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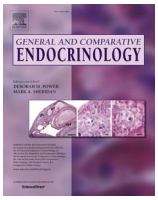

IGF-1 receptor inhibitor OSI-906 reduces growth in nestlings of a wild passerine

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ABSTRACT

Young animals need to grow to a large body size fast to maximise their survival prospects until sexual maturity. However, body size varies substantially in wild populations, and neither the selection pressures maintaining this variation, nor the regulatory mechanisms are well understood. IGF-1 administration has been shown to accelerate growth, but this does not necessarily imply that natural variation in growth rate is IGF-1 dependent. To test the latter we administered OSI-906 to pied flycatcher *Ficedula hypoleuca* nestlings, which has an inhibitory effect on IGF-1 receptor activity. We performed the experiment in two breeding seasons to test the prediction that blocking the IGF-1 receptor downregulates growth. As predicted, OSI-906 treated nestlings had lower body mass and reached a smaller structural size than siblings receiving a vehicle only, with the mass difference being most profound at the age preceding the highest body mass growth rate. The IGF-1 receptor inhibition effect on growth varied with age and year of study, and we discuss possible explanations. The OSI-906 administration results indicate that natural variation in growth rate is regulated by IGF-1, and constitutes a novel tool to study causes and consequences of growth variation, but details of the underlying mechanism still need to be resolved.

1. Introduction

The early postnatal growth phase is among the animal's first stages in its lifelong endeavour to maximise Darwinian fitness. It is generally accepted that young animals need to grow to a large body size and do it fast to maximise their survival prospects until sexual maturity. However, growth rates are not always maximised, as is evident from a phenomenon known as 'catch-up growth': the acceleration of growth rate following a period of reduced growth (Metcalfe and Monaghan, 2001). This suggests that fast growth somehow has a detrimental effect on fitness, but how such a cost arises is poorly understood (Dmitriew, 2011; Flatt and Heyland, 2011; Lodjak and Verhulst, 2020).

Optimal growth patterns and body size evolution is ideally studied through direct manipulations of growth rate, but conducting 'clean' experimental manipulations of growth rates is challenging. In some species and/or life stages growth rate can be manipulated through changes in the ambient temperature, for example in fish (e.g., Lee et al., 2013) and avian embryos (e.g., Vedder et al., 2018). However, most experimental manipulations of growth have changed energy management indirectly, for example, by changing brood size, parental foraging efficiency, or by food supplementation (e.g., Gerritsma et al., 2022; Griffioen et al., 2019; Lodjak et al., 2022; Lodjak et al., 2014; Paul et al., 2019; Schubert et al., 2009; Seress et al., 2020; Stahlschmidt and Adamo, 2015; Williams, 2018). While these approaches have yielded important insights with respect to growth, these treatments do not allow us to distinguish between the effects of changes in the resource budget and changes in resource allocation, and in particular the latter is of interest in the context of the optimal growth rate.

Another approach is through the manipulation of hormones that manipulate the ways young animals use their resources (Spencer et al., 2009; Spencer and Verhulst, 2007; Wood et al., 2018). However, when the administered hormones have pleiotropic effects, as is the case with for example glucocorticoids and many other hormones, this complicates the interpretation of the results because of uncertainty over the mechanism through which hormones modulate growth rate. We assume however that this is less of an issue when administering hormones with more specific effects in the context that they are administered. With this assumption in mind, studies have succefully accelerated growth using insulin-like growth factor 1 (IGF-1) (Lendvai et al., 2021; Lodjak et al., 2017) and thyroid hormones (Cossin-Sevrin et al., 2022; Hsu et al., 2021). We note however that while on the one hand, the finding that IGF-1 administration accelerates growth demonstrates that there is a

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potential for nestling birds to accelerate growth through an increase in IGF-1 levels, it does not shed light on the question of whether the observed natural variation in growth rate is dependent on IGF-1 levels. In the current study, we aimed to address this question by implementing a novel protocol to slow growth and reduce body size by inhibiting the insulin and insulin-like signalling (IIS) axis. This approach builds on studies using genetic models of mice and fish, where embryos that lacked a functional IGF-1 receptor ($igf1r^{-/-}$) achieved a lower embryonic growth rate (Liu et al., 1993; Schlueter et al., 2007). Building on this effect, OSI-906 is used as an anti-tumour treatment, but to our best knowledge, it has not yet been used as an experimental tool to manipulate growth rate and/or body size. Birds are a particularly good system to manipulate growth using OSI-906, because, in contrast to mammals, birds do not have a functional IGF-2 receptor (Nordin et al., 2014); therefore, the IGF signalling uses the primarily IGF-1 receptor and insulin receptor exclusively to a small extent. We administered OSI-906 during two breeding seasons to pied flycatcher (*Ficedula hypoleuca*) nestlings to test the prediction that inhibiting the IGF1 receptor (IGF1r) activity would reduce growth rate and body size.

2. Material and methods

2.1. Study system

The study was carried out in May / June 2021 and 2022 in a coniferous forest dominated by Scots pine (*Pinus sylvestris*) near Kilingi-Nõmme (58°7′N, 25°5′E) in Estonia. Nest boxes were mounted on tree trunks at a height of 1.5–1.8 m and checked at regular intervals to obtain precise laying dates, clutch sizes, and hatching dates of the first egg (hatch date = day 0 post-hatch). For a more detailed description of the standard field protocol, see Lodjak et al. (2015).

Mean (±SD) clutch size was 6.56 (±0.63) in 2021 and 6.77 (±0.53) in 2022; the number of chicks at the age of 3 days (start of the experiment) was 6.04 (±0.99) in 2021 and 6.36 (±0.84) in 2022; the number of fledglings was 6.01 (±0.97) in 2021 and 6.36 (±0.84) in 2022.

Climatic conditions in the experimental periods (see below) were similar in the two years of study (median daily mean temperature: 2021: 18.55 °C, IQR = 3.52 °C; 2022: 16.4 °C, IQR = 1.65 °C; relative humidity: 2021: 70.0%, IQR = 18.0%; 2022: 75.0%, IQR = 17.0%).

2.2. Manipulation protocol

Within every brood (2021: n = 36 broods; 2022: n = 21 broods), and at the age of 3 days post-hatch, four nestlings with the same hatching date were randomly (using a mobile app) assigned to either the OSI-906 treatment (two nestlings) or the control treatment (two nestlings). OSI-906 is a highly selective inhibitor of IGF1r, with lower activity on the insulin receptor (Ir) (Jones et al., 2015; Mulvihill et al., 2009; Puzanov et al., 2015), that impedes ligand-induced activation of downstream pathways, including PI3K-Akt, ERK1/2, and P70S6K, and inhibits cell proliferation (Mulvihill et al., 2009). All nestlings received 200 μl of a 15% DMSO solution (10 times in total) orally daily. In the OSI-906 treatment, a dosis of 40 μg/g of body mass of a pre-fledging nestling (13 g) was used, which amounted to an OSI-906 concentration of 2.6 mg/ml. The concentration, and hence the OSI-906 dosis, was held constant throughout the experiment. OSI-906 was diluted in a 15% DMSO solution following the manufacturer's solubility estimates and previous studies (note that solubility estimates might differ between manufacturers); the compound is not soluble in water. OSI-906 was purchased from Axon Biochemicals (Netherlands) and designed for oral administration. Nestlings of the control group received the vehicle solution that differed only by not containing OSI-906.

All nestlings were individually marked during the experiment with a non-toxic marker, coloured plastic rings, and metal rings. The body mass of nestlings was measured daily (ages from 3 to 13 days) with a digital scale to the nearest 0.01 g. At age 13 days, we measured tarsus length (precision 0.1 mm), wing length (precision 1.0 mm), and total length of head and bill (precision 0.1 mm) to estimate the structural size of nestlings at the end of the experiment.

Experiments were carried out under license 188 of the Animal Procedures Committee of the Estonian Ministry of Agriculture.

2.3. Statistical analysis

The experimental effect was analysed with linear mixed models, with either body mass, tarsus length, wing length, head-bill length, or condition as the dependent variable. In the case of body mass, experiment (factor with two levels), age (factor with 11 levels), year (factor with two levels), and time-of-day (continuous variable) were used as explanatory variables. Since we wanted to know how the experimental effect depended on age and year, we included a three-way interaction 'treatment*age*year' (and all lower-level interactions) in the model. To account for the non-independence of repeated measurements on nestlings and of nestlings within a brood, we included a chickID and broodID as random factors, where the chickID was nested in broodID. The models with other dependent variables were very similar, but did not include age (fixed effect) or chickID (random term) since these variables were measured only once. The condition was defined as body mass residuals from the linear model with tarsus length (Green, 2001). Statistical analysis was done using R v4.0.3 (R Development Core Team, 2021) with *lme4* (Bates et al., 2015), *emmeans* (post hoc analysis and effect sizes) (Lenth et al., 2018), and *car* (type II SS; to aid the interpretation of main effects and interactions in the same model) packages (Fox and Weisberg, 2019). All tests were two-tailed.

3. Results and discussion

Body mass did not differ between the treatments prior to the first OSI-906 administration at the age of 3 days ($t = 0.875$, $df = 568$, $p = 0.38$). OSI-906 caused a significant reduction in the growth rate during the first half of the nestling period (maximum reduction at ages 4–6 days; daily mass gain; Fig. 1A), but OSI-906 treated nestlings grew faster than control nestlings in the second half of the nestling phase (Fig. 1A, Table S2a and b). Nevertheless, body mass was significantly lower when compared to controls at all ages from the age of 4 days onwards ($F_{1,160.6} = 100.12$, $p < 0.001$; Fig. 1B; see Supplementary Material Table S1 for all full models), but the mass difference varied with time. The treatment effect on body mass peaked at ages 6–8 days (average Cohen's d over both years at ages 6–8 days: 2.48), but, due to 'catch-up' growth in the second half of the nestling period, the treatment effect on body mass was substantially smaller close to fledging (average Cohen's d over the years at age 13 days: 0.60). The growth depressing effect is consistent with the findings of various biomedical studies on cancer and recovery from pathological changes with neonatal to 7-week-old mice (Sun et al., 2016; Tajima et al., 2017). In conclusion, OSI-906 reduced growth rate, also when considered over the entire nestling period. Still, a more detailed inspection of the growth pattern revealed a more complex pattern, with the effect size depending strongly on age.

Because structural size was measured once, just before fledging, we can only investigate the net treatment effect on size over the entire nestling period. Approaching fledging age, OSI-906 treated nestlings were smaller in their linear dimensions: tarsus length ($F_{1,160.3} = 81.50$, $p < 0.001$; Fig. 1C; average Cohen's d over the years: −1.40), wing length ($F_{1,160.3} = 89.18$, $p < 0.001$; Fig. 1D; Cohen's d: −1.44), head and bill length ($F_{1,160.2} = 98.93$, $p < 0.001$; Fig. 1E; Cohen's d: −1.52). Table S3 in the Supplementary Material gives an overview of size measurements themselves, and Table S4 offers details for the post hoc analysis to increase the clarity of the results. Given that the experimental effect on mass growth depended strongly on age (Fig. 1A), and that the temporal growth pattern differs between the three linear dimensions, with wing length growing later than the tarsus and head + bill length, it is notable that the experimental effect sizes of the three different linear

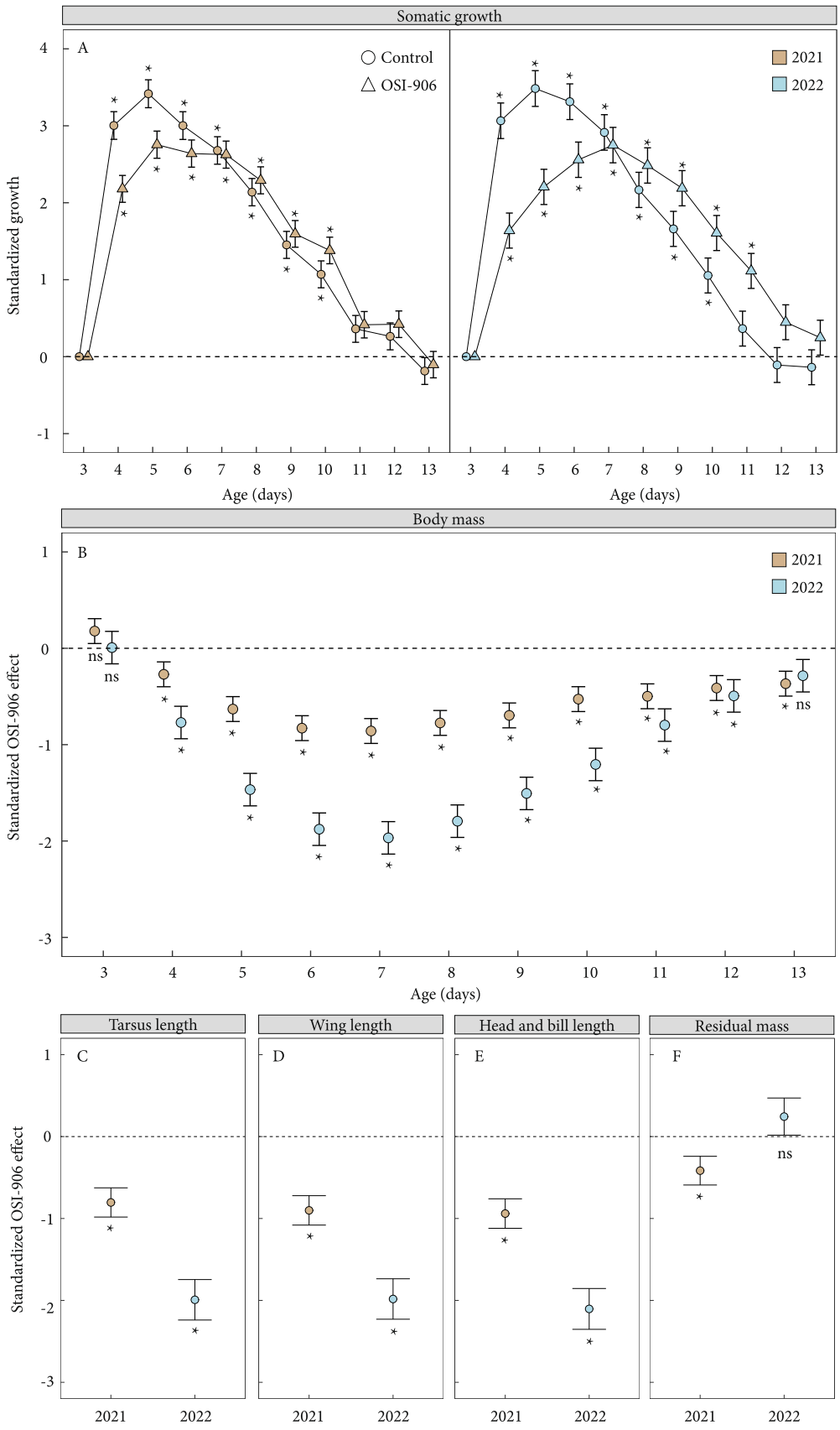

Fig. 1. Growth rate (A; daily mass gain), body mass (B) difference of OSI-906 treated nestlings relative to control nestlings with advancing age. Tarsus length (C), wing length (D), head and bill length (E), and residual mass (F) are shown as a difference of OSI-906 treated nestlings relative to control nestlings at the age of 13 days (pre-fledging stage). The data shown are standardized effect sizes (Cohen's d ± SE). Colours denote different study years.

dimensions were very similar. Residual mass at fledging age was not affected by OSI-906 treatment over the years combined ($F_{1,159.4} = 0.60$, $p = 0.44$; average Cohen's d over the years: 0.02; Fig. 1F). Thus we conclude that OSI-906 treatment resulted in smaller birds without affecting condition as reflected in residual mass. The effect on body size is consistent with biomedical studies reporting IGF-1r effects on bone tissue development. Firstly, IGF-1r mediates the growth and differentiation of osteoblasts, and the reduction of IGF-1R function results in osteoblasts shifting growth and differentiation processes from IGF1r to Ir (Buck et al., 2010; Fulzele et al., 2007). Therefore, osteoblast proliferation and differentiation and the interplay between osteoblasts and osteoclasts are modulated through both IGF1r and Ir, of which OSI-906 has been shown to decrease the activity (Cannata et al., 2010; Mulvihill et al., 2009). Secondly, the reduction of IGF-1R function is able to decrease the linear size and body mass through chondrocytes by inducing their hypoproliferation and increased apoptosis (Yakar and Isaksson, 2016). However, most studies do not differentiate between mass and size, and hence the link between OSI-906 and structural size remains poorly described.

Exogenous IGF-1 administration increased the nestling growth rate in the same population (Lodjak et al., 2017). While this demonstrates that nestlings could potentially increase their IGF-1 levels, and thereby their rate of growth, IGF-1 administration does not shed light on the extent to which the unmanipulated growth rate was regulated through IGF-1. Our current experiment fills this gap, by showing the mirror effect of IGF-1 administration, i.e. reducing the rate of growth. The results of the two treatments are not complete mirror images however. The IGF-1 administration resulted in a gradually increasing effect on body mass up to fledging (Lodjak et al., 2017), and we therefore expected a gradual OSI-906-dependent decrease in growth rate to smaller body mass compared to control nestlings. Instead, we observed a clear age-dependency of the OSI-906 effect (Fig. 1B).

We can only speculate on the mechanism explaining the age-dependence of the OSI-906 effect, but we suggest our protocol may have played a role. We administered a fixed OSI-906 dosis throughout the nestling period, which implies that the dosis per unit body mass decreased with age due to growth. While this may explain why the effect size on growth decreased over almost the entire age range after an initial strong increase, it does not by itself explain why the growth rate of treated nestlings was higher than the growth rate of control nestlings in the latter half of the nestling phase, because even if the OSI-906 dosis per unit body mass decreased, the control group received no OSI-906 at all. However, it is well established that birds can perform 'catch-up growth' following a period of suppressed growth (Metcalfe and Monaghan, 2001), and the OSI-906-caused growth backlog is therefore likely to have induced catch-up growth. We therefore interpret the observed growth rate as the net outcome of the OSI-906 effect on the one hand, decreasing with age due to the decreasing mass specific dosis, and the 'catch-up' effect, which increased with an increasing growth backlog, but decreased again towards the end of the nestling period. Based on this explanation, we predict that stopping the OSI-906 administration at some point during the growth phase would have resulted in an even stronger return to the mass observed in the control nestlings, while an increasing OSI-906 dosis with age would have maintained a larger mass difference up to fledging age. Additionally, when conducting an OSI-906 receptor inhibition experiment from the age of 7 days onwards, in conjunction with the previously mentioned experiment, we can observe to what degree the continuous blockade of IGF-1r earlier in life could have affected the body mass change in the second half of the nestling phase. Further experimentation is required to test these hypotheses, and thereby fine-tune the use of OSI-906 as a tool to manipulate the growth rate.

An additional factor likely to have played a role in the temporal dynamics of the treatment effect on growth rate is the earlier finding that IGF-1 levels of small passerines, including pied flycatchers, decrease with age during the nestling phase (Lodjak et al., 2017; Lodjak et al., 2014). It seems reasonable to expect that blocking the IGF-1 receptor with OSI-906 will have a larger effect on growth when IGF-1 levels are high, potentially explaining why the treatment effect on growth rate declined with age. In this context, it is worth mentioning that the mechanism underlying the experimental effect remains to be resolved. For example, temporal dynamics of IGF-1 receptors remain to be studied, which may be important given that hormone efficacy will be the outcome of the interplay between hormone levels and receptor density. Of particular importance will be to establish whether the manipulations of IGF-1 and IGF-1 receptors exert their effect through resource allocation only, or whether these manipulations also affect resource acquisition, through interaction with siblings and the parents that provide food. Resolving this issue may require a better understanding of the physiological mechanisms regulating growth. The rodent studies that observed an initial OSI-906–dependent body mass reduction followed by a body mass recovery to control levels suggested that the modulation of glucose metabolism, insulin tolerance and fat metabolism are among the factors to consider (Shirakawa et al., 2020; Tajima et al., 2017).

Although the temporal pattern in effect size on mass was very similar in the two years, effect sizes differed between the years ($F_{1,2079.01} = 7.31$, $p < 0.001$). In particular, peak effect sizes were much more profound in 2022, compared to 2021 (average Cohen's d of year effect over the ages 6–8 days: 1.94), while towards the end of the nestling period, the effect on mass was similar in the two years. Similar year differences in effect size were observed for experimental effects on structural size: tarsus length ($F_{1,159.8} = 17.33$, $p < 0.001$; Fig. 1C; Cohen's d of the year effect over the treatments combined was −1.19), wing length ($F_{1,159.8} = 14.36$, $p < 0.001$; Fig. 1D; Cohen's d: −1.08), and head and bill length ($F_{1,159.8} = 16.62$, $p < 0.001$; Fig. 1E; Cohen's d: −1.16). Because experimental effects on mass towards the end of the nestling period were similar in the two years, while the effect on linear size was stronger in 2022, there was a significant treatment by year interaction with respect to condition ($F_{1,159.1} = 6.23$, $p = 0.01$). Post-hoc analysis revealed a significant negative treatment effect in 2021 ($t = 2.18$, $df = 160.0$, $p = 0.03$; Cohen's d: −0.38), but a non-significant positive treatment effect of similar magnitude in 2022 ($t = 1.48$, $df = 159.0$, $p = 0.14$; Cohen's d: +0.33). In conclusion, the nestlings' response to hormonal receptor inhibition was considerably stronger in 2022 compared to 2021. With respect to the mechanism causing the difference in magnitude of the experimental effect between the two years, we note that clutch size, brood size and nestling mortality, did not differ between the two years (see methods). However, control nestlings reached a higher peak body mass in 2022, and at a younger age (11 days, one day earlier compared to 2021); mass gain (±SE) from the start of the experiment (age of 3 days) to the peak body mass for control nestlings was 9.47 g (±0.10 g; age of 11 days) in 2021, and 9.82 g (±0.12 g; age of 10 days) in 2022 ($F_{1,102.85} = 6.97$, $p = 0.009$). Presumably, environmental conditions in 2022 were such that the adults could provision their offspring at a higher rate. That the experimental effect size was larger in 2022 may be directly related to the higher growth, simply because when the growth rate is higher there is more scope to suppress it.

In conclusion, the use of OSI-906, an IGF-1 receptor inhibitor, results in an age-specific change in growth rate and reduction of body size, providing a further characterization of IGF-1 in growth regulation. However, the extent to which two closely related hormones, insulin and IGF-2, are impacted by OSI-906′s inhibition of the IGF-1 receptor and how these three hormones interact to produce the observed body mass phenotype require further investigation.

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CRediT authorship contribution statement

Jaanis Lodjak: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Visualization, Writing - original draft, Writing - review & editing. **Marko Mägi**: Data curation, Methodology, Writing - review editing. **Simon Verhulst:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygcen.2023.114293.

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