Science AMA Series: I am Dr. Albert Li, CEO of IVAL. We provide products and research to improve drug development and make drugs safer and more effective before they reach clinical trials. AMA!

Dr$_{A}$$albert_{L}i$[1]$andr/ScienceAMAs$[1]

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April 17, 2023

Abstract

Hello, r/Science! I am Albert Li, President and CEO of In Vitro ADMET Laboratories (IVAL), located in Columbia, MD and Malden, MA. For the past three decades, I have devoted my scientific career to the improvement and application of human-based in vitro experimental systems (experiments done outside of a living body) in the development of pharmaceuticals. In 2004, I founded IVAL, an organization dedicated to creating innovative approaches to the evaluation of human drug properties. We strive to develop products and preclinical applications that help scientists study how the body processes a compound, how that compound interacts with others already in the body, and predict any potential harm that the compound may cause. This improves the drug discovery process, allowing for more accurate prediction of drug safety and efficacy in the early phases of drug research and ensuring that only the safest and most promising candidates move on to clinical trials. One achievement in this effort is the Integrated discrete Multiple Organ Co-Culture experimental tool (IdMOC). This testing plate consists of multiple wells that can be seeded with cells from different organs. These wells are then connected by an overlying medium, which allows for well-to-well communication, mimicking the way organs communicate within the body. Researchers can then apply a test compound to the target cell type and assess how the compound might travel through the body and affect other organs. In addition to providing far more complete information on drug metabolism and interaction, the IdMOC can allow for the refinement, reduction, and replacement of live animal usage in drug research. This not only aides animal welfare but also creates more accurate data, since the use of human cells can provide human-specific information that cannot be obtained with laboratory animals. We also work on optimizing cryopreservation of primary human and animal cells, particularly hepatocytes, a major cell type found in the liver. Hepatocytes play an important role in metabolizing outside compounds and altering them so that they can be excreted from the body. This makes them vital to drug research and development. Cryopreservation is an ideal method for long term storage and allows researchers to have a steady supply of cells available for experimentation. We have a (newly minted) blog http://invitroadmetlabs.com/ as well as Twitter https://twitter.com/InVitroADMET and Facebook https://www.facebook.com/In-Vitro-ADMET-Laboratories-LLC-441026892766841/timeline/ . Here are links to a few of our recent papers: Evaluation of Adverse Drug Properties with Cryopreserved Human Hepatocytes and the Integrated Discrete Multiple Organ Co-culture (IdMOC) System http://www.ncbi.nlm.nih.gov/pubmed/26191380 (Full Text) In Vitro Heptocyte-based Experimental Systems http://www.ncbi.nlm.nih.gov/pubmed/24805059 (Abstract) Evaluation of Human Hepatocytes under Prolonged Culture http://www.ncbi.nlm.nih.gov/pubmed/25313020 (Abstract) A Novel Plated Hepatocyte Relay Assay (PHRA) for In Vitro Evaluation of Hepatic Metabolic Clearance of Slowly Metabolized Compounds http://www.ncbi.nlm.nih.gov/pubmed/26282592 (Epub Ahead of Print) Also with me today is IVAL researcher Yang Qian (YQ) out Social Media Coordinator, Allison Isberg (AI), who will be helping us take questions and type answers. We will be back to answer your questions at 1 pm ET (10 am PT, 5 pm UTC), Feel free to AUA about in vitro drug research and development, drug toxicology, cryopreservation of cells, biomedical entrepreneurship, or anything else you have in mind! Edit AI- Hey everyone, that's about all we have time for today. Thank you so much for your questions; Dr. Li really enjoyed

answering them! And thank you to the r/Science mods for setting this up. If you're interested in following more of our research, please feel free to follow the Twitter or send a PM to this account. If anyone is interested in full copies of any of our papers, PM this account and we should be able to get those to you. We will check back again and answer any more questions if possible. Thanks again!

the WINNOWER

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DR_ALBERT_LI R/SCIENCE

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We have a (newly minted) blog http://invitroadmetlabs.com/ as well as Twitter https://twitter.com/InVitroADMET and Facebook https://www.facebook.com/In-Vitro-ADMET-Laboratories-LLC-441026892766841/timeline/ .

Here are links to a few of our recent papers: Evaluation of Adverse Drug Properties with Cryopreserved Human Hepatocytes and the Integrated Discrete Multiple Organ Co-culture (IdMOC) System http://www.ncbi.nlm.nih.gov/pubmed/26191380 (Full Text) In Vitro Heptocyte-based Experimental Systems http://www.ncbi.nlm.nih.gov/pubmed/24805059 (Abstract) Evaluation of Human Hepatocytes under Prolonged Culture http://www.ncbi.nlm.nih.gov/pubmed/25313020 (Abstract) A Novel Plated Hepatocyte Relay Assay (PHRA) for In Vitro Evaluation of Hepatic Metabolic Clearance of Slowly Metabolized Compounds http://www.ncbi.nlm.nih.gov/pubmed/26282592 (Epub Ahead of Print)

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If you're interested in following more of our research, please feel free to follow the Twitter or send a PM to this account. If anyone is interested in full copies of any of our papers, PM this account and we should be able to get those to you. We will check back again and answer any more questions if possible. Thanks again!

READ REVIEWS

WRITE A REVIEW

CORRESPONDENCE:

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Background: **One of the biggest issues, for the aging population perspective, is polypharmacy. Almost one in 3 elderly Americans (> 65) takes 8 or more drugs on a daily basis, with an average of 18 prescriptions per year. Between 10 and 30 percent of the inpatients are admitted for a drug problem. While I cannot figure out the societal cost (and burden), polypharmacy is clearly a problem that we do not handle well.**

Question 1: **Can you tell us how IVAL evaluates drug-drug interactions of more than pair-wise combinations? Given the above, we really need to go beyond that type of evaluation.**

Question 2: **By some estimates, there are 84 drug metabolizing enzymes - this includes house-keeping genes and ABC transporters, not just CYPs. Are you monitoring such effects? Is it necessary to understand which ones are in play?**

Question 3: **LZ Benet classifies drugs according to extent of metabolism and (FDA) solubility - he calls it BDDCS (since 2005). Would you benefit from categorizing ADRs according to BDDCS? For example, transporters are less of an influence on BDDCS class 3, but may play a major role in Class 2 drugs.**

milagr05o5
Good afternoon. That is a fantastic question. Evaluation of drug-drug interactions (DDI) currently mainly is focused on pharmacokinetic drug interactions: how one drug affects the metabolism and clearance of another drug. We ask the following questions: 1. DDI victim potential: We define which drug metabolism pathways are involved in the metabolism of a drug. Then we can project which drugs that are currently in the market can cause drug interactions. For instance, if a drug is metabolized by P450 isoform 3A4 (CYP34), then CYP3A4 inhibitors such as erythromtycin and ketoconazole are likely to cause drug interactions. CYP3A4 inhibitors will inhibit metabolism of the drug, causing slower metabolic clearance, leading to higher than expected plasma drug concentration. The result is toxicity. A good example is seldane/ketoconazole interactions, leading to cardiotoxicity. Using this principle, we can project the effects of polypharmacy.

I will post this and continue to answer the question.

How do you feel the balance is being struck between the need for raising costs for drug research via prices, and the need for affordable drugs by consumers?

Are there some people striking the balance better than others, and are there people who you see as profiteering?

AdrianBlake
There are several questions and comments of drug costs so I will address this important issue here.

The cost for developing a drug has escalated dramatically. We had a conference early this year at our Boston Hepatocyte Technology Center (BHTC) on this topic with Joe DiMasi of Tuft's as our keynote speaker. The cost for developing a new drug is now estimated at $1.5 billion, taking an average of 15-20 years. This is an astronomical sum, but, to the pharmaceutical company, it is still financially attractive. A block buster drug (e.g. statins when they first enter the market) can make over $1 billion per year.

First let's ask the question of why is it so difficult to come up with a new drug. The short answer is: we do not know whether a new drug works, or how safe it is until it is tested in humans.

Efficacy: It is one of the major reasons drug candidates fail in clinical trials. Drug candidates that work in nonhuman animals often are not efficacious in human.

Safety: This is a major concern in drug development. First of all, drug candidates found safe in animals often have unacceptable safety profiles in humans during clinical trials. Worse of all, many drugs found safe in Phase I, II, III clinical trials have been found to have unacceptable adverse drug effects after marketing, leading to withdrawal or blackbox warnings.

So the key to enhance the efficiency of drug development is to accurately predict human efficacy and safety.

At IVAL, we believe that using human cells, especially primary cells isolated from human organs, can help define human drug properties. We are now able to accurately predict human drug-drug interactions. We can accurately identify drugs that cause acute liver failures. We continue to develop new experimental systems to further this goal.

What new developments or research areas are you most excited about?

Weedwums

1. Human enterocytes (intestinal cells) to model oral drug absorption and metabolism - our new project.
2. Human pharmacology: application of human cells (e.g. hepatocytes) to discover new drug targets
3. Human drug toxicity: definition of human drug toxicity using in vitro human cell systems.

There are more - but you can see that I am very human-centric.

How would you compare your research and daily work 5 years in the past to what you think it will evolve to 5 years in the future?

I_double_doge_dare_u

I have witnessed very positive changes. The idea that animals are different from human - a well-established scientific concept, is finally getting acceptance. You may find that hard to believe. But imagine yourself as a toxicologist in pharma: your job is to make sure that the drug candidates you are proposing to move on to clinical trial are "safe" per FDA. So you perform your two or three species safety studies that are required, and hope to obtain Investigative New Drug (IND) approval from FDA for clinical trials. You are rewarded for this and therefore there is no incentive for you to consider the question of whether the drug candidates found safe in animals are toxic to human. In the past 5 years, I witness finally that pharma is now putting human safety as the ultimate goal upfront as they should be. Every pharma has an investigative toxicology program so that drug candidates can be evaluated with human-based tests, hopefully thereby removing human-toxic drug candidate, before subjecting them to animal testing. All said, there is still great resistance to make judgment of human drug toxicity based on mechanistic, investigative experiments. This is an area that I will continue to push.

I will talk also about something we are very proud of: human hepatocytes. In the five years, finally human hepatocytes are used routinely by pharmaceutical industry for drug metabolism and drug-drug interaction studies. You would not believe how long (20 years) I have to continue to publish, and to speak, on the advantages of human hepatocytes before this now universal acceptance. You will still find researchers who prefer HepG2 cells: an old human hepatocyte model that is defective due to the lack of drug metabolizing enzyme activities, but they are now a minority whom I believe will eventually see the light.

In our company, we will continue to develop relevant experimental systems to provide data to

reproduce that found in human in vivo. One of our new projects is the isolation and cryorpreservation of human enterocytes (intestinal cells responsible for drug absorption and metabolism). You will hear about this soon - very exciting system for the evaluation of bioavailability (how much a drug is absorbed after oral ingestion), food-drug interactions, herbal medicine-drug interactions, and enterotoxicology.

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Explain to me in detail how the IdMOC is *possible*? In other words, how did you initially defeat criticism of the IdMOC? What kinds of criticism was it originally met with? What kind of criticism can it not overcome?

usesdirectquotes
IdMOC: Integrated discrete multiple organ co-culture, models the entire human body, with multiple organs co-cultured as physically separated entities but interconnected by an overlying medium, akin to blood connecting all our organs. We very quickly were supported by EPA in the Toxcast program, and have published with CDC on cigarette smoke, and the US Army in the proof-of-concept of the provision of liver metabolism on the toxicity on nonhepatic cells. It is now getting more attention as we have published more on it. Our next model will be IdMOC with multiple organs, with multiple cell types per organ.

A major criticism is that IdMOC does not employ 3-dimensional cell culture, and there is no blood flow. 3-d cell culture and microfluidics is the latest trends. We are now developing 3-d liver systems and will

apply that to IdMOC. In terms of flow, I am not convinced that flow per se is important. Most microfluidic system involve flow and recirculation, meaning that after one recirculation, everything is mixed - no different from a non-flow system. We can simply model that by shaking our IdMOC plate.

The challenge of IdMOC is that it takes a long time for scientists to accept a new platform (think "hepatocytes"). I believe that it will be readily accepted, hopefully before I retire.

Do you have any suggestions for how someone passionate about working to improve the pharmaceutical industry (specifically the drug discovery process) could "plug in" and find opportunities to make a difference? I got my degree in chemistry because I wanted to fix the problems I saw growing up with chronically ill family members, but working for several pharmaceutical companies and hearing all the news about the price hikes has discouraged me about the direction the industry is headed. Any advice is appreciated, and thank you for the AMA!

tiny-dino
You will be successful, as you are passionate about problem solving, and obviously capable (I was also a chem major).

I would not be discouraged about the pharmaceutical industry. It is still the best industry to work in: curing human diseases to me remains the most interesting, challenging, and rewarding endeavor.

Try joining a small pharma: you will find it most rewarding.

What's the greatest achievement you'd say you've accomplished over your time as CEO?

terminalhack
To be well-regarded both in science and in business. In Vitro ADMET is now well-recognized as the best "hepatocyte" company. I am especially proud of the establishment of our Boston facility to serve the Boston-Cambridge pharmaceutical community. Making many great friends all over world through science and business.

In you opinion, what is holding back the development of new treatment options? Have we exhausted the diseases that can be cured by a small molecule drug? Or are the standards set by the FDA to bring a drug to market too high? Or is it that drug development is just a really challenging problem and will remain this way for the foreseeable future?

Thanks

jostmey
We are moving away from random testing to hypothesis driven testing in drug development. Opportunities abound for the development of better drugs: more efficacious, less toxic, drugs - both small molecules and biologics.

I have great respect for the reviewers of FDA. They are often open-minded, logical, scientific and reasonable. Definitely not the check-the boxes type.

If we continue to emphasize on early understanding of human drug properties and without blindly relying on animal experimentation, we will make great strides.

1. **I read a while back that there was a drug being tested on rats that stopped heroin addicted rats from craving the substance permanently. The scientists conducting this study, however, could not get the funding or FDA approval to take their study to the next step in the process**

of research and develop towards and eventual drug for human heroin addicts. Is this true? If so, who would want to stop the research into something like this and why?

2. **read the article a while back, some of my memory from it may be incorrect. Also, didn't double check the source.**
3. **Besides government grants, grants from colleges, and private funds; are there ways to expand funding the research and development of medications/ treatments for the more serious diseases facing humanity? Especially vs. the type of money that pharmaceutical companies provide for things like acne products or more minimal health issues. How big is that gap of funding?**
4. **I want to thank you for all of your hard work and dedication. I think that the research you are doing is absolutely amazing! I have been taking several different medications since the age of 16 (am now 23), and I worry about the side effects that these drugs could have on my kidneys and liver. I truly admire you, sir.**

****posted via mobile, please excuse grammer and spelling. Also, not the most informed on the issues in my questions, but I do understand the science in this discussion**

WarDamnMoon
Thanks for posting your questions. I do not know about the study you refer to.

Drug discovery and development requires extensive funding and organization. Usually, it starts with a professor with an interesting discovery, leading to him/her forming a company with substantial venture capital funding, and culminate in the company receiving milestone payments from pharmaceutical companies which also with serve as development and marketing partners.

Please continue to remain healthy - taking only medications that are required and proven to be effective. Don't trust any unauthorized medications - especially "natural" remedies.

Take care.

Hi there,

This question will be asked in many forms today but I will try to specific it as much as possible. The Martin Shkrelli case where he purchased orphan drugs and skyrocketed price really upset the public. However, many individuals maintain a dislike to Pharma due to (what I believe to be false) a belief that Pharma is just trying to get more and more money while holding their health hostage. As a graduate student, I don't have that opinion of Big Pharma at all. As a member of the industry, do you believe that profits is always the number one priority or do you believe that pharma attempts to price their products to make R&D such as the kinds of things you proposal a reality.

Thanks!

gammadeltat
I believe in the good of human nature. The focus of pharmaceutical industry should be relief of human sufferings via development of cures. I have met many pharmaceutical scientists with great passion in what they are doing and see themselves as doing good for the world. An organization needs to be profitable to survive, but profitability should not be the sole reason for existence. I believe that great companies have strong visions, with the vision being advancement of human conditions, not profitability.

I've always felt that in-vitro testing wouldn't be particularly useful in replacing animal models since it doesn't indicate a whole organism response and I'm so glad to find you have worked a way around this. I'm wondering if your innovations have been accepted by the pharmaceutical industry given that animal models have been used for so long. Is there resistance to adopting

your approaches? If so, what are the concerns and criticisms you face?

happy-little-atheist

I think that resistance to in vitro testing is based on our believe that we will never understand the whole organism, and therefore testing in animals is the only way to go. That is absolutely out-of-date. Using relevant in vitro systems, we now can gain knowledge about human effects of drugs that, due to species difference, cannot be obtained with animals. A case in point is that for drug-drug interaction evaluation, FDA, EMA, Japan Health Ministry all require only human in vitro evaluation - no animal experimental required. All because we understand the huge different between human and animals in drug metabolism. The same will happen (already happening) to toxicology and pharmacology.