# Summary - Pyruvate Dehydrogenase Complex Deficiency (PDCD)

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**Clinical Trials - from Drug Discovery to Drug Approval** (slide 1)
Navigating the path to drug development and approval, especially for rare diseases, is a difficult journey, much like the literary character, Odysseus, faced choosing between the lesser of two very real dangers (Scylla vs. Charybdis) while attempting to reach his end point.

Pyruvate Dehydrogenase Complex (PDC) is the largest enzyme in the body and most animal cells. PDC plays the critical role of converting substrate fuels, such as carbohydrates, to energy by irreversibly converting pyruvate (a molecule formed in the cytoplasm by glycolysis) to Acetyl-CoA. By doing so, PDC links glycolysis in the cytoplasm to in the TCA cycle (also called the citric acid cycle and Krebs cycle) in the mitochondria.

**Energy is Life!**

- PDC's role in the energy production is very complex and critical for survival as energy as ATP is needed to fuel the body and cells.
- Pathways and cofactors involved in mitochondrial energetics (slide 2) are depicted in great detail.
- Glucose in the cytoplasm is broken down to pyruvate via glycolysis (left side of the slide).
- Pyruvate then has many fates -
  -- forms amino acids for protein synthesis

  -- forms the backbone for fat synthesis

  -- conversion to alanine

  -- conversion to lactate - a potential problem with PDCD and many mitochondrial diseases is lactic acidosis, occurring due to an inefficient conversion of pyruvate into the mitochondria to then be acted on within the pyruvate dehydrogenase complex to form Acetyl-CoA in the TCA cycle (lower center of slide).

  -- Glucose carbon from pyruvate enters the TCA cycle, and then the PDC and various enzymes (depicted in blue), and vitamins and cofactors (depicted in green) in the TCA cycle generate negatively charged electrons (e-), which then traverse the respiratory chain (also called the electron transport chain) (lower right side of the slide).

1. Ultimately, the respiratory chain has two major functions:

- converts oxygen a person breathes to water
- converts ADT to ATP the major energy source for all cellular work (adenosine *di*phosphate to adenosine *tri*phosphate)

2. PDC plays a pivotal role in cellular energy metabolism, and, as a consequence, when things go awry with the expression or activity of this critical enzyme, energy failure may supervene.

**Natural History of PDCD** (slide 3)

Review of 371 PDCD Cases

- Any of the component parts of the PDC can be mutated and become dysfunctional, leading to PDCD. The vast majority of mutations, however, are nuclear DNA and found in the "business end" of the molecule, namely E1alpha subunit mutations. This subunit blocks off the carbon dioxide from pyruvate, ultimately leading to the conversion of Acetyl-CoA.
- Most individuals with PCDC have clinical onset within the first few days to weeks of life. Diagnoses in the neonatal period (less than 4 weeks of age) is spurred by unrelenting lactic acidosis. PDCD is the most common cause of congenital lactic acidosis (CLA) with increased blood and/or CSF(cerebral spinal fluid obtained via spinal tap) lactate and lactate/pyruvate (L/P) ratio greater than or equal to 20. Normal L/P ratio under normal conditions in a healthy individual is 10-15/1. Heavy exercise, a fever, an infection, or even eating a meal can elevate lactate levels many fold. In healthy individuals, these increases are transient and baseline is restored quickly. In patients with PDCD, the ratio is usually 10-20/1. In Respiratory Chain Diseases (RCD), the ratio is higher. The sensitivity and specificity of the L/P ratio test is not always reliable. Some children with RDC and PDCD may have normal L/P ratios and this test alone cannot be used to make a diagnosis.
- Affected individuals with heterozygous PDCD (a partial defect with 2 different alleles of a gene - one healthy and one with the PDCD mutation) are extremely rare. This individual could be asymptomatic or have a mild presentation. Heterozygosity with PDCD is more commonly discovered after two heterozygous individuals have an affected homozygous (both alleles mutated) child. The process to diagnosis an adult with PDCD is the same process used with children. Acquired defects to the PDC can also cause symptomatology in adults and children.
- Most common clinical signs and symptoms in children:
  - Developmental delay (cognitive and physical milestones are not met)
  - Hypotonia (low tone) and muscle weakness
  - Seizures
- Brain Imaging
  - Enlarged ventricles
  - Brain atrophy, especially of the cortex
  - Other structural abnormalities
  - Leigh syndrome (bilateral symmetric degeneration of basal ganglia, brain stem, and cerebellum)
- Most patients die within months to a few years after diagnosis, but a few with mild mutations live into adulthood. CLA in neonatal period points to a dire prognosis.

**What is a Rare Disease** (slide 4)

- In the US, rare disease is defined as having a frequency of less than one case per 200,000 as defined by Congress with the Orphan Products Act (1983).

- About 5,000-6,000 diseases qualify as a rare disease, including PDCD.
- About 12 million Americans are affected by rare disease.
- Historically, funding for rare disease research, including clinical and drug development research, has fallen into a "Valley of Death," which describes a dead period of time between the discovery of a potential new treatment for a rare disease and the subsequent licensing, testing, and approval of any treatments. Many drugs for rare diseases languish on shelves due to a lack funding available for clinical trials. Drug approval is not pursued by pharmaceutical companies due to the limited financial reward common with rare disease therapies.
- The Orphan Products Act established mechanisms by which funding and protection for drugs developed for rare diseases could occur, essentially like having a patent, albeit for limited amount of time.
- Although this act has helped get hundreds of drugs approved for rare diseases, **no FDA-approved drugs for any primary mitochondrial disease are available**.

**A Possible Therapy for PDCD** (slide 5)

- Dichloroacetate (DCA) or "vinegar with a kick!" is an investigational drug used for many years for the treatment of genetic mitochondrial diseases, including PDCD.
- DCA is also used for other conditions.
- The molecule is a simple one, acetic acid (vinegar) except that 2 hydrogen ions have been substituted by 2 chloride ions (top of slide) and is provided as a sodium salt, specifically sodium DCA.
- Doses given are in the mg/kg/day range, which is 10,000 times the concentration found in the environment.
- DCA is ubiquitous in biosphere and humans cannot avoid exposure to this molecule (micrograms/kg/day exposure range).
  - DCA is a TCE metabolite, an industrial solvent used by dry cleaners and airlines.
  - DCA is a disinfection byproduct of water chlorination. Humans drink, bathe, prepare foods, and are generally surrounded by chlorinated water.
  - DCA is also present in fog and rain.
- The concentration of DCA in the environment is about 1/10,000th of what is administered for Mito therapy. The molecule is the same, but the amount of exposure is vastly different - milligrams vs. micrograms!

**How DCA Works** (slide 6)

- Regulates the activity of PDC.
- Review - breaks down glucose to pyruvate, crosses the mitochondrial membrane, converts to Acetyl-CoA, enters the TCA cycle, and makes ATP/energy.
- PDC is regulated by many checks and balances, the most dominant check and balance is facilitated by reversible phosphorylation. A phosphate group, when attached to PDC, phosphorylates it, rendering PDC inactive and no longer able to convert pyruvate to Acetyl-CoA. This reaction is handled by an enzyme Pyruvate Dehydrogenase Kinase (PDK). The opposite effect can occur when PDC loses a phosphate group and reconstitutes the active enzyme which is facilitated by the enzyme Pyruvate Dehydrogenase Phosphatase (PDP). DCA acts by inhibiting the action of PDK, thereby preventing the phosphorylation of PDC and keeping PDC in an

active form. This benefit occurring through all cells, such as heart, liver, brain, muscle, etc.

**Preliminary Findings** (slide 7)

- Diverse anecdotal evidence of benefit, coupled with DCA's fundamental ability to work on this key regulator of metabolism, gave hope that the drug would work in children with multiple, congenital forms of lactic acidosis.
- In the early 1990s, Alexander, diagnosed with PDCD with an abnormally high serum lactic acid level, came to University of Florida with his mom. Alexander was 18 months old, unable to track stimuli visually or auditorily, and was very floppy to the point of being unable to sit up on his own. One hour after a single dose of DCA, Alexander was able to track auditory stimuli and over the course of that day, his lactate level became normal. The next morning, following the second dose of DCA, much to the amazement of his mother and others, Alexander sat up unaided. The family returned home to California with DCA. The ensuing months brought videotapes of the progress Alexander continued to make in gaining his milestones. Alexander showed signs of a small infection and was observed in the hospital as a precaution. In 3 days, Alexander had passed away from that respiratory illness due to the inability of his body to mount enough energy to fight this illness.
- Other children were given DCA as well with good clinical responses and a subsequent lowering of lactic acid levels, giving enough preliminary support to conduct a clinical trial.

**What is a Clinical Trial?** (slides 8 -11)

- An experiment in which the subjects are humans.
- Prospective (gathering data from this point and into the future), not retrospective (gathering data from past events or medical chart review).
- Often involves a novel intervention or novel use of an established intervention (drug, vaccine, gene, food, or device, for example).
- Investigational New Drug (IND) permit held by sponsor or investigator.
- Investigators include physicians, nurses, dietitians, laboratory technicians, biostatisticians, collectively coming together as one team.
- Common venues for rare disease trials are academic health centers.

**Phases of a clinical trial**:

- **Phase I** - Drug metabolism and dose ranging studies in healthy volunteers. Dosing, safety, and how the drug is metabolized by the body are studied.
- **Phase II** - Blinded (unknown if patient receives the study drug) or open label studies (known if patient receives study drug) in the target population for safety and efficacy. The target population encompasses the group for which the drug is ultimately intended. DCA's target population is PDCD patients. Any drug metabolism, safety, or dosing difference between the Phase I healthy individuals and the Phase II target population is also evaluated. Hints of efficacy may be obtained as well.

- **Phase III** - Randomized, double-blind, placebo-controlled study in target population for hard data on safety and efficacy. Phase II studies are need to ensure that bias does not affect study results.

-- Randomized - the arm of the study (active treatment arm or placebo arm) that the patient will follow is determined by a flip of a coin (or like randomizing procedure).

-- Double-blind - neither the patient, nor the treating physician, nor any other staff knows when or if the patient is receiving active treatment or placebo.

-- Placebo-controlled - some patients exclusively receive the study drug or treatment and some patients exclusively receive a placebo - a harmless substance that has no effect, used as a control. A placebo crossover design study includes a point whereby participants change study arms, although the timing of that change and whether drug or placebo is received remains blind to all.

- Safeguards and ombudsmen - many checks and balances are in place to ensure safety.
  - New drug applications (NDA) are submitted to the Food and Drug Administration (FDA), requiring one or more pivotal Phase II trials. FDA oversight ensures maximal safety. Foreign studies may or may not help drug approval.
  - Further safeguards are placed by the Institutional Review Board (IRB) within the hospital or facility level where the ethical aspects and safety profile of the study are monitored on a regular basis.
  - The Data Safety Monitoring Board (DSMB) is comprised of independent experts in the field who have no part in the actual study, but are able to look at the unblinded progress of the trial and recommend changes in the protocol or even a premature discontinuation of the trial if warranted. Unintentional toxicity or data revealing continuation of giving the placebo over the actual medication is unethical give good cause to alter the study course.

**First Randomly controlled Trial Results for CLA (2006)** (slide 12-13)

- Cohort - 43 children with an average age of 5.6 years at entry. 11 children with PDCD and 32 children with Respiratory Chain Defects (RC) with or without known mtDNA mutation.
- Patient outcome
  - DCA was significantly effective in lowering LA levels, even after a high carbohydrate meal, which often precipitates or exacerbates LA (see figure on the left side of the slide 12). DCA is a potent LA lowering drug and potentially can allow for liberalization of diet in children often treated with the high fat, ketogenic diet. Fats are used as an alternative source of energy given that dumping glucose from carbohydrates into the PDC can give rise to elevated lactate levels. Use of this diet has never been researched for safety and efficacy.
  - After the blind was broken, results of the clinical impression of nurses, neurologists, and pediatricians participating in the study showed that there was no real discernible effect of DCA as compared to placebo (see figure on right side of the slide 12). The tool is limited because there were no clinical measures in place to evaluate children with mitochondrial disease as no such tool as been developed.

- DCA treatment continued as open label therapy, and over the course of time, there was continued lactate lowering effect in blood and CSF, documenting that DCA did not lose effect over time (see left figure on slide 13). Over about a decade a 40% mortality rate was documented, but nearly all the deaths were in the children with the RC defects (see figure on ride side of slide 13). In fact, the top line reflects that only one child with PDCD died during the course of the 10 year follow up, pointing research toward DCA use in PDCD in the future.

**Between a Rock and a Hard Place** (slide 14)

- Scylla
  - Non-patentable molecule because DCA is so simple and has been available for years, so Pharma is not interested.
  - First trial showed no obvious clinical benefit, again hurting Pharma interest.
- Charybdis
  - Rare disease research is very tough to do, tougher to fund, and even more difficult to run clinical trials. Huge geographic nets must be cast to even find study subjects due to the rare nature of the disease and hinders replication of the study. The study above gathered subjects from around the world, including New Zealand.
  - The question of whether researchers should find greener pastures elsewhere with more common issues that would be easier to fund or stick with DCA research becomes the issue at hand. Decision made to continue DCA research.

**Pivotal Trial of DCA in PDCD** (slide 15)

- Trial design - based on previous study and by working with the FDA:
  - Four-year duration, recruiting 24-30 children ages 1 month to 18 years
  - Placebo-controlled
  - Double-blind
  - Crossover trial, followed by open label phase option
    - Each patient is own control
    - All patients receive DCA
    - Randomized
    - Novel survey tool, primarily utilizing parental/guardian home assessments as the primary efficacy tool, called OBSRO measure

**Observer Reported Outcome (OBSRO) Measure** (slide 16):

- Represents a major effort by PDCD parent organizations and FDA.
- Prospectively evaluates how patient feels and functions at home.
- Stipulated by FDA and Primary Efficacy Outcome measure, the results of which may lead to drug approval.
- Novel tool for mitochondrial disease
- Daily assessment of multiple domains, for example: motor, neurological, GI, nutrition, general health, etc. Assessment requires about 5 minutes at the end of every day.
- Uploaded daily by reporting to Data Coordinating Center (DCC) for data management and analysis.
- Patient clinic visits number about 5 over the 10-month crossover period, then every 6 months during the open label phase (months to years).

**Potential Obstacles and Limitations** (slide 17)

- Recognition of conflict within the rare disease professional community about Randomized Controlled Trials (RCTs) because many faced with devastating illnesses in their patients shy away from studies utilizing placebos in lieu of other Mito cocktails or treatments. Yet, those cocktails or treatments become antidotal, never leading to sound results nor approval by the FDA because no rigorous or scientific evaluation exists regarding safety and efficacy. The second slide shows the cofactors needed for normal PDC activity, explaining the rationale behind why these cofactors are a part of the Mito cocktail.
- Funding problem can delay trial and discourage investigators.
- Single center study can limit FDA enthusiasm as multicenter trials are preferred.
- Eligible patients can be lost due to logistics of travel and due to competing trials.
- Small population of PDCD patients require a large and effective catchment net, even internationally.
- Consensus on diagnosis criteria, which can be frustrating, humbling and educational.
- Importance of choosing validated assessment tools, which is especially pressing given that few tools for mitochondrial disease exist.
- Questionable applicability of key outcome measures.

**Applying the Lessons - DCA/PDCD Clinical Trial** (slide 18)

- Evaluation of DCA for PDCD therapy is promising at this time.
- Multicenter study is possible.
- PDCD organizations and collaborative centers around the US are willing to participate in this trial (see map denoting potential locations).
- Medosome Biotec is interested in commercializing DCA genotyping kit. Dosing would be based on this genotyping.

**WE NEED YOUR HELP!** (slide 19)

- **Advocate!**
  -- Families, caregivers - as potential participants in this study
  -- UMDF landing page (www.umdf.org/pdcd)
  -- Private donors are needed for funding
- **Participate!**
  -- Phase III Trial
- **Benefit!**
  -- DCA is/is not safe and effective therapy for PDCD
  -- If FDA approved, DCA could be covered by insurance
  -- Pioneering the first approved drug for any primary (congenital) mitochondrial disease

**Summary** - **Energy is life!** (slide 20)

PDC is a critical enzyme, not a player in only mitochondrial disease, but also a potential player in diabetes, heart disease, pulmonary disease, cancer, and other disorders.

Molecules that stimulate this enzyme, such as DCA, have wide possibilities for both understand disease pathology and intervention.

**Additional Reading**

NIH Public Access: The spectrum of pyruvate dehydrogenase complex deficiency: Clinical, Biochemical and Genetic features in 371 Patients. Patela, K.P., Stacpoole, P.W.

Nord: PCCD

Therapeutic Potential of Dichloroacetate for Pyruvate Dehydrogenase Complex Deficiency. Berendzen, K., Stacpoole, PW.

UMDF

For more trial information contact Dr. Stacpoole at psw@ufl.edu