ACS AMA: Hi, Reddit! I am Donna Huryn, a medicinal chemist at the University of Pittsburgh's School of Pharmacy. Ask me anything about medicinal chemistry / drug discovery in academia.

AmerChemSocietyAMA [1] and r/Science AMAs[1]

[1]Affiliation not available

April 17, 2023

Abstract

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the WINNOWER

REDDIT

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ACS AMA

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Hi Donna, and than you for doing this AMA.

I'll be honest, I've always been a pretty big skeptic when it comes to expanding the role of academia doing drug discovery. The skill set required to do lead optimization, model development, trial design etc. is just so different from what is often selected for in academia. Further, the incentive system is hard to get right in an academic setting - publish or perish doesn't mesh well with an environment where we know a priori that the vast majority of drug ideas, let alone drug candidates, will fail.

So I guess my questions for you are:

- what do you perceive as the advantages of drug development in an academic setting vs. a more corporate setting?
- what do you consider your biggest successes since you've started this initiative?

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- your biggest failures, and the lessons learned?

SirT6

Yes, I completely understand the skepticism. In fact, I share some of it. Your question asked about "drug development" if you mean true development – I agree it is not something done well in academia. But, as far as the earlier discovery phase, if you carefully choose you academic drug discovery projects you can be successful - but you need to exploit your strengths and differences. Rare diseases are one such case – these drug discovery projects rarely take place in large pharma, and you may have access to a world expert in a protein or a disease, or a particular technology down the hall that can expedite projects by getting access to animal models and patients rapidly. I like to think that pharma has the breadth of expertise but academia has a depth.

Another difference / advantage is that you can take some risks to try new approaches in academia that may be harded to justify in industry. One example of success that comes to mind is related to Alzheimer's Disease. While industry was focusing on beta-amyloid, some in academia were focusing on tau, which was less well validated at the time. My collaborators did proof of concept studies, and pointed people into a new direction and provided some validation. Given the clinical failures of secretase inhibitors, there is now more focus on tau.

The biggest disappointment is that for multiple projects - we have very interesting, promising compounds, but in academia it is sometimes difficult to take them any futher than in vitro and cellular activity. Lots of examples of this. Finding collaborators who have the ability, will and funds to do animal studies is challenging. One of the benefits of NCI's chemical Biology Consortium is that for projects accepted – all those resources are there and available. Lessons learned include establishing all the collaborators you need early on, and picking projects very carefully according to ones you can have an impact on.

do you think the employment landscape of medicinal chemists is changing? im particularly interested in your take on: the number of medicinal chemistry jobs available in the US (and how that will change in the future) and if degree preferences are changing (e.g. Can you get a job with a PhD in med. chem. Or is it still total synthesis/raw organic chemistry based? Maybe chemical biology?)

Justdis

I started my career in pharma in the late 80's - and certainly there have been enormous changes since then. While I don't have hard numbers in front of me, my observations are that students are now getting medicinal chemistry jobs in big pharma and biotech, more so than several years ago. I don't think medicinal chemistry jobs are going away any time soon, but they may be in smaller companies vs. big pharma. My opinion is that the desire for a background in total synthesis has not gone away - the feeling is that it is hard to know how to design and synthesize small molecules, and it is not a skill easily taught. Chemical Biology may not be as desirable since the depth of experience in synthesis may be missing. A degree in Med Chem seems to be gaining more favor that it was when I was in school, especially if the project is complex and requires some sophisticated chemistry.

How valuable is QSAR in finding new drug candidates? Have chemists generally found "most" usable drugs, or do we have a lot more to discover?

Can you tell us more about bioassays and testing kinetics in animal models?

What are the top five or ten notable compounds you know of in any phase trials? (aka, what's cookin' good, Chef?)

Not exactly a question, but can you explain the general processes, restrictions on chemicals, paperwork, and how you go from precursor, to chemistry, to purification and cleanup, to produced drug?

Can you explain the general requirements and general processes for being able to produce/manage/handle scheduled compounds? (From each schedule)

Will your drugs be able to save my kidneys in ten years? Haha.

This is an endlessly fascinating and exciting field to be in. Super glad you posted an AMA!!

NeuroNerd4Mit

Lots of questions here - so I will only answer a few: I am an eternal optimist - so I think there are lots more drugs to discover! We use QSAR frequently - especially when we don't have a solved x-ray or cryo-EM structure to rely on. For your kidneys - we hope so! We are working on an exciting project where the initial hits were found in a zebrafish screen.

How has genetic research impacted drug discovery? Are the molecular pathways associated with increased risk useful for therapeutic targets? Or has this approach been more of a bust than a bang?

p1percub

The answer to your first question is definitely. There are multiple examples of gene mutations associated with disease becoming targets for drug discovery, and even successful drugs. A few examples include Gleevec which targets gene product that is specifically mutated in certain cancers and Kalydeco which targets a very specific mutation found in cystis fibrosis patients. Understanding the genetics of these diseases focused research efforts. There are other examples of drugs in clinical trials whose targets were discovered based on mapping the human genome . However, there are also examples where the genetics suggested a target, but drugs were not effective. Alzheimer's Disease is a great example – where mutations in genes for certain enzymes was linked to the familial form of the disease, but drugs affecting these same targets failed in clinical trials. Genes associated with increased risk (vs. cause) are also being pursued (for example in Alzheimer's) but those are less advanced.

I feel that personalized medicine is going to be pretty big in the drug world, as your genome can determine what side effects you will encounter. Do you take any of this into account yet-how far are we from really personalizing medications?

harambay

Yes, in some ways this is taken into account and has been for some time. Drug discovery programs typically evaluate effects on certain metabolizing enzymes (Cyps). It is known these enzymes vary in individuals - by race and by gender. By evaluating several of them, you can get a warning of whether certain groups of people will be more sensitive or prone to toxicity than others. A drug example - Kalydeco- is one where only a very small percentage of cystic fibrosis patients benefit – they must have a specific mutation in the CF gene. It is a good example of personalized medicine.

Hi, Dr. Huryn -- what's your viewpoint regarding the validity of cannabidiol as a treatment for cancer?

Is the academic community allowed to study it despite prohibition still being in effect on a federal level?

Thanks very much for participating here.

sighbourbon

I am not that familiar with the data. But, there is considerable work on cannabinoids in academia, so it seems that any restrictions can be dealt with.

Thank you for doing this AMA, Donna.

I'm an Organic Chemistry student in Europe (graduating next year) and I had always been charmed by large, complex synthetic challenges. I've found that medicinal chemistry could be a personal challenge and a satisfying job for me. I would like to ask you some questions about your world (if they are similar to the ones already asked or they have already been answered, I'll go read them myself):

- What are the modern challenges of medicinal chemistry?
- What do i need to do to try become a medicinal chemist?
- Is the job market already saturated for someone like me?
- What are the skills that are useful to have in my portfolio? And how can I learn those skills? Are there some useful resources?
- What is one of your work-day like?
- Do you still go in the lab and set up reactions and the like? That's the most enjoying part of the chemistry "world" to me.

Have a nice day.

alleluja

I'll try to answer some of these questions: As a scientist - there are still lots of challenges for medicinal chemists. The same old ones are still there - finding compounds with the right potency and properties. But more recent challenges are - understanding how to design small molecules that interrupt protein-protein interactions a priori; understanding better how to manipulate a structure so it adopts a specific conformation are just a few.
Medicinal chemists have strong backgrounds in synthetic organic chemistry - so make sure you have been exposed to different types of chemistry and molecules. Getting used to reviewing biological data, and understanding what it tells you is another important skill. My work day is pretty varied, which I like. I usually spend some time writing - either grants, reports or manuscripts. I also spend a lot of time in meetings - with students and with collaborators (sometimes one on one, and sometimes as a group). Many of my collaborators are remote - so lots of teleconferences or skype calls. Spending time reviewing data and designing the next experiments is also a big component. I also teach. Sadly, I miss setting up reactions :(

I've heard nothing but terrible things about working in the pharmaceutical industry as a chemist. I've been told the pay sucks, the standards are insane (makes sense though, it is medicine), and it is very cutthroat so I have avoided any jobs in that field.

Is there any validation to this?

kevoizjawesome

I haven't worked in pharma for 10 years, but I can say I LOVED IT. It was exciting to be working on

interesting scientific projects were everyone was working towards the same goal. I learned from my colleagues and liked being part of a bigger effort of developing new drugs.

As I watch the Amazon being stripped of it's botanical diversity with continued deforestation I can't help but fear we are losing valuable potential for future medicines. Do you share this fear? Is this a topic among your colleagues? Just curious.

OnThe65thSquare

We talk a lot of the potential for natural products as drugs, since they have been such a valuable source and there is a lot of discussion about how to resurrect the area,. The de-forestation is a concern, but honestly not one that I have considered. There are many challenges – including as you mention preserving the ecosystem. Other challenges include assuring that the home country retains some rights (or a reward) for drugs that may result, but that these agreements are not so onerous that it becomes a barrier for further research. There are some very interesting approaches to finding new natural products – both in the environment and in the lab - looking at new sources and genetically engineering organisms to make new "natural products"

What would you recommend as beginner reading material to understanding medicinal chemistry? (Other then analytical/organic/biochemistry)

With the giant leap forwards in the last 50 years for synthetic chemistry, cell bio, and molecular biology, and computers why has success rates for new drug candidates fallen?

Ekap2

There are a number of medicinal chemistry books available. Some are more useful for beginners than others. Reading reviews/ drug annotations, perspectives etc in journals like J. Med. Chem. or ACS MCL is also a great way to start to learn.
As to your second question - lots of reasons, but this is a question many have tried to answer. Only a few include: higher regulatory hurdles and higher expectations of drug candidates.

What advice would you give to someone interested in pursuing a PhD in medicinal chemistry?

Would you take the same career path if you had the chance to do it over again? What would you do differently?

needmoremullins

I am grateful that I had a career in industry and now in academia. The experiences I had and the things I learned in industry have really helped me in academia. I would not have done it any differently. The advice I would give is to make sure your medicinal chemistry projects are high quality projects, that will be respected by colleagues in academia and industry. That the assays are valid and all the tools you need to succeed are available, and the target is one that is worth pursuing. The quality of academic medicinal chemistry projects vary greatly - make sure you have one of the best ones.

Is there any valid research or data that proves that changing ones pH to a more alkaline state can lead to a healthier body and a body that can resist cancer growth?

urkellurker

no

Thanks for coming to talk with us!

A few years ago, a friend of mine worked at a startup that took a combinatorial/robotics approach to drug discovery: try thousands of things in parallel, see if anything works. That startup didn't succeed. But more generally, have any significant discoveries come from a combinatorial approach? Are people still doing that?

asbruckman

Our Alzheimer's project at Wyeth on gamma secretase inhibitors started with a hit from a combinatorial library (~300,000 compounds screened - 2 hits that came out of 6K compound of very similar compounds). This evolved compound advanced to clinical trials. We would not have had a starting point without the combinatorial library hit. Today, people are doing less of the original combinatorial library - BUT are applying a lot of the same strategies and techniques. For example - instead of making analogs of a hit or lead one at a time - we do things in parallel and make many close analogs simultaneously. Lots of labs are using parallel and automated equipment that really started with combinatorial chemistry.

As I understand it (and as I'm always trying to explain to others who want to try the next "miracle cure"), just about anything will kill cancer cells in a petri dish, but most of those molecules won't make good drugs. Can you give a very general outline of the difference between a useful drug and - say - hand sanitizer?

nezumipi

Useful drug: effective in treating the disease without side effects that outweigh the beneficial effects; Able to be administered to a patient in a practical manner and still have the same benefits as in a petri dish

Hi, and thanks for the opportunity!

There is a lot of coverage in the news about the opioid epidemic, including some conflicting information about children and police officers who have been harmed via skin contact.

Statements by doctors from the AMA seem to discredit those claims. But they have also point out that transdermal delivery of similar drugs is a common method of treatment.

What is your opinion about the potential for opioids being taken up through skin contact? Should people be worried?

Thanks again - I hope my question isn't too far out of the scope of this discussion.

robertson4379

I have not followed this area. However, usually drugs that are delivered transdermally also include excipients that enhance skin absorption - they are not pure drug.

Hello Dr. Huryn and thank you for taking the time to do this AMA,

I just have two questions: Where does the technology for computer aided drug design stand currently? And, what improvements could make drug design/discovery easier in the future?

Thanks Again,

Cooper

CDeruiter5963

Virtually everyone uses some form of computer aided drug design - some more sophisticated than others, and for different aspects. We are pretty good about drug design for well characterized enzymes for which there are many x-ray structures. Areas for opportunity include modeling targets for which structures haven't been solved, and highly dynamic proteins. The success rate for virtual screening should be better than it is - which suggests there is more to learn. There is a lot of interest in understanding how on- and off-rates of small molecules binding to their targets impact biological effects - and this area is not one that is well modeled by computational methods.

Hi Donna, thanks so much for taking time to do this.

I am currently a resident of Philadelphia so both Pittsburgh and Penn have been schools I have been looking at for college. I am taking my first year of Chemistry next year in the form of AP Chemistry and I am interested in hearing your academic process for people who may also be interested in medicinal chemistry.

What was high school like? What did you do both in school and out to get to where you got? College? The years after? What interested you in medicinal chemistry?

I believe it would be interesting to get some insight from a person in that field. Thank you so much.

Madison360

My best advice is to try to get some lab experience. Sadly, this is hard to do for a HS student, particularly in PA since there are many costly requirements for lab heads in order to have a minor in the lab. But, there are several summer programs (one at Penn for sure) where you can do real experiments. Rutgers/ Douglas College also used to have a great summer program - not sure if they still do. HS was pretty uninspiring for science for me. (In fact, my HS chemistry teacher was shocked when I told him I got a PhD, in chemistry) I went to Cornell, and found that I really liked chemistry. I wanted to do organic chemistry, and went to graduate school to do organic synthesis. I had a class I loved at Cornell all about synthesis - and I think that inspired me. At Penn, I went to a lecture by Noal Cohen - a scientist from Roche who talked about synthesizing complex products and using them to make new drugs, and I knew that was what I wanted to do. I found it appealing to work on a project where my efforts contributed to something as important as discovery new drugs for people.

Why have motor neuron diseases been such a black box? It seems like our understanding of things like ALS, PLS, Huntington's etc. has not progressed very much. In your estimation how far away are we from treatment or a cure? I know rituluozole is considered a treatment, but it's not very effective. Thanks!

Wonka_Raskolnikov

This is a huge disappointment and frustration. Probably far from a cure, but maybe a little closer to some treatments. One problem is that it is hard to study some of these diseases because they are in the brain, and in some, the disease may start well before symptoms - so you are treating and studying the disease at later stages not early stages when it may be more effect to treat. Another is that many

are probably caused by aggregation of proteins, and this phenomena is not something medicinal chemists have developed strategies to reverse or inhibit.

As an undergrad aiming to go into drug development, what are the best things you can do to maximize the chance of success in entering the industry? Also, do you feel that total organic synthesis is being phased out by natural product synthesis even in the drug development world?

Thanks!!

Neobladesman

Strong academic credentials and experience in a lab. If you have an opportunity to do undergraduate research - take it. Not clear on your distinction between total organic synthesis vs. NP synthesis in your second question.

In a year, I will be starting my PhD in Pharmaceutical Sciences, specializing in Pharmacogenomics. Do you have any advice for the years to come?

NintendoNoNo

Work hard, show you can solve problems, keep up with the literature, and perfect your communication (writing and verbal) skills. (sorry - pretty generic advice)

Currently a chem major biological emphasis. Would medicinal chem be a good way to further my education?

mygingersoul

If you mean a class, yes. It will give you a good perspective in the area. But, also taking classes in biochemistry and pharmacology and chemical biology would also be useful. Practice writing - this always helps regardless of discipline.