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Mayo Researchers Prepare to Launch Clinical Trial Using Gene Therapy for Knee Osteoarthritis

A Mayo research team led by Christopher H. Evans, Ph.D., plans to use a viral vector to introduce an anti-arthritis gene into the knee joints of patients with osteoarthritis (OA). Dr. Evans is director of Mayo Clinic's Rehabilitation Medicine Research Center and associate director, translation, for Mayo Clinic's Musculoskeletal Regeneration Program. Funded by a Department of Defense grant, the study's primary goals are to evaluate the safety of gene therapy for knee OA, as well as the treatment's possible effects on joint structure and clinical efficacy.

Approximately 27 million Americans have OA, and the disease is incurable, largely untreatable and the major cause of disability among older adults. Earlier research has established that interleukin-1 (IL-1) is a key intra-articular mediator of the pathophysiology of OA, and that its natural inhibitor, the IL-1 receptor antagonist (IL-1Ra), is a promising therapeutic.

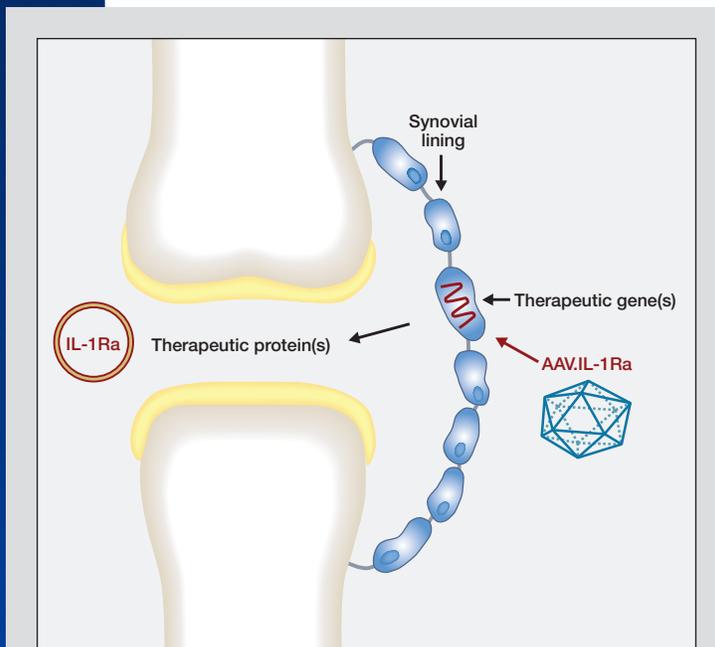
"Using traditional technology, IL-1Ra is impossible to deliver to joints in a sustained fashion," says Dr. Evans. "Gene delivery is a solution to this problem."

The team has developed a recombinant adeno-associated virus (AAV) carrying the IL-1Ra cDNA (sc-AAV2.5IL-1Ra) as a therapeutic for injection into joints with OA. "The efficacy of this agent has been shown in preclinical animal models, and its safety has recently been confirmed in a large, audited, pharmacology/toxicology study under Good Laboratory Practice (GLP) conditions," says Dr. Evans.

The team plans to conduct a phase I safety study in nine human subjects with moderate OA of the knee. The gene therapeutic will be injected into the index knee joint of nine patients with OA of the knee in a dose-escalation manner, and the patients will be followed for one year.

The research team also hopes to study these secondary outcomes:

- Expression of IL-1Ra in synovial fluid and serum
- Possible presence of viral genomes in peripheral blood
- Possible humoral or cell-mediated immune responses to the viral vector and IL-1Ra
- Possible effect on joint structure, as determined by MRI



Transfer of the IL-1Ra gene to the synovial lining of the joint using AAV as the vector. This leads to intra-articular expression of the therapeutic protein IL-1Ra.



Christopher H. Evans, Ph.D.

- Possible clinical efficacy, as determined by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and pain scores

Right now, the team is awaiting the manufacture of clinical-grade vector. Once the vector is delivered, Dr. Evans expects the team to enroll and treat patients in early 2017.

The Musculoskeletal Regeneration Program is based at Mayo Clinic's campus in Rochester, Minnesota. Physicians and scientists in this new program are focused on the repair of diseased or injured tendons, ligaments, cartilage, muscle and bone using advanced stem cell and tissue

engineering platforms. This work involves a multidisciplinary team encompassing orthopedic surgery, sports medicine, physical medicine and rehabilitation, and rheumatology, with the common goal to improve the current standard of care. These emerging regenerative technologies, focusing on structural repair and functional restoration, are poised to provide innovative solutions that address unmet patient needs. In separate studies, Mayo researchers are using preclinical animal models to explore the possible use of gene therapy to regenerate cartilage and heal bone.

Mayo Researchers Evaluate Telerehabilitation Tools



Allen W. Brown, M.D.

Telerehabilitation (TR) has been shown to improve access to care and expand continuity of care for people with disabling conditions and for individuals living far from health care providers. A wide variety of assessment and treatment interventions are currently delivered to patients using remote monitoring systems and other information and communication technologies that provide rehabilitation.

Led by physiatrist Allen W. Brown, M.D., director of brain rehabilitation research at Mayo Clinic's campus in Rochester, Minnesota, Mayo researchers are currently involved in a feasibility study that examines the use of TR to treat patients who have stroke-induced upper limb motor impairment. This study is a joint effort between Mayo Clinic and ReAbility Online, an initiative of Gertner Institute, located in Israel.

The recent development of advanced sensor and remote monitoring technologies has enabled an increasing number of TR applications to be deployed into the home. While early telecare projects looked to provide basic follow-up services and caregiver support, more recent work has developed and deployed systems to provide home-based exercise monitoring, diet and medication compliance tracking, and other more dynamic interventions.

The aims of this study are to 1) assess the feasibility of and satisfaction with providing a telerehabilitation service directed at treating upper limb

motor impairment in individuals with stroke and 2) measure the change in affected limb function during the study period.

Study methods

This study will employ the ReAbility Online system, which is designed to provide a home-based telerehabilitation program to improve the motor, cognitive and functional status of people who have had a stroke-acquired disorder of brain

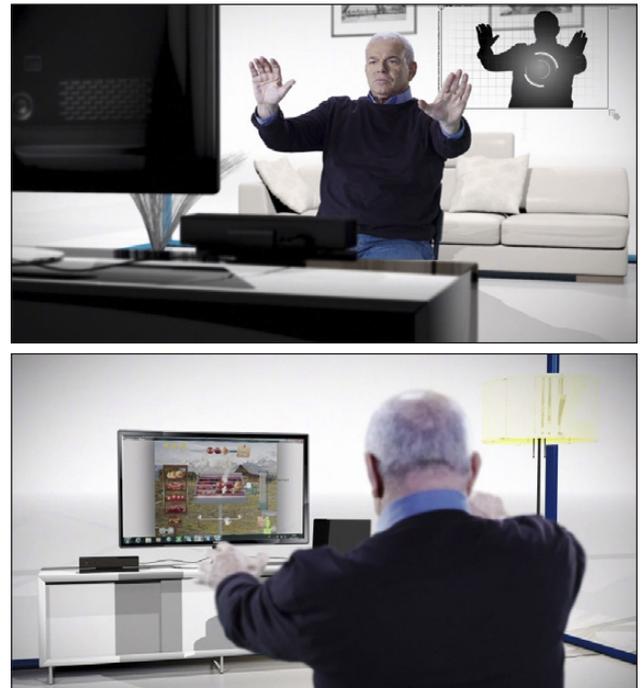


Figure 1. Side and back views of a client using the ReAbility Online telerehabilitation system at home. Photos reprinted with permission from ReAbility Online.

function. The program's commercially available sensor tracking system has been adapted to record upper limb and trunk movements to control a variety of functional tasks and motor activities (Figure 1).

Although this sensor is now widely used in medical and entertainment settings, the clinical team from ReAbility Online has uniquely adapted the software to comply with all key rehabilitation intervention principles. Its capabilities thus extend far beyond "biogaming" activities to provide a truly clinically relevant and valid treatment experience.

The system leads patients through a variety of individually tailored games and functional tasks that span a range of motor and cognitive levels, including several that target activity of the lower limb and grasp (Figure 2). The system provides:

1. Programmable levels of difficulty
2. Targeted auditory feedback of results, performance and progress related to the virtual tasks
3. Offline exercise protocols for independent use by the patient (with sporadic "checkups" by the clinician)
4. Storage of performance data generated during both online and offline sessions for subsequent interpretation and recommendations by the clinician

Both the patient and clinician become aware of the occurrence of any compensatory movements, which are easier for the patient to make but maladaptive in terms of the rehabilitation process. In order to document this latter problem, ReAbility Online can determine the extent to which the targeted and compensatory movements are detected accurately. In this way, the system provides both immediate and long-term feedback in the form of "knowledge of results" and "knowledge of performance" to enhance cognitive-motor learning.

Dr. Brown and colleagues are hopeful that this feasibility study will provide data to support a larger clinical trial of this intervention to determine whether it offers additional benefits compared with the benefits of usual care.

For more information

ReAbility Online. The Gertner Institute.

http://www.gertnerinst.org.il/e/health_society/ReAbility_online.

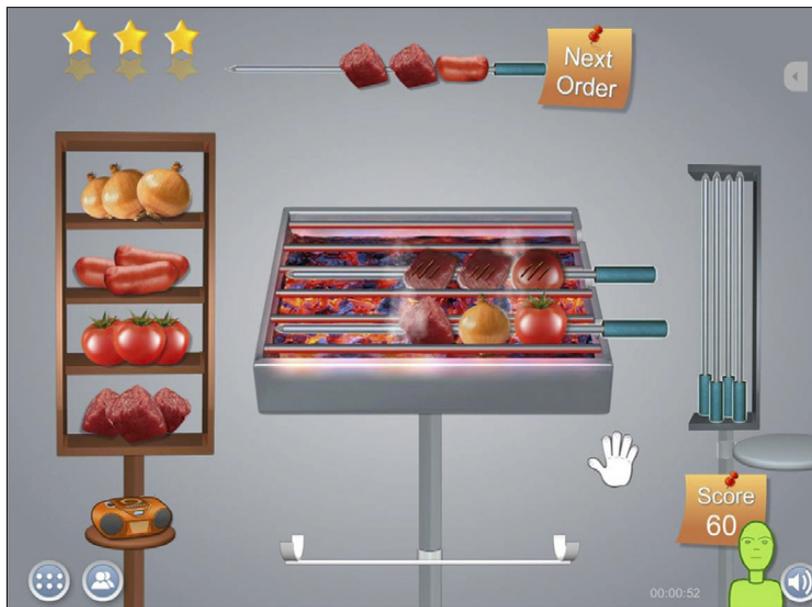


Figure 2. A screenshot from the ReAbility Online grill game in which the user prepares kebabs by using touch-screen selection of food items in accordance with a displayed menu. The user must cope with several simultaneous tasks involved in the grilling activity (preparing a kebab, placing it on the grill, turning it over while preparing the next kebab, removing the first kebab while turning the second kebab and preparing a third kebab, and so on). This activity has moderate motor and moderate to high cognitive requirements. The level of difficulty may be adjusted by changing the number of kebabs that need to be prepared. Photos reprinted with permission from ReAbility Online.

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scientific videos and online referrals

Education Opportunities

11th Mayo Clinic Medical and Surgical Spine Course: Comprehensive Cervical Spine Update 2017

Jan. 13-14, 2017, in Phoenix

This course covers current and emerging spine topics driving national change in the quality and delivery of care. Participants learn new skills via didactics, case presentations and multiple skills labs.

Rehabilitation Medicine Update in Orlando 2017

Feb. 3-5, 2017, in Orlando, Fla.

This course covers multiple techniques and topics, including spine care, amputee, ultrasound injection, stem cell therapies for musculoskeletal injuries, spinal cord injuries, traumatic brain injury, pain, EMG, lymphedema and more.

Pain Medicine for the Non-Pain Specialist 2017

Feb. 16-18, 2017, in Palm Desert, Calif.

This course targets the integration of pain services across disciplines to address the international movement toward improved pain control. The course includes spine care review, pharmacologic management with opioid and nonopioid strategies, and updates on common chronic pain conditions.

Mayo Wound Symposium 2017 - General Session

Feb. 23-25, 2017, in Rochester, Minn.

This course provides the latest diagnostic and treatment strategies for comprehensive wound management. Multiple educational formats offer comprehensive wound management strategies (from basics to high level) to meet the continuing education needs of both novice and expert wound care providers.

Sports Medicine for the Primary Care Clinician 2017

March 24-26, 2017, in Orlando, Fla.

This conference gives attendees confidence to accurately diagnose and treat sports-related conditions and the knowledge to determine appropriate testing and referral criteria. Topics include musculoskeletal conditions and procedural techniques that primary care clinicians can use for athletes and active individuals.

For more information: Visit <https://ce.Mayo.edu/physical-medicine-and-rehabilitation/pmr>, call 800-323-2688 (toll-free) or email cme@mayo.edu.

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