

cellular-extract concentrations obtained by use of the fully developed HFE will be at least  $10^3$  times those obtained by means of state-of-the-art extraction methods heretofore used in environmental microbiology.

*This work was done by Adrian Ponce of Caltech and Donald Obenhuber of National*

*Research Council for NASA's Jet Propulsion Laboratory. Further information is contained in a TSP (see page 1).*

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## Activating STAT3 Alpha for Promoting Healing of Neurons

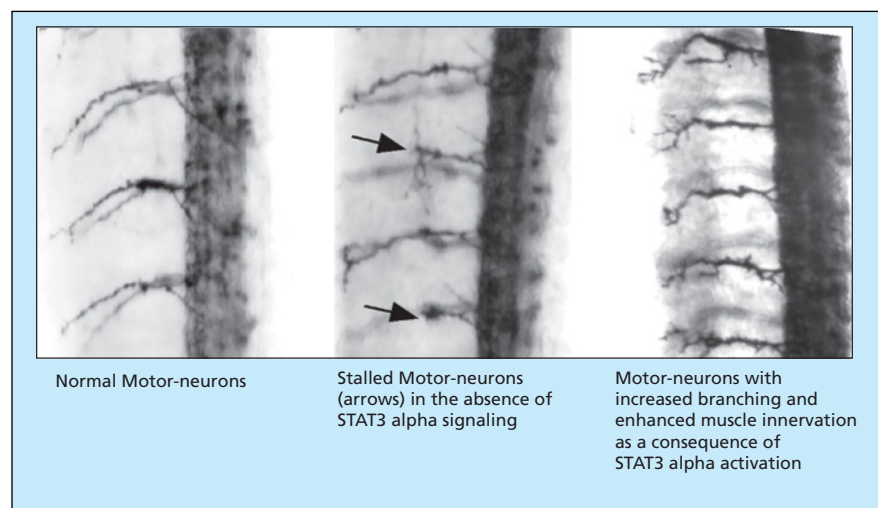
Natural anti-apoptotic, pro-axogenic mechanisms are stimulated artificially.

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A method of promoting healing of injured or diseased neurons involves pharmacological activation of the STAT3 alpha protein. Usually, injured or diseased neurons heal incompletely or not at all for two reasons: (1) they are susceptible to apoptosis (cell death); and (2) they fail to engage in axogenesis — that is, they fail to re-extend their axons to their original targets (e.g., muscles or other neurons) because of insufficiency of compounds, denoted neurotrophic factors, needed to stimulate such extension. The present method (see figure) of treatment takes advantage of prior research findings to the effect that the STAT3 alpha protein has anti-apoptotic and pro-axogenic properties.

As used here, “STAT” signifies “signal transducer and activator of transcription.” “STAT3 alpha” is the name of one of a number of transcription factors and of the gene responsible for producing it. Transcription factors activate the expression of other genes and otherwise generally regulate gene expression. The STAT3 alpha protein is activated in response to such extracellular factors as hormones and growth factors as well as the aforementioned neurotrophic factors. The STAT3 alpha protein associates with trans-membrane receptors for these extracellular factors. When activated by growth factors and hormones, STAT3 alpha prevents apoptosis.

Recent findings from the Life Sciences and Microgravity Division of Ames Research Center now show that when activated by neurotrophic factors STAT3 alpha, in addition to preventing apoptosis, also promotes innervation. The natural activation of the STAT3 alpha protein is effected by phosphorylation of a specific tyrosine amino acid. Upon such phosphorylation, two STAT3 alpha mol-



**Motor Neurons** visualized by a dark staining reaction are seen exiting the spinal cord, from the right side of each panel, innervating adjacent muscle tissue.

ecules can form a homo-dimer. The tyrosine on a given STAT3 protein molecule that becomes phosphorylated resides on a flexible activation loop sequence that binds to a pocket, denoted the SH2 domain, of another STAT3 protein molecule. Upon homo-dimerization, STAT3 alpha is retained in the nucleus of cells, where it binds specific deoxyribonucleic acid (DNA) sequences and activates the expression of nearby genes. Thus, homo-dimerized STAT3 alpha protein is part of a signal-transduction complex that relays chemical signals from hormones, growth factors, and neurotrophic factors outside the cell directly to the DNA inside the cell. In so doing, it activates genes that exert anti-apoptotic and axogenic effects.

Hence, the present method is based on the design of a new class of pharmacological agents (homo and heteroditopic Janus molecules) to promote artificial dimerization and pharmacological activa-

tion of therapeutic targets, in this case the STAT3 alpha protein. The precise location of each atom in the STAT3 homo-dimer is known and it is possible to use this structural information along with molecular modeling and docking programs to rationally design a Janus molecule having the correct sizes and shape, and/or to bind to STAT3 alpha preferentially to other proteins that are similar to STAT3 alpha. The compound can be synthesized by techniques that are well established in the pharmaceutical industry and can be formulated to be administered alone or in combination with other therapeutic compounds.

*This work was done by Greg Conway of Ames Research Center.*

*This invention is owned by NASA, and a patent application has been filed. Inquiries concerning rights for the commercial use of this invention should be addressed to the Ames Technology Partnerships Division at (650) 604-2954. Refer to ARC-15475-1.*