Targeting Synaptic Loss In Alzheimer’s Disease

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Dr. Stuart Lipton, whose lab discovered memantine (Namenda) for use in Alzheimer’s disease, recently published his work on a newer version of the drug, called NitroMemantine. As readers of this newsletter will recall, neurons are covered with receptors. Receptors bind to neurotransmitters. Some receptors are located within synapses (connections between two neurons) while other receptors are outside of the synaptic region. These are so called extrasynaptic receptors.

In AD, it is thought that activation of NMDA receptors by the neurotransmitter glutamate, specifically at the extra-synaptic NMDA receptors, leads to neuronal damage. The drug memantine blocks the activation of these synapses and is thought to protect neurons from degenerating.

NitroMemantine consists of memantine conjugated to nitroglycerin, both of which are already FDA-approved drugs. It selectively blocks these extrasynaptic NMDA receptors with high potency.

Why are these extra-synaptic NMDA receptors becoming activated in the first place? It turns out that beta-amyloid leads to the overproduction of glutamate by activating specific cells called astrocytes. Astrocytes are supportive cells in the brain and they produce a neurotransmitter called glutamate. Dr. Lipton’s group found that when astrocytes are exposed to high levels of beta-amyloid, they produce high levels of glutamate which in turn activate extrasynaptic NMDA receptors. And, this activation leads to neuronal demise.

Dr. Lipton’s team showed that by using NitroMemantine, neurons can be protected at an even earlier stage in animal models of AD. The data from this study warrant further testing of NitroMemantine in AD.
AD Meds May Reduce Heart Risk

By Elizabeth DeVita Raeburn
Contributing Writer, MedPage Today

Alzheimer's patients taking cholinesterase inhibitors (ChEIs) to improve cognitive function were at reduced risk for MI and death, a study found.

In the study, patients who'd taken a ChEI had a 34% lower risk for MI or death than those who hadn't [hazard ratio 0.66, 95% confidence interval (CI) 0.56-0.78], Peter Nordstrom, MD, PhD, of Umea University in Sweden, and colleagues reported online June 4 in the *European Heart Journal*
The cohort consisted of 7,073 subjects with a mean age of 78.9 from the national Swedish Dementia Registry, begun in 2007. It includes approximately 90% of new dementia diagnoses made in Swedish clinics.

The researchers used registry data on patients followed for up to 2009 days, during which time 831 had an MI or died. The researchers obtained information regarding MIs and deaths through a national health registry and tracked prescription drug usage from another national registry that tracks both prescription and nonprescription drugs.

Dose appeared to make a difference in the benefit conferred by ChEIs. Patients taking the highest doses of one of three different ChEIs (donepezil 10 mg, rivastigmine >6 mg, galantamine 24 mg) had the lowest risk of MI (HR 0.35, 95% CI 0.19-0.64) or death (HR 0.54, 95% CI 0.43-0.67) compared with patients who’d never taken them.

Risk reduction was also similar in case-control cohorts matched for potential confounders such as age, gender, cognitive function, and presence of CVD, they said.
"The interesting thing about the findings is that it had previously been thought that patients with cardiovascular disease should not be taking cholinesterase inhibitors," Sahil Parikh, MD, of UH Harrington Heart & Vascular Institute and not part of the study, told *MedPage Today*.

"In an interesting comparative analysis," Parikh added, "the authors looked at another anti-Alzheimer's dementia drug called memantine in which case patients who took the drug versus those who didn't had similar results in terms of myocardial infarction and all-cause mortality."

The findings by the Swedish team also hint of the possibility that cholinesterase inhibitors could reduce the risk of cardiovascular events in cognitively intact individuals.

ChEIs were introduced in the mid-1990s for treatment of mild-to-moderate Alzheimer's disease. They work by interfering with the breakdown of acetylcholine, a neurotransmitter that tends to be low in Alzheimer's patients.

The drugs are known for certain negative side effects -- largely gastrointestinal -- due to the reduced acetylcholine breakdown, one of the study's authors, Nordstrom told *MedPage Today*.

The research team decided to do the study after a literature review turned up signs of potentially positive cardiovascular side effects, said Nordstrom.

"There were ... data both from animal studies and clinical studies suggesting that ChEIs both have anti-inflammatory properties, and treatment with ChEI animal models showed favorable effects after myocardial infarctions," he said.
AD Meds May Reduce Heart Risk continued...

The researchers wrote that the protective effect observed in the current study might be due to ChEIs' anti-inflammatory properties since "... atherosclerosis, which underlies most forms of CVD, is considered to be an inflammatory disease."

Donald LaVan, MD, of the Perelman School of Medicine at the University of Pennsylvania and a spokesperson for the American Heart Association, said the heart benefits seen in the study might also be due to the fact that acetylcholine causes slowing of the heart rate, "which is similar to what we saw with beta-blockers in the past."

LaVan said the research was worth pursuing further. "They have come across an observation that is relatively new and unreported in the past," he said.

But there were "glitches" in the study that need fine tuning going forward, said LaVan. Statin use was not included in the sensitivity analysis for confounders; the authors didn't document the MIs themselves; and the study was retrospective and ongoing. "They have to do this in a really carefully controlled, double-blinded situation so there's no misinterpretation of data," he said.

The authors agreed. "The major limitation of the present study is its observational design," they wrote. "It would be of value if the findings could be confirmed in a randomized, controlled trial."

Though the authors adjusted for numerous confounders, there could also be others, they wrote, that they did not have access to, which might influence the findings.

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Sanford-Burnham Researchers Develop New Drug That Reverses Loss Of Brain Connections In Alzheimer’s

By Sanford-Burnham Medical Research Institute

NitroMemantine is the first drug to halt the progression of synaptic loss and to even restore these connections between nerve cells. The combination drug is now headed for clinical trials.

The first experimental drug to boost brain synapses lost in Alzheimer's disease has been developed by researchers at Sanford-Burnham Medical Research Institute. The drug, called NitroMemantine, combines two FDA-approved medicines to stop the destructive cascade of changes in the brain that destroys the connections between neurons, leading to memory loss and cognitive decline.

The decade-long study, led by Stuart A. Lipton, M.D., Ph.D., professor and director of the Del E. Webb Center for Neuroscience, Aging, and Stem Cell Research, who is also a practicing clinical neurologist, shows that NitroMemantine can restore synapses, representing the connections between nerve cells (neurons) that have been lost during the progression of Alzheimer’s in the brain. The research findings are described in a paper published June 17 by the Proceedings of the National Academy of Sciences of the United States of America (PNAS).

The focus on a downstream target to treat Alzheimer's, rather than on amyloid beta plaques and neurofibrillary tangles—approaches which have shown little success—"is very exciting because everyone is now looking for an earlier treatment of the disease," Lipton said. "These findings actually mean that you might be able to intercede not only early but also a bit later." And that means that an Alzheimer’s patient may be able to have synaptic connections restored even with plaques and tangles already in his or her brain.

Targeting lost synapses

In their study, conducted in animal models as well as brain cells derived from human stem cells, Lipton and his team mapped the pathway that leads to synaptic damage in Alzheimer’s. They found that amyloid beta peptides, which were once thought to injure synapses directly, actually induce the release of excessive amounts of the neurotransmitter glutamate from brain cells called astrocytes that are located adjacent to the nerve cells.

Normal levels of glutamate promote memory and learning, but excessive levels are harmful. In patients suffering from Alzheimer’s disease, excessive glutamate activates extrasynaptic receptors, designated eNMDA receptors (NMDA stands for N-methyl-D-aspartate), which get hyperactivated and in turn lead to synaptic loss.

Continued on next page...
Sanford-Burnham Researchers Develop New Drug That Reverses Loss Of Brain Connections In Alzheimer’s continued...

How NitroMemantine works

Lipton’s lab had previously discovered how a drug called memantine can be targeted to eNMDA receptors to slow the hyperactivity seen in Alzheimer’s. This patented work contributed to the FDA approval of memantine in 2003 for the treatment of moderate to severe Alzheimer’s disease. However, memantine’s effectiveness has been limited. The reason, the researchers found, was that memantine—a positively charged molecule—is repelled by a similar charge inside diseased neurons; therefore, memantine gets repelled from its intended eNMDA receptor target on the neuronal surface.

In their study, the researchers found that a fragment of the molecule nitroglycerin—a second FDA-approved drug commonly used to treat episodes of chest pain or angina in people with coronary heart disease—could bind to another site that the Lipton group discovered on NMDA receptors. The new drug represents a novel synthesis connecting this fragment of nitroglycerin to memantine, thus representing two FDA-approved drugs connected together. Because memantine rather selectively binds to eNMDA receptors, it also functions to target nitroglycerin to the receptor. Therefore, by combining the two, Lipton’s lab created a new, dual-function drug. The researchers developed 37 derivatives of the combined drug before they found one that worked, Lipton said.

By shutting down hyperactive eNMDA receptors on diseased neurons, NitroMemantine restores synapses between those neurons. "We show in this paper that memantine's ability to protect synapses is limited," Lipton said, "but NitroMemantine brings the number of synapses all the way back to normal within a few months of treatment in mouse models of Alzheimer’s disease. In fact, the new drug really starts to work within hours."

To date, therapies that attack amyloid plaques and neurofibrillary tangles have failed. "It's quite disappointing because I see really sick patients with dementia. However, I'm now optimistic that NitroMemantine will be effective as we advance to human trials, bringing new hope to both early and later-stage Alzheimer’s patients," Lipton said.

Stuart Lipton's Research Focus
Neurodegenerative and Neuromuscular Diseases, Alzheimer's Disease, Amyotrophic Lateral Sclerosis (Lou Gehrig’s Disease), HIV-Associated Dementia, Huntington's Disease, Parkinson's Disease, Stroke, Traumatic Injury, Spinal Cord Injury, Brain Injury

The Lipton laboratory studies molecular mechanisms of neurodegenerative diseases and stroke, including the role of excessive stimulation of ion channels and intracellular signaling pathways in nerve cells. Among the laboratory's accomplishments and ongoing activities are (i) the development of the first glutamate receptor/channel antagonist drug (Memantine), representing the most recent therapeutic to be clinically approved for the treatment of Alzheimer's disease by the European Union and the FDA, (ii) discovery with colleagues of the posttranslational protein modification termed S-nitrosylation (reaction of NO with a critical thiol group to control protein function), (iii) characterization of signaling events leading to neuronal injury and apoptosis in AIDS, and (iv) discovery and cloning of the transcription factor MEF2C that programs Embryonic Stem Cells to become nerve cells in the brain and whose knock down in the brain of rodents and humans causes Autism Spectrum Disorders (ASD). These studies have led to the development of the first neuroprotective drugs to be administered successfully to humans to combat various neurodegenerative and vascular diseases of the brain.

Watch Dr. Lipton describe his research
Scientists at Washington University School of Medicine in St. Louis have measured a significant and potentially pivotal difference between the brains of patients with an inherited form of Alzheimer’s disease and healthy family members who do not carry a mutation for the disease.

Researchers have known that amyloid beta, a protein fragment, builds up into plaques in the brains of Alzheimer’s patients. They believe the plaques cause the memory loss and other cognitive problems that characterize the disease. Normal brain metabolism produces different forms of amyloid beta.

The new study shows that research participants with genetic mutations that cause early-onset Alzheimer’s make about 20 percent more of a specific form of amyloid beta – known as amyloid beta 42 – than family members who do not have the Alzheimer’s mutation.

Scientists found another, more surprising difference linked to amyloid beta 42 in mutation carriers: signs that amyloid beta 42 drops out of the cerebrospinal fluid much more quickly than other forms of amyloid beta. This may be because amyloid beta 42 is being deposited on brain amyloid plaques.

“These results indicate how much we should target amyloid beta 42 with Alzheimer’s drugs,” said Randall Bateman, MD, the Charles F. and Joanne Knight Distinguished Professor of Neurology. “We are hopeful that this and other research will lead to preventive therapies to delay or even possibly prevent Alzheimer’s disease.”

The study appears June 12 in Science Translational Medicine.

In addition to helping develop treatments for inherited Alzheimer’s, investigations of these conditions have helped scientists lay the groundwork for advances in treatment of the much more common sporadic forms of the disease.

Three forms account for most of the amyloid beta found in the cerebrospinal fluid: amyloid beta 38, 40 and 42. Earlier studies of the human brain after death and using animal research had suggested that amyloid beta 42 was the most important contributor to Alzheimer’s. The new study not only confirms this connection but also quantifies overproduction of amyloid beta 42 for the first time in living human brains.
Bateman, who co-developed a technique that measures the rate at which amyloid beta is produced and cleared from the cerebrospinal fluid, contacted several Washington University colleagues to see if they could develop a way to analyze the types of amyloid beta being produced in the brain.

Bateman, metabolism expert Bruce Patterson, PhD, and biomedical engineer Donald Elbert, PhD, created a new mathematical model to describe the production and clearance of amyloid beta.

The scientists applied the model to data from 11 research participants with Alzheimer’s mutations and 12 related family members who did not have the genetic errors that cause Alzheimer’s. The model let the scientists compare the production rates of the protein’s different forms, revealing an increase in amyloid beta 42 production in subjects with an Alzheimer’s gene.

“Working in isolation, any one of us would likely have gotten the wrong answer, or no answer,” Elbert said. “Bringing our different skill sets together let us tackle a very complex physiological problem.”

Scientists are testing the new model on data from approximately 100 Alzheimer’s patients.

“We hope that our new insights about the production and clearance of amyloid beta proteins will pave the way for future studies aimed at understanding and altering the metabolic processes that underlie this devastating disease,” Patterson said.
HHS Releases 2013 Alzheimer’s Disease Plan Update

Plan updated to show achievements, newly set goals in research, care and services

U.S. Department of Health and Human Services released the National Plan to Address Alzheimer’s Disease: 2013 Update, a follow-up to the initial plan released in May 2012. The update reflects our national progress towards accomplishing the goals set a year ago, as well as new and revised action steps.

The plan, ordered under the 2011 National Alzheimer’s Project Act, includes: finding ways to prevent and effectively treat Alzheimer’s disease by 2025; enhancing care for Alzheimer’s patients; expanding support for people with dementia and their families; improving public awareness; and carefully tracking data to support these efforts. The Plan was developed collaboratively by experts in aging and Alzheimer’s disease from federal, state, private and non-profit organizations.

“Over the past year, the Plan has provided a framework for the progress made to relieve the burden of dementia on individuals, families, our health care system and our economy,” HHS Secretary Kathleen Sebelius said. “Researchers are expanding their work on prevention and treatment and we are getting clinicians the tools they need to help people with the disease. By enhancing collaboration between the public and private sectors, the Plan is breaking down walls that have prevented the sharing of expertise, data and resources needed to combat the disease and provide the best care possible.”

Highlights over the past year include:

- National Institutes of Health, part of HHS, brought together international experts for the Alzheimer’s Disease Research Summit 2012: Path to Treatment and Prevention, which developed important recommendations on how best to advance research.

- Multiple new Alzheimer’s research projects were funded in 2012, including two major new clinical trials, genetics sequencing, and development of innovative new cellular models for Alzheimer’s.

- The Health Resources and Services Administration issued grants that helped provide training to more than 10,000 health care providers on topics from dementia diagnosis to effective behavior management for people with dementia and their caregivers.

- HHS launched the widely praised website, www.alzheimers.gov to increase public awareness and connect people with a diagnosis and their caregivers with important resources. The site had more than 200,000 visits in the first ten months.

The update plan also identifies additional action steps that HHS and its partners will take.
HHS Releases 2013 Alzheimer’s Disease Plan Update continued...

These include:

- A unified Alzheimer’s disease training curriculum for primary care providers will be developed to help deliver high-quality dementia care. Researchers will investigate avoidable hospitalization and emergency department use among those with Alzheimer’s disease and the best interventions for reducing them.

- Detection of elder abuse and neglect will be expanded through aging networks and program providers who work with the Alzheimer’s population. Demonstration grants will be awarded to help promote legal services groups that assist families and communities impacted by Alzheimer’s.

- An expanded Dementia Capability Toolkit will be developed for state and local health networks to better help them provide dementia services in their communities.

For more information about Alzheimer’s disease, visit www.alzheimers.gov

National Plan to Address Alzheimer’s Disease: 2013 Update

now available at

An Alzheimer’s disease protein controls the speed at which materials move through brain cells, and defects could lead to deadly pileups of the kind seen in neurodegenerative disease, a new publication finds.

Imagine if you could open up your brain and look inside.

What you would see is a network of nerve cells called neurons, each with its own internal highway system for transporting essential materials between different parts of the cell.

When this biological machinery is operating smoothly, tiny motor proteins ferry precious cargo up and down each neuron along thread-like roadways called microtubule tracks. Brain cells are able to receive information, make internal repairs and send instructions to the body, telling the fingers to flex or the toes to curl.

But when the neuron gets blocked, this delicate harmony deteriorates. One result: diseases like Alzheimer’s.

Understanding such blockages and how traffic should flow normally in healthy brain cells could offer hope to people with neurodegenerative diseases.

Toward that end, a research team led by University at Buffalo biologist Shermali Gunawardena, PhD, has shown that the protein presenilin plays an important role in controlling neuronal traffic on microtubule highways, a novel function that previously was unknown.

The research results were published online on May 24 in the journal Human Molecular Genetics (http://bit.ly/ZqxSJ5). Gunawardena’s co-authors are Ge Yang of Carnegie Mellon University and Lawrence S. B. Goldstein of the Howard Hughes Medical Institute and the University of California, San Diego.

Inside the nerves of fruit fly larvae, presenilin helped to control the speed at which molecular motors called kinesins and dyneins moved along neurons. When the scientists halved the amount of presenilin present in the highway system, the motors moved faster; they paused fewer times and their pauses were shorter.

Given this data, Gunawardena thinks that tweaking presenilin levels may be one way to free up traffic and prevent dangerous neuronal blockages in patients with Alzheimer’s disease.

“Our major discovery is that presenilin has a novel role, which is to control the movement of motor proteins along neuronal highways,” said Gunawardena, an assistant professor of biological sciences. “If this regulation/control is lost, then things can go wrong. This is the first time a protein that functions as a controller of motors has been reported.

“In Alzheimer’s disease, transport defects occur well before symptoms, such as cell death and amyloid plaques, are seen in post-mortem brains,” she added. “As a result, developing therapeutics targeted to defects in neuronal transport would be a useful way to attack the problem early.”

The findings are particularly intriguing because scientists have known for several years that presenilin is involved in Alzheimer’s disease.

Continued on next page...
Presenilin rides along neuronal highways in tiny organic bubbles called vesicles that sit atop the kinesin and dynein motors, and also contain a second protein called the amyloid precursor protein (APP). Presenilin participates in cutting APP into pieces called amyloid beta, which build up to form amyloid plaques in patients with Alzheimer’s disease.

Such buildups can lead to cell death by preventing the transport of essential materials—like proteins needed for cell repair—along neurons.

The findings of the new study mean that presenilin may contribute to Alzheimer’s disease in at least two ways: not just by cleaving APP, but also by regulating the speed of the molecular motors that carry APP along neuronal highways.

“More than 150 mutations in presenilin have been identified in Alzheimer’s disease,” Gunawardena said. “Thus, understanding its function is important to understanding what goes wrong in Alzheimer’s disease.”

To track the movement of the kinesins and dyneins, the team tagged their cargo with a yellow fluorescent protein. This enabled the scientists to view the molecular motors chugging along inside the neuron under a microscope in a living animal. A special computer program then analyzed the motors’ paths, revealing more details about the nature of their movement and how often they paused.

Expression of human APP in fly larval nerves causes axonal blockages (arrows, top panel) which are rescued by reductions in presenilin. Expression of human APP in fly larval brains causes cell death (arrows, bottom panel) which are rescued by reductions in presenilin.

Credit: Shermali Gunawardena
By Rachel Champeau
UCLA

FINDINGS:

UCLA researchers have found that older adults who regularly used a brain-fitness program on a computer demonstrated significantly improved memory and language skills.

The UCLA team studied 69 dementia-free participants, with an average age of 82, who were recruited from retirement communities in Southern California. The participants played a computerized brain-fitness program called Dakim BrainFitness, which trains individuals through more than 400 exercises in the areas of short- and long-term memory, language, visual-spatial processing, reasoning and problem-solving, and calculation skills.

The researchers found that of the 69 participants, the 52 individuals who over a six-month period completed at least 40 sessions (of 20–25 minutes each) on the program showed improvement in both immediate and delayed memory skills, as well as language skills.

The findings suggest that older adults who participate in computerized brain training can improve their cognitive skills.

IMPACT:

The study's findings add to a body of research exploring whether brain fitness tools may help improve language and memory and ultimately help protect individuals from the cognitive decline associated with aging and Alzheimer's disease.

Age-related memory decline affects approximately 40 percent of older adults. And while previous studies have shown that engaging in stimulating mental activities can help older adults improve their memory, little research had been done to determine whether the numerous computerized brain-fitness games and memory training programs on the market are effective in improving memory. This is one of the first studies to assess the cognitive effects of a computerized memory-training program.

AUTHORS:

Authors of the study were Karen Miller, Ph.D., an associate clinical professor at the Semel Institute for Neuroscience and Human Behavior at UCLA, and Prabha Siddarth, Ph.D., a research statistician in psychiatry and biobehavioral sciences at the Semel Institute. Both are available for interviews.

FUNDING:

The study was funded in part by Dakim, manufacturer of Dakim BrainFitness, the computerized program used in the study. Miller and Siddarth have served as consultants on the development of the software included in the program.

JOURNAL:

The study is published in the July issue of the American Journal of Geriatric Psychiatry.

Prabha Siddarth
(Courtesy of UCLA Health System)
Caring for a person with Alzheimer’s disease can be a tough job with many demands and challenges. To help, the Alzheimer’s Disease Education and Referral (ADEAR) Center offers more than 25 tip sheets—many now available for mobile devices in .epub and .mobi (Kindle) formats.

The popular tip sheets offer brief, easy-to-understand information on a range of issues, from bathing and driving to disaster preparedness and personality changes. They can help caregivers of people at any stage of the disease—mild, moderate, or severe.

Users of tablets, smartphones, and e-readers with an e-book app can now view and download select tip sheets for their mobile devices from the ADEAR website at www.nia.nih.gov/alzheimers/topics/caregiving:

- Managing Personality and Behavior Changes (PDF, 977K) (E-pub, 180K) (Kindle, 166K)
- Bathing (PDF, 645K) (E-pub, 189K) (Kindle, 157K)
- Exercise and Physical Activity (PDF, 1.1M) (E-pub, 278K) (Kindle, 186K)
- Changes in Communication Skills (PDF, 902K) (E-pub, 206K) (Kindle, 192K)
- Holiday Hints (PDF, 485K) (E-pub, 180K) (Kindle, 167K)
- Helping Family and Friends Understand Alzheimer’s Disease (PDF, 555K) (E-pub, 243K) (Kindle, 157K)
- Helping Kids Understand Alzheimer’s Disease (PDF, 790K) (E-pub, 185K) (Kindle, 169K)
- Disaster Preparedness (PDF, 617K) (E-pub, 227K) (Kindle, 144K)
- Driving Safety (PDF, 701K) (E-pub, 223K) (Kindle, 143K)
- Wandering (PDF, 840K) (E-pub, 200K) (Kindle, 187K)

For more Alzheimer’s disease resources, visit www.nia.nih.gov/alzheimers, or contact the ADEAR Center at 1-800-438-4380 (toll-free) or adear@nia.nih.gov. The ADEAR Center is a service of the National Institute on Aging, part of the National Institutes of Health.
ADCS Trials Enrolling...

Studies That Will Be Open for Enrollment Soon

For Information: http://www.adcs.org/Studies/clinicalResearchStudy.aspx

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation. Understanding of this form of Alzheimer’s disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.