# JOURNAL CLUB

## Meaning, definition, exploration

**Dr Karamallah S Mahmood**

# Journal Club

Journal club is a regular gathering of scientists to discuss a **scientific paper** found in a research journal.

e.g Monthly research presentations first Tuesday of the month.

Journal clubs are usually organized around **a defined subject** in basic or applied research.

# Journal Club/ History

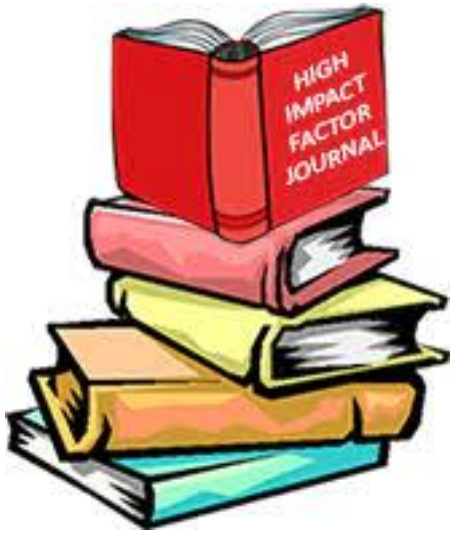
The earliest references to a journal club was found in a book of memoirs by Sir James Paget, a British surgeon, who describes a group at St. Bartholomew's Hospital in London in the mid-19th century as "*a kind of club ... a small room near the Hospital-gate where we could sit and read the journals*."

Sir William Osler established the first formalized journal club at McGill University in Montreal in 1875.

# Article Selection .. Do and Don't

**DO**

- Article should report original research




- Topics that will generate conversation
- You should also be aware of how much information the audience will have

nature Science Cell PNAS THE LANCET nature medicine
The NEW ENGLAND JOURNAL of MEDICINE nature genetics nature biotechnology nature COMMUNICATIONS Journal of Virology nature methods
nature chemical biology Cancer Cell Immunity nature immunology JAMA nature cell biology
Molecular Cell Cell Research THE PLANT CELL jbc

# Article Selection Do and Do not

**DO NOT**

- No reviews (they don't have the methods sections)
- Meta-analyses only if you have a compelling reason for presenting
- Don't choose industry sponsored articles.

# Journal Club Goals

- Keep informed about new development
- Promote evidence-based research
- Demonstrate continuing education
- Learn critical appraisal skills generally
- Improve reading

# Journal Club Goals …. Cont.

- Generate novel research ideas
- They allow researchers and students at varying stages of education to discuss topics.
- Help students to develop analytical and presentation skills

# Prepare Yourself

- Read the article critically
- Understand the background and the experimental details
- Think about the decisions the authors made regarding the design the study
- Remember: the audience has a range of experience

# Journal Club Practical Example/
# Medical School - University of Dundee – 22/03/2017

**Synergistic effects of ion transporter and MAP kinase pathway inhibitors in melanoma**

Karamallah Al-Yousuf

*Nature Communications* **volume7**, Article number: 12336 (2016)

New | Delete Archive Junk | Sweep Move to Categories ••• Unc

All folders

Top results

Cancer-Admin
Journal Club Paper 20/03/2017
Dear all Please see attached paper from ...

Cancer-Admin
Journal Club Paper 12/12/2016
Dear all Please see attached paper fro...

Cancer-Admin
Journal club Paper 24/03/2016
Dear all Please see attached paper fro...

All results

Karamallah Al-Yousuf ...
JC 16/04/2018
...Karamallah Al-Yousuf K Journal clu...

BioMedBadass
A Day in the Life of a Principle In 27/03/2018
...activities ahead...11 am lecture, paper to...

Martina Elias (Staff)

pdf Karam's JC March 2017....
1 MB

Download

Action Items

Dear all

Please see attached paper from Karam for the Journal Club on Wednesday 22nd March 2017. Hugh can you please see that your paper is approved by John Hayes and Mark Saville and email it to cancer-admin@dundee.ac.uk by Thursday 23rd March 2017.

Many thanks.

Morag

JH

John Hayes (Staff)
Mon 20/03/2017, 15:19

Dear Karam,

I am happy with the paper. I was out of the lab on Friday, and could not read it. Is Mark happy with the paper?

# Outline the content of the Article

***Authors and funding source***

Who are the authors?
Their previous work?
Has it been reliable?
Who paid for the study?

**Correspondent:**

## Prof Sean J. Morrison Ph.D.

President-elect, International Society for Stem Cell Research (2014-2015)

Senior Editor, eLife (2014-2015)

***Currently***

The Director of the Children's Medical Center Research Institute at UT Southwestern

An Investigator of the Howard Hughes Medical Institute.

## *Research Interests*

Cancer stem cell biology

Melanoma cell proliferation and metastasis

Stem cell aging

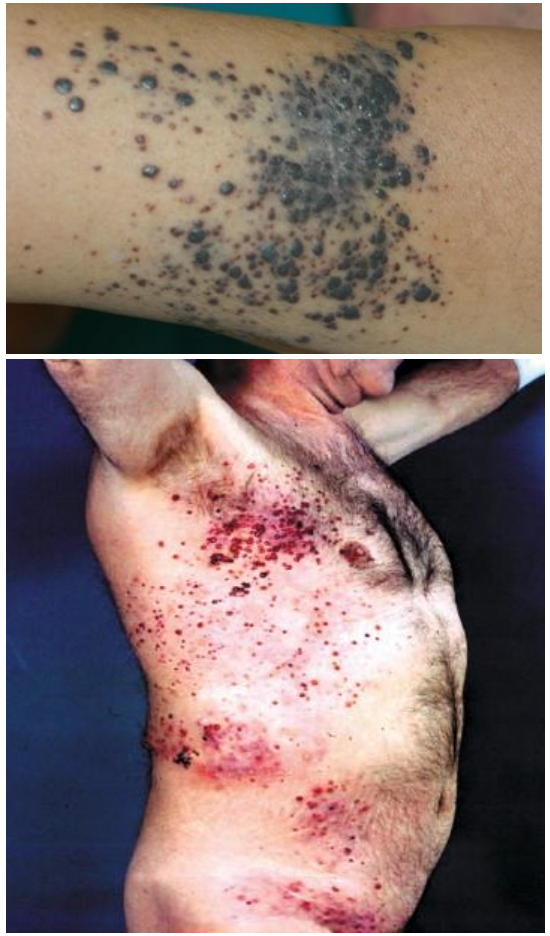
Stem cell self-renewal

# Outline the content of the Article

***Background***

What is the context and motivation for doing the study?

# Malignant Melanoma: 1979-2012



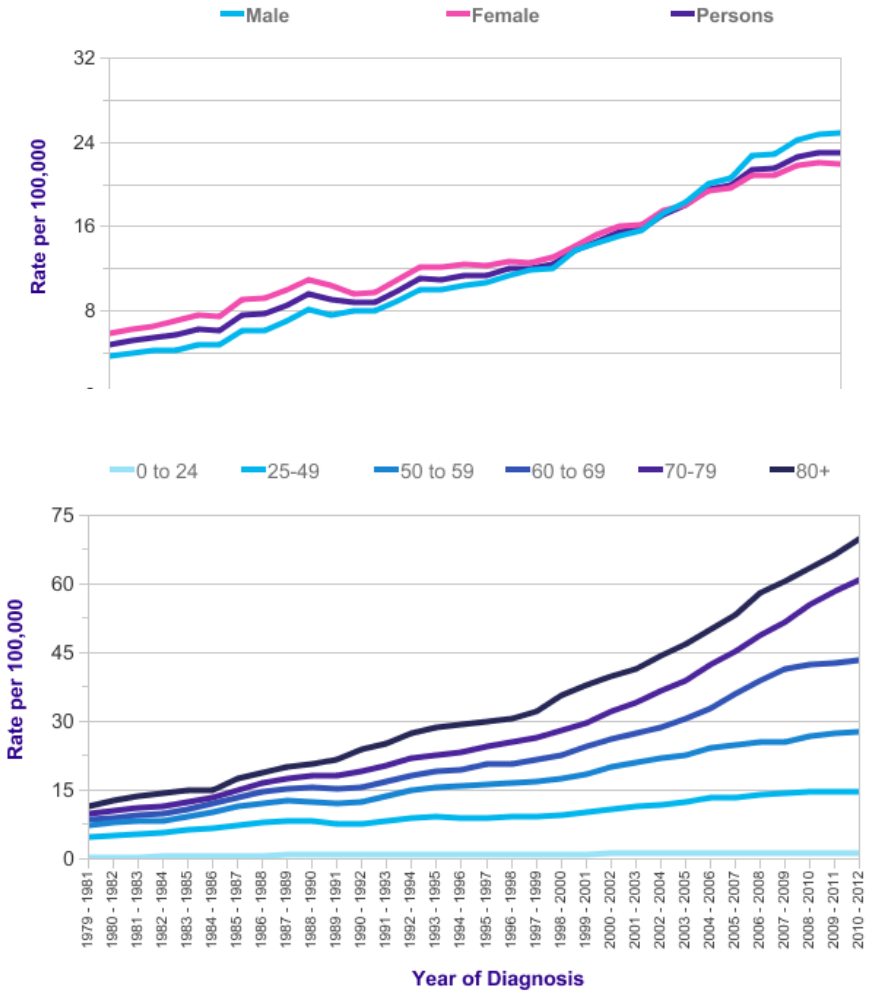
*Lancet Oncol* 2003; 4 748–59

**Melanoma is a malignant cancer of melanocytes**

**Most commonly originating from the skin.**

**Very poor prognosis**

**European Age-Standardised Incidence Rates per 100,000 Population, by Sex/ Age, Great Britain, 1979-2012**



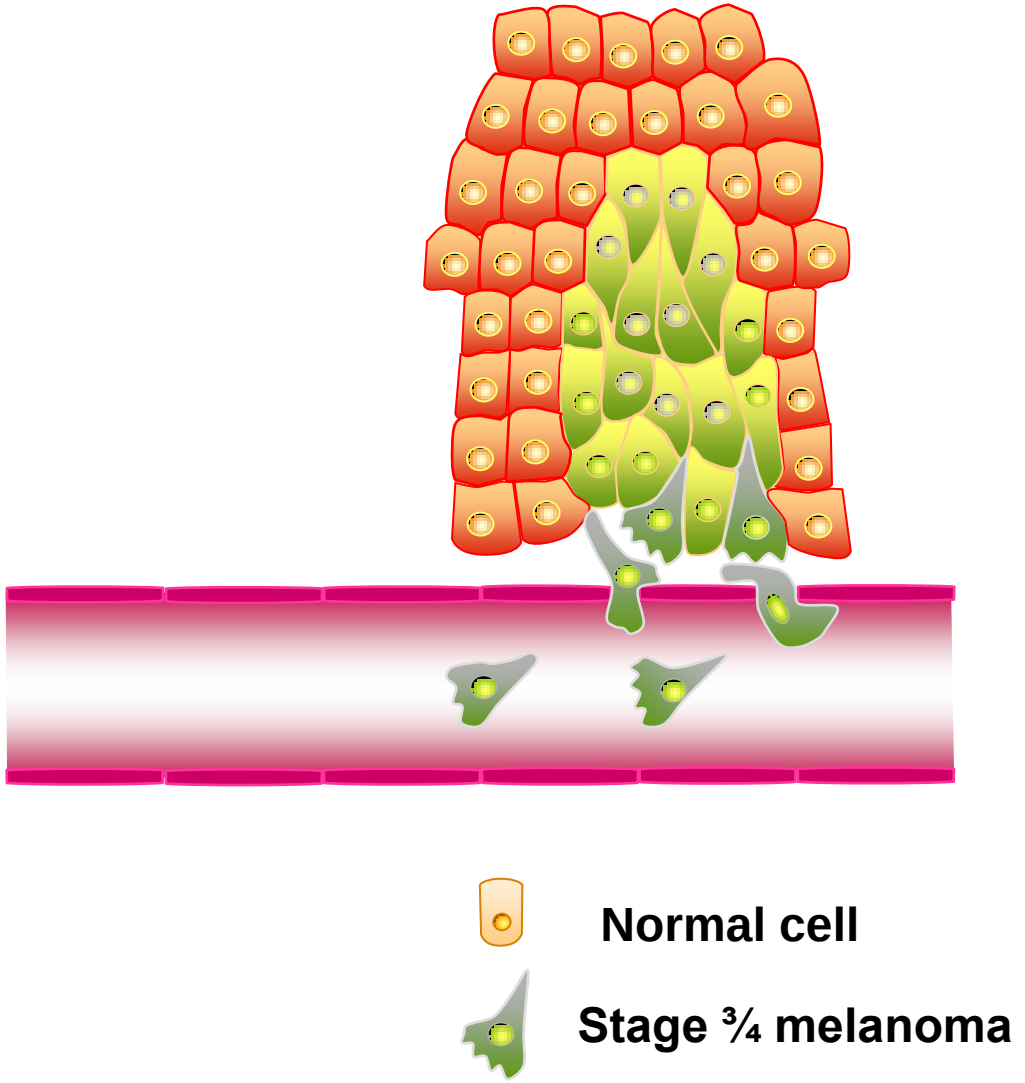

Source: cruk.org/cancerstats

CANCER RESEARCH UK

The traditional anti-melanoma drugs do not produce a satisfactory therapeutic response in melanoma patients.

- Traditional chemotherapies …. Ineffective/ side effects
- Targeted therapies …. resistance
- Immunotherapies ….. severe immune-related adverse effects (irAEs)

It is still challenging to develop a drug that joins efficacy and safety in Stage 3/4 of the disease.

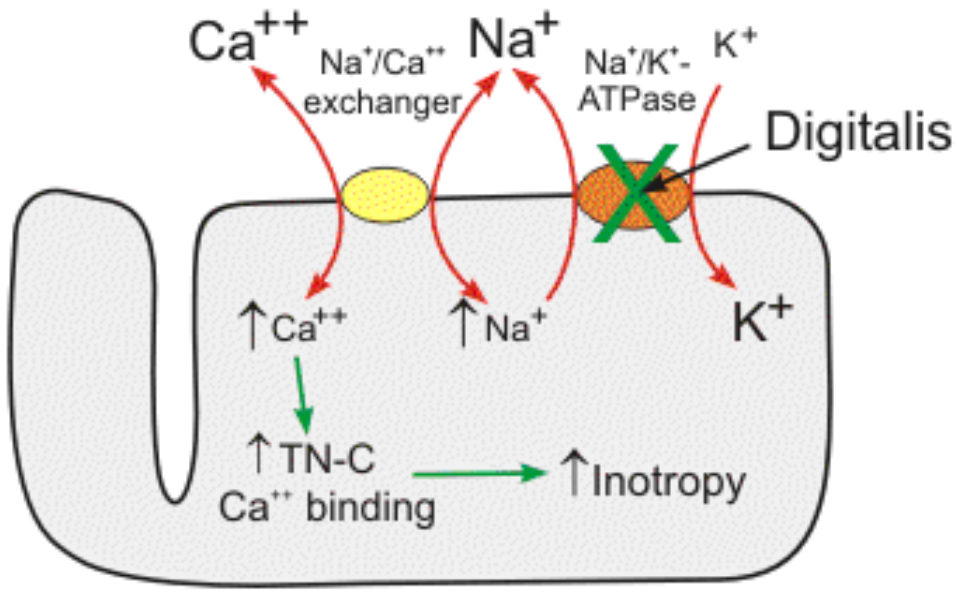


For decades congestive **heart failure** has been treated with the plant-derived digitalis cardiac glycosides

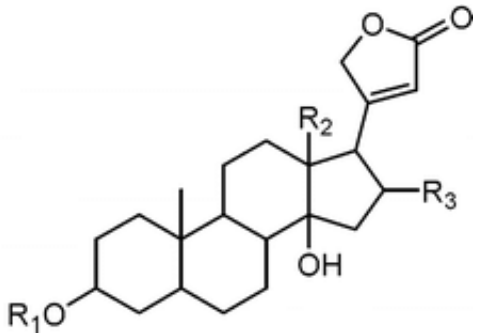
**Digitalis cardiac glycosides** increase force of contraction of failing cardiac muscle and reduce cardiac conduction rate.

Increased force of contraction of cardiac muscle induced by cardiac glycosides is the result of inhibition of **Na,K-ATPase**.

Raised intracellular Na+ concentration limits Ca2+ extrusion via the 3Na+/Ca2+ exchanger, leading to enhanced Ca2+ uptake into the SR by the Ca-ATPase and increased calcium-induced calcium release during excitation-contraction coupling




| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| digitoxin (**1**) | $(digitoxose)_3$ | H | H |
| digitoxigenin (**2**) | H | H | H |
| digoxin (**3**) | $(digitoxose)_3$ | OH | H |
| digoxigenin (**4**) | H | OH | H |
| gitoxin (**5**) | $(digitoxose)_3$ | H | OH |
| gitoxigenin (**6**) | H | H | OH |




*J. Nat. Prod.*, **2005**, *68* (11), 1642–1645

## Plant Sources

**a. Digitalis purpurea.**
Digitoxin, gitoxin, gitalin
**b. Digitalis lanata**
Digoxin, digitoxin, gitoxin
**c. Strophanthus kombe** Strophanthin
**d. Strophanthus gratus** Ouabain

*Digitalis purpurea* (Common Foxglove)

## PHARMACOKINETICS OF CARDIAC GLYCOSIDES

| | DIGOXIN | DIGITOXIN |
|---|---|---|
| ABSORPTION (ORAL) | 40 – 75% | 90 –100% |
| PROTEIN BINDING | LOW | EXTENSIVE |
| HALF LIFE | 39 HOURS | 168 HOURS |
| METABOLISM | LOW | EXTENSIVE |
| EXCRETION | PREDOMINANTL RENAL | PARTLY RENAL |
| Vd (L/Kg) | 6.3 | 0.6 |
| THERAPEUTIC PLASMA CONCENTRATION | 0.5 – 2 ng/ml | 10 – 25ng/ml |
| TOXIC PLASMA CONC. | > 2ng/ml | > 35 ng/ml |
| DAILY DOSE (SLOW LOADING OR MAINT) | 0.125 – 0.5mg | 0.05 – 0.2mg |
| RAPID DIGITALIZING DOSE | 0.5 – 0.75mg 8 HRLY X 3 DOSES | 0.2 - .4mg 12 HRLY X 3 DOSES |
| TIME FOR PEAK EFFECT | 3 – 6 HOURS | 6 – 12 HOURS |

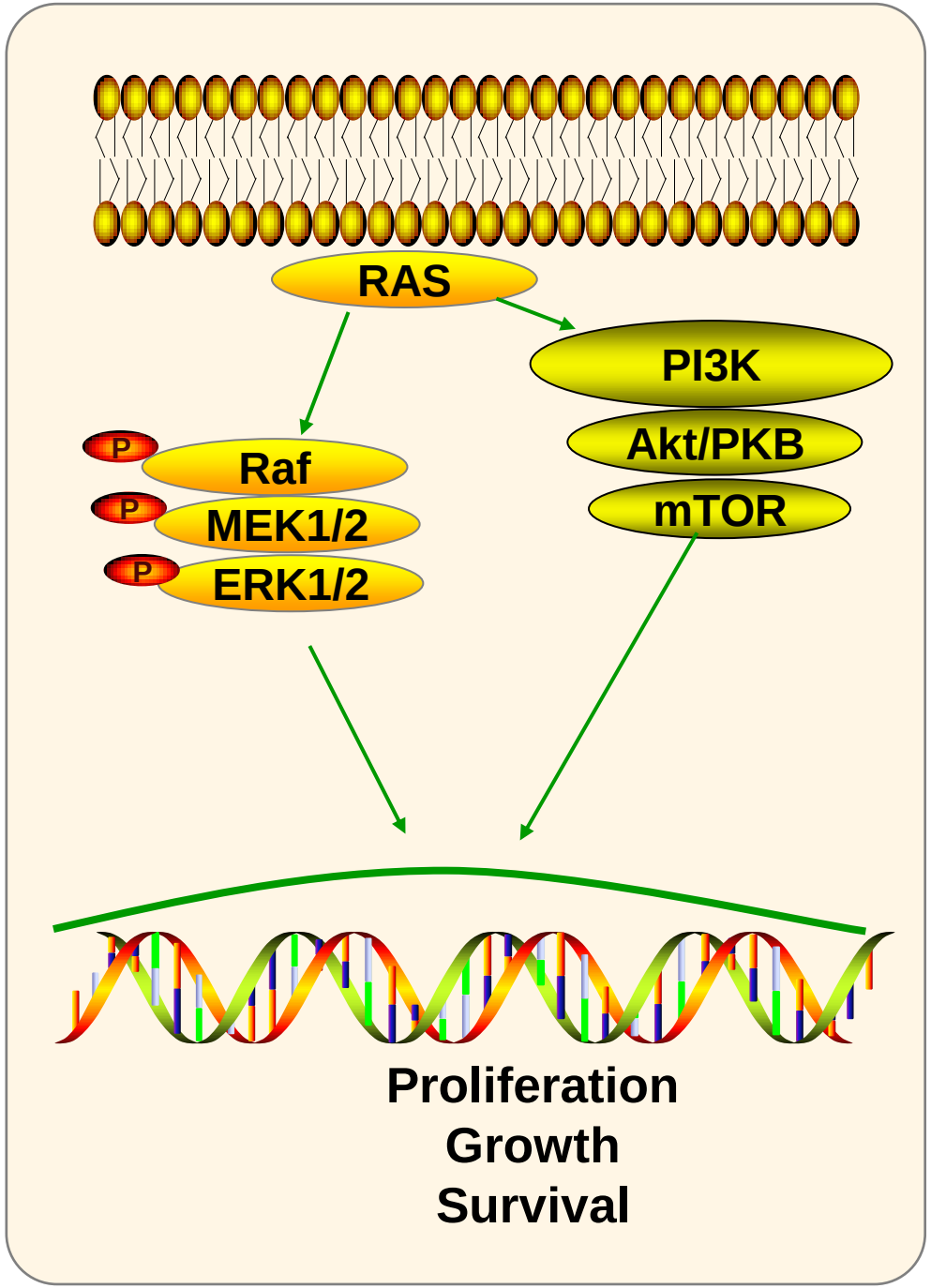
http://howmed.net/pharmacology/cardiac-glycosides-digoxin-and-digitoxin/

The **Mitogen-Activated Protein Kinase** (MAPK) Pathway

When bound by their ligand, various receptor tyrosine kinases lead to ERK activation, which triggers cell proliferation and anti-apoptotic pathways.

ERK also activates DUSP (dual-specificity phosphatases) and Sprouty, which negatively feed back on ERK and RAS, respectively. In melanomas with $BRAF^{V600E}$ mutations, the MAPK pathway is activated from the level of RAF.

*Clin Cancer Res* 2010; 16:3329,

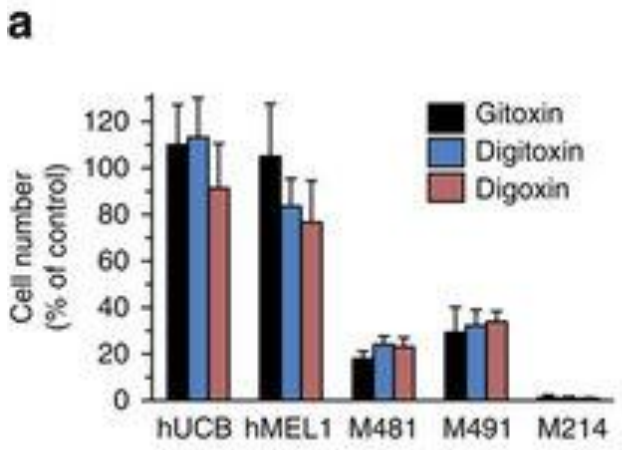


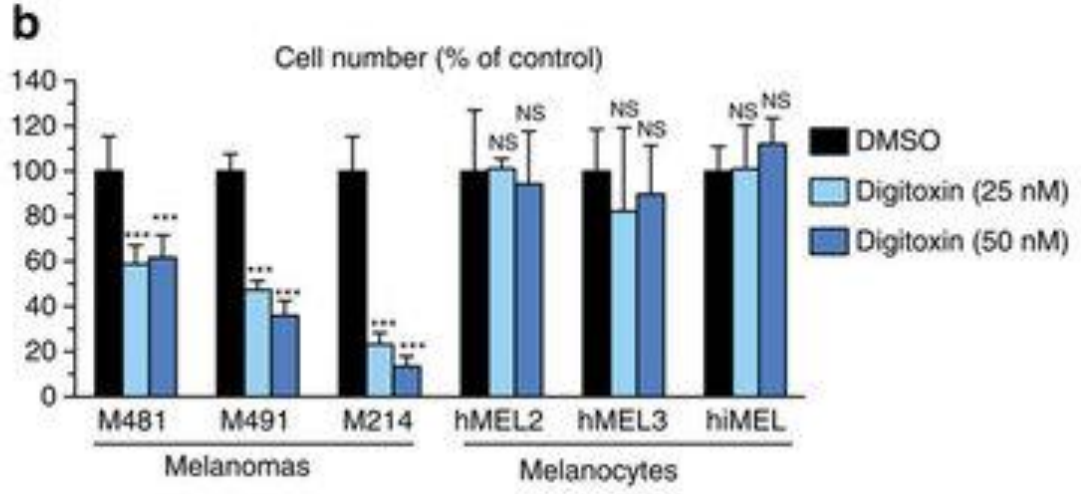
# Outline the content of the Article …Cont.

***Results***

What did they find?
Consider both the statistical significance and the effect size-the magnitude of difference between the groups.

**Figure 1**: Cardiac glycosides are preferentially toxic to melanomas by inhibiting the ATP1A1 $Na^+/K^+$ ATPase.



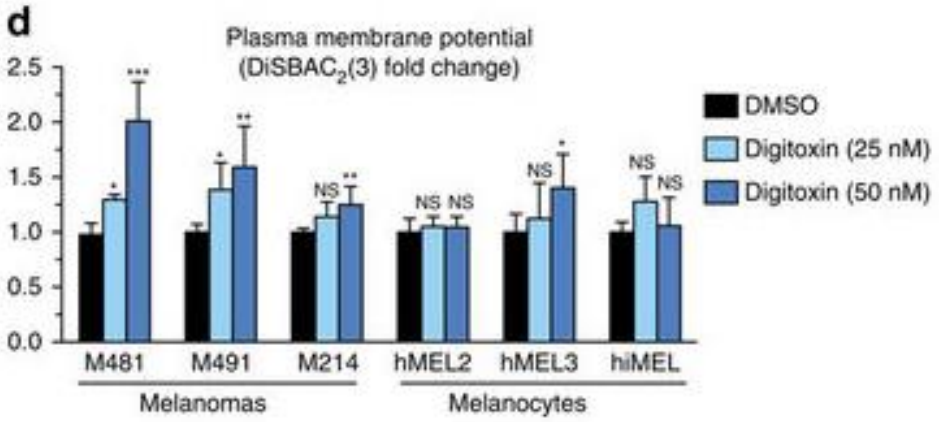



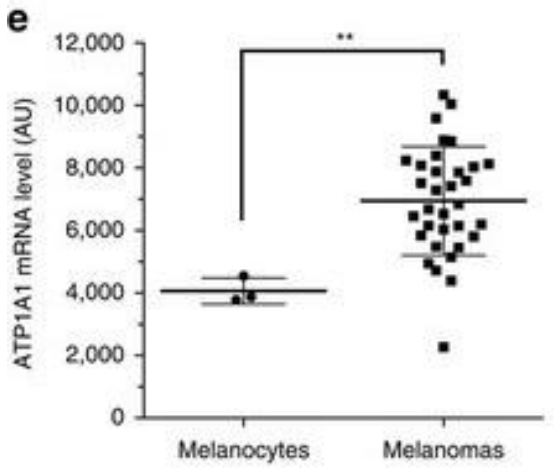

c

| Digitoxin | |
|---|---|
| Cell | IC50 (nM) |
| M481 | 15±15 |
| M514 | 17 |
| M651 | 23 |
| A375 | 27 |
| M711 | <30 |
| M214 | 30±18 |
| M610 | 34±20 |
| M491 | 33 |
| M715 | 40 |
| M499 | 65 |
| UM12 | 123±61 |
| M498 | 137 |
| M701 | 238±182 |
| M741 | 251 |
| M528 | 398±70 |
| M405 | 1,540 |
| hUCB | 22,200 |

Falls within therapeutic range

Above therapeutic range




$DiSBAC_2(3)$ is a lipophilic dye which accumulates and fluoresces in depolarized membranes

# Outline the content of the Article .. Cont.

***Conclusions***

What did they conclude?

# Conclusions

- ✓ Necroptosis depends on receptor interacting protein 1 (RIP1) and particularly occurs under caspase-deficient conditions.
- ✓ The targeted induction of necroptosis represents a promising strategy to overcome apoptosis resistance in cancer.

- ✓ pan-caspase inhibitors facilitated 5-FU-induced necroptosis, which was mediated by autocrine secretion of tumor necrosis factor α (TNF-α).

- ✓ TNF-α production was driven by nuclear factor κB (NF-κB) and required RIP1 kinase.

- ✓ Necroptotic cell death as an important effector mechanism of 5-FU-mediated anti-tumoral activity.

# Outline the content of the Article …Cont.

***Discussion***

What are the possible biases of the study?

Is the study design appropriate to answer the question?

Estimate the likelihood that each of biases has affected the validity of the study, and what direction would affect results.


- ✔ Very through paper,
- ✔ Wide range techniques,
- ✔ Well written,
- ✔ Logical steps,
- ✔ *In vitro, in vivo* and clinical work,
- ✔ **Novel pan-caspase inhibitor IDN-7314 in combination**
- ✔ **MOA, necroptosis by NF-κB and RIP1.**
- ✔ **Two different caspase inhibitors**

- ✖ Another malignant tumour,
- ✖ Two different caspase inhibitors, *in vitro* and *in vivo*
- ✖ Future work,
- ✖ Some data haven't been shown, page 6


# Thanks