Seizing Life, episode 54
Epilepsy Drug Development: The Journey Begins
Guest: Dr. James Cloyd
(Transcript)

Kelly Cervantes:	00:00	Hi, I'm Kelly Cervantes, and this is Seizing Life, a biweekly podcast produced by Cure Epilepsy.
Kelly Cervantes:	00:18	Today on Seizing Life, we begin a special series examining the drug development process from its initial stages, through FDA approval. With the COVID-19 pandemic and the accelerated quest to develop a vaccine, we all have a new interest in the drug development process. So we thought it would be a good time to take a closer look at the process on a more typical timeline, with a focus on epilepsy drug development.
Kelly Cervantes:	00:42	To get us started. I'm happy to welcome Dr. James Cloyd to the podcast. Dr. Cloyd in the Lawrence C. Weaver Endowed-Chair in Orphan Drug Development and Director of the Center for Orphan Drug Research at the University of Minnesota College of Pharmacy. He is also a member of the Cure Epilepsy Scientific Advisory Council. He is here today to explain the early stages of the drug development process, from drug discovery through preclinical studies. Dr. Cloyd, thank you so much for joining us today on Seizing Life.
Dr. James Cloyd:	01:15	Kelly, thank you for inviting me to join you and your audience today. This is a very important topic that means so much to the millions of individuals and their families who must deal with epilepsy.
Kelly Cervantes:	01:28	2020 has made amateur epidemiologists and pharmacists out of so many of us as we watch COVID and the drug trials and all of these things that are going on, but I just don't think that many people actually understand the process that it takes from recognizing the problem to the FDA approving a drug that people can use. I would love, and we'll dive in deeper a little later on, but just to give us a basic foundation, what are those steps from recognition of the problem to the drug being on the market?
Dr. James Cloyd:	02:07	With regard to development of new therapies for epilepsy, it begins actually in basic neuroscience where we learn what causes seizures and what causes epilepsy. And as that is described and understood, you begin to identify something called a target. That's some part of the human body where you can do something, you can intervene to correct the problem, prevent the seizure or prevent the epilepsy. Once you know that target, you can then literally design molecules that will work at that target to either block or intervene in some way.

Dr. James Cloyd:	02:49	The next step after that is you take that molecule and synthesize it, you actually make it. And then you begin a series of tests starting at a very basic level, perhaps with cells and then laboratory animals. And then when you've done all that and you also have some idea of how you could make this product or how you could make this molecule into a drug, you put all of that together and you submit something called a IND, it's a new drug application. That goes to the FDA. They will take a look up the work that you've already done and what you propose to do in humans, and they will determine if it's safe to proceed.
Dr. James Cloyd:	03:30	If you get that approval, you then would carry out. A series of studies, often with healthy volunteers first, then with small numbers of the patients who would be the users of this medication, and this would be a small clinical trial. And then the last phase would be to conduct a relatively large clinical trial to ascertain whether the drug actually works and if it is safe.
Dr. James Cloyd:	03:58	Once you've done all of that and compile all of that information, both the preclinical and the clinical into a document called the new drug application, that's shortened to NDA, you submit that to the FDA. And after usually about a year's review, the FDA will determine whether or not you, the manufacturer, can go ahead and market the drug. And if you do get approval, patients and families then will have a new medication to use for the various types of epilepsies. So that's a thumbnail sketch of something like a 10 to 12 year journey from start to finish.
Kelly Cervantes:	04:36	Yeah, that's intense. That is a long, long journey.
Dr. James Cloyd:	04:42	I should mention that in addition to designing brand new molecules, another approach is to take drugs that are already on the market, but modify them in some way so that you either get more effectiveness or reduced adverse effects. And then there's actually a third way, and that's where we find literally serendipity, that something that's available perhaps as a natural product or a plant product can be beneficial. And the best example of that is the component of medical marijuana known as CBD.
Kelly Cervantes:	05:19	So now I want to dive a little deeper into each of these stages, and I really want to start with that basic research. What does that entail? Who is doing that research and who's funding it? Because you can't get to any of the other steps if you don't have that basic research as a fundamental starting block.
Dr. James Cloyd:	05:41	You're absolutely right. It is the crucial step and it's one of the most important ways in which we find new drugs to either

prevent seizures or prevent epilepsy. You begin through doing research in the area of how the brain works and what, within the brain, causes seizures to occur. And this is really basic work. It may be genetic in nature. It may be examining cells from human tissue, or it could be from animal models, but it's really at the basic core.

Dr. James Cloyd: 06:20 And then the people that most commonly do this are in academe, but it is also carried out by investigators in both large pharmaceutical companies and even smaller pharmaceutical companies that may have sort of a special expertise in a particular area of epilepsy research.

Dr. James Cloyd: 06:40 Now, who funds this research? And this is really a critical question. Most of the large grants funded through the NIH generally require that you have something called preliminary data. Well, if you have a brand new idea and you want to study it, very often, you don't have brand new data, you're starting from scratch. So organizations like Cure become indispensable in providing that early support. It doesn't have to be a lot of money, but it has to be enough so that the investigator can carry out these very early stage investigations to find out if there's a target.

Dr. James Cloyd: 07:16 Other funding could come from grants or contracts from pharma, and that too is important. And there are occasions where the NIH will provide funding at this earliest of stages. And then not to forget, internal funding within typically universities will also provide this starter funding to allow an investigator to explore a brand new approach to understanding the underlying triggers for epilepsy and seizures, and then ultimately identify a target.

Kelly Cervantes: 07:50 You know, I've read some of these proposals that Cure has gotten for the basic research and it's not always the sexiest of research. It can be very complicated and difficult to understand for a lay person, but this piece is so integral. And as a proud member of Cure's board, it, it just makes me so excited and so happy and so proud of our organization, that this is something that we prioritize.

Brandon: 08:25 Hi, this is Brandon from Cure Epilepsy. Since 1998, Cure Epilepsy has raised over $70 million to fund more than 240 epilepsy research projects in 15 countries. Learn what you can do to support epilepsy research by going to cureepilepsy.org. Now, back to Seizing Life.

Kelly Cervantes:	08:45	So the next phase after basic research is the drug discovery process?
Dr. James Cloyd:	08:53	Exactly. And it too is basic. I don't want to misrepresent just how early and how basic the process is. So these advances in understanding the underlying causes and triggers and mechanisms for epilepsy then hopefully will identify something called a target, that is to say it's a part of our biology where it seems that if we can intervene, we could have a new therapy.
Dr. James Cloyd:	09:24	And with that information, medicinal chemists using what's called computational chemistry can take a look at the target and then begin to design molecules, literally design on their computer molecules that might interact at that target. And in fact, you earlier referenced COVID 19 and the vaccines that are coming forth. That's very much the way in which these vaccines were developed early on. It was through understanding the virus, where it was vulnerable, and then how you would design a molecule, a vaccine that might result in a trigger for the inherent antibodies that we're trying to create with the vaccine. So that next step is to find a molecule generally through computation, computational chemistry, that could work at that site.
Kelly Cervantes:	10:22	So you're talking about a specific, they discover that there is a specific gene or a specific chemical interaction that is occurring in the brain, and they identify that, whatever it is, and decide that they are going to go in and intervene chemically.
Dr. James Cloyd:	10:42	That's right. That's exactly what happens. But I want to emphasize that this very early stage is often done, generally it's done through what's called in silico or through computer processes. So at this point, we actually haven't even synthesized the molecule. It's all theoretical.
Kelly Cervantes:	11:02	So who is doing this work? Where is it being done?
Dr. James Cloyd:	11:07	Again, academicians, and then more likely than in the very basic neuroscience research, this is also being done in pharma. And there are incredible scientists, both in large pharmaceutical companies and even smaller ones that have this remarkable capability of translating these advances in neuroscience into a potential drug. So those are the primary groups involved in this part of drug development.
Kelly Cervantes:	11:39	So we have the basic research. That is then used to identify some sort of mechanism in the brain that can ideally be

manipulated to prevent seizures from occurring. And then what happens next?

Dr. James Cloyd: 11:54 Then, the scientist, the medicinal chemist in general would propose one or more molecules that could be beneficial, and the next step in that journey is then to actually make or synthesize these molecules. And understand that even fairly simple molecules could be modified in hundreds, maybe thousands of ways. So very often, particularly in pharma, the scientist may make hundreds or even thousands of molecules that have the potential to work at that target.

Dr. James Cloyd: 12:37 And so the next step after that is you actually have to make the drug, you have to synthesize it, and that's not always easy. It could be a lengthy synthesis process, or it could be a very expensive process. And so it takes a bit of time to actually synthesize and make available these, these molecules, these chemicals, if you will.

Dr. James Cloyd: 13:03 And then the next step after that is you actually start to test to see if these molecules hit the target. And there's been an innovation in drug development over the last 15 or 20 years which is called high throughput screening. Now, high, here it means simply a large number, and throughput means a fairly rapid way to screen hundreds, maybe thousands of molecules to see which ones hit the target and how tightly and how avidly they hit the target. And out of that, you then begin to narrow down the number of molecules which you want to further investigate.

Kelly Cervantes: 13:43 So in this sort of preclinical testing phase, what are the specific goals? And again, who is it that's doing this research and who is funding it?

Dr. James Cloyd: 13:52 The goal of all this early drug development work is to try to narrow down the number of molecules so that you end up with something called a lead compound. And the phrase means exactly what it sounds. The compound is the drug, the molecule, and lead means it's your best bet at this point.

Dr. James Cloyd: 14:15 So you take that lead molecule, or maybe it's several molecules, and you begin a series of tests that now take you into laboratory animals. Usually these are animals where they have some type of seizure or epilepsy typically artificially created. Now, how do you do that? Well, you can do some manipulation of the brain, either chemically, clinically, or electrically. You can actually breed animals genetically so that they have a propensity for seizures. And whatever point you try, whatever

model you're, when I say model, a laboratory model, you then begin to administer these drugs to see, one, if they appear to work, and two, if they are reasonably safe. And as you move along, you may have to circle back to get rid of your lead compound and find an alternative because either the drug wasn't as effective as you had hoped, or it's creating adverse effects or toxicities that are unacceptable.

Dr. James Cloyd: 15:23 So that's the next phase is this testing in animal models to see if the compound is showing evidence of benefit. And that's really what your goal is as you proceed through this preclinical part of drug development is to isolate and get a compound that has two, three actually, characteristics; it appears to work, it appears to be safe, and lastly, you could actually make it into a drug product that humans can take. Again, there are academicians at major universities that carry out this work, but more and more as we move along, you're going to see that pharmaceutical manufacturers take a greater and greater role in this aspect of drug development.

Kelly Cervantes: 16:12 Now, is that because of cost or profitability, or both?

Dr. James Cloyd: 16:18 Well, cost is high for preclinical drug development, number one. Number two, a lot of this work isn't necessarily innovative. It's using techniques and research that have been well-described, and that may not be the kind of work that the NIH typically funds. Although there are exceptions where there is great unmet need, and in those cases, the NIH will step in and try to provide funding to carry out the necessary work.

Dr. James Cloyd: 16:51 Now, the last part of that is that these latter steps that we've described are highly regulated. They have to be done with great quality and great precision by FDA rules. And lots of university researchers don't have the resources to carry out the research at that depth and degree of quality, though I want to be clear, the work done in universities is of very high quality, but it may not be possible for an academic researcher to look at the safety in a thousand laboratory animals, whereas with pharmaceutical manufacturers, that is a possibility.

Dr. James Cloyd: 17:39 So those are some of the reasons why you begin to see this shift from academic institutions to pharmaceutical manufacturers. Now, there's one other element to this before that document, the IND is submitted to the FDA, and that is you need to get some idea of the kinds of doses you're going to use initially in humans, and you're going to need to show that you can make a product, a capsule, a tablet, a solution that has the qualities and then the requirements needed for use in humans, and that you

can actually make it, that you have some evidence that you can actually make the drug product that's needed.

Kelly Cervantes: 18:26 All right. So we have gone through our testing phase. We tested it on animals and now it's time to submit that IND document that you had mentioned to the FDA.

Dr. James Cloyd: 18:39 That IND has basically three elements. One, it compiles all the information you have that you've obtained during the preclinical phase. That includes the likelihood that it'll work, that it's safe, and by safe, I mean not only does it not have any typical adverse effects, these drugs are also tested to make sure they don't cause things like cancer or alterations in fetuses of laboratory animals.

Dr. James Cloyd: 19:11 You put that together, you put the information you have about the manufacturing of the possible product, and then the next phase is you propose in this IND what you are planning to do in the early phases of clinical studies. And then the last part of the IND is to provide information on the investigators that are going conduct these clinical trials in humans, including patients.

Dr. James Cloyd: 19:41 You put all of that together, and by the way, these are documents that can run thousands of pages, and you submit that to the FDA for their review. And that review often takes months or longer, but once the FDA agrees that it's safe, and I want to emphasize safe to proceed into human trials, the investigators, or in the case of sponsors, pharmaceutical manufacturers can proceed.

Kelly Cervantes: 20:09 So 20 years ago, there was just a handful of medications and therapies available to treat epilepsy. And then, within the last 5, 10, 15 years, all of a sudden we had seen this surge. I use that word lightly because, as we know, we still have one third of epilepsy patients who are drug resistant, but that there are more options available to choose from. What caused this surge, and can we hope for it to continue?

Dr. James Cloyd: 20:46 Well, let answer your last question first. I think undoubtedly it will continue, and there are three reasons why you're seeing this renaissance. First, the investment, made generally by the NIH, but other and also non-for-profit organizations such as Cure, in understanding the basic processes of epilepsy and seizures, because it's there that you begin to see where there could be new targets. And one of the very promising areas is understanding the role of genetics in the cause of epilepsy, particularly epilepsy syndromes.

Dr. James Cloyd:	21:24	So that area of science has just exploded, and therefore has opened up the door to develop brand new novel molecules for treatment. But there's also another process that's now gone on, and that's called repurposing. Repurposing simply means that you have a medication that's available, and by one mechanism or another, you conclude that it may be beneficial in epilepsy. And one of the ways in which you determine that is knowing some of these new causes. Basically, what it takes is taking these available medications, knowing how they work, and then linking that to these advances in basic neuroscience to see if a drug already available might attack a target, might work at a target that was not the original purpose for the medication.
Dr. James Cloyd:	22:19	And then lastly, and CBD is a really great example, is that families have become increasingly involved in looking at ways to treat family members who have severe seizures, and they're taking a look at what might be out there, what might be available. And it was in fact family members, parents, who were looking at some evidence that medical marijuana might be beneficial that triggered the research into the development of a prescription product for some epilepsy syndromes.
Dr. James Cloyd:	22:57	So that's the reason why you're seeing this explosion, if you will, in new therapies. And I think that the underlying reason for that is going to continue so long as we continue to invest in basic neuroscience research.
Kelly Cervantes:	23:13	Now, it is no secret that epilepsy research in and of itself is underfunded significantly compared to the number of people that it affects. Are there other programs that exists outside of Cure, outside of the NIH, outside of universities to really help push this along?
Dr. James Cloyd:	23:39	Yes, there is. And several decades ago, the NIH's Neurology Institute decided that in order to accelerate the development of new therapies for epilepsy, they would create a screening program and fund it through grants. The screening program was located at the University of Utah and has been in existence since then. The program offers anybody who has a compound that might be beneficial in epilepsy, the opportunity to provide that compound to the screening program at the University of Utah, and the scientists there would then undertake a series of tests to see if the drug works in their various animal models.
Dr. James Cloyd:	24:26	They do this at no cost. They keep the information that could be proprietary confidential so that the individual or organization submitting the compound will maintain the potential benefit from knowing how the drug works or doesn't. That program has

screened, as I understand it, thousands of compounds. And today, thanks to that program, we have a number of drugs approved for epilepsy that were shown to be effective through their screening program.

Kelly Cervantes: 25:00 But that's absolutely incredible. And it's heartening in some ways to know that this is epilepsy specific, that this type of program exists for all of those affected by epilepsy and seizures. I am just so grateful for all of the information that you shared with us today. I feel like I personally got a crash course in how all of this works and I'm just very grateful for your time and sharing your years of expertise and knowledge with myself and all of our listeners today. So thank you so, so much.

Dr. James Cloyd: 25:37 Again, my pleasure. This was an enjoyable session, and I just want to just compliment Cure on their focus in supporting both basic and applied research in epilepsy, particularly the development of new therapies. So thank you.

Kelly Cervantes: 25:53 Thank you. Thank you, Dr. Cloyd, for sharing your knowledge and expertise to provide us with an understanding of the early stages of the drug development process. Cure Epilepsy was founded with the understanding that basic science is the foundation on which all new therapies and drugs for epilepsy will be built. For over 20 years, we have supported scientific investigators and their ideas through our research grant program. During that time, scientists have accumulated a wealth of new knowledge regarding seizures and produced new drug options for epilepsy, but we won't stop until we've reached our goal, a world without epilepsy. To help us reach that goal, please visit cureepilepsy.org/donate. Your support and generosity are greatly appreciated. Thank you.

Brandon: 26:53 The opinions expressed in this podcast do not necessarily reflect the views of Cure. The information contained herein is provided for general information only and does not offer medical advice or recommendations. Individuals should not rely on this information as a substitute for consultations with qualified healthcare professionals who are familiar with individual medical conditions and needs. Cure strongly recommends that care and treatment decisions related to epilepsy and any other medical condition be made in consultation with a patient's physician or other qualified healthcare professionals who are familiar with the individual's specific health situation.