

and vegan dairy alternatives. Currently, the growth of vegan alternatives to cows' milk is a strong market driver. Preferring drinks made from soy, oat, spelt or almonds, many consumers now avoid cows' milk products for ethical or allergic/intolerance reasons but don't want to miss out on its inherent nutritional benefits. By adding natural calcium carbonate to these products, manufacturers can take a contemporary approach to fortification. In addition, compared with synthetically produced calcium salts, naturally derived calcium sources are not only a better match for modern consumer demands, but also convince because of their high calcium content. Calcium carbonate is a globally recognized source of calcium that allows for health claims. In order to be able to make a "high in calcium" claim in the EU, a food item must contain 30% of the recommended daily allowance (RDA) per serving size. A dosage of 15% allows for a "source of calcium" claim. Because of its high total calcium content (approximately 40%), calcium carbonate can be incorporated at low concentrations to minimize the cost of fortification for manufacturers.

Outlook

Omya has developed a natural calcium carbonate portfolio comprising different brands in order to offer the perfect functionality for all types of applications – from food fortification to nutritional supplementation. Thanks to its role as a global distributor, Omya also possesses a comprehensive portfolio of multipurpose ingredients, such as natural food colors,

yeast extracts, stevia, vitamins and other food supplements. The combination of its vast application know-how and its huge armory of ingredients enables the company to develop holistic and tailored formulations to suit all demands. Thus, the company can support manufacturers who are looking to target the bone health market in multiple ways. Osteoporosis should no longer be thought of as an inevitable part of growing old. By focusing on prevention and lifestyle changes, including physical activity and nutrition, people all over the world can avoid much of its devastating impact.

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Omya at SupplySide West 2017

At booth M179, Omya will present natural and functionalized calcium carbonates for food, nutraceutical, pharmaceutical and personal care applications. Its distribution company in North America, Lipscomb Chemical, is the technical sales organization that partners with leading specialty ingredients producers for these markets.

Using *in vivo* models to support development of nutraceuticals that promote healthy ageing

The importance of healthy ageing.

Medical developments and improvements to factors such as food supply and sanitation have contributed to lengthening of human lifespan, which based on OECD statistics¹ has been increasing at a rate of close to 2 years per decade in recent history. Despite this relatively rapid increase in lifespan, there is evidence that healthspan – essentially the number of years that an individual remains in relative good health and free from disease – has not increased at the same rate². So, although we may be living longer, our quality of life in these extra years is not necessarily very high.

Age is a major risk factor in many diseases; whether that is certain cancers, cardiovascular disease, neurodegenerative diseases such as Alzheimer's, or declines in our immune system (immunosenescence) or strength (sarcopenia). The process of ageing is not simply the result of accumulation of damage in an individual's cells over time that leads to a breakdown in their function. Instead ageing involves a coordinated programme of changes, including notable differences to an individual's epigenome^{3,4}. For better or for worse, how an individual interacts with their environment can impact this ageing program. As such, positive changes to factors such as diet and lifestyle can promote healthy ageing, and help to delay the onset of these negative age-related conditions.

At Sibelius, we believe that Nutraceuticals can make a great contribution towards healthy ageing, but there is a clear need to demonstrate the clinical benefits that such products can offer. In part this is due to increasing pressure coming from regulators, with requirements to provide clinical evidence to support any marketing claims. However, there is also a need to develop products with proven benefits to help a growing consumer segment to make informed decisions about the products that they choose to purchase and use.

In vivo models and managing the risk of demonstrating clinical benefits.

Well publicised drug-development costs from the pharmaceutical industry – as high as \$2.9bn to take a single drug to market⁵ – demonstrate that proving clinical benefits is a lengthy, costly, and risky process. Although development costs in the Nutraceutical industry may not be on this scale, effective management of risks is just as crucial to success.

Just as with the Pharmaceutical industry, clinical trials can make a major contribution to Nutraceutical development costs. It is therefore critical to minimise expensive failures at this stage. Pre-clinical *in vitro* and *in vivo* research, are commonly used to support the identification and characterisation of potential new treatments. *In vivo* models in particular play an important role in allowing the safety, efficacy, pharmacology, and pharmacokinetics of potential new treatments to be assessed in whole living organisms prior to application in humans.

In vivo studies are designed to bridge the gap between fundamental research and the clinic, and in line with the principles of "fail fast", they help to manage risk before committing to increased spending at later, more expensive stages of a development pipeline. The successful translation of results from *in vivo* models into application in humans is dependent on a number of factors; but notably a combination of the organism that is used as the model, and the underlying causes of the disease being tested (e.g. biochemical or genetic mechanisms) and how similar this is to the condition in humans.

The number of orthologs – related genes between species

that arose from the same ancestral gene before the species diverged – provides a crude indication of how similar different species are, and therefore to some extent how good a model they might represent. Around 85% of human genes have orthologs in rats and mice – two very commonly used *in vivo* models – and this rises to above 90% in primates.

C. elegans as an *in vivo* model.

The roundworm *Caenorhabditis elegans* is an invertebrate and more distantly related to humans than the previously mentioned vertebrate models, with a genome that contains orthologs for between 40% and 80% of human genes^{6,7}. *C. elegans* has many of the features that are desired in a model species including: small size, high fecundity, short generation time, translucent bodies, a fully sequenced genome, and genetic tractability (see review⁸). The worm provides a whole organism model with many physiological similarities to humans, such as a digestive system and a nervous system. Such features led to it being proposed as a model organism by Nobel prize winning scientist Sydney Brenner in the 1970s⁹. Since then it has been heavily used in biological and biomedical research, including areas such as development and cell death, and oncology, and these efforts have led to two Nobel prizes. *C. elegans* was also the first animal to have its genome sequenced¹⁰. Lastly, it is recognized as one of the two preferred whole organism models that support the 3Rs initiative in animal research (Refine, Reduce, Replace).

In the context of healthy ageing, *C. elegans* provides a very good model. A significant amount of research into ageing and longevity has been conducted in the worm¹¹ and the core pathways that regulate ageing are well conserved across almost all species tested; from yeast and worms through to insects and mammals. This makes it much more likely that treatments with positive effects on the regulation of cellular health and ageing can be successfully translated across from these diverse species to humans. For example common interventions such as calorie- or dietary-restriction, or treatments with compounds such as rapamycin, have been shown to extend lifespan in essentially all organisms that they have been tested in.

Chronoscreen™: supporting the development of novel Nutraceuticals to promote healthy ageing.

At Sibelius we take advantage of *C. elegans* small size and short lifespan, together with the conservation of ageing-related pathways between species, to screen potential Nutraceutical ingredients for beneficial effects on ageing in a high throughput manner (See summary in Figure 1). By taking advantage of the genetic tools available for *C. elegans* – including the use of fluorescent markers such as Green Fluorescent Protein (GFP) – our proprietary Chronoscreen™ technology enables us to track the movements of the translucent worms throughout their lifetime. This way we can measure the lifespan in populations of worms in response to treatment with different Nutraceutical ingredients to identify those with positive effects.

Extension of lifespan on Chronoscreen™ indicates that the tested ingredient has had a beneficial effect on the regulation of cellular ageing, and therefore has delayed the onset of age-related conditions in the worm. Given the strong conservation of the pathways of cellular ageing between species, our premise is that these ingredients should also have beneficial effects in humans, with the potential to delay the onset of one or more age related conditions.

Having identified ingredients showing biological activity, it is important to understand the specific activities of these ingredients and what end-points should be considered in any

Chronoscreen™

The Science Behind Sibelius

BOTANICAL AND PROBIOTIC

Chronoscreen™ is Sibelius' patented technology, which allows the identification of biologically active natural products by measuring Chronological Lifespan Extension in the model organism *C.elegans*.



We Co-develop

We bring ingredients with validated biological activity – delivering Chronological Lifespan Extension (CLS) on Chronoscreen; and tools for claim substantiation.

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Fruit d'Or cranberry seed oil approved by Health Canada for maintenance of good health

. . . Cranberry seed oil is a foodceutical, cosmeceutical and nutraceutical ingredient

Fruit d'Or Nutraceuticals has received Natural Product Number (NPN #80079040) from Health Canada's Natural and Non-prescription Health Products Directorate (NNHPD), for both Cran Naturelle and Cran d'Or cranberry seed oil. Fruit d'Or Cranberry Seed Oil is registered with an NPN claim as a, "source of omega-3 and omega-6 fatty acids for the maintenance of good health. Source of antioxidants. Source of oleic acid." Each tablespoon (15 ml) contains 34.8% ALA, 36.6% LA and 19.9% Oleic acid.

"This is a major breakthrough for culinary applications. Fruit d'Or is the first to extract the oil from the cranberry seed and earn this health claim of taking one tablespoon daily, or as directed by a healthcare practitioner, for the maintenance of good health. And because Health Canada has recognized that our cranberry seed oil is safe for consumption, it does not have to be GRAS-approved," says Stephen Lukawski, director of global sales and product development, Fruit d'Or Nutraceuticals.

"No other fruit oil has this combination of omega 3, 6 and 9 in these high amounts," Lukawski continues. "This news is a home run for the food industry around the world to use Fruit d'Or cranberry seed oil as a functional artisanal oil." The rich, golden oil is flavor neutral with no aftertaste.

He adds, "No chemicals are used in our cold-pressed extraction method, which was developed to preserve the cranberry seed oil's phospholipid content and its abundant natural antioxidants." Fruit d'Or cranberry seed oil is a rich source of vitamin E tocopherols and tocotrienols, as well as sterols.

Cranberry seed oil is also creating exciting new cosmeceutical opportunities

Demand for Fruit d'Or cranberry seed oil is also increasing for its skin care and anti-aging benefits. Cranberry seed oil is one of the most unsaturated oils available, making it an ideal moisturizing ingredient. With a composition of more than 95 percent fatty acids, cranberry seed oil may protect and reestablish the protective lipid barrier of the skin. It has excellent oxidative stability, a pleasant odor and texture, and the ideal 1:1 ratio of omega 3 to omega 6. "Essential fatty acids are nourishing, protective, aid in the formation and maintenance of cellular membranes and are essential to the formation of prostaglandins to reduce inflammation," confirms Lukawski.

Due to its stability and the protective characteristics of its high vitamin E content, cranberry seed oil is an excellent ingredient for products requiring stabilizing, emulsifying and penetrating actions to enhance the fatty acids and other components within its health product composition.

"By using a cold-pressed extraction method with no excipients, the multitude of beneficial compounds and

biological activities housed within Fruit d'Or cranberry seed oil are retained," explains Lukawski. "The bioavailability of these ingredients in skin care applications may enhance the regeneration, healing, protection and ultimately the beautification of the skin."

Formulators are excited by cranberry seed oil's versatility

Lukawski confirms that Fruit d'Or is already working with nutraceutical and cosmetic companies to combine its cranberry seed oil with vitamins, chia and other trending ingredients. "We are welcoming all researchers and formulators to embrace cranberry seed oil by putting this superstar ingredient into their dietary supplements, blending it with vitamin D and other fatty oils such as CoQ10, selling it on its own, using it for skincare products or to complement other dietary oils such as those found in fish oil," he says.



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In keeping with Fruit d'Or Nutraceutical's commitment to ongoing research, Lukawski says the company is excited to further investigate the benefits of the beta sitosterol found in cranberry seed oil, which has been linked to prostate health.

He also reconfirms the company's farm-to-table advantages. "Fruit d'Or produces its own cranberries and cranberry concentrate so they can control the quality from farm to factory, seed to table. Having a one-stop shop prevents the possibility of adulteration and degradation while protecting the health and safety of consumers. Vertical integration by Fruit d'Or allows for control of the supply chain and maintains a standardized quality that delivers on promise," states Lukawski.

Those interested in learning more about the advantages of Fruit d'Or cranberry seed oil, and of working with Fruit d'Or Nutraceuticals, should visit www.bestcranberry.com

beneficial effects against. Given the broad use of *C. elegans* in biomedical research, it is often possible to validate beneficial effects against models in the worm that have been developed for specific human diseases, ranging from Alzheimer's to metabolic syndrome¹⁴.

The use of *in vivo* models on platforms such as Chronoscreen™, allows us to identify novel Nutraceutical ingredients, or novel applications for existing ingredients, with greater confidence that these benefits will translate across to utilisation in human. Furthermore, the quantitative nature of the lifespan and gene expression readouts enable comparison of equivalent Nutraceutical ingredients from different sources, or which have undergone different extraction or processing procedures. Such a comparison can support developers' efforts to optimise the activity of final products. Similarly, such methods, either alone or in combination with fractionation, together with biochemical analyses, can potentially be used to identify the active Nutraceutical compounds originating from complex mixtures such as plant extracts.

Sibelius' research has proven that Chronoscreen™ in combination with gene expression analysis can be successfully applied for biological testing of a broad range of natural products and ingredients. This provides a very powerful toolset to help elucidate indications benefiting from particular treatments – either where the indication is not known, or where it requires further substantiation – or for identifying new indications benefiting from already established ingredients. This toolset is likely to prove very useful in the screening and substantiation of probiotic claims for the increasing numbers of strains being developed.

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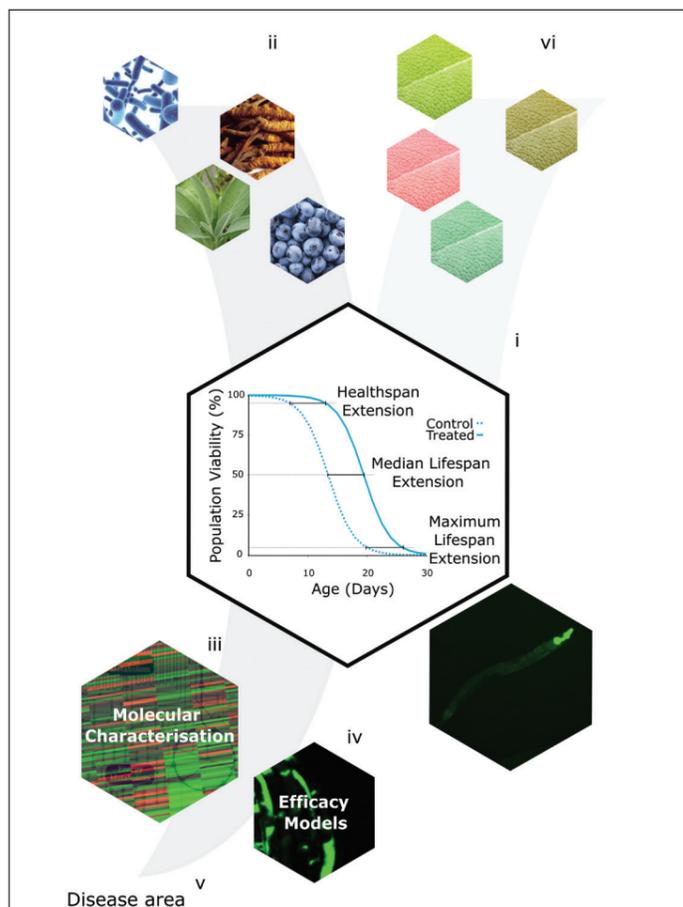


Figure 1

(i) Chronoscreen™ enables the measurement of lifespan in the model organism *C. elegans*. (ii) Libraries of Nutraceutical ingredients can be screened on Chronoscreen™ to identify those that extend lifespan and delay the onset of age-related diseases. (iii) Molecular characterisation, through the measurement of changes in gene expression in response to treatment with ingredients identified as active on Chronoscreen™, improves our understanding of how the Nutraceutical ingredient is causing a beneficial biological effect. (iv) Biomedical research in *C. elegans* has led to the development of efficacy models for multiple diseases, allowing Nutraceutical ingredients to be tested for beneficial effects against some specific diseases. (v) Such down-stream characterisation of active ingredients allows the identification of relevant diseases or conditions to be considered in future clinical applications of the ingredients. (vi) Testing of different fractions (or sources) of Nutraceutical ingredients for activity on Chronoscreen™, combined with measuring the biochemical differences between the fractions, also has the potential to identify active fractions and individual compounds within the Nutraceutical, which is often a complex mixture such as a plant extract.

potential clinical applications. Measuring of gene expression changes in the worm in response to treatments with active ingredients enables the genes and pathways that are up- or down-regulated to be identified. Taken alone this may give clues as to the activity of the ingredient, but it is also possible to take advantage of the wealth of gene expression data that exists from other species to improve understanding of such responses. For example, our analysis has shown orthologs of genes that respond to rapamycin treatment in worms¹² show a significant overlap with genes that respond to rapamycin treatment in human cell cultures¹³. Such approaches allow gene expression patterns in *C. elegans* to be associated with similar patterns in human gene expression, which supports the identification of diseases that the ingredient may show