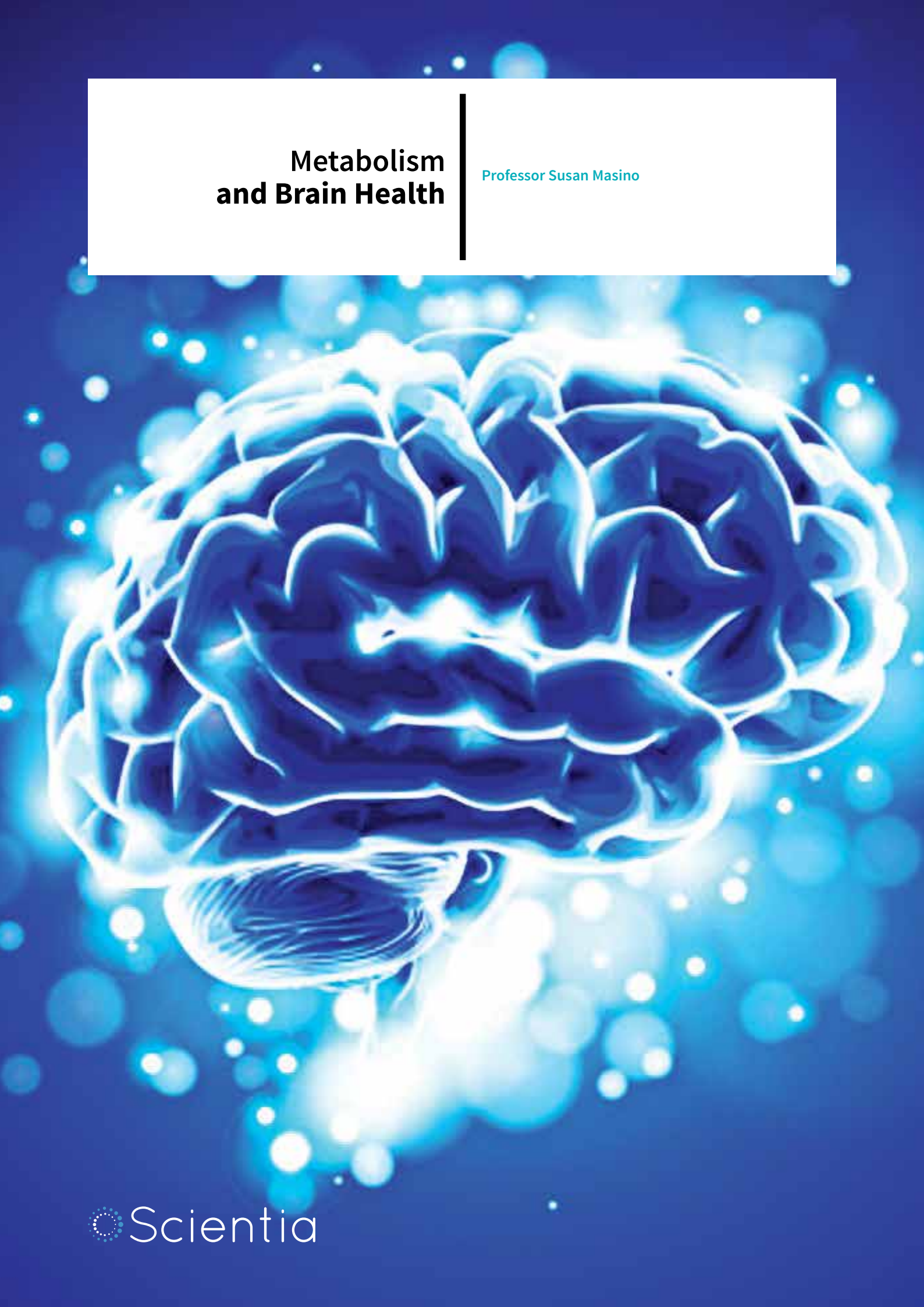
Metabolism and Brain Health

Professor Susan Masino



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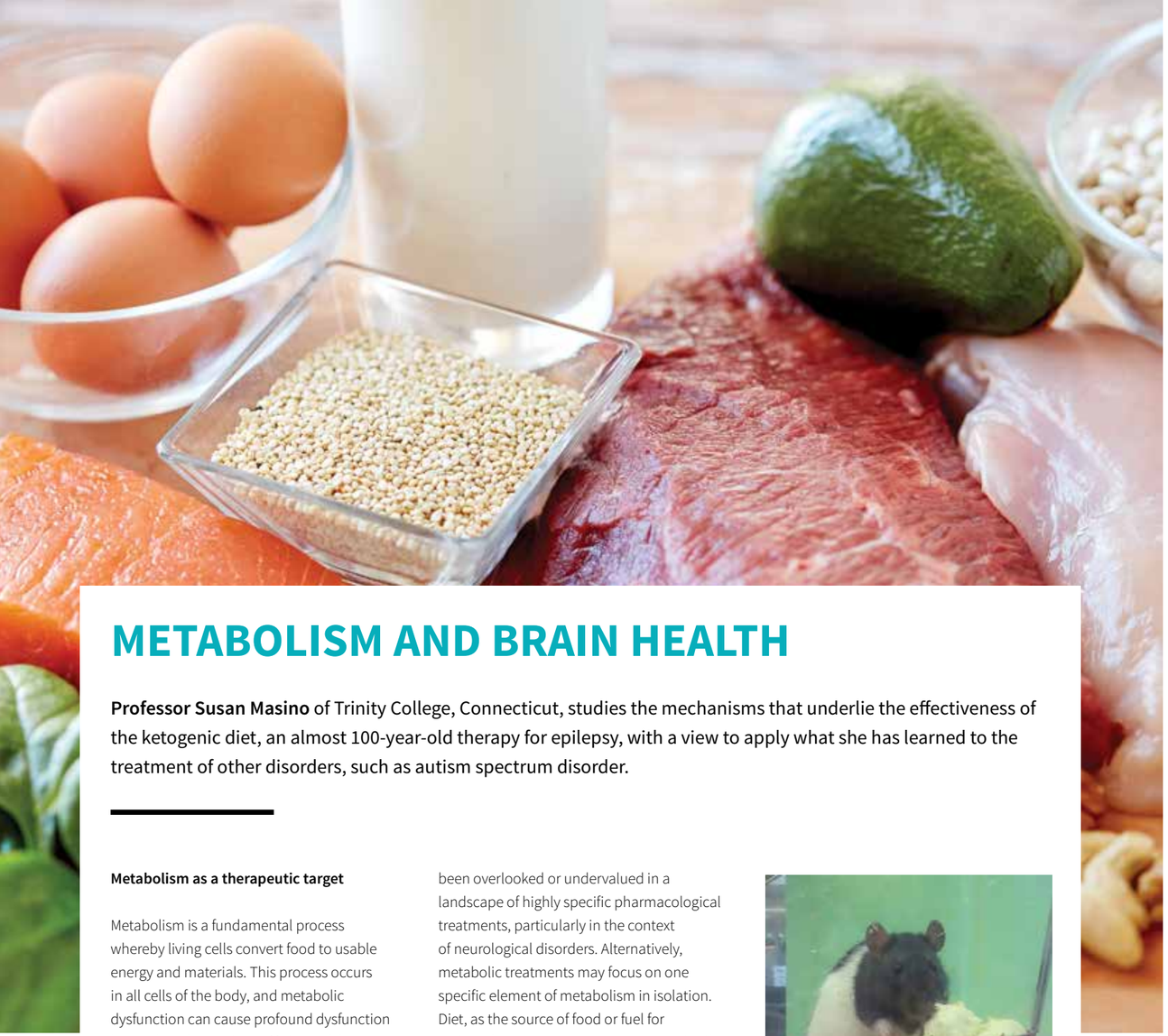

METABOLISM AND BRAIN HEALTH

Professor Susan Masino of Trinity College, Connecticut, studies the mechanisms that underlie the effectiveness of the ketogenic diet, an almost 100-year-old therapy for epilepsy, with a view to apply what she has learned to the treatment of other disorders, such as autism spectrum disorder.

Metabolism as a therapeutic target

Metabolism is a fundamental process whereby living cells convert food to usable energy and materials. This process occurs in all cells of the body, and metabolic dysfunction can cause profound dysfunction in physiological systems. Not surprisingly, metabolic disturbance may play a major role in numerous diseases, including neurological diseases, even those it is not typically a therapeutic target. Classical pharmacological approaches aim to identify and modulate highly specific targets that contribute to the symptoms of disease - or its underlying cause, if known. However, the goal of specificity notwithstanding, many pharmacological treatments cause off-target side effects or produce unforeseen consequences by modulating their targets in ways that would not occur under normal physiological conditions. Furthermore, pharmacological effects are often not long lasting, requiring chronic repeated treatment – and are often masking their target symptoms rather than promoting or restoring health.
As metabolism is ubiquitous it has perhaps been overlooked or undervalued in a landscape of highly specific pharmacological treatments, particularly in the context of neurological disorders. Alternatively, metabolic treatments may focus on one specific element of metabolism in isolation. Diet, as the source of food or fuel for metabolic processes, has enormous potential in treating metabolic disorders and in overall health and disease prevention. Changing our diet can have multifaceted and lasting effects on our physiology, providing a simple but highly effective means to ameliorate diseases by maintaining healthy metabolism. Moreover, the disease-modifying changes brought about by changing diet can help us to learn more about our physiology and the root of the disease processes that afflict it, and could contribute to the development of more effective pharmaceutics that can target the underlying cause of the disease, rather than palliative treatment of symptoms.

While diet-modification and metabolic approaches do not fit with the highly specific targeting of traditional pharmacology, producing change in multiple physiological systems at once may be what is required to

Rat tucking in to a ketogenic meal.
Credit: David Ruskin

effect significant therapeutic benefit, and particularly in patients for which traditional pharmacological therapies have failed. Furthermore, due to its high metabolic demand, brain function may be particularly sensitive to metabolic problems. This requires a paradigm shift, from the treatment of specific symptoms of a specific disease, to the modulation of metabolism throughout the body to support and enhance overall health and optimise metabolic processes to negate existing dysfunction. This approach has gained significant support recently.

However, this is somewhat of a renaissance, as this concept is not new. One such example of a therapeutic diet for the treatment of epilepsy is the ketogenic diet, which has been in existence for nearly 100 years.

The ketogenic diet and epilepsy

The ketogenic diet has been in use for the treatment of epilepsy since 1921. It had long been noticed that fasting reduced the incidence of epileptic seizures and the ketogenic diet was developed to circumvent the obvious limitations of fasting as a long-term treatment. Patients on the ketogenic diet limit strictly their intake of carbohydrates, and eat sufficient but not excessive protein, meaning that the majority of their energy is derived from dietary fats which are converted into ketone bodies. These ketone bodies can pass into the brain and are used instead of carbohydrate-derived glucose as a source of energy.
The diet is often prescribed for patients for whom conventional pharmacological anti-convulsant therapies have failed – but is arguably underutilised. Professor Masino tells Scientia about the advantages of the ketogenic diet for particular epileptic patients: ‘Today there are many drugs available to control epileptic seizures, yet this metabolic therapy can stop seizures even when all medications fail: for some patients a ketogenic diet is superior to all known drug treatments.’ The mechanisms underlying the therapeutic effects of the ketogenic diet in epilepsy are unclear. However, Professor Masino has posited a theory based on a molecule with inherent involvement in the metabolic process: adenosine.

The ketogenic diet and the adenosine hypothesis

Adenosine is a nucleoside neuromodulator that is involved in cell energy transfer; it is the core of adenosine triphosphate (ATP), the main cell energy molecule. Adenosine is regulated in response to cell stress and metabolic demand and it has been shown to have neuroprotective, anti-seizure and disease modifying properties. Professor Masino tells Scientia about the importance of adenosine and how her early work with it has shaped her current hypothesis: ‘Adenosine immediately links cell energy (ATP is successively dephosphorylated into adenosine) and neural activity (adenosine is a neuromodulator acting at G-protein coupled receptors) and exerts lasting epigenetic changes as a product of DNA

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Credit: McCarron Art

methylation. Initially, adenosine was hailed as an endogenous neuroprotective molecule that increased during events like hypoxia or injury. My initial electrophysiological research in the laboratory of Tom Dunwiddie helped to reveal the dynamic regulation of adenosine by diverse ongoing physiological changes at the cellular level. This led to my current hypothesis on the regulation of adenosine by ketogenic diet.’ She explains the therapeutic potential and limitations of adenosine as a standalone therapy and how she believes it links with the ketogenic diet: ‘Adenosine has long been a highly coveted therapeutic target as an anticonvulsant and a neuroprotectant, but peripheral side effects have made drug development challenging. Both a ketogenic diet and adenosine can stop seizures that are refractory to all available medications, and both link metabolism to neuronal activity. Therefore, if a ketogenic diet increases adenosine signalling it sheds light on two long standing mysteries: 1) how does a ketogenic diet work, and 2) how can we regulate adenosine.’ The team has investigated the ketogenic diet in rodents, to determine if adenosine signalling is increased.

Key findings to date

The team has discovered some compelling evidence for adenosine’s involvement in the ketogenic diet’s effects. They observed changes in adenosine signalling in the brains of rats that had been fed a ketogenic diet. They found that the effectiveness of the ketogenic diet in preventing seizures is eliminated in animals that do not possess adenosine receptors or in those that are administered a drug that inhibits the action of these receptors, suggesting that adenosine’s action on its receptors is a key mediator of the ketogenic anti-seizure effect in epilepsy. Recent work suggests that a ketogenic diet may have long-term epigenetic effects via adenosine signalling independent of adenosine receptors, providing a potential explanation for the long-term therapeutic effects experienced by some epilepsy patients on the ketogenic diet even after cessation of the diet. The team has some preliminary evidence that these effects are mediated through changes in DNA methylation. However, Professor Masino is determined to see if the findings the team had made concerning the ketogenic

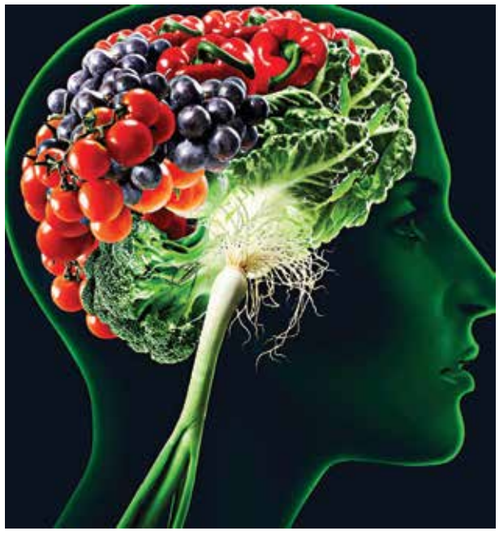
diet and adenosine are relevant to other neurological conditions, in keeping with the concept that metabolic therapies could be applicable to maintenance and enhancement of overall health: 'It turns out that adenosine is neuroprotective, but not just during pathological events. I believe that it promotes a dynamic homeostasis, which is essential for a healthy brain. In fact, we are beginning to appreciate that both adenosine and the ketogenic diet regulate brain function in a homeostatic way and may have disease-modifying properties. This could yield a new approach where rather than treating a specific disease we focus on restoring health.'

Beyond epilepsy – autism spectrum disorder

Based on a parallel hypothesis about autism spectrum disorder and adenosine the team broadened the scope of their research and began to study the effect of the ketogenic diet in a mouse model of autism spectrum disorder. While dietary treatments, such as the gluten-free diet, have been considered for autism previously, none were shown to be broadly effective in clinical trials. One small clinical study had previously shown that the ketogenic diet might have potential in the treatment of autism, but it was not a standard protocol and there has been little follow up. Professor Masino's team investigated the effect of the ketogenic diet in a mouse model of autism and was able to show a reduction in autistic behaviours compared with mice fed a normal diet. This included a reduction in repetitive behaviours such as grooming alongside increased sociability and awareness of social cues. The team was curious if the anti-seizure effects of the ketogenic diet were involved in its ability to reduce autistic behaviours, given that patients with autism spectrum disorder often experience seizures. However, the mice demonstrated no electrical or behavioural evidence of seizures, and no evidence of overall changes in brain activity when fed a ketogenic diet – suggesting that even though the ketogenic diet does stop seizures, the improved behaviours were not due to this effect. The results are exciting – a subset of patients with autism spectrum disorder have co-morbid epilepsy, and severely affected patients who also have seizures tend to have very poor outcomes. An established therapy such as the ketogenic diet could be particularly helpful in treating patients with autism spectrum disorder and seizures and may already be eligible for ketogenic diet therapy.

Looking to the future

Professor Masino explains her hopes for metabolic therapy, including complementary or synergistic co-therapies: 'New research has provided evidence that alternatives which can substitute for or complement the ketogenic diet – and potentially augment its efficacy – may be close at hand. Evidence is also mounting that for some people ketogenic diets can reverse chronic health conditions and provide general health benefits beyond treating any particular disease. Understanding key mechanisms underlying the success of metabolic therapy is of the highest biomedical significance: it is anticipated these mechanisms will apply to provide breakthroughs for multiple common, chronic, and poorly-treated disorders.' She explains that, for her, the multifaceted nature of dietary therapies is their key strength in treating complex and multifaceted disease states: 'While the ketogenic diet in particular is challenging conceptually for those who want to identify very specific mechanisms, I see this as a strength whereby a different set of key mechanisms may be needed address any disorder. Traditionally the ketogenic diet has been used to treat epilepsy, and my hypothesis about the ketogenic diet and adenosine predicted additional conditions that would benefit from this metabolic approach, such as



'Evidence is mounting that for some people ketogenic diets can reverse chronic health conditions and provide general health benefits beyond treating any particular disease.'

pain and autism spectrum disorder. These are challenging conditions with diverse underlying causes, and we are actively pursuing the short and long term efficacy and mechanisms of metabolic therapy in these and other conditions.' While the research group is interested in identifying the mechanisms underlying the efficacy of metabolic treatments, such as the ketogenic diet, Professor Masino would like to see healthcare providers and legislators adopt a more pre-emptive treatment approach to brain health, where disease modification and improvement in overall health are adopted in conjunction with treating specific symptoms and targets: 'Ultimately my real passion is brain health – I believe it should be part of all of our health visits – and it should be a top priority for public policy decisions and funding. A brain-health focused approach could prevent or delay disease, and complement any disease-specific treatment. I believe a key place to start is with our food system. We subsidise production of processed foods and refined carbohydrates and then pay the medical bills for the chronic diseases they precipitate. People who eat a higher proportion of subsidised food – often refined carbohydrates – have worse cardiometabolic health. I am sure that the conclusion would be the same for brain health, and the economic and societal costs of neurological disorders are staggering.'

Meet the researcher

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Susan Masino obtained her PhD from the University of California, Irvine in 1996, following which she pursued postdoctoral research at the University of California, Irvine and the University of Colorado. She is currently the Vernon Roosa Professor of Applied Science and appointed jointly in the Psychology Department and Neuroscience Program at Trinity College, Connecticut. She is a member of the Society for Neuroscience, American Epilepsy Society and American Physiological Society, among others. She studies the regulation of adenosine and mechanisms underlying the ketogenic diet with a focus on brain health and neurological conditions such as epilepsy and autism.

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