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## REPORT

## AGE Breakers

by Carmia Borek, PhD

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For all the promise of youth-restoring remedies none has ever reversed the process of aging. Now, for the first time, researchers at Alteon Inc. ([alteonpharma.com](http://alteonpharma.com)) have developed a drug that rejuvenates hearts and blood vessels, stiffened with age, by breaking up molecules that cause the trouble.



Glucose is the prime source of fuel for generating energy; but glucose has its dark side. Glucose can bind tightly to proteins and form abnormal (glycated) complexes that progressively damage tissue elasticity. An increased stiffness in the cardiovascular system, which leads to high blood pressure and an overworked heart, is one of the striking features of aging. By breaking these abnormal glucose-protein bonds, the drug ALT-711 can reverse the damage and restore elasticity to blood vessels and heart. Extensive animal studies and ongoing clinical trials show ALT-711 as a potential treatment for a wide range of aging-related disorders.

Since the early 1900s food chemists have known that glucose reacts with amino acids in proteins to form yellow-brown products with cross-linked structures. The Maillard reaction process—named after its discoverer—is the source of color, flavor and texture in cooking; it toughens and discolors food, for example, turning a roasting turkey golden brown or darkening a slice of toast. During the 1970s and 1980s, research done by Dr. A. Cerami and other investigators showed that the glucose-amino acid complexes, called advanced glycation endproducts (AGEs), also form slowly in vivo, on the surface of long-lived proteins such as collagen and elastin, in blood vessels and heart muscle, and crystallin in the lens. Once advanced glycation endproducts are formed they interact with neighboring proteins to produce pathological crosslinks that toughen tissues. The formation of advanced glycation endproducts and AGE-crosslinks are non-enzymatic processes and cannot be reversed by enzymes that disrupt protein bonds. It has been suggested that no other molecule has the versatility of structure and the potential toxic effects on proteins as advanced glycation endproducts. These molecules destroy normal protein structure, inhibit protein physiological function and cause damage that leads to irreversible disease conditions in vital organs.

## AGEs effects on tissues

Since advanced glycation endproducts are by nature permanently bound to collagen and other long lived proteins, they accumulate continuously on vessel walls and other tissues, progressively crosslinking collagen and restricting its flexibility. The rate of advanced glycation endproducts' accumulation and the degree of stiffness they produce are proportional to blood glucose levels and the length of time these levels persist. Evidence that advanced glycation endproducts are important contributors to a loss of elasticity is provided by observations that high blood sugar (hyperglycemia) in young diabetic rats accelerates the stiffening of the heart muscle (myocardium) and that chemicals that inhibit the formation of advanced glycation endproducts prevent the stiffening of the tissues. Additional supporting evidence comes from human observations. People with diabetes, whose high blood glucose is not readily restored to normal, show substantially larger amounts of advanced glycation endproducts in their tissues. They also show increased stiffness, compared to age matched non-diabetic individuals. Age-related cardiovascular disorders that are linked to advanced



glycation endproducts—atherosclerosis, hypertension, stroke and heart failure—are frequent complications in diabetes. In fact it has been suggested that diabetes is an accelerated form of aging. Conversely, it is speculated that increased longevity associated with reduced caloric intake may be due to lower amounts of advanced glycation endproducts formed in the body.

#### AGEs and cardiovascular damage

Restricted movements due to advanced glycation endproduct crosslinking of collagen are especially damaging in blood vessels and the myocardium, whose normal functions depend on flexibility and distensibility. Loss of elasticity in the aorta, the major artery transporting blood from the heart, leads to high systolic blood pressure (systolic hypertension) and high pulse pressure (the gap between systolic and diastolic blood pressure). An increase in arterial stiffness intensifies the workload on the heart and is one of the causes of myocardial enlargement (hypertrophy) and heart failure.

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Advanced glycation endproduct crosslinking and loss of elasticity in the myocardium gradually affect the left ventricle of the heart that pumps oxygen-rich blood into circulation. Increasing stiffness suppresses ventricular contractility, damages its ability to fill with blood (diastolic ventricular filling) and reduces blood delivery into the circulation (decreased output). Stiffness of the myocardium increases diastolic blood pressure, as arterial stiffness increases systolic blood pressure and pulse pressure. Epidemiological studies have shown that increased vessel stiffness is a reliable predictor of cardiovascular disease and mortality.

#### Other AGE induced damage

Considering that collagen is the most abundant protein in the body—a major protein in skin, bones, cartilage, tendons, teeth and the cardiovascular system—advanced glycation endproduct crosslinking of collagen can produce widespread damaging effects.

Advanced glycation endproduct formation also generates free radicals that can add to the damage inflicted by AGE crosslinking of proteins. For example, free radicals can react with components in blood vessels to form fatty plaques that further increase the risk of atherosclerosis, heart disease and stroke, in a cardiovascular system already compromised by loss of elasticity. Advanced glycation endproducts have been found in brain tissue and have been implicated in the pathology of Alzheimer's disease, by inducing oxidative stress and causing structural modification of beta amyloid proteins that play a significant role in the disease.

Advanced glycation endproducts are also involved in other aging-related conditions, seen frequently in diabetes. AGEs damage the kidney, causing leakage in blood vessels, a thickening of the glomerulus walls and the filtering system, and renal failure. Progressive advanced glycation endproduct damage to blood vessels in the retina (retinopathy) results in blindness.

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### AGE crosslink breakers

Once formed, advanced glycation endproducts and the crosslinks they produce were considered permanent structures. But research at Alteon, in collaboration with other researchers, has yielded a new class of pharmaceutical compounds that can break established AGE crosslinks and restore the cardiovascular system to a more 'youthful' state of elasticity. The lead Alteon AGE breaker is ALT-711 (3-phenacyl-4, 5-dimethylthiazolium chloride). ALT-711 inserts itself into AGE crosslinks, separates and cleaves the linked molecules and releases the proteins. The safety of ALT-711 and its efficacy in reversing age-related cardiovascular damage have been confirmed in animals and in phase I and phase IIa clinical trials.

### Preclinical research with ALT-711

Studies in aging dogs (around 10 years old) showed that ALT-711 reversed the age-related increased stiffness of the myocardium within four weeks after the dogs received a daily dose of 1mg/kg of ALT-711. Treatment with the AGE breaker reduced left ventricle stiffness by approximately 40%, and improved cardiac function, as measured by the left ventricle's increased diastolic volume (due to increased flexibility), improved stroke volume (ventricular performance) and decreased diastolic pressure.

Studies on the effects of ALT-711 on healthy older rhesus monkeys showed that an injection of 10 mg/kg ALT-711, every other day for three weeks, improved the flexibility of all vessel walls, increased blood flow to the heart and enhanced blood delivery from the left ventricle into circulation. The improved vascular flexibility persisted over time, with maximum improvement seen six weeks after the end of ALT-711 treatment, and a gradual return to baseline 39 weeks after treatment was stopped. Improvement in cardiac functions persisted longer, continuing until the end of the study, at 39 weeks.

### Clinical studies with ALT-711

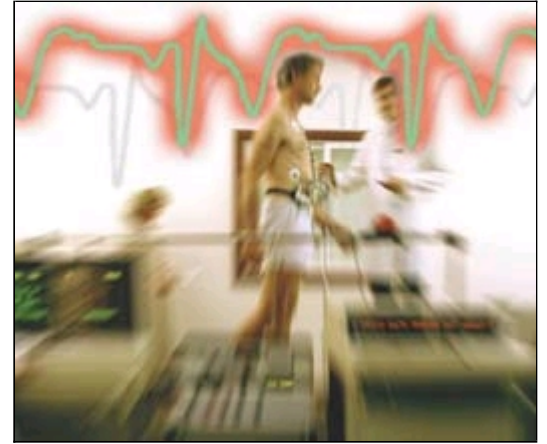
During normal development glucose binds to proteins in a regulated manner, facilitated by enzyme action (enzymatic glycosylation), and natural crosslinking of collagen occurs, as part of normal tissue dynamics. These enzymatic glycosylations differ from the pathological AGE crosslinks that are formed non-enzymatically and are detrimental to health.

### Phase I clinical studies, which were done to determine the safety of ALT

711 in humans, had to demonstrate that the drug does not disrupt normal structure and function in tissues. According to an Alteon Inc. spokesperson, the studies were carried out in the Netherlands and showed that ALT-711 had no side effects. It did not disrupt natural enzymatic glycosylation sites or break peptide bonds (chains of amino acids that form the protein), which maintain the structure and integrity of the collagen chain. Thus, ALT-711 appeared to be selective for breaking AGE crosslinks without interfering with normal tissue processes.

### Phase IIa—the study and the results

The Alteon phase IIa clinical trial was conducted to evaluate the safety and efficacy of ALT-711 in improving cardiovascular function. The study was a randomized, double blind, placebo controlled trial, conducted at nine US clinical centers, including the Johns Hopkins University Medical Center and the National Institute on Aging. Researchers tested the effects of ALT-711 on blood pressure and vascular elasticity in 93 individuals (48 females and 45 males) over the age of 50. The selected participants had measurable stiffened arteries with a systolic



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Results of the Phase IIa trial showed that ALT-711 was safe and well tolerated. Patients who received ALT-711 for eight weeks had a statistically significant lowering of arterial pulse pressure.

blood pressure of at least 140 mmHg and pulse pressure of at least 60 mmHg.

They were assigned randomly to receive ALT-711 at daily doses of 210 mg (63 individuals) or placebo (31 individuals), for eight weeks. Participants in the study who were under treatment for hypertension remained on their medications throughout the course of the clinical trial.

Results of the phase IIa trial showed that ALT-711 was safe and well tolerated. Patients who received ALT-711 for eight weeks had a statistically significant lowering of arterial pulse pressure, a -5.6 mmHg drop in the treated group, compared to a -0.5mmHg drop in patients receiving placebo. This is an important result since high pulse pressure—the gap between systolic and diastolic pressure—is probably the best predictor of cardiovascular risk for most individuals. Mean arterial pressure showed a trend downwards in both groups (by 2-5 mmHg). ALT-711 significantly improved large artery compliance and distensibility (volume capacity) by 11% to 18%, compared to placebo, as measured by the ratio of stroke volume (ventricular performance) to pulse pressure. The increase in compliance indicated greater vascular flexibility. As reported, ALT-711 did not alter cardiac output or peripheral vascular resistance (total resistance to blood flow that thwarts left ventricular emptying), as compared to placebo.

The results were presented at the 50th annual meeting of the American College of Cardiology, in Orlando Florida, March 19, 2001, by Dr. David Kass, Professor of Medicine and Biomedical Engineering at Johns Hopkins University School of Medicine. Dr. Kass was Principal Investigator of the phase IIa trial and has written a joint manuscript for publication.

Phase IIa was successful in demonstrating proof of principle that ALT-711 improves cardiovascular performance, including vessel stiffness—a better predictor of cardiovascular risk than peripheral vascular resistance.

Dr. Kass considers the results of phase IIa impressive. When questioned on the unchanged cardiac output and peripheral vascular resistance following ALT-711 treatment, which differed from results in the animal studies, he suggested that there was probably some increase in cardiac output and fall in peripheral vascular resistance, since mean blood pressure was decreased by ALT-711 and the three parameters are linked. The lack of detection may have resulted because only about 25% of the patients had isolated systolic hypertension, where systolic blood pressure is greater than 160 mmHg and is accompanied by normal diastolic pressure, less than 90 mmHg. The next Alteon study, which will include more patients with this condition and continue over a longer period of time, will further evaluate the effects of ALT-711 on peripheral vascular resistance and cardiac output.

Dr. Lakatta, Chief of the Laboratory of Cardiovascular Disease at the National Institute of Health and an investigator on the phase IIa study, considers the phase IIa results exciting. “Current available cardiovascular treatments do not target vascular stiffening and as a result are not optimal for the treatment of isolated systolic hypertension.” ALT-711, which selectively increases the distensibility of the large artery and reduces pulse pressure, offers a novel approach for treating this condition.

#### Future studies with AGE breakers

Guidelines for the management of hypertension, published by the World Health Organization-International Society for Hypertension, emphasize that pulse pressure and arterial stiffness are important predictors of general cardiovascular risk; a 10 mmHg drop in pulse pressure correlates with a 35% reduction in cardiovascular mortality. Phase IIa showed a significant lowering of pulse pressure with ALT-711 treatment, compared to placebo.

Alteon is planning a phase IIb clinical trial. The randomized, double blind, placebo controlled, clinical study will test the effects of multiple doses of ALT-711 in improving isolated systolic hypertension. The trial will be set up in 42 clinical sites, and involve several hundred patients.

Other pathological conditions caused by advanced glycation endproducts, including kidney dysfunction and damaged vision, may also benefit in the future from AGE breakers. Crosslinking of collagen and elastin are the source of skin aging, caused by advanced glycation endproducts and free radicals. It may be that such damage can be reversed by AGE breakers, restoring youthful elasticity to aging skin.

ALT-711 is one of over 350 AGE breakers developed by Alteon or acquired by the company. Plans are to test some of the other compounds in treating skin aging and in ophthalmic use, including the treatment of diabetic retinopathy.

#### What aging humans can do today

#### Preventing The Glycation Process

If ALT-711 is ever approved by the FDA, it will enable aging humans to reverse the effects of glycation, one of the most devastating consequences of aging. Glycation causes proteins to degrade throughout the body, which results in a wide range of age-associated degenerative diseases.

Glycation occurs when a glucose molecule binds to a protein molecule to form a non-functioning structure in the body. These non-functioning structures destroy the body's proteins resulting in the development of cataract, muscle atrophy, arterial stiffening, skin wrinkling, dementia and a host of other disorders.

ALT-711 is not yet approved by the FDA. As soon as it becomes available, it may be the first drug that every health conscious person takes since all aging humans suffer from some degree of glycation. In the meantime, the best that humans can do is to consume substances such as carnosine or aminoguanidine that can help prevent, but not reverse, the glycation process.

There are compounds that can interfere with the glycation process. One of these agents is a drug available in Europe called aminoguanidine. The suggested dose of aminoguanidine is 300

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mg a day.

A nutrient that may have broader mechanisms of action in protecting against glycation is an amino acid peptide called carnosine. The dose of carnosine needed to protect against glycation is 1000 mg a day. Carnosine is now available in high-potency form and many Life Extension members take carnosine because of its multi-modal effects in protecting against glycation and other pathological processes involved in molecular aging.

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