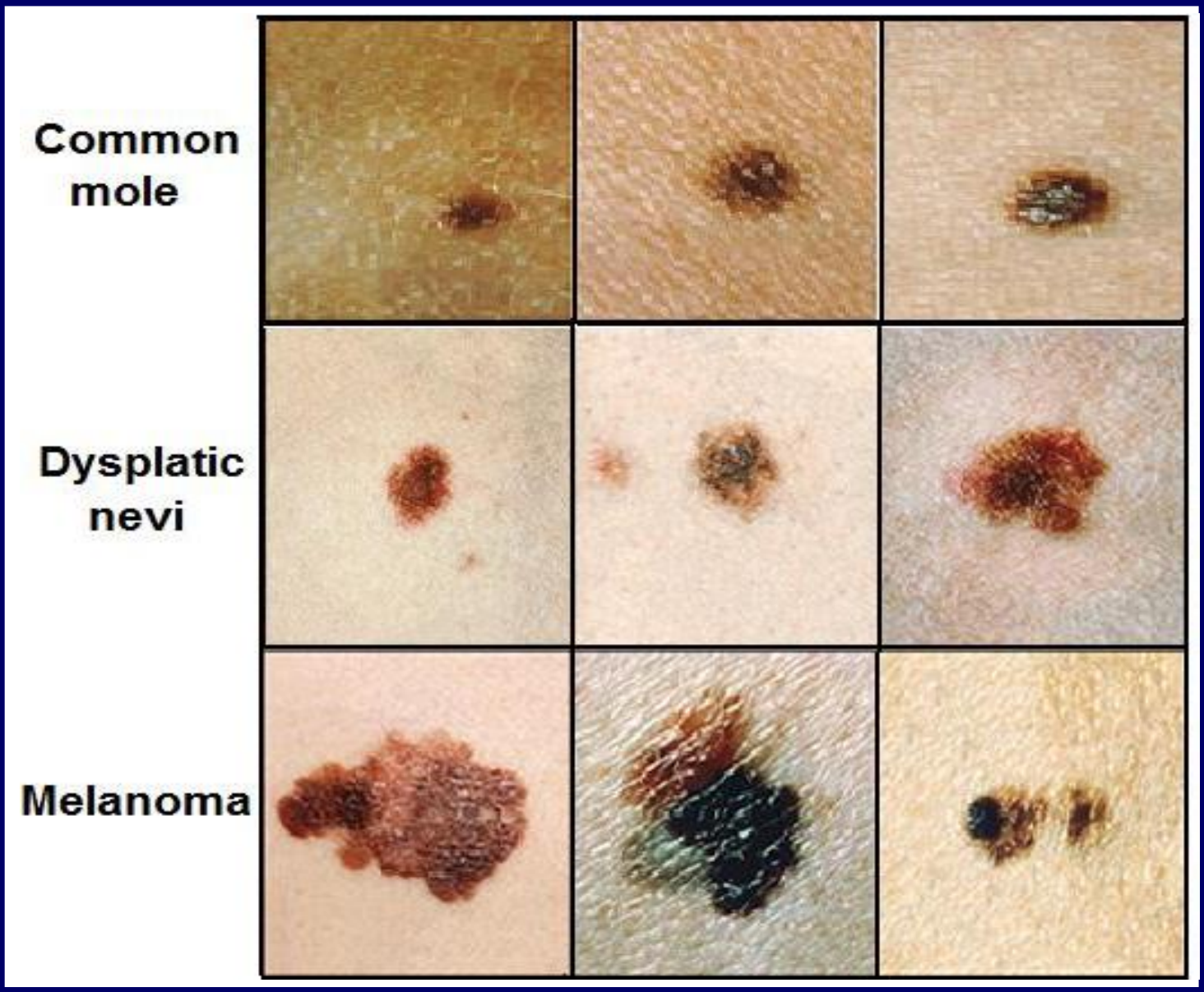


The **Scholars** Programme

The role of centrosomes in melanoma progression

2016-17

Teacher Name: Dr S. Patel

Pupil Name _____

The Scholars Programme – 2015/16 – Pupil Feedback Report

Grade	Marks	What this means
1st	70+	Performing to an excellent standard at **first year undergraduate level/A-level**
2:1	60-69	Performing to a good standard at **first year undergraduate level/A-level**
2:2	50-59	Performing to an excellent standard at **A-level/GCSE level**
3rd	40-49	Performing to a good standard at **A-level/GCSE level**
Workings towards a pass	0-39	Workings towards a pass
Did not submit	DNS	No assignment received

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

Name of Teacher	Dr S. Patel		
Title of Assignment	Compare and contrast the risk factors, preventative measures and prognosis (depending on tumour stage) of melanoma and a cancer of your choice. Explain whether there is a relationship between extra centrosomes and your chosen cancer (research-based evidence required).		
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 teacher should give an explanation in this section:

Learning Feedback Comment 1 -	
What you did in relation to this Key Learning Priority	**How you could improve in the future**
Learning Feedback Comment 2 -	
What you did in relation to this Key Learning Priority	**How you could improve in the future**
Learning Feedback Comment 3 -	
What you did in relation to this Key Learning Priority	**How you could improve in the future**
Resilience Comment	
How you showed learning resilience during the course	**How you could build learning resilience in the future**

Contents

Course Rationale Page 4
Mark Scheme Page 5
Glossary of Keywords Page 6
Additional Glossary of Keywords Page 7
Tutorial 1 Page 8
- True or false Page 8
- Think pair share Page 8
- Label the epidermis Page 10
- Tutorial 1 Homework – Baseline Test Page 10

Tutorial 2 Page 11
- Label the epidermis for changes driving melanoma Page 12
- Think pair share Page 13
- Tutorial 2 Homework Page 14

Tutorial 3 Page 15
- Tutorial 3 Homework Page 18

Tutorial 4 Page 20
- Tutorial 4 Homework Page 23

Tutorial 5 Page 24
- Label figure 7 Page 24
- Conclusion from figure 8 Page 25
- Conclusion from figure 9 Page 26
- Future studies Page 26
- Tutorial 5 Homework Page 27

Tutorial 6 Page 28
Bibliography Page 30
University Applications Guidance Page 32

Course Rationale

Skin cells called melanocytes have an important role in giving skin colour. Importantly, melanocytes protect us from the damaging effects of the sun ultraviolet (UV) rays. They do this by making pigment in unique structures called melanosomes which protect surrounding cells of the skin from DNA damage. Apart from their protective role, melanocytes are implicated in the most lethal form of skin cancer known as melanoma. Melanoma is one of the fastest growing cancers worldwide. The incident rate of melanoma has increased more rapidly in both the UK (5th most common cancer) and USA than any other cancer. Both environmental (exposure to UV) and genetic factors (individual's pigmentation tone, changes to DNA etc) appear to contribute to melanomagenesis whereby melanocytes accumulate genetic changes that lead to abnormal growth and spread.

Through this course you will initially learn the basics of melanocyte biology and in relation to my own research you will further learn about centrosomes (an important cellular organelle for accurate cell division) and how they are thought to have a role in melanoma progression. In the final stages of the course, you will produce an essay-based assignment on a cancer of your choice. In this essay you will address risk factors, preventative measures and prognosis depending on tumour stage and investigate whether there is any evidence for the role of centrosomes in that particular cancer. By the end of this course you will be exposed to how new scientific theories are tested and what conclusions could be drawn to assist future research.

Mark Scheme

Key Skill	1st	2.2
Research Skills	☐ All sources are correctly referenced in Harvard style. ☐ Uses reliable, relevant and balanced range of sources. ☐ Comprehensive research is evidenced; sources of information go beyond the obvious choices and those suggested throughout the course. ☐ Evidence of in-depth research highlighting comparative and contrasting factors between two different cancers.	☐ Sources are mostly but not always referenced correctly. ☐ A limited range of sources have been used. ☐ Sources used may be unreliable; inappropriate for the subject; limited attempt made to balance these with other sources. ☐ Evidence of incomplete research highlighting comparative and contrasting factors between two different cancers.
Language/content	☐ Scientific vocabulary is used correctly and effectively - shows a detailed understanding of the concepts covered. ☐ Accurate and complete findings on the cancer of choice.	☐ Uses simple vocabulary effectively but struggles with more challenging vocabulary. ☐ Scientific vocabulary may be used incorrectly at times. ☐ Incomplete findings on the cancer of choice.
Communication	☐ Essay has an organised and logical sequence. ☐ Almost faultless spelling, punctuation and grammar. ☐ Writing is of an appropriate style for the scientific document and follows stylistic techniques.	☐ Parts of the essay are poorly organised and lacks a coherent structure. ☐ Spelling, punctuation and grammar are weak in places. ☐ Inconsistent use of style throughout a complete document which results in a lack of clarity.

Glossary of Keywords

Aneuploidy – when cells acquire a change in chromosome numbers.

Basement membrane (skin) – A specialised matrix that forms a sheet separating epithelial cells from stromal cells. For example, found between the junction of the epidermis and dermis in the skin.

Benign nevus – This lesion consists of abnormally proliferating melanocytes that have acquired oncogenic mutations such as in $BRAF^{V600E}$ (50-60% cases) and NRAS (15-20% cases).

Centrosome – An organelle in the cytoplasm that contains two centrioles and has a role in generating the bipolar spindle for correct segregation of the genetic material.

Centrosome amplification – When more than two centrosomes are generated.

DNA – The genetic material of cells.

Melanin – A pigment (yellow-red, brown-black) synthesised by melanocytes**.**

Melanogenesis - The process by which melanin is synthesis.

Melanoma (skin) – This is the most lethal type of skin cancer that arises due to transformation of melanocytes in the epidermal layer of the skin.

Melanosomes – These contain melanin and are found in the cytoplasm of melanocytes. Once matured, they are subsequently transferred to surrounding keratinocytes to impart pigmentation.

Metastatic – The spread of cancer cells to other sites of the body from the origin of the tumour.

Oncogenes – Genes that can transform cells (cancer-inducing).

Radial growth phase (RGP) – Stage of melanoma in which the transformed cells spread within or near the epidermis and do not invade the deeper dermis as their growth is keratinocyte-dependent.

Senescence – A phenomenon whereby normal cells reach a stage of irreversible growth arrest due to their limited proliferative lifespan.

Skin melanocyte – These are specialised cells that reside in the epidermis and hair follicles and have an important role in giving skin and hair colour, respectively.

S-phase – A phase of the cell cycle in which both the DNA and centrosome are duplicated.

Tumour suppressor genes – Genes whose inactivation (partial or complete) leads to an increased chance of cancer development.

Tumour progression – Multi-step process of transforming a normal cell into a tumour cell.

Vertical growth phase (VGP) – Stage of melanoma in which the transformed cells invade the deeper dermis and are capable to metastasise.

Additional Glossary of Keywords

Tutorial 1 – Skin anatomy

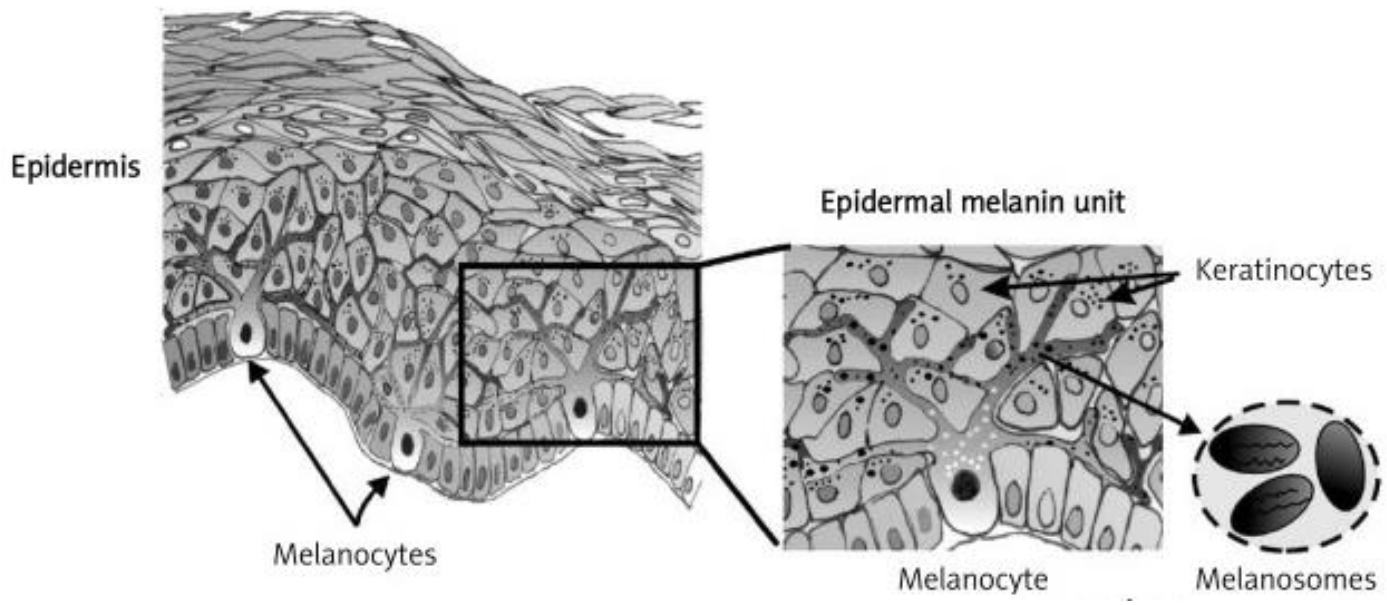


Figure 1 – Structure of the epidermis. Melanocytes transfer melanosomes through their dendritic processes to the surrounding keratinocytes. The ratio of melanocyte to keratinocytes in the epidermal basal layer is around 1:10 and changes in the epidermal melanin unit to around 1:30-40. Figure taken from Cichorek et al. (2013).

What is the Purpose of Tutorial 1?

- To give students an overview of the course.
- To introduce the anatomy of the skin.

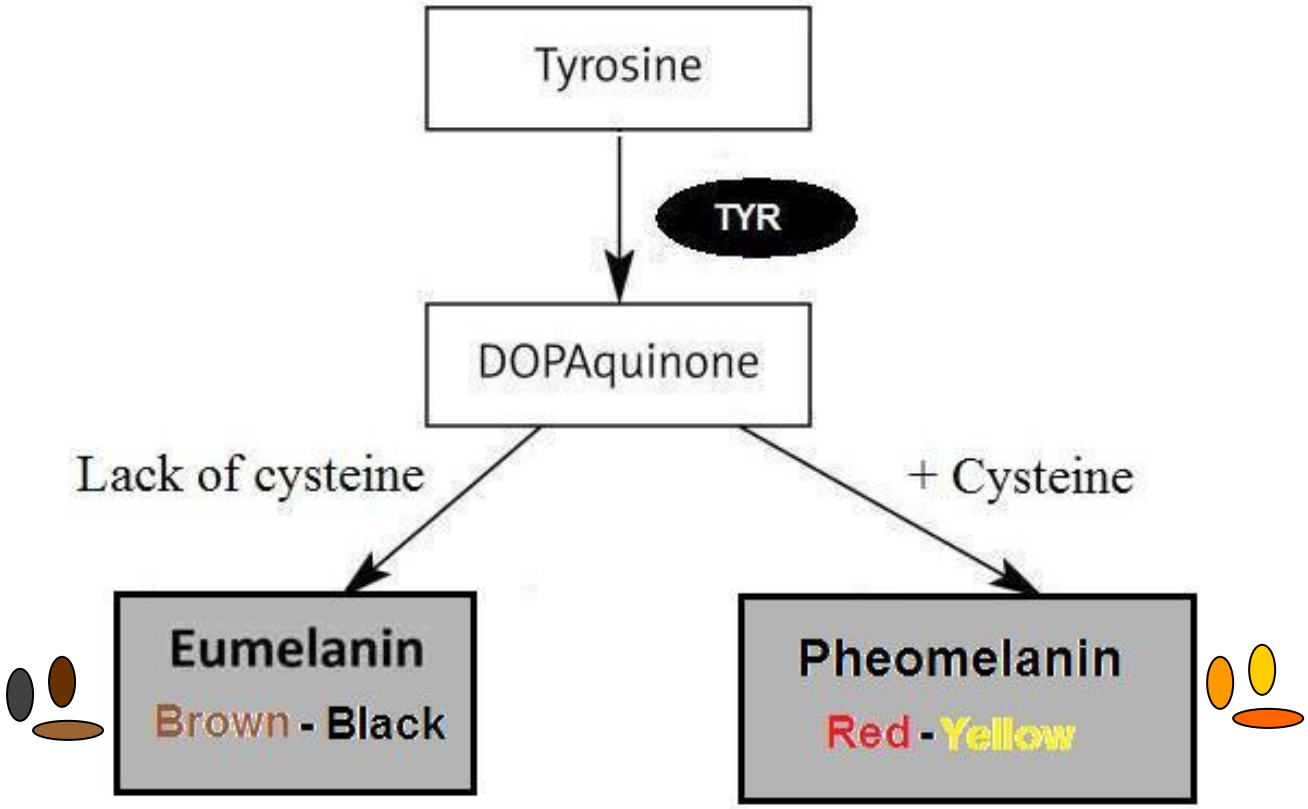
True or false

1. Skin is the largest organ in the body. (T/F)
2. Our skin weighs around 5Kg. (T/F)
3. The thickness of skin varies from 0.5cm to 4.0 cm. (T/F)
4. People who have more than 50 moles have a greater chance of developing melanoma. (T/F)
5. People with fair skin are more likely to develop melanoma. (T/F)

Think pair share

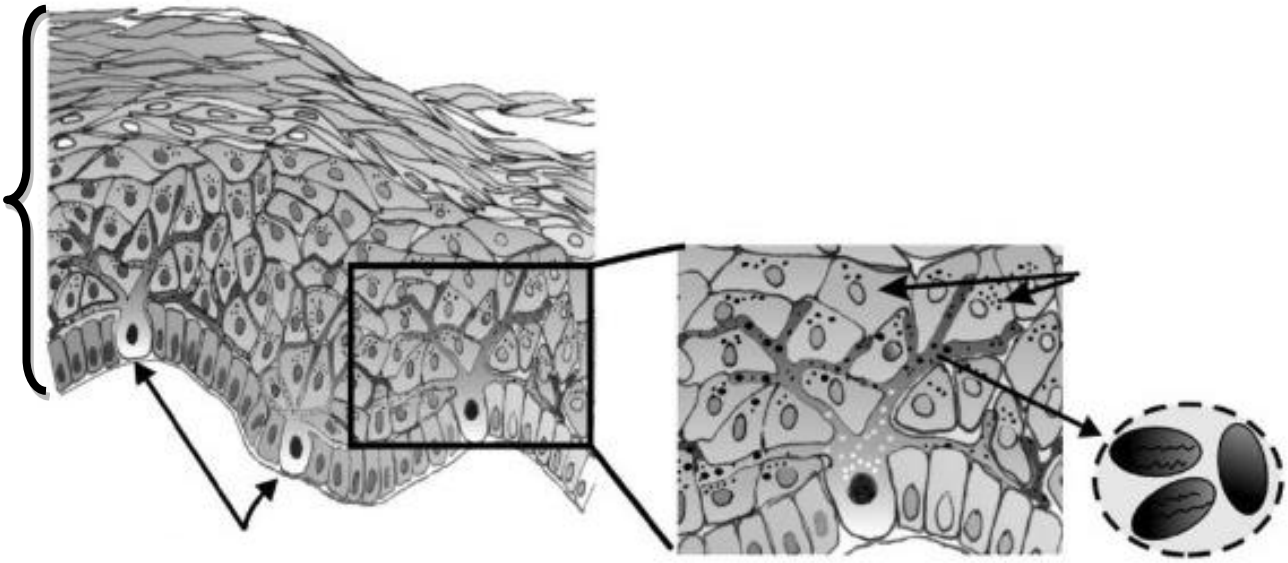
What gives us all a different skin colour?

Melenogenesis



Notes:

Label the epidermis



Melanocytes	Melanosomes	Keratinocytes	Epidermal melanin unit	Epidermis

Tutorial 1 – Baseline Test/Homework

The homework assignment for the first tutorial is a baseline test to see your initial level of attainment in this subject area. The assignment will test for some or all of the subject specific skills that are required later in the final assignment. However, it is shorter than the final assignment and will be an introduction to the subject as well as a challenge!

Do not worry too much about doing 'well' or 'badly' on the baseline test, it takes into account the fact that you may not be familiar with the subject area. It is designed to help you and your teacher identify where you are at the start of the programme and to help you measure your progress along the way.

Task 1: In less than 500 words describe the cell cycle (Interphase – G1/S/G2 and mitosis). Make sure to include key events that take place in each phase. Briefly describe how centrosomes ensure correct partition of the DNA?

Task 2: For a cancer of your choice briefly note down the progressive stages of cancer development.

Refer to www.cancerresearch.co.uk as a starting point.

Tutorial 2 – Stages of melanoma progression

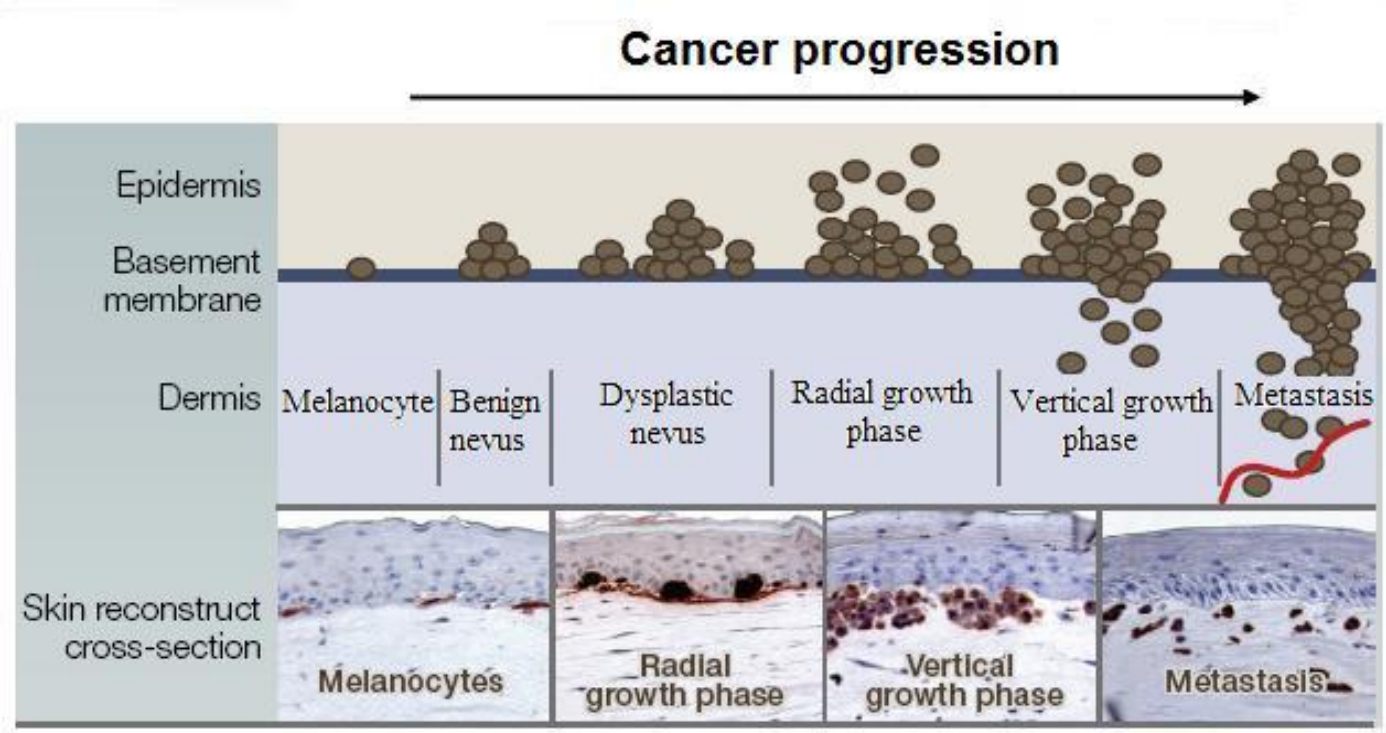


Figure 2 – Brief graphical presentation of melanoma progression. Figure taken from Vultur, Herlyn (2013).

What is the Purpose of Tutorial 2?

- To understand the stages (melanocyte-RGP-VGP-melanoma) of melanoma progression.

Senescence

Before we look at the different stages of melanoma progression it is important to understand that senescence is an anti-cancer mechanism that our cells possess. Cellular senescence was first described by Hayflick (Hayflick, Moorhead 1961) as a phenomenon whereby normal cells reach a stage of irreversible growth arrest due to their limited proliferative lifespan. In somatic cells, cellular senescence is also induced due to the accumulation of unrepaired DNA and the expression of oncogenes such as $BRAF^{V600E}$ (Michaloglou et al. 2005). Cancer cells have to evade senescence in order to replicate indefinitely.

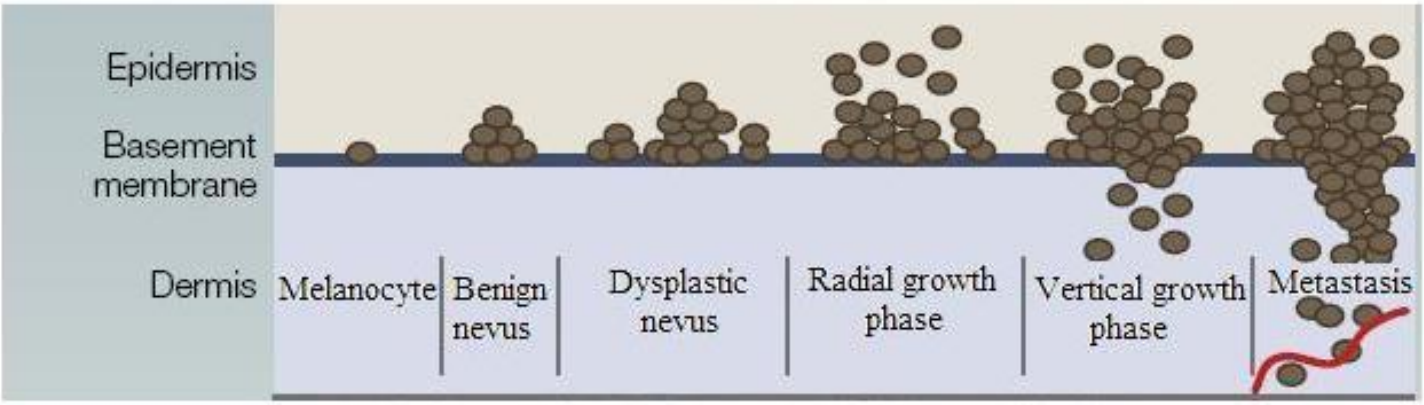
Notes:

Stages of melanoma

The formation of the benign nevus marks the first step in **melanomagenesis.** This lesion consists of abnormally proliferating melanocytes that have acquired oncogenic mutations such as in $BRAF^{V600E}$ (50-60% cases) and NRAS (15-20% cases) (Giuliano et al. 2011, Bennett 2008). As a result, oncogene-induced senescence is triggered via the expression of p16 (tumour suppressor protein). The next stage of melanoma progression is the **dysplastic nevi** in which one functional copy of p16 may be lost (Soo et al. 2011). This results in delayed senescence which allows the nevus to grow further until senescence is triggered by the remaining functional allele of p16 or p53 (another tumour suppressor protein) (Soo et al. 2011).

Further aberrations to the p16 pathway leads to the radial growth phase (RGP) of melanoma in which the second copy of p16 may also be lost. RGP cells spread within or near the epidermis and do not invade the deeper dermis as their growth is keratinocyte-dependent (Soo et al. 2011). The final stage of melanoma progression is known as the vertical growth phase (VGP). VGP cells invade the deeper dermis and are capable to metastasise (Soo et al. 2011). This phase is no longer dependent on keratinocytes and thus requires further defects that repress **apoptosis**, for example, loss of PTEN (Soo et al. 2011).

Label the epidermis for changes driving melanoma



1) one copy of p16 lost
2) BRAF and NRAS mutations
3) second copy of p16 lost
4) This stage is not dependent on keratinocytes
5) This stage is dependent on keratinocytes

Think pair share

Which stage of melanoma do you think would be the hardest to treat? Why?

Summarise some of the changes acquired by melanocytes in order to become cancerous.

Notes:

Tutorial 2 – Homework: Answer the below questions

1. What are centrosomes?

2. In a non-dividing cell how many centrosomes would you expect to see?

3. In a cell undergoing cell division how many centrosomes would you expect to see?

4. If a cell had three centrosomes would it be abnormal? If yes, why?

Tutorial 3 – Normal Vs extra centrosomes

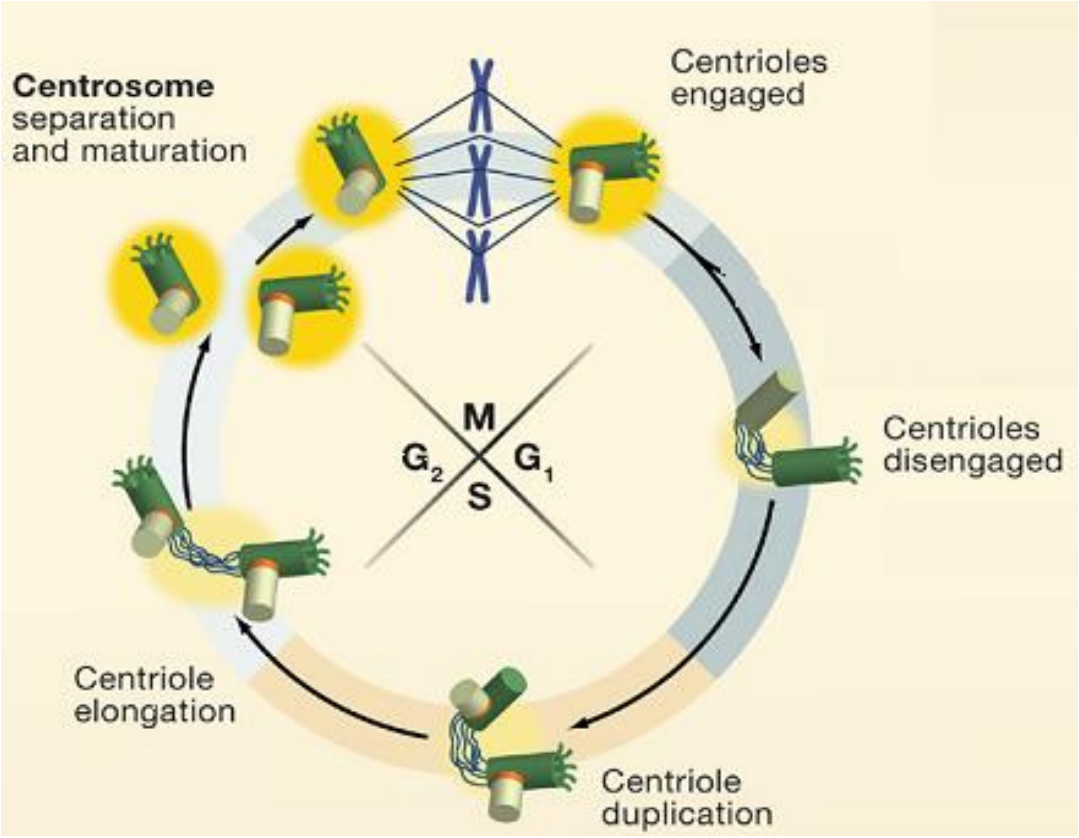


Figure 3: The centrosome duplication cycle. Figure taken from Nigg, Raff (2009).

What is the Purpose of Tutorial 3?

- To understand how a cell may acquire extra centrosomes in different ways.

Under normal conditions, during every cell cycle the centrosome duplicates only once, as shown in **Figure 3**, and is regulated to be in coordination with the DNA replication cycle (Tsou, Stearns 2006, Hinchcliffe, Sluder 2001).

Centrosome numerical defects

There are a number of ways in which may result the cell to acquire extra centrosomes. Firstly, if the centrosome cycle becomes deregulated then more than one round of centrosome duplication can occur within the same S-phase (termed centrosome overduplication - **Figure 4A**). Secondly, the cell may fail cytokinesis and as a consequence the daughter cell inherits two centrosomes/four centrioles with tetraploidy (termed centrosome accumulation - **Figure 4B** (Nigg, Raff 2009). Thirdly, duplicated centrosomes could split due to the abrogation of the mechanism underlying centriole pairing. This leads to uncontrolled splitting of the paired centrioles, which results in the generation of three or four separate organelles each of which might be counted as an individual centrosome **(Figure 4C).**

There are other mechanisms but for the purpose of simplification we will not discuss all.

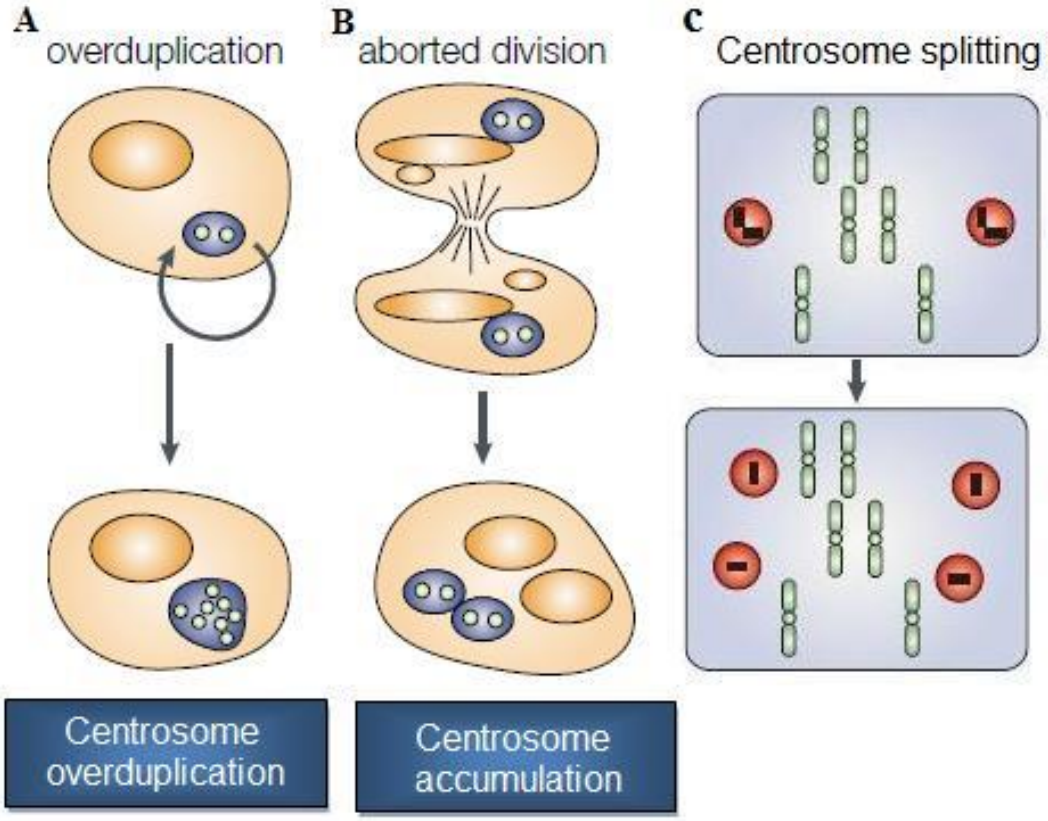


Figure 4 – Centrosome amplification. **(A)** Deregulated centrosome duplication within the same S-phase can lead to centrosome overduplication. **(B)** Failure of cell division can lead to the accumulation of centrosomes with tetraploidy. **(C)** Cell containing two normal centrosomes vs. split centrioles that generates extra centrosomes. Figure taken from Nigg (2002).

Extra centrosomes and cancer

The link between extra centrosomes and cancer was first mentioned over a century ago by Boveri (1914). He hypothesised that abnormal centrosome numbers would result in **multipolar spindles (Figure 5)**, potentially disturbing the process of equal chromosome distribution leading to malignancy. Indeed, the vast majority of cancer cells display centrosome aberrations in terms of acquiring extra or "supernumerary" centrosomes, that is more than two (termed centrosome amplification) (D'Assoro, Lingle & Salisbury 2002, Brinkley 2001). It has become increasingly apparent that supernumerary centrosomes are not only indicative of malignancy but from emerging evidence they may also drive malignant transformation (Ogden, Rida & Aneja 2013, Nigg 2006).

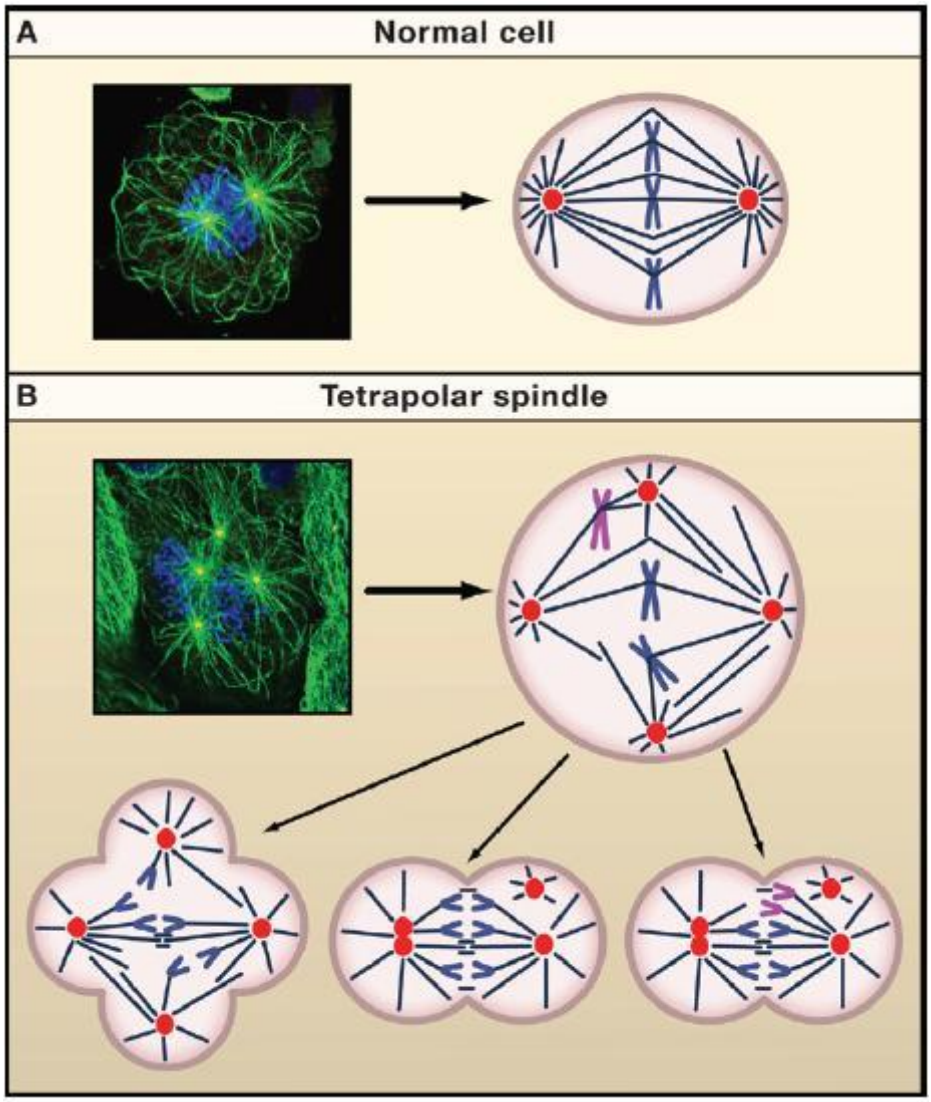


Figure 5 – Spindle formation in normal vs. abnormal cell with extra centrosomes. Figure taken from Nigg, Raff (2009).

Notes:

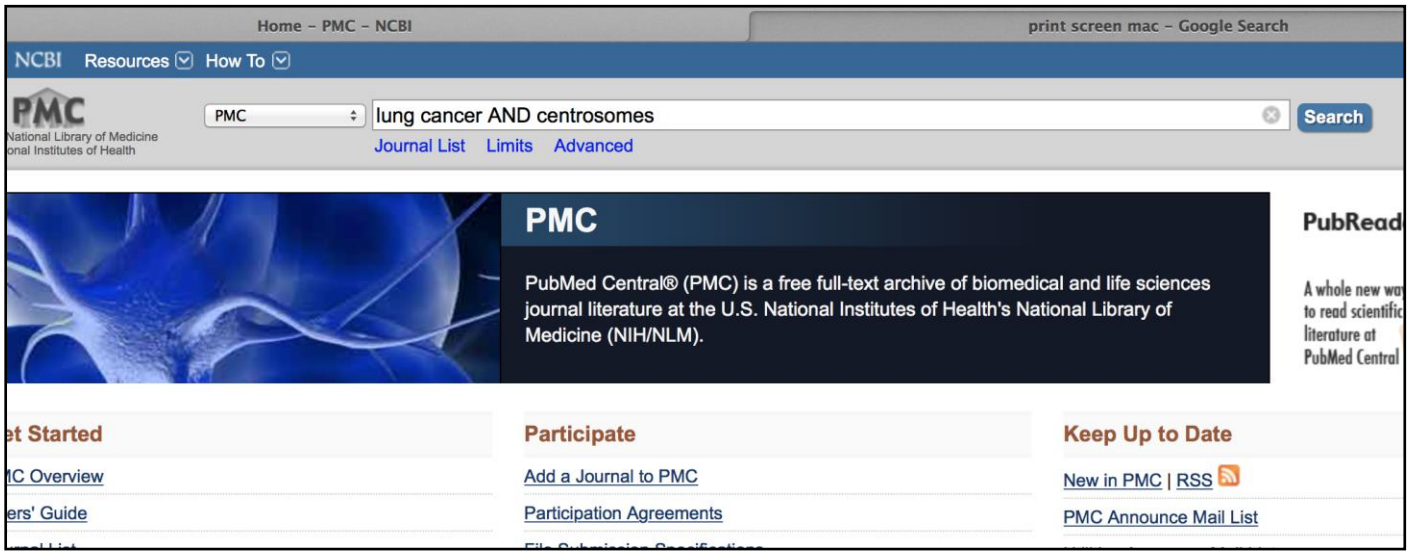
Tutorial 3 – Homework:

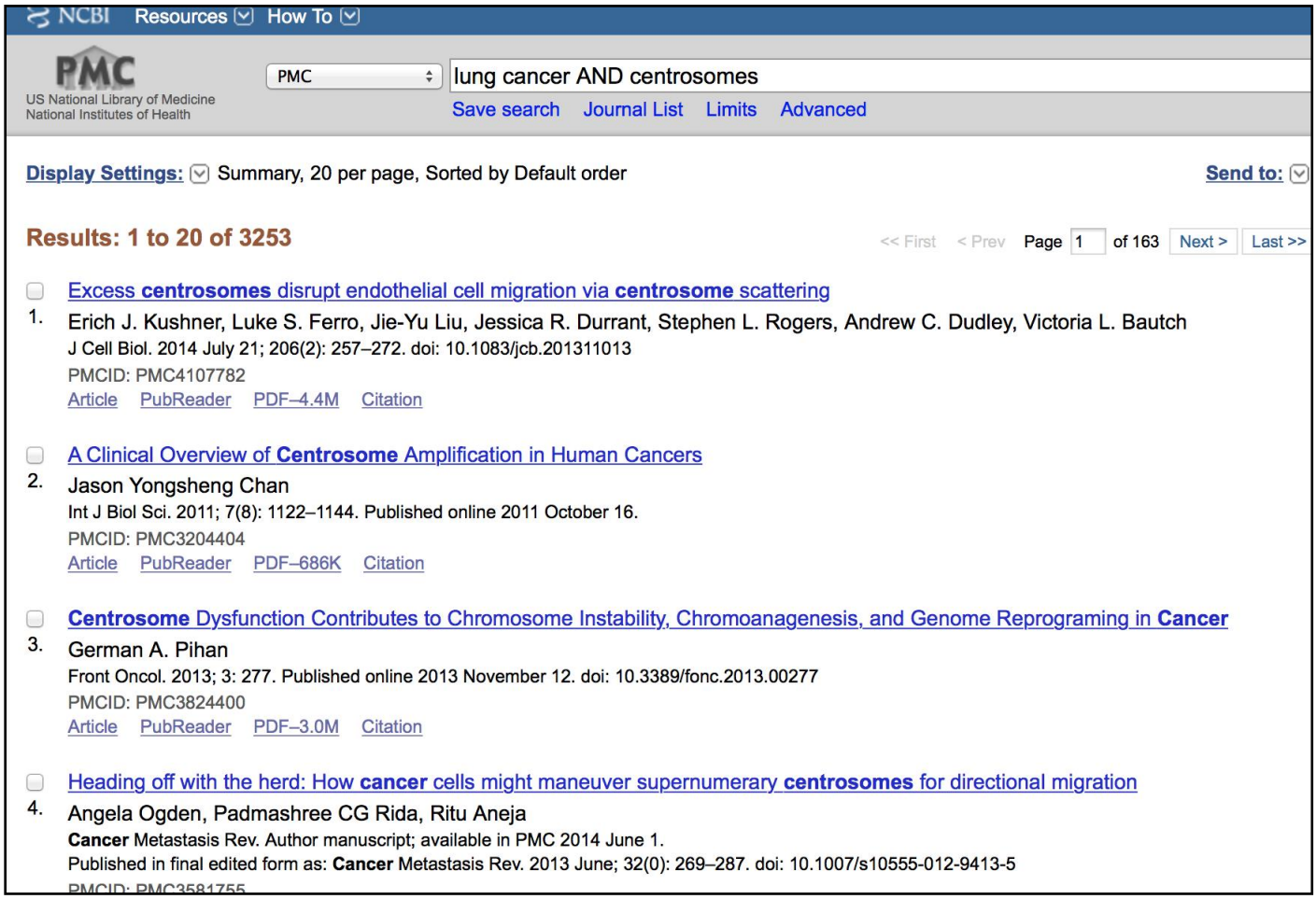
From the current literature (pubmed central) find at least three research papers describing a connection between extra centrosomes and cancer. Select at least three different cancers. Summarise the key findings of each paper.

Extra guidance:

Website: http://www.ncbi.nlm.nih.gov/pmc/

In the search text type the cancer of your choice + (AND) centrosomes





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Int J Biol Sci. 2011; 7(8): 1122–1144.
Published online 2011 Oct 16.
PMCID: PMC3204404

A Clinical Overview of Centrosome Amplification in Human Cancers

Jason Yongsheng Chan[✉]

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Abstract

Go to:

The turn of the 21st century had witnessed a surge of interest in the centrosome and its causal relation to human cancer development - a postulate that has existed for almost a century. Centrosome amplification (CA) is frequently detected in a growing list of human cancers, both solid and haematological, and is a candidate "hallmark" of cancer cells. Several lines of evidence support the progressive involvement of CA in the transition from early to advanced stages of carcinogenesis, being also found in pre-neoplastic lesions and even in histopathologically-normal tissue. CA constitutes the major mechanism leading to chromosomal instability and aneuploidy, via the formation of multipolar spindles and chromosomal missegregation. Clinically, CA may translate to a greater risk for initiation of malignant transformation, tumour progression, chemoresistance and ultimately, poor patient prognosis. As mechanisms underlying CA are progressively being unravelled, the centrosome has emerged as a novel candidate target for cancer treatment. This Review summarizes mainly the clinical studies performed to date focusing on the mechanisms underlying CA in human neoplasia, and highlights the potential utility of centrosomes in the diagnosis, prognosis and treatment of human cancers.

Keywords: Boveri hypothesis, chromosomal instability, aneuploidy, centrosome, aurora kinase, p53

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Simultaneous Aurora-A/STK15 overexpression and centrosome amplification induce chromosomal instability i [BMC Cancer. 2007]

The centrosome in normal and transformed cells. [DNA Cell Biol. 2004]

Centrosome amplification in tumorigenesis. [Cancer Lett. 2012]

See reviews...

See all...

Cited by other articles in PMC

Loss of KLF14 triggers centrosome amplification and tumorigenesis [Nature Communications. 1/01]

Notes:

Tutorial 4 – Extra centrosomes in melanoma progression

What is the Purpose of Tutorial 4?

- To understand how scientific hypothesis are drawn.
- To introduce a few hypothesis on extra centrosomes and melanoma progression.

At this stage you will appreciate the connection between extra centrosomes and cancer and how there has been an increased focus in this field of research. Currently there have been no studies focusing on centrosomes in melanoma progression. However, we do have evidence in the literature for a role of p16 in centrosome duplication. Therefore, my own research focused on investigating whether there was a correlation between extra centrosomes and melanoma stage. Secondly, I wanted to know whether p15 (a tumour suppressor protein that has the same molecular functions as p16 – previously discussed) had a role in controlling centrosome duplication in melanocytes. Some of the objectives of my study were:

1. To find out if cells from later stages of melanoma progression display a higher proportion of centrosome numeric abnormality (3 or more centrosomes).
2. To then analyse whether the expression or deficiency of p15 and/or p16 correlates with centrosome numeric integrity across each disease stage (melanocyte– RGP – VGP – metastatic melanoma).

Methods used to answer my questions

I first selected around 5 cell lines (a strain of cells that have been adapted to grow indefinitely **in culture**) from each stage of melanoma.

1. To find out if cells from increasing stages of melanoma progression would display a higher proportion of centrosome numeric abnormality, **immunocytochemistry** was utilised to observe the number of cells with more than two centrosomes in all cell lines. Centrosomes were identified by staining the cells for **γ-tubulin**. **Figure 6** shows the immunocytochemistry images of centrosome staining in **HeLa cells** which do not display any centrosome numeric abnormality. This was a **control experiment**. The main results will be discussed in the next tutorial.
2. Secondly, to investigate a link between p15 and/or p16 and centrosome duplication I examined the p15 and p16 protein expression status - determined by **Western blotting** - in all selected cell lines derived from various stages of melanoma progression (melanocytes to melanoma).

Notes on methods:

Immunocytochemistry -

Western blotting -

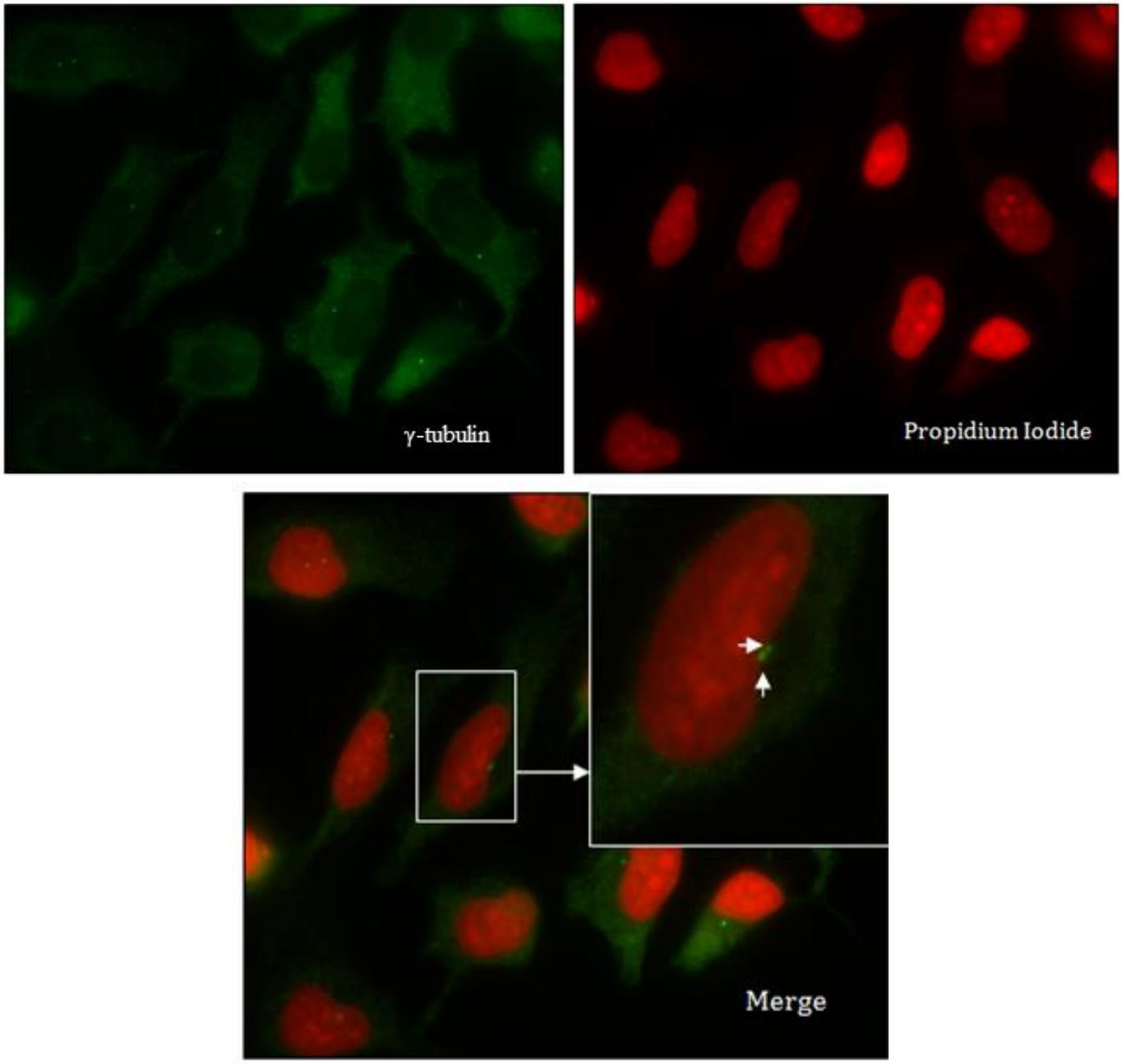

Figure 6 - Immunostaining on HeLa cells (control cells without abnormal centrosome numbers). γ-tubulin (green) to identify centrosomes, propidium iodide (red) to stain nuclei and arrows in the merge panel indicate centrosomes at higher magnification.

Tutorial 4 – Homework: Draft Assignment

To complete a draft plan of the final assignment (must include the research part).

Points for consideration:

- Look through the mark scheme on page 6.
- Finalise which will be your cancer of choice.
- Start thinking about the layout of your essay (which subheadings will you have?)
- Have you considered a range of sources to extract all the relevant information?
- Are you able to reference according to Harvard style? Note that this handbook has been referenced in Harvard style throughout and an example bibliography can be found on page 30.

Tutorial 5 – Data analysis and conclusions

What is the Purpose of Tutorial 5?

- To analyse some original data.
- To evaluate and draw conclusions from the data.
- To understand how future studies are formulated.

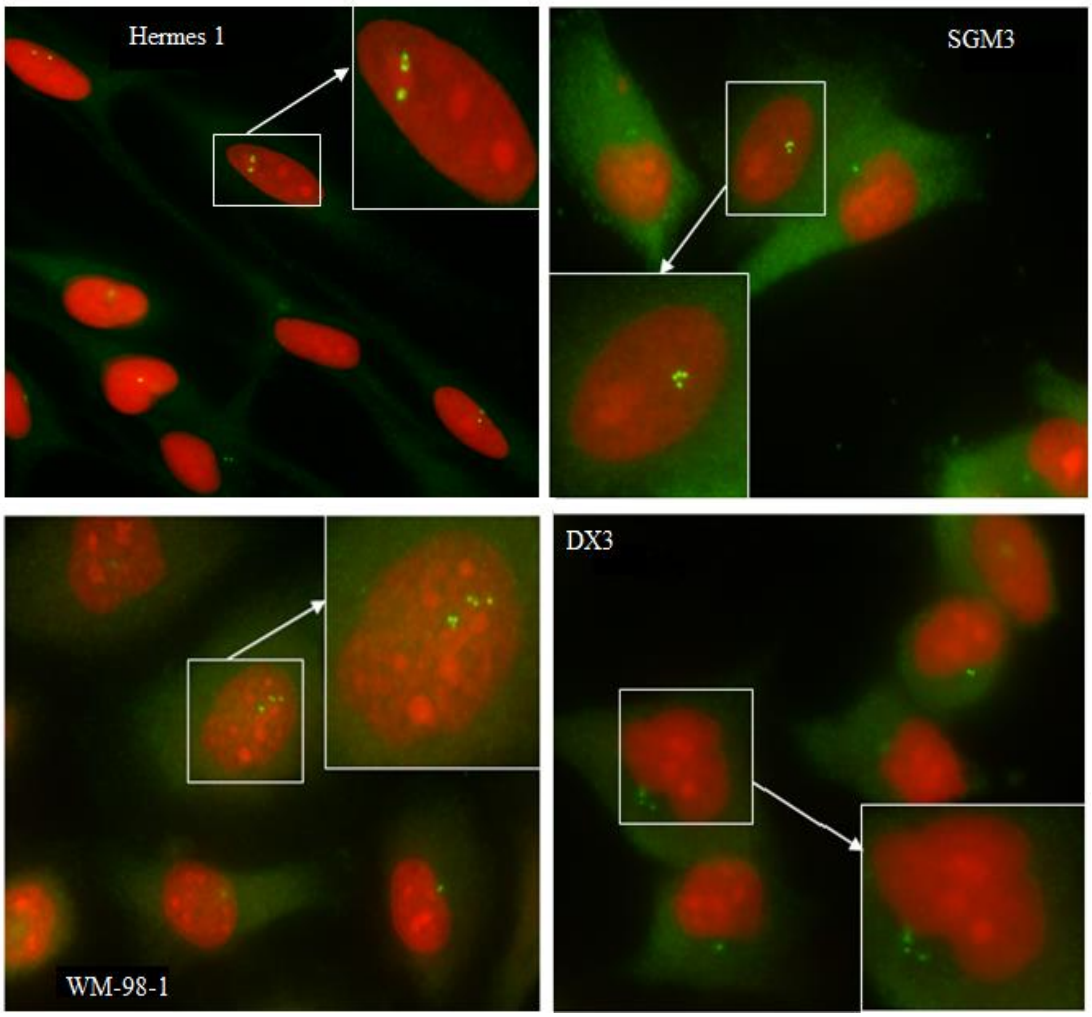

Figure 7 - Immunostaining of centrosomes (γ-tubulin, green) and nuclei (propidium iodide, red). All insets show centrosomes at a higher magnification. **Hermes I –** melanocyte cell line**; SGM3 –** RGP cell line**; WM-98-1 –** VGP cell line**; DX3 –** melanoma cell line.

The above figure shows immunocytochemistry images from four different cell lines. It is important to note that although all four have cells with extra centrosomes they also contain normal cells with the expected number of centrosomes.

Task – label on the above diagram which cells are normal and which are abnormal in terms of centrosome numbers.

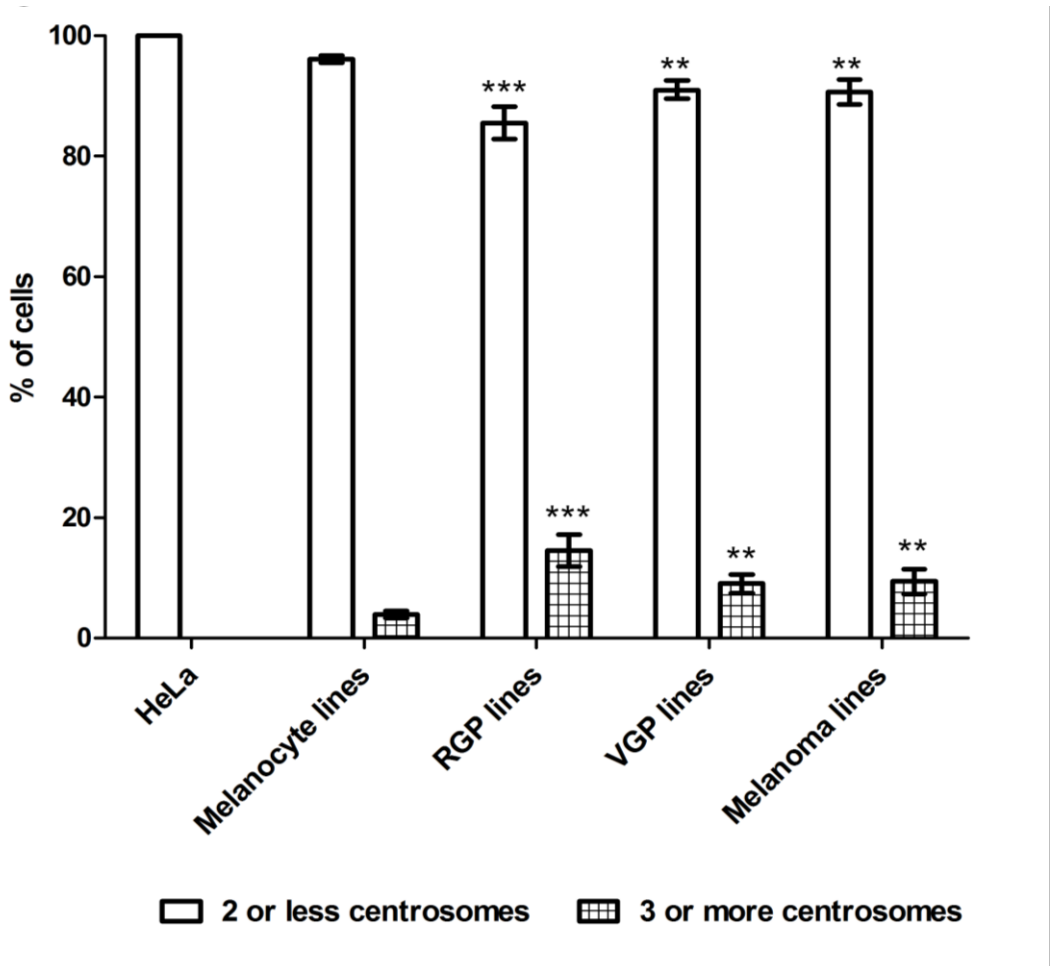

Figure 8 - Combined data by tumour stage showing the proportion of centrosome abnormality (3 or more centrosomes). Average percentage of cells with 2 (or <) or 3 (or >) centrosomes across five melanocyte lines, five RGP lines, four VGP lines and three melanoma lines. Statistical significance is marked as $p<0.05$ (*), $p<0.01$ (**) and $p<0.001$ (***). The level of statistical significance shown is that relative to the % of cells in melanocyte lines for each category (2 or less and 3 or more centrosomes).

Task – From figure 8 what conclusion can you draw?

-
-
-
-

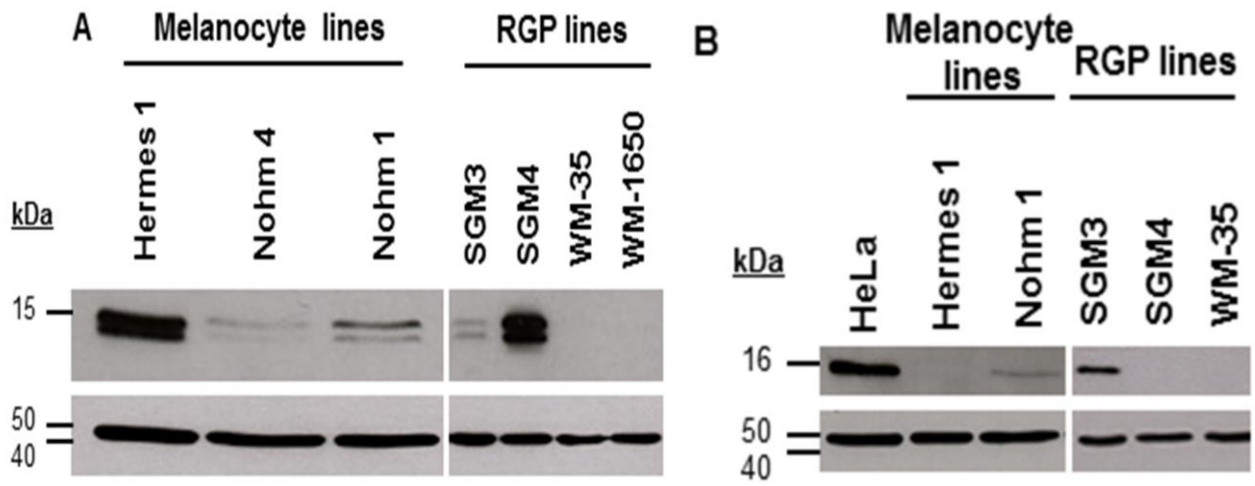

Figure 9 - Western blotting. Analysis of p15 **(A)** and p16 **(B)** expression in melanocyte and RGP lysates, respectively, to determine the p15 and p16 status of the cell lines used in this study. β-actin was probed as a loading control on all blots.

Task – From figure 9 what conclusions can you draw?

-
-
-
-

Future studies

1.
2.
3.
4.

Tutorial 5 – Homework: Final Assignment

Compare and contrast the risk factors, preventative measures and prognosis (depending on tumour stage) of melanoma and a cancer of your choice. **Explain** whether there is a relationship between extra centrosomes and your chosen cancer (research-based evidence required).

Word-count: 2000

In-text referencing

Font size 12

Bibliography at the end (Harvard style) – see page 30 for guidance.

Students need to first introduce the cancer of their choice and briefly state current statistics for incidence, mortality etc. In the main body they are required to compare and contrast each factor in the cancer of their choice and melanoma. Lastly, they are required to carry out a literature search in order to explain whether there is any evidence for the role of centrosomes in cancer (their chosen one) progression. Students will be awarded their final mark based on the mark scheme on page 6.

Tutorial 6 – Feedback

What is the Purpose of Tutorial 6?

- Reflect on skills learned on the programme with a view to encouraging resilience.
- Receive feedback on final assignment.

What are the key questions?

- What strengths have I demonstrated in my work and what areas of development are there left for me to address?
- What steps do I need to take to improve my academic output?

Activity 2 – Marking your own

Using the mark scheme, identify three things you did well and three things you could improve.

What went well?

1.

2.

3.

What could be improved?

1.

2.

3.

Activity 3 – Responding to feedback

Read through your feedback sheet and highlight on your assignment where you received positive feedback (one colour) and areas for improvement (different colour). You might find it helpful to annotate this with a brief comment or two.

(Acknowledgement: The structure and the activities in this feedback tutorial were first designed by Hannah Manktelow in January 2015. We have repeated them here as they demonstrate thoughtful and excellent planning, and can be used by all tutors to ensure a successful and productive feedback tutorial.)

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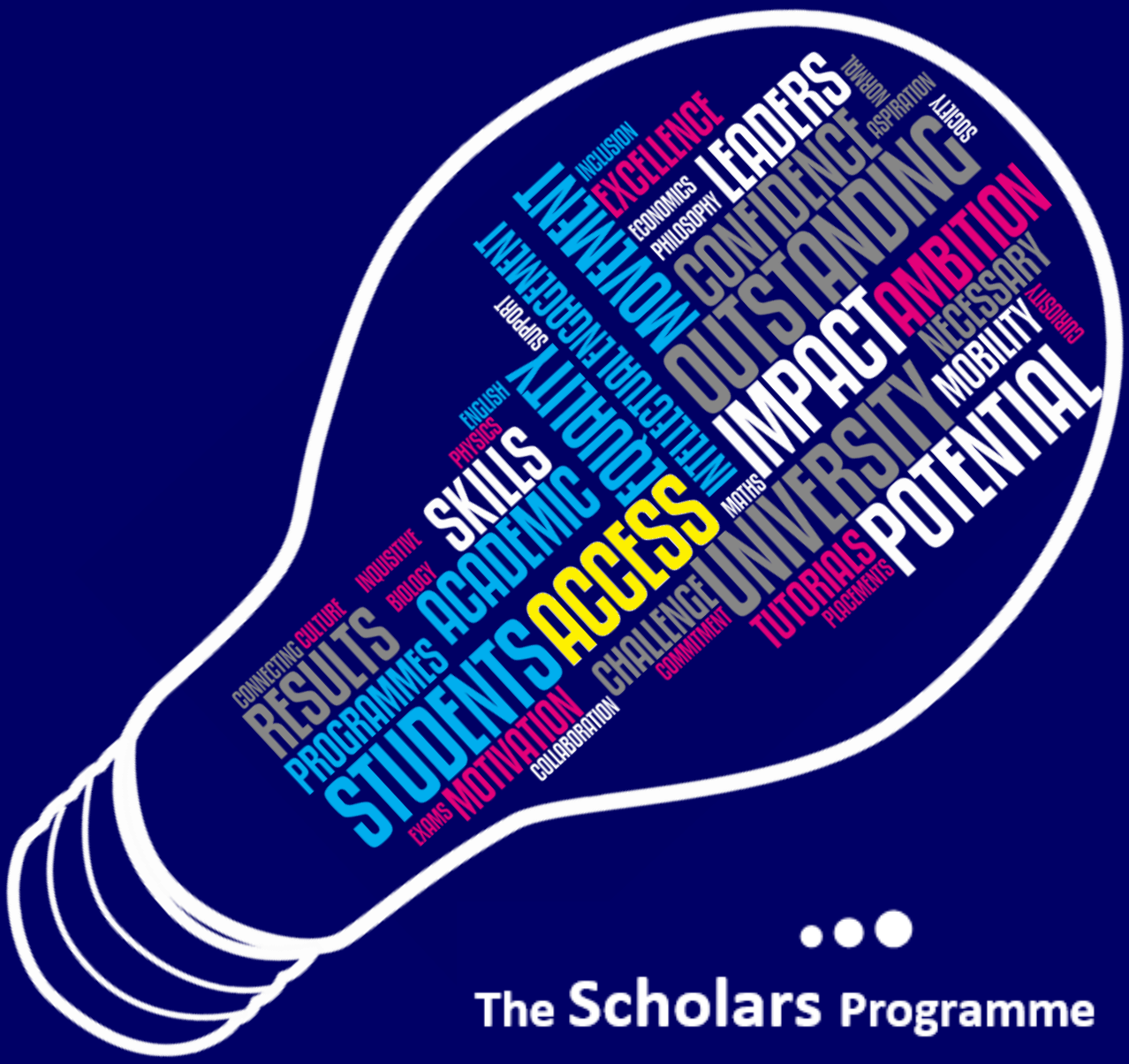

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