

Deciduous Therapeutics

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DECIDUOUS
THERAPEUTICS

Restoring immune surveillance to tackle age-related diseases

Deciduous Therapeutics is developing a novel class of immuno-therapies designed to systemically clear senescent cells and to treat co-morbidities of aging.

The gradual accumulation in tissues and organs of permanently damaged cells that don't die, known as senescent cells, is a hallmark of aging. Both intra- and extracellular stimuli—chemical or physical, including DNA damage, oncogene activation, infection, oxidative damage, and mechanical stress—can cause cells to enter a senescent state. In addition to showing resistance to cell death, senescent cells are characterized by a senescence-associated secretory phenotype (SASP), whereby they secrete pro-inflammatory and tissue-remodelling factors that result in detrimental local and systemic effects. Because senescent cells are found at pathogenic sites in many major age-related chronic diseases, they are a promising target for anti-aging therapeutics.

"There is a lot of excitement around senescence and significant efforts are underway to find drugs that remove senescent cells or mitigate their effects," said Anil Bhushan, professor of medicine at University of California, San Francisco (UCSF), United States (US) and co-founder of the biotech company Deciduous Therapeutics. However, the promise of therapies to eliminate senescent cells is yet to be realised. "It is difficult to target senescent cells directly since there is no universal method to identify them; many of their features, including the anti-apoptotic pathways they rely on, are not exclusive to senescent cells and exist in many healthy cells such as neurons, beta cells, and immune cells," he explained.

A unique immune-mediated approach

Research by Bhushan and others has shown that senescent cells act as sensors of damage. They signal that something is awry and attract immune cells, which in turn can orchestrate their elimination. Thus, failure of our immune surveillance system facilitates the accumulation of pathogenic senescent cells. By restoring the immune-mediated clearance of senescent cells, Deciduous Therapeutics stands apart from other companies that are developing senolytic agents that are often compromised by intractable off-target effects (Fig. 1).

"We discovered that a subtype of cells that sit between the innate and adaptive immune system were dramatically dysfunctional where senescent cells were accumulating," Bhushan said. His team showed in two different mouse models of disease that the number and function of these invariant natural killer T (iNKT) cells was significantly reduced in tissues with high levels of senescent cells¹. Importantly, transient activation of iNKT cells by a small molecule therapy was sufficient to eliminate senescent cells in vivo, culminating in disease resolution.

Deciduous Therapeutics was founded when Regis

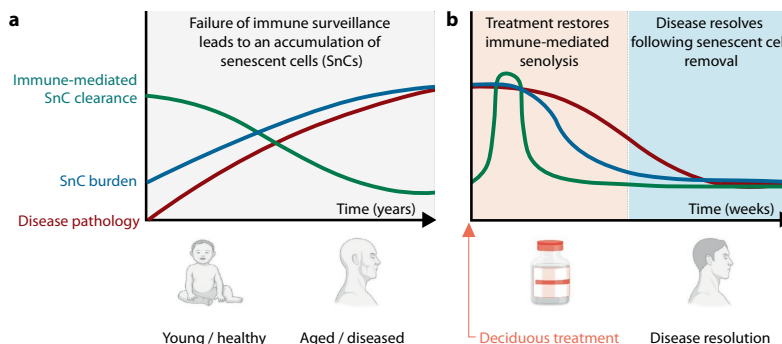


Fig. 1 | Restoration of natural killer T cells ablates senescent cells and resolves disease. a, Senescent cells accumulate owing to a failure in immune surveillance and drive age-related diseases. **b**, Deciduous's novel immunotherapy restores immune surveillance, resulting in the ablation of senescent cells and culminating in disease resolution within weeks. Created with BioRender.com

Kelly, director of the California Institute for Quantitative Biosciences (QB3) at UCSF, introduced Bhushan to life sciences entrepreneur, Robin Mansukhani. "Bhushan's findings on the effects of immune-mediated clearance of senescent cells on a number of diseases, including type 1 diabetes, which is not linked to age, caught my eye as an incredible opportunity to systemically improve health. I had considered senescence only in the context of aging, but after seeing Bhushan's early data, I realised that his immune-based approach had the potential to revolutionize the field," he said. "Prior to meeting Anil, I had been studying early senolytic approaches and found the premise of senescence removal to be promising but felt that the off-target effects of senolytics combined with the need for frequent dosing would become a translational bottleneck."

As Mansukhani, now CEO and co-founder of Deciduous Therapeutics, explained, "rather than target a non-specific anti-apoptotic pathway on senescent cells, Deciduous is focused on directly restoring the body's natural immune response to senescent cells. We believe nature and thereby the immune system provide the best roadmap for the safe and effective removal of senescent cells."

Applying immune-based senolysis

Bhushan's initial work showed that a tool compound, alpha-galactosylceramide (α GalCer) could be used to activate iNKT cells and reduce senescent cells in adipose tissue, leading to durable improvements in blood glucose levels, insulin resistance and HbA1c levels in diet-induced obese mice. Subsequently, to demonstrate the widespread utility of immune-based senolysis, the company applied the approach to a severe model of pulmonary fibrosis. In this study, a single treatment at the peak of disease resulted in the

ablation of senescent cells in the lung and attenuation of key fibrotic and inflammatory markers, which ultimately resolved fibrosis. Deciduous Therapeutics has used computational assisted design to synthesise a suite of proprietary therapies that could be used in the clinic to re-activate tissue-resident iNKT cells.

To date, the company's lead program has shown single-dose efficacy in resolving both metabolic and fibrotic diseases along with a favorable safety profile at doses significantly higher than the efficacious dose. "We can induce a safe and transient activation of iNKT cells in multiple models with our lead therapy and are continuing to investigate the effects in additional age-related comorbidities," Mansukhani said.

The company has appointed a diverse set of advisors including Eric Verdin, CEO of the Buck Institute for Research on Aging, California, Paul Wolters, director of research of the ILD program at UCSF, Max Krummel, Chair of ImmunoX at UCSF, Kristen Fortney, CEO of BioAge Labs, California, and James Peyer, CEO of Cambrian Biopharma. Deciduous's financial supporters include venture groups from the US, Europe and Asia, and Deciduous has been the recipient of Golden Ticket awards from AbbVie and Eisai.

Overall, Deciduous's long-term vision is to provide a globally accessible immune therapy that can be intermittently administered to systemically treat age-related comorbidities.

1. Arora, S. et al. *Med* 2, 938-950 (2021).

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