Novel AMPK activators for the treatment of Type 2 Diabetes and related metabolic diseases

Pascual Sanz

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GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española
farmaindustria

Content:

1.- The Institutions: - Spanish National Research Council (CSIC)
- Network of Excellence on Rare Diseases (CIBERER-ISCiii)

2.- The Product: New indol-derivatives

a) Target Indications: AMP-activated protein kinase (AMPK)

b) Innovative mechanism of action. Chemical characteristics

c) Current status of development

d) Differential features facing the market

e) IPR protection

f) Pitfalls & Risks to be considered

3.- Partnering Opportunities

1.- The Institutions: - Spanish National Research Council (CSIC)
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CSIC
CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

- Largest public research organization
- 21 different Center/Institutes in the Biology and Biomedical field

ibv INSTITUTO DE BIOMEDICINA DE VALENCIA CSIC

- 11 scientific groups in different research areas: structural biology, genomics, pathophysiology of disease, etc.

- **Nutrient Signalling Unit**. Dr. Sanz: Role of AMPK in cell physiology, regulation of its activity by post-translational modifications

ciberer
CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED DE ENFERMEDADES RARAS

- Network of Excellence on Rare Diseases
- 62 scientific groups, leading the research on different rare diseases

- **U742**: Dr. Pascual Sanz: Rare diseases related to glucose metabolism dysfunction, i.e. Lafora Disease (progressive myoclonus epilepsy)

2a.- The target: AMP-activated protein kinase (AMPK)

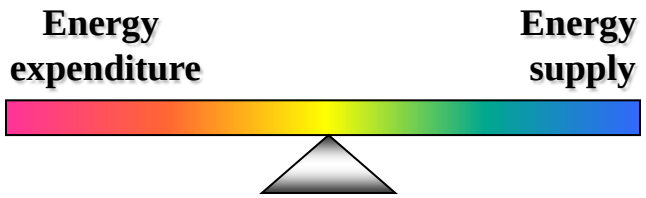
"Energy sensor"

[AMP]:[ATP] **Stress signals**

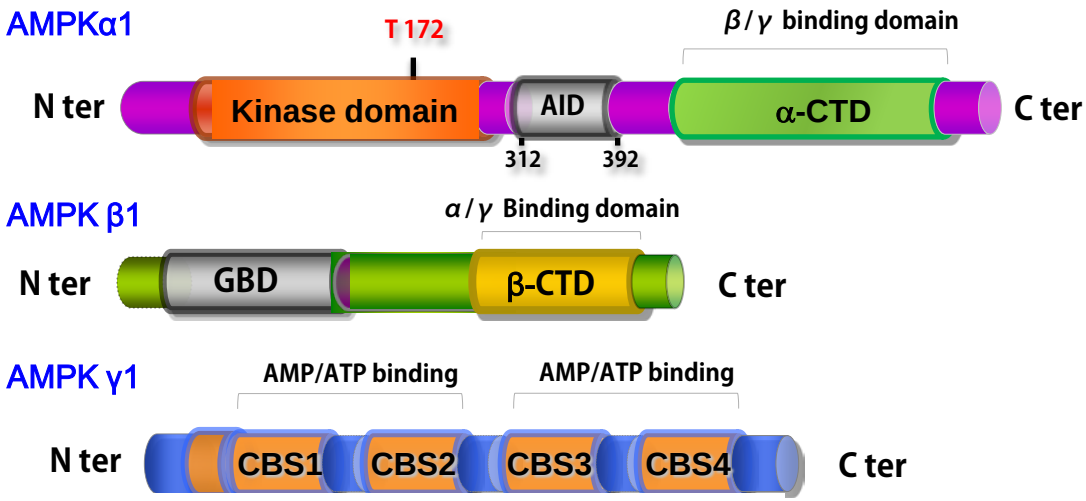
AMPK-P

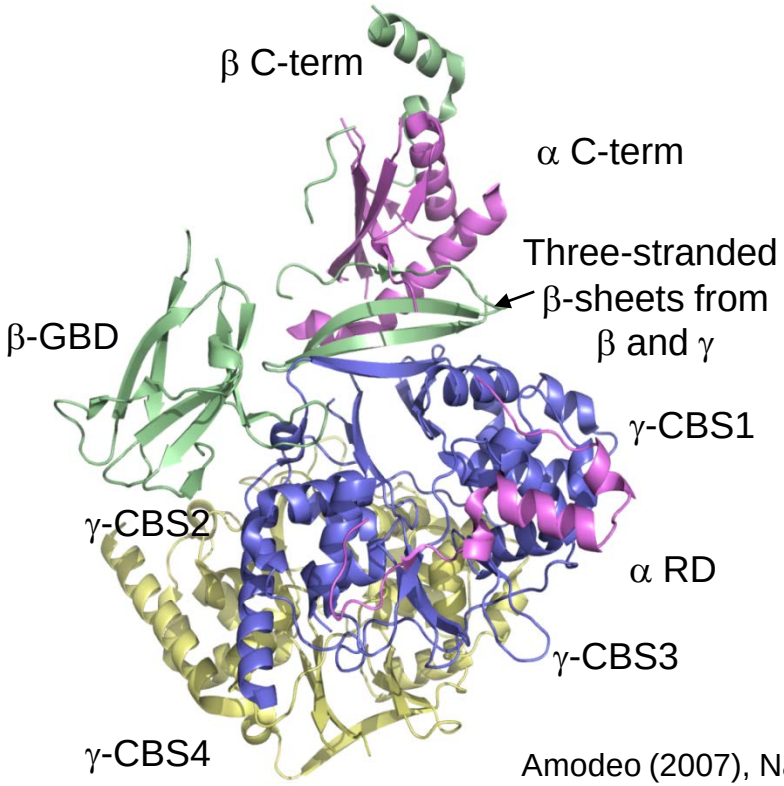
↓ **Anabolism** ↑ **Catabolism**

Long term effects:
Regulation of gene expression



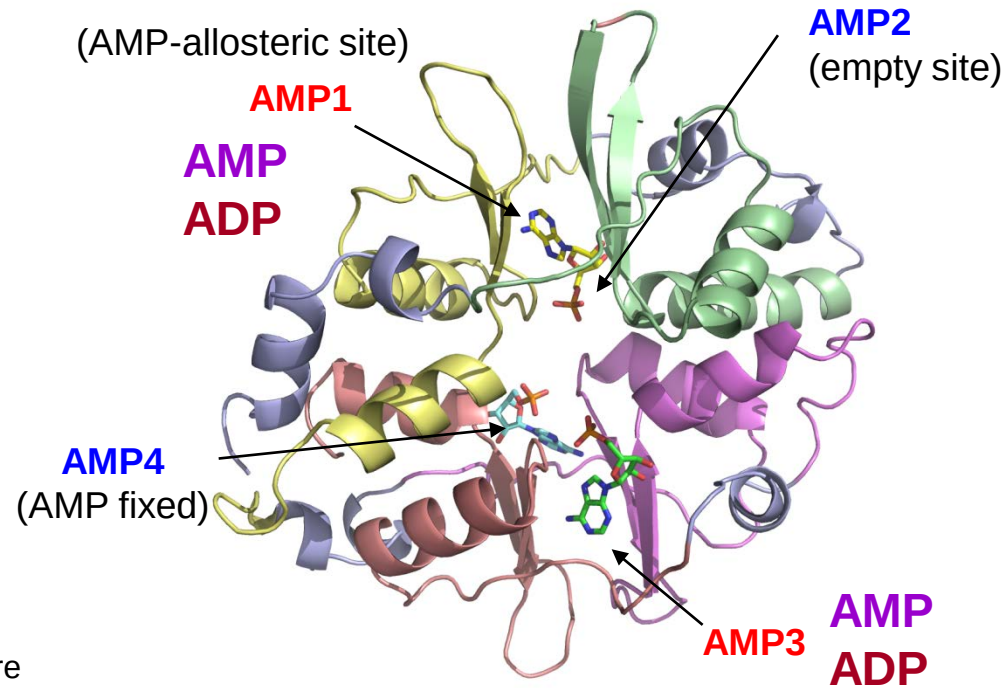
AMPK structure and modulation





Amodeo (2007), Nature

AMP allosteric regulation of AMPK activity

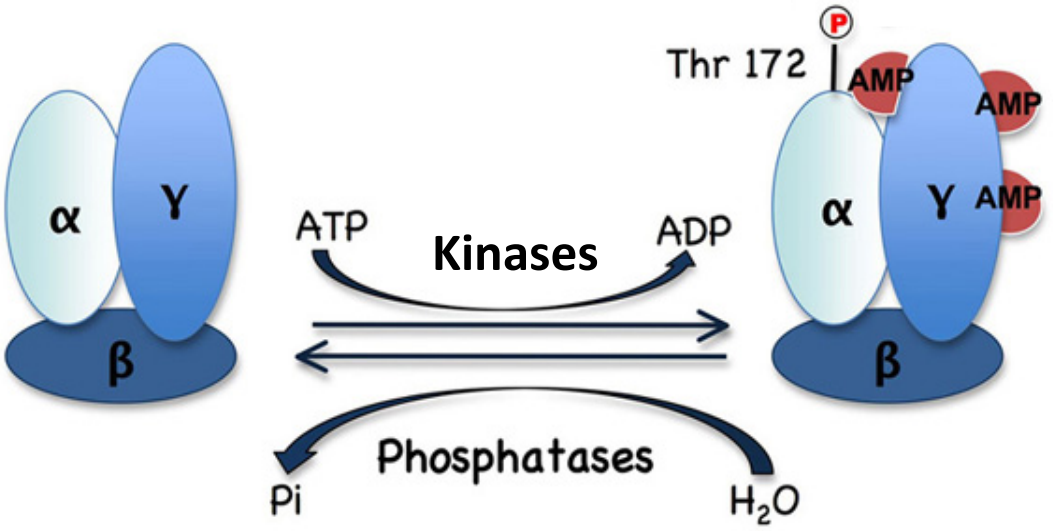


AMPK regulation

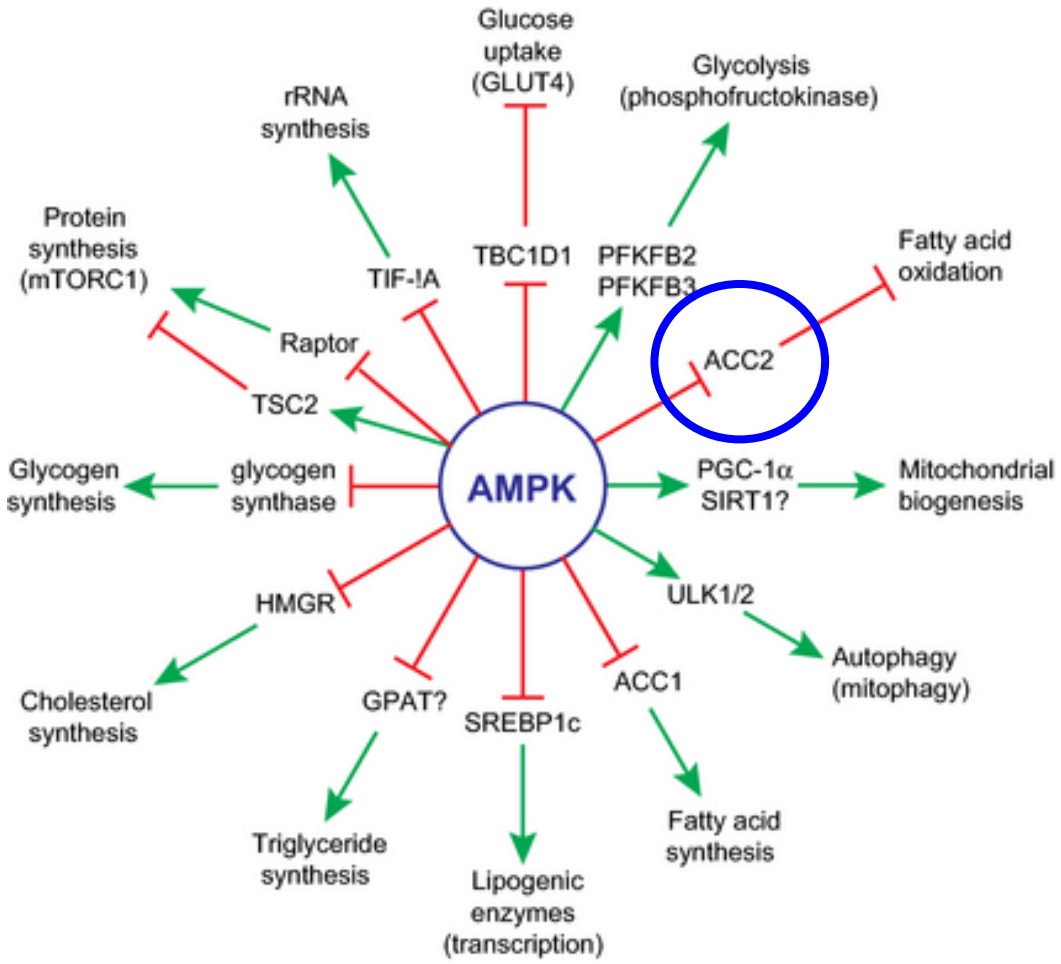
AMP allosteric activation: 10 fold

Phosphorylation α-subunit: 100 fold

} 1000 fold



AMPK as a metabolic regulator



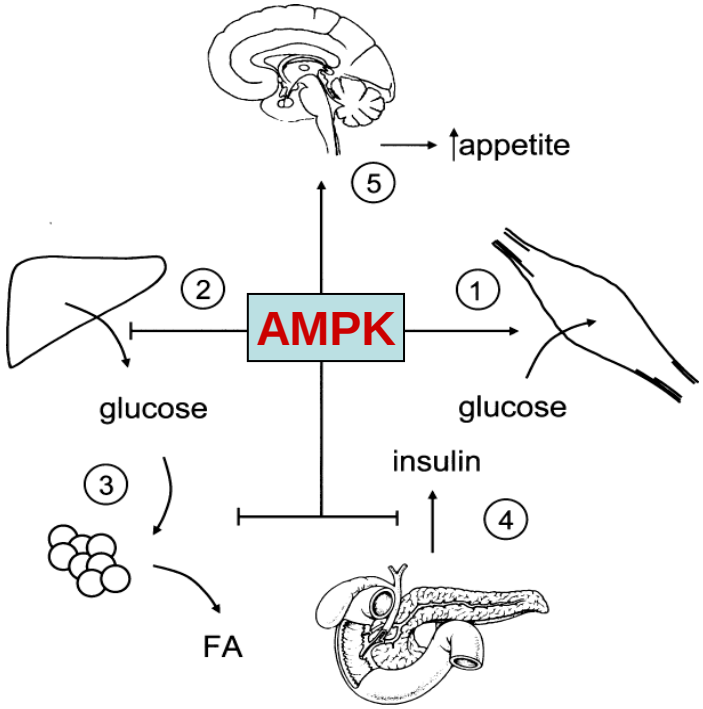
Catabolic pathways

Anabolic pathways

Hardie, 2014 J. Internal Med. 276:543

AMPK, Diabetes and Obesity

1) Activation of AMPK by exercise or by pharmacological activators may be useful to correct the metabolic defects of patients suffering from insulin resistance, type 2 diabetes and obesity.



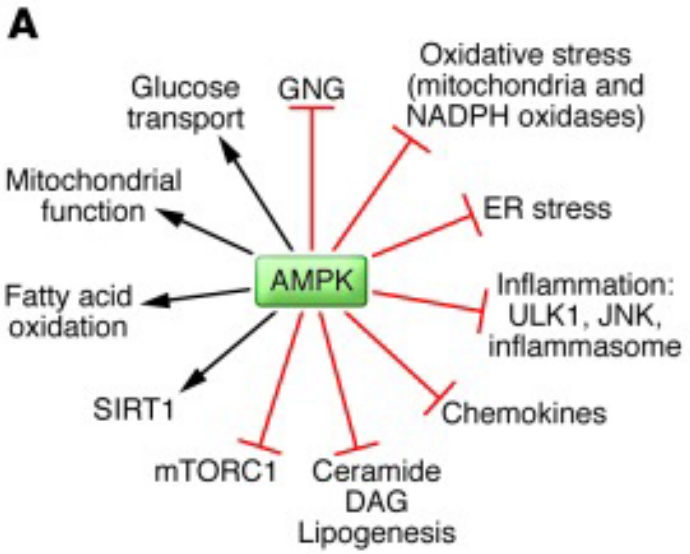
2) Metformin (oral antidiabetic drug) is able to activate AMPK.

3) In addition to its action on peripheral tissues, AMPK plays a role at the CNS.

AMPK: additional roles

1) Role of AMPK in inflammatory disease

- AMPK attenuates production of inflammatory cytokines
- By enhancing fatty acid oxidation, AMPK attenuates production of proinflammatory diacylglycerol
- AMPK attenuates oxidative stress



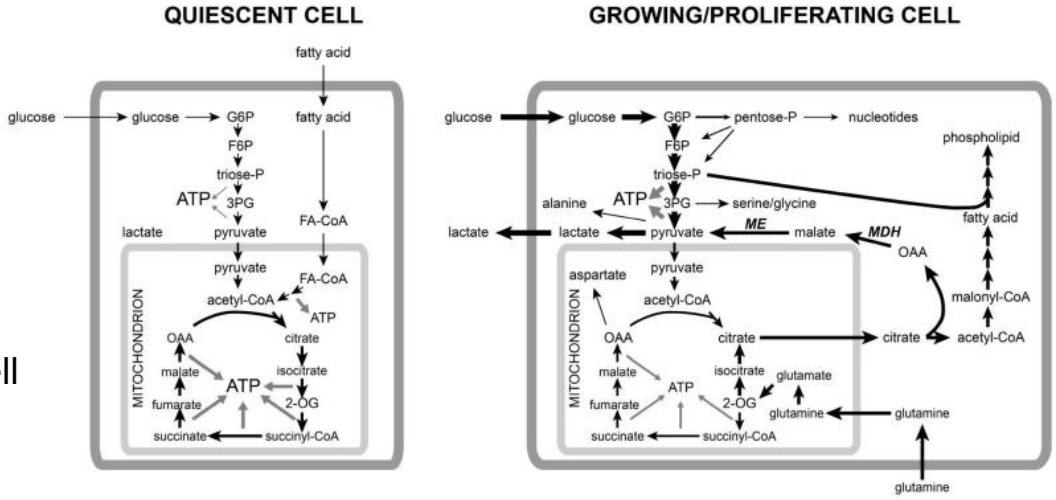
Hardie, 2014 J. Internal Med. 276:543

Dandapani M, Hardie DG. Biochem Soc Trans. 2013, 41:687

Ruderman et a., 2013 J Clin Inves 123: 2764

2) Role of AMPK in cancer

- AMPK activation tends to promote the more energy-efficient **oxidative metabolism**, thus opposing the switch to aerobic glycolysis observed in many tumour cells
- AMPK **inhibits mTOR function**, preventing cell proliferation

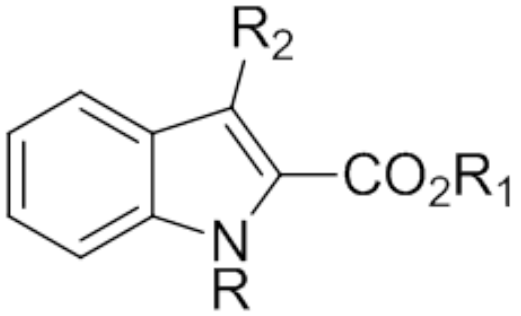


2b.- Innovative mechanisms of action

a) Chemical characteristics.

New indole-derivatives

Dr. Ana Castro
Instituto de Química Médica (CSIC)



- **Small** molecules
- **Simple** synthesis procedure
- **Inexpensive** starting material
- **Pharmacological profile** related to the chemical class of R substituents
- **Lead compounds** for further optimization

IQM_AC1303 IQM_AC1311 IQM_AC1316

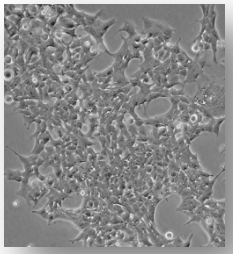
2b.- Innovative mechanisms of action

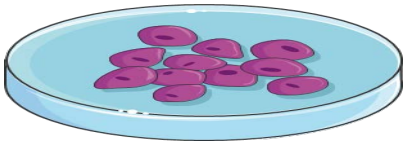
b) *In silico* ADME Properties.

Compound	IQM_AC1303	IQM_AC1311	IQM_AC1316
QPlogS[a]	-5.123	-7.090	-5.949
QPPCaco[b]	91.988	282.733	214.357
QPPMDCK[c]	47.721	160.617	119.077
HumanOralAbsorption (%)[d]	85.952	95.420	85.392

[a] Predicted aqueous solubility [range of 95% of drugs: −6.5 to +0.5].
[b] Apparent Caco-2 cell permeability (nm/s) [<25, poor; >500, excellent]
[c] Apparent MDCK cell permeability (nm/s) [<25, poor; >500, excellent].
[d] Human oral absorption in gastro-intestinal tract [<25% is poor].
(*QikProp Program, Schrödinger*)

2c.- Current status of development





HEK293 cells

1 hour

5 mM phenformin

or

IQM_ACs

Cell extracts

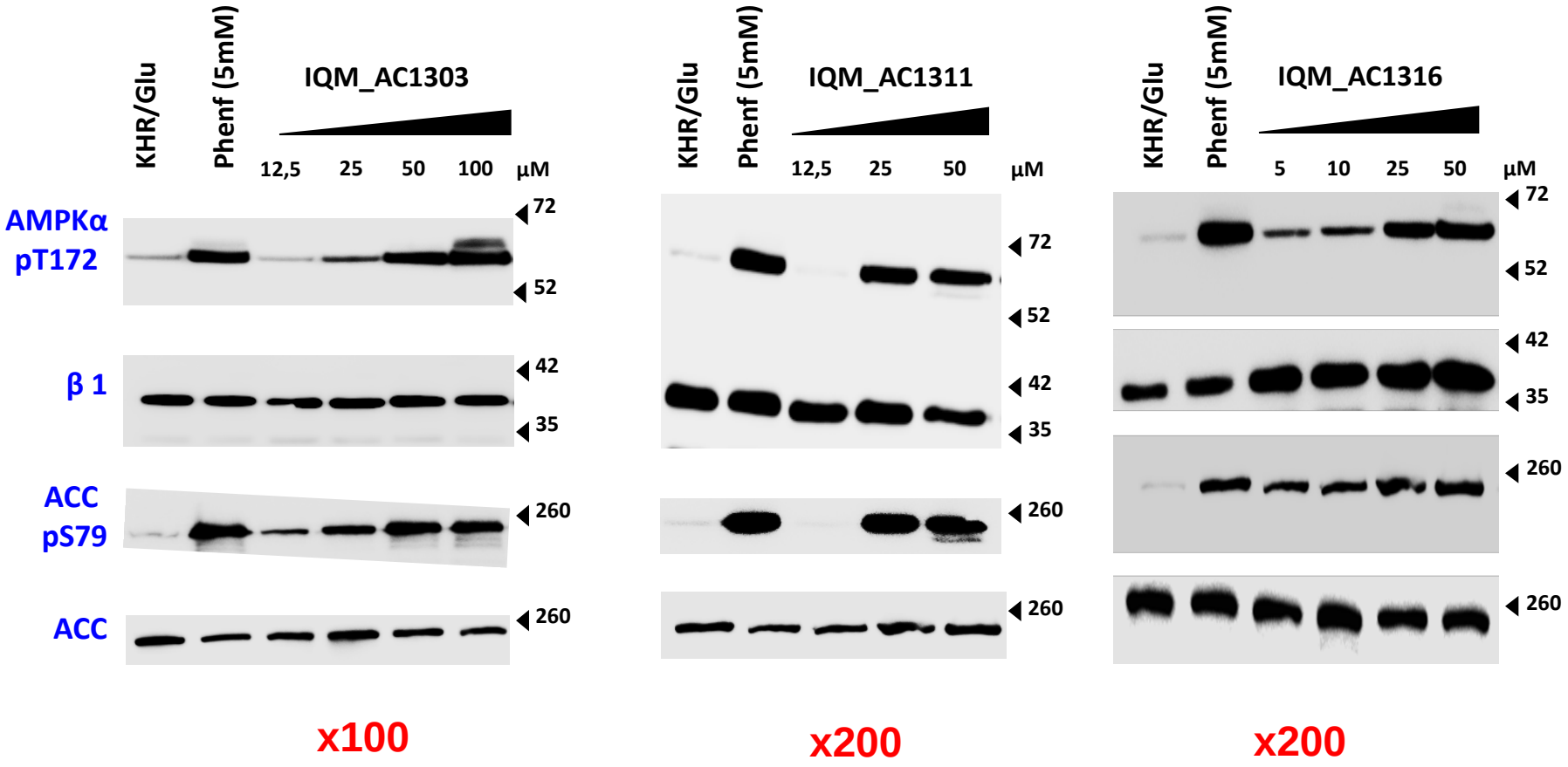
pT172-AMPK/AMPK

pACC/ACC

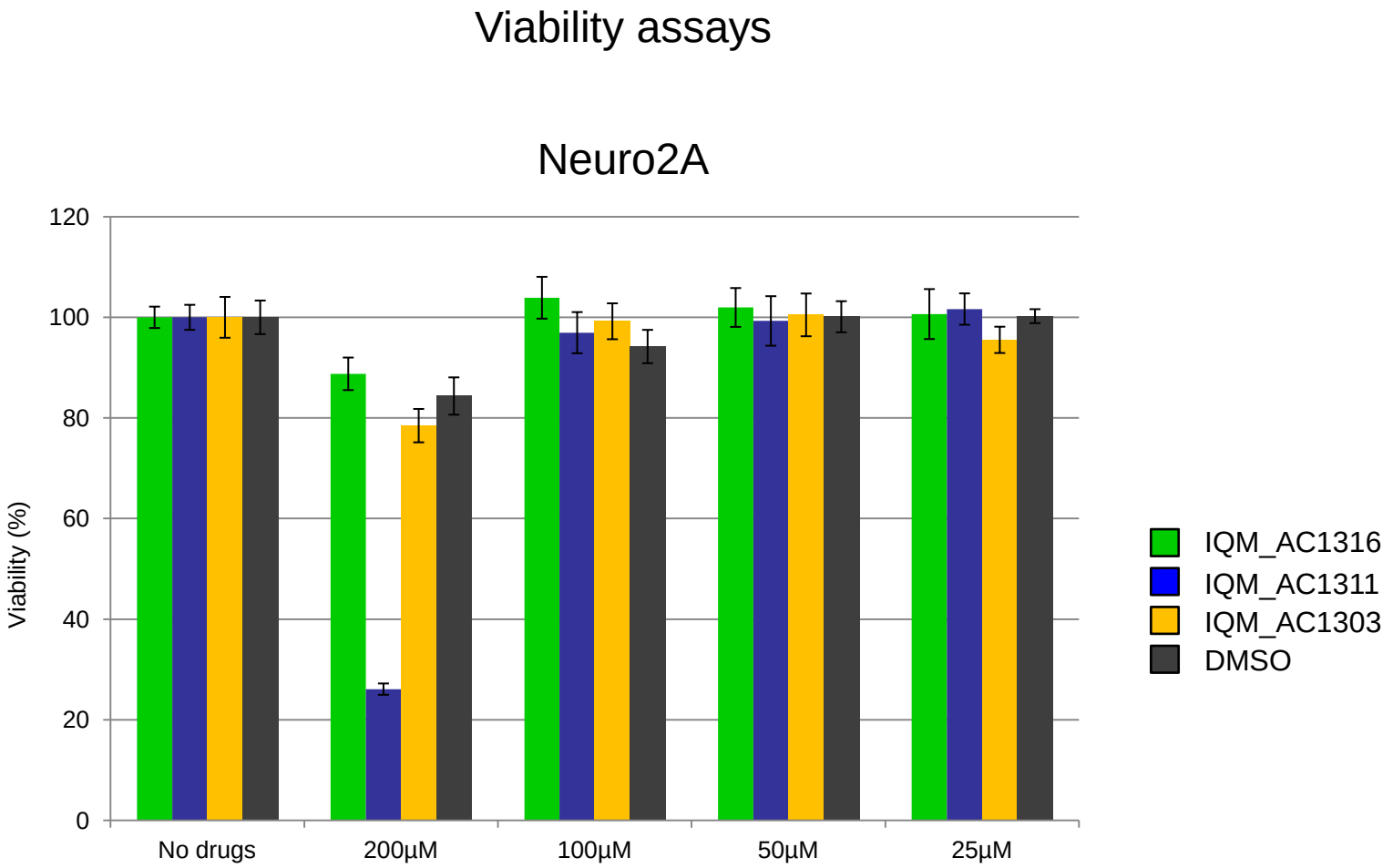
IQM_ACs compounds are:
water soluble,
entry cells,
and exerts there their function

2c.- Current status of development

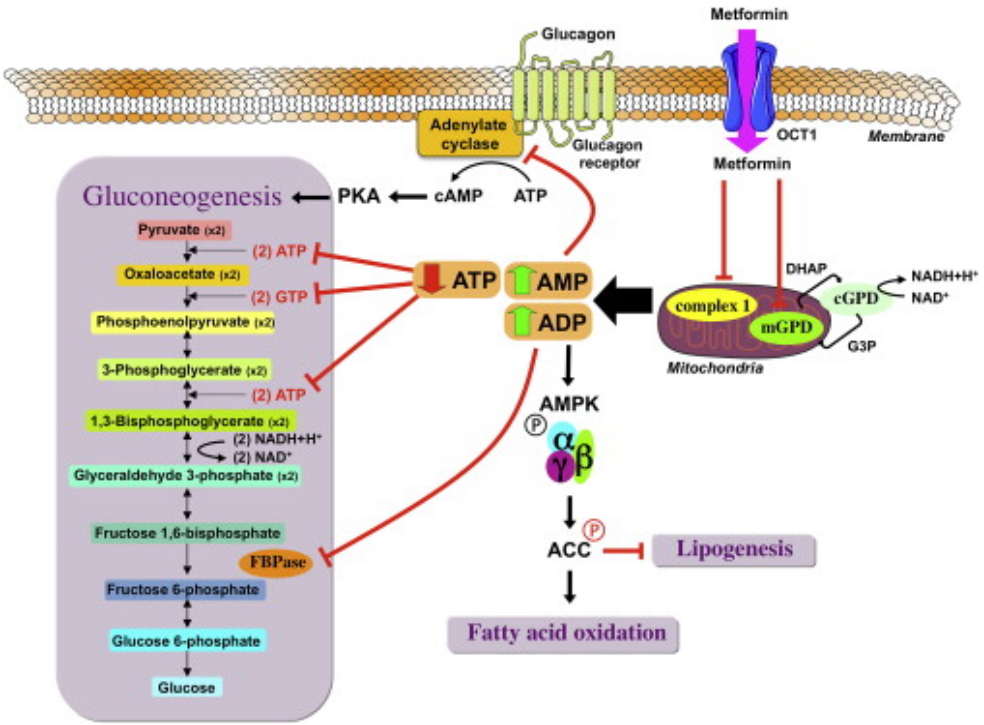
Effect of products on AMPK activity



2c.- Current status of development

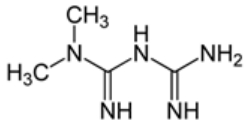


2d.- Differential features facing the market



Foretz et al., 2014 Cell Metab 20:953

Metformin



But

- High dose of around 2g/day
- Indirect activator of AMPK, through inhibition of complex-I of the respiratory chain
- AMPK-independent effects
- Main function at the liver

Adverse effects

- Risk of lactic acidosis
- Gastrointestinal disturbance

Pernicova et al., 2014 Nat. Rev.Endocrinol 10:143
Pryor et al., 2015. Biochem J. 471:307

2e.- IPR protection

Autores: Ana Castro Morera, Pascual Sanz Bigorra, Marta Vela Ruiz y Maria Adelaida Garcia-Gimeno.
Título: Derivados de indol para la prevención y/o tratamiento de diabetes y trastornos metabólicos relacionados.
N° de registro: PCT/ES2015/070677 Año: 2015
Paises: España y países cubiertos por la PCT.
Entidad titular: Consejo Superior de Investigaciones Científicas y Centro de Investigación Biomédica en Red (CIBER).

2f.- Pitfalls & Risks to be considered

- No data on the mechanism of action of the new compounds

- No data on the action of the new compounds on alternative signaling pathways

- Project in early stages of drug development

3.- Partnering Opportunities

- Companies with interest to license our research work
- Companies with interest to grant *in vivo e*xperiments to evaluate IQM_AC products in a model of diabetes
- Companies with interest to grant a project centered in the optimization of IQM_AC derivatives or alternative AMPK activators

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