WHITE PAPER

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Immunotherapy's Next Chapter: **In-Vivo Modulation, Cross-Disease Expansion, and the Need for Flexible CRO Models**

Investors are increasingly backing in-vivo application-ready immune-modulating medicines; therapies that reprogram the immune system inside the body, as a pragmatic alternative to complex cell therapies requiring ex-vivo manipulation (programming). The appeal is clear; broader patient reach, lower costs of goods (COGS), faster scale-up and platform extensibility across multiple indications in oncology and immunology. At the same time, oncology-first biotechs are intentionally expanding into autoimmune diseases to maximise their technology across immune contexts - strengthening pipelines and creating more resilient value creation paths.

As pipelines expand across oncology and autoimmunity, development models also need to keep pace. Many biotechs and pharma are looking for CRO partners who can adapt fluidly by shifting between full-service portfolio support and more tailored functional outsourcing. For smaller biotechs, especially where in-house resources may be limited, having a flexible partner can make the difference in running trials smoothly, keeping sites engaged and ensuring high-quality data across diverse programs.

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The Science: Trending Mechanisms in 2025

Biotechs are focusing on immune pathways that can be tuned for activation in cancer or tolerisation in autoimmunity. The most active areas include:

- Checkpoint inhibitors next-gen targeting: TIGIT, LAG-3, TIM-3; bispecifics (e.g., PD-1+ LAG-3).
- CD47–SIRPα axis for myeloid reprogramming.
- Adenosine (CD73/CD39/A2A) blockade.
- Engineered cytokines: biased IL-2, IL-15, IL-12, IL-18.
- Costimulatory agonists: 4-1BB, OX40, CD27.
- Innate sensors: cGAS–STING, TLR agonists.
- TGF-β and myeloid suppression blockers.
- T/NK-cell engagers with half-life extension.
- Genetic medicines in vivo: LNPs, AAVs, tolerising vaccines.
- Targeted delivery: antibody-directed LNPs, depot/oncolytic vectors.

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R&D Investment Baseline

A recent Springer Nature study (2023) estimated that (after accounting for attrition and applying a cost of capital at 10.5%) the clinical-stage R&D investment required to bring a new cell or gene therapy to market is approximately US$1.94 billion (95% CI: US$1.40B–US$2.49B).

This figure underscores the capital intensity of cell-based modalities compared with antibody-based immunotherapies, which leverage established development and manufacturing pathways.

Commercial Pricing and Economics

- Cell Therapy (CAR-T, Tecartus): US$373,000 for a treatment infusion at list price (Drugs.com) with higher real-world costs due to hospitalisation, monitoring and AE management.

- Checkpoint Inhibitor (pembrolizumab: Keytruda): ~US$112,500 per patient at list price (NHS England).

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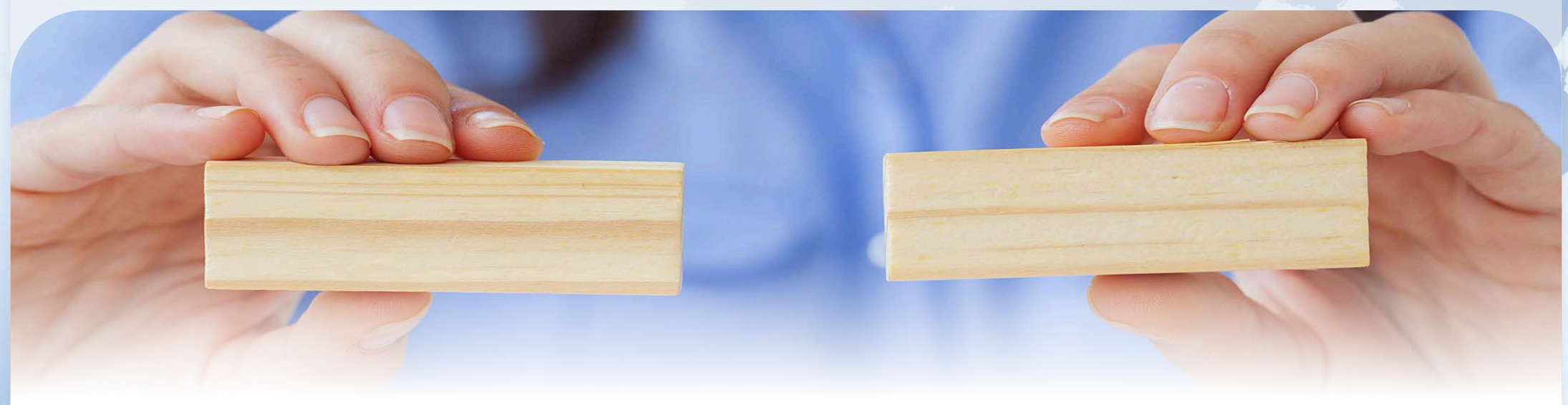
Comparative Implications

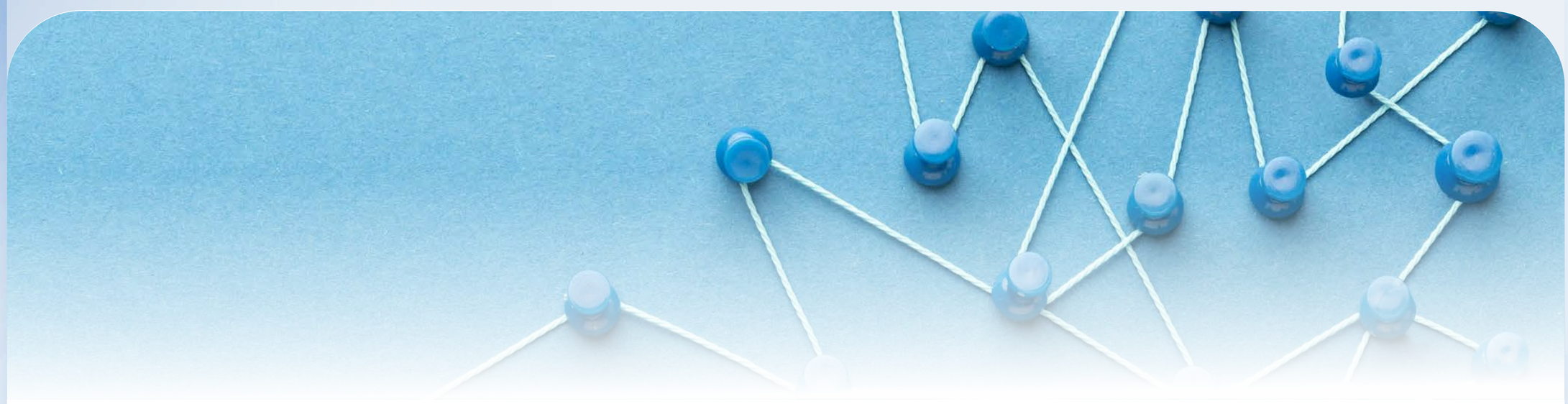


- Cell therapies carry both higher upfront R&D costs and (due to complex single therapy preparation and complex patient management) dramatically higher per-patient costs than in-vivo biological immunotherapies.

- In-vivo modalities (e.g. engineered cytokines, mRNA delivery or gene therapy) offer the programmability of cell therapy but with scalability and pricing models closer to biologics.

Investors view this as a superior economic model; repeatable dosing, chronic-use revenue potential and fewer manufacturing bottlenecks versus bespoke autologous approaches.

Oncology → Autoimmunity: A Strategic Expansion



A major shift is underway as oncology biotechs increasingly extend their immune-modulating platforms into autoimmune disease. The underlying science makes this possible as many immune pathways are inherently bidirectional.

So, while in fighting the tumour we need to activate pathways to drive stronger immune effector responses (e.g. through checkpoint inhibition, cytokine biasing, myeloid reprogramming), in autoimmune pathology we need better control of the overactive immune system (e.g. through Tregs expansion, tolerise autoreactive T and B cells, checkpoint activation or dampen inflammatory circuits). By extending the reach of their technologies across diverse therapeutic areas, oncology-first biotechs are capturing growing interest from investors and strategic partners.

Number of Oncology Biotech and Pharma Expanding into Autoimmune Diseases 2023-2025 (Zymewire November 2025)

· 2023: 105
· 2024: 232
· 2025: 514 (YTD)

Economic Rationale

- Platform leverage: One delivery stack (e.g. targeted LNP + mRNA payloads) can support multiple oncology and autoimmune programs.

- Broader TAM & smoother cadence: Autoimmune trials offer larger patient pools and clearer biomarker endpoints - de-risking development.

- Partnership gravity: Pharma demand is high for platforms that span oncology and immunology - improving BD optionality.

- Operational readiness: Expansion across immune contexts requires CRO partners able to adapt trial operations to different disease areas and regulatory expectations, not just replicate oncology playbooks.

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Conclusion

While ex-vivo therapy has made a significant advancement in selected (mainly onco-hematology) tumour management, it has not managed to change the overall global treatment paradigm in oncology. At the same time, in-vivo immunotherapy has matured into a cost-effective, scalable and versatile alternative to cell therapy, with economics that align more closely with antibody drugs than autologous CAR-Ts. With over 500 oncology biotechs already moving into autoimmunity in 2025 (per Zymewire, as of November 2025), the sector is pivoting toward cross-disease immune modulation.

The winners will not just be those with the best platforms, but also those with the most adaptable operating models which leverage CRO partnerships that can pivot between fixed and hybrid outsourcing to support portfolio expansion, site engagement and trial data integrity. For investors, this dual-use orientation; *amplify when you must, tolerise when you can*, is strengthened by an execution strategy that scales with the science.

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With 15+ years in life sciences, Paul has led global commercial growth, strengthened CRO brands, and driven strategic expansion. As CCO at Optimapharm, he oversees global sales and marketing, fosters client partnerships, and shapes the company's commercial vision and growth strategy.

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