“Metformin: A drug for all reasons?”

Professor Chris R. Triggle, PhD, FBPhS.

Weill Cornell Medicine - Qatar
Speaker:

Christopher R. Triggle, Phd, FBPhS

- Has no relevant financial relationship to disclose
- and WILL BE DISCUSSING off-label or investigational use of products or services...Metformin
As faculty members of Weill Cornell Medicine - Qatar we are committed to providing transparency for any and all external relationships prior to giving an academic relationship.

I, Chris Triggle (Professor of Pharmacology), declare that I do NOT have a financial interest in commercial products or services or any conflicts of interest related to this lecture entitled:

“Metformin: A drug for all reasons?”
Lecture Objectives

• Summarize the basic pharmacology of metformin – particularly with reference to its use in the treatment of T2DM and its vasculoprotective effects.

• Evaluate the evidence of putative anti-cancer effects of metformin.

• Identify other potential indications for metformin.

ALSO:
Some Shakespeare
A little bit of history.
A little bit of German Renaissance art.
A little bit of controversy – why concentration matters.
And something for fans of Star Trek
PERSONALISED / PRECISION

– a Drug for All Reasons?
IF The Bard Of Avon was giving this talk today he might well re-phrase a well known speech from Julius Caesar, Act 3 Scene 2 and say:

“I COME TO PRAISE METFORMIN AND _ NOT _ TO BURY IT”

BUT ------
If Mary Poppins hadn't supplied the spoonful of sugar, maybe her charges wouldn't have needed metformin in the first place!
50+ years ago:
Pharmacotherapy for diabetes 1966

- **INSULINS** – animal origins (beef and or pork).

- **ORAL HYPOGLYCAEMICS:**
  - a. **Sulfonylureas:** tolbutamide & chlorpropamide
  - a. **Biguanides:** phenformin – FDA withdraws late 1978 (metformin used in UK)

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mechanism</th>
<th>I⁰ action</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>metformin</td>
<td>Activates AMPK; microbiome?</td>
<td>Hepatic glucose production</td>
<td>Experience; No hypoglycaemia; no weight gain; ↓CVD</td>
<td>GI SE; lactic acidosis (v.rare); VitB12 deficiency; Cls: CKD</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>glyberide</td>
<td>Closes $K_{\text{ATP}}$ ↑ insulin secretion</td>
<td></td>
<td>Extensive experience</td>
<td>Hypoglycaemia; weight gain =3-4 Kg; CV events?</td>
</tr>
<tr>
<td>Meglitinidines “prandins”</td>
<td>repaglinide</td>
<td>Closes $K_{\text{ATP}}$ ↑ insulin secretion</td>
<td></td>
<td>Postprandial excursions</td>
<td>Hypoglycaemia; weight gain; CV events?</td>
</tr>
<tr>
<td>Thiazolidinediones (Glitazones)</td>
<td>pioglitazone</td>
<td>PPARγ activation ↑ insulin sensitivity</td>
<td>No hypoglycaemia; Good lipid profile</td>
<td>Weight gain 4-5 Kg; edema/CHF; bone fractures; bone cancer?</td>
<td></td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>acarbose</td>
<td>Inhibits intestinal α-glucosidase ↑ intestinal absorption</td>
<td>No hypoglycaemia; Postprandial excursions</td>
<td>Only modest efficacy; GI issues; compliance? SS</td>
<td></td>
</tr>
<tr>
<td>GLP-1 analogues</td>
<td>Exenatide</td>
<td>GLP-1 receptor agonists ↑ Insulin secretion/satiety; ↓ glucagon secretion</td>
<td>No hypoglycaemia; weight reduction; improved β-cell function; CV benefits?</td>
<td>GI SEs; injections acute pancreatitis - controversial? SSS</td>
<td></td>
</tr>
</tbody>
</table>
| DPP-4 inhibitors       | sitagliptin | Enhances GLP-1 GLP-1 | Oral; No hypoglycaemia and well tolerated | Modest efficacy HbA1c; angioedema | $$ $$
| SGLT-2 inhibitors      | FLOZINS | ↓glucose kidney                               | Weight reduction; no hypoglycaemia? CV PROTECTION? | NEW; dehydration; UTI. Ketoacidosis? SSS |
HISTORY
# Traditional Plant Medicines as Treatments for Diabetes

<table>
<thead>
<tr>
<th>Plants</th>
<th>Location of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aconitum carmichaeli</td>
<td>Orient</td>
</tr>
<tr>
<td>Allium cepa</td>
<td>Asia, Europe, Middle East</td>
</tr>
<tr>
<td>Allium sativum</td>
<td>Asia, Europe, Middle East</td>
</tr>
<tr>
<td>Amorphophallus konjac</td>
<td>Orient</td>
</tr>
<tr>
<td>Anemarrhena asphodeloides</td>
<td>Orient</td>
</tr>
<tr>
<td>Atractylodes japonica</td>
<td>Orient</td>
</tr>
<tr>
<td>Blighia sapida</td>
<td>Africa, Central America</td>
</tr>
<tr>
<td>Catharanthus roseus</td>
<td>Africa, Asia, Europe, Australasia</td>
</tr>
<tr>
<td>Coccinia indica</td>
<td>Asia</td>
</tr>
<tr>
<td>Cyamopsis tetragonolobus</td>
<td>Asia</td>
</tr>
<tr>
<td>Dioscorea japonica</td>
<td>Orient</td>
</tr>
<tr>
<td>Eleutherococcus senticosus</td>
<td>Orient</td>
</tr>
<tr>
<td>Emericella quadrilineata</td>
<td>Asia</td>
</tr>
<tr>
<td>Ephedra distachya</td>
<td>Orient</td>
</tr>
<tr>
<td>Ficus benghalensis</td>
<td>Asia</td>
</tr>
<tr>
<td>Galega officinalis</td>
<td>Europe</td>
</tr>
<tr>
<td>Ganoderma lucidum</td>
<td>Orient</td>
</tr>
<tr>
<td>Gymnema sylvestre</td>
<td>Asia, South Africa</td>
</tr>
<tr>
<td>Lithospermum erythrorhizon</td>
<td>Orient</td>
</tr>
<tr>
<td>Lupinus termis</td>
<td>Middle East</td>
</tr>
<tr>
<td>Momordica charantia</td>
<td>Asia, Australasia, Central America,</td>
</tr>
<tr>
<td></td>
<td>West Africa</td>
</tr>
<tr>
<td>Momordica foetida</td>
<td>West Africa</td>
</tr>
<tr>
<td>Oryza sativa</td>
<td>Orient</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>Orient</td>
</tr>
<tr>
<td>Panax quinquefolium</td>
<td>Orient</td>
</tr>
<tr>
<td>Saccharum officinarum</td>
<td>Orient</td>
</tr>
<tr>
<td>Tecomastans</td>
<td>Central and South America, Middle</td>
</tr>
<tr>
<td></td>
<td>East, West Africa</td>
</tr>
<tr>
<td>Trigonella foenumgraecum</td>
<td>Asia, Europe</td>
</tr>
<tr>
<td>Vaccinium myrtillus</td>
<td>Europe, North America</td>
</tr>
</tbody>
</table>

- **Guanidine** - - galegine
- **Synthalin A & B**, polyethylene biguanides 1926-1940, liver & kidney problems
- **Pentamidine**
- **Trypanosomiasis & Chagas Disease**

Galega officinalis, French lilac, which in Germany was called “plague herb”, contain numerous guanidine derivatives, including galegine which cause hypoglycaemia. Goat's rue is widely used internationally as a galactogogue.

Galegine was, unsuccessfully, evaluated as an anti-hyperglycaemic drug in the 1920/30s. Synthetic biguanides phenformin & metformin were evaluated in 1950s.

Galegine  phenformin (phen-ethyl; Ciba Geigy)  metformin (dimethyl)
Metformin: 10 out of 10

1. Introduced in UK in 1958 with ~ 60 years of clinical knowledge.
3. Estimated 150 million patients currently use metformin worldwide.
4. Cardiovascular (microvascular) protective (UKPDS data).
5. Low risk of hypoglycaemia.
6. No weight gain; modest weight loss.
7. Orally effective, safe and relatively free of side effects.
8. Generic and therefore comparatively inexpensive.
10. Studies as an anti-ageing drug?
Want it or not - metformin in the drinking water?

Estimated urinary excretion ~250,000 Kg/day

Pharmaceuticals and personal care products found in the Great Lakes above concentrations of environmental concern

Benjamin D. Blair, Jordan P. Crago, Curtis J. Hedman, Rebecca D. Klaper

HIGHLIGHTS

- Pharmaceuticals and personal care products (PPCPs) were monitored in Lake Michigan.
- Fifty-four PPCPs were assessed in surface water and sediment on six dates.
- Many PPCPs, such as metformin, were detected 3.2 km away from the shore.
- Hydrophobic compounds were detected in sediment at concentrations up to 510 ng g⁻¹.
- Using a risk quotient, the ecosystem risk was found to be high for many PPCPs.
Metformin – A drug for ALL reasons?

First clinical use in France & United Kingdom in 1957/8, but not until 1995 in USA and now >150 million people prescriptions/year.
Metformin Acts on Two Different Molecular Pathways to Enhance Adult Neural Precursor Proliferation/Self-Renewal and Differentiation

Michael Fatt, Karolynn Hsu, Ling He, Fredric Wondisford, Freda D. Miller, David R. Kaplan, and Jing Wang

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http://dx.doi.org/10.1016/j.stemcr.2015.10.014
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)


UK Prospective Diabetes Study (UKPDS) Group*

**RISK REDUCTION WITH METFORMIN**: Based on data from a randomised control trial over a period of 10.7 years of 1704 overweight newly diagnosed T2DM patients. Diet vs. [metformin](https://en.wikipedia.org/wiki/Metformin) vs. intensive blood-glucose control with [chlorpropamide](https://en.wikipedia.org/wiki/Chlorpropamide), [glibenclamide](https://en.wikipedia.org/wiki/Glibenclamide) or [insulin](https://en.wikipedia.org/wiki/Insulin). The metformin (alone) treated group showed decreased diabetes-related endpoints, diabetes-related death and all cause mortality.

**CONCLUSION**: On balance, treatment (of T2DM) with metformin appears to be advantageous as a first-line pharmacological therapy in diet-treated overweight patients with T2DM.
From Professor Lebovitz
2014 EASD Virtual Meeting:
http://www.easdvirtualmeeting.org/resources/18622

UKPDS: Diabetes-Related Deaths in Metformin Study

- Conventional (n=411)
- Intensive (n=951)
- Metformin (n=342)

M vs C
P=0.017

M vs I
P=0.11

Improved Endothelial Function With Metformin in Type 2 Diabetes Mellitus

Kieren J. Mather, MD,* Subodh Verma, MD, PhD,† Todd J. Anderson, MD‡

Indianapolis, Indiana; and Toronto and Calgary, Canada

OBJECTIVES
This study was designed to assess the effect of metformin on impaired endothelial function in type 2 diabetes mellitus.

BACKGROUND
Abnormalities in vascular endothelial function are well recognized among patients with type 2 (insulin-resistant) diabetes mellitus. Insulin resistance itself may be central to the pathogenesis of endothelial dysfunction. The effects of metformin, an antidiabetic agent that improves insulin sensitivity, on endothelial function have not been reported.

METHODS
Subjects with diet-treated type 2 diabetes but without the confounding collection of cardiovascular risk factors seen in the metabolic syndrome were treated with metformin 500 mg twice daily (n = 29) or placebo (n = 15) for 12 weeks. Before and after treatment, blood flow responses to intraarterial administration of endothelium-dependent (acetylcholine), endothelium-independent (sodium nitroprusside) and nitrate-independent (verapamil) vasodilators were measured using forearm plethysmography. Whole-body insulin resistance was assessed on both occasions using the homeostasis model (HOMA-IR).

RESULTS
Subjects who received metformin demonstrated statistically significant improvement in acetylcholine-stimulated flows compared with those treated with placebo (p = 0.0027 by 2-way analysis of variance), whereas no significant effect was seen on nitroprusside-stimulated (p = 0.27) or verapamil-stimulated (p = 0.40) flows. There was a significant improvement in insulin resistance with metformin (32.5% reduction in HOMA-IR, p = 0.01), and by stepwise multivariate analysis insulin resistance was the sole predictor of endothelium-dependent blood flow following treatment (r = −0.659, p = 0.0012).

CONCLUSIONS
Metformin treatment improved both insulin resistance and endothelial function, with a strong statistical link between these variables. This supports the concept of the central role of insulin resistance in the pathogenesis of endothelial dysfunction in type 2 diabetes mellitus. This has important implications for the investigation and treatment of vascular disease in patients with type 2 diabetes mellitus. (J Am Coll Cardiol 2001;37:1344–50) © 2001 by the American College of Cardiology
“You are only as old as your endothelium”- Rudolf Altschul, 1954
Endothelial dysfunction - Defined as an impaired vascular relaxation to endothelium-dependent vasodilators such as acetylcholine & bradykinin or an impaired flow-mediated vasodilatation response. It is an early (earliest) indicator of arterio- and atherosclerosis.

Q. Can a short exposure of endothelial cells to metformin improve endothelial function and enhance eNOS-P?

Protocol:
Mouse ECs cultured in either normal or high glucose and effects of 50μM metformin on ser1177eNOS and sirtuin 1 (SIRT1) determined.

Answer:
Yes.

Metformin improves endothelial function in aortic tissue and microvascular endothelial cells subjected to diabetic hyperglycaemic conditions

Biochemical Pharmacology 2015

Suparna Ghosh\textsuperscript{a,1}, Arun P. Lakshmanan\textsuperscript{a,1}, Mu Ji Hwang\textsuperscript{b}, Haidar Kubba\textsuperscript{b}, Ahmed Mushannen\textsuperscript{b}, Chris R. Triggle\textsuperscript{a,b}, Hong Ding\textsuperscript{a,b,*}

\textsuperscript{a}Department of Pharmacology, Weill Cornell Medical College in Qatar, P.O. Box 24144, Education City, Doha, Qatar
\textsuperscript{b}Medical Education, Weill Cornell Medical College in Qatar, P.O. Box 24144, Education City, Doha, Qatar

50μM metformin not only improves endothelial function in blood vessels from diabetic mice but this can also be correlated with protection of eNOS function.
50μM metformin not only improves endothelial function in blood vessels from diabetic mice but this can also be correlated with protection of eNOS function.
SIRTUINS are the “Seven Samurai” in the regulation of metabolism & ageing

The sirtuins 1-7 are histone deacetylases (HDACs) that require NAD+ as a co-factor. They were named after their homology to the Saccharomyces cerevisiae gene silent information regulator 2 (Sir2). In yeast and the nematode, C. elegans, Sir2 mediates the effects of calorie restriction to extend life span.
The Fountain of Youth by Lucas Cranach – Berlin National Museum

1546 - FIRST DEMONSTRATION OF EFFECTIVENESS OF GENE THERAPY WITH SIRT1
Inspired by Lucas Cranach’s art we demonstrated that metformin prevents high glucose-induced endothelial cell senescence via a SIRT1-dependent mechanism.

SUMMARY: Pretreatment of mouse microvascular endothelial cells maintained in high glucose [HG] with 50μM metformin prevents HG-induced endothelial cell senescence. siRNA-knockdown of the NAD-dependent deacetylase – sirtuin-1 and metformin promotes deacetylation of eNOS and pro-angiogenic activity.

NOTE: Sirtuin-1 has been previously shown to be downregulated in cells that have high insulin resistance and inducing sirtuin-1 expression increases insulin sensitivity.
Metformin protects endothelial cells against high glucose-induced senescence

1. DHE Staining

2. β-galactosidase activity

MMECs treated with NG (11mM) and HG (40mM) along with metformin (50μM) for 72 hr. 1. DHE staining showing the ROS levels, 2. β-galactosidase activity as a measure of senescence.
In absence of SIRT1 metformin no longer reduces effects of HG on β-galactosidase activity

MMECs transfected with control and SIRT1 siRNAs and then treated NG (11 mM) along with metformin (50μM). SIRT1 knockdown showed increased β-galactosidase activity as a measure of senescence. Metformin treatment does not show any effect in reducing the β-galactosidase activity.
Knockdown of SIRT1 mimics effects of HG on protein expression/acetylation

In absence of SIRT1 metformin now has no “rescue effect” on protein expression/acetylation.

MMECs transfected with control and SIRT1 siRNAs and then treated NG (11 mM) along with metformin (50μM). SIRT1 knockdown showed increased Ac-Foxo1, Ac-p53 and p21 levels.
microRNAs – small non-coding molecules with RNA-silencing actions: Role in regulation of vascular function:

**Angiogenesis**
- miR-126, miR-221/222
- miR-17-92, miR-23-24
- miR-16, miR-424
- miR-130, miR-132
- miR-101, miR-200b

**Inflammation**
- miR-126, miR-21, miR-181b
- miR-10a, miR-31, miR-17
- miR-155, miR-150, miR-17-92
- miR-424, miR-17-5b, miR-20a
- miR-106a, miR-146

**Diabetic Nephropathy**
- miR-192, miR-377, miR-93, miR-29c, miR-21 and miR-25
- miR-146a

**Diabetic Heart /ECs**
- miR-320, miR-221/222
- miR-133, miR-1
- miR-206, miR-125b, miR-503

**Diabetic Retinopathy**
- miR-146, miR-155
- miR-132, miR-21
- miR-34, miR-220b, miR-29

**EC senescence**
- miR-34a, miR-217
- miR-200, miR-146a

miR-34a – tumour suppressor & via binding within 3’ UTR of SIRT1 reduces sirtuin 1 expression
miR34a increased in HG but reduced by metformin

Mean ± S.E.M of miR-34a expression normalized to U6 small nuclear RNA as an endogenous control

SO HOW DOES METFORMIN MEDIATE ITS EFFECTS?
Distribution of SLC transporters for metformin

Liver

OCT1

MATE1

Extrusion from liver

metformin

Kidney

OCT2

MATE1/2

Expression of SLCs in cardiovascular system?

ORAL METFORMIN

PMAT/OCT1&3

apical membrane

basement membrane

GI

OCT1

OCT1

apical membrane

basement membrane

Via bloodstream unchanged metformin is distributed throughout body

Unchanged metformin is eliminated through urine
Metformin inhibits mitochondrial Complex 1?

THE ZOMBIE LITERATURE
Metformin: Reduces hyperglycaemia; protects endothelium; reduces cell growth.

Adapted from: Triggle & Ding: Acta Physiologica 2017
In 1984 Bonora et al reported that IV administered metformin has no effect on plasma glucose in non-diabetic patients.

1) “Novel Gut-Based Pharmacology of Metformin in Patients with Type 2 Diabetes Mellitus” Antonella Napolitano, GSK, PLOS ONE July 2014 | Volume 9 | Issue 7 | e100778

Metformin affects gut microbiome and enhances entero-hepatic recirculation of bile acids, modulation of gut microbiota and changes in gut hormones, especially GLP-1.


NOTE: the metformin concentration in the jejenum peaks at 500 μg/g, 30–300 times greater than plasma concentrations.
Mechanism of Metformin: A Tale of Two Sites

Diabetes Care 2016;39:187–189 | DOI: 10.2337/dci15-0013

B
- Met XR (Upper Gut Absorption)
  - Bio-Avail. ~50%
  - LG Accum. ~50%
  - HGP
  - Met GLP → FPG

C
- Met DR (Lower Gut Release)
  - Bio-Avail. ~25%
  - LG Accum. ~75%
  - HGP
  - Met GLP → FPG

Ruisheng Song
Yes, concentration does matter!

MetforminAction: ConcentrationsMatter

LingHe1 and Fredric E. Wondisford1,*
1Division of Metabolism, Department of Pediatrics, Physiology and Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.
*Correspondence: fwondis1@jhmi.edu http://dx.doi.org/10.1016/j.cmet.2015.01.003

Metformin has been used for nearly a century and is now the most widely prescribed oral anti-diabetic agent worldwide. Yet how metformin acts remains only partially understood and controversial. One key reason may be that almost all previous studies were conducted with supra-pharmacological concentrations (doses) of metformin, 10–100 times higher than maximally achievable therapeutic concentrations found in patients with type 2 diabetes mellitus.
Drug Selectivity Depends on Concentration

[Yohimbine] (log molar)

-9 -8 -7 6 -5 -4 -3 -2 -1

- \( \alpha_2 \)-adrenergic receptor blockade
- 5-HT receptor blockade
- \( \alpha_1 \)-adrenergic receptor blockade
- local anesthetic
- MAO inhibitor
- anti-cholinesterase
“Ye cannae change the Laws of Pharmacokinetics”

YE CANNAE CHANGE

THE LAWS OF PHARMACOKINETICS
Steady-state pharmacokinetics of metformin is independent of the \textit{OCT1} genotype in healthy volunteers

Mette Marie Hougaard Christensen\textsuperscript{1} \cdot Kurt Højlund\textsuperscript{2} \cdot Ole Hother-Nielsen\textsuperscript{2} \cdot Tore Bjerregaard Stage\textsuperscript{1} \cdot Per Damkier\textsuperscript{1,3} \cdot Henning Beck-Nielsen\textsuperscript{2} \cdot Kim Brøsen\textsuperscript{1}

**Plasma metformin concentration–time curve**

PEAK concentration is in ng/ml peak \(\sim 16\mu\text{M}\)
Metformin & Cancer: Is it a Paracelsus effect, or selective toxicity?

“The dose makes the poison”.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Standard clinical use</th>
<th>In vivo preclinical studies</th>
<th>In vitro laboratory studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250 to 2250 mg/day</td>
<td>750 mg/kg per day</td>
<td>2 to 50 mM</td>
</tr>
<tr>
<td>Relative Dose*</td>
<td>0.15 to 1.0</td>
<td>2 to 45</td>
<td>25 to 1000</td>
</tr>
</tbody>
</table>

CONCENTRATIONS MATTER! In this study the investigators used metformin concentrations 8.0mM, 25mM, 50mM & 150mM.
To achieve a plasma concentration of 100 mM in man you would need to give an oral dose of >5 Kg!
Does metformin protect against cancer?

BMJ 2005

RESEARCH POINTERS

Metformin and reduced risk of cancer in diabetic patients
Josie M M Evans, Louise A Donnelly, Alistair M Emslie-Smith, Dario R Alessi, Andrew D Morris

Metformin, widely given to patients with type 2 diabetes, works by targeting the enzyme AMPK (AMP activated protein kinase), which induces muscles to take up glucose from the blood. A recent breakthrough has found the upstream regulator of AMPK to be a protein kinase known as LKB1. LKB1 is a well recognised tumour suppressor. Activation of AMPK by metformin and exercise requires LKB1, and this would also explain why exercise is beneficial in the primary and secondary prevention of certain cancers. We hypothesise that metformin use in patients with type 2 diabetes may reduce their risk of cancer.

What this paper suggests
Metformin may reduce the risk of cancer in patients with type 2 diabetes

What research is needed now
A more rigorous cohort study, before experimental work is initiated

However, rather than a direct anti-proliferative effect:
1/ Suppression of gluconeogenesis (G-6-P, PEPCK) and hyperinsulinemia would reduce tumour growth – particularly when insulin sensitive.
2/ Tumour cells highly dependent on glycolysis (Warburg effect) that would be inhibited by metformin (HKI & HKII).
Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis

C. Coyle*, F. H. Cafferty, C. Vale & R. E. Langley

MRC Clinical Trials Unit at University College London, London, UK

This 2016 review by Coyle et al concludes that there is a particular benefit for metformin in colorectal and prostate cancer.

ACTIVE TRIALS:
1. The Metformin Active Surveillance Trial – a Phase III trial of metformin vs. placebo given before primary therapy in assessing time to progression in low-risk prostate cancer.
2. The STAMPEDE Trial – a randomised phase III trial of metformin vs. placebo. Aims to evaluate whether the addition of metformin improves survival in the treatment of hormonenaïve, high-risk, localised and metastatic prostate cancer.
3. In colorectal cancer, a phase III trial of metformin versus standard care assessing recurrence and survival in stage III disease is now in set-up phase in South Korea.
Insulin  Growth Factor  GF Receptor  

PI3K  

AKT  

AMPK  

LKB1  

Micro RNAs  

SIRT1  

Rheb  

Rheb  

Raptor  

mTOR  

TSC1  

TSC2  

AMPK  

mTOR  

Triggle & Ding - unpublished
Autophagy, a catabolic process involving protein/organelle degradation and autophagosomes / lysosomes, serves a dual role in cancer:

1. **a tumour suppressor mechanism** that prevents the accumulation of damaged proteins and organelles.

2. **a mechanism of cell survival** that promotes the growth of established tumors - tumour cells activate autophagy in response to cellular stress and/or increased metabolic demands and enable cell survival.

3. **Metformin** has been reported to both promote and inhibit autophagy via AMPK-dependent and –independent mechanisms.
Glucose starvation initiates ER Stress & activates the Akt/mTOR pathway, BUT inhibited by metformin.

**NOTE:** significant increase in the mTOR inhibitory Raptor phosphorylation (pRap; S792)
Glucose starvation & metformin is anti-angiogenic

2mM metformin decreases SIRT1

Samuel & Triggle unpublished

2mM metformin enhances TSP1

---

[Diagram showing the effects of glucose and metformin on SIRT1 and TSP1 expression]
Concentration-Dependent Effects of Metformin

< 100 μM metformin is “endothelial protective” – protects against HG-induced senescence, enhances eNOS activity, enhances angiogenesis: AMPK-dependent?

>500 μM metformin has anti-angiogenic actions, inhibits autophagy, reduces cell survival: AMPK independent?
Conclusions

• Multiple targets for metformin, but note concentration dependence.

• **Therapeutic levels** modulate eNOS and SIRT1 function in endothelial cells = endothelial / vascular protective.

• Effects of metformin on endothelium linked to SIRT1/ microRNA34a & AMPK (?)

• “**Paracelsus levels**” of metformin have anti-angiogenic action and promote apoptosis (data not shown) – and might explain anti-cancer effects of metformin. BUT can such high levels be reached in cancer cells with therapeutic doses (as for diabetes) of metformin? Possibly IF there is an imbalance in the expression of inward versus extrusion transporters for the drug.
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Ms. Tina Bharani, Merna Hussein & Mr. Tarek Taha – Medical students

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Dr. Rohit Upadhyay
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- Profs. Aimin Xu/Paul Vanhoutte - University of Hong Kong

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