

# Johns Hopkins Engineering

## Immunoengineering

**Immunoengineering—Pathogens**

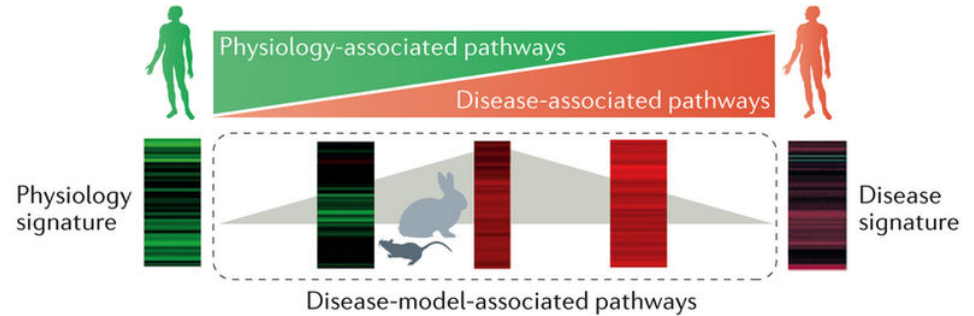
Therapeutic Discovery Process

# Drug Discovery Process

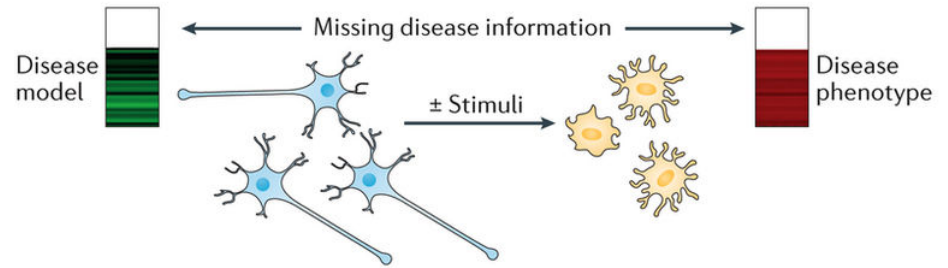
## 1. Define Disease Phenotype

## 2. Replicate in *in vitro* setting

**a** Disease knowledge integration



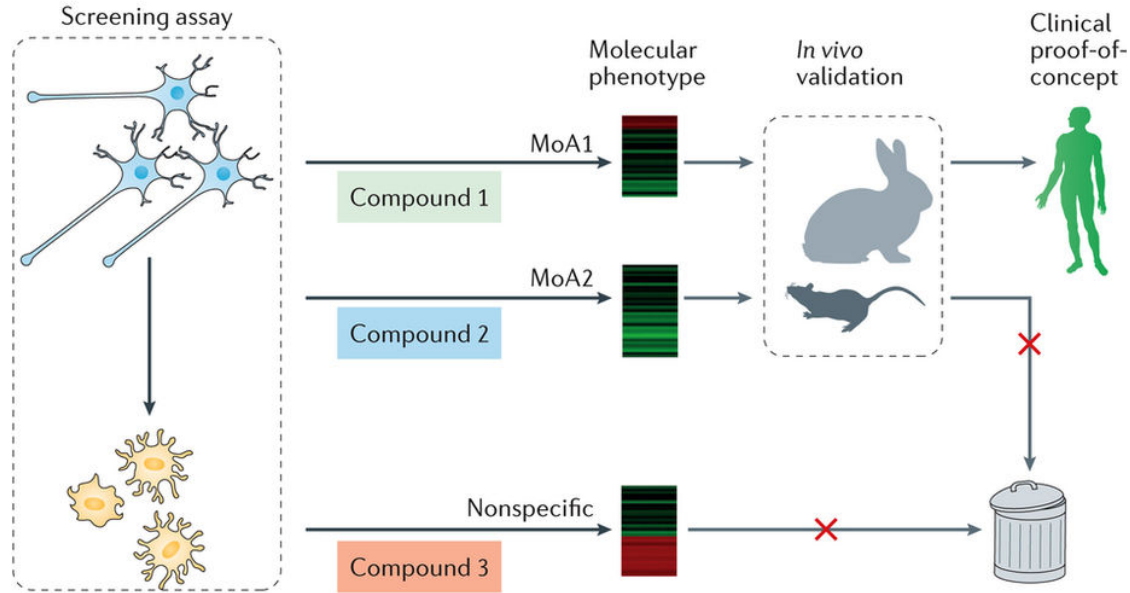
**b** Incorporation and assessment of disease relevance in cells



# Drug Discovery Process

## 3. Screen Compounds in vitro, then in vivo

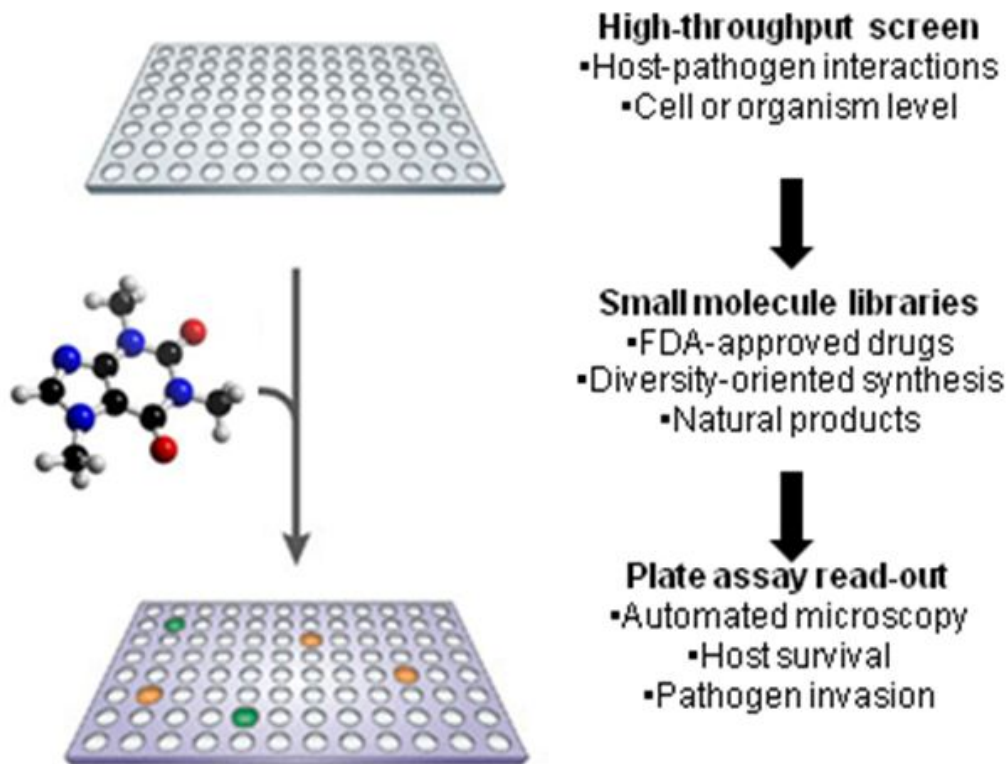
c PDD compound screening and validation



# Therapeutic Discovery Approaches

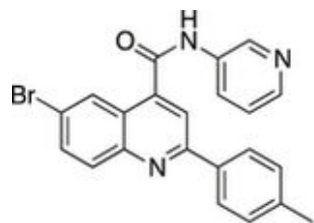
- Large scale screens
- Mechanistically inspired
- Combinatorial approaches
- New tools for discovery

# High-throughput Compound Screening



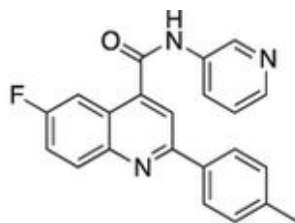
# Example: Antimalarial

- Screened 4,731 compounds
- Chemical evolution



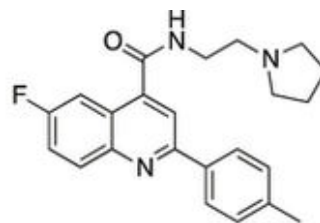
Hit from screen

Pf(3D7)  $EC_{50}$  0.12  $\mu$ M  
Calculated  $\log(P)$  4.3  
Solubility not determined  
Mouse cli. 5.3 ml min<sup>-1</sup> g<sup>-1</sup>



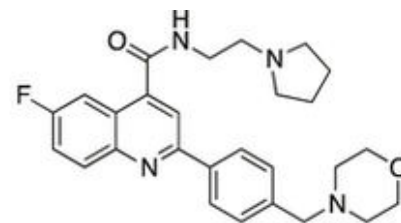
DDD102542

Pf(3D7)  $EC_{50}$  0.35  $\mu$ M  
Calculated  $\log(P)$  3.7  
Solubility 36  $\mu$ M  
Mouse cli. 8.6 ml min<sup>-1</sup> g<sup>-1</sup>



DDD103679

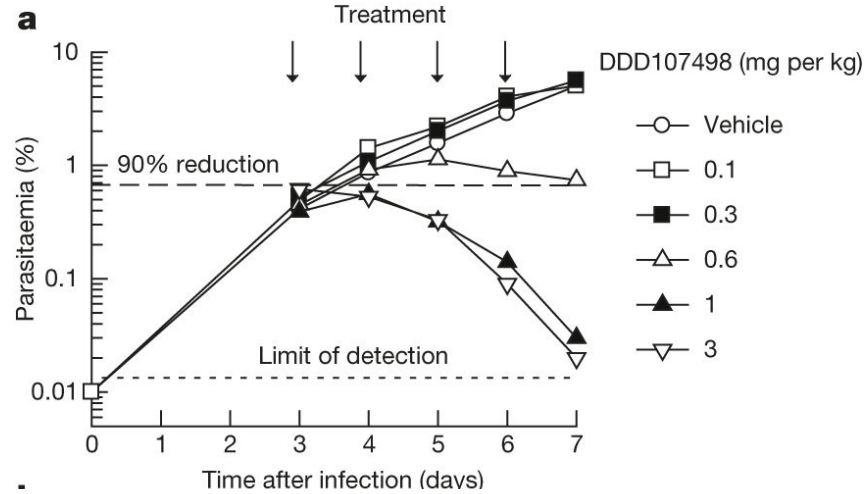
Pf(3D7)  $EC_{50}$  0.70  $\mu$ M  
Calculated  $\log(P)$  3.7  
Solubility 180  $\mu$ M  
Mouse cli. 3.4 ml min<sup>-1</sup> g<sup>-1</sup>



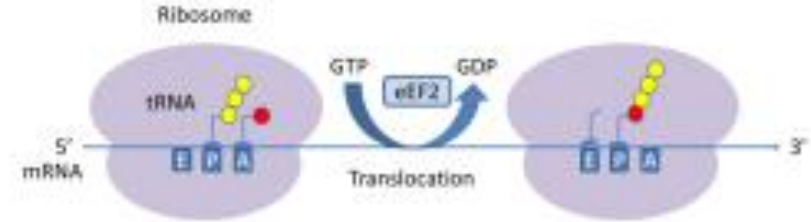
DDD107498

Pf(3D7)  $EC_{50}$  0.001  $\mu$ M  
Calculated  $\log(P)$  3.2  
Solubility 216  $\mu$ M  
Mouse cli. < 0.9 ml min<sup>-1</sup> g<sup>-1</sup>

# Example: Antimalarial

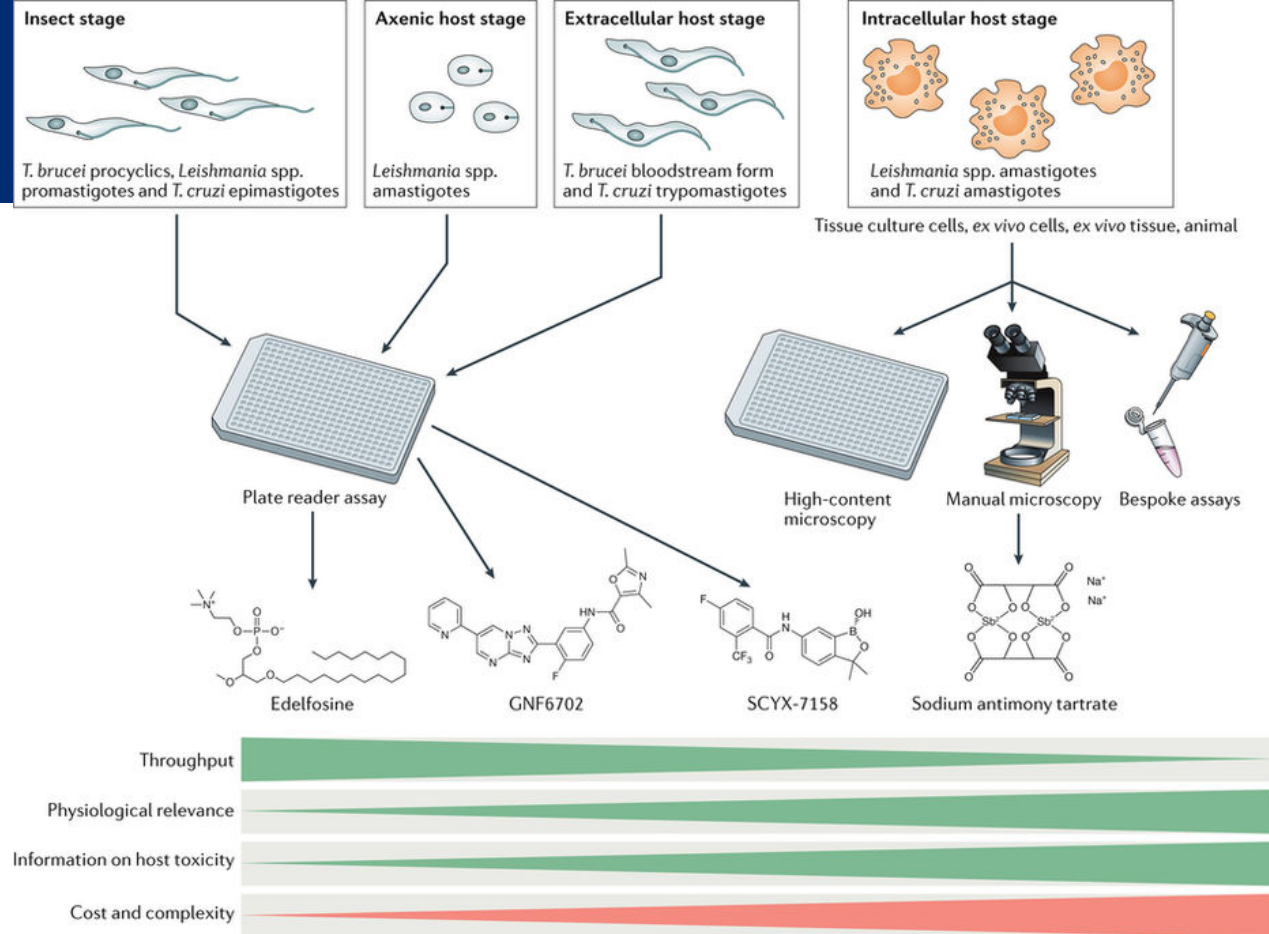


**a**



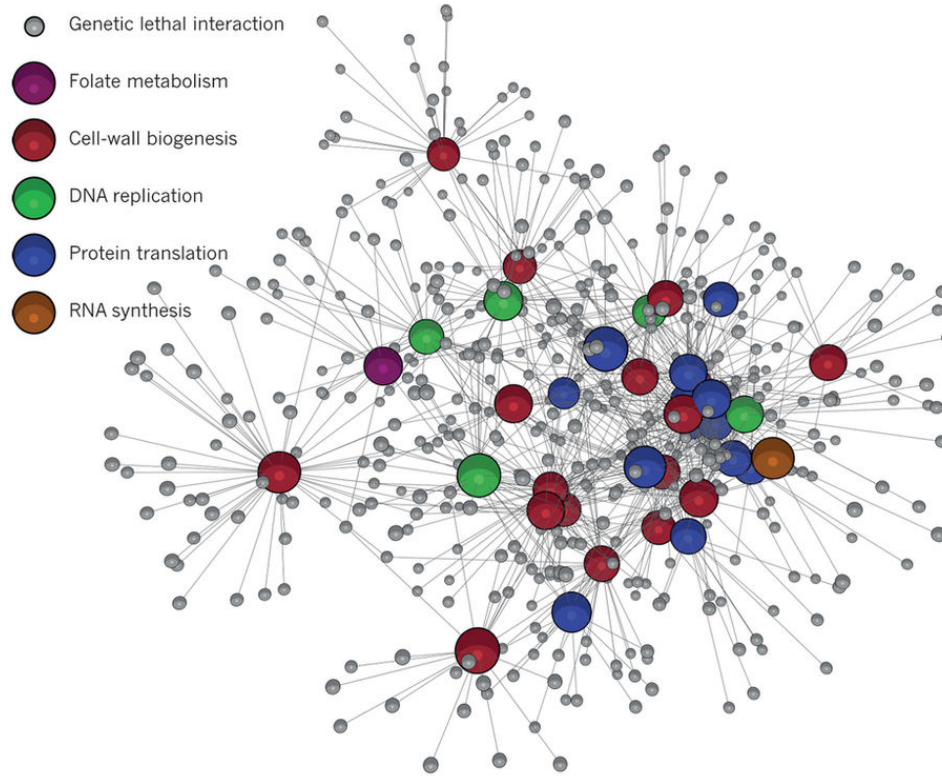
Baragaña, Beatriz, et al. "A novel multiple-stage antimalarial agent that inhibits protein synthesis." *Nature* 522.7556 (2015): 315.

# Limitations to Screening

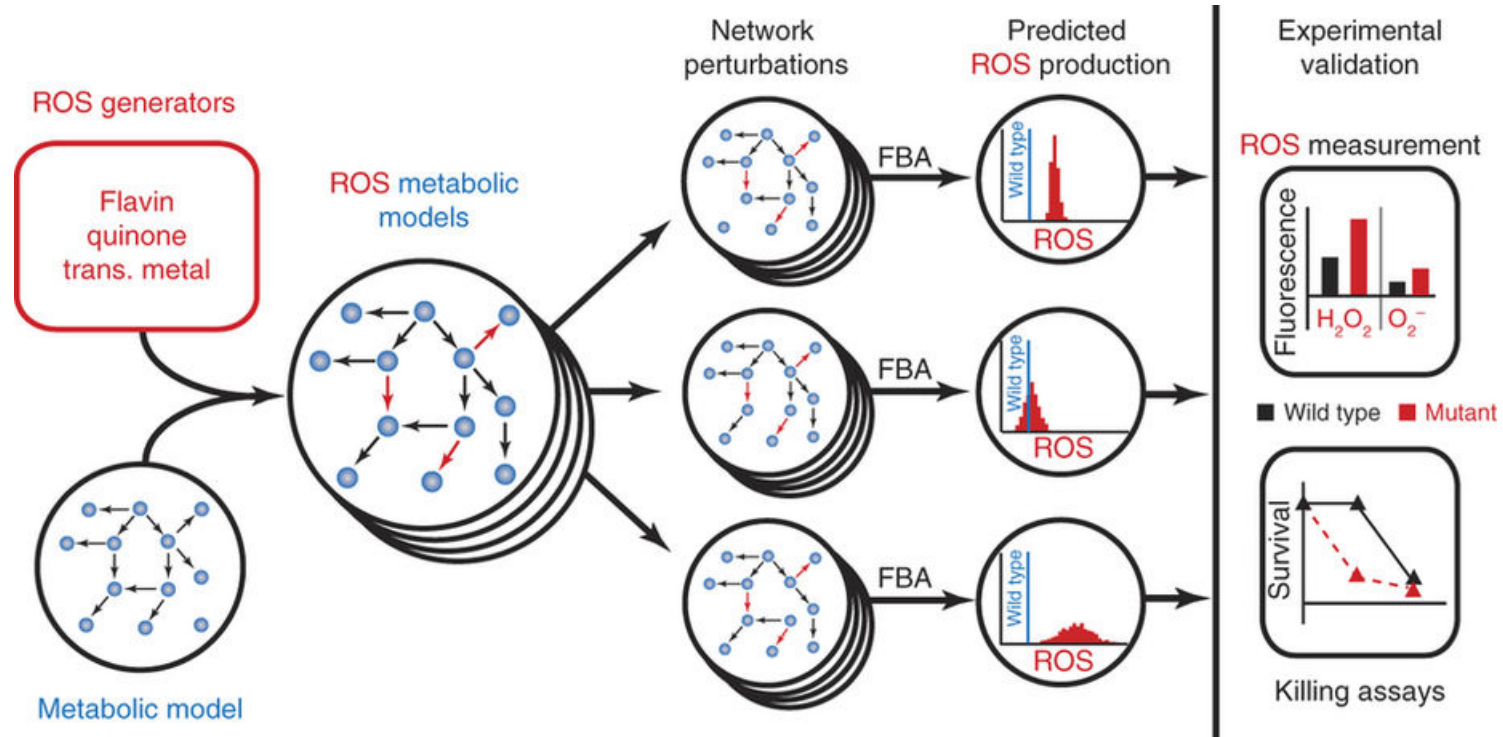




# Discovery Based on Inspiration of Biology



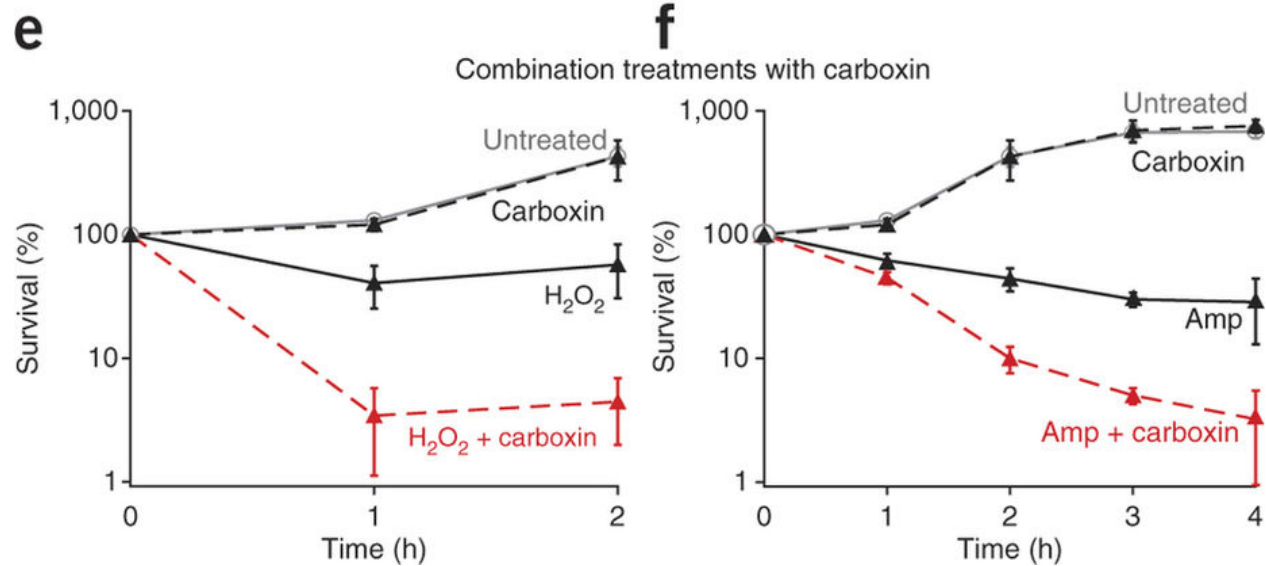
# Example: Enhancing Antibiotics



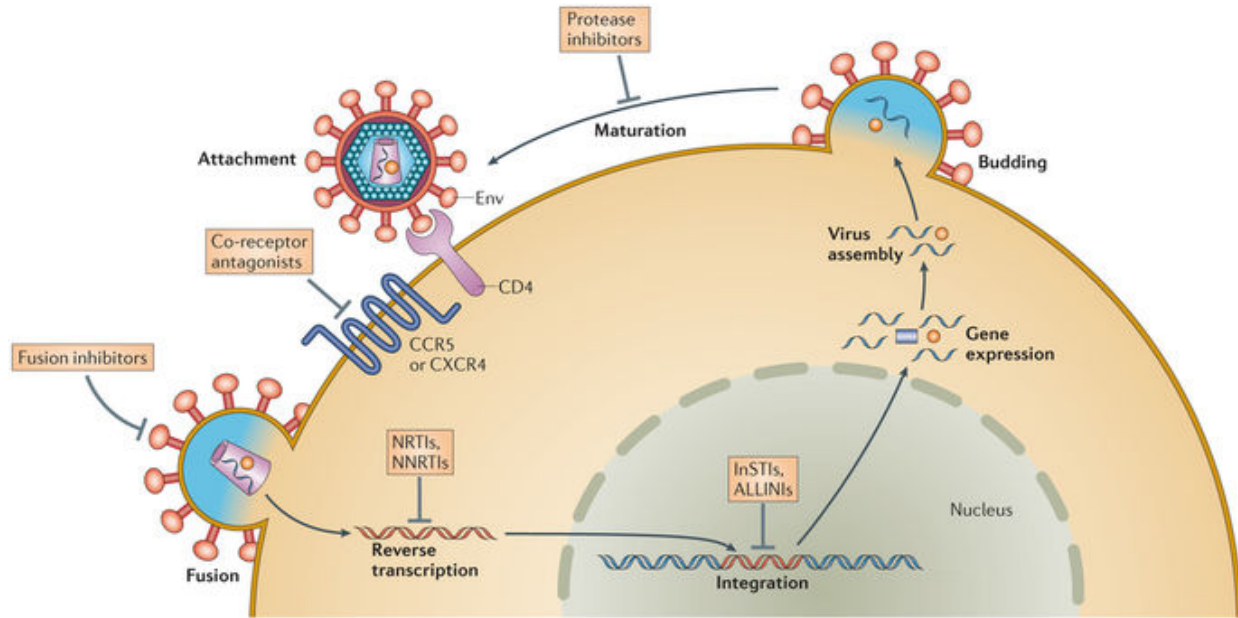
Ronaldson, Mark P., et al. "Potentiating antibacterial activity by predictably enhancing endogenous microbial ROS production." *Nature biotechnology* 31.2 (2013): 160.

# Example: Enhancing Antibiotics

- Model to predict ROS targets
- ROS target synergize with antibiotics



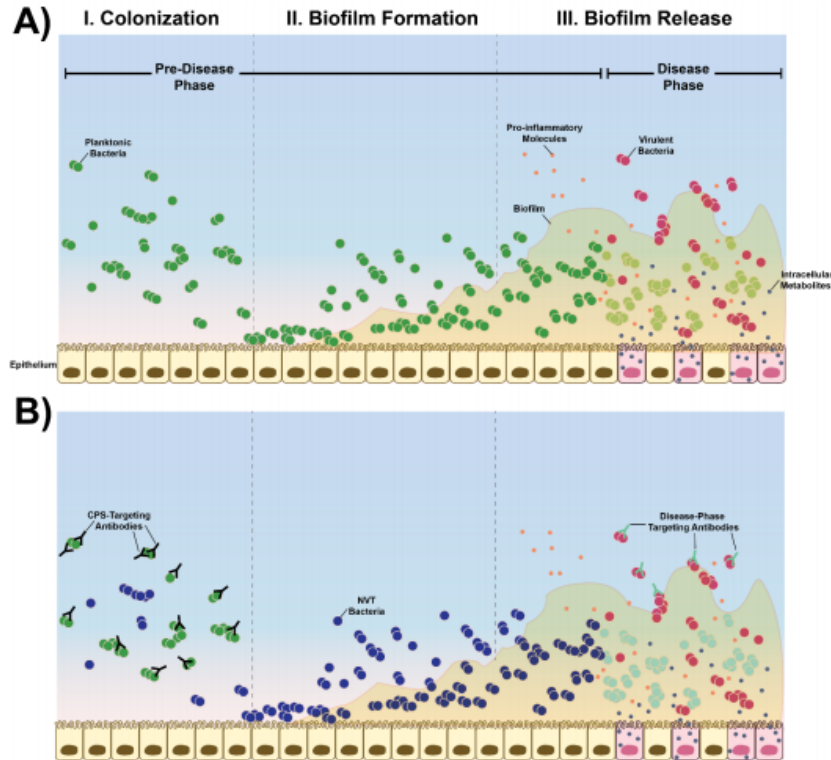
# Combinatorial Approaches



Nature Reviews | Microbiology

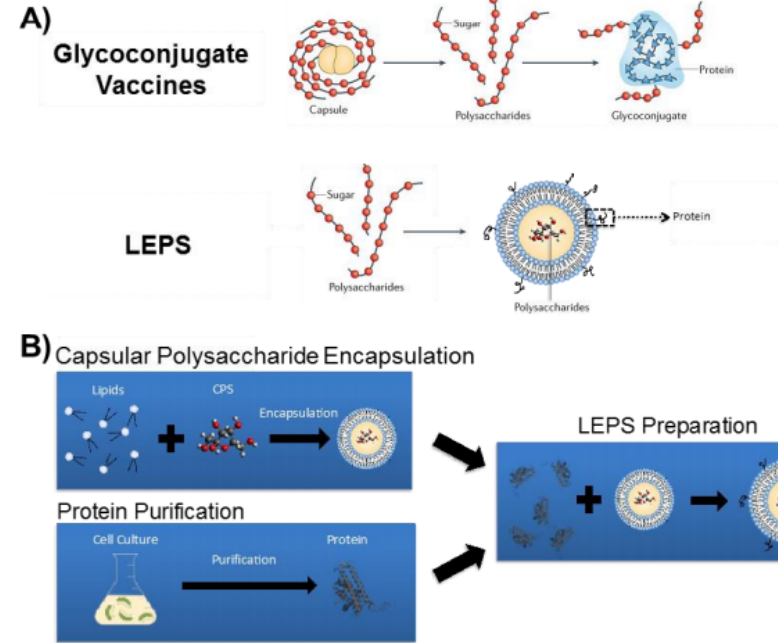
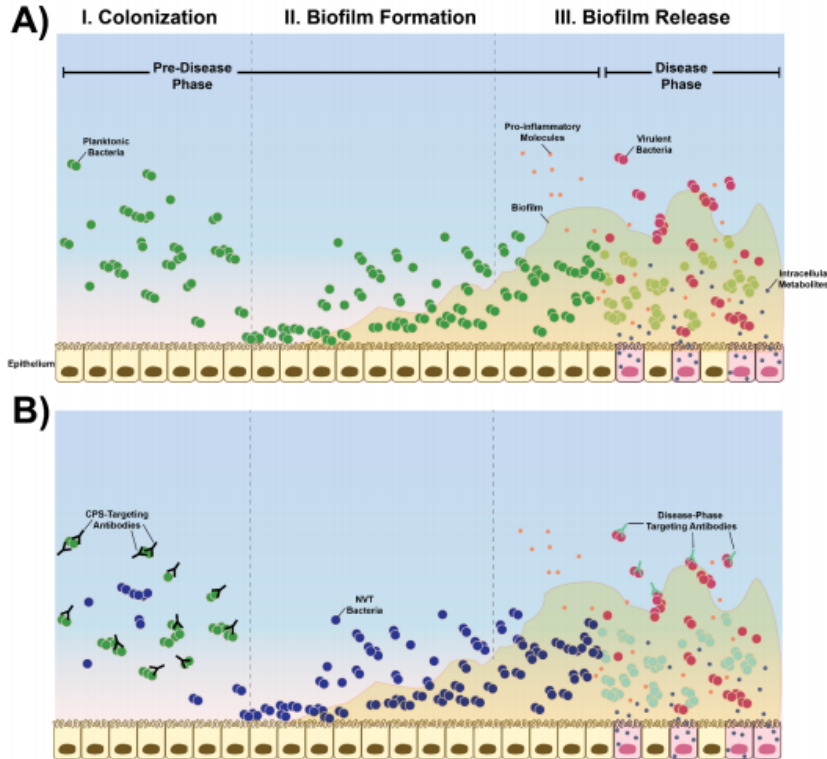
Laskey, Sarah B., and Robert F. Siliciano. "A mechanistic theory to explain the efficacy of antiretroviral therapy." *Nature Reviews Microbiology* 12.11 (2014): 772.

# Combinatorial Approach – Commensal Vaccine



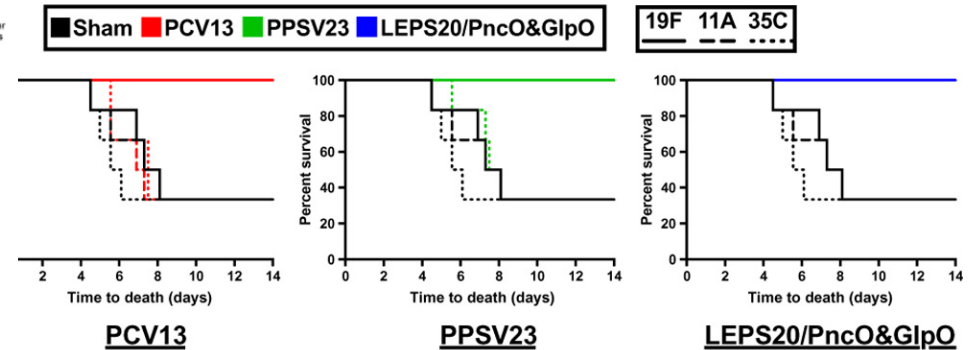
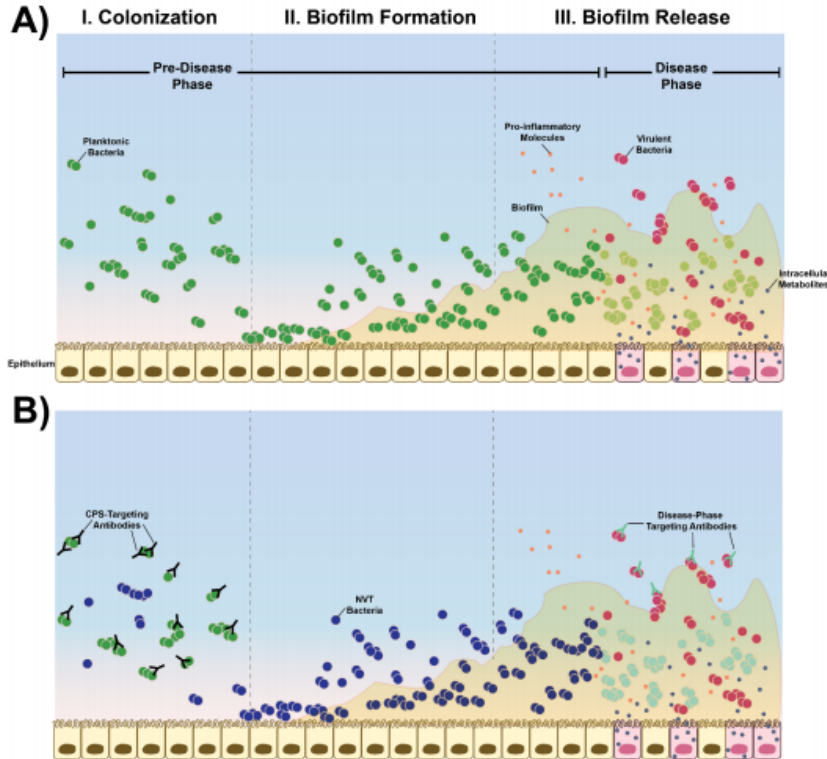
Jones, Charles H., et al. "Comprehensive vaccine design for commensal disease progression." *Science Advances* 3.10 (2017): e1701797.

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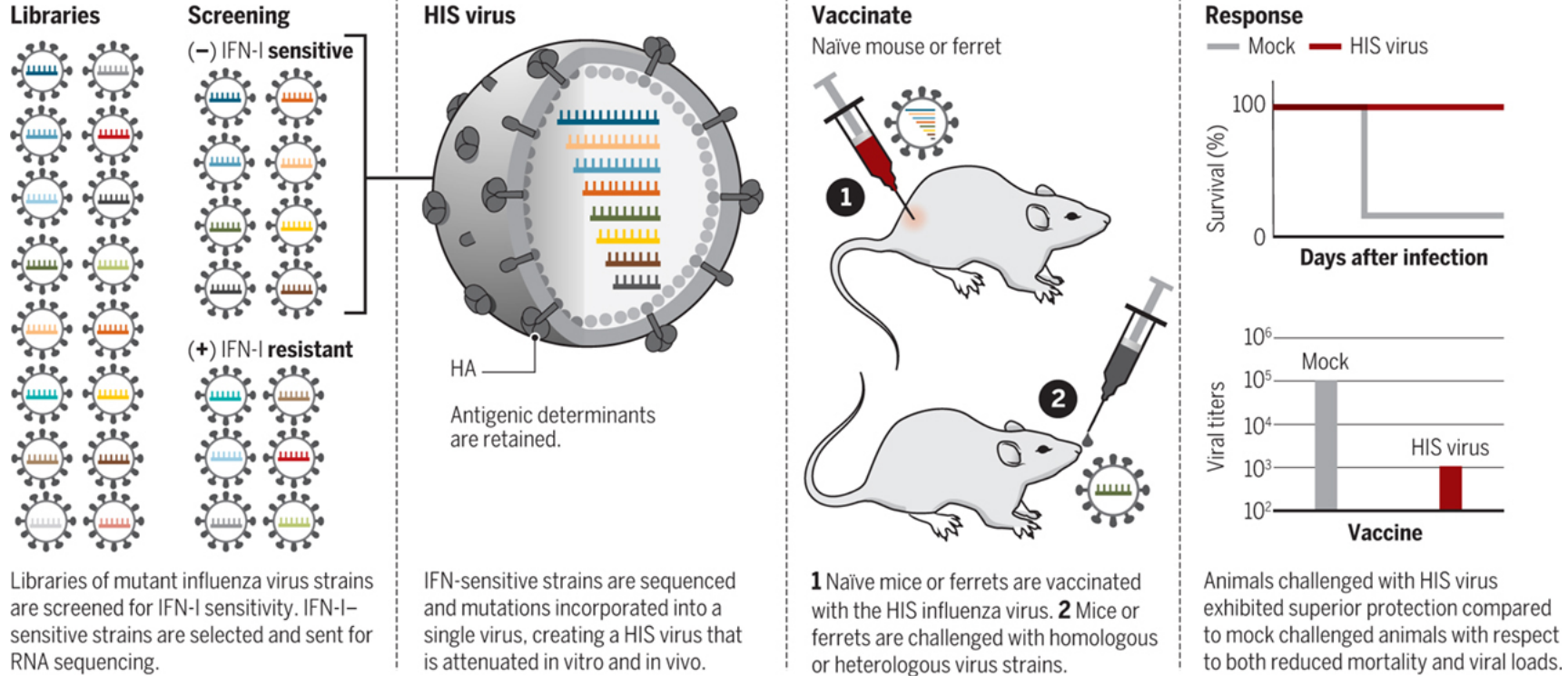
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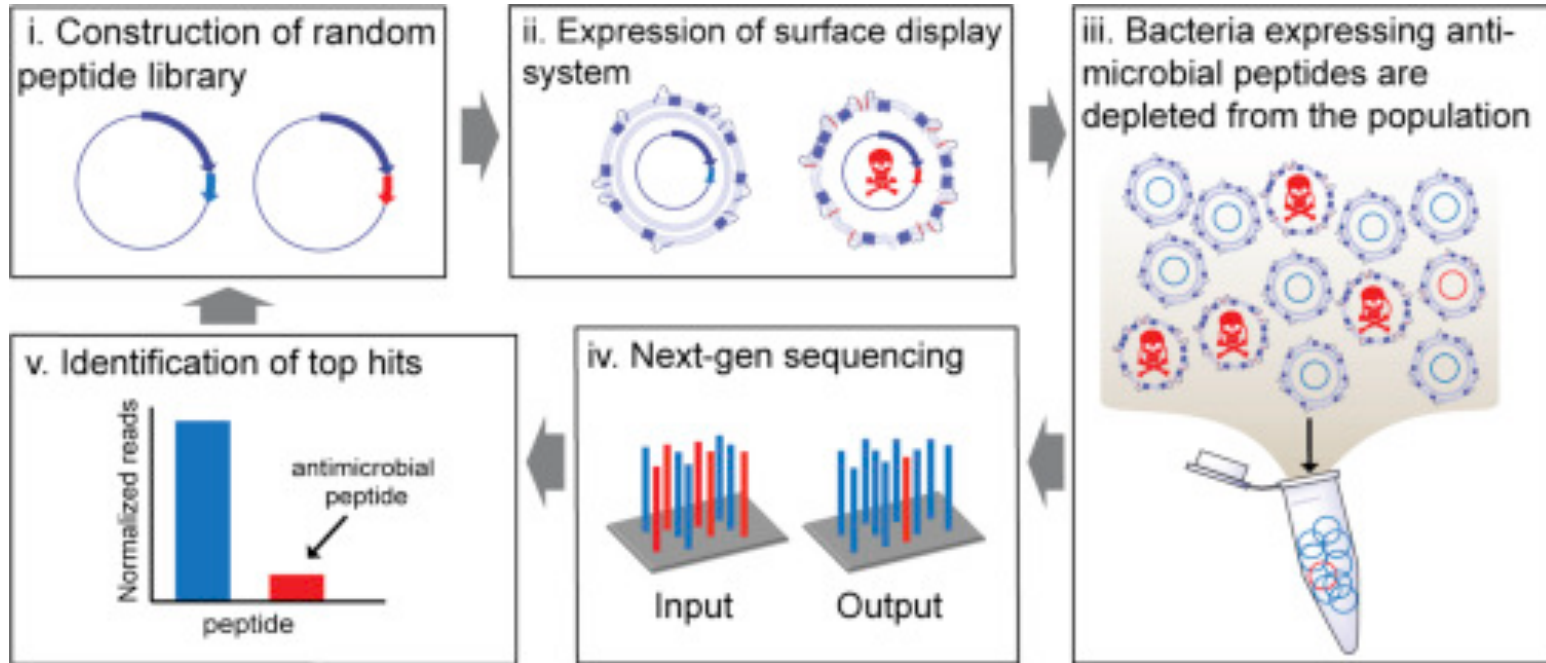


# New Tools for Target Discovery - Vaccine

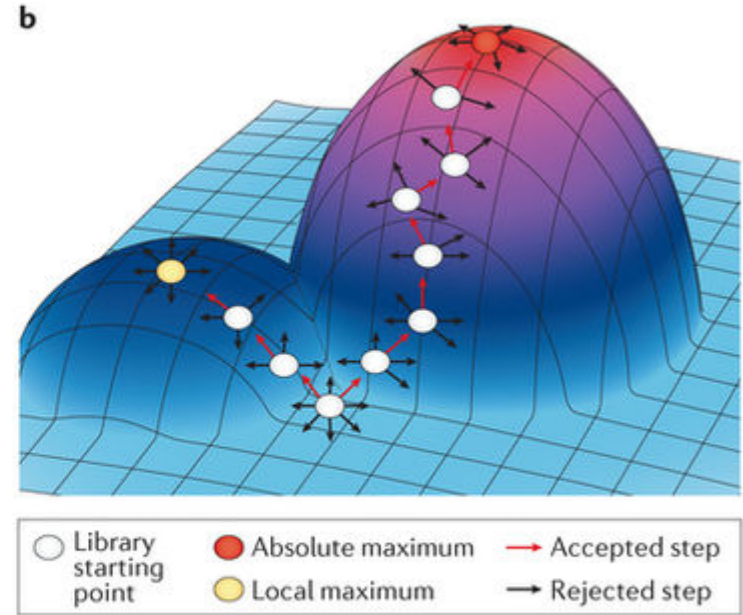
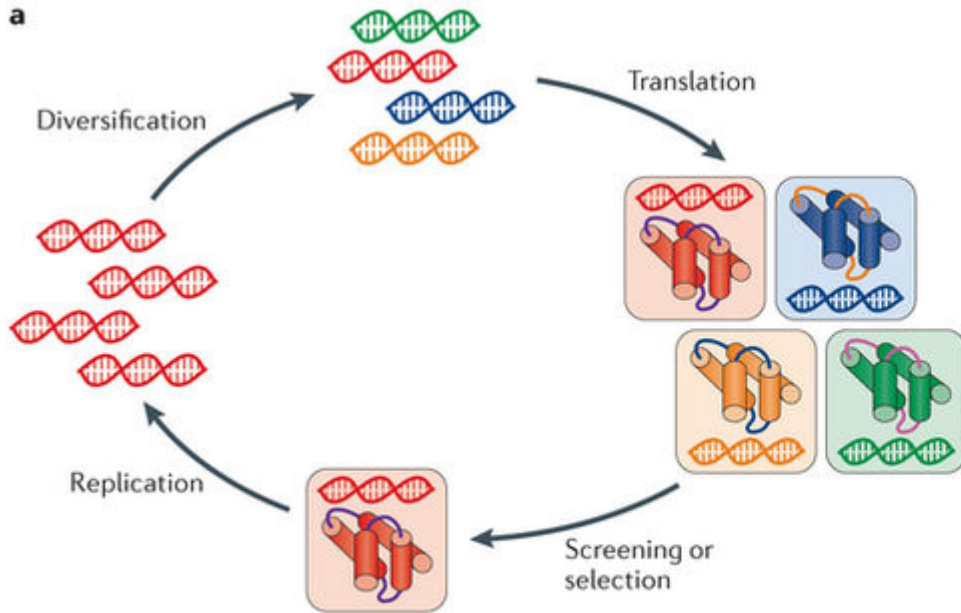




# New Tools for Target Discovery - Antibiotics

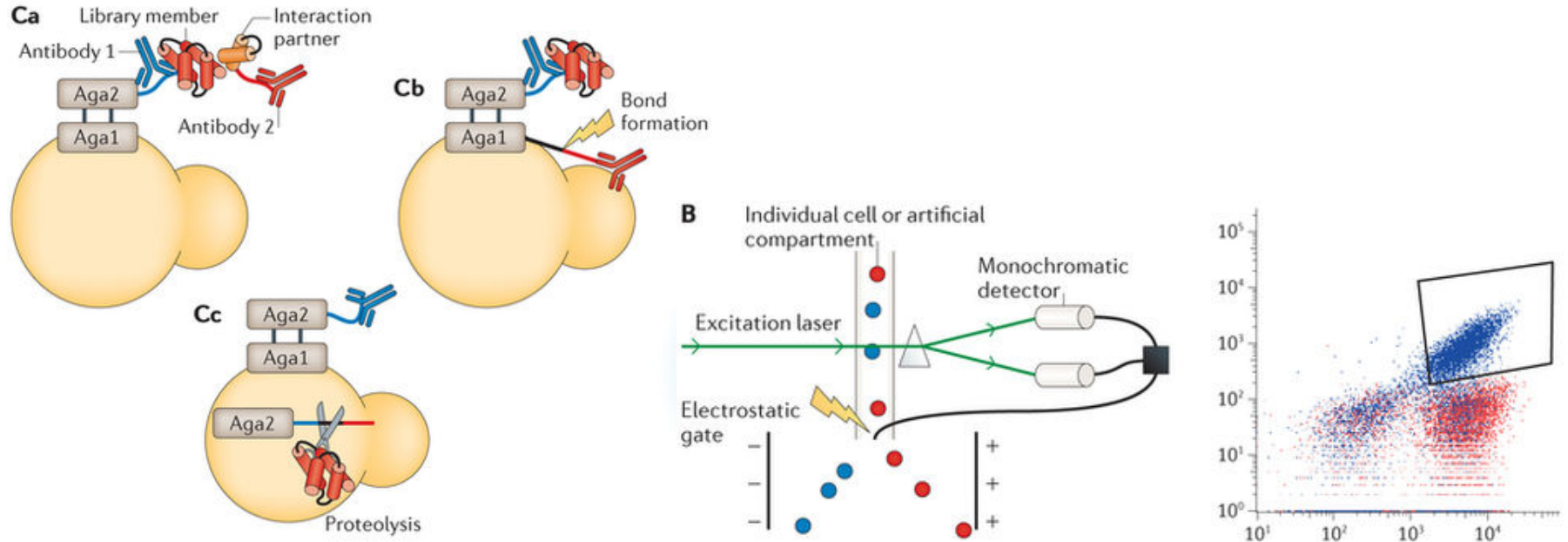


# New Tools for Drug Discovery – Directed Evolution



Nature Reviews | **Genetics**

# New Tools for Drug Discovery – Directed Evolution



Approach	Advantages	Disadvantages
High volume	<ul style="list-style-type: none"> <li>+ Many opportunities for success, enabling success</li> <li>+ Not require prior knowledge lead to novel finding</li> <li>+ Compound may already be approved</li> </ul>	<ul style="list-style-type: none"> <li>- May not be as specific</li> <li>- Requires assay to be high throughput and may require significant framework</li> <li>- Requires library to be established</li> </ul>
Mechanistic insight	<ul style="list-style-type: none"> <li>+ Leads to direct and specific therapy</li> <li>+ Potentially more potent than random hits</li> <li>+ Can potentially lead to cure rather than treatment</li> </ul>	<ul style="list-style-type: none"> <li>- Requires more resources</li> <li>- Higher chance of failure</li> <li>- Takes longer</li> </ul>
Combination therapies	<ul style="list-style-type: none"> <li>+ Increased potency than relying on one mechanism</li> <li>+ May be able to use two or more existing therapies</li> </ul>	<ul style="list-style-type: none"> <li>- Safety and side effects a concern</li> <li>- Regulatory hurdles</li> </ul>
New tools	<ul style="list-style-type: none"> <li>+ Increase throughput</li> <li>+ Increase insight</li> </ul>	<ul style="list-style-type: none"> <li>- Tools may not be available or require significant expertise</li> <li>- Tools are still not refined to always be predictive</li> </ul>



JOHNS HOPKINS

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*of* ENGINEERING