Artificial intelligence identifies new small-molecule senolytics

We used graph neural networks trained on experimental data to identify senolytic compounds from vast chemical libraries of over 800,000 compounds and discovered structurally diverse senolytics that have potent in vitro and in vivo activity, as well as favorable medicinal chemistry properties.

This is a summary of:
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The mission

The selective removal of senescent (non-dividing) cells extends healthspan and enhances chemotherapy efficacy in mice[1,2]. Senolytics are small molecules that can mediate healthy aging by selectively eliminating senescent cells, but their clinical application has been limited by poor bioavailability and adverse effects[1]. The discovery of novel senolytics with unprecedented chemical structures can advance their development as a class of therapeutics, helping to promote healthy aging and address diseases such as fibrosis and inflammation.

We previously applied artificial intelligence (AI) approaches, including graph neural networks, to the discovery of bioactive small molecules such as antibiotics[3]. In computational science, graphs are data structures comprising two components, nodes (or vertices) and edges, and graph neural networks are deep learning models that can infer information from graphs. Translating this AI-driven approach to the discovery of senolytics would open up this promising therapeutic space to software, enabling us to identify drug candidates from chemical spaces (sets of all possible compounds with determined properties) of over 1 billion compounds[4] at a scale that could not be accomplished by experimental testing alone. This AI-driven approach would also enable subsequent models to be retrained on the basis of new data, and the process of compound curation, experimentation and model retraining could be iterated to build accurate models that help us to productively mine vast chemical libraries in silico and design new senolytic small molecules de novo.

The solution

We evaluated 2,352 compounds (largely FDA-approved drugs and drugs undergoing clinical trials) for senolytic activity in a cell-based model of therapy (etoposide chemotherapy)-induced senescence. We defined active compounds on the basis of their ability to decrease senescent cell viability without substantially decreasing control cell viability, and we used this initial dataset to train graph neural networks to predict senolytic activity on the basis of chemical structure (Fig. 1a). For each compound, the model performs 'message passing' — a pattern of mathematical operations based on the atoms (nodes) and bonds (edges) in the compound structure — and outputs a number between 0 and 1 that represents the probability that the input compound has senolytic activity. We applied the model to 804,959 compounds in silico and identified 2,565 compounds as active (having prediction scores > 0.4).

Next, we performed computational filtering to select candidate compounds on the basis of no promiscuous reactivity (the property of a compound to also interact with unrelated targets), favorable pharmacokinetics and structure novelty. We tested 216 compounds that passed these filters at the bench; 25 of them exhibited senolytic activity (Fig. 1b), yielding a working hit rate of 11.6% that was substantially higher than the percentage of active compounds (1.9%) in our training data. Of the validated hits, three compounds were similarly selective as ABT-737 (a known senolytic) and had senolytic activity in a model of replicative senescence (induced by repeated cell divisions). These compounds also seem to possess favorable medicinal chemistry properties, including low molecular weights, no hemolytic activity and no genotoxicity, while potentially acting on apoptosis regulators Bcl-2 proteins (ABT-737 targets). Intraperitoneal injections of one compound in aged mice decreased the levels of aging biomarkers (senescence-associated β-galatosidase and mRNA expression of *Cdkn2a* and *Cdkn1a* (also known as *p16* and *p21*, respectively) in the kidneys compared with vehicle treatment.

The implications

Our approach demonstrates that combining high-throughput phenotypic screens with AI-driven modeling can facilitate the discovery of structurally diverse senolytics. Because our approach can also select candidate molecules on the basis of computationally inferred properties (such as favorable medicinal chemistry), the selected compounds can help to overcome the limitations of current senolytics. Furthermore, for small molecules, senolytic activity can be inferred from chemical structure. We anticipate that the design and development of additional AI-driven models will enable the generation of more tunable and programmable senolytics.

We used models of therapy-induced and replicative senescence, but senescence is a complex pathway that can also be activated by factors that include oncogene expression and oxidative stress. Further work should study whether the senolytics discovered using any one model system are as effective in other models. How well AI-driven models can identify structurally unprecedented compounds depends on the diversity of the training set; we plan to train next-generation models using data obtained from high-throughput screens of more extensive chemical spaces.

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EXPERT OPINION

"This impressive work uses deep learning techniques to explore diverse molecular structures for use as novel senolytics. The authors demonstrate that 'cheminformatics' can be used to design promising new anti-aging drugs, which they then test. Laudably, they also share their software pipeline to accelerate future molecular discovery." **Andrew Rutenberg, Dalhousie University, Halifax, Nova Scotia, Canada.**

FIGURE

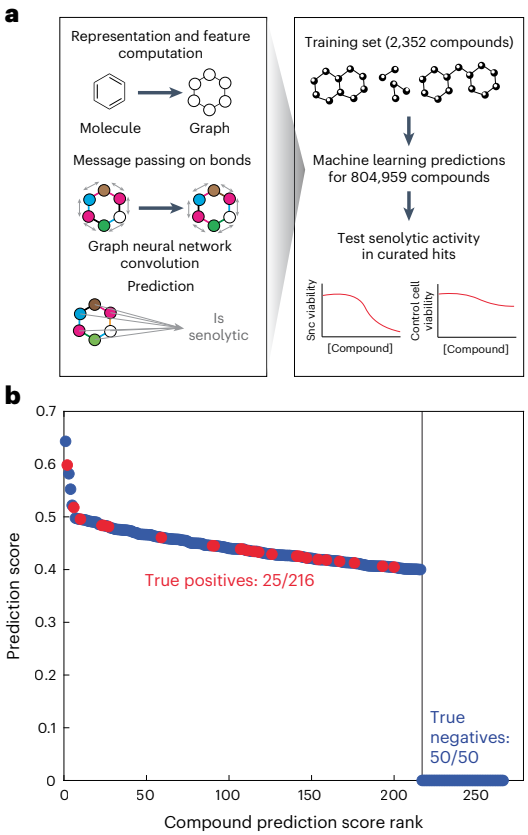

Fig. 1 | Discovering senolytics with graph neural networks. a, Schematic of the approach. We screened 2,352 compounds, including known senolytics, for senolytic activity, and we used the data to train graph neural networks to predict the senolytic activities of 804,959 compounds. Compounds predicted to be active were tested for senolytic activity in vitro. Snc, senescent cell. **b**, Rank-ordered prediction scores of 266 (216 high-ranking and 50 low-ranking) curated and tested compounds. Red points indicate tested compounds that were found to be active.

BEHIND THE PAPER

We have long been interested in age-related diseases. The unmet need for therapies that target age-related diseases is high: fibrosis and resulting organ failure account for at least one third of all deaths worldwide[5]. Senolytic therapies promise to address various age-related diseases, but few senolytic compounds are known. Hence, senolytic discovery remains an important area of research for the field.

Like antibiotics, and unlike drugs discovered using mechanism-guided approaches, senolytics are defined by their ability to target a specific phenotype[1]. This feature presented an attractive opportunity to apply the approaches we have developed for antibiotics (which leverage the use of phenotypic information) to senolytics. Although our final models were trained on only 45 active compounds, we were excited that our predictions were substantively enriched for senolytic compounds, and that several structurally novel compounds were as selective as ABT-737 while possessing more favorable medicinal chemistry properties. **F.W.**

REFERENCES

1. Kirkland, J. L. & Tchkonia, T. Senolytic drugs: from discovery to translation. *J. Intern. Med.* **288**, 518–536 (2020). **This review presents an overview of previously discovered senolytics and their therapeutic potential.**
2. Wakita, M. et al. A BET family protein degrader provokes senolysis by targeting NHEJ and autophagy in senescent cells. *Nat. Commun.* **11**, 1935 (2020). **This paper shows that a BET family protein degrader is senolytic and eliminates chemotherapy-induced senescent cells in mice, increasing the efficacy of chemotherapy.**
3. Stokes, J. M. et al. A deep learning approach to antibiotic discovery. *Cell* **180**, 688–702.e13 (2020). **This paper demonstrates that graph neural networks can be applied to discover small molecules with antibacterial activity.**
4. Irwin, J. J. et al. ZINC20—A free ultralarge-scale chemical database for ligand discovery. *J. Chem. Inf. Model.* **60**, 6065–6073 (2020). **This paper introduces ZINC20, the latest version of an influential small molecule database, which contains about 2 billion compounds.**
5. Rockey, D. C., Bell, P. D. & Hill, J. A. Fibrosis—a common pathway to organ injury and failure. *N. Engl. J. Med.* **372**, 1138–1149 (2015). **This review discusses the biology that underlies fibrosis.**

FROM THE EDITOR

"When this paper was submitted, it stood out to us because it demonstrated that deep learning can be used to discover new senolytic small molecules. This in silico approach enables the field to identify candidate drugs more easily, compared with other discovery methods (for example, in vitro screening). The ultimate aim is to derive a greater variety of senolytics, and with this work we are one crucial step closer." **Editorial Team, *Nature Aging*.**