SABPA 13th Annual Biomedical Forum

By SABPA-Orange County / Los Angeles Chapter

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For

Selected Presentations

The Roller Coaster of Antibacterial Drug Discovery and Development in an Era of Multidrug Resistance

Ian Critchley, Ph.D., Vice President, Clinical Microbiology, Allergan

History:

- Fleming's accidental Discovery of Penicillin
- Traditional antibiotic R&D, nearly all all discovered before 1970s
- The Golden Era – many in the pipelines in 70s, 80s, and 90s
- Fewer antibiotics approved in the 21st century (13 antibiotics since 2000)

Lots of drugs vs few targets:

- Most antibiotics directed against a few well known targets
- Inhibition of DNA replication, inhibition of protein, metabolite cell wall synthesis, injury to cell wall.

Resistance mechanism

- Enzymatic degradation of antibiotic
- Decreased uptake or accumulation of the drug
- Altered antimicrobial target

History of methicillin resistance staphylococcus aureus (MRSA): *mecA* gene and altered *PBP2a*
Reason for the MRSA

- Lethal targets for beta lactam antibiotics are penicillin binding proteins (PBPs)
- MRSA acquired a modified PBP encoded by mecA gene (PBP2a)

Response to the MRSA

- Approved agents with activity
- Vancomycin, Linezolid, Tedizolid, Daptomycin, Tigecycline, Telavancincin, Ceftaroline, Delafloxacin

Treating gram-negative pathogens: an unmet need

- Quinolones – last antibiotic new class to treat gram negative bacilli first discovered over 40 years ago
- "For gram positives, we need better drugs, for gram negatives, we need any drugs" John Bartlett, MD

Four major areas of need

- ESBL-producing enterobacteriaceae, serious, 26000 cases, 1700 deaths in US per year
- MDR P. Aerugino, 6000 cases, 400 deaths in US per year
- Carbapenem resistant, enterobacteriaceae, urgent 9300 cases 610 deaths in US per year
- Metallo beta lactamase producers, very rare

Cephalosporins and gram-negative coverage
Second and third generation cephalosporins, developed to extend coverage of gram negative pathogens including pseudomonas

- ESBL (extended spectru beta lactamase) and AmpC
- Increased use of carbapenems
- KPC (Killed 11 patients)

New beta lactam beta lactamase inhibitors

- Ceftazime-avibactam, Allergan Pfizer, approved
- Ceftolozane-tazobactam, Merck, approved
- Meropenme-vaborbactam, Melinta, approved
- Imipenem-relebactam, Merck, phase 3

Avibactam new inhibitor for class A and C beta lactamases
Expanded spectrum of activity against contemporary US CAZ-NS isolates

In the pipeline

- Eravacycline, Tetraphase, fluorocyclic tetracycline,
- Plazomycin, Achaogen, neoglycoside
- Cefiderocol, Shionogi, Cephalosporin

The Challenges of genomics based discovery

- Lack of chemical diversity among compounds
- Binding to or inhibiting cell free targets in screen did not always translate into activity
- Compound prone to mutational resistance

Antibacterial drug development

- Difficult to treat
- Low returns on investment
- Restricted use on formularies/antimicrobial stewardship
- AST device development
- Unpredictable and challenging regulatory pathways

What is being done about it

- FDA safety and innovation act
- Legislation reauthorize the PDUFA
- Incentives to spur antibacterial and antifungal R&D
- Provision modeled after the GAIN act

Gain act identifies high priority pathogens

- Qualified infections disease products (QIDP) benefits
- Advancement of critically needed antibody: priority review, fast track
- If approved, 5-year extension of hatch Waxman exclusivity

Labeling compliance – advertising & promotion of medical devices – Regulatory considerations

Raymond W. Brullo, PhD, DPM, Compliance officer, FDA office of regulatory affairs

Topics

- CDRH jurisdiction
- Background guidance
- Surveillance and enforcement
- Labeling – promotional violation examples

CDRH jurisdiction

- Division of premarket and labeling compliance (DPLC)
- DPLC is the division within the office of compliance (OC)
- Enforce premarket clearance and approval
- Enforce labeling and promotion and advertising requirements

Final General wellness guidance

- Policy for low risk devices
- Suitable for device that promote a healthy lifestyle, not treat diseases
- CDRH does not intent to examine low risk general wellness products within the meaning of the FD&C Act

Low risk product is not invasive or implanted

- Example: app that plays music to soothe and relax to manage stress
- Claim “related to only stress management”, not disease or medical condition
- Product does not pose risk if regulatory controls are not applied

Patient preference information

- Benefit risk guidance, for a list of benefit factors, risk factors, go to FDA.gov
- Help companies conduct their own benefit risk assessments
- Clarifies how the CDRH assesses the benefits and risks
- Consider relevant reliable info relating to patient perspective and real world data in addition to traditional scientific and clinical data

Surveillance and enforcement

- Compliance action approach
- Focused on the impact on patients
- Risk based on significant violations

Surveillance tools

- Inspections
- Promotional materials disseminated to the public
- The internet is helpful resource for DPLC
- Outreach initiatives: supporting the centers strategic plan, partnering with patients

Common problems

- Third party sellers
- Claims for products intended to remedy the lastest outbreak or natural disaster
- Breaking commitment made during the premarket review process
- Exceeding boundaries of enforcement
- Misuse of exempt product classifications

From Starr Edwards valve to TMVR-60 years of innovation in treating Heart Valve Diseases

Shouyan Lee, PhD, Founder and CTO, Joy Medical and Medical Implant

What is heart valve disease?

- Insufficiency (door not full closed)
- Stenosis (Door opening restricted)

The legend of 1958: Albert Starr, MD and Margaret and Lowell Edwards
Since 1960, 175000 total implants were performed

Keys to innovation across multi discipline
Starr-Edwards: medicine and hydraulics
TAVIL Interventional Cardiology and material sciences

Keys to innovation: timing, timing is everything
Starr Edwards: cardio pulmonary bypass
TAVI: Shape memory material, delivery system
Polymer valve: first prototype made of silicone, but rapture right away

Keys to innovation: failure is part of innovation

Clinical Result is the final Judgment

Panel Discussion: Fundraising for Startup

Moderator: **Guangqiang Jiang**, Ph.D., CTO & co-founder, Axonics Modulation Technologies
Panelists:
Jinsong Ni, Ph.D., CEO & CSO, Cloudbreak Therapeutics
Libin Cui, Ph.D., Founder and CEO, Akeagen
Eric Tang, Ph.D., Chairman, ZD Medical
Guorong Xu, Ph.D., Vice President, Innomed Medical Device
Wendy Hua, Ph.D., Managing partner, Cybernaut US venture capital funds

Moderator: Going from a stable income to starting a company is a big step. How did you become an entrepreneur? What motivates you to start your own company?

Ni: In my case, you may not find it inspiring, but it is true. In other cases, when people get out of school, they want to become an entrepreneur. But I was forced to be in that position. I worked at Pfizer for 3 years and 15 years at Allergan. Leaving comfortable life from Allergan, you have to give up a lot. Luckily Allergan help me transfer. 3 years ago Allergan restructured, I was laid off. One of the benefits about being laid off from big pharma is package. I had to decide: do I want to go back to big pharm again or do I want to start something new? I start the company for ocular development. When I look back it is not easy. That's my story about transferring.

Tang: I was a biologist and a JD. I worked at Wall Street for many years. In 2008-9 the financial crisis happened. I thought about starting a company and I know some people in China. I told my wife that If I fail in three years, I will come back; if I succeed, I will sell it and still come back. In the medical device field, there was a very high demand in China at the time. In 2008-9 my partner and I started our own company. We made a lot of mistakes at the beginning, I thought I knew a lot about China and I have done deals. It turns out that I knew little.

Cui: I graduated from grad school in 1992. I was inspired by Genentech, which was started with a scientist and an entrepreneur. We thought that maybe we could do something like Genentech. Two years ago, I started the Akeagen because of the dream that I realized. In the US it is not easy. Fortunately, I had good supporters. At the beginning, I had the idea but not any investment except the three Fs. Later we went well and got the preA funding. This year we will try to get series A funding.

Xu: I mostly worked in SoCal since 1992. In 2014, I had a chance to work at North Cal. The Start-ups and micro-companies made me think that I should do the same thing. There are so many reasons. For me, my kids are older and I had certain financial freedom. I visited China and science and technology parks. Most of the companies were found with people from the US. At the time Chinese govs had the support funding. So at the beginning of 2015, I started.

Hua: I had the entrepreneurship in my blood. One day I said to my roommate that I want to be a CEO. At the time, innovation was not big in China and my parents don't have high expectation for me. I just followed my heart. I had an internship when I was in China and my first job was negotiation during the investment process. I helped Plug and Play to set up the headquarter in China. Now we have invested over 50 companies in the US and a lot of them want to start a subsidiary in China.

Moderator: My second question is, what are the biggest change that you have made during the transition?

Ni: For me the change is that as scientists, we are conservative and cautious. But as an entrepreneur you have to do the opposite. At the beginning I wrote disclaimers, but the investors do not always appreciate that. They think that if you don't even have confidence then how can I believe in you.

Cui: My opinion is that you have to be honest. For me the biggest change is that as a scientist, you just have to deal with your experiments. But as an entrepreneur you have to multitask with many different things and deal with a lot of people.

Xu: If you run your own business, you have so many responsibilities for your employee, investors, and government. One person has to play different roles.

Moderator: What is your opinion on the gap between the Chinese pharma and the ones here?

Cui: I think in Chinese industry there was no real innovation before, but things changed a lot in the past two years. Chinese FDA made changes and encouraged innovation. So for us there is a good chance to do something for Chinese drug industry to be innovative.

Tang: Device side, gap here is huge. Almost 100% are owned by foreign companies. But there are a lot of opportunities. We acquired a company in LA in 2015, a spinoff from USC. By acquiring a company in the US and spent 3.5 years, we become one of the top companies that have this advanced technology. With the help from the US company, the China company in Hangzhou grew very quickly. Hangzhou developed their own product after our effort. Chinese gov. does encourage innovations.

Moderator: For fundraising, you want to go out and raise money. What are the essential things that you have to have before raising money?

Xu: I think the most important is that you have to have good business plan and senior management team. Otherwise VC will not be interested.

Cui: I think you have to be kind to the people around you. First is your family, they support you. Second, the seed that we had is from friends. When you have something, a prototype then we

have the confidence to show it off. She went to our lab and saw that it is very interesting. She asked if she can invest. If you do your job and have a prototype, you will have the money. Right now we are doing series A fundraising. This time is different, we still depend on people, so she brings the VC to us. Some said we want more data, some said they want to invest in the later rounds. So be patient and do your own job. This time we went to Shenzhen and we got an award and attention. It is not easy, but not that hard.

Hua: For very early stage we look at the team. We at least look at the CEO who should be good at marketing, and the CTO with good technology. In China we do a screening first, we look at business and technology. If they do not pass our screening, we won't look at them. There are many different passes, mainstream and not mainstream. The technology has to be at the top. If the technology is not top, the CTO has to be top. For business-wise, we look at people that have technology background. Top-tier PhDs who are outgoing and have business mindset are preferable.

Ni: Seed money is hard and important, we had two provision patent and no data. So seed investor takes a lot of risks. Seed money is the toughest and the next round is easy, it is just a validation of your company and it becomes a lot of easier.

Moderator: Do you have any lessons and experience that you would like to share when you go out. What kind of money you are targeting?

Tang: When you start, here and China are different. It is good to start with angels. Find someone who are VIPs in the industry, they do not only bring in money but also resources. In my case, as soon as our company and the products are ready, people approached us, and only at that time we thought that we were ready to take institutional money. Because private money is more flexible, I recommend to take angels' money at the beginning until you reach certain stage.

Q: Other perspective on common mistakes that we should avoid?

Hua: For angel investors, they can bring in resources. So in the early stage, think less about how much money or valuation but look for big names. There is a little trick. You need to think for investors and think about exit. There are only three ways: stay private, go public or you sell it. Then you look at the companies that are IPO. So if you find some companies that are pioneers, you can find good targets and talk to them ASAP, at least to get feedbacks. As long as you get some feedbacks to get some standard, that is good. Second is to get acquired. For some people if you want to sell a drug at certain phase, you need to know how to fit the standard of the company that wants to buy, or talk to the client to ASAP. Just try to talk to them. Plan ahead and think as investors are very important.

Q: Any advice for an academic person?
If you can patent, if you can collaborate with university then you can apply for SBIR. The key is that your technology has to be the top-notch.

Q: How do you deal with unreasonable “coal boss” investors?
Tang: Generally speaking, don’t take their money
Hua: An very practical advice: raise your valuation to compensate for what you are facing.

Q: How do you get the money, people and technology together to get things going?

Xu: Get fund first. No one works for you for free.

Cui: Get a patent, investors saw something tangible, otherwise get three Fs. If you really want to start, just start and the resource will come to you.

Ni: Seed investors just invest in you. So that is the seed money, not so much about the team. If you work yourself to the best they will come.

Moderator: The IPs are important. That is one side of the story. For medical device world you have to look at the patents what has been filed. Do your freedom to operate dual diligence.

Q: When you raise money, as owners how much share do you want to give up each time? And as investors, how much share do you want to get when you give money?

Hua: Typically, first round angel 20%, when you IPO the investors take 50%.

Xu: Depend on the value of your company

Cui: I agree that it all depends on valuation. If you have higher then you can dilute less.

Ni: Early investors don’t want to take too much. If they take too much you don't get motivated. Smart investors don’t want to control your company.

Tang: If you are a professor and don’t want to quit you job, the founding team will have 20-30%, 15-18% is reserved for managers and employees, and the rest is reserved for investors. The VC can find the CEO to run the company. Lots of company follow this path. That is in the US and the spin-off from universities. This is one model for professors. How much do you want to raise? Most of companies I have seen eventually did not end up with what they want to begin with. At the early stage get as much as possible, no one cares about who owns the company until you are successful.