HHS/FDA/Center for Biologics Evaluation and Research (CBER): Joint Studies for Potential Treatments of Joint Disorders for Americans

Using human gene studies as well as mouse and amphibian embryos, we discovered several proteins involved in the growth and development of joints that appear to have great potential as treatments for joint disorders caused by structural damage.

Lead Agency:

HHS/FDA/Center for Biologics Evaluation and Research (CBER)

Agency Mission:

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

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Partner Agencies:

National Institute of Dental and Craniofacial Research (NIDCR)
NIDCR is one of the National Institutes of Health (NIH)

General Description:

Trauma (accident or injury), normal wear and tear, disease, and cancer surgery can all damage specific tissues and organs. The ideal treatment for repairing this damage would restore the tissue or organ to 'like new' condition.

But before researchers can design such treatments, they must first have a detailed understanding of the biochemical processes the body itself uses to make these specific structures.

Among the most important elements that guides the growth of tissues and organs are biochemical signals called growth factors--proteins that trigger specific, immature cells to mature into a cell that is committed to a particular identity, such as a bone cell rather than a cartilage cell. The body uses dozens of different growth factors that cooperate under

normal circumstances to direct proper formation of developing embryos as well as to repair tissues during the life of an individual.

Our laboratory uses a combination of experimental approaches to understand the role of growth factors in triggering growth and repair of tissues in the joints. We use a variety of strategies to identify and study several previously unknown growth factors crucial to the development of joints in vertebrates (e.g., humans). Specifically, we use conventional rodent models for studying bone and cartilage formation and use the embryos of the South African clawed frog (Xenopus) to work out the detailed biology of the growth factors that control joint development and other processes. In addition, we analyzed DNA from families affected by genetic disorders that lead to short stature and deformed limbs to identify the specific DNA sequence changes that caused two different clinical syndromes, thus confirming the role of the factors identified in human disease.

Our work has led to the discovery of several novel growth factors, the most important of which are Cartilage-Derived Morphogenetic Proteins (CDMP) 1, 2, and 3, and Frzb.

CDMPs 1 and 2 are found only in joint cartilage, and appear to be required for normal joint formation. For example, individuals who lack a functioning gene for CDMP1 are very short and have deformed limbs. Therefore, CDMP growth factors are now being evaluated to determine if they offer potential as therapies for joint disorders.

Unlike the CDMPs, the job of Frzb is to block the activity of other growth factors that belong to a group of molecules called Wnts. The family of Wnt growth factors is crucial to the formation and repair of many tissues, including joints; but when these growth factors are overexpressed (i.e., the genes that code for them are too active and make too much growth factor) the Wnt proteins sometimes trigger uncontrolled growth, that is, they cause cancer. Therefore, our work with Frzb and Wnts has the potential to lead to new strategies for repairing joints as well as for diagnosing and treating certain forms of cancer.

While both CDMPs and Frzb growth factors might prove useful as stand-alone therapies, it is more likely that they will be most valuable when used in combination with other growth factors, living cells, and various natural or synthetic biomaterials to manufacture various tissue-engineered medical products.

We are currently trying to identify at the molecular level other crucial biochemical steps that make up the signaling systems triggered by these growth factors. We hope this work will help us better understand these pathways that become active “downstream,” after the initial growth factor signal.

The outcome of these studies would likely contribute to the design of improved products to repair joint disease. In addition, our finding could help improve techniques for testing products under clinical development in order to predict how well they will work in the clinic.

We are currently preparing for submission to scientific publications several manuscripts that describe our work in these areas.

Excellence: What makes this project exceptional?

We suggested, years ahead of most investigators in the field, that the processes controlling many types of tissue repair—especially skeletal repair—was generally similar to the processes that control embryonic development.

We tested the idea in two ways. First, we tested the activity of growth factors that we identified in newborn mammals to determine their effects in developing frog embryos; and then we searched both frog and fish embryos for growth factors that might be useful therapies for human joint diseases.

Both approaches were successful and enabled FDA researchers and their colleagues at the National Institutes of Health to obtain patents for molecules now proposed for testing in human clinical trials for the repair of damaged joints.

Also of interest is the fact we combined laboratory research techniques commonly used in embryology (in our case, frog embryos) with genetic studies of both mice and human families afflicted with certain short stature syndromes. This rather unconventional approach to the study enabled us to find key growth factors more efficiently and economically than would have been possible with conventional approaches.

Significance: How is this research relevant to older persons, populations and/or an aging society?

Since virtually all older individuals develop joint damage, this work is relevant to a large and growing population of Americans.

Effectiveness: What is the impact and/or application of this research to older persons?

New therapies based on our growth factor discoveries could significantly improve the quality of life of the many older persons who develop joint damage (e.g., osteoarthritis), and help them retain their independent functioning.

Innovativeness: Why is this research exciting and newsworthy?

The findings hold promise for more effective treatments to repair, or perhaps even completely reconstruct, damaged joint tissues, eliminating the need for artificial joints.