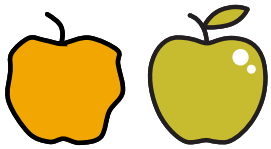
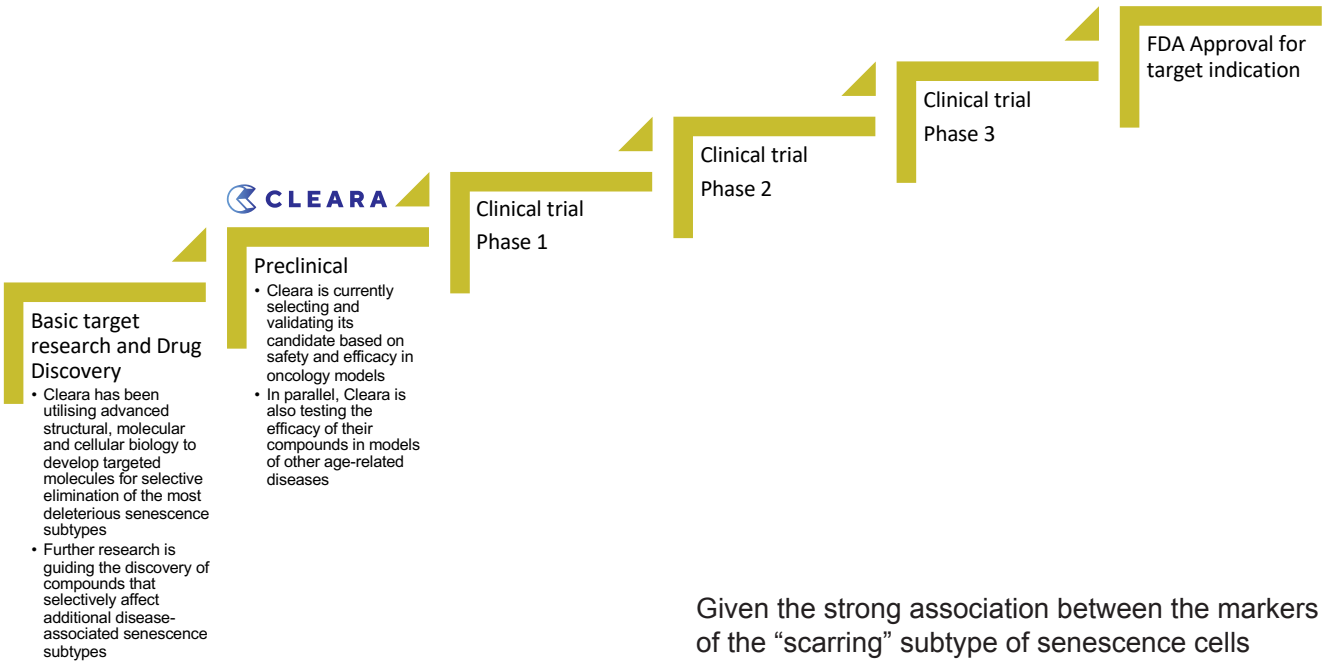


Pre-Clinical and Clinical Studies

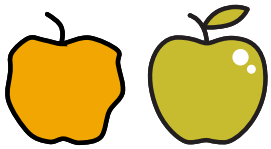


Cleara's drug candidates have been found to be efficacious in several independent oncology models using sensitive biomarkers that reflect the burden of target senescent subtypes and pharmacokinetic experiments to validate target occupation at desired location.

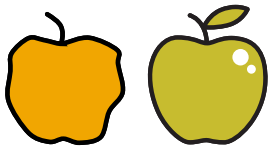
The third generation of FOXO4-based anti-senescence drugs has shown efficacy in counteracting signs of chemotoxicity and restoring healthspan in mouse models for fast and natural aging (www.cell.com/cell/fulltext/S0092-8674(17)30246-5). Metrics included fur density, behaviour, renal function and reducing senescent cell burden. A major improvement of Cleara's fourth generation FOXO4 peptides is improved on-target binding, biomarker engagement and shelf-life (from days to months), as well as improved plasma stability after administration. Cleara is currently in the process of selecting and validating its 4th generation candidate based on safety and efficacy readouts in oncology models.

Given the strong association between the markers of the "scarring" subtype of senescence cells and cancer cells, particularly in surviving cancer cells post chemo- or radiation therapy, there is the potential for stratifying oncology indications based on such markers and it also provides an opportunity for an ultra-targeted cancer therapy. Cleara is considering several endpoints for their clinical trials that are dependent on the type of cancer they ultimately target. This ranges from reduction in primary tumour volume to the prevention of metastases.

Cleara's strategy facilitates identification of novel senescent sub-population and disease relationships that can then be molecularly dissected to develop novel compounds (or iterate on existing ones) that target various disease states. Further, its biomarker discovery efforts will provide them with valuable data that can be used to optimise senotherapeutic strategies to ensure clinical trial success. In summary, Cleara is taking the necessary steps to improve the safety profile and potency of their flagship candidates in the efforts of translating results to individuals with therapy-resistant cancer and other chronic diseases.



Technology Platform Analysis	Description	Cleara
Class of Senotherapeutic	Senolytic, Senomodulator, SA-immunomodulator, Senoblocker.	Senolytic: Targeting a specific cellular mechanism that prevents apoptosis in damages senescent cells to restore induction of apoptosis in these cells selectively.
Target specificity	Features of therapeutic that facilitate targeting of senescent cells without off-target effects; dependent on senescent biomarkers	Cleara Biotechnology utilises its advanced structural, molecular and cellular biology know-how to identify mechanisms specific to senescent subtypes and design compounds to specifically target these mechanisms.
Delivery	Approaches (local or systemic), technologies (delivery vehicle), and formulations needed to safely and reliably deliver therapeutic to its target.	Cleara utilises a special chemical formulation (D-Retro-Inverso cell penetrating peptides) with significantly superior stability and plasma half-life, that is administered via subcutaneous injection.
Adaptability	Foundational technology that can be utilised to systematically improve, or build upon, robustness of therapeutic.	Cleara's deep know-how enables identification and characterization of new senescence subtypes, underlying mechanisms, and development of targeted modulators.
Regulation	Context specific control over therapeutic action once it has reached its target (spatial, temporal, sensitivity, degradation).	Cleara's flagship product targets a particular protein-protein interaction which is specific to damaged senescent cell subtypes, ensuring exclusive activity in the target cell type.
Toxicity	Level of damage that therapeutic can cause to organism; can include, but not limited to: off-target effects, on-target side effects, immunogenicity, etc.	Cleara is focused on specifically designing and developing compounds that selectively target mechanisms that are exclusively altered in distinct senescent cell subtypes. The selective targeting, which is limited to senescent subtypes, reduces the potential for on-target side effects that may contribute to toxicity, while the specific design for a particular target limits the potential for off-target side effects.



Cleara's platform technology is dependent on deep biomarker analysis of various senescent sub-populations that drive disease followed by the synthesis of novel compounds that target and clear these sub-populations based on biomarker profiles. It is Cleara's belief that their strongest and most important differentiator is the ability for patient selection based on a defined set of biomarkers. Cleara uses multiple biomarkers for efficacy, e.g. by advanced image-based mass cytometry, amongst others, on tissues and tumours. This greatly improves the power of senescent subtype-detection and patient selection which is critical for optimising efficacy and improving clinical trial outcomes.

Safety and Risks

Many of the senolytic drugs used to clear senescent cells cause profound toxic side effects due to lack of specificity toward senescent cells or pathogenic senescent cell sub-populations. A large part of the issue is the challenge of characterising senescence heterogeneity and the overall lack of sensitive biomarkers for senescence. Cleara's founders built their technological and business strategy with the knowledge that there are no "golden bullets" that can target pathogenic senescent sub-populations for every single chronic disease. More personalised, niche directed approaches are required for the development of drug pipelines that are destined for clinical success.

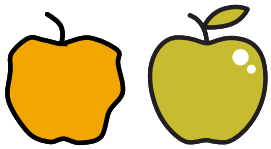
Cleara uses high resolution biomarker characterisation to design senolytic drugs that target pathogenic subsets of senescent cells that accumulate a high amount of damage and are "precisely the type of cell that needs to be removed" for a given pathology (in this case, oncology applications). One major benefit of Cleara's therapeutic strategy is that the compounds in the drug pipeline are rigorously designed and the mechanism of action is carefully elucidated. This means Cleara can use biomarkers to predict senescent cell specific sensitivity to their therapeutics. This has been successfully achieved with *in vitro* models, in 3D organoids and in mice.

According to Cleara, "markers that are being targeted by most other senotherapeutics are associated with phenotypes and processes in cells that may not need to be eliminated". This could lead to off-target effects and deleterious effects on physiology over time, especially if administered frequently. With their advanced biomarker imaging and bioinformatic technologies, Cleara aims to create a comprehensive and personalised senotherapeutic strategy that is optimised for patient safety and therapeutic success.

Target Market

Cleara's flagship products are focused on targeting late-stage cancer which had a market size valued at $63.18 billion in 2020 and is expected to reach $161.67 billion by 2027, a CAGR of 12.3% from 2021 to 2027. Late-stage cancer is one of the major concerns in the healthcare sector due to its fast progression and high mortality rate. Treatment of late-stage cancer, which often involves metastasis, is often not curable and is mainly focused on providing palliative care. Market growth is driven by the rising incidence of cancer and the unmet medical needs of patients that are eager for more promising therapeutic options. Cleara's technological strategy which includes personalised biomarker profiling and precision targeting of senescent populations driving late-stage cancer pathology holds promise to have a big impact within a disease demographic that has had a very poor prognosis to date.

Given that damage-induced senescent cells have been identified in several tissues associated with age-related pathologies, particularly in cancer and fibrosis, Cleara has the potential to focus on several different target groups. In the near term, the company is focusing its efforts on patients with tumours that display a specific damage associated signature. Once this shows clinical success, the company can use its advanced bioinformatics

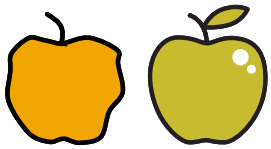


approaches and imaging technologies to expand their market and design novel peptides (or iterate on existing FOXO4 peptides) to target additional indications and mechanisms that are associated with various senescent sub-populations that drive disease.

Success Factors

Team and Reputation

- Cleara Biotech has a strong team with proven expertise on understanding and targeting subtypes of senescence within the fields of structural biology (NMR, FA), molecular biology (protein-protein binding), cell biology, animal studies and pharmacology. Its C-suite covers multiple aspects of a successful senotherapeutic start-up including entrepreneurship, senescence subtype expertise, peptide design and optimisation, as well as business insights;
- Cleara operates as an umbrella company and greatly benefits from its relationship with founding investor Apollo Health Ventures and Cambrian BioPharma which remain deeply involved in guiding the company's overall strategy, R&D strategy and connecting with potential co-investors;
- Peter de Keizer is scientific founder and a leading expert in the field of aging and cellular senescence. Peter trained in the lab of Judith Campisi where he gained pioneering experience in the field of senescence. Peter is an associate professor of "Senescence in Cancer and Aging" at the University of Utrecht in Netherland and has several high impact and highly cited papers (Cell, Cancer Research, Oncogene, etc.) on senescence in cancer and aging. Peter's work has been featured in over 100 mainstream international media channels and he is a recurring guest on aging and senescence podcasts and panel discussions;
- Marco Demaria is co-founder of Cleara Biotech and a leading scientist in cellular and molecular biology, aging research, cancer and cellular senescence. Marco trained in the lab of Judith Campisi, along with Peter de Keizer, and has several high impact and highly cited papers (Cancer Discovery, Nature Medicine, Cell) that have been largely influential in the field of senescence and cancer. Marco has served several roles as: scientific advisor to Deep Knowledge Life Sciences, consultant at Unity, editorial board member at Aging Cell, and associate professor at the European Research Institute for the Biology of Aging. Marco has an extraordinary track record in academic publications and his insights played a key role in the development of Cleara's scientific platform;
- Tobias Madl is a cofounder at Cleara and a leader in structural biology with expertise in biophysics, bioinformatics, metabolomics and molecular biology. Tobias is an associate professor and faculty member at multiple institutes across the globe where he studies and teaches about age related diseases and molecular medicines. Tobias has played a key role in the development of Cleara's drug design platform and therapeutic strategy;
- Cleara biotech benefits from a stellar advisory board, including Dr Yvonne Angell (pharmaceutical leader in synthetic and analytical chemistry), Professor Boudewijn Burgering (key opinion leader in the field of FOXO therapeutics), and Professor Onno Kranenburg and Dr Jeanine Roodhart, MD (experts in preclinical and clinical oncology, respectively).
- Cleara's key partnerships are a crucial component driving its success within the senotherapeutics field. Cleara has partnerships with three academic centres as well as being the industrial leader of three academic consortia. These partnerships play a critical role in Cleara's business and scientific strategy and help promote their mission, ensure capital and attract skilled experts into the company. Cleara's scientific founder Peter de Keizer regularly speaks at scientific and partnering conferences to promote the therapeutic potential of Cleara's programs;



- The current team has a strong breadth of knowledge (especially within the field of senescence) that has aided development of its therapeutic pipeline and technological platform. Given that Cleara is beginning to expand into medically defined areas (i.e. oncology) with its lead candidate, the company would benefit from new team members that can support its preclinical development, manufacturing, as well as medical translation manager to lead clinical development (IND, clinical trial design, etc.). Alternatively, Cleara is open to out licencing its oncology program to a strategic partner.

Intellectual Property

- Cleara Biotechnology's advanced know-how including mechanistic and structural insights into the biology of distinct senescence subtypes and dense network of partnerships gives it plenty of opportunities for developing intellectual property based on the design of innovative therapeutic candidates and discovery of novel senescent biomarkers based for senescence subtype specific molecular characteristics;
- Cleara recently optimised its flagship FOXO4 peptides and attained significant new IP which is fully owned by Cleara. These peptides were modified to improve potency and stability to address key requirements for clinical translation. The company also owns IP on surface biomarkers for senescent cells. This allows Cleara to detect senescent cells pre- and post-therapy;
- Cleara is filing additional IP based on novel "mechanism of action" discoveries made when testing its fourth generation FOXO4 peptides as well as IP on new biomarkers of senescence;
- Cleara plans to expand its label towards several other oncology applications and iterate on its technology to create new IP for therapeutics that address other chronic diseases of aging, such as fibrosis;
- Cleara is currently performing additional efficacy studies on its flagship product to narrow down which patient segment is most responsive to its therapeutic for oncology applications;
- Due to the company's rigorous approach of defining biomarkers that are indicative of senotherapeutic success in defined patient segments, they will have unique insights for clinical trial design. This provides Cleara great potential of not only attaining clinical trial success with their flagship product, but also generating IP for a range of oncology and chronic disease applications.

Funding

- Cleara's founding investor is Apollo Health Ventures, and Cambrian BioPharma is a co-investor;
- The company will begin raising Series A funding in Q3 2021 to progress their oncology program into the clinic, and is also considering strategic partnership for its programs;
- After validation of Cleara's flagship product for the first oncology application, there is vast potential for expansion to other types of cancer and age-related diseases. The Series A funding will enable the company to explore additional preclinical animal efficacy models to validate patient selection and efficacy for their oncology indications and additional models for chronic disease application.