

DOMANDA DI CONTRIBUTO (L. 401/90)

2025
Svezia

Elementi generali

Titolo (in Italiano)	Il canale del cloruro muscolare CLC-1 come bersaglio farmacologico: un approccio strutturale e funzionale combinato
----------------------	--

Ente proponente italiano

Struttura	Consiglio Nazionale delle Ricerche
Dp./Ist.	Istituto di Biofisica

Responsabile scientifico italiano

Titolo	Dott.
Cognome	PUSCH
Nome	MICHAEL
Qualifica	Dirigente di Ricerca (Enti Pubblici Ricerca)

Descrizione delle attività in programma

Sintesi

The muscle chloride channel CLC-1 is mutated in myotonia congenita, a disorder characterized by delayed muscle relaxation that presents a significant health burden to affected individuals, often impairing their quality of life. Recently CLC-1 has been also recognized as a promising drug target for myasthenia gravis and other hypo-excitability diseases. Cryo-electron microscopy (cryoEM) has emerged as a revolutionary tool in structural biology, enabling the visualization of biological macromolecules at near-atomic resolution. For ion channels, the combination of structure determination in association with channel targeting drugs and functional characterization using high resolution electrophysiology offers unprecedented molecular insight and has the potential to enable personalized medicines. Here, we will extend an ongoing fruitful collaboration on inhibitor bound CLC-1 structures combined with patch clamp electrophysiology and site-directed mutagenesis to determine cryoEM structures and characterize mutants with elevated affinity for two established CLC-1 inhibitors. Furthermore, we will determine structures and functionally characterize myotonia causing dominant negative disease mutants, in the absence and presence of CLC-1 binding drugs. The intention is to yield pioneering insights into fundamental disease-causing mechanisms of dominant myotonia and how inhibition of CLC-1 can be optimized that will serve as a framework, and inspire future activities in these research fields for further basic research and drug-design efforts against CLC-1 related disorders. Moreover, in an extensive exchange program of young scientists, we intend to transfer the complementary know-how of our two laboratories. Collectively, our integrative approach of bridging the gap between structural and functional studies provides an exceptional opportunity towards the development of CLC-1 targeting therapies for a variety of skeletal muscle excitability disorders.