XXX PhD Program in Sciences and Medical Biotechnology

Università del Piemonte Orientale "Amedeo Avogadro"

Novara

ANNUAL REPORT 2014-2015

Dr. Alessio Baricich, MD

Section 1: Scientific activity

Section 2: Didactic and educational activities

SECTION 1: SCIENTIFIC ACTIVITY

1.1 RESEARCH PROJECT

Project title: PKAnkle++: A multifunctional, parallel kinematics device for ankle rehabilitation

Scientific background

The foot and ankle complex involves multiple segments which can influence the interaction between the lower limb and the ground during gait and balance [1]. It is critically involved in gait biomechanics, mainly during the stance phase. The first contact of the foot, body progression and power generation in terminal stance require an optimal ankle mobility, in order to obtain a correct body progression [2]. Unfortunately, several clinical pictures can cause a mobility reduction in ankle joint, reducing the functional status of the patients by affecting their mobility.
Ankle mobility can be affected by several pathologies and it can be involved both in neurological and orthopaedic diseases. First, upper motor neuron syndrome is a leading cause of disability which can be caused by several neurological diseases (e.g. stroke, multiple sclerosis, cerebral palsy). Loss of motor control and pathological fixed postures are common problems in the Upper Motor Neuron Syndrome (UMNS). The equinovarus foot is the commonest posture seen in the lower extremity of these patients. Equinovarus limits dorsiflexion motion during single limb support when the foot is stationary. The lack of available dorsiflexion results in hyperextension thrust of the knee and retrained forward translation of the body centre of gravity. Commonly, equinovarus in addition to loss of motor control alters the cyclical kinematic pattern of the lower limb and trunk during gait, inducing compensations for the noninvolved limb, pain, fatigue and impaired function. The compensatory movements necessary for ambulation produce exaggerated lateral displacements of the centre of gravity which results in increased energy expenditure and negatively impact the patients' activities of daily living. Rehabilitation therapies addressing prevention/treatment of stiffness and equinovarus focus on passive mobilization. The goal is to maintain the passive range of ankle motion. Besides stretching of the plantar flexor muscles, also inversion and eversion mobilization is important to allow proper foot contact and base support. In addition, several orthopaedic conditions can affect ankle mobility: trauma (e.g. sprain, fractures), inflammatory arthtritis, post-surgery disability [3][4]. Moreover, in older people specific ankle impairments have been described as significant determinants of balance and functional ability [5].

In this context, the Institute of Industrial Technologies and Automation at National Research Council (CNR-ITIA, Milano, Italy) developed PKankle (Fig. 1), a patent-pending robotic device, based on a fully-parallel kinematic architecture, designed for the rehabilitation of the ankle-foot complex [6][7][8]. Its kinematics allows the foot to rotate, with good approximation, about its instantaneous centre of rotation, enabling movements in almost all the foot rotational workspace. It features an integrated load cell for measuring subject interaction forces/torques and a synchronized electromyographic acquisition system in order to analyze patient's muscular activity.

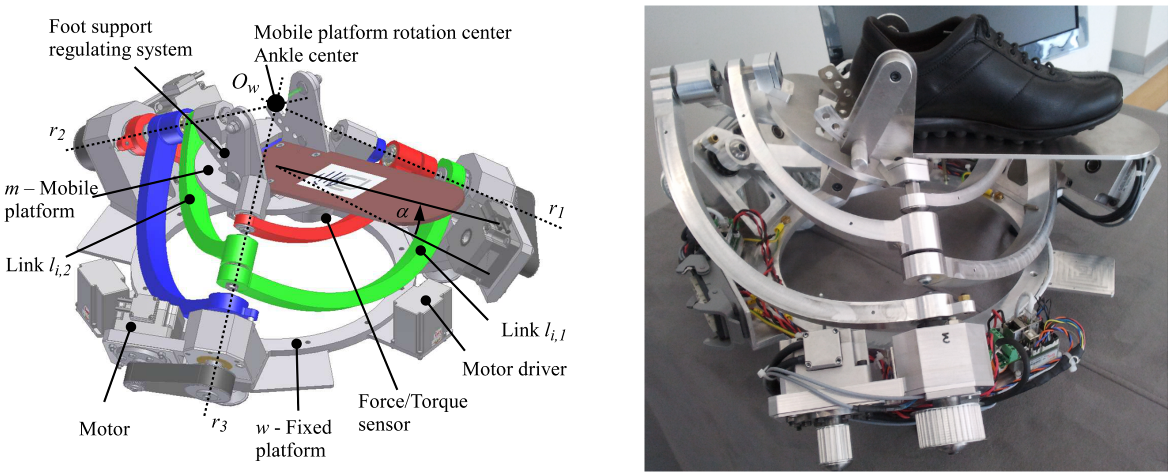

Fig. 1. PKankle prototype

Aim:

The aim of **PKankle++ project** is focused on expanding the functionalities and the application scenarios allowed by the currently existing PKankle device.

It will focus on these aspects :

- Implementation of force-based and EMG-based control modalities, enabling the execution of patient-in-the-loop rehabilitation therapies, even by patient with limited mobility capabilities.
- Sensorization of the foot support with a pressure-sensitive foot insole for real-time monitoring of the plantar pressure distribution [9].
- Integration of a Functional Electrical Stimulation (FES) module to realize a Hybrid Assistive System (HAS).
- Interface to a high-level software application targeted to the end user, characterized by easiness of use and database storage, satisfying requirements of applicability in a real clinical environment.
- Development of currently missing ergonomic elements, required for an actual exploitation of the system by clinicians and patients, optimizing setup time and expanding the scope of use. Particular attention will be placed on the development of an ergonomic foot support and a patient's positioning system to enable the execution of exercises in different patient positions

Clinical usability tests will be performed to assess the implemented functionalities.
PKankle++ will be empowered by new functionalities to interact with the patient in a multi-modal and multi-sensor-based way, paying attention to ergonomic aspects, outstandingly important in a medical device physically interacting with the patient.

Methods

The whole design process will be carried out exploiting a Human-Centred Design (HCD) approach by means of co-design methodologies which empower end users to be more outspoken about their needs and their satisfaction during the development of a product.
Co-design method instils a sense of ownership in the end user and stakeholders. It is a process of co-determination based upon a set of common aims and purposes between the designers and the

patients. Involving all parties at an early stage enables the designer to cost-effectively support for the long-term design and evaluation of the designed product.
A co-design strategy has a number of advantages:

- The direct link between the designer and end user ensured that the design decision making process results in the minimum of iterative cycles of development.
- The less well defined, qualitative areas of opinion and satisfaction for the product functionalities and desirability of use are also addressed.
- Iterative design cycles, in the form of co-design, enable the optimum compromise to be achieved quickly.

The primary purpose of the Human Centred Design research is to test out a model of experience-based design. This involves using patients' direct experiences of the existing product to design and improve it. '*Experience'* is an extremely valuable source of knowledge, through which the designers and the different parties will be able to identify those parts of the design interventions where the patients' feelings and opinion of the use of the product – both positive and negative – are being most strongly formed ('touch points'), therefore where improvement efforts need to be focused.
Examination of these touch points at later stage will enable the team of the consortium and patients to identify design principles which will be then applied to the design and improvements of the product.
Iterative cycles will be made in the product development, where each cycle is an essential opportunity to learn: for designers, to learn what is really possible, and for medical researchers, to learn what is really needed, allowing step-by-step updating and redefinition of target properties and reprioritization of tasks. This will allow for convergence of the two main streams in the project, i.e. of design activity and medical research and development.

The partners involved in PK ankle++ project are:

- CNR, Institute of Industrial Technologies and Automation (Milano, Italy)
- Brunel University, Human-Centred Design Institute (London, UK)
- Università del Piemonte Orientale, Physical and Rehabilitative Medicine - Department of Health Sciences (Novara, Italy)

Preliminary results

PKankle++ addresses a number of scientific and technological issues to achieve its final aim.
In terms of Technology Readiness Level, the project has the ambitious aim of reaching Level 7, *System Prototype Demonstration in Operational Environment*, starting from different functional devices already existing but not so far integrated in a single device.
To the authors' knowledge no commercial system features the set of characteristics foreseen for PKankle++. It aims at going beyond the state of the art being a hybridly assistive system allowing multi-degrees-of-freedom patient-in-the-loop ankle rehabilitation, featuring a high level of customization of the therapy and accurate monitoring of performed treatments. A great compatibility to patients' needs will be obtained merging peculiarities of the parallel kinematic structure of the core mechanism together with design improvements expected by adopting the Human Centred Design approach.

Some of the PKankle++ peculiar characteristics and advances beyond the state are:

1. Ankle-foot kinematic compatibility

The use of robots in the ankle-foot neuro-rehabilitation for impaired subjects has to meet challenging requirements in terms of compatibility between the movements allowed by the machine and the physiological movements of the foot. The most prominent factor for such compatibility is the fine alignment between human and robotic articulations, mostly intended as rotational axes, in order not to induce unwanted internal forces.

Notwithstanding several available robotic devices, improvements in state-of-the-art solutions are pursued in clinical practice because of some limitations in existing ankle-foot rehabilitation machines. In a simplified model (Fig. 2), the ankle-foot complex can be modelled as a three-segment system, connected by two ideal hinge joints: the talocrural and the subtalar joints [9]. Along the proximal-distal direction, the first joint represents the talo-crural articulation and determines the flexion-extension movement of the foot (rotation by f_u about u_u). This hinge joint has a fixed rotation axis defined as the axis that ideally connects the malleoli. The second joint represents the sub-talar articulation: in the standard anatomical position, it can be described by an oblique axis running approximately from antero-medio-superior to postero-latero-inferior regions of the foot (rotation by f_l about u_l). Actually a) the rotation axis direction of the former is not fixed [11][12] and b) the latter approximates the combined effect of the subtalar and mid-tarsal joints which should be modelled with an instantaneous helical axis instead of by a merely rotational joint [12][13]. Given the complex kinematics of the ankle-foot complex, a six-degrees-of-freedom device would be the best solution to comply as faithfully as possible with its mobility (Rutgers Ankle [14]).

With the aim of realizing a relatively simple device but flexible enough to well comply with the actual range of motion and mobility of the ankle-foot complex, CNR-ITIA developed PKankle exploiting the three-degree of freedom fully-parallel spherical kinematic architecture developed by Gosselin [15], configuring the actual centre of rotation of the foot support (O_w in Fig.1) nearby the minimum distance point between u_u and u_l (O_f in Fig. 2). This feature overcomes limitations existing in other non-wearable devices [16][17][18][19], whose instantaneous centre of rotation is under the foot, distant from the actual ankle articulation, leading to possible unnatural physiological proprioception and causing the knee not to be steady during rehabilitation movements [7].

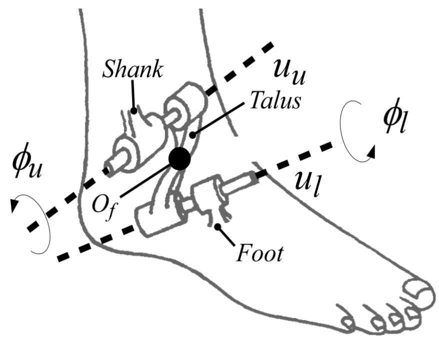

Fig. 2. Mechanical model of the ankle-foot complex, as reported in [9]

2. Multimodal interactions for ankle rehabilitation

Continuous passive joint mobilisation consists in a smooth, continuous joint mobilisation and is a technique commonly used to address the problems related to pain, stiffness and range of motion of the ankle in post-injury or post-surgical rehabilitation treatment, in order to allow an earlier return to mobility or an increase in gait autonomy. PKankle can provide a continuous passive mobilisation of ankle joint, and it can be also equipped with EMG signal analysis, in order to analyse the muscle activation pattern during exercise activity. This is a relevant point, due to the fact that muscle activity is strictly related to active stability of ankle: monitoring this activity permits to better focus on specific rehabilitation training. In addition, in neurological patients this device allows a strict analysis of stretch-related activity of spastic muscle, a key point in UMNS patients' rehabilitation.

MONITORING

- Neuromuscular activation pattern (surface EMG)
- Pressure insole
- Force/torque sensor (Ankle torques)

TREATMENT CUSTOMIZATION/CONTROL MODALITIES

- Passive
- Admittance (with force sensor/with forces estimated from pressures)
- Movement triggered by EMG
- FES [20]

However, a rehabilitation system in weight-bearing exercise modality must be able to measure not only the mobilization degree of the joint, but also the forces involved during the exercise.
In order to allow this requirement, the PKankle is integrated with a force pressure system which permits a precise force analysis during rehabilitation activity.

3. Patient positioning

The proprioception of ankle joint is a key feature in motor control for stability in stance during gait. As a consequence of it, an ideal passive joint mobilization system should consider also the possibility of a weight-bearing exercise modality to better train proprioceptive control of the ankle. In order to reach this goal, the patients should be positioned in different modalities, depending on its movement ability, e.g. in standing or seated position (Fig. 3). For example, neurological patients could be unable to maintain the upright position, and they could require a weight-bearing exercise with a comfortable seat. The currently existing devices (refer to References) focuses on the importance of the kinematics without giving enough importance, according to PKankle++ team, to ergonomic aspects and possibility to be exploited in different positions.

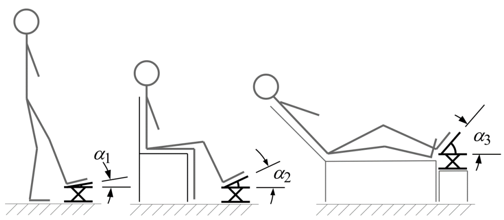

Fig. 3. Use of PKankle in different patient's

4. Human centred design

"*There is a clear potential to improve innovation performance and competitiveness at company and national level through the use of design.*" [21].

Human Centred Design (HCD) is a fundamental area of contact between the business, design, manufacturing and scientific communities. HCD includes all elements of knowledge which are required to design products or services which are physically, cognitively and emotionally intuitive to their users. Human centred design and sustainable design have been identified by many as the multidisciplinary paradigms which will characterise 21st century products and services. A current difficulty in the EU and in many other industrialised societies is the fragmented nature of our academic and industrial base, which divides knowledge into compartmental units along disciplinary lines. HCD is, instead, an approach which takes a holistic and multidisciplinary view of the development and marketing of commercial products and services. The growing importance of HCD was highlighted in the February 2007 edition of the Harvard Business Review in a special report treating "Breakthrough Ideas for 2007". In the special report, an article written by Eric Von Hippel of the MIT Business School explained why Denmark considers human centred innovation vital to its economic growth [22]. The article further states that "recent research shows that the 70% to 80% of new product development that fails does so not for lack of advanced technology but because of a failure to understand users' needs.". The role of the human centred designer is a relatively transparent figure who does not impose his or her preferences on a project, but, instead, conveys and translates the will of the people in order to empower them through the final design solution with ultimate goal of enhancing human wellbeing. The HCD approach will bring techniques that communicate, interact, empathise & stimulate the people involved, obtaining an understanding of their needs, desires and meaningful experiences.

Next steps

The results from PKankle++ project could have a significant clinical impact in rehabilitative medicine.
In fact, from an epidemiological point of view, ankle joint impairment is a relevant problem, described in several clinical conditions including neurological (e.g stroke, multiple sclerosis) and orthopaedic diseases (e.g. ankle sprains, ankle fractures, post-surgery disability).
For example, ankle-foot complex impairment, described as equinovarus foot, is a frequent cause of gait and balance impairment in stroke survivors, and stroke is a leading cause of long-term disability; worldwide, 15 million people suffer a stroke each year: one-third are left permanently disabled [23] [24]. In addition to this, in United States the incidence of ankle sprain injury is 2.15 per 1000 person-years [25], and ankle fracture incidence is between 107 and 184 per 100,000 person-year [26].
As a consequence of these numbers, it is clear that rehabilitation of the ankle is a key point in several clinical pictures, in order to increase patients' mobility by improving gait ability.

The project's goal is focused on demonstration of the effectiveness of a rehabilitation treatment of the ankle-foot complex performed through robotic device. The robotic therapy will be task-oriented, intensive, reproducible and repeatable by using high precision motors and advanced software that characterize PKankle++.
After the preliminary acceptability and applicability tests, performed during the first stages of the project, well-designed studies with large numbers of participants will be planned in order to demonstrate the level of efficacy of robotic rehabilitation programs through PKankle++ to restore functional ability and to establish this robot-assisted therapy as an integral part of ankle-foot rehabilitation.
The potential beneficiary patient groups are orthopaedic trauma patients, oncological patients, and patients with neurological diseases such as stroke, Parkinson's disease and Multiple Sclerosis. Incidence of these problems/diseases correlates with age and, given the demographic changes, increase of patients is expected.

It is hypothesized that the PKankle++ treatment will reduce the disability in the medium and long-term, the number and severity of complications leading to a better quality of life.
Therefore, the effects on the following factors will be evaluated: disability, patient safety, muscle strength, ambulation capacity, risk of falls, functional outcomes such as activities of daily living, length of rehabilitation programs.
The success of the PKankle++ rehabilitation therapy will be to find out correlation results between the amount of residual motor-functional capacity and the level of autonomy achieved during the period of treatment, in order to demonstrate the effectiveness of the robotic treatment in obtaining comparable or better outcomes than the duration of rehabilitation program.
Advantages in terms of engagement of healthcare staff involved are desirable.
Last but not least, the industrial product design sector driving this project has a strong spin-off to other industries relevant to this project. The European Commission notes in their report 'Design as a driver of user-centred innovation' (2009) that good design can increase sales revenues and profit margins by differentiating products and services, making them more valuable to customers. The field of design is a key part of the 'super-creative core' as defined by Richard Florida in 2002, which is fully engaged in the creative process and a driving force of future economic growth. In a report of the Harvard Business Review treating 'Breakthrough Ideas for 2007', the design-related concept of human centred innovation has been considered as vital to economic growth. As a result the design-driven research on the ankle device can directly contribute to innovation and competitiveness for a large number of sectors and industries where these technologies have applications: not only design, (health)care and consumer goods, but also mechanical engineering, electrical engineering and systems engineering. In this way it contributes directly to Europe 2020 targets on employment and R&D.

The team involved in this project will define all PKankle++ requirements, taking advantage of the available multidisciplinary skills.

- **CNR-ITIA (Milano, Italy)** will be in charge of defining technical requirements focusing on: mechatronic modules to be integrated (e.g. the mechatronic foot support for bilateral training functionalities); the overall requirements and design guidelines of the multimodal controller structure.
- **Brunel University, Human-Centred Design Institute (London, UK)** will perform patient-centred co-design activity involving qualitative design research to uncover patients' needs, issues and wishes related to comfort and usability of the ankle support. This will be done through a variety of primary research activities such as in-depth contextual interview, co-creation sessions with different key stakeholders (e.g. not just users, but also doctors, engineers etc.). The design researchers will ensure the involvements of all key stakeholders (consumers, healthcare professionals, etc.) within the defined context of ankle rehabilitation. The qualitative data collected in context mapping contain a number of recorded (audio and video) stories related to the explored context. Transcriptions of these records and also the verbal protocols are analysed to explore the context and uncover the unexpected directions to broaden the designers' view. The results are communicated to the consortium in an informative and inspirational form using persona displays and backed up with written reports for future reference.
- **Università del Piemonte Orientale, Physical and Rehabilitative Medicine - Department of Health Sciences (Novara, Italy)** will define requirements in order to allow efficacy and safety of passive joint mobilization, both in seated and weight-bearing position; analyse body weight support system for weight bearing exercise; define monitoring systems (EMG, force pressure measurements) in different exercise protocols.

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1.2 ORAL COMMUNICATIONS

Il trattamento della spasticità: approccio multiprofessionale
Versilia Hospital, Lido di Camaiore, February 6th 2015

Chemodenervazione e spasticità
Fondazione S. Maugeri IRCSS, Milano, June 12th 2015

Le basi del recupero post-lesionale. Stabilizzazione o cronicità: modificabilità a distanza
XV Congress of SIRN, Italian Society of Neurological Rehabilitation. Novara, April 16-18th 2015

Muscle targeting nel trattamento della spasticità
XV Congress of SIRN, Italian Society of Neurological Rehabilitation. Novara, April 16-18th 2015

1.3 CONGRESS CONTRIBUTIONS

Analisi impedenziometrica quantitativa delle alterazioni muscolari in pazienti affetti da stroke cronico.
XV Congress of SIRN (Italian Society of Neurological Rehabilitation). Novara, April 16-18 2015

Il trattamento della spasticità post ictus con tossina botulinica: analisi dei percorsi di trattamento post-inoculo in Italia
XV Congress of SIRN (Italian Society of Neurological Rehabilitation). Novara, April 16-18 2015

Post stroke spasticity as a condition: a new perspective on patient's evaluation
9th World Congress of the International Society of Physical and Rehabilitation Medicine (ISPRM 2015). Berlin, june 19-23 2015

Applicabilità di un programma di esercizio per il morbo di Parkinson in un setting di comunità: studio pilota su efficacia, sicurezza e compliance.
43° Congress of SIMFER (Italian Society of Physical and Rehabilitative Medicine). Ferrara, october 4-7 2015. (Accepted)

A single-sensor wearable system for gait analysis in stroke patients: a pilot study
3rd European Congress of NeuroRehabilitation. Vienna, December 1-4 2015 (Accepted)

1.4 LIST OF INDEXED PUBLICATIONS

Santamato A, Micello MF, Panza F, Fortunato F, **Baricich A**, Cisari C, Pilotto A, Logroscino G, Fiore P, Ranieri M. Can botulinum toxin type A injection technique influence the clinical outcome of patients with post-stroke upper limb spasticity? A randomized controlled trial comparing manual needle placement and ultrasound-guided injection techniques. J Neurol Sci. 2014 Dec 15;347(1-2):39-43. doi: 10.1016/j.jns.2014.09.016. PubMed PMID: 25263601.

Santamato A, Micello MF, Ranieri M, Valeno G, Albano A, **Baricich A**, Cisari C, Intiso D, Pilotto A, Logroscino G, Panza F. Employment of higher doses of botulinum toxin type A to reduce spasticity after stroke. J Neurol Sci. 2015 Mar 15;350(1-2):1-6. doi: 10.1016/j.jns.2015.01.033. Review. PubMed PMID: 25684341.

Invernizzi M, Carda S, Molinari C, Stagno D, Cisari C, **Baricich A**. Heart Rate Variability (HRV) modifications in adult hemiplegic patients after botulinum toxin type A (nt-201) injection. Eur J Phys Rehabil Med. 2015 Aug;51(4):353-9. PubMed PMID: 25051207.

Santamato A, Micello MF, Valeno G, Beatrice R, Cinone N, **Baricich A**, Picelli A, Panza F, Logroscino G, Fiore P, Ranieri M. Ultrasound-Guided Injection of Botulinum Toxin Type A for Piriformis Muscle Syndrome: A Case Report and Review of the Literature. Toxins (Basel). 2015 Aug 10;7(8):3045-56. doi: 10.3390/toxins7083045. Review. PubMed PMID: 26266421; PubMed Central PMCID: PMC4549739.

Baricich A, Grana E, Carda S, Santamato A, Cisari C, Invernizzi M. High doses of onabotulinumtoxinA in post-stroke spasticity: a retrospective analysis. J Neural Transm. 2015 Sep;122(9):1283-7. doi: 10.1007/s00702-015-1384-6. PubMed PMID: 25724294.

SECTION 2: DIDACTIC AND EDUCATIONAL ACTIVITIES

2.1 Attended Seminars and Lessons of PhD Program at Università del Piemonte Orientale

November 28th 2014
Humoral responses to HCV infection and clinical outcomes
Prof. Arvind Patel

December 4th 2014
Uncovering the role of β-HPV in field cancerization: a collaboration in progress
Prof. Girish Patel

December 5th 2015
Focus on the liver: from basics of NAFLD to hot topics in HBV & HCV infections"
Prof. Rifaat Safadi

December 16th 2014
From the legend of Prometheus to regenerative medicine
Prof. Antonio Musarò

December 17th 2014
Microglia microvesicles: messengers from the diseased brain
Prof. Furlan

January 19th, 2015
Anticancer strategy Targeting cancer cell metabolism in ovarian cancer
Prof. Dr Yong-Sang Song

January 20th, 2015
Different molecular mechanisms regulate hepatocyte differentiation during the transitions between epithelial and mesenchymal states
Dr Tonino Alonzi,

January 21st, 2015
Targeting the liver to cure myocarditis: a lesson from a model of STAT3-dependent auto-immune myocarditis
Prof. Valeria Poli

January 27th, 2015
Myeloid cells as therapeutic target in cancer
Prof. Antonio Sica

April 9th 2015
Signal control in iNKT cell development and function
Dr. Xiaoping Zhong,

April 21st, 2015
Actin-based mechanisms in the control of gene expression and cell fate
Prof. Percipalle

May 14th 2015
Conflicting interests and scientific communication. What ethical standards to apply? How effective are these standards in practice?
Kathleen Ruff

May 25th 2015
Ribosomopathies
Prof. Steve Ellis

May 27th 2015
Basis of scientific research
Prof. Nicoletta Filigheddu

2.2 Attended Congresses

TOXINS 2015: Basic Science and Clinical Aspects of Botulinum and Other Neurotoxins.
Lisbon, January 14-17 2015.

XV Congress of SIRN, Italian Society of Neurological Rehabilitation.
Novara, April 16-18 2015

9th World Congress of the International Society of Physical and Rehabilitation Medicine (ISPRM 2015).
Berlin, june 19-23 2015

Novara, september 22th 2015.

Dr Alessio Baricich, MD