MedImmune
A member of the AstraZeneca Group

What is Net Present Value and Why is it Killing My Research?

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DriveAB Septermber 2017

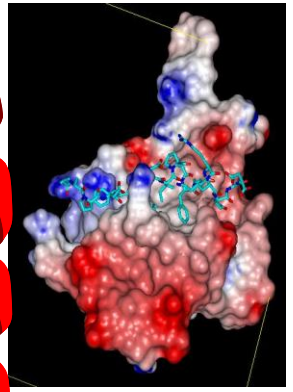
Sept 6, 2017

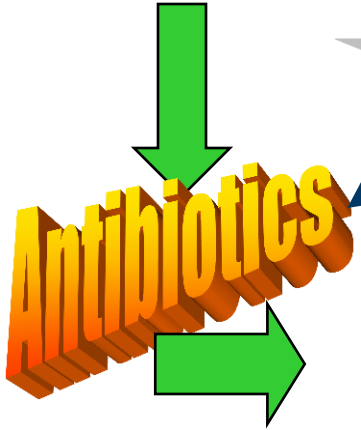
Welcome to the Movement!

- Pierre Meulien: "The Drive AB Movement" is now the time?
- Thanks to Stephan Harbarth for serving as the P.I. For Drive AB and the Judy Hackett for making me do this.
- Awareness is high (good!). But..."knowledge is quite low (very bad!!).“
- Sharon Brennan: "Twenty-three years of Pseudomonas..." And that Pseudomonas was spelled with a Capital R."

Scientific Issues in Antibacterial Discovery

1850-presen





optimization

1990s

Why has target based drug discovery failed?

THE FOUR QUESTIONS?

- Are our scientists in this field incompetent?
- Have these projects been under-resourced?
- Are there important differences between antibacterial targets and other targets?
- Are these failures only “apparent” and not real?

- And What do these questions have to do with Orville and Wilbur Wright?

Do we really need new antibacterial drugs?

"The time has come to close the book on infectious diseases. We have basically wiped out infection in the United States."
-attrib. **William Stewart, U.S. Surgeon General, 1967**

"Emerging infectious diseases are a continuing threat to the health of U.S. citizens and of people around the world. They cause suffering and death and impose an enormous financial burden on society."
- **David Satcher, U.S. Surgeon General, 2000**

The reality is that infectious diseases are the second leading cause of death worldwide and the third leading cause of death in developed countries (and are actually gaining on cardiovascular disease and cancer in the US and elsewhere)

And then there is the problem of AMR!

Problems with AMR

Ed Whiting: "A big and wicked problem." But let us be careful to not preach about the pending apocalypse. Fernando Baquero cautioned us at meeting in early 2016 in Stockholm not to use phrases like "entering a post antibiotic era". We heard this morning that only a small proportion of bacterial strains are highly multidrug resistant with adverse clinical outcomes. But it is a small fraction of a very large number. Yehuda Carmeli: Resistance rates in *E. coli* and *K. pneumoniae* - constant in (some) developed countries; there has been or will be "stabilization" but the curves are affected by infection control procedures (France vs. Italy). Ignatz Semmelweis and Didier Pittet were/are right! But what were the fates of Semmelweis and Alexander Fleming?

Signs of Progress?

- "Stewardship has improved." Indeed hospital MRSA levels have dropped in the U.S. And in some other geographies. In fact we are using fewer doses of antibiotics and less antibiotics in meat animals as growth promoters. (Although quantification is “imperfect.”)

The antibacterial market

- The global market for antibacterial agents has remained relatively flat in the recent past
  - But at $24-26 billion isn't it still attractive?
  - Do we believe the market will reach $32B in 2010? (it didn't)?
- Save for resistance there are many safe and effective antibiotics
  - I.e. the bar for new agents is high
- New agents launched that have targeted resistance have not done well commercially
  - Synercid & Linezolid*
- There is increasing pressure to use less antibiotics and cheaper ones as well

The Economics Does Not Work

- Kevin Outterson: "Economics vs. Evolution." And according to Thomas Carlyle (Victorian historian): "Economics is the dismal science." Decision making in Big Pharma is flawed: bad data (bad assumptions) are worse than no data.
- Ramanan Laxminarayan: :The "diversity value" of novel antibiotics, "antibiotics are fundamentally different."

What is “Net Present Value”

and why is it killing my research?

- What is NPV?
  - The value of future cash flow after discounting to today’s money $NPV=x(1+k)^n$
  - rNPV = risk-adjusted (the later stage the project the lower the risk (e.g. Phase III antibacterials have an 87% “success rate”)
    - **Basically it is what a (future) product is worth in today’s money**
- Used as a tool to rate projects across therapeutic research areas

Portfolio Optimization

•Project Therapeutic Class	•Risk Adj. NPV*
•MusculoSkeletal	•1,150
•Neuroscience	•720
•Oncology	•300
•Vaccines	•160
•Injectable Antibiotic (Gm+)	•100
•MS- Psoriasis	•60
•Liver Transplant	•20
•Oral Contraceptive	•10

*In millions of dollars

The Effects of Public Policy

- “The Infamous 10% Delta Issue”
- FDA’s 1992 Points to Consider document for determining delta for the lower margin for non-inferiority is adequate, especially when 2 Phase 3 trials are done for a specific indication.

Cure Rate	Delta
90+%	10%
80 - 89 %	15%
< 80 %	20%

- No evidence that new agents approved to treat serious infections, especially those involving resistant pathogens, are less effective than previously approved products.
- Moreover, the medical community will quickly recognize a new agent that might be less effective.
- A 10 percentage point lower margin is a substantial disincentive due to much larger sample sizes resulting in increased development time and costs.
- WHAT IS EFFICACY CREEP?

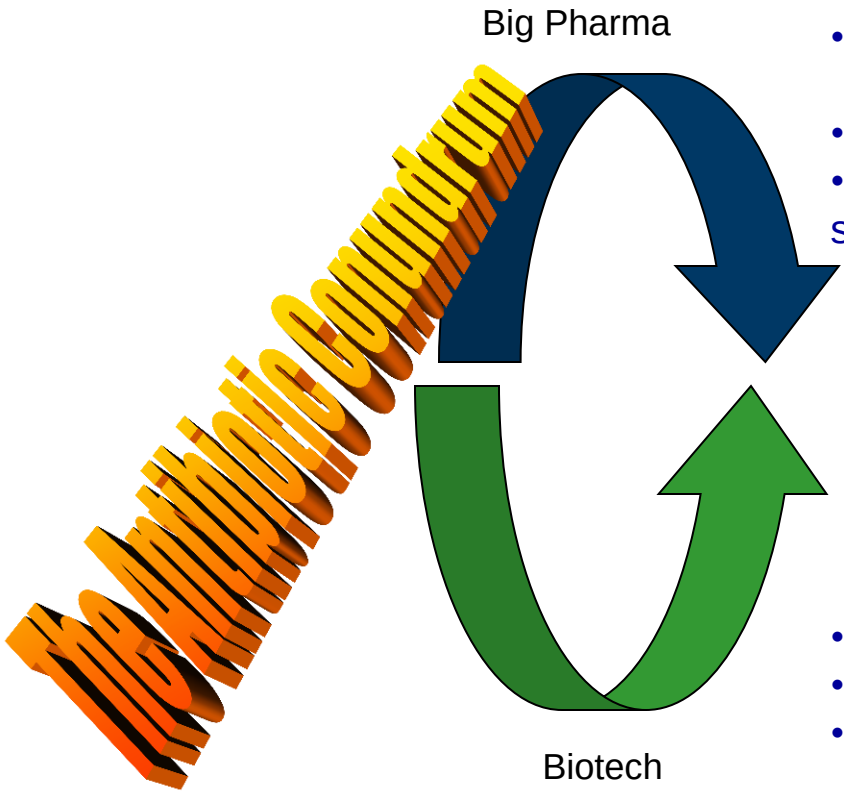
Consequences of a 10% delta

- Increased cost and time will lead to fewer new agents being developed, overuse of existing agents, and a higher consumer price for new products.
- Increased Time to Conduct Clinical Trials
  - Increases time to drug availability
- Increased Number of Investigators
  - Increasing use of ex-US investigators

rNPVs with a 10% delta

• Project Therapeutic Class	• Risk Adj. NPV • (post 10% delta)
• MusculoSkeletal	• 1150
• Neuroscience	• 720
• Oncology	• 300
• Vaccines	• 160
• MS-Psoriasis	• 60
• Injectable Antibiotic (Gm+)	• 35
• Liver Transplant	• 20
• Oral Contraceptive	• 10

Will Biotech pick up the slack?



- Return on investment insufficient
  - Costs of Ph. III
- Prioritization (remember the NPV)
- Lack of Pipeline compounds of sufficient scale
  - Promise of genomics "unfulfilled"

- Costs of Ph. III are the same
- Lack of large Pharma partners
- Risks of "going it alone"
  - Bad data = death

Disclaimer

- The US FDA has an impossible job
  - They must counterbalance the demands to the public and the policy makers with the commercial and technical realities of drug discovery and deveopment
- The Public
  - Increasing demands that NMEs (new medical entities) be highly effective, absolutely safe, cheap (free is more like it), and instantly available
- The Industry
  - Cost containment (mainly in smaller clinical trials)
  - Faster review (and decision) times
- The use of Advisory Panels complicates the process
  - Expertise can be an issue (not always the right people for the job)
  - Focus on “safety uber alles” has led to demands for more and more clinical data

So what's up with Ketek?

- Telithromycin - a new form of macroclide, a "ketolide," with excellent activity vs. macrolide and pen. resistant *S. pneumoniae*
- Aventis runs the largest safety trial in history (24,000 patients) finding Ketek comparable in safety to Augmentin (amox/clav)
- Currently marketed in Europe with over 1.5+ million patients treated with no major AEs
  - Issues?: elevated liver enzymes & some blurred vision; clinical efficacy vs. resistant strains
  - Is it safe? (Moellering & Shlaes analysis)
- Despite (maybe because of) this wealth of clinical data the US FDA requested "further analysis"
- Maybe we should call it "TELOthromycin"

The Consequences

- The antibiotic pipeline may be rather dry other the next decade
- What will we have for VRSA, CO-MRSA, MDR-*Klebsiella, Pseudomonas, Acinetobacter*?
  - **Not much!**
- Who is going discover and develop these products?
- Big Pharma will make its money elsewhere
  - **Mainly by developing drugs for chronic conditions and move further away from “life saving” medications**
  - **And how we are going to ensure that developing countries have access to drugs that they need but legitimately cannot afford?**

Can Changes in Public Policy Encourage Antibacterial Drug Discovery and Development?

What does not work for antibacterial research

- The Orphan drug program
- More and more and more resource-intense clinical trials (and long term post-marketing obligations)
- Killing the market
- Longer exclusivity for anti-infective drugs (note that the later years are heavily discounted in the NPV calculation) (unless it is “fungible”
- What about paying a “bounty”? Now called an M.E.R.

Changes in Public Policy

- How do we change the NPV Calculation?
  - Charge more money for anti-bacterial drugs
    - **How about some respect for Intellectual Property!!**
      - But the trend is in the opposite direction (apparently it is more important to stop the downloading of music on line then it is protect the public from bootleg or counterfeit drugs)
  - Make antibacterial drug discovery more efficient (can public policy actually help?)
  - Smaller clinical trials
    - **But the trend is in the opposite direction**
  - Easier/faster regulatory approval
    - **But the trend is in the opposite direction**

How about an enhanced R&D tax credit??

Funding, Funding, Funding

- We need better scientists who study microbiology, especially pathogens
  - Try and find a young scientist who knows anything about bacterial physiology
- We need to fund studies on anti-bacterial drug resistance
  - No, this does not mean more surveys or MIC accounting
- And we obviously need public funding on developing novel approaches to targets, assays and drug discovery

Where will our scientists come from?

- Man-Wah Tan "{Academic} funding has been abysmal." We have basically lost most of a generation of (potential) microbiologists. However the funding of academic research in the U.S. HAS improved. "I think there is hope."
- Laura Piddock: "How on earth do we get {academia to engage industry}." Rolf Muller: "Where do they come from if not academia?"

Improve the Regulatory Climate

- Trials allowing for multiple indications using a much smaller number of patients
  - Pool pathogens
- Surrogate endpoints (e.g. microbiological)
- A clear and feasible path to an indication for resistance (on the label!)
  - Now it’s just a tease
- A primary bacteremia indication?
  - **Yes but within reason**
- Promotion for quality of life indications
- Promotion for pharmacoeconomics

“It’s all about the trials.” Robert Arbeit, MD

- How about thinking outside the box?
- Do Phase III trials as part of a broader Clinical Trials Network
  - **The FDA has cited (and used as a guide) historic data in past cases**
  - **Agree before hand with regulatory authorities on the target efficacy rate, based on historic norms, for a specified minimum number of evaluable patients (e.g. 65% clinical cure rate in hospital acquired pneumonia in 500 patients)**
  - **Define an “acceptable” side effect profile**
- This is really win-win
  - **Significantly lower costs and reduce risks**
  - **We will actually end up with more patients tested on the study drug!**

Let’s talk incentives

Are there “economic” solutions

- Christine Årdal: "The Four Models" which looked more like an integrated framework which requires "Coordination." "Grants are fundamental." In my view especially in academia!! And then transitioning to SMEs? "Focus on priority pathogens." "Fill the gaps {in the pipeline}."
- Will Market Entry Rewards provide a sufficient incentive to keep (Large? Medium? Small?) companies engaged? Are there are (more politically palatable) incentives: E.g. Priority review vouchers (fungible) the first in 2009 for Coartem (Novartis)? R&D tax credits?
- But if the industry takes the money it has obligations (in terms of access and pricing) delinkage vs. linkage! Access and stewardship linked to funding. Dominque Monnet: "there should be rules for use of a new antibiotic."

Innovation – Science and Funding

- Speaking different languages...defining the terms. What is innovation? I can't really define it maybe It is like pornography: I know it when I see it. (From Potter Stewart)
- Where do we find innovation? SMEs, academia, big pharma? Rex and Outterson: "Pay for infrastructure" using the metaphor of paying for the firehouse and firemen. The metaphor I would use is the story of the Pied Piper of Hameln: It is now time to pay the piper. But the money may actually be there!! The ISS cost in excess of $150B (2010 dollars) and that is not counting maintenance costs!
- "The money needs to go into the SMEs.“

Coordination

- We must do better
- Focus: MDR gram negative bacteria and Ursula Theuretzbacher "the pipeline does not address the public health needs." Push mechanisms... discovery grants broaden the base and then prioritize...increase, coordinate, optimize (ICO) and do it globally. (Global Collaboration Hub on AMR R&D are we there yet?...G20; GARD-P funding! Hurray!
- Coordination...NIAID should also be at the table e.g. The ARLG (Antibiotic Resistance Leadership Group). Build the CTN! Incorporate Drive-Dx!

Thankyou for your attention

“If you don’t go to their funeral then they won’t go to yours.”

Lawrence Peter (Yogi) Berra

"Remember, hope is a good thing, maybe the best of things, and no good thing ever dies.“

Stephen King - The Shawshank Redemption.