Treatments are lacking ALS

NDR's goals are simple, bring promising therapies to ALS patients and know which treatment is appropriate for a patient by evaluating biomarkers. Classically, the path to licensed treatment and testing drugs starts in the laboratory. Treatments are then tested in mice models of ALS, and then safety and effectiveness studies and conducted in people.

State of the art

The Healey ALS platform is a strategy when multiple treatments, selected by a group of expert ALS scientists and the Healey Center Science advisory board, are tested, and evaluated simultaneously in people. Each drug is given to a patient and at some point, the patient switches to another drug. In this paradigm, patients are not given multiple drugs. Trehalose is on the current platform. One advantage to the ALS platform is that placebo group data is shared and that decreases costs and speeds discovery. The current 2020 platform is testing:

- Zilucoplan – inhibits complement C5
- Verdiperstat – oral myeloperoxidase inhibitor reduces microglial activation
- CNM-Au8 – nanocrystalline gold, supports cellular metabolism
- Pridopidine – selective S1R agonist, shown benefit in A93A model reduces toxic protein aggregates and ameliorates muscle fiber wasting
- IC14 – targets CD14; chronic hyper-activated (dysregulated) CD14 is detrimental; soluble CD14 in blood is associated with ALS progression.

Information silos impede progress!

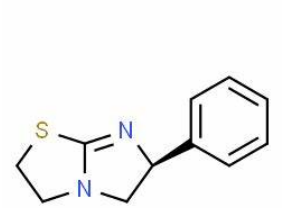
The silo effect is everywhere! In science, an information silo is the drilling down on a topic by a group of scientists. The effect of silos in chronic illnesses that are connected by a common root pathology was explained to NDR by Dr. Robert Naviaux. (Control + click to hear his presentation). Breaking out of the silo approach can lead to discovery and a paradigm change. A promising success in polyneuritis equi (PNE) treatment was observed for this untreatable clinical condition in horses when looking for *something else* led to unexpected results. Data from sarcocystosis experiments directly led to a treatment for equine demyelinating polyneuropathy.

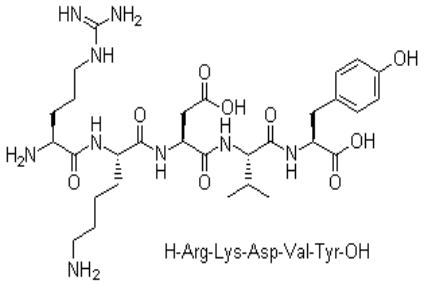
Polyneuritis is a syndrome with multiple causes. PNE had no treatment, no diagnostic bioassays, and newer technology wasn't being applied to discoveries that were reported in the older literature. The EPM *information silo* didn't optimize past discoveries that could be applied to horse disease. Changing the paradigm of EPM in the equine community required an effective disease model, the ability to identify and monitor disease and still, will require eliminating information silos.

Research and discovery in ALS

ALS is complicated, both in disease pathogenesis and genetics. ALS has two licensed treatments, sub-optimal bioassays, frustrating animal models, and 20 years of failed clinical trials. Urgent needs to evaluate potential treatments are biomarkers and disease models.

Some treatments have been lost to the annals of time. Levamisole HCl and thymopoietin are two such treatments. It is possible these molecules will have a place in combination therapies for ALS. We are testing them in ALS mouse models and will publish the data when results are in. These treatments lost favor because levamisole HCl causes undesirable side effects in 5% of people and thymopoietin was short lived. These issues are not insurmountable, and we are trying to develop levamisole HCl analogs without side effects. Another goal is to make the active peptide (thymopentin) longer lived, and if possible, an oral drug. If these goals are achieved, the ALS patient could benefit.





Another aspect of ALS is the altered energy metabolism that occurs as disease progresses. Dysregulated energy pathways may be modulated with a product called secretome. Secretome is the combination of growth factors and cytokines that stem cells produce when placed in a bioreactor. Secretome was shown to extend the life of a strain of mice that express an ALS phenotype. Hopefully, with NDR's support, secretome will be placed in a clinical trial in 2021.

The phenomena of muscle wasting in ALS is a process of neurogenic muscle atrophy instigated by neurodegeneration, a direct effect of disconnecting (die-back) neurons from the muscles they control. There are pathways that are down-regulated in atrophied muscles, one significat pathway is PI3K/Akt. The role of a key modulator protein (CTMP) was identified, CTMP decreases PI3K/Akt signaling. Inhibiting CTMP in post-sciatic nerve injury and in knock-out mouse models restores muscle mass. Understanding these associations may lead to new therapies for ALS patients. An additional finding in this novel research is that atropy and cell degredation markers can be measured and monitored. It is yet to be determined if these cytokines could be used as biomarkers for disease, we remain hopeful.

Another approach to providing ALS treatments is investigating combinations of treatments that are already licensed for neurodegenerative diseases and finding a synergetic combination could change lives. An example is phenylbutyrate and TUDCA, this combination is being tested in a clinical trial with promising results. It took two college students, not intrenched in the ALS information silo, to come up with the idea. Synergistic combination therapy is a good approach and one we are funding. There are some treatments that are mildly beneficial, Riluzole and Edavarone, that could be modified to exert a greater effect. This is another idea and a project NDR is funding.

It is vitally important to find biomarkers to diagnose the disease processes present in ALS because the pathology changes over time. ALS is a spectrum of pathologies and giving the clinician the tools to identify real time disease would alter their approach to an individual's treatment. We support a laboratory that is looking at markers for stressed tissue, altered fat metabolism, and immune check point signaling. Another research path to identify biomarkers is metabolomics. Metabolomics is the study of the chemical processes involving metabolites. Metabolites are small molecule substrates, intermediates, and products of cell metabolism. As we identify biomarkers it will be important to translate them into a test format and put

a kit in the doctor's office. We have a project funded with that goal in mind, it's called wax-on-paper biosensing chip technology.

As we try and pin-point measurable factors that can give us a clue to the disease process, it may be as important to know how pathways are down regulated. What are these processes that are no longer available to the body to maintain homeostasis? Are the loss of functional pathways as important as pathways that are running at high gear? Inflammation is an example. We already mentioned the down regulation of PI3K/Akt by CTMP and inhibiting CTMP could be therapeutic. Are there other molecules that significantly inhibit pathways that become pathologic in ALS, when compared to the healthy person? Are the inhibited pathways just a matter of control points or is the DNA inhibited by epigenetic mechanisms? We are well underway in this type of analysis and will report the findings as soon as we have something.