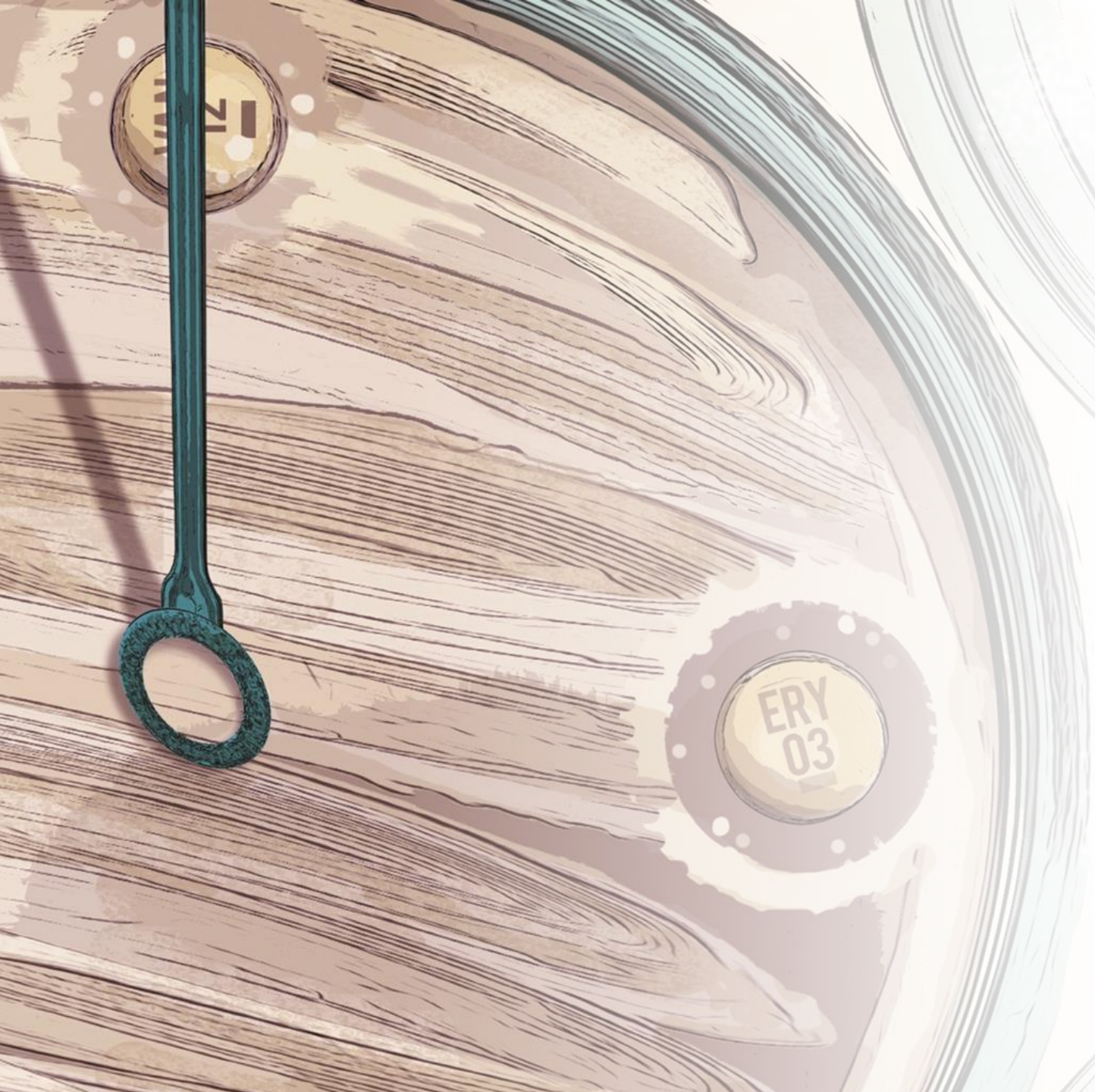


Drug Repurposing For Antimicrobial Discovery

- Joint Graduate Seminar
- Supervisor: Dr. Xiao Yang
- Student: Lorena (LI, Haojun)
  1st year MPhil candidate
- Date: 2019 December 11
- Department: Microbiology

Centre for Health Protection
Department of Health
The Government of the Hong Kong Special Administrative Region

A A A 繁 简

Enter search keyword(s)

Hot searches: Vaccine, Influenza, Tear Gas, Hand, Foot and Mouth Disease, Heart Diseases

About | Health Topics | Recommendations | Resources | Statistics | Media Room | Others

Antimicrobial Resistance (AMR)

Home > Feature Topic > Antimicrobial Resistance (AMR)

- Communicable Diseases
- Non-Communicable Diseases and Healthy Living
- Healthy Life Course
- Organ Donation
- Travel Health
- Health and Hygiene
- Antimicrobial Resistance
- Poisoning

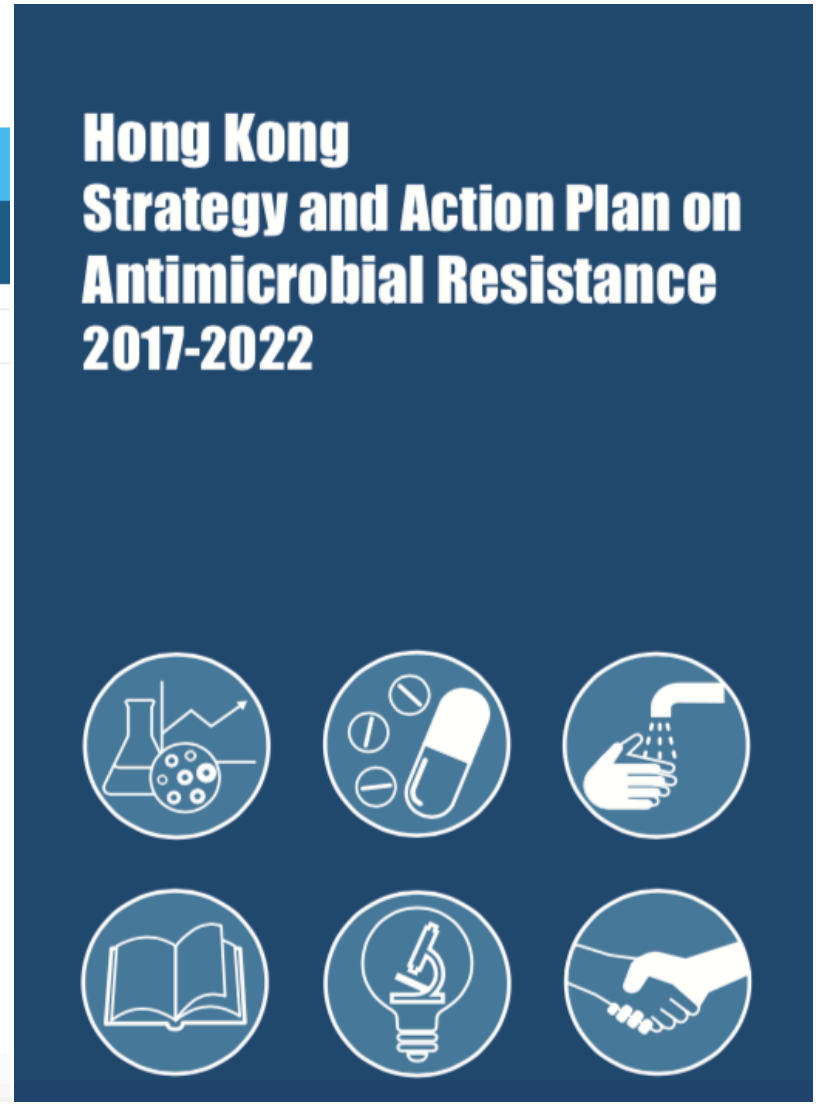
- General Public
- Health Professionals
- Institutions & Schools
- Business & Workplace

Antimicrobial Resistance (AMR)

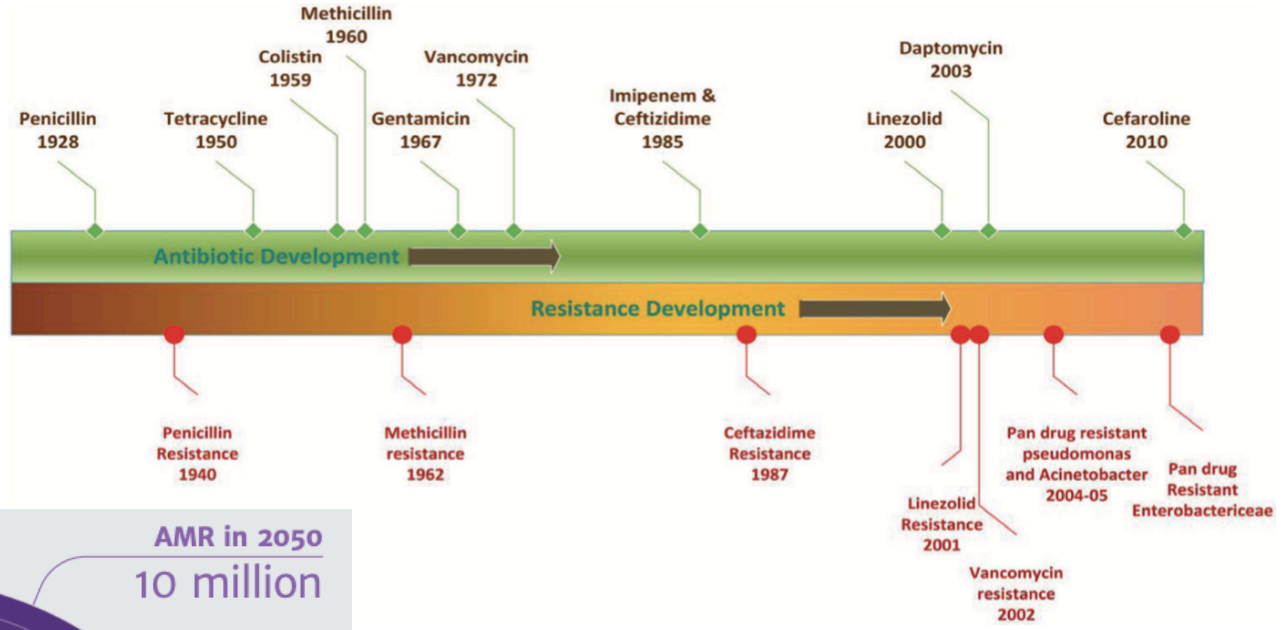
18 November 2019

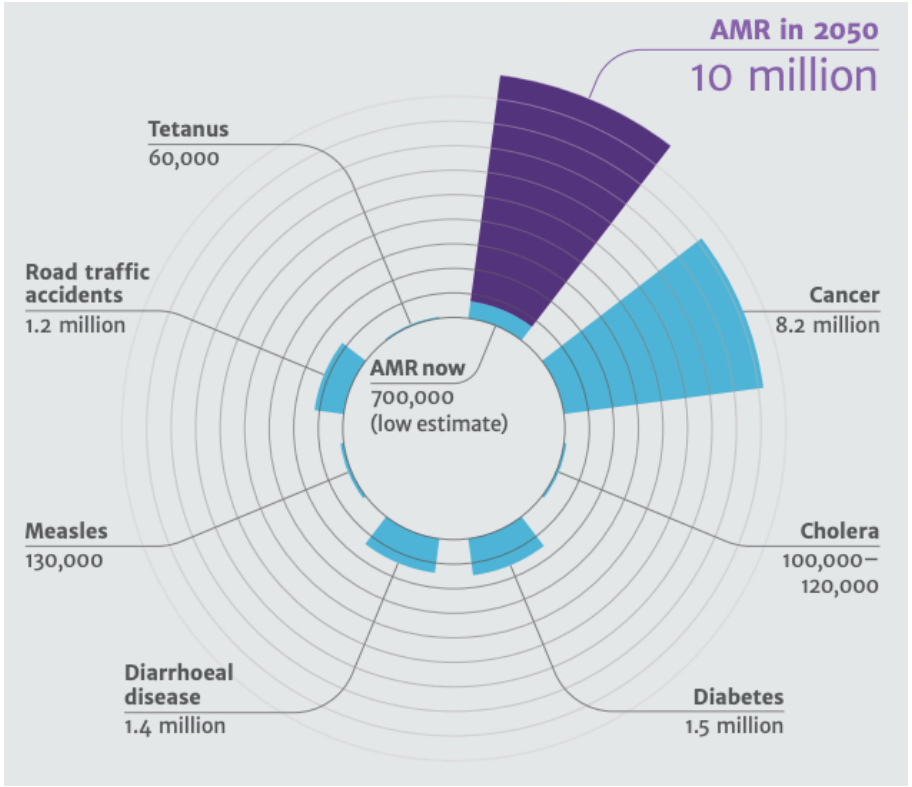
抗菌素 Antimicrobial Resistance 耐藥性

香港抗菌素耐藥性策略及行動計劃
The Hong Kong Strategy and Action Plan on Antimicrobial Resistance



Global situation





In 2050…

10 million death/year

100 trillion dollars/year≒275 × Hong Kong GDP(2018)

Neelam Taneja *et al.* (2019)

Jim O'Neill *et al.* (2016)

Drug repurposing

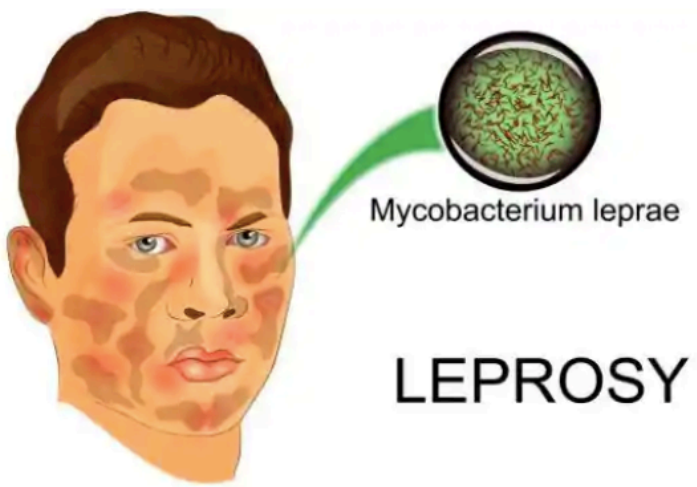
- Using a drug that was developed or approved to treat one disease as a treatment for another
- Formulation / Dosage / Combination/ Delivery
- Re-write the fate of drug

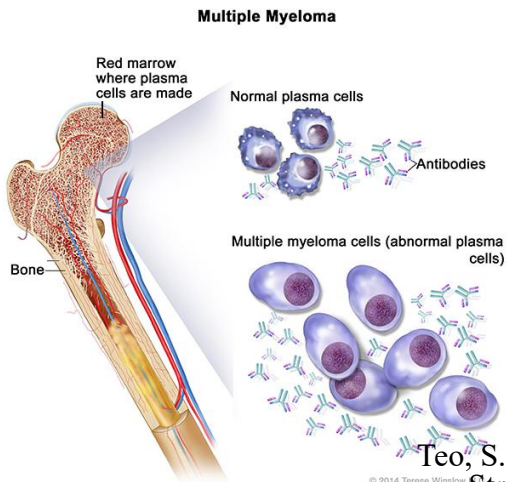
Examples

Thalidomide

In the past
- Developed for morning sickness
- Birth defect: “seal limbs”

Now
- 1998: leprosy
- 2006: multiple myeloma





Teo, S. K. et al. (2002)
Strasser, K. (2002)

Examples

Aspirin

In the past

- Nonsteroidal anti-inflammatory Drugs (NSAIDs)
- Pain, fever, inflammation

Now

- 2015: Prevent colorectal cancer ——325 mg/day

ELSEVIER

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Gastroenterology

Aspirin for the prevention of colorectal cancer

X. Garcia-Albeniz, MD, Research Fellow [a], A.T. Chan, MD, MPH, Assistant Professor of Medicine [b,*]

[a] Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave., Boston, MA 02114, USA
[b] Gastrointestinal Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St., Boston, MA 02114, USA

U.S. Preventive Services TASK FORCE

Search USPSTF Website | E-mail Updates | Text size: a A A

Home
Recommendations
Published Final Recommendations
Recommendations in Progress
Copyright Notice
Information for Health Professionals
Information for Consumers
Public Comments and Nominations
Methods and Processes
About the USPSTF
Newsroom
Announcements

You are here: Home » Recommendations for Primary Care Practice » Published Recommendations » Recommendation Summary » Final Recommendation Statement : Final Recommendation Statement

Final Recommendation Statement

Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Preventive Medication

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

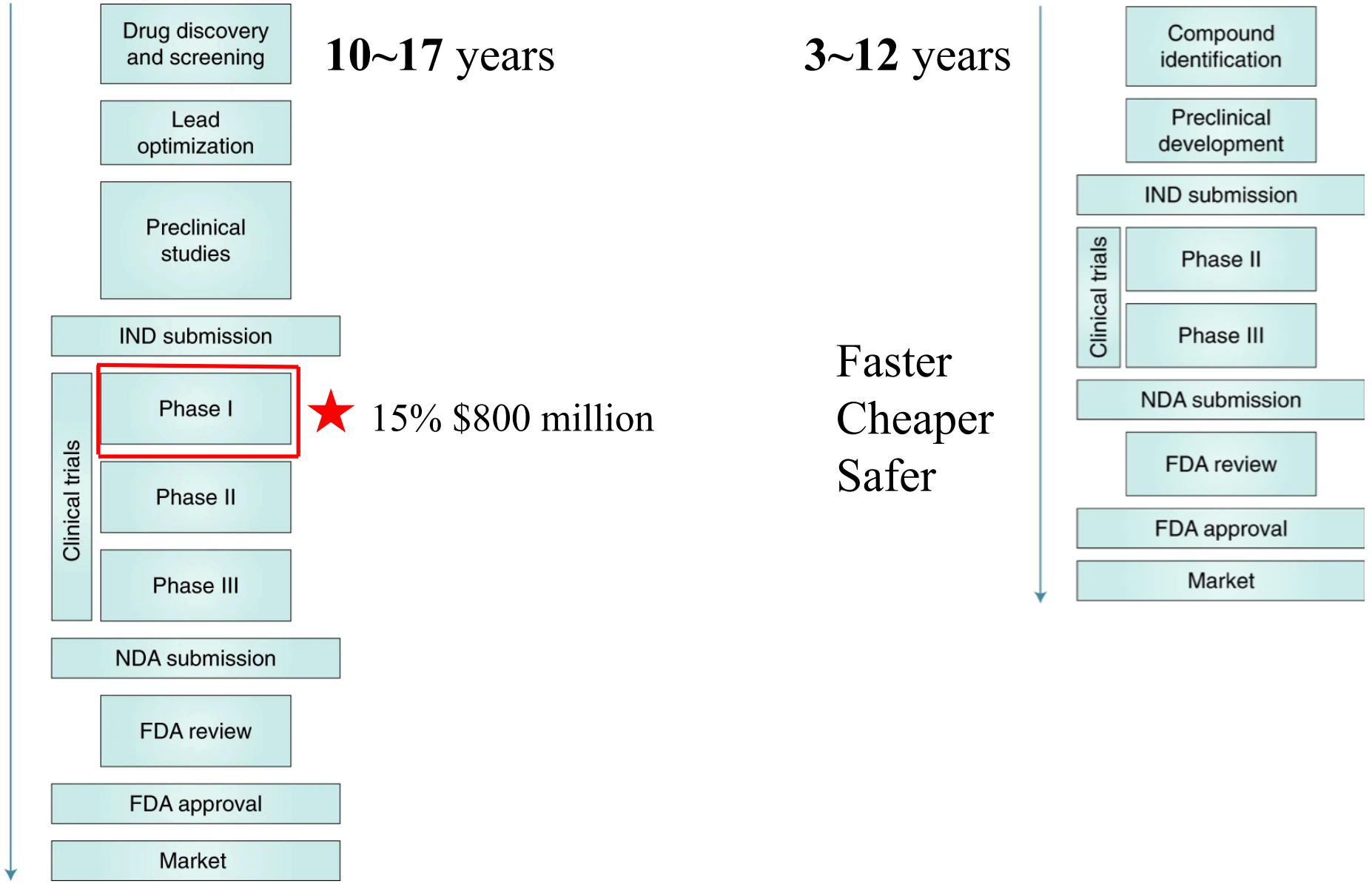
Table of Contents

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B

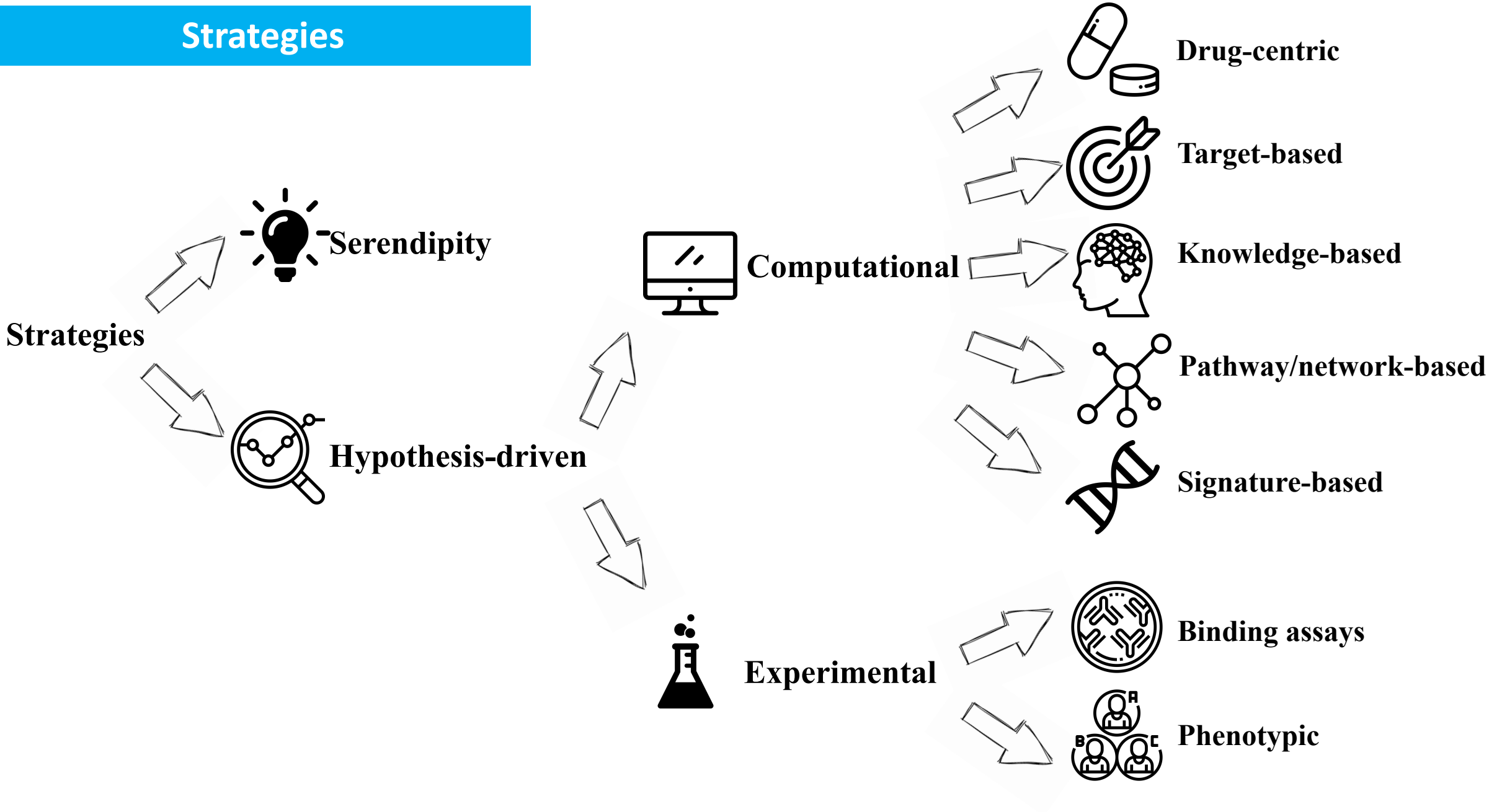
Advantages

Conventional VS Repurposing

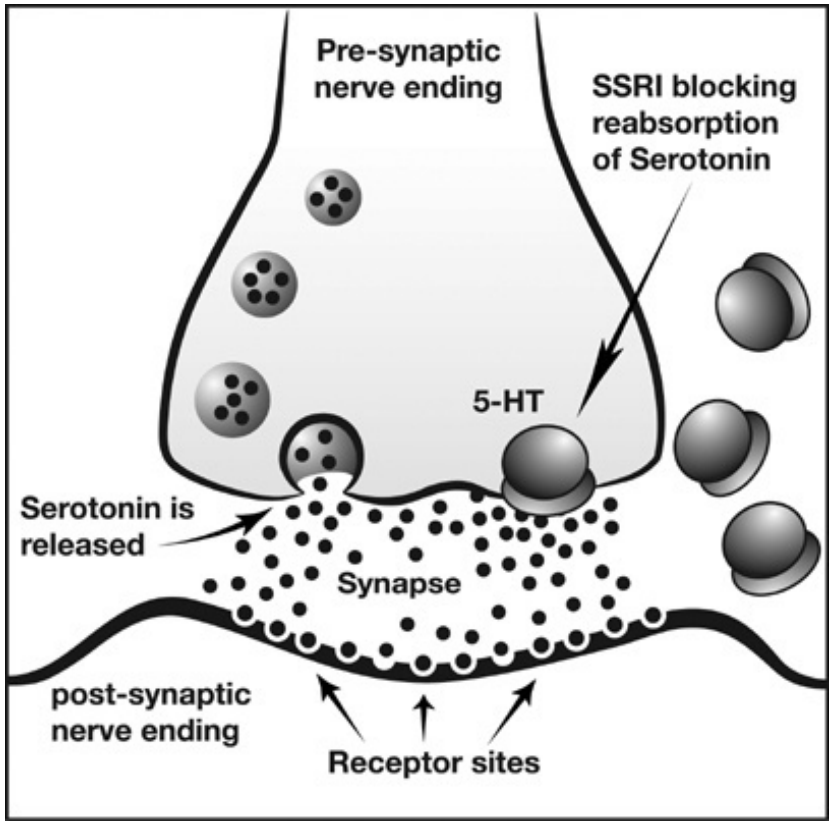


Farha, M.A *et al.* (2019)

Strategies


Strategies
Serendipity
Hypothesis-driven
Computational
Drug-centric
Target-based
Knowledge-based
Pathway/network-based
Signature-based
Experimental
Binding assays
Phenotypic

Sertraline



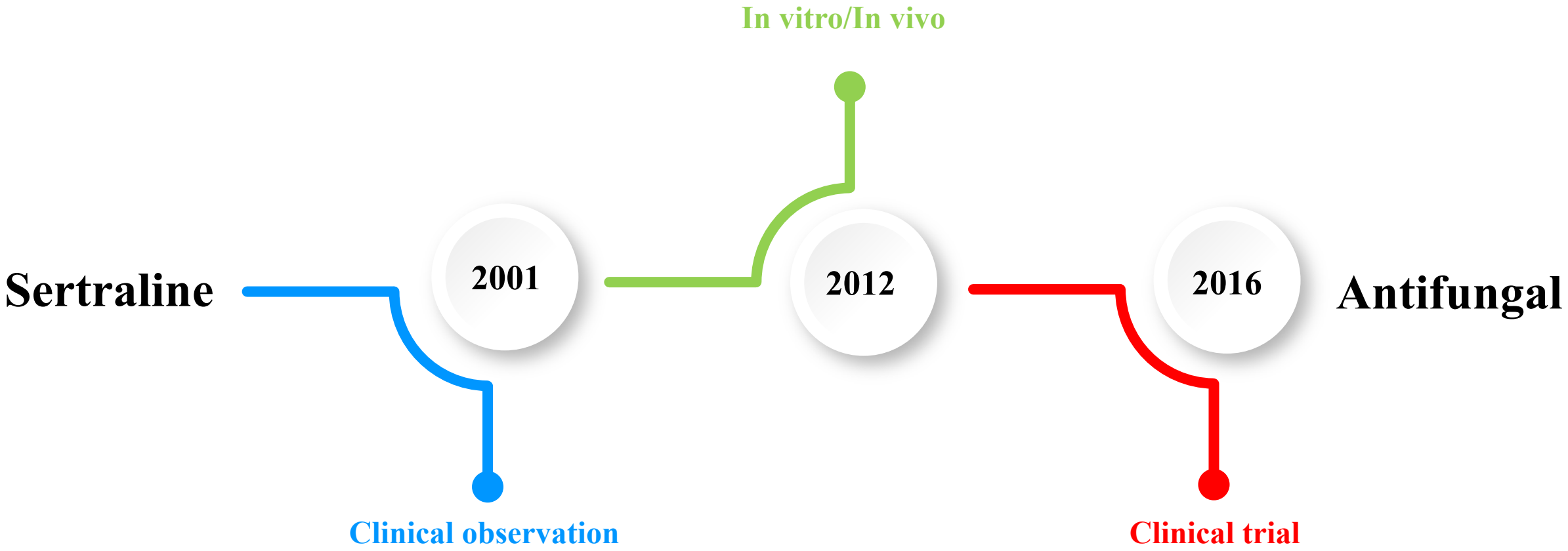
SSRIs
Selective
Serotonin
Reuptake
Inhibitors

→ Depression

→ Antifungal ?

www.ocduk.org/overcoming-ocd/medication/how-ssri-work/

Timeline



Lass-Florl, C. *et al.* (2001)

Zhai, B. *et al.* (2012)

Rhein, J. *et al.* (2016)

2001 Clinical observation

3 patients

Premenstrual Dysphoric Disorder (PMDD)
+
Recurrent Vulvovaginal Candidiasis (VVC)

Sertraline →

100µL Fungal suspensions
+
100µL Sertraline dilutions

48 h
35 °C →

Table 1. Fungicidal concentrations of sertraline against *Candida* species.

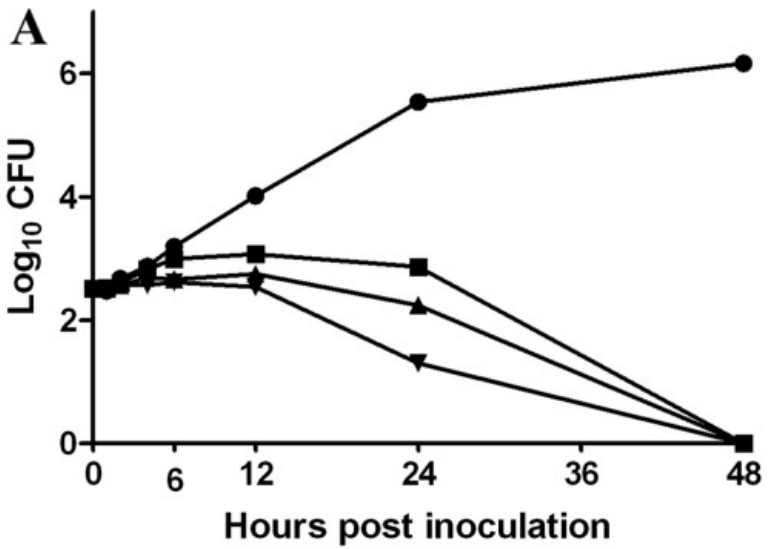
Fungi, isolate	Yeast suspension, cfu/mL	MFC range at 48 h, µg/mL
Candida albicans		
1	4.3–5 × 10^3	14–29
2	2.7–4 × 10^3	7–14
CBS 5982	1.4–4 × 10^3	3–7
Candida glabrata		
1	1.2–2 × 10^3	14–29
2	1–5 × 10^3	14–29
Candida tropicalis		
1	1.3–2 × 10^3	7
2	1.2–4 × 10^3	3–7
Candida parapsilosis		
ATCC 22019	2–3.1 × 10^3	14–29

→ **Antifungal activity was observed.**

Lass-Florl, C. *et al.* (2001)

2012 In vitro testing

Time course assay of cell viability



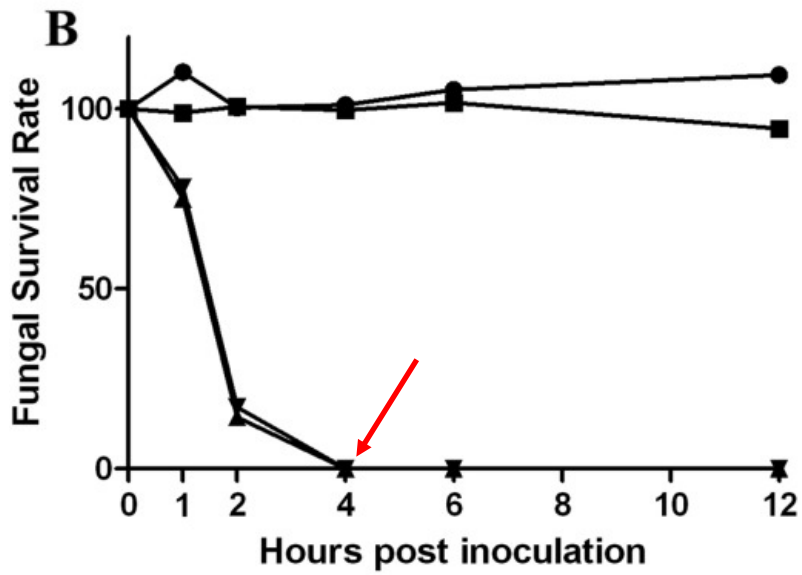
→ **Proliferative**

Efficiency : FLC+SRT > SRT > FLC

MIC_{90}
Cryptococcus H99
6 μg/ml

fungistatic ?

fungicidal ?



→ **Quiescent**

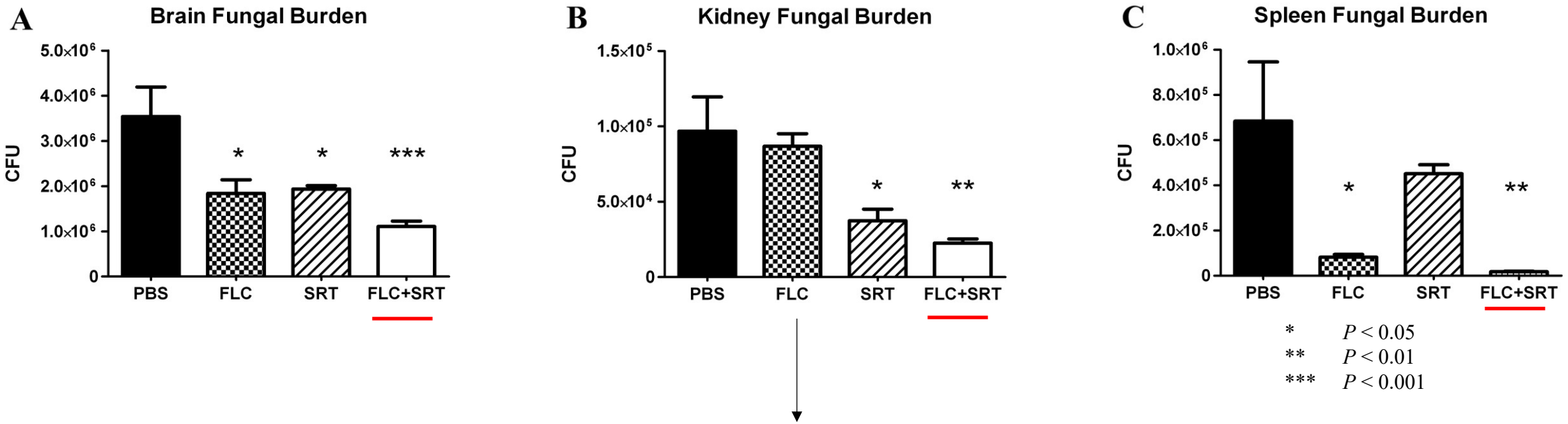
Sertraline is **fungicidal** against *Cryptococcus* regardless of whether cells are growing or not.

Zhai, B. *et al.* (2012)

2012 In vivo efficacy

4 groups

Control (PBS)
Fluconazole(FLC),
Sertraline(SRT),
Fluconazole+ Sertraline(FLC+ SRT)



- **Sertraline displays antifungal activity in systemic cryptococcosis.**
- **The combination is a more effective than either drug alone due to strong synergy.**

Zhai, B. *et al.* (2012)

2016 Clinical trial

172 HIV patients
+ cryptococcal meningitis

antifungal therapy
+
adjunctive sertraline

first **60** patients——assess safety and tolerability

2 weeks
induction therapy

100 mg/d (n=17)
200 mg/d (n=12)
300 mg/d (n=14)
400 mg/d (n=17)

+

8 weeks
consolidation therapy

200 mg/d

+

112 patients
randomly assigned (1:1)

2 weeks
induction therapy

200 mg/d (n=48)
300 mg/d (n=36)
400 mg/d (n=28)

+

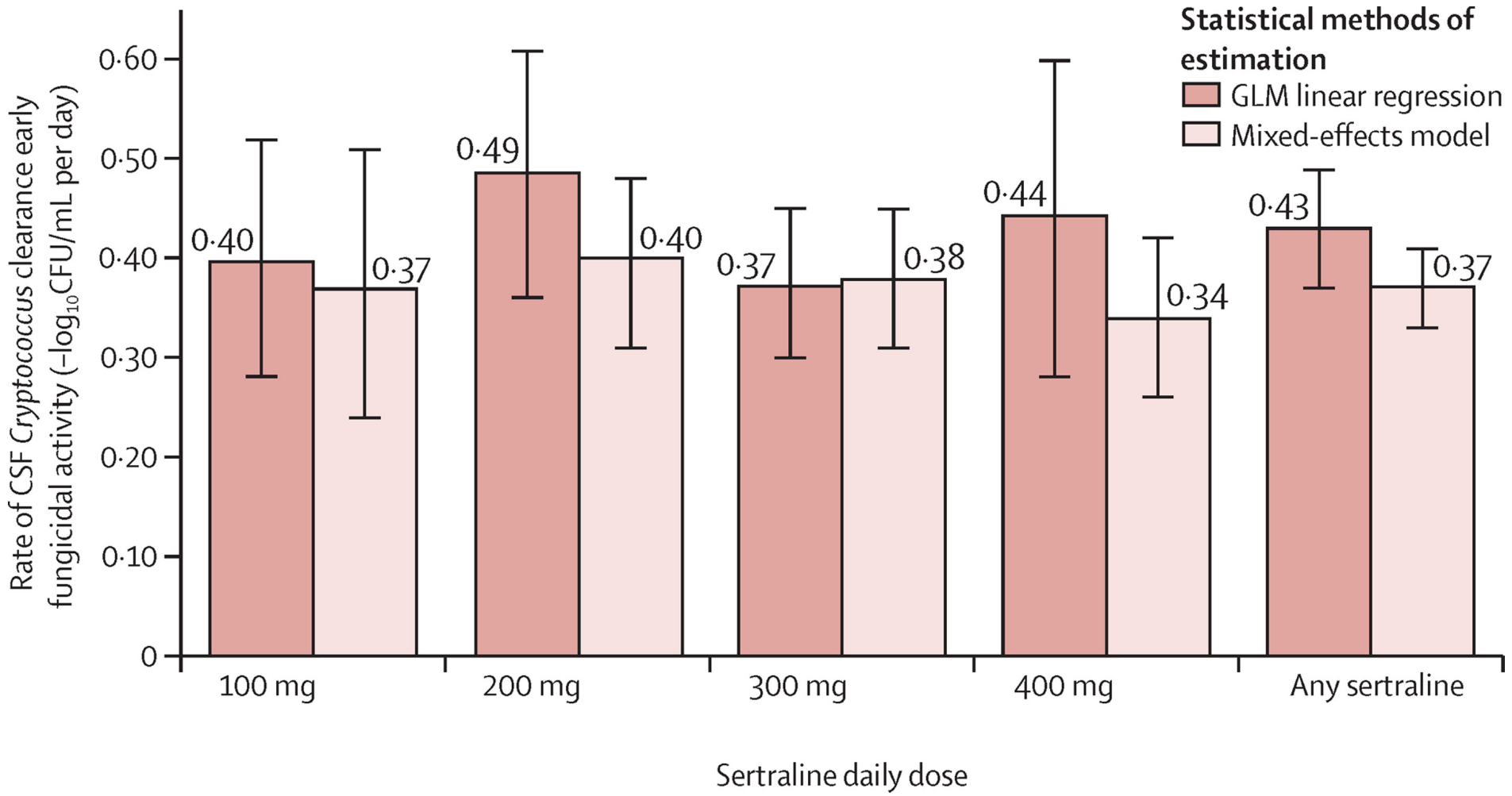
8 weeks
consolidation therapy

200 mg/d

Final population

100 mg/d (n=17)
200 mg/d (n=60)
300 mg/d (n=50)
400 mg/d (n=45)

2016 Clinical trial



1. Participants receiving any sertraline dose averaged a CSF clearance rate of **–0.37** colony forming units/mL/day (95% CI –0.41 to –0.33).

Rhein, J. *et al.* (2016)

2016 Clinical trial

	Sertraline dose cohort				Sertraline, all (n=172)	Sertraline, p value (n=172)
	100 mg (n=17)	200 mg (n=60)	300 mg (n=50)	400 mg (n=45)		
14-day CSF sterility*	6/14 (43%)	25/41 (61%)	22/43 (51%)	20/40 (50%)	73/138 (53%)	0·61
Paradoxical IRIS†	0/3 (0%)	1/14 (7%)	0/15 (0%)	1/11 (9%)	2/43 (5%)	0·58
Culture-positive relapse‡	0	0	0	0	0	..
2-week mortality	5/17 (29%)	8/60 (13%)	12/50 (24%)	13/45 (29%)	38/172 (22%)	0·21
12-week mortality	10/17 (59%)	20/60 (33%)	21/50 (42%)	18/45 (40%)	69/172 (40%)	0·30

2. Incidence of paradoxical immune reconstitution inflammatory syndrome(IRIS) was **5%**.

   IRIS: a collection of inflammatory disorders associated with paradoxical worsening of preexisting infectious processes following the initiation of antiretroviral therapy (ART) in HIV-infected individuals.

3. **No** cases of relapse occurred over the 12-week study period.

Rhein, J. *et al.* (2016)

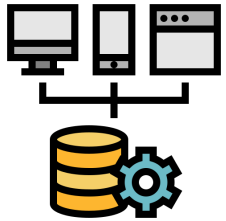
2016 Clinical trial

- Faster cryptococcal CSF clearance
- Lower incidence of IRIS
- Lower relapse rates

→ **Sertraline is a promising adjunctive antifungal therapy.**

Challenges

- Experimental data
- Clinical data

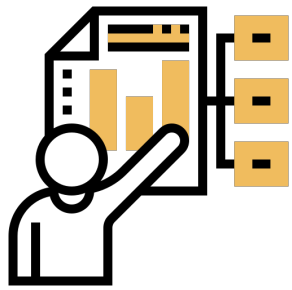


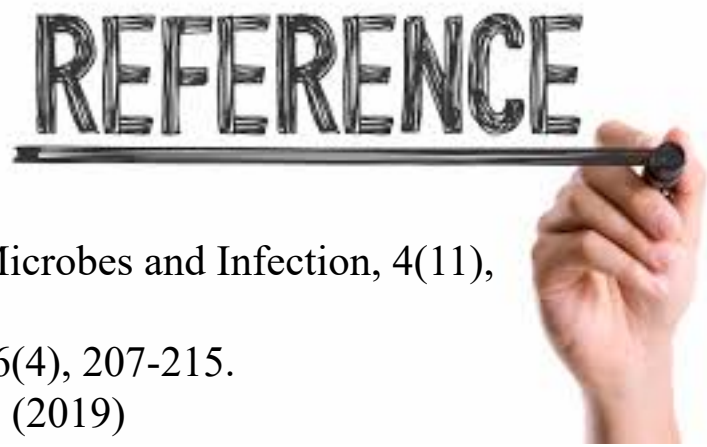
- Integrative platforms
- Clinical pharmacology

- Regulatory requirements
- Intellectual property

Conclusion

- Drug repurposing holds strong promise in complementing traditional drug discovery.
- A systematic application of repurposing strategies improves its feasibility.
- Repurposing drugs could provide breakthrough therapies for antimicrobial resistance.





1. Teo, S. K., Resztak, K. E., Scheffler, M. A. et al. (2002). Thalidomide in the treatment of leprosy. Microbes and Infection, 4(11), 1193-1202.
2. Strasser, K., & Ludwig, H. (2002). Thalidomide treatment in multiple myeloma. Blood Reviews, 16(4), 207-215.
3. Farha, M.A., Brown, E.D. Drug repurposing for antimicrobial discovery. *Nat Microbiol* **4,** 565–577 (2019)
4. Theuretzbacher, U., Outterson, K., Engel, A. *et al.* The global preclinical antibacterial pipeline. *Nat Rev Microbiol* (2019)
5. Pushpakom, S., Iorio, F., Eyers, P. A *et al.* (2018). Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discovery, 18*,41.
6. Campos, A. I., & Zampieri, M. (2019). Metabolomics-Driven Exploration of the Chemical Drug Space to Predict Combination Antimicrobial Therapies. *Molecular Cell, 74*(6), 1291-1303.e1296.
7. Ribeiro da Cunha, B.; Fonseca, L.P.; Calado, C.R.C. Antibiotic Discovery: Where Have We Come from, Where Do We Go? Antibiotics 2019,8 45.
8. Parvathaneni, V., Kulkarni, N. S., Muth, A., & Gupta, V. (2019). Drug repurposing: a promising tool to accelerate the drug discovery process. Drug Discovery Today, 24(10), 2076-2085.
9. Gns, H. S., Gr, S., Murahari, M., & Krishnamurthy, M. (2019). An update on Drug Repurposing: Re-written saga of the drug's fate. Biomedicine & Pharmacotherapy, 110, 700-716.
10. li, Yvonne & Jones, Steven. (2012). Drug repositioning for personalized medicine. Genome medicine. 4. 27. 10.1186/gm326.
11. Lass-Florl, C., Dierich, M. P., Fuchs, D., Semenitz, E. & Ledochowski, M. Antifungal activity against Candida species of the selective serotonin-reuptake inhibitor, sertraline. Clin. Infect. Dis. 33, E135–E136 (2001).
12. Zhai, B., Wu, C., Wang, L., Sachs, M. S. & Lin, X. The antidepressant sertraline provides a promising therapeutic option for neurotropic cryptococcal infections. Antimicrob. Agents Ch. 56, 3758–3766 (2012).
13. Rhein, J. et al. Efficacy of adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis: an open-label dose-ranging study. Lancet Infect. Dis. 16, 809–818 (2016).


Thank you