Production of inhibin analogs: Generating potential

World leaders with over 30 years' experience in inhibin research, Hudson Institute scientists have developed novel inhibin analogs that overcome the challenges preventing its use in both the laboratory and clinic.

The hormone inhibin stimulates bone mass and strength, and is known to be decreased in post-menopausal women suffering osteoporosis. Its full potential is yet to be realised, as production of this protein at scale is extremely challenging. In this patented technology, our team describes the modification and production of inhibin analogs, and their use in the treatment or prevention of disease.

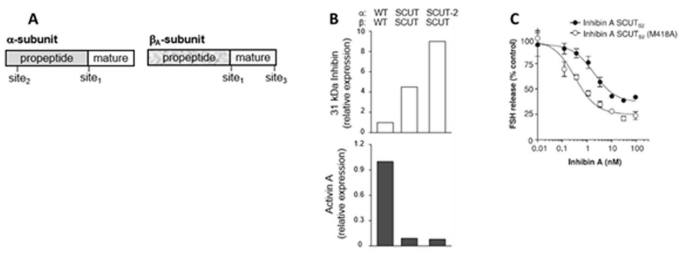
Summary

Inhibins are a non-steroidal gonadal hormone, best characterised for their role in regulating reproductive function. Recent research suggests that inhibins have pleiotropic actions, and are expressed in many organ systems throughout the body. Of particular interest, inhibin has been shown to stimulate bone growth, leading to suggestions of its potential as a therapeutic for osteoporosis.

Inhibin A and Inhibin B are heterodimers, made up of an α-subunit linked to a β-subunit. Two β-subunits linked together forms activin, a protein with often opposing actions to inhibin. Overexpression of inhibin also results in expression of activin, and separating the two proteins is extremely challenging. The inability to produce stable and purified active recombinant inhibin has hindered studies into its potential use as a therapeutic agent or diagnostic tool.

Current methods of recombinant inhibin production are inefficient with low yield, and multiple steps of purification are required to isolate recombinant inhibin using currently available systems. Our researchers have overcome these hurdles using their system for the production of engineered purified, potent, active inhibin analogs.

Key data



Key modifications to both the α-subunit and β-subunit are required to overcome the difficulties in expressing and purifying recombinant inhibin (A). The "SuperCut" variant, with changes at site$_1$, is produced at increased levels (B) while the "SuperCut-2" version, with a further modification at site$_2$, is produced at greater levels again. The change at site$_3$ renders any residual inhibin inactive. The protein is tagged to allow for purification. The resulting proteins are active, as demonstrated by a LβT2 gonadotrope FSH bioassay (C).

Applications and market

Development of recombinant inhibin as a tool for research or diagnostics

Inhibin is currently used in diagnostic tests for Down syndrome and some ovarian cancers. It has potential as a diagnostic marker for infertility and pregnancy-related conditions. Inhibin has also been implicated in erythropoiesis, eye development, adrenal gland growth and function, and regulation in the immune system. The potential clinical utility of inhibin has yet to be explored to its utmost potential. The analogs engineered by our team could form the basis for testing and developing treatments for a range of indications. The research use of inhibin can also be expanded, allowing for a more detailed understanding of this hormone.

Development of novel therapeutics

Circulating inhibin levels dramatically decrease during menopause. This loss of inhibin at menopause may contribute to decreased bone mass in osteoporosis, and inhibin A has been shown to restore bone growth in in vivo models of bone degeneration. Many current treatment strategies for osteoporosis aim only to slow disease progression, and adverse side effects mean patient compliance with current therapeutics is low. There is a need for the development of novel treatments which can increase bone mass and strength in osteoporosis patients.

Up to 50% of women, and 20% of men aged over 50 years, suffer from osteoporosis. The estimated prevalence of this disease is 200 million worldwide, with an expected increase ahead as the population ages. The direct cost for osteoporosis fracture in the US was USD17 billion in 2001; in the EU it was over €32 million in 2000 and is expected to reach €77 million in 2050.

Publication

Walton et al. (2016) A novel, more efficient approach to generate bioactive inhibins. Endocrinology. 157(7):2799-2809.

Inventors

The team is led by internationally respected molecular biologist and expert in reproductive endocrinology, Professor Craig Harrison, whose research focuses on the structural and functional characterisation of transforming growth factor β (TGF-β) proteins to understand their role in reproduction and human disease.

IP position

PCT/AU2016/051156 filed November 2016 – 'Inhibin Analogs.'

The patent application has been prepared and refined by Dr John Hughes, patent attorney and partner at Davies Collison cave, in conjunction with the Inventors Professor Craig Harrison and Dr Kelly Walton.

Development pathway

A suite of improved inhibin analogs is under development, as is scaled-up production and purification of industry-grade inhibin. Our team are currently seeking opportunities for co-investment, licensing or collaboration to further develop the inhibin program, including use of inhibin as a research tool, and proof of concept in vivo testing in preclinical models of bone diseases.

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- Cancer
- Endocrinology and metabolism
- Fetal, infant and child health
- Immunology and infectious diseases
- Reproductive health and biology
- Women's health

Opportunities for collaboration and partnership

Partnership opportunities include:

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- Reproductive, women's and children's health
- Regenerative medicine
- Infectious disease, inflammation and immunology
- Diagnostics and biomarkers

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Key Indicators

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