The Balgrist

OPTIONS FOR PERSONALISED MUSCLE REHABILITATION

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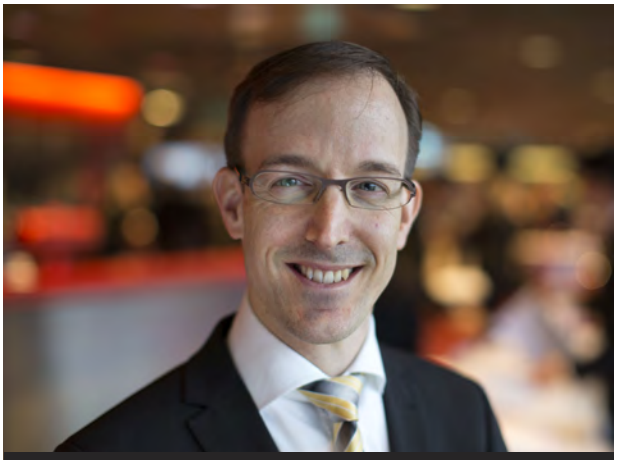
Horizon 2020: What full association means for Swiss research

Philipp Langer, Head of the EU Framework Programmes section, SERI, highlights Switzerland's participation in Horizon 2020 now it has full association

Up until the end of 2016, Switzerland was only partially associated with Horizon 2020, the European Union's latest framework research programme. National measures were put in place to finance Swiss project participations in areas of Horizon 2020, to which Switzerland was not associated. Since the beginning of 2017 Switzerland has become fully associated with Horizon 2020. Philipp Langer, Head of the EU Framework Programmes section at the State Secretariat for Education, Research and Innovation (SERI), looks back on the period of partial association and explains how things are likely to continue over the coming years.



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Philipp Langer, State Secretariat for Education, Research and Innovation, Head EU Framework Programmes

What is Switzerland's official position regarding Horizon 2020?

Switzerland's official position over the last 3 years has always been the same, namely, the desire for full association to Horizon 2020. There is great satisfaction because this association to all parts of the Horizon 2020 Programme has been in place since 1 January 2017. Researchers from Switzerland can now participate in all sections of the 8th Programme generation (Horizon 2020 and the Euratom Programme), just as they could under FP6 and FP7, between 2004 and 2013. In addition, Switzerland is also able to take part as an observer when it comes to defining the programme's content and strategy.

Did the impediments of the last 3 years cause problems for higher education institutions and researchers in Switzerland?

The possibility of participating in the Horizon 2020 research framework programme is extremely important for Swiss institutions and businesses involved in research and innovation. For one thing, collaborative projects allow Swiss actors to position themselves in international networks at the cutting edge of their scientific field. Moreover, the possibility of applying for individual funding (e.g. ERC grants) allows researchers in Switzerland to measure themselves against the world's greatest talents and is a key argument in drawing the best researchers to Swiss institutions, particularly cantonal universities, federal institutes of technology and universities of applied sciences. Obtaining such a grant brings with it prestigious recognition, which is extremely important in a researcher's career.

Over the last 3 years, Switzerland was only able to participate to a limited extent in Horizon 2020, both in terms of content and duration: researchers in Switzerland were only able to participate in a third of the Horizon 2020 as associated partners, and this was only until the end of 2016. Besides, even this partial association as of September 2014 has only been possible because Switzerland granted citizen from Croatia de facto the same treatment in terms of

free movement of persons as other European countries. As of 2017, Switzerland had only 2 options: full participation as an associated country or total exclusion from the Programme. The uncertainty that reigned over the least 3 years regarding Switzerland's partner status within Horizon 2020 diminished our country's appeal. Including Swiss partners in a given project, who were considered a risk for that project, so they were sometimes disregarded by international consortiums. The upshot was a significant drop in Swiss participation, a problematic situation as international connection is a key factor for Switzerland's standing as a scientific location.

What further possibilities are open to Switzerland with full association?
Full association status in Horizon 2020 allows Switzerland to sit as an observer on the programme's various advisory groups at European level and contribute to defining research topics and other strategic aspects. This is important for a number of reasons. On the one hand, calls for the topics of cooperative projects at European level are defined in a more top-down manner than in Switzerland, and that takes place in the advisory groups for each area covered by Horizon 2020 (health, ICT, environment, space, energy, climate, and transport). On the other, the funding available through Horizon 2020 (some €80 billion, over 7 years) is so important that each rule associated with these programmes (for example, the obligation to publish findings in Open Access journals) has a real impact on the way in which research and innovation is conducted throughout Europe.

During the period of partial association between 2014 and 2016, Switzerland was considered a third country for certain programme sections of Horizon 2020. The federal government took over the funding of Swiss elements of the projects. What will happen to these projects now that Switzerland is again fully associated?
Projects already underway that have received funding under Horizon 2020 will not be affected by the change in Switzerland's participation status: Their source of funding is assured for the full duration of the project. SERI will continue to fund projects submitted to Brussels by researchers in Switzerland and positively evaluated between 2014 and 2016. This affects around 1,000 projects with a financing volume of around 600 million Swiss francs. The last of these projects are expected to conclude in 2023. Until then, SERI has to maintain the structures set up to implement the transitional measures.

After the uncertainty and stress surrounding Horizon 2020 between 2014 and 2016, can we now expect calmer times ahead?
The period between 2014 and 2016 was fairly work intensive. For all projects where Swiss researchers could still submit projects, but did no longer receive funding by the EU, we had to set up the whole national project funding system within a short space of time, which involved putting in place a new legal basis and creating a new IT database (the former database dated from 1993). The national funding of projects with a normal duration of 4 to 6 years, as opposed to paying a set annual contribution to Brussels, meant we had to make adjustments to the annual payment appropriations involving hundreds of millions of francs. That is still having an impact on the federal budget.

Depending on political developments between the EU and Switzerland, the future should be somewhat more ordered, yet implying double work: In addition to assuring the obligations that come with full association with the managing bodies in Brussels, SERI also has to ensure the continued project-based funding of researchers in Switzerland. Administering the 1,000 or so nationally funded projects will be particularly time consuming between 2018 and 2020, because that is when the detailed project invoices will be due. The Horizon 2020 projects are also more extensive than earlier EU projects. But it was clear from the outset that Switzerland's third country status would require the setting up of the necessary administration.

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The Balgrist

Options for Personalised Muscle Rehabilitation

By Prof. Dr. Martin Flück

Introductory synopsis

Soft tissues (muscle, tendon and ligaments) demonstrate a graded capacity to respond to the impact of external stimuli with molecular and cellular adjustments that improves their capacity to withstand the original impact. The molecular-diagnostic assessment of muscle's adaptive potential provides indications on how bottlenecks in the current therapy of musculoskeletal defects can be overcome. This may permit to personalise surgical and rehabilitative approaches to maximise adaptive stimuli and allow a faster and stronger recovery of handicapped individuals.

Conditioning of 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). This is grounded in the fact that both reduce mobility and quality of life, and accrue the risk of developing hypertension and metabolic disease all of which increase morbidity. This menace arises due to a reduction in the force producing capacity (i.e. strength) and metabolic fitness of skeletal muscle with prolonged unloading due to inactivity, injury or disease. Based on epidemiological evidence it is estimated that associated costs accrue to 2,000 CHF per year and person (3). Musculoskeletal health is thus an important financial substrate in Western society.

Physical exercise is the most complete counter-measure to enhance functional capacity of frail individuals, and halt energy expenditure-related diseases, such as hypertension, type II diabetes, metabolic syndrome, and even certain forms of cancers (1). Both endurance and resistance forms of exercise are now active part of the rehabilitation program of patient groups suffering from musculoskeletal and metabolic affections. The underlying processes involve an activity-induced enhancement of metabolic turnover within musculoskeletal tissues, the cardio-vasculature and the liver, which provide fuels for the higher energy demand during exercise. In consequence, lean-to-fat mass is favorably affected through quantitative and qualitative adaptations in skeletal muscle's contractile and metabolic makeup. It is estimated that the latter physical therapies and associated lifestyle interventions represent a considerable market size summing to a total of US$1.49 Trillion (4). Therapeutic measures based on diagnostic

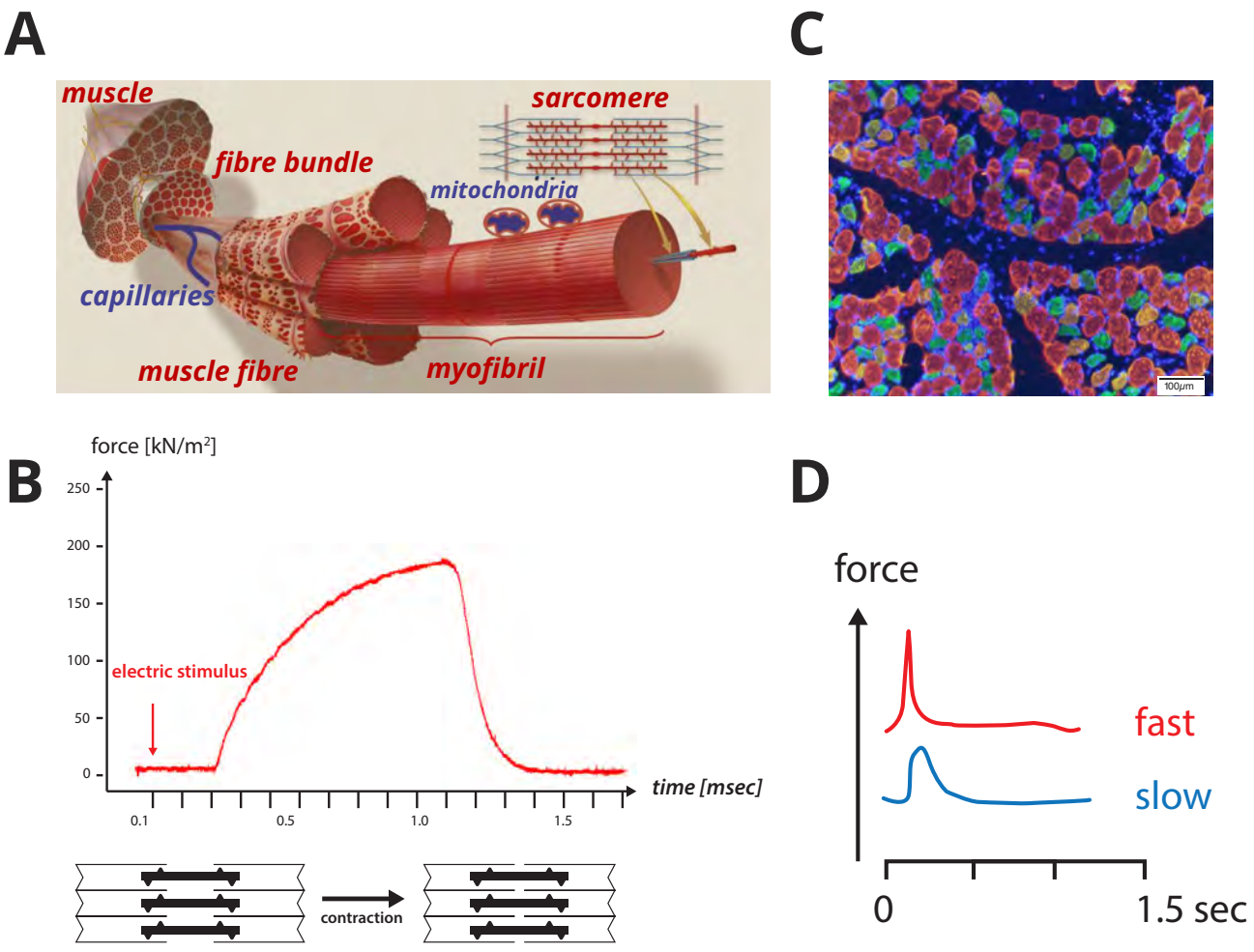


Figure 1: Scheme of contractile aspects on muscle function. A) Illustration of the cellular elements underpinning metabolic and contractile function of skeletal muscle. Adapted from Scientific American. B) Line graph of the relationship between force production and elapsed time after electric pacing of fibre contraction. Below the shortening of sarcomeres with contraction is indicated. C) Microscopic image of slow (green) and fast (red) type fibres as detected in a cross-section of a muscle biopsy. D) Different force production and time lag between slow and fast muscle fibres.

information on muscle plasticity thus would offer a considerable socio-economic potential for musculoskeletal medicine. Today the introduction of these applications in the health care sector is underdeveloped.

Research approach and strategy

The laboratory for muscle plasticity at Balgrist deploys state-of-the-art methodology to expose the molecular and cellular mechanisms underpinning unsolved musculoskeletal phenomena of the Orthopaedic patient. The aim is to identify biological bottlenecks which targeting opens venues for novel interventions that can halt muscle deconditioning and degeneration. Specific emphasis is put on genetic and myocellular biomarkers which predict the outcome of surgical interventions and rehabilitative measures. The aspiration being the transfer identified knowledge into personalised measures, which improve musculo-skeletal health and quality of life of the patient.

By 2016 the laboratory has integrated its activities in brand new research facilities at Balgrist Campus. The setting offers a unique combination of dry- and wetlabs in a unique open space landscape that fosters interactions between academic, industrial and medical partners. The following sections highlight active areas and scientific background of our research towards a personalised approach to musculoskeletal health.

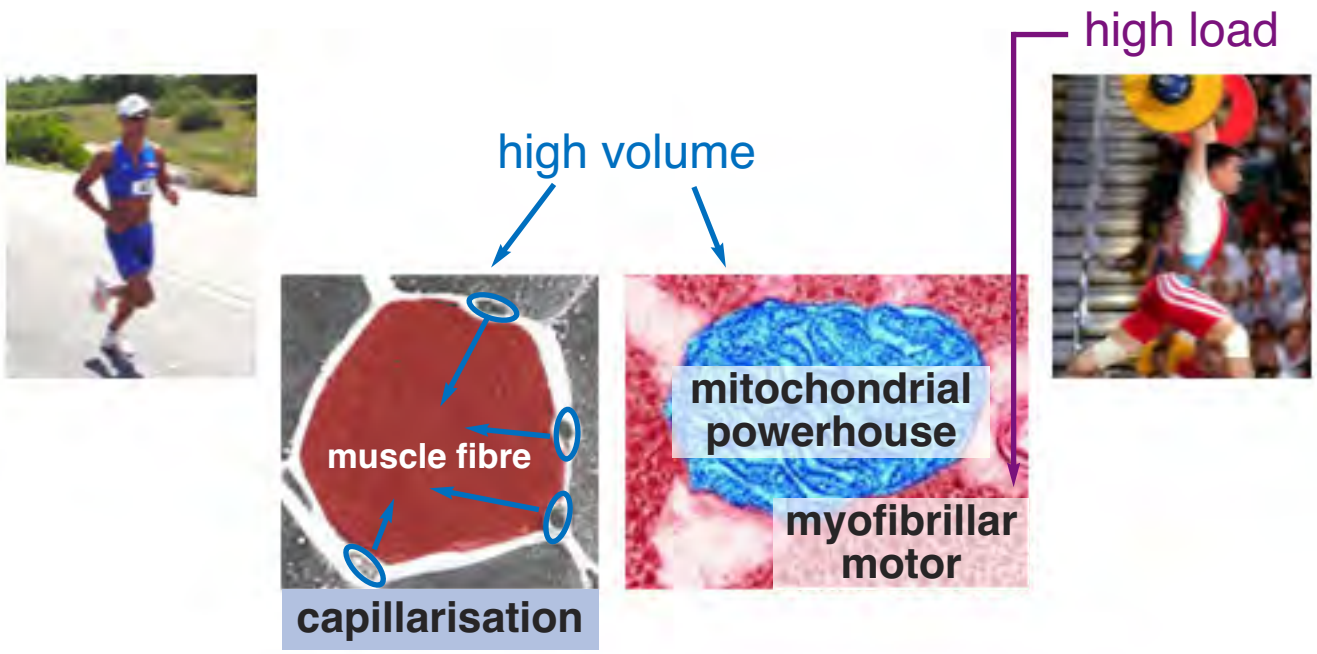


Figure 2: The two main exercise stimuli of muscle plasticity. Sketch summarising the reciprocal influence of high volume type, and high load exercise stimuli, on contractile and metabolic composition of muscle fibres. High load-low volume type contractions during resistance exercise increase the force producing capacity of muscle through effects on the myofibrillar motor; producing radial growth of myofibrils. By contrast, high volume-low load typed of contraction during intense endurance exercise improve the supply of energy to muscle fibres by increasing the content of the cellular powerhouse, the mitochondria, and capillaries.

Background

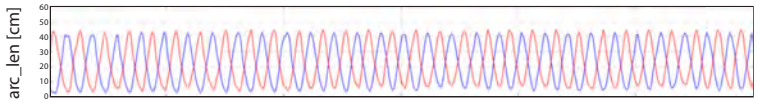
Skeletal muscle function relies on shortening of the embedded muscle cells (fibres) and this depends on bioenergetic processes (Fig. 1). Depending on the composition and anatomy of the muscle, this results in a varied capacity for force production. On one hand this implicates the content and cross-sectional area of slow and fast contractile types of muscle cells, which defines muscle strength. On the other hand, it includes the content of mitochondria and capillaries which set fatigue resistance of contracting muscle. Both features are conditioned in a pulsatile manner by muscle use because there is a natural degradation of muscle material due to wear-and-tear of cellular structures. Wasted muscle material must therefore 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. Muscle conditioning through mechanical and metabolic factors is amply illustrated by the different outcome of resistance type versus endurance type of Sports activities on force and energy producing components of skeletal muscle (Fig. 2).

Maximising the stimulus of rehabilitation

In clinical practice, it is appreciated that certain individuals demonstrate a handicap to develop functionally relevant adaptations with exercise rehabilitation as efficiently as healthy subjects. As the response of muscle plasticity is graded to the intensity and volume of exercise, much of the reduced capacity of patients to adapt to exercise may be explained by an insufficiently high workload. This is particularly critical in patients with cardio-vascular disease, which present the incapacity to allocate sufficient metabolic resources to exercising cardiac and skeletal muscle during the manifold increase in energy demand with onset of exercise.

A

B



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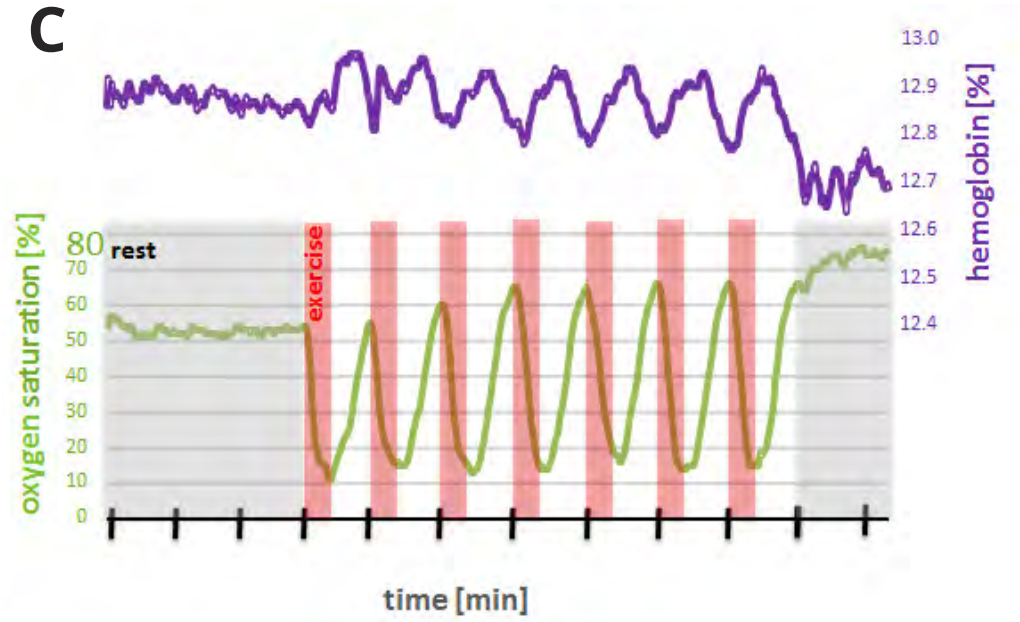


Figure 3: Cardiovascular exercise on a soft robot. A) Soft-robotic device allowing enhanced mechanical loading of exercising muscle in an individual fashion for both legs. B, C) Mechanical characteristics of loading left (blue) and right leg (red) during one work interval (B) and metabolic characteristics (i.e. oxygen saturation) during seven work intervals (C) of interval type exercise on the soft robot.

We have started a clinical investigation to overcome metabolic bottlenecks which alleviate the improvement of metabolic fitness and strength in certain cardiac patients with cardio-rehabilitation. The aim is to test the suitability and effectiveness of special forms of pedalling exercise on a soft-robotic device which reduce metabolic load through requesting lengthening type (i.e. eccentric) contractions (Fig. 3A). The implicated higher metabolic efficiency compared to shortening type (i.e. concentric) contractions is mediated through a spring-like mechanism that retrieves mechanical energy being stored in the molecular structures of soft tissues in skeletal muscle and tendon. However, this comes at the cost of an increased wear- and tear, which produces a degree of muscle fibre damage, especially in untrained individuals. It is therefore important to reduce the strain experienced by muscle fibres during eccentric exercise to an acceptable level. Towards this end the inbuilt sensors of the soft robot and the additional application of oxygen sensors allow to monitor and dose the nutritive mechanical and metabolic stimuli that impact on muscle during the exercise. We expect that this data will provide valuable information to tailor the mix of metabolic and mechanical stimuli during exercise to the genotypic and physiological condition of the patient to optimise the improvement of metabolic fitness and strength with cardio-rehabilitative training.

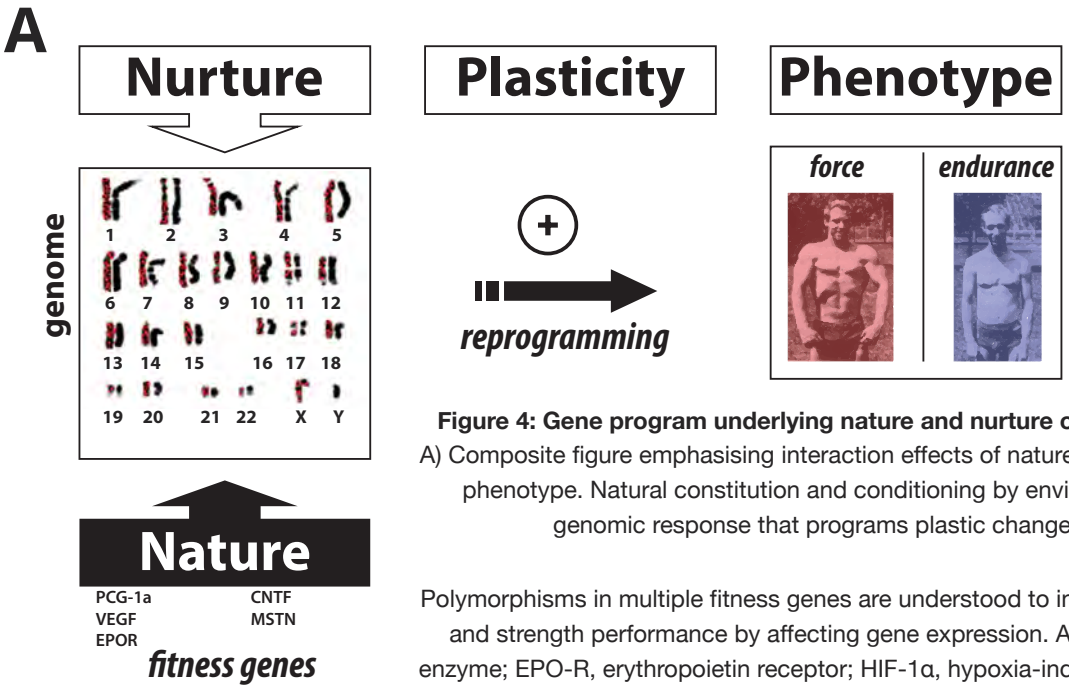
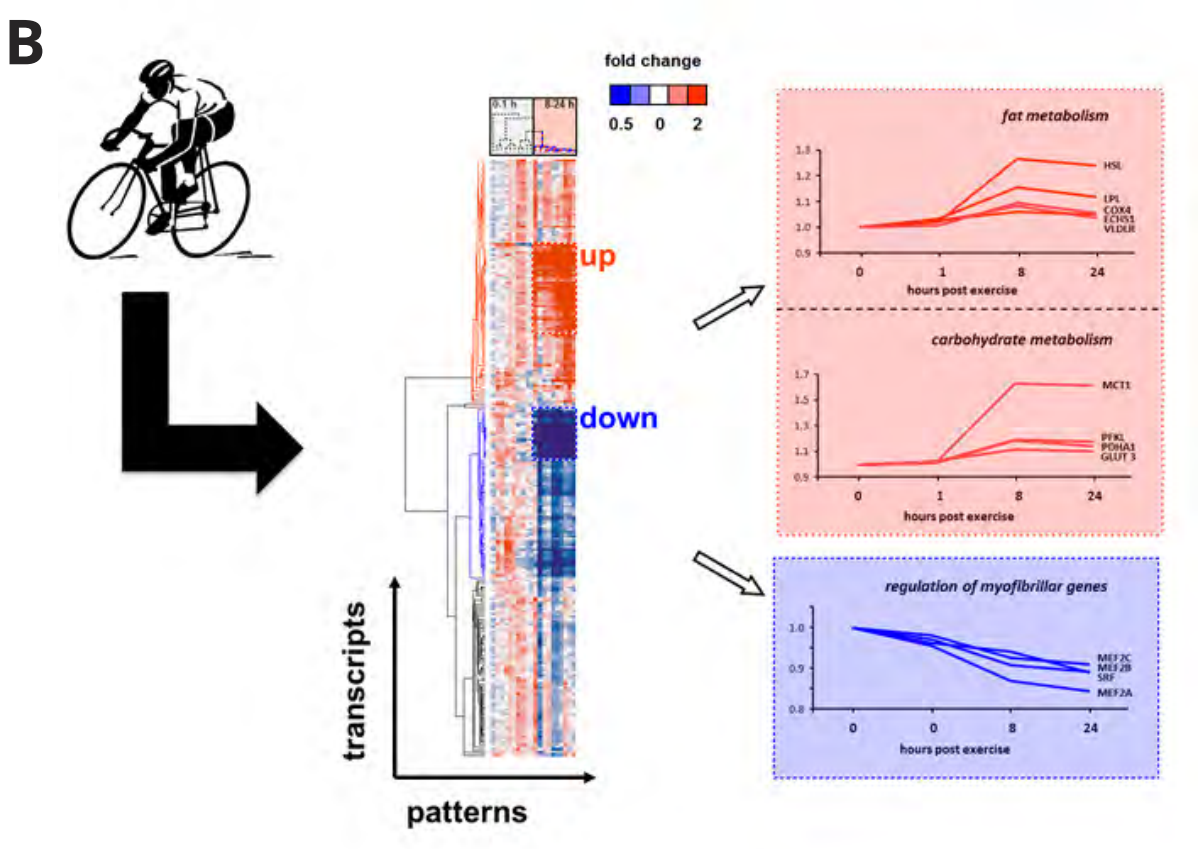


Figure 4: Gene program underlying nature and nurture of the exercise phenotype. A) Composite figure emphasising interaction effects of nature and nurture on the muscle phenotype. Natural constitution and conditioning by environmental stimuli activate a genomic response that programs plastic changes of the muscle phenotype.

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.



B) Drawing summarising the gene transcript response in knee extensor muscle over the first 24 hours after exhaustive bicycle type endurance exercise. Gene transcript levels resolve as a pattern of high (red) and low abundant gene transcripts. A maximal response is seen 8-24 hours after exercise for gene transcripts that program aerobic metabolism of fat and glucose (up-regulated) and regulation of contractile genes (down-regulated). The names and response of representative gene transcripts are given. For more information see Flueck 2009.

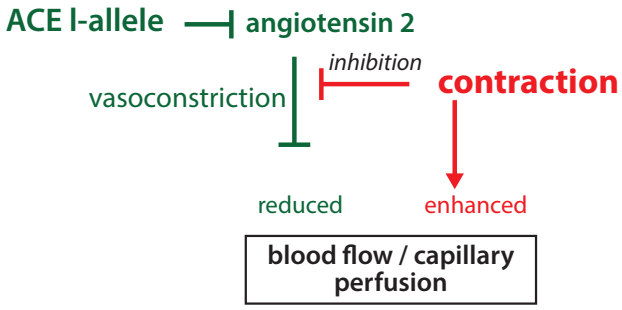


Figure 5: ACE-I/D genotype dependent muscle plasticity. Scheme how ACE-angiotensin 2 mediated vasoconstriction, which reflects the reduction in the diameter of arterioles, affects perfusion of downstream blood vessels. The ACE insertion allele (ACE-I) and the onset of muscle contractions affects capillary perfusion, and blood flow, and possibly muscle oxygenation in opposite ways.

In our investigation, we specifically apply an interval-type of pedalling exercise to allow subjects to recover after one-minute bouts of work. This results in a repeated pattern of muscle de-oxygenation and enhanced muscle strain which returns to near normal levels in the resting phase between work intervals (Fig. 3B/C). This would normally allow subjects with lower fitness to perform the training sessions. Results from a first cohort of healthy subjects emphasises that the lengthening type interval exercise on the soft robot approach is well tolerated and reduces cardiovascular metabolic load to a level that is safe for the cardiovascular patient, compared to shortening type exercise, and can be tailored in an individual fashion to the performance characteristics of the patient.

Genetic explanation for inter-individual variability

It is an appreciated, but often ignored fact that considerable variability exists between subjects regarding the conditioning of muscle function by physical training. A number of polymorphism in so called fitness genes are now understood to influence the exercise phenotype through affecting adaptations to training (Fig. 4A). Our research has pointed out that gene-mediated regulation of muscle plasticity may explain this genetic influence (5). Molecular measurements would be useful to develop effective rehabilitative interventions, or define stimuli that improve the efficiency of a training stimulus. Yet commercial considerations on the cost and financially interest groups have prevented to introduce this approach into a practical application.

In fact, specific adjustments of muscle composition with physical training are reflected in a genomic response in exercised muscle which programs muscle adaptation. The response involves the biosynthesis (transcription) of diffusible gene copies which program muscle remodelling through instructing the making of proteins. The response pattern of the synthesised gene transcripts is specific for the exercise stimulus distinguishing between endurance and resistance type of exercise (Fig. 4B). For instance, after exhaustive endurance exercise, transcript concentrations of genes for aerobic metabolism are increased in relation to exercise intensity and cumulate with repetition of exercise during training. By contrast transcripts for anabolic processes are elevated after load bearing exercise. Measurements of transcript levels thus offer an improved temporal resolution and sensitivity compared to classical physiological measures of muscle strength and aerobic performance to identify adaptations with training.

The aspiration of the laboratory for muscle plasticity is to apply gene-mediated mechanisms to predict and enhance the responsiveness of musculoskeletal function in the (orthopaedic) patient to surgical repair and rehabilitative exercise. Towards this end we identified that a specific insertion/deletion polymorphism in the gene for blood vessel associated angiotensin converting enzyme (ACE) modifies muscle adaptations in response to endurance training through affecting the production of the peptide angiotensin 2 (5). Specifically, genotypes with the insertion allele were associated with an improved trainability of endurance performance. Our results delineated that the

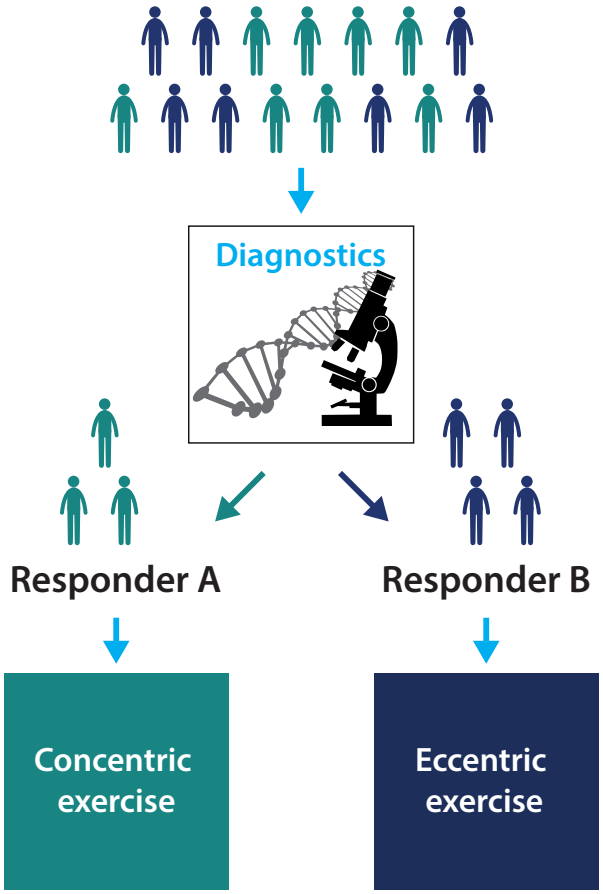


Figure 6: A personalisation approach for musculoskeletal rehabilitation. Drawing emphasising how diagnostics involving genotyping (and microscopic analysis of bioptic samples) may be used to draw personalised recommendation on the suitable form of exercise to drive muscle plasticity of the (cardiovascular) patient.

superior trainability of aerobic performance in ACE insertion allele carriers is reflected in larger gains of muscle mitochondria and lipid stores that assist the production of aerobic energy for contraction (5). We identified that the improved adaptations of metabolic processes in ACE insertion allele carriers, are related to a better capillary perfusion and glucose utilisation during intense exercise (6); and compares to the effect of ACE inhibition through oral intake of anti-hypertensive medication (7; 8). The observed effects emphasise that perfusion dependent muscle deoxygenation drives adaptations of aerobic metabolism in exercised muscle and that this response is modified through the vasoconstrictory action of the ACE product angiotensin 2 (Fig. 5).

Introducing gene based personalisation to exercise rehabilitation

Given the importance of oxygen de-oxygenation as adaptive stimuli for muscle plasticity we have initiated a clinical trial (ACE-REHAB) to test whether the effect of rehabilitative exercise in cardiovascular patients can be enhanced in non-responders based on the ACE-I/D genotype (Fig. 6). Results from the first cardiac patients are encouraging essentially supporting the feasibility of a personalised approach into cardio-rehabilitation. They show that the devised interval-type protocol on the soft robot is successful to sizeably improve blood pressure regulation, muscle strength and endurance capacity within 3 weeks of training already.

Focus on rotator cuff disease

The rotator cuff is a complex group of skeletal muscles, which facilitate shoulder function (Fig. 7A). 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 condition affecting a considerable portion of the population. Aging associated factors

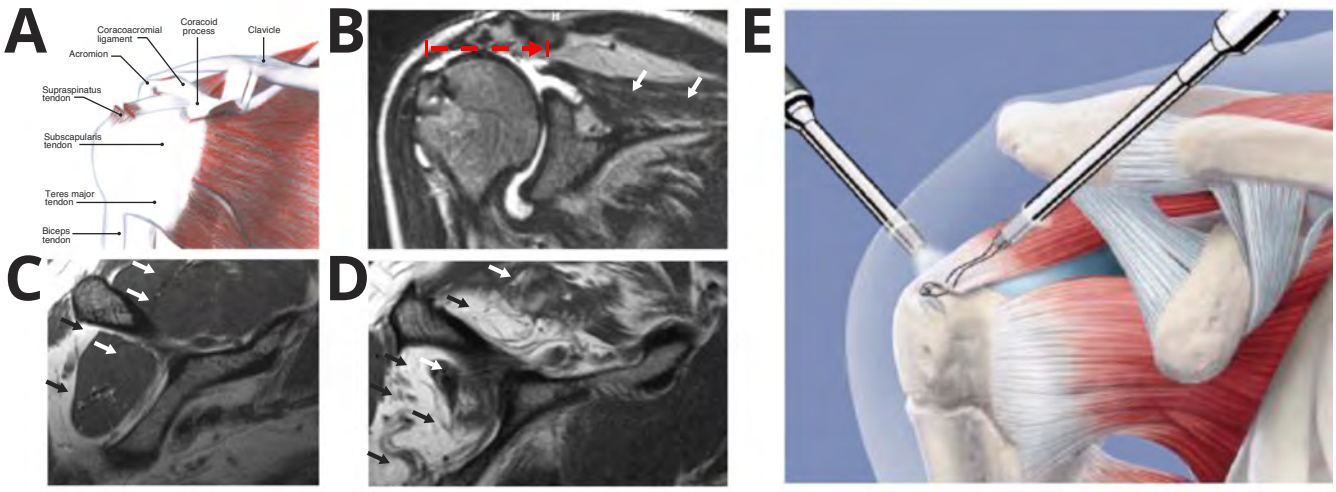


Figure 7: Muscle deterioration with rotator cuff disease. A) Drawing of the human rotator cuff with the indication of a rupture of supraspinatus tendon (redrawn from MendMeShopTM © 2011). Coronary (B) and sagittal (C, D) images of a MRI scan of the shoulder at different depth of a patient at two time 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 arthroscopic procedure used to anchor the torn tendon stump to the bone.

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. 7B-D). Beyond limiting shoulder kinematics this leads to degeneration of the glenohumeral joint; leaving no other option than to surgically replace the joint with an expensive endoprosthesis. Surgical interventions aimed at repairing the affected shoulder muscle involve the reattachment of the ruptured tendon to the bone via an anchor (Fig. 7E). 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 treatment of patients with rotator cuff disease, we have initiated 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 which unfortunately is incomplete in a proportion of subjects. The goal being to reintegrate the gathered knowledge into a personalised decision taking aimed at optimising surgical repair and rehabilitation of the torn rotator cuff.

Outlook

In a next phase the laboratory for muscle plasticity aims at translating the insight gleaned on the genetic markers of clinical muscle plasticity into novel applications which allow personalised surgery and rehabilitation. Towards this end we call for interactions with academic and industrial partners, and health care providers, being interested in developing our research approach and findings into applicable interventions which can maximise the rehabilitative effect. This process comes with the challenge to engage in a dialogue with the society to resolve arising medico-legal matters.

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