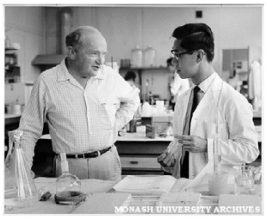
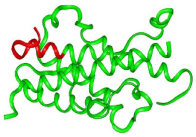
AOD9604 history

- Late 1970s to early 1990s – Bornstein & Ng with co-workers discover multifunctional domains of hGH:
  - Diabetogenic or hyperglycemic (increases blood sugar)
  - Hypoglycemic (decreases blood sugar)
  - Lactogenic (milk)
  - Somatogenic (muscle)
  - Lipolytic (fat)



- 1990s
  - Ng's focus shifts from searching for a cure to diabetes to a cure for obesity due to correlation between obesity and diabetes
  - R&D into lipolytic component of hGH confirms lipolytic and anti-lipogenic actions of C-terminal hGH peptides
  - Obese rodents treated with daily AOD peptides, showed reduction in body weight with no apparent adverse effects
  - No effect on non-obese rodents



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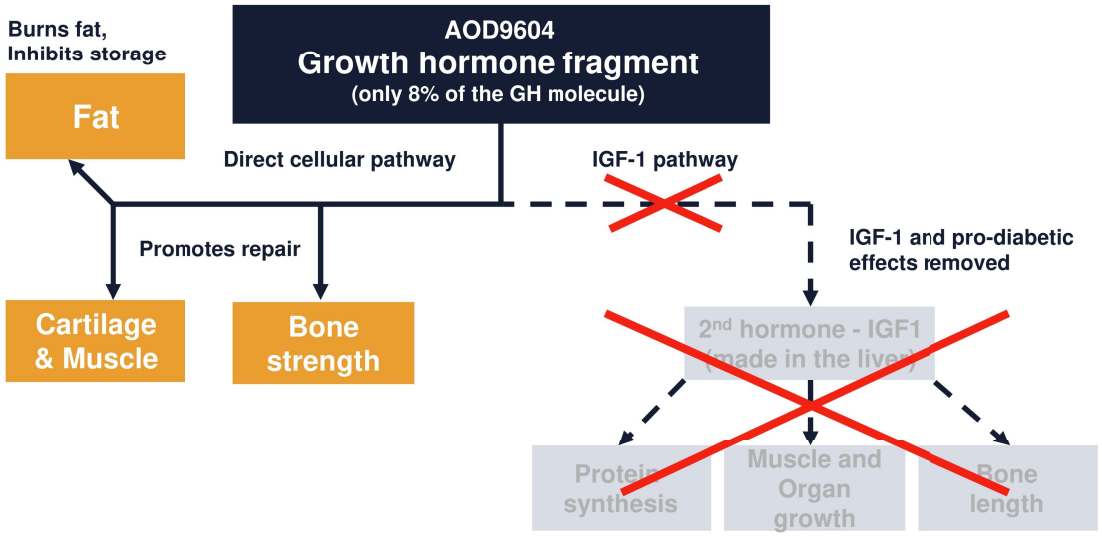
What is AOD9604?



Growth Hormone activates both the IGF-1 (crossed out) and direct cellular pathways. AOD9604 does not act on the IGF-1 pathway which causes significant insulin resistance and other negative side-effects

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AOD9604 at Metabolic

- Small, structurally conserved, fragment (<9%) of Growth Hormone(GH)
  - GH has many positive effects - promoting fat loss, lean muscle mass, bone & cartilage repair, pain relief
  - GH negative properties and safety concerns: pro-diabetic, induction of IGF-1, oedema, tumourigenesis, not orally available
- AOD9604 maintains some positive effects of GH
  - weight loss, bone strength, stem cell differentiation towards bone, cartilage and muscle repair
- AOD9604 advantages
  - Positive effects of GH with:
    - No induction of IGF-1
    - Anti-diabetic
    - Flexible delivery options - Injectable, oral, transdermal, potentially other
- Metabolic invested >$50 million deriving excellent safety data for AOD in animals and from extensive human clinical trials for obesity
- Human GRAS status

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Prior experience with AOD9604 in human obesity programme

- Safety and tolerability
  - Excellent safety profile in formal pre-clinical toxicology studies – acute and chronic dosing (More et al 2014)
  - Excellent results so far in two IV and four oral safety & efficacy studies in wide dose range involving 925 human subjects (Stier et al 2013)
  - No IGF-1 changes in animals or humans
- Efficacy
  - Reproducible weight loss in rodent models of obesity. Data independently verified (Lierop et al 2010, big pharma study 2005)
  - Clinical trial data indicated efficacy but was insufficient for Metabolic to progress to phase 3 trials in obesity
  - Note: Metabolic efficacy data similar in extent to full length GH in other published studies
- New Indications
  - Research programs in bone and joint
  - Strong case developed for osteoarthritis (OA)
  - Large potential in soft tissue repair and pain

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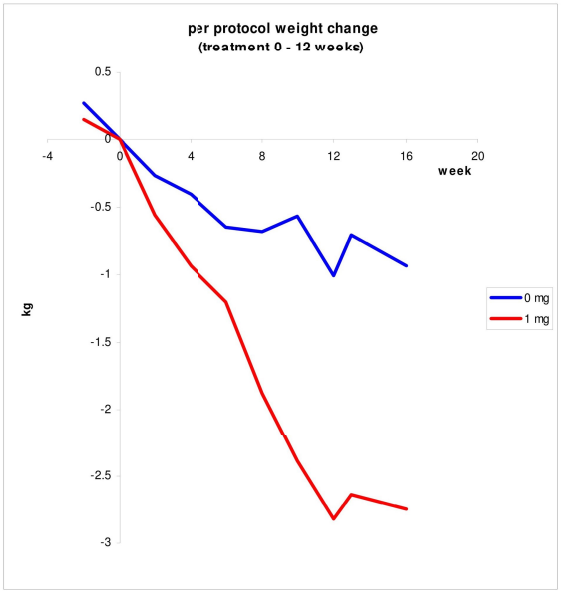
Phase 2, 3-Month Daily Oral Efficacy Trial



n = 300 patients
6 dose groups of 50 treated
– 0mg, 1mg, 5mg, 10mg, 20mg & 30 mg

Weight loss, All, 1mg, primary endpoint: p = 0.10

Weight loss, Females, 1mg: p = <0.04

Rate of weight loss, All, 1mg, secondary EP: p = <0.001

Rate of waistline reduction, all treated: p = <0.001 to 0.01

Trends and subgroup analyses - all groups
Suggested improvement in metabolic profiles :
•lipid profiles (LDL down, HDL/LDL up);
•progression to diabetes (IGT) recuced; and
•improved waistline measurements

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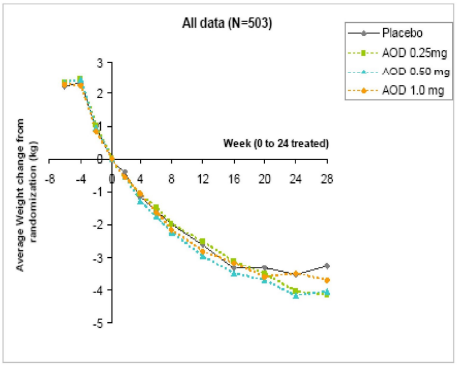
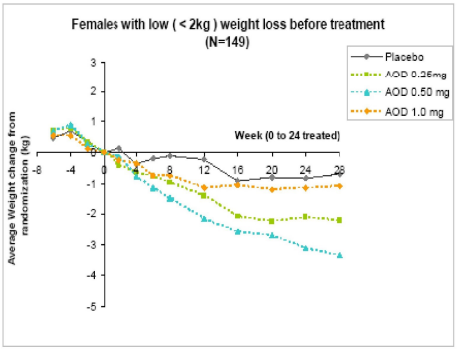
Phase 2, 24 Week Oral Efficacy Trial* results indicate limited effect on obesity





- Explored doses = or <1mg
- Oral availability issue may have thwarted efficacy
- Drug regimen complicated by changing from capsule to tablet
- Tough diet and exercise program washed out drug effect
  - Placebo in 6th trial lost 2.8kgs over 12 weeks
  - Placebo in 5th trial lost 1.0kgs over 12 weeks
- 2nd graph shows drug worked in 149 females who did not comply with formal diet and exercise program

* Trial not in compliance with FDA guidelines

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Meta-analysis of Non-complying females

Meta-analysis of non-complying women in Trial 5 & OPTIONS (Trial 6)

OUTCOME (Change in ... from baseline)	Comparison to the placebo	Change	P value
Weight (kg)	Combined - AOD9604 1mg	-1.403	0.0111
Weight (kg)	Combined - AOD9604 1mg / 0.5mg	-1.709	0.0003
Waist circumference (cm)	Combined - AOD9604 1mg / 0.5mg	-2.245	0.0247
BMI (kg/m^2)	Combined - AOD9604 1mg / 0.5mg	-0.622	0.0004
Systolic Blood Pressure (mmHg)	Trial 5 - AOD9604 1mg	-5.454	0.0414
Diastolic Blood Pressure (mmHg)	Trial 5 - AOD9604 1mg	-3.719	0.0421

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Safety of AOD9604 in Chronic Studies

Details of Chronic Exposure of Animals and Humans to AOD9604

Species	Number	Route of Delivery	Multiple of Human Daily Dose Equivalent (Assuming a conservative effective dose of 0.5mg/day)	Time Period of Dosing
Sprague Dawley Rats	20	Intravenous	280 (70mg/m^2)	4 weeks
Cynomolgus Monkeys	6	Intravenous	480 (120mg/m^2)	4 weeks
Wistar Rats	42	Oral gavage	2,800 (700mg/m^2)	26 weeks
Cynomolgus Monkeys	14	Oral gavage	2,400 (600mg/m^2)	39 weeks
Humans	38	Intravenous	4 to 64	Single dose
Humans	17	Capsule	108	Single dose
Humans	27	Capsule	18 to 108	7 days
Humans	238	Capsule	2, 10, 20, 40 & 60	12 weeks
Humans	377	Tablet	0.5, 1 & 2	24 weeks

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Recent Developments

- 2010
  - Unearthed the 'black market' trade in AOD9604
- 2011
  - Prof Grynpas study discovered the potent activity of AOD9604 on stem cells
  - Patented new applications of AOD9604 for muscle, cartilage, OA, pain and other indications
  - BodyShaper cosmetic product introduced by Phosphagenics containing AOD
- 2012
  - Conditional GRAS status achieved
  - Profs Grynpas & Kandel proved AOD's profound effect on progenitors for repair of muscle and cartilage
- 2013
  - Prof Kwon study showed positive effects in a rabbit model of Osteoarthritis
  - Unexpected discovery that AOD9604 has a significant effect on reducing pain
  - Large amount of anecdotal data showing efficacy in doctor prescribed AOD
- 2014
  - Compounding pharmacies, increased 'Black market' trade, GRAS status

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Osteoarthritis Market

- Osteoarthritis is a very common, chronic, debilitating disease that affects the joints in humans and companion animals
- A common ageing disease. Affects 33.6% of US adults over 65 (US Center for Disease Control & Prevention 2005)
- Global market $4.6bn in 2011 growing at 3.8% pa (Global Data)
- Current drugs offer only symptomatic relief, many generics eg systemic and topical NSAIDS, intra-articular Hyaluronic acid
- Common disease – Regulators have a high expectation of safety in any new drugs eg NGF Mabs. AOD has a GRAS status
- Pain relief has be demonstrated in trials and in anecdotal data

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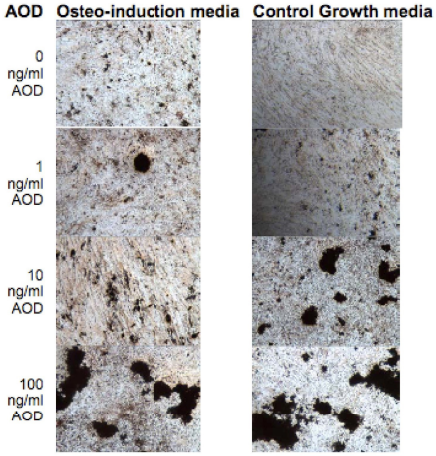
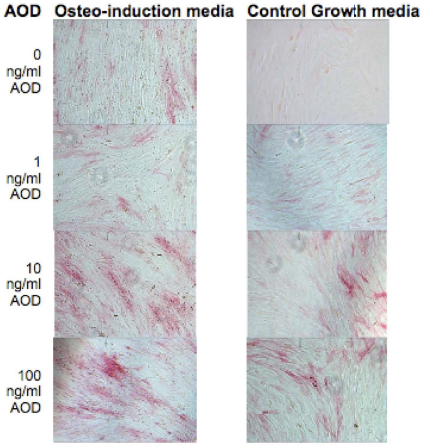
AOD9604 rationale for use in osteoarthritis

- GH positive effects on connective tissue (direct & via IGF-1):
  - GH reduces pain in fibromyalgia trials (Cuatrecasas et al 2012)
  - Intra-articular hGH is effective in rabbit OA models and enhances activity of Hyaluronic acid (Kim et al 2010)
- AOD9604 has positive effects on joint tissues in vitro
  - AOD promotes osteogenesis in MSC treated in vitro +/- osteogenic media
  - AOD promotes Myoblast differentiation in vitro and Chondrocyte production of Collagen and Proteoglycan
- AOD9604 has positive effects in animal models of bone and joint disease
  - Ovarectomized rat model of osteoporosis- bone quality
  - Collagenase-induced OA rabbit model – lameness and joint architecture
- AOD9604 pharmaceutical profile is suitable for osteoarthritis
  - Intra-articular, systemic or topical delivery
  - Extensive acute, chronic and reproductive animal and human safety database
  - Low cost of goods at large scale manufacture

AOD9604 promotes osteogenesis in adipose mesenchymal stem cells





AOD9604 also promotes murine myoblast differentiation and collagen and proteoglycan production by bovine chondrocytes *in vitro*

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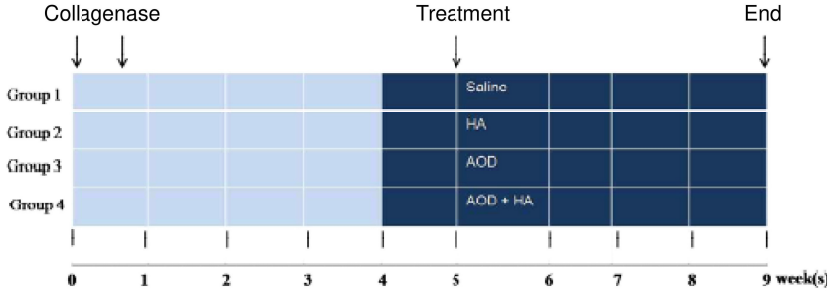
AOD9604 in osteoarthritis

- Rabbit collagenase model of osteoarthritis (Kim et al 2010)
- AOD given as a single intra-articular injection had similar efficacy to Hyaluronic acid (HA) on cartilage repair and recovery from lameness
- AOD combined with HA was significantly more effective than each given alone



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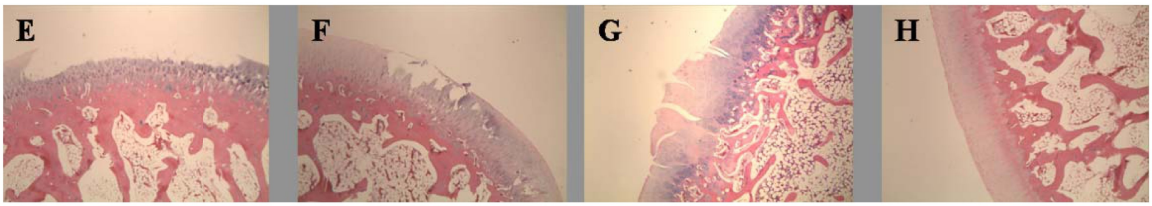
AOD9604 in rabbit osteoarthritis model

H&E stained rabbit knee joints, collagenase-induced arthritis model



Saline control | HA treated | AOD treated | AOD plus HA

	Group	Lameness period (day)	Macroscopic score	Histological score
Saline	G1	25 ± 2	4.2 ± 0.7	7.8 ± 0.6
HA	G2	15 ± 3*	2.5 ± 0.5*	4.6 ± 0.7*
AOD	G3	16 ± 2*	3.0 ± 0.5*	5.7 ± 1.3*
AOD & HA	G4	11 ± 4*,†	1.3±0.5*,†	2.5 ± 0.7*,†

Data are expressed as mean ± SD (n=8). * Significant differences compared with G1; $P<0.05$.

†Significant differences compared with G2 and G3; $P<0.05$.

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AOD9604 for osteoarthritis:

- Benign safety and tolerability profile based on animal studies and 925 human subjects
- Novel mechanism of action protected by patents, one filed Dec 2012
- Bone, cartilage and muscle repair with positive effects on mesenchymal stem cells
- Effective (and safe) by Intra-articular injection (combination with HA)
- Early recovery from lameness suggests pain relief effect
  - Opportunity for early clinical POC trials with sc or ia AOD9604
- Potential for once daily oral delivery
  - Systemic effects on metabolic profile advantageous in OA patients
- Cost of Goods and Manufacturing straightforward

- **Excellent profile for Osteoarthritis treatment in human and veterinary medicine**

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AOD9604 Manufacturing

- AOD9604 can be made by solid & liquid phase chemical synthesis and by recombinant means
- Feasibility work undertaken on both processes
- Previous trials, new clinical studies in OA and pharmacy API supplied by chemical synthesis
- For large scale market supply a fermentation approach is likely to be the most cost-effective. Will reduce COGs to 2c to 6c per dose (cf 6c to 12c for chemical synthesis)

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