On the Hunt for Modifiers

寻找修饰基因

Monica Coenraads & Dr. Neul Discuss a Newly Funded Project

MC: Hello everyone. This is Monica Coenraads, skyping in from Connecticut. I am the Executive Director of Rett Syndrome Research Trust and I'm speaking today to Dr. Jeffrey Neul. A lot you will probably already be familiar with Dr. Neul . He is the co-director of the Rett Clinic at Texas Children's Hospital. He's currently running a clinical trial and some of many of you may also know him from the natural history study. Good morning Dr. Neul. Thank you so much for joining us and taking time from your busy schedule.

莫妮卡：各位好。我是莫妮卡，从 Connecticut 州使用 sky 连线通话。我是 RSRT 的执行总监。今天，我要和 Jeffrey Neul 博士谈谈。你们当中很多人可能已经很熟悉 Jeffrey Neul 博士了，他是得克萨斯州儿童医院的 Rett 诊所的主任。目前，他在进行一个临床试验，你们可能已经从 rett 的自然发展研究中认识他了。早上好，Jeffrey Neul 博士，非常感谢你百忙之中抽出时间参与这次探讨。

JN: Good morning and thank you for taking the time to talk with me

Jeffrey Neul 博士：早上好，也谢谢你腾出时间与我讨论。

MC: So today we're going to be talking to Dr. Neul about a new project that RSRT and Dr. Neul are launching and it has to do with the topic that many of you have heard about already: the search for modifier genes. RSRT has been funding for a number of years a project on in the lab of Dr. Monica Justice who is using mouse models to try to identify mutations in other genes that lessen the severity of having no MECP2 or a mutated MECP2. Because the cost of sequencing and has gotten more manageable (cheaper) and also because the bioinformatics capabilities are much greater, we can now start thinking about home looking for modifier genes in human patients. So this project Dr. Neul will be spearheading is going to sequence the exxome of high-functioning children who have any MECP2 mutations but whom wouldn't naturally be diagnosed with Rett because they don't meet the criteria. In the hopes that we might be able to find secrets in their genome that might help other kids because it would open up potential targets for therapeutics. So the three-year project with a $350,000 budget. Let's jump in, Dr. Neul, I'd like to start us off by asking you if you can just tell us a bit about nuts and bolts of this project.

莫妮卡：今天，我们要和 Jeffrey Neul 博士讨论一下他和 RSRT 发起的新项目，这是关于你们已经听说的一个主题：寻找修饰基因。RSRT 已经多年资助 Monica Justice 博士实验室，他们使用老鼠模型来寻找在其他基因上的，可以减轻缺失或者突变的 mecp2 蛋白的症状严重程度的基因。由于基因测序的成本日渐可控（更便宜），也因为生物信息学的长足发展，现在，我们能够开始考虑在人体上寻找这样的修饰基因了。Neul 博士将会对那些有 mecp2 突变，但是功能却很好的孩子进行外显子测序。这些孩子并没有被诊断为 rett，因为他们没有那些典型症状，但是，确有 mecp2 突变。我们希望能够找到那些基因上的秘密使她们免于 rett 症状，这将为其他的 rett 孩子打开治疗的途径。所以，我们有了这个为期三年，35 万美元的项目。Neul 博士，我们来问你些问题，你来告诉我们关于这个项目的一些基本原理吧。

JN: This project really came about because I had found people in my clinic who are coming to see me who were referred because they had mutations in MECP2, common mutations that cause Rett Syndrome, and these people didn't have Rett Syndrome. It really fascinated me why you could have such variation in the clinical presentation. You could have people who maybe were diagnosed with autism or pervasive developmental disorder yet had that same mutation. There are a lot of potential causes and we ruled out the ones we knew like X-chromosome inactivation in these people. That didn't explain it so there must be something more. So I was interested in trying to figure out how to find genetic modifiers. Here Baylor College of Medicine, I was very familiar and initially started helping Monica Justice with her modifier strain in mice a so obviously that's a great avenue, an idea that there are genetic modifiers in Rett Syndrome that may make the phenotype, the clinical features, less severe. If we can find it in mice, I think that idea would be that maybe we can find in people. As you said, the exact details of the technical aspects in terms of sequencing and bioinformatics has advanced dramatically to make this I'm a realistic idea.

Neul 博士：这个项目是源于我的一些发现，一些来我的诊所就诊的病人，是由于发现了 mecp2 的突变而被引荐过来的，这些突变都是常见的会导致 rett 的，但是她们却没有 rett。这很使我着迷，为什么她们在临床上有这样的表现。他们可能是被诊断为自闭症或者全面发育紊乱，但却有和 rett 相同的突变。这有很多潜在的原因，我们也排除了诸如 X 染色体激活模式不同的原因。这无法解释，一定有其他原因。这样，我就非常感兴趣去尝试如何找到基因上的修饰者。在 Baylor 药学院，我很熟悉，而且最初也帮助 Monica Justice 在老鼠身上寻找修饰基因，想法就是 Rett 综合征的修饰基因使得她们的临床症状没有那么严重，很明显，这受益匪浅。如果我们能在老鼠身上找到，我想我们可能也能在人身上找到。如你所言，测序与生物信息学有了长足的进步，使得这个想法变得现实。

So the nuts and bolts of it is that we are through the natural history study, which has been an ongoing project funded by the NIH and IRSF, we've accumulated a very large amount of clinical data on people with Rett Syndrome and so we looked at that and said we can take people who are clinically very severe or very mild, so they are at the ends of the distribution of severity, and try to use those as the subjects to sequence all the genes in their body. Now the issue that we have, and one of the big challenges moving forward, is that although that [the Natural History Study] has been a great resource to get a number people to do this study, we still want to capture more people. From the Natural History Study, we can probably identify about a hundred people total on the two ends, fifty people who are more severe and fifty people who are milder, who have typical disease-causing mutations but we know that there are a number of other people out there who had mutations who are so mild maybe they even have been recognized as Rett. So one of our big challenges is to tap into those groups of people and recruit then to do this study that I am describing now.

原理就是我们通过自然发展研究（这是 IRSF 和 NIH 资助的正在进行的项目），积累了大量临床数据，这样，我们能看到那些临床上很严重或者很轻微的病人，她们在严重程度分布的两端，用她们作为研究对象，测序她们的基因。现在，我们前进中遇见的巨大挑战就是我们还需要更多的病人进行研究，尽管自然发展研究项目提供了相当多的病例。基于自然发展研究项目，我们大概能找到在两端的一百个左右的病例，50 人很严重，50 人较轻微，这些轻微的患者具有 mecp2 突变，但却表现出很轻微的症状。我们面临的一个巨大的挑战就是招募这些病人参与研究。

MC: So can you tell us since were able to also go outside Natural History Study and tap into other kids, I think it is going to be really important to figure out what are the criteria that we're going to be looking at, what symptoms are you looking at? So can you tell us a little bit about the type of individual that we're trying to find so that if someone watching says this says hey, that that sounds like my child? What are we looking for?

莫妮卡：既然我们能够超越自然发展研究的范围，招募其他的病人，我想你们要寻找的病人的条件就非常重要，都有哪些标准，有哪些症状？能告诉我们一些你们要寻找的个体的类型吗？像我的孩子，她能说“这个”，或者“嗨”。你们要找什么样的？

JN: It's a great question and a challenging one because we only have very broad strokes of what kind of things would look for. What I would say is that we want to find anybody who has a mutation MECP2, especially people who have a mutation in MECP2 who do not meet the clinical features of typical Rett Syndrome. There are a handful of these people and I think they're hard to identify because we had yet to identify real distinctive characteristics.

Of the people that I do know of, they have a variety of social interaction abnormalities, some learning problems, and the degree of severity can be variable. We had some we had one child who really was very rather high functioning, had some obsessive-compulsive and attention issues, but actually had a relatively normal IQ. Whereas some of the other children had pretty severe autistic features and they spoke but only in very short sentences, but didn't have any hand problems. So I think we have to cast a broad net and it's hard for me to tell exactly clinically. The one thing I will say is that more and more girls who don't have the clinical features of Rett Syndrome for are getting tested for MECP2 mutations. So we're identifying more these people. So if those people ever show up, we would love to hear from them and try to enroll in this study.

Neul 博士：这是非常好的问题，也是很有挑战性的。因为我们只有对于要招募的个体的非常宽泛的描述。我能说的是，我们要找有 mecp2 突变的任何人，特别是是那些没有典型的 rett 临床症状的人。有这么一群人，但是非常难以识别，因为我们没有真正的识别特征。就人们目前所知，症状包括社交异常，学习问题，但是严重程度的差异也很大。我们有一个病例，具备相当高的功能，有一些强迫症和注意力方面的问题，但是，却有相对正常的智商。然而，另外一些孩子，有很严重的自闭症特征，她们仅仅说很短的句子，却没有任何手部问题。所以，我认为我们必须广撒网，我很难确切告诉你临床上的症状。还有一个我要说的就是越来越多的孩子并没有临床上的 rett 症状却被查出 mecp2 突变。所以，目前我们在寻找更多的这样的人。所以，一旦他们出现了，我将会非常乐于知道他们，并且把他们纳入我的研究。

MC: These might be kids who have language even though it's not at age level but who have language, who motorically, are in pretty good shape, who walk and run, who can climb the stairs, who have some hand function.

莫妮卡：那就是这样的孩子：她们有语言，但也许和年龄不相称；运动能力不错，能跑能走，能爬楼梯，有部分手部功能。

JN: All those things definitely

Neul 博士：正是。

MC: Let's be broad and give you an opportunity to assess them and rule them in or rule them out.

莫妮卡：那就让我们宽松一些，使得你有机会去评估她们，来看看是否纳入她们进入研究。

JN: Yes.

Neul 博士：是的。

MC: If I and others, through things like social media, get the word out and if parent says this could be my daughter what do they do? What should they do?

莫妮卡：如果我或者他人，通过媒体什么的，知道这些，然后说我的女儿可能是（他们要找的人），他们应该怎么做，做什么？

JN: A very easy thing to do is contact RSTR and I know that RSRT will definitely put them in touch with me. They can also directly call the Bluebird Clinic at Texas Childrens Hospital (the number is 832 822 7388).

Neul 博士：非常简单，联系 RSRT，RSRT 会和我联系。他们也可以直接联系得克萨斯儿童医院的蓝鸟诊所，电话 832 822 7388

MC: And ask to speak to you?

莫妮卡：直接与你对话？

JN: Yes, they can leave their information. If they can't get in touch with me [directly], the office will get in touch, and I will get back to them.

Neul 博士：是的，他们可以留下他们的信息，如果他们没有能直接与我联系上，办公室也会联系我，我会回复他们。

MC: As you suggested, they can also contact me at RSRT and I can start to put some preliminary information together and pass it on to you. Do you think that you will have to see these kids in person or do you think with Skype and videos and talking to the parents you'll be able to get a clinical picture?

莫妮卡：你建议是他们可以联系我，我能整合一些初期的基本信息，再转递给你。你觉得我们必须要亲自看看那些孩子吗？使用 skype，或者录像，或者和家长对话，你能做一些临床了解吗？

JN: I would love to see people in person but I understand the challenges of traveling and so I think we can try and work out things that can be done by phone calls, Skype, exchanging medical information and I think I can make a pretty decent assessments if they're not meeting the situation for Rett Syndrome.

Neul 博士：我非常想亲自见见这些人，但是我也理解旅行是一个挑战。所以我想我们可以尝试通过电话，skype 来完成，交换信息。我想我能做出非常正式的评估，如果他们并不具备 rett 的症状。

MC: One of the aspects of this project that I found attractive is that all of the sequencing data and all of the phenotypic data will be deposited in a database, the national database for Autism research which is an NIH funded program, and will be available to the scientific community. I think is really valuable to share this information. Can you speak to that a little bit and also addressed what safeguards are put in place to protect the genetic information of individuals?

莫妮卡：关于这个项目的另一个我觉得有吸引力的方面就是所有的测序数据，所有表征数据都会存储在数据库里，就是 NIH 资助的自闭症研究的国家数据库，这些数据也会对科学团体所开放。我想分享这些信息是非常有价值的。你能说说并且解释一下这些个人的基因数据有什么安保措施吗？

JN: Sharing genetic information amongst researchers is really critical because any one individual may not be able to really understand everything in genetics and I think that it's become the standard practice that genetic information is deposited into databases for other researchers to tap into, and for them may be explore it in ways that the primary search didn't think of in the first place. Now this does raise certain safety issues of privacy and concerns like that, but I'm we try and the NIH has devised a variety of methods to try to prohibit people using this information in ways that they shouldn't. This means using it in for discriminatory practices or denying insurance, and so really there are no names associated with any of the information that's placed there and although it's "a public databases", it's actually not just broadly available. You have to be approved researcher to be able to access the data and so there's a standardized process to go through to establish that you are really somebody who has a legitimate scientific reason to look at the data. So there's no names, and the access is really restricted to legitimate scientific purposes.

Neul 博士：在研究者当中分享基因信息是很重要的，因为任何一个人可能都不能真正了解基因学的全部。我想，和其他研究者分享数据库里的基因信息，也使他们可以第一时间用主流以外的方式探索这些数据，这已成为一种标准行为。这就引起一些隐私方面的安全的担心，但是，NIH 已经使用了多种方法以禁止人们以不当的方式使用数据。这意味着不能进行歧视性的行为，以及用来拒绝给予保险，而且，任何信息都不和姓名相联系。尽管它叫"公共数据库"，也不是那种广泛的"公共"，只有被批准的研究者才能进入数据库，

还有一套标准的流程来确认你确实就是那个合法的科学目的来查看数据的人。。总之，没有姓名，权限仅限于有合法的科学研究目的的。

MC: Now the concept of modifiers certainly is not unique to Rett Syndrome. This is a well-known genetic scenario that that happens probably in every disease, right? It helps to explain why some people are more severe/less severe, why they might do well with a certain drugs are not do well with another, why some people are susceptible to disease and not. So I just wanted to make that point.

莫妮卡：修饰基因的概念对于 rett 综合征来说并不是独一无二的。总所周知，这样的情况在其他基因疾病也可能发生。这有助于解释为什么人们会有严重，或者不那么严重的症状，为什么有些药物对某些人有效，而其他一些人却不行，为什么有些人易患病，而另一些却不会。我想说明下这一点。

JN: Yes, it's absolutely true. People have known for a while some of the things like certain susceptibility to bad side effects of drugs, certain genetic changes can predict if you're going to react badly to a drug, so that is really the beginning that this concept that we call personalized medicine where some people have genetic risks that are unique to themselves. Then you can look at their genetic composition and help guide their therapies. So in that situation, you can help decide if someone can be on a drug or not. More recently people have been pushing this idea of a modifier and really probably the best example was in cystic fibrosis where they were able to identify changes in gene that determine how likely it was that someone was going to get another infection, a bacterial infection. It really gave insight into the disease process that people didn't realize. It really will probably both help initially, it would help if you look at their genes and could say you're more at risk for getting this bacterial infection so we may need to change our therapies, but it also hopefully will provide insight into the pathology so you can modify the treatments for everyone to prevent these things. That's really where we wanted see a project like this go. What we hope is that we'll be able to find genetic modifiers of Rett Syndrome and not so we could predict if someone might be more severe or less severe, but really if we could find genetic changes that are protective, if we could understand what those genetic change are doing to the function of these proteins, then we might be able to mimic this with drugs and that's really where we want to go with this kind of project. We want to find things that will give us an insight to develop new therapies.

Neul 博士：是的，完全正确。人们已经知道一些事实，诸如一些人容易对药物产生副作用，某些基因的不同可以预测你会对某种药物产生糟糕的副作用。我们称之为个性化药物，

还在萌芽阶段，某些人基因风险相对于其他人来说是独特的。因此，你可以具体分析每个人的基因特性，用来指导治疗手段。这样的情况下，你可以决定某人是否用某药。最近，一些人推出修饰体这个想法，有个最好的例子大概就是囊肿性纤维化。患者有能够识别的不同基因，来预测他们多大可能性患上其他感染，细菌感染。这给了我们以前没有意识到的深刻洞察病程的机会。这在两方面都能有所帮助，如果我们看到他们的基因，我们可能会说：你有比较高的风险患这种细菌感染，我们需要改变我们的治疗方案；另一方面，也非常有希望提供我们关于病理的更深刻的观察，从而你能为每个人调整治疗方案预防这些事情的发生。这就是我们在这个项目上想看见的东西。我们希望对于 rett 综合征能找到这样的修饰基因，这样我们不仅能预测患者的严重程度，还可以找到是哪些基因产生这些保护作用，如果我们能够理解那些基因变化对于蛋白功能产生的影响，我们就能够用药物去模拟它，这就是这个项目想做的。我们想找到一些能带给我们更深地了解 rett 的机会从而开发一些新的治疗方法。

MC: When the proposal went to the peer review process, the reviewers were not shy about saying this is a rather high-risk proposal. In terms a building a resource for the scientific community, that's not high risk. This is going to be a database that hopefully will grow over time and will be a rich resource of information. Now whether will actually be able to identify modifiers is the risky piece. But I think that's where foundations like ours should fund riskier projects that might not be funded through more traditional agencies. Also, it's the kind of thing that we won't know until we do it.

莫妮卡：当这个提案进入对等评估阶段时，评估者毫不避讳地说这是一个相当高风险的计划。就构建一个科学团体的资源而言，风险不是那么高。这个将会希望成为一个随时间不断增长的数据库，成为一个丰富的信息源。现在，无论实际上能识别修饰基因与否，都是风险相当高的。但是，我想，传统基金中，哪里会有像我们这样的基金去支持这些高风险的项目呢？而且，我们不去做，我们怎么会知道呢？

JN: Absolutely, and I think you really hit the nail on the head there. You know, the NIH, by its very nature, is extraordinarily conservative and it really takes a foundation to say look we want to take a chance because we think this has a high reward and we're going to put some money in because hopefully that parlays into, like you said, a broader project that once you establish that it's working, you can seek outside funding. I think that this is a great way to parlay into larger funding. But I think it is absolutely true; this is a risky project by the nature and like you said, the reviewers were not shy about that and I think we all understand that's the nature of it. I think the main point is that it is risky for us with the relatively small sample we have to discover modifier, but I think where there is low or no risk, is that we will have this banked information linked to clinical information that can be mined for a long

time. So, what we say is the pure discovery, that just from this genetic information we will be able to find modifiers has a high degree of risk. However we know from the mouse work that there are modifiers and there are more genetic modifiers in mice that just need further refined or yet to be discovered. As we learn more those with the sequencing data available and publicly available to researchers, they'll be able to mine that database and determine if their favorite gene candidate is present in the human populations, if mutations in these genes are present, and that will really give a lot of strength to show that those animal work or those the ideas really pan out well because their existent in humans.

Neul 博士：是这样的。我想你说出了我心中所想。你知道，NIH，由于它的本质，是尤其地保守，你确实需要让基金会说，看，我们要抓住这个机会，因为我们认为它是高回报的，我们把钱放进去因为我们希望它大大地增值，如你所言，一个宽泛的项目，一旦你证实它是可行的，你可以去寻找外部的资助。我想，这是一个使资金增值的一个很好的方式。但是，我想这（你所说的）是绝对正确的，本质上，这是一个非常有风险的项目，也如你所言，评估者直言不讳，我想我完全理解。我想要点是由于相对小的样本下，我们去发现修饰基因是风险比较高的，但是，如果我们有大量和临床信息相关的数据，可供我们长时间挖掘的，风险就会降低，甚至没有风险。我们所说的是指单纯的发现，从这些基因信息，仅仅从基因信息发现修饰基因是高风险的。但是，我们从老鼠模型中已经知道存在修饰基因，老鼠身上有许多的修饰基因，只需要进一步完善和有待发掘而已。我们从对公共开放的测序数据中了解越多，我们就越能够挖掘数据库，识别那些最有力的基因候选者是否在人类身上也有。如果那些基因突变也存在（人身上），这就能给我们有力的证据说那些在老鼠身上有效的基因能够推广出去，因为它们在人身上也存在。

MC: So this is a project where we are really seeking partnership with the Rett community at large. We need your help. Dr. Neul has X number of patients within his natural history study but there's lots more individuals out there and if what we describe sounds reminiscent about your child, or a child that you may have met on somewhere along your Rett journey, then we really encourage you to contact me or contact Dr. Neul and let's determine whether your child may help us figure out how we might be able to help all Rett kids. So thank you very much Dr. Neul.

莫妮卡：所以，这就是我们真正寻找的与 rett 团体自由合作的项目。我们需要你的帮助，Neul 博士，以及那些在自然发展研究项目中的病人，还有好多局外的病人。如果我们的表述使你缅怀起关于你孩子的一些往事，或者在你与 rett 的历程中曾经在某处遇见过那样的孩子，我们鼓励你联系我，或者 Neul 博士，让我们来看看你的孩子是否能使我们能去帮助其他的 rett 孩子。非常感谢你，Neul 博士。

JN: One final thing I want to add to what you just said. I think the people we are extremely interested in are people who have MECP2 mutations but do not have Rett Syndrome. However we also very interested in the very high functioning people with Rett Syndrome. So people that really do have Rett Syndrome, but who maybe can speak in sentences and maybe can write some but they do really carry a true diagnosis of Rett Syndrome. We're definitely interested in those people too.

Neul 博士：最后我想就我们所说的多说一句，我想，我们最感兴趣的个体是那些具有 mecp2 突变，却没有症状的。但是，我们也对那些有 rett 综合征但是却有高度功能的病人很感兴趣。所以，那些 rett 综合征患者，或者能说句子，或者能写，但确实被诊断为 rett，我们同样对这些患者感兴趣。

MC: Okay. Well, we wish you a lot of luck and we look forward to getting updates and sharing them with our community.

莫妮卡：OK，好的，我们希望你好运，我们盼望着你的进展，和我们的群体分享。