Cascades: Improving TB Drug Treatment

New Drugs, New Regimens, New Opportunities for MDRTB

Credit: Elizabeth Griot

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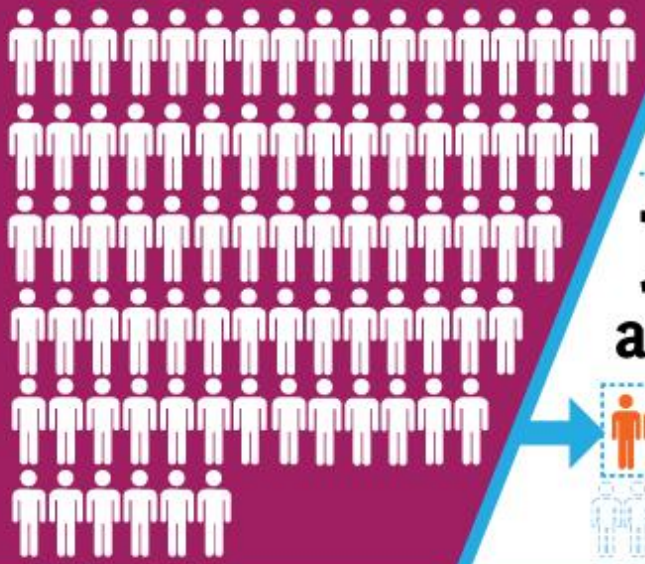
ACCESS TO EFFECTIVE DR-TB TREATMENT

81% of people with DR-TB don't get effective treatment



of the **19%** that do,

ONLY

HALF are cured.

WE NEED BETTER TREATMENT NOW

IT CAN TAKE

DAY 1
20 pills swallowed + 1 painful injection

START

DAY 240
4,800 pills swallowed
240 painful injections received

DAY 365
7,300 pills swallowed

DAY 730
14,600 pills swallowed

FINISH

2 YEARS TO TREAT DRUG-RESISTANT TB

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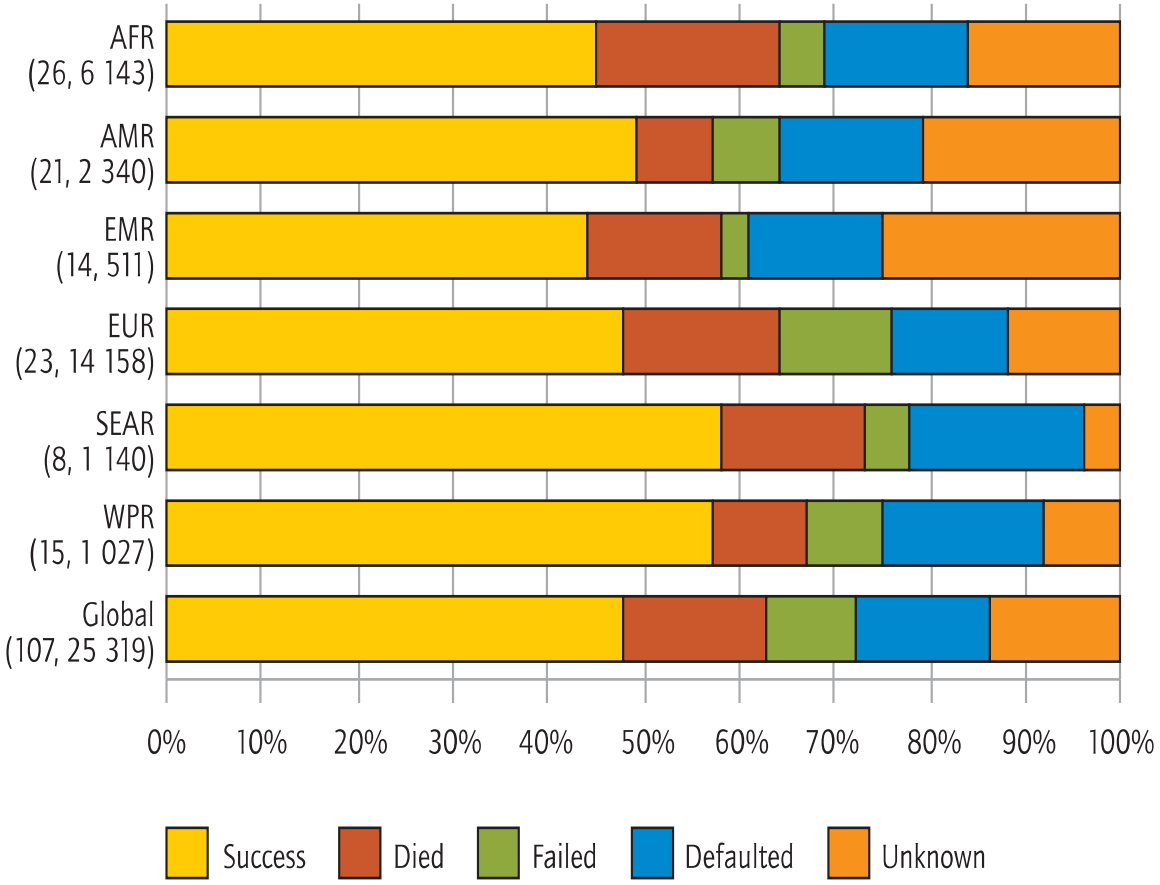
FIGURE 4.8 **Treatment outcomes for patients diagnosed with MDR-TB by WHO region, 2009 cohorts.**
The number of countries reporting outcomes for at least one case, followed by total cases with outcome data, shown beside each bar.



The issues - DRTB treatment

Old – last approved new drug was 50 years ago

Long – Treatment takes two years

Complex – multiple tablets, 8 months of injectable agents, needs tailored to individual resistance patterns. Hard to scale-up.

Expensive – Can cost up to $3000 in drug costs alone

Toxic – Side effects range from hearing loss to intractable nausea to psychosis

Inadequate – high default rates, low cure rates, generates further resistance, no paediatric FDC

Unproven – No RCT or prospective trials exist for the current regimen.

Game Changer: An Ideal Regimen

1. Contain at least two new classes of drug and does not combine drugs of same class
2. Effective against MDR and XDR
3. Contain 3 to 5 effective drugs
4. All-oral, simple dosing schedule
5. Good side effect profile with limited monitoring
6. Duration 6 months or less
7. Have minimal interactions with anti-retrovirals
8. Efficacy 80% or higher

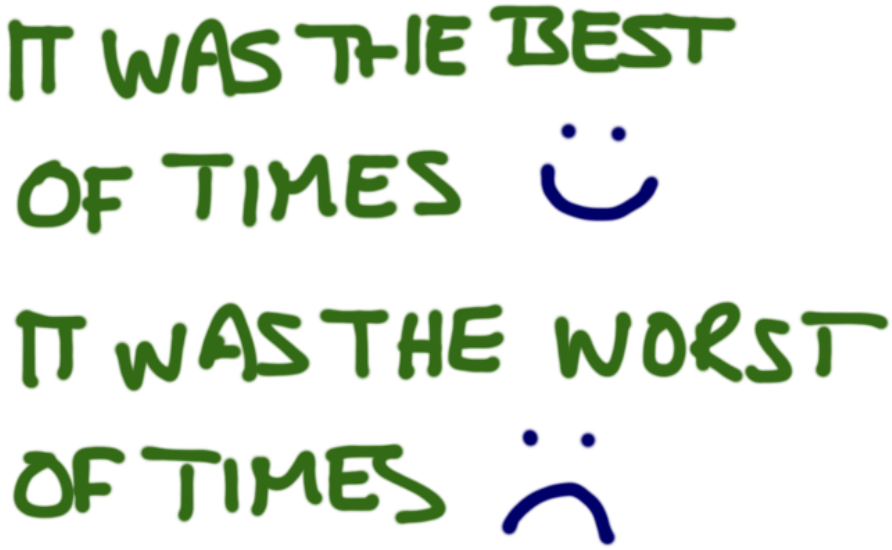
- Patient effects
  - Increase adherence
  - Increase cure
  - Patients will not have to “shut down” their lives for 2 years
- Health system effects
  - Decentralizable
  - Enables task shifting
- Market effects
  - Consolidates demand
  - Allows increased pooling (more country regimens harmonized)
  - No injectable=potential lower costs
  - Larger volume market can support generic competition

Global TB Drug Pipeline [1]

Discovery

Lead Optimization

- Cyclopeptides
- Diarylquinoline
- DprE Inhibitors
- InhA Inhibitor
- LeuRS Inhibitor
- Macrolides
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Ruthenium(II) Complexes
- Spectinamides
- Translocase-1 Inhibitor



Phase III

- elamanid (PC-67683)
- tifloxacin
- oxifloxacin
- fapentine

Chemical classes: fluoroquino
benzothiazinone

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

[2] Combination regimens: NC-001 -(J-M-Pa-Z), phase 2a, NCT01215851; NC-002-(M-Pa-Z), phase 2b, NCT01498419; NC-003-(C-J-Pa-Z), phase 2a, NCT01691534; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), phase 2b, NCT01785186.

RKING GROUP
ON NEW TB DRUGS

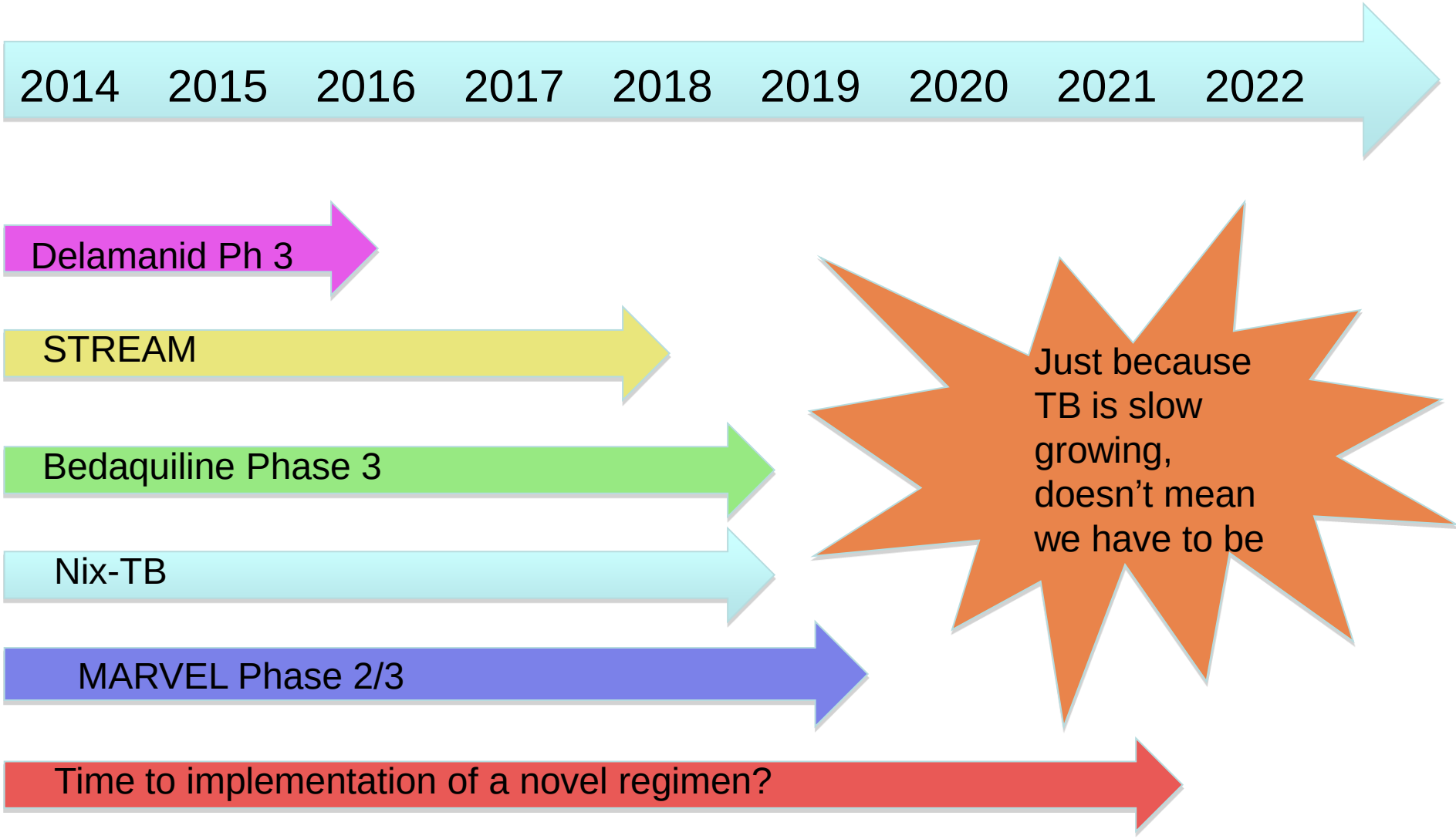
www.newtbdrugs.org

Updated: June 2013

Trials

- STREAM (4KCMEHZP/5MEZC)
  - 9 months (key populations), higher efficacy (?), WHO endorsed for operational research and countries taking up OR
  - 7 drugs up front, injectable, ? Efficacy with SLD resistance, cost still $2000
- STREAM additional arms
  - Potential for addition of BDQ and elimination of injectable
  - Shorter duration?
- MARVEL (JPaULZ various combos)
  - All-oral, use of >2 new classes, 6 months?
  - Timeline?
- Nix (JPaU+/-Z)
  - All-oral, use of >2 new classes, 6-8 months
  - XDR-only

How Long Will We Wait?



Accelerating Access to Current and Future Tools

- Use diagnostics to uncover the epidemic
- Price – breaking the paradigm of expensive regimens, especially MICs
- Availability
  - Compassionate use
  - Wide registration applications and speedy approval
  - Ensure antibiotic stewardship (COE? Private sector select sites?)
- Rapid adoption of new drugs and regimens
  - WHO advice and guidelines – how much data is sufficient?
  - Scale up STREAM as OR for key populations
  - Potential for market consolidation – especially if broadly effective regimen
- Speed new trials
  - Use of 6 month or EOT conversion
  - Internal controls slowing results? What is our SOC?
  - Regulatory pathways for accelerated approval of novel regimens
  - Improve access to medicines and data on study drugs….

Yeah, Heard It All Before….

Innovative Medicines Initiative

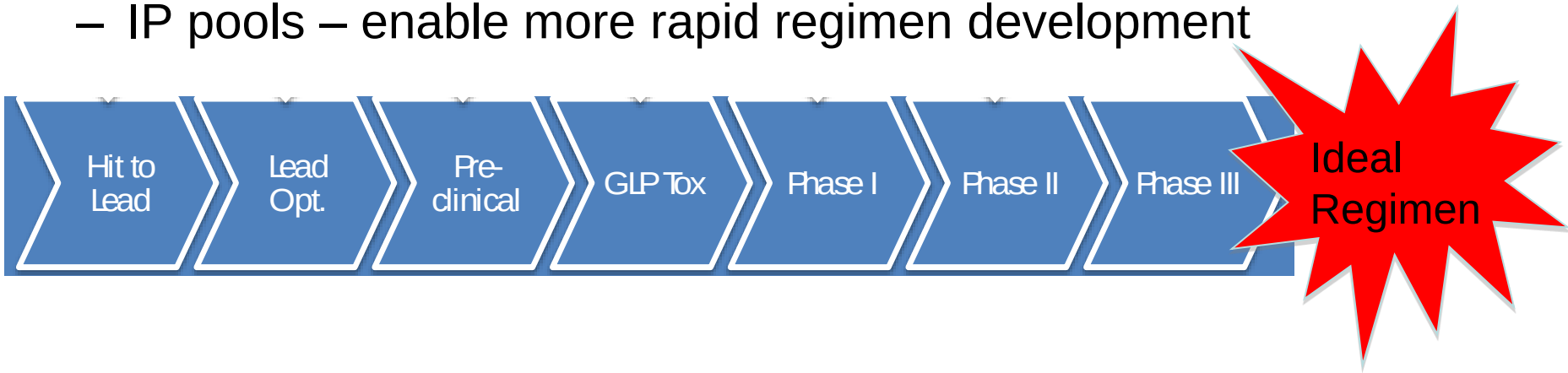
RESIST-TB
Research Excellence to Stop TB Resistance

WIPO | Re:Search
Sharing Innovation
in the Fight Against
Neglected Tropical Diseases

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Incentivizing R&D for Public Health

- De-link R&D goals from eventual profit motivation
  - Increases public health needs driving R&D
  - Facilitates collaboration
- Opportunity for change?
  - Push mechanisms – grants linked to TPPs
  - Pull mechanisms – variable rewards that incentivize sharing IP and based on meeting TPP (including regimen development)
  - IP pools – enable more rapid regimen development



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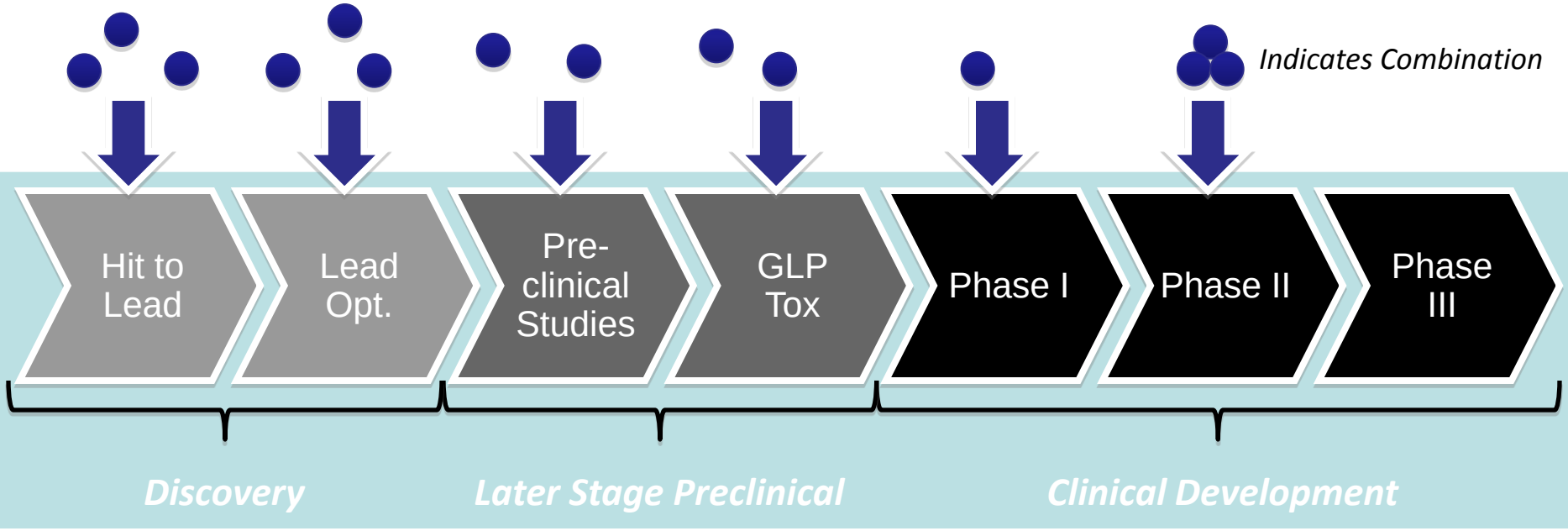
A Different Path



Small, early-stage Milestone Prize (Size 1; mix of small financial and recognition prizes) for licensing the compound to the Open Collaborative Framework

Milestone Prize (Size 2) for entering clinical development (Phase I)

Milestone Prize (Size 3) for combination regimen successfully completing Phase II

Legend

- Various TB Compounds
- Milestone Prizes
- Grant funding

Grant funding for studies from the fund

Grant funding for Phase III from existing and new sources

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Thank you!