

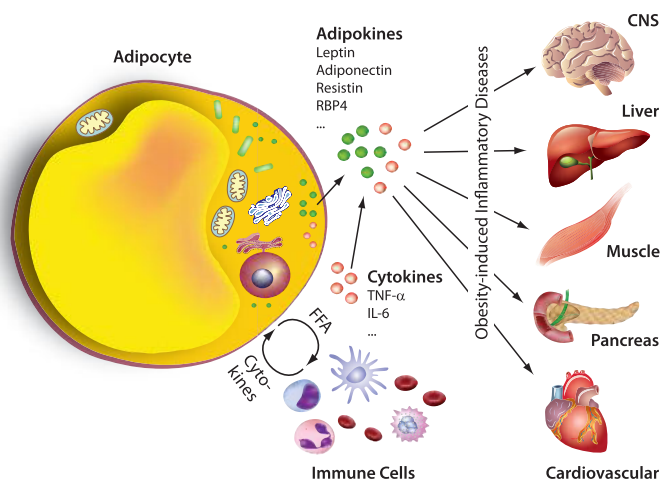
4th Edition

Obesity & Diabetes Research

Focus: White & Brown Fat Cells as Endocrine Tissues

Two major types of adipose tissue exist in mammals, white (WAT) and brown adipose tissue (BAT) composed mainly of white (see below **Figure**) or brown adipocytes (see page 8), respectively. **White adipose tissue (WAT)** is found throughout the body, primarily under the skin (subcutaneous fat that has no adverse effects and may even be protective against metabolic syndrome) as well as in larger deposits in the abdomen (visceral fat that is associated with insulin resistance and increased risk of metabolic disease). White adipocytes act as storage cells for neutral triacylglycerols, storing excess calories for use in times of scarcity. WAT contributes to whole body insulation and actively communicates with key organs to maintain metabolic homeostasis by secreting adipokines.

Adipokines are defined generally as biologically active substances produced in white adipose tissue (WAT) that act in an autocrine/paracrine or endocrine fashion and communicate with the brain, heart, vasculature, liver and muscle. Some adipokines are produced exclusively or predominantly by adipose tissue, whereas others may be produced in a variety of different tissues. The diversity of the adipokines is considerable, in terms of both, protein structure and function. Adipokines include classical cytokines (e.g. TNF- α , IL-6), chemokines (e.g. MCP-1), proteins of the alternative complement system (e.g. Adipsin), proteins involved in vascular hemostasis (e.g. PAI-1), the regulation of blood pressure (Angiotensinogen), lipid metabolism (e.g. RBP4), glucose homeostasis (e.g. Adiponectin, Leptin, Progranulin, Nampt/Visfatin/PBEF, Resistin, Vaspin, Omentin, Lipocalin-2, Apelin, DPP-4, CTRPs, selected ANGPTLs), angiogenesis (e.g. VEGF, NGF) and lipid mobilization (Zinc- α -2-glycoprotein). Adipokines have either pro-inflammatory or anti-inflammatory activities and exhibit a wide range of functions including the regulation of food intake and body weight homeostasis, insulin sensitivity, cell proliferation and angiogenesis, immunity, inflammation or vascular homeostasis. During obesity (see page 4), adipokines are dysregulated and create a state of **chronic low-grade inflammation** responsible for the different obesity-linked pathologies and the onset of insulin resistance. Although **brown adipose tissue (BAT)** also produces adipokines (see page 8), the endocrine role of BAT in metabolic diseases is not fully investigated. A growing interest in adipokines and myokines as biomarkers of low-grade inflammation and metabolic diseases emerges.



SELECTED REVIEW ARTICLE

Two Faces of White Adipose Tissue with Heterogeneous Adipogenic Progenitors: I. Hwang & J.B. Kim; *Diabetes Metab. J.* 43, 752 (2019)

FIGURE: Schematic interaction between adipocytes and immune cells.

Adapted from H. Cao; *J. Endocrinol.* 220, T47 (2014)

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KEY Adipokines: Novel Biomarkers and Regulators of Diabetes, Obesity, Insulin Resistance and Inflammation

Adiponectin

Adiponectin is an important adipocyte-derived anti-inflammatory hormone that regulates metabolism of lipids and glucose. Its receptors (AdipoR1, AdipoR2, T-cadherin) appear to exert actions in peripheral tissues by activating the AMP-activated protein kinase, p38-MAPK, PPAR α and NF- κ B and exerting a wide range of beneficial physiological actions, including antidiabetic, anti-inflammatory, anti-atherosclerotic and cardioprotective effects. Adiponectin is the most abundant adipokine in the circulation and its levels are substantially altered in obesity, type 2 diabetes, cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), obesity-related inflammation and various cancers.

ELISA KITS	THE STANDARDS	PID	SIZE	SENSITIVITY	RANGE	SAMPLES
Adiponectin (human) ELISA Kit		AG-45A-0001Y	96 wells 2 x 96 wells	100 pg/ml	0.5 to 32 ng/ml	C, P, S, U
Adiponectin (mouse) ELISA Kit		AG-45A-0004Y	96 wells 2 x 96 wells	50 pg/ml	0.125 to 8 ng/ml	C, P, S
Adiponectin (rat) ELISA Kit		AG-45A-0005Y	96 wells 2 x 96 wells	50 pg/ml	0.375 to 24 ng/ml	C, P, S
RECOMBINANT PROTEINS		PID	SIZE	SOURCE	ENDOTOXIN	SPECIES
Adiponectin (human) (rec.)		AG-40B-0030	50 μ g	HEK 293 cells	<0.01EU/ μ g	Hu
Adiponectin (mouse) (rec.)		AG-40B-0026	50 μ g	HEK 293 cells	<0.01EU/ μ g	Ms

Nampt [Visfatin; PBEF]

Nicotinamide phosphoribosyltransferase (NAMPT) is a regulator of the intracellular NAD⁺ pool. Through its NAD⁺-biosynthetic activity, NAMPT influences the activity of NAD⁺-dependent enzymes, thereby regulating cellular metabolism. In addition to its enzymatic function, extracellular NAMPT (also called Visfatin or PBEF1) has cytokine-like activity. Altered levels are associated with various metabolic disorders, including obesity, nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes by influencing the oxidative stress response, apoptosis, lipid and glucose metabolism, inflammation and insulin resistance. NAMPT plays a crucial role in cancer cell metabolism and is often overexpressed in tumor tissues, making it an attractive therapeutic cancer drug target.

ELISA KITS	THE STANDARDS	PID	SIZE	SENSITIVITY	RANGE	SAMPLES
Nampt (human) ELISA Kit		AG-45A-0006Y	96 wells 2 x 96 wells	30 pg/ml	0.125 to 8 ng/ml	S
Nampt (human) (IntraCellular) ELISA Kit		AG-45A-0008Y	96 wells 2 x 96 wells	30 pg/ml	0.25 to 16 ng/ml	L
Nampt (mouse/rat) Dual ELISA Kit		AG-45A-0007Y	96 wells 2 x 96 wells	50 pg/ml	0.5 to 32 ng/ml	S
RECOMBINANT PROTEINS		PID	SIZE	SOURCE	ENDOTOXIN	SPECIES
Nampt (human) (rec.)		AG-40A-0031Y	10 μ g 3 x 10 μ g	HEK 293 cells	<0.01EU/ μ g	Hu
Nampt (mouse) (rec.) (enzymatically active)		AG-40B-0179	50 μ g	HEK 293 cells	<0.01EU/ μ g	Ms
Nampt (mouse) (rec.)		AG-40A-0056Y	10 μ g 3 x 10 μ g	CHO cells	<0.01EU/ μ g	Ms
POTENT INHIBITORS		PID	SIZE	From The Manufacturer BULK AVAILABLE		
CHS-828		AG-CR1-0064	5 mg 25 mg			
FK-866		AG-CR1-0011	1 mg 5 mg			

Retinol-binding Protein 4 [RBP4]

The physiological role of RBP4 is transport of retinol from the liver to peripheral tissues. RBP4 is produced in hepatocytes and adipocytes. Excessive visceral fat accumulation, followed by the development of inflammation and consequently a hormonal adipose tissue dysfunction is in direct relation with excessive RBP4 expression, orchestrated by GLUT4. Circulating RBP4 inhibits the signal pathways stimulated by insulin in skeletal muscle cells, resulting in the development of insulin resistance. Altered levels are associated with various metabolic disorders, including obesity, cardiovascular disease, nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes.

ELISA KITS	PID	SIZE	SENSITIVITY	RANGE	SAMPLES
RBP4 (human) ELISA Kit (Quantitative)	AG-45A-0035Y	96 wells 2 x 96 wells	380 pg/ml	0.39 to 25 ng/ml	C, P, S, U
RBP4 (human) Competitive ELISA Kit	AG-45A-0010Y	96 wells 2 x 96 wells	1 ng/ml	0.001 to 5 μ g/ml	C, P, S, U
RBP4 (mouse/rat) Dual ELISA Kit	AG-45A-0012Y	96 wells 2 x 96 wells	60 pg/ml	0.188 to 12 ng/ml	C, S, U

Progranulin [PGRN]

Progranulin (PGRN) is a cysteine rich secreted protein, expressed in epithelial cells, immune cells, neurons and adipocytes. PGRN was first identified as a growth factor and recently characterized as an adipokine implicated in obesity, insulin resistance and rheumatic disease. At a central level, PGRN acts as a neurotropic and neuroprotective factor and protects from neural degeneration. PGRN has pleiotropic actions and participates in several processes, such as inflammation or tumorigenesis.

Tag-free Progranulins

- Higher activity compared to tagged Progranulins
- Suitable for *in vitro* and *in vivo* studies
- Reflects the native sequence with no additional amino acids
- Affinity purified
- Low endotoxin levels (<0.01 EU/ μ g)

ELISA KITS	PID	SIZE	SENSITIVITY	RANGE	SAMPLES
Progranulin (human) ELISA Kit	AG-45A-0018Y	96 wells 2 x 96 wells	32 pg/ml	0.063 to 4 ng/ml	C, P, S, U
Progranulin (mouse) ELISA Kit	AG-45A-0019Y	96 wells 2 x 96 wells	60 pg/ml	0.125 to 8 ng/ml	C, S
Progranulin (rat) ELISA Kit	AG-45A-0043Y	96 wells 2 x 96 wells	40 pg/ml	0.063 to 4 ng/ml	C, S
RECOMBINANT PROTEINS	PID	SIZE	SOURCE	ENDOTOXIN	SPECIES
Progranulin (human) (rec.) (untagged)	AG-40A-0188Y	10 μ g 50 μ g	HEK 293 cells	<0.01 EU/ μ g	Hu
Progranulin (mouse) (rec.) (untagged)	AG-40A-0189Y	10 μ g 50 μ g	HEK 293 cells	<0.01 EU/ μ g	Ms
Progranulin (rat) (rec.) (untagged)	AG-40A-0196Y	10 μ g 50 μ g	HEK 293 cells	<0.01 EU/ μ g	Rt

Vaspin [Visceral Adipose Tissue-derived Serpin; Serpin A12]

Vaspin, a serine protease inhibitor, is an insulin-sensitizing adipokine that has been isolated from both visceral and subcutaneous white adipose tissue. Vaspin is suggested to regulate immune responses and inflammation and was found to be correlated with various metabolic parameters. Vaspin represents a novel biomarker for obesity and impaired insulin sensitivity and might serve as a new therapeutic target of metabolic syndrome diseases, such as obesity-related insulin resistance and inflammation.

ELISA KITS	PID	SIZE	SENSITIVITY	RANGE	SAMPLES
Vaspin (human) ELISA Kit	AG-45A-0017Y	96 wells 2 x 96 wells	12 pg/ml	0.016 to 1 ng/ml	C, P, S
RECOMBINANT PROTEINS	PID	SIZE	SOURCE	ENDOTOXIN	SPECIES
Vaspin (human) (rec.)	AG-40A-0064Y	10 μ g 3 x 10 μ g	HEK 293 cells	<0.01 EU/ μ g	Hu
Vaspin (mouse) (rec.)	AG-40A-0094	10 μ g	HEK 293 cells	<0.1 EU/ μ g	Ms
ANTIBODIES	PID	SIZE	ISOTYPE/SOURCE	APPLICATION	SPECIES
anti-Vaspin (human), mAb (VP63)	AG-20A-0045	50 μ g 100 μ g	Mouse IgG1 κ	IHC, WB	Hu
anti-Vaspin (mouse), pAb	AG-25A-0075	100 μ g	Rabbit	WB	Ms

Zinc- α -2-glycoprotein [ZAG]

Zinc- α -2-glycoprotein (ZAG) is expressed in the major white fat depots and in the interscapular brown fat of mice defining it as an adipokine. ZAG has been shown to stimulate lipolysis in *in vitro* and *in vivo* experiments. Data from genetic studies suggest that ZAG may be a candidate gene for body weight regulation. ZAG is up-regulated in urine from diabetic patients and is reported to be associated with several diseases, such as cancers, metabolic syndrome and acute sepsis.

ELISA KITS	PID	SIZE	SENSITIVITY	RANGE	SAMPLES
Zinc-α-2-glycoprotein (human) TurboELISA™ Kit	AG-48B-1000	96 wells	0.23 ng/ml	0.9375 to 60 ng/ml	C, P, S
Zinc-α-2-glycoprotein (human) Matched Pair Detection Set	AG-46B-0008	5 x 96 wells	100 pg/ml	0.0156 to 1 ng/ml	C, P, S
RECOMBINANT PROTEIN	PID	SIZE	SOURCE	ENDOTOXIN	SPECIES
Zinc-α-2-glycoprotein (human) (rec.)	AG-40B-0146	10 μ g 50 μ g 3 x 50 μ g	E. coli	<0.1 EU/ μ g	Hu

A Complete Panel of Adiponectin, Nampt, RBP4, Progranulin, Vaspin and ZAG Proteins & Antibodies is available on www.adipogen.com

IL-36 Cytokines – Protective Role in Obesity & Metabolic Diseases

Interleukin-36 α , β and γ (IL-36 α , β and γ), members of the interleukin-1 (IL-1) family, are pro-inflammatory cytokines mainly involved in skin inflammatory diseases, but also in the inflammation of lung or gut. Recently, the lab of Prof. Patrick T. Walsh (Trinity College Dublin, Ireland) describes in Nature Communication a new protective role of the IL-36 family of cytokines in obesity and metabolic diseases. They observed that IL-36 γ is increased in serum of obese patients with diabetes, indicating that elevated IL-36 cytokines may play a protective role in reducing blood sugar levels. IL-36 cytokines function by changing the composition of the intestinal microbiome towards a more metabolically healthy state. IL-36 cytokines enhance mucus secretion from goblet cells in the colon, which promote the outgrowth of the commensal bacterial strain *Akkermansia muciniphila*, known to play an important protective role against obesity and metabolic dysfunction.

LIT: Interleukin-36 cytokines alter the intestinal microbiome and can protect against obesity and metabolic dysfunction: F. Giannoudaki, et al.; Nat. Commun. 10, 4003 (2019)

ELISA KITS	PID	SIZE	SENSITIVITY	RANGE	SAMPLES
IL-36α (human) ELISA Kit	AG-45B-0013	96 wells	4 pg/ml	7.8 to 500 pg/ml	C, P, S
IL-36γ (human) ELISA Kit	AG-45B-0008	96 wells	3 pg/ml	3.9 to 250 pg/ml	C, S
IL-36β (human) Matched Pair Detection Set	AG-46B-0009	5 x 96 wells	10 pg/ml	15.6 to 1000 pg/ml	C

Also Available:

NEW **IL-36 α /IL-36 γ (human) Tandem ELISA Kit**
AG-45B-4502

*Visit our Website for a
Complete Range of
IL-36-related Reagents!*

Other Obesity-related Proteins & Antibodies

PROTEINS	PID
Calreticulin (human) (rec.) (His)	AG-40A-0132
Clusterin (secretory form) (human) (rec.)	AG-40A-0050Y
Clusterin (nuclear form) (human) (rec.) (His)	AG-40A-0047
Clusterin (nuclear form) (mouse) (rec.) (His)	AG-40A-0057
CREB-binding Protein (mouse) (rec.) (His)	AG-40T-0016
CTHRC1 (human) (rec.)	AG-40B-0157
CTHRC1 (mouse) (rec.)	AG-40B-0154
FABP1 (human) (rec.) (His)	AG-40A-0039T
FABP3 (human) (rec.) (untagged)	AG-40B-6002
FABP4 (human) (rec.) (His)	AG-40A-0035
FTO (human) (rec.) (His)	AG-40A-0112
FTO (mouse) (rec.) (His)	AG-40A-0127
IDO (human) (rec.) (His) (highly active)	AG-40B-0161
Lipocalin-2 (human) (rec.)	AG-40B-6001
NAD Kinase (human) (rec.) (His) (highly active)	AG-40T-0091
NMNAT1 (human) (rec.) (His) (highly active)	AG-40T-0092
NMNAT3 (human) (rec.) (His) (highly active)	AG-40T-0093
Omentin (human) (rec.)	AG-40B-0042
PEDF (human) (rec.)	AG-40B-0077
PEDF (mouse) (rec.)	AG-40B-0118
Resistin (human) (rec.)	AG-40A-0010Y
Resistin (mouse) (rec.)	AG-40A-0011

ANTIBODIES	PID
Calreticulin (human), mAb (CR213-2AG)	AG-20A-0079
Calreticulin (human), pAb	AG-25A-0094
Clusterin (human), pAb	AG-25A-0099
Clusterin (mouse), pAb	AG-25A-0054
FABP3 (human), pAb	AG-25A-0040
FABP4 (human), pAb	AG-25A-0041
FTO (human), mAb (AG103)	AG-20A-0092
FTO (mouse), mAb (FT62-6)	AG-20A-0083
IDO (human), mAb (ID 177)	AG-20A-0035
IDO (mouse), pAb	AG-25A-0032
MPC-2, mAb (JCM-1)	AG-20B-0071
NMNAT2 (human), mAb (Nady-1)	AG-20A-0087
Obestatin (human), pAb	AG-25A-0043
PEDF (human), mAb (rec.) (Serpy-1-4)	AG-27B-0014
RELM- β (mouse), mAb (MRB 46L)	AG-20A-0026
Resistin (human), mAb (HRES106)	AG-20B-0076
Resistin (human), pAb	AG-25A-0013
Resistin (mouse), mAb (MRES06)	AG-20A-0004
Resistin (mouse), mAb (MRES18)	AG-20B-0077
Resistin (rat), mAb (RRES07)	AG-20A-0015
Stearoyl-CoA Desaturase-1 (mouse), pAb	AG-25A-0031
TDO (human), pAb	AG-25A-0106
TRB-3 (human), pAb	AG-25A-0059

Obesity & Immunometabolism

During **obesity**, excess fat accumulates in adipose tissue leading to low-grade chronic inflammation. Obesity is a major risk factor for many metabolic diseases, especially diabetes and cardiovascular diseases, increasing the risk of hypertension, hyperglycemia and dyslipidemia, recognized as the **metabolic syndrome**. Obesity is also linked to a broad spectrum of pathological disorders including neurodegenerative diseases, airway disorders and cancer.

Dysregulation in **adipokines secretion**, adipocyte mitochondrial dysfunction, alteration in the gut microbiota composition are among factors involved in the development of obesity and its associated metabolic disorders. During obesity, a modulation of immune cells is observed (see below section immunometabolism and **Figure**). In **lean healthy adipose tissue**, Th2 cells and eosinophils secrete Th2 cytokines IL-4, IL-10 and IL-13 leading to an anti-inflammatory macrophage M2 phenotype, ensuring tissue remodeling. In **obese adipose tissue**, overnutrition leads to bigger adipocytes, which coupled with various cellular stress consequently leads to the recruitment of different immune cells and the development of a pro-inflammatory environment.

Immunometabolism describes the ability of the immune system to communicate and coordinate systemic metabolic homeostasis. Immunometabolism can be studied at macroscopic level, the whole-body metabolism and at microscopic level, the cellular bioenergetics of immune cells. Adipose tissue illustrates best the interdependency of both arms of immunometabolism (whole-body metabolism and the microscopic metabolism) and provides examples of changes in both the lean and obese states (see **Figure**). Lean adipose tissue is characterized by an enrichment of immune cells whose phenotype and cytokine profiles maintain a state of type 2 immunity necessary for the health of the tissue. Obesity is characterized by an accumulation of inflammatory immune cells and loss of protective lymphocytes due to change in the composition of fatty acids, glucose and oxygen availability that may provide different metabolic substrates to immune cells and adipocytes.

SELECTED REVIEWS: Extrinsic and Intrinsic Immunometabolism Converge: Perspectives on Future Research and Therapeutic Development for Obesity: H.L. Caslin & A.H. Hasty; *Curr. Obes. Rep.* 3, 210 (2019) • Obesity: a neuroimmunometabolic perspective: C.M. Larabee, et al.; *Nat. Rev. Endocrinol.* 16, 30 (2020)

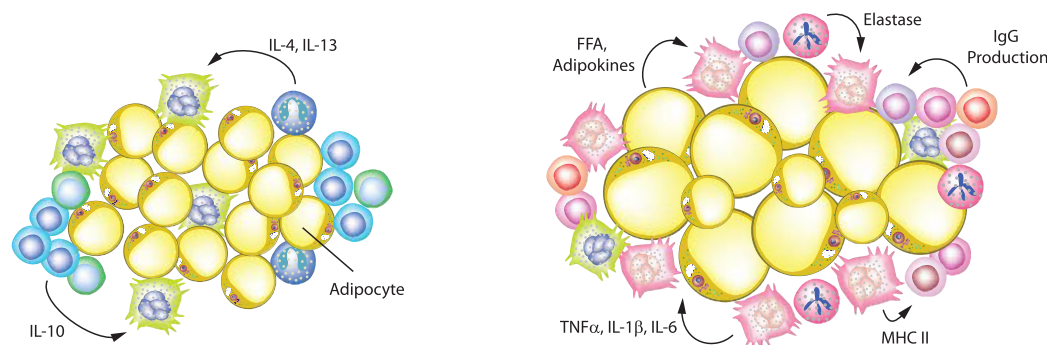


FIGURE: Modulation of immunometabolism during obesity.

Adapted from H.L. Kammoun, et al.; *Rev. Endocr. Metab. Disord.* 15, 31 (2014)

Lean Adipose Tissue – Anti-Inflammatory Milieu

Immune cells promoting:
Remodeling Tissue, Immune Surveillance

Obese Adipose Tissue – Pro-Inflammatory Milieu

Immune cells promoting:
Insulin Resistance, Chemotaxis, Lipolysis



Immunometabolism Modulators

AdipoGen Life Sciences offers a broad range of small molecule modulators of glycolysis, TCA cycle, fatty acid oxidation, fatty acid synthesis and amino acid pathways, as well as IDO1 and Nampt inhibitors.

Atpenin A5 (synthetic) (OXPHOS inhibitor) **BULK**

AG-CN2-0100 250 µg | 1 mg

Heptelidic acid (GAPDH inhibitor) **UNIQUE**

AG-CN2-0118 250 µg | 1 mg

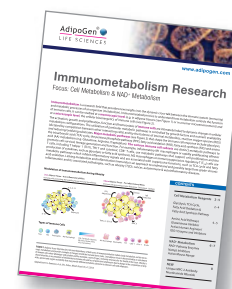
Itaconate (PFKII and SDH inhibitor) **BULK**

AG-CN2-0426 1 g | 5 g

STF-31 (Nampt inhibitor) **NEW**

AG-CR1-3693 1 mg | 5 mg | 25mg

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Immunometabolism
Brochure!



Obesity & Angiogenesis

Adipose tissue is the most dynamic and plastic organ in adults. Upon exposure to different metabolic challenges, adipose tissue has the capacity to either expand or shrink according to the nutrient status. Elasticity of adipose tissue is tightly related with angiogenesis, the growth of new blood vessels, and angiogenesis plays an essential role in the modulation of adipogenesis and obesity. In growing adipose tissue, the new blood vessels contribute to adipogenesis by performing multiple functions, such as providing nutrients and oxygen to nourish adipocytes, removing waste products from the adipose tissue, carrying monocytes and neutrophils that can affect adipocyte function and also providing adipose precursors and stem cells [1].

There exist several pro-angiogenic factors secreted by adipocytes, such as leptin, adiponectin, vascular endothelial growth factor-A (VEGF-A), VEGF-B and angiopoietins (mainly ANG-1 and ANG-2) that function by stimulating proliferation and migration of endothelial cells. A recent study [2] demonstrates that angiopoietin-2 (ANG-2) overexpression induces a pro-angiogenic program in white adipose tissue (WAT), protecting against high fat diet (HFD)-induced metabolic challenges. Decreasing the angiopoietin-2 levels using a neutralization antibody (anti-Angiopoietin-2, mAb (rec.) (blocking) (Angy-2-1) (AG-27B-0016PF)) confirms the beneficial effects of endogenous ANG-2. Mechanistically, increasing vascular function and decreasing adipose tissue inflammation contribute to the beneficial effects of ANG-2. Due to the essential role of angiogenesis in the modulation of adipogenesis and obesity, anti-angiogenesis therapy has emerged as a potential treatment for obesity.

LIT: [1] Role of VEGFs in metabolic disorders. M. di Somma, et al.; *Angiogenesis* (Epub ahead of print) (2019) • [2] Angiopoietin-2 in white adipose tissue improves metabolic homeostasis through enhanced angiogenesis: Y.A. An, et al.; *Elife* 29, 6 (2017)

NEW

Potent ANG-2 Blocking Antibodies

anti-Angiopoietin-2, mAb (rec.) (blocking) (Angy-2-1) (preservative free)

AG-27B-0016PF 100 µg | 500 µg | 1mg

anti-Angiopoietin-2 (human), mAb (rec.) (blocking) (Angy-1-4) (preservative free)

AG-27B-0015PF 100 µg | 500 µg | 1mg

Also Available:

Angiopoietin-2 (human) (rec.) AG-40B-0114

Angiopoietin-2 (mouse) (rec.) AG-40B-0131

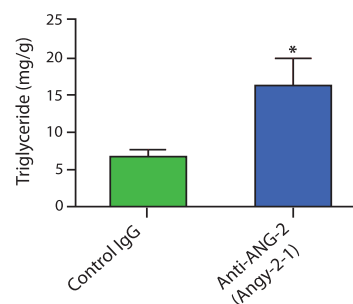


FIGURE: Antagonizing Angiopoietin-2 *in vivo* with anti-ANG-2, mAb (rec.) (blocking) (Angy-2-1) (AG-27B-0016PF) increases triglyceride levels.

METHOD: After High Fat Diet (HFD) challenges for five weeks in wild-type C57BL/6 mice, control IgG (left panel) or anti-ANG-2 (Clone Angy-2-1) blocking antibody (right panel) (4 µg/g body weight; twice/week) were administered and afterwards the mice underwent metabolic analyses of the triglycerides levels from both groups.

Vascular Endothelial Growth Factor [VEGF]-related Reagents

PROTEINS	PID	SIZE	SOURCE	ENDOTOXIN	SPECIES
VEGF 164 (mouse) (rec.)	AG-40T-0044	5 µg 20 µg	Sf9 cells	n.d.	Ms
VEGF 165 (human) (rec.)	AG-40T-0043	5 µg 20 µg	E. coli	n.d.	Hu
VEGF 165 (human) (rec.)	AG-40T-0045	5 µg 20 µg	Sf9 cells	n.d.	Hu
VEGFR-1, Soluble (human) (rec.)	AG-40T-0049	5 µg 20 µg	Sf9 cells	n.d.	Hu
ANTIBODIES	PID	SIZE	ISOTYPE	APPLICATION	SPECIES
VEGF-A (human), mAb (3(6D3))	AG-20T-0105	200 µg	Mouse IgG1	ELISA, WB, FUNC	Hu
VEGFR-1 (human), mAb (EWC)	AG-20T-0106	100 µg	Mouse IgG1	ELISA, WB	Hu
VEGFR-1 (human), mAb (EWF)	AG-20T-0107	100 µg	Mouse IgG1	ELISA, IP, WB	Hu

A Complete Panel of Angiogenesis-related Reagents is available on www.adipogen.com

Factors that Regulate WAT Browning and Thermogenesis

Brown adipose tissue (BAT) found in hibernating animals, also exists in human where it represents 1% to 2% of fat and is found in the cervical, axillary and paraspinal regions. Beige/brite adipose tissue is a type of brown fat that is composed of cells interspersed within WAT that are capable of transforming into brown-like adipocytes following cold exposure, adrenergic or other stimulations. In contrast to white adipocytes, with large unilocular lipid droplets, brown and beige adipocytes have multilocular droplets and high mitochondrial density. Brown adipose tissue (BAT) is the main site of adaptive thermogenesis, using a specific brown fat protein, uncoupling protein 1 (UCP1) that dissipates the mitochondrial membrane potential energy as heat instead of producing ATP. The ability of BAT to protect against obesity and metabolic diseases has traditionally been attributed to its capacity to utilize glucose and lipids for thermogenesis. However, BAT might also have a secretory role, which could contribute to the systemic consequences of BAT activity. Several BAT-derived molecules (called **Batokines**) acting in a paracrine, autocrine or endocrine manner have been identified. These **Batokines** control expansion and activity of BAT and the extent of browning of white adipose tissue (see **Figure**). They also promote hypertrophy and hyperplasia of BAT, vascularization, innervation and blood flow, processes that are all associated with BAT recruitment when thermogenic activity is enhanced. Some **Batokines** also target peripheral tissues such as liver, pancreas, white adipose tissue, bone and heart, and affect systemic metabolism by interacting with the central nervous system (CNS).

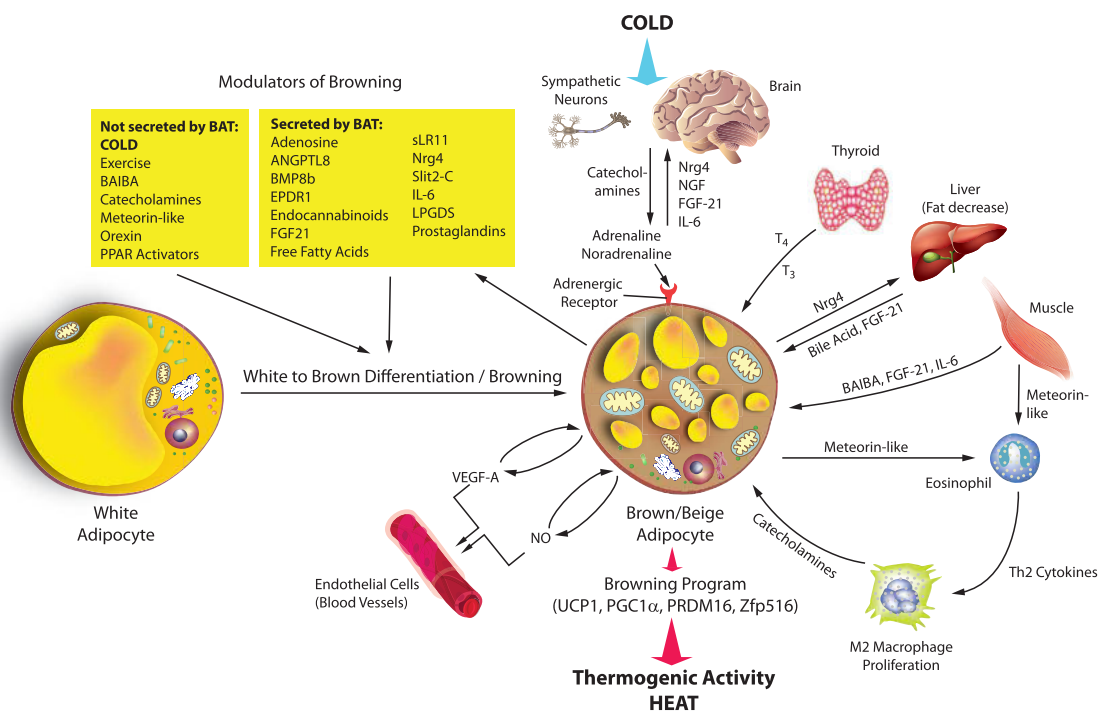
REVIEWS: New Advances in Adaptive Thermogenesis: UCP1 and Beyond: E.T. Chouchani, et al.; Cell Metabolism 29, 27 (2019) • Importance of adipocyte browning in the evolution of endothermy: M. Jastroch & F. Seebacher; Philos. Trans. R Soc. Lond. B Biol. Sci. 375, 20190134 (2020)

Overview of Important Batokines:

- **Fibroblast Growth Factor 21 (FGF-21)** is induced in BAT by cold exposure and induces the thermogenic program in brown adipocytes. FGF-21 is also expressed in organs such as liver or skeletal muscle. Metabolic benefits of FGF-21 include weight loss, glucose and lipid metabolism and insulin sensitivity. FGF-21 also acts directly in the brain.
- **Interleukin-6 (IL-6)**, released by skeletal muscle and by BAT in response to exercise, promotes insulin sensitivity, is required for the induction of browning of WAT and acts on the pancreas and the brain (see page 10).
- **Nrg4 (Neuregulin-4)** is a cold-induced adipokine, highly expressed in adipose tissue, enriched in brown fat. It promotes neurite outgrowth and protects against diet-induced insulin resistance and hepatic steatosis through attenuating hepatic lipogenic signaling.
- **CTHRC1 (Collagen Triple Helix Repeat Containing 1)** is expressed in BAT but its role is still unclear.
- **Soluble form of the LDL Receptor (sLR11)** suppresses thermogenesis in brown adipocytes, by binding to BMP receptors, despite being increased by cold-induced activation in BAT.
- **Angiopoietin-like 8 (ANGPTL8 or Betatrophin)** is induced in BAT in response to cold. ANGPTL8 can repress the activity of lipoprotein lipase.
- **BMPs (Bone Morphogenetic Protein)** promote brown fat formation and act on the central nervous system to regulate thermogenesis.
- **VEGF-A and VEGF-B (Vascular Endothelial Growth Factor A and B)** regulate angiogenesis, thermogenesis and macrophage function (see page 7).
- **Slit2-C** activates a thermogenic PKA pathway in adipocytes.
- **Lipocalin Prostaglandin D Synthase (LPGDS)** synthesizes D-series prostaglandins. It is highly regulated in BAT and plays a role in lipid and carbohydrate utilization.
- **Adenosine** is released from BAT during stimulation of sympathetic nerves and activates a thermogenic program. Adenosine protects mice from diet-induced obesity.
- **Endocannabinoid system** and metabolites, such as **FFA (Free Fatty Acid)**, **Retinaldehyde**, **Retinoic Acid** and **Lactate** are released from BAT and play a role in thermogenic activation.
- **Ependymin-related Protein 1 (EPDR1)** is a new batokine that is vital for development into a functional thermogenic adipocyte.

FIGURE: The autocrine and paracrine factors released by brown adipocytes.

Adapted from F. Villarroya, et al.; Nat. Rev. Endocrinol. 13, 26 (2017)



Browning Inducers not expressed by BAT:

- **Cold exposure** is a strong inducer of brown cells. Thermogenic activity is regulated by a canonical β -adrenergic receptor pathway via the sympathetic nervous system. The **TRPM8 channel** is a cold-sensing cation channel present in sensing neurons that has a role in detecting environmental temperature.
- **Catecholamines** activate β -adrenergic receptors at the surface of brown adipocytes and increase the intracellular cAMP level to activate the thermogenic program.
- **PPARs** are master regulators of adipogenesis. Recently, PPAR- γ activators thiazolidinediones were shown to promote WAT browning as well (see page 11).
- Cold-induced conversion of cholesterol to **Bile acid** shapes the gut microbiome and promotes adaptive thermogenesis.

- The neuropeptide **Orexin and its Receptors** are also involved in the induction of browning and affect brown fat thermogenesis.
- **Meteorin-like Protein** is a novel adipokine expressed by adipose tissue being downregulated upon caloric restriction. Meteorin-like is secreted by muscles during exercise and converts white adipose cells into brown fat tissue. This activation of fat browning is the consequence of a direct effect of meteorin-like on eosinophils in WAT that secretes IL-4 and IL-13, which promotes the activation of adipose tissue macrophages as well as the thermogenic program.
- **T3** (Triiodothyronine) and T4 exert effects locally to promote thermogenesis.
- **3-Aminoisobutyric acid (BAIBA)** is a browning molecule secreted from contracting muscles.

Protein Modulators & Inducers of Brown Adipose Tissue (BAT)

RECOMBINANT PROTEINS	PID	SIZE	SOURCE	ENDOTOXIN	SPECIES
Betatrophin [ANGPTL8] (human):Fc (human) (rec.)	AG-40B-0145	10 μ g 3 x 10 μ g	HEK 293 cells	<0.1EU/ μ g	Hu
Betatrophin [ANGPTL8] (mouse) (rec.)	AG-40B-0144	10 μ g 3 x 10 μ g	CHO cells	<0.1EU/ μ g	Ms
Betatrophin [ANGPTL8] (mouse):Fc (human) (rec.)	AG-40B-0142	10 μ g 3 x 10 μ g	HEK 293 cells	<0.1EU/ μ g	Ms
FGF-21 (human) (rec.)	AG-40A-0091Y	10 μ g 50 μ g	HEK 293 cells	<0.1EU/ μ g	Hu
FGF-21 (human):Fc (human) (rec.)	AG-40A-0095	10 μ g 50 μ g	HEK 293 cells	<0.1EU/ μ g	Hu
FGF-21 (mouse) (rec.)	AG-40B-0143	10 μ g 3 x 10 μ g	HEK 293 cells	<0.01EU/ μ g	Ms
FGF-21 (mouse) (rec.)	CHI-MF-102FGF21	10 μ g 50 μ g	HEK 293 cells	<0.06EU/ μ g	Ms
FGF-21 (mouse):Fc (human) (rec.)	AG-40A-0097	10 μ g 50 μ g	HEK 293 cells	<0.1EU/ μ g	Ms
Meteorin-like (mouse) (rec.)	AG-40B-0149	10 μ g 3 x 10 μ g	HEK 293 cells	<0.1EU/ μ g	Ms
Neuregulin-4 (human) (rec.)	AG-40B-0155	10 μ g 3 x 10 μ g	E. coli	<0.01EU/ μ g	Hu
Neuregulin-4 (mouse) (rec.)	AG-40B-0159	10 μ g 3 x 10 μ g	E. coli	<0.01EU/ μ g	Hu, Ms
NEW Slit2 (C fragment) (human) (rec.)	AG-40B-0168	10 μ g 3 x 10 μ g	HEK 293 cells	<0.01EU/ μ g	Hu

Various WAT/BAT Browning Inducers

YM-254890 (Potent and selective $G_{\alpha q}$ family inhibitor)

AG-CN2-0509 500 μ g | 1 mg

3-Aminoisobutyric acid (Contraction-induced myokine)

AG-CR1-3596 250 mg | 1 g

Harmine (UCP1-dependent thermogenesis inducer)

AG-CN2-0510 10 mg | 50 mg | 250 mg

Miglitol (α -Glucosidase inhibitor)

AG-CR1-3635 10 mg | 50 mg

Papaverine . HCl (PDE10A inhibitor)

AG-CN2-0414 1 g | 5 g

PF-2545920 (PDE10A inhibitor)

AG-CR1-3636 1 mg | 5 mg | 25 mg

Rutin . trihydrate (Brown fat activator)

AG-CN2-0408 5 g

Succinate [Succinic acid] (Metabokine/BAT activator)

AG-CN2-0521 1 g | 5 g

NEW

CL 316,243

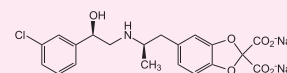
AG-CR1-3699

1 mg | 5 mg

Formula: $C_{20}H_{18}ClNO_7 \cdot 2Na$

MW: 419.8, 46.0

CAS: 138908-40-4



Potent and selective β_3 -adrenoceptor agonist ($EC_{50}=3nM$). Increases brown adipose tissue thermogenesis. Induces functionally active mitochondrial UCP in white fat.

UCP1-dependent Thermogenesis Inducers through CK2

CK2 Inhibitor 10

AG-CR1-3626

1 mg | 5 mg

CX-4945 . HCl

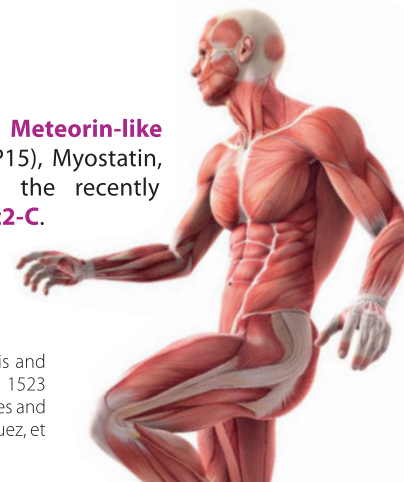
AG-CR1-3629

1 mg | 5 mg | 25 mg

Myokines: Muscle, Exercise & Obesity

Exercise training enhances muscular endurance and strength, expends calories, exerts beneficial effects on systemic metabolism and combats the development of common diseases such as obesity and type 2 diabetes, by adaptive structural and metabolic changes in skeletal muscle, including a change in the type of muscle fiber, mitochondrial biogenesis and angiogenesis. Additionally, skeletal muscles secrete cytokines and growth factors, called **myokines** that can potentially act in an autocrine, a paracrine and/or an endocrine manner to modulate metabolic, inflammatory and other processes. Several contraction-regulated myokines have been described including **ANGPTL4**, Apelin, BDNF, **FGF-21**, FSTL1, **IL-6**, **IL-7**, **IL-8**,

IL-15, **Irisin**, **LIF**, MCP-1, **Meteorin-like protein**, Myonectin (CTRP15), Myostatin, PAI-1, **PEDF**, **VEGF** and the recently described **Asprosin** or **Slit2-C**.



SELECTED REVIEWS:

Myokines in metabolic homeostasis and diabetes: J. Eckel; Diabetologia **62**, 1523 (2019) • Crosstalk between adipokines and myokines in fat browning: A. Rodríguez, et al.; Acta Physiol. **219**, 362 (2017)

Myokine: Protein or metabolite that is produced and secreted by muscle fibers and exerts either paracrine or endocrine effects.

NEW

Asprosin

Asprosin is a new fasting-induced protein hormone that targets the liver to increase plasma glucose levels. Asprosin is the C-terminal cleavage product of the protein Fibrillin-1. Asprosin is secreted from white adipose tissue and increases hepatic glucose production by using cAMP as a second messenger, leading to activation of protein kinase A in the liver. Reduction of asprosin levels protect against metabolic syndrome-associated hyperinsulinism.

ELISA KITS	PID	SIZE	SENSITIVITY	RANGE	SAMPLES	
Asprosin (human) Matched Pair Detection Set	AG-46B-0011	5 x 96 wells	100 pg/ml	0.156 to 10 ng/ml	C, S	
RECOMBINANT PROTEIN	BULK AVAILABLE	PID	SIZE	SOURCE	ENDOTOXIN	SPECIES
Asprosin (human) (rec.) (His)	AG-40B-0174T	10 µg 100 µg	E. coli	<0.1EU/µg		Hu
ANTIBODIES	PID	SIZE	ISOTYPE/SOURCE	APPLICATION	SPECIES	
anti-Asprosin, mAb (Birdy-1)	AG-20B-0073	100 µg	Mouse IgG1	WB		Hu, Ms
anti-Asprosin (human), mAb (Birdy-2)	AG-20B-0074	100 µg	Mouse IgG2a	WB		Hu

Selected Myokines: Interleukin-6 and Irisin

Several cytokines including IL-6, IL-7, IL-8, IL-15, LIF and MCP-1 have been shown to be secreted from muscle after endurance. IL-6 is the best characterized myokine implicated as a co-inducer of the development of obesity-associated insulin resistance, which precedes the development of type 2 diabetes (T2D). The role of irisin is still under debate. Initially, described as a browning inducer, recent studies suggest an involvement of irisin in cortical bone mass, β cell proliferation, insulin secretion, in synaptic plasticity and memory in Alzheimer's Disease models.

LIT: Physical activity and muscle-brain crosstalk: B.K. Pedersen; Nat. Rev. Endocrinol. **15**, 383 (2019) • Myokines: The endocrine coupling of skeletal muscle and bone: M. Gomasasca, et al.; Adv. Clin. Chem. **94**, 155 (2020)

PROTEINS	PID	SIZE	SOURCE	ENDOTOXIN	SPECIES
IL-6 (human) (rec.) (His)	CHI-HF-20106	10 µg 50 µg	HEK 293 cells	<0.01EU/µg	Hu
IL-6 (human):Fc (human) (rec.)	CHI-HF-21006	50 µg 3 x 50 µg	CHO cells	<0.06EU/µg	Hu
IL-6 (mouse):Fc (human) (rec.)	AG-40B-0108	10 µg 3 x 10 µg	HEK 293 cells	<0.01EU/µg	Ms
Irisin (rec.) (CHO)	AG-40B-0136	10 µg 3 x 10 µg	CHO cells	<0.01EU/µg	Hu, Ms
Irisin (rec.) (E. coli) (untagged)	AG-40B-0103	10 µg 5 x 10 µg	E. coli	<0.1EU/µg	Hu, Ms
ELISA KITS	PID	SIZE	SENSITIVITY	RANGE	SAMPLES
Cymax IL-6 (human) ELISA Kit	YIF-LF-EK0260	96 wells	1.160 pg/ml	4.68 to 300 pg/ml	C, P, S, L
Cymax IL-6 (mouse) ELISA Kit	YIF-LF-EK0270	96 wells	1.138 pg/ml	7.8 to 500 pg/ml	C, P, S, L
Cymax IL-6 (rat) ELISA Kit	YIF-LF-EK0224	96 wells	26.643 pg/ml	62.5 to 4000 pg/ml	C, P, S, L
Irisin Competitive ELISA Kit	AG-45A-0046Y	96 wells 2 x 96 wells	1 ng/ml	0.001 to 5 µg/ml	C, P, S

SAMPLES: C: Cell Culture Supernatant, P: Plasma, S: Serum; U: Urine; L: Cell Lysate; F: CSF

APPLICATIONS: FUNC: Functional Application; ICC: Immunocytochemistry; IHC: Immunohistochemistry; IP: Immunoprecipitation; WB: Western blot

FORMULATION: PF = Preservative free

SPECIES: Dg = Dog; Hu = Human; Mo = Monkey; Ms = Mouse; Rt = Rat; Rb = Rabbit

BULK**IBMX****Enhances Differentiation of 3T3-L1 Cells****IBMX [3-Isobutyl 1-methylxanthine]**

AG-CR1-3512-M500 500 mg
 AG-CR1-3512-G001 1 g

BULK**Streptozotocin****STANDARD Diabetes Inducer****Streptozotocin**

AG-CN2-0046-M050 50 mg
 AG-CN2-0046-M250 250 mg
 AG-CN2-0046-G001 1 g

AMPK Modulators

AMPK (AMP-activated protein kinase) plays a role in cellular energy homeostasis, regulating several intracellular systems including hepatic fatty acid oxidation and ketogenesis, inhibition of cholesterol synthesis, lipogenesis and triglyceride synthesis, stimulation of skeletal muscle fatty acid oxidation and muscle glucose uptake as well as modulation of insulin secretion by pancreatic β cells.

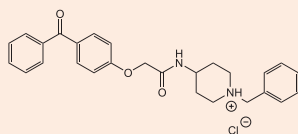
SELECTED REVIEW ARTICLE: Past strategies and future directions for identifying AMP-activated protein kinase (AMPK) modulators: S.E. Sinnott & J.E. Brenman; Pharmacol. Ther. 143, 111 (2014)

BULK**AdipoRon . HCl (water soluble)****Original Source**

AG-CR1-0156

10 mg | 50 mg

Formula: $C_{27}H_{28}N_2O_3 \cdot HCl \cdot H_2O$
MW: 428.5 . 36.5 . 18.0
CAS: 924416-43-3 (free base)



AdipoR agonist. AMPK & PGC1 α activator. Improves diabetes.

AICAR (Potent AMPK activator)**BULK**

AG-CR1-0061 10 mg | 50 mg | 100 mg

Compound 112254 . HCl (water soluble) (AMPK activator)

AG-CR1-0157 10 mg | 50 mg

Metformin . HCl (AMPK activator)**NEW**

AG-CR1-3689 1 g | 5 g

MOTS-c (human) (AMPK inducer)**NEW**

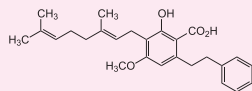
AG-CP3-0026 1 mg | 5 mg

PPAR (Peroxisome Proliferator-activated Receptor) Agonists**NEW****Amorfrutin B**

AG-CN2-0464

500 μ g | 1 mg

Formula: $C_{26}H_{32}O_4$
MW: 408.5
CAS: 1174387-94-0
Source: *Amorpha fruticosa*



Natural PPAR γ agonist with potent glucose-lowering properties.

Also available: **Amorfrutin A (AG-CN2-0462)**

GW1929 (Selective PPAR γ agonist)**BULK**

AG-CR1-0116 1 mg | 5 mg | 25 mg

GW501516 (Potent and selective PPAR δ agonist)**NEW**

AG-CR1-3641 1 mg | 5 mg | 25 mg

Ionomycin (free acid) (PPAR γ ligand with a unique binding mode)

AG-CN2-0416 1 mg | 5 mg

Pioglitazone (Selective PPAR γ agonist)**BULK**

AG-CR1-0067 1 mg | 5 mg | 25 mg

Rosiglitazone . maleate (Potent PPAR γ agonist)**BULK**

AG-CR1-3571 25 mg | 100 mg | 1 g

Pseudolaric acid B (PPAR α agonist)AG-CN2-0083 100 μ g | 1 mg**Troglitazone (Potent and selective PPAR γ agonist)**

AG-CR1-3565 5 mg | 25 mg

WY-14643 [Pirinixic acid] (Potent PPAR α activator)

AG-CR1-3566 10 mg | 50 mg | 250 mg

Astaxanthin (PPAR α agonist & PPAR γ antagonist)**BULK**

AG-CN2-0055 5 mg | 25 mg

Ciglitazone (Selective PPAR γ agonist)**BULK**

AG-CR1-0033 1 mg | 5 mg | 25 mg

Selection of a Broad Range of Metabolic Research Reagents

NEW

N1-Guanyl-1,7-diaminoheptane [GC7]

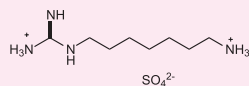
AG-CR1-3702

10 mg | 50 mg

Formula: C₈H₂₂N₄O₄S

MW: 270.0

CAS: 150417-90-6



Cell permeable competitive deoxyhypusine synthase (DHPS) inhibitor. Blocks OXPHOS in macrophages and is a useful tool for immunometabolism research.

AK-7 (Brain-permeable SIRT2 inhibitor)

AG-CR1-3511

5 mg | 25 mg

Amlexanox (Selective TBK1 and IKKε inhibitor)

AG-CR1-3579

10 mg | 50 mg

AP-III-a4 . HCl (HNE inhibitor)

AG-CR1-3696

1 mg | 5 mg

AZD 7545 (Potent PDK2 inhibitor)

AG-CR1-3692

1 mg | 5 mg | 10 mg

BMS-309403 (Potent and selective FABP4 inhibitor)

AG-CR1-3640

1 mg | 5 mg | 25 mg

3,4-Dimethoxychalcone (Caloric restriction mimetic)

AG-CN2-0531

10 mg | 50 mg | 250 mg

EM574 (Orexigenic; Motilin receptor agonist)

AG-CN2-0102

250 µg | 1 mg

Emodin (Potent selective 11β-HSD1 inhibitor)

AG-CN2-0457

50 mg | 250 mg

Empagliflozin (SGLT-2 inhibitor)

AG-CR1-3619

10 mg | 50 mg

(+)-Etomoxir . Na (CPT-1a inhibitor)

AG-CR1-3688

5 mg | 25 mg

Glyburide (USP) (Antidiabetic)

AG-CR1-3613

1 g | 5 g | 10 g

LATEST INSIGHT

L-Glutamine (Linking Obesity to Inflammation)

AG-CR1-3534

1 g | 5 g

LIT: P. Petrus, et al.; Cell Metab. 31, 375 (2020)

GW311616A (Potent HNE inhibitor)

AG-CR1-3632

1 mg | 5 mg | 25 mg

Isoliquritigenin (Antidiabetic/Antihyperglycemic)

AG-CN2-0459

10 mg | 50 mg

Kaempferitrin (Insulinomimetic/Hypoglycemic)

AG-CN2-0039

1 mg | 5 mg

Linagliptin (DPP4 inhibitor)

AG-CR1-3618

10 mg | 50 mg

Narciclasine (Anti-obesity agent)

AG-CN2-0524

500 µg | 1 mg

Neuromedin U-25 (human) (NMUR1/NMUR2 agonist)

AG-CP3-0031

1 mg | 5 mg

Niclosamide (Neuropeptide Y4 receptor ligand)

AG-CR1-3643

100 mg | 1 g

AG-CR1-3644 [Ethanolamine]

25 mg | 100 mg

Orlistat (DAGLα inhibitor/Antiobesity)

AG-CN2-0050

50 mg | 250 mg

Pellitorine (α-Glucosidase inhibitor)

AG-CN2-0009

1 mg | 5 mg | 25 mg

Suramin . 6Na (SIRT1 & SIRT5 inhibitor)

AG-CR1-3575

50 mg

(±)-Verapamil . HCl (USP) (Antidiabetic)

AG-CR1-3627

100 mg | 1 g | 5 g

Withaferin A (Leptin sensitizer)

AG-CN2-0490

1 mg | 5 mg | 10 mg

Visit our Website for a Complete Overview!

BULK

Long-acting Antidiabetic Peptides

Liraglutide (GLP-1 receptor agonist)

AG-CP3-0034

1 mg | 5 mg | 25 mg

Semaglutide . AcOH (GLP-1 receptor agonist)

AG-CP3-0032

1 mg | 5 mg | 25 mg

LATEST INSIGHT

Microbiota-related Reagents

Indole-3-carbinol

AG-CR1-3637

500 mg | 5 g

trans-Indole-3-acrylic acid

AG-CR1-3677

250 mg | 1 g

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