Introduction
The slogan “Today’s Science, Tomorrow’s Medicines” captures the essence of translational medicine. High-quality science as a basis for understanding disease processes is brought to the table by academia. Industry provides the knowhow for drug development, clinical trials and marketing. Together, in an active collaboration between the private sector and universities, discoveries in basic science will be translated more effectively into medicines, changing patients’ therapies and impacting their lives.

Two recent projects in translational medicine are presented in this issue of the Neurotransmitter. The first describes the development of a novel immunotherapeutic strategy for the treatment of amyotrophic lateral sclerosis (ALS), a devastating neurodegenerative disease. The second example is taken from the area of health technology and describes the development of a robotic rehabilitation device to accelerate neurorehabilitation following spinal cord injury or brain insults such as stroke.

Both of these projects in translational medicine were selected and supported by the Swiss Federal Council in 2009 as part of its economic stabilization measures.

Immunotherapy of Amyotrophic Lateral Sclerosis
A common theme underlying many neurodegenerative diseases is the deposition of pathogenic protein aggregates derived from normally occurring endogenous brain proteins. In ALS, one of the most severe forms of motor neuron degeneration, two pathogenic protein aggregates, consisting of superoxide dismutase 1 (SOD1) or TAR DNA-binding pro-

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Beyond Translational Medicine

Translational medicine is a popular and frequently used term. However, the understanding of what translational medicine means varies widely within the biomedical science community. Most frequently, translational medicine is understood as the effective translation of basic scientific discoveries at the “bench” into application in clinical medicine at the “bedside” and vice versa, from the bedside to the bench (Phase 1 of translational medicine). For others, the scope of translational medicine is much broader and also includes translation of findings from clinical trials to their acceptability, effectiveness and cost efficiency in routine practice (Phase 2) as well as the conversion of effective treatment and prevention strategies into sustainable public health solutions (Phase 3). Hence, since the focus of translation is science and research, the term translational medicine should be replaced by the more precise term translational research (or science) in medicine. Independent of these ongoing discussions about its exact definition, the common goal of all translational medicine is to let patients, populations and society profit in one form or the other from new scientific discoveries.

In this issue of the *Neurotransmitter*, two examples of translational research in medicine are exemplified. The first example highlights the value of the bedside to the bench approach, since the recombinant monoclonal antibodies developed against a disease-specific protein aggregate that is pathogenic for amyotrophic lateral sclerosis (ALS) are originally derived from humans and have now been successfully tested in a transgenic ALS mouse model. In order to close the translational Phase 1 circle, it is now important to take the way back to the patient and to test the therapeutic potential of the recombinant antibodies at the bedside. The second example is different. It takes engineering sciences to the bedside and demonstrates an impressive progress in robot-assisted neurorehabilitation of injured arms. This project illustrates in a paradigmatic way the importance of a synergistic and effective collaboration between academia and industry. In fact, independent of any definition of translational medicine, industrial knowhow is of paramount importance for effective implementation of the full translational research chain, be it in the “from bench to bedside” context alone or in its wider scope, including socioeconomic and political public health aspects.

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Beyond Translational Medicine

The number of healthy motor neurons in wildtype mice (top) is strongly reduced in ALS mice (control). These neurons are partially rescued by anti-SOD1 antibody (NI-204 A).

The formation of novel pathogenic protein conformations can be accompanied by a humoral immune response, resulting in the generation of specific B-cells. They encode antibodies which, experimentally, can bind with, neutralize and clear the pathogenic protein aggregates. Thus, recombinant human monoclonal antibodies, derived from human B-cell memory, with high affinity and selectivity for aggregated SOD1 represent a novel class of therapeutic antibodies. Human antibodies were found to show high affinity binding with SOD1 pathogenic aggregates. When released from affected cells, the pathogenic protein aggregates can bind with their cognate physiological counterparts in unaffected neighboring cells and force them to adopt pathological conformations as well. This process of prion-like infectivity ultimately causes the spread of protein aggregation from cell to cell and throughout the central nervous system. Over time, the motor neuron function deteriorates and the patients’ neurological status progressively declines. In human subjects, the formation of novel pathogenic protein conformations can be accompanied by a humoral immune response, resulting in the generation of specific B-cells. They encode antibodies which, experimentally, can bind with, neutralize and clear the pathogenic protein aggregates. Thus, recombinant human monoclonal antibodies, derived from human B-cell memory, with high affinity and selectivity for aggregated SOD1 represent a novel class of therapeutic antibodies. Human antibodies were found to show high affinity binding with SOD1 pathogenic aggregates. When released from affected cells, the pathogenic protein aggregates can bind with their cognate physiological counterparts in unaffected neighboring cells and force them to adopt pathological conformations as well. This process of prion-like infectivity ultimately causes the spread of protein aggregation from cell to cell and throughout the central nervous system. Over time, the motor neuron function deteriorates and the patients’ neurological status progressively declines. In human subjects, the formation of novel pathogenic protein conformations can be accompanied by a humoral immune response, resulting in the generation of specific B-cells. They encode antibodies which, experimentally, can bind with, neutralize and clear the pathogenic protein aggregates. Thus, recombinant human monoclonal antibodies, derived from human B-cell memory, with high affinity and selectivity for aggregated SOD1 represent a novel class of therapeutic antibodies. Human antibodies were found to show high affinity binding with SOD1 pathogenic aggregates. When released from affected cells, the pathogenic protein aggregates can bind with their cognate physiological counterparts in unaffected neighboring cells and force them to adopt pathological conformations as well. This process of prion-like infectivity ultimately causes the spread of protein aggregation from cell to cell and throughout the central nervous system. Over time, the motor neuron function deteriorates and the patients’ neurological status progressively declines.

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in the picomolar range with high target specificity. The efficacy of the human antibodies was tested in transgenic mouse models for ALS. These transgenic mice express a familial ALS-causing mutated human SOD1 transgene and develop signs of motor neuron disease followed by progressive motor neuron degeneration and death within five to six months. Intrathecal antibody treatment showed signs of motor neuron rescue, with 70% more large motor neurons in the lumbar spinal cord of antibody-treated as compared to vehicle-treated transgenic mice. In functional analyses, the antibody treatment delayed the onset of behavioral symptoms, as shown by better motor performance, and ameliorated muscle atrophy, reflected by a delayed decrease of body weight. Taken together, recombiant human-derived monoclonal antibodies against SOD1 aggregates have in vivo efficacy in delaying, preventing and reversing signs of motor neuron degeneration in transgenic mouse models of ALS. Because of the human origin of their cDNA, they have 100% human amino acid sequences combined with natural human heavy and light chain pairing, high affinity and selectivity, resulting in excellent probability for fast, as well as safe, translation into therapeutic clinical use as a treatment for ALS in human patients.

**Robot-Assisted Neurorehabilitation of the Arm**

Following spinal cord injury or stroke, the movement of legs and arms is often compromised. Regaining proper movement by rehabilitation is frequently an arduous and longwinded process. Robot-assisted rehabilitation devices have therefore been developed which assist and accelerate this process by providing regular, patient-specific training, independent of a therapist. A training device for the recovery of leg movements, the Lokomat, was developed earlier and is now marketed world-wide by the industry partner Hocoma AG. More recently, a robotic device for the training of arm movements, called ARMin, was designed and developed only to the stage of a laboratory prototype. The device had to be considerably improved for commercialization and the transfer to a standardized clinical setting. For example, the device did not provide any quantitative outcome measures that would have allowed the assessment of the patients’ rehabilitation status. Furthermore, the device was not optimized for serial production and sales with respect to function and design. The aim of the RANA project, Robot-Assisted Neurorehabilitation of the Arm, was therefore to optimize ARMin and turn it into a commercial product. The novel features of ARMin include i) improved maneuverability, ii) optimal assist-as-needed controllers that make the device “mechanically invisible” in phases when not needed, iii) several virtual activities of daily living tasks on a screen, iv) 18 channel force sensors to record the complete load interaction between user and robot, and v) robot-assistive assessment routines to quantify the biomechanical function and performance of the patient. The latest ARMin model is being tested on several tetraplegic patients by Armin Curt’s team at the Spinal Cord Injury Center, Balgrist University Hospital to evaluate the novel assessment functions. Additionally, in the Berufsgenossenschaftliche Unfallklinik Murnau, a version of the ARMin device upgraded with the newly developed RANA software is being tested in order to evaluate the responsiveness of ARMin to neurological patients. During the entire project, there has been a continuous transfer of knowledge about electro-mechanical design, safety concepts and clinical experience from the academic laboratories to the industrial partner, Hocoma AG. Six ARMin beta versions have now been developed. The device has attracted overwhelming interest at international conferences and medical device fairs. The first series of regular ARMin devices was delivered in December 2011. Further improvements for patients are expected to arise from future research on the biological mechanisms of recovery, which might help to identify predictors for the optimal choice of therapeutic methods (e.g. robot-aided therapy) and timing of therapy.
The cover story of this newsletter describes two NCCR Neuro projects which were selected following a special call for transfer projects addressed to all NCCRs in Switzerland. The results show very impressively that the long-term developments of this NCCR have enabled us to design new monoclonal antibodies against SOD1 protein aggregates in ALS in only two years. Based on the same principles, earlier NCCR work produced a new immunotherapy against Alzheimer’s disease, which is now being studied in phase I human clinical trials. Four of the 14 CTI projects (Grants of the Commission for Technology and Innovation) of this NCCR, the new spin-off Neurimmune Therapeutics AG, and two collaboration agreements with Biogen Idec AG accelerated the transfer of this knowhow into application. Since 2001, our spinal cord repair project has designed and tested a new antibody against the neural regeneration-blocking protein NOGO-A. In collaboration with Novartis AG, humanized antibodies against spinal cord injury have been developed and are about to enter phase II clinical trials.

The second project of our cover story in robot-assisted neurorehabilitation shows another successful transfer of new NCCR technology into the clinic, here in collaboration with the company Hocoma AG. In addition to the robot ARMin, several other novel technical solutions have been developed to support therapy of patients with stroke, spinal cord injury, cerebral palsy, apraxic syndrome and dementia. Knowledge transfer was boosted by seven CTI projects and the foundation of a new spin-off YouRehab AG.

NCCR Neuro technology development also contributed successfully to the area of laboratory equipment. The Center of Assessment of Rodent Behavior invented new fully-automated cages to monitor the behavior of rodents more professionally and efficiently (see figure below). The products, including consulting in rodent behavior analysis, were commercialized with the help of three NCCR spin-off companies: Intellilage Solutions GmbH, Neurospex GmbH and New-Behavior AG. A total of 61 patent applications have been filed and 17 license agreements have been signed for all the inventions of the NCCR Neuro so far. All research activities have resulted in more than 1800 peer-reviewed publications in the neuroscience and engineering communities.

Wolfgang Knecht
Deputy Director NCCR Neuro

IntelliMaze with a central IntelliCage: A fully automated compact behavioral laboratory for efficient simultaneous behavioral testing of up to 16 mice without presence of humans. The central IntelliCage is a “classroom” for mice learning the same task, while individual mice are tested for other abilities in connected test boxes coined collectively IntelliMaze.