# WORKED EXAMPLE

## Therapeutic Gut Hormone Research
## Imperial College London

Professor Stephen Bloom
and team at
Hammersmith Campus
in West London

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# What is required for drug discovery in Academia?

Knowledge of drug discovery

Scientific opportunity

Team resource (money)

University mechanism

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# Knowledge of Drug Discovery

Physician in AHSC

Extensive consultancy for industry

Work with small biotech

Member of MHRA, NIBSC etc

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# Scientific Opportunity

Worked with human systems and basic science

Trained as peptide chemist

Nearly 40 years in research

Large team

Aware of gaps in therapeutics

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# Team Resource

My research team is 20 scientists

Built up financial reserves (spent £15 million)

Skill with molecular biology, receptors, animal physiology, peptide chemistry, assays, human infusions

Management experience.

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# University Mechanism

Imperial a technical university

History of consultancy and working with industry

Innovations considerable experience

Own Venture Capital

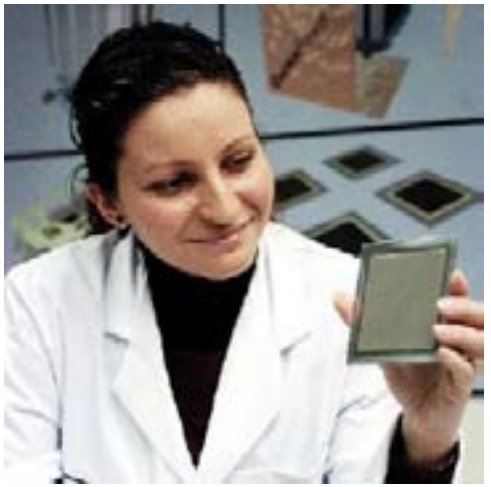
# An enterprise culture

## SLIDE TAKEN FROM THE OFFICIAL PROMOTIONAL PRESENTATION FOR IMPERIAL COLLEGE

**89** Established equity holdings in spin-out companies

**157** Commercial agreements under management

**150+** Licence agreements



**Example spin-out company - Thiakis**

» Obesity drug company founded by Steve Bloom & John Burt

» Sold to US-based Wyeth Pharmaceuticals in Dec 08 for up to £100M payable to all shareholders

» A significant proportion of this income will flow back to College under the revenue share agreement

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# The Problem

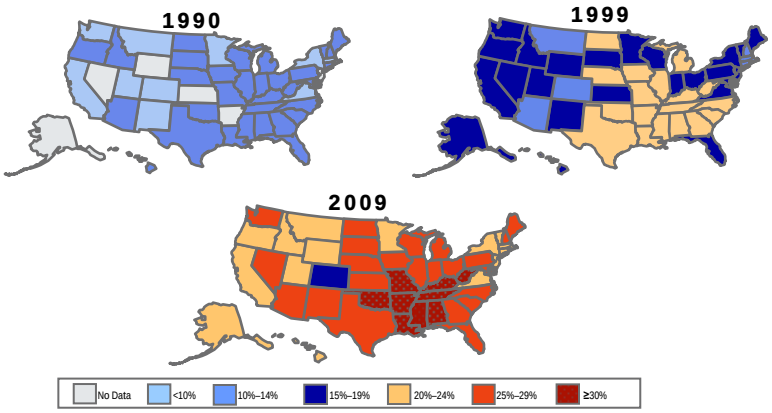
**Obesity, and its main complication, diabetes, is very common and increasing at an accelerating rate.**

Over 20% of UK adults are obese according to the WHO criterion (BMI ≥30 kg/m$^2$) resulting in an estimate 800 premature UK deaths per week.

*Obesity directly causes 95% of diabetes.*

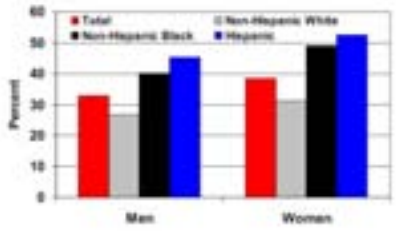
The International Diabetes Federation estimates about 285 million people worldwide had diabetes in 2010 and as many as 438 million could have the condition by 2030.

**Obesity Trends Among U.S. Adults**
1990, 1999, 2009




**By 2050 1 in 3 citizens born in USA will be diabetic**
**Centers for Disease Control and Prevention**

Estimated lifetime risk of developing diabetes for individuals born in the United States in 2000




Narayan et al, JAMA, 2003

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# Abject Therapeutic Failure

## Current & Coming Anti-obesity Agents

| Agent | Action | Company | Status | Comment |
|---|---|---|---|---|
| Orlistat | Lipase inhibition | Roche | Marketed for obesity | Safe, poor efficacy, significant side effects |
| Exenatide | GLP1 mimetic | Lilly/Amylin | Marketed diabetes | Injection, moderate to good efficacy, safe, nausea |
| Liraglutide | GLP1 mimetic | Novo Nordisk | Marketed diabetes | Nausea, hypoglycaemia, fairly effective |
| Pramlintide | Amylin agonist | Amylin | Marketed diabetes | Poor efficacy, injection |
| Phentermine | Adrenergic | Generic | Marketed initial obesity therapy only | Only three months, limited efficacy, CVS concerns |
| Sibutramine | Amine uptake inhibition | Abbott | No longer marketed | Poor efficacy, may have risks |
| Rimonabant | CB1 partial antagonist | Sanofi Aventis | No longer marketed | Moderate efficacy, some side effects (depression) |
| Cetilistat | Lipase inhibition | Alizyme | Phase III | Safe, poor efficacy, side effects |
| Qnexa (Phentermine + Topiramate) | Adrenergic + Amine | Vivus | Phase III/FDA | Effective (15% wt loss), possible toxicity |
| Lorcaserin | 5HT 2c agonist | Arena | Phase III/FDA | Moderate efficacy (8% wt loss), headache |
| Contrave (Bupropion + Naltrexone) | Opioid antag + Amine uptake inhib | Orexigen | Phase III/FDA | Effective (10% wt loss), safety unclear |
| Metreleptin + Pramlintide | Leptin + Amylin agonists | Amylin | Phase II | Injection, nausea, effectiveness in obese? |
| Intranasal PYY3-36 | Gut hormone | Nastech | Phase II | Nasal, nausea, uncertain efficacy |
| Bupropion + Zonisamide | Unclear | Orexigen | Phase II | Effective, toxicity |
| Oleyl Estrone | Unclear | Manhattan | Phase II | Unclear |
| Y5 antag | Inhib NPY Y5 R | Shionogi | Phase II | Poor efficacy |
| Tesofensine | Unclear | Neurosearch | Phase II | Unclear |
| OAP 189 | Oxyntomodulin agonist | Pfizer | Phase I | Injection, Chronic effect on wt unclear |
| Glucagon/GLP1 agonist | Gluc/GLP1 agonist | | Phase I | Injection, Chronic effect on CHO tolerance unclear |
| CB1 antagonists | CB1 antag | Vernalis,Merck,Pfizer | Various | Reasonable efficacy, depression, nausea etc |

**Past 25 years 123 products, only one now marketed for obesity.**

Orlistat is the only agent currently on the market for obesity and only 1% of subjects continue beyond a year due to significant side effects and poor efficacy.

Life long therapy requires excellent safety.

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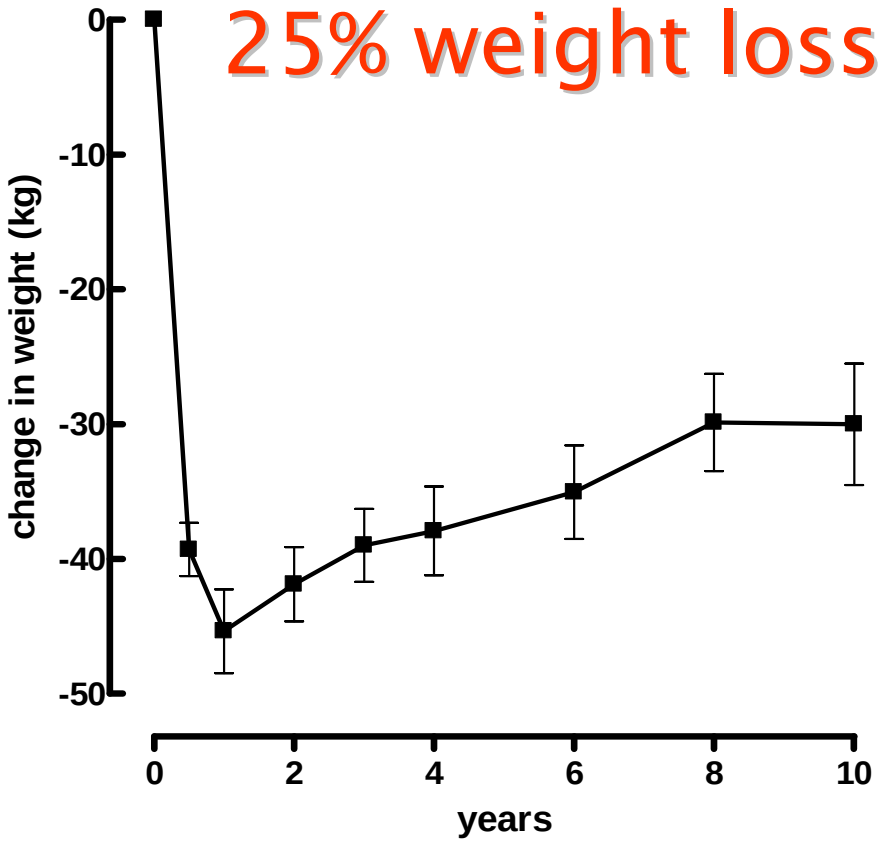
# What does "cure" obesity?




Roux-en-Y gastric bypass

*adapted from:* Sjöström et al, New Engl J Med 2004; 351: 2683-93

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# Bariatric Surgery - excellent long term outcome

## Bariatric Surgery only successful therapy

Sjostrom et al, Sweden, NEJM 2007

Prospective controlled study, 4000 subjects

Gastric Bypass group 10 year wt loss 25%

Adams et al, USA, NEJM 2007

Retrospective cohort study

Gastric Bypass, 7 years, 15000 subjects

## Myocardial Infarct & Cancer rates halved

Expensive, significant death rate, 50% morbidity and can't be adjusted.

Works by sending satiety gut hormone signals fooling the brain that the gut is full.

Chronic elevation of satiety gut hormones associated with improved life expectation!

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# Current Therapeutic Team Work

letters to nature

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**Supplementary Information** accompanies the paper on *Nature*'s website (http://www.nature.com/nature).

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**Competing interests statement**

The authors declare that they have no competing financial interests.

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## Gut hormone $PYY_{3-36}$ physiologically inhibits food intake

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**Food intake is regulated by the hypothalamus, including the melanocortin and neuropeptide Y (NPY) systems in the arcuate nucleus[1]. The NPY Y2 receptor (Y2R), a putative inhibitory presynaptic receptor, is highly expressed on NPY neurons[2] in the arcuate nucleus, which is accessible to peripheral hormones[3]. Peptide $YY_{3-36}$ ($PYY_{3-36}$), a Y2R agonist[4], is released from the gastrointestinal tract postprandially in proportion to the calorie content of a meal[5–7]. Here we show that peripheral injection of $PYY_{3-36}$ in rats inhibits food intake and reduces weight gain. $PYY_{3-36}$ also inhibits food intake in mice but not in Y2r-null mice, which suggests that the anorectic effect requires the Y2R. Peripheral administration of $PYY_{3-36}$ increases c-Fos immunoreactivity in the arcuate nucleus and decreases hypothalamic *Npy* messenger RNA. Intra-arcuate injection of $PYY_{3-36}$ inhibits food intake. $PYY_{3-36}$ also inhibits electrical activity of NPY nerve terminals, thus activating adjacent pro-opiomelanocortin (POMC) neurons[8]. In humans, infusion of normal postprandial concentrations of $PYY_{3-36}$ significantly decreases appetite and reduces food intake by 33% over 24 h. Thus, postprandial elevation of $PYY_{3-36}$ may act through the arcuate nucleus Y2R to inhibit feeding in a gut–hypothalamic pathway.**

The orexigenic NPY and the anorectic alpha melanocyte-stimulating hormone (α-MSH) systems of the hypothalamic arcuate nucleus are involved in the central regulation of appetite[1]. However, the potential mechanisms that signal meal ingestion directly to these hypothalamic-feeding circuits are unclear. $PYY_{3-36}$ is a gut-derived hormone that is released postprandially in proportion to the calories ingested[5]. We therefore investigated the effects of peripheral administration of $PYY_{3-36}$ on feeding.

An intraperitoneal (i.p.) injection of $PYY_{3-36}$ to freely feeding rats before the onset of the dark phase significantly decreased subsequent food intake (Fig. 1a). A similar inhibition of feeding was seen after i.p. injection in rats fasted for 24 h (Supplementary Information Fig. 1). A time course of the plasma $PYY_{3-36}$ concentrations after i.p. injection of $PYY_{3-36}$ showed a peak at 15 min after injection, which was within the normal postprandial range (peak $PYY_{3-36}$ 15 min after i.p. injection of 0.3 μg per 100 g (body weight), $99.3 \pm 10.4\ pmol\ l^{-1}$; peak postprandial $PYY_{3-36}$, $112.1 \pm 7.8\ pmol\ l^{-1}$; $n = 8$–10 per group), suggesting that physiological concentrations of $PYY_{3-36}$ inhibit feeding. $PYY_{3-36}$ did not affect gastric emptying (percentage of food ingested remaining in the stomach at 3 h (ref. 9): $PYY_{3-36}$, 36 ± 1.9%; saline, 37.4 ± 1.0%; $n = 12$). $PYY_{3-36}$ that was administered i.p. twice daily for 7 d reduced cumulative food intake (7-d cumulative food intake: $PYY_{3-36}$, 187.6 ± 2.7 g; saline, 206.8 ± 2.3 g; $n = 8$ per group, $P < 0.0001$) and decreased body weight gain ($PYY_{3-36}$, 48.2 ± 1.3 g; saline, 58.7 ± 1.9 g; $n = 8$ per group, $P < 0.002$; Fig. 1b).





## A role for glucagon-like peptide-1 in the central regulation of feeding

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**The sequence of glucagon-like peptide-1 (7–36) amide (GLP-1) is completely conserved in all mammalian species studied, implying that it plays a critical physiological role[1]. We have shown that GLP-1 and its specific receptors are present in the hypothalamus[2,3]. No physiological role for central GLP-1 has been established. We report here that intracerebroventricular (ICV) GLP-1 powerfully inhibits feeding in fasted rats. ICV injection of the specific GLP-1-receptor antagonist, exendin (9-39)[4], blocked the inhibitory effect of GLP-1 on food intake. Exendin (9-39) alone had no influence on fast-induced feeding but more than doubled food intake in satiated rats, and augmented the feeding response to the appetite stimulant, neuropeptide Y. Induction of *c-fos* is a marker of neuronal activation[5]. Following ICV GLP-1 injection, *c-fos* appeared exclusively in the paraventricular nucleus of the hypothalamus and central nucleus of the amygdala, and this was inhibited by prior administration of exendin (9-39). Both of these regions of the brain are of primary importance in the regulation of feeding[6]. These findings suggest that central GLP-1 is a new physiological mediator of satiety.**

We report that ICV administration of GLP-1 reduces food intake in fasted rats, with greater effect at higher doses (Fig. 1b). ICV injection of GLP-1 in rats at the beginning of the dark (feeding) phase also results in a profound decrease in feeding (Fig. 1a). When administered intraperitoneally up to a dose of 500 μg, GLP-1 did not affect early dark-phase feeding (data not shown), suggesting that the action of GLP-1 on food intake is through central rather than peripheral mechanisms. A reduction in locomotor activity is a well defined part of the satiety sequence and follows nutrient ingestion[7]. In a subgroup of the animals given ICV GLP-1 at the beginning of the dark phase, locomotor activity was monitored by the frequency of line-crossing[8]. A significant reduction in activity was seen after ICV administration of GLP-1 (10 μg; 41 ± 7% of control activity, $P < 0.05$; 100 μg; 32 ± 9%, $P < 0.01$, $n = 8$ per group) compared to controls. Following ingestion of a palatable meal[9], the reduction in activity was similar to that observed following ICV injection of GLP-1 (10 μg) (palatable meal; 54 ± 19% of control activity, $P < 0.05$, $n = 6$). Although not assessed formally, the behaviour of the GLP-1-treated animals could not be distinguished, by observation, from those fed a palatable meal[10]. Fragments of GLP-1 are inactive peripherally[11]. To establish the specificity of GLP-1 on feeding,





We discovered the satiety action of these gut hormones.

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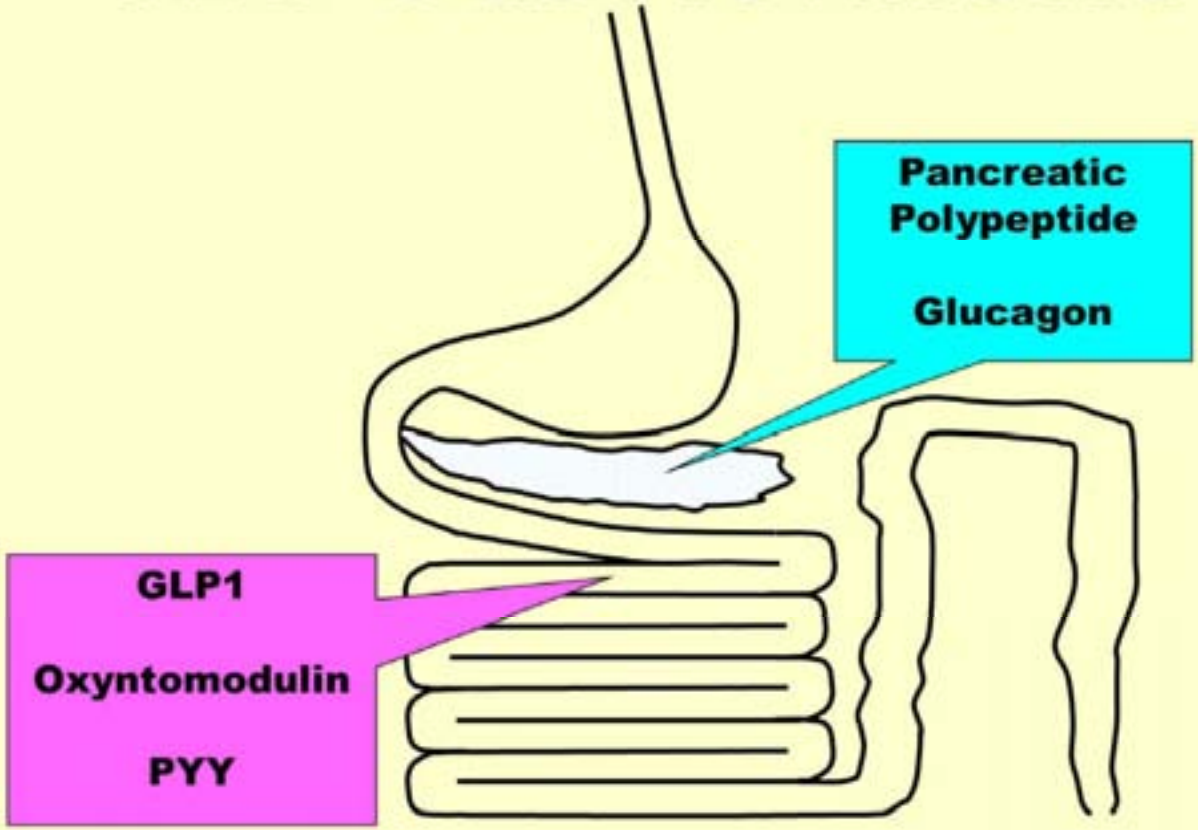
# Current Therapeutic Team Work

## The Gut Hormones




We work on five hormones to mimic safe physiological satiety.

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# Current Therapeutic Team Work

**SATIETY PEPTIDE STATUS**

Oxyntomodulin analogue being developed by Pfizer (Phase 1/2).
Pancreatic polypeptide analogue (Phase 1/2) ready to licence.

PYY funded through phase I in man, in laboratory.
GLP1 funded in discovery, in laboratory.
Glucagon funded in discovery, in laboratory.

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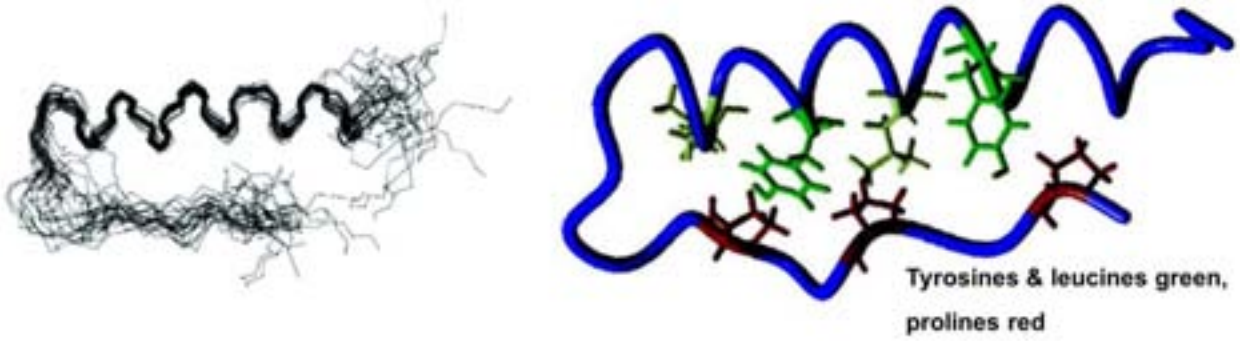
# Current Therapeutic Team Work

## PYY 1-36




We've produced hundreds of analogues of PYY to improve action and render the basic molecule long acting. Each has been extensively tested in animals, and chemically, and the very best chosen for further development.

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# Current Therapeutic Team Work

**GLP1 analogues established for diabetes mellitus - some weight loss.**

**We showed that a natural GLP1 family member, oxyntomodulin, had the additional action of increasing energy expenditure.**

**This produced much better weight loss*.**

**Both GLP1 analogues limited by nausea. For example at first dose of 10ug (usual therapeutic dose) of Byetta 2/3rds of subject feel sick and 1/3rd vomit.**

**We have designed a second generation series of GLP1 analogues with enhanced insulin stimulation, improved weight loss, long action and low nausea potential.**

*Dakin et al **Endocrinology** 2004, 145, 2687., Wynne et al **Diabetes** 2005, 54, 2390. , Wynne et al **Int J Obesity** 2005, 30, 1729., Liu et al **Int J Obesity** 2010, 34, 1715.

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# The Academic Therapeutic Team

| NAME | POST | WT/PT ON PROJECT |
|---|---|---|
| Steve Bloom | Professor & Head | Whole Time |
| James Minnion | Senior Post Doc | Whole Time |
| Tricia Tan | Consultant Physician | Part Time |
| Nima Khandan-Nia | Finance Manager | Part Time |
| Beverly Hull | Administrator | Part Time |
| Mohammad Ghatei | Professor | Part Time |
| Ben Field | Clinical Lecturer | Part Time |
| Joy Cuenco-Shillito | Senior Technician | Whole Time |
| Jamie Plumer | PhD student | Whole Time |
| Katherine Simpson | Clinical PhD Student | Whole Time |
| Jenny Parker | PhD student | Whole Time |
| Klara Hostomska | PhD student | Whole Time |
| Tanya Stezhka | Technician | Whole Time |
| Sagen Zac-Varghese | Clinical Lecturer | Whole Time |
| Rachel Troke | PhD student | Whole Time |
| Victoria Salem | Clinical PhD Student | Whole Time |


## HISTORY

- 1970 Steve Bloom began work on gut hormones and their roles.
- 1990 onwards demonstrated major CNS effects on appetite circuits.
- Aug 2005 published academic 4 week at home blinded study of oxyntomodulin in volunteers – very good weight loss achieved.
- Devised convenient once a day analogues for wt loss, IPR protected.


## HISTORY

- 2004 Dr John Burt and myself incorporated a new company, Thiakis.
- Exclusive licence from Imperial to develop oxyntomodulin and PYY.
- Worked with Nastech on nasal delivery - licence fee was received.
- Operated for two years on this fee.
- Ongoing research in the Imperial College.
- Visited many venture capital companies – unsuccessful!


# HISTORY

- March 2006 selected TKS1225 as the development analogue.
- Aug 2006 £10M venture funding for Thiakis.
- Engaged CROs to undertake GMP synthesis, pathtox, pharmacy and phase I trial.
- No toxicity, easy to synthesise and stable.
- Saw food intake reduction.


## HISTORY

- Dec 2008 sold to Wyeth for £100M (3 tranches).
- Wyeth bought by Pfizer a week later.
- OAP-189 is still in current development.

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# Conclusion

Successful drug development in academia not necessarily cheaper

Spot gaps or novel solutions

Drive to succeed can be strong

May have less distractions

Maybe intellectual atmosphere increases success

Grant environment now helpful but still has rigidities