Targeted clearance of senescent-cells with CAR-T: a commercial analysis for a promising therapy in the treatment of ageing associated diseases.

This report analyses the commercialisation potential of the breakthrough in targeted senescent cell clearance with CAR-T. Patent ID: (WO2020160518).

The strategy entails engineering immune cells to specifically target senescent-cells to prevent or alleviate senescence-related diseases, such as cancer, Alzheimer's, and fibrosis.

Although the technology is still in its early preclinical stages, the manufacturing and scalability difficulties in cell and gene therapy (CGT) necessitate forward planning to stay ahead of the challenges. This study focuses beyond projected conclusion of clinical trials, to plan commercial operations in a region that can support the full potential of this technology, enter markets with significant unmet need and to offer rationale for early stage investment.

The global burden of ageing

In 2018, the WHO officially classified ageing as a disease, it is the greatest risk factor for the chronic diseases responsible for the majority of morbidity, mortality, and health-care costs worldwide. Increasingly the cellular mechanisms of ageing contributing to disease are being investigated, spurring billions of dollars in investment.

What is senescence and its role in disease

Tissue ageing is caused by cells that leave the quiescent state and accumulate with age, known as senescence. These senescent-cells accumulate in sites of ageing-associated disease and secrete components that disrupt tissue structure and function.

This leads to ageing-associated diseases, such as atherosclerosis, cancer and fibrosis. Ultimate goal of reducing senescent-cell burden is to enhance **health-span** by removing their associated inflammatory phenotype that progresses to multiple ageing-associated diseases.

What is the current market for senolytics

Senolytics are compounds that kill zombie cells by inhibiting anti-apoptotic pathways, however the therapies are transient and **may produce off-target effects** (Kobbe,2019).

The primary senolytics that have been investigated for therapy include Fisetin and the combination of Src-kinase inhibitor Dasatinib and flavonoid Quercetin, currently in phase 2/3 trials. However, some senescent-cells do serve a function such as in wound repair and do not secrete the pathogenic inflammatory cytokines that are released in the secretory-phenotype (SASP) of non-replicative senescent-cells (Wilkinson, 2020). The problem comes when there are too many senescent-cells which produce the SASP and induce inflammation.

Therefore the identification of cellular-senescence markers for **selective targeting** provides a potent tool for senescence clearance only where it is needed.

Targeted clearance of senescent-cells with CAR-T

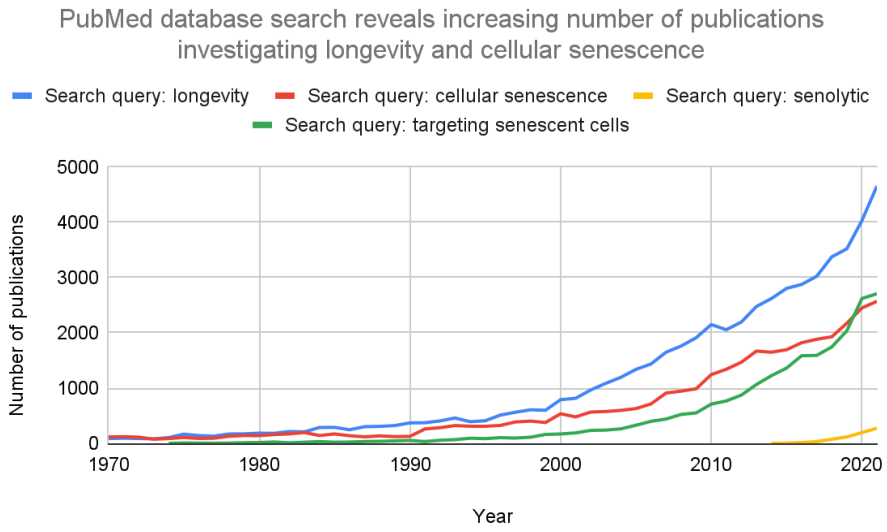
CAR-T therapies, which modify the patient’s own T-cells and reinject them to kill cancer cells, are saving lives of people who were previously deemed untreatable. Senescent-cells have similarities to cancer cell

phenotypes, notably in evasion of the immune system and resistance to apoptosis. Just like with cancer therapies, we could harness the immune system to recognise senescent-cells..

In this approach, T-cells are extracted from a patient's blood and genetically modified to express a receptor for **uPAR**, a cell-surface protein that is induced during senescence. CAR-T cells are then proliferated and infused back into the patient.

Viability

Research into senescence has exploded in the last decade, revealing senescence spreads like a cancer mediated by the SASP which can lead to senescence in neighbouring cells and pathogenic inflammation.



It has been revealed that senescent-cells over time evade the immune system, leading to their accumulation in ageing. uPAR has been demonstrated to be highly expressed in tissues from patients with senescence-associated disorders and animal model studies found uPAR specific CAR-T cells efficiently ablated senescent-cells in vitro and in vivo (Amor et al. Nature, 2020).

Value of platform technologies

Globally, VC firms invested over $52 billion in biotech startups between 2019-2021, over 60% of which was invested in platform-technologies (Leclerc, 2022). CAR-T manufacturing takes a platform approach when adopting pre-optimized production processes that extends to various disease areas. This favours the value potential of the technology since the senescent-cell burden is implicated across multiple diseases, with significant investor interest in targeting solid tumours.

The market

Economic value of targeting longevity

The value of statistical life model was recently utilised to assess the economic value of increasing lifespan. Extending life-expectancy by one year equates to $38 trillion, and by 10 years, $367 trillion (Sinclair, 2021).

Nearly every nation in the world ties their investment in medical research to the definition of a disease. The US for example, allocates more than 80% of its budget to over 2,500 research institutions where out of 285 diseases researched, attention ageing has grown 188% from $2.5 billion in 2014 to $5.6 billion in 2021 (NIH,2020). The largest % growth in funding aside from Alzheimer's disease.

However, investigating the 2018 $3.5 billion budget for ageing research revealed less than 3 percent of the funding for “ageing research” was actually for the study of the biology of ageing. And attention to ageing in other advanced nations is sparse, a direct result of the view that ageing is an inevitable part of life rather than a treatable disease.

Due to the dramatically rising prevalence of age-related comorbidities, a treatment targeting ageing is valuable as the impact will be felt across multiple diseases. The value model incentivises government backing of technologies that may serve as a treatment for severe unmet need, and longer term be utilised in the treatment of extending health-spans.

For the purpose of patient enrollment and gaining government or investor backing, the first indications initially targeted should be where there is greatest unmet need. For instance, the biggest company in senolytics, Unity Biotechnology, lost their initial clinical trial for osteoarthritis and is now concentrating on eye illnesses for which there is presently no effective treatment.

Initially the scope of therapies can be focused towards three main disease areas identified with severe unmet need, where the patient populations have been analysed across geographies:

Patient population with severe unmet need

Indication	EU	US	Asia
Alzheimer's Disease	7,000,000	6,500,000	23,000,000
In the absence of effective therapies, the estimated number of people with Alzheimer's will reach over 130 million by 2050			
PDAC	100,000	57,000	143,363
Devastating malignancy with an extremely poor prognosis, as shown by a 1-year survival rate of around 18% for all stages of the disease			
IPF	111,000	250,000	171,000
There is no cure for IPF and currently available drugs can only slow the disease down, and do not stop, or reverse the disease			
Total	**7,211,000**	**6,807,000**	**23,314,363**

1. World Alzheimer Report 2021, Dementia in the Asia Pacific Region
2. Global trends in pancreas cancer among Asia-Pacific population, Association of facility type with overall survival in patients with nonsurgically managed pancreatic cancer
3. European IPF Patient Charter: unmet needs and a call to action for healthcare policymakers, Annual ILD Day to Drive Awareness of Interstitial Lung Disease on Sept. 14

This reveals Asia as the largest patient population for initial indications, where Asia is undergoing a demographic shift to an ageing population that has implications on the economy and strained healthcare systems. It presents rationale for government and private research funding in a technology that has the potential to target ageing-related disease.

Pre-Launch Stakeholders

Due to biotechnology being a knowledge intensive industry, its commercial pathway should consider different global, national and local stakeholders. Pre-launch, the key stakeholders are involved in regulatory approval and funding, which as been analysed across regions:

Geography of capital raisings in 2020

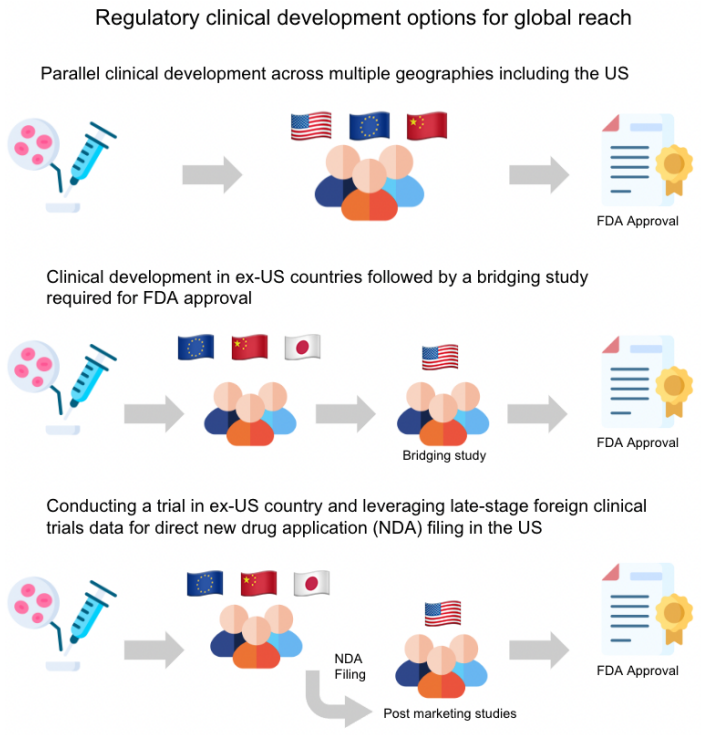
	Biotech based in China	Biotech based in Europe	Biotech based in North America	Biotech based in Japan	Biotech based in Singapore
Deals in Europe	11	567	133	3	6
Deals in China	493	14	33	3	5
Deals North America	64	164	2,295	20	12
Deals in Japan	1	2	9	56	0
Other Geographies	9	17	48	4	23
Total	578	764	2,518	86	46

All data generated in Global Data Deals Index, figures accurate as of November 2022

Average regulatory review time of marketing authorization:

	China	EU (EU27)	US	Japan	Singapore
Regulatory Authority	NMPA	EMA	FDA	PMDA	The HSA
Priority Review	3 months	4 months	6 months	6-8 months	8 months
Standard review	6 months	6 months	10 months	6-8 months	-

Because it enables authorization in other developed countries, the US remains the preferred jurisdiction for regulatory approval. In order to reach the target patient population in Asia whilst maintaining global reach, the product would have the following options:

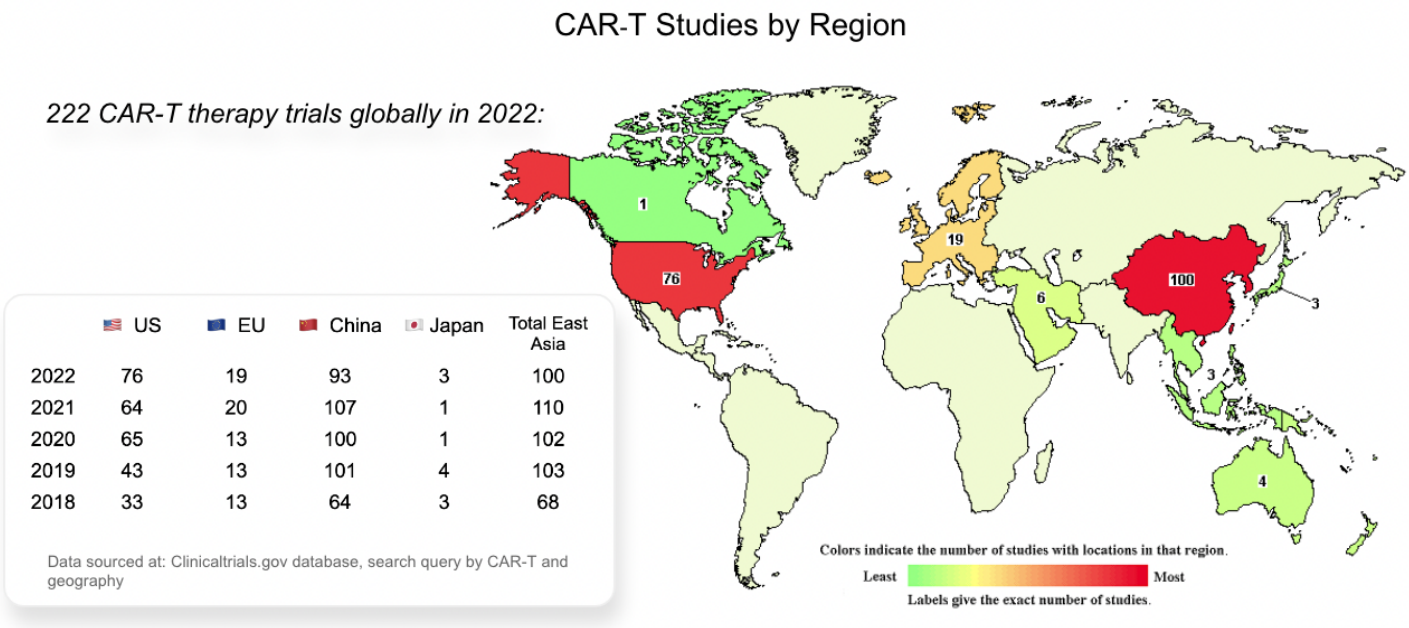


In recent years, the US FDA has approved several compounds developed by Chinese companies based on results from trials conducted in ex-US locations but required cross regional studies to be conducted since it is difficult to generalise the study results from differences in the patients' ethnicity.

Strategic Alliances

Biotechnology is an industry that has been defined as extremely strategic alliance oriented (Hagedoorn, 1993), where breakthroughs occur as a result of interactions between different entities such as research centres, VC firms, and IP protection authorities. Cooperation is best facilitated in a conductive environment such as Biotechnology clusters. Locating within an innovation cluster provides a competitive advantage through proximity to funding and access to “star scientists”.

This raises the question as to where innovations in CGT are concentrated: analysing clinical trials in CAR-T treatments indicates that China leads in the number of active studies, followed by the United States.



	US	EU	China	Japan	Total East Asia
2022	76	19	93	3	100
2021	64	20	107	1	110
2020	65	13	100	1	102
2019	43	13	101	4	103
2018	33	13	64	3	68

Data sourced at: Clinicaltrials.gov database, search query by CAR-T and geography

Geographic analysis of commercial potential for longevity biotech

Mckinsey's Biotech Innovation index identifies the US as leading in the number of patents, quantity of newly launched biotech, early stage finance, and impact of newly launched products. However the Asian biotech market leads in scaling; by value of late stage capital raised and IPOs. Its impact factor has grown faster than the US and EU markets by 55% from 2015-17 and 2018- 20.

Despite Asia's position as the world's third largest pharmaceutical market, it has undergone a shift from producing generics to developing innovative technologies. An examination of patents, funding, and entrepreneurship indicators space indicates China as a regional leader for APAC in R&D, biopharma production:

	EU	North America	China	Singapore	Japan	Leader
Gross domestic expenditure on Research and Development in 2020	2.32	3.45	2.4	1.89	3.26	North America
Ease of doing business rank 2020	-	-	3	2	30	Singapore
Charges for the use of intellectual property, receipts (BoP, current US$, 2021)	$167 B	$133 B	$11.7 B	$11.7 B	$48 B	China
Patent applications, residents	23,381	274,038	1,344,817	1,778	227,348	China
Patent applications, nonresidents	22,337	357,699	152,342	11,487	61,124	China
Researchers in R&D (per million people)	4,257	4,821	1,585	7,287	5,455	Singapore
Scientific and technical journal articles (2018)	524,444	482,864	528,263	11,459	98,793	China
Total tax and contribution rate (% of profit) 2019	40	30.6	59.2	21	46.7	Singapore
Value of venture capital financing worldwide in 2020, by region (billion U.S. dollars)	33.4	134	87.1	-	-	North America
The Venture Capital & Private Equity Country Attractiveness Index (2021 ranking)	-	1	7	6	3	North America
Global Innovation Index (2022 Score)	*Switzerland ranked 1st in region (64.6)*	*US ranked 1st in region (61.8)*	*Ranked 3rd in region (55.3)*	*Ranked 2nd in region (57.3)*	*Ranked 4th in region (53.6)*	EU
Growth in R&D spend 2022 *(Global Innovation Index)*	-	*5%*	*9.6%*	-	*-2.70%*	China

Data sources: UNESCO Institute for Statistics, World bank IBRD indicators (https://archive.doingbusiness.org/en/data), iese VCPE index (https://blog.iese.edu/vcpeindex/), WIPO Global Innovation Index 2022

Biopharmaceutical production in China benefits from cheaper development, due to the availability of advanced infrastructure, technology, and skilled resources at lower price. Resultantly many businesses are seeking to deliver cancer treatments created in China to the US at lower price points. This presents a promising opportunity to establish a global footprint by partnering with international biopharma corporations wanting to invest in innovative therapeutic modalities and serves as rationale for basing operations in China.

Since 2015, the Chinese government has invested heavily to spur innovation in biotech, both to address significant local unmet healthcare needs and to compete on the global arena (Frew, 2008). As such there is access to a large and diverse patient population for enrollment in trials

Implementation

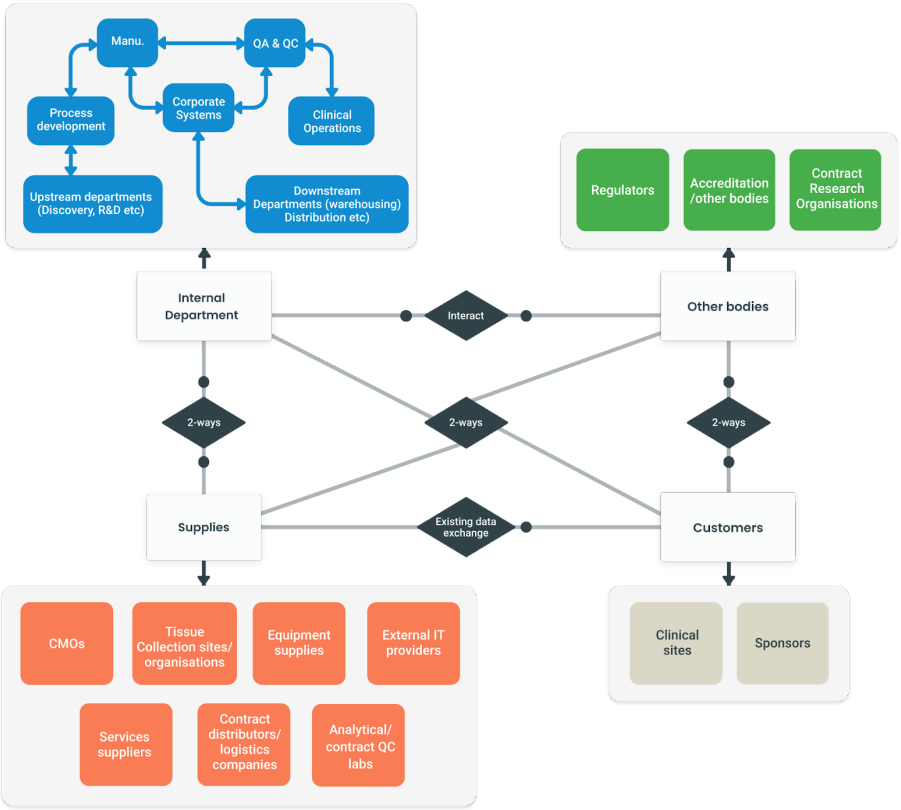
Establishing a biotech corporation is one of the most unpredictable and complex entrepreneurial endeavours in terms of technological requirement, capital intensity, and lengthy time to market (Patzelt, 2008).

Recent developments have shown that CGT can be commercialised and delivered rapidly at a global scale. However, the personalised and variable nature of manufacturing processes present novel challenges to development and expansion. It will be necessary to solve several problems to achieve the potential benefits:

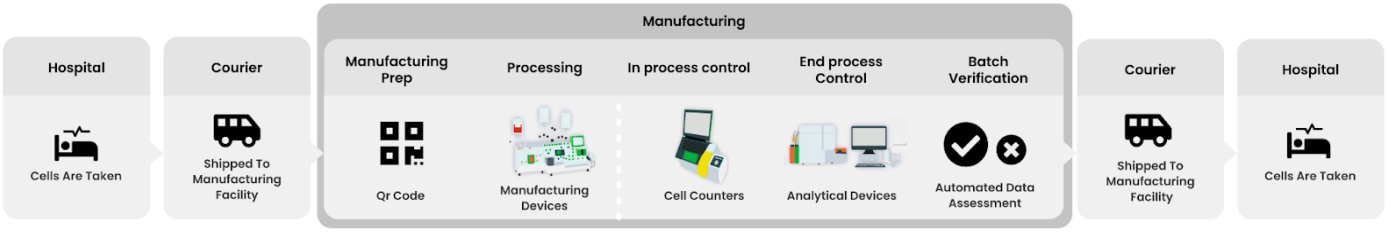
- High cost of goods (average cost for CGT drug products $500k-$2m per dose)
- Access to individuals trained in CGT therapy processes
- Availability of GMP manufacturing space
- Cash intensive R&D process for CGT therapies

Despite the mitigations by aiming development within the bio-pharmaceutical cluster to foster strategic alliances, China did feature the least researchers in R&D per million people of the regions analysed which could present an obstacle in access to highly trained individuals.

The graphic below illustrates complex processes involved in the collection, manufacturing and distribution of a CGT involving multiple stakeholders, who may be in different facilities across the globe:



A key consideration to explore in the preclinical stage would be the use of allogenic or autologous cells, since additional complexity arises when manufacturing involves processes performed at more than one location. Collection via hospital and transportation to a GMP facility for example:

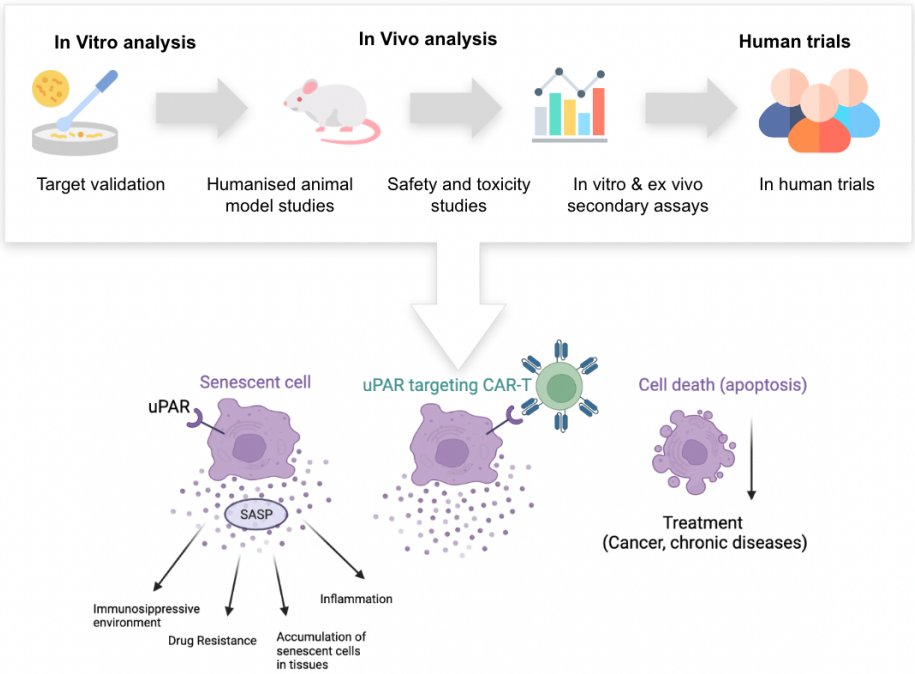


Foreign investment in China

CGT has been declared a strategic priority by major Chinese authorities, in line with technology initiatives to boost innovation. However, regulation contradicts these attempts by declaring foreign investors are not authorised to collaborate with Chinese firms on the development of CGT. Access to China is more difficult for overseas participants, however "pilot zones" assist to circumvent this issue. Hope City and Medicine Connect, for example, offer early access and treatment of patients with medicines that have been licensed elsewhere but not in China and free trade zones like Shanghai Pudong have emerged where regulations promote access to conduct studies for innovative medicines such as CGTs. However, there are only 1.5 doctors for every 1,000 people (Ministry of Health 2007), and medical-insurance coverage has dropped to less than 10% in rural regions making affordability of generic pharmaceuticals, let-alone biotech items, difficult.

Experiment

Currently this approach has only been validated in vitro and in vivo in animal models. To demonstrate feasibility the therapy will be tested in clinical trials. The unmet need is important as CGT is considered high cost and high risk, since once injected into the patient the effects are irreversible. Clinicians would be far more likely to prescribe an experimental therapy in cases where there is little or no other option and such a solution would likely also gain accelerated approval under fast track designations.



Conclusion

This study presents a regional analysis to determine a plan to commercialise the identified lead indications for significant unmet need. A major challenge is government recognition for the need to extend health-spans by targeting the cause of ageing related disease. The burden of ageing in Asia and thriving biotech ecosystem would provide a favourable location with government-industry partnerships. A strategy for global approval to reach wider markets has been proposed and considers the benefits of China as a region for fostering strategic partnerships. The scope of the report is limited in considering only a few of the challenges for a CGT commercialisation strategy.

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**All diagrams made in google drawings or biorender, Analysis tables cite data sources below*

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