MANCHESTER 1824
The University of Manchester

COURSE SAMPLE

TRANSFORMATIVE ONCOLOGY

COURSE SAMPLE

CONTENTS

UNDERSTANDING CHALLENGES OF TUMOUR BIOLOGY

INTRODUCTION TO CELL TOXICITY

Over the next two weeks we will begin to look at the toxicity of treatment at the cellular level starting with the basics of cell death. We will cover why cell death is a normal and important stage of tissue growth and how controlling a cell's demise can reduce the impact on surrounding cells enabling an organism to continue to grow. Then we will dissect the mechanisms of cell death drawing on the most recent understanding in the field and begin to understand at a conceptual level how cancer cells evolve to use some of the normal cellular functions to their advantage, enabling them to survive.

LEARNING OBJECTIVES

By the end of this section you will be able to:

- Demonstrate a mechanistic understaning of cytotoxicity
- Reflect on the key issues of tumout/host toxicity

WHAT IS CYTOTOXICITY?

Cell death is a normal event which occurs when the functions of that cell are no longer needed, or if the cell becomes damaged in a way which cannot be repaired.

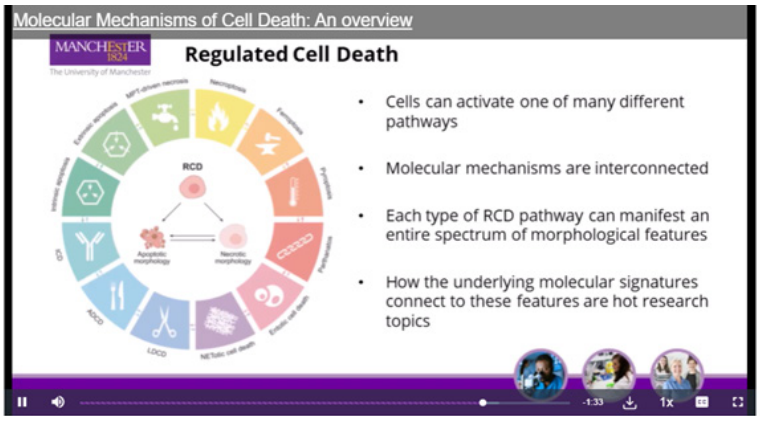
In a healthy multicellular organism, cell death is a critical part of developmental and regulatory processes which allow the organism to control and regulate its cellular components and maintain homeostasis.

Cell death is also important for when things go wrong either due to cell damage or disease. If the cell's internal machinery is unable to repair the damage, the cell will undergo regulated cell death to limit the impact on surrounding cells or tissue. In simple terms, two main types of cell death occur: regulated or accidental.

- Regulated Cell Death (RCD) - relies on dedicated molecular machinery to control the cell's demise.
- Accidental Cell Death (ACD) - the instantaneous and catastrophic demise of cells due to exposure to physical (temperature, pressure, radiation), chemical (extreme pH variations) or mechanical (shear forces).

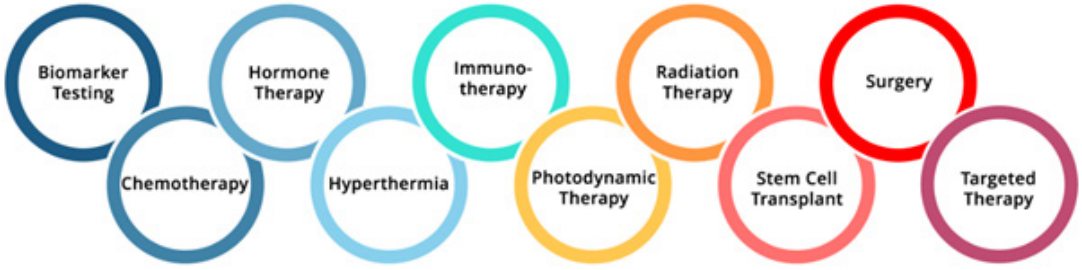
AN OVERVIEW OF THE UNDERLYING MOLECULAR MECHANISMS OF CELL DEATH

In the next video, we will take a bird's eye view of the current understanding around cell death with a general introduction into the molecular mechanisms involved. We will explore the requirements for formulated guidance around the definition and explanation of cell death from morphological, biochemical and functional perspectives.
You are encouraged to take notes for your portfolio so you can reflect on your learning later.



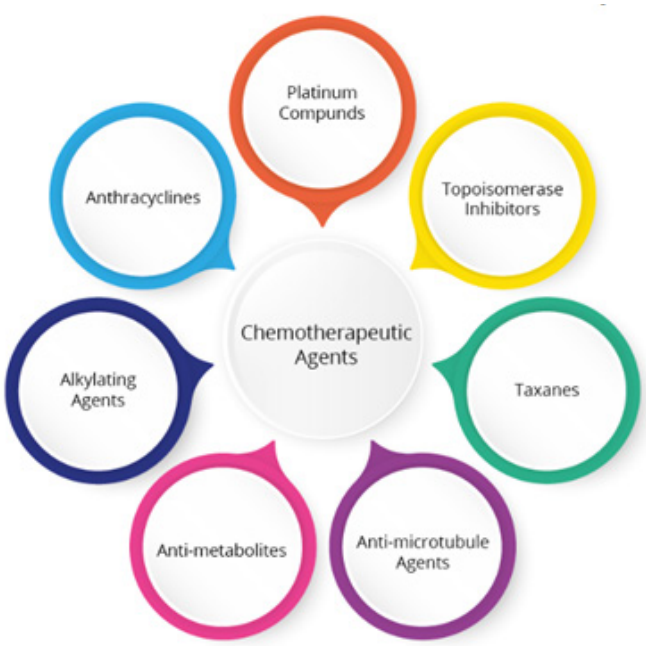
OVERVIEW OF TREATMENT STRATEGIES

It is important to understand these different treatment approaches and appreciate the impact and effects of toxicity resulting from the different treatment strategies and combinations.



CHEMOTHERAPY

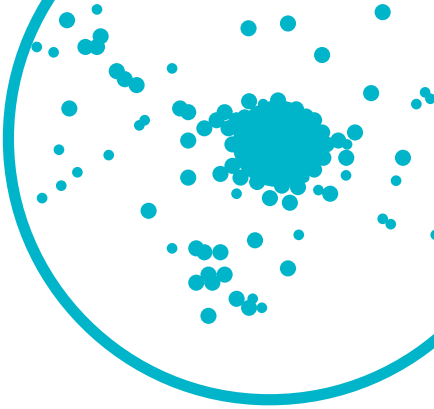
Chemotherapy is a type of cancer treatment that uses drugs to kill cancer cells. Please spend a couple of minutes exploring the various chemotherapy treatment examples. If required, please download the transcript for an accessible version.



Think: Reflecting on your progress

We encourage you to make notes of your thoughts as you work through the materials. As we move towards your final comprehension assignment, focus on integrating your understanding, and draw on some of the ideas and opinions of experts in the field.

Please use the **Questions for the tutor** discussion forum on Blackboard to send any questions our way, and we will endeavour to answer them!



IMPORTANCE OF PRECISION MEDICINE IN CANCER TREATMENT

INTRODUCTION

In this section, we'll explore the valuable role of molecular characterisation in various aspects of cancer care. This not only includes identifying actionable targets, but also selecting the right treatment dose and duration. We'll also delve into its significance in immunotherapy approaches and biomarker development.

LEARNING OBJECTIVES

By the end of this section you will be able to:

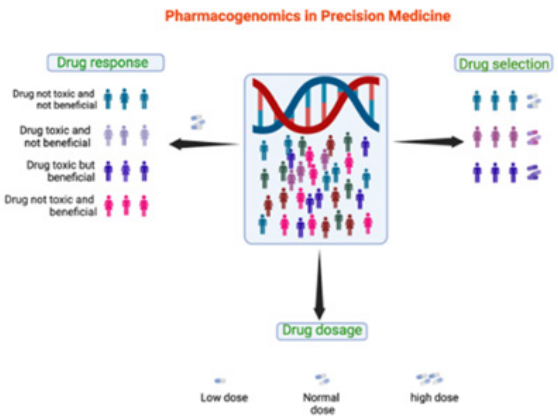
- Understand the ethical considerations attached to personalised medicine
- Gain critical insights into appropriate methodologies and ket considerations
- Critically reflect on current practice to seek new approaches
- Analyse and evaluate multi-modal data to identify high risk populations

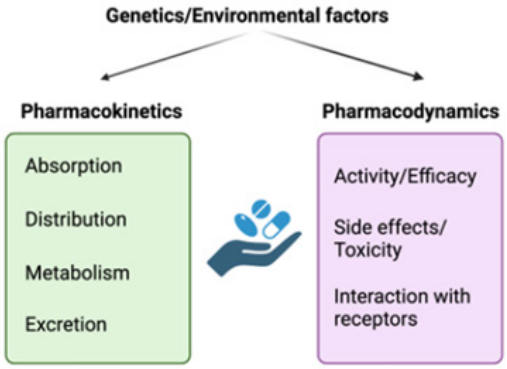
PHARMACOGENOMICS

Understanding drug response is crucial for precision in oncology. The variability in drug response is influenced by factors like pharmacokinetics and pharmacodynamics. Genetic and enviornmental variations impact how drugs interact with the body. Pharmacodynamics relates to the drug's action on the whole body, while pharmacokinetics pertains to how to body processes the drug.

Tumour denomic analysis aids in choosing therapies, predicting side effects, and determining the appropriate dosage. Besides genomics, host-related factors also play a role in drug response. Generally, tumour heterogeneity contributes more to pharmacodynamic variability than pharmacokinetics variability.

PHARMACOGENOMICS IN PRECISION ONCOLOGY





PHARMACOGENOMICS IN PRECISION ONCOLOGY

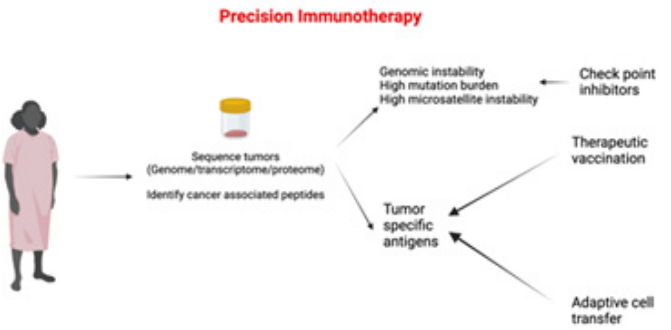
PRECISION IMMUNOTHERAPY

Immunotherapy is a cancer treatment that uses the patient's own immune system to fight cancer cells and potentially cure the disease. The main types of immunotherapy are checkpoint inhibitors, CAR T-cell therapy, and cancer vaccines.

However, the response to immunotherapy is not always good, and there are a number of factors that can affect this, including low participation in clinical trials, the lack of well-established biomarkers of response and, high costs.

To improve the effectiveness of immunotherapy, we need to identify patient-specific neoantigens or patient specific immune suppressive mechanisms. Advanced single-cell technologies, peptidomics can help us to invesitgate these mechanisms.

Additionally, it is important to understand how immunotherapy works in combination with other cancer treatments, such as radiotherapy and chemotherapy, so that we can develop more precise and effective treatment regimens in the future.



TYPES OF CANCER VACCINE

Cancer vaccines: There are two main types of cancer vaccines: prophylactic and therapeutic.

- Prophylactic vaccines: These are conventional vaccines that prevent infections by oncogenic viruses, such as the human papillomavirus (HPV) which can cause certain cancers.

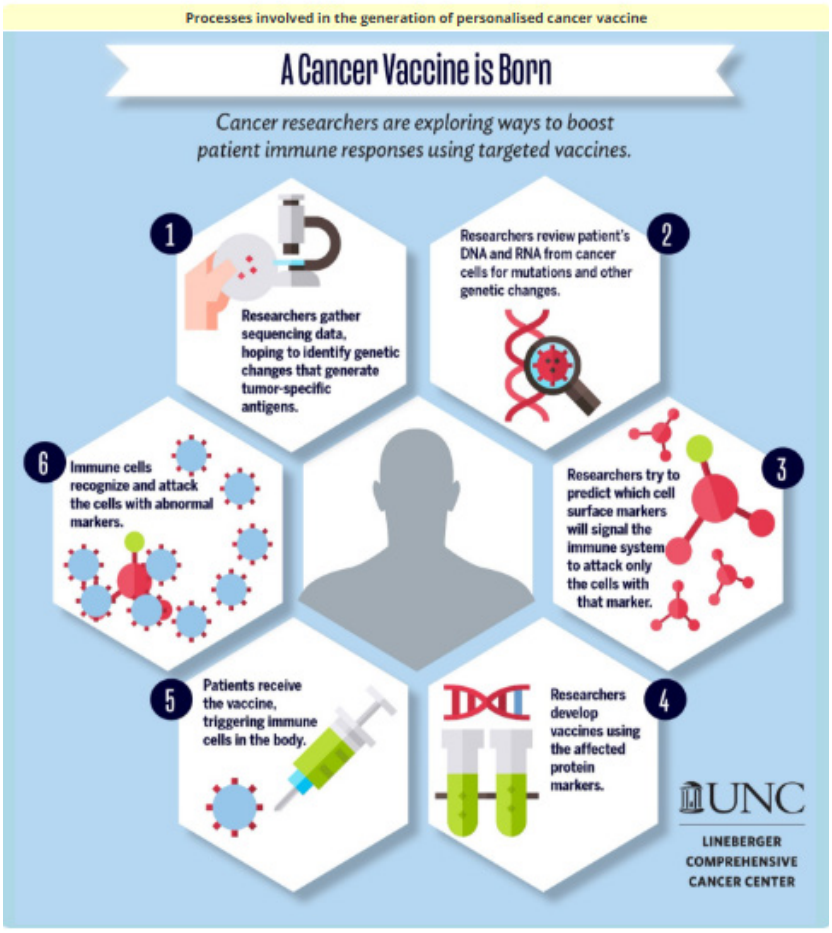
- Therapeutic vaccines: These vaccines harness tumour-associated antigens to boost the immune system and attack cancer cells. The source of these tumour-specific antigens can be whole tumours, tumour cells, proteins, peptides, DNA or RNA.

Therapeutic cancer vaccines can be further classified based on two factors:

- The identity of the tumour antigens: This refers to the specific molecules targeted by the vaccine.

- Whether priming of antigen-presenting cells occurs in situ or ex vivo: In situ priming happens within the body, while ex vivo priming occurs outside the body, for example, in a lab.

Anonymous antigens (those of unknown identity) can be co-localised with antigen-presenting cells either ex vivo or in situ. Predefined vaccines may require personalised approaches to target unique antigens, or they may be designed to target features shared across tumour types.

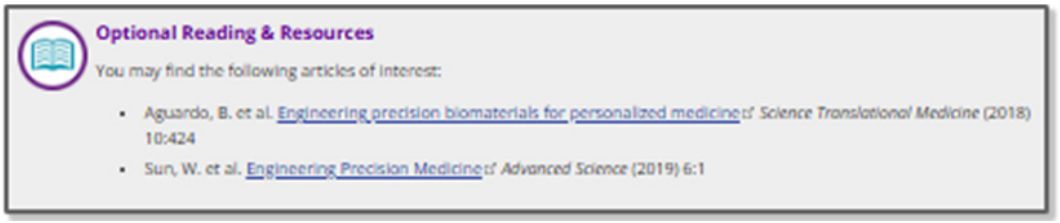


PROGNOSTIC BIOMARKERS

Understanding tumour biology is essential for developing effective and targeted cancer treatments. Inter and Intra patient heterogeneity, however, makes it difficult to achieve sustained responses. Biomarkers that can identify responders to specific treatments can help to avoid side effects in non-responders. In addition, identification of specific molecular alterations can also (e.g. BCR-ABL or HER2 amplification) can indicate treatment possibilities. The development and use of cancer biomarkers is therefore key to implementing precision oncology approaches. Biomarkers ar efeatures of tumour cells or the surrounding microenvironment that can be used to accurately diagnose, predict prognosis, or predict response to treatment.

Some of the prognostic biomarkers linked to different features of tumours in different types of cancers are listed here.

Somatic mutations	**Cellular Pathways**	**Gene expression**
Germline mutations	**DNA methylation**	**Serum protein levels**
Patient characteristics	**Cell surface phenotype**	**Image Biomarkers**



Optional Reading & Resources

You may find the following articles of interest:

- Aguardo, B. et al. Engineering precision biomaterials for personalized medicine// *Science Translational Medicine* (2018) 10:424
- Sun, W. et al. Engineering Precision Medicine// *Advanced Science* (2019) 6:1

SECTION SUMMARY

Identifying actionable targets remains a cornerstone of precision medicine, but tumour molecular profiling offers so much more. It informs personalised dosing, minimises side effects and guides optimal treatment choices. Leveraging engineering alongside omics data can dramatically accelerate the selection of the right treatment and the development of new drugs.

BRANCHES OF ONCOLOGY

MEDICAL ONCOLOGY

In this unit, over the next two weeks, we are going to be looking at how we give systemic treatment to patients with cancer, and how those treatments and treatment-pathways that would be over branches of oncology. In the second week, will look a little bit more at how these treatments are changing and might continue to change in the future, as oncology continues to develop. And you will have the chance to see two interviews with experts in the field. The aim of these two weeks is to think about and understand the guiding principles of medical oncology, how we assess a treatment plan for an individual patient and develop your problem solving skills.

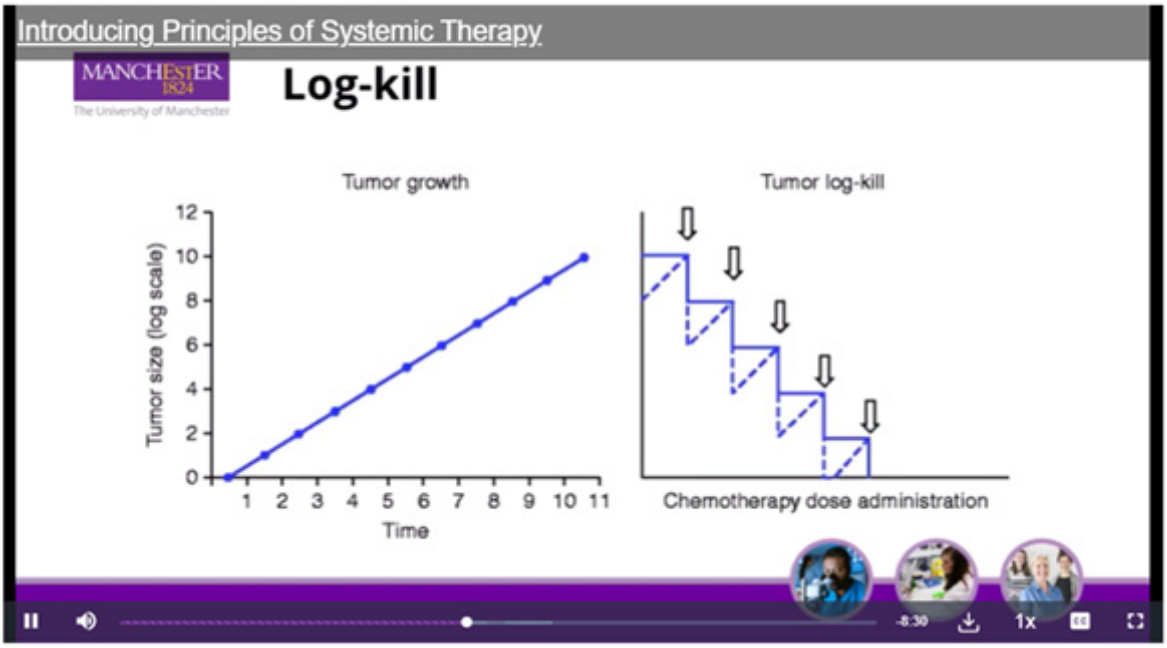
LEARNING OBJECTIVES

By the end of this section you will be able to:

- Explain the principles of medical oncology
- Assess the treatment needs of individual patients and construct an appropriate treatment plan
- Demonstrate efficient and effective problem-solving regarding treatment selection based on clinical evidence

DIFFERENT PATHWAYS OF SYSTEMIC THERAPY TREATMENT

This first video will introduce the key concepts behind the different ways systemic therapy is delivered.



Transcript Slides

Essential Reading

Please read the following article:

- DeVita, V. T. and Chu, E. (2008) A History of Cancer Chemotherapy *Cancer Research* 68(21) 8643-8653

Recommended reading

- Selli C. and Sims A. H. (2019) Neoadjuvant Therapy for Breast Cancer as a Model for Translational Research *Breast Cancer (Auckland)* Vol. 13

ACTIVITY: MATCH THE TREATMENT TYPE

The aim of this activity is to consolidate the knowledge from the video. Can you match the description of the patients' treatment to the type of treatment pathway?

Treatment Pathways

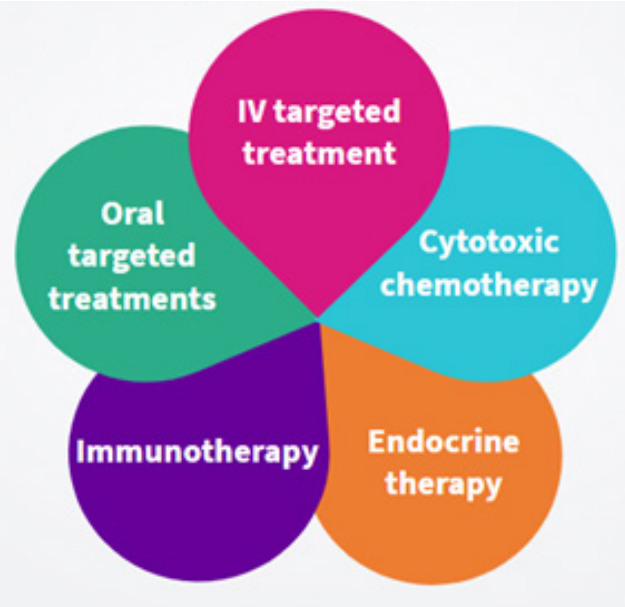
Can you match the description of the patients' treatment to the type of treatment pathway?

Please drag the boxes from the left to the spaces on the right, based on the corresponding descriptive text

Neoadjuvant	Treatment given without the intent of cure	
Support	This is treatment given before a main treatment, usually surgery, but sometimes chemotherapy	
Maintenance	Careful symptom management, may include psychological or nutritional support and physical symptom control	
Curative	Therapy given to maintain/lengthen the progression-free survival	
Adjuvant	Some cancers can be cured with systemic therapy alone, even in the metastatic setting	
Palliative	Given after a main treatment, often surgery.	

TYPES OF SYSTEMIC CANCER TREATMENT

Systemic cancer treatment can be broadly split into these groups.



Essential reading

Please read the following article:

- Kennedy, L. B. and Salama, A. K. S. (2020) A review of cancer immunotherapy toxicity *CA: a Cancer Journal for Clinicians* 70, 86-104

Recommended reading

- Loprinzi, C. L., Lacchetti, C. and Bleeker, J. et al. (2020) Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update *J Clin Oncol* 38:3325
- Hussaini, S. M. Q., Gupta, A. and Dusetzina, S. B. (2022) Financial Toxicity of Cancer Treatment *JAMA Oncol.* 8(5), 788

Padlet Activity: Potential challenges of treatment pathways

In the last activity we explored toxicity associated with systemic anti-cancer therapy. This can have a particular impact when a patient is undergoing several different types of treatment.

Identify three key challenges in the different treatment pathways we have explored. In no more than 200 words explain how systemic anti-cancer therapy toxicity may play a part in these challenges.

Share your answers on the **Padlet: Potential challenges of treatment pathways** found in the *Padlet: peer-shared activities* section on the Blackboard menu.

Discussion: Submit your questions for the Medical Oncology tutorial

Ahead of next week's optional synchronous tutorial, please submit any questions you may have in relation to cancer medicine. There will be an opportunity for you to ask your questions live. The session will be recorded and made available if you are unable to attend.

ESTABLISHED AND EXPERIMENTAL THERAPEUTICS

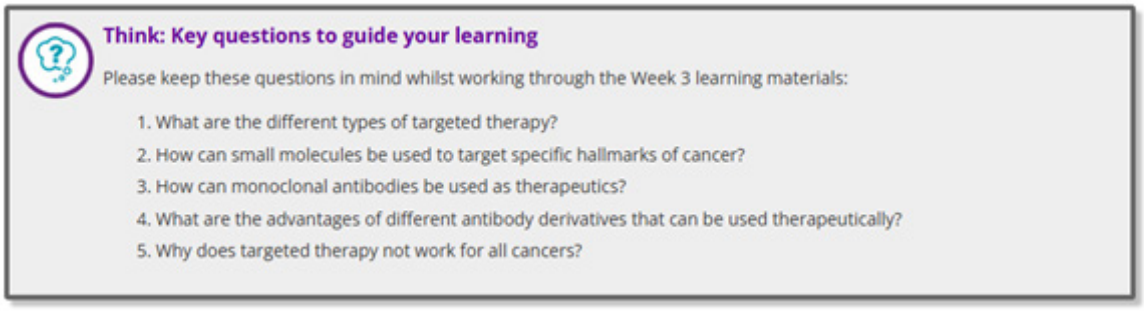
INTRODUCING TARGETED THERAPY

The focus of this section will be on targeted therapy. We'll explore how specific genetic and molecular vulnerabilities of cancer cells linked to various tumour hallmarks can be exploited as therapeutic targets. We'll discuss the strengths and limitations of two main types of targeted therapy: small molecules and antibody-based therapeutics. And in particular, given the success of antibodies within the clinical setting, we'll focus on examples of how antibody approaches work to eliminate cancer cells. This will link with learning from the first two weeks of this unit when we discussed a specific type of antibody therapy against immune checkpoints.

LEARNING OBJECTIVES

By the end of this section you will be able to:

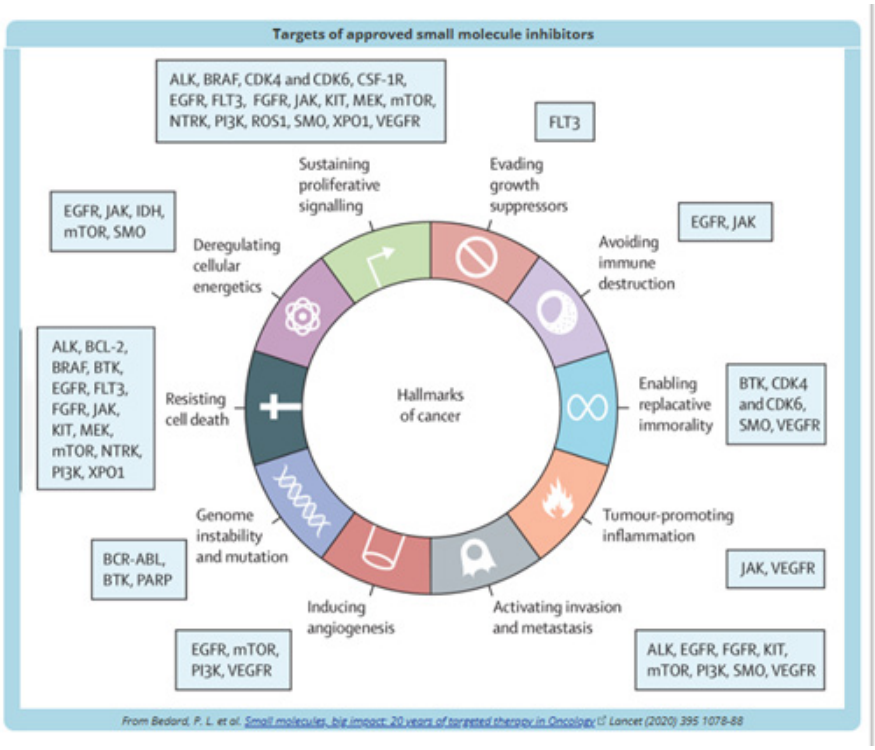
- Understand how specific molecular and genetic vulnerabilities can be used to therapeutically target cancer cells
- Have an insight into the range of different targeted therapies available
- Gain an understanding of the limitations of targeted therapy



PRINCIPLES OF TARGETED THERAPY

The principle of targeted therapy is to attack specific molecular vulnerabilities in cancer cells using either small molecules or monoclonal antibodies (mAb), which have more precise targeting effects than standard treatments such as chemotherapy. These approaches differ in their basic properties and have distinct mechanisms of action that elicit anti-cancer activity. The concept of molecularly targeted therapy is analogous to the 'magic bullet' concept first proposed by Paul Ehrlich in the 1800s. We will consider examples of small molecule and antibody based therapeutics to illustrate how this approach works.

Small molecule inhibitors have been developed that target a number of different vulnerabilities across a spectrum of cancer types. Based on the specific mutational and biological drivers that underpin the development of the given tumour type, small molecules may be used to target a variety of pathways (hallmarks), including those that regulate DNA damage/repair, cell death, oncogenic signalling, angiogenesis, endocrine signals, and metabolism. Examples of clinically approved targets are summarised below.



Essential Reading & Resources

Please read the following review paper which will provide a broad overview of small molecule targeted therapy approaches in cancer. **In particular, you should focus on the categories of small molecule inhibitor and lessons learned sections (the latter will be important later on when discussing mechanisms of resistance).** We expect you to have a good understanding of these aspects of the paper.

- Bedard, P. L. et al. Small molecules, big impact: 20 years of targeted therapy in Oncology *Lancet* (2020) 395 1078-88

Consider figure 3.3.1b

- **How can we use small molecule inhibitors to target specific hallmarks of cancer?**
- **How effective do you think targeting a specific hallmark will be?**
- **Is it better to use drugs which may target multiple hallmarks simultaneously?**

Recommended Reading

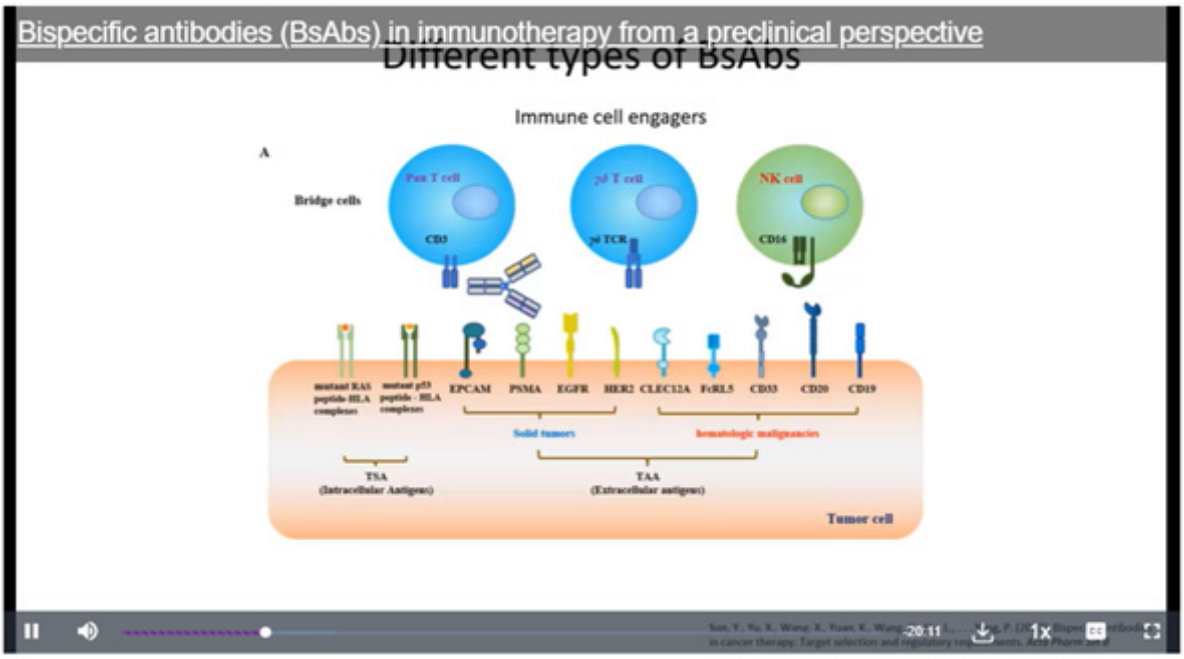
If you are interested and want to read more, this review also provides a good overview of current small molecule targeted therapy approaches:

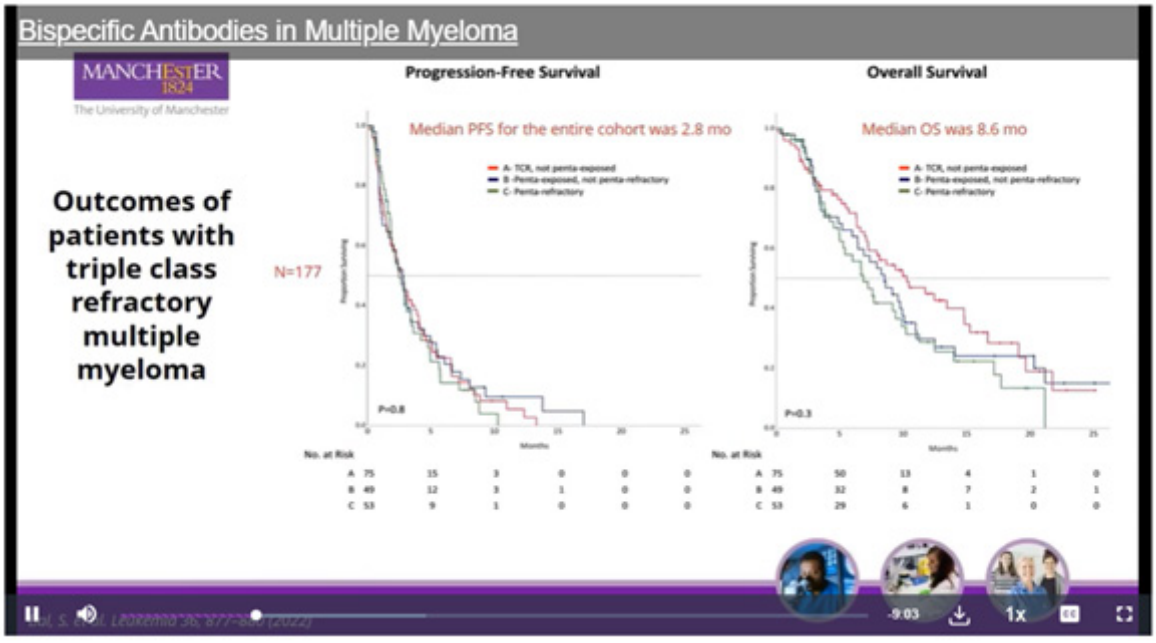
- Zhong, L. et al. Small molecules in targeted cancer therapy: advances, challenges and future perspectives *Signal Transduction and Targeted Therapy* (2021) 6(1) 201

BISPECIFIC ANTIBODIES AS AN EMERGING NEW FORM OF TARGETED THERAPY

We have heard previously about the use of monoclonal antibodies as a form of targeted therapy. Often antibodies are used because of their unique specificity for a defined target. Combinations of different antibodies can also be used to help enhance efficacy further. However, this approach can be refined through the use of bispecific antibodies, which can simultaneously engage two epitopes: one on the tumour cell and one on an immune effector cell, for example.

The following two recordings will provide more information on bispecific antibodies. First, Dr Xiaomeng Wang, a discovery scientist working on cancer immunotherapy, will provide an introduction to bispecific antibodies and how they work. Then Dr Emma Searle, a consultant haematologist at the Christie Hospital, will provide perspective on the clinical use of bispecific antibodies for the management of multiple myeloma.





Reading & Resources

Please read the following review which will give you an overview of how different antibody derivatives can be used therapeutically for the treatment of cancer:

- Jin, S. et al. Emerging new therapeutic antibody derivatives for cancer treatment *Signal Transduction and Targeted Therapy* (2022) 7, 39

We do not expect you to know everything covered in the review, but you are expected to have a good basic understanding of the different types of antibody derivative, and how they can be used as therapeutics.

These additional YouTube videos provide a brief overview of antibody structure and function:

- Therapeutic antibodies (Part 1): structure and function
- Therapeutic antibodies (Part 2): mechanism of action
- Therapeutic antibodies (Part 3): antibody-drug conjugates

If you cannot access YouTube, please see the transcript document for all three parts.

Transcript

3.3.4 Padlet Activity: Antibody Derivatives Analysis

Once you have read the Jin et al. review as a guide, consider the following classes of antibody derivative (you may need to carry out further research and reading).

- BiTE
- Antibody drug conjugate
- Antibody- fusion protein
- ScFv

For each, write a short definition (three or four sentences), describing the nature of the derivative, and the advantage of using this approach to target cancer cells. You should also include a specific example.

Once you have completed this, share your findings on the **Antibody Derivatives Analysis Padlet** found in the *Peer-shared Activities (Padlet)* section on Blackboard.

Read and respond to your peers' contributions, with the aim of identifying the strengths and limitations of each approach.

TRANSFORMATIVE ONCOLOGY

Through studying this fully online, part-time course, you will learn knowledge and skills to make a difference in the oncology field. Whether you are keen to further develop your understanding of the current models you are using in a pre-clinical setting; looking to move towards discovery, translational or data science or even into a patient-facing role.

manchester.ac.uk/transformativeoncology

studyonline@manchester.ac.uk