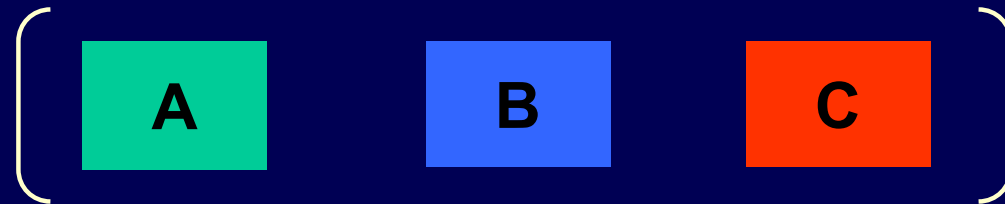


Pattern Recognition Tumor Targeting (PRTT)

A Pattern is a Set of Biomolecules



Pattern ABC is present if and only if all three elements A, B, and C are present

The role of target patterns is to allow the detection of cancer cells.

Elements of Patterns can be

- On the tumor cell surface
- In the microenvironment
- Inside the tumor cell
- Or combinations of the above

The Logic of PRTT Drugs



Are all the elements of the pattern present ?

Yes



Kill Cell

No



Spare Cell

Specificity is for the pattern not the individual elements.

The Design of PRTT Drugs

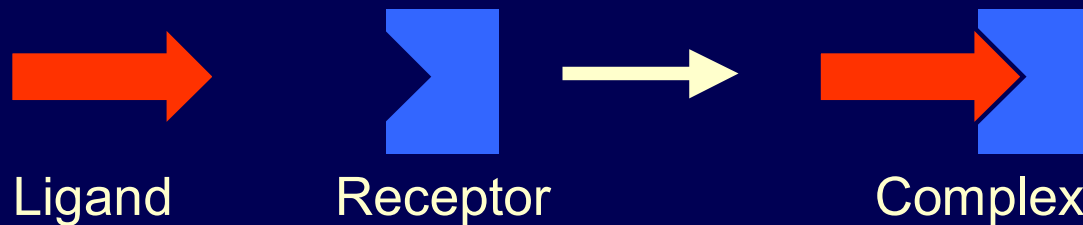
The basic principles of the design of PRTT drugs are simple and involve the use of a small number of modular components.

There are only two ways that a target can interact with a drug

- It can bind to the drug
- It can trigger a chemical change in the drug

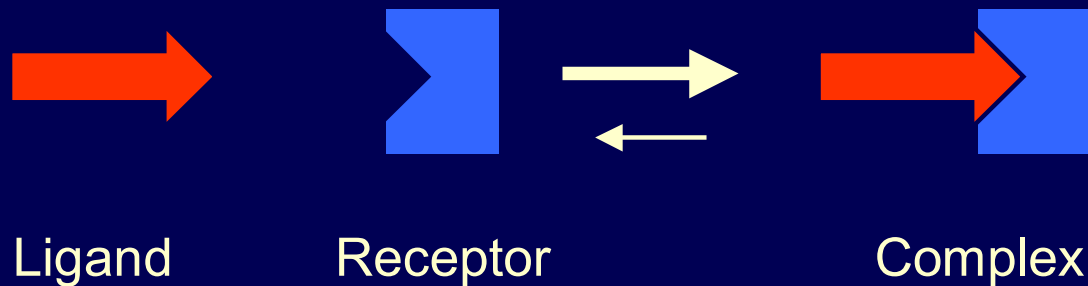
These define the key building blocks of drugs: ligands and triggers.

Targeting Ligands



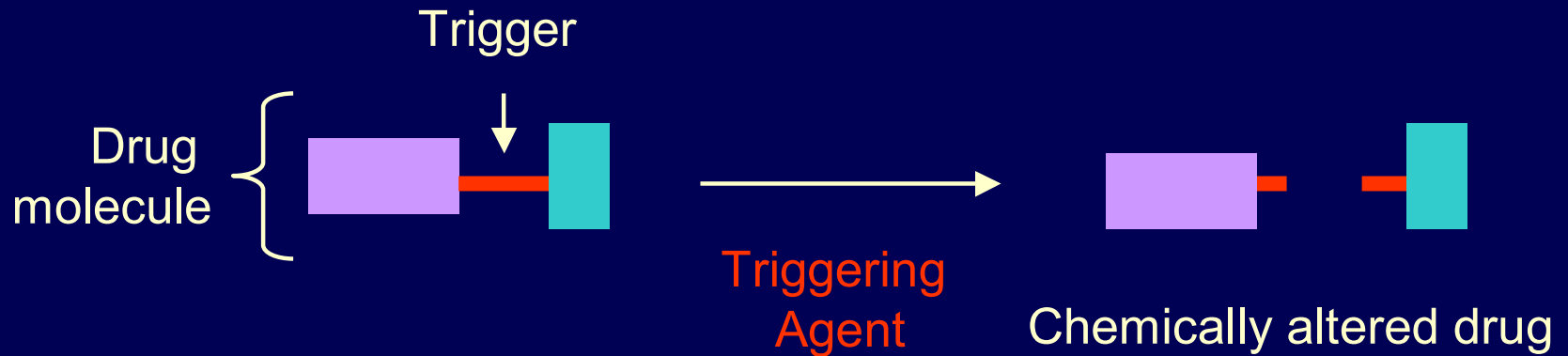
Ligands are chemical groups that bind together like a lock and key to target receptors.

Targeting Ligands are Used to Localize Drug to the Target



If the binding is tight then the drug will localize at receptor sites. In the ideal, binding is specific and irreversible.

Triggers and Triggering Agents



Triggers are chemical groups then when acted upon by a triggering agent undergo a chemical change. Enzymes can serve as triggering agents.

Triggers Have Many Uses

- To turn on or off a chemical process
- To activate a toxin
- To inactivate a toxin
- To unmask a ligand
- To release a toxin

Other Modular Drug Components

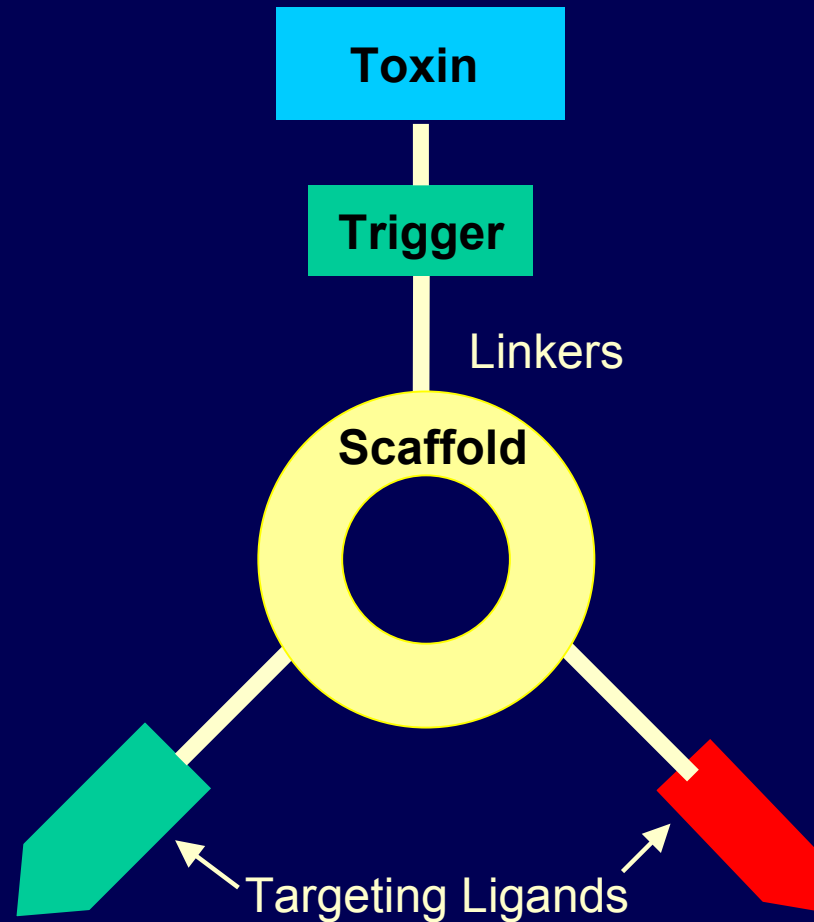
Linkers: provide structure and connect different groups of the drug molecule

Effector Agents: kill the cell

Male Ligands and Female Adaptors: bind tightly together

Other groups can be added to confer additional specialized functions.

Modular Component-Based Design Drug



A variety of modular designs are possible.

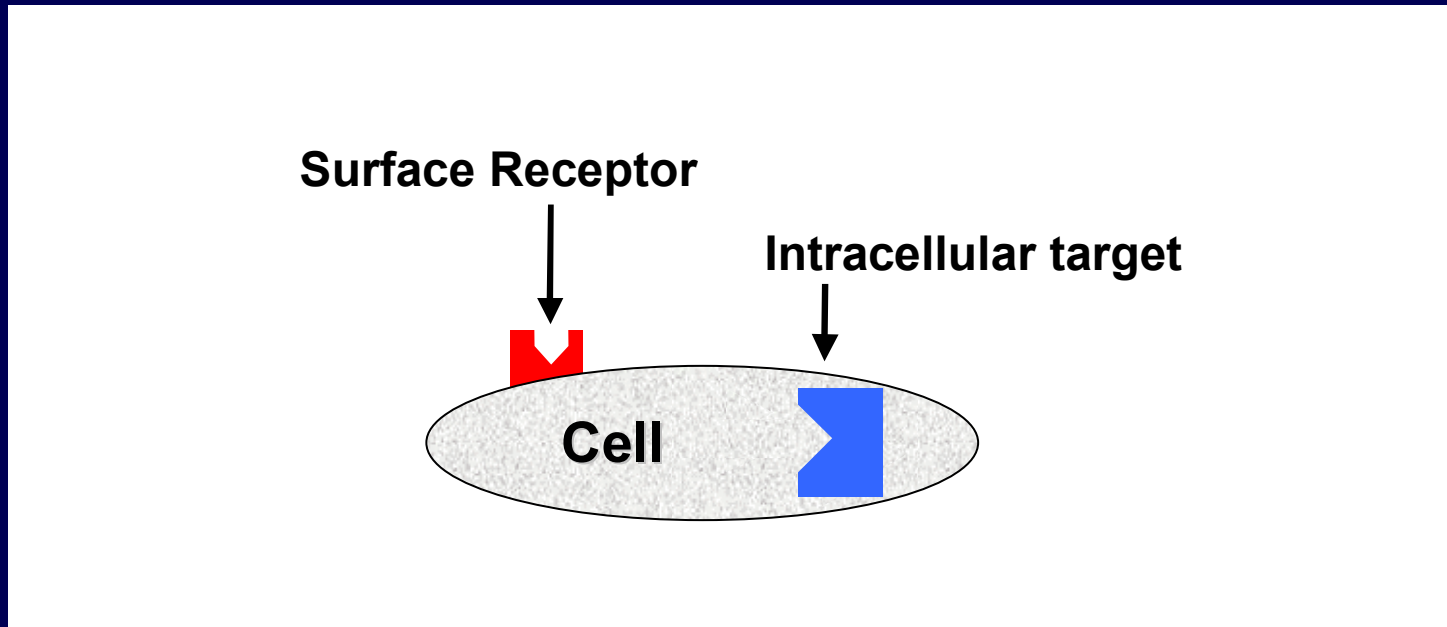
There are a Many PRTT Approaches

- Targeted delivery of a targeted agent
- Targeted Delivery of a Trigger Activated Drug
- Independently targeted synergistically toxic drugs
- Multi-site binding
- Exponential Pattern Recognition Targeting
- Other

Targeted Delivery of a Targeted Cytotoxic Agent

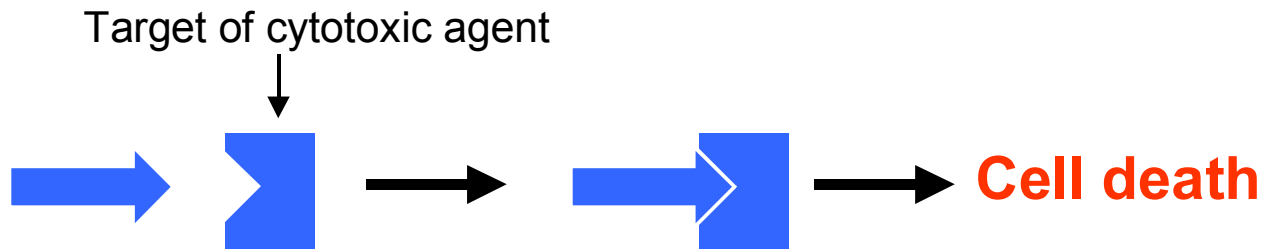
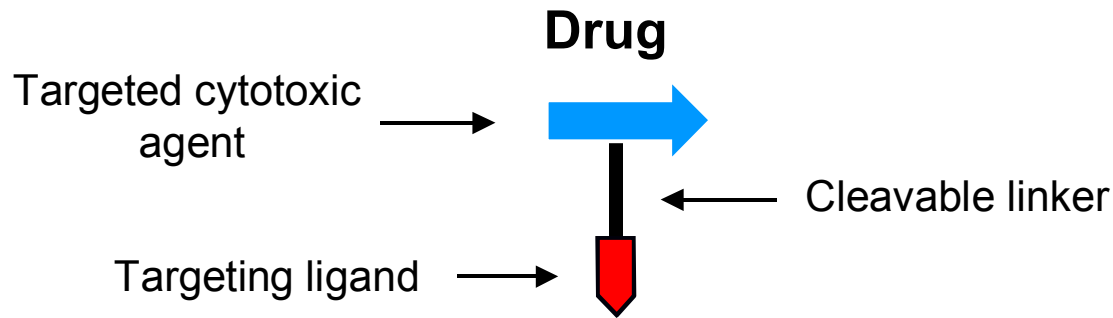
**This method is the simplest
and requires no new drug
delivery technology**

The Pattern is a Surface Receptor and Intracellular Target

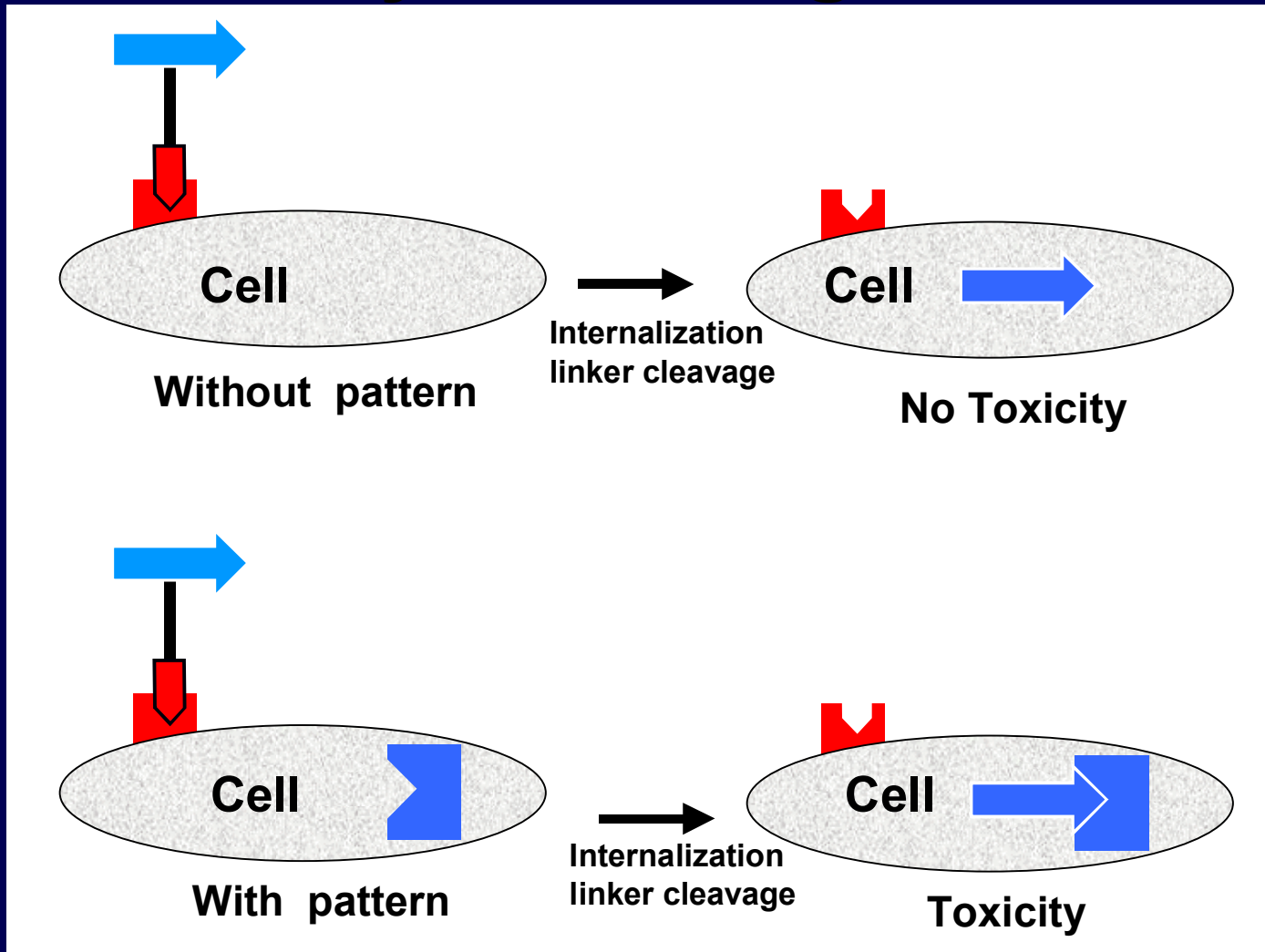


For cell killing both must be present

Targeted Delivery of a Targeted Cytotoxic Agent

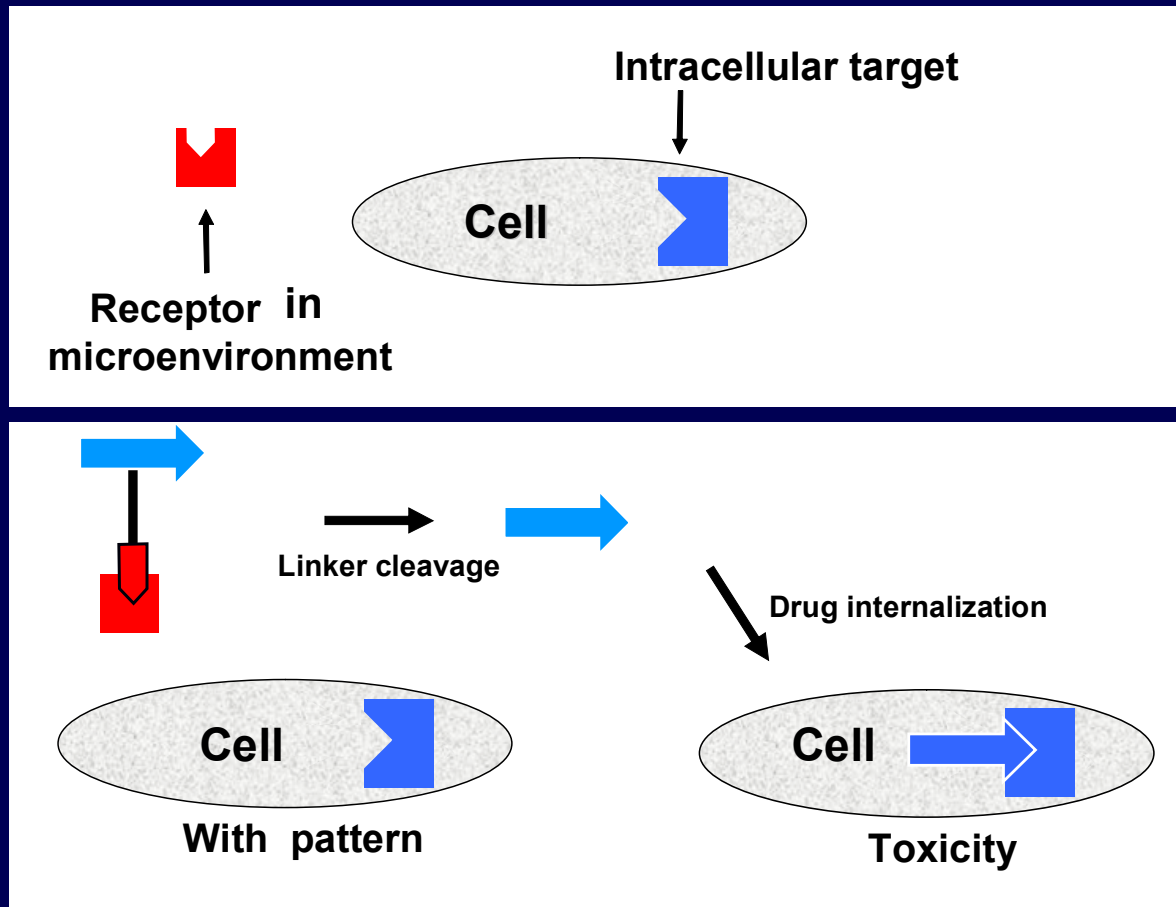


Targeted Delivery of a Targeted Cytotoxic Agent



The cytotoxic agent is toxic only if its target is present

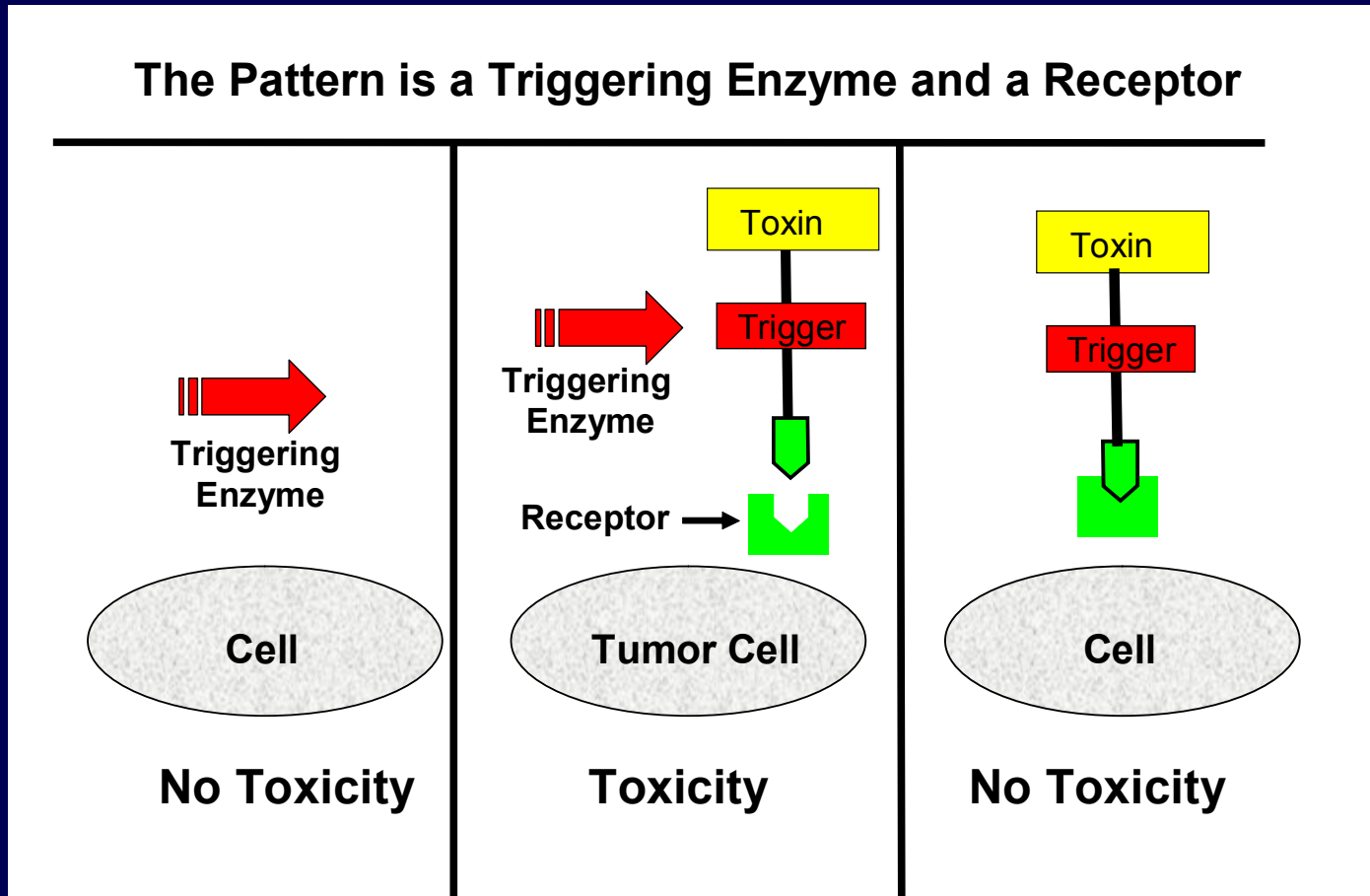
The Targeting Receptor Can Also be in the Tumor Cell Microenvironment



Targeted Delivery of a Trigger Activated Drug

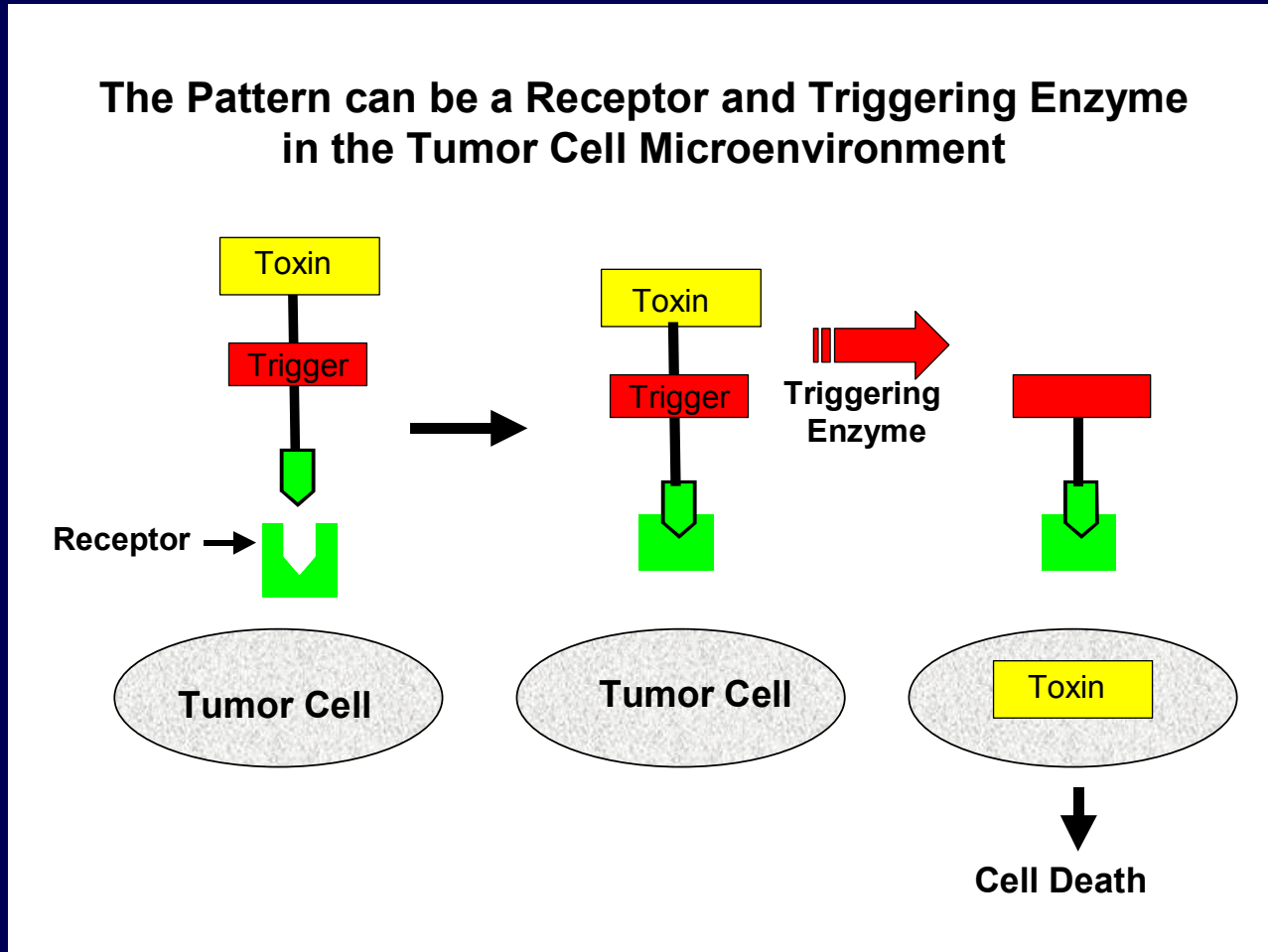
Targeted Delivery of a Trigger Activated Drug

The Pattern is a Triggering Enzyme and a Receptor



Only cells that have both the target receptor and the triggering enzyme will be killed.

Targeted Delivery of a Trigger Activated Drug



The drug is targeted to the microenvironment, released by the triggering enzyme, diffuses to the tumor cell and kills it.

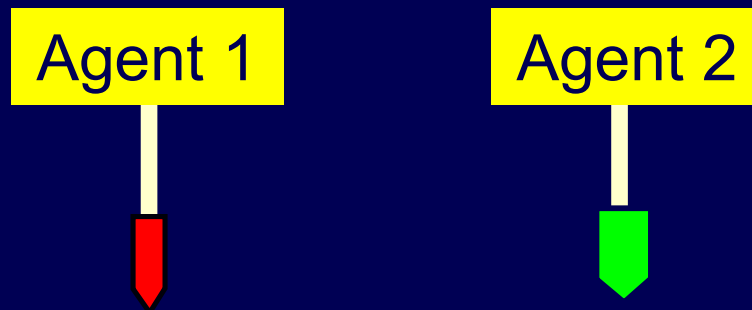
Advantages of Releasing a Toxin into the Tumor Micro-Environment

- Invasiveness is a property of both the cancer cell and its microenvironment
- A zone of toxicity is created making it easier to kill all the cancer cells

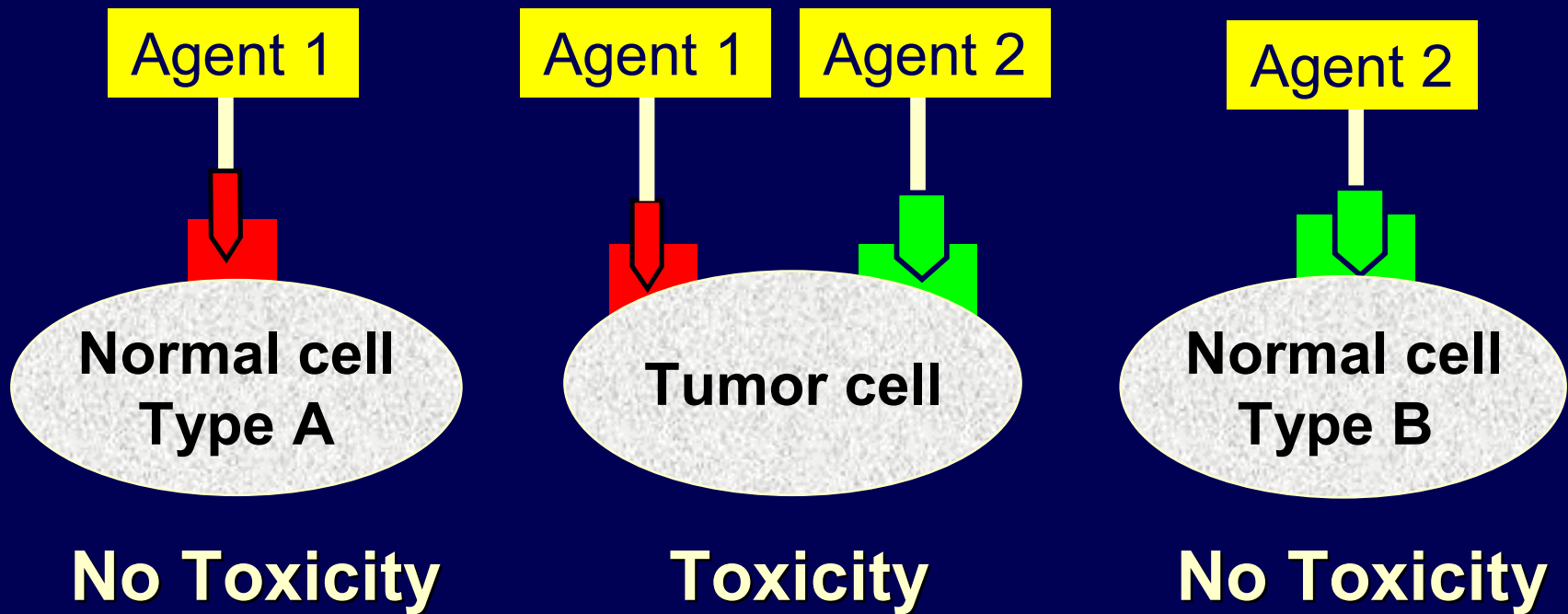
PRTT approaches that produce a zone of toxicity are strongly preferred over those that target individual cancer cells.

**Paired, Independently
Targeted, Synergistically
Toxic Drugs**

Paired, Independently Targeted Synergistically Toxic Drugs



Individually, Agent 1 and Agent 2 are Nontoxic, But Toxic in Combination:



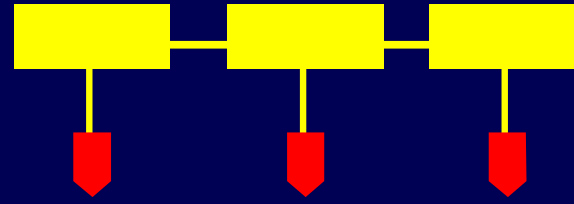
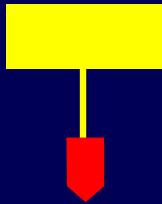
Multi-Site Binding

Multi-Site Binding and Pattern Recognition

Multi-site binding can give an enormous increase in the tightness of binding compared to single site binding

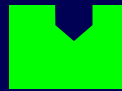
A Ten Billion Times Increase in Affinity due to Three Site Binding

Vancomycin



Tri-Vancomycin

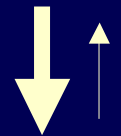
Ala-Ala



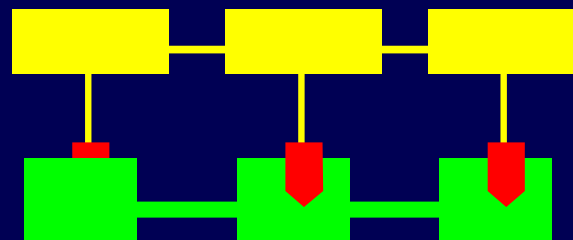
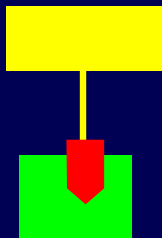
Tri-Ala-Ala

$$K_d = 10^{-6}$$

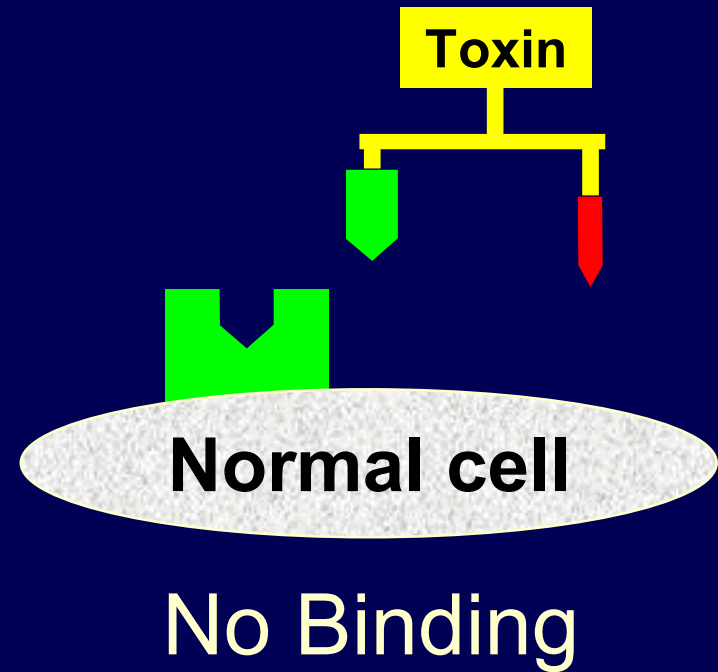
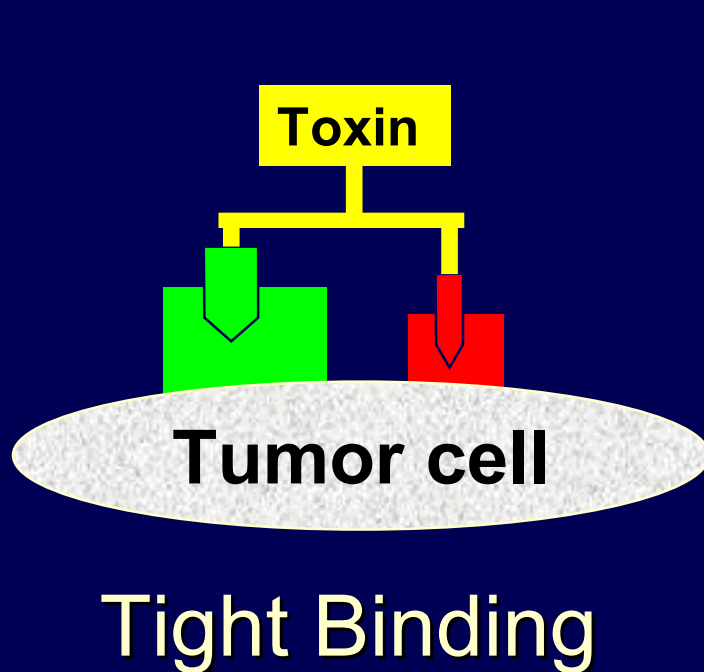
↓ ↑



$$K_d = 10^{-17}$$



Multi-Site Binding



At low concentrations the drug can bind tightly to cells with the target pattern without binding to cells that express only one element of the pattern

Advantages of Multi-Site Binding

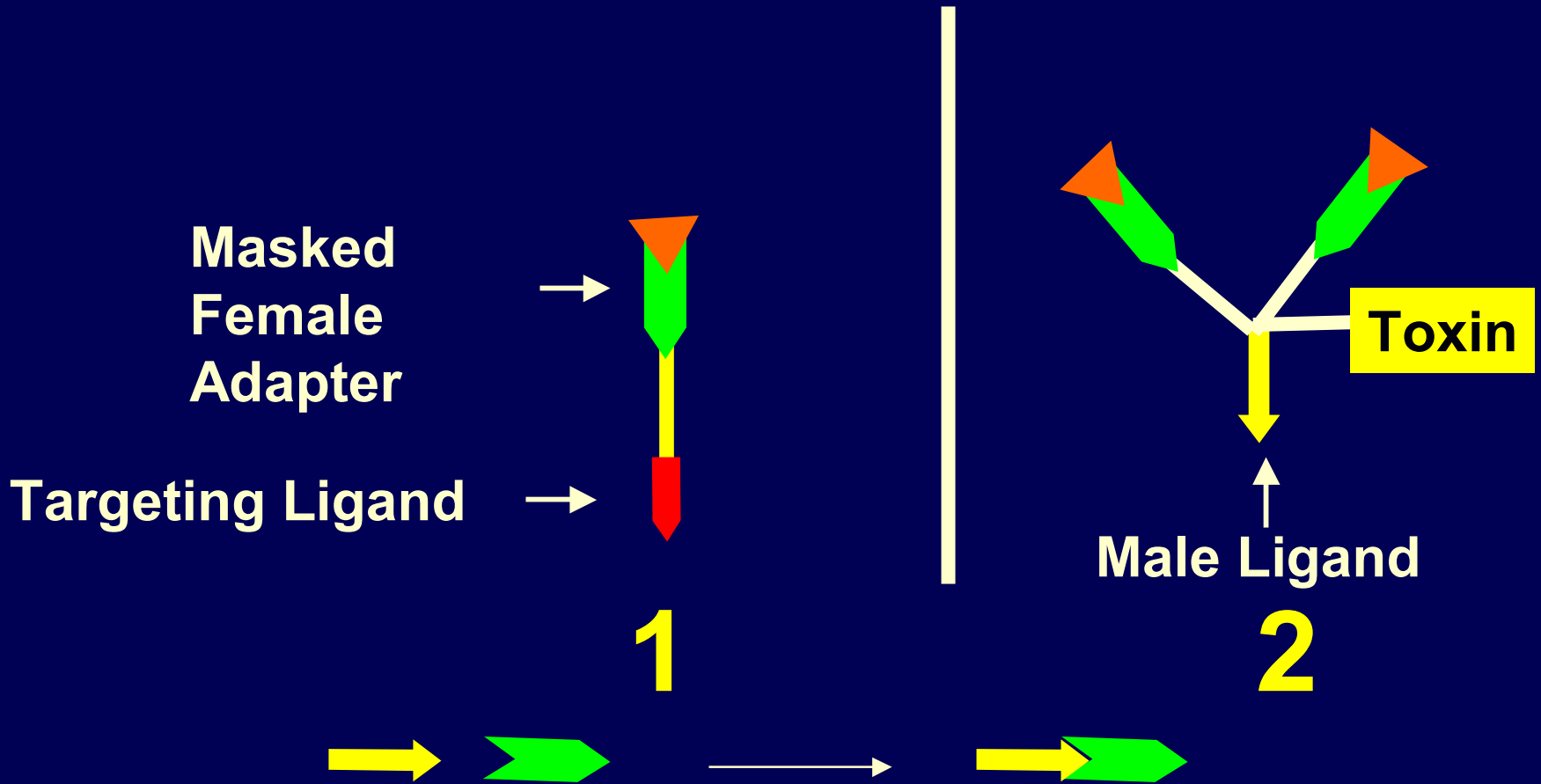
- Specificity for the pattern
- Potency
- Slow off rate
- Immense reductions in the dose of drug required
- Reductions in side effects

Exponential Pattern Recognition Targeting

**From one receptor create two,
from two create four**

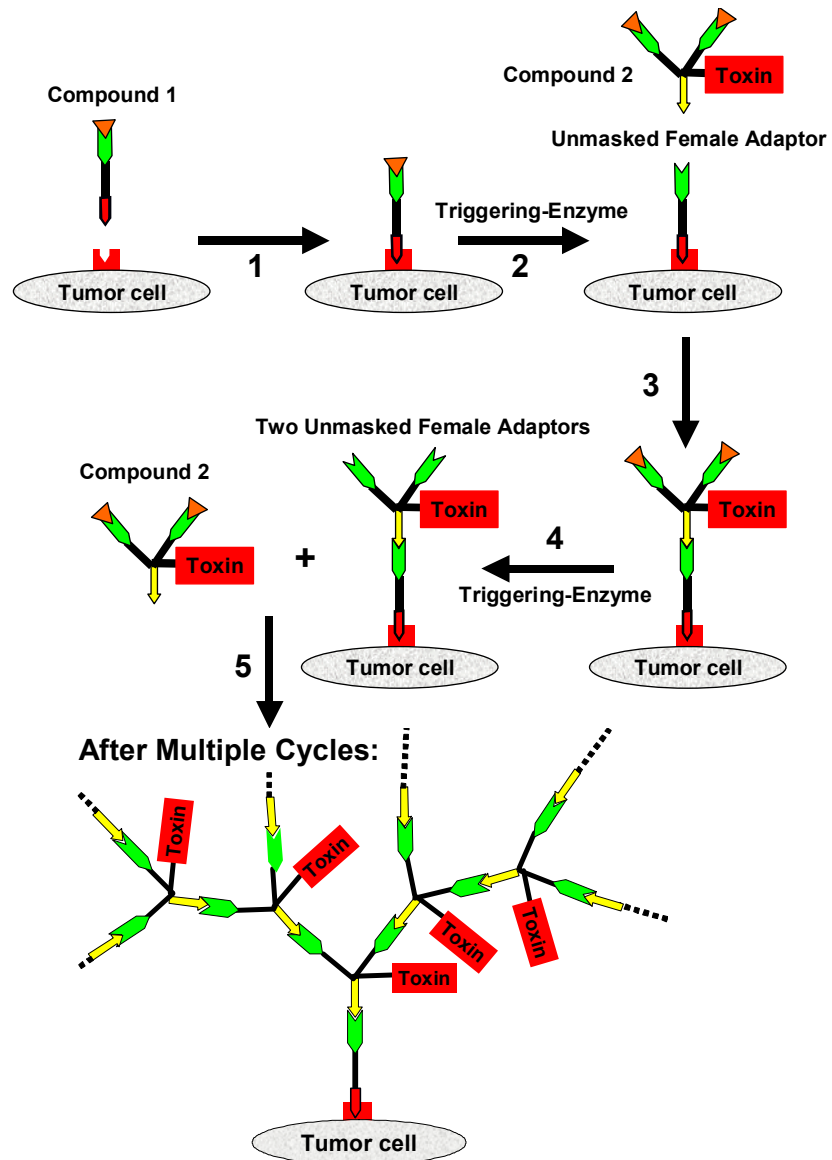
In this method specificity is for the pattern of a receptor and a triggering enzyme

Components of Exponential Pattern Recognition Targeting



The male and female parts bind with very high affinity.

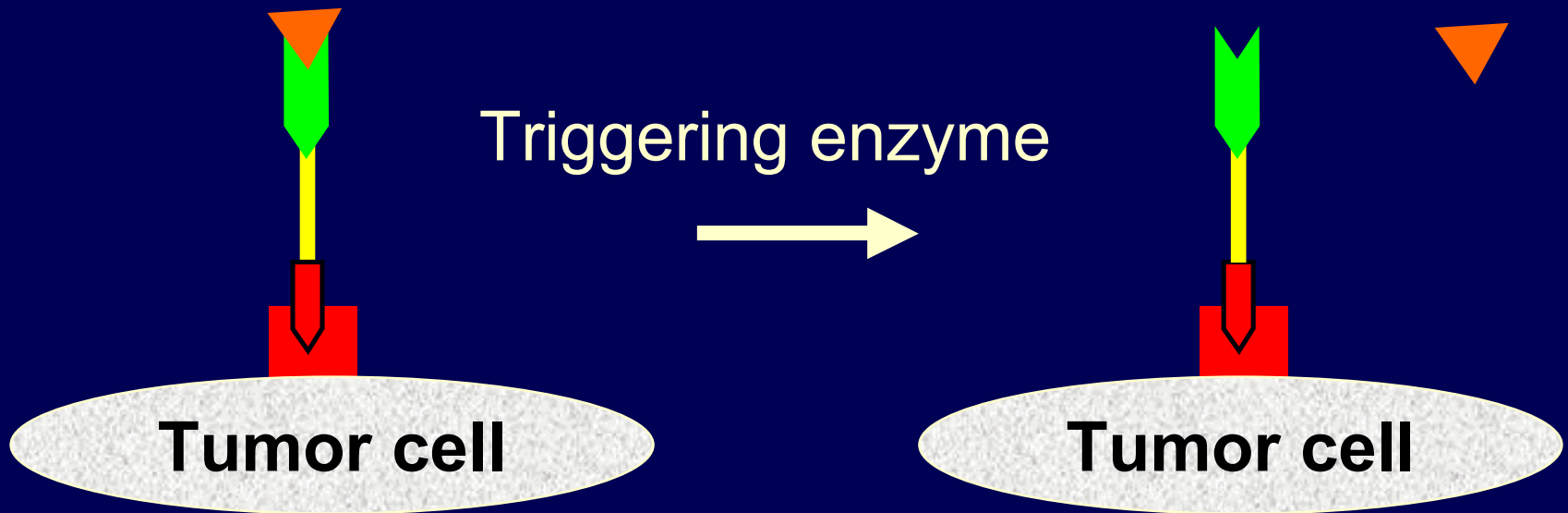
The Mechanism of Exponential PRTT



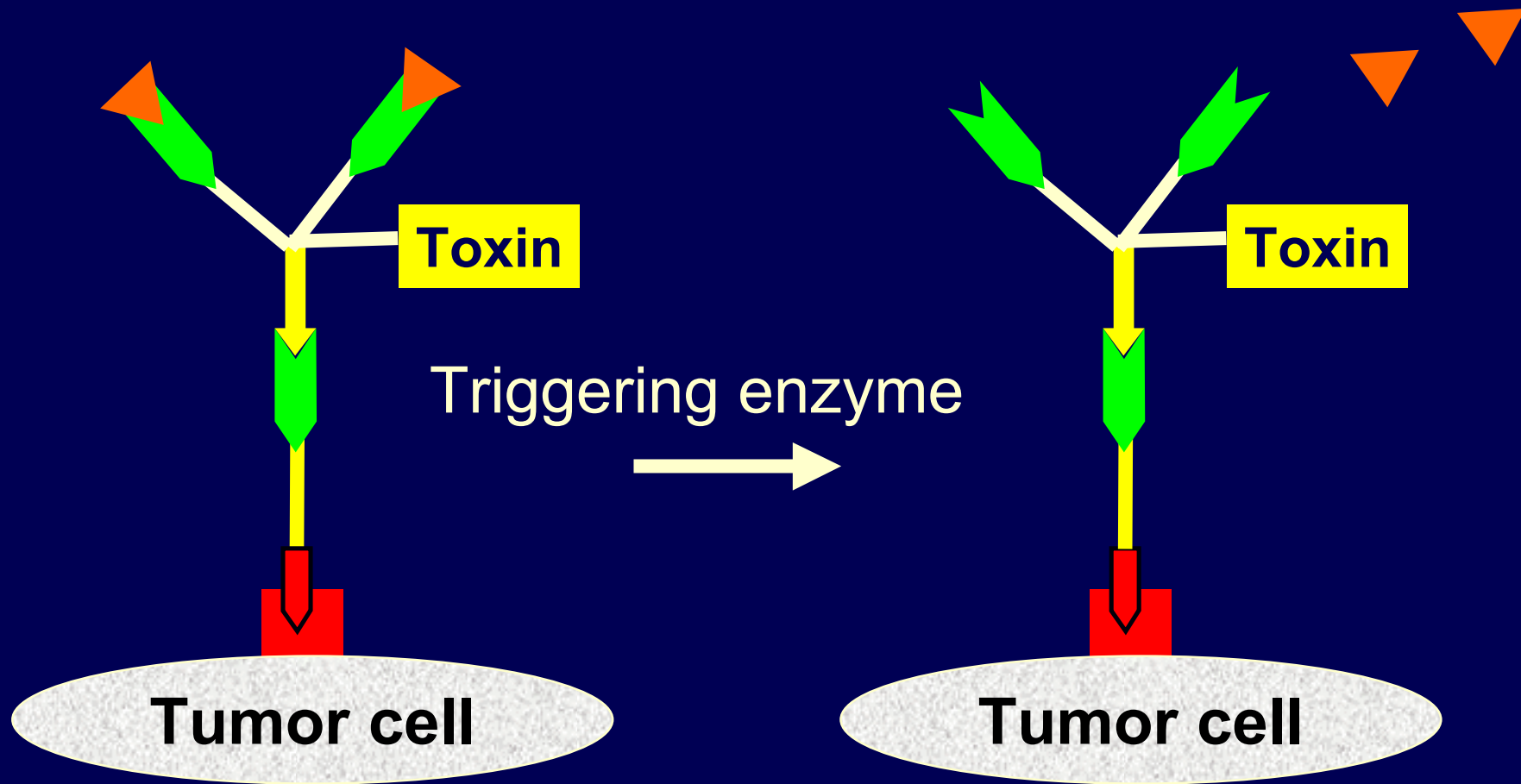
Triggering Enzymes Unmask the Female Adaptor

- Many enzymes that are over-expressed by tumors can be utilized
- The triggering enzyme can also be independently targeted to tumor cells

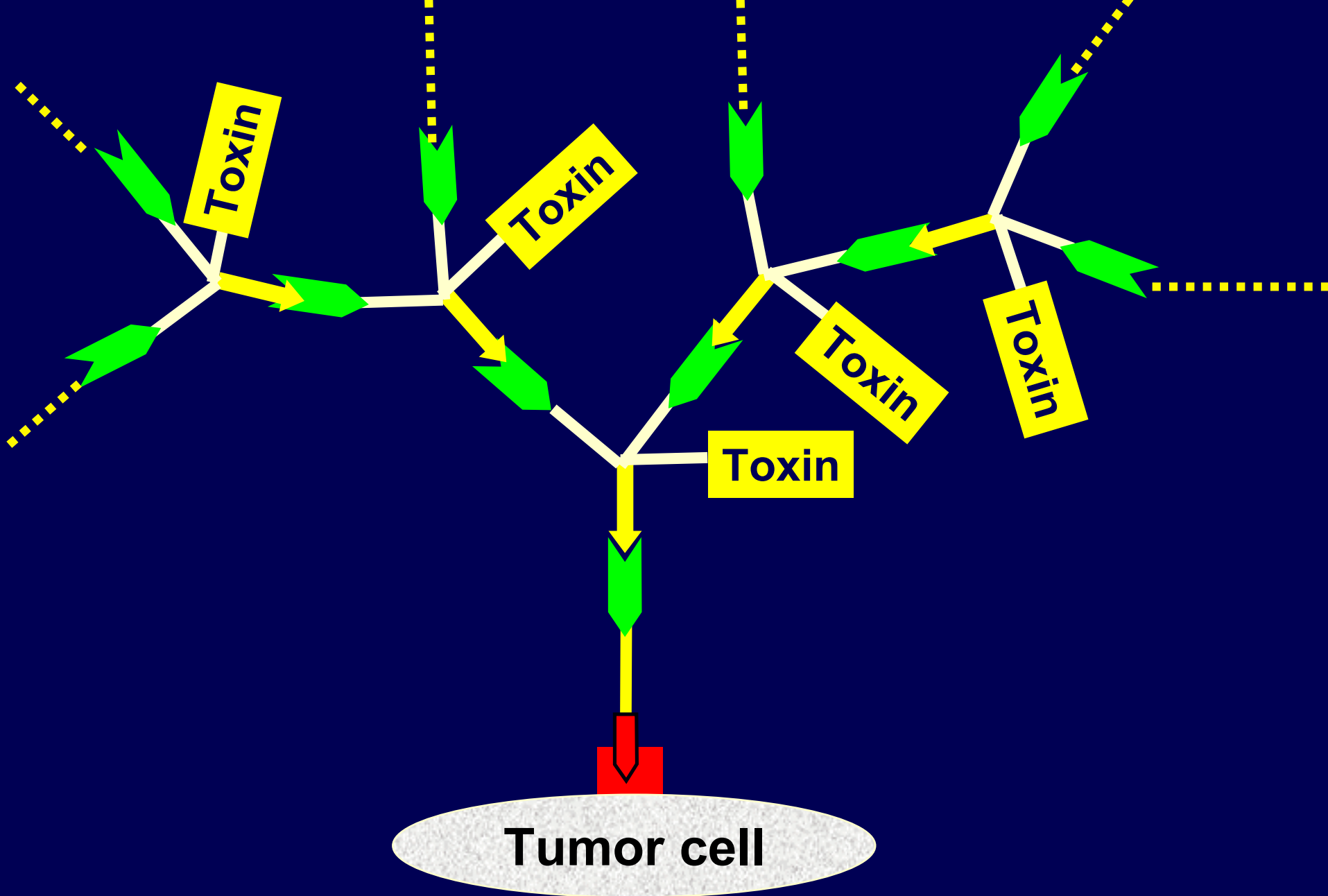
Exponential Pattern Recognition Targeting



- 1.) Component 1 binds to cell receptors.
- 2.) Triggering enzyme(s) unmask female adapter.

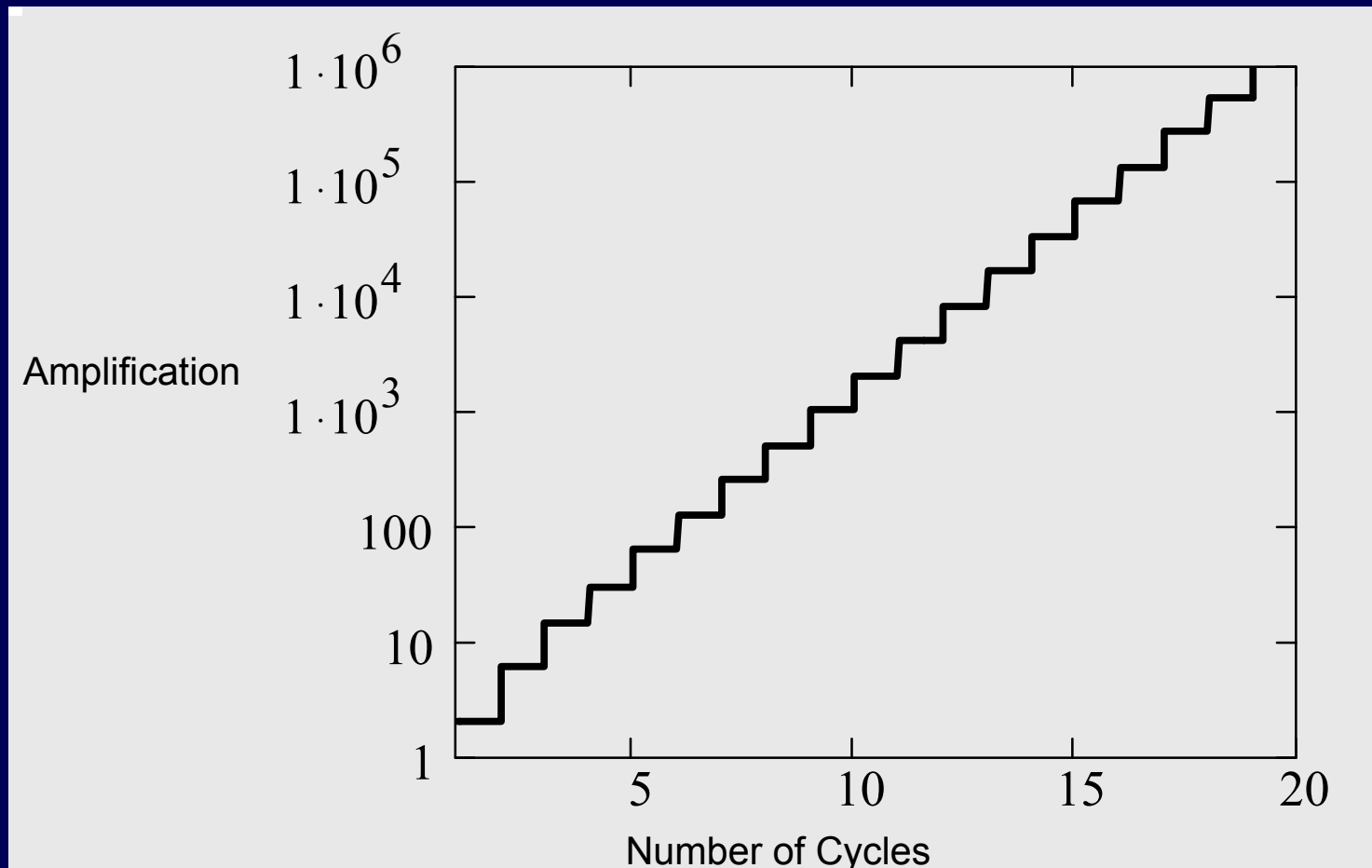


- 3.) Component 2 binds to the unmasked female adaptor.
- 4.) The triggering enzyme unmasks twice as many new female adaptors.



Repetition of the cycle can deposit a large quantity of drug in a tree like structure

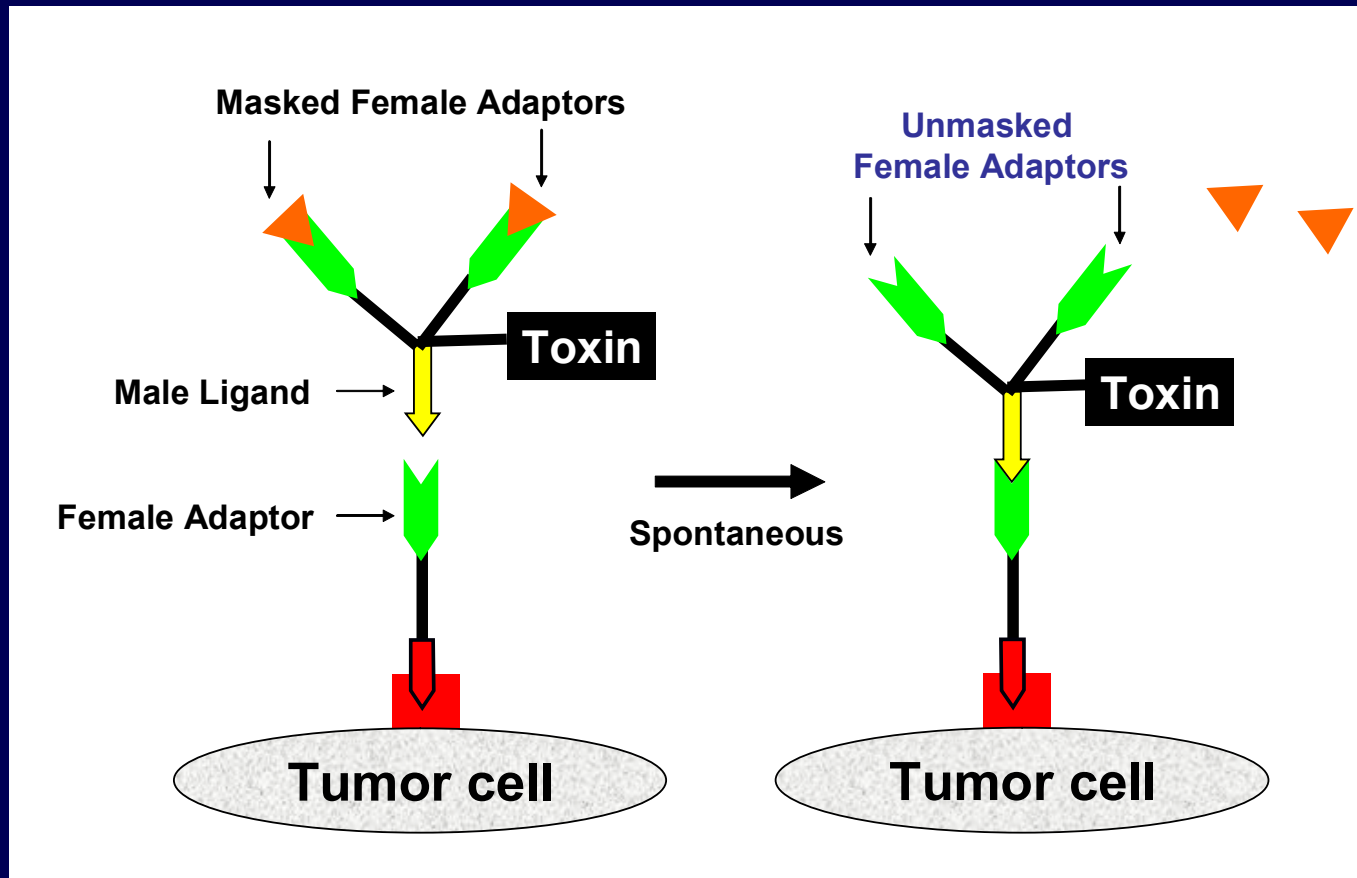
Massive Amounts of Drug can be Delivered to a Tumor Cell



The quantity can increase exponentially

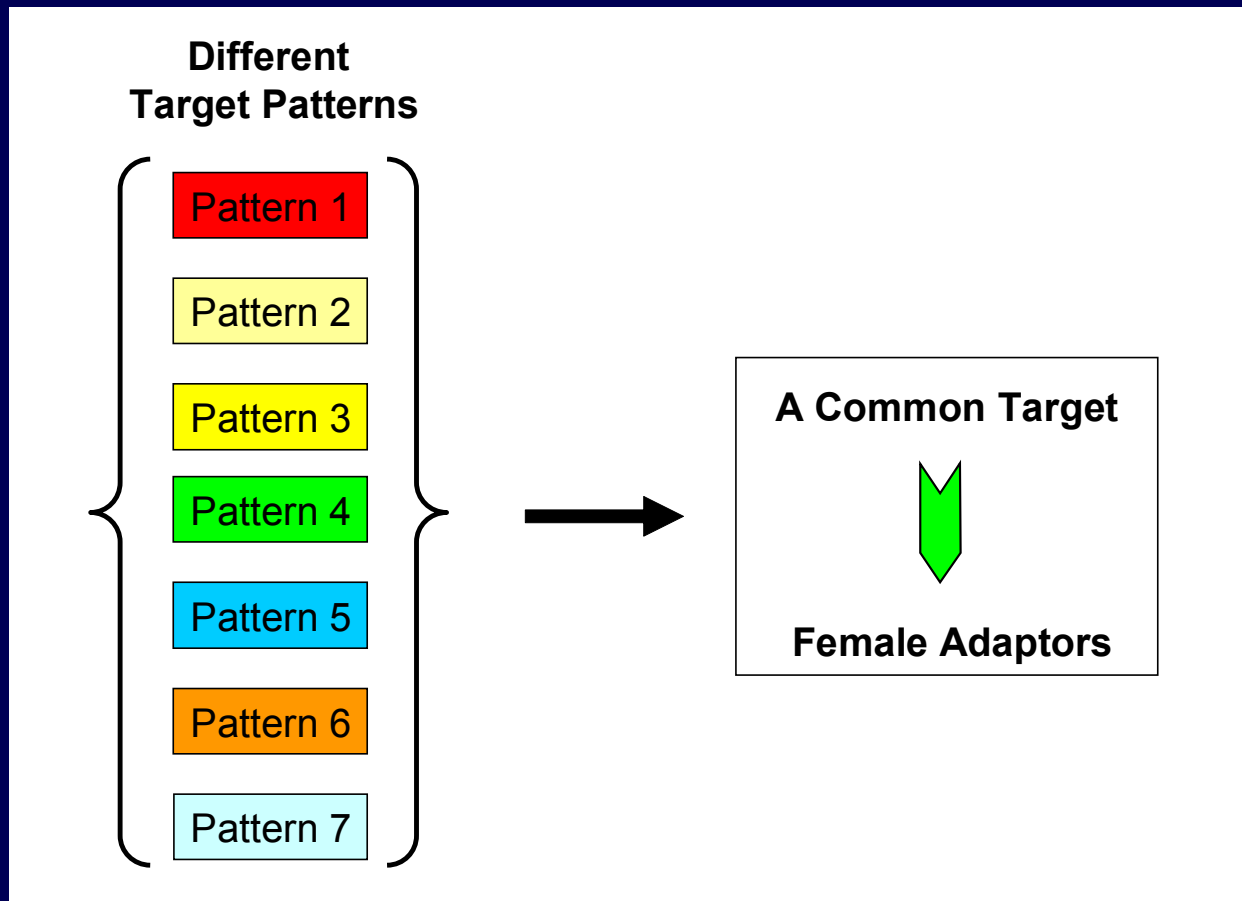
**Self-Amplifying
Exponential Pattern
Recognition Targeting**

Self-Amplifying Exponential PRTT



The very binding of a male ligand and female adaptor creates two new female adaptors without the need for a triggering enzyme.

Female Adaptors can Transform Different Patterns into a Common Target



This can enable the efficient delivery of multiple drugs to each target pattern and prevent the development of drug resistance.

Many PRTT technologies can be developed by combining these basic approaches

The science and technology needed to develop PRTT exists today