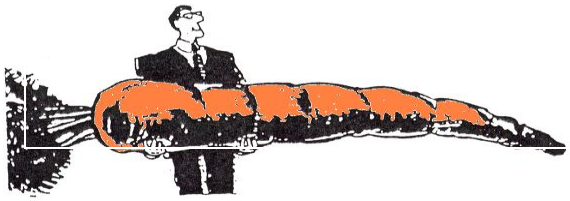

Carotenoid & Retinoid News

May 2019
Vol. 28, No. 1

CARIG EVENTS AT ASN

Several upcoming CARIG sponsored events will be held at Nutrition 2019 in Baltimore, MD. The CARIG 2019 symposium will take place at 1:00 pm on June 7, 2019, Friday afternoon, before the Saturday opening of the Nutrition 2019 program. The title is "**Carotenoids and Vitamin A for Pregnancy, Lactation, and Early Life Nutrition: New Findings and Considerations for Dietary Guidelines**" (organized by Nancy Moran and Elizabeth Johnson).

The Symposium will be held in rooms 314/315 and open at 1:00 with an introduction, followed by the Olson Lecturer A. Catharine Ross, PhD who will speak on "**Carotenoid and Vitamin A DRIs for Pregnancy and Early Life - What Comes Next and Special Considerations"** from 1:15- 2:00 pm.

The following field experts will also be presenting during the symposium:

2:00 - 2:30 **Prenatal:** Loredana Quadro, PhD- Novel roles for apo-carotenoids during prenatal development.

3:00 – 3:30 **Infant Feeding:** Mario Ferruzzi, PhD- Carotenoids and vitamin A in human milk and bioavailability differences between human milk and infant formula

3:30- 4:00 **Infant Development:** Carol Cheatham, PhD- Novel roles of carotenoids in cognitive development.

4:00 - 4:30 **Metabolism in Lactation and in Toddlers:** Veronica Lopez-Teros, PhD- How mathematical modeling of carotenoid and vitamin A metabolism in mothers and children can be used to define their nutritional needs.

4:30 - 5:00 **Q&A, Panel Discussion:** The next frontiers in studying carotenoids and vitamin A in pregnancy, lactation, and the first 24 months of life.

We will also have a business meeting (5:30 pm) and a CARIG trainee poster competition and award session (6:30-8:30 pm) during the annual social following the CARIG Conference.

We would like to thank **Abbott Nutrition, Amway/Nutrilite, Kemin, Hass Avocado Board,** and **ZeaVision** for their generous support of the 2019 CARIG symposium.

We encourage attendance at the CARIG sponsored or co-sponsored Oral/Poster sessions during the Nutrition 2019 conference. These sessions include:

6/8 1:00 - 3:00 Oral Session (OR05) Carotenoids and Retinoids: From Mechanisms to Human Health (I)

6/9 8:00 - 5:00 Poster Session: Carotenoids and Retinoids

6/9 10:00 - 11:30 Poster Theater Flash Session (FS06) Carotenoids and Retinoids: From Mechanisms to Human Health (II)

6/10 8:00 - 2:45 Poster Session: Neuroscience, Cognitive Function and Chronobiology

6/11 10:30- 12:30 Oral Session (OR32) Nutritional Effects on Brain, Cognition, and Chronobiology

CARIG Travel Awards!

CARIG will award at least two monetary prizes, based on a poster competition to be held in conjunction with the CARIG reception at Nutrition 2019 on Friday, June 7, 2019. Graduate, undergraduate, and postdoctoral trainees are eligible. Posters must address carotenoid and/or vitamin A research. For those assigned an oral presentation rather than a poster at Nutrition 2019, printed copies of your slides with a print copy of your abstract and a small banner may be used for the CARIG poster competition. No advance registration is required to participate in the poster competition. Contact: Nancy Moran (Nancy.Moran@bcm.edu).

STUDENT SPOTLIGHT

Ambria Crusan, PhD Student University of Minnesota.
Ambria is a third year PhD student working under Dr. Susan Raatz. Her work focuses on carotenoids and adiposity, specifically on inflammation and post-consumption factors that attenuate carotenoid concentrations in serum. She is also a Registered Dietitian and mom to a 4 month old. She is a co-Student Representative for the year 2018-2019 and excited for the CARIG symposium at Nutrition 2019!

UPCOMING EVENTS

June 7, 2019: **CARIG Annual Symposium, Nutrition 2019, Baltimore, MD.**
Contact**:** Nancy Moran, CARIG RIS Chair, Email: Nancy.Moran@bcm.edu

American Society for Nutrition
Excellence in Nutrition Research and Practice
NUTRITION 2019
Where the Best in Science & Health Meet
JUNE 8 - 11, 2019 | BALTIMORE, MARYLAND

Website: http://meeting.nutrition.org/

EUROCAROTEN

November 26-29, 2019: **International Conference on Carotenoid Research and Applications in Agro-Food and Health (EUROCAROTEN COST FINAL MEETING), Lemesos, Cyprus.**
Website: https://www.eurocaroten.eu/?q=lemesos2019

July 12-17, 2020: **19th International Symposium on Carotenoids, Toyama, Japan**

The 19th International Symposium on Carotenoids
12-17 July, 2020 Toyama, Japan

Website: http://www.carotenoid.org/index.html

SAVE THE DATE!

June 14-19, 2020: **FASEB**
The 5th International Conference on
Retinoids:
New Developments in Basic Science & Translational Applications
Loews Ventana Resort, Tucson, AZ, USA
Website: www.faseb.org/src

July 5-7, 2021: **Brain and Ocular Nutrition 2021, Cambridge, UK.** Website**:** www.bonconference.org

2021 (Date TBD Jan-March): **The 11th Gordon Research Conference on Carotenoids.**

FORTHCOMING / RECENT MEDIA

EUROCAROTEN
https://www.cost.eu/actions/CA15136/#tabs|Name:overview Is developing a series of non-technical videos about carotenoids. The videos have subtitles available in many languages and the target audience is the general public.
https://www.youtube.com/watch?v=I3cXnznY7X8

SIGHT AND LIFE Magazine: Double Burden of Malnutrition, December 10, 2018. PO Box 2116, 4002 Basel, Switzerland, tel: 41-61-815-8756, Website**:** www.sightandlife.org

Calling for Proposals!
Special CARIG Collection for ASN's *Current Developments in Nutrition* journal

Current Developments in Nutrition has asked CARIG to propose a special CARIG-themed collection of articles to publish in their journal. CARIG may submit one proposal.
Please contact the current CARIG Chair, Nancy E. Moran, PhD (nancy.moran@bcm.edu), with your ideas! **Proposals are due to CDN on September 13, 2019.** Decisions will be made by September 30th. CDN expects to help fund 5-6 proposals. The top-rated proposal will qualify for 100% waiver of open access publication fees. Other proposals may receive 25–50% discounts in article processing charges beyond standard member rates. Selection criteria will include timeliness of the topic, quality of the proposed papers, alignment with CDN scope, and credentials of the guest editor. The general expectation is that each collection would contain 4–8 papers that could include a combination of review papers and original research papers. Peer-review of manuscripts would be chaperoned by a Guest Editor nominated by the RIS group.

HIGHLIGHTED ONGOING FEEDING TRIALS

As the benefits of carotenoid and retinoid consumption receive increased mainstream attention, dietitians and consumers alike find themselves seeking ways to increase consumption. CARIG Researchers have responded - with a number of human feeding trials currently being conducted throughout the society. Dr. Naiman Khan's Body Composition and Nutritional Neuroscience Laboratory Group at the University of Illinois at Urbana-Champaign currently has 2 ongoing feeding trials aimed at studying the impact of carotenoid supplementation through whole food sources. Look for these studies to be presented at various ASN 2019 CARIG sponsored sessions!

Persea Americana for Total Health (PATH) Study

(Clinical Trial: NCT02740439)
Participants receive a daily meal for 12-weeks either containing one HASS avocado, or an isocaloric and macronutrient matched control meal. Outcomes include the impact of avocado intake on measures of macular pigmentation, serum carotenoid status, and subsequent measures of cognitive function.

Studying How to Elevate Lutein and Learning (SHELL) Study

(Clinical Trial: NCT03521349)
Child participants (ages 7-12) receive 2 daily muffins for 4-weeks either containing whole egg, or an isocaloric and macronutrient matched egg white muffin. Outcomes include the impact of egg yolk intake on measures of macular pigmentation and subsequent measures of cognitive function.

HIGHLIGHTED NEW RESEARCH

Duration of Retinol Isotope Dilution Studies with Compartmental Modeling Affects Model Complexity, Kinetic Parameters, and Calculated Vitamin A Stores in US Women

Retinol isotope dilution (RID) indirectly estimates vitamin A (VA) status. Multicompartment modeling of RID data is used to refine study designs and equations to calculate VA stores. Previous studies suggest that VA in slowly turning over pools is not traced if follow-up is not long enough; however, shorter RID studies are being investigated. Few long-term models have been published. We determined the effect of time on mathematical models of VA kinetics, model parameters, and outcomes. In this longitudinal study, women were given 2.0 μmol [14,15]-$^{13}C_2$-retinyl acetate. Blood samples were staggered from 4h to 152d; the fraction of dose in serum was modeled with compartmental models. Four model-time categories were created: full models that used all data and truncated shorter studies of 14, 27, and 52 d. Outcomes included number of compartments to adequately model serum data, kinetic parameters, total traced VA mass, and time-to-dose equilibration. To gain insight into longer follow-up, an additional participant was given 17.5 μmol $^{13}C_4$-VA, and data were modeled as long as enrichment was above baseline (5 y). Longer follow-up times affected kinetic parameters and outcomes. Compared with the 14-d models, long-term full models required an additional compartment for adequate and had whole-body half- compared with 135 d, time-to-dose equilibration compared with 18.9 d, and total traced mass compared with 476 μmol VA. Extended RID sampling alters numerous mathematically modeled, time-dependent outcomes in women. Length of study should be considered when using mathematical models for calculating total-body VA stores or kinetic parameters related to VA turnover.

Gannon BM, et al.
J Nutr, 148(8):1387-1396 (2018)

Retinoids induce antagonism between FOXO3A and FOXM1 transcription factors in human oral squamous cell carcinoma (OSCC) cells.

To gain a greater understanding of oral squamous cell carcinoma (OSCC) we investigated the actions of all-trans-retinoic acid (RA; a retinoid), bexarotene (a pan-RXR agonist), and forkhead box (FOX) transcription factors in human OSCC-derived cell lines. RA and bexarotene have been shown to limit several oncogenic pathways in many cell types. FOXO proteins typically are associated with tumor

suppressive activities, whereas FOXM1 acts as an oncogene when overexpressed in several cancers. RA and/or bexarotene increased the transcript levels of FOXO1, FOXO3A, and TRAIL receptors; reduced the transcript levels of FOXM1, Aurora kinase B, and vascular endothelial growth factor A; and decreased the proliferation of OSCC-derived cell lines. Also, RA and/or bexarotene influenced the recruitment of FOXO3A and FOXM1 to target genes. Additionally, FOXM1 depletion reduced cell proliferation, decreased transcript levels of downstream targets of FOXM1, and increased transcript levels of TRAIL receptors. Overexpression of FOXO3A decreased proliferation and increased binding of histone deacetylases 1 and 2 at the FOXM1, AURKB, and VEGFA promoters. This research suggests novel influences of the drugs RA and bexarotene on the expression of FOXM1 and FOXO3A in transcriptional regulatory pathways of human OSCC.

Osei-Sarfo K, Gudas LJ
PLoS One, 14(4):epub (2019)

Dietary vitamin and carotenoid intake and risk of age-related cataract.

Existing studies suggest that dietary vitamins and carotenoids might be associated with a reduced risk of age-related cataract (ARC), although a quantitative summary of these associations is lacking. The aim of this study was to conduct a meta-analysis of randomized controlled trials (RCTs) and cohort studies of dietary vitamin and carotenoid intake and ARC rise. The adjusted RRs and corresponding 95% CIs for the associations of interest in each study were extracted to calculate pooled estimates. Dose-response relations were assessed with the use of generalized least-squares trend estimation. We included 8 RCTs and 12 cohort studies in the meta-analysis. Most vitamins and carotenoids were significantly associated with reduced risk of ARC in the cohort studies, including vitamin A, vitamin C, vitamin E, β-carotene, and lutein or zeaxanthin. In RCTs, vitamin E or β-carotene intervention did not reduce the risk of ARC significantly compared with the placebo group. Further dose-response analysis indicated that in cohort studies the risk of ARC significantly decreased by 26% for every 10-mg/d increase in lutein or zeaxanthin intake by 18% for each 500-mg/d increase in vitamin C intake by 8% for each 5-mg/d increase in β-carotene intake and by 6% for every 5 mg/d increase in vitamin A intake. Higher consumption of certain vitamins and carotenoids was associated with a significant decreased risk of ARC in cohort studies, but evidence from RCTs is less clear.

Jiang H, et al.
Am J Clin Nutr, 109(1):43-54 (2019)

Quantification of Lutein + Zeaxanthin Presence in Human Placenta and Correlations with Blood Levels and Maternal Dietary Intake

Lutein + zeaxanthin (L + Z) are carotenoids recognized in eye health, but less is known about their status during pregnancy. While quantified in maternal and umbilical cord blood, they have never been analyzed in placenta. The purpose of this study is to quantify combined L + Z concentrations in human placenta and correlate with levels in maternal dietary intake, maternal serum, and umbilical cord blood. The proportions of combined L + Z were compared within diet, placenta, maternal serum, and umbilical cord blood among additional carotenoids (lycopene, β-cryptoxanthin, α-carotene, and β-carotene). This Institutional Review Board approved cross-sectional study enrolled 82 mother-infant pairs. Placenta, maternal serum, and umbilical cord blood samples were analyzed for carotenoids concentrations. Mothers completed a food frequency questionnaire and demographic/birth outcome data were collected. L + Z were present in placenta, median 0.105 micrograms/gram (mcg/g) and were significantly correlated with maternal serum ($r = 0.57$; $p < 0.001$), umbilical cord blood levels ($r = 0.49$; $p = 0.001$), but not dietary intake ($p = 0.110$). L + Z were the most prevalent in placenta (49.1%) umbilical cord blood (37.0%), but not maternal serum (18.6%) or dietary intake (19.4%). Rate of transfer was 16.0%, the highest of all carotenoids. Conclusively, L + Z were identified as the two most prevalent in placenta. Results highlight unique roles L + Z may play during pregnancy.

Thoene, M, et al.
Nutrients, 11(134): 1-12 (2019)

The effects of lutein and zeaxanthin on resting functional connectivity in older Caucasian adults: a randomized controlled trial

The carotenoids lutein (L) and zeaxanthin (Z) accumulate in retinal regions of the eye and have long been shown to benefit visual health. A growing literature suggests cognitive benefits as well, particularly in older adults. The present randomized controlled trial sought to investigate the effects of L and Z on brain function using resting state functional magnetic resonance imaging (fMRI). It was hypothesized that L and Z supplementation would (1) improve *intra*-network integrity of default mode network (DMN) and (2) reduce *inter*-network connectivity between DMN and other resting state networks. 48 community-dwelling older adults (mean age = 72 years) were randomly assigned to receive a daily L (10 mg) and Z (2 mg) supplement

or a placebo for 1 year. Resting state fMRI data were acquired at baseline and post-intervention. A dictionary learning and sparse coding computational framework, based on machine learning principles, was used to investigate intervention-related changes in functional connectivity. DMN integrity was evaluated by calculating spatial overlap rate with a well-established DMN template provided in the neuroscience literature. *Inter*-network connectivity was evaluated via time series correlations between DMN and nine other resting state networks. Contrary to expectation, results indicated that L and Z significantly increased rather than decreased *inter*-network connectivity (Cohen's $d = 0.89$). A significant *intra*-network effect on DMN integrity was not observed. Rather than restoring what has been described in the available literature as a "youth-like" pattern of intrinsic brain activity, L and Z may facilitate the aging brain's capacity for compensation by enhancing integration between networks that tend to be functionally segregated earlier in the lifespan.

Lindbergh, CA, et al.
Brain Imaging and Behavior, 2019

RECENT REVIEWS

Carotenoids, vitamin A, and their association with the metabolic syndrome: a systematic review and meta-analysis

Modifiable factors that reduce the burden of the metabolic syndrome (MetS), particularly plant-derived biomarkers, have been a recent focus of rising interest. This systematic review and meta-analysis, which follows PRISMA guidelines, evaluates evidence from a period of 20 years that links vitamin A and carotenoids with the occurrence of MetS and following the PRISMA guidelines. PubMed and Cochrane databases (January 1997 through March 2017) were systematically assessed for studies, including case-control, cross-sectional, and cohort studies, that evaluated the associations of MetS with carotenoids and retinyl esters and retinol (vitamin A). Key measures of associations were harmonized into odds ratios (ORs) and 95% confidence intervals (95%CI) of MetS per 1 standard deviation (SD) of exposure using forest plots and random effects models that pooled data points from 11 cross-sectional studies. Begg's funnel and harvest plots were constructed. An inverse association between total carotenoids and MetS was found [ORpooled, 0.66; 95%CI, 0.56-0.78; 1 SD ~ 0.82 μmol/L; n = 5 studies]. This association was the strongest for β-carotene, followed by α-carotene and β-crypotoxanthin. No association was detected between retinol and MetS (ORpooled, 1.00; 95%CI, 0.88-1.13; 1 SD ~ 2.14 μmol/L; n = 6 studies). Publication bias was absent, and harvest plots indicated consistency upon replication for β-carotene and total carotenoid exposures. This review and meta-analysis suggests that, unlike retinol, total and individual carotenoids were inversely related to MetS.

Beydoun, MA, et al.
Nutr Rev, 77(1): 32-45 (2019)

β-carotene in Obesity Research: Technical Considerations and Current Status of the Field

Over the past decades, obesity has become a rising health problem as the accessibility to high calorie, low nutritional value food has increased. Research shows that some bioactive components in fruits and vegetables, such as carotenoids, could contribute to the prevention and treatment of obesity. Some of these carotenoids are responsible for vitamin A production, a hormone-like vitamin with pleiotropic effects in mammals. Among these effects, vitamin A is a potent regulator of adipose tissue development, and is therefore important for obesity. This review focuses on the role of the provitamin A carotenoid β-carotene in human health, emphasizing the mechanisms by which this compound and its derivatives regulate adipocyte biology. It also discusses the physiological relevance of carotenoid accumulation, the implication of the carotenoid-cleaving enzymes, and the technical difficulties and considerations researchers must take when working with these bioactive molecules. Thanks to the broad spectrum of functions carotenoids have in modern nutrition and health, it is necessary to understand their benefits regarding to metabolic diseases such as obesity in order to evaluate their applicability to the medical and pharmaceutical fields

Coronel J, et al.
Nutrients, 11(4):842 (2019)

Vitamin A signaling and homeostasis in obesity, diabetes, and metabolic disorders

Much evidence has accumulated in the literature over the last fifteen years that indicates vitamin A has a role in metabolic disease prevention and causation. This literature proposes that vitamin A can affect obesity development and the development of obesity-related diseases including insulin resistance, type 2 diabetes, hepatic steatosis and steatohepatitis, and cardiovascular disease. Retinoic acid, the transcriptionally active form of vitamin A, accounts for many of the reported associations. However, a

number of proteins involved in vitamin A metabolism, including retinol-binding protein 4 (RBP4) and aldehyde dehydrogenase 1A1 (ALDH1A1, alternatively known as retinaldehyde dehydrogenase 1 or RALDH1), have also been identified as being associated with metabolic disease. Some of the reported effects of these vitamin A-related proteins are proposed to be independent of their roles in assuring normal retinoic acid homeostasis. The primary focus of the review is on the effects that vitamin A *per se* and proteins involved in vitamin A metabolism have on adipocytes, adipose tissue biology, and adipose-related disease, as well as on early stage liver disease, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

Blaner WS
Pharm & Therapeutics, epub (2019)

Determinants and Determination of Carotenoid Bioavailability from Infant Food Formulas and Adult Nutritionals Including Liquid Dairy Products

Carotenoids are typically tetraterpenoid phytochemicals that cannot be synthesized by humans, some of which such as β-carotene can be metabolized into vitamin A. Sufficient carotenoid intake and tissue levels have been associated with several health benefits including the reduction of cardiovascular diseases and some types of cancer and also the amelioration of age-related macular degeneration. Carotenoids and their metabolites have also been related to reduced inflammation and oxidative stress via interacting with transcription factors, such as NF-κB and Nrf-2, as well as with the nuclear receptors retinoic acid receptor/retinoid X receptor, implicated in immune functions and cellular differentiation. Therefore, carotenoids are important for growth and development. They could mark beneficial constituents in infant food formulas and adult nutritionals, the latter typically constituting protein-rich liquid foods targeting meal replacements. Carotenoids may be present by nature (typically below 20 µg/100 mL) or following fortification (up to 200 µg/100 mL), such as for lutein and β-carotene. However, carotenoid bioavailability may be low and variable, especially in low-fat items. Although most infant foods and adult nutritionals are rich in lipids and proteins, facilitating absorption and availability of carotenoids, unfortunately, very little data is available. In addition, carotenoid detection for such lipid-rich matrices may be challenging as a result of low concentrations and matrix effects. This review aims to highlight considerations for carotenoid bioavailability from infant food formula and adult nutritionals as well as summarize detection methods for carotenoids from these items.

Bohn, T
Journal of AOAC Intl, 102:1-15 (2019)

Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies

High dietary intake or blood concentrations (as biomarkers of dietary intake) of vitamin C, carotenoids, and vitamin E have been associated with reduced risk of cardiovascular disease, cancer, and mortality, but these associations have not been systematically assessed. We conducted a systematic review and meta-analysis of prospective studies of dietary intake and blood concentrations of vitamin C, carotenoids, and vitamin E in relation to these outcomes. We searched PubMed and Embase up to 14 February 2018. Summary RRs and 95% CIs were calculated with the use of random-effects models. Sixty-nine prospective studies (99 publications) were included. The summary RR per 100-mg/d increment of dietary vitamin C intake was 0.88 (95% CI: 0.79, 0.98, I^2 = 65%, n = 11) for coronary heart disease, 0.92 (95% CI: 0.87, 0.98, I^2 = 68%,n = 12) for stroke, 0.89 (95% CI: 0.85, 0.94, I^2 = 27%, n = 10) for cardiovascular disease, 0.93 (95% CI: 0.87, 0.99, I^2 46%, n = 8) for total cancer, and 0.89 (95% CI: 0.85, 0.94, I^2 = 80%, n = 14) for all-cause mortality. Corresponding RRs per 50-µmol/L increase in blood concentrations of vitamin C were 0.74 (95% CI: 0.65, 0.83, I^2= 0%, n = 4), 0.70 (95% CI: 0.61, 0.81, I^2= 0%, n = 4), 0.76 (95% CI: 0.65, 0.87, I^2 = 56%, n = 6), 0.74 (95% CI: 0.66, 0.82, I^2 = 0%, n = 5), and 0.72 (95% CI: 0.66, 0.79, I^2 = 0%, n = 8). Dietary intake and/or blood concentrations of carotenoids (total, β-carotene, α-carotene, β-cryptoxanthin, lycopene) and α-tocopherol, but not dietary vitamin E, were similarly inversely associated with coronary heart disease, stroke, cardiovascular disease, cancer, and/or all-cause mortality. Higher dietary intake and/or blood concentrations of vitamin C, carotenoids, and α-tocopherol (as markers of fruit and vegetable intake) were associated with reduced risk of cardiovascular disease, total cancer, and all-cause mortality. These results support recommendations to increase fruit and vegetable intake, but not antioxidant supplement use, for chronic disease prevention.

Aune, D, et al.
J Clin Nutr,108:1069–1091 (2018)

Registration for CARIG RIS

Many International Carotenoid Society members are also participants in the Carotenoid and Retinoid Interactive Research Group (CARIG) RIS associated with the American Society of Nutrition. If you attend ASN's Nutrition meeting, the CARIG meeting, and are also a member of ASN, it is important that you log onto your ASN NutriLink profile and join the CARIG RIS. We receive benefits from ASN including the opportunity to schedule space during the Nutrition meeting for the CARIG Symposium, so it is extremely important for members to identify their participation in the CARIG RIS. Membership in the RIS has declined because members did not update profiles during their renewal process. You can join the CARIG RIS on ASN's NutriLink website at: https://nutrilink.nutrition.org/home

CARIG Steering Committee 2018-2019

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•Wendy White- Iowa State
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•Xiao-Ming Gong- Texas Tech

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E-mail:	lisa.jahns@ars.usda.gov
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