



HOPE FOR A CURE

From Molecule to Medicine

An exciting behind-the-scenes journey through
the drug development process

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HOPE FOR A CURE

Medical research has undergone a tremendous revolution in the last decade. Since the early '90s, scientists have discovered and developed more than 300 new treatments for more than 150 conditions. A great many diseases that used to be fatal can now be alleviated, contained or cured.

And yet there are still many more diseases than treatments. People are also living longer and are therefore more likely to be affected by (chronic) conditions. Disease affects not only the patient, but also those around him. Aside from the individual suffering, there is also the issue of the soaring costs of health care.

The need for new and even more effective drugs is greater than ever. But there is also a need for preventive treatments for diseases, and diagnostics to discover diseases at the earliest stage possible, and biomarkers to distinguish between the various subtypes of a disease. Because these allow us to develop targeted treatment for every patient. Every patient is unique and deserves a personalized approach.. Take for example 'intelligent' forms of administration which increase a patient's comfort and therapy adherence.

But we go one step further in our commitment. You may not be ill yet, but we would like to be your guide and continuously monitor your state of health. Spectacular developments in electronics, and digital access to global data are providing us with amazing opportunities. We would like to guide you on the right course, in sickness and in health, providing advice to meet your needs.

This brochure takes you on a behind-the-scenes journey into the world of drug research and development. We will look at the complete course from molecule to medicine: basic research, preclinical and clinical trials, registration, price and reimbursement, production, sales and marketing, and further follow-up. A journey that takes years, with spiraling investment costs due to the latest innovative techniques being used. At the same time we have to comply with increasingly stringent criteria, for example in the area of registration, and the pressure on prices is relentless. We are looking to a future where patients and their families have a new sense of hope. Hope for treatment that is personalized, with the ultimate goal of a complete cure.

THE HUMAN BODY IS A MIRACLE

Your body is a staggeringly intricate system, but you are generally unaware of the constant stream of miraculous activity that keeps you alive, alert and functioning.

You are amazing

You started life as a single cell, virtually exploding into existence as a fully-formed human being in just nine months. Such dizzying growth means that an adult human is made up of more than 100 trillion (100,000,000,000,000) cells. That's 10,000 times more cells in a single person than there are people on Earth.

Your body contains more than 200 different types of cells, which make up organs like the heart and help keep your body working. Red blood cells, for example, carry oxygen from the lungs to body tissues while white blood cells protect the body from disease. Incredibly, all these cell types came from the initial division of just one cell.

Awesome facts

- Over 70 years, a typical human heart will beat more than 2.5 billion times.
- The airways and cavities in an adult's lungs have about the same surface area as a tennis court.
- Every five seconds, a human produces enough energy to carry an apple to the top of the Empire State Building.
- A human body contains millions of nerve cells that, in one second, can ferry messages between the toes and the brain ten times.



THE CELL

A marvel of engineering on a miniaturized scale.

Human cells are so small that some structures can only be seen with an electron microscope. Yet these microscopes are powerful enough to magnify a cell around 500,000 times, enough to make an ant look two kilometers long!

Your cells contain organelles; structures that carry out specific functions like tiny versions of our body's organs. Mitochondria power your cells by converting food into energy while the cytoskeleton contains small tubes and filaments that act like your bones, giving the cell its structure. The biggest organelle is the cell's nucleus.

The secrets of the cell: Instructions for you

In the cell's nucleus, scientists have discovered a wealth of information. Each of your cells contains a molecular instruction manual with 3 billion 'letters', called bases, formed into more than 20,000 'words', known as genes. Scientists working on the Human Genome Project aim to read every word. This 'book of life', known as your genome, describes how to copy, construct and maintain your molecules, tissues and organs. It's what makes you unique.

Your instruction manual is written in a substance called DNA – short for deoxyribonucleic acid. It consists of two long strands of repeating molecules that coil

around each other like a vine or a spring in a structure called a double helix.

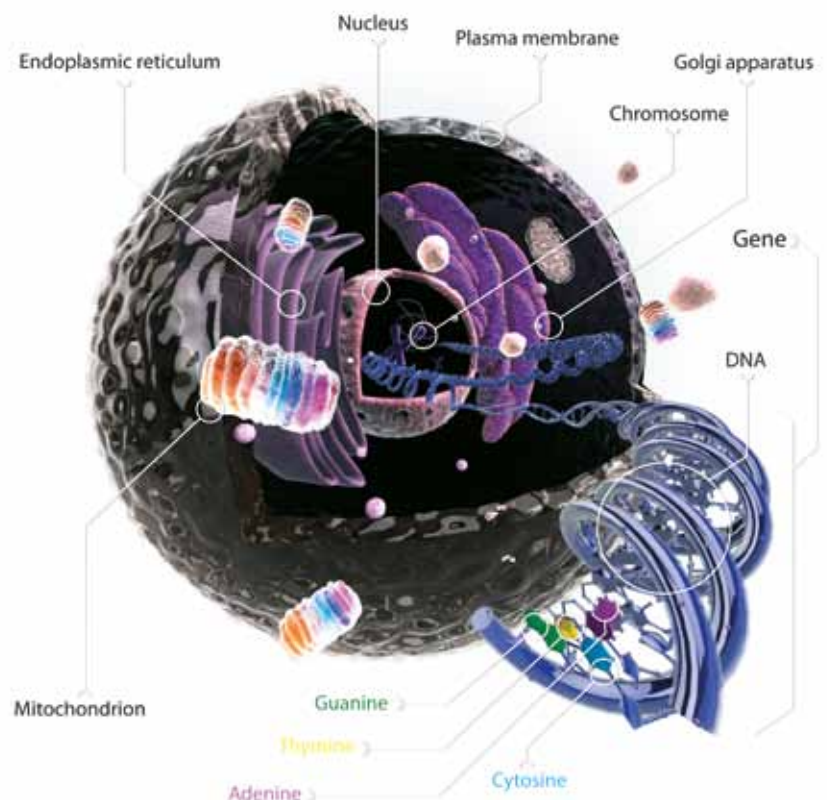
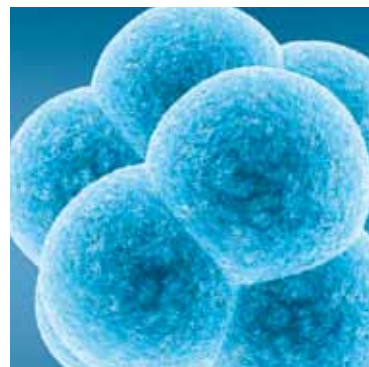
Protruding from these strands are DNA's four 'letters', molecules called Adenine (A), Cytosine (C), Guanine (G) and Thymine (T). A binds to T and C binds to G, locking the two strands together like the teeth of a zip.

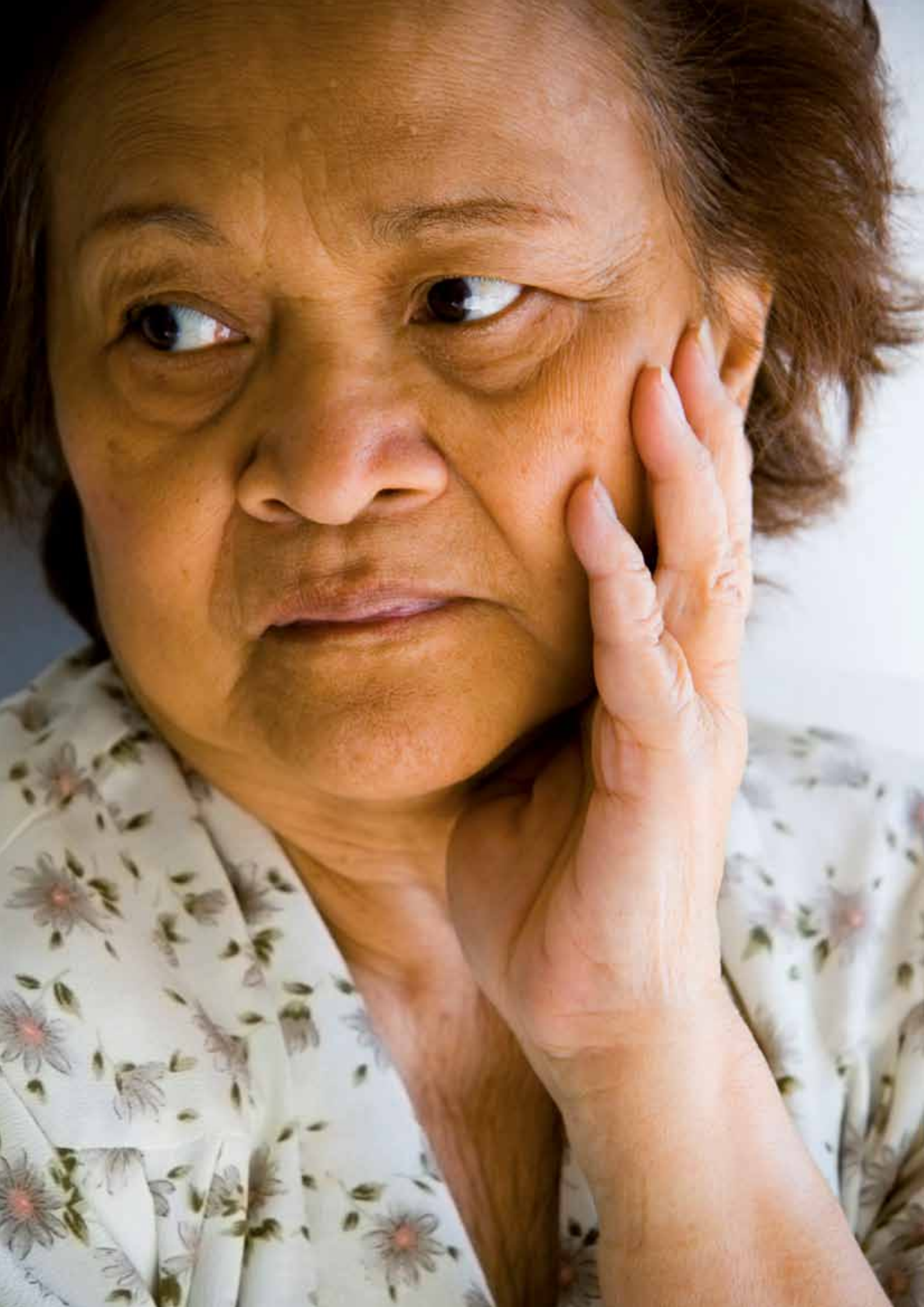
Heart tissue, liver tissue, skin and blood are distinctly different and have dramatically different functions. Yet, astonishingly, each cell contains the same DNA. Your cells are literate – despite being mindless! Astoundingly, your cells read, write and edit this instruction manual. When the cell copies itself or needs to create new proteins – the most impor-

tant types of molecule in a cell – it unzips its DNA. Molecules called polymerases act like intelligent pens, writing out the sequence of bases onto new strands.

Molecules

The building blocks of all physical objects, including people and this brochure, are tiny particles called atoms. Molecules are a relatively stable arrangement of two or more atoms held together by strong chemical bonds. Many molecules are made up of several different types of atoms – these are called compounds. For example, water molecules contain two hydrogen atoms and one oxygen atom. Molecules, such as DNA, contain many atoms.





THE HUMAN BODY IS VULNERABLE

Your body, although incredible, is not invincible.

Like a machine, your body can break down.

The body can break down



Your DNA code may contain mistakes, your lifestyle can damage your body, you may get a “bug” in your system or you simply age. A complex mix of these causes many diseases. You need good health to enjoy life, whatever your age. But illness stops you turning your dreams into reality.

A bug in the system

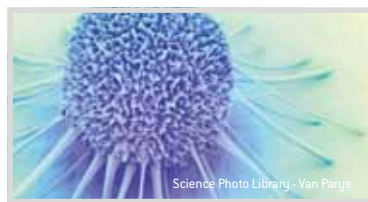
Viruses, such as those that cause flu and chicken pox, work much like computer viruses. They are stray bits of DNA code that break into cells, hijack their manufacturing machinery and use this to churn out multiple copies of the virus. Bacteria, like those that cause food poisoning, are tiny creatures that rapidly grow, feed and reproduce within your body.

Your immune system acts like your body’s army, finding and destroying harmful invaders. It flags up cells, viruses or bacteria with a different genetic code to you and eliminates them. Unfortunately, it is not perfect and some attackers can go undetected or overwhelm you.

Bugs in your code

Your DNA code, like computer code, can contain errors that cause your body to malfunction. Some of these are passed from one generation to the next, while

others occur during your life. If you suffer from cancer, a cell starts endlessly duplicating itself because its program



has copied incorrectly or is corrupted. Your cells reproduce and copy their DNA billions of times a day but, incredibly, they make so few mistakes that only about 1 in 27 of us will suffer cancer before the age of 50!

Living on the brink

AIDS has killed 25 million people to date, making it one of the most destructive pandemics in history. It is caused by the HIV virus, which invades immune system cells, leaving sufferers open to life-threatening infections. The HIV virus writes itself into a cell’s DNA so that the cell manufactures viruses. HIV is a poorer proof-reader than your own cells and often copies its DNA incorrectly so that the new viruses are quite different from the original. It is because HIV is constantly changing, that it is difficult to treat.

One third of the world’s population is currently infected with the bacteria that cause tuberculosis (TB) and anyone infected has a 10% chance of suffering from TB during their lifetime. People with weakened immune systems are especially at risk of developing this often deadly lung disease. AIDS sufferers, for example, are ten times more likely to develop TB and often live in developing countries where TB infection is also

more prevalent. In Africa, for example, 30 - 50 % of the population is infected with TB, compared to 5% in the West.

The first antibiotic to treat TB was discovered 50 years ago, but treatment remains very difficult. Sufferers need to take four antibiotics continuously for six to nine months, which many find difficult to do. Failing to take the antibiotics gives the one in ten million bacteria that survive treatment the time to multiply and spread. The hunt continues, therefore, for a drug that can treat TB faster and kill the bacteria that survive treatment with existing antibiotics. There is renewed hope due to a new drug in our pipeline. In conjunction with social and political programs, and in combination with existing antibiotics, this new drug has the potential to be a powerful weapon in the fight against TB.

Fast Facts - Diseases

We know of 30,000 diseases worldwide, ¾ of these cannot be treated effectively, according to the World Health Organization, while others are very difficult to treat.





OUR SCIENTIFIC KNOWLEDGE IS GROWING

Fortunately, science is always evolving. Scientific advances increase our understanding of the human body - from unraveling the structure of DNA and reading its text, to understanding the errors in our genetic code that can cause cancer and delay the onset of brain diseases like Alzheimer's.

Cracking life's code

Life scientists working for research organizations, universities or pharmaceutical companies face a constant challenge to

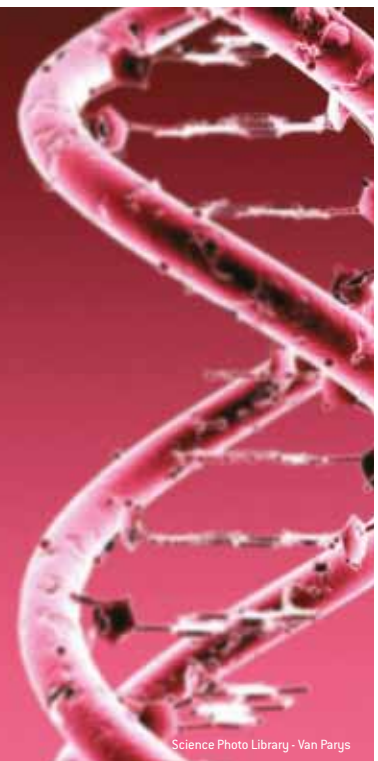
transform this expanding knowledge into effective new treatments to bring relief from suffering to millions worldwide.

The next 10 years in medicine should be a time of great excitement for science and hope for all humanity.

The Human Genome Project

Until 1990, scientists had not decoded most of our genetic instruction manual, and didn't understand how its letters and words contributed to human disease. Then, the US Government paid scientists to record or 'sequence' all the genes in our genome. Soon, researchers in UK, Japan, Germany, France and China joined in the international Human Genome Project (HGP). The project was well underway when, in May 1998, an ambitious company announced it could sequence the entire human genome in just three years using a radical new technique called 'shotgun sequencing'. Both teams raced to be first to publish a human genome and finished neck-and-neck, with a draft of the genome, in 2000.

Sequencing the human genome has fuelled the discovery of disease genes and the search for new treatments. More than 1,000 genes are known to be involved in disease to-date. Identifying a disease gene is essential so that researchers can answer questions like: What does the gene do? Which genes work together? How can a gene be rendered powerless to cause disease? By answering these questions, scientists can begin to develop new treatments, which are even more effective and have fewer side effects than those available today.

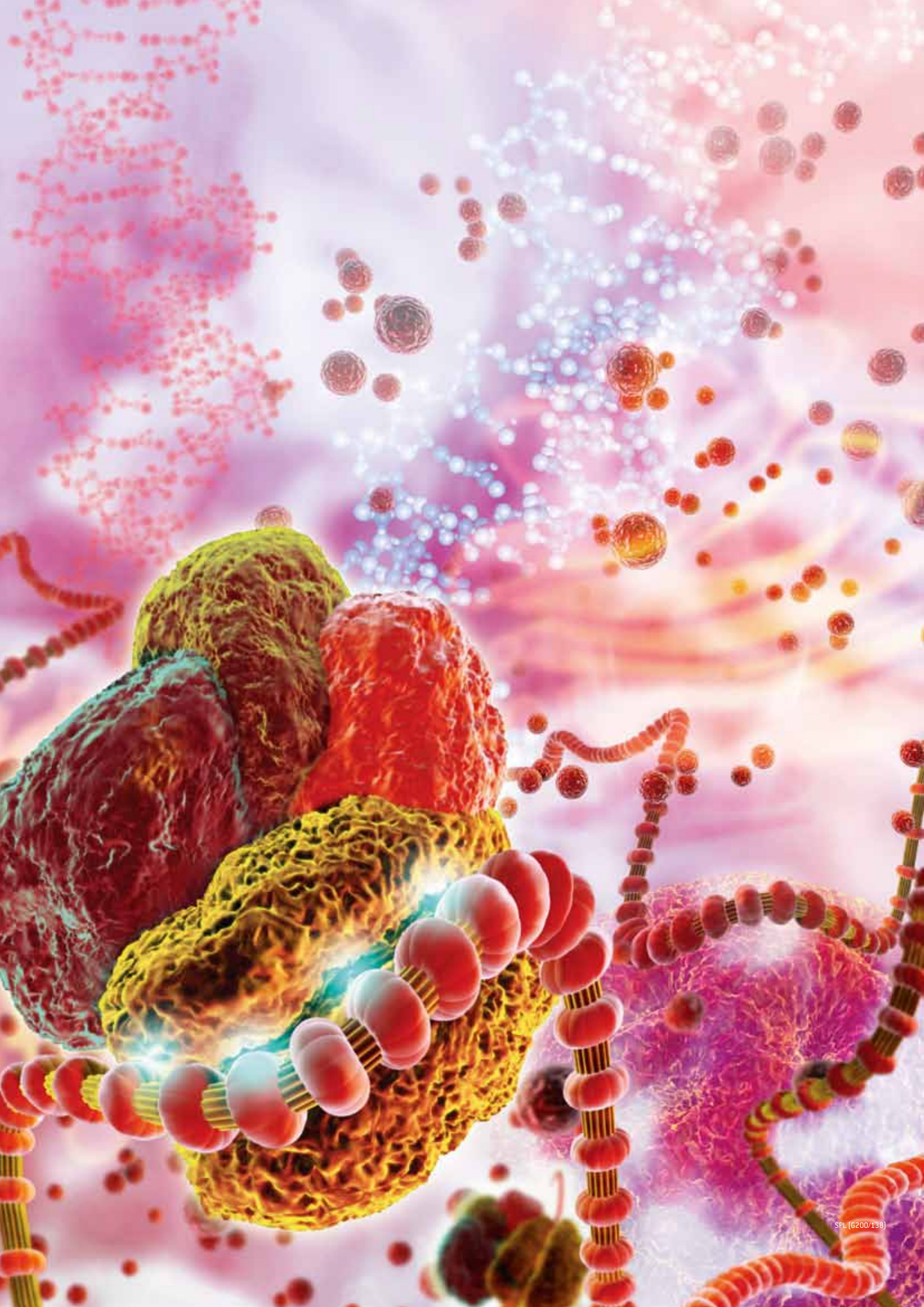


Science Photo Library - Van Parys



Did you know?

- If we wrote down our DNA, it would fill 200 volumes the size of a 1000-page telephone directory.
- It would take 9.5 years to read out loud the 3 billion 'letters' in our DNA at a rate of 10 bases per second!



DETECTIVE WORK

Researchers learn from scientific discoveries and use this knowledge in their search for new medicines and their quest to learn how diseases are caused.

The drug discovery process begins by finding diseases that have few, effective treatments and identifying drug targets that could be the starting points for new ones. In many diseases, one or more proteins in the body do not work correctly. Proteins form most of the structures in cells and participate in every process within them. Most drugs act on specific proteins so scientists must find the proteins connected to a disease before they can develop a drug which affects them.

Alternatively, they can start by measuring the effects of different potential



Science Photo Library - Van Parys

drugs on an animal, a patient or in the lab and then investigate which proteins or 'drug targets' it affects.

Finding a needle in a haystack

With millions of bases, hundreds of thousands of proteins, trillions of cells and numerous processes occurring in each cell daily, finding the drug target is like looking for a needle in a haystack. The challenge is comparable to a treasure hunt with many enticing clues about where to dig, but where almost nothing is found but large, empty holes.

It can take years to find a valid target and, to succeed, scientists must turn detective. Like modern detectives, scientists use and develop innovative technology to find, select and evaluate potential targets before starting a drug discovery research program.

Amongst the most promising technologies are RNA interference, which can silence genes, and DNA microarray, a matrix of tiny dots which help us to understand the many simultaneous activities of a whole host of genes.

Since the drug discovery process is very long, complex and expensive, and only a small number of targets can be developed at once, scientists use filtering technologies to choose the right targets.

Did you know

- There are around 30,000 genes in the human body of which perhaps 5,000 play a key role in disease. For example, defects in a gene called BRCA2 makes women more likely to suffer breast cancer.
- Out of the 100,000 or so different proteins in the human body, and the many molecules found in harmful organisms like bacteria, scientists only understand 324 molecules well enough to use them as a human drug target.

The tiniest helping hand

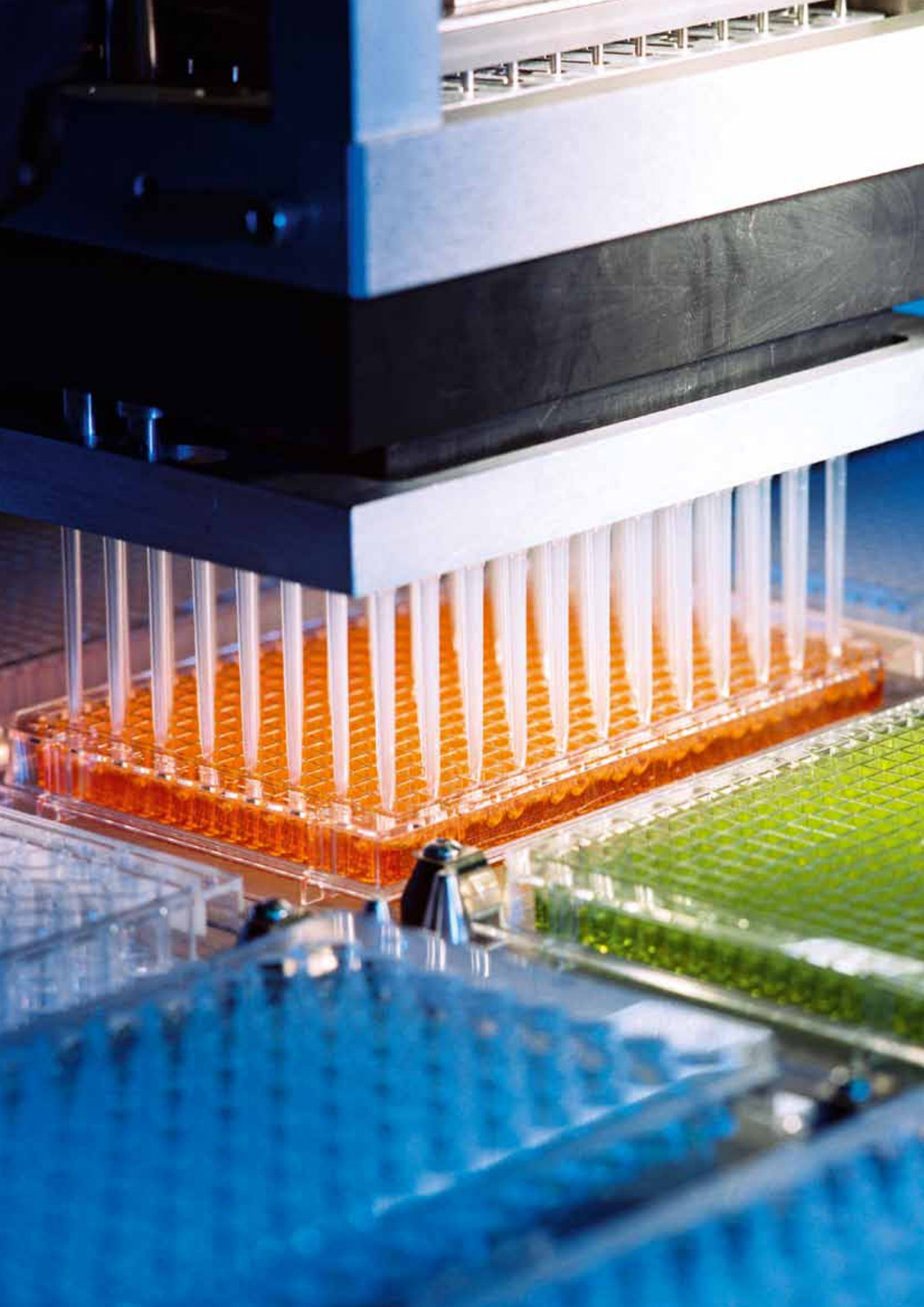
The Human Genome Project was a first step towards understanding what each gene does. Not to mention the complex interactions between the genes and the proteins that they instruct!

This is where microarrays can lend a helping hand: enabling the activity of thousands of genes to be followed in a single experiment. At any time, a cell is only running

certain sections of code in its DNA program. Microarrays can detect, for example, which genes are 'switched on' and producing proteins in diseased cells compared to healthy cells. Microarrays are so-called because they consist of thousands of molecules arranged in a regular pattern of microscopic dots on a solid surface, such as a glass, silicon or plastic chip.

Silencing genes

Imagine a molecule that can 'switch off' any pre-selected human gene, including those involved in causing disease. The recent discovery of a technique (RNA interference) to silence genes has opened exciting new medical horizons. Scientists hope to identify potential new targets for the development of novel drugs faster, by watching what happens when they 'switch off' certain genes.



SEEKING A MOLECULAR KEY

Once scientists understand a protein's relationship to a disease, their next challenge is to discover the molecular key that fits the protein's lock and can make it work correctly.

Deciding to develop a drug against a particular target is a big commitment in terms of time and money. After a pharmaceutical company settles upon a target, it can take about 12 years to bring a new drug to patients.

Some proteins – called enzymes – are shaped like locks and speed up chemical reactions by binding to molecules, just like a lock fits a key. Once scientists have tracked down which protein (or proteins) is the disease culprit, their next challenge is to discover a molecular key that fits the protein's lock and can make it work correctly. They transform this key into a new drug. Hitting upon the right substance is a daunting task.

With a little help from nature

Many drugs in use were originally derived from natural sources. The first written record of humans using natural substances, such as licorice, to treat illnesses like coughs and parasitic infections was found on clay tablets in Mesopotamia (in the modern Middle East) that may be nearly 5000 years old.

Scientists still develop drugs from nature by isolating and purifying the molecules that produce beneficial effects. Consider the discovery of trabectedin, a drug for treating cancer derived from sea squirts.

Cracking the lock

During the Second World War, a famous physicist called Richard Feynman was working in a top-secret US laboratory. He amused himself by cracking combination locks and amazed his colleagues

by opening safes full of confidential documents. Scientists discovering drugs are master code-breakers too. They use the same tricks as Feynman to discover the right molecular combination to crack their protein lock.

Fortunately, they can check every combination more efficiently. They don't just hope the right key will turn up. Scientists called structural biologists use X-rays to examine the molecular structure of the protein lock. In the lab, combinational chemists create whole libraries of slightly different keys by combining simple molecules into more complex ones. The chemists can also use powerful search engines and databases to look for other natural or synthetic compounds with desirable properties.

Then, just like Feynman, they figure out how the locks work so they don't have to try every combination. Rapid increases in computer power have meant scientists can model the behavior and interactions of proteins and molecules in tremendous detail and over fractions of a second, allowing them to design keys from scratch. This is called molecular modeling. These scientists are experts in bioinformatics – using computers to solve biological problems.

The search continues

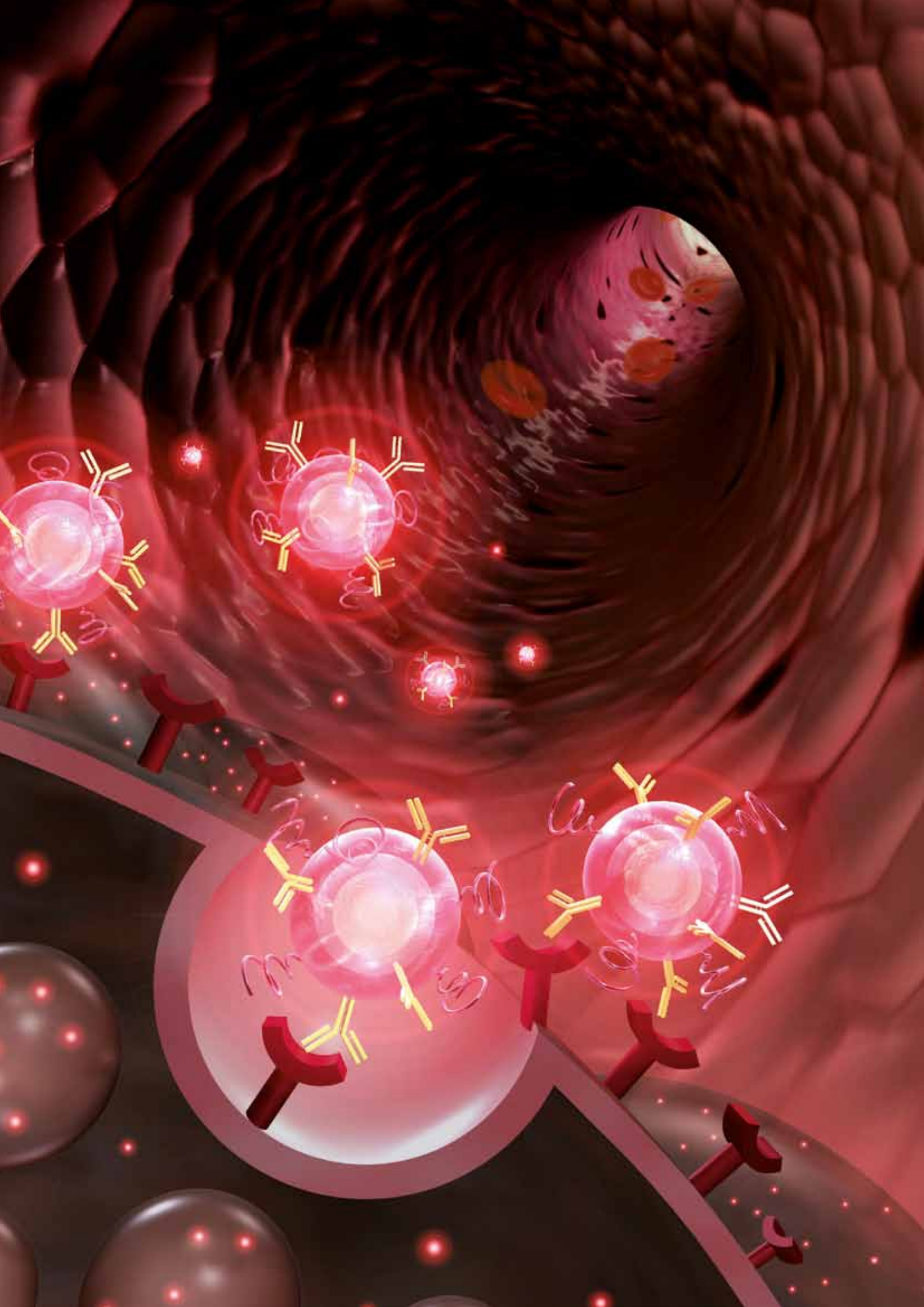
This search can yield literally millions of potential drug candidates. Synthetically bolting molecules together, in particular, vastly increases the number of possible substances. Even a relatively simple molecule can be varied slightly to produce a library of 100s or 1000s of possible combinations.

In the search for the key, scientists then need to test every one of these. Modern laboratories have automated this process and, using high-throughput-screening, can screen up to 100,000 substances every day. Robots squirt whole cells, cell components or purified proteins into several hundreds or thousands of tiny tubes, each containing a different possible molecular key. The scientists observe whether any of these molecular keys fit the protein lock, what they do to the cell components or how they act inside a cell. By screening, they identify several hundred 'hits' – likely candidates to be made into a drug.

Small or large molecular keys

Most medicines today are small molecule drugs. These are a diverse group or substances derived from nature or manufactured in the lab which generally have a low molecular weight. Molecular weight is the sum of all the weights of the atoms in a molecule.

Large molecules or 'biologics' are being used increasingly to develop novel and targeted treatments. These are proteins derived from living sources such as mammalian cells and grown in an artificial environment. They can be 200 or more times the size of small molecules. Biologics will play a major role in a wide variety of diseases.



FROM MOLECULES TO MEDICINE

The compounds with the greatest potential to be developed into safe and effective medicines are selected and proceed through preclinical, chemical and pharmaceutical development.

Cutting the keys

The next step is 'hit confirmation'. Scientists known as medicinal chemists check that their 'hits' didn't happen by accident because, for example, the molecule happened to fit the wrong 'lock' (since proteins may have several 'locks' that fit).

Next, they examine each 'hit' to check it resembles existing drugs by, for example, dissolving them in water. Again, many 'hits' don't make the grade because, for example, too much of a substance is needed to open the lock. To improve the remaining keys, a 'hit explosion' is created. The chemists generate a burst of molecules similar to the original 'hit' in the hope that a closely-related key will work better.

The molecular keys they select are like key blanks that fit the lock but don't turn. During the 'lead optimization' stage, medicinal chemists improve each key, or 'lead', by switching some of its atoms and molecules around. Their aim is to make the new drug safer and more efficient with fewer side effects. Sometimes they test and change it hundreds of times. Once the pharmaceutical company is happy with the result, it patents the drug – this means no one can copy its hard work.



Preclinical development

At this stage, the scientists have discovered a whole bunch of possible keys. But do they treat the disease and are they safe?

It is the role of preclinical development to quickly and cost-effectively identify which compounds are unlikely to succeed in humans. Scientists test whether the drug is toxic (toxicity), the effects it has on the body (pharmacodynamics) and what happens to it (pharmacokinetics), for example, how it travels through the body, is broken down and is eventually excreted as urine or feces (known collectively as ADME). At any point, a potential candidate may be rejected because it is harmful or doesn't work effectively. It is expensive to discover that a drug is toxic or ineffective when it's almost ready to be sold, so scientists do their utmost at this stage to find that out.

Preclinical tests are performed in test tubes and some have to be done on animals. Regulations in Europe, the USA and other countries ensure that animal experiments are only performed where necessary and are humane. Drug companies are trying to reduce the number of animal experiments needed by, for example, adopting new techniques for measuring trace doses of drugs in the human body – too small to cause any harm.

Scientists also make sure the new drug can be produced in sufficient quantities to meet patient demand.



Drug delivery of challenging molecules

During preclinical development, scientists also investigate whether drugs should be swallowed or injected, for example, to reach the right part of the body. Side-effects affecting certain parts of the body can be reduced if the drug bypasses them.

Forgetting to take your pills can affect how well they work. Recent advances in drug delivery are helping to overcome this problem. Tablets that slowly release their drug over 24 hours can transform the lives of patients with mental illnesses, like schizophrenia, because they don't have to remember to take multiple tablets daily to stop their symptoms returning.

It's difficult for some drugs to stay in or reach the right part of the body because, for example, they don't dissolve well in water. Once scientists discover this, they can change the way the drug is delivered so it is more effective and they can continue developing a promising drug.

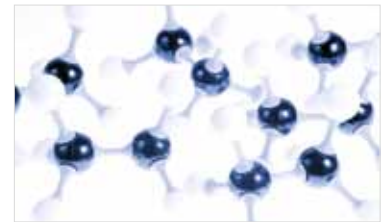


BRINGING A NEW DRUG TO LIFE

During preclinical development, new drugs were tested outside the human body. Now, the scientists are ready to study the drug in people, to test its ability to treat the disease.

Clinical trials are the last critical step before the drug is sent to be approved for sale. Admittedly, the path from the lab bench to the marketplace is long and costly, but to ensure new drugs are safe and effective, no corners can be cut. After all, lives hang in the balance.

The most commonly performed clinical trials test new drugs, medical devices or other treatments on patients in strictly controlled settings, and are required before the authorities will approve the treatment.



Unique challenges arise at every step

The drug must pass through three clinical stages before it can be launched – this is the longest part of the entire drug development process and takes around 6 years to complete:



1

Phase 1: Scientists test the new drug on a group of 20 – 100 volunteers to find the best dose to give and to see if it has any side effects. The volunteers are usually healthy people who want to help society battle diseases.

2

Phase 2: The new drug is tested on 100 – 500 volunteer patients with the disease to test whether it works and to continue to study its safety. Patients participating in clinical trials have their health carefully monitored and are the first people to receive a potentially revolutionary new treatment.

3

Phase 3: Thousands of patients in many different hospitals are treated with the new drug which is compared to existing treatments. The aim is to see whether the new drug is better than what has gone before.

Many drugs fail during these clinical studies because they don't perform in people as they did in the lab. The trial results are sent to a regulator appointed by government, such as the US Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMA). The regulator's mission is to protect public health by checking that the company has carried out enough tests and that these tests show the drug to be efficacious and safe. They will only allow the drug to be sold when they are convinced that this is the case.

The testing doesn't stop when the drug hits the market, Phase 4 trials are conducted to study the long-term effects of

the drug, any rare side effects and other diseases it may treat.

Why so long?

Only certain people are eligible to take part in each clinical trial and the biggest barrier to completing studies is encouraging enough people to take part. Cancer trials, by their very nature, take months or years to complete since it takes that long to see if the treatment works in any one person.

OVERVIEW FROM MOLECULE TO

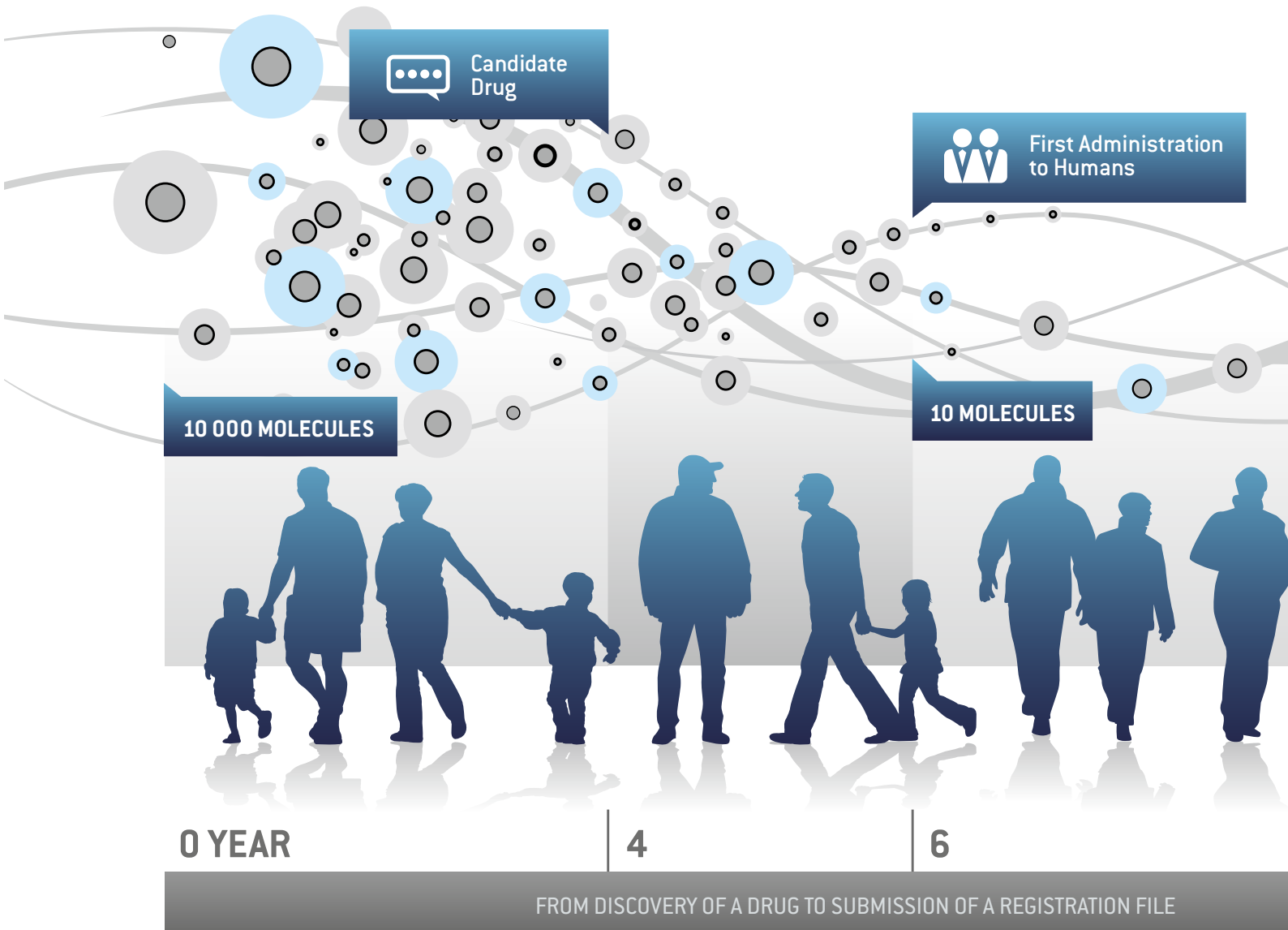
 BASIC RESEARCH	 PRECLINICAL DEVELOPMENT	 CLINICAL TRIALS
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There are a great many medical problems that remain unsolved. And there could be a whole lot more to come. There is a global need for new treatments for (chronic) diseases - such as HIV, cancer and central nervous system disorders.

The most promising molecules become candidate drugs! We go on to test these in a test-tube, on cells (in vitro), or in live laboratory animals (in vivo).

If the candidate drug is safe enough to be tested the clinical trials begin in healthy volunteers (phase I) (phase II and III). We investigate the safety and efficacy of the candidate drug, and how it behaves in the body (absorption, distribution, excretion).

High-Throughput Screening	From Hit to Lead	Lead Optimization	Preclinical Development	PHASE I	PHASE II	PHASE III
			Formulation	>20-100 healthy volunteers	>100-500 patients	>1000-5000 patients
			Upscaling			Production Preparation



 Internal pipeline
  External pipeline

FROM DISCOVERY OF A DRUG TO SUBMISSION OF A REGISTRATION FILE

0 MEDICINE



REGISTRATION

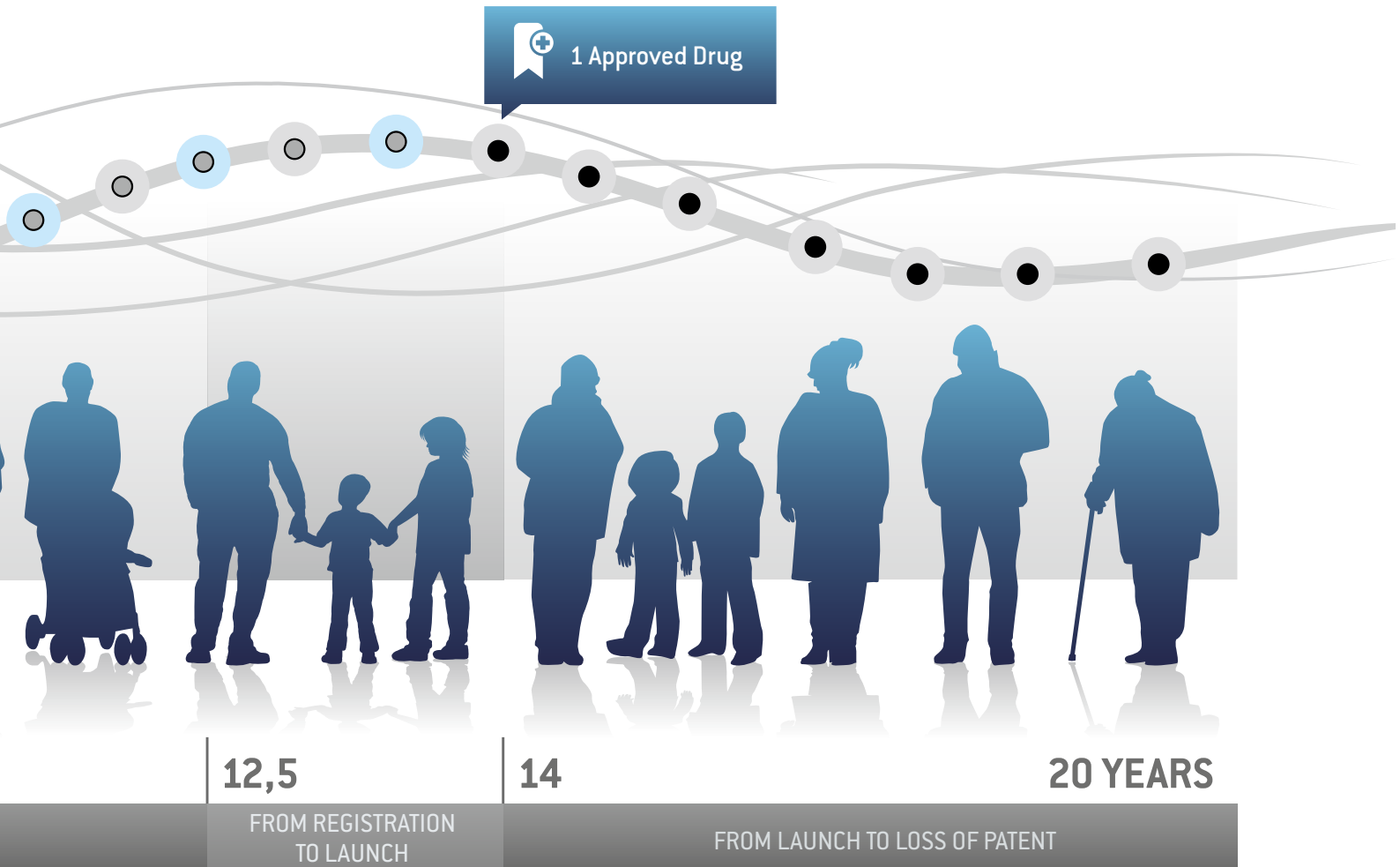
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Only registered drugs can be brought to market. Which is why we have to submit a file containing all the data from the basic, preclinical and clinical research to the government.



COMMERCIALIZATION

Once the drug has been registered, production gets into full swing. We provide information to the medical profession, and request a price and reimbursement from the authorities. Once these are obtained, we can distribute the drug to our customers. The safety of the drug is then continually monitored in patients around the world.



AVERAGE COST OF A DRUG 1,250,000,000 EURO



R&D AND PRODUCTION

WORKING TOGETHER

Registering a drug used to be the last step in Research & Development and the first step in Production. Now Production gets involved in the development phase, long before the launch of a drug. And R&D helps Production long after the launch.

During the registration, price and reimbursement stage of a drug, the production department has already started firing on all cylinders. Once the reimbursement has been allocated, the drug is immediately distributed to all those countries where the registration applies. This usually includes all EU member states at the same time, because most drugs are registered today via the European procedure. This means that in the run up to the launch date huge stocks of the drugs must be ready and waiting in our warehouse.

Balancing objectives

R&D no longer passes on the baton after registration to Production. Now both departments work together for practically the whole life cycle of a drug. At a very early stage R&D and Production lay down the production definition: from formulation to production, analysis, packaging and distribution. R&D focuses on the formulation of the active substance in an administration form. Production then finds a cost-effective and feasible way to produce, analyze, package and distribute the drug on a large scale.

Built-in quality

The close collaboration between R&D and Production raises the quality of the development and production process to a higher level. R&D takes into account the experiences of Production. Formulations that have been made in the development lab using small devices in small quantities (kilos), need to be produced by Production using different, bigger apparatus on a commercial scale (tons). This upscaling process sometimes causes

Production problems that never arise in the laboratory. In addition, R&D provide Production with detailed information on the production parameters that affect the quality of the finished product.

Technological innovation

Increasing the batch and reducing the unit production cost is a constant challenge for Production. What this means in real terms is that the latest technological developments need to be applied to production and analysis processes. That's the only way to stay competitive in the pharmaceutical sector. And to anticipate and give detailed answers to the questions from the registration authorities. For example, on the presence of impurities or breakdown products in our drug. These can be tracked down much better with the latest (more sensitive) analysis methods. If necessary we can adapt the production process and even the formulation of the drug to obtain an even purer product.

Top quality drugs

Quality control ensures that the entire production process is carried out according to Good Manufacturing Practice (GMP). So all procedures are laid down in SOP's or Standard Operating Procedures, and the personnel are trained and qualified to implement them. The analysis laboratories continuously check the quality and stability of the drugs delivered by Production. These must comply fully with the guidelines in the registration file. Together, Production and R&D work out how to 'label' drugs invisibly by,

for example, adding a harmless tracer so that an original product can always be distinguished from illegal counterfeit products.

Running like clockwork

So, how does the finished product get to the customer on time? Well, it's all down to the planning unit in Production which converts sales forecasts into a practical schedule for production and distribution. For example, it signals that new machines need developing (engineering) for production or packaging of drugs. Or for packaging and information leaflets in line with the registration requirements. And it arranges the transport of the drugs under the correct conditions (e.g. fridge temperature) to the customers.





PRICE AND INFORMATION

Who decides on the price and reimbursement of a drug? Which aspects are taken into consideration? And who presents the drug to the medical profession?

Our health economy specialists at Health Economics, Market Access & Reimbursement (HEMAR) prepare the price and reimbursement file. By the end of phase 2 clinical trials they start communicating with R&D and Medical Affairs to determine the value of the new medication.

Their concern is what public price we should demand for the drug to recover our costs.

Can we defend the price in the face of existing treatments? Have we presented sufficient scientific arguments about the therapeutic (added) value of the drug to obtain and maintain reimbursement?

In most countries, the price of a new drug that enters the market is determined on the basis of a negotiation with the national authorities. In some countries, the price level is free and can be determined by the company. Throughout its life cycle, the price of a drug may fluctuate, based on changing market circumstances or because of re-negotiations with the authorities. Because the reimbursement is always made with public money, its level and conditions are always the result of a negotiation with the authorities, the sick funds and the health insurance companies.

Information and advertising

After the official launch of the drug, and to a limited extent also during the price and reimbursement procedure, our medical representatives visit members of the medical profession. They talk about all the details in the patient information leaflet (PIL). If the doctor has a question that cannot be answered by the PIL, then the representative sends it to our medical department who contacts the doctor. That department also gives lectures at medical conferences and organizes scientific meetings with specialists from the health care sector in order to pres-

ent information about the drug and its scientific background.

All the activities that we organize for those active in health care are strictly regulated by the government. In addition, we have developed industry rules to which all companies must adhere. All those rules come under the policy of Health Care Business Integrity. After the launch the drug is made available worldwide. This is the point at which new side effects sometimes come to light, brought to our attention via spontaneous reports from doctors or pharmacists, or by the systematic research of the company itself (sometimes enforced by the European Medicines Agency (EMA), e.g. for biological molecules).

The value of medicines

Medicines remain the prime target of healthcare cost control, despite the fact that, there is growing evidence of the added value of medicines in the healthcare context, both in terms of global cost savings as well as increasing the quality of care. Medicines can not only provide the best treatment for many diseases, but can also generate savings by substantially reducing costs in other branches of healthcare (hospital stays, disability, etc.).

- Each year Cardiovascular Disease (CVD) causes over 4.3 million deaths in Europe and over 2.0 million deaths in the European Union. Overall CVD is estimated to cost the EU economy €192 billion a year. (Source: European Heart Network)
- Some 30-80% of the adult population in the WHO European Region is overweight. Obesity affects up to a third of the adult population in the region. Almost 400 million adults in the region are estimated to be overweighted and about 130 million, obese. Obesity cre-

ates a major economic burden through loss of productivity and income, and consumes 2-8% of overall health care budgets. (Source: World Health Organization).

The value of innovation

We're living longer and better than at any time in history. In part, this is due to pharmaceutical advances, small and large. Life expectancy is higher than ever, and we're making progress against the most serious diseases we face. New, innovative medicines will assume an increasingly prominent role in the way we improve health for future generations. The value of innovation tends to be split in three categories: breakthrough innovation, incremental innovation and marginally innovative. Not only breakthrough innovation is 'real' innovation, but also incremental improvements to existing medicines, which treat diseases in new and better ways, are easier or safer to use or have fewer side effects. Although molecularly similar, their therapeutic properties are often substantially different. They offer alternatives enabling the doctor to treat with greater precision the needs of individual patients.





GIVING PATIENTS RENEWED HOPE

The miniaturization of electronics, and the digital highway present us with great opportunities. Both to monitor your health even more effectively and to design treatment with 'intelligent' and personalized medication.

Our challenge is to develop and produce new medicines to treat patients around the world more effectively. But we are more than just drug manufacturers. For us, every patient is unique and deserves 'personalized' treatment. What are our aims? Continuous follow-up of your health and the diagnosis of your illness at a very early stage. Medication that is effective and user-friendly, support from your personal carers, and follow-up after treatment. Working in a team with your doctor, pharmacist and other health care workers we want to be your personal guide in sickness and health. How does the future look if all the pieces of the puzzle that we have already completed or are still perfecting, fall into place? Here's a taste of what's to come...

Sensor talks to mobile

The miniaturization of electronics means that we can develop really small sensors that can be worn effortlessly on your body. They register physical parameters (e.g. blood pressure, heart rate, glucose levels, movement, cardiac activity) around the clock. If you are in the vicinity of your mobile phone, then the sensors send their data automatically (via Bluetooth) to a website where they are converted into health data. You and your doctor can then request this data. That way you get expert advice to suit your needs.

Personalization

What medicine works best for you? We can use biomarkers (e.g. in your blood) to trace your illness at the earliest possible stage. Our knowledge about diseases (precise cause, subtypes, etc.) and genes is growing with every passing day. On the basis of the diagnosis of (the sub-

type of) your disease, and your genetic profile, we select the drug that will be most effective for you. Our current HIV treatment is a wonderful example of this personalization.

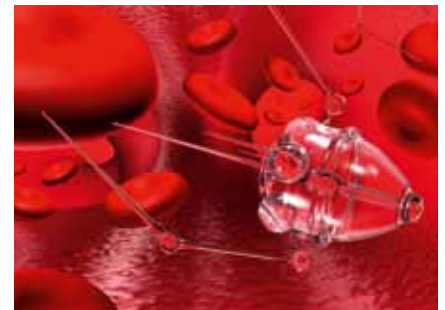
'Intelligent' packaging and administration form

It's not always easy to adhere correctly and faithfully to your treatment. Those patient leaflets can be a boring read, can't they? Useful pictograms on the packaging are a much better way of giving you the most important information. And a personal photo on the box (e.g. of your family) will encourage you to take to your medication every day. If however you sometimes forget to take your medication, don't panic. A ring tone in the packaging is there to remind you. And then, once you've taken a tablet, the packaging automatically registers the date, time and which tablet you took. When you, your doctor or pharmacist scan in the packaging you can see your therapy adherence profile. 'Intelligent' forms of administration for drugs also increase your comfort. For example, forms with prolonged action, or automatic release (e.g. after a signal from a sensor).

Digital highway

We use data from anonymous patients around the world to customize your treatment in this way. We expand our knowledge about diseases and patients' response to medicines. The exchange of anonymous patient data between health portals, hospitals, doctors and laboratories around the world is a must for this

purpose. And the digital access points for opening or keeping open this data, and managing this data, is our ultimate challenge for the future.



Our vision of the future ...

A cancer patient is on the operation table, a piece of tumor is cut away. That piece is put on a chip, which takes only a few minutes to determine the type of tumor and the genetic profile of the patient. The doctor immediately knows which drug to prescribe to fight the tumor. And then he administers it in the form of a minuscule thread directly into the tumor.

An epilepsy patient is wearing a cap or hat which contains a tiny device to measure his brain activity on a continual basis. It is a minuscule ECG device, no bigger than a sugar cube.

If it records abnormal brain activity predicting an epilepsy attack, the patient immediately receives a dose of a drug via an 'intelligent' mechanism to suppress the attack. The patient can then continue safely on his way!

ONE TEAM, ONE MISSION

We embrace science and research to bring innovative solutions to advance the health of millions of people worldwide

