TransCon CNP, a sustained-release prodrug of C-type natriuretic peptide, prevents premature synchondroses closure in an achondroplasia mouse model

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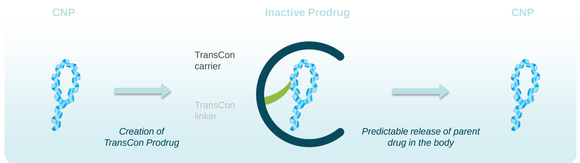
Background

Achondroplasia (ACH), the most common form of human dwarfism, is caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 (FGFR3) gene, a key negative regulator of endochondral ossification.

Inhibition of chondrocyte proliferation and terminal differentiation results in premature closure of the cartilaginous synchondroses, including within the craniofacial bones, with resulting stenosis of the craniocervical junction and foramen magnum. Clinical sequelae include hydrocephalus and cardiorespiratory dysfunction that contribute to an increased mortality among infants with ACH.

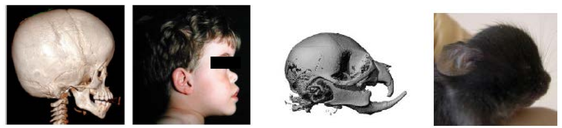
CNP levels appear to correlate with height velocity in ACH.[1] Vosoritide, a mutated CNP analogue in phase 3 development, is being assessed for its effects on bone growth in patients with ACH.[2,3] However, the impact of CNP on craniofacial development in ACH remains to be elucidated.



TransCon CNP, a once-weekly CNP prodrug, is being developed for use in ACH. In its prodrug form, CNP is transiently bound to an inert TransCon carrier via the TransCon linker. Through autohydrolysis, fully active CNP is released, providing sustained exposure.

Background

The aim of this study was to investigate the ability of TransCon CNP to rescue abnormal craniofacial bone formation in mice exhibiting a severe dwarfism phenotype similar to ACH.



The mouse ACH model displays similar craniofacial anomalies as seen in human ACH, including macrocephaly and modification of the head and midface.

Methods

Newborn mice harboring the murine-equivalent ACH (*Fgfr3*$^{Y367C/+}$) phenotype were administered TransCon CNP (5.6 mg CNP/kg/day; n=9) or vehicle (n=6) for 15 days and compared to wild type (*Fgf3*$^{+/+}$) mice.

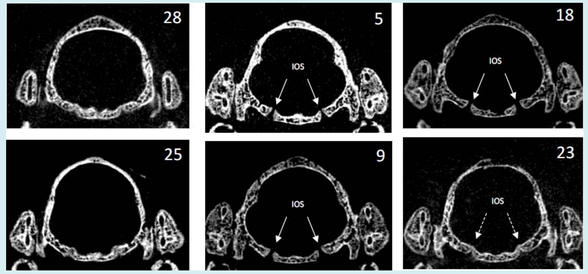
Based on µCT (Skyscan 1172, Voltage 80V, 100mA, 100ms exposure time, resolution 18.5 mm scaled to avoid subjectivity) scan assessments, the anterior intra-occipital (IOSA) synchondroses were classified as open (cartilage present), partially closed, or closed (cartilage absent).

To evaluate the effect of TransCon CNP on skull morphology, images that most clearly demonstrated normalization were reviewed. Foramen magnum, fontanels, and overall skull shapes were assessed as a proxy for calvaria ossification and compared to wild type mice.

Results

TransCon CNP was shown to counteract premature closure of the anterior intraoccipital synchondroses in *Fgfr*$^{3Y367C/+}$ mice leading to an increased size of the foramen magnum (numbers indicate individual animals).

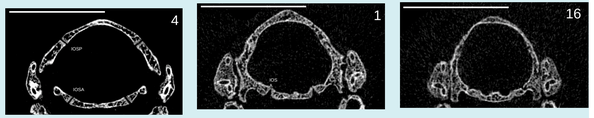
Foramen magnum with the IOSA:



Vehicle | TransCon CNP | TransCon CNP

TransCon CNP-treated mice demonstrated a foramen magnum shape more similar to wild type than that of vehicle-treated mice.

Foramen magnum shape comparison:

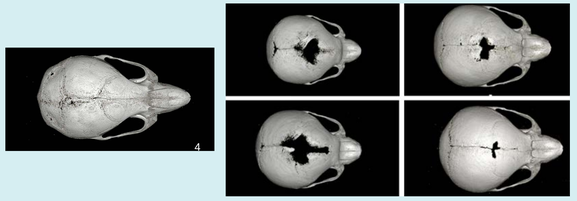


Wild Type | TransCon CNP | Vehicle

Results

TransCon CNP-treated mice demonstrated a fontanel and overall skull shape more similar to wild type than that of vehicle-treated mice.

Superior skull view:



Wild Type | Vehicle | TransCon CNP

Conclusions

In a murine model of ACH, TransCon CNP prevented the closure of synchondroses and resulted in an improvement in foramen magnum and skull shape, suggesting normalization of the overall skull contour.

These results suggest that the early administration of TransCon CNP may alleviate the risk of foramen magnum stenosis that leads to some of the most serious clinical complications of ACH.

[1]Olney, R.C., et al., J Clin Endocrinol Metab, 2015. **100**(2): p. E355-9.
[2]Wendt, D.J., et al., J Pharmacol Exp Ther, 2015. **353**(1): p. 132-49.
[3]Biomarin 2016, R&D Day