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TITLE: Dietary Genistein and Prostate Cancer Chemoprevention

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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The disease of cancer is usually attacked at time of diagnosis, and even chemoprevention is not usually considered until adulthood. Our hypothesis is that windows of development hold the key for chemoprevention of prostate cancer. We have previously demonstrated that genistein is bioavailable to the rat prostate and that life-time exposure to physiological concentrations of genistein suppressed the development of chemically-induced prostate cancer. The purpose of our research is to determine if there is a developmental window for this chemoprevention and the mechanism (s) of chemoprevention. The importance of this lies in the need to know, prior to initiation of human trials, if we need to expose infants and/or adults to get maximum chemoprevention. We have proposed to accomplish this in a dietary model at "physiological concentrations". To date, we have demonstrated that neonatal and prepubertal exposure to genistein via the diet does not alter development of the prostate buds in 21 and 35 day old rats. Chemoprevention experiments are in progress to determine the critical period of exposure for protection against chemically-induced prostate cancer in rats.

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Introduction

The disease of cancer is usually attacked at time of diagnosis, and even chemoprevention is not usually considered until adulthood. Our **hypothesis** is that windows of development hold the key for chemoprevention of prostate cancer. We have previously demonstrated that life-time exposure to physiological concentrations of genistein suppressed the development of chemically-induced prostate cancer. We have shown that genistein is bioavailable to the prostate. We have also demonstrated that genistein did not readily cross the placenta, hence we don't believe that the gestational period plays a significant role in the protective effect. On the other hand, it is primarily during the first weeks of postnatal life that prostate differentiation takes place, a period that may be influenced by genistein. The purpose of our proposed research is to determine if there is a developmental window for this chemoprevention and the mechanism (s) of chemoprevention. The importance of this lies in the need to know, prior to initiation of human trials, if we need to expose infants and/or adults to get maximum chemoprevention. We propose to accomplish this in a dietary model at "physiological concentrations".

Body

Aim 1. To determine if a specific window of development (prepubertal only, adult only or life-time) is responsible for genistein chemoprevention of prostate cancer. This will be done on the following groups of rats.
Group A) genistein via the diet from birth throughout life to confirm that postnatal lifetime exposure only protects against prostate cancer.
Group B) genistein in the diet from birth until 35 days of age only.
Group C) genistein in the diet starting at 90 days of age, 20 days after cancer initiation.
Group D) no genistein in the diet as positive controls.

This was to be initiated in the first year and to be completed in the second year. The breeders were purchased, the rats bred, treated with the carcinogenesis protocol, and exposed to genistein in the diet as listed above. The rats will be necropsied and the histopathology evaluations carried out in year 2.

Aim 2. To investigate prostate gland morphology in the dorsal and lateral lobes of the prostates of 21 and 35 day old rats exposed ± genistein in the diet, starting at birth. Months 6-12. This work is complete.

Prostate Bud Perimeter (mm) in 21 Day Old Male Rats*

	DP	LP1	LP2
Control	0.65 ± 0.01	0.67 ± 0.02	0.61 ± 0.02
Genistein	0.66 ± 0.02	0.61 ± 0.02	0.60 ± 0.02

Prostate Bud Perimeter (mm) in 35 Day Old Male Rats*

	DP	LP1	LP2
Control	1.13 ± 0.03	1.15 ± 0.04	1.05 ± 0.03
Genistein	1.14 ± 0.03	1.15 ± 0.03	0.97 ± 0.02

*These 21 and 35 day old rats were exposed to 250 mg genistein/kg AIN-76A diet, starting at birth. DP: dorsal prostate; LP1: lateral prostate lobe 1; LP2: lateral prostate lobe 2. No statistical significance was detected for prostate bud perimeter from genistein compared to control treated rats.

These data demonstrate that neonatal/prepubertal genistein in the diet does not alter prostate gland development. The significance of this will be revealed with the chemoprevention data (Specific Aim 1). Should we get prostate cancer chemoprevention with neonatal/prepubertal genistein exposure, this will suggest that genistein is not altering prostate gland development as the cellular mechanism of chemoprevention.

Aim 3. To investigate the potential of genistein to regulate sex steroid receptor expression as mechanism of prostate cancer prevention. This is to be carried out during year 2. This work is already in progress.

Aim 4. To investigate DNA methylation of AR, ER alpha and ER beta as imprinting mechanism of action. This is to be carried out during year 3.

Key Research Accomplishments

Dietary genistein given during the neonatal and prepubertal periods did not alter cellular morphology of prostate development in 21 and 35 day old rats.

Reportable Outcomes

None.

Request for Modification

Budget: Ms. Natalie Durr has been the primary technician on this project, but she is leaving in August for pharmacy school. We intend to hire Mr. Glen Puckett as replacement for animal care and to assist with biological assays. Drs. Nadejda Lopatina and Jun Wang (25% each) will assist with necropsy, processing of tissues/tumors, and measurement of sex steroid receptor expression in the rat prostate. Dr. Eltoum's percent effort (10%) remains the same for histopathology. Dr. Lamartiniere's percent effort will be decreased to 15% effort to accommodate the budget. However, this will not compromise the work, especially with the addition of Dr. Lopatina to the project and the increased effort of Dr. Wang. The total personnel and fringe budget remains the same, as does the total direct cost. I am enclosing a detailed second year budget that has same totals as the original budget. Also, enclosed is a copy of Dr. Lopatina's biographical sketch.

Conclusion

Neonatal/prepubertal genistein in the diet does not alter prostate bud perimeter in 21 and 35 day old rats. This demonstrates that genistein is not capable of altering developmental of the rat prostate.

The work of Aim 2 is complete. Data from Aims 1 and 3 are expected in year 2. The work of this grant is progressing as outlined in the Statement of Work.

Appendices

The biographical sketch of Dr. Lopatina is enclosed.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Nadejda Lopatina	Research Instructor in Pharmacology and Toxicology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Moscow State University, Moscow, Russia	M.S.	1974	Virology
Academy of Medical Sciences, Institute of Biomedical Chemistry. Moscow, Russia	Ph.D.	1980	Biochemistry

A. Positions and Honors.

1974-1976: Research Associate, Institute of Biomedical Chemistry, Moscow, Russia,
1976-1990: Research Scientist, Biomedical Chemistry, Moscow, Russia
1990-1994: Senior Research Scientist, Institute of Biomedical Chemistry, Moscow, Russia,
1994-1997: Visiting Scientist, National Center for Toxicological Research, Jefferson, AR
1997-1998: Research Associate, UAMS Little Rock, AR,
1998-1999: Visiting Scientist, National Center for Toxicological Research, Jefferson, AR,
2001-2003: Associate, Center for Aging and Biology Department, University of Alabama at Birmingham, Birmingham, AL
2003-present: Research Instructor, Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL

B. Selected peer-reviewed publications (in chronological order).

Lopatina NG, Suchkov SV, Kulikov SM, Nikolskaya II and Debov SS. Site specificity of isolated DNA-cytosine methyltransferases from Shigella sonnei 47 cells. Biokhimiya 1985;50(10):1691-1700. (Russian).

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C. Research Support.

None