New technology: Bio-orthopaedics

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Cartilage repair, which is my main focus of study, has impressively expanded in recent years thanks to the insights provided by stem-cell research. When I began my medical career in 1983 very little of what is shared knowledge today was studied and discussed in the scientific community. Remembering the curiosity that led me to pursue this line of research, I also see that innovation in cartilage repair has shaped the entire development of my professional life. Partly as a coincidence, partly as a choice, as it so often happens, the tight connection between my life and this aspect of medical research has turned me into an enthusiastic witness of the major advancements made possible by cellular biology and bioengineering techniques in orthopaedics.

Cartilage is a thin layer of specialized connective tissue lining the joint surfaces, whose properties enable almost frictionless joint movement and protection to the underlying bone from excessive load and trauma during its movement. As this tissue is avascular, once damaged it fails to heal on its own[1]. Current anti-inflammatory based therapies can inhibit pain caused by the damage and delay the progress of cartilage and bone loss, but it does not regenerate these tissues. This implies that if untreated, cartilage damage only worsens over time, inevitably leading patients towards a downward path of reduced mobility, pain and eventually surgery[2-3].

Unfortunately, traditional surgical procedures are quite unsatisfactory in long-term evaluation and often lead to joint replacement. A joint replacement may represent the only option left in the case of severe cartilage damage. It aims to improve the patient’s conditions and quality of life and often does so for a while, but this remains to be an extremely invasive surgical procedure and marks an irreversible turning point in patient care. It is far from safe of uncertain outcomes and not exempt from risks of infection. In young and middle aged patients, however, active individual prosthetic surgery is plagued by a short life-span of a few years, as the replaced joint quickly wears out damaging the underlying bone as well. Pain, depression and lost workdays make the life of these people often sad and difficult.

Cartilage injury leads quickly to arthritis, resulting in a major reduction in the functional capacity of the person and representing a huge social cost. In the last 50 years, studies have been focused towards artificial joint prostheses made of different materials that are more sophisticated and more expensive, and all this represent a huge business for companies producing this technology but not for our social health care system. Over the next 50 years, the challenge will be to prevent wear and tear of tissues and to regenerate damaged cartilage, muscle, ligament or nervous tissue to restore function and delay the onset of osteoarthritis.

The impact of bone and cartilage pathologies is not only experienced by the individual patient but also at the social level, in terms of therapeutic treatments and loss of income. Patients with impaired mobility tend to become a lifelong burden to the health care system. Joint replacement, it should be added, is not an inexpensive medical procedure: artificial joints are made of costly materials, surgery is heavy, and recovery is long and strenuous. This is why repairing cartilage, possibly as soon as the first lesions appear, may change people’s life for the better in the long run and, at the same time, represent a cost-effective alternative to prosthetic surgery, an issue which is particularly pressing nowadays in Western democracies, faced as they are with increased health needs and dwindling budgets[4]. In Italy alone, for example, the number of people suffering from musculoskeletal injuries has been estimated as 10% of the entire population.

For all these reasons, the trend is now going towards preventive interventions and therapeutic solutions that can lead to an enhancement of tissue regeneration and the reduction of degenerative mechanisms. This is happening thanks to cutting edge research that has succeeded in jump starting the data from the lab and bringing straight into the operating room and the physician’s office in a short span of time. I am convinced that what is currently in progress will produce youngest offspring of orthopaedics, and bio-orthopaedics represents the beginning of an exciting era, which promises to be very rewarding.

Bio-orthopaedics, whose common goal can be broadly summarised as the attempt to regenerate damaged joint tissue by activating healing processes at the molecular level with pulsed electromagnetic field, and offer innovative surgical and non-surgical strategies[5-6].

We are now able to do what was deemed impossible 15 years ago: people now do not have to suffer from these cartilage problems. In the past we would just have to learn to accept to live with the morbidity brought about by these problems and eventually accept the fate of a joint replacement. Now these cartilage damages can be prevented, alleviated and repaired if necessary with the help of ortho-biologics. A very promising alternative to surgery, which is becoming mainstream in outpatient treatment, is relatively simple in preparation and use is platelet-rich plasma (PRP)[7-9]. This entails injecting centrifuged
portions of a patient’s blood directly into the injured area, which catalyzes the body’s instincts to repair muscle, bone and other tissue. PRP preparations have been used both in surgical and outpatient procedures in the treatment of several musculoskeletal problems with effective results[10-14]. Described also by Espregueira-Mendes, the influence of platelet rich plasma on chondrogenic differentiation and proliferation of chondrocytes (personal communication). Mishra[15] suggested in their study that PRP treatment given to elbow epicondylar tendinosis patients prior to surgery can prevent the necessity to undergo the surgical procedure. Other studies reported clinical efficacy of PRP applications in soft tissue surgical and conservative treatments; furthermore, PRP combined with proper nutrition (control of BMI), exercise and life-style, can act as a preventive agent in chronic and degenerative musculoskeletal disease.

Recent studies have documented the effectiveness of factors in chondrogenesis and preventing degeneration of the joints. Nakagawa reported at the 7th World Congress of International Cartilage Repair Society in Warsaw, Poland. 2007 the in vitro efficacy of autologous PRP in stimulating the proliferation and collagen synthesis of human chondrocytes, suggesting the use of this method in the treatment of cartilage defects.

In animal studies Frisbie[16] reported clinical and histologic improvement in osteoarthritic affected joints of horses after treatment with PRP. Wu et al[17] in an experimental study done on animals showed the effectiveness of intra-articular injections of PRP with chondrocytes growing in vivo that resulted in the formation of new cartilage tissue.

In clinical studies Anitua[18] showed that an intra-articular injection of PRP could induce an increase in production of hyaluronic acid structure and promote angiogenesis and cell proliferation.

Cugat[19] used platelet-rich growth factors (PRGF) to treat chondral defect in athletes and obtained good results, according to their experiences for other connective tissue repair, they showed that PRGF in physiological concentration is effective for the recovery of connective tissue furthermore local treatment is safe and does not alter the systemic concentrations of these proteins. Kon presented at the 8th World Congress of the International Cartilage Repair Society Miami, USA, 2009, a study including a group of 60 patients with symptomatic degenerative disease of the knee joints treated with three autologous PRP intra-articular injections weekly compared with homogenous group of 60 patients treated with hyaluronic acid intra-articular injections; the 12 months follow up showed statistically significant (P < 0.005) superiority of PRP group in the 3 KOOS subscales.

In our institution we used a L-PRP according to Dohan Ehrenfest et al[19] classification, in treating early arthritis. We presented at the XVIII International Congress on Sports Rehabilitation and Traumatology Isokinetic, Bologna, Italy, 2009 a group of 50 patients treated with PRP injections we followed up 23 patients with grade 3 and 4 chondral defects of the knee and a mean age of 44.3 years, 13 cases with previous knee surgeries. We collected pain visual analogue scale and Knee Osteoarthritis Outcome Score at pre-treatment and 6-12 months post treatment; preliminary results are encouraging showing a trend towards improvement in both scores.

Finally several authors[20-25] reported the use of growth factors and PRP preparations to stimulate mesenchymal stem cells (MSCs) proliferation for chondrogenesis. Drengek et al[23] reported in their in vitro study that PRP has proliferative effects on autologous MSCs and chondrocytes, suggesting advantages for one-step surgical procedure in cartilage transplantation using a combination of cells and growth factors. Mishra[24] concluded in their study that PRP enhances MSCs proliferation and suggested that PRP causes chondrogenic differentiation of MSCs in vitro. These results were also evident in an in vivo study done by Milano presented at the 54th Annual Meeting of the Orthopaedic Research Society in San Francisco, USA, 2008 the animal study showed a more effective cartilage repair after microfracture associated to hydrogel scaffold with PRP. Nishimoto[25] suggested that simultaneous concentration of PRP and bone marrow cells, acting as a sources of growth factors and “working cells”, could play important roles in future regenerative medicine.

Flooded with often contradictory information about stem-cell research, public opinion finds it difficult to distinguish between what is myth and what is fact. Scientists and doctors often fail to spell out their knowledge in a language accessible to anyone, for reasons that go from poor communicative skills to the power imbalance that still characterises the doctor-patient relation and the defence of one’s professional monopoly. The media too often leads to believe unrealistic promises and scepticism brought by misinformation. Instead, stem-cell research applied to orthopaedics is no longer a myth, but is grounded in actual facts and successes.

Many ongoing studies are providing us with promising information[26-46].

Giannini described the application in the ankle of mesenchymal stem cells with “one-step” technique[47].

We presented a preliminary report on mesenchymal stem cells implantation for full thickness cartilage lesions treatment at the 8th World Congress of the International Cartilage Repair Society in Miami, USA, 2009, showing encouraging data on MSCs implantation to treat grade III and IV chondral lesions. Also at the 8th World Congress of the International Cartilage Repair Society World Miami, USA 2009 Milkovic described chondrogenic potential of adipose-derived stem cells for cartilage repair.

Mandelbaum at the 26th Annual Meeting of Arthroscopy Association of North America, San Diego, California, 2007 described expected upcoming future directions in the next generation cell based therapy.

To be fully understood and applied, however, this kind of innovation requires that all different stakeholders involved, researchers, doctors, health managers, patients and more generally citizens, engage in a more participatory and meaningful debate about its benefits and ultimate goals for the entire community. It is only this kind of collective engagement that will hopefully move bio-orthopaedics from the edge to the centre of patient care.

Combined with proper nutrition, exercise and life-style, this procedure can act as a preventive agent in chronic and degenerative musculo-skeletal disease.

In spite of the successes of bio-orthopaedics, which I have
bBriefly tried to summarise above, there are still scientific and social obstacles to overcome. First, owing to the rapid pace of its development, cartilage repair is still going through an experimental phase, which needs to stand the test of time and produce long-term and reliable results, in order to be fully acknowledged by the scientific community. As for the specific Italian situation, though consensus is growing, not all orthopaedic doctors are unanimous in their support of bio-engineering techniques, as these require a very different approach to treating musculoskeletal pathologies.

REFERENCES


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新技术：生物矫形学

软骨修复是我主要的研究领域，随着干细胞研究的深入，软骨修复研究在近几十年得到了广泛的发展。我于 1983 年开始医学生涯时还很少有资源共享的说法，而现在我们能够在科学会中对相关研究进行研究和讨论。我还记得是好奇心使我开始了这项研究，我发现这项软骨修复的创新技术贯穿于我整个职业生涯，一部分由于巧和，一部分由于选择，使我的生活和生物研究紧密结合，让软骨再生研究成为我以后一直坚持的研究领域。

软骨是关节面特殊结缔组织内层的一个薄层，其性质是能够使人完成无摩擦的关节运动，并且对运动时可能存在的负荷或外伤进行保护。软骨是没有血管的，一旦损伤无法完全自我修复。目前抗炎的治疗可以抑制由损伤引起的疼痛，延迟软骨和骨的丢失进程，但不能使组织再生。这意味着如不进行处理，软骨损伤会随着时间的变化而加重。传统的外科操作长期评估不满意，经常会导致关节置换。全关节置换是严重软骨损伤患者的唯一选择。关节置换的目的是提高患者的生活质量，但常常是暂时的。

对于外科一个有效的选择，是用富含血小板血浆治疗门诊患者，需要通过离心机使患者的血液注射到损伤部位，促进自身修复。最近的研究显示，该技术可以使韧带和腱纤维再生，使损伤的软骨恢复，这种方法具有微创性，而且价格较低。

目前关于干细胞研究的对立信息非常多，公众的观点认为该研究很难区分什么是虚幻的，什么是现实的。科学家和医生很难用语言将他们所知的信息告诉所有人，原因还是医患关系的自我保护。而媒体多用脱离现实的保证和怀疑进行误报。但干细胞在骨科的应用已经不再是虚构，而是现实的和成功的，很多研究给我们提供了希望的信息。要完全的了解和应用这种创新技术，需要不同的人群参与，如研究员、医生、卫生管理者、患者和更多的普通民众，通过更多的参与和讨论来探讨其对整个社会的利益和极限。只有通过这种集体讨论形式才能促进生物骨科学从边缘走到中心位置。

结合适当的营养、练习和生活方法，这种方法可以在慢性和退行性肌与骨骼损伤中起到预防的作用。

尽管我试着简要的对生物骨科学所取得的成绩做上述概括，还仍然有很多科学和社会的障碍需要克服。该领域发展很快，但软骨修复仍要经过实验阶段，要确定实验时间，生产周期和得到可靠的结果。以得到科学会公认。关于意大利的特殊情况，虽然意见一致的比较多，但并不是所有骨科医师都支持生物工程技术，因为这项技术要求完全不同的入路治疗肌与骨骼损伤。


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