

OAK RIDGE ASSOCIATED UNIVERSITIES

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT NO. ORAU91-0002

INITIAL ABSTRACT

REGIONAL NEONATAL ASSOCIATES FOR

COOPERATIVE STUDY OF PLATELET-ACTIVATING FACTOR (PAF)

Oak Ridge Associated Universities, Inc. (ORAU) and Regional Neonatal Associates (RNA) will collaborate to combine ORAU's research on the platelet-activating factor (PAF) and RNA's research involving the treatment of Hyaline membrane disease.

The purpose of the research is to obtain preliminary information which can be used to develop an application for funding from a federal agency for a complete study which, if funded, will be a collaborative effort between investigators at ORAU and RNA.

Scientists at the two facilities will obtain biological materials, specifically pulmonary lavage fluids and blood from preterm infants with respiratory disease, and undertake a study of the role of PAF on the pulmonary surfactant. RNA will be responsible for obtaining approval from the Human Use Committee at the University of Tennessee Medical Center in Knoxville and for the identification of infants to be used in the study and the collection of materials. ORAU will be responsible for transporting the materials to the Medical Sciences Division laboratories and performing the technical analysis. RNA will also document that all required institutional review board assurances and reviews have been obtained by the Hospital for the clinical protocol to support this research collaboration. It is agreed that the research under this agreement will be on the biological materials and not the infants.

The study will be the beginning of an increased understanding of the causes and treatments of Hyaline Membrane Disease on preterm infants. If expanded into further study, the results could lead to improved protocols for dealing with preterm infants with a wide range of respiratory distress. In addition to the basic scientific knowledge which will accrue from the study, this project offers an excellent opportunity to apply the gains in cellular biology and specifically PAF acquired from years of DOE-supported research to a practical medical need.

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Summary Report for Cooperative Research
and Development Agreement

(CRADA ORAU 91-0002)

Fred Snyder

Lipid inflammatory mediators are thought to play an important role in the pathogenesis of the respiratory distress syndrome, including neonatal lung injury and bronchopulmonary dysplasia (BPD). One such mediator is platelet-activating factor (PAF), a potent bioactive phospholipid that induces adverse airway, vascular, and microcirculatory responses. To study the role of PAF in neonatal lung disease, we used an ¹²⁵I-radioimmunoassay to measure PAF in whole blood and tracheal lavage in 22 ventilated, very low birthweight infants at 1, 3, 5, 9, 21 and 28 days after birth. Infants developing BPD were significantly smaller and of younger gestational age. PAF was found in the pulmonary lavage and blood of ventilated infants as early as one day after birth. Blood PAF levels rose linearly from 3-21 days after birth in those infants developing BPD and was significantly increased in comparison to babies with BPD at 1-5 days after birth and to those without BPD three weeks after birth. Lavage levels of PAF increased with acute injury (pneumothorax, pneumonia) but were not associated with BPD. Our results indicate PAF could be associated with the pathogenesis of BPD.

We suggest that as a consequence of the pathophysiologic processes associated with BPD (hypoxia, barotrauma and inflammation), PAF is released by pulmonary cells. Our preliminary data indicate that low birthweight infants also have lower PAF acetylhydrolase levels in cord blood and tracheal lavage as compared to adults. Therefore, it is possible the increased levels of PAF in the blood of low birthweight infants might be due to persistent transient increases in PAF alveolar levels ("PAF spikes") coupled with lower blood acetylhydrolase activities and could be important in the development of symptoms associated with BPD.

Future plans for this project call for completing the enzymatic study of acetylhydrolase activity in pulmonary lavage of the BPD infants. Because of the limited funds available for this pilot study, we do not expect the statistical analysis of the

enzymatic results and correlation with clinical parameters to be completed until later this year. It is hoped that at some future time some of this preliminary information will be useful in preparing a proposal for substantial funding of this project. The results of this research is relevant to DOE-sponsored work at ORAU that pertains to respiratory distress during lung injury.

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