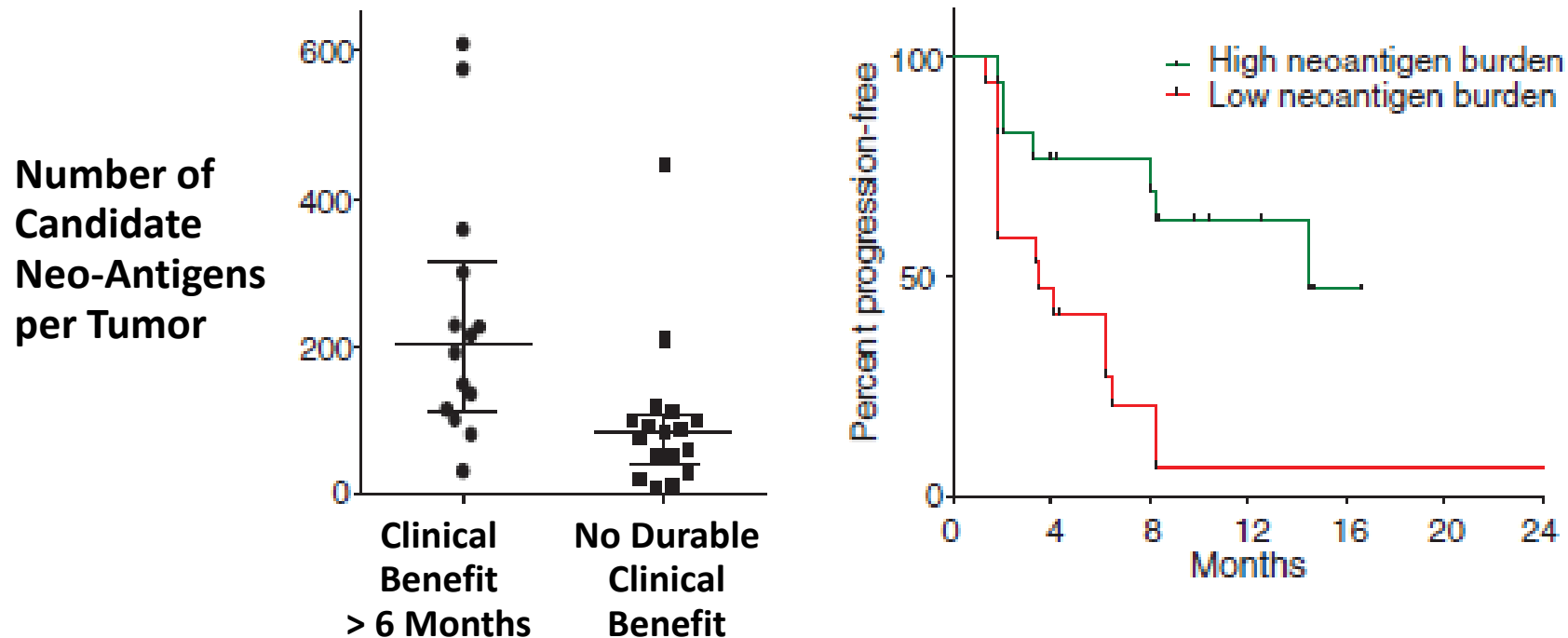
Disrupting the leukocyte-cancer interaction augments the effects of chemotherapy



Lung metastases



Burden of neo-antigens predicts benefit from PD-1 blockade with pembrolizumab in non-small cell lung cancer



Precision Molecularly-Targeted Therapy of Cancer Will Work Best When Combined With Chemotherapy (= Phenotypic Targeting)

