
Global Report on Obesity

Survey of Market Participants and Emerging Technologies in Obesity

Module #1

What's What. Clinical need, Obesity challenges and current standards of Care.

In this report we provide an understanding of Obesity's epidemiology, the current treatments, trends worldwide, relative benefits of treatments, and the direction of future treatments.

Module #2

What's Now. Current Players and Market Structure.

Here we take a look at the current marketplace; the current players, market share, treatments options, mechanisms of action. Complete review of drugs on the market today, their relative strengths and weakness, with profiles of the leading competitors and their technologies.

Module #3

What's Next. Future Players and Technologies.

This report anticipates a future marketplace by way of new and emerging technology-based companies. We assess their conceptual strengths, weaknesses, and approval expectations to evaluate prospects for success.

Module #4

Who's Who. The Ecosystem. Directory of Important Institutions and Individuals.

The directory comprises an invaluable resource to understand the important competitors and the roles they play in the overall ecosystem. Includes: organization, key contact information, analysis, major events, publications, key management biographies for all the important investment houses, associations, publications, research institutions, foundations and thought leaders.

OneMedResearch

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Global Report on Obesity

Obesity's intensification and increasing cost to the health care system composes a growing epidemic. An estimated 30% of the US population is considered obese with 6% marked severely or morbidly obese. The combined comorbidities of obese patients are collectively regarded as the biggest single drain on the country's health care system, which is an estimated \$300 billion annual bill.

Yet despite the problem's size, there has been little in the way of new drugs coming to market. The total count is two approved drugs in the last five years and none in the preceding 13 years.

The objective of this research report is to identify the new opportunities and give investors an overall understanding of the obesity market. The full report which is packaged into four sections, contains insight on:

- 32 companies with obesity drugs in development.
- 11 drugs at some stage of the FDA approval. (US only).
- 21 distinct drug targets with non-scientific summaries.
- 18 mechanism of action (MOA) with summaries.

The report also includes profiles of seven promising new entrants as a look at the major actors serving this market:

- 14 venture, private equity funds with active investments.
- Business development contacts and major strategic investors.
- 24 professional groups, non-profits, associations, media outlets and influencers.

We have a master report which totals 50 pages 140 citations which is then divided into 4 separate reports:

- 1. What's What.** The need, challenges current status.
- 2. What's Now.** Current players and market structure.
- 3. What's Next.** Future players and technologies.
- 4. Who's Who.** Directory of important institutions and individuals.

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We encourage readers to make suggestions and if possible alert us to additional companies or technologies that may be imminent. An update to this report planned for Release in late October 2015.

For additional information about the report and research services contact us at tkinze@onemedmarket.com or visit www.onemedmarket.com.

Module 3: What's Next

What's Next. Future Players and Technologies. This report will look at the future expected marketplace. The new and emerging companies and the technologies being developed, drug targets and mechanisms of action. Strengths and weaknesses of their concepts and expectations as to approvals as well as profiles of the leading players, their technologies and prospects for success.

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Drugs in the Approval Pipeline

New entrants that are currently developing anti-obesity drugs can be broadly classified into two groups.

1. **Phase III.** This group consists of drugs currently undergoing clinical trials, and that also look promising with a strong possibility of entering the market soon (Phase III Drugs).
2. **Preclinical, Phase I and Phase II.** The final group consists of drugs that are currently undergoing clinical investigation or are in development, but have not at this point provided well-developed data on efficacy and safety in humans for obesity treatment (Preclinical, Phase I and Phase II Drugs). We will discuss these three groups in the next section:

Phase III Drugs & Promising Phase II Drugs

Regeneron's drug Candidate (REG-3030) (GLP-1), Adipose's drug Candidate "Sipho" and "Sipho-2" and Strongly "Sipho" are currently in Phase III trials. There are also two companies who have strong Phase II drug profiles that have gotten significant backing from investors and they are Edgewise, Inc's "Sipho" and Rhythm Pharmaceuticals "RIP-100".

Regeneron's Candidate (REG-3030) is a space molecule that is purchased from Abnova Therapeutics Limited, is partnered with Takeda Pharmaceuticals to commercialize the drug. It is expected that this drug will come to market in 2023 as a result of promising clinical studies. This product exhibits the activity of space, which is a

specific enzyme that is secreted by the digestive tract and processed, and blocks the absorption of fat from the gut, resulting in reduced body weight. It is expected that they will seek FDA approval based on the results of their phase II clinical trials, a 52-week parallel-controlled study to evaluate the efficacy and safety study, a 24-week and 52-week open-label safety study in obese patients with type 2 diabetes and hypertension. The result of the efficacy study demonstrates that candidate used every three times daily was superior to placebo at the primary endpoint with an average body weight reduction of 2.7% in treated compared to 1.1% in placebo-treated. The clinical trials have also demonstrated that candidate has a good safety profile and is well tolerated. Compared to the other type 3 inhibitors, such as orlistat (Xenical) on the market, candidate has a better safety profile.

Strongly Siphonol is also an orally available acting small molecule non-peptide GLP-1/GIP receptor antagonist. GLP-1 affects appetite signaling, which plays a role in meal initiation and regulation of energy balance, and is important under conditions of food deprivation or reduced weight. As GLP-1 antagonist can potentially be effective in reducing a negative energy balance leading to reduced body weight. In addition, as GLP-1 antagonist could be particularly effective for weight loss maintenance in maintaining individuals below their usual weight by inhibiting GLP-1 signaling. Clinical studies of siphonol have shown that 25% of the patients and 15% of their weight relative to 12% of the patients taking placebo.

Edgewise will report to other promising Phase II drugs, Edgewise, whose main drug candidate is Siphonol is a

Intunivon: Beltransk was licensed from OGD Pharma. Zolger raised over \$115 million from investors before going public in June 2014.

Beltransk (OZG-442) is a novel obesity therapy that is a malonyl-CoA: acetyl-CoA transferase (MCD) 1 inhibitor, an enzyme that helps produce fatty acids. MCD1 inhibitors work by reestablishing balance in the way the body stores and utilizes fat. Inhibitors of MCD1 reduce the generation of new fatty acid molecules in the liver and help convert stored fats into energy. Beltransk targets this enzyme and restores balance to the production and metabolism of fat leading to positive metabolic changes. Beltransk is interesting in that, while current drugs are expected to trick the body into thinking that it is full, this drug will change the way the body metabolizes fat. The most common side effects seen in clinical studies are nausea, vomiting and diarrhea, with no serious side effects arising. They have received funding to the tune of \$115.2 million in 7 rounds from 9 investors. Their investors include Atlas Venture, Greatpoint Venture, Third Rock Ventures, Atlas Partners, EA Capital Management, Brookside Capital, Wernick, McCay Financial, and Oxford Finance Corporation.¹⁷

Zolger has initiated Phase II trial for their beltransk drug in October 2014. The "best PWS" trial Beltransk Efficacy Safety and Tolerability in PWS, is a randomized, double-blind, placebo-controlled trial in obese adolescents (12 years of age and older) and adults with Prader-Willi syndrome to evaluate food-related behaviors, total body fat mass, and safety of beltransk. The "best PWS" trial is expected to enroll 84 patients at 14 different sites across the United States.¹⁸ One issue with Zolger's clinical studies is the sample size, with participants in the study roughly numbered at 120 compared to other anti-obesity clinical studies where the sample size > 2000. This raises questions about the efficacy of their drug when exposed to a larger sample size as well as if the safety profile will change if the drug is administered to a population size with a broader metabolic profile.

Rhythm Pharmaceutical is another company that has shown promise in the development of a novel anti-obesity drug. Rhythm is a biopharmaceutical company that is involved in the development of peptide therapeutics. They have received a total of \$34.3

million from 6 investors. In the most recent fund round in September 2013 they obtained \$1.4 million. They have received significant investment support from the Michael J. Fox Foundation (Parkinson Research), Third Rock Ventures, Ignis, New Enterprise Associates, MFW Capital, Fluor Venture Investments.¹⁹

Their drug candidate RM-492 is a melanocortin 4 (MC4) receptor agonist. It has been proposed that genetic defects in the MC4 gene could cause obesity.²⁰ Previous studies using other MC4 agonists were not productive, since they caused increases in blood pressure. RM-492 on the other hand is quite safe and retains the specificity and functionality of the naturally occurring hormone, which activates MC4. Additionally, RM-492 does not appear to effect blood pressure based on Phase I clinical trials. They commenced Phase II clinical trials in January 2013,²¹ with this trial being designed to evaluate the effect of RM-492 on weight loss and safety in obese subjects treated for three months. The trial also assessed the effect of the drug on glucose and insulin resistance. With this trial being completed last month, initial results show that the RM-492 increased energy expenditure significantly.²² It has been suggested that RM-492 could achieve double-digit weight loss. Patients treated for 8 weeks had an average of 13.5%. The RM-492 is administered as subcutaneous injection.

Enter Therapeutics is another company that has a promising portfolio of drugs for obesity treatment. They recently merged with Merit Therapeutics so as to enlarge their drug portfolio. The company was formerly known as Adipoferrin Inc. and then changed its name in 2011. They were founded by Third Rock Ventures with \$34 million investment, but had to shut down in December 2014. However, in 2015, Enter merged with Merit Therapeutics, a company focused on developing cardiovascular therapies and became a combined entity under the name Enter Therapeutics.²³ Their drugs work through the brown fat mechanism and include PFM25, Fx02, TRPA4, Thermo1 and Adipocal. Studies have shown that inhibition of Adipocal induced classic brown fat characteristics, including increased expenditure, lowered glucose levels and weight gain. Also other studies have demonstrated that Thermo1, a long chain fatty acid-CoA thioesterase that is highly enriched in brown fat, plays an important role in regulating energy homeostasis.²⁴ PFM25 is active in stimulating brown fat development.

TABLE 10: FDA Approved & Phase I/II/III companies that are poised enter in the obesity drug market.^{77,78}

Mechanism of Action	Company	Drug	Target	Status
Central serotonergic signaling	Hydrex	HY-019	5-HT _{2C} receptor	Phase II
	Strongbridge	SB-297090 (S-2970)	5HT _{2C} receptor	Phase II
Peripheral peptide hormone signaling	Amgen	Saralix (Saralix)	GLP-1	Phase II
	Phase	Orlistat (Xenical)	ORX	Phase I recruiting
	Therapeutics	TRX-200	ORX	Phase I
Peripheral hormone signaling	Merck	MR-002	PP	Phase I completed
	Amgen	Desamorelin (AMG 001)	AgRP	Phase II
	TTM	Orlistat	Peripheral 11 and 14 receptors	Phase II
Adipose tissue hormone signaling	Amgen/Genentech	Metformin	Leptin	Phase II
Inhibition of lipase	Alnylam/Genentech/Sangart	Orlistat (Xenical)	Adipose lipase	Phase II

Abbreviation list:

- GLP-1: Glucagon-like peptide 1
- MR-002: Melanocortin 4 Receptor
- NDN: New Drug Application
- PP: Peripherally administered
- ORX: Orlistat
- 5HT_{2C}: Serotonergic 5
- ORX: Orlistat
- PP: Peripherally administered

<http://www.clinicaltrials.gov/ct2/show/study?term=obesity&rank=1>

Mechanism of Action

- ① **MC4 pathway**, an important cell signaling mechanism is involved in the regulation of energy expenditure, homeostasis, and appetite. Genetic defects in the genes associated with in MC4 pathway leads to early-onset and severe obesity confirming MC4's role in weight regulation.⁷⁹
- ② **Neuropeptide Y (NPY)** is a potent appetite stimulating (orexigenic) neuropeptide, and blockade of its cognate receptors NPY Y1 and NPY Y5 (NPYxR) is considered an important anti-obesity drug target.⁸⁰
- ③ **Byetta** suppresses appetite by delaying the movement of food from the stomach into the small intestine leading to a feeling of satiety and reduced appetite.
- ④ **Obinipitide** is an analog of two peptide hormones that are associated with food intake and appetite regulation and are known to play a role as satiety signals.⁸¹
- ⑤ **Lipase Inhibitors** such as Cametor (Cetilistat) inhibits the activity of lipase, a lipolytic enzyme, secreted by the digestive tract and pancreas, and block the absorption of fat from the gut, resulting in reduced body weight.⁸²

TABLE 11: Company Profile of New Entrants in the Market

Companies	CEO	Year Founded	Location	Drug	Funds Raised	Investors	Drug Phase	Mode of Administration
Adipose Therapeutics (Boston)	Don Brannan	2007	San Diego, CA	Wegovy (semaglutide), Retatrineriv, Baxlo, Tirzepatide	\$70 M (2012)	NA	Phase III	Subcutaneous Injection
Orion Therapeutics (Boston)		2011	Boston, MA	Wegovy and Retatrineriv	\$100 M	First Round Ventures	NA	NA
Regeneron SA / Regeneron (Tarrytown)	Paul Stoffa	1988	Boston, MA / Tarrytown, NY	Compound 1096	NA	NA	Phase III	Oral
Novo Nordisk	Carsten Thomsen	1919	Denmark / Bagsvaerd, Denmark	Wegovy	NA	NA	Phase Approved	Subcutaneous Injection
Orange Therapeutics	Michael Brown	2010	La Jolla, CA	Compound 1096 (semaglutide)	Phase I Company	NA	Phase Approved	Oral
Bluebird bio (Boston)	Scott Gottlieb (ex-NIH)	2008	Boston, MA	Wegovy	\$100 M	<ul style="list-style-type: none"> • Michael J. Fox Foundation (Phase I/IIa) • First Round Ventures • Gen • New Enterprise Associates • BPC Capital • First Round Ventures 	Phase I	Subcutaneous Injection
Strategic Bio	John Kelly	2010	San Diego, CA	Wegovy	NA	NA	Phase III	Oral
EdgeBio	Thomas F. Hughes	2010	San Diego, CA	Wegovy	\$100 M (Phase I/II) \$100 M	<ul style="list-style-type: none"> • Bluebird bio • LinePoint Ventures • First Round Ventures • BPC Capital 	Phase I	Subcutaneous Injection
Orion Therapeutics	NA	2010	Boston, MA	Retatrineriv (based on existing active ingredient)	\$1.2 M	LinePoint	Phase III	NA

Companies	CEO	Year Founded	Location	Drug	Funds Raised	Investors	Drug Phase	Mode of Administration
Genentech Therapeutics	Scott Cook	2005	Hayward, CA	Oral Drug Delivery Platform	\$750.2 M	<ul style="list-style-type: none"> Genentech GGP Capital New Enterprise Associates New Leaf Venture Partners Frontier Capital 	Pre-clinical	Subcutaneous Injection, Medical Device
Genentech Phase 4/5	Dr. Mark Sarnat	2006	San Diego, CA	201529	\$5	Warner Capital Management	Phase 1	Subcutaneous Injection
TRG Phase 4/5	Dr. Wolfgang	2005	San Diego, CA	Genesys	\$10.2 M	<ul style="list-style-type: none"> LifePointFund Gen GGP Capital Index Ventures New Partners GGP Genentech Life Sciences Venture 2.0 	Phase 2	Subcutaneous Injection
Genentech Research Corporation	Dr. John Brannon	2005	Hayward, CA	Adipex	\$5	GGP Capital Management	Phase 1	Subcutaneous Injection
Genentech Pharmaceutical	Dr. John Brannon	2004	San Diego, CA	Oral Drug Delivery Platform	\$5	GGP	Phase 1 Early Stage	\$5
Genentech Therapeutics	Dr. Steven Lee	2012	San Diego, CA	GGP 1.0	\$5	GGP Ventures	Pre-clinical	Subcutaneous Injection
Genentech 1.0	Dr. Steve Lee	2012	San Diego, CA	Genentech Commercial Model	\$10.2 M	<ul style="list-style-type: none"> Warner Capital Management Index Partners GGP Ventures GGP Capital Genentech Ventures GGP Life Sciences 	\$5	Medical Device
Genentech Pharmaceutical	Dr. Steve Lee	2011	San Diego, CA	Genentech 1.0	\$1 M	<ul style="list-style-type: none"> GGP Ventures Genentech GGP Capital Genentech Ventures GGP Life Sciences GGP 	Pre-clinical	\$5

Pre-Clinical Innovations on Horizon

There are several companies that are currently working on developing anti-obesity drugs. The efficacy and safety of these drugs have not been significantly proven clinically, but they have the potential.

These companies are summarized in **Table 11**. The most promising of these companies are **TNO Pharma, Zealand Pharma A/S, Global Pharma and Intance Therapeutics**.

TNO Pharma is located in Copenhagen, Denmark. It is focused on developing new drugs that target **FTS** receptors. Their lead compound is **Obimiprotin**, which targets the treatment of obesity, is in Phase II clinical study. **Obimiprotin (TNO3336)** is a synthetic analogue of two natural human hormones, **PYY3-36** and **pancreatic polypeptide PP**, which are normally released during food consumption. They also recently announced that a second obesity compound entered Phase III studies in early 2014. This drug, **TNO3637** is a first in class, second generation **GBC** receptor antagonist. Another drug in their portfolio is **TNO3335**, which is a selective **5H** receptor antagonist, and is currently in clinical development Phase III for treatment of obesity.¹⁴

Zealand Pharma A/S is also another small company that is focused on type 2 diabetes and obesity and is poised to provide some novel obesity solutions. Their main drug target for obesity is **2P1219**, which is currently undergoing Phase I study. **2P1219** is a once-daily dual acting glucagon/GLP-1 peptide receptor agonist for subcutaneous administration. Zealand A/S Pharma has partnered for the commercialization of its obesity pipeline with **Boehringer Ingelheim** and **Dr. Lilly**.¹⁵ **2P1219** will be similar to **Saxenda**, in mechanism, though it would be interesting to see if there are any significant changes in the drug efficacy profile.

Global Pharma has developed a peptide with rapid and substantial weight loss efficacy with a novel Mechanism of Action. It increases **PGC-1** in muscle and **UCP1** in white adipose tissue which turns white fat into brown fat. The origin for the drug started about a decade ago. Prof. Wan Shik Kim, PhD (Medical School of Seoul University, Seoul, Korea) initiated extensive research and experiments with fat protein, a small protein encoded by **UCP1** that is essential for heat production ("fat" stands for Trans activator of transcription). Dr. Kim's research has shown that the small fat protein alone can induce a dramatic weight loss in animal models, mimicking the wasting syndrome observed in untreated **AIDS** victims. They have seen as much as 20% weight reduction, at least all of them from reduction of fat, in animal studies.

Intance Therapeutics is another small company that currently has some anti-obesity drugs in its pipeline. Intance is different from the other companies listed in that it is also a drug delivery company. They have developed a subcutaneous micro-pump technology to address some of the primary obstacles that are encountered in developing safe drug therapies in obesity. This drug delivery method employs the "iNANO drug delivery platform" and will be paired with some of their peptide technologies. They are headquartered in Hayward, CA. Intance is evaluating a series of human peptides for delivery with its micro-pump technology.¹⁶

Another interesting company that needs to be noted is **Raxat Therapeutics**. Raxat Therapeutics has developed a novel drug that after a single injection into subcutaneous fat will convert white adipose tissue (**WAT**) into brown adipose tissue (**BAT**). The name of Raxat's drug candidate is **RX-12** which is a potential first in class, injectable drug currently in pre-clinical development for the reduction of fat cell mass.¹⁷ They are also assessing the feasibility of making this drug available in an oral form. Their main investor is **W.B. Star Line Serial Ventures**. This is quite similar to the drug being made by Global.

Furthermore, small subsets of companies are developing anti-obesity drugs, but are relative unestablished at this point. They are using novel methodologies to address obesity. One of these is

Compass Therapeutics whose candidate drug CPN04 is a calcium channel blocker used in a nasal formulation to block olfactory activity and reduce food intake.¹⁷ As a result it can be classified as an anorexigen drug. The advantage of CPN04 is that it is a small molecule that is well tolerated in humans and is readily manufactured. Based on its prior use in humans for certain other disorders, Compass believes it will be eliminating some of the drawbacks typically associated with anorexigen compounds. They have started human testing in 2012. There are companies like **Innovative Therapeutics Agil**, whose main therapy is the lipolytic receptor derived peptides and proteins that could potentially be used for treating obesity.

Another worthy mention is **Verve Pharmaceuticals**, which is also developing a new set of drugs that are referred to as "verve fat blockers." At the moment they have generated preclinical proof of concept with two obesity

technologies that will prevent de novo fat cell formation. They recently discovered that compounds that will act on some targets were found to reduce body fat and body weight in obese mice and prevented fat as well as weight gain in lean mice placed on a high fat diet. Although no human trials have been performed, it is expected that these fat blockers will reduce fat cell number leading to a better endocrine profile and reduced appetite.

Also since these fat blockers do not act on the CNS, they will avoid some of the side effects associated with current drugs on the market. It is expected that this technology will also have several therapeutic indications including the prevention of weight gain in general, regaining of fat after weight loss and drug induced weight gain.¹⁸

The drugs in **Table 12** are either in the research phase in which lead identification is currently being done or in the preclinical stage. These drugs have been indicated for both type 2 diabetes and obesity in animal models, but not in a human trial model.

Company	Drug Target	Phase	Location	MOA	Notes
Genentech	GLP-1	Preclinical	Marlborough, MA	GLP-1 (Olanzapine) acylated peptide 2; inhibitor which reduces TG synthesis	
UCR Life Sciences	Not disclosed	Preclinical	South Korea	Not disclosed	Collaboration with Genentech Pharmaceuticals
Wintona/Takeda Pharma Group	Long-chain (18:1) n-3	Phase 2	Japan	Reduce glucose transporter 2 (GLUT2) inhibitor	Has shown clinical efficacy in weight loss in 2013. Has been approved for Type 2 Diabetes
Wintona/Takeda Pharma Group/Novartis	Long-chain	Preclinical	Osaka, Japan	GLP-1 receptor inhibitor; peptide 4 analog	
Wintona Group/Novartis/Novartis Inc.	Not disclosed	Preclinical	Wilmington, DE	GLP-1 inhibitor agent	
Medtronic	GLP-1R	Phase III (2015)	San Diego, CA	GLP-1 receptor agonist	Investigate drug for reducing beta cell function; company not yet focused on obese obesity
UCR Therapeutics	Human Acid (non-obligate)	Preclinical	Barcelona, Spain	Targeting secretory PIP2 in Pancreatic ACPG neurons	GLP-1 in the research phase with patent awarded in 2014
Novartis Research at the University of Geneva	Human	Preclinical	Geneva, Geneva	Not disclosed	Early research going on in US
Novartis	Human (GLP-1R)	Phase II (2015)	Basel, Switzerland	Anti-obesity compound; compound of telaprevir	Phase II trial showed positive results in 2013
Novartis Therapeutics/Takeda Pharma Inc.	GLP-1R	Preclinical	Osaka, Japan	GLP-1 agonist	Takeda Pharma owns right to GLP-1R but was purchased by Novartis Therapeutics
Novartis Therapeutics	GLP-1R agonist	Preclinical	Osaka, Japan	Wintona/Novartis (GLP-1) agonist that inhibits glucose effect	
Pharm Group plc	GLP-1 (Olanzapine)	Preclinical	London, United Kingdom	Purified Peptide Extract	
Pharm Group plc	GLP-1R	Phase 2	Cambridge, MA	GLP-1R agonist	

Company	Drug Target	Phase	Location	MOA	Notes
Sanofi Novartis Roche	GLP-1 agonists	Phase 3	Copenhagen, Denmark	Type 2 diabetes insulin inhibitor	Approved by Sanofi in 2014
Novartis Roche Takeda T. J. Novartis T. J. Novartis	GLP-1 agonists	Phase 3	Germany, UK, Canada, Canada	GLP-1 agonist	GLP-1 agonists act in the stomach to reduce the reabsorption of glucose into the bloodstream. This can act to weight loss. The first GLP-1 agonist to receive market approval in the U.S. is Novartis and Roche's GLP-1 agonist, Exenatide (Byetta).
Novartis Roche	GLP-1 agonists	Phase 3 to study and Phase 3 for Canada	Canada, Canada	GLP-1 agonist	Phase 3 to study and currently in Phase 3 trials
Novartis Roche Takeda T. J. Novartis	GLP-1 agonists	Phase 3	High Point, NC	Small molecule inhibitor of appetite related protein (MCH)	Agonist Receptor Protein (MCH), is a central antagonist of MCH-R and MCH-R and is an integral component in the metabolic processes that regulate feeding behavior and body weight
Novartis Roche	GLP-1 agonists	Phase 3	India	GLP-1 agonist	
Novartis Roche	GLP-1 agonists	Phase 3	India	GLP-1 agonist	

Mechanism of Action

- ❶ **Melanin concentrating hormone (MCH)** is an appetite stimulating peptide that affects food intake and body weight regulation. MCH peptide regulates energy homeostasis through the MCH1 receptor by stimulating feeding and promoting glucose, insulin and leptin levels. Blocking MCH1 receptor reduces food intake in rats and leads to body weight and fat stores reduction.⁹²
- ❷ **Leptin**, is a hormone made exclusively by fat cells, regulates both metabolism and appetite. Leptin resistance is a proposed reason for obesity. One cause of leptin resistance is the impaired transport of leptin receptors through the blood-brain barrier. A leptin therapy that can effectively transport across the blood-brain barrier could prove effective in treating obesity.
- ❸ **Somatostatin** vaccine induces body's immune system to produce anti-somatostatin antibodies and thus inhibiting its function. Somatostatin functions by antagonizing growth hormone and insulin-like growth factor, both of which increase metabolism, fat breakdown, and muscle build-up leading to weight loss.⁹³
- ❹ **ZAG** is an adipokine (cell signaling proteins) secreted by adipose (fat) tissue involved in the mobilization and utilization of fat and thus plays a key role in fat cell metabolism.⁹⁴
- ❺ **Ghrelin** is involved in appetite stimulation, suppression of insulin secretion and weight gain via its receptor GH secretagogue receptor type 1a (GHS-R1a). Antagonists to ghrelin receptors may reverse its effects.¹⁰¹
- ❻ **MC4 receptor** is associated with feeding behavior and energy homeostasis. It has been shown that agonists (eg., alpha-MSH) exert anorectic effects similar to the mechanism of Rhythm's RM-493.

Some of the drugs we listed in **Table 12** have a lot of potential if they are able to show efficacy in future clinical studies. Also observed is the emergence of nucleic acid technology such as nLife Therapeutics and ISIS "ISIS-FGFR4RX" to target obesity.

Product Comparison/Differentiation

The new entrants to the market are comprised of both peptide and small molecule drugs.* These new generation compounds act by inducing

anorectic and/or fat burning effects via a wide variety of cellular mechanisms as shown in **Table 13**.

TABLE 13: Comparison of New Entrants in the Market

Company (Compound)	Molecule Type	Mode of Administration	Effect	Mechanism of Action	Price	Clinical Stage
TRF Peptides (TRF Peptides)	TRF	Subcutaneous Injection	Anorectic	Peptide hormone signaling. Peptide binds to and activates TRF receptors.	\$6	Phase II
Amesobut Research (Amesobut)	TRF	Subcutaneous Injection	Fat Burning	Targets adipose tissue and binding to TRF receptors (lipogenesis inhibition)	\$6	Phase I
Adipose Tissue (Adipose Tissue)	TRF	Subcutaneous Injection	Anorectic	Adipose tissue hormone signaling, TRF receptor agonist	\$6	Phase II
Orlistat (Orlistat)	SM	SM	Anorectic	Caloric intake restriction that blocks fat absorption to reduce fat intake	\$6	Phase II Early Stage
Orlistat Therapeutics (Orlistat)	TRF	SM	Fat Burning	Increase brown fat and reduce energy expenditure	\$6	SM
Insulin Therapeutics (Insulin Therapeutics)	TRF or SM (Insulin)	SM	SM	Modulation of specific proteins	\$6	Preclinical
Insulin Therapeutics (Insulin Therapeutics)	TRF	Subcutaneous Injection Medical device	SM Anorectic	SM Anorectic	\$6	Preclinical
Insulin SM (Insulin SM)	SM	SM	Fat Burning	Insulin promotes lipid uptake (brown fat)	\$6	Phase II
Insulin SM (Insulin SM)	TRF	Subcutaneous Injection	Anorectic	Insulin promotes TRF signaling TRF 2 agonist	\$1,000	Phase II

Company (Compound)	Molecule Type	Mode of Administration	Effect	Mechanism of Action	Price	Clinical Stage
Merck (Tosyn)	PP-1	Oral Solution	Fat burning	Increase SIRT, increase energy expenditure, and increase fat metabolism, reduce appetite	\$6	Preclinical
Genzyme Therapeutics (Eliquis)	SM	Oral	Appetite	Neuroendocrine dysregulation pathway inhibitor	\$1000	FDA Approved
Novartis Therapeutics (AZD 1225)	SM	Subcutaneous injection Oral formulation is being tested	Fat burning	Effect: appetite	\$6	Preclinical
Hydrex Pharmaceuticals (HYD-402)	SM	Subcutaneous injection	Appetite	Reduce appetite, increase fat metabolism	\$6	Phase II
Strategic Bio (SMB-001)	SM	Oral	Appetite	Central neuroendocrine signaling (GPR119, 419 receptor antagonist, SIRT activator)	\$6	Phase II
Novo Pharmaceuticals (NN-700, NN-710, NN-720)	SM	SM	Appetite, Fat burning	Reduce neuroendocrine serotonergic inhibition (5HT2C-antagonist)	\$6	Preclinical
Adigen, Inc. (Adigen-1)	SM	Subcutaneous injection	Fat burning	Inhibition of synthesis of fatty acid in liver	\$6	Phase II
Novartis Pharma AG (GSK2330672)	PP-1	Subcutaneous injection	Appetite, Fat burning	Inhibits peptide hormones signaling GPR119 receptor agonist	\$6	Phase I

Abbreviation list:

MOLECULE TYPE

SM Small Molecule

PP-1 Peptide

TARGET ORGAN

SMO Stomach

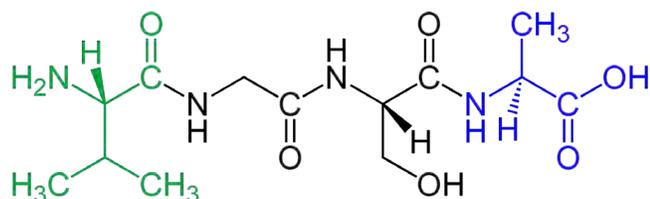
SMI White Adipose Tissue

EFFECT

SMO/SMI Reduce food intake and increase feelings of satiety

Note on Peptides & Small Molecules

*Peptide drugs offer high efficacy, high specificity, lower toxicity, and a wide range of target selectivity in contrast to small molecule drugs. However, small molecules exhibit higher stability, oral bioavailability, and lower production costs. Due to these characteristics peptide drugs are usually administered parenteral (subcutaneous injection) in contrast to orally administered small molecules.¹⁰²



Peptides (from Gr. **πεπτός**, “digested”, derived from **πέσσειν**, “to digest”) are naturally occurring biological molecules. They are short chains of amino acid monomers linked by peptide (amide) bonds. The covalent chemical bonds are formed when the carboxyl group of one amino acid reacts with the amino group of another. The shortest peptides are dipeptides, consisting of 2 amino acids joined by a single peptide bond, followed by tripeptides, tetrapeptides, etc. A **polypeptide** is a long, continuous, and unbranched peptide chain. Hence, peptides fall under the broad chemical classes of biological oligomers and polymers, alongside nucleic acids, oligosaccharides and polysaccharides, etc.

Peptides are distinguished from proteins on the basis of size, and as an arbitrary benchmark can be understood to contain approximately 50 or fewer amino acids. Proteins consist of one or more polypeptides arranged in a biologically functional way, often bound to ligands such as coenzymes and cofactors, or to another protein or other macromolecule (DNA, RNA, etc.), or to complex macromolecular assemblies. Finally, while aspects of the lab techniques applied to peptides *versus* polypeptides and proteins differ (e.g., the specifics of electrophoresis, chromatography, etc.), the size boundaries that distinguish peptides from polypeptides and proteins are not absolute: long peptides such as amyloid beta have been referred to as proteins, and smaller proteins like insulin have been considered peptides.

Note on Small Molecules

In molecular biology and pharmacology, a **small molecule** is a low molecular weight (<900 daltons) organic compound that may help regulate a biological process, with a size on the order of 10^{-9} m. Most drugs are small molecules.

The upper molecular weight limit for a small molecule is approximately 900 daltons, which allows for the possibility to rapidly diffuse across cell membranes so that they can reach intracellular sites of action. In addition, this molecular weight cutoff is a necessary but insufficient condition for oral bioavailability. Finally, a lower molecular weight cutoff of 500 daltons (as part of the “rule of five”) has been recommended for small molecule drug development candidates based on the observation that clinical attrition rates are significantly reduced if the molecular weight is kept below this 500 dalton limit.

Pharmacology usually restricts the term to a molecule that binds to a specific biopolymer—such as protein or nucleic acid—and acts as an effector, altering the activity or function of the biopolymer. Small molecules can have a variety of biological functions, serving as cell signaling molecules, as drugs in medicine, as pesticides in farming, and in many other roles. These compounds can be natural (such as secondary metabolites) or artificial (such as antiviral drugs); they may have a beneficial effect against a disease (such as drugs) or may be detrimental (such as teratogens and carcinogens). Biopolymers such as nucleic acids and proteins, and polysaccharides (such as starch or cellulose) are not small molecules—though their constituent monomers—ribo- or deoxyribonucleotides, amino acids, and monosaccharides, respectively—are often considered small molecules. Very small oligomers are also usually considered small molecules, such as dinucleotides, peptides such as the antioxidant glutathione, and disaccharides such as sucrose.

Small molecules may also be used as research tools to probe biological function as well as leads in the development of new therapeutic agents. Some can inhibit a specific function of a multifunctional protein or disrupt protein-protein interactions.

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(Module 3)

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