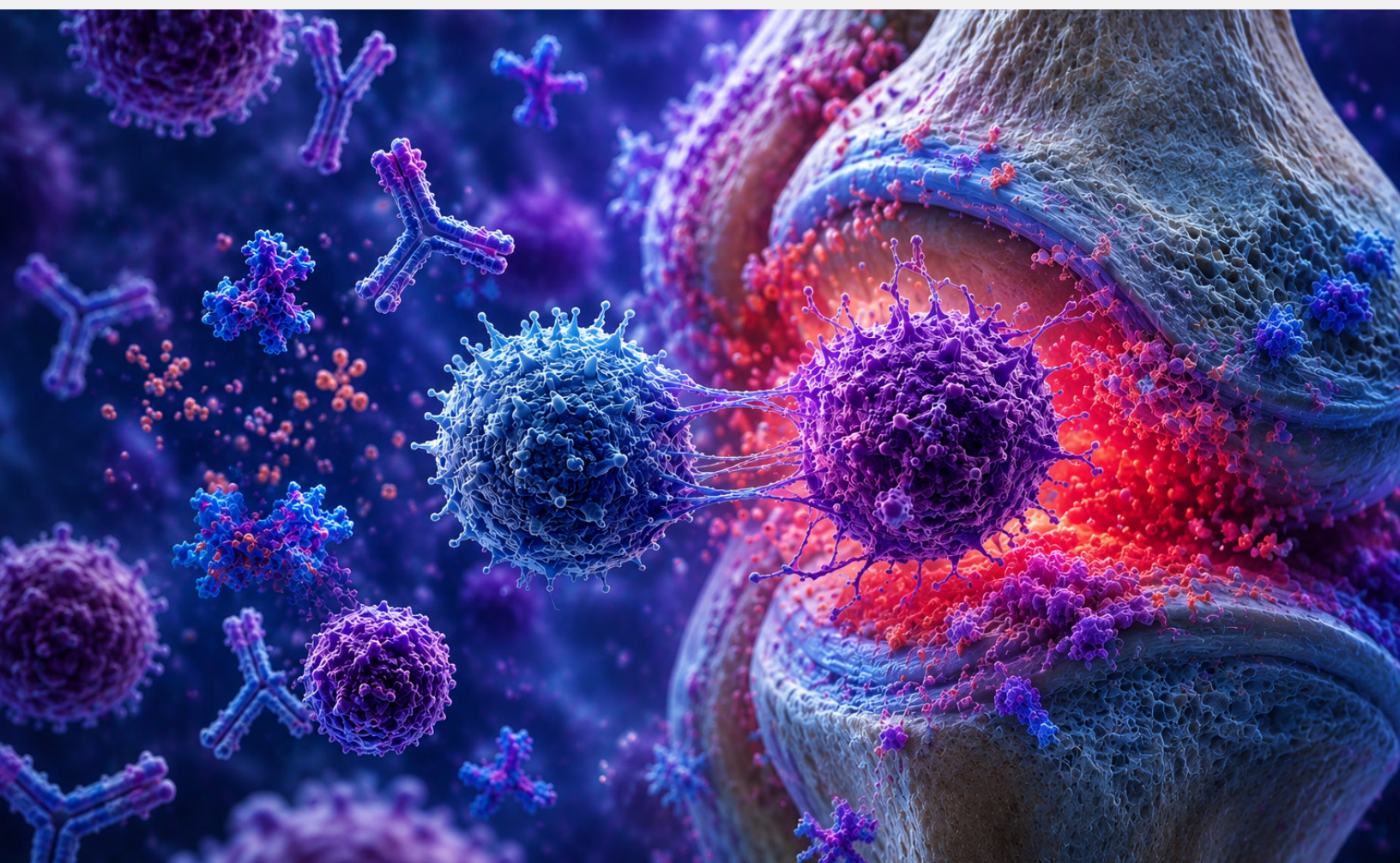


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Q&A: The Shift Toward Precision Immunology in Rheumatology Trials

Advances in immunology, biomarker science, and translational medicine are reshaping autoimmune drug development, moving sponsors beyond one-size-fits-all approaches to clinical trial design. We spoke with Dr. Mila Grieg, MD, PhD, vice president of medical affairs, head of Immunology and Inflammation, Allucent Center of Expertise (ACE), about why precision immunology is gaining momentum, what it means for clinical development, and how sponsors can position themselves for success.

For years, rheumatology development has centered on broad immunosuppression. What is driving the industry's shift toward more targeted, precision-based approaches today?

Broad immunosuppression took the field a long way, but we've reached its ceiling. Even with our best biologics and targeted synthetic DMARDs, a substantial proportion of patients never achieve low disease activity or remission. "Difficult-to-treat" rheumatoid arthritis is now a formally defined EULAR entity precisely because so many patients cycle through mechanism after mechanism without durable benefit. At the same time, broadly suppressing the immune system carries a cumulative cost in infection risk and long-term toxicity.

The clinical motivation is straightforward: we've been treating highly heterogeneous diseases as though they were one disease, and group averages conceal large populations of non-responders.

What has changed is that the science and the technology have caught up with that problem. Today, single-cell and spatial sequencing, high-dimensional immunophenotyping, multi-omics, and advanced imaging allow us to characterize the immune drivers of disease in individual patients rather than relying solely on diagnostic labels. Just as importantly, these technologies have become scalable and affordable enough to be integrated into clinical development programs rather than remaining confined to academic laboratories.

There's also a commercial imperative. The TNF and IL-pathway landscape is increasingly crowded, making differentiation based on modest average effect sizes more difficult. Sponsors need to demonstrate to

regulators and payers that they're treating the right patients rather than all comers. When persistent unmet need, improved mechanistic understanding, enabling technology, and competitive pressure converge, you get the inflection point we're seeing today.

The term "precision medicine" is often associated with oncology. What does precision immunology look like in rheumatology and autoimmune disease?

It's a useful comparison, but also a slightly misleading one.

In oncology, precision medicine often means identifying a druggable mutation and matching it to a targeted therapy. Autoimmune diseases don't behave that way. They're polygenic, dynamic, and driven by networks of immune cells and cytokines rather than a single mutation. The dominant pathway can also shift over the course of disease and in response to prior treatment.

Precision immunology is really about matching mechanism to patient: identifying which immune pathway is dominant in a given patient, or subgroup of patients, at a given point in time and selecting therapy accordingly.

We're already seeing early proof of concept. Lupus patients with a high type I interferon signature are more likely to respond to interferon-pathway blockade. In rheumatoid arthritis, synovial tissue analysis can distinguish a B-cell-rich pathotype that's showed greater treatment effect with B-cell depletion from one better suited to IL-6 blockade.

There's also a temporal dimension. Precision isn't only about selecting the right patient. It's also about identifying the right window for intervention and treating to a defined target.

That said, it's important to be candid about where the field stands today. Precision immunology remains earlier in its evolution than precision oncology. Very few predictive biomarkers are in routine clinical use, and many leading investigators still describe true precision medicine in rheumatoid arthritis as a moonshot. The promise is real, but so is the distance still to travel.

As our understanding of disease biology improves, how are sponsors rethinking patient populations and enrichment strategies?

The fundamental shift is that study populations are increasingly defined biologically rather than solely by clinical classification criteria.

Historically, sponsors enrolled patients who met ACR/EULAR criteria and hoped a treatment signal would emerge from a broad population. Increasingly, they begin by asking which biological subgroup is most likely to respond to a particular mechanism of action and build the trial around that hypothesis.

It's also important to distinguish between different types of enrichment. Some strategies reduce heterogeneity by narrowing the study population and minimizing biological noise. Prognostic enrichment selects patients who are more likely to experience the outcome of interest, improving event rates and reducing sample size. Predictive enrichment goes a step further by selecting patients who are more likely to respond to a specific therapeutic mechanism.

Successful enrichment strategies balance several considerations. Is the targeted pathway actually active in the patient? How do disease stage and prior treatment history influence the underlying immunobiology? Can biomarker assays be delivered reliably across study sites? And perhaps most importantly, will the enriched population ultimately support the label sponsors hope to defend with regulators and payers?

One of the biggest mistakes is locking a biomarker hypothesis too early. Narrowing a pivotal study around a subgroup identified in a small exploratory dataset, and then failing to replicate those findings, remains one of the most expensive mistakes in precision drug development.

What are some of the biggest challenges sponsors face when translating precision immunology into successful clinical development programs?

The first challenge is the biomarker validation gap. The literature contains an enormous number of promising biomarkers, but very few have been analytically and clinically validated for use in regulated clinical trials. Moving an assay from an academic setting to a reproducible, GCP-compliant test suitable for clinical development is demanding work that's often underestimated.

The second is operational complexity. Many of the most informative biomarkers require specialized sampling procedures, central laboratories, cold-chain logistics, and, in some cases, real-time assay turnaround to determine patient randomization. Comparatively few sites can deliver all of that consistently.

Patient identification presents another challenge. Biomarker-positive patients are, by definition, less common, leading to higher screen-failure rates, slower recruitment, and increased costs. At the same time, immune biology is dynamic, meaning biomarker status may change with disease state or prior therapy, complicating both eligibility and interpretation.

Finally, there's an organizational challenge. Precision development programs require translational science, clinical operations, laboratory medicine, biostatistics, and regulatory teams to work together from the outset rather than sequentially. For emerging biotech's in particular, resource constraints can make it tempting to postpone biomarker work. In reality, that's often the point where an experienced development partner adds the greatest value: helping de-risk both the biomarker strategy and operational execution before expensive pivotal studies begin rather than discovering problems during them.

As patient populations become more narrowly defined, how does that impact recruitment, site selection, and overall trial execution?

It changes almost everything about feasibility, and it changes it earlier than many sponsors expect.

Recruitment planning now starts with the prevalence of the biomarker rather than the prevalence of the disease. A narrower eligible population means higher screen-failure rates, longer enrollment timelines, and often the need for more sites across more countries to achieve recruitment targets.

Site selection also becomes more complex. Sponsors need both patient access and technical capability within the same institution: the ability to perform specialized procedures, handle sample collection and processing correctly, and return reliable assay results within required timelines. That often pushes studies toward academic and specialist centers, creating an important trade-off. While those sites can improve data quality, they may also reduce the representativeness and diversity of the study population—something regulators increasingly expect sponsors to address proactively.

Execution, meanwhile, becomes tightly coordinated around laboratory operations. When assay results determine patient eligibility or randomization, central laboratory turnaround times directly affect enrollment.

Site training and sample handling become critical, because a mishandled sample isn't simply a protocol deviation: it can mean losing an otherwise eligible patient.

Patient burden also becomes a key operational consideration. Additional procedures, more screening visits, and higher screen-failure rates can all affect recruitment and retention. Incorporating patient-centric design, minimizing unnecessary visits, and using decentralized approaches where appropriate are no longer simply best practices. They're increasingly essential to successful trial execution.

Beyond patient selection, where do you see the greatest opportunities for biomarkers to guide internal development decisions?

This is where biomarkers may deliver the greatest value, yet it's often the least discussed application.

Target engagement comes first. Pharmacodynamic biomarkers can answer one of the most fundamental questions in early development: is the drug doing what it was designed to do, in humans, at the intended dose? That distinction matters because a disappointing clinical outcome may reflect either an ineffective therapeutic hypothesis or inadequate drug exposure: two very different conclusions that require very different decisions.

Biomarkers also strengthen dose selection. Exposure-response relationships built on pharmacodynamic data provide a far more rational basis for Phase III dose selection than clinical endpoints alone in small early-stage studies. Given the increasing regulatory emphasis on dose optimization, generating that evidence early can significantly reduce downstream risk.

They're equally valuable for proof of concept, providing molecular evidence of biological activity before clinical endpoints mature and enabling smaller, faster studies. Perhaps most importantly, biomarkers can support objective go/no-go decisions. Pre-specified biomarker-based futility criteria allow sponsors to stop unsuccessful programs before they consume the time and resources required for late-stage development.

Biomarkers don't simply improve individual trials— they improve portfolio decision-making by helping sponsors

invest in the programs most likely to succeed.

How are regulators viewing the increasing use of biomarker-driven strategies in rheumatology, and what should sponsors be considering early in development?

Regulators are genuinely supportive of biomarker-driven development, and they've built the infrastructure to support it through biomarker qualification programs, guidance on enrichment strategies, innovative trial designs, and companion diagnostic development. They recognize that studying the right therapy in the right patients benefits everyone.

What they won't accept, however, is imprecision.

Sponsors must demonstrate analytical and clinical validation, clearly define the biomarker's context of use, and pre-specify how it will be used within the study rather than relying on post hoc subgroup analyses.

That places a premium on early planning. Sponsors should engage regulators earlier than may feel comfortable through pre-IND meetings, scientific advice procedures, and biomarker qualification pathways where appropriate. If a biomarker will determine patient eligibility, diagnostic development should proceed alongside therapeutic development rather than becoming an afterthought.

It's equally important to validate assays early and bank patient samples with appropriate consent. One of the costliest mistakes is reaching a pivotal trial with a compelling biomarker subgroup that emerged only through exploratory analyses and lacks the evidence needed for regulatory acceptance.

Looking ahead, which emerging technologies or scientific advances do you believe will have the greatest impact on precision immunology over the next five years?

Cell therapy has the potential to reshape the field more dramatically than any other recent advance.

CD19-directed CAR-T therapy has already produced drug-free remissions in patients with severe lupus, systemic sclerosis, and myositis, raising the possibility of resetting the immune system rather than suppressing it indefinitely. Newer approaches, including dual-target constructs and off-the-shelf allogeneic therapies, aim to make these treatments more scalable.

At the same time, it's important to keep those findings in

perspective. The studies remain relatively small, long-term durability is still being established, and significant questions remain around safety, patient selection, and predictors of response. The field itself still considers these approaches to be in their infancy.

Beyond cell therapy, advances in single-cell sequencing, spatial multi-omics, and artificial intelligence are expected to further improve target discovery and patient stratification. As these technologies become more accessible, they'll enable increasingly sophisticated analyses that integrate molecular data, imaging, electronic health records, and digital biomarkers.

The common thread is that development is moving toward smaller, biomarker-rich, adaptive clinical trials, and toward operational capabilities that many organizations have yet to fully build.

If there is one misconception you would like sponsors to move beyond when it comes to precision medicine in rheumatology, what would it be?

The biggest misconception is that precision medicine can be added to a development program later.

Precision isn't something to layer onto a successful Phase III study. It's a development philosophy that

needs to be built in from first-in-human studies through sample banking, biomarker exploration, assay validation, and early regulatory engagement. Attempting to retrofit precision strategies typically produces interesting exploratory findings that ultimately can't support registration.

It's also important to recognize that the oncology model doesn't transfer directly to autoimmune disease. In rheumatology, the answer is unlikely to be a single biomarker that neatly matches one patient to one therapy. More often, precision will rely on combinations of biomarkers that reflect dynamic immune pathways rather than static mutations.

Finally, precision medicine isn't only for large pharmaceutical companies. Smaller and emerging biotech's often have the most to gain because concentrating limited development budgets on the patients most likely to respond can dramatically improve the probability of success.

The key shift is recognizing that precision isn't an added expense—it's an investment in reducing the single greatest cost in drug development: late-stage failure. Sponsors that build precision into development from the beginning will be the ones best positioned to shape the next generation of rheumatology innovation.



Dr. Mila Grieg

MD, PhD, vice president of medical affairs, head of Immunology and Inflammation, Allucent Center of Expertise (ACE)

Mila Grieg is a seasoned medical and clinical development leader with more than 26 years of experience in medicine and clinical research. She holds both MD and PhD degrees and brings a strong clinical foundation, having practiced medicine for 10 years before transitioning to clinical research and development.

Over the past 20 years at Allucent, Mila has held increasingly senior medical leadership roles, providing medical strategy, clinical execution, and oversight for more than 50 clinical trials across Phases I-IV. Her

therapeutic expertise spans immunology and inflammation, rheumatology, allergy, infectious diseases, and vaccines, with extensive experience in immune-mediated and inflammatory diseases, including rheumatoid arthritis.

As vice president, Medical Affairs and head of the Allucent Center of Expertise for Immunology and Inflammation, Mila leads medical and therapeutic strategy across immunology and inflammation. She partners closely with clinical operations, business development, and scientific teams to develop integrated clinical development and service solutions, bringing extensive experience in rheumatology, immune mediated diseases, and strategic partnerships.

Throughout her career, Mila has combined deep clinical research expertise with strategic medical leadership, supporting sponsors across early- and late-stage development and contributing to innovative approaches to clinical trial design, medical strategy, and execution in immunology and inflammation.



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