Antifungal Drug R&D Comes of Age

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I will share these slides via my newsletter/blog

Please note these details!

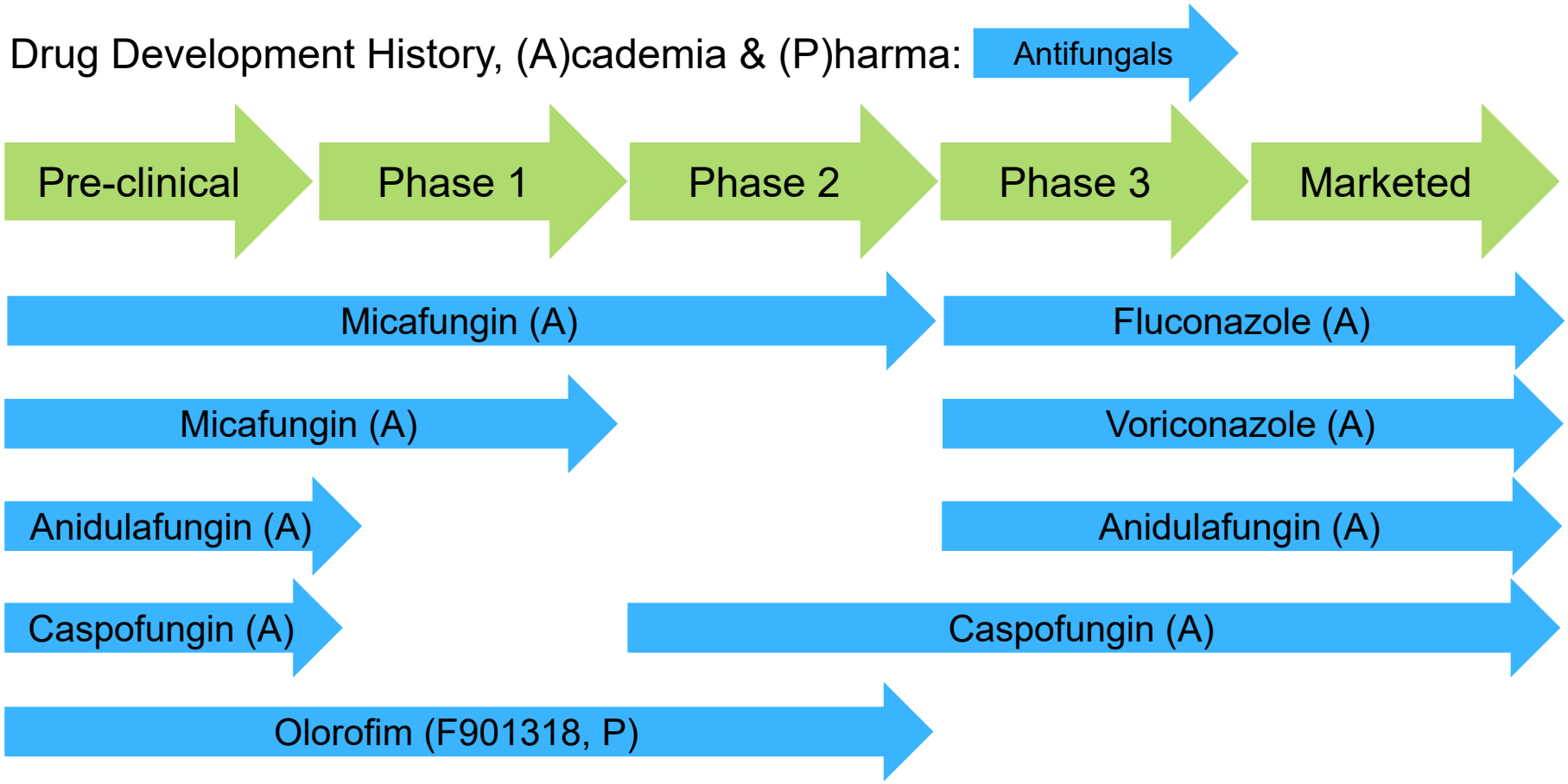
Agenda

- Introduction
- What does it take to invent & deliver a new drug?
- Evolving regulatory paradigms
- Evolving payor paradigms
- Summary
- Resources

Thank you!

- I am honored to have been asked to give this talk
- I have been a student of mycology for 33 years!
  - *Many* beloved mentors: Jack Bennett, Elias Anaissie, Bill Dismukes, Jack Edwards, June Kwon-Chung, Jacky Sobel, David Stevens, Gail Triggs, Doug Webb, Temple Williams
- I have followed a somewhat winding career path
  - 1987-2002: Academic medicine (99% antifungal)
  - 2003-present: Development within regulated Industry
    - Antibacterial then antifungal
  - As this is part of what makes me qualified to discuss this subject, a bit more detail is helpful…

Qualifications: A continuous focus on drug development!



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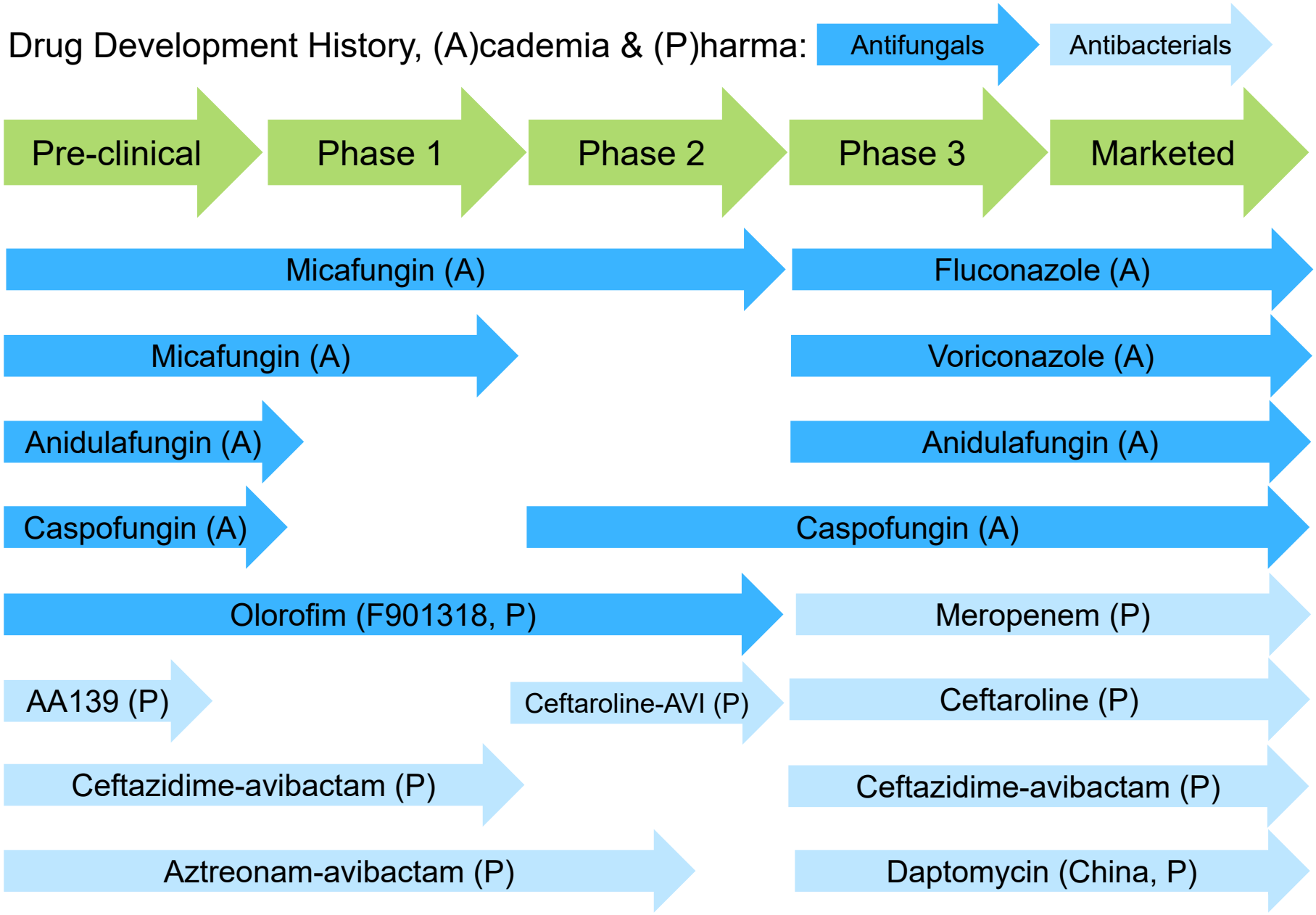

With that in mind…

- This talk will be tour of the ideas I find most relevant to developing novel therapeutics
- The focus will mostly be from mid-Discovery to Registration: The very early stages of target discovery will be covered only incidentally
- The topics are
  - Biased by my personal experience and lessons learned
  - Often drawn from the antibacterial world – there are more similarities than differences between antifungals & antibacterials
- For avoidance of doubt, note that I work with a company that has novel antifungal in Phase 2 (F901318, olorofim)
  - Details on it were shared at the pipeline session yesterday
  - I will draw on a lesson from its development program, but only with the intent of showing how this idea can be generalized

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  - A focus on Unmet Need
  - Multiple disciplines: Biology, MedChem, Tox, CMC, PK-PD
- Evolving regulatory paradigms
- Evolving payor paradigms
- Summary
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Unmet Need

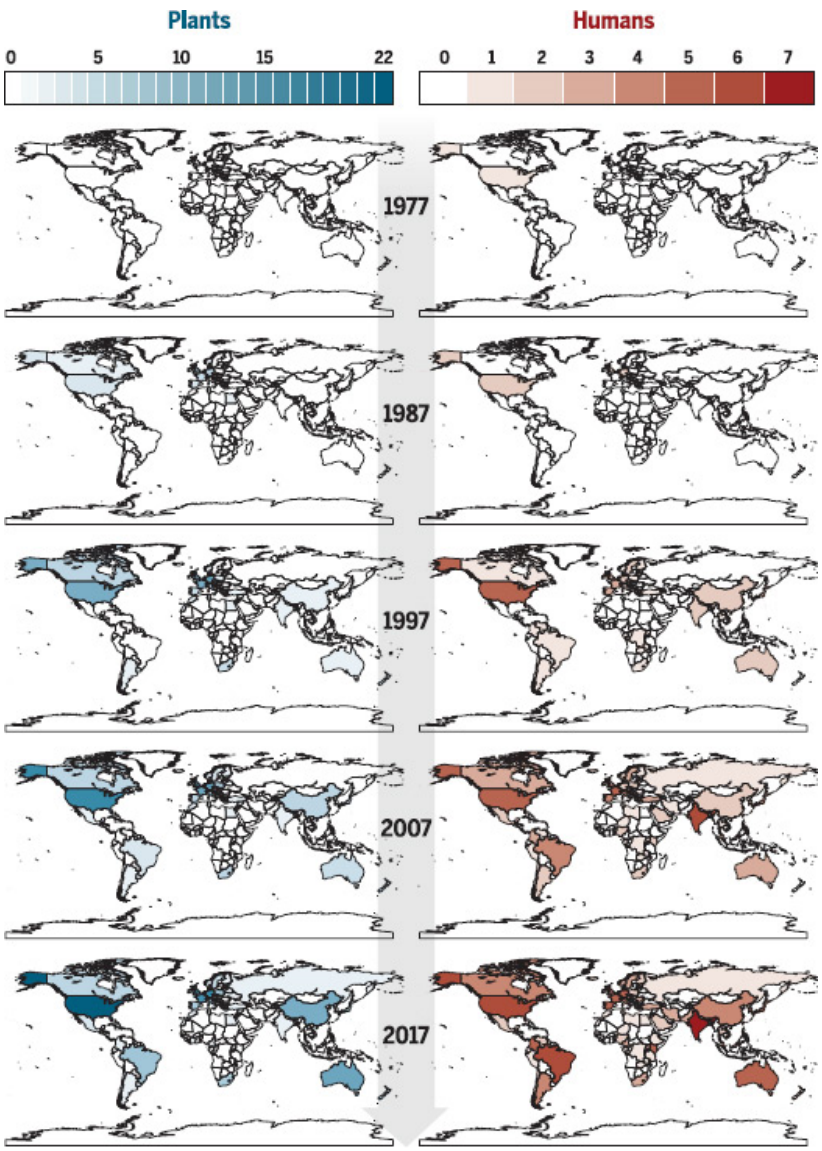
- Every product needs a clear value
  - This is true of everything, not just antimicrobials
- But, making good on this can be subtle
  - How do you prove its advantages in the clinic?
  - Harder than you'd think … and we'll come to that
- The best advantages are durable & visible
  - Novel mechanism: Not *required*, but a great start
  - Oral: So few things do this!
  - Spectrum and low frequency of (mutation to) resistance
  - Drug-like properties: Plays well with other drugs and with key body systems

Unmet Need in Mycology: Abundant!

- Novel mechanisms: *We have so few on the market*
  - Amphotericins, azoles, candins, terbinafine, 5-FC
  - Exciting: Several novel mechanisms are in the clinic now
- Oral: *As yet, only the azoles, terbinafine, and 5-FC*
- Spectrum: *Resistance is seemingly everywhere!*
  - *Candida*, esp. *C. auris*: Azoles & candins
  - *Aspergillus*: Azoles & amphotericins (the cryptic species have turned out to be very interesting)
- And then there are the places where current agents struggle in one way or another
  - E.g., we still can't always cure coccidioidomycosis!
- I could go on, but a picture tells a thousand words…

Fisher, 2018[1]

- Shown at right is the rate of antifungal resistance over time for plant and human products.
- Darker = more resistance
- Resistance advances!



1. Fisher et al., Science 360:739–742, 2018

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Many Disciplines in Drug R&D

- Biology, MedChem, Tox, CMC, ADME, PK-PD, Regulatory, Clinical Operations … a long list
  - It takes a substantial team to create a new drug!
- Being selective, I'm going to look at Discovery Biology (briefly) and then at Tox, CMC, PK-PD, and Regulatory in more detail

Biology: The role of Academia

Drakeman 2014[1]: Origins of priority review NMEs, 1998-2012

Sector	NBEs	NCEs	Fast track
Biotech	24 (92%)	65 (48%)	49 (70%)
Pharma	2 (8%)	71 (52%)	21 (30%
Totals	26	136	70

In short, small companies (often launched from academic insights) really power the pharmaceutical industry.

But, the move from Biology to Pharmaceuticals is a big leap!

[1]Drakeman DL. Benchmarking biotech and pharmaceutical product development. Nat Biotechnol. 2014;32(7):621-5.
NME = New Molecular Entity; NBE = New Biological Entity; NCE = New Chemical Entity

Toxicology: Key idea #1

- You need to study supratherapeutic exposures of new agent *and its metabolites* in 2 animal species
- Serious fungal infections often require prolonged therapy: your studies must run for long periods
  - 0-90 days of exposure: day-for-day coverage in man
  - 180 days: (generally) enough for indefinite exposure
- Metabolites can be tricky. You can try to predict human metabolites but you don't *know* until Ph1
  - Sometimes you have to do additional studies
  - Forewarned is forearmed. Be sure your investors know!

Toxicology: Key idea #2

- Don't panic! *Everything* has toxicity
- Your job is to triangulate three things
  - Exposure that you think required (PK-PD! See next)
  - The nature of the toxicity (monitorable? reversible?)
  - The Unmet Need you are addressing
- This is your first look at benefit-risk (B-R)!
  - B-R needs be B >>>>>> R for vaginal candidiasis
  - B-R can be B ≥ R for (say) curative therapy of CNS cocci
- Advice: Have a PK-PD expert & a medic on your toxicology team
  - CARB-X + GARDP workshops this year on toxicology
  - Watch my newsletter for access to same

CMC: Chemistry, Manufacturing, & Controls

- How does a molecule become a physical medicine (tablet, injectable, etc.) to give to a human?
- I knew *nothing* about this before joining Industry
- You must plan for
  - Early materials for preclinical studies
  - GMP (Good Manufacturing Practice) materials for human studies
  - Sufficient quantity at scale & on stability for Ph3 and registration
- This is a science unto itself
  - In parallel with the IND/MAA (you've heard of those), you also file an IMPD (Investigational Medicinal Product Dossier) of equal length
- Advice: Start early! Have a CMC guru on your team
  - Great CARB-Xed + GARDP workshop from 2017 on this:
  - Search for "amr.solutions 2017 bootcamp"

PK-PD: Overview

- PK-PD (pharmacokinetics-pharmacodynamics) is now a key element of antibacterial programs
  - Strong PK-PD is the reason a smaller trial program is acceptable proof of drug utility
- Antifungal PK-PD has lagged a bit
  - Fewer agents; Effect measures (esp. moulds) harder to validate
- But, significant progress has been made[1]
  - MIC methods standardized & at least as good as antibiotics
  - *Candida*: PD targets now known for azoles & candins
  - *Aspergillus*: Galactomannan and quantitative PCR as endpoints
  - Other tools: Beta-D-glucan, for example
- For a novel product, the hard part is defining a PD target that has meaning

1. Hope W, Drusano GL, Rex JH. Pharmacodynamics for antifungal drug development: an approach for acceleration, risk minimization and demonstration of causality. JAC 71:3008-19, 2016.

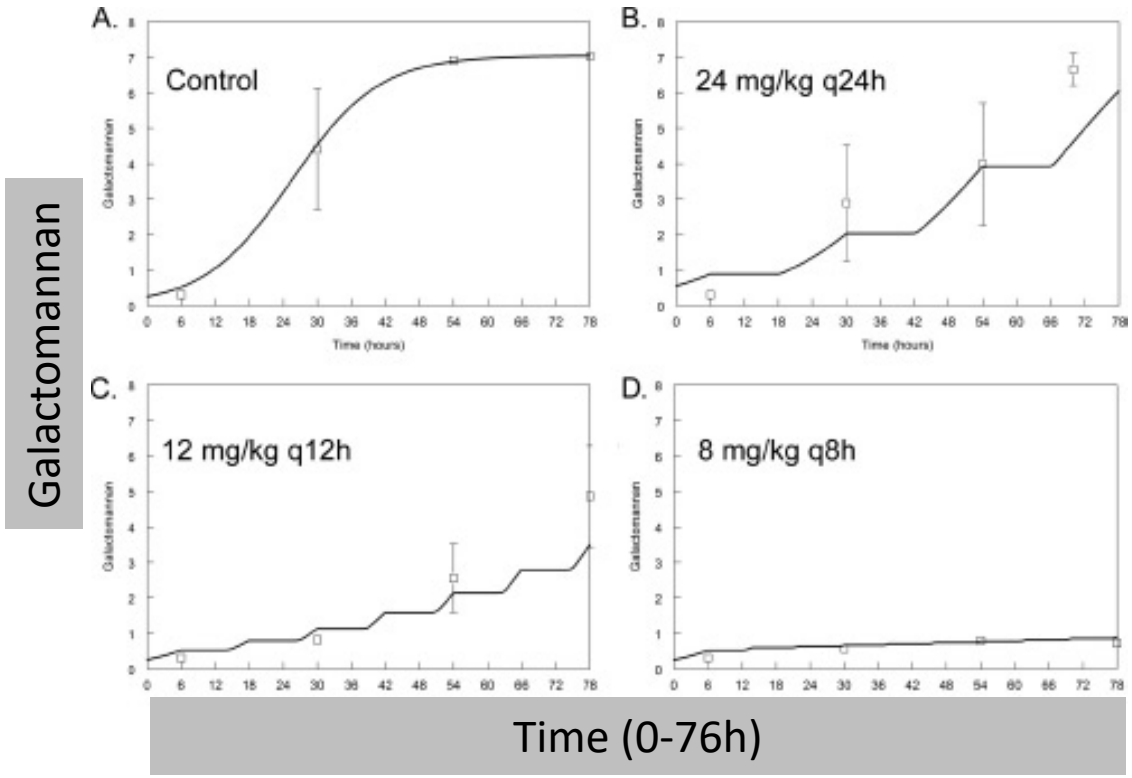
PK-PD: Defining a PD target

- Known class (e.g., new azole, new carbapenem)
  - You can lean on precedent
  - Compound class predicts PD parameter & approximate target value
- Novel class: This gets interesting!
  - It is typically true in animal model that you can push drug exposures to levels producing 100% effects on your endpoint of choice
  - Those exposure may not be needed in man
  - Those exposure may even be unattainable in man
- So, how much PK-PD is enough?
  - W. Hope (ECCMID 2018): It's enough when "I would be prepared to be the first person to administer a new compound to a *patient*"
  - There's a fair bit written on this, but one idea that has helped me a lot has been the emerging idea of cross-class benchmarking…

PK-PD of new anti-mould agent[1]

Activity includes Aspergillus *spp.*

- What is the PD parameter?
  - How do we analyze?
- Answer:
  - Dose-fractionation in neutropenic mouse model of pulmonary aspergillosis
  - Galactomannan response (y-axis) vs. time (x-axis)



- **Results:** Control in Panel A. Same total dose in Panels B-D
  - **PD parameter:** Must be time > threshold
  - **Summary effect metric:** Area-Under-the-GM-Curve

1. Hope WW, McEntee L, Livermore J, Whalley S, Johnson A, Farrington N, et al. Pharmacodynamics of the orotomides against *Aspergillus fumigatus*: New Opportunities for Treatment of Multidrug-Resistant Fungal Disease. MBio. 2017;8(4):1-17.

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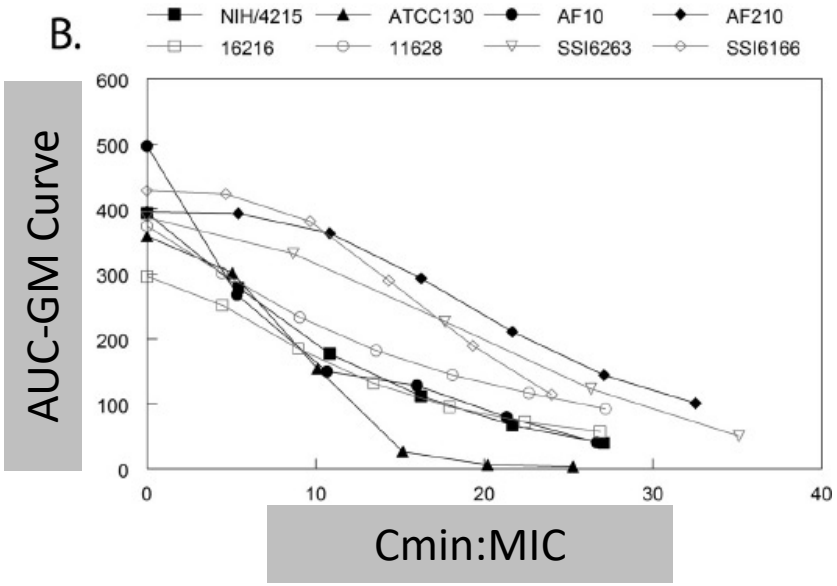

Novel agent

- Above, see AUC-GM-Curve vs. Cmin:MIC for 8 isolates
  - 4 (each) azole-S and –R strains
- How much is enough?
  - Animal model ≠ human illness
  - Arbitrary intensity & response

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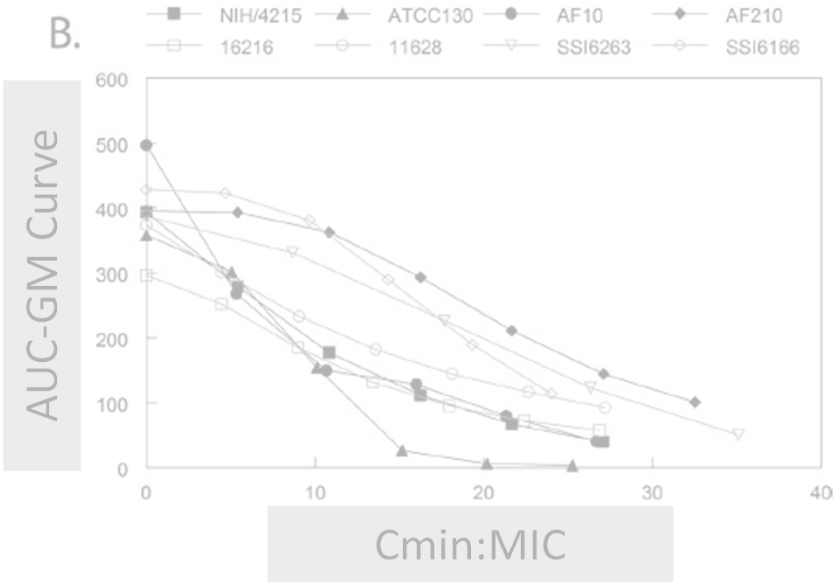

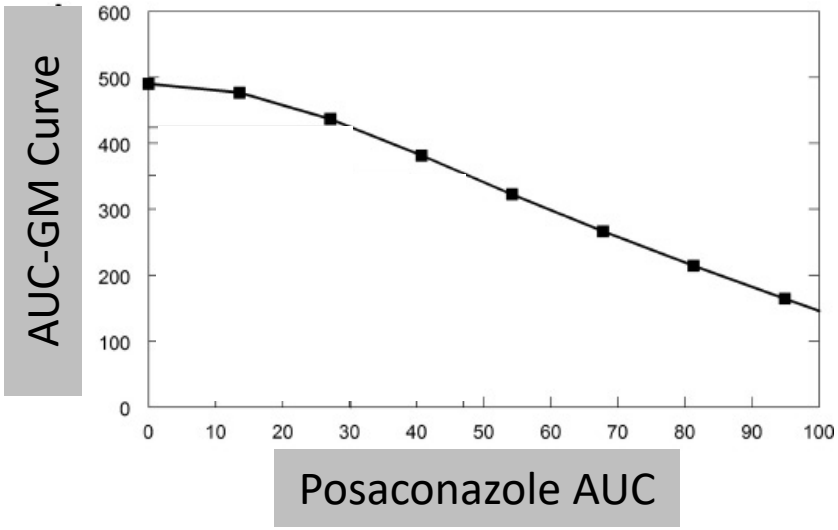

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Posaconzole as a benchmark

- Posa's AUC vs. AUC-GM
- Same animal strain
- Same lab
- Same infection model

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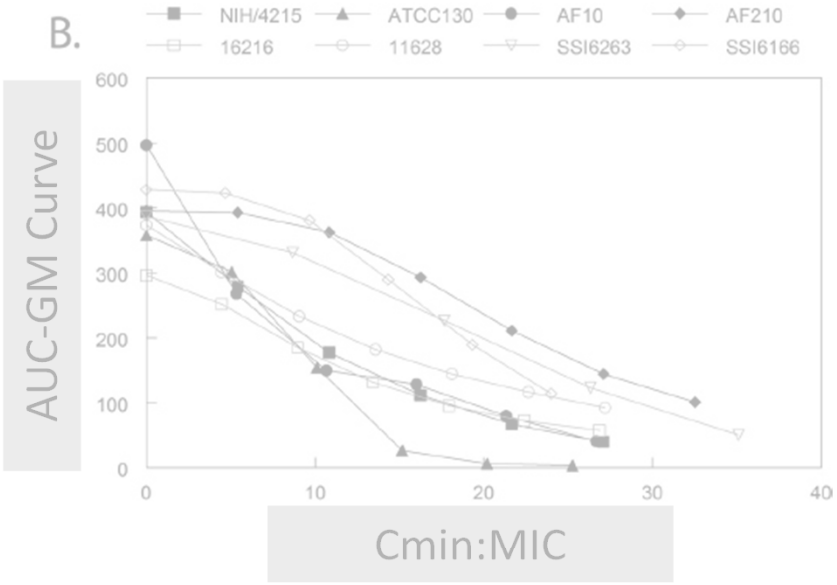

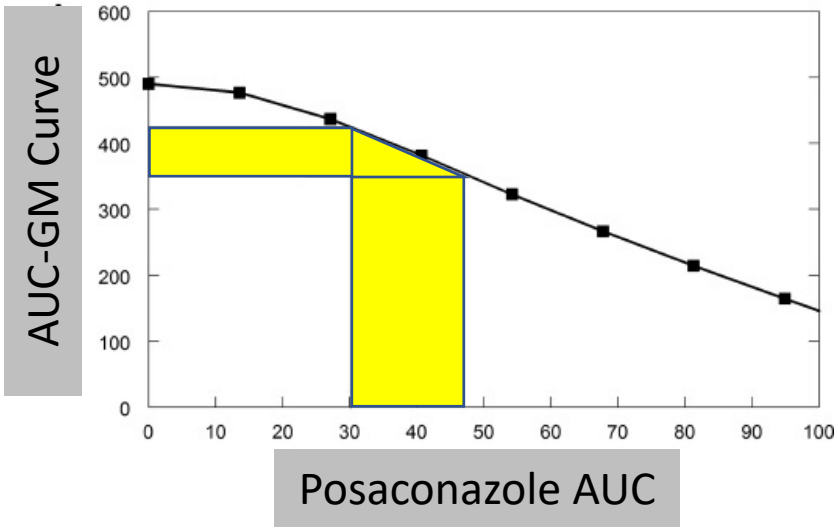

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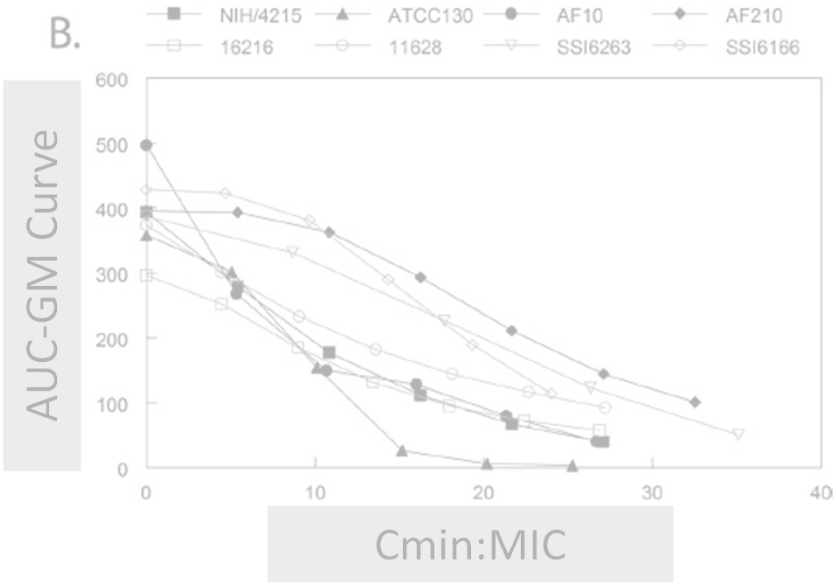

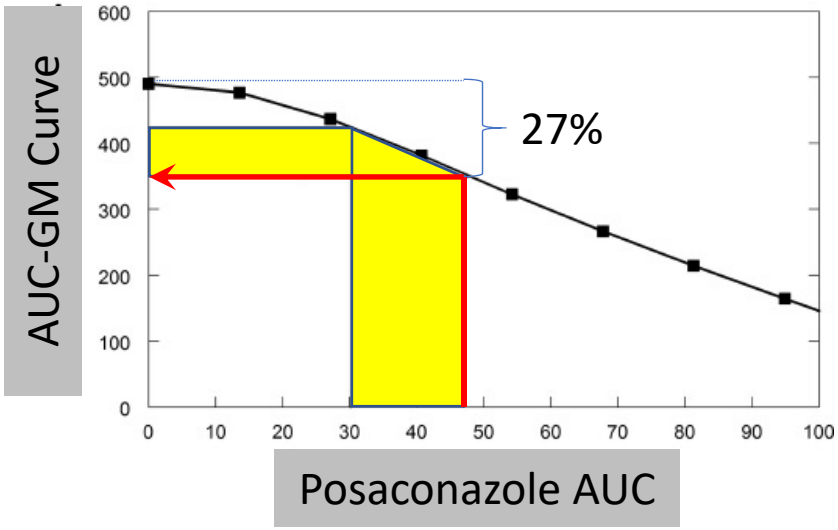

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- Human data show strong response at AUC_{24} of 30-47 mg·h/L (Walsh CID 2007, 44;2-12)
- At 95% **upper bound** on human exposures, 27% drop in GM AUC

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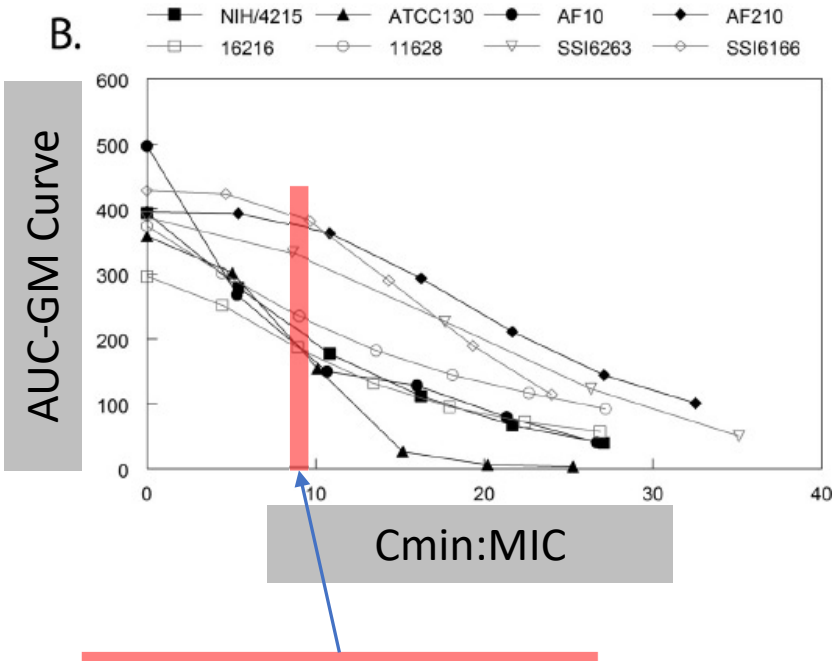

Now, work backwards for NEW

- 27% drop is at Cmin:MIC ~9
- This, in turn, yields an efficacy target of Cmin of 0.1-0.3 mg/L
- Exposures *in* this range should equal the effect of the maximal posaconazole exposure

Similar results with…

- Rabbit model
- Survival as an endpoint
- Histopathology as an endpoint
- For more detail: Hope 2017[1]

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  - Preview: A fungal case-study
  - Lessons from antibacterial development
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Applications in Mycology

- Isavuconazole's registration program
  - 1x NI RCT*: ISA vs. voriconazole in (azole-susceptible) Invasive Aspergillosis (IA)
  - 1x salvage: Open-label study for mucormycosis
    - Control groups drawn from literature and Fungiscope

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- Why this pair of studies?
- What is the relevance of a study in azole-susceptible infections?
- Why not just study difficult infections?

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Brief sidebar

Trial Design 101: Two study designs – *everything* reduces to one of these

- Superiority studies
  - X vs. Y, with an aim to show X beats Y
  - TEST vs. placebo or TEST vs. Standard of Care
  - Preferred design – result is unambiguous
  - Everybody likes the idea of Better
- Non-inferiority (NI) studies
  - X vs. Y, with an aim to show X ≈ Y
  - Messy, harder to do accurately, confusing
- But, we (almost) always use NI for new antibiotics
  - **Why?**

Key Ideas: 1 of 3

The paradox of antibiotics

- We want new drugs for bad bugs
  - The superiority of NEW is easily shown in the lab on the basis of MIC testing or in animal models of infection
- But, asking for clinical data leads to a problem
  - Trials must (usually) be designed to avoid superiority
  - Instead, we must use non-inferiority designs showing similar activity relative to another active agent
- Example: Limb-threatening infection due to MRSA*
  - It is not ethical to randomize to methicillin vs. NEW
  - Must instead do something like vancomycin vs. NEW
  - Must NOT enroll if resistant to NewDrug or comparator

*MRSA = Methicillin-resistant *Staphylococcus aureus*

This idea is very, very hard

- Non-life-threatening illness (e.g., migraine)
  - Delayed effective therapy is not dangerous
- Cancer: Placebo is (usually) not possible, but there is always room to improve on 5- or 10-year survival
- **Infections: We routinely produce Cure of potentially fatal illness**
  - And, it's hard to improve on Cured
- But, the idea of non-inferiority is confusing
  - "We want a *better* drug."
  - I get it, but insisting on clinical superiority before approving new agents means progress only when/if the pipeline (again) becomes inadequate
- Next 2 slides: Let's discuss in two other ways

In Infection, superiority means something bad has happened: Plazomicin and CRE[1]

- In 2012-13, colistin was the only alternative for CRE. A study of plazomicin vs. colistin-based SOC[2] for CRE was plausible
- Plazomicin wins, but efforts to control CRE made it very hard to find cases & enroll (note small N). Cost was $1m/case!
- And, 40% mortality is not good!
- Future studies will need to use plazomicin (or one of the other new agents with comparable data) as the comparator

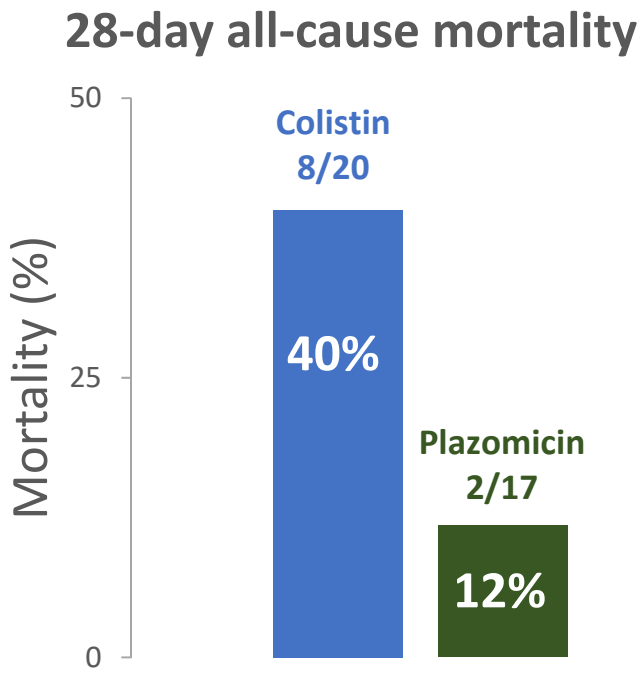

Figure adapted from slide 24 the Jan 2017 Achaogen corporate presentation. Downloaded 24 Feb 2017 from http://files.shareholder.com/downloads/AMDA-2JY46Z/3956962155x0x922829/80C50E00-4B27-4F84-B13F-55DE31AABA28/AKAO-Corporate-Deck-January-2017.pdf

1. CRE = Carbapenem-resistant Enterobacteriaceae
2. SOC = Standard of Care

But, superiority trials are used in other areas! Tell me again: *Why not in Infection?*

	Migraine	Cancer	Infection
1. Durable cure is routine	No	No	*Yes*
2. Placebo is routinely acceptable	Yes	*No*	*No*
3. Transmissible resistance arises → new agents always needed	No	No	*Yes*
4. New agents are really for use…	Today	Today	*Tomorrow*[1]

Points 1 & 2: Superiority is routinely used in some areas not but others

- *Migraine (non-life-threatening example):* Placebo with rescue is possible
- *Cancer:* Durable cure is not routine and continual improvement (e.g., improve 5- or 10-year survival) is hence possible. Also, resistance is not transmissible.
- *Human Infection:* Placebo not usually acceptable & it's hard to improve on Cured!

Points 3 & 4: We need to develop new anti-infectives despite this limitation

- There are negative Public Health issues if superiority is (or becomes) possible!

1. This points to part of the reason why new antibiotics suffer from several forms of market failure. For more on this, see the DRIVE-AB report, various blogs on John's website, and any of Kevin's various publication (the 11 Apr 2018 op-ed in *STAT News* is a very good place to start: https://www.statnews.com/2018/04/11/innovation-new-antibiotics-fight-superbugs/).
2. For reference, the corresponding answers in Animal Health are Yes, Yes, Maybe & Today. See this cite for more on Animal Health issues: Page SW, Gautier P. Use of antimicrobial agents in livestock. Rev Sci Tech 31:145-88, 2012.

Solution: The (emerging) 2-study path for new traditional antibiotics

- 1x NI RCT* vs. a good comparator
  - UDR (Usual Drug Resistance) setting: **both agents are predicted to be active**
  - Done in one of the major indications (cUTI, cIAI, etc.)
- 1x salvage study for highly Resistant pathogens
  - Randomized vs. Best-Alternative Therapy (BAT) if possible, Open-label if N too small for this
- Example: Plazomicin initial registration program
  - NI RCT: 1x complicated UTI NI RCT vs. meropenem
  - Salvage: 1x study in CRE vs. colistin (prior slide)

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Key Ideas: 2 of 3

About narrow-spectrum agents…

- This is the concept of "Tier C" pathways[1]
  - Rare pathogens, (only) MDR pathogens, rare diseases
  - Small trial programs, just barely (or not) powered
- Can this be done? Yes, but it's not an easy out
  - Do not think of this as simpler, faster, or cheaper
  - It's not (just) a regulatory hurdle – the strength of evidence will become frustrating
- See recent IDSA whitepaper and FDA workshops
  - Boucher et al. "Developing Antimicrobial Drugs for Resistant Pathogens, Narrow-spectrum Indications, and Unmet Needs." J Infect Dis 216: 228-36, 2017
  - My blog notes: 13 Apr 2017 + 5 May 2017 workshops

[1]Rex JH, Eisenstein BI, Alder J, Goldberger M, Meyer R, Dane A, et al. A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. Lancet Infect Dis. 2013;13(3):269-75.

Key Ideas: 3 of 3

Agents that Augment

- Example: Virulence inhibitor or such
  - Not sufficient alone: Must also give an active agent (e.g., toxin inhibitor + active 2nd agent)
- Distinctive hurdles
  - **Base therapy needs to work**
    - Might protect a base therapy from emergence of resistance but doesn't solve existing resistance problems
  - Dose: Lack of an MIC → harder to apply PK-PD
    - If the PK-PD rationale has gaps, it may become harder to validate dose/exposure logic
  - Superiority problem: Must show NEW + OLD > OLD
  - May need a novel endpoint to show value

Superiority & Endpoints

- Ultimately, must study NEW + SOC vs. SOC
  - We will want to see that NEW + SOC **is superior to** SOC
  - And this superiority must be grounded in how the patient feels, functions, or survives
- Are there settings where this might be possible?
  - Endocarditis is a good candidate: more rapid bloodstream clearance might have a measurable clinical effect
  - Chronic infections (many fungal infections!) may also offer scope for showing improvement
- **Endpoints:** Would different endpoints help?
  - How would you show a clinical benefit for reduced rate of onset of resistance? Can you show this at a community level?
  - A challenging question! Whatever is proposed must be compelling.
- Finally, know that this is not a regulatory problem per se
  - The agencies are simply the first to point out the issue
  - Why should I use this? Why should I pay for this?

Applications in Mycology

- Isavuconazole's registration program
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Applications in Mycology

- Isavuconazole's registration program
  - 1x NI RCT: ISA vs. voriconazole in (azole-susceptible) Invasive Aspergillosis (IA): UDR* setting. N = 123 vs. 108
  - 1x salvage: Open-label for mucor: N = 37
    - Control groups drawn from literature and Fungiscope
  - For both, similar efficacy to control

- Why this pair of studies?
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*UDR = Usual Drug Resistance

Applications in Mycology

- Isavuconazole's registration program used this idea
  - 1x NI RCT*: ISA vs. voriconazole in (azole-susceptible) Invasive Aspergillosis (IA): UDR setting. N = 123 vs. 108
  - 1x salvage: Open-label for mucor: N = 37
    - Control groups drawn from literature and Fungiscope
  - For both, similar efficacy to control
- Future agents will likewise apply these tools
  - ISA: Advantages are real but hard to show clinically
  - There may a little more scope for showing superiority with antifungals, but it is generally a tough road
  - Requiring **clinical** data on superiority for every future drug creates a Catch-22 that must be avoided

*NI RCT: Non-Inferiority design Randomized Controlled Trial. See extended discussion of these trials in Rex JH et al.: Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. Clinical Infectious Diseases 65: 141-146, 2017.

Agenda

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Current economic model is broken

- Current approach to antibiotics
  - Everyone is delighted to have a new antibiotic
  - But, use is delayed and deferred in effort to preserve new antibiotic
- Stewardship perspective: Entirely rational
- Economic perspective: A financial loss
  - Many analyses show same thing
  - It is not financially rational to do antibiotic R&D
- Problem: Current pay-per-use model reimburses for only a piece of the value

Pop Quiz #1: Have you used a fire extinguisher today?

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Actually, we can get more concrete. Are you using a fire extinguisher <u>right now?</u>

Antibiotic benefits go beyond simple use

But, we don't (yet) have an agreed way to capture that value

Antibiotics are the fire extinguishers of medicine!

- **Enabling value:** Many surgical and medical procedures rely on prophylaxis with effective antibiotics.
- **Option or insurance value:** We may want to have an antibiotic in reserve before we really need it, so it's ready if resistance arises or worsens.
- **Diversity value:** Having multiple antibiotics may reduce selection pressure and delay resistance.

The Fix: New Incentive Models

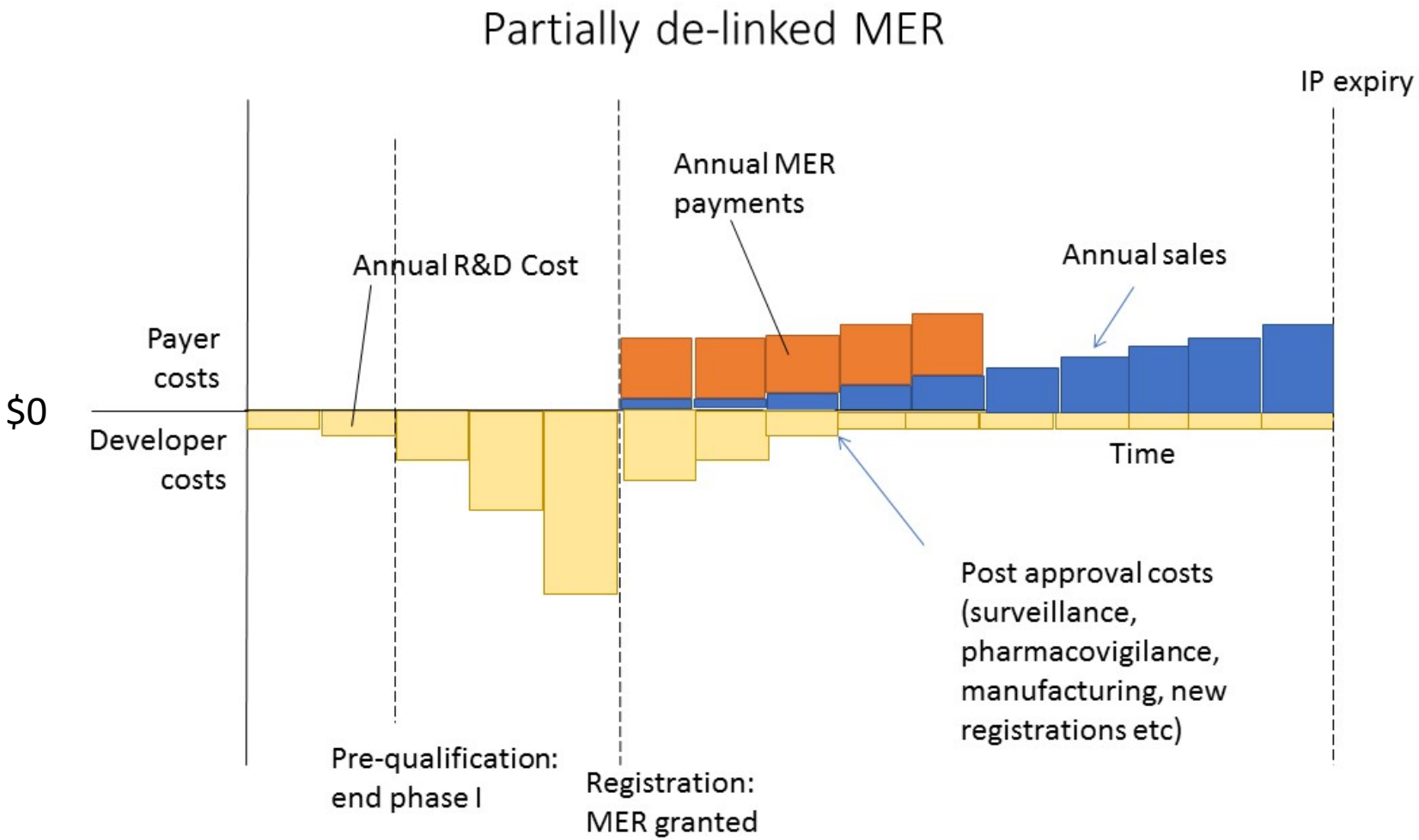
- Three major reports[1]
  - DRIVE-AB, UK AMR Review, Duke-Margolis paper
  - Links below or, search “john rex amr blog davos”
- Recommendation: Two types of incentives
  - Push: More grants and coordination of grants
    - We’re doing this: CARB-X, Novo’s REPAIR, NIAID, etc.
  - Pull: Market entry rewards & Long-term continuity
- The two *Pull* ideas require a bit of explanation

[1]http://drive-ab.eu/; https://amr-review.org/; https://healthpolicy.duke.edu/PAVE

Pull #1: Market Entry Reward (MER)

- How do we separate usage from payment?
- Essence of the solution
  - A defined sum of money (a MER) is given on registration of an interesting new antibiotic
  - The MER is independent of volume of use
- The company still sells the drug
  - But, the company does not actively market
  - There may be other stewardship / access requirements
  - Fundamentally, the MER is intended to provide (most of) the financial reward
- A picture is helpful…

MER, illustrated. This is one pattern



Ardal, C., J. A. Rottingen, A. Opalska, A. J. Van Hengel and J. Larsen (2017). "Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance." Clin Infect Dis 65(8): 1378-1382.

Pull #2: Long-term continuity model

The problem of off-patent & forgotten antibiotics

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia ☆

Céline Pulcini [a,*], Simone Mohrs [b], Bojana Beovic [c], Inge Gyssens [d,e], Ursula Theuretzbacher [f], Otto Cars [b] on behalf of the ESCMID Study Group for Antibiotic Policies (ESGAP), ReAct Working Group on Old Antibiotics [1]

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ABSTRACT

The objective of this study was to update a 2011 survey, conducted on behalf of the ESCMID Study Group for Antibiotic Policies (ESGAP), studying the availability of old but clinically useful antibiotics in North America, Europe and Australia. This follow-up survey was performed in 2015 in 40 countries among specialists from the pharmaceutical, infectious diseases and microbiology sectors in North America, Europe and Australia in order to assess the availability through usual marketing processes of 36 systemic antibiotics (addition of 3 antibiotics compared with the 2011 survey) selected for their ability to treat infections caused by resistant bacteria and their unique value for specific criteria. The questionnaire was sent by e-mail to national contacts belonging to ESGAP and ReAct networks. In all, 39 of the 40 countries participated in this survey. The number of available antibiotics differed considerably from one drug to another as well as from one country to another (e.g. 7 antibiotics available in Estonia, 24 in France). Overall, 25/36 selected antibiotics were marketed in 20/39 countries or less. From 2011 to 2015 (data available for both periods in 37 countries for 33 antibiotics), the number of available selected antibiotics increased in 13 countries and decreased in 17. In conclusion, despite the ongoing bacterial resistance crisis, the situation regarding the availability of 'forgotten antibiotics' has worsened since 2011. Urgent measures are needed to ensure better availability of these antibiotics on a global scale as a conservation measure to ensure sustainable and responsible use of antibiotics.

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Why is this? Pop quiz #2

- What does it cost per year to maintain the plant that makes a sterile injectable so that you can make at least 1 vial per year?
- Please consider
  - Cost for the building
  - Cost for the staff
  - Cost for record-keeping
  - Etc.

Long-Term Continuity Model

- **Idea:** Use a long-term procurement process for antibiotics with fragile supply chains
  - Contract for 10-year supply of a drug
  - Good test cases would be “access” antibiotics on WHO’s Essential Medicine List (e.g., benzylpenicillin)
- **Beneficial side effect:** Testing a long-term supply continuity model can also test the aspects of implementation of a MER

Putting it together

- There are still many puzzles to be solved and we don't (yet) have a viable MER model
  - What is the value of a new antibiotic?[1]
  - Do all antibiotics have the same value?[2]
  - Who will pay? How will payment be delivered?
- I am hopeful (there are serious discussions in US and EU), but I am also realistic
  - I assume the future market will be a mixture of the current model (pay per fire) and a MER model
- What does this mean for you?

1. Sertkaya A et al. Analytical framework for examining the value of antibacterial products. Report to US DHHS. United States Department of Health and Human Services. 2014;Downloaded 17 June 2014 from http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm.
2. Rex JH, Outterson K. Antibiotic Reimbursement in a Sales-Delinked Model: Context and a Benchmark-Based Global Approach. The Lancet Infectious Disease. 2016;16:500-5.

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Implication: Novelty above all

- Fire extinguishers come in different categories
  - You only need one of each!
- Incremental extensions
  - Some of this is OK
  - But, it will only go so far
- Easily articulated scientific value is the best path to economic value
  - Novel mechanisms
  - Novel molecular basis of resistance
  - Addressing strong Unmet Need

- **And, this is true both in the current market model and any MER-based future model. Not all products will earn a MER!**

Implications for Medical Mycology

- The focus in the prior work (DRIVE-AB, etc.) has been 99% on antibacterial compounds
  - The only fungus-focused elements are in the US
  - The GAIN Act[1], QIDP[2], and LPAD[2] all recognize the Unmet Need for fungi
  - Current discussions in the US on other incentives also include (by extension) the fungi
- We need to keep building awareness of the fungi
  - Developed countries in Europe and Asia (and societies within them!) need to develop incentives
  - Involvement with lobbying groups is way to contribute

1. GAIN: Generating Antibiotic Incentives Now, the 2012 legislation in the US that created the QIDP designation
2. QIDP: Qualified Infectious Diseases Product, a designation that gives a product additional exclusivity as well Fast Track and Priority Review status
3. LPAD: Limited Population Pathway for Antibacterial and Antifungal Drugs, the Act in which Congress emphasized the need to products that (a) treat a serious/life-threatening bacterial or fungal infection, (b) target a clinically relevant and limited population, and (c) address an unmet need.

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Summary perspective & advice

- Start early and ensure expertise in key areas
  - CMC, PK-PD, Tox, and regulatory
- Study the antibacterial literature
  - Attend (or at least listen to) as many FDA Advisory Committees as possible
  - The isavuconazole AdComm is a good place to start
  - Attend the major meetings, especially the ASM-ESCMID development meeting series (#3 is in Lisbon this year)
- Focus on strong approaches to Unmet Need
  - Don’t waste your time on minor improvements
- My newsletter is a good way to hear about events
  - http://amr.solutions

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Read, Listen, & Learn

- FDA guidances
  - The full collection: ucm064980.htm, with a focus on this group: cIAI: ucm321390.pdf; cUTI: ucm070981.pdf; Nosocomial pneumonia: UCM234907.pdf; Skin infection: UCM071185.pdf;
  - LPAD: UCM610498.pdf
- FDA Advisory Committees: Attend or listen by webcast to **every AdComm**. These are free master classes. I can't emphasize this one strongly enough.
- EMA guidances
  - Core antibacterial guidance: WC500003417.pdf
  - "The addendum": WC500153953.pdf
  - PK-PD: WC500210982.pdf
  - Pediatric antibacterials: WC500247102.pdf
- Papers
  - Rex, Talbot et al. Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. CID. 2017;65:141-6.
  - Boucher, Ambrose, et al. White Paper: Developing Antimicrobial Drugs for Resistant Pathogens, Narrow-spectrum Indications, and Unmet Needs. JID. 2017;216:228-36.
  - Hope, Drusano, & Rex. Pharmacodynamics for antifungal drug development: an approach for acceleration, risk minimization and demonstration of causality. JAC 2016;71(11):3008-19.
- 2017 GARDP + CARB-X Bootcamp on CMC: http://amr.solutions/blog/summary-slides-from-carb-x-gardp-bootcamps-5-8-sep-2017-asm-escmid-conference

Thanks for listening!

Antifungal Drug R&D Comes of Age

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