Evolution of Cell Therapies: From Autologous to iPSC

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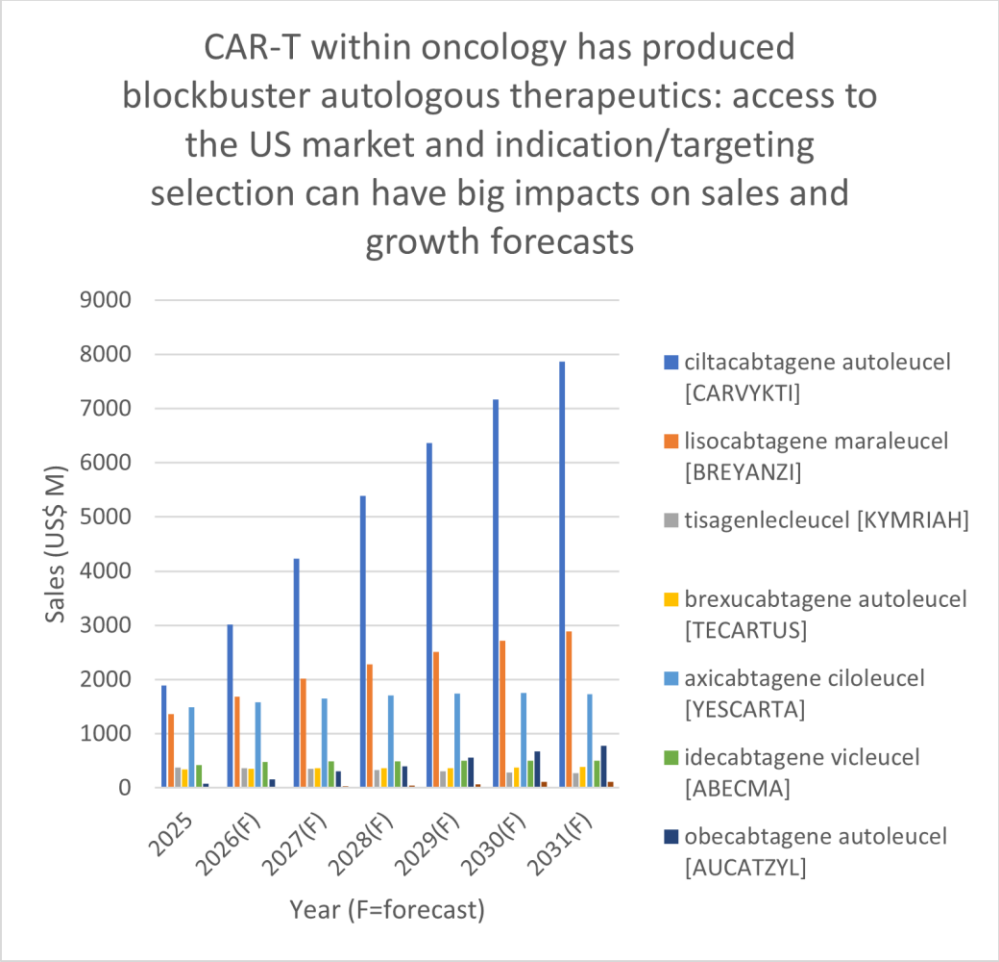
In last month's piece we had a look at non-gene modified/non-stem cell autologous and allogeneic cell therapies (first-generation) that pioneered the cell therapy space and noted some of the key weaknesses constraining clinical development, patient access and revenue generation for early innovators.

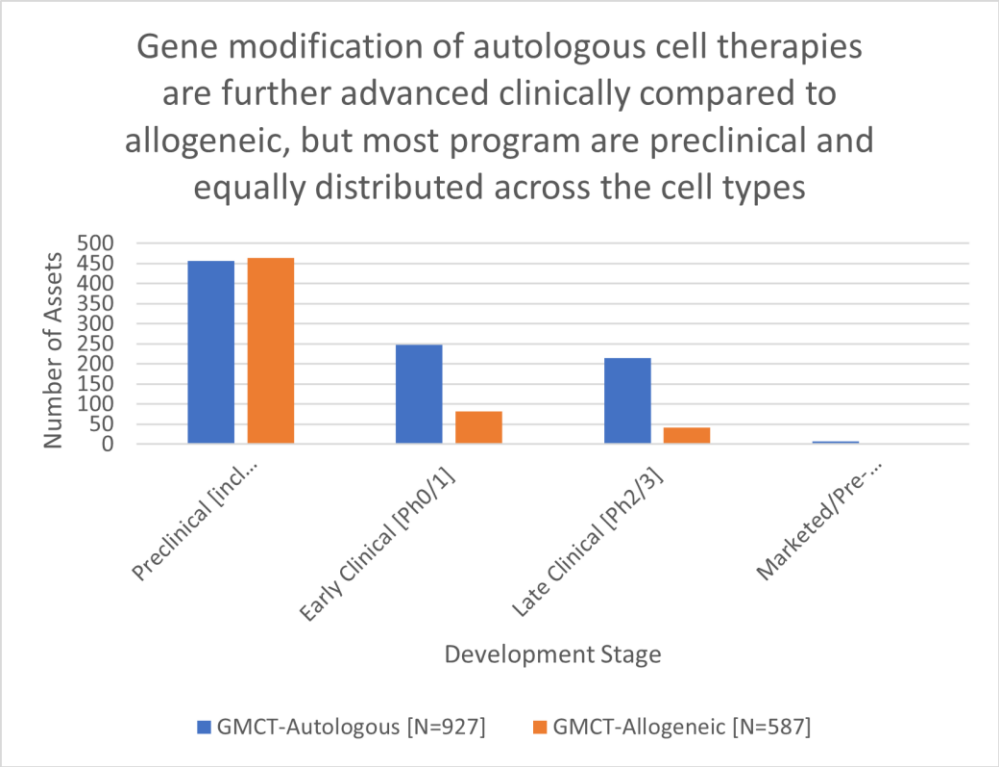
Approved and marketed autologous CAR-T therapy in oncology has clearly anchored the gene modified autologous cell therapy space (second-generation).



There are no currently approved gene modified non-stem cell allogeneic cell therapies (Ebvallo – EMA approved – is an enriched allogeneic T-cell product approved by the EMA but is not technically gene modified). Phase II readouts for allogenic CAR-T products from Allogene (cema-cel; Primary Mediastinal B-Cell Lymphoma) and Cellectis (lasme-cel; Follicular Lymphoma) are expected to have a big impact on further development of allogenic CAR-T, but also perhaps more broadly in other indications if funding is redirected into competing technologies.

Advances in gene modifying technologies and cell manufacturing that heralded the advent of CAR-T therapies has supported a robust

preclinical and development pipeline for non-stem cell gene modified autologous and allogeneic cell types so therapeutic options in multiple indications, not just oncology, should continue to emerge.



However, despite these advances many of the limitations noted in the previous piece remain for gene modified autologous and allogeneic cell therapies:

- For patients with rapidly progressing disease, manufacturing time is critical,

- The quality of the final therapy is intrinsically linked to the health of the patient's starting cells. Up to a third of intended CAR-T patients may not receive treatment, primarily due to disease progression and/or manufacturing failures,

- The bespoke nature of autologous manufacturing drives high Cost of Goods (COGs) which constrains pricing flexibility and market access,

- Additionally, safety profiles for these first-generation autologous therapies carry significant risks. Yescarta carries a black box warning for cytokine release syndrome (CRS) and neurologic toxicities (ICANS), necessitating stringent monitoring requirements that often mandate hospitalization,

- Gene editing to prevent rejection by the host and improve persistence are difficult in a primary cell setting. Allogene utilizes TALEN (Transcription Activator-Like Effector Nuclease) technology and anti-CD52 mAbs,

- Allogeneic therapies can still face "batch-to-batch" variability inherent in using different donors (this risk can be mitigated by enhanced selection procedures) and primary cells have a finite expansion capacity before reaching senescence, limiting the size of any single master cell bank,

- Limited efficacy of allogenic relative to autologous to date has driven further developments in manufacturing of autologous and a leapfrog to in vivo approaches that leverage in situ cell modifications, leaving allogeneic approaches struggling.

Third Generation: The iPSC Revolution

The emergence of induced pluripotent stem cell (iPSC) platforms represents a critical step in the evolutionary arc of cell therapies. iPSCs are adult somatic cells (e.g., fibroblasts or cord blood cells)

reprogrammed into a pluripotent state, capable of infinite self-renewal and differentiation into any cell type. This technology enables the creation of a Clonal Master Cell Bank (MCB), fundamentally changing the manufacturing economics and consistency of cell therapy:

- iPSCs have an infinite ability to expand, allowing companies to generate a master cell bank from a single clone. A single bioreactor run can produce over 1,000 doses of a CAR-T therapy,

- Every dose is derived from the same starting Master Cell Bank, batch-to-batch variability is virtually eliminated,

- Cells derived from a single donor at one point in time negate the need for continuous donor recruitment and re-qualification,

- iPSC platforms enable complex, multiplexed gene editing to be performed at the stem cell level before differentiation,

- Full characterization of single clones ensures all desired edits are present and no off-target effects have occurred. This allows for the generation of multiple gene deletions and bi-allelic insertions with relative ease and consistency,

- Sophisticated "armoring" and "stealth" features can be engineered:

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    - Century's CNTY-308 incorporates "Allo-Evasion 5.0" technology, which includes edits like CD300a TASR and IgG-degrading enzymes to prevent rejection,

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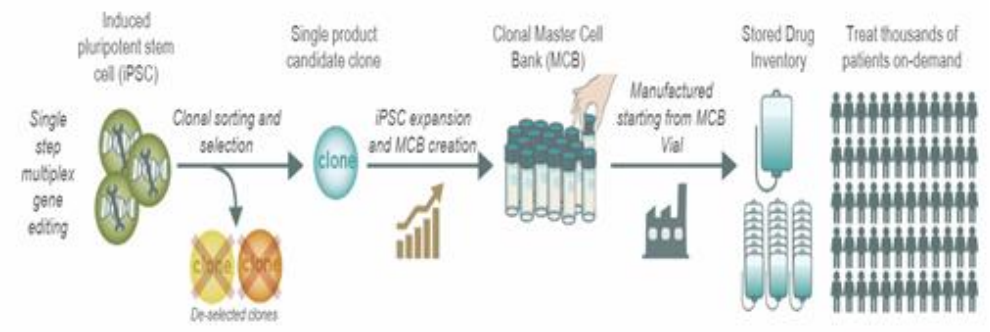
    - Lineage Cell Therapeutics utilizes a hypoimmune iPSC line with B2M deletion (to reduce CD8+ T-cell rejection) and HLA-E insertion (to mitigate NK-cell response),

- iPSC-derived therapies are cryopreserved and stored, ready for on-demand use,

- Scalability of iPSC manufacturing drives a dramatic reduction in the Cost of Goods (COGs), moving cell therapy economics closer to that of monoclonal antibodies [single-digit thousands of dollars per patient].



Clearly iPSC's can be derived from autologous and allogeneic sources and many of the same considerations for non-iPSC for each type apply. For the purposes of the remainder of this piece, we will focus on allogeneic sources based on the potential for multiplexed gene editing to address the main limitations of safety and immunogenicity as exemplified by programs at: Century [CNTY-101, CNTY-108], Fate [FT819] and Lineage [OpRegen].

Strategic Partnerships

The transition from first-generation autologous therapies to third-generation scalable, off-the-shelf allogeneic iPSC platforms has necessitated a fundamental restructuring of the biopharmaceutical deal landscape. Unlike autologous therapies, where value is primarily generated through clinical logistics and patient management, the next-generation cell therapy ecosystem relies heavily on the aggregation of distinct intellectual property (IP) domains: cell sourcing (iPSC master banking), precision gene editing (CRISPR, TALEN, Allo-Evasion), and differentiation protocols. Consequently, the period leading up to this year has been defined by a web of licensing agreements, strategic alliances, and subsequent realignments designed to de-risk these novel modalities and secure freedom to operate in a crowded IP landscape.

Partnership	Origin Date	Revised Date	iPSC Product	Partnership Attributes
Allogene - Notch	2019	2024 2025	T cell	Limited exclusive target rights and Roche acquired Notch (collaboration with potential competitor)
Century – Fujifilm Cellular Dynamics	2018	2023	NK cell	Clonal Master Cell Bank and scalable production for Century with complex licensing: Non-exclusive reprogramming, exclusive differentiation, non-exclusive autoimmune differentiation
Century – BMS	2022	2025	T cells NK cells	Termination - loss of large pharma partner but regain of program control and realisation of collaboration revenue
Sernova – Evotec	2022	N/A	islet cells	Device engineering company gains exclusive license to unlimited cell supply to transform into integrated therapeutics company through co-funding arrangement
Lineage – Factor	2023	2026	hypoimmune clonal master cell bank	Best-in-class component strategy for Lineage pipeline validates Factor platform both technically and financially
Lineage – Roche	2025	N/A	retinal cell	Milestone payment in 2026 validates Lineage program and late-stage financial/clinical support in a high barrier indication
Help – CR Sanjiu	2025	N/A	cardiomyocyte	Investment by large clinical/sales backer accelerates Help programs in large China markets, supports development in key RoW areas and validates fully automated and robotic production platform

De-risking Through Specialization and Partnership

The analysis of the deals space over the last 5 years reveals a clear trend toward specialization. No single company seems to be attempting to own the entire spectrum (Cells + Edits + Manufacturing + Clinical) in isolation.

- Cell Sourcing: Companies like Century and Sernova rely on partners (FCDI, Evotec) for the foundational iPSC banking, acknowledging that establishing clinical-grade master banks is a multi-year, capital-intensive process,

- Editing Technologies: Access to CRISPR (Arbor) and TALEN (Cellectis) is secured through licensing rather than internal discovery. This allows therapeutic developers to swap editing engines if legal or technical hurdles arise,

- Differentiation Protocols: In the Notch/Allogene and FCDI/Century deals, the value lies in the *protocols* to turn a stem cell into a specific therapeutic cell (T-cell, NK cell). These protocols are trade secrets that define the product's potency,

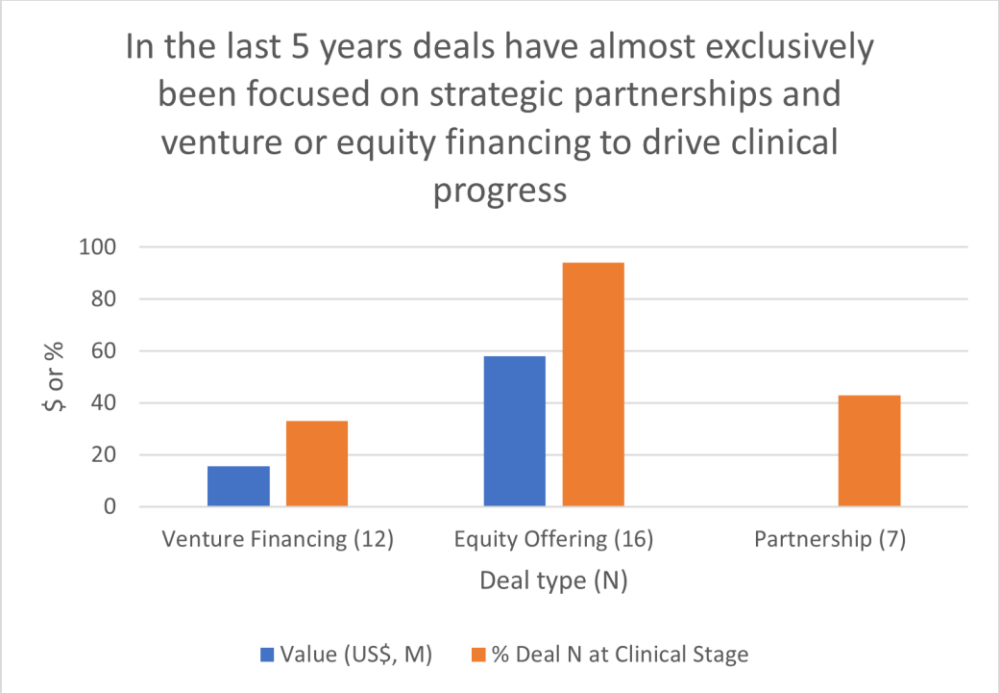
- Allo-Evasion: The Lineage/Factor and Allogene/Cellectis deals focus on "invisibility" edits (knocking out TRAC/CD52/B2M, modifications to HLA-E). Securing these specific edits is crucial because the IP landscape for gene editing is a minefield; licensing ensures freedom to operate without infringing on foundational CRISPR/TALEN patents,

- Manufacturing Scale: Sernova's reliance on Evotec is explicitly driven by the need for "biologic-scale" manufacturing. Evotec's

bioreactor capabilities allow Sernova to envision a product for millions of diabetics, which would be impossible with manual donor processing,

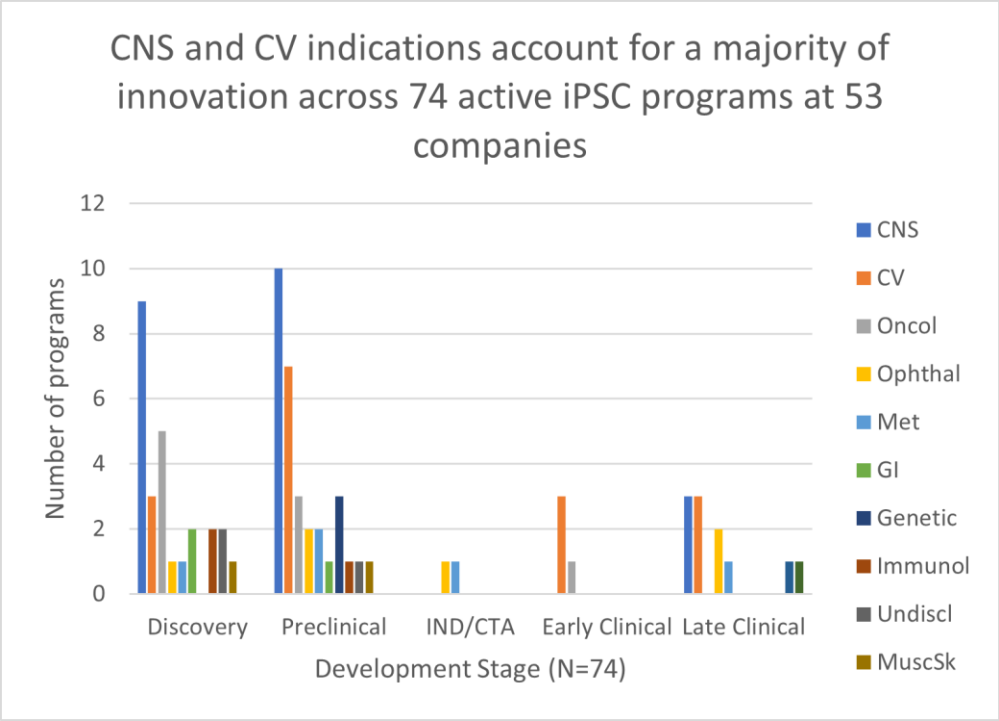
- Regulatory Muscle: Lineage's partnership with Roche and Allogene's (indirect) tie to Servier provide the regulatory infrastructure to manage global pivotal trials, which are operationally beyond the reach of mid-cap biotechs.

- Regional Strength: Help's partnership with CR Sanjiu exercises the regulatory, clinical and sales muscle to drive patient access in large markets.



Indications and Commercialization Shifting Gears

While oncology birthed the cell therapy revolution (see above), advances in iPSC manufacturing and manipulation are pushing the indications space wider from anchor points in CV and CNS.



Autoimmune diseases are rapidly becoming the proving ground for iPSC platforms due to the potential for deep, drug-free remission (immune reset) without the complex barriers of the tumor microenvironment.

Century Therapeutics is aggressively advancing this frontier. Their lead candidate, CNTY-101 (CD19 CAR-iNK), is currently enrolling in the CARAMEL Phase 1/2 trial for systemic lupus erythematosus (SLE), lupus nephritis (LN), and other B-cell mediated diseases, with preliminary data expected in 2026. Their follow-on candidate, CNTY-308 (CD19 CAR-iT), which incorporates "Allo-Evasion 5.0" technology to prevent rejection, is slated to enter the clinic in 2026.

Fate Therapeutics is positioning its iPSC platform to standardize treatment for autoimmunity with FT819 (CD19 iPSC-CAR T) already demonstrating complete B-cell ablation and remission in early patients, with a pivotal trial planned for 2026. The ability to manufacture these cells at scale allows for a "mAb-like" cost structure, essential for treating prevalent conditions like lupus.

Lineage Cell Therapeutics , in collaboration with Roche/Genentech, is advancing OpRegen (RPE cells) for geographic atrophy through Phase 2a. Success here would further validate the "cell transplant" model — replacing specific lost cell types rather than just killing cancer cells.

Sumitomo Pharma and Cuopris Inc in what may be considered a world first, received approval in Japan on Feb 19, 2026, for allogeneic iPS cell-derived dopaminergic neural progenitor cells for Parkinson's disease (Amchepry, raguneprocel) and cardiomyocyte sheets for ischaemic heart disease (RiHEART).

And on that last note a bit of speculation on the bright future of iPSC cell therapies...

Horizon	Key Theme	Critical Milestones & Technologies
5-Year	**Validation**	Clinical POC for iPSC in Autoimmune (SLE/LN). Second iPSC commercial approval (HF, AMD, T1D). "No-preconditioning", “multi-dosing” regimens validated on the back of multiplexed editing.
10-Year	**Industrialization**	COGS <$5,000 via fully automated "Cell Foundries". Solid tumor efficacy (RCC, Ovarian) becomes mainstream. Functional cures for Type 1 Diabetes firmly established.
50-Year	**Regeneration**	Routine cell transplants for aging organs (Retina, CNS, Heart). Longevity therapies targeting "inflammaging" (Tregs). Convergence of ex vivo cell replacement and in vivo reprogramming.

And on that note, will in vivo approaches leapfrog the entire ex vivo cell space? Probably not fully (but more on that in a future piece). Like most therapeutic spaces there is enough heterogeneity in human pathobiology to warrant multiple therapeutic modalities. The rational build-out on effective autologous approaches suggests that established cornerstone therapies and technical evolution in the cell therapy space will continue to benefit patients for decades to come by a variety of modalities and mechanisms.

All raw data derived from AlphaSense and GlobalData.