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

Pascual Sanz

Madrid, 17 de noviembre de 2015
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)
- Network of Excellence on Rare Diseases (CIBERER-ISCiii)

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

- 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"

\[
\frac{[\text{AMP}]}{[\text{ATP}]}
\]

Stress signals

AMPK-P

↓ Anabolism  ↓  Catabolism

Long term effects:

Regulation of gene expression

Energy expenditure  Energy supply
AMPK structure and modulation

AMPK α1
N ter - Kinase domain - AID - α-CTD - C ter

AMPK β1
N ter - GBD - β-CTD - C ter

AMPK γ1
N ter - CBS1 - CBS2 - CBS3 - CBS4 - C ter

AMP allosteric regulation of AMPK activity

β C-term
α C-term
Three-stranded β-sheets from β and γ
γ-CBS1
γ-CBS2
γ-CBS3
γ-CBS4

β-GBD
γ-CBS1
γ-CBS2
γ-CBS3
γ-CBS4

β-GBD
γ-CBS1
γ-CBS2
γ-CBS3

AMP4 (AMP fixed)
AMP1 (AMP-allosteric site)
AMP2 (empty site)
AMP3

Amodeo (2007), Nature
AMPK regulation

AMP allosteric activation: 10 fold
Phosphorylation α-subunit: 100 fold

1000 fold

AMP allosteric activation

Phosphorylation α-subunit
AMPK as a metabolic regulator

Anabolic pathways

Catabolic pathways

Hardie, 2014 J. Internal Med. 276:543
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**

- **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.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IQM_AC1303</th>
<th>IQM_AC1311</th>
<th>IQM_AC1316</th>
</tr>
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<tbody>
<tr>
<td>QPLogS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-5.123</td>
<td>-7.090</td>
<td>-5.949</td>
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<tr>
<td>QPPCaco&lt;sup&gt;b&lt;/sup&gt;</td>
<td>91.988</td>
<td>282.733</td>
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<tr>
<td>QPPMDCK&lt;sup&gt;c&lt;/sup&gt;</td>
<td>47.721</td>
<td>160.617</td>
<td>119.077</td>
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<td>HumanOralAbsorption (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>85.952</td>
<td>95.420</td>
<td>85.392</td>
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</tbody>
</table>

<sup>a</sup> Predicted aqueous solubility [range of 95% of drugs: −6.5 to +0.5].

<sup>b</sup> Apparent Caco-2 cell permeability (nm/s) [<25, poor; >500, excellent]

<sup>c</sup> Apparent MDCK cell permeability (nm/s) [<25, poor; >500, excellent].

<sup>d</sup> 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

<table>
<thead>
<tr>
<th></th>
<th>KHR/Glu</th>
<th>Phenf (5mM)</th>
<th>IQM_AC1303</th>
<th>12.5</th>
<th>25</th>
<th>50</th>
<th>100</th>
<th>μM</th>
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<td>AMPKα</td>
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<td>260</td>
</tr>
</tbody>
</table>

- **IQM_AC1303**: 12.5, 25, 50, 100 μM
- **IQM_AC1311**: 12.5, 25, 50 μM
- **IQM_AC1316**: 5, 10, 25, 50 μM

*Images show protein levels at different concentrations.*
2c. - Current status of development

Viability assays

Neuro2A

Viability (%)

No drugs  200µM  100µM  50µM  25µM

IQM_AC1316  IQM_AC1311  IQM_AC1303  DMSO
2d.- Differential features facing the market

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

Foretz et al., 2014 Cell Metab 20:953

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


Países: 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* experiments 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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