

It takes two to tango: Combination therapy for cancer



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Why we need combination therapy

- Cancer is a collection of malignant cells that tend to behave differently.
- Monotherapy is prone to inducing drug resistance.

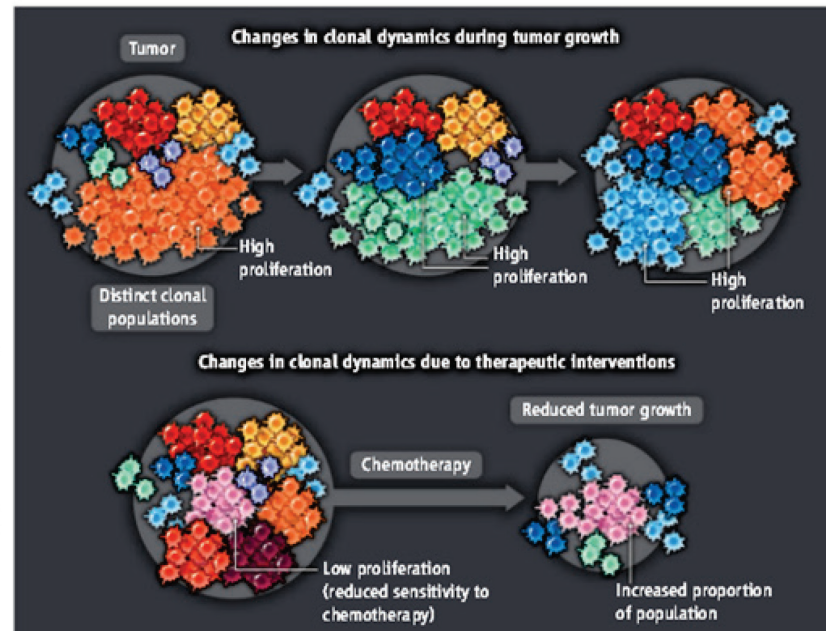
Cancer Cell Phenotypes, in Fifty Shades of Grey

Andriy Marusyk and Kornelia Polyak

Intratumor heterogeneity refers to biological differences between malignant cells originated within the same tumor. Possible explanations for this include genetic heterogeneity (resulting from the inherent genetic instability of cancer combined with evolutionary dynamics) and cell differentiation hierarchies in tumor cell populations (1–3). However, the results of Kreso *et al.* (4) on page 543 of this issue strongly suggest that biological differences between tumor cells can be due to additional mechanisms.

To explore functional heterogeneity within tumors, Kreso *et al.* traced the fates of single cell–derived clones from 10 different human primary colorectal tumors over multiple serial transplantations in mouse xenografts. Analysis of copy number alterations and deep sequencing for mutational hotspots in 42 cancer genes revealed that a number of xenografts retained the genomic profile of the primary tumor, whereas in some cases the first transplant and the parental tumor displayed substantial genetic differences

Intratumor heterogeneity is a major obstacle in successfully eradicating tumors.



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Why we need combination therapy



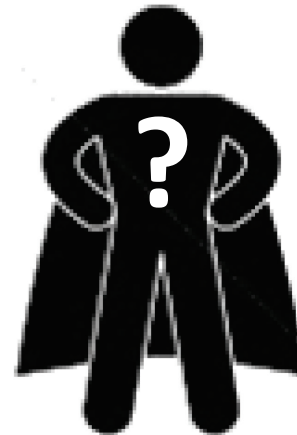
I could destroy the green ones easily, but not the tall ones. I can't do this alone!



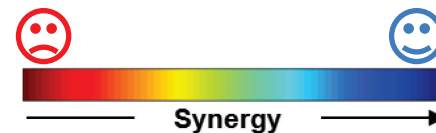
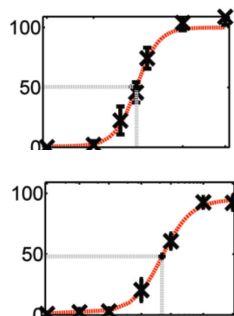
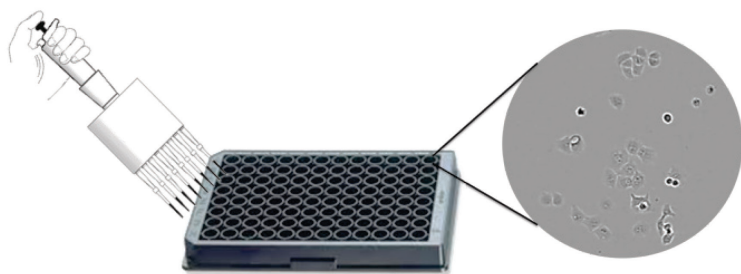
A feisty dwarf

- Who could help save the day?
- How do we identify this person?

How do we identify synergistic pairs?



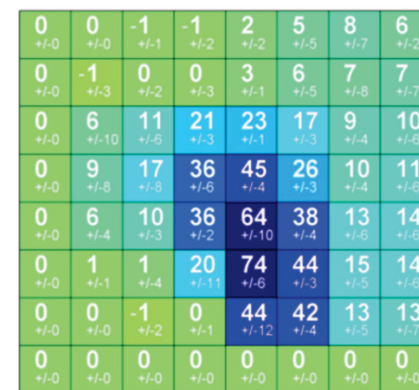
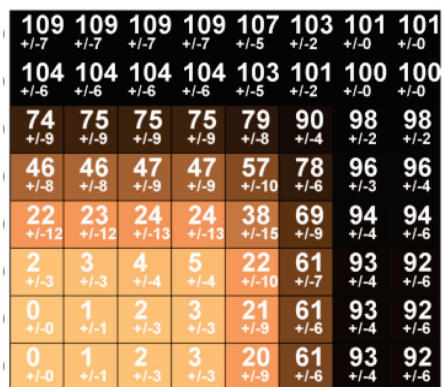
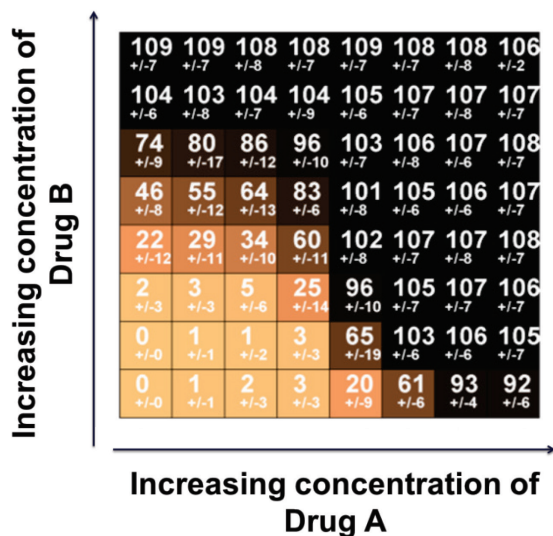
How we assess synergy in the lab



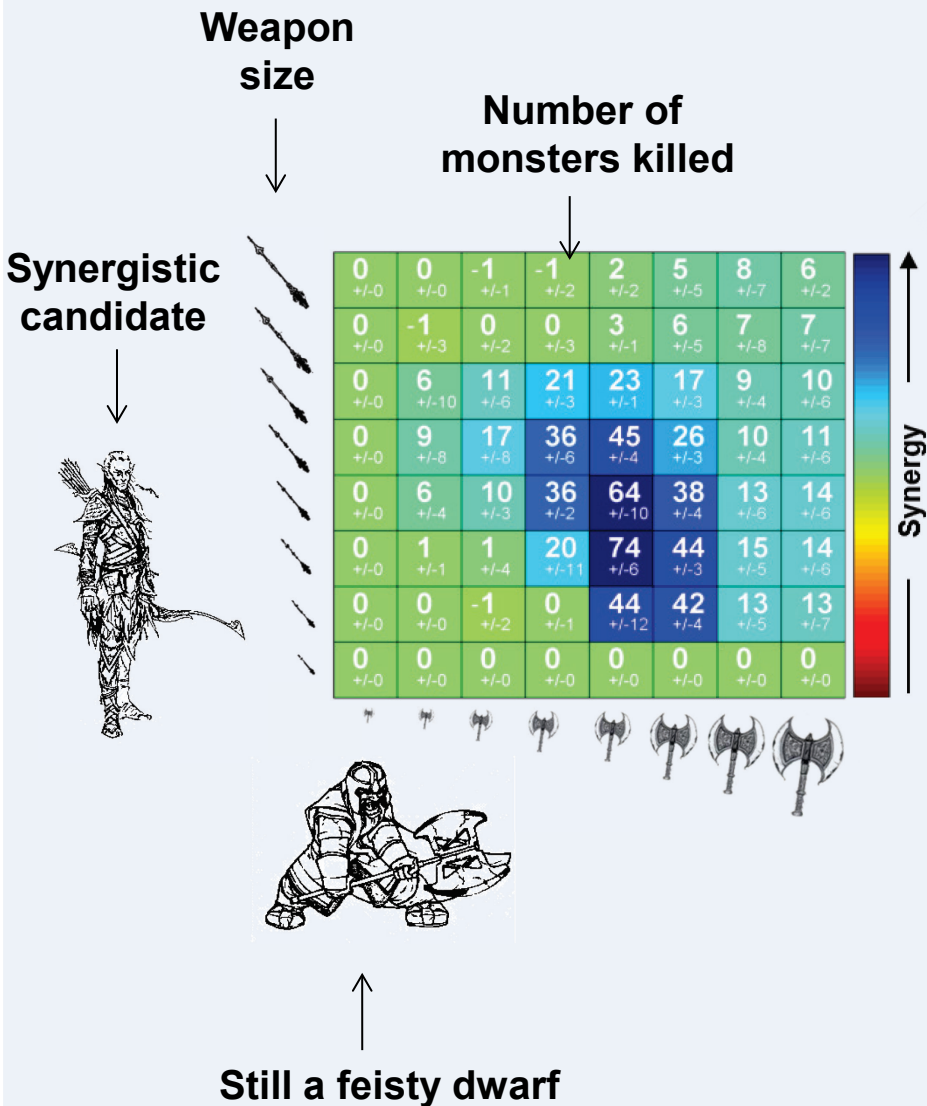
Experimental data

Model prediction

Data - Prediction



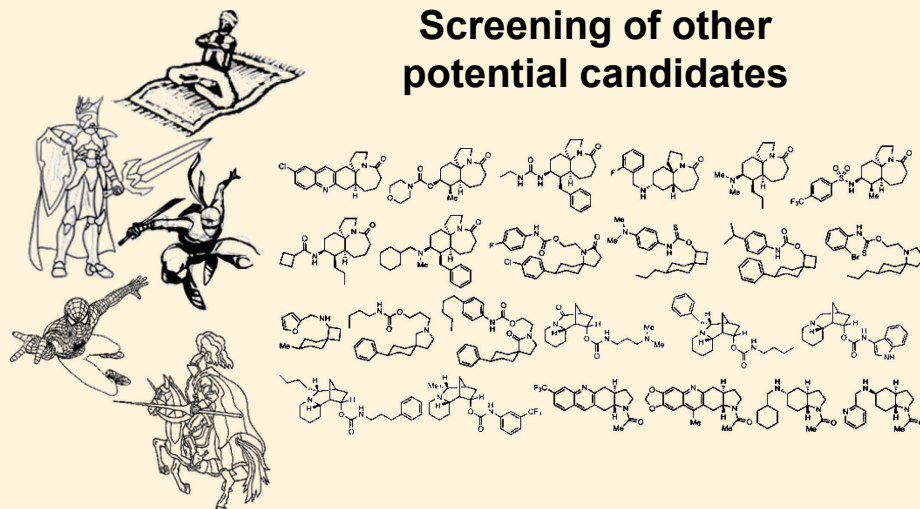
How we assess synergy in the lab



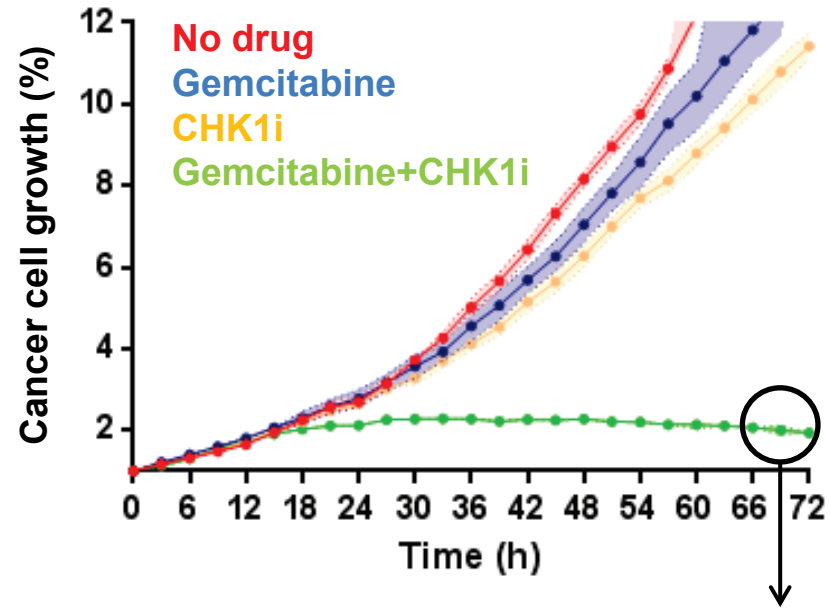
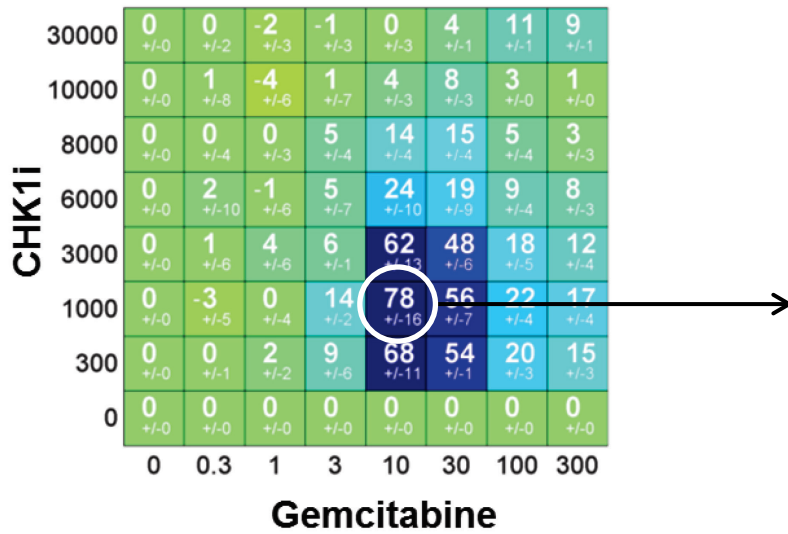
In some cases, antagonism occurs.



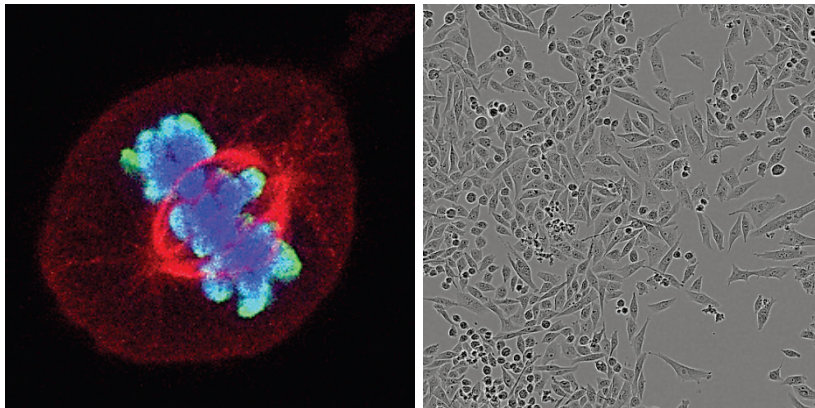
Screening of other potential candidates



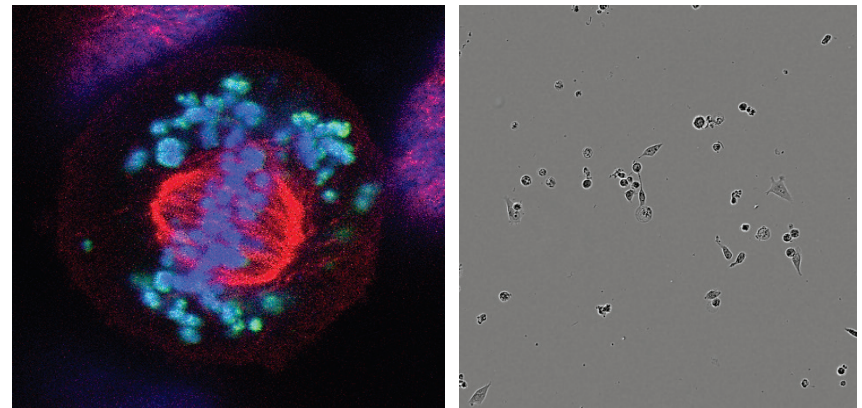
How we assess synergy in the lab



No drug



Gemcitabine+CHK1i



Summary

- **Combination therapy is an attractive approach for cancer treatment.**
- **Mathematical modelling enables high-throughput assessment of combination therapies in vitro.**
- **Quantitative assessment of combination therapies could reveal important mechanistic understanding.**
 - **Right dose**
 - **Right time**
 - **Right drug cocktails**

Acknowledgement

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