BroadcastMed | Grand Rounds: Chemistry to Clinic: The Nanosyn Approach to Bridging the Gaps in Translational Research

SPEAKER 1: So welcome to CTSA grand rounds. As many in the audience will be aware, and CATS and Mayo have entered upon a process of trying to enter the field of drug discovery. And as part of that, we've been searching for and finding strategic partners that span the spectrum of the drug discovery activities. And already-- we're about three or four years into it-- in my belief, it's transformed the way that Mayo investigators have done science.

Whereas previously investigators would do science with the goal of getting papers and grants, now there's a third goal. And that is to move their research towards developing new technologies and new therapies. And so today we have the great pleasure of hearing from one of our new strategic partners, Nanosyn.

There's been two Mayo investigators who have worked extensively with Nanosyn already. And so we're very pleased to have with us three representatives from Nanosyn-- Nikolai Sepetov, who's going to be giving our keynote presentation today. He's the CEO and Chief Scientific Officer. Olga Isakova, who's the executive vice president for business operations, and Kevin Greenman, who's the senior director for chemistry.

Time precludes me from going through all of the accomplishments for all three of these distinguished guests, so instead I'll talk a little bit about Nanosyn itself. It was founded in 1998 by Nikolai and Olga. And their activities span, truly, the breadth of the drug discovery spectrum, from high throughput screening, to lead compound optimization, medicinal chemistry, GMP facilities, and now they're entering the domain of looking at epigenetic regulators-- all of which are key tools for the Mayo clinicians to use.

They've already subcontracted with numerous groups in academia, big pharma, and, as mentioned, Mayo. They have offices on the West Coast and offices in Research Triangle Park. And we look forward to hearing the presentation. And the purpose of today's presentation is, really, is an introduction between Mayo investigators and our friends at Nanosyn, but also to spur new collaborations and new partnerships. So Nikolai, welcome and thank you, and we look forward to your presentation.

NIKOLAI SEPETOV: First, I would like to say, I'm extremely honored to be here. We have two collaborations with Mayo Clinic. And one of, probably, the biggest impressions of my last year was our visit to a Mayo Clinic in Scottsdale. We have multiple, multiple collaborators, and this is a scientific discussion.

You have your teleconference, when you have some scientists on either side. You are discussing some scientific issue, and we had multiple discussions with Dr. Stuart. And he is a good scientist with very sharp thinking. And it's nice to talk with him on teleconference.

I'm coming in Scottsdale, and we are going, and he sees his patients, and they're looking at him with respect and hope. And I was so amazed, you know-- you are a doctor. You are cure disease. And in the same time, you are a scientist, and you are working.

This is amazing. And I respect you so much. And I feel great honor to be here, and to tell about what we are doing, and what we can do together.

I have in my presentation three parts. I always like to tell people what-- actually, I would like to discuss. First part of this is to present to us, and to present how we see drug discovery today, because it's very different from what it was tomorrow.

Second part, it will be a presentation of only a few technologies which we have, and as this is a very tiny piece of what we can offer, I will use them because after this, we'll have two case studies. We have two collaborations with [INAUDIBLE]. And we use this technology for this collaboration. And I would like you to be familiar with this because, to say, only, we are using fragment screening without understanding what is this, probably it's not a good idea.

And after this it will be two case studies. And they're very different, and they're different on purpose. Because, usually when we have doctors coming to us, they have two pretty different ideas. One of ideas is about targets because they studied some disease, and they found something which may cause this disease, and they would like to study this target to find something which will work.

Second group of people which are coming to pass. This is people who study something. They found a compound which has interesting properties, which can do something very useful, but it's not ideal because this is patented, because this is not active enough, because this is not selective enough, and they need us to help make this compound more valuable and move this to a next step of development. And I will have these two case studies, which will reflect both of [INAUDIBLE].

This slide is disclosures. I have absolutely nothing to disclose. I don't have conflict of interest, and I can move to my next slide. What I would like to discuss here. I would like to discuss how to do drug discovery in environment of academia or a small biotech company. Because this is very different from big pharma, when you have all tools. You have a lot of funds which allow you to do-- and we are talking about, what you can do small players.

And when I'm saying small, this is more about finding, but not about ideas which you have. And I would like to discuss how you can move, and you can move pretty successfully, even if you don't have everything what you need for this, and how to make these with small, manageable units, and to move from one step to another step, moving the approach. We'll talk a little about our screening technology, and we'll talk about how we can collaborate.

I included this slide on purpose, because you see this probably 100 times. And I'm not willing to discuss this because every time when we are coming to this slide, people are a little scared. They are saying, OK, this is at least 15 years. We need to have at least one billion money to develop any drug.

And actually, this is not about us, because you and us, we are on the left side of the flight. We are doing pre-discovery. We are doing early drug discovery. When it will come to do phase 1, phase 2, phase 3, it will require billions, or millions, of money, and it's done much better in big pharma than done in academia or [INAUDIBLE].

From [INAUDIBLE], we will discuss about left side of this. But what is important here, this is how to move your project to a moment when big players will be interested. And this is probably key for what we're doing here. And actually, we see pretty clear substantially changed landscape in drug discovery.

First, big pharma is going away from early drug discovery. First, this is too risky, to long away, and, even now, more than 50% of all drugs originated in academia or small offices. You have much more small company, you have pure virtual company.

We have companies when people, four or five people, they don't have even lab. They have only offices. But they are coming with ideas. They understand what has be done. And after this, they can outsource work which they are doing.

Foundation of academia. It's taken a bigger and bigger role because of their deep understanding of biology and because it's changing in a landscape of [INAUDIBLE]. We are saying, actually, the idea fully integrated companies, when you have in one company chemistry, biology, pharmacology, which will need to have funding of dozens or hundreds of millions of dollars to develop some drugs-- that's actually changing for smaller, lean companies which can have the core expertise, which know what has to be done, and everything else done outside of this.

And obviously, this required to have a contract research organization, which can take some work load from these new players because you don't need to have HTS for all the life of your project. You need to have HTS at very beginning, when you will discover something, and, after this, you'll need to have another species which will help you.

And this is not related to drug discovery. This is related to lean thinking. I would like you to think about your project very differently. Not extensive when everything comes with-- we put in project and, after this, we will see.

How to combine mass production when we need to have-- HTS when you need to have 100,000 compounds to screen with very focused development, when you need to do this. And to make an efficient way, this is probably not only science-- this is not pharmacology. It's not chemistry or biology. And I would advise to read this book, excellent book, and, you know, to think about how you will organize your project.

About our company. We are 17-year-old. We started this, the two of us. Now we have 70 people. We have our discovery in Santa Clara, and we have our [INAUDIBLE] facility in Santa Rosa. We have multiple compounds, which we moved from very initial stage to defilement to clinical study. And we have compounds which were developed with us, and now these own market. We we'll talk about this in a few minutes. More than 50% of them have PhD degree.

And last three, which may be important, we are completely US-based. It means your intellectual property will not go outside. We are not doing drug discovery ourself. Our best scientists will work for you.

And at the very beginning, we decided we will not take any IP from our operator. We are paid as money. We are helping you to develop new drug. And we would like you to keep rights for your drug because you will need to have these rights to progress your project later, when you need to share these rights with a bigger player. And for this, you need to keep everything in your hands.

Started 17 years ago doing only chemistry. In 2008, we acquired [INAUDIBLE] discoveries of our partner, but it will allow us to build our biology. [INAUDIBLE] this year, [INAUDIBLE] from stage to stage, the moment when our compound is going to clinical trials, and our client will say, guys, when will you have your GMP?

Now we have GMP. It means we can take your project to phase 1, phase 2, and we have even commercial product. In 2011, we move in to a new building, and now we are doing more and more integrated drug discovery when we are taking project from very beginning, and we are providing biology, chemistry, scale up, and [INAUDIBLE] production.

More than 200 customers in these 17 years. Very big players, biotech companies, and you see, on bottom of this, we have a lot of academia. We know how to work with people who do not have industrial experience. And we are ready to share this experience.

And you understand this is probably the most successful biotech, but it was 150 were not successful. But we know the experience. And we would like to share this experience because you don't need to repeat mistakes which other people are doing.

And we had a very successful company, and maybe the most successful company, what we have, this is Plexxicon. And I would like to talk a couple of words about this. They are our client for 15 years. They develop a BRAF inhibitor, and you see what happened in this patient before and after.

This is a great success. This is good for patients. This is saving people. But this is also a financial success because they spent $70 million in all these 10 or 15 years, and they were sold to [INAUDIBLE] for $1 billion.

And how they managed this? They managed this with making this step by step, moving project from a small population of patients to a large population of patients.

And during today's discussion, we had multiple times when I said maybe we need to learn something from this, use this, and it will help us to move [INAUDIBLE]. A couple of technologies which we will discuss later. As I said, we acquired Amphora Discovery. And Amphora Discovery it was a spin-off of [INAUDIBLE]. They are doing microfluidics.

They took $100 million and built a factory to do HTS-based on high throughput screening. They made mistakes, which I would like you to avoid. They went too broad, and they burned $100 million.

And we acquired them, which is good for us and good for you because you can use now these resources for your research. And we have a library. We have 200,000 compounds which we can use. We have HTS factory. And we have a lot of assays which they developed. Most of these assays are based on microfluidics technology. And I will take a couple of words to tell about this.

Microfluidics technology, this is the best way to screen, biochemical screen. What we are doing? We are taking your substrate. This substrate has to be fluorescent labeled. And in many cases, this is peptide.

After this, you are mixing this substrate with an enzyme. You wait until reaction will proceed. And after this, you inject in-- I'm sorry, I might.

We have on right side, this is microchip. We will [INAUDIBLE] from plate. And we'll separate your product and substrate. And you will have a picture which we have on right lower corner when you can measure concentration of your substrate and [INAUDIBLE] of your product.

And now, if you will add any compound which will change this ratio-- for example, [INAUDIBLE] less product, it means we have an inhibitor, and you can measure this. If you an activator, it will be in the opposite direction, and you can measure this. And you can measure this very precisely.

And you can use this safe for kinases, phosphatases, [INAUDIBLE] enzyme [INAUDIBLE], and you will change mobility of substrate. And you don't need to read everything what is here because the most important is-- this is extremely precise.

We can measure this ratio with precision of a few percent. It means you can detect very, very low inhibition or [INAUDIBLE]. And we have largest in the world [INAUDIBLE]. We can screen millions of compounds.

And we can not only screen millions of compounds, but we can profile a lot of compounds because we have already more than 500 assays which are in place and may be done any moment when you need to do this. They may be done on an HTS mode, when we will screen these, or they can be done on profiling mode, when you need to know what component, actually, you already got, and if it will have [INAUDIBLE].

And we have 300 kinases. We have a lot of epigenetic targets. Actually, it's increasing every day. We have [INAUDIBLE]. We have around 70 proteases and so on. And from this point of view, if you have something which you need to measure, visit our website. Maybe we already have this assay, and we don't need to do this.

If we don't have assay, we are developing this, and we will discuss this in a few minutes. Second technology which we developed and we have our own twist of these technologies-- this is fragment-based drug discovery. This is probably the most interesting direction in medicinal chemistry and drug discovery.

To develop something you need to have a starting point. Before starting point, people we're making mostly by HTS. You are screening 1,000, or 100,000, sometimes a million compounds. You are finding some compound, and after this, you can optimize this.

Analysis of [INAUDIBLE], it was done multiple, multiple times, and, very often, heats which are coming from HTS, not good enough. You cannot develop a drug for them because it will be not efficient enough. And people started to think how to increase probability success for these, and they started to move to idea, for development, we don't need to have final compound. We need to have [INAUDIBLE] compound-- compound which is similar to a drug, but smaller it may be.

And next step, it was the development of the fragment approach, when we are taking very small pieces of molecule, and you are screening these, and you are trying to find hint of what may be active. And this technology is now very popular, and it has different colors.

Sometimes it's used in structural biology, when you are using x-ray to determine how exactly it will be. We are using this in a slightly different way. We are trying to understand what is important for interaction. And after this, it allows us to make our HTS much more focused and much more efficient. Because we are small players.

To screen one million compounds around at $0.50 each, this is half a million. If you can achieve the same screening small amounts of material, it will allow you to move to the next level much faster, which is very, very important for us.

To do this, we are using an extremely high precision of microfluidics because most of people would like to measure IC50. And for IC50, you need to have, sometimes, a pretty high concentration. We can measures this extremely precisely. And, in this case, we are detecting a very small change in activity of our enzymes that to allows us to do this.

We are doing this also differently because we have [INAUDIBLE] microfluidics machines. And in this case, what we can do? We can take the same collection of compounds and screen it against multiple targets, and screen against our target. After this, you have information not only what is compound making with your target, but also what is making with another target, which allows you to think about if I would like to take this component in development, if it's promiscuous.

What is important for my task today-- activity or selectivity? And we are using this. And it works pretty well.

[INAUDIBLE] technology, which we will discuss today, this is high-speed chemistry. Every time we are doing drug development, you have a few cycles. You are designing your compound. You are making your component. You are screening your compound, and you are designing the next compound based on these data.

And it will be done on a different level of drug discovery. At a stage when you have heat expansion, it means you found an original compound, and you need to select which series you will take in development. You will do absolutely the same when you will do lead optimization when you have less compounds, but in any case, it will be cycles which you need to repeat.

And the key is to make the cycle as fast as you can. Because, at this moment, you are not interested to have high yield chemistry. Because when it comes to process development, you will need to make kilos of material. This is important. On this stage, time and efficiency, this is the most important.

And we built infrastructure which allows us to produce multiple compounds. We are making up to 3,000 compounds per week for multiple projects. And we are doing this [INAUDIBLE] and our chemists-- and we have extremely good chemists-- they are making these compounds. They are not trying to optimize synthetic route. And we are using a lot of instrumentation.

We have 20 [INAUDIBLE] machines, which allow us to take these compounds, [INAUDIBLE] these compounds, and move this to screening because we would like to get information as early as possible because, after this, we will design next compound. And for these, we have a lot of starting reagants. We have a lot of instrumentation. You have a lot of processes, and it worked well. And it worked well for all of these 17 years for which our company has existed.

And now we are coming to two case studies. First, it was this Dr. Stuart from Scottsdale And before we'll go to real data-- this is how small players have to work.

First, you have to look at your project and split this project in manageable units. Because you don't have money to move project from very beginning to very end. And so you need to decide what you will do on every step and increase value of your project. And always, the increase of value has to be more than money which you spent to move from one step to another.

And in this case, this is a target-centric project. When Dr. Stuart sees his patient, measures something, and he's finding some target which may be important. And he's saying, OK, first what we need, we need to have compounds which we would like to use as drug in the future.

But what do we need for this? First, you need to find a starting point. Second, you need to see your starting point, it's good enough to support your development. And after this, you need to develop this to a stage, when you have intellectual property. When you have something valuable which you can fight for.

And, from this point of view, on this state of the target, you have only three parameters which are important for you-- activity, selectivity, and IP. And as usual, you have a limited budget and you have very tight time line. Because if you will develop these later than your competitors, it's not good enough.

And usually, interesting ideas are in the air, and if somebody started to work, especially in the academic world, you know, other people, you know, also thinking if it may be important for here. And here this is a limited budget. In a few months, and we have to move this.

This is real time line. From moment when Dr. Stuart came to us, and moment when we were [INAUDIBLE], because it was a new target, do fragment screening because limited budget, we cannot screen 100,000 compounds. We decided to make this only 30,000, because it was fund which was available.

Doing HTS itself, and to conform everything what we worked, this is real, it took from the end of March to beginning of June.

First, we need to develop an assay. How are we developing an assay. I said, we have microfluidics technology. And in this case, we are converting our substrate to product. And we have to separate them. And we have largest in the world collection of substrate for microfluidics.

We are putting all of them in [INAUDIBLE]. We are screening, and you see most of compound-- red, this is enzyme. Blue is without enzyme. And most of substrates do not work. In disease case, you have only one peak.

But if enzyme is working, you have two peaks, and you understand, this is substrate. You have your substrate. You're optimizing. You are determining everything what you have to do-- you know, [INAUDIBLE] and [INAUDIBLE] coming to HTS.

We run around 150 HTS campaign at around 100 fragment campaign. We know how to do this. You don't need to worry about this. We will determine operands. We will prepare this for screening.

And in this case, at first we screen a fragment library, which allows us to find key features of future molecules. And after this, we went back to a diverse library which we have. We have a 130,000 compound library. We selected plate which may have compound which have a higher probability to be active.

And we screen these, confirm these, screen-- and, for this project, for this project, we have a new target. And for new target, it's important to find a highly selective compound. A highly selective compound, you need to proof your concept. You have to prove compounds which you make working on this target. And this is key for this disease.

And to be sure we have this, as I said, we acquired assets off Amphora. And Amphora has 130,000 compound library, which was screened against 100 targets. It means, when we are finding new hits, we have instant selectivity. We have already the 100 targets, which we know it was screened, which is not active.

This is a statistic for this. And we screened 30,098 compounds. And you see, we have pretty good hit rate. And we have more than 200 compounds with six times [INAUDIBLE] noise, which is more than enough to do. Extremely important step, when you need to have professional experiences. This is, you have 200 hits. And after this, you need to select series, which will be good to take in as a development.

And this is not, I like this, and I don't like this. This is [INAUDIBLE]. This is potential issues. And this is economy because you need to move fast. You need to have something which-- and this is series 1, which has good activity and selectivity. Good IP issue.

But probably, with synthesis, because difficult to synthesize this. And second, what is only very experienced medicinal chemists can say-- OK guys, we might have a potential problem here because we have doubled bond b in [INAUDIBLE], it means it may be nonspecific interaction with something.

And from this point of view, not throwing away, but this is priority [INAUDIBLE]. And we have multiple series, and issues of series will be analyzed, checked, and we have these, IP, so-so because many examples. But easy to synthesize.

It was not referenced to our target, and our target is GRK6. And [INAUDIBLE] for kinases. It means we are pretty good on IP, even structured itself. We are taking this, and, again, don't pay attention on all the details because it was prepared for some project meeting. And we can expand this series to a matter of days.

We got compound, 18 animals, excellent selectivity against 230 kinases which we have here. And now we can use these compound, first, for our target validation, because we can use these and say, OK, it's hitting only this enzyme, and it's still in cancer cell, and, high probability, it may be a real target.

Second, Because it's come apart. And we can take this component in further development. In this case, we are thinking about drugs. It depends on funding which you have, how much appetite you have for drug discovery.

And, if you decided to take second route, I have to tell-- from the very beginning-- this is not easy. Because, if from very beginning, [INAUDIBLE] concentrated mostly on activity, selectivity, and IP, now you need to worry about cell-based activity, about physical chemical properties, about stability, about off-target activity, and so on, and so on.

But it's possible. We did this multiple times. And if you decide to do this with us, we will be ready to help you.

Second project, this is this Dr. [INAUDIBLE], which was very different. We have molecule. And it was multiple research already with this molecule saying this molecule is extremely good for something. I'm not biologist, and I will not go into details because now we are discussing strategy.

Even patent exist for this. But it's already existed for many years. It means, if you will take this molecule and move this molecule in development, at the moment when you will have your drug, you will have only one year to recover all costs, which is far not enough.

And from this point of view, most of pharma companies simply will not take this. Not because chemist is bad. Not because of Sciences. But everything is fine

but this is real world. And you need to think about how the drug industry works. And it may be not only a short patent life. Compound may be not active enough. It may be not selective enough. It has some not desirable property. And this is situation when we have something, and we need to improve this. And we need to improve this creating new IP because, without IP, nobody will take this in future development because it costs a lot of money. And you need to recover them.

The same problem, not enough money because nobody is yet interested. It may be more. When you will prove what you are doing, this is good enough. And you have to understand, if you have a molecule, and you are planning to change something, it will be two consequences.

First, I've had a lot of discussions about repositioning a drug. And people are thinking, OK, we have a drug. Now we will take this. We'll make it slightly better. And it will help us. It will not help us because, if they will consider this as a new component, then you have to start everything from the beginning. You know, you need to do toxicology studies, [INAUDIBLE].

Second, every time when you are making even a small change in your molecule, it will change everything. It will change interaction with your target. And you need to think about activity. It will change physical chemical properties. It means that it will be distributed a different way. It will change interaction with another target, and you to need deal with this.

But its the same model approach. You have to say, I cannot solve all problem. I need to solve them one by one. First problem here, it's already solved because we have hit. This is not a Dr. [INAUDIBLE] project when we need to develop something. In this case, we have compound CP2, but now we need to change this.

In this case case, we are starting with heat expansion. And after this, we will [INAUDIBLE] some compound which we can consider as potential-- I would say, advanced heat. We need to optimize this to move this on next level.

First, we need to find a compound which will be active enough. And for this, you have to use something which you can do because, obviously, in this case, we have proof of concept in animals. But to take this component and use this in animals, it will be too expensive, and if everything will work fine, its fine.

But what compound which is [INAUDIBLE] not active. It may be not active because it's not active, because it's not penetrate inside, because its just not stable enough. And in this case, you have to choose cell-based screening. I would prefer to use this as a biochemical screen to confirm activity.

But in this case, lack of targets, which was clear and [INAUDIBLE] this moment. Now, the situation is changing. In this case, we are using cell-based screening. [INAUDIBLE] synthesizing some compounds. We have CP2, and we see some of the compounds working the same as CP2, some of compounds much worse, but some of compounds even better.

And now, we are can this compound and what has to be next step? Logical way, it has to be in-vivo model. [INAUDIBLE] not, because if you are [INAUDIBLE] in in-vivo model, and it does not work, you don't know why.

And the next step has to be something which is not exciting but has to be done. You need to see stability of your compound. You need to see if your compound will penetrate in brain. Because it doesn't matter how good your compound is-- if it's not a place of action, nothing will happen.

And we are doing this, and you see our compound, its good enough. They are stable enough. They penetrate in brain.

And in this case, now we can move to next level. And now you need to cross your fingers because if it works, it works. And in this case, it works.

If it does not work, you need to go in square one, and you can to rethink your approach because, if your biochemical screens say it compound is active, if your stability screens saying compound is stable and penetrate, and if it does not work, maybe your hypothesis was not right, and you need to start this. In this case, we are in a very [INAUDIBLE] situation, and we have here.

Actually, it's supposed to be s.k. study it supposed to be case study when they are taking advanced heat and moving these two pre-clinical candidates, this is work which was done by Kevin in the last three years.

We got exciting results. You know, we had a very difficult target. It was moved. It was licensed, but we were not allowed to talk about this today. They are planning to make an announcement themselves, and--

And if Dr. [INAUDIBLE] project will continue, what will happen? We have very exciting result. But this is not an end of road because, after this, you need to set criteria, which you have to meet to move this compound to clinic. And this is a criteria about activity, about [INAUDIBLE] properties, about selectivity. This is a long way. But even now, we are in project which has some value. And probably, somebody may be interested and invest money to move this project.

This is our conclusion, what we have there in good place. Filing patent in progress. And all rights belongs to my team. What will happen next? May happen, may not, we have some example when it's happened.

You can come to us and say, guys, now we are ready to move in clinical trial. We need to have compound, which will be synthesized, and facility which you prove to FDA. We have this facility. It's approved more than 30 years.

We have process development group there. We can develop process. We can synthesize compounds, and we can provide these compounds for clinical trials. And we can make this from grams to kilograms.

This is done-- this is a joint venture with a French public company. It means we can move your compound even in [INAUDIBLE] production. But I'm looking at what you are doing here. And I understand, probably, the diagnostic development may be very beneficial for your organization.

But, in this case, we may be very good partners for you when we have [INAUDIBLE] facility, which allows us to produce diagnostic. And we have a couple of commercial products with Abbott diabetes care.

I would like you to think about full cycle, when we will discover something. We will help you to develop, and we will move this in a market together. And I supposed we have, if not, but most of tools which you need to move your project from current moment to great success.

And I made this on time. And I'm ready to take any questions.