

INSTITUTE FOR MOLECULAR BIOSCIENCE

THE EDGE

INFLAMMATION

*The latest in research
and discovery*



**CAN IT BE STOPPED?
LATEST STUDIES
ON PREVENTION
AND CURE**

**INFLAMMATION
AND DIET
EVERYTHING YOU
SHOULD KNOW**

**INFLAMMASOME
HOLDING THE KEY
TO NEW THERAPIES?**



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One-third of deaths in Australia are due to inflammatory-driven diseases. At the Institute for Molecular Bioscience, we are leading the way in finding solutions.

You can help too, find out how imb.uq.edu.au

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INSTITUTE OF MOLECULAR BIOSCIENCE

Welcome

Inflammation is our response to infection and injury, a necessary way for the body to fight back against invaders. But inflammation has a dark side. When it doesn't switch off, or is activated inappropriately, the result is chronic, ongoing inflammation, a complex, system-wide condition that we increasingly see at the heart of many diseases of the 21st century.

The World Health Organization's projected causes of mortality, which estimates the global percentage of people who will die from a particular disease or injury each year, is dominated by inflammation-related diseases. Cardiovascular disease is the world's biggest killer, responsible for 31 per cent of all deaths, and is related to inflammation. Infectious diseases (16 per cent), cancer (16 per cent), some injuries (9 per cent), respiratory disease (6 per cent), digestive diseases (4 per cent), dementia/Alzheimer's (4 per cent) and diabetes (3 per cent) all involve inflammation, as does sepsis, which is responsible for many maternal and infant deaths (5 per cent of global deaths). These statistics don't even begin to touch on the emotional and economic burden that inflammatory diseases place on people all around the world, each and every day.

Despite its involvement in numerous medical conditions, inflammation is still not well understood. To combat this issue, in 2014 the Institute for Molecular Bioscience at The University of Queensland established a research centre dedicated to identifying, preventing and treating the underlying causes of inflammatory diseases: the IMB Centre for Inflammation and Disease Research.

Our mission is to help solve some of the world's greatest health challenges.



Professor
Brandon
Wainwright

Our scientists are delving into inflammation at the molecular level to advance our knowledge of its causes and progression, and to make strides towards better outcomes for people with inflammatory diseases.

We are also committed to educating and empowering non-scientists through improving the community's understanding of scientific topics. This magazine is the first in a series in which we will explore some of the most pressing issues facing our local and global communities. We have named this series *The Edge* in recognition that our research sits at the edge of scientific knowledge, and to reflect our mission to push the boundaries of the known and make discoveries that help solve some of the world's greatest health and environmental challenges.

Within these pages, you will find more information on inflammation and some of the diseases it underlies, some actionable tips on prevention, and updates on the research that is bringing hope for the future.

Professor Brandon Wainwright
IMB Director

What is inflammation?

The body's 'Goldilocks' response can kill or cure

We all know inflammation when we see it – the red and painful cut, the hot, swollen thumb we've hit with a hammer, or the angry welt of an insect bite.

Those are all outward signs of the process initiated by many systems in our body in response to danger, in the form of a physical injury, an infection, or even our own body not behaving as it should.

Inflammation is a vital short-term response to a sudden insult, whether that is injury, infection or both. Messenger proteins, known as cytokines, are released to signal the danger and our system responds with the tools to fix the problem.

Pain, swelling, redness and heat are the classic external signs of this process.

Inflammation is a shapeshifter. It is both a symptom of injury or disease, and at the same time the cause of symptoms.

The pain warns us to take care and notifies us of the insult; an area may become swollen as fluids are moved to the injury; heat and redness follow as increased blood flow brings cells to start the healing process, and hormone-like messaging systems can order the blood to clot to close a wound.

When pathogens like bacteria or viruses are present, the immune response involves dispatching white blood cells to fight off and kill the infection.

If all goes well, inflammation will subside and our bodies return to normal as the damage is healed or the pathogen is destroyed.

But inflammation is a "Goldilocks" condition – too little and our bodies can be overwhelmed by infection or fail to heal; too much and it can cause crippling health problems of its own.

Where the immune system cannot be returned to normal because our body fails to heal, or environmental factors such as smoking or diet maintain a threat,

Acute vs chronic – what's the difference?

Acute inflammation is the first line of defence against injury or infection. It is usually a sign that your body has taken the first step towards healing but this response can also be involved in illness, such as sepsis. Acute inflammation comes on quickly, lasts a matter of days, but can be fatal.

Chronic inflammation, by contrast, comes on slowly and can last for months, or even years. It is persistent inflammation that tries to rectify a problem, such as an autoimmune disease or ongoing exposure to environmental or lifestyle irritants such as pollution or smoking. Acute inflammation, if not resolved, can turn into chronic inflammation.

The mechanics of the response can be similar as for an emergency, but as the injury or infection cannot be resolved, the distress signals continue. The consequences of this persistent inflammation are one or more of a raft of health conditions.

Inflammation becomes the problem and not the solution.

inflammation goes into overdrive and can continue to signal danger. Scientists now understand that this long-term inflammatory response, known as chronic inflammation, can lead to many chronic diseases.

So inflammation is a shapeshifter. It can be both a symptom of injury or disease, or a cause of symptoms.

Scientists and doctors are only beginning to build a detailed understanding of the many moving parts of this complex system. As they do, they are devising strategies to control inflammation and provide new approaches to tackle many important and common diseases.

BY THE NUMBERS

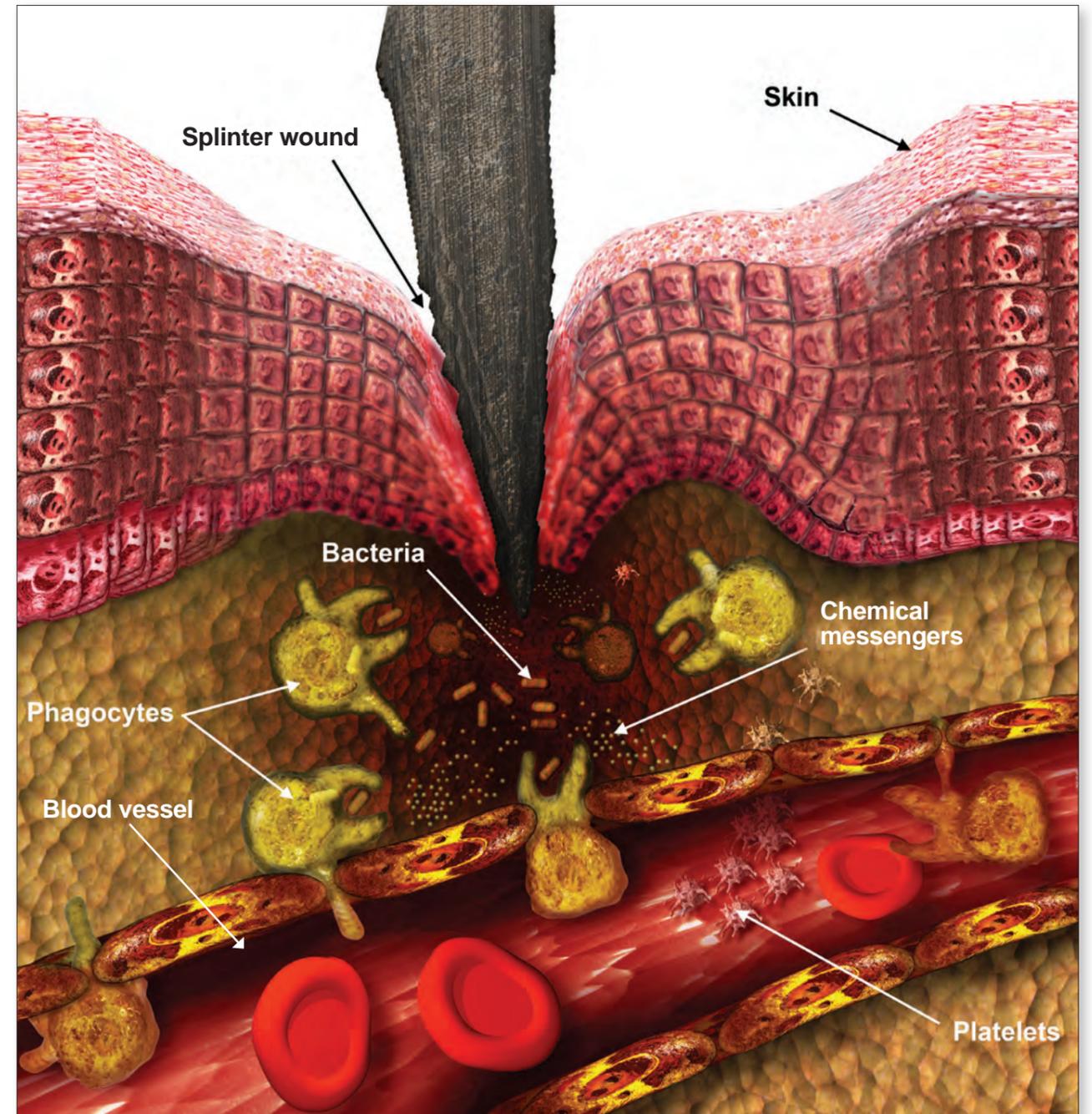
Alzheimer's disease affects 10 per cent of people aged over 65. Among those aged 85 or more that rises to

25%



How inflammation works

A complex set of steps involving many of the body's systems



The inflammatory response begins when damaged tissue releases chemical signals that, among other functions, cause blood vessels to become porous. Phagocytes – the cells which protect the

body by engulfing foreign particles and bacteria – then move from the blood vessel into the affected tissue to attack bacteria and clean up debris. Platelets move to the wound to cause blood clotting.

The aim is to return the tissue to the way it was before the injury. With chronic inflammation, the process does not stop and, instead of attacking a foreign invader and protecting us from disease, the inflammation now attacks the body itself.

Some common inflammatory diseases

Chronic problems and their causes

The definition of an inflammatory disease can be a little confusing. Inflammation is a response present in many diseases – it is the reason for your sore throat and runny nose when you have a cold, for example.

Typically, those symptoms last for only for a short period of time before your body returns to normal – indeed that is the purpose of inflammation.

When we talk of inflammatory diseases we are talking about ongoing inflammation that does not return your body to its original healthy state.

There are a range of factors that can cause inflammation overload: lifestyle, such as smoking and diet; genetics; and pollutants in the environment. There are also many autoimmune diseases, where your body's immune system turns on itself, which lead to chronic inflammation.

BY THE NUMBERS

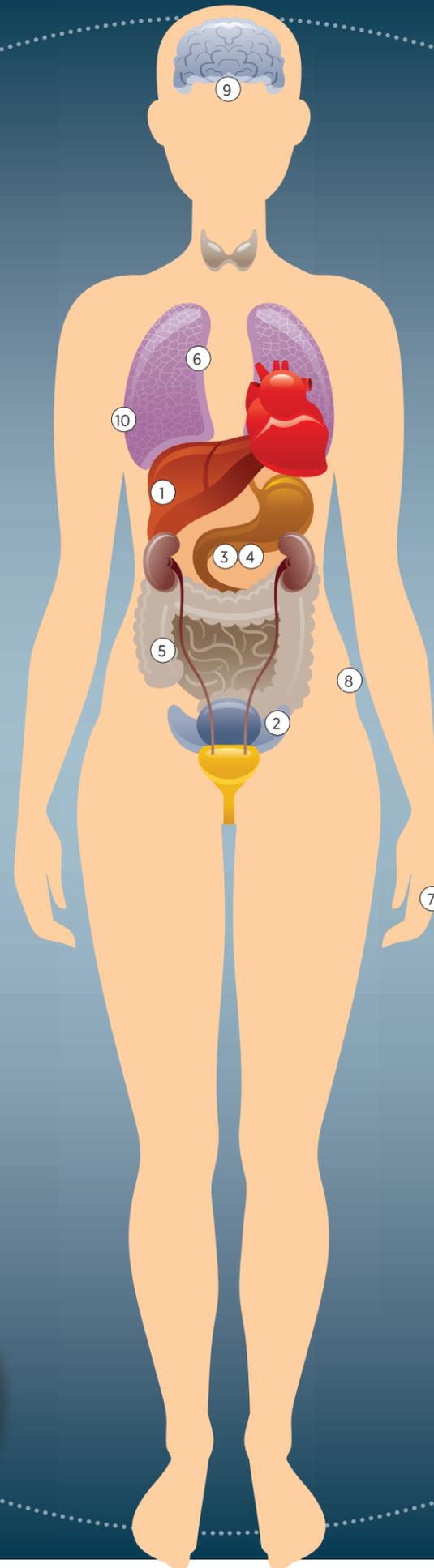
Half of us have a chronic condition, and these conditions are responsible for most deaths

50%

BY THE NUMBERS

About 458,000 Australians have rheumatoid arthritis, affecting 2.3% of women and 1.5% of men

458k



2. Endometriosis

Tissue similar to the uterus lining grows in other parts of the body, such as the abdominal cavity, where the resulting inflammation can cause excruciating pain. The disease can be better managed by addressing pro-inflammatory factors.

1. Fatty liver disease

Fatty liver disease can be caused by poor diet, which can set off an inflammatory response. Unchecked, this response can lead to cirrhosis, liver cancer, liver failure, and can ultimately result in death.

10. Cancer

Inflammation caused by chronic infection, inflammatory diseases or environmental factors plays a multi-faceted role in certain cancers, as a primary cause and by helping tumours grow and spread.

9. Alzheimer's and Parkinson's diseases

Over the past decade, inflammation due to a sustained immune response in the brain has been linked to these two progressive neurodegenerative disorders.

8. Obesity

With obesity, there is an over-accumulation of fatty tissue, which produces and releases a variety of inflammatory messengers making obesity an underlying condition for many inflammatory and metabolic diseases.

3. Type 2 diabetes mellitus

Low-grade inflammation is common in type 2 diabetes sufferers but we are only beginning to understand the role inflammation may play in the development of the disease.

4. Type 1 diabetes mellitus

The immune system attacks and destroys insulin-producing cells in the pancreas. Symptoms include increased thirst, frequent urination, hunger, fatigue and blurred vision.

5. Inflammatory bowel disease (IBD)

Umbrella term for ulcerative colitis and Crohn's disease. The immune system attacks the gut lining causing diarrhoea, abdominal pain, fever and weight loss.

6. Asthma

Inflammation causes the lining of the airways to swell, narrowing them and making breathing difficult. It also causes the airways to produce more mucus and makes them more sensitive to asthma triggers.

7. Rheumatoid arthritis

A painful condition associated with inflammation in the joints. In advanced cases, it can cause damage to the heart, lungs, kidneys, skin, eyes and other tissues.

Time to read the warning signs

The indicators that say it's time to see a doctor

Chronic inflammation increases your risk of several serious diseases. While only your doctor, through blood tests, can provide a definite diagnosis of a particular inflammatory disease, there are some warning signs to watch for.

You should be particularly on guard if you have certain lifestyle risks such as smoking, excessive drinking of alcohol or being overweight.

A common cause of inflammatory illnesses, however, are autoimmune conditions in which your immune system mistakenly attacks your body.

Some autoimmune diseases target only one organ, as is the case with type 1 diabetes, which

attacks the pancreas. Others, such as lupus, affect the whole body, and some, such as rheumatoid arthritis, target a specific part of the body but cause collateral damage in a wide range of places.

But while each has different effects on our bodies, there are some common symptoms that might suggest it is time to visit your GP.

Most of us will recognise the symptoms of acute inflammation – pain, redness, swelling and heat. The symptoms of chronic inflammation can be similar but they are usually subtler and easy to dismiss as just the aches and pains associated with ageing.



Most of us will recognise the symptoms of acute inflammation – pain, redness, swelling and heat.

Symptoms of chronic inflammation

Common symptoms of chronic inflammation can range from mild to severe and last for several months or even years. They include:



Fatigue

Being tired all the time, even when you first wake up, could be a warning sign that your body is expending too much energy on an inflammatory response.



Aches and pains, especially in the joints

Common to most inflammatory conditions. Joint pain can be an indicator of autoimmune diseases, but also of chronic inflammation at the site of an old injury or in response to conditions such as osteoarthritis. But if you have any chest or abdominal pain, especially if combined with other symptoms, please see a doctor.



Skin rashes

Eczema or psoriasis can be a symptom of some inflammatory conditions. And while there are many other causes, if you have a consistent rash it may be worth having a doctor check it out.



Digestive problems

Diarrhoea, constipation or bloating – especially when they go on for a long period of time – could be a sign that your gut lining is inflamed. Because your digestive system is designed to extract nutrients and speed them to the entire body, inflammation here can lead to system-wide symptoms.



Allergies

While allergies are not necessarily an indicator that you are suffering from chronic inflammation, consistent watery eyes and a runny nose, especially when there are no other obvious external triggers, could be a warning sign. It may not be an allergy at all, but excessive mucus production as your body copes with inflammation.

What you can do for an ounce of prevention

We can't stop our bodies from responding to danger but we can take steps to keep it under control

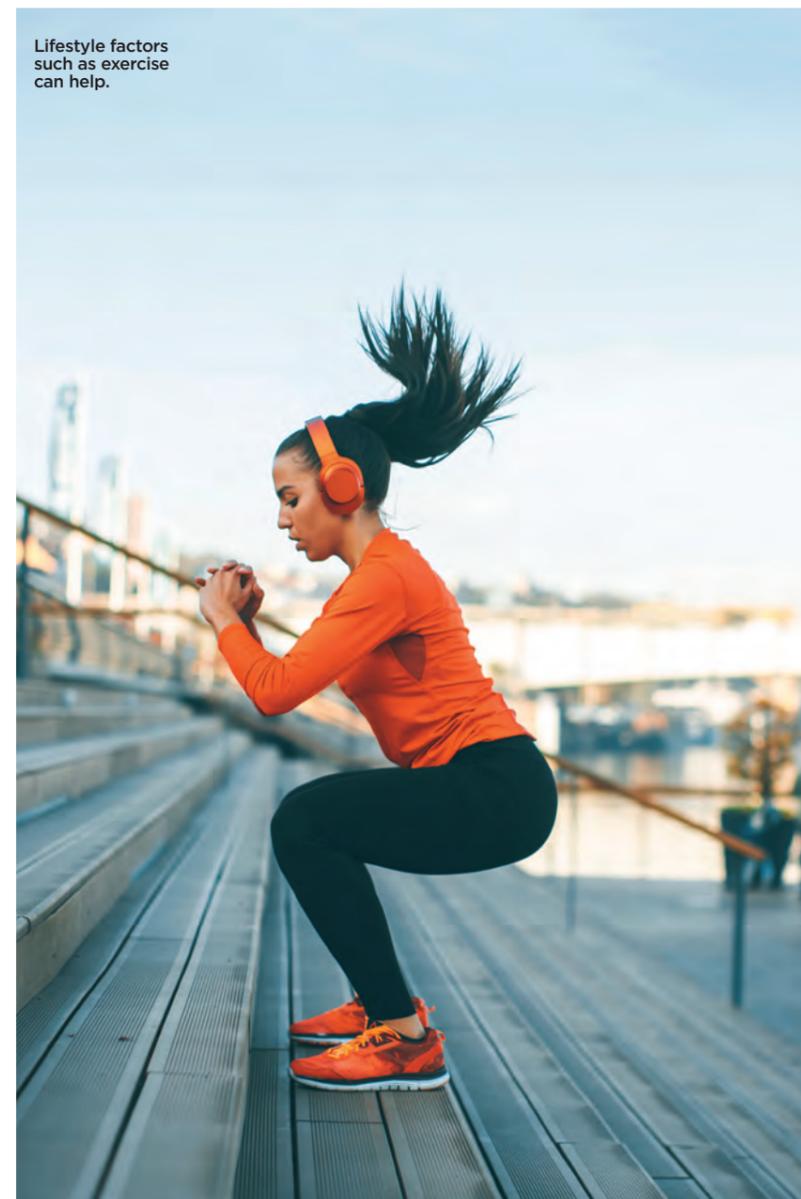
In a world awash with inflammatory triggers, and an explosion of chronic diseases linked to dietary and environmental factors, there are several concrete steps you can take to reduce risk.

Prevention is better than a cure. You may not be able to change your genetic risk factors, but by avoiding the environmental signals that trigger

inflammation such as poor diet and cigarette smoke, you can reduce the risk of developing inflammatory diseases.

While there will never be a silver bullet to protect us from the harmful effects of out-of-control inflammation, we now know enough about it to develop strategies to reduce the harmful effects of unhealthy inflammation.

Lifestyle factors such as exercise can help.



Inflammation busters

Here are five things you can do to reduce your risk of developing diseases associated with chronic inflammation.



1. Improve your diet

Make sure you are eating a balanced diet that includes omega-3-rich fish, whole grains and fruits and vegetables in a range of colours, while avoiding foods that can make inflammation worse (see pages 18–19).



2. Stop smoking

This may seem obvious, given that the harmful effects of smoking are well known, but it is important. Smoking tobacco is linked to increased inflammation throughout the body.



3. Maintain a healthy weight

Obesity is an inflammatory trigger in its own right. Fat cells react with the immune system to increase inflammation.



4. Exercise

Regular exercise can help to reduce stress and inflammation, and also help with weight loss.



5. Manage stress

While stress in an acute form can help us perform better under pressure, if it goes on too long it can be damaging. Chronic stress, depression and anxiety have all been associated with inflammation.

Is the 21st century turning against us?

Genetic, environmental and lifestyle factors all play a role in inflammatory diseases

Why do we hear of more and more diseases that are “inflammatory” by nature? There are two reasons, says Professor Jennifer Stow from IMB.

“One is that we have an ageing population, and ageing is associated with more chronic disease,” she says.

The second reason is our environment: “We live in an inflammatory world that we’ve created for ourselves.”

Inflammation is a very ancient response designed to be triggered by things such as pathogens or injury.

But now we assault our bodies with all sorts of things – air pollution, cigarette smoke, food additives, stress, alcohol and many more.

All of these can act as environmental danger signals that trigger inflammation, often subtly in the background.

Environmental factors, including dietary choices, can lead to so-called “lifestyle diseases”, such as type 2 diabetes, where chronic inflammation is a major factor.

And as IMB’s Dr Larisa Labzin explains, the problem is made worse when the immune system doesn’t receive the signal that the threat has been neutralised, and the immune system can turn off. Then you get more and more inflammation.

“In the case of an infection, the inflammatory and immune responses to pathogens such as bacteria or viruses enable them to be killed and degraded,” she says. “But if it’s against something inert that’s made its way into the body – silica particles or asbestos fibres, for example –

We assault our bodies with all sorts of things that it interprets as dangerous – air pollution, cigarette smoke, food additives, stress.

you’re mounting an immune response against something that can’t really be destroyed by our immune system. So, our usual weapons are useless against them.

“That’s when you get chronic inflammation that’s not being turned off.”

And so the body itself becomes subject to collateral damage.

There is a similar outcome with autoimmune diseases, although for different reasons.

The root causes of many of these diseases, which include rheumatoid arthritis, Addison’s disease, lupus and type 1 diabetes, are not yet completely understood, but the mechanics are well established.

Instead of attacking bacteria, viruses or other sources of infection, the immune system attacks healthy organs and tissues. For example, in rheumatoid arthritis, our immune cells destroy the insulin-producing cells in the pancreas.

“This abnormal response also drives constant inflammation, further contributing to disease processes,” says Professor Matt Sweet, an immune system specialist at IMB.

Chronic inflammation is rapidly becoming synonymous with disease in the 21st century.



It’s a dangerous world

Some of the environmental inflammatory factors we face:



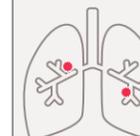
Air pollution

Studies have found that increased exposure to fine particulate matter in air pollution is associated with elevated inflammation markers in the blood. This inflammation can contribute to the incidence of heart attack and stroke.



Smoking

Smoking is a major factor in a range of inflammatory diseases. Not only is it linked to cardiovascular and respiratory diseases, but also to increased levels of inflammatory markers and accelerated atherosclerosis. It is a major risk factor for rheumatoid arthritis. It increases the risk of developing Crohn’s disease and may aggravate



Asbestos

Asbestos exposure is the cause of a range of lung diseases. While the biology of this is complex, exposure to asbestos leads to chronic inflammation and scarring of the connective tissue in the lungs.



Stress

Stress triggers the production of cortisol, the flight-or-flight stress hormone that plays a role in inflammation, and can interfere with the body’s ability to control it. Physical stress, such as a sporting injury, can also trigger excessive inflammation, sometimes years later.



Toxic chemicals

Your body can determine that certain chemicals are harmful and launch an immune and inflammatory response to them, whether you are exposed through the air, by touching them or through a wound.

Autoimmune or inflammatory?

- Inflammatory diseases are not the same as autoimmune diseases, although the dividing line is often blurred.
- The difference lies in the immune system. Inflammatory diseases are those in which your innate immune system – the first line of defence against infection – launches an inflammatory response that does not stop.
- In autoimmune diseases, your adaptive immune system attacks your body as if it were an invader. That can lead to inflammation and inflammation-related conditions.

The silent threat in fatty liver disease

Inflammation can determine whether you develop a more aggressive version

Fatty liver disease affects nearly one third of Australians. In most cases, it will cause no lasting liver health problems, but for the unlucky ones in whom it sets off a prolonged inflammatory response, it is potentially very serious.

Unchecked, the disease can lead to cirrhosis, liver cancer and liver failure, and can ultimately result in death.

While excessive drinking of alcohol is a well-known cause of liver disease, the most common variety is non-alcoholic fatty liver disease. A poor diet is frequently to blame, with obesity, diabetes, and metabolic syndrome the top risk factors.

"Non-alcoholic fatty liver disease (NAFLD) affects 25 per cent of the population," says Professor Elizabeth Powell, a hepatologist with Queensland Health. "But it's the inflammatory response to liver injury that can determine the outcome of the injury."

The most serious type of fatty liver disease, with inflammation and liver cell injury, is known as steatohepatitis. Inflammation is a common factor in the progression of three other key liver diseases: alcoholic hepatitis; and viral hepatitis B and C.

"Inflammation underpins them all," says Professor Powell. "Persistent inflammation triggers the development of fibrosis – scarring in the liver – and progressive scarring over many years can lead to cirrhosis."

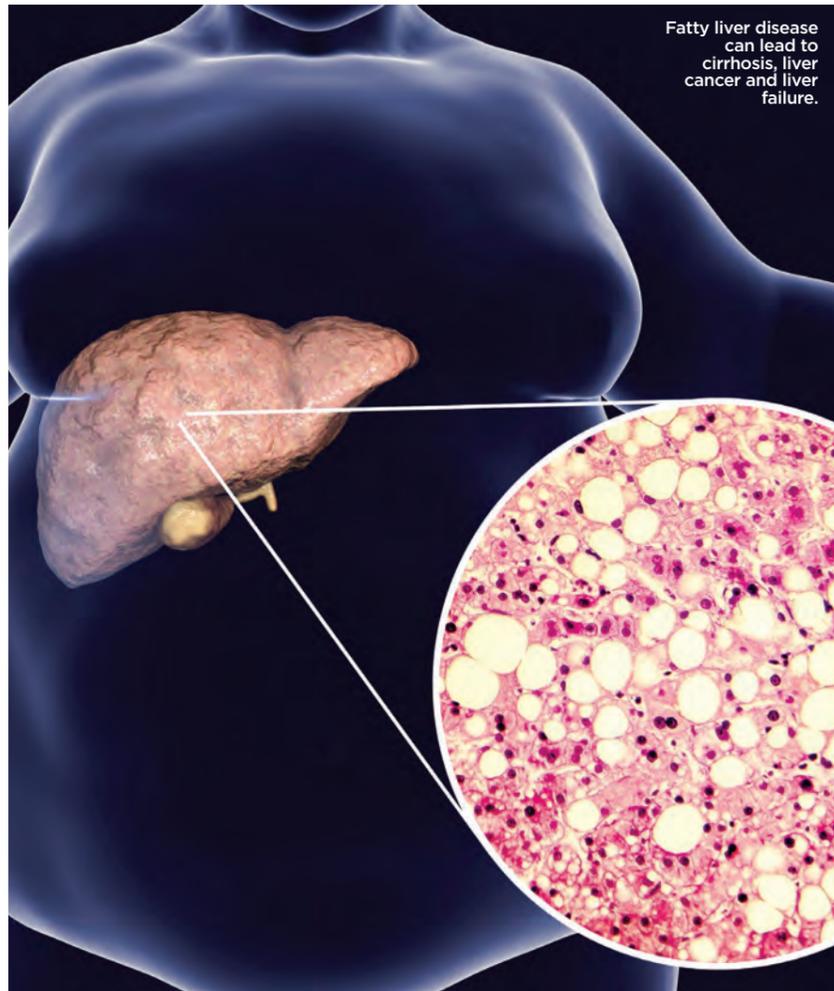
Patients with cirrhosis are at risk of developing complications of advanced liver disease including hepatocellular cancer – the primary form of liver cancer.

Liver cancer is one of the fastest-growing causes of cancer death in Australia and has one of the poorest prognoses. It has a five-year survival rate of just 16 per cent, a statistic that appalls Professor Powell.

"It is particularly troubling because most liver cancer is potentially preventable if the cause of chronic liver disease is identified early and interventions are undertaken to treat it," she says.

In the case of viral hepatitis, there are treatments that can cure or suppress the disease before it leads to the more serious

Liver cancer is now one of the fastest-growing causes of cancer death in Australia and has one of the poorest prognoses.



problems caused by inflammation. Antiviral therapies can cure hepatitis C in the majority of cases, and long-term treatment of hepatitis B can suppress the virus and reduce liver inflammation.

The good news is that only about five per cent of people with fatty liver develop clinically significant liver disease. The bad news is that there are, so far, no medications to treat it.

"There are a number of problems that we need to address," says Professor Powell. "The obvious one is the lack of therapies to treat it."

"And the other major issue is the need for biomarkers that can detect which patients are at risk of disease progression. If we had a good biomarker for inflammation, that

BY THE NUMBERS

Fatty liver disease affects nearly one third of the Australian population

33%

would be really important to detect the small subset of patients at risk from non-alcoholic steatohepatitis."

It's yet another window on the potentially life-changing consequences of better understanding inflammation.

How our bodies can help drive cancer

The inflammatory response can both orchestrate tumour growth and aid its spread

The link between inflammation and cancer was first suggested by Prussian physician Rudolf Virchow in 1863 after he found white blood cells – immune cells – in some cancerous tumours.

He thought that constant "irritation" caused by the immune system could be driving their development, and termed cancer "the wound that doesn't heal" – not a bad way to describe chronic inflammation.

Scientists now understand that inflammation does play a multi-faceted role in certain cancers – not only as a primary cause, but also as a key component that helps tumours grow and even provides the means by which they spread throughout the body.

The inflammation that leads to cancer can be caused by chronic infection, inflammatory diseases or environmental factors that expose the body to harmful chemicals – this last factor could be the result of smoking, excessive drinking, poor diet or exposure to asbestos, for example.

A third of stomach cancer deaths are caused by infection with the bacterium *Helicobacter pylori*, which can set off a chronic inflammatory response. This is similar to the progression to cancer that can occur with fatty liver disease or viral infections of hepatitis B and hepatitis C, which can lead to inflammation of the liver that causes scarring, and can, in turn, result in liver cancer.

What about aspirin?

Many studies have investigated whether an anti-inflammatory medication such as aspirin could reduce the risk of cancer but without any definite findings.

Major lifestyle changes remains the best bet for risk reduction – stop smoking, lose weight, drink less, exercise more and eat well.

Researchers believe that some of the highly reactive molecules containing oxygen and nitrogen released during the inflammatory response are capable of causing DNA damage in cells, which, if not repaired, can play a role in the development of cancer.

The inflammatory response to a primary tumour is also now understood to help orchestrate the growth of cancer cells, as well as helping them spread – the devastating "metastasis" that can turn a treatable primary tumour into a terminal illness.

The inflammatory response sends out signals for immune cells to infiltrate the tumour (see page 5). These produce proteins that, among other responses, muster forces to increase the blood supply carrying oxygen and nutrients to the affected region.

While this increased blood supply is designed to promote healing and recovery, it can have the opposite effect if the tumour hijacks the body's own nutrient supply and drainage systems – the blood and lymphatic vessels respectively – to help spread the cancer cells to other organs.

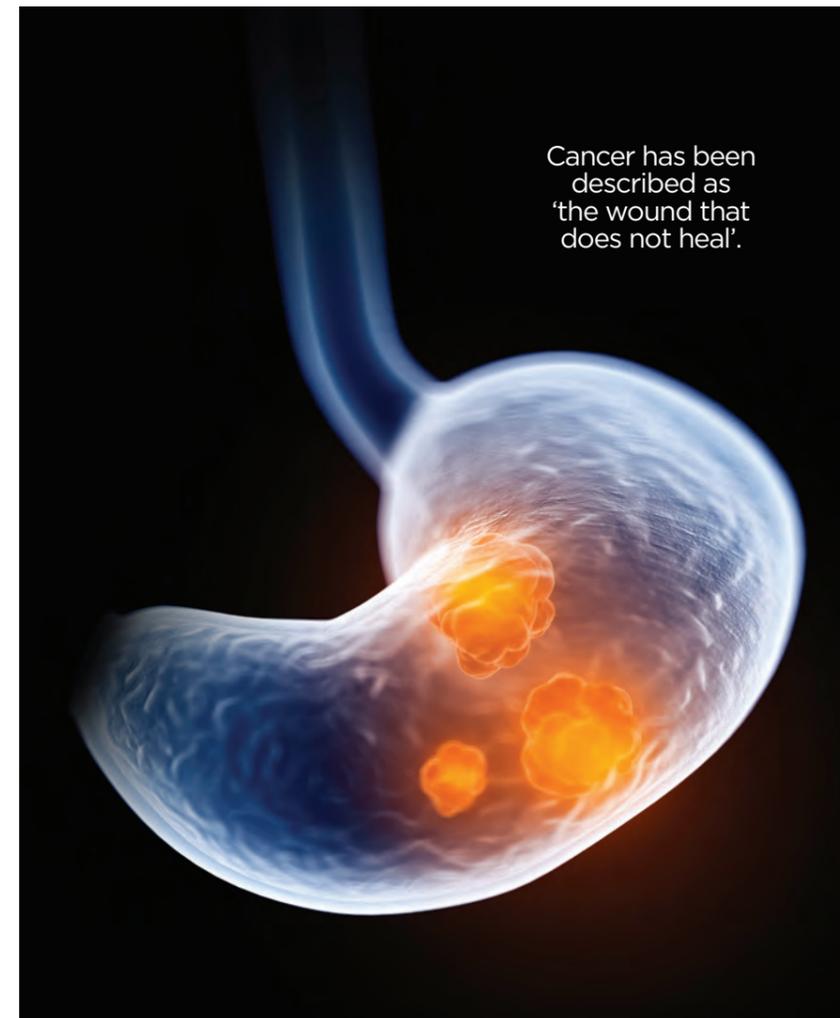
"Many studies have implicated inflammation in the ability of a primary cancer to spread throughout our body," says IMB's Professor Matt Sweet.

Researchers now face the challenge of using our knowledge of inflammation to reduce the chance of cancer developing in the first place.

BY THE NUMBERS

One in two Australians will be diagnosed with cancer by age 85

50%



Autoimmunity: when your body turns on itself

How targeting the body's messaging system offers hope of treatment



In chronic inflammatory diseases, the attack phase never ends.

Professor Jennifer Stow

One of the most powerful chemical messengers is tumour necrosis factor, or TNF, which can be released by immune cells to kill tumours. In inflammatory and autoimmune diseases, the excessive release of TNF promotes ongoing waves of inflammation, causing tissue damage, pain and suffering.

Researchers found that blocking the action of TNF with drugs like Infliximab and Enbrel helps many patients with rheumatoid arthritis.

The results have been impressive, with 70 per cent of rheumatoid arthritis patients showing reduced inflammation and symptoms.

"Unfortunately these treatments don't do much for the other 30 per cent of patients," says Professor Stow. "But they stand as a wonderful proof of concept that we can successfully target the messengers to turn off inflammation. The job of researchers now is to identify additional drug targets to treat all patients."

In autoimmune diseases, the immune system attacks its own tissues, leading to inflammation. The membranes lining the joints are often affected and over time can suffer irreversible damage.

But the damage can go well beyond that, devastating the kidneys, lungs, skin, and eyes.

Why do our defences suddenly turn on us? One of the most frustrating things about inflammation in most chronic diseases is that we don't know exactly what triggers it.

Viral or bacterial infection may play a major role, but environmental and hereditary factors are also at play.

We know, for example, that there is a strong genetic component in up to 60 per cent of cases of rheumatoid arthritis, an autoimmune disease associated with inflammation in the joints and other tissues. Ageing, on the other hand, is a major factor in systemic lupus erythematosus, although as it is most common in women and specific ethnicities, it

also has a hereditary component.

The inflammation causing these diseases starts out as a normal response.

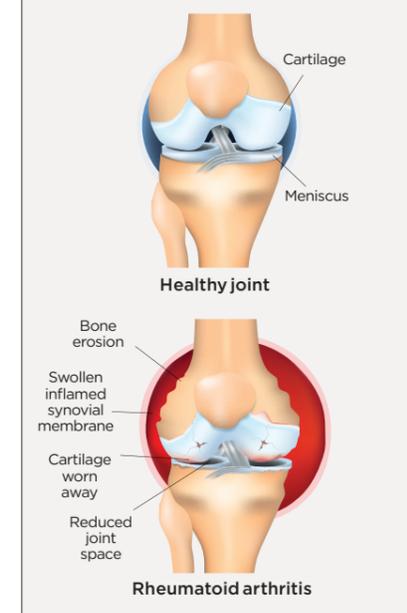
"The attack phase of inflammation is designed to be short and robust and is normally followed by a repair phase to heal any bystander damage done to surrounding tissues," says IMB's Professor Jennifer Stow.

But in chronic inflammatory and autoimmune diseases, the attack phase never ends.

The repair phase is also impaired or inadequate in these chronic conditions, resulting in tissue damage that causes pain and leads to loss of organ function.

With no single cure currently available for autoimmune diseases, researchers have turned to inflammation as the target for possible treatments. One strategy has been to look at how immune cells are activated in the first place, and the role of cytokines – chemical messengers that help to orchestrate the body's responses.

How rheumatoid arthritis strikes



How reducing inflammation is helping ease endo pain

Diet, exercise and physio have become part of the 'toolbox' for managing endometriosis

Jessica Taylor was diagnosed with endometriosis six years ago after a series of frustrating misdiagnoses.

It's a common story for women with the debilitating, painful condition in which tissue similar to that of the uterus lining grows in other parts of the body.

Inspired to help other women with endometriosis, Jessica took the reins as president of the Endometriosis Association (Qld), or QENDO. Through this position, she met IMB's Professor Grant Montgomery, a 30-year patron of QENDO.

Jessica was immediately struck by his work on the genetic factors involved with endometriosis. They forged a strong relationship, and QENDO now raises funds to support Professor Montgomery's research.

"His work is like no other, and so we've tried to make it our mission to give him as much support as we can," Jessica says.

Both Jessica and Professor Montgomery are determined to help advance knowledge of endometriosis, which can seriously impact the lives of the one in nine women it affects.

"Some girls aren't able to work. They're often in crippling amounts of pain," says Jessica. "I have fainted before because of the pain. It just washes over you like a wave. It just shoots at you and it can be at any time; you don't even see it coming."

While researchers such as Professor Montgomery work on untangling the contribution of genetics to endometriosis, women are taking some comfort from an understanding of its inflammatory dimension.

"We know that inflammation causes pain in the pelvic area, and it can become very sore," Jessica says. "But when we reduce the factors that cause inflammation, we see – and I've seen it in



Jessica Taylor suffers from endo and backs IMB research.

We know that inflammation causes pain in the pelvic area, and it can become rather sore. But when we reduce the factors that cause inflammation, we see ... significant benefits.

Jessica Taylor

myself – significant benefits. The disease can be better managed."

Jessica describes it as part of the "toolbox" to handle endometriosis.

"There are lots of things that you can do – diet, exercise, and pelvic floor physio. But it's also important to work with gynaecologists and psychologists. Psychology is a really important tool to help you work through emotions that can come with managing the disease."

Reducing inflammation and building up the immune system through diet can also play a role in living well with endometriosis.

"Some people affected with endometriosis can see great results when

working with allied health professionals such as a dietitian. Certain diets can cause a flare. If you can reduce your triggers that can cause inflammation, such as caffeine or sugar, while increasing the amount of whole grains, vegetables and fruits, it can really help," says Jessica.

"It is really important to understand that what works for one person may not be effective for another. Working with a dedicated team will help you build your toolbox and understand your condition and triggers. Women can then start to see a reduction of the symptoms caused by inflammation."

BY THE NUMBERS

One in nine women suffers from endometriosis, a debilitating and painful condition

11%

STEPH SAUNDERS, LET ME WONDER PHOTOGRAPHY

Venomous animals hold hope for bowel disease

Peptides derived from our deadliest creatures could become next-generation drugs

Not everyone celebrates Australia's plentiful supply of venomous animals, but to the country's 100,000 people with inflammatory bowel disease (IBD) they could be a godsend, offering hope for a treatment to relieve an often hidden, painful struggle.

IBD is an umbrella term for many debilitating conditions – two of which are Crohn's disease and ulcerative colitis – which cause a range of symptoms including abdominal pain, weight loss, fever, diarrhoea, rectal bleeding and fatigue.

As is common with inflammatory problems, we don't know exactly what causes the condition, although there appears to be a genetic element and it may be triggered by an infection.

While the symptoms are bad enough, complications that arise from IBD can be even worse – bowel obstructions, an increased risk of colon cancer and perforated colon.

Until recently there have been few treatments other than general anti-inflammatory steroids and a family of drugs called the aminosalicylates, which are of limited value.

"The response to these lessens as the disease worsens," says IMB's Associate Professor Mark Smythe, a chemist looking for molecules that might stop the inflammatory process in the stomach and intestines in its tracks.

But these potential new drugs present their own challenges.

To the digestive system, proteins are seen simply as food – no different from a steak that needs to be broken down. These proteins can be injected to better effect, but if taken orally as a pill they are digested before they can reach the tissues.

"So we developed a new set of molecules called constrained peptides," says Associate Professor Smythe.

"They're smaller than the large protein molecules so they can be taken orally. But they're big enough to block the really difficult inflammatory targets that underpin IBD."

These smaller constrained peptide-based drugs can also be aimed exclusively at affected gastrointestinal inflammatory targets and do not block the response in healthy tissue, which means patients can take the treatment for longer, with fewer side effects.

And that's where our venomous animals come in – their toxins are abundant in constrained peptides and, realising this, Associate Professor Smythe had his eureka moment.

"I thought it was interesting that there was this niche where nature had evolved all these molecules. So why aren't we using them?"

He set about developing drugs using the same constrained peptides that nature uses, but engineering them with completely new functions and improved potency: the ability to bind to the target and stay bound for as long as possible.

I thought it was interesting that there was this niche where nature had evolved all these molecules. So why aren't we using them?

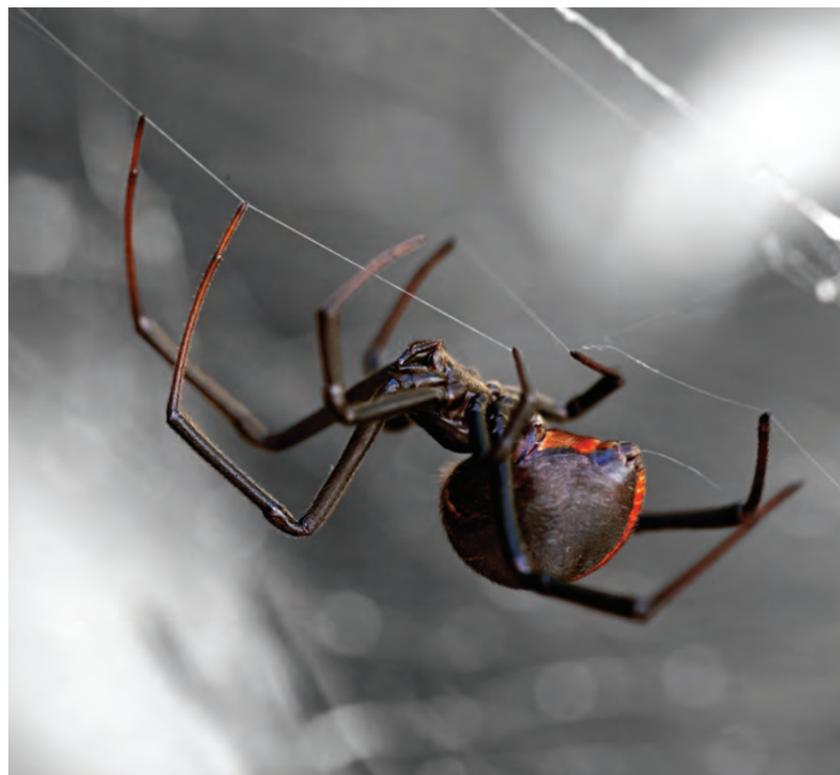
Associate Professor Mark Smythe

While constrained peptide treatments for IBD are not available to patients yet, Associate Professor Smythe helped launch a company, Protagonist Therapeutics, to develop them as drugs.

While early stage trials so far are promising, there is still a long way to go before they are in general use, and even then, they will not help every patient.

"IBD is a very heterogeneous disease; in other words, it comprises lots of different pathways gone awry. These drugs could work for around 20 per cent of patients," Associate Professor Smythe estimates.

But for the many people whose lives are burdened with the effects of IBD, those must sound like odds worth taking.



BY THE NUMBERS

IBD costs Australia \$3.1 billion each year in hospital costs, productivity losses and financial and economic costs

\$3.1bn

A new pathway to asthma relief

Proteins that play a role in asthma attacks are being targeted for new treatments

Nearly everyone knows someone who lives with asthma – it's one of the most common lung conditions in the world, affecting some 300 million people. What many people may not know is the origin of this sometimes life-threatening affliction: asthma is an inflammatory disease.

This means that if scientists can discover the pathways that lead to an asthma attack, it may be possible to develop drugs that target the underlying causes of airway inflammation.

The hallmark symptoms of wheezing and shortness of breath arise from an inflammatory response that causes the chest muscles to tighten and the airways to become inflamed, constricted and to produce extra mucus. Breathing becomes difficult and, in severe cases, the asthma attack can prove fatal.

While many triggers can set off an attack – exercise, respiratory viruses, or exposure to cigarette smoke – the most common is an allergic reaction to airborne particles of pollen, mould or house dust mites.

Allergic asthma affects 10 per cent of Australians and is the one of the most common reasons for hospitalisation of children under five years of age.

There is no cure for asthma, so management of the condition focuses on controlling the symptoms, usually by the initial use of a steroid 'puffer' or 'inhaler'. The only way to prevent some attacks is to avoid triggers.

In the search for better ways to treat asthma, researchers are trying to understand exactly how the inflammatory response to allergens works.

IMB's Professor David Fairlie and colleagues have discovered proteins that activate immune system receptors, an action which in turn plays a significant role in setting off inflammation in an asthma attack.

Previous research had shown that one immune system receptor in the lungs plays a big role in the response that leads to an asthma attack.

What researchers didn't know was exactly how this worked – something Professor Fairlie and colleagues at IMB set out to better understand.

Once they learned how the receptor triggered lung inflammation leading to asthma, they were able to design and develop a potential new experimental drug



that disrupts the action of the receptor.

What's even more exciting for asthmatics is that this potential drug worked on mice when given orally. This could pave the way for a pill to stop the allergic asthma and associated inflammation in its tracks.

While that's still some way off, and would require extensive clinical trials before being made available to patients, it does show that there may be new ways to tackle allergic asthma more effectively than is the case today.

"Current treatments for allergic asthma in humans have major limitations," Professor Fairlie said. "Our results show that there may be a new way to disrupt the inflammatory response in the lungs, which offers the promise of new and improved treatments in the future."

Path of most resistance



Healthy (left) and unhealthy bronchial tubes. The respiratory muscle tightening in the right-hand tube causes constricted breathing.

Diet is your best bet

Our choice of food can either fight or fan inflammation

One of the precautionary steps you can take to avoid chronic inflammatory conditions is to improve your diet.

While some foods increase the risk of chronic inflammation and its symptoms, a healthy diet rich in the right foods can help keep chronic inflammation in check, even when its causes may be beyond our control, as in the case of autoimmune conditions.

What's more, a healthy diet will help you maintain a healthy weight and avoid obesity – itself a major cause of chronic inflammation.

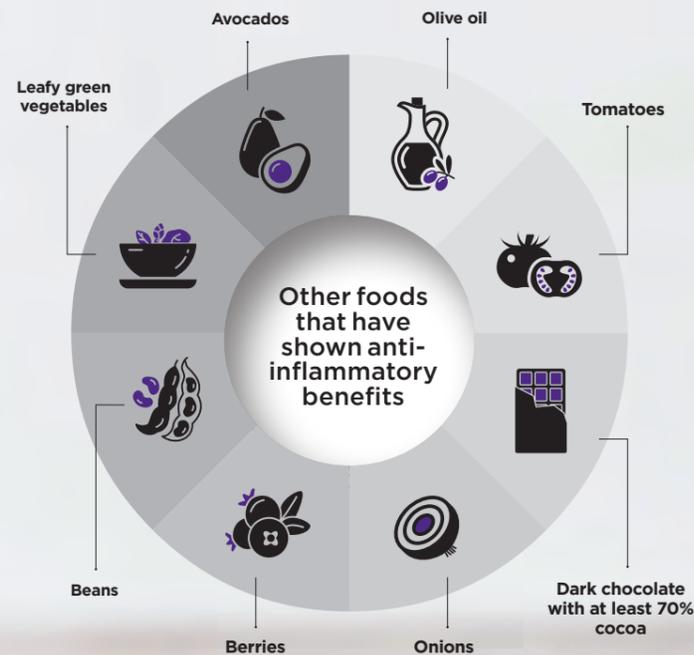
On the positive side of the ledger are all the foods that contribute to a nutrient-rich dietary pattern, including healthy fats, fruit,

vegetables, and whole cereals and grains.

What we call the “Mediterranean diet” contains many of these foods that are high in antioxidants, compounds that may help fight inflammation.

Foods rich in omega-3 fats, such as oily fish like salmon, mackerel and sardines, as well as linseed oil and walnuts, have been found to help reduce inflammation, particularly when it's associated with conditions such as rheumatoid arthritis.

Some of the compounds in broccoli and related vegetables such as cauliflower, kale and Brussels sprouts may help prevent a range of chronic diseases, and this may be thanks to anti-inflammatory actions of the antioxidants they are rich in.



What we call the ‘Mediterranean diet’ contains many of these foods that are high in antioxidants, compounds that may help fight inflammation.



Foods that can make inflammation worse

1. Added sugar and refined carbohydrates

Diets high in added sugar have been linked to inflammatory uric acid, insulin resistance and heart disease. Apart from direct inflammatory effects, excessive added sugar has been linked to obesity, diabetes, fatty liver disease and cancer. Avoid sugary drinks, and choose whole grains over refined white breads and cereals.

2. Alcohol

Although some studies have shown that light-to-moderate consumption of red wine can have anti-inflammatory benefits, too much alcohol can cause inflammatory problems in your gut and liver. Alcohol can also cause gout, an inflammatory form of arthritis.

3. Artificial trans fats

While the bad publicity these have received in recent years means they are being used less, trans fats are still found in some highly processed and deep-fried takeaway foods. They are created by adding hydrogen to unsaturated fats to make them more stable. The telltale words to look for in the ingredients list are “hydrogenated oils”.

4. Processed meat

Processed meat, including sausages, bacon, salami and ham, have been linked to cancer, particularly bowel cancer, with the World Health Organization classifying them as a Group 1 carcinogen. One of the mechanisms underlying this link is believed to be an inflammatory response by colon cells.

Gut feelings

How the microbes that live inside you affect your health

Good bacteria are vital for good health. There are trillions of these microscopic cells living inside us, along with other microorganisms including viruses and fungi. Collectively, they form a community of microbes – a complex ecosystem called the microbiome.

These microbes can and do live in lots of places in and on our bodies, including our mouth, nose and skin. But they are most often found in our digestive system, particularly in the large intestine. This

community of microbes is referred to as the gut microbiome.

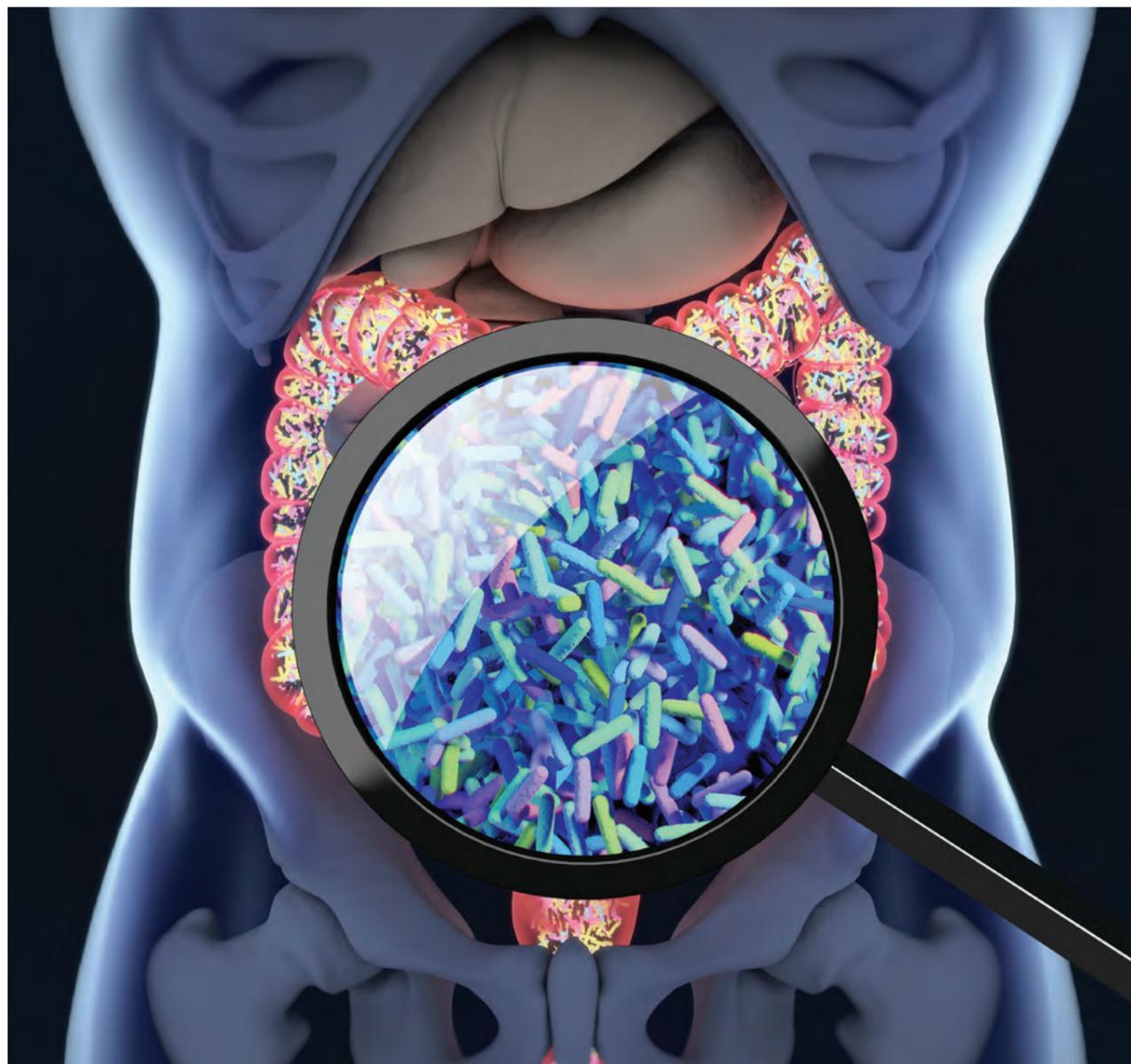
Scientists have long known that the microbiome is important for our health. It helps keep our digestive systems running smoothly, breaking down food for nutrients and transforming vitamins into useful forms.

But scientists are finding more and more functions linked to the microbiome, and realising that its impacts are more widespread than previously thought. For example, altered gut bacteria have

First steps

Three Fs for good gut health, according to Professor Tim Spector, head of the British Gut Project:

- ▣ Fibre – and plenty of it
- ▣ Fruit and veg – in as many varieties as possible
- ▣ Felines – spending time with animals increases your microbial diversity



Scientists are finding more and more functions linked to the microbiome, and realising that its impacts are more widespread than previously thought.

been found in obese mice, and in many different disease states. The gut microbiome might even affect our mental health, with some evidence linking it to disorders such as depression and anxiety, although we still can't be sure it causes those conditions. And at least one study has shown that there is a correlation between microbiome diversity and sleep quality.

What we can say for sure is that changes to the microbiome are present when there are inflammatory diseases. While it is too early to tell if one causes the other, it means that an altered gut microbiome can be a biomarker for disease. Scientists have observed changes in the composition of the microbiome taking place in inflammatory diseases such as type 2 diabetes and fatty liver disease.

The exact mechanisms are not always clear, but it appears that some microbes, or molecules that they produce, can move from the gut to affect organs such as the liver to cause inflammation.

The good news is that while you may not be able to see your microbiome, you can change it. Environmental factors play a big role, determining the bacteria to which you are exposed.

You should also avoid the unnecessary use of antibiotics, both to avoid killing your good gut bacteria and also to help prevent the development of antibiotic resistance.

The most important factor, though, is the food you eat. A good diet, along the guidelines you can read on pages 18 and 19, will help support good bacteria and keep your gut – and you – healthy.

BY THE NUMBERS

The percentage of our gut microbiome that is unique to each individual

66%

INSTITUTE OF MOLECULAR BIOSCIENCE

RESEARCHER PROFILE

Professor Kate Schroder



Professor Kate Schroder heads IMB's Inflammasome Laboratory, which she set up in 2013. It was a return home for her, having completed her PhD at IMB in 2005, before moving to Switzerland to work with a famous Swiss immunologist.

It was when working under Professor Jürg Tschopp that she became hooked on the biology of inflammasomes – inflammation-generating molecular machines that trigger immune cells to respond to an infection or injury (see page 24).

She is unravelling the secrets of these protein complexes. The work is paying off, with potential new therapies about to be rolled out in clinical trials through a startup company based in part on Professor Schroder's research.

The company, Inflazome Ltd, attracted one of the largest investments in Australian university intellectual property when it raised A\$22 million in its first round of funding and A\$63 million in its second round recently.

The capital is being used to develop compounds that are designed to switch off the inflammasome – to turn off unhealthy inflammation in disease.

This could be a gamechanger in treating inflammatory diseases – those associated with the innate immune system – which include many human diseases, such as gout, diabetes, neurodegenerative diseases and cancers.

The link between inflammasomes and autoimmune diseases is much less clear than that between inflammasomes and inflammatory diseases.

"Inflazome is advancing the compounds with the aim of developing new treatments for inflammatory disease where there are significant unmet needs, such as Parkinson's disease," Professor Schroder says.

Inflamm-ageing

Is ageing accelerated by inflammation?

There is no doubt that chronic inflammation is a major contributing factor in many of the diseases we associate with getting older. Parkinson's and Alzheimer's diseases are inflammatory by nature, and chronic inflammation is a risk factor in diabetes, atherosclerosis and cancer – all conditions that we are more likely to develop as we age.

But why should inflammation leave us so susceptible to increased incidence of these diseases as we get older? In many respects, the answer may be simply that as we age,

What happens as we get older?

Older people often have high levels of pro-inflammatory markers in the blood and other tissues.

Some clinical trials suggest that reducing inflammation can prevent cardiovascular diseases, but there are few studies on other chronic diseases of old age and those there are, so far are inconclusive.

Obesity contributes to age-related disease because visceral fat produces proinflammatory compounds that activate the immune system and drive inflammation.



As you age, your immune system ages too, and you lose control over the inflammatory processes.

Professor Ian Henderson

we slow down – we may become less active, exercise less and gain weight. Chronic inflammation plays precisely into this sort of feedback loop.

The older you are, the more you have been exposed to environmental factors, and past injuries can come back to haunt us.

“I think inflammation is the great driver of ageing,” says Professor Ian Henderson. “We’re all a product of our own history.”

“If you’re young and you have an injury, it heals and it doesn’t bother you when you’re 20. It doesn’t bother you at 25 or 30, but when you get to 60 it begins to cause you problems.”

These examples of inflammation occurring decades after the event are also true of infection.

“As you age, your immune system ages too, and you lose control over the inflammatory processes,” says Professor Henderson.

Older people do have consistently elevated levels of inflammatory chemical messengers, especially interleukin-6 (IL-6), which is called into action by the protein response system known as the inflammasome (see page 24), and tumour necrosis factor (TNF). The suppression of which has proved useful in the treatment of rheumatoid arthritis and other inflammatory conditions (see page 14).

But higher levels of these chemical messengers are also linked to other factors such as smoking, and many others.

“If you don’t sleep, for example, you become more inflammatory,” says Professor Henderson. “You can connect a lot of the non-infectious diseases to inflammation.”

BY THE NUMBERS

Dementia and Alzheimer’s disease is the leading cause of death for females in Australia at

11%

INSTITUTE OF MOLECULAR BIOSCIENCE

RESEARCHER PROFILE

Professor Matt Sweet



What controls ‘innate immunity’, our broad defence system that triggers inflammation when invading microbes, cellular damage or noxious stimuli are detected in the body?

That’s what Professor Matt Sweet’s laboratory is studying, seeking to understand how ‘pattern recognition receptors’ (PRRs) – the families of molecules that our immune system use to detect danger – work, in the hope of controlling them to treat inflammation-mediated diseases or harnessing their power to treat infectious diseases.

“Inflammation is tasked with trying to eliminate the danger, whether it’s an infection or an injury, and return the system to normal,” he says. “We used to think inflammation had a role in only a limited number of conditions, but we now appreciate that it actually is *driving* disease, causing pain, discomfort and loss of function in many, many different diseases.”

Inflammation is the body’s way of focussing defences in an area where

danger is afoot and where repair work is needed. But in chronic conditions – like arthritis, diabetes, Alzheimer’s, inflammatory bowel disease and chronic liver disease – inflammation often drives the loss of function of the particular organ, or organs, that is characteristic of the progression of that disease, for example joints in arthritis.

“We’re trying to understand how different pattern recognition receptors are awakened, how they drive antimicrobial responses that enable immune cells to kill infectious agents, and how they drive destructive inflammation in different disease settings,” he adds. “If we can understand how various pattern recognition receptors function, we can then manipulate them in different ways to combat both infectious and inflammatory diseases.”

The little protein engine that could

The inflammasome may help us control inflammation at a molecular level

Of all the elements that make up the inflammatory response, none is more intriguing than the inflammasome – a machine-like protein complex at the heart of inflammation and disease.

Inflammasomes are part of the innate immune system and operate at a molecular level. They are triggered when an infection is detected and then activate specific cytokines – messenger proteins that tell immune cells that they should respond to the threat.

But inflammasomes can also be triggered by non-microbial molecules that might indicate an injury. Genetic mutations in inflammasome components can be inherited and also cause inflammatory disorders.

When everything is working as it should, the threat is resolved, and the inflammasome's in-built timer switch ensures that the inflammasome only operates for a specific length of time.

As the head of IMB's Centre for Inflammation and Disease Research, Professor Kate Schroder, explains, "but if the inflammasome continues to fire, inflammation can become chronic, with disastrous results".

Inflammasome-linked cytokines have been identified as the drivers of the inflammatory

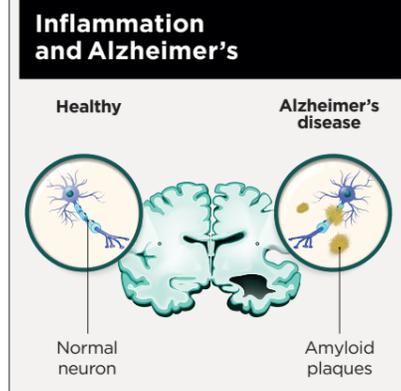
If the disturbance can't be cleared...these molecular machines continue to fire, resulting in neurodegenerative damage from the sustained inflammation.

Professor Kate Schroder



Professor Kate Schroder.

INSTITUTE OF MOLECULAR BIOSCIENCE



component of numerous chronic diseases including gout, diabetes, Alzheimer's disease and fatty liver disease.

"If the disturbance can't be cleared, such as in the case of amyloid plaques in Alzheimer's disease, these molecular machines continue to fire, resulting in neurodegenerative damage from continuous inflammation."

Professor Schroder is studying how the inflammasome works during infection and how it can misfire in human inflammatory disease. By understanding how unhealthy inflammation begins, she hopes to design

new strategies to treat many common diseases.

One experimental strategy used in Professor Schroder's lab is to use gene-editing technologies to alter the inflammasome's in-built timer, in effect, turning up or down the volume on unhealthy inflammation to understand its impact on disease.

Another clinical strategy is the development of drugs that could inhibit the inflammation response, which are currently being commercialised by drug development company, Inflazome Ltd.

Cutting off the power to slow things down

Could macrophages' unique metabolism be the key to disrupting inflammation?

Could we turn the immune system's own power plant against it to control out-of-control inflammation? Professor Matt Sweet thinks so.

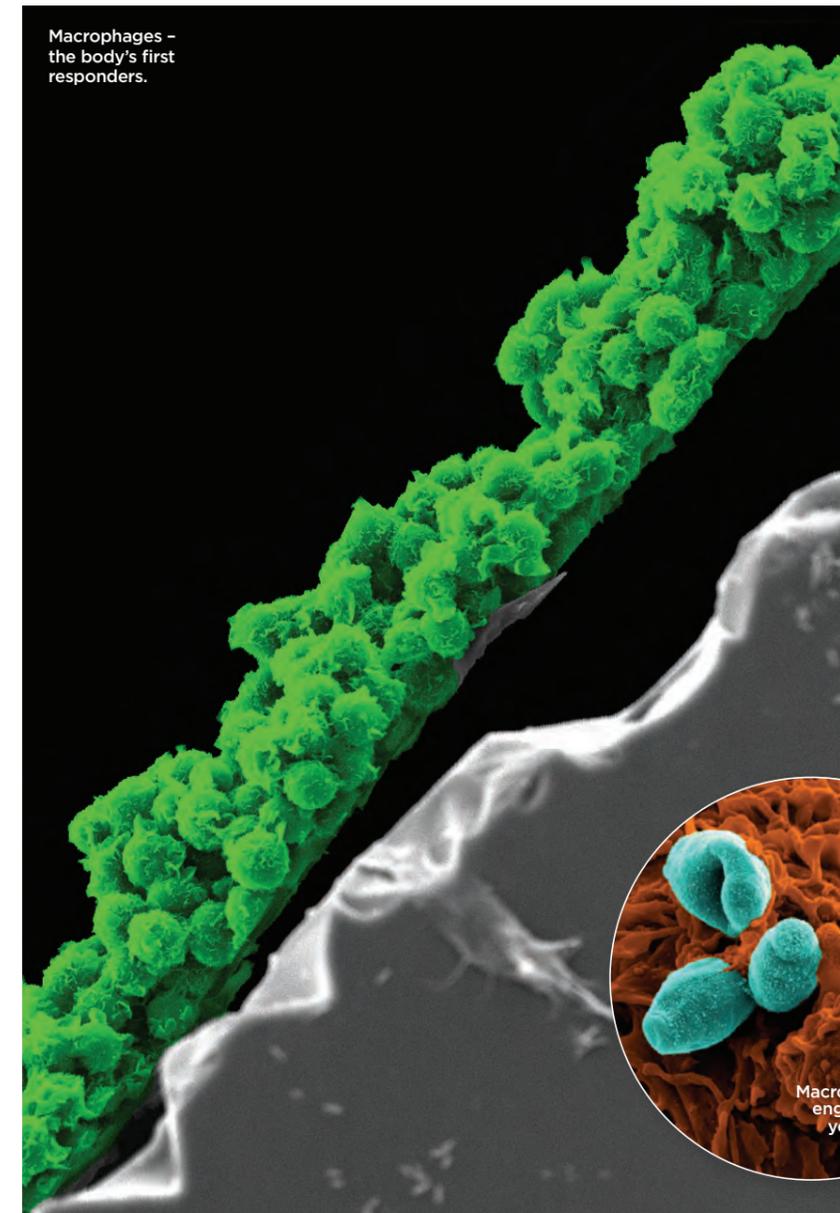
The IMB Group Leader specialises in the study of innate immune cells – the first responders to environmental threats – and

much of his work involves macrophages, the cells that protect the body by engulfing dangerous intruders such as bacteria.

Macrophages identify these intruders and set the inflammatory response in action by releasing cytokines – proteins that activate other immune cells.

If we can turn off or dim the switch, it will enable us to shut down inflammation when it goes awry.

Professor Matt Sweet



Macrophages – the body's first responders.

"But in order for the macrophages to do so, they need to reprogram their metabolic pathways," says Professor Sweet.

Macrophages need energy, as do all cells. The traditional powerhouses in the cell are mitochondria, which break down nutrients to create the energy-rich molecule adenosine triphosphate (ATP).

"Mitochondria are very good at making ATP," says Professor Sweet. "But it's a relatively slow process, which is fine if the macrophage is just hanging out in the tissue, helping to make sure everything runs smoothly."

But when danger appears, macrophages need to swing rapidly into action, resulting in sudden huge energy demands.

"Macrophages need to manufacture a whole lot of molecules really quickly," says Professor Sweet. "So there is another metabolic pathway, glycolysis, that is much less efficient at making ATP than mitochondria, but much faster."

And so as the macrophage responds to its changing environment, it makes a sudden switch, reprogramming its metabolism to turn on glycolysis, the process that breaks down glucose to generate energy.

That led Professor Sweet to wonder if we could use this unique process to close down the macrophage power supply and so disrupt, or even stop, the inflammatory response.

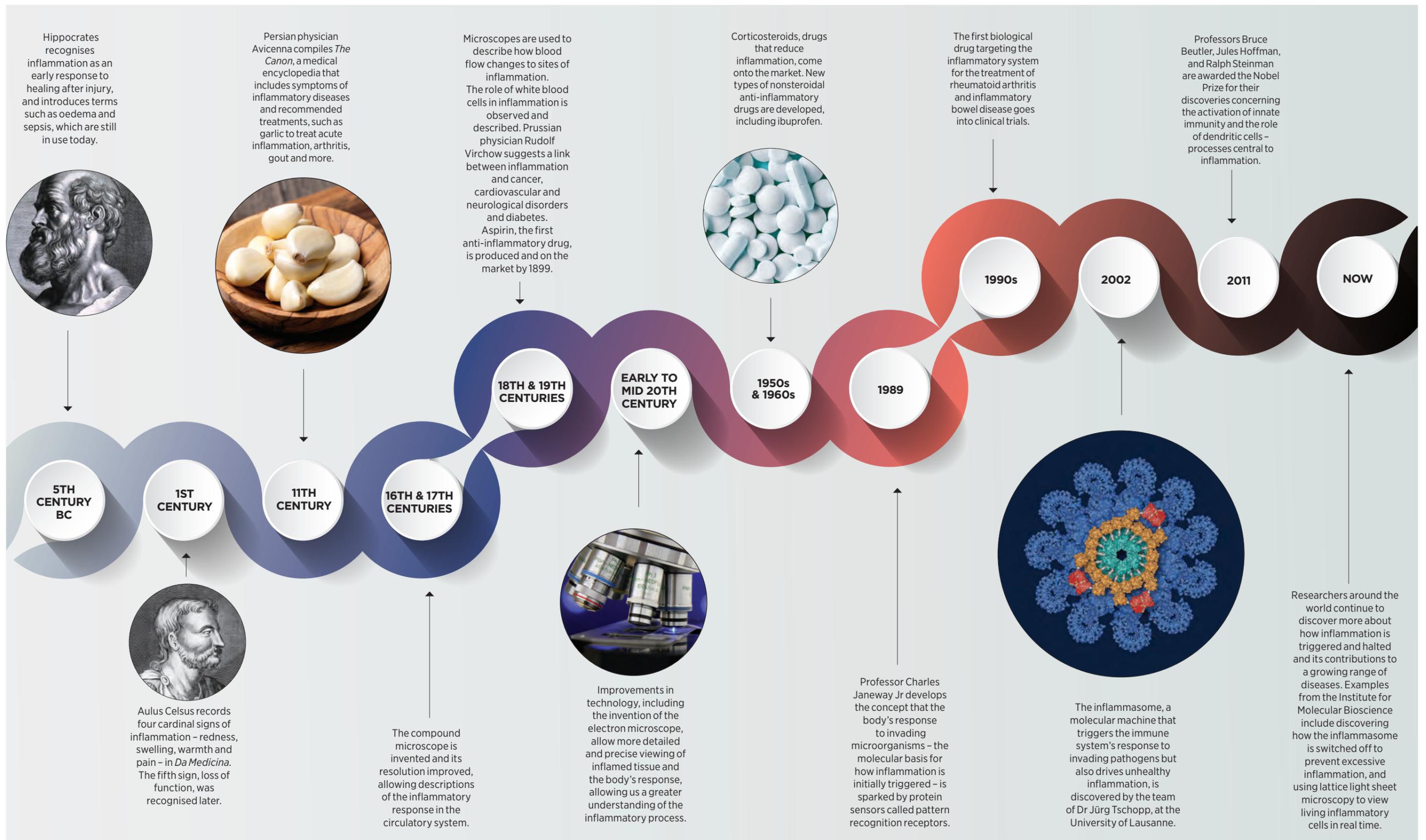
"If we can turn off or dim the switch, it will enable us to shut down inflammation when it goes awry," he says.

Professor Sweet and his team have already identified a key element that controls the switch for power production.

"The enzyme represents a potential target by which we may be able to block inflammation by reprogramming immune cell metabolism," he says.

The inflammation timeline

The ancients knew how to recognise inflammation and described accurately how it manifests itself. As technology has improved, so has our understanding of its impact.





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