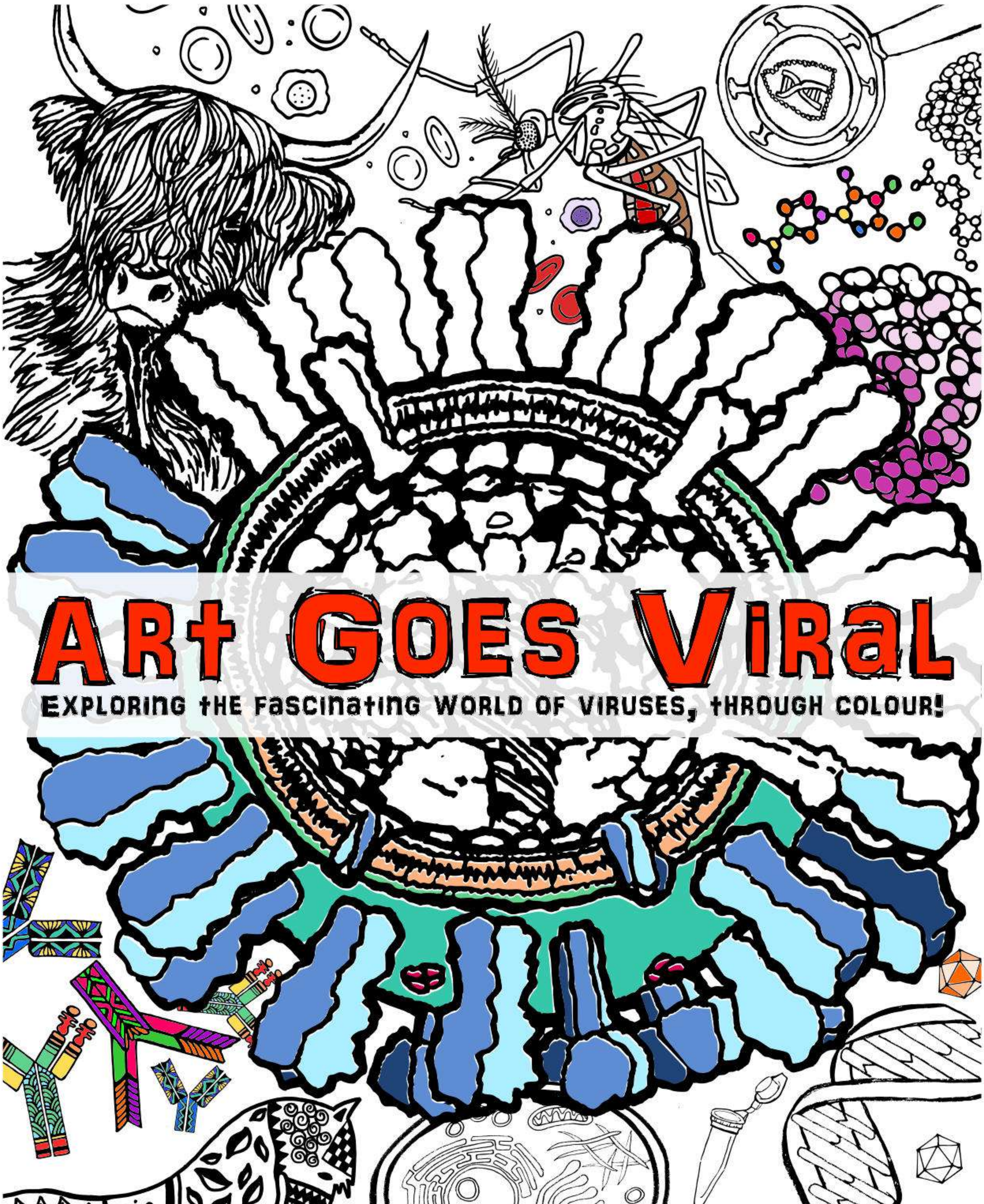

Art Goes Viral

Exploring the fascinating world of viruses, through colour!

Medical Research Council MRC

CVR Medical Research Council University of Glasgow Centre for Virus Research

University of Glasgow
Via Veritas Vita

For further information please contact us at http://www.gla.ac.uk/researchinstitutes/iii/cvr/contact/

Art Goes Viral

At the MRC-University of Glasgow Centre for Virus Research (CVR) we know that, like viruses, creativity is contagious. To help spread the fun, we have designed our very own colouring book!

Illustrated and written by CVR scientists, we hope this book gives you a bit of welcome relief from the daily stresses of life, while inspiring you with interesting facts about viruses and the incredible research underway at our research centre in Glasgow.

Viruses are tiny, yet they never cease to amaze us. So, pick up a pencil and take yourself on a journey of virology discovery.

Go forth and be vibrant with colour.

Best wishes from the CVArt Team

'Creativity is contagious – pass it on'
Albert Einstein

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What are Viruses?

1. What is a Virus?

Ed Hutchinson

A virus is a set of instructions which cause a cell to copy them and release those copies inside tiny, infectious particles. Though viruses are extremely small, they are also extremely common – more so than anything else in the natural world.

To replicate, viruses take control of the normal activities of cells. The top of this image shows the replication of herpes simplex virus, which causes cold sores. On the left, a virus particle binds to and enters a cell, releasing genetic instructions. These cause the cell to make many more copies of the virus, which can be seen emerging on the right.

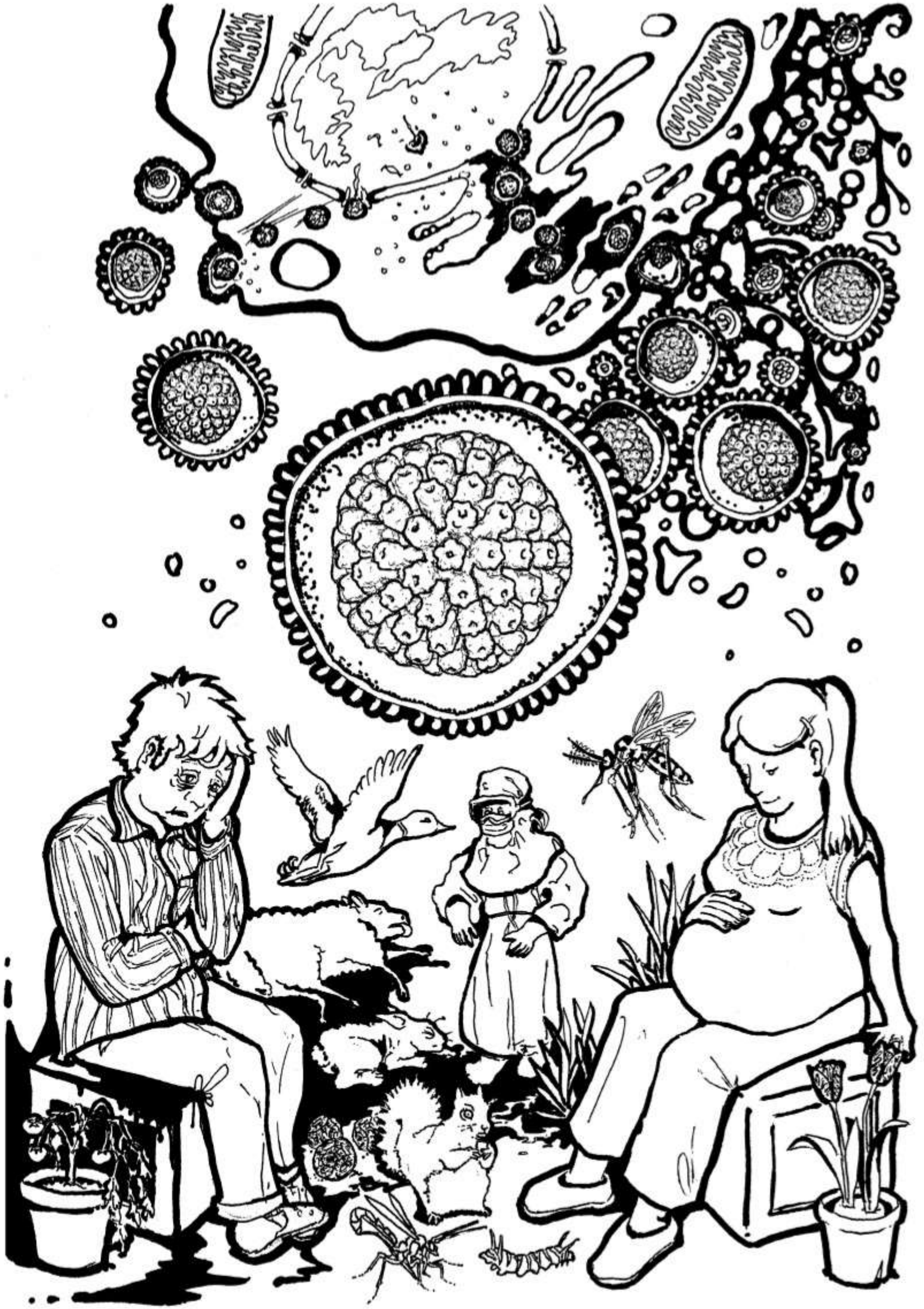
As viruses are too small to see, they are most noticeable when they cause disease. Viruses cause many of the most common, and some of the most serious, diseases of humans, domesticated animals and plants. However, many, perhaps most, viruses have adapted to exploit their hosts with few effects, and some even provide their hosts with benefits.

Did you know?

Viruses have many different effects. Some viruses cause apparent disease – here a human experiences fever, a sheep collapses from bluetongue virus and the tomato spotted wilt virus does as its name suggests. In the background, a medical worker dons protective clothing to avoid infection with the lethal Ebola virus. A mosquito can spread many diseases, viruses included.

Viewed in the right light, viral diseases can have some benefits. Viruses kill marine plankton (shown greatly enlarged) in ways which help to keep nutrients circulating in the oceans. In the UK **squirrel parapoxvirus** causes a fatal disease in red squirrels but is carried with few effects by North American grey squirrels, allowing them to spread across the country. The same situation in reverse helped European humans, and their diseases, to colonise the Americas. Parasitoid wasps have a relationship with **polydnaviruses**, which do not harm them but allow them to disable the immune defences of the caterpillars they lay their eggs inside. Humans have used the **myxoma virus** to control the spread of rabbits in Australia, and tulip breaking virus to create pretty patterns on flower petals.

Some viruses cause no apparent disease in their main hosts. Ducks, for example, can carry **avian influenza viruses** without showing obvious disease. Some viruses even benefit their hosts directly. Certain panic grasses can grow in scalding hot volcanic soils due to a relationship between the grass, a fungus, and a virus. We ourselves carry many viruses without ill effects, and our own genomes contain the remains of viral genes. Most are decayed and dormant, but some prove very useful. In particular, a former viral gene, very similar to a gene found in **retroviruses** such as **HIV**, plays a critical role in forming the placenta during pregnancy.



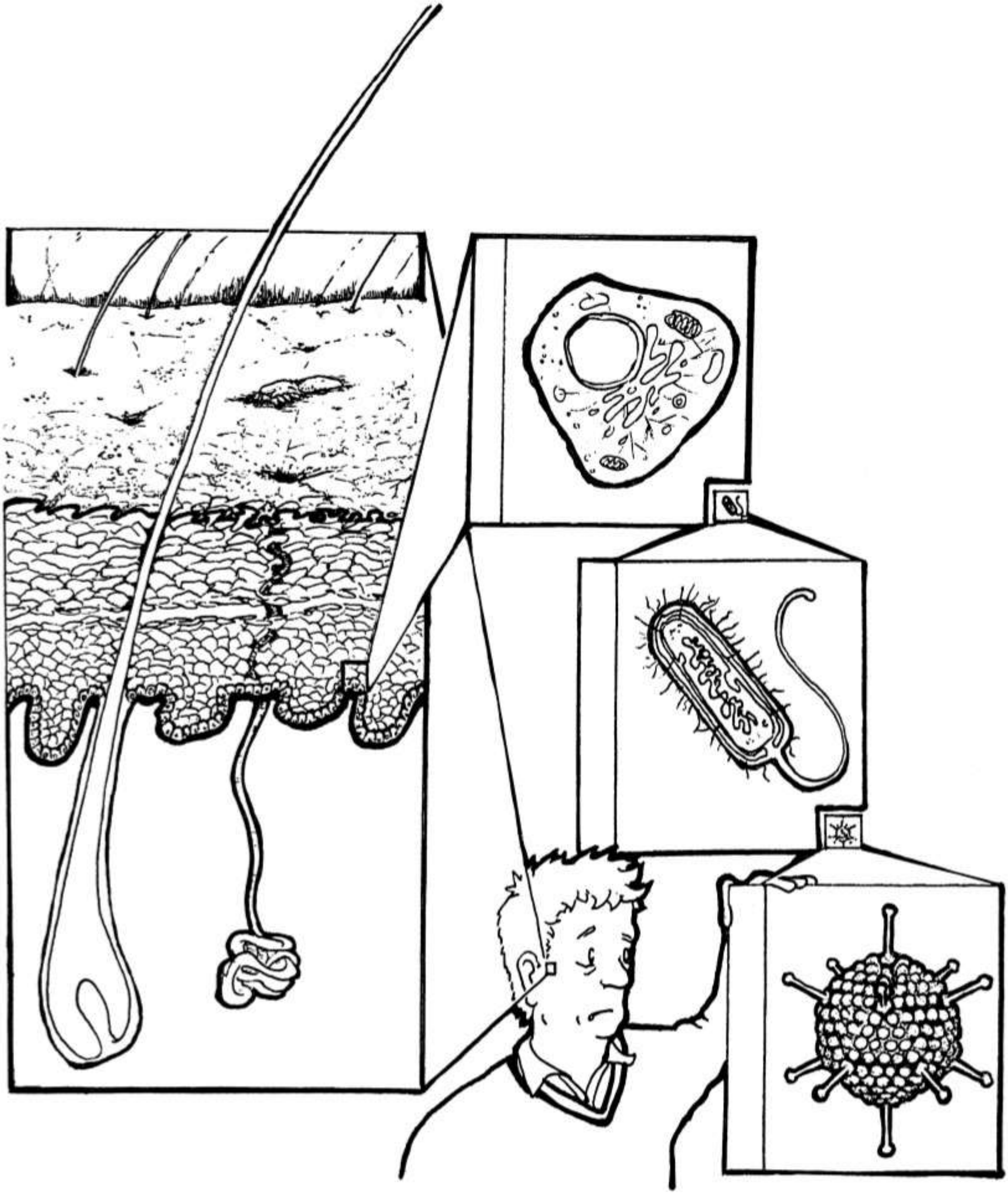
2. Different scales of life

Ed Hutchinson

Most cells in our body are slightly too small to be seen with the naked eye – just under a tenth of a millimetre across. The cells in skin can be seen on the left of this image – a hair and a sweat gland pass through layers of living cells and, above them, a tough crust of dead, dried skin cells protects our body and is eventually shed as dust. In the distance an eyelash mite can be spotted – a tiny and typically harmless resident of our faces. Its body length is only a few times longer than one of our skin cells, and most of us don't realise we carry them.

Zooming in on a single cell reveals that despite their tiny size our cells have an extremely complex internal architecture. It also allows us to see bacteria – also a type of cellular life, though very distantly related to us. Bacterial cells, such as the gut bacterium ***Escherichia coli*** shown here, are typically ten times smaller than our own cells and have a less complex internal structure.

Ten times smaller again are typical viruses, such as this **adenovirus**. Virus particles are not cells, and by themselves they do very little. They are simply containers for instructions which, once infected, cells can be forced to follow.



3. How big are viruses?

Ed Hutchinson

Viruses are extremely small.

We are used to thinking about very large things, such as mountains and cities, and scaling them down to maps. This skill can be used in reverse to think about how big we are compared to very small things, such as viruses. Try putting your hand on this map, which shows the city between the CVR and the main campus of the University of Glasgow at a 1:25,000 scale. Now try and imagine that your hand is really as big as the map features it covers. On your giant hand, your fingernails would be the size of city blocks, the creases in your skin would be the size of roads, and your hairs would be about as thick as person is tall.

On the surface of your city-spanning hand, each skin cell is the size of the table you may be sitting at to read this – a substantial thing, but slightly too small to make out with the naked eye.

Each of the many bacteria clinging to you is about the size of a coffee mug.

And a single virus particle, as shown above, would be the size of a pebble.

There is room for a lot of pebbles on that giant hand of yours.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4. What do viruses look like?

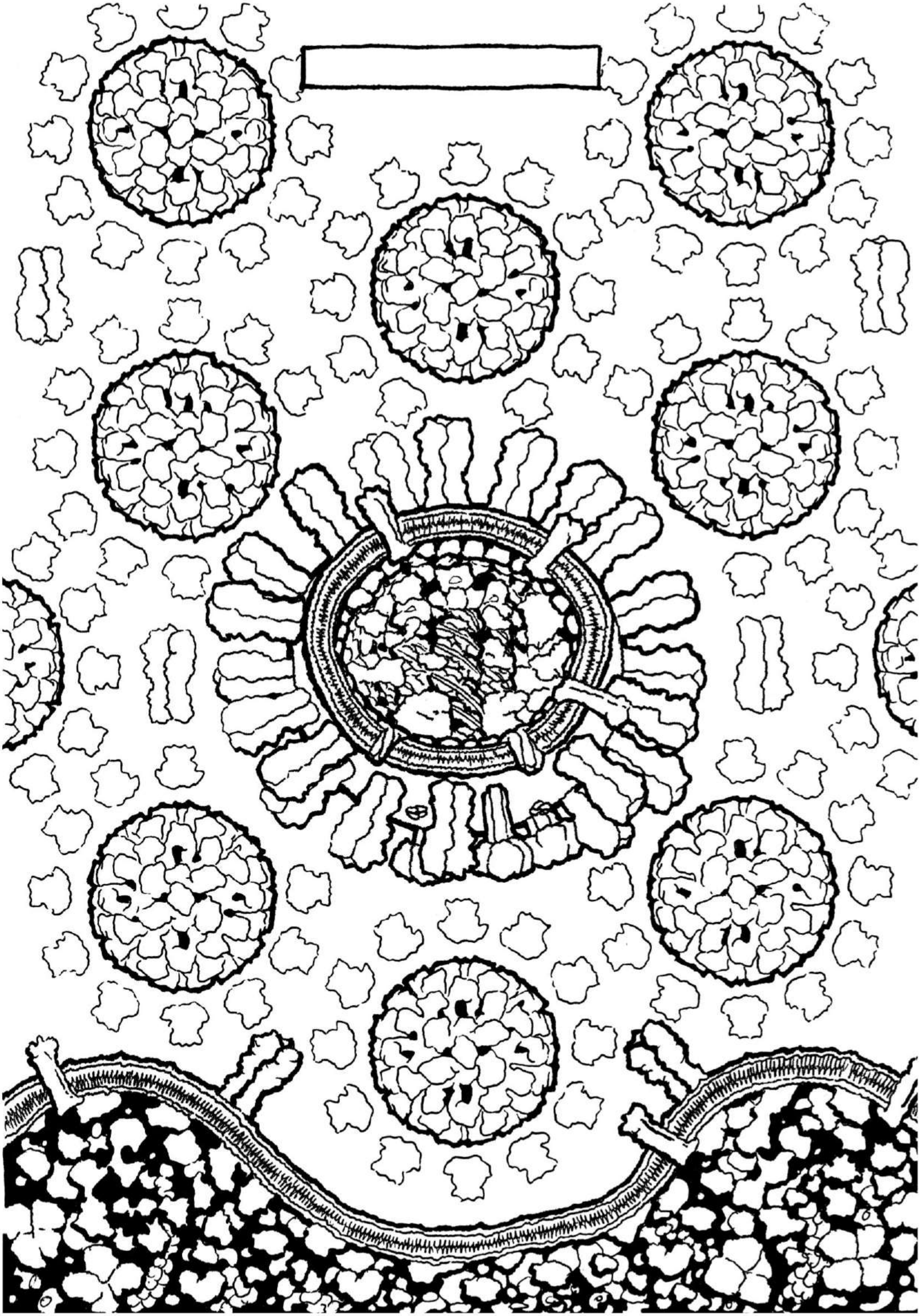
Ed Hutchinson

When we think of viruses, we tend to think of the virus particles that carry them from one cell to another. Virus particles, also referred to as **virions**, are the containers for carrying viral genes between cells. The genes themselves can be encoded in double strands of DNA, much like our own, but they can also be stored in other ways. Some viruses use single strands of DNA, while others use the related molecule RNA (although our cells do contain RNA, they do not use it for the long-term storage of genetic information).

Virus particles are simple structures, made of a small number of proteins in a repeating pattern. This pattern is typically either a helix, which makes a rod-shaped particle, or an icosahedron, which makes a ball-shaped particle. Some viruses will also scoop up membranes and other structures from the host cell.

Virus particles need to bind to new cells to infect them, and so they are covered in spikes which allow them to grab hold of and enter cells. Antibodies which bind to these spikes can stop viruses infecting cells, and vaccines often work by training our bodies to produce antibodies that can do this.

This image shows a virus particle of **influenza virus**, which causes respiratory infections in humans, surrounded by virus particles of **feline calicivirus**, which causes respiratory infections in cats. The bar at the top is 0.1 microns - a ten millionth of a metre, or a ten thousandth of a millimetre. Below is the surface of a cell, from which the **influenza virus** has scooped up a membrane. The **feline calicivirus** particles are each made of exactly 180 copies of a coat protein, which is shown surrounding them. Also in the background are the protein spikes that **influenza virus** particles use to bind to and enter cells.



5. What are viruses made of?

Ed Hutchinson

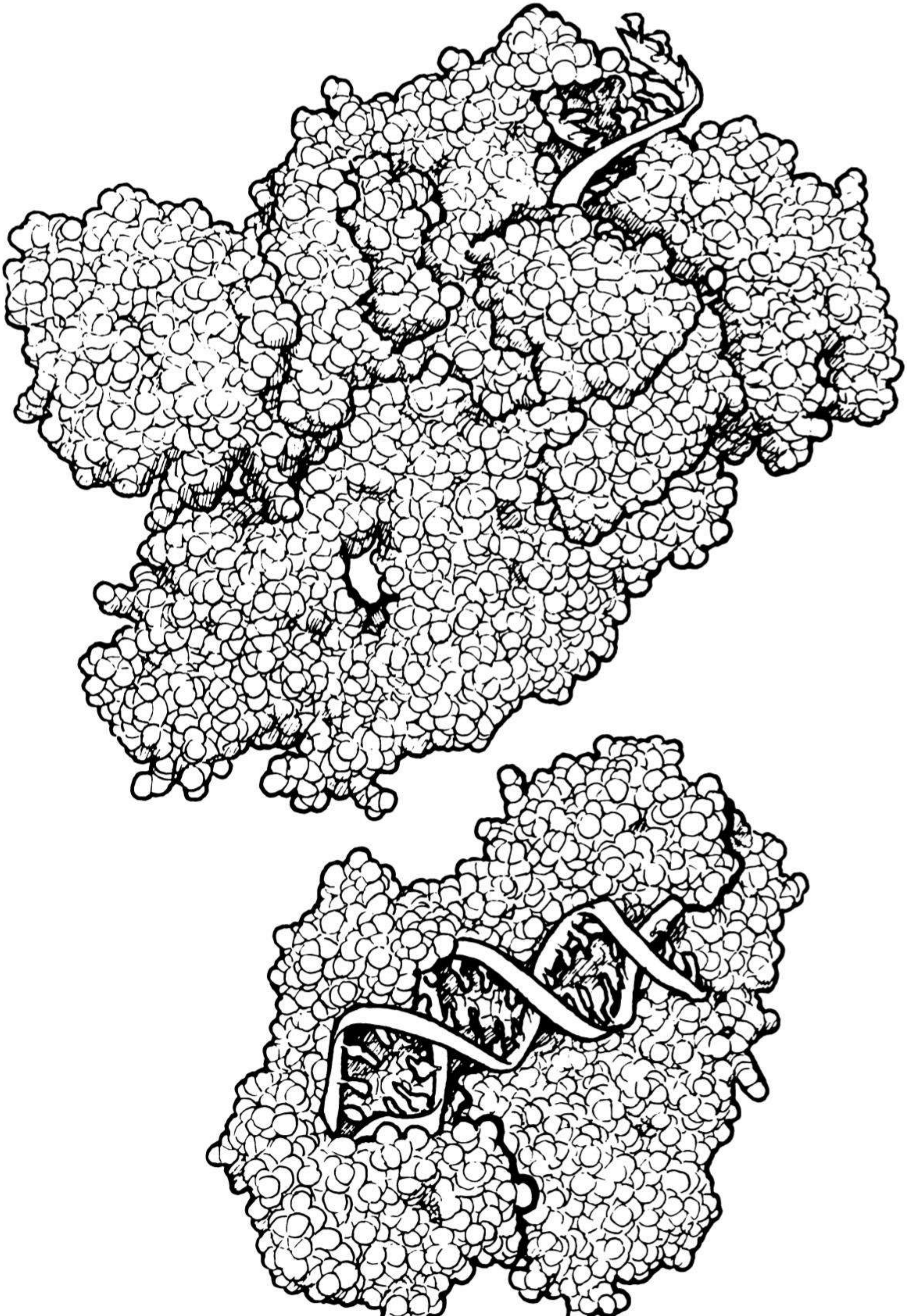
On the last page, we explained that virus particles contain genetic instructions, encoded in strands of DNA or RNA. These genetic instructions cause host cells to make proteins, which are assembled with new copies of the viral genes, and in some cases membranes, to produce new virus particles.

Some of these proteins are encoded by many different viruses, and suggests that all viruses are related to each other. These viral 'hallmark' proteins are not encoded by anything else in the natural world. As an example, this image shows two proteins which can directly copy RNA. This is something our own cells cannot do – although our cells do make RNA, they do this indirectly by copying a DNA template. At the top are three influenza virus proteins, which act together to copy RNA to make more RNA. Below is an HIV protein, which copies an RNA template to make DNA. Carbon atoms in the protein are drawn as spheres and RNA (bound to the influenza proteins) and DNA (bound to the HIV protein) are shown as ribbons.

Did you know?

Viruses are ancient. The uniqueness of viral hallmark proteins and their presence in very different viruses suggests that viruses have been evolving separately from all other life for a long time. Indeed, it seems likely that the relationships between some viruses are extremely ancient – quite possibly more ancient than the last common ancestor of all cells.

Even before cells, there was life. And it seems that, even then, there were viruses.



Viruses in Health and Disease

6. How do viruses make us sick?

Stephanie Cumberworth

Viral infection doesn't always cause disease, but when it does it can cause some unpleasant symptoms. Sometimes this is due to the virus itself, altering how our bodies function, to increase their spread. However, in the fight against infection your own body can leave you feeling under the weather, through a complex set of processes collectively known as 'inflammation'.

How viruses make you sick:

The 'winter vomiting bug', **norovirus**, affects the gastrointestinal system and causes vomiting and diarrhoea to aid its spread. Respiratory viruses such as **influenza** (flu) and the common cold (caused by many different viruses, including **rhinovirus**) make us sneeze and cough to spread virus particles through water droplets. **HIV** destroys our immune system to avoid detection. Other viruses grow better when they force our cells to divide, which can lead to cells dividing uncontrollably as cancer; for example, some **Human Papillomaviruses** (HPV) have been associated with cancer.

Inflammation:

Viral infection is detected by immune cells near the area injured by infection, which alert and recruit circulating immune cells from the bloodstream using **cytokines**. Cytokines are specialised molecules which act as 'breadcrumbs' to guide new immune cells to fight at the site of infection (pictured opposite). Inflammation itself is damaging to the body and in excess causes the symptoms of the most severe viral diseases including haemorrhagic fevers and encephalitis. During haemorrhagic fever, blood vessels become leaky causing bleeding; **Ebola** virus and **dengue virus** can cause haemorrhagic symptoms. Encephalitis is a condition where the brain becomes inflamed and can be caused by viruses such as **Japanese encephalitis virus** and **tick-borne encephalitis virus**.

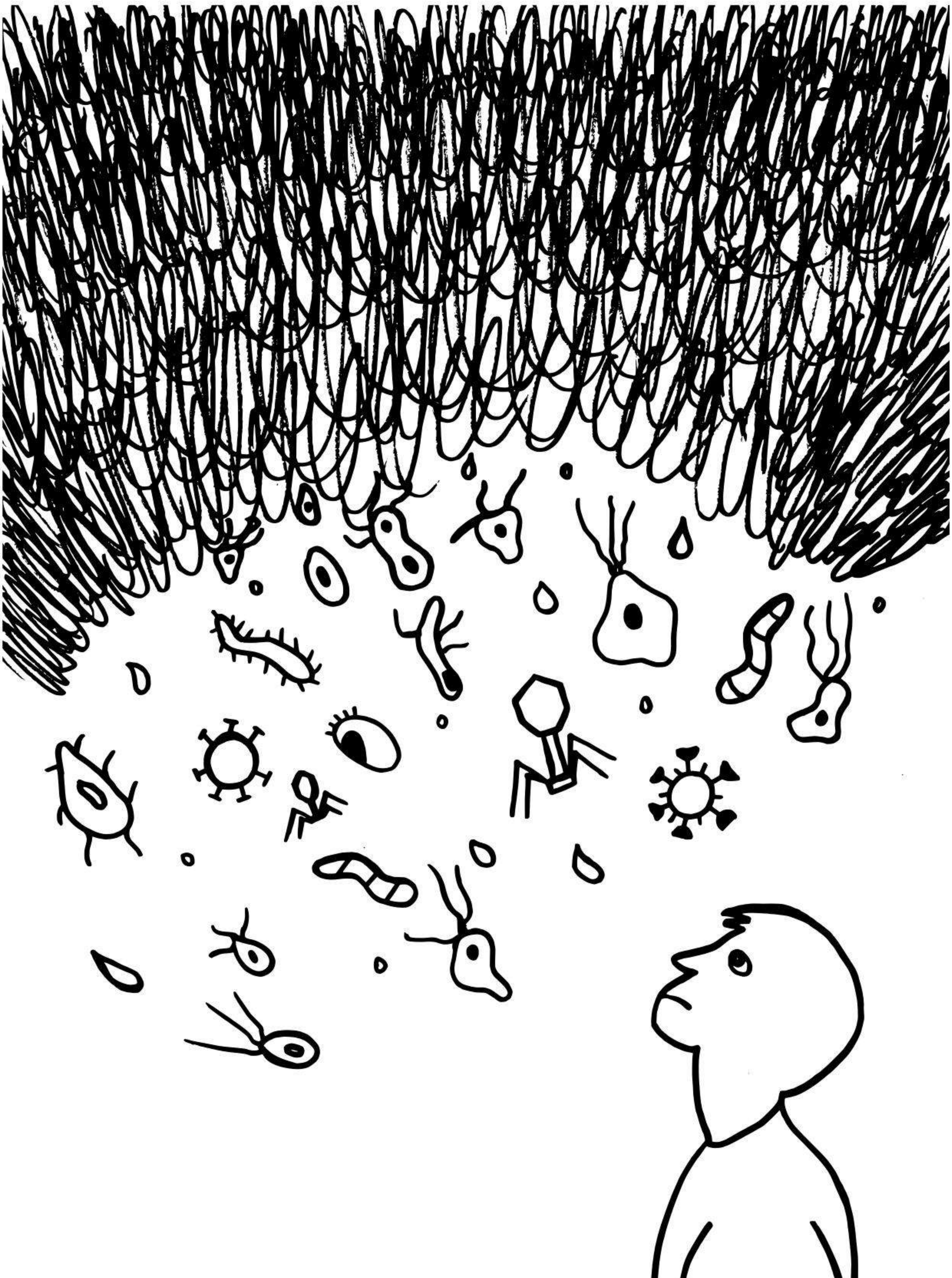
7. Co-infections

Joanna Crispell

Even before we are born, we are exposed to infections from our mothers within the womb. Once we come out into the world, there are many different **viruses, bacteria** and **fungi** that can infect us all at the same time. It can sometimes feel like a scary attack, like in the picture! But our **immune system** is constantly battling these infections, which is why you're not sick all of the time.

Did you know?

Researchers at the CVR are trying to study the pattern of respiratory disease within the Glasgow area using data collected since 2005. They have found that if you are infected with one particular kind of virus, then another specific virus will be the most likely to infect you next. The opposite is also true, some viruses cannot infect a host at the same time, as they are incompatible. These viruses are in competition with each other to infect you first.



8. Viral Hepatitis

Weronika Witkowska

Viral hepatitis is a term for inflammation of the liver due to viral infection. The culprits are known as **hepatitis A, B, C, D and E viruses**. Despite their name, the various ‘hepatitis’ viruses which infect the liver are not related, and the term hepatitis only refers to the symptoms they create. Reduced liver function due to viruses may cause joint, muscle and abdominal pain, tiredness and yellowing of the skin and eyes (jaundice) and in the long term may induce scarring of the liver (cirrhosis) and possibly liver cancer.

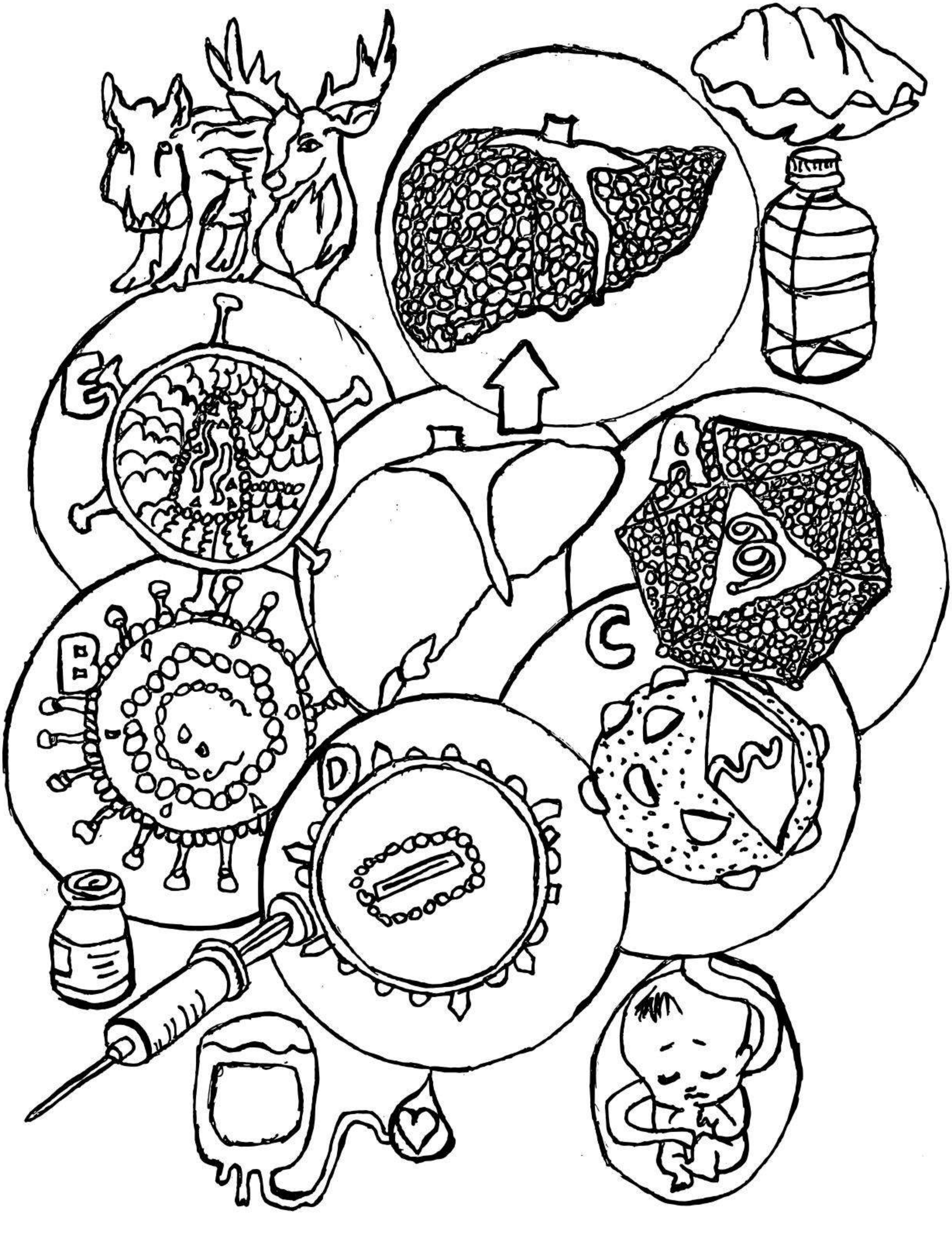
Hepatitis A Virus (HAV) and Hepatitis E Virus (HEV) are found in areas with poor sanitation, where infection occurs due to drinking water or eating food contaminated with faeces. HEV can also come from undercooked pork or wild animals' meat. Fortunately, infection tends to pass within a few months with no treatment required. A vaccine for HAV is also available to prevent infection in people traveling to affected areas.

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) occur worldwide and can cause infections lasting only a few months, or long-lasting life-threatening illnesses. Both viruses are spread via the blood through activities such as sharing needles or razors, unprotected sex or sometimes from a mother to her unborn child. Over 90% of people can be cured with the latest HCV treatment but unfortunately there is no effective vaccine. Luckily there is both a vaccine and treatment for HBV. Unfortunately, patients must rely on treatment for their entire life.

Hepatitis D Virus (HDV) can only infect people, who are also infected by HBV and infection happens in the same way for both. HBV vaccine provides an effective protection against the infection.

Did you know?

Scientists at the CVR are working towards a vaccine for Hepatitis C virus!


E
A
B
C
D

9. Oncolytic Viruses

Yasmin Parr

Not all viruses cause disease, some can be used to help us! Scientists are working with viruses so they can be used to treat cancer. These cancer-destroying viruses are referred to as 'oncolytic.' Oncolytic viruses are designed to:

FIND the tumour

INFECT the cancerous cells

REPLICATE in the cancerous cells

Cause cell DEATH and release of newly made virus particles

Importantly, these viruses are designed to specifically replicate in cancerous cells without affecting the patient's normal healthy cells. One example of a virus currently in trial for cancer therapy is **Herpes Simplex Virus (HSV) 1716**. Herpes simplex virus can replicate in many different types of cells, has a very stable genome and has a number of genes that it doesn't need, which can be easily changed or deleted in the lab.

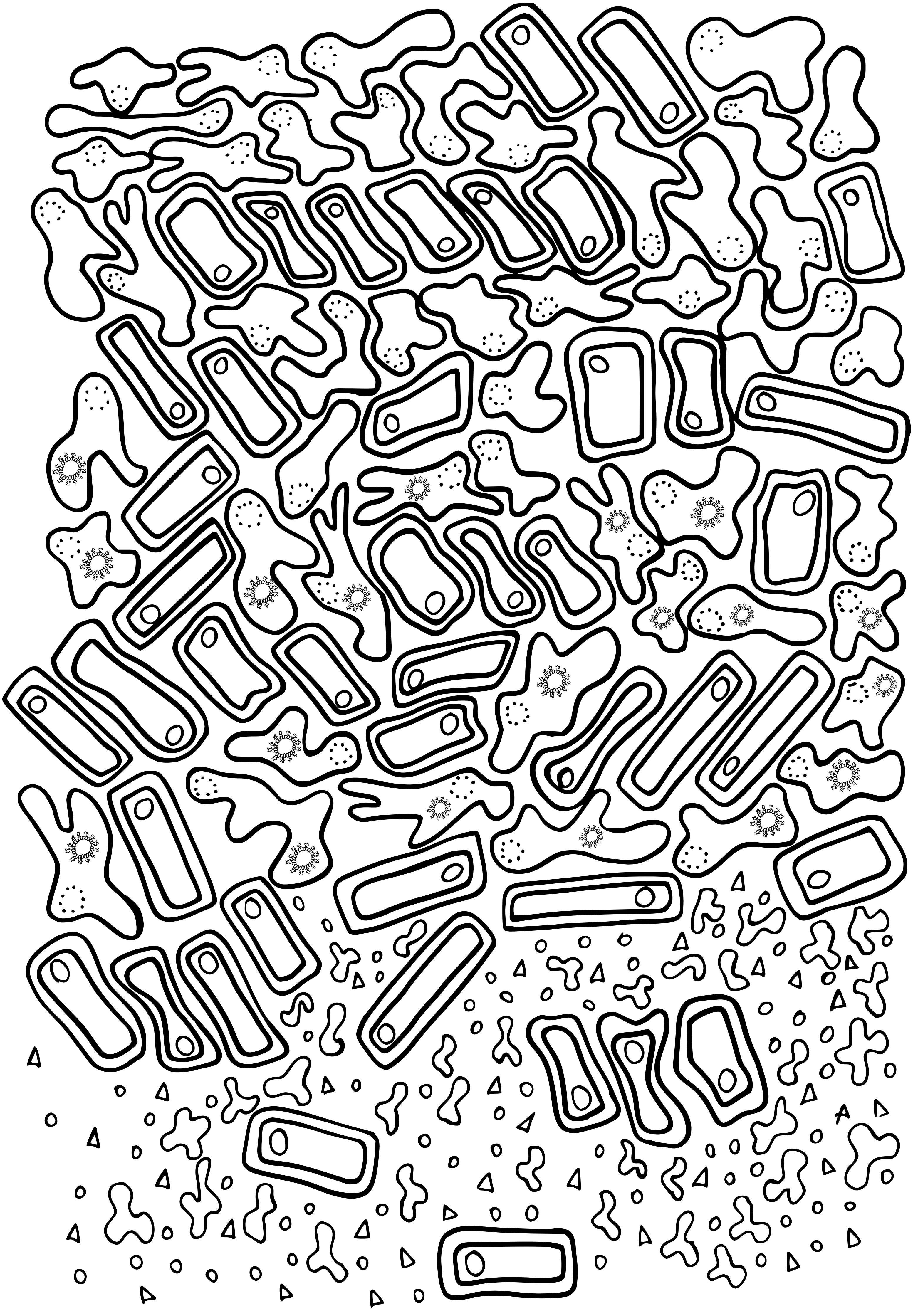
HSV1716 is a type of HSV that has been modified so that it can only replicate in cancerous cells (making it a great candidate for oncolytic virus therapy).

Scientists are also investigating the possibility of using oncolytic viruses in combination with already existing cancer therapies.

Did you know?

HSV is the virus responsible for cold sores!

Not all oncolytic viruses directly cause cell death, some help the immune response find and target cancer cells. Other candidates being considered as potentially oncolytic are adenovirus (common cold virus), vaccinia virus and measles virus.



Different Viruses, Different Hosts

10. Arboviruses

Stephanie Cumberworth

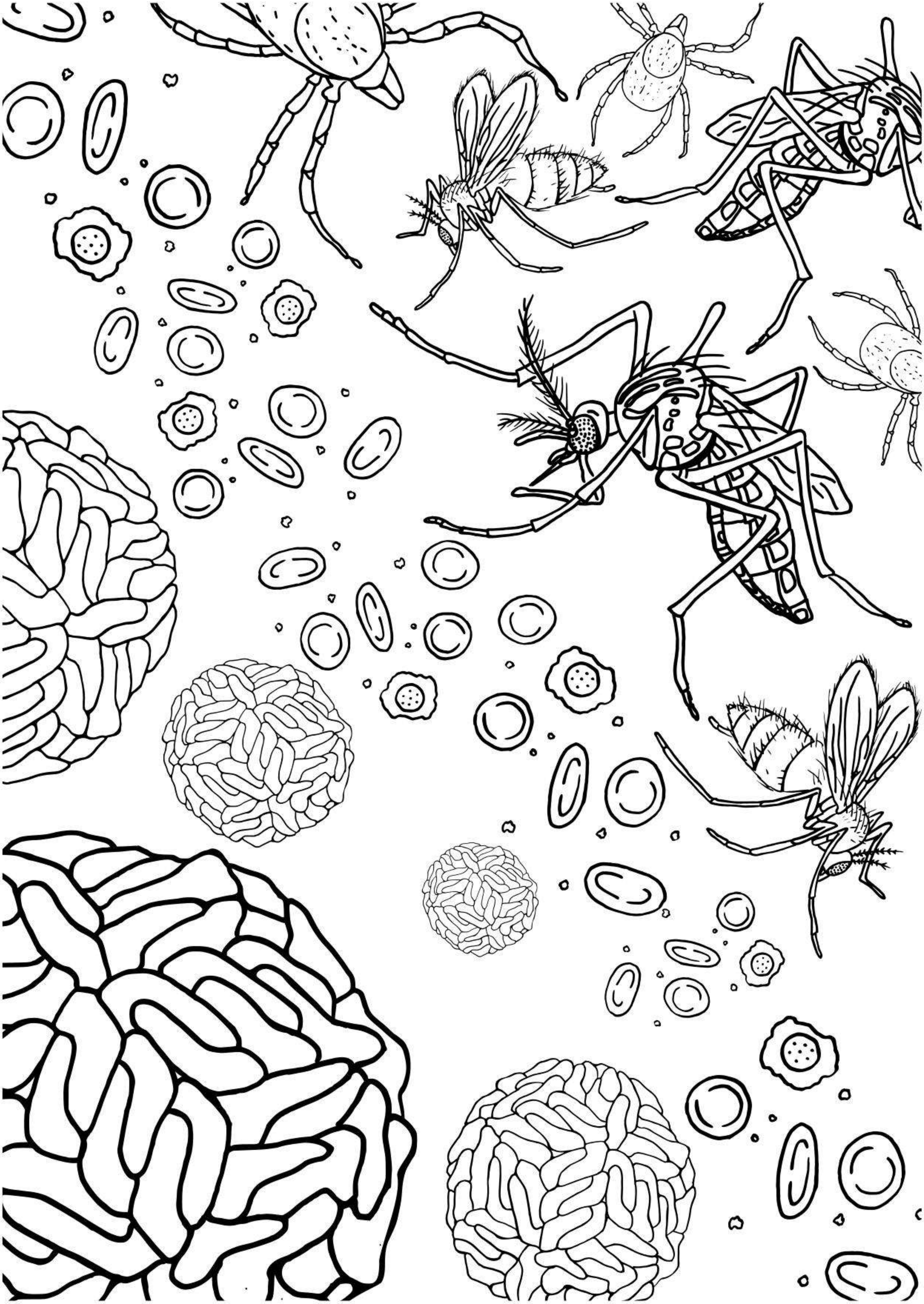
ARthropod BOrne VIRUSES

Arboviruses are transmitted by biting insects (or arthropods) such as ticks, midges, sand-flies and mosquitoes. There are over 500 different arboviruses including **Zika virus, dengue virus, chikungunya virus, West Nile virus** and **tick-borne encephalitis virus**. They can have a major impact on the health of humans and animals around the world, and are often classed as emerging or re-emerging pathogens.

When a mosquito feeds, it will take around 2 microliters of blood - that's only two thousandths of a millilitre! When the mosquito feeds on an infected animal, it will swallow virus along with the blood. Once inside the mosquito the virus must escape the gut and spread to the salivary glands. When the virus reaches the salivary glands, the mosquito can transmit the virus when it takes its next meal. The mosquito also injects molecules into the bite site to numb it and prevent the stimulation of the immune response. Although most viruses have an animal host as part of their transmission cycle, some of them can be spread from human to human via the bites of an infected arthropod, allowing urban epidemics to develop.

Did you know?

Only female mosquitoes take blood meals!
They need the extra supplements in blood to produce eggs and reproduce.



11. Orbiviruses

Alexandra Hardy

Some viruses specifically infect animals, such as domestic pets, livestock and wild animals. These pathogens have a major impact on animal welfare because they can cause severe disease. When they affect the farming industry, viruses are also responsible for serious economic losses. Orbiviruses are a group of viruses which have a wide range of hosts, but which mostly cause disease in animals.

A good example of an Orbivirus is **Bluetongue Virus (BTV)**, a virus of significant veterinary importance. It is present worldwide and can infect sheep, cattle, goats, and other wild ruminants such as deer, buffalo and antelope. BTV is an arbovirus which means that it isn't directly transmitted between animals, but relies on a vector species: in this case, small biting midges spread the virus when they consume a blood meal from an infected host. BTV is responsible for bluetongue disease which tends to be more severe in sheep than in other species. Symptoms can include fever, swelling of the face, bleeding and difficulties in breathing.

Did you know

The term "bluetongue" refers to rare cases where the swelling of the tongue is very severe and reduced oxygen delivery causes it to turn blue!

African Horse Sickness Virus (AHSV) also belongs to the same virus family as BTV. As such, it has a very similar structure and is also transmitted by midges, but it infects a very different range of hosts. Zebras and donkeys can be affected by AHSV but rarely experience symptoms, whereas infection of horses is often fatal.

12. Morbilliviruses

Yasmin Parr

Morbilliviruses are a closely related and highly infectious group of viruses that infect many different animals. These viruses can cause huge outbreaks and are associated with high death rate and devastating disease.

Did you know?

The word 'morbili' comes from the Latin word 'morbus' meaning disease!

Measles virus is a major cause of childhood death and disease. You may associate measles viruses with a fever and rash, but this virus can also cause life threatening disease. There are highly effective vaccines available to protect us against measles.

Did you know?

Not everyone is lucky enough to be vaccinated! Some people don't have access to vaccines because of where they live or because their general health is poor. By getting vaccinated you are not only protecting yourself but you are protecting others around you! If enough of the population is vaccinated we can stop the spread of the virus. This is known as herd immunity.

Canine Distemper Virus (CDV) can infect many wild carnivores and not just dogs! CDV attacks the gastrointestinal tract and the central nervous system. Although there is no cure for CDV, we have effective vaccines! CDV poses a threat to many endangered species such as the Giant Panda and the Amur Tiger.

Rinderpest was eradicated in 2011 due to the use of successful vaccines, only the second virus to be wiped out in this way. Rinderpest was an infection of cattle, buffalo and other hoofed animals. This virus caused devastating disease, economic loss and famines.

Peste des Petits Ruminants Virus (PPRV) infects small ruminants and causes disease in sheep and goats. PPRV has been announced as a target for active eradication by the World Health Organisation. They are aiming for eradication by 2030.

13. Retroviruses

Yasmin Parr

Retroviruses are different from other viruses in the way they replicate. They have a unique protein that copies their RNA genes into DNA. The hosts cell's DNA is then cut and the viral genes are inserted into the gap, integrating them permanently into the host cell's genome. If viral DNA is integrated into the genome of a germline cell DNA (a sperm or egg) the viral genetic material can be passed down through generations.

Did you know?

Around 8-10% of the human genome is made up of retroviral DNA!

A retrovirus that you have probably heard of is **HIV** (Human Immunodeficiency Virus). The World Health Organisation estimates that 35 million people worldwide are infected with HIV. HIV infects cells of the immune system, which normally help protect your body against pathogens. This makes it difficult to recover from infection and makes you more likely to become infected with other pathogens. A very similar virus infects cats, known as **FIV** (Feline Immunodeficiency Virus).

FeLV (Feline Leukaemia Virus) is another example of a retrovirus. Some cats infected with FeLV can naturally recover, whereas others develop FeLV-associated diseases such as leukaemia, lymphoma and anaemia. Research is underway at the CVR to help understand why these different outcomes of infection occur. FeLV prevalence has greatly decreased due to the use of successful vaccination and diagnostic testing.

Did you know?

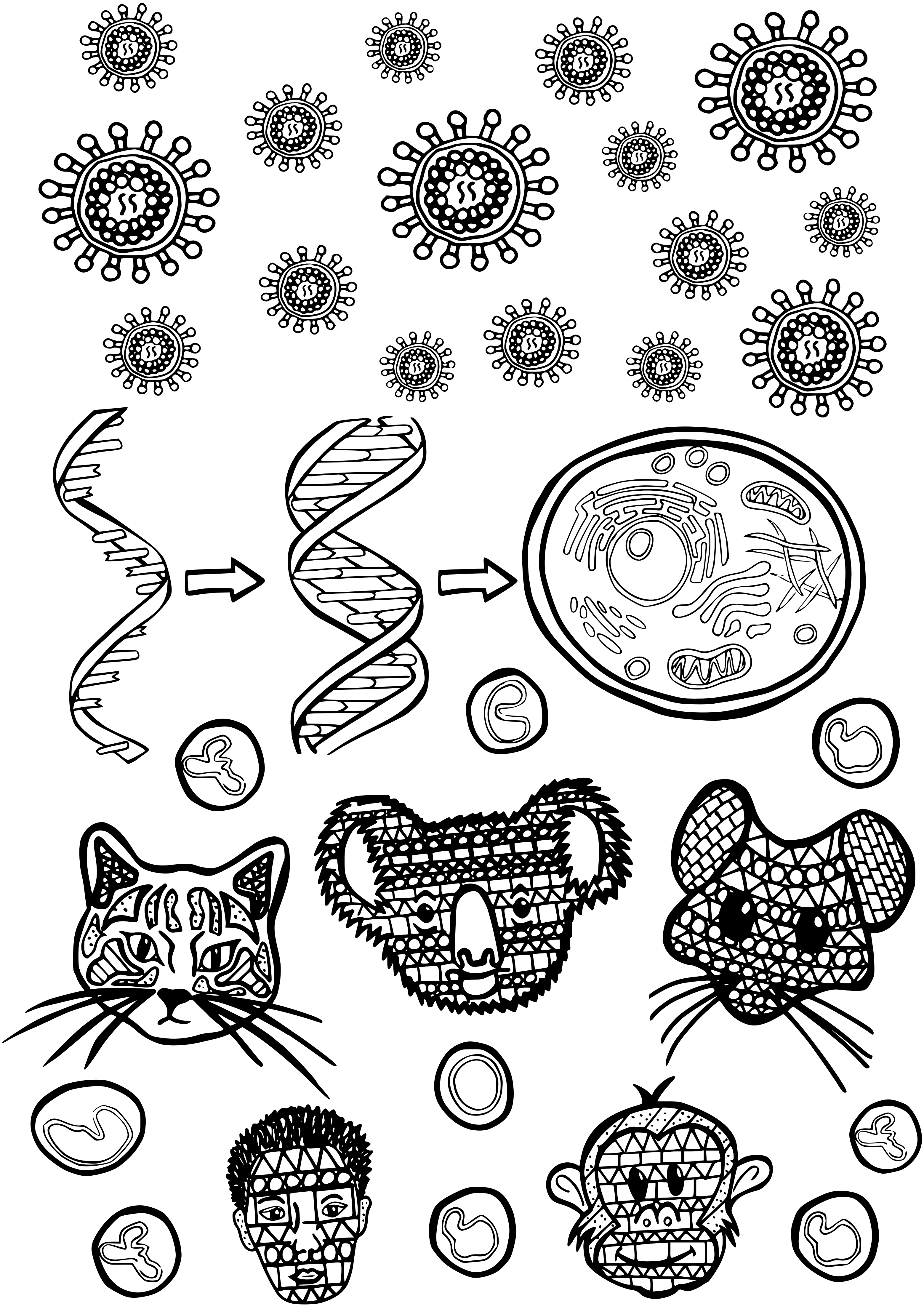
FeLV was discovered at the University Glasgow in 1964 by Professor Bill Jarrett.

Other examples of retroviruses include:

MuLV (Murine Leukaemia Virus)

SIV (Simian Immunodeficiency Virus)

KoRV (Koala Retrovirus)



14. Zoonotic Diseases

Joanna Crispell

The word **zoonosis** describes an infectious disease that can be spread from animals to humans. Just under two thirds of all human pathogens (including viruses, bacteria and fungi) are zoonotic. That's a lot of diseases from other animals! Some zoonotic diseases are caused by rabies virus, Ebola virus and West Nile virus.

A well-known zoonotic disease is **Influenza A Virus (IAV)**. Some of the animals that can be infected by IAVs are shown in the image. It is a disease that begins in wild birds such as ducks, and can then sometimes jump from one species to another. Here you can see that pigs can infect humans with IAV, which is what caused the global **swine flu** outbreak of 2009. Another animal that can be infected by IAV is the horse. In the early 2000s, horses passed IAV infection to dogs. Some of the researchers at the CVR are studying this horse to dog jump to figure out how it happened. There are many other animals that can be infected by IAVs, including chickens, seals, and even whales.

Did you know?

Even though influenza A viruses almost always cause respiratory infections in humans, in birds they affect the gastrointestinal tract (the stomach and intestines). Birds can spread infection through their faeces, rather than by sneezing or coughing. The first person to discover that influenza A viruses came from birds (Robert Webster) wasted a lot of time swabbing their throats, before he realised he needed to swab the other end of the bird!

Controlling Viruses

15. Our cells' own immune response

Connor Bamford

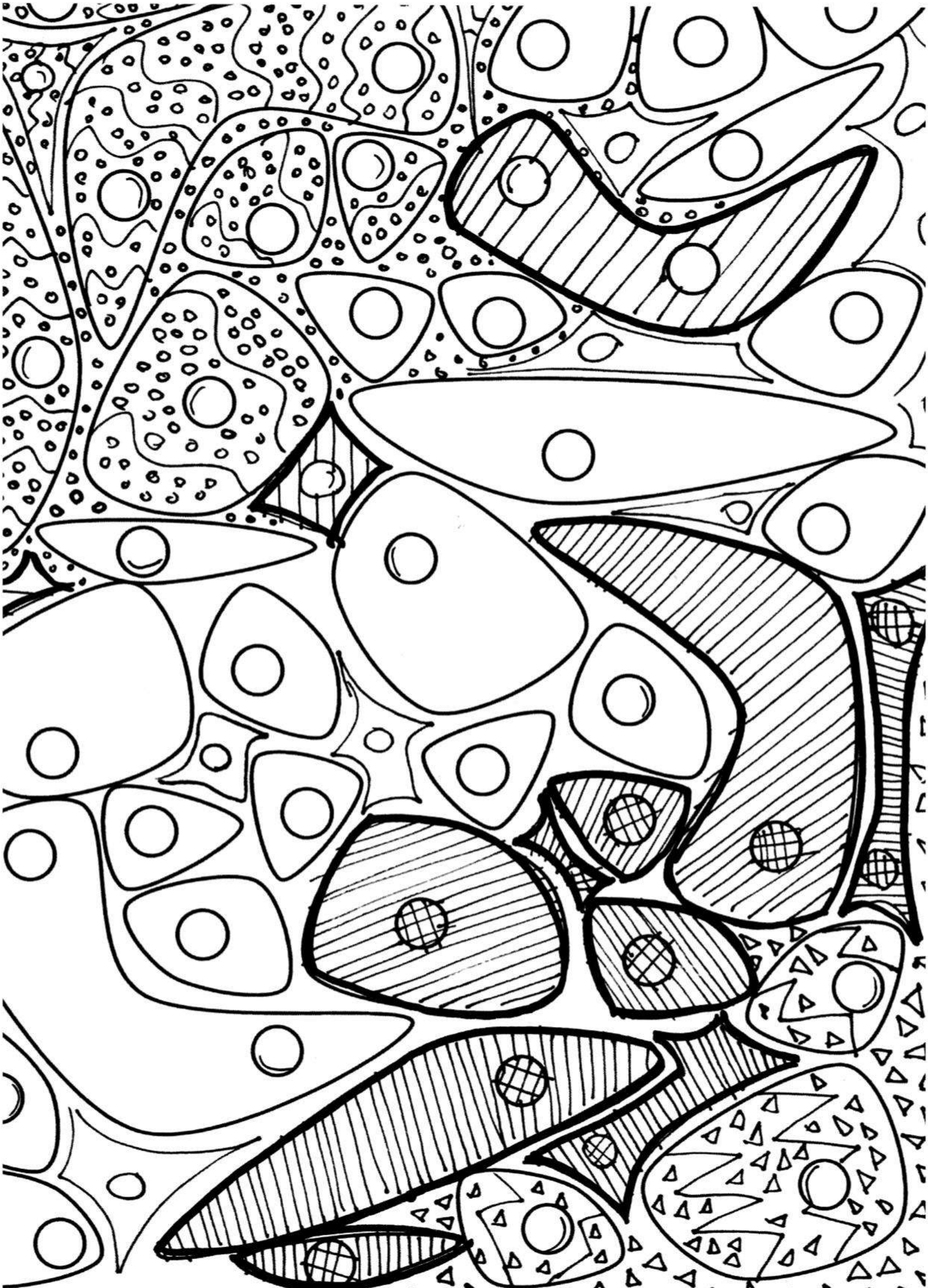
Viruses need to infect cells within our body to survive, and sometimes this leads to disease. Our body does not usually rely on medicines to defend itself against viral infection; we have our own defences against viruses and this is what protects us against infection (most of the time). We refer to all our defences as our **immune system**. Together our immune system stops viruses at many different steps in the virus' life-cycle and can even remember past infections, blocking them rapidly when we see them again, which is the basis of **immunisation**. Stopping viruses from infecting our cells can stop us getting sick.

One of the earliest defences that our bodies have is known as the **interferon response**. This is the natural ability of our own cells to block virus infection in the very first minutes-to-hours following exposure to the virus. This response relies upon the rapid detection of incoming viruses and the release of a protein called interferon, which signals to nearby cells that a virus is nearby and that they should start making hundreds of antiviral proteins to block the impending infection. Think of interferon as our bodies' own natural antiviral medicine.

Ideally, interferon would stop all viruses infecting us but viruses have evolved the means to escape or block our antiviral response. Viruses achieve this by making their own proteins that interfere with our ability to mount an interferon response. In the image opposite we have two infections by two distinct viruses: one that can block our cells' immune response (circles, top left) and one that cannot (triangles, bottom right). Infected cells are marked by wavy or angular lines. Cells that have started an interferon response are shaded with straight lines.

Did you know?

Humans produce hundreds – maybe thousands – of different genes involved in the interferon response. Many of these have no known function but are presumed to slow down an infection. CVR scientists are trying to understand how viruses interact with these genes.



16. How to find your ISGs

Connor Bamford

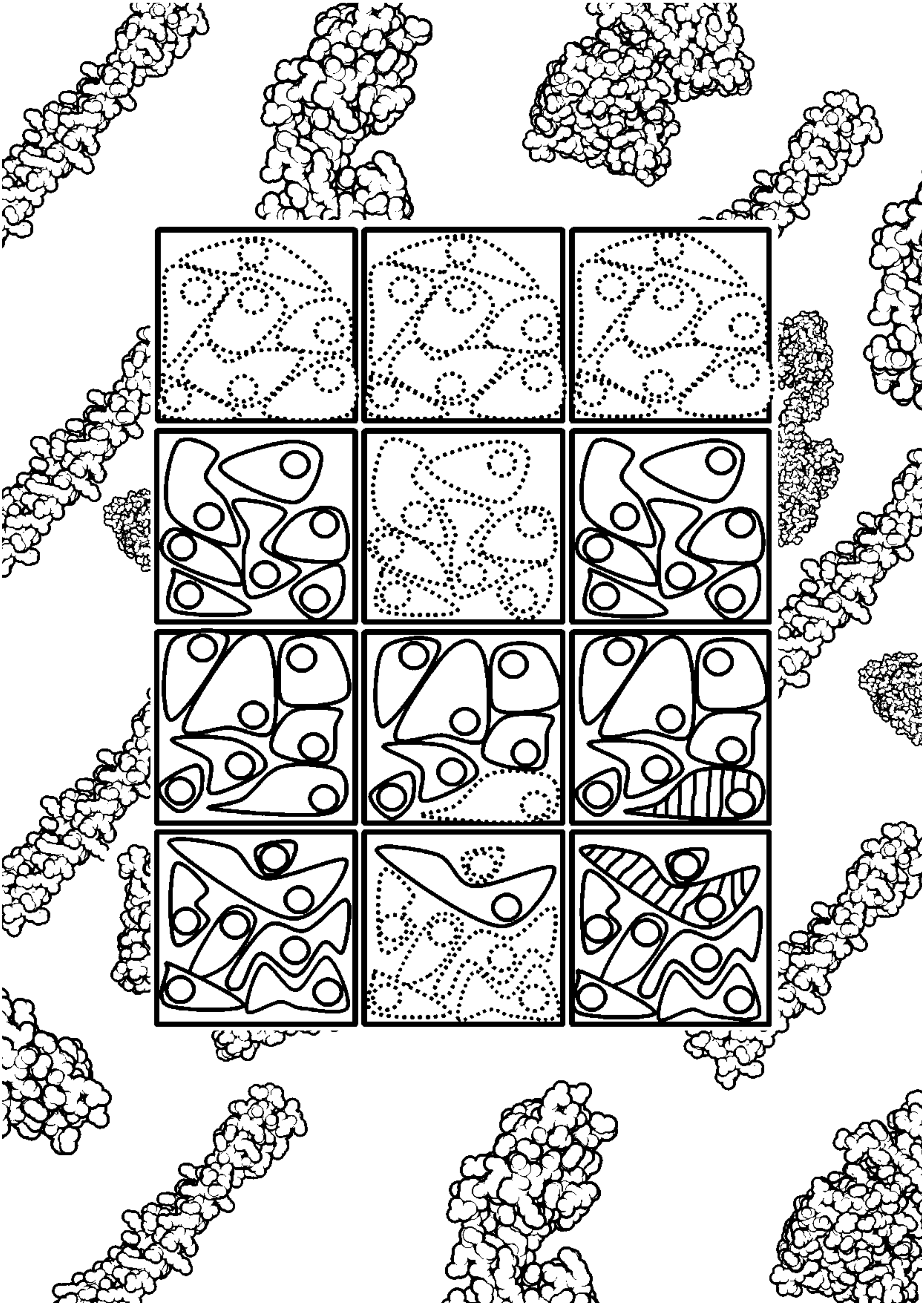
Interferon makes our own cells produce large amounts of specific proteins from **'interferon-stimulated genes'** or **ISGs**. Understanding how these ISGs work is a major area of research because of their ability to protect us from infections. However, finding which ISGs act to block an infection is very difficult because typically, hundreds of genes get made all at the same time. Teasing apart which ones block any particular virus takes a lot of work. But it can be done and scientists at the CVR are doing so.

One way scientists are doing this is by isolating individual ISGs and asking whether they are capable of blocking infection on their own, when they are produced by cells in the lab. Researchers can now can produce hundreds of ISGs (red) individually inside cells, add virus (green), and see whether an ISG can block an infection by simply counting how many green cells there are by looking down a special kind of microscope.

In the image opposite you can see three columns and four rows of boxes with cells inside them. Each row shows three panels of cells producing a single kind of ISG. Row one has no ISG; row two makes interferon (or every ISG); row three makes a newly discovered ISG and row four makes another new ISG. Each column highlights the production of the ISG (column A); cells infected by the virus (column B) or a combination of both (column C). Cells with ISG or virus inside them are shown by filled lines while 'empty' cells are shown by dashed lines. Can you find the ISG that is blocking the virus infection? HINT: look at column B.

Did you know?

Examples of ISGs that defend our cells from viruses include TRIM5 proteins (which can bind directly to viral proteins and stop them working), APOBEC (which scrambles virus genomes and stops them completing more infections) and tetherin (a protein that physically binds or tethers certain viruses to the outside of cells and prevents ongoing infection). Some of these antiviral proteins are shown in the image opposite.



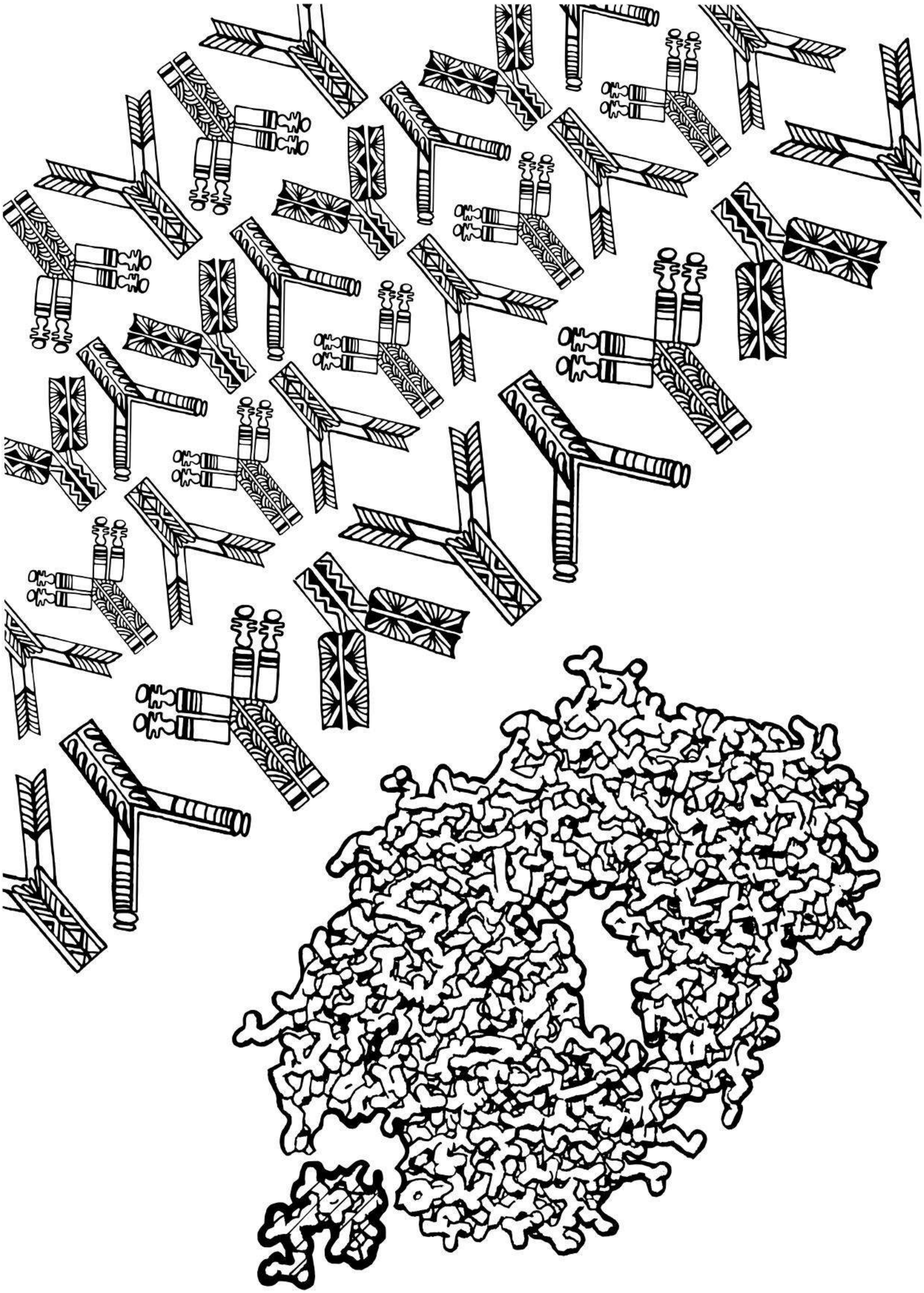
17. Antibodies

Alexandra Hardy

Antibodies are proteins produced by the immune system which can bind specifically to pathogens such as bacteria or viruses. They are made up of different structural units but have a general Y shape. At one end (the extremities of the two branches) the antibodies can attach to pathogens, and at the other end (the leg of the Y) they can interact with other immune cells to shape the immune response. The interaction between antibodies and pathogens is highly specific: antibodies only recognise a very precise pattern called an **'epitope'** whose structure matches their own, very much as a **key** will only recognise one specific **lock**. The tip regions of the antibodies are extremely variable, allowing our bodies to generate thousands of different antibodies which increases the chances of a specific antibody recognising a specific pathogen. Once our bodies have been exposed to a pathogen, they learn how to make the antibodies that recognise it, so the next time they encounter it they can mount an efficient response.

Did you know?

The AP33 antibody is an example of a well-understood antibody, developed here in the CVR. It is able to stop the hepatitis C virus by binding to a protein on the outside of its virus particle. One of the 'arms' of the AP33 antibody is represented here, showing its specific interaction with the viral protein. You can see that the tip of the arm wraps neatly around the viral protein, and will be able to attach to it. Identifying effective antibodies such as this one can be an important step in the development of new vaccines.



18. Antivirals

When our own body's defences aren't good enough

Connor Bamford

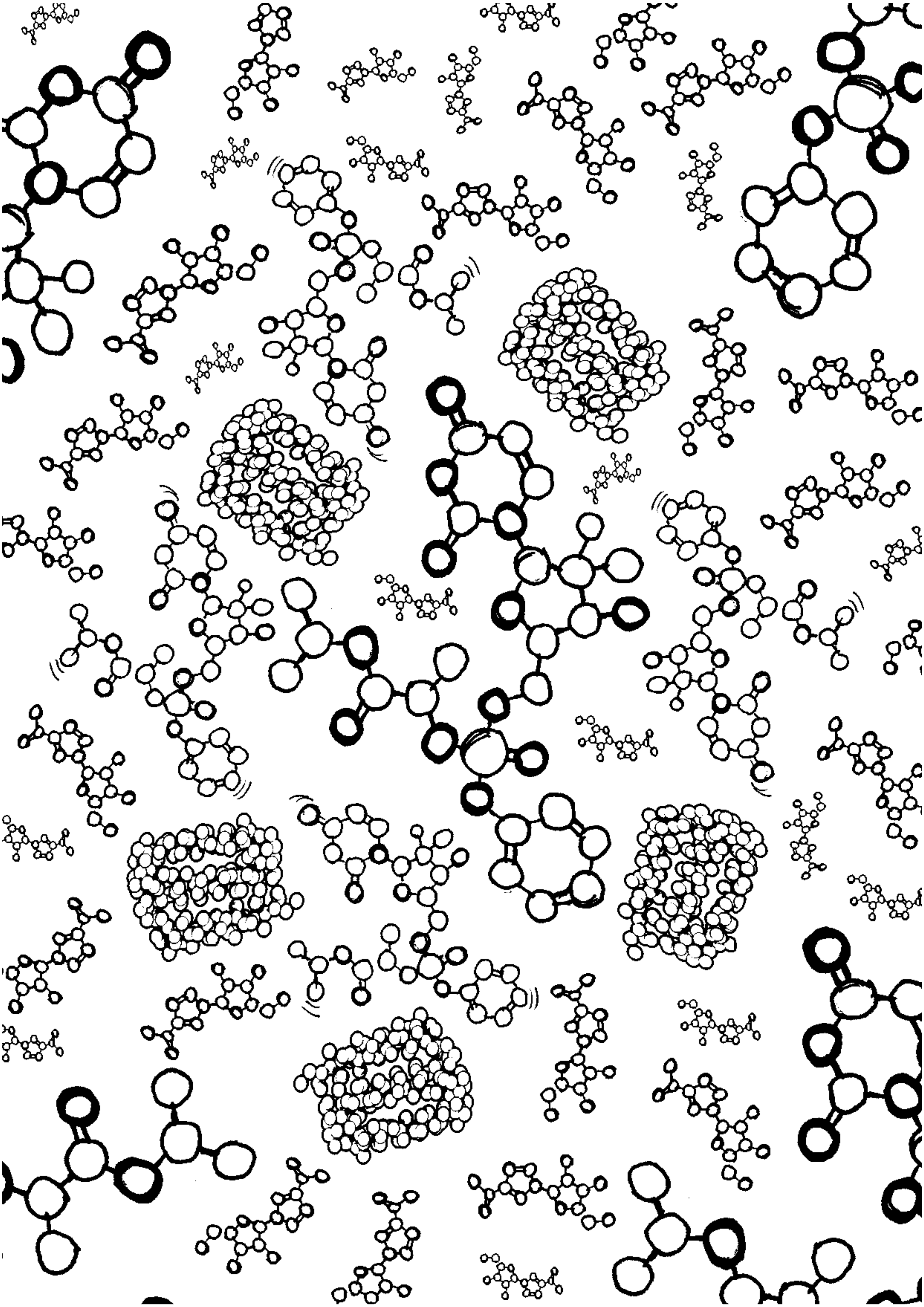
Most of the time we can ward off infections with ease with our own immune system but sometimes we need help in the form of medicines. This might be because some people's immune systems are weaker than others or because some viruses are just too good at evading our defences. When we need to, we are able to harness the power of antiviral drugs to cure or slow down viral infections when our body can't.

Decades of research by scientists across the world has led to the development of highly successful antiviral drugs. Among the best examples of antiviral drugs we have are medicines against **hepatitis C virus**, which is a very serious infection that can lead to fatal liver damage, and even cancer. The drugs we have now act directly on the virus to stop it replicating inside our cells and can cure nearly every person infected, if they take their medicine correctly. However, it has not always been that way.

We have made improvements in our medicines in the last two to three decades. From the 1980s doctors would prescribe **human interferon alpha** to patients with hepatitis C virus but this protein-based drug (which is a natural, antiviral protein found in all animals with backbones) was not always effective, had to be used for up to one year, and could have many unpleasant side-effects. Recently, new small molecule drugs have become available that bind to the hepatitis C virus directly and stop it from infecting you in as little as a couple of months. Some of these medicines are shown opposite.

Did you know?

Other examples of antiviral drugs include those able to prevent human immunodeficiency virus (HIV) infection and suppress viral replication, turning a fatal illness into a chronic condition; those that can stop influenza viruses from spreading from one cell to another; and those that stop herpes simplex viruses, protecting people from cold sores and fatal conditions such as the rare brain infection caused by some herpes viruses.



19. Resistance

When the drugs don't work

Connor Bamford

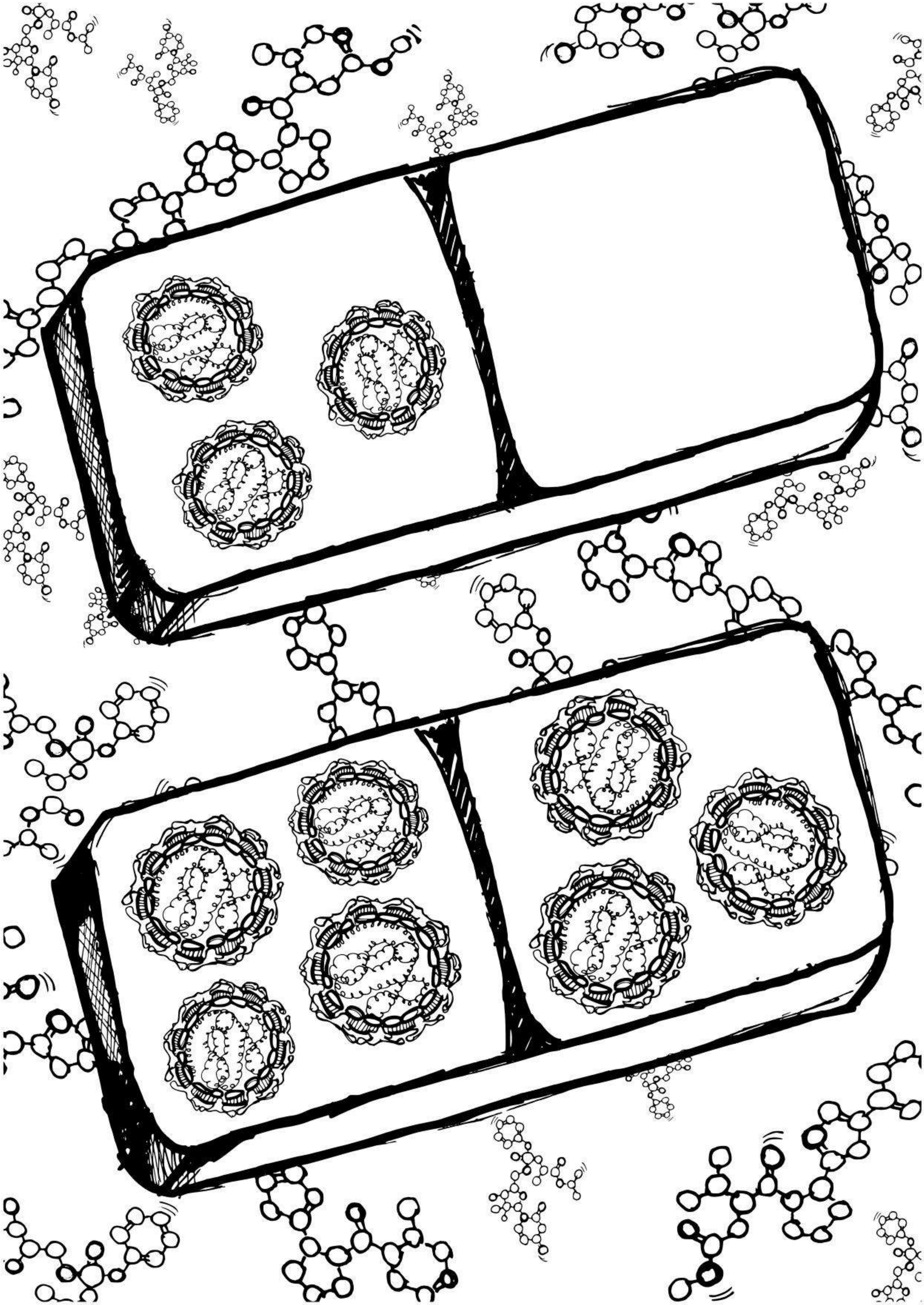
Sometimes doctors in the clinic notice that their antiviral medicines no longer work against a virus that should be sensitive to those drugs. If this is the case doctors have to find new antiviral drugs to fight the **'resistant' virus** and this isn't always easy. This phenomenon is known as antiviral resistance and it can be a very serious issue for patients. Like any living things, viruses evolve and can adapt to their surroundings and environment, including the presence of a drug that interferes with their growth. Viruses become resistant by changing the structure of their proteins so as to block, inactivate or avoid the drug's effects.

We can notice this resistance by looking at the **viral genome** (the collection of all the viral genes), which is made up of a type of chemical called a nucleic acid (DNA or RNA). Genomes from resistant viruses look different from those from sensitive viruses. This difference is spelled out in the precise ordering of the building blocks that are linked together to form the nucleic acid (chemicals named **A, T, C** and **G**). The order of these encodes proteins, and changes in nucleic acids ultimately cause changes in proteins that block the drug from working.

The image opposite demonstrates two different scenarios in the clinic when treating a viral infection such as **hepatitis C virus**. The top pill represents one patient (before and after treatment). On the left they have virus, but it is all gone following treatment with antiviral medicine (presumably because it was not resistant). The bottom pill shows what happens when you treat someone with a resistant virus: the virus does not disappear when you are given the medicine! Virus that is still there can continue to cause disease, and spread to new hosts.

Did you know?

Understanding antiviral resistance is major area of scientific interest. Finding ways to track resistance in patients and ways to get around it are becoming increasingly important. Scientists and clinicians are now using super sensitive technology to determine accurately the entire genome sequence of viruses from patients to rapidly and sensitively follow them and monitor the development of resistance.



20. Fighting Viruses With Bacteria

Stephanie Cumberworth

Wolbachia is a bacterium which is naturally present in many insect species, including ladybirds and butterflies. It is not normally present in ***Aedes aegypti*** mosquitoes, which are responsible for transmitting arboviruses (see above) that cause significant diseases in humans such as **dengue virus, chikungunya virus** and **Zika virus**. Effective vaccines and treatments are not available for many arboviruses that cause human disease; therefore, an alternative to limit virus transmission is to target the insects which spread them. ***Wolbachia*** carrying mosquitos have a reduced ability to produce virus and could be used to limit virus spread from ***Aedes aegypti*** mosquitoes to humans.

Did you know?

Wolbachia carrying mosquitos have been released into the wild. Small scale releases in Australia, Malaysia, Colombia, Vietnam and Brazil are part of efforts to reduce viruses spread by *Aedes aegypti* mosquitos. Researchers from the CVR are involved in some of these projects.

Understanding Viruses

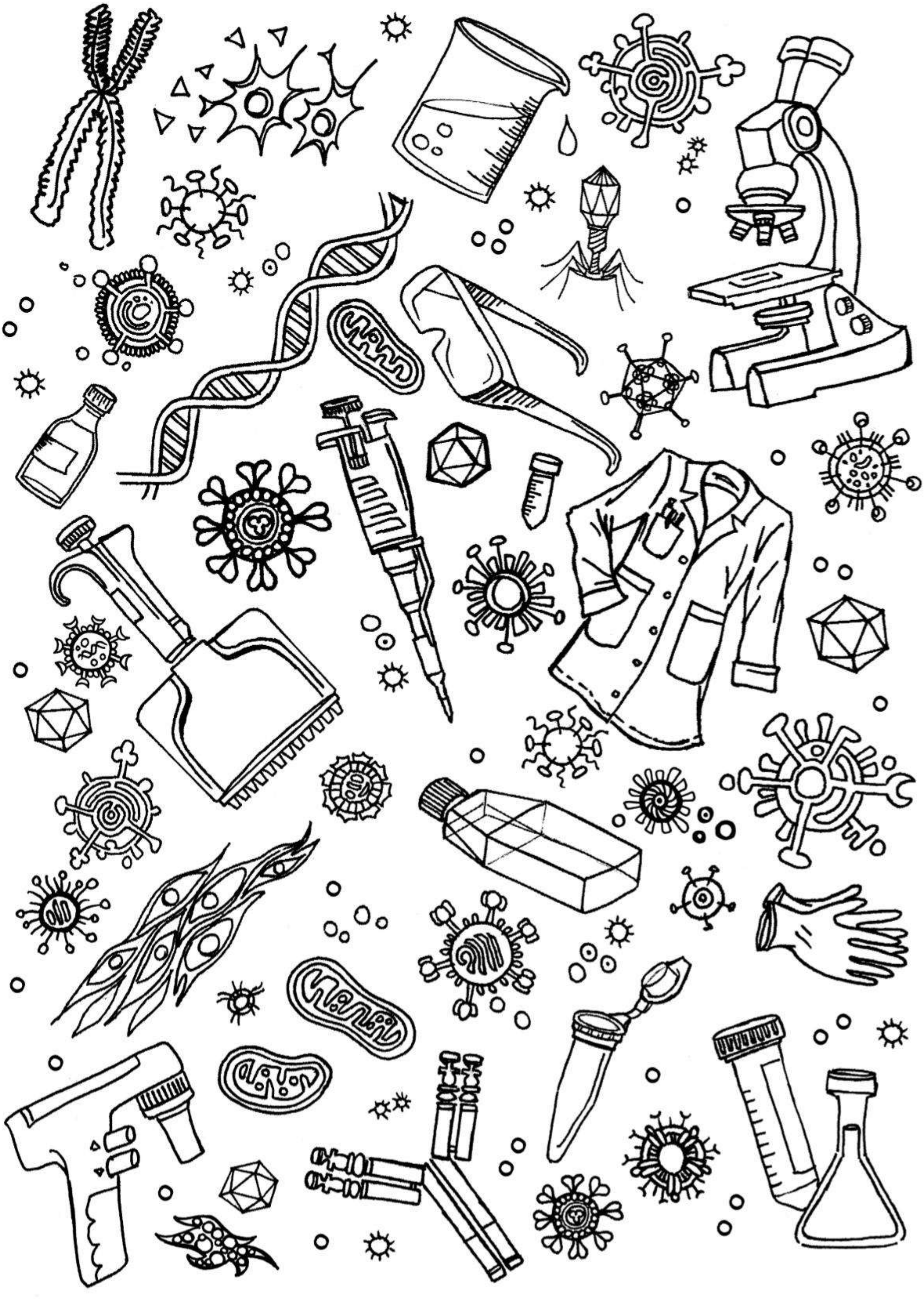
21. Studying Viruses

Alexandra Hardy

The study of viruses is referred to as **virology**. It is crucially important to increase our understanding of how viruses can replicate and how they cause disease in order to develop specific treatments.

Scientists are able to grow certain viruses using cells in the lab, which makes it easier to study them. Researchers can, for example, focus on the **genetic information** contained in the virus, or try and determine the exact composition of virus particles. They can also investigate which parts of host cells viruses interact with, and how they modify the cell's behaviour.

A **micropipette** is a very commonly used tool in the lab to collect and dispense very small, precise volumes of liquid. It has a piston at the top which creates a vacuum, enabling liquid to be collected at the other end. Can you spot the micropipette amongst all the other lab equipment?



22. Viral Diagnosis

Weronika Witkowska

Diagnosing viruses is in many cases a crucial component to the wellbeing of today's world population. In general terms, the methods used for diagnosing viruses can be divided into three categories: **direct detection, indirect detection** and **serology**. Any viral diagnosis starts with the collection of a clinical sample, usually in the form of blood, other body fluids or excretions or sometimes biopsies.

Direct detection

As we described previously, viruses are made up of building blocks which are unique signatures of each virus. Scientists can look for these signatures directly by using powerful microscopes to diagnose a viral infection. Alternatively, an individual building block such as nucleic acid or viral surface protein can be used. **Polymerase Chain Reaction (PCR)** is most commonly used for nucleic acid detection. This method multiplies nucleic acids to over a billion copies which makes it much easier to analyse them in the laboratory. Detection of parts of viral proteins using antibodies is known as antigen detection.

Indirect detection

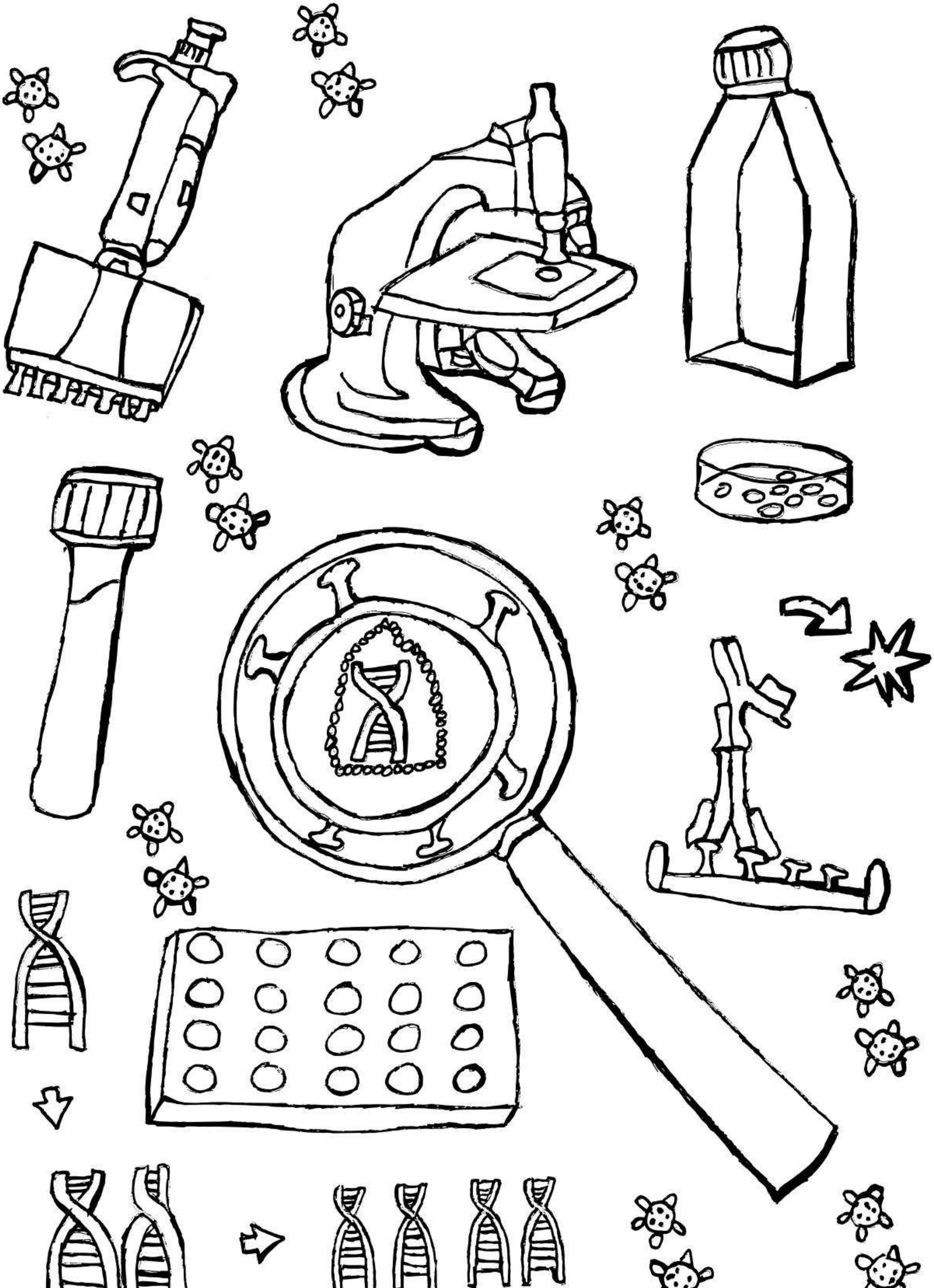
In indirect detection, a clinical sample is added to a cell culture system, an egg or animal model to grow the virus and isolate it. Most laboratories usually rely on cell culture as other methods are expensive, difficult to maintain, and require the use of animals. In cell cultures, some viruses are likely to have very dramatic effects on cells – for example causing cells to die or burst!

Serology

Serology is a way of detecting what pathogens your body has been exposed to in the past. Any time the human body encounters viruses our immune system recognises them as 'foreign' and prepares a unique defensive mechanism. This mechanism often relies on the production of antibodies, which bind viruses and help in the eradication of infection. Every antibody has a unique shape and thus it can only bind one virus type. The detection of antibodies in the clinical samples shows that the patient has previously been exposed to the virus and learnt to recognise it - this is the basis of all serological tests. **Enzyme Linked Immunosorbent Assays (ELISAs)** are the most commonly used diagnostic tests, and these are also the basis of over-the-counter pregnancy tests!

Did you know?

Scientists are trying to make even cheaper, more sensitive and faster tests for viral diagnosis.



23. Discovering Viruses

Joanna Crispell

Even though some viruses are very well known to researchers, there are many undiscovered viruses in the world. The more we know about them, the better prepared we will be if they ever become emerging viruses.

This image tells the story of the discovery of **Zika virus**. This virus is now infamous for an outbreak in South America in 2015, which led to infected mothers giving birth to babies with illnesses including **microcephaly** (a smaller than expected brain and head). But the virus was first discovered in 1947 in Uganda by **Alexander Haddow**, a researcher who was born here in Glasgow. He was part of a group of scientists who were hunting for yellow fever virus in the Zika Forest of Uganda. They had built platforms high in the trees where monkeys were kept in cages as **'sentinels'** (animals used to detect any infection present). They took blood from one of these monkeys and injected it into mice that then became sick. By doing this, the researchers discovered a new virus that they named after the forest it was found in. So, it was actually an accidental discovery in the hunt for a different virus!

Did you know?

Researchers at the CVR are studying Zika virus. They are collaborating with other scientists worldwide to find out why a virus, which had been known for almost 70 years, suddenly started causing a different type of disease leading to widespread illness in babies.

Glossary

Aedes aegypti - a species of mosquito which is a prominent **vector** of human viruses

Arbovirus - arthropod borne **virus**

Arthropod - invertebrate animal with an exoskeleton, including insects such as mosquitos and arachnids such as ticks

Bacterium - a type of single-celled organism. Bacteria are very distantly related to us and their **cells** are different from our own - typically smaller, and without the internal chamber, called a nucleus, in which our **cells** store their **DNA**. Like **viruses**, some bacteria cause noticeable **disease** but many more live harmlessly on and in our bodies and even promote our health.

Cell - the basic building block of every living thing, whether it consists of single cell or many cells working together. Your own body is built from tens of trillions of cells, fulfilling thousands of specialised roles. Cells are separated from the outside world by a **membrane**, within which they organise huge numbers of molecular machines that allow them to use nutrients to create energy and produce new molecules. Most cells also contain **genetic** instructions, in the form of **DNA**.

Cytokine - signalling molecules sent out as a message by an **cell** in response to infection or injury. Cytokines alter the behaviour of surrounding cells and can also attract **immune cells.**

Disease - an abnormal, harmful state.

DNA - an abbreviation of the name of a chemical (deoxyribonucleic acid) which stores **genetic** instructions in our **cells** and in certain **viruses**.

Encephalitis - **inflammation** of brain

Endemic area - an area where an **infection** is constantly present without external introduction.

Emerging - a **virus** or other **pathogen** which has increased in frequency or has altered its geographic range, often resulting in an outbreak, is said to be emerging.

Evolution - changes in a species from one generation to the next. These changes are driven by the fact if a particular variant of a **gene** make a member of the species better at reproducing in its current environment, there will be more individuals carrying that version of the **gene** in the next generation. **Viruses** have a very high mutation rate and a very short generation time. As a result, they can evolve incredibly quickly.

Fungi - a kingdom of life including yeasts, molds, and mushrooms. Numerous fungi make a living on our bodies, though they rarely cause **disease** unless our **immune systems** are weakened, and never cause mushrooms.

Gene - An instruction about how to make a protein or a strand of RNA, encoded in the precise form of a chemical (typically **DNA**, though some viruses use **RNA**) which can be copied and passed on to the next generation.

Genome - the complete set of **genes** of a **cell** or a **virus**.

Host - something whose resources have been taken over to make more copies of an infectious agent such as a **virus**. Can refer either the whole organism or to an individual **cell**.

Infectious - able to take over a **host** and use its resources to reproduce. As **viruses** cannot generate their own biochemical resources, they must be infectious by definition if they are going to reproduce.

Inflammation - the body's reaction to infection or injury. Visible signs include an area of the body becoming red, swollen and often painful.

Immune System - an enormously varied and complex system of **cells** and signals used by our bodies to control infections and repair injuries.

Jaundice - a condition where the skin and whites of eyes become yellow due to a build-up of a substance called bilirubin in blood and tissues of the body.

Membrane - when describing **cells**, a thin flexible layer of fats which separates the liquid inside a **cell** (or a region inside the **cell**) from the liquid outside. Membranes typically have **proteins** attached to them, and some **viruses** wrap membrane from their **host cell** around them.

Pathogen - something that causes **disease**. **Infectious** pathogens include certain **viruses**, as well as **bacteria**, **fungi** and parasites.

Protein - a type of chemical used by living things for a huge range of different purposes. Some proteins drive chemical reactions, others link together to form structures or link specific targets together, and others physically haul parts of the cell around. **Viruses** uses proteins to protect their **genomes** as they move from **cell** to **cell** inside **virus particles** - and **virus particles** can be targeted by proteins produced by the **host**, such as antibodies.

RNA - an abbreviation of the name of a chemical (ribonucleic acid) which in our cells makes short-lived 'working' copies of the genetic instructions stored in **DNA**, as well as acting as components in some molecular machines. Some **viruses** use RNA to encode their **genomes**, something that is not done by any **cell**.

Ruminant - even toed hoofed mammals that gain their nutrition from a plant based diet such as cows, sheep, goats, deer and antelope.

Sanitation - provision of facilities for clean drinking water supply and adequate sewage disposal

Sentinels - an animal used to provide advanced warning of a danger, for example an **emerging virus**.

Wolbachia - a **bacterium** which infects a wide range of **arthropods**, though without always causing obvious **disease**. Somewhat unusually for a **bacterium**, *Wolbachia* lives inside infected insect **cells**.

Vector - an organism (often a biting **arthropod**) that can transmit an **infectious pathogen** between different **hosts**.

Virus - a set of **genetic** instructions that cause a **host cell** to copy them and release those copies inside **virions**.

Virus particle - also referred to as a **virion**. The case which protects a **virus**' **genome** as it is transmitted from one **host cell** to the next. Though only a single stage in viral replication, the virus particle is still what most people - including most virologists - think of when they think '**virus**.'

Zoonosis - an **infection** in a **host** species other than the one in which it normally spreads.

Who We Are

Connor Bamford

Following completion of his PhD at Queen's University Belfast in his home country of Northern Ireland, Connor is currently a postdoctoral research scientist at the MRC-University of Glasgow Centre for Virus Research working on how our immune system works to control viral infections like hepatitis C virus. In his spare time he likes to play guitar and make his very own beer!

Joanna Crispell

Joanna is from Northern Ireland (though born in Brazil), and has almost finished her PhD at the CVR studying equine influenza virus. She has now moved to Dublin to work in science communication at the Science Gallery. She loves live music, science, and crafting.

Stephanie Cumberworth

Stephanie is from West Yorkshire, England, and moved to Glasgow in 2015 to start her PhD. She studies Zika virus interactions within the central nervous system, working in the Kohl group. In her spare time Stephanie enjoys all things theatrical and attends dance workshops.

Alexandra Hardy

Alex is from France, where she originally trained as a vet before deciding to move into research. She is now doing a PhD on Bluetongue virus at the CVR, investigating virus-host interactions in different host species. Alex loves to travel and 'wander' up Scottish Munros.

Ed Hutchinson

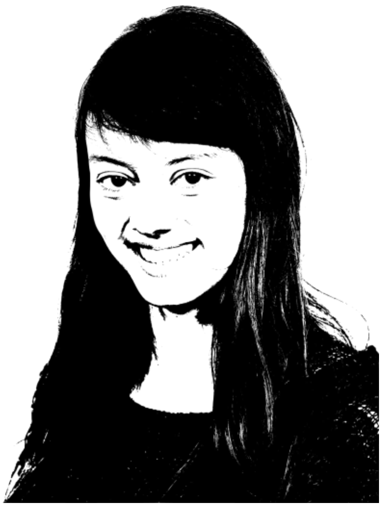
Ed is a Research Fellow, and leads a group who study the molecular biology of influenza viruses. He is originally from the UK, and worked in Cambridge and Oxford before moving to the CVR in 2016.

Yasmin Parr

Yasmin is a PhD student studying feline leukaemia virus at the CVR. She grew up in Campbeltown, Argyll and moved to study at the University of Glasgow where she obtained a MSci in Veterinary Biosciences (with honours). Her interests include live music, animals and photography.

Siobhan Petrie

Siobhan is the CVR Communications Officer and all round 'scicom ninja'. She has a BSc Hons in Biomedical Sciences and over 10 years' experience working in events and communications. Siobhan provides support to deliver our CVR public engagement activities



Weronika Witkowska

Weronika is a PhD student at the CVR and her project focuses on improving ways of diagnosing Hepatitis C virus. She is originally from Poland but has lived in the UK for over 11 years. Weronika has a passion for martial arts, particularly taekwondo.

Acknowledgements

We would like to thank Michaela Jayne Conley (CVR) for help with preparing images of virus particles, and Claire Donald and Ilaria Epifano (CVR), Hannah Forrest (Microbiology Society), Eliza Wolfson (http://lizawolfson.co.uk/), and Kris McConnell for comments and advice. And thank you for your colouring - we hope you enjoyed the viruses as much as we do.

The Centre for Virus Research (CVR)

Understanding viruses. Improving health.

Our vision:
To be the world-leading virology research centre, understanding viruses and viral diseases through innovative science.

Our mission:
To carry out fundamental research on viruses and viral diseases, translating the knowledge gained for the improvement of health and benefit of society.

Our vision and mission are realised through the pursuit of discovery science, generating new knowledge and improved understanding of the fundamental properties of viruses, the pathogenesis of the diseases they cause and the mechanisms of viral emergence and spread, and developing new strategies for the diagnosis, control and treatment of viral diseases.
Our research expertise is broad based, spanning molecular and structural virology, virus-cell interactions, viral pathogenesis, virus ecology, virus genomics and bioinformatics. Through linking approaches at the molecular, cellular, host, population and ecosystem level we strive to understand viruses and improve health.

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