SARCONEOS (API BIO101) targets Mas receptor within the protective arm of the renin angiotensin system and proves efficacy in various models of muscle wasting

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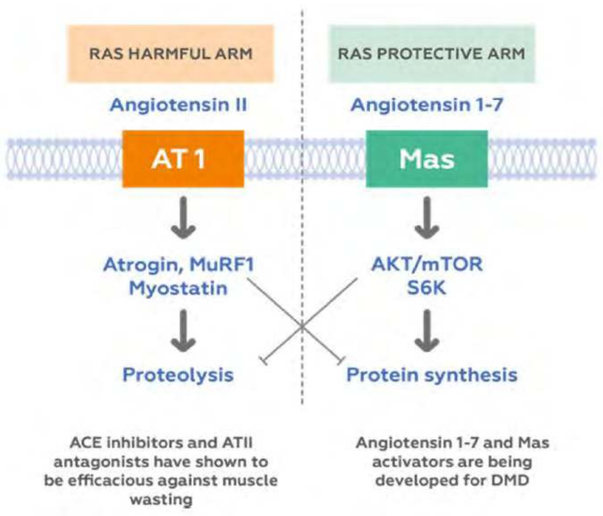
Abstract

Background. Muscle wasting affections such as sarcopenia and disuse atrophy lead to a progressive or temporary decrease in mobility and reduced quality of life. The drug candidate BIO101, a first-in-class drug targeting Mas receptor, has been developed pre-clinically and clinically for its potential on muscle quality and function. BIO101 is the API of Sarconeos currently tested in clinical IIb trial in patients with sarcopenia.
Objectives. The aim of this work was to demonstrate and characterize the impact of BIO101 on models of sarcopenia and disuse atrophy.
Methods. Adult (12-month-old) and aged (22-month-old) C57BL6/J mice were assessed for running performance after 14 weeks of oral treatment with BIO101 at 50mg/kg*day. Young (8-week-old) mice continuously administered orally at the same dose were assessed for muscle mass and specific maximal force at completion of the 14-day hindlimb immobilization. The impact of BIO101 on mouse and human myoblasts differentiation was determined by q-PCR, western blot and fluorescence microscopy. Mitochondrial respiration and biogenesis were evaluated using a Seahorse XF Analyzer and the Mitotracker Deep red dye, respectively.
Results. Old BIO101-treated animals ran significantly faster than old control animals (+17%) which demonstrated that BIO101 compensated for the significant aging-related loss of maximal running velocity. In young animals, BIO101 treatment prevented the loss of muscle functionality and improved muscle strength by 17,5% after 14 days of immobilization compared to vehicle-treated muscles. Improvement of muscle function demonstrated in young and old treated-animals, immobilized or not, was consistent with *in vitro* findings in terms of mitochondrial function and anabolism. BIO101 increased mitochondrial mass (+75%) and oxygen consumption rate in myotubes (+23% in spare respiratory capacity). The percentage of myogenin-positive cells was significantly increased after continuous BIO101 exposure (+ 80%) consistently with increased fusion index and number of nuclei/myotube, suggesting an acceleration of differentiation process by the drug candidate.
Conclusion. These studies demonstrate the overall beneficial properties of BIO101 on muscle cell function in two distinct physiopathological contexts and brings together evidences for improved anabolism and mitochondrial function. These results support the clinical development of Sarconeos in sarcopenic patients and warrant further studies in other muscle wasting indications.

Introduction

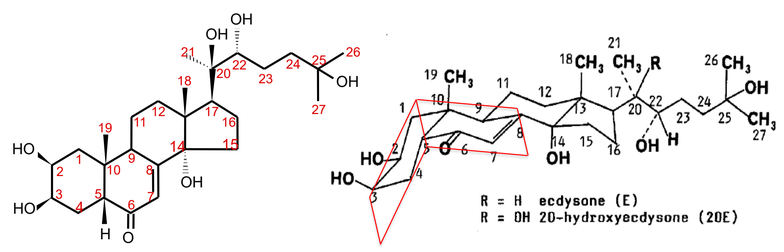
About Sarconeos: Sarconeos is a first-in-class drug candidate based on the activation of the MAS receptor (major player of the renin-angiotensin system) that had demonstrated meaningful activity in animal models of muscular dystrophies. Sarconeos has already entered clinical Phase IIb (SARA-INT) in patients with sarcopenia, an age-related degeneration of skeletal muscles, leading to loss of mobility in elderly people. BIO101 is the active principal ingredient of Sarconeos.
BIO101 received an Orphan Drug Designation (ODD) for Duchenne muscular dystrophy in EU on the 27th of June 2018 and in US on the 10th of May 2018. FDA IND application will be submitted by the end of 2018. Biophytis clinical programme for DMD (MYODA) will start in the first quarter of 2019.

About the renin angiotensin system (RAS): Growing evidence demonstrates that the activation of the renin angiotensin system contributes to muscle wasting and loss of strength leading to sarcopenia. Both observational studies and randomized clinical trials are suggesting that inhibition of the renin angiotensin system may avert sarcopenia and improve skeletal muscle strength and physical performance.



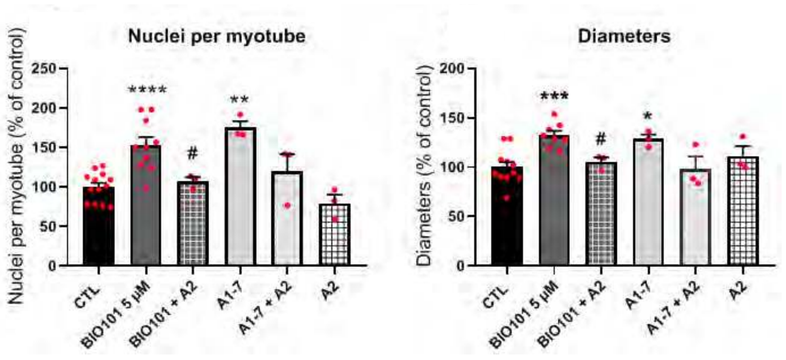
Results

20-hydroxyecdysone



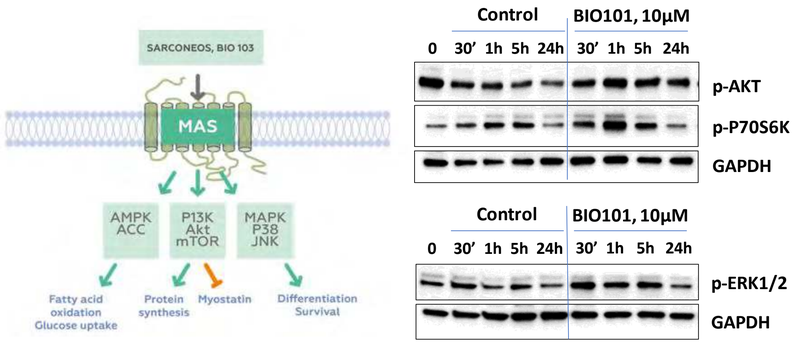
- Ecdysteroids are found throughout the whole plant kingdom
- They are believed to protect plants by acting as endocrine disrupters or/and feeding deterrents
- Because of its particular structure 20-E does not interact with human steroid receptors
- Development of an original process to obtain 20-E at a pharmaceutical grade: **BIO101**

Target engagement



→ BIO101 mimics the activity of Mas endogenous ligand Ang 1-7 on myoblast differentiation. BIO101 activity on myoblast differentiation is inhibited by a Mas specific inhibitor (A2 or A779). BIO101 activity on myoblast is inhibited by Mas siRNA (not shown).

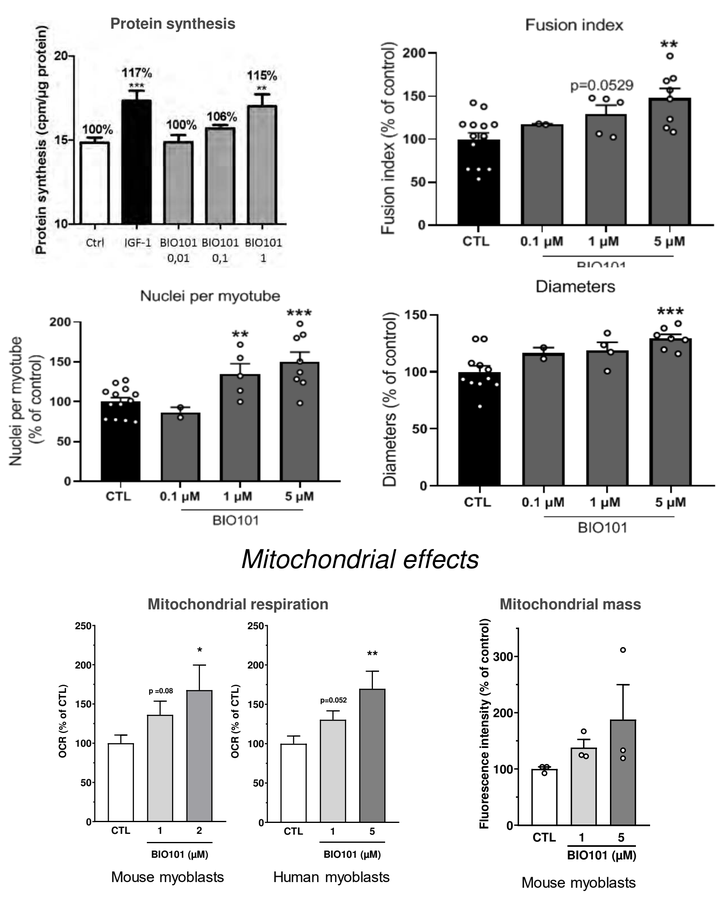
Signaling pathways



→ BIO101 activates AKT, MAPK and AMPK signaling pathways in myoblasts.

Dose-dependent target engagement *in vitro*

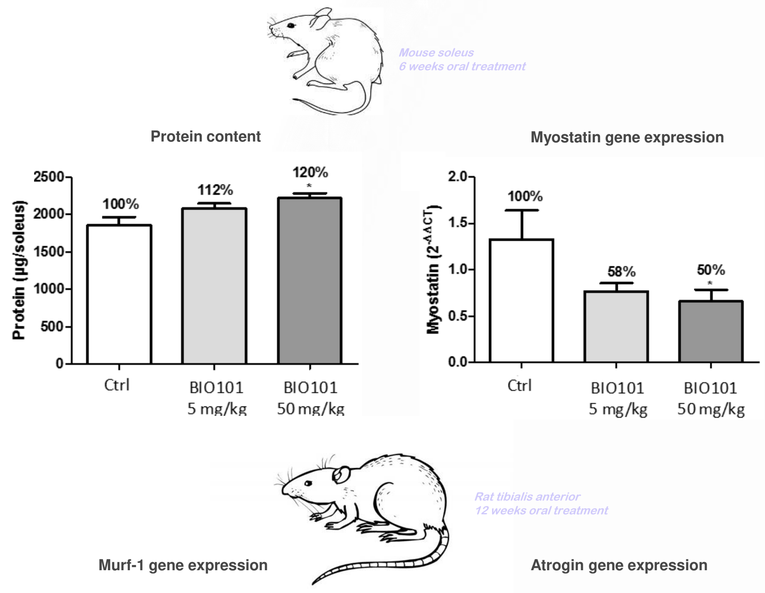
Anabolic effects



Mitochondrial effects

→ BIO101 demonstrates beneficial effects on both anabolism and mitochondrial respiration in myocytes.

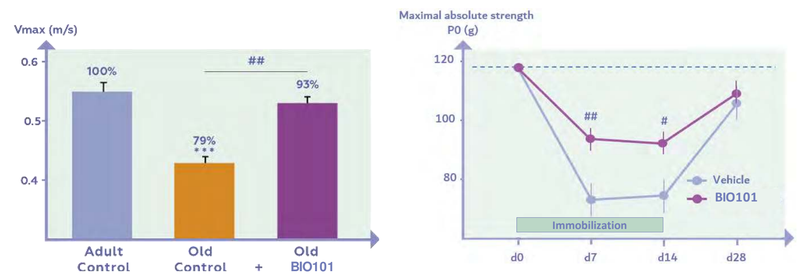
Dose-dependent target engagement *in vivo*



→ BIO101 is responsible for an increase in muscle protein content in treated mice consistent with a partial inhibition of myostatin gene expression. In rats, it inhibits the gene expression of two important regulators of ubiquitin-mediated protein degradation in skeletal muscle.

Proofs of concept in muscle wasting indications

Sarcopenia and disuse atrophy

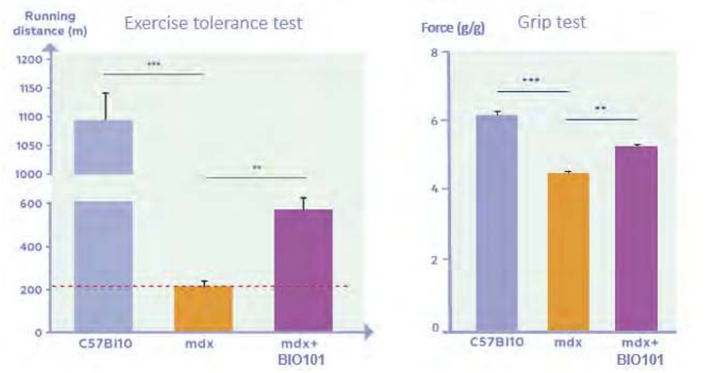


Adult: 16-month-old C57Bl6J female mice
Old: 26-month-old C57Bl6J female mice
Daily oral treatment for 14-weeks (50 mg/kg*day)

20-week-old C57Bl6J female mice
Hind limb immobilization for 14 days (d0-d14)
Daily oral treatment for 28 days (d0-d28) (50 mg/kg*day)

→ BIO101 is responsible for a significant protection against muscle function loss during ageing and disuse

Duchenne Muscular Dystrophy



20-week-old mdx C57Bl10 male mice. Daily oral treatment for 60 days (50 mg/kg*day).
Exercise tolerance test and four limb grip test

→ BIO101 is responsible for a significant protection against muscle function loss arising from a genetic alteration

Conclusions

These results demonstrate the potential of BIO101, a ***first-in-class small molecule*** Mas activator, in the improvement of muscle functionality.
Most interestingly, (1) energy metabolism (mitochondrial respiration), (2) myoblast differentiation as well as (3) the activation of signaling pathways involved in anabolism (Akt/mTOR) and regeneration (MAPK) known for being in various indications of muscle wasting are all significantly improved by BIO101.
Taken together, these results warrant further preclinical and clinical developments of BIO101.

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