

[REDACTED] [REDACTED]

Title: Phototoxicity of drugs and nanoparticles in the human eye

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Abstract

If awarded, a Faculty Research Grant would enable me to capitalize on a peer-reviewed invitation to conduct research this summer in collaboration with my two post-doctoral fellows (Albert Wielgus, Ph.D. and Baozhong Zhao, Ph.D) at the National Institutes of Environmental Health Sciences (NIEHS), a North Carolina located unit of the National Institute of Health (NIH). Fordham's support is critical for five reasons:

- (i) I do not have laboratory space at Fordham, and this type of collaboration is essential if I am to access the multimillion dollar photophysical equipment and human ocular tissues my research requires;
- (ii) Due to the untimely death of the PI (Colin Chignell, July 2008) at the NIEHS' Photobiology laboratory, I have become the scientific head of this laboratory, requiring my presence as current titular PI for the successful completion of the projects that are the subject of this proposal;
- (iii) Due to Federal budget cuts, in 2010 the NIEHS will not be able to cover my costs of travel and stay at their facility as in past years, and I will also have to cover some of my cost of supplies;
- (iv) The NIEHS has, however, donated HPLC [High Pressure Liquid Chromatogram] equipment with fluorescence detectors (valued at \$20,000) to Fordham's Department of

Natural Sciences through my initiative, the cost for packing and shipping of which would also be covered under this grant;

(v) In addition to the two scholarly articles I intend to produce from this summer's research for submission [Toxicology and Applied Pharmacology, Photochemistry Phtobiology]the NIEHS also anticipates making external grants available in my area of "nanosafety" for 2011-12, for which my work at their facility this summer will place me in an advantageous position.

Background

Everyone over the age of 65 is susceptible to developing cataracts and macular degeneration. In the next 30 years over 24 % of the population of the United States will be over the age of 65 and are therefore at risk for these blinding disorders. Although sight may be restored by an operation to remove cataracts, there is currently no effective treatment for retinal or macular degeneration. My ongoing research is to identify environmental risk factors that lead to these age-related blinding diseases and examine ways to prevent such damage. In addition to environmental hazards, there are dyes, drugs, over the counter medications and nanoparticles that can dramatically enhance phototoxic reactions in the human eye leading to early development (i.e., at 40 years old) of cataracts and macular or retinal degeneration.

The NIEHS facility at which I have been conducting this research for the past 12 years is a multidisciplinary lab that allows me access to multimillion dollar laser and photochemical equipment. During the summer of 2008 and my Spring 2009 Faculty Fellowship I developed at NIEHS an *in vitro* system using human lens epithelial cells to define phototoxic properties of nanoparticles with potential to damage the human lens.

(Phototoxicity and cytotoxicity of fullerol in human lens epithelial cells. Roberts JE, Wielgus AR, Boyes WK, Andley U, Chignell CF. Toxicology and Applied Pharmacology 2008 Apr 1;228(1):49-58.

In previous years at NIEHS, I have proven that ocular exposure to UVA and UVB (lens) or Visible blue light (430 nm) (retina) alone or in the presence of drugs or herbs (St. John's Wort) increases the human risk for developing cataracts and retinal degeneraton

(Wielgus AR, Chignell CF, Miller DS, Van Houten B, Meyer J, Hu DN, Roberts JE. Phototoxicity in Human Retinal Epithelial Cells Promoted by Hypericin, a Component of St. John's Wort. Photochem Photobiol. (2007) 83(3):706-13)

Summer 2010 I will investigate how nanoparticles (fullerols), used for drug delivery to the eye, may cause very early retinal degeneration. I am also examining the potential for fluoroquinolone (i.e. cipro) antibiotics to cause early damage to the human lens. The final purpose of my research is to remove, modify or quench these toxic agents in order to prevent the formation of early or late onset cataracts and macular degeneration. These *in vitro* experiments are currently in progress and are expected to be completed by September 2010.

Contribution

Cataracts and age-related macular degeneration (AMD) are the most common causes of visual impairment in the elderly. Although there is a genetic component to these blinding disorders, clinical and epidemiology studies have confirmed that environmental hazards (sunlight, phototoxic drugs and herbal medications) are major risk factors in initiating cataracts and AMD. All of these environmental hazards induce the formation of free radicals and reactive oxygen species (ROS) in the eye. The aged eye has limited protection against

free radicals and ROS, thus environmental hazards can put older people at severe risk of serious ocular damage. I have modeled this synergistic effect between environmental hazards and age by studying the interaction of sunlight with endogenous photoactive substances (xanthurenic acid, lipofuscin, A2E) whose production increases dramatically with age.

I have previously defined the damage to human ocular tissues induced by the endogenous agents. I am now defining the ocular damage induced by exogenous agents using *in vitro* and photophysical techniques. The ultimate goal is to develop appropriate strategies to ameliorate or prevent age related, environmental, drug and nanoparticle induced cataracts and macular or retinal degeneration.

Specifically, before attempting to define the effect of photoprocesses on biological systems, it is essential to get precise information about wavelength, photochemical yields/reaction rates, and biological targets. Mechanisms may be further defined through examination of the effects on the target molecules in live cells. This knowledge will facilitate risk assessment in humans and promote development of more sensitive ways to measure and screen for damage in individuals and in populations. Furthermore, once the mechanisms of damage are known, phototoxic agents can be modified to inhibit detrimental processes or to improve the efficacy of beneficial reactions.

Consequently, my research involves a multidisciplinary approach:

1) *in vitro*:

i. Models for Cataract formation Human Lens Epithelial Cells:

An *in vitro* model system (using human lens epithelial cells from human eyes) has been set up to determine potential phototoxicity of fluoroquinolone antibiotics and demonstrate specific damage end points (oxidative DNA damage, lipid peroxidation, apoptosis/necrosis, membrane damage, mitochondrial damage).

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Cataracts and age-related macular degeneration (AMD) are the most common causes of visual impairment in the elderly. In the next 30 years over 24 % of the population of the United States will be over the age of 65 and are therefore at risk for these blinding disorders. As stated at the outset of this proposal, not only will a Fordham Faculty Research Grant prove pivotal in supporting my longstanding line of research during a critical juncture in its funding, bring needed resources to the University, and provide a platform for future external support, it will prevent interruption of work that is already proving integral to our fight to preserve the sight of millions of Americans.

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