How to Co-Develop Two (or More) New Agents

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Goals Multi-targeted Approach in Cancer Therapy

* Improve efficacy
* Delay development of resistance
* Conduct more efficient trials

Targeted Agent Approval Example

Agent(s)	Efficacy	Safety			
	ORR	SCC	Pyrexia	↑ AST	↓WBC
Trametinib + Dabrafenib	76%	7%	71%	60%	62%
Dabrafenib	54%	19%	26%	15%	21%

ORR: Overall response rate, SCC: Squamous cell carcinoma

Combination Therapy

* Combination of two or more approved agents
* Adding a new investigational agent to approved agents
* **Combination of two or more new investigational agents**

FDA Guidance: Co-Development of Two or More New Agents

- Criteria for Co-Development of New Agents
  - Intended to treat a serious disease or condition
  - **Strong biological rationale** for use of the combination
  - Non-clinical or limited clinical study suggest significant therapeutic advance
  - Compelling reason that new agents cannot be developed independently

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

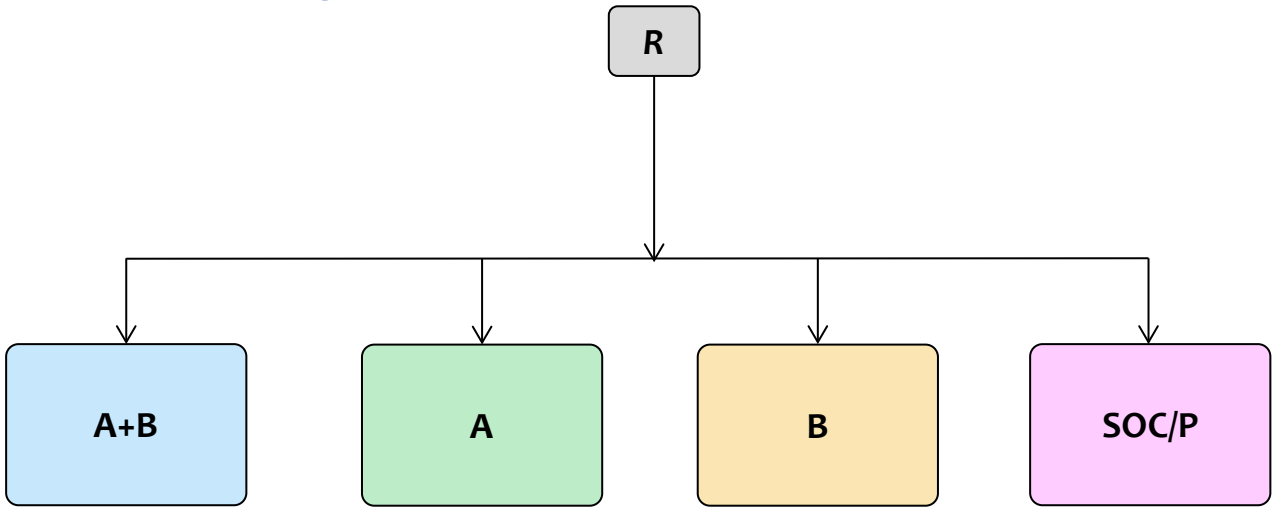
Considerations for Co-Development of New Agents in the "Omics" Era

* Trial design considerations
* Target(s) Selection
* Agent(s) Selection
* Dose and dosing schedule finding

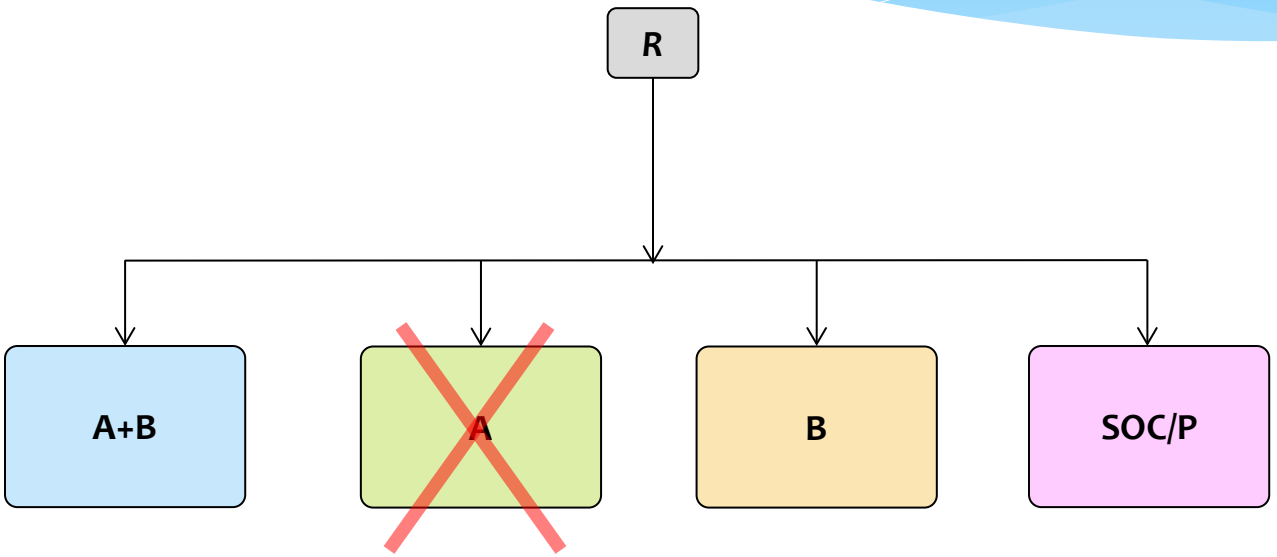
Trial Design Considerations

Proof of Concept Studies: Randomized Trials Designs

- **Scenario 1 (Conventional Multi-factorial Model)**
  - Each new investigational drug alone has activity and they can be administered separately



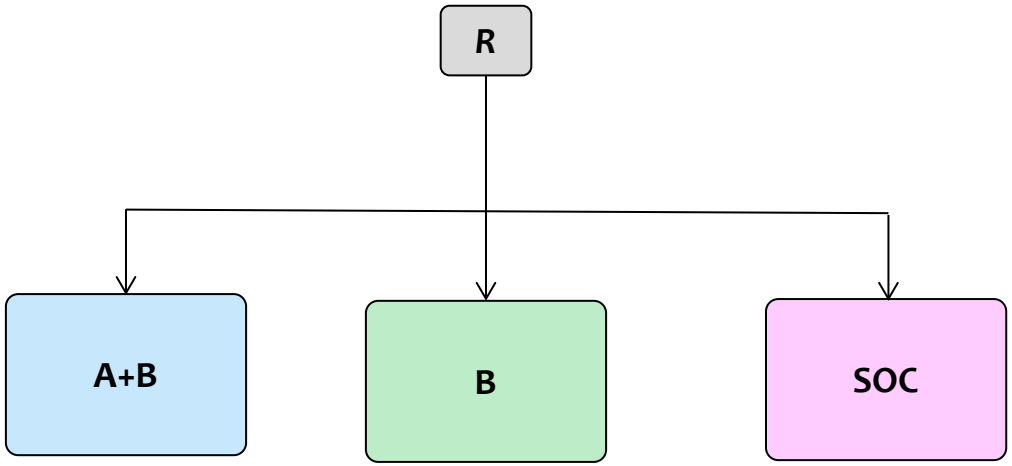
Adaptive Design



* Interim futility analysis

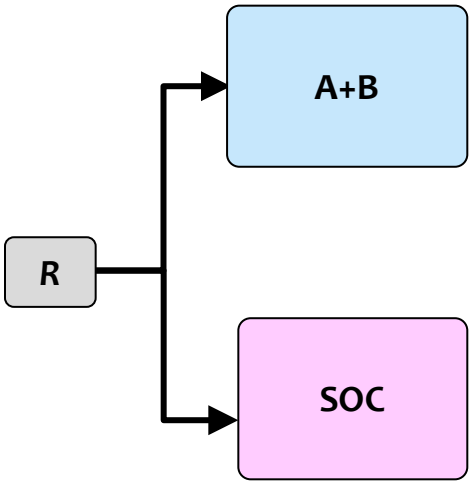
Randomized Trials Designs

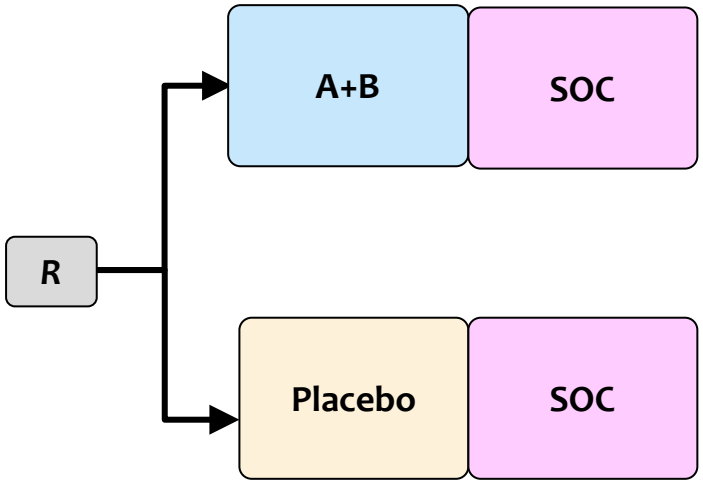
* **Scenario 2:** When administered separately, one new investigational drug in the combination is active (A) and one is inactive (B)



When Isolation of Effect of Both Agents Is Not Required

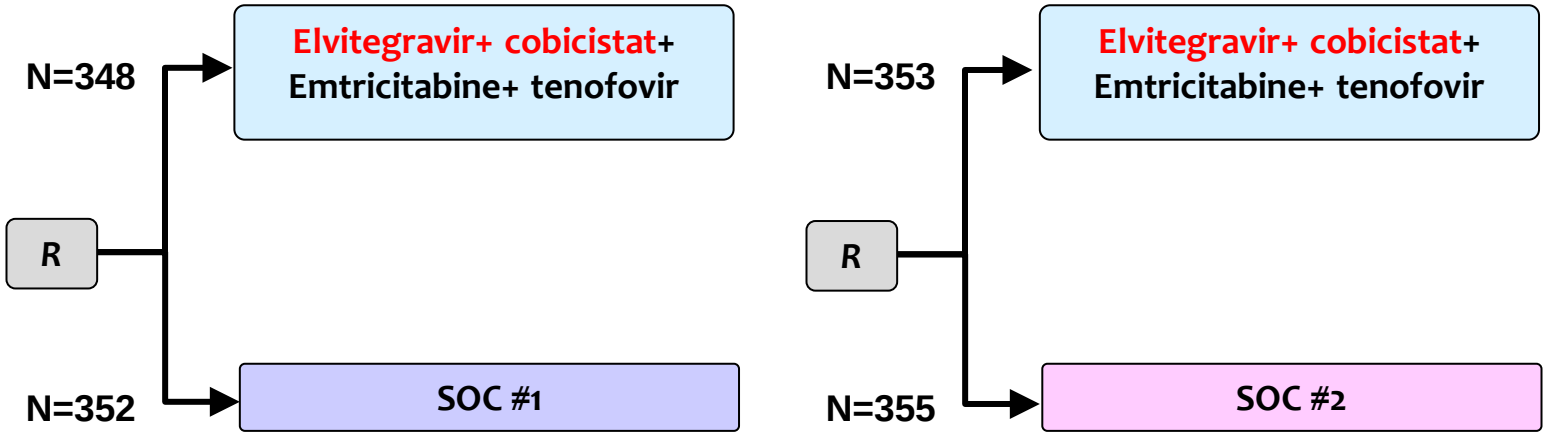
* **Scenario 3:** The individual new investigational drugs in the combination cannot be administered separately



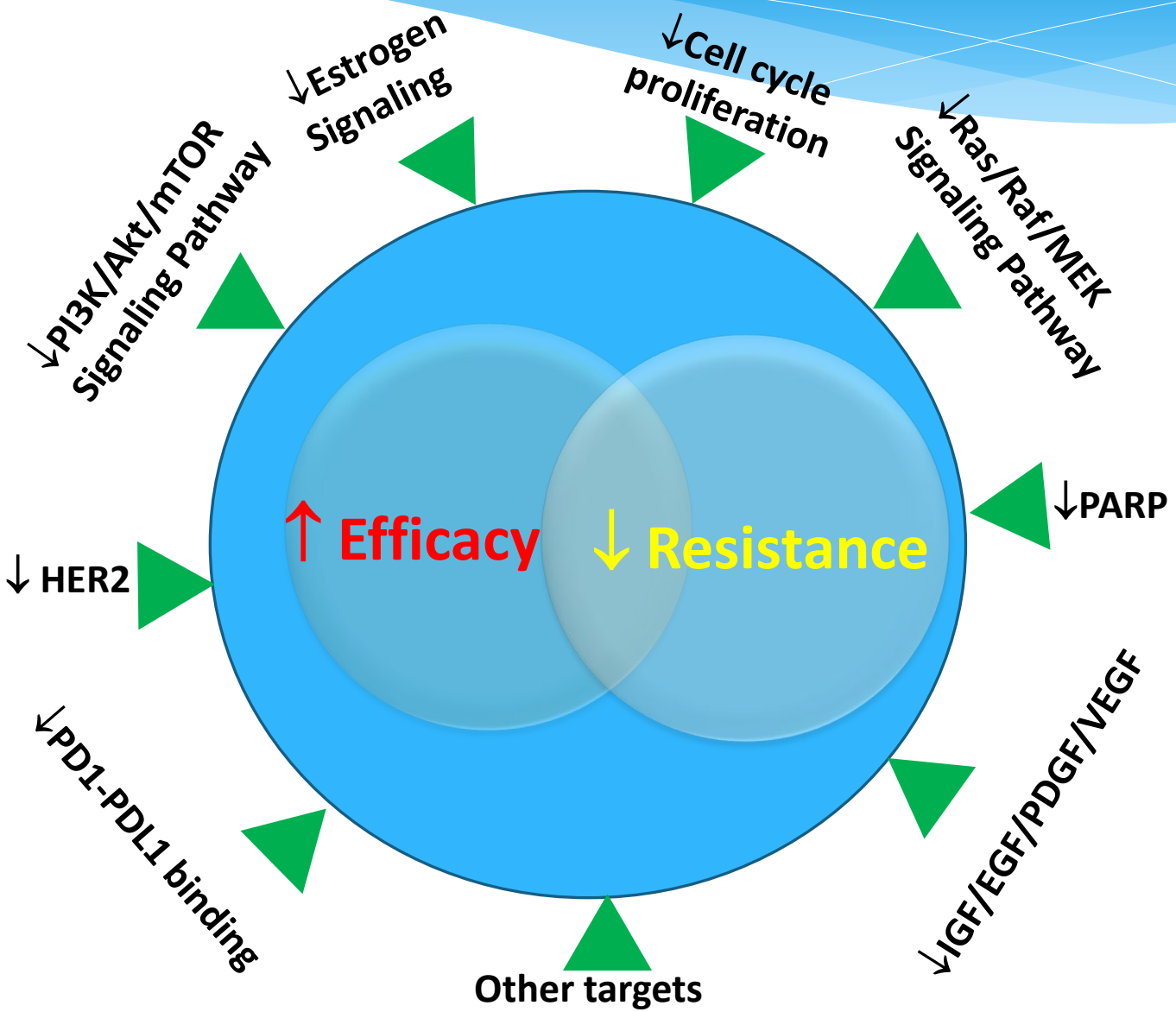


HIV Drug Approval 2012

- Stribild combination pill
  - Contains two previously approved HIV drugs (emtricitabine and tenofovir) plus **two** new drugs (elvitegravir and cobicistat)
- **Biologic rational of the combination**: Cobicistat, a pharmacokinetic enhancer, inhibits the enzyme that metabolizes elvitegravir and is used to prolong the effect of it



Target(s) Selection

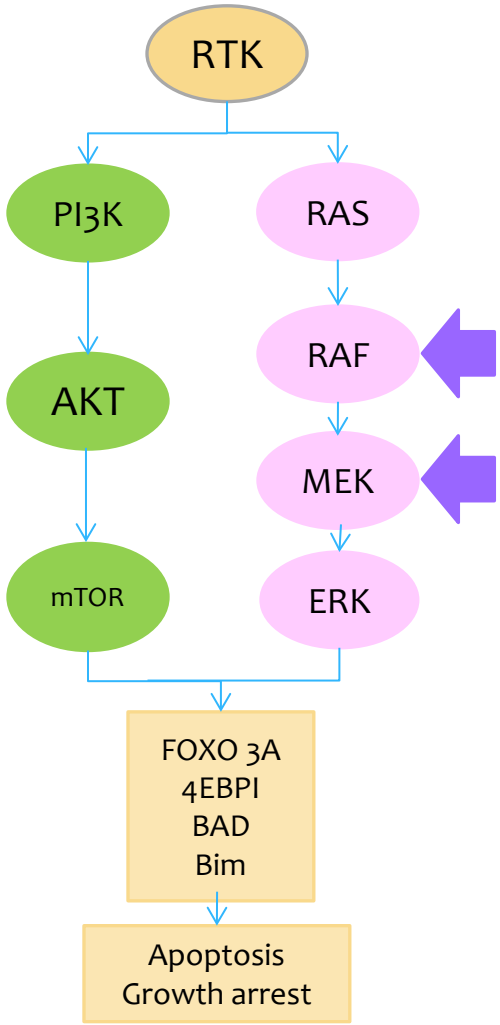

↓Estrogen Signaling
↓Cell cycle proliferation
↓Ras/Raf/MEK Signaling Pathway
↓PI3K/Akt/mTOR Signaling Pathway
↑ Efficacy
↓ Resistance
↓PARP
↓ HER2
↓PD1-PDL1 binding
↓IGF/EGF/PDGF/VEGF
Other targets

Methods of Target(s) Selection

- Methods to evaluate and prioritize the best potential combinations:
  - Large-scale unbiased *in silico* or experimental biology methods
  - Hypothesis-driven approaches
    - genomics, proteomics and other omics technologies

Al-Lazikani B. et al, Nature biotechnology 2012

Target(s) Selection: Combinatorial Options



- **Vertical (within one oncogenic pathway)**
  - **Adding MEK inh to BRAF inh**
- Horizontal (across two 'parallel' pathways)
  - Adding AKT inh to MEK inh
- Same target (receptor)
  - Pertuzumab+ trastuzumab

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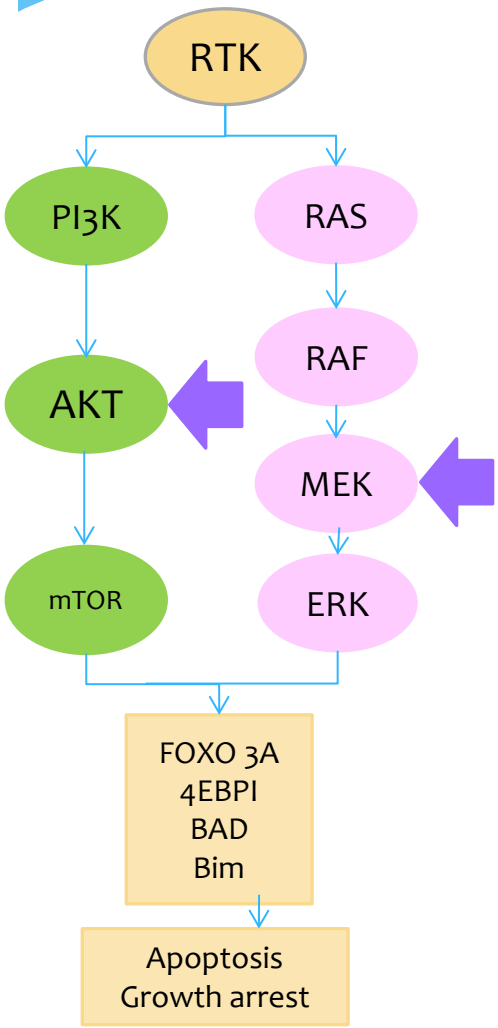

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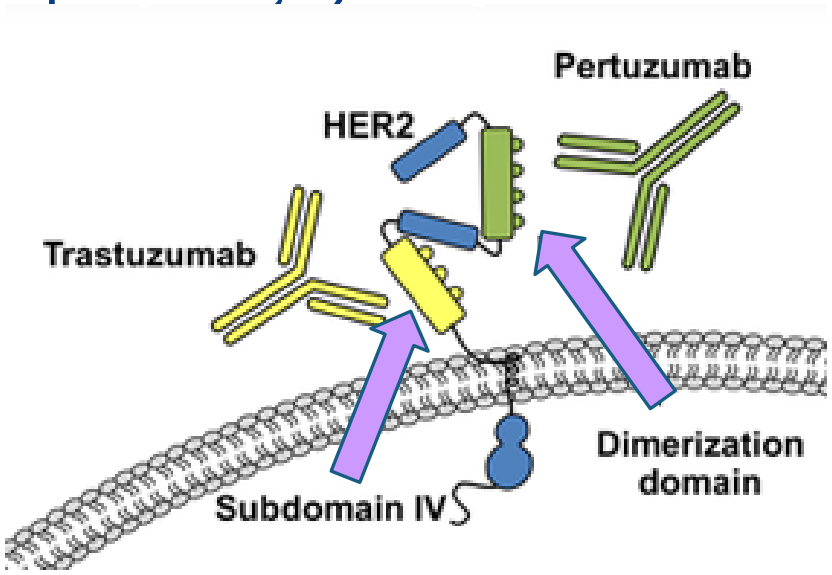


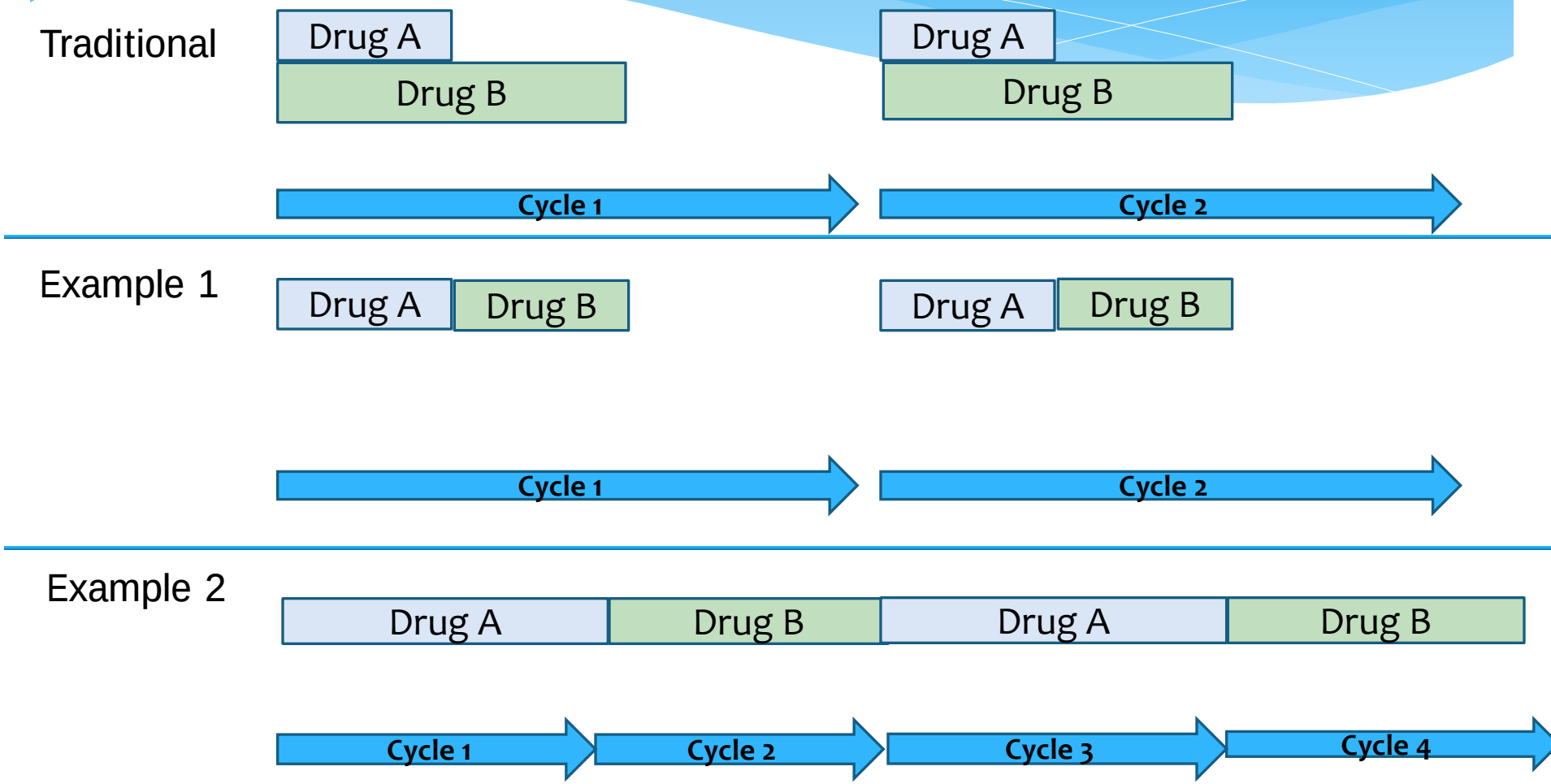
Agent(s) Selection

Agent(s) Selection: Smart Drugs!

- Specific and selective for target(s)
- Promising preliminary activity (preclinical/clinical)
- Human safety data (DLT, MTD, etc)
- Have activity across multiple dose levels
  - To allow flexibility for combinatorial strategies

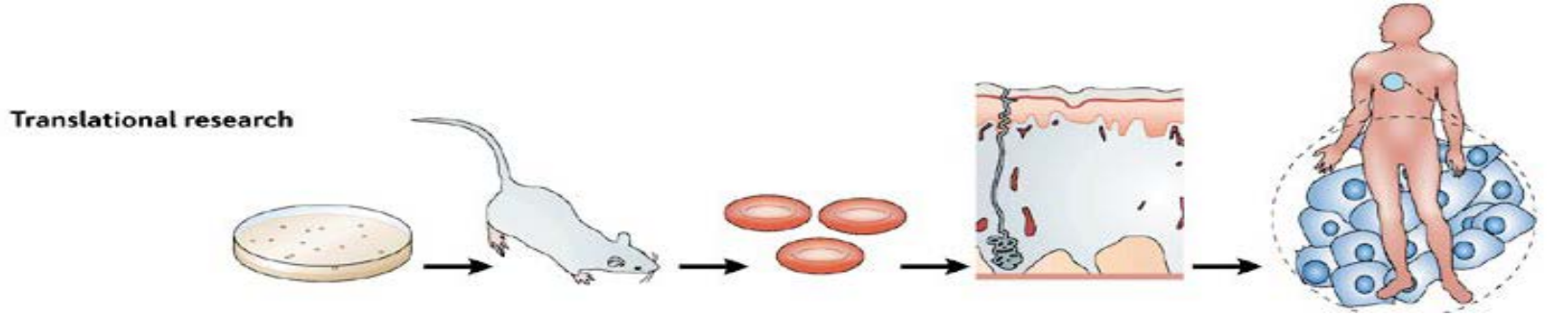
Dose and dosing schedule finding

Alternative Dosing Schedules to Minimize Overlapping Toxicity



Methods: Dose and dosing schedule finding

- Pre-clinical
  - *In silico* models (PBPK modeling, evolutionary modeling, etc), *in vitro* and *in vivo studies*
- Clinical
  - Adaptive Phase 1 single agent & combination studies



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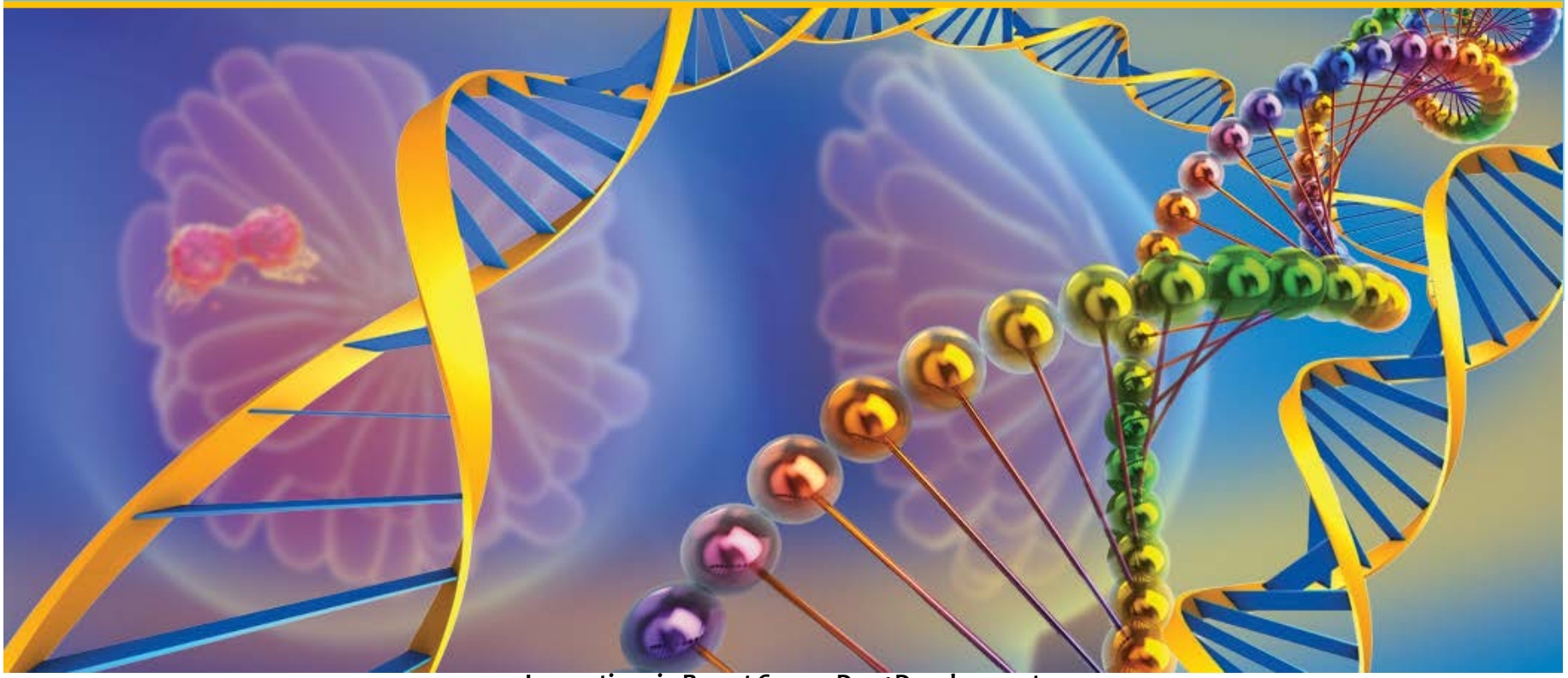
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