Summary of Scientific Working Group Discussion - December 8th 2012

Background

As a follow up to the summary from the *1st International Conference on Resveratrol and Health* (Resveratrol2010), a scientific working group was convened and compiled an updated set of recommendations. The group met on December 8th 2012 at the University of Leicester, Leicester, United Kingdom, following Resveratrol2012, the *2nd International Conference on Resveratrol and Health*.

Based on the published scientific literature and the data made available during the previous 2½ days of the conference, the task of the group was to formulate evidence-based recommendations for:

- The use of resveratrol
- Proposed research on resveratrol for the coming years

There was extensive focus on the human intake of resveratrol since there are promising results in the literature indicating prevention of lifestyle diseases. This interest in the human intake of resveratrol is driven by increasing desire of the general population for "natural medicine" and by the commercial interests of a large number of suppliers of nutritional ingredients and cosmetic actives or natural products.

Therefore, an evidence-based scientific evaluation taking into account state-of-art knowledge on resveratrol research is needed.

The conference covered a broad range of topics:

1. Resveratrol and cancer
2. Resveratrol and cardiovascular health
3. Resveratrol and diabetes
4. Resveratrol and osteoporosis
5. Resveratrol and neuroprotection
6. Resveratrol and longevity
7. Resveratrol and inflammation
8. Delivery, absorption and metabolism of resveratrol
9. Combinatory effect of resveratrol and other components
10. Regulation of autophagy by resveratrol
11. Naturally occurring resveratrol and derivatives
12. New *in vivo* models for testing resveratrol

The members of the working group were:

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Recommendations for the use of resveratrol

1. **Can resveratrol be recommended in the prevention or treatment of human diseases or for improving human health?**

   Conclusion:

   - There are not yet unequivocal scientific data to support the recommendation of resveratrol for disease prevention in humans or for human lifespan extension. Two long-term (one year) clinical studies from one research group showed that consuming a low dose of resveratrol (up to 16 milligrams (mg) per day) together with grape phenolics, decreased cardiovascular disease risk in patients undergoing primary or secondary prevention of cardiovascular disease. More long-term (greater than six months) clinical trials with larger sample sizes are needed to confirm the impact of these and other promising studies.
   - Although clinical trials with encouraging results have been completed in the past two years or are currently underway, there is not yet sufficient evidence to unequivocally support a therapeutic effect of resveratrol for the treatment of any specific condition, either alone or in combination with other natural compounds or formulations.
   - Preliminary clinical evidence has demonstrated potential benefits with regards to changes in biomarkers and/or physiological parameters that are consistent with health promotion, particularly in the area of endothelial vasodilator function. There are conflicting results on the effect of resveratrol on insulin sensitivity, although most studies report improvements in insulin sensitivity in humans, while other studies find no effect of resveratrol on insulin sensitivity.

2. **Are there observed "side effects" caused by the intake of resveratrol in humans?**

   Conclusion:

   - No adverse effects were observed in humans receiving resveratrol as a single agent in short-term studies (75 mg per day for 12 weeks or up to 1500 mg per day for 4 weeks). No adverse effects were reported in two clinical trials (up to one-year) involving the administration of up to 16 mg resveratrol in combination with other grape polyphenols.
   - Some side effects of resveratrol have been reported at doses at and above 1 gram (g) per day whereas other studies observed no side effects up to 1.5 gram per day. At and above 2.5 grams per day, the observed side effects include diarrhea, vomiting, nausea and evidence of liver dysfunction in patients with non-alcoholic fatty liver disease. A proprietary formulation based on resveratrol (5 g SRT501 per day) demonstrated renal toxicity in multiple myeloma patients, although it remains unclear whether this was due to resveratrol per se, or some component of the matrix in which it was delivered. Renal toxicity was not observed when the same formulation was administered to healthy controls, type 2 diabetics, or patients with mitochondrial encephalomyopathy, lactic acidosis, and atroke-like episodes (MELAS) syndrome.

- No side effects were reported in long-term clinical trials involving administration up to 16 mg resveratrol in combination with other grape polyphenols in poly-medicated subjects undergoing primary and secondary prevention of cardiovascular disease**.** However, the potential for adverse drug-resveratrol interactions, based on indirect evidence, needs to be evaluated further in clinical trials.

3. What is the relevant dose of resveratrol?

Conclusion:

- A relevant or optimal dose for resveratrol has yet to be established in human studies and will almost certainly vary depending on the condition / disease being treated and a risk-benefit analysis for the population concerned.
- In short-term trials, doses in the range of 10 mg to 2.0 g per day have shown efficacy. However, of the studies reported to date, there is no compelling evidence for a larger beneficial effect at higher doses. More comprehensive dose-response experiments are needed.

4. What valid data are available confirming an effect in mammalian experimental animals?

Conclusion:

- There is sufficient evidence for a chemopreventive effect of resveratrol on the development of cancer in the mouse skin. There are promising results on the prevention of colon and prostate cancer in animals. The effects of resveratrol on other cancer types need to be investigated in more detail prior to recommending clinical trials.
- There is sufficient evidence to suggest that resveratrol enhances vascular health and reduces hypertension, heart failure, and ischemic heart disease in experimental animal models (including pigs).
- There is sufficient evidence that resveratrol improves insulin sensitivity, reduces serum glucose levels in multiple animal models, protects against high fat diet-induced obesity, and improves diabetic kidney disease in rodents.
- Resveratrol induced neuroprotective effects in experimental rodent models of injury or degeneration, but chronic studies are lacking.
- No evidence exists to show that resveratrol increases lifespan in healthy mammals; however, it increases survival in obese and progeroid mice.
- There is evidence suggesting that resveratrol can partially mimic the transcriptional and physiological effects of a calorie restricted diet which is known to slow the aging process and extend lifespan in diverse species.
- In rats, resveratrol is well-tolerated no toxicological effects are observed in the range of 700-1000 mg per kilogram bodyweight per day.

5. Which relevant (overall) actions of resveratrol have been documented?

Resveratrol has multiple direct targets, and numerous additional targets have been discovered since 2010. There is not yet sufficient evidence to link a specific direct target to a specific health benefit. Our understanding of mechanisms of action are further complicated by metabolism of resveratrol, including by the gut microbiota.

Reported effects include:

- Modulation of cell proliferation and apoptosis
- Modulation of angiogenesis
- Inhibition of metastasis
- Modulation of redox status
- Suppression of adipogenesis and stimulation of adipocyte lipolysis
- Stimulation of osteogenesis
- Modulation of mitochondria activity
- Modulation of pro-inflammatory signaling pathways
- Modulation of DNA damage
- Modulation of xenobiotic metabolism
- Modulation of glutamate metabolism
- Estrogenic activity / anti-estrogenic activity
- Enhanced endothelial function
- Modulation of autophagy

Overall conclusions:

- To date, published evidence from human trials is not sufficiently strong to justify the recommendation of chronic resveratrol consumption by humans for any given indication.
- New animal data and recent short-term clinical trials are promising and indicate the need for further long-term human clinical trials (generally more than six months depending on the condition).
- The use of resveratrol is not an alternative to maintaining a healthy lifestyle.

Several relevant research areas have been proposed, but the task of the group was to pinpoint general directions that may serve as guidelines for the research community over the next few years. These recommendations are from scientists representing various fields.

The recommendations for future resveratrol research:

- Clinical trials should aim to identify the optimum dose(s) to be used for specific indications in selected populations.
- Further evaluations of potential side effects (e.g., endocrine effects) are warranted.
- Clinical studies should be initiated, especially focusing on the effect of resveratrol on the development of colorectal and skin cancers.
- Long-term clinical studies should be conducted to evaluate the impact of resveratrol on cardiovascular diseases, prevention of osteoporosis and cognitive function.
- Short- and long-term studies in humans (up to six months and more than six months, respectively) are needed in order to demostrate the potential benefits of resveratrol on metabolic syndrome and brain disease (e.g., neurodegenerative disease, ischemia, and dementia).
- Further studies are needed to elucidate the bio-distribution and degradation of resveratrol *in vivo* including the biological effects of resveratrol metabolites; studies should also address the interactions between resveratrol and the gut microflora.
- Additional studies should address the modulation of drug metabolism by resveratrol (especially cytochrome P450 mediated metabolism).
- There is a need for preparation of an internationally-standardized resveratrol reference product for analytical purposes and to allow for comparing the effects of resveratrol in different clinical studies.
- Future studies should address the combinatory effects of resveratrol with other compounds and developments of relevant models to show the combinatory effect are needed.
- Identification / development of relevant biomarkers for health promoting, disease-preventive and disease specific therapeutic applications
- Further studies should evaluate the effect of resveratrol on inflammation which is recognized as a general condition relevant to several lifestyle diseases.

- Long-term preclinical studies in nonhuman primates may be appropriate to determine the effect of resveratrol on diet-induced metabolic disorders, such as development of insulin resistance.
- There is a need to establish a biobank for samples obtained from clinical trials involving resveratrol.
- Our understanding of the preventative effect of resveratrol for conditions like cardiovascular disease and diabetes will require support from governmental (e.g., NIH and/or EU) and non-governmental sources (private companies).