Pricing of Antibiotics & Proposals to Strengthen the Pipeline

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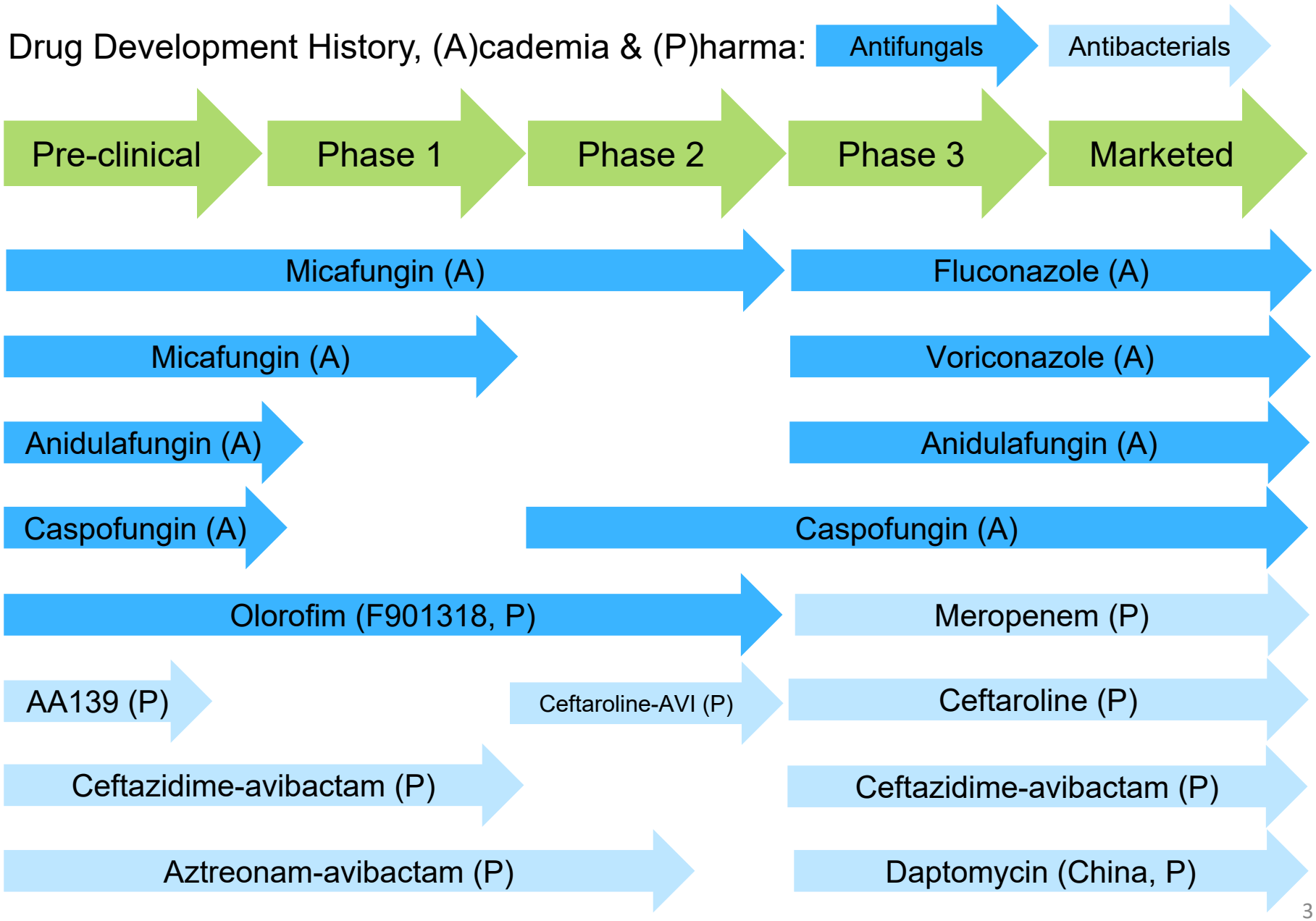
Slides happily shared

Disclosures

- John H. Rex, MD, is Chief Medical Officer & Director, F2G, Ltd.; Editor-in-Chief, AMR.Solutions; Operating Partner & Consultant, Advent Life Sciences; and Adjunct Professor of Medicine, McGovern Medical School, Houston, TX
- He sits on the scientific advisory boards of Bugworks Research, Inc.; Basilea Pharmaceutica; Forge Therapeutics, Inc.; Novo Holdings; and Roche Pharma Research & Early Development
- He is a shareholder in AstraZeneca Pharmaceuticals; F2G, Ltd; Advent Life Sciences; Zikani Therapeutis; and Bugworks Research, Inc.
- He has received consulting fees from Phico Therapeutics; ABAC Therapeutics; Polyphor, Ltd.; Heptares Therapeutics, Ltd.; Gangagen, Ltd.; Meiji Seika Pharma; Basilea Pharmaceutica International Ltd.; Allecra Therapeutics GmbH; Forge Therapeutics, Inc.; SinSa Labs; AtoxBio; Peptilogics; F. Hoffmann-LaRoche, Ltd.; Novo Holdings; Innocoll; Vedanta; Progenity; Nosopharm SA; Roivant Sciences; and Shionogi Inc.

- The opinions expressed are his own and do not necessarily reflect the opinion of any of the groups with which he works.

CV: A pragmatic focus on advancing antimicrobials



Agenda

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- Antibiotics are the fire extinguishers of medicine
  - This analogy is very informative
- The pipeline is remarkably small and shallow
  - Useful agents will be few and are costly to develop
- The key fixes are now well understood
  - Push funding that germinates new ideas
  - Pull funding that creates a level economic playing field
  - Preventing stagnation by leveraging failure
- Summary

Pop Quiz: Have you used a fire extinguisher today?

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Let's be more concrete.
Are you using a fire extinguisher <u>right now?</u>

Fundamental starting points

- Antibiotics enable all of health care:
  - Safety net for surgery, cancer therapy, and essentially everything else
  - Fire extinguishers (or fire departments) of medicine
  - Infrastructure for civilization

- Stated differently…

Speaker personal opinion.

STEDI: Antibiotic value beyond mere use

But, we don't (yet) have an agreed way to capture these values

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Antibiotics are the fire extinguishers of medicine!

The "STEDI" values of antibiotics

Value	Description of benefit
Spectrum	Replacing broad spectrum agents with narrow spectrum agents and thereby reducing collateral damage to the microbiome
Transmission	Avoiding pathogen spread to the wider population by effectively treating patients
Enablement	Availability of effective treatment enables other types of medical interventions (eg, surgery, oncology)
Diversity	Having a range of treatment options reduces selection pressure
Insurance	Having an agent available in case of a sudden or significant increase in the prevalence of pathogens resistant to existing agents

Table from Outterson K, Rex JH. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Translational Research*, 2020. The STEDI concept was adapted from Rothery et al. Framework for Value Assessment of New Antimicrobials. http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf, 2018.

Fire extinguisher value: $0 vs. ∞

COVID as an example

- Thought experiment. *Let's hop in a time machine…*
  - You own a company that has developed a novel small molecule with broad activity vs. all Coronaviridae
  - You've shown that it shortens the duration of URI symptoms for the coronoviridae strains that cause URI
  - There is in vitro activity for SARS and MERS but no clinical data as no cases
- You receive FDA & EMA approval in 1 Jan 2019
  - What are your sales during 2019?
  - Could you have stayed in business?
  - What's the fix?

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  - What's the fix? *Delinked Pull rewards that are independent of use*

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  - Value of the molecule in 2021? *If it had been used early on to contain the outbreak in Wuhan, total sales might be low … but the value to the global community would nonetheless be enormous*

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Antibiotics are hard to discover

- Easy to find: Targets
  - Multiple bacterial genomes are fully sequenced
- Easy to find: Things that kill bacteria
  - Bleach works quite well, as do steam and fire
- Hard to find: Kills bacteria & is safe
  - Failures: physical properties, pharmacology, safety
  - Need high levels to penetrate bug → high doses
    - Typical lipid-lowering agent: 5-20 mg/day
    - Typical antibiotic: 100-2000 mg/day
- The impact of all of this…

Payne DJ et al. Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nat Rev Drug Discov 2007;6:29-40.

The pipeline is thin

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Pew's Analysis of Antibiotics in Clinical Development

42	**4**	**17**	**11**	**1 in 4**
Antibiotics in development	Have new drug applications submitted	Could treat infections caused by certain Gram-negative bacteria	Could address urgent threats gonorrhea or *C. difficile*	Is a novel drug class or novel mechanism of action

As of June 2019[8]

"...resistance will eventually develop to those [antibiotics] that are approved, it is clear that there are too few drugs in development to meet current and anticipated patient needs."

—Pew Charitable Trusts, September 2019[8]

True novelty requires years of effort

Completely new classes are higher risk and even slower

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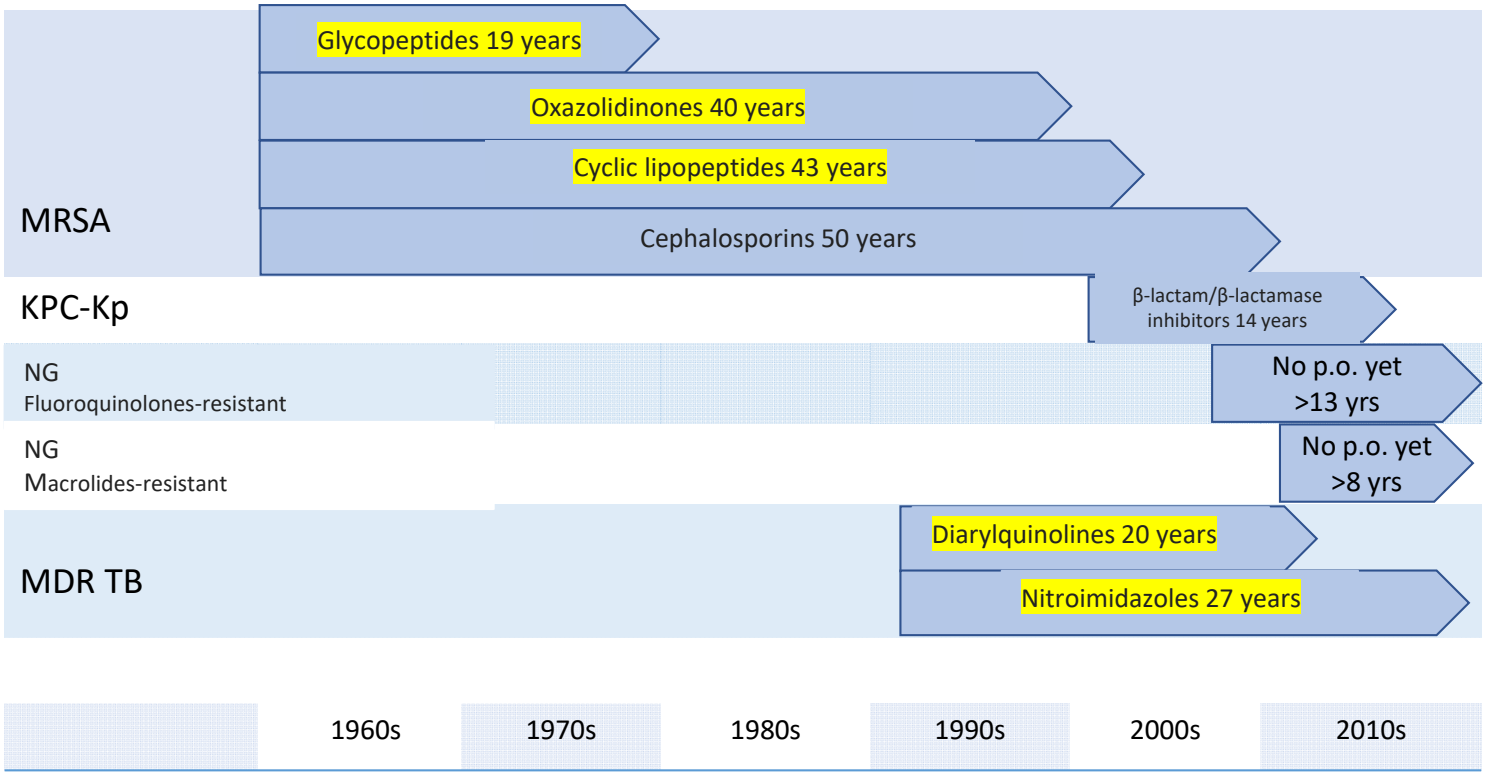
Time from discovery to FDA approval



Sources: CDC AR Threats 2019, at 35; MRSA 1960 (Jevons MP 1961. BMJ); KPC-Kp 2001 (Yigit H, et al. AAC 2001); NG-CR 2007 (CDC, MMWR 2007); NG-AR 2012 (Soge OO, et al, STD 2012); MDR-TB 1992 (Vallarino ME, et al., Pub H Rep 1992). Drug approvals: Vancomycin approved 1958, but US usage did not grow until 1979 (Kirst HA 1998. AAC). Other approvals from Drugs@FDA.gov. For emergence of MRSA resistant to ceftaroline prior to its FDA approval, see Kelley WL et al., AAC 2015.

Graphic borrowed and adapted from Kevin Outterson, July 2020

That time & effort comes at a cost

- Average cost to approval[1] = $1.3b
- Running costs of a drug in its first 10 years: $350m[2]
  - $100m in post-approval commitments: pediatrics, etc.
  - $25m/year to run the plant that makes your drug, surveillance, pharmacovigilance
- All together: ~$1.7b per molecule
  - Usage-based income will not recover those costs[3,4]
  - New antibiotics often have ≤ $25m/year in sales
- Can it be done for substantially less?
  - On average, no. There are no discounts or regulatory shortcuts for being small or large, for-profit or non-profit, degree of novelty, etc.
  - Small company models are already very, very lean[5]

[1]Wouters J, et al. *JAMA* 2020;323:844–53. AMR.Solutions: "Melinta, Part 2 / Bankruptcy Is Not The End / Post-Approval Costs For An Antibiotic", available at https://amr.solutions/2020/01/07/melinta-part-2-bankruptcy-is-not-the-end-post-approval-costs-for-an-antibiotic/. [3]AMR.Solutions: "Mandatory Reading: Alan Carr's Jan 2020 Antibacterial And Antifungal Market Review", available at: https://amr.solutions/2020/01/28/mandatory-reading-alan-carrs-jan-2020-antibacterial-and-antifungal-market-review/. [4]AMR.Solutions: "What Does An Antibiotic Cost To Develop? What Is It Worth? How To Afford It?", available at: https://amr.solutions/2020/03/06/what-does-an-antibiotic-cost-to-develop-what-is-it-worth-how-to-afford-it/. [5]Drakeman DL. Benchmarking biotech and pharmaceutical product development. Nat Biotechnol, 32(7): 621-5, 2014.

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Push and Pull are both needed

- Substantial public thinking over the past 10+ years
  - UK AMR Review; DRIVE-AB project; US legislative efforts; Swedish pilot project, EU Pharma strategy, and more
- Key insights: We need 2 different kinds of funding
  - Push incentives that encourage work to start: Grants
    - $750m for Discovery to Phase 1: CARB-X, Novo REPAIR, etc.
    - $1b for Phase 2-3: AMR Action Fund
    - Lots of (mostly small) companies have entered the fray
  - Pull incentives paid ***on successful approval***
- Many papers on this, see amr.solutions for more
  - In particular, the 1 Sep 2020 newsletter is a good start
  - https://amr.solutions/2020/09/01/reimbursing-for-innovative-antibiotics-encouraging-updates-from-the-amr-conference/

Pull equalizes the economics

- A Pull Incentive rewards creation of a valuable new therapy
  - Key: It is paid on approval and is independent of actual use
  - Analogy: We don't pay fire fighters per fire; we pay to be ready
- With multiple global calls for Pull*, it is starting to emerge
  - The UK subscription pilot as a benchmark: The "Netflix" model
  - GBP 10m/yr x 10 years for a good antibiotic whether used or not
  - The UK is 3% of the G20: 100m x 33 = GBP 3.3b ≈ $4b
- This is right on target: Economic research says ~$2-4b is the global value of a new antibiotic
- So, how do we engage and extend?
  - Wealthy countries need to contribute their fair share
  - Targets must be fair and consistently available
  - So far, the only sizeable further effort is in the US (PASTEUR Act)

*US: PACCARB (https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf) and PASTEUR Act (https://www.congress.gov/bill/116th-congress/senate-bill/4760/text); EU: IMI DRIVE-AB: http://drive-ab.eu/drive-ab-outputs/drive-ab-reports/ and 2020-25 EU Pharmaceutical Strategy (https://ec.europa.eu/health/human-use/strategy_en), UK: AMR Review: https://amr-review.org/ and UK pilot itself: https://amr.solutions/2020/03/29/uk-antibiotic-subscription-pilot-implies-pull-incentive-of-up-to-4b-across-the-g20/

Why $2-$4b as the reward?

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- What does a new antibiotic *really* cost?
  - As noted above, $1.7b all-in would be a good guess
- A reward in the range of ~$2-4b balances the risk
  - Substantial modeling has been done on this
  - A reward of this size makes antibiotics ≅ cancer drugs
  - DRIVE-AB[1], ERG review[2], UK AMR Review[3], PACCARB[4]
- Investment will occur if reward is predictable
  - Pharma & VCs will take on the technical risk
  - Reward should be triggered by approval

[1]DRIVE-AB: http://drive-ab.eu/drive-ab-outputs/drive-ab-reports/. [2]Sertkaya et al. https://aspe.hhs.gov/report/analytical-framework-examining-value-antibacterial-products. [3]UK AMR Review: https://amr-review.org/. [4]PACCARB incentives: https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf

Pull awards can guide R&D

- Think of R&D as a big ship … *a 10- to 15-year-long ship*
  - Big ships turn slowly, but they do turn
- Pull awards tied to desired features will turn the ship
  - Novelty, Indications, and Spectrum can all be measured[1]
  - The UK Pilot has published a point scoring system[2]
- Key: Targets must be held constant
  - Products coming to approval at any given time are the result of decisions made a decade or more previously
- This is an involved topic. For an extended discussion…
  - AMR.Solutions:[3] "Assessing Antibiotic Value: DTR, Fire Extinguishers, And A View From Australia"
  - The idea of Difficult-to-Treat-Resistance (DTR) is a noteworthy build on features such as novelty and spectrum

[1]Rex JH, Outterson K. Antibiotic Reimbursement in a Sales-Delinked Model: Context and a Benchmark-Based Global Approach. The Lancet Infectious Disease, 16: 500-5, 2016. [2]Search for "slide 25" on https://amr.solutions/2020/03/29/uk-antibiotic-subscription-pilot-implies-pull-incentive-of-up-to-4b-across-the-g20/. [3]https://amr.solutions/2020/06/07/assessing-antibiotic-value-dtr-fire-extinguishers-and-a-view-from-australia/

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(Real) Failure is a critical tool

- I had to live this one to fully understand it
  - No one wants their project to fail
  - No one wants their salary to be at risk
  - Most people do not like uncertainty
- Impact: The system will adapt to protect jobs
  - There's always one more tempting experiment!
  - Unless really forced, projects will *Never. Ever. Stop.*
- Core lesson: Real failure must be possible
  - Clear targets and clear funding boundaries are needed to force projects to sink or swim
  - Without same, projects/companies will go on & on

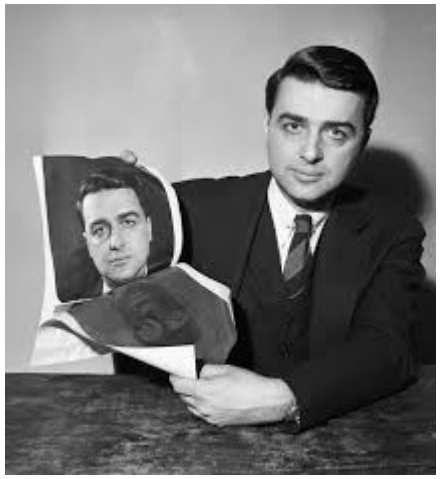
The power of Small vs. Large

- (Small) Biotech's sweet spot: Trying and discarding
  - 70% of FDA Fast Track products are from small biotech[1]
  - Why? "The biotech industry is nearly perpetually short of cash … most biotech companies will run out of cash within three years without further funding."
- (Large) Pharma's sweet spot: Global delivery
  - The multinationals have a network that simply cannot be recreated by a small company
- A predictable Pull incentive leverages both levels
  - Biotech will invest and then Pharma will buy in
  - It's a win-win: We get the clarity of the marketplace (no zombie projects!) while aligning use with stewardship

[1]Drakeman 2014 Nature Biotech 32:621-625

Summary

Our head is round so that our thinking can change direction (Francis Picabia)



Don't undertake a project unless it is manifestly important and nearly impossible (Edwin Land)

Summary

- The AMR problem is now well-defined
  - After 10 years of effort, we really understand the issues
  - Antibiotics are the Fire Extinguishers of Medicine
    - Like other infrastructure, we must buy them in advance
- The possible solutions are now well studied
  - Push funding is familiar and is having an effect
  - The big mental shift is in Pull
- It takes years of effort to find novel new agents
  - Reward must match required risk
  - The pressure of Sink or Swim is critical to success
  - Delinked Pull ties together creativity and stewardship

#FireExtinguishersOfMedicine