Bile Acid-Activated Receptors, Intestinal Microbiota and the Treatment of Metabolic Disorders

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Disclosure

Member of the scientific advisory board of BAR Pharmaceuticals, a company that is currently involved in developing FXR and GPBAR1 ligands

I have received research grants from BAR Pharmaceuticals in the last 2 years

I have been a co-founder of Intercept Pharmaceuticals and I’m listed as a co-inventor in several patents related to FXR and GPBAR1 ligands
The gut microbiota

Targets:
- Immune system
- Endocannabinoids
- Hormones
- Bile acids
- SCFAs
- Biogenic amines
- Xenometabolites

Composition of bile acids in the gallbladder and feces of microbiota

Redrawn From: Ridlon J M et al. J. Lipid Res. 2006;47:241-259
The intestinal microbiota shapes a gradient of FXR and GPBAR1 ligands throughout the intestine.

Relative percent of individual bile acids:
- Bile
  - Others: 1%
  - UDCA: 2%
  - DCA: 25%
  - CDCA: 35%
  - CA: 35%

Preferential activity:
- FXR
- GPBAR1

 Preferential activity in Feces:
- Others: 28%
- UDCA: 2%
- LCA: 28%
- DCA: 34%
- CDCA: 2%
- CA: 2%

Mice only:
- αMCA
- βMCA
- ωMCA
- HCA
- HDCA

Cholesterol:
- CDCA
- CA
- DCA
- LCA

Glp-1

Mice only
# Bile acid activated receptors (BARs)

<table>
<thead>
<tr>
<th>Nuclear receptors</th>
<th>Natural bile acid ligands</th>
<th>Synthetic ligands</th>
</tr>
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<tbody>
<tr>
<td>Farnesoid X receptor</td>
<td>CDCA=LCA=DCA&gt;CA</td>
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<tr>
<td>PXR</td>
<td>LCA&gt;DCA&gt;CA</td>
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<tr>
<td>Vitamin D receptor</td>
<td>3-oxo-CA=LCA&gt;LCA&gt;DCA&gt;CA</td>
<td></td>
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<tr>
<td>LXR</td>
<td>Hyocholic and Hy-DCA</td>
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<th>G-protein coupled receptors</th>
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<td>Sphingosine 1-phosphate receptor 2</td>
<td>Taurine or glycine conjugate DCA,LCA</td>
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<td>EGF-R</td>
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*OCA, Obeticholic acid (6-ECDCA, INT-747) is a dual FXR-GPBAR1 ligand (EC_{50} ≈400 nM for FXR and ≈900 nM for GPBAR1)

° UDCA is a very weak agonist for GPBAR1 (EC_{50}=50 µM)

GW4064 and Px-104 are non steroidal FXR ligand
Fexaramine is a poorly absorbed, intestinal FXR agonist
BAR502,BAR504 and BAR704 are steroidal non bile acids ligands for GPBAR1 and FXR

Novel FXR and GPBAR1 ligands

- **BAR501**: Selective GPBAR1 agonist
- **BAR704**: Selective FXR agonist
- **BAR502**: Dual FXR and GPBAR1 agonist
GPBAR1 agonist

BAR501

Concentration/response curve to BAR501 in vitro. HEK293 cells transfected with GPBAR1 and cAMP-responsive element (CRE) cloned upstream to a luciferase reporter

BAR501 induces the release of GLP-1 in vitro from Glutag cells.

Claudio D’Amore; et al.; J. Med. Chem. 2014, 57, 937-954.DOI: 10.1021/jm401873d
BAR501 is a selective GPBAR1 (TGR5) ligand with no activity toward FXR.

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<td>Affinity (µM)</td>
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Mode of binding of BAR501 on GPBAR1

Claudio D’Amore; et al.; *J. Med. Chem.* 2014, 57, 937-954. DOI: 10.1021/jm401873d
GPBAR1 and intestinal inflammation
GPBAR1 is expressed by cells of innate immunity

Vavassori P. et al. *The Journal of Immunology* November 15, 2009 vol. 183 no. 10 6251-6261
**GPBAR1 is essential to maintain intestinal immune homeostasis**

**Mucin staining**

**Zonulin-1**

**Ocludin**

**E-cadherin**

**Dextran FITC**

**Intestinal permeability**

GPBAR1-expressing leukocytes are recruited into the intestinal mucosa in response to inflammation.


doi:10.1371/journal.pone.0025637
GPBAR1 regulates the intestinal leukocyte trafficking

- **GPBAR1 relative mRNA expression (x10^-5)**
  - CD4 T cells
  - CD8 T cells
  - B cells
  - MØ cells

- **Colon Length (cm)**
  - 0.00
  - 0.05
  - 0.10

- **Ratio W/L (g/cm)**
  - 0.00
  - 0.05
  - 0.10

- **Ulcers (mm^2)**
  - 0
  - 20
  - 40
  - 60
  - 80

GPBAR1 activation promotes a phenotypic shift of intestinal macrophages

GPBAR1 regulates the intestinal leukocyte trafficking

**GPBAR1 regulates the leukocyte trafficking in the intestine**

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<th>% CD11b+ of live cells</th>
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GPBAR1 regulates the intestinal leukocyte trafficking by promoting IL-10 secretion

GPBAR1 regulates the intestinal leukocyte trafficking by promoting IL-10 secretion

GPBAR1 and NAFLD/NASH
Gpbar1<sup>−/−</sup> mice show minor abnormalities when fed a HFD in comparison to wild type mice

Carino et al. Gpbar1 agonism promotes a Pgc-1α-dependent browning of white adipose tissue and energy expenditure and reverses diet-induced steatohepatitis in mice” (SREP-17-19426) online publication in Scientific Reports on the 20<sup>th</sup> of October 2017. DOI:10.1038/s41598-017-13102-y
**Gpbar1**<sup>−/−</sup> mice have increased physical activity

![Graph showing increased physical activity](image)

Activation of GPBAR1 reverses liver steatosis

Carino et al. Gpbar1 agonism promotes a Pgc-1α-dependent browning of white adipose tissue and energy expenditure and reverses diet-induced steatohepatitis in mice” (SREP-17-19426) online publication in Scientific Reports on the 20th of October 2017. DOI:10.1038/s41598-017-13102-y
BAR501 reverses liver steatosis in NASH model

Carino et al. Gpbar1 agonism promotes a Pgc-1α-dependent browning of white adipose tissue and energy expenditure and reverses diet-induced steatohepatitis in mice” (SREP-17-19426) online publication in Scientific Reports on the 20th of October 2017. DOI:10.1038/s41598-017-13102-y
BAR501 reverses liver fibrosis in NASH model

Sirius red staining

16 weeks HFD

HFD

HFD+ BAR501

16 weeks HFD
9 weeks BAR501 15 mg/kg

Carino et al. Gpbar1 agonism promotes a Pgc-1α-dependent browning of white adipose tissue and energy expenditure and reverses diet-induced steatohepatitis in mice” (SREP-17-19426) online publication in Scientific Reports on the 20th of October 2017. DOI:10.1038/s41598-017-13102-y
BAR501 increases the expression of GLP-1 in the intestine

Gene expression in the intestine after 16 weeks HFD-F

Carino et al. Gpbar1 agonism promotes a Pgc-1α-dependent browning of white adipose tissue and energy expenditure and reverses diet-induced steatohepatitis in mice” (SREP-17-19426) online publication in Scientific Reports on the 20th of October 2017. DOI:10.1038/s41598-017-13102-y
BAR501 increases the Weight of brown adipose tissue

Carino et al. Gpbar1 agonism promotes a Pgc-1α-dependent browning of white adipose tissue and energy expenditure and reverses diet-induced steatohepatitis in mice” (SREP-17-19426) online publication in Scientific Reports on the 20th of October 2017. DOI:10.1038/s41598-017-13102-y
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BAR501 does not increase gallbladder volume

Gallbladder weight (mg)

Carino et al. Gpbar1 agonism promotes a Pgc-1α-dependent browning of white adipose tissue and energy expenditure and reverses diet-induced steatohepatitis in mice” (SREP-17-19426) online publication in Scientific Reports on the 20th of October 2017. DOI:10.1038/s41598-017-13102-y
GPBAR1 is a vasodilatory receptor

Gpbar1 agonism reverses liver endothelial dysfunction

Gpbar1 is expressed by and modulates the response of liver sinusoidal cells to endothelin (ET)-1

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Dual FXR and GPBAR1 ligands

The prototype of semi-synthetic dual FXR and GPBAR1 ligands is the 6-ECDCA, also known as INT-747 and obeticholic acid (OCA)
Dual FXR and GPBAR1 ligands

Obeticholic acid

CDCA
Endogenous FXR agonist

TLCA
Endogenous GPBAR1 agonist

6-ECDCA
Synthetic dual FXR/GPBAR1 agonist

D’Amore et al. J Med Chem 2014
This agent was originally described as selective FXR ligand (Pellicciari et. Al. J Med Chem 2002) and demonstrated to protect the liver in models of non-obstructive cholestasis (Fiorucci S., et al. JPET 2004) and liver fibrosis (Fiorucci et al. Gastroenterology 2004).

Later on, Rizzo et al. have shown that OCA is a dual FXR and GPBAR1 ligand (Mol. Pharmacol 2010)

More recently, it has been reported that OCA activates FXR with a EC$_{50}$ of $\approx$ 500 nM and GPBAR1 with EC$_{50}$ of $\approx$ 900 nM (D’Amore et al. J Med Chem 2014) in transactivation assay.
BAR502 is dual non-bile acids FXR and GPBAR1 ligand

**FXR agonism**

- EC$_{50}$: 2 µM
- % Maximal Response

**GPBAR1 (TGR) agonism**

- EC$_{50}$: 0.4 µM
- % Maximal Response

### Ligand Performance Table

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### Efficacy Table

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BAR502 modulates FXR-regulated genes in isolated hepatocytes

D’Amore et al. J Med Chem 2014
BAR502 and NASH in HFD mice

BAR502 administered for 8 weeks to mice fed a high fat diet reduces body weight and increase insulin sensitivity
BAR502 reverses NASH like features in HFD mice

Naive

HFD

HFD + BAR502

BAR502

Steatosis score

Inflammation score

*  

#
BAR502 administered for 8 weeks to mice fed a HFD Promotes the browning of adipose tissue

BAR502 administered for 8 weeks to mice fed a HFD Promotes the browning of adipose tissue

Fibrosis score

rel. mRNA expr.

Naive
HFD
HFD+ BAR502

Fibrosis score

rel. mRNA expr.

αSMA
COL1α1

Naive
HFD
HFD+ BAR502
BAR502 administered for 8 weeks to mice fed a high fat diet
Activates FXR and GPBAR1 in the liver (A) and intestine (B)
BAR502 administered for 8 weeks to mice fed a HFD promotes the browning of adipose tissue.

White adipose tissue

UCP1

HFD

HFD+BAR502

rel. mRNA expr.
Gpbar1 and side effects

- A potential side effect of GPBAR1 activation is the itching.
- Alemi et al. JCI 2014 have suggested that GPBAR1 (TGR5) mediates the itch and analesia induced by bile acids and other GPBAR1 ligands in mice.

Itching is a common side effect of obeticholic acid.

Up to 70% of side effects reported in post-marketing surveillance of OCA (up to August 31, 2017) are due itching.
Cipriani et al. Impaired Itching Perception in Murine Models of Cholestasis Is Supported by Dysregulation of GPBAR1 Signaling.

PLOS ONE | DOI:10.1371/journal.pone.0129866 July 15, 2015
Cipriani et al. Impaired Itching Perception in Murine Models of Cholestasis Is Supported by Dysregulation of GPBAR1 Signaling. PLOS ONE | DOI:10.1371/journal.pone.0129866 July 15, 2015
Gpbar1 and FXR and itching

Alkaline Phosphatase

AST (U/L)

GP-BAR1+/+

GP-BAR1−/−

Lesions per field

CYP7a1 rel. expr.

SHP rel. expr.

OSTα rel. expr.

BSEP rel. expr.

CTRL ANIT ANIT+502

Gpbar1+/+ Gpbar1−/−

CYP7a1 rel. expr.
Cipriani et al. Impaired Itching Perception in Murine Models of Cholestasis Is Supported by Dysregulation of GPBAR1 Signaling.

PLOS ONE | DOI:10.1371/journal.pone.0129866 July 15, 2015
Conclusions

FXR and GPBAR1 were discovered approx. 20 years ago (1995 and 2002 respectively).
So far only a very limited number of compounds that target FXR (and GPBAR1) have been proved effective in treating liver disorders.

The first generation of FXR ligands based on the CDCA scaffold have shown poor safety profile and very narrow therapeutic window.

While explanations might be several, this poor safety profile could be the consequence of avid retention in liver cells.
Conclusions

• BAR501 and BAR502 are non-bile acid ligands for GPBAR1 and FXR.

• Preclinical pharmacology shows that these agents in contrast to semi-synthetic agonists based on the CDCA scaffold have a completely novel metabolic profiles and do not accumulate in the body even when administered at fairly high doses (30 mg/kg/d) for several weeks.

• Preclinical toxicology in rats and dogs shows that BAR502 has a robust safety profile (LD >900 mg/kg).

• But.....clinical studies are needed.
Thanks

- GI and hepatology unit at the University of Perugia Medical Schol.
  Dr. Michele Biagioli
  Dr. Adriana Carino
  Dr. Silvia Marchianò
  Dr. Fiorucci Chiara
  Past fellows
  Dr. Andrea Mencarelli
  Dr. Barbara Renga
  Dr. Sabrina Cipriani

- The GI and Surgery units
  Dr. Eleonora Distrutti
  Prof. Annibale Donini and its surgical team
  The Department of Pharmacology University of Naples «Federico II»
  Prof. Angela Zampella and its chemistry team.
  The Italian University Switzerland (Lugano)
  Dr. Vittorio Limongelli
The human GI microbiota

The *gut microbiota* is the community of microorganisms that normally live in the human digestive tract performing a number of useful functions for their hosts. The average human body, consisting of $\approx 10^{13}$ cells, has about ten times that number of microorganisms in the gut (100 trillion). Bacteria make up most of the microbiota in the colon and 60% of the dry mass of feces. **5 phyla contribute the large majority of human bacteria**

The gene catalogue - characterized by a metagenomic approach - indicates the microbe genome encodes for 3,364 non-redundant genes suggesting that no more than ~1,150 bacterial species are abundant enough to be detected in the feces. With most individuals harboring approximately 160 different bacterial species and 99% of intestinal microbiome derives from 30-40 species

BAR501 remodels liver genes expression

Gene expression in the liver after 16 weeks HFD +F

Carino et al. Gpbar1 agonism promotes a Pgc-1α-dependent browning of white adipose tissue and energy expenditure and reverses diet-induced steatohepatitis in mice” (SREP-17-19426) online publication in Scientific Reports on the 20th of October 2017. DOI:10.1038/s41598-017-13102-y
Exposure of LSEC to BAR501, along with other GPBAR1 ligands, increases the expression of CSE; BAR501 recruits CREB in its active form to a region of human CSE promoter that contains two CREB binding sites, resulting in a functional increase of CSE activity.
Gpbar1 is vasodilatory receptor

Endothelial cells

- GP-BAR1
- L-NIO
- eNOS
- cAMP
- CREB
- CRE1 CRE2
- CSE
- Transcription
- FXR
- TR1
- CDCA
- PAG

Smooth muscle cells

- CDCA
- LCA
- BKCa
- Muscarinic receptors
- Iberiotoxin
- K+
- Ca
- H2S
- NO

### Main metabolites

| Short-chain fatty acids (SCFA): acetate, propionate, butyrate, isobutyrate and others | Clostridial clusters IV and XIVa of *Firmicutes*, including species of *Eubacterium*, *Roseburia*, *Faecalibacterium*, and *Coprococcus* | Energy source for colonic epithelial cells, anti-tumor activities on colorectal cancer. Modulate insulin resistance in metabolic syndrome and type 2 diabetes |

### Main Bacteria

| Bile acids. Human: LCA and DCA, mouse: (ω-MCA, UDCA, hyodeoxycholic acid, hyocholic acid) | *Lactobacillus*, *Bifidobacteria*, *Enterobacter*, *Bacteroides*, *Clostridium* | Essential for absorption of dietary fats and lipid-soluble vitamins and act as signaling molecule through FXR, GPBAR1, PXR, VDR and other BARs* |

### Signaling pathways


| Indole derivatives: N-acetyltryptophan, indoleacetate, indoleacetylglucose, indole, indoxyl sulfate, indole-3-propionate, melatonin, melatonin 6-sulfate, serotonin, 5-hydroxyindole | *Clostridium sporogenes*, *E. coli* | AhR ligands. Anti-inflammatory effects. Unknown metabolic activities |

| Vitamins: vitamin K, vitamin B12, biotin, folate, thiamine, riboflavin, pyridoxine | *Bifidobacterium* | Complementary source to endogenous vitamins. Unclear metabolic effects |

| D-lactate, formate, methanol, ethanol, succinate, lysine, glucose, urea, α-ketoisovalerate, creatine, creatinine, endocannabinoids, 2-arachidonoylglycerol (2-AG), N-arachidonoylethanolamide, LPS, etc. | *Bacteroides*, *Pseudobutyrivibrio*, *Ruminococcus*, *Faecalibacterium*, *Subdoligranulum*, *Bifidobacterium*, *Atopobium*, *Firmicutes*, *Lactobacillus* | Variety of biological functions. Unclear metabolic effects |

| Polyamines | *Campylobacter jejuni*, *Clostridium saccharolyticum* | Anti-inflammatory and antitumoral effects. Unclear metabolic effects |

| Phenolic, benzoyl, and phenyl derivatives | *Clostridium difficile*, *F. prausnitzii*, *Bifidobacterium*, *Subdoligranulum*, *Lactobacillus* | PXR ligands. Regulation of xenobiotic metabolism. Unclear metabolic effects |

| Lipids: conjugated fatty acids, LPS, peptidoglycan, acylglycerols, sphingomyelin, cholesterol, phosphatidylycholines, phosphoethanolamines, | *Bifidobacterium*, *Roseburia*, *Lactobacillus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Clostridium* | Anti-inflammatory and pro-inflammatory activities. Modulation of immune system, insulin receptor and insulin sensitivity. cholesterol and tryglycerols |

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*From Fiorucci & Distrutti Trends Mol Med 2015*
Gpbar1 activation in liver sinusoidal cells results in an Akt-dependent phosphorylation of FoxO1 that detach from the ET-1 promoter, thus blocking ET-1 transcription.

GPBAR1 is a potential therapeutic target thought that it is still unclear whether potential side effects would prevent its exploitation in liver diseases.