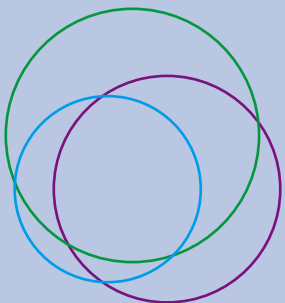


# A FOCUS ON MUSCULOSKELETAL FUNCTION RESEARCH



## A focus on musculoskeletal function research

An interview with Professor Dr Martin Flück at the Laboratory for Muscle Plasticity at Balgrist University Hospital. Here he explains his fascinating research around musculoskeletal function, including the post-operation recovery of patients that have undergone surgery due to the rupture of a rotator cuff tendon.

To set the scene, Professor Dr Martin Flück at the Laboratory for Muscle Plasticity at Balgrist University Hospital introduces us to the excellent research that takes place at the Department of Orthopaedics. He tells us that the main part of their work concerns musculoskeletal function, namely the muscles and as such, they are currently focussing on the post-operation recovery of patients that have undergone shoulder surgery due to the rupture of a rotator cuff tendon. They are also trying to identify biomarkers that may predict the existing and unsuccessful healing or a better response.

Martin then explains that this aforementioned approach is a unique one. In that context, what has been investigated involves the interplay of constitutional factors such as genes and conditional factors such as physical exercise for muscle and body fitness. This, Martin adds, may improve recovery through better nurturing and he highlights that another major aspect of the work at the Department of Orthopaedics is the interaction with the shoulder surgery team, to identify how to tackle clinically relevant problems. While the details of these cannot be revealed now, Martin can tell us that these concern the delay in the recovery from musculoskeletal injury where for instance the knee is concerned. Certainly, he argues that the muscle must play a major role when it comes to stabilising the joint via direct and indirect pathways. The key question is to figure out to what extent specific

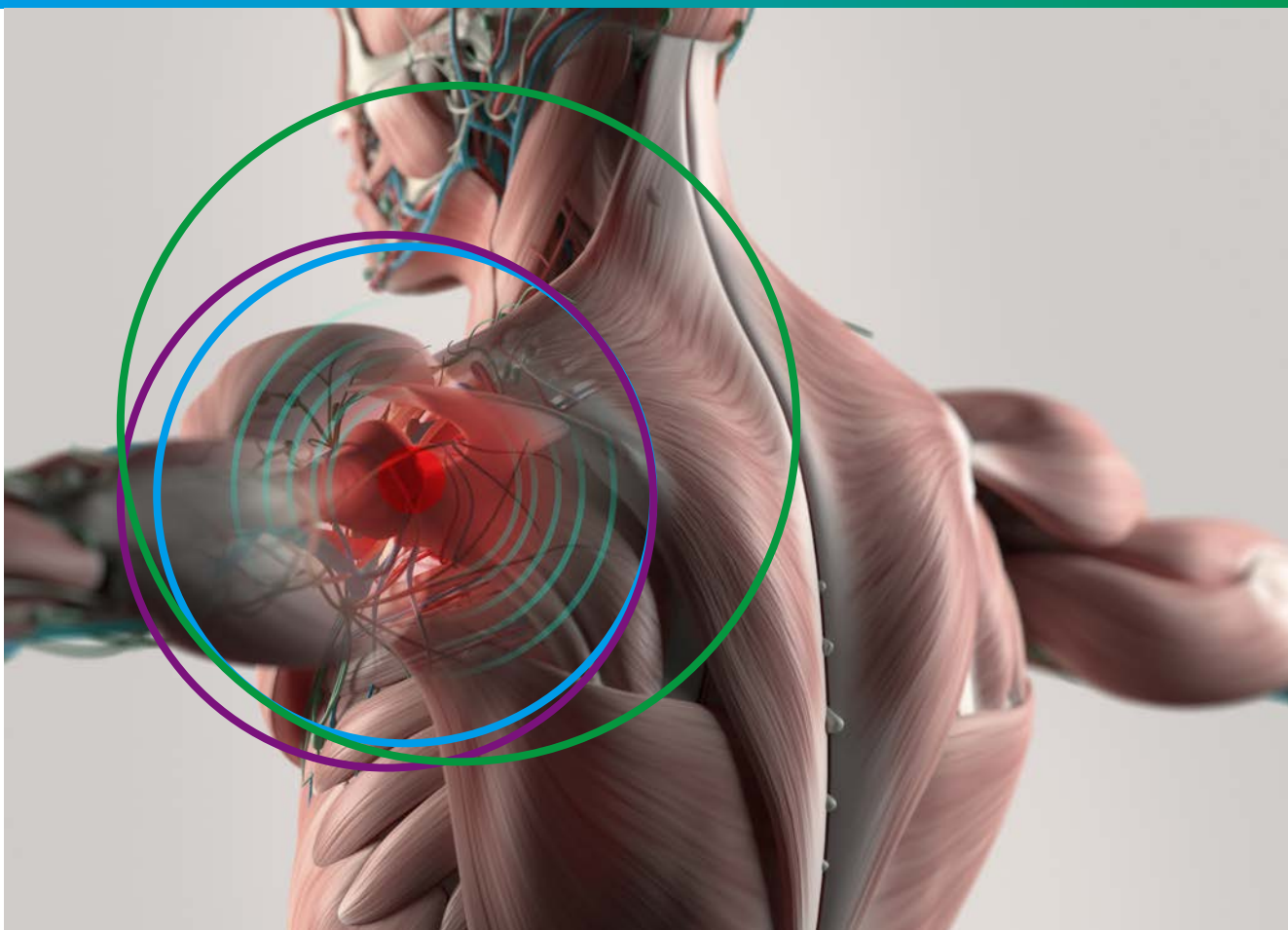
muscles, and the associated activity- dependent remodeling soft and hard tissues of the musculoskeleton, contribute to this.

### **Maintaining the highest standards of quality and performance**

The conversation then moves to detail Martin's reflections on how as a privately administrated university hospital, Balgrist University Hospital is committed to maintaining the highest standards of quality and performance. We know that Balgrist University Hospital represents the Department of Orthopaedics of The University of Zurich (UZH) and has a very good share of doctors and students, Martin notes. He then expands this point, focussing on the crucial role of research at the Balgrist Campus.

“Balgrist University Hospital invests in continuing education and collaboration with universities including the polytechnic school, ETH Zurich who perform research. Research is only performed internally in a competitive manner and is presented and evaluated for its merits and the Campus offers a platform to solve actual questions the patients have through that interaction.

“Then there is a scientific board who is continually evaluating projects and these are also perceived through the congress participation that we all undertake as surgeons and students. However, I still



identify some topics that were underdeveloped but consequently, I have recently seen adaptations by recruiting a new professor. While the preventative aspects were not fully exploited but it now looks like we have initiatives to get that rolling in a much better way than previously.”

### **A new generation of therapies for weak muscles**

Martin then tells us about the research taking place at the Balgrist Campus into personalised interventions which are helping pave the way for a new generation of therapies for weak muscles. He underlines that the research here is divided into three areas.

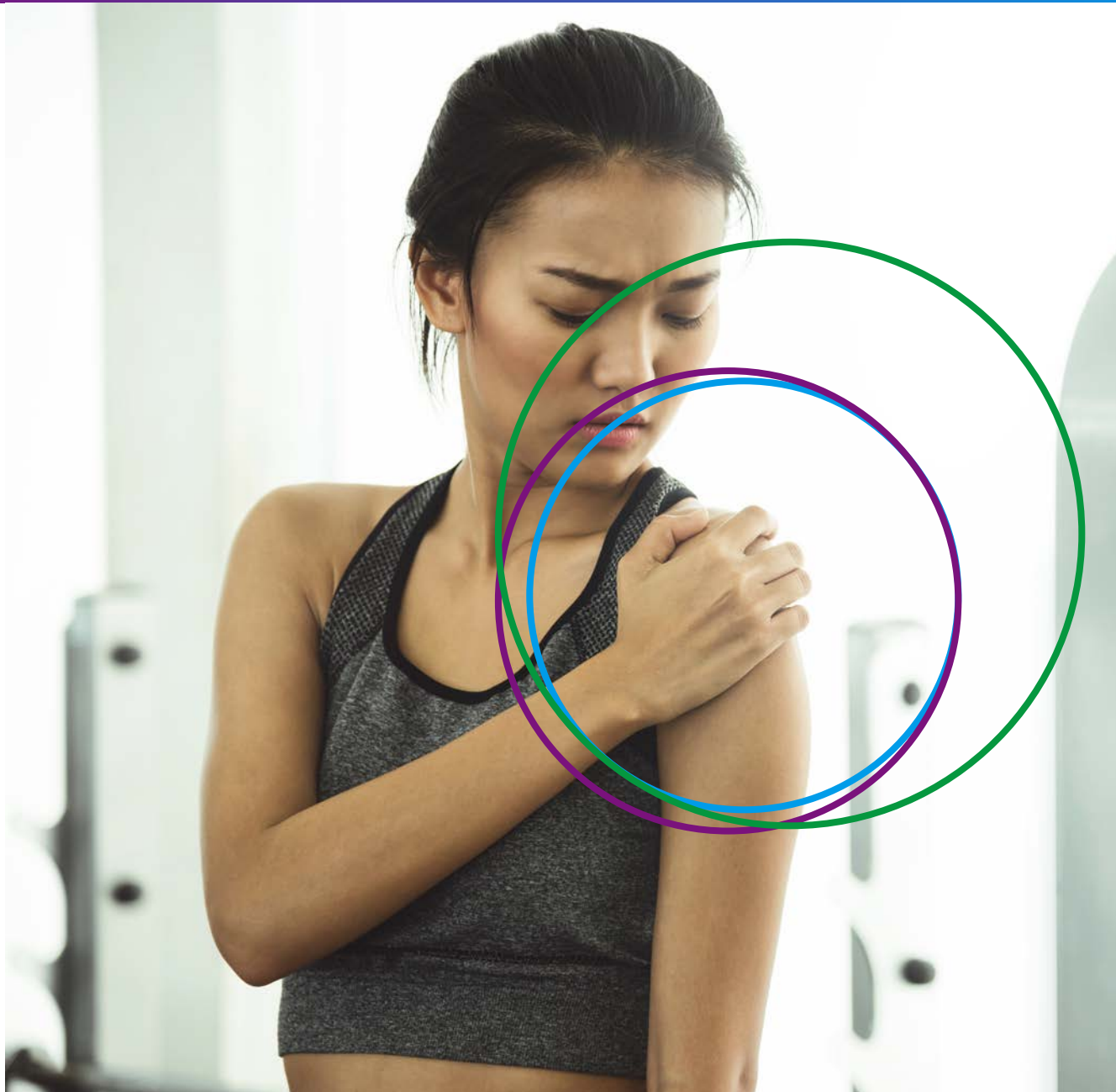
“The first study **MARK-GEROT** focuses on the healing of the tendon reconstruction – there we try to identify markers that improving recovery from injury-related muscle loss after reconstructive surgery by predicting the healing response and personalizing the rehabilitative measures to optimize the reconditioning of the muscle-tendon composite. Biomarkers of muscle composition are the subject of unpublished results from the MARK-GEROT investigation for

which congress abstracts are available. There are two other pieces of research output, one concerns an accepted paper where we set out ways to help cardiovascular patients to improve during rehabilitation.

“This is quite interesting because much research has been done recently on this, showing that not all patients benefit to an equal degree to standard exercise paradigms by improving muscle function through an increase in strength and/or fatigue resistance. Muscle is a very big ingredient of it because it allows them to be active and, therefore, to train, and then improve the quality of life and gain independence. We found in a recently published **study** that there are genetic markers that reflect muscle condition, which can be helped by training which is also modified by specific medications, so have a pattern of **how we can then treat patients in the future** (see Mathes et al - 2015).

“When we first wrote that report, the first patients being treated with a personalized exercise paradigm on a soft-robotic device showed quite a dramatic rehabilitation through personalised types of training





(Fitze, Franchi, Popp, Ruoss, Catuogno, Camenisch, Lehmann, Schmied, Niederseer, Frey, Martin Flück, Concentric and Eccentric Pedaling-Type Interval Exercise on a Soft Robot for Stable Coronary Artery Disease Patients: Towards a Personalized Protocol, JMIR RESEARCH PROTOCOLS, 2019 Mar 27;8(3):e10970. doi: 10.2196/10970. This is an interdependent research approach and now, we don't know how to apply it because it involves cardiovascular and rehabilitation individuals, as well as the work of basic scientists who are conducting the measurements to help us identify easily accessible markers that allow to rate progress during rehabilitation. We will have to see how that develops in terms of sustainable economic pipelines because they change paradigms.”

This is a major challenge because it may involve relocating patients to other hospitals, where trained physiotherapists and equipment is available, Martin stresses. This has been an issue when you consider the patient numbers that are necessary to render the approach financially viable. In some instances, such an approach has worked in rehabilitation but not in the field of personalised medicine.

Martin then tells us that the third area of research entitled BACK-GENE to detail is where Balgrist University Hospital has patients from the chiropractors who suffer from chronic non-specific low back pain, where a specific hypothesis is followed. The indication here is that such patients suffer from relative deficiency in muscle perfusion

where basically, **the muscle dries out of nutrients** during longer activities, demanding the stabilization of the upper trunk (Valdivieso et al. 2018). Martin adds that Balgrist University Hospital is close to completing a study on this, which includes functional tests for back muscle mobility, as well as mental and physical aspects and how these relate to genetics. We also find out that in an already published paper that alludes to this hypothesis, that a good condition of the back muscles is already part of the prevention. But Martin notes that specific groups could be helped if they specifically train the strength and perfusion of the back muscles.

### **The conditioning of skeletal muscle structure**

The interview then goes on to reveal something about the work of the laboratory for muscle plasticity which investigates the mechanisms that underlie the conditioning of skeletal muscle structure and function during recovery from surgical interventions and rehabilitation. Martin responds by saying that a number of studies have been conducted during the past 20 years concerning healthy subjects and from these, they know the factors and the conditions necessary to maintain muscle. Martin explains more about this to us.

“These include muscle strength and endurance which interplay to help people conduct activities. We have been using that information in very extreme models to prove it as indicated in the work of published astronauts and in this very controlled situation we can show that it is the volume and intensity of exercise that directs strength and endurance (**Rittweger et al. Sarcolab pilot study into skeletal muscle’s adaptation to long-term spaceflight. NPJ Microgravity** 4: 18, 2018. doi: 10.1038/s41526-018-0052-1). On board the international space station, we can monitor every step taken, so this translates into **a study we published in 2018** which follows people over 16 years after knee surgery (Flück et al, Knee Extensors Muscle Plasticity Over a 5-Years Rehabilitation Process After Open Knee Surgery. *Front Physiol* 9: 1343, 2018. doi: 10.3389/fphys.2018.01343). Here, we showed that the response is relatively slow and

variable but related to measures of the prior muscle activity. So the key factor of a successful rehabilitation is that exercise is done sufficiently frequent or intense. Because it took the patients more than a year muscle volume and force to recover to acceptable levels conservative prescriptions may not be enough if started too late after a prolonged period of inactivity. If untreated this eventually leads to an imbalance between the operated, respective to the non- operated leg.

“There was, therefore, a call for a very specific focus on training which is just not sufficient. In a way, that poses new social questions about how much people train? Those that train very hard will improve more but some are not used to doing that. The study is a retrospective and the current ways of rehabilitation are already better than what they were 16 years ago but still, there seems to be a very distinct lack of recovery when we talk about reduced muscle fitness that persists for a year but people should consider themselves as professional athletes for at least a couple of months. Only under those conditions do they recover.”

Martin then tells us about a non-complicated wrist fracture he suffered from in July 2018 when he was run over while riding his bike. Following the advice given by his doctor, Martin nearly recovered functionally just three weeks later. This was due to the load and volume of low-impact exercise on the wrist that Martin carried out which allows the bone and the muscle to maintain a minimum function, so aggressive training was possible. While it was a simple fracture without a dislocation, Martin believes this is a good case study to show how bone fracture works in athletes, but this is not a method of recovery that most people would normally accept. Nevertheless, there is really good expertise around, for example, when it comes to professional football players. Following on from an already published book (*Muscle Injuries in Sports* 1st Edition, Kindle Edition, by Hans-W. Müller-Wohlfahrt, Peter Uebliacker, William E. Garrett Jr, Lutz Hänsel, Thieme, ISBN-10: 9783131624710), Martin then draws our attention to how we find out more about how to tackle the problem surgeons face when



“ This, Martin adds, may improve recovery through a better nurturing and he highlights that another major aspect of the Department of Orthopaedics work is the interaction with the shoulder surgery team to identify how to tackle clinically relevant problems. ”

prescribing rehabilitative measures which stand the risk of provoking a recurrent failure of the operated soft/hard tissue. As such, he calls for individual subjects who are willing to do so to adopt an educated and physically motivated attitude to the rehabilitation process.

#### **The emphasis of the research team**

As this interview draws to a close, Martin speaks about the emphasis of the research team at the Balgrist Hospital Orthopaedics Clinics when it comes to the major musculoskeletal affections that

exist. In terms of raw numbers, it is already known which fractures or musculoskeletal effects are associated with generalized effects on the connected musculoskeleton and that not all of those are tackled at the Balgrist Hospital, Martin says before adding his concluding remarks.

“We tackle those that involve a very active joint that may be involved in movement or propulsion rather than posture control, so we look at the spinal aspects but not too much because the delicate interventions there are directed by the surgeon. So, our work involves the active joint that concerns the



shoulder and the knee and all the attached muscles where we know that rehabilitation programmes are available and can be improved. This indicates that the muscle is a very active ingredient for recovery through the mechanical forces that it generates to allow the tendon and bone to grow correctly.

“While it is not yet accepted, which is in a way paradoxical, I do gene therapies and if you go to an international congress you can see that there is a very active part of research advocating biologicals as treatment. To some extent, and for obvious reasons of safety, gene therapy does not yet meet

acceptance in the surgical field, which is a contrast to what we have seen in other areas before. We find that in models of Achilles tendon injury and repair in the rat, we can, in part, echo the problems of muscle reconditioning.”

Martin concludes that this is a really important area to mention because it is really hard to find the perception for innovative approaches directed to personalise musculoskeletal rehabilitation when people are for economic reasons often resistant to resource-intensive applications but in contrast, this is a most active part of Martin’s own research. ■



# The mechanisms that govern skeletal muscle function

In this second interview, Professor Dr Martin Flück reveals how his research aims to shed light on the mechanisms that govern skeletal muscle function in health and disease, with the goal of translating the findings into more effective clinical applications

To kick things off, Professor Dr Martin Flück explains how the research at the Laboratory for Muscle Plasticity at Balgrist University Hospital aims to shed light on the mechanisms that govern skeletal muscle function in health and disease, with the goal of translating the findings into more effective clinical applications. Martin notes that the approach of a head of a department is to make a patient-directed question that you must elucidate in a laboratory setting and he adds that the mechanisms in this respect need to be described in a coherent manner. This is because the words used to describe active processes when it comes to the muscle can be wrongly used and do not match what we would use to describe the biology of the patient. Martin then continues these themes in his own words, including the importance of accelerating translation for the benefit of the patient.

“We have been investing much in rediscovering older ideas – ones that surgeons originally rejected – based upon an incomplete description of the time course of muscle degeneration following a musculoskeletal injury. Previously, they looked at what happened in rotator cuff disease quite late in the degenerative process, which is quite common when a tendon ruptures, but much of the negative remodelling has already occurred at this point. As such, things have to be checked early on which brings us back to a previous hypothesis that was rejected, Martin tells us. He goes on to expand this point in his own words.

“Basically, our approach is to translate the clinical problem in an experimental scenario that allows to test therapies for emerging bottlenecks in the recovery of musculoskeletal function of the patient. In this respect we now revisit early ideas for solutions of the negative remodeling of the injured muscle-tendon tissue composite which were set out 15 years ago, but rejected based on preliminary studies with negative outcome. We do this because we identify that the first window of opportunity for treatment after injury and reconstructive surgery, is short and not addressed experimentally, and consequently a number of active mechanisms were overlooked.

This can be explained for example by the destruction of the cellular powerhouse, mitochondria, with immobilization that was not considered important; but we now know now that this exerts a dominant negative influence on the maintenance of muscle mass and fatigue resistance. Based on these findings one can reasonably argue that the treatment of disuse-related aspects of musculoskeletal disease, such as after tendon rupture, should start early, before the deterioration of clinical endpoints such as a loss in strength and fatigue resistance of muscle can be diagnosed and established as a chronic disability.

We also have a window of opportunity here to translate what we see in other muscle affections, such as during recovery from anterior cruciate



ligament injury and repair and cardiovascular disease (CVD) that also involves the **deconditioning of peripheral skeletal muscle** (Flück et al, 2018). The critical factor here is how long the muscle is in a semi-stable state after an injury before it enters into a devastating spiral of muscle wasting. So, we aim to provide evidence in a coherent manner for how many days and weeks you can keep using the muscle before surgery needs to take place. We now know, for instance, when muscle loss occurs and when it transfers into fat.”

### **The power of medication and the importance of timing**

While it is not one of his main priorities, Martin then shares his thoughts on educating the patients in this respect, as a dentist would when advising that teeth should be brushed three times daily but if one does not follow such advice then things will go bad. When it comes to translation for the benefit of the patient, Martin believes that while very simple forms of medication are available, such as steroids, there are new drugs on the market that have passed governmental tests, and as such, their use is safe for humans to ingest.

Martin’s opinion is that the power of existing medication can be improved by timing when it is taken so that muscle deterioration can be delayed. For example, if medication is administered under neuromuscular electric stimulation during the first two weeks after injury when surgery typically does not take place because the patient is in a lot of pain and experiencing tissue swelling. This approach is the way forward, according to Martin, who adds that he works hard with the surgeons because they are not used to working in such a manner, so a rethinking of priorities is therefore essential when you have the first meeting with a patient.

### **The benefits of excellent research facilities**

The conversation then turns to explore Martin’s thoughts on the superb new research facilities at the Balgrist Campus, and the benefit they have had on the valuable work and research at the campus. We

find out how different parts of the Balgrist Campus are grouped together to enable easier access to research facilities and the pipelines are, therefore, tighter. In addition, there are other routines which allow for the acceleration of research because new investments have been made for the functional exploitation of muscle structure during movement.

Martin says that while his research output has not yet concretely benefited from the new facilities, interactions with other scientists who carry out anatomical measurements of the muscle has been a plus for him. “It is much easier for the students or researchers to train using these methods to measure muscle volume, get a 3D image and analyse the muscle. The facilities are good because they are open during weekdays and the weekend so people can come in and get things turned around.”

### **State-of-the-art methods and technologies**

This compelling interview continues, with Martin keen to detail the very important role that state-of-the-art methods and technologies play in the field of muscle research when it comes to the work taking place at the Balgrist Campus and in their fruitful cooperation with the Functional Genomics Center of the University of Zurich / ETH. Knowledge gathering can be accelerated, Martin reveals, in terms of exploiting paradigms in more breadth and in a higher resolution. State-of-the-art methods and technologies enable the measurement of multiple species and the use of powerful tools that enable researchers to work at a very fast pace. Still much work needs to be done in the field, Martin underlines.

“We still need good knowledge on the cell, biological, chemical and anatomical aspects of disease because it can be misleading to rely solely on results from one novel method. An image tool can always be used to draw conclusions about the raw numbers but nevertheless, combining that in a very elegant approach that relates to a systems biology that people advocate was raised at a **conference around 11 years ago** (Flück et al.



“ So, we aim to provide evidence for the Duration of the window of opportunity during which reconstructive surgery and Rehabilitation has to start before irreversible Damage occurs in musculoskeletal tissues after injury. ”



2008). “Now, we get biomarkers that allow us to screen patients out of the acceleration of numbers that we can relate to the relevant sizes of muscle, and we can more easily determine something in blocks, for example, or by a simple genetic test.”

### **Personalised sports medicine and exercise rehabilitation**

When it comes to disruptive ideas for personalised sports medicine and exercise rehabilitation, Martin says that one of his thoughts around this is the problem of getting economically viable pipelines established for medics. If it be for reasons of wisdom, or economic causes, the medical profession has typically been shy when it was to implement paradigm shifting approaches this demanded the reconsideration of established clinical routines. Now, it is about how a patient is aware of a problem and goes to a doctor to seek a solution. Sometimes, a doctor has a fair and good knowledge, but a researcher can be very well-informed about an aspect of health that perhaps a doctor doesn't know about. It might be that a doctor needs to do a literature search but although ultimately powerful and justified, this slows down decision taking. The latter in fact is a very active area of Research and Development in the Polytechnical School of Zurich (ETH) to identify faster and more comprehensive ways to approach a disease, Martin notes.

“Here, progressive methods could be used for other treatments even if it is not generally accepted nowadays. For example, if you had a bone fracture as I did, would you only do the training they tell you to do or would you do more, especially if you are experienced in physical training and know the limits of (your) human performance and capacity for the improvement through the stimulation of musculoskeletal plasticity? Would you train hard to ensure a better recovery? Or do you want to get access to treatment that some people are using, such as biohacking that concerns legally allowed biological principles? For example, there are ways in which people can enrich their stem cells and reinject into them during training.





Balgrist University Hospital: view of the Clinic

“Gene therapy won’t solve everything and when looking at this field of atrophy, it needs to be administered in doses because that is how we grow. We renew, or grow, our active muscles one by one, 1% every day. Using this method repeatedly is way too much for the health system, indeed, we don’t visit a doctor daily for two years, so we may anticipate to inject the agent in small doses. People who do biohacking reinject their stem cells when training daily for one month and then either stop or continue. This is not good for control and it is questionable if you carry this out in large numbers. But this is how these processes work. Improvements in strength and endurance rely on adaptations in muscle and tendons to (daily) repeated stimuli that if reach a specific threshold of mechanical or metabolic overload. The potency of it is enhanced by a high load of medication but the problem is that it uses far too many resources from the perspective of the health practitioner. Certainly, it is getting too expensive, so how do we deal with

that? There will be big solutions to translate and in some cases, to abandon stem cell gene therapy for patients with many risks; but if it works, it will be quite disruptive. Martin then details his thoughts on rehabilitation after muscle injury occurs.

“Another more practical consideration is the contribution of the chiropractor or physiotherapist in rehabilitation. In the U.S., as the American Academy of Orthopaedic Surgeons sees it, the post-operative rehabilitation is conditioned by new ideas on the load, the intensity and volume of training. Physiotherapy often takes over that part but may overrule the researcher and possibly the orthopaedic surgeons because they have greater experience, and the pharmacist has even more experience of the drug.

“The well-trained physiotherapist is knowledgeable about rehabilitative interventions the patient should do post-operatively during musculoskeletal rehabilitation to achieve maximal benefit. The physiotherapist will



do what is allowed in the window of intervention for the patient but maybe it could be done more aggressively and earlier? We have seen how in some hospitals in Germany, that certain post-operative interventions are starting much earlier to allow lymphatic drainage and reperfusion, for instance, after anterior cruciate ligament surgery. We know that this is very beneficial for healing from the experience of other surgeries as it is applied worldwide. So – this is something that we should actively pursue – that the physiotherapist or the people with knowledge of that aspect have more to say. This is the current practice of the American Academy of Orthopaedic Surgeons and hasn't yet been fully carried over to larger parts of Switzerland.

“What is also a problem is that because there is an economic pipeline, defining within which duration post-operative interventions can be performed in a hospital setting. New knowledge on therapeutic interventions which would extend beyond this window, or which are complicated to carry out in ambulant sessions of rehabilitation, may fall out of consideration for an implementation. This is particular concern for the reconditioning of an atrophied muscle, which must be tackled as early as possible by enhancing (or mimicking) the mechanical and metabolic load of an active muscle. There is a classic study from a famous English researcher which clearly shows that immediately after bone fracture, the contractile activity of concerned muscle groups must be increased for instance with sessions of neuromuscular electric stimulation (NMES) to maintain its protein balance.”

Martin adds that studies have been done around these aforementioned areas but they had not been carried out for a long enough duration to really gain benefit from. NMES may be used for some very high profile sports individuals, such as the number one acrobatic skier who has treatment at the Balgrist University Hospital and uses EMS for an hour or two daily which works. While there are not enough resources to understand how it works, the patient needs to be willing to do NMES for many months or years as shown successfully in rare cases of tetraplegic patients, Martin stresses, which is disruptive.

“I know of athletes using EMS at night and I know it works but there is a big disconnect between the basic knowledge and how you apply it. Only committed people use EMS, often externally through Balgrist University Hospital. The patient will stay in the hospital for a month and this approach works but this method it is only disruptive if it is translated to all patients and the benefit for society would be great.”

### **The priorities for musculoskeletal disorders**

Martin then sheds light on the priorities ahead for the diagnostics, treatment and rehabilitation of all musculoskeletal disorders. He says that his priorities for the future are very practical ones, in terms of the areas identified in this interview which need to be pursued. A willingness to change the system is needed, Martin notes and adds that if a treatment is available, it is important to ask at the Balgrist University Hospital with whom one can collaborate to apply such a genetic test. This involves much rethinking of the legal procedures when it comes to data protection and risk around genetic tests, Martin tells us.

In closing, Martin underlines that there is an issue today around health insurance because you cannot fully evaluate people in terms of numbers. Martin asks us to imagine that if we own a car and there is a problem with it then we go to the garage to get it repaired so that it works properly. This helps us to understand Martin's areas of research, and that Balgrist University Hospital sends out people who can walk again even though they may have a functional deficit following treatment but thresholds are not set to provide the patient with a map of the individual aspects of its musculoskeleton which require further improvement through therapy and training to empower a full regain of functional work capacity. Martin develops this point and adds his concluding remarks to this in-depth interview.

“Translating effective measures for the patient is a priority, so that they recover and that the form of treatment given is acceptable, such as gene therapy. Of course, gene therapy is far too



“ The well-trained physiotherapist is knowledgeable about rehabilitative interventions the patient should do post-operatively during musculoskeletal rehabilitation to achieve maximal benefit. ”

expensive but the question is how can you do that? Do you have a risk priority in some areas? Or do you have the basic genetic tests that predict that such an approach will not help some patients, the health system or even the hospital?

“The priority must be to substitute for a subtle, often unnoticed, genetic deficit with an effective treatment which is what we do in the cardiovascular field, where with a non-responder to rehabilitation we try to have another treatment that the patient can respond to.

“Finally, I want to add that I am not connected with my European colleagues who have two approaches. One is a centralised setting tied to the way the state is organised, such as in the UK, the Netherlands and Scandinavian countries that rely on an institutional monarchy who have specifically robust, but sometimes rigid, ways of tackling some diseases. But interestingly, there is a disconnect in terms of what we aim to do in Switzerland where we have a federal system to gather information and administer a solution in a totally different way.



“In the UK, for example, there are the state organs to indicate how to pursue new treatments best based on a centralised database. In Switzerland, we gather information from our individual datasets and I see from my experience of working in different cultures that despite the possibilities for innovation provided by the latter approach, it sometimes lacks effective power for translation on a large scale. We need a solution to direct preventive and curative treatments in a more individual and economically viable manner to the entire spectra of the

population. But to do so, we should combine a well-informed population-based approach with the innovative powers of an individualized approach, possibly by changing the organization of the health care system.” ■



# The Balgrist

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