A Quest into **Muscle Plasticity**

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Laboratory for Muscle Plasticity

The Balgrist

A Quest into Muscle Plasticity

Introductory synopsis

Soft tissues (muscle, tendon and ligaments) demonstrate a pronounced ability to respond to the impact of external stimuli with molecular and cellular adjustments that improves their capacity to withstand impact. The diagnostic assessment of muscle's adaptive potential provides indications on how bottlenecks in the current therapy of musculoskeletal defects can be overcome. The aim being to innovate surgical and rehabilitative approaches to permit the handicapped individual to maximise adaptive stimuli and processes.

Muscle health is an economic factor

Plasticity is described as the ability of an organism to change its phenotype in response to changes in the environment. This has its place in body homeostasis, especially regarding the implication of skeletal muscle in bodily actions. Through its mechanical actions in locomotion, posture and speech, muscle facilitates interactions with the environment and affects energy expenditure. The reduction of muscles' functional ability thus develops an important negative impact on our human capacity.

Muscle weakness and associated poor fatigue resistance is a major challenge to modern Western Society [1, 2]. It arises due to a reduction in the force producing capacity of skeletal muscle with prolonged unloading due to inactivity (disuse), injury or disease. The consequent reduction in strength negatively affects physical fitness and mobility; which lowers the quality of life. Based on epidemiological evidence it is estimated that associated costs accrue to 2000 CHF per year and person (Fig. 1).[3] Musculoskeletal health is thus an important financial substrate in Western society.

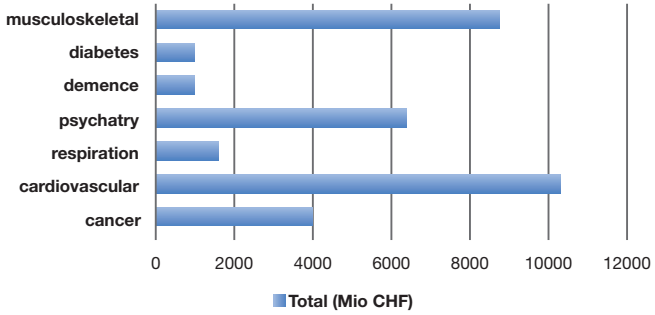


Figure 1: Health care cost in 2011 of the 7 major non-transmissive diseases.

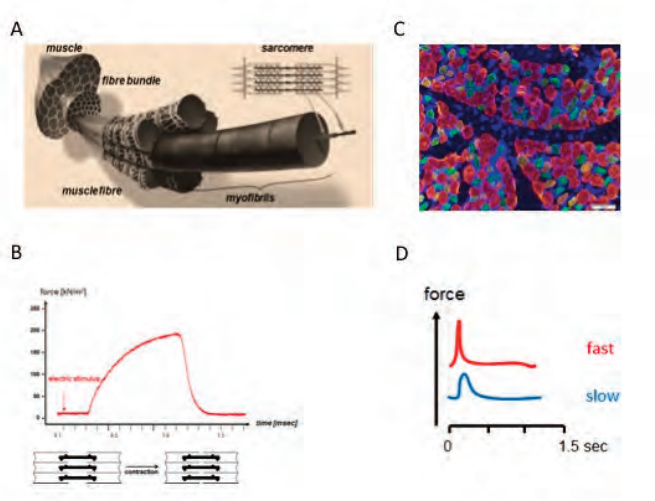


Figure 2: Scheme of electrically paced muscle contraction.

A) Illustration of the cellular organisation of skeletal muscle. Key elements of the cellular makeup are depicted. Adapted from Scientific American. B) Line graph of the relationship between force production and time after electric activation of fiber contraction. Below the shortening of sarcomeres with contraction is indicated. C) Microscopic image of slow (green) and fast (red) type fibers as detected in a cross-section of a muscle biopsy. D) Different force production and time lag between slow and fast muscle fibers.

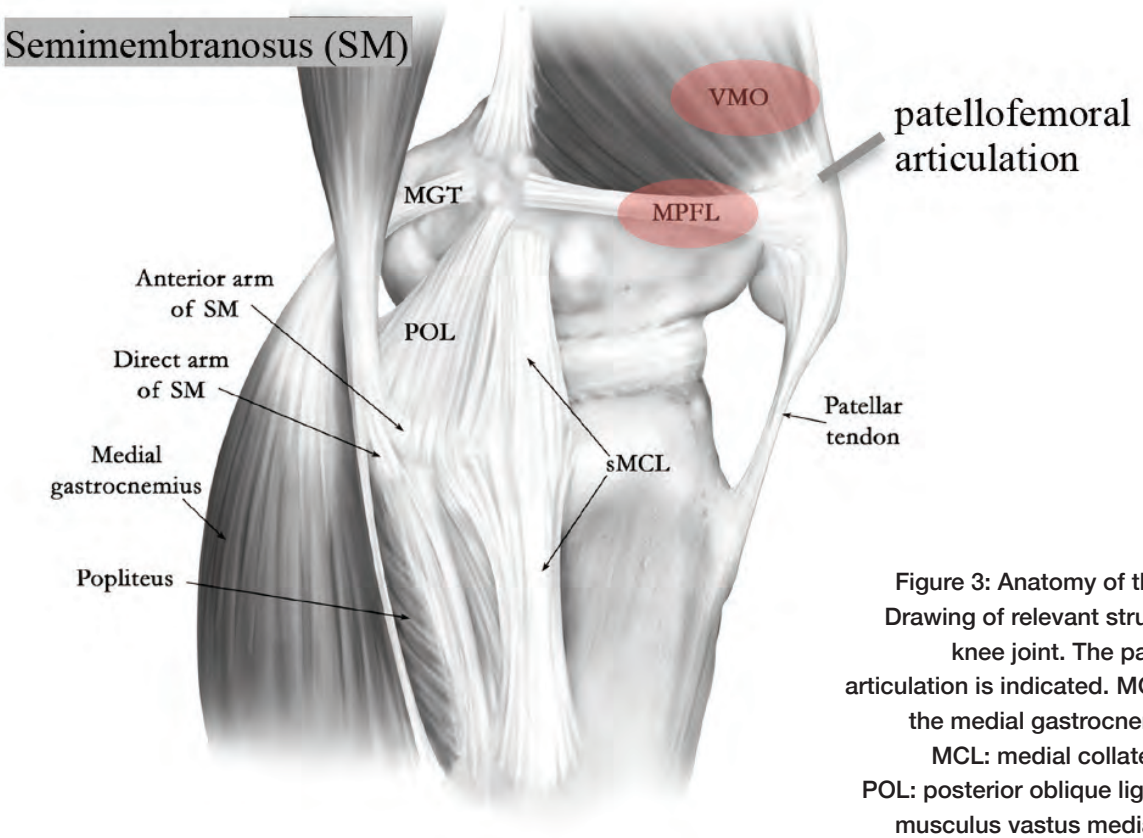


Figure 3: Anatomy of the knee joint. Drawing of relevant structures of the knee joint. The patella-femoral articulation is indicated. MGT: tendon of the medial gastrocnemius muscle, MCL: medial collateral ligament, POL: posterior oblique ligament, VMO: musculus vastus medialis obliquus.

Our research focus

The strategic aim of the Laboratory for Muscle Plasticity at Balgrist University Hospital is to expose the molecular and cellular mechanisms underpinning muscle affections in clinical situation ranging from simple exertion-induced soreness to major musculoskeletal disease of striated muscle; and more so their reversion with rehabilitation. This is done within the goal to identify biological bottlenecks which targeting opens venues for novel interventions that can halt muscle deconditioning and degeneration. Specific emphasis is put on the myocellular processes of rehabilitative and therapeutic measures after orthopedic surgery. Towards this end we focus on patient groups, whose musculo-skeletal health and quality of life could benefit from an improvement in muscle function.

Research approach and strategy

The laboratory for muscle plasticity at Balgrist deploys state-of-the-art methodology to optimise surgical approaches and rehabilitation based on genetic and physical constitution. The research is embedded in the Orthopaedic Hospital of the University of Zurich. By 2016 it will extend its patient tailored biomedical research by integrating its activities in the Musculoskeletal Research at Balgrist Campus. The following sections highlight active areas and scientific background of our research towards a personalised approach to musculoskeletal health.

Background

Skeletal muscle function relies on shortening of the embedded muscle cells (fibres) and this depends on bioenergetic processes (Fig. 2). The resulting in the capacity for force production, which is dictated by the composition and anatomy of skeletal muscle. Especially this implicates the volume content and cross sectional area of slow and fast contractile types of myofibrils, mitochondria and capillaries.

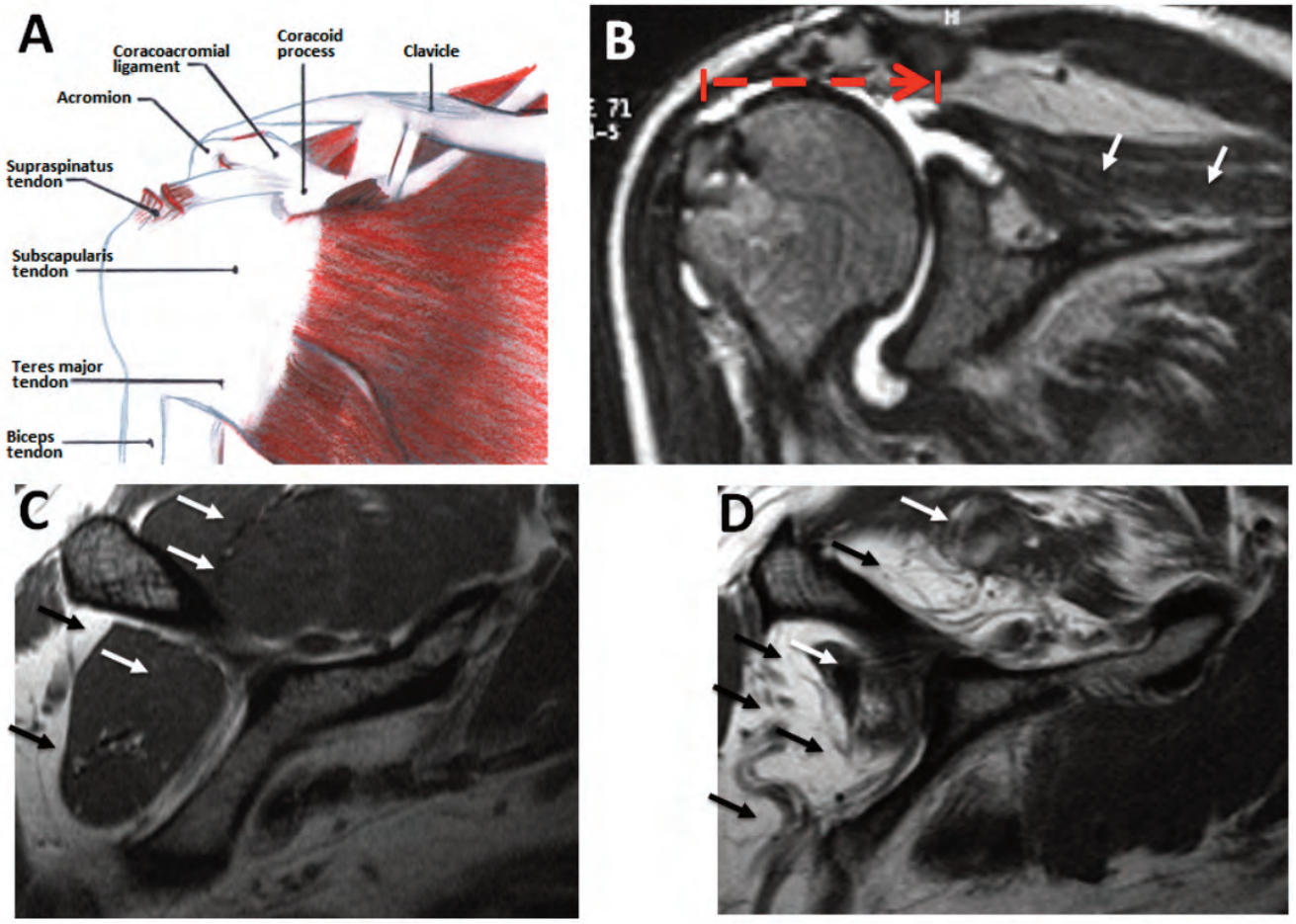


Figure 4: Fatty atrophy with tears of the rotator cuff.

A) Drawing of the human rotator cuff with the indication of a rupture of supraspinatus tendon (redrawn from MendMeShopTM © 2011). Coronary (B) and sagittal (C, D) images of a MRI scan of the shoulder at different depth of a patient at two time points after a full tear of the supraspinatus muscle tendon. The rate of retraction respective to the site of supraspinatus tendon attachment is indicated with a stippled, red arrow in panel B. Fat tissue (indicated by black arrows) appears in white above the darker contrast of muscle and bony tissue (white arrows). E) Sketch of the surgical procedure used to anchor the torn tendon stump to the bone.

These cellular variables define the maximal force (strength) and fatigue resistance of contraction. Both features are conditioned in a pulsatile manner by muscle use. This occurs because there is a natural degradation of muscle material due to wear-and-tear of cellular structures. The wasted muscle material must be replaced through the activation of biosynthesis. Mechanical stress with weight bearing contractions is a potent stimulus for the activation of these synthetic pathways. Energy flux is its most important modulator. The specific conditioning muscle through physiological factor is amply illustrated by the different outcome of strength type versus endurance type Sports activities that involve a high load or high repetition number of contractions, respectively.

The underlying regulation involves the activation of a molecular program that is embedded in our genes and which dictates the proteins to be made, i.e. expressed. The study of gene expression allows exposing the relationship between the dose and duration of exercise and the resulting effect on muscle function. This knowledge is important to develop rehabilitative interventions, or define stimuli that produce a functional outcome. Therapeutic measures based on information on muscle plasticity thus would offer a considerable socio-economic potential for

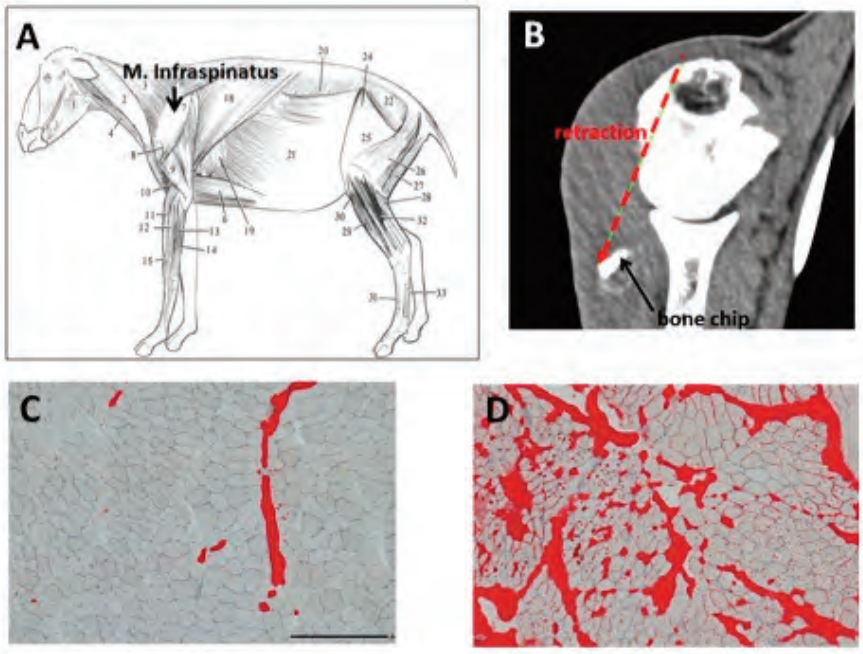


Figure 5: Degeneration of the rotator cuff after tendon release in a sheep model.

A) Sketch depicting the location of the infraspinatus muscle, which is targeted for tendon release via osteotomy of the greater tuberosity. B) Computed tomography image visualizing the retraction of infraspinatus muscle (based on the detached bone chip) after tendon release. C, D) Microscopic images visualizing the increased fat content of infraspinatus muscle in one sheep after 16 weeks of tendon release (D) compared to baseline levels (C). Fat was detected by Oil Red O staining (red) of cross-sections from the bioptic samples. Single muscle fibres can be identified based on the contrast provided by the sarcolemma. Bar indicates 500 micrometer.

musculoskeletal medicine but its application in the management of health care is underdeveloped today.

Repair mechanisms after rupture of the anterior cruciate ligament

As a joint the knee exerts the important task of translating and potentiating forces being produced in the upper, large thigh muscles via the lever arm of the femoro-patellar articulation (Fig. 3A). This function is essential to counteract the forces of gravity through the extension of the knee. On the downside, however, the knee joint is exposed to particularly high rates of mechanical stress. This may damage anatomical structures that stabilise the knee joint if the resulting mechanical strain exceeds the typical safety factor for musculoskeletal tissues. This is especially true for mechanical impact on ligaments that operate in the lateral direction, such as the anterior cruciate ligament (ACL) and medial patella-femoral ligament (MPFL; Fig. 3B). Their integrity is challenged by biomechanical vectors that operate in transverse direction to the movement of the knee joint. This is for instance the case with intense physical activity in Sports and during manual labour. The resulting incident is relatively frequent and affects 1 in 1750 individuals each year [4]. Because it renders the function of the affected knees unstable, repair of the damaged soft tissue is strongly indicated. This requires orthopaedic surgery and subsequent physical procedures to support the functional recovery of the re-attached ligament and connected muscle as it is weakened due to the prior injury and enhanced catabolism during unloading. Typically this is initiated by resistive type of exercise. The dose-effect relationships for musculoskeletal adaptations with rehabilitation, which define the therapeutic success of orthopaedic surgery, are not well defined.

Towards this end we pursue an investigation to define the time course of molecular and cellular adaptations in a major knee extensor muscle with exercise based rehabilitation subsequent to surgical repair of the ruptured ACL. This study is inspired by our results showing that eccentric types of endurance activity such as seen with downhill sports activities (skiing) represent a potent intervention to strengthen the musculo-tendinous structures that operate on the knee joint. We expect that our study will provide important information as to quality and effect size of the rehabilitation for the deconditioned muscle and knee function.

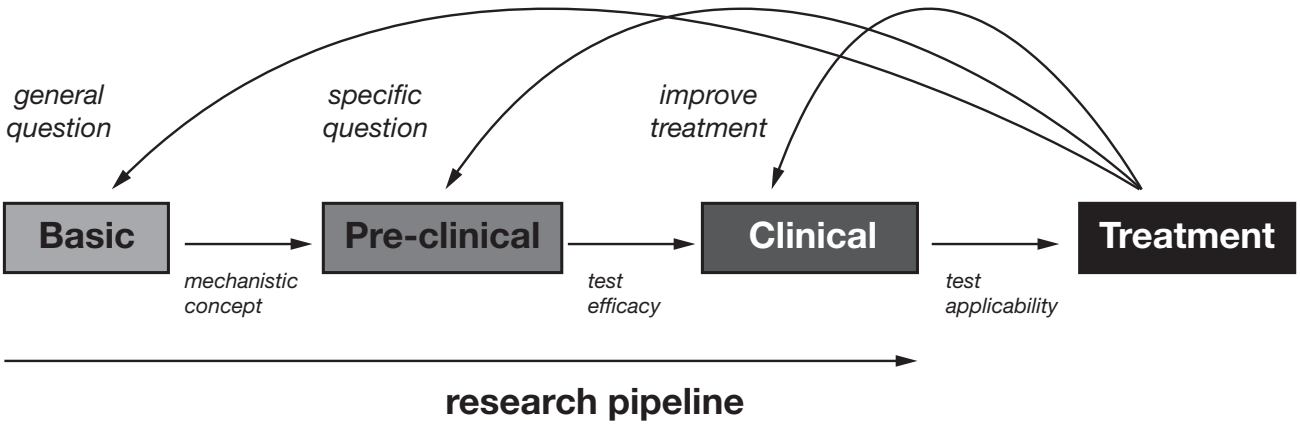


Figure 6: Research approach.

Scheme of the conceptual path of the research strategy of our integrated studies towards improved treatment of the orthopaedic patient.

Focus on rotator cuff disease

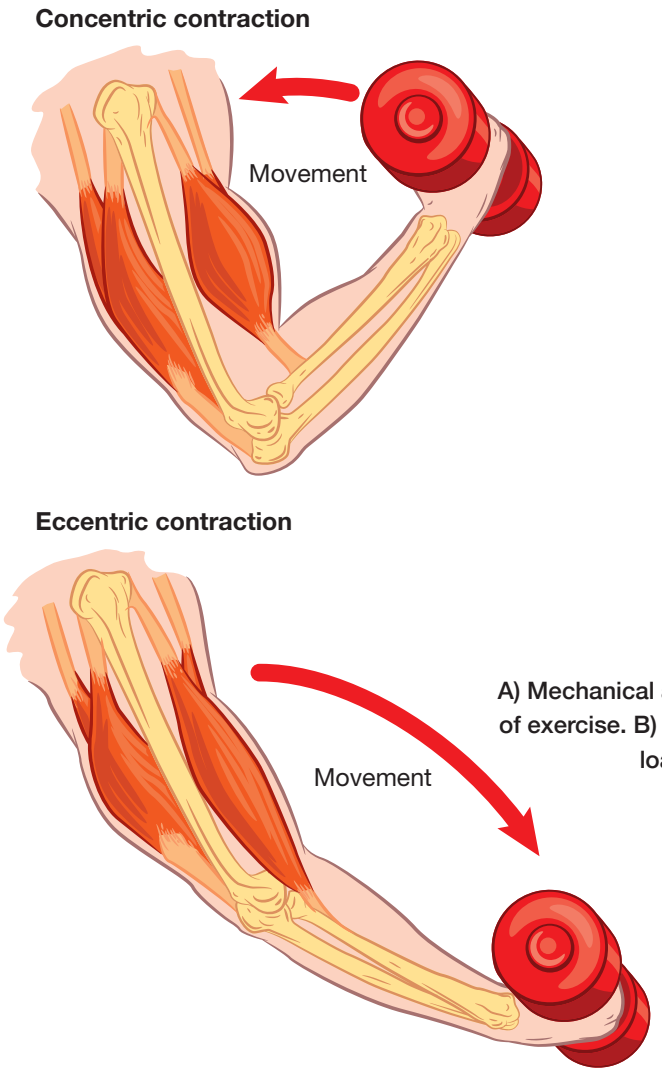
The rotator cuff is a complex group of skeletal muscles, which facilitate shoulder function (Fig. 4A). This involves important actions such as internal and external rotation as well as the abduction of the arm.

Full or partial tears of rotator cuff tendons are a relatively frequent and affect a considerable portion of the population. Aging associated factors and injury represent the major cases of the disease. Thereby current numbers indicate that 40% of subject above sixty years of age demonstrate tears of the rotator cuff. This severely complicates daily activities as it renders the accentuation of the upper extremity in one or more direction hard to impossible. If left untreated, shoulder function is permanently affected because the detached muscle degenerates by shrinkage of muscle cells and their conversion into fat tissue (Fig. 4B-D). Eventually this limits kinematics of respective joints which has the ultimate consequence in the degeneration of the glenohumeral joint. At this point no other option remains than to surgically replace the joint with an expensive endoprosthesis to reinstate limb function. Surgical interventions aimed at repairing the affected shoulder muscle involve the reattachment of the ruptured tendon to the bone via an anchor. Thereby the prevention of adipogenic and atrophic processes in the detached muscle is a priority to warrant optimal surgical repair of the ruptured muscle-tendon unit.

Towards improving the therapy of rotator cuff disease we investigate the time course of molecular and cellular alterations in animal models of the ruptured rotator cuff (Fig. 5). The aim is to map the mechano-regulated patho-biological process and risk factors of muscle degeneration, which contribute to the healing of muscle-tendon complex. Specific emphasis is put on testing the effectiveness of pharmacological compounds targeting the degradation of structural anchors of the contractile apparatus in muscle fibres.

The knowledge is integrated in a clinical trial in which we characterise morphological and genetic biomarkers of the healing response of rotator cuff muscle after surgical repair of the detached tendon. This is motivated by the reported contribution of heritable factors to the healing of the reattached rotator cuff. The aim is to reintegrate the gathered knowledge into personalised surgical approaches and therapies that do more efficiently prevent detractions in shoulder muscle function in critical responder groups (Fig. 6).

A



B

Figure 7: Exercise adaptation.

A) Mechanical and metabolic characteristics of eccentric and concentric forms of exercise. B) Exercise on a soft-robotic device allows to enhance mechanical loading of exercising muscle in an individual fashion for both legs.

Maximising the stimulus of rehabilitation

It is firmly established that repeated exercise can improve muscle's strength and metabolic fitness. It is however often not taken into account that certain individuals demonstrate a handicap to perform at a sufficiently high level to show functional adaptations respond at a much lower degree.

A bodily handicap is specifically indicated for patients with cardiovascular disease. Incidentally these subjects could profit considerably from an improvement in muscle fitness as this counteracts the looming risk to develop cardiovascular disease and associated systemic consequences. This defect typically consists in the incapacity of the cardiovascular patient to allocate metabolic resources to cardiac and skeletal muscle with an increase in demand (i.e. exercise).

Towards the alleviation of metabolic bottlenecks, we have started a clinical investigation in which we test the suitability of special forms of cardiovascular exercise on a soft-robotic device (Fig. 7). This tool allows enhancing mechanical loading to exercising muscle at a lower metabolic cost in an individual fashion for both legs. We hope this potentially boost improvements in muscle power as it allows subjects with lower fitness to perform the training sessions.

Gene therapy to accelerate muscle healing after Achilles tendon rupture

Achilles tendons are submitted to forces above n 6-fold the body weight. Consequently, injury of the Achilles tendon may occur with short physical activities that involve a large degree of gravitational loading. The injuries are relatively common affecting an estimated 7 per 100000 subjects in the general population [5]. Rapid reattachment of the tendon stump is a requirement to prevent irreversible degeneration of the ruptured soft tissue and wasting of the concerned muscle due to reduced mechanical impact upon tendon rupture. The concomitant deconditioning of muscle reduces mobility and consequently the quality of life.

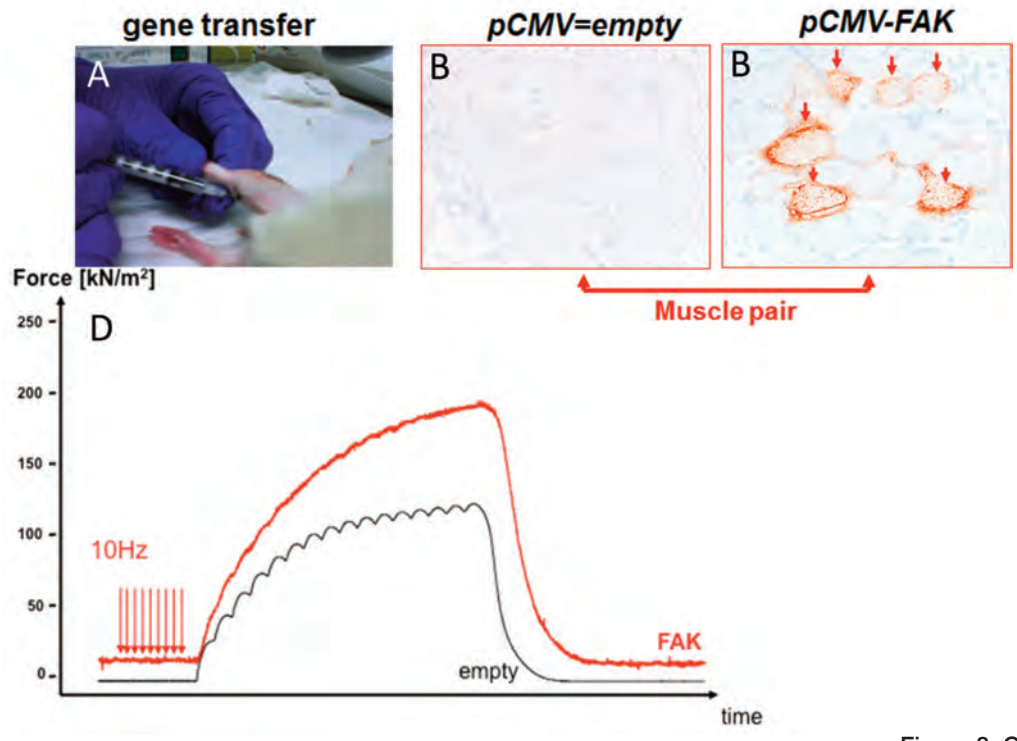


Figure 8: Gene therapy.

A) Composite figure depicting delivery of the mechano sensor focal adhesion kinase (FAK) into a lower extremity muscle of a rat. A gene vector is injected into the muscle and uptake is stimulated by electropulsing. B,C) Microscopic image visualising the amount of FAK (orange) in muscle fibres of a muscle being injected with a vector that carries the FAK gene or an empty control. D) Consequent effect of forced FAK expression (red) versus empty control (blue) on specific force (in Newton per square meter of the muscle cross section). Note the higher force in the muscle with forces FAK expression.

Despite high quality literature on how to diagnose and treat Achilles tendon rupture surgically, limited mechanistic understanding exists on how to tailor effective countermeasures to prevent muscle atrophy, especially physiotherapy [5].

This is important because the healing period requires time and is often not-productively invested. This has financial and social repercussions for the affected individual which is often month away from work. Towards this goal we have initiated studies to determine the effectiveness of a gene therapeutic approach to halt muscle atrophy. The intervention is directed to boost mechano-sensitive biochemical pathway that control muscle size and muscle force (Fig. 8). The long-term goal would be to extend successful approaches into a clinical trail.

Exercise genes that predict the response

It is a fact that considerable variability exists in the population regarding physical strength and endurance as well as their conditioning by training. This has evident implications for rehabilitative interventions aimed at re-establishing the musculoskeletal function. In a last, larger research project, we have therefore initiated studies into the mechanism underlying variability in muscle plasticity. In this context, we assess the extent to which muscular adaptations are associated with molecular determinants. We thereby focus on selected gene polymorphisms which affect the muscle phenotype in animals by modifying the function of important regulators of muscle plasticity (Fig. 9). The aim being to disentangle the mechanism underlying the responsiveness in healthy subjects to mechanical (i.e. strength type) and metabolic (i.e. endurance type) stimuli interventions and to translate this knowledge to the patient.

Outlook

The laboratory for muscle plasticity will continue research in this area in Balgrist Campus that provides a unique combination of dry and wetlabs

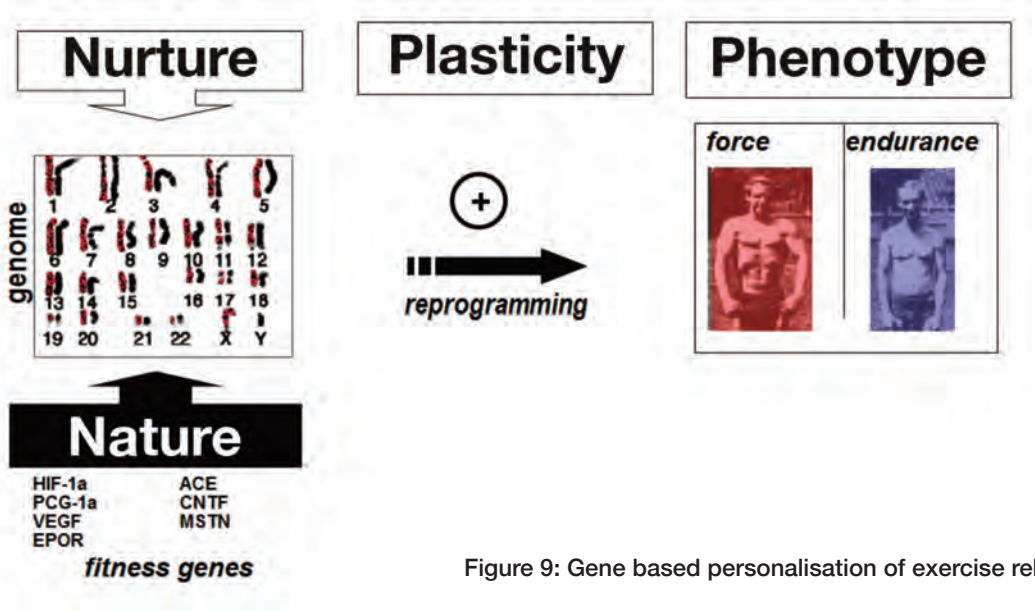


Figure 9: Gene based personalisation of exercise rehabilitation.

Composite figure emphasizing interaction effects of nature and nurture on the muscle phenotype. Natural constitution and conditioning by environmental stimuli activate a genomic program that instructs plastic changes of the muscle phenotype. It involves the production of diffusible gene messengers that act as actuators of performance by instructing the making of proteins. Polymorphisms in multiple fitness genes are understood to influence gains in endurance and strength performance by affecting gene expression. ACE, angiotensin-converting enzyme; EPO-R, erythropoietin receptor; HIF-1α, hypoxia-induced factor 1alpha; MSTN, myostatin; VEGF, vascular endothelial growth factor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

Figure 10: Virtual view of the Balgrist Campus. More information is available at http://www.balgristcampus.ch/de/

in a unique open space landscape that fosters interactions between academic, industrial and medical partners on questions driven by the orthopaedic patient (Fig. 10). Towards this end we call for interactions with academic and industrial partners being interested to develop our research areas in a joint venture.

Further reading

1. Booth FW, Chakravarthy MV, Gordon SE, Spangenburg EE. Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. J Appl Physiol 93(1): 3-30, 2002.

2. Dean E, Physical therapy in the 21st century (Part I): toward practice informed by epidemiology and the crisis of lifestyle conditions. Physiother Theory Pract 25(5-6): 330-53, 2009.

3. Statistical Yearbook of Switzerland, Swiss Federal Statistical Office (publisher), NZZ Verlag, 2014, ISBN 978-3-03823-874-4.

4. Griffin LY, Noncontact Anterior Cruciate Ligament Injuries: Risk factors and prevention strategies, Journal of the American Academy of Orthopaedic Surgeons 8: 141-150,2008

5. Glazebrook MA, New guidelines to address acute Achilles tendon ruptures, AAOS Now, March 2010, http://www.aaos.org/news/aaosnow/mar10/research1.asp).

Additional information:
Webpages: http://www.balgrist.ch/en/Home/Research-and-Education/Orthopaedics/Muskelplastizitaet.aspx

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