362 Inhibin analogues for post-menopausal osteoporosis treatment

Asset Overview

Product Type	Protein
Indication	Menopausal complications (Post-menopausal osteoporosis)
Current Stage	Lead optimization
Target(MoA)	Engineered inhibin mutants
Brief Description	We have developed super-inhibin analogues that can be used to prevent osteoporosis and weight gain during menopause, and beyond. The potential for inhibin therapeutics has been challenged by the concomitant production of activins, which induces cachexia in inhibin-null mice. We have identified mutations that eliminate activin formation in the production of potent inhibin analogues that can be used develop a first inhibin replacement therapy.
Organization	Monash University

Differentiation

□ **Inhibin can decrease FSH level**

- Follicle-Stimulating Hormone (FSH) increases the risk of postmenopausal osteoporosis by stimulating osteoclast differentiation
- Activin and inhibin are two closely related protein complexes activin enhances FSH biosynthesis and secretion inhibin downregulates FSH synthesis and inhibits FSH secretion

□ **A novel, more efficient approach to generate bioactive inhibins**

- Gonadal-derived inhibins are essential factors in mammalian reproduction, negatively regulating pituitary production of FSH
- Declines in inhibin levels across the menopause transition correlate with not only an increase in FSH but also a rapid decrease in bone mass

□ **Inhibins are difficult to produce recombinantly**

- Inhibins are difficult to produce, and their expression is always accompanied by production of activins (subunit homodimers), the proteins they antagonize. We showed that inhibin A noncovalently associated with its prodomain was more potent (20-fold) than mature inhibin A, indicating an important role of the prodomain in inhibin bioactivity
- The production of potent inhibin analogs in the absence of activin activity will greatly facilitate the investigation of the therapeutic potential of gonadal hormones on bone and other tissues

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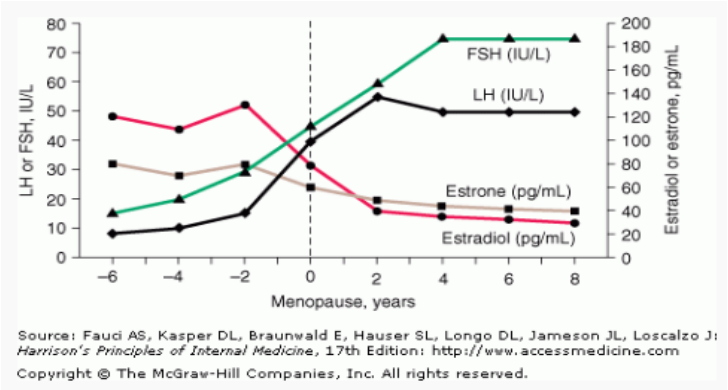
Key Data

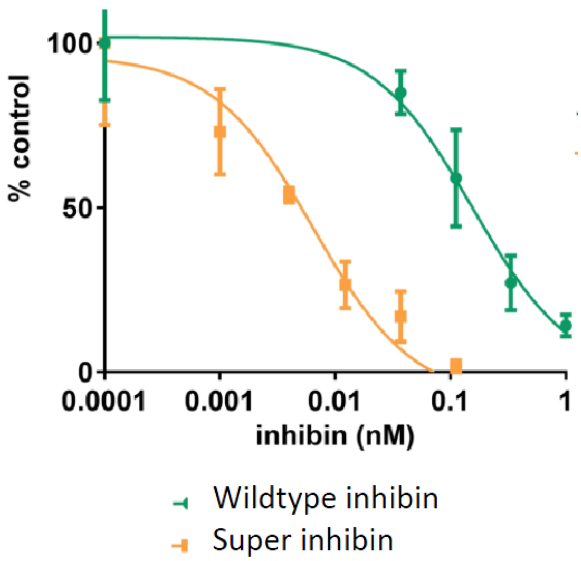
FSH increases the risk of postmenopausal osteoporosis



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Circulating inhibin levels decrease dramatically across the menopause transition and inversely correlate with increased serum FSH.

Inhibin suppression of activin-mediated luciferase activity in COV434 cells



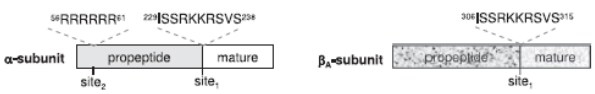


Table 1. Ratio of Inhibin to Activin Produced After Transient Transfection of HEK293F Cells With Wild-Type and SCUT Constructs

α-Subunit	βA-Subunit	Ratio Inhibin to Activin (Mean ± SD)
WT	WT	1.5 ± 0.7
SCUT	WT	24.8 ± 0.3
WT	SCUT	2.2 ± 0.3
SCUT	SCUT	68.7 ± 7.3

Abbreviation: WT, wild type.

Potency of Inhibin analogue. Activity read out for inhibin analogues in suppressing activin-mediated cells luceriferase reporter response.

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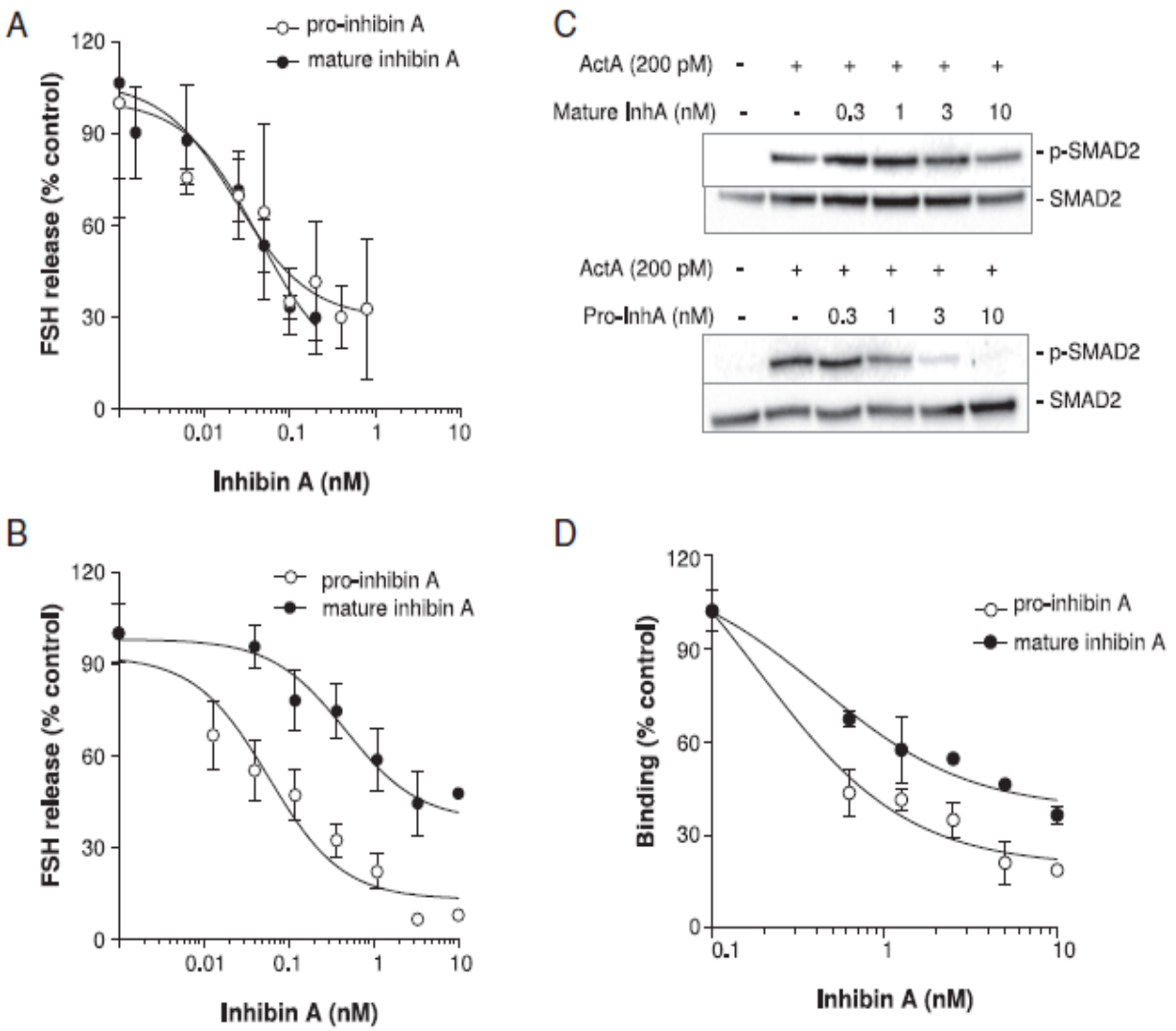
Proinhibin A is a more potent activin antagonist than mature inhibin A in specific settings



Analysis of proinhibin bioactivity. The ability of proinhibin A to suppress activin-induced FSH release was compared with mature inhibin A in both rat pituitary cell cultures (A) and mouse gonadotrope LT2 cells (B). (C) The ability of proinhibin A to suppress activin-induced SMAD2 phosphorylation was also assessed in LT2 cells. Cells were treated with 150 pM activin A in the presence of increasing doses of proinhibin A or mature inhibin A. (D) The ability of proinhibin and mature inhibin A to displace 125I-inhibin A binding to betaglycan was assessed in transfected HEK293T cells.

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Intellectual Property

Patent No.	PCT-AU2016-051156
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Status	Application Pending
Country	US, AU

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