Playing a Role in History

Clinical Trials Key to Vanquishing Scourges Through the Years

Who doesn't secretly dream of playing an important role in the history of the world? Most people want to be remembered in some way. People who participate in clinical trials are doing just that. How, you wonder? By volunteering for clinical trials, study participants play a vital role in the long history of clinical trials.

Many people think that clinical trials are a recent phenomenon, but in fact they date back to ancient times. The earliest documented clinical trial is mentioned in the Old Testament. In the first chapter of the Book of Daniel, King Nebuchadnezzar of Babylon conquered Israel and ordered that several Jewish youths be brought to his palace where they would be fed and taught as though they were his own children. One of the youths, Daniel, did not want to disgrace himself by eating the king’s meat and drinking his wine. He suggested to the king’s head eunuch, Melzar, that instead they be allowed to eat a mixture of peas and beans called pulse and drink only water. Melzar feared the king’s anger should the youths become sick on a diet of beans and water. So Daniel suggested an experiment – allow some of the youths to eat pulse and drink water for 10 days, while the others eat meat and drink wine and to watch them carefully. After 10 days, the children that ate pulse and drank water were healthier than those who ate the meat and drank the wine. Convinced, Melzar gave all of them only pulse and water at future meals.

In 1025 A.D. Avicenna, an early Persian physician, introduced the first rules for conducting what are now called clinical trials in The Canon of Medicine. These rules and principles for testing the effectiveness of substances and medications formed the basis of modern clinical trials by providing a logical method for measuring and comparing effects.

One of the most famous clinical trials was James Lind’s 1747 demonstration aboard the HMS Salisbury that citrus fruits could cure scurvy, the bane of sailors. He fed various acidic substances to groups of afflicted sailors. The group that ingested oranges and lemons mostly recovered in six days. Although he proved that citrus fruit could cure and even prevent scurvy, the fruits were not included in ship rations due to their high cost. It was not until 50 years later that the British Navy made lemon juice an essential part of the Naval diet. Soon after that, lemon juice was replaced by lime juice because of its lower cost. It has been postulated that is the reason why British sailors, and later on all British citizens, were nicknamed “limeys” by Americans.
The next clinical trial of sorts occurred in 1789 with English physician Edward Jenner. Noting the common observation that milkmaids did not generally get smallpox, Jenner theorized that the fluid in the blisters which milkmaids received from cowpox (a disease similar to smallpox but much less virulent) protected the milkmaids from smallpox. On 14 May 1796, Jenner tested his theory by inoculating James Phipps, a neighbor’s eight year old child. Jenner inoculated Phipps with the blister fluid from a milkmaid. This produced a fever and some uneasiness, but no great illness. Later, he injected Phipps with infectious material which surely would have caused smallpox. No disease followed. Jenner reported that later the boy was again challenged with material and again showed no sign of infection. He tested his theory in a series of 23 subjects, and proved vaccination could work in reducing the incidence of smallpox infection.

In 1884 French physician Louis Pasteur inoculated a nine year-old boy with a rabies antidote. The boy had been bitten by a rapid dog and several physicians were sure the boy would die without some kind of treatment. Although nervous about experimenting on the child he relented under pressure from the boy’s mother. The boy survived.

The first placebos (non-active ingredients) were used in 1863 and in 1923. The word placebo, Latin for “I shall please”, dates back to a Latin translation of the Bible by Jerome. It was first used in a medicinal context in the 1700s. In 1785 it was defined as a “commonplace method or medicine” and in 1811 it was defined as “any medicine adapted more to please than to benefit the patient.”

In 1948 the first trial using randomization, control groups and “double blinding” (where neither the doctor nor patient knows if the patient is getting the study drug or placebo) was conducted by the Medical Research Council for using streptomycin to treat tuberculosis.

Unfortunately, there have also been abuses in the name of research. Unethical experiments conducted by the Nazis in concentration camps led to strict regulation of medical experiments on human beings: the Nuremburg Code and the Declaration of Helsinki. Sadly these declarations held little weight in the United States which is why the iniquitous Tuskegee experiment, an observational study of 400 African American men with syphilis continued for 40 years until it was brought to light in 1970 and closed down for not treating the men with penicillin, a known cure for the disease.

That scandal led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In 1979 the commission issued The Belmont Report that stipulated ethical principles and requirements for clinical trials.

Fortunately there have been many more positive benefits from clinical research than abuses. There is not a drug on the market today that has not been studied extensively. Every time you take ibuprofen for a headache or strained muscle, an acid reducer for a stomach ache or use an inhaler for asthma, remember that you can use these drugs because someone agreed to participate in a clinical research trial. Participation in a clinical study blazes the trail toward a treatment for Alzheimer’s, just like Lind, Jenner and Pasteur were pioneers in their time to find treatments for diseases that plagued their communities. — ADIN
Researchers studying peptides using the Gordon supercomputer at the San Diego Supercomputer Center (SDSC) at the University of California, San Diego have found new ways to elucidate the creation of the toxic oligomers associated with Alzheimer’s disease.

Igor Tsigelny, a research scientist with SDSC, the UCSD Moores Cancer Center, and the Department of Neurosciences, focused on the small peptide called amyloid-beta, which pairs up with itself to form dimers and oligomers.

The scientists surveyed all the possible ways to look at the dynamics of conformational changes of these peptides and the possibility that they might organize into the oligomers theorized to be responsible for the degenerative brain disease. In the February 14 issue of the Journal of Alzheimer’s Disease, the researchers suggest their results may generate new targets for drug development.

“Our research has identified amino acids for point mutations that either enhanced or suppressed the formation and toxicity of oligomer rings,” said Tsigelny, the study’s lead author. “Aggregation of misfolded neuronal proteins and peptides may play a primary role in neurodegenerative disorders, including Alzheimer’s disease.”

Tsigelny also noted that recent improvements in computational processing speed have allowed him and other researchers to use a variety of tools, including computer simulations, to take new approaches to examining amyloid-beta, which has proven too unstable for traditional approaches such as x-ray crystallography.

The researchers investigated the single and dimer forms of the peptide with a combination of computational methods including molecular dynamics, molecular docking, molecular interactions with the membrane, as well as mutagenesis, biochemical, and electron microscopy studies. They then looked at how those dimers interacted with additional peptides and which larger structures resulted. The researchers found that depending on their configurations, some dimers did not lead...
oligomers implicated in the development of Alzheimer’s disease.

“Remarkably, we showed a greater diversity in amyloid-beta dimers than previously described,” said Eliezer Masliah, professor of pathology and medicine at UC San Diego, and a member of the research team. “Understanding the structure of amyloid-beta dimers might be important for the design of small molecules that block formation of toxic oligomers.”

Based on their results, the researchers were able to identify key amino acids that altered the formation and toxicity of oligomer rings. “Our data is only theoretical, but there is a good chance the oligomers we have been modeling exist for real,” noted Masliah. “Some important recent publications have come out that support our work.”

The in silico experiments allowed the single amyloid-beta monomers to associate randomly, according to Masliah. However, he noted that within the brains of Alzheimer’s patients, the formation of oligomers and fibrils depends on any number of biochemical influences such as peptide concentration, oxidation, neurotoxins, and acidity.

According to the researchers, their work implicates a more dynamic role for the amyloid-beta dimers than previously thought. It also suggests that the way dimers form and then grow into larger structures is a rapidly changing process.

“This, as well as previous results, suggests that targeting selected amyloid-beta dimers may be important in an effort to ameliorate the episodic memory described in mild cognitive impairment and the early stages of Alzheimer’s disease,” said Masliah.

Masliah and Tsigelny’s collaborators included UC San Diego’s Yuriy Sharikov, Valentina Kouznetsova, Jerry Greenberg, Wolfgang Wrasidlo, Tania Gonzalez, Paula Desplats, Sarah E. Michael, Margarita Trejo-Morales, and Cassia Overk.

Single amyloid-beta monomers can pair up to form a variety of dimers that can aggregate into larger peptide rings that reside on cell membranes such as those pictured. This process has been implicated in the development of Alzheimer’s disease. This visualization shows the possible rings which have the most favorable energies of interactions with the membrane. The residues are colored white to represent apolar or hydrophobic areas, green for the polar or hydrophilic areas, blue to show a positive charge, and red to show a negative charge. 
Image by Igor Tsigelny, SDSC and UC San Diego; Eliezer Masliah, UC San Diego
A new initiative called the Accelerating Medicines Partnership (AMP) will contribute $129.5 million toward the search for biomarkers and therapeutic targets for Alzheimer’s disease, the National Institutes of Health announced February 4. The goal is to speed up the discovery of treatments in critical and underserved areas of medicine. In addition to funding AD, another $100 million will be spent on Type 2 diabetes and the autoimmune disorders rheumatoid arthritis and lupus, with other diseases to be funded later. About half the money will come from the National Institutes of Health (NIH), and 10 industry partners will donate the rest. Several nonprofit organizations, including the Alzheimer’s Association and USAgainstAlzheimer’s, will help guide the research in collaboration with the Food and Drug Administration. All data and analyses from AMP projects will be made publicly available. The AMP website provides more information, including a list of industry and not-for-profit partners.

For Alzheimer’s disease, the new effort intends to fill two gaps in the present state of the research, said George Vradenburg of USAgainstAlzheimer’s. One is for better biomarkers to track disease in preclinical populations and show if a drug is working. The second is for validated therapeutic targets beyond amyloid and tau. “That will increase the number of shots on goal,” said Vradenburg. Most Alzheimer’s drug candidates have failed in clinical trials, and none have been approved in the last decade. The NIH estimates about a 95 percent failure rate for new drugs for any disorder, and AMP aims to improve this average.

Current AD biomarkers, such as PET amyloid imaging and cerebrospinal fluid (CSF) Aβ and tau, identify people on course to develop the disease, but do not track well with clinical outcomes (see Nov 2012 conference story). Researchers would like to find a surrogate biomarker because that would speed up clinical trials, lower costs, and might allow more drugs to be tested. PET tau tracers, which label neurofibrillary tangles in the brain, show promise in this regard (see Nov 2013 conference story). In addition, some researchers think that electroencephalography (EEG), which directly measures synaptic activity, might reflect cognitive status better than do current biomarkers (see Nov 2012 conference story).

To more fully test these two markers, AMP will fund the addition of PET tau imaging and EEG to three existing prevention trials: the Dominantly Inherited Alzheimer Network trial, the Alzheimer’s Prevention Initiative ApoE4 trial, and the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) trial. EEG and tau imaging may also be added to a Phase 2 AD study of the approved cancer drug sargramostim. This recombinant granulocyte macrophage colony-stimulating factor pumps up the innate immune system, said Neil Buckholtz, who directs the neuroscience division at the National Institute on Aging. The sargramostim trial received $2.2 million in NIH funding in 2013, and is run by Sanofi Aventis, Cambridge, Massachusetts, one of the AMP partners, in collaboration with scientists at Baylor College of Medicine, Houston. The 24-week trial will test the drug in people with mild cognitive impairment to see if it clears amyloid deposits and slows cognitive decline.

While the biomarker portion of the project will receive the bulk of AMP funding, some money will also support three studies that are searching for new therapeutic targets by developing network models of AD (see Sep 2013 news story). These studies, led by Philip De Jager at Brigham and Women’s Hospital, Boston; David Bennett at Rush University Medical Center, Chicago; Eric Schadt at the Icahn School of Medicine at Mount Sinai, New York; and Todd Golde at the University of Florida, Gainesville, were funded by the NIH in 2013. AMP support will enable the creation of a shared database and help coordinate the efforts of the three groups, Buckholtz said.

—Madolyn Bowman Rogers

In a technological tour de force, researchers at Albert Einstein College of Medicine of Yeshiva University have published two studies in the January 24, 2014 issue of the journal, Science, that provide an unparalleled window into how the brain makes memories. Such insights into the molecular basis of memory formation have never before been achieved in animals.

Einstein researchers developed a mouse in which they fluorescently tagged all molecules of messenger RNA (mRNA) that code for the beta-actin protein – a key structural protein found in large amounts in neurons and considered a key player in making memories. mRNA is a family of RNA molecules that copy DNA's genetic information and translate it into the proteins that make life possible.

The researchers then stimulated neurons in the mouse's hippocampus, where memories are made and stored, and watched fluorescently glowing beta-actin mRNA molecules form in the nuclei of neurons and travel within dendrites, the neuron's branched projections. They discovered that mRNA in neurons is regulated through a novel process described as “masking” and “unmasking,” which allows beta-actin protein to be synthesized from the mRNA.

As readers of this blog will recall, neurons communicate with each other at synapses. Studies over the past 30 years have demonstrated that repeated stimulation increases the strength of synaptic connections by changing the shape of synapses. Beta-actin protein plays an important role in physically strengthening these connections. Memories are thought to be encoded when stable, long-lasting synaptic connections form between neurons in contact with each other.

The relevance of such research in the field of AD cannot be overstated. By seeing the physical nature of memory formation, we can now look at this process in various disease states, including memory robbing diseases such as AD. Further, we can better understand how beta-amyloid may perhaps interfere with the brain's memory machinery.

Michael Rafii, MD, PhD
Director, Memory Disorders Clinic
Medical Core Director, ADCS
UC San Diego
Avoiding Harmful Byproducts of Heat-Processed Foods Protects Against Risk of Alzheimer’s Disease and Diabetes

Modifying Dietary Intake of Advanced Glycation Endproducts, or AGES, Bolsters Body’s Defenses Against Alzheimer’s and Metabolic Syndrome, Say Mount Sinai Researchers

by Sid Dinsay, Mount Sinai Health System

Advanced glycation endproducts, or AGES, are compounds commonly found in the so-called “Western diet,” and previously have been linked to increased body weight, diabetes, and possibly Alzheimer’s disease. Now, researchers at the Icahn School of Medicine at Mount Sinai have shown that AGES also cause brain changes similar to Alzheimer’s disease and pre-diabetes. AGES, which naturally occur at low levels in the body, are found in high levels mostly in heat-processed animal food products, such as grilled or broiled meats; Mount Sinai researchers showed that consumption of such foods by mice raised the body’s level of AGES, which, among other effects, suppressed levels of sirtuin, or SIRT1, a key “host defense” shown to protect against Alzheimer’s disease as well as metabolic syndrome, a pre-diabetic state.

The studies suggest that reducing the intake of AGES could help open “new therapeutic avenues” for the treatment of Alzheimer’s dementia, as well as diabetes. The paper was first published in the journal Proceedings of the National Academy of Sciences.

“Age-associated dementia or Alzheimer’s disease is currently epidemic in our society and is closely linked to diabetes. Our studies of both animals and human subjects confirm that AGE-rich foods are a lifestyle-driven reality with major health implications. The findings point to an easily achievable goal that could reduce the risk of these conditions through the consumption of non-AGE-rich foods, for example, foods that are cooked or processed under lower heat levels and in the presence of more water – cooking methods employed for centuries,” said Helen Vlassara, MD, Professor and Director of the Division of Experimental Diabetes and Aging in the Brookdale Department of Geriatrics at Mount Sinai. “While more research needs to be done to discover the exact connection of food AGES to metabolic and neurological disorders, the new findings again emphasize the importance of not just what we eat, but also how we prepare what we eat. By cutting AGES, we bolster the body’s own natural defenses against Alzheimer’s disease as well as diabetes.”

Dr. Vlassara and her team of researchers at Mount Sinai previously identified AGES as a culprit leading to diabetes and increased body weight, and showed that decreasing the intake of AGES lowers related health risks and restores the body’s natural defenses. For this study, Dr. Vlassara tracked cognitive health in mice (and humans) that ingested AGES at the high levels typical of a Western diet to determine whether AGES caused neurodegeneration by suppression of a substance called SIRT1, a deacetylase that regulates neuronal, immune, and endocrine function; SIRT1 is found suppressed in individuals with neurodegenerative and metabolic diseases, such as diabetes or pre-diabetes or simply aging.

The Mount Sinai researchers found that the mice kept on a diet high in AGES – similar to Western diet - had high levels of AGE in their brains, and suppressed SIRT1 in their blood and brain tissue compared with mice that were fed a diet low in AGES. Those mice also developed declines in cognitive and motor abilities; and deposits of amyloid-β, a component of the plaques characteristic of Alzheimer’s disease. They also had metabolic syndrome, a combination of medical conditions
with increased risk of diabetes and heart disease; The mice fed a low AGE diet remained free of these conditions.

In addition, Dr. Vlassara’s team conducted a clinical study of healthy humans over the age of 60 with high blood levels of AGEs. The study showed that, over a nine-month period, those subjects with high blood levels of AGEs developed cognitive decline, signs of insulin resistance and SIRT1 suppression, while those with low blood AGEs remained healthy. Taken together, these results suggest that consumption of foods high in AGEs can suppress production of SIRT1, contributing over time not only to metabolic syndrome, but also to dementia.

These studies were funded through the National Institutes of Health’s National Institute on Aging and the National Institute of Diabetes and Digestive and Kidney Diseases.
Alzheimer’s disease is the most common cause of late-life dementia. The disorder is thought to be caused by a protein known as amyloid-beta, or Abeta, which clumps together in the brain, forming plaques that are thought to destroy neurons. This destruction starts early, too, and can presage clinical signs of the disease by up to 20 years.

For decades now, researchers have been trying, with limited success, to develop drugs that prevent this clumping. Such drugs require a “target” — a structure they can bind to, thereby preventing the toxic actions of Abeta.

Now, a new study out of UCLA suggests that while researchers may have the right target in Abeta, they may be missing the bull’s-eye. Reporting in the Jan. 23 issue of the Journal of Molecular Biology, UCLA neurology professor David Teplow and colleagues focused on a particular segment of a toxic form of Abeta and discovered a unique hairpin-like structure that facilitates clumping.

“Every 68 seconds, someone in this country is diagnosed with Alzheimer’s,” said Teplow, the study’s senior author and principal investigator of the NIH-sponsored Alzheimer’s Disease Research Center at UCLA. “Alzheimer’s disease is the only one of the top 10 causes of death in America that cannot be prevented, cured or even slowed down once it begins. Most of the drugs that have been developed have either failed or only provide modest improvement of the symptoms. So finding a better pathway for these potential therapeutics is critical.”

The Abeta protein is composed of a sequence of amino acids, much like “a pearl necklace composed of 20 different combinations of different colors of pearl,” Teplow said. One form of Abeta, Abeta40, has 40 amino acids, while a second form, Abeta42, has two extra amino acids at one end.

Abeta42 has long been thought to be the toxic form of Abeta, but until now, no one has understood how the simple addition of two amino acids made it so much more toxic than Abeta40.

In his lab, Teplow and his colleagues used computer simulations in which they looked at the structure of the Abeta proteins in a virtual world. The researchers first created a virtual Abeta peptide that only contained the last 12 amino acids of the entire 42–amino-acid-long Abeta42 protein. Then, said Teplow, “we just let the molecule move around in a virtual world, letting the laws of physics determine how each atom of the peptide was attracted to or repulsed by other atoms.”
By taking thousands of snapshots of the various molecular structures the peptides created, the researchers determined which structures formed more frequently than others. From those, they then physically created mutant Abeta peptides using chemical synthesis.

“We studied these mutant peptides and found that the structure that made Abeta42 Abeta42 was a hairpin-like turn at the very end of the peptide of the whole Abeta protein,” Teplow said.

The hairpin turn structure was not previously known in the detail revealed by the researchers, “so we feel our experiments were novel,” he said. “Our lab is the first to show that it is this specific turn that accounts for the special ability of Abeta42 to aggregate into clumps that we think kills neurons. Abeta40, the Abeta protein with two less amino acids at the end of the protein, did not do the same thing.”

Hopefully, the work of the Teplow laboratory presents what may the most relevant target yet for the development of drugs to fight Alzheimer’s disease, the researchers said.

Other authors on the study included Robin Roychaudhuri, Mingfeng Yang, Atul Deshpande, Gregory M. Cole and Sally Frautschy, all of UCLA, and Aleksey Lomakin and George B. Benedek of the Massachusetts Institute of Technology.

Funding for the study was provided by grants from the State of California Alzheimer’s Disease Research Fund, a UCLA Faculty Research Grant, the National Institutes of Health (AG027818, NS038328) and the James Easton Consortium for Alzheimer’s Drug Discovery and Biomarkers.
ADCS Clinical Trials

The following trials have begun but not all sites are up and able to enroll participants. Check the web pages for sites able to screen and check back periodically as the pages are updated as sites come online.

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness
http://adcs.org/Studies/SNIFF.aspx

http://adcs.org/Studies/A4.aspx

http://dian-info.org/

For further information on all ADCS clinical trials please visit:
http://adcs.org/Studies/clinalResearchStudy.aspx

https://twitter.com/ADCSComm

https://www.facebook.com/pages/Alzheimers-Disease-Research/114211355284888?v=wall