Apolipoprotein AI as Therapy for Atherosclerosis: Does the Future of Preventive Cardiology Include Weekly Injections of the HDL Protein?

Sergio Fazio,1,2 and MacRae F. Linton,1,3
Departments of Medicine1, Pathology2, and Pharmacology1
Vanderbilt University Medical Center, Nashville, TN USA

A major reason why current guidelines on lipid management focus on reducing the amount of circulating low-density lipoprotein (LDL) cholesterol through the body is because of the availability of powerful LDL-lowering medications, namely the statins, which are ideal agents for long-term use and have proven their effectiveness in large randomized clinical trials (1). However, it is also widely accepted that other aspects of lipid metabolism could produce important therapeutic targets to control the epidemic of atherosclerosis and consequent cardiovascular disease. Interventions on the HDL side of a patient’s lipid profile typically have been based on the concept that raising HDL cholesterol levels will reduce atherosclerosis. This expectation comes from epidemiological observations consistently showing an inverse correlation between HDL cholesterol levels and cardiovascular event rates (i.e., myocardial infarctions) (2, 3). Nonetheless, direct evidence that raising HDL cholesterol levels will reduce cardiovascular risk is scarce and incomplete.

Clinical therapies used to increase HDL cholesterol include smoking cessation, regular physical activity, weight loss, as well as medications such as statins, fibrates, and niacin. The mechanism through which statins raise HDL concentrations is not known and the effect is limited to a few percentage points; however, this “HDL effect” of statins might partly explain the clinical benefits observed in the treatment groups of different clinical trials. For example, in the Air Force/Texas Coronary Artery Prevention Study (AFCAPS/TexCAPS) study, the patients who experienced the greatest benefit from statin usage were individuals with low HDL, and this protective effect might have been due in part to the increase in HDL produced by lovastatin (4). Of the lipid-lowering medications currently used in practice, niacin has the strongest effect on HDL cholesterol (increases average 30–35%). Niacin also exhibits significant salutary effects on cardiovascular disease (5), which can partly be attributed to the effect on HDL levels—although it is well known that this medication beneficially modulates all parameters of the lipid profile.

Fibrates are agonists for the peroxisome proliferator–activated receptor (PPAR) α, a transcriptional regulator of several genes including that for apolipoprotein (apo) AI, the main protein of HDL (6). The use of fibrates effects a 10–20% increase in HDL. Fibrates have also shown evidence of cardiovascular benefits in controlled clinical trials, but these benefits appear to diminish and disappear when baseline LDL levels are higher than 130 mg/dl (7, 8). Among the most exciting new therapeutic molecules on the horizon are cholesteryl ester transfer protein (CETP) inhibitors, agents that can increase HDL by more than 80% (9).

The measurement of HDL cholesterol levels represents only one measure of the status of the reverse cholesterol transport (RCT) system (Box 1).

**Box 1. Reverse cholesterol transport.**
Reverse cholesterol transport (RCT) is the pathway through which excess cellular cholesterol is collected from peripheral tissues and transported to the liver via the bloodstream. The carrier of this cholesterol is the high-density lipoprotein (HDL) particle. The HDL starts its maturation process as a lipid-free protein called apolipoprotein AI (apoAI), which is mainly produced by the liver and intestine. ApoAI can engage a membrane transporter on the cell surface called ABCA-1, resulting in the translocation of cholesterol and phospholipids from the membrane to the nascent lipoprotein. An enzyme associated with the HDL, lecithin–cholesterol acyl transferase (LCAT), esterifies the cellular cholesterol and packages it inside the particle, which becomes spherical and progressively larger as the process continues. The large, mature HDL is capable of exchanging cholesterol with very low–density lipoprotein (VLDL) in plasma and, more importantly, can be recognized by the HDL receptor in the liver [the human scavenger receptor class B type 1 (SR-B1)], resulting in the selective removal of the cholesterol cargo and the initiation of a new cycle of maturation for the once again lipid-free apoAI. Even though arterial macrophages do not produce apoAI, they need it to get rid of their excess cholesterol via ABCA-1. Interventions aimed at providing apoAI to the macrophages within the plaque have demonstrated that the vascular effect of modulating RCT does not necessarily require increasing the level of plasma HDL cholesterol.

Therefore, it is possible that, unlike what we have learned with the LDL pathway, where improved metabolism means lower plasma concentrations, interventions that exert large beneficial effects on RCT might only translate into relatively minor increases in plasma HDL cholesterol levels. Taking this idea to its extreme, one could also envision improvements in RCT without any measurable changes in HDL cholesterol levels or, paradoxically, with reductions in HDL (Figure 1). Surprisingly, this has been the case with the apoAIMilano mutation, which differs from wild-type apoAI by only one amino acid: R173C (10). Carriers of this HDL mutant have been identified on the basis of low HDL cholesterol levels and concomitant longevity (11). Human HDL that contains apoAIMilano appears to undergo faster catabolism, which explains the lower levels of HDL cholesterol and apoAI in the plasma of carriers (12). Reportedly, apoAIMilano has a superior ability over normal apoAI to drive cellular cholesterol efflux, the first step of RCT (13). Thus, at the time when almost every clinician thinks of...
The use of injected apolipoproteins to affect atherosclerosis has been practiced in experimental systems for many years. Injections of apoE, an apolipoprotein similar in structure to apoAI, have a significant effect on reducing the size of lipid–cholesterol plaques in hypercholesterolemic rabbits \(14, 15\). Similarly, injections of normal apoAI have been said to demonstrate the feasibility of an atherosclerosis-reducing intervention aimed at modulating RCT \(16\). Also, studies in transgenic mice have revealed that overexpression of human apoAI has a protective effect against diet-induced atherosclerosis \(17, 18\), and positive results have been observed in studies of adenoviral-mediated overexpression of human apoAI in mice as well \(19\). In all these cases, however, the injection or expression of apolipoproteins had measurable and beneficial effects on plasma lipid concentrations, and this could have easily explained the vascular changes. Injected apoAlMilano has been used in animals to show a direct vascular effect, but because these interventions were undertaken with large amounts of apolipoprotein, they caused increases in HDL cholesterol and total apoAI levels \(20, 21\). However, the concept that apoAI might influence lipid–cholesterol plaque size and composition irrespective of plasma HDL concentrations has been validated in other studies that showed that the expression of normal human apoAI by arterial macrophages, due to transgenic expression or retroviral transduction of bone marrow cells, significantly reduces atherosclerosis without affecting HDL cholesterol levels \(22–24\). Therefore, if macrophages acquire the ability to secrete the HDL protein even in small amounts, large changes on the atheroma will follow without increases in HDL cholesterol.

Another problem that has marred the investigations on apoAlMilano is that none of the studies compares the effects of the mutant with that of the normal apoAI, which is in itself capable of activating cholesterol efflux and of stimulating RCT. In this context it is important to emphasize that increasing the plasma level of apoAI is the benchmark of current pharmacological options affecting HDL.

Results of a study by Nissen et al. on the effect of apoAlMilano injections in patients with atherosclerosis have recently been published \(25\). In this study a small group of patients received either saline infusion or five weekly injections of two different dosages of apoAlMilano–containing phospholipid particles. In just five weeks, two repeat intravascular ultrasound (IVUS) evaluations demonstrated an effect on the plaque reported as a 4% regression in total atheroma (i.e., an accumulated lipid–cholesterol plaque) volume. This study is, in many ways, remarkable, as it shows the clinical applicability of a therapeutic concept that has been tossed around by experimentalists for nearly twenty years, and demonstrates that the arterial plaque in human subjects is a plastic tissue that can undergo quick volume regression. However, the study has limitations in scope and relevance that need to be considered. First, the authors did not feel compelled to evaluate the effect of apoAlMilano vis-à-vis that of normal apoAI. Similar to previous work in experimental animals, these results cannot be interpreted as sure evidence that it was indeed the peculiar structure of apoAlMilano, and not the general apoAI effect, that produced the vascular changes. What is even more surprising is that the authors did not monitor changes in HDL cholesterol or any other plasma lipid parameters. This is a tremendous missed opportunity, because correlating the vascular effects with any changes in plasma HDL cholesterol levels would have allowed for a better prediction of the future therapeutic use of this medication. For example, if the injected apoAlMilano raised HDL, this would support the widely held notion that HDL increases are good, but at the same time, might make the results less physiologically relevant considering that apoAlMilano depresses circulating HDL levels in carriers by virtue of its quick turnover. On the other hand, if the HDL cholesterol levels were reduced by the injections of apoAlMilano, this intervention might not receive widespread acceptance in clinical practice, as physicians may not be ready to adopt a strategy that can only be monitored through a change in a biochemical parameter (HDL) that would appear to move in the wrong direction.

Another interesting aspect of this study was the absence of a dose-dependent effect of apoAlMilano on the IVUS outcomes. The dosages used were hefty, either 15 or 45 mg/kg, and would be expected to increase significantly the concentration of total apoAI in plasma. However, because the effect of normal apoAI on atherogenesis (i.e., plaque formation) is dose-dependent, these results indicate either that apoAlMilano has a dominant-negative effect on the plasma apoAI pool, or that even the smaller injection dose of apoAlMilano was above the pharmacologic titration range. It is impossible at this time to know whether the protective effects of the mutant protein were indeed due to its specific impact on RCT or to a non-specific increase in the apoAI pool.

Finally, the importance of this study is somewhat reduced by the small number of patients enrolled, which resulted in the lack of statistical significance for the comparisons between treatment and placebo groups. However, the effect of the active intervention on atheroma volume in individual patients (in comparison to their own baseline levels) was undeniably positive and significant, whereas standard angiography on these same patients failed to show any differences due to treatment. This confirms that IVUS is an excellent methodology to investigate coronary status \(26\), with more sensitivity than angiography and possibly better predictive power for clinical outcomes. This latter point remains to be proven, however, as small volume changes in early plaques might not translate into significant clinical benefits.

The best stance for the informed clinicians and clinical researchers eager to learn about new therapeutic interventions in
Figure 1. ApoAI, HDL cholesterol, and the atheroma. A. Under physiological conditions, the production rate of apoAI is the main determinant of HDL cholesterol levels, and both correlate well with the extent of cholesterol efflux from peripheral cells. The macrophage cluster in the atheroma is depicted as an example. B. The most common reason for low HDL is reduced production or increased elimination of lipid poor apoAI, resulting in impaired cholesterol efflux from peripheral cells. C. The apoAI Milano reduces HDL through increased catabolism of mature HDL. This is not associated with vascular deterioration because the production rate of apoAI is normal and its ability to collect cellular cholesterol is increased. D. A strategy based on increasing the amount and availability of normal apoAI in the vessel wall results in vascular benefits without any changes in plasma HDL cholesterol levels (see text for details).
atherosclerosis is to wait for better and more complete data on the usefulness of injectable apoAI (either the wild-type protein or its natural or synthetic variants) in improving RCT and vascular health. To provide the final evidence of benefits, a study should be designed with clinical outcomes as primary endpoints. Given the rapidity of the anatomical changes induced by apoA1Milano effects on endpoints such as angina could be detected in less than a year using the right population size. Such a study would address the untapped potential in practice for an acute and aggressive pharmacologic modulation of the arterial plaque.

For cardiovascular interventions based on apoAI injections to become standard practice in preventive cardiology, we must accept that the goal of these therapies is to activate cholesterol efflux from the plaque. We should be prepared to discover that, in some instances, monitoring changes in plasma lipoprotein levels induced by pharmacological interventions may not be an adequate way to assess clinical benefits. What is needed to resolve the issue of potential dissociation between HDL/apoAI levels and clinical effects is a reliable methodology to measure RCT.

Acknowledgments

The authors are supported by National Institutes of Health grants HL53989, HL58427, HL57986, and HL65405. MFL is an Established Investigator of the American Heart Association. We would like to thank Dwayne Dove for helpful discussions and for the production of the figure.

References


8. The BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The Bezafibrate Infarction Prevention (BIP) study. Circulation 102, 21–27 (2000). A study similar in design and statistical power to the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). However, here the HDL raising effect of the fibrate did not produce clinical benefits because the baseline LDL was too high.


A Neurogenic Theory of Depression Gains Momentum

Rosanne M. Thomas and Daniel A. Peterson
Department of Neuroscience, The Chicago Medical School
North Chicago, IL USA

No neuropathological hallmarks exist for depression, despite decades of research investigating the cause of this significant public health problem. The hippocampus increasingly has been implicated as a key brain system involved in depressive disorders, as it influences many functions impaired in depressed individuals, including mood and cognitive difficulties, adverse responses to stress, and altered neuroendocrine functions. An emerging hypothesis linking hippocampal neurogenesis and its control to the cause and subsequent cure of depression is attractive to neuroscientists and clinicians alike. Alterations in hippocampal morphology—including decreased synaptic plasticity and decreased neurogenesis—occur both in animal models of depression and in humans (1). The hippocampus is one of only two areas in the brain clearly shown to exhibit neurogenesis throughout the life of mammals, including humans (2, 3). Recent evidence demonstrates that these newly generated neurons display action potentials, establish synapses, and may function as mature dentate granule cells (4).

The functional purpose of continued neuronal birth has received much speculation. As environmental enrichment increases the rate of neurogenesis, one possibility is that the decreased hippocampal neurogenesis found with depression may reflect an impaired ability to cope with novelty and complexity (5). This hypothesis is supported by work correlating neurogenesis with reactivity to novelty where hyperactive rats exhibited lower rates of cell proliferation in response to novelty compared to low-reactive animals (6). This linkage between neurogenesis and depression was recently advanced by a report from the laboratory of Rene Hen and colleagues advocating a causal relationship between increased neurogenesis and amelioration of depressive behavior in mice (7).

Neurogenesis is a complex series of events resulting in the generation of new neurons from a pool of more primitive progenitor or stem cells (Figure 1). This process occurs during development of the nervous system and, to a more limited extent, during adulthood (8). The rate of adult neurogenesis is not static, but changes in response to environmental factors. Whether such modulation affects the rate of proliferation or the survival of new neurons will differentially influence the net outcome on neuronal number (9). It is the integration of these differentiated, new neurons into the existing neural circuitry that will likely determine the long-term effect of neurogenesis. A variety of stimuli may positively or negatively alter neurogenesis (Figure 2) (10–14), for example, stress is a potent reducer of adult neurogenesis (15–17). Given that stress is a factor implicated in psychiatric illness such as depression, it is plausible that this stress-induced reduction in neurogenesis may be one aspect of the pathophysiology of depression.

Many antidepressants stimulate hippocampal cell proliferation, the first stage of neurogenesis (18, 19). Indeed, the latency of onset of clinical efficacy with antidepressant medication may be the time required to restore “depressed” neurogenesis and allow for maturation of new neurons. Different classes of psychotropic drugs facilitate hippocampal neurogenesis through modulation of various neurotransmitters suggesting that a

**Figure 1. Process of neurogenesis.** Neurogenesis in the adult hippocampus is a process that includes progression from cell proliferation through lineage commitment and functional integration. **A.** Self-renewal and Proliferation Phase. Resident neural stem cells in the subgranular zone (SGZ) below the hippocampal dentate gyrus (DG) occasionally undergo cell cycle, producing progeny that either retain their stem-cell-like nature (self-renewal) or begin a process of lineage commitment as neural progenitor cells (green). The progenitor cells act as a reserve of cells that can be expanded under the influence of environment factors, such as antidepressants. **B.** Survival and Differentiation Phase. Under appropriate environmental conditions, some progenitor cells (green) progress in their lineage commitment (yellow) and move into the granule cell layer where they begin to express markers characteristic of mature neurons (red). This represents the process of differentiation into neurons. Other progenitor cells may commit to become astrocytes or die (X). This process is typically complete within one or two weeks from the progenitor cell's “birthdate” when it exits from cell cycle. **C.** Maturation and Functional Integration Phase. Newly generated neurons eventually establish a morphology consistent with neuronal function such as the elaboration of a dendritic arbor, formation of dendritic spines and synapses, axonal extension, and the ability to conduct action potentials.

**Figure 2. Some environmental factors reported to modulate the rate of neurogenesis.** See (10) for a complete review.
Viewpoint

Table 1. Response of Neurogenesis to Administration of Neuroleptic Drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Effect on Neurogenesis</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>SNRI</td>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td>Tianeptine</td>
<td>SSRE</td>
<td>+</td>
<td>26</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>+</td>
<td>7, 9, 18, 27</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>SNRI</td>
<td>+</td>
<td>18</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>MAOI</td>
<td>+</td>
<td>18</td>
</tr>
<tr>
<td>Imipramine</td>
<td>TCA</td>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Antipsychotic</td>
<td>No effect</td>
<td>9</td>
</tr>
<tr>
<td>Lithium</td>
<td>Mood stabilizer</td>
<td>No effect</td>
<td>29, 30</td>
</tr>
</tbody>
</table>

For detailed reviews see (1) and (19).

SNRI, selective norepinephrine reuptake inhibitor; SSRE, selective serotonin reuptake enhancer; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

Although the role of neurogenesis in human depression is of primary interest, for ethical reasons it is not possible to design studies using human subjects because our current method of detecting new neurons requires administration of thymidine analogs. Therefore, it is essential to utilize animal models to elucidate those adaptive molecular responses that lead to the proliferation and neurogenesis and appear to ameliorate depressive behavior. Animal models of depression, though numerous, are elusive in their ability to define depression and instead rely on various behavioral outcome measures. Most animal models of depression quantify the behavioral effects to various stressors. In fact, antidepressant efficacy is deduced from the medication’s ability to diminish such behavioral effects. These behaviors closely resemble human symptoms of depression and animals exposed to natural and laboratory stress exhibit diminished appetite, sexual drive, grooming, and social behavior (25).

Santarelli et al. adapted a novelty-suppressed feeding test as their measure of the behavioral effects of antidepressants (7). In this test, latency-to-begin-eating is used as an index of anxiety-like behavior. Mice receiving antidepressants exhibited a 35% reduction in latency compared to those receiving vehicle. This reduced latency was correlated with a 60% increase in proliferating hippocampal cells. The specificity of fluoxetine to reduce latency was shown by their ineffectiveness on 5-HT₁A receptor-null mice. To demonstrate the requirement of neurogenesis for this effect, the authors blocked hippocampal neurogenesis by localized X-irradiation, which abolished the effect of antidepressants on latency.

Because blocking neurogenesis blocked the behavioral effects of antidepressants, this study provides evidence for a causal effect for the rate of neurogenesis on depression (7). However, there are some limitations to the strength of this interpretation, primarily because the mice in the report of Santarelli et al. were not exposed to stress and were thus baseline, “non-depressed” animals. Some groups of mice were subjected to stress to evaluate the integrity of their limbic structures following X-irradiation, but no data for the effects of antidepressant administration was reported for these groups [online supplementary material to (7)]. For instance, it is interesting that Santarelli et al. found that both proliferation and differentiation of new neurons was increased with antidepressants [online supplementary material to (7)]. In contrast to Malberg and Duman (9) who found that stressed animals showed elevated proliferation but not differentiation or survival of new neurons in response to antidepressant administration. Differences in the animal models of depression studied may account for these observed differences in neuronal differentiation and underscore the need for additional lines of evidence to be presented to strengthen the proposed relationship between neurogenesis and depression.

If diminished hippocampal neurogenesis is indeed the neuropathological hallmark of depression, then antidepressant administration may be only one way to treat this disease. It may be possible that other conditions that increase neurogenesis (Figure 2) could likewise provide antidepressant effects. Additionally, if depression is a disease of neurogenesis, then it may be possible to predict risk factors for depression based on factors that decrease neurogenesis (Figure 2). The neural circuitry involved in depression is widespread and it may be too soon to conclude that hippocampal neurogenesis is exclusively implicated as the neurobiological basis of depression. Although the assertion of Santarelli et al. linking depression and neurogenesis is provocative and provides a conceptual framework for further investigation, it may be premature to define such a causal relationship. The development of more effective pharmacological intervention for depression aimed at modulating neurogenesis will depend on further elucidation of the mechanisms regulating neurogenesis and the determination of the functional role of newly generated neurons in the adult brain.

References
extensive review article discussing the molecular, cellular and structural adaptations underlying the therapeutic responses of different antidepressants and their resulting induction of brain plasticity.


6. Lemaire, V., Aurousseau, C., LeMoai, M., and Abrous, D.N. Behavioral trait of reactivity to novelty is related to hippocampal neurogenesis. Eur. J. Neurosci. 11, 4006–4014 (1999). The authors showed inter-individual differences in behavioral reactivity to novelty and found that neurogenesis in the dentate gyrus is correlated with this behavioral trait.


8. Cameron, H.A. and McKay, R.D.G. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. J. Comp. Neurol. 435, 406–417 (2001). The authors asserted that the rate of neurogenesis might have been underestimated as a result of low BrdU doses. They used a high dose of BrdU to attempt to quantify the number of newly generated granule cells in the dentate gyrus.

9. Malberg, J.E. and Duman, R.S. Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. Neuropsychopharmacology 28, 1562–1571 (2003). The authors demonstrated that exposure to inescapable shock decreased hippocampal cell proliferation and could be reversed by fluoxetine treatment but did not affect long-term cell survival or differentiation.


14. Lee, J., Duan, W., Long, J.M., Ingram, D.K., and Mattson, M.P. Dietary restriction increases the number of newly generated neural cells, and induces BDNF expression, in the dentate gyrus of rats. J. Mol. Neurosci. 15, 99–108 (2000). Limiting food intake results in an increased survival of newly generated hippocampal neurons and also elevates hippocampal levels of BDNF, providing evidence that this neurotrophin may act as a survival, and/or differentiation factor for hippocampal neuronal stem cells.

15. Czeh, B., Welt, T., Fischer, A.K., Erhardt, A., Schmitt, W., Muller, M.B., Toschi, N., Fuchs, E., and Keck, M.E. Chronic psychosocial stress and concomitant repetitive transcranial magnetic stimulation: Effects on stress hormone levels and adult hippocampal neurogenesis. Biol. Psych. 52, 1057–1065 (2002). The authors found that chronic psychosocial stress resulted in a significant increase of stress hormone levels and suppressed proliferation and survival of newly generated cells in the hippocampus. Concomitant repetitive transcranial magnetic stimulation treatment normalized the elevated stress hormones, mildly attenuated the decrement of proliferation, and further suppressed survival rate of BrdU-labeled cells.


treatment may be a mechanism by which loss of hippocampal neurons is overcome.


Rosanne Thomas, MSPT, (left) is an Assistant Professor of Physical Therapy at the Chicago Medical School, teaching neurological treatment approaches in the doctor of physical therapy program. She received an advanced masters degree in neurological physical therapy in 1996 and maintains a part-time clinical practice focusing on improving functional outcomes for patients with neurological dysfunction. In addition to her academic and clinical duties, RT is a PhD candidate in the Neuroscience Graduate Program at the Chicago Medical School and is doing her dissertation work in Dr. Peterson’s lab. Her work focuses upon the environmental modification of adult neurogenesis in models of acute stress. Given her diverse professional background, RT’s goal is to bridge the gap between basic science research and clinical application.

Daniel A. Peterson, PhD, (right) is an Associate Professor of Neuroscience at the Chicago Medical School where he is director of the Laboratory for Neural Repair and Neurogenesis and Director of the University’s Microscopy and Imaging Facility. DP earned his PhD at the University of Otago School of Medicine (New Zealand) and completed a post-doctoral fellowship in the Department of Neurosciences at the University of California, San Diego. After serving as a Staff Scientist in the Laboratory of Genetics at the Salk Institute for Biological Studies in La Jolla, California, DP joined the faculty of the Chicago Medical School in 1998. His research focuses on the regulation of neurogenesis in the adult brain, particularly as a function of aging, and the development of strategies to repair the nervous system using a combination of stem cell and gene therapy approaches. DP’s research is supported by grants from the National Institute on Aging. Address correspondence to DAP. Email: Daniel.Peterson@finchcms.edu; fax (847)-578-8545.