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Carmel Diagnostics – Biomarker discovery for Neurodegenerative diseases

Carmel diagnostics is interested in participating as partner in IMI2 - Call 23: ***Accelerating biomarker discovery to support therapeutics development for neurodegenerative diseases.*** Carmel developed a system that measures Oxidative Stress **(OS)** and Oxidizability in body fluids. **OS** plays a major role in the pathogenesis of Neurodegenerative diseases.

TCL – A tool for using OS as biomarker

TCL holds the potential to play a clinically meaningful role as a diagnostic and prognostic marker in those disease states where OS is known to play a key role, including **neurodegenerative diseases**, autoimmune disorders, and diseases with abnormalities of O_2 supply and utilization.

Measuring OS—Current Limitations

It is generally accepted that many diseases are the result of cellular deterioration due to molecules called free radicals. Free-radical damage is known as Oxidative Stress (OS), and when measured effectively OS can serve as a diagnostic and prognostic biomarker of disease progression and severity. Studies indicate that OS is of central importance in: 1) **neurodegenerative diseases**, 2) inflammatory states such as infection, arthritis and heart failure, 3) diseases in which oxygen delivery is impaired, such as heart attack, stroke, sepsis and heart failure, 4) disease characterized by abnormal stress responses, such as PTSD. Free radicals, which are the source of OS, are believed to play a role in a wide variety of human diseases ranging from heart disease, **neurodegenerative diseases (NGD)** and even the normal aging process. However, a major obstacle in translating these hypotheses to clinically useful tools has been the lack of a reliable approach to assess OS status (OS status is sometimes known as the "redox state"). This is because most methods to measure OS lack specificity and/or sensitivity, are too slow, expensive or complicated, or are too invasive for human investigation.
Carmel Diagnostics developed and validated novel non-invasive and minimally invasive assays that are based on the measurement of OS in blood, cerebrospinal fluid (CSF), tears and other biologic and organic fluids and materials using a patented process known as *thermochemiluminescence* (TCL). The assay runs on the Company's proprietary, patented platform technology known as the TCL Analyzer™. In stark contrast to existing assays for OS that target a single source or particular molecule, TCL analyzes systemic levels of OS, providing critical information about disease status. In short, TCL and the TCL Analyzer ™ are game changers, being the first and only tool available to make OS a useful biomarker.

Neurodegenerative diseases (NGD) and OS: Oxidative molecular damage has been broadly implicated in the pathogenesis of Alzheimer's, Parkinson, ALS and Huntington. Patients with

those diseases have associated oxidative molecular damage in the brain, and many peripheral tissues, including blood leukocytes, serum, and plasma. Indices of oxidative substrate damage, such as F2-isoprostanes, 8-hydroxy-2-deoxyguanosine (8-OHdG) and 4-hydroxynonenal (4-HNE), are augmented in NGD patients' blood relative to control values.

Measurement of OS in Human Biofluids: An Unmet Medical Challenge

The above examples clearly illustrate a clinical need for improved methodologies to detect and monitor OS in human biofluids and tissues in the context of NGD and inflammation. Current methods involve measurement of specific analytes accruing from ROS-mediated modifications of lipids, proteins and nucleic acids and/or determining the status of enzymatic and low-molecular weight antioxidant compounds. The latter often invoke complex, labor-intensive and expensive apparati such as HPLC-EC, mass spectrometry, gas chromatography and multi-enzyme biochemical assays. **The advent of an accurate, reliable, rapid, minimally invasive, high-throughput and inexpensive method to achieve these objectives would represent an important breakthrough in the clinical evaluation of redox homeostasis and oxidative tissue damage in human NGD and inflammation**. It **would facilitate strategies to ameliorate ROS-mediated injury in various stages of the NGD process.** As described below, TCL fulfils many of the criteria for an ideal probe of OS in human blood and other biofluids.

Thermochemiluminescence (TCL) - Technology

The detection of electronically excited species (EES) in body fluids by TCL may provide an important diagnostic and prognostic tool in the management of diverse human pathological conditions. Examples of EES are triplet excited carbonyls (TEC) derived from lipid and protein components which emit photons detectable by TCL during the heating of biological fluids. The corresponding TCL curves can be used as sensitive and reproducible kinetic models for measuring the magnitude and duration of oxidative processes in minute samples of human biofluids.

The TCL assay is performed using a desktop-sized, robust and easy to use platform that has been engineered with Carmel Diagnostics' proprietary mechanical, photometric and bioinformatic technology. Single use, disposable cuvettes are filled with 50 microliters of serum plasma, CSF, tears or other biologic fluid. This procedure takes about 8 minutes per sample to complete. The device is suitable for routine laboratory use or point-of-care applications and has been successfully employed by Carmel Diagnostics' clinicians and scientists as a rapid, cost-effective and minimally invasive (venipuncture) method for the determination of the OS status in patients with heart failure as well as for Embryo Selection in IVF process. (peer reviewed articles are available). TCL is an in-vitro diagnostic device (IVD); more specifically, it is a molecular diagnostic assay. TCL is unique among IVDs as it possesses characteristics of both chemical and non-chemical markers. Because TCL is

measuring a condition, or state, that is ubiquitous in biologic processes (i.e., OS and oxidation), it is detectable in almost any disease state and in virtually all biologic fluids and materials. However, because there are variations among the OS profiles of different disease states, the OS profile can be used to make distinctions within and among various disease states. In the case of NGD, **the application of TCL as a probe for relatively simple, real-time monitoring of oxidative substrate damage in human fluids would constitute a quantum leap forward from the complex ascertainment of multiple oxidatively-modified chemical targets and enzyme activities. The sensitivity, reliability and user-friendliness of TCL would assure that redox perturbations potentially worsening inflammation in a host of acute and chronic human afflictions, would be detected at the earliest stages permitting timely and effective therapeutic interventions. The ease with which TCL can be applied in these conditions might also provide important prognostic information and facilitate the evaluation of novel pharmaceuticals in clinical trials.**

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