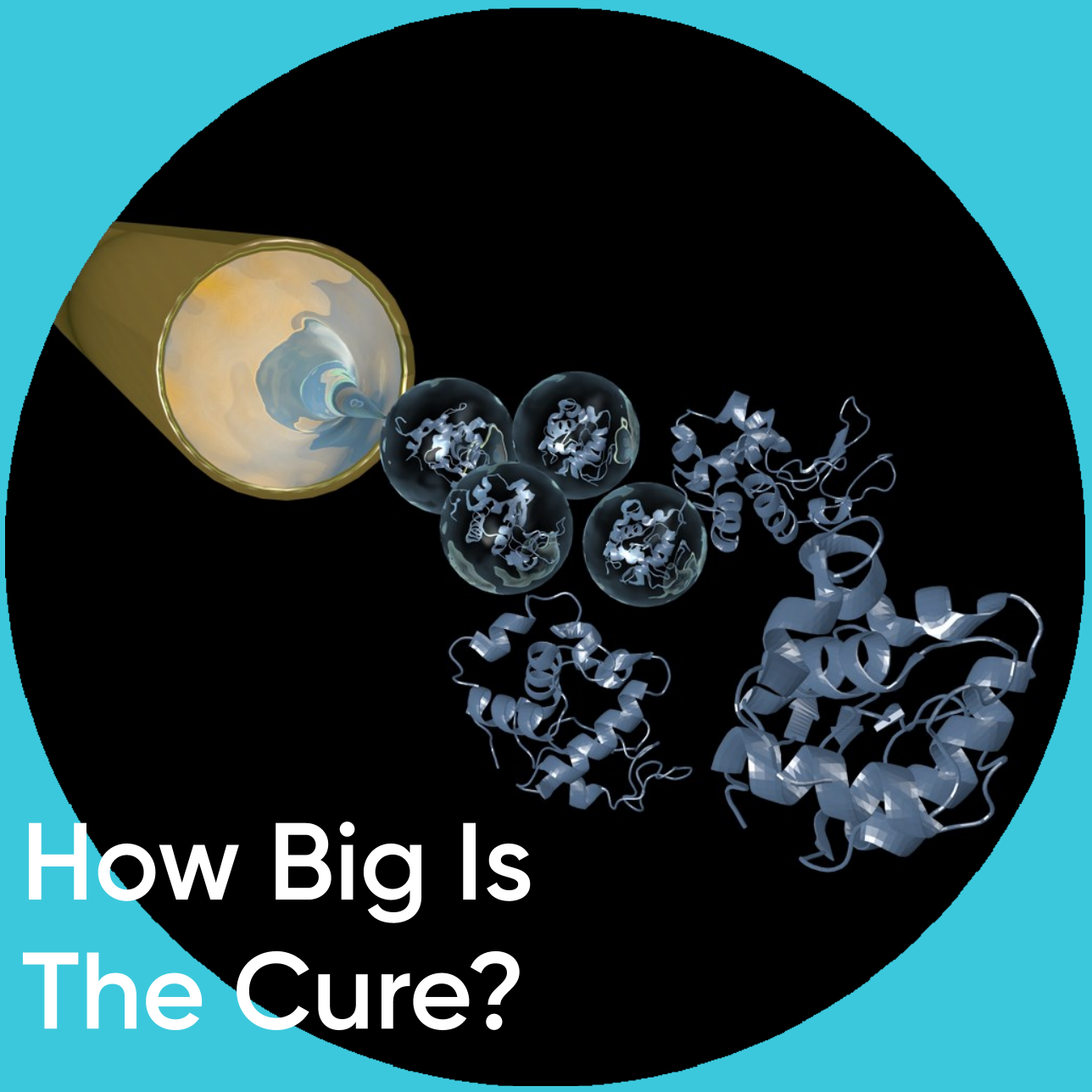

How Big Is The Cure?

Pupil Name

Handbook Designed by

Timetable and Assignment Submission

Timetable – Tutorials

Tutorial	Date	Time	Location
1	**26/11/2018**	**2:00PM**	**Cambridge Trip**
2	**11/12/2018**	**4:00PM**	**Yellow Lab**
3	**08/01/2019**	**4:00PM**	**Yellow Lab**
4	**15/01/2019**	**4:00PM**	**Yellow Lab**
5	**22/01/2019**	**4:00PM**	**Yellow Lab**
6	**05/02/2019**	**4:00PM**	**Yellow Lab**
7 (Feedback)	**26/02/2019**	**4:00PM**	**Yellow Lab**

Timetable – Homework Assignments

Homework Assignment	Description	Due Date
Tutorial 1	**Complete the questions at the end of tutorial 1**	**10/12/2018**
Tutorial 2	**Read the article and complete the sentences about it**	**07/01/2019**
Tutorial 3	**Calculate the mass to charge ratios for the 3 species**	**14/01/2019**
Tutorial 4	**Calculate the mass of Semi-Sweet from the mass spectra**	**21/01/2019**
Tutorial 5	**Complete the $P2Y_1$ problems and draft your essay**	**04/02/2019**
Tutorial 6	**Using feedback provided, finish your essay**	**18/02/2019**

Assignment Submission – Lateness and Plagiarism

Lateness	
Submission after midnight on 19 February	10 marks deducted
Plagiarism	
Some plagiarism	10 marks deducted
Moderate plagiarism	20 marks deducted
Extreme plagiarism	Automatic fail

Uni Pathways – Pupil Feedback Report

Grade	Marks	What this means
1st	70+	Performing to an excellent standard at A-level
2:1	60-69	Performing to a good standard at A-level
2:2	50-59	Performing to an excellent standard at GCSE
3rd	40-49	Performing to a good standard at GCSE
Working towards a pass	0-39	Performing below a good standard at GCSE
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 RIS teacher			
Title of Assignment			
Name of Pupil			
Name of School			
ORIGINAL MARK / 100		FINAL MARK / 100	
DEDUCTED MARKS		FINAL GRADE	

If marks have been deducted (e.g. late submission, plagiarism) the PhD tutor should give an explanation in this section:

Knowledge and Understanding
Enter feedback here
Critical Evaluation/Problem Solving
Enter feedback here
Structure and Presentation
Enter feedback here
Resilience Comment
Enter feedback here

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Course Rationale

Countless diseases are treated on a daily basis. But what exactly is being treated? How do these drugs work? How are new drugs being discovered for dangerous diseases? During this cause we will address these questions and see how modern research is making a difference to them.

We will look into what exactly a disease is, what can cause them and how they can be treated by drugs. We will investigate where drugs can come from and how they can be developed into new treatments that are available to us all.

We will learn about the analytical technique called mass spectrometry and specifically what we can learn about proteins using it. We will explore several aspects of the techniques including ionization and mass detection and then see how this can be applied to targets for disease as a first step in drug discovery. We will also learn to critically compare different techniques that enable similar discoveries.

By weighing proteins and drugs we will learn, how big is the cure?

STEM Mark Scheme

- The problem set will be weighted 50% and the research problem question the other 50%.
- PhD tutor will give one overall mark for the problem set and three sub-marks for the research problem set: 1) Knowledge and Understanding; 2) Critical Evaluation (problem solving); 3) Structure and Presentation (see mark scheme below), and the average of the problem set and research problem question..

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 • Good understanding of all the relevant topics. • Scientific terms are defined and used accurately throughout • 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 • Good understanding of most the relevant topics • Scientific terms are used accurately but not always clearly defined. • 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 • Good understanding on some of the relevant topics but occasional confusion on others. • Scientific terms are used mostly accurately with occasional confusion and often not defined. • 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 • Evaluative points are consistently explicit/ systematic/reasoned/ justified • Effective critiques on the reliability of sources provided • Consistently demonstrate clear, analytical and logical steps to solving	• Mostly description but some assessment of the value or significance of what is described • Evaluative points are mostly explicit/ systematic/reasoned/ justified • Some evidence of critiques on the reliability of sources provided • 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 • Evaluative points are at times explicit/ systematic/reasoned/ justified • Limited evidence of critiques on the reliability of sources provided • 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 • The introduction clearly outlines how the essay/report will deal with the issues • The conclusion summarises all the main points clearly and concisely • All calculations, formulas and methods are clearly structured, clear to follow and correct • Tables and graphs are effectively constructed including appropriate headings, units and scales. • All sources are referenced correctly in an agreed format	• Ideas are presented in paragraphs and arranged in a structure that is mostly appropriate for the assignment • The introduction adequately describes how the essay/report will deal with the issues • The conclusion summarises most of the main points clearly • Calculations, formulas and methods are mostly structured, clear to follow and correct • Most tables and graphs are well constructed • Most sources are referenced correctly in an agreed format	• Ideas are presented in paragraphs and arranged in a structure • The introduction mentions how the essay/report will deal with the issues • The conclusion summarises some of the main points clearly • Calculations, formulas and methods are not always structured, clear to follow and correct. • Some tables and graphs are well constructed but contains some errors • Some sources are referenced correctly in the agreed format with occasional errors

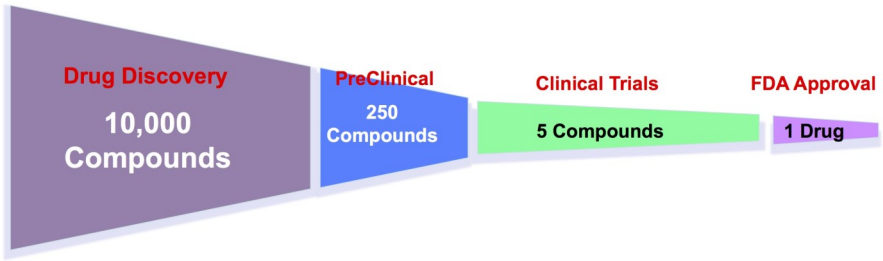
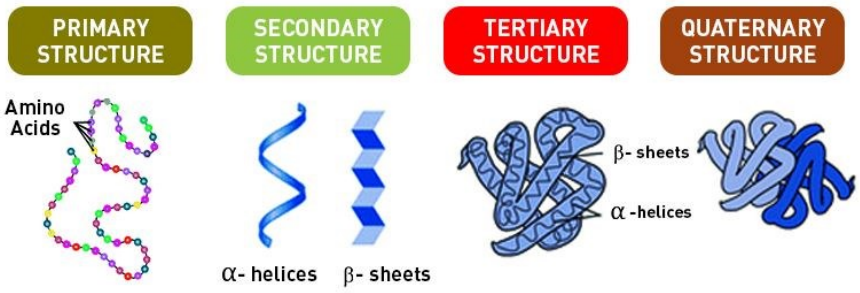
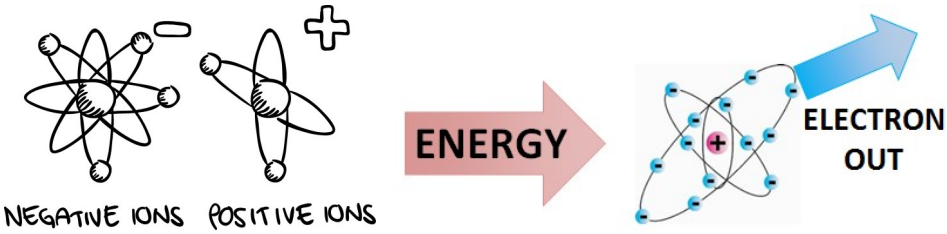
Final Assignment Guidelines

- Includes a problem set worth 50% of the marks and a written portion of 1000 words worth 50% of the marks.

Subject Vocabulary

Word	Definition	In a sentence
Disease	A disorder of in an organism that causes specific symptoms.	
Protein	A single or collection of molecules that exist within cells and perform specific functions.	
Ion	An atom or molecule that carries an electrical charge due to the loss or gain of electrons.	
Ionization	A process that causes an atom or molecule to lose or gain electrons, generating an ion.	
Mass to Charge Ratio	A quantity by which ions are commonly measured, calculated by dividing its mass by its charge.	
Mass Spectrometry	A method using instruments to measure the mass to charge ratio of an ion	
Electrospray	An ionization technique that produces ions by application of a high voltage to a solution.	
Mass Peak	The highest point in a mass spectra for an ion that is used to measure its mass to charge ratio.	
Drug Screening	The process of testing a large selection of compounds to find which interact with a protein.	
Drug Cocktail	A mixture of compounds that may be useful drugs.	

Knowledge Organisers

Key Concepts	
What is a disease	Diseases are abnormal conditions that negatively affects the structure or function of a part of an organism. They cause specific symptoms that affect specific parts of the effected organism.
What causes disease	Diseases may be caused by other organism such as bacteria that can be transmitted between people. They may also be caused by defects in specific parts of the body that cause them to not function properly.
How are diseases treated	Diseases can be prevented by minimising the risk of contracting them. They can be treated by drugs and techniques that manage symptoms. They can sometimes be cured by drugs that remove the cause.
What is drug screening	
What are proteins	
What is an ion	
What is mass to charge ratio	Mass to charge ratio = mass ÷ charge
What is mass spectrometry	Mass spectrometry is a technique that uses instruments to both generate ions from sample molecules and separate them based on their mass to charge ratio, allowing this value to be measured.
How are mass spectra interpreted	Each ion gives a peak at its mass to charge ratio, with an intensity proportional to its abundance. Mass = mass to charge ratio x charge An average of the mass for each peak will give the most reliable value

Tutorial 1 – How Can We Treat Diseases?

What is the Purpose of Tutorial 1?

- Review what you know about disease
- Discuss ideas about how diseases can be treated
- Learn where new drugs can come from

What do you know about disease?
Write down any words associated with disease that you can think of?

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Sort the words the group came up with into the following categories.

Causes	Symptoms	Definitions
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Define a disease in your own words.

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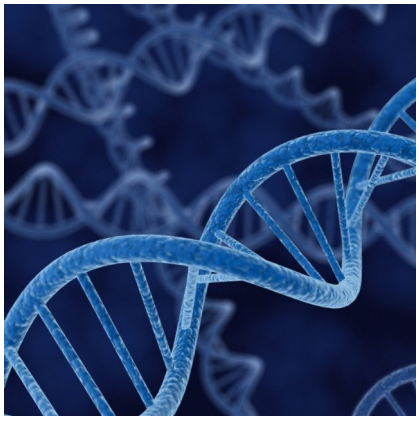
What can cause disease?



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How can diseases be treated?
Sort the listed treatments into the correct category.

Paracetamol, Insulin, MMR Vaccine, Sunscreen, Penicillin, Malaria Pills, Surgery

Prevention	Treatment	Cure
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Where can new drugs be found?
Here are some examples of drugs you may know and their original source.

Aspirin | Morphine | Vitamin C | Insulin

Willow Tree | Poppies | Citrus Fruit | Pork Pancreas

If you wanted to find a new drug where would you look?

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How can we go from source to cure?

Selection of Natural and Synthetic Compounds

Drug Screening

Active Compounds

Pre-Clinical Trials

Potential Drugs

Clinical Trials

Licensed Drug

What do we mean by drug screening and why is it important?

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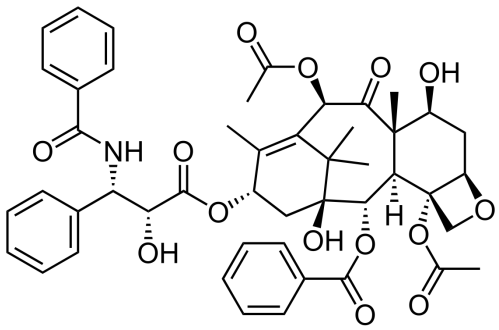
How Paclitaxel was discovered

In 1955 the Cancer Chemotherapy National Service Centre was set up to screen anticancer activity in submitted compounds.

One chemist began screening compounds from plants, testing about 1,000 plant species each year.

One botanist submitted a sample of bark from a pacific yew tree which was effective against cancer cells.

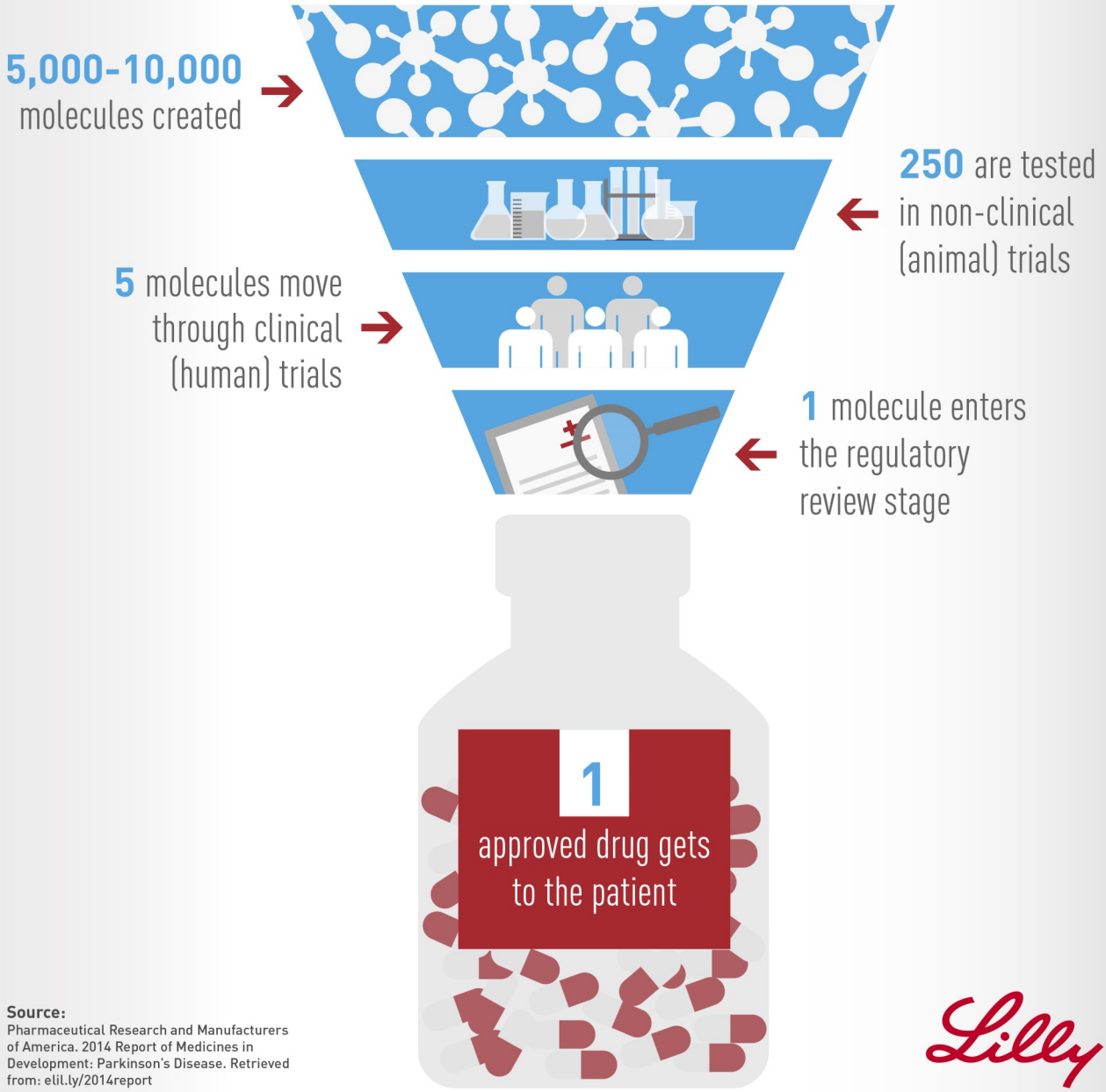
Chemists then began working on isolating the active compound in the bark. It took 1,000 kg of bark to get only 10g of pure material!



Pre-clinical trials in mice showed this isolated compound was an effective treatment for leukaemia.

Clinical trials in humans showed a remarkable response in patients taking the drug and it was licensed for use in a variety of cancers.

DRUG DISCOVERY BY THE NUMBERS



Source:
Pharmaceutical Research and Manufacturers of America. 2014 Report of Medicines in Development: Parkinson's Disease. Retrieved from: elil.ly/2014report

Lilly

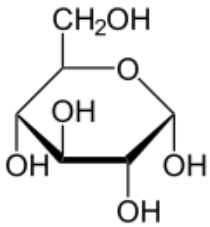
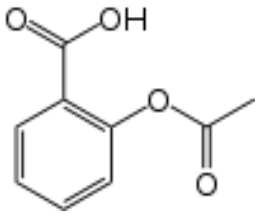
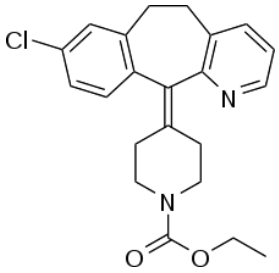
Homework 1

Complete the following sentences

A disease is a condition that ..... affects the structure or ..... of a part of an ..... . They cause specific ..... in the affected organism.

A ..... is a chemical substance used in the ..... , treatment or ..... of a disease.

Calculate the relative atomic mass of the following drug molecules

Glucose	Aspirin	Loratadine
$C_6H_{12}O_6$	$C_9H_8O_4$	$C_{22}H_{23}ClN_2O_2$
		
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In a short paragraph, describe how new drugs can be discovered

Use ideas discussed in tutorial 1, considering where the initial compound can be found and how this is developed into a licensed drug

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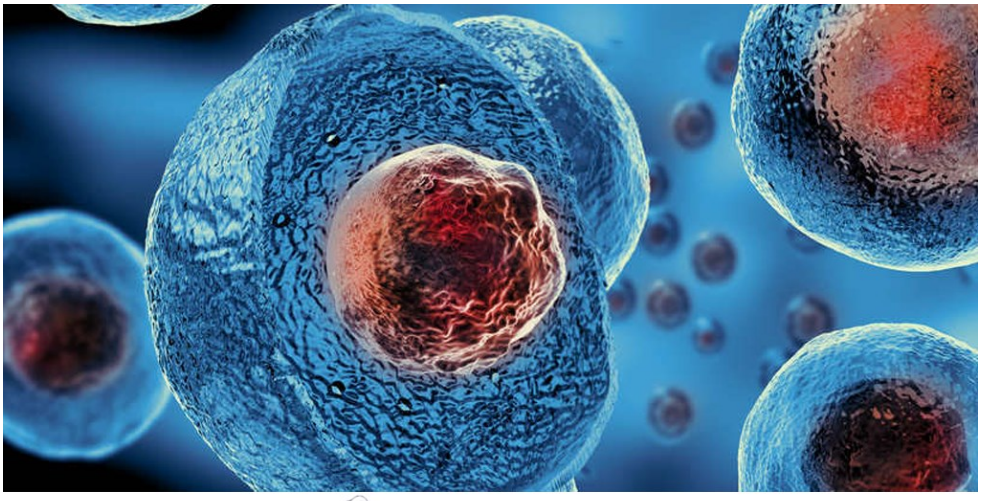
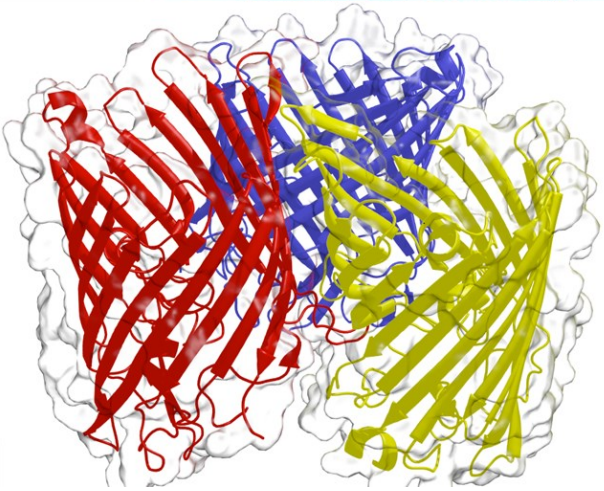
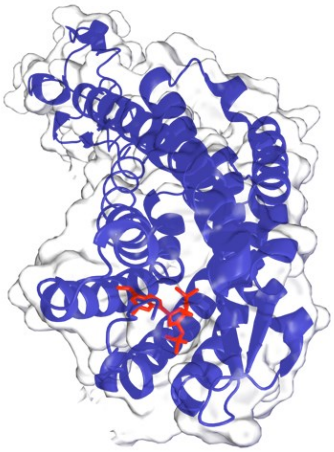
Tutorial 2– How Do Drugs Work?







What is the Purpose of Tutorial 2?

- Learn what proteins are
- Learn what a protein looks like
- Learn how drugs interact with proteins

Let's build a cell! Use the materials provided to build a cell.
Draw and label a diagram of this.

How can drugs enter a cell?
Write down your thoughts, discuss them with your partner, then share them with the group.

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What is a protein?

A protein is .....
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Proteins can be found .....
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They perform functions such as .....
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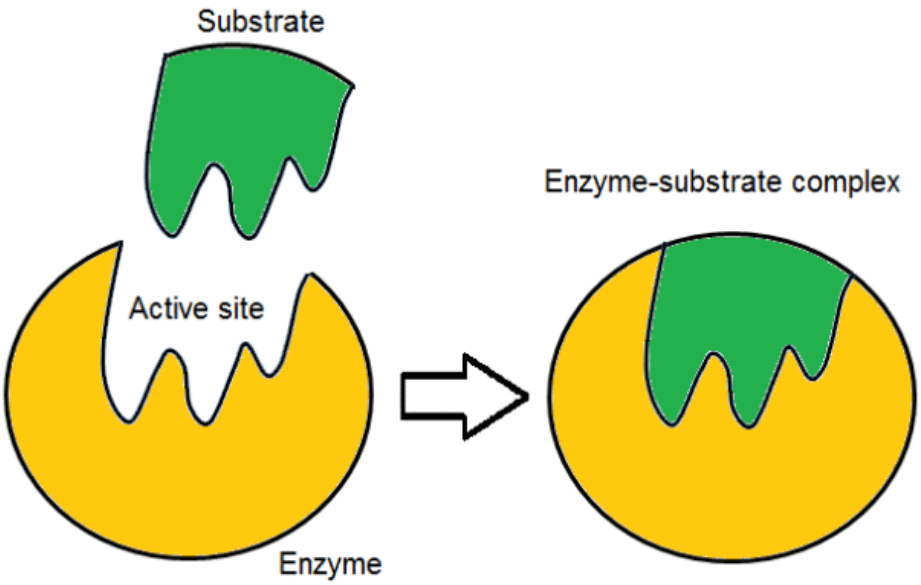
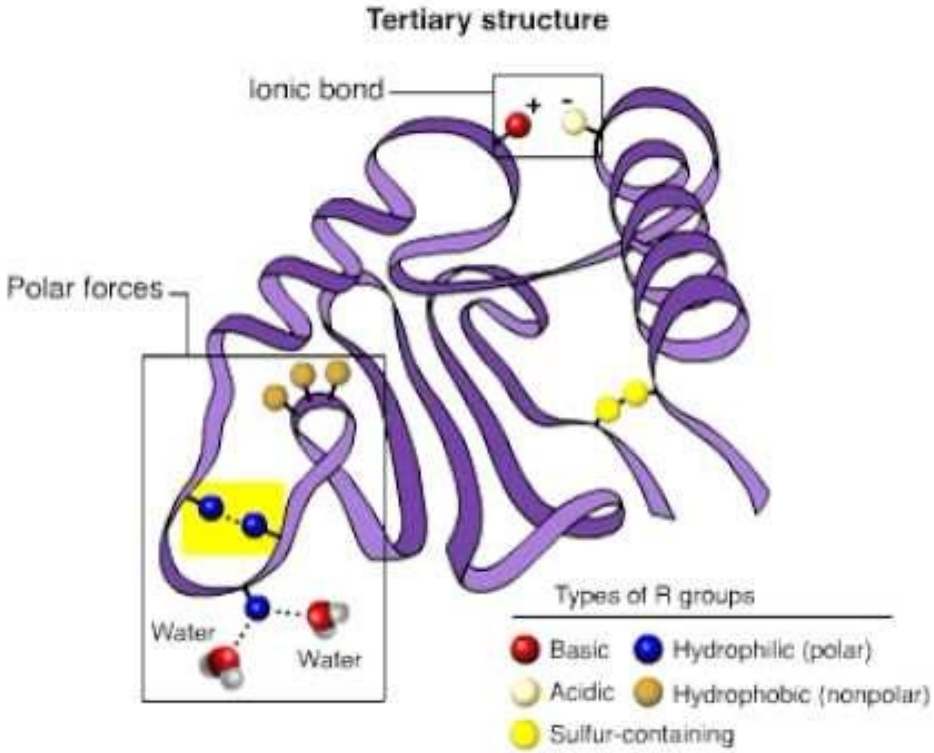
What does a protein look like?
Build a protein using the handout given to you.
Draw a diagram of it.

How do drugs interact with proteins?





The main factors influencing drug binding are

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Homework 2

On the following page is an article about a protein called alpha-synuclein. Read this and use the information to complete the following sentences.

Alpha-synuclein is found in the ..... although its function is unknown.

Evidence suggests that alpha-synuclein is significant in ..... disease.

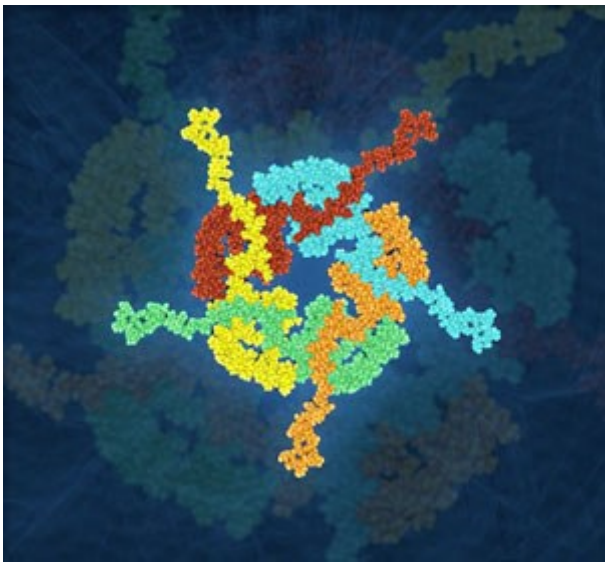
In familial cases of the disease the alpha-synuclein gene produces either too ..... of the protein or an ..... form of the protein.

This suggests that therapies should be developed that ..... gene expression or block its aggregation.

Alpha-synuclein may also be useful as a ..... , i.e. a species that is present in individuals with the disease that can be measured and used in the diagnosis of the disease.

A ..... is being trialled that targets alpha-synuclein by binding to it and clearing it from the brain.

Alpha-synuclein and Parkinson's Disease



What is alpha-synuclein?

Alpha-synuclein (also *α-synuclein*) is a protein whose function in the healthy brain is currently unknown. It is of great interest to Parkinson's researchers because it is a major constituent of Lewy bodies, protein clumps that are the pathological hallmark of Parkinson's disease.

In the several years since its discovery, alpha-synuclein has been the focus of intensive efforts by basic Parkinson's disease researchers working to definitively characterize the protein's role in Parkinson's and its potential as a target for neuroprotective therapies. Despite this, there are still more questions than answers as to whether and how alpha-synuclein plays a direct causative role in Parkinson's disease.

What is alpha-synuclein?

What is the latest research into the role that alpha-synuclein plays in Parkinson's disease?

There is compelling evidence from recent studies that alpha-synuclein may play a role in the development of both (rare) familial and (more common) sporadic cases of Parkinson's disease.

For a very small subset of Parkinson's patients, hereditary variability in the alpha-synuclein gene contributes to developing the disease. In these rare cases of familial Parkinson's disease, the alpha-synuclein gene produces either too much alpha-synuclein protein or an abnormal form of the protein — unusual events believed by some researchers to be toxic to brain cells and to result in neuron dysfunction.

Furthermore, alpha-synuclein is the primary structural component of Lewy bodies, suggesting that protein aggregation plays a role in sporadic Parkinson's disease as well.

These findings support the development of Parkinson's disease therapies that reduce alpha-synuclein gene expression or block its aggregation. Such therapies could potentially prevent or delay the onset of Parkinson's disease, or halt or slow its progression.

What's more, alpha-synuclein pathology has been found to exist in some body systems not traditionally associated with Parkinson's disease, as well as in patients who did not experience any clinical features of Parkinson's. For this reason, study of alpha-synuclein is crucial to test the emerging hypothesis that Parkinson's disease affects many areas of the central nervous system beyond the substantia nigra, and even extends beyond the boundaries of the central nervous system. This hypothesis has gained attention in recent years as appreciation has grown for the diversity of the clinical features of Parkinson's disease.

Finally, research is ongoing to determine whether alpha-synuclein may have a potential use as a biomarker of Parkinson's disease.

What attempts have been made to develop an alpha-synuclein therapy

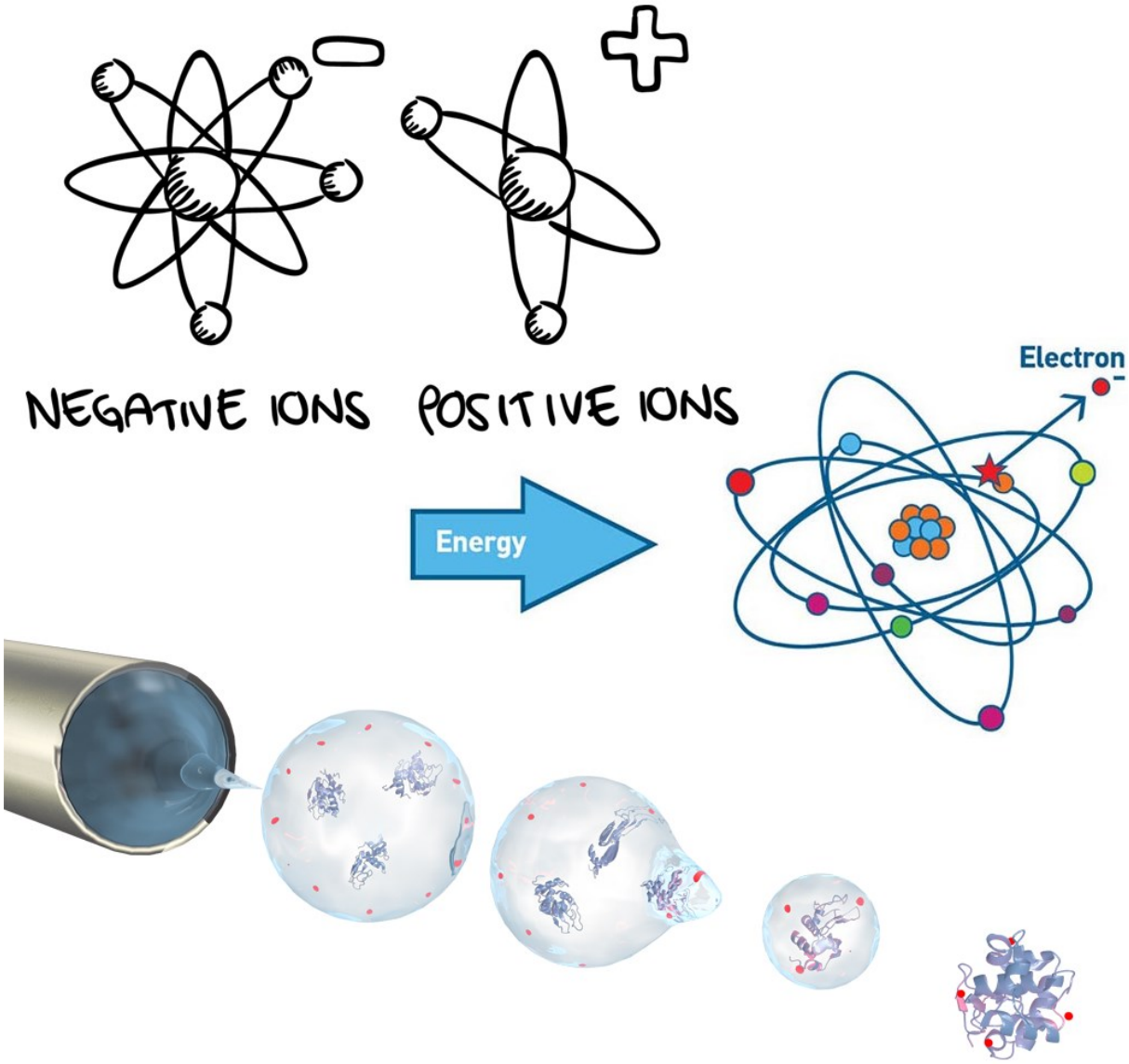
A vaccine approach targeting alpha-synuclein in Parkinson's patients is now in the clinic. The vaccine candidate, from Austrian biotech AFFiRiS, works by binding to alpha-synuclein and subsequently clearing it from the brain. It is now in the first stages of clinical testing.

Other approved compounds that have been shown to stop synuclein clumping, and to break up existing clumps, are moving forward in pre-clinical testing.

As of January 2012, The Michael J. Fox Foundation had invested over $47 million in projects targeting alpha-synuclein.

Alpha-synuclein and Parkinson's Disease
https://www.michaeljfox.org/understanding-parkinsons/living-with-pd/topic.php?alpha-synuclein

Tutorial 3 – Can We Look At Single Proteins?



What is the Purpose of Tutorial 3?

- Learn what an ion is
- Learn how we can form ions
- Learn how to assign charge states

What is an ion?
Write down your thoughts, discuss them with your partner, then share them with the group.

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Define an ion

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How is an ion formed?

What are the charges of the following ions?

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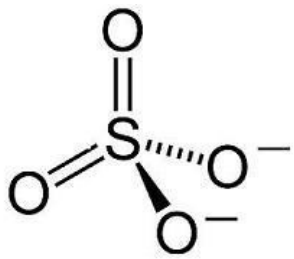
Mass to charge ratio

Ions are usually measured by their mass to charge ratio.

Mass to charge ratio = mass ÷ charge

Example

Sulphate Ion



Chemical Formula = SO_4^{2-}

Relative Atomic Mass = 1 x 32 + 4 x 16
= 96

Charge = 2-

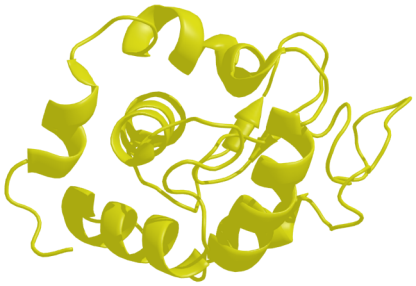
Mass to Charge Ratio = mass ÷ charge
= 96 ÷ 2
= 48

Work out the mass to charge ratio for the previous 3 ions.

Large molecules, including proteins can have multiple charge states as there are several chemical groups that may or may not be charged.

Example

Lysozyme



Mass = 14,000

Possible Charge States = 6+ , 7+ and 8+

Mass to Charge Ratios = 14,000 ÷ 6 = 2,333
= 14,000 ÷ 7 = 2,000
= 14,000 ÷ 8 = 1,750

The amount of charge can also depend on the way the ions were formed.

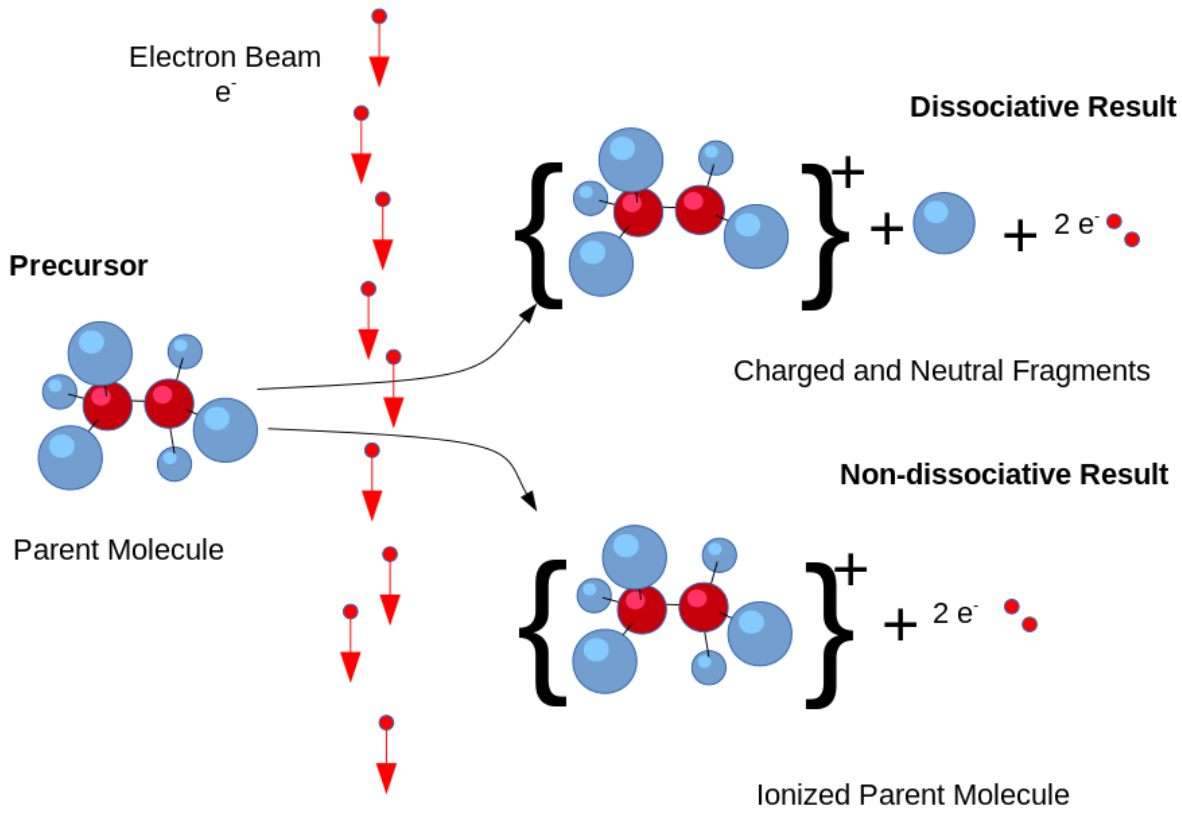
Ionization Techniques:

There a several ways that ions can be generated from neutral species.

These involve adding or removing electrons from a species by applying energy from an external source.

Below are three of the most common techniques used.

1. Electron Impact Ionization (EI)



Key features:

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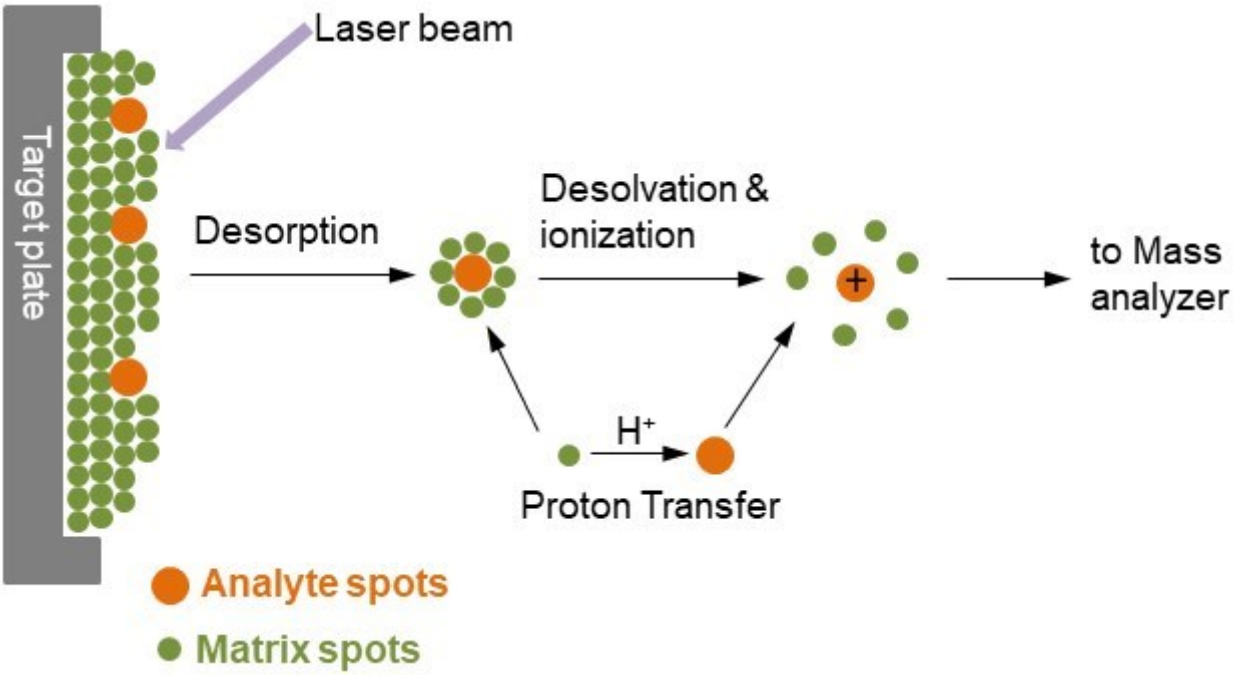
2. Matrix Assisted Laser Desorption Ionization (MALDI)



Key features:

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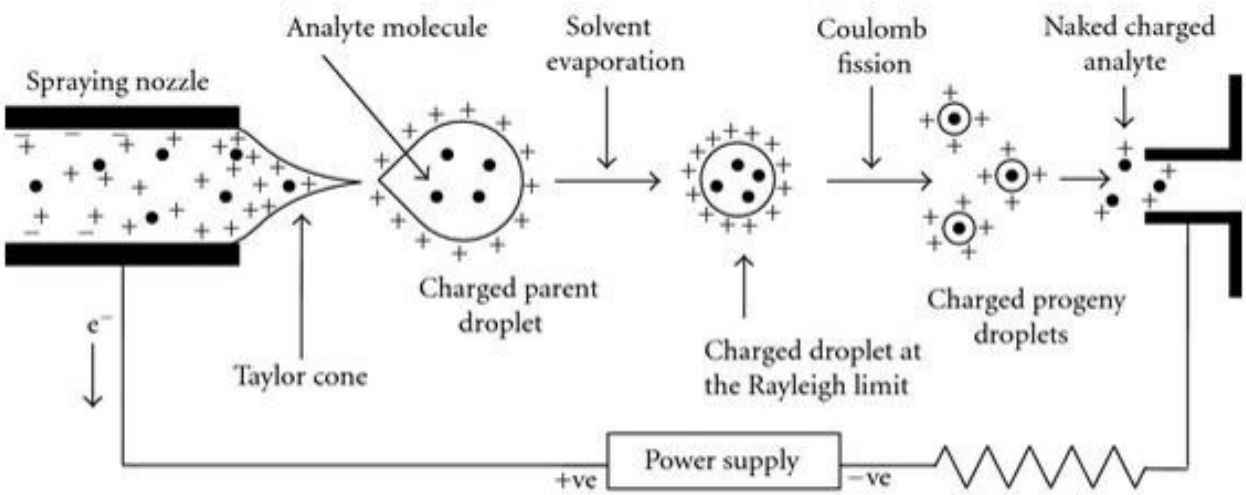
3. Electrospray Ionization (ESI)



Key features

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Homework 3

Calculate the mass to charge ratio for the following species:

1. Aluminium 3+

Al^{3+}

Mass

26.98

Charge

3+

Mass to Charge Ratio

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Space for calculations

2. Carbonate

CO_3^{2-}

Mass

60.01

Charge

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Mass to Charge Ratio

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Space for calculations

3. BSA (Bovine Serum Albumin)

Mass

66,000

Possible Charge States

15+ 16+ 17+

Possible Mass to Charge Ratios

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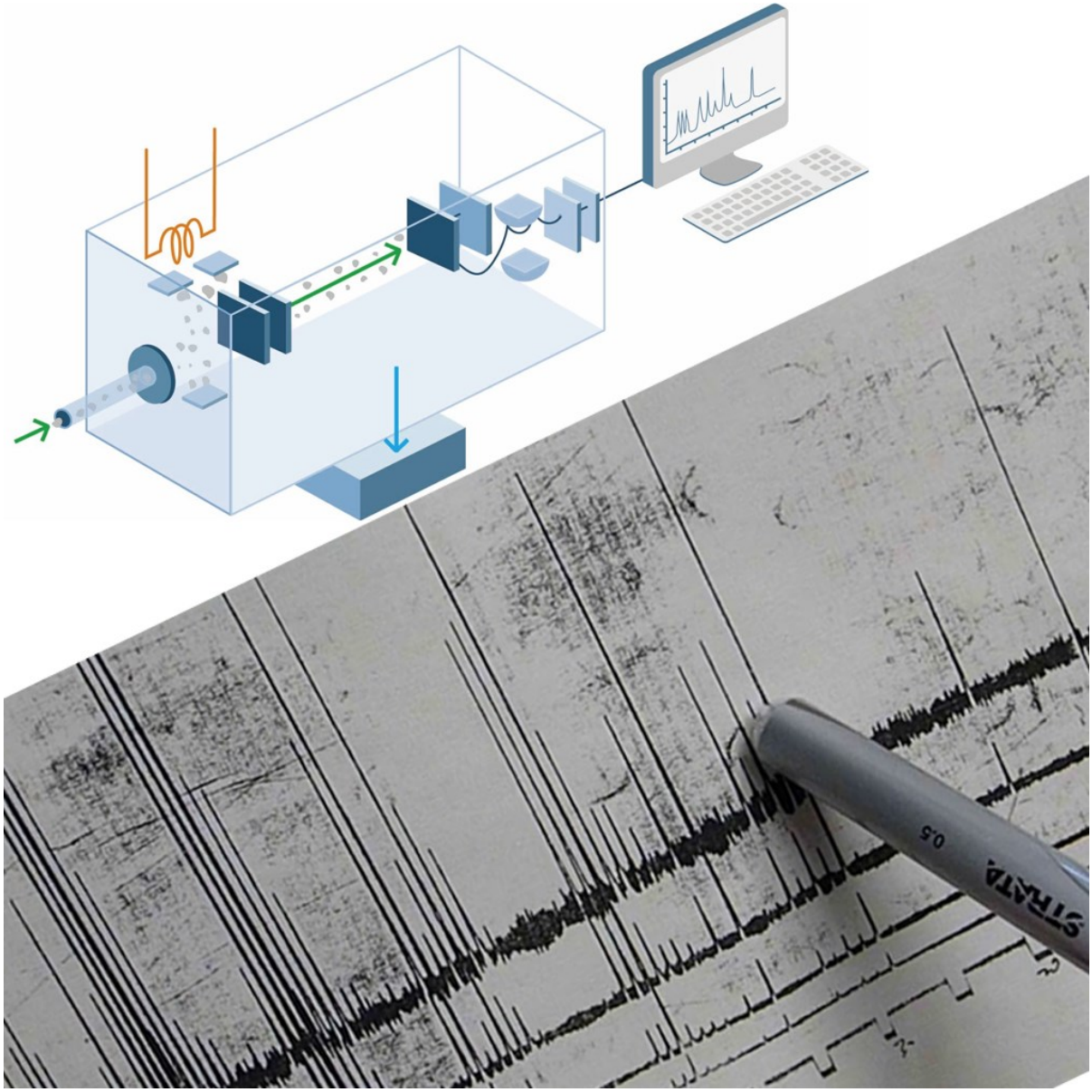
Space for calculations

Tutorial 4 – How Heavy Is An Ion?



What is the Purpose of Tutorial 4?

- Learn how forces work on ions
- Learn how ions can be separated by size
- Learn how to calculate the mass of an ion

What factors change how ions react in an electronic field?

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Draw an electric field.
Add the paths for ions of light, medium and heavy mass.

For one of the ions add the change in the path for a higher and lower charge

What is Mass Spectrometry

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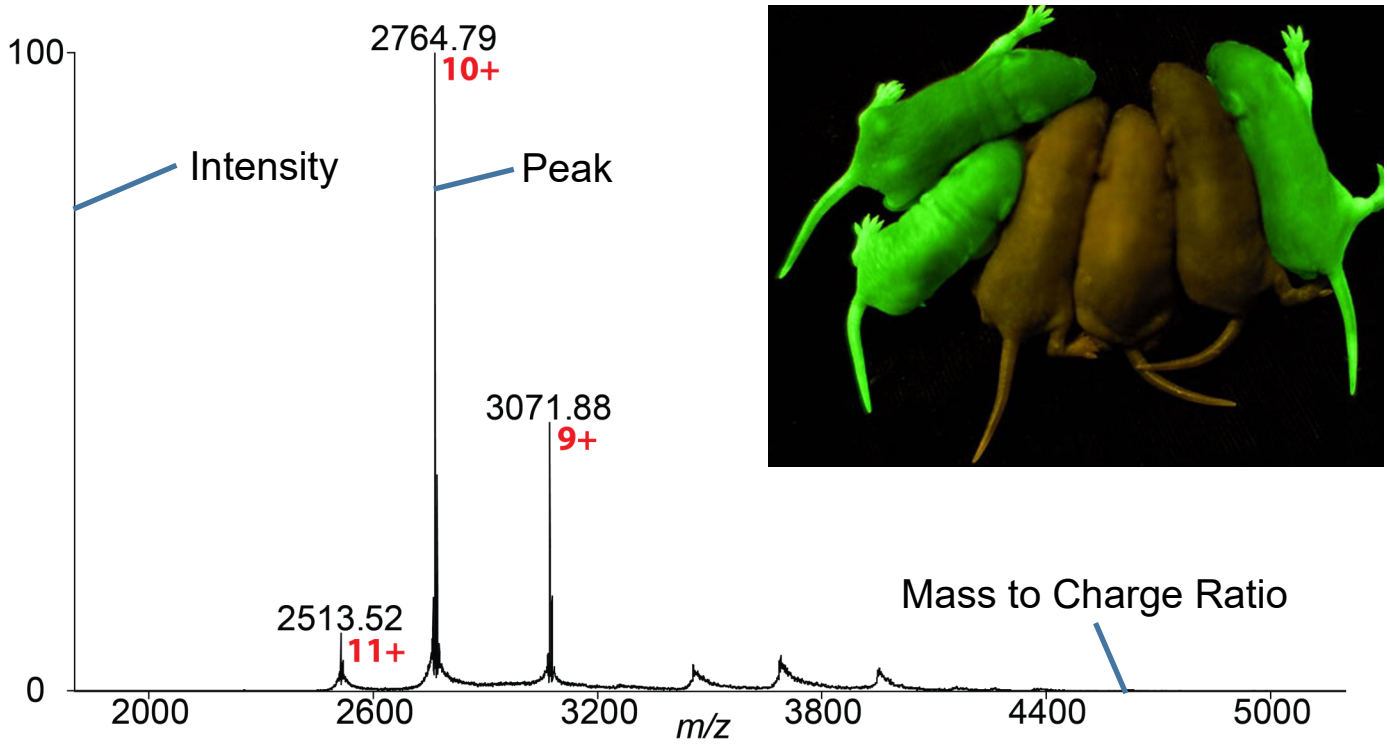
Below is a mass spectra for a protein called GFP (Green Fluorescent Protein), a protein found in a jellyfish that glows bright green.



In this spectra the intensity (y-axis) is shown for each mass to charge ratio (x-axis).

A peak in the spectrum indicates that there is an ion in the sample with that mass to charge ratio. The size of the peak indicates the amount of each ion.

How can we calculate the mass of GFP?

We learnt before that

Mass to Charge Ratio = Mass ÷ Charge

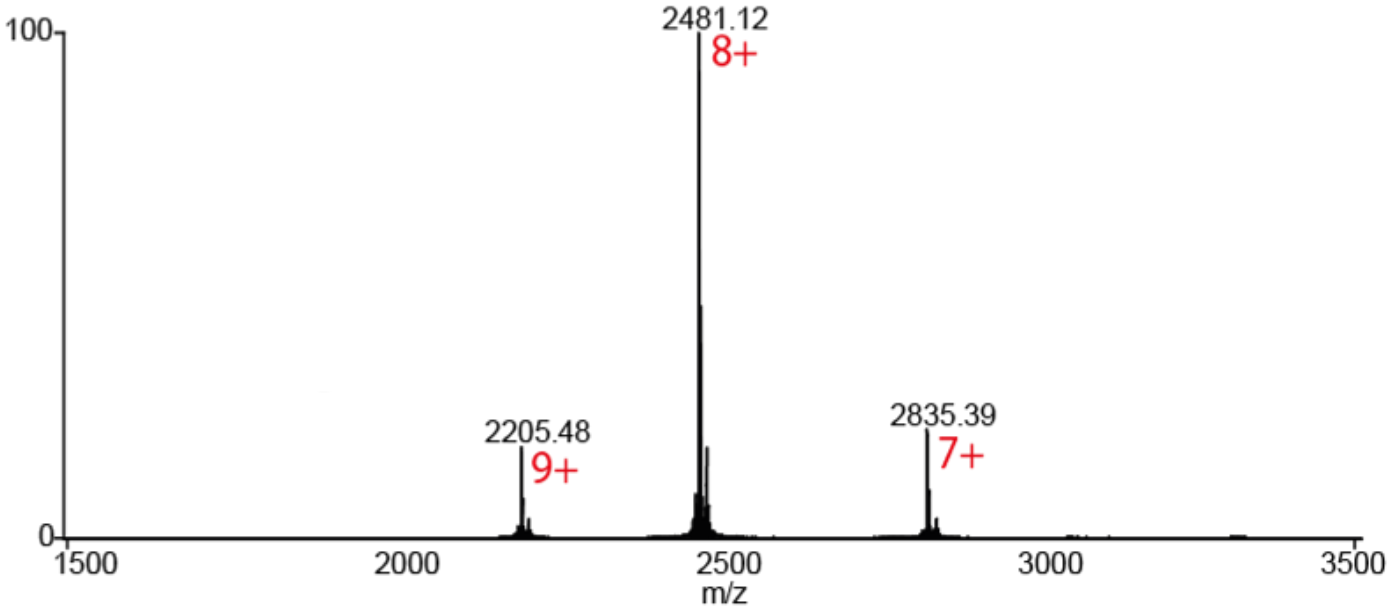
This can be rearranged to

Mass = Mass to Charge Ratio x Charge

To get the mass we need to multiply the mass to charge ratio for each peak by its charge. Taking an average of the mass calculated for each peak gives a more reliable result.

mass	= 2,513	x	11	= 27,643
	= 2,764	x	10	= 27,640
	= 3,071	x	9	= 27,639
average	= (27,643 + 27,640 + 27,639) ÷ 3			
	= 27,640			

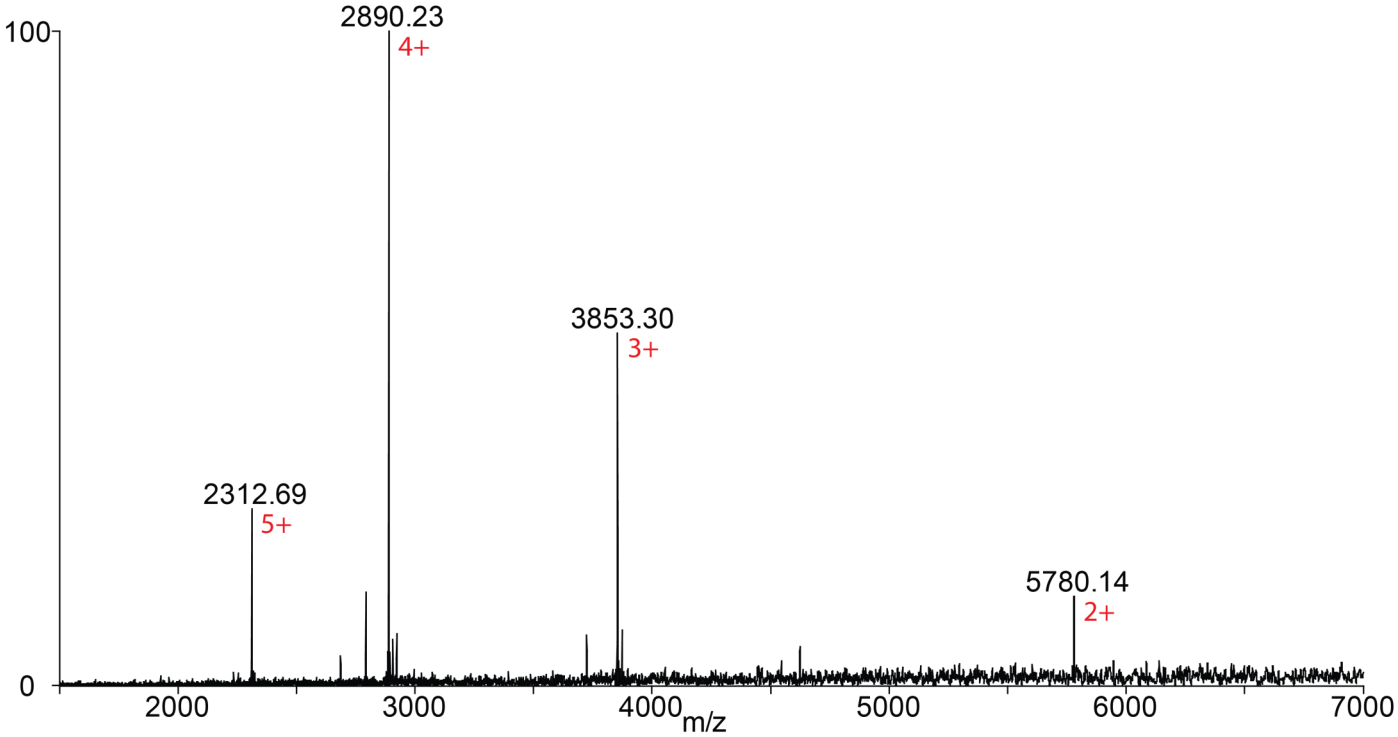
Below is a mass spectra for a protein called KRas which is an important target in treating several types of cancer.



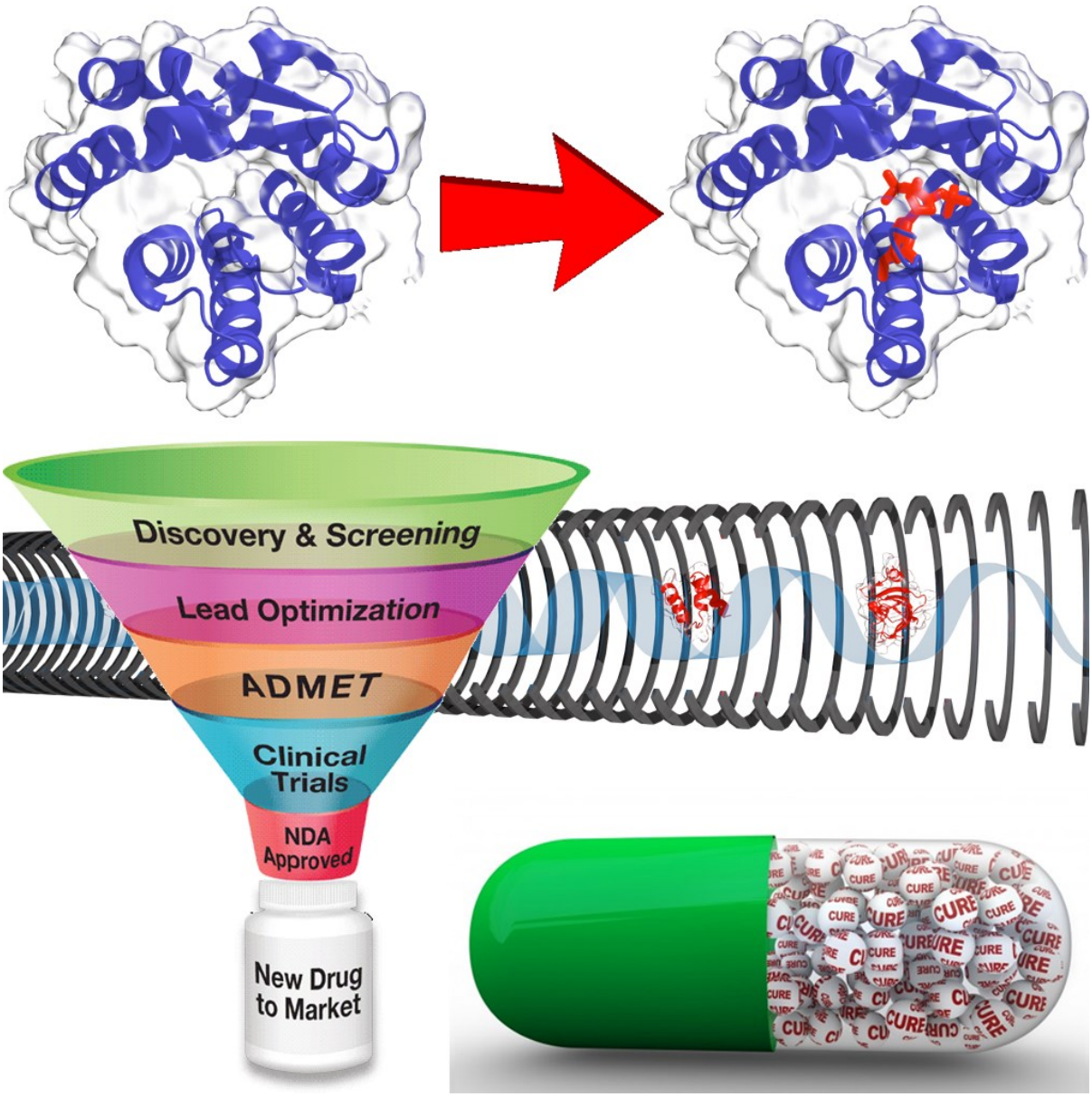
Calculate the mass of KRas

Homework 4

Calculate the mass of Semi-Sweet, a sugar transport found across many plants and animals, from the spectra below



Tutorial 5 – How Can We Find New Drugs?



What is the Purpose of Tutorial 5?

- Learn how drug binding can be measured by mass spectrometry
- Learn how drug screening is performed

How would a drug binding to a protein affect the mass spectra?
Draw what you think would happen on a whiteboard.
Then compare it to your partners.
Summarise the effect below:

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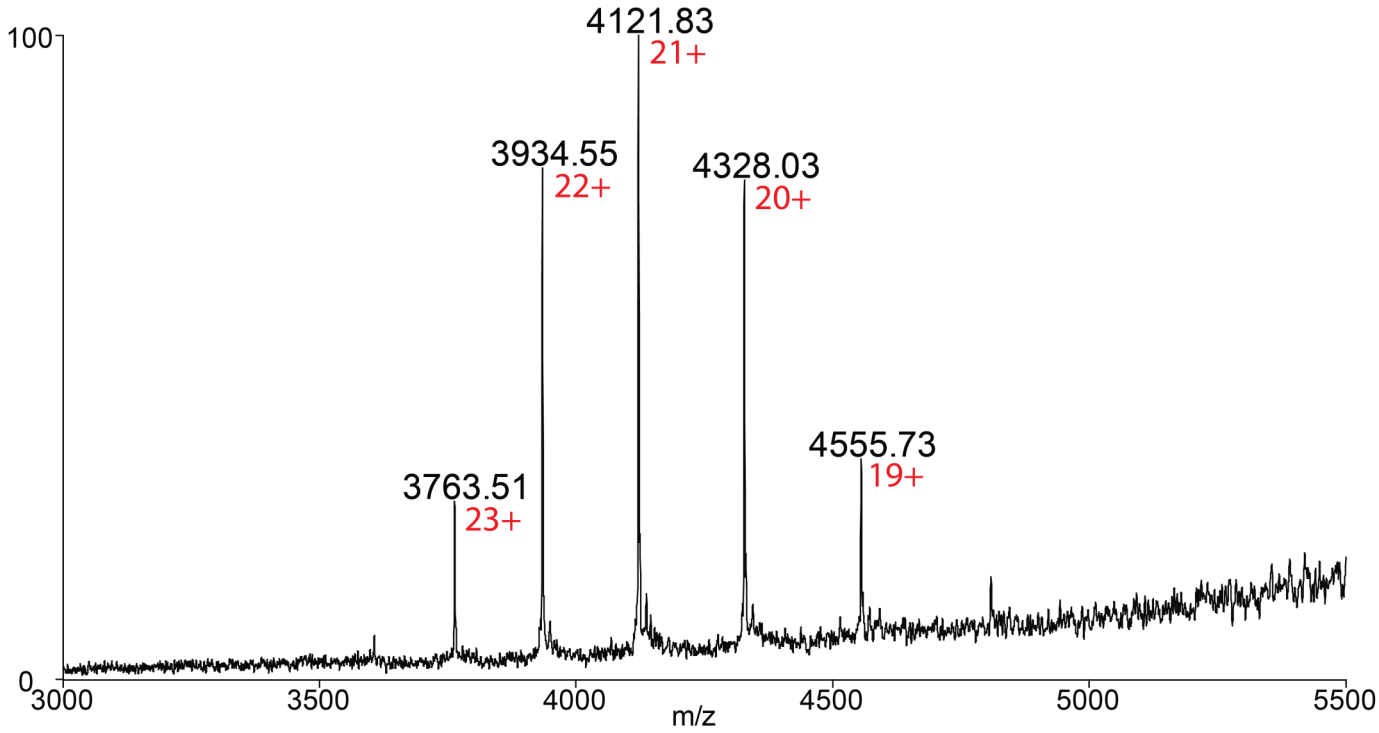
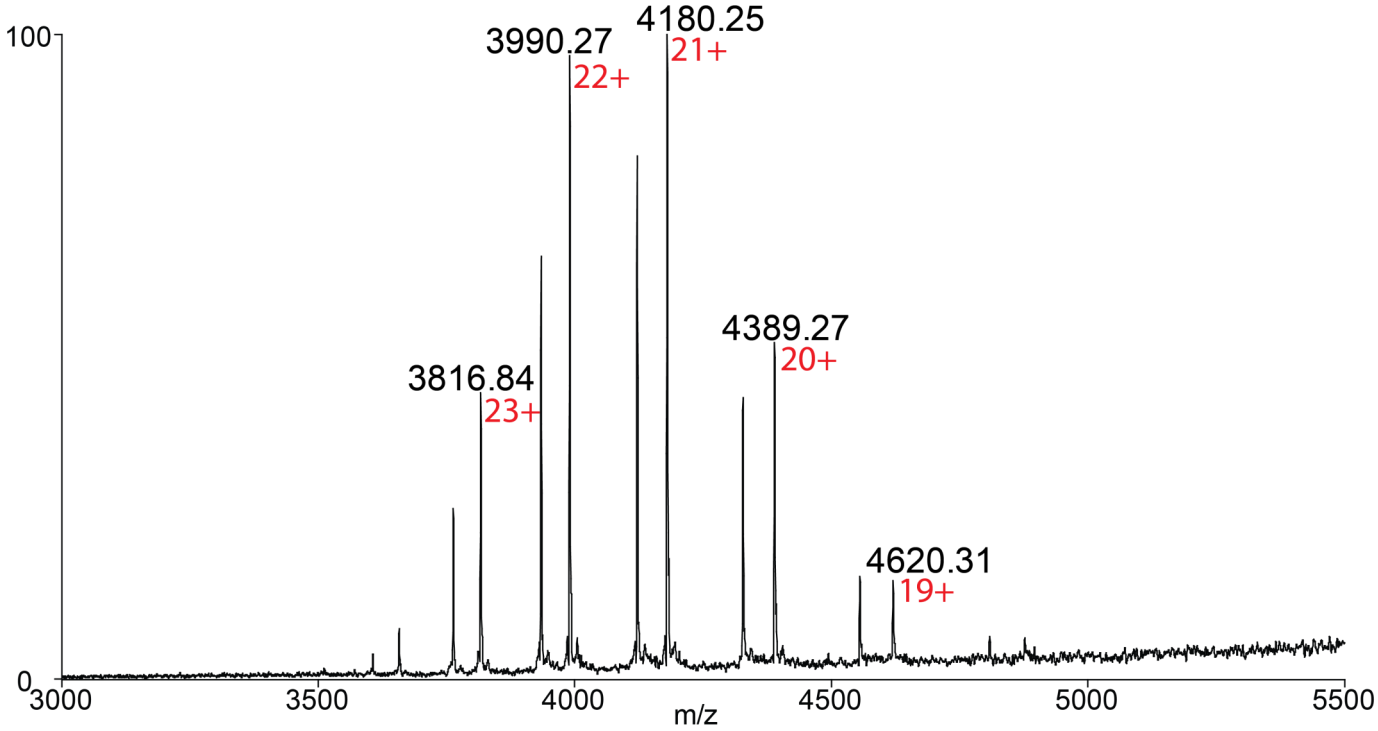
PVD Binding to fvpA

Below is a spectra of Ferric Hydroxymate Receptor, which transports iron into cells in certain bacteria, calculate its mass.



An iron carrying molecule called ferric-pyoverdine (Pvd) has been added to the protein. Below is the resulting spectra, only the new peaks are labelled.



What causes the new peaks?

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Calculate the mass of Pvd.

Imagine you have a protein you want to find a new drug for, how could you use mass spectrometry to find one.

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Homework 5

The first spectra on the next page is of a protein called $P2Y_1$, a protein responsible for platelet aggregation and a key target for anti-thrombotic therapy.

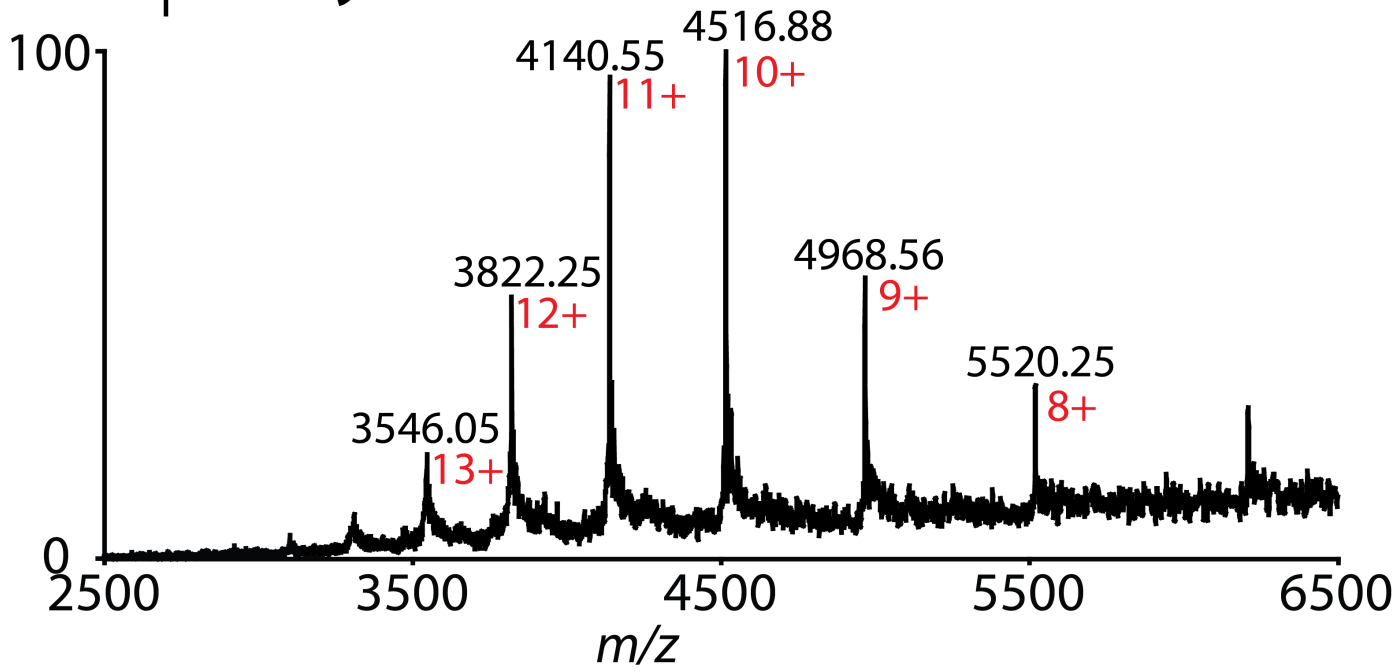
Calculate the mass of $P2Y_1$

You will need to rearrange and use the equation from tutorial 4

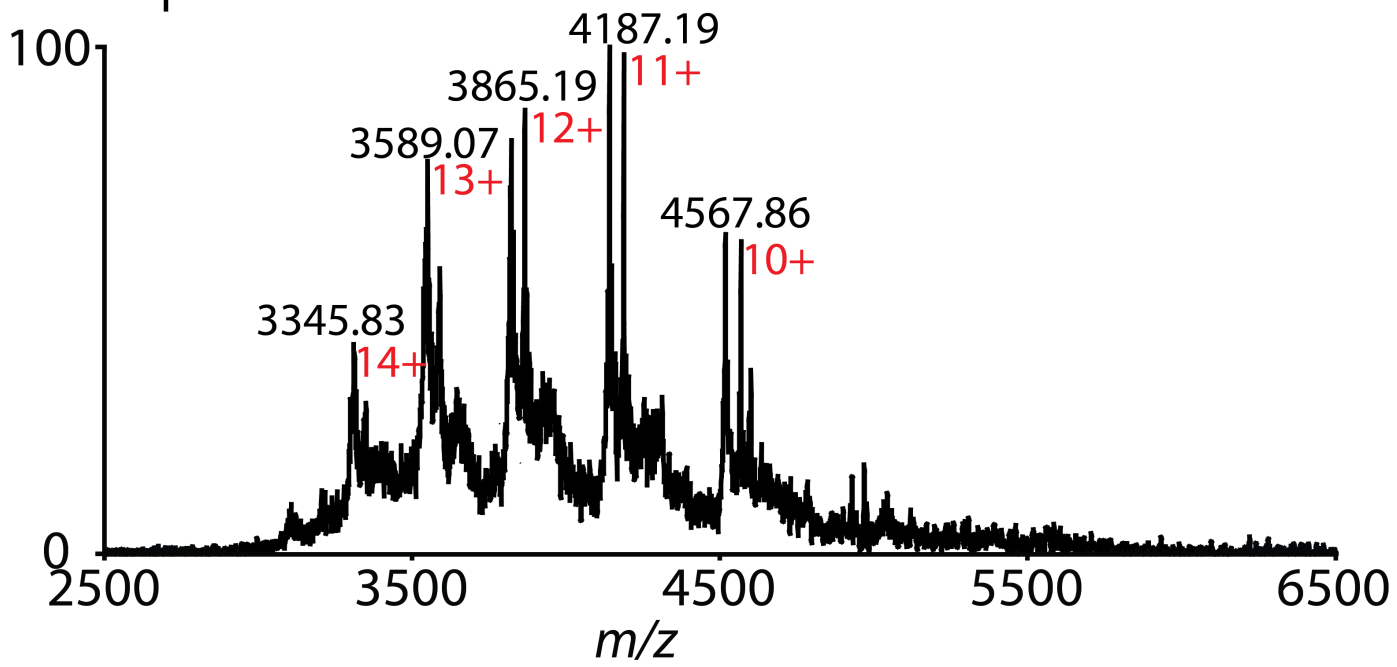
Mass to Charge Ratio = Mass ÷ Charge

Remember that averages give more accurate results.

$P2Y_1$ Only



$P2Y_1$ With Drug Cocktail



Drug	Mass
MRS2500	561.16
MRS2211	428.68
PSB 0739	563.56
PSB 1115	350.35
Ticlopidine Hydrochloride	263.79

The second spectra on the previous page shows $P2Y_1$ after the addition of a 'cocktail' of 5 potential drugs, only the new peaks for the protein with the drug bound are labelled.

Calculate the mass of $P2Y_1$ and determine which of the drugs is binding to it and a potential candidate for further development.

Remember that when a drug binds to a protein it will increase the mass of the species by an amount equal to the mass of the drug.

Drug screening by mass spectrometry, as shown with $P2Y_1$, is only one possible technique that may be involved in the drug discovery process.

Using the ideas discussed over the course of these tutorials, write an short essay titled:

How is mass spectrometry useful in the drug discovery process?

This should be:

- A word processed essay
- Up to 1,000 words in length

You should consider:

- The stages involved in drug discovery
- How mass spectrometry fits into the drug discovery timeline
- What extra information mass spectrometry provides
- How this information informs further drug development

You should include:

- The title of the essay
- An clear introduction that outlines the contents of the essay
- Paragraphs organized into a logical structure around the key ideas
- A conclusion that summarises they key points discussed

You should pay attention to:

- Accurate spelling, punctuation and grammar
- Using a formal writing style appropriate for an essay

Tutorial 6 – Feedback tutorial

What is the Purpose of Tutorial 6?

- To receive feedback on final assignments.
- To share examples of best practice with the other pupils in your group.
- To write targets for improvement in school lessons.

To reflect on the programme including what was enjoyed and what was challenging.

Final assignment feedback

What I did well…	What I could have improved on…

My target for future work is…

Tutorial 7 – Feedback tutorial

What is the Purpose of Tutorial 7?

- To receive feedback on final assignments.
- To share examples of best practice with the other pupils in your group.
- To write targets for improvement in school lessons.

To reflect on the programme including what was enjoyed and what was challenging.

Final assignment feedback

What I did well…	What I could have improved on…

My target for future work is…

Reflecting on Uni Pathways

What did you most enjoy about Uni Pathways?

What did you find challenging about the programme?	How did you overcome these challenges?

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:

1. **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].

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.

Notes

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