Farah Saeed

in support of WORLD CANCER RESEARCH DAY

September 24th

2024 Campaign

INNOVATION IN CANCER RESEARCH DRIVES PROGRESS TOWARDS HEALTH EQUITY

Hippo signalling and cancer

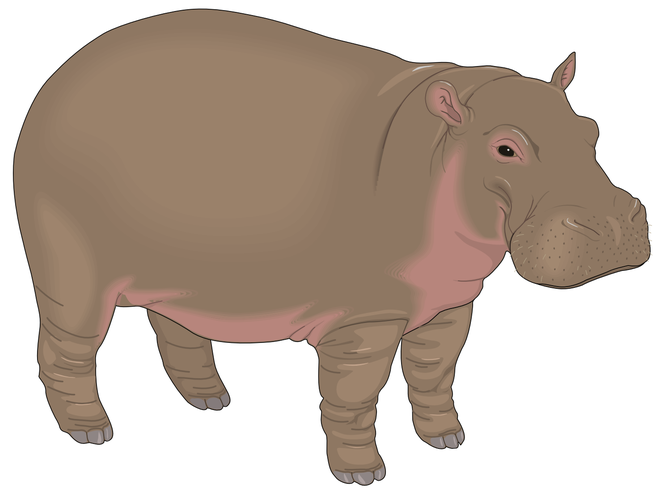
By Dr Hafsa Waseela Abbas

Hippo is an Ste20 protein kinase enzyme.

It has many key roles:

- · **Control the size of the organ through development and homeostasis**
- · **Proliferation**
- · **Degeneration of neurones**
- · **Cell survival**
- · **Apoptosis**

(Fu *et al*. 2022; Mueller *et al.* 2018; Akyala and Peppelenbosch, 2018; University of Michigan, 2020)



GLOSSARY

Apoptosis: A type of cell death.
Differentiation: Changes to cell shape and function when unspecialised cells become specialised for specific functions.
Enzyme: A type of protein that speeds up a chemical reaction.
Homeostasis: The maintenance of the internal environment of the body by adjusting to optimal conditions for survival e.g. water and ion concentration, glucose levels and temperature.
Neurone: Another term of a nerve cell that transmits electrical signals in the body
Proliferation: increased growth
Protein kinase: It modifies other proteins only through phosphorylation to help regulate cellular processes.
Phosphorylation – The addition to phosphate to molecule.

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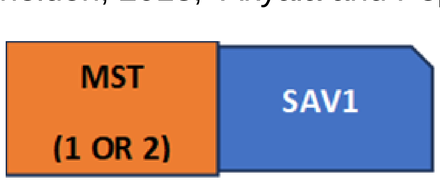
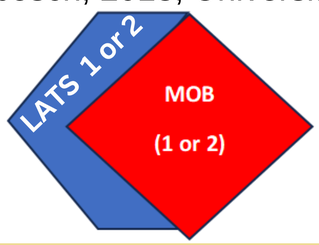
There are several key players involved in the pathway:

- **Striatin-interacting phosphatase and kinase (STRIPAK): It is a complex that contains kinases and phosphatases. Striatin is a key modulator in cell adhesion.**
- **Mammalian Ste20-like serine/threonine kinase 1/2 (MST1/2): It has a similar role to Hippo. an upstream regulator of YAP, controls organ size, cell proliferation, and induces apoptosis.**
- **Protein Salvador homologue 1 (SAV1) – scaffold protein of MST1/2**
- **MOBKL1A/B – scaffold protein of LATS1/2.**
- **Large tumour suppressor kinase 1/2 (LATS1/2) - serine/threonine kinases in the AGC kinase family.**
- **The transcriptional enhanced associated domain (TEAD) family - transcriptional coactivator**
- **Yes-associated protein 1 (YAP) à They are transcriptional coactivators that binds to the TEAD1-4 to conduct cell proliferation, apoptosis and self-renewal of stem cells.**
- **WW-domain-containing transcription regulator 1 (TAZ) – the paralog of YAP**

(Fu *et al*. 2022; Shi, Jiao and Zhou, 2016; Talukdar and Chatterji, 2023; Mueller *et al*. 2018; Sheldon, 2018; Akyala and Peppelenbosch, 2018; University of Michigan, 2020)





GLOSSARY

- **Paralog: They are homologous (same) genes that swerves from one another within a species (Sheldon, 2018).**
- **Scaffold protein: They bind two or more proteins which increases signalling more efficiency (Hata and Iida, 2024).**
- **Stem cells: Undifferentiated cells that can divide and make cells that have a specialised roles to function in tissues and organs.**
- **Transcriptional coactivator: It is also known as transcriptional coregulator. It binds to a transcription factor to form multiprotein complexes. The complex activates and increase the transcription of different genes and influence cellular signals. Some co-regulators repress transcription (Talukdar and Chatterji, 2023)**
- **Tumour suppressor: A gene that encodes a protein to stop cancer growth.**

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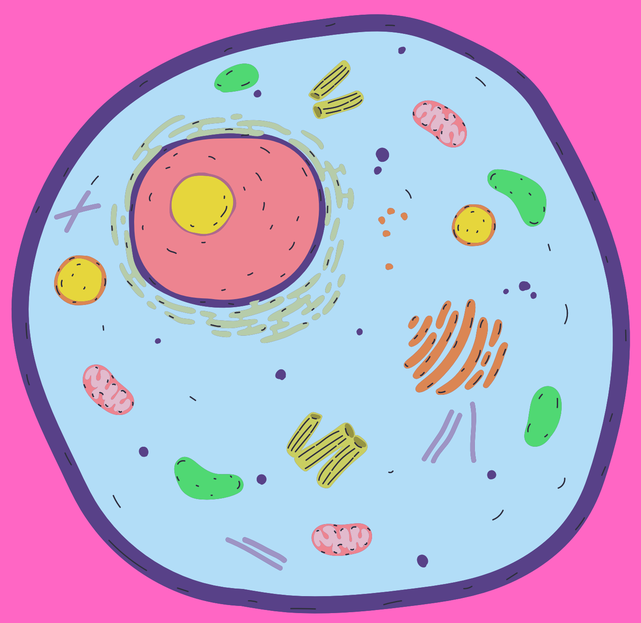
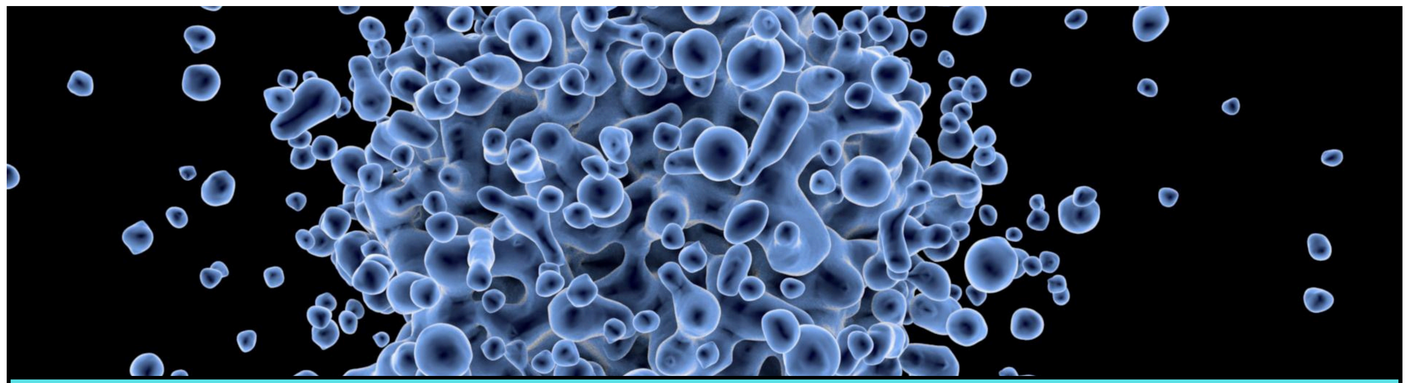
Key regulatory processes:

- **YAP proteins**
- **Cell polarity and cell-to-cell interaction**
- **G-protein-coupled receptors.**

(Fu *et al*. 2022; Mueller *et al*. 2018; Sheldon, 2018; Akyala and Peppelenbosch, 2018; University of Michigan, 2020)





GLOSSARY

- **Cell polarity is the distribution of proteins, organelles (parts of a cell) in different forms unevenly. It is important in how cells divide, develop and differentiate (Nelson, 2003).**
- **G protein-coupled receptors (GPCRs) are receptor proteins found on the cell surface. They mediate lots of roles that are triggered by signals outside the cell, for instance, fat molecules, hormones, small proteins and neurotransmitters (chemicals) (Zhang e*t al.* 2023).**

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HIPPO PATHWAY ON

1. STRIPAK complex regulates MST1/2 and MAP4Ks.
2. The activity of MST1/2 increases when bound with its scaffold protein SAV1.
3. MST1/2 interacts with its scaffold protein SAV1 can phosphorylate LATS1/2 serine/threonine kinase and its scaffold protein MOB1A/B with assistance of WWC1-3 – other scaffold proteins.
4. MAP4K also can activate LATS1/2 without SAV.
5. The phosphorylated MOB1 promote activation of LATS1/2.
6. The activated form of LATS1/2 phosphorylate transcriptional co-activator Yes-Associated Protein (YAP) and lowers the activity and can also inactivate YAP or its paralog TAZ. It can mediate oxidative stress-induced neural death
7. Phosphorylated YAP cannot translocate to the nucleus and bind to its transcriptional coactivator TEAD to induce transcription.
8. Instead, it is targeted for degradation. Yap is held in the cytoplasm bound to a 14-3-3 protein or degraded by the proteasome.

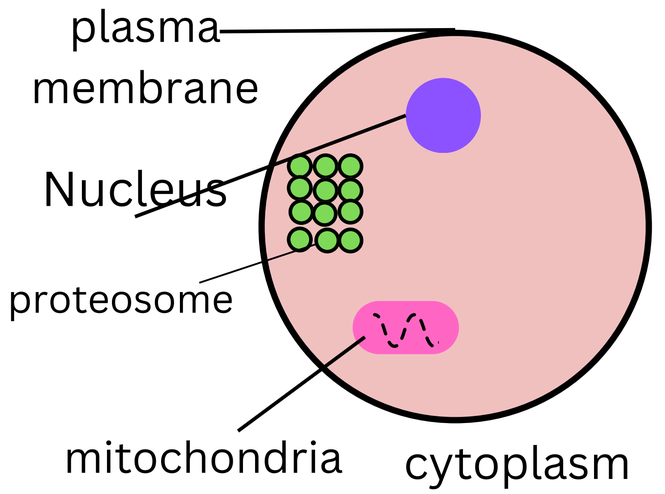
GLOSSARY

Proteosome: A structure within the cytoplasm that degrades proteins.

Nucleus: A structure found in the cell that contains genetic material and controls the cell

Cytoplasm: A jelly-like structure where chemical reactions takes place via structures called organelles.

Plasma membrane: It surrounds each cell and controls what enters and leaves the cell.



(Fu *et al*. 2022; Mueller *et al*. 2018; Sheldon, 2018; Akyala and Peppelenbosch, 2018; University of Michigan, 2020)

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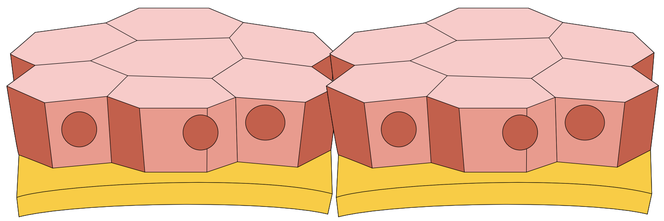
(Fu *et al*. 2022; Mueller *et al*. 2018; Sheldon, 2018; Akyala and Peppelenbosch, 2018; University of Michigan, 2020)

HIPPO PATHWAY OFF

1. When not phosphorylated, The YAP protein translocates into the nucleus where it binds and activates the transcription factor TEAD (transcriptional enhancer activator domain).
2. The YAP/TEAD complex activates the transcription of genes involved in cell survival, proliferation and prevents apoptosis, hypertrophy and alterations in pathways involved in metabolism.

DNA

RNA



Epithelial cell

GLOSSARY

- **Hypertrophy:** increase in size of tissue caused by the large size of the cells rather than proliferation.
- **Phosphorylation**: The addition of phosphate groups to a molecule.
- **protein: A large molecule made up of amino acids as building blocks.**
- **Metabolism:** A series of chemical and physical reaction changes to support life.
- **Apoptosis**: A type of cell death
- **Transcription**: The process of using DNA as a template to make the single strand of nucleotide called ribonucleic acid (RNA).

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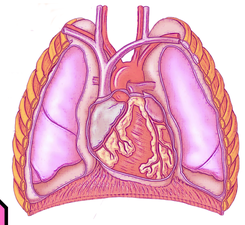
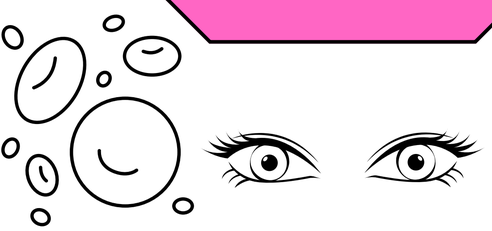
(Fu *et al*. 2022; Mueller *et al*. 2018; Sheldon, 2018; Akyala and Peppelenbosch, 2018; University of Michigan, 2020)

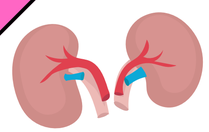
DYSREGULATION OF THE HIPPO PATHWAY

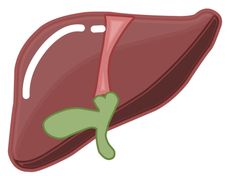
Dysregulation can lead to:

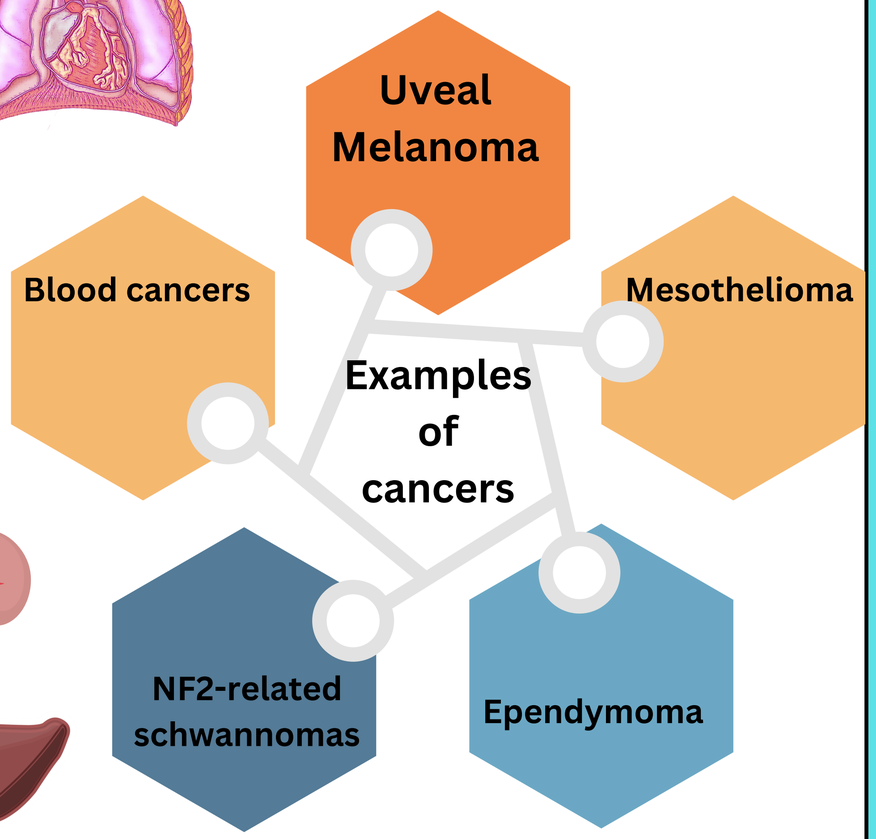
- **Diseases of the heart and lungs**
- **Diseases of the liver and kidneys**
- **Disease of the eyes**
- **The immune system stops working properly.**











GLOSSARY

- **Uveal melanoma: This is the cancer that occurs in the uveal tract, a layer which is below the outer layer of the eye (Sclera).**
- **Mesothelioma: It is a single layer of cancer cells found on outer layer of heart (pericardium) or the lungs (pleural membrane) or the abdominal cavity which has the intestines and stomach (peritoneum).**
- **Ependymoma: A tumour of non-nerve cells called glial cells that align the ventricles of the brain.**
- **Schwannomas - tumour arises from schwann cells whose normal function is to protect nerve cells from electric shock.**
- **Blood: Fluid that contains a variety of cells, proteins, fragments, hormones and water that travels around the body for its defined functions**
- **Immune system: It contains different types of cells and proteins that protect the body from infection and disease-causing microbes.**

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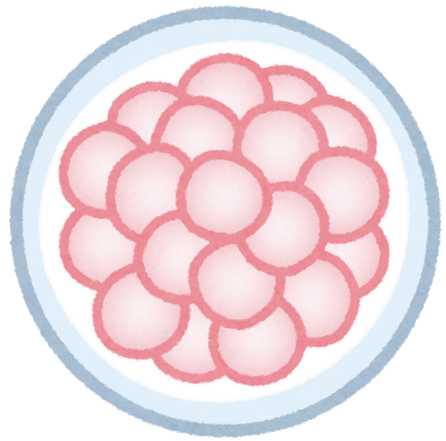
THE LINK BETWEEN HOW CANCER IS FORMED AND PROGRESSED WITH HIPPO PATHWAY.

MST1/2 and LATS 1 /2 act as tumour suppressors and there is a decrease expression caused by a progressive loss of nerve cells (neurodegeneration).

The YAP/TAZ proteins act as oncoproteins where the levels in the nucleus and activity elevates as the growth of cancer cells also increases.

Recent study discovered that TAZ proteins is essential for cancer stem cells to potentiate and grow.

Another recent study discovered that YAP suppresses the growth of cancer in the colon and rectum (large intestine) in primary and secondary cancers. Evidence was also found in breast , blood and neuroendocrine tumours.(Fu, *et al*. 2022; Baroja, *et al.* 2024)



GLOSSARY

Oncoproteins – They are proteins that increase the transformation of cells into tumour cells by influencing cell proliferation and death (Castel, Rauen and McCormick, 2020)

Nucleus – A structure that is part of the cell, it contains genetic material and its main role is to control the cell.

Cancer stem cells: They are a type of cell found in tumours that share similar characteristics as normal stem cells through self-renewal and differentiation. Cancer stem cells also shares similar characteristics as tumour cells to maintain tumour heterogeneity, evade apoptosis, continuously proliferate, invasion, migration, metastasis and chemotherapeutic resistance (Chu *et al.* 2024; Mayo Clinic, 2024)

Primary Cancer: The primary or original site of where the cancer initiates (Eldridge, 2023)

Secondary Cancer: The growth of the cancer to other organs where it spreads (metastasis)either through the blood or lymph nodes (Eldridge, 2023)

Tumour suppressor : A gene that encodes a protein to stop cancer growth

Neuroendocrine tumour: Tumour arising in specialised cells called neuroendocrine cells that influences both nerves and hormones especially the pituitary gland and adrenal.

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THE LINK BETWEEN HOW CANCER METASTASES WITH THE HIPPO PATHWAY.

LAT1/2, MST1/2, YAP and TAZ can cause tumour metastasis.

Primary cancer	Secondary cancer
Lung and lymph nodes	Breast cancer metastasis
Brain	Lung cancer metastasis

First method of metastasis

- Hippo pathway regulate migration and invasion of cells
- High levels of YAP/TAZ increase activation of Epithelial-to-mesenchymal (EMT) transition. It suppresses against migration and invasion of cells

(Fu, *et al*. 2022; Baroja, *et al.* 2024)

Second method of metastasis

- Suppress anoikis – a type of cell death where attachment between cells and extracellular matrix (ECM).
- LIMO domain only 3 (LMO3) inhibit anokis to increase metastasis in the liver and suppress Hippo.

GLOSSARY

- **Extracellular matrix (ECM): This network contains proteins and sugar secreted from plants and animal cells to strengthen, support, organize, and communicate with other cells.**
- **Epithelial–mesenchymal transition (EMT) – single layer of cells (epithelial cells) have characteristics of mesenchymal cells (Manfioletti and Fedele, 2022). Mesenchymal cells are small cells that can differentiate into cells that produce connective tissue, for instance, osteoblasts (bone), preadipocytes (fat), fibroblasts, and chondroblasts (cartilage) (Sendic, 2023).**

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(Fu, *et al*. 2022; Baroja, *et al.* 2024)

THE LINK BETWEEN DRUG RESISTANCE WITH THE HIPPO PATHWAY.

Key players of chemotherapy resistance are: YAP, TAZ, MST1 and LATS1/2 proteins.

YAP and TAZ overexpression or translocation to nucleus decrease the efficacy of the following chemotherapeutic agents:

- cisplatin
- Doxorubicin
- 5-flouracil
- Taxol.

Downregulation of LATS1/2 cause resistance against chemotherapeutic agents:

- Cisplatin
- 5-flouracil.

CISPLATIN and 5-Flouracil can cause resistance in both methods

(Fu, *et al*. 2022; Baroja, *et al.* 2024)

H O W

GLOSSARY

Efficacy – power to produce the effect.

Efflux – flown out ump out unwanted toxic substances through specific efflux pumps

Cytokine -protein molecule released when activated by antigen they are involved in how cells communicate and mediate immune response. Key examples are interleukins, interferons and lymphokines.

Myeloid-derived suppressor cells (MDSC): They are derived from neutrophils and monocytes (types of white blood cells) with strong immunosuppressive function (Akkari *et al*., 2024).

Tumour-associated -macrophages (TAM): They are found in the tumour microenvironment where they support cancer cell growth, metastasis and induce immunosuppression. This opposes the normal function of macrophages that engulf microorganisms (Christofides *et al*. 2022)

Causes of chemotherapy resistance:

- **Stemness – it enables cancer stem cells to self-renew and differentiate**
- **Metabolising drugs decrease its efficacy decrease concentration.**
- **Efflux of drugs**

For example:

YAP activation can sensitize pancreatic cancer cells to gemcitabine by decreasing the number of drug efflux transporters and become more active and potent.

- **Myeloid-derived suppressor cells and Tumour-associated macrophages (TAM) are immunosuppressive in tumour microenvironment which contribute to resistance. How? YAP can directly induce CXCL5 cytokine which attract myeloid-derived suppressor cells and CCL2 cytokine to attract TAM.**

This suggests Yap tumour promoting and tumour suppressive.

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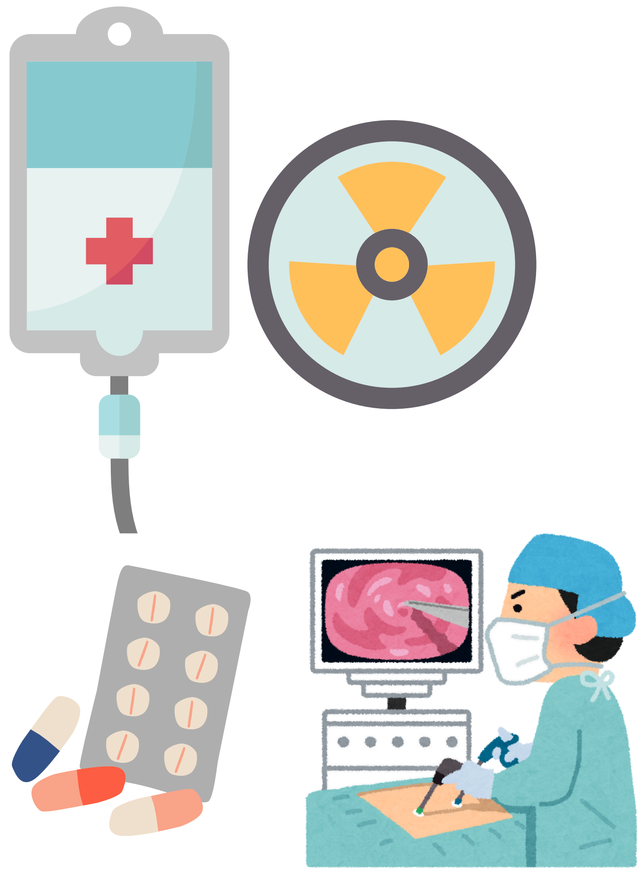
NEW DEVELOPMENTS OF THERAPEUTIC STRATEGIES FOR THE HIPPO PATHWAY.

Small molecule inhibitors

Aim: To block function of YAP/TAZ-TEAD transcription factor. This helped improve efficacy and removes cancers with mutations.

Key example: Verteporfin
Role: It blocks the binding of YAP/TAZ to TEAD1-4
It also has ability to target non-YAP e.g. autophagy and TNF signallling.



Other effects of blocking YAP/TAZ-TEAD:

- **Decrease expression of immune checkpoint proteins, this help prevent immunesuppression and increase activity of a type of white blood cell: T cells**
- **Increase expression of major histocompatibility complex (MHC) molecules who play a vital role in initiating anti-tumour immune response.**
- **On the contrary it helps stop the activity of neutrophils.**

New generation – TEAD inhibitors competitively bind to a region in TEAD proteins which can cause instability and prevent interaction with YAP/TAZ

(Fu, *et al*. 2022; Baroja, *et al.* 2024)

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NEW DEVELOPMENTS OF THERAPEUTIC STRATEGIES FOR THE HIPPO PATHWAY.

Further experiments are done but is unknown which approach is suitable and response varies with different types of cancer.

Phase 1 assess YAP/TAZ-TEAD inhibitors in patients with mesothelioma and other cancers that have NF2/LATS1/LATS2 mutations and tumours with functional YAP/TAZ fusions.

There was a positive partial response for 7 of 69 patients: six had refractory mesothelioma (Two NF2 mutant cancers, three NF2 normal (wild-type) cells and one unknown) and one NF2 mutant sarcoma

Partial response whilst the other patients had stable disease.

(Fu, *et al*. 2022; Baroja, *et al.* 2024; Bergoug *et al.* 2020))

Phase 2 clinical data consisted of Ionis preclinical data from xenograft models on the following cancers:

- **head and neck tumours**
- **Hepatocellular carcinoma**
- **Epidermoid carcinoma**
- **Squamous cell carcinoma**

Non-Hippo pathway therapeutic targets

YAP/TAZ inhibitors that are not driven by non-Hippo components but senior researchers have stated that measuring proliferation in 2D or 3D monocultures of cancer cells may not be reliable.

Combination therapies with YAP/TAZ-TEAD inhibitors may increase the efficacy of targeted and chemotherapies by reducing therapy resistance.

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CHALLENGES IN CANCER TREATMENT WITH HIPPO PATHWAY

Resistance may occur in response interaction with non-Hippo pathway components:

- **Loss of Ras protein function causes the YAP/TEAD2 complex to join with E2F (gene regulators) to increase cell proliferation and survival.**
- **YAP/TEAD signalling induce senescence-like dormant state that increases cancer cells to resist to EGFR/MEK inhibitors and risk of recurrent disease.**
- **YAP/TAZ activity increase drug resistance to EGFR, KRAS and MEK inhibitors by reactivating MAPK signalling pathway and MRAS protein.**
- **YAP/TAZ activity increases expression of drug efflux transporters e.g. ABCG2 and MDR1 – this causes cancer cells to pump toxic substances outside the cell.**
- **Side effects of YAP/TAZ-TEAD inhibition could damage the kidney.**

(Fu, *et al*. 2022; Baroja, *et al.* 2024)

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