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Respiratory Disease and RNA Therapy

A breath of fresh air

Q&A with Dr Rocio Martinez-Nunez

In the UK, 1 in 5 people are directly affected by respiratory disease costing the NHS £11 billion annually. With increasing contributing risk factors, such as air pollution, incidence rates continue to rise at ~1.5% per year. In recent years, few drug classes have garnered more attention than RNA therapies. By harnessing the cells' own machinery, these utilitarian molecules can produce therapeutic and antigenic proteins in addition to modulating malicious cellular processes.

RNA therapeutics comprise of a rapidly expanding category of drugs that possess the potential to change the standard of care for respiratory disease and actualize personalized medicine. Although RNA-based therapeutics have made real breakthroughs in the production, purification, stabilization and delivery of RNA to cells, key challenges still remain.

With this in mind, we spoke to Dr Rocio Martinez-Nunez at King's College London to discuss current challenges and future opportunities across RNA and respiratory disease.

Interview led by Adam Richardson,
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Dr Rocio T Martinez-Nunez is a molecular biologist with 16 years of experience in RNA biology in academic and research centers. Rocio has a BSc in Biology from The Complutense University of Madrid, Spain, and completed her PhD at the University of Southampton, UK. In addition, she worked as a postdoctoral researcher at the University of California Santa Cruz RNA Centre, USA, and the University of Southampton, UK.

During the first two years of the COVID-19 pandemic, she led the installation of open-source automation at hospitals in Spain and King's College London's COVID-19 testing program. Her research centers on understanding RNA expression modulation during inflammation and infection, with a particular focus on asthma. Her goal is to reveal and understand novel pathways about how cells deal with their own and external (viral) RNAs for future therapeutic intervention in inflammatory and infectious diseases.

What are the latest research trends in asthma and respiratory diseases?

There is a significant movement in the respiratory field to invest more in data science, specifically the type of technology or methodology we should be applying. There have already been pockets of people doing it in the US and Europe. But there is still a lack of consensus on certain challenges, partly because it's a very complex disease. So, a debate remains about "What is driving the disease?" especially when you encounter patients who are not the usual type. However, it is more acknowledged now that you need multi-faceted data to inform research using clinical parameters like biomarkers rather than taking an exploratory approach. There is also a recognition that we need to push the boundaries of "what we think we know" and explore new avenues of research.

Respiratory diseases have very complex pathologies - where does RNA fit?

RNA biology used to be considered by a lot of people as basic biology. But it is a fast-moving area and it's exciting to see new discoveries, things you didn't know existed before.

Most of the leaps in progress in the translational field in understanding RNA complexity and applying it to patients have been in neurodevelopmental and the nervous system - the brain has one of the most complex RNA processing patterns among all the tissues. But there are several genetically inherited diseases that are caused by mutations in genes that lead to bad RNA. So, it is a field in which the translational aspects of RNA biology have to be studied more to establish understanding across different tissues, but the therapeutic potential is enormous.

Currently, not enough is known about RNA processing. There was a wave of "oh, my goodness, this is really important", but people seemed to lose interest quickly. We should remember, though, to pursue science because it will bring important treatment changes rather than because it's fashionable. Yes, you can publish a fascinating paper, but we have to consider what it will actually change. Where does it lead? What is the end goal of the research?

What are the key challenges in getting RNA to a specific cell or tissue type, and what can we learn and improve on for patients in the future?

Specificity has always been a problem in drug delivery. In terms of RNA therapy, the most successful story is the new COVID-19 vaccines. But before that, there was work by the biochemist Adrian Krainer at Cold Spring Harbour, who developed the first genetic treatment for Spinal Muscular Atrophy. The clinical trials were so successful that the teams did not wait to end the trials and swapped all placebo patients onto the treatment. Through basic RNA biology, he helped to develop a therapy that meant these children had improved motor function.

When RNA is made, it needs to undergo a series of maturation events, one of which involves removing non-coding regions (introns) and sticking together protein-coding regions (exons) in a process called splicing. Adrian Krainer used basic biology of splicing to 'convert' the product of one gene into the one that is defective in patients with SMA. Amazingly, this is not more well-known, even though it was revolutionary for these patients and a landmark moment in the potential of RNA as a therapy.

And then, with the arrival of COVID, RNA vaccines made a real impact on the public for the first time. Public perception was that RNA was brand new gene therapy. When actually, the research wasn't new. It had been in development behind the scenes for ten years or more.

Something that must change in the field, in general, is the ability to communicate that these therapies and technologies, and the biology behind them, often exist long before the general public becomes aware of them. A transparent approach could increase awareness and trust in RNA as a therapeutic.

One RNA challenge is the delivery to specific organs. With asthma, patients who have severe asthma typically don't respond well to therapy anyway. And those who do respond to treatment usually respond to inhaled therapy which is well delivered but usually involves strong steroids. Currently, new treatments which were not around a few years ago, are systemic intravenous therapies that patients receive over different intervals of time. These new therapies have revolutionized the lives of many asthma patients, but there's still no cure. So that means you must treat patients for life to control inflammatory mediators and immune cells like T cells or eosinophils, all key parts in the pathogenesis of asthma.

Interestingly, all these drugs are based on research carried out 15 to 20 years ago. Many of these therapies aim to reduce either the numbers or effects of eosinophils, with some aiming to decrease a specific type of inflammation driven by epithelial cells. These therapies are safe and have improved the lives of many patients with severe asthma. However, there's a fear when you say RNA or DNA therapy – with an implication that you're modifying something irreversibly – that you may cause some long-term damage or something weird or bad. And that's something that I think we need to do a better job of explaining to people.

One of the beauties of RNA is that the molecule gets in, it does what it should do, and then it gets degraded relatively quickly, unlike other drugs that can stick around. All drugs have secondary effects, but we take them because they offer a benefit over disease. We test them thoroughly in clinical trials, and the process is very regulated. Unfortunately, I think many of these messages have not been delivered very well to the public.

Do we need to do more in terms of patient and physician education?

Absolutely, because nowadays, if you tell a patient, "I'm going to give you an RNA vaccine", they are more knowledgeable about what it is. But pre-pandemic, there would have been much more anxiety around it.

It is also important for physicians to communicate and clearly explain all therapy-related options to their patients. Even more so because everyone Googles symptoms and diseases. Immunomodulators such as antibodies are widely used, acknowledged, and safe and have been revolutionary in medicine. But, probably at the start, they created anxiety – RNA is next. So yes, I think there is a lack of communication with patients and physicians and even between different disciplines in science.

The same applies to data science, where we could be getting a lot more from the mass of data generated. If you are not a data scientist, you won't know where to start as it's essentially another language! The good news is there is a push from the respiratory community to make these resources more accessible.

Where do you think the responsibility lies for improving access to, and understanding data?

Since the data usually comes from us, I think the responsibility should start there. We should share it without fear that someone will take it and use it for their self-gain without acknowledgement.

We also need to do a better job with funding because, depending on the funding scheme, there are sometimes questions about 'Who owns the data?', 'Can you share it?, or 'How can you share it?'. Although with major funding bodies, the general consensus is to share all data without restrictions. We need to help people understand that you get a lot more for your money when you openly share your findings. You're enriching a pool, from which you can also take and make it better. That is the way forward. We need to communicate that better to some pharmaceutical companies who have lots of data.

We should engage with their advocacy and patient groups for them to know how to communicate about how the data translates into science with their patients. There are two reasons for this. Firstly, because we can't do everything. Secondly, they do a much better job than we do in terms of those communications, and that's why they are there -- they provide a great way of engaging with that particular population. They know their patients well. It's the same with physicians - patients will generally trust them. We must ensure basic science is easily digestible and comes from a well-researched standpoint.

What are the main factors why so many RNAs have failed to commercialize?

Firstly, there is the perception that "you're changing my genes." There have also been damaging, peer-reviewed papers in credible journals that you can still find today that stand for the RNA of a vaccine getting integrated into your cellular DNA. I do not comprehend how that has not been rejected and withdrawn already. That's a massive thing. And we still have to fight that perception.

Secondly, there are the scientific challenges of making it stable and tolerable. **The work done by many researchers, particularly Karikò and colleagues, really paved the way for us to understand how RNA is sensed in cells – and what modifications can be made to make it more stable, more efficient, and less immunogenic.**

Immunogenic meaning that it triggers an immune response – we want some of that, but not a really big one. That has now been overcome – the COVID-19 vaccines' success is proof of that.

We also need to better understand the disease itself – for example, in chronic inflammation, such as asthma, the underlying cause(s) are not understood, so we need to invest more in discovery science. This is the only way that we will discover new targets for therapies.

Do you think that RNA and RNA binding proteins (RBPs) could change the course of patient-centric treatments for different diseases?

Yes, because with personalized medicine, we're getting closer to being able to profile an individual. I don't think we should do total RNA sequencing – even if, theoretically, you could do it as you see it in the movies, it doesn't make sense. But you can consider certain transcripts associated with certain proteins as biomarkers in diseases such as asthma – a mini-screen, if you may, similar to when you get a blood test.

I believe that RNA binding proteins (RBPs), on which my research is focused, have great potential! **There are more RBPs that control RNA processing and function than there are transcription factors that initiate RNA transcription from our genes, but they are not yet making it into headlines or university curriculums. I believe that we will get there... But you can at least consider them as candidates and as biomarkers.** We already see in my lab that they determine how steroids work or how we process viruses.

One idea, for example, would be to incorporate RBPs in screening panels. Asthma clinics already measure things in blood that have been born out of basic research – certain cytokines and signaling molecules between cells. So, what we want to do in the lab now is bring these RBPs to those panels to say, 'Now, look, if you don't have enough of 'X', you shouldn't be treated with 'Y' because it's going to do something completely different, or the therapy won't work well. I think they can be very good biomarkers, and one day, I envision they could be used as therapeutics too.

Is it possible that every patient will be screened for their RNA Binding Protein transcript profile (RBPome) to create more tailored treatments in the future?

Hopefully, but I think we are far away from that because we don't know enough yet.

Heterogeneity is one of the main challenges in patients with severe asthma – this means that patients are very different clinically. We now have more biological treatments, which have made a huge impact on some of these patients, but not all, and indeed, too many remain symptomatic, with asthma being a massive health burden in their daily lives. So, whilst there are guidelines, it also comes down to the physician's experience, and they decide which biological treatment the patient will receive.

If we have not been able to come up with decisive markers to aid treatment decisions, then maybe we have not been looking in the right area. From what we see in the lab, some RBPs are quite determinant for certain signaling pathways that we know a lot about, theoretically at least. And that's what I would like our lab to bring to the table, saying, 'Look, RBPs exist and matter. They modulate this very well-known biological pathway'. When you look at the levels of RBPs in certain patients, it's pretty determinant what happens with certain signaling pathways. So, if you measure them beforehand, you will have an excellent idea about their response to treatment and their immune activation profile.

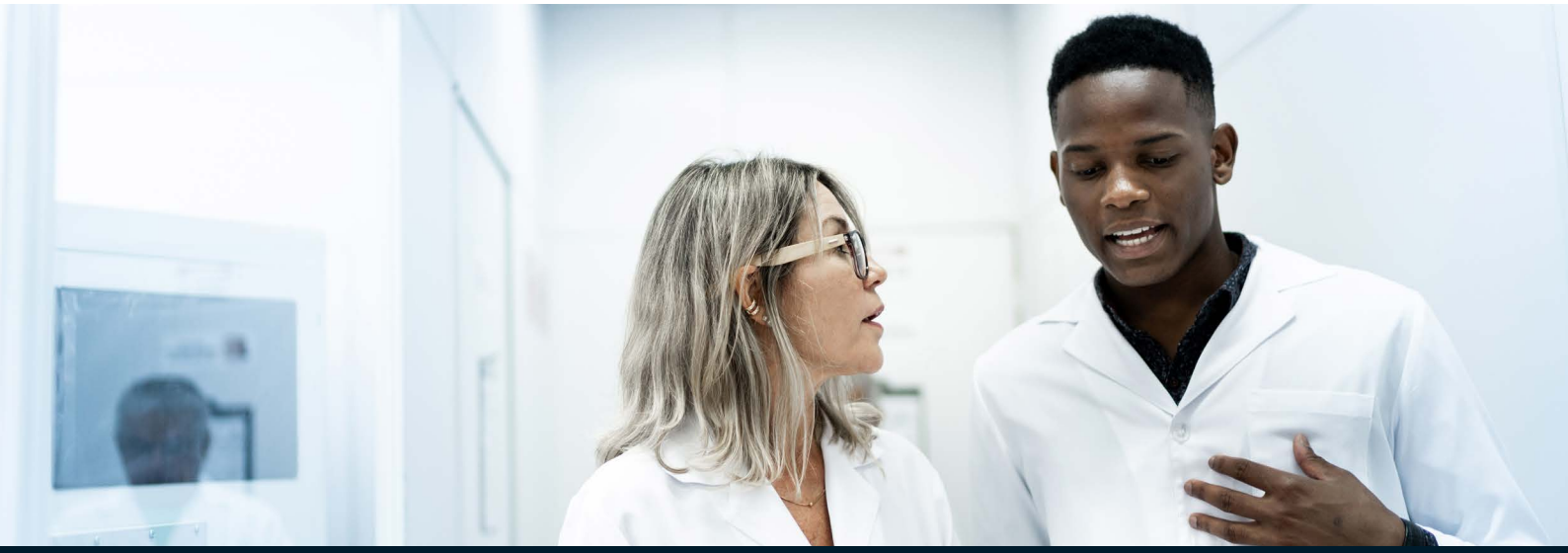
Interestingly, even after integrating many different datasets, we still haven't developed a signature that sharply defines different types of patients. That happens a lot in chronic inflammation because it's very complex. So, we probably need to take a step back and understand more about the disease at new levels, to understand this complexity. And the RBPome is still a great unknown.

How would you go about segmenting patients into profiles? Is it a case of collecting enough data to make a logical decision? Or is there more that we could do in terms of data sharing?

We need to reach a point where we all share data whilst obviously respecting patients' wishes and within the remit of anonymity and ethical approvals.

Everyone needs to be willing to share, which the 'pure bioinformatics' community does very well. Biology and translational sciences are heading in that direction, but it's still not enough. In bioinformatics, you make a program, and the dream is to share it with the world for everyone to use. For many years in biology, the dream has been 'I do something unique that only I can do, which makes me special'. But thankfully, that attitude is changing – and it is the way we can actually advance, much, much faster.

Right now, so much information is out there that it has almost become an intoxication of data. We need to have a better consensus to inform each other better; otherwise, we will continue to make the same mistakes. **Collecting more and more data also needs an endpoint – more data is not more information. It is about how we analyze the data, what it tells us, and what we learn from it to design the next steps to further dissect the underlying biology.** But we're definitely moving in the right direction.



What diagnostic techniques do you see in the future? For example, as an asthmatic patient, do you really want to take bronchial brushings every time you go to the clinic?

In diagnostics, you want something non-invasive that does not burden anyone.

When you profile certain types of asthma, e.g., blood and exhaled sampling, non-invasive things like Fractional Exhaled Nitric Oxide (FeNO) and Forced Expiratory Volume (FEV) are good. But although it has systemic influences, it is a local disease, so blood may not give you enough information.

Nasal sampling may be an excellent way to go. It is much less invasive than a bronchoscopy, and thanks to COVID, we all now know how to put a swab inside our noses! If you sample the lungs, you will understand what is happening, and with that, look for surrogates in more accessible places such as the nose. This is particularly relevant in patients where sampling is trickier because they are very unwell. They don't represent the majority in asthma, although they comprise most of the clinic and asthma-associated costs.

We know that cost and stability are significant challenges in RNA. Is sensitivity of detection a big issue too?

Sensitivity is not a big issue anymore. We can now sequence a single cell... Costs have come down a lot too.

In sequencing, dealing with a large amount of data is one of the biggest challenges. We need to find a way to make that less cumbersome. There are some great resources and companies that can help when approaching data, which is a step in the right direction. And we also need to educate more people in data science.

I don't think it makes sense to fully sequence patients routinely, but creating a panel for those challenging-to-treat patients would help, rather than a 'let's screen everyone approach'. It has to be cost-effective, and it can be cost-effective. We could have a small panel with newly researched molecules that could be available for when current markers fail to inform you – if they don't work, we should be replacing them. So that's where I would implement more complex technologies and multi-plex panels with polymerase chain reaction (PCR; a technique to assess levels of RNA that is made by our genes).

The pharmaceutical industry is trying to make these methods more affordable; otherwise, you only treat the wealthy. In terms of basic research, we can do more to make sequencing more accessible and relevant to the patient. So, for example, you can carry out genome-wide experiments in a small population. Then you generate a panel for a validation cohort, which is more tailored, precise, and cost-effective.

With a bank of traditional systemic biologics available, what would drive the choice of treating with an RNA therapy over a biologic for a physician?

Both have their place. RNA is more modulatory and time-limited, and you can be very cell-specific. For example, if you encapsulate RNAs in lipids, you can engineer them to express a certain receptor so they will go to specific cells. Biologics are great, but they tend to be systemic.

Another reason is that with RNA, you don't remove absolutely everything; you can modulate the excess back to a baseline level. So, I see RNA as more of a homeostatic molecule, a chisel, as opposed to a hammer. On some occasions, you need a hammer. In many others, a chisel. You can go more towards homeostasis and normal regulation vs trying to wipe it out completely depending on the need of the patient.

Do you think there's an issue with pharma, academics, or society, in general, trying to move from vaccines to a place in therapy where you manipulate the protein?

I think there used to be a lot more fear. One of the good things about the vaccines is that they've put the word 'RNA' out into the world. They have proven that they work, that RNA is safe, and that has increased people's trust in them. These molecules can be really beneficial for you. I know that sounds like a very loose concept. But I think that's one massive step that has changed things.

Particularly for certain genetically inherited diseases, I don't see how you can treat those patients unless you change the gene or the product of the gene in its RNA form because that is what causes the disease in the first place. A defect in the genome makes a defect in the RNA, leading to no protein or bad protein... It is as close as a cure that you can get rather than a treatment.

The COVID-19 RNA vaccines have paved the way for us to see that RNA is a therapeutic possibility. They proved to be the perfect case study for tolerability, safety and speed of development. Now we can work on improving their longevity and develop novel treatments for other diseases.

Summary

Despite the considerable advances in RNA research in recent years, there remain significant translational challenges and unmet needs in understanding and treating respiratory diseases. As we look to the future, there are numerous potential opportunities to improve the treatment of patients with respiratory diseases and increase the awareness and understanding of RNA as a therapy.

Early and comprehensible communication about RNA from scientists across industries will be vital to improving public trust further, and multidisciplinary engagement and collaboration between scientists, physicians, charities, and pharma companies are key to that. Also, we should push for the discovery and utilization of RNA biomarkers to improve the diagnostic capabilities of severe asthma patients through the open sharing of big data across academia and pharma. Adding and bringing together layers of complexity by overlaying different RNA datasets, including RNA-sequencing and RBPomics, to understand further the heterogeneity of respiratory disease can be key for us to discover novel biological pathways that can be targeted in these patients.

Through more investment in basic science, translating discoveries into clinical research, and public engagement, we are in an exciting era for the RNA field in respiratory science, where we can all work together to truly make an impact to improve the lives of millions of people.

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