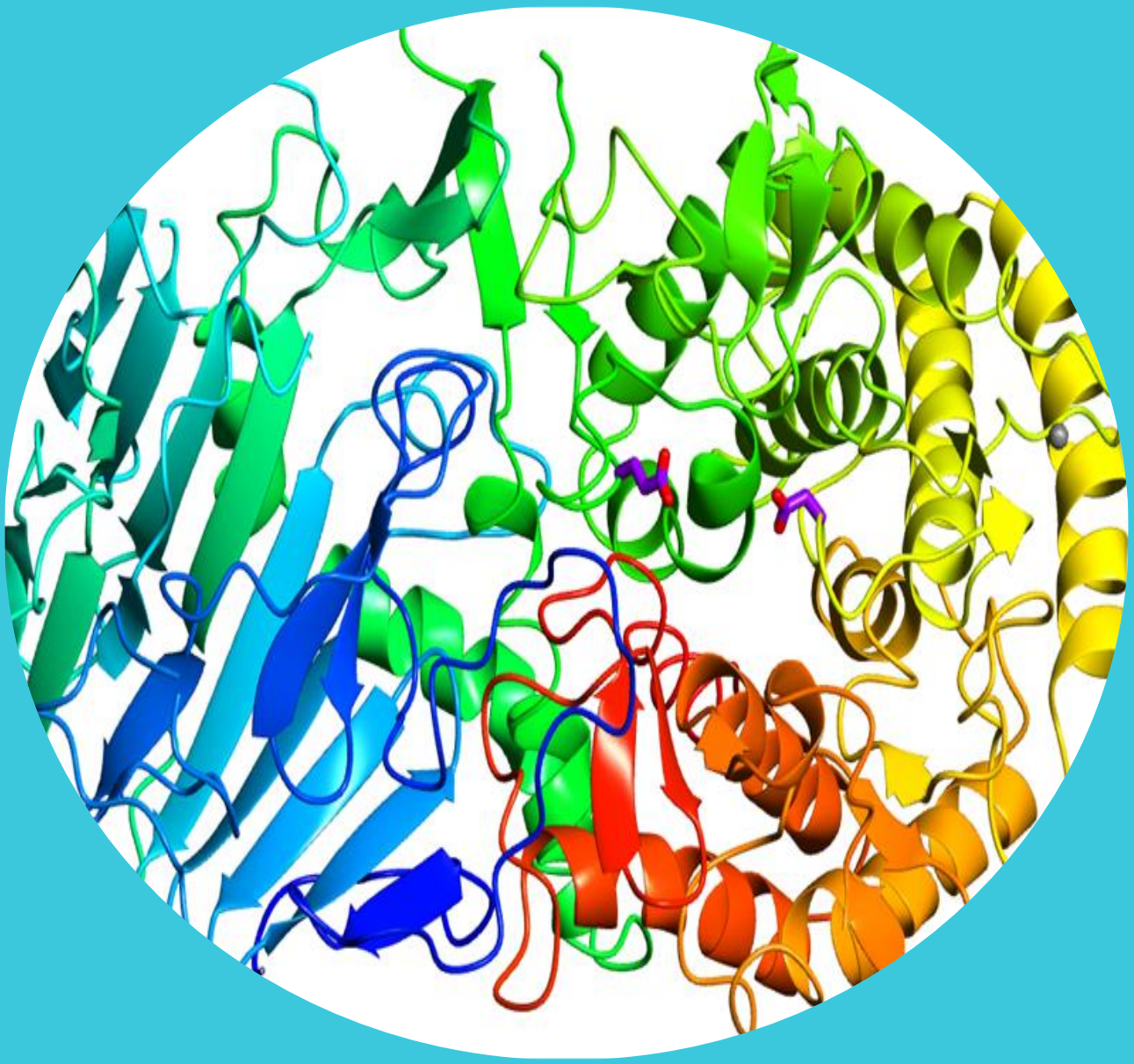

# 3D or not 3D: The shape of the protein

| | |
|---|---|
| Pupil Name | |
| Handbook Designed by | Dr Breen |

# Timetable and Assignment Submission

## Timetable – Tutorials

| Tutorial | Date | Time | Location |
|---|---|---|---|
| 1 | | | |
| 2 | | 15:00 | |
| 3 | | 15:00 | |
| 4 | | 15:00 | |
| 5 | | 15:00 | |
| 6 (Feedback) | | 15:00 | |
| 7 (Feedback) | | 15:00 | |

## Timetable – Homework Assignments

| Homework Assignment | Description | Due Date |
|---|---|---|
| Tutorial 1 | Baseline Assignment | |
| Tutorial 2 | Match the disease to the protein! | |
| Tutorial 3 | Read the articles and answer the questions. | |
| Tutorial 4 | Completion of workbook and glossary | |
| Tutorial 5 | Final assignment | |

## Assignment Submission – Lateness and Plagiarism

| Lateness | |
|---|---|
| Submission after midnight on 9th August | 10 marks deducted |
| **Plagiarism** | |
| Some plagiarism | 10 marks deducted |
| Moderate plagiarism | 20 marks deducted |
| Extreme plagiarism | Automatic fail |

Cover Image: The 3D structure of TxGH116. Data collected to 2.6 Å at Diamond Light Source Oxfordshire. PDB ID: 5FJS (Charoenwattanasatien et al, 2016) [1]

# Uni Pathways – Pupil Feedback Report

| Grade | Marks | Guidance |
|---|---|---|
| 1st | 70+ | |
| 2:1 | 60-69 | |
| 2:2 | 50-59 | |
| 3rd | 40-49 | |
| Working towards a pass | 0-39 | |
| Did not submit | DNS | *No assignment received by The Brilliant Club* |

| Lateness | |
|---|---|
| Any lateness | 10 marks deducted |
| **Plagiarism** | |
| Some plagiarism | 10 marks deducted |
| Moderate plagiarism | 20 marks deducted |
| Extreme plagiarism | Automatic fail |

| | | | |
|---|---|---|---|
| Name of PhD Tutor | Dr Breen | | |
| Title of Assignment | 3D or not 3D: The Shape of the Protein | | |
| Name of Pupil | | | |
| Name of School | Harris Academy Bermondsey | | |
| ORIGINAL MARK / 100 | | FINAL MARK / 100 | |
| DEDUCTED MARKS | | FINAL GRADE | |

If marks have been deducted (e.g. late submission, plagiarism) Dr Breen will give an explanation in this section:

| Learning Feedback Comment 1 - *Referencing information sources* | |
|---|---|
| | How you could improve in the future |
| **Learning Feedback Comment 2 – *Generating your own evidence-based ideas*** | |
| | How you could improve in the future |
| **Learning Feedback Comment 3 – *Conducting own research*** | |
| | How you could improve in the future |
| **Resilience** | |
| | How you could build learning resilience in the future |

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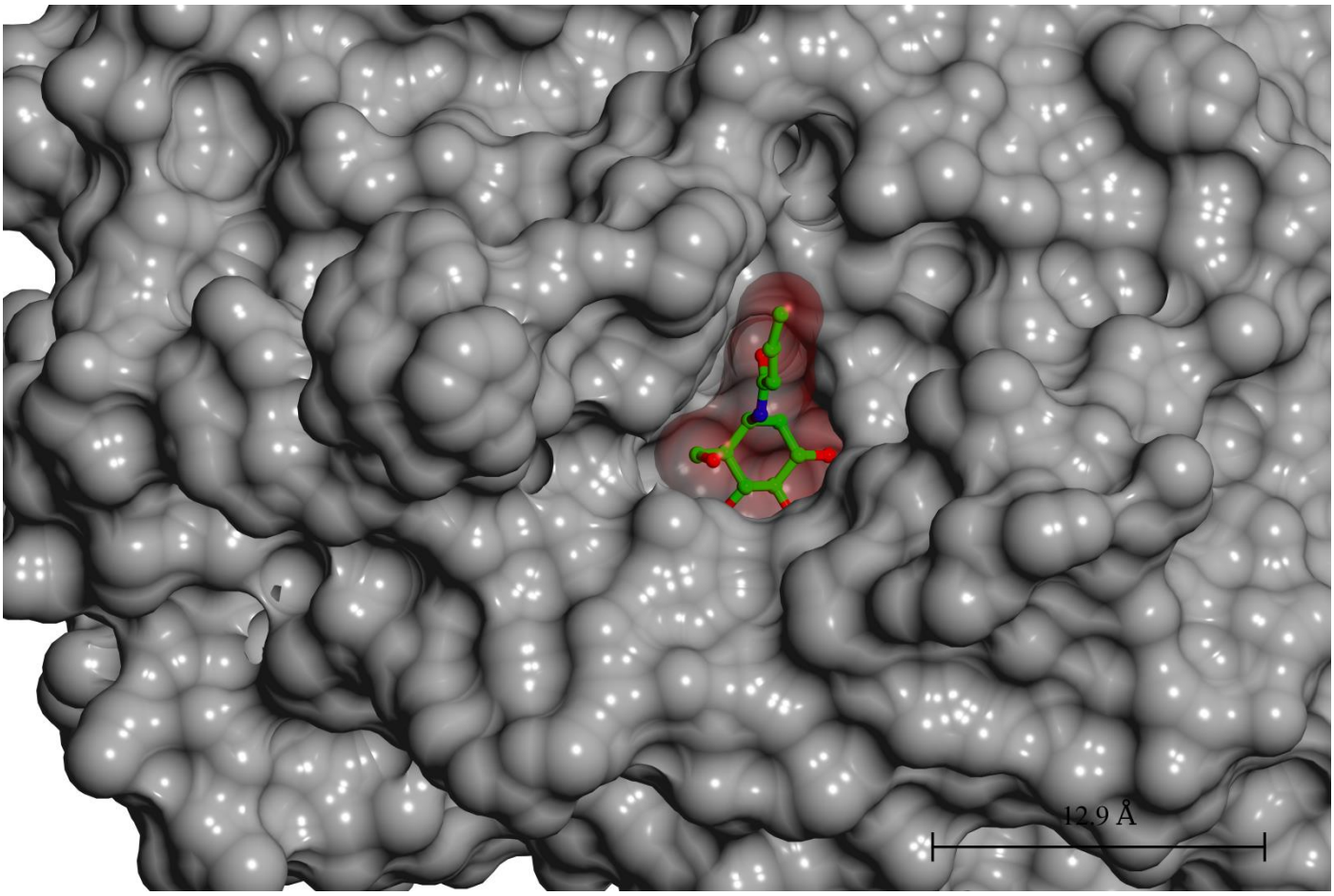
# Course Rationale

In this course, we will investigate how the 3D shape of an enzyme affects its role and function. With this knowledge, we will be able to consider how "misfolding" or loss of 3D shape can prevent an enzyme from performing the necessary reactions within a human cell, and how this can be linked to certain diseases and illnesses (pathologies).

From what we have learnt about protein folding, we will be able to consider medical approaches to treating diseases where a loss of enzyme function has occurred. These approaches can range from the entire replacement of an enzyme to small molecule "chaperone" drugs than can assist an enzyme in folding correctly.

The viability of many drugs is not only dependant on how they are able to treat a patient, but the cost to the manufacturer and how much demand there is for the treatment. After considering these different approaches, we can discuss the impact of the availability cost of medical treatment on patients with rare, or "orphan", diseases.




*A small molecular chaperone bound into the active site of the bacterial enzyme TxGH116. Data for this image was collected via x-ray crystallography using the Diamond Light Source in Oxfordshire and many, many experiments set up by Dr Breen for her PhD thesis (Breen, 2017)* [2]

# Mark Scheme

| Skills | 1st (70-100) | 2:1 (60-69) | 2:2 (50-59) |
|---|---|---|---|
| Knowledge and Understanding | ▪ All content included is relevant to the general topic and to the specific question/title<br>▪ Good understanding of all the relevant topics.<br>▪ Scientific terms are defined and used accurately throughout<br>▪ Clear justification on how the content included is related to the specific issues that are the focus of the assignment | ▪ Most of the content included is relevant to the general topic and to the specific question/title<br>▪ Good understanding of most the relevant topics<br>▪ Scientific terms are used accurately but not always clearly defined.<br>▪ Adequate justification on how the content included is related to the specific issues that are the focus of the assignment | ▪ Some of the content included is relevant to the general topic and to the specific question/title<br>▪ Good understanding on some of the relevant topics but occasional confusion on others.<br>▪ Scientific terms are used mostly accurately with occasional confusion and often not defined.<br>▪ Some justification on how the content included is related to the specific issues that are the focus of the assignment |
| Critical Evaluation / Problem solving | ▪ Moved beyond description to an assessment of the value or significance of what is described<br>▪ Evaluative points are consistently explicit/systematic/reasoned/justified<br>▪ Effective critiques on the reliability of sources provided<br>▪ Consistently demonstrate clear, analytical and logical steps to solving problems | ▪ Mostly description but some assessment of the value or significance of what is described<br>▪ Evaluative points are mostly explicit/systematic/reasoned/justified<br>▪ Some evidence of critiques on the reliability of sources provided<br>▪ Some examples of solving problems but not consistently clear, analytical and logical | ▪ Only description with minimal assessment of the value or significance of what is described<br>▪ Evaluative points are at times explicit/systematic/reasoned/justified<br>▪ Limited evidence of critiques on the reliability of sources provided<br>▪ Demonstrate clear steps to solving problems but not consistently analytical or logical |

| | | | |
|---|---|---|---|
| Structure and Presentation | ▪ Ideas are presented in paragraphs and arranged in a logical structure that is appropriate for the assignment<br>▪ The introduction clearly outlines how the essay/report will deal with the issues<br>▪ The conclusion summarises all the main points clearly and concisely<br>▪ Tables and graphs are effectively constructed including appropriate headings, units and scales.<br>▪ All sources are referenced correctly in an agreed format<br>Oral presentations meet the time constraints +/- 20 seconds<br>Oral presentations make use relevant media and all images are credited appropriately | ▪ Ideas are presented in paragraphs and arranged in a structure that is mostly appropriate for the assignment<br>▪ The introduction adequately describes how the essay/report will deal with the issues<br>▪ The conclusion summarises most of the main points clearly<br>▪ Most tables and graphs are well constructed<br>▪ Most sources are referenced correctly in an agreed format<br>Oral presentations meet the time constraints +/- 45 seconds<br>Oral presentations uses some relevant media and images are credited appropriately | ▪ Ideas are presented in paragraphs and arranged in a structure<br>▪ The introduction mentions how the essay/report will deal with the issues<br>▪ The conclusion summarises some of the main points clearly<br>▪ Some tables and graphs are well constructed but contain some errors<br>▪ Some sources are referenced correctly in the agreed format with occasional errors<br>Oral presentations over or under run by more than one minute.<br>Oral presentations uses irrelevant media or none and images are not credited appropriately |

# Subject Vocabulary

Fill this in as the course continues (Some have been done for you!)

| Word | Definition | In a sentence |
|---|---|---|
| Protein | | |
| Enzyme | | |
| DNA | | |
| Drug | | |
| Hypothesis | | |
| Catalyst | | |
| Orphan disease | | |
| Pathological | | |
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# Knowledge organiser:

**Tutorial 1: Infectious and non-infectious disease.**
Proteins are made as the cell translates the DNA code into amino acids. The chains of amino acids fold into complex 3D shapes. Changes in the DNA code can disrupt the protein, occasionally preventing it from fulfilling it's role.

Diseases involving the DNA code can be inherited. If only a very few people across the world have a particular disease, it is called an "orphan disease".

**Tutorial 2: Missing proteins and the Lock & Key hypothesis**
Enzymes are proteins that perform a chemical reaction. If a person is lacking a particular enzyme, they can suffer from an illness.

Each enzyme only acts on one substrate, which is determined by the shape of the enzyme. This is called the lock and key hypothesis.

**Tutorial 3: What is a drug?**
A drug is any substance that we can take that causes a change in the body. Some drugs are cheap and easy to make, some are much more complicated.

Proteins can be drugs, and they are very hard to produce as they must have the correct 3D shape as well as all the correct amino acids.

**Tutorial 4: Replace an enzyme?**
We can manufacture certain enzymes in laboratories by changing the DNA in bacteria and yeast. This is how insulin is made.
The bigger the protein, the more complicated it is to create correctly.

**Tutorial 5: Making things fold!**
A more simple approach could be to make the "incorrect" enzymes in a patient the right shape by forcing them to fold. This uses small molecules called chaperones. These chaperones are cheaper to make and easier to give to patients.

**Tutorial 6: Feedback**

## Learning outcomes. I can...

- Describe an enzyme
- State what happens to protein if DNA is changed
- Describe an orphan drug
- Evaluate the costs of drugs and the effect this has on patients

## Key terms:

| | |
|---|---|
| Protein | Organic compound made up of amino acid molecules. |
| Enzyme | Enzymes are proteins that function as biological catalysts |
| Pathology | A disease or illness. A pathogen is an agent that can cause disease.. |
| Translation | The process when cells translate a DNA sequence into amino acids |
| DNA | A chain of nucleic acids. This is how cells store information. |
| Amino acids | These are the building blocks of proteins. There are 20 different amino acids. |
| Lock & key hypothesis | The lock & key hypothesis describes how the active site of an enzyme determines what substrate it can act on.. |
| Enzyme | A catalyst is a molecule that can speed up a chemical reaction without being changed by the reaction. |

# Tutorial 1: Infectious and non-infectious diseases

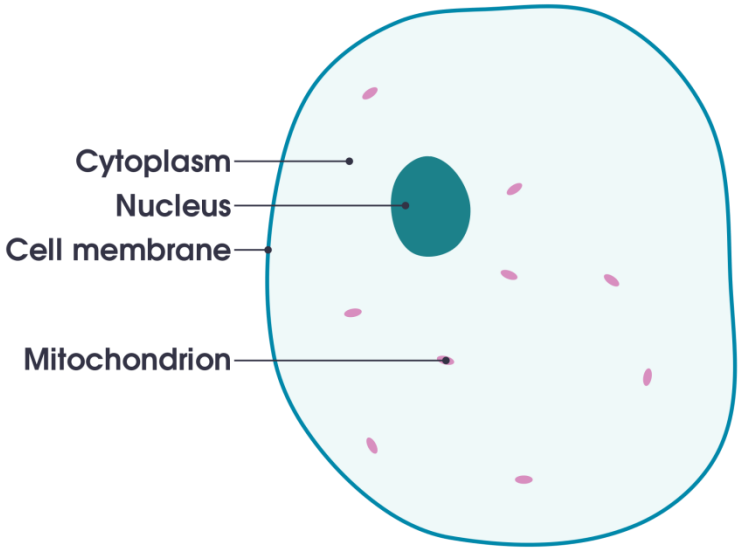
Starter: What is an infectious disease? What can cause them? What is a non-infectious disease? What can cause these?

Use the two post-it notes to write down your answers to these questions.

What is the purpose of tutorial 1?

- To define what a protein is
- To understand how changes in DNA can lead to changes in a protein
- To define what an orphan disease and an orphan drug are
- To understand how a change in DNA can lead to a rare disease

## DNA: information codes




Inside the nucleus of a cell, information is stored as DNA. This DNA is organised as chromosomes (long sections of DNA). Humans have 23 pairs of chromosomes. You inherit one set of chromosomes from each parent.

A gene is a small section of DNA on a chromosome. Each gene can code for a particular sequence of amino acids to make a specific protein.

## How do we get protein from DNA?

DNA contains only 4 bases – GATC. A cell can use this code to produce all the proteins that we need. However, proteins are made up from 20 different amino acids. How can we code for 20 different things from only 4?

Can you think of an example where you use only a few things (perhaps 26?) to mean a lot more depending on the order, grouping and location?

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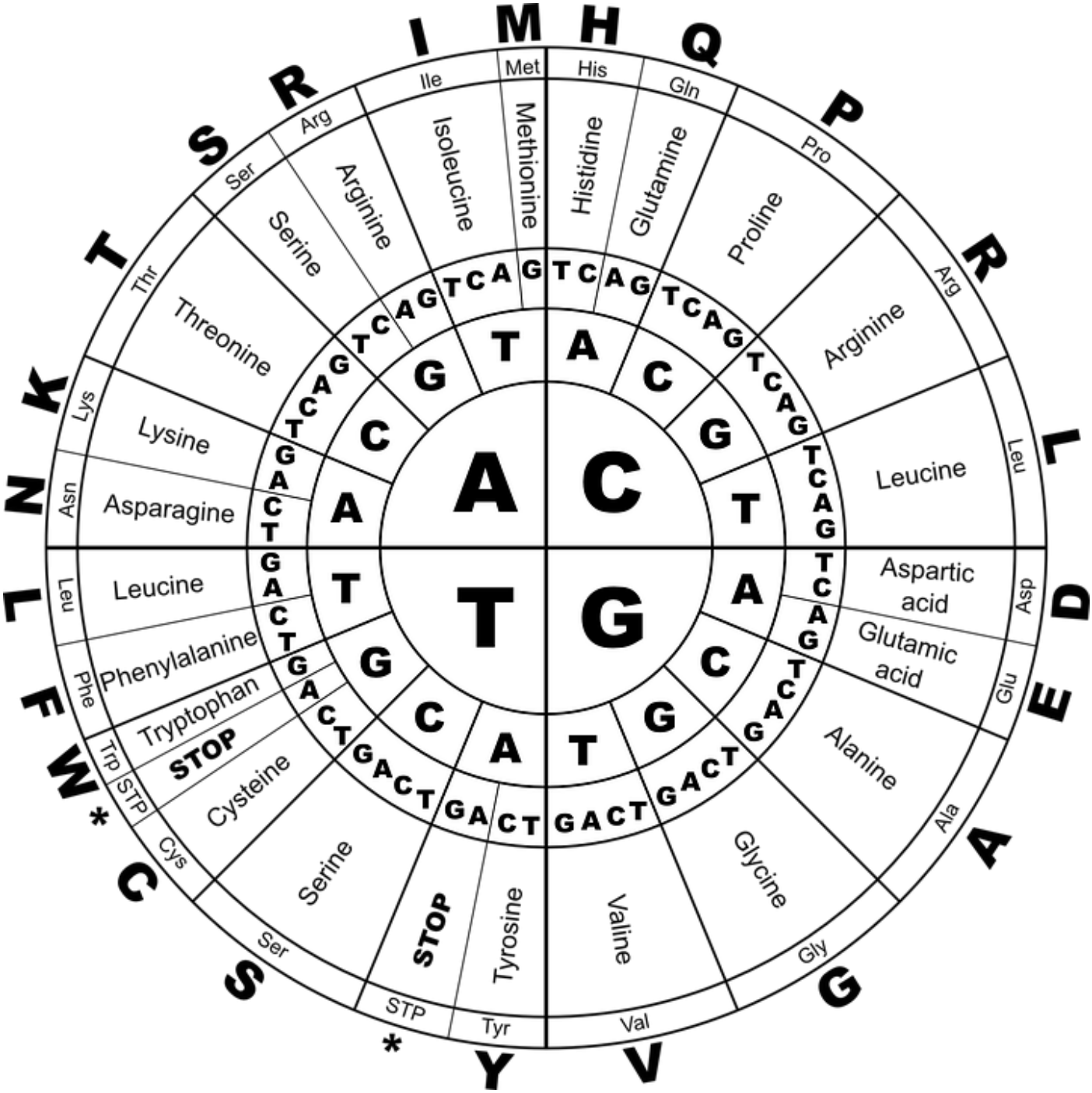
Dr Breen says:
Remember, DNA is made up of bases and proteins are made up of amino acids.




Using this chart – can you translate the following DNA strings into their single letter amino acid code? Start on the inside of the ring. Remember, bases are grouped in threes.
Use the chart above and the extra space to write your own short phrase in DNA, swap with a partner and see if you can translate each other's messages!

TCTTGTATAGAGAATTGTGAGTAA

TCTACGCGTATCAATGGTTCATAA

Thinking point: what happens to the amino acid messages when one of the bases in the DNA sequence is changed, deleted or a new one is added? Write down your thoughts, and then we will share your ideas with the group.

## Orphan Diseases

A rare disease is a disease (usually genetic) that affects a very small number of people worldwide. 5,000 to 7,000 distinct rare diseases exist, and although 8% of the population of the European Union is affected by one, each disease only occurs in a handful of cases (Breen et al, 2018) [3].

The terms "rare disease" and "orphan disease" can be used interchangeably, and often are. However, orphan disease particularly means those diseases that are *so* rare that medical treatment may be lacking, misunderstood or unsupported.

Disease examples:

| Disease | Number of people effected in the UK | How easy do you think it would be for a person with this disease to receive medical treatment at a hospital in London? |
|---|---|---|
| Sickle cell disease | 12, 500 to 15, 000 | |
| Cystic fibrosis | ~ 10, 400 | |
| Amyotrophic lateral sclerosis (ALS) | ~ 4,000 | |
| Gaucher's disease | 325 | |

**In 2013 the United Kingdom government published *The UK Strategy for Rare Diseases* which "aims to ensure no one gets left behind just because they have a rare disease", which detailed recommendations for care and treatment across the UK.**

Rare disease day is an observance day held on the last day of February. The aim is to raise awareness of rare diseases and help support the patients and families of those who have them.

## Homework 1: Baseline assignment

What is an orphan disease and why might they occur in a patient? Why might a patient with an orphan disease struggle to get medical treatment?

When answering this question, include what we have spoken about in the tutorial and your own thoughts on the matter.

Include at least one example of a rare disease beyond those that we have spoken about in class. You will find it helpful to compare rare diseases to those that are more common in the population.

Write 400 words, these can be handwritten or typed.

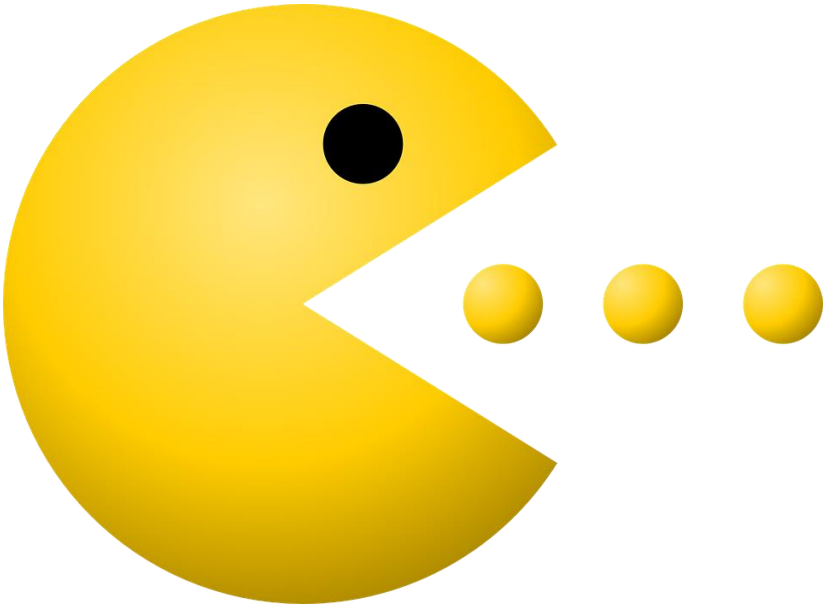
# Notes

# Tutorial 2: Missing proteins and the Lock & Key hypothesis

What is the purpose of tutorial 2?

- To consider what might lead to a deficiency in a certain protein
- To be able to give examples of diseases where a protein is missing
- To be able to describe the Lock and Key hypothesis and understand how this affects an enzymes behaviour

Enzymes are proteins that function as biological catalysts. So, they are molecules that speed up a chemical reaction without being changed by the reaction.

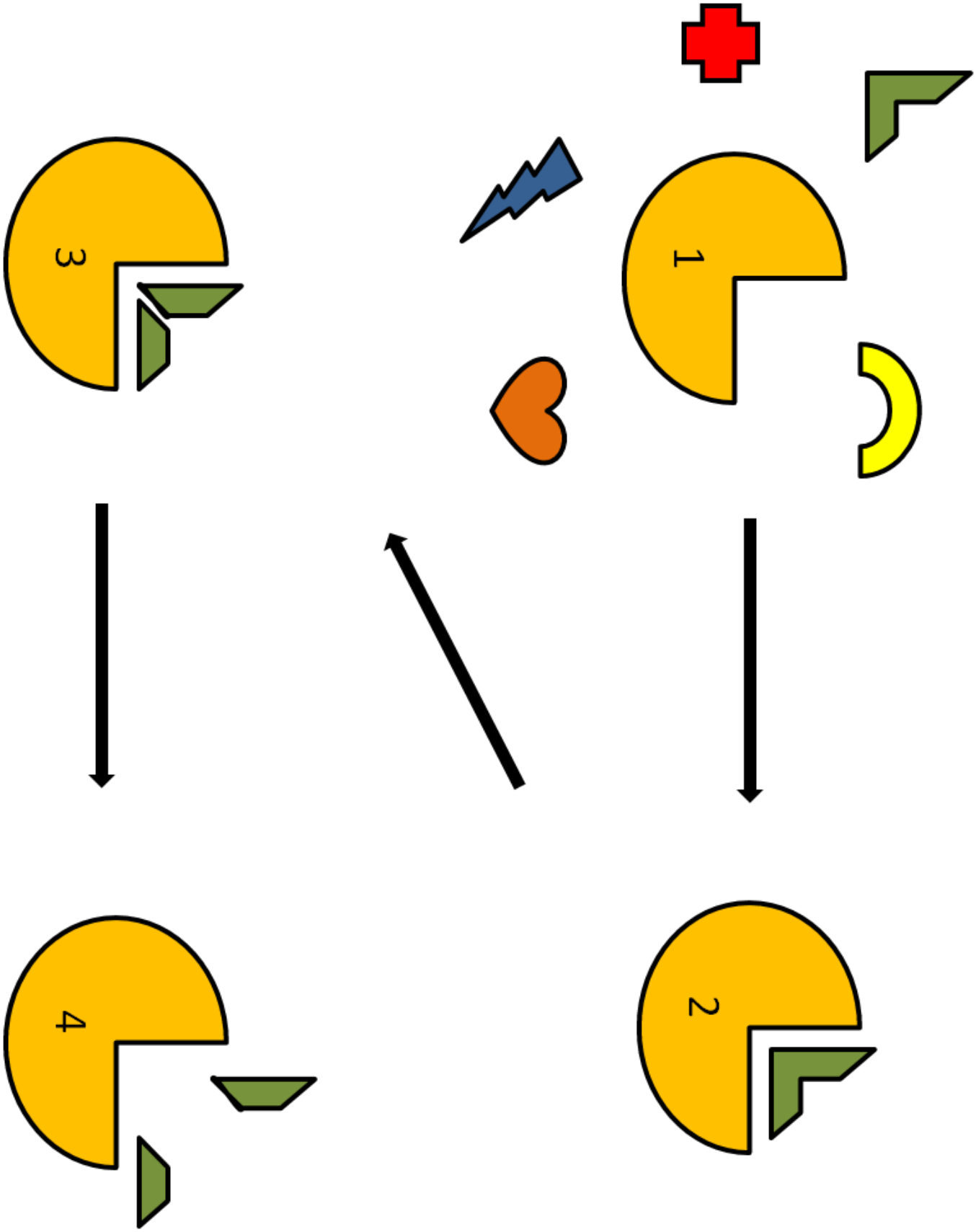


| What sort of reaction might an enzyme perform? | Where might you find an enzyme performing this job? |
|---|---|
| | |

There are approximately 75, 000 different enzymes in the human body. Each one of these performs a very particular role. Whilst we can group the various enzymes into categories (for example proteases catalyse the breakdown of proteins into amino acids in the stomach and small intestine and lipases catalyse the breakdown of fats and oils into fatty acids and glycerol in the small intestine), each enzyme only catalyses one reaction.

What might be controlling what reaction an enzyme can catalyse?

Clue: consider the figure on the next page. What factor is controlling which molecule the enzyme is acting on?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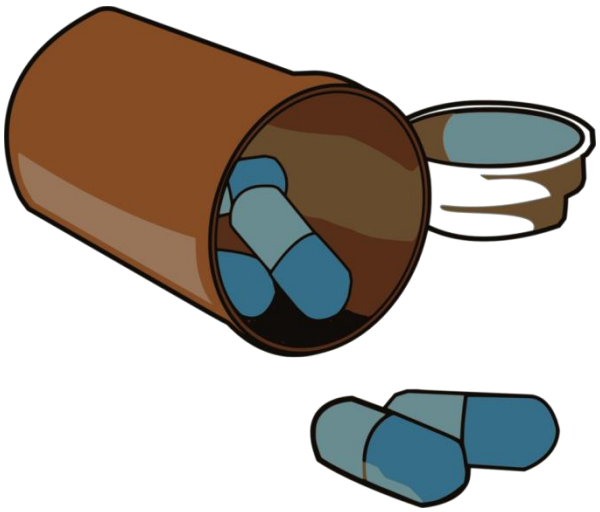
The Lock and Key Hypothesis. In your own words:

Homework 2: Complete the proteins and disease match up game on the next page. You will need to do your own research to find the answers!

| Disease: | Linked protein: |
| --- | --- |
| Huntington's | Insulin |
| Diabetes | GBA1 |
| Sickle cell disease | Huntingtin |
| Gauchers disease | Haemoglobin |
| Creutzfeldt-Jakob disease | CFTR protein |

Some diseases are linked to faults or deficiencies in single proteins. Match up the disease with the linked protein – some will be easier to find out about than others!

# Tutorial 3: What is a drug?

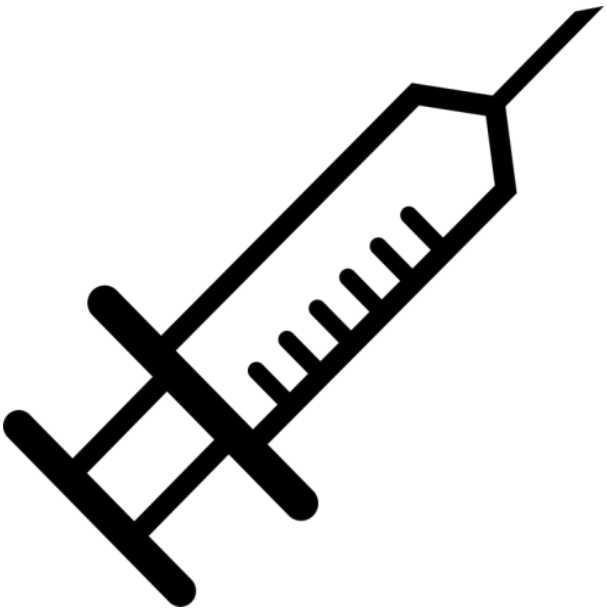


Drugs can come as pills, drinks, injections, patches and aerosols. But what makes something a drug?

What is the purpose of tutorial 3?

- To be able to define the term "drug"
- To consider the potential role of proteins as drugs
- To understand how important the 3D shapes of proteins are in the role that they play

| How would you define "drug"? | What are some examples of drugs? |
|---|---|
| | |



What did all your examples of drugs have in common?

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How would you change your definition of "drug" after the group discussion?

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_____
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_____

Can a protein be a drug? What about an enzyme?

_____
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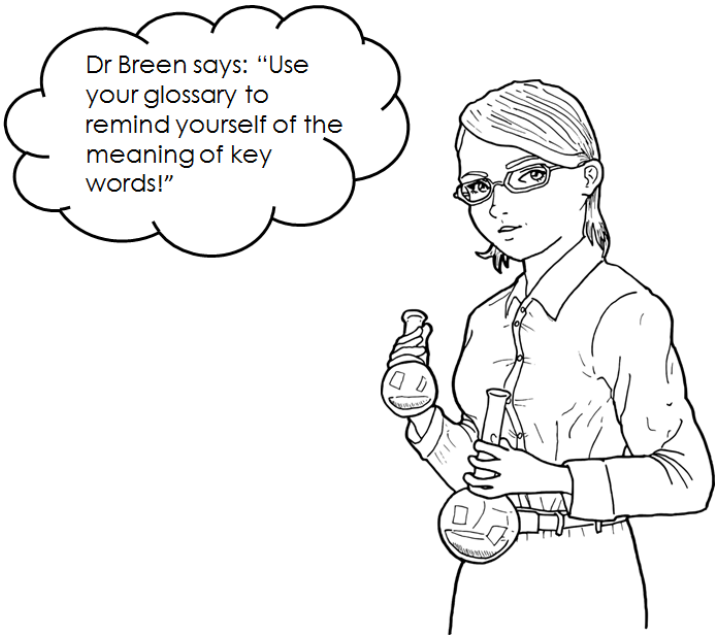
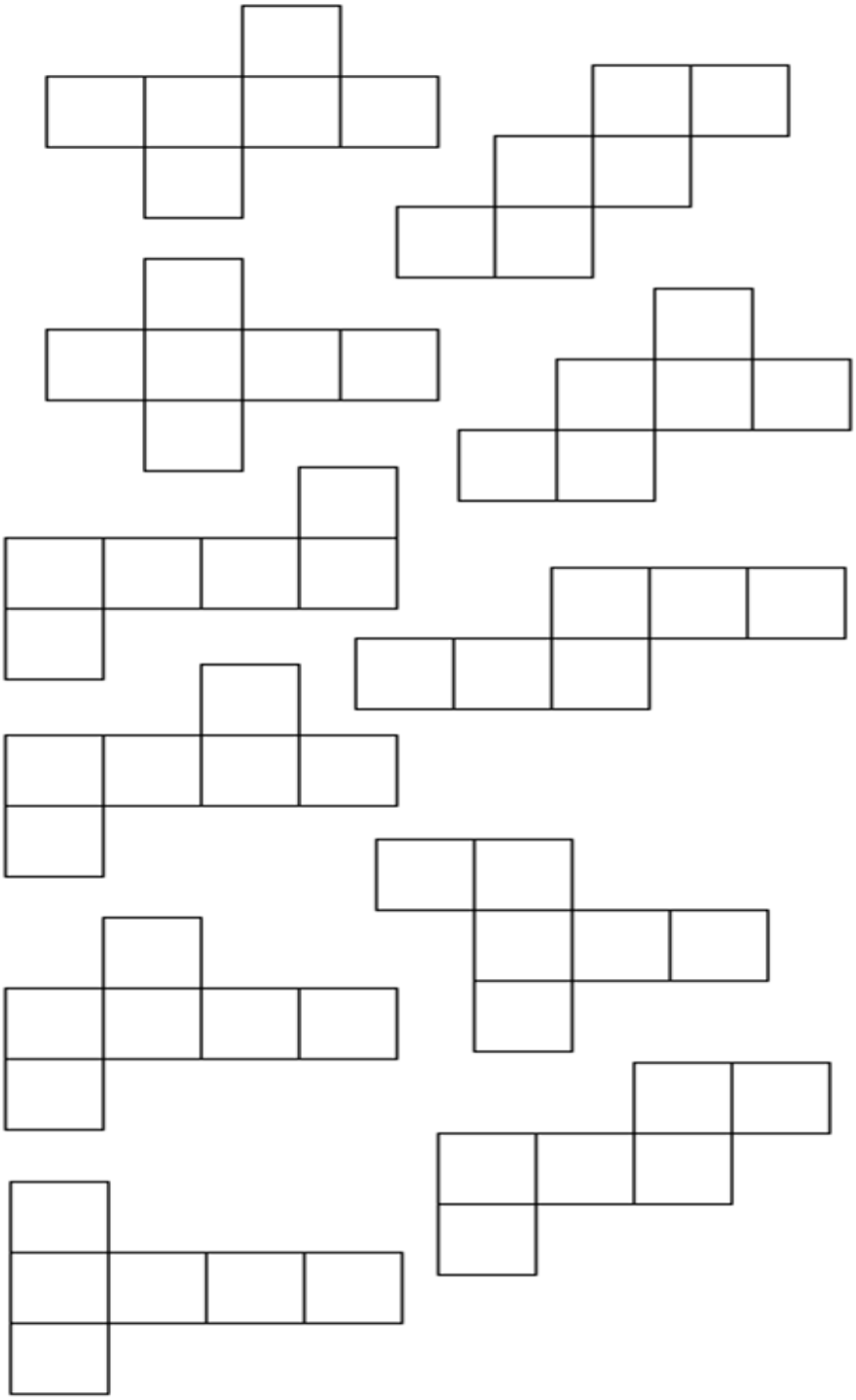



Think about:
When would you use a protein (especially an enzyme!) as a drug?
Can you think of some examples?



Look at all these plans! How many squares are they all made up of?

_____

What 3D shape could you make out of them all?

_____

Now cut out a couple of the plans from the handout and have a go at folding them.

How many shapes can you actually make from each one? (it doesn't need to be a "closed" shape)

_____

How much does the shape of the 2D plan predict the potential 3D shape?

_____

If each plan was made up from 60 or more squares, how would this affect the number of different 3D shapes that you could make?

_____

Fold one of the plans into an interesting shape. Give your partner the same plan, but do not allow them to see the shape that you have made! How could you guide them to fold the same shape as you without talking or touching or pointing?
Clue: consider the original plan!

# Notes

## Homework 3: Reading and research

Read the two articles attached as Appendices 2 and 3 (Boseley, 2018, Triggle 2014) [4,5]. And answer these questions:

- How much does it cost to develop a new drug?
- What does QALY stand for and how does it affect drug cost?
- The drug sofosbuvir can cure hepatitis C – why does the NHS not give it to every patient who is infected?
- How much more expensive is paroxetine in the USA compared to the UK?

Additionally, note down any thoughts and opinions you have on the topic. You may wish to do some additional research to back up your ideas. We will discuss your ideas in the next tutorial.

# Notes

# Tutorial 4: Replace an enzyme?

What is the purpose of Tutorial 4?

- To consider our thoughts and opinions on the access to and the costs of medical treatment for rare diseases
- To understand how we might create a protein we are interested in using recombinant expression
- To understand the costs associated with drug production

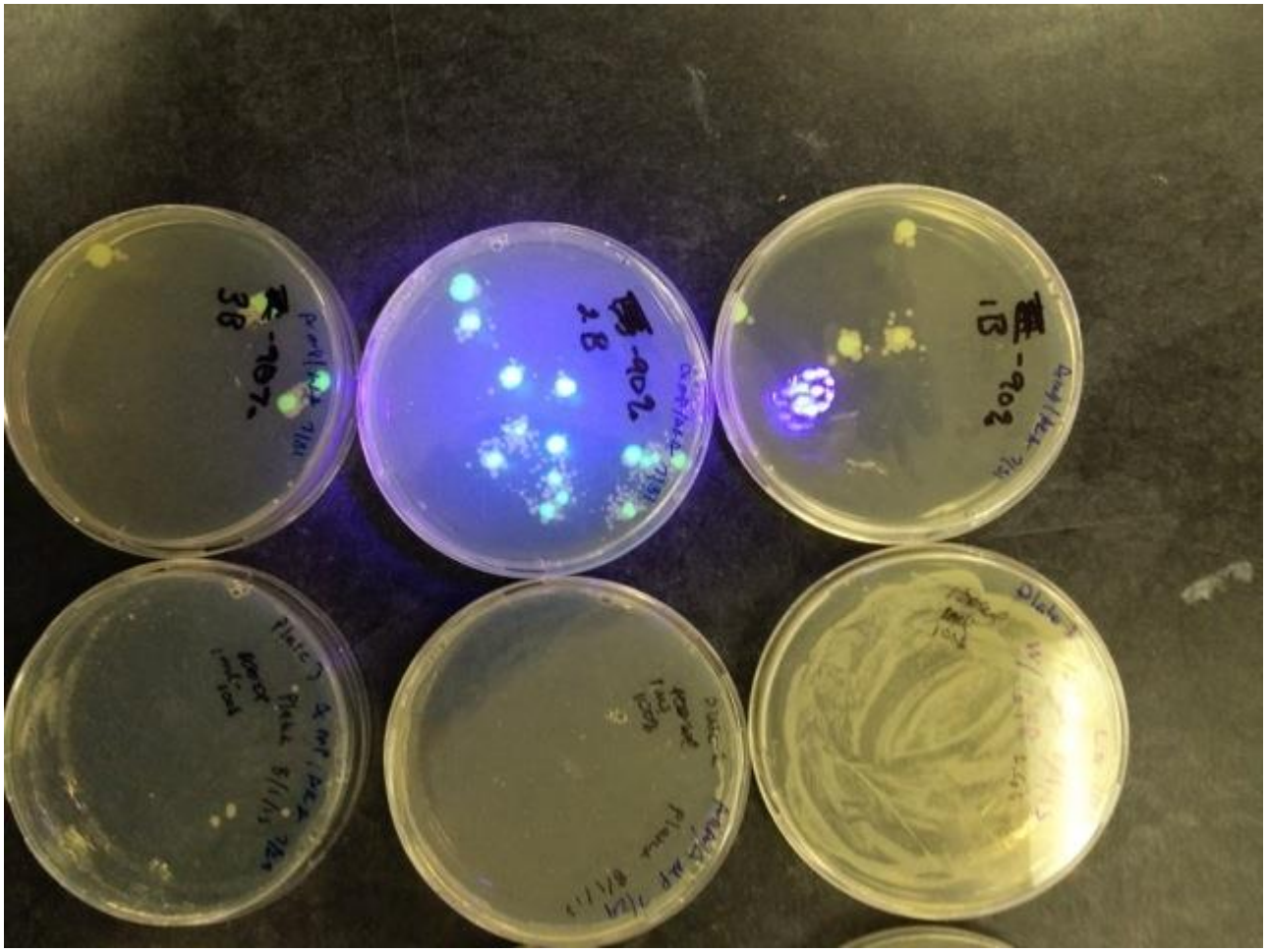


*Image: Wiki Commons*

What is going on in this picture?
All of the bacteria on the plates are types of E.coli, what might be difference inside them?

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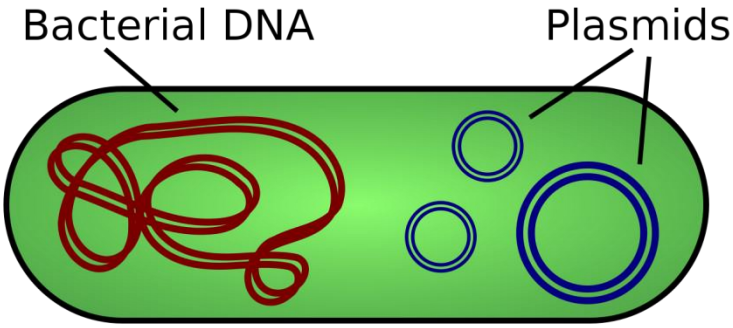



Image: Wiki commons

Bacteria cells do not have a nucleus. Instead they contain two different types of DNA – chromosomal DNA and plasmid DNA.

We can insert new plasmids into bacteria, giving them new genetic information that we have chosen and designed.

What effect might this have on the bacteria?
What might we be trying to achieve?

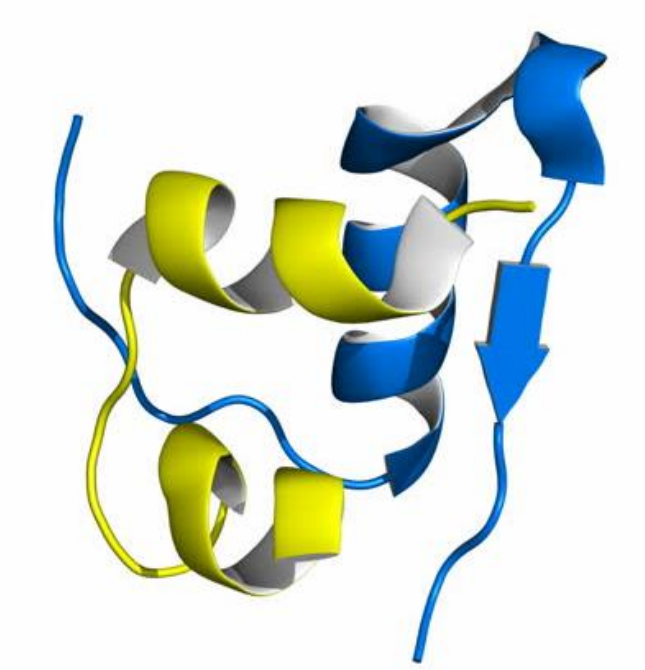
You can buy a kilo of paracetamol for less than £4, and the drug will last for years in its tablet form. However, most forms of insulin must be kept refrigerated and it can cost well over £70 for only 10 mg.

Insulin can be made in both bacteria and yeast cells and is *relatively* simple to produce. Do you think other protein drugs will cost more, less or similar to insulin?

---

In 2014, there were 421,300 people using insulin in the UK, a number that keeps increasing.

Considering your previous reading, and our group discussions in previous tutorials, do you think having a large number of people requiring a drug improves individual patient access to the medicine? What effect do you think this has on the price of the drug?



The structure of insulin. Image: Wiki commons

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Consider this image of insulin, and compare it to the image of GBA2 on the front cover – which do you think would easier to produce in a laboratory?

_____

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_____

**Homework 4**: Complete your notes for this session and fill out any missing terms in your glossary! For next tutorial, please bring in a (clean!) t-shirt.

# Tutorial 5: Making things fold!

What is the purpose of tutorial 5?

- To understand how a small molecule drug could help a faulty enzyme to fold correctly
- To be able to consider the benefits of using a small molecule drug over a recombinant enzyme drug
- To be ready to complete the final assignment!

But first, some translation!

*Conjugation of a known, mechanism-based glycosidase inhibitor to sensitive fluorophores yielded unexpectedly potent and selective probes for quantifying active lysosomal glucocerebrosidase. These conjugates could prove to be invaluable tools for diagnosing and studying Gaucher disease. (Goddard-Borger et al, 2010)* [6]

So, what does this all mean?

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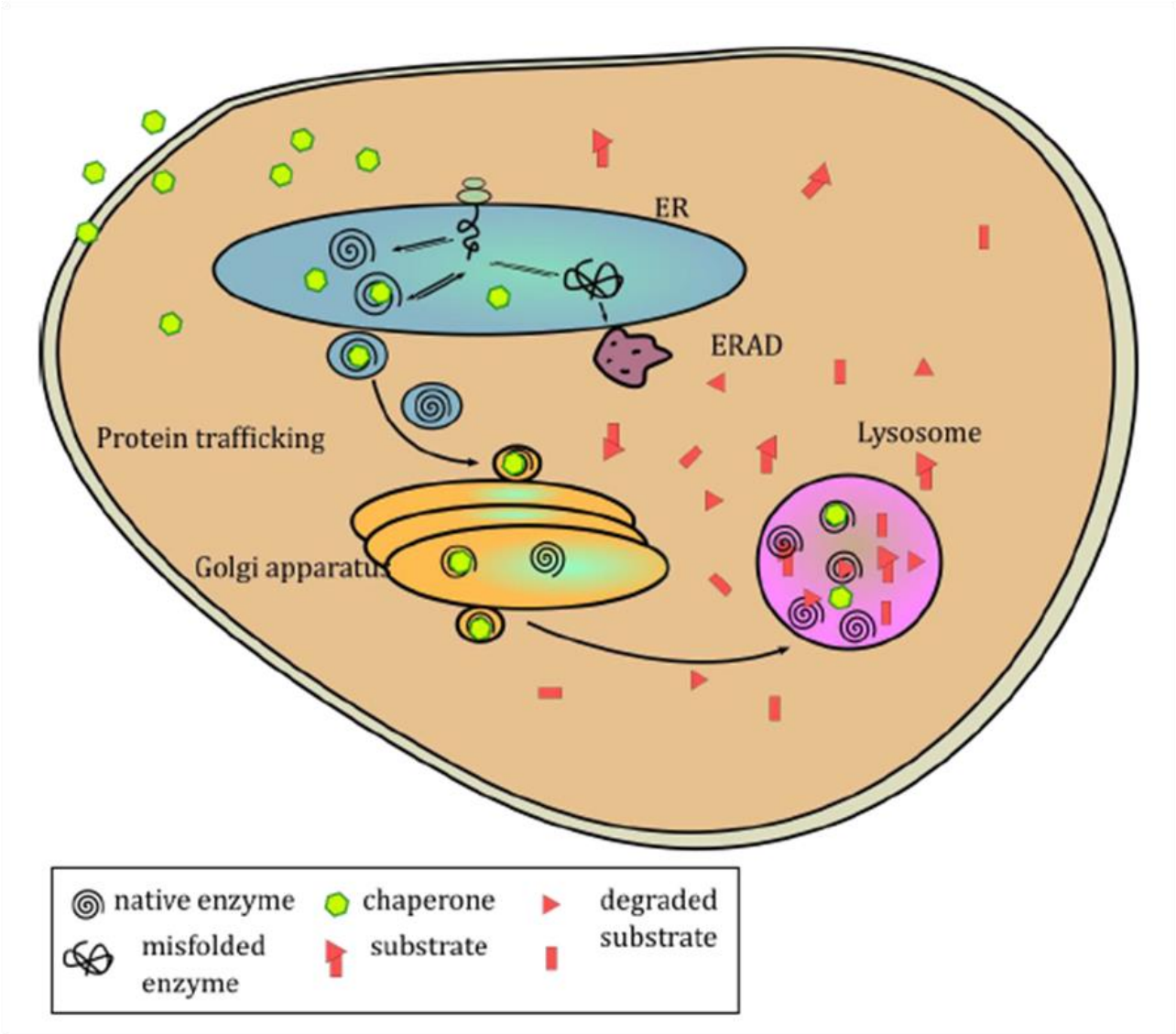
## Small molecule chaperones




*I have given you some space to write your own notes and explanations for the chaperone process. This is university style note taking. Draw your own diagrams to help yourself remember!*

How did the T-shirt folder help show this effect?

## Final assignment:

*You must complete both parts to achieve your grade.*

1) How can research into the use of small molecular chaperones as potential drug compounds help those that suffer from so-called "orphan diseases"?
   *Write 1000 words, including examples of diseases. Reference your sources currently. You may include figures, graphs and diagrams to help your argument.*

2) Create and present a 5 minute presentation about a rare disease of your choice.
   *This can be a disease we have discussed in a tutorial or one that you find yourself. Included information on the cause of the disease, relevant statistics, current and previous treatment approaches.* You will present in front of the group and other teachers in the science dept.

*Top tips:*
*See your success criteria handout – have you completed all the criteria?*
*Use your baseline assignment to help you get started!*
*The mark scheme is on page 6 – this will help you to target your writing and presentation.*

# Tutorial 6 – Feedback tutorial

## What is the Purpose of Tutorial 6?

- To receive feedback on final assignments.
- To share your thoughts and work so far with the other students
- To write targets for improvement in school lessons and your assignments
- To reflect on the programme including what you enjoyed and what was challenging.

## Final assignment feedback

| What I did well… | What I can improve on… |
|---|---|
| • | • |
| • | • |
| • | • |

| My target for future work is… |
|---|
| |

## Reflecting on Uni Pathways

| What did you most enjoy about Uni Pathways? |
| --- |
| • <br><br>• <br><br>• |

| What did you find challenging about the programme? | How did you overcome these challenges? |
| --- | --- |
| • <br><br>• <br><br>• | • <br><br>• <br><br>• |

# Appendix 1 – Referencing correctly

When you get to university, you will need to include references in the assignments that you write, so we would like you to start getting into the habit of referencing in your Brilliant Club assignment. This is really important, because it will help you to avoid plagiarism. Plagiarism is when you take someone else's work or ideas and pass them off as your own. Whether plagiarism is deliberate or accidental, the consequences can be severe. In order to avoid losing marks in your final assignment, or even failing, you must be careful to reference your sources correctly.

## What is a reference?

A reference is just a note in your assignment which says if you have referred to or been influenced by another source such as book, website or article. For example, if you use the internet to research a particular subject, and you want to include a specific piece of information from this website, you will need to reference it.

## Why should I reference?

Referencing is important in your work for the following reasons:

- It gives credit to the authors of any sources you have referred to or been influenced by.
- It supports the arguments you make in your assignments.
- It demonstrates the variety of sources you have used.
- It helps to prevent you losing marks, or failing, due to plagiarism.

## When should I use a reference?

You should use a reference when you:

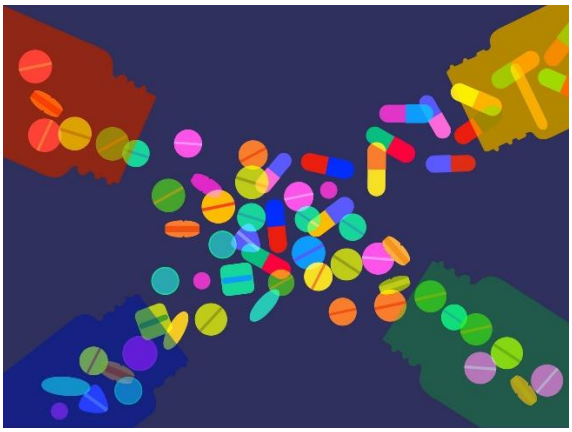
- Quote directly from another source.
- Summarise or rephrase another piece of work.
- Include a specific statistic or fact from a source.

## How do I reference?

There are a number of different ways of referencing, and these often vary depending on what subject you are studying. The most important to thing is to be consistent. This means that you need to stick to the same system throughout your whole assignment. Here is a basic system of referencing that you can use, which consists of the following two parts:

**A marker in your assignment**: After you have used a reference in your assignment (you have read something and included it in your work as a quote, or re-written it your own words) you should mark this is in your text with a number, e.g. [1]. The next time you use a reference you should use the next number, e.g. [2].
**Bibliography**: This is just a list of the references you have used in your assignment. In the bibliography, you list your references by the numbers you have used, and include as much information as you have about the reference. The list below gives what should be included for different sources.
**Websites** – Author (if possible), title of the web page, website address, [date you accessed it, in square brackets].
E.g. Dan Snow, 'How did so many soldiers survive the trenches?', http://www.bbc.co.uk/guides/z3kgjxs#zg2dtfr [11 July 2014].
**Books** – Author, date published, title of book (in italics), pages where the information came from.
E.g. S. Dubner and S. Levitt, (2006) *Freakonomics*, 7-9.
**Articles** – Author, 'title of the article' (with quotation marks), *where the article comes from* (newspaper, journal etc.), date of the article.
E.g. Maev Kennedy, 'The lights to go out across the UK to mark First World War's centenary', Guardian, 10 July 2014.

# Appendix 2:



## Why do new medicines cost so much, and what can we do about it?

*The cost of new drugs is putting increasing pressure on people in both rich and poor countries. We explain why it's a burning issue*

by Sarah Boseley *Health editor, The Guardian*

9th April 2018

Main image: Getty Photograph: Getty

**Why does it matter what medicines cost?**

If you are lucky enough to live in a country with comprehensive state-funded healthcare, such as the UK, you probably have no idea how much medicines really cost. But it can be a lot. Some drugs that have been around for ages are very cheap – aspirin, for instance, costs pence. It's been out of patent and made by numerous companies competing to undercut each other's price for decades. But new medicines, protected by 20-year patents, can cost hundreds of pounds a packet and sometimes thousands. The new breast cancer drug Kadcyla weighed in at a starting price of £90,000 per patient per year in the UK in 2015, though the manufacturer has now agreed a hefty discount for the NHS.

It is an increasing pressure on all health systems around the world. In 2017, NHS England put its annual drugs bill at £16bn, £9bn of which is GPs prescribing, and said it was rising at 7% a year – faster than the overall NHS budget.

**Isn't that really just a problem for poor countries?**

No. The new drugs that cure the liver disease hepatitis C were launched at a price that elicited squeals of pain from the UK, Western Europe and the United States, as well as India and Romania, which both have high numbers of infections. In the US, the drug sofosbuvir (brand name Sovaldi), launched at a cost of $1,000 a pill. In the UK, the manufacturer Gilead was asking £35,000 for a 12-week course, with some patients needing 24 weeks. It was soon clear that no country was going to be able to treat everybody who needed them, even though hepatitis C is a killer in the long term and the drugs are – unusually – a cure.

In the UK, the National Institute for Health and Care Excellence (Nice), which decides whether drugs are value for money, said yes to hepatitis C drugs, provided Gilead gave a discount. The drugs would save years of expensive NHS treatment, including liver transplants. But the government balked at the cost of treating everybody – an estimated 160,000 people are infected. Normally the deal is that the NHS must introduce any drug Nice approves, but in this case it chose to phase it in, treating the sickest first and making others wait, which was unprecedented.

In the US, the cost was out of the question for many people without good health insurance cover. The prices of new cancer drugs have also been prohibitive.

**Didn't drug prices crop up in the US election?**

Yes. The cost of drugs became a hot political potato. Hillary Clinton promised to bring down high prices, and Donald Trump also gave the subject a mention. The row wasn't triggered by hepatitis C, though, or even cancer, but by a scandal concerning the hiked prices of old drugs that caused a huge public outcry in summer 2015 and made Martin Shkreli, then chief executive of Turing Pharmaceuticals (he has had to resign since), the "most hated man in America". That's quite an accolade.

Old drugs are out of patent, which means any company can make them, and usually the price drops very low because of the competition. But Shkreli was an entrepreneur who saw no reason why selling drugs should be any different from selling cars: corner the market and hike the price. He did it a few times, but the one that caused all the trouble was a very cheap drug called pyrimethamine, trade name Daraprim. Daraprim had been out of patent for a very long time, having been approved by the US Food and Drug Administration in 1953. It is an anti-parasitic drug given to people with toxoplasmosis infection, particularly where they have weak immune systems because of Aids or pregnancy and cannot easily fight it off. Shkreli bought the drug from another company in August 2015 and hiked the price by 5,000%. It went up overnight from $13.50 per pill to $750.

**So medical drugs are not like Chryslers or Porsches in the public mind, then?**

It would seem not. The anger was clear evidence that people think medicines are a special case and that people have a moral right to affordable treatment. There is quite a tension between that view and the pursuit by pharmaceutical companies of profit for shareholders in the free market.

**So how much does it cost to make a medicine?**

Ah – that's the $64bn question. Well, no, it doesn't cost $64bn to create a drug, but there is a great deal of heated debate about the real cost. The biggest issue is what you factor in. The big pharma companies say you have to calculate not only the (usually cheap) cost of the raw ingredients and manufacturing, but also the cost of research and development of the drug – and also the R&D costs of all the drugs that fail to get to market. Clinical trials to test new drugs for safety and find out how well they work cost millions of dollars, and many drugs look good in the lab or in animals but don't work in humans – or there are serious side effects. Research pharma companies need to set those costs for failures against the profits from the drugs that work – it's the only way they can afford to keep looking for new medicines, they say.
The Tufts Center for the Study of Drug Development in Boston, Massachusetts, which produces estimates for the cost of making a medicine every few years, accepts that argument. Drug development is a long process, taking as long as 10 years, it says. It's expensive. The centre's latest figure for the cost of developing a prescription drug that gets marketing approval, published in the Journal of Health Economics in March 2016, is a colossal $2.558bn. The analysis, Tufts says, was based at least in part on information from 10 pharma companies on 106 randomly selected drugs that were first tested in human subjects anywhere in the world from 1995 to 2007.

**Does anybody contest that figure of $2.6bn per drug?**

Yes. There are now a lot of campaigners calling for greater access to medicines in both rich and low-income countries. They are not impressed with the argument that pharma should cost in its failures. And furthermore, they say that often the best drugs were invented in university labs, paid for from public funds, so that should also be taken into account. In these cases, they say, the pharma companies buy up promising potential drugs and do the large-scale testing and development.

**But if pharma companies insist they have to charge high prices because of their high costs, what can be done?**

That's been much debated in recent years. The first big access-to-medicines movement was sparked by Aids in Africa. The inequity of thousands dying for lack of drugs while people with HIV in San Francisco were alive and well on medication became a huge issue. Campaigners succeeded in enlisting the Indian generic company Cipla to make super-cheap versions of the HIV triple-drug combinations in 2001 that cost $100 a person a year instead of $10,000.

**Why didn't the rules on patents stop that?**

Patents normally apply for about 20 years but have to be registered in each country where the drug is sold. That stops other companies making rival copies that might compete to push the prices down. But India had different intellectual property rules at the time, which meant the HIV drugs patents did not apply there. So India's generics companies became the pharmacy for the developing world. But the rules have since changed and attempts to make cheap copies of new drugs such as the hepatitis C medicines in India have been subject to long battles in court.

**At least health services can save money by using cheap copies once drug patents run out.**

Yes. The good news for hard-pressed health services everywhere is that it is now possible to make cheap copies of "biologics" as well. These are much harder to copy, because they contain living cells or blood or proteins, not just simple chemicals. Many cancer drugs are biologics and for some time many doctors had doubts that the so-called biosimilars would work as well as the originals. But now it is clear they do. And the Royal Marsden cancer hospital in London says one year's use of the first cancer biosimilar, a version of rituximab to treat lymphomas, has saved the NHS £80m. They estimate the health service could save £200m to £300m a year – maybe more – by embracing the biosimilars coming along, which include a version of the breast cancer drug trastuzumab, better known as Herceptin.
But campaigners say patients with cancers and other life-threatening diseases who don't have loads of money cannot just wait for the patents to run out.

**Is it just radical campaigning groups that are trying to get the prices of the patented medicines down?**

No. Médecins Sans Frontières, winner of a Nobel prize, has played a big part through its access campaign, which started in 1999, proclaiming "medicines shouldn't be a luxury", but the issue has also more recently been taken up in the United Nations. It's about the cost of drugs that the entire world needs, including new antibiotics the pharma companies have stopped trying to invent because they can't make a profit on them.
The World Health Organization is strong on access to medicines for all and also has a list of essential medicines that all countries are advised they should stock. A UN high-level panel on access to medicines spent the best part of a year deliberating over the issues, with members from pharma companies as well as civil society and academics. It said the current setup has failed to come up with the drugs we need, whether antibiotics for all of us or cures for Zika and Ebola in low-income countries where there isn't a market because people have no money (and because some terrifying diseases are rare). It tried to balance the conflicting demands of trade and the right to health in its final report in September 2016, in which it backed "delinkage" of the costs of R&D from the eventual price of the drug. That's possible if you can have some sort of deal funded by governments or philanthropists that rewards companies for getting a much-needed drug like an antibiotic into the hands of doctors, so they would not make their money from sales.

**What next?**

The UN report has given everybody food for thought and is still being discussed. "The world must take bold new approaches," it said, but that won't happen quickly. The majority of big pharma, with the possible exception of GSK, whose then chief executive Sir Andrew Witty was on the panel, was unenthusiastic about the report. That might be mainly because it supported governments' right to invoke a get-out from the World Trade Organization's Trips agreement to bypass drug patents and make cheap versions in the interests of public health (the 2001 Doha declaration). But as happened with Aids, each new crisis over access to medicines – whether concerning a common liver disease or a rare cancer, and particularly over the antibiotics that are under threat and vital to all our lives – is likely to put pressure on companies to find ways to bring the costs of medicines down.

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# Appendix 3

## Anatomy of the cost of a new drug

By Nick Triggle *Health correspondent, BBC News*
7 August 2014

*Image copyright Thinkstock*

The cost of drugs is in the headlines following the decision by NHS watchdog NICE that a new cancer treatment should not be funded. Its cost? More than £90,000 per patient for an extra six months of life. But how are such figures reached?
The drug - Kadcyla - was developed by Roche. And for commercial reasons it has so far not revealed the methods behind its pricing strategy.

But to really understand the cost of developing a new drug you have to go back to the very earliest stages of the process.

*Image copyright SPL*

There are a number of important milestones in the journey - and at each point development can come to a halt if the treatment is found not to be viable. Drug development essentially begins in the lab with research on animals, such as mice.

Only one in 10 potential treatments in the lab actually reach the clinical trial stage on humans. And from there only a fifth will make it through all three phases. The most common reasons for discontinuation are the effect of the treatment being too weak, the side-effects too great or the market for the treatment too small.

Then comes the regulatory and marketing stage. It is a process that takes at least a decade for most drugs - and is therefore a costly process. The Association of British Pharmaceutical Industry estimates it costs £1.15bn on average to get a drug to market. That is in line with what most academics have estimated, including the Office of Health Economics.

But its report, The Research and Development Cost of a New Medicine, published in 2012, warned that working out average costs should be treated with caution as they could vary greatly depending on

where the treatment was targeted. The study said costs in cancer and neurology tended to be the highest because of the lower success rates and longer development times.

Nonetheless, the report said, only about 10% of the overall cost was actually accounted for by the lab tests and clinical trials - the so-called research and development end.
A more important factor is the cost of capital - that is related to the fact that the money has to be found upfront many years before the pharmaceutical firm sees anything back.

## Other factors

And when it comes to pricing, companies also have to take into account the anticipated market for the drugs. The smaller the market, the more they have to charge. Covering the costs of treatments that have not made it this far is also important, as the APBI admits.

A spokeswoman said: "For every one successful medicine, there are thousands of unsuccessful medicines and this has to be taken into account when making pricing decisions."

Drug firms have also been complaining about the cost of the regulatory hoops they have to jump through to get their treatments licensed. In the US that is the responsibility of the Food and Drug Administration and in Europe it's the European Medicines Agency.

## Horse-trading

Once that has been achieved, the drug has to be marketed and - in terms of the NHS - get through the appraisal process. In England, this is done by the National Institute for Health and Care Excellence. The group uses a method called quality-adjusted life years (QALY) for assessing the value of new drug treatments. A similar system is used by the Scottish Medicines Consortium, while officials in Wales and Nothern Ireland tend to rely heavily on NICE analyses.

The formula looks at the cost of using a drug for a year and weighs it against how much someone's life can be extended and improved. Generally if a treatment costs more than £20,000 to £30,000 per QALY, it would not be recommended as cost-effective by NICE. Although for end-of-life treatments NICE will go to twice that amount.

As there has been with Kadcyla, there can be a period of negotiation on price. While that appears not to have been successful this time, it has worked in the past. Two years ago NICE initially rejected prostate cancer drug abiraterone for not being cost-effective. Approval was eventually given when the manufacturer offered a lower undisclosed price.

So after this complicated and complex process, the final price is determined by some good, old-fashioned horse-trading.

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# Notes

3D or not 3D:

The shape of the protein

Key Stage 4 Programme

researchersinschools.org