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# Designing the next generation of vaccine adjuvants

Derek O'Hagan, Ed Lavelle, Jay T Evans, and Ari Joffe

INTERVIEW

"Novel adjuvants will emerge when they clearly differentiate themselves and show inherent value that others cannot match."

Charlotte Barker (Commissioning Editor, *Vaccine Insights*) speaks with **Derek O'Hagan** (GSK R&D), **Ed Lavelle** (Trinity College Dublin), **Jay T Evans** (Inimmune Corporation), and **Ari Joffe** (NIAID, NIH) about the state of vaccine adjuvant development, including drivers for new adjuvant innovation, advances in mechanistic understanding, and key barriers to clinical translation.

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**Q** Do we need new adjuvants? If so, where are the greatest needs?

**DOH** Recently, we have seen large vaccine players licensing or even acquiring adjuvants that are pretty well established. When it comes

to low- and middle-income countries (LMICs), the goal is mainly to access established adjuvants. I think neither is surprising: getting approval of a novel adjuvant in a vaccine product is challenging and difficult so it is natural to gravitate towards what worked in the past.

I spent a couple of decades working on MF59 oil-in-water emulsions, and now you see many companies following a similar path towards emulsions. That is not to say there is no path for new adjuvants, or that we do not need them, but people will naturally follow what has succeeded previously, unless there is a clear delineating signal that a new approach is genuinely better. Better can mean improved supply chain or lower cost, but ideally it means enabling a product that would not otherwise be possible.

There is scope to bring in new, unproven adjuvants, but it will be an uphill struggle. It always has been. If anything, now that more adjuvants are approved, there may be further consolidation around established approaches.

JTE I would add that new adjuvants moving into developed markets versus LMICs tend to have a slightly different focus. In LMICs, where disease burden and unmet need are high, thermostability, cost, and availability are central questions. In developed markets, what is driving new adjuvants is innovation: whether that is taking an existing adjuvant and formulating or delivering it in a new way, or developing something entirely new that solves a problem the current adjuvants do not. Whether that is pushing a T helper response in a specific direction, or a platform that meets a market current adjuvants cannot serve.

In both markets, I think new adjuvants are needed, and both incremental improvements and complete redesigns are happening in the space.

EL One question worth raising is how effective current adjuvants are at driving CD8+ T cell responses. There is ongoing discussion in the cancer vaccine space about this. We may be better at driving CD8+ T cells with adjuvants such as AS01 or Matrix-M than people sometimes assume, though measuring those responses in humans, particularly in the relevant tissues rather than the circulation, remains a challenge.

Cancer vaccines in general may be a source of innovation – the challenges are very different, increasing the odds that something genuinely new might be discovered.

AJ As long as there is a need for new and improved vaccines, I see a need for new and improved adjuvants. We have vaccines that work well, vaccines that could work better, and diseases where we have no vaccines at all. In those latter two categories, novel adjuvants are likely how we are going to solve the problem. Yes, there are difficulties in bringing novel adjuvants to market, but that is precisely where they are most needed.

DOH It is worth noting that traditional adjuvants are not always the best solution. Adjuvants play a key role across a number of vaccine products, but different modalities may be better suited to different problems. The energy in oncology right now seems to have shifted toward RNA, with late stage trial data suggesting genuine promise for cancer vaccines. The LNP delivery system is itself an adjuvant, and there is significant innate signaling remaining in the RNA, so adjuvant effects are present even in that setting. Not every problem calls for a classical adjuvant, but there is certainly a role for them.


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Ari Joffe

**Q** If different adjuvants are capable of inducing protective immunity when used with the same vaccine antigen, do we need many different adjuvants?

**AJ** While it is true that different adjuvants can induce protective immunity when used with the same antigen, I argue that 'protective immunity' is not a clearly defined endpoint that represents ideal protection. For example, a vaccine may provide protection from challenge within a relatively brief window of time. In this case, choosing a different adjuvant may achieve more durable protection. Similarly, a novel vaccine may be aiming for sterilizing immunity that completely prevents infection and transmission (beyond just protection from disease and/or death). Having different adjuvants available would help here as well. Overall, I think that we are in a better position to develop new and effective vaccines when we have multiple well-characterized adjuvants to choose from and clearly defined goals for the type of protection we want to provide.

**Q** How does a deeper mechanistic understanding advance adjuvant discovery and development? Where are the most important gaps in our knowledge?

**AJ** I am a huge proponent of studying adjuvant mechanism. We can imagine a utopian future for vaccine design, in which we perfectly understand how all adjuvants work, how antigens behave, and how the other components of a vaccine system function. In that world we could achieve pure rational design of new vaccines and have a high level of certainty that they would work. Of course, we are nowhere near that point, and may never fully get there – but it is a worthy goal to strive toward.

Indeed, we are already moving in that direction. Many new adjuvants are now designed to target specific receptors, and we are learning more about how older adjuvants work. For example, we know that emulsion adjuvants are associated with strong humoral responses, and that informs formulation choices. As our mechanistic understanding deepens, I think we will see more genuinely rational vaccine design.

Where are the gaps? Honestly, there are many. Our understanding of adjuvant mechanism is constrained by our understanding of the immune system itself. As fundamental immunology advances so will our understanding of how adjuvants work.

**EL** The field has been transformed over the last two decades. As we entered the 2000s, we did not know the inflammasome existed. We did not know that intracellular self-DNA or RNA could activate responses, or what the cGAS-STING pathway was. It is no surprise that we could not work out adjuvant mechanisms, when we did not even know the pathways existed. And there is still much more to discover; for example, how mitochondrial stress, endoplasmic reticulum stress, or membrane disruption contributes to adjuvant activity.

Understanding these mechanisms will enable refinements. That might mean making formulations smaller or larger, more or less cationic, or more or less hydrophobic. I do not expect we will have entirely rationally designed adjuvants in the future. We will probably still be using emulsions, alum, and liposomes 20 years from now. But understanding the physicochemical factors that regulate their innate immune activity gives us tools to improve them. For example, inflammasome story was important even though it did not ultimately explain how alum works: it demonstrated that specific innate signaling pathways can be triggered by what seemed like old-fashioned adjuvants, and that kicked the field forward.

JTE Mechanistic understanding is absolutely critical from a safety perspective, and a regulatory requirement for new adjuvants entering Phase 1 trials. If you are seeing off-target effects, you need to understand the mechanism. That applies not just to negative effects, but also beneficial off-target effects, as we have seen with BCG and shingles vaccines containing AS01 adjuvant.

We are still in an era where a significant proportion of antigen–adjuvant combination and formulation selection is trial and error, although we are getting more sophisticated. As Ari said, we know emulsions tend to drive antibody responses. We know liposomal formulations typically drive cellular responses. But I could not tell you today whether Matrix-M, AS01, a Toll-like receptor (TLR) 7/8 agonist, or some other adjuvant would drive the right response for a given pathogen. Understanding trafficking and what is happening in the draining lymph node after vaccination with different antigen–adjuvant combinations will help us predict this more reliably. The ultimate goal is to predict safety and potential off-target effects more accurately.

DOH This makes me reflect on how far the field has come. When I started, we only had alum and it is mechanism was a complete black box. Then I worked on MF59, and the path to licensure in the US required us to explain what it did and how, which drove a lot of mechanistic work, made possible by new analytical techniques. Early gene expression profiling at the injection site and in the local lymph node was revealing, showing much greater activation with MF59 than alum.

Stanford immunologist Bali Pulendran's recent work showing that MF59 can induce CD8 responses in mice via a unique pathway of cell death came as a surprise to us, but it illustrates the point: there are still new insights to be found even in the most established adjuvants. The question is whether it is more productive to dig deeper into adjuvants that are already working, or to hypothesize new mechanisms and discover molecules that target them.

JTE There are still fundamental questions about alum itself. Whether absorption of the antigen for co-delivery to a lymph node or to a cell really matters, whether the depo hypothesis has any merit, whether inflammasome activation is central: all of these remain open. For the more defined synthetic adjuvants, there is still a long way to go in understanding their impact at the injection site, in the draining lymph node, and systemically.

AJ In addition to formulation, route of administration matters enormously. An adjuvant delivered intramuscularly may not work the same way delivered intradermally or intranasally. It is hard to imagine fully elucidating mechanism across all of these contexts, but having a specific, defined question is essential.

EL Understanding mechanism will also tell us about safety. Why alum is so safe is actually a key question we have not fully answered. Understanding what alum is doing may give insights into why injection-site reactions are limited, and that is important both for informing new designs and for knowing what to avoid.

DOH This explains why alum is such a solid foundation. It is safe, effective, inexpensive, stabilizes antigens, allows pre-filled syringes, and is fridge stable. An attractive approach is combining alum with TLR agonists, precisely because it builds on a platform with a strong safety record.

**Q** What are the most exciting new directions in the adjuvant space?

EL One of the most exciting frontiers, which we have touched on, is taking the vaccinee into account. The immune system shifts substantially with age: a neonate, an infant, an adult, and an elderly individual are all different immunologically. AS01 has shown that it is possible to vaccinate elderly populations very effectively with potent adjuvants.

We are only scratching the surface of whether the same adjuvants hit the same targets in both sexes, whether the relevant innate targets differ in neonates, and how immune senescence affects adjuvant responsiveness in older adults.

There are probably specific targets in elderly populations that could be exploited for diseases where effective vaccines do not yet exist, such as C. difficile or certain antimicrobial resistance pathogens. Understanding which innate targets are preserved in elderly immune systems could guide the design of vaccines specifically for that population.

AJ The mRNA space is particularly exciting for adjuvant research. We know the LNP appears to act as an adjuvant in its own right. But this opens up an entirely new realm: the possibility of encoding adjuvants genetically, just as antigens are encoded in mRNA vaccines. The mechanism of a genetically encoded adjuvant may be entirely different from the same molecule delivered as a recombinant protein. There are a lot of unknowns, and to me that is exactly what makes it exciting.

The other area I find compelling is systems immunology, machine learning, and big data approaches applied to adjuvant research. I am not an expert in those fields, but the potential to use machine learning to dig through the large datasets being generated through vaccine development to give better mechanistic insight and better predictive power is genuinely exciting.

JTE I would add innovation in adjuvants for LMICs. We are starting to see breakthroughs. One good example is the synthetic adjuvant Alhydroxiquim-II used in the Covaxin vaccine: a small-molecule synthetic that can be manufactured at kilogram scale, has thermostability advantages, and does not require ultra-cold storage. Synthetic adjuvants that have been in development for 20 years are just now starting to make it through the regulatory process, and there is potential for lower cost and large-scale manufacturing.

Another thing I would highlight is innovation in single-cell omics and spatial omics. Studies are finding substantial changes in lipidomics and metabolomics in response to adjuvants, which we knew nothing about 5 years ago. Understanding how delivery systems impact lipidomics and metabolomics will help with mechanism and safety alike.

"There is a lot of interest in mucosal and alternative delivery, but the question is whether that interest is justified in cases where injectable vaccines work well."
Derek O'Hagan

DOH There are now many adjuvants available for injectable products, but a great deal of interest in alternative delivery routes, and those routes likely require different adjuvants altogether. The adjuvant systems established for injectable vaccines are probably not going to succeed by alternative routes. Mucosal adjuvants, in particular, have been set back by some serious missteps that made the area more difficult to revisit.

Most mucosal vaccines we can currently make are live attenuated, where the pathogen is doing the work at the mucosal site. We cannot yet accomplish mucosal vaccination effectively with recombinant proteins or RNA, despite many years of trying. Figuring out how to do that is probably where we need to make the next major advance.

## Q Do we need mucosal-specific adjuvants? What are the most promising approaches?

EL We should not try to make mucosal vaccines for everything. We should focus on infectious diseases where we are confident that a local mucosal response will be more protective than an optimal circulating IgG response. In the intestinal tract, that probably includes rotavirus, cholera, C. difficile, and Helicobacter pylori. For the respiratory tract, we know injectable vaccines for COVID-19, influenza, and pneumococcal disease protect against severe outcomes. Could a mucosal vaccine give sterilizing immunity and stop people getting sick at all? Probably, but the question is whether the gap justifies the challenge.

Where there is clearly a gap is where we have no vaccine at all. The dmLT adjuvant for oral vaccines is probably the most advanced example: it is now in Phase 2 trials for enterotoxigenic Escherichia coli vaccines and looks safe and immunogenic. If we found one orally active adjuvant that became a product, that could change the field significantly.

DOH I agree – there is a lot of interest in mucosal and alternative delivery, but the question is whether that interest is justified in cases where injectable vaccines work well. We have an intranasal flu vaccine that is demonstrably more effective in young children than the injectable, yet it has never really taken off as a major product. That undermines arguments about convenience and ease of administration.

That said, there is an interesting new development: intranasal flu vaccine is now available direct to consumer, so people can receive it at home without going to a doctor or pharmacy. That changes the access equation entirely, and it will be interesting to see whether uptake shifts as a result.

JTE Mucosal vaccines have been a topic of discussion for the 20-plus years I have been in this space. There is undoubtedly a place for them, but it is pathogen-specific, and there needs to be a genuine unmet need. For respiratory infections such as influenza, COVID-19, and RSV, the biggest challenges are durability and breadth. If a mucosal vaccine could give more cross-protective neutralizing antibodies, that would be a compelling advance.


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> Jay T Evans

For the gastrointestinal tract, mucosal IgA protection can be critical. For intradermal delivery, the immunology is compelling in animal studies, but local inflammation at the injection site is a significant barrier to patient acceptance.

DOH To add to Jay's point about skin delivery: one of the perceived attractions is that it could be dry, stable, and easy to distribute direct to consumer. The local reaction question is real, but if we can address that, the distribution and access advantages could be significant.

JTE One additional point not yet raised: cost of alternate delivery devices can be a real barrier to LMIC access. Manufacturing costs for intradermal microneedle patches or actuated intranasal spray devices are higher than for a standard liquid formulation and needle. These are solvable problems, but they need to be part of the design brief from the start.

EL I remain very positive about mucosal vaccines. Some genuinely significant innovations have emerged in the last couple of years. The prime-pull approach, where an injectable vaccine primes for mucosal responses that can then be boosted with adjuvant alone, is particularly interesting if it holds up in humans. Retinoic acid-containing formulations that imprint mucosal homing capacity are another avenue. If we can demonstrate in humans that certain injectable vaccines create this kind of mucosal priming capacity, that changes the calculus considerably.

There are also some de-risking data on mucosal intranasal adjuvants. A synthetic TLR4 agonist is in a Phase 2 clinical trial by the intranasal route. For oral delivery, there is a need for better enteric formulation strategies, and for exploring what happens when adjuvants that have only been tested parenterally make it through the gut. There is a lot of innovation still to happen.

Q Why are new adjuvants not reaching the clinic? What are the roadblocks?

JTE COVID produced a real breakthrough, with some new technologies moving into the market far more rapidly than they otherwise would have. But there is a huge gap between the hundreds of adjuvants in preclinical research and the handful of adjuvants approved for use in commercial products.

Pharmaceutical companies often do not engage with adjuvants until they have been through Phase 1 and have a safety record. From a biotech perspective, it is difficult to raise funding for an adjuvant-only company unless you have a full vaccine platform behind it. There is a recognized valley of death between fundamental adjuvant discovery and the de-risked Phase 1 data that larger companies want to see. Funding from BARDA and DARPA has begun to fill that gap, but there is still significant work to do.

"For mucosal vaccines, the bar is much lower: there is essentially nothing available for many applications, so the opportunity is enormous."
Ed Lavelle

**AJ** I totally agree. Clinical trials are a necessary and unavoidable step, and they are expensive. Academic investigators may do excellent preclinical work, demonstrate mechanism, and build a compelling case for an adjuvant, but then have no clear path to get into clinical testing. That is the valley of death Jay described. At the NIH, we are focused primarily on basic research and early preclinical studies, but we do fund some early clinical trials, and we make introductions to agencies such as BARDA. We are also investing in organoid-type systems to enable additional preclinical de-risking, because the more you can de-risk at the preclinical stage, the better the case for investment in early clinical trials.

**DOH** I feel the pain of this challenge firsthand at GSK. AS01, AS03, and AS04 are in products. We are still working to get traction for AS34 and AS37, trying to convince internal project teams to take them into the clinic. The path of least resistance, even internally, is to go with what has been established. Projects want to de-risk, and that means using adjuvants with a clinical track record.

However, the broader trajectory is actually quite positive: originally there was just alum, then MF59, now five or six adjuvants. COVID accelerated progress further, and we have seen major licensing deals and acquisitions. Novel adjuvants will emerge when they clearly differentiate themselves and show inherent value that others cannot match.

**EL** The challenge now is that if you are developing a new injectable adjuvant, you are trying to beat something that is already very effective. You need to have the right protective antigens and show that the ideal immune response cannot be achieved with existing tools.

For mucosal vaccines, the bar is much lower: there is essentially nothing available for many applications, so the opportunity is enormous.

## BIOGRAPHIES

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