Cytokinetics

Cytokinetics: harnessing the therapeutic potential of muscle contractility through innovative research

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Experts in the modulation of muscle contractility

Cytokinetics is a late-stage biopharmaceutical company focused on the discovery and development of first-in-class muscle activators as potential treatments for conditions characterized by compromised or declining muscle function. Over the years, the company has developed unparalleled expertise in muscle biology and function. By focusing on investigational agents that target muscle contractility, we aspire to develop treatment options that may improve the lives of people who have severe, debilitating diseases.

Our long-standing interest in the cytoskeleton led us to focus on the discovery of small molecules that modulate skeletal and cardiac muscle contractility specifically by targeting the sarcomere. The contractility of these muscle types is relevant to certain neuromuscular and cardiovascular diseases. At Cytokinetics, we believe targeting muscle contractility has the potential to unlock treatments for diseases characterized by impaired muscle function. Our investigational agents are engineered with the intent of increasing muscle force, power and function as well as delaying the onset of muscle fatigue.

The sarcomere: the fundamental unit of muscle contraction

Our skeletal muscle contractility program is focused on the direct activation of the sarcomere, the basic unit of muscle contraction. The skeletal sarcomere is a highly ordered cytoskeletal structure composed of skeletal muscle myosin, actin and regulatory proteins, including the troponins and tropomyosin (**see Fig. 1**).

Fast skeletal muscle troponin

The troponin complex on the actin thin filaments of striated muscle (cardiac, fast-twitch skeletal and slow-twitch skeletal) comprises troponin C, troponin I and troponin T, proteins that regulate contraction of cardiac and skeletal muscle. Troponin C is responsible for binding calcium to activate muscle contraction. One approach to increase muscle contractility is to slow the rate of calcium release from fast skeletal muscle troponin C. Slowing the release of calcium would improve the sensitivity of troponin to calcium and increase the production of muscle force at submaximal neuromuscular input[1]. By directly improving the function of skeletal muscle, fast skeletal muscle troponin activators (FSTAs), could enhance functional performance and the quality of life of patients with medical conditions characterized or complicated by muscle weakness or wasting.

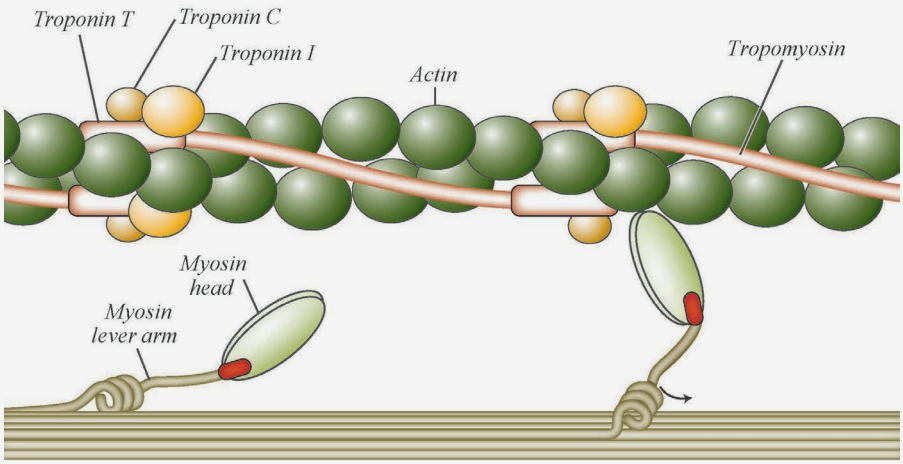

Figure 1 | Thin and thick filaments of the sarcomere. Myosin (light green), a motor protein, powers the muscle to contract by 'grabbing' onto actin (dark green) and 'flexing'. When the myosin releases the actin, the muscle relaxes. This process is regulated by troponin.

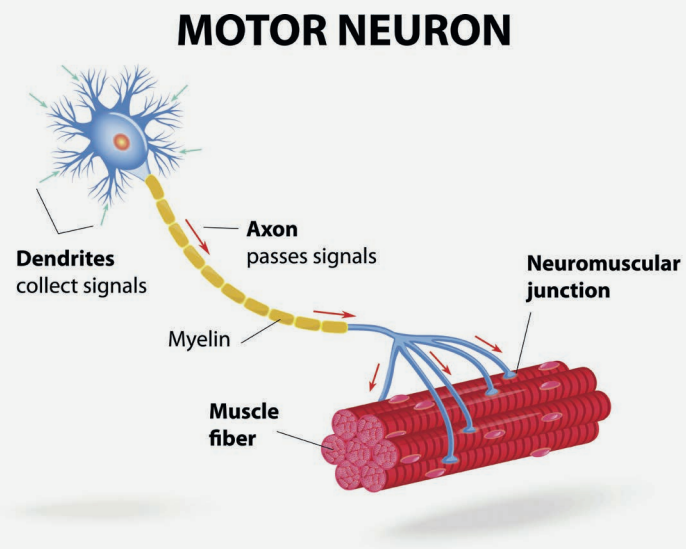

Figure 2 | Motor neuron. As motor neurons in the brain and spinal cord progressively die, the brain can no longer send signals to skeletal muscle fibers, resulting in muscle weakness and atrophy.

Unmet need in amyotrophic lateral sclerosis

ALS, also known as Lou Gehrig's disease, is the most common motor neuron disease. It is a rapidly progressive neurodegenerative disorder that primarily involves motor neurons in the brain and spinal cord, which innervate skeletal muscles (**see Fig. 2**). Clinical symptoms of ALS include progressive weakness, muscle wasting and spasticity. Treatment options for ALS are limited, and the disease affects as many as 30,000 people in the United States, with an estimated 5,600 new cases diagnosed each year[2]. In most cases of ALS, the cause is not well understood, but a combination of environmental and genetic risk factors may have a role. Familial ALS, the inherited form of the disorder, affects approximately 5–10% of patients[3].

The average age of onset of ALS is 58–60 years[4], and the average life expectancy is 3–4 years after diagnosis. As muscles become progressively weaker, the loss of independence and increasing difficulty of performing activities of daily living greatly affect patients' quality of life. Patients in the terminal stage of the disease often require ventilatory support and feeding via gastrostomy[5].

In ALS, muscle weakness results from limited (submaximal) neuromuscular input to the sarcomere caused by motor neuron damage and death, which strains the ability of surviving motor neurons to stimulate muscle effectively[1]. Amplifying the response of the sarcomere to submaximal motor neuronal input could improve muscle force generation and function in patients with ALS. One way to do this is to increase the calcium sensitivity of the troponin–tropomyosin regulatory complex, the calcium sensor in the sarcomere that regulates force generation[1].

Vital capacity: a meaningful clinical indicator of disease progression

All patients with ALS eventually show some degree of respiratory muscle dysfunction. Respiratory failure is the most common cause of death in ALS, so early detection of respiratory muscle dysfunction is important[6]. Signs of declining respiratory muscle function, such as dyspnea, are often evident only during heavy exertion and go unnoticed in the early stages of disease[7]. Therefore, understanding the role of respiratory muscle weakness in ALS is crucial in monitoring disease progression.

Vital capacity is a measure of respiratory muscle strength and is measured either as forced vital capacity (FVC) or slow vital capacity (SVC)[8]. A decrease in FVC or SVC indicates declining respiratory function and is an important prognostic indicator of disease progression and a predictor of mortality[9]. Regular tests of pulmonary function can identify early signs of respiratory dysfunction and predict the onset of respiratory failure. Additionally, frequent respiratory evaluations are crucial for clinicians to identify patients who could benefit from noninvasive ventilation, an intervention that has been associated with improved survival[10].

Cytokinetics' commitment to muscle-biology-driven treatments

We are passionate about advancing muscle-biology-driven treatments for diseases characterized by compromised muscle function, weakness and fatigue to address the urgent unmet medical needs of patients with these disorders. Toward this end, Cytokinetics is collaborating with Astellas Pharma Inc. to research, develop and commercialize FSTAs. We are driven to improve the lives of people fighting ALS by applying our understanding of the mechanics of muscle function and contractility to the discovery and development of novel treatments that aim to directly improve muscle function and performance, potentially delaying disease progression and preserving independence.

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