KDDF
Korea Drug Development Fund

Asset #1
NIH

La Protein as a Novel Regulator of Osteoclastogenesis

Therapeutic Area	Bone Disease	**Indications**	Osteoporosis, Paget's Disease, Fibrous Dysplasia
Modality	Protein	**Development Stage**	Hit to Lead/Lead Optimization

Overview

Background

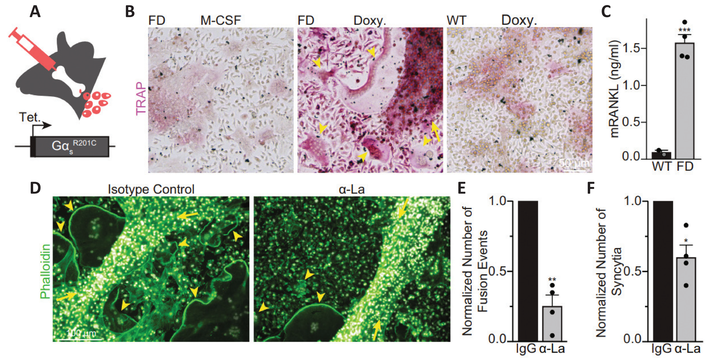
- Millions of patients in the United States are afflicted by a host of bone diseases rooted in the dysfunction of osteoclasts, specialized cells originating from the macrophage/monocyte lineage. This array of conditions encompasses Paget's disease, osteoporosis, fibrous dysplasia and osteolytic bone metastasis. The prevailing standard of care for these disorders relies on broad-spectrum treatments that either coat the skeletal system or inhibit osteoclast development, aiming to modulate osteoclastogenesis. To address the limitations of these approaches and mitigate the off-target side effects associated with them, novel therapies are imperative, ones that specifically target osteoclast fusion.

Technology Advantages

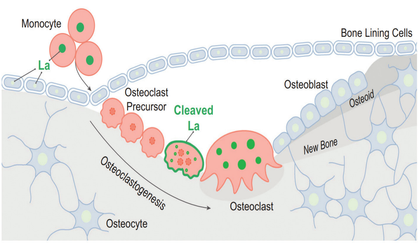
- Technology addresses most major forms of – and therefore the largest addressable markets for – bone disease
- Enables precise regulation of osteoclast fusion and function
- Potential to prevent off-target side-effects associated with current therapies

Key Data

α-La treatment suppresses ectopic osteoclast formation in fibrous dysplasia explants



(A) Illustration of ex vivo bone marrow culture system based on a tetracycline-inducible model of FD. (B) The culture of these FD explants in the presence of M-CSF alone resulted in numerous adherent cells but no multinucleated, tartrate-resistant acid phosphatase positive (TRAP)+ osteoclasts. In contrast, addition of Doxy to induce FD-like phenotype, resulted in the rapid development of fibrous cell clumps (arrow) and numerous multinucleated, TRAP+ osteoclasts (arrowheads) that were not observed in explants from wild-type littermates, lacking the inducible GαsR201C element. © Doxy-induced osteoclastogenesis was accompanied by a ~17-fold increase in mRANKL produced by the explants. (D, E, F) Importantly, α-La mAb blocked osteoclast fusion elicited by the addition of Doxy to FD explants by ~60% and reduced the number of multinucleated osteoclasts observed by ~40%



(G) An illustration of changes in the steady-state level and cellular localization of La protein in the process of osteoclast formation. La (green) carries out its canonical, ancient function in the nuclei of all eukaryotic cells as an essential RNA-binding protein. First, La dissipates as circulating monocytes become osteoclast precursor cells. When osteoclast commitment is initiated by RANKL, La returns but is quickly cleaved by proteases and shuttled to the surface of osteoclasts. At the surface of fusing osteoclasts, La plays a novel role as a membrane fusion manager. When osteoclasts arrive at the "right size" for their biological function, surface La dissipates and is replaced by canonical, non-cleaved La that returns to the nuclei of mature osteoclasts.

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-US2022-018639 (2022.03.03)

Patent Family
PCT

Publication(s)

- Whitlock, J. M. et al. (2023). Cell surface-bound La protein regulates the cell fusion stage of osteoclastogenesis. Nature Communications, 14(1).